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*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b02771 • Publication Date (Web): 09 Jan 2018

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## Bedford-type palladacycle catalyzed Miyaura-borylation of aryl halides with tetrahydroxydiboron in water

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Arwa A. Makki<sup>†</sup>, Nagaiyan Sekar<sup>‡</sup> and Jörg Eppinger<sup>†\*</sup>

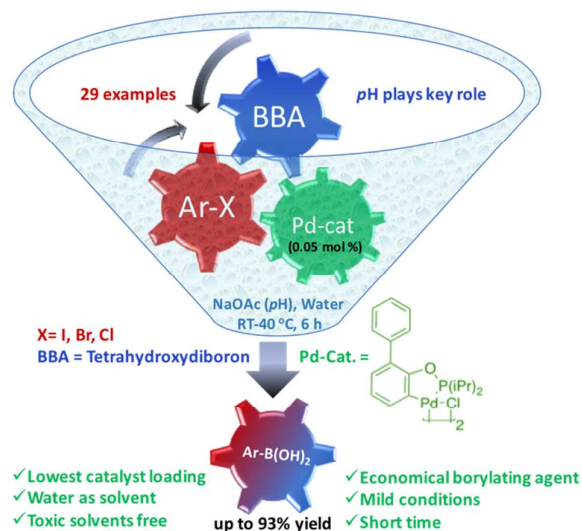
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### Abstract:

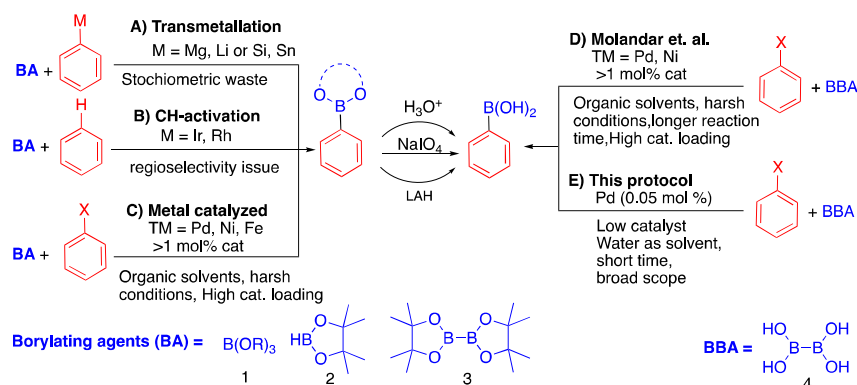


A mild aqueous protocol for palladium catalyzed Miyaura borylation of aryl iodides, aryl bromides and aryl chlorides with tetrahydroxydiboron (BBA) as a borylating agent is developed. The developed methodology requires low catalyst loading of Bedford-type palladacycle catalyst (0.05 mol %) and works best under mild reaction conditions at 40 °C in short time of 6 hours in water. In addition, our studies show that for Miyaura borylation using BBA in aqueous condition, maintaining a neutral reaction pH is very important for reproducibility and higher yields of corresponding borylated products. Moreover, our protocol is applicable for a broad range of aryl halides, corresponding borylated products are obtained in excellent yields up to 93% with 29 examples demonstrating its broad utility and functional group tolerance.

**Keywords:** Miyaura-borylation, Palladacycle, Tetrahydroxydiboron, Arylboronic acids

## Introduction

Arylboronic acids provide a unique combination of stability, mild Lewis acidity, low toxicity and distinct reactivity profile, therefore a tremendous interest in synthesis and applications of arylboronic acids, and their corresponding intermediates exists.<sup>1</sup> Notably arylboronic acids and their corresponding esters and trifluoroborates are widely explored as a substrate for numerous organic transformations. In last decade arylboronic acids are well explored for various cross-coupling reactions, such as Suzuki-Miyaura coupling, the Hosomi-Sakurai allylation<sup>2</sup> and the oxidative Chan-Lam coupling.<sup>3</sup> Moreover, other applications includes 1,4-additions<sup>4</sup> and 1,2-additions<sup>5</sup> of boronic acids to Michael acceptors and aldehydes, e.g. the Petasis borono-Mannich reaction<sup>6</sup>. Particularly in bioorganic and medicinal chemistry, arylboronic acids serve as valuable tool for a broad range of applications including sensors molecules,<sup>7</sup> enzyme inhibitors or in vivo alteration of cellular functions.<sup>8</sup> Recently many catalytic protocols for amide or peptide synthesis have been reported using various arylboronic acid derivatives as catalysts.<sup>9</sup> Therefore due to their wide applications in synthetic chemistry, as well as in biology, there are numerous methods reported for the synthesis of arylboronic acids (Scheme 1).



**Scheme 1.** Metal based borylation protocols

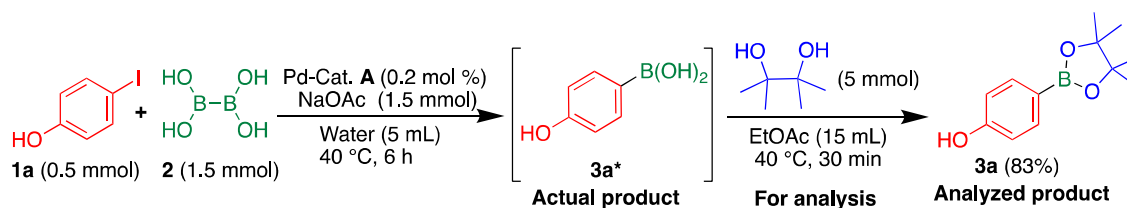
Traditionally arylboronic acids were prepared by a metal-halogen exchange approach using stoichiometric amount of organolithium<sup>10</sup> or Grignard-reagents<sup>11</sup>, but offers only limited tolerance to functional groups and also generates stoichiometric amount of toxic waste

(Scheme 1, **A**). To address these issues several research groups, including those of Smith,<sup>12</sup> Hartwig,<sup>13</sup> Miyaura<sup>14</sup> and Marder<sup>15</sup> have recently reported efficient catalytic borylation protocols by C-H activation of aromatic compounds using iridium or rhodium catalysts, but regioselectivity is determined by steric and electronic factors, which represents a major drawback (Scheme 1, **B**). Currently, transition-metal-catalyzed Miyaura borylation of aryl halides therefore provide the most versatile access to arylboronic acids,<sup>16</sup> as it combines high functional group tolerance and selectivity. Yet, most of these reported catalytic borylation methods typically require the use of expensive pinacolato-boron precursors. In addition, reaction of pinacolato-boron with aryl halide gives arylboronic ester as a product instead of arylboronic acid, necessitating an additional deprotection step which ultimately generates additional stoichiometric amount of waste (Scheme 1, **C**). In this regard Molander *et al.* reported a palladium-catalyzed borylation protocol, which employed economical and greener bis-boronic acid (BBA) also known as tetrahydroxydiboron as a boron source in ethanol as a solvent. The resulting diethyl boronic esters converted in situ into the more stable trifluoroborates or even directly applied in cross-coupling reactions (Scheme 1, **D**).<sup>17</sup> This represents a major step towards more atom economic and sustainable synthesis of organo-boronic acids. Thereafter many other transition metals based catalytic protocols were reported for borylation of aryl halides.<sup>18</sup> Recently nice progress has been made in photoinduced borylation<sup>18b,19</sup>, as well as organo-catalytic borylation<sup>18b,20</sup> protocols. However overall most of the reported borylation protocols requires use of toxic and environmental hazardous organic solvents, high catalyst loading, higher temperature (reflux or >80 °C) and longer reaction time, which limits its wide applications. Nevertheless, it would be more economically and industrially appealing to develop a water based, greener borylation protocol for direct synthesis of aryl boronic acids using tetrahydroxydiboron (BBA) with lowest possible catalyst loading, in shorter time, under mild reaction conditions.<sup>21</sup> Particularly compared to toxic organic solvents, water is safe to handle, greener, economically and

