Direct C7 Functionalization of Tryptophan. Synthesis of Methyl (S)-2-((tert-Butoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propanoate.

The MIT Faculty has made this article openly available. Please share how this access benefits you. Your story matters.

| As Published | http://dx.doi.org/10.15227/orgsyn.092.0373 |
| Publisher | PubMed Central |
| Version | Author's final manuscript |
| Accessed | Thu Dec 13 17:16:16 EST 2018 |
| Citable Link | http://hdl.handle.net/1721.1/109768 |
| Terms of Use | Creative Commons Attribution-Noncommercial-Share Alike |
| Detailed Terms | http://creativecommons.org/licenses/by-nc-sa/4.0/ |
Direct C7 Functionalization of Tryptophan. Synthesis of Methyl (S)-2-((tert-Butoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propanoate

Kazuma Amaike, Richard P. Loach, and Mohammad Movassaghi

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139, United States

Graphical abstract

Procedure

Methyl (S)-2-((tert-Butoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propanoate (3)

A flame-dried, 500-mL two-necked round-bottomed flask, equipped with a 3.5 cm football-shaped magnetic stir bar and thermometer, is charged with N-Boc-L-tryptophan methyl ester (1, 6.31 g, 19.8 mmol, 1.0 equiv), (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (328 mg, 0.500 mmol, 0.025 equiv), and 4,4′-di-tert-butyl-2,2′-bipyridine (266 mg, 0.991 mmol, 0.05 equiv) (Note 1). The flask is sealed with a rubber septum secured by copper wire and placed under a nitrogen atmosphere after three successive vacuum–argon cycles conducted slowly using a needle inlet through the septum (Figure 1). Fresh anhydrous tetrahydrofuran (180 mL) (Note 2) is introduced into the flask via a syringe to afford a dark brown solution. Using a syringe, 4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) (2, 14.4 mL, 99.1 mmol, 5.00 equiv) (Note 1) is added in a single portion, whereupon the solution rapidly changes color.

We acknowledge financial support by NIH-NIGMS (GM089732 and GM074825) and the NSF under CCI Center for selective C–H functionalization (CHE-1205646). R.P.L. thanks the Fonds de Recherche du Québec – Nature et Technologies for a postdoctoral fellowship. K.A. acknowledges support from the Institute of Transformative Bio-Molecules, Nagoya University, and the NSF program for Science Across Virtual Institutes for a summer fellowship.

1Address: Massachusetts Institute of Technology, Department of Chemistry, 77 Massachusetts Avenue, 18-290, Cambridge, MA 02139. movassag@mit.edu.

2THF was purchased from Fisher Scientific and purified by the method of Grubbs et al.3 under positive argon pressure.
from brown to dark red. This reaction solution is stirred and maintained at 60 °C. After 13 h, TLC analysis indicates complete consumption of starting material 1 (Notes 3 and 4).

The reaction solution is cooled to 23 °C, and is concentrated under reduced pressure (20 mmHg, 30 °C) to afford a dark brown residue. Acetic acid (20.0 mL) (Note 1) is slowly added to this residue to give a brown solution, followed by addition of palladium(II) acetate (223 mg, 0.991 mmol, 0.05 equiv) (Note 1) in a single-portion. The mixture is stirred under a nitrogen atmosphere at 30 °C for 12 h (Note 5), at which time TLC analysis indicates complete consumption of the 2,7-dibororated intermediate. The reaction mixture is then cooled to 23 °C, filtered through Celite using a glass-sintered funnel (9 cm diameter, 4 cm height), and the filter cake is rinsed with ethyl acetate (3 × 150 mL). The filtrate is washed with saturated aqueous sodium bicarbonate (500 mL), the layers are separated, and the aqueous layer is extracted with ethyl acetate (2 × 300 mL). The organic layers are combined, dried over anhydrous sodium sulfate (15 g), filtered, and concentrated under reduced pressure (20 mmHg, 30 °C). The resulting brown residue is purified by flash column chromatography on silica gel (eluent: 5% acetone, 15% dichloromethane, 80% hexanes) (Note 6) to provide a light yellow solid. The solid is recrystallized (Note 7) to afford N-Boc-7-boro-tryptophan methyl ester 3 as a white powdery solid 4.09–4.29 g (46.5–48.8%) (Notes 8 and 9) (Figure 2).

