Synthesis of Nonsymmetrical 5-Aryl-2-indolopyrrole Derivatives via Controlled Mono Suzuki–Miyaura Cross-Coupling on *N*-Boc-2,5-dibromopyrrole

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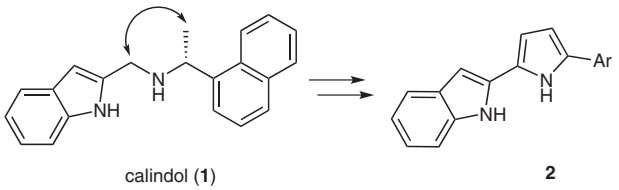
Dedicated to Professor Akira Suzuki on the occasion of his receiving the Nobel Prize in Chemistry

Abstract: The first example of mono Suzuki–Miyaura cross-coupling of *N*-Boc-2,5-dibromopyrrole with a boronic acid (indol-2-ylboronic acid) is reported. The resulting 2-indolyl-5-bromopyrrole derivative was in turn coupled with a variety of aryl- or heteroarylboronic acids thereby providing the corresponding non-symmetrical 2,5-disubstituted pyrroles in good to excellent yields. The *tert*-butoxycarbonyl (Boc) groups could be easily removed to give the completely deprotected products.

Key words: cross-coupling, Suzuki–Miyaura, indole, pyrrole, palladium-catalyzed

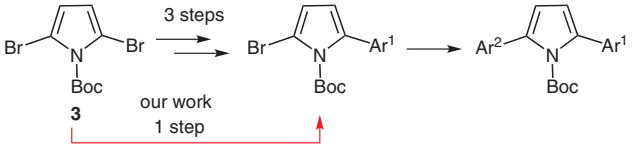
As part of a medicinal chemistry project aimed at the preparation of rigid analogues of the calcium sensing receptor[1] agonist, calindol (**1**),[2] developed in our laboratory, the synthesis of 2-(2-indolyl)-5-arylpyrrole derivatives of type **2** was targeted (Scheme 1).



Scheme 1 Rigidification strategy

Recent efforts toward the preparation of 2,5-di(hetero)arylpyrroles have mainly made use of metal-catalyzed, particularly palladium-catalyzed, coupling reactions starting from suitably functionalized pyrroles.[3] Two different substitution patterns can be distinguished, each of which requires a separate strategy. Thus, the more easily accessible symmetrically substituted 2,5-diarylpyrroles have been obtained, for example, by Sinha using Stille coupling of a 2,5-di(tri-*n*-butyl)stannylpyrrole with two equivalents of aryl bromide,[4] while Sugihara and co-workers described the single-step, double Suzuki–Miyaura coupling of *N*-Boc-2,5-dibromopyrrole (**3**) with an azulene pinacolboronate.[5] Alternatively, a double C–H activation on 1-(2,6-dichlorobenzoyl)pyrrole allowed Itahara[6] to prepare 2,5-diphenyl pyrroles, whereas an N-methylated version of the latter was obtained in low yield by way of direct palladium-catalyzed 2-arylation of *N*-methylpyrrole using phenyl iodide.[7]

More challenging is the preparation of unsymmetrical 2,5-diarylpyrroles, that is, in which two different coupling partners are introduced. Most of the methods described for this purpose resort to step-wise coupling/pyrrole activation/coupling strategies. For example, two successive in situ generations of pyrrolezinc chloride allowed Sadighi to introduce, at high temperature and under air-free conditions, different aryl groups at the C-2 and C-5 positions of pyrrole via a C–H activation process.[8] Using a similar strategy, Sames prepared 2-phenyl-5-(4-carboxymethyl)phenyl pyrrole, but in moderate yield and requiring a long reaction time.[9] Vachal and co-workers described the palladium-catalyzed cross-coupling of 1-methyl-2-(tri-*n*-butyl)stannylpyrrole with iodobenzene, followed by C-5 bromination of the product and subsequent Suzuki–Miyaura coupling with a substituted phenylboronic acid.[10] Willis, on the other hand, successfully developed the desymmetrization of *N*-Boc-2,5-dibromopyrrole (**3**) by prior *n*-butyllithium-mediated exchange of one bromine atom with a trimethylsilyl group and subsequent reversion to the bromine after the first Suzuki–Miyaura cross-coupling reaction (Scheme 2).[11]



Scheme 2 Willis' desymmetrization strategy and our approach

None of these studies included indole as one of the coupling partners with pyrrole. Moreover, all these methods are multistep procedures, and for an eventual structure–activity study of molecules of type **2**, we were interested in developing a more rapid access to these compounds. As a wide variety of aryl and heteroarylboronic acids are commercially available the application of two successive Suzuki–Miyaura couplings on an easily accessible 2,5-dibromopyrrole derivative appeared to be the best route to this goal.[12] Only a few examples of mono Suzuki–Miyaura cross-couplings on a symmetrical dihalogenated substrate (phenyl,[13] pyridine,[12a,14] thiophene[15]), followed

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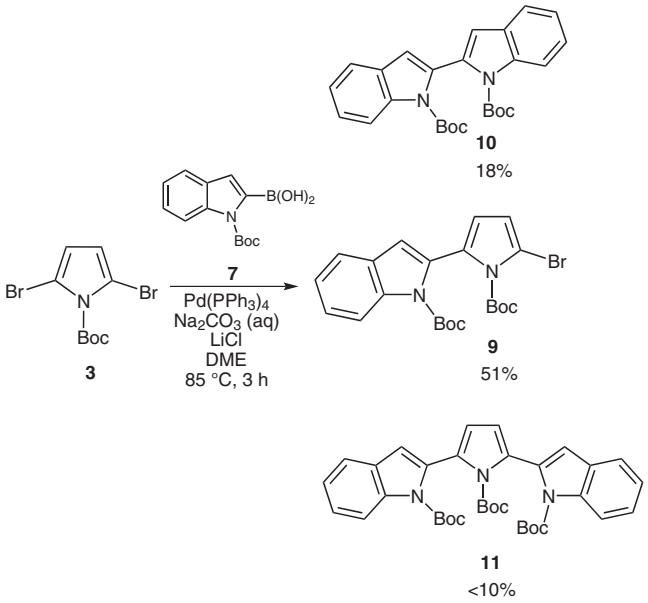
by a second coupling have been described. The success of such reactions depends on the deactivation of the second oxidative addition of palladium after the first coupling of an electron-donating boronic acid.[12a] As far as the selective introduction of two different aryl groups at the C-2 and C-5 positions of pyrrole is concerned, only the use of 1-methyl-2,3,4,5-tetrabromopyrrole as substrate has been described.[16] However, the reaction failed when cleavable N-protecting groups were used instead of *N*-methyl. Since, in the context of our medicinal chemistry program mentioned above, only N-deprotected pyrrole derivatives of type **2** were required, this procedure was not suitable for our objectives. In this paper, we report the first controlled mono-coupling of an arylboronic acid (that is, an N-protected indol-2-ylboronic acid) with *N*-Boc-2,5-dibromopyrrole (**3**) followed by a second coupling reaction with a different arylboronic acid to give the corresponding non-symmetrical 2,5-disubstituted-*N*-Boc-pyrrole derivatives. The latter could be easily deprotected to give the desired compounds of type **2**.[17]

