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Palladium-catalyzed direct arylation using free NH_2 substituted thiophene derivatives with inhibition of amination type reaction

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ABSTRACT

The palladium-catalyzed direct arylation at C2 or C5 of free NH_2 substituted thiophene derivatives was found to proceed in moderate to high yields using a variety of aryl halides. The choice of potassium acetate as the base was found to be crucial to inhibit the amination reaction and to promote the direct arylation.

1. Introduction

Heteroarenes bearing aryl substituents display important biological or physical properties and their preparation represents an important field of research in organic chemistry.[1] In recent years, the palladium-catalyzed direct arylation of heteroaromatics has emerged as a very powerful tool for the preparation of arylated heteroaromatics.[2–5] However, there are still important limitations in terms of heteroaromatics functional group tolerance for this coupling procedure. Direct arylations of thiophenes substituted by nitrile, carbonyl, ester, methylalcohol as the functional groups have been described.[4f,6] On the other hand, the use of heteroaromatics bearing free NH_2 substituents has attracted much less attention. To our knowledge, only purine derivatives or pyrazoles bearing a free NH_2 function have been employed.[7,8] Some protected amines have also been used.[9–13]

However, the direct use of thiophenes bearing unprotected functions, such as NH_2 would be more useful in organic synthesis since it would allow to avoid the *protection/deprotection sequence*, and would provide a more environmentally and economically attractive access to such arylated thiophenes. Therefore, the discovery of effective conditions, for the direct coupling of such thiophenes with aryl halides, would be a considerable advantage for industrial applications and for sustainable development.

We have recently reported preliminary results on the direct arylation of some thiophenes bearing a free NH_2 substituent.[14] Here, we wish to report on the scope of this reaction using a set of electronically and sterically diverse aryl halides. The regioselectivity of the coupling with some thiophene derivatives bearing unprotected amino functions was also studied.

2. Results and discussion

We decided to employ methyl 3-amino-4-methylthiophene-2-carboxylate as the test substrate for our study. Carbon C2 of this substrate is blocked by an ester, which can be easily removed. This commercially available compound is a precursor of articaine (Fig. 1), which is actually the most widely used local dental anaesthetic in several European countries.

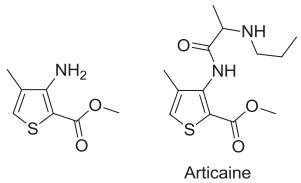

Fig. 1. Articaine and its precursor.

First, we examined the influence of the base, solvent, catalyst precursor and reaction temperature for the coupling of 4-trifluoromethylbromobenzene with methyl 3-amino-4-methylthiophene-2-carboxylate (Scheme 1, Table 1). In the course of this reaction, several compounds were produced. However, the amination

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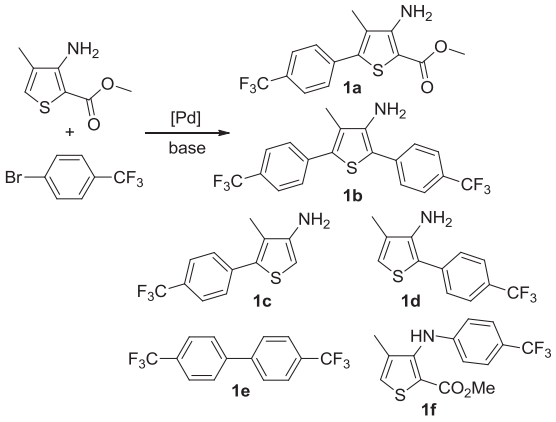


Scheme 1.

Table 1
Influence of the reaction conditions on the selectivity for the arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with 4-(trifluoromethyl)bromobenzene (Scheme 1)

Entry	Solvent	Base	Catalyst	Temp (°C)	Conv. (%)	Ratio **1a**/**1b**/**1c**/**1e**
1	DMAc	K_2CO_3	$PdCl(C_3H_5)(dppb)$	150	5	—
2	DMAc	Na_2CO_3	$PdCl(C_3H_5)(dppb)$	150	13	2:0:1:8
3	DMAc	Cs_2CO_3	$PdCl(C_3H_5)(dppb)$	150	11	2:1:4:0
4	DMAc	CsOAc	$PdCl(C_3H_5)(dppb)$	150	98	43:37:12:2
5	DMAc	NaOAc	$PdCl(C_3H_5)(dppb)$	150	43	28:5:5:4
6	DMAc	KOAc	$PdCl(C_3H_5)(dppb)$	150	100	19:66:11:3
7	DMAc	KOAc	$PdCl(C_3H_5)(dppb)$	120	100	93:3:1:1[a]
8	NMP	KOAc	$PdCl(C_3H_5)(dppb)$	120	100	84:2:3:10
9	DMF	KOAc	$PdCl(C_3H_5)(dppb)$	120	93	84:4:0:5
10	Toluene	KOAc	$PdCl(C_3H_5)(dppb)$	120	63	58:0:0:5
11	Di-*n*-butyl ether	KOAc	$PdCl(C_3H_5)(dppb)$	120	46	41:0:0:0:4[b]
12	CPME	KOAc	$PdCl(C_3H_5)(dppb)$	120	52	37:0:0:0:3[b,c]
13	DMAc	KOAc	$Pd(OAc)_2$[d]	120	100	78:15:6:1
14	DMAc	KOAc	$Pd(OAc)_2$/dppb	120	92	83:1:0:8
15	DMAc	KOAc	½ $[PdCl(C_3H_5)]_2$	120	100	78:0:6:9
16	DMAc	KOAc	½ $[PdCl(C_3H_5)]_2$/dppe	120	100	92:1:1:6
17	DMAc	KOAc	½ $[PdCl(C_3H_5)]_2$/2 PPh_3	120	83	75:2:0:5

Conditions: [Pd] (0.02 equiv), 4-(trifluoromethyl)bromobenzene (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), base (2 equiv), 20 h. Conversion of 4-(trifluoromethyl)bromobenzene. Traces of 4-(trifluoromethyl)benzene were also observed in some cases.

[a] Compound **1a** was isolated in 82% yield.

[b] Reaction time: 48 h.

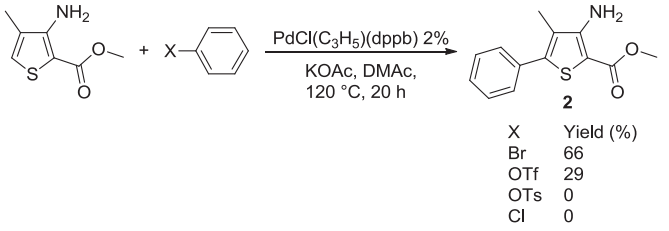
[c] CPME: cyclopentyl methyl ether, 13% of debromation was observed.

