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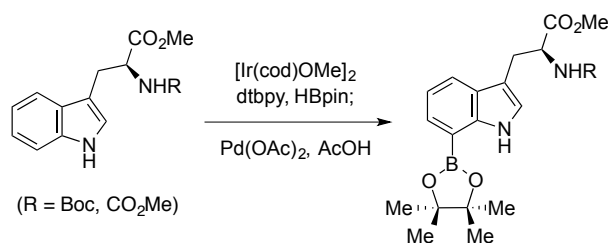
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## C7-Derivatization of C3-Alkylindoles Including Tryptophans and Tryptamines

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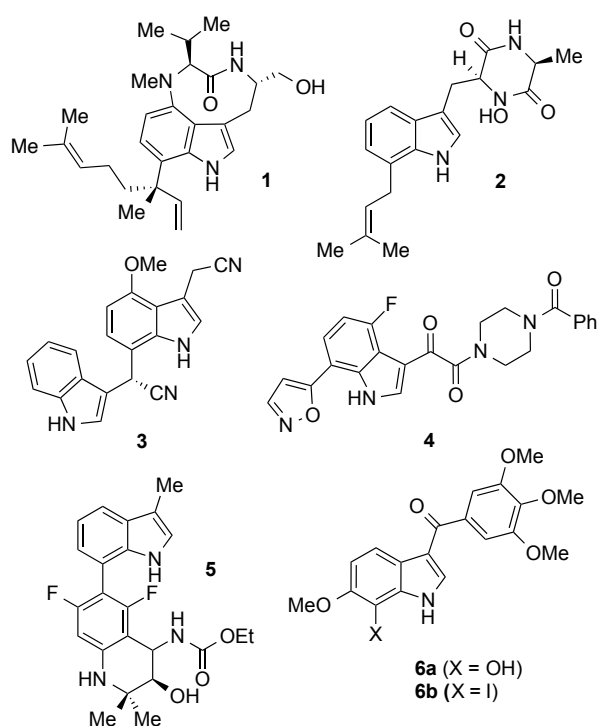


## Abstract Graphic

## Abstract

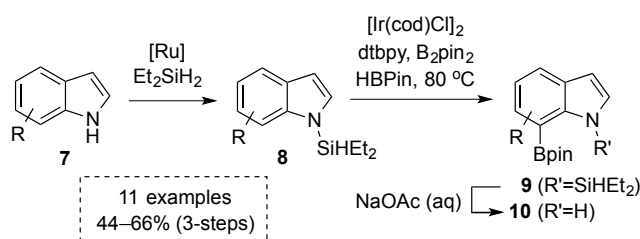
A versatile strategy for C7-selective boronation of tryptophans, tryptamines, and 3-alkylindoles, by way of a single-pot C2/C7-diboronation–C2-protodeboronation sequence is described. The combination of a mild iridium-catalyzed C2/C7-diboronation followed by an in situ palladium-catalyzed C2-protodeboronation allows efficient entry to valuable C7-boroindoles that enable further C7-derivatization. The versatility of the chemistry is highlighted by the gram-scale synthesis of C7-boronated *N*-Boc-L-tryptophan methyl ester and the rapid synthesis of C7-halo, C7-hydroxy, and C7-aryl tryptophan derivatives.

Indole derivatives are prevalent in many natural products and pharmaceutical compounds, often as complex tryptophan- and tryptamine-derived substructures.<sup>1</sup> The demand for such diversely substituted indolic structures has led to the development of ever more efficient and direct methods for their synthesis, none more so than in the nascent field of C–H functionalization.<sup>2–6</sup> Within this realm, some inventive and practical chemistry has been developed to functionalize different positions around the indole ring, mainly through the innate reactivity of the C2,<sup>3</sup> C3,<sup>4</sup> and C5<sup>5</sup> sites, and to a lesser extent C4 and C6.<sup>6</sup> The growing number of structurally and biologically fascinating natural and unnatural products bearing an indole substituent at C7 (i.e. **1–6**, Figure 1), has generated further interest in methods that expedite functionalization at this position.<sup>7–11</sup> Many such targets, including chloropectin I,<sup>8</sup> the teleocidins (i.e. **1**),<sup>9</sup> the indole-glyoxamide class of HIV-1 attachment inhibitors (i.e. **4**),<sup>10</sup> and the 3-aryloindole isosteres of combretastatin (**6**),<sup>11</sup> have been shown to exhibit potent biological activities.



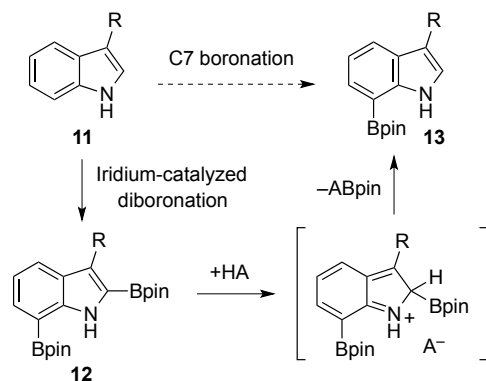
**Figure 1.** Representative biologically active C7-substituted indoles.

Selective C7 indole functionalization has proven particularly challenging in the case of tryptamine and tryptophan derivatives. In the latter case, the most commonly used strategies target 7-bromotryptophan, which requires either enzymatic processes<sup>12</sup> or a multistep synthesis from 7-bromoindole.<sup>9g,13</sup> Our group's continuing goal to unearth and expand new avenues for the elaboration of complex indole-derived natural products spurred our interest in addressing this challenge.<sup>14</sup> Herein we wish to report a practical and versatile one-pot method for C7 boronation of C3-substituted indoles, including tryptophans and tryptamines, in turn permitting rapid C7 indole functionalization via the corresponding C7-boronated products.



**Scheme 1.** Silane-directed C7 boronation of indoles.

In the last decade, important inroads into C7 indole functionalization have been made through metal-catalyzed arene and heteroarene C–H boronations.<sup>15,16</sup> Of particular relevance to us were the reports into iridium-catalyzed indole boronations,<sup>17</sup> which Smith<sup>17c</sup> and later James<sup>17e</sup> showed would proceed selectively at C7 in the presence of C2 substituents to block the inherently greater azole reactivity. An interesting substrate in Smith's study was 2-trimethylsilyl indole, which was boronated in 76% yield under their conditions, with subsequent desilylation affording a 7-boroindole in 88% yield.<sup>17c</sup> Then in 2010, Hartwig's group utilized a variant of their hydrosilyl-directed *ortho*-boronation chemistry<sup>18,19</sup> as a platform for the first truly C7-selective boronation reaction. Their 3-step methodology exploited the N1-appended silane directing group on indole **8** to enable regioselective boronation to 7-boroindole **9** (Scheme 1).<sup>18c</sup>

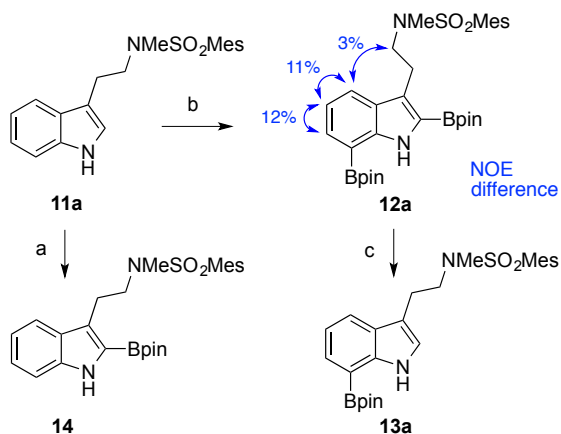


**Scheme 2.** Planned synthesis of C7-borotryptamines.

Inspired by these studies, we sought to develop a more streamlined process for direct conversion of tryptamines and tryptophans to the corresponding C7-boronated indoles. By taking advantage of the more nucleophilic/basic C2 position of these C3-substituted indoles (i.e. **11**), we have now been able to fashion a two-step, one pot procedure for C7-selective boronation. This methodology provides an expedient means for C7 derivatization of these compounds on a large scale through direct activation of unfunctionalized tryptamines and tryptophans. The premise behind this diboronation/protodeboronation sequence was our recognition of the high propensity of five-membered heterocycles to readily undergo C2 protodeboronation.<sup>20–24</sup> Indeed, this oft-maligned side reaction of Suzuki–Miyaura cross couplings involving C2-boronated indoles,<sup>14a,g,21a–h</sup> furans<sup>22</sup> and thiophenes,<sup>23</sup> has been extensively studied in acidic media.<sup>24</sup> Thus, a synthetic operation was envisioned involving iridium-catalyzed boronation of C3-substituted indole **11**, first at C2,<sup>17</sup> and then C7, to give diboronated indole **12**, followed by acidic workup to induce ipso-protonation, re-aromatization, and cleavage of the carbon–boron bond to afford 7-boroindole **13** (Scheme 2).

