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A concise synthesis of novel naphtho[*a*]carbazoles and benzo[*c*]carbazoles

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Abstract—Starting from simple indole precursors the synthesis of naphtho[*a*]carbazoles and benzo[*c*]carbazoles is described. Key steps include the use of the Suzuki–Miyaura reaction to afford 2- or 3-aryl substituted indoles, as well as a potassium *t*-butoxide and light assisted aromatic ring-forming reaction.

1. Introduction

Indolocarbazoles such as rebeccamycin **1** and staurosporine **2** display a range of biological activities that make them attractive compounds to synthetic and medicinal chemists.[1–4] As a result, the synthesis of many analogues, for example, **3** and **4** and the benzo- and naphtho-fused carbazoles such as **5** and **6** (Fig. 1), have been described. Compound **3** has been found to be a potent tyrosine kinase inhibitor of vascular endothelial growth factor R2,[5] while isogranulatimide **4** has been described as an G2 checkpoint inhibitor.[5a] The naphtho- and benzo-fused carbazoles (although rarely found in Nature) are of interest owing to their potential as antitumour agents.

For example, the synthetic naphtho[*a*]carbazole[6] **5** is a potential candidate for cancer treatment as a result of DNA intercalative binding properties[7] and the well-known indole/naphthalene bioisotery,[8] while benzo[*c*]carbazole **6**[9] shows promising profiles for intra-cyclin dependent kinase selectivity. In general it has been found that modification of the indolo[2,3-*a*]carbazole framework can lead to products with very different useful pharmacological properties and biological activities.[5]

In these laboratories, we have developed novel methodology for the synthesis of benzo[*a*]carbazoles and pyrido[2,3-*a*]-carbazoles[10,11] by means of a novel light- and base-assisted cyclization reaction to form a centrally-positioned aromatic

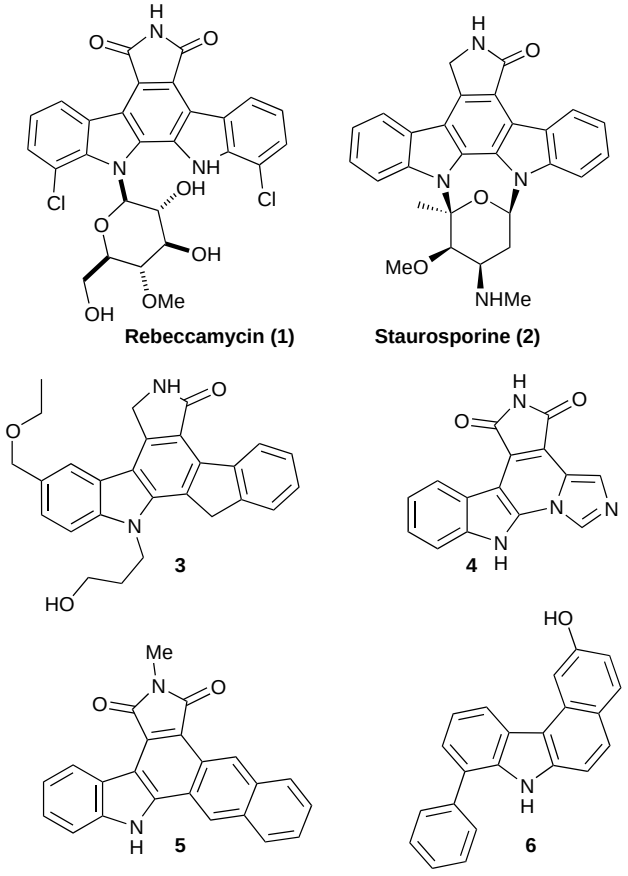

Figure 1. Representative biologically active indolocarbazoles and naphtho- and benzo-fused carbazoles.

Keywords: Suzuki–Miyaura reaction; Carbazoles; Antitumour; Potassium *t*-butoxide.
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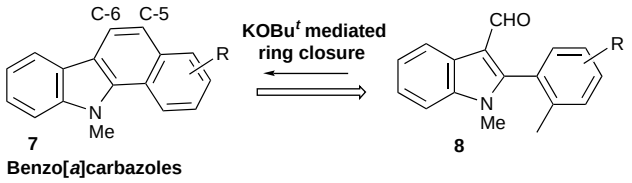


Figure 2. Retrosynthesis of benzo[*c*]carbazoles.

ring (Fig. 2). For benzo[*a*]carbazoles **7**, for example, the last step entails the construction of the C-5/C-6 bond (i.e., **8**→**7**) by our novel ring-forming reaction.[11]

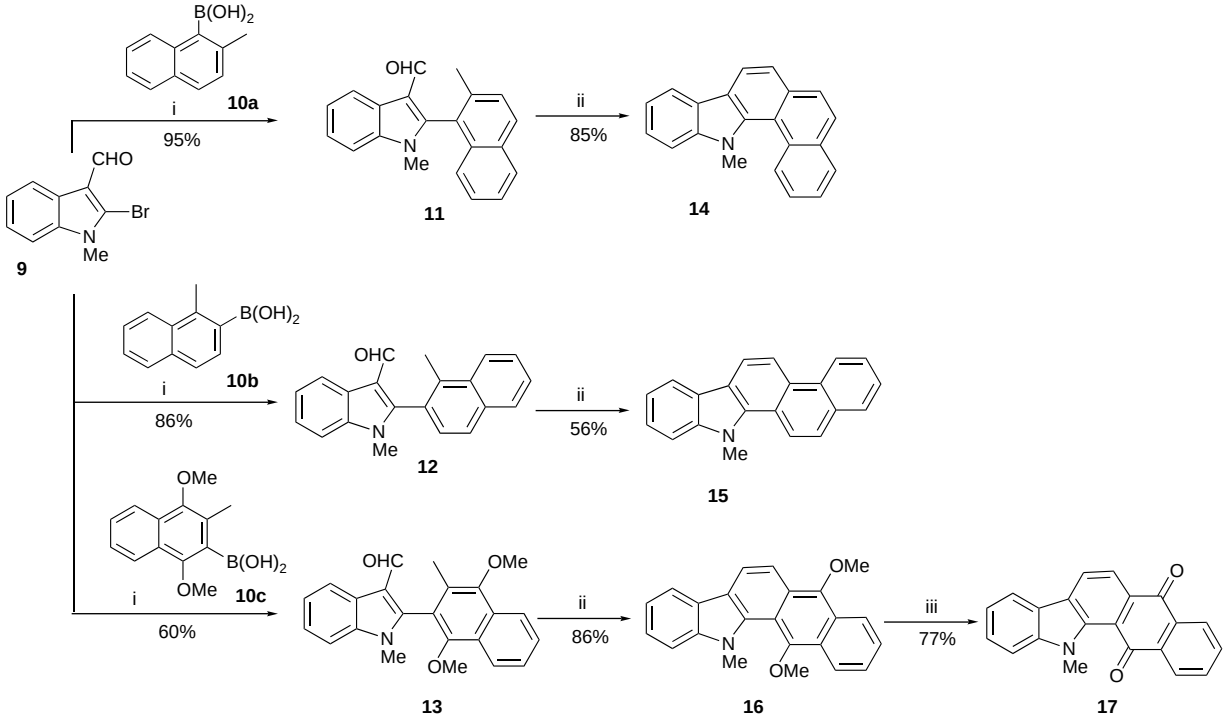
2. Results and discussion

As part of our ongoing programme we wished to extend the methodology developed for the synthesis of benzo[*a*]carbazoles to the synthesis of naphtho[*a*]-fused carbazoles and carbazoles containing rings fused onto the *c*-face. These extensions are described in this paper.[12]

As a starting point for this work we believed that treatment of the readily available *N*-methyl-2-bromoindole-3-carbaldehyde **9**[11] with a number of naphthaleneboronic acids, as we had done previously for benzeneboronic acids would provide easy access to naphtho[*a*]carbazoles. However, since the desired naphthaleneboronic acids were not commercially available, the initial task was to synthesize them. Boronic acid **10a** was prepared by treating 1-bromo-2-methylnaphthalene[13] with *n*-BuLi followed by the addition of trimethyl borate and then hydrochloric acid. The more challenging synthesis of boronic acid **10b** involved treatment of 1-methylindene with KOBu^t and $CHBr_3$ to give 2-bromo-1-methylnaphthalene,[14] which was treated in the same manner as 1-bromo-2-methylnaphthalene to afford 1-methyl-2-naphthylboronic acid **10b**. Boronic acid **10c** was synthesised as described previously.[15] Treatment of **10a–c** with **9** under aqueous Suzuki–Miyaura coupling reaction conditions afforded the desired biaryl compounds **11**, **12** and **13** in good yields (Scheme 1). It was clear from the spectroscopic data that the desired products had been formed. In particular, the presence of the aromatic methyl protons in the range of δ 2.2–2.5 in the ^{1}H NMR spectra were a good indication that the reaction had proceeded. Exposure of each of these substrates (**11**, **12** and **13**) to reaction conditions (KOBu^t, DMF, hν) that we have developed for forming new aromatic rings gave the desired naphtho-fused carbazoles **14**, **15** and **16** in fair to good yields (56–86%).[11,15] Naphthocarbazole **16** could also be oxidised with ceric ammonium nitrate to afford quinone **17**.[16]

As depicted in the retrosynthesis in Figure 3, we planned to extend this synthesis to benzo[*c*]carbazoles such as **18** from indoles such as **19** or **20** containing a substituted aromatic ring at the 3-position. Examination of the retrosynthesis shows that a carbonyl-containing substituent is required *ortho* to the biaryl linkage, either on the benzene ring or the indole nucleus. In addition, either the benzene ring or the indole nucleus must possess a methyl substituent at the 2-position. The biaryl linkage for both possible retrosynthesis could be formed, as before, using Suzuki–Miyaura coupling methodology.

