Ligand-less palladium-catalyzed direct 5-arylation of thiophenes at low catalyst loadings

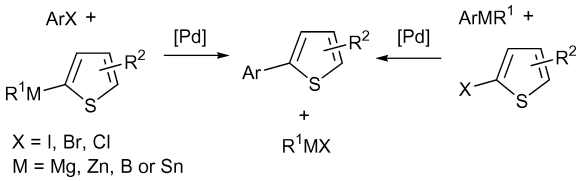
Julien Roger,[a] Franc Požgan[b] and Henri Doucet*[a]

Received 10th November 2008, Accepted 5th January 2009
First published as an Advance Article on the web 6th February 2009
DOI: 10.1039/b819912d

Ligand-less $Pd(OAc)_2$ provides a very efficient catalyst for the direct 5-arylation of thiophene derivatives. With this catalyst, a low palladium concentration (0.1–0.001 mol%) should be employed in order to obtain high yields of coupling products. At higher concentrations a fast formation of inactive "Pd black" generally occurs. Substrates/catalysts ratios up to 100000 can be employed with the most reactive aryl bromides. A very wide variety of functional groups is tolerated on both coupling partners. The major waste of this reaction is HBr associated with KOAc. Therefore this procedure is more economically and environmentally attractive than the traditional cross-coupling procedures employing organometallic derivatives.

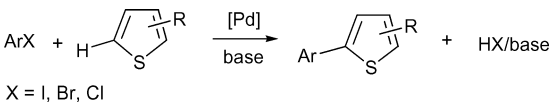
Introduction

In recent years, much attention has been given to the synthesis of arylthiophenes, due to the biological or physical properties demonstrated by this class of compounds.[1] 2-Arylthiophene derivatives can be prepared by classical palladium-catalyzed cross-coupling procedures such as Suzuki,[2] Stille[3] or Negishi[4] type reactions. These reactions are performed using an organometallic derivative of the thiophene with an aryl halide or using an organometallic derivative of an aryl with a halothiophene (MR^1 = ZnX, SnR_3 $B(OR)_2$) (Scheme 1). The major drawback of these reactions is that they require the preparation of organometallic derivatives and also provide either an organometallic or a salt (MX) as a by-product.



Scheme 1

In 1990, Ohta and co-workers reported the direct arylation of thiophenes with aryl halides *via* a C–H bond activation of thiophene in medium to good yields using 5 mol% $Pd(PPh_3)_4$ as catalyst.[5] Since these results, this methodology has been demonstrated to be very powerful for the synthesis of 2-arylthiophenes.[6,7] This reaction is attractive for the environment since the major by-product is HX (X = I, Br or Cl) associated to a base instead of a metallic salt using more classical coupling procedures. Moreover, no preparation of an organometallic derivative is required reducing the number of steps to prepare these compounds (Scheme 2).



Scheme 2

The major disadvantage of this reaction is the relatively high catalyst loadings which are actually employed for such couplings. So far, most of these reactions have been performed using 1–10 mol% palladium catalyst.[5,8,9] Moreover, in most cases, palladium was associated with 1–20 mol% of monophosphines[8] or diphosphines as ligands.[9] Only a few examples of ligand-free palladium procedures have been reported.[10–12] An intramolecular cyclisation of a substituted benzothiophene using 10 mol% $Pd(OAc)_2$ in the absence of ligand or stabilizing agent gave the target products in 60–100% yields.[10] However, in most cases, for ligand-free palladium procedures, a stoichiometric amount of an ammonium salt or of a crown ether was added to the reaction mixture as palladium-stabilizing agent, increasing the amount of wastes.[11,12] Additionally, to the best of our knowledge, such ligand-less palladium couplings using low catalyst concentration have not been reported.

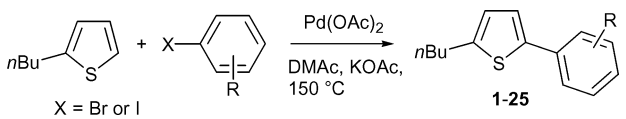
Recently, de Vries and co-workers have reported that Heck and Suzuki reactions can be performed under very low catalyst loadings (0.1–0.01 mol%) using a ligand-free catalyst $Pd(OAc)_2$.[13,14] They have demonstrated that, when $Pd(OAc)_2$ is employed as catalyst precursor at elevated temperature, soluble palladium(0) colloids or nanoparticles are formed. With this ligand-less catalytic system, the Heck or Suzuki reactions takes place *via* the interaction of the arylating agent with the palladium atoms in the outer rim of the nanoparticles. This leads to formation of monomeric or dimeric anionic palladium complexes that undergo the usual catalytic steps. However, this promising procedure has not yet been extended to C–H activation reactions.

[a]*UMR 6226 CNRS-Université de Rennes, "Catalyse et Organometalliques", Campus de Beaulieu, 35042, Rennes, France. E-mail: henri.doucet@univ-rennes1.fr; Tel: +33 (0)2 23 23 63 84*
[b]*Faculty of Chemistry and Chemical Technology, University of Ljubljana Aškerčeva 5, SI-1000, Ljubljana, Slovenia. E-mail: franc.pozgan@fkkt.uni-lj.si*

For the past few years we have been studying the efficiency of palladium catalysts for activation followed by arylation or vinylation of C–H bonds of heteroaromatics such as furans,[15a,b] thiazoles,[15c] benzoxazoles.[15d,e] We have already reported preliminary results for the direct 5-arylation of thiophenes using ligandless $Pd(OAc)_2$ as catalyst.[16] Here, we wish to report on the use of the "de Vries procedure" for palladium-catalyzed 5-arylation of a large set of thiophene derivatives using a wide variety of aryl bromides under very low catalyst loadings.

Results and discussion

First, we examined the reactivity of a variety of *para*-substituted aryl bromides and also iodobenzene with 2-*n*-butylthiophene (Scheme 3, Table 1). The coupling of the electron-deficient aryl bromides, 4-bromoacetophenone, 4-bromobenzophenone, 4-bromobenzaldehyde, 4-(trifluoromethyl)bromobenzene or 4-bromobenzonitrile with 2-*n*-butylthiophene proceeded in high yields using only 0.1–0.001 mol% catalyst (Table 1, entries 3–10). With these substrates the target compounds **2–6** were selectively obtained in very high turnover numbers (TONs) of 1900–85000. Poorly activated 4-fluorobromobenzene was found to be slightly less reactive, and 0.1 mol% catalyst had to be employed in order to obtain a high conversion of the starting material and a good yield of **7** (81%) (Table 1, entry 11). As expected, a lower reactivity of the deactivated aryl bromide, 4-bromoanisole, was observed. Using 0.1 mol% catalyst, a yield of 62% of **9** was obtained (Table 1, entry 14). With this substrate, an increase of the catalyst loading to 1 mol% led to



Scheme 3

Table 1 Reaction of 2-*n*-butylthiophene with *para*-substituted aryl bromides or iodobenzene (Scheme 3)

