Suzuki Cross-Coupling Reaction of Benzylic Halides with Arylboronic Acids in the Presence of a Tetraphosphine/Palladium Catalyst

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Abstract: The *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl) cyclopentane–$[PdCl(C_3H_5)]_2$ system catalyses efficiently the Suzuki cross-coupling reaction of benzylic halides with arylboronic acids. A wide variety of benzylic bromides or chlorides and functionalised arylboronic acids lead selectively to the corresponding diarylmethane adducts in good yields. Furthermore, this catalyst can be used at low loading in many cases.

Key words: catalysis, palladium, tetraphosphine, arylboronic acids, benzylic halides

Diarylmethane derivatives are fundamental building blocks in organic synthesis and their preparation is an important industrial goal. The palladium-catalysed so-called Suzuki cross-coupling reaction should be a powerful method for the synthesis of such compounds.[1] Organoboron reagents exhibit greater functional group compatibility than organozinc or Grignard reagents. Moreover, the innocuous nature of boronic acids, which are generally non-toxic and thermally, air-, and moisture-stable, is a practical advantage of the Suzuki reaction, relative to the other coupling processes. However, the procedure suffers generally from high catalyst loading due to the fast decomposition of the catalyst. In recent years, several thermally stable palladium catalysts have been successfully used for Suzuki reactions,[2] but most of the results, which have been described with these catalysts, were obtained for the coupling of aryl halides. With these catalysts, relatively few results have been reported for the coupling of benzylic halides. Most of the results were described with the popular but unstable catalyst $Pd(PPh_3)_4$.[3,4] Recently, an alternative procedure for the synthesis of 3-arylprop-1-ene derivatives by Pd-catalysed coupling of various arylboronic acids with allylic acetates has also been described.[5]

The nature of the 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[6] phosphine ligand, tedicyp[7,8] (Figure 1). We have reported recently several results obtained in Suzuki cross-coupling using tedicyp as ligand.[9] For example, a TON (turnover number) of 96 000 000 for the reaction of 4-bromobenzophenone with phenylboronic acid has been obtained.[9b] We have also reported some results using tedicyp ligand with sterically hindered aryl bromides,[9d] heteroaryl bromides,[9c] aryl chlorides,[9e] vinylhalides[9g] and with a variety of arylboronic acids.[9f] Here, in order to further establish the requirements for a successful Suzuki cross-coupling reaction, we wish to report the reaction of benzylic halides with a variety of arylboronic acids using tedicyp as the ligand.

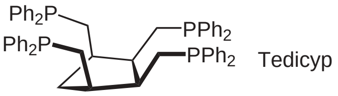
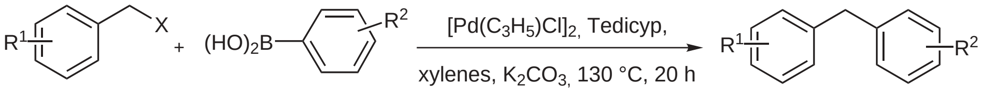


Figure 1

For this study, based on previous results,[9] xylene was chosen as the solvent and potassium carbonate as the base (Scheme 1). The reactions were performed at 130 °C under argon in the presence of a ratio 1/2 of $[Pd(C_3H_5)Cl]_2$/tedicyp as catalyst.



