



# Tetrakisphosphine/palladium-catalysed Suzuki cross-coupling with sterically hindered aryl bromides and arylboronic acids

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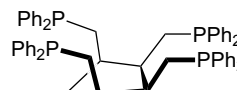
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**Abstract**—*cis,cis,cis*-1,2,3,4-Tetrakis(diphenylphosphinomethyl)cyclopentane/[PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>] system efficiently catalyses the Suzuki cross-coupling of sterically hindered substrates. Very high turnover numbers can be obtained for the coupling of sterically hindered aryl bromides with benzenboronic acid or for the coupling of bromobenzene with sterically hindered arylboronic acids. On the other hand the formation of tri-*ortho*-substituted biaryl adducts requires higher catalyst loading. © 2001 Elsevier Science Ltd. All rights reserved.

Atropisomerism in biaryl derivatives is important due to their biological properties; therefore their preparation is an important goal.<sup>1</sup> Palladium-catalysed Suzuki cross-coupling reaction<sup>2</sup> between sterically hindered aryl halides and arylboronic acids is one of the most efficient methods for the synthesis of these compounds. In general, these palladium catalysts are associated with the triphenylphosphine ligand.<sup>3</sup> 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 1–10% of the catalyst must be used. In recent years, a few bulky monodentate ligands have been successfully used for Suzuki cross-coupling reaction.<sup>4</sup> However, most of the results, which have been described with these ligands, were obtained for the coupling of *meta*- or *para*-substituted aryl halides or arylboronic acids. Few results have been reported using *ortho*-substituted substrates.<sup>5</sup> One of the most active catalysts for such substrates is Herrmann's palladacycle.<sup>5a</sup> A very efficient catalyst has also been prepared with the bulky ligand (*o*-biphenyl)P(*t*-Bu)<sub>2</sub>.<sup>5b</sup> Another efficient catalytic system uses a palladium–phosphite complex.<sup>5d</sup> Finally, a sulfur-containing palladacycle and a ferrocene derivative also efficiently promote the cross-coupling of sterically demanding substrates.<sup>5e,f</sup> However, to our knowledge, the efficiency of tetrakisphosphine ligands for the coupling of *ortho*- and di-*ortho*-sub-

tuted arylbromides and arylboronic acids has not been reported.

The nature of phosphine ligands on complexes has a tremendous influence on the rate of catalysed reactions. In order to obtain highly stable palladium catalysts we have prepared the new tetrakisphosphine ligand,<sup>6</sup> *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane or Tedicyp<sup>7</sup> (Fig. 1) in which four diphenylphosphino groups are stereospecifically bound to the same face of a cyclopentane ring. The presence of these four phosphines close to the metal centre seems to increase the coordination of the ligand to the metal centre and therefore increase the stability of the catalyst. We have recently reported the first results obtained in allylic substitution,<sup>8</sup> for Heck reaction<sup>9</sup> and for Suzuki cross-coupling using Tedicyp as the ligand.<sup>10</sup> For example, a turnover number (TON) of  $2.8 \times 10^7$  for the coupling of 4-bromobenzophenone with benzenboronic acid had been observed. A high efficiency was also observed for the cross-coupling of activated aryl chlorides.<sup>11</sup> In this paper, we wish to report on Suzuki cross-coupling in the presence of sterically hindered aryl bromides and arylboronic acid using Tedicyp as the ligand.



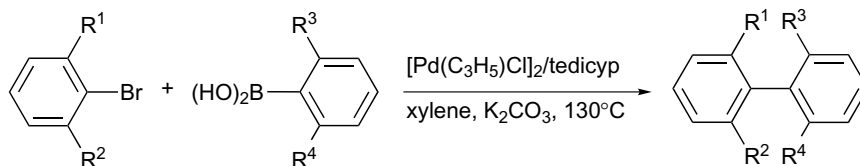
Tedicyp

Figure 1.

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First, we tried to evaluate the importance of the presence of one *ortho* substituent on the arylbromide on the rate of the reaction. For this study, based on our previous results,<sup>10</sup> xylene was chosen as the solvent and potassium carbonate as the base. The reactions were performed at 140°C in the presence of a 1/2 ratio of  $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2/\text{Tedicyp}]$  as catalyst. Although this catalyst is quite air-stable,<sup>9</sup> the reactions were performed under argon. Using these conditions, we observed that the coupling of 2-methylbromobenzene with ben-

zeneboronic acid in the presence of a 0.00001% catalyst led to the biaryl adduct in 88% yield (TON  $8.8 \times 10^6$ ) (Scheme 1, Table 1, entry 6). A conversion of 75% was obtained using similar conditions with 4-methylbromobenzene (TON  $7.5 \times 10^6$ ) (entry 4). With 1-fluoro-2-bromobenzene, 2-bromoanisole, 2,4-dimethoxy-bromobenzene or 1-bromonaphthalene similar reaction rates were observed (TONs  $7.1 \times 10^5$ – $4.3 \times 10^6$ ) (entries 7–13). Next, we tried to evaluate the difference of reaction rate between mono- and di-*ortho*-substituted arylbromides,



Scheme 1.

