Palladium-Catalysed C2 or C5 Direct Arylation of 3-Substituted Thiophenes with Aryl Bromides

Jia Jia Dong, David Roy, Reny Jacob Roy, Marina Ionita, Henri Doucet*

Institut Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 'Catalyse et Organometalliques', Campus de Beaulieu, 35042 Rennes, France
Fax +33(2)23236939; E-mail: henri.doucet@univ-rennes1.fr
Received 1 July 2011; revised 29 July 2011

Abstract: The $Pd(OAc)_2$/dppb system was found to be an efficient catalyst for the direct arylation of 3-substituted thiophene derivatives. The regioselectivity of the arylation strongly depends on the thiophene substituent and also on the nature of the aryl bromide. When using 3-formyl, 3-cyano, 3-methyl, 3-hydroxymethyl or 3-bromothiophene, the 2-arylated thiophenes were obtained with 76–95% regioselectivity; whereas, the arylation of 3-formylthiophene diethylacetal or 3-acetylthiophene gave the 5-arylated thiophenes with 52–90% regioselectivity. The use of congested aryl bromides favours the arylation at C5. These reactions were performed using only 0.1 mol% of catalyst. Moreover, this procedure has been found to be tolerant to a variety of functional groups on the aryl bromide such as formyl, propionyl, benzoyl, nitrile, and nitro.

Key words: catalysis, palladium, thiophenes, arylation, C–H bond activation

Substituted thiophenes continue to attract the attention of synthetic organic chemists, due to their inherent biological activity and physical properties. Conventional methods for the synthesis of aryl thiophenes include metal catalysed cross-coupling reactions such as Suzuki, Stille, and Negishi type reactions,[1] which permit the coupling of aryl halides with organometallic derivatives of thiophenes. Nevertheless, these procedures require the appropriate functionalisation of one or both of the coupling partners, and they produce stoichiometric amounts of metallic salts as by-products. Moreover, when functionalised thiophene derivatives are employed, the access to the corresponding organometallic derivatives might be tricky.

The direct coupling of functionalised thiophenes with aryl halides via a C–H bond activation/functionalisation should provide a cost-effective and environmentally attractive procedure for the preparation of functionalised aryl thiophenes. The selective C5 arylation of 2-substituted thiophenes via a palladium-catalysed C–H bond activation[2–4] has been largely described in recent years.[5,6] The polyarylation of 3-thiophenecarboxylic acid has been reported by Miura and co-workers.[7] On the other hand, the palladium-catalysed regiocontrolled direct arylation of 3-substituted thiophenes has attracted less attention.[8–14] In 2003 Sharp and co-workers have reported conditions that allow the regioselective arylation of methyl 3-thiophenecarboxylate.[8] The use of $Pd(PPh_3)_4$ in toluene gave selectively the 2-arylated thiophene; whereas $Pd_2(dba)_3$ in NMP gave a mixture of 2- and 5-arylated thiophenes in a 15:51 ratio. In 1998, Lemaire and co-workers reported the direct arylation of 3-formyl, 3-cyano, and 3-nitrothiophene with aryl iodides.[9] In most cases, they obtained mixtures of 2-arylated and 2,4-diarylated thiophenes together with a good amount of homocoupled product of the aryl iodide. For example, 3-formylthiophene reacted with iodobenzene using $Pd(OAc)_2$ (8 mol%), PPh_3 (16 mol%), and K_2CO_3 in DMF at 140 °C to give 2-phenyl-3-formylthiophene in 35% yield.[10] Bilodeau and co-workers have examined the regioselectivity of the arylation of 3-methylthiophene with bromobenzene using $Pd[(P(t\text{-}Bu)_3]_2$ as the catalyst. They obtained a mixture of the 2- and 5-phenylated thiophenes in a 3.3:1 ratio (30% yield of 2-phenylation and 9% yield of the 5-phenylated thiophene).[11] Recently, Fagnou and co-workers have reported the direct arylation of 3-*n*-hexylthiophene with 4-bromonitrobenzene.[12] A mixture of C2 and C5 arylation products was obtained in a 1.3:1 ratio. Therefore, in order to obtain selectively the arylation at C2 or at C5, they blocked one position (C2 or C5) using a chloro substituent. The direct arylation of 3-methoxythiophene has been explored by Borghese and co-workers.[13] With this reactant, the 2-arylated thiophenes were obtained regioselectively in 28–60% yields. Rhodium catalysts have also been found to promote the direct arylation at C2 of 2-methoxythiophene.[15,16]

In summary, if some different catalysts and reaction conditions have been employed for such couplings, the influence of the nature of the substituent at C3 of thiophenes on the regioselectivity of the arylation remains unclear. Moreover, only a few examples of direct arylation of 3-formylthiophene, 3-methylthiophene, 3-bromothiophene, and 3-cyanothiophene have been described; and to our knowledge, 3-thiophenemethanol, ethyl thiophen-3-ylacetate, and 3-formylthiophene diethylacetal have never been employed. Thus, it would be useful to develop a simple procedure, employing low catalyst loadings and a variety of functionalised aryl bromides, allowing the direct arylation of 3-substituted thiophenes to obtain either arylation at C2 or at C5 in a regioselective manner. Moreover, a better understanding of the influence of electronic and steric parameters on the regioselectivity of the arylation is also highly desirable. We have already reported preliminary results for such couplings using 3-formyl-

SYNTHESIS 2011, No. 21, pp 3530–3546
Advanced online publication: 07.09.2011
DOI: 10.1055/s-0030-1260213; Art ID: Z66011SS

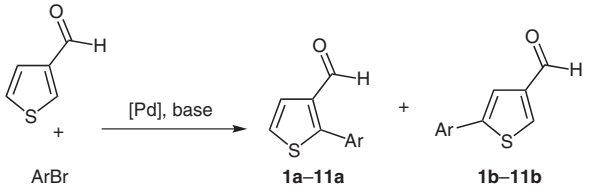
thiophenes.[17] Here we report on the regioselectivity of the palladium-catalysed direct arylation of a wide variety of 3-substituted thiophenes with a set of aryl bromides.

Initially our efforts were directed towards palladium-catalysed direct arylation of 3-formylthiophene with 4-bromobenzonitrile (Scheme 1, Table 1). The reaction was found to produce a mixture of **1a** and **1b** in a 79:21 ratio, using only 0.1 mol% of $Pd(OAc)_2$ as the catalyst, in the presence of KOAc as the base and DMA (dimethylacetamide) as the solvent at 150 °C. In order to improve the regiocontrol of the arylation, we performed a series of experiments using various solvents, bases, and catalysts. Bases exhibit a considerable difference of efficiency and regioselectivity for this reaction (Table 1, entries 1–9). Carbonates or KF led to the formation of the C2 arylated thiophene **1a** in lower regioselectivities than KOAc or NaOAc. The NMR of the crude mixtures using KOAc was found to be cleaner than with NaOAc. Next, we examined the influence of the solvent. The use of DMF or NMP resulted in low to moderate conversions of 4-bromobenzonitrile, and the regioselectivity of the arylation was not improved (Table 1, entries 10 and 11). In the presence of xylene, the coupling products **1a** or **1b** were not detected (Table 1, entry 14). The selectivity of the reaction was also slightly dependent on the catalyst. We observed that $[Pd(C_3H_5)Cl]_2$, in the absence of phosphine, exhibits a high regioselectivity (80%) towards the product **1a** (Table 1, entry 19). Similar regioselectivities (80–81% of **1a**) were obtained in the presence of $Pd(OAc)_2$ associated to the phosphine ligands dppb, dppe, dppf, PPh_3, and PCy_3 (Table 1, entries 12, 13, 15–18). The GC and NMR analysis of the crude mixtures revealed that the reaction performed with $Pd(OAc)_2$ associated to dppb was very clean. With this catalyst **1a** was isolated in 57% yield (Table 1, entry 13). Therefore, this catalyst precursor was selected to explore the scope and limitations of this reaction using various aryl bromides.

Table 1 Influence of the Reaction Conditions on the Arylation of 3-Formylthiophene with 4-Bromobenzonitrile (Scheme 1)[a]

Entry	Solvent	Base	Catalyst	Temp (°C)	Conv. (%)	Ratio (%) **1a/1b**
1	DMA	KOAc	$Pd(OAc)_2$	150	100	79:21
2	DMA	KF	$Pd(OAc)_2$	130	70	69:31
3	DMA	Cs_2CO_3	$Pd(OAc)_2$	130	50	mixture[b]
4	DMA	Na_2CO_3	$Pd(OAc)_2$	130	52	72:28
5	DMA	K_2CO_3	$Pd(OAc)_2$	130	82	62:38
6	DMA	K_3PO_4	$Pd(OAc)_2$	130	2	traces
7	DMA	NaOAc	$Pd(OAc)_2$	130	100	79:21
8	DMA	KOAc	$Pd(OAc)_2$	130	76	78:22
9	DMA	CsOAc	$Pd(OAc)_2$	130	100	71:29
10	DMF	KOAc	$Pd(OAc)_2$	130	55	75:25
11	NMP	KOAc	$Pd(OAc)_2$	130	20	mixture
12	DMA	KOAc	$Pd(OAc)_2$/dppb[c]	130	100	81:19
13	DMA	KOAc	$Pd(OAc)_2$/dppb[c]	150	100	81:19[d,e]
14	xylene	KOAc	$Pd(OAc)_2$/dppb[c]	130	0	–
15	DMA	KOAc	$Pd(OAc)_2$/dppe[c]	130	100	80:20
16	DMA	KOAc	$Pd(OAc)_2$/dppf[c]	150	100	80:20[d]
17	DMA	KOAc	$Pd(OAc)_2$/2 PPh_3[f]	130	100	81:19
18	DMA	KOAc	$Pd(OAc)_2$/2 PCy_3[f]	150	100	80:20[d]
19	DMA	KOAc	$[Pd(C_3H_5)Cl]_2$	130	100	80:20

[a] Conditions: [Pd] (0.1 mol%), 4-bromobenzonitrile (1 mmol), 3-formylthiophene (2 mmol), base (2 mmol), solvent (3 mL), 16 h; conversions and ratios of **1a**/**1b** were determined by GC and NMR.
[b] The formation of an important amount of biphenyl-4,4′-dicarbonitrile was observed.
[c] Diphosphine ligand used: 0.1 mol%.
[d] 3-Formylthiophene used: 1.5 mmol.
[e] Isolated yield of **1a**: 57%.
[f] PPh_3 or PCy_3 used: 0.2 mol%.



