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Efficient coupling of heteroaryl halides with arylboronic acids in the presence of a palladium–tetraphosphine catalyst

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Abstract

Cis,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane:·1/2[PdCl(C_3H_5)]$_2$ system catalyses the Suzuki cross-coupling of heteroaryl halides with a range of arylboronic acids with very high ratio substrate/catalyst in good yields. Substrates such as pyridines, quinolines, thiophenes, an indole, pyrimidines or a furane have been used successfully.

Keywords: Tetraphosphine; Palladium; Suzuki-coupling; Arylboronic acids; Heteroaryl halides

1. Introduction

Heterobiaryls have important biological properties [1]. The palladium-catalysed cross-coupling reaction between heteroaryl halides and arylboronic acids provides a very efficient method for the preparation of heterobiaryls derivatives [2,3]. Organoboron reagents exhibit greater functional group compatibility than organozinc or Grignard reagents. Moreover, the innocuous nature of boronic acids, which are generally nontoxic and thermally, air-, and moisture-stable, is a practical advantage of the Suzuki reaction, relative to many other cross-coupling processes. As a consequence the Suzuki cross-coupling reaction has found wide application in organic synthesis. However, this procedure suffer generally from high catalyst loading. Since a few years some very efficient catalyst have been described for Suzuki reaction [4]. For example bulky phosphites such as P(*O*-2,4-^{t}Bu$_2$C$_6$H$_3$)$_3$ or P(*O*-^{i}Pr)$_3$ have been used successfully [4]. A carbene ligand also leads to the formation of palladium catalysts that are more efficient than those of triphenylphosphine for this reaction [4g]. A very efficient catalyst for this reaction has been prepared with the bulky ligand (*o*-biphenyl)P(^{t}Bu)$_2$ [4c,e]. However, most of the results, which have been described with these ligands, were obtained for the coupling of simple aryl halides. Few results have been reported using heteroaromatic substrates [1,5]. In this paper we wish to report our results for the coupling of several heteroaromatic substrates with a variety of arylboronic acids using a tetraphosphine/palladium catalyst.

The nature of the phosphine ligand on complexes has an important influence on the stability of the catalysts and on the rate of catalysed reactions. In order to find more stable and more efficient palladium catalysts, we have prepared the new tetrapodal [6] phosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp **1** (Fig. 1) [7a] in which the four diphenylphosphinoalkyl groups are stereospecifically bound to the same face of the cyclopentane ring.

We have reported recently that the complex formed by association of **1** with [PdCl(C_3H_5)]$_2$ is an extremely efficient catalyst for allylic substitution, Heck vinylation reaction [7] and for the Suzuki cross-coupling of arylhalides with arylboronic acids [8]. Some preliminary results using heteroarylbromides have been reported [8c]. Now, we wish to describe the results obtained with several heteroaryl halides and a variety of arylboronic acids using **1** as ligand.

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Tedicyp 1

Fig. 1.

2. Experimental

2.1. General

All reactions under argon were run using vacuum lines in Schlenk tubes in oven-dried glassware. In order to avoid contamination with palladium residues, the reactions were performed in brand new Pyrex tubes for chromatography inserted in Schlenk tubes with new stirring bars; dry xylene was added in the Schlenk tube for the transmission of the temperature of the oil bath to the Pyrex tubes. Xylene analytical grade (98%) was not distilled before use. Some of the aryl halides were distilled before use. Potassium carbonate (99+) was used without drying. The reactions were followed by GC and NMR for high boiling point substrates and by GC for low boiling point substrates. ^{1}H (400 or 300 MHz) spectra were recorded in $CDCl_3$ solutions. Chemical shift (δ) are reported in ppm relative to $CDCl_3$. Flash chromatography were performed on silica gel (230–400 mesh) eluting with ether–pentane mixtures.

2.2. Catalytic procedure

As a typical experiment, the reaction of aryl halide (10 mmol), arylboronic acid (15 or 20 mmol) and K_2CO_3 (2.76 g, 20 mmol) at 130 °C during 20 h in dry xylene (10 ml) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/1/2 $[PdCl(C_3H_5)]_2$ complex under argon affords the corresponding products after addition of water, extraction with ether or dichloromethane, separation, drying ($MgSO_4$), evaporation and chromatography on silica gel.

2.3. Coupling products with halopyridines (Table 1)

2-Phenylpyridine (**2**): (Table 1, entry 2), 2-bromopyridine (0.95 ml, 10 mmol), Pd complex (0.1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-phenylpyridine in 62% (0.96 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 4.8$ Hz, 1H), 7.90 (d, $J = 6.8$ Hz, 2H), 7.63 (m, 2H), 7.42–7.30 (m, 3H), 7.13 (m, 1H).

2-(2-Methylphenyl)pyridine (**3**): (Table 1, entry 4), 2-bromopyridine (0.95 ml, 10 mmol), Pd complex (1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(2-methylphenyl)pyridine in 80% (1.35 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.69$ (d, $J = 4.9$ Hz, 1H), 7.72 (td, $J = 7.7$ and 1.7 Hz, 1H), 7.39 (m, 2H), 7.28–7.24 (m, 4H), 2.36 (s, 3H).

3-Phenylpyridine (**4**): (Table 1, entry 5), 3-bromopyridine (0.95 ml, 10 mmol), Pd complex (1×10^{-2} μmol) and benzeneboronic acid (1.83 g, 15 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-phenylpyridine in 98% (1.52 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.85$ (d, $J = 1.7$ Hz, 1H), 8.60 (dd, $J = 4.9$ and 1.7 Hz, 1H), 7.85 (dt, $J = 8.0$ and 1.7 Hz, 1H), 7.60 (m, 2H), 7.50–7.35 (m, 3H), 7.29 (dd, $J = 8.0$ and 4.9 Hz, 1H).