During initial investigations into the diboronation of tryptamine, introduction of a mesitylsulfonyl on the amine side chain helped avoid some of the undesired aryl boronations that we first observed when utilizing phthalimido,<sup>25</sup> benzenesulfonyl or *p*-nitrobenzenesulfonyl protective groups. Furthermore, the

use of  $N^\alpha$ -methylated mesitylsulfonamide **11a** (Scheme 3) would also permit direct mapping of a C7-derivatized tryptamine onto many of the biologically interesting cyclotryptamine natural products that carry an  $N^\alpha$ -methyl substituent.<sup>26</sup> As confirmation of the order of ring boronation, exposure of tryptamine **11a** to 1 equivalent of boronating reagent, in conjunction with 2 mol% [Ir(cod)OMe]<sub>2</sub> and 4 mol%, 4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy), delivered the C2-boronated product **14** in 68% yield (Scheme 3). Under these conditions, a minor amount (<10%) of the 2,7-diboronated product **12a** was also generated, an observation previously noted by James and coworkers in their microwave-assisted C2-boronation of *N*-Boc-tryptophan methyl ester.<sup>17e</sup> In our case, inclusion of a second equivalent of bis(pinacolato)diboron under the same conditions (see (a), Scheme 3) led to substantial decomposition. Attempts to remedy this by extending the reaction time to 16 h at ambient temperature however only increased slightly the conversion to 2,7-diborotryptamine **12a**, with 2-borotryptamine **14** still the major product. While switching to *n*-hexane as solvent and using higher catalyst loadings improved substantially the conversion of precursor **11a** to the desired product **12a** (>75% by NMR), these more forcing conditions led to only 27% yield of the desired product being isolated. After further optimization, tetrahydrofuran (see conditions (b), Scheme 3) proved to be the optimal solvent for full incorporation of the second boron at C7, delivering tryptamine **12a** in 80% yield. At slightly elevated reaction temperatures and/or prolonged times, triboronated tryptamine, resulting from further boronation at C5 of diborotryptamine **12a**, was also observed in minor amounts. Our regiochemical assignment of the two newly formed carbon–boron bonds in compound **12a** was confirmed by 1D NOE difference experiments (Scheme 3).



**Scheme 3.** Initial screening of C2/C7 boronations. Conditions: (a)  $[\text{Ir}(\text{cod})\text{OMe}]_2$  (2 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mol%),  $(\text{Bpin})_2$  (1 equiv),  $\text{CH}_2\text{Cl}_2$ , 60 °C, 3 h, 68%. (b)  $[\text{Ir}(\text{cod})\text{OMe}]_2$  (2 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4 mol%),  $(\text{Bpin})_2$  (2 equiv), THF, 65 °C, 20 h, 80%. (c) TFA (10 equiv),  $\text{CH}_2\text{Cl}_2$ , 23 °C, 15 min, 81%.

Guided by the wealth of literature on acid-promoted protodemetalations of heteroarenes,<sup>21o,22e,23b,24,27,28</sup> we were then able to extend our diboronation procedure to one that also included in situ C2 protodeboronation. After initial success in converting diboroindole **12a** into 7-boroindole **13a** by simple exposure to trifluoroacetic acid (i.e. conditions (c) in Scheme 3),<sup>28</sup> we then explored using the same conditions once the C2/C7 diboronation of tryptamine **11a** (i.e. conditions (a) in Scheme 3) had been allowed to run its course. To minimize bis-protodeboronation and recovery of starting material **11a**, the reaction mixture was first diluted with dichloromethane prior to addition of trifluoroacetic acid. Gratifyingly, addition of an equal volume (relative to tetrahydrofuran) of trifluoroacetic acid at 0 °C to a 3:2 (v:v) dichloromethane–THF solution afforded 7-borotryptamine **13a** in 60% yield (entry 1, Table 1).

Entry	Substrate	Product	Yield <sup>a</sup>
1 <sup>b</sup>			60%
2			66%
3			54% 58% <sup>c</sup>
4			84% 82% <sup>d</sup> 72% <sup>c</sup>
5			63%

<sup>a</sup> Isolated yield after purification. <sup>b</sup> Boronation conducted at 80 °C.

<sup>c</sup> 2<sup>nd</sup> step: Pd(OAc)<sub>2</sub> (5 mol%), AcOH, 30 °C. <sup>d</sup> Gram-scale reaction.

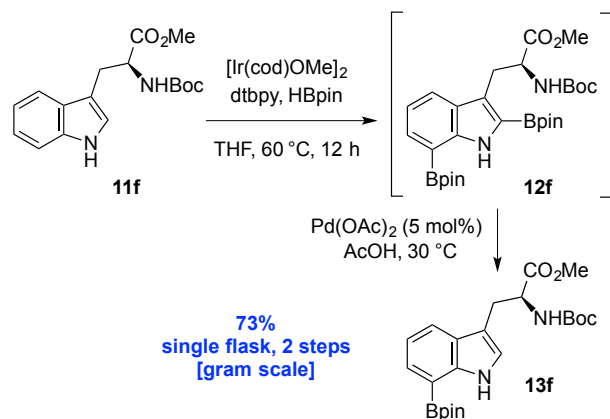
**Table 1.** Rapid synthesis of C7-boronated 3-substituted indole derivatives.

We next focused on applying our one pot diboronation/protodeboronation regimen to other valuable C3-substituted indole derivatives (Table 1).<sup>29</sup> We were pleased to confirm that changing the tryptamine protective group to a methyl carbamate in substrate **11b** was in no way detrimental to the outcome of our reaction, and improved our yield of 7-borotryptamine to 66% for carbamate **13b** (entry 2). We also found that the time and temperature for initial diboronation could be tempered without needing to increase the stoichiometry of reagents. Apart from tryptamine **11a** (entry 1, Table 1), a temperature of



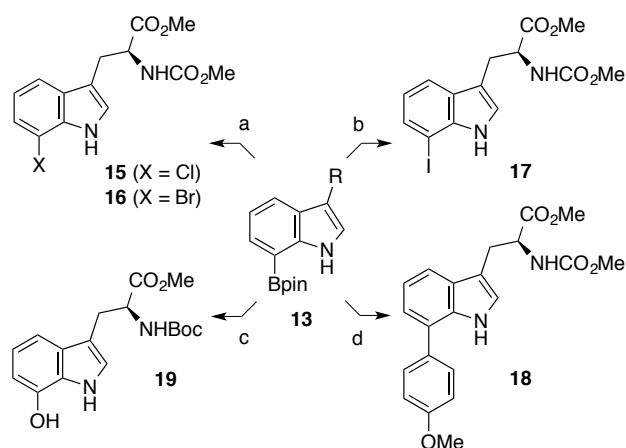
60 °C and reaction time of 4–7 h was found to be ideal for most of the diborinations (entries 2–5, Table 1).<sup>30,31</sup> The applicability of this protocol to other 3-substituted indoles was also highlighted by the efficient conversion of indoles **11c** and **11e** to 7-boroindoles **13c** and **13e**, respectively (entries 3 and 5). In the latter case (entry 5), the presence of a primary alcohol did not impede diboronation of tryptophol **11e** from proceeding just as efficiently as was observed with 3-methylindole **13c**, as evidenced by the 63% yield for 7-borotryptophol **13e**. Importantly, selective boronation of tryptophan derivative **11d** to the corresponding 7-borotryptophan **13d** was achieved in 84% yield (entry 4).

