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Direct Arylation of Thiophenes *via* Palladium-Catalysed C–H Functionalisation at Low Catalyst Loadings

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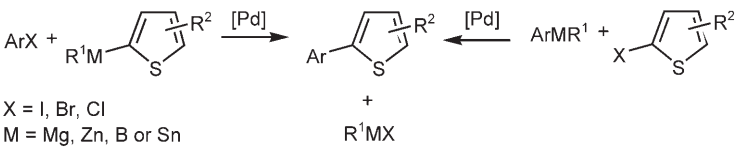
Abstract: Palladium associated with *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane (Tedicyp) was found to promote the direct 2-arylation of a variety of thiophene derivatives *via* C–H functionalisation in good yields using very low catalyst loadings. Electron-deficient, electron-excessive or sterically-congested aryl bromides are tolerated. Moreover, several substituents on the aryl bromide or thiophene derivatives such as acetyl, formyl, nitrile, nitro, ester, methoxy, fluoro or trifluoromethyl are tolerated. The most reactive aryl bromides were coupled with thiophenes derivatives using as little as 0.1–0.01 mol% catalyst.

Keywords: aryl halides; atom economy; C–H activation; palladium; thiophenes

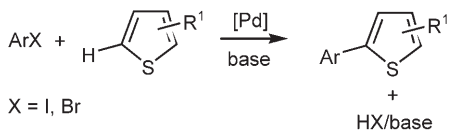
Introduction

A great deal of attention has been given to the synthesis of arylthiophenes, mainly due to the biologically or physical properties demonstrated by this class of compounds.[1] The cross-coupling reaction of thiophenes with aryl derivatives provides an efficient method for the synthesis of a wide variety of arylthiophenes. These cross-coupling reactions were generally performed using an organometallic derivative of the thiophene with an aryl halide or using an organometallic derivative of an aryl with an halothiophene 8metal = MgX,[2] ZnX,[2] SnR_3[3] $B(OR)_2$[4]] using a palladium or a nickel catalyst (Scheme 1). The major drawbacks of these reactions is that they requires the preparation of organometallic derivatives and also provides either an organometallic or a salt (MX) as by-product.

In 1990, Ohta et al. reported the direct arylation of thiophenes, furans or thiazoles with aryl halides *via* C–H activation of thiophene in medium to good yields using 5 mol% $Pd(PPh_3)_4$ as catalyst.[5] Since these exciting results, the direct arylation of heteroaryl derivatives with aryl halides has proved to be a powerful method for the synthesis of heterobiaryls (Scheme 2). Recent results such as those reported by Miura, Sanford, Fagnou, Lemaire, or Lautens have definitively demonstrated that the direct palladium-catalysed arylation of pyridines, furans, thiophenes, thiazoles, oxazoles or indoles is a very simple, efficient and environmentally friendly procedure for the preparation of heterobiaryls.[6]



Scheme 1.



Scheme 2.

The direct coupling of thiophenes with aryl halides *via* C–H activation/functionalisation at low catalyst loadings would provide a cost-effective and environmentally attractive procedure for the preparation of such compounds. A few results have already been reported for this coupling. In most cases, simple palladium salts or Pd associated with monodentate ligands were employed, and, relatively high catalysts loadings were generally employed. For example, the direct arylation of thiophene-2-carbonitrile, 2-formylthiophene or a thienothiophene with aryl iodides using 5 mol% $Pd(OAc)_2$ as catalyst and *n*-Bu_4NBr as additive led to the biaryl products in moderate to good yields.[7a,b,e] The coupling of thiophene derivatives with aryl iodides has also been described using 3 mol% $PdCl_2$ (dppb) or 5 mol% $PdCl_2(PPh_3)_2$ as catalysts and AgF or $AgNO_3$ as bases.[7c,d] The arylation of thiophenes using aryl bromides has also been described.[8] Using the monodentate electronically rich and sterically congested ligand P(*o*-biphenyl)(*t*-Bu)$_2$ and 10 mol% $Pd(OAc)_2$, Miura and co-workers have arylated phenylthiophenes, thiophene-3-carbonitrile or 2,2′-bithiophene.[8a,c,d] The arylation of methyl 3-thiophene carboxylate with 5 mol% $Pd(PPh_3)_4$ gave the 2-arylated thiophene in 67% yield using an electron-deficient aryl bromide. On the other hand, bromobenzene led to a lower yield of 52%.[8b] Finally, the regioselective 2-arylation of 3-methoxythiophene has been reported recently.[8e] The reaction was performed in DMF in the presence of KOAc, *n*-Bu_4NBr, and 10 mol% of $Pd(OAc)_2$ at 80 °C with either aryl iodide or bromide derivatives.

