Suzuki Coupling Reactions of Heteroarylboronic Acids with Aryl Halides and Arylboronic Acids with Heteroaryl Bromides Using a Tetraphosphine/ Palladium Catalyst

Isabelle Kondolff, Henri Doucet,* Maurice Santelli*

UMR 6180 CNRS and Université d'Aix-Marseille III: 'Chirotechnologies: catalyse et biocatalyse', Laboratoire de Synthèse Organique, Faculté des Sciences de Saint Jérôme, Université d'Aix-Marseille III, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

Fax +33(4)91983865; E-mail: henri.doucet@univ.u-3mrs.fr; E-mail: m.santelli@univ.u-3mrs.fr

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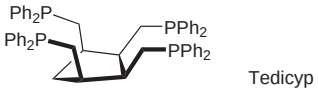
Abstract: *cis*,*cis*,*cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ efficiently catalyses the Suzuki reaction of heteroarylboronic acids with aryl bromides and also the coupling of arylboronic acids with heteroaryl bromides. The coupling of thiopheneboronic acids, 3-furanboronic acid and 3-pyridineboronic acid with a variety of aryl bromides gave the corresponding adducts in good yields. However, in most cases, better results in terms of substrate/catalyst ratio were obtained for the reaction of heteroaryl bromides with arylboronic acids.

Key words: heteroaryl bromides, arylboronic acids, Suzuki reaction, heteroarylboronic acids

Heterobiaryls have important biological properties and their preparation is an important industrial goal. The palladium-catalysed cross-coupling reaction between heteroaryl halides and arylboronic acids provides a very efficient method for the preparation of heterobiaryl derivatives.[1,2] The reverse reaction using heteroarylboronic acids and aryl halides has attracted less attention, and most of the results have been described with $Pd(PPh_3)_4$ as catalyst.[3–6] However, this ligand can be labile under some coupling conditions especially at elevated temperature and gives palladium black which is generally inactive. In recent years, a few other catalysts have been tested in the Suzuki coupling of these heteroarylboronic acid derivatives.[7–15] Fu et al. have reported the coupling of 2-thiopheneboronic acid with 4-bromo-*N*,*N*-dimethylaniline using 0.5% $Pd_2(dba)_3$ and 1.2% P(*t*-Bu)$_3$ as catalyst.[7] 2-(2′,6′-Dimethoxybiphenyl)dicyclohexylphosphine with 2–3% $Pd_2(dba)_3$ is also an efficient catalyst for the coupling of 3-pyridineboronic acid with aryl halides.[8] Dppf as ligand gave satisfactory results with a thiophene and a pyridineboronic acid.[9,10] A few other coupling reactions using these heteroarylboronic acids have also been described in the presence of palladium nanoparticles, supported catalysts or in ionic liquids.[11–15]

In order to obtain stable and efficient palladium catalysts, we have prepared the tetraphosphine ligand, *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp[16] (Figure 1). We have already reported results obtained in allylic substitution,[16] Heck,[17] Sonogashira[18] and Suzuki reactions[19] using this ligand. We have also described several results for the Suzuki coupling of heteroaryl halides with arylboronic acids.[20] However, we have not studied the reverse reaction using heteroarylboronic acids with aryl halides. In order to further establish the requirements for successful Suzuki coupling reactions for the synthesis of arylthiophenes, arylfuranes or arylpyridines with our catalyst, we herein report on the relative reaction rates for the coupling of heteroarylboronic acids with aryl bromides and heteroaryl bromides with arylboronic acids.



Tedicyp

Figure 1

For this study, based on previous results,[20] xylene was used as the solvent and K_2CO_3 as the base. The reactions were performed at 130 °C under argon in the presence of a 1:2 ratio of $[Pd(C_3H_5)Cl]_2$/Tedicyp as catalyst (Scheme 1). We first studied the reactivity of 2-thiopheneboronic acid, 3-thiopheneboronic acid and 3-furanboronic acid with a range of aryl bromides (Scheme 1, Table 1).

