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ARTICLE TYPE

Synthesis of Heteroarenes Dyads from Heteroarenes and Heteroarylsulfonyl Chlorides *via* Pd-Catalyzed Desulfitative C–H bond Heteroarylations

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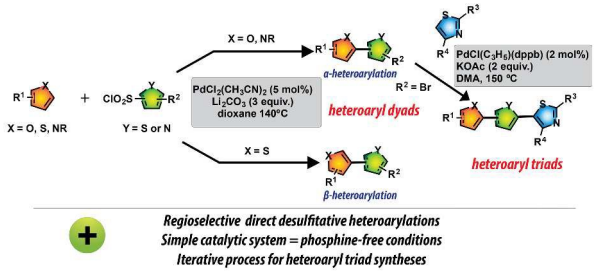
We report herein on the palladium-catalyzed direct heteroarylation of heteroarenes (e.g., pyrroles, furans, and thiophenes) in which heteroarylsulfonyl chlorides are used as coupling partners through a desulfitative cross-coupling. These C–H bond functionalizations occurred at the α-position in the case of pyrrole and furan derivatives, while in the case of thiophenes the C–H bonds at β position have been heteroarylated. This methodology represents a very simple access to heteroaryl dyads. Moreover, some examples of heteroaryl triads have been synthetized *via* iterative C–H bond arylations.



Introduction

Polyheteroaromatic compounds are well represented in organic chemistry. This motif is present in many pharmaceuticals. For examples, RITA an heteroaryl triads containing a furan 2,5-substituted by thiophenes, is a potent multi-target drug against cancer.[1] ER-38930, which possesses a pyrazole core, was also shown to markedly activate transactivation of the RARR receptor.[2] Benzofuranyl-pyrrole derivative **I** act as potent retinoic acid receptor α agonist.[3] Prodigiosine is a bright red tripyrrole pigment isolated from Serratia marcescens, which displays several biological activities such as antibacterial, anticoccidial, antimalarial, and antifungal activities, and is often used as a biochemical tool. Polyheteroaromatics can be also found in organometallic chemistry as ligands (e.g., bipyridines, polythiophenes, …) and for the preparation of electronic devices.

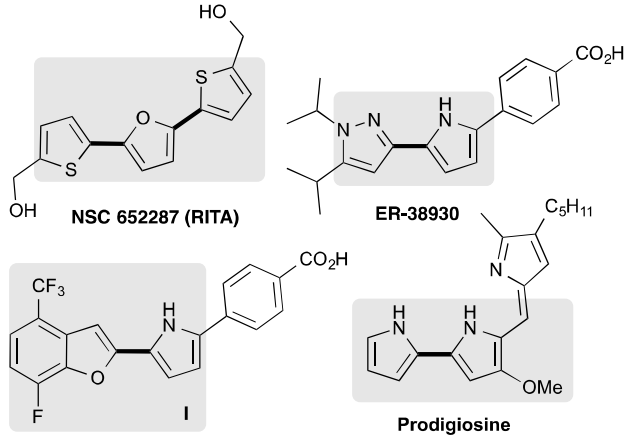


Figure 1. Relevant bioactive polyheteroaryl compounds

The abundance of polyheteroaromatic structures in organic compounds led to intense efforts to develop new methods for their synthesis over the last few decades.[4] Palladium catalysis is a very useful tool for the C–C bond formation.[5] The synthesis of heteroaryl dyads has been widely reported using palladium catalysis from organometallic reagents with heteroaryl halides (Figure 2A). Major contributions focused on the synthesis of C2–C2' heteroaryl dyads –which found some applications as electronic devices–[6] but a few examples of the synthesis C3–C2' or C3–C3' heteroaryl dyads have been also reported using trialkyl(heteroaryl)stannane derivatives and 2-haloheteroaryls,[7] or 3-haloheteroaryls.[7b, 8] On the other hand, palladium-catalyzed direct C–H bond arylation has emerged as one of the most suitable and eco-friendly alternative for the formation of C–C bonds, because of a simpler access to reactants with generation of lower amount of waste.[9] Palladium-catalyzed direct arylation of heteroarenes with heteroaryl halides for the formation of C2–C2' or C2–C3' heteroaryl dyads has been reported,[10] which includes intramolecular reactions,[11] moreover some applications in the synthesis of electronic devices were also described (Figure 1B).[12]

More recently, we reported the use of benzenesulfonyl chlorides as an original alternative to aryl halides for the direct arylation of heteroarenes through palladium-catalyzed desulfitative C–H bond functionalizations.[13] Benzenesulfonyl chlorides exhibits several advantages such as commercial availability for many of them at an affordable cost including heteroarylsulfonyl chlorides. They can also be easily prepared from sulfonic acids or sulfur substrates by chlorination.[14] In addition, palladium-catalyzed direct arylation of thiophenes with benzenesulfonyl chlorides offered different regioisomers than the reaction performed with aryl bromides.[13a] In the course of our previous study on Pd-catalyzed desulfitative cross-coupling

reactions, we demonstrated on one example that methyl 3-(chlorosulfonyl)thiophene-2-carboxylate might be used as coupling partner to afford a 3–3' dithiophene derivative in good yield (Figure 1C). To the best of our knowledge, this is the only example of such desulfitative direct heteroarylation reported in the literature. As a wide scope of heteroarylsulfonyl chlorides are commerically available and due to the lack of information concerning their reactivities in palladium-catalyzed desulfitative cross-coupling, their potentials in the synthesis of heteroaryl dyads and triads needed to be studied (Figure 1D).