It should be noted that in all these examples the only other side product recovered from the two-step sequence was a minor amount of starting material **11a–e** (<5%). The fact that traces of starting material **11a** were also observed upon converting pure 2,7-diborotryptamine **12a** to 7-borotryptamine **13a** suggested that the conditions in the second step may cause unwanted C7 protodeboronation. This led us to focus our efforts on further optimization of the C2 protodeboronation step. More specifically, to make our process more amenable to *N*<sup>α</sup>-Boc-protected tryptophans,<sup>17d,e</sup> it was deemed necessary to move toward a milder protodeboronation that obviated the use of trifluoroacetic acid.



**Scheme 4.** Optimized C7 boronation of *N*-Boc-tryptophan.

The diboronation of *N*-Boc-tryptophan methyl ester **11f** proceeded smoothly under the optimal iridium-catalyzed conditions (Scheme 4). Diborotryptophan **12f** could be isolated by concentration of the reaction mixture and purified by flash column chromatography in ca. 88% yield.<sup>32</sup> After investigation of a range of basic and acidic conditions, we found that C2 protodeboronation of **12f** could be efficiently promoted by a catalytic amount of palladium(II) acetate in acetic acid.<sup>21a-h</sup> The optimal temperature for this step of 30 °C delivered **13f** in 85% yield (2.0 mmol scale) from tryptophan **12f**. Further still, the dried crude mixture from the diboronation of **11f** could also be subjected to these same protodeboronation conditions to provide **13f** in 73% yield on gram scale, once more rendering this a two step, one pot method (Scheme 4). Compared to the conditions used in Table 1, this alternative procedure gave similar yields of 58% and 72%, respectively, for the C7 boronation of indole **11c** (entry 3, Table 1) and tryptophan **11d** (entry 4, Table 1).



**Scheme 5.** Derivatization of 7-tryptophans. Conditions: (a) **13d**, (i) for **15**: CuCl<sub>2</sub>·2H<sub>2</sub>O, MeOH, H<sub>2</sub>O, 80 °C, 3 h, 93%; (ii) for **16**: CuBr<sub>2</sub>, MeOH, H<sub>2</sub>O, 80 °C, 5 h, 76%. (b) **13d**, Cu<sub>2</sub>O, NaI, aq NH<sub>3</sub>/MeOH, 23 °C, 14 h, 85%. (c) **13f**, (i) 30% aq H<sub>2</sub>O<sub>2</sub>, 2% aq NaOH, THF, 23 °C, 30 min, 65%; (ii) 50% aq NH<sub>2</sub>OH, MeOH, 23 °C, 21 h, 86%. (d) **13d**, *p*-bromoanisole, SPhos, Pd<sub>2</sub>(dba)<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>, PhMe, 80 °C, 12 h, 76%.

The broader utility of this one-pot boronation protocol for the rapid synthesis of 7-substituted tryptamines and tryptophans is highlighted by the facile conversion of 7-boroindole **13** to a variety of derivatives (Scheme 5). The 7-borotryptophan **13d** was converted to the corresponding 7-chloro-, 7-bromo-, and 7-iodotryptophan derivatives **15–17**, respectively, in high yields using mild copper-mediated conditions.<sup>18c,33</sup> Similarly, compound **13d** could undergo efficient Suzuki–Miyaura cross coupling to furnish C7-arylated product **18** (Scheme 5).<sup>34</sup> Another valuable transformation was the peroxide-mediated oxidation of 7-borotryptophan **13f** that delivered the corresponding phenol **19** in 65% yield.<sup>35</sup> Interestingly, aqueous hydroxylamine in methanol also proved highly efficient for this oxidation, with these milder conditions providing compound **19** in 86% yield.<sup>36</sup>

In summary, we have described a direct, practical, and scalable methodology for the one-pot conversion of C3-alkylindoles to the corresponding C7-boronated derivatives. The synthesis and study of a series of C2/C7-diboronated 3-alkylindoles and development of conditions for C2-selective protodeboronation of these C2/C7-diboronated indoles, including tryptophan and tryptamine derivatives, was described (Scheme 3, Table 1). The value of this strategy as an expedient means for rapid C7 derivatization of C3-alkylindoles was underscored by the gram-scale synthesis of C7-boronated *N*-Boc-L-tryptophan methyl ester (Scheme 4), providing a rapid entry to various unnatural amino acid derivatives (Scheme 5).

## Experimental Section

**General Methods.** All reactions were performed in oven- or flame-dried round-bottomed flasks, reinforced screw-capped pressure tubes or modified Schlenk (Kjeldahl shape) flasks. The flasks were fitted with rubber septa and reactions were conducted under a positive pressure of argon. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash column

chromatography was performed as described by Still et al. using silica gel (60 Å pore size, 40–63 µm, 4–6% H<sub>2</sub>O content).<sup>37</sup> Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or an aqueous solution of ceric ammonium molybdate (CAM) followed by heating (<1 min) on a hot plate (~250 °C). Unless otherwise stated, all chemicals and solvents were obtained from commercial sources and used as received with the following exceptions: dichloromethane, tetrahydrofuran, hexane, toluene, methanol, and triethylamine were purified by the method of Grubbs et al. under positive argon pressure.<sup>38</sup> Proton (<sup>1</sup>H) and carbon (<sup>13</sup>C) nuclear magnetic resonance spectra were recorded with 600 MHz, 500 MHz and 400 MHz spectrometers. Proton nuclear magnetic resonance (<sup>1</sup>H NMR) spectra are reported in parts per million on the δ scale and are referenced from the residual protium in the NMR solvent (CDCl<sub>3</sub>: δ 7.24 (CHCl<sub>3</sub>); CD<sub>3</sub>OD: δ 3.31 (CH<sub>3</sub>OH)). Data is reported as follows: chemical shift [multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, st = sextet, sp = septet, m = multiplet, app = apparent, br = broad), coupling constant(s) in Hertz, integration. Carbon-13 nuclear magnetic resonance (<sup>13</sup>C NMR) spectra are reported in parts per million on the δ scale and are referenced from the carbon resonances of the solvent (CDCl<sub>3</sub>: δ 77.23; CD<sub>3</sub>OD: δ 49.15). Assignments of <sup>13</sup>C chemical shifts for boron-bound carbons were not made owing to the effect of quadrupolar relaxation on the intensity of these signals.<sup>39</sup> Data is reported as follows: chemical shift. Infrared data (IR) were obtained with a FTIR and are reported as follows: [frequency of absorption (cm<sup>-1</sup>), intensity of absorption (s = strong, m = medium, w = weak, br = broad)]. High-resolution mass spectrometric data (HRMS) were recorded on a FT-ICR-MS spectrometer using electrospray ionization (ESI) source or direct analysis in real time (DART) ionization source.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*,2,4,6-tetramethylbenzenesulfonamide (11a):** Triethylamine (1.80 mL, 12.9 mmol, 1.04 equiv) was added via syringe to a solution of tryptamine (2.0 g, 12.4 mmol, 1 equiv)

