

## Reactivity of 3-(pyrrol-1-yl)thiophenes in Pd-catalysed direct arylations

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

► **To cite this version:**

Imen Smari, Chiraz Youssef, Hamed Ben Ammar, Bechir Ben Hassine, Jean-François Soulé, et al..  
Reactivity of 3-(pyrrol-1-yl)thiophenes in Pd-catalysed direct arylations. *Tetrahedron*, Elsevier, 2015,  
71 (37), pp.6586-6593. 10.1016/j.tet.2015.03.022 . hal-01149179

**HAL Id: hal-01149179**

**<https://hal-univ-rennes1.archives-ouvertes.fr/hal-01149179>**

Submitted on 6 May 2015

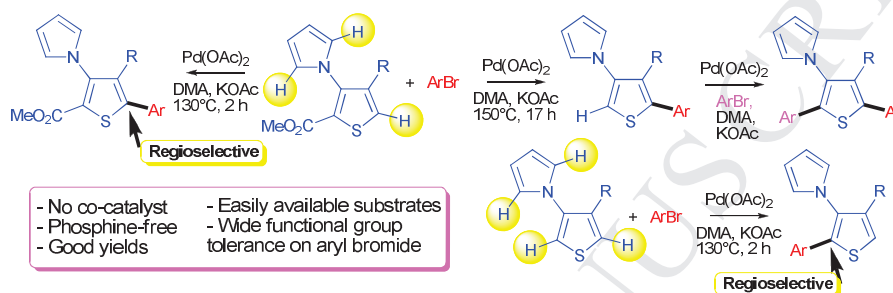
**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

## Reactivity of 3-(Pyrrol-1-yl)thiophenes in Pd-Catalysed Direct Arylations

Leave this area blank for abstract info.

Imen Smari,<sup>a,b</sup> Chiraz Youssef,<sup>b</sup> Hamed Ben Ammar,<sup>b\*</sup> Bechir Ben Hassine,<sup>b</sup> Jean-François Soulé,<sup>a</sup> and Henri Doucet,<sup>a\*</sup>



# Reactivity of 3-(Pyrrol-1-yl)thiophenes in Pd-Catalysed Direct Arylations

Imen Smari,<sup>a,b</sup> Chiraz Youssef,<sup>b</sup> Hamed Ben Ammar,<sup>b\*</sup> Bechir Ben Hassine,<sup>b</sup> Jean-François Soulé,<sup>a</sup> and Henri Doucet,<sup>a\*</sup>

<sup>a</sup> Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes

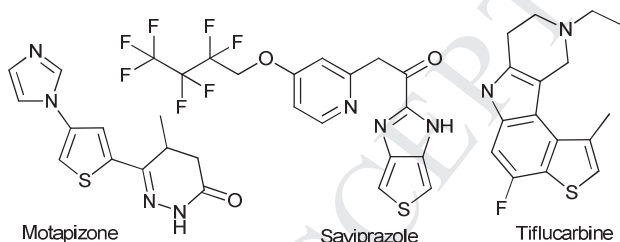
"Organométalliques: Matériaux et Catalyse", Campus de Beaulieu, 35042 Rennes, France.

<sup>b</sup> Laboratoire de Synthèse Organique Asymétrique et Catalyse Homogène, (UR 11ES56) Université de Monastir, Faculté des Sciences de Monastir, avenue de l'environnement, Monastir 5000, Tunisie. Fax: (+216) 73 500 278; Tel: (+216) 73 500 275.

**Abstract**— The regioselectivity of the Pd-catalysed direct arylation of 3-(pyrrol-1-yl)thiophene derivatives was investigated. Conditions allowing either the regioselective arylation at C2 or at C5 of the thiophene ring are reported. From methyl 3-(pyrrol-1-yl)thiophene-2-carboxylate using KOAc as the base, DMA as the solvent and only 1 mol% Pd(OAc)<sub>2</sub> catalyst, the target 5-arylated thiophenes were obtained in moderate to good yields with a wide variety of aryl halides; whereas the use of 1-(4-methylthiophen-3-yl)pyrrole affords the C2-arylated thiophenes. The sequential palladium catalysed 2,5-diheteroarylation of such 3-(pyrrol-1-yl)thiophene is also reported allowing the access to thiophenes bearing two different aryl units at C2 and C5. A pyrazole bearing an ester substituent at C4 and a pyrrole substituent at C5 was only aryolated at C2 on the pyrrole ring.

## 1. Introduction

Both thiophene and pyrrole derivatives represent important structures due to their biological and/or physical properties. For example, Motapizone<sup>1a</sup> is used against platelet aggregation, Saviprazole<sup>1b</sup> is a gastric proton pump inhibitor and Tiflucarbine<sup>1c</sup> displays antidepressant properties (Fig. 1). Due to these properties, the discovery of simple accesses to a variety of thiophene or pyrrole derivatives remains an important challenge for organic chemists.



**Figure 1.** Examples of bioactive thiophene derivatives

As early as in 1985-1992, Ohta et al. reported the direct arylation of heteroaromatics with aryl halides via a C–H bond activation using Pd(PPh<sub>3</sub>)<sub>4</sub> catalyst.<sup>2</sup> Since these results, the Pd-catalysed direct arylation of several heteroaryls using aryl halides as the coupling partners has proved to be a very powerful method for a simpler and greener access to a wide variety of arylated heterocycles.<sup>3,4</sup> This method is very attractive as it avoids the preparation of an organometallic derivative and as the

major by-products of the reaction are a base associated to HX, instead of metallic salts.<sup>5</sup>

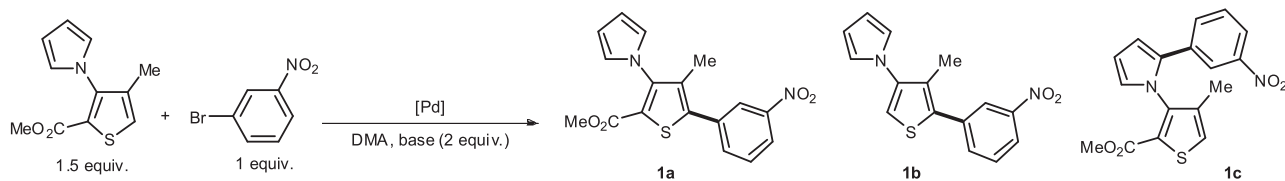
The direct arylation of a variety of thiophene and pyrrole derivatives has been reported in recent years.<sup>6,7</sup> However, to our knowledge, the reactivity of a thiophene substituted by a pyrrole unit at C3 and also of a 5-pyrrolylpyrazole for Pd-catalysed direct arylations has not been described. Therefore, the reactivity for direct arylation of such substrates needed to be investigated.

Here, we wish to report (i) conditions allowing a regioselective arylation of a 3-(pyrrol-1-yl)thiophene derivative, (ii) a one pot procedure with arylation at C5 of the thiophene derivative followed by decarboxylation at C2 and (iii) the sequential arylation to prepare 2,5-diarylated thiophenes with two different aryl units.

## 2. Results and discussion

Based on previous results, for this study DMA was initially chosen as the solvent and KOAc as the base.<sup>8</sup> The reactions were performed at 130-150 °C under argon in the presence of Pd(OAc)<sub>2</sub> or PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalysts. First, using only 1 mol% Pd(OAc)<sub>2</sub>, the reaction of 1 equiv. of 3-bromonitrobenzene with 1.5 equiv. of methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate as the coupling partners at 150 °C during 17 h affords selectively the *in situ* decarboxylated C5-arylation product **1b** in 78% yield (Table 1, entry 1). On the other hand, the reaction performed under the same reaction conditions, but after only 2 h affords a mixture of **1a** and **1b** in a 83:17 ratio (Table 1, entry 2).

