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PALLADIUM- OR NICKEL-CATALYZED COUPLING REACTION OF DIALKOXYBORANES WITH CHLOROARENES: ARYLATION OF 1,3,2-DIOXABOROLANES OR 1,3,2-DIOXABORINANES[†]

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Abstract – The borylation of electron-deficient aryl chlorides with pinacolborane proceeded in the presence of Bu_4NI and a catalytic amount of $Pd(dba)_2$ / bis(2-di-*tert*-butylphosphinophenyl) ether. The combination of $NiCl_2(dppp)$ catalyst and Bu_4NBr was also efficient for the borylation of aryl chlorides.

Arylboronic acids and their esters are versatile reagents for modern organic synthesis, particularly with reactions involving carbon–carbon bond formation through the Suzuki-Miyaura cross-coupling reaction.[1] The versatility of this methodology renders arylboronates attractive targets for synthesis. In recent years, the palladium-catalyzed borylation of aryl electrophiles with bis(pinacolato)diboron[2] or 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (pinacolborane, **1a**)[3–7] has proved to be a general and powerful method for carbon–boron bond formation. In particular, **1a** is a cheaper and more atom-economical boron source. Although numerous catalyst systems have been reported to affect the borylation using **1a**, the use of aryl iodides or bromides is often necessary. Despite several advantages of employing aryl chlorides **2**, examples of the borylation of **2** with **1a** are rare.[8] We demonstrated the first examples of the palladium-catalyzed borylation of **2**; however, this method was only applicable to aryl chlorides having electron-donating groups at *para*-position.[6] Thereafter, the scope of **2** in the palladium-catalyzed borylation was somewhat improved by Buchwald and his colleague.[7] However, there has been no successful report of the borylation of aryl chlorides having electron-withdrawing groups on the aromatic rings. In this paper, we wish to report an efficient protocol for the transition-metal-catalyzed borylation of

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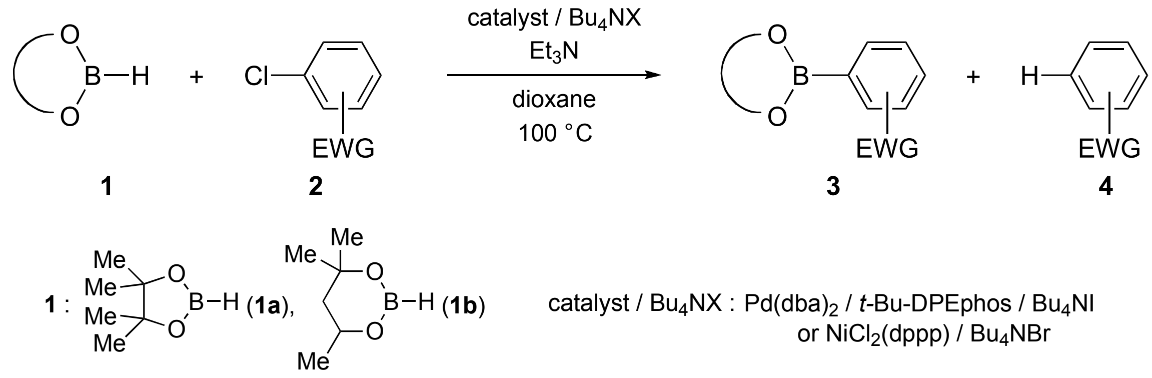
[†] This paper is dedicated to Professor Akira Suzuki on the occasion of his 80th birthday.

electron-deficient aryl chlorides **2** using cyclic dialkoxyboranes **1** (Scheme 1).



Scheme 1. Borylation of Electron-Deficient Aryl Chlorides

As a test for the optimization of reaction parameters, **1a** and ethyl 4-chlorobenzoate (**2a**) were selected as reaction partners. The results are summarized in Table 1. The borylation of such an electron-deficient aryl chloride using Pd(dba)$_2$ and bis(2-di-*tert*-butylphosphinophenyl) ether (*t*-Bu-DPEphos) as a catalyst gave only 13% yield of the borylated product **3a** due to a strong tendency to produce the reduced arene **4a** (entry 1).[6] Recently, we reported that addition of an iodide anion source improved the selectivity on the analogous silylation of aryl halides with hydrosilanes.[9] We then examined a treatment with additional 2 equiv of tetrabutylammonium halides, and found that the borylation proceeded selectively in the presence of Bu$_4$NI (entry 2). Bu$_4$NBr or Bu$_4$NCl was less effective (entries 3 and 4). Although the mechanism for this borylation is unclear at the present stage, the role of iodide ion may be attributed to the halide ligand exchange of the arylpalladium(II) halide intermediate.[3,9]

Table 1. Reaction of Ethyl 4-Chlorobenzoate (**2a**) with Pinacolborane (**1a**)[a]