in dichloromethane (60 mL) at 23 °C under an argon atmosphere. A sample of 2-mesitylenesulfonyl chloride (2.6 g, 11.9 mmol, 0.96 equiv) was added cautiously, resulting in a slight exotherm. After 1 h, the reaction mixture was diluted with diethyl ether (500 mL) and was washed with distilled water (300 mL). The aqueous layer was removed and the organic layer was acidified to pH 1–2 by slow addition of aqueous hydrochloric acid (1N, 600 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 300 mL), was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure. The residue was dissolved in toluene and concentrated (2 × 100 mL) to give *N*-(2-(1*H*-indol-3-yl)ethyl)-2,4,6-trimethylbenzenesulfonamide **S1** as a yellow solid. This material was sufficiently clean to be used in the next step without further purification; Mp: 92–95 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.15 (br-s, 1H), 7.44–7.27 (m, 2H), 7.17 (dd, *J* = 7.5, 8.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.83 (s, 2H), 4.51 (t, *J* = 6.0 Hz, 1H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.45 (s, 6H), 2.26 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 142.3, 139.2, 136.7, 133.5, 132.1, 127.0, 122.8, 122.5, 119.7, 118.6, 111.7, 111.5, 42.6, 25.5, 22.9, 21.1. FTIR (thin film, cm<sup>-1</sup>): 3397 (br-s), 1604 (m), 1458 (s), 1317 (s), 1153 (s), 1076 (m), 744 (s), 656 (s). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>19</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub>S, [M+H<sup>+</sup>]: 343.1475, found: 343.1466. TLC (30% ethyl acetate in hexanes), R<sub>f</sub> = 0.36 (CAM, UV). The sulfonamide **S1** was dissolved in dimethylformamide (60 mL), and 1,8-diazabicyclo[5.4.0]undec-7-ene (7.18 mL, 48.0 mmol, 3.87 equiv) was added. A sample of dimethyl sulfate (2.88 mL, 30.0 mmol, 2.42 equiv) was added and the reaction mixture was stirred at 23 °C. After 3 h, another sample of 1,8-diazabicyclo[5.4.0]undec-7-ene (7.18 mL, 48.0 mmol, 3.87 equiv) and dimethyl sulfate (2.88 mL, 30.0 mmol, 2.42 equiv) was added. After 3 h, the reaction mixture was diluted with diethyl ether (200 mL) and was washed with aqueous hydrochloric acid (1N, 500 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution (2 × 300 mL) and brine (300 mL), and was dried over anhydrous sodium sulfate. The organic layer was filtered, was concentrated under reduced pressure, and the resulting brown

residue was purified by flash column chromatography (silica gel, 4 × 8 cm, eluent: 50% ethyl acetate in hexanes) to afford *N*-methyl sulfamide **11a** as an orange powder (3.30 g, 77.3% over 2 steps); Mp: 104–105 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.03 (br-s, 1H), 7.36 (d, *J* = 7.5 Hz, 1H), 7.32 (app-dd, *J* = 0.5, 8.0 Hz, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 7.0 Hz, 1H), 6.94 (d, *J* = 2.0 Hz, 1H), 6.87 (s, 2H), 3.43–3.38 (m, 2H), 3.32–2.97 (m, 2H), 2.84 (s, 3H), 2.55 (s, 6H), 2.27 (s, 3H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 142.5, 140.5, 136.4, 132.4, 132.0, 127.3, 122.2, 122.1, 119.5, 118.6, 112.6, 111.3, 49.6, 33.1, 23.9, 22.9, 21.2. FTIR (thin film, cm<sup>-1</sup>): 3403 (br-s), 1604 (m), 1457 (s), 1309 (s), 1148 (s), 949 (s), 742 (s), 727 (s). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>20</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub>S, [M+H]<sup>+</sup>: 357.1631, found: 357.1617. TLC (30% ethyl acetate in hexanes), R<sub>f</sub> = 0.49 (CAM, UV).

***N*-(2-(2,7-Bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)-*N*,2,4,6-tetra-**

**methylbenzenesulfonamide (12a):** A round-bottomed flask equipped with a stir bar was charged sequentially with bis(pinacolato)diboron (142 mg, 560 μmol, 2.00 equiv), tryptamine **11a** (100 mg, 281 μmol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (3.7 mg, 5.6 μmol, 2.0 mol%), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (3.0 mg, 11 μmol, 4.0 mol%). The flask was placed under an argon atmosphere, anhydrous tetrahydrofuran (1.4 mL) was added to the flask and the resulting red/brown solution was stirred at 65 °C. After 20 h, the volatiles were then removed under reduced pressure, and the resulting black residue was purified by flash column chromatography (eluent: 25% ethyl acetate in hexanes) to afford **12a** as a white foamy solid (136 mg, 80.1%); Mp: 163.5–165 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 20 °C): δ 9.06 (br-s, 1H), 7.62 (dd, *J* = 1.0, 7.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 6.96 (t, *J* = 7.0 Hz, 1H), 6.72 (s, 2H), 3.27–3.20 (m, 2H), 3.19–3.12 (m, 2H), 2.97 (s, 3H), 2.46 (s, 6H), 2.21 (s, 3H), 1.39 (s, 12H), 1.33 (s, 12H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 20 °C): δ 143.1, 142.2, 140.4, 132.4, 131.8, 131.5, 127.0, 125.0, 122.9, 119.0, 84.0, 83.9, 50.6, 32.5, 25.2, 25.1, 23.4, 22.9, 21.2. FTIR (thin film, cm<sup>-1</sup>): 3455 (m), 2978 (m), 2930 (m), 1598 (m), 1551 (m), 1372 (s), 1320 (s), 1292 (s), 1141 (s),

683 (m). HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $C_{32}H_{47}B_2N_2O_6S$ ,  $[M+H]^+$ : 609.3360, found: 609.3371.

TLC (20% ethyl acetate in hexanes),  $R_f$  = 0.47 (CAM, UV).

***N*,2,4,6-Tetramethyl-*N*-(2-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)-**

**benzenesulfonamide (13a):** A sample of diborotryptamine **12a** (500.0 mg, 822  $\mu$ mol, 1 equiv) in a 25-mL round-bottomed flask was flushed three times with argon, then was dissolved in anhydrous dichloromethane (8.0 mL) and was cooled to 0 °C. Trifluoroacetic acid (0.620 mL, 8.34 mmol, 10.2 equiv) was then added dropwise via a gas tight syringe and the colorless reaction solution was stirred at 0 °C for 5 min, before warming to 23 °C over 10 min. After a further 5 min, the resulting light green solution was concentrated under reduced pressure to leave a pale green residue, which was purified by flash column chromatography on silica gel (eluent: 20% ethyl acetate in hexanes) to provide the boronic ester **13a** as a white foamy solid (320 mg, 80.7%). Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data; Mp: 44–44.5 °C.  $^1H$  NMR (600 MHz,  $CDCl_3$ , 20 °C):  $\delta$  9.03 (br-s, 1H), 7.62 (d,  $J$  = 7.0 Hz, 1H), 7.47 (d,  $J$  = 7.8 Hz, 1H), 7.05 (app-t,  $J$  = 7.3 Hz, 1H), 7.01 (d,  $J$  = 1.7 Hz, 1H), 6.86 (s, 2H), 3.39 (t,  $J$  = 7.7 Hz, 2H), 3.00 (t,  $J$  = 8.0 Hz, 2H), 2.85 (s, 3H), 2.55 (s, 6H), 2.27 (s, 3H), 1.38 (s, 12H).  $^{13}C$  NMR (150 MHz,  $CDCl_3$ , 20 °C):  $\delta$  142.4, 141.5, 140.3, 132.4, 131.9, 129.3, 126.0, 122.1, 122.0, 118.9, 112.0, 83.9, 49.7, 33.0, 25.1, 23.8, 22.9, 21.1. FTIR (thin film,  $cm^{-1}$ ): 3457 (s), 2978 (s), 2936 (s), 1605 (m), 1592 (m), 1372 (s), 1328 (s), 1151 (s), 729 (w). HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $C_{26}H_{36}BN_2O_4S$   $[M+H]^+$ : 483.2498, found: 483.2488. TLC (5% acetone, 15% dichloromethane, 80% hexanes),  $R_f$  = 0.11 (CAM, UV).