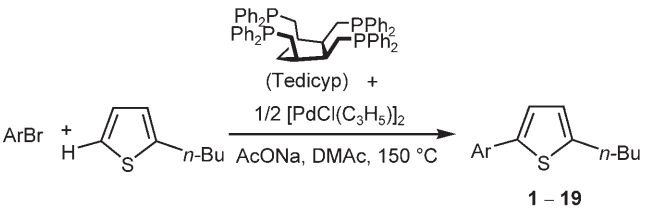
If monophosphine ligands such as PPh_3 or P(*o*-biphenyl)(*t*-Bu)$_2$ and the bidentate ligand dppb have been successfully used for the coupling of thiophene derivatives with aryl halides *via* C–H activation, to the best of our knowledge, the efficiency of polydentate ligands for such couplings has not been demonstrated. It should be noted that the reported reactions were generally performed using quite high catalyst loadings (3–10 mol%). Moreover, the presence of additives such as *n*-Bu_4NBr or expensive reagents such as AgF or $AgNO_3$ was necessary in several cases. Therefore, an effective and selective procedure, which does not require the presence of additives, allowing high substrate/catalyst ratios for the coupling of these challenging substrates with both electron-rich, electron-poor or sterically congested aryl bromides and using non-expensive bases needs to be found to provide an industrially viable process.

Results and Discussion

In order to obtain more efficient palladium catalysts we have prepared the tetrapodal phosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp (Scheme 3)[11] in which the four diphenylphosphino groups are stereospecifically bound to the same face of the cyclopentane ring. Using this ligand, very high turnover numbers (TONs) have been obtained for Suzuki, Heck, Sonogashira or Negishi cross-coupling reactions.[12,13] Recently, we also described the direct coupling of furan derivatives with a wide variety of aryl halides.[14] The palladium is shown by NMR to circulate around the 4 phosphorus atoms under the "pressure to coordinate" of the 4 phosphino groups maintained in a half-space. This "pressure to coordinate" is certainly responsible for the high TONs obtained with this catalyst both by an increase of the stability of the catalyst and by an easier reductive elimination step for several cross-coupling reactions. In this paper, we report on the efficiency of this catalytic system for the challenging coupling reaction of aryl bromides with thiophenes derivatives *via* C–H activation/functionalisation.

First, we tried to determine the best reaction conditions for the coupling of 2-*n*-butylthiophene with 4-bromoacetophenone. Using bases such as Na_2CO_3, K_2CO_3, KOH or NaOH disappointing results were obtained using the catalytic system $[PdCl(C_3H_5)]_2$/Tedicyp (0.1 mol%) in DMAc at 150 °C. In the presence of DMF or xylene as solvents low conversions were also obtained. On the other hand with AcONa as base and DMAc as solvent, a complete conversion of 4-bromoacetophenone and an high yield of product **1** was obtained using 0.1 mol% catalyst and 65% using as little as 0.01% catalyst (Table 1, Scheme 3, entries 1 and 2). It should be noted that this reaction is very selective in favour of the 5-arylation. The 3- or 4-arylated thiophenes were not observed by GC or NMR analysis of the crude mixtures.

Using these reaction conditions, we tried to determine the scope and limitations of the Tedicyp-palladium catalytic system for the arylation of 2-*n*-butylthiophene (Table 1). Several functionalised electron-rich, electron-poor *para*- or *ortho*-substituted aryl bromides have been employed. Very impressive TONs of 680–7100 were obtained using *para*-substituted electron-



Scheme 3.

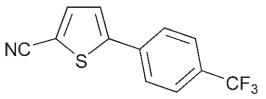
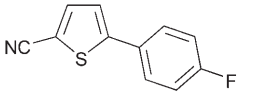
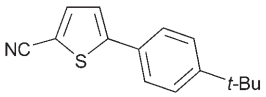
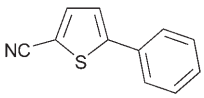
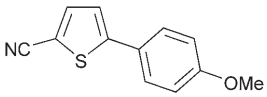
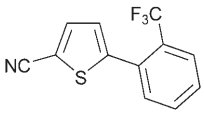
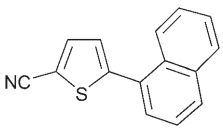
Table 1. Palladium-catalysed reaction of aryl halides with 2-*n*-butylthiophene (Scheme 3).[a]