Scheme 1

3-Formylthiophene was coupled to a set of aryl bromides using 0.1 mol% $Pd(OAc)_2$ associated to 0.1 mol% dppb as the catalytic system and KOAc as the base (Table 2). The reactions performed with *para*-substituted electron-deficient aryl bromides proceed conveniently in most cases. High regioselectivities in favour of C2 arylation were observed using 4-bromobenzaldehyde, 4-bromopropiophenone, 4-bromobenzophenone, and 4-bromonitrobenzene, resulting in 55–61% yields of the products **2a**–**5a** (Table 2, entries 3 and 5–7). *meta*-Substituted aryl bromide, 3-bromobenzonitrile, gave **6a** in 58% yield (Table 2, entry 9). A slightly lower regioselectivity in favour of C2 arylation was observed when *ortho*-substituted aryl bromides were employed. 2-Bromobenzaldehyde and 2-bromobenzonitrile gave mixtures of regioisomers **a/b** in 76:24 and 77:23 ratios, respectively (Table 2, entries 10 and 11). This is certainly due to the steric hindrance of these aryl bromides. Pyridines or quinolines are π-electron deficient heterocycles and therefore, their oxidative addition to palladium is, in general, relatively easy. 3-Bromopyridine and 3-bromoquinolines gave the regioisomers **10a** and **11a** with 83 and 82% regioselectivity, respectively (Table 2, entries 14 and 15).

Table 2 2-Arylation of 3-Formylthiophene (Scheme 1)[a]

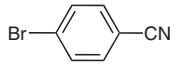
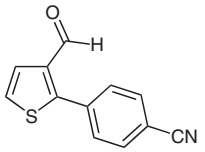
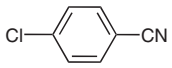
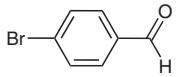
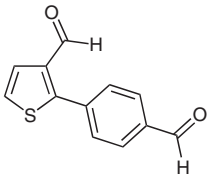
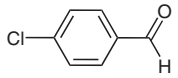
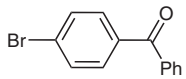
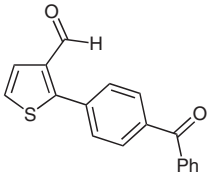
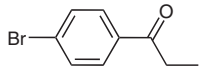
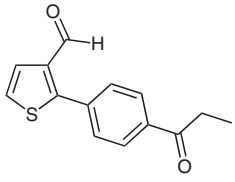
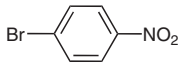
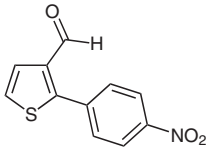
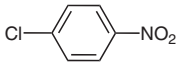
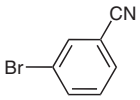
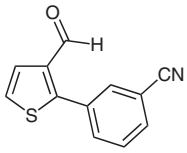
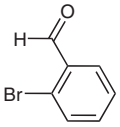
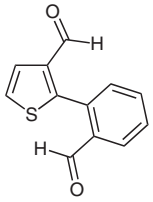
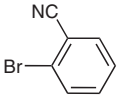
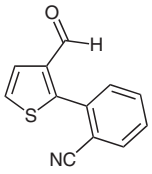
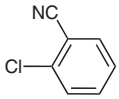
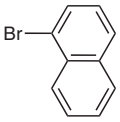
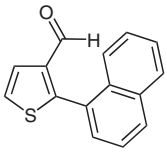
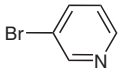
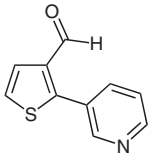
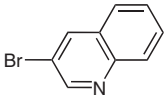
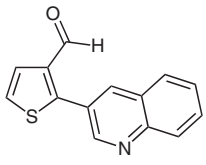
Entry	Aryl halide	Major product	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
1		 **1a**	81:19	57
2			–	0[c]
3		 **2a**	85:15	55
4			–	0[c]
5		 **3a**	84:16	56
6		 **4a**	86:14	58

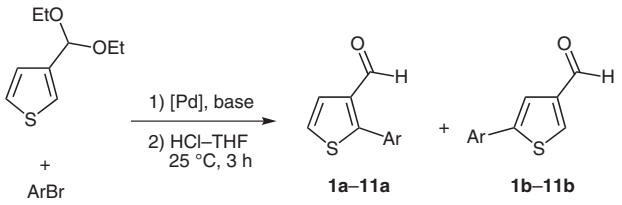
Table 2 2-Arylation of 3-Formylthiophene (Scheme 1)[a] (continued)

Entry	Aryl halide	Major product	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
7		 **5a**	85:15	61
8			–	0[c]
9		 **6a**	80:20	58
10		 **7a**	76:24	44
11		 **8a**	77:23	48
12			–	0 [c]
13		 **9a**	80:20	52
14		 **10a**	83:17	54
15		 **11a**	82:18	50

[a] Conditions: $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl halide (1 mmol), 3-formylthiophene (1.5 mmol), KOAc (2 mmol), DMA (3 mL), 150 °C, 16 h.
[b] Isolated yields of regioisomers **a**.
[c] $Pd(OAc)_2$: 1 mol%; dppb: 1 mol%.

The coupling of 2- or 4-chlorobenzonitriles, 4-chloroacetophenone, and 4-chloronitrobenzene with 3-formylthiophene using 1 mol% $Pd(OAc)_2$ associated to 1 mol% dppb at 150 °C was also studied. However, using these reaction conditions, no formation of desired coupling products was detected, and the aryl chlorides were recovered unreacted (Table 2, entries 2, 4, 8, and 12). For such challenging substrates more efficient catalysts should be employed.[5u]

Next, the reactivity of 3-formylthiophene diethylacetal with 4-bromobenzonitrile was examined (Scheme 2, Table 3). A similar set of reaction conditions were employed, identical with those used for 3-formylthiophene, and again, KOAc as the base was found to give a good conversion of the aryl bromide and also a quite regioselective arylation (Table 3, entries 1–9). However, with this substrate, the C5 arylation was predominant. This might be due to steric factors, as carbon C2 of 3-formylthiophene diethylacetal is more hindered than carbon C2 of 3-formylthiophene. The use of other solvents such as NMP or DMF did not allow to improve the regioselectivity of the arylation (Table 3, entries 10 and 11). Again, the cleanest NMR of the crude mixtures was obtained using $Pd(OAc)_2$/dppb as the catalyst precursor, KOAc as the base, and DMA as the solvent at 150 °C (Table 3, entry 13). Using these reaction conditions, the ratio of product **1a/1b** was 24:76 and the yield in **1b** was 53%.



Scheme 2

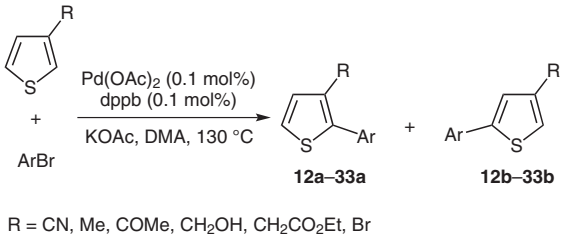
Then, the arylation of 3-formylthiophene diethylacetal with several aryl bromides was explored (Table 4). In the presence of aryl bromides electronically and sterically similar to 4-bromobenzonitrile, such as 4-bromobenzaldehyde, 4-bromobenzophenone, and 4-bromopropiophenone, similar regioselectivities (76–78% of 5-arylation) and yields were obtained (Table 4, entries 2–4). On the other hand, when the sterically congested aryl bromides, 2-bromobenzonitrile, 2-bromobenzaldehyde, and 1-bromonaphthalene were employed, the regioselectivities of the arylation in favour of regioisomers **7b–9b** were increased to 83–88% (Table 4, entries 7–9). In the presence of 3-bromopyridine or 3-bromoquinoline, the compounds **10b** and **11b** were obtained with 64% and 70% regioselectivity, respectively (Table 4, entries 10 and 11).

Next, the influence of other substituents at the 3-position of thiophene on the regioselectivity of the arylation was studied using similar reaction conditions (Scheme 3). First, 3-cyanothiophene was coupled with 4-bromobenzonitrile, 4-bromobenzaldehyde, 4-bromonitrobenzene, and 3-bromopyridine (Table 5). We observed that the formation of the 2-arylated products **12a–15a** was predominant in all cases (79–83%). This regioselectivity was expected, as the hindrance and electronic properties of cyano and formyl as substituents are quite similar.