environmentally friendly solvent. Therefore, in the last decade there is growing interest for water based cross-coupling reactions and many water based catalytic protocols have been reported particularly with major contributions by Beller,<sup>22</sup> Plenio,<sup>23</sup> Shaughnessy,<sup>24</sup> Leadbeater<sup>25</sup> and Lipshutz.<sup>26</sup> However the water based protocol under mild reaction conditions for a Miyaura-borylation is rarely explored. In this regard, we believe that Bedford-type catalysts has good potential for developing aqueous protocols with low catalyst loading.<sup>27</sup> Recently, we reported a new Bedford-type palladacycle as effective catalyst for aqueous Sonogashira and Suzuki cross-coupling reactions.<sup>28a, 28b</sup> Therefore in continuation with our interest for development of aqueous catalytic protocols,<sup>28</sup> herein we report application of our developed Bedford-type palladacycle catalyst (Table 1, Cat. A) for Miyaura-borylation of aryl halides with tetrahydroxydiboron (BBA) in water, notably reactions proceed under mild reaction conditions, in short time with lowest catalyst loading (0.05 mol %) (Scheme 1, E).

## Result and Discussion

We started our initial optimization study with borylation of 4-iodophenol (**1a**) with tetrahydroxydiboron (**2**) in presence of 0.2 mol % of Bedford-type palladacycle catalyst (Cat. A) and sodium acetate as base in water at 40 °C (Scheme 2) under argon atmosphere. To our surprise almost 83% yield of borylated product **3a** was obtained in 6 hours (Table 1, entry 1).

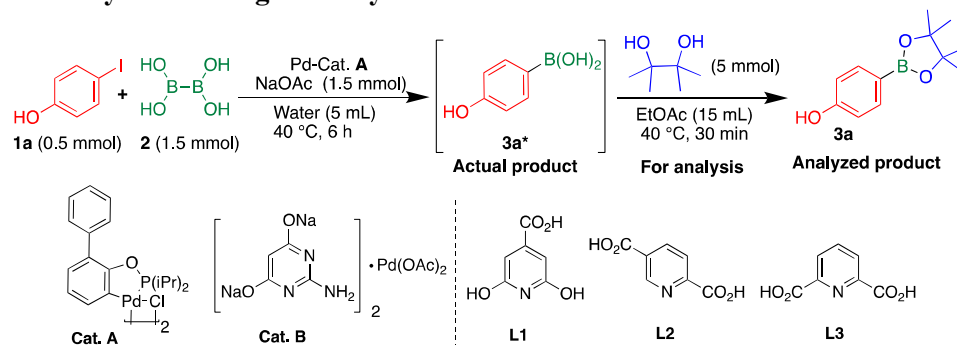


**Scheme 2. Test experiment for borylation using Bedford-type palladacycle Catalyst A**

It should be noted that the direct quantification of borylated product (4-hydroxyphenyl)boronic acid (Scheme 2, **3a\***) from aqueous phase is difficult and suffers from

low reproducibility. Therefore, the product **3a\*** was subsequently converted into the respective pinacol ester 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (Scheme 2, **3a**) and then GC yield of **3a** was measured. This conversion of **3a\*** into **3a** tremendously reduced the fluctuations of GC yields therefore same procedure is followed throughout our studies. Next test reaction was performed in air atmosphere and result in a significant drop in yields of **3a** to around 20 % (Table 1, entry 2). Therefore, for next studies all the reactions were performed under argon atmosphere and with degassed water. Subsequently effect of addition pattern and pre-stirring were checked and it's noteworthy to mention that there is no effect of addition pattern or pre-stirring observed. Near quantitative yields of borylated product **3a** were obtained in all cases up to 83% yield. Encouraged by our initial test experiments, we investigated the influence of catalyst loading of Catalyst A on borylation (Table 1, entries 1-5) and it was observed that 0.05 mol % of Catalyst A is sufficient to get 96% yield of **3a** (Table 1, entry 4).

**Table 1. Catalyst screening for borylation<sup>a</sup>**



entry	catalyst (mol %)	yield (%) <sup>b</sup>
1	Cat. A (0.20)	83, (5) <sup>c</sup>
2	Cat. A (0.20)	20 <sup>d</sup>
3	Cat. A (0.10)	99, (1) <sup>c</sup>
4	Cat. A (0.05)	96
5	Cat. A (0.01)	67
6	Cat. B (0.10)	0
7	Na <sub>2</sub> PdCl <sub>4</sub> (0.10)	0
8	K <sub>2</sub> PdCl <sub>4</sub> (0.10)	0
9	Pd(NO <sub>3</sub> ) <sub>2</sub> (0.10)	0
10	Pd(OAc) <sub>2</sub> (0.10)	0
11	PdCl <sub>2</sub> (0.10) / L1 (0.10)	0

12	PdCl <sub>2</sub> (0.10) / <b>L2</b> (0.10)	0
13	PdCl <sub>2</sub> (0.10) / <b>L3</b> (0.10)	0
14	Pd(OAc) <sub>2</sub> (0.10) / XPhos (0.30)	0

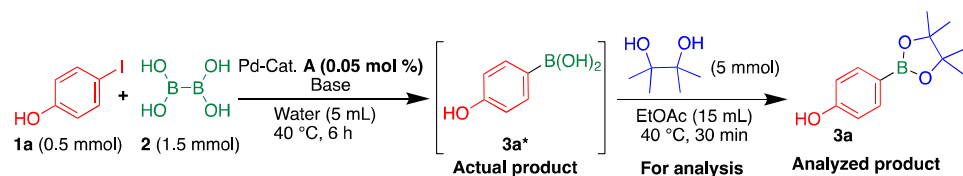
<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), Pd-catalyst, NaOAc (1.5 mmol), degassed water (5 mL), 40 °C, 6 h under argon atmosphere. <sup>b</sup>GC yield of **3a**. <sup>c</sup>Dehalogenated product (phenol). <sup>d</sup>Under air atmosphere.

Next to select the best catalyst for borylation, we screened various other palladium catalysts (Table 1, entries 6-14), including Davis' catalyst **B**<sup>8h</sup> and surprisingly, only catalyst **A** found to be the best catalyst under aqueous conditions.

Thereafter we studied the effect of base because it is a known fact that for organic solvent based borylation protocols, the nature of the added base strongly influences yields of the corresponding borylated products (**3**).<sup>16a</sup> Therefore, we investigated the influence of base type, concentration and structure of bases on the yield of borylated product **3a** in the aqueous medium (Table 2). We checked the effect of base stoichiometry using sodium acetate (NaOAc) as base (Table 2, entries 1 to 6). Notably in the absence of base only trace amount of product **3a** was observed, while further addition of excess of BBA without any base improved the yield up to 60% but requires longer time 48 hours (Table 2 entry 1). However, it was observed that 3 equivalence of sodium acetate is sufficient for achieving higher yield of **3a** up to 99% in 6 hours confirms the importance of base for borylation in water (Table 2, entry 4). Interestingly the addition of 2 to 4 equivalence of sodium acetate results in near quantitative yields of **3a** (Table 2, entries 3-5), while further decrease or increase in base concentrations only lead to incomplete conversions (Table 2, entries 2 and 6). After knowing the strong influence of base concentration on borylation secondly, to investigate the effect of structure of bases we screened various bases such as carbonates, hydroxides, phosphate, amine, borax etc (Table 2, entries 7 to 20). From overall base screening, we conclude that the nature of base as well as concentration of the base mainly influences the reaction pH and the reaction pH mainly determines the yield of borylation product **3a** (Table 2). From the overall base study, it was observed that high yields of product **3a** were mainly achieved for reactions performed in

a narrow pH window of 6.7 to 7.7 except few exceptions (Table 2). Interestingly, in a pH study we observed that addition of the Lewis acid  $\text{ScCl}_3$  generated high yields of **3a** even at an acidic pH of 5.3 (table 2, entry 8). However, with addition of  $\text{Zn}(\text{OAc})_2$  alone, without any base, the pH of reaction becomes 5.6 but did not result in a detectable **3a** formation (table 2, entry 9). Therefore, we further investigated the influence of different additives on the yield of **3a** (Table 3). For more details on effect of base and pH please see the supporting information.