[d] $Pd(OAc)_2$ (0.01 equiv).

product **1f** was not detected. On the other hand, the 2,5-diarylated product **1b** and the decarboxylated product **1c** were obtained in relatively high yields in some cases. We initially examined the influence of the nature of the base on the product distribution for this reaction using DMAc as the solvent. DMAc is known to be a suitable solvent for direct arylations of heteroaromatics.[2] K_2CO_3, Na_2CO_3 or Cs_2CO_3 gave poor conversions of 4-(trifluoromethyl)bromobenzene, and target compound **1a** was obtained only in traces (Table 1, entries 1–3). The use of acetates as the base gave better results and the desired compound **1a** was obtained in 19–43% selectivity together with moderate to large amounts of **1b** and **1c** (Table 1, entries 4–6). It should be noted that the inter- or intramolecular palladium-catalyzed amination of some 3-aminothiophenes with aryl bromides have been described using Cs_2CO_3 or K_3PO_4 as the bases in toluene.[15] Interestingly, acetates appear to be not suitable to catalyze amination reaction, as not trace of **1f** was detected. The good performance of acetates as the base for direct arylation is consistent with a concerted metallation deprotonation (CMD) pathway.[16] Then, in order to reduce the amount of decarboxylated products, we performed the reaction at 120 °C instead of 150 °C. At this temperature, in the presence of KOAc as the base, DMAc as the solvent and $PdCl(C_3H_5)(dppb)$ as the catalyst, **1a** was obtained in 82% yield (Table 1, entry 7).

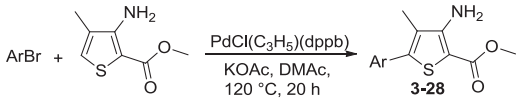
Quite similar results were obtained in the presence of 1,2-bis(diphenylphosphino)ethane (dppe) as the ligand; whereas, the use of PPh_3 led to a lower conversion of the aryl bromide (Table 1, entries 16 and 17). The use of ethers, such as cyclopentyl methyl ether (CPME) or di-*n*-butyl ether as solvents led selectively to **1a**, but moderate conversions of 4-trifluoromethylbromobenzene were observed (Table 1, entries 11 and 12).

We also compared the reactivity of bromobenzene, chlorobenzene, phenyltosylate and phenyltriflate using similar reaction conditions (Scheme 2). As expected, no reaction was observed in the presence of phenyltosylate and chlorobenzene. The oxidative addition of such compounds to palladium is probably too slow under these conditions. On the other hand, a moderate yield of 29% in **2** was obtained with phenyltriflate. However, the highest yield was obtained using bromobenzene.



Scheme 2.

Then, the scope of the coupling of methyl 3-amino-4-methylthiophene-2-carboxylate with a set of *para*-, *meta*-, or *ortho*-substituted aryl bromides and also with heteroaryl bromides was investigated (Scheme 3, Tables 2–5).

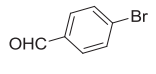
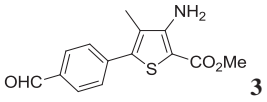
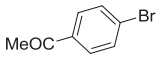
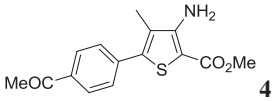
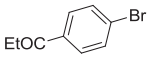
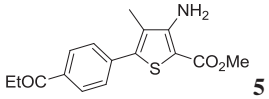
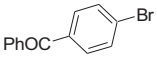
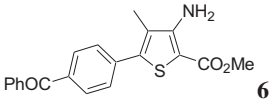
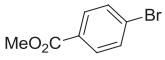
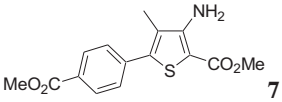
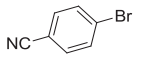
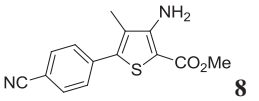
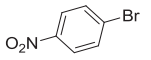
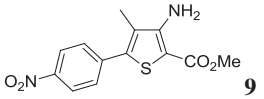
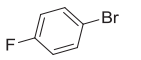
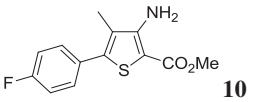
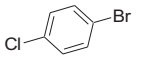
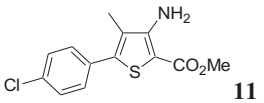
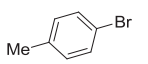
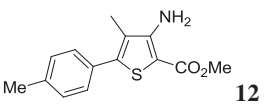
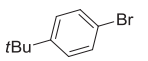
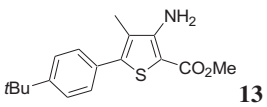
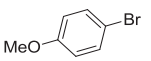
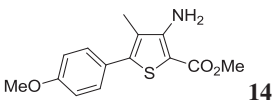
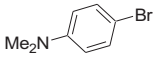
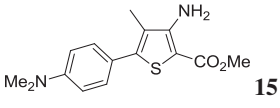


Scheme 3.

The reactions performed with *para*-substituted electron-deficient aryl bromides and 2 mol % $PdCl(C_3H_5)(dppb)$ as the catalyst proceed conveniently in most cases (Table 2). Selective 5-arylations were observed using 4-bromobenzaldehyde, 4-bromoacetophenone, 4-bromopropiophenone, methyl 4-bromobenzoate, 4-bromobenzo nitrile, 4-bromonitrobenzene or 4-bromofluorobenzene, resulting in 74–90% yields of the products **3**–**10** (Table 2, entries 1–12). It should be noted that even 4-chlorobromobenzene could be employed to give **11** in 84% yield (Table 2, entry 13). In the course of this reaction, no cleavage of the C–Cl bond was observed, allowing further transformations. Even the electron-rich aryl bromides 4-bromotoluene or 4-*tert*-butylbromobenzene gave the desired coupling products **12** and **13** in good yields (Table 2, entries 14 and 15). On the other hand, 4-bromoanisole gave **14** in a lower yield of 58% due to a partial conversion; and the strongly deactivated aryl bromide, 4-bromo-*N*,*N*-dimethylaniline was recovered unreacted (Table 2, entries 16 and 17).