The coupling of 2-thiopheneboronic acid with iodobenzene, bromobenzene, 4-bromoacetophenone, 4-bromoanisole or 2-bromotoluene gave the expected 2-arylthiophenes in good yields in the presence of 1–5% catalyst (Table 1, entries 1, 2, 4, 6, 8 and 9). Similar reaction rates were observed with electron-poor and electron-rich aryl bromides indicating that with this heteroarylboronic acid, the oxidative addition of the aryl halide is not rate-limiting. Higher reaction rates were observed for the coupling reactions in the presence of 3-thiopheneboronic acid. With 4-bromoacetophenone, 4-bromobenzaldehyde, 4-bromobenzonitrile, 4-bromoanisole or 2-bromotoluene the reactions were performed using 0.4–0.1% catalyst (Table 1, entries 11, 12, 16–21 and 25). Then, in order to determine the must powerful method for the synthesis of these compounds, we determined the reaction rates for the coupling reactions using 2-bromothiophene or 3-bromothiophene with a few arylboronic acids. In most cases, much faster reactions were observed, and substrates/

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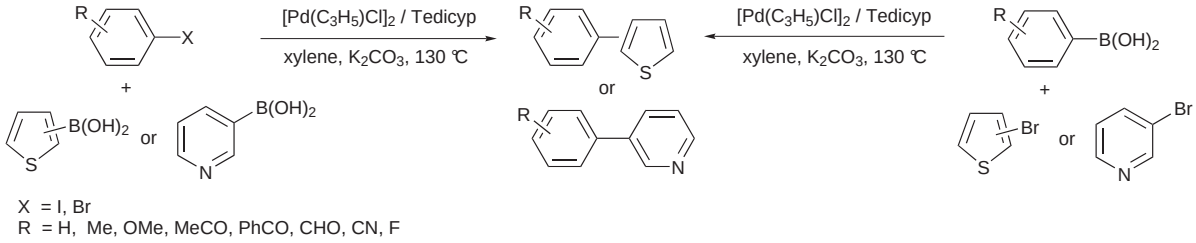

Scheme 1

catalyst ratios up to 1000000:1 have been used successfully (Table 1, entries 3, 5, 7, 10, 15, 24 and 26). However, the functional groups on the arylboronic acid have an important influence on the reaction rates. For example the coupling of 2-bromothiophene with 4-acetylbenzeneboronic acid and 4-methoxybenzeneboronic acids were performed using 0.1% and 0.0001% catalyst, respectively (Table 1, entries 5 and 7).

The reaction rates using 3-furanboronic acid and aryl halides are similar to those obtained with 3-thiopheneboronic acid. With this heteroarylboronic acid, iodobenzene, 4-bromoacetophenone, 4-bromobenzonitrile or 2-bromotoluene gave the arylfuran adducts in good yields in the presence of 0.4–0.1% catalyst (Table 1, entries 27, 28, 30, 31 and 33–35). The reverse reaction using 3-bromofuran and arylboronic acids also gave the expected 3-arylfurans in the presence of 0.1–0.4% catalyst (Table 1, entries 29, 32 and 37). However, these reactions were performed at a lower temperature (90 °C) due to the low boiling point of 3-bromofuran. We had previously reported that the coupling of 5-bromo-2-furaldehyde with arylboronic acids proceeds with very high TONs.[20]

A few reactions were also performed with 3-thiophene and 3-furanboronic acids at lower temperatures (90 °C). With 3-thiopheneboronic acid the reactions were slower, but satisfactory TONs of 300 and 225 were obtained with 4-bromoacetophenone and 4-bromoanisole (Table 1, entries 13, 14, 22 and 23). On the other hand, with 3-furanboronic acid, 2-bromotoluene was recovered unreacted (Table 1, entry 36).

Next, we studied the synthesis of 3-arylpyridines by coupling 3-pyridineboronic acid with several aryl bromides and also by the reaction of 3-bromopyridine with arylboronic acids (Table 2). Very slow reactions were observed with 3-pyridineboronic acid, and 2–10% catalyst had to be used in order to obtain high yields of adducts (Table 2, entries 1, 3, 4, 6, 8, 10, 11, 13, 15 and 18). These results revealed a minor substituent effect of the aryl bromide on the reaction rate, indicating that again, with 3-pyridineboronic acid as coupling partner, the rate-limiting step of the reaction is not the oxidative addition of the aryl bromide. The reverse coupling reactions using 3-bromopyridine and arylboronic acids gave much more satisfactory results in terms of substrate/catalyst ratio. The reactions were performed using 0.1–0.001% catalyst (Table 2, entries 2, 5, 7, 9, 12, 14, 16, 17, 19 and 20).