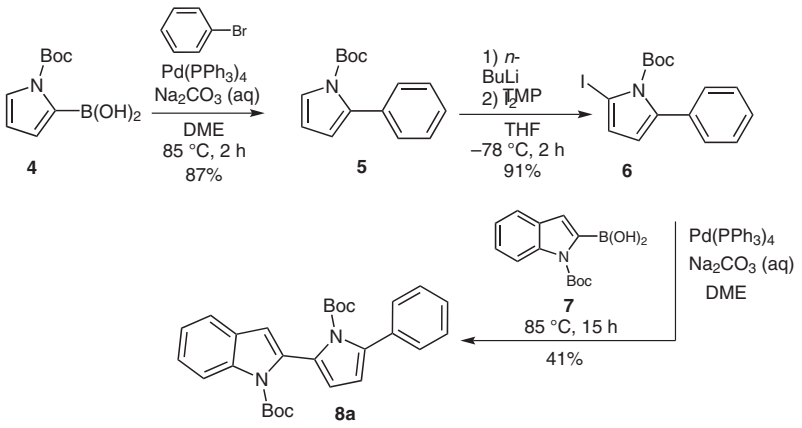
For purposes of comparison, we decided to first synthesize the simplest derivative of type **2**, that is, the 2-indolyl-5-phenylpyrrole derivative **8a**, by a classical step-wise procedure.[17] Thus, *N*-Boc-pyrrol-2-ylboronic acid (**4**)[18] was coupled with bromobenzene using tetrakis(triphenylphosphine)palladium(0) and sodium carbonate in 1,2-dimethoxyethane to give the 2-phenylpyrrole derivative **5** in 87% yield (corresponding to an 81% yield starting from pyrrole) (Scheme 3). Compound **5** was treated with *n*-butyllithium and 2,2,6,6-tetramethylpiperidine (TMP) in tetrahydrofuran for two hours followed by the addition of 1.1 equivalents of iodine to afford, selectively, the 5-iodopyrrole derivative **6** which was isolated in 91% yield. A second Suzuki–Miyaura coupling between **6** and *N*-Boc-indol-2-ylboronic acid (**7**) then provided the desired unsymmetrical disubstituted pyrrole **8a** in 41% yield. The overall yield for the five-step preparation of **8a** from pyrrole was 30%.

We next attempted to prepare compound **8a** directly from *N*-Boc-2,5-dibromopyrrole (**3**)[19]by way of two successive Suzuki–Miyaura coupling reactions. Thus, using conditions described by Fürstner[20]for palladium-catalyzed coupling of **7** with pyrrole-2-triflate, treatment of **3** with 1.2 equivalents of **7** in 1,2-dimethoxyethane in the presence of tetrakis(triphenylphosphine)palladium(0) (8 mol%), sodium carbonate and lithium chloride provided, after three hours at 85 °C, the mono-coupled product **9** in 51% yield (Scheme 4). The only by-products observed were the bis-indole homo-coupled derivative **10**, formed in approximately 18% yield, as estimated by ^{1}H NMR spectroscopy, and *N*-Boc-2,5-diindolylpyrrole **11**, the yield of which was estimated to be less than 10%. Attempts to increase the yield of **9** by varying the number of equivalents of lithium chloride (1–3) or the amount of palladium catalyst were not successful.[21] Interestingly, attempted mono-coupling of **3** with phenylboronic acid or pyridin-3-ylboronic acid, instead of with **7**, was unsuccessful, providing mainly starting material and unidentified degradation products.



Scheme 4 Mono Suzuki–Miyaura cross-coupling on pyrrole **3**

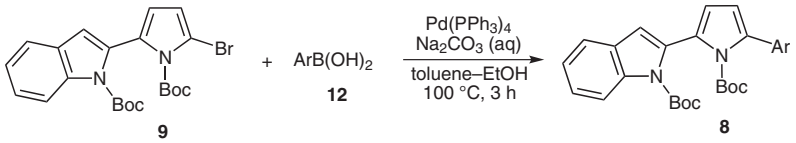
Compound **9** was then engaged in a second Suzuki coupling reaction with phenylboronic acid using the same reaction conditions as for the first indole-pyrrole coupling

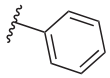
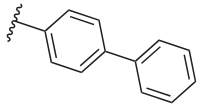
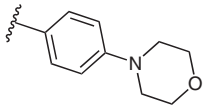
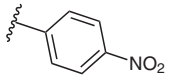
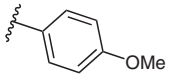
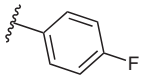
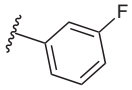
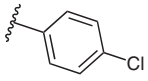
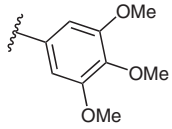
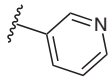
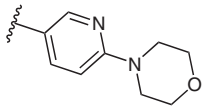
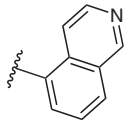


Scheme 3 Linear strategy for the preparation of target compound **8a**

reaction. This provided the unsymmetrical 2,5-disubstituted pyrrole derivative **8a** in 55% yield (Table 1, entry 1). However, the use of toluene–ethanol (4:1) instead of 1,2-dimethoxyethane as reaction solvent, allowing heating of the reaction mixture at 100 °C instead of 85 °C, improved the yield of compound **8a** to 84%. The latter was thus obtained in only four steps and in 38% overall yield starting from pyrrole, thereby demonstrating the superiority of this methodology compared to the step-wise procedure (Scheme 3) in which **8a** was obtained in five steps and in

Table 1 Second Suzuki–Miyaura Cross-Coupling on *N*-Boc-2-Bromo-5-indolopyrrole Derivative **9**[a]



Entry	Ar	Product	Yield (%)
1		**8a**	84 (55)[b]
2		**8b**	79
3		**8c**	52
4		**8d**	75
5		**8e**	81
6		**8f**	98
7		**8g**	82
8		**8h**	54
9		**8i**	88
10		**8j**	33
11		**8k**	76
12		**8l**	32

[a] Reactions were performed with **9**, $ArB(OH)_2$ (1.5 equiv), $Pd(PPh_3)_4$ (10 mol%) and Na_2CO_3 (2 M, 6.0 equiv) in a mixture of toluene–EtOH (4:1) at 100 °C for 3 h.

[b] Reaction was performed with **9**, $PhB(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$ (8 mol%), Na_2CO_3 (2 M, 4.0 equiv) and LiCl (1.0 equiv) in DME at 85 °C for 3 h.

30% overall yield from pyrrole. These improved conditions were then applied to a variety of aryl- and heteroarylboronic acids **12**, as shown in Table 1.

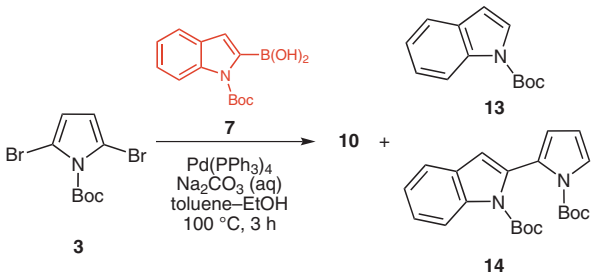
In the case of arylboronic acids, the yields of the unsymmetrical coupling products **8b–8i** were consistently good to excellent. Thus, introduction of the sterically hindered biphenyl group gave product **8b** in 79% yield (Table 1, entry 2) while the presence of either electron-withdrawing (nitro) or electron-donating (methoxy, trimethoxy) provided the corresponding products **8d**, **8e** and **8i**, respectively, in 75–88% yields (Table 1, entries 4, 5 and 9). The lower yield of the 4-phenylmorpholine derivative **8c** (52%, Table 1, entry 3) was ascribed to the relative instability of the starting non-commercial boronic acid.[22] The use of halogenated arylboronic acids was also successful as demonstrated by formation of the 4-fluorophenyl and 3-fluorophenyl derivatives **8f** and **8g** in yields of 98% and 82%, respectively (Table 1, entries 6 and 7); however, the 4-chlorophenyl derivative **8h** was obtained in a more moderate 54% yield (Table 1, entry 8).

Altogether, electronic effects seemed to have little effect on the outcome of the second Suzuki coupling reaction.

This second coupling reaction was also attempted using heteroarylboronic acids. Interestingly, while the pyridinomorpholine product **8k** was obtained in higher yield than its phenylmorpholine analogue **8c** (76% versus 52%, Table 1, entries 11 and 3), the unsubstituted pyridine derivative **8j** was obtained in considerably lower yield than its phenyl counterpart **8a** (33% and 84%, Table 1, entries 10 and 1) using, in all cases, exactly the same reaction conditions. The 5-isoquinolinyl derivative **8l** was obtained in a relatively modest but exploitable 32% yield (Table 1, entry 12). The use of stronger bases, different palladium catalysts and solvents, as well as microwave irradiation, did not lead to higher yields of **8j** and **8l**.

