An Efficient Catalyst System for Palladium-Catalyzed Borylation of Aryl Halides with Pinacolborane

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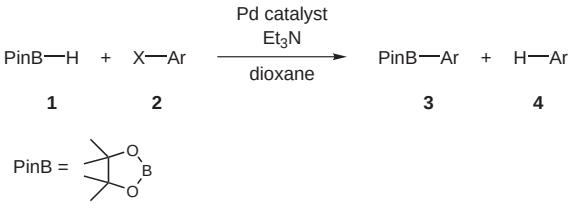
Abstract: The combination of $Pd(dba)_2$ and bis(2-di-*tert*-butylphosphinophenyl)ether has proven to be efficient for the cross-coupling of pinacolborane with aryl bromides and chlorides. The substrate scope is broad and the present system enables the synthesis of *ortho*-, *meta*-, and *para*-substituted electron-rich and -deficient arylboronates.

Key words: boron, palladium, catalysis, cross-coupling, ligands

Arylboronic acids and their esters are useful intermediates in organic synthesis, particularly with reactions involving carbon–carbon bond formation through the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1] Various methods are now available for their preparation. Above all, the palladium-catalyzed cross-coupling reactions of tetra(alkoxo)diborons[2] or dialkoxyboranes[3–8] with organic electrophiles have emerged as a general and powerful method for carbon–boron bond formation. The borylation using dialkoxyborane, such as pinacolborane (**1**), is an atom-economical method, more economically profitable as **1**, and cheaper than bis(pinacolato)diboron. We demonstrated the first examples of the palladium-catalyzed borylation of aryl halides **2** with **1** to provide arylboronates **3** (Equation 1).[3] Although our original procedure using $PdCl_2$(dppf) was found to work effectively for most aryl iodides, aryl bromides were often problematic with undesirable reduced arenes **4**. Recently, the Buchwald phosphine ligand[5] and DPEphos[8] have been utilized as efficient supporting ligands for the palladium-catalyzed borylation of aryl bromides. Whereas the scope of the aryl halides **2** in the palladium-catalyzed borylation has been improved, these catalyst systems still had some drawbacks, for example the reactions of electron-deficient or *ortho*,*ortho*′-disubstituted bromides produced only poor yields, and no example of the borylation of aryl chlorides was provided. In this paper, we wish to report a general protocol for the palladium-catalyzed borylation of aryl halides **2** using **1**. The present catalyst system using a bulky and electron-rich bis-phosphine ligand overcomes many limitations of the previous methods.



Equation 1 Palladium-catalyzed borylation using pinacolborane

An initial screening was performed using several phosphine ligands **L1**–**L8** (Figure 1) for the coupling reaction of **1** and ethyl 4-bromobenzoate (**2a**). These results are summarized in Table 1. The treatment of **2a** (1 equiv) with **1** (2 equiv) and Et_3N (3 equiv) in the presence of 5 mol% of $Pd(dba)_2$ and the phosphine ligand (Pd:P = 1:2) in dioxane at 80 °C was found to lead to the corresponding arylboronate **3a**. The formation of ethyl benzoate (**4a**) by reduction of the starting **2a** was the major side reaction. For the electron-deficient **2a**, the use of ligands **L1**, DPPF (**L3**), and DPEphos (**L6**), which have been utilized for the borylation of aryl iodides and electron-rich aryl bromides, did not provide the desired product **3a** as expected (entries 1, 3, 6).[3,5,8] Recently, it has been revealed that DiPPF (**L4**)[9] and DtBPF (**L5**)[10] were effective ligands for other palladium-catalyzed carbon–heteroatom bond forming processes. Bearing these reports in mind, we postulated that bis-phosphines having dialkylphosphino groups together with large bite angles created by backbones, such as **L4** and **L5**, could be efficient supporting ligands for the borylation. We then examined the chelating alkylphosphines. Employing **L4** and *i*-Pr-DPEphos (**L7**), however, gave poor yields of **3a** due to the extensive formation of **4a** (entries 4 and 7). Among the many trials using electron-rich and sterically hindered bidentate phosphines, we were pleased to observe that the use of *t*-Bu-DPEphos (**L8**) remarkably improved the yield and selectivity, although the formation of **4a** could not be completely suppressed (entry 8).[11]