Table 3 Influence of the Reaction Conditions on the Arylation of 3-Formylthiophene Diethylacetal with 4-Bromobenzonitrile (Scheme 2)[a]

Entry	Solvent	Base	Catalyst	Temp (°C)	Conv. (%)	Ratio (%) **1a/1b**
1	DMA	KOAc	$Pd(OAc)_2$	150	90	25:75
2	DMA	KF	$Pd(OAc)_2$	130	30	28:72
3	DMA	Cs_2CO_3	$Pd(OAc)_2$	130	8	24:76
4	DMA	Na_2CO_3	$Pd(OAc)_2$	130	22	28:72
5	DMA	K_2CO_3	$Pd(OAc)_2$	130	11	32:68
6	DMA	K_3PO_4	$Pd(OAc)_2$	130	0	–
7	DMA	NaOAc	$Pd(OAc)_2$	130	70	26:74
8	DMA	KOAc	$Pd(OAc)_2$	130	77	23:77
9	DMA	CsOAc	$Pd(OAc)_2$	130	80	29:71
10	DMF	KOAc	$Pd(OAc)_2$	130	80	24:76
11	NMP	KOAc	$Pd(OAc)_2$	130	82	25:75
12	DMA	KOAc	$Pd(OAc)_2$/dppb[b]	130	100	27:73
13	DMA	KOAc	$Pd(OAc)_2$/dppb[b]	150	100	24:76[c]
14	DMA	KOAc	$Pd(OAc)_2$/dppe[b]	130	90	25:75
15	DMA	KOAc	$Pd(OAc)_2$/2 PPh_3[d]	130	90	24:76
16	DMA	KOAc	$[Pd(C_3H_5)Cl]_2$	130	92	25:75

[a] Conditions: [Pd] (0.1 mol%), 4-bromobenzonitrile (1 mmol), 3-formylthiophene diethylacetal (2 mmol), base (2 mmol), solvent (3 mL), 16 h, conversions and ratios of **1a/1b** determined by GC and NMR.
[b] Diphosphine ligand: 0.1 mol%.
[c] 3-Formylthiophene diethylacetal (1.5 mmol); isolated yield of **1b**: 53%.
[d] PPh_3: 0.2 mol%.



Scheme 3

Table 4 5-Arylation of 3-Formylthiophene Diethyl Acetal (Scheme 2)[a]

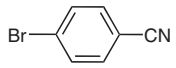
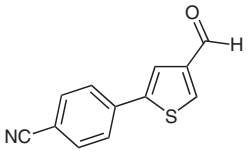
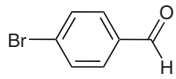
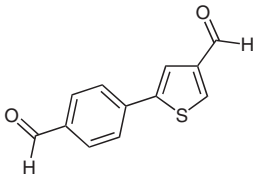
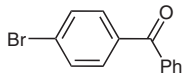
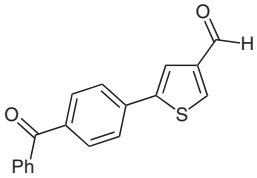
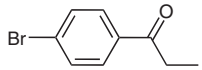
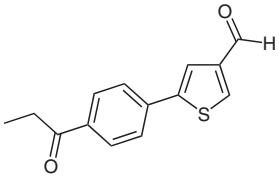
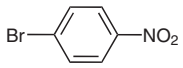
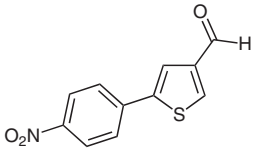
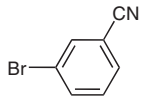
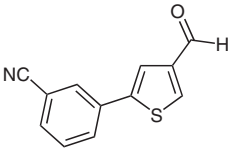
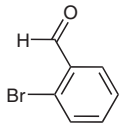
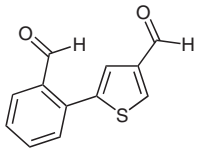
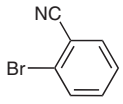
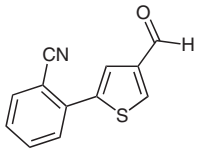
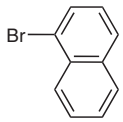
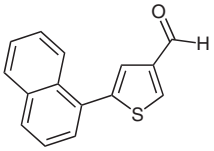
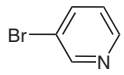
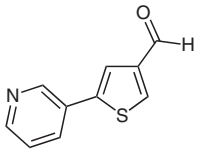
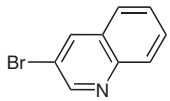
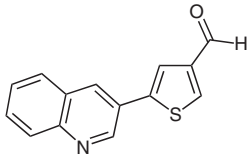
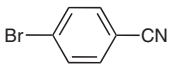
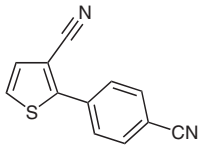
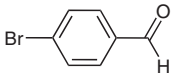
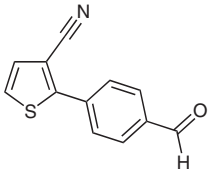
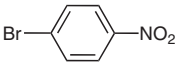
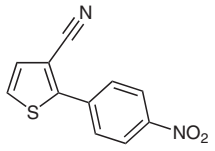
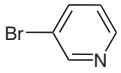
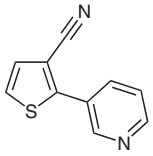
Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **b** (%)[b]
1		 **1b**	24:76	53
2		 **2b**	24:76	48
3		 **3b**	22:78	50
4		 **4b**	24:76	48
5		 **5b**	28:72	53
6		 **6b**	28:72	55
7		 **7b**	12:88	40
8		 **8b**	17:83	62

Table 4 5-Arylation of 3-Formylthiophene Diethyl Acetal (Scheme 2)[a] (continued)

Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **b** (%)[b]
9		 **9b**	13:87	51
10		 **10b**	36:64	42
11		 **11b**	30:70	40

[a] Conditions: 1. $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl bromide (1 mmol), 3-formylthiophene diethyl acetal (1.5 mmol), KOAc (2 mmol), DMA (3 mL), 150 °C, 16 h; 2. HCl, THF, 25 °C, 3 h.
[b] Isolated yields of regioisomers **b**.

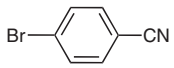
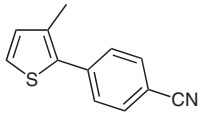
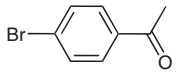
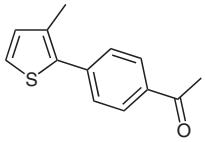
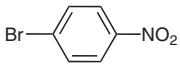
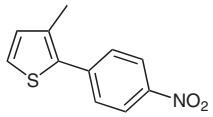
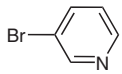
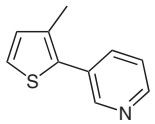
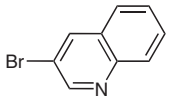
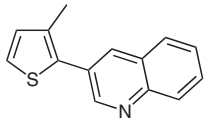
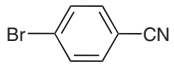
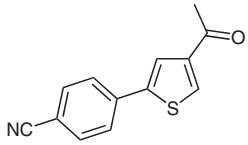
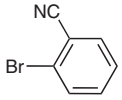
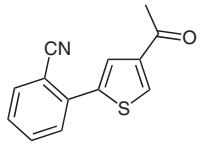
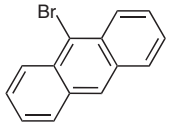
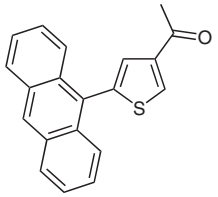
Table 5 Direct Arylation of 3-Cyanothiophene with Aryl Bromides (Scheme 3)[a]

Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
1		 **12a**	80:20	60
2		 **13a**	78:22	58
3		 **14a**	83:17	64
4		 **15a**	79:21	40

[a] Conditions: $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl bromide (1 mmol), 3-cyanothiophene (2 mmol), KOAc (2 mmol), DMA (3 mL), 130 °C, 20 h.
[b] Isolated yields of regioisomers **a**.

Then, the reactivity of a thiophene bearing an electron-donating group at C3 was examined using the same reaction conditions (Table 6). For 3-methylthiophene, a regioselectivity similar to that obtained for 3-formylthiophene or 3-cyanothiophene was observed. The 2-aryl-3-methylthiophenes **16a**–**20a** were obtained in 45%–69% yields with 82–87% regioselectivities (Table 6). These results reveal that with our reaction conditions, the regioselectivity of the arylation of thiophenes mainly depends on the steric properties of the substituents at C3 rather than on their electronic properties.

Table 6 Direct Arylation of 3-Methylthiophene or 3-Acetylthiophene with Aryl Bromides (Scheme 3)[a]

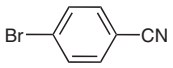
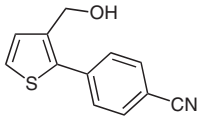
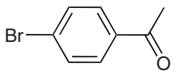
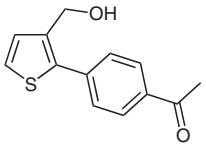
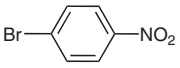
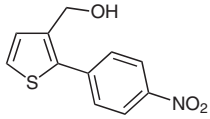
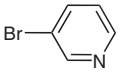
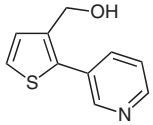
Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
1		 **16a**	87:13	65
2		 **17a**	86:14	64
3		 **18a**	84:16	62
4		 **19a**	82:18	45
5		 **20a**	87:13	69
6		 **21b**	48:52	38[c]
7		 **22b**	25:75	57[a]
8		 **23b**	10:90	73[a]

[a] Conditions: $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl bromide (1 mmol), 3-methylthiophene or 3-acetylthiophene (2 mmol), KOAc (2 mmol), DMA (3 mL), 130 °C, 20 h.
[b] Isolated yields of regioisomers **a**.
[c] Isolated yields of regioisomers **b**.

