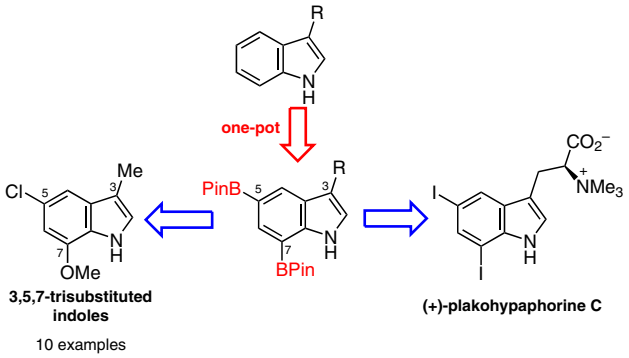
Synthesis A. S. Eastabrook, J. Sperry Feature

Synthetic Access to 3,5,7-Trisubstituted Indoles Enabled by Iridium-Catalyzed C–H Borylation

Andrew S. Eastabrook
Jonathan Sperry*

School of Chemical Sciences, 23 Symonds Street, University of Auckland, Auckland, New Zealand
j.sperry@auckland.ac.nz

Published as part of the Special Topic *Modern Strategies for Borylation in Synthesis*



Received: 13.03.2017
Accepted after revision: 10.04.2017
Published online: 08.05.2017
DOI: 10.1055/s-0036-1589018; Art ID: ss-2017-z0155-fa

Abstract A one-pot conversion of 3-substituted indoles into their 5,7-diboryl derivatives is reported. The simultaneous functionalization of the C5-H and C7-H sites is achieved using an iridium-catalyzed triborylation-protodeborylation sequence. The 5,7-diborylindoles are useful intermediates that can be readily derivatized into a variety of indoles possessing the rare 3,5,7-trisubstitution pattern, including the natural product (+)-plakohypaphorine C.

Key words iridium, C–H borylation, indole, natural product, plakohypaphorine

The indole ring system is present in a huge amount of biologically active natural products and pharmaceuticals.[1] Given the wide range of biological activity displayed by indole derivatives,[2] efficient methods that provide access to indoles bearing new and rare substitution patterns are highly coveted.[3] We were particularly interested in developing a simple route to 3,5,7-trisubstituted indoles (Figure 1), a substitution pattern that is rare in the literature. A general approach to 3,5,7-trisubstituted indoles using Mori–Ban and Larock cyclizations has been reported,[4] but this methodology requires *ortho*-haloanilines that are not easily attainable. There are limited examples of 3,5,7-trisubstituted indoles being prepared using a variety of cyclization strategies,[5] C7-H functionalization of 3,5-disubstituted indoles[6,7] and the electrophilic substitution of 5,7-disubstituted indoles at C3.[8] Conceptually, the simplest route to 3,5,7-trisubstituted indoles would be to simultaneously functionalize the C5-H and C7-H positions on 3-substituted indoles, substrates that are commercially available or easily prepared. Herein we report a simple C–H borylation procedure that facilitates the conversion of 3-substituted indoles into 3,5,7-trisubstituted indoles, including the natural product (+)-plakohypaphorine C.

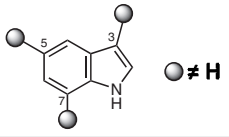
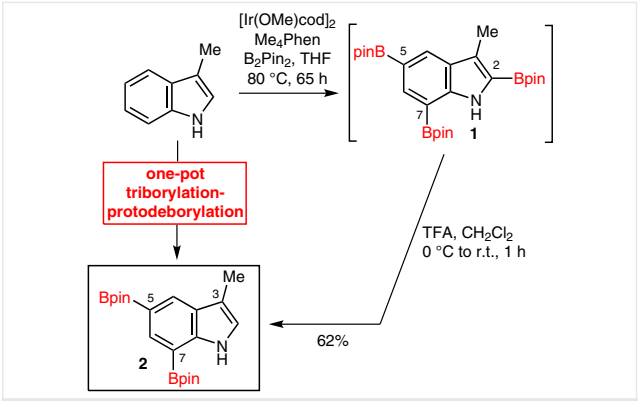


Figure 1 3,5,7-Trisubstituted indoles

We have previously reported that 3-substituted indoles undergo iridium-catalyzed triborylation[9] at C2-H, C5-H, and C7-H.[10] It was envisaged that this procedure could be modified to access 3,5,7-trisubstituted indoles by conducting a selective C2-protodeborylation[11] after the triborylation event. When 3-methylindole (skatole) was subjected to the previously reported triborylation conditions,[10] the triborylindole **1** was formed as the sole product. Concentration of the reaction mixture followed by subjecting the crude material to acid-mediated protodeborylation[11a] gave the 3-methyl-5,7-diborylindole **2** in a simple, good-yielding one-pot process (Scheme 1).

Having successfully functionalized the C5-H and C7-H sites of skatole with excellent pot-economy, the derivatization of diborylated indole **2** was subsequently investigated (Scheme 2). The 5,7-dichloro-, 5,7-dibromo-, and 5,7-diiodoskatoles **3**–**5** were easily attainable using standard halodeborylation chemistry.[12] Subjecting **2** to simultaneous Suzuki couplings with iodobenzene provided the 3-methyl-5,7-diphenylindole (**6**). Upon subjecting **2** to the Chan–Lam conditions reported by Batey,[13] 3-methyl-5,7-dimethoxyindole was formed and subsequently protected as the *tert*-butyl carbamate **7** for stability reasons. Indoles differentially substituted at the C5 and C7 sites are also accessible



Scheme 1 One-pot preparation of 3-methyl-5,7-diborylindole **2**

(Scheme 2). By reducing the amount of copper acetate and methanol in the Chan–Lam coupling, the reaction occurred regioselectively at the C7-boronate in **2** to give **8**, which was itself readily converted to the differentially substituted indoles **9**–**12** using the same chemistry described above. All of the indoles in Scheme 2 are novel.