**Table 2. Influence of base and pH on borylation yields<sup>a</sup>**



entry	base (mmol)	pH <sup>b</sup>	yield (%) <sup>c</sup>
1	No base	5.9	4, 14 <sup>d</sup> , 60 <sup>e</sup>
2	NaOAc (0.5)	6.1	42, (2) <sup>f</sup>
3	NaOAc (1)	6.2	97, (3) <sup>f</sup>
4	NaOAc (1.5)	6.7	99
5	NaOAc (2)	6.8	99, (1) <sup>f</sup>
6	NaOAc (2.5)	6.9	45, (2) <sup>f</sup>
7	KOAc (1.5)	6.8	47, (1) <sup>f</sup>
8	NaOAc (1.5) / $\text{ScCl}_3$ (1.5)	5.3	90
9	$\text{Zn}(\text{OAc})_2$ (1.5)	5.6	0
10	NaHCOO (1.5)	6.7	99
11	$\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ (0.5)	7.6	99
12	$\text{Na}_2\text{B}_4\text{O}_7 \cdot 10\text{H}_2\text{O}$ (1.5)	8.4	12
13	$\text{NaH}_2\text{PO}_4$ (1.5)	4.4	63
14	$\text{Na}_2\text{HPO}_4$ (1.5)	8.0	49
15	$\text{Na}_3\text{PO}_4$ (1.5)	9.2	0
16	$\text{Na}_2\text{CO}_3$ (1.5)	9.1	0
17	$\text{Cs}_2\text{CO}_3$ (1.5)	9.4	0, (2) <sup>f</sup>
18	NaOH (1.5)	9.4	0, (1) <sup>f</sup>
19	$\text{NEt}_3$ (1.5)	9.6	0
20	KOtBu (1.5)	9.0	0

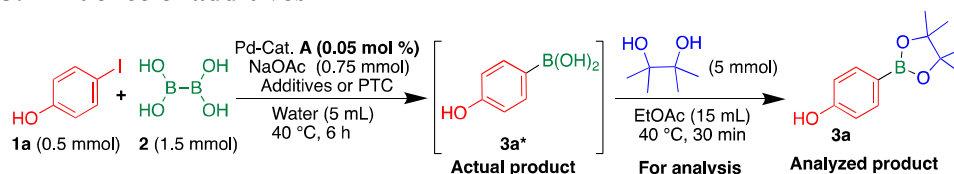
<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), base, Catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h under argon atmosphere. <sup>b</sup>Initial pH of the reaction measured after 10 min at 40 °C in a separate vessel, which was prepared with the exception of catalyst addition. <sup>c</sup>GC yield of **3a**. <sup>d</sup>2<sup>nd</sup> addition of 1.5 mmol of BBA after 24 h; total reaction time 48 h. <sup>e</sup>2<sup>nd</sup> and 3<sup>rd</sup> addition of 1.5 mmol BBA after 24 h and 36 h; total reaction time 48 h. <sup>f</sup>Dehalogenated product (phenol).

The effect alkali halides as additives (1.5 eq.), along with base sodium acetate (1.5 eq.) were checked, which leads to moderately improved yields of **3a** (Table 3, entries 2-8)



compare with 1.5 equivalence of sodium acetate alone (Table 3, entry 1). Various phase transfer catalysts were checked along with sodium acetate (1.5 eq.) (Table 3, entries 9-11). It was observed that the addition of phase transfer agents like PEG-2000,  $\alpha$ -cyclodextrin or cetyltrimethylammonium chloride (CTMA) has actually a negative effect on borylation of **1a** and results in lower yield of **3a** (Table 3, entries 9-11). Therefore, based on our optimization studies about effect of base, influence of reaction pH (Table 2) and effect of additives (Table 3) on borylation of **1a**, best results were obtained with the use of 3 equivalence of sodium acetate (pH 6.7) without using any additives (Table 2, entry 4)

**Table 3. Influence of additives<sup>a</sup>**



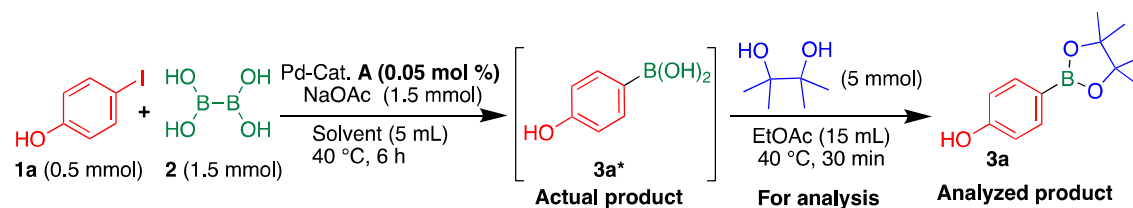
entry	additive (mmol)	yield (%) <sup>b</sup>
1	----	50
2	KCl (0.75)	53, (1) <sup>c</sup>
3	NaCl (0.75)	68, (2) <sup>c</sup>
4	NaBr (0.75)	64, (1) <sup>c</sup>
5	KBr (0.75)	82, (1) <sup>c</sup>
6	LiBr (0.75)	80, (2) <sup>c</sup>
7	NaI (0.75)	80, (1) <sup>c</sup>
8	NaF (0.75)	57, (5) <sup>c</sup>
9	PEG-2000 (0.05)	33
10	$\alpha$ -cyclodextrine (0.05)	34
11	CTMA (0.05)	47

<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), NaOAc (0.75 mmol), additives, catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h under argon atmosphere. <sup>b</sup>GC yield of **3a**. <sup>c</sup>Dehalogenated product (phenol).

Next, we checked the effect of different organic solvents with or without water as co-solvent (Table 4, column A and column B). Firstly, it was observed that the addition of organic co-solvent in 1:1 ratio with water, reduces the yield of **3a** dramatically in most cases (Table 4, entry 1 compare with entries 2-9 for column A). Among the eight organic solvents tested as co-solvent with water notably only methanol, THF and dichloromethane (biphasic)

gave good yield of **3a**, however, at the expense of noticeable formation of the dehalogenated phenol as side product (Table 4, column A entries 2, 4 and 5). Secondly it was noticed that in pure solvents catalyst **A** shows only very low (Table 4, column B entry 3) or no catalytic activity (Table 4, column B entries 4-9) except for water and methanol which gives 99% yield of **3a**. A reduced solubility of the base and BBA in organic solvents may be partially responsible for the observed loss in activity for borylation in pure solvents. Moreover, water is nontoxic, economical and greener solvent, therefore it is selected as solvent of choice over methanol for our next studies on borylation of aryl halides (Table 4, entry 1, column B). Our study on solvent screening confirms a crucial role of water in promoting the borylation reaction (Table 4). In addition, effect of water volume was also checked and 5 mL of water found to be sufficient for achieving higher yields of **3a**, while in time study reaction already completes with in 6 hours.