In order to confirm these observations, the slightly more congested thiophene, 3-acetylthiophene (Table 6, entries 6–8) was used. To our knowledge, so far this reactant has not been employed for palladium-catalysed direct arylations. In the presence of 4-bromobenzonitrile, and 0.1 mol% $Pd(OAc)_2$ associated to 0.1 mol% dppb as the catalytic system, an almost equimolar amount of regioisomers **a** and **b** was formed, and the 5-arylated product **21b** was isolated in 38% yield (Table 6, entry 6). It was also observed that the regioselectivity shifts to the predominant formation of 4-acetyl-2-arylthiophenes **22b** or **23b** in the presence of sterically more hindered aryl bromides. For example, with 2-bromobenzonitrile, the product **22b** was obtained in 57% yield with 75% regioselectivity. The very bulky aryl bromide, 9-bromoanthracene led to a highly regioselective arylation at C5, forming **23b** in 73% yield with 90% regioselectivity (Table 6, entry 8). Under these reaction conditions, the regioselectivity of the arylation mostly depends on the steric influence of both coupling partners.

To our knowledge, the direct arylation of 3-thiophenemethanol has also not been reported.[18] The use of such substrate bearing an unprotected functions would be very useful in organic synthesis since it would allow to avoid the protection/deprotection sequence, and therefore should provide a more environmentally and economically attractive access to such arylated heteroaromatics. Moreover, the presence of such functional group on thiophene might have an influence on the regioselectivity of the arylation due to a possible coordination of the hydroxy group to palladium. It was observed that when the reaction is performed in DMA with $Pd(OAc)_2$ (0.1 mol%) associated to dppb (0.1 mol%) using KOAc as the base, the reaction of 4-bromobenzonitrile with 3-thiophenemethanol gives predominantly the arylation at C2 (ratio C2/C5 = 79:21) (Table 7, entry 1). This result indicates that with these reaction conditions, the presence of such hydroxymethyl function at C3 has almost no influence on the regioselectivity. This is consistent with the previously reported results using 2-thiophenemethanol.[18] It should be noted that the use of *n*-Bu_3N as the base gave no coupling product

Table 7 Direct Arylation of 3-Thiophenemethanol with Aryl Bromides (Scheme 3)[a]

Entry	Aryl bromide	Major product	Conversion (%)	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
1		 **24a**	100	79:21	66
2			0	–	0[c]
3			68	95:5	35[d]
4			mixture	–	0[e]
5			mixture	–	0[f]
6		 **25a**	100	81:19	65
7		 **26a**	100	82:18	55
8		 **27a**	100	82:18	69

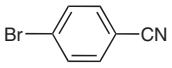
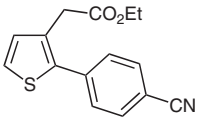
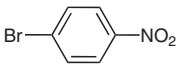
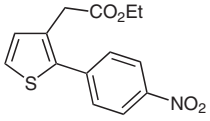
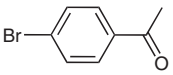
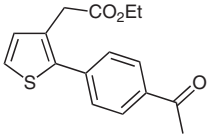
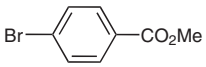
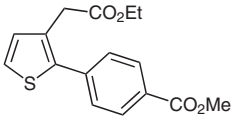
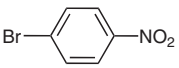
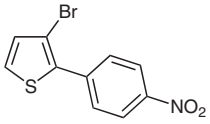
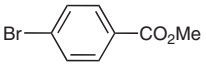
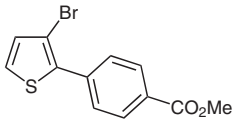
[a] Conditions: $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl bromide (1 mmol), 3-thiophenemethanol (2 mmol), KOAc (2 mmol), DMA (3 mL), 130 °C, 20 h.
[b] Isolated yields of regioisomers **a**.
[c] *n*-Bu_3N as the base.
[d] Xylene as the solvent.
[e] Cs_2CO_3 as the base.
[f] CsOAc as the base.

24a (Table 7, entry 2). On the other hand, a better regioselectivity in favour of the arylation at C2 was observed in xylene, but only a partial conversion of 4-bromobenzonitrile was obtained (Table 7, entry 3). Sharp and co-workers have already reported that the use of toluene as the solvent favours the arylation at C2.[8] Then, the reactivity of three other aryl bromides with thiophene-3-methanol was examined. 4-Bromoacetophenone, 4-bromonitrobenzene, and 3-bromopyridine gave the products **25a**–**27a** in 55–69% yields with 81–82% regioselectivities (Table 7, entries 6–8).

A few reactions using ethyl 3-thiophenylacetate as the reactant was also performed (Table 8). In DMA using 0.1 mol% $Pd(OAc)_2$ and 0.1 mol% dppb as the catalytic system, the C2 arylated thiophenes **28a**–**31a** were obtained in 51–63% yields with 69–76% regioselectivities. It should be noted that the use of xylene as the solvent instead of DMA gave only a slightly more regioselective reaction, and a poor conversion of 4-bromobenzonitrile of only 27% was obtained (Table 8, entry 3). *n*-Bu_3N was found to be an ineffective base for this reaction (Table 8, entry 2).

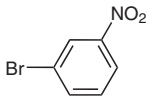
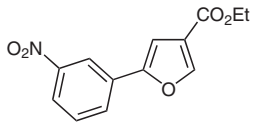
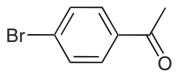
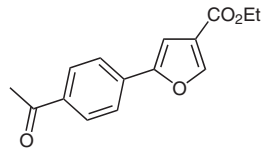
Then, the direct arylation of 3-bromothiophene using our reaction conditions was studied (Table 8, entries 7 and 8). Fagnou and co-workers have reported the direct arylation of this thiophene derivative with 4-iodoanisole using 5 mol% $Pd(OAc)_2$ associated to 10 mol% of an electron-rich phosphine ligand at 60 °C. They obtained the arylation at C2 in 72% yield.[14] Using 0.1 mol% $Pd(OAc)_2$ associated to 0.1 mol% of dppb at 130 °C and 4-bromo-

Table 8 Direct Arylation of Ethyl 3-thiopheneacetate or 3-Bromothiophene with Aryl Bromides (Scheme 3)[a]

Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **a** (%)[b]
1		 **28a**	69:31	61
2			–[c]	0
3			76:24[d]	–
4		 **29a**	73:27	63
5		 **30a**	76:24	53
6		 **31a**	76:24	51
7		 **32a**	89:11	58
8		 **33a**	93:7	46

[a] Conditions: $Pd(OAc)_2$ (0.1 mol%), dppb (0.1 mol%), aryl bromide (1 mmol), ethyl 3-thiopheneacetate or 3-bromothiophene (2 mmol), KOAc (2 mmol), DMA (3 mL), 130 °C, 20 h.
[b] Isolated yields of regioisomers **a**.
[c] *n*-Bu_3N as the base.
[d] Xylene as the solvent, conversion of 4-bromobenzonitrile 27%.

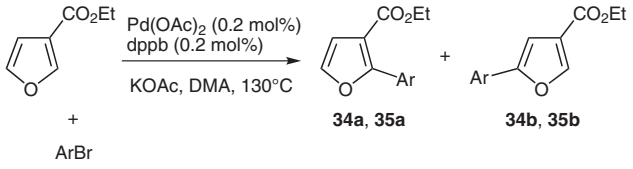
Table 9 Direct Arylation of Ethyl 3-Furoate with Aryl Bromides (Scheme 4)[a]

Entry	Aryl bromide	Major product	Ratio **a/b**	Yield of regioisomer **b** (%)[b]
1		 **34b**	28:72	45
2		 **35b**	26:74	43

[a] Conditions: $Pd(OAc)_2$ (0.2 mol%), dppb (0.2 mol%), aryl bromide (1 mmol), ethyl 3-furoate (2 mmol), KOAc (2 mmol), DMA (3 mL), 130 °C, 20 h.
[b] Isolated yields of regioisomers **b**.

nitrobenzene or methyl 4-bromobenzoate, the products **32a** and **33a** were obtained with high regioselectivities of 89% and 93%, but in moderate yields of 58% and 46% due to the formation of some unidentified side-products.

Finally, the regioselectivity of the arylation of the 3-substituted furan, ethyl 3-furoate, was studied (Scheme 4). Sharp and co-workers had observed that the use of Pd/C as the catalyst in NMP led to the formation of 5-arylated ethyl 3-furoate **34b** in 42% yield, whereas, the use of 5 mol% $Pd(PPh_3)_4$ in toluene led to **34a** in 73% yield.[8] We observed that using our reaction conditions, 0.2 mol% $Pd(OAc)_2$ associated to 0.2 mol% dppb in DMA, the major product was **34b** (Table 9, entry 1). A similar regioselectivity was observed for the coupling with 4-bromoacetophenone to give **35b** in 43% yield with 74% regioselectivity (Table 9, entry 2).



