4,4,6-Trimethyl-1,3,2-dioxaborinane: A Practical Reagent for Palladium-Catalyzed Borylation of Aryl Halides

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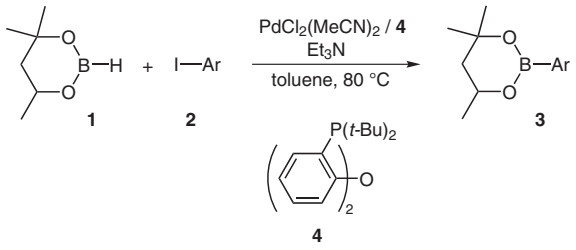
Abstract: The palladium-catalyzed borylation of aryl iodides with 4,4,6-trimethyl-1,3,2-dioxaborinane is described. The mild reaction conditions employed allow for aryl iodides with a wide variety of functional groups to be tolerated. The products of this borylation were coupled with aryl halides to give biaryls in good yields.

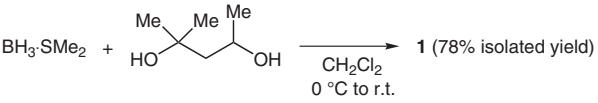
Key words: boron, palladium, catalysis, cross-coupling, aryl halides

Arylboronic acids and their esters are useful intermediates in organic synthesis, particularly in carbon–carbon bond formations using the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1] Various methods are now available for their preparation. 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 in carbon–boron bond formation. We have demonstrated the first examples of palladium-catalyzed borylation using commercially available 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane) and 1,3,2-benzodioxaborole (catecholborane) to give the corresponding arylboronates.[3] Pinacolborane has become one of the most popular borylation reagents, predominantly because the resulting pinacol boronates display excellent aqueous and chromatographic stability. It can be synthesized simply by reaction of equimolar amounts of borane and pinacol;[9] however, pinacol is extremely expensive. Consequently, we have sought an alternative borylation reagent; in this paper, we wish to report a palladium-catalyzed borylation of aryl iodides **2** using 4,4,6-trimethyl-1,3,2-dioxaborinane (**1**) (Scheme 1).[10]



Scheme 1

We thought that 4,4,6-trimethyl-1,3,2-dioxaborinane **1** was a promising borylation reagent because of its high stability.[10] Traditionally, the synthesis of **1** has been accomplished by the reduction of 2,2′-oxybis(4,4,6-trimethyl-1,3,2-dioxaborinane).[10b] It is interesting to note that **1** can be easily prepared from the borane-methyl sulfide complex and hexylene glycol by a similar procedure to that used in the preparation of pinacolborane (Scheme 2).[9] Not only is hexylene glycol less expensive, but this reaction also led to a better yield when compared to pinacol. Thus, using **1** is more economically profitable than using pinacolborane.



Scheme 2

In order to optimize reaction conditions, 4-iodoanisole (**2a**) was used as the substrate in the palladium-catalyzed borylation using **1**. Table 1 lists the phosphine ligands tested and the subsequent results. Although the combination of $PdCl_2(MeCN)_2$ and phosphine ligands, (PPh_3, DPPF[3] and DPEphos,[7] Table 1, entries 1, 3 and 4), gave the desired arylboronate **3a** in moderate to good yields (74–84%, by GC analysis), there was also considerable amounts of anisole **5a** (15–20%). We recently reported the use of bis(2-di-*tert*-butylphosphinophenyl)ether (**4**, *t*-Bu-DPEphos) as a supporting ligand for a palladium-catalyzed borylation using pinacolborane,[8] which also proved to be an efficient catalyst system here and gave smaller amounts of **5a** (3% yield, Table 1, entry 5). Examining a variety of bases showed that the use of a tertiary amine was essential for this borylation and that triethylamine proved to be the most effective base. A good result was obtained using toluene as a solvent, while the use of 1,4-dioxane resulted in lower selectivity. Thus, the optimized conditions were determined to be 4-iodoanisole (**2a**, 1.0 equiv), **1** (1.5 equiv), Et_3N as base (3.0 equiv) and 3 mol% of palladium catalyst prepared in situ from $PdCl_2(MeCN)_2$ and *t*-Bu-DPEphos **4**, in toluene at 80 °C under a nitrogen atmosphere.