**Table 4. Influence of solvents<sup>a</sup>**

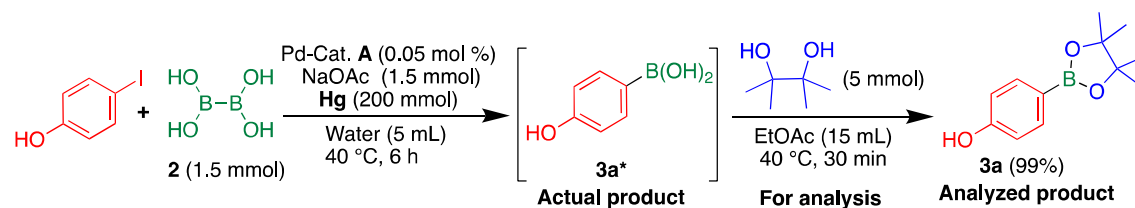


entry	solvent	[A] solvent + water (1:1) yield (%) <sup>b</sup>	[B] only Solvent yield (%) <sup>b</sup>
1	Water	-	99
2	MeOH	91, (9) <sup>c</sup>	99
3	EtOH	52, (18) <sup>c</sup>	18
4	THF	87, (13) <sup>c</sup>	6
5	DCM	86, (14) <sup>c</sup>	0
6	ACN	63, (7) <sup>c</sup>	0, (3) <sup>c</sup>
7	DMSO	31, (1) <sup>c</sup>	0
8	Acetone	15	0
9	EtOAc	0	0

<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2** (1.5 mmol), NaOAc (1.5 mmol), catalyst **A** (0.05 mol %), solvent (5 mL) or 1:1 solvent and water (2.5 + 2.5 mL), 40 °C, 6 h under argon atmosphere. <sup>b</sup>GC yield of **3a**. <sup>c</sup>Dehalogenated product (phenol).

From overall optimization study our final optimized conditions for achieving highest yield for Miyaura borylation under mild reaction conditions are aryl halide (**1**, 0.5 mmol), tetrahydroxydiboron (**2**, 1.5 mmol), catalyst **A** (0.05 mol %), sodium acetate (1.5 mmol) under inert atmosphere and reaction at 40 °C for 6 h.

After this optimization it is important to eliminate any possibility of in-situ formed nano-palladium particles catalyzing the Miyaura borylation. Because the BBA driven Miyuara borylation occurs under reaction conditions, which are moderately reducing and hence may prone for the formation of Pd nanoparticles. However, we did not observed emergence of colour during borylation, which typically is indicative for metallic nanoparticles. Moreover, to answer the question, if in situ formed palladium nanoparticles are the catalytically active species or Bedford-type palladacycle catalyst **A**, a mercury drop test was performed. A mercury drop test is widely used to test exclude possibility of catalysis by nanoparticles because amalgamation with mercury should only deactivate heterogeneous metal particle catalyst, yet is not expected to occur for a ligated homogenous Pd(II) species.<sup>29</sup> Interestingly in our test experiment despite the addition of 400 eq. of mercury to the catalytic reaction 99% yields of **3a** was obtained (Scheme 3). Therefore, the possibility of a nanoparticulated promoted borylation is ruled out and our test experiment (Scheme 3) confirms that palladacycle catalyst **A** is the actual catalyst for the Miyuara borylation reaction under our optimized reaction conditions.



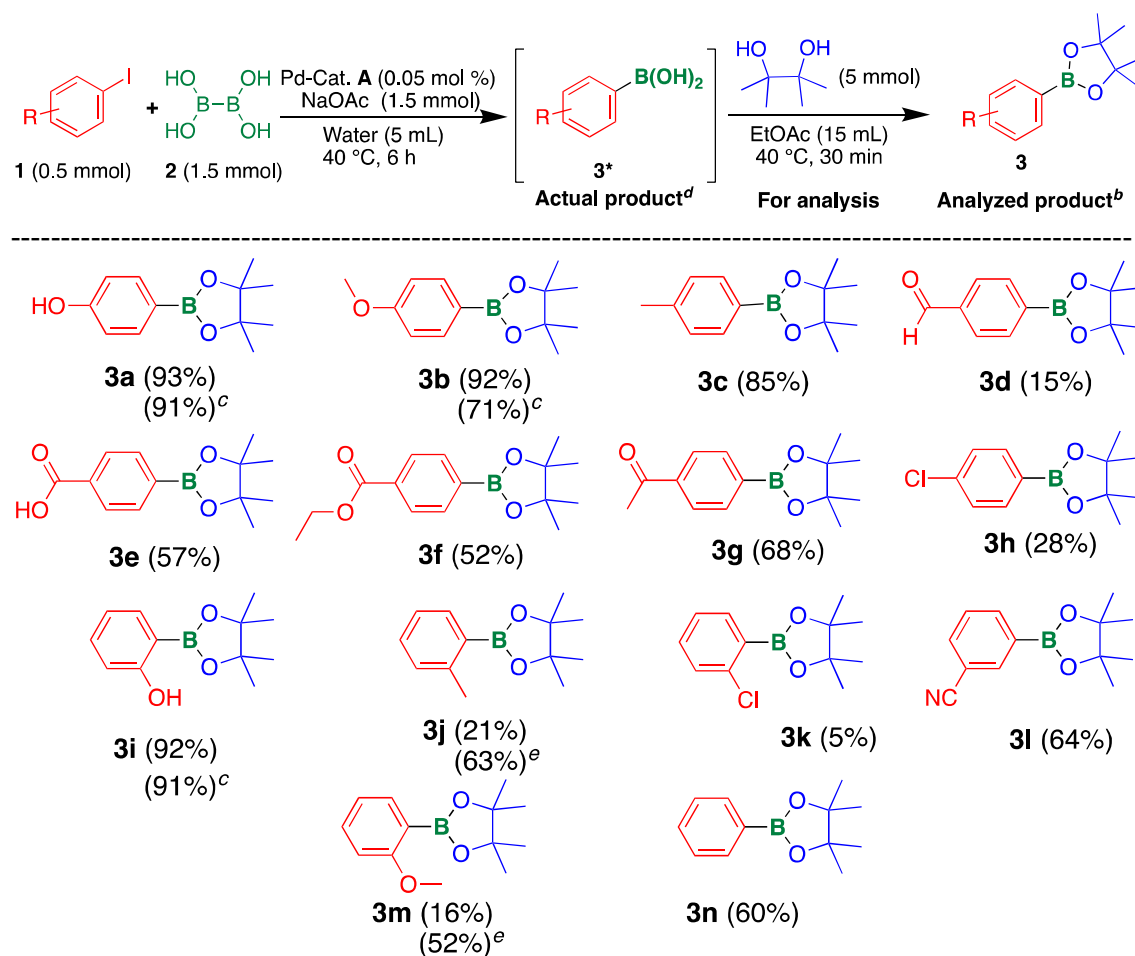
**Scheme 3.** A mercury drop test to confirm role of Pd-catalyst