In summary, in the presence of the Tedicyp/palladium complex, the Suzuki cross-coupling of some heteroarylboronic acids such as 3-thiopheneboronic acid or 3-furanboronic acid with aryl bromides can be performed with as little as 0.1% catalyst. On the other hand, with 2-thiopheneboronic acid and 3-pyridineboronic acid the reactions are quite slow and were performed with 1–10% catalyst. With these heteroarylboronic acid derivatives similar reaction rates were generally observed in the presence of 4-bromoacetophenone or 4-bromoanisole indicating that the rate-limiting step of these reactions does not seem to be the oxidative addition of the aryl halides to palladium. In order to obtain higher TONs for the synthesis of these products, we also studied the reverse reactions using arylboronic acids and heteroaryl bromides. We observed that in most cases, much higher reaction rates were obtained for the coupling of bromothiophenes or 3-bromopyridine with arylboronic acids. For this reason, for the synthesis of arylthiophene or arylpyridine derivatives, the boronic acid function should preferably be located on the aryl and the halide on the heteroaryl rather than the reverse.

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Table 1 Suzuki Reaction with Thiophene and Furan Derivatives Catalysed by the Tedicyp/Palladium Complex[a,21]

Entry	Aryl halide	Arylboronic acid	Substrate/catalyst ratio[b]	Product	Yield (%)[c]
1	Iodobenzene	2-Thiopheneboronic acid	100:1	**1**	82 (96)
2	Bromobenzene	2-Thiopheneboronic acid	50:1	**1**	(47)
3	2-Bromothiophene	Benzeneboronic acid	100000:1	**1**	88
4	4-Bromoacetophenone	2-Thiopheneboronic acid	100:1	**2**	80 (86)
5	2-Bromothiophene	4-Acetylphenylboronic acid	1000:1	**2**	90
6	4-Bromoanisole	2-Thiopheneboronic acid	50:1	**3**	81
7	2-Bromothiophene	4-Methoxyphenylboronic acid	1000000:1	**3**	85
8	2-Bromotoluene	2-Thiopheneboronic acid	20:1	**4**	87 (100)
9	2-Bromotoluene	2-Thiopheneboronic acid	50:1	**4**	(40)
10	2-Bromothiophene	2-Methylphenylboronic acid	100000:1	**4**	89
11	4-Bromoacetophenone	3-Thiopheneboronic acid	250:1	**5**	77 (82)
12	4-Bromoacetophenone	3-Thiopheneboronic acid	1000:1	**5**	(55)
13	4-Bromoacetophenone	3-Thiopheneboronic acid	250:1	**5**	(84)[d]
14	4-Bromoacetophenone	3-Thiopheneboronic acid	1000:1	**5**	(30)[d]
15	3-Bromothiophene	4-Acetylphenylboronic acid	250:1	**5**	86
16	4-Bromobenzaldehyde	3-Thiopheneboronic acid	250:1	**6**	81 (90)
17	4-Bromobenzaldehyde	3-Thiopheneboronic acid	1000:1	**6**	(45)
18	4-Bromobenzonitrile	3-Thiopheneboronic acid	250:1	**7**	85 (96)
19	4-Bromobenzonitrile	3-Thiopheneboronic acid	1000:1	**7**	(77)
20	4-Bromoanisole	3-Thiopheneboronic acid	250:1	**8**	84 (97)
21	4-Bromoanisole	3-Thiopheneboronic acid	1000:1	**8**	(42)
22	4-Bromoanisole	3-Thiopheneboronic acid	250:1	**8**	(90)[d]
23	4-Bromoanisole	3-Thiopheneboronic acid	1000:1	**8**	0[d]
24	3-Bromothiophene	4-Methoxyphenylboronic acid	1000000:1	**8**	75
25	2-Bromotoluene	3-Thiopheneboronic acid	1000:1	**9**	84 (90)
26	3-Bromothiophene	2-Methylphenylboronic acid	1000000:1	**9**	93
27	Iodobenzene	3-Furanboronic acid	250:1	**10**	83 (100)
28	Iodobenzene	3-Furanboronic acid	1000:1	**10**	(35)
29	3-Bromofuran	Benzeneboronic acid	1000:1	**10**	91 (100)[d]
30	4-Bromoacetophenone	3-Furanboronic acid	250:1	**11**	81 (98)
31	4-Bromoacetophenone	3-Furanboronic acid	1000:1	**11**	(84)
32	3-Bromofuran	4-Acetylphenylboronic acid	250:1	**11**	87 (94)[d]
33	4-Bromobenzonitrile	3-Furanboronic acid	250:1	**12**	68
34	2-Bromotoluene	3-Furanboronic acid	250:1	**13**	81 (90)
35	2-Bromotoluene	3-Furanboronic acid	1000:1	**13**	(28)
36	2-Bromotoluene	3-Furanboronic acid	100:1	**13**	0[d]
37	3-Bromofuran	2-Methylphenylboronic acid	250:1	**13**	70[d]