As noted above, the second Suzuki coupling to form compounds **8** from 2-bromo-5-indolylpyrrole derivative **9** was favored using toluene–ethanol (4:1) as the reaction medium, while the first coupling reaction to give **9** itself was conducted in 1,2-dimethoxyethane. With the objective of conducting both coupling reactions in the same solvent system (thereby avoiding the necessity of an intermediate work-up step), coupling of *N*-Boc-dibromopyrrole (**3**) with indol-2-ylboronic acid **7** was attempted in toluene–ethanol, that is, under the optimized reaction conditions of the second coupling reaction (Scheme 5). Surprisingly, no trace of the mono-coupled indole–pyrrole product **9** was found. Instead, only the debrominated form of **9** was observed (that is, compound **14** obtained in 10% isolated yield) together with the products of indole homocoupling **10** (14% yield) and deborylation **13** (27%). The necessity of using different solvent systems in order to optimize the yields of each of the two coupling steps thus seems apparent.

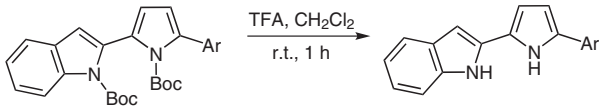
In view of the pharmacological potential of this new family of triaromatic compounds, simultaneous removal of both *N*-Boc groups was then studied (Table 2). Treatment



Scheme 5 Importance of the nature of the solvent on the first mono cross-coupling

of compounds **8** with trifluoroacetic acid in dichloromethane (1:1) at room temperature for one hour gave good (61%) to high (86%) yields of the bis-deprotected products **2a** and **2e–2i** (Table 2, entries 1 and 3–7). Only the nitrophenyl derivative **8d** gave a less satisfactory yield of deprotected product **2d** (32%, Table 2, entry 2). In the case of the two substrates having a heteroaryl moiety (**8j** and **8l**), the use of tetrabutylammonium fluoride instead of trifluoroacetic acid, under the same reaction conditions, proved to be necessary to remove the protecting groups in high yield (100% and 75%, respectively, Table 2, entries 8 and 9).

Table 2 Double Deprotection of Compounds **8**



8 **2**

Entry	Substrate	Product	Yield (%)
1	**8a**	**2a**	61
2	**8d**	**2d**	32
3	**8e**	**2e**	78
4	**8f**	**2f**	86
5	**8g**	**2g**	73
6	**8h**	**2h**	86
7	**8i**	**2i**	78
8	**8j**	**2j**	100[a]
9	**8l**	**2l**	75[a]

[a] TBAF–THF (1:1) at reflux for 4 h.

In conclusion, we have developed an efficient strategy for the synthesis of non-symmetrical 2-indolyl-5-aryl- and -heteroarylpyrroles from symmetrical *N*-Boc-2,5-dibromopyrrole (**3**) by successive and selective coupling of first, an indol-2-ylboronic acid, followed by an aryl- or heteroarylboronic acid. Structural diversity can thus be achieved in only two steps instead of the multi-step processes described until now. Furthermore, the use of the *tert*-butoxycarbonyl N-protecting group allows deprotec-

tion of the final products in typically high yields under mild conditions. Finally, the present procedure is complementary to our recently-described one-pot, simultaneous double Suzuki–Miyaura coupling reaction on *N*-Boc-2,5-dibromopyrrole (**3**) the success of which required the use, however, of arylboronic acids possessing significantly divergent electronic characters.[23]

Melting points were measured in capillary tubes on a Büchi B-540 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer. Proton NMR (^{1}H) spectra were recorded using Bruker 500 MHz or 300 MHz Avance spectrometers. Carbon NMR (^{13}C) spectra were recorded at 125 MHz or 75 MHz, using a broadband decoupled mode with the multiplicities obtained using a JMOD or DEPT sequence. Chemical shifts (δ) are reported in parts per million (ppm). NMR experiments were carried out in deuterochloroform ($CDCl_3$), deuteromethanol (CD_3OD) or deuterodimethylsulfoxide [$(CD_3)_2SO$]. Mass spectra were obtained either with an LCT (Micromass) instrument using electrospray ionization (ES), or using a Time-of-Flight analyzer (ESI-MS) for the high-resolution mass spectra (HRMS). Elemental analyses were performed on a Perkin Elmer CHN 2400 analyzer with detection by catharometry. Thin-layer chromatography was performed on silica gel 60 F254 on aluminum plates (Merck) and visualized under a UVP Mineralight UVLS-28 lamp (254 nm) and with ninhydrin and phosphomolybdic acid in ethanol. Flash chromatography was conducted on Merck silica gel 60 (40–63 μm) at medium pressure (300 mbar) or on CombiFlash (Serlabo Technologies). All reagents were obtained from commercial suppliers unless otherwise stated. Where necessary, organic solvents were routinely dried and/or distilled prior to use and stored over molecular sieves under nitrogen.

N-*tert*-Butoxycarbonyl-2-phenyl-1*H*-pyrrole (5)

To a stirred soln of **4** (0.25 g, 1.18 mmol), bromobenzene (0.13 g, 0.86 mmol), $Pd(PPh_3)_4$ (0.05 g, 43 μmol) in DME (15 mL) at r.t. under Ar was added a soln of Na_2CO_3 (0.38 g, 3.56 mmol) in H_2O (5 mL). The mixture was heated at reflux for 2 h, cooled and evaporated. CH_2Cl_2 (15 mL) was added and the organic layer was washed with H_2O (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated in vacuo. Chromatography (heptanes–EtOAc, 90:10) of the crude reaction product gave **5** (0.16 g, 87%) as a yellow oil.

R_f = 0.58 (heptanes–EtOAc, 90:10).

IR (neat): 1650, 1316, 1044 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 6 H), 6.30–6.28 (m, 1 H), 6.26–6.24 (m, 1 H), 1.41 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.4, 135.1, 134.5, 129.2, 127.6, 127.2, 122.5 (C-4), 114.4 (C-3), 110.6 (C-2), 83.5, 27.6.

MS (ESI): *m*/*z* = 266.1 [M + Na$^+$].

N-*tert*-Butoxycarbonyl-5-iodo-2-phenyl-1*H*-pyrrole (6)

To a dry 25 mL round-bottomed flask was added THF (1 mL) and 2,2,6,6-tetramethylpiperidine (TMP) (169 μl, 994 μmol). The mixture was cooled to –80 °C and *n*-BuLi (0.62 mL of a 1.6 M soln in hexanes, 994 μmol) was added dropwise, the temperature being maintained below –65 °C. The mixture was stirred for 1 h at –78 °C, compound **5** (161 mg, 662 μmol) in THF (1 mL) was added and the mixture stirred for 2 h at –78 °C. I_2 (185 mg, 729 μmol) in THF (1 mL) was then added and stirring was continued for 2 h at –78 °C. Sat. aq Na_2SO_3 soln (2 mL) was introduced and after 15 min, CH_2Cl_2 (10 mL) was added. The organic layer was washed with H_2O (3 × 5 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated in vacuo to give **6** (293 mg, 91%) as a red oil.

R_f = 0.54 (heptanes–EtOAc, 90:10).

IR (neat): 2925, 1681, 1316, 1140 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.42–7.28 (m, 5 H), 6.56 (d, *J* = 3.4 Hz, 1 H), 6.22 (d, *J* = 3.4 Hz, 1 H), 1.33 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.1, 138.9, 134.2, 128.2, 128.0, 127.4, 123.2, 114.8, 85.0, 66.2, 27.3.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{16}INO_2Na$ [M + Na$^+$]: 392.0124; found: 392.0135.

N-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-2-phenyl-1*H*-pyrrol-5-yl)-1*H*-indole (8a)

To a stirred soln of **6** (70 mg, 190 mol) in DME (1.5 mL) at r.t. under Ar were added *N*-Boc-indol-2-ylboronic acid (**7**) (45 mg, 172 μmol), a soln of Na_2CO_3 (77 mg, 724 μmol) in H_2O (0.5 mL) and $Pd(PPh_3)_4$ (10 mg, 9 μmol). The resulting mixture was heated at 85 °C for 15 h, then cooled and evaporated. CH_2Cl_2 (5 mL) was added and the organic layer was washed with H_2O (3 × 3 mL) and brine (3 mL), dried over $MgSO_4$ and evaporated in vacuo. Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8a** (32 mg, 41%) as a white powder.