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3 Finally, under optimized reaction conditions the substrate scope of our Miyuara borylation  
4 protocol to aryl halide substrates is explored to check its wide applicability (Table 5-7).  
5 Firstly, we started our study with borylation of aryl iodides **1a** to **1n** (Table 5) and effect of  
6 various functional groups was checked (Table 5, entries **3a-3h**). Interestingly various *para*  
7 substituted functionalities on iodobenzene such as hydroxy (**1a**), methoxy (**1b**), methyl (**1c**),  
8 aldehyde (**1d**), acid (**1e**), ester (**1f**), acetyl (**1g**), chloro (**1h**) and cyano (**1i**) group are well  
9 tolerated and borylated products **3a** to **3h** and **3i** obtained in good to excellent yield up to  
10 93%. It was observed that aryl iodides with electron donating groups or water-solubilizing  
11 groups are converted smoothly to borylated product **3** with higher yields. However, aryl  
12 iodides with electron-withdrawing groups tend to generate low yields of corresponding  
13 borylated product **3**. Next various *ortho* and *meta* substituted iodobenzene **1i** to **1m** were  
14 screened and product **3i** to **3l** were obtained in good to moderate yields. However, for  
15 iodobenzene derivative **1j** and **1m** only 21% and 16% yield respectively of product **3j** and **3m**  
16 was obtained, which was improved further up to moderate 63% and 52% yield by extending  
17 reaction time up to 24 hours. Moreover, borylation of unsubstituted iodobenzene **1n** give 60%  
18 yield of product **3n** under optimized reaction condition. It was observed that with the  
19 exception of a 2-hydroxy substituent, the steric hindrance, which is introduced by *ortho*-  
20 substituents, strongly reduces the reactivity of the aryl iodides for borylation. In addition,  
21 lower yields in some exceptional cases can attribute to the lower substrate solubility of  
22 corresponding aryl iodides in water. We also tried to explore the substrate scope for  
23 heteroaromatic iodides and electronic withdrawing aryl iodides with substituents such as CF<sub>3</sub>  
24 and NO<sub>2</sub> groups but because of very low solubility of these derivatives in water no product  
25 formation was observed (See SI, Table S2).  
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52 During substrate scope study for aryl iodides it was observed that electron rich aryl iodides  
53 gave more than 90% yield of borylated product **3**. Therefore, with the aim to develop mildest  
54 conditions, we repeated borylation reactions of **1a**, **1b** and **1h** at only 20 °C, interestingly still  
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more than 90% yields of **3a**, **3b** and **3h** was obtained within 6 hours (Table 5, entries for **3a**, **3b** and **3j**). It should be noted that in 2006, Van Aken *et al.*<sup>30</sup> introduced the Eco-scale as a metrics to evaluate green organic synthesis protocols. A respective analysis establishes an Eco-scale value of 88.5 points for the borylation of 4-iodophenol (**1a**), 4-iodoanisole (**1b**) and 2-iodophenol (**1h**) by our protocol (See SI, Table S1), which comes already close to the score of 100 points for an “ideal” reaction. This study confirms the added advantage of our protocol.

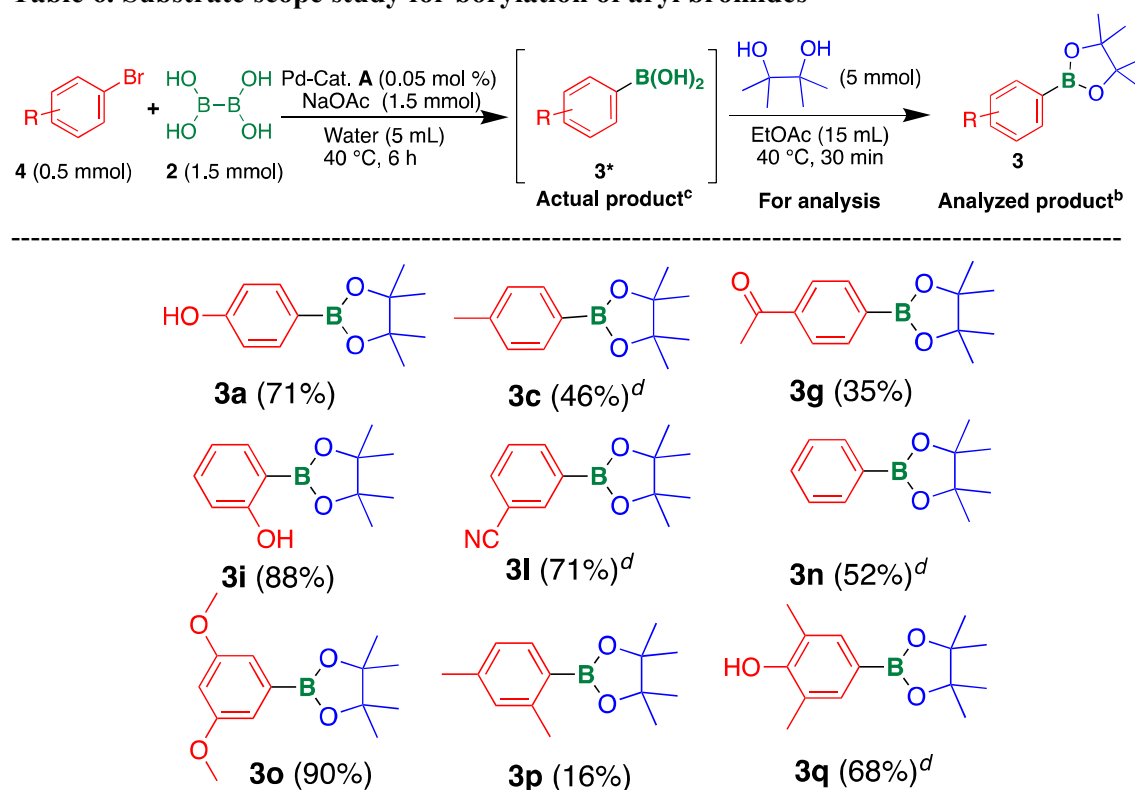
**Table 5. Substrate scope study for borylation of aryl iodides<sup>a</sup>**



<sup>a</sup>Reaction conditions: **1** (0.5 mmol), **2** (1.5 mmol), NaOAc (1.5 mmol), catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h under argon atmosphere. <sup>b</sup>All yields mentioned in brackets are isolated yields of product **3**. <sup>c</sup>Reaction carried out at room temperature. <sup>d</sup>Corresponding arylboronic acid **3\*** are the actual products in all cases only for analysis purpose they are converted to pinacol ester **3**. <sup>e</sup>Reaction time 24 h.

Secondly, we extended applicability of Bedford-type palladacycle catalyzed protocol for aryl bromides (Table 6). It was observed that hydroxy (**4a** and **4i**), cyano (**4l**) and methoxy (**4o**) substituted aryl bromides gave higher yields of corresponding borylated product **3a**, **3i**, **3l** and **3o**. However, in case of acetyl substituted phenyl bromide **4g** moderate yield of **3g** was obtained, while for 2,4-dimethyl substituted phenyl bromide **4p** lowest yield of product **3p** was obtained. Furthermore, by extending the reaction time to 24 hours for aryl bromides **4c**, **4n** and **4q** good yields of product **3c**, **3n** and **3q** up to 90%.