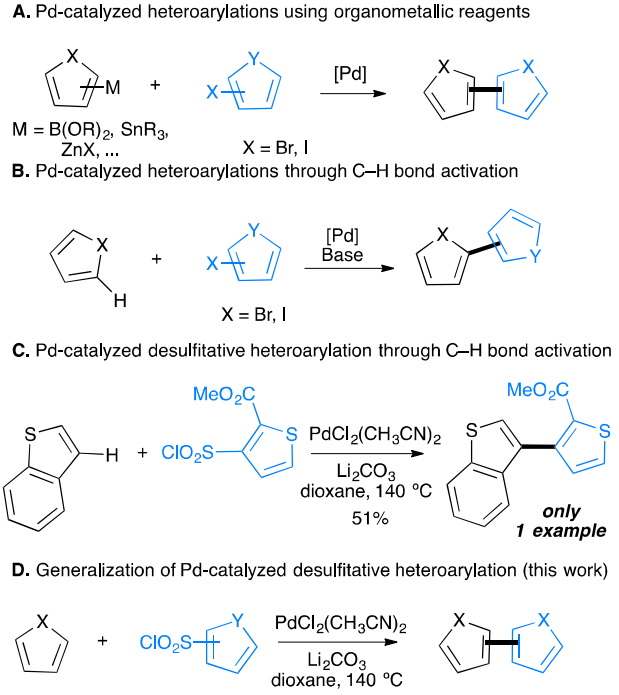
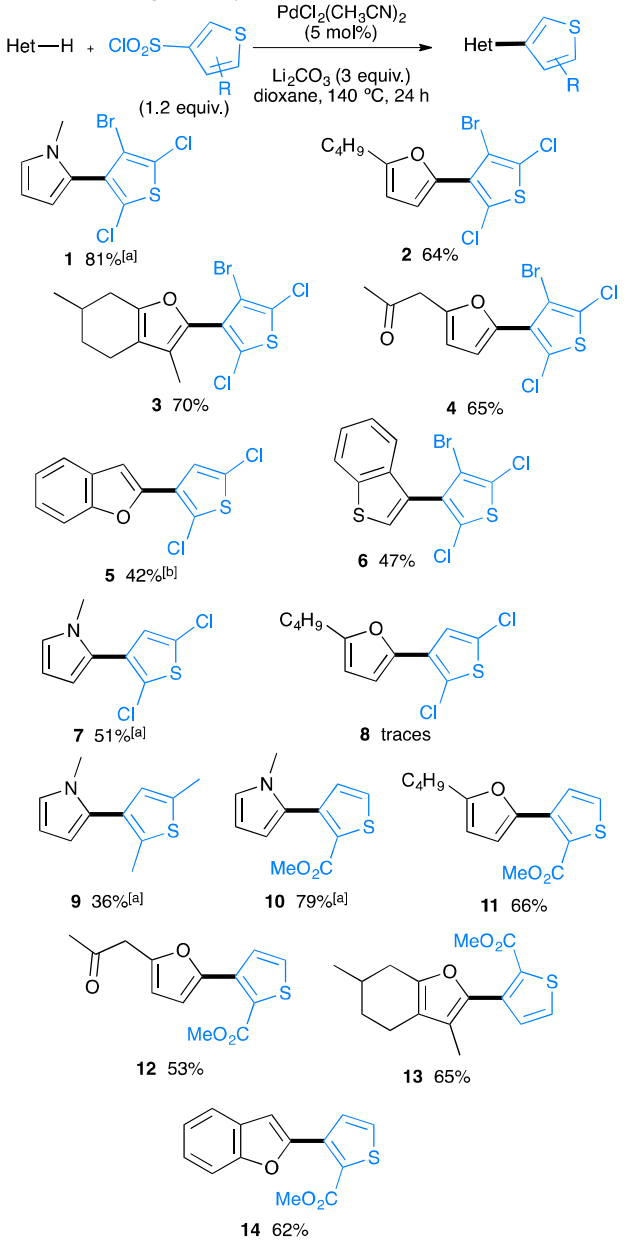


Figure 2. Palladium-catalyzed heteroarylation reactions

Result and Discussion

Firstly, we decided to investigate the reactivity of thiophene-3-sulfonyl chloride in palladium catalyzed desulfitative arylation reaction of 5-membered rings containing one heteroelement. We selected a fully substituted thiophene-3-sulfonyl chloride to prevent homocoupling side reactions. We attempted the heteroarylation of 1-methylpyrrole with 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride as heteroarylating agent using our previous best reaction conditions for such desulfitative C–H bond arylations,[13c] namely 5 mol% $PdCl_2(CH_3CN)_2$ in the presence of 3 equiv. of lithium carbonate in dioxane at 140 °C. We found that the reaction proceeded smoothly to afford the 2-heteroarylation product **1** in 81% yield. It is important to note that all C-halogen bonds including the C–Br one were untouched during the reaction, which allows further transformations. Then, we attempted the reaction using furan derivatives as the coupling partners. Both 2-*n*-butylfuran and menthofuran were regioselectively heteroarylated at C5-position to give **2** and **3** in 64% and 70% yields, respectively. Interestingly, the reaction conditions tolerates enolizable ketone substituent as 1-(furan-2-yl)propan-2-one reacted with 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride to provide the desired arylated product **4** in 65% yield. The reaction performed with benzofuran as the starting material led to the unexpected debrominated coupling product **5** in 42% yield. Benzothiophene was arylated at C3-position to give the desired thiophene dyad **6** in moderate yield.

Nevertheless, this result could be an opening wedge in original and efficient synthesis of 3,3'-bithiophene derivatives. We investigated next the reactivity of other thiophene-3-sulfonyl chlorides. Thiophene bearing only chloro or methyl substituents at the positions 2 and 5 afforded the coupling products with 1-methylpyrrole **7** and **9** in lower yields of 51% and 36%, respectively. Moreover, no reaction occurred between 2,5-dichlorothiophene-3-sulfonyl chloride and 2-*n*-butylfuran. Finally, we found that the reaction proceeded in high yield with a thiophene-3-sulfonyl chloride bearing an electron-withdrawing group at C2. Indeed, the desulfitative heteroarylation in which methyl 3-(chlorosulfonyl)thiophene-2-carboxylate was used as coupling partner allowed the formation of the desired products **10-14** in good yields whatever the heteroarene.