Entry	Aryl halide	Substrate/ catalyst ratio	Prod.	Yield (%)
1	Iodobenzene	1000	**1**	63 (49)
2	Iodobenzene	10000	**1**	52 (46)
3	4-Bromoacetophenone	10000	**2**	100 (85)
4	4-Bromobenzophenone	10000	**3**	100 (86)
5	4-Bromobenzaldehyde	1000	**4**	100 (89)
6	4-Bromobenzaldehyde	10000	**4**	19
7	4-(Trifluoromethyl)-bromobenzene	10000	**5**	100 (90)
8	4-(Trifluoromethyl)-bromobenzene	100000	**5**	85
9	4-Bromobenzonitrile	1000	**6**	100 (88)
10	4-Bromobenzonitrile	10000	**6**	30
11	4-Bromofluorobenzene	1000	**7**	98 (81)
12	4-Bromotoluene	1000	**8**	73 (67)
13	4-Bromoanisole	100	**9**	60 (50)
14	4-Bromoanisole	1000	**9**	76 (62)
15	4-Bromo-*N*,*N*-dimethylaniline	100	**10**	0
16	4-Bromo-*N*,*N*-dimethylaniline	1000	**10**	0

Conditions: $Pd(OAc)_2$, aryl halide (1 mmol), 2-*n*-butylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

Table 2 Reaction of 2-*n*-butylthiophene with *meta*- or *ortho*-substituted aryl bromides (Scheme 3)

Entry	Aryl bromide	Substrate/ cat. ratio	Prod.	Yield (%)
1	3-Bromobenzaldehyde	1000	**11**	100 (88)
2	3-Bromoacetophenone	1000	**12**	100 (91)
3	3-Bromoacetophenone	10000	**12**	65
4	3-(Trifluoromethyl)-bromobenzene	1000	**13**	100 (93)
5	3,5-Bis(trifluoromethyl)-bromobenzene	10000	**14**	100 (90)
6	2-Bromobenzaldehyde	1000	**15**	91 (84)
7	2-Bromoacetophenone	1000	**16**	0
8	2-(Trifluoromethyl)-bromobenzene	1000	**17**	100 (92)
9	2-Bromobenzonitrile	10000	**18**	81 (67)
10	1-Bromonaphthalene	1000	**19**	100 (87)
11	2-Bromotoluene	100	**20**	52 (42)
12	2,6-Difluorobromobenzene	1000	**21**	94 (86)

Conditions: $Pd(OAc)_2$, aryl bromide (1 mmol), 2-*n*-butylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

a lower yield of product **9** (50%) (Table 1, entry 13). This result was confirmed using the strongly deactivated aryl bromide: 4-bromo-*N*,*N*-dimethylaniline. In the presence of 0.1 mol% or 1 mol% of catalyst no conversions were detected (Table 1, entries 15 and 16). For this ligand-free procedure, under higher palladium concentrations, so-called "palladium black" forms more rapidly. The concentration of active palladium species is not increased, and the conversions of aryl bromides are not improved. Therefore, this ligand-free procedure is limited to relatively reactive substrates.

Surprisingly, this ligand-free procedure was also found to give disappointing results using iodobenzene. With this very reactive aryl halide, moderate conversions of 52 and 63% and yields of 46 and 49% of **1** were obtained using 0.01 or 0.1 mol% catalyst (Table 1, entries 1 and 2). In the course of this reaction, the formation of side-products was also observed. The major one was biphenyl arising from the homocoupling of iodobenzene.

Then, we studied the reactivity of *meta*- and *ortho*-substituted aryl bromides with 2-*n*-butylthiophene (Table 2, Scheme 3). As expected, *meta*-substituted aryl bromides gave quite similar results than the *para*-substituted ones. For example, 3-bromoacetophenone gave **12** with a TON of 6500, whereas a TON of 10000 had been obtained using 4-bromoacetophenone (compare Table 2, entry 3 with Table 1, entry 3). In general, *ortho*-substituents on aryl halides have a more important effect on the rates and yields of palladium-catalysed reactions, due to their different steric hindrance and coordination properties. *Ortho*-substituted 2-bromobenzonitrile reacted with 2-*n*-butylthiophene leading to the expected product **18** in a high TON of 8100 (Table 2, entry 9). 2-Bromobenzaldehyde, 2-(trifluoromethyl)bromobenzene or 1-bromonaphthalene also led to the desired 5-arylated thiophenes **15–17** in good yields and TONs of 910–1000 (Table 2, entries 6, 8 and 10). On the other hand, 2-bromoacetophenone gave no coupling product (Table 2, entry 7). This is probably due to some coordination of the acetyl function to palladium. A low reactivity was observed using 2-bromotoluene. With this non-activated congested substrate, the product **20** was obtained in 42% yield using 1 mol% catalyst (Table 2, entry 11). This lower reactivity probably comes from

Table 3 Reaction of 2-*n*-butylthiophene with heteroaryl bromides (Scheme 3)

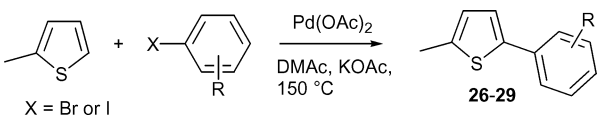
Entry	Heteroaryl bromide	Substrate/ cat. ratio	Prod.	Yield (%)
1	3-Bromopyridine	1000	**22**	100 (91)
2	3-Bromopyridine	10000	**22**	53
3	3-Bromoquinoline	1000	**23**	100 (90)
4	3-Bromoquinoline	10000	**23**	23
5	5-Bromopyrimidine	1000	**24**	100 (88)
6	2-Bromo-5-methylthiophene	100	**25**	0
7	2-Bromo-5-methylthiophene	1000	**25**	0

Conditions: $Pd(OAc)_2$, heteroaryl bromide (1 mmol), 2-*n*-butylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

a slow oxidative addition to palladium. On the other hand, the di-*ortho*-substituted 2,6-difluorobromobenzene gave the target conpound **21** in good yield using only 0.1 mol% catalyst (Table 2, entry 12).

Palladium chemistry involving heterocycles has its unique characteristics stemming from the heterocycles' inherently different structural and electronic properties in comparison to the corresponding carbocyclic aryl compounds.[1] Pyridines, quinolines or pyrimidines are π-electron deficient heterocycles, while thiophenes or furans are π-electron excessive. If the oxidative addition of the aryl bromides to the palladium complex is the rate-limiting step of the reaction with this catalyst, the reactions should be slower with thiophenes or furans than with pyridines. We observed that the coupling of 3-bromopyridine, 3-bromoquinoline or 5-bromopyrimidine proceeded nicely using only 0.1–0.01 mol% catalyst and gave **22–24** in 88–91% yields (Table 3, entries 1–5). On the other hand, 2-bromo-5-methylthiophene gave no coupling product **25** using 0.1 or 1 mol% catalyst (Table 3, entries 6 and 7). This result seems to confirm that the oxidative addition of the aryl bromide to palladium is the rate-limiting step of the catalytic cycle with this catalyst. With such challenging substrates, palladium associated to phosphine ligands should be prefered as catalysts.[7c]

Then, we examined the reactivity of 2-methylthiophene (Scheme 4, Table 4). Due to its very similar electronic and steric properties with 2-*n*-butylthiophene, we expected to obtain similar reaction rates with this substrate. Indeed, we observed almost identical TONs. 4-Bromobenzaldehyde and 4-bromobenzonitrile gave **26** and **27** in 2800 and 2300 TONs, respectively (Table 4, entries 1–4). 4-Fluorobromobenzene was slighly less reactive (Table 4, entry 5). Again, only a partial conversion of 4-bromoanisole was observed to give **29** in 41% isolated yield (Table 4, entry 6).