Next, we decided to apply this methodology to natural product synthesis. (+)-Plakohypaphorine C is an unusual diiodinated tryptophan derivative isolated from the Caribbean marine sponge *Plakortis simplex*[14] (Figure 2). Plakohypaphorine C shows good antihistamine activity, reducing histamine-induced contractions on isolated guinea pig ileum.[15]

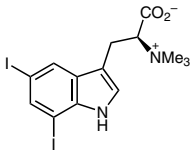


Figure 2 (+)-Plakohypaphorine C

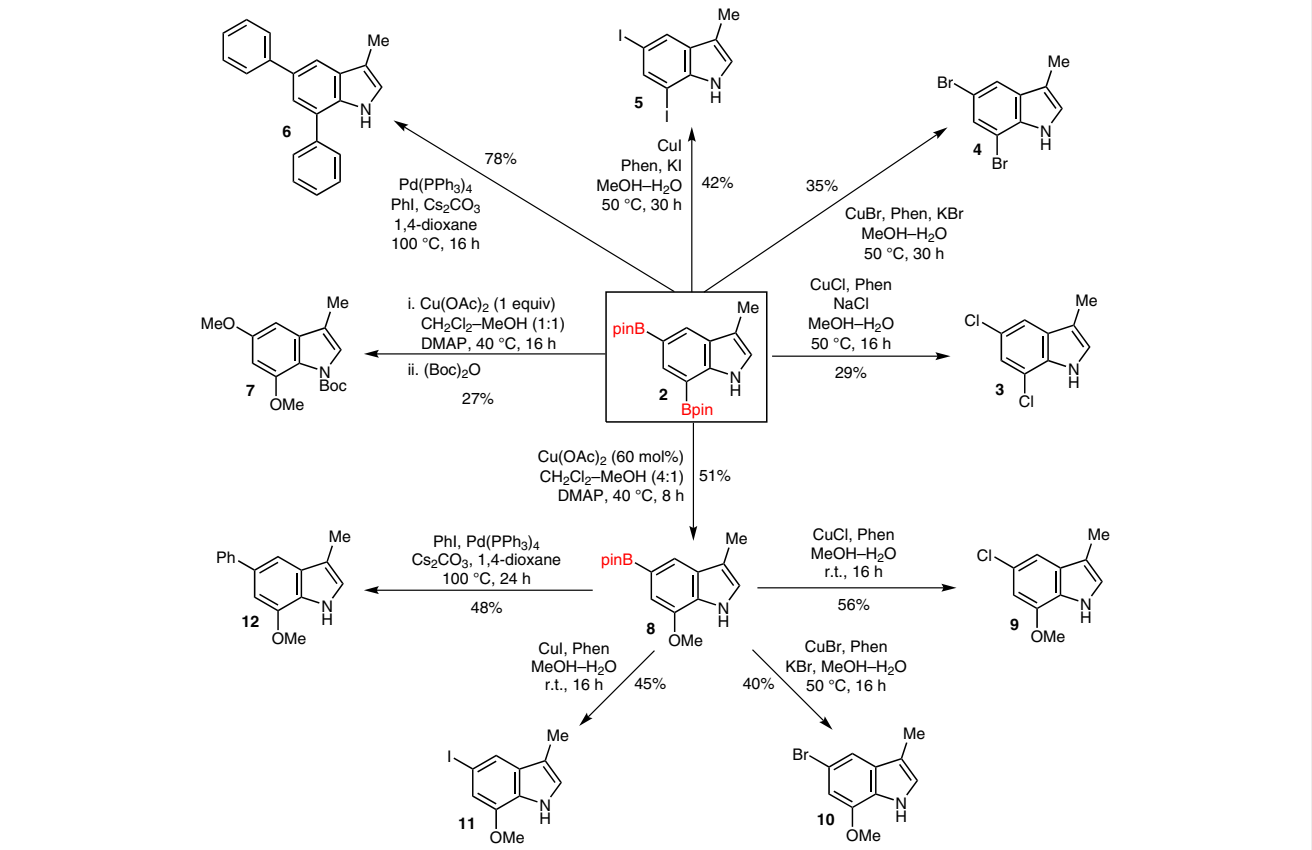
The synthesis of (+)-plakohypaphorine C began with subjecting diprotected tryptophan **13**[10] to a one-pot triborylation-protodeborylation process to give **14**. In this instance, the protodeborylation step was carried out using $Pd(OAc)_2$/AcOH[11a] so as to prevent cleavage of the Boc group. Diiododeborylation gave the 5,7-diiodotryptophan **15**, which underwent Boc-removal, trimethylation, and ester hydrolysis to give (+)-plakohypaphorine C (Scheme 3). The spectroscopic data were in agreement with the isolation report[14,16] and the optical rotation of synthetic plakohypaphorine C {$[\alpha]_D^{22}$ +23.4 (*c* 0.1, MeOH–TFA, 8:1)} was in agreement with the literature value {$[\alpha]_D^{25}$ +29.1 (*c* 0.1, MeOH–TFA, 8:1)}.[14]

In conclusion, we have developed a procedure to transform 3-substituted indoles into their 5,7-diboryl derivatives by way of a one-pot iridium-catalyzed triborylation-protodeborylation sequence. The resulting 5,7-diborylindoles are useful synthetic intermediates that can be derivatized into a variety of indoles possessing the rare 3,5,7-trisubsti-