Mp 141–142 °C; R_f = 0.36 (heptanes–CH_2Cl_2, 50:50).

IR (neat): 2982, 1753, 1724, 1332, 1297 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.5 Hz, 1 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.42–7.39 (m, 4 H), 7.38–7.35 (m, 2 H), 7.29–7.26 (m, 1 H), 6.69 (s, 1 H), 6.32 (d, *J* = 3.1 Hz, 1 H), 6.28 (d, *J* = 3.1 Hz, 1 H), 1.47 (s, 9 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 149.2, 137.0, 136.8, 134.4, 132.1, 128.8, 128.5, 128.2, 127.8, 127.2, 124.6, 122.7, 120.5, 115.8, 114.1, 112.7, 111.6, 83.6, 83.2, 27.9, 27.2.

Anal. Calcd for $C_{28}H_{30}N_2O_4$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.34; H, 6.63; N, 6.13.

N-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-2-bromo-1*H*-pyrrol-5-yl)-1*H*-indole (9), *N*,*N*′-Di-*tert*-butoxycarbonyl-1*H*,1′*H*-2,2′-biindole (10) and *N*,*N*′-Di-*tert*-butoxycarbonyl-2,2′-(*N*-*tert*-butoxycarbonyl-1*H*-pyrrole-2,5-diyl)-di-1*H*-indole (11)

To an oven-dried round-bottomed flask was added *N*-Boc-2,5-dibromo-1*H*-pyrrole (**3**)[18] (1.20 g, 3.71 mmol) and $Pd(PPh_3)_4$ (0.36 g, 0.31 mmol) in DME (40 mL). The mixture was degassed with Ar. *N*-Boc-indol-2-ylboronic acid (**7**) (1.16 g, 4.46 mmol), a soln of Na_2CO_3 (2.36 g, 14.84 mmol) in H_2O (11 mL) and LiCl (0.16 g, 3.71 mmol) were added. The reaction mixture was degassed with Ar and heated at 85 °C for 3 h. After cooling to r.t., the soln was filtered through a thin pad of Celite, the pad rinsed with EtOAc (15 mL) and the filtrate concd under reduced pressure. Chromatography (heptanes–EtOAc, 98:2) of the crude residue gave the desired product **9** (875 mg, 51% by NMR) as a colorless oil contaminated with the homocoupled indole product **10** ($C_{26}H_{28}N_2O_4$) (179 mg, 18% by NMR).

R_f = 0.40 (heptanes–EtOAc, 90:10).

IR (neat): 2981, 2933, 1745, 1720, 1334, 1307 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.35–8.31 (m, 1 H), 7.60–7.54 (m, 1 H), 7.40–7.33 (m, 1 H), 7.32–7.23 (m, 1 H), 6.58 (s, 1 H), 6.37 (d, *J* = 3.6 Hz, 1 H), 6.24 (d, *J* = 3.6 Hz, 1 H), 1.44 (s, 9 H), 1.21 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 148.0, 137.0, 132.1, 131.7, 128.7, 124.8, 122.9, 120.5, 115.8, 115.6, 114.9, 111.3, 102.6, 84.7, 83.6, 27.8, 27.4.

Anal. Calcd for $C_{22}H_{25}N_2O_4Br{\cdot}0.22C_{26}H_{28}N_2O_4$: C, 59.83; H, 5.64; N, 6.14. Found: C, 59.74; H, 5.59; N, 6.11.

Continued elution of the column gave pure compound **10**.[17]

R_f = 0.36 (heptanes–EtOAc, 90:10).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.2 Hz, 2 H), 7.59 (d, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.6 Hz, 2 H), 7.27 (t, *J* = 8.2 Hz, 2 H), 6.67 (s, 2 H), 1.26 (s, 18 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 137.0, 132.1, 128.7, 124.8, 122.8, 120.6, 115.7, 111.2, 83.4, 27.7.

MS (ESI): *m*/*z* = 455.2 [M + Na^+], 355.1 [M – Boc + Na^+].

Further elution of the column gave pure compound **11**.

R_f = 0.28 (heptanes–EtOAc, 90:10).

IR (neat): 2980, 1741, 1720, 1331, 1315, 745 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 7.5 Hz, 2 H), 7.35 (t, *J* = 8.5 Hz, 2 H), 7.25 (t, *J* = 7.5 Hz, 2 H), 6.57 (s, 2 H), 6.31 (s, 2 H), 1.48 (s, 18 H), 1.08 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 148.7, 137.0, 132.3, 128.9, 128.4, 124.6, 122.8, 120.5, 116.0, 114.2, 111.2, 83.5, 83.2, 28.0, 27.5.

HRMS (ESI): *m*/*z* calcd for $C_{35}H_{39}N_3O_6Na$ [M + Na^+]: 620.2724; found: 620.2737.

N-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-2-aryl-1*H*-pyrrol-5-yl)-1*H*-indoles 8; General Procedure

To an oven-dried round-bottomed flask was added compound **9** (1.0 equiv) and $Pd(PPh_3)_4$ (10 mol%) in a mixture of toluene–EtOH (4:1). The reaction mixture was degassed with Ar, and aryl or heteroaryl boronic acid [$ArB(OH)_2$] **12** (1.5 equiv) and a soln of Na_2CO_3 (6.0 equiv) in H_2O (1 mL) were added. The reaction mixture was again degassed with Ar and heated to 100 °C for 3 h before cooling to r.t. The soln was then filtered through a thin pad of Celite (eluting with EtOAc) and the filtrate was concd under reduced pressure. Chromatography (gradient elution) using the appropriate solvents gave the desired product.

N-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-2-phenyl-1*H*-pyrrol-5-yl)-1*H*-indole (8a)

Following the general procedure, compound **9** (61 mg, 132 μmol) was treated with phenylboronic acid (24 mg, 198 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8a** (50 mg, 84%) as a white powder which was identical to that prepared from compound **6**.

Biphenyl-4-ylboronic Acid

To a dry 25 mL round-bottomed flask was added 4-bromobiphenyl (990 mg, 4.25 mmol) in THF (20 mL). The mixture was cooled to –80 °C and *n*-BuLi (8.49 mmol) was added dropwise whilst keeping the temperature below –65 °C. The reaction mixture was stirred for 1 h at –78 °C and then trimethylborate (1.32 g, 12.74 mmol) was added, and the mixture stirred for a further 10 min at –78 °C and then for 1 h at r.t. NaOH (4% aq soln in H_2O, 10 mL) was added and the mixture was evaporated. EtOAc (20 mL) was added and the soln acidified to pH 5–6 using HCl (1 M; 4 mL). The organic layer was washed with H_2O (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated in vacuo to give biphenyl-4-ylboronic acid as a white powder which was used in the Suzuki cross-coupling step without further purification.

N-*tert*-Butoxycarbonyl-2-[*N*-*tert*-butoxycarbonyl-2-(biphenyl-4-yl)-1*H*-pyrrol-5-yl]-1*H*-indole (8b)

Following the general procedure, compound **9** (110 mg, 238 μmol) was treated with biphenyl-4-ylboronic acid (71 mg, 358 μmol). Chromatography (heptanes–EtOAc, 85:15) of the crude reaction product gave **8b** (100 mg, 79%) as a brown oil.

R_f = 0.79 (heptanes–EtOAc, 85:15).

IR (neat): 1743, 1726, 1333, 1304, 1154, 1138 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 8.5 Hz, 1 H), 7.67–7.62 (m, 4 H), 7.59 (d, *J* = 7.9 Hz, 1 H), 7.49–7.46 (m, 4 H), 7.39–7.36 (m, 2 H), 7.29–7.26 (m, 1 H), 6.67 (s, 1 H), 6.33 (s, 2 H), 1.47 (s, 9 H), 1.14 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 142.9, 140.8, 140.0, 137.0, 136.5, 133.3, 132.0, 128.8, 128.7, 128.4, 127.3, 127.2, 127.1, 126.6, 124.6, 122.8, 120.5, 115.8, 114.2, 113.0, 111.6, 83.8, 83.3, 27.9, 27.3.