3Thin layer chromatography was performed using pre-coated (0.25 mm) silica gel 60 F-254 plates purchased from SiliCycle (eluent: 5% acetone, 15% dichloromethane, 80% hexanes): Compound 1 \( R_T = 0.06 \) (CAM, UV), Compound 3 \( R_T = 0.17 \) (CAM, UV), Compound 4 \( R_T = 0.26 \) (CAM, UV).
4The intermediate N-Boc-2,7-diborotryptophan methyl ester (4, see Scheme 2) could be isolated in ca. 88% yield as a white solid, by flash column chromatography over silica gel (eluent: 5% acetone, 15% dichloromethane, 80% hexanes) (Note 6) of the crude mixture after the diboration step (see Discussion section, Scheme 2). This product contained trace impurities (<5%) but was not subjected to further chromatographic purification due to its sensitivity toward C2 protodeboronation. For reference, data for flash column chromatography over silica gel (eluent: 5% acetone, 15% dichloromethane, 80% hexanes) (Note 6) of the crude mixture is obtained in fractions 21–54.
5Longer exposure to these protodeboronation conditions led to isolation of trace amounts (<5%) of N-Boc-L-tryptophan methyl ester (1), resulting from proto-deboronation of product 3.
6Flash column chromatography (9.0 cm diameter, 17 cm height) was performed using silica gel (60-Å pore size, 40–63 µm, standard grade, Zeochem). The residue was loaded using dichloromethane (15 mL). After 500 mL of initial elution, fraction collection (50 mL fractions) is begun, and elution is continued with 2.7 L of eluent (5% acetone, 15% dichloromethane, 80% hexanes). The compound is obtained in fractions 21–54.
7The chromatographed product was poured into a 125 mL Erlenmeyer flask and 30 mL of hexanes/chloroform (3:1) was added. The mixture was heated to its boiling point (70 °C), and 5 mL portions of hexanes/chloroform (3:1) were added until the total volume was 55 mL (the solid was not completely dissolved). The mixture was cooled to 23 °C, capped and left to stand for 13 h, then placed in a fridge at 4 °C for 48 h. The recrystallized solid was then filtered with a glass-sintered funnel, washing 3 times with cooled hexanes.
8The analytical data for tryptophan derivative 3 is as follows: 1H NMR (500 MHz, CDCl₃) \& & 1.39 (s, 18H), 1.40 (s, 6H), 3.33 (dd, \( J = 14.0, 10.0 \) Hz, 1H), 3.46 (dd, \( J = 14.0, 4.5 \) Hz, 1H), 3.70 (s, 3H), 3.46–4.28 (m, 1H), 6.00 (d, \( J = 6.8 \) Hz, 1H), 7.11 (t, \( J = 7.2 \) Hz, 1H), 7.60 (d, \( J = 6.8 \) Hz, 1H), 7.77 (d, \( J = 8.0 \) Hz, 1H), 9.21 (br-s, 1H); 13C NMR (125 MHz, CDCl₃, 20 °C) \& & 24.9, 25.2, 27.4, 28.2, 28.5, 52.3, 55.5, 79.4, 84.0, 84.6, 119.4, 123.1, 123.2, 127.0, 131.9, 143.1, 155.9, 173.7; FTIR (neat) cm⁻¹: 3451 (br-s), 2979 (s), 1718 (s), 1596 (m), 1588 (s), 1436 (m), 1368 (m), 1293 (m), 1229 (s), 1167 (m), 1135 (s), 1050 (m), 851 (m); HRMS (ESI, TOF) (m/z) calc’d for C₂₉H₇O₄B₁₂Na [M+Na]⁺: 593.3202; found: 593.3204; mp 105–106 °C.
9Mosher ester analysis provided an enantiomeric excess of >98% for the alcohol obtained from reduction of a sample of ester 1 that had been made by proto-deboronation of 7-borotryptophan 3 (see Note 5). This is in full agreement with the expectation that this procedure does not erode the enantiopurity of 7-borotryptophan 3 with respect to tryptophan 1.
Handling and Disposal of Hazardous Chemicals

The procedures in this article are intended for use only by persons with prior training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as “Prudent Practices in the Laboratory” (The National Academies Press, Washington, D.C., 2011 www.nap.edu). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in Organic Syntheses, chemical-specific hazards are highlighted in red “Caution Notes” within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