X = Cl, Br
R^1 = H, Me, F, Cl, NO_2, CF_3, CN, CO_2Me
R^2 = H, Me, F, MeO, NO_2, CHO, CF_3, COMe

Scheme 1

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First, we have investigated the Suzuki cross-coupling reaction with benzyl bromide The reaction with phenylboronic acid can be performed with as little as 0.0001% catalyst (entries 1 and 2). Using similar conditions, in absence of catalyst, most of the benzylbromide was recovered unreacted and the formation of a mixture of side products which seems to contain traces of diphenylmethane was observed. Then the reaction with several *para*-, *meta*- and *ortho*-substituted arylboronic acids in the presence of catalyst was examined. The results presented in the Table 1 show a strong influence of the substituents at the arylboronic acids on the reaction rate, however this influence does not come from the electronic factors on the arylboronic acid: in the presence of 4-methoxy or 4-fluorophenylboronic acids the reactions required 0.001–0.0001% catalyst (entries 3–7). Higher catalyst loadings were required for arylboronic acids containing functional groups such as nitro, formyl or acetyl (entries 8–10 and 15). The lower reaction rates observed with these functionalised arylboronic acids probably does not comes from the transmetallation rate of the arylboronic acid with the palladium catalyst, but more likely, from poisoning of the catalyst by the impurities or the functional groups of these arylboronic acids.[9f] Then, we studied the reaction with sterically congested arylboronic acids such as 2-methyl-, 2-methoxy-, 2-acetyl- or 2,4,6-trimethylphenylboronic acids. With these substrates, the coupling products were obtained with TONs of 84 000, 56 000, 910 and 810, respectively (entries 12–18).

Next, we studied the influence of the substituents on the benzylic bromides. Electron-withdrawing groups at the aryl have a minor influence on the reaction rates. 4-Nitrobenzyl bromide, 4-trifluoromethylbenzyl bromide, 4-cyanobenzyl bromide, methyl 3-(bromomethyl)benzoate and 3-chlorobenzyl bromide with phenylboronic acid led to the corresponding disubstituted methanes in the presence of 0.01–0.0001% catalyst (entries 21, 30, 33, 42 and 44). The *ortho*-substituted 2-fluorobenzyl bromide also gave the expected adduct in high TON: 83 000 (entry 45). On the other hand, the sterically hindered 2-methylbenzyl bromide led to a much slower reaction. With this substrate a TON of 910 was obtained (entry 46). In a few cases the formation of a side product resulting from the homocoupling of the benzylic bromide was also observed (entries 23 and 26).

Table 1 Palladium-Tedicyp Catalysed Suzuki Cross-Coupling Reactions with Benzylic Bromides (Scheme 1)[10,11,a]

Entry	R-Br	Arylboronic acid	Ratio substrate/catalyst	Yield (%)[b]
1	Benzyl bromide	Phenylboronic acid	100000	99 (91)
2	Benzyl bromide	Phenylboronic acid	1000000	58
3	Benzyl bromide	4-Methoxyphenylboronic acid	1000	100 (88)
4	Benzyl bromide	4-Methoxyphenylboronic acid	10000	63
5	Benzyl bromide	4-Methoxyphenylboronic acid	100000	30
6	Benzyl bromide	4-Fluorophenylboronic acid	100000	100 (82)
7	Benzyl bromide	4-Fluorophenylboronic acid	1000000	40
8	Benzyl bromide	3-Nitrophenylboronic acid	100	74 (60)
9	Benzyl bromide	3-Formylphenylboronic acid	250	100 (74)
10	Benzyl bromide	3-Formylphenylboronic acid	1000	45
11	Benzyl bromide	3,5-Bistrifluoromethylphenylboronic acid	10000	89 (77)
12	Benzyl bromide	2-Methylphenylboronic acid	100000	100 (84)
13	Benzyl bromide	2-Methoxyphenylboronic acid	10000	81
14	Benzyl bromide	2-Methoxyphenylboronic acid	100000	56
15	Benzyl bromide	2-Acetylphenylboronic acid	1000	100 (91)
16	Benzyl bromide	2,4-Difluorophenylboronic acid	1000	100 (85)
17	Benzyl bromide	2,4-Difluorophenylboronic acid	10000	70
18	Benzyl bromide	2,4,6-Trimethylphenylboronic acid	1000	87 (81)
19	Benzyl bromide	Thiophene-2-boronic acid	250	62 (55)
20	4-Nitrobenzyl bromide	Phenylboronic acid	100000	100 (78)
21	4-Nitrobenzyl bromide	Phenylboronic acid	1000000	87
22	4-Nitrobenzyl bromide	4-Methoxyphenylboronic acid	1000	100 (84)
23	4-Nitrobenzyl bromide	4-Methoxyphenylboronic acid	10000	74[c]

Table 1 Palladium-Tedicyp Catalysed Suzuki Cross-Coupling Reactions with Benzylic Bromides (Scheme 1)[10,11,a] (continued)

