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Synthesis of biheteroaryl derivatives by tetraphosphine/palladium-catalysed Suzuki coupling of heteroaryl bromides with heteroarylboronic acids

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Abstract

The synthesis of biheteroaryl derivatives by palladium-catalysed Suzuki cross-coupling reaction of heteroaryl bromides with heteroarylboronic acids is a challenging reaction due to the electronic and/or poisoning properties of these heteroaryl compounds. Through the use of $[PdCl(C_3H_5)]_2$/*cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane as a catalyst, a range of heteroaryl bromides undergoes Suzuki reaction with heteroarylboronic acids such as thiophene-, furan- or pyridineboronic acid derivatives in good yields. This catalyst can be used at low loadings with several substrates. In general bromopyridines were found to be more reactive than bromothiophenes or bromofuranes.

Keywords: Tetraphosphine; Palladium; Suzuki coupling; Heteroarylboronic acids; Heteroaryl halides

1. Introduction

Heteroaryls are the most common motif found in pharmaceutically active compounds. The palladium-catalysed Suzuki reaction is a powerful method for the preparation of heteroaryl derivatives [1,2]. However, if the Suzuki coupling of heteroarylboronic acids with aryl halides or the reaction of arylboronic acids with heteroaryl halides has been largely explored, the reaction using heteroarylboronic acids with heteroaryl halides has attracted less attention [3–25]. In fact, one of the major limitations of the Suzuki coupling, is its inability to maintain the efficacy exhibited for the coupling of simple aryls when heterocycles are employed as coupling partners, especially when both partners are heterocycles. For electronic or poisoning reasons, the reaction with such substrates is generally much slower than with simple aryl derivatives and it generally requires high catalyst loadings. A few ligands have been successfully employed for the reaction with these substrates. The first one was triphenylphosphine; however, the catalyst formed by association of this ligand with palladium complexes is not very efficient in terms of the substrate/catalyst ratio and in general 3–10 mol% catalyst had to be used [3–8]. In recent years, new palladium catalysts have been successfully employed for the coupling of heteroarylboronic acids with heteroaryl halides [9–25]. For instance, interesting results using monophosphine–palladium complexes, especially with sterically congested and electron-rich phosphine ligands, have been reported [9–14]. For example, Capretta and co-workers reported that a phosphaadamantane ligand (4 mol%) associated with $Pd_2(dba)_3$ (1.2 mol%) is a powerful system for the reaction of 2-thiopheneboronic acid with a 2-chloropyridine [10]. Wei et al. described the efficiency of $P(Cy)_3$ or $P(t\text{-}Bu)_3$ as ligands (6 mol%) for the coupling of a bromoimidazole with 3-pyridineborane [11]. Fu and co-workers have also reported the cross-coupling of 3-pyridineboronic acid with several chloro- or bromopyridine derivatives using 4 mol% catalyst of $P(Cy)_3$ associated with $Pd_2(dba)_3$ [12]. The Suzuki coupling reactions of heteroaryl chlorides with potassium 3-pyridyltrifluoroborates or pyridineboronic acids have been accomplished in good

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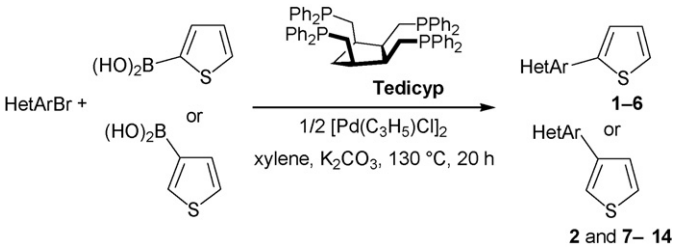


Scheme 1.

yields by Buchwald and co-workers with the ligands S-Phos (6 mol%) or dicyclohexyl-(2′,4′,6′-triisopropyl-biphenyl-2-yl)-phosphane (4 mol%) [13,14]. Diphosphine ligands have also been used successfully for the coupling of these heteroaryl derivatives [15–22]. For example, potassium 3-thiophenetrifluoroborate and heteroaryl halides gave high yields of biaryls using 1–2 mol% of $PdCl_2$(dppf) as catalyst [16]. Good yields were also obtained for the coupling of a chloropyrimidine and 3-thiopheneboronic acid with 1,1′-bis(di-*tert*-butylphosphino)ferrocene and $Pd(OAc)_2$ (5 mol%) [22]. A 2-pyridine aldoxime-based Pd(II)-complex (0.7 mol%) covalently anchored via the oxime moiety to a glass/polymer composite material was employed in cross-coupling reactions of heteroaryl halides, with 3-thiopheneboronic acid under thermal as well as microwave irradiating conditions in water [23].

Although mono- or diphosphine ligands and palladacycles have been successfully used for the Suzuki reaction of heteroarylboronic acids with heteroaryl bromides, to the best of our knowledge, the efficiency of polydentate phosphine ligands for such couplings has not been demonstrated. Moreover, an effective and selective method for the reaction with these challenging substrates using high substrate/catalyst ratios still needs to be developed.

In order to find more efficient palladium catalysts, we have prepared the tetrapodal phosphine ligand, Tedicyp (Scheme 1) [26]. The idea of the design of this ligand was that intermediate Pd(0) species have to be protected by internal ligation against possible decomposition pathways through under-ligation and subsequent colloid formation. We have reported several results [27] obtained in Heck reaction [28], Sonogashira [29] and Suzuki cross-coupling [30], using Tedicyp as ligand. We have also reported the reaction of heteroaryl halides with arylboronic acids [31] and the coupling of heteroarylboronic acids with arylbromides [32]. Herein, in order to further establish the requirements for a successful Suzuki reaction, we report that the catalyst composed of Pd and Tedicyp ligand provides a powerful system for the cross-coupling of heterocyclic substrates, such as thiophene-, furan- or pyridineboronic acids with heteroaryl bromides. The presence of this polydentate ligand on palladium might reduce the poisoning of the catalyst or reverse this poisoning process when strongly coordinating substrates such as sulphur or nitrogen-containing reactants or products are used. With these heteroaryl derivatives the "steric pressure" of the Tedicyp ligand might also accelerate the reductive elimination in the catalytic cycles to form the biheteroaryl compound.