Entry	Aryl bromide	Ratio substrate/catalyst	Product	Yield [%]
1	4-Bromoacetophenone	1000	**1**	100 (81)
2	4-Bromoacetophenone	10000	**1**	65
3	4-Bromobenzaldehyde	1000	**2**	100 (87)
4	4-Bromobenzaldehyde	10000	**2**	71
5	4-Bromobenzophenone	250	**3**	94 (79)
6	4-Bromobenzophenone	1000	**3**	68
7	Methyl 4-bromobenzoate	1000	**4**	100 (83)
8	Methyl 4-bromobenzoate	10000	**4**	24
9	4-Trifluoromethylbromobenzene	1000	**5**	100 (81)
10	4-Trifluoromethylbromobenzene	10000	**5**	60
11	4-Bromobenzonitrile	1000	**6**	100 (80)
12	4-Bromobenzonitrile	10000	**6**	50
13	4-Bromonitrobenzene	100	**7**	100 (86)
14	4-Bromonitrobenzene	1000	**7**	89
15	Iodobenzene	100	**8**	100 (80)
16	Iodobenzene	1000	**8**	43
17	4-*tert*-Butylbromobenzene	250	**9**	100 (83)
18	4-*tert*-Butylbromobenzene	1000	**9**	51
19	4-Bromoanisole	100	**10**	100 (79)
20	4-Bromoanisole	250	**10**	64
21	2-Trifluoromethylbromobenzene	100	**11**	100 (84)
22	2-Trifluoromethylbromobenzene	1000	**11**	88
23	2-Fluorobromobenzene	100	**12**	100 (87)
24	2-Fluorobromobenzene	1000	**12**	95
25	2-Bromotoluene	100	**13**	100 (79)
26	2-Bromotoluene	1000	**13**	82
27	1-Bromonaphthalene	100	**14**	100 (81)
28	1-Bromonaphthalene	1000	**14**	48
29	2,4,6-Trimethylbromobenzene	250	**15**	54 (49)
30	2,4,6-Triisopropylbromobenzene	50	**16**	39 (37)
31	3-Bromopyridine	250	**17**	100 (81)
32	3-Bromopyridine	1000	**17**	91
33	3-Bromoquinoline	250	**18**	100 (79)
34	3-Bromoquinoline	1000	**18**	55
35	4-Bromoisoquinoline	100	**19**	100 (87)
36	4-Bromoisoquinoline	250	**19**	60

[a] *Conditions:* catalyst: $[Pd(C_3H_5)Cl]_2$/Tedicyp: 1/2 see ref.[11], aryl halide: 1 mmol., 2-*n*-butylthiophene: 2 mmol., AcONa: 2 mmol., DMAc, 20 h, 150 °C, yield determined by GC and NMR, yields in parenthesis are isolated.

deficient bromoarenes such as 4-bromobenzophenone, 4-bromobenzaldehyde, 4-trifluoromethylbromobenzene or 4-bromobenzonitrile (Table 1, entries 3–14). On the other hand, the electron-rich 4-bromoanisole or 4-*tert*-butylbromobenzene gave the 5-arylation products **9** and **10** in good yields but in lower TONs of 160 and 510, respectively (Table 1, entries 17–20). With our catalyst, for the arylation of 2-*n*-butylthiophene with aryl bromides the rate-limiting step seems to be the oxidative addition of the aryl bromide to palladium. Iodobenzene was found to be quite reactive with a TON of 430 (Table 1, entries 15 and 16). The coupling of 2-*n*-butylthiophene with *ortho*-substituted aryl bromides also proceeds nicely. 4-Trifluoromethylbromobenzene, 2-fluorobromobenzene, 2-bromotoluene or 1-bromonaphthalene gave the arylated thiophene **11**–**14** in 480–950 TONs (Table 1, entries 21–28). With the Tedicyp/palladium catalyst precursor, even the sterically challenging very congested di-*ortho*-substituted 2,4,6-trimethylbromobenzene or 2,4,6-triisopropylbromobenzene led to the expected coupling products **15** and **16**, however, in lower TONs of 135 and 19 (Table 1, entries 29 and 30). The functional group tolerance of this reaction is worthy of note. Substituents such as acetyl, formyl, benzoyl, ester, nitrile, nitro, trifluoromethyl, fluoro or methoxy have been used successfully. The reactivity of three heteroaryl bromides using our catalyst was also examined. 3-Bromopyridine or 3-bromoquinoline led to the 5-arylated 2-*n*-butylthiophenes **17** and **18** in good yields and TONs using as little as 0.4–0.1 mol% catalyst (Table 1, entries 31–34). A slightly slower reaction was observed with 4-bromoisoquinoline, probably for steric reasons (Table 1, entries 35 and 36).

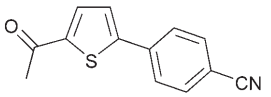
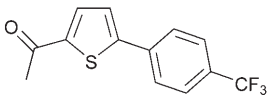
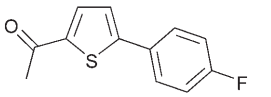
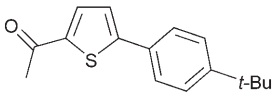
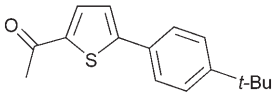
Table 2. Tedicyp-Pd-catalysed reaction of aryl halides with thiophene-2-carbonitrile (Scheme 4).[a]