HRMS (ESI): *m*/*z* calcd for $C_{34}H_{34}N_2O_4Na$ [M + Na^+]: 557.2426; found: 557.2416.

4-Morpholinophenylboronic Acid

To a dry 25 mL round-bottomed flask was added 4-(4-bromophenyl)morpholine (500 mg, 2.40 mmol) in THF (10 mL). The mixture was cooled to –80 °C and *n*-BuLi (4.81 mmol) was added dropwise whilst keeping the temperature below –65 °C. The mixture was stirred for 1 h at –78 °C and then trimethylborate (749 mg, 7.21 mmol) was added. The resulting mixture was stirred for 10 min at –78 °C and then for 1 h at r.t. NaOH (4% aq soln in H_2O, 5 mL) was added and the reaction mixture was evaporated. EtOAc (10 mL) was added and the soln was acidified to pH 5–6 using HCl (1 M; 2 mL). The organic layer was washed with H_2O (3 × 5 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated in vacuo to give 4-morpholinophenylboronic acid as a white powder which was used in the Suzuki cross-coupling step without further purification.

N-*tert*-Butoxycarbonyl-2-[*N*-*tert*-butoxycarbonyl-2-(4-morpholinophenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8c)

Following the general procedure, compound **9** (54 mg, 117 μmol) was treated with 4-morpholinophenylboronic acid (36 mg, 175 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8c** (33 mg, 52%) as a brownish-colored oil.

R_f = 0.36 (heptanes–EtOAc, 70:30).

IR (neat): 1735, 1724, 1332, 1303, 1138 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.2 Hz, 1 H), 7.57 (d, *J* = 7.6 Hz, 1 H), 7.35 (t, *J* = 8.2 Hz, 1 H), 7.30 (d, *J* = 8.9 Hz, 2 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 6.93 (d, *J* = 8.9 Hz, 2 H), 6.63 (s, 1 H), 6.28 (d, *J* = 3.4 Hz, 1 H), 6.20 (d, *J* = 3.4 Hz, 1 H), 3.89 (t, *J* = 4.6 Hz, 4 H), 3.23 (t, *J* = 4.6 Hz, 4 H), 1.44 (s, 9 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.3, 150.1, 149.3, 137.0, 136.9, 132.3, 129.4, 128.8, 127.7, 125.8, 124.5, 122.7, 120.4, 115.8, 114.8, 114.0, 112.1, 111.4, 83.4, 83.2, 66.9, 49.0, 27.9, 27.3.

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{37}N_3O_5Na$ [M + Na^+]: 566.2631; found: 566.2647.

N-*tert*-Butoxycarbonyl-2-[*N*-*tert*-butoxycarbonyl-2-(4-nitrophenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8d)

Following the general procedure, compound **9** (71 mg, 154 μmol) was treated with 4-nitrophenylboronic acid (39 mg, 231 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8d** (58 mg, 75%) as a yellow oil.

R_f = 0.40 (heptanes–EtOAc, 80:20).

IR (neat): 1753, 1727, 1511, 1316, 1303 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.3 Hz, 1 H), 8.27 (d, *J* = 8.5 Hz, 2 H), 7.60 (d, *J* = 7.5 Hz, 1 H), 7.54 (d, *J* = 8.5 Hz, 2 H), 7.38 (dd, *J* = 8.3 Hz, *J* = 2.1 Hz, 1 H), 7.28 (dd, *J* = 7.5 Hz, *J* = 2.1 Hz, 1 H), 6.67 (s, 1 H), 6.41 (d, *J* = 3.4 Hz, 1 H), 6.35 (d, *J* = 3.4 Hz, 1 H), 1.46 (s, 9 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 149.0, 146.6, 140.7, 136.9, 134.5, 131.2, 130.1, 128.8, 128.7, 124.9, 123.3, 122.9, 120.6, 115.8, 114.9, 114.6, 111.8, 84.5, 83.5, 27.9, 27.3.

Anal. Calcd for $C_{28}H_{29}N_3O_6$: C, 66.79; H, 5.80; N, 8.34. Found: C, 66.51; H, 5.93; N, 7.96.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(4-methoxyphenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8e)**

Following the general procedure, compound **9** (83 mg, 180 μmol) was treated with 4-methoxyphenylboronic acid (41 mg, 270 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8e** (71 mg, 81%) as a white powder.

Mp 108–109 °C; R_f = 0.41 (heptanes–EtOAc, 80:20).

IR (neat): 1747, 1729, 1333, 1310, 1132 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.34–8.33 (m, 1 H), 7.58–7.55 (m, 1 H), 7.38–7.26 (m, 4 H), 6.94 (d, *J* = 8.7 Hz, 2 H), 6.64 (s, 1 H), 6.28 (d, *J* = 3.4 Hz, 1 H), 6.21 (d, *J* = 3.4 Hz, 1 H), 3.86 (s, 3 H, CH_3O), 1.45 (s, 9 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.9, 150.0, 149.3, 137.0, 136.6, 132.3, 129.7, 128.8, 127.8, 126.9, 124.5, 122.7, 120.4, 115.8, 114.0, 113.4, 112.3, 111.4, 83.5, 83.2, 55.2, 27.9, 27.3.

Anal. Calcd for $C_{29}H_{32}N_2O_5$: C, 71.29; H, 6.60; N, 5.73. Found: C, 71.33; H, 6.58; N, 5.52.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(4-fluorophenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8f)**

Following the general procedure, compound **9** (87 mg, 189 μmol) was treated with 4-fluorophenylboronic acid (40 mg, 283 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8f** (88 mg, 98%) as a white powder.

Mp 161–162 °C; R_f = 0.54 (heptanes–CH_2Cl_2, 30:70).

IR (neat): 1747, 1720, 1315, 1145, 1134 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.35–8.32 (m, 1 H), 7.60–7.57 (m, 1 H), 7.40–7.33 (m, 3 H), 7.29–7.28 (m, 1 H), 7.13–7.07 (m, 2 H), 6.66 (s, 1 H), 6.31 (d, *J* = 3.2 Hz, 1 H), 6.24 (d, *J* = 3.2 Hz, 1 H), 1.47 (s, 9 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8–160.5 (d, $^1J_{C-F}$ = 246.5 Hz), 150.0, 149.2, 136.9, 135.7, 132.0, 130.5–130.3 (d, $^3J_{C-F}$ = 8.2 Hz), 130.2, 128.8, 128.3, 124.6, 122.8, 120.5, 115.8, 115.0–114.7 (d, $^2J_{C-F}$ = 22.0 Hz), 114.1, 112.9, 111.5, 83.8, 83.3, 27.9, 27.3.

Anal. Calcd for $C_{28}H_{29}FN_2O_4 \cdot 0.2H_2O$: C, 70.04; H, 6.17; N, 5.83. Found: C, 70.14; H, 6.22; N, 5.86.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(3-fluorophenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8g)**

Following the general procedure, compound **9** (96 mg, 207 μmol) was treated with 3-fluorophenylboronic acid (44 mg, 311 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8g** (80 mg, 82%) as a white powder.

Mp 118–119 °C; R_f = 0.74 (heptanes–EtOAc, 80:20).

IR (neat): 1748, 1725, 1330, 1321, 1154, 1140, 1128 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.34–8.32 (m, 1 H), 7.60–7.57 (m, 1 H), 7.40–7.34 (m, 2 H), 7.29–7.28 (m, 1 H), 7.18–7.17 (m, 1 H), 7.08–7.01 (m, 2 H), 6.66 (s, 1 H), 6.31 (d, *J* = 3.4 Hz, 1 H), 6.29 (d, *J* = 3.4 Hz, 1 H), 1.46 (s, 9 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0–160.7 (d, $^1J_{C-F}$ = 245.4 Hz), 150.0, 149.0, 136.9, 136.5–136.4 (d, $^3J_{C-F}$ = 2.7 Hz), 135.4, 131.7, 129.3, 129.2, 128.8–128.7 (d, $^3J_{C-F}$ = 3.3 Hz), 124.7, 124.3–124.2 (d, $^4J_{C-F}$ = 2.2 Hz), 122.8, 120.5, 115.8, 115.7–115.4 (d, $^2J_{C-F}$ = 22.1 Hz), 114.2–113.9 (d, $^2J_{C-F}$ = 22.1 Hz), 114.1, 113.3, 111.7, 83.9, 83.3, 27.9, 27.3.