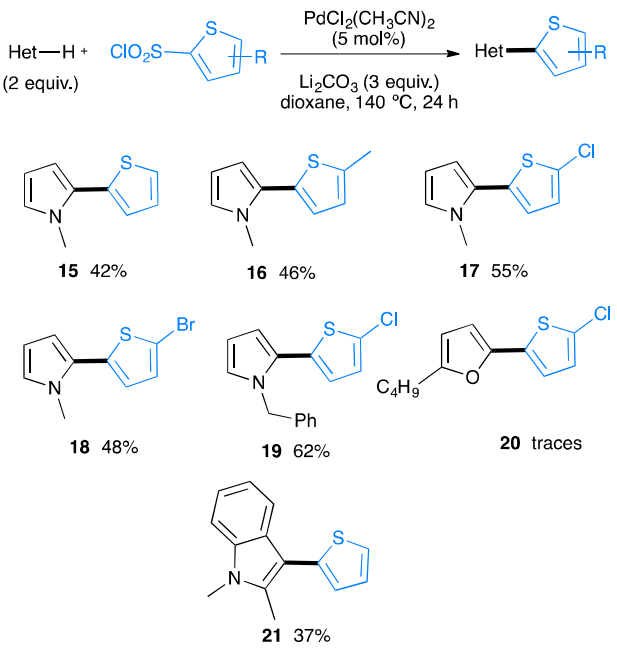


[a] 1-Methylpyrrole (2 equiv.), $HetArSO_2Cl$ (1 equiv.); [b] Reaction performed from 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride

Scheme 1. Palladium-catalyzed direct desulfitative heteroarylations using thiophene-3-sulfonyl chloride derivatives.

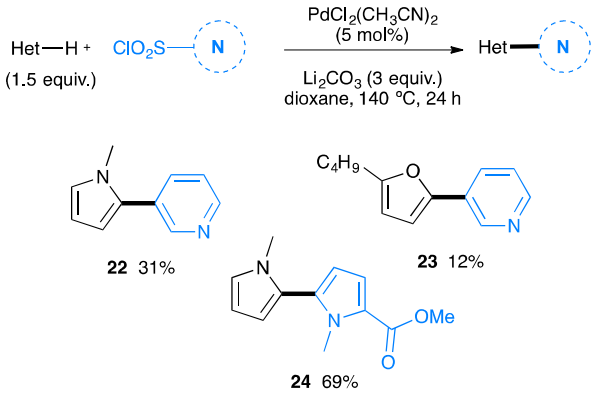
We next turned our attention to the reactivity of thiophene-2-

sulfonyl chlorides as the heteroarylating agents in such coupling reactions (Scheme 2). Overall, these derivatives displayed a lower reactivity than their 3-substituted homologues. Unsubstituted thiophene-2-sulfonyl chloride was coupled with 1-methylpyrrole to furnish 1-methyl-2-(thiophen-2-yl)pyrrole (**15**) in 42% yield. Then, we studied the influence of substituents at the C5 position on thiophene-2-sulfonyl chlorides. With thiophene-2-sulfonyl chloride substituted by a C5 methyl substituent, a slightly better yield of 46% in favor of the desired coupling product **16** was obtained. Chloro or bromo substituents at the C5 position of thiophene-2-sulfonyl chlorides were also tolerated by the reaction conditions to afford the thiophenylpyrrole derivatives **17** and **18** in 55% and 48% yields, respectively. Again, these reaction conditions were completely chemoselective, as C–X bond was not involved in the direct arylation process, allowing further transformations through iterative processes. 1-Benzylpyrrole has been heteroarylated affording **19** in 62% yield using the most reactive 5-chlorothiophene-2-sulfonyl chloride; whereas, 2-*n*-butylfuran was found to be unreactive. 3-Heteroarylated 1,2-dimethylindole **21** was synthetized in moderate yield using 2-thiophene-2-sulfonyl chloride.



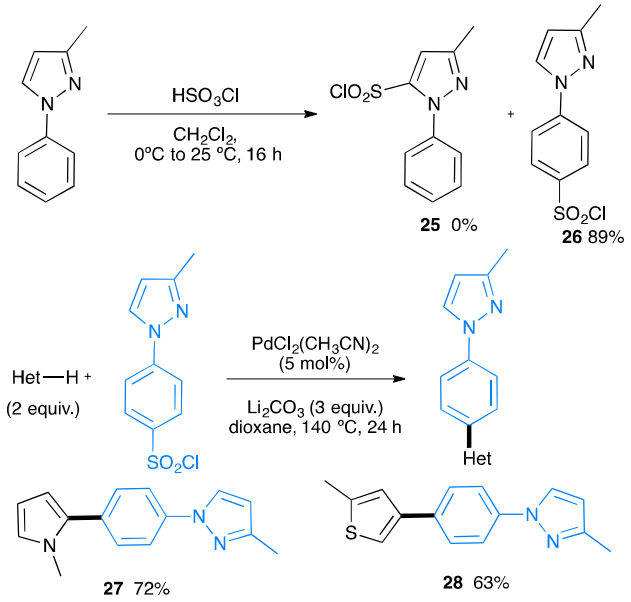
Scheme 2. Palladium-catalyzed direct desulfitative heteroarylations using thiophene-2-sulfonyl chloride derivatives.

Next, we examinated the reactivity of nitrogen containing heteroarylsulfonyl chloride derivatives as the heteroarylating agents (Scheme 3). Pyridine-3-sulfonyl chloride displayed a very low reactivity. For example, the coupling products with 1-methylpyrrole or 2-*n*-butylfuran gave **22** and **23** in only 31% and 12% yields, respectively. This heteroarylpyridine synthesis pathway is not attractive compared to the reaction performed using 3-bromopyridine as the arylation agent through also a C–H bond activation.[15] On the other hand, the preparation of 2-bromo-1-methylpyrrole is challenging due to over-bromination or decomposition,[16] whereas 1-methylpyrrole-2-sulfonyl chlorides can be easily prepared from 1-methylpyrroles by chlorosulfonylation using chlorosulfuric acid. Moreover, some pyrrole-2-sulfonyl chlorides are commercially available. The reaction between 1-methylpyrrole and methyl 5-(chlorosulfonyl)-1-methylpyrrole-2-carboxylate allowed the formation of pyrrole dyad **24** in 69% yield.