3-(4-Methoxyphenyl)pyridine (**5**): (Table 1, entry 8), 3-bromopyridine (0.95 ml, 10 mmol), Pd complex (0.1 μmol) and 4-methoxyphenylboronic acid (3.04 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(4-methoxyphenyl)pyridine in 82% (1.52 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.81$ (s, 1H), 8.53 (d, $J = 4.9$ Hz, 1H), 7.81 (d, $J = 8.0$ Hz, 1H), 7.48 (d, $J = 8.7$ Hz, 2H), 7.31 (dd, $J = 8.0$ and 4.9 Hz, 1H), 6.94 (d, $J = 8.7$ Hz, 2H), 3.80 (s, 3H).

3-(4-Fluorophenyl)pyridine (**6**): (Table 1, entry 10), 3-bromopyridine (0.95 ml, 10 mmol), Pd complex (0.1 μmol) and 4-fluorophenylboronic acid (2.10 g, 15 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(4-fluorophenyl)pyridine in 96% (1.66 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.82$ (d, $J = 1.5$ Hz, 1H), 8.63 (d, $J = 4.7$ Hz, 1H), 7.85 (d, $J = 7.8$ Hz, 1H), 7.50 (dd, $J =$ 8.7 and 5.3 Hz, 2H), 7.38 (dd, $J = 7.8$ and 4.7 Hz, 1H), 7.15 (dd, $J = 8.7$ and 8.7 Hz, 2H).

3-(3-Trifluoromethylphenyl)pyridine (**7**): (Table 1, entry 11), 3-bromopyridine (0.95 ml, 10 mmol), Pd complex (1×10^{-2} μmol) and 3-trifluoromethylphenylboronic acid (3.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(3-trifluoromethylphenyl)pyridine in 71% (1.58 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.82$ (d, $J = 1.5$ Hz, 1H), 8.61 (d, $J = 4.7$ Hz, 1H), 8.02 (s, 1H), 7.96 (d, $J = 7.7$ Hz, 1H), 7.88 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.55 (m, 1H), 7.29 (dd, $J = 8.7$ and 5.3 Hz, 1H).

3-(2-Methylphenyl)pyridine (**8**): (Table 1, entry 12), 3-bromopyridine (0.95 ml, 10 mmol), Pd complex (1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(2-methylphenyl)pyridine in 87% (1.47 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.76$ (s, 1H), 8.15 (dd, $J = 5.5$ and 1.9 Hz, 1H), 7.81 (dt, $J = 7.7$ and 1.9 Hz, 1H), 7.51 (dd, $J = 7.7$ and 5.5 Hz, 1H), 7.35–7.16 (m, 4H), 2.67 (s, 3 H, CH_3).

4-Phenylpyridine (**9**): (Table 1, entry 14), 4-bromopyridine hydrochloride (1.94 g, 10 mmol), Pd complex

Table 1
Palladium catalysed Suzuki cross-coupling reactions with halopyridines

Entry	Aryl halide	Arylboronic acid	Ligand	Product	Ratio substrate/catalyst	Yield (%)	TON
1	2-Bromopyridine	Benzeneboronic acid	**1**	**2**	10 000	100 [a]	10 000
2	2-Bromopyridine	Benzeneboronic acid	**1**	**2**	100 000	62	62 000
3	2-Bromopyridine	2-methylphenylboronic acid	**1**	**3**	1000	100 [a]	1000
4	2-Bromopyridine	2-methylphenylboronic acid	**1**	**3**	10 000	80	8000
5	3-Bromopyridine	Benzeneboronic acid	**1**	**4**	1 000 000	98 [b c]	980 000
6	3-Bromopyridine	Benzeneboronic acid	**1**	**4**	10 000 000	25 [a]	2 500 000
7	3-Bromopyridine	Benzeneboronic acid	dppe	**4**	100 000	82	82 000
8	3-Bromopyridine	4-methoxyphenylboronic acid	**1**	**5**	100 000	82	82 000
9	3-Bromopyridine	4-methoxyphenylboronic acid	**1**	**5**	1 000 000	12 [a]	120 000
10	3-Bromopyridine	4-fluorophenylboronic acid	**1**	**6**	100 000	96 [b d]	96 000
11	3-Bromopyridine	3-trifluoromethylphenylboronic acid	**1**	**7**	1 000 000	71	710 000
12	3-Bromopyridine	2-methylphenylboronic acid	**1**	**8**	10 000	87	8700
13	4-Bromopyridine	Benzeneboronic acid	**1**	**9**	10 000	100 [a e]	10 000
14	4-Bromopyridine	Benzeneboronic acid	**1**	**9**	1 000 000	81 [e]	810 000
15	4-Bromopyridine	4-fluorophenylboronic acid	**1**	**10**	100 000	85 [e]	85 000
16	4-Bromopyridine	2-methylphenylboronic acid	**1**	**11**	100 000	59 [e]	59 000
17	2-Chloropyridine	Benzeneboronic acid	dppe	**2**	1000	40 [f]	400
18	2-Chloropyridine	Benzeneboronic acid	**1**	**2**	10 000	89	8900
19	3-Chloropyridine	Benzeneboronic acid	**1**	**4**	250	94	235
20	3-Chloropyridine	Benzeneboronic acid	**1**	**4**	1000	20 [a]	200
21	4-chloropyridine	Benzeneboronic acid	**1**	**9**	1000	86	860
22	3-Iodopyridine	Benzeneboronic acid	**1**	**4**	1 000 000	96	960 000
23	3-Iodopyridine	Benzeneboronic acid	**1**	**4**	10 000 000	40 [a]	4 000 000
24	5-Bromopyridine-3-carboxamide	Benzeneboronic acid	**1**	**12**	10 000	93	9300
25	2-amino-5-Bromo pyridine	Benzeneboronic acid	**1**	**13**	10 000	85	8500

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/ligand 1/2, see Ref. [7a], ArX (one equivalent), $ArB(OH)_2$ (two equivalent), K_2CO_3 (two equivalent), xylene, 130 °C, 20 h, isolated yields.
[a] GC yield.
[b] $ArB(OH)_2$ (1.5 equivalents).
[c] 115 h.
[d] 90 h.
[e] 4-Bromopyridine hydrochloride was used directly with three equivalent of K_2CO_3.
[f] 72 h.

