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Palladium-catalyzed direct 5-arylation of formyl- or acetyl-halothiophene derivatives

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ABSTRACT

$Pd(OAc)_2$ was found to catalyze the direct arylation of some functionalized halothiophene derivatives allowing the synthesis in only one step of polyfunctionalized arylated thiophenes. In the presence of 2-acetyl-3-chlorothiophene, 2-acetyl-4-chlorothiophene, 2-acetyl-3-bromothiophene diethylacetal or 2-(4-bromothiophen-2-yl)-[1,3]dioxolane, and a variety of aryl bromides, the 5-arylation products were obtained in moderate to high yields employing only 0.5 mol% catalyst. On the other hand, the use of 2-formyl-3-chlorothiophene, 2-acetyl-3-bromothiophene or 2-formyl-3-bromothiophene gave disappointing results.

1. Introduction

The arylation of heteroaromatics, such as thiophenes, furans, pyrroles, thiazoles or oxazoles is an important field for research in organic synthesis due to the biological and physical properties of such compounds. Palladium catalyzed Suzuki, Stille or Negishi cross-couplings are among the most important methods to perform such arylation reactions [1]. However, they require the preparation of an organometallic derivative and provide a metallic salt (MX) as by-product. Therefore, these reactions are generally not economically and environmentally very attractive. In 1990, Ohta et al. reported the arylation of thiophenes, furans or thiazoles with aryl halides, *via* a C–H bond activation, in moderate to good yields using 5 mol% $Pd(PPh_3)_4$ as the catalyst [2]. Since these exciting results, the palladium-catalyzed direct arylation of heteroaryl derivatives with aryl halides or triflates has proved to be a powerful method for the synthesis of arylated heterocycles [3–8]. This method provides cost-effective and environmentally attractive procedure for the preparation of arylated heteroaromatics due to the reduced number of steps, reduced amount of waste, and due to the wider diversity of available compounds. Actually, one of the major drawbacks of this reaction is the substrate scope, which is quite limited [6]. A few examples of palladium-catalyzed direct arylations of formyl- or acetyl-thiophenes have been reported [7]. Some direct coupling reactions of halothiophenes with aryl halides, where the integrity of the C–Br or C–Cl bond of the halothiophene was maintained, have also been reported [8]. On the other hand, to our knowledge, so far, no example of palladium catalyzed arylations of halogenated carbonylthiophenes *via* C–H bond activation has been described (Fig. 1).

The use of such functional halothiophenes for direct arylation would be useful, as they would give a simple access to a wide variety of polyfunctionalised thiophenes useful for material chemistry or pharmaceutical applications. For example, some 2-carbonylthiophene derivatives are bioactive (Fig. 2) [9].

Moreover, the access to boron or organometallic derivatives of functional halothiophenes might be tricky or fastidious [10]. To our knowledge, the synthesis and use of organometallic derivatives of 2-formyl- or 2-acetyl-halothiophenes for the preparation of the corresponding 5-arylated thiophenes has not been reported so far. For these reasons, we decided to examine the influence of such substituents on thiophene derivatives, for the palladium-catalyzed direct coupling with aryl bromides.

2. Results and discussion

First, we studied the coupling of 2-acetyl-4-chlorothiophene with several aryl bromides employing 0.5 mol% $Pd(OAc)_2$ as the catalyst and KOAc as the base. These phosphine-free catalyst reaction conditions allowed the successful coupling of several aryl bromides to more simple thiophene derivatives [7f]. We observed that using such conditions, the 5-arylated thiophenes **1**–**10** were obtained with high isolated yields (Scheme 1, Table 1). With this

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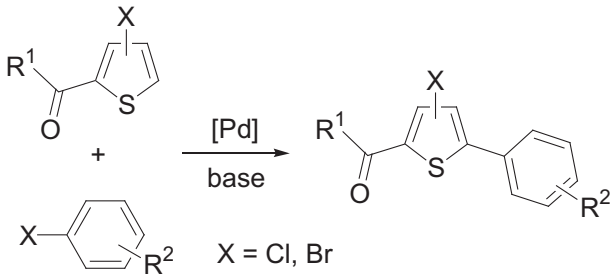


Fig. 1. Arylation of 2-carbonylthiophenes.

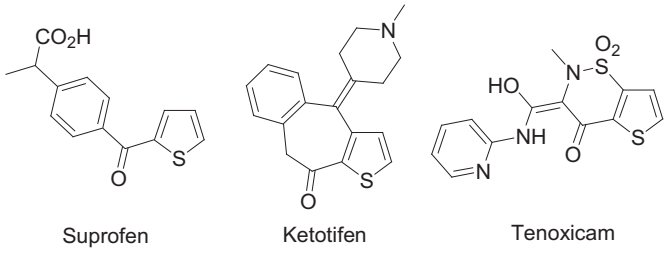


Fig. 2. Examples of bioactive 2-carbonylthiophene derivatives.

procedure, the priority for the arylation of this 2,4-disubstituted thiophene is clearly the 5-position. Moreover, no formation of by-products such as thiophene oligomers due to the oxidative addition of this chlorothiophene to palladium was detected during the course of these reactions. We examined the scope and limitations of this reaction using *para*-, *meta*- or *ortho*-substituted aryl bromides and also heteroaryl bromides (Table 1). 4-Bromoacetophenone, 4-bromobenzonitrile, 4-(trifluoromethyl)bromobenzene or (4-bromophenyl)-acetonitrile gave **1**–**4** in 81–93% yields (Table 1, entries 1–4). Even the deactivated aryl bromide, 4-*tert*-butylbromobenzene led to the expected coupling product **5** in good yield (Table 1, entry 5). A lower yield was obtained in the presence of 2-bromobenzonitrile due to a partial conversion of this aryl bromide. With this congested reactant, **8** was obtained in 76% yield (Table 1, entry 8). Pyridines are probably the most common heterocyclic motif found in pharmaceutically active compounds [11]. Therefore, preparative methods of biheteroaryl derivatives containing pyridines remain an essential research topic in organic synthesis [12]. 3- or 4-Bromopyridines were also found to give the coupling products **9** and **10** in high yields; whereas, 5-bromopyrimidine gave **11** in only 46% due to a partial conversion of this aryl bromide (Table 1, entries 9–11).

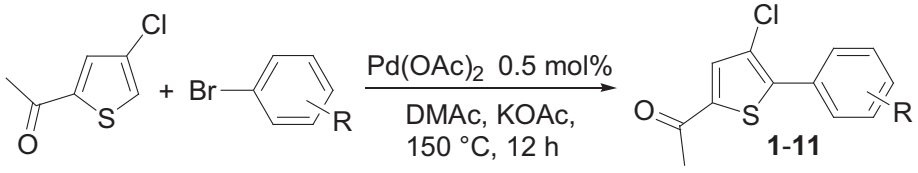
Next, in order to determine the influence of the chloride position on the thiophene derivative, we studied the reactivity of 2-acetyl- or 2-formyl-3-chlorothiophenes with 4-bromobenzonitrile (Schemes 2 and 3, Table 2). Surprisingly, the reactivity of these two thiophene derivatives was found to be different. Four aryl bromides were successfully coupled with 2-acetyl-3-chlorothiophene (Scheme 2, Table 2). Even if some by-products were formed, the expected 5-arylation products **12**–**15** were obtained in relatively good yields using either electron-deficient aryl bromides or 2-bromonaphthalene. On the other hand, the reaction of 2-formyl-3-chlorothiophene with 4-bromobenzonitrile gave no desired coupling product **16** (Scheme 3). At 120 °C, most of the starting material was recovered unreacted, whereas at 150 °C an extensive decomposition of these reactants was observed by gas chromatography and NMR analysis of the crude mixtures.

Then, we examined the reactivity of 2-acetyl- or 2-formylbromothiophenes for these direct arylation reactions (Schemes 4–9, Tables 3–5). The oxidative addition of bromothiophenes to palladium should be easier than the oxidative addition of chlorothiophenes, and the formation of larger amounts of undesired product arising from partial polymerization of these substrates was expected. In the presence of 2-formyl-4-bromothiophene, using 4-bromobenzaldehyde as the coupling partner, the 5-arylation product **17** was obtained in moderate yields, together with several by-products (Scheme 4, Table 3). On the other hand, in the presence of or 4-bromobenzonitrile the major product of the reaction was **18**, due to the debromation of this thiophene derivative (Table 3, entry 2). A few other aryl bromides, such as 4-bromoacetophenone, 3-bromobenzaldehyde or (4-bromophenyl)-acetonitrile were also employed, but led to mixtures of products, which were not purified, as we had observed that, in the presence of 2-(4-bromothiophen-2-yl)-[1,3]dioxolane, much higher yields could be easily obtained (Scheme 5, Table 4).