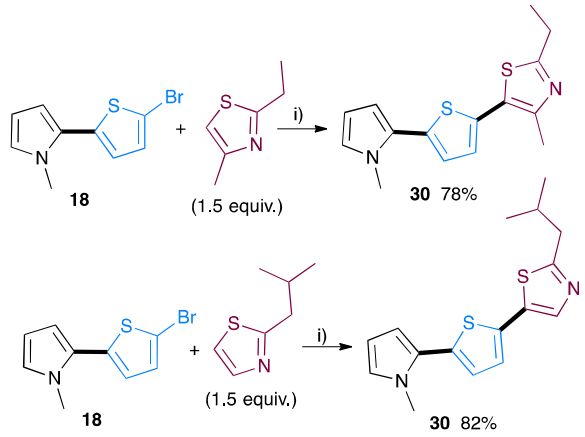
Scheme 3. Palladium-catalyzed direct desulfitative heteroarylations using nitrogen-containing sulfonyl chloride derivatives.

In order to get a wider substrate scope, the synthesis of a pyrazole unit bearing a chlorosulfonyl function was attempted. Starting from 3-methyl-1-phenylpyrazole, we expected that the use of chlorosulfonic acid would provide the pyrazole **25**, in which the chlorosulfonyl function would be introduced at the C5-position. However, we only observed the formation of the regioisomer **26**, which is formed by the activation of the *para* C–H bond of the phenyl ring (Scheme 4, top). This regioselectivity is different to the bromination of pyrazole with NBS, which proceeds at the pyrazole C4-position. With substrate **26** in hands, we investigated its reactivity in palladium-catalyzed desulfitative arylations for the synthesis of (hetero)aryl triads (Scheme 4, bottom). The arylation of 1-methylpyrrole took place at the expected C2 position allowing the formation of the triaryl **27** in 72% yield, while 2-methylthiophene was arylated at the C4-position to give the desired product **28** in 63% yield. It is important to note that such triaryls exhibit a similar structure to N6022, which is a potent *S*-nitrosoglutathione reductase inhibitor in clinical development–[17] and this elegant synthetic pathway might provide an easier access to new analogues.



Scheme **4**. Synthesis of (hetero)aryl triads from 4-(3-methylpyrazol-1-yl)benzenesulfonyl chloride via Pd-catalyzed direct desulfitative arylation.

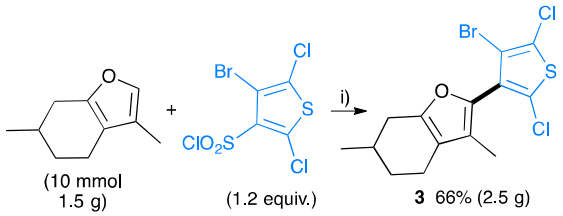
Finally, thanks to the high chemoselectivity of these palladium-catalyzed desulfitative heteroarylations, in which the C-Br bonds remained untouched, we conducted a second direct arylation for the synthesis of heteroaryl triad compounds (Scheme 5). As examples, the derivative **18,** which bears a C-Br bond at C2-position on the thiophene ring, was heteroarylated –using our previous reaction conditions–[10i] affording the triad **29** and **30** in 78% and 82% yields, respectively, through a C–H bond activation of thiazoles.



i) $PdCl(C_3H_5)(dppb)$ (2 mol%), KOAc (2 equiv.), DMA, 150 °C, 16 h.

Scheme 5. Application to the synthesis of heteroaryl triads.

As heteroaryl dyads are important building blocks in the preparation of pharmaceuticals or electronic devices, we demonstrated the scalability of Pd-catalyzed desulfitative heteroarylation. The reaction was conducted on 10 mmol scale and afforded 2.5 g of the compound **3** after purification (Scheme 6).



i) $PdCl_2(CH_3CN)_2$ (5 mol%), Li_2CO_3 (3 equiv.), 1,4-dioxane, 140 °C, 24 h

Scheme 6. Application to gram-scale synthesis.

Although the exact mechanism is not completely elucidated, we can propose a reasonable pathway for palladium-catalyzed direct heteroarylation of heteroarenes (Figure 3). Based on Dong and co-workers report,[18] the first step might be an oxidative addition of the heteroarylsulfonyl chloride to Pd(II) to afford the Pd(IV) intermediate **A**. Then, a SO_2 extrusion occurred to afford electrophilic aryl-palladium(II) specie **B**. An electrophilic palladation of thiophene at β-position affords the intermediate **C**; whereas with pyrroles and furans, the electrophilic palladation occurred at α-position affording **E** intermediate. Then, the base assisted the rearomatization process gives the intermediates **D** and **F**, which undergo reductive elimination to afford the desired arylated products and regenerates the Pd(II) catalysts. However, a Pd(0)/P(II) catalytic cycle cannot be excluded.

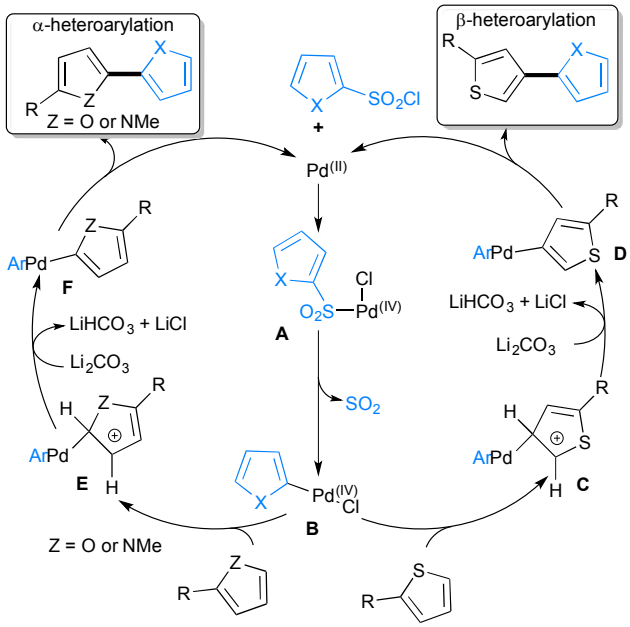


Figure 3. Proposed mechanism for palladium-catalyzed desulfitative heteroarylation reactions.