Table 1. Suzuki cross-coupling catalysed by the Tedicyp–palladium complex (Scheme 1)<sup>12</sup>

Entry	Aryl bromide	Boronic acid	Ratio substrate/catalyst	Yield (%) <sup>a</sup>
1	Bromobenzene	Benzeneboronic acid	1 000 000	100 <sup>b</sup>
2	Bromobenzene	Benzeneboronic acid	10 000 000	75
3	4-Bromotoluene	Benzeneboronic acid	1 000 000	100 <sup>b</sup>
4	4-Bromotoluene	Benzeneboronic acid	10 000 000	75
5	2-Bromotoluene	Benzeneboronic acid	1 000 000	91
6	2-Bromotoluene	Benzeneboronic acid	10 000 000	88
7	1-Bromo-2-fluorobenzene	Benzeneboronic acid	1 000 000	87
8	1-Bromo-2-fluorobenzene	Benzeneboronic acid	10 000 000	43
9	2-Bromoanisole	Benzeneboronic acid	1 000 000	71
10	1-Bromo-2,4 dimethoxybenzene	Benzeneboronic acid	1 000 000	100 <sup>b</sup>
11	1-Bromo-2,4 dimethoxybenzene	Benzeneboronic acid	5 000 000	28
12	1-Bromonaphthalene	Benzeneboronic acid	1 000 000	82
13	1-Bromonaphthalene	Benzeneboronic acid	10 000 000	42
14	1-Bromo-2,6-dimethylbenzene	Benzeneboronic acid	1 000 000	88
15	1-Bromo-2,6-diethylbenzene	Benzeneboronic acid	1 000 000	88
16	1-Bromo-2,4,6-triisopropylbenzene	Benzeneboronic acid	1 000 000	92
17	9-Bromoanthracene	Benzeneboronic acid	1 000 000	93
18	9-Bromoanthracene	Benzeneboronic acid	10 000 000	32 <sup>b</sup>
19	1-Bromo-2-methylnaphthalene	Benzeneboronic acid	1 000 000	60
20	Bromobenzene	2-Methylphenylboronic acid	1 000 000	88
21	Bromobenzene	2-Methylphenylboronic acid	10 000 000	43 <sup>b</sup>
22	2-Bromotoluene	2-Methylphenylboronic acid	1 000 000	85
23	1-Bromo-2,6-dimethylbenzene	2-Methylphenylboronic acid	1000	83
24	1-Bromo-2-methoxynaphthalene	2-Methylphenylboronic acid	1000	89
25	Bromobenzene	2,6-Dimethylphenylboronic acid	10 000	78
26	Bromobenzene	2,6-Dimethylphenylboronic acid	100 000	43 <sup>b</sup>
27	2-Bromotoluene	2,6-Dimethylphenylboronic acid	100	100 <sup>b</sup>
28	2-Bromotoluene	2,6-Dimethylphenylboronic acid	1000	12
29	1-Bromonaphthalene	2,6-Dimethylphenylboronic acid	100	36
30	1-Bromo-2,6-dimethylbenzene	2,6-Dimethylphenylboronic acid	50	0
31	Bromobenzene	1-Naphthaleneboronic acid	100 000	100 <sup>b</sup>
32	Bromobenzene	1-Naphthaleneboronic acid	1 000 000	92
33	Bromobenzene	1-Naphthaleneboronic acid	10 000 000	50 <sup>b</sup>
34	2-Bromotoluene	1-Naphthaleneboronic acid	1 000 000	90
35	2-Bromotoluene	1-Naphthaleneboronic acid	10 000 000	43 <sup>b</sup>
36	1-Bromo-2,6-dimethylbenzene	1-Naphthaleneboronic acid	100	85 <sup>b</sup>
37	1-Bromo-2-methylnaphthalene	1-Naphthaleneboronic acid	100	94
38	1-Bromo-2-methylnaphthalene	1-Naphthaleneboronic acid	1000	82
39	1-Bromo-2-methoxynaphthalene	1-Naphthaleneboronic acid	1000	90

Conditions: catalyst  $[\text{Pd}(\text{C}_3\text{H}_5\text{Cl})_2/\text{ligand}]$  1/2 see: Ref. 7, ArBr (1 equiv.), ArB(OH)<sub>2</sub> (2 equiv.), K<sub>2</sub>CO<sub>3</sub> (2 equiv.), xylene, 140°C, 20 h.

<sup>a</sup> Isolated yields.

<sup>b</sup> GC yields.

and we observed that even very hindered aryl bromides could be coupled efficiently with benzenboronic acid. For example, with 9-bromoanthracene, 1-bromo-2,6-dimethylbenzene, 1-bromo-2,6-diethylbenzene and 1-bromo-2,4,6-triisopropylbenzene high conversions were obtained in the presence of 0.0001% catalyst (TONs  $8.8 \times 10^5$ – $3.2 \times 10^6$ ) (entries 14–18) showing a not very significant effect of the *ortho*-substituents of the aryl bromide on the rate of the reaction. In all cases, only traces (<3%) of homocoupling of the boronic acid were observed.

