Palladium Catalysed Cross-Coupling of Aryl Bromides with Functionalised Arylboronic Acids in the Presence of a Tetraphosphine Ligand

Marie Feuerstein, Florian Berthiol, Henri Doucet,* Maurice Santelli*

Laboratoire de Synthèse Organique associé au CNRS, Faculté des Sciences de Saint Jérôme, 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)]$_2$ system catalyses efficiently the cross-coupling of aryl bromides with functionalised arylboronic acids. The electronic properties of the arylboronic acids seem to have a minor influence on the reaction rate. Better results were generally obtained for the reaction of electron poor aryl bromides associated with electron rich arylboronic acids rather than the contrary.

Key words: catalysis, palladium, tetraphosphine, arylboronic acids, aryl bromides

Biaryl compounds are fundamental building blocks in organic synthesis and their preparation is an important industrial goal.[1] Palladium catalysed Suzuki cross-coupling reaction is one of the most powerful methods for the synthesis of such compounds.[2] In general, these palladium catalysts are associated with triphenylphosphine ligand. Even if the catalyst formed by association of this ligand with palladium complexes is efficient in terms of yield of adduct, the efficiency in terms of ratio substrate/catalyst is generally low and 1 to 10% of the catalyst must be used. In recent years, several more stable palladium catalysts have been successfully used for Suzuki cross-coupling reaction.[3] However, most of the results which have been described with these catalysts, were obtained for the coupling of phenylboronic acid. Relatively few results have been reported with functionalised arylboronic acids.[4] One of the most active catalyst for such substrates has been prepared with the bulky ligand (*o*-biphenyl)P(*t*-Bu)$_2$.[4c] A resin-bound catalyst was also found to enable Suzuki reaction with functionalised arylboronic acids in high yields.[4f] An other efficient catalytic systems uses a palladium–diazabutadiene complex.[4i] A palladium–carbene complex also efficiently promotes the cross-coupling of methoxybenzeneboronic acids.[4e] However, to our knowledge, the efficiency of tetraphosphine ligands for the coupling of functionalised arylboronic acids has not been reported.

The nature of phosphine ligand has an important effect on the rate of transition-metal catalysed reactions. In order to find more efficient palladium catalysts we have prepared the tetrapodal[5] phosphine ligand, *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp[6a] (Figure 1). All four phosphines probably cannot bind at the same time to the same palladium centre, but the presence of these four phosphines close to the metal centre seems to increase the coordination of the ligand to the palladium complex and therefore increase the stability of the catalyst. We have reported recently the first results obtained in Suzuki cross-coupling[7] using Tedicyp as ligand. For example, a TON (turnover number) of 96 000 000 for the coupling of 4-bromoacetophenone with benzeneboronic acid had been observed.[7e] Palladium catalyst prepared with dppe as ligand is generally less active by a factor of ten.[7a,b] We had also reported a few results using Tedicyp ligand with 4-methoxy- and 4-fluorobenzeneboronic acids. Generally lower TONs were obtained with these substrates, but the reason of these results was not clear.[7b] Here, in order to further establish the requirements for a successful Suzuki cross-coupling reaction, we wish to report on the influence of several electron-donating and electron-withdrawing functions on the arylboronic acid using Tedicyp as the ligand.

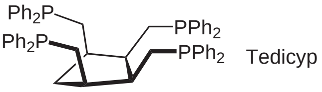
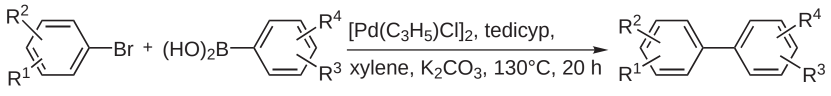


Figure 1

First, we have investigated the Suzuki reaction of several *para* substituted arylboronic acids with arylhalides in the presence of the system [PdCl(C_3H_5)]$_2$/2 Tedicyp in xylenes at 130 °C (Scheme 1, Table 1). The results presented in Table 1 unfold a strong influence of the substituents of the arylboronic acids on the reaction rate.