(1×10^{-2} μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 4-phenylpyridine in 81% (1.26 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.63$ (d, $J = 5.8$ Hz, 2H), 7.61 (d, $J = 5.8$ Hz, 2H), 7.49–7.44 (m, 5H).

4-(4-Fluorophenyl)pyridine (**10**): (Table 1, entry 15), 4-bromopyridine hydrochloride (1.94 g, 10 mmol), Pd complex (0.1 μmol) and 4-fluorophenylboronic acid (2.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 4-(4-fluorophenyl)pyridine in 85% (1.47 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.63$ (d, $J = 5.6$ Hz, 2H), 7.60 (d, $J = 5.6$ Hz, 2H), 7.46 (dd, $J = 8.8$ and 5.3 Hz, 2H), 7.06 (dd, $J = 8.8$ and 8.7 Hz, 2H).

4-(2-Methylphenyl)pyridine (**11**): (Table 1, entry 16), 4-bromopyridine hydrochloride (1.94 g, 10 mmol), Pd complex (0.1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 4-(2-methylphenyl)pyridine in 59% (1.00 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.60$ (d, $J = 5.8$ Hz, 2H), 7.25–7.14 (m, 6H), 2.21 (s, 3H).

5-Phenylpyridine-3-carboxamide (**12**): (Table 1, entry 24), 5-bromopyridine-3-carboxamide (2.01 g, 10 mmol), Pd complex (1 μmol) and and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 5-phenylpyridine-3-carboxamide in 93% (1.84 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.99$ (s, 2H), 8.41 (s, 1H), 8.06 (s, 1H), 7.78 (s, 1H), 7.55 (m, 2H), 7.47–7.42 (m, 3H).

2-Amino-5-phenylpyridine (**13**): (Table 1, entry 25), 2-amino-5-bromopyridine (1.73 g, 10 mmol), Pd complex (1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-amino-5-phenylpyridine in 85% (1.44 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.21$ (d, $J = 2.0$ Hz, 1H), 7.50 (dd, $J = 8.6$ and 2.0 Hz, 1H), 7.34–7.20 (m, 5H), 6.42 (d, $J = 8.6$ Hz, 1H), 4.51 (br.s, 2H).

2.4. Coupling products with haloquinolines (Table 2)

3-Phenylquinoline (**14**): (Table 2, entry 1), 3-bromoquinoline (1.36 ml, 10 mmol), Pd complex (1×10^{-2}

Table 2
Palladium catalysed Suzuki cross-coupling reactions with haloquinolines

Entry	Aryl halide	Arylboronic acid	Ligand	Product	Ratio substrate/catalyst	Yield (%)	TON
1	3-Bromoquinoline	Benzeneboronic acid	**1**	**14**	1 000 000	82	820 000
2	3-Bromoquinoline	Benzeneboronic acid	dppe	**14**	100 000	83	83 000
3	3-Bromoquinoline	2-Methylphenylboronic acid	**1**	**15**	100 000	60	60 000
4	4-Bromoisoquinoline	Benzeneboronic acid	**1**	**16**	10 000	68	6800
5	2-Chloroquinoline	Benzeneboronic acid	**1**	**17**	10 000	88	8800
6	2-Chloroquinoline	Benzeneboronic acid	**1**	**17**	100 000	30 [a]	30 000
7	2-Chloroquinoline	1-Naphthaleneboronic acid	**1**	**18**	1000	90	900
8	2-Chloroquinoline	2-Methylphenylboronic acid	**1**	**19**	1000	91	910
9	2-Chloroquinoline	2-Methylphenylboronic acid	**1**	**19**	10 000	37 [a]	3700

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/ligand 1/2, see Ref. [7a], ArX (one equivalent), $ArB(OH)_2$ (two equivalents), K_2CO_3 (two equivalents), xylene, 130 °C, 20 h, isolated yields.
[a] GC yield.

μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-phenylquinoline in 82% (1.68 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.18$ (s, 1H), 8.27 (d, $J = 2.2$ Hz, 1H), 8.14 (d, $J = 8.5$ Hz, 1H), 7.85 (d, $J = 8.2$ Hz, 1H), 7.70 (m, 3H), 7.58-7.49 (m, 3H), 7.42 (m, 1H).

3-(2-Methylphenyl)quinoline (**15**): (Table 2, entry 3), 3-bromoquinoline (1.36 ml, 10 mmol), Pd complex (0.1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(2-methylphenyl)quinoline in 60% (1.31 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.91$ (s, 1H), 8.15 (d, $J = 8.3$ Hz, 1H), 8.09 (s, 1H), 7.85 (d, $J = 8.3$ Hz, 1H), 7.73 (m, 1H), 7.58 (m, 2H), 7.32 (m, 3H), 2.31 (s, 3H).

4-Phenylisoquinoline (**16**): (Table 2, entry 4), 4-bromoisoquinoline (2.08 g, 10 mmol), Pd complex (1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 4-phenylisoquinoline in 68% (1.39 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.28$ (s, 1H), 8.50 (s, 1H), 8.04 (d, $J = 7.9$ Hz, 1H), 7.90 (d, $J = 7.9$ Hz, 1H), 7.69-7.62 (m, 2H), 7.52-7.35 (m, 5H).

2-Phenylquinoline (**17**): (Table 2, entry 5), 2-chloroquinoline (1.31 ml, 10 mmol), Pd complex (1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-phenylquinoline in 88% (1.81 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.00$ (m, 3H), 7.82 (dd, $J = 8.6$ and 8.9 Hz, 1H), 7.63–7.48 (m, 3H), 7.36–7.27 (m, 4H).

2-(1-Naphthyl)quinoline (**18**): (Table 2, entry 7), 2-chloroquinoline (1.31 ml, 10 mmol), Pd complex (10 μmol) and 1-naphthaleneboronic acid (3.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(1-naphthyl)quinoline in 90% (2.30 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.31$ (d, $J = 8.5$ Hz, 1H), 8.21 (d, $J = 8.5$ Hz, 2H), 7.96 (m, 2H), 7.86 (d, $J = 8.3$ Hz, 1H), 7.77 (m, 2H), 7.68 (d, $J = 8.5$ Hz, 1H), 7.64–7.48 (m, 4H).