The reactivity of 2-acetyl-4-bromothiophene for direct arylation is very low (Scheme 5). Only a moderate conversion of 4-bromopropiophenone was observed in the presence of this heteroaromatic after 16 h at 150 °C. Moreover, the desired compound **19a** was only obtained in a very low yield. The major product of this reaction was the debrominated compound **19b**, which was isolated in 22% yield. The lower reactivity of 2-acetyl-4-bromothiophene compared to 2-acetyl-4-chlorothiophene might come from the larger steric hindrance of bromo vs chloro substituents.

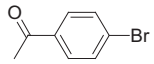
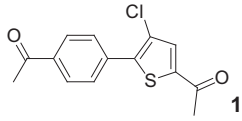
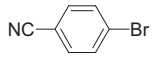
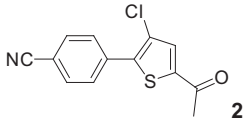
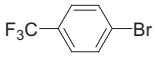
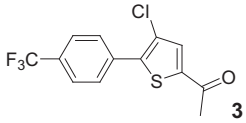
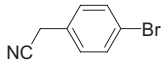
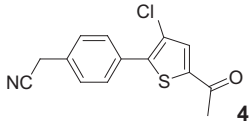
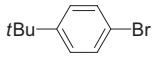
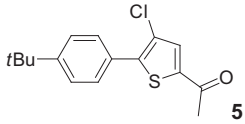
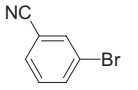
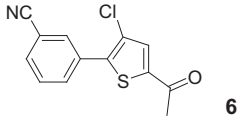
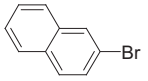
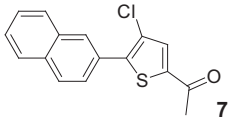
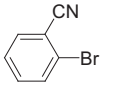
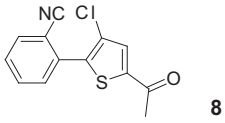
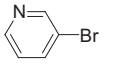
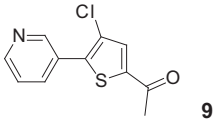
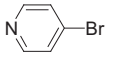
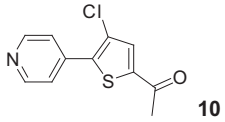
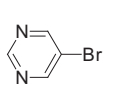
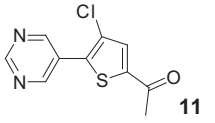
2-Acetyl-3-bromothiophene failed to afford the desired target product **20** when reacted with 4-bromobenzaldehyde (Scheme 6), but the formation of several unidentified by-products was observed. The reaction of 2-formyl-3-bromothiophene with 4-bromobenzonitrile was also unsatisfactory (Scheme 7). None of various experimental conditions tested allowed the isolation of the desired coupling product **21**. Yet, the formation of several unidentified by-products was evidenced by GC and NMR analysis of the crude mixture, as observed previously with 2-formyl-3-chlorothiophene.

The initial attempts to couple aryl bromides using 2-(4-bromothiophen-2-yl)-[1,3]dioxolane at 150 °C during 20 h gave mixtures of products. On the other hand, the reactions performed at 100 °C during 4 h gave the desired coupling products **22**–**35** in very high yields (Scheme 8, Table 4). Under these conditions, only traces of by-products were detected by NMR and GC analysis of the crude mixtures. Thiophenes are electron-rich heterocycles. Therefore, the oxidative addition of bromothiophenes to palladium often requires the use of palladium associated to phosphine ligands and/or elevated reaction temperatures [8d,13]. Consequently, the use for these reactions of $Pd(OAc)_2$ without the addition of phosphine ligand as the catalyst, at a moderate reaction temperature (100 °C) allows a very selective oxidative addition of the aryl bromide to palladium; during which the C–Br bond of this bromothiophene remains untouched. Several aryl bromides were successfully



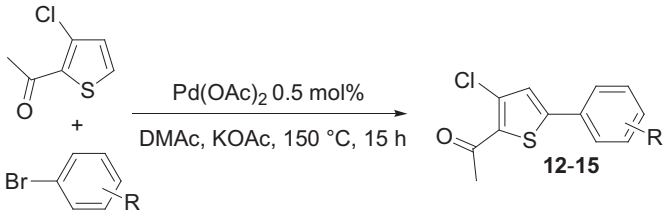
Scheme 1. Direct 5-arylation of 2-acetyl-4-chlorothiophene.

Table 1
Direct 5-arylation of 2-acetyl-4-chlorothiophene with bromobenzene derivatives (Scheme 1).

Entry	Aryl bromide	Product	Yield (%)
1		 **1**	98 (87)
2		 **2**	96 (88)
3		 **3**	96 (93)
4		 **4**	90 (81)
5		 **5**	95 (80)
6		 **6**	98 (85)
7		 **7**	90 (82)
8		 **8**	80 (76)
9		 **9**	98 (80)
10		 **10**	78 (73)
11		 **11**	52 (46)

Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-acetyl-4-chlorothiophene (2 mmol), KOAc (2 mmol), DMAc, 150 °C, 12 h, under argon, GC and NMR yields, yields in parentheses are isolated.

employed in this reaction. For example, 4-bromobenzaldehyde, 4-bromobenzonitrile, 4-bromoacetophenone, 4-bromopropiophenone or 4-bromobenzophenone gave the desired compounds **22**–**26** in 85–90% yields (Table 4, entries 1–5). Even the poorly activated aryl bromide, 4-bromofluorobenzene gave the desired 5-arylation product **28** in good yield (Table 4, entry 7). As expected, the *meta*-substituted aryl bromides, 3-bromobenzaldehyde or 3-bromobenzonitrile gave the products **30** and **31** in high yields (Table 4, entries 9 and 10). 2-Bromonaphthalene was also found to be reactive under these reaction conditions and gave **32** in 90% yield (Table 4, entry 11). Pyridines or pyrimidines are π-electron deficient; whereas, thiophenes are π-electron excessive. Therefore, in a reaction mixture containing both a bromothiophene and a bromopyridine (or a bromopyrimidine), the oxidative addition of the bromopyridine to palladium should be easier. As expected, we observed that the reaction of 3-bromopyridine or 5-bromopyrimidine with 2-(4-bromothiophen-2-yl)-[1,3]dioxolane led to **34** and **35** in good yields (Table 4, entries 13 and 14).



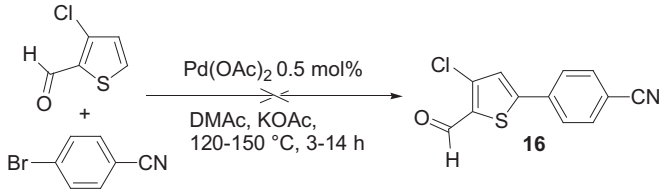
Scheme 2. Direct arylation of 2-acetyl-3-chlorothiophene.

Again, the use of an aldehyde function protected as an acetal gave more satisfactory results (Scheme 9, Table 5). The coupling of 2-formyl-3-bromothiophene diethylacetal with three aryl bromides using only 0.5 mol% $Pd(OAc)_2$ as the catalyst gave the desired compounds **36**–**38** in moderate yields.

Finally, we also performed a few direct 5-arylation reactions of 2-chlorothiophene using our phosphine-free catalyst procedure (Scheme 10, Table 6). A few examples of palladium-catalyzed direct 5-arylations of this reactant have already been reported in the literature [8a,f] However, these reactions were performed using either a relatively high catalysts loading (5 mol% [8a]) or palladium was associated to a phosphine ligand [8f] We observed that, in the presence of only 0.5 mol% $Pd(OAc)_2$ as the catalyst, the reaction of 2-chlorothiophene with electron-deficient aryl bromides generally gave the desired coupling products in good yields.