Scheme 1

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Table 1 Palladium–Tedicyp Catalysed Cross-Coupling (Scheme 1)[8,a]

Entry	R^1	R^2	R^3	R^4	Ratio substrate/ catalyst	Yield (%)[b]
1	4-MeCO	H	2-Me	H	1 000 000	82 (78)
2	4-MeO	H	2-Me	H	1 000 000	81 (76)
3	2-Me	6-Me	2-Me	H	10 000	83 (76)
4	4-MeCO	H	4-MeO	H	1 000 000	(80)
5	4-MeCO	H	4-MeO	H	10 000 000	62
6	4-MeO	H	4-MeO	H	1 000 000	82 (74)
7	2-Me	6-Me	4-MeO	H	100 000	97 (95)
8	4-MeCO	H	2-MeO	H	1 000 000	91 (85)
9	4-MeO	H	2-MeO	H	1 000 000	53
10	2-Me	6-Me	2-MeO	H	10 000	66 (65)
11	4-MeCO	H	2-F	4-F	100 000	53
12	4-MeO	H	2-F	4-F	10 000	60
13	2-Me	6-Me	2-F	4-F	1 000	67 (60)
14	4-MeCO	H	4-CF$_3$	H	1 000 000	60 (58)
15	4-MeO	H	4-CF$_3$	H	100 000	75
16	2-Me	6-Me	4-CF$_3$	H	10 000	98 (95)
17	4-MeCO	H	2-CF$_3$	H	10 000	80 (78)
18	4-MeO	H	2-CF$_3$	H	10 000	76
19	2-Me	6-Me	2-CF$_3$	H	1 000	10
20	4-MeCO	H	3-CF$_3$	5-CF$_3$	100 000	100 (98)
21	4-MeO	H	3-CF$_3$	5-CF$_3$	100 000	92
22	2-Me	6-Me	3-CF$_3$	5-CF$_3$	10 000	97 (95)
23	4-MeCO	H	4-MeCO	H	100 000	66 (60)[c]
24	4-MeO	H	4-MeCO	H	250	94 (90)
25	2-Me	6-Me	4-MeCO	H	250	100 (90)
26	4-MeCO	H	2-MeCO	H	10 000	100 (94)[c]
27	4-MeO	H	2-MeCO	H	10 000	90 (88)[c]
28	4-MeCO	H	3-NO$_2$	H	10 000	58
29	4-MeO	H	3-NO$_2$	H	10 000	24[c]
30	4-F	H	4-MeO	H	100 000	80 (78)
31	4-F	H	2-Me	6-Me	10 000	48
32	2-F	4-F	4-MeO	H	100 000	65 (62)
33	2-F	4-F	2-Me	6-Me	1 000	22
34	4-CF$_3$	H	4-MeO	H	100 000	100 (97)
35	4-CF$_3$	H	4-MeO	H	1 000 000	72
36	4-CF$_3$	H	2-Me	6-Me	10 000	25
37	2-CF$_3$	H	4-MeO	H	100 000	100 (96)
38	2-CF$_3$	H	4-MeO	H	1 000 000	28
39	3-CF$_3$	5-CF$_3$	4-MeO	H	1 000 000	99 (96)
40	3-CF$_3$	5-CF$_3$	4-MeO	H	10 000 000	35
41	3-CF$_3$	5-CF$_3$	2-Me	6-Me	10 000	33
42	2-MeCO	H	4-MeO	H	100 000	66
43	4-MeCO	H	2-Me	6-Me	10 000	60
44	3-NO$_2$	H	4-MeO	H	100 000	90 (86)[c]
45	3-NO$_2$	H	4-MeCO	H	10 000	75 (69)[c]

[a] Conditions: catalyst see ref.,[6a] ArBr (1 equiv), ArB(OH)$_2$ (2 equiv), K$_2$CO$_3$ (2 equiv), xylene, 130 °C, 20 h, GC or NMR yields.

[b] Yields in brackets are isolated.

[c] Solvent: xylenes/DMF: 1/1 for solubility reasons.

Electron-withdrawing groups in the arylboronic acid are unfavourable in a few cases, while an electron-donation group is favourable. For example, a turnover number of 6 200 000 can be achieved with this catalyst for the reaction of 4-bromoacetophenone with 4-methoxybenzeneboronic acid (entry 5) whereas the coupling of 4-bromoanisole with 4-acetylbenzeneboronic acid led to a much lower TON of 234 (entry 24). However, high TONs are obtained for the coupling of 4-trifluoromethylbenzeneboronic acid with 4-bromoacetophenone or 4-bromoanisole (entries 14 and 15) indicating a minor electronic effect of the substituents on the arylboronic acid on the reaction rate.

Several reactions were also performed using 3-nitrobenzeneboronic acid (entries 28 and 29). With this substrate low TONs were observed.