**Table 6. Substrate scope study for borylation of aryl bromides<sup>a</sup>**

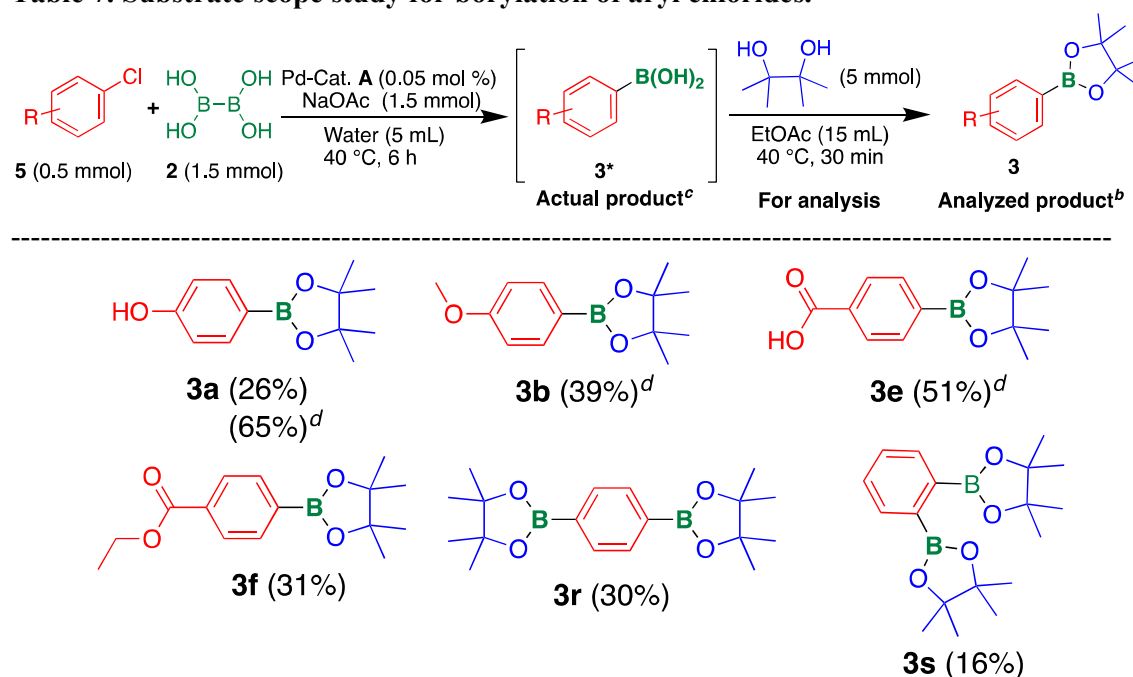


<sup>a</sup>Reaction conditions: **4** (0.5 mmol), **2** (1.5 mmol), NaOAc (1.5 mmol), catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h. <sup>b</sup>All yields mentioned in brackets are isolated yields of product **3**. <sup>c</sup>Corresponding arylboronic acid **3\*** are actual products in all cases only for analysis converted to pinacol ester **3**. <sup>d</sup>Reaction time 24 h.

Finally, aryl chlorides (**5**), which are known to be economically, but difficult substrates for catalytic reactions were tested for borylation (Table 7). As expected borylation of aryl chloride required longer reaction times and excess use of BBA. However, it should be noted that with our protocol the borylation of aryl chlorides could be performed under very mild reaction conditions, notably with low catalyst loading of catalyst **A** 0.05 mol % at 40 °C in

water. Interestingly aryl chlorides such as **5a**, **5b**, **5e**, **5f**, were smoothly converted into the corresponding borylated product **3a**, **3b**, **3e** and **3f**. However, because of excess use of BBA and longer reaction time diborylation of 4-chloro iodobenzene (**5r**) and 2-chloro iodobenzene (**5s**) to product **3r** and **3s** was observed. From overall substrate scope study, it was observed that our Bedford-type palladacycle catalyzed borylation protocol has wide applications under mild reaction conditions.

**Table 7. Substrate scope study for borylation of aryl chlorides.<sup>a</sup>**

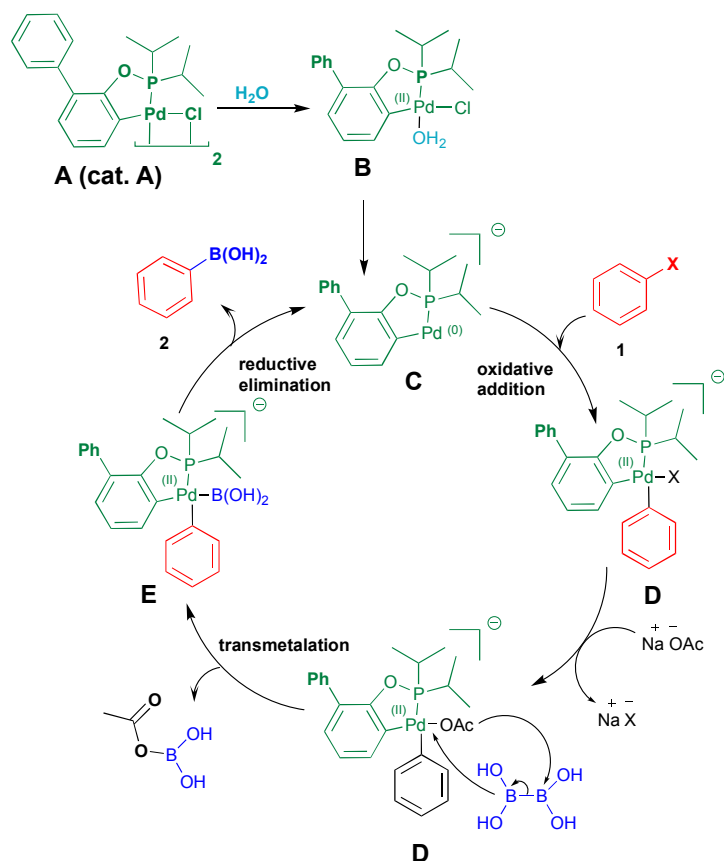


<sup>a</sup>Reaction conditions: **5** (0.5 mmol), **2** (1.5 mmol), NaOAc (1.5 mmol), catalyst **A** (0.05 mol %), water (5 mL), 40 °C, 6 h, under argon atmosphere. <sup>b</sup>All yields mentioned in bracket are isolated yields of product **3**. <sup>c</sup>Corresponding arylboronic acid **3\*** are actual products in all cases only for analysis converted to pinacol ester **3**. <sup>d</sup>2<sup>nd</sup> and 3<sup>rd</sup> addition of 3 eq. BBA after 12 and 36 h, total reaction time 72 h.

### Mechanism

The precatalyst **Cat. A** is dimer (**A**) and as soon as water is added to the reaction flask containing **Cat. A**, the dimer **A** breaks down and convert to Pd (II) intermediate (**B**). The bulky isopropyl substituents on the phosphorous center are electron rich and well shielded against cleavage by nucleophilic attack therefore a well-balanced steric bulk stabilizes the palladacyclic motive. Based on our previous mechanistic study on Suzuki coupling we believe that in situ an undercoordinated, palladacyclic anionic Pd(0) species (**C**) forms which might be the active catalytic species. In next step, oxidative addition of arly halide (**1**) occurs to the

palladium intermediated **C** which results in the formation of intermediate **D**. In next step the halide group is replaced by acetate and forming intermediate **E**. Thereafter the transmetalation occurs forming an intermediated **F** which undergo the reductive elimination and result in formation of product arylboronic acid (**2**) and regenerate the catalytically active intermediate **C** which continues the catalytic cycle.



## Conclusion

We have developed a new Bedford-type palladacycle catalyzed mild aqueous protocol for the Miyaura-borylation using a water-soluble boron source tetrahydroxydiboron (BBA). The developed methodology requires low catalyst loading of (0.05 mol%) and works best under mild reaction conditions at maximum  $40\text{ }^\circ\text{C}$  or even at room temperature in short time of 6 hours in water. Our results reveal that good to excellent yields of aryl boronic acids can be achieved in water, therefore eliminating the need of toxic organic solvents for borylation. In



1  
2  
3 addition, our studies show that maintaining a neutral reaction pH is very important for  
4  
5 reproducibility and higher yields of corresponding products. We believe that our reported  
6  
7 studies on the effect of pH, will be very helpful for developing new aqueous borylation  
8  
9 protocols. Nevertheless, our protocol is applicable for a broad range of aryl halides and  
10  
11 corresponding borylated products were obtained in excellent yields up to 94% with 29 such  
12  
13 examples demonstrating its broad utility and functional group tolerance.  
14  
15

