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An efficient synthesis of sterically hindered arylboronic acids

Hao Fang,[a,b] Gurpreet Kaur,[b] Jun Yan[b] and Binghe Wang[b,*]

[a]*School of Pharmacy, Shandong University, No. 44 Wenhuaxi Road, Jinan 250012, China*
[b]*Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, 33 Gilmer St. S.E., Atlanta, GA 30303, USA*

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Abstract—Boronic acids are important intermediates and molecular recognition moieties in a wide variety of applications. In our research, we have found that the synthesis of *ortho*-substituted arylboronic acids is problematic with the commonly used bis(pinacolato)diboron in palladium-mediated borylation reactions. As a substitute, we have found that bis(neopentyl glycolato)diboron is a much more efficient borylation agent for the synthesis of sterically hindered *ortho*-substituted arylboronic acids.

Boronic acids are important intermediates in organic synthesis and are useful for the development of biologically active agents.[1] For example, boronic acids have been widely used in Suzuki cross-coupling reactions,[2] protection of diols,[3] Diels–Alder reaction,[4] selective reduction of aldehydes,[5] asymmetric synthesis of amino acids,[6] and as amidation catalysts.[7,8] In addition, boronic acids have been used in biological applications[1] as sensors for carbohydrates,[9,10] artificial lectins (boronolectins) targeting cell surface carbohydrates,[11,12] selective transporters of nucleosides, saccharides and nucleotides,[13,14] enzyme inhibitors,[1,15] and therapeutic agents in boron neutron capture therapy (BNCT) of certain brain tumors.[16]

Generally, two methods are used to synthesize arylboronic acid or ester compounds. One is the transmetalation between an arylmetal and a boron halide or alkoxide;[17] the other is the recently developed $PdCl_2$(dppf)-catalyzed borylation of aryl halides,[18] triflates,[19,20] and diazonium[21,22] with a tetra(alkoxy)diboron[18,19,21] or dialkoxyborane reagent.[20,23] The palladium-catalyzed method can be used for the borylation of substrates that contain functional groups such as cyano, nitro, amino, hydroxyl, ester, and carbonyl groups, which may not be compatible with organometallic agents such as *n*-butyllithium. Currently, bis(pinacolato)diboron is the most widely used agent in palladium mediated borylation reactions due to its commercial availability and good stability in the presence of water and during chromatography.[24]

In our on-going research in the design and synthesis of new fluorescent boronic acids,[11,25,26] we were in need of *ortho*-substituted arylboronic acids. In the synthesis of such boronic acids, we encountered many problems when bis(pinacolato)diboron was used as the borylation agent. For example, complicated reaction mixtures were obtained in the preparation of *ortho*-methoxy-substituted phenylboronic acid, which led to low yields (about 20%).[26] Similar results have also been reported in the literature,[18] although a few exceptions were reported when aryltriflates were used instead of arylhalides.[19] Baudoin et al. utilized pinacolborane $(Me_4C_2O_2)BH$ to synthesize phenylpinacol boronic esters from *ortho*-substituted aryl bromides and found the best catalyst being $Pd(OAc)_2$ in the presence of 2-(dicyclohexyl phosphino)biphenyl which is a sterically hindered phosphine ligand,[23] although the yields were still poor when functional groups such as nitro (20%), acetyl (0%), and Boc protected amino group (40%) were present. Later Miyaura's group reported that $Pd(dba)_2/PCy_3$ could be used to carry out borylation of some *ortho*-substituted chloroarenes (nitro and methoxy) by using bis(pinacolato)diboron (70% yield based on GC after 48 h of reaction).[27] Most recently, a new *N*-heterocyclic carbene–palladium catalyst was used to borylate *ortho*-methoxy substituted aryldiazonium with good yields using bis(pinacolato)diboron.[22]

Keywords: Palladium-catalyzed borylation; Bis(neopentyl glycolato)diboron; *ortho*-Arylboronic acids.