To examine the scope of this reaction, borylations of representative aryl halides were examined under these conditions (Table 2). Previous borylation reactions using pinacolborane tolerated various functional groups owing to the inert nature of the pinacolborane.[3,8] As shown in

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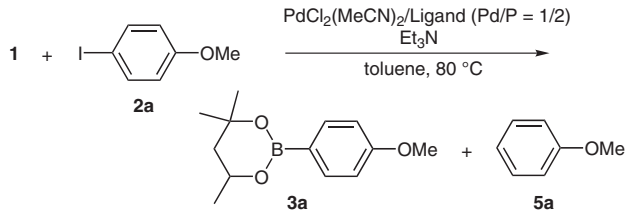
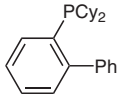
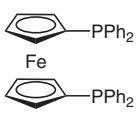
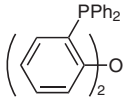
Table 1 Screening of Ligands for Borylation of **2a**[a]



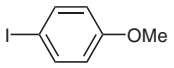
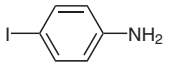
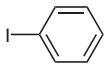
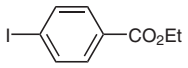
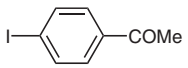
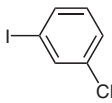
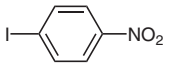
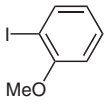
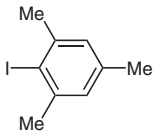
Entry	Ligand	Yield (%)[b]	
		3a	**5a**
1[c]	PPh_3	84	15
2[c]		23	0
3	 DPPF	74	20
4	 DPEphos	83	15
5	**4**	97	3

[a] Reaction conditions: **2a** (0.5 mmol), **1** (0.75 mmol), Et_3N (1.5 mmol), $PdCl_2(MeCN)_2$ (15 μmol), ligand (15 μmol) in toluene (2 mL) at 80 °C for 4 h.
[b] GC yields based on **2a**.
[c] 30 μmol of phosphine ligand was used.

Table 2, the present procedure using **1** is similarly tolerant of a variety of common functional groups. Thus, aryl iodides **2** containing NH_2 (Table 2, entry 2), CO_2Et (Table 2, entry 4), COMe (Table 2, entry 5), CN (Table 2, entry 6), and NO_2 (Table 2, entry 7) were all efficiently converted to the corresponding products **3**. In all cases listed in Table 2, small amounts of the reduced by-product were produced, but purification by bulb-to-bulb distillation or flash column chromatography was simple as the resulting boronates **3** exhibited excellent stability in aqueous workup and chromatography. Both the yield and the product selectivity were almost independent of the electronic and steric requirement. The differences in the yields and the selectivity between substrates bearing electron-donating (Table 2, entries 1 and 2) or electron-withdrawing groups (Table 2, entries 4–7) were not particularly large and the sterically hindered **2h** and **2i** (Table 2, entries 8 and 9) were also coupled with **1** without any difficulty. Accordingly, the present reaction provides a simple and widely available procedure for the synthesis of arylboronates **3**.

In order to demonstrate the synthetic utility of the arylboronates **3**, we proceeded to examine the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[1,11] The results are summarized in Table 3 and show that a variety of substituted biaryls can be obtained in high yields. The

Table 2 Borylation of **2** with **1** (Scheme 1)[a]

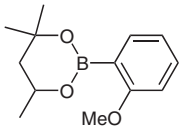
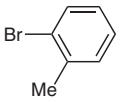
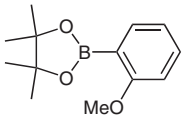
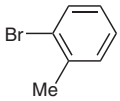
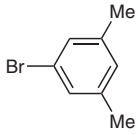
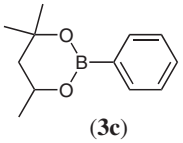
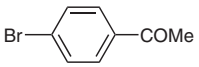
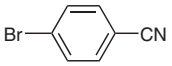
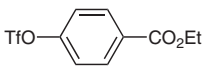
Entry	Aryl halide **2**	Yield (%)[b]
1[c]	 (**2a**)	86 (**3a**)
2[c]	 (**2b**)	72 (**3b**)
3	 (**2c**)	93 (**3c**)
4	 (**2d**)	78 (**3d**)
5	 (**2e**)	80 (**3e**)
6	 (**2f**)	86 (**3f**)
7	 (**2g**)	77 (**3g**)
8	 (**2h**)	89 (**3h**)
9	 (**2i**)	88 (**3i**)

[a] Reaction conditions: **2** (0.5 mmol), **1** (0.75 mmol), Et_3N (1.5 mmol), $PdCl_2(MeCN)_2$ (15 μmol), **4** (15 μmol) in toluene (2 mL) at 80 °C for 16 h.
[b] Isolated yields based on **2**.
[c] The reaction was carried out for 4 h.

reaction of 2-bromotoluene with 2-(2-methoxyphenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane (**3h**) took place smoothly in *N*,*N*-dimethylformamide at 100 °C in the presence of potassium phosphate and 3 mol% of $Pd(PPh_3)_4$ (Table 3, entry 1). When compared to the corresponding pinacol boronate (Table 3, entry 2), the difference in reactivity between these two compounds was very small.