\* Corresponding author. Tel.: 00-33-2-23-23-63-84; fax: 00-33-2-23-23-69-39; e-mail: [henri.doucet@univ-rennes1.fr](mailto:henri.doucet@univ-rennes1.fr)



**Scheme 2.** Regioselectivity of the palladium catalysed direct arylation using methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate and 3-bromonitrobenzene as the coupling partners

**Table 1.** Influence of the reaction conditions for the palladium catalysed direct arylation using methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate and 3-bromonitrobenzene as the coupling partners (Scheme 2)

Entry	Catalyst (mol%)	Base	Time (h)	Temp (°C)	Ratio <b>1a</b> : <b>1b</b> : <b>1c</b>	Yield in <b>1a</b> or <b>1b</b> (%)
1	Pd(OAc) <sub>2</sub> (1)	KOAc	17	150	0:100:0	76 of <b>1b</b>
2	Pd(OAc) <sub>2</sub> (1)	KOAc	2	150	83:17:0	-
3	Pd(OAc) <sub>2</sub> (1)	KOAc	2	130	93:7:0	78 of <b>1a</b>
4	Pd(OAc) <sub>2</sub> (1)	CsOAc	17	150	49:51:0	-
5	Pd(OAc) <sub>2</sub> (1)	CsOAc	2	130	94:6:0	78 of <b>1a</b>
6	Pd(OAc) <sub>2</sub> (1)	NaOAc	17	150	23:77:0	-
7	Pd(OAc) <sub>2</sub> (1)	NaOAc	2	130	69:31:0	-
8	Pd(OAc) <sub>2</sub> (1)	Cs <sub>2</sub> CO <sub>3</sub>	17	150	0:100:0	77 of <b>1b</b>
9	PdCl(C <sub>3</sub> H <sub>5</sub> )(dppb) (2)	KOAc	17	150	14:86:0	70 of <b>1b</b>

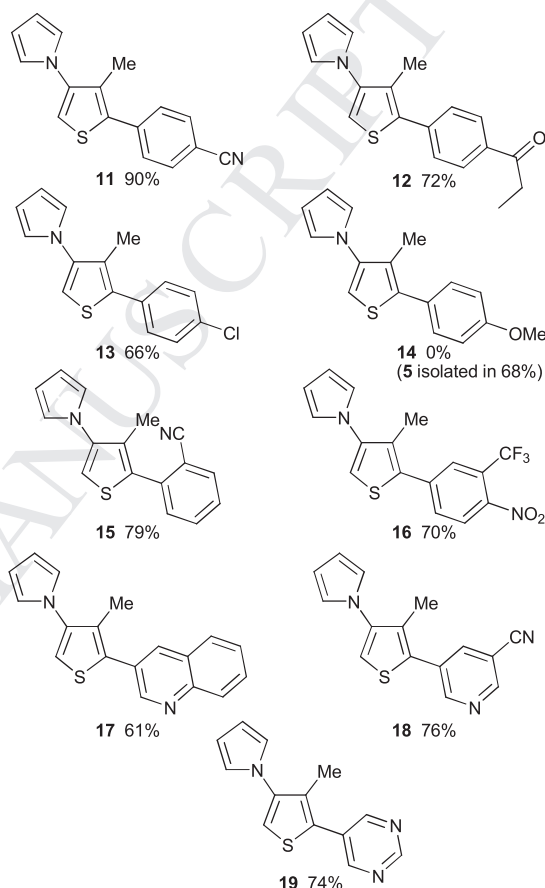
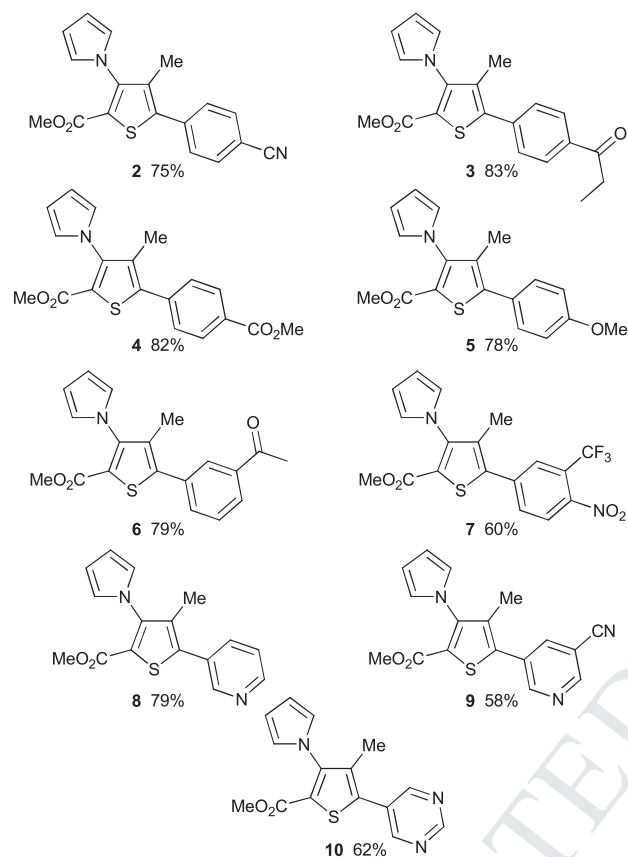
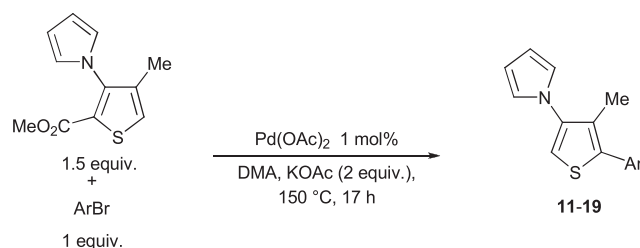
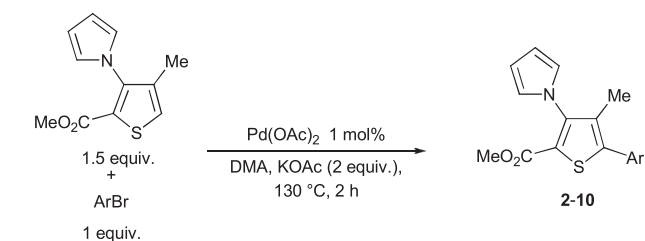
Conditions: 3-bromonitrobenzene (1 equiv.), 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (1.5 equiv.), base (2 equiv.), DMA, isolated yields, complete conversion of 3-bromonitrobenzene was observed in all cases.

It should be noted that in both cases no arylation at the pyrrole ring to afford **1c** was observed by GC/MS analysis of the crude mixture. A lower temperature led to an increase in the selectivity for **1a**, as at 130 °C ratio **1a**:**1b** was 93:7 and **1a** was isolated in 78% yield (Table 1, entry 3). Then, we examined the influence of the nature of the base for this reaction. The use of CsOAc instead of KOAc at 150 °C afforded lower amounts of decarboxylated product **1b**, and at 130 °C a 94:6 ratio (**1a**:**1b**) was obtained, with 78% isolated yield of **1a** (Table 1, entries 4 and 5). NaOAc led to mixtures of products **1a** and **1b**, whereas Cs<sub>2</sub>CO<sub>3</sub> afforded exclusively **1b** (Table 1, entries 6-8). The use of 2 mol% PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst<sup>8b</sup> instead of 1 mol% Pd(OAc)<sub>2</sub>, also affords **1b** although in slightly lower yield (Table 1, entry 9).