2. Experimental

2.1. General

All reactions were run under argon using vacuum lines in Schlenk tubes in oven-dried glassware. DMF was not distilled before use. Commercial heteroarylboronic acids and heteroaryl halides were used without purification. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^{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).

2.2. Preparation of the Pd–Tedicyp catalyst [26]

Preparation of the Pd–Tedicyp catalyst: an oven-dried 40 mL Schlenk tube, equipped with a magnetic stirring bar under argon atmosphere, was charged with $[Pd(C_3H_5)Cl]_2$ (30 mg, 81 μmol) and Tedicyp (140 mg, 162 μmol). Ten milliliters of anhydrous DMF were added, then the solution was stirred at room temperature for 10 min. The appropriate catalyst concentration was obtained by successive dilutions.

2.3. Catalytic procedure for Suzuki reactions

In a typical experiment, the heteroaryl halide (1 mmol), heteroarylboronic acid (2 mmol) and K_2CO_3 (0.276 g, 2 mmol) were dissolved in xylene (3 mL) under an argon atmosphere. The prepared Pd–Tedicyp catalyst complex (see tables) was then transferred to the reaction flask via cannula. The reaction mixture was stirred at 130 °C for 20 h. The solution was diluted with H_2O (5 mL), and then the product was extracted three times with CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product was purified by silica gel column chromatography.

2.4. Coupling products (Tables 1–4)

[*2,2′*]*Bithiophene* (***1***) (Table 1, *entry 1*): From 2-bromothiophene (0.163 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **1** was obtained in 92% (0.153 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (dd, J = 5.0, 3.6 Hz, 2H), 7.17 (dd, J = 3.6, 1.0 Hz, 2H), 7.20 (dd, J = 5.0, 1.0 Hz, 2H).

[*2,3′*]*Bithiophene* (***2***) (Table 1, *entry 3*): From 3-bromothiophene (0.163 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **2** was obtained in 73% (0.121 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.03 (dd, J = 4.5, 3.8 Hz, 1H), 7.17–7.21 (m, 2H), 7.30–7.39 (m, 3H).

3-(Thiophen-2-yl)-furan (***3***) (Table 1, *entry 5*): From 3-bromofuran (0.147 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **3** was obtained in 90% (0.135 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (bs, 1H), 7.02 (dd, J = 5.1,

Table 1
Palladium–Tedicyp catalysed Suzuki coupling reactions with thiopheneboronic acids and heteroaryl bromides (Scheme 1)

Entry	Aryl bromide	Heteroarylboronic acid	Ratio substrate/catalyst	Product	Yield (%)[a]
1	2-Bromothiophene	2-Thiopheneboronic acid	20	**1**	100 (92)
2	2-Bromothiophene	2-Thiopheneboronic acid	50	**1**	23
3	3-Bromothiophene	2-Thiopheneboronic acid	20	**2**	85 (73)
4	3-Bromothiophene	2-Thiopheneboronic acid	50	**2**	21
5	3-Bromofuran	2-Thiopheneboronic acid	100	**3**	100 (90)[b]
6	3-Bromofuran	2-Thiopheneboronic acid	250	**3**	8[b]
7	2-Bromopyridine	2-Thiopheneboronic acid	100	**4**	100 (94)
8	2-Bromopyridine	2-Thiopheneboronic acid	250	**4**	56
9	3-Bromopyridine	2-Thiopheneboronic acid	20	**5**	100 (93)
10	3-Bromopyridine	2-Thiopheneboronic acid	50	**5**	36
11	4-Bromopyridine	2-Thiopheneboronic acid	20	**6**	100 (81)
12	4-Bromopyridine	2-Thiopheneboronic acid	50	**6**	89
13	2-Bromothiophene	3-Thiopheneboronic acid	100	**2**	99 (88)
14	2-Bromothiophene	3-Thiopheneboronic acid	250	**2**	83
15	3-Bromothiophene	3-Thiopheneboronic acid	100	**7**	100 (96)
16	3-Bromothiophene	3-Thiopheneboronic acid	250	**7**	76
17	3-Bromofuran	3-Thiopheneboronic acid	100	**8**	100 (91)[b]
18	3-Bromofuran	3-Thiopheneboronic acid	250	**8**	5[b]
19	2-Bromopyridine	3-Thiopheneboronic acid	1,000	**9**	100 (90)
20	2-Bromopyridine	3-Thiopheneboronic acid	10,000	**9**	10
21	3-Bromopyridine	3-Thiopheneboronic acid	100	**10**	100 (89)
22	3-Bromopyridine	3-Thiopheneboronic acid	250	**10**	95
23	4-Bromopyridine	3-Thiopheneboronic acid	250	**11**	100 (91)
24	4-Bromopyridine	3-Thiopheneboronic acid	1,000	**11**	89
25	5-Bromopyrimidine	3-Thiopheneboronic acid	1,000	**12**	85 (77)
26	5-Bromopyrimidine	3-Thiopheneboronic acid	10,000	**12**	39
27	3-Bromoquinoline	3-Thiopheneboronic acid	250	**13**	96 (87)
28	4-Bromoisoquinoline	3-Thiopheneboronic acid	100	**14**	80 (75)

[a] Conditions—catalyst: $[ClPd(C_3H_5)]_2$/Tedicyp = 1:2, aryl bromide (1 mmol), thiopheneboronic acid (2 mmol), K_2CO_3 (2 mmol), xylene, 130 °C, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.
[b] Reaction performed at 90 °C.

