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Lithium aminoborohydrides **17**. Palladium catalyzed borylation of aryl iodides, bromides, and triflates with diisopropylaminoborane prepared from lithium diisopropylaminoborohydride

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ABSTRACT

The Alcaraz–Vaultier borylation of aryl halides and triflates is reported utilizing diisopropylaminoborane ($BH_2N(^iPr)_2$) prepared from the corresponding lithium aminoborohydride (LAB reagent). $BH_2N(^iPr)_2$, prepared by reacting lithium diisopropylaminoborohydride with trimethylsilyl chloride, provided the most consistent isolated yields from this reaction. Catalytic amounts of palladium dichloride produced the highest yields from aryl iodides, while catalytic tris(dibenzylideneacetone)dipalladium(chloroform) provided the best yields for aryl bromides and triflates. This route to boronic acids is mild enough to tolerate various functionalities and for the first time employs aryl triflates as substrates for the Alcaraz–Vaultier borylation. In addition, it was found that both boronic acid and ester compounds could be isolated from the reaction mixture utilizing simple work-up procedures. Treatment of the reaction intermediate with an acid/base work-up provided the corresponding boronic acid, while treating the same intermediate with a diol, such as neopentyl glycol, afforded the corresponding boronic ester.

1. Introduction

Aryl boronic acids remain important reagents widely used throughout organic chemistry due to their unique reactivity in cross-coupling reactions.[1a,b] Over the last decade there has been a significant expansion in the use of boronic acids with researchers developing synthetic, medicinal, and biological applications for these versatile compounds.[2] As potential pharmaceutical agents, boronic acids have been used in the development of enzyme inhibitors,[3a] boron neutron capture therapy (BNCT) agents,[3b] feedback controlled drug delivery polymers,[3c,d] saccharide sensors,[3e] and antibody mimics for cell-surface polysaccharides.[3f,g] Synthetic applications include the use of boronic acids in metal catalyzed cross-coupling reactions,[1a,b] in Diels–Alder reactions,[1c] as chiral auxiliaries,[1d–h] as protecting groups,[1f] and as precursors of boron enolates.[1i]

The extensive expansion in the utility of functionalized aryl boronic acids has prompted researchers to explore new and more efficient methods for their preparation. The currently established method for the production of arylboronic acids is the reaction of an aryl lithium or Grignard reagent with an excess of a trialkylborate, usually trimethyl-, triethyl-, or triisopropylborate, followed by acid hydrolysis.[4] Unfortunately, these methods require previous preparation of the organometallic species, which is not always trivial and only tolerated by a restricted number of functional groups. In addition, Grignard reagents have poor selectivity and often give mixtures of the mono- and dialkylated products.[5]

Several new methods for the synthesis of aryl boronic acids using various transition metals have been reported. These procedures involve the cross-coupling of a boron source, such as a tetra (alkoxo)diboron derivative (BisPin)[6] or dialkoxyborane derivatives (Pinacolborane or neopentylborane),[7] with aryl halides or aryl triflates in the presence of catalytic palladium.[6,7] Unfortunately, these methods often require an excess of relatively expensive boron donors and high temperatures. However, this route to boronic acids is still widely used in industry due to its tolerance of various functional groups. The most significant challenges associated with these methods are the high cost associated with the catalytic components, catalyst decomposition, and the isolation of products free from heavy metal impurities.

A novel method was more recently reported for the production of aryl boronic acids from non-halogenated precursors through metal catalyzed C–H activation.[8] This method is very attractive due to its functional group tolerance but still suffers from many of the aforementioned drawbacks as the transition metal catalyzed

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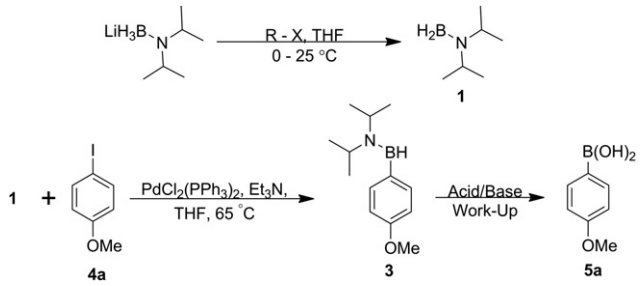
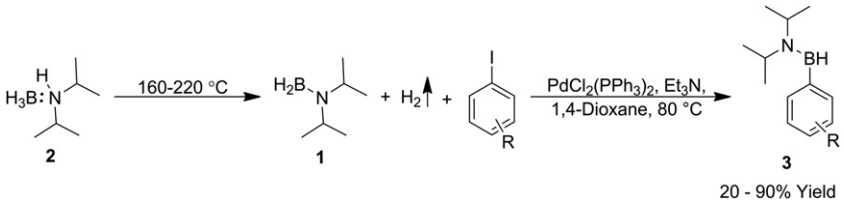
synthesis of boronic acid derivatives discussed above. Metal catalyzed C–H activation also has the added challenge of controlling the regioselectivity of activation in unsymmetrical substrates.

In addition to trialkyl borates and boronic esters, other boron sources have also been used to synthesize boronic acids. Recently, Alcaraz–Vaultier reported a palladium catalyzed borylation of aryl and alkenyl halides using monomeric dialkylaminoboranes (aminoboranes), such as diisopropylaminoborane **1**, as an inexpensive boron source.[9] However, the aminoboranes used in the Alcaraz–Vaultier borylation were synthesized by thermal decomposition of the corresponding amineborane **2** at high temperatures. This produces the desired aminoborane **1** with concomitant evolution of hydrogen gas (Scheme 1). These aminoboranes were then reacted with various aryl iodides and bromides in the presence of bis(triphenylphosphine) palladium dichloride [$PdCl_2(PPh_3)_2$] producing the corresponding aryl(dialkylamino)boranes in yields ranging from 20 to 90% (Scheme 1). The aryl(dialkylamino)borane products are useful intermediates that can be converted into other boronic acid derivatives.