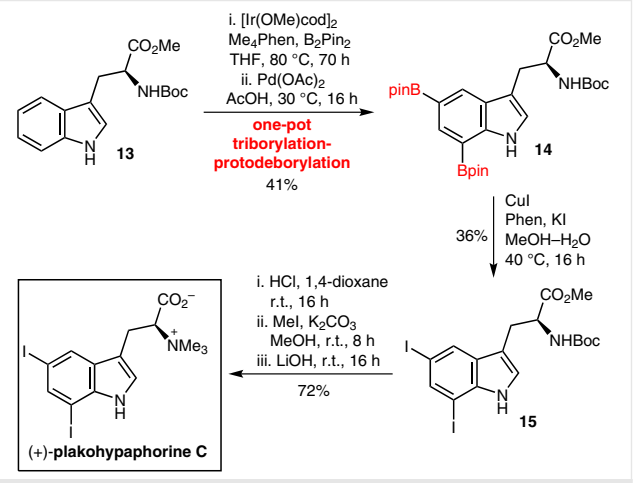
Biographical sketches

Andrew Eastabrook obtained his B.Sc. (Hons) in Medicinal Chemistry in 2014 from the University of Auckland, New Zealand. He is currently a Ph.D. student working on the application of C–H borylation reactions to the functionalisation of heteroaromatics under the supervision of Associate Professor Jonathan Sperry.

Jonathan Sperry obtained his B.Sc. (Hons) in Biological and Medicinal Chemistry in 2002 from the University of Exeter, UK. He conducted his Ph.D. under the supervision of Professor Chris Moody at the same institution, before moving to New Zealand where he spent 3.5 years as a postdoctoral researcher with Distinguished Professor Margaret Brimble at the University of Auckland. He took up a lectureship at the same institution in 2009, where he is currently an Associate Professor and a Royal Society of New Zealand Rutherford Discovery Fellow.



Scheme 2 Synthesis of 3,5,7-trisubstituted indoles **3–12**; Phen = phenanthroline



Scheme 3 Synthesis of (+)-plakohypaphorine C

tution pattern. The utility of this methodology has been demonstrated in a short synthesis of the natural product (+)-plakohypaphorine C.

All reactions were carried out in oven-dried glassware under a N_2 atmosphere, unless otherwise stated. Analytical TLC was performed using 0.2 mm silica plates and compounds were visualized under 365 nm ultraviolet irradiation followed by staining with either alkaline $KMnO_4$ or ethanolic vanillin solution. IR spectra were obtained as thin films between NaCl plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). Melting points were recorded on a melting point apparatus and are uncorrected. NMR spectra were recorded as indicated on an NMR spectrometer operating at 500, 400, and 300 MHz for ^1H nuclei and 125, 100, and 75 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the TMS peak recorded as δ (0.00 ppm) in $CDCl_3$/TMS solvent, or the residual acetone (δ = 2.05), $CHCl_3$ (δ = 7.24), DMSO (δ = 2.50), or MeOH (δ = 3.31) peaks. The ^{13}C NMR values were referenced to the residual acetone (δ = 29.9), $CHCl_3$ (δ = 77.1), DMSO (δ = 39.5), or MeOH (δ = 49.0) peaks. ^{13}C NMR values are reported as chemical shift δ and assignment. ^1H NMR shift values are reported as chemical shift δ, multiplicity (standard abbreviations), coupling constant (*J* in Hz), relative integral, and assignment. Assignments are made with the aid of DEPT 90, DEPT 135, COSY, NOESY, and HSQC experiments. High-resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a microTOF mass spectrometer.

3-Methyl-5,7-bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (2)

In a sealed tube, a mixture of 3-methylindole (100 mg, 0.76 mmol), bis(pinacolato)diboron (971 mg, 3.80 mmol), $[Ir(OMe)cod]_2$ (30 mg, 6 mol%), and 3,4,7,8-tetramethyl-1,10-phenanthroline (22 mg, 12 mol%) in THF (4 mL) was heated to 80 °C for 65 h. The reaction mixture was cooled to r.t. and concentrated in vacuo. The resulting crude material was suspended in CH_2Cl_2 (15 mL) at 0 °C and TFA (0.58 mL) was added dropwise. The mixture was allowed to warm to r.t., then stirred for 1 h. Sat. aq $NaHCO_3$ (30 mL) was added and the whole extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (19:1) as eluent gave the title compound (180 mg, 0.47 mmol, 62%) as a colorless solid; mp 134.6–137.4 °C.

IR (neat): 2980, 1596, 1489, 1451, 1428, 1380, 1359, 1297, 1269, 1205, 1133, 1090, 1047, 1029, 992, 966, 905, 850, 798, 733, 755, 696 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.36 (s, 12 H, 4 × CH_3), 1.38 (s, 12 H, 4 × CH_3), 2.35 (d, *J* = 0.7 Hz, 3 H, CH_3), 6.99 (s, 1 H, ArH), 8.14 (s, 1 H, ArH), 8.22 (s, 1 H, ArH), 8.99 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.8 (CH_3), 25.0 (4 × CH_3), 25.1 (4 × CH_3), 83.4 (2 × C), 83.8 (2 × C), 112.0 (C), 121.6 (CH), 127.0 (C), 130.1 (CH), 135.9 (CH), 143.6 (C); 2 C not observed.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{21}H_{31}B_2NO_4 + H]^+$: 384.2519; found: 384.2512.

5,7-Dichloro-3-methylindole (3)

To a suspension of **2** (100 mg, 0.26 mmol) in MeOH (7.2 mL) and H_2O (0.8 mL) were added NaCl (46 mg, 0.79 mmol), 1,10-phenanthroline (19 mg, 0.10 mmol, 40 mol%), and CuCl (5.0 mg, 0.05 mmol, 20 mol%). The reaction mixture was heated to 50 °C and stirred for 16 h under air. H_2O (30 mL) was added, and the whole was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (4:1) as eluent gave the title compound (15 mg, 0.08 mmol, 29%) as a white solid; mp 87.0–92.6 °C.