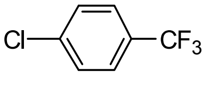
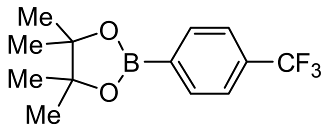
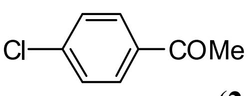
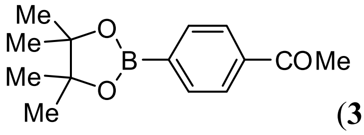
entry	catalyst	additive	yield (%)[b]	
			3a	**4a**
1	Pd(dba)$_2$/*t*-Bu-DPEphos[c]	none	13	65
2		Bu$_4$NI	84	12
3		Bu$_4$NBr	57	30
4		Bu$_4$NCl	36	45
5	NiCl$_2$(dppp)[d]	none	5	5
6		Bu$_4$NI	74	11
7		Bu$_4$NBr	85	7
8		Bu$_4$NCl	29	19

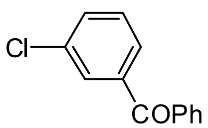
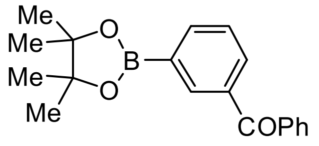
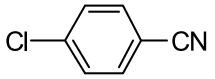
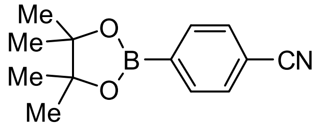
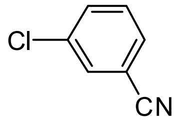
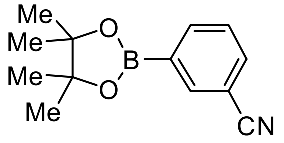
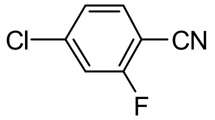
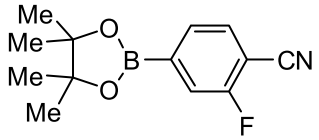
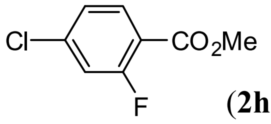
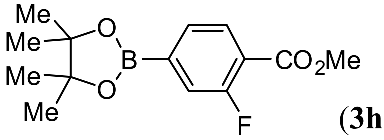
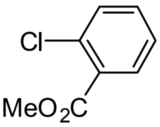
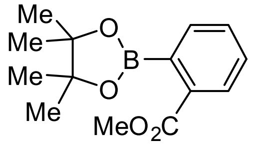
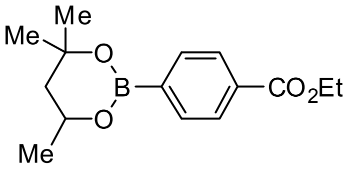
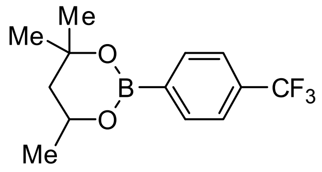
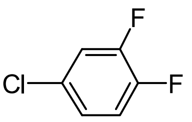
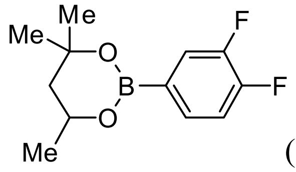
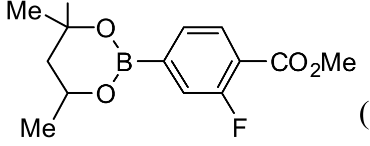
[a] Reaction conditions: **2a** (0.25 mmol), **1a** (0.50 mmol), Et_3N (0.75 mmol), catalyst (5 mol%), additive (0.50 mmol), in dioxane at 100 °C. [b] GC yields are based on **2a**. [c] The reactions were carried out for 24 h in 1 mL of dioxane by using a catalyst prepared in situ from $Pd(dba)_2$ (12.5 μmol) and *t*-Bu-DPEphos (12.5 μmol). [d] The reactions were carried out for 48 h in 0.25 mL of solvent.

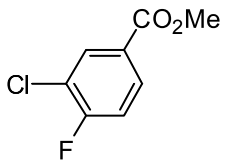
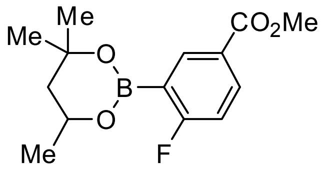
It is known that the borylation of aryl halides was also performed using $NiCl_2(dppp)$ as a catalyst; however, no successful example of the borylation of aryl chlorides **2** has appeared.[10] Gratifyingly, this coupling work was achieved with the aid of tetrabutylammonium halides in analogy with the above palladium-catalyzed reaction, whereas the absence of tetrabutylammonium halides gave no satisfactory result as expected (entry 5). Thus, the $NiCl_2(dppp)$ catalyst proved to be highly efficient for the borylation of **2a** in the presence of Bu_4NBr (entry 7), although replacing the halide anion of tetrabutylammonium salts gave lower yields under the same conditions (entries 6 and 8).