Scheme 4

In summary, we have described here on the influence of several substituents at C3 of thiophene derivatives on the regioselectivity of palladium-catalysed direct arylations. Although the electronic properties of such substituents on thiophene seem relatively limited, their steric properties are important. Thiophenes substituted at C3 by a methyl, a cyano, a formyl, a hydroxymethyl, and a bromo gave the 2-arylated thiophenes in quite high regioselectivities. On the other hand, the presence of an acetyl or a formyl protected as an acetal at C3 led to a predominant formation of 5-arylated thiophenes. Therefore, this reaction gives a simple access to either 2-aryl-3-formylthiophenes or 2-aryl-4-formylthiophenes. The steric hindrance of the aryl bromides has also an influence on the regioselectivity. Larger amounts of C5 arylated thiophenes were generally obtained in the presence of *ortho*-substituted aryl bromides. This procedure should be industrially and environmentally attractive as it employ only 0.1 mol% palladium catalyst, has proved to be tolerant to a variety of functional groups on the aryl bromide such as formyl, propionyl, benzoyl, nitrile, and nitro and as the major by-products are AcOH/KBr instead of metallic salts using more classical coupling procedures. Moreover, no prior preparation of an organometallic derivative is required for these couplings, reducing the number of required steps to obtain these arylated thiophenes.

All chemical reactants and metal complexes were obtained from commerical sources and used without further purification. DMA analytical grade (99%) was not distilled before use. KOAc (99+%) was employed. All reactions were run under argon using vacuum lines in Schlenk tubes in oven-dried glassware. Flash chromatographies were performed on silica gel (230–400 mesh).

Reaction of 3-Formylthiophene with Aryl Bromides (Products 1a–11a); General Procedure

In a typical experiment, the aryl bromide (1 mmol), 3-formylthiophene (0.168 g, 1.5 mmol), and KOAc (0.196 g, 2 mmol) were introduced in an oven-dried Schlenk tube, equipped with a magnetic stirring bar. Then, $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), dppb (0.42 mg, 0.001 mmol), and DMA (3 mL) were added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a preheated oil bath at 150 °C and the reactants were allowed to stir for 16 h. Then, the reaction mixture was analysed by GC and NMR to determine the ratio of regioisomers **a/b** and the conversion of the aryl bromide. The solvent was removed by heating of the reaction vessel under vacuum and the residue was charged directly onto a silica gel column. The products were eluted, using an appropriate ratio of Et_2O and pentane (Table 2).

4-(3-Formylthiophen-2-yl)benzonitrile (1a)

The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **1a** in 57% (0.122 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 5.3 Hz, 1 H), 7.62 (d, *J* = 5.3 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 2 H), 7.80 (d, *J* = 8.3 Hz, 2 H), 9.89 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 113.6, 118.5, 127.0, 127.9, 131.1, 133.0, 136.5, 138.3, 154.4, 185.2.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.67; H, 3.22.

4-(3-Formylthiophen-2-yl)benzaldehyde (2a)
The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **2a** in 55% (0.118 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 5.3 Hz, 1 H), 7.62 (d, *J* = 5.3 Hz, 1 H), 7.70 (d, *J* = 8.3 Hz, 2 H), 8.02 (d, *J* = 8.3 Hz, 2 H), 9.89 (s, 1 H), 10.11 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 126.8, 127.7, 130.5, 131.1, 136.9, 137.7, 138.2, 153.8, 185.5, 191.8.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.69; H, 3.69.

4-(3-Formylthiophen-2-yl)benzophenone (3a)
The reaction of 4-bromobenzophenone (0.260 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **3a** in 56% (0.163 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 5.3 Hz, 1 H), 7.46–7.63 (m, 6 H), 7.81–7.92 (m, 4 H), 9.90 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 126.5, 127.5, 128.8, 130.4, 130.5, 130.9, 133.2, 135.7, 137.5, 138.1, 138.5, 154.4, 185.6, 196.1.

Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14. Found: C, 73.82; H, 4.29.

4-(3-Formylthiophen-2-yl)propiophenone (4a)
The reaction of 4-bromopropiophenone (0.212 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **4a** in 58% (0.141 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.5 Hz, 3 H), 3.01–3.12 (m, 2 H), 7.36 (d, *J* = 5.3 Hz, 1 H), 7.60–7.64 (m, 3 H), 8.08 (d, *J* = 8.3 Hz, 2 H), 9.90 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.5, 32.4, 126.4, 127.5, 128.9, 130.7, 136.1, 137.6, 138.0, 154.4, 185.6, 200.3.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.91; H, 4.92.

4-(3-Formylthiophen-2-yl)nitrobenzene (5a)
The reaction of 4-bromonitrobenzene (0.199 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **5a** in 61% (0.142 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 5.3 Hz, 1 H), 7.64 (d, *J* = 5.3 Hz, 1 H), 7.72 (d, *J* = 8.3 Hz, 2 H), 8.37 (d, *J* = 8.3 Hz, 2 H), 9.92 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.5, 127.3, 128.1, 131.3, 138.3, 138.5, 148.6, 152.1, 185.1.

Anal. Calcd for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02. Found: C, 56.72; H, 3.05.

3-(3-Formylthiophen-2-yl)benzonitrile (6a)
The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **6a** in 58% (0.123 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 5.3 Hz, 1 H), 7.59–7.82 (m, 5 H), 9.86 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 113.8, 118.3, 126.7, 127.7, 130.2, 133.1, 133.3, 133.6, 134.7, 138.1, 152.4, 185.1.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.62; H, 3.28.

2-(3-Formylthiophen-2-yl)benzaldehyde (7a)
The reaction of 2-bromobenzaldehyde (0.186 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **7a** in 44% (0.095 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.72 (m, 5 H), 8.10 (d, *J* = 5.3 Hz, 1 H), 9.65 (s, 1 H), 10.01 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 126.9, 127.2, 128.9, 130.5, 133.0, 134.0, 134.2, 135.8, 140.2, 150.1, 185.0, 190.7.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.58; H, 3.81.

2-(3-Formylthiophen-2-yl)benzonitrile (8a)
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **8a** in 48% (0.102 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 5.3 Hz, 1 H), 7.56–7.94 (m, 5 H), 9.75 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 114.2, 117.7, 127.3, 127.6, 130.2, 132.5, 133.2, 134.0, 137.6, 139.3, 149.2, 184.7.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.41; H, 3.40.

1-(3-Formylthiophen-2-yl)naphthalene (9a)[19]
The reaction of 1-bromonaphthalene (0.206 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **9a** in 52% (0.123 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 5.3 Hz, 1 H), 7.50–7.65 (m, 4 H), 7.67 (d, *J* = 5.3 Hz, 1 H), 7.80–8.03 (m, 3 H), 9.52 (s, 1 H).

3-(3-Formylthiophen-2-yl)pyridine (10a)
The reaction of 3-bromopyridine (0.157 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **10a** in 54% (0.102 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.46 (m, 2 H), 7.61 (d, *J* = 5.3 Hz, 1 H), 7.84 (d, *J* = 7.8 Hz, 1 H), 8.71 (m, 2 H), 9.85 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 124.0, 126.7, 127.6, 128.2, 137.6, 138.3, 150.4, 150.8, 151.4, 185.4.

Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73. Found: C, 63.52; H, 3.63.

3-(3-Formylthiophen-2-yl)quinoline (11a)
The reaction of 3-bromoquinoline (0.208 g, 1 mmol) and 3-formylthiophene (0.168 g, 1.5 mmol) afforded the product **11a** in 50% (0.119 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 5.3 Hz, 1 H), 7.61–7.93 (m, 4 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 8.30 (s, 1 H), 9.05 (s, 1 H), 9.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 123.8, 125.4, 126.2, 126.3, 126.8, 127.1, 128.4, 129.7, 135.9, 137.0, 146.9, 149.2, 150.3, 183.8.

Anal. Calcd for $C_{14}H_9NOS$: C, 70.27; H, 3.79. Found: C, 70.33; H, 3.66.

Reaction of 3-Formylthiophene Diethyl Acetal with Aryl Bromides (Products 1b–11b); General Procedure
In a typical experiment, the aryl bromide (1 mmol), 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol), and KOAc (0.196 g, 2 mmol) were introduced in an oven-dried Schlenk tube, equipped

with a magnetic stirring bar. Then, $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), dppb (0.42 mg, 0.001 mmol), and DMA (3 mL) were added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a preheated oil bath at 150 °C and the reactants were allowed to stir for 16 h. After cooling to r.t., THF (5 mL) and aq HCl (pH 2, 5 mL) were added, and the mixture allowed to stir for 3 h. The reaction mixture was analysed by GC and NMR to determine the ratio of regioisomers **a/b** and the conversion of the aryl bromide. After separation and drying ($MgSO_4$), the solvent was removed under vacuum, and the residue was charged onto a silica gel column. The products were eluted, using an appropriate ratio of Et_2O and pentane (Table 4).

4-(4-Formylthiophen-2-yl)benzonitrile (1b)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **1b** in 53% (0.113 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.70–7.80 (m, 4 H), 7.85 (d, *J* = 1.2 Hz, 1 H), 8.18 (d, *J* = 1.2 Hz, 1 H), 9.94 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 112.2, 118.9, 122.9, 126.8, 133.3, 137.6, 137.7, 144.3, 144.4, 185.2.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.41; H, 3.47.

4-(4-Formylthiophen-2-yl)benzaldehyde (2b)
The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **2b** in 48% (0.103 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.81(d, *J* = 8.3 Hz, 2 H), 7.96 (d, *J* = 8.3 Hz, 2 H), 7.88 (s, 1 H), 8.17 (s, 1 H), 9.94 (s, 1 H), 10.05 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.8, 126.8, 131.0, 136.3, 137.5, 139.1, 144.3, 145.1, 185.3, 191.7.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.53; H, 3.81.