Entry	Aryl halide	Ratio substrate/catalyst	Product		Yield [%]
1	4-Trifluoromethylbromobenzene	250		**20**	100 (83)
2	4-Trifluoromethylbromobenzene	1000			93
3	4-Fluorobromobenzene	250		**21**	100 (81)
4	4-Fluorobromobenzene	1000			96
5	4-*tert*-Butylbromobenzene	100		**22**	72 (67)
6	Iodobenzene	250		**23**	100 (86)
7	Iodobenzene	1000			63
8	4-Bromoanisole	100		**24**	68 (61)
9	2-Trifluoromethylbromobenzene	1000		**25**	100 (82)
10	2-Trifluoromethylbromobenzene	10000			17
11	1-Bromonaphthalene	250		**26**	100 (84)
12	1-Bromonaphthalene	1000			61

[a] *Conditions:* catalyst: $[Pd(C_3H_5)Cl]_2$/Tedicyp: 1/2 see ref.[11], aryl halide: 1 mmol, thiophene-2-carbonitrile: 2 mmol, AcONa: 2 mmol, DMAc, 20 h, 150 °C, yield determined by GC and NMR, yields in parenthesis are isolated.

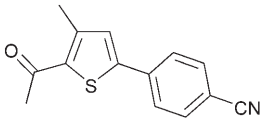
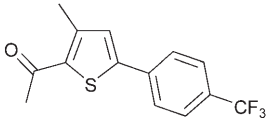
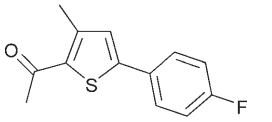
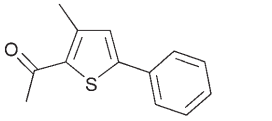
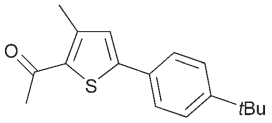
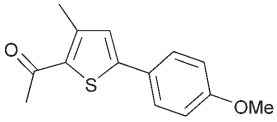
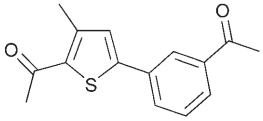
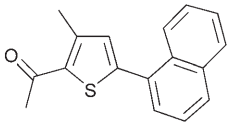
Then, the reactivity of five other thiophene derivatives has been examined (Table 2, Table 3, Table 4, Scheme 4, Scheme 5, Scheme 6). Thiophene-2-carbonitrile was also found to be a suitable substrate for low-catalyst loading coupling reactions (Table 2, Scheme 4). However, the presence of the electron-

Table 3. Tedicyp-Pd-catalysed reaction of aryl halides with 2-acetylthiophene (Scheme 4).[a]

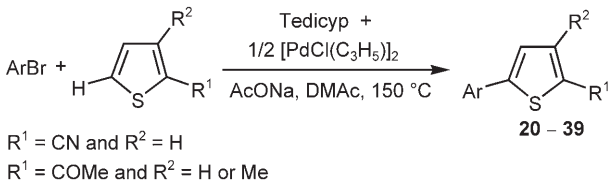
Entry	Aryl halide	Ratio substrate/catalyst	Product		Yield [%]
1	4-Bromobenzonitrile	100		**27**	100 (81)
2	4-Bromobenzonitrile	1000			80
3	4-Trifluoromethylbromobenzene	100		**28**	100 (76)
4	4-Fluorobromobenzene	100		**29**	100 (75)
5	4-*tert*-Butylbromobenzene	100		**30**	70 (66)
6	1-Bromonaphthalene	100		**31**	100 (77)

[a] *Conditions:* catalyst: $[Pd(C_3H_5)Cl]_2$/Tedicyp: 1/2 see ref.[11], aryl bromide: 1 mmol, 2-acetyl thiophene: 2 mmol, AcONa: 2 mmol, DMAc, 20 h, 150 °C, yield determined by GC and NMR, yields in parenthesis are isolated.

Table 4. Tedicyp-Pd-catalysed reaction of aryl halides with 2-acetyl-3-methylthiophene (Scheme 4).[a]

Entry	Aryl halide	Ratio substrate/catalyst	Product	Yield [%]
1	4-Bromobenzonitrile	100	 **32**	100 (71)
2	4-Bromobenzonitrile	1000		80
3	4-Trifluoromethylbromobenzene	100	 **33**	100 (74)
4	4-Trifluoromethylbromobenzene	1000		95
5	4-Fluorobromobenzene	100	 **34**	100 (80)
6	4-Fluorobromobenzene	1000		93
7	Iodobenzene	100	 **35**	100 (77)
8	Iodobenzene	1000		78
9	4-*tert*-Butylbromobenzene	100	 **36**	70 (54)
10	4-Bromoanisole	100	 **37**	100 (70)
11	3-Bromoacetophenone	100	 **38**	100 (68)
12	1-Bromonaphthalene	100	 **39**	60 (44)

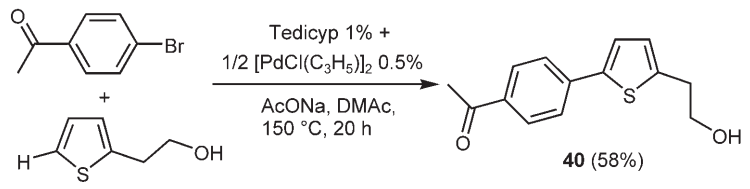
[a] *Conditions:* catalyst: $[Pd(C_3H_5)Cl]_2$/Tedicyp: 1/2 see ref.[11], aryl halide: 1 mmol, 2-acetyl-3-methylthiophene: 2 mmol, AcONa: 2 mmol, DMAc, 20 h, 150 °C, yield determined by GC and NMR, yields in parenthesis are isolated.