## 16 17 18 **Experimental section**

19  
20 **General Information:** NMR spectra were recorded on BrukerBioSpin 400, 500, 600 or 700  
21  
22 MHz spectrometer at 297 K. Chemical shifts in ppm are referenced to the residual signal of  
23  
24 the solvent ( $\text{CDCl}_3$ ,  $\delta_H = 7.26$  and  $\delta_C = 77.16$  ppm).<sup>33a</sup> Coupling constants  $J$  are given in Hz  
25  
26 and signal multiplicities are abbreviated as: s (singlet), d (doublet), t (triplet), vt (virtual  
27  
28 triplet), q (quartet), m (multiplet) and br (broad). As already known in literature in  $^{13}\text{C}$  the  
29  
30 carbon next to the boron tend to be broadened beyond the limits of detection due to the  
31  
32 quadrupolar relaxation of  $^{11}\text{B}$ .<sup>1</sup> MS: High resolution (HR-MS) was measured by the CORE  
33  
34 LABS of King Abdullah University of Science and Technology at a LTQ Orbitrap from  
35  
36 Thermo Scientific. Low resolution (LC-MS or MS by direct injection) spectra were recorded  
37  
38 on a TSQ Vantage MS from Thermo Scientific. For the combination of gas chromatography  
39  
40 with mass spectroscopic detection (GC-MS), a GC from Agilent 7890 A with an Agilent  
41  
42 5975C instrument for MS detection (inert XL EI/CI MSD with Triple-Axis Detector, EI,  
43  
44 70 eV) was used. GC/MS Method (80-280 °C DB-5MS): Initial 80 °C, 3 min; Ramp  
45  
46 25 °C/min, 280 °C, 6 min; total 17 min. Thin layer chromatography was performed using  
47  
48  $\text{SiO}_2$  pre-coated glass plates (Merck 60, F-254). The chromatograms were examined under  
49  
50 UV light at 254 nm and 365 nm and by staining of the TLC plate with a 0.1 mM solution of  
51  
52 10-hydroxybenzo[*h*]quinolone (HBQ) in ethanol, followed by heating with a heat gun.<sup>33b</sup> If  
53  
54 not stated otherwise, reactions were run under argon atmosphere in Carousel 12 Plus<sup>TM</sup>  
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56  
57  
58  
59  
60

1  
2  
3 Reaction Stations from *Radleys*, which allow simultaneously stirring and heating of up to 12  
4  
5 reactions. HPLC-grade water was used as the solvent and degassed by prior to use by three  
6  
7 *freez-pump-thaw* cycles. All reagents were obtained from commercial sources and used  
8  
9 without further purification unless stated otherwise. Column chromatography was performed  
10  
11 using silica gel 60 (0.040-0.063 mm) from Merck, but much like other carboxylic acids the  
12  
13 boronic acid interact strongly with silica gel.<sup>25</sup> Thus prolonged exposure to silica has to be  
14  
15 avoided. Solvents were used in HPLC grade.

### 16 17 18 **Synthesis of the palladacycle catalyst A<sup>[27a]</sup>**

#### 19 20 21 **Step 1. ([1,1'-Biphenyl]-2-yloxy)diisopropylphosphine (*Ligand A*)<sup>27a</sup>**

22  
23  
24 In a Schlenk tube 2-phenylphenol (1.70 g, 10.0 mmol, 1.0 eq.) was dissolved in 50 mL of  
25  
26 dry toluene and triethylamine (1.51 g, 14.9 mmol, 1.5 eq.) was added. After stirring the  
27  
28 solution for 15 min at r.t. chlorodiisopropylphosphine (1.51 g, 9.9 mmol, 0.95 eq.) was added.  
29  
30 The reaction mixture was refluxed for 16 h. After cooling to r.t. pentane (50 mL) was added.  
31  
32 A white solid precipitated, which was removed by filtration through a pad of Celite® and  
33  
34 washed with pentane (3 × 10 mL). The combined organic fractions were evaporated to  
35  
36 dryness *in vacuo* yielding the phosphiniteligand (2.63 g, 92%), which was used without further  
37  
38 purification.  
39  
40  
41  
42  
43

#### 44 45 **Step II. Synthesis of $[\{\text{Pd}(\mu\text{-Cl})\{\kappa^2\text{-P,C-P}(\text{iPr})_2(\text{OC}_6\text{H}_3\text{-2-Ph})\}\}_2]$ (*Catalyst A*)<sup>27a</sup>**

46  
47 In a Schlenk tube ([1,1'-Biphenyl]-2-yloxy)diisopropylphosphine (2.63 g, 9.9 mmol, 1.0  
48  
49 eq.) and PdCl<sub>2</sub> (1.75 g, 9.9 mmol, 1.0 eq.) were dissolved in dry toluene (50 mL). The  
50  
51 reaction mixture was refluxed for 19 h. After cooling to r.t. the solvent was removed *in vacuo*.  
52  
53 The residue was extracted with DCM (20 mL) and filtered through a pad of Celite®. The  
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60

product was precipitated from the organic solution by addition of ethanol, collected by filtration and recrystallized from DCM/EtOH.

**General procedure for the Bedford-type palladacycle catalyzed Miyaura-borylation of aryl halides with tetrahydroxydiboron in water and identification by Pinacol-esterification:**

214  $\mu$ L of a 1.16 mM stock solution of palladacycle **1**<sup>[16a]</sup> in DCM are added to the reaction tube followed by evacuation of the flask for 5 min to evaporate the solvent. NaOAc (123 mg, 1.5 mmol, 3 eq.), tetrahydroxydiboron (134 mg, 1.5 mmol, 3 eq.) and aryl halide (0.5 mmol) are added before the flask atmosphere is changed to argon gas. 5 mL of degassed water are added and the reaction mixture is stirred vigorously (1500 rpm) at 40 °C for 6 h. Subsequently, 2 mL of 3 M HCl are added to quench the reaction. The acidic aqueous phase is extracted with EtOAc (3x 5 mL) and dried over MgSO<sub>4</sub>. Addition of Pinacol (600 mg) to the organic phase and stirring at 40 °C for 1 h yields the boronic acid pinacolato-ester, which was purified by column chromatography on silica gel (pet ether/ethyl acetate combination) to afford the pure product.. Final Products are confirmed by GCMS, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopic analysis.

([1,1'-Biphenyl]-2-yloxy)diisopropylphosphine (**Ligand A**)<sup>27a</sup> Yield: 92% (2.63 g). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.61-7.58 (m, 2H), 7.51-7.43 (m, 3H), 7.39-7.32 (m, 3H), 7.10 (m, 1H, t,  $J(\text{H,H})= 7.5$  Hz), 1.86 (dvt, 2H,  $J(\text{P,H})= 2.9$  Hz,  $J(\text{H,H})= 9.1$  Hz), 0.06 (dd, 6H,  $J(\text{P,H})= 11.4$  Hz,  $J(\text{H,H})= 7.0$  Hz); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  156.2, 138.9, 132.6, 130.8, 130.0, 128.6, 127.8, 126.9, 121.7, 118.2, 28.3, 17.7, 17; <sup>31</sup>P-NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  150.8.

[{Pd( $\mu$ -Cl){ $\kappa^2$ -P,C-P(iPr)<sub>2</sub>(OC<sub>6</sub>H<sub>3</sub>-2-Ph)}<sub>2</sub>}] (**Catalyst A**)<sup>27a</sup> Yield: 43% (1.9 g) <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.55 (m, 1H), 7.49-7.47 (m, 2H), 7.39-7.36 (m, 2H), 7.30-7.28 (m, 1H), 7.08-7.07 (m, 1H), 6.88-6.86 (m, 1H), 2.45-2.42 (m, 2H), 1.31-1.26 (m, 12H); <sup>13</sup>C-NMR (126

MHz, CDCl<sub>3</sub>)  $\delta$  161.8, 139.2, 136.3, 136.1, 129.1, 128.3, 128.1, 126.9, 126.8, 122.7, 122.5, 29.7, 17.8, 17.1; <sup>31</sup>P-NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  201.4, 200.1.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3a**):<sup>19b</sup> Yield: 93% (102 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (d, *J* = 10 Hz, 2H), 6.82 (d, *J* = 10 Hz, 2H), 1.33 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  158.5, 136.9, 114.9, 83.8, 24.9.