Next, we studied the influence of hindered arylboronic acids for this reaction, and we noticed that similar reaction rates were obtained for the cross-coupling of bromobenzene with 2-methylbenzene boronic acid (TON  $4.3 \times 10^6$ ) (entry 21) than for the coupling of 2-bromotoluene with benzenboronic acid (TON  $8.8 \times 10^6$ ) (entry 6). This result indicates that the transmetallation of sterically hindered boronic acids with the palladium centre occurs very rapidly. High reaction rates were also observed for the coupling of bromobenzene with the sterically hindered 2,6-dimethylphenylboronic acid and 1-naphthaleneboronic acid (entries 25, 26, 32 and 33).

On the other hand, a very important steric effect for the cross-coupling of *ortho*-substituted arylbromides with di-*ortho*-substituted arylboronic acids or for di-*ortho*-substituted arylbromides with *ortho*-substituted arylboronic acids was observed. For example, the coupling of 1-bromo-2,6-dimethylbenzene with 2-methylbenzenboronic acid led to the biaryl adduct in a TON of 830 (entry 23). Finally, we tried the coupling of 1-bromo-2,6-dimethylbenzene with 2,6-dimethylbenzenboronic acid in the presence of 2% catalyst; however, no coupling adduct was observed due to a very fast decomposition of the catalyst. In order to obtain more information on the influence of the steric factors on the rate of this reaction, we performed a competitive reaction using an equimolar mixture of benzenboronic acid and 2,6-dimethylbenzenboronic acid in the presence of 1-bromo-2,6-dimethylbenzene (Scheme 2). We only observed the formation of the coupling products with benzenboronic acid and in this case the decomposition of the catalyst was not observed.

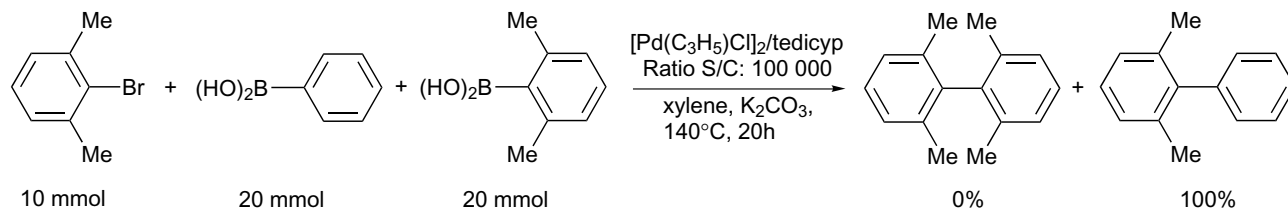
The respective rates of these reactions with sterically hindered substrates suggest that, in the presence of

this catalyst, the rate-determining step of the reaction is not the oxidative addition of the arylbromide. The rate-determining step seems to be the transmetallation of the boronic acid with the palladium centre due to a sterically hindered *ortho*-substituted aryl-Pd intermediate. However, a slower C–C bond formation from the Pd-biaryl intermediate due to a steric effect is also possible.

In conclusion, the use of the tetradentate ligand Tedicyp associated with a palladium complex provides a convenient catalyst for the cross-coupling of sterically hindered aryl bromides with arylboronic acids. This catalyst is more efficient than the complex formed with triphenylphosphine and related ligands. This efficiency probably comes from the presence of the four diphenylphosphinoalkyl groups stereospecifically bound to the same face of the cyclopentane ring, which probably increases the coordination of the ligand to the metal and prevents precipitation of the catalyst. As expected, both the steric hindrance of the arylbromides and the steric hindrance of the boronic acids have an effect on the rate of this reaction. If the presence of one *ortho* substituent on one of the substrates has almost no influence on the rate of the reaction, the presence of two *ortho* substituents on one of the substrates or one *ortho* substituent on both substrates has some influence on the rate of the reaction. However, with all these substrates, high TONs are generally observed. The reaction can be performed with as little as 0.00001% catalyst without further optimisation of the reaction conditions. Due to the high price of palladium, the practical advantage of such low catalyst loading reactions can become increasingly important for industrial processes. On the other hand, the formation of tri-*ortho*-substituted biaryl compounds led to much lower reaction rates and the presence of 0.1–1% catalyst is required, showing a very significant steric effect on the rate of the reaction. These results represent an environmentally friendly procedure. Further applications of this ligand will be reported in due course.

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Scheme 2.

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- As a typical experiment, the reaction of 2,4,6-triisopropyl bromobenzene (2.83 g, 10 mmol), benzenboronic acid (2.44 g, 20 mmol) and K<sub>2</sub>CO<sub>3</sub> (2.76 g, 20 mmol) at 140°C for 20 h in dry xylene (10 mL) in the presence of *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl)cyclopentane/[PdCl(C<sub>3</sub>H<sub>5</sub>)<sub>2</sub>]<sub>2</sub> complex (0.00001 mmol) under argon affords the corresponding biaryl product after evaporation and filtration on silica gel in 92% (2.57 g) isolated yield.