Anal. Calcd for $C_{28}H_{29}FN_2O_4 \cdot 0.2H_2O$: C, 70.04; H, 6.17; N, 5.83. Found: C, 70.04; H, 6.07; N, 5.76.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(4-chlorophenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8h)**

Following the general procedure, compound **9** (64 mg, 139 μmol) was treated with 4-chlorophenylboronic acid (33 mg, 208 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8h** (37 mg, 54%) as a brown oil.

R_f = 0.72 (heptanes–EtOAc, 80:20).

IR (neat): 3048, 1748, 1720, 1330, 1309 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.34–8.31 (m, 1 H), 7.59–7.57 (m, 1 H), 7.39–7.33 (m, 4 H), 7.30–7.24 (m, 2 H), 6.65 (s, 1 H), 6.30 (d, *J* = 3.4 Hz, 1 H), 6.26 (d, *J* = 3.4 Hz, 1 H), 1.45 (s, 9 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 149.1, 136.9, 135.5, 133.2, 132.8, 131.9, 129.8, 128.8, 128.6, 128.1, 124.7, 122.8, 120.5, 115.8, 114.2, 113.1, 111.6, 83.9, 83.3, 27.9, 27.3.

Anal. Calcd for $C_{28}H_{29}ClN_2O_4 \cdot 0.1H_2O$: C, 67.97; H, 5.95; N, 5.66. Found: C, 68.01; H, 5.94; N, 5.48.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(3,4,5-trimethoxyphenyl)-1*H*-pyrrol-5-yl]-1*H*-indole (8i)**

Following the general procedure, compound **9** (82 mg, 180 μmol) was treated with 3,4,5-trimethoxyphenylboronic acid (57 mg, 270 μmol). Chromatography (PE–EtOAc–heptanes, 63:7:30) of the crude reaction product gave **8i** (87 mg, 88%) as a white powder.

Mp 78–79 °C; R_f = 0.20 (heptanes–EtOAc, 80:20).

IR (neat): 3129, 1736, 1730, 1333, 1310, 1128 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.3 Hz, 1 H), 7.57 (d, *J* = 7.5 Hz, 1 H), 7.36 (dd, *J* = 8.3 Hz, *J* = 1.1 Hz, 1 H), 7.26 (dd, *J* = 7.5 Hz, *J* = 1.1 Hz, 1 H), 6.65 (s, 1 H), 6.61 (s, 2 H), 6.29 (d, *J* = 3.4 Hz, 1 H), 6.26 (d, *J* = 3.4 Hz, 1 H), 3.90 (s, 3 H, CH_3O), 3.88 (s, 6 H, 2 × CH_3O), 1.46 (s, 9 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8, 150.0, 149.2, 137.5, 136.9, 136.6, 131.8, 129.8, 128.8, 128.2, 124.7, 122.8, 120.4, 115.8, 113.9, 112.6, 111.7, 105.8, 83.6, 83.2, 60.9, 56.0, 27.9, 27.3.

Anal. Calcd for $C_{31}H_{36}N_2O_7$: C, 67.87; H, 6.61; N, 5.11. Found: C, 67.66; H, 6.55; N, 4.84.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(pyridin-3-yl)-1*H*-pyrrol-5-yl]-1*H*-indole (8j)**

Following the general procedure, compound **9** (102 mg, 221 μmol) was treated with pyridin-3-ylboronic acid (41 mg, 332 μmol). Chromatography (heptanes–EtOAc, 70:30) of the crude reaction product gave **8j** (33 mg, 33%) as an orange oil.

R_f = 0.20 (heptanes–EtOAc, 70:30).

IR (neat): 1726, 1302, 1134 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.67 (br s, 1 H), 8.57 (d, *J* = 4.9 Hz, 1 H), 8.31 (d, *J* = 8.2 Hz, 1 H), 7.70 (d, *J* = 7.9 Hz, 1 H), 7.58 (d, *J* = 7.6 Hz, 1 H), 7.38–7.32 (m, 2 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 6.66 (s, 1 H), 6.34 (d, *J* = 3.4 Hz, 1 H), 6.32 (d, *J* = 3.4 Hz, 1 H), 1.46 (s, 9 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.9, 149.3, 149.0, 148.1, 136.9, 135.8, 133.1, 131.7, 130.5, 129.2, 128.7, 124.7, 122.8, 122.7, 120.5, 115.8, 114.4, 114.0, 111.6, 84.2, 83.3, 27.9, 27.3.

Anal. Calcd for $C_{27}H_{29}N_3O_4 \cdot 0.3EtOAc$: C, 69.61; H, 6.63; N, 8.64. Found: C, 69.52; H, 6.27; N, 8.37.

***N-tert*-Butoxycarbonyl-2-[*N-tert*-butoxycarbonyl-2-(6-morpholinopyridin-3-yl)-1*H*-pyrrol-5-yl]-1*H*-indole (8k)**

Following the general procedure, compound **9** (57 mg, 123 μmol) was treated with 6-morpholinopyridin-3-ylboronic acid (54 mg, 185 μmol). Chromatography of the crude reaction product (PE–EtOAc–heptanes, 63:7:30) gave **8k** (51 mg, 76%) as a white powder.

Mp 111–112 °C; R_f = 0.28 (heptanes–EtOAc, 90:10).

IR (neat): 1726, 1604, 1305, 1111, 744 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 8.2 Hz, 1 H), 8.25 (d, *J* = 2.1 Hz, 1 H), 7.57–7.53 (m, 2 H), 7.35 (t, *J* = 8.2 Hz, 1 H), 7.26 (t, *J* = 7.9 Hz, 1 H), 6.68 (d, *J* = 8.2 Hz, 1 H), 6.63 (s, 1 H), 6.30 (d, *J* = 3.4 Hz, 1 H), 6.22 (d, *J* = 3.4 Hz, 1 H), 3.85 (t, *J* = 4.9 Hz, 4 H), 3.57 (t, *J* = 4.9 Hz, 4 H), 1.43 (s, 9 H), 1.12 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.3, 150.0, 149.2, 147.1, 145.3, 138.2, 136.9, 134.0, 132.2, 128.8, 128.1, 124.6, 122.8, 120.4, 115.8, 114.4, 112.7, 111.3, 105.7, 83.8, 83.3, 66.8, 45.6, 27.9, 27.3.

Anal. Calcd for $C_{31}H_{36}N_4O_5$: C, 68.36; H, 6.66; N, 10.29. Found: C, 68.24; H, 6.63; N, 10.11.

Isoquinolin-5-ylboronic Acid

To a dry 25 mL round-bottomed flask was added 5-bromoisoquinoline (500 mg, 2.40 mmol) in THF (10 mL). The mixture was cooled to –80 °C and *n*-BuLi (4.81 mmol) was added dropwise whilst keeping the temperature below –65 °C. The mixture was stirred for 1 h at –78 °C and then trimethylborate (749 mg, 7.21 mmol) was added. The mixture was stirred for 10 min at –78 °C and then for 1 h at r.t. NaOH (4% aq soln in H_2O, 5 mL) was added and the reaction mixture was evaporated. EtOAc (10 mL) was added and the soln was acidified to pH 5–6 using HCl (1 M; 4 mL). The organic layer was washed with H_2O (3 × 5 mL) and brine (5 mL), dried over $MgSO_4$ and evaporated in vacuo to give isoquinolin-5-ylboronic acid as a white powder which was used in the Suzuki cross-coupling step without further purification.

***N*-*tert*-Butoxycarbonyl-2-[*N*-*tert*-butoxycarbonyl-2-(isoquinolin-5-yl)-1*H*-pyrrol-5-yl]-1*H*-indole (8l)**

Following the general procedure, compound **9** (108 mg, 234 μmol) was treated with isoquinolin-5-ylboronic acid (49 mg, 281 μmol). Chromatography (heptanes–EtOAc, 70:30) of the crude reaction product gave **8l** (38 mg, 32%) as a brown oil.

