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PALLADIUM-CATALYZED BORYLATION OF ARYL IODIDES WITH 2,3-DIHYDRO-1*H*-BENZO[*d*][1,3,2]DIAZABOROLES

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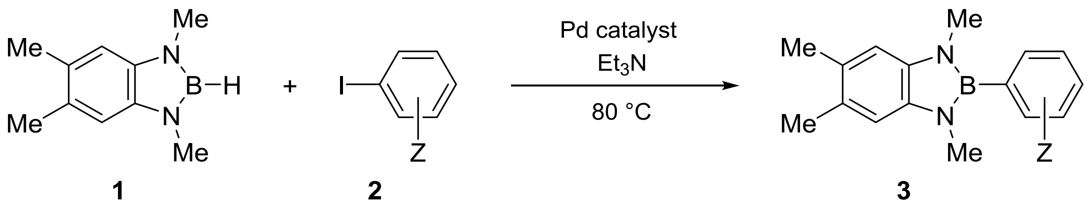
This paper is dedicated to Professor Victor Snieckus on the occasion of his 77th birthday.

Abstract – The palladium-catalyzed borylation of aryl iodides with 2,3-dihydro-1*H*-benzo[*d*][1,3,2]diazaboroles was achieved. The mild reaction conditions employed allowed for the inclusion of a wide variety of functional groups in aryl iodides to be tolerated. Additionally, the borylated products can be transformed into the corresponding boronic acids or their esters under acidic conditions.

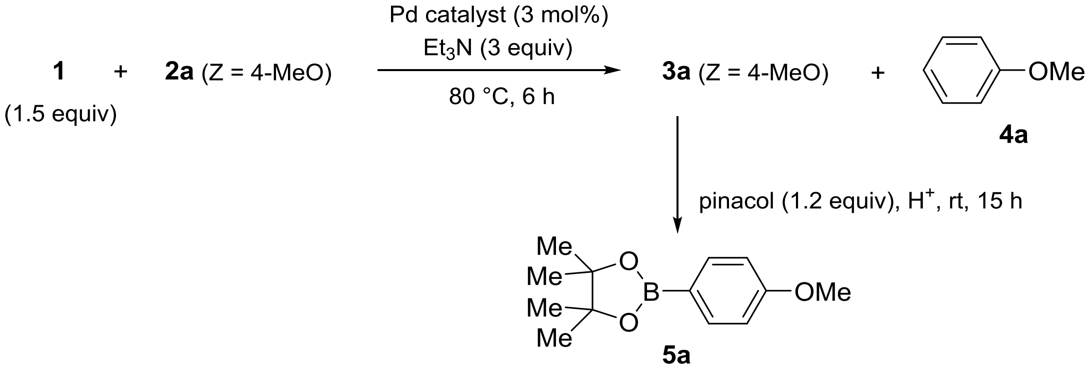
The synthesis of arylboronic acids and their esters has attracted a great deal of interest due to the versatility of such compounds in modern organic chemistry.[1] Although a number of methods exist for aryl C–B bond construction, the borylation of aryl halides with hydroboranes has proved to be an atom-economical and powerful method for preparation of functionalized arylboronates.[2,3] Our and other groups successfully introduced several cyclic dialkoxyboranes to participate in the catalytic borylation of aryl halides. Above all, pinacolborane has become one of the most popular boron sources,[4] predominantly because of the high level of functional group compatibility; however, some sensitive functional groups, such as a free hydroxy and a formyl group, were not well tolerated.[5] Based on our success in this area, we have sought an alternative boron source; in this paper, wish to report the palladium-catalyzed borylation of aryl iodides **2** with 1,3,5,6-tetramethyl-2,3-dihydro-1*H*-benzo[*d*][1,3,2]diazaborole (**1**)[6] (Scheme 1). To the best of our knowledge, the present work is the first example of the di(amino)boranes for the borylation of C–halogen bonds. Although there are previous studies on the palladium-catalyzed borylation using aminoboranes ($R_2N–BH_2$) as boron sources, improvements of functional group tolerance have not been demonstrated in the literatures.[7]



Scheme 1. Borylation of aryl iodides **2** with 2,3-dihydro-1*H*-benzo[*d*][1,3,2]diazaboroles **1**

