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# Palladium-catalyzed borylation of L-tyrosine triflate derivative with pinacolborane: practical route to 4-borono-L-phenylalanine (L-BPA) derivatives

Shinya Iimura *, Wenxue Wu *

*Chemical Development, Lexicon Pharmaceuticals, 350 Carter Road, Princeton, NJ 08540, USA*

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ABSTRACT

Efficient palladium-catalyzed borylation of protected L-tyrosine triflate with pinacolborane was achieved despite previous reports to the contrary. In addition to the use of an inexpensive boron source, the reaction was carried out in the presence of only 0.5 mol % palladium catalyst. Furthermore, the borylation can be performed using pinacolborane prepared in situ from pinacol and borane–diethylaniline complex. This represents a practical entry to 4-borono-L-phenylalanine (L-BPA) derivatives.



4-Boronophenylalanine (BPA)[1] and its derivatives have attracted much interest in medicinal as well as in synthetic communities. $^{10}$B-enriched BPA, especially the L isomer (L-$^{10}$BPA),[2] has been extensively studied for the treatment of melanoma, glioma, and other tumors in Boron Neutron Capture Therapy (BNCT).[3] L-BPA-containing peptides[4] may be used as precursors to tritiated phenylalanine-containing peptides[4a] or as potential biosensors.[4c] Additionally, L-BPA derivatives have been extensively employed as building blocks for the synthesis of biologically interesting molecules.[5] As a result, quite a few synthetic approaches to these compounds have been reported over the last two decades.[5a,6] Among the existing synthetic methods, borylation of a tyrosine triflate appears to be one of the most straightforward approaches. In fact, borylation of a tyrosine triflate derivative using bis(pinacolato)diboron was reported.[6f] Although this borylation proceeded smoothly under Miyaura's conditions,[7] a high catalyst loading (8 mol %) was used. Additionally, the reagent bis(pinacolato)diboron is expensive and not atom-economical as only half of the boron is active. To improve the efficiency of this approach, inexpensive pinacolborane was also employed.[8,9] However, this reaction appeared to be rather challenging with protected tyrosine triflates (**1a, 1c, and 1d**) according to the literature reports (Table 1).[5a,6h] Therefore, the borylation with pinacolborane was achieved using more expensive iodophenylalanine derivatives (**1b** and **1e**) and a relatively high catalyst loading (3 mol %). Encouraged by a recent progress on transition metal-catalyzed borylation,[10] we decided to revisit this reaction using the more readily available L-tyrosine triflate derivatives.

We chose triflate **1a**[11] as the model substrate for our investigations. Initial catalyst screening results indicated that the problem was not only the reactivity of the triflate, but also the formation of the reduction side product **3** (Table 2, entries 1 and 2).[8] A recently reported nickel-based catalyst system was also ineffective in this case (entry 3).[12] Surprisingly, the reaction proceeded smoothly to give the desired product **2a** in good yields under standard Masuda conditions (entries 4 and 5),[8] contrary to the unsuccessful result reported previously under very similar conditions (Table 1, substrate **1a**). Further optimizations indicated that solvent had a minor effect on the reaction, with dioxane being slightly better than other solvents (entries 5–8). On the other hand, selection of the base was critical for the control of side product **3** (entries 5, 9–15). Tertiary amines such as triethylamine, diisopropylethylamine, and *N*-methylmorpholine (NMM) gave excellent results, whereas strongly coordinating bases such as DABCO and DMAP as well as inorganic bases such as potassium acetate, potassium carbonate, and cesium carbonate gave **3** as the predominant product (entries 11–15). Though an undesired side reaction for the borylation, the reduction could be further exploited for the deoxygenation of the substituted tyrosines via triflates.[13]