IR (neat): 3452, 2920, 2857, 1565, 1556, 1467, 1397, 1380, 1344, 1304, 1285, 1233, 1195, 1080, 1068, 857, 826, 801, 766, 742, 683 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.28 (d, *J* = 0.6 Hz, 3 H, CH_3), 7.04 (s, 1 H, ArH), 7.18 (d, *J* = 1.4 Hz, 1 H, ArH), 7.45 (d, *J* = 1.0 Hz, 1 H, ArH), 8.10 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 112.8 (C), 116.8 (C), 117.3 (CH), 121.4 (CH), 123.6 (CH), 124.8 (C), 130.2 (C), 132.1 (C).

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $[C_9H_7{}^{35}Cl_2N - H]^-$: 197.9883; found: 197.9879.

5,7-Dibromo-3-methylindole (4)

To a suspension of **2** (100 mg, 0.26 mmol) in MeOH (7.2 mL) and H_2O (0.8 mL) were added KBr (93 mg, 0.78 mmol), 1,10-phenanthroline (19 mg, 40 mol%), and CuBr (7 mg, 20 mol%). The resulting mixture was heated at 50 °C for 30 h under air. H_2O (30 mL) was added and the whole was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (9:1) as eluent gave the title compound (26 mg, 0.09 mmol, 35%) as a colorless solid; mp 73.7–79.9 °C.

IR (MeOH): 3090, 2980, 2936, 1686, 1618, 1442, 1393, 1349, 1289, 1233, 1204, 1053, 991, 856, 842 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (d, *J* = 0.8 Hz, 3 H, CH_3), 7.02 (d, *J* = 0.8 Hz, 1 H, ArH), 7.45 (d, *J* = 1.5 Hz, 1 H, ArH), 7.64 (d, *J* = 1.1 Hz, 1 H, ArH), 8.07 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 105.0 (C), 112.1 (C), 112.8 (C), 120.9 (CH), 123.4 (CH), 126.3 (CH), 130.6 (C), 133.8 (C).

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $[C_9H_7{}^{79}Br_2N - H]^-$: 285.8872; found: 285.8881.

5,7-Diiodo-3-methylindole (5)

To a suspension of **2** (100 mg, 0.26 mmol) in MeOH (7.2 mL) and H_2O (0.8 mL) were added KI (130 mg, 0.78 mmol), 1,10-phenanthroline (19 mg, 40 mol%), and CuI (10 mg, 20 mol%). The reaction mixture was heated at 50 °C for 30 h under air. H_2O (15 mL) was added and the whole was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with H_2O (15 mL) and brine (15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (9:1) as eluent gave the title compound (42 mg, 0.11 mmol, 42%) as a pale yellow solid; mp 77.2–83.9 °C.

IR (neat): 3436, 3056, 2909, 2850, 2172, 1704, 1681, 1597, 1559, 1535, 1489, 1447, 1434, 1413, 1377, 1336, 1297, 1272, 1231, 1200, 1141, 1092, 1075, 981, 912, 865, 842, 819, 801, 755, 726, 698 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (d, *J* = 0.9 Hz, 3 H, CH_3), 6.99 (d, *J* = 0.8 Hz, 1 H, ArH), 7.78 (d, *J* = 1.3 Hz, 1 H, ArH) 7.86 (d, *J* = 0.7 Hz, 1 H, ArH), 7.97 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.9 (CH_3), 82.3 (C), 112.8 (C), 122.8 (CH), 128.0 (CH), 130.5 (C), 137.1 (CH), 137.5 (C); 1 C not observed.

HRMS (ESI): *m*/*z* $[M - H]^-$ calcd for $[C_9H_7I_2N - H]^-$: 381.8595; found: 381.8599.

3-Methyl-5,7-diphenylindole (6)

To a solution of **2** (50 mg, 0.13 mmol) in 1,4-dioxane (2.5 mL) were added iodobenzene (57 mg, 0.28 mmol), $Pd(PPh_3)_4$ (20 mol%, 30 mg), and Cs_2CO_3 (212 mg, 0.65 mmol). The reaction mixture was heated at 100 °C under an atmosphere of N_2 for 16 h. H_2O (10 mL) was added and the whole was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using toluene–hexanes (3:1) as eluent gave the title compound (29 mg, 0.10 mmol, 78%) as a colorless oil.

IR (MeOH): 3426, 2915, 1648, 1600, 1496, 1470, 1453, 1438, 1356, 1336, 1302, 1254, 1182, 1076, 1051, 1028, 965, 908, 869, 801, 753, 696, 656 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.41 (d, *J* = 0.8 Hz, 3 H, CH_3), 7.03 (d, *J* = 0.9 Hz, 1 H, ArH), 7.32 (t, *J* = 7.3 Hz, 1 H, ArH), 7.38–7.54 (m, 6 H, ArH), 7.67–7.72 (m, 4 H, ArH), 7.78 (d, *J* = 1.3 Hz, 1 H, ArH), 8.15 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.8 (CH_3) 112.6 (C), 116.7 (CH), 121.8 (CH), 122.5 (CH), 125.7 (C), 126.4 (CH), 127.5 (3 × CH), 128.3 (2 × CH), 128.7 (2 × CH), 129.2 (2 × CH), 129.3 (C), 133.5 (C), 133.7 (C), 139.2 (C), 142.6 (C).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{21}H_{17}N + H]^+$: 284.1434; found: 284.1427.