2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3b**):<sup>19a</sup> Yield: 92% (108 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (d, *J* = 10 Hz, 2H), 6.89 (d, *J* = 10 Hz, 2H), 3.83 (s, 3H), 1.33 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  162.2, 136.6, 113.4, 83.6, 55.2, 24.9.

4,4,5,5-tetramethyl-2-(p-tolyl)-1,3,2-dioxaborolane (**3c**):<sup>19a</sup> Yield: 85% (93 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.86 (d, 2H), 7.29 (d, 2H), 2.46 (s, 3H), 1.43 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  141.3, 135.0, 128.6, 83.6, 24.9, 21.8.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzaldehyde (**3d**):<sup>19a</sup> Yield: 15% (17 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.04 (s, 1H), 7.96 (d, *J* = 8 Hz, 2H), 7.86 (d, *J* = 8 Hz, 2H), 1.36 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  192.8 (s), 138.2 (s), 135.3, 128.8, 84.5, 25.0.

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**3e**):<sup>32a</sup> Yield: 57% (71 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  10.01 (s, 1H), 8.10 (d, 2H), 7.91 (d, 2H), 1.36 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  172.3, 134.8, 129.3, 84.4, 25.0.

Methyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (**3f**):<sup>19a</sup> Yield: 52% (72 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.93 (d, <sup>3</sup>*J* = 8 Hz, 1H), 7.53-7.48 (m, 2H), 7.43-7.38 (m, 1H), 3.90 (s), 1.40 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  168.6, 133.5, 132.3, 131.9, 129.1, 128.9, 84.2, 52.4, 25.0.

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2  
3 1-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (**3g**):<sup>19a</sup> Yield: 68% (84  
4 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.90 (dd,  $J$  = 8 Hz, 4H), 2.61 (s, 3H), 1.35 (s, 12H); <sup>13</sup>C-  
5 NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  198.6, 139.1, 135.0, 127.4, 84.3, 26.9, 25.0.  
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9  
10 2-(4-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3h**):<sup>19a</sup> Yield: 28% (33 mg). <sup>1</sup>H-  
11 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.73 (d,  $J$  = 8 Hz, 2H), 7.74 (d,  $J$  = 8 Hz, 2H), 1.34 (s, 12H); <sup>13</sup>C-  
12 NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  137.7, 136.3, 128.1, 84.2, 25.0.  
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16  
17 2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3i**):<sup>32b</sup> Yield: 92% (101 mg). <sup>1</sup>H-  
18 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.81 (s, 1H), 7.62 (d,  $J$  = 7.6 Hz, 1H), 7.34 (t,  $J$  = 7.4 Hz, 1H),  
19 6.90-6.87 (m, 2H), 1.38 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  163.7, 135.8, 133.9, 119.6,  
20 115.5, 84.5, 24.9.  
21  
22  
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26 4,4,5,5-Tetramethyl-2-(o-tolyl)-1,3,2-dioxaborolane (**3j**):<sup>19a</sup> Yield: 68% (69 mg). <sup>1</sup>H NMR  
27 (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.68 (dd,  $J$  = 7.7, 1.6 Hz, 1H), 7.23 (td,  $J$  = 7.5, 1.6 Hz, 1H), 7.07 (m, 2H),  
28 2.46 (s, 3H), 1.26 (s, 12H).  
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33  
34 2-(2-chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3k**):<sup>19a</sup> Yield: 5% (6 mg). <sup>1</sup>H-  
35 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.72 (d, 1H), 7.33-3.38 (m, 2H), 7.25 (t, 1H), 1.39 (s, 12H); <sup>13</sup>C-  
36 NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  139.6, 136.5, 131.9, 129.4, 125.8, 84.1, 24.8.  
37  
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41  
42 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzotrile (**3l**):<sup>19b</sup> Yield: 64% (73 mg). <sup>1</sup>H-  
43 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  8.09 (s, 1H), 8.00 (d, <sup>3</sup> $J$  = 5 Hz, 1H), 7.72 (d, <sup>3</sup> $J$  = 5 Hz, 1H), 7.47  
44 (t, <sup>3</sup> $J$  = 7.6 Hz, 1H), 1.35 (s, 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  138.8, 138.5, 134.5, 128.5,  
45 119.0, 112.15, 84.6, 24.9.  
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51 2-(2-methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3m**):<sup>32c</sup> Yield: 52% (61 mg).  
52 <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  7.60 (dd,  $J$  = 7.3, 1.8 Hz, 1H), 7.31 (ddd,  $J$  = 8.4, 7.3, 1.9 Hz,  
53 1H), 6.86 (td,  $J$  = 7.3, 0.9 Hz, 1H), 6.80 – 6.74 (m, 1H), 3.75 (s, 3H), 1.27 (s, 12H).  
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56

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3 4,4,5,5-Tetramethyl-2-phenyl-1,3,2-dioxaborolane (**3n**):<sup>19a</sup> Yield: 60% (61 mg). <sup>1</sup>H-NMR  
4 (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.82 (d, *J* = 8 Hz, 2H), 7.47 (t, *J* = 8 Hz, 1H), 7.38 (t, *J* = 8 Hz, 2H),  
5 1.36 (s, 12H). <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  135.2, 131.7, 128.2, 84.2, 25.3.  
6  
7

8  
9  
10 2-(3,5-dimethoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3o**):<sup>32c</sup> Yield: 90% (119  
11 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  6.95 (d, 2H), 6.57 (t, 1H), 3.81 (s, 6H), 1.34 (s, 12H);  
12 <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  160.4, 111.6, 104.6, 84.0, 55.5, 24.9.  
13  
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17 2-(2,4-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**3p**):<sup>32d</sup> Yield: 16% (19 mg).  
18 <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.78 (d, 1H), 7.08 (d, 2H), 2.62 (s, 3H), 2.41 (s, 3H), 1.42 (s,  
19 12H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  145.0, 140.9, 136.2, 130.8, 125.6, 83.2, 24.9, 22.2,  
20 21.5.  
21  
22  
23

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26  
27 2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**3q**):<sup>32e</sup> Yield: 68% (84  
28 mg). <sup>1</sup>H-NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.46 (s, 2H), 2.24 (s, 6H), 1.33 (s, 12H); <sup>13</sup>C-NMR (126  
29 MHz, CDCl<sub>3</sub>)  $\delta$  155.2, 135.6, 131.0, 83.6, 24.9, 15.7.  
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31  
32

33  
34 1,4-bis(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3r**):<sup>19a</sup> Yield: 30% (50 mg). <sup>1</sup>H-  
35 NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  7.81 (s, 4H), 1.35 (s, 24H); <sup>13</sup>C-NMR (126 MHz, CDCl<sub>3</sub>)  $\delta$  134.0,  
36 84.0, 25.0.  
37  
38  
39

40  
41  
42 1,2-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene (**3s**):<sup>32f</sup> Yield: 16% (26 mg). <sup>1</sup>H-  
43 NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.64 (q, *J* = 3.0 Hz, 2H), 7.37 (q, *J* = 3.0 Hz, 2H), 1.37 (s, 24H);  
44 <sup>13</sup>C-NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  133.5, 129.2, 84.0, 25.0.  
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#### 50 51 **Acknowledgment:**

52  
53 This work was supported by the King Abdullah University of Science and Technology  
54 (KAUST baseline funding and GCR grant FIC/2010/07). Authors are gratefully  
55  
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acknowledging support from King Abdullah University of Science and Technology (KAUST), Saudi Arabia.

**Supporting Information:** Copies of GCMS,  $^1\text{H}$  and  $^{13}\text{C}$  NMR of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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