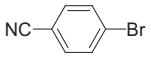
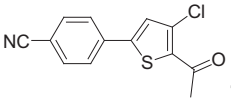
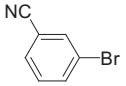
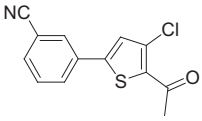
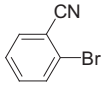
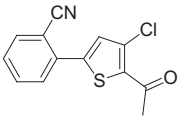
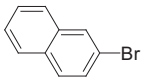
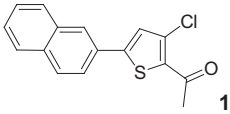
3. Conclusion

In summary, we have demonstrated that a variety of halothiophenes are successfully applicable in direct palladium catalyzed arylation reactions, including those that possess electron withdrawing groups such as acetyl, formyl- or electron-neutral groups. Using as little as 0.5 mol% of $Pd(OAc)_2$ as the catalyst precursor, the direct 5-arylation of 2-acetyl-3-chlorothiophene or 2-acetyl-4-chlorothiophene generally proceeds in high yields. With bromothiophene derivatives, protected carbonyl functions and moderate reaction temperatures are mandatory to avoid unwanted oligomerisation processes. When appropriate reactions conditions are employed, both 2-formyl-3-bromothiophene diethylacetal and 2-(4-bromothiophen-2-yl)-[1,3]dioxolane can be arylated on C5 in moderate to good yields. On the other hand, the use of 2-formyl-3-



Scheme 3. Attempts of direct arylation of 2-formyl-3-chlorothiophene.

Table 2
Direct 5-arylation of 2-acetyl-3-chlorothiophene with bromobenzene derivatives (Scheme 2).

Entry	Aryl bromide	Product	Yield (%)
1		 **12**	81 (68)
2		 **13**	70 (61)
3		 **14**	90 (70)
4		 **15**	70 (60)

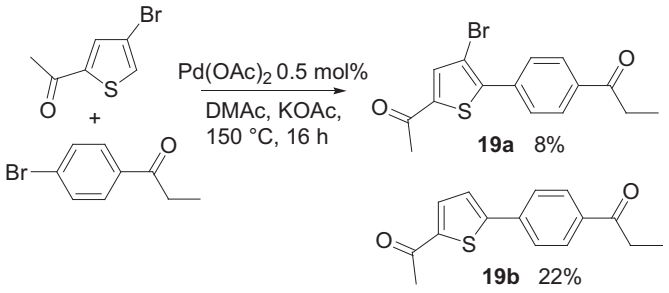
Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-formyl-3-chlorothiophene (2 mmol), KOAc (2 mmol), DMAc, 150 °C, 15 h, under argon, GC and NMR yields, yields in parentheses are isolated.

bromothiophene, 2-formyl-4-bromothiophene or 2-acetyl-4-bromothiophene gave disappointing results. It should be noted that a wide range of functions such as formyl, acetyl, propionyl, benzoyl, nitrile, fluoro or trifluoromethyl on the aryl bromide is tolerated. Satisfactory results were also obtained using heteroaryl bromides. This reaction gives a very simple access to relatively complex molecules in only one step. This quite low catalyst loading procedure is economically and environmentally attractive. The major by-products are AcOH/KBr instead of metallic salts with more classical 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.

4. Experimental

4.1. General remarks

All reactions were run under argon in Schlenk tubes using vacuum lines. DMAc analytical grade was not distilled before use. Potassium acetate (99+) was used. Commercial aryl bromides and thiophene derivatives were used without purification. ^1H and ^{13}C spectrum were recorded with Bruker 200 MHz spectrometer in $CDCl_3$ solutions. Chemical shift are reported in ppm relative to



Scheme 5. Direct 5-arylation of 2-acetyl-4-bromothiophene.

$CDCl_3$ (7.25 for ^1H NMR and 77.0 for ^{13}C NMR). Flash chromatography were performed on silica gel (230–400 mesh).

4.2. General procedure

As a typical experiment, the reaction of the aryl bromide (1 mmol), the halothiophene derivative (2 mmol) and KOAc (0.196 g, 2 mmol) at 100–150 °C (see tables or schemes) during 3–20 h (see tables or schemes) in DMAc (4 mL) in the presence of $Pd(OAc)_2$ (see tables or schemes) under argon affords the corresponding product after extraction with dichloromethane, evaporation and filtration on silica gel (pentane/ether).

4.2.1. 1-[4-(5-Acetyl-3-chlorothiophen-2-yl)-phenyl]-ethanone (*1*)

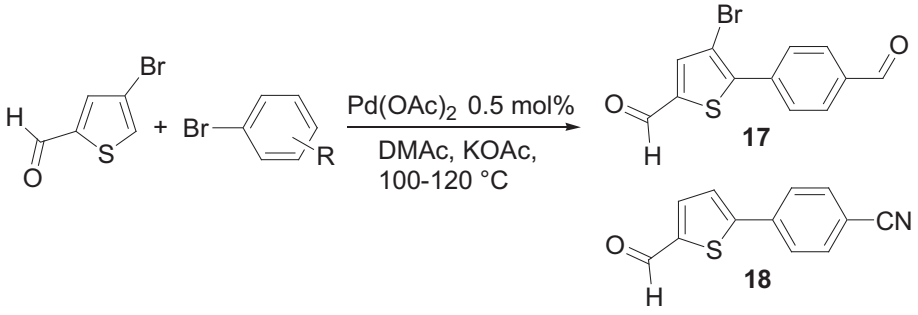
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **1** in 87% (0.242 g) isolated yield. ^1H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, $J = 8.2$ Hz, 2H), 7.80 (d, $J = 8.2$ Hz, 2H), 7.59 (s, 1H), 2.64 (s, 3H), 2.57 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.6, 190.1, 143.5, 142.2, 137.5, 136.2, 134.2, 129.2, 129.1, 123.7, 27.1, 26.8. Elemental analysis: calcd (%) for $C_{14}H_{11}ClO_2S$ (278.75): C 60.32, H 3.98; found: C 60.40, H 3.90.

4.2.2. 4-(5-Acetyl-3-chlorothiophen-2-yl)-benzonitrile (*2*)

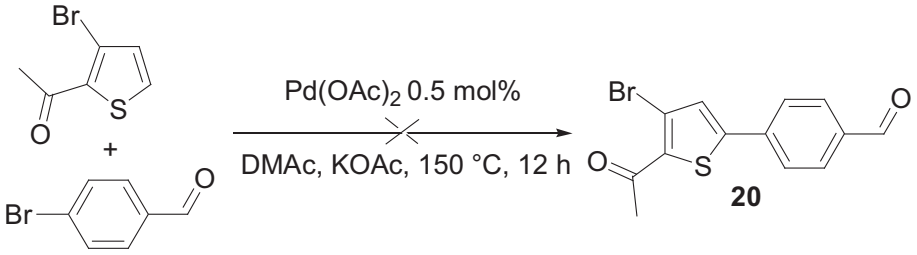
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **2** in 88% (0.230 g) isolated yield. ^1H NMR (200 MHz, $CDCl_3$): δ 7.84 (d, $J = 8.2$ Hz, 2H), 7.77 (d, $J = 8.2$ Hz, 2H), 7.62 (s, 1H), 2.60 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.0, 142.8, 142.3, 136.2, 134.2, 133.0, 129.7, 123.7, 118.7, 113.2, 26.8. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.49, H 2.89.

4.2.3. 1-[4-Chloro-5-(4-trifluoromethylphenyl)-thiophen-2-yl]-ethanone (*3*)

The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc



Scheme 4. Direct 5-arylation of 2-formyl-4-bromothiophene.



Scheme 6. Attempts of direct arylation of 2-acetyl-3-bromothiophene.

(0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **3** in 93% (0.283 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.83 (d, J = 8.2 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.61 (s, 1H), 2.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 189.6, 142.6, 141.9, 134.8, 133.6, 131.0 (q, J = 32.5 Hz), 129.1, 125.8 (q, J = 3.8 Hz), 124.0 (q, J = 273.0 Hz), 122.9, 26.3. Elemental analysis: calcd (%) for $C_{13}H_8ClF_3OS$ (304.72): C 51.24, H 2.65; found: C 51.30, H 2.57.

*4.2.4. [4-(5-Acetyl-3-chlorothiophen-2-yl)-phenyl]-acetonitrile (**4**)*

The reaction of (4-bromophenyl)-acetonitrile (0.196 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **4** in 81% (0.223 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.59 (s, 1H), 7.45 (d, J = 8.2 Hz, 2H), 3.83 (s, 2H), 2.57 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 188.7, 142.5, 140.2, 132.7, 130.2, 130.1, 128.4, 127.4, 121.2, 116.3, 25.3, 22.5. Elemental analysis: calcd (%) for $C_{14}H_{10}ClNOS$ (275.75): C 60.98, H 3.66; found: C 60.87, H 3.80.