N-Boc-3-Methyl-5,7-methoxyindole (7)

To a solution of **2** (100 mg, 0.26 mmol) in CH_2Cl_2 (5 mL) and MeOH (5 mL) were added $Cu(OAc)_2{\cdot}H_2O$ (52 mg, 0.26 mmol), 4-dimethylaminopyridine (64 mg, 0.52 mmol), and molecular sieves 4 Å (500 mg). The reaction mixture was stirred at 40 °C under an atmosphere of air for 16 h. The mixture was filtered through a pad of $MgSO_4$, then H_2O (20 mL) was added, and the whole was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq NH_4Cl (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using PE–EtOAc (4:1) as eluent gave a colorless oil. This oil was suspended in THF (1 mL) to which NaH (21 mg, 0.52 mmol) and $(Boc)_2O$ (113 mg, 0.52 mmol) were added. The reaction mixture was stirred at r.t. for 16 h. H_2O (20 mL) was added and the whole extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with sat. aq NH_4Cl (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using PE–EtOAc (19:1) as eluent gave the title compound (21 mg, 0.07 mmol, 27%) as a colorless oil.

IR (acetone): 2977, 2936, 1751, 1717, 1606, 1577, 1489, 1451, 1421, 1389, 1366, 1332, 1277, 1237, 1209, 1149, 1068, 1048, 1021, 995, 941, 908, 855, 815, 765, 739, 725, 670 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.60 (s, 9 H, 3 × CH_3), 2.19 (d, *J* = 1.4 Hz, 3 H, CH_3), 3.86 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.46 (d, *J* = 2.2 Hz, 1 H, ArH), 6.51 (d, *J* = 2.2 Hz, 1 H, ArH), 7.28 (d, *J* = 1.2 Hz, 1 H, ArH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 28.1 (3 × CH_3) 55.7 (CH_3), 55.9 (CH_3), 82.6 (C), 93.1 (CH), 97.3 (CH), 115.8 (C), 119.7 (C), 126.1 (CH), 134.6 (C), 148.9 (C), 149.6 (C), 156.9 (C=O).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{16}H_{21}NO_4$ + Na]$^+$: 314.1363; found: 314.1359.

7-Methoxy-3-methyl-5-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)indole (8)

To a solution of **2** (50 mg, 0.13 mmol) in CH_2Cl_2 (4 mL) and MeOH (1 mL) was added $Cu(OAc)_2{\cdot}H_2O$ (15 mg, 60 mol%), DMAP (19 mg, 1.2 equiv) and molecular sieves 4 Å (150 mg). The reaction mixture was stirred at 40 °C for 8 h. The reaction mixture was filtered through Celite®, washing with CH_2Cl_2 (3 × 15 mL), then concentrated in vacuo. Purification by flash chromatography on silica gel using PE–EtOAc (9:1) as eluent gave the title compound (19 mg, 0.07 mmol, 51%) as a colourless solid; mp 81.6–83.5 °C.

IR (neat): 3328, 2978, 2935, 1631, 1617, 1596, 1489, 1463, 1451, 1425, 1378, 1351, 1314, 1290, 1270, 1231, 1206, 1171, 1141, 1091, 1051, 995, 970, 913, 876, 858, 844, 835, 817, 799, 755, 711, 692 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.38 (s, 12 H, 4 × CH_3), 2.33 (d, *J* = 0.8 Hz, 3 H, CH_3), 3.99 (s, 3 H, CH_3), 6.93 (d, *J* = 0.8 Hz, 1 H, ArH), 7.05 (s, 1 H, ArH), 7.76 (s, 1 H, ArH), 8.12 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.9 (CH_3), 24.9 (4 × CH_3), 55.4 (CH_3), 83.5 (2 × C), 106.7 (CH), 112.9 (C), 120.2 (CH), 121.2 (CH), 129.1 (C), 129.5 (C), 145.6 (C); 1 C not observed.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{16}H_{22}BNO_3$ + Na]$^+$: 310.1581; found: 310.1588.

5-Chloro-7-methoxy-3-methylindole (9)

To a solution of **8** (14 mg, 0.049 mmol) in MeOH (4.5 mL) and H_2O (0.5 mL) were added CuCl (4.8 mg 0.049 mmol) and 1,10-phenanthroline (8.8 mg, 0.049 mmol). The reaction mixture was stirred at r.t. for 16 h. H_2O (20 mL) was added and the whole was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (9:1) as eluent gave the title compound (5.3 mg, 0.027 mmol, 56%) as a colorless oil.

IR (MeOH): 3433, 2925, 2856, 1718, 1575, 1481, 1454, 1385, 1372, 1311, 1294, 1244, 1227, 1177, 1135, 1084, 1057 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (d, *J* = 1.0 Hz, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 6.61 (d, *J* = 1.7 Hz, 1 H, ArH), 6.94 (q, *J* = 1.1 Hz, 1 H, ArH), 7.16 (d, *J* = 1.3 Hz, 1 H, ArH), 8.07 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 55.6 (CH_3), 103.1 (CH), 111.3 (CH), 112.0 (C), 122.2 (CH), 124.9 (C), 133.0 (C), 134.1 (C), 146.1 (C).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for [$C_{10}H_{10}{}^{35}ClNO$ – H]$^-$: 194.0378; found: 194.0374.

5-Bromo-7-Methoxy-3-methylindole (10)

To a solution of **8** (15 mg, 0.052 mmol) in MeOH (1.8 mL) and H_2O (0.2 mL) were added CuBr (2.0 mg, 20 mol%), 1,10-phenanthroline (1.9 mg, 20 mol%), and KBr (9 mg, 0.076 mmol). The reaction mixture was stirred at 50 °C for 16 h. H_2O (20 mL) was added and the whole was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (9:1) as eluent gave the title compound (5.0 mg, 0.021 mmol, 40%) as a colorless oil.