After optimization of the reaction conditions, we investigated the scope of the borylation of the aryl chlorides **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. In the first part of this study, the palladium catalyst system was applied to the coupling of various aryl chlorides **2** with **1a**.[11] The present process was extremely tolerant of a variety of common functional groups. Thus, the presence of functional groups, such as an ester (entries 8 and 9), ketone carbonyl (entries 3 and 4), and cyano groups (entries 5–7), in the starting **2** did not interfere with the outcome of the present reaction. In contrast, an *ortho* substituent prevented the borylation of **2i**, although moderate yield was still obtained (entry 9). The use of the catalyst derived from $Pd(dba)_2$ and *t*-Bu-DPEphos demonstrated exceptional level of functional group toleration, but the $NiCl_2(dppp)$ system lacked generality; i.e., several attempts at the selective nickel-catalyzed borylation of **2** having ketone carbonyl and cyano groups were unsuccessful.

Table 2. Borylation of Representative **2** with **1**

entry	**1**	**2**	condition[a]	**3**	yield (%)[b]
1	**1a**	 (**2b**)	A	 (**3b**)	84
2[c]	**1a**	**2b**	B	**3b**	81
3	**1a**	 (**2c**)	A	 (**3c**)	87

4[c]	**1a**	 (**2d**)	A	 (**3d**)	70
5	**1a**	 (**2e**)	A	 (**3e**)	80
6	**1a**	 (**2f**)	A	 (**3f**)	88
7	**1a**	 (**2g**)	A	 (**3g**)	74
8	**1a**	 (**2h**)	A	 (**3h**)	70
9[c]	**1a**	 (**2i**)	A	 (**3i**)	57
10	**1b**	**2a**	B	 (**3j**)	86
11	**1b**	**2b**	B	 (**3k**)	77
12[c]	**1b**	 (**2j**)	B	 (**3l**)	81
13	**1b**	**2h**	B	 (**3m**)	89

14	**1b**	 (**2k**)	B	 (**3n**)	59

[a] The reactions were carried out at 100 °C for 24 h by using **2** (0.50 mmol), **1** (1.0 mmol), Et_3N (1.5 mmol), Bu_4NX (1.0 mmol), and catalyst (25 μmol), unless otherwise noted The catalyst, Bu_4NX, and solvent are as follows. Condition A: Pd(db**a**)$_2$ (25 μmol), *t*-Bu-DPEphos (25 μmol), and Bu_4NI in dioxane (2 mL). Condition B: $NiCl_2$(dppp) (25 μmol) and Bu_4NBr in dioxane (0.5 mL). [b] Isolated yields are based on **2**. [c] The reactions were conducted for 48 h.

Quite recently, 4,4,6-trimethyl-1,3,2-dioxaborinane (**1b**) has been used as a borylating reagent to achieve the palladium-catalyzed borylation of aryl halides; however, this method was limited to aryl iodides and bromides.[12] The second portion of this work involved the application of our protocol to the catalytic borylation of electron-deficient aryl chlorides **2** with **1b**. While the Pd(dba)$_2$/*t*-Bu-DPEphos/Bu_4NI system was not suitable for the reaction of aryl chlorides with **1b**, we were pleased to observe that the nickel-catalyzed borylation could be carried out in the presence of Bu_4NBr. At present, we have no definitive explanation for the superior efficiency of the nickel catalyst for **1b**. Several functionalized aryl chlorides **2** containing ester group (entries 10, 13, and 14) and fluorine atom (entries 11−14) were efficiently converted to the corresponding products **3**.

In conclusion, we have developed a general method for the arylation of cyclic dialkoxyboranes **1** using electron-deficient aryl chlorides **2** as arylating reagents. The Pd(dba)$_2$/*t*-Bu-DPEphos or $NiCl_2$(dppp) catalyst system was effective for the coupling of aryl chlorides, and the selective borylation proceeded by a treatment with additional tetrabutylammonium halides in either case. Further investigations to broaden the scope of the organic electrophiles are currently underway in our laboratory.

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11. *General Procedure*. In a glove box, Pd(dba)$_2$ (25 μmol) and *t*-Bu-DPEphos (25 μmol) were placed in a screw-capped vial containing a stir bar, and dissolved in 2 mL of 1,4-dioxane. After being stirred for 1 h at room temperature, Et_3N (1.5 mmol), Bu_4NI (1.0 mmol), aryl chloride **2** (0.50 mmol), and **1a** (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 100 °C for 24 h. The resulting mixture was allowed to cool to room temperature, 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**.
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