2-(2-Methylphenyl)quinoline (**19**): (Table 2, entry 8), 2-chloroquinoline (1.31 ml, 10 mmol), Pd complex (10 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(2-methylphenyl)quinoline in 91% (2.00 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.18$ (d, $J = 8.4$ Hz, 2H), 7.84 (d, $J = 7.4$ Hz, 1H), 7.73 (dd, $J = 7.7$ and 7.0 Hz, 1H), 7.54 (m, 3H), 7.34 (m, 3H), 2.43 (s, 3H).

2.5. Coupling products with a bromoindole, bromopyrimidines and a bromothiazole (Table 3)

5-Phenylindole (**20**): (Table 3, entry 2), 5-bromoindole (1.96 g, 10 mmol), Pd complex (0.1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 5-phenylindole in 90% (1.74 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.06$ (brs, 1H), 7.96 (s, 1H), 7.76 (d, $J = 8.5$ Hz, 2H), 7.52 (m, 3H), 7.45–7.35 (m, 2H), 7.20 (t, $J = 3.1$ Hz, 1H), 6.67 (m, $J = 3.1$ Hz, 1H).

5-(2-Methylphenyl)indole (**21**): (Table 3, entry 3), 5-bromoindole (1.96 g, 10 mmol), Pd complex (0.1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 5-(2-methylphenlyl)indole as a red liquide in 70% (1.45 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.00$ (brs, 1H), 7.64 (s, 1H), 7.41 (d, $J = 8.4$ Hz, 1H), 7.38–7.29 (m, 4H), 7.24 (m, 2H), 6.62 (s, 1H), 2.27 (s, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta =$ 140.0, 135.7, 134.7, 133.7, 130.3, 130.2, 127.7, 126.7, 125.6, 124.7, 123.7, 121.0, 110.5, 102.6, 20.7. MS (70 ev); *m/z* (%): 207 (100) [M^+], 207 (87), 204 (19), 179 (20), 178 (16), 103 (13), 89 (15), 63 (11), 50 (13).

5-Phenylpyrimidine (**22**): (Table 3, entry 5), 5-bromopyrimidine (1.59 g, 10 mmol), Pd complex (0.1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pen-

Table 3
Palladium catalysed Suzuki cross-coupling reactions with a bromoindole, bromopyrimidines and a bromothiazole

Entry	Aryl halide	Arylboronic acid	Product	Ratio substrate/catalyst	Yield (%)	TON
1	5-Bromoindole	Benzeneboronic acid	**20**	10 000	100 [a]	10 000
2	5-Bromoindole	Benzeneboronic acid	**20**	100 000	90	90 000
3	5-Bromoindole	2-Methylphenylboronic acid	**21**	100 000	70	70 000
4	5-Bromopyrimidine	Benzeneboronic acid	**22**	10 000	100 [a]	10 000
5	5-Bromopyrimidine	Benzeneboronic acid	**22**	100 000	78	78 000
6	5-Bromopyrimidine	Benzeneboronic acid	**22**	1 000 000	8 [a]	80 000
7	5-Bromopyrimidine	2-Methylphenylboronic acid	**23**	10 000	80	8000
8	2-Chloropyrimidine	Benzeneboronic acid	**24**	100	100 [a]	100
9	2-Chloropyrimidine	Benzeneboronic acid	**24**	1000	58	580
10	2-Chloropyrimidine	2-Methylphenylboronic acid	**25**	100	87	87
11	2-Bromothiazole	Benzeneboronic acid	**26**	10 000	60	6000
12	2-Bromothiazole	2-Methylphenylboronic acid	**27**	100	85	85
13	2-Bromothiazole	2-Methylphenylboronic acid	**27**	1000	30 [a]	300

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/tedicyp: 1/2 see Ref. [7a], ArX (one equivalent), $ArB(OH)_2$ (two equivalents), K_2CO_3 (two equivalents), xylene, 130 °C, 20 h, isolated yields.
[a] GC yield.

tane: 3/7) to give 5-phenylpyrimidine in 78% (1.22 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.13$ (s, 1H), 8.85 (s, 2H), 7.49–7.39 (m, 5H).

5-(2-Methylphenyl)pyrimidine (**23**): (Table 3, entry 7), 5-bromopyrimidine (1.59 g, 10 mmol), Pd complex (1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 5-(2-methylphenyl)pyrimidine as a white solid in 80% (1.36 g) isolated yield. M.p. 120 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta =$ 9.23 (s, 1H), 8.75 (s, 2H), 7.35–7.18 (m, 4H), 2.27 (s, 3H). ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 156.9, 156.5, 135.6, 135.3, 134.0, 130.8, 129.8, 129.0, 126.4, 20.2. MS (70 ev); *m/z* (%): 170 (100) [M^+], 169 (26), 116 (26), 115 (54), 89 (11), 63 (10).

2-Phenylpyrimidine (**24**): (Table 3, entry 9), 2-chloropyrimidine (1.14 g, 10 mmol), Pd complex (10 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-phenylpyrimidine in 58% (0.91 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.82$ (d, $J = 4.8$ Hz, 2H), 8.46 (d, $J = 7.3$ Hz, 2H), 7.50 (m, 3H), 7.20 (t, $J = 4.8$ Hz, 1H).

2-(2-Methylphenyl)pyrimidine (**25**): (Table 3, entry 10), 2-chloropyrimidine (1.14 g, 10 mmol), Pd complex (100 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(2-methylphenyl)pyrimidine in 87% (1.48 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.94$ (d, $J = 4.9$ Hz, 2H), 7.72 (d, $J = 7.2$ Hz, 1H), 7.60–7.49 (m, 3H), 7.20 (t, $J = 4.9$ Hz, 2H), 2.53 (s, 3H).