R_f = 0.29 (heptanes–EtOAc, 70:30).

IR (neat): 1737, 1731, 1310, 1142, 1119 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.30 (s, 1 H), 8.51 (d, *J* = 6.1 Hz, 1 H), 8.19 (br s, 1 H), 8.00 (d, *J* = 7.9 Hz, 1 H), 7.74–7.72 (m, 1 H), 7.68–7.65 (m, 1 H), 7.61–7.60 (m, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.28–7.25 (m, 2 H), 6.75 (s, 1 H), 6.46 (d, *J* = 3.1 Hz, 1 H), 6.36 (d, *J* = 3.1 Hz, 1 H), 1.61 (s, 9 H), 0.80 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.2, 150.1, 148.6, 142.4, 142.3, 135.9, 130.9, 130.6, 129.1, 128.9, 128.0, 127.7, 127.6, 127.3, 127.2, 127.1, 124.5, 122.7, 120.7, 115.8, 114.6, 114.5, 111.2, 83.5, 83.3, 28.2, 26.9.

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{32}N_3O_4$ [M + H^+]: 510.2383; found: 510.2369.

***N*,*N*′-Di-*tert*-Butoxycarbonyl-1*H*,1′*H*-2,2′-biindole (10), *N*-*tert*-Butoxycarbonylindole (13) and *N*-*tert*-Butoxycarbonyl-2-(*N*-*tert*-butoxycarbonyl-2-1*H*-pyrrolyl)-1*H*-indole (14)**

To an oven-dried round-bottomed flask was added compound **3** (109 mg, 337 μmol) and $Pd(PPh_3)_4$ (39 mg, 34 μmol) in a mixture of toluene–EtOH (4:1) and the mixture degassed with Ar. *N*-Boc-indol-2-ylboronic acid (**7**) (132 mg, 506 μmol) and a soln of Na_2CO_3 (215 mg, 2.02 mmol) in H_2O (1 mL) were added. The reaction mixture was degassed with Ar and heated at 100 °C for 3 h. After cooling to r.t., the soln was filtered through a thin pad of Celite, the pad rinsed with EtOAc (10 mL) and the filtrate concd under reduced pressure. Chromatography (heptanes–EtOAc, 98:2) of the crude reaction product gave *N*-Boc-indole **13** (20 mg, 27%).

Continued elution of the column gave pure **14** (21 mg, 24%) as a colorless oil.

R_f = 0.46 (heptanes–CH_2Cl_2, 65:35).

IR (neat): 1726, 1452, 1334, 1319, 1153, 1123 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.28 (d, *J* = 7.9 Hz, 1 H), 7.55 (d, *J* = 7.6 Hz, 1 H), 7.48–7.45 (m, 1 H), 7.34 (t, *J* = 7.9 Hz, 1 H), 7.24 (t, *J* = 7.6 Hz, 1 H), 6.58 (s, 1 H), 6.30–6.28 (m, 1 H), 6.26–6.25 (m, 1 H), 1.42 (s, 9 H), 1.27 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.0, 149.0, 137.0, 131.9, 128.7, 126.4, 124.5, 122.6, 122.2, 120.4, 115.7, 115.6, 111.1, 110.4, 83.6, 82.8, 27.9, 27.6.

MS (ESI): *m*/*z* = 382.2 [M^+].

Further elution of the column gave pure compound **10** (20 mg, 10%) identical with that prepared above.

Deprotection of Compounds 8; General Procedures

Procedure A

A soln of **8** in CH_2Cl_2 (1 mL) was treated under Ar with TFA (1 mL) and the resulting soln was stirred at r.t. for 1 h. The mixture was evaporated and the residue was taken up in acetone, filtered through a thin pad of K_2CO_3 (eluting with acetone) and the solvent was evaporated under reduced pressure to give product **2**.

Procedure B

A soln of **8** in THF (1 mL) was treated under Ar with TBAF in THF (1.33 mL) and the resulting soln was heated at reflux for 4 h. The mixture was then cooled and evaporated. EtOAc (5 mL) was added and the organic layer was washed with H_2O (3 × 3 mL) and brine (3 mL), dried over $MgSO_4$ and evaporated in vacuo. Chromatography (gradient elution) using appropriate solvents gave the desired product **2**.

2-(5-Phenyl-1*H*-pyrrol-2-yl)-1*H*-indole (2a)

Following procedure A, compound **8a** (25 mg, 55 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2a** (9 mg, 61%) as a brown powder.

Mp 210–212 °C; R_f = 0.36 (heptanes–EtOAc, 70:30).

IR (neat): 3333, 3254 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 10.57 (br s, 1 H, NH), 10.31 (br s, 1 H, NH), 7.64–7.62 (m, 2 H), 7.39–7.35 (m, 1 H), 7.29–7.23 (m, 3 H), 7.11–7.07 (m, 1 H), 6.96–6.92 (m, 1 H), 6.89–6.86 (m, 1 H), 6.86 (s, 1 H), 6.58–6.56 (m, 1 H), 6.54–6.52 (m, 1 H).

^{13}C NMR (75 MHz, C_3D_6O): δ = 137.7, 134.0, 133.7, 132.9, 130.3, 129.6, 127.8, 126.8, 124.7, 121.9, 120.5, 120.3, 111.5, 108.5, 108.2, 97.4.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{15}N_2$ [M + H^+]: 259.1235; found: 259.1209.

2-[5-(4-Nitrophenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2d)

Following procedure A, compound **8d** (42 mg, 83 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2d** (8 mg, 32%) as a black oil.

R_f = 0.16 (heptanes–EtOAc, 80:20).

IR (neat): 3350, 3305, 1678, 1594, 1511, 1261 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 11.10 (br s, 1 H, NH), 10.59 (br s, 1 H, NH), 8.24 (d, *J* = 9.2 Hz, 2 H), 7.98 (d, *J* = 9.2 Hz, 2 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.39 (d, *J* = 7.6 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.98 (d, *J* = 3.7 Hz, 1 H), 6.89 (s, 1 H), 6.79 (d, *J* = 3.7 Hz, 1 H).

^{13}C NMR (75 MHz, C_3D_6O): δ = 147.0, 139.6, 139.5, 137.9, 131.9, 131.7, 128.2, 125.2, 124.5, 122.5, 120.8, 120.5, 112.2, 111.7, 109.5, 98.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{12}N_3O_2$ [M – H^+]: 302.0941; found: 302.0930.

2-[5-(4-Methoxyphenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2e)
Following procedure A, compound **8e** (39 mg, 80 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2e** (18 mg, 78%) as a black powder.

Mp 196–197 °C; R_f = 0.19 (heptanes–EtOAc, 80:20).

IR (neat): 3434, 3387, 1237 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 10.64 (br s, 1 H, NH), 10.48 (br s, 1 H, NH), 7.68 (d, *J* = 8.9 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.05 (t, *J* = 7.3 Hz, 1 H), 7.00–6.99 (m, 1 H), 6.96 (d, *J* = 8.9 Hz, 2 H), 6.76 (s, 1 H), 6.67–6.66 (m, 1 H), 6.52–6.51 (m, 1 H), 3.82 (s, 3 H, CH_3O).

^{13}C NMR (75 MHz, C_3D_6O): δ = 159.3, 137.7, 134.2, 130.4, 126.6, 126.1, 126.0, 125.4, 121.8, 120.3, 120.2, 115.0, 111.4, 108.3, 107.0, 97.0, 55.6.

Anal. Calcd for $C_{19}H_{16}N_2O{\cdot}0.5H_2O{\cdot}0.5C_3H_6O$: C, 73.63; H, 6.03; N, 8.38. Found: C, 73.61; H, 5.93; N, 7.99.

2-[5-(4-Fluorophenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2f)
Following procedure A, compound **8f** (35 mg, 73 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2f** (17 mg, 86%) as a grey powder.

Mp 198–199 °C; R_f = 0.38 (heptanes–EtOAc, 80:20).