IR (MeOH): 3428, 2920, 2852, 1562, 1477, 1447, 1385, 1370, 1310, 1291, 1276, 1244, 1227, 1175, 1081, 1055 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.27 (d, *J* = 1.0 Hz, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 6.73 (d, *J* = 1.4 Hz, 1 H, ArH), 6.93 (d, *J* = 1.0 Hz, 1 H, ArH), 7.32 (d, *J* = 1.4 Hz, 1 H, ArH), 8.08 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 55.6 (Me), 95.5 (C), 105.6 (CH), 111.9 (C), 112.1 (C), 114.4 (CH), 122.0 (CH), 130.5 (C), 146.3 (C).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for [$C_{10}H_{10}{}^{79}BrNO$ – H]$^-$: 237.9873; found: 237.9870.

5-Iodo-7-methoxy-3-methylindole (11)

To a solution of **8** (11 mg, 0.038 mmol) in MeOH (4.5 mL) and H_2O (0.5 mL) were added CuI (7.3 mg 0.038 mmol) and 1,10-phenanthroline (6.9 mg, 0.038 mmol). The reaction mixture was stirred at r.t. for 16 h. H_2O (20 mL) was added and the whole was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using hexanes–EtOAc (9:1) as eluent gave the title compound (5.0 mg, 0.017 mmol, 45%) as a colorless oil.

IR ($CDCl_3$): 3431, 2923, 2858, 1620, 1560, 1471, 1445, 1421, 1405, 1385, 1388, 1309, 1289, 1264, 1248, 1228, 1174, 1088, 1055 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.26 (s, 3 H, CH_3), 3.92 (s, 3 H, OCH_3), 6.87 (d, *J* = 1.3 Hz, 1 H, ArH), 6.89 (q, *J* = 0.9 Hz, 1 H, ArH), 7.54 (d, *J* = 1.3 Hz, 1 H, ArH), 8.08 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.7 (CH_3), 55.6 (CH_3), 110.8 (CH), 111.5 (C), 121.1 (CH), 121.7 (CH), 126.1 (C), 131.5 (C), 146.5 (C), 153.0 (C).

HRMS (ESI): *m*/*z* [M – H]$^-$ calcd for [$C_{10}H_{10}INO$ – H]$^-$: 285.9734; found: 285.9737.

7-Methoxy-3-methyl-5-phenylindole (12)

To a solution of **8** (25 mg, 0.087 mmol) in 1,4-dioxane (1 mL) were added iodobenzene (27 mg, 0.13 mmol), $Pd(PPh_3)_4$ (10 mol%, 10 mg), and Cs_2CO_3 (85 mg, 0.26 mmol). The reaction mixture was heated at

100 °C under an atmosphere of N_2 for 24 h. H_2O (10 mL) was added and the whole was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using toluene–PE (1:1) as eluent gave the title compound (10 mg, 0.042 mmol, 48%) as a colorless oil.

IR (MeOH): 3422, 2934, 2857, 1628, 1586, 1477, 1450, 1427, 1408, 1385, 1373, 1322, 1304, 1278, 1221, 1165, 1077, 1052, 1027 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 2.35 (d, *J* = 1.1 Hz, 3 H, CH_3), 4.01 (s, 3 H, CH_3), 6.88 (d, *J* = 1.1 Hz, 1 H, ArH), 6.97 (d, *J* = 1.1 Hz, 1 H, ArH), 7.31 (tt, *J* = 7.4, 1.0 Hz, 1 H, ArH), 7.38 (s, 1 H, ArH), 7.44 (t, *J* = 7.5 Hz, 2 H, ArH), 7.66 (dd, *J* = 7.8, 1.0 Hz, 2 H, ArH), 8.09 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 9.8 (CH_3), 55.4 (CH_3), 102.1 (CH), 110.4 (CH), 112.6 (C), 121.8 (CH), 126.2 (C), 126.3 (CH), 127.5 (2 × CH), 128.6 (2 × CH), 129.9 (C), 133.7 (C), 143.1 (C), 146.1 (C).

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{16}H_{15}NO$ + Na]$^+$: 260.1046; found: 260.1045.

5,7-Bis(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)-*N*-(*tert*-butoxycarbonyl)-L-tryptophan Methyl Ester (14)

N-Boc-L-tryptophan methyl ester (**13**; 150 mg, 0.47 mmol), bis(pinacolato)diboron (600 mg, mmol), $[Ir(OMe)cod]_2$ (29 mg, 9 mol%), and 3,4,7,8-tetramethyl-1,10-phenanthroline (20 mg, 18 mol%) were suspended in THF (3 mL) in a sealed tube and the reaction mixture was heated to 80 °C for 70 h. The mixture was cooled to r.t. and concentrated in vacuo. The resulting crude material was suspended in AcOH (0.5 mL) and $Pd(OAc)_2$ (11 mg, 10 mol%) was added. The reaction mixture was stirred at 30 °C for 16 h. Sat. aq $NaHCO_3$ (15 mL) was added and the whole was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (15 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using PE–EtOAc (4:1) as eluent gave the title compound (111 mg, 0.19 mmol, 41%) as a colorless solid; mp 207.9–211.6 °C; $[\alpha]_D^{20}$ +25.4 (*c* 1.0, EtOAc).