Scheme 4

The functionalised thiophene, thiophene-2-carbonitrile can also be employed with this ligand-less palladium procedure (Scheme 5, Table 5). When this substrate was reacted with 4-bromoacetophenone it gave very selectively the expected

Table 4 Reaction of 2-methylthiophene with aryl bromides (Scheme 4)

Entry	Aryl bromide	Substrate/ catalyst ratio	Prod.	Yield (%)
1	4-Bromobenzaldehyde	1000	**26**	100 (89)
2	4-Bromobenzaldehyde	10000	**26**	28
3	4-Bromobenzonitrile	1000	**27**	100 (92)
4	4-Bromobenzonitrile	10000	**27**	23
5	4-Bromofluorobenzene	1000	**28**	95 (87)
6	4-Bromoanisole	1000	**29**	48 (41)

Conditions: $Pd(OAc)_2$, aryl bromide (1 mmol), 2-methylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

Table 5 Reaction of thiophene-2-carbonitrile with aryl bromides (Scheme 5)

Entry	Aryl bromide	Substrate/ catalyst ratio	Prod.	Yield (%)
1	4-Bromoacetophenone	10000	**30**	100 (80)
2	4-Bromobenzaldehyde	1000	**31**	100 (85)
3	4-Bromobenzaldehyde	10000	**31**	79
4	Methyl 4-bromobenzoate	1000	**32**	100 (87)
5	Methyl 4-bromobenzoate	10000	**32**	57
6	4-(Trifluoromethyl)-bromobenzene	10000	**33**	97 (90)
7	4-Bromobenzonitrile	1000	**34**	100 (89)
8	4-Bromobenzonitrile	10000	**34**	68
9	4-Bromofluorobenzene	10000	**35**	97 (84)
10	4-*tert*-Butylbromobenzene	1000	**36**	72 (62)
11	4-*tert*-Butylbromobenzene	10000	**36**	44
12	4-Bromoanisole	1000	**37**	87 (77)
13	4-Bromo-*N*,*N*-dimethylaniline	1000	**38**	0
14	3-Bromobenzonitrile	10000	**39**	100 (89)
15	2-Bromobenzaldehyde	1000	**40**	98 (87)
16	2-(Trifluoromethyl)-bromobenzene	10000	**41**	100 (90)
17	2-Bromobenzonitrile	10000	**42**	100 (91)
18	2-Bromoanisole	1000	**43**	0
19	3-Bromopyridine	10000	**44**	98 (86)
20	3-Bromopyridine	100000	**44**	46

Conditions: $Pd(OAc)_2$, aryl bromide (1 mmol), thiophene-2-carbonitrile (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

Scheme 5

product **30** in a very high TON of 10000 and 80% isolated yield (Table 5, entry 1). Quite similar TONs of 5700–9700 were obtained using the other electron-deficient *para*-substituted aryl bromides, 4-bromobenzaldehyde, methyl 4-bromobenzoate, 4-(trifluoromethyl)bromobenzene or 4-bromobenzonitrile (Table 5, entries 2–8). Good yields and TONs were also obtained using 4-*tert*-butylbromobenzene or 4-bromoanisole. With these two deactivated substrates, TONs of 4400 and 870 were obtained, respectively (Table 5, entries 10–12). Again, the strongly deactivated aryl bromide 4-*N*,*N*-dimethylaniline was found to be unreactive using this procedure (Table 5, entry 13). Electron-deficient *meta*- and *ortho*-substituted aryl bromides reacted with thiophene-2-carbonitrile gave **39–42** in 980–10000 TONs (Table 5, entries 14–17). On the other hand,

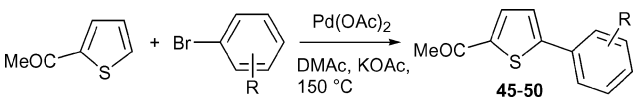
Table 6 Reaction of 2-acetylthiophene with aryl bromides (Scheme 6)

Entry	Aryl bromide	Substrate/ catalyst ratio	Prod.	Yield (%)
1	4-Bromoacetophenone	1000	**45**	91 (78)
2	Methyl 4-bromobenzoate	1000	**46**	89 (76)
3	Methyl 4-bromobenzoate	10000	**46**	36
4	4-(Trifluoromethyl)-bromobenzene	1000	**47**	94 (80)
5	4-(Trifluoromethyl)-bromobenzene	10000	**47**	81
6	4-Bromobenzonitrile	1000	**48**	90 (78)
7	4-Bromobenzonitrile	10000	**48**	15
8	4-Bromofluorobenzene	1000	**49**	92 (79)
9	4-Bromoanisole	1000	**50**	78 (63)

Conditions: $Pd(OAc)_2$, aryl bromide (1 mmol), 2-acetylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

the deactivated and congested aryl bromide: 2-bromoanisole was recovered unreacted (Table 5, entry 18).

The coupling reactions using 2-acetylthiophene were found to be less selective than those in the presence of 2-alkylthiophenes or thiophene-2-carbonitrile. With this substrate, the formation of some side-products was observed with most aryl bromides, mostly due to some arylation of the acetyl function. Therefore, the isolated yields of desired products **45–50** were slightly lower (Scheme 6, Table 6). However, also with this substrate, the reactions can be performed using only 0.1–0.01 mol% catalyst when using electron-poor aryl bromides (Table 6, entries 1–7). For the coupling of 4-fluorobromobenzene or 4-bromoanisole, we used 0.1 mol% catalyst (Table 6, entries 8 and 9).