Scheme 2. Synthesis of a boronic acid from $BH_2N(^iPr)_2$ prepared from a LAB reagent.

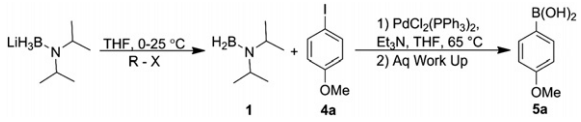
Closer examination of our procedures for the preparation of aminoboranes revealed that aminoboranes prepared from LAB and methyl iodide (MeI) contained trace amounts of lithium borohydride ($LiBH_4$), while aminoboranes prepared from LAB and trimethylsilyl chloride (TMSCl) did not.[12] Since the reaction of **1** prepared from LAB and MeI produced variable yields of **5a**, we decided to test



Scheme 1. Preparation of a boronic acid derivative from an aminoborane.

We recently published a mild synthesis of various monomeric and dimeric aminoboranes from the corresponding lithium aminoborohydride (LAB) reagents.[10] Our procedure was conducted at ambient temperatures without the evolution of hydrogen gas. In a preliminary study, we reported that the aminoborane **1**, prepared from the corresponding LAB reagent, could be used in the Alcaraz–Vaultier borylation.[10] When we probed the generality of this reaction we observed that the yields of boronic acid varied depending on the synthetic route used to prepare aminoborane **1**. A systematic study revealed the cause of the variable yields obtained in this reaction and allowed us to expand the scope of this reaction to include aryl triflates. Herein we report our result of the optimized borylation of aryl iodides, bromides, and triflates using diisopropylaminoborane prepared from lithium diisopropylaminoborohydride.

Table 1
Aminoborane optimization study[a]



Entry	R-X	Additive	Yield%
1	CH_3I	None	50
2	TMSCl	None	76
3	TMSCl	$LiBH_4$[b]	45

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl iodide, 2 equiv aminoborane, 5 equiv of triethylamine, and 5 mol % palladium catalyst.
[b] $LiBH_4$ (20 mol %) was added to the reaction after addition of the aminoborane.

2. Results and discussion

2.1. Synthesis of boronic acids

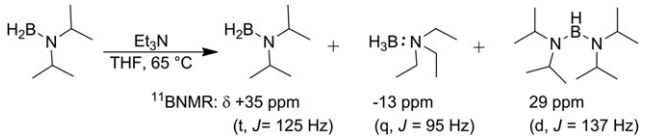
Aminoboranes are typically prepared in situ in tetrahydrofuran (THF) from LAB reagents and used as such.[11] We decided to investigate whether the aminoboranes prepared from LAB reagents could be used in the Alcaraz–Vaultier borylation.[9] Thus, the synthesis of aryl(dialkylamino)borane **3** from **1** was carried out in THF and its formation was followed by ^{11}B NMR spectroscopy of aliquots withdrawn periodically from the reaction (Scheme 2). After 12 h of reflux the formation of **3** was confirmed by ^{11}B NMR spectroscopy of the reaction mixture. However, a simple acid/base work-up provided the corresponding boronic acid in only 50% yield (Table 1, entry 1). Moreover, these results could not be reliably reproduced and yields varied from reaction to reaction warranting further optimization.

this borylation reaction using pure **1** prepared from LAB and TMSCl (Table 1, entries 1 and 2). It should be pointed out that the use of **1**, contaminated with $LiBH_4$, causes a black precipitate of palladium metal. The reaction of **1**, prepared from LAB and TMSCl, and iodoanisol **4a** resulted in a significantly higher and reproducible yield of **5a** (Table 1, entry 2). We also noted the absence of palladium-black precipitation in this reaction. These results indicated that the $LiBH_4$ contaminant, present in **1** prepared from the reaction of LAB and MeI, is causing the lower and variable yields of **5a** by reducing the palladium salt to palladium-black.[13] In addition, $LiBH_4$ may reduce the aryl halide to the corresponding hydrocarbon by palladium catalyzed proto-dehalogenation. A similar reaction was reported by Lipshutz et al. for the palladium catalyzed reduction of aryl triflates by amineboranes.[14]

In an effort to confirm that $LiBH_4$ was causing the lower and variable yields of **5a**, we spiked pure **1** with 20 mol % $LiBH_4$ and used it in the borylation reaction (Table 1, entry 3). The addition of

$LiBH_4$ caused the precipitation of palladium-black and resulted in a significantly reduced yield of **5a** consistent with earlier results. These results confirmed that the presence of $LiBH_4$ is detrimental to this borylation reaction. Consequently, we carried out our optimization studies using pure **1** prepared from LAB and TMSCl.

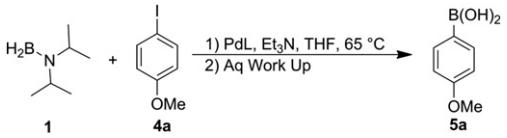
We next turned our attention to optimize the stoichiometry of this borylation reaction. Previous studies have used 2 equiv of **1** for complete borylation of aryl and alkenyl haldies.[9] To confirm this stoichiometry, a solution of 2 equiv of **1** was added to 1 equiv of triethylamine and heated to reflux. After 15 h of reflux an aliquot of the reaction was analyzed via ^{11}B NMR spectroscopy. This analysis revealed a disproportionation of aminoborane **1** as evidenced by two additional signals in the ^{11}B NMR spectra. From the chemical shift and multiplicity of the signals we assigned these peaks as triethylamine-borane and *N*,*N*,*N*′,*N*′-tetraisopropylboranediamine (Scheme 3). Since these disproportionation products are inactive boron donors, the borylation reaction requires an excess of **1** for complete borylation of the aryl or alkenyl halide. Consequently, we utilized two equiv of aminoborane **1** for all further borylation reactions.