These procedures must be conducted at one’s own risk. Organic Syntheses, Inc., its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Indole derivatives are prevalent in many natural products and pharmaceutical compounds, mostly in the form of often-complex tryptophan and tryptamine-derived motifs. The demand for such diversely substituted indole structures has led to the development of a wide range of methods for indole functionalization. With regards to tryptophan and tryptamine derivatives, selective functionalization at indole C7 has proven especially difficult, with few methods available that are direct and readily scalable. We sought to explore a direct C7 functionalization method for 3-substituted indoles by utilizing arene C–H boronation as a means to this end. Of particular relevance to us were reports into iridium-catalyzed indole boronations, which Smith had initially shown in 2006 would proceed selectively at C7 with C2-substituted indoles. These studies inspired us to investigate a more streamlined process for direct C7 boronation of tryptophan and tryptamine substrates in a single operation. By taking advantage of the more nucleophilic/basic C2 position of C3-substituted indoles, our two-step single-flask procedure provides expedient access to the corresponding C7-boronated compounds on multi-gram scale through direct C7 activation of non-functionalized tryptamines and tryptophans. The premise behind this diboronation/protodeboronation sequence was our recognition of the high propensity of five-membered heterocycles to undergo rapid C2 protodemetalation.

Examination of conditions for the diboronation of various N-protected tryptamines demonstrated that exposure to excess pinacolborane (5 equiv), catalytic amounts of
[Ir(cod)OMe]$_2$, and 4,4’-di-tert-butylbipyridine in tetrahydrofuran at 60 °C, was sufficient to ensure full boronation at C2 and C7.\textsuperscript{9} Consistent with our C2 protodeboronation hypothesis, these 2,7-diboronated indoles can be dissolved in dichloromethane followed by addition of trifluoroacetic acid to cleanly afford the desired 7-boronated indole derivatives.

As we were interested in converting these two steps into a single-flask operation, we first explored simple acidification of the reaction medium once the diboronation was complete. However, mere addition of an equivolume (with respect to tetrahydrofuran) of trifluoroacetic acid at 0 °C led to global protodeboronation and recovery of starting material. Gratifyingly, dilution of the reaction mixture with dichloromethane followed by the addition of trifluoroacetic acid at 0 °C, led to the desired C2-protodeboronated tryptamine in 60% yield for the two-step process (entry 1, Table 1).\textsuperscript{9}

We then focused our attention on expanding the substrate scope (Table 1) to other 3-substituted indoles. In all but one case (entry 1), a temperature of 60 °C and reaction time of 4–7 h was found to be ideal for the diboronation reactions (entries 2–5, Table 1).\textsuperscript{9} These results highlighted the general compatibility of our protocol with alcohol, carbamate, ester, and sulfonamide functional groups. The excellent yield obtained for a C7-boronated tryptophan derivative (entry 4, Table 1) and its ready conversion to the corresponding 7-halo, 7-hydroxy and 7-aryl tryptophan derivatives (Scheme 1) further highlight the versatility of this chemistry.\textsuperscript{9}

The 2,7-diborotryptophan 4 (Scheme 2), resulting from C2/C7 diboronation of N-Boc tryptophan methyl ester (1) using our standard iridium-catalyzed conditions,\textsuperscript{9} could be isolated chromatographically (ca. 88%. Note 4) from the crude reaction mixture after removal of volatiles.

We have developed milder conditions than those described in Table 1 for the C2 protodeboronation of the intermediate 2,7-diborotryptophan 4. After exploring a range of additives in acetic acid, it was found that C2-selective protodeboronation of 2,7-diborotryptophan 4 could be engendered by inclusion of catalytic quantities of palladium(II) acetate. The optimal temperature for this step was found to be 30 °C, delivering the desired N-Boc 7-borotryptophan methyl ester 3 in 85% yield (Scheme 2). Further still, the dried crude mixture from the diboronation step could also be subjected to the same palladium-catalyzed protodeboronation conditions, once more rendering this a two-step single-flask operation as described above.\textsuperscript{9}