*4.2.5. 1-[5-(4-tert-Butylphenyl)-4-chlorothiophen-2-yl]-ethanone (**5**)*

The reaction of 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **5** in 80% (0.234 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, J = 8.2 Hz, 2H), 7.59 (s, 1H), 7.50 (d, J = 8.2 Hz, 2H), 2.57 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.2, 153.1, 140.8, 134.4, 128.9, 128.8, 126.2, 121.9, 35.3, 31.6, 26.7. Elemental analysis: calcd (%) for $C_{16}H_{17}ClOS$ (292.82): C 65.63, H 5.85; found: C 65.79, H 5.97.

*4.2.6. 3-(5-Acetyl-3-chlorothiophen-2-yl)-benzonitrile (**6**)*

The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **6** in 85% (0.222 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.68–7.55 (m, 2H), 2.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.0, 142.5, 141.9, 134.0, 133.4, 133.1, 132.9, 132.5, 130.2, 123.5, 118.5, 113.7, 26.8. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.70, H 2.87.

*4.2.7. 1-(4-Chloro-5-naphthalen-2-ylthiophen-2-yl)-ethanone (**7**)*

The reaction of 2-bromonaphthalene (0.207 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **7** in 82% (0.235 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.20 (s, 1H), 8.02–7.85 (m, 4H), 7.58–7.40 (m, 3H), 1.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.1, 145.3, 141.4, 134.3, 133.7, 133.5, 129.2, 129.0, 128.9, 128.8, 128.2, 127.6, 127.3, 126.3, 122.4, 26.8. Elemental analysis: calcd (%) for $C_{16}H_{11}ClOS$ (286.78): C 67.01, H 3.87; found: C 67.14, H 4.03.

*4.2.8. 2-(5-Acetyl-3-chlorothiophen-2-yl)-benzonitrile (**8**)*

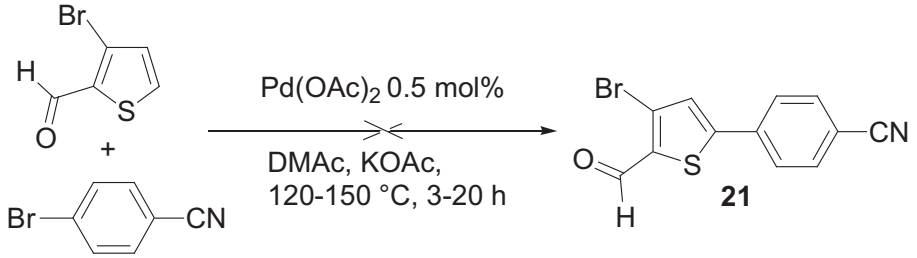
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **8** in 76% (0.199 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, J = 8.0 Hz, 1H), 7.75–7.45 (m, 4H), 2.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.1, 143.8, 140.2, 134.9, 134.0, 133.3, 133.1, 132.0, 130.3, 125.8, 117.7, 113.9, 26.9. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.47, H 2.99.

*4.2.9. 1-(4-Chloro-5-pyridin-3-ylthiophen-2-yl)-ethanone (**9**)*

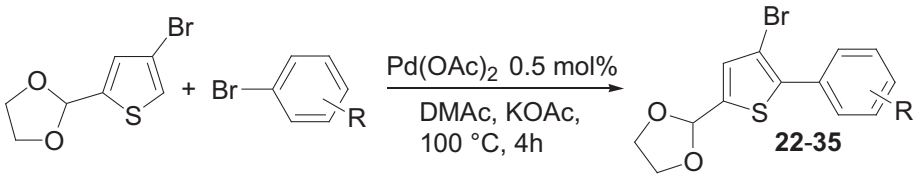
The reaction of 3-bromopyridine (0.158 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **9** in 80% (0.190 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.91 (s, 1H), 8.65 (d, J = 4.8 Hz, 1H), 7.99 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.40 (dd, J = 7.8, 4.8 Hz, 1H), 2.56 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.0, 150.5, 149.6, 142.4, 141.1, 136.3, 134.0, 128.1, 123.9, 123.5, 26.8. Elemental analysis: calcd (%) for $C_{11}H_8ClNOS$ (237.71): C 55.58, H 3.39; found: C 55.72, H 3.50.

*4.2.10. 1-(4-Chloro-5-pyridin-4-yl-thiophen-2-yl)-ethanone (**10**)*

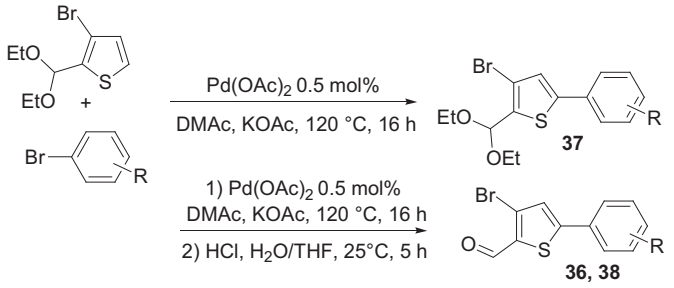
The reaction of 4-bromopyridine hydrochloride (0.194 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **10** in 73% (0.173 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.73 (d, J = 4.7 Hz, 2H), 7.63 (d, J = 4.7 Hz, 2H), 7.28 (s, 1H), 2.59 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 189.6, 150.4, 142.5, 140.9, 138.9, 133.8, 123.8, 122.5, 26.4.



Scheme 7. Attempts of direct arylation of 2-formyl-3-bromothiophene.



Scheme 8. Direct 5-arylation of 2-(4-bromothiophen-2-yl)-[1,3]dioxolane.



Scheme 9. Direct arylation of 2-acetyl-3-bromothiophene diethylacetal.

Elemental analysis: calcd (%) for $C_{11}H_8ClNOS$ (237.71): C 55.58, H 3.39; found: C 55.40, H 3.31.

*4.2.11. 1-(4-Chloro-5-pyrimidin-5-ylthiophen-2-yl)-ethanone (**11**)*

The reaction of 5-bromopyrimidine (0.159 g, 1 mmol), 2-acetyl-4-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 12 h affords the product **11** in 46% (0.110 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.28 (s, 1H), 9.08 (s, 2H), 7.66 (s, 1H), 2.61 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 192.2, 158.9, 156.3, 143.6, 133.8, 133.4, 128.6, 124.7, 26.9. Elemental analysis: calcd (%) for $C_{10}H_7ClN_2OS$ (238.69): C 50.32, H 2.96; found: C 50.40, H 3.07.

*4.2.12. 4-(5-Acetyl-4-chlorothiophen-2-yl)-benzonitrile (**12**)*

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-3-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 15 h affords the product **12** in 68% (0.178 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75–7.65 (m, 4H), 7.34 (s, 1H), 2.72 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 189.9, 146.7, 138.3, 136.4, 133.0, 129.2, 127.8, 126.3, 118.2, 112.9, 29.7. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.47, H 2.97.

*4.2.13. 3-(5-Acetyl-4-chlorothiophen-2-yl)-benzonitrile (**13**)*

The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-3-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 15 h affords the product **13** in 61% (0.159 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.89 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.29 (s, 1H), 2.72 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 189.8, 146.5, 137.9, 133.6, 132.6, 130.2, 130.0, 129.3, 129.2, 127.3, 117.9, 113.7, 29.7. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.25, H 3.14.

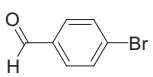
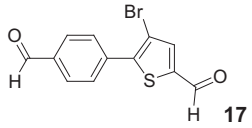
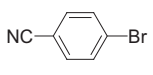
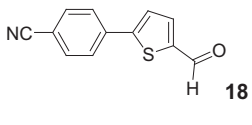
*4.2.14. 2-(5-Acetyl-4-chlorothiophen-2-yl)-benzonitrile (**14**)*

The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-3-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 15 h affords the product **14** in 70% (0.183 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.81 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.54 (t, J = 7.8 Hz, 1H), 2.73 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.0, 144.6, 138.8, 135.3, 134.5, 133.4, 130.2, 129.6, 129.5, 128.8, 117.8, 110.4, 29.8. Elemental analysis: calcd (%) for $C_{13}H_8ClNOS$ (261.73): C 59.66, H 3.08; found: C 59.35, H 3.24.