Scheme 6

Then, we employed 2-acetylthiophene ethylene acetal as coupling partner (Scheme 7, Table 7). This reactant is commercially available on large scale at an affordable cost. With this substrate, we expected to reduce the formation of side-products. Moreover, the direct access to protected 5-aryl-2-acetylthiophenes might be very convenient in total synthesis. We observed that, in all cases, the desired 5-arylated thiophenes were obtained very cleanly. Almost no side-products were formed in the presence of this reactant. Using *para*-substituted electron-deficient aryl bromides, the compounds **51–54** were obtained in 2800–9800 TONs (Table 7, entries 1–7). 4-*tert*-Butylbromobenzene or 4-bromoanisole gave **55** and **56** in lower TONs of 620 and 810, respectively (Table 7, entries 8 and 9). The *ortho*-substituted 2-bromobenzaldehyde, 2-bromobenzonitrile or 1-bromonaphthalene also gave the expected 5-arylation products **57–59** using only 0.1–0.01 mol% catalyst (Table 7, entries 10–14). In the presence of the same catalyst loadings, heteroaromatic substrates, 3-bromopyridine or 4-bromoisoquinoline gave **60** and **61** in very high yields (Table 7, entries 15–17). 2-Formylthiophene reacted with a variety of aryl bromides gave the desired products **62–68** in 31–78% isolated yields using 0.1 mol% catalyst (Scheme 8, Table 8). The formation of a small

Table 7 Reaction of 2-acetylthiophene ethylene acetal with aryl bromides (Scheme 7)

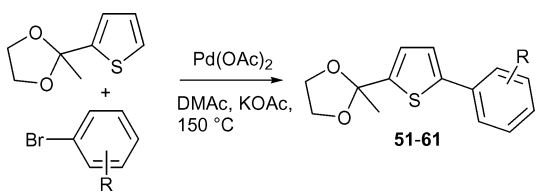
Entry	Aryl bromide	Substrate/ catalyst ratio	Prod.	Yield (%)
1	4-Bromobenzaldehyde	1000	**51**	100 (89)
2	4-Bromobenzaldehyde	10000	**51**	53
3	4-(Trifluoromethyl)-bromobenzene	10000	**52**	98 (87)
4	4-Bromobenzonitrile	1000	**53**	100 (89)
5	4-Bromobenzonitrile	10000	**53**	39
6	4-Bromofluorobenzene	1000	**54**	100 (88)
7	4-Bromofluorobenzene	10000	**54**	28
8	4-*tert*-Butylbromobenzene	1000	**55**	62 (56)
9	4-Bromoanisole	1000	**56**	81 (72)
10	2-Bromobenzaldehyde	1000	**57**	100 (88)
11	2-Bromobenzaldehyde	10000	**57**	16
12	2-Bromobenzonitrile	1000	**58**	100 (90)
13	1-Bromonaphthalene	10000	**59**	100 (87)
14	1-Bromonaphthalene	1000	**59**	74
15	3-Bromopyridine	1000	**60**	100 (91)
16	3-Bromopyridine	10000	**60**	50
17	4-Bromoisoquinoline	1000	**61**	100 (88)

Conditions: $Pd(OAc)_2$, aryl bromide (1 mmol), 2-acetylthiophene ethylene acetal (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.

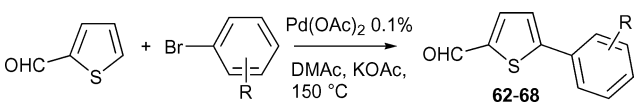
Table 8 Reaction of 2-formylthiophene with aryl bromides (Scheme 8)

Entry	Aryl bromide	Prod.	Yield (%)
1	4-Bromobenzaldehyde	**62**	78 (67)
2	4-(Trifluoromethyl)-bromobenzene	**63**	85 (77)
3	4-Bromobenzonitrile	**64**	96 (78)
4	4-Bromofluorobenzene	**65**	95 (76)
5	4-*tert*-Butylbromobenzene	**66**	40 (31)
6	4-Bromoanisole	**67**	78 (68)
7	3-Bromopyridine	**68**	72 (65)

Conditions: $Pd(OAc)_2$ (0.001 mmol), aryl bromide (1 mmol), 2-formylthiophene (2 mmol), KOAc (2 mmol), DMAc, 20 h, 150 °C, GC and NMR yields, yields in parentheses are isolated.



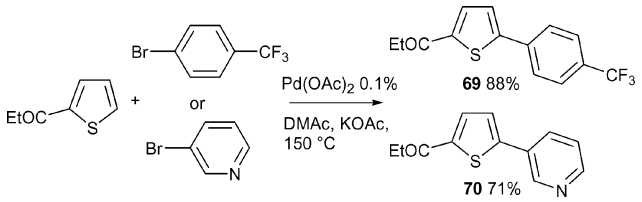
Scheme 7



Scheme 8

amount of unidentified side-products was observed in all cases thus lowering the yields. Again, electron-deficient aryl bromides generally gave higher yields than the electron-rich ones.

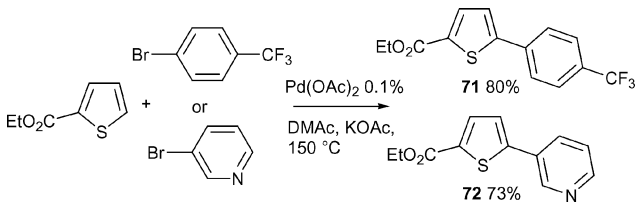
As expected, 2-propionylthiophene gave quite similar results than 2-acetylthiophene (Scheme 9). The formation of lower amounts of side-products than with 2-acetylthiophene was observed. The reaction of 2-propionylthiophene with 4-(trifluoromethyl)bromobenzene or 3-bromopyridine gave



Scheme 9

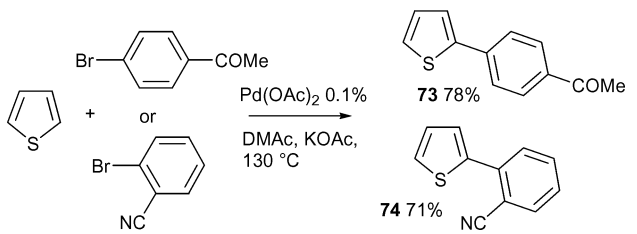
69 and **70** in 88 and 71% yields, respectively, employing 0.1 mol% catalyst.

Next, a thiophene substituted by an ester function in 2 position was employed (Scheme 10). Ethyl 2-thiophenecarboxylate coupled with 4-(trifluoromethyl)bromobenzene or 3-bromopyridine gave **71** and **72** in good yields using again only 0.1 mol% catalyst.



Scheme 10

Finally, thiophene was employed as reactant (Scheme 11). Using 4-bromoacetophenone or sterically hindered 2-bromobenzonitrile in the presence of as little as 0.1 mol% $Pd(OAc)_2$, the compounds **73** and **74** were obtained in 78 and 71% yields, respectively.



Scheme 11

Conclusions

We have demonstrated that, using this ligand-free procedure, the direct 5-arylation *via* C–H bond activation of thiophene derivatives proceeded in moderate to very high yields. In the presence of as little as 0.1–0.001 mol% of $Pd(OAc)_2$ as catalyst precursor, a wide range of aryl bromides were selectively arylated. With this ligand-free procedure, an increase of the catalyst loading to 1 mol% generally led more rapidly to aggregation of palladium to form so-called "palladium black" and gave lower yields of coupling products. This procedure gave the best results using electron-deficient aryl bromides, and several functions such as acetyl, benzoyl, nitro, nitrile, fluoro or trifluoromethyl are tolerated. Deactivated or congested aryl bromides also gave satisfactory results in some cases. Several functions on the thiophene derivative are also tolerated. This ligand-less low catalyst loading procedure is economically and environmentally attractive. There is no need to eliminate phosphine derivatives at the end of the reaction. Under such low catalyst concentration, palladium stabilizing agents such as ammonium salts, are useless, thus reducing the amount of wastes. With this C–H activation procedure, no preparation of an organometallic derivative is required, reducing the number of steps and therefore the mass of waste product to prepare these compounds, compared to Negishi, Stille or Suzuki type coupling reactions. Moreover, as it should be possible to recover most of DMAc, the major waste is the relatively non-toxic AcOH/KBr instead of metallic salts with more classical coupling procedures. For these reasons, the methodology developed here is very promising for the sustainable synthesis of 5-arylthiophenes.