Scheme 3. Disproportionation reaction between triethylamine and $BH_2N(^iPr)_2$.

We next screened various palladium catalysts in the reaction of **1** with **4a** as shown in Table 2. Previously used bis(triphenylphosphine)palladium(II) chloride catalyst afforded only moderate yield of **5a** (Table 2, entry 1). It should be noted that this palladium catalyst is relatively more expensive and air sensitive when compared to other palladium catalysts used in the present study. On the other hand, the relatively inexpensive and stable palladium dichloride ($PdCl_2$) catalyst provided the highest yield of **5a** (Table 2, entry 2). $PdCl_2$ not only improved the isolated yield of **5a** but also lowered the overall cost of this borylation reaction per mol of substrate, making it the best choice for this borylation reaction. We investigated the generality and scope of this reaction using a series of aryl iodides **4a**–**h** with **1**. The results are summarized in Table 3.

Table 2
Palladium catalyst optimization for the reaction of $BH_2N(^iPr)_2$ and iodoanisol[a]

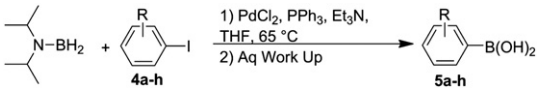


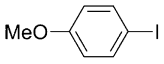
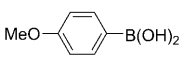
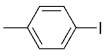
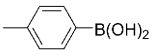
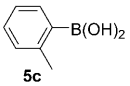
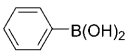
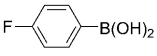
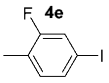
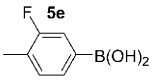
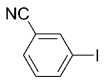
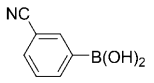
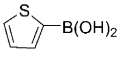
Entry	Palladium source	Additive	Isolated % yield	Palladium cost[b] ($/mmol)
1	$PdCl_2(PPh_2)_2$	None	76	14
2	$PdCl_2$	20 mol % PPh_3	89	5
3	$Pd(OAc)_2$	20 mol % PPh_3	85	9
4	$Pd_2(DBA)_3 \cdot CHCl_3$	20 mol % PPh_3	87	13[c]

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl iodide, 2 equiv aminoborane, 5 equiv triethylamine, and 5 mol % palladium catalyst.
[b] Prices as of January 2010.
[c] Price to synthesize in house following the procedure in Ref. 13.

The reaction of aryl iodides with **1** in the presence of $PdCl_2$ resulted in isolation of the corresponding boronic acids in good to excellent yields (Table 3). Aryl iodides bearing an electron donating group (EDG), such as methoxy or methyl, afforded the corresponding boronic acids in high yields. For example, *p*-methoxyphenylboronic acid **5a** was obtained in 89% isolated yield from **4a**. Conversely, substrates containing an electron withdrawing group

Table 3
Boronic acid synthesis from $PdCl_2$, $BH_2N(^iPr)_2$, and aryl iodides[a]

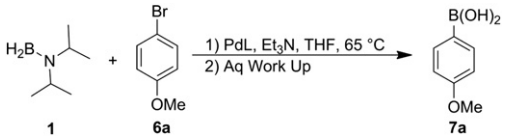


Entry	Aryl iodide	Boronic acid	Isolated % yield
1	 **4a**	 **5a**	89
2	 **4b**	 **5b**	84
3	 **4c**	 **5c**	73
4	 **4d**	 **5d**	80
5			57
6	 **4e** **4f**	 **5e** **5f**	50
7	 **4g**	 **5g**	20
8	 **4h**	 **5h**	99

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl iodide, 2 equiv aminoborane, 5 equiv triethylamine, 5 mol % palladium catalyst, and 20 mol % triphenylphosphene.

(EWG), such as nitrile, chloro, or fluoro, afforded the corresponding boronic acid in diminished yields. For instance, 3-cyanophenylboronic acid **5g** was obtained in 20% isolated yield from **4g**, while 4-fluorophenylboronic acid **5f** was isolated in 57% yield from **4a**. In both cases unreacted starting material was recovered from the reaction mixture. Unfortunately, aryl iodides containing chloro substituents only resulted with recovery of the starting material with no formation of the desired boronic acid products. Aryl iodides bearing *ortho*-substituents produced the corresponding boronic acids in lower yields compared to analogous *meta*- and *para*- substituted compounds. These depressed yields are likely due to steric retardation at the oxidative addition step. For example, *o*-methylphenylboronic acid **5c** obtained in 73% isolated yield from **4c**. The highest yield was obtained from 2-iodothiophene **4h** providing the corresponding boronic acid **5h** in 99% isolated yield. Unfortunately, *N*-heterocycles, such as iodopyridine, iodoquinoline, and iodopyrazole, did not undergo this borylation reaction and only starting material was recovered from these reactions. We next applied the above optimized conditions to synthesize boronic acids from aryl bromides. The results are summarized in Table 4. As shown in Table 4, the optimized reaction conditions did not perform as well with aryl bromide substrates (Table 4, entry 2). This difference in reactivity between aryl iodides and bromides may be due to the difference in the activation barrier of the oxidative addition step.[15] In an effort to optimize the yield of **7a** from **6a**, several palladium catalysts