3.5 Hz, 1H), 7.08 (m, 1H), 7.19 (dd, J = 5.1, 1.4 Hz, 1H), 7.43 (dd, J = 3.5, 1.4 Hz, 1H), 7.67 (s, 1H).

2-(Thiophen-2-yl)-pyridine (***4***) (Table 1, *entry 7*): From 2-bromopyridine (0.158 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **4** was obtained in 94% (0.151 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (dd, J = 5.1, 3.6 Hz, 1H), 7.11–7.15 (m, 1H), 7.38 (dd, J = 5.1, 1.2 Hz, 1H), 7.57 (dd, J = 3.6, 1.2 Hz, 1H), 7.61–7.68 (m, 2H), 8.55 (d, J = 4.8 Hz, 1H).

3-(Thiophen-2-yl)-pyridine (***5***) (Table 1, *entry 9*): From 3-bromopyridine (0.158 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **5** was obtained in 93% (0.150 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, J = 4.3, 4.0 Hz, 1H), 7.31 (dd, J = 8.0, 4.9 Hz, 1H), 7.35 (m, 2H), 7.85 (dt, J = 8.0, 1.7 Hz, 1H), 8.52 (bs, 1H), 8.88 (bs, 1H).

4-(Thiophen-2-yl)-pyridine (***6***) (Table 1, *entry 11*): From 4-bromopyridine (0.158 g, 1 mmol), 2-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **6** was obtained in 81% (0.131 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (dd, J = 5.0, 3.6 Hz, 1H), 7.40 (dd, J = 5.0, 1.0 Hz, 1H), 7.46 (d, J = 5.8 Hz, 2H), 7.44 (d, J = 3.6 Hz, 1H), 8.58 (bs, 2H).

[3,3′]Bithiophene (***7***) (Table 1, *entry 15*): From 3-bromothiophene (0.163 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **7** was obtained in 96% (0.159 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.34 (m, 4H), 7.36 (dd, J = 3.0, 1.5 Hz, 2H).

3-(Thiophen-3-yl)-furan (***8***) (Table 1, *entry 17*): From 3-bromofuran (0.147 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **8** was obtained in 91% (0.137 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (d, J = 1.0 Hz, 1H), 7.20 (dd, J = 4.9, 1.3 Hz, 1H), 7.26 (dd, J = 2.8, 1.3 Hz, 1H), 7.34 (dd, J = 4.9, 2.8 Hz, 1H), 7.44 (t, J = 1.7 Hz, 1H), 7.66 (s, 1H).

2-(Thiophen-3-yl)-pyridine (***9***) (Table 1, *entry 19*): From 2-bromopyridine (0.158 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.001 mmol), product **9** was obtained in 90% (0.145 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (ddd, J = 6.8, 4.7, 1.2 Hz, 1H), 7.38 (dd, J = 5.1, 3.1 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.64 (dd, J = 5.1, 1.3 Hz, 1H), 7.68 (ddd, J = 8.5, 6.8, 1.8 Hz, 1H), 7.90 (dd, J = 3.1, 1.3 Hz, 1H), 8.60 (d, J = 4.7 Hz, 1H).

3-(Thiophen-3-yl)-pyridine (***10***) (Table 1, *entry 21*): From 3-bromopyridine (0.158 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **10** was obtained in 89% (0.143 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.36 (m, 1H), 7.39 (dd, J = 5.0, 1.2 Hz, 1H), 7.43 (dd, J = 5.0, 2.9 Hz, 1H), 7.52 (m, 1H), 7.87 (d, J = 8.0 Hz, 1H), 8.52 (bs, 1H), 8.88 (bs, 1H).

Table 2
Palladium–Tedicyp catalysed Suzuki coupling reactions with thiopheneboronic acid derivatives and heteroaryl bromides (Scheme 2)

Entry	Aryl bromide	Heteroarylboronic acid	Ratio substrate/catalyst	Product	Yield (%)[a]
1	3-Bromothiophene	2-Acetyl-5-thiopheneboronic acid	20	–	0
2	3-Bromopyridine	2-Acetyl-5-thiopheneboronic acid	20	**15**	40 (32)
3	2-Bromothiophene	2-Formyl-3-thiopheneboronic acid	20	**16**	45 (37)
4	3-Bromothiophene	2-Formyl-3-thiopheneboronic acid	50	**17**	73 (67)
5	3-Bromofuran	2-Formyl-3-thiopheneboronic acid	20	**18**	100 (93)[b]
6	3-Bromofuran	2-Formyl-3-thiopheneboronic acid	100	**18**	83[b]
7	2-Bromopyridine	2-Formyl-3-thiopheneboronic acid	20	**19**	19 (11)
8	3-Bromopyridine	2-Formyl-3-thiopheneboronic acid	20	**20**	82 (78)
9	4-Bromopyridine	2-Formyl-3-thiopheneboronic acid	10	**21**	90 (82)
10	2-Bromothiophene	2-Benzothiopheneboronic acid	10	**22**	37 (29)
11	3-Bromothiophene	2-Benzothiopheneboronic acid	10	**23**	31 (25)
12	2-Bromopyridine	2-Benzothiopheneboronic acid	100	**24**	100 (89)
13	2-Bromopyridine	2-Benzothiopheneboronic acid	250	**24**	97
14	4-Bromopyridine	2-Benzothiopheneboronic acid	100	**25**	100 (90)
15	4-Bromopyridine	2-Benzothiopheneboronic acid	250	**25**	61
16	2-Bromothiophene	4-Dibenzothiopheneboronic acid	100	**26**	78 (66)
17	3-Bromothiophene	4-Dibenzothiopheneboronic acid	250	**27**	100 (94)
18	2-Bromopyridine	4-Dibenzothiopheneboronic acid	1,000	**28**	100 (91)
19	2-Bromopyridine	4-Dibenzothiopheneboronic acid	10,000	**28**	30

[a] Conditions—catalyst: $[ClPd(C_3H_5)]_2$/Tedicyp = 1:2, aryl bromide (1 mmol), heteroarylboronic acid (2 mmol), K_2CO_3 (2 mmol), xylene, 130 °C, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.
[b] Reaction performed at 90 °C.