Experimental section

General procedure

As a typical experiment, the reaction of the aryl halide (1 mmol), thiophene derivative (2 mmol) and KOAc (0.196 g, 2 mmol) at 150 °C during 20 h in dry DMAc (3 mL) in the presence of $Pd(OAc)_2$ under argon affords the corresponding coupling product after extraction with dichloromethane, evaporation and filtration on silica gel: pentane/ether: 1/4 or ether for compounds **10**, **22**, **23**, **24**, **38**, **44**, **60**, **61** and **68**.

2-*n*-Butyl-5-phenylthiophene[7a] (1). Iodobenzene (0.204 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **1** in 46% (0.100 g) yield.

4-(5-*n*-Butylthiophen-2-yl)acetophenone[7a] (2). 4-Bromo-acetophenone (0.199 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **2** in 85% (0.220 g) yield.

4-(5-*n*-Butylthiophen-2-yl)benzophenone[7a] (3). 4-Bromobenzophenone (0.261 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **3** in 86% (0.275 g) yield.

4-(5-*n*-Butylthiophen-2-yl)benzaldehyde[7a] (4). 4-Bromo-benzaldehyde (0.185 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **4** in 89% (0.217 g) yield.

2-*n*-Butyl-5-[4-(trifluoromethyl)phenyl]thiophene[7a] (5). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **5** in 90% (0.256 g) yield.

4-(5-*n*-Butylthiophen-2-yl)benzonitrile[7a] (6). 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) and KOAc (0.196 g, 2 mmol) affords **6** in 88% (0.212 g) yield.

2-*n*-Butyl-5-(4-fluorophenyl)thiophene (7). 4-Bromofluorobenzene (0.175 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) and KOAc (0.196 g, 2 mmol) affords **7** in 81% (0.190 g) yield.

2-*n*-Butyl-5-*p*-tolylthiophene (8). 4-Bromotoluene (0.171 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **8** in 67% (0.154 g) yield.

2-*n*-Butyl-5-(4-methoxyphenyl)thiophene[7a] (9). 4-Bromoanisole (0.187 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) **9** in 62% (0.153 g) yield.

3-(5-*n*-Butylthiophen-2-yl)benzaldehyde (11). 3-Bromo-benzaldehyde (0.185 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **11** in 88% (0.215 g) yield.

3-(5-*n*-Butylthiophen-2-yl)acetophenone (12). 3-Bromo-acetophenone (0.199 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **12** in 91% (0.235 g) yield.

2-*n*-Butyl-5-[3-(trifluoromethyl)phenyl]thiophene (13). 3-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **13** in 93% (0.264 g) yield.

2-[3,5-Bis(trifluoromethyl)phenyl]-5-*n*-butylthiophene (14). 3,5-Bis(trifluoromethyl)bromobenzene (0.293 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **14** in 90% (0.317 g) yield.

2-(5-*n*-Butylthiophen-2-yl)benzaldehyde (15). 2-Bromo-benzaldehyde (0.185 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **15** in 84% (0.205 g) yield.

2-*n*-Butyl-5-[2-(trifluoromethyl)phenyl]thiophene[7a] (17). 2-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **17** in 92% (0.262 g) yield.

2-(5-Butylthiophene-2-yl)benzonitrile (18). 2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **18** in 67% (0.162 g) yield.

2-*n*-Butyl-5-(naphthalen-1-yl)thiophene[7a] (19). 1-Bromonaphthalene (0.207 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **19** in 87% (0.232 g) yield.

2-Butyl-5-*o*-tolylthiophene[7a] (20). 2-Bromotoluene (0.171 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **20** in 42% (0.097 g) yield.

2-*n*-Butyl-5-(2,6-difluorophenyl)thiophene (21). 2,6-Difluorobromobenzene (0.193 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **21** in 86% (0.217 g) yield.

3-(5-*n*-Butylthiophen-2-yl)pyridine[7a] (22). 3-Bromopyridine (0.158 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **22** in 91% (0.198 g) yield.

3-(5-*n*-Butylthiophen-2-yl)quinoline[7a] (23). 3-Bromoquinoline (0.208 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **23** in 90% (0.240 g) yield.

5-(5-*n*-Butylthiophen-2-yl)pyrimidine (24). 5-Bromopyrimidine (0.159 g, 1 mmol) and 2-*n*-butylthiophene (0.280 g, 2 mmol) affords **24** in 88% (0.192 g) yield.

4-(5-Methylthiophen-2-yl)benzaldehyde (26). 4-Bromobenzaldehyde (0.185 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) affords **26** in 89% (0.180 g) yield.

4-(5-Methylthiophen-2-yl)benzonitrile (27). 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) affords **27** in 92% (0.183 g) yield.

2-(4-Fluorophenyl)-5-methylthiophene (28). 4-Bromofluorobenzene (0.175 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) affords **28** in 87% (0.168 g) yield.

2-(4-Methoxyphenyl)-5-methylthiophene[17a] (29). 4-Bromoanisole (0.187 g, 1 mmol) and 2-methylthiophene (0.196 g, 2 mmol) affords **29** in 41% (0.084 g) yield.

5-(4-Acetylphenyl)thiophene-2-carbonitrile (30). 4-Bromoacetophenone (0.199 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **30** in 80% (0.182 g) yield.

5-(4-Formylphenyl)thiophene-2-carbonitrile (31). 4-Bromobenzaldehyde (0.185 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **31** in 85% (0.181 g) yield.

Methyl 4-(5-cyanothiophen-2-yl)benzoate (32). Methyl 4-bromobenzoate (0.215 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **32** in 87% (0.212 g) yield.

5-[4-(Trifluoromethyl)phenyl]thiophene-2-carbonitrile[7a] (33). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **33** in 90% (0.228 g) yield.

5-(4-Cyanophenyl)thiophene-2-carbonitrile[17b] (34). 4-Bromobenzonitrile (0.182 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **34** in 89% (0.187 g) yield.

5-(4-Fluorophenyl)thiophene-2-carbonitrile[7a] (35). 4-Bromofluorobenzene (0.175 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **35** in 84% (0.171 g) yield.

5-(4-*tert*-Butylphenyl)thiophene-2-carbonitrile[7a] (36). 4-*tert*-Butylbromobenzene (0.213 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **36** in 62% (0.150 g) yield.

5-(4-Methoxyphenyl)thiophene-2-carbonitrile[7a] (37). 4-Bromoanisole (0.187 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **37** in 77% (0.166 g) yield.

5-(3-Cyanophenyl)thiophene-2-carbonitrile (39). 3-Bromobenzonitrile (0.182 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **39** in 89% (0.187 g) yield.

