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## An efficient synthesis of sterically hindered arylboronic acids

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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. © 2005 Elsevier Ltd. All rights reserved.

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

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;<sup>17</sup> the other is the recently developed PdCl<sub>2</sub>(dppf)-catalyzed borylation of aryl halides,<sup>18</sup> triflates,<sup>19,20</sup> and diazonium<sup>21,22</sup> with a tetra(alkoxy)diboron<sup>18,19,21</sup> or dialkoxyborane reagent.<sup>20,23</sup> 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(pina-

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colato)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.<sup>24</sup>

In our on-going research in the design and synthesis of new fluorescent boronic acids,<sup>11,25,26</sup> 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%).<sup>26</sup> Similar results have also been reported in the literature,<sup>18</sup> although a few exceptions were reported when aryltriflates were used instead of arylhalides.<sup>19</sup> 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,<sup>23</sup> 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)<sub>2</sub>/PCy<sub>3</sub> 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).<sup>27</sup> Most recently, a new N-heterocyclic carbenepalladium catalyst was used to borylate *ortho*-methoxy substituted aryldiazonium with good yields using bis(pinacolato)diboron.<sup>22</sup>

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

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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, orthobromonitrobenzene (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%).<sup>23</sup> In contrast, the corresponding reactions using bis(neopentyl glycolato)diboron as the borylation



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Entry	1	Product 3	Time (h)	<b>3</b> (%) <sup>a</sup>
1	OCH <sub>3</sub> Br	OCH3 O2N	2	72
2	la NH <sub>2</sub> Br		2	69
3	1b NHBoc Br	3b Ab = B = B = B = B = B = B = B = B = B =	4	65
4	NO <sub>2</sub> Br	$\langle $ $B_{0}^{NO_{2}} $ $B_{0}^{NO_{2}} $	3	68
5	F Br 1e		4	(90)
6	CO <sub>2</sub> CH <sub>3</sub> Br	3f	4	80
7	CN Br		6	73
8	o Br Ih		3	70
9	NHBoc Br 1i	NHBoc NHBoc B(OH) <sub>2</sub> 3i	12	35
10	Br N-Boc	B(OH) <sub>2</sub>	12	85
11	OH Br Ik		12	5
12			8	70
13	CHO Br Im		12	7

<sup>a</sup> Isolated yield after flash chromatography. Yields in parentheses are GC yields.

agent gave over 68% isolated yields for both nitro (entry 4) and acetyl substituent (entry 8).

On a somewhat different note, where steric hindrance may not necessarily be a factor, the borylation of quinoline bromide also benefited from using bis(neopentyl glycolato)diboron instead of bis(pinacolato)diboron as the borylation agent. For example, in the borylation of 8-bromoquinoline derivatives (entries 9 and 10), Suzuki coupling product was the major product when bis(pinacolato)diboron was used as a borylation agent in the presence of KOAc.<sup>28</sup> However, when bis(neopentyl glycolato)diboron was used, Suzuki coupling product was not formed in the reaction mixture and the corresponding 8-quinoline boronic acid was easily obtained.

It does need to be noted that entry 13 (with a formyl substituent) gave less than 10% yield of the desired product with the formation of 20% Suzuki coupling product and the recovery of 50% of the starting material. In addition, entry 11 (hydroxyl group) gave only 5% yield of the desired product with over 85% of the starting material recovered, while the corresponding iodide (entry 12) gave a good yield (70%). It is not clear why the hydroxyl group (entry 11) and the formyl group (entry 13) presented special problems. In an effort to improve the yields for entries 11 and 13, we also examined whether different catalysts would be able to facilitate these two reactions. Previous work by Baudoin and co-workers<sup>23</sup> and Miyaura and co-workers<sup>27</sup> indicates that a more reactive palladium catalyst may be able to improve yield of entry 11. Several air stable and more active palladium catalysts, such as [(t-Bu)<sub>2</sub>P(OH)]<sub>2</sub>-PdCl<sub>2</sub>(POPd),  $\{[(t-Bu)_2P(OH)][(t-Bu)_2P(O^{-})]PdCl\}_2$ (POPd1), and [(t-Bu)<sub>2</sub>P(OH)PdCl<sub>2</sub>]<sub>2</sub> (POPd2), have been employed for cross-coupling reactions of aryl chloride,<sup>29-32</sup> and also for borylation of 5-bromofluorescein diacetate.33 Therefore, the new active palladium catalyst, POPd, was examined in the borylation of 2-bromophenol and 2-bromobenzaldehvde.

Different palladium catalysts and solvents were examined in order to search for a condition that would give a reasonable borylation yield from 2-bromophenol (Table 2). The results showed that the POPd facilitates the borylation reaction and works better than  $Pd(PPh_3)_4$ and PdCl<sub>2</sub> (dppf) in DMSO (entries 1–3). When the temperature was raised to 120 °C, 40% of the desired borylation product was obtained, with the remaining portion being the unreacted starting material (entry 4). When the solvent was changed to toluene and dioxane, the debromo product (4) was the main product (entries 6 and 7). Therefore, it seems that for the borylation of 2-bromophenol using POPd in DMSO at 120 °C gives the best yield. When applying the same conditions to the borylation of 2-bromobenzaldehyde, the starting material completely disappeared with the formation of 35% (isolated yield) of the desired borylation product and the remaining being the Suzuki coupling product.

In conclusion, palladium catalyzed borylation of arylbromide is a very convenient way for the preparation of arylboronic acids. However commonly used borylation  
 Table 2. Different palladium catalysts in the borylation of 2-bromophenol and 2-bromobenzaldehyde

X Br 1 k X = m X =	Catalyst, KOAc	S k	X = -OH X = -OH	<b>4 k</b> X = -OH <b>m</b> X = -CHO
Entry	Catalyst (mol%)	Solvent	Heating method (temp °C, time)	Product ratio 1k:3k:4k <sup>a</sup>
1	$Pd(PPh_3)_4$ (6)	DMSO	100, 12 h	100:0:0
2	PdCl <sub>2</sub> (dppf) (6)	DMSO	100, 12 h	93:7:0
3	POPd (3)	DMSO	80, 12 h	78:22:0
4	POPd (3)	DMSO	120, 12 h	60:40:0
5	POPd (3)	DMF	80, 12 h	74:27:0
6	POPd (3)	Toluene	80, 12 h	0:27:73 <sup>b</sup>
7	POPd (3)	Dioxane	80, 12 h	0:10:80 <sup>b</sup>

<sup>a</sup> Determined by GC–MS.

<sup>b</sup> Determined by <sup>1</sup>H NMR.

reagent, bis(pinacolato)diboron, gives low yields and side reactions for *ortho*-substituted bromoarenes, possibly due to the steric hindrance of the *ortho* substituent. This problem can be overcome by using a less hindered borylation agent, bis(neopentyl glycolato)diboron, in most of the cases. With the two cases (*ortho* substituent being a hydroxyl or a formyl group) that give low yields of the borylation product, the problem can be addressed by using a new and more active palladium catalyst, such as POPd.

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## Supplementary data

The supplementary data, including general experimental procedures and NMR data, is available online with the paper in ScienceDirect. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.064.

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