IR (neat): 3440, 3415, 1231 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 10.72 (br s, 1 H, NH), 10.45 (br s, 1 H, NH), 7.80–7.75 (m, 2 H), 7.52–7.49 (m, 1 H), 7.37–7.35 (m, 1 H), 7.20–7.14 (m, 2 H), 7.10–7.04 (m, 1 H), 7.02–6.97 (m, 1 H), 6.80–6.79 (m, 1 H), 6.70–6.69 (m, 1 H), 6.62–6.61 (m, 1 H).

^{13}C NMR (75 MHz, C_3D_6O): δ = 162.9–159.7 (d, $^1J_{C–F}$ = 243.0 Hz), 136.8, 132.2, 131.9, 129.4, 126.9, 125.7, 125.6, 121.1, 119.6, 119.4, 115.4 (d, $^2J_{C–F}$ = 21.4 Hz), 110.6, 107.6, 107.3, 96.5.

Anal. Calcd for $C_{18}H_{13}FN_2{\cdot}0.3H_2O{\cdot}0.3C_3H_6O$: C, 75.89; H, 5.19; N, 9.36. Found: C, 76.09; H, 5.55; N, 8.96.

2-[5-(3-Fluorophenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2g)
Following procedure A, compound **8g** (37 mg, 78 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2g** (16 mg, 73%) as a grey powder.

Mp 191–192 °C; R_f = 0.45 (heptanes–EtOAc, 80:20).

IR (neat): 3434, 3410, 1184 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 10.65 (br s, 1 H, NH), 10.36 (br s, 1 H, NH), 7.45–7.35 (m, 3 H), 7.29–7.21 (m, 2 H), 6.95–6.77 (m, 3 H), 6.67 (s, 1 H), 6.59–6.54 (m, 2 H).

^{13}C NMR (75 MHz, C_3D_6O): δ = 165.0–161.8 (d, $^1J_{C–F}$ = 243.0 Hz), 136.9, 135.2–135.1 (d, $^3J_{C–F}$ = 8.8 Hz), 131.8 (d, $^4J_{C–F}$ = 2.7 Hz), 131.7, 130.6–130.5 (d, $^3J_{C–F}$ = 8.8 Hz), 129.4, 127.6, 121.2, 119.8, 119.7–119.6 (d, $^4J_{C–F}$ = 2.7 Hz), 119.5, 112.3–112.0 (d, $^2J_{C–F}$ = 21.4 Hz), 110.7, 110.3–110.0 (d, $^2J_{C–F}$ = 22.5 Hz), 108.4, 107.7, 96.9.

Anal. Calcd for $C_{18}H_{13}FN_2{\cdot}0.45H_2O{\cdot}0.45C_3H_6O$: C, 74.84; H, 5.39; N, 9.02. Found: C, 74.84; H, 5.28; N, 9.08.

2-[5-(4-Chlorophenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2h)
Following procedure A, compound **8h** (28 mg, 57 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2h** (15 mg, 86%) as an orange powder.

Mp 202–203 °C; R_f = 0.40 (heptanes–EtOAc, 80:20).

IR (neat): 3430, 3390, 827 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 7.62 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 7.5 Hz, 1 H), 7.25 (d, *J* = 8.7 Hz, 2 H), 7.21 (d, *J* = 7.3 Hz, 1 H), 6.92 (t, *J* = 7.5 Hz, 1 H), 6.86 (t, *J* = 7.5 Hz, 1 H), 6.65 (s, 1 H), 6.55 (d, *J* = 3.8 Hz, 1 H), 6.53 (d, *J* = 3.8 Hz, 1 H).

^{13}C NMR (75 MHz, C_3D_6O): δ = 137.6, 132.6, 132.5, 131.7, 130.2, 129.6, 128.1, 126.1, 126.0, 122.0, 120.5, 120.3, 111.5, 108.8, 108.6, 99.8.

Anal. Calcd for $C_{18}H_{13}ClN_2{\cdot}0.55H_2O{\cdot}0.55C_3H_6O$: C, 70.53; H, 5.24; N, 8.37. Found: C, 70.58; H, 5.21; N, 8.25.

2-[5-(3,4,5-Trimethoxyphenyl)-1*H*-pyrrol-2-yl]-1*H*-indole (2i)
Following procedure A, compound **8i** (36 mg, 65 μmol) and TFA (1 mL) were stirred in CH_2Cl_2 (1 mL). After treatment, the eluent was evaporated to give **2i** (18 mg, 78%) as a black powder.

Mp 193–194 °C; R_f = 0.06 (heptanes–EtOAc, 80:20).

IR (neat): 3395, 3337, 1120 cm^{-1}.

^1H NMR (500 MHz, C_3D_6O): δ = 11.44 (br s, 1 H, NH), 11.27 (br s, 1 H, NH), 7.31–7.26 (m, 2 H), 7.00 (br s, 2 H), 6.88–6.78 (m, 2 H), 6.51–6.50 (m, 2 H), 6.44–6.43 (m, 1 H), 3.77 (s, 6 H, 2 × CH_3O), 3.60 (s, 3 H, CH_3O).

^{13}C NMR (75 MHz, C_3D_6O): δ = 154.7, 137.9, 137.6, 134.1, 133.3, 130.3, 129.8, 127.8, 121.4, 120.0 (2 × C), 111.9, 108.6, 108.0, 102.6, 97.1, 60.6, 56.6.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{21}N_2O_3$ [M + H^+]: 349.1549; found: 349.1552.

2-[5-(Pyridin-3-yl)-1*H*-pyrrol-2-yl]-1*H*-indole (2j)
Following procedure B, compound **8j** (31 mg, 67 μmol) in THF (1 mL) was treated with TBAF in THF (1.33 mL). Chromatography [20% EtOAc in a mixture of CH_2Cl_2–MeOH–NH_4OH, 38:17:2 (soln B)] of the crude reaction product gave **2j** (17 mg, 100%) as an orange oil.

R_f = 0.62 (CH_2Cl_2–soln B, 80:2).

IR (neat): 3374, 3354, 1596 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 8.89 (d, *J* = 1.8 Hz, 1 H), 8.33–8.32 (m, 1 H), 8.11 (dt, *J* = 7.9 Hz, *J* = 1.8 Hz, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.43–7.42 (m, 1 H), 7.35 (d, *J* = 7.9 Hz, 1 H), 7.07 (t, *J* = 7.9 Hz, 1 H), 6.99 (t, *J* = 7.6 Hz, 1 H), 6.77 (s, 1 H), 6.71 (d, *J* = 4.0 Hz, 1 H), 6.65 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 146.6, 145.5, 138.3, 132.8, 132.7, 131.1, 130.6, 130.3, 129.9, 125.4, 122.3, 120.7, 120.4, 111.6, 109.8, 108.7, 97.7.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_3$ [M + H^+]: 260.1187; found: 260.1188.

5-[5-(1*H*-Indol-2-yl)-1*H*-pyrrol-2-yl]isoquinoline (2l)
Following procedure B, compound **8l** (34 mg, 67 μmol) in THF (1 mL) was treated with TBAF in THF (1.33 mL). Chromatography (EtOAc) of the crude reaction product gave **2l** (15 mg, 75%) as a yellow oil.

R_f = 0.33 (EtOAc).

IR (neat): 3395, 3354, 1618 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 9.39 (br s, 1 H, NH), 9.21 (s, 1 H), 9.01 (br s, 1 H, NH), 8.44 (d, *J* = 6.0 Hz, 1 H), 8.07 (d, *J* = 6.0 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 7.3 Hz, 1 H), 7.64–7.59 (m, 2 H), 7.38 (d, *J* = 7.5 Hz, 1 H), 7.19 (td, *J* = 7.5 Hz, *J* = 1.1 Hz, 1 H), 7.13 (td, *J* = 7.3 Hz, *J* = 1.1 Hz, 1 H), 6.70–6.68 (m, 2 H), 6.61–6.59 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, 152.8, 150.4, 143.3, 143.2, 133.8, 130.1, 130.0, 129.2, 129.1 (2 × C), 127.1, 127.0, 122.0, 120.3, 120.2, 118.6, 111.6, 110.7, 107.3, 97.3.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{16}N_3$ [M + H^+]: 310.1344; found: 310.1349.

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