5-(2-Formylphenyl)thiophene-2-carbonitrile (40). 2-Bromobenzaldehyde (0.185 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **40** in 87% (0.186 g) yield.

5-(2-Trifluoromethylphenyl)thiophene-2-carbonitrile[7a] (41). 2-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **41** in 90% (0.228 g) yield.

5-(2-Cyanophenyl)thiophene-2-carbonitrile (42). 2-Bromobenzonitrile (0.182 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **42** in 91% (0.191 g) yield.

5-(Pyridin-3-yl)thiophene-2-carbonitrile (44). 3-Bromopyridine (0.158 g, 1 mmol) and thiophene 2-carbonitrile (0.218 g, 2 mmol) affords **44** in 86% (0.160 g) yield.

1-[4-(5-Acetylthiophen-2-yl)phenyl]ethanone[17c] (45). 4-Bromoacetophenone (0.199 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **45** in 78% (0.191 g) yield.

Methyl 4-(5-acetylthiophen-2-yl)benzoate[17d] (46). Methyl 4-bromobenzoate (0.215 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **46** in 76% (0.198 g) yield.

1-{5-[4-(Trifluoromethyl)phenyl]thiophen-2-yl}ethanone[7a] (47). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **47** in 80% (0.216 g) yield.

4-(5-Acetylthiophen-2-yl)benzonitrile[7a] (48). 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **48** in 78% (0.177 g) yield.

1-[5-(4-Fluorophenyl)thiophen-2-yl]ethanone[7a] (49). 4-Bromofluorobenzene (0.175 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **49** in 79% (0.174 g) yield.

1-[5-(4-Methoxyphenyl)thiophen-2-yl]ethanone[17e] (50). 4-Bromoanisole (0.187 g, 1 mmol) and 2-acetylthiophene (0.252 g, 2 mmol) affords **50** in 63% (0.146 g) yield.

4-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzaldehyde (51). 4-Bromobenzaldehyde (0.185 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **51** in 89% (0.244 g) yield.

2-Methyl-2-{5-[4-(trifluoromethyl)phenyl]thiophen-2-yl}-1,3-dioxolane (52). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **52** in 87% (0.273 g) yield.

4-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzonitrile (53). 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **53** in 89% (0.242 g) yield.

2-[5-(4-Fluorophenyl)thiophen-2-yl]-2-methyl-1,3-dioxolane (54). 4-Bromofluorobenzene (0.175 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **54** in 88% (0.233 g) yield.

2-[5-(4-*tert*-Butylphenyl)thiophen-2-yl]-2-methyl-1,3-dioxolane (55). 4-*tert*-Butylbromobenzene (0.213 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **55** in 56% (0.169 g) yield.

2-[5-(4-Methoxyphenyl)thiophen-2-yl]-2-methyl-1,3-dioxolane (56). 4-Bromoanisole (0.187 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **56** in 72% (0.199 g) yield.

2-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzaldehyde (57). 2-Bromobenzaldehyde (0.185 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **57** in 88% (0.241 g) yield.

2-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]benzonitrile (58). 2-Bromobenzonitrile (0.182 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **58** in 90% (0.244 g) yield.

2-Methyl-2-(5-naphthalen-1-yl)thiophen-2-yl)-1,3-dioxolane (59). 1-Bromonaphthalene (0.207 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **59** in 87% (0.258 g) yield.

3-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]pyridine (60). 3-Bromopyridine (0.158 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **60** in 91% (0.225 g) yield.

4-[5-(2-Methyl-1,3-dioxolan-2-yl)thiophen-2-yl]isoquinoline (61). 4-Bromoisoquinoline (0.208 g, 1 mmol) and 2-acetylthiophene ethylene acetal (0.340 g, 2 mmol) affords **61** in 88% (0.262 g) yield.

5-(4-Formylphenyl)thiophene-2-carbaldehyde[17f] (62). 4-Bromobenzaldehyde (0.185 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **62** in 67% (0.145 g) yield.

5-[4-(Trifluoromethyl)phenyl]thiophene-2-carbaldehyde[17g] (63). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **63** in 77% (0.197 g) yield.

4-(5-Formylthiophen-2-yl)benzonitrile[17h] (64). 4-Bromobenzonitrile (0.182 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **64** in 78% (0.166 g) yield.

5-(4-Fluorophenyl)thiophene-2-carbaldehyde[17i] (65). 4-Bromofluorobenzene (0.175 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **65** in 76% (0.157 g) yield.

5-(4-*tert*-Butyl-phenyl)thiophene-2-carbaldehyde (66). 4-*tert*-Butylbromobenzene (0.213 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **66** in 31% (0.076 g) yield.

5-(4-Methoxyphenyl)thiophene-2-carbaldehyde[10] (67). 4-Bromoanisole (0.187 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **67** in 68% (0.149 g) yield.

5-(Pyridin-3-yl)thiophene-2-carbaldehyde[17j] (68). 3-Bromopyridine (0.158 g, 1 mmol) and 2-formylthiophene (0.224 g, 2 mmol) affords **68** in 65% (0.123 g) yield.

1-{5-[4-(Trifluoromethyl)phenyl]thiophen-2-yl}propan-1-one (69). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and 2-propionylthiophene (0.280 g, 2 mmol) affords **69** in 88% (0.250 g) yield.

1-[5-(Pyridin-3-yl)thiophen-2-yl]propan-1-one (70). 3-Bromopyridine (0.158 g, 1 mmol) and 2-propionylthiophene (0.280 g, 2 mmol) affords **70** in 71% (0.154 g) yield.

Ethyl 5-[4-trifluoromethyl)phenyl]thiophene-2-carboxylate (71). 4-(Trifluoromethyl)bromobenzene (0.225 g, 1 mmol) and ethyl 2-thiophenecarboxylate (0.312 g, 2 mmol) affords **71** in 80% (0.240 g) yield.

Ethyl 5-(pyridin-3-yl)thiophene-2-carboxylate (72). 3-Bromopyridine (0.158 g, 1 mmol) and ethyl 2-thiophenecarboxylate (0.312 g, 2 mmol) affords **72** in 73% (0.170 g) yield.

1-(4-Thiophen-2-ylphenyl)-ethanone (73)[17k]. 4-Bromoacetophenone (0.199 g, 1 mmol) and thiophene (0.420 g, 5 mmol) affords **73** in 78% (0.158 g) yield.

2-Thiophen-2-yl-benzonitrile (74)[17l]. 2-Bromobenzonitrile (0.182 g, 1 mmol) and thiophene (0.420 g, 5 mmol) affords **74** in 71% (0.132 g) yield.

Acknowledgements

This research was supported by a Marie Curie Intra-European Fellowships within the 6th European Community Framework Programme. J. R. is grateful to "Ministère de la Recherche" for a grant. We thank P. H. Dixneuf for useful discussions.