*4.2.15. 1-(3-Chloro-5-naphthalen-2-ylthiophen-2-yl)-ethanone (**15**)*

The reaction of 2-bromonaphthalene (0.207 g, 1 mmol), 2-acetyl-3-chlorothiophene (0.321 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 15 h affords the product **15** in 60% (0.172 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.93–7.85 (m, 3H), 7.71 (d, J = 8.2 Hz, 1H), 7.59–7.50 (m, 2H), 7.37 (s, 1H), 2.73 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.3, 150.2, 136.8, 134.0, 133.7, 129.9, 129.6, 129.5, 128.8, 128.3, 127.6, 127.5, 126.7, 125.6, 123.7, 30.1. Elemental analysis: calcd (%) for $C_{16}H_{11}ClOS$ (286.78): C 67.01, H 3.87; found: C 67.10, H 3.98.

Table 3
Direct 5-arylation of 2-formyl-4-bromothiophene with bromobenzene derivatives (Scheme 4).

Entry	Aryl bromide	Product	Reaction time (h)	Temp. (°C)	Yield (%)
1		 **17**	24	100	60 (54)
2		 **18**	6	120	(20)

Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-formyl-4-bromothiophene (2 mmol), KOAc (2 mmol), DMAc, under argon, GC and NMR yields, yields in parentheses are isolated.

Table 4
Direct 5-arylation of 2-(4-bromothiophen-2-yl)-[1,3]dioxolane with bromobenzene derivatives (Scheme 8).

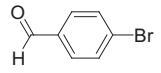
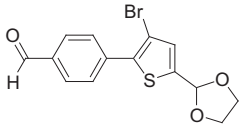
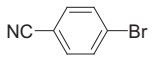
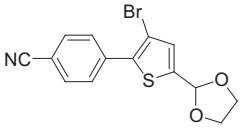
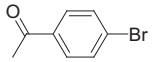
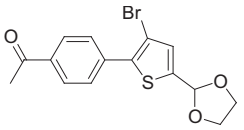
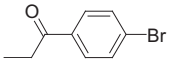
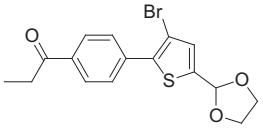
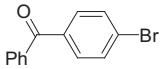
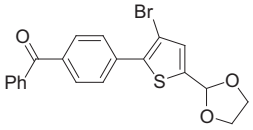
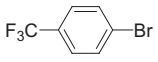
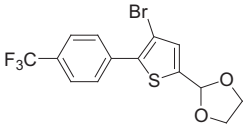
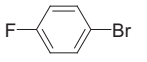
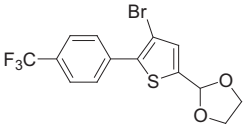
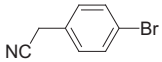
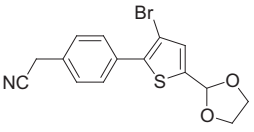
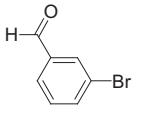
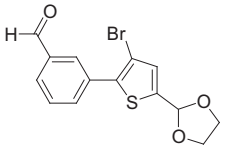
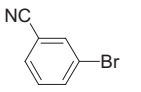
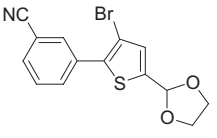
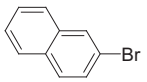
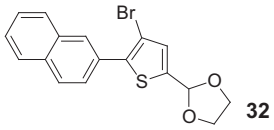
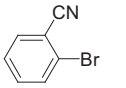
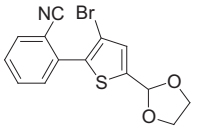
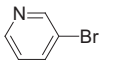
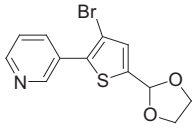
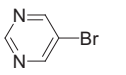
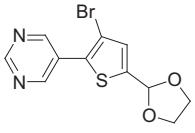
Entry	Aryl bromide	Product	Yield (%)
1		 **22**	95 (89)
2		 **23**	96 (87)
3		 **24**	97 (90)
4		 **25**	95 (88)
5		 **26**	96 (85)
6		 **27**	92 (84)
7		 **28**	95 (84)
8		 **29**	93 (84)
9		 **30**	93 (87)
10		 **31**	97 (86)

Table 4 (*continued*)

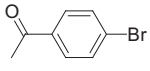
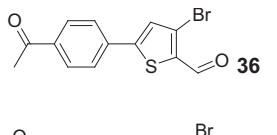
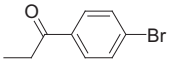
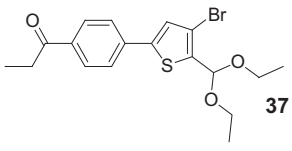
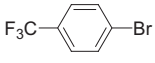
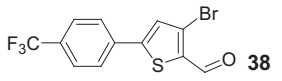
Entry	Aryl bromide	Product	Yield (%)
11		 **32**	95 (90)
12		 **33**	95 (85)
13		 **34**	87 (78)
14		 **35**	79 (69)

Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (2 mmol), KOAc (2 mmol), DMAc, 100 °C, 4 h, under argon, GC and NMR yields, yields in parentheses are isolated.

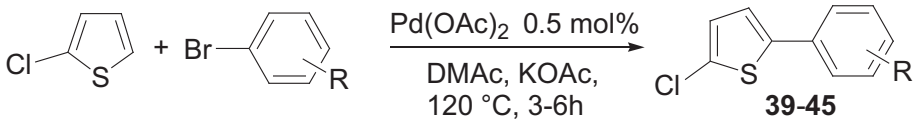
4.2.16. 4-Bromo-5-(4-formylphenyl)-thiophene-2-carbaldehyde (**17**)

The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), 2-formyl-4-bromothiophene (0.470 g, 2 mmol) and KOAc (0.382 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 24 h affords the product **17** in 54% (0.159 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.10 (s, 1H), 9.91 (s, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.89 (d, J = 8.3 Hz, 2H), 7.78 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.8, 182.2, 142.8, 140.2, 137.9, 137.0, 131.7, 130.4,

Table 5
Direct 5-arylation of 2-formyl-3-bromothiophene diethylacetal with bromobenzene derivatives (Scheme 9).

Entry	Aryl bromide	Product	Yield (%)
1		 **36**	51
2		 **37**	54
3		 **38**	50

Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-formyl-3-bromothiophene diethylacetal (2 mmol), KOAc (2 mmol), DMAc, 120 °C, 16 h, under argon, GC and NMR yields, yields in parentheses are isolated. The deprotection of the aldehyde function to form product **36** and **38** was performed by the stirring of the crude mixture at room temperature during 5 h using an $HCl \cdot H_2O$/THF solution.



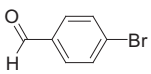
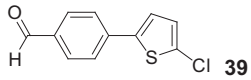
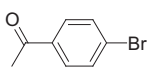
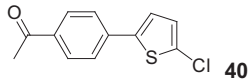
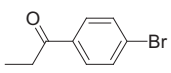
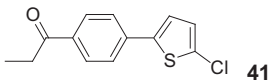
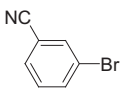
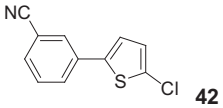
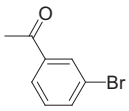
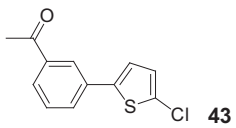
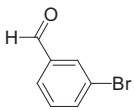
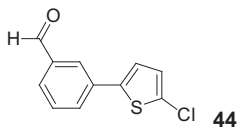
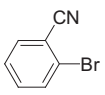
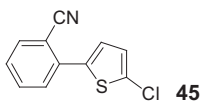
Scheme 10. Direct 5-arylation of 2-chlorothiophene.

130.1, 110.3. Elemental analysis: calcd (%) for $C_{12}H_7BrO_2S$ (295.15): C 48.83, H 2.39; found: C 49.01, H 2.18.

*4.2.17. 4-(5-Formylthiophen-2-yl)-benzonitrile (**18**) [7f]*

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-formyl-4-bromothiophene (0.470 g, 2 mmol) and KOAc (0.382 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 6 h affords the product **18** in 20% (0.043 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.96 (s, 1H), 7.85–7.75 (m, 5H), 7.50 (d, J = 4.0 Hz, 1H).

Table 6
Direct 5-arylation of 2-chlorothiophene with bromobenzene derivatives (Scheme 10).