As the first option we choose to attempt the synthesis using the disconnection leading to the placement of the carbonyl on the 2-position of the indole nucelus (i.e., **19**, Fig. 4). We believed that further disconnection would lead to a 3-bromoindole derivative such as **21**. The synthesis of **21a**



Scheme 1. Reagents and conditions: (i) 10 mol% $Pd(PPh_3)_4$, DME/EtOH, 2 M aq Na_2CO_3, reflux 48 h; (ii) KOBu^t, DMF, hν, 80 °C, 10 min; (iii) CAN, THF, rt.

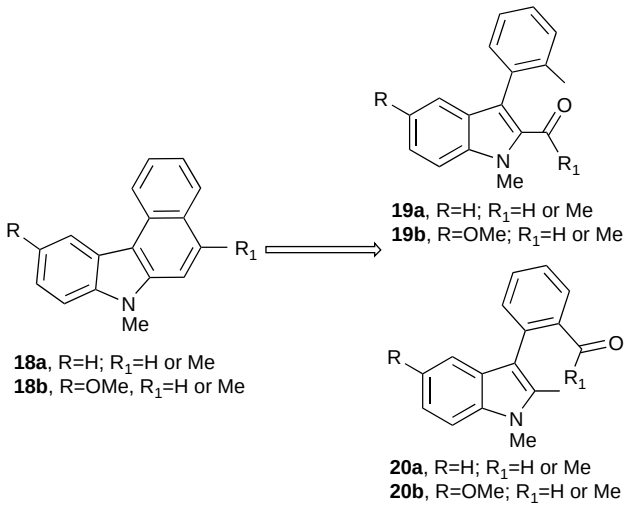


Figure 3. Retrosynthesis of benzo[*c*]carbazoles.

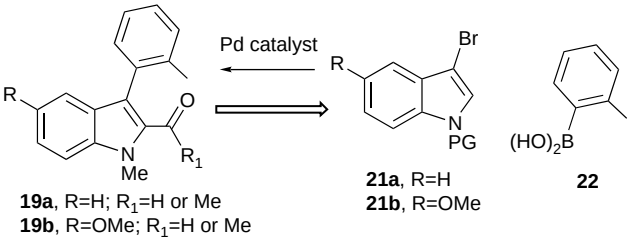


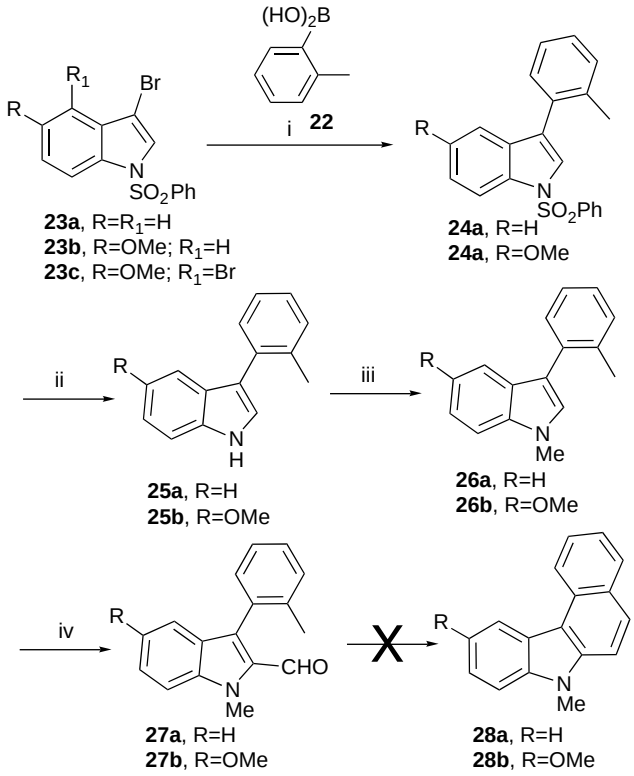
Figure 4. Retrosynthesis of **19**.

($PG{=}SO_2Ph$) has been described in the literature[17] and the toluene boronic acid **22** is commercially available and has been made and used many times in our laboratories. We thought that the carbonyl containing substituent at C-2 of the indole nucleus could be introduced once the aromatic ring had been placed at C-3 of the indole by means of a Suzuki–Miyaura coupling reaction.

The synthesis commenced with the preparation of the known compound **23a**[17] as well as its 5-methoxy analogue **23b**. The analogue **23b** was prepared by bromination of 5-methoxyindole followed by protection of the resulting 3-bromo-5-methoxyindole with phenylsulfonyl chloride to afford **23b** in 65% over two steps. If the steps were reversed and 5-methoxy-1-(phenylsulfonyl)-1*H*-indole was treated with bromine significant amounts of **23c** were isolated unless the reaction was done very carefully.

Treatment of both **23a** and **23b** under Suzuki–Miyaura reaction conditions with toluene boronic acid **22** provided the desired 3-aryl substituted indoles **24a** and **24b** in good yield (Scheme 2). In order to introduce the aldehyde substituent at the 2-position of the indole nucleus the phenylsulfonyl group on the indole nitrogen was removed and replaced by a methyl in a two-step procedure.

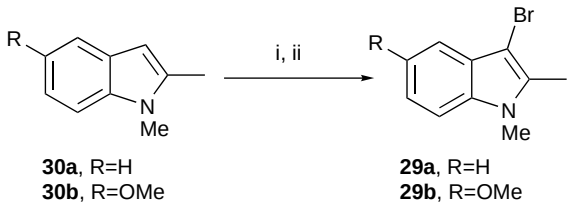
The first step was accomplished with K_2CO_3 in MeOH to give **25a** and **25b** and the second by exposure of the free indole nitrogen to $(MeO)_2SO_2$ and NaH to afford **26a** and **26b**. Attachment of the formyl group at C-2 was achieved by treatment of **26a** and **26b** under classical



Scheme 2. Reagents and conditions: (i) 10 mol% $Pd(PPh_3)_4$, DME, aq K_2CO_3, reflux, 18 h, **24a**, 100%; **24b**, 99%; (ii) MeOH, K_2CO_3, reflux, **25a**, 93%; **25b**, 96%; (iii) $(MeO)_2SO_2$, THF, NaH, rt, **26a**, 99%; **26b**, 99%; (iv) $POCl_3$, DMF, reflux, **27a**, 60%; **27b**, 27%; (v) $KOBu^t$, DMF, hν, 80 °C, 10 min, no reaction.

Vilsmeier–Haack reaction conditions to provide **27a** and **27b** in mediocre to poor yields of 60 and 27%, respectively. We were now in a position to attempt the base mediated ring closure reaction to hopefully yield the desired products **28a** and **28b**. To our surprise all attempts at this reaction failed to produce the desired products and the only detectable products from this reaction were the result of deformylation yielding **26a** and **26b**.[18] Hence the alternative retrosynthesis outlined in Figure 3 giving intermediates **20a** and **20b** was pursued in which the positions of the carbonyl and methyl substiuent were interchanged.