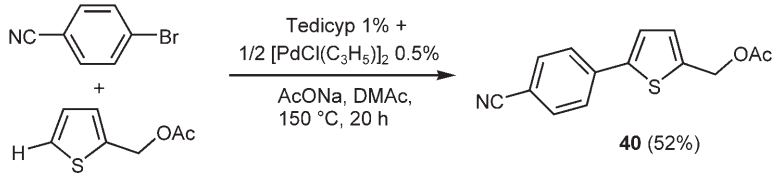
Scheme 4.

withdrawing substituent nitrile on the thiophene appears to slow down the reaction. For example, with electron-deficient aryl bromides such as 4-trifluoromethylbromobenzene or 4-fluorobromobenzene the presence of 0.1 mol% catalyst gave high yields of the corresponding 5-arylated thiophene-2-carbonitrile (Table 2, entries 1–4). The electron-rich bromoarenes 4-*tert*-butylbromobenzene and 4-bromoanisole also led selectively to the 5-arylated products, however in lower TONs of 72 and 68, respectively (Table 2, entries 5 and 8). Using iodobenzene a higher TON of 630 was obtained (Table 2, entries 6 and 7). The reactivity of the two *ortho*-substituted aryl bromides, 2-trifluoromethylbromobenzene and 1-bromonaphthalene was also examined, and, in both cases, good results in terms of yields of products **25** and **26**, and TONs were obtained (Table 2, entries 9–12). These observations seems to confirm that the oxidative addition of the aryl bromide to palladium is the rate-limiting step of the catalytic cycle.

The electron-deficient 2-acetylthiophene reacted with activated aryl bromides such as 4-bromobenzonitrile or 4-trifluoromethylbromobenzene to give the coupling products **27** and **28** in high yields and TONs of 800 and 100, respectively (Table 3, entries 1–3). With this thiophene derivative, the electron-rich aryl bromide 4-*tert*-butylbromobenzene or sterically hin-



Scheme 5.



Scheme 6.

dered 1-bromonaphthalene led to **30** and **31** in TONs of 70 and 100, respectively (Table 3, entries 5 and 6).

Quite similar results were obtained with 2-acetyl-3-methylthiophene (Table 4). The 5-arylated thiophenes were obtained selectively using 4-bromobenzonitrile, 4-trifluoromethylbromobenzene or 4-fluorobromobenzene in high TONs of 800, 950 and 930, respectively (Table 4, entries 1–6). The electron-rich or congested aryl bromides 4-*tert*-butylbromobenzene, 4-bromoanisole or 1-bromonaphthalene led to lower TONs of 70, 100 and 60, respectively (Table 4, entries 9, 10 and 12). In summary, the presence of the electron-withdrawing goups nitrile of acetyl in 2 position on the thiophene led in most cases to slower reactions than the couplings preformed with 2-*n*-butylthiophene.

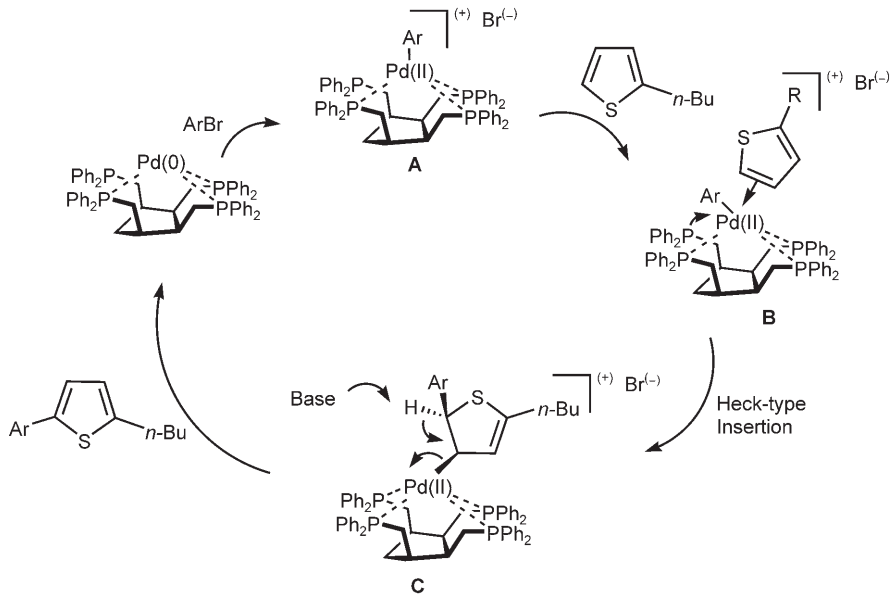
Thiophenes bearing functionalised alkyl side chains are also tolerated by this reaction. For example, 2-(2-thienyl)ethanol reacted with 4-bromoacetophenone to give the 5-arylated thiophene in 58% yield (Scheme 5).