Table 4
Palladium catalyst optimization for the reaction of $BH_2N(^iPr)_2$ and bromoanisol[a]



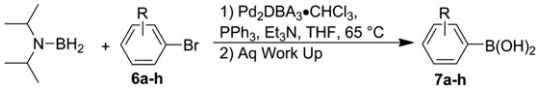
1 6a 7a

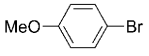
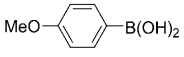
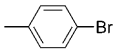
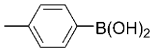
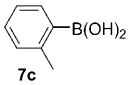
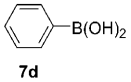
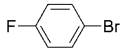
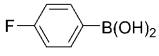
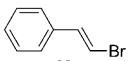
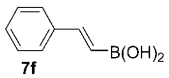
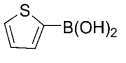
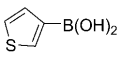
Entry	Palladium source	Additive	Isolated % yield	Palladium cost[b] ($/mmol)
1	$PdCl_2(PPh_2)_2$	None	64	14
2	$PdCl_2$	20 mol % PPh_3	33	5
3	$Pd(OAc)_2$	20 mol % PPh_3	27	9
4	$Pd_2(DBA)_3 \cdot CHCl_3$	20 mol % PPh_3	85	13[c]

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl bromide, 2 equiv aminoborane, 5 equiv triethylamine, and 5 mol % palladium catalyst.
[b] Prices as of January 2010.
[c] Price to synthesize in house following the procedure in Ref. 13.

were screened (Table 4). We found that tris(dibenzylideneacetone) dipalladium(chloroform)[16] ($Pd_2DBA_3 \cdot CHCl_3$) produced the highest yield of **7a** from the reaction of **6a** with **1** (Table 4, entry 4).[17] With the optimized borylation of aryl bromides at hand, various aryl bromides **6a**–**j** were reacted with **1** in the presence of $Pd_2DBA_3 \cdot CHCl_3$ in an effort to probe the extent of this reaction. These results are summarized in Table 5.

Table 5
Boronic acid synthesis from $Pd_2DBA_3 \cdot CHCl_3$, $BH_2N(^iPr)_2$, and aryl bromides[a]



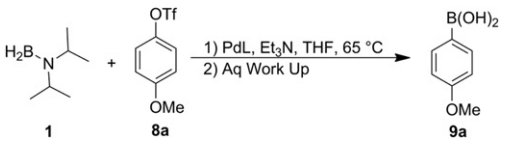
Entry	Aryl bromide	Boronic acid	Isolated % yield
1	 6a	 7a	85
2	 6b	 7b	80
3	 6c	 7c	35
4	 6d	 7d	34
5	 6e	 7e	40
6	 6f	 7f	51
7	 6g	 7g	87
8	 6h	 7h	72

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl bromide, 2 equiv aminoborane, 5 equiv triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphene.

The reaction of **1** with various aryl bromides in the presence of $Pd_2DBA_3 \cdot CHCl_3$ produced the corresponding boronic acids in moderate to excellent yields (Table 5). In general, yields were slightly lower than previously obtained with analogous aryl iodides. This depression in observed yields is thought to be due to the lower reactivity of the carbon–bromide bond as compared to the carbon–iodide bond.[15] Reactivity trends that were previously observed with aryl iodides containing EWG and EDG substituents were also observed with aryl bromides (Table 5, entries 1–5). For example, *p*-bromoanisol **6a** produced **7a** with an excellent 85% isolated yield, while 1-bromo-4-fluorobenzene was converted to **7e** with a moderate 40% isolated yield. Additionally, aryl bromides containing chloride or nitrile groups produced very little to no yields of the corresponding boronic acids with recovery of the starting material from the reaction mixture. Heterocyclic bromides, such as 2-bromothiophene **6g** and 3-bromothiophene **6h**, provided the corresponding boronic acids **7g** and **7h** in 87% and 72% isolated yields, respectively. Once again *N*-heterocycles, including bromopyridine, bromoquinoline, and *N*,*N*-dimethylaniline, were unreactive in this borylation reaction. Finally, the 1-alkenylboronic acid (*E*)-styrylboronic acid **7f** was obtained from the corresponding alkenylbromide **6f** in 51% isolated yield. The moderate yield obtained in this reaction is likely due to proto-deborylation of the vinyl boronic acid during the acid/base work-up.

We subsequently attempted to expand the scope of this borylation reaction to include aryl mesylates, tosylates, and triflates using the optimized procedures developed above for aryl iodides and bromides. When aryl mesylates or tosylates were reacted with **1** under our optimized reaction conditions only starting material was recovered. ^{11}B NMR spectroscopy analysis of aliquots withdrawn periodically indicated that intermediate **3** was not formed in these reactions. However, we were pleased to find the reaction of *p*-methoxyphenyl triflate[18] **8a** with **1** in the presence $Pd_2DBA_3 \cdot CHCl_3$ afforded the corresponding boronic acid in a very good yield (Table 6, entry 4). With the discovery that aryl triflates can be utilized in this borylation reaction, we next probed the scope and generality of this new reaction. These results are summarized in Table 7.