IR (neat): 3451, 3348, 2979, 1754, 1699, 1591, 1504, 1371, 1332, 1313, 1265, 1210, 1137, 1065, 963, 851, 686, 694 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.35 (d, *J* = 4.0 Hz, 12 H, 4 × CH_3), 1.38 (s, 12 H, 4 × CH_3), 1.42 (s, 9 H, 3 × CH_3), 3.33 (t, *J* = 5.4 Hz, 2 H, CH_2), 3.72 s, (3 H, CH_3), 4.63 (m, 1 H, CH), 5.05 (d, *J* = 8.0 Hz, 1 H, NH), 7.05 (d, *J* = 2.2 Hz, 1 H, ArH), 8.13 (d, *J* = 0.9 Hz, 1 H, ArH), 8.15 (s, 1 H, ArH), 9.19 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 24.8 (2 × CH_3), 25.0 (6 × CH_3), 27.8 (CH_2), 28.3 (3 × CH_3), 52.2 (CH_3), 54.0 (CH), 79.7 (C), 83.4 (2 C), 83.8 (2 C), 110.2 (C), 122.9 (CH), 126.2 (C), 129.9 (CH), 136.1 (CH), 143.3 (C), 155.3 (C=O), 172.7 (C=O); 2 C not observed.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{29}H_{44}B_2N_2O_8$ + Na]$^+$: 593.3186; found: 593.3174.

5,7-Diiodo-*N*-(*tert*-butoxycarbonyl)-L-tryptophan Methyl Ester (15)

To a suspension of **14** (70 mg, 0.12 mmol) in MeOH (6.5 mL) and H_2O (0.7 mL) were added CuI (4.6 mg, 20 mol%), 1,10-phenanthroline (8.8 mg, 40 mol%), and KI (62 mg, 0.37 mmol). The reaction mixture was heated to 40 °C for 16 h, then H_2O (20 mL) was added, and the whole was extracted with EtOAc (3 × 20 mL). The combined organic extracts were washed with sat. aq NH_4Cl (20 mL) and brine (20 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel using PE–EtOAc (4:1) as eluent gave the title compound (25 mg, 0.04 mmol, 36%) as a colorless solid; mp 129.8–131.6 °C; $[\alpha]_D^{22}$ +27.7 (*c* 1.0, MeOH).

IR (neat): 3399, 2974, 1693, 1500, 1455, 1365, 1201, 1160, 1061 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.45 (s, 9 H, 3 × CH_3), 3.15 – 3.25 (m, 2 H, CH_2), 3.71 (s, 3 H, CH_3), 4.62–4.64 (m, 1 H, CH), 5.09 (d, *J* = 7.8 Hz, 1 H, NH), 7.03 (d, *J* = 1.9 Hz, 1 H, ArH), 7.79 (d, *J* = 1.2 Hz, 1 H, ArH), 7.81 (d, *J* = 1.0 Hz, 1 H, ArH), 8.20 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 28.4 (CH_2 + 3 × CH_3), 52.4 (CH_3), 54.0 (CH), 80.1 (C), 83.0 (C), 111.5 (C), 124.0 (CH), 128.0 (CH), 129.8 (C), 137.4 (C), 137.6 (CH), 155.0 (C=O), 172.3 (C=O); 1 C not observed.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for [$C_{17}H_{20}I_2N_2O_4$ + Na]$^+$: 592.9405; found: 592.9405.

(+)-Plakohypaphorine C

The entire sequence was conducted at room temperature.

To a solution of **15** (24 mg, 0.042 mmol) in 1,4-dioxane (1 mL) was added a solution of HCl in 1,4-dioxane (4.0 M, 0.5 mL). The reaction mixture was stirred for 16 h and concentrated in vacuo. The crude material was suspended in MeOH (3 mL) and K_2CO_3 (23 mg, 0.17 mmol) and MeI (0.02 mL, 0.25 mmol) were added. The mixture was stirred for 6 h and then a 1 M solution of LiOH in H_2O (1 mL) was added. The mixture was stirred for 16 h and concentrated in vacuo. Purification by reverse phase chromatography using a gradient of H_2O to H_2O–MeOH (6:4) as eluent gave the title compound (15 mg, 0.030 mmol, 72%) as a pale yellow solid; mp 212.2–215.0 °C (Lit.[14] mp not stated); $[\alpha]_D^{22}$ +23.4 (*c* 0.1, MeOH–TFA, 8:1) {Lit.[14] $[\alpha]_D^{25}$ +29.1 (*c* 0.1, MeOH–TFA, 8:1)}.

IR (neat): 3265, 1623, 1439, 1025, 958, 861, 846, 816 cm^{-1}.

^1H NMR (DMSO-d_6, 500 MHz): δ = 3.18 (s, 9 H, 3 × CH_3), 3.22–3.09 (m, 2 H, CH_2), 3.66 (dd, *J* = 10.3, 3.4 Hz, 1 H, CH), 7.24 (s, 1 H, ArH), 7.69 (d, *J* = 0.8 Hz, 1 H, ArH), 8.01 (d, *J* = 1.0 Hz, 1 H, ArH), 11.04 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6, 125 MHz): δ = 23.0 (CH_2), 51.0 (3 × CH_3), 78.4 (CH), 78.7 (C), 82.5 (C), 110.6 (C), 126.2 (CH), 127.1 (CH), 129.9 (C), 135.9 (CH), 137.1 (C), 166.7 (C=O).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{14}H_{16}I_2N_2O_2$ + H]$^+$: 498.9374; found: 498.9378.

Acknowledgment

We are indebted to the Royal Society of New Zealand for support through the Rutherford Discovery Fellowship Scheme. We thank Professor Orazio Scafati (Dipartimento di Farmacologia Sperimentale, Università degliStudi di Napoli 'Federico II') for helpful discussions regarding the spectroscopic data for plakohypaphorine C.

Supporting Information

Supporting information for this article is available online at https://doi.org /10.1055/s-0036-1589018.