With the solvent (dioxane) and base (NMM) selected, additional catalyst screening was performed. As the data in Table 3 indicate that $PdCl_2$(dppf) is a superior catalyst for this transformation (entries 1–8). Although DPEphos (**4**) was reported to be good ligands for borylation of halides with pinacolborane,[14] it did not perform well in this reaction (entry 7). The reaction did not proceed at all when $PdCl_2$ was used (entry 9), probably due to its low solubility in the solvent system. $NiCl_2$(dppf) was also inactive for the reaction despite a higher catalyst loading (entry 10). It is worth noting that $PdCl_2$(dppf) catalyst loading can be reduced from 3 mol % to only 0.5 mol % without problems (Table 3, entries 1, 11, and 12).[15] In fact, the conversion seemed to improve slightly as the catalyst loading was decreased from 3 mol % to 0.5 mol %. To the best of our knowledge, this is the first example for Miyaura–Masuda borylation of an aryl triflate using such a low-catalyst loading.[16] The data in Table 3 also suggest that the reaction may be sensitive to the base/pinacolborane charges as well as their ratio. Thus, the reaction slowed considerably when the amount of pinacolborane

* Tel.: +1 609 466 6080; fax: +1 609 466 3562 (S.I.).
*E-mail address:* siimura@lexpharma.com (S. Iimura).

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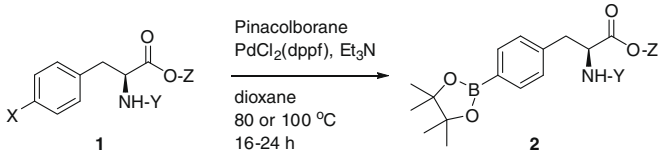
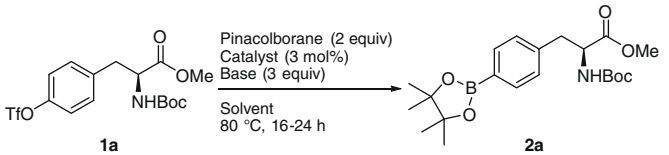
**Table 1**
Previously reported borylation of tyrosine triflate derivatives with pinacolborane

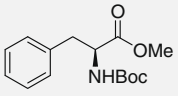



| Substrate | X | Y | Z | Yield (%) | Ref. |
|---|---|---|---|---|---|
| **1a** | OTf | Boc | Me | <5 (**2a**) | 5a |
| **1b** | I | Boc | Me | 72 (**2a**) | 5a |
| **1c** | OTf | Cbz | Bn | Very poor (**2b**) | 6h |
| **1d** | ONf | Cbz | Bn | 58 (**2b**) | 6h |
| **1e** | I | Cbz | Bn | 82 (**2b**) | 6h |

**Table 2**
Initial screening for borylation of **1a** with pinacolborane




| Entry | Catalyst | Base | Solvent | Yield[a] (%) | | |
|---|---|---|---|---|---|---|
| | | | | **2a** | **3** | **1a** |
| 1 | $Pd(PPh_3)_4$ | NMM | Dioxane | 5 | 4 | 91 |
| 2[b] | $Pd(OAc)_2/PCy_3$ | $Et_3N$ | Dioxane | 6 | 12 | 82 |
| 3[c] | $NiCl_2(dppp)_2$ | $Et_3N$ | Toluene | <5 | — | — |
| 4[d] | $PdCl_2(dppf)$ | $Et_3N$ | Dioxane | 69[e] | 9 | 13 |
| 5 | $PdCl_2(dppf)$ | $Et_3N$ | Dioxane | 87 | 6 | 7 |
| 6 | $PdCl_2(dppf)$ | $Et_3N$ | ACN | 85 | 13 | 2 |
| 7 | $PdCl_2(dppf)$ | $Et_3N$ | Toluene | 79 | 13 | 8 |
| 8 | $PdCl_2(dppf)$ | $Et_3N$ | MeTHF | 83 | 9 | 8 |
| 9 | $PdCl_2(dppf)$ | *i*-$Pr_2NEt$ | Dioxane | 82 | 8 | 10 |
| 10 | $PdCl_2(dppf)$ | NMM | Dioxane | 88 | 4 | 7 |
| 11 | $PdCl_2(dppf)$ | DABCO | Dioxane | 9 | 73 | 18 |
| 12 | $PdCl_2(dppf)$ | DMAP | Dioxane | 0 | 99[f] | 1 |
| 13 | $PdCl_2(dppf)$ | KOAc | Dioxane | 3 | 97 | 0 |
| 14 | $PdCl_2(dppf)$ | $K_2CO_3$ | Dioxane | 21 | 79 | 0 |
| 15 | $PdCl_2(dppf)$ | $Cs_2CO_3$ | Dioxane | 3 | 97 | 0 |