Table 6
Palladium catalyst optimization for the reaction of $BH_2N(^iPr)_2$ and *p*-methoxyphenyl triflate[a]



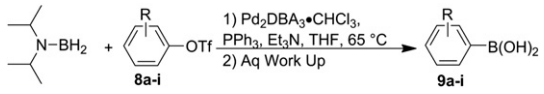
1 8a 9a

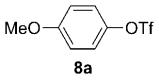
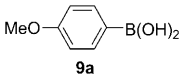
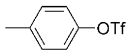
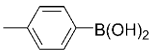
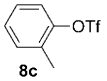
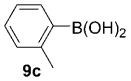
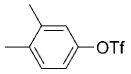
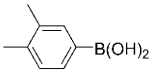
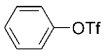
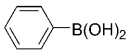
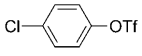
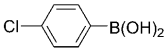
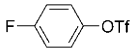
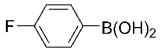
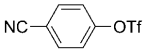
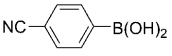
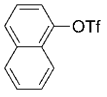
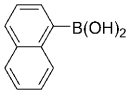
Entry	Palladium source	Additive	Isolated % yield	Palladium cost[b] ($/mmol)
1	$PdCl_2(PPh_2)2$	None	0	14
2	$PdCl_2$	20 mol % PPh_3	0	5
3	$Pd(OAc)_2$	20 mol % PPh_3	0	9
4	$Pd_2(DBA)_3 \cdot CHCl_3$	20 mol % PPh_3	87	13[c]

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl triflate, 2 equiv aminoborane, 5 equiv triethylamine, and 5 mol % palladium catalyst.
[b] Prices taken from a leading chemical manufacturer in January 2010.
[c] Price to synthesize in house following the procedure in Ref. 13.

The reaction of various aryl triflates with **1** in the presence of $Pd_2DBA_3 \cdot CHCl_3$ produced the corresponding boronic acids with generally better yields then analogous aryl iodide and bromide compounds (Table 7). This increase in observed yields is likely due to the much higher reactivity of the aryl triflate bond toward palladium oxidative insertion.[15] Even aryl triflates containing EWG substituents afforded the corresponding boronic acid in good to excellent yields. For example, *p*-chlorophenylboronic acid **9f** was obtained in 97% yield from **8f** while both aryl iodide and bromide

Table 7
Boronic acid synthesis from $Pd_2DBA_3 \cdot CHCl_3$, $BH_2N(^iPr)_2$, and aryl triflates[a]



Entry	Aryl triflate	Boronic acid	Isolated % yield
1	 **8a**	 **9a**	87
2	 **8b**	 **9b**	86
3	 **8c**	 **9c**	78
4	 **8d**	 **9d**	85
5	 **8e**	 **9e**	74
6	 **8f**	 **9f**	97
7	 **8g**	 **9g**	81
8	 **8h**	 **9h**	70
9	 **8i**	 **9i**	82

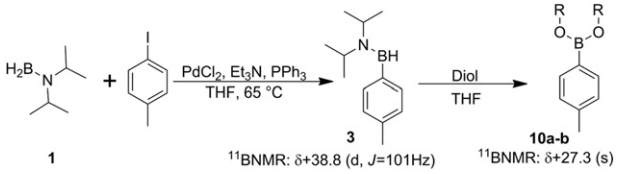
[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl triflate, 2 equiv aminoborane, 5 equiv triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphene.

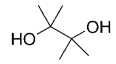
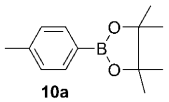
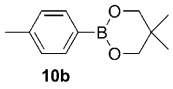
compounds containing the same functionality failed to produce any product whatsoever. *p*-Fluorophenyl triflate **8g** also gave the corresponding boronic acid **9g** in 81% yield, a yield much higher than what was realized with analogous aryl iodide **4e** and bromide **6e** compounds. Additionally, *p*-cyanophenylboronic acid **9h** was isolated in 70% yield from **8h**. It should be pointed out that analogous cyano-substituted aryl iodide or bromide substrates gave very poor yield in this reaction. Napthyl triflate **8i** was also found to be an excellent substrate for this borylation reaction affording 1-naphthylboronic acid **9i** in 82% isolated yield. However, only starting material was recovered from the analogs napthyl iodo- and bromo-compounds. As observed before, nitrogen containing triflates did not produce the corresponding boronic acids and only starting material was recovered from the reactions. Overall, aryl triflates performed better then analogous iodo- and bromo-compounds and tolerated functional groups in this borylation reaction.

2.2. Synthesis of aryl boronic esters

Hindered aryl boronic acid esters are relatively more air-stable than analogous boronic acids.[6b,7a,19,20a] Consequently, they are used more frequently in organic synthesis as substitutes for the corresponding boronic acids. For these reasons, we wanted to isolate aryl boronic acid esters directly from this borylation reaction. Gratifyingly, quenching the reaction mixture with neopentyl glycol afforded the corresponding aryl boronic acid ester, as evidenced by ^{11}B NMR spectroscopic analysis (Table 8). The boronic acid ester obtained from 1-iodo-4-methylbenzene was isolated in 95% yield and identified as 5,5-dimethyl-2-*p*-tolyl-1,3,2-dioxaborinane **10b** (Table 8, entry 2). Quenching the above reaction mixture with pinacol also afforded the corresponding pinacol boronic acid ester **10a** in 90% isolated yield (Table 8, entry). However, quenching with ethylene glycol or 1,3-propanediol resulted in the corresponding boronic acid ester contaminated with boronic acids. This result shows that 1,3-dioxaborolane and 1,3-dioxaborinanes are more susceptible to hydrolysis when compared to pinacol esters. In order to expand the scope and generality of this synthesis of aryl boronic

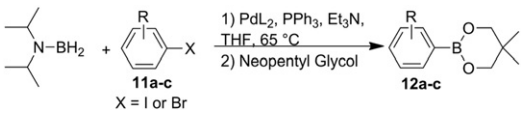
Table 8
Aryl boronic ester synthesis from diols[a]

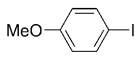
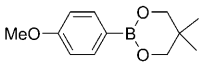
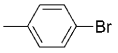
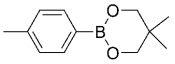
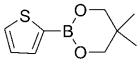


Entry	Diol	Boronic ester	Isolated % yield
1		 **10a**	90
2		 **10b**	95

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl halide, 2 equiv aminoborane, 5 equiv triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphene. Boronic ester was formed by treating the reaction mixture with 6 equiv of a diol.