Notes and references

1 J. J. Li and G. W. Gribble, *Palladium in Heterocyclic Chemistry*, Pergamon, Amsterdam, 2000.

2 (*a*) I. Kondolff, H. Doucet and M. Santelli, *Synlett*, 2005, 2057; (*b*) N. Kuhnert, C. Patel and F. Jami, *Tetrahedron Lett.*, 2005, **46**, 7575; (*c*) S. P. G. Costa, R. M. F. Batista, P. Cardoso, M. Belsley and M. M. M. Raposo, *Eur. J. Org. Chem.*, 2006, 3938; (*d*) A. N. Cammidge, V. H. M. Goddard, H. Gopee, N. L. Harrison, D. L. Hughes, C. J. Schubert, B. M. Sutton, G. L. Watts and A. J. Whitehead, *Org. Lett.*, 2006, **8**, 4071; (*e*) J.-H. Li, Q.-M. Zhu and Y.-X. Xie, *Tetrahedron*, 2006, **62**, 10888; (*f*) V. Promarak, A. Pankvuang and S. Ruchirawat, *Tetrahedron Lett.*, 2007, **48**, 1151; (*g*) C.-L. Deng, S.-M. Guo, Y.-X. Xie and J.-H. Li, *Eur. J. Org. Chem.*, 2007, 1457; (*h*) L. M. Klingensmith, M. M. Bio and G. A. Moniz, *Tetrahedron Lett.*, 2007, **48**, 8242; (*i*) D. P. Hagberg, T. Marinado, K. M. Karlsson, K. Nonomura, P. Qin, G. Boschloo, T. Brinck, A. Hagfeldt and L. Sun, *J. Org. Chem.*, 2007, **72**, 9550; (*j*) E. Paunescu, N. Matuszak and P. Melnyk, *Tetrahedron*, 2007, **63**, 12791; (*k*) I. Kondolff, H. Doucet and M. Santelli, *J. Het. Chem.*, 2008, **45**, 109.

3 (*a*) C. Fave, Y. Leroux, G. Trippe, H. Randriamahazaka, V. Noel and J.-C. Lacroix, *J. Am. Chem. Soc.*, 2007, **129**, 1890; (*b*) D. Kim, J. K. Lee, S. O. Kang and J. Ko, *Tetrahedron*, 2007, **63**, 1913; (*c*) N. Negishi, Y. Ie, M. Taniguchi, T. Kawai, H. Tada, T. Kaneda and Y. Aso, *Org. Lett.*, 2007, **9**, 829; (*d*) J. Ohshita, S. Kangai, H. Yoshida, A. Kunai, S. Kajiwara, Y. Ooyama and Y. Harima, *J. Organomet. Chem.*, 2007, **692**, 801; (*e*) J. Ohshita, S. Kangai, Y. Tada, H. Yoshida, K. Sakamaki, A. Kunai and Y. Kunugi, *J. Organomet. Chem.*, 2007, **692**, 1020; (*f*) A. Pietrangelo, M. J. MacLachlan, M. O. Wolf and B. O. Patrick, *Org. Lett.*, 2007, **9**, 3571; (*g*) P.-L. T. Boudreault, S. Wakim, N. Blouin, M. Simard, C. Tessier, Y. Tao and M. Leclerc, *J. Am. Chem. Soc.*, 2007, **129**, 9125; (*h*) C. Zhao, Y. Zhang and M.-K. Ng, *J. Org. Chem.*, 2007, **72**, 6364; (*i*) M. Endou, Y. Ie, T. Kaneda and Y. Aso, *J. Org. Chem.*, 2007, **72**, 2659; (*j*) X. Zhang, Y. Qu, L. Bu, H. Tian, J. Zhang, L. Wang, Y. Geng and F. Wang, *Chem. Eur. J.*, 2007, **13**, 6238; (*k*) S. Lois, J.-C. Flores, J.-P. Lere-Porte, F. Serein-Spirau, J. J. E. Moreau, K. Miqueu, J.-M. Sotiropoulos, P. Baylere, M. Tillard and C. Belin, *Eur. J. Org. Chem.*, 2007, 4019.

4 (*a*) B. Betzemeier and P. Knochel, *Angew. Chem. Int. Ed. Eng.*, 1997, **36**, 2623; (*b*) J. Sirieix, M. Ossberger, B. Betzemeier and P. Knochel, *Synlett*, 2000, 1613; (*c*) M. Iyoda, K. Nakao, T. Kondo, Y. Kuwatani, M. Yoshida, H. Matsuyama, K. Fukami and S. Nagase, *Tetrahedron Lett.*, 2001, **42**, 6869; (*d*) W.-L. Jia, D.-R. Bai, T. McCormick, Q.-D. Liu, M. Motala, R.-Y. Wang, C. Seward, Y. Tao and S. Wang, *Chem. Eur. J.*, 2004, **10**, 994; (*e*) F. F. Kneisel, M. Dochnahl and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 1017; (*f*) K. Krascsenicsova, P. Walla, P. Kasak, G. Uray, C. O. Kappe and M. Putala, *Chem. Commun.*, 2004, 2606.

5 A. Ohta, Y. Akita, T. Ohkuwa, M. Chiba, R. Fukunaga, A. Miyafuji, T. Nakata, N. Tani and Y. Aoyagi, *Heterocycles*, 1990, **31**, 1951.

6 (*a*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (*b*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (*c*) T. Satoh and M. Miura, *Chem. Lett.*, 2007, **36**, 200; (*d*) H. Doucet and J. C. Hierso, *Curr. Opin. Drug Discov. Devel.*, 2007, **10**, 672; (*e*) L.-C. Campeau, D. R. Stuart and K. Fagnou, *Aldrichimica Acta*, 2007, **40**, 35.

7 (*a*) A. Battace, M. Lemhadri, T. Zair, H. Doucet and M. Santelli, *Adv. Synth. Catal.*, 2007, **349**, 2507; (*b*) J. Roger and H. Doucet, *Org. Biomol. Chem.*, 2008, **6**, 169; (*c*) F. Derridj, A. L. Gottumukkala, S. Djebbar and H. Doucet, *Eur. J. Inorg. Chem.*, 2008, 2550.