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$/Tedicyp (1:2),[16] ArX (1 equiv), arylboronic acid (2 equiv), K_2CO_3 (2 equiv), xylene, 20 h, 130 °C, under argon.
[b] Substrate/catalyst ratio based on aryl halide.
[c] Isolated yields; yields in parenthesis correspond to GC and NMR yields.
[d] Reaction temperature: 90 °C

Table 2 Suzuki Reaction with Pyridine Derivatives Catalysed by the Tedicyp/Palladium Complex[a,21]

Entry	Aryl bromide	Arylboronic acid	Substrate/catalyst ratio[b]	Product	Yield (%)[c]
1	Bromobenzene	3-Pyridineboronic acid	33:1	**14**	75
2	3-Bromopyridine	Benzeneboronic acid	1000000:1	**14**	98[e,20b]
3	4-Bromobenzophenone	3-Pyridineboronic acid	20:1	**15**	82 (100)
4	3-Bromobenzaldehyde	3-Pyridineboronic acid	20:1	**16**	84 (100)
5	3-Bromopyridine	3-Formylphenylboronic acid	100:1	**16**	87 (100)
6	4-Fluorobromobenzene	3-Pyridineboronic acid	10:1	**17**	84
7	3-Bromopyridine	4-Fluorophenylboronic acid	100000:1	**17**	96[e,20b]
8	4-Bromoanisole	3-Pyridineboronic acid	20:1	**18**	80
9	3-Bromopyridine	4-Methoxyphenylboronic acid	100000:1	**18**	82[20b]
10	2-Bromoacetophenone	3-Pyridineboronic acid	20:1	**19**	80 (100)
11	2-Bromoacetophenone	3-Pyridineboronic acid	50:1	**19**	(49)
12	3-Bromopyridine	2-Acetylphenylboronic acid	1000:1	**19**	77
13	2-Bromotoluene	3-Pyridineboronic acid	20:1	**20**	85 (100)
14	3-Bromopyridine	2-Methylphenylboronic acid	10000:1	**20**	87[20b]
15	1-Bromonaphthalene	3-Pyridineboronic acid	10:1	**21**	84
16	3-Bromopyridine	1-Naphthaleneboronic acid	10000:1	**21**	77
17	3-Bromopyridine	1-Naphthaleneboronic acid	100000:1	**21**	(56)
18	2,6-Dimethylbromobenzene	3-Pyridineboronic acid	20:1	**22**	85 (98)
19	3-Bromopyridine	Mesitylboronic acid	1000:1	**23**	91 (100)
20	3-Bromopyridine	Mesitylboronic acid	10000:1	**23**	(70)

[a] Conditions: catalyst $[Pd(C_3H_5)Cl]_2$ /Tedicyp 1:2,[16] ArBr (1 equiv), arylboronic acid (2 equiv), K_2CO_3 (2 equiv), xylene, 20 h, 130 °C, under argon.
[b] Substrate/catalyst ratio based on the aryl halide.
[c] Isolated yields; yields in parenthesis correspond to GC and NMR yields.
[d] $PhB(OH)_2$ (1.5 equiv), 115 h.
[e] $PhB(OH)_2$ (1.5 equiv), 90 h.

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(21) A typical experiment (Table 1, entry 11): Thiophene-3-boronic acid (0.256 g, 2 mmol), 4-bromo-acetophenone (0.199 g, 1 mmol) and K_2CO_3 (0.276 g, 2 mmol) at 130 °C over 20 h in xylene (3 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/$[PdCl(C_3H_5)]_2$ complex (0.004 mmol) under argon afforded the corresponding product after evaporation and filtration through silica gel; yield: 0.156 g, 77%. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.98 (d, 2 H, *J* = 8.3 Hz), 7.68 (d, 2 H, *J* = 8.3 Hz), 7.57 (dd, 1 H, *J* = 2.5, 1.7 Hz), 7.43–7.40 (m, 2 H), 2.61 (s, 3 H).