Table 9
Aryl boronic ester synthesis from $BH_2N(^iPr)_2$, aryl iodides and bromides, and palladium[a]



Entry	Aryl halide	Boronic ester	Isolated % yield
1	 **11a**	 **12a**	99[b]
2	 **11b**	 **12b**	90[c]
3	 **11c**	 **12c**	89[c]

[a] Reactions conducted on a 2.5 mmol scale with 1 equiv aryl halide, 2 equiv aminoborane, 5 equiv triethylamine, 5 mol % palladium catalyst and 20 mol % triphenylphosphene.
[b] $PdCl_2$ catalyst used.
[c] $Pd_2DBA_3 \cdot CHCl_3$ catalyst used.

acid esters, the intermediates obtained from the reaction of various aryl halides with **1** and a palladium catalyst were treated with neopentyl glycol to afford the corresponding neopentyl glycol boronic esters. These results are summarized in Table 9.

Several aryl iodides and bromides could be converted to the corresponding aryl boronic esters with comparable or superior yields to the analogous boronic acids (Table 8). The higher yields obtained for these boronic esters are likely due to increased stability of the hindered boronic acid esters. Isolation of boronic acid esters from the reaction mixture requires a simple quench of the reaction with a diol, such as neopentyl glycol, followed by removal of the palladium by filtration and subsequent extraction of the desired product. On the other hand, isolation of analogous boronic acids required several steps and extreme pHs to obtain a pure product. The harsh conditions required for the isolation of boronic acids likely results in proto-deborination leading to lower isolated yields of the desired compound. Consequently, hydrolytically unstable boronic acids are best isolated as the corresponding boronic acid esters directly from the reaction mixture.

3. Conclusion

The reactivity of aminoborane **1** prepared from LAB reagents was evaluated in the palladium-catalyzed Alcaraz–Vaultier borylation of aryl iodides, bromides, and triflates. It was found that use of **1**, prepared in situ from the corresponding LAB reagent and TMSCl, resulted in the highest yields of the corresponding boronic acids. It was observed that the presence of $LiBH_4$ in this borylation reaction resulted in the precipitation of palladium-black, significantly lowering isolated yields of the desired products. After screening various palladium catalysts, palladium dichloride was found to be the most effective catalyst with aryl iodides. However, $Pd_2DBA_3{\bullet}CHCl_3$ worked the best for aryl bromides and triflates. Depending on the work-up procedure used, we were able to isolate either boronic acids or the corresponding esters from the reaction mixture. When the reaction was subjected to an acid/base work-up the corresponding boronic acid was isolated, whereas boronic acid esters were obtained when the reaction mixture was quenched with a diol, such as neopentyl glycol. Isolation of boronic acids from the reaction of **1** with aryl iodide- and bromide- compounds resulted in moderate to excellent yields. Though the borylation of aryl iodides and bromides was found to be incompatible with many functional groups, the borylation of aryl triflates were highly tolerant to a wide range of functionalities. In summary, a wide variety of boronic acids and esters were synthesized from the corresponding aryl iodides, bromides, and triflates with moderate to excellent yields using mildly synthesized aminoborane **1** and fairly inexpensive palladium catalysts.

4. Experimental section

4.1. General methods

All reactions were performed in oven-dried and argon-cooled glassware. All air and moisture-sensitive compounds were introduced through a rubber septum via a syringe or cannula. Anhydrous THF was distilled from sodium-benzophenone. The aminoboranes used in these reactions were synthesized via published procedures and used in situ without any purification.[10,11] ^1H NMR, ^{13}C NMR, and ^{11}B NMR spectra were recorded at 500 MHz (^1H), 126 MHz (^{13}C), and 165 MHz (^{11}B). All ^{11}B NMR chemical shifts are reported relative to the external standard BF_3/Et_2O (δ=0). All ^1H NMR and ^{13}C NMR chemical shifts are reported in δ units relative to the respective solvent of the NMR sample.

4.2. General procedure for the synthesis of boronic acids from the reaction of aryl iodides, bromides, or triflates with $BH_2N(^iPr)_2$ in the presence of a palladium catalyst

Triphenylphosphene (0.131 g, 0.5 mmol, 20 mol %), *p*-iodoanisol (0.585 g, 2.5 mmol), and triethylamine (1.78 mL, 12.5 mmol) were added to a 50 mL round-bottomed flask equipped with a sidearm, condenser, and stir bar. This solution was then degassed by alternating vacuum and argon three times. Palladium dichloride (0.023 g, 0.13 mmol, 5 mol %) was then added under positive argon pressure. After stirring at room temperature for 15 min, diisopropylaminoborane (5 mL, 1 M solution in THF, 5 mmol) was added and the reaction mixture was degassed again by alternating vacuum and argon three times. The reaction solution was then heated to reflux. After 12 h of reflux the reaction was cooled to 0 °C and 6 mL of methanol was added through the condenser slowly (*Caution*: exothermic reaction with evolution of hydrogen). After 15 min of stirring all the solvent was removed under reduced pressure to yield a black solid. This solid was dissolved with sodium hydroxide (3 M, 8 mL) and subsequently washed with hexanes (3×10 mL). The aqueous layer was then cooled to 0 °C (ice bath) and acidified to pH ≤1 with concentrated HCl, with the boronic acid usually precipitating out as a white solid. The aqueous fraction was then extracted with diethyl ether (3×10 mL). The organic fractions were combined, dried with magnesium sulfate and filtered. The solvent was then removed under reduced pressure yielding a white solid.