In our initial screening experiments, 4-iodoanisole (**2a**) was used as substrates for discovery of suitable reaction conditions.[8] The results are summarized in Table 1. The treatment of **2a** with **1** (1.5 equiv), Et_3N (3 equiv), and $PdCl_2$(dtbpf) (DtBPF = 1,12-bis(di-*tert*-butylphosphino)ferrocene, 3 mol%)[9] in 1,4-dioxane at 80 °C followed by esterification with pinacol and aq. HCl afforded the corresponding arylboronate **5a** in 81% yield in two steps, although the reaction suffered from the formation of dehalogenated byproduct **4a** as a result of reduction of the C–I bond (entry 1). The Suzuki–Miyaura coupling reaction between **3a** and starting **2a** was completely suppressed; i.e., no homo-coupled 4,4'-dimethoxy-1,1'-biphenyl was observed.[10] The commonly employed catalysts, such as $PdCl_2$(dppf), $PdCl_2(PPh_3)_2$, and Pd[P(*t*-Bu)$_3$]$_2$,

Table 1. Borylation of 4-iodoanisole (**2a**) with **1**[a]



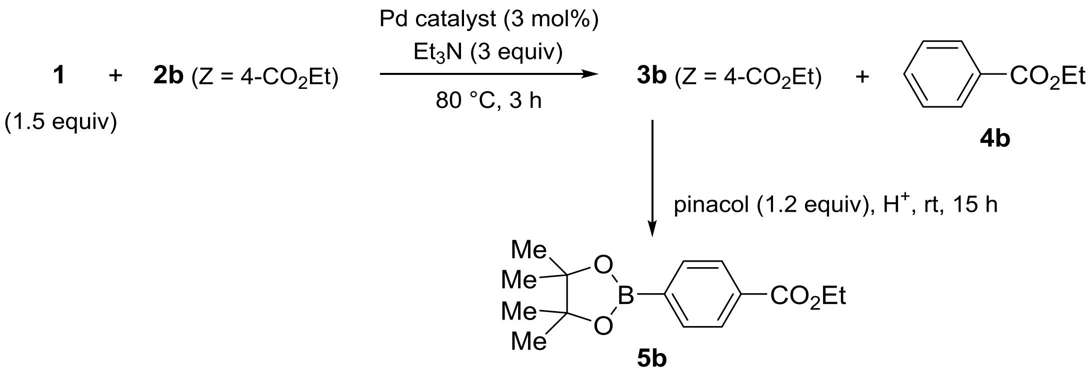
entry	catalyst	solvent	yield (%)[b]	
			5a	**4a**
1	$PdCl_2$(dtbpf)	dioxane	81	13
2	$PdCl_2$(dppf)	dioxane	58	24
3	$PdCl_2(PPh_3)_2$	dioxane	55	16
4	Pd[P(*t*-Bu)$_3$]$_2$	dioxane	68	15
5	$PdCl_2$(dtbpf)	toluene	79	10
6	$PdCl_2$(dtbpf)	DMF	68	32

[a] The borylation of **2a** (0.250 mmol) with **1** (0.375 mmol) was carried out with Et_3N (0.75 mmol) and a catalyst (5 mol%) in a solvent (1 mL) at 80 °C for 6 h. Pinacol (0.3 mmol) and HCl aq. were added to the mixture and the reaction was continued for 15 h at rt. [b] GC yields are based on **2a**.

gave unsatisfactory results (entries 2–4). As for the reaction solvent, 1,4-dioxane and toluene were found to be superior to DMF (entries 1, 5 and 6).

With the optimized conditions in hand, we next investigated the substrate scope. However, it became apparent that the above conditions were somewhat limited in substrate scope; i.e., the reaction of ethyl 4-iodobenzoate (**2b**) gave moderate yield and selectivity (Table 2, entry 1).[11] Therefore, palladium catalysts, and solvents were again evaluated for the borylation of electron-deficient aryl iodides with **1**. Among the catalysts examined in this study, the use of Pd[P(*t*-Bu)$_3$]$_2$ improved the selectivity of the borylation of **2b** (entry 5).[12] From Table2, it is evident that toluene was the best solvent for the reaction (entry 6). Since the Pd[P(*t*-Bu)$_3$]$_2$ catalyst was inefficient for the borylation to electron-rich aryl iodides (Table 1, entry 3), two reaction conditions compensate for their defects each other.