Entry	Aryl bromide	Product	Reaction time (h)	Yield (%)
1		 **39**	12	92 (80)
2		 **40**	6	89 (70)
3		 **41**	3	84 (76)
4		 **42**	3	88 (78)
5		 **43**	3	70 (57)
6		 **44**	3	90 (75)
7		 **45**	6	85 (73)

Conditions: catalyst: $Pd(OAc)_2$ (0.005 mmol), aryl bromide (1 mmol), 2-chlorothiophene (2 mmol), KOAc (2 mmol), DMAc, 120 °C, 3 h, under argon, GC and NMR yields, yields in parentheses are isolated.

*4.2.18. 1-[4-(5-Acetyl-3-bromo-thiophen-2-yl)-phenyl]-propan-1-one (**19a**) and 1-[5-(4-acetylphenyl)-thiophen-2-yl]-ethanone (**19b**)*

The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), 2-acetyl-4-bromothiophene (0.410 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 150 °C during 16 h affords **19a** in 8% (0.027 g) and the by-product **19b** in 22% (0.054 g) isolated yield. **19a**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.07 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.67 (s, 1H), 3.05 (q, J = 7.6 Hz, 2H), 2.60 (s, 3H), 1.13 (t, J = 7.6 Hz, 2H). **19b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.03 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 4.0 Hz, 1H), 7.44 (d, J = 4.0 Hz, 1H), 3.05 (q, J = 7.6 Hz, 2H), 2.61 (s, 3H), 1.13 (t, J = 7.6 Hz, 2H).

*4.2.19. 4-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzaldehyde (**22**)*

The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **22** in 89% (0.302 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.91 (d, J = 8.4 Hz, 2H), 7.37 (s, 1H), 6.08 (s, 1H), 4.12 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.7, 152.5, 144.5, 137.1, 130.9, 129.5, 128.6, 115.6, 107.3, 99.5, 65.9. Elemental analysis: calcd (%) for $C_{14}H_{11}BrO_3S$ (339.21): C 49.57, H 3.27; found: C 49.70, H 3.41.

*4.2.20. 4-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzonitrile (**23**)*

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **23** in 87% (0.292 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.37 (s, 1H), 6.08 (s, 1H), 4.11 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.6, 144.9, 133.4, 129.5, 128.6, 118.5, 115.4, 113.8, 107.5, 99.5, 66.0. Elemental analysis: calcd (%) for $C_{14}H_{10}BrNO_2S$ (336.20): C 50.01, H 3.00; found: C 50.13, H 2.89.

*4.2.21. 4-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-acetophenone (**24**)*

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **24** in 90% (0.318 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.06 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.4 Hz, 2H), 7.36 (s, 1H), 6.08 (s, 1H), 4.11 (m, 4H), 2.65 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.5, 152.9, 144.1, 138.0, 129.6, 129.4, 128.2, 115.7, 107.0, 99.5, 65.9, 27.1. Elemental analysis: calcd (%) for $C_{15}H_{13}BrO_3S$ (353.23): C 51.00, H 3.71; found: C 51.14, H 3.80.

*4.2.22. 1-[4-(3-Bromo-5-[1,3]dioxolan-2-ylthiophen-2-yl)-phenyl]-propan-1-one (**25**)*

The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **25** in 88% (0.323 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.05 (d, J = 8.4 Hz, 2H), 7.84

(d, J = 8.4 Hz, 2H), 7.34 (s, 1H), 6.06 (s, 1H), 4.11 (m, 4H), 3.04 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.2, 153.0, 144.1, 137.8, 129.4, 129.3, 128.2, 115.6, 106.8, 99.5, 65.9, 32.4, 8.6. Elemental analysis: calcd (%) for $C_{16}H_{15}BrO_3S$ (367.26): C 52.33, H 4.12; found: C 52.17, H 4.01.

4.2.23. 4-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzophenone (**26**)

The reaction of 4-bromobenzophenone (0.261 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **26** in 85% (0.353 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98–7.80 (m, 6H), 7.70–7.45 (m, 3H), 7.38 (s, 1H), 6.09 (s, 1H), 4.13 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.0, 153.2, 144.1, 138.8, 137.5, 133.2, 131.3, 130.5, 129.4, 128.9, 128.0, 115.7, 106.9, 99.6, 65.9. Elemental analysis: calcd (%) for $C_{20}H_{15}BrO_3S$ (415.30): C 57.84, H 3.64; found: C 57.98, H 3.80.

4.2.24. 2-[4-Bromo-5-(4-trifluoromethylphenyl)-thiophen-2-yl]-[1,3]dioxolane (**27**)

The reaction of 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **27** in 84% (0.319 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.87 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H), 7.38 (s, 1H), 6.09 (s, 1H), 4.13 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 152.5, 144.2, 132.0 (q, J = 32.5 Hz), 129.3, 128.5, 126.7 (q, J = 3.8 Hz), 124.0 (q, J = 272.3 Hz), 115.5, 107.2, 99.5, 65.9. Elemental analysis: calcd (%) for $C_{14}H_{10}BrF_3O_2S$ (379.19): C 44.34, H 2.66; found: C 44.47, H 2.51.

4.2.25. 2-[4-Bromo-5-(4-fluorophenyl)-thiophen-2-yl]-[1,3]dioxolane (**28**)

The reaction of 4-bromofluorobenzene (0.175 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **28** in 84% (0.277 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.73 (dd, J = 8.5, 4.8 Hz, 2H), 7.32 (s, 1H), 7.19 (d, J = 8.5 Hz, 2H), 6.07 (s, 1H), 4.11 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 163.4 (d, J = 250.9 Hz), 153.0, 142.5, 129.7 (d, J = 8.5 Hz), 128.6, 127.4 (d, J = 3.4 Hz), 116.3 (d, J = 22.0 Hz), 105.5, 98.9, 65.4. Elemental analysis: calcd (%) for $C_{13}H_{10}BrFO_2S$ (329.19): C 47.43, H 3.06; found: C 47.32, H 3.19.

4.2.26. [4-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-phenyl]-acetonitrile (**29**)

The reaction of 4-bromophenylacetonitrile (0.196 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **29** in 84% (0.294 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2H), 7.45 (d, J = 8.2 Hz, 2H), 7.33 (s, 1H), 6.06 (s, 1H), 4.11 (m, 4H), 3.82 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 153.2, 142.8, 131.7, 128.9, 128.7, 128.4, 117.3, 115.4, 105.9, 99.2, 65.5, 23.5. Elemental analysis: calcd (%) for $C_{15}H_{12}BrNO_2S$ (350.23): C 51.44, H 3.45; found: C 51.30, H 3.40.

4.2.27. 3-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzaldehyde (**30**)

The reaction of 3-bromobenzaldehyde (0.185 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **30** in 87% (0.295 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.18 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.7 Hz, 1H), 7.35 (s, 1H), 6.06 (s, 1H), 4.11 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.7, 152.8, 143.9, 137.5, 133.5, 130.9, 130.5, 129.4, 129.2, 115.6, 106.8, 99.5, 65.9. Elemental analysis: calcd (%) for $C_{14}H_{11}BrO_3S$ (339.21): C 49.57, H 3.27; found: C 49.79, H 3.14.

4.2.28. 3-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzonitrile (**31**)

The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **31** in 86% (0.289 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.00 (d, J = 7.8 Hz, 1H), 7.96 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.37 (s, 1H), 6.09 (s, 1H), 4.13 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.4, 144.5, 133.5, 132.2, 131.5, 130.7, 129.2, 118.2, 115.3, 114.2, 107.4, 99.4, 65.9. Elemental analysis: calcd (%) for $C_{14}H_{10}BrNO_2S$ (336.20): C 50.01, H 3.00; found: C 50.10, H 3.11.

4.2.29. 2-(4-Bromo-5-naphthalen-2-yl-thiophen-2-yl)-[1,3]dioxolane (**32**)

The reaction of 2-bromonaphthalene (0.207 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **32** in 90% (0.325 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.27 (s, 1H), 8.00–7.80 (m, 4H), 7.60–7.52 (m, 2H), 7.37 (s, 1H), 6.10 (s, 1H), 4.13 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.9, 142.8, 134.0, 133.6, 129.6, 129.3, 129.0, 128.2, 127.8, 127.7, 127.5, 125.3, 116.2, 106.0, 99.7, 65.9. Elemental analysis: calcd (%) for $C_{17}H_{13}BrO_2S$ (361.25): C 56.52, H 3.63; found: C 56.67, H 3.50.