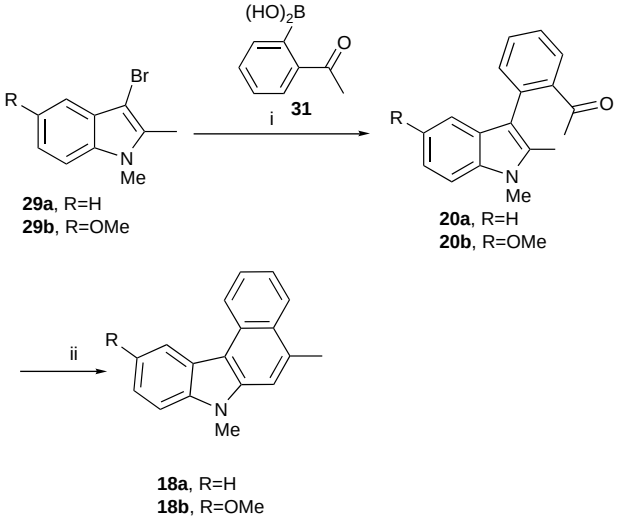
In order to achieve the synthesis of **20a–b**, suitable 2-brominated indole precursors **29a** and **29b** were prepared (Scheme 3). Exposure of 2-methylindole **30a** to molecular bromine followed by protection of the indole nitrogen by *N*-methylation afforded **29a** in good yield. The synthesis of methoxyindole **29b** was accomplished from **30b**, but in this case the bromination of **30b** was accomplished with



Scheme 3. Reagents and conditions: **30a**→**29a** (i) Br_2, DMF, rt, 99%; (ii) $(MeO)_2SO_2$, NaH, THF, 18 h, 99%. **30b**→**29b** (i) NBS, CH_2Cl_2, cat. SiO_2, 30 min, 99%; (ii) $(MeO)_2SO_2$, NaH, THF, 48 h, 94%.

N-bromosuccinimide (NBS), as the use of molecular bromine resulted in simultaneous bromination of the electron-rich aromatic ring. Both **29a** and **29b** were unstable and had to be used immediately in subsequent steps.

Treatment of both **29a** and **29b** under non-aqueous Suzuki–Miyaura coupling conditions with the commercially available boronic acid **31** resulted in the formation of the desired biaryl compounds **20a** and **20b** in good yields (Scheme 4). Exposure of **20a** and **20b** to potassium *t*-butoxide in the presence of light gave the desired benzo[*c*]carbazoles **18a** and **18b** in good yield. Clear evidence for the formation of the products was provided by spectroscopy. For example, in the ^{1}H NMR spectrum of **18a** an aromatic methyl at δ 2.79 was present and it was noted that both the acetyl methyl and the methyl at the 2-position of the indole nucleus of the starting material **20a** were no longer observed.



Scheme 4. Reagents and conditions: (i) 20 mol% $Pd(PPh_3)_4$, DMF, K_3PO_4, 100 °C, 65 h, **20a**, 83%; **20b**, 80%; (ii) $KOBu^t$, DMF, hν, 80 °C, 10 min, **18a**, 71%; **18b**, 70%.

In conclusion, we have been able to show that both [*a*]-fused naphtho- and [*c*]-fused benzocarbazoles can be synthesised from simple indole precursors using our well developed aromatic ring-forming reaction.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded either on a Bruker ADVANCE 300 (300.132 MHz for ^{1}H, 75.473 for ^{13}C), a Bruker DRX-400 (400.132 MHz for ^{1}H, 100.625 for ^{13}C) or a Bruker AC-200 (200.13 MHz for ^{1}H, 50.32 for ^{13}C) spectrometer at the frequency indicated. *J*-values are given in Hz. Infra-red spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer, or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or a VG 70 SEQ mass spectrometer. Macherey-Nagel Kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography, and Macherey-Nagel Kieselgel 60 (particle size 0.040–0.063 mm) was used for preparative flash chromatography. All solvents used for reactions and chromatography were distilled prior to use. THF and Et_2O were freshly distilled from sodium benzophenone ketyl under nitrogen.

3.1.1. 1-Bromo-2-methylnaphthalene. A solution of Br_2 (0.40 mL, 7.8 mmol) in acetic acid (2 mL) was added dropwise to a solution of 2-methylnaphthalene (1.01 g, 7.10 mmol) and anhydrous KOAc (0.75 g, 7.8 mmol) in AcOH (2 mL). After the mixture had been stirred for 15 min it was added to CH_2Cl_2 (20 mL) and the solution was washed with saturated aq $NaHCO_3$ (30 mL) and H_2O (20 mL). The residue obtained upon evaporation was purified by column chromatography (20% EtOAc–hexane) to obtain the product, 1-bromo-2-methylnaphthalene (1.43 g, 92%) as a clear oil. The spectral data agreed with that described in the literature.[13]

3.1.2. 2-Bromo-1-methylnaphthalene. $KOBu^t$ (2.10 g, 18.6 mmol) was stirred in 25 mL anhydrous Et_2O under N_2 atmosphere. Redistilled 1-methylindene (2.01 g, 15.5 mmol) was added dropwise to yield an orange slurry. Freshly distilled $CHBr_3$ (4.85 g, 19.6 mmol) was then added dropwise over a period of 35 min. The slurry became pink, then red and finally a deep red-violet with precipitation of solid material. The reaction mixture was periodically cooled to 20 °C while it was stirred for 2.5 h. The mixture was then quenched with water (50 mL) and extracted with Et_2O (3×50 mL) followed by brine. The mixture was filtered and dried with $MgSO_4$ to give brown oil. The oil was slurred in 37.5 mL of absolute EtOH and 0.50 g of KOH and heated at reflux for 30 min. Hexane (50 mL) was added and the mixture was heated for 30 min and filtered. The mixture was then rinsed with hexane (3×50 mL) and the solution was finally evaporated on a rotary evaporator. The crude material was then purified by column chromatography (5–20% EtOAc–hexane) to give the product, 2-bromo-1-methylnaphthalene (3.8 g, 38%) as a yellow oil. The ^{1}H and ^{13}C NMR spectral data agreed with that described in the literature.[14]

3.1.3. 2-Methyl-1-naphthylboronic acid 10a. *n*-BuLi (1.2 M, 3.9 mL, 4.7 mmol) was added dropwise to a solution of 1-bromo-2-methylnaphthalene (1.01 g, 4.57 mmol) in THF (30 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, then $B(OMe)_3$ (1.39 g, 1.50 mL, 13.4 mmol) was added. The resulting mixture was stirred at −78 °C for a further 30 min and then allowed to warm to rt. The reaction mixture was acidified with aq 10% HCl solution and extracted with Et_2O (3×30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under vacuum to afford an off-white crystalline material, 2-methyl-1-naphthylboronic acid **10a** (0.74 g, 87%), which was used without further purification or characterization.

3.1.4. 1-Methyl-2-naphthylboronic acid 10b. *n*-BuLi (1.4 M, 2.1 mL, 2.9 mmol) was added dropwise to a solution of 2-bromo-1-methylnaphthalene (0.50 g, 2.3 mmol) in THF (15 mL) at −78 °C. The reaction mixture was then treated as described above and $B(OMe)_3$

(0.70 g, 0.75 mL, 6.7 mmol) was added. An off-white crystalline material, 1-methyl-2-naphthylboronic acid **10b** (0.39 g, 93%) was produced, which was used without further purification or characterization.

3.1.5. 1,4-Dimethoxy-3-methyl-2-naphthylboronic acid 10c. 2-Bromo-1,4-dimethoxy-3-methylnaphthalene was prepared according to Ref. 19. This was then treated as described above to afford the desired boronic acid **10c**.[15]

3.2. Representative procedure for the Suzuki coupling reactions

3.2.1. 1-Methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde 11. A solution of 2-bromo-1-methyl-1*H*-indole-3-carbaldehyde **9** (0.100 g, 0.420 mmol) in DME (2 mL) was deoxygenated by passing N_2 through the mixture for 5 min. The deoxygenated mixture was added to $Pd(PPh_3)_4$ (10 mol%, 0.048 g, 0.040 mmol) and stirred under N_2 for 10 min at rt. A solution of 2-methyl-1-naphthylboronic acid **10a** (0.110 g, 0.591 mmol) in EtOH (1.5 mL) was deoxygenated and added to the reaction mixture. The mixture was stirred for a further 10 min. A deoxygenated 2 M aq Na_2CO_3 solution (3.0 mL, 6.0 mmol) was added and the reaction mixture was stirred at rt for 5 min before being heated at reflux for 2 days. The mixture was cooled to rt and quenched with H_2O (20 mL). The organic material was extracted with CH_2Cl_2 (3×30 mL) and the solvent was evaporated under reduced pressure. The crude product was subjected to column chromatography (2–10% EtOAc–hexane) to afford 1-methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde **11** as an off-white solid (0.120 g, 95%). Mp 146–147 °C; ν_{max}/cm^{-1} 1655 (C=O), 1579 (ArC=C), 1501, 1466, 1444 and 1421; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.28 (3H, s, $ArCH_3$), 3.42 (3H, s, NCH_3), 7.23 (1H, m, Ar-H), 7.35–7.51 (6H, m, 6×Ar-H), 7.91 (1H, d, J=8.0 Hz, Ar-H), 7.96 (1H, d, J=8.5 Hz, Ar-H), 8.48 (1H, m, Ar-H) and 9.45 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 20.5 ($ArCH_3$), 30.2 (NCH_3), 109.8 (Ar-CH), 116.4 (Ar-C), 122.3 (Ar-CH), 123.3 (Ar-CH), 123.8 (Ar-CH), 124.4 (Ar-C), 125.0 (Ar-CH), 125.3 (Ar-C), 125.7 (Ar-CH), 127.4 (Ar-CH), 128.1 (2×Ar-CH), 130.2 (Ar-CH), 131.7 (Ar-C), 133.6 (Ar-C), 137.3 (Ar-C), 137.6 (Ar-C) and 149.4 (Ar-C), 186.0 (CHO); MS m/z 299 (M^+, 100%), 284 (38), 282 (55), 254 (19) and 127 (14); HRMS calcd for $C_{21}H_{17}NO$: 299.1310, found: 299.1307.