References

(1) (a) Gribble, G. W. *Indole Ring Synthesis: From Natural Products to Drug Discovery*; Wiley: New York, **2016**. (b) Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, **1970**. (c) Ban, Y.; Murakami, Y.; Iwasawa, Y.; Tsuchiya, M.; Takano, N. *Med. Res.*

Rev. **1988**, *8*, 231. (d) Sundberg, R. J. *Indoles*; Academic Press: New York, **1996**. (e) Pindur, U.; Lemster, T. *Curr. Med. Chem.* **2001**, *8*, 1681. (f) Ramirez, A.; Garcia-Rubio, S. *Curr. Med. Chem.* **2003**, *10*, 1891. (g) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

(2) (a) Taylor, R. D. M.; MacCoss, M.; Lawson, A. D. G. *J. Med. Chem.* **2014**, *57*, 5845. (b) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257. (c) de Sá Alves, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Mini. Rev. Med. Chem.* **2009**, *9*, 782.

(3) (a) Vicente, R. *Org. Biomol. Chem.* **2011**, *9*, 6469. (b) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (c) StC Black, D.; Channon, M. F.; Clayton, K. A.; Condie, G. C.; Harper, J. B.; Kumar, N.; Pchalek, K.; Wahyuningsih, T. D. *ARKIVOC* **2006**, *(vii)*, 67.

(4) (a) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synlett* **2005**, 3071. (b) Charrier, N.; Demont, E.; Dunsdon, R.; Maile, G.; Naylor, A.; O'Brien, A.; Redshaw, S.; Theobald, P.; Vesey, D.; Walter, D. *Synthesis* **2006**, 3467.

(5) (a) Zhang, J.; Yin, Z.; Leonard, P.; Wu, J.; Sioson, K.; Liu, C.; Lapo, R.; Zheng, S. *Angew. Chem. Int. Ed.* **2013**, *52*, 1753. (b) Feu, K. S.; Deobald, A. M.; Narayanaperumal, S.; Corrêa, A. G.; Paixão, M. W. *Eur. J. Org. Chem.* **2013**, 5917. (c) Boyd, E. M.; Sperry, J. *Org. Lett.* **2015**, *17*, 1344. (d) Jensen, T.; Pedersen, H.; Bang-Andersen, B.; Madsen, R.; Jørgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 888. (e) Outlaw, V. K.; Townsend, C. A. *Org. Lett.* **2014**, *16*, 6334. (f) Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.

(6) (a) Shen, F.; Tyagarajan, S.; Perera, D.; Krska, S. W.; Maligres, P. E.; Smith, M. R. III; Maleczka, R. E. Jr. *Org. Lett.* **2016**, *18*, 1554. (b) Xu, L.; Zhang, C.; He, Y.; Tan, L.; Ma, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 321. (c) Song, Z.; Antonchick, A. P. *Org. Biomol. Chem.* **2016**, *14*, 4804. (d) Frese, M.; Sewald, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 298. (e) Winkelblech, J.; Li, S.-M. *ChemBioChem* **2014**, *15*, 1030.

(7) For the enzymatic prenylation of a 7-substituted tryptophan at C5, see: Yu, X.; Liu, Y.; Xie, X.; Zheng, X.-D.; Li, S.-M. *J. Biol. Chem.* **2012**, *287*, 1371.

(8) (a) Plancq, B.; Lafantaisie, M.; Companys, S.; Maroun, C.; Ollevier, T. *Org. Biomol. Chem.* **2013**, *11*, 7463. (b) Taheri, A.; Lai, B.; Cheng, C.; Gu, Y. *Green Chem.* **2015**, *17*, 812. (c) Komnatnyy, V. V.; Taveras, K. M.; Nandurkar, N. S.; Le Quement, S. T.; Givskov, M.; Nielsen, T. E. *Eur. J. Org. Chem.* **2015**, 3524.

(9) (a) Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056. (b) Sulanga, P.; Chotana, G. A.; Holmes, D.; Reichle, R. C.; Maleczka, R. E. Jr.; Smith, M. R. III *J. Am. Chem. Soc.* **2006**, *128*, 15552. (c) Lo, W. F.; Kaiser, H. M.; Spannenberg, A.; Beller, M.; Tse, M. K. *Tetrahedron Lett.* **2007**, *48*, 371. (d) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (e) Robbins, D. W.; Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 4068. (f) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (g) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864. (h) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287.

(10) Eastabrook, A. S.; Sperry, J. *Aust. J. Chem.* **2015**, *68*, 1810.

(11) (a) Loach, R. P.; Fenton, O. S.; Amaike, K.; Siegel, D. S.; Ozkal, E.; Movassaghi, M. *J. Org. Chem.* **2014**, *79*, 11254. (b) Amaike, K.; Loach, R. P.; Movassaghi, M. *Org. Synth.* **2015**, *92*, 373. (c) Kallepalli, V. A.; Gore, K. A.; Shi, F.; Sanchez, L.; Chotana, G. A.; Miller, S. L.; Maleczka, R. E. Jr.; Smith, M. R. III *J. Org. Chem.* **2015**, *80*, 8341.

(12) Partridge, B. M.; Hartwig, J. F. *Org. Lett.* **2013**, *15*, 140.

(13) Quach, T. D.; Batey, R. A. *Org. Lett.* **2003**, *5*, 1381.

(14) Campagnuolo, C.; Fattorusso, E.; Taglialatela-Scafati, O. *Eur. J. Org. Chem.* **2003**, 284.

(15) Borelli, F.; Campagnuolo, C.; Capasso, R.; Fattorusso, E.; Taglialatela-Scafati, O. *Eur. J. Org. Chem.* **2004**, 3227.

(16) See the Supporting Information for full details.