Entry	R-Br	Arylboronic acid	Ratio substrate/catalyst	Yield (%)[b]
24	4-Nitrobenzyl bromide	3-Nitrophenylboronic acid	1000	100 (79)
25	4-Nitrobenzyl bromide	3-Formylphenylboronic acid	250	86 (64)
26	4-Nitrobenzyl bromide	2,4-Difluorophenylboronic acid	250	100 (80)[d]
27	4-Nitrobenzyl bromide	2,4-Difluorophenylboronic acid	1000	85
28	4-Nitrobenzyl bromide	2-Methoxyphenylboronic acid	1000	100 (92)
29	4-Nitrobenzyl bromide	2-Methoxyphenylboronic acid	10000	66
30	4-Trifluoromethylbenzyl bromide	Phenylboronic acid	100000	94 (87)
31	4-Trifluoromethylbenzyl bromide	4-Methoxyphenylboronic acid	1000	100
32	4-Trifluoromethylbenzyl bromide	4-Methoxyphenylboronic acid	10000	49
33	4-Cyanobenzyl bromide	Phenylboronic acid	10000	100 (86)
34	4-Cyanobenzyl bromide	4-Fluorophenylboronic acid	1000	100 (84)
35	4-Cyanobenzyl bromide	4-Methoxyphenylboronic acid	1000	100 (81)
36	4-Cyanobenzyl bromide	4-Methoxyphenylboronic acid	10000	68
37	4-Cyanobenzyl bromide	3-Nitrophenylboronic acid	250	100 (75)
38	4-Cyanobenzyl bromide	3-Nitrophenylboronic acid	1000	85
39	4-Cyanobenzyl bromide	2-Methoxyphenylboronic acid	1000	100 (92)
40	4-Cyanobenzyl bromide	2-Methoxyphenylboronic acid	10000	63
41	Methyl 3-(bromomethyl)benzoate	Phenylboronic acid	10000	100 (95)
42	Methyl 3-(bromomethyl)benzoate	Phenylboronic acid	100000	85
43	Methyl 3-(bromomethyl)benzoate	2-Acetylphenylboronic acid	1000	100 (88)
44	3-Chlorobenzyl bromide	Phenylboronic acid	100000	90 (85)
45	2-Fluorobenzyl bromide	Phenylboronic acid	100000	89 (83)
46	2-Methylbenzyl bromide	Phenylboronic acid	1000	98 (91)

[a] Conditions: catalyst, see ref.[7], RBr (1 equiv), arylboronic acid (2 equiv), K_2CO_3 (2 equiv), xylene, 130 °C, 20 h, GC or NMR yields.

[b] Yields in parentheses are isolated.

[c] 20% of homocoupling of 4-nitrobenzylbromide was also observed.

[d] 12% of homocoupling of 4-nitrobenzylbromide was also observed.

Then, we studied the Suzuki cross-coupling reaction with benzylic chlorides. As illustrated in Table 2, in all cases much slower reactions rates were observed than with benzylic bromides. With these benzylic chlorides the rate-determining step seems to be the oxidative addition to the palladium complex. The reaction of benzyl chloride with phenylboronic acid led to the coupling adduct with a TON of 470 (entries 1 and 2). Similar reactions rates were observed in the presence of substituted arylboronic acids. For example, TONs of 580 and 230 were obtained in the presence of 4-methoxyphenylboronic acid and 2-acetylphenylboronic acid (entries 4 and 6). As expected, a lower TON was obtained in the presence of the sterically congested 2,4,6-trimethylphenylboronic acid (entry 8). In the presence of functionalised benzyl chlorides, similar results were obtained indicating a minor influence of electronic factors at the benzyl chlorides on the reaction rates (entries 9-15). For example, 4-methoxybenzyl chloride and 3,5-dinitrobenzyl chloride in the presence of phenylboronic acid led to very similar TONs of 610 and 840 (entries 13 and 15). Finally, 1,4-bis(chloromethyl)benzene with phenylboronic acid gave the expected diaddition adduct: 1,4-dibenzylbenzene, however, with this substrate a low TON was observed (entry 16).