The following compounds were prepared in a similar manner.

3.2.2. 1-Methyl-2-(1-methyl-2-naphthyl)-1*H*-indole-3-carbaldehyde 12. The product **12** was isolated as an off-white solid (0.162 g, 86%) from **9** (0.150 g, 0.630 mmol) and **10b** (0.164 g, 0.882 mmol). Mp 184–186 °C; IR ν_{max}/cm^{-1} 1652 (C=O), 1610, 1579 and 1528 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.52 (3H, s, $ArCH_3$), 3.53 (3H, s, NCH_3), 7.35–7.43 (4H, m, 4×Ar-H), 7.61–7.67 (2H, m, 2×Ar-H), 7.83 (1H, d, J=8.4 Hz, Ar-H), 7.93–7.96 (1H, m, Ar-H), 8.11–8.14 (1H, m, Ar-H), 8.43–8.46 (1H, m, Ar-H), 9.61 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$) 17.0 ($ArCH_3$), 31.0 (NCH_3), 110.2 (Ar-CH), 116.6 (Ar-C), 122.6 (Ar-CH), 123.7 (Ar-CH), 124.3 (Ar-CH), 125.0 (Ar-CH), 125.6 (Ar-C), 125.9 (Ar-C), 126.9 (Ar-CH), 127.5 (2×Ar-CH), 128.1 (Ar-CH), 129.2 (Ar-CH), 132.9 (Ar-C), 134.3 (Ar-C), 135.9 (Ar-C), 137.8 (Ar-C), 152.2 (Ar-C), 186.6 (CHO); MS m/z 299 (M^+, 78%), 284 (100), 282 (74), 254 (24); HRMS calcd for $C_{21}H_{17}NO$: 299.1310, found: 299.1309.

3.2.3. 1-Methyl-2-(1,4-dimethoxy-2-methyl-3-naphthyl)-1*H*-indole-3-carbaldehyde 13. The product **13** was isolated as a yellow solid (0.224 g, 60%) from **9** (0.247 g, 1.04 mmol) and **10c** (0.359 g, 1.46 mmol). Mp 147–148 °C; IR ν_{max}/cm^{-1} 1655 (C=O) and 1593 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.16 (3H, s, $ArCH_3$), 3.55 and 3.60 (each 3H, s, 2×OCH_3), 3.95 (3H, s, NCH_3), 7.37–7.47 (3H, m, 3×Ar-H), 7.57–7.67 (2H, m, 2×Ar-H), 8.13–8.20 (2H, m, 2×Ar-H), 8.42–8.45 (1H, m, Ar-H), 9.73 (1H, s, CHO); δ_C (75 MHz; $CDCl_3$), 13.8 ($ArCH_3$), 30.4 (NCH_3), 61.5 and 62.0 (2×OCH_3), 109.9 (Ar-CH), 115.8 (Ar-C), 119.4 (Ar-C), 122.0 (Ar-CH), 122.4 (Ar-CH), 122.9 (Ar-CH), 123.0 (Ar-CH), 123.7 (Ar-CH), 125.2 (Ar-C), 126.3 (Ar-CH), 126.3 (Ar-C), 127.1 (Ar-C), 127.7 (Ar-CH), 129.9 (Ar-C), 137.6 (Ar-C), 147.2 (Ar-C), 150.4 (Ar-C), 152.2 (Ar-C), 185.6 (CHO); MS m/z 360 (M^++1, 25%) 359 (M^+, 100), 344 (23), 329 (20), 328 (68) and 285 (17); HRMS calcd for $C_{23}H_{21}NO_3$: 359.1521, found: 259.1535.

3.3. Representative procedure for the ring-forming reactions

3.3.1. 13-Methyl-13*H*-naphtho[1,2-*a*]carbazole 14. $KOBu^t$ (0.06 g, 0.53 mmol) was added to 1-methyl-2-(2-methyl-1-naphthyl)-1*H*-indole-3-carbaldehyde **11** (0.045 g, 0.15 mmol) dissolved in dry DMF (6 cm^3) and was heated under N_2 atmosphere at 80 °C while being irradiated with a high pressure mercury lamp through a quartz filter for 10 min. The reaction mixture was quenched with H_2O (50 mL) and extracted with Et_2O (3×50 mL). The organic layer was dried with $MgSO_4$ and filtered. It was then evaporated and subjected to column chromatography (10–20% EtOAc–hexane) to afford the product **14** (0.034 g, 85%) as an off-white solid. Mp 113–115 °C; IR ν_{max}/cm^{-1} 1616 (ArC=C), 1559 and 1527; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.78 (3H, s, NCH_3), 7.31–7.34 (1H, m, Ar-H), 7.49–7.61 (4H, m, 4×Ar-H), 7.70 (1H, d, J=8.1 Hz, Ar-H), 7.74 (1H, d, J=8.7 Hz, Ar-H), 7.86 (1H, d, J=8.7 Hz, Ar-H), 7.93 (1H, d, J=7.9 Hz, Ar-H), 8.15 (1H, d, J=7.7 Hz, Ar-H), 8.22 (1H, d, J=8.1 Hz, Ar-H) and 8.66 (1H, d, J=8.1 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 37.6 (NCH_3), 111.2 (Ar-CH), 118.2 (Ar-C), 119.3 (Ar-CH), 120.0 (Ar-CH), 120.6 (Ar-CH), 121.3 (Ar-CH), 123.9 (Ar-C), 124.8 (Ar-C), 125.1 (Ar-CH), 125.7 (2×Ar-CH), 125.9 (Ar-CH), 127.7 (2×Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-C), 132.1 (Ar-C), 132.4 (Ar-C), 140.0 (Ar-C) and 145.9 (Ar-C); MS m/z 281 (M^+, 100%), 266 (18), 265 (19) and 141 (9); HRMS calcd for $C_{21}H_{12}N$: 281.1204, found: 281.1203.

The following compounds were prepared in a similar manner.

3.3.2. 11-Methyl-11*H*-naphtho[2,1-*a*]carbazole 15. The product **15** was isolated as an off-white solid (0.045 g, 56%) from **12** (0.085 g, 0.28 mmol). Mp 213–216 °C; IR ν_{max} ($CHCl_3$)/cm^{-1} 1617 and 1572 (ArC=C), 1466, 1437 and 1407; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.43 (3H, s, NCH_3), 7.30–7.35 (1H, m, Ar-H), 7.50–7.71 (4H, m, 4×Ar-H), 7.86

(1H, d, J=9.2 Hz, Ar-H), 7.94 (1H, d, J=7.6 Hz, Ar-H), 8.20 (1H, d, J=7.8 Hz, Ar-H), 8.35 (1H, d, J=8.7 Hz, Ar-H), 8.60 (1H, d, J=8.7 Hz, Ar-H), 8.71 (1H, d, J=9.2 Hz, Ar-H) and 8.82 (1H, d, J=8.3 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 34.4 (NCH_3), 109.0 (Ar-CH), 114.8 (Ar-CH), 119.2 (Ar-CH), 119.5 (Ar-CH), 119.8 (Ar-CH), 120.7 (Ar-C), 121.0 (Ar-CH), 122.8 (Ar-C), 123.5 (Ar-CH), 125.3 (Ar-CH), 125.8 (Ar-CH), 126.1 (Ar-CH), 126.7 (Ar-CH), 128.4 (Ar-CH), 129.7 (Ar-C), 131.1 (Ar-C), 131.2 (Ar-C), 137.0 (Ar-C) and 141.6 (Ar-C), (one quaternary C not observed); MS m/z 281 (M+, 100%), 266 (22), 252 (3) and 140 (2); HRMS calcd for $C_{21}H_{15}N$: 281.1204, found: 281.1209.