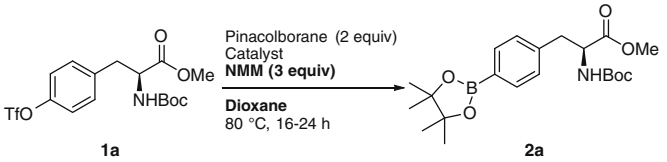



[a] HPLC yield.
[b] $Pd(OAc)_2$, 2.5 mol %; $PCy_3$, 5 mol %.
[c] $NiCl_2(dppp)$, 10 mol %; dppp, 10 mol %.
[d] Pinacolborane (1.5 equiv), 100 °C.
[e] 63% isolated yield.
[f] 98% isolated yield.

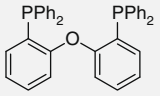
alone was reduced (entry 13), whereas it was unchanged when the amount of NMM alone was reduced (entry 14). Moreover, the yield was unchanged when both pinacolborane and the base amounts were reduced (entry 15). These interesting findings suggest that there may be some subtleties in the mechanism of borylation using pinacolborane. Importantly, under the optimized conditions (1.5 equiv pinacolborane), the isolated yield was 94% after chromatography (entry 15).

The product **2a** thus prepared proved to be enantiopure by chiral HPLC, suggesting that no racemization occurred during the borylation reaction. It is worth noting that a lower chiral purity (94% ee) of **2a** was reported for the reaction of the iodide substrate **1b**.[5a] These results indicate that the present reaction conditions can preserve the stereochemical integrity of a base-sensitive chiral

**Table 3**
Optimization for borylation of **1a** with pinacolborane

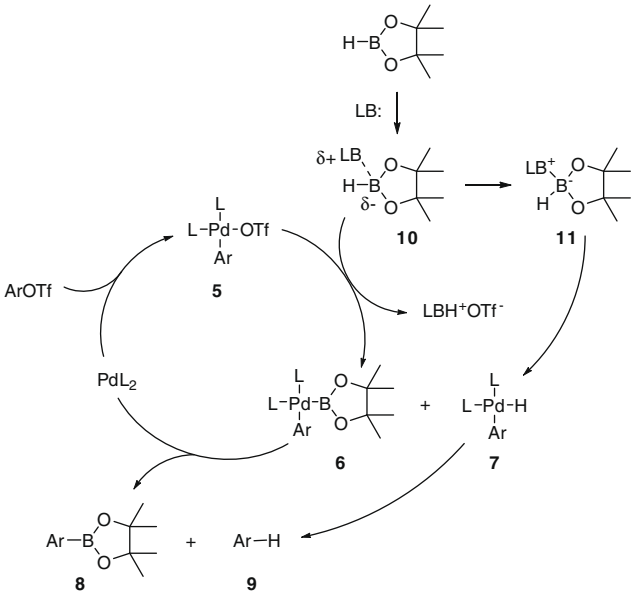



| Entry | Pd catalyst/ligand (mol %) | Yield[a] (%) | | |
|---|---|---|---|---|
| | | **2a** | **3** | **1a** |
| 1 | $PdCl_2(dppf)$ (3) | 88 | 4 | 7 |
| 2 | $PdCl_2(PCy_3)_2$ (3) | 0 | 0 | — |
| 3 | $Pd(OAc)_2$ (3) | 2 | 15 | 83 |
| 4 | $Pd(OAc)_2$ (3)/dppf (3) | 60 | 9 | 31 |
| 5 | $Pd(OAc)_2$ (3)/dppp (3) | 42 | 9 | 49 |
| 6 | $Pd(OAc)_2$ (3)/dppb (3) | 34 | 10 | 56 |
| 7 | $Pd(OAc)_2$ (3)/**4** (3) | 34 | 5 | 61 |
| 8 | $Pd(OAc)_2$ (3)/BINAP (3) | 10 | 4 | 86 |
| 9 | $PdCl_2$ (3)/dppf (3) | 0 | 0 | 100 |
| 10 | $NiCl_2(dppf)$ (5) | 0 | 0 | 100 |
| 11 | $PdCl_2(dppf)$ (2) | 90 | 4 | 6 |
| 12 | $PdCl_2(dppf)$ (0.5) | 95 | 3 | 2 |
| 13[b] | $PdCl_2(dppf)$ (0.5) | 60 | 3 | 36 |
| 14[c] | $PdCl_2(dppf)$ (0.5) | 97 (95)[d,e] | 1 | 2 |
| 15[b,c] | $PdCl_2(dppf)$ (0.5) | 96 (94)[d,e] | 2 | 1 |