Then, using the most effective reaction conditions for coupling with and without decarboxylation (DMA, KOAc, Pd(OAc)<sub>2</sub>, 130 °C 2 h or 150 °C 17 h), we explored the scope of this reaction using a variety of aryl bromides as the coupling partner (Schemes 3 and 4).

First, we investigated the reaction of methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate using 1 mol% Pd(OAc)<sub>2</sub> catalyst with a set of aryl bromides at 130 °C during 2 h in order to obtain the non-decarboxylated products (Scheme 3). The reaction with the *para*-substituted aryl bromides, 4-bromobenzonitrile, 4-bromopropiophenone or 4-bromoanisole proceeds very smoothly to afford the target products **2-5** in 75-83% yields. *Meta*-substituted 3-bromoacetophenone and also 4-bromo-1-nitro-2-(trifluoromethyl)benzene also react nicely to give **6** and **7** in 79% and 60% yields, respectively. 3-Bromopyridine, 5-bromonicotinonitrile

and 5-bromopyrimidine were also successfully coupled with methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate, without decarboxylation, to afford **8-10** in 58-79% yields.

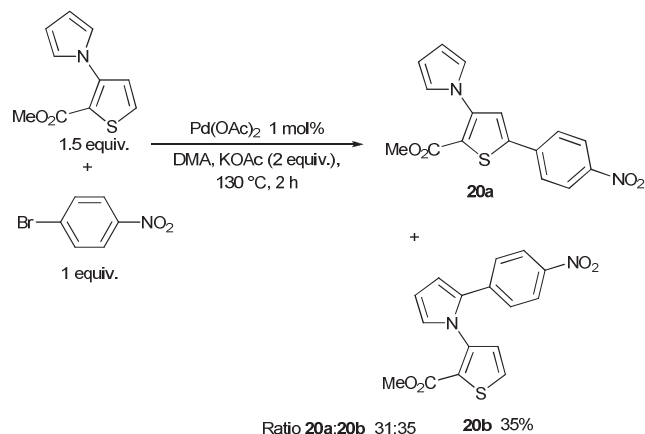


**Scheme 3.** Scope of the C5-arylation of methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate

The scope of the C5-arylation with *in situ* decarboxylation was also studied (Scheme 4). From 4-cyano-, 4-propionyl- and 4-chlorobromobenzene, after 17 h at 150 °C, the decarboxylated C5-arylated thiophenes **11-13** were obtained in good yields. On the other hand, no formation of the desired decarboxylated product **14** was observed in the presence of the electron-rich 4-bromoanisole as only product **5** was formed (68%). The decarboxylation step appears to be favoured by the presence of electron-withdrawing substituents on the arene. In the presence of 2-bromobenzonitrile and 4-bromo-1-nitro-2-(trifluoromethyl)benzene, **15** and **16** were obtained in 79% and 70% yields, respectively. Then, three heteroarenes were employed. 3-Bromopyridine, 5-bromonicotinonitrile and 5-bromopyrimidine also afforded the desired decarboxylated products **17-19** in good yields.

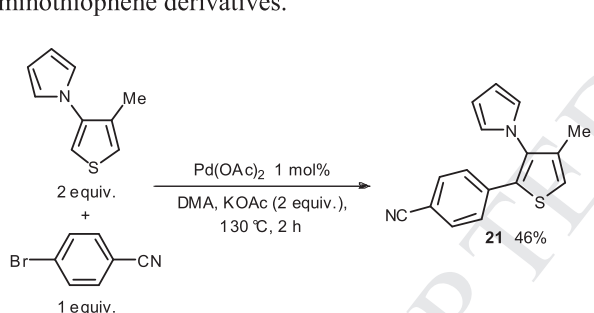
**Scheme 4.** Scope of the C5-arylation of methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate with *in-situ* decarboxylation

The selectivity of the arylation of 3-(pyrrol-1-yl)thiophene derivatives appears to be very sensitive to the steric hindrance of the pyrrolyl moiety. The presence of a substituent at C4 on the thienyl ring seems to be crucial to control the selectivity. Indeed, in the presence of methyl 3-(pyrrol-1-yl)thiophene-2-carboxylate and 4-bromobenzonitrile as coupling partner, the formation of a mixture of the 5-arylated thiophene **20a** and 2-arylated pyrrole **20b** in a 31:35 ratio was observed under the same reaction conditions (Scheme 5).



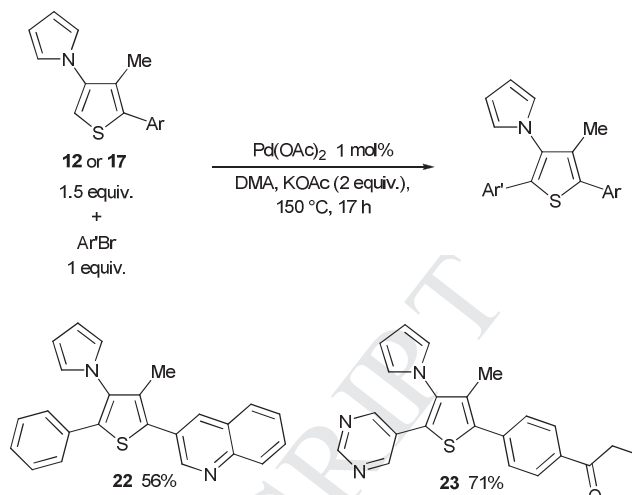
**Scheme 5.** Regioselectivity of the arylation of methyl 3-(pyrrol-1-yl)thiophene-2-carboxylate

The regioselectivity of the arylation of 1-(4-methylthiophen-3-yl)pyrrole was also investigated (Scheme 6). In the presence of 4-bromobenzonitrile and 1 mol% Pd(OAc)<sub>2</sub> catalyst, the regiospecific formation of the C2-arylated product **21** was observed which indicates that the most reactive position of a 3-pyrrolylthiophene is the carbon C2 of the thienyl ring. Therefore, this result confirms that an ester substituent at C2 on the thienyl ring acts as a blocking group, allowing for selective arylation at C5 position. A similar regioselectivity trend for direct arylations had been previously observed using 3-aminothiophene derivatives.<sup>9</sup>



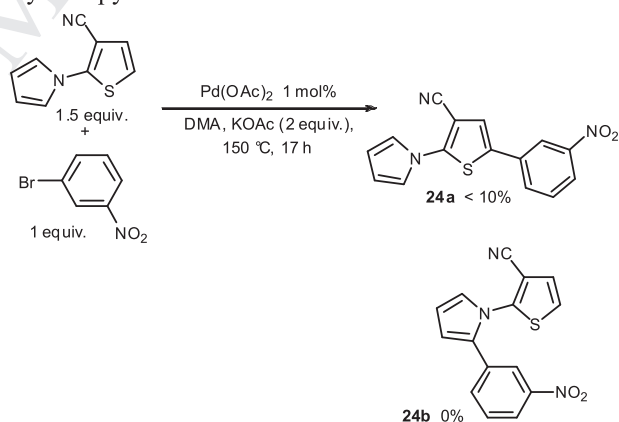
**Scheme 6.** Regioselectivity of the arylation of 1-(4-methylthiophen-3-yl)pyrrole

The reactivity of the arylated thiophene derivatives **12** and **17** for C5 arylation was then evaluated (Scheme 7). Such arylations would allow the preparation of non-symmetrically 2,5-diarylated thiophene derivatives. From **17** and bromobenzene the desired product **22** was obtained in 56% yield. **12** reacted with 5-bromopyridine also affords the desired 2,5-diarylated thiophene **23** in good yield.