4-(Thiophen-3-yl)-pyridine (***11***) (Table 1, *entry 23*): From 4-bromopyridine (0.158 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **11** was obtained in 91% (0.147 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (m, 2H), 7.52 (d, J = 5.5 Hz, 2H), 6.68 (t, J = 2.0 Hz, 1H), 8.62 (bs, 2H).

5-(Thiophen-3-yl)-pyrimidine (***12***) (Table 1, *entry 25*): From 5-bromopyrimidine (0.159 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.001 mmol), product **12** was obtained in 77% (0.125 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (dd, J = 5.0, 1.4 Hz, 1H), 7.49 (dd, J = 5.0, 2.9 Hz, 1H), 7.59 (dd, J = 2.9, 1.4 Hz, 1H), 8.95 (bs, 2H), 9.13 (s, 1H).

3-(Thiophen-3-yl)-quinoline (***13***) (Table 1, *entry 27*): From 3-bromoquinoline (0.208 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **13** was obtained in 87% (0.184 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (dd, J = 5.1, 2.9 Hz, 1H), 7.51 (dd, J = 5.1, 1.5 Hz, 1H), 7.56 (t, J = 8.2 Hz, 1H), 7.65 (dd, J = 2.9, 1.5 Hz, 1H), 7.70 (td, J = 8.2, 1.5 Hz, 1H), 7.85 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.30 (d, J = 1.5 Hz, 1H), 8.92 (bs, 1H).

4-(Thiophen-3-yl)-isoquinoline (***14***) (Table 1, *entry 28*): From 4-bromoisoquinoline (0.208 g, 1 mmol), 3-thiopheneboronic acid (0.256 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **14** was obtained in 75% (0.158 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (dd, J = 4.9, 1.4 Hz, 1H), 7.44 (dd, J = 3.0, 1.4 Hz, 1H), 7.48 (dd, J = 4.9, 3.0 Hz, 1H), 7.61 (td, J = 8.1, 1.5 Hz, 1H), 7.69 (td, J = 8.1, 1.5 Hz, 1H), 8.02 (d, J = 8.1 Hz, 2H), 8.55 (bs, 1H), 9.23 (bs, 1H).

2-Acetyl-5-(Pyridin-3-yl)-thiophene (***15***) (Table 2, *entry 2*): From 3-bromopyridine (0.158 g, 1 mmol), 2-acetyl-5-thiopheneboronic acid (0.340 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **15** was obtained in 32% (0.065 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 7.32–7.36 (m, 1H), 7.37 (d, J = 4.0 Hz, 1H), 7.67 (d, J = 4.0 Hz, 1H), 7.90 (dt, J = 7.9, 1.5 Hz, 1H), 8.59 (bd, J = 3.8 Hz, 1H), 8.90 (bs, 1H).

2-Formyl-3-(thiophen-2-yl)-thiophene (***16***) (Table 2, *entry 3*): From 2-bromothiophene (0.163 g, 1 mmol), 2-formyl-3-thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **16** was obtained in 37% (0.072 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, J = 5.1, 3.6 Hz, 1H), 7.25–7.30 (m, 2H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 7.68 (dd, J = 5.1, 1.2 Hz, 1H), 10.14 (d, J = 1.2 Hz, 1H).

2-Formyl-3-(thiophen-3-yl)-thiophene (***17***) (Table 2, *entry 4*): From 3-bromothiophene (0.163 g, 1 mmol), 2-formyl-3-thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.02 mmol), product **17** was obtained in 67% (0.130 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.28 (m, 2H), 7.43–7.50 (m, 2H), 7.71 (dd, J = 5.1, 1.2 Hz, 1H), 10.00 (d, J = 1.2 Hz, 1H).

2-Formyl-3-(furan-3-yl)-thiophene (***18***) (Table 2, *entry 5*): From 3-bromofuran (0.147 g, 1 mmol), 2-formyl-3-thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **18** was obtained in 93% (0.166 g) yield. Oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (d, J = 1.1 Hz, 1H), 7.18 (d, J = 4.9 Hz, 1H), 7.54 (t, J = 1.7 Hz, 1H), 7.71–7.74 (m, 2H), 10.04 (d, J = 1.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.1, 129.6, 129.9, 134.5, 141.4, 141.5, 143.9, 160.0, 183.1; MS (70 eV); *m/z* (%) 178 ($M^{\bullet+}$, 87); $C_9H_6O_2S$: Calcd C 60.66, H 3.39; Found C 60.76, H 3.24.

2-Formyl-3-(pyridin-2-yl)-thiophene (***19***) (Table 2, *entry 7*): From 2-bromopyridine (0.158 g, 1 mmol), 2-formyl-3-

thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **19** was obtained in 11% (0.021 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30–7.35 (m, 1H), 7.43 (d, J = 5.0 Hz, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.72 (dd, J = 5.0, 1.1 Hz, 1H), 7.80–7.92 (m, 1H), 8.72 (m, 1H), 10.51 (d, J = 1.1 Hz, 1H).

2-Formyl-3-(pyridin-3-yl)-thiophene (***20***) (Table 2, *entry 8*): From 3-bromopyridine (0.158 g, 1 mmol), 2-formyl-3-thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.05 mmol), product **20** was obtained in 78% (0.148 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, J = 4.9 Hz, 1H), 7.43 (dd, J = 7.8, 4.9 Hz, 1H), 7.77–7.83 (m, 2H), 8.63 (d, J = 4.2 Hz, 1H), 8.74 (bs, 1H), 9.85 (d, J = 1.0 Hz, 1H).

2-Formyl-3-(pyridin-4-yl)-thiophene (***21***) (Table 2, *entry 9*): From 4-bromopyridine (0.158 g, 1 mmol), 2-formyl-3-thiopheneboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.1 mmol), product **21** was obtained in 82% (0.155 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 4.9 Hz, 1H), 7.41 (d, J = 4.9 Hz, 2H), 7.80 (dd, J = 4.9, 1.1 Hz, 1H), 8.75 (bs, 2H), 9.90 (d, J = 1.1 Hz, 1H).