***N*,2,4,6-Tetramethyl-*N*-(2-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)-**

**benzenesulfonamide (14):** A round-bottomed flask equipped with a stir bar was charged sequentially with bis(pinacolato)diboron (71.1 mg, 280  $\mu$ mol, 1.00 equiv), tryptamine **11a** (100 mg, 280  $\mu$ mol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (3.7 mg, 5.6  $\mu$ mol, 2.0 mol%), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (3.0 mg, 11 mmol, 4.0 mol%). After flushing with argon for 5 min, anhydrous

dichloromethane (1.4 mL) was added to the flask and the resulting red solution was stirred at 60 °C. After 3 h, the volatiles were removed under reduced pressure, and the resulting black residue was purified by flash column chromatography (eluent: 25% ethyl acetate in hexanes) to afford **14** as a white foamy solid (91.6 mg, 67.7%); Mp: 42–43 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.34 (br-s, 1H), 7.26 (t, *J* = 8.0 Hz, 2H), 7.16 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1H), 6.95 (ddd, *J* = 1.0, 7.0, 8.0 Hz, 1H), 6.74 (s, 2H), 3.32–3.27 (m, 2H), 3.21–3.17 (m, 2H), 2.98 (s, 3H), 2.49 (s, 6H), 2.21 (s, 3H), 1.33 (s, 12H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 142.2, 140.3, 138.2, 132.3, 132.0, 131.8, 127.9, 125.2, 123.8, 119.4, 111.4, 84.0, 50.4, 32.5, 25.1, 23.4, 22.9, 21.2. FTIR (thin film, cm<sup>-1</sup>): 3395 (br-m), 2975 (s), 1550 (s), 1315 (s), 1144 (s), 730 (s). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>26</sub>H<sub>36</sub>BN<sub>2</sub>O<sub>4</sub>S, [M+H]<sup>+</sup>: 483.2498, found: 483.2490. TLC (30% ethyl acetate in hexanes), R<sub>f</sub> = 0.41 (CAM, UV).

***N*,2,4,6-Tetramethyl-*N*-(2-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)-benzenesulfonamide (13a):** A pressure tube was charged sequentially with (1,5-cyclooctadiene)-(methoxy)iridium(I) dimer (5.0 mg, 7.5 μmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4.0 mg, 15 μmol, 5.0 mol%), and tryptamine **11a** (107 mg, 300 μmol, 1 equiv). The contents of the reaction vessel were kept under an argon atmosphere. Freshly distilled anhydrous tetrahydrofuran (2 mL) was then introduced to the flask via a gas tight syringe to afford a dark brown solution. Pinacolborane (218 μL, 1.50 mmol, 5.00 equiv) was added in a single portion via a gas tight syringe to afford a red solution. The pressure tube was sealed and was stirred at 80 °C for 21 h and 15 min. The tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added under an argon atmosphere. Trifluoroacetic acid (2 mL) was then added dropwise via a gas tight syringe to afford a clear orange solution. The solution was stirred at 0 °C for 10 min and was then warmed to 23 °C and was stirred for 5 h and 15 min. The resulting solution was diluted with dichloromethane (50 mL) and was washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure. The resulting



1 brown residue was purified by flash column chromatography on silica gel (eluent: 5% acetone, 15%  
2 dichloromethane, 80% hexanes) to provide the boronic ester **13a** (86.4 mg, 59.6%). All data was in  
3 accordance with that obtained from the aforementioned protodeboronation of **12a**.  
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8 **Methyl (2-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethyl)carbamate (13b):**

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10 A pressure tube was charged sequentially with (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (5.0  
11 mg, 7.5  $\mu\text{mol}$ , 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4.0 mg, 15  $\mu\text{mol}$ , 5.0 mol%) and  
12 tryptamine methyl carbamate<sup>40</sup> **11b** (67.0 mg, 307  $\mu\text{mol}$ , 1 equiv). The contents of the reaction vessel  
13 were kept under an argon atmosphere. Freshly distilled anhydrous tetrahydrofuran (2 mL) was  
14 introduced to the flask via a gas tight syringe to afford a dark brown solution. Pinacolborane (218  $\mu\text{L}$ ,  
15 1.50 mmol, 4.86 equiv) was added in a single portion via a gas tight syringe, at which point the  
16 solution turned bright red. The pressure tube was sealed and the reaction mixture was stirred at 60 °C  
17 for 6 h and 15 min, was then cooled to 0 °C, whereupon anhydrous dichloromethane (3 mL) was added  
18 under an argon atmosphere. Trifluoroacetic acid (2 mL) was then added dropwise via a gas tight  
19 syringe to afford an orange solution. The solution was stirred at 0 °C for 10 min and was then warmed  
20 to 23 °C and was stirred for 2 h and 30 min. The solution was diluted with dichloromethane (50 mL)  
21 and was washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was  
22 dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure. The  
23 resulting brown residue was purified by flash column chromatography on silica gel (eluent: 10%  
24 acetone, 20% dichloromethane, 70% hexanes) to provide the boronic ester **13b** (70.0 mg, 66.2%) as a  
25 white waxy solid. Structural assignments were made with additional information from gCOSY, HSQC,  
26 and gHMBC data; Mp: 138–140 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 20 °C):  $\delta$  9.07 (br-s, 1H), 7.71 (d, *J* =  
27 7.8 Hz, 1H), 7.64 (d, *J* = 6.9 Hz, 1H), 7.13 (app-t, *J* = 7.3 Hz, 1H), 7.09 (br-s, 1H), 4.71 (br-s, 1H),  
28 3.63 (s, 3H), 3.49 (app-q, 2H), 2.97 (app-t, 2H), 1.37 (s, 12H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 20 °C):  $\delta$   
29 157.2, 141.7, 129.6, 126.3, 122.4, 122.2, 119.1, 112.4, 84.0, 52.2, 41.4, 25.9, 25.1. FTIR (thin film,  
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cm<sup>-1</sup>): 3451 (s), 2978 (s), 2939 (s), 1713 (s), 1522 (m), 1373 (m), 1135 (s), 966 (w), 684 (m). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>18</sub>H<sub>26</sub>BN<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 345.1994, found: 345.1996. TLC (10% acetone, 20% dichloromethane, 70% hexanes), R<sub>f</sub> = 0.21 (CAM, UV).

**3-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (13c):** A pressure tube was charged sequentially with (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (5.0 mg, 7.5 μmol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4.0 mg, 15 μmol, 5.0 mol%) and 3-methylindole **11c** (39.0 mg, 0.297 mmol, 1 equiv). The contents of the reaction vessel were kept under an argon atmosphere. Anhydrous tetrahydrofuran (2 mL) was introduced to the flask under an argon atmosphere to afford a clear dark brown solution. Pinacolborane (218 μL, 1.50 mmol, 5.05 equiv) was added in a single portion via a gas tight syringe, the pressure tube was sealed and the resulting red solution was stirred at 60 °C. After 5 h and 30 min, the reaction contents were cooled to 0 °C and anhydrous dichloromethane (3 mL) was added under an argon atmosphere. Trifluoroacetic acid (2 mL) was then added dropwise via a gas tight syringe to afford an orange solution that was stirred at 0 °C for 10 min and then warmed to 23 °C and stirred for a further 3 h. The resulting solution was diluted with dichloromethane (50 mL) and was washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure to give a brown residue that was purified by flash column chromatography on silica gel (eluent: 1.5% acetone in hexanes) to provide the boronic ester **13c** (41.0 mg, 53.6%) as a white waxy solid. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data; Mp: 46–47 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.94 (br-s, 1H), 7.69 (d, *J* = 7.9 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 0.6 Hz, 1H), 2.33 (s, 3H), 1.37 (s, 12H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 20 °C): δ 141.5, 129.2, 127.3, 122.5, 121.6, 118.7, 111.2, 83.9, 25.1, 9.8. FTIR (thin film, cm<sup>-1</sup>): 3462 (s), 2977 (s), 2923 (m), 1607 (m), 1592 (m), 1437 (m), 1371 (s), 1136 (s), 848 (m).

HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $C_{15}H_{21}BNO_2$   $[M+H]^+$ : 258.1673, found: 258.1668. TLC (5% diethyl ether in hexanes),  $R_f$  = 0.26 (CAM, UV).

**Alternative Procedure, 3-Methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (13c):**

Anhydrous tetrahydrofuran (11 mL) was added via syringe to 3-methylindole **11c** (201 mg, 1.53 mmol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (25.4 mg, 38.3  $\mu$ mol, 2.50 mol%), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (20.6 mg, 76.6  $\mu$ mol, 5.00 mol%) sealed in a flame-dried round-bottomed flask under an argon atmosphere to result in a dark brown solution. Pinacolborane (1.10 mL, 7.66 mmol, 5.00 equiv) was introduced in a single portion via a gas tight syringe, and the resulting red solution was stirred at 60 °C for 8 h. After cooling to 23 °C and removal of volatiles under reduced pressure, the subsequent brown residue was dissolved in acetic acid (4.0 mL) and palladium(II) acetate (17.2 mg, 76.6  $\mu$ mol, 5.00 mol%) was added and the resulting mixture was stirred under argon at 30 °C. After 8 h, the mixture was cooled to 23 °C and was filtered through celite with ethyl acetate (150 mL) as eluent. The filtrate was washed with saturated aqueous sodium bicarbonate solution (200 mL) and the organic layer was dried over anhydrous sodium sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (eluent: 1.5% acetone in hexanes) to provide the boronic ester **13c** (228 mg, 57.9%) as a white waxy solid. All data for **13c** was in accordance with that obtained from the previous procedure.

**(S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl))-1H-indol-3-yl)propanoate (13d):** A pressure tube was charged sequentially with (1,5-cyclooctadiene)(methoxy)-iridium(I) dimer (5.0 mg, 7.5  $\mu$ mol, 2.5 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (4.0 mg, 15  $\mu$ mol, 5.0 mol%) and L-tryptophan methyl ester **11d** (83.0 mg, 300  $\mu$ mol, 1 equiv). The contents of the reaction vessel were kept under an argon atmosphere. Anhydrous tetrahydrofuran (2 mL) was introduced to the flask via a gas tight syringe to afford a clear dark brown solution. Pinacolborane (218  $\mu$ L, 1.50 mmol, 5.00 equiv) was then added in a single portion via a gas

tight syringe, the pressure tube was sealed and the resulting red solution was stirred at 60 °C. After 4 h, the tube was subsequently cooled to 0 °C and anhydrous dichloromethane (3 mL) was added via a gas tight syringe. Trifluoroacetic acid (2 mL) was added dropwise via a gas tight syringe to afford an orange solution that was stirred at 0 °C for 10 min, then was warmed to 23 °C and was stirred for a further 5 h and 15 min. The resulting solution was diluted with dichloromethane (50 mL) and was washed with saturated aqueous sodium bicarbonate solution (50 mL). The organic layer was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (eluent: 8% acetone, 30% dichloromethane, 62% hexanes) to provide the boronic ester **13d** (101 mg, 83.5%) as a white powder. Structural assignments were made with additional information from gCOSY, HSQC, and gHMBC data; Mp: 151–152 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 20 °C): δ 9.16 (br-s, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.13 (app-t, *J* = 7.3 Hz, 1H), 7.05 (d, *J* = 1.7 Hz, 1H), 5.28 (d, *J* = 8.1 Hz, 1H), 4.68 (q, *J* = 2.8 Hz, 1H), 3.66 (s, 3H), 3.64 (s, 3H), 3.30 (d, *J* = 4.7 Hz, 2H), 1.37 (s, 12H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, 20 °C): δ 172.6, 156.5, 141.3, 129.5, 126.5, 122.9, 122.2, 119.2, 109.3, 83.9, 54.5, 52.4, 52.3, 28.0, 25.0. FTIR (thin film, cm<sup>-1</sup>): 3448 (s), 2979 (s), 2953 (m), 1722 (s), 1591 (m), 1516 (s), 1374 (m), 1329 (m), 1134 (s), 684 (w). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>20</sub>H<sub>28</sub>BN<sub>2</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 403.2050, found: 403.2030. TLC (10% acetone, 20% dichloromethane, 70% hexanes), R<sub>f</sub> = 0.19 (CAM, UV).

**Alternative Procedure, (S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl))-1H-indol-3-yl)propanoate (13d):** Anhydrous tetrahydrofuran (6 mL) was added to L-tryptophan methyl ester **11d** (203 mg, 735 μmol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (12.2 mg, 18.4 μmol, 2.50 mol%), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (9.8 mg, 37 μmol, 5.0 mol%) sealed in a flame-dried round-bottomed flask under an argon atmosphere. Pinacolborane (530 μL, 3.68 mmol, 5.00 equiv) was added to the resulting dark brown solution in a single portion via a gas

1 tight syringe, and the resulting red solution was stirred at 60 °C. After 8 h, the mixture was allowed to  
2 cool to 23 °C and the volatiles were removed under reduced pressure to give a brown residue. Acetic  
3 acid (1.8 mL) and palladium(II) acetate (8.3 mg, 37 μmol, 5.0 mol%) were added and the resulting  
4 mixture was stirred under argon at 30 °C. After 18 h, the mixture was allowed to cool to 23 °C and  
5 filtered through celite with ethyl acetate (100 mL) as eluent. The filtrate was washed with saturated  
6 aqueous sodium bicarbonate solution (150 mL) and the organic layer was dried over anhydrous sodium  
7 sulfate, was filtered, and was concentrated under reduced pressure. The resulting brown residue was  
8 purified by flash column chromatography on silica gel (eluent: 8% acetone, 30% dichloromethane,  
9 62% hexanes) to provide the boronic ester **13d** (213 mg, 72.3%) as a white powder. All data for **13d**  
10 was in accordance with that obtained from the previous procedure.  
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25 **2-(7-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)ethan-1-ol (13e):** A pressure tube  
26 was charged sequentially with (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (20.4 mg, 30.7 μmol,  
27 2.42 mol%), 4,4'-di-*tert*-butyl-2,2'-bipyridine (16.5 mg, 61.4 μmol, 4.84 mol%) and tryptophol **11e**  
28 (205 mg, 1.27 mmol, 1 equiv). The contents of the reaction vessel were kept under an argon  
29 atmosphere. Freshly distilled anhydrous tetrahydrofuran (10 mL) was introduced to the flask via a gas  
30 tight syringe to afford a dark brown solution. Pinacolborane (895 mL, 6.17 mmol, 4.87 equiv) was  
31 added in a single portion via a gas tight syringe, at which point the solution turned bright red. The  
32 pressure tube was sealed and the reaction mixture was stirred at 60 °C for 7 h, was then cooled to 0 °C,  
33 whereupon anhydrous dichloromethane (15 mL) was added under an argon atmosphere.  
34 Trifluoroacetic acid (10 mL) was then added dropwise via a gas tight syringe to afford an orange  
35 solution. The solution was stirred at 0 °C for 10 min and was then warmed to 23 °C and was stirred for  
36 4 h. The reaction solution was diluted with dichloromethane (100 mL) and was washed with saturated  
37 aqueous sodium bicarbonate solution (2 × 200 mL). The organic layer was concentrated under reduced  
38 pressure, was dissolved in pentane/diethyl ether (2:1, 300 mL), and was washed with water (5 × 300  
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mL). The organic layer was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure to leave a yellow residue that was purified by flash column chromatography on silica gel (eluent: 15% ethyl acetate in hexanes) to give a white solid. This material was vacuum-dried (6–8 mTorr) for 48 h at 70 °C to remove remaining pinacol, and 7-borotryptophol **13e** was obtained as a white solid (227 mg, 62.7%); Mp: 78–78.5 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 9.12 (br-s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.0 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.13 (s, 1H), 3.92–3.86 (m, 2H), 3.05 (t, *J* = 6.2 Hz, 2H), 1.73 (br-s, 1H), 1.40 (s, 12H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 142.3, 130.2, 127.0, 123.2, 123.1, 119.7, 112.3, 84.5, 63.4, 29.5, 25.7. FTIR (thin film, cm<sup>-1</sup>): 3457 (br), 2978 (s), 1684 (s), 1559 (m), 1437 (m), 1374 (w), 1329 (w), 1135 (w), 1048 (s), 668 (m). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>16</sub>H<sub>23</sub>BNO<sub>3</sub> [M+H]<sup>+</sup>: 288.1766, found: 288.1763. TLC (30% ethyl acetate in hexanes), R<sub>f</sub> = 0.24 (CAM, UV).