**Scheme 7.** C5-arylation of 2-aryl-3-methyl-4-(pyrrol-1-yl)thiophenes

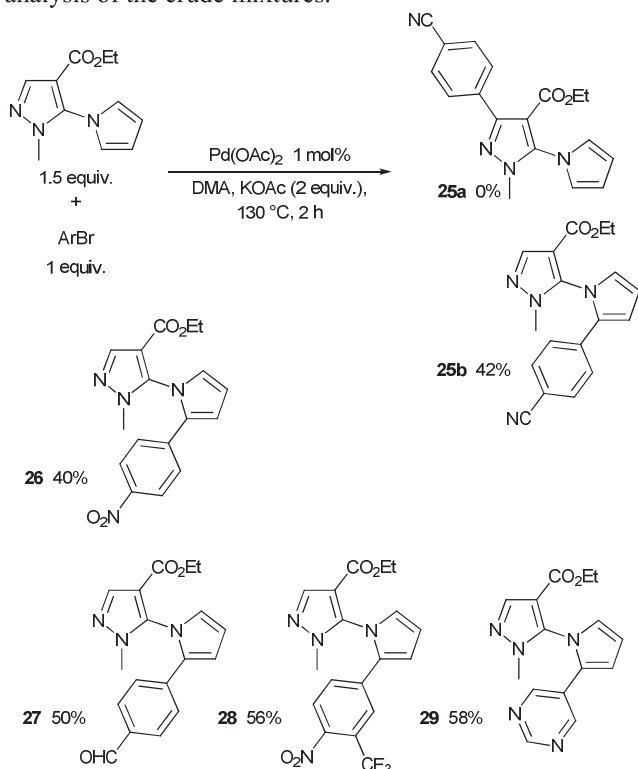
The reactivity of 2-(pyrrol-1-yl)thiophene-3-carbonitrile in the presence of 3-bromonitrobenzene was also investigated (Scheme 8). A permutation of the electron-withdrawing (pyrrolyl) and electron-donating (ester or cyano) substituents on the thiophene was found to drastically modify the reactivity. In the presence of 1 mol% Pd(OAc)<sub>2</sub> catalyst and KOAc as base, the expected product **24a** was obtained in a very low yield and the C2-arylated pyrrole **24b** was not observed.



**Scheme 8.** Reactivity of 2-(pyrrol-1-yl)thiophene-3-carbonitrile

We also explored the reactivity of a pyrazole bearing a pyrrole substituent at C5 and an ester at C4 (Scheme 9). As the position C3 of pyrazoles derivatives generally exhibits a poor reactivity, the formation of product **25b** was expected. Indeed, 4-bromobenzonitrile and this 5-(pyrrol-1-yl)pyrazole in the presence of 1 mol% Pd(OAc)<sub>2</sub> and KOAc in DMA at 130 °C, 2 or 17 h affords the C2-arylated pyrrole **25b** in 42% yield. No formation of **25a** was observed. A similar regioselectivity was observed in the presence of 4-bromonitrobenzene, 4-bromobenzaldehyde, 4-bromo-1-nitro-2-(trifluoromethyl)benzene and 5-bromopyrimidine as the coupling partners, and products **26-29** were obtained in

40–58% yields, respectively. The formation of diarylation products in trace amounts was also observed by GC/MS analysis of the crude mixtures.



**Scheme 9.** Arylation of ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate

In conclusion, thiophenes bearing a pyrrole unit at C3 and a methyl at C4 were found to react exclusively at the thienyl ring. We established that 1 mol% of air stable palladium Pd(OAc)<sub>2</sub> catalyst and KOAc as base at 130 °C promotes 5-arylation of methyl 3-(pyrrol-1-yl)thiophene-2-carboxylate without decarboxylation; whereas, at 150 °C a C5 arylation followed by an in situ decarboxylation was observed. On the other hand, 1-(4-methylthiophen-3-yl)-pyrrole was selectively arylated at carbon C2 of the thienyl ring. From the decarboxylated 5-arylated thiophenes, the direct arylation at C2 position of thiophene was also found to be possible, and affords 2,5-diheteroarylated thiophenes bearing two different aryl units. A pyrazole bearing an ester substituent at C4 and a pyrrole substituent at C5 was only arylated at C2 on the pyrrole ring.

### Acknowledgments

We thank the Centre National de la Recherche Scientifique, “Rennes Metropole”, “UTIQUE” and Scientific Ministry of Higher Education Research of Tunisia for providing financial support.

### Experimental section

#### General Remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMA analytical grade was not distilled before use. KOAc (99%) was used. Commercial heteroarenes and aryl bromides were used without purification. The reactions were followed by GC and NMR. <sup>1</sup>H and <sup>13</sup>C spectra were recorded with a Bruker 400 MHz spectrometer in CDCl<sub>3</sub> solutions. Chemical shifts are reported in ppm relative to CDCl<sub>3</sub> (7.25 for <sup>1</sup>H NMR and 77.0 for <sup>13</sup>C NMR). Flash chromatography was performed on silica gel (230–400 mesh).

#### General procedure

In a typical experiment, the thiophene derivative (1.5 mmol), aryl bromide (1 mmol), KOAc (0.196 g, 2 mmol) and Pd(OAc)<sub>2</sub> (2.24 mg, 0.01 mmol) or PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) (12.1 mg, 0.02 mmol), were dissolved in DMA (5 mL) under an argon atmosphere. The reaction mixture was stirred at 130 or 150 °C for 2 or 17 h (see schemes). Then, the reaction was stirred at 30–40 °C in vacuum (0.4 mbar) to remove the solvent, and the product was purified by silica gel column chromatography.

**Preparation of the PdCl(C<sub>3</sub>H<sub>5</sub>)(dppb) catalyst:**<sup>10</sup> An oven-dried 40 mL Schlenk tube equipped with a magnetic stirring bar under argon atmosphere, was charged with [Pd(C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (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. <sup>31</sup>P NMR (81 MHz, CDCl<sub>3</sub>) δ = 19.3 (s).

#### Methyl 4-methyl-5-(3-nitrophenyl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (**1a**)

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 3-bromonitrobenzene (0.202 g, 1 mmol) at 130 °C during 2 h product **1a** was obtained in 78% (0.267 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.37 (s, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 7.8 Hz, 1H), 6.76 (t, *J* = 2.0 Hz, 2H), 6.37 (t, *J* = 2.0 Hz, 2H), 3.78 (s, 3H), 2.07 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.5, 148.5, 143.8, 139.8, 135.1, 134.7, 134.2, 130.0, 125.2, 123.7, 123.3, 121.9, 109.3, 52.3, 12.8.

C<sub>17</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>S (342.37): Calcd C 59.64, H 4.12; Found C 59.41, H 4.27.

#### 1-(4-Methyl-5-(3-nitrophenyl)thiophen-3-yl)-pyrrole (**1b**)

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 3-bromonitrobenzene (0.202 g, 1 mmol) at 150 °C during 17 h product **1b** was obtained in 76% (0.216 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.37 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 7.8 Hz, 1H), 7.26 (s, 1H), 6.88 (t, *J* = 2.0 Hz, 2H), 6.36 (t, *J* = 2.0 Hz, 2H), 2.22 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  148.5, 141.0, 136.3, 134.7, 135.7, 130.8, 129.7, 123.7, 122.4, 121.9, 117.9, 109.3, 13.1.  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$  (284.33): Calcd C 63.36, H 4.25; Found C 63.50, H 4.37.