The protected thiophene-2-methanol led to the 5-arylated thiophene derivative in moderate yield using the electron-deficient aryl bromides, 4-bromobenzonitrile (Scheme 6). However, the formation of a few unidentified side-products was also observed.

We had previously reported that Tedicyp and $[Pd(C_3H_5)Cl]_2$ were found to promote the direct arylation of furans *via* C–H functionalisation in good yields using very low catalyst loadings.[14] For example, 2-*n*-butylfuran reacts with a variety of aryl bromides in good yields and high turnover numbers (TONs) (up to 1000) in most cases. The reactivity of a few other furan derivatives had also been examined. For example, 2-methylfuran-3-carboxylic acid ethyl ester reacted with activated aryl bromides such as 4-bromoacetophenone or 4-bromobenzonitrile to give the coupling products in very high TONs of 5100 and 9800, respectively. Protected furfuryl alcohol also led to the 5-arylated compounds in high TONs and good yields using electron-deficient aryl bromides and in 75 TON with an electron-excessive aryl bromide. In short, the reactivity of furans and thiophenes for this reaction is quite similar, and lead to the coupling products in high yields and TONs in several cases. However, there is some difference of reactivity between these heteroaromatics. Although 2-*n*-butylthiophene appears to be more reactive than 2-*n*-butylfuran in most cases, on the other hand, the arylation of protected furfuryl alcohol gave better results than using protected thiophene-2-methanol. Both with furans and thiophene derivatives, the presence of electron-withdrawing substituents on the heteroaromatic is tolerated.

Several mechanism have been suggested for the C–H activation/functionalisation of heteroarenes.[6c] With our catalyst we believe that reaction might proceed *via* a classical oxidative addition of the aryl bromide to a palladium(0) complex followed by a Heck type insertion of the thiophene to give the intermediate **C** (Scheme 7). On this intermediate the Pd on carbon 4 and the H on carbon 5 are in an *anti* orientation. As *anti* β-eliminations are quite difficult, we assume that a base-assisted elimination of the proton on carbon 5 followed by an aromatisation and elimination of Pd occurs. A migration of the palladium to the 2-position of the 2-*n*-butylthiophene followed by a β-elimination into the alkyl side chain is also possible, but is not supported by an experiment performed with D_2O (no incorporation of deuterium on the benzylic CH_2 of 2-*n*-butylthiophene). The β-eliminations using other thiophene derivatives can be expained with the same mechanism. Then, with all these substrates, a reductive elimination assisted by the base regenerates the Pd(0) (Scheme 7). However, an electrophilic aromatic substitution type mechanism is also possible for this reaction.

The high TONs obtained with the Tedicyp/palladium probably mainly come from a high thermal stabili-



Scheme 7.

ty of the catalyst. However, the structure of this catalyst has certainly also some influence on some steps of the catalytic cycle. For steric reasons, the oxidative addition of the aryl bromide and the coordination of the thiophene derivatives to palladium are probably not accelerated by presence of a tetraphosphine ligand. On the other hand, the insertion of the thiophene derivatives in the Ar–Pd bond, and especially the β-elimination and/or the reductive elimination of HBr to regenerate the Pd(0) complex might be accelerated by the steric factors and recoordination pressure of the phosphines.

Conclusions

In summary, the coupling of aryl bromides with a variety of thiophene derivatives proceeds nicely using the tetradentate ligand Tedicyp associated to a palladium complex. The reaction can be performed with as little as 0.01 mol% catalyst with the most reactive substrates instead of 3–10 mol% with the reported procedures. The electron-deficient thiophenes, thiophene-2-carbonitrile or 2-acetylthiophenes are slightly less reactive than the electron-neutral 2-*n*-butylthiophene. Electron-poor, electron-rich or sterically congested aryl bromides have been used successfully. Even the sterically very congested 2,4,6-triisopropylbromobenzene gave the coupling product. Moreover, a wide range of functions such as methoxy, fluoro, trifluoromethyl, acetyl, formyl, benzoyl, carboxylate, nitro or nitrile on the aryl bromide are tolerated. We believe that this system compares favourably with other catalyst systems that have been reported for this process. The efficiency of this catalyst probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring which probably increases the coordination of the ligand to the metal, prevents the precipitation of the catalyst and could also accelerate the insertion, the β-elimination or the reductive elimination steps in the catalytic cycle. Moreover, these thiophenes are commercially available. This is a practical advantage of this reaction.