3.3.3. 5,13-Dimethoxy-12-methyl-12*H*-naptho[2,3-*a*]-carbazole 16. The product **16** was isolated as a pale yellow solid (0.050 g, 81%) from **13** (0.065 g, 0.18 mmol). Mp 133–135 °C; IR ν_{max} /cm^{-1} 1605 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.81 (3H, s, NCH_3), 4.17 and 4.25 (each 3H, s, 2×OCH_3), 7.33–7.38 (1H, m, Ar-H), 7.49–7.58 (3H, m, 3×Ar-H), 7.63 (1H, d, J=8.2 Hz, Ar-H), 8.09 (2H, s, 2×Ar-H), 8.14 (1H, d, J=7.8 Hz, Ar-H), 8.33–8.37 (1H, m, Ar-H) and 8.42–8.45 (1H, m, Ar-H); δ_C (75 MHz; $CDCl_3$) 37.2 (NCH_3), 62.0 and 63.0 (2×OCH_3), 110.7 (Ar-CH), 115.0 (Ar-CH), 115.4 (Ar-C), 119.1 (Ar-C), 119.3 (Ar-CH), 119.4 (Ar-CH), 120.3 (Ar-CH), 122.4 (Ar-CH), 122.7 (Ar-CH), 124.0 (Ar-C), 124.7 (Ar-CH), 124.8 (Ar-C), 125.4 (Ar-CH), 125.5 (Ar-CH), 125.6 (Ar-C), 125.7 (Ar-C), 137.9 (Ar-C), 143.3 (Ar-C), 147.1 (Ar-C) and 148.7 (Ar-C); MS m/z 342 (M^++1, 34%), 341 (M^+, 80), 327 (20), 326 (100), 312 (16), 311 (42), 310 (44), 282 (8), 170 (14), 163 (10), 155 (14), 149 (18) and 69 (13); HRMS calcd for $C_{23}H_{19}NO_2$: 341.1416, found: 341.1411.

3.3.4. 12-Methyl-5*H*-naphtho[2,3-*a*]carbazole-5,13-(12*H*)-dione 17. Carbazole **16** (10 mg, 0.0029 mmol) in THF was stirred together with cerium(IV) ammonium nitrate (7 mg, 0.013 mmol) at rt for 30 min. Water was added to the reaction mixture and the organic material was extracted into Et_2O (3×20 mL). The combined organic layers were dried with $MgSO_4$ and filtered. The organic solvent was then evaporated and subjected to column chromatography (20–40% EtOAc–hexane) to afford the product **17** as an orange solid (7 mg, 77%). mp193–195 °C; IR ν_{max}/cm^{-1} 1644 (C=O), 1621 and 1594 (ArC=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.03 (3H, s, NCH_3), 7.32–7.37 (1H, m, Ar-H), 7.54–7.63 (2H, m, 2×Ar-H), 7.74–7.83 (2H, m, 2×Ar-H), 8.13 (1H, d, J=7.8 Hz, Ar-H), 8.24–8.30 (3H, m, 3×Ar-H) and 8.40 (1H, d, J=8.0 Hz, Ar-H); δ_C (75 MHz; $CDCl_3$) 36.0 (NCH_3), 110.5 (Ar-CH), 119.0 (Ar-CH), 120.8 (Ar-CH), 120.9 (Ar-CH), 121.9 (Ar-C), 125.2 (Ar-CH), 126.7 (Ar-CH), 126.8 (Ar-CH), 128.3 (Ar-CH), 131.1 (Ar-C), 132.6 (Ar-C), 133.2 (Ar-C), 133.4 (Ar-CH), 133.9 (Ar-CH), 135.4 (Ar-C), 140.0 (Ar-C), 143.2 (Ar-C), 145.5 (Ar-C), 183.7 (C=O) and 191.8 (C=O); MS m/z 312 (M^+, 22%), 311 (92), 310 (100), 297 (33), 282 (8), 254 (11), 155 (5) and 127 (7); HRMS calcd for $C_{21}H_{13}O_2N$: 311.0946, found: 311.0946.

3.3.5. 3-Bromo-1-(phenylsulfonyl)-1*H*-indole 23a. 1-(Phenylsulfonyl)-1*H*-indole (2.00 g, 7.77 mmol) was dissolved in CH_2Cl_2 (60 mL). To the resulting solution, Br_2 (1.37 g, 0.440 mL, 8.55 mmol) was added dropwise. The red reaction mixture was then stirred at rt for 4.5 h, and then poured into a saturated solution of aq $NaHCO_3$ (80 mL). The resulting two layers were separated, and the organic layer successively washed with aq $Na_2S_2O_3$ (60 mL), H_2O (60 mL), brine (60 mL) and then dried with $MgSO_4$ mixed with charcoal. The solvent was removed under reduced pressure and the crude residue was purified by chromatography (20% EtOAc–hexane) to afford the product **23a** (2.58 g, 99%) as light orange crystals. Mp 125–126 °C, lit. (125–127 °C);[17] δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 7.29–7.57 (6H, m, 6×Ar-H), 7.63 (1H, s, 2-H), 7.87–7.91 (2H, m, 2×Ar-H) and 7.99 (1H, d, J=8.3 Hz, Ar-H); δ_C (50 MHz; $CDCl_3$) 99.8 (Ar-C), 113.6 (Ar-CH), 120.0 (Ar-CH), 124.0 (Ar-CH), 124.7 (Ar-CH), 125.8 (Ar-CH), 126.8 (2×Ar-CH), 129.3 (Ar-C), 129.4 (2×Ar-CH), 134.1 (Ar-CH), 134.2 (Ar-C) and 137.8 (Ar-C).[17]

3.3.6. 3-Bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole 23b. 5-Methoxyindole (200 mg, 1.36 mmol) was dissolved in DMF (5 mL). To the resulting solution Br_2 (219 mg, 0.070 mL, 1.37 mmol) dissolved in DMF (5 mL) was added dropwise within a few minutes at rt while stirring. The end point of the reaction was easily detectable by the appearance of the halogen colour (light brown). The reaction mixture was then poured onto ice and H_2O (50 mL) containing 0.5% NH_3 and 0.1% sodium metabisulphite. The white precipitate formed was then filtered, washed with cold H_2O and dried. Recrystallization was carried out from EtOH/H_2O to give fluffy white crystals (256 mg, 83%) of 3-bromo-5-methoxy-1*H*-indole. To an ice-cold mixture of powdered NaOH (55 mg, 1.37 mmol) and tetrabutylammonium bromide (3.7 mg, 0.015 mmol) in dry CH_2Cl_2 (3 mL) under N_2 was added solid 3-bromo-5-methoxy-1*H*-indole (100 mg, 0.442 mmol) followed by the addition of phenylsulfonyl chloride (94 mg, 0.068 mL, 0.53 mmol). The reaction mixture was then stirred vigorously at rt for 2 h. The white precipitate that formed was filtered off and the solid was purified by silica gel column chromatography (20% EtOAc–hexane) to afford the product **23b** (126 mg, 78%) as a white solid. Mp 131–133 °C; IR ν_{max} ($CHCl_3$)/cm^{-1} 1615 and 1583 (ArC=C), 1475, 1447, 1435 and 1375; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.84 (3H, s, OMe), 6.89 (1H, d, J=1.2 Hz, 4-H), 6.98 (1H, dd, J=6.8, 1.2 Hz, 6-H), 7.42–7.46 (2H, m, 2×Ar-H), 7.53–7.58 (1H, m, 2×Ar-H), 7.58 (1H, s, 2-H), 7.84–7.86 (2H, m, Ar-H) and 7.89 (1H, d, J=6.8 Hz, 7-H); δ_C (75 MHz; $CDCl_3$) 55.7 (OMe), 99.8 (3-C), 101.9 (Ar-CH), 114.7 (Ar-CH), 115.4 (Ar-CH), 125.4 (Ar-CH), 126.8 (2×Ar-CH), 128.8 (Ar-C), 129.3 (2×Ar-CH), 130.8 (Ar-C), 134.0 (Ar-CH), 137.8 (Ar-C) and 157.1 (5-C); MS m/z 367 (M+, 64%), 365 (64), 226 (98), 224 (100), 211 (14), 209 (14), 183 (21), 181 (16), 178 (25), 124 (21), 102 (16), 81 (15), 77 (51) and 69 (36); HRMS calcd for $C_{15}H_{12}Br^{79}NO_3S$: 364.9721, found: 364.9722.