Conclusions

In summary, we have developed a new methodology for the one-step synthesis of heteroaryl dyads based on palladium-catalyzed desulfitative heteroarylation through a C–H bond activation of heteroarenes. We established that 5 mol% $PdCl_2(CH_3CN)_2$ catalyst in the presence of Li_2CO_3 as base in dioxane promotes the desulfitative heteroarylation of a variety of heteroarenes such as thiophenes, furans, and pyrroles –which is the most reactive

substrates– with diverse heteroarylsulfonyl chlorides as coupling partners. Thiophene-3-sulfonyl chloride derivatives generally displayed a high reactivity, while thiophene-2-sulfonyl chloride derivatives have been smoothly reacted only with 1-methylpyrrole. Other heteroarylsulfonyl chlorides containing nitrogen atom have also been successfully used. It is important to note that with heteroarylsulfonyl chlorides, uncommon functionalization at the C3-position occured with thiophenes. Moreover, other regioisomers could be obtained using chlorosulfonylation instead of bromination, as demonstrated with a 1-phenylpyrazole. In addition, such cross-coupling reactions are very chemoselective as C–Br bonds were untouched allowing iterative direct arylations for the synthesis of heteroaryl triads in only two steps.

Experimental section

General: All reactions were carried out under argon atmosphere with standard Schlenk-tube techniques. HPLC grade 1,4-dioxane was used and stored under argon without further purification. ^{1}H NMR spectra were recorded on Bruker GPX (400 MHz or 300 MHz) spectrometer. Chemical shifts (d) 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.

Preparation of the PdCl(C_3H_5)(dppb) catalyst:[19] 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 powder was used without purification. (^{31}P 381 MHz, $CDCl_3$) δ = 19.3 (s).

General procedure for synthesis of heteroarylated heteroarenes: To a 25 mL oven dried Schlenk tube, heteroarylsulfonyl chloride (1–1.2 mmol), heteroarenes (1–4 mmol), Li_2CO_3 (0.222 g, 3 mmol), 1,4-dioxane (2 mL) and $PdCl_2(CH_3CN)_2$ (12.9 mg, 0.05 mmol) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 140 ºC (oil bath temperature) for 24 h (see tables and schemes). After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the heteroarylated heteroarens.

2-(4-Bromo-2,5-dichlorothiophen-3-yl)-1-methylpyrrole (1): 1-Methylpyrrole (0.162 g, 2 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.330 g, 1 mmol) affords **1** in 81 % (0.252 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.78 (t, *J* = 2.3 Hz, 1H), 6.26 (t, *J* = 3.1 Hz, 1H), 6.22 (dd, *J* = 1.9 and 3.6 Hz, 1H), 3.50 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 132.0, 126.6, 123.8, 123.5, 123.0, 114.0, 111.5, 107.9, 34.4.

Elemental analysis: calcd (%) for $C_9H_6BrCl_2NS$ (311.02): C 34.76, H 1.94; found: C 34.85, H 2.07.

2-(4-Bromo-2,5-dichlorothiophen-3-yl)-5-butylfuran (2): 2-*n*-Butylfuran (0.124 g, 1 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.396 g, 1.2 mmol) affords **2** in 64 % (0.227 g) yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.70 (d, *J* = 3.3 Hz, 1H), 6.12 (d, *J* = 3.3 Hz, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 1.69 (quint., *J* = 7.6 Hz, 2H), 1.41 (sext., *J* = 7.6 Hz, 2H), 0.95 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 150.4, 136.5, 122.1, 116.9, 116.3, 105.3, 103.5, 99.3, 23.1, 20.8, 15.3, 6.8.

Elemental analysis: calcd (%) for $C_{12}H_{11}BrCl_2OS$ (354.08): C 40.71, H 3.13; found: C 40.82, H 3.36.

2-(4-Bromo-2,5-dichlorothiophen-3-yl)-3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran (3): Menthofuran (0.150 g, 1 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.396 g, 1.2 mmol) affords **3** in 70% (0.266 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.71 (dd, *J* = 5.1 and 16.4 Hz, 1H), 2.47-2.33 (m, 2H), 2.27-2.18 (m, 1H), 2.01-1.97 (m, 1H), 1.90 (s, 3H), 1.88-1.82 (m, 1H), 1.46-1.35 (m, 1H), 1.1 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 151.7, 138.4, 130.6, 125.9, 123.2, 121.0, 118.5, 112.8, 31.5, 31.2, 29.6, 21.6, 20.2, 9.3.

Elemental analysis: calcd (%) for $C_{14}H_{13}BrCl_2OS$ (380.12): C 44.24, H 3.45; found: C 44.37, H 3.56.

1-(5-(4-Bromo-2,5-dichlorothiophen-3-yl)furan-2-yl)propan-2-one (4): 1-(Furan-2-yl)propan-2-one (0.124 g, 1 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.396 g, 1.2 mmol) affords **4** in 70% (0.248 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.75 (d, *J* = 3.2 Hz, 1H), 6.35 (d, *J* = 3.2 Hz, 1H), 3.77 (s, 2H), 2.22 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.6, 148.9, 144.8, 128.6, 124.2, 124.1, 112.7, 110.4, 109.7, 43.4, 29.4.

Elemental analysis: calcd (%) for $C_{11}H_7BrCl_2O_2S$ (354.04): C 37.32, H 1.99; found: C 37.59, H 1.81.

2-(2,5-Dichlorothiophen-3-yl)benzofuran (5): Benzofuran (0.118 g, 1 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.396 g, 1.2 mmol) affords **5** in 42% (0.113 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61 (d, *J* = 7.7 Hz, 1H), 7.5 (d, *J* = 7.7 Hz, 1H), 7.35-7.32 (m, 2H), 7.28-7.23 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 153.8, 148.9, 128.7, 128.3, 127.1, 125.1, 125.0, 123.2, 122.5, 121.3, 111.2, 104.8.

Elemental analysis: calcd (%) for $C_{12}H_6Cl_2OS$ (269.14): C 53.55, H 2.25; found: C 53.81, H 2.37.

3-(4-Bromo-2,5-dichlorothiophen-3-yl)benzo[*b*]thiophene (6): Benzothiophene (0.134 g, 1 mmol) and 4-bromo-2,5-dichlorothiophene-3-sulfonyl chloride (0.396 g, 1.2 mmol) affords **6** in 47% (0.171 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.94-7.91 (m, 1H), 7.55-7.51 (m, 1H), 7.49 (s, 1H), 7.41 (q, *J* = 5.3 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.6, 137.4, 133.5, 128.1, 128.1, 128.0, 124.7, 124.4, 123.6, 123.2, 122.8, 112.8.