In summary, we have established that the tedicyp-palladium system is not limited to Suzuki reactions of aryl halides; benzylic halides are also efficiently coupled. In the presence of the tedicyp/palladium complex, the Suzuki reaction of benzylic halides including the couplings of chlorides with a wide variety of arylboronic acids can be performed with as little as 0.0001% catalyst. Due to the high price of palladium, the practical advantage of such low catalyst loadings can become increasingly important for industrial processes. The functional group tolerance is remarkable, substituents such as fluoro, methyl, methoxy, acetyl, nitro, formyl, cyano or ester are tolerated. As expected, both the steric hindrance of the benzylic halides and the steric hindrance of the boronic acids have an effect on the reaction rates.

Table 2 Palladium-Tedicyp Catalysed Suzuki Cross-Coupling Reactions with Benzylic Chlorides (Scheme 1)[10,a]

Entry	R-Cl	Arylboronic acid	Ratio substrate/catalyst	Yield (%)[b]
1	Benzyl chloride	Phenylboronic acid	250	100 (91)
2	Benzyl chloride	Phenylboronic acid	1000	47
3	Benzyl chloride	4-Methoxyphenylboronic acid	250	92 (87)
4	Benzyl chloride	4-Methoxyphenylboronic acid	1000	58
5	Benzyl chloride	2,4-Difluorophenylboronic acid	250	55 (52)
6	Benzyl chloride	2-Acetylphenylboronic acid	250	100 (92)
7	Benzyl chloride	2-Methoxyphenylboronic acid	250	75 (72)
8	Benzyl chloride	2,4,6-Trimethylphenylboronic acid	100	45 (41)
9	4-Fluorobenzyl chloride	Phenylboronic acid	250	100 (95)
10	4-Fluorobenzyl chloride	Phenylboronic acid	1000	56
11	4-Nitrobenzyl chloride	Phenylboronic acid	1000	100 (83)
12	4-Nitrobenzyl chloride	4-Methoxyphenylboronic acid	1000	100 (80)[c]
13	4-Methoxybenzyl chloride	Phenylboronic acid	1000	87 (61)
14	3,5-Dinitrobenzyl chloride	Phenylboronic acid	250	100 (93)
15	3,5-Dinitrobenzyl chloride	Phenylboronic acid	1000	84
16	α,α′-Dichloro-*p*-xylene	Phenylboronic acid	100	60 (54)[d]

[a] Conditions: catalyst, see ref.[7], RCl (1 equiv), arylboronic acid (2 equiv), K_2CO_3 (2 equiv), xylene, 130 °C, 20 h, GC or NMR yields.
[b] Yields in parentheses are isolated.
[c] 7% of homocoupling of 4-nitrobenzylchloride was also observed.
[d] Phenylboronic acid: 3 equivalents.

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(10) As a typical experiment, the reaction of 4-cyanobenzyl bromide (1.00 g, 5.1 mmol), 4-methoxyphenylboronic acid (1.55 g, 10.2 mmol) and K_2CO_3 (1.4 g, 10.2 mmol) at 130 °C during 20 h in anhydrous xylene (10 mL) in the presence of *cis*,*cis*,*cis*-1,2,3,4-tetrakis(diphenylphosphinomethyl) cyclopentane–$[PdCl(C_3H_5)]_2$ complex (0.0051 mmol) under argon affords the corresponding adduct after extraction with ether, evaporation and filtration on silica gel (dichloromethane) in 81% (0.92 g) isolated yield. 4-(4-Methoxyphenylmethyl)benzonitrile: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.59$ (d, $J = 8.3$ Hz, 2 H, Ar), 7.29 (d, $J = 8.3$ Hz, 2 H, Ar), 7.11 (d, $J = 8.6$ Hz, 2 H, Ar), 6.88 (d, $J = 8.6$ Hz, 2 H, Ar), 4.00 (s, 2 H, CH2), 3.82 (s, 3 H, OMe).