**Methyl 5-(4-cyanophenyl)-4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (2)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol) at 130 °C during 2 h product **2** was obtained in 75% (0.241 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.76 (d,  $J = 8.0$  Hz, 2H), 7.61 (d,  $J = 8.0$  Hz, 2H), 6.74 (t,  $J = 2.0$  Hz, 2H), 6.36 (t,  $J = 2.0$  Hz, 2H), 3.78 (s, 3H), 2.06 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  141.1, 139.2, 136.4, 132.5, 130.8, 129.3, 121.9, 118.6, 118.2, 111.2, 109.3, 13.3.

$\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$  (322.38): Calcd C 67.06, H 4.38; Found C 67.24, H 4.27.

**Methyl 4-methyl-5-(4-propionylphenyl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (3)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromopropiophenone (0.213 g, 1 mmol) at 130 °C during 2 h product **3** was obtained in 83% (0.293 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (d,  $J = 8.0$  Hz, 2H), 7.60 (d,  $J = 8.0$  Hz, 2H), 6.75 (t,  $J = 2.0$  Hz, 2H), 6.36 (t,  $J = 2.0$  Hz, 2H), 3.77 (s, 3H), 3.04 (q,  $J = 7.6$  Hz, 2H), 2.06 (s, 3H), 1.25 (t,  $J = 7.6$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  199.8, 160.6, 143.7, 141.5, 137.7, 136.5, 133.6, 128.9, 128.3, 127.2, 121.8, 109.0, 52.0, 31.7, 12.7, 8.0.

$\text{C}_{20}\text{H}_{19}\text{NO}_3\text{S}$  (353.43): Calcd C 67.97, H 5.42; Found C 67.87, H 5.34.

**Methyl 5-(4-(methoxycarbonyl)phenyl)-4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (4)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and methyl 4-bromobenzoate (0.215 g, 1 mmol) at 130 °C during 2 h product **4** was obtained in 82% (0.291 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.13 (d,  $J = 8.0$  Hz, 2H), 7.58 (d,  $J = 8.0$  Hz, 2H), 6.75 (t,  $J = 2.0$  Hz, 2H), 6.36 (t,  $J = 2.0$  Hz, 2H), 3.95 (s, 3H), 3.77 (s, 3H), 2.06 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.4, 160.7, 143.9, 141.7, 137.9, 133.7, 130.1, 128.9, 127.2, 122.0, 109.3, 109.2, 52.3, 52.1, 12.8.

$\text{C}_{19}\text{H}_{17}\text{NO}_4\text{S}$  (355.41): Calcd C 64.21, H 4.82; Found C 64.02, H 4.99.

**Methyl 5-(4-methoxyphenyl)-4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (5)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromoanisole (0.187 g, 1 mmol) at 130 °C during 2 h product **5** was obtained in 78% (0.255 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.43 (d,  $J = 8.0$  Hz, 2H), 6.99 (d,  $J = 8.0$  Hz, 2H), 6.75 (t,  $J = 2.0$  Hz, 2H), 6.35 (t,  $J = 2.0$  Hz, 2H), 3.96 (s, 3H), 3.76 (s, 3H), 2.02 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  161.2, 160.2, 144.0, 143.5, 132.3, 130.4, 126.0, 123.2, 122.1, 114.5, 109.1, 55.5, 52.2, 12.9.

$\text{C}_{18}\text{H}_{17}\text{NO}_3\text{S}$  (327.40): Calcd C 66.03, H 5.23; Found C 65.89, H 5.07.

**Methyl 5-(3-acetylphenyl)-4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (6)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 3-bromoacetophenone (0.199 g, 1 mmol) at 130 °C during 2 h product **6** was obtained in 79% (0.268 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.08 (s, 1H), 7.99 (d,  $J = 8.0$  Hz, 1H), 7.69 (d,  $J = 8.0$  Hz, 1H), 7.58 (t,  $J = 7.6$  Hz, 1H), 6.75 (t,  $J = 2.0$  Hz, 2H), 6.35 (t,  $J = 2.0$  Hz, 2H), 3.76 (s, 3H), 2.65 (s, 3H), 2.04 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  197.2, 160.7, 143.7, 141.7, 137.6, 133.9, 133.4, 133.2, 129.2, 128.6, 128.4, 124.3, 121.9, 109.0, 52.1, 26.6, 12.6.

$\text{C}_{19}\text{H}_{17}\text{NO}_3\text{S}$  (339.41): Calcd C 67.24, H 5.05; Found C 67.02, H 5.30.

**Methyl 4-methyl-5-(4-nitro-3-(trifluoromethyl)phenyl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (7)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromo-1-nitro-2-(trifluoromethyl)benzene (0.270 g, 1 mmol) at 130 °C during 2 h product **7** was obtained in 60% (0.246 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (d,  $J = 8.0$  Hz, 1H), 7.95 (s, 1H), 7.84 (d,  $J = 8.0$  Hz, 1H), 6.75 (t,  $J = 2.0$  Hz, 2H), 6.38 (t,  $J = 2.0$  Hz, 2H), 3.79 (s, 3H), 2.08 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.3, 144.0, 138.5, 138.1, 135.2, 133.0, 128.2 (q,  $J = 5.3$  Hz), 126.4, 125.9, 124.5 (q,  $J = 34.4$  Hz), 121.8 (q,  $J = 273.9$  Hz), 121.9, 109.5, 52.4, 12.9.

$\text{C}_{18}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_4\text{S}$  (410.37): Calcd C 52.68, H 3.19; Found C 52.74, H 3.04.

**Methyl 4-methyl-5-(pyridin-3-yl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (8)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 3-bromopyridine (0.158 g, 1 mmol) at 130 °C during 2 h product **8** was obtained in 79% (0.235 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.77 (s, 1H), 8.66 (d,  $J = 4.2$  Hz, 1H), 7.80 (d,  $J = 7.9$  Hz, 1H), 7.41 (dd,  $J = 7.9, 4.2$  Hz, 1H), 6.75 (s, 2H), 6.36 (s, 2H), 3.77 (s, 3H), 2.05 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.7, 149.7, 149.5, 143.9, 138.9, 136.2, 134.1, 129.7, 125.1, 123.6, 122.0, 109.2, 52.2, 12.7.

$\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$  (298.36): Calcd C 64.41, H 4.73; Found C 64.55, H 4.58.



**Methyl 5-(5-cyanopyridin-3-yl)-4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (9)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 5-bromonicotinonitrile (0.183 g, 1 mmol) at 130 °C during 2 h product **9** was obtained in 58% (0.187 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.26 (s, 1H), 8.89 (s, 2H), 6.74 (t, *J* = 2.0 Hz, 2H), 6.37 (t, *J* = 2.0 Hz, 2H), 3.79 (s, 3H), 2.07 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.4, 158.2, 156.2, 143.9, 135.2, 134.5, 128.2, 126.2, 121.9, 109.4, 52.3, 12.7.

C<sub>17</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S (323.37): Calcd C 63.14, H 4.05; Found C 63.00, H 4.24.

**Methyl 4-methyl-5-(pyrimidin-5-yl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (10)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 5-bromopyrimidine (0.159 g, 1 mmol) at 130 °C during 2 h product **10** was obtained in 62% (0.185 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.26 (s, 1H), 8.86 (s, 2H), 6.75 (t, *J* = 2.0 Hz, 2H), 6.37 (t, *J* = 2.0 Hz, 2H), 3.79 (s, 3H), 2.07 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.3, 158.2, 156.2, 143.9, 135.2, 134.5, 128.2, 126.2, 121.9, 109.4, 52.4, 12.7.

C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>S (299.35): Calcd C 60.18, H 4.38; Found C 60.01, H 4.24.