8 For direct 2- or 5-arylations of thiophenes using palladium associated to monophosphine ligands: (*a*) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467; (*b*) R. R. Hark, D. B. Hauze, O. Petrovskaia and M. M. Joullie, *Can. J. Chem.*, 2001, **79**, 1632; (*c*) T. Okazawa, T. Satoh, M. Miura and M. Nomura, *J. Am. Chem. Soc.*, 2002, **124**, 5286; (*d*) B. Glover, K. A. Harvey, B. Liu, M. J. Sharp and M. F. Tymoschenko, *Org. Lett.*, 2003, **5**, 301; (*e*) C. W. G. Fishwick, R. Grigg, V. Sridharan and J. Virica, *Tetrahedron*, 2003, **59**, 4451; (*f*) A. Yokooji, T. Satoh, M. Miura and M. Nomura, *Tetrahedron*, 2004, **60**, 6757; (*g*) E. M. Beccalli, G. Broggini, M. Martinelli, G. Paladino and C. Zoni, *Eur. J. Org. Chem.*, 2005, 2091; (*h*) K. Kobayashi, A. Sugie, M. Takahashi, K. Masui and A. Mori, *Org. Lett.*, 2005, **7**, 5083; (*i*) L. Joucla, A. Putey and B. Joseph, *Tetrahedron Lett.*, 2005, **46**, 8177; (*j*) M. Nakano, T. Satoh and M. Miura, *J. Org. Chem.*, 2006, **71**, 8309; (*k*) J. Fournier, Dit Chabert, G. Chatelain, S. Pellet-Rostaing, D. Bouchu and M. Lemaire, *Tetrahedron Lett.*, 2006, **47**, 1015; (*l*) A. Martins, D. Alberico and M. Lautens, *Org. Lett.*, 2006, **8**, 4827; (*m*) K. Kobayashi, M. S. Mohamed, Ahmed and A. Mori, *Tetrahedron*, 2006, **62**, 9548; (*n*) A. K. Mohanakrishnan, P. Amaladass and J. A. Clement, *Tetrahedron Lett.*, 2007, **48**, 539; (*o*) H. A. Chiong and O. Daugulis, *Org. Lett.*, 2007, **9**, 1449; (*p*) E. David, S. Pellet-Rostaing and M. Lemaire, *Tetrahedron*, 2007, **63**, 8999; (*q*) P. Amaladass, J. A. Clement and A. K. Mohanakrishnan, *Tetrahedron*, 2007, **63**, 10363; (*r*) H. Ohno, M. Iuchi, N. Fujii and T. Tanaka, *Org. Lett.*, 2007, **9**, 4813; (*s*) S. H. Wunderlich and P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7685; (*t*) G. L. Turner, J. A. Morris and M. F. Greaney, *Angew. Chem. Int. Ed.*, 2007, **46**, 7996; (*u*) E. David, J. Lejeune, S. Pellet-Rostaing, J. Schulz, M. Lemaire, J. Chauvin and A. Deronzier, *Tetrahedron Lett.*, 2008, **49**, 1860.

9 For direct 2- or 5-arylations of thiophenes using palladium associated to diphosphine ligands: (*a*) K. Masui, A. Mori, K. Okano, K. Takamura, M. Kinoshita and T. Ikeda, *Org. Lett.*, 2004, **6**, 2011; (*b*) K. Masui, H. Ikegami and A. Mori, *J. Am. Chem. Soc.*, 2004, **126**, 5074.

10 I. C. F. R. Ferreira, M.-J. R. P. Queiroz and G. Kirsch, *Tetrahedron*, 2003, **59**, 3737.

11 For direct 2- or 5-arylations of thiophenes using $Pd(OAc)_2$ and an ammonium salt: (*a*) L. Lavenot, C. Gozzi, K. Ilg, I. Orlova, V. Penalva and M. Lemaire, *J. Organomet. Chem.*, 1998, **567**, 49; (*b*) M. Smet, J. Van, Dijk and W. Dehaen, *Synlett*, 1999, 495; (*c*) J. Fournier, Dit Chabert, C. Gozzi and M. Lemaire, *Tetrahedron Lett.*, 2002, **43**, 1829; (*d*) J. Fournier, Dit Chabert, L. Joucla, E. David and M. Lemaire, *Tetrahedron*, 2004, **60**, 3221; (*e*) A. Borghese, G. Geldhof and L. Antoine, *Tetrahedron Lett.*, 2006, **47**, 9249; (*f*) S. H. Mashraqui, M. Ashraf and S. G. Ghadigaonkar, *Synlett*, 2006, 2423; (*g*) K. Mitsudo, P. Thansandote, T. Wilhelm, B. Mariampillai and M. Lautens, *Org. Lett.*, 2006, **8**, 3939.

12 (*a*) E. David, J. Perrin, S. Pellet-Rostaing, J. Fournier, dit Chabert and M. Lemaire, *J. Org. Chem.*, 2005, **70**, 3569; (*b*) E. David, C. Rangheard, S. Pellet-Rostaing and M. Lemaire, *Synlett*, 2006, 2016.

13 (*a*) A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org. Lett.*, 2003, **5**, 3285; (*b*) M. T. Reetz and J. G. de Vries, *Chem. Commun.*, 2004, 1559; (*c*) J. G. de Vries, *Dalton Trans.*, 2006, 421.

14 A. Alimardanov, L. Schmieder-van, de Vondervoort, A. H. M. de Vries and J. G. de Vries, *Adv. Synth. Catal.*, 2004, **346**, 1812.

15 (*a*) A. Battace, M. Lemhadri, T. Zair, H. Doucet and M. Santelli, *Organometallics*, 2007, **26**, 472; (*b*) A. L. Gottumukkala and H. Doucet, *Adv. Synth. Catal.*, 2008, **350**, 2183; (*c*) A. L. Gottumukkala and H. Doucet, *Eur. J. Inorg. Chem.*, 2007, 3629; (*d*) F. Derridj, S. Djebbar, O. Benali-Baitich and H. Doucet, *J. Organomet. Chem.*, 2008, **693**, 135; (*e*) A. L. Gottumukkala, F. Derridj, S. Djebbar and H. Doucet, *Tetrahedron Lett.*, 2008, **49**, 2926.

16 F. Požgan, J. Roger and H. Doucet, *ChemSusChem*, 2008, **1**, 404.

17 (*a*) D. R. Shridhar, M. Jogibhukta, P. S. Rao and V. K. Handa, *Synthesis*, 1982, 1061; (*b*) V. Tralic-Kulenovic, G. Karminski-Zamola, L. Racane and L. Fiser-Jakic, *Heterocyclic Commun.*, 1998, **4**, 423; (*c*) E. L. Anderson, J. E. Casey, Jr., M. Emas, E. E. Force, E. M. Jensen, R. S. Matz and D. E. Rivard, *J. Med. Chem.*, 1963, **6**, 787; (*d*) F. F. Kneisel, M. Dochnahl and P. Knochel, *Angew. Chem. Int. Ed.*, 2004, **43**, 1017; (*e*) J. C. Meslin, Y. T. N′Guessan and H. Quiniou, *Tetrahedron*, 1975, **31**, 2679; (*f*) S. P. G. Costa, R. M. F. Batista, P. Cardoso, M. Belsley and M. M. M. Raposo, *Eur. J. Org. Chem.*, 2006, 3938; (*g*) S. Ando, J.-i. Nishida, H. Tada, Y. Inoue, S. Tokito and Y. Yamashita, *J. Am. Chem. Soc.*, 2005, **127**, 5336; (*h*) S. Mallena, M. P. H. Lee, C. Bailly, S. Neidle, A. Kumar, D. W. Boykin and W. D. Wilson, *J. Am. Chem. Soc.*, 2004, **126**, 13659; (*i*) J. C. Bussolari and D. C. Rehborn, *Org. Lett.*, 1999, **1**, 965; (*j*) T. E. Barder and S. L. Buchwald, *Org. Lett.*, 2004, **6**, 2649; (*k*) S. Sase, M. Jaric, A. Metzger, V. Malakhov and P. Knochel, *J. Org. Chem.*, 2008, **73**, 7380; (*l*) B. Sain and J. S. Jagir, *J. Org. Chem.*, 2008, **55**, 2545.