4-(4-Formylthiophen-2-yl)benzophenone (3b)
The reaction of 4-bromobenzophenone (0.260 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **3b** in 50% (0.146 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.48–7.63 (m, 3 H), 7.72–7.91 (m, 7 H), 8.15 (s, 1 H), 9.93 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.3, 126.1, 128.8, 130.4, 131.4, 133.0, 137.2, 137.3, 137.5, 137.8, 144.2, 145.5, 185.3, 196.2.

Anal. Calcd for $C_{18}H_{12}O_2S$: C, 73.95; H, 4.14. Found: C, 74.02; H, 4.38.

4-(4-Formylthiophen-2-yl)propiophenone (4b)
The reaction of 4-bromopropiophenone (0.212 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **4b** in 48% (0.117 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.5 Hz, 3 H), 2.96–3.07 (m, 2 H), 7.79 (d, *J* = 8.3 Hz, 2 H), 7.81 (s, 1 H), 8.01 (d, *J* = 8.3 Hz, 2 H), 8.13 (s, 1 H), 9.90 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 8.6, 32.2, 122.2, 126.3, 129.3, 136.8, 137.3, 137.5, 144.2, 145.4, 185.3, 200.3.

Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.79; H, 4.97.

4-(4-Formylthiophen-2-yl)nitrobenzene (5b)
The reaction of 4-bromonitrobenzene (0.199 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **5b** in 53% (0.123 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2 H), 7.88 (s, 1 H), 8.21 (s, 1 H), 8.30 (d, *J* = 8.3 Hz, 2 H), 9.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 123.5, 124.9, 126.9, 138.0, 139.6, 143.9, 144.3, 147.8, 185.1.

Anal. Calcd for $C_{11}H_7NO_3S$: C, 56.64; H, 3.02. Found: C, 56.51; H, 3.09.

3-(4-Formylthiophen-2-yl)benzonitrile (6b)
The reaction of 3-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **6b** in 55% (0.117 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51–7.66 (m, 2 H), 7.78–7.89 (m, 3 H), 8.15 (s, 1 H), 9.92 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 113.8, 118.6, 122.4, 129.8, 130.4, 130.5, 132.1, 134.8, 137.2, 144.0, 144.2, 185.2.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.53; H, 3.42.

2-(4-Formylthiophen-2-yl)benzaldehyde (7b)
The reaction of 2-bromobenzaldehyde (0.186 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **7b** in 40% (0.086 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52–7.72 (m, 4 H), 8.05 (s, 1 H), 8.25 (s, 1 H), 9.95 (s, 1 H), 10.20 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 127.1, 128.8, 129.6, 131.8, 134.2, 134.6, 136.7, 138.1, 141.4, 143.6, 185.2, 191.5.

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73. Found: C, 66.74; H, 3.62.

2-(3-Formylthiophen-2-yl)benzonitrile (8b)
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **8b** in 62% (0.132 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.44–7.81 (m, 4 H), 7.94 (s, 1 H), 8.22 (s, 1 H), 9.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 111.0, 118.6, 125.9, 129.1, 130.2, 133.6, 134.7, 136.7, 137.5, 141.7, 143.8, 185.1.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.69; H, 3.42.

1-(4-Formylthiophen-2-yl)naphthalene (9b)
The reaction of 1-bromonaphthalene (0.206 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **9b** in 51% (0.121 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.53–7.58 (m, 4 H), 7.70 (s, 1 H), 7.92–8.23 (m, 3 H), 8.23 (s, 1 H), 9.99 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 125.3, 125.6, 125.7, 126.7, 127.3, 128.8, 128.9, 129.7, 131.3, 131.9, 134.2, 137.4, 143.6, 144.5, 185.6.

Anal. Calcd for $C_{15}H_{10}OS$: C, 75.60; H, 4.23. Found: C, 75.62; H, 4.33.

3-(4-Formylthiophen-2-yl)pyridine (10b)
The reaction of 3-bromopyridine (0.157 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **10b** in 42% (0.079 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 (m, 1 H), 7.78 (s, 1 H), 7.92 (m, 1 H), 8.14 (s, 1 H), 8.60 (d, *J* = 4.2 Hz, 1 H), 8.91 (s, 1 H), 9.92 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.1, 124.3, 129.6, 134.0, 137.1, 142.9, 144.2, 147.5, 149.9, 185.2.

Anal. Calcd for $C_{10}H_7NOS$: C, 63.47; H, 3.73. Found: C, 63.39; H, 3.45.

3-(4-Formylthiophen-2-yl)quinoline (11b)
The reaction of 3-bromoquinoline (0.208 g, 1 mmol) and 3-formylthiophene diethyl acetal (0.279 g, 1.5 mmol) afforded the product **11b** in 40% (0.075 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.50–7.91 (m, 4 H), 8.11–8.17 (m, 2 H), 8.33 (s, 1 H), 9.20 (s, 1 H), 9.94 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 122.3, 123.1, 126.7, 128.0, 128.3, 129.7, 130.4, 132.6, 137.1, 143.2, 144.3, 148.0, 148.5, 185.2.

Anal. Calcd for $C_{14}H_9NOS$: C, 70.27; H, 3.79. Found: C, 70.24; H, 3.81.

Reactions of Other 3-Substituted Thiophenes with Aryl Bromides (Products 12a–20a, 21b–23b, and 24a–33a); General Procedure
In a typical experiment, the aryl bromide (1 mmol), thiophene (1.5 mmol), and KOAc (0.196 g, 2 mmol) were introduced in an oven-dried Schlenk tube, equipped with a magnetic stirring bar. Then, $Pd(OAc)_2$ (0.22 mg, 0.001 mmol), dppb (0.42 mg, 0.001 mmol), and DMA (3 mL) were added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a preheated oil bath at 130 °C and the reactants were allowed to stir for 16 h. Then, the reaction mixture was analysed by GC and NMR to determine the ratio of regioisomers **a/b** and the conversion of the aryl bromide. The solvent was removed by heating of the reaction vessel under vacuum and the residue was charged directly onto a silica gel column. The products were eluted, using an appropriate ratio of Et_2O and pentane (Tables 5– 8).

4-(3-Cyanothiophen-2-yl)benzonitrile (12a)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-cyanothiophene (0.218 g, 2 mmol) afforded the product **12a** in 60% (0.126 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 5.3 Hz, 1 H), 7.49 (d, *J* = 5.3 Hz, 1 H), 7.78 (d, *J* = 8.3 Hz, 2 H), 7.90 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.1, 113.5, 115.6, 118.5, 127.7, 128.6, 131.4, 133.4, 135.9, 151.2.

Anal. Calcd for $C_{12}H_6N_2S$: C, 68.55; H, 2.88. Found: C, 68.57; H, 2.83.

4-(3-Cyanothiophen-2-yl)benzaldehyde (13a)
The reaction of 4-bromobenzaldehyde (0.186 g, 1 mmol) and 3-cyanothiophene (0.218 g, 2 mmol) afforded the product **13a** in 58% (0.123 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 5.3 Hz, 1 H), 7.47 (d, *J* = 5.3 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 2 H), 8.02 (d, *J* = 8.3 Hz, 2 H), 10.09 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 107.9, 115.8, 127.4, 128.7, 130.9, 131.3, 137.0, 137.1, 152.0, 191.7.

Anal. Calcd for $C_{12}H_7NOS$: C, 67.58; H, 3.31. Found: C, 67.61; H, 3.34.

4-(3-Cyanothiophen-2-yl)nitrobenzene (14a)
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 3-cyanothiophene (0.218 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **14a** in 64% (0.147 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 5.3 Hz, 1 H), 7.53 (d, *J* = 5.3 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 2 H), 8.35 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.4, 115.5, 124.9, 128.1, 129.0, 131.5, 137.7, 148.4, 150.6.

Anal. Calcd for $C_{11}H_6N_2O_2S$: C, 57.38; H, 2.63. Found: C, 57.43; H, 2.59

3-(3-Cyanothiophen-2-yl)pyridine (15a)[10]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 3-cyanothiophene (0.218 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **15a** in 40% (0.074 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34 (d, *J* = 5.3 Hz, 1 H), 7.40–7.46 (m, 2 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 8.68 (d, *J* = 4.4 Hz, 1 H), 8.90 (s, 1 H).

4-(3-Methylthiophen-2-yl)benzonitrile (16a)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-methylthiophene (0.196 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **16a** in 65% (0.129 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H), 6.98 (d, *J* = 5.3 Hz, 1 H), 7.32 (d, *J* = 5.3 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 7.71 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.6, 110.8, 119.3, 125.6, 129.6, 132.1, 132.7, 135.4, 136.1, 139.9.

Anal. Calcd for $C_{12}H_9NS$: C, 72.33; H, 4.55. Found: C, 72.40; H, 4.52

4-(3-Methylthiophen-2-yl)acetophenone (17a)
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and 3-methylthiophene (0.196 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **17a** in 64% (0.138 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (s, 3 H), 2.65 (s, 3 H), 6.98 (d, *J* = 5.3 Hz, 1 H), 7.30 (d, *J* = 5.3 Hz, 1 H), 7.59 (d, *J* = 8.3 Hz, 2 H), 8.02 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.6, 27.0, 125.0, 129.0, 129.2, 132.0, 134.9, 135.8, 136.9, 140.0.

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59. Found: C, 72.24; H, 5.62

4-(3-Methylthiophen-2-yl)nitrobenzene (18a)[20]
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 3-methylthiophene (0.196 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **18a** in 62% (0.135 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 7.00 (d, *J* = 5.3 Hz, 1 H), 7.35 (d, *J* = 5.3 Hz, 1 H), 7.65 (d, *J* = 8.3 Hz, 2 H), 8.29 (d, *J* = 8.3 Hz, 2 H).