4.2.30. 2-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-benzonitrile (**33**)

The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **33** in 85% (0.286 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (d, J = 7.4 Hz, 1H), 7.80–7.55 (m, 3H), 7.40 (s, 1H), 6.12 (s, 1H), 4.13 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 147.7, 144.5, 133.1, 132.2, 130.1, 129.2, 126.8, 116.2, 113.3, 111.6, 109.1, 98.0, 64.5. Elemental analysis: calcd (%) for $C_{14}H_{10}BrNO_2S$ (336.20): C 50.01, H 3.00; found: C 50.07, H 2.84.

4.2.31. 3-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-pyridine (**34**)

The reaction of 3-bromopyridine (0.158 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **34** in 78% (0.243 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.93 (s, 1H), 8.70 (d, J = 4.2 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.46 (dd, J = 7.9, 4.2 Hz, 1H), 7.42 (s, 1H), 6.09 (s, 1H), 4.14 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 151.2, 150.5, 148.8, 144.2, 135.2, 129.2, 124.3, 115.4, 107.4, 99.5, 65.9. Elemental analysis: calcd (%) for $C_{12}H_{10}BrNO_2S$ (312.18): C 46.17, H 3.23; found: C 46.04, H 3.11.

4.2.32. 5-(3-Bromo-5-[1,3]dioxolan-2-yl-thiophen-2-yl)-pyrimidine (**35**)

The reaction of 5-bromopyrimidine (0.159 g, 1 mmol), 2-(4-bromothiophen-2-yl)-[1,3]dioxolane (0.470 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 100 °C during 4 h affords the product **35** in 69% (0.216 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.30 (s, 1H), 9.10 (s, 2H), 7.42 (s, 1H), 6.10 (s, 1H), 4.10 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 159.5, 155.4, 146.1, 145.8, 129.3, 114.8, 108.9, 99.3, 66.0. Elemental analysis: calcd (%) for $C_{11}H_9BrN_2O_2S$ (313.17): C 42.19, H 2.90; found: C 42.02, H 2.77.

*4.2.33. 4-(5-Formyl-3-bromothiophen-2-yl)-acetophenone (**36**)*

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-acetyl-3-bromothiophene diethylacetal (0.530 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 16 h affords, after deprotection using an $HCl \cdot H_2O$/THF solution, the product **36** in 51% (0.158 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.99 (s, 1H), 8.04 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H), 7.45 (s, 1H), 2.65 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 196.9, 182.7, 151.4, 137.8, 136.6, 136.0, 129.3, 128.7, 126.3, 120.9, 26.7. Elemental analysis: calcd (%) for $C_{13}H_9BrO_2S$ (309.18): C 50.50, H 2.93; found: C 50.61, H 2.97.

*4.2.34. 1-[4-(4-Bromo-5-diethoxymethylthiophen-2-yl)-phenyl]-propan-1-one (**37**)*

The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), 2-acetyl-3-bromothiophene diethylacetal (0.530 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 16 h affords the product **37** in 54% (0.215 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.99 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.28 (s, 1H), 5.73 (s, 1H), 3.72 (m, 4H), 3.03 (q, J = 7.5 Hz, 2H), 1.32–1.20 (m, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.3, 143.2, 138.3, 137.7, 136.5, 129.2, 127.4, 125.8, 110.0, 98.2, 62.3, 32.2, 15.5, 8.7. Elemental analysis: calcd (%) for $C_{18}H_{21}BrO_3S$ (397.33): C 54.41, H 5.33; found: C 54.29, H 5.42.

*4.2.35. 3-Bromo-5-(4-trifluoromethylphenyl)-thiophene-2-carbaldehyde (**38**)*

The reaction of 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), 2-acetyl-3-bromothiophene diethylacetal (0.530 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 16 h affords, after deprotection using an $HCl \cdot H_2O$/THF solution, the product **38** in 50% (0.168 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.43 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 182.7, 151.0, 136.6, 135.3, 131.7 (q, J = 32.5 Hz), 128.7, 126.5, 126.4 (q, J = 3.8 Hz), 123.7 (q, J = 272.2 Hz), 120.8. Elemental analysis: calcd (%) for $C_{12}H_6BrF_3OS$ (335.14): C 43.01, H 1.80; found: C 43.20, H 1.90.

*4.2.36. 4-(5-Chlorothiophen-2-yl)-benzaldehyde (**39**)*

The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 12 h affords the product **39** in 80% (0.178 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.01 (s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.1 Hz, 2H), 7.23 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.7, 141.5, 139.6, 135.7, 131.9, 130.9, 128.0, 126.0, 124.7. Elemental analysis: calcd (%) for $C_{11}H_7ClOS$ (222.69): C 59.33, H 3.17; found: C 59.43, H 3.10.

*4.2.37. 4-(5-Chlorothiophen-2-yl)-acetophenone (**40**)*

The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 6 h affords the product **40** in 70% (0.165 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.97 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H), 2.64 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.6, 141.8, 138.3, 136.4, 131.4, 129.6, 127.9, 125.6, 124.2, 27.0. Elemental analysis: calcd (%) for $C_{12}H_9ClOS$ (236.72): C 60.89, H 3.83; found: C 60.97, H 4.00.

*4.2.38. 4-(5-Chlorothiophen-2-yl)-propiophenone (**41**)*

The reaction of 4-bromopropiophenone (0.213 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 3 h affords the product **41** in 76% (0.190 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H), 3.02 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 199.8, 141.5, 137.7, 135.8, 130.9, 128.8, 127.4, 125.2, 123.7, 31.8, 8.3. Elemental analysis: calcd (%) for $C_{13}H_{11}ClOS$ (250.74): C 62.27, H 4.42; found: C 62.40, H 4.31.

*4.2.39. 3-(5-Chlorothiophen-2-yl)-benzonitrile (**42**)*

The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 3 h affords the product **42** in 78% (0.171 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.72 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 1H), 7.14 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 140.4, 135.3, 131.4, 131.3, 130.3, 130.0, 129.1, 127.9, 124.1, 118.8, 113.7. Elemental analysis: calcd (%) for $C_{11}H_6ClNS$ (219.69): C 60.14, H 2.75; found: C 60.24, H 2.89.

*4.2.40. 3-(5-Chlorothiophen-2-yl)-acetophenone (**43**)*

The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 3 h affords the product **43** in 57% (0.135 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.16 (d, J = 3.7 Hz, 1H), 6.93 (d, J = 3.7 Hz, 1H), 2.65 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 197.6, 141.6, 137.8, 134.2, 130.0, 129.9, 129.3, 127.6, 127.3, 125.0, 123.1, 26.7. Elemental analysis: calcd (%) for $C_{12}H_9ClOS$ (236.72): C 60.89, H 3.83; found: C 60.69, H 3.78.

*4.2.41. 3-(5-Chlorothiophen-2-yl)-benzaldehyde (**44**)*

The reaction of 3-bromobenzaldehyde (0.185 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 3 h affords the product **44** in 75% (0.167 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.07 (s, 1H), 8.03 (s, 1H), 7.85–7.75 (m, 2H), 7.57 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 3.7 Hz, 1H), 6.95 (d, J = 3.7 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 191.8, 141.1, 137.0, 134.7, 131.1, 130.3, 129.8, 129.1, 127.4, 126.1, 123.3. Elemental analysis: calcd (%) for $C_{11}H_7ClOS$ (222.69): C 59.33, H 3.17; found: C 59.12, H 3.01.

*4.2.42. 2-(5-Chlorothiophen-2-yl)-benzonitrile (**45**)*

The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol), 2-chlorothiophene (0.237 g, 2 mmol) and KOAc (0.196 g, 2 mmol) with $Pd(OAc)_2$ (1.12 mg, 0.005 mmol) in DMAc at 120 °C during 6 h affords the product **45** in 73% (0.160 g) isolated yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (d, J = 7.7 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.48–7.36 (m, 2H), 7.01 (d, J = 3.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$): δ 138.2, 137.0, 134.8, 133.5, 132.4, 129.8, 128.3, 127.7, 127.5, 118.7, 113.7. Elemental analysis: calcd (%) for $C_{11}H_6ClNS$ (219.69): C 60.14, H 2.75; found: C 60.00, H 2.59.