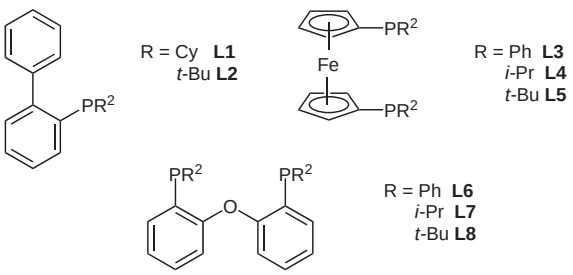


Figure 1 Phosphine ligands

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Table 1 Screening of Ligands for Borylation of Ethyl 4-Bromobenzoate (**2a**)[a]

Entry	Ligand	Yield (%)[b]	
		3a	**4a**
1[c]	L1	0	0
2[c]	L2	6	44
3	**L3**, DPPF	0	40
4	**L4**, DiPPF	11	80
5	**L5**, DtBPF	75	15
6	**L6**, DPEphos	0	46
7	**L7**, *i*-Pr-DPEphos	15	62
8	**L8**, *t*-Bu-DPEphos	84	16

[a] Reaction conditions: **2a** (0.5 mmol), **1** (1.0 mmol), Et_3N (1.5 mmol), $Pd(dba)_2$ (25 mmol), ligand (25 mmol), in dioxane (2 mL) at 80 °C for 6 h.
[b] GC yields are based on **2a**.
[c] 50 mmol of phosphine ligand was used.

After optimization of the reaction conditions, we investigated the scope of the borylation of the aryl halides **2** using **1**. These results are presented in Table 2. For all the cases listed in Table 2, small amounts of reduced by-products **4** were produced, but their isolation was very easy. The present process was extremely tolerant of a variety of common functional groups. Thus, the presence of functional groups, such as an ester (Table 1), ketone carbonyl (Table 2, entry 2), cyano (entry 3), and nitro groups (entry 4), in the starting **2** did not interfere with the outcome of the present reaction. The use of the catalyst derived from $Pd(dba)_2$ and **L8** demonstrated a good deal of generality, and the differences in the yields among the electronic characteristics of the substituent on the aryl bromides **2** (X = Br) were not particularly large. In addition, the sterically hindered bromides **2g–i** also gave the corresponding arylboronates **3** in high yields (entries 6–8). It is noteworthy that the reactions of the *ortho*,*ortho′*-disubstituted bromides **2h** and **2i**, which were problematic substrates in previous catalyst systems,[5,8] proceeded in high yields (entries 7 and 8). The present system enables the synthesis of *ortho*-, *meta*-, and *para*-substituted electron-rich and -deficient arylboronates **3** from the corresponding bromides **2**.

Although aryl chlorides are less reactive for the palladium-catalyzed processes than their bromide and iodide counterparts, these substrates are often more readily available from commercial sources and less expensive.[12] Thus, we then turned our attention toward the application of aryl chlorides **2** (X = Cl) for the palladium-catalyzed borylation using **1**. The present catalyst system also proved to be highly efficient for the electron-rich aryl chlorides **2j** and **2k**, although the reaction temperature of 120 °C was required (entries 9 and 10). To the best of our knowledge, this is the first example of the selective borylation of aryl chlorides with **1**. However, several attempts at the borylation of the electron-deficient aryl chloride **2l** were unsuccessful as the presence of electron-withdrawing substituents remarkably increased the yield of **4a** (entry 11).