2-Phenylthiazole (**26**): (Table 3, entry 11), 2-bromothiazole (1.64 g, 10 mmol), Pd complex (1 μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 4/6) to give 2-phenylthiazole in 60% (0.97 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.03$ (m, 2H), 7.85 (d, $J = 3.5$ Hz, 1H), 7.50–7.40 (m, 3H), 7.37 (d, $J = 3.5$ Hz, 1H).

2-(2-Methylphenyl)thiazole (**27**): (Table 3, entry 12), 2-bromothiazole (1.64 g, 10 mmol), Pd complex (100 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 4/6) to give 2-(2-methylphenyl)thiazole in 85% (1.49 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 3.4$ Hz, 1H), 7.70 (d, $J = 7.4$ Hz, 1H), 7.37 (d, $J = 3.4$ Hz, 1H), 7.32–7.24 (m, 3H), 2.57 (s, 3H).

2.6. Coupling products with halothiophenes (Table 4)

2-Phenylthiophene (**28**): (Table 4, entry 1), 2-iodothiophene (2.10 g, 10 mmol), Pd complex (10^{-2} μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-phenylthiophene in 100% (1.60 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (d, $J = 7.2$ Hz, 2H), 7.44 (dd, $J = 2.8$ and 1.6 Hz, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.37 (d, $J = 3.8$ Hz, 1H), 7.33 (d, $J =$ 5.0 Hz, 1H), 7.13 (dd, $J = 5.0$ and 3.8 Hz, 1H).

2-(4-Methoxyphenyl)thiophene (**29**): (Table 4, entry 6), 2-bromothiophene (1.63 g, 10 mmol), Pd complex (10^{-2} μmol) and 4-methoxyphenylboronic acid (3.04 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(4-methoxyphenyl)thiophene in 85% (1.62 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.52$ (d, $J = 8.7$ Hz, 2H), 7.20 (m, 2H), 7.05 (dd, $J = 5.1$ and 3.8 Hz, 1H), 6.90 (d, $J =$ 8.7 Hz, 2H), 3.83 (s, 3H).

2-(4-Fluorophenyl)thiophene (**30**): (Table 4, entry 7), 2-bromothiophene (1.63 g, 10 mmol), Pd complex (0.1

Table 4
Palladium catalysed Suzuki cross-coupling reactions with halothiophenes

Entry	Aryl halide	Arylboronic acid	Product	Ratio substrate/catalyst	Yield (%)	TON
1	2-Iodothiophene	Benzeneboronic acid	**28**	1 000 000	100	1 000 000
2	2-Iodothiophene	Benzeneboronic acid	**28**	10 000 000	5 [a]	500 000
3	2-Bromothiophene	Benzeneboronic acid	**28**	100 000	88	88 000
4	2-Bromothiophene	Benzeneboronic acid	**28**	1 000 000	58 [a]	580 000
5	2-Bromothiophene	4-Methoxyphenylboronic acid	**29**	100 000	100 [a]	100 000
6	2-Bromothiophene	4-Methoxyphenylboronic acid	**29**	1 000 000	85	850 000
7	2-Bromothiophene	4-Fluorophenylboronic acid	**30**	100 000	95	95 000
8	2-Bromothiophene	4-Fluorophenylboronic acid	**30**	1 000 000	10 [a]	100 000
9	2-Bromothiophene	1-Naphthaleneboronic acid	**31**	1 000 000	94	940 000
10	2-Bromothiophene	2-Methylphenylboronic acid	**32**	100 000	89	89 000
11	2-Bromothiophene	2-Methylphenylboronic acid	**32**	1 000 000	26 [a]	260 000
12	3-Bromothiophene	Benzeneboronic acid	**33**	10 000 000	74	7 400 000
13	3-Bromothiophene	4-Methoxyphenylboronic acid	**34**	1 000 000	75	750 000
14	3-Bromothiophene	4-Fluorophenylboronic acid	**35**	100 000	85	85 000
15	3-Bromothiophene	1-Naphthaleneboronic acid	**36**	100 000	91	91 000
16	3-Bromothiophene	1-Naphthaleneboronic acid	**36**	1 000 000	61 [a]	610 000
17	3-Bromothiophene	2-Methylphenylboronic acid	**37**	1 000 000	93	930 000

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/ligand 1/2, see Ref. [7a], ArX (one equivalent), $ArB(OH)_2$ (two equivalents), K_2CO_3 (two equivalents), xylene, 130 °C, 20 h, isolated yields.
[a] GC yield.

μmol) and 4-fluorophenylboronic acid (2.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(4-fluorophenyl)thiophene in 95% (1.69 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.75$ (dd, $J = 8.8$ and 5.2 Hz, 2H), 7.45 (m, 2H), 7.28 (m, 3H).

2-(1-Naphthyl)thiophene (**31**): (Table 4, entry 9) 2-bromothiophene (1.63 g, 10 mmol), Pd complex (10^{-2} μmol) and 1-naphthaleneboronic acid (3.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(1-naphthyl)thiophene in 94% (1.98 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.22$ (d, $J = 8.2$ Hz, 1H), 7.9–7.85 (m, 2H), 7.58 (d, $J = 7.0$ Hz, 1H), 7.52–7.44 (m, 4H), 7.25 (m, 1H), 7.17 (m, 1H).

2-(2-Methylphenyl)thiophene (**32**): (Table 4, entry 10), 2-bromothiophene (1.63 g, 10 mmol), Pd complex (0.1 μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 2-(2-methylphenyl)thiophene in 89% (1.55 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.40$ (dd, $J = 5.7$ and 2.7 Hz, 1H), 7.33 (dd, $J = 5.0$ and 1.2 Hz, 1H), 7.27–7.21 (m, 3H), 7.10–7.05 (m, 2H), 2.43(s, 3H).

3-Phenylthiophene (**33**): (Table 4, entry 12), 3-bromothiophene (1.63 g, 10 mmol), Pd complex (10^{-3} μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-phenylthiophene in 74% (1.19 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 7.2$ Hz, 2H), 7.42 (m, 1H), 7.38–7.35 (m, 4H), 7.27 (m, 1H).