Table 2. Borylation of ethyl 4-iodobenzoate (**2b**) with **1**[a]

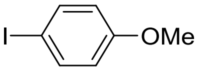
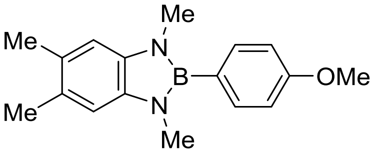
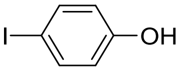
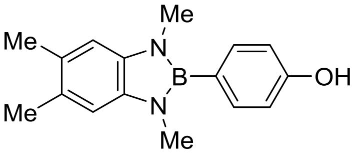
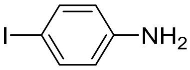
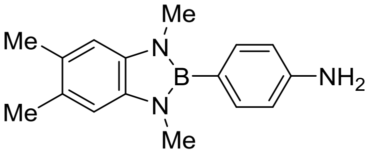
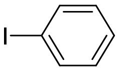
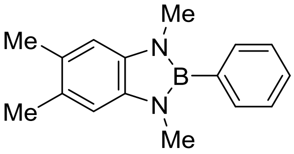
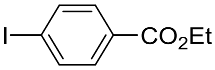
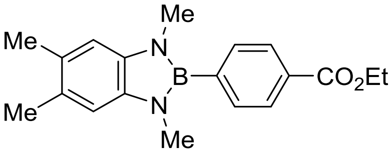
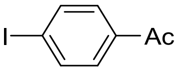
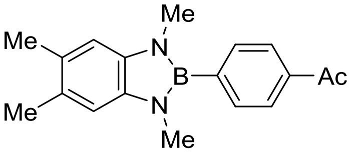
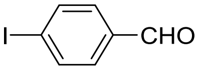
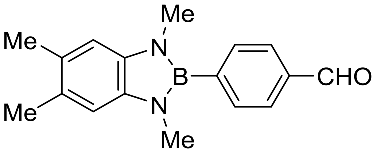
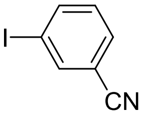
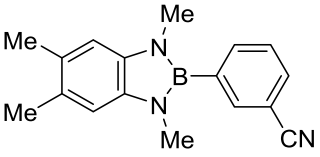


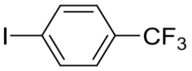
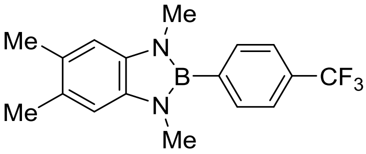
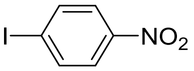
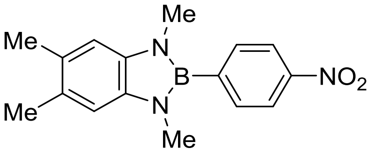
entry	catalyst	solvent	yield (%)[b]	
			5b	**4b**
1	PdCl$_2$(dtbpf)	dioxane	62	20
2	PdCl$_2$(dppf)	dioxane	trace	7
3	PdCl$_2$(PPh$_3$)$_2$	dioxane	trace	7
4	Pd[P(*t*-Bu)$_3$]$_2$	dioxane	74	10
5	Pd[P(*t*-Bu)$_3$]$_2$	toluene	77	9
6	Pd[P(*t*-Bu)$_3$]$_2$	DMF	56	13

[a] The borylation of **2b** (0.250 mmol) with **1** (0.375 mmol) was carried out with Et$_3$N (0.75 mmol) and a catalyst (5 mol%) in a solvent (1 mL) at 80 °C for 3 h. Pinacol (0.3 mmol) and HCl aq. were added to the mixture and the reaction was continued for 15 h at rt. [b] GC yields are based on **2b**.

The results obtained with various aryl iodides **2**, giving the borylated products **3**, are listed in Table 3.[13] Yields reported in this table refer to isolated yields of **3**. The first part of Table 3 involves the application of PdCl$_2$(dtbpf)-catalyzed borylation to electron-rich aryl iodides (entries 1, 3 and 4). In the second portion, the reaction conditions using Pd[P(*t*-Bu)$_3$]$_2$ were applied to the borylation of electron-neutral (entry 2) and -deficient aryl iodides (entries 6–11). These present methods were extremely tolerant of a variety of common functional groups, such as OH (entry 2), NH_2 (entry 3), CO_2Et (entry 5), COMe (entry 6), CHO (entry 7), CN (entry 8), and NO_2 (entry 10) groups. It is noteworthy that aryl iodides **2** containing hydroxy or formyl groups were efficiently borylated without protection.[5]

Table 3. Borylation of representative aryl iodides **2** with **1**

entry	aryl iodide **2**	product **3**	conditions^{a}	yield (%)^{b}
1	 (**2a**)	 (**3a**)	A	80
2	 (**2c**)	 (**3c**)	A	84
3	 (**2d**)	 (**3d**)	A	85
4	 (**2e**	 (**3e**)	B	79
5	 (**2b**)	 (**3b**)	B	69
6	 (**2f**)	 (**3f**)	B	79
7	 (**2g**)	 (**3g**)	B^{c}	84
8	 (**2h**)	 (**3h**)	B	72