2-(Thiophen-2-yl)-benzo[b]thiophene (***22***) (Table 2, *entry 10*): From 2-bromothiophene (0.163 g, 1 mmol), 2-benzothiopheneboronic acid (0.356 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.1 mmol), product **22** was obtained in 29% (0.063 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (dd, J = 4.7, 3.7 Hz, 1H), 7.27–7.36 (m, 3H), 7.33 (t, J = 6.5 Hz, 1H), 7.39 (s, 1H), 7.72 (dd, J = 6.5, 1.3 Hz, 1H), 7.77 (dd, J = 6.5, 1.3 Hz, 1H).

2-(Thiophen-3-yl)-benzo[b]thiophene (***23***) (Table 2, *entry 11*): From 3-bromothiophene (0.163 g, 1 mmol), 2-benzothiopheneboronic acid (0.356 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.1 mmol), product **23** was obtained in 25% (0.054 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28–7.44 (m, 5H), 7.51 (s, 1H), 7.74 (dd, J = 6.5, 1.7 Hz, 1H), 7.78 (dd, J = 6.5, 1.7 Hz, 1H).

2-(Benzo[b]thiophen-2-yl)-pyridine (***24***) (Table 2, *entry 12*): From 2-bromopyridine (0.158 g, 1 mmol), 2-benzothiopheneboronic acid (0.356 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **24** was obtained in 89% (0.188 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19 (ddd, J = 7.3, 5.0, 1.1 Hz, 1H), 7.30–7.37 (m, 2H), 7.72 (td, J = 7.3, 1.9 Hz, 1H), 7.76–7.90 (m, 4H), 8.62 (dd, J = 5.0, 1.0 Hz, 1H).

4-(Benzo[b]thiophen-2-yl)-pyridine (***25***) (Table 2, *entry 14*): From 4-bromopyridine (0.158 g, 1 mmol), 2-benzothiopheneboronic acid (0.356 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.01 mmol), product **25** was obtained in 90% (0.190 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (t, J = 4.5 Hz, 1H), 7.40 (t, J = 4.5 Hz, 1H), 7.60 (d, J = 3.2 Hz, 2H), 7.75 (s, 1H), 7.84 (ddd, J = 9.2, 4.5 Hz, 2H), 8.67 (bs, 2H).

4-(Thiophen-2-yl)-dibenzothiophene (***26***) (Table 2, *entry 16*): From 2-bromothiophene (0.163 g, 1 mmol), 4-dibenzothiopheneboronic acid (0.456 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.01 mmol), product **26** was obtained in 66% (0.176 g) yield. Oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (dd, J = 5.2, 3.5 Hz, 1H), 7.39–7.54 (m, 5H), 7.64 (m, 1H), 7.87 (dd, J = 6.2, 3.0 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 8.17 (dd, J = 6.2, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.6, 121.7, 122.62, 124.3, 124.5, 124.9, 125.5, 125.6, 126.5, 126.9, 127.8, 129.8, 135.6, 136.6, 139.4, 142.4; MS (70 eV); *m/z* (%) 266 ($M^{\bullet+}$, 100); $C_{16}H_{10}S_2$: Calcd C 72.14, H 3.78; Found C 71.97, H 3.57.

4-(Thiophen-3-yl)-dibenzothiophene (***27***) (Table 2, *entry 17*): From 3-bromothiophene (0.163 g, 1 mmol), 4-dibenzothiopheneboronic acid (0.456 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.004 mmol), product **27**

Table 3
Palladium–Tedicyp catalysed Suzuki coupling reactions with 3-furanboronic acid or 2-benzofuranboronic acid and heteroaryl bromides (Scheme 3)

Entry	Aryl bromide	Heteroarylboronic acid	Ratio substrate/catalyst	Product	Yield (%)[a]
1	3-Bromothiophene	3-Furanboronic acid	100	**8**	100 (94)
2	3-Bromothiophene	3-Furanboronic acid	1,000	**8**	59
3	2-Bromopyridine	3-Furanboronic acid	250	**29**	100 (88)
4	2-Bromopyridine	3-Furanboronic acid	1,000	**29**	10
5	3-Bromopyridine	3-Furanboronic acid	250	**30**	100 (90)
6	3-Bromopyridine	3-Furanboronic acid	1,000	**30**	95
7	4-Bromopyridine	3-Furanboronic acid	1,000	**31**	100 (92)
8	4-Bromopyridine	3-Furanboronic acid	10,000	**31**	89
9	5-Bromopyrimidine	3-Furanboronic acid	250	**32**	85 (77)
10	5-Bromopyrimidine	3-Furanboronic acid	1,000	**32**	39
11	3-Bromoquinoline	3-Furanboronic acid	250	**33**	82 (69)
12	3-Bromoquinoline	3-Furanboronic acid	1,000	**33**	36
13	4-Bromoisoquinoline	3-Furanboronic acid	250	**34**	68 (61)
14	2-Bromothiophene	2-Benzofuranboronic acid	250	**35**	100 (91)
15	2-Bromopyridine	2-Benzofuranboronic acid	1,000	**36**	100 (94)
16	3-Bromopyridine	2-Benzofuranboronic acid	250	**37**	88 (64)
17	3-Bromopyridine	2-Benzofuranboronic acid	1,000	**37**	68
18	4-Bromopyridine	2-Benzofuranboronic acid	1,000	**38**	100 (90)
19	4-Bromopyridine	2-Benzofuranboronic acid	10,000	**38**	95

[a] Conditions—catalyst: $[ClPd(C_3H_5)]_2$/Tedicyp = 1:2, aryl bromide (1 mmol), heteroarylboronic acid (2 mmol), K_2CO_3 (2 mmol), xylene, 130 °C, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.

was obtained in 94% (0.250 g) yield. Oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.63 (m, 6H), 7.75 (dd, J = 2.8, 1.3 Hz, 1H), 7.86 (dd, J = 4.1, 2.2 Hz, 1H), 8.10 (d, J = 7.5 Hz, 1H), 8.19 (dd, J = 4.1, 2.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.3, 121.7, 122.6, 122.8, 124.5, 124.9, 125.0, 126.1, 126.3, 126.8, 127.5, 131.7, 135.7, 136.4, 139.4, 141.0; MS (70 eV); *m/z* (%) 266 ($M^{\bullet+}$, 100); $C_{16}H_{10}S_2$: Calcd C 72.14, H 3.78; Found C 72.27, H 3.97.