**(S)-Methyl 2-(((tert-butoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propanoate (13f):** *N*-Boc-L-tryptophan methyl ester **11f** (1.01 g, 3.18 mmol, 1 equiv), (1,5-cyclooctadiene)(methoxy)iridium (I) dimer (52.8 mg, 79.6 μmol, 2.50 mol%), and 4,4'-di-*tert*-butyl-2,2'-bipyridine (42.7 mg, 159 μmol, 5.00 mol%) were sealed in a flame-dried round-bottomed flask under an argon atmosphere and anhydrous tetrahydrofuran (32 mL) was added. To the resulting dark brown solution was added pinacolborane (2.31 mL, 15.9 mmol, 5.00 equiv) in a single portion via a gas tight syringe, and the resulting red solution was stirred at 60 °C for 12 h. After cooling to 23 °C and removal of volatiles under reduced pressure, the subsequent brown residue was dissolved in acetic acid (3.5 mL) and palladium(II) acetate (35.7 mg, 0.159 mmol, 5.00 mol%) was added. The mixture was stirred under argon at 30 °C for 10 h, then was cooled to 23 °C and was filtered through celite, with ethyl acetate (50 mL) as eluent. The filtrate was washed with saturated aqueous sodium bicarbonate solution (50 mL) and the organic layer was dried over anhydrous sodium sulfate, was filtered and was concentrated under reduced pressure. The resulting brown residue was purified by

flash column chromatography on silica gel (eluent: 5% acetone, 15% dichloromethane, 80% hexanes) to provide the 7-borotryptophan derivative **13f** as a white powder (1.03 g, 73.1%); Mp: 152–153 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 9.11 (br-s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.04 (s, 1H), 5.03 (d, *J* = 8.0 Hz, 1H), 4.65–4.57 (m, 1H), 3.65 (s, 3H), 3.29 (d, *J* = 5.0 Hz, 2H), 1.41 (s, 9H), 1.37 (s, 12H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 172.9, 155.4, 141.5, 129.7, 126.8, 122.9, 122.5, 119.3, 109.8, 84.0, 79.9, 54.4, 52.4, 28.5, 28.1, 25.2. FTIR (thin film, cm<sup>-1</sup>): 3451 (br-s), 2978 (m), 1745 (s), 1714 (s), 1592 (m), 1493 (s), 1436 (m), 1373 (m), 1329 (m), 1167 (m), 1134 (s), 1050 (m), 966 (s), 914 (s), 849 (m). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>23</sub>H<sub>34</sub>BN<sub>2</sub>O<sub>6</sub> [M+H]<sup>+</sup>: 445.2520, found: 445.2515. Anal. calc'd for C<sub>23</sub>H<sub>33</sub>BN<sub>2</sub>O<sub>6</sub>: C, 62.17; H, 7.49; N, 6.30, found: C, 62.24; H, 7.42; N, 6.24. TLC (5% acetone, 15% dichloromethane, 80% hexanes), R<sub>f</sub> = 0.28 (CAM, UV).

**(S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-chloro-1H-indol-3-yl)propanoate (15):** To a methanol solution (2.4 mL) of 7-borotryptophan **13d** (80.5 mg, 200 μmol, 1 equiv) was added an aqueous solution (2.4 mL) of copper(II) chloride dihydrate (102 mg, 670 μmol, 3.35 equiv). The resulting mixture was stirred for 3 h at 80 °C, then cooled to 23 °C and was diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, were dried over anhydrous sodium sulfate, were filtered and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to provide tryptophan **15** as a white needles (57.7 mg, 92.7% yield); Mp: 118.5–119 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.33 (br-s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.0 Hz, 1H), 7.08–7.01 (m, 2H), 5.22 (d, *J* = 7.5 Hz, 1H), 4.72–4.64 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.27 (d, *J* = 5.0 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 172.5, 156.6, 133.6, 129.2, 123.6, 121.9, 120.7, 117.5, 117.0, 111.4, 54.6, 52.63, 52.57, 28.3. FTIR (thin film, cm<sup>-1</sup>): 3341 (br-s), 2952 (s), 1709 (s), 1521 (m), 1439

(s), 1341 (m), 1205 (m), 1082 (m), 895 (s), 843 (s), 779 (s), 738 (s). HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $C_{14}H_{16}ClN_2O_4$   $[M+H]^+$ : 311.0793, found: 311.0808. TLC (25% ethyl acetate in hexanes),  $R_f$  = 0.17 (CAM, UV).

**(S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-bromo-1*H*-indol-3-yl)propanoate (16):** To a methanol solution (2.4 mL) of 7-borotryptophan **13d** (80.5 mg, 200  $\mu$ mol, 1 equiv) was added an aqueous solution (2.4 mL) of copper(II) bromide (134 mg, 600  $\mu$ mol, 3.00 equiv). The resulting mixture was heated at 80 °C for 4 h and 30 min. The reaction mixture was cooled to 23 °C and was diluted with ethyl acetate (10 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2  $\times$  10 mL). The combined organic layers were washed with brine, were dried over anhydrous sodium sulfate, were filtered and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to provide tryptophan **16** as a light yellow powder (54.2 mg, 76.2% yield); Mp: 123–124 °C.  $^1H$  NMR (500 MHz,  $CDCl_3$ , 20 °C):  $\delta$  8.30 (br-s, 1H), 7.46 (d,  $J$  = 7.5 Hz, 1H), 7.32 (d,  $J$  = 7.5 Hz, 1H), 7.04 (d,  $J$  = 1.0 Hz, 1H), 6.99 (t,  $J$  = 8.0 Hz, 1H), 5.23 (d,  $J$  = 8.0 Hz, 1H), 4.72–4.64 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.26 (d,  $J$  = 5.0 Hz, 2H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ , 20 °C):  $\delta$  172.5, 156.6, 135.0, 128.9, 124.8, 123.6, 121.1, 118.1, 111.5, 105.1, 54.6, 52.64, 52.57, 28.4. FTIR (thin film,  $cm^{-1}$ ): 3335 (br-s), 2952 (s), 1707 (s), 1521 (m), 1437 (s), 1337 (m), 1203 (m), 1077 (m), 882 (s), 827 (s), 777 (s), 738 (s). HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $C_{14}H_{16}BrN_2O_4$   $[M+H]^+$ : 355.0288, found: 355.0281. TLC (25% ethyl acetate in hexanes),  $R_f$  = 0.17 (CAM, UV).