Experimental Section

General Remarks

DMAc analytical grade (99%) was not distilled before use. AcONa (99+%) was used. All reactions were run under argon using vacuum lines in Schlenk tubes in oven-dried glassware. ^{1}H (300 MHz) and ^{13}C (75 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shift (δ) are reported in ppm relative to $CDCl_3$. Flash chromatographies were performed on silica gel (230–400 mesh).

Preparation of the Pd-Tedicyp Catalyst[11]

An over-dried 40-mL Schlenk tube equipped with a magnetic stirring bar, under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_5$ (4.2 mg, 11.6 μmol) and Tedicyp (20 mg, 23.2 μmol). 2.5 mL of anhydrous DMAc were added, then the solution was stirred at room temperature for 10 min. This catalyst solution was used directly for the catalysed reactions.

General Procedure

In a typical experiment, the aryl halide (1 mmol), thiophene derivative (2 mmol) and AcONa (2 mmol) were dissolved in DMAc (3 mL) under an argon atmosphere. The prepared Pd-Tedicyp catalyst complex was then transferred to the re-

action flask *via* cannula. The reaction mixture was stirred at 150 °C for 20 h. The solution was diluted with H_2O (5 mL), then the product was extracted with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed under vacuum. The crude product was purified by silica gel column chromatography.

1-[4-(5-Butylthiophen-2-yl)phenyl]ethanone (1): The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **1** in 81 % (0.209 g) isolated yield.

4-(5-Butylthiophen-2-yl)benzaldehyde (2): The reaction of 4-bromobenzaldehyde (0.185 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **2** in 87 % (0.212 g) isolated yield.

[4-(5-Butylthiophen-2-yl)-phenyl]phenylmethanone (3): The reaction of 4-bromobenzophenone (0.261 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **3** in 79 % (0.253 g) isolated yield.

4-(5-Butylthiophen-2-yl)benzoic acid methyl ester (4): The reaction of methyl 4-bromobenzoate (0.215 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **4** in 83 % (0.228 g) isolated yield.

2-Butyl-5-(4-trifluoromethylphenyl)thiophene (5): The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **5** in 81 % (0.230 g) isolated yield.

4-(5-Butylthiophen-2-yl)benzonitrile (6): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **6** in 80 % (0.193 g) isolated yield.

2-Butyl-5-(4-nitrophenyl)thiophene (7): The reaction of 4-bromonitrobenzene (0.202 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **7** in 86 % (0.225 g) isolated yield.

2-Butyl-5-phenylthiophene (8): The reaction of iodobenzene (0.204 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **8** in 80 % (0.173 g) isolated yield.

2-Butyl-5-(4-*tert*-butylphenyl)thiophene (9): The reaction of 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **9** in 83 % (0.226 g) isolated yield.

2-Butyl-5-(4-methoxyphenyl)thiophene (10): The reaction of 4-bromoanisole (0.187 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **10** in 79 % (0.194 g) isolated yield.

2-Butyl-5-(2-trifluoromethylphenyl)thiophene (11): The reaction of 2-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **11** in 84 % (0.239 g) isolated yield.

2-Butyl-5-(2-fluorophenyl)thiophene (12): The reaction of 2-fluorobromobenzene (0.175 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **12** in 87 % (0.204 g) isolated yield.

2-Butyl-5-(*o*-tolyl)thiophene (13): The reaction of 2-bromotoluene (0.171 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **13** in 79 % (0.182 g) isolated yield.

2-Butyl-5-(naphthalen-1-yl)-thiophene (14): The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **14** in 81 % (0.215 g) isolated yield.

2-Butyl-5-(2,4,6-trimethylphenyl)thiophene (15): The reaction of 2,4,6-trimethylbromobenzene (0.195 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **15** in 49 % (0.127 g) isolated yield.

2-Butyl-5-(2,4,6-triisopropylphenyl)thiophene (16): The reaction of 2,4,6-triisopropylbromobenzene (0.283 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.02 mmol) affords the corresponding product **16** in 37 % (0.127 g) isolated yield.

3-(5-Butylthiophen-2-yl)pyridine (17): The reaction of 3-bromopyridine (0.158 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **17** in 81 % (0.176 g) isolated yield.

3-(5-Butylthiophen-2-yl)quinoline (18): The reaction of 3-bromoquinoline (0.208 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **18** in 79 % (0.211 g) isolated yield.

4-(5-Butylthiophen-2-yl)isoquinoline (19): The reaction of 4-bromoisoquinoline (0.208 g, 1 mmol), 2-*n*-butylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **19** in 87 % (0.232 g) isolated yield.

5-(4-Trifluoromethylphenyl)thiophene-2-carbonitrile (20): The reaction of thiophene-2-carbonitrile (0.218 g, 1 mmol), 4-trifluoromethylbromobenzene (0.225 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **20** in 83 % (0.210 g) isolated yield.