Elemental analysis: calcd (%) for $C_{12}H_5BrCl_2S_2$ (364.10): C 39.59, H 1.38; found: C 39.79, H 1.12.

2-(2,5-Dichlorothiophen-3-yl)-1-methylpyrrole (7): 1-Methylpyrrole

(0.162 g, 2 mmol) and 2,5-dichlorothiophene-3-sulfonyl chloride (0.251 g, 1 mmol) affords **7** in 51% (0.118 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.79 (s, 1H), 6.73 (dd, *J* = 1.8 and 3.1 Hz, 1H), 6.27 (dd, *J* = 1.8 and 3.1 Hz, 1H), 6.22 (t, *J* = 3.1 Hz, 1H), 3.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 130.8, 127.9, 126.1, 125.1, 124.1, 123.5, 110.6, 107.9, 34.8.

Elemental analysis: calcd (%) for $C_9H_7Cl_2NS$ (232.12): C 46.57, H 3.04; found: C 46.71, H 3.32.

2-(2,5-Dimethylthiophen-3-yl)-1-methylpyrrole (9): 1-Methylpyrrole (0.162 g, 2 mmol) and 2,5-dimethylthiophene-3-sulfonyl chloride (0.211 g, 1 mmol) affords **9** in 36% (0.069 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.68 (t, *J* = 2.3 Hz, 1H), 6.58 (s, 1H), 6.19 (t, *J* = 3.1 Hz, 1H), 6.07 (dd, *J* = 1.7 and 3.5 Hz, 1H), 5.52 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 135.2, 134.8, 129.8, 128.8, 127.4, 122.0, 109.0, 107.3, 34.5, 15.3, 14.0.

Elemental analysis: calcd (%) for $C_{11}H_{13}NS$ (191.29): C 69.07, H 6.85; found: C 69.33, H 7.05.

Methyl 3-(1-methylpyrrol-2-yl)thiophene-2-carboxylate (10): 1-Methylpyrrole (0.162 g, 2 mmol) and methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (0.241 g, 1 mmol) affords **9** in 79% (0.175 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.51 (d, *J* = 5.1 Hz, 1H), 7.07 (d, *J* = 5.1 Hz, 1H), 6.77 (t, *J* = 2.3 Hz, 1H), 6.23-6.21 (m, 2H), 3.81 (s, 3H), 3.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.0, 139.5, 132.2, 131.9, 130.0, 128.4, 127.3, 123.2, 109.6, 107.5, 52.0, 34.4.

Elemental analysis: calcd (%) for $C_{11}H_{11}NO_2S$ (221.27): C 59.71, H 5.01; found: C 59.87, H 5.28.

Methyl 3-(5-butylfuran-2-yl)thiophene-2-carboxylate (11): 2-*n*-Butylfuran (0.124 g, 1 mmol) and methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (0.289 g, 1.2 mmol) affords **11** in 66% (0.174 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53 (d, *J* = 5.3 Hz, 1H), 7.48 (d, *J* = 3.3 Hz, 1H), 7.44 (d, *J* = 5.3 Hz, 1H), 6.12 (d, *J* = 3.1 Hz, 1H), 3.88 (s, 3H), 2.68 (t, *J* = 7.5 Hz, 2H), 1.67 (quint., *J* = 7.5 Hz, 2H), 1.41 (sext., *J* = 7.5 Hz, 2H), 0.95 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.4, 156.8, 147.3, 137.2, 130.1, 128.5, 122.8, 113.9, 107.5, 52.0, 30.2, 27.9, 22.3, 13.9.

Elemental analysis: calcd (%) for $C_{14}H_{16}O_3S$ (264.34): C 63.61, H 6.10; found: C 63.85, H 6.27.

Methyl 3-(5-(2-oxopropyl)furan-2-yl)thiophene-2-carboxylate (12): 1-(Furan-2-yl)propan-2-one (0.124 g, 1 mmol) and methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (0.289 g, 1.2 mmol) affords **12** in 53% (0.140 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.53-7.47 (m, 2H), 7.46-7.42 (m, 1H), 6.33 (d, *J* = 2.9 Hz, 1H), 3.87 (s, 3H), 3.75 (s, 2H), 2.19 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 203.5, 162.2, 148.7, 148.1, 136.4, 130.2, 128.5, 123.9, 113.9, 110.8, 52.0, 43.4, 29.1.

Elemental analysis: calcd (%) for $C_{13}H_{12}O_4S$ (264.30): C 59.08, H 4.58; found: C 59.26, H 4.81.

Methyl 3-(3,6-dimethyl-4,5,6,7-tetrahydrobenzofuran-2-yl)thiophene-2-carboxylate (13): Menthofuran (0.150 g, 1 mmol) and methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (0.289 g, 1.2 mmol) affords **13** in 65% (0.189g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.46 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 5.1 Hz, 1H), 3.84 (s, 3H), 2.71 (dd, *J* = 5.4 and 16.5 Hz, 1H), 2.49-2.33 (m, 2H), 2.27-2.19 (m, 1H), 2.00-1.93 (m, 1H), 1.91 (s, 3H), 1.90-1.82 (m, 1H), 1.46-1.44 (m, 1H), 1.1 (d, *J* = 6.6 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.1, 150.6, 142.0, 137.2, 130.2, 129.9, 126.5, 119.9, 119.2, 52.0, 31.4, 31.3, 29.6, 21.6, 20.2, 9.8.

Elemental analysis: calcd (%) for $C_{16}H_{18}O_3S$ (290.38): C 66.18, H 6.25; found: C 66.42, H 6.39.

Methyl 3-(benzofuran-2-yl)thiophene-2-carboxylate (14): Benzofuran (0.118 g, 1 mmol) and methyl 3-(chlorosulfonyl)thiophene-2-carboxylate (0.289 g, 1.2 mmol) affords **14** in 62% (0.160g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.97 (d, *J* = 1.0 Hz, 1H), 7.74 (d, *J* = 5.3 Hz, 1H), 7.65 (dd, *J* = 1.4 and 7.7 Hz, 1H), 7.53 (d, *J* = 5.4 Hz, 1H), 7.50-7.49 (m, 1H), 7.33 (ddd, *J* = 1.5, 7.1 and 8.2 Hz, 1H), 7.28-7.22 (m, 1H), 3.93 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 162.1, 154.3, 150.2, 136.4, 130.3, 129.4, 129.2, 126.5, 125.2, 122.9, 121.8, 111.0, 108.8, 52.2.