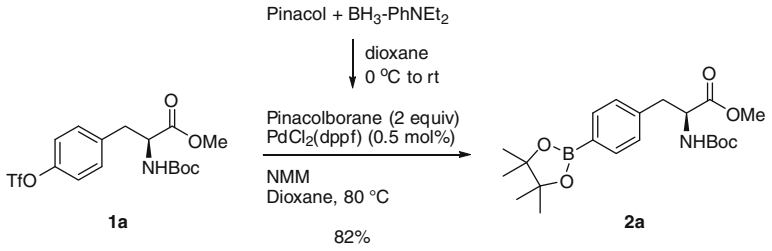



[a] HPLC yield.
[b] Pinacolborane (1.5 equiv).
[c] NMM (1 equiv).
[d] Isolated yield.
[e] >99% ee.

center. While it is unclear why the reaction was not successful in the previous attempts,[5a,6h] a working mechanism improved upon that proposed by Masuda[8b] can be used to explain the sensitivities of the reaction profile to the type of bases (Scheme 1). Oxidative addition of the active palladium (0) species to form the palladium (II) intermediate (**5**) is unlikely a rate-limiting step in this reaction. During the rate-limiting transmetalation step, either the pin-




**Scheme 1.** Possible working mechanism for the borylation.




**Scheme 2.** Borylation using pinacolborane prepared in situ.

acolboron or the hydrogen atom can be transferred to give species **6** and **7**, respectively, which upon fast reductive eliminations result in borylation product **8** and reduction product **9**, respectively. We propose that the bases employed in this reaction may form complexes **10** and **11** with pinacolborane depending on the Lewis basicity of the bases employed. A weakly coordinating Lewis base, such as trialkylamines, likely forms the weakly bound complex **10** whereas a strongly coordinating Lewis base, such as DABCO and DMAP, likely forms the strongly bound complex **11**. Due to the oxophilic nature of boron, the oxygen-centered bases possibly also form the strongly bound complex **11**. The weakly bound complex **10** activates the borylation pathway, whereas the strongly bound 'ate' complex **11** prefers the hydride transfer pathway.[17] This mechanism is consistent with the results summarized in Table 2.

In order to further improve the efficiency of the reaction for large-scale manufacture, it was carried out using pinacolborane prepared in situ (Scheme 2). The less active and more stable borane–diethylaniline complex was shown to be optimal for this pinacolborane preparation.[18] The reaction proceeded to give **2a** in 82% isolated yield.

In conclusion, an efficient borylation of a tyrosine triflate was achieved with the use of the inexpensive pinacolborane reagent in excellent yields and without racemization. Contrary to the previous reports, modified Masuda conditions were sufficient to achieve satisfactory results. The catalyst loading can be reduced to as low as 0.5 mol %. Additionally, the borylation can be carried out using pinacolborane prepared in situ from borane–diethylaniline complex, further reducing the cost. This work provides a practical and concise synthesis of protected 4-boronophenylalanine, which can be either used directly as a building block in Suzuki coupling reactions or converted to L-BPA using known procedures.[6g]

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## Supplementary data

General methods, typical borylation procedure, preparative procedure of **1a**, copies of $^{1}H$ and $^{13}C$ NMR spectra of compounds **1a**, **2a**, and **3**, and chiral HPLC chromatograms for **2a** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.006.

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