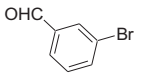
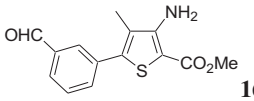
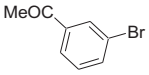
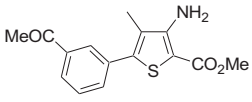
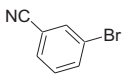
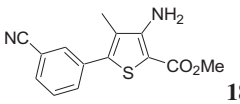
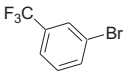
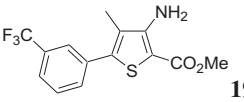
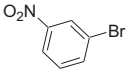
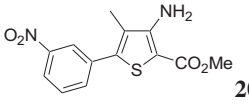
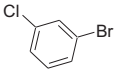
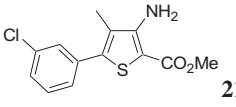
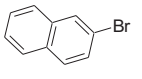
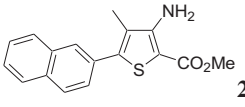
As the use of 1 mol % of the phosphine-free catalyst $Pd(OAc)_2$ has also been found to promote efficiently the direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate in the presence of 4-(trifluoromethyl)bromobenzene (Table 1, entry 13); this air stable and easily available catalyst was also evaluated with a few other aryl bromides. Good yields in **4**, **8** and **9** were obtained with 4-bromoacetophenone, 4-bromobenzonitrile and 4-bromonitroben

Table 2
Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with *para*-substituted aryl bromides (Scheme 3)

Entry	Aryl bromide	Product	Yield (%)
1		 **3**	87
2			44[a]
3		 **4**	90
4			91[a]
5		 **5**	86
6		 **6**	74
7		 **7**	74
8		 **8**	87
9			70[a]
10		 **9**	83
11			78[a]
12		 **10**	89
13		 **11**	84
14		 **12**	81
15		 **13**	67
16		 **14**	58
17		 **15**	0

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.
[a] $Pd(OAc)_2$ (0.01 equiv).

Table 3
Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with *meta*-substituted aryl bromides (Scheme 3)

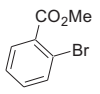
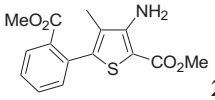
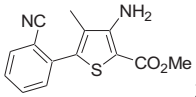
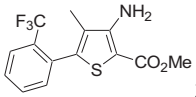
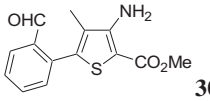
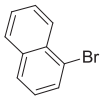
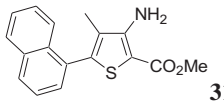
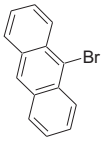
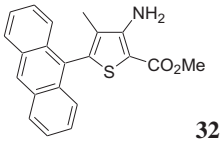
Entry	Aryl halide	Product	Yield (%)
1		 **16**	83
2		 **17**	74
3		 **18**	90
4			45[a]
5		 **19**	92
6			43[a]
7		 **20**	79
8		 **21**	74
9		 **22**	80
10		**23**	70
11		**24**	69
12		**25**	51
13		**26**	42

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.
[a] $Pd(OAc)_2$ (0.01 equiv).

zene and 1 mol % $Pd(OAc)_2$ (Table 2, entries 4, 9 and 11). On the other hand, a moderate conversion of 4-bromobenzaldehyde and a low yield of 44% in **3** was obtained using this catalyst (Table 2, entry 2).

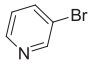
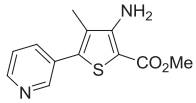
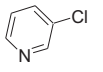
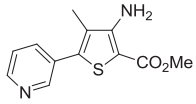
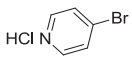
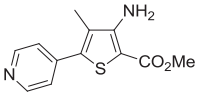
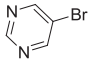
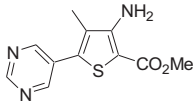
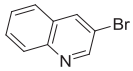
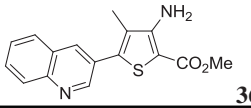
As expected, the reactivity of the *meta*-substituted aryl bromides is similar to the reactivity of the *para*-substituted. The use of electron-deficient aryl bromides, such as 3-bromobenzaldehyde, 3-bromobenzonitrile, 3-(trifluoromethyl)bromobenzene or 3-bromonitrobenzene gave **16**–**20** in very high yields (Table 3,

Table 4
Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with *ortho*-substituted aryl bromides (Scheme 3)

Entry	Aryl bromide	Product	Yield (%)
1		 **27**	87
2		 **28**	90
3			38[a]
4		 **29**	88
5			30[a]
6		 **30**	0
7		 **31**	65
8		 **32**	51

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.
[a] $Pd(OAc)_2$ (0.01 equiv).

Table 5
Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with heteroaryl bromides (Scheme 3)

Entry	Aryl bromide	Product	Yield (%)
1		 **33**	77
2		 **33**	0
3		 **34**	89[a]
4		 **35**	76
5		 **36**	70

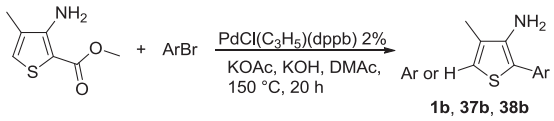
Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.
[a] KOAc (3 equiv).

entries 1–3, 5 and 6). 2-Bromonaphthalene or 6-methoxy-2-bromonaphthalene also led to the desired coupling products **22** and **23** in good yields (Table 3, entries 9 and 10). The arylation of methyl 3-amino-4-methylthiophene-2-carboxylate with unprotected iodoanilines also proceeds using the same reaction conditions. From 3-iodoaniline, **24** was obtained in 69% yield (Table 3, entry 11). Functionalized iodoanilines gave the arylation products **25** and **26** in moderate yields (Table 3, entries 12 and 13). It should be noted that, with 3-bromoaniline, no formation of product **24** was detected.

Then, the reactivity of a set of *ortho*-substituted aryl bromides was studied (Table 4). Electron-deficient and quite congested substrates, such as methyl 2-bromobenzoate, 2-bromobenzonitrile or 2-trifluoromethylbromobenzene were also found to be reactive under these reaction conditions and gave **27**–**29** in 87–90% yields (Table 4, entries 1, 2 and 4). On the other hand, in the presence of 2-bromobenzaldehyde, no formation of **30** was detected (Table 4, entry 6). With this substrate, the formation of several unidentified products was observed. The coupling with 1-bromonaphthalene proceed to give **31** in 65% yield (Table 4, entry 7). Finally, the sterically very congested substrate, 9-bromonaphthalene was employed and the target compound **32** was obtained in 51% yield (Table 4, entry 8).

Pyridines are probably the most common heterocyclic motif found in pharmaceutically active compounds. Therefore, preparative methods of biheteroaryl derivatives containing pyridines remain an essential research topic in organic synthesis. We observed that the coupling of 3- or 4-bromopyridines, with methyl 3-amino-4-methylthiophene-2-carboxylate using 2 mol % $PdCl(C_3H_5)(dppb)$ as the catalyst proceed nicely to give **33** and **34** in good yields (Table 5, entries 1 and 3). On the other hand, the use of 3-chloropyridine as coupling partner gave no product **33** (Table 5, entry 2). The reactivity of 5-bromopyrimidine and 3-bromoquinoline was also examined, and the desired coupling products **34** and **36** were obtained in 76% and 70% yields, respectively (Table 5, entries 4 and 5).

As the decarboxylation of methyl 3-amino-4-methylthiophene-2-carboxylate in the presence of a relatively strong base is quite easy, we examined the reactivity of this substrate using a mixture of KOH and KOAc as the bases (Scheme 4, Table 6). Using these conditions, in the presence of 3-bromopyridine or 4-bromotoluene as the coupling partners, only the 2-arylated products **37b** and **38b** were isolated. No formation of the other regioisomers or diarylated thiophenes was detected.