To gain insight into the reason of such results, we undertook a series of competitive reactions using an equimolar mixture of 4-methoxybenzeneboronic acid and 3,5-bistrifluoromethylbenzene-boronic acid in the presence of arylbromides (Scheme 2). We observed in both cases the formation of a mixture of the coupling products. Ratios of 41/59 and 42/58 between the 4-methoxyphenylaryl adduct **a** and the 3,5-bistrifluoromethylphenylaryl adduct **b** were obtained. These results reveal that slightly higher reaction rates can be obtained with electron-withdrawing groups on the arylboronic acid. In fact, the lower reaction rates observed in some cases with the arylboronic acids bearing electron-withdrawing groups apparently does not comes from the transmetallation rate of the arylboronic acid with the palladium catalyst, but more likely from the poisoning of the catalyst by the impurities or the functions of the arylboronic acids. In order to confirm this, we have recrystallized some of the arylboronic acids and better results were obtained in some cases. For example, a TON of 100 000 instead of 8 000 for the coupling of 3,5-bistrifluoromethylbenzeneboronic acid with 4-bromoacetophenone was obtained after recrystallization (entry 20).

Then, we studied the influence of *ortho* substituents on the arylboronic acid for the coupling with 4-bromoacetophenone or 4-bromoanisole. Higher TONs were obtained using a methyl or a methoxy substituent (entries 1, 2, 8 and 9) rather than a trifluoromethyl or an acetyl (entries 17, 18, 26 and 27). Here also the purity of the substrates seems to be an important factor for a successful reaction.

Finally, the coupling in the presence of the sterically hindered substrates 2,6-dimethylbromobenzene or 2,6-dimethylbenzeneboronic acid has been studied. The reactions rates are much lower, however most of the reactions could be performed with substrate/catalyst ratios of 1 000–10 000. In general, better results were obtained for the coupling of 2,6-dimethylbromobenzene with functionalised arylboronic acids (entries 3, 7, 10, 13, 16 and 22) than for the coupling of functionalised arylbromides with 2,6-dimethylbenzeneboronic acid (entries 31, 33, 36, 41 and 43).

In summary, in the presence of the Tedicyp/palladium complex, the Suzuki cross-coupling of several functionalised arylboronic acids can be performed with as little as 0.00001% catalyst. A wide range of functions such as methoxy, fluoro, acetyl, nitro or trifluoromethyl is tolerated. In order to obtain high turnover numbers, electron-withdrawing substituents of the substrates should be located on the aryl bromide. If the functions and the purity of the arylboronic acid have an influence on the catalyst, their electronic properties have a minor influence on the reaction rate. For this reason the electron-donating substituents of the reaction should be located on the arylboronic acid. When disappointing results are obtained with functionalised arylboronic acids, they should be recrystallized.

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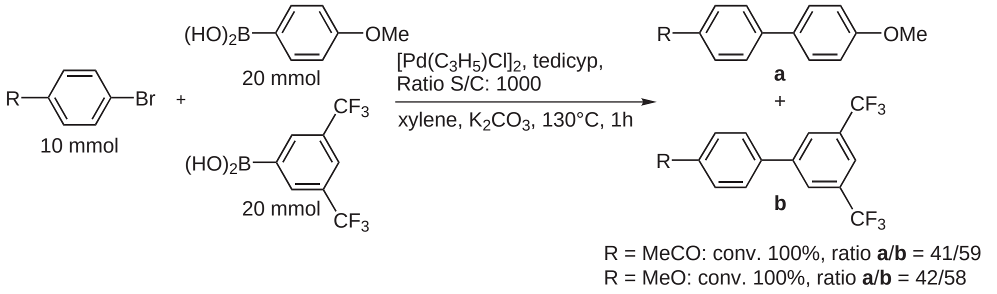

Scheme 2

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(8) As a typical experiment, the reaction of 4-bromoaceto phenone (1.99 g, 10 mmol), 4-methoxybenzeneboronic acid (3.04 g, 20 mmol) and K_2CO_3 (2.8 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/$[PdCl(C_3H_5)]_2$ complex (0.00001 mmol) under argon affords the corresponding adduct after extraction with dichloromethane, evaporation and filtration on silica gel (dichloromethane/diethyl ether: 1/5) in 80% (1.81 g) isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 8.5$ Hz, 2 H), 7.64 (d, $J = 8.5$ Hz, 2 H), 7.56 (d, $J = 8.7$ Hz, 2 H), 6.99 (d, $J = 8.7$ Hz, 2 H), 3.85 (s, 3 H), 2.62 (s, 3 H).