2-(Dibenzothiophen-4-yl)-pyridine (***28***) (Table 2, *entry 18*): From 2-bromopyridine (0.158 g, 1 mmol), 4-dibenzothiopheneboronic acid (0.456 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.001 mmol), product **28** was obtained in 91% (0.238 g) yield. Oil ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (dd, J = 7.6, 4.9 Hz, 1H), 7.42–7.50 (m, 2H), 7.59 (t, J = 7.6 Hz, 1H), 7.83 (td, J = 7.6, 1.7 Hz, 1H), 7.91 (dd, J = 4.5, 3.0 Hz, 1H), 7.99 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 7.5 Hz, 1H), 8.20 (t, J = 5.1 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.86 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.9, 121.3, 122.1, 122.1, 122.4, 124.1, 124.5, 125.0, 126.7, 133.4, 134.8, 136.7, 137.3, 137.7, 142.0, 148.5, 156.2; MS (70 eV); *m/z* (%) 261 ($M^{\bullet+}$, 100); $C_{17}H_{11}NS$: Calcd C 78.13, H 4.24; Found C 78.29, H 4.00.

2-(Furan-3-yl)-pyridine (***29***) (Table 3, *entry 3*): From 2-bromopyridine (0.158 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **29** was obtained in 88% (0.128 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (dd, J = 1.8, 0.8 Hz, 1H), 7.13 (ddd, J = 7.5, 4.6, 1.1 Hz, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.49 (dd, J = 1.8, 0.5 Hz, 1H), 7.66 (td, J = 7.5, 1.9 Hz, 1H), 8.02 (s, 1H), 8.58 (d, J = 4.6 Hz, 1H).

3-(Furan-3-yl)-pyridine (***30***) (Table 3, *entry 5*): From 3-bromopyridine (0.158 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **30** was obtained in 90% (0.130 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.69 (dd, J = 0.9, 1.7 Hz, 1H), 7.27 (ddd, J = 8.0, 4.9, 1.0 Hz, 1H), 7.50 (t, J = 1.7 Hz, 1H), 7.70–7.79 (m, 2H), 8.48 (dd, J = 4.9, 1.1 Hz, 1H), 8.74 (dd, J = 3.4, 1.1 Hz, 1H).

4-(Furan-3-yl)-pyridine (***31***) (Table 3, *entry 7*): From 4-bromopyridine (0.158 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.001 mmol), product **31** was obtained in 92% (0.133 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.73 (dd, J = 1.9, 1.0 Hz, 1H), 7.36 (d, J = 4.5 Hz, 2H), 7.52 (t, J = 1.9 Hz, 1H), 7.86 (d, J = 1.0 Hz, 1H), 8.57 (d, J = 4.5 Hz, 2H).

5-(Furan-3-yl)-pyrimidine (***32***) (Table 3, *entry 9*): From 5-bromopyrimidine (0.159 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **32** was obtained in 77% (0.113 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, J = 1.8, 1.0 Hz, 1H), 7.55 (t, J = 1.8 Hz, 1H), 7.82 (t, J = 1.0 Hz, 1H), 8.84 (s, 2H), 9.10 (s, 1H).

3-(Furan-3-yl)-quinoline (***33***) (Table 3, *entry 11*): From 3-bromoquinoline (0.208 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **33** was obtained in 69% (0.135 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (dd, J = 1.9, 1.0 Hz, 1H), 7.50–7.58 (m, 2H), 7.67 (td, J = 8.3, 1.5 Hz, 1H), 7.81 (d, J = 8.3 Hz, 1H), 7.90 (s, 1H), 8.08 (d, J = 8.3 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 9.07 (d, J = 2.4 Hz, 1H).

4-(Furan-3-yl)-isoquinoline (***34***) (Table 3, *entry 13*): From 4-bromoisoquinoline (0.208 g, 1 mmol), 3-furanboronic acid (0.224 g, 2 mmol), K_2CO_3 (0.276 g, 2 mmol) and Pd complex (0.004 mmol), product **34** was obtained in 61% (0.119 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (dd, J = 1.9, 1.0 Hz, 1H), 7.56–7.78 (m, 4H), 8.00 (d, J = 8.6 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 8.51 (s, 1H), 9.20 (s, 1H).

2-(Thiophen-2-yl)-benzofuran (***35***) (Table 3, *entry 14*): From 2-bromothiophene (0.163 g, 1 mmol), 2-benzofuranboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.004 mmol), product **35** was obtained in 91% (0.182 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 7.10 (dd, J = 5.4, 3.6 Hz, 1H), 7.15–7.30 (m, 3H), 7.45–7.57 (m, 3H).

2-(Benzofuran-2-yl)-pyridine (***36***) (Table 3, *entry 15*): From 2-bromopyridine (0.158 g, 1 mmol), 2-benzofuranboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.001 mmol), product **36** was obtained in 94% (0.183 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.40 (m, 4H), 7.58 (dd, J = 7.6, 0.8 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.90 (t, J = 7.8 Hz, 1H), 8.00 (d, J = 7.8 Hz, 1H), 8.71 (d, J = 4.3 Hz, 1H).