To verify the feasibility of the reaction on a common laboratory scale, the borylation of **2a** was repeated on a 5-mmol scale (see the experimental section). In this case, the amounts of **1**, the catalyst, and the solvent were lowered. The reducing the amount of the reagents would be desirable to limit the amount of waste generation from this procedure, especially if the borylation was performed on a preparative scale. Actually, the present system was applied to the larger scale synthesis of **3a** without any difficulty.

In conclusion, we have developed a general method for the borylation of aryl halides **2** with pinacolborane **1** using $Pd(dba)_2$/*t*-Bu-DPEphos (**L8**) as the catalyst. The substrate scope was significantly broad and included electron-deficient and sterically hindered aryl bromides and electron-rich aryl chlorides. This catalyst system has the widest substrate scope of any reported to date. Further investigations to broaden the scope of the organic electrophiles are currently underway in our laboratory.

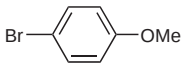
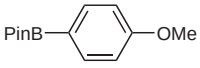
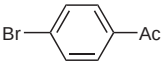
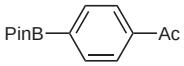
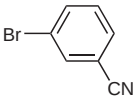
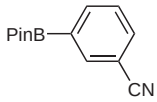
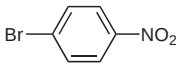
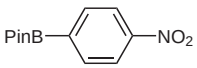
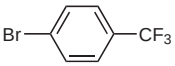
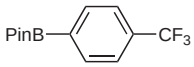
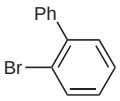
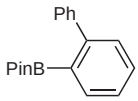
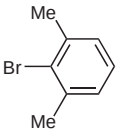
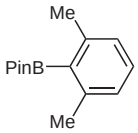
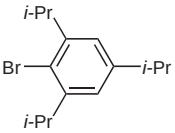
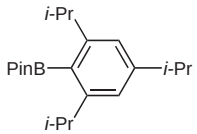
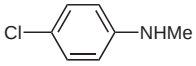
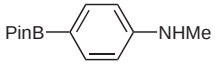
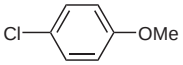
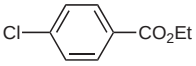
Palladium-Catalyzed Borylation of Aryl Halides; General Procedure (Table 1 and Table 2)

In a glove box, $Pd(dba)_2$ (25 μmol) and *t*-Bu-DPEphos (**L8**, 25 μmol) were placed in a screw-capped vial, and dissolved in 2 mL of 1,4-dioxane. After being stirred for 30 min, Et_3N (1.5 mmol), the aryl halide **2** (0.50 mmol), and pinacolborane (**1**, 1.0 mmol) were successively added. The vial was sealed with a cap and removed from the glove box. The reaction mixture was then stirred at 80–100 °C for 6 h. After the reaction, the mixture was diluted with Et_2O, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by Kugelrohr distillation to give the desired arylboronate **3**. The products **3a–c**, **3e**[3] and **3h**[5] were identified by comparison of their ^1H NMR data with those reported in the literature. Other boronates **3d**,**f**,**g**,**i**,**j** were characterized by ^1H NMR and ^{13}C NMR spectroscopy and HRMS analysis.[13]

Large-Scale Preparation of Arylboronates; General Procedure

A flask with a septum inlet was charged with $Pd(dba)_2$ (28 mg, 0.05 mmol), **L8** (25 mg, 0.05 mmol), and a magnetic stirring bar, and then flushed with nitrogen. Dioxane (10 mL), Et_3N (2.0 mL, 14 mmol), **2a** (1.14 g, 4.97 mmol), and **1** (0.87 mL, 6 mmol) were added by syringe. After being stirred for 16 h at 80 °C, the mixture was extracted with Et_2O (10 mL). The extract was washed with brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by Kugelrohr distillation to give 1.11 g (81% yield) of **3a**.