**4-(3-Methyl-4-(pyrrol-1-yl)thiophen-2-yl)benzotrile (11)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromobenzotrile (0.182 g, 1 mmol) at 150 °C during 17 h product **11** was obtained in 90% (0.238 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.26 (s, 1H), 6.86 (t, *J* = 2.0 Hz, 2H), 6.34 (t, *J* = 2.0 Hz, 2H), 2.20 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 141.2, 139.2, 136.5, 132.5, 130.8, 129.4, 121.9, 118.5, 118.2, 111.3, 109.3, 13.2.

C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>S (264.34): Calcd C 72.70, H 4.58; Found C 72.49, H 4.37.

**1-(4-(3-Methyl-4-(pyrrol-1-yl)thiophen-2-yl)phenyl)propan-1-one (12)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromopropiophenone (0.213 g, 1 mmol) at 150 °C during 17 h product **12** was obtained in 72% (0.212 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.21 (s, 1H), 6.86 (t, *J* = 2.0 Hz, 2H), 6.33 (t, *J* = 2.0 Hz, 2H), 3.04 (q, *J* = 7.6 Hz, 2H), 2.20 (s, 3H), 1.26 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 200.1, 141.0, 139.0, 137.4, 135.8, 130.2, 128.9, 128.4, 121.9, 117.6, 109.1, 31.8, 13.3, 8.2.

C<sub>18</sub>H<sub>17</sub>NOS (295.40): Calcd C 73.19, H 5.80; Found C 73.00, H 5.89.

**1-(5-(4-Chlorophenyl)-4-methylthiophen-3-yl)pyrrole (13)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromochlorobenzene (0.191 g, 1 mmol) at 150 °C during 17 h product **13** was obtained in 66% (0.180 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.42 (s, 4H), 7.16 (s, 1H), 6.85 (t, *J* = 2.0 Hz, 2H), 6.33 (t, *J* = 2.0 Hz, 2H), 2.15 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 140.7, 137.3, 133.8, 133.0, 130.2, 129.5, 128.9, 121.9, 116.8, 109.1, 13.1.

C<sub>15</sub>H<sub>12</sub>ClNS (273.78): Calcd C 65.80, H 4.42; Found C 65.88, H 4.28.

**2-(3-Methyl-4-(pyrrol-1-yl)thiophen-2-yl)benzotrile (15)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 2-bromobenzotrile (0.182 g, 1 mmol) at 150 °C during 17 h product **15** was obtained in 79% (0.208 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.82 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.60-7.47 (m, 2H), 6.91 (t, *J* = 2.0 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 2H), 2.12 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 140.3, 138.0, 133.8, 133.4, 132.7, 132.3, 131.8, 128.6, 121.9, 118.3, 117.9, 113.6, 109.2, 13.2.

C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>S (264.34): Calcd C 72.70, H 4.58; Found C 72.54, H 4.33.

**1-(4-Methyl-5-(4-nitro-3-(trifluoromethyl)phenyl)thiophen-3-yl)pyrrole (16)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 4-bromo-1-nitro-2-(trifluoromethyl)benzene (0.270 g, 1 mmol) at 150 °C during 17 h product **16** was obtained in 70% (0.246 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.01 (d, *J* = 8.0 Hz, 1H), 7.93 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 1H), 6.84 (t, *J* = 2.0 Hz, 2H), 6.34 (t, *J* = 2.0 Hz, 2H), 2.21 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 146.6, 141.4, 139.7, 134.5, 132.6, 131.9, 128.0 (q, *J* = 5.5 Hz), 125.8, 124.2 (q, *J* = 34.0 Hz), 121.7 (q, *J* = 272.5 Hz), 121.9, 119.1, 109.5, 13.3.

C<sub>16</sub>H<sub>11</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>S (352.33): Calcd C 54.54, H 3.15; Found C 54.47, H 3.07.

**3-(3-Methyl-4-(pyrrol-1-yl)thiophen-2-yl)quinoline (17)**

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 3-bromoquinoline (0.208 g, 1 mmol) at 150 °C during 17 h product **17** was obtained in 61% (0.177 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.07 (s, 1H), 8.22 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.8 Hz, 1H), 6.89 (t, *J* = 2.0 Hz, 2H), 6.35 (t, *J* = 2.0 Hz, 2H), 2.24 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.5, 147.2, 141.0, 135.2, 134.7, 130.6, 129.8, 129.3, 127.9, 127.8, 127.6, 127.2, 121.8, 117.7, 109.2, 13.1.

$\text{C}_{18}\text{H}_{14}\text{N}_2\text{S}$  (290.38): Calcd C 74.45, H 4.86; Found C 74.67, H 5.01.

#### 5-(3-Methyl-4-(pyrrol-1-yl)thiophen-2-yl)nicotinonitrile (18)

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 5-bromonicotinonitrile (0.183 g, 1 mmol) at 150 °C during 17 h product **18** was obtained in 76% (0.201 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.94 (s, 1H), 8.87 (s, 1H), 8.04 (s, 1H), 7.31 (s, 1H), 6.85 (t,  $J = 3.1$  Hz, 2H), 6.34 (t,  $J = 3.1$  Hz, 2H), 2.19 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  152.6, 150.8, 141.2, 138.7, 131.9, 131.8, 131.2, 121.9, 119.0, 116.1, 109.5, 13.1.

$\text{C}_{15}\text{H}_{11}\text{N}_3\text{S}$  (265.33): Calcd C 67.90, H 4.18; Found C 68.06, H 4.29.

#### 5-(3-methyl-4-(pyrrol-1-yl)thiophen-2-yl)pyrimidine (19)

From methyl 4-methyl-3-(pyrrol-1-yl)thiophene-2-carboxylate (0.318 g, 1.5 mmol) and 5-bromopyrimidine (0.159 g, 1 mmol) at 150 °C during 17 h product **19** was obtained in 74% (0.178 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.20 (s, 1H), 8.87 (s, 2H), 7.30 (s, 1H), 6.85 (t,  $J = 3.1$  Hz, 2H), 6.34 (t,  $J = 3.1$  Hz, 2H), 2.19 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  157.6, 156.3, 141.3, 131.9, 130.7, 129.2, 122.0, 118.9, 109.6, 13.1.

$\text{C}_{13}\text{H}_{11}\text{N}_3\text{S}$  (241.31): Calcd C 64.70, H 4.59; Found C 64.41, H 4.38.

#### Methyl 5-(4-nitrophenyl)-3-(pyrrol-1-yl)thiophene-2-carboxylate (20a) and Methyl 3-(2-(4-nitrophenyl)-pyrrol-1-yl)thiophene-2-carboxylate (20b)

From methyl 3-(pyrrol-1-yl)thiophene-2-carboxylate (0.310 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol) at 130 °C during 2 h a mixture of **20a** and **20b** was obtained in a 31:35 ratio. After column chromatography, product **20b** was obtained in 35% (0.115 g) yield, and product **20a** was isolated in low yield.

**20a**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.35 (d,  $J = 8.0$  Hz, 2H), 7.81 (d,  $J = 8.0$  Hz, 2H), 7.44 (s, 1H), 7.09-7.06 (m, 2H), 6.39-6.35 (m, 2H), 3.89 (s, 3H).

**20b**:  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.06 (d,  $J = 8.0$  Hz, 2H), 7.52 (d,  $J = 5.2$  Hz, 1H), 7.22 (d,  $J = 8.0$  Hz, 2H), 6.97 (t,  $J = 1.3$  Hz, 1H), 6.91 (d,  $J = 5.2$  Hz, 1H), 6.64 (dd,  $J = 3.6, 1.6$  Hz, 1H), 6.43 (t,  $J = 3.3$  Hz, 1H), 3.71 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  160.4, 145.7, 142.1, 139.1, 132.9, 130.6, 128.4, 127.1, 127.0, 125.0, 123.6, 112.5, 110.2, 52.2.