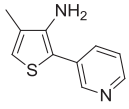
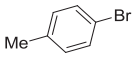
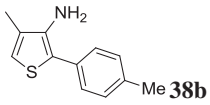
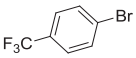
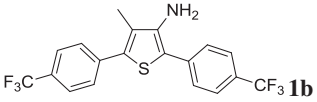
Scheme 4.

We also performed a 2,5-diarylation reaction using 2 equiv of the aryl bromide, 1 equiv of the thiophene derivative and a mixture of KOH and KOAc as the base (Table 6, entry 3). The target 2,5-diarylated product **1b** was obtained in 70% yield.

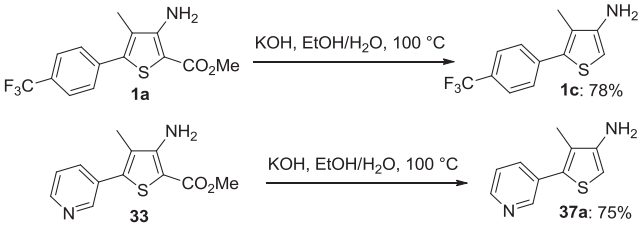
It should be noted that products **1c** or **37a** could be obtained in good yields by decarboxylation of **1a** or **33** using basic conditions (Scheme 5). Therefore, the presence of the ester substituents at carbon C2 of thiophene appears to be useful to block this reactive carbon and to provide alternative regioisomeric arylthiophenes.

Then, we examined the reactivity of 3-amino-4-methylthiophene (Scheme 6, Table 7). As expected, the direct arylation of this substrate with 4-(trifluoromethyl)bromobenzene gave regioselectively the C2 arylated product **1d** (Table 7, entry 1).

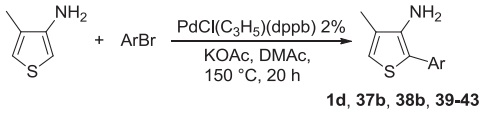
Table 6
Direct arylation of methyl 3-amino-4-methylthiophene-2-carboxylate in the presence of KOH (Scheme 4)

Entry	Aryl bromide	Product	Yield (%)
1		 **37b**	66
2		 **38b**	64
3		 **1b**	70[a]

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (2 equiv), KOAc (1.5 equiv), KOH (1.5 equiv), DMAc, 20 h, 150 °C.
[a] Aryl bromide (2 equiv), methyl 3-amino-4-methylthiophene-2-carboxylate (1 equiv).

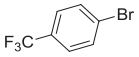
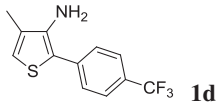
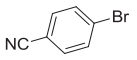
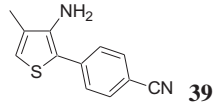
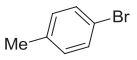
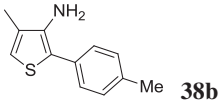
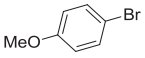
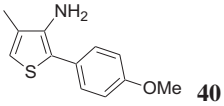
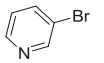
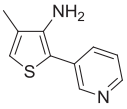
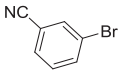
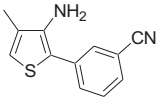
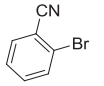
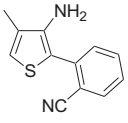
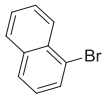
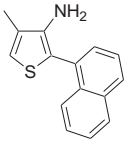


Scheme 5.



Scheme 6.

Table 7
Direct arylation of 3-amino-4-methylthiophene (Scheme 6)

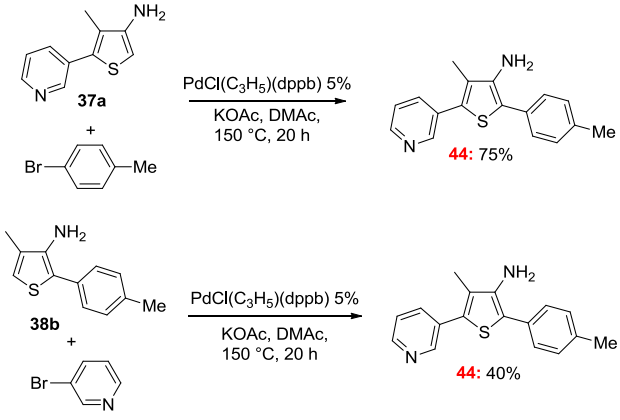
Entry	Aryl bromide	Product	Yield (%)
1		 **1d**	77
2		 **39**	85
3		 **38b**	79
4		 **40**	62
5		 **37b**	78
6		 **41**	83
7		 **42**	80
8		 **43**	75

Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), 3-amino-4-methylthiophene (2 equiv), KOAc (2 equiv), DMAc, 20 h, 150 °C.

This high regioselectivity in favour of the arylation at carbon C2 might be due either to the coordination of the amino substituent to palladium or from electronic factors. Several other aryl bromides were coupled with 3-amino-4-methylthiophene, and both electron-deficient and electron-rich aryl bromides, such as 2-, 3- or 4-bromobenzonitriles or 4-bromoanisole gave the C2 arylated thiophene **39**–**42** in good yields (Table 7, entries 2, 4, 6 and 7).

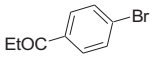
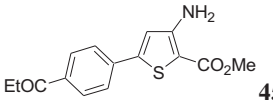
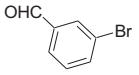
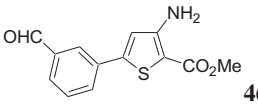
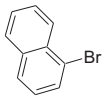
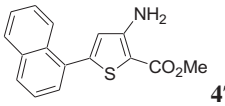
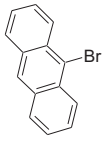
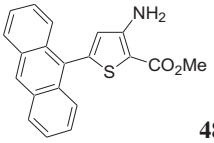
The synthesis of a wide variety of 2,5-diarylated thiophenes bearing a free NH_2 substituent at C3 is also possible. Moreover, this method allows to introduce the aryls at C2 or C5 in any order. Therefore, it is possible to choose the most suitable sequence of reactions in order to obtain the highest yield. For example, compound **37a** reacted with 4-bromotoluene gave **44** in 75% yield (Scheme 7, top); whereas, the reaction of **38b** with 3-bromopyridine led to **44** in only 40% yield (Scheme 7, bottom).