Table 2 Palladium-Catalyzed Borylation of Representative **2** with **1**

Entry	Aryl Halide **2**	Product **3**	Condition	Yield (%)[a]
1	 **2b**	 **3b**	100 °C, 6 h	91
2	 **2c**	 **3c**	80 °C, 6 h	78
3	 **2d**	 **3d**	80 °C, 6 h	79
4	 **2e**	 **3e**	80 °C, 2 h	76
5	 **2f**	 **3f**	80 °C, 6 h	82
6	 **2g**	 **3g**	100 °C, 6 h	86
7	 **2h**	 **3h**	100 °C, 6 h	82
8	 **2i**	 **3i**	100 °C, 6 h	72
9	 **2j**	 **3j**	120 °C, 24 h	81
10	 **2k**	**3b**	120 °C, 24 h	86
11	 **2l**	**3a**	120 °C, 24 h	10[b]

[a] Isolated yields are based on **2**.
[b] GC yield. The GC analysis also indicated the formation of **4a** in 87% yield.

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(11) *t*-Bu-DPEphos (**L8**) was prepared from diphenylether and $(t\text{-Bu})_2$PCl by a similar procedure for the preparation of DPEphos. See: Kranenburg, M.; Vanderburgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081.

(12) For a review of the palladium-catalyzed couplings of aryl chlorides, see: Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed.* **2002**, *41*, 4176.

(13) Compound **3d**: ^{1}H NMR ($CDCl_3$): δ = 1.35 (s, 12 H), 7.47 (t, *J* = 7.9 Hz, 1 H), 7.73 (d, *J* = 7.9 Hz, 1 H), 8.01 (d, *J* = 7.9 Hz, 1 H), 8.09 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 24.81, 84.46, 111.95, 118.79, 128.36, 134.37, 138.37, 138.73. HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}BNO_2$ [M^+]: 229.1274; found: 229.1312. IR (KBr): 2228 cm^{-1}.
Compound **3f**: ^{1}H NMR ($CDCl_3$): δ = 1.36 (s, 12 H), 7.61 (d, *J* = 7.9 Hz, 2 H), 7.92 (d, *J* = 7.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 24.98, 84.25, 124.29 (q, *J* = 4 Hz), 124.13 (q, *J* = 272 Hz), 132.80 (q, *J* = 32 Hz), 135.21. HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}BF_3O_2$ [M^+]: 272.1196; found: 272.1229.
Compound **3g**: ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 12 H), 7.30–7.50 (m, 8 H), 7.71 (d, *J* = 7.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 24.55, 83.69, 126.23, 126.79, 127.74, 128.92, 129.08, 130.03, 134.40, 143.19, 147.46. HRMS (EI): *m*/*z* calcd for $C_{18}H_{21}BO_2$ [M^+]: 280.1635; found: 280.1629.
Compound **3i**: ^{1}H NMR ($CDCl_3$): δ = 1.21 (d, *J* = 6.7 Hz, 6 H), 1.25 (d, *J* = 6.7 Hz, 12 H), 1.37 (s, 12 H), 2.84 (sept, *J* = 6.7 Hz, 1 H), 2.98 (sept, *J* = 6.7 Hz, 2 H), 6.93 (s, 2 H). ^{13}C NMR ($CDCl_3$): δ = 24.01, 24.55, 24.98, 34.00, 34.49, 83.61, 119.63, 149.72, 151.86. HRMS (EI): *m*/*z* calcd for $C_{21}H_{35}BO_2$ [M^+]: 330.2730; found: 330.2773.
Compound **3j**: ^{1}H NMR ($CDCl_3$): δ = 1.32 (s, 12 H), 2.86 (d, *J* = 5.5 Hz, 3 H), 3.92 (br s, 1 H), 6.58 (d, *J* = 8.5 Hz, 2 H), 7.65 (d, *J* = 8.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 24.79, 30.22, 83.13, 111.38, 136.26, 151.74. HRMS (EI): *m*/*z* calcd for $C_{13}H_{20}BNO_2$ [M^+]: 233.1587; found: 233.1611.
IR (KBr): 3425, 3401, 3375 cm^{-1}.