3-(4-Methoxyphenyl)thiophene (**34**): (Table 4, entry 13), 3-bromothiophene (1.63 g, 10 mmol), Pd complex (10^{-2} μmol) and 4-methoxyphenylboronic acid (3.04 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(4-methoxyphenyl)thiophene in 75% (1.43 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.53$ (d, $J = 8.5$ Hz, 2H), 7.38–7.35 (m, 3H), 6.95 (d, $J = 8.5$ Hz, 2H), 3.85 (s, 3H).

3-(4-Fluorophenyl)thiophene (**35**): (Table 4, entry 14), 3-bromothiophene (1.63 g, 10 mmol), Pd complex (0.1 μmol) and 4-fluorophenylboronic acid (2.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(4-fluorophenyl)thiophene in 85% (1.51 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (dd, $J = 8.8$ and 5.2 Hz, 2H), 7.45 (dd, $J = 8.8$ and 8.2 Hz, 2H), 7.14–7.02 (m, 3H).

3-(1-Naphthyl)thiophene (**36**): (Table 4, entry 15), 3-bromothiophene (1.63 g, 10 mmol), Pd complex (0.1 μmol) and 1-naphthaleneboronic acid (3.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(1-naphthyl)thiophene in 91% (1.91 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (d, $J = 8.1$ Hz, 1H), 7.90 (d, $J = 8.7$ Hz, 1H), 7.86 (dd, $J = 6.4$ and 3.1 Hz, 1H), 7.52–7.46 (m, 5H), 7.42 (m, 1H), 7.32 (dd, $J = 4.9$ and 1.3 Hz, 1H).

3-(2-Methylphenyl)thiophene (**37**): (Table 4, entry 17), 3-bromothiophene (1.63 g, 10 mmol), Pd complex (10^{-2} μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 3/7) to give 3-(2-methylphenyl)thiophene in 93% (1.62 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.34$ (dd, $J = 4.9$ and 3.0 Hz,

1H), 7.31–7.18 (m, 5H), 7.14 (dd, $J = 4.9$ and 1.4 Hz, 1H), 2.34 (s, 3H).

2.7. Coupling products with a bromofurane (Table 5)

5-Phenyl-2-furaldehyde (**38**): (Table 5, entry 1), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and benzeneboronic acid (2.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-phenyl-2-furaldehyde in 96% (1.65 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.63$ (s, 1H), 7.80 (d, $J = 8.3$ Hz, 2H), 7.48–7.32 (m, 3H), 7.28 (d, $J = 3.7$ Hz, 1H), 6.81 (d, $J = 3.7$ Hz, 1H).

5-(4-Methoxyphenyl)-2-furaldehyde (**39**): (Table 5, entry 5), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and 4-methoxyphenylboronic acid (3.04 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-(4-methoxyphenyl)-2-furaldehyde in 96% (1.94 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.59$ (s, 1H), 7.75 (d, $J = 8.9$ Hz, 2H), 7.29 (d, $J = 3.8$ Hz, 1H), 6.95 (d, $J = 8.9$ Hz, 2H), 6.70 (d, $J = 3.8$ Hz, 1H), 3.85 (s, 3H).

5-(4-Fluorophenyl)-2-furaldehyde (**40**): (Table 5, entry 6), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and 4-fluorophenylboronic acid (2.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-(4-fluorophenyl)-2-furaldehyde in 62% (1.18 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.50$ (s, 1H), 7.67 (dd, $J = 6.6$ and 5.3 Hz, 2H), 7.19 (d, $J = 3.7$ Hz, 1H), 7.01 (dd, $J = 6.6$ and 5.3 Hz, 2H), 6.66 (d, $J = 3.7$ Hz, 1H).

5-(3-Trifluoromethylphenyl)-2-furaldehyde (**41**): (Table 5, entry 7), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and 3-trifluoromethylphenylboronic acid (3.80 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-(3-trifluoromethylphenyl)-2-furaldehyde in 88% (2.11 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.65$ (s, 1H), 8.02 (s, 1H), 7.96 (d, $J = 7.7$ Hz, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.55 (t, $J = 7.8$ Hz, 1H), 7.32 (d, $J = 3.8$ Hz, 1H), 6.90 (d, $J = 3.8$ Hz, 1H).

5-(1-Naphthyl)-2-furaldehyde (**42**): (Table 5, entry 8), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and 1-naphthaleneboronic acid (3.44 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-(1-naphthyl)-2-furaldehyde in 55% (1.22 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.58$ (s, 1H), 8.34 (d, $J = 7.9$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.80 (d, $J = 7.3$ Hz, 1H), 7.57-7.49 (m, 4H), 7.33 (d, $J = 3.6$ Hz, 1H), 6.86 (d, $J = 3.6$ Hz, 1H).

5-(2-Methylphenyl)-2-furaldehyde (**43**): (Table 5, entry 9), 5-bromo-2-furaldehyde (1.75 g, 10 mmol), Pd complex (10^{-2} μmol) and 2-methylphenylboronic acid (2.72 g, 20 mmol). The residue was purified by column chromatography (ether–pentane: 2/8) to give 5-(2-methylphenyl)-2-furaldehyde in 92% (1.71 g) isolated yield. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 9.70$ (s, 1H), 7.82 (m, 1H), 7.37 (d, $J = 3.6$ Hz, 1H), 7.32 (m, 4H), 6.77 (d, $J = 3.6$ Hz, 1H), 2.58 (s, 3H).