As the amino substituent on thiophenes appears to have a very strong directing effect in the course of direct arylation reactions, the regioselectivity of the coupling with methyl 3-aminothiophene-2-carboxylate was unpredictable. In the presence of 1-bromonaphthalene, we observed the formation of a mixture of the 4- and 5-arylated products **47b** and **47** in 12% and 52% yields, respectively (GC ratio **47**/**47b**=77:23) (Table 8, entry 3). On the other hand, the reaction with the electron-deficient aryl bromides, 4-bromopropiophenone or 3-bromobenzaldehyde and with the congested aryl bromides 9-bromoanthracene gave the C5 arylated products **45**, **46** and **48** in higher regioselectivities (Table 8, entries 1, 2 and 4). In the presence of 9-bromoanthracene, the C4



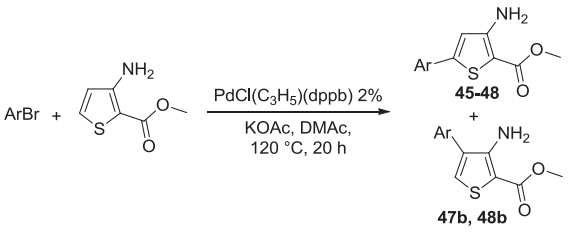
Scheme 7.

Table 8
Direct arylation of methyl 3-aminothiophene-2-carboxylate (Scheme 8)

Entry	Aryl bromide	Product	Yield (%)
1		 **45**	51
2		 **46**	67
3		 **47**	52[a]
4		 **48**	39[b]

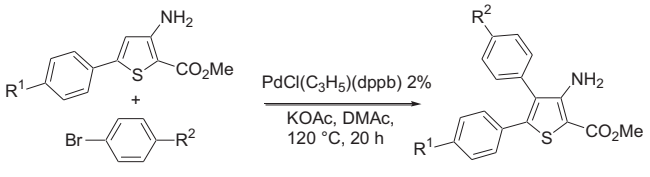
Conditions: $PdCl(C_3H_5)(dppb)$ (0.02 equiv), aryl bromide (1 equiv), methyl 3-aminothiophene-2-carboxylate (2 equiv), KOAc (2 equiv), DMAc, 20 h, 120 °C.
[a] Product **47b** corresponding to a C4 arylation was also isolated in 12%.
[b] Product **48b** corresponding to a C4 arylation was also isolated in 4%.

arylated product was obtained in only 4% yield, whereas the C5 arylated product **48** was isolated in 39% yield.



Scheme 8.

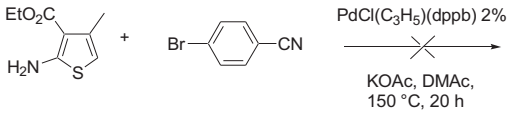
The arylation at C4 of 3-aminothiophenes is possible (see Table 8). Therefore, we examined the C4 arylation of two methyl 3-amino-5-arylthiophene-2-carboxylates with aryl bromides (Scheme 9). The desired coupling products **49** and **50** were obtained in moderate yields due to a partial conversion of the aryl bromides.



R^1	R^2	Product	Yield (%)
H	CF_3	**49**	48
*t*Bu	COMe	**50**	45

Scheme 9.

Then, we examined the influence of the substituents distribution on the thiophene ring. A permutation of the amino and ester substituents was found to drastically modify the thiophene reactivity. No formation of coupling products was detected in the presence of 4-bromobenzonitrile using similar reaction conditions (Scheme 10).



Scheme 10.

3. Conclusions

In summary, we have demonstrated that, when appropriate reaction conditions are employed, the palladium-catalyzed direct arylation at C2 or C5 of some free NH_2 substituted thiophene derivatives with aryl bromides proceed nicely. The choice of KOAc as the base inhibits the amination reaction and promotes the direct arylation. This result is consistent with a concerted metallation deprotonation mechanism.[16] A wide variety of substituents, such as propionyl, acetyl, formyl, benzoyl, ester, nitrile, nitro, trifluoromethyl, fluoro, chloro or methoxy on the aryl bromide are tolerated. To our knowledge, this is the first method for direct arylation of free NH_2 substituted thiophenes. The most reactive carbon of 3-aminothiophenes appears to be the carbon C2. However, the presence of an ester substituent at C2 was found to be useful to block this highly reactive position to provide the 5-arylated thiophenes. This procedure is attractive as it allows to prepare arylated heteroaromatics bearing free NH_2 substituents without protection/deprotection sequence and therefore should provide a 'greener' and more economic access to such compounds.

4. Experimental

4.1. General remarks

All reactions were performed in Schlenck tubes under argon. DMAc analytical grade was not distilled before use. Potassium acetate 99+ was used. Commercial aryl bromides and thiophene derivatives were used without purification. ^1H (300 MHz), ^{13}C (75 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^1H: 7.26 and ^{13}C: 77.0). Flash chromatography was performed on silica gel (230–400 mesh).

4.2. General procedure for the synthesis of products 1a and 2–36

As a typical experiment, the reaction of 4-(trifluoromethyl)bromobenzene (0.225 g, 1 mmol), methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) and KOAc (0.196 g, 2 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) under argon affords methyl 3-amino-4-methyl-5-(4-trifluoromethylphenyl)-thiophene-2-carboxylate **1a** after extraction with dichloromethane, evaporation and filtration on silica gel (pentane/ether) in 82% (0.258 g) yield.

*4.2.1. 4-Methyl-2,5-bis-(4-trifluoromethylphenyl)-thiophen-3-ylamine (**1b**).* 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol), methyl 3-amino-4-methylthiophene-2-carboxylate (0.171 g, 1 mmol), KOH (0.084, 1.5 mmol) and KOAc (0.147 g, 1.5 mmol) in the presence of $PdCl(C_3H_5)(dppb)$ (12.2 mg, 0.02 mmol) in DMAc at 150 °C during 20 h affords **1b** in 70% (0.281 g) yield.

*4.2.2. 4-Methyl-5-(4-trifluoromethylphenyl)-thiophen-3-ylamine (**1c**).* Methyl 3-amino-4-methyl-5-(4-trifluoromethylphenyl)-thiophene-2-carboxylate **1a** (0.315 g, 1 mmol) and KOH (0.067 g, 1.2 mmol) were stirred at 100 °C during 15 h in a mixture EtOH/H_2O (3/1 mL). After addition of an HCl solution to reach pH 7, the

solution was washed with saturated aq $NaHCO_3$. After extraction with dichloromethane, evaporation and filtration on silica gel, **1c** was obtained in 78% (0.201 g) yield.

*4.2.3. 4-Methyl-2-(4-trifluoromethylphenyl)-thiophen-3-ylamine (**1d**).* 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol), 3-amino-4-methylthiophene (0.228 g, 2 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords **1d** in 77% (0.198 g) yield.

*4.2.4. 4,4′-Bis-(trifluoromethyl)biphenyl (**1e**).* This side-product was detected using GC/MS.

*4.2.5. Methyl 3-amino-4-methyl-5-phenylthiophene-2-carboxylate (**2**).*[17] Bromobenzene (0.157 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **2** in 66% (0.163 g) yield.