3-(3-Methylthiophen-2-yl)pyridine (19a)[21]
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 3-methylthiophene (0.196 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **19a** in 45% (0.078 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 6.98 (d, *J* = 5.3 Hz, 1 H), 7.28–7.37 (m, 2 H), 7.79 (d, *J* = 5.3 Hz, 1 H), 8.60–8.78 (m, 2 H).

3-(3-Methylthiophen-2-yl)quinoline (20a)
The reaction of 3-bromoquinoline (0.207 g, 1 mmol) and 3-methylthiophene (0.196 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **20a** in 69% (0.155 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 7.03 (d, *J* = 5.3 Hz, 1 H), 7.34 (d, *J* = 5.3 Hz, 1 H), 7.55–7.88 (m, 3 H), 8.13–8.21 (m, 2 H), 9.08 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.4, 125.2, 127.5, 128.1, 128.3, 128.5, 129.7, 129.9, 131.8, 134.4, 135.2, 135.3, 147.3, 151.3.

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92. Found: C, 74.59; H, 4.94

4-(4-Acetylthiophen-2-yl)benzonitrile (21b)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-acetylthiophene (0.252 g, 2 mmol), KOAc (0.196 g, 2 mmol) afforded the product **21b** in 38% (0.086 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 7.72 (s, 4 H), 7.85 (s, 1 H), 8.08 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.1, 111.4, 118.4, 124.2, 126.1, 132.7, 132.9, 137.5, 142.8, 143.5, 191.9.

Anal. Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99. Found: C, 68.66; H, 3.95

2-(4-Acetylthiophen-2-yl)benzonitrile (22b)
The reaction of 2-bromobenzonitrile (0.182 g, 1 mmol) and 3-acetylthiophene (0.252 g, 2 mmol) afforded the product **22b** in 57% (0.129 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.58 (s, 3 H), 7.47–7.80 (m, 4 H), 7.95 (s, 1 H), 8.15 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 27.9, 110.8, 118.7, 127.4, 128.8, 130.2, 133.6, 133.8, 134.7, 137.0, 140.8, 143.5, 192.4.

Anal. Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99. Found: C, 68.75; H, 3.94

9-(4-Acetylthiophen-2-yl)anthracene (23b)
The reaction of 9-bromoanthracene (0.255 g, 1 mmol) and 3-acetylthiophene (0.252 g, 2 mmol) afforded the product **23b** in 73% (0.220 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.66 (s, 3 H), 7.43–7.55 (m, 4 H), 7.66 (s, 1 H), 7.84–8.08 (m, 4 H), 8.33 (s, 1 H), 8.57 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 28.0, 125.8, 126.5, 126.7, 128.9, 129.0, 129.3, 131.5, 132.0, 134.2, 140.8, 143.2, 192.9.

Anal. Calcd for $C_{20}H_{14}OS$: C, 79.44; H, 4.67. Found: C, 79.48; H, 4.63.

4-(3-Hydroxymethylthiophen-2-yl) benzonitrile (24a)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and 3-thiophenemethanol (0.228 g, 2 mmol) afforded the product **24a** in 66% (0.142 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.67 (s, 2 H), 7.17 (d, *J* = 4.7 Hz, 1 H), 7.38 (d, *J* = 4.7 Hz, 1 H), 7.50–7.80 (m, 4 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 58.5, 111.1, 118.6, 126.0, 129.5, 130.0, 132.4, 138.3, 138.4, 139.1.

Anal. Calcd for $C_{12}H_9NOS$: C, 66.95; H, 4.21. Found: C, 66.87; H, 4.30.

1-[4-(3-Hydroxymethylthiophen-2-yl)phenyl]ethanone (25a)
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and 3-thiophenemethanol (0.228 g, 2 mmol) afforded the product **25a** in 65% (0.151 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.60 (s, 3 H), 4.68 (s, 2 H), 7.20 (d, *J* = 4.7 Hz, 1 H), 7.32 (d, *J* = 4.7 Hz, 1 H), 7.60 (d, *J* = 8.1 Hz, 2 H), 7.97 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.5, 58.7, 125.5, 128.7, 129.0, 129.8, 135.9, 138.0, 138.5, 139.7, 197.6.

Anal. Calcd for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.10; H, 5.32.

[2-(4-Nitrophenyl)thiophen-3-yl]methanol (26a)
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 3-thiophenemethanol (0.228 g, 2 mmol) afforded the product **26a** in 55% (0.129 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.68 (s, 2 H), 7.21 (d, *J* = 4.7 Hz, 1 H), 7.39 (d, *J* = 4.7 Hz, 1 H), 7.70 (d, *J* = 8.1 Hz, 2 H), 8.21 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 58.5, 123.9, 126.4, 129.5, 130.2, 138.6, 138.7, 140.3, 146.8.

Anal. Calcd for $C_{11}H_9NO_3S$: C, 56.16; H, 3.86. Found: C, 56.04; H, 3.98.

(2-Pyridin-3-ylthiophen-3-yl)methanol (27a)
The reaction of 3-bromopyridine (0.158 g, 1 mmol) and 3-thiophenemethanol (0.228 g, 2 mmol) afforded the product **27a** in 69% (0.132 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.62 (s, 2 H), 7.21 (d, *J* = 4.7 Hz, 1 H), 7.25–7.40 (m, 2 H), 7.82 (d, *J* = 7.2 Hz, 1 H), 8.44 (d, *J* = 4.5 Hz, 1 H), 8.63 (s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 57.9, 123.4, 125.2, 129.8, 130.1, 136.2, 136.4, 138.7, 148.1, 149.1.

Anal. Calcd for $C_{10}H_9NOS$: C, 62.80; H, 4.74. Found: C, 62.87; H, 4.61.

Ethyl [2-(4-Cyanophenyl)thiophen-3-yl]acetate (28a)
The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol) and ethyl 3-thiophenylacetate (0.340 g, 2 mmol) afforded the product **28a** in 61% (0.165 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 3.72 (s, 2 H), 4.21 (q, *J* = 7.5 Hz, 2 H), 7.11 (d, *J* = 5.1 Hz, 1 H), 7.37 (d, *J* = 5.1 Hz, 1 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 7.70 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.6, 61.1, 111.3, 118.6, 125.7, 129.8, 130.4, 130.9, 132.4, 138.4, 138.6, 170.8.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; Found: C, 66.51; H, 4.78.

Traces of **28b** were also isolated.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 3.70 (s, 2 H), 4.21 (q, *J* = 7.5 Hz, 2 H), 7.21 (s, 1 H), 7.41 (s, 1 H), 7.68–7.72 (m, 4 H).

Ethyl [2-(4-Nitrophenyl)thiophen-3-yl]acetate (29a)
The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and ethyl 3-thiophenylacetate (0.340 g, 2 mmol) afforded the product **29a** in 63% (0.183 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 3.72 (s, 2 H), 4.21 (q, *J* = 7.5 Hz, 2 H), 7.12 (d, *J* = 5.1 Hz, 1 H), 7.40 (d, *J* = 5.1 Hz, 1 H), 7.69 (d, *J* = 8.1 Hz, 2 H), 8.28 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.4, 34.8, 61.5, 124.2, 126.3, 130.1, 130.7, 131.5, 138.3, 140.8, 147.0, 171.0.

Anal. Calcd for $C_{14}H_{13}NO_4S$: C, 57.72; H, 4.50. Found: C, 57.64; H, 4.65.

Traces of **29b** were also isolated.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 3.70 (s, 2 H), 4.21 (q, *J* = 7.5 Hz, 2 H), 7.28 (s, 1 H), 7.45 (s, 1 H), 7.71 (d, *J* = 8.1 Hz, 2), 8.26 (d, *J* = 8.1 Hz, 2 H).

Ethyl [2-(4-Acetylphenyl)thiophen-3-yl]acetate (30a)
The reaction of 4-bromoacetophenone (0.199 g, 1 mmol) and ethyl 3-thiophenylacetate (0.340 g, 2 mmol) afforded the product **30a** in 53% (0.153 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.5 Hz, 3 H), 2.62 (s, 3 H), 3.65 (s, 2 H), 4.19 (q, *J* = 7.5 Hz, 2 H), 7.10 (d, *J* = 5.1 Hz, 1 H), 7.32 (d, *J* = 5.1 Hz, 1 H), 7.58 (d, *J* = 8.1 Hz, 2 H), 8.00 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 26.6, 34.6, 61.0, 125.2, 128.6, 129.4, 130.2, 130.4, 136.0, 138.6, 139.3, 171.0, 197.5.

Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59. Found: C, 66.48; H, 5.75.

Traces of **30b** were also isolated.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.5 Hz, 3 H), 2.63 (s, 3 H), 3.65 (s, 2 H), 4.19 (q, *J* = 7.5 Hz, 2 H), 7.18 (s, 1 H), 7.38 (s, 1 H), 7.66 (d, *J* = 8.1 Hz, 2 H), 7.95 (d, *J* = 8.1 Hz, 2 H).

Methyl 4-(3-Ethoxycarbonylmethylthiophen-2-yl)benzoate (31a)

The reaction of methyl 4-bromobenzoate (0.215 g, 1 mmol) and ethyl 3-thiophenylacetate (0.340 g, 2 mmol) afforded the product **31a** in 51% (0.155 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.5 Hz, 3 H), 3.65 (s, 2 H), 3.93 (s, 3 H), 4.19 (q, *J* = 7.5 Hz, 2 H), 7.10 (d, *J* = 5.1 Hz, 1 H), 7.32 (d, *J* = 5.1 Hz, 1 H), 7.56 (d, *J* = 8.1 Hz, 2 H), 8.08 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1, 34.6, 52.2, 61.0, 125.1, 129.2, 129.9, 130.2, 130.3, 138.4, 139.4, 166.7, 171.0.