4.3. General procedure for the synthesis of an aryl boronic ester from the reaction of aryl iodides or bromides with $BH_2N(^iPr)_2$ in the presence of a palladium catalyst

Triphenylphosphine (0.131 g, 0.5 mmol, 20 mol %), *p*-iodoanisol (0.585 g, 2.5 mmol), and triethylamine (1.78 mL, 12.5 mmol) were added to a 50 mL round-bottomed flask equipped with a sidearm, condenser, and stir bar. This solution was then degassed by alternating vacuum and argon three times. Palladium dichloride (0.023 g, 0.13 mmol, 5 mol %) was then added under positive argon pressure. After stirring at room temperature for 15 min diisopropylaminoborane (5 mL, 1 M THF, 5 mmol) was added and the reaction mixture was degassed again by alternating vacuum and argon three times. The reaction solution was then heated to reflux. After 12 h of reflux the reaction was cooled to 0 °C and neopentyl glycol (6 mL, 1 M solution in THF, 6 mmol) was slowly added through the condenser. After warming to 25 °C and stirring for 15 min. 1 M HCl (6 mL) was added and the mixture was filtered through a pad of Celite. The mixture was then extracted with diethyl ether (3×10 mL), combining all the organic fractions together. The organic fractions were then washed with a brine solution (2×10 mL), dried with magnesium sulfate and filtered. The solvent was removed under reduced pressure yielding 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane as a yellow oil.

4.4. Spectral data

*4.4.1. 4-Methoxyphenylboronic acid (**5a**) (**7a**) (**9a**)[21].* Off-white solid, ^1H NMR (500 MHz, MeOH-d_4) δ 3.74 (s, 1H), 6.84 (d, 2H, J=8.5 Hz), 7.64 (d, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 53.9, 112.7, 135.2, 161.5; ^{11}B NMR (160 MHz, MeOH) δ +28.7; EM (ESI): m/z (M+) calcd for $C_9H_{14}BO_3$ 181.10260, found 181.10305.

*4.4.2. 4-Tolylboronic acid (**5b**) (**7b**) (**9b**)[21].* Off-white solid, ^1H NMR (500 MHz, $CDCl_3$) δ 2.45 (s, 3H), 7.33 (d, 2H, J=8.0 Hz), 8.14 (d, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 128.9, 133.7, 135.9,

143.1; ^{11}B NMR (160 MHz, MeOH) δ +29.1; EM (ESI): m/z (M+) calcd for $C_9H_{14}BO_2$ 165.11054, found 165.10814.

*4.4.3. 2-Tolylboronic acid (**5c**) (**7c**) (**9c**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.86 (s, 3H), 7.31 (d, 1H, J=8.0 Hz), 7.35 (t, 1H, J=7.5 Hz), 7.49 (t, 1H, J=7.5 Hz), 8.26 (d, 1H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.3, 125.4, 130.8, 132.4, 137.5, 146.5; ^{11}B NMR (160 MHz, MeOH) δ +28.5; EM (ESI): m/z (M+) calcd for $C_9H_{13}BNaO_2$ 187.10383, found 187.09008.

*4.4.4. Phenylboronic acid (**5d**) (**7d**) (**9e**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (t, 2H, J=7.5 Hz), 7.62 (t, 1H, J=7.5 Hz), 8.27 (d, 2H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 128.1, 132.9, 135.8; ^{11}B NMR (160 MHz, MeOH) δ +28.5; EM (ESI): m/z (M+) calcd for $C_8H_{12}BO_2$ 151.08092, found 151.09249.

*4.4.5. 4-Fluorophenylboronic acid (**5e**) (**7e**) (**9g**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (t, 2H, J=9.0 Hz), 8.24 (t, 2H, J=8.5 Hz); ^{13}C NMR (125 MHz, MeOD) δ 112.2 (d, J_F=20 Hz), 134.0 (d, J_F=8 Hz) 162.7 (d, J_F=246 Hz); ^{11}B NMR (160 MHz, MeOD) δ +28.5; EM (ESI): m/z (M+) calcd for $C_8H_{11}BO_2F$ 169.08972, found 169.08307.

*4.4.6. 3-Fluoro-4-methylphenylboronic acid (**5f**).* Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 2.21 (s, 3H), 7.13 (t, 1H, J=7.0 Hz), 7.29 (s, 1H), 7.35 (s, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 14.7, 120.7, 120.8, 130.6, 132.1, 162.6 (d, J_F=242); ^{11}B NMR (160 MHz, MeOH-d_4) δ +28.8; EM (ESI): m/z (M+) calcd for $C_9H_{13}BFO_2$ 183.10495, found 183.09872.

*4.4.7. 3-Cyanophenylboronic acid (**5g**)*[22]. Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.45 (t, 1H, J=8.0 Hz), 7.67 (d, 1H, J=8.0 Hz) 7.96 (m, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 111.2, 118.7, 128.1, 133.0, 137.1, 137.9; ^{11}B NMR (160 MHz, MeOH-d_4) δ +27.6.