*4.2.6. Methyl 3-amino-5-(4-formylphenyl)-4-methylthiophene-2-carboxylate (**3**).* 4-Bromobenzaldehyde (0.185 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **3** in 87% (0.239 g) yield.

*4.2.7. Methyl 5-(4-acetylphenyl)-3-amino-4-methylthiophene-2-carboxylate (**4**).* 4-Bromoacetophenone (0.199 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **4** in 90% (0.260 g) yield.

*4.2.8. Methyl 3-amino-4-methyl-5-(4-propionylphenyl)-thiophene-2-carboxylate (**5**).* 4-Bromopropiophenone (0.213 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **5** in 86% (0.261 g) yield.

*4.2.9. 3-Amino-5-(4-benzoylphenyl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**6**).* 4-Bromobenzophenone (0.261 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **6** in 74% (0.260 g) yield.

*4.2.10. Methyl 3-amino-5-[4-(methoxycarbonyl)phenyl]-4-methylthiophene-2-carboxylate (**7**).* Methyl 4-bromobenzoate (0.215 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **7** in 74% (0.226 g) yield.

*4.2.11. Methyl 3-amino-5-(4-cyanophenyl)-4-methylthiophene-2-carboxylate (**8**).* 4-Bromobenzonitrile (0.182 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **8** in 87% (0.237 g) yield.

*4.2.12. Methyl 3-amino-4-methyl-5-(4-nitrophenyl)-thiophene-2-carboxylate (**9**).* 4-Bromonitrobenzene (0.202 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **9** in 83% (0.242 g) yield.

*4.2.13. Methyl 3-amino-5-(4-fluorophenyl)-4-methylthiophene-2-carboxylate (**10**).* 4-Bromofluorobenzene (0.175 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **10** in 89% (0.236 g) yield.

*4.2.14. Methyl 3-amino-5-(4-chlorophenyl)-4-methylthiophene-2-carboxylate (**11**).* 4-Bromochlorobenzene (0.192 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **11** in 84% (0.236 g) yield.

*4.2.15. Methyl 3-amino-4-methyl-5-p-tolylthiophene-2-carboxylate (**12**).* 4-Bromotoluene (0.171 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **12** in 81% (0.212 g) yield.

*4.2.16. Methyl 3-amino-5-(4-tert-butylphenyl)-4-methylthiophene-2-carboxylate (**13**).* 4-*tert*-Butylbromobenzene (0.213 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **13** in 67% (0.203 g) yield.

*4.2.17. Methyl 3-amino-5-(4-methoxyphenyl)-4-methyl-thiophene-2-carboxylate (**14**).* 4-Bromoanisole (0.187 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **14** in 58% (0.161 g) yield.

*4.2.18. Methyl 3-amino-5-(3-formylphenyl)-4-methylthiophene-2-carboxylate (**16**).* 3-Bromobenzaldehyde (0.185 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **16** in 83% (0.228 g) yield.

*4.2.19. 5-(3-Acetylphenyl)-3-amino-4-methyl-thiophene-2-carboxylic acid methyl ester (**17**).* 3-Bromoacetophenone (0.199 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **17** in 74% (0.214 g) yield.

*4.2.20. Methyl 3-amino-5-(3-cyanophenyl)-4-methylthiophene-2-carboxylate (**18**).* 3-Bromobenzonitrile (0.182 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **18** in 90% (0.245 g) yield.

*4.2.21. Methyl 3-amino-4-methyl-5-(3-trifluoromethylphenyl)-thiophene-2-carboxylate (**19**).* 3-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **19** in 92% (0.290 g) yield.

*4.2.22. 3-Amino-4-methyl-5-(3-nitrophenyl)-thiophene-2-carboxylic acid methyl ester (**20**).* 3-Bromonitrobenzene (0.202 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **20** in 79% (0.231 g) yield.

*4.2.23. 3-Amino-5-(3-chlorophenyl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**21**).* 3-Bromochlorobenzene (0.192 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **21** in 84% (0.208 g) yield.

*4.2.24. Methyl 3-amino-4-methyl-5-naphthalen-2-ylthiophene-2-carboxylate (**22**).* 2-Bromonaphthalene (0.207 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **22** in 80% (0.238 g) yield.

*4.2.25. 3-Amino-5-(6-methoxynaphthalen-2-yl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**23**).* 2-Bromo-6-methoxynaphthalene (0.237 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **23** in 70% (0.229 g) yield.

*4.2.26. 3-Amino-5-(3-aminophenyl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**24**).* 3-Iodoaniline (0.219 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **24** in 69% (0.181 g) yield.

*4.2.27. 3-Amino-5-(4-amino-3-chlorophenyl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**25**).* 2-Chloro-4-iodoaniline (0.253 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **25** in 51% (0.151 g) yield.

*4.2.28. 3-Amino-5-(4-amino-3-ethoxycarbonyl-phenyl)-4-methyl-thiophene-2-carboxylic acid methyl ester (**26**).* Ethyl 2-amino-5-

iodobenzoate (0.291 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **26** in 42% (0.140 g) yield.

*4.2.29. Methyl 3-amino-5-(2-methoxycarbonylphenyl)-4-methylthiophene-2-carboxylate (**27**).* Methyl 2-bromobenzoate (0.215 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **27** in 87% (0.266 g) yield.

*4.2.30. Methyl 3-amino-5-(2-cyanophenyl)-4-methylthiophene-2-carboxylate (**28**).* 2-Bromobenzonitrile (0.182 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **28** in 90% (0.245 g) yield.

*4.2.31. 3-Amino-4-methyl-5-(2-trifluoromethylphenyl)-thiophene-2-carboxylate (**29**).* 2-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **29** in 88% (0.277 g) yield.

*4.2.32. Methyl 3-amino-4-methyl-5-naphthalen-1-ylthiophene-2-carboxylate (**31**).* 1-Bromonaphthalene (0.207 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **31** in 65% (0.193 g) yield.

*4.2.33. Methyl 3-amino-5-anthracen-9-yl-4-methylthiophene-2-carboxylate (**32**).* 9-Bromoanthracene (0.257 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **32** in 51% (0.177 g) yield.

*4.2.34. Methyl 3-amino-4-methyl-5-pyridin-3-ylthiophene-2-carboxylate (**33**).* 3-Bromopyridine (0.158 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **33** in 77% (0.191 g) yield.

*4.2.35. Methyl 3-amino-4-methyl-5-pyridin-4-ylthiophene-2-carboxylate (**34**).* 4-Bromopyridine hydrochloride (0.194 g, 1 mmol), methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) and KOAc (0.294 g, 3 mmol) affords **34** in 89% (0.221 g) yield.