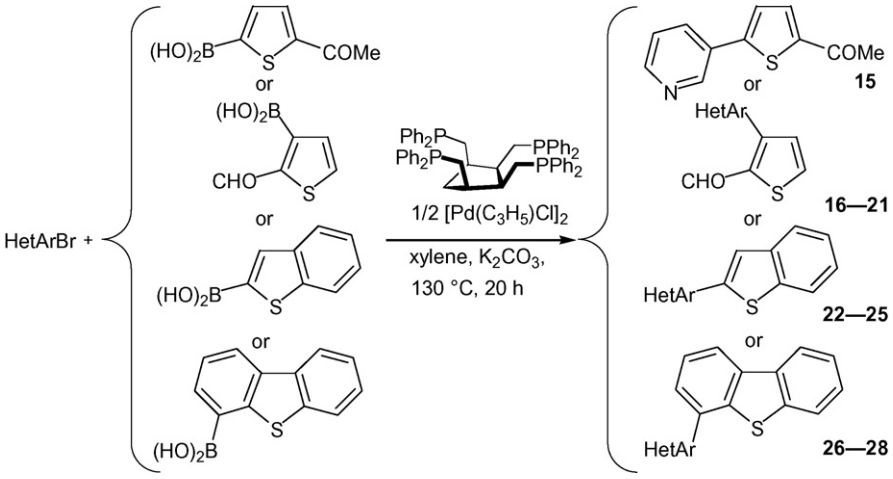
3-(Benzofuran-2-yl)-pyridine (***37***) (Table 3, *entry 16*): From 3-bromopyridine (0.158 g, 1 mmol), 2-benzofuranboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.004 mmol), product **37** was obtained in 64% (0.125 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (s, 1H), 7.28–7.32 (m, 2H), 7.35 (t, J = 7.9 Hz, 1H), 7.59 (d, J = 8.3 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 8.29 (d, J = 7.9 Hz, 1H), 8.69 (bs, 1H), 9.23 (bs, 1H).

4-(Benzofuran-2-yl)-pyridine (***38***) (Table 3, *entry 18*): From 4-bromopyridine (0.158 g, 1 mmol), 2-benzofuranboronic acid (0.312 g, 2 mmol), K_2CO_3 (0.324 g, 2 mmol) and Pd complex (0.001 mmol), product **38** was obtained in 90% (0.176 g) yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.38 (t, J = 8.5 Hz, 1H), 7.55 (d, J = 8.5 Hz, 1H), 7.64 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 2.9 Hz, 2H), 8.70 (bs, 2H).

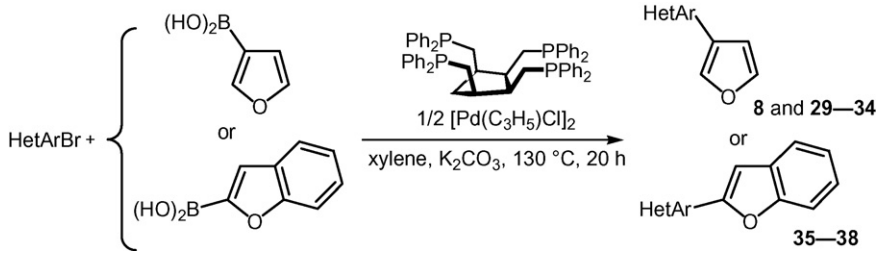
CAS Registry No.: **1**, 492-97-7; **2**, 2404-89-9; **3**, 27521-81-9; **4**, 3319-99-1; **5**, 21298-53-3; **6**, 21298-54-4; **7**, 3172-56-3; **8**, 27521-83-1; **9**, 21298-55-5; **10**, 21308-81-6; **11**, 21308-82-7; **12**, 5875-02-7; **13**, 56421-85-3; **14**, 112370-12-4; **15**, 187540-78-9; **16**, 91545-61-8; **17**, 91545-62-9; **19**, 150711-16-3; **20**, 16970-91-1; **21**, 166450-81-3; **22**, 55164-48-2; **23**, 55164-49-3; **24**, 38210-35-4; **25**, 133617-47-7; **29**, 55484-05-4; **30**, 55484-06-5; **31**, 27079-81-8; **32**, 560994-06-1; **33**, 104967-58-0; **34**, 112370-10-2; **35**, 65246-50-6; **36**, 7035-05-4; **37**, 7035-06-5; **38**, 7035-04-3.

3. Results and discussion

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 [2]. Pyridines or quinolines are π-electron deficient. Thiophenes or furanes are π-electron excessive. If the oxidative addition of the aryl halides



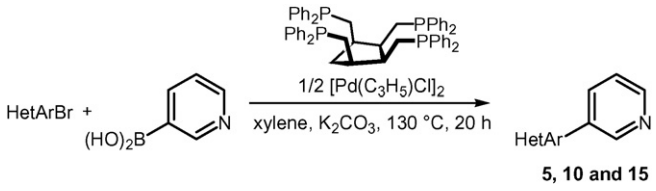
Scheme 2.



Scheme 3.

to the palladium complex is the rate-limiting step of the reaction with this catalyst, the reactions should be slower with bromothiophenes or bromofuranes than with bromopyridines or bromoquinolines. Furthermore palladium(II) possesses strong thiophilicity. This is reflected in the poisoning effects of the sulphur atom on some palladium-catalysed reactions. This poisoning effect has also been observed in the presence of nitrogen atoms. For this reason, the position of the halide on a heteroaromatic ring has an important effect on the reactions rates.

We describe here successively the reactions of bromopyridines, bromoquinolines, bromothiophenes, a bromopyrimidine and a bromofuran with thiopheneboronic acid derivatives (Schemes 1 and 2, Tables 1 and 2), furanboronic acid derivatives (Scheme 3, Table 3), and finally a pyridineboronic acid (Scheme 4, Table 4). For this study, based on previous results [31,32], xylene was chosen as the solvent and potassium carbonate as the base. The reactions were generally performed under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst. In order to achieve high substrate/catalyst ratios, we have generally performed the reactions at an elevated temperature: 130 °C.



Scheme 4.