3.3.7. 3,4-Dibromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole 23c. 5-Methoxy-1-(phenylsulfonyl)-1*H*-indole (2.00 g, 6.97 mmol) was dissolved in CCl_4 (60 mL). To the resulting solution, Br_2 (1.22 g, 0.40 mL, 7.67 mmol) was added dropwise. The red reaction mixture was then stirred at rt for 4.5 h, and then poured into saturated solution of aq $NaHCO_3$ (80 mL). The resulting two layers were separated, and the organic layer successively washed with aq $Na_2S_2O_3$ (60 mL), water (60 mL), brine (60 mL) and then dried with $MgSO_4$ mixed with charcoal. The solvent was removed

under reduced pressure and the crude residue was purified by chromatography (10% EtOAc–hexane) to afford the product **23c** (2.53 g, 82%) as orange crystals. Mp 129 °C; IR ν_{max}/cm^{-1} 1600, 1582, 1561 (ArC=C), 1462, 1449, 1415 and 1375; δ_H (400 MHz; $CDCl_3$; Me_4Si) 3.91 (3H, s, OCH_3), 6.98 (1H, d, $J=9.1$ Hz, 6-H), 7.44–7.49 (2H, m, 2×Ar-H), 7.56–7.60 (1H, m, Ar-H), 7.67 (1H, s, 2-H), 7.83–7.87 (2H, m, 2×Ar-H) and 7.94 (1H, d, $J=9.1$ Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 57.7 (OCH_3), 98.9 (3-C)[a], 103.9 (4-C)[a], 111.6 (Ar-CH), 113.5 (Ar-CH), 127.2 (2× Ar-CH), 127.5 (Ar-C), 128.5 (Ar-CH), 129.8 (Ar-C), 129.9 (2×Ar-CH), 134.7 (Ar-CH), 137.8 (Ar-C) and 153.6 (5-C); MS *m/z* 347 (M^+, 100%), 445, (68), 443 (36), 415 (15), 306 (46), 304 (100), 302 (51), 289 (26), 265 (21), 261 (24), 256 (35), 214 (26), 132 (22), 130 (22), 97 (21), 85 (17), 83 (30), 81 (38), 77 (53), 73 (40), 71 (29), 69 (82), 67 (27), 60 (32), 57 (53), 56 (20), 55 (74), 51 (20), 43 (80), 41 (86) and 39 (19); HRMS calcd for $C_{15}H_{11}^{79}Br_2NO_3S$ 442.8826, found: 442.8944. The position of the bromine atom was determined by NOE spectroscopy.

3.3.8. 2-Methylphenylboronic acid 22. 1-Bromo-2-methylbenzene (5.00 g, 3.50 mL, 29.3 mmol) was dissolved in THF (30 mL) and cooled to −78 °C. *n*-Butyllithium (25.1 mL, 32.2 mmol) was added dropwise and the resulting white suspension was stirred at −78 °C under an atmosphere of nitrogen for 30 min. After this time trimethyl borate (9.11 g, 9.8 mL, 37.7 mmol) was added dropwise and the reaction mixture stirred for a further 30 min at −78 °C. The reaction mixture was then gradually warmed to rt and acidified with 10% aq HCl and extracted with CH_2Cl_2 (3× 60 mL) and the combined organic extracts were dried with $MgSO_4$. The inorganic solids were filtered off and the solvent removed under reduced pressure to afford white crystalline material **23** in quantitative yield. The product was then used without any further purification or characterisation.[20]

3.3.9. 3-(2-Methylphenyl)-1-(phenylsulfonyl)-1*H*-indole 24a. A solution of 3-bromo-1-(phenylsulfonyl)-1*H*-indole **23a** (0.25 g, 0.74 mmol) in DME (6 mL) was deoxygenated by passing through it a fast stream of N_2 for 5 min. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 86 mg, 0.074 mmol) and stirred under an atmosphere of N_2 at rt for 10 min. A solution of 2-bromophenylboronic acid **22** (0.15 g, 1.1 mmol) in 96% EtOH (2 mL) was also deoxygenated and added to mixture. The mixture was stirred for another 10 min followed by the addition of a deoxygenated aq Na_2CO_3 solution (3.2 mL, 6.3 mmol). The resulting mixture was further stirred at rt under N_2 for 10 min. The mixture was then heated at reflux for 18 h under N_2. The mixture was cooled to rt and quenched with H_2O (20 mL). The organic material was extracted into CH_2Cl_2 (3×30 mL), the combined organic extracts dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% EtOAc–hexane) to afford the product **24a** (0.26 g, 100%) as a light orange oil. IR ν_{max}/cm^{-1} 1523 (ArC=C), 1425 and 1374; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.19 (3H, s, $ArCH_3$), 7.19–7.41 (7H, m, 7×Ar-H), 7.41–7.46 (2H, m, 2×Ar-H), 7.51–7.54 (2H, m, 2×Ar-H), 7.90–7.93 (2H, m, 2×Ar-H) and 8.05–8.08 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.3 ($ArCH_3$), 113.8 (Ar-CH), 120.7 (Ar-CH), 123.5 (Ar-CH), 123.7 (Ar-C), 124.0 (Ar-CH), 124.9 (Ar-CH), 125.8 (Ar-CH), 126.7 (2×Ar-CH), 127.9 (Ar-CH), 129.2 (2×Ar-CH), 130.4 (Ar-CH), 130.5 (Ar-CH), 130.7 (Ar-C), 131.8 (Ar-C), 133.8 (Ar-CH), 135.0 (Ar-C), 136.8 (Ar-C) and 138.1 (Ar-C); MS *m/z* 348 (M^+ + 1, 15%), 347 (M^+, 61), 207 (18), 206 (100), 204 (18), 178 (31), 103 (4) and 77 (10); HRMS calcd for $C_{21}H_{17}NO_2S$ 347.0980, found: 347.0980.

3.3.10. 5-Methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole 24b. A solution of 3-bromo-5-methoxy-1-(phenylsulfonyl)-1*H*-indole **23b** (2.21 g, 6.04 mmol) in DME (48 mL) was deoxygenated by passing through it a fast stream of N_2 for 5 min. This deoxygenated solution was added to $Pd(PPh_3)_4$ (10%, 0.70 g, 0.60 mmol) and stirred under an atmosphere of N_2 at rt for 10 min. A solution of 2-bromophenylboronic acid **22** (1.23 g, 9.07 mmol) in 96% ethanol (16 mL) was also deoxygenated and added to mixture. The mixture was stirred for another 10 min followed by the addition of deoxygenated aq 2 M Na_2CO_3 (26 mL, 51.3 mmol) solution. The resulting mixture was further stirred at rt under N_2 for 10 min. The mixture was then heated at reflux for 18 h under N_2. The mixture was cooled to rt and quenched with H_2O (80 mL). The organic material was extracted into CH_2Cl_2 (3×80 mL), the combined organic extracts dried with $MgSO_4$ and the solvent evaporated under reduced pressure. The crude residue was purified with column chromatography (20% EtOAc–hexane) to afford the product **24b** (2.25 g, 99%) as white crystals. Mp 127–128 °C (MeOH); IR ν_{max}/cm^{-1} 1616, 1558 (ArC=C), 1540, 1521, 1506, 1458 and 1365; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.18 (3H, s, $ArCH_3$), 3.73 (3H, s, OCH_3), 6.72 (1H, d, $J=2.5$ Hz, 4-H), 6.96 (1H, dd, $J=8.7$, 2.5 Hz, 6-H), 7.26–7.32 (4H, m, 4×Ar-H), 7.41–7.47 (3H, m, 3×Ar-H), 7.51–7.53 (1H, m, Ar-H), 7.86–7.90 (2H, m, 2×Ar-H) and 7.94–7.97 (1H, dd, $J=9.0$, 0.4 Hz, Ar-H); δ_C (50 MHz; $CDCl_3$) 20.3 ($ArCH_3$), 55.7 (OCH_3), 102.9 (Ar-CH), 114.0 (Ar-CH), 114.8 (Ar-CH), 124.0 (Ar-C), 124.9 (Ar-CH), 125.8 (Ar-CH), 126.7 (2×Ar-CH), 128.0 (Ar-CH), 129.2 (2×Ar-CH), 129.7 (Ar-C), 130.4 (Ar-CH), 130.5 (Ar-CH), 131.8 (Ar-C), 131.9 (Ar-C), 133.7 (Ar-CH), 136.9 (Ar-C), 138.1 (Ar-C) and 156.8 (5-C); MS *m/z* 378 (M^+ + 1, 25%), 377 (M^+, 100), 237 (15), 236 (80), 205 (14), 204 (19), 192 (9), 165 (10) and 77 (10); HRMS calcd for $C_{22}H_{19}NO_3S$ 377.1086, found: M^+ 377.1078.