*4.2.36. Methyl 3-amino-4-methyl-5-(pyrimidin-5-yl)thiophene-2-carboxylate (**35**).* 5-Bromopyrimidine (0.159 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 3 mmol) affords **35** in 76% (0.189 g) yield.

*4.2.37. Methyl 3-amino-4-methyl-5-quinolin-3-ylthiophene-2-carboxylate (**36**).* 3-Bromoquinoline (0.208 g, 1 mmol) and methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol) affords **36** in 70% (0.209 g) yield.

*4.2.38. 4-Methyl-2-pyridin-3-ylthiophen-3-ylamine (**37b**).* 3-Bromopyridine (0.158 g, 1 mmol), methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol), KOH (0.084, 1.5 mmol) and KOAc (0.147 g, 1.5 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) in DMAc at 150 °C during 20 h affords **37b** in 66% (0.125 g) yield.

*4.2.39. 4-Methyl-2-p-tolylthiophen-3-ylamine (**38b**).* 4-Bromotoluene (0.171 g, 1 mmol), methyl 3-amino-4-methylthiophene-2-carboxylate (0.342 g, 2 mmol), KOH (0.084, 1.5 mmol) and KOAc (0.147 g, 1.5 mmol) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) in DMAc at 150 °C during 20 h affords **38b** in 64% (0.130 g) yield.

*4.2.40. 4-Methyl-5-pyridin-3-ylthiophen-3-ylamine (**37a**).* Methyl 3-amino-4-methyl-5-pyridin-3-ylthiophene-2-carboxylate **33** (0.248 g, 1 mmol) and KOH (0.067 g, 1.2 mmol) were stirred at 100 °C during 15 h in a mixture EtOH/H_2O (3/1 mL). After addition of an HCl solution to reach pH 7, the solution was washed with saturated aq $NaHCO_3$. After extraction with dichloromethane, evaporation and filtration on silica gel, **37a** was obtained in 75% (0.142 g) yield.

*4.2.41. 4-(3-Amino-4-methylthiophen-2-yl)benzonitrile (**39**).* 4-Bromobenzonitrile (0.182 g, 1 mmol), 3-amino-4-methylthiophene (0.226 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) affords **39** in 85% (0.182 g) yield.

*4.2.42. 2-(4-Methoxyphenyl)-4-methylthiophen-3-amine (**40**).* 4-Bromoanisole (0.187 g, 1 mmol), 3-amino-4-methylthiophene (0.226 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) affords **40** in 62% (0.136 g) yield.

*4.2.43. 3-(3-Amino-4-methylthiophen-2-yl)benzonitrile (**41**).* 3-Bromobenzonitrile (0.182 g, 1 mmol), 3-amino-4-methylthiophene (0.226 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) affords **41** in 83% (0.178 g) yield.

*4.2.44. 2-(3-Amino-4-methylthiophen-2-yl)benzonitrile (**42**).* 2-Bromobenzonitrile (0.182 g, 1 mmol), 3-amino-4-methylthiophene (0.226 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) affords **42** in 80% (0.171 g) yield.

*4.2.45. 4-Methyl-2-(naphthalen-1-yl)thiophen-3-amine (**43**).* 1-Bromonaphthalene (0.207 g, 1 mmol), 3-amino-4-methylthiophene (0.226 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) affords **43** in 75% (0.179 g) yield.

*4.2.46. 4-Methyl-5-pyridin-3-yl-2-p-tolylthiophen-3-ylamine (**44**).* 4-Bromotoluene (0.171 g, 1 mmol), 4-methyl-5-pyridin-3-ylthiophen-3-ylamine **37a** (0.380 g, 2 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (30.5 mg, 0.05 mmol) affords **44** in 75% (0.210 g) yield.

*4.2.47. Methyl 3-amino-5-(4-propionylphenyl)thiophene-2-carboxylate (**45**).* 4-Bromopropiophenone (0.213 g, 1 mmol), methyl 3-aminothiophene-2-carboxylate (0.314 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords **45** in 51% (0.147 g) yield.

*4.2.48. Methyl 3-amino-5-(3-formylphenyl)thiophene-2-carboxylate (**46**).* 3-Bromobenzaldehyde (0.185 g, 1 mmol), methyl 3-aminothiophene-2-carboxylate (0.314 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords **46** in 67% (0.175 g) yield.

*4.2.49. Methyl 3-amino-5-naphthalen-1-yl-thiophene-2-carboxylate (**47**) and methyl 3-amino-4-naphthalen-1-yl-thiophene-2-carboxylate (**47b**).* 1-Bromonaphthalene (0.207 g, 1 mmol), methyl 3-aminothiophene-2-carboxylate (0.314 g, 2 mmol) and KOAc (0.196 g, 2 mmol) in the presence of $PdCl(C_3H_5)$(dppb)

(12.2 mg, 0.02 mmol) in DMAc at 120 °C during 20 h affords the products **47** in 52% (0.147 g) and **47b** in 12% (0.034 g) yields.

*4.2.50. Methyl 3-amino-5-(anthracen-9-yl)thiophene-2-carboxylate (**48**) and methyl 3-amino-4-(anthracen-9-yl)thiophene-2-carboxylate (**48b**).* 9-Bromoanthracene (0.257 g, 1 mmol), methyl 3-aminothiophene-2-carboxylate (0.314 g, 2 mmol) and KOAc (0.196 g, 2.0 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords methyl 3-amino-5-(anthracen-9-yl)thiophene-2-carboxylate **48** in 39% (0.130 g) and **48b** in 4% (0.013 g) yields.

*4.2.51. Methyl 3-amino-5-phenyl-4-[4-(trifluoromethyl)phenyl]thiophene-2-carboxylate (**49**).* 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol), methyl 3-amino-5-phenylthiophene-2-carboxylate (0.466 g, 2 mmol) and KOAc (0.196 g, 2 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords **49** in 48% (0.181 g) yield.

*4.2.52. Methyl 4-(4-acetylphenyl)-3-amino-5-(4-tert-butylphenyl) thiophene-2-carboxylate (**50**).* 4-Bromoacetophenone (0.199 g, 1 mmol), methyl 3-amino-5-(4-*tert*-butylphenyl)thiophene-2-carboxylate (0.578 g, 2 mmol) and KOAc (0.196 g, 2 mmol) at 120 °C during 20 h in DMAc (3 mL) in the presence of $PdCl(C_3H_5)$(dppb) (12.2 mg, 0.02 mmol) under argon affords **50** in 45% (0.183 g) yield.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tet.2012.06.053.