First, to examine the influence between the 2- and 3-boronated positions of thiophene on the coupling, we studied the reactivity of 2- and 3-thiopheneboronic acids with several aryl bromides (Scheme 1, Table 1). With 3-thiopheneboronic acid, good results were obtained for the coupling with bromothiophenes, bromopyridines, 5-bromopyrimidine, a bromofuran or bromoquinolines (Table 1, entries 13–28). TONs of 100–3900 were obtained with this arylboronic acid. In all cases, the reactions with 2-thiopheneboronic acid led to lower TONs of 20–140 (Table 1, entries 1–12). Using this substrate, the highest TON was obtained for the coupling with 2-bromopyridine: 140 (Table 1, entry 8). On the other hand, the reaction of 3-thiopheneboronic acid with 2-bromopyridine gave a TON of 1000 (Table 1, entries 19 and 20).

These results suggest that with 2-thiopheneboronic acid, a possible interaction between the sulphur atom and the palladium complex has a decelerating effect on the reaction rate. The electron-rich aryl bromide 3-bromothiophene and electron-poor 3-bromopyridine led to similar TONs, indicating that in several cases, the oxidative addition of the heteroaryl bromides to palladium is not the rate-limiting step of the catalytic cycle for the coupling with 2-thiopheneboronic acid (Table 1, entries 4 and 10). A similar observation had been made with simple aryl bromides [32]. We had also previously observed that slightly higher reaction rates could be obtained when there are electron-withdrawing substituents on the arylboronic acid. However, in general their electron properties do not seem to have a large influence on the transmetallation rate with the palladium catalyst [30d]. In fact, the relatively low reaction rates observed

Table 4
Palladium–Tedicyp catalysed Suzuki coupling reactions with 3-pyridineboronic acid and heteroaryl bromides (Scheme 4)

Entry	Aryl bromide	Ratio substrate/catalyst	Product	Yield (%)[a]
1	2-Bromothiophene	50	**5**	100 (92)
2	3-Bromothiophene	20	**10**	100 (94)
3	3-Bromothiophene	50	**10**	60
4	2-Acetyl-5-bromothiophene	20	**15**	100 (90)
5	2-Acetyl-5-bromothiophene	50	**15**	80

[a] Conditions—catalyst: $[ClPd(C_3H_5)]_2$/Tedicyp = 1:2, aryl bromide (1 mmol), 3-pyridineboronic acid (2 mmol), K_2CO_3 (2 mmol), xylene, 130 °C, 20 h, yields are GC and NMR conversions, yields in parenthesis are isolated.

in some cases with some 2-thiopheneboronic acids more likely come from the poisoning of the catalyst by the coordinating properties of this class of substrates which often rendered the catalytic reactions totally ineffective.

We also examined the reactivity of four thiopheneboronic acid derivatives (Scheme 2, Table 2). The presence of electron-withdrawing substituents on these substrates led to lower TONs than the corresponding unsubstituted compounds. With 2-acetyl-5-thiopheneboronic acid or 2-formyl-3-thiopheneboronic acid the coupling products were obtained in medium to good yields with 8–83 TONs (Table 2, entries 1–9). The coupling of 2-benzothiopheneboronic acid with heteroaryl bromides also proceeds in low to medium TONs of 3–242 (Table 2, entries 10–15). With these three thiopheneboronic acid derivatives lower TONs were obtained with bromothiophenes as coupling partner than with bromopyridines. 4-Dibenzothiopheneboronic acid gave more satisfactory results in terms of substrate/catalyst ratio. The couplings of this substrate with bromothiophenes or 2-bromopyridine led to high TONs of 78–3000 (Table 2, entries 16–19).

Then, we examined the reactivity of 3-furanboronic acid and 2-benzofuranboronic acid (Scheme 3, Table 3). Furan is also a π-electron-excessive heteroarene; however, with this substrate no poisoning effect due to the coordination of the heteroatom to the palladium centre should be observed. We were pleased to find that this substrate can react successfully with 3-bromothiophene, 2-, 3-bromopyridines or 3-bromoquinoline with as little as 0.4–0.1 mol% catalyst (Table 3, entries 1–13). The highest TON: 8900 was obtained using 4-bromopyridine as coupling partner. Quite similar results were obtained with 2-benzofuranboronic acid (Table 3, entries 14–20). With this substrate, the reactions gave high yields of the arylated products **35**–**38** with a TON of 250 using 2-bromothiophene and TONs of 1000–9500 with 2-, 3-, or 4-bromopyridines.

Pyridines are probably the most common heterocyclic motif found in pharmaceutically active compounds. Therefore, preparative methods of biheteroaryl containing pyridines remains an essential research topic in organic synthesis. We performed a few coupling reactions between 3-pyridineboronic acid with bromothiophenes (Scheme 4, Table 4). These couplings required 2 mol% catalyst in order to obtain satisfactory yields of products **5**, **10** and **15**. The reverse reaction using 3-bromopyridine and 3-thiopheneboronic acid led to an higher TON of 235 (Table 1, entry 22).

4. Conclusion

In summary, we have established that the Tedicyp–palladium system is an efficient catalyst for the coupling of heteroarylboronic acids with heteroaryl bromides. To the best of our knowledge, this work represents one of the most wide-ranging studies reported so far for the preparation of biheteroaryls via the Suzuki coupling. Since the electronic properties of heteroarylboronic acids appears to have a minor influence on the reactions rates, their coordinative/poisoning properties to palladium seems to have a decisive influence. On the other hand, the electronic properties of the heteroaryl bromide often have an important effect on the yields and rates of the reactions. In general, better results were obtained for the coupling with the electron-poor bromopyridines than with the electronically rich bromothiophenes. It should be noted that a large part of these biheteroaryl products could behave as bidentate ligands with palladium and therefore act as poisons for the catalyst. With this Pd–tetraphosphine catalyst, several reactions could be performed with as little as 0.1% catalyst without further optimisation of the reaction conditions. However, it remains quite difficult to predict the most suitable combination of reactants in order to prepare these biheteroaryls using low catalyst loadings.

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