In conclusion, 4,4,6-trimethyl-1,3,2-dioxaborinane **1** was found to promote the palladium-catalyzed borylation of aryl iodides. From an economical point of view, **1** is a less expensive borylating reagent than pinacolborane. In addition, **1** tolerates various functional groups and the resulting boronates **3** exhibit good reactivity for converting the

Table 3 Suzuki–Miyaura Cross-Coupling Reaction of **3**[a]

Entry	Arylboronate	Aryl halide	Yield (%)[b]
1	 (**3h**)		93
2			97
3	**3h**		85
4	 (**3c**)		90
5	**3c**		97
6	**3c**		98

[a] Reaction conditions: arylboronate (0.25 mmol), aryl bromide (0.25 mmol), K_3PO_4 (0.75 mmol), $Pd(PPh_3)_4$ (7.5 μmol) in DMF (1 mL) at 100 °C for 2 h.
[b] GC yields.

boron functionality and excellent stability in aqueous workup and chromatography. Further studies are currently underway to expand the scope of organic halides and dialkoxyboranes.

All experiments were carried out under a nitrogen atmosphere using oven-dried glassware. NMR spectra were recorded on a JEOL JMN-A500 spectrometer. Mass spectra were obtained at an ionization potential of 70 eV with a JEOL JMS-SX102 spectrometer. Bis(2-di-*tert*-butylphosphinophenyl)ether (**4**) was prepared by a known method.[8]

Synthesis of 4,4,6-Trimethyl-1,3,2-dioxaborinane

A flask equipped with a distillation apparatus and an oil bubbler was flushed with nitrogen, charged with CH_2Cl_2 (10 mL) and hexylene glycol (2.6 mL, 20 mmol) through the septum inlet with a syringe and cooled to 0 °C. Then $BH_3{\cdot}SMe_2$ (2.0 mL, 20 mmol) was added dropwise leading to effervescence. After the mixture was stirred for 2 h at 0 °C and for 1 h at r.t., distillation under reduced pressure afforded 2.0 g (78% yield) of 4,4,5-trimethyl-1,3,2-dioxaborinane (**1**), bp 45 °C at 35 mmHg.

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

In a glove box, $PdCl_2(MeCN)_2$ (15 μmol) and *t*-Bu-DPEphos **4** (15 μmol) were placed in a screw-capped vial and dissolved in 2 mL of toluene. After being stirred for 30 min, Et_3N (1.5 mmol), the aryl iodide **2** (0.50 mmol) and 4,4,5-trimethyl-1,3,2-dioxaborinane **1** (0.75 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 °C for 16 h. After the reaction was complete, 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 or flash column chromatography (hexane–Et_2O) to give the desired arylboronate **3**. All products **3** were characterized by ^1H and ^{13}C NMR spectroscopy and HRMS analysis.

3a

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.1 Hz, 3 H), 1.35 (s, 3 H), 1.36 (s, 3 H), 1.57 (dd, *J* = 6.8, 11.6 Hz, 1 H), 1.84 (dd, *J* = 2.8, 6.8 Hz, 1 H), 3.81 (s, 3 H), 4.32 (br s, 1 H), 6.86 (d, *J* = 8.6 Hz, 2 H), 7.75 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.25, 28.41, 31.59, 46.32, 55.29, 65.09, 71.04, 113.23, 135.66, 161.47.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}BO_3$: 234.1427; found: 234.1399.

3b

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (d, *J* = 6.1 Hz, 3 H), 1.34 (s, 3 H), 1.35 (s, 3 H), 1.56 (dd, *J* = 6.8, 12.2 Hz, 1 H), 1.83 (dd, *J* = 2.8, 6.8 Hz, 1 H), 3.79 (br s, 2 H), 4.30 (br s, 1 H), 6.65 (d, *J* = 8.0 Hz, 2 H), 7.62 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.29, 28.16, 31.36, 46.10, 64.71, 70.60, 114.11, 135.29, 148.37.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}BNO_2$: 219.1430; found: 219.1479.

3c

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.1 Hz, 3 H), 1.36 (s, 3 H), 1.37 (s, 3 H), 1.58 (dd, *J* = 6.8, 11.9 Hz, 1 H), 1.86 (dd, *J* = 2.8, 6.8 Hz, 1 H), 4.34 (br s, 1 H), 7.33 (t, *J* = 7.0 Hz, 2 H), 7.4–7.8 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.20, 28.13, 31.27, 46.01, 64.93, 70.92, 127.40, 130.29, 133.72.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{17}BO_2$: 204.1321; found: 204.1346.