2.8. Registry no.

2, 1008-89-5; **3**, 10273-89-9; **4**, 1008-88-4; **5**, 5958-02-1; **6**, 85589-65-7; **7**, 5957-99-3; **8**, 90395-49-6; **9**, 939-23-1; **10**, 39795-58-9; **11**, 30456-66-7; **12**, 43083-19-8; **13**, 39774-25-9; **14**, 1666-96-2; **15**, 57479-09-1; **16**, 612-96-4; **17**, 19571-30-3; **18**, 24702-41-8; **19**, 52146-06-2; **20**, 66616-72-6; **22**, 34771-45-4; **24**, 7431-45-0; **25**, 188527-65-3; **26**, 1826-11-5; **27**, 39187-97-8; **28**, 825-55-8; **29**, 42545-43-7; **30**, 58861-48-6; **31**, 4632-51-3; **32**, 99846-56-7; **33**, 2404-87-7; **34**, 82437-75-0; **35**, 153312-51-7; **36**, 17574-57-1; **37**, 16939-08-5; **38**, 13803-39-9; **39**, 34070-33-2; **40**, 33342-17-5; **41**, 52130-30-0; **42**, 51792-36-0; **43**, 110360-09-3.

Table 5
Palladium catalysed Suzuki cross-coupling reactions with 5-bromo-2-furaldehyde

Entry	Arylboronic acid	Ligand	Product	Ratio substrate/catalyst	Yield (%)	TON
1	Benzeneboronic acid	**1**	**38**	1 000 000	96	960 000
2	Benzeneboronic acid	**1**	**38**	10 000 000	67 [a]	6 700 000
3	Benzeneboronic acid	**1**	**38**	100 000 000	23 [a]	23 000 000
4	Benzeneboronic acid	dppe	**38**	1 000 000	87	870 000
5	4-Methoxyphenylboronic acid	**1**	**39**	1 000 000	96	960 000
6	4-Fluorophenylboronic acid	**1**	**40**	1 000 000	62	620 000
7	3-Trifluoromethylphenylboronic acid	**1**	**41**	1 000 000	88	880 000
8	1-Naphthaleneboronic acid	**1**	**42**	1 000 000	55	550 000
9	2-Methylphenylboronic acid	**1**	**43**	1 000 000	92	920 000

Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/ligand 1/2, see Ref. [7a], 5-bromo-2-furaldehyde (one equivalent), $ArB(OH)_2$ (two equivalents), K_2CO_3 (two equivalents), xylene, 130 °C, 20 h, isolated yields.

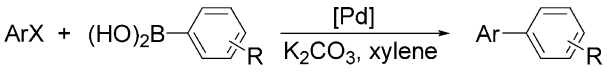
[a] GC yield.

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. Pyridines or quinolines are π-electron deficient. Thiophenes or furanes are π-electron excessive. If the oxidative addition of the aryl halides to the palladium complex is the rate-limiting step of the reaction with this catalyst, the reactions should be slower with thiophenes or furanes than with pyridines or quinolines.

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 atom. 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 a range of arylboronic acids with halopyridines, haloquinolines, halothiophenes, a bromoindole, bromopyrimidines, a bromothiazole and a bromofurane (Scheme 1). For this study, based on previous results [8], 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. The substrates and product are thermally stable so, in order to obtain high ratio substrate/catalyst, we have performed the reactions at an elevated temperature: 130 °C. However, the Suzuki cross-coupling reactions also proceed at lower temperature in the presence of this catalyst [8f]. When these reaction conditions are used, no induction period is observed.



2-43

ArX:

2-chloropyridine
3-chloropyridine
4-chloropyridine
2-bromopyridine
3-bromopyridine
4-bromopyridine
3-iodopyridine
5-bromopyridine-3-carboxamide
2-amino-5-bromopyridine
2-chloroquinoline
3-bromoquinoline
4-bromoisoquinoline
5-bromoindole
2-chloropyrimidine
5-bromopyrimidine
2-bromothiazole
2-bromothiophene
3-bromothiophene
2-iodothiophene
5-bromo-2-furaldehyde

R = H, 4-F, 4-MeO, 3-CF_3, 2-Me

Scheme 1.

3.1. Reactions with halopyridines

Due to the abundance of halopyridines, Suzuki cross-coupling reaction if a very powerful method for the preparation of arylpyridines.

First, we studied the influence of position of the bromo substituent on pyridines on the rate of the coupling with benzeneboronic acid. Due to the electronegativity of the nitrogen atom, the α and γ positions of halopyridines should be the most susceptible to the oxidative addition to Pd(0) [2]. In fact, we observed higher TON's for the coupling of β- and γ-substituted bromopyridines with benzeneboronic acid (2 500 000 and 810 000, respectively) (Table 1, entries 5, 6, 13 and 14) than with the α-substituted 2-bromopyridine (62 000) (Table 1, entries 1 and 2). These results seem to indicate that with this α-substituted bromopyridine, a possible interaction between the nitrogen atom and the palladium complex has a decelerating effect on the reaction rate. With this substrate the oxidative addition is probably not the rate-limiting step of the reaction.

Next, we tried to evaluate the influence of the substituents on the arylboronic acid on the rate of this reaction, so we investigated the coupling of 4-fluoro-, 4-methoxy- and 3-(trifluoromethyl)-benzeneboronic acids with bromopyridines. Lower reaction rates were observed with all these functionalised arylboronic acids than with simple phenylboronic acid (entries 8–11 and 15). Coupling of 4-fluoro-, 4-methoxy- and 3-(trifluoromethyl)benzeneboronic acids with 3-bromopyridine led to products coupling adducts with TON's of 96 000, 120 000 and 710 000, respectively. Sterically hindered 2-methylphenylboronic acid in the presence of 2-, 3- and 4-bromopyridines led to the coupling products with TON's of 8000, 8700 and 59 000, respectively (entries 3, 4, 12 and 16).

We have also investigated the reactivity of chloropyridines. As expected the oxidative addition of 2- and 4-chloropyridines to Pd(0) is faster than for 3-chloropyridine. 2-Chloropyridine is the most reactive and a TON of 8 900 has been obtained for the coupling with benzeneboronic acid (Table 1, entries 17 and 18). With 4-chloropyridine and 3-chloropyridine TONs of 860 and 235 are observed respectively (entries 19–21). These results seem to indicate that in the presence of these chloropyridines the oxidative addition of palladium is the rate-limiting step of the reaction. On the other hand, the reaction in the presence of 3-iodopyridine led to the coupling adduct in a very high TON of 4 000 000 (entries 22 and 23).