Elemental analysis: calcd (%) for $C_{14}H_{10}O_3S$ (258.29): C 65.10, H 3.90; found: C 65.31, H 4.17.

1-Methyl-2-(thiophen-2-yl)pyrrole (15): 1-Methylpyrrole (0.162 g, 2 mmol) and thiophene-2-sulfonyl chloride (0.182 g, 1 mmol) affords **15** in 42% (0.069 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25 (d, *J* = 5.1 Hz, 1H), 7.06 (dd, *J* = 3.8 and 5.1 Hz, 1H), 7.02 (d, *J* = 3.8 Hz, 1H), 6.72-6.68 (m, 1H), 6.35-6.30 (m, 1H), 6.16 (t, *J* = 4.0 Hz, 1H), 3.71 (s, 3H).

This is a known compound and the spectral data are identical to those reported in literature.[20]

1-Methyl-2-(5-methylthiophen-2-yl)pyrrole (16): 1-Methylpyrrole (0.162 g, 2 mmol) and 5-methylthiophene-2-sulfonyl chloride (0.182 g, 1 mmol) affords **16** in 46% (0.082 g) yield.

^{1}H NMR (400 MHz, DMSO-*d*-6) δ (ppm) 6.90 (s, 1H), 6.82 (s, 1H), 6.81 (s, 1H), 6.14 (s, 1H), 6.01 (s, 1H), 3.66 (s, 3H), 2.43 (s, 3H).

This is a known compound and the spectral data are identical to those reported in literature.[21]

2-(5-Chlorothiophen-2-yl)-1-methylpyrrole (17): 1-Methylpyrrole (0.162 g, 2 mmol) and 5-chlorothiophene-2-sulfonyl chloride (0.217 g, 1 mmol) affords **17** in 55% (0.109 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45 (d, *J* = 4.1 Hz, 1H), 7.03 (dd, *J* = 1.6 and 3.8 Hz, 1H), 6.93 (d, *J* = 4.1 Hz, 1H), 6.83 (t, *J* = 2.3 Hz, 1H), 6.21 (dd, *J* = 2.6 and 4.1 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.1, 138.6, 131.6, 130.2, 128.1, 127.0, 119.0, 108.7, 35.8.

Elemental analysis: calcd (%) for C_9H_8ClNS (197.68): C 54.68, H 4.08; found: C 54.89, H 3.83.

2-(5-Bromothiophen-2-yl)-1-methylpyrrole (18): 1-Methylpyrrole (0.162 g, 2 mmol) and 5-bromothiophene-2-sulfonyl chloride (0.217 g, 1 mmol) affords **18** in 48% (0.116 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.39 (d, J = 4.0 Hz, 1H), 7.04 (d, J = 4.0 Hz, 1H), 7.01 (dd, J = 1.9 and 4.1 Hz, 1H), 6.81 (t, J = 2.3 Hz, 1H), 6.19 (dd, J = 2.6 and 4.1 Hz, 1H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 145.2, 132.3, 130.6, 130.2, 128.1, 121.2, 119.0, 108.7, 35.8.

Elemental analysis: calcd (%) for C_9H_8BrNS (242.13): C 44.64, H 3.33; found: C 44.97, H 3.12.

1-Benzyl-2-(5-chlorothiophen-2-yl)pyrrole (19): 1-Benzylpyrrole (0.314 g, 2 mmol) and 5-bromothiophene-2-sulfonyl chloride (0.217 g, 1 mmol) affords **19** in 62% (0.169 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41-7.26 (m, 5H), 7.1 (d, J = 7.9 Hz, 2H), 6.63 (t, J = 2.6 Hz, 1H), 6.14 (t, J = 3.4 Hz, 1H), 6.10-6.08 (m, 1H), 5.09 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 137.4, 136.6, 134.2, 128.9, 128.7, 128.6, 126.8, 126.6, 120.7, 108.3, 106.9, 106.7, 50.3.

Elemental analysis: calcd (%) for $C_{15}H_{12}ClNS$ (273.78): C 65.81, H 4.42; found: C 66.07, H 4.61.

1,2-Dimethyl-3-(thiophen-2-yl)-indole (21): 1,2-Dimethylindole (0.290 g, 2 mmol) and thiophene-2-sulfonyl chloride (0.182 g, 1 mmol) affords **21** in 37% (0.084 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.80 (d, J = 7.8 Hz, 1H), 7.27-7.35 (m, 2H), 7.22 (ddd, J = 0.9, 7.1 and 8.0 Hz, 1H), 7.11-7.18 (m, 2H), 7.09 (dd, J = 0.9 and 3.7 Hz, 1H), 3.73 (s, 3H), 2.56 (s, 3H).

This is a known compound and the spectral data are identical to those reported in literature.[22]

3-(1-Methylpyrrol-2-yl)pyridine (22): 1-Methylpyrrole (0.162 g, 2 mmol) and pyridine-3-sulfonyl chloride (0.178 g, 1 mmol) affords **22** in 31% (0.049 g) yield.

^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.66-8.65 (m, 1H), 8.48-8.47 (m, 1H), 7.87-7.85 (m, 1H), 7.45-7.42 (m, 1H), 6.91-6.90 (m, 1H), 6.28-6.26 (m, 1H), 6.11-6.08 (m, 1H), 3.66 (s, 3H)

This is a known compound and the spectral data are identical to those reported in literature.[21]

3-(5-Butylfuran-2-yl)pyridine (23): 2-*n*-Butylfuran (0.186 g, 1.5 mmol) and pyridine-3-sulfonyl chloride (0.178 g, 1 mmol) affords **23** in 12% (0.024 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.88 (m, 1H), 8.49 (m, 1H), 7.85 (d, J = 7.4 Hz, 1H), 7.25 (m, 1H), 6.62 (d, J = 3.2 Hz, 1H), 6.07 (d, J = 3.2 Hz, 1H), 2.68 (t, J = 7.4 Hz, 2H), 1.67 (quint., J = 7.4 Hz, 2H), 1.42 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H).