**(S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-iodo-1*H*-indol-3-yl)propanoate (17):** A round bottomed flask was charged with copper(I) oxide (2.9 mg, 20  $\mu$ mol, 10 mol%) and 28% aqueous ammonia (62  $\mu$ L, 500  $\mu$ mol, 2.5 equiv), and the resulting mixture was stirred under air at 23 °C for 15 min. 7-borotryptophan **13d** (80.5 mg, 200  $\mu$ mol, 1 equiv), sodium iodide (150 mg, 1.00 mmol, 5.00 equiv) and methanol (0.6 mL) were then added to the reaction solution and stirring under air was



continued at 23 °C for 14 h. The resulting solution was concentrated under reduced pressure, and the residue was dissolved in water (5 mL). This aqueous solution was then extracted with ethyl acetate (3 × 20 mL), and the combined organic layers were dried over anhydrous sodium sulfate, were filtered, and were concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel (eluent: 25% ethyl acetate in hexanes) to provide tryptophan **17** as a white solid (68.5 mg, 85.1% yield); Mp: 119–119.5 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.13 (br-s, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 2.0 Hz, 1H), 6.88 (t, *J* = 8.0 Hz, 1H), 5.19 (d, *J* = 8.0 Hz, 1H), 4.71–4.65 (m, 1H), 3.66 (s, 3H), 3.65 (s, 3H), 3.25 (d, *J* = 5.5 Hz, 2H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 172.5, 156.6, 138.1, 131.1, 127.8, 123.3, 121.6, 119.0, 111.8, 54.5, 52.64, 52.57, 28.5. FTIR (thin film, cm<sup>-1</sup>): 3464 (br-s), 1708 (s), 1517 (m), 1432 (s), 1333 (m), 1202 (m), 1075 (m), 776 (s), 666 (s). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>14</sub>H<sub>16</sub>IN<sub>2</sub>O<sub>4</sub> [M+H]<sup>+</sup>: 403.0149, found: 403.0151. TLC (25% ethyl acetate in hexanes), R<sub>f</sub> = 0.14 (CAM, UV).

**(S)-Methyl 2-((methoxycarbonyl)amino)-3-(7-(4-methoxyphenyl)-1*H*-indol-3-yl)propanoate (18):**

A dry round-bottomed flask was charged sequentially with 7-borotryptophan **13d** (80.5 mg, 200 μmol, 1 equiv), tris(dibenzylideneacetone)dipalladium(0) (9.1 mg, 10 μmol, 5.0 mol%), SPhos (8.2 mg, 20 μmol, 10 mol%) and tribasic potassium phosphate (84.9 mg, 400 μmol, 2.00 equiv), was sealed and placed under an argon atmosphere. Toluene (0.8 mL) was added, and to the resulting red-brown slurry *p*-bromoanisole (30.0 μL, 239 μmol, 1.20 equiv) was added via syringe in a single portion. The resulting dark green reaction mixture was stirred at 80 °C for 12 h, then was cooled to 23 °C and filtered through celite, with ethyl acetate as eluent. The filtrate was concentrated under reduced pressure to yield a residue that was purified by flash column chromatography on silica gel (eluent: 40% ethyl acetate in hexanes) to provide tryptophan **18** as a white waxy solid (58.5 mg, 76.4% yield); Mp: 165 °C (decomp.). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 20 °C): δ 8.26 (br-s, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.49 (dd, *J* = 7.3 Hz, 1.3 Hz, 1H), 7.20–7.14 (m, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.99 (s, 1H), 5.24 (d, *J*

= 7.5 Hz, 1H), 4.74–4.67 (m, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.65 (s, 3H), 3.31 (d,  $J = 5.5$  Hz, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ , 20 °C):  $\delta$  172.7, 159.3, 156.7, 134.3, 131.5, 129.5, 128.1, 125.7, 123.1, 122.2, 120.5, 117.6, 114.8, 110.6, 55.6, 54.7, 52.6, 52.5, 28.2. FTIR (thin film,  $\text{cm}^{-1}$ ): 3374 (br-s), 2952 (s), 1710 (s), 1610 (s), 1513 (s), 1438 (m), 1355 (m), 1247 (m), 1056 (s), 1029 (s), 836 (s), 799 (m), 748 (s). HRMS (ESI, TOF) ( $m/z$ ): calc'd for  $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_5$   $[\text{M}+\text{H}]^+$ : 383.1601, found: 383.1617. TLC (40% ethyl acetate in hexanes),  $R_f = 0.29$  (CAM, UV).

**(S)-Methyl 2-((tert-butoxycarbonyl)amino)-3-(7-hydroxy-1H-indol-3-yl)propanoate (19):**

*Conditions (i).* A sample of *N*-Boc tryptophan boronic ester **13f** (20.2 mg, 45.5  $\mu\text{mol}$ , 1 equiv) was dissolved in anhydrous tetrahydrofuran (0.5 mL) and a solution of 2% aqueous sodium hydroxide was added (0.5 mL), followed by slow addition of 30% (wt) aqueous hydrogen peroxide (51.5  $\mu\text{L}$ , 455  $\mu\text{mol}$ , 10.0 equiv). The resulting purple reaction solution was stirred for 30 min at 23 °C and then quenched by addition of a solution of saturated ammonium hydroxide/saturated ammonium chloride (3:1, 5 mL). After extracting with ethyl acetate ( $3 \times 5$  mL), the organic layers were combined and washed with brine ( $2 \times 10$  mL), were dried over anhydrous sodium sulfate, were filtered and were concentrated under reduced pressure. The resulting brown residue was purified by flash column chromatography on silica gel (eluent: 15% acetone, 15% dichloromethane, 70% hexanes) to afford phenol **19** as an off white solid (9.8 mg, 64.6%). *Conditions (ii).* To a sample of *N*-Boc tryptophan boronic ester **13f** (25.3 mg, 56.9  $\mu\text{mol}$ , 1 equiv) in methanol (1.0 mL) was added 50% aqueous hydroxylamine (18.8  $\mu\text{L}$ , 285  $\mu\text{mol}$ , 5.00 equiv) and the resulting white slurry was stirred at 23 °C. After 3 h another dose of 50% aqueous hydroxylamine (18.8 mg, 285  $\mu\text{mol}$ , 5.00 equiv) was added, and the reaction was stirred at 23 °C. After 15 h the reaction mixture had turned into a light brown solution, at which time TLC analysis indicated complete disappearance of starting material. The reaction was diluted with water (5 mL) and was extracted with ethyl acetate ( $3 \times 5$  mL). The organic layers were combined and were washed sequentially with saturated aqueous ammonium chloride ( $2 \times$

10 mL), saturated aqueous sodium bicarbonate (10 mL), and brine (10 mL), before being dried over anhydrous sodium sulfate. After filtration and concentration under reduced pressure, the resulting brown residue was purified by flash column chromatography on silica gel (eluent: 15% acetone, 15% dichloromethane, 70% hexanes) to afford phenol **19** as an off white powder (16.8 mg, 86.3%); Mp: 185 °C (decomp.). <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, 20 °C): δ 7.02 (d, *J* = 7.0 Hz, 1H), 7.01 (s, 1H), 6.83 (t, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 4.40–4.37 (m, 1H), 3.65 (s, 3H), 3.20 (d, *J* = 14.5, 5.5 Hz, 1H), 3.08 (d, *J* = 14.5, 8.2 Hz, 1H), 1.39 (s, 9H). <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, 20 °C): δ 174.9, 157.9, 144.8, 130.9, 128.1, 124.1, 120.7, 111.3, 111.0, 106.8, 80.8, 56.3, 52.7, 29.0, 28.8. FTIR (thin film, cm<sup>-1</sup>): 3384 (br), 2899 (m), 1684 (s), 1583 (m), 1506 (m), 1437 (w), 1368 (m), 1164 (m). HRMS (ESI, TOF) (*m/z*): calc'd for C<sub>17</sub>H<sub>23</sub>N<sub>2</sub>O<sub>5</sub> [M+H]<sup>+</sup>: 335.1601, found: 335.1614. TLC (15% acetone, 15% dichloromethane, 70% hexanes), R<sub>f</sub> = 0.17 (CAM, UV).

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## ASSOCIATED CONTENT

## Supporting Information.

Copies of  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of all products described in the experimental section. This material is available free of charge via the Internet at <http://pubs.acs.org>

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