$\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_4\text{S}$  (328.34): Calcd C 58.53, H 3.68; Found C 59.01, H 3.55.

#### 4-(4-Methyl-3-(pyrrol-1-yl)thiophen-2-yl)benzonitrile (21)

From 1-(4-methylthiophen-3-yl)-pyrrole (0.326 g, 2 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol) at 130 °C during 2 h product **21** was obtained in 46% (0.121 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (d,  $J = 8.0$  Hz, 2H), 7.07 (s, 1H), 7.02 (d,  $J = 8.0$  Hz, 2H), 6.59 (t,  $J = 2.0$  Hz, 2H), 6.33 (t,  $J = 2.0$  Hz, 2H), 2.08 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  136.8, 136.7, 136.6, 134.8, 132.4, 127.2, 121.3, 120.8, 118.6, 111.0, 110.1, 13.6.

$\text{C}_{16}\text{H}_{12}\text{N}_2\text{S}$  (264.34): Calcd C 72.70, H 4.58; Found C 72.78, H 4.79.

#### 3-(3-Methyl-5-phenyl-4-(pyrrol-1-yl)thiophen-2-yl)quinoline (22)

From 3-(3-methyl-4-(pyrrol-1-yl)thiophen-2-yl)quinoline **17** (0.435 g, 1.5 mmol) and bromobenzene (0.157 g, 1 mmol) at 150 °C during 17 h product **22** was obtained in 56% (0.205 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.11 (s, 1H), 8.27 (s, 1H), 8.15 (d,  $J = 8.0$  Hz, 1H), 7.89 (d,  $J = 8.0$  Hz, 1H), 7.76 (t,  $J = 7.8$  Hz, 1H), 7.61 (t,  $J = 7.8$  Hz, 1H), 7.30-7.24 (m, 3H), 7.07 (d,  $J = 8.0$  Hz, 2H), 6.71 (t,  $J = 2.0$  Hz, 2H), 6.33 (t,  $J = 2.0$  Hz, 2H), 2.17 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  150.5, 137.5, 135.8, 135.0, 133.7, 131.8, 129.9, 129.4, 128.8, 128.1, 127.9, 127.7, 127.3, 127.1, 121.7, 109.7, 12.9.

$\text{C}_{24}\text{H}_{18}\text{N}_2\text{S}$  (366.48): Calcd C 78.66, H 4.95; Found C 78.54, H 5.11.

#### 1-(4-(3-Methyl-5-(pyrimidin-5-yl)-4-(pyrrol-1-yl)thiophen-2-yl)phenyl)propan-1-one (23)

From methyl 4-methyl-5-(4-propionylphenyl)-3-(pyrrol-1-yl)thiophene-2-carboxylate **3** (0.529 g, 1.5 mmol) 5-bromopyrimidine (0.159 g, 1 mmol) at 150 °C during 17 h product **23** was obtained in 71% (0.264 g) yield.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.05 (s, 1H), 8.26 (s, 2H), 8.08 (d,  $J = 8.7$  Hz, 2H), 7.63 (d,  $J = 8.7$  Hz, 2H), 6.68 (t,  $J = 2.0$  Hz, 2H), 6.39 (t,  $J = 2.0$  Hz, 2H), 3.05 (q,  $J = 7.6$  Hz, 2H), 2.16 (s, 3H), 1.27 (t,  $J = 7.6$  Hz, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  200.0, 157.4, 154.2, 138.0, 137.1, 136.3, 133.5, 129.3, 128.8, 128.6, 126.8, 121.2, 110.9, 31.9, 12.9, 8.2.

$\text{C}_{22}\text{H}_{19}\text{N}_3\text{OS}$  (373.47): Calcd C 70.75, H 5.13; Found C 70.82, H 5.01.

#### 5-(3-Nitrophenyl)-2-(pyrrol-1-yl)thiophene-3-carbonitrile (24a)

From 2-(pyrrol-1-yl)thiophene-3-carbonitrile (0.261 g, 1.5 mmol) and 3-bromonitrobenzene (0.202 g, 1 mmol) at 150 °C during 17 h product **24a** was obtained in <10% (0.029 g) yield. This compound was not isolated in pure form.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.38 (s, 1H), 8.29 (d,  $J = 8.0$  Hz, 1H), 7.84 (d,  $J = 8.0$  Hz, 1H), 7.63 (t,  $J = 7.8$  Hz, 1H), 7.27 (t,  $J = 2.0$  Hz, 2H), 6.44 (t,  $J = 2.0$  Hz, 2H).

#### Ethyl 5-(2-(4-cyanophenyl)-pyrrol-1-yl)-1-methylpyrazole-4-carboxylate (25b)

From ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate (0.328 g, 1.5 mmol) and 4-bromobenzonitrile (0.182 g, 1 mmol) at 130 °C during 2 h product **25b** was obtained in 42% (0.134 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.98 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.88-6.80 (m, 1H), 6.69-6.66 (m, 1H), 6.49 (t, *J* = 3.1 Hz, 1H), 4.14 (q, *J* = 7.6 Hz, 2H), 3.40 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.3, 141.1, 139.6, 136.1, 133.3, 132.5, 126.4, 126.2, 118.6, 112.4, 111.7, 110.2, 110.1, 60.4, 35.7, 14.1.

C<sub>18</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub> (320.35): Calcd C 67.49, H 5.03; Found C 67.66, H 4.78.

#### Ethyl 1-methyl-5-(2-(4-nitrophenyl)-pyrrol-1-yl)-pyrazole-4-carboxylate (26)

From ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate (0.328 g, 1.5 mmol) and 4-bromonitrobenzene (0.202 g, 1 mmol) at 130 °C during 2 h product **26** was obtained in 40% (0.136 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.13 (d, *J* = 8.0 Hz, 2H), 8.02 (s, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 3.1 Hz, 1H), 6.79-6.75 (m, 1H), 6.54 (t, *J* = 3.1 Hz, 1H), 4.18 (q, *J* = 7.6 Hz, 2H), 3.46 (s, 3H), 1.20 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.3, 146.1, 141.1, 138.0, 133.1, 126.6, 126.3, 124.1, 113.0, 111.9, 110.2, 60.4, 35.7, 14.1.

C<sub>17</sub>H<sub>16</sub>N<sub>4</sub>O<sub>4</sub> (340.33): Calcd C 59.99, H 4.74; Found C 60.11, H 4.59.

#### Ethyl 5-(2-(4-formylphenyl)-pyrrol-1-yl)-1-methylpyrazole-4-carboxylate (27)

From ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate (0.328 g, 1.5 mmol) and 4-bromobenzaldehyde (0.185 g, 1 mmol) at 130 °C during 2 h product **27** was obtained in 50% (0.161 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.98 (s, 1H), 7.99 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 3.1 Hz, 1H), 6.74-6.70 (m, 1H), 6.50 (t, *J* = 3.1 Hz, 1H), 4.16 (q, *J* = 7.6 Hz, 2H), 3.40 (s, 3H), 1.17 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 191.4, 161.4, 141.1, 139.8, 137.5, 134.5, 133.9, 130.2, 126.4, 126.2, 112.3, 111.6, 110.1, 60.3, 35.7, 14.1.

C<sub>18</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> (323.34): Calcd C 66.86, H 5.30; Found C 67.04, H 5.07.