This is a known compound and the spectral data are identical to those reported in literature.[23]

Methyl 1,1'-dimethyl-1*H*,1'*H*-[2,2'-bipyrrole]-5-carboxylate (24): 1-Methylpyrrole (0.162 g, 2 mmol) and methyl 5-(chlorosulfonyl)-1-methylpyrrole-2-carboxylate (0.238 g, 1 mmol) affords **24** in 69% (0.151 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.99 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 1.8 Hz, 1H), 6.64 (t, J = 2.0 Hz, 1H), 6.13 (d, J = 2.2 Hz, 2H), 3.95 (s, 3H), 3.83 (s, 3H), 3.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 130.1, 128.1, 127.6, 122.5, 120.3, 116.8, 115.9, 107.4, 107.2, 51.1, 36.8, 35.0.

Elemental analysis: calcd (%) for $C_{12}H_{14}N_2O_2$ (218.26): C 66.04, H 6.47; found: C 66.14, H 6.63.

4-(3-Methylpyrazol-1-yl)benzenesulfonyl chloride (26): To a solution of chlorosulfuric acid (5 mL) in CH_2Cl_2 (5 mL) a solution of 3-methyl-1-phenylpyrazole (1.58 g, 10 mmol) in CH_2Cl_2 (5 mL) was slowly added at 0 ºC, then the resulting mixture was warm-up to room temperate and stirred during 16 h. Then, the crude mixture was poured in ice and the solid was collected by filtration of affords **26** in 89% (2.28 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.01 (d, J = 8.9 Hz, 2H), 7.91 (s, 1H), 7.84 (d, J = 8.9 Hz, 2H), 6.32 (s, 1H), 2.35 (s, 3H).

3-Methyl-1-(4-(1-methylpyrrol-2-yl)phenyl)pyrazole (27): 1-Methylpyrrole (0.162 g, 2 mmol) and 4-(3-methylpyrazol-1-yl)benzenesulfonyl chloride (0.257 g, 1 mmol) affords **27** in 72% (0.171 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.83 (d, J = 2.5 Hz, 1H), 7.69 (d, J = 8.6 Hz, 2H), 7.47 (d, J = 8.6 Hz, 2H), 6.74 (t, J = 2.3 Hz, 1H), 6.28-6.26 (m, 2H), 6.23 (t, J = 3.0 Hz, 1H), 3.68 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.5, 138.7, 133.6, 131.0, 129.4, 127.2, 123.8, 118.7, 108.7, 107.8, 107.6, 35.0, 13.7.

Elemental analysis: calcd (%) for $C_{15}H_{15}N_3$ (237.31): C 75.92, H 6.37; found: C 76.14, H 6.59.

3-Methyl-1-(4-(5-methylthiophen-3-yl)phenyl)pyrazole (28): 2-Methylthiophene (0.196 g, 2 mmol) and 4-(3-methylpyrazol-1-yl)benzenesulfonyl chloride (0.257 g, 1 mmol) affords **28** in 63% (0.160 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.82 (d, J = 2.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.21 (d, J = 1.5 Hz, 1H), 7.07 (s, 1H), 6.26 (d, J = 2.4 Hz, 1H), 2.54 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.6, 141.1, 140.8, 138.8, 134.0, 127.4, 127.1, 124.5, 119.1, 118.0, 107.6, 15.5, 13.7.

Elemental analysis: calcd (%) for $C_{15}H_{14}N_2S$ (254.09): C 70.83, H 5.55; found: C 71.12, H 5.41.

2-Ethyl-4-methyl-5-(5-(1-methylpyrrol-2-yl)thiophen-2-yl)thiazole (29): 2-(5-Bromothiophen-2-yl)-1-methylpyrrole (0.242 g, 1 mmol), 2-ethyl-4-methylthiazole (0.191 g, 1.5 mmol), KOAc (0.194 g, 2 mmol) and $PdCl(C_3H_5)$(dppb) (12.1 mg, 0.02 mmol), were dissolved in DMA (3 mL) under an argon atmosphere. The reaction mixture was stirred at 150 °C for 16 h. After evaporation of the solvent, the product was purified by silica gel column chromatography to afford **29** in 78% (0.225 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.02 (d, J = 3.8 Hz, 1H), 6.96 (d, J = 3.8 Hz, 1H), 6.73-6.70 (m, 1H), 6.36 (dd, J = 1.4 and 3.0 Hz, 1H), 6.17 (t, J = 3.0 Hz, 1H), 3.75 (s, 3H), 2.98 (q, J = 7.6 Hz, 2H), 2.57 (s, 3H), 1.40 (t, J = 7.6 Hz, 3H).

This is a known compound and the spectral data are identical to those reported in literature.[10i]

2-Isobutyl-5-(5-(1-methylpyrrol-2-yl)thiophen-2-yl)thiazole (30): 2-(5-Bromothiophen-2-yl)-1-methylpyrrole (0.242 g, 1 mmol), 2-isobutylthiazole (0.212 g, 1.5 mmol), KOAc (0.194 g, 2 mmol) and $PdCl(C_3H_5)(dppb)$ (12.1 mg, 0.02 mmol), were dissolved in DMA (3 mL) under an argon atmosphere. The reaction mixture was stirred at 150 °C for 16 h. After evaporation of the solvent, the product was purified by silica gel column chromatography to afford **30** in 81% (0.248 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.70 (s, 1H), 7.07 (d, J = 3.7 Hz, 1H), 6.92 (d, J = 3.7 Hz, 1H), 6.71 (dd, J = 1.9 and 2.7 Hz, 1H), 6.36 (dd, J = 1.9 and 3.7 Hz, 1H), 6.17 (dd, J = 2.7 and 3.7 Hz, 1H), 3.75 (s, 3H), 2.87 (d, J = 7.2 Hz, 2H), 2.18-2.08 (m, 1H), 1.02 (d, J = 6.7 Hz, 6H)

^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 169.1, 137.5, 135.0, 132.1, 131.7, 126.6, 125.6, 125.1, 124.6, 110.4, 108.2, 42.4, 35.4, 29.8, 22.3.

Elemental analysis: calcd (%) for $C_{16}H_{18}N_2S_2$ (302.45): C 63.54, H 6.00; found: C 63.82, H 5.79.

Notes and references

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