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References

[1] J.J. Li, G.W. Gribble, Palladium in Heterocyclic Chemistry. Pergamon, Amsterdam, 2000.
[2] (a) A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani, Y. Aoyagi, Heterocycles 31 (1990) 1951;

(b) Y. Aoyagi, A. Inoue, I. Koizumi, R. Hashimoto, K. Tokunaga, K. Gohma, J. Komatsu, K. Sekine, A. Miyafuji, J. Kunoh, R. Honma, Y. Akita, A. Ohta, Heterocycles 33 (1992) 257.
[3] (a) D. Alberico, M.E. Scott, M. Lautens, Chem. Rev. 107 (2007) 174;
(b) T. Satoh, M. Miura, Chem. Lett. 36 (2007) 200;
(c) H. Doucet, J.C. Hierso, Curr. Opin. Drug Discov. Devel. 10 (2007) 672;
(d) B.-J. Li, S.-D. Yang, Z.-J. Shi, Synlett (2008) 949;
(e) G.P. McGlacken, L.M. Batman, Chem. Soc. Rev. 38 (2009) 2447;
(f) F. Bellina, R. Rossi, Tetrahedron 65 (2009) 10269;
(g) L. Ackermann, R. Vincente, A.R. Kapdi, Angew. Chem. Int. Ed. 48 (2009) 9792;
(h) J. Roger, A.L. Gottumukkala, H. Doucet, ChemCatChem 2 (2010) 20.
[4] For selected examples of palladium-catalysed direct arylations of thiophenes:
(a) B. Glover, K.A. Harvey, B. Liu, M.J. Sharp, M.F. Tymoschenko, Org. Lett. 5 (2003) 301;
(b) K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita, T. Ikeda, Org. Lett. 6 (2004) 2011;
(c) A. Yokooji, T. Satoh, M. Miura, M. Nomura, Tetrahedron 60 (2004) 6757;
(d) K. Mitsudo, P. Thansandote, T. Wilhelm, B. Mariampillai, M. Lautens, Org. Lett. 8 (2006) 3939;
(e) S.H. Mashraqui, M. Ashraf, S.G. Ghadigaonkar, Synlett (2006) 2423;
(f) A. Borghese, G. Geldhof, L. Antoine, Tetrahedron Lett. 47 (2006) 9249;
(g) P. Amaladass, J.A. Clement, A.K. Mohanakrishnan, Tetrahedron 63 (2007) 10363;
(h) F. Požgan, J. Roger, H. Doucet, ChemSusChem 1 (2008) 404;
(i) M. Nakano, H. Tsurugi, T. Satoh, M. Miura, Org. Lett. 10 (2008) 1851;
(j) J. Roger, H. Doucet, Org. Biomol. Chem. 6 (2008) 169;
(k) N. Arai, T. Miyaoku, S. Teruya, A. Mori, Tetrahedron Lett. 49 (2008) 1000;
(l) F. Derridj, J. Roger, F. Geneste, S. Djebbar, H. Doucet, J. Organomet. Chem. 694 (2009) 455;
(m) S. Yanagisawa, K. Ueda, H. Sekizawa, K. Itami, J. Am. Chem. Soc. 131 (2009) 14622;
(n) R.V. Smaliy, M. Beauperin, H. Cattey, P. Meunier, J.-C. Hierso, J. Roger, H. Doucet, Y. Coppel, Organometallics 28 (2009) 3152.
[5] For examples of palladium-catalysed direct arylations using a halopyrazole:
(a) F. Bellina, S. Cauteruccio, L. Mannina, R. Rossi, S. Viel, Eur. J. Org. Chem. (2006) 693.
[6] For examples of palladium-catalysed direct arylations using formyl- or acetyl-heteroarenes: (a) M.S. McClure, B. Glover, E. McSorley, A. Millar, M.H. Osterhout, F. Roschangar, Org. Lett. 3 (2001) 1677;
(b) J. Fournier Dit Chabert, L. Joucla, E. David, M. Lemaire, Tetrahedron 60 (2004) 3221;
(c) C.-H. Park, V. Ryabova, I.V. Seregin, A.W. Sromek, V. Gevorgyan, Org. Lett. 6 (2004) 1159;
(d) M. Parisien, D. Valette, K. Fagnou, J. Org. Chem. 70 (2005) 7578;
(e) B.B. Toure, B.S. Lane, D. Sames, Org. Lett. 8 (2006) 1979;
(f) G.L. Turner, J.A. Morris, M.F. Greaney, Angew. Chem. Int. Ed. 46 (2007) 7996;
(g) A.L. Gottumukkala, H. Doucet Adv, Synth. Catal. 350 (2008) 2183;
(h) J. Roger, H. Doucet, Adv. Synth. Catal. 351 (2009) 1977;
(i) J. Roger, H. Doucet, Tetrahedron 65 (2009) 9772;
(j) Y. Fall, C. Reynaud, H. Doucet, M. Santelli, Eur. J. Org. Chem. (2009) 4041;
(k) J.J. Dong, J. Roger, F. Pozgan, H. Doucet, Green Chem. 11 (2009) 1832.
[7] For examples of palladium-catalysed direct arylations using formyl- or acetyl-thiophenes: (a) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura, M. Nomura, Bull. Chem. Soc. Jpn. 71 (1998) 467;
(b) L. Lavenot, C. Gozzi, K. Ilg, I. Orlova, V. Penalva, M. Lemaire, J. Organomet. Chem. 567 (1998) 49;
(c) T. Okazawa, T. Satoh, M. Miura, M. Nomura, J. Am. Chem. Soc. 124 (2002) 5286;
(d) K. Masui, H. Ikegami, A. Mori, J. Am. Chem. Soc. 126 (2004) 5074;
(e) A. Battace, M. Lemhadri, T. Zair, H. Doucet, M. Santelli, Adv. Synth. Catal. 349 (2007) 2507;
(f) J. Roger, F. Požgan, H. Doucet, Green Chem. 11 (2009) 425;
(g) B. Liegault, D. Lapointe, L. Caron, A. Vlassova, K. Fagnou, J. Org. Chem. 7 (2009) 1826;
(h) J.J. Dong, J. Roger, H. Doucet, Tetrahedron Lett. 50 (2009) 2778.
[8] For examples of palladium-catalysed direct arylations using halothiophenes:
(a) J. Hassan, C. Gozzi, E. Schulz, M. Lemaire, J. Organomet. Chem. 687 (2003) 280;
(b) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui, A. Mori, Org. Lett. 7 (2005) 5083;
(c) K. Kobayashi, M.S. Mohamed Ahmed, A. Mori, Tetrahedron 62 (2006) 9548;
(d) F. Derridj, A.L. Gottumukkala, S. Djebbar, H. Doucet, Eur. J. Inorg. Chem. (2008) 2550;
(e) N. Masuda, S. Tanba, A. Sugie, D. Monguchi, N. Koumura, K. Hara, A. Mori, Org. Lett. 11 (2009) 2297;
(f) B. Liégault, I. Petrov, S.I. Gorlesky, K. Fagnou, J. Org. Chem. 75 (2010) 1047;
(g) O. René, K. Fagnou, Org. Lett. 12 (2010) 2116.
[9] (a) P.A. Todd, R.C. Heel, Drugs 30 (1985) 514;
(b) S.M. Grant, K.L. Goa, A. Fitton, E.M. Sorkin, Drugs 40 (1990) 412;
(c) J.P. Gonzalez, P.A. Todd, Drugs 34 (1987) 289.
[10] (a) F. Denat, H. Gaspard-Iloughmane, J. Dubac, Synthesis (1992) 954;
(b) A. Mucci, F. Parenti, R. Cagnoli, R. Benassi, A. Passalacqua, L. Preti, L. Schenetti, Macromolecules 39 (2006) 8293;
(c) G.A. Chotana, V.A. Kallepalli, R.E. Maleczka Jr., M.R. Smith III, Tetrahedron 64 (2008) 6103.
[11] V. Bonnet, F. Mongin, F. Trecourt, G. Breton, F. Marsais, P. Knochel, G. Queguiner, Synlett (2002) 1008.
[12] L. Ackermann (Ed.), Modern Arylation Methods, Wiley-VCH, Weinheim, 2009.
[13] (a) J.P. Wolfe, R.A. Singer, B.H. Yang, S.L. Buchwald, J. Am. Chem. Soc. 121 (1999) 9550;
(b) I. Kondolff, H. Doucet, M. Santelli, J. Heterocycl. Chem. 45 (2008) 109.