References and notes

1. (a) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Amsterdam, 2000; (b) Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, NY, 2002; Part III, p 213; (c) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1470.
2. (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238; (b) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200–205; (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; (d) Li, B.-J.; Yang, S.-D.; Shi, Z.-J. *Synlett* **2008**, 949–957; (e) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269–10310; (f) Ackermann, L.; Vincente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792–9826; (g) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20–40; (h) Fischmeister, C.; Doucet, H. *Green Chem.* **2011**, *13*, 741–753.
3. (a) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R.; Miyafuji, A.; Nakata, T.; Tani, N.; Aoyagi, Y. *Heterocycles* **1990**, *31*, 1951–1958; (b) Aoyagi, Y.; Inoue, A.; Koizumi, I.; Hashimoto, R.; Miyafuji, A.; Kunoh, J.; Honma, R.; Akita, Y.; Ohta, A. *Heterocycles* **1992**, *33*, 257–272.
4. For selected recent examples of palladium-catalysed direct arylations from our laboratory: (a) Dong, J. J.; Roger, J.; Požgan, F.; Doucet, H. *Green Chem.* **2009**, *11*, 1832–1846; (b) Smaliy, R. V.; Beaupérin, M.; Cattey, H.; Meunier, P.; Hierso, J.-C.; Roger, J.; Doucet, H.; Coppel, Y. *Organometallics* **2009**, *28*, 3152–3160; (c) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977–1990; (d) Fall, Y.; Reynaud, C.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2009**, 4041–4050; (e) Dong, J. J.; Roger, J.; Verrier, C.; Martin, T.; Le Goff, R.; Hoarau, C.; Doucet, H. *Green Chem.* **2010**, *12*, 2053–2063; (f) Požgan, F.; Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2010**, *352*, 696–710; (g) Beydoun, K.; Zaarour, M.; Williams, J. A. G.; Doucet, H.; Guerchais, V. *Chem. Commun.* **2012**, 1260–1262.
5. For recent examples of direct arylations of thiophenes: (a) David, E.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron* **2007**, *63*, 8999–9006; (b) Amaladass, P.; Clement, J. A.; Mohanakrishnan, A. K. *Tetrahedron* **2007**, *63*, 10363–10371; (c) Nakano, M.; Tsurugi, H.; Satoh, T.; Miura, M. *Org. Lett.* **2008**, *10*, 1851–1854; (d) Bheeter, C. B.; Bera, J. K.; Doucet, H. *J. Org. Chem.* **2011**, *76*, 6407–6413; (e) Shibahara, F.; Yamaguchi, E.; Murai, T. *Chem. Commun.* **2010**, 2471–2473; (f) Tanaka, S.; Tamba, S.; Tanaka, D.; Sugie, A.; Mori, A. *J. Am. Chem. Soc.* **2011**, *133*, 9700–9703; (g) Baghbanzadeh, M.; Pilger, C.; Kappe, C. O. *J. Org. Chem.* **2011**, *76*, 8138–8142; (h) Ueda, K.; Yanagisawa, S.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8946–8949.
6. For examples of palladium-catalysed direct arylations using thiophenes bearing formyl-, acetyl-, nitrile-, silyl, halo- or methylalcohol substituents: (a) Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467–473; (b) Lavenot, L.; Gozzi, C.; Ilg, K.; Orlova, I.; Penalva, V.; Lemaire, M. *J. Organomet. Chem.* **1998**, *567*, 49–55; (c) Okazawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 5286–5287; (d) Hassan, J.; Gozzi, C.; Schulz, E.; Lemaire, M. *J. Organomet. Chem.* **2003**, *687*, 280–283; (e) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074–5075; (f) Kobayashi, K.; Sugie, A.; Takahashi, M.; Masui, K.; Mori, A. *Org. Lett.* **2005**, *7*, 5083–5085; (g) Kobayashi, K.; Mohamed Ahmed, M. S.; Mori, A. *Tetrahedron* **2006**, *62*, 9548–9553; (h) Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834; (i) Dong, J. J.; Roger, J.; Doucet, H. *Tetrahedron Lett.* **2009**, *50*, 2778–2781; (j) Liégault, B.; Petrov, I.; Gorlesky, S. I.; Fagnou, K. *J. Org. Chem.* **2010**, *75*, 1047–1060; (k) Rene, O.; Fagnou, K. *Org. Lett.* **2010**, *12*, 2116–2119; (l) Beydoun, K.; Doucet, H. *ChemSusChem* **2011**, *4*, 526–534; (m) Chen, L.; Roger, J.; Bruneau, C.; Dixneuf, P. H.; Doucet, H. *Chem. Commun.* **2011**, 1872–1874; (n) Schipper, D. J.; Fagnou, K. *Chem. Mater.* **2011**, *23*, 1594–1600.
7. For examples of palladium-catalysed direct arylations using purine derivatives: (a) Cerna, I.; Pohl, R.; Hocek, M. *Chem. Commun.* **2007**, 4729–4730; (b) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125–6137; (c) Cerna, I.; Pohl, R.; Klepetarova, B.; Hocek, M. *J. Org. Chem.* **2008**, *73*, 9048–9054; (d) Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009**, *74*, 5810–5821; (e) Sahnoun, S.; Messaoudi, S.; Brion, J.-D.; Alami, M. *Org. Biomol. Chem.* **2009**, *7*, 4271–4278; (f) Cerna, I.; Pohl, R.; Klepetarova, B.; Hocek, M. *J. Org. Chem.* **2010**, *75*, 2302–2308; (g) Storr, T. E.; Strohmeier, J. A.; Baumann, C. G.; Fairlamb, I. J. S. *Chem. Commun.* **2010**, 6470–6472.
8. For examples of palladium-catalysed direct arylations using free-(NH_2) pyrazoles: Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Adv. Synth. Catal.* **2012**, *354*, 747–750.
9. For intramolecular cyclizations of aniline derivatives: Ackermann, L.; Althammer, A.; Mayer, P. *Synthesis* **2009**, 3493–3503.
10. For examples of palladium-catalysed direct arylations using protected 2-aminothiazoles: (a) Priego, J.; Gutierrez, S.; Ferritto, R.; Broughton, H. B. *Synlett* **2007**, 2957–2960; (b) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449–1451.
11. For an example of palladium-catalysed intramolecular direct arylations using a protected 2-aminofuran: Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716–1724.
12. For examples of palladium-catalysed direct arylations using protected 2- or 3-aminothiophenes: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Synthesis* **2008**, 136–140; (b) Roger, J.; Doucet, H. *Eur. J. Org. Chem.* **2010**, 4412–4425.
13. For an example of palladium-catalysed intramolecular direct arylation using an aminothiophene derivative: Ferreira, I. C. F. R.; Queiroz, M.-J. R. P.; Kirsch, G. *Tetrahedron* **2003**, *59*, 3737–3743.
14. Derridj, F.; Roger, J.; Djebbar, S.; Doucet, H. *Org. Lett.* **2010**, *12*, 4320–4323.
15. (a) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *Tetrahedron* **2006**, *62*, 11100–11105; (b) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Tetrahedron* **2007**, *63*, 690–702.
16. (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755; (b) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126.
17. Migianu, E.; Kirsch, G. *Synthesis* **2002**, 1096–1100.