[*] Corresponding author. Tel.: +1 404 651 0289; fax: +1 404 654 5827; e-mail: wang@gsu.edu

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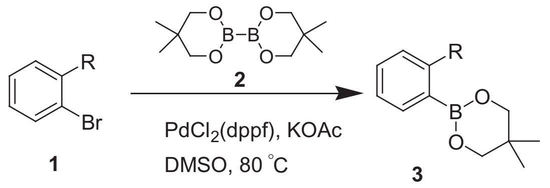
So far, research in this area has been focused on examining the effect of different leaving groups or designing or experimenting new palladium catalysts. We envisioned that some of the problems might be overcome by manipulating the steric bulkiness of the borylation agent. In our very first example, we examined the borylation of 2-methoxy-5-nitrophenylbromide using the new commercially available bis(neopentyl glycolato)diboron **2** in the presence of $PdCl_2$ (dppf) and observed much improved yield compared with the reaction using bis(pinacolato)diboron as the borylation agent (72% vs 20%) under similar conditions (Scheme 1). Such results suggested that the steric bulkiness of the tetra(alkoxy)diboron agent may play an important role in the borylation of other *ortho*-substituent arylhalide (bromide in this case) and a less hindered bis(neopentyl glycolato)diboron might be used to overcome the side reaction problems associated with the use of sterically bulky bis(pinacolato)diboron.

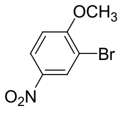
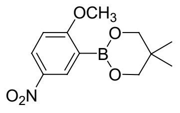
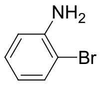
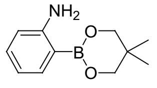
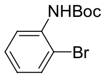
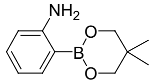
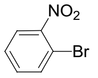
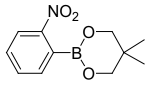
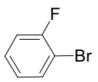
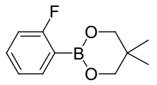
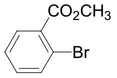
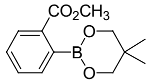
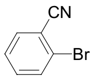
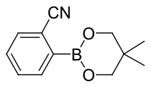
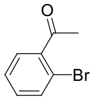
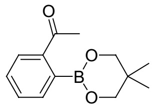
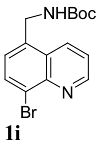
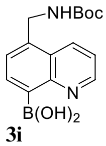
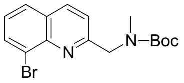
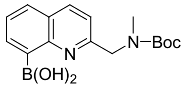
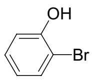
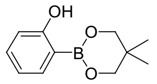
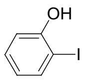
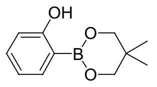
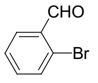
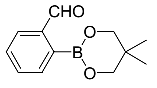
In order to understand the scope of the effect of the steric bulkiness of the borylation agent, we were interested in examining the borylation of a series *ortho*-substituted arylhalides. As a first step, we optimized the reaction conditions with respect to the solvent and base used. As expected and has been observed with reactions using the bis(pinacolato)diboron borylation agent, DMSO was the best solvent and KOAc was the best base. Toluene and dioxane exhibited low reaction rate with more debromo product. The reaction did not work when using triethylamine as base.

The borylation of 12 additional arylhalides were studied using this method (entries 2–13, Table 1). In most cases, the reaction was completed within 4 h. Good (65%) to excellent (90%) yields were obtained in most cases except with 8-quinoline analog (entry 9, 35%), 2-bromophenol (entry 11, 5%), and 2-bromobenzaldehyde (entry 13, 7%). Unexpectedly, borylation of Boc protected 2-bromoaniline (entry 3) gave the deprotected aniline neopentyl glycolato boronate. The mechanism through which the Boc group was cleaved is unclear. Comparing with literature and our own research results, the yields were much better than the reactions using bis(pinacolato)diboron or pinacolborane as the borylating agent. For example, *ortho*-bromonitrobenzene (entry 4) and 2-bromomethylphenylketone (entry 8) gave yields in the range of 0–20% when pinacolborane was used as the borylating agent.[23] Even when the corresponding iodoarene was used for the nitrobenzene analog, the yield was still low (44%).[23] In contrast, the corresponding reactions using bis(neopentyl glycolato)diboron as the borylation



Scheme 1.

Table 1. Reaction of representative **1** with **2**

Entry	**1**	Product **3**	Time (h)	**3** (%)[a]
1	 **1a**	 **3a**	2	72
2	 **1b**	 **3b**	2	69
3	 **1c**	 **3b**	4	65
4	 **1d**	 **3d**	3	68
5	 **1e**	 **3e**	4	(90)
6	 **1f**	 **3f**	4	80
7	 **1g**	 **3g**	6	73
8	 **1h**	 **3h**	3	70
9	 **1i**	 **3i**	12	35
10	 **1j**	 **3j**	12	85
11	 **1k**	 **3k**	12	5
12	 **1l**	 **3k**	8	70
13	 **1m**	 **3m**	12	7

[a] Isolated yield after flash chromatography. Yields in parentheses are GC yields.