*4.4.8. Thiopen-2-ylboronic acid (**5h**) (**7g**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.13 (s, 1H), 7.59 (s, 2H); ^{13}C NMR (125 MHz, MeOH-d_4) 127.4, 130.9; ^{11}B NMR (160 MHz, MeOH-d_4) δ +26.8; EM (ESI): m/z (M+) calcd for $C_4H_5BO_2S$ 157.05865, found 157.04891.

*4.4.9. (E)-Styrylboronic acid (**7f**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 6.18 (d, 1H, J=18.0 Hz), 7–7.3 (m, 5H) 7.42 (d, 1H, J=7.0 Hz); ^{13}C NMR (125 MHz, MeOH-d_4) δ 126.6, 127.6, 127.9, 128.3, 137.8, 146.9; ^{11}B NMR (160 MHz, MeOH-d_4) δ +32.4; EM (ESI): m/z (M+) calcd for $C_8H_9BNaO_2$ 171.05905, found 171.05878.

*4.4.10. Thiophen-3-ylboronic acid (**7h**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.28 (s, 1H) 7.36 (s, 1H) 7.84 (s, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 124.6, 127.3, 131.6, 134.3; ^{11}B NMR (160 MHz, MeOH-d_4) δ +27.0.

*4.4.11. 3,4-Dimethylphenylboronic acid (**9d**).* Off-white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (s, 3H), 2.65 (s, 3H), 7.54 (s, 1H), 8.24 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.0, 20.5, 128.2, 129.7, 133.7, 136.3, 137.0, 141.8; ^{11}B NMR (160 MHz, MeOH) δ +29.3; EM (ESI): m/z (M+) calcd for $C_8H_{11}BNaO_2$ 173.07764, found 173.07443.

*4.4.12. 4-Chlorophenylboronic acid (**9f**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOD) δ 5.70 (d, 2H, J=7.0 Hz), 6.04 (d, 2H, J=6.5 Hz); ^{13}C NMR (125 MHz, MeOD) δ 125.7, 133.4; ^{11}B NMR (160 MHz, MeOD) δ +30.4; EM (ESI): m/z (M+) calcd for $C_6H_{11}BClO_2$ 185.04943, found 185.05351.

*4.4.13. 4-Cyanophenylboronic acid (**9h**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOD) δ 7.04 (d, 2H, J=8.0 Hz), 7.23 (d, 2H, J=8.5 Hz); ^{13}C NMR (125 MHz, MeOD) δ 116.8, 129.0, 132.4; ^{11}B NMR (160 MHz, MeOD) δ +28.3; EM (ESI): m/z (M+) calcd for $C_9H_{11}BNO_2$ 176.09440, found 176.08774.

*4.4.14. Naphthalen-2-ylboronic acid (**9i**)*[21]. Off-white solid, ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.48 (m, 2H), 7.76–7.89 (m, 4H), 8.24 (m, 1H); ^{13}C NMR (125 MHz, MeOH-d_4) δ 126.8, 127.7, 128.7, 129.6, 131.4, 135.7; ^{11}B NMR (160 MHz, MeOH-d_4) δ +29.3; EM (ESI): m/z (M+) calcd for $C_{12}H_{13}BNaO_2$ 223.09631, found 223.09008.

*4.4.15. 4,4,5,5-tetramethyl-2-p-tolyl-1,3,2-dioxaborolane (**10a**)*[23]. Yellow Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38 (s, 8H), 2.40 (s, 3H), 7.23 (d, 2H, J=8.0 Hz), 7.77 (d, 2H, J=8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.8, 24.9, 83.7, 128.7, 135.0, 141.5; ^{11}B NMR (160 MHz, $CDCl_3$) δ +31.3.

*4.4.16. 2-(4-methylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**10b**)*[6b,7a,20a]. Yellow Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 6H), 2.41 (s, 3H), 3.80 (s, 4H), 7.23 (d, J=8.0 Hz), 7.77 (d, 2H, J=6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 22.0, 31.9, 72.4, 128.5, 134.1, 140.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ +27.1; EM (ESI): m/z (M+) calcd for $C_{12}H_{18}BO_2$ 205.14448, found 205.13944.

*4.4.17. 2-(4-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**12a**)*[6b,7a,20a]. Yellow Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 6H), 3.76 (s, 4H), 3.80 (s, 3H), 6.92 (d, 2H, J=8.5 Hz), 7.83 (d, 2H, J=9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 32.0, 55.1, 72.4, 113.4, 128.9, 132.4, 135.9, 162.1; ^{11}B NMR (160 MHz, $CDCl_3$) δ +27.0; EM (ESI): m/z (M+) calcd for $C_{12}H_{18}BO_3$ 221.12795, found 221.13435.

*4.4.18. 2-(4-methylphenyl)-5,5-dimethyl-1,3,2-dioxaborinane (**12b**)*[6b,7a,20a]. Yellow Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10 (s, 6H), 2.41 (s, 3H), 3.80 (s, 4H), 7.23 (d, J=7.5 Hz), 7.78 (d, 2H, J=5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.7, 22.0, 31.9, 72.4, 128.5, 134.1, 140.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ +27.1; EM (ESI): m/z (M+) calcd for $C_{12}H_{18}BO_2$ 205.14448, found 205.13944.

*4.4.19. 5,5-dimethyl-2-(thiophen-2-yl)-1,3,2-dioxaborinane (**12c**)*[6b,7a,20a]. Yellow Oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 6H), 3.77 (s, 4H), 7.20 (s, 1H), 7.58 (s, 1H), 7.63 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.9, 72.5, 128.2, 131.5, 135.8; ^{11}B NMR (160 MHz, $CDCl_3$) δ +25.5; EM (ESI): m/z (M+) calcd for $C_9H_{14}BO_2S$ 197.08817, found 197.08021.

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