Anal. Calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 63.20; H, 5.41.

Traces of **31b** were also isolated.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.5 Hz, 3 H), 3.64 (s, 2 H), 3.92 (s, 3 H), 4.19 (q, *J* = 7.5 Hz, 2 H), 7.17 (s, 1 H), 7.37 (s, 1 H), 7.64 (d, *J* = 8.1 Hz, 2 H), 8.02 (d, *J* = 8.1 Hz, 2 H).

3-Bromo-2-(4-nitrophenyl)thiophene (32a)

The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol) and 3-bromothiophene (0.326 g, 2 mmol) afforded the product **32a** in 58% (0.165 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 5.3 Hz, 1 H), 7.39 (d, *J* = 5.3 Hz, 1 H), 7.82 (d, *J* = 8.1 Hz, 2 H), 8.23 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.5, 123.8, 126.9, 129.6, 132.4, 135.5, 139.3, 147.2.

Anal. Calcd for $C_{10}H_6BrNO_2S$: C, 42.27; H, 2.13. Found: C, 42.34; H, 2.21.

Methyl 4-(3-Bromothiophen-2-yl)benzoate (33a)

The reaction of methyl 4-bromobenzoate (0.215 g, 1 mmol) and 3-bromothiophene (0.326 g, 2 mmol) afforded the product **33a** in 46% (0.137 g) yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.94 (s, 3 H), 7.07 (d, *J* = 5.1 Hz, 1 H), 7.33 (d, *J* = 5.1 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 2 H), 8.08 (d, *J* = 8.1 Hz, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 52.2, 108.5, 125.9, 128.7, 129.7, 129.4, 132.0, 136.9, 137.2, 166.6.

Anal. Calcd for $C_{12}H_9BrO_2S$: C, 48.50; H, 3.05. Found: C, 48.41; H, 3.24.

Ethyl 5-(3-Nitrophenyl)furan-3-carboxylate (34b)[8]

3-Bromonitrobenzene (0.202 g, 1 mmol), ethyl 3-furoate (0.280 g, 2 mmol), and KOAc (0.196 g, 2 mmol) were introduced in an oven-dried Schlenk tube, equipped with a magnetic stirring bar. Then, $Pd(OAc)_2$ (0.44 mg, 0.002 mmol), dppb (0.84 mg, 0.002 mmol), and DMA (3 mL) were added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a preheated oil bath at 130 °C and the reactants were allowed to stir for 20 h. Then, the reaction mixture was analysed by GC and NMR to determine the ratio of regioisomers **a/b** and the conversion of the aryl bromide. The solvent was removed by heating of the reaction vessel under vacuum and the residue was charged directly onto a silica gel column. The product was eluted, using an appropriate ratio of Et_2O and pentane to afford the product **34b** in 45% (0.117 g) yield (Table 9).

Ethyl 5-(4-Acetylphenyl)furan-3-carboxylate (35b)

Similar procedure as for **34b** using 4-bromoacetophenone (0.199 g, 1 mmol). Product **35b** was isolated in 43% (0.111 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 7.5 Hz, 3 H), 2.60 (s, 3 H), (q, *J* = 7.5 Hz, 2 H), 7.09 (s, 1H), 7.73 (d, *J* = 8.4 Hz, 2 H), 7.98 (d, *J* = 8.4 Hz, 2 H), 8.05 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 26.2, 60.4, 106.5, 121.3, 123.5, 128.6, 133.5, 135.9, 147.3, 153.6, 162.4, 196.9.

Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.70; H, 5.54.

Acknowledgment

We thank the Centre National de la Recherche Scientifique and 'Rennes Metropole' for providing financial support.

References

(1) (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, **2000**. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, **2002**, Part III, 213.

(2) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951.

(3) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (c) Campeau, L.-C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* **2007**, *40*, 35. (d) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (e) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949. (f) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 548. (g) McGlacken, G. P.; Batman, L. M. *Chem. Soc. Rev.* **2009**, *38*, 2447. (h) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (i) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20. (j) Fischmeister, C.; Doucet, H. *Green Chem.* **2011**, *13*, 741.

(4) For recent examples of palladium-catalysed direct arylation or vinylation of heteroaromatics with aryl halides from our laboratory, see: (a) Gottumukkala, A. L.; Doucet, H. *Adv. Synth. Catal.* **2008**, *350*, 2183. (b) Gottumukkala, A. L.; Derridj, F.; Djebbar, S.; Doucet, H. *Tetrahedron Lett.* **2008**, *49*, 2926. (c) Fall, Y.; Doucet, H.; Santelli, M. *ChemSusChem* **2009**, *2*, 153. (d) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (e) Fall, Y.; Reynaud, C.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2009**, 4041. (f) Dong, J. J.; Roger, J.; Pozgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 1832. (g) Derridj, F.; Gottumukkala, A. L.; Djebbar, S.; Doucet, H. *Eur. J. Inorg. Chem.* **2008**, 2550. (h) Roger, J.; Doucet, H. *Tetrahedron* **2009**, *65*, 9772. (i) Roger, J.; Verrier, C.; Le Goff, R.; Hoarau, C.; Doucet, H. *ChemSusChem* **2009**, *2*, 951. (j) Ionita, M.; Roger, J.; Doucet, H. *ChemSusChem* **2010**, *3*, 367. (k) Fall, Y.; Doucet, H.; Santelli, M. *Synthesis* **2010**, 127.

(5) For selected examples of palladium-catalysed direct arylations of thiophenes, see: (a) Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Appl. Catal., A* **1999**, *182*, 399. (b) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286. (c) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (d) Masui, K.;

Mori, A.; Okano, K.; Takamura, K.; Kinoshita, M.; Ikeda, T. *Org. Lett.* **2004**, *6*, 2011. (e) Yokooji, A.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2004**, *60*, 6757. (f) Mitsudo, K.; Thansandote, P.; Wilhelm, T.; Mariampillai, B.; Lautens, M. *Org. Lett.* **2006**, *8*, 3939. (g) Mashraqui, S. H.; Ashraf, M.; Ghadigaonkar, S. G. *Synlett* **2006**, 2423. (h) Amaladass, P.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2007**, *63*, 10363. (i) Turner, G. L.; Morris, J. A.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2007**, *46*, 7996. (j) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999. (k) Arai, N.; Miyaoku, T.; Teruya, S.; Mori, A. *Tetrahedron Lett.* **2008**, *49*, 1000. (l) Derridj, F.; Roger, J.; Geneste, F.; Djebbar, S.; Doucet, H. *J. Organomet. Chem.* **2009**, *694*, 455. (m) Smaliy, R. V.; Beauperin, M.; Cattey, H.; Meunier, P.; Hierso, J.-C.; Roger, J.; Doucet, H.; Coppel, Y. *Organometallics* **2009**, *28*, 3152. (n) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826. (o) Roger, J.; Pozgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 425. (p) Dong, J. J.; Roger, J.; Doucet, H. *Tetrahedron Lett.* **2009**, *50*, 2778. (q) Dong, J. J.; Roger, J.; Verrier, C.; Martin, T.; Le Goff, R.; Hoarau, C.; Doucet, H. *Green Chem.* **2010**, *12*, 2053. (r) Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Org. Lett.* **2010**, *12*, 4320. (s) Laidaoui, N.; Miloudi, A.; El Abed, D.; Doucet, H. *Synthesis* **2010**, 2553. (t) Beydoun, K.; Doucet, H. *J. Organomet. Chem.* **2011**, *696*, 1749. (u) Roy, D.; Mom, S.; Beaupérin, M.; Doucet, H.; Hierso, J.-C. *Angew. Chem. Int. Ed.* **2010**, *49*, 6650.

(6) For examples of palladium-catalysed intramolecular direct 2-arylations of 3-substituted thiophenes, see: Mori, A.; Arai, N.; Hatta, T.; Monguchi, D. *Heterocycles* **2010**, *80*, 103.

(7) For examples of palladium-catalysed direct polyarylations of 3-substituted thiophenes, see: (a) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851. (b) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, 2471.

(8) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.

(9) Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 49.

(10) Fournier dit Chabert, J.; Marquez, B.; Neville, L.; Joucla, L.; Broussous, S.; Bouhours, P.; David, E.; Pellet-Rostaing, S.; Marquet, B.; Moreau, N.; Lemaire, M. *Bioorg. Med. Chem.* **2007**, *15*, 4482.

(11) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350.

(12) Liégault, B.; Petrov, I.; Gorlesky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047.

(13) Borghese, A.; Geldhof, G.; Antoine, L. *Tetrahedron Lett.* **2006**, *47*, 9249.

(14) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *9*, 2116.

(15) Yanagisawa, S.; Ueda, K.; Sekizawa, H.; Itami, K. *J. Am. Chem. Soc.* **2009**, *131*, 14622.

(16) Yanagisawa, S.; Sudo, T.; Noyori, R.; Itami, K. *Tetrahedron* **2008**, *64*, 6073.

(17) Dong, J. J.; Doucet, H. *Eur. J. Org. Chem.* **2010**, 611.

(18) Roger, J.; Pozgan, F.; Doucet, H. *Adv. Synth. Catal.* **2010**, *352*, 696.

(19) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 3140.

(20) Roth, G. P.; Farina, V. *Tetrahedron Lett.* **1995**, *36*, 2191.

(21) Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem.* **2005**, *48*, 224.