5-(4-Fluorophenyl)thiophene-2-carbonitrile (21): The reaction of 4-fluorobromobenzene (0.175 g, 1 mmol), thiophene-2-carbonitrile (0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **21** in 81 % (0.165 g) isolated yield.

5-(4-*tert*-Butylphenyl)thiophene-2-carbonitrile (22): The reaction of 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), thiophene-2-carbonitrile (0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **22** in 67 % (0.162 g) isolated yield.

5-Phenylthiophene-2-carbonitrile (23): The reaction of iodobenzene (0.204 g, 1 mmol), thiophene-2-carbonitrile

(0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **23** in 86% (0.159 g) isolated yield.

5-(4-Methoxyphenyl)thiophene-2-carbonitrile (24): The reaction of 4-bromoanisole (0.187 g, 1 mmol), thiophene-2-carbonitrile (0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **24** in 61% (0.131 g) isolated yield.

5-(2-Trifluoromethylphenyl)thiophene-2-carbonitrile (25): The reaction of 2-trifluoromethylbromobenzene (0.225 g, 1 mmol), thiophene-2-carbonitrile (0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.001 mmol) affords the corresponding product **25** in 82% (0.208 g) isolated yield.

5-(Naphthalen-1-yl)thiophene-2-carbonitrile (26): The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), thiophene-2-carbonitrile (0.218 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.004 mmol) affords the corresponding product **26** in 84% (0.197 g) isolated yield.

4-(5-Acetylthiophen-2-yl)benzonitrile (27): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-acetylthiophene (0.252 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **27** in 81% (0.184 g) isolated yield.

1-[5-(4-Trifluoromethylphenyl)thiophen-2-yl]-ethanone (28): The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-acetylthiophene (0.252 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **28** in 76% (0.205 g) isolated yield.

1-[5-(4-Fluorophenyl)thiophen-2-yl]ethanone (29): The reaction of 4-fluorobromobenzene (0.175 g, 1 mmol), 2-acetylthiophene (0.252 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **29** in 75% (0.165 g) isolated yield.

1-[5-(4-*tert*-Butylphenyl)thiophen-2-yl]ethanone (30): The reaction of 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-acetylthiophene (0.252 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **30** in 66% (0.170 g) isolated yield.

1-[(5-Naphthalen-1-yl)-thiophen-2-yl]ethanone (31): The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), 2-acetylthiophene (0.252 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **31** in 77% (0.194 g) isolated yield.

4-(5-Acetyl-4-methylthiophen-2-yl)benzonitrile (32): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **32** in 71% (0.171 g) isolated yield.

1-[3-Methyl-5-(4-trifluoromethylphenyl)thiophen-2-yl]-ethanone (33): The reaction of 4-trifluoromethylbromobenzene (0.225 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **33** in 74% (0.210 g) isolated yield.

1-[5-(4-Fluorophenyl)-3-methylthiophen-2-yl]ethanone (34): The reaction of 4-fluorobromobenzene (0.175 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **34** in 80% (0.187 g) isolated yield.

1-(3-Methyl-5-phenylthiophen-2-yl)ethanone (35): The reaction of iodobenzene (0.204 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **35** in 77% (0.166 g) isolated yield.

1-[5-(4-*tert*-Butylphenyl)-3-methylthiophen-2-yl]ethanone (36): The reaction of 4-*tert*-butylbromobenzene (0.213 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **36** in 54% (0.147 g) isolated yield.

1-[5-(4-Methoxyphenyl)-3-methylthiophen-2-yl]ethanone (37): The reaction of 4-bromoanisole (0.187 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **37** in 70% (0.172 g) isolated yield.

1-[5-(3-Acetylphenyl)-3-methylthiophen-2-yl]ethanone (38): The reaction of 3-bromoacetophenone (0.199 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **38** in 68% (0.175 g) isolated yield.

1-[3-Methyl-5-(naphthalen-1-yl)thiophen-2-yl]ethanone (39): The reaction of 1-bromonaphthalene (0.207 g, 1 mmol), 2-acetyl-3-methylthiophene (0.280 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **39** in 44% (0.117 g) isolated yield.

1-[4-(5-Hydroxyethylthiophen-2-yl)phenyl]ethanone (40): The reaction of 4-bromoacetophenone (0.199 g, 1 mmol), 2-thiophen-2-yl-ethanol (0.256 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **40** in 58% (0.143 g) isolated yield.

Acetic acid 5-[(4-cyanophenyl)thiophen-2-yl]methyl ester (41): The reaction of 4-bromobenzonitrile (0.182 g, 1 mmol), methyl thiophene-2-acetate (0.312 g, 2 mmol) and AcONa (0.164 g, 2 mmol) with the palladium complex (0.01 mmol) affords the corresponding product **41** in 52% (0.134 g) isolated yield.

Supporting Information Available

Characterization data for compounds **1**–**40**.

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