References


Appendix

Chemical Abstracts Nomenclature (Registry Number)

\[N\text{-Boc-}\text{-L-tryptophan methyl ester: L-tryptophan, } N\text{-[(1,1- dimethylethoxy)carbonyl]-}(13139-14-5)\text{ (1,5-Cyclooctadiene)(methoxy)iridium(I) dimer: bis[(1,2,5,6-\eta)-1,5-}
\text{cyclooctadiene]di-\mu-methoxydi-}; (12148-71-9)\text{ 4,4'-Di-}\text{-tertButyl-2,2'-bipyridine: 2,2'-}
\text{Bipyridine, 4,4'-bis(1,1-dimethylethyl)-}; (72914-19-3)\text{ 4,4,5,5-Tetramethyl-1,3,2-}
\text{dioxaborolane: 1,3,2-Dioxaborolane, 4,4,5,5-tetramethyl-}; (25015-63-8)\text{ Palladium(II)}
\text{acetate: Acetic acid, palladium(2+) salt (2:1); (3375-31-3)}
\]

\[(S)\text{-Methyl 3-(2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)-2-(cyclohexylamino)propanoate}\]

\[\text{1H, 500 MHz, CDCl}_3, 20 \text{ °C}\]
(S)-Methyl 3-(2,7-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)-2-(tert-butoxycarbonylamino)propanoate
methyl (S)-2-(((tert-butoxycarbonyl)amino)-3-(7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolano-2-yl)-1H-indol-3-yl)propanoate
Kazuma Amaike is pursuing his graduate studies in Professor Kenichiro Itami’s group at Nagoya University, Nagoya, Japan. His studies focus on a range projects related to C–H activation and the synthesis of natural products. In 2013, he joined the laboratory of Professor Mohammad Movassaghi at MIT as a visiting graduate student via the National Science Foundation CCI Center for selective C–H functionalization.
Richard Loach was born in Birmingham (U.K.) and graduated from Imperial College, London in 2003 with a B.Sc. in Chemistry. In 2007 he joined the research group of Professor John Boukouvalas at Laval University in Québec (Canada), earning his Ph.D. in 2013 for his studies on the total syntheses of novel γ-hydroxybutenolide natural products. In 2014, he was granted a FRQNT fellowship to pursue his postdoctoral research in Professor Mohammad Movassaghi’s group at MIT. He is currently working on the total synthesis of alkaloid natural products.

Mohammad Movassaghi carried out his undergraduate research with Professor Paul A. Bartlett at UC Berkeley, where he received his B.S. degree with Honors in chemistry in 1995. He completed his graduate studies in Professor Andrew G. Myers’ group as a Roche predoctoral fellow at Harvard University. In 2001, Mo joined Professor Eric N. Jacobsen’s group at Harvard University as a Damon Runyon Cancer Research Foundation postdoctoral fellow. In 2003, he joined the faculty at MIT and his research program focuses on the total synthesis of alkaloids in concert with the discovery and development of new reactions for organic synthesis.

Danilo Pereira de Sant’Ana was born in Rio de Janeiro-RJ, Brazil. He received his B.S. and M.S. degrees at the Federal University of Rio de Janeiro, Brazil (UFRJ) (2008) under the supervision of Prof. Paulo Roberto Ribeiro Costa. He got his Ph.D. in cotutelle between the State University of Campinas-SP, Brazil (UNICAMP) and National Graduate School of Chemistry, Montpellier, France (ENSCM) (2014) under the supervision of Prof Luiz Carlos Dias and Jean-Marc Campagne. He is currently a Postdoctoral Fellow with Prof. Richmond Sarpong at UC Berkeley, working on the total synthesis of prenylated indole alkaloid natural products.
Figure 1.
Reaction Apparatus (photo provided by checkers)
Figure 2.
Reaction Product 3 (photo provided by authors)
Scheme 1.
Representative derivatization of a C7-boronated tryptophan
Scheme 2.
Two step sequence for C7 boronation of N-Boc tryptophan 1
Table 1
Rapid synthesis of C7-boronated 3-substituted indole derivatives

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>NMeSO&lt;sub&gt;2&lt;/sub&gt;Mes</td>
<td>NMeSO&lt;sub&gt;2&lt;/sub&gt;Mes</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>NHCO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>NHCO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>66%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>54%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>58%&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>NHCO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>NHCO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>84%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>82%&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>OH</td>
<td>OH</td>
<td>63%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yield after purification.

<sup>b</sup>Boronation conducted at 80 °C.
2nd step: Pd(OAc)$_2$ (5 mol%), AcOH, 30 °C.

Gram-scale reaction.