(11) Analytical data of selected products: Table 1 (entry 11): $\delta =$ 7.71 (s, 1 H, Ar), 7.62 (s, 2 H, Ar), 7.35–7.10 (m, 5 H, Ph), 4.09 (s, 2 H, CH_2); Table 1 (entry 16): $\delta =$ 7.30–7.00 (m, 5 H, Ph), 7.08 (m, 1 H, Ar), 6.80 (m, 2 H, Ar), 3.94 (s, 2 H, CH_2); $C_{13}H_{10}F_2$ (204.2): calcd. C 76.46, H 4.94; found C 76.62, H 4.71; MS (EI, 70 eV) *m/z* (%): 204(100) [M^+]; Table 1 (entry 18): $\delta =$ 7.25–7.10 (m, 3 H, Ph), 7.01 (d, $J =$ 7.2 Hz, 2 H, Ph), 6.89 (s, 2 H, Ar), 4.02 (s, 2 H, CH_2), 2.29 (s, 3 H, Me), 2.20 (s, 6 H, Me); Table 1 (entry 25): $\delta =$ 9.96 (s, 1 H, CHO), 8.14 (d, $J =$ 8.7 Hz, 2 H, Ar), 7.85–7.35 (m, 4 H, Ar), 7.33 (d, $J =$ 8.7 Hz, 2 H, Ar), 4.14 (s, 2 H, CH_2); $C_{14}H_{11}NO_3$ (214.2): calcd. C 69.70, H 4.60; found C 70.01, H 4.72; MS (EI, 70 eV) *m/z* (%): 241(100) [M^+]; Table 1 (entry 26): $\delta =$ 8.12 (d, $J =$ 8.7 Hz, 2 H, Ar), 7.34 (d, $J =$ 8.7 Hz, 2 H, Ar), 7.11 (m, 1 H, Ar), 6.82 (m, 2 H, Ar), 4.03 (s, 2 H, CH_2); $C_{13}H_9F_2NO_2$ (249.2): calcd. C 62.65, H 3.64; found C 62.52, H 3.74; MS (EI, 70 eV) *m/z* (%): 249(100) [M^+]; Table 1 (entry 28): $\delta =$ 8.08 (d, $J =$ 8.6 Hz, 2 H, Ar), 7.32 (d, $J =$ 8.6 Hz, 2 H, Ar), 7.25 (m, 1 H, Ar), 7.09 (d, $J =$ 7.3 Hz, 1 H, Ar), 6.89 (m, 2 H, Ar), 4.03 (s, 2 H, CH_2), 3.77 (s, 3 H, Me); Table 1 (entry 35): $\delta =$ 7.60 (d, $J =$ 7.8 Hz, 2 H, Ar), 7.29 (d, $J =$ 7.8 Hz, 2 H, Ar), 7.10 (d, $J =$ 8.5 Hz, 2 H, Ar), 6.88 (d, $J =$ 8.5 Hz, 2 H, Ar), 4.00 (s, 2 H, CH2), 3.82 (s, 3 H, Me); Table 1 (entry 39): $\delta =$ 7.53 (d, $J =$ 7.3 Hz, 2 H, Ar), 7.28 (d, $J =$ 7.3 Hz, 2 H, Ar), 7.23 (m, 1 H, Ar), 7.07 (d, $J =$ 7.4 Hz, 1 H, Ar), 6.87 (m, 2 H, Ar), 4.00 (s, 2 H, CH_2), 3.78 (s, 3 H, Me); Table 1 (entry 43): $\delta =$ 7.83 (m, 1 H, Ar), 7.79 (s, 1 H, Ar), 7.67 (d, $J =$ 7.6 Hz, 1 H, Ar), 7.39 (t, $J =$ 7.6 Hz, 1 H, Ar), 7.30 (m, 3 H, Ar), 7.20 (d, $J =$ 7.6 Hz, 1 H, Ar), 4.31 (s, 2 H, CH2), 3.86 (s, 3 H, Me), 2.46 (s, 3 H, Me); $C_{17}H_{16}O_3$ (268.3): calcd. C 76.10, H 6.01; found C 75.87, H 6.21; MS (EI, 70 eV); *m/z* (%): 268(36) [M^+].