3.3.11. 3-(2-Methylphenyl)-1*H*-indole 25a. 3-(2-Methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **24a** (0.028 g, 0.080 mmol) was dissolved in MeOH (20 mL) at rt under N_2. K_2CO_3 (1.78 g, 12.9 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of N_2 for 18 h. The mixture was allowed to cool to rt, filtered and the filtrate concentrated under reduced pressure. H_2O (15 mL) was added to the crude material and slowly acidified to pH 2–4 with aq 10% HCl. The aq portion was saturated with solid NaCl and the organic material extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were washed with H_2O (2×20 mL), brine (2× 20 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography (20% EtOAc–hexane) to afford product **25a** (0.16 g, 93%) as a light yellow oil. IR ν_{max}/cm^{-1} 3487 (NH) and 1523 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.31

(3H, s, $ArCH_3$), 7.09–7.33 (6H, m, 6×Ar-H), 7.37–7.44 (2H, m, 2×Ar-H), 7.52 (1H, dd, $J=7.9$, 1.1 Hz, Ar-H) and 8.09 (1H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 111.2 (Ar-CH), 117.4 (Ar-C), 119.9 (Ar-CH), 120.1 (Ar-CH), 122.1 (Ar-CH), 122.7 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.1 (Ar-C), 130.3 (Ar-CH), 130.9 (Ar-CH), 134.4 (Ar-C), 135.8 (Ar-C) and 136.8 (Ar-C); MS *m/z* 208 ($M^+ +1$, 16%), 207 (M^+, 100), 206 (63), 204 (16), 178 (15) and 102 (10); HRMS calcd for $C_{15}H_{13}N$ 207.1048, found: 207.1050.

3.3.12. 5-Methoxy-3-(2-methylphenyl)-1*H*-indole 25b. 5-Methoxy-3-(2-methylphenyl)-1-(phenylsulfonyl)-1*H*-indole **24b** (0.30 mg, 0.80 mmol) was dissolved in MeOH (30 mL) at rt under N_2. K_2CO_3 (1.76 g, 12.7 mmol) was added to the solution and the reaction mixture heated to reflux under an atmosphere of N_2 for 18 h. The mixture was allowed to cool to rt, filtered and the filtrate concentrated under reduced pressure. H_2O (30 mL) was added to the crude material and slowly acidified to pH 2–4 with 10% HCl. The aq portion was saturated with solid NaCl and extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were washed with H_2O (2×30 mL), brine (2×30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to column chromatography (20% EtOAc–hexane) to afford product **25b** (0.18 g, 96%) as a light yellow oil. IR ν_{max}/cm^{-1} 3417 br (NH) 1624 and 1603 (ArC=C), 1582, 1545, 1481, 1455 and 1439; δ_H (400 MHz; $CDCl_3$; Me_4Si) 2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, OCH_3), 6.89 (1H, dd, $J=8.7$, 2.5 Hz, 6-H), 6.93 (1H, d, $J=2.5$ Hz, Ar-H), 7.11 (1H, d, $J=2.5$ Hz, Ar-H), 7.25–7.34 (4H, m, 4×Ar-H), 7.40–7.42 (1H, m, ArH) and 8.09 (1H, br s, N-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 55.9 (OCH_3), 101.6 (Ar-CH), 111.9 (Ar-CH), 112.6 (Ar-CH), 117.3 (Ar-C), 123.5 (Ar-CH), 125.6 (Ar-CH), 126.7 (Ar-CH), 127.5 (Ar-C), 130.3 (Ar-CH), 130.8 (Ar-CH), 131.0 (Ar-C), 134.6 (Ar-C), 136.9 (Ar-C) and 154.4 (5-C); MS *m/z* 238 ($M^+ +1$, 17%), 237 (M^+, 100), 222 (51), 206 (12), 194 (17) and 165 (11); HRMS calcd for $C_{16}H_{15}NO$ 237.1155, found: 237.1164.

3.3.13. 1-Methyl-3-(2-methylphenyl)-1*H*-indole 26a. To a solution of 3-(2-methylphenyl)-1*H*-indole **25a** (0.45 g, 2.2 mmol) in THF (10 mL) was added dimethyl sulfate (1.8 mol equiv, 0.50 g, 0.37 mL, 3.9 mmol) followed by NaH (50% in oil, 0.12 g, 5.2 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (3×50 mL), combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **26a** (481 mg, 99%); IR ν_{max}/cm^{-1} 1653, 1634 and 1616 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.32 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3), 7.00 (1H, s, 2-H), 7.07–7.26 (1H, m, Ar-H), 7.28–7.41 (6H, m, 6×Ar-H) and 7.49–7.54 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 20.8 ($ArCH_3$), 32.7 (NCH_3), 109.3 (Ar-CH), 115.9 (Ar-C), 119.4 (Ar-CH), 120.2 (Ar-CH), 121.7 (Ar-CH), 125.6 (Ar-CH), 126.5 (Ar-CH), 127.5 (Ar-CH), 130.3 (Ar-CH), 130.8 (Ar-CH), 132.2 (Ar-C), 134.5 (Ar-C) and 136.7 (Ar-C), (one quaternary C not observed); MS *m/z* 221 (M^+, 100%), 220 (57), 204 (13) and 178 (9); HRMS calcd for $C_{16}H_{15}N$ 221.1204, found: 221.1199.

3.3.14. 5-Methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole 26b. To a solution of 5-methoxy-3-(2-methylphenyl)-1*H*-indole **25b** (175 mg, 0.737 mmol) in THF (10 mL) was added dimethyl sulfate (0.14 g, 0.10 mL, 1.1 mmol) followed by NaH (50% in oil, 0.043 g, 1.8 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×30 mL), combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **26b** (183 mg, 99%); IR ν_{max}/cm^{-1} 1618 and 1603 (ArC=C), 1576, 1559 and 1542; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.33 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3)[a], 3.79 (3H, s, OCH_3)[a], 6.90–6.94 (2H, m, 2×Ar-H), 6.99 (1H, s, 2-H), 7.22–7.25 (3H, m, 3×Ar-H), 7.30–7.32 (1H, m, Ar-H) and 7.39–7.41 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 32.9 (NCH_3), 55.9 (OCH_3), 101.7 (Ar-CH), 110.1 (Ar-CH), 112.1 (Ar-CH), 115.5 (Ar-C), 125.6 (Ar-CH), 126.5 (Ar-CH), 127.8 (Ar-C), 128.1 (Ar-CH), 130.4 (Ar-CH), 130.7 (Ar-CH), 132.1 (Ar-C), 134.6 (Ar-C), 136.7 (Ar-C) and 154.3 (5-C); MS *m/z* 252 ($M^+ +1$, 27%), 251 (M^+, 100%) 236 (54), 218 (15), 208 (9) and 165 (8); HRMS calcd for $C_{17}H_{17}NO$ 251.1310, found: 251.1296.

3.3.15. 1-Methyl-3-(2-methylphenyl)-1*H*-indole-2-carbaldehyde 27a. DMF (0.30 g, 0.30 mL, 4.1 mmol) was added to $POCl_3$ (0.42 g, 0.25 mL, 2.71 mmol) at 0 °C under an atmosphere of N_2. The resulting salt was treated with a solution of 1-methyl-3-(2-methylphenyl)-1*H*-indole **26a** (300 mg, 1.36 mmol) in toluene (6 mL). The resulting reaction mixture was heated at reflux for 42 h under N_2 atmosphere. The reaction mixture was then cooled to rt, quenched with water and the excess $POCl_3$ neutralised with Na_2CO_3. The crude product was extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts dried with $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% EtOAc–hexane) to afford product **27a** (202 mg, 60%) as a light brown oil. IR ν_{max}/cm^{-1} 1709 (C=O) and 1608 (ArC=C); δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.18 (3H, s, $ArCH_3$), 4.16 (3H, s, NCH_3), 7.11–7.15 (1H, m, Ar-H), 7.23–7.44 (7H, m, 7×Ar-H) and 9.66 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.9 ($ArCH_3$), 32.2 (NCH_3), 110.8 (Ar-CH), 121.3 (Ar-CH), 122.9 (Ar-CH), 125.9 (Ar-CH), 126.7 (Ar-C), 127.7 (Ar-CH), 128.7 (Ar-CH), 130.7 (Ar-CH), 131.7 (Ar-C), 131.8 (Ar-C), 131.9 (Ar-C), 132.5 (Ar-CH), 138.2 (Ar-C), 140.0 (Ar-C) and 184.2 (CHO); MS *m/z* 250 ($M^+ +1$, 18%), 249 (M^+, 100), 234 (32), 232 (69), 220 (18), 217 (24) and 204 (18); HRMS calcd for $C_{17}H_{15}NO$ 249.1154, found: 249.1158.