Two functionalised bromopyridines: 5-bromopyridine-3-carboxamide and 2-amino-5-bromopyridine have also been cross-coupled efficiently with benzeneboronic acid in the presence of 0.01% catalyst (entries 24 and 25).

3.2. Reactions with haloquinolines

For Suzuki reactions of haloquinolines, we observed behavior similar to that of halopyridines. Three haloquinolines have been used (Table 2). For the reaction with 3-bromoquinoline high TONs of 820 000 and 60 000 were observed in the presence of benzeneboronic acid and 2-methylphenylboronic acid (Table 2, entries 1 and 3). On the other hand, sterically congested 4-bromoisoquinoline led to the coupling adduct with a lower TON of 6800 (Table 2, entry 4). As expected, the reactivity of 2-chloroquinoline is very similar to 2-chloropyridine and the reaction proceed even in the presence of sterically congested arylboronic acids such as 1-naphthaleneboronic acid or 2-methylphenylboronic acid (Table 2, entries 5–9).

3.3. Reactions with a bromoindole a bromopyrimidine and a bromothiazole

Halo-substituted indole, pyrimidines or thiazole, which have also the potential to bind to palladium through nitrogen or sulfur, are suitable substrates for Suzuki reactions. TON's of 90 000 and 78 000 were obtained for the coupling with 5-bromoindole and 5-bromopyrimidine with phenylboronic acid (Table 3, entries 1–7). Much slower reactions were observed with 2-chloropyrimidine and 2-bromothiazole (entries 8–13). With these two substrates the poisoning effects of the heteroelements seems to be more important.

3.4. Reactions with halothiophenes

Thiophenes are π-electron-excessive heterocycles. Oxidative addition to palladium should be slower with bromothiophenes, than with bromopyridines however we observed in general similar or higher reaction rates with these π-electron excessive heterocycles than with π-electron deficient heterocycles such as bromopyridines. This observation suggests that in most cases the oxidative addition of the heteroaryl bromides is not the rate-limiting step with this catalyst. 3-Bromothiophene led to the coupling product with a very high TON of 7 400 000 (Table 4, entry 12). It should be noted that the reaction performed with $[PdCl(C_3H_5)]_2$ as catalyst in absence of ligand in the presence of 4% catalyst led to the biaryl adduct in a very low TON of 8. The highest TON obtained for the reaction with 2-bromothiophene was 580 000 (entry 4). These results suggest that with this α-substituted bromothiophene, a possible interaction between the sulphur atom and the palladium complex has a decelerating effect on the reaction rate. These 2- and 3-bromothiophene also led to the coupling adducts in high TON's in the presence of functionalised or sterically congested arylboronic acids (entries 9–11 and 15–17).

3.5. Reactions with a bromofurane

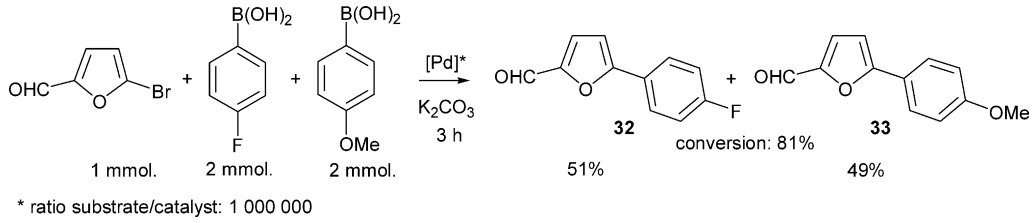
Furan is a π-electron-excessive heteroarene, however, we observed a very fast oxidative addition of 5-bromo-2-furaldehyde to palladium. Moreover, with this substrate no poisoning effect of the heteroatom was observed, and a very high TON was obtained in the presence of benzeneboronic acid: 23 000 000 (Table 5, entry 3). Coupling with 4-methoxy, 4-fluoro and 3-trifluoromethylbenzeneboronic acid also led to the corresponding coupling adducts with TON's of 960 000, 620 000, 880 000 respectively (entries 5–7). Next, we studied the reaction with the sterically congested arylboronic acids: 1-naphthaleneboronic acid and 2-methylphenylboronic acid. With this substrates, the coupling products were obtained with TONs of 550 000 and 920 000 (entries 8 and 9).

In order to have a more accurate idea of the influence of the electronic factor of the substituents of the arylboronic acid on the reaction rate we performed a competitive reaction using an equimolar mixture of 4-fluorobenzeneboronic acid and 4-methoxybenzeneboronic acid in the presence of 5-bromo-2-furaldehyde. We observed the formation of an almost equimolar mixture of coupling products (Scheme 2). This result seems to indicate that the lower reaction rates observed with functionalised arylboronic acids more likely comes from partial poisoning of the catalyst rather than from electronic factors.

Finally, in order to present a simple procedure using a commercially available ligand, we performed a few reactions with dppe as ligand (Tables 1, 2 and 5). Palladium catalyst prepared with dppe is less active than with **1** by a factor of ten; however dppe–Pd complex is much more stable and efficient than the popular but unstable catalyst $Pd(PPh_3)_4$. With dppe TON's of 82 000, 83 000 and 870 000 were obtained for the coupling of benzeneboronic acid with 3-bromopyridine, 3-bromoquinoline and 5-bromo-2-furaldehyde, respectively.

4. Conclusion

The Tedicyp–palladium complex provides a convenient catalyst for the cross-coupling of several heteroaromatics with arylboronic acids. In the presence of this catalyst heteroaromatics such as pyridines, quinolines, thiophenes, an indole or a furane led to the coupling products in good yields. The position of the halide on the heteroaromatic has an important effect on the reaction rate and faster reactions are generally observed with β- and γ- than with α-heteroaryl bromides. This catalyst system is also tolerant of electronic and steric variation in the arylboronic acid component. With some substrates, the reaction can be performed with as little as



Scheme 2.

0.00001% catalyst. To date, only a few other ligands have achieved this objective. In all cases, only traces (< 1%) of homocoupling products were observed with this catalyst. These results represent economically attractive procedures and due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes.

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