9	 (**2i**)	 (**3i**)	B	83
10	 (**2j**)	 (**3j**)	B	72

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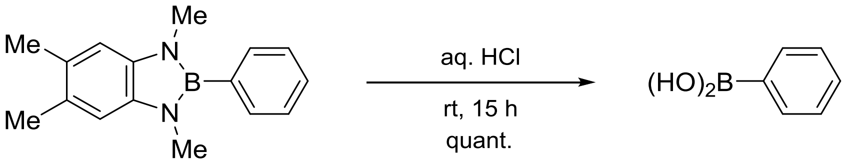
[a] Condition A: **2** (0.250 mmol), **1** (0.375 mmol), Et_3N (0.75 mmol), $PdCl_2(dtbpf)$ (3 mol%), dioxane (1 mL) at 80 °C for 6 h. Condition B: **2** (0.250 mmol), **1** (0.375 mmol), Et_3N (0.75 mmol), $Pd[P(t\text{-}Bu)_3]_2$ (3 mol%), toluene (1 mL) at 80 °C for 3 h. [b] Isolated yields are based on **2**. [c] At 80 °C for 1 h.

As shown in Tables 1 and 2, the borylated products **3** can be transformed into the corresponding arylboronates. Then, in order to expand this method to other boron compounds, we explored the conversion of **3** into arylboronic acids (Scheme 2). The deprotection of the diamine moiety of **3** was achieved by the use of aq. HCl at room temperature, in which the corresponding boronic acid was obtained in quantitative yield.[10] Since deprotection of arylboronates requires somewhat harsh conditions,[14] it is meaningful that the diamines were much easier to remove than the diols.



3e

Scheme 2. Deprotection of **3e** to phenylboronic acid

In summary, we have developed a general protocol for the palladium-catalyzed borylation of aryl iodides **2** with 1,3,5,6-tetramethyl-2,3-dihydro-1*H*-benzo[*d*][1,3,2]diazaborole (**1**). The use of two different catalysts for electron-rich and electron-deficient halides, respectively, is important for achieving good product selectivities. For electron-rich substrates, $PdCl_2(dtbpf)$ gave the best results, whereas for electron-deficient substrates, $Pd[P(t\text{-}Bu)_3]_2$ was preferred. These reaction conditions displayed a broad scope and excellent functional group compatibility. In addition, we have shown that the conversion of the borylated products **3** to the corresponding boronic acids or their esters occurred under acidic conditions. Further studies are currently underway to expand the scope of this transformation.

ACKNOWLEDGEMENTS

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9. For the $PdCl_2$(dtbpf)-catalyzed cross-coupling reactions, see: (a) B. H. Lipshutz and B. R. Taft, *Org. Lett.*, 2008, **10**, 1329; (b) G. A. Grasa and T. J. Colacot, Org. Lett., 2007, **9**, 5489.
10. 2-Aryl-1,3-dimethyl-2,3-dihydro-1*H*-naphtho[1,8-*de*][1,3,2]diazaborinines are inactive to Suzuki–Miyaura cross-coupling reaction. Furthermore, 1,8-diaminonaphthalene is quantitatively removable by treatment with aqueous acids. See: (a) H. Noguchi, K. Hojo, and M. Suginome, *J. Am. Chem. Soc.*, 2007, **129**, 758; (b) H. Noguchi, T. Shioda, C.-M. Chou, and M. Suginome, *Org. Lett.*, 2008, **10**, 377.
11. Although still preliminary, the borylation of aryl bromides was much slower and gave a lower yield and selectivity. The treatment of ethyl 4-bromobenzoate with **1** (1.5 equiv) and Et_3N (3 equiv) with 5 mol% of $PdCl_2$(dtbpf) in dioxane at 100 °C for 8 h was found to lead to **3b** (37% yield) and **4b** (45% yield).
12. For the $Pd[P(t\text{-}Bu)_3]_2$-catalyzed silylation of aryl iodides, see: (a) Y. Yamanoi, T. Taira, J. I. Sato, I. Nakamula, and H. Nishihara, *Org. Lett.*, 2007, **9**, 4543; (b) Y. Yamanoi, *J. Org. Chem.*, 2005, **70**, 9607.
13. The general procedure is as follows. In a glove box, **1** (0.375 mmol), **2** (0.25 mmol), and Pd catalyst (7.5 µmol), and Et_3N (0.75 mmol) were placed in a screw-capped vial containing a stir bar, and dissolved in 1.0 mL of solvent. The vial was sealed with a cap equipped and removed from the glove

box. The reaction mixture was then stirred at 80 °C for 3–6 h. The resulting mixture was allowed to cool to room temperature, diluted with toluene, washed with brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give the desired product **3**.

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