#### Ethyl 1-methyl-5-(2-(4-nitro-3-(trifluoromethyl)phenyl)-pyrrol-1-yl)-pyrazole-4-carboxylate (28)

From ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate (0.328 g, 1.5 mmol) and 4-bromo-1-nitro-2-(trifluoromethyl)benzene (0.270 g, 1 mmol) at 130 °C during 2 h product **28** was obtained in 56% (0.228 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.99 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.59 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 3.1 Hz, 1H), 6.80-6.75 (m, 1H), 6.54 (t, *J* = 3.1 Hz, 1H), 4.16 (q, *J* = 7.6 Hz, 2H), 3.48 (s, 3H), 1.18 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 161.1, 141.1, 139.0, 136.6, 131.9, 129.0, 127.1, 126.0, 125.4 (q, *J* = 5.6 Hz), 124.5 (q, *J* = 34.0 Hz), 121.6 (q, *J* = 273.7 Hz), 113.6, 112.2, 110.5, 60.5, 35.7, 14.0.

C<sub>18</sub>H<sub>15</sub>F<sub>3</sub>N<sub>4</sub>O<sub>4</sub> (408.33): Calcd C 52.95, H 3.70; Found C 52.79, H 3.89.

#### Ethyl 1-methyl-5-(2-(pyrimidin-5-yl)-pyrrol-1-yl)-pyrazole-4-carboxylate (29)

From ethyl 1-methyl-5-(pyrrol-1-yl)-pyrazole-4-carboxylate (0.328 g, 1.5 mmol) and 5-bromopyrimidine (0.159 g, 1 mmol) at 130 °C during 2 h product **29** was obtained in 58% (0.172 g) yield.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 9.02 (s, 1H), 8.45 (s, 2H), 7.96 (s, 1H), 6.87 (t, *J* = 3.1 Hz, 1H), 6.75-6.70 (m, 1H), 6.53 (t, *J* = 3.1 Hz, 1H), 4.13 (q, *J* = 7.6 Hz, 2H), 3.48 (s, 3H), 1.18 (t, *J* = 7.6 Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 160.8, 156.5, 153.7, 140.8, 138.7, 128.3, 125.9, 125.7, 111.9, 111.7, 110.2, 60.1, 35.3, 13.7.

C<sub>15</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub> (297.31): Calcd C 60.60, H 5.09; Found C 60.41, H 5.27.

#### References

- (a) Schulz, V.; Fischer, W.; Hanselle, U.; Huhmann, W.; Zietsch, V. *Eur. J. Clin. Pharmacol.* **1986**, *31*, 411-414; (b) Herling, A. W.; Scholl, T.; Bickel, M.; Lang, H. J.; Scheunemann, K. H.; Weidmann, K.; Rippel, R. *Pharmacology* **1991**, *43*, 293-303; (c) Maj, J.; Rogoz, Z.; Sowinska, H.; Zalewski, Z. *Pol. J. Pharmacol. Pharm.* **1987**, *39*, 63-74.
- (a) Akita, Y.; Inoue, A.; Yamamoto, K.; Ohta, A.; Kurihara, T.; Shimizu, M. *Heterocycles* **1985**, *23*, 2327-2333.; (b) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951-1958; (c) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Miyafuji, A.; Kunoh, J.; Honma, R. Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257-272.
- For reviews on Pd-catalysed C-H functionalisations: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174-238; (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200-205; (c) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949-957; (d) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269-10310; (e) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949-957; (f) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792-9826; (g) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20-40; (h) Wu, X.-F.; Anbarasan, P.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 7316-7319; (i) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254; (j) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960-9009; (k) Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369-375; (l) Kuzhushkov, S. I.; Potukuchi, H. K.; Ackermann, L. *Catal. Sci. Technol.* **2013**, *3*, 562-571; (m) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, *356*, 17-117; (n) He, M.; Soulé, J. F.; Doucet, H. *ChemCatChem* **2014**, *6*, 1824-1859; (o) Yuan, K.; Soulé, J. F.; Doucet, H. *ACS Catal.* **2015**, *5*, 978-991.
- For selected examples of Pd-catalysed direct arylations from our laboratory: (a) Beydoun, K.; Zaarour, M.; Williams, J. A. G.; Doucet, H.; Guerschais V. *Chem. Commun.* **2012**, *48*,

- 1260-1262; (b) Fu, H. Y.; Chen, L. Doucet, H. *J. Org. Chem.* **2012**, *77*, 4473-4478; (c) Zhao, L.; Bruneau, C.; Doucet, H. *Chem. Commun.* **2013**, *49*, 5598-5600.
5. (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*, Pergamon: Amsterdam, **2000**; (b) Negishi, E. Ed. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, 2002; Part III, p 213; (c) Schnürch, M.; Flasič, R.; Khan, A. F.; Spina M.; Mihovilovic, M. D.; Stanetty, P. *Eur. J. Org. Chem.* **2006**, 3283-3307; (d) Ackermann, L. *Modern arylation methods*, Wiley, **2009**.
6. For selected examples of Pd-catalysed direct arylations of thiophene derivatives: (a) Masui, K.; Ikegami H.; Mori, A. *J. Am. Chem. Soc.*, **2004**, *126*, 5074-5075; (b) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999-9006; (c) Amaladass, P.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2007**, *63*, 10363-10371; (d) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851-1854; (e) Liégault, B.; Petrov, I.; Gorlesky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047-1060; (f) Chen, L.; Roger, J.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *Chem. Commun.* **2011**, *47*, 1872-1874; (g) Yuan, K.; Doucet, H. *Chem. Sci.* **2014**, *5*, 392-396.
7. For selected examples of Pd-catalysed direct arylations of pyrrole derivatives: (a) Toure, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *8*, 1979-1982; (b) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Li, Y.-Z.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1473-1476; (c) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826-1834; (d) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977-1990; (e) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517-9520; (f) Nadres, E. T.; Lazareva, A.; Daugulis, O. *J. Org. Chem.* **2011**, *76*, 471-483; (g) Vakuliuk, O.; Koszarna, B.; Gryko, D. T. *Adv. Synth. Catal.* **2011**, *353*, 925-930; (h) Wu, M.; Luo, J.; Xiao, F.; Zhang, S.; Deng, G.-J.; Luo, H.-A. *Adv. Synth. Catal.* **2012**, *354*, 335-340; (i) Florentino, L.; Aznar, F.; Valdes, C. *Chem. Eur. J.* **2013**, *19*, 10506-10510; (j) Ehlers, P.; Petrosyan, A.; Baumgard, J.; Jopp, S.; Steinfeld, N.; Ghochikyan, T. V.; Saghyan, A. S.; Fischer, C.; Langer, P. *ChemCatChem* **2013**, *5*, 2504-2511; (k) Zhao, L.; Bruneau, C.; Doucet H. *ChemCatChem* **2013**, *5*, 255-262; (l) Jin, R.; Yuan, K.; Chatelain, E.; Soulé, J.-F.; Doucet H. *Adv. Synth. Catal.* **2014**, *356*, 3831-3841.
8. (a) Roger, J.; Požgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 425-432; (b) Xu, Y.; Zhao, L.; Li, Y.; Doucet, H. *Adv. Synth. Catal.* **2013**, *355*, 1423-1432.
9. Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Org. Lett.* **2010**, *12*, 4320-4323.
10. Cantat, T.; Génin, E.; Giroud, C.; Meyer G.; Jutand, A. *J. Organomet. Chem.* **2003**, *687*, 365-376.

**Keywords:** palladium, catalysis, C-H bond activation, thiophenes pyrroles, direct arylation, aryl halides