3d

^1H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.1 Hz, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.40 (t, *J* = 6.3 Hz, 3 H), 1.60 (dd, *J* = 7.0, 11.9 Hz, 1 H), 1.88 (dd, *J* = 3.1, 7.0 Hz, 1 H), 4.36 (br s, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 7.86 (d, *J* = 8.5 Hz, 2 H), 7.98 (d, *J* = 8.5 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.34, 23.14, 28.17, 31.22, 45.97, 60.89, 65.20, 71.32, 128.34, 131.82, 133.73, 167.03.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}BO_4$: 276.1533; found: 276.1577.

3e

^1H NMR (500 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.1 Hz, 3 H), 1.38 (s, 3 H), 1.39 (s, 3 H), 1.61 (dd, *J* = 7.0, 12.2 Hz, 1 H), 1.89 (dd, *J* = 2.8, 6.9 Hz, 1 H), 2.61 (s, 3 H), 4.36 (br s, 1 H), 7.88 (d, *J* = 8.6 Hz, 2 H), 7.90 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.10, 26.72, 28.13, 31.17, 45.92, 65.19, 71.33, 127.06, 133.90, 138.28, 198.68.

HRMS (EI): *m*/*z* calcd for $C_{14}H_{19}BO_3$: 246.1427; found: 246.1416.

3f

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 6.7 Hz, 3 H), 1.37 (s, 3 H), 1.38 (s, 3 H), 1.60 (dd, *J* = 6.8, 11.6 Hz, 1 H), 1.90 (dd, *J* = 3.1, 6.8 Hz, 1 H), 4.36 (br s, 1 H), 7.43 (t, *J* = 7.3 Hz, 1 H), 7.66 (d, *J* = 7.3 Hz, 1 H), 8.01 (d, *J* = 7.3 Hz, 1 H), 8.09 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.06, 28.12, 31.42, 45.93, 65.37, 71.60, 111.58, 119.38, 128.03, 133.53, 137.65, 137.91.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{16}BNO_2$: 229.1275; found: 229.1304.

3g

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.1 Hz, 3 H), 1.39 (s, 3 H), 1.40 (s, 3 H), 1.62 (dd, *J* = 7.0, 12.2 Hz, 1 H), 1.91 (dd, *J* = 3.1, 7.0 Hz, 1 H), 4.38 (br s, 1 H), 7.95 (d, *J* = 8.6 Hz, 2 H), 8.15 (d, *J* = 8.6 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.04, 28.14, 31.13, 45.89, 65.47, 71.72, 122.13, 134.65, 149.87.

HRMS (EI): *m*/*z* calcd for $C_{12}H_{16}BNO_4$: 249.1173; found: 249.1156.

3h

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 6.1 Hz, 3 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 1.63 (dd, *J* = 7.0, 11.9 Hz, 1 H), 1.86 (dd, *J* = 3.1, 7.0 Hz, 1 H), 3.80 (s, 3 H), 4.38 (br s, 1 H), 6.82 (d, *J* = 7.3 Hz, 1 H), 6.92 (t, *J* = 7.3 Hz, 1 H), 7.31 (t, *J* = 7.3 Hz, 1 H), 7.59 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 23.11, 28.07, 31.18, 45.85, 55.70, 65.06, 71.02, 110.80, 120.18, 131.06, 135.38, 163.43.

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}BO_3$: 234.1427; found: 234.1415.

3i

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 6.1 Hz, 3 H), 1.35 (s, 3 H), 1.41 (s, 3 H), 1.63 (dd, *J* = 6.8, 12.2 Hz, 1 H), 1.91 (dd, *J* = 3.1, 6.8 Hz, 1 H), 2.21 (s, 3 H), 2.31 (s, 6 H), 4.37 (br s, 1 H), 6.75 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.16, 21.82, 23.20, 28.02, 31.17, 46.24, 65.22, 71.32, 127.13, 137.75, 139.97.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}BO_2$: 246.1792; found: 246.1830.

Palladium-Catalyzed Biaryl Coupling; Typical Procedure (Table 3)

A mixture of 2-(2-methoxyphenyl)-4,4,6-trimethyl-1,3,2-dioxaborinane (**3h**) (0.25 mmol), 2-bromotoluene (0.25 mmol), K_3PO_4 (0.75 mmol), and $Pd(PPh_3)_4$ (7.5 μmol) in DMF (1 mL) was stirred at 100 °C for 2 h. The resulting mixture was diluted with toluene and washed with H_2O. The GC analysis of the organic layer indicated the formation of the desired biaryl in 93% yield.

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References and Notes

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