3.3.16. 5-Methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole-2-carbaldehyde 27b. DMF (0.124 g, 0.13 mL, 1.70 mmol) was added to $POCl_3$ (0.17 g, 0.10 mL, 1.1 mmol) at 0 °C under an atmosphere of N_2. The resulting salt was treated with a solution of 5-methoxy-1-methyl-3-(2-methylphenyl)-1*H*-indole **26b** (140 mg, 0.557 mmol) in toluene (4 mL). The reaction mixture was then heated to reflux for 42 h under N_2 atmosphere. The reaction mixture was then cooled to rt, quenched with water and excess $POCl_3$ neutralised with Na_2CO_3. The crude product was extracted into CH_2Cl_2 (3×30 mL), the combined organic

extracts dried with $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by column chromatography (20% EtOAc–hexane) to afford product **27b** (156 mg, 27%) as a brown oil. IR ν_{max}/cm^{-1} 1716 (C=O), 1654 and 1617 (ArC=C); δ_H (400 MHz; $CDCl_3$, $MeSi_4$) 2.23 (3H, s, $ArCH_3$), 3.78 (3H, s, NCH_3), 4.17 (3H, s, OCH_3), 6.75 (1H, d, $J=2.3$ Hz, 4-H) and 7.15 (1H, dd, $J=9.1$, 2.3 Hz, 6-H), 7.28–7.41 (5H, m, 5×Ar-H) and 9.63 (1H, s, CHO); δ_C (50 MHz; $CDCl_3$) 20.6 ($ArCH_3$), 33.1 (NCH_3), 56.0 (OCH_3), 100.6 (Ar-CH), 109.9 (Ar-CH), 116.1 (Ar-C), 120.9 (Ar-C), 125.8 (Ar-CH), 127.0 (Ar-CH), 130.5 (Ar-CH), 130.6 (Ar-CH), 131.6 (Ar-C), 132.7 (Ar-CH), 133.0 (Ar-C), 133.8 (Ar-C), 136.8 (Ar-C), 156.5 (5-C) and 190.4 (CHO); MS *m/z* 280 ($M^+ +1$, 30%), 279 (M^+, 100), 264 (19), 262 (38), 247 (16), 218 (9), 206 (10), 204 (9), 192 (6), 165 (9) and 152 (6); HRMS calcd for $C_{18}H_{17}NO_2$ 279.1259, found: 279.1253.

3.3.17. 1-[2-(1,2-Dimethyl-1*H*-indol-3-yl)phenyl]-ethanone 20a. (a) 2-Methyl-1*H*-indole (1.00 g, 7.62 mmol) was dissolved in DMF (7.5 mL). A solution of Br_2 (1.22 g, 0.390 mL, 7.62 mmol) in DMF (7.5 mL) was added to the reaction mixture and the resulting solution was stirred at rt under N_2 atmosphere for 4 h. After this time the reaction mixture was poured into an ice-cold mixture of H_2O (10 mL), a 25% aq NH_3 solution (10 mL) and an aq solution of $NaHSO_3$ (10 mL). The resulting precipitate was then dissolved in CH_2Cl_2 (20 mL). The organic layer was sequentially washed with H_2O (20 mL), aq NaCl (20 mL), dried with $MgSO_4$ and concentrated in vacuo. The residue was then loaded on a silica gel column and eluted with 20% EtOAc–hexane to afford the desired product 3-bromo-2-methyl-1*H*-indole (1.61 g, 100%) as an off-white solid. δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.40 (3H, s, 2-CH_3), 7.13–7.23 (3H, m, 3×Ar-H), 7.45–7.47 (1H, m, 7-H) and 8.0 (1H, br s, NH); δ_C (50 MHz; $CDCl_3$) 12.2 (2-CH_3), 100.3 (3-C), 112.0 (7-C), 121.5 (Ar-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 128.2 (Ar-C), 130.3 (Ar-C) and 136.7 (Ar-C).[21]

(b) To the intermediate 3-bromo-2-methyl-1*H*-indole (1.60 g, 7.60 mmol) in THF (50 mL) was added dimethyl sulfate (1.44 g, 1.08 mL, 11.4 mmol) followed by sodium hydride (50% in oil, 0.44 g, 18 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (35 mL), extracted with Et_2O (3×40 mL), the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **30a**[22] (1.68 g, 99%) which was used immediately in the next reaction. δ_H (200 MHz; $CDCl_3$; $MeSi_4$) 2.36 (3H, s, 2-CH_3), 3.59 (3H, s, NCH_3), 7.12–7.20 (3H, m, 3×Ar-H) and 7.45–7.49 (1H, m, Ar-H); δ_C (50 MHz; $CDCl_3$) 12.4 (2-CH_3), 33.5 (NCH_3), 102.4 (3-C), 112.9 (Ar-CH), 121.9 (Ar-CH), 122.3 (Ar-CH), 123.2 (Ar-CH), 128.7 (Ar-C), 130.8 (Ar-C) and 137.2 (Ar-C).

(c) Boronic acid **31** (0.29 g, 1.7 mmol) was dissolved in DMF (1.5 mL) and O_2 removed from the solution by three freeze-thaw cycles. 3-Bromo-1,2-dimethyl-1*H*-indole **30a** (0.20 g, 0.89 mmol), K_3PO_4 (0.57 g, 2.7 mmol) and $Pd(PPh_3)_4$ (20 mol%, 0.21 g, 0.18 mmol) were added sequentially under an Ar atmosphere. The reaction flask was sealed tightly and heated at 100 °C for 65 h. After this time the reaction mixture was cooled and followed by the addition of saturated solution of brine (10 mL). The reaction mixture was extracted with Et_2O (4×15 mL), and the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–hexane) afforded the biaryl compound **20a** as a yellow-brown oil (0.19 g, 83%); IR ν_{max}/cm^{-1} 1683 (C=O) and 1614 and 1596 (ArC=C), 1558, 1541 and 1472; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 1.88 (3H, s, 2-CH_3), 2.26 (3H, s, CH_3CO), 3.74 (3H, s, NCH_3), 7.32 (1H, d, $J=8.2$ Hz, Ar-H), 7.18–7.24 (1H, m, Ar-H), 7.25–7.31 (1H, m, Ar-H), 7.37–7.44 (3H, m, 3×Ar-H) and 7.50–7.55 (1H, m, Ar-H), 7.63 (1H, d, $J=7.7$ Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 10.9 (2-CH_3), 29.3 (NCH_3), 29.8 (CH_3CO), 108.8 (Ar-CH), 112.9 (Ar-C), 118.6 (Ar-CH), 120.0 (Ar-CH), 121.5 (Ar-CH), 126.8 (Ar-CH), 127.4 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 132.1 (Ar-CH), 133.8 (Ar-C), 134.6 (Ar-C), 136.7 (Ar-C), 142.2 (Ar-C) and 205.0 (CH_3CO); MS *m/z* 264 ($M^+ +1$, 20%), 263 (M^+, 100), 262 (11), 249 (14), 248 (68), 245 (16), 234 (10), 233 (21), 218 (14), 204 (16) and 144 (10); HRMS calcd for $C_{18}H_{17}NO$: 263.1310, found: M^+263.1312.

3.3.18. 1-[2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3yl)-phenyl]ethanone 20b. (a) 5-Methoxy-2-methyl-1*H*-indole (600 mg, 3.72 mmol) was dissolved in CH_2Cl_2 (4 mL). To the resulting solution was added a small amount (ca. 100 mg) of silica gel followed by *N*-bromosuccinimide (660 mg, 3.72 mmol). The resulting mixture was stirred at rt for 30 min under an atmosphere of N_2. The reaction was quenched with H_2O (30 mL), extracted with CH_2Cl_2 (3×50 mL), the combined organic extracts were dried with $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by column chromatography (20% EtOAc–hexane) to afford 3-bromo-5-methoxy-2-methyl-1*H*-indole (870 mg, 99%). δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.38 (3H, s, 2-CH_3), 3.87 (3H, s, OCH_3), 6.80 (1H, dd, $J=8.7$, 2.1 Hz, 6-H), 6.91 (1H, d, $J=1.5$ Hz, 4-H), 7.12 (1H, d, $J=8.7$ Hz, 7-H) and 7.89 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 12.4 (2-CH_3), 55.8 (OCH_3), 90.0 (3-C), 100.0 (6-C), 111.5 (Ar-CH), 112.3 (Ar-CH), 128.1 (Ar-C), 129.6 (Ar-C), 133.1 (Ar-C) and 154.7 (5-C).

(b) To a solution of 3-bromo-5-methoxy-2-methyl-1*H*-indole (350 mg, 1.46 mmol) in THF (10 mL) was added dimethyl sulfate (0.28 g, 0.21 mL, 2.2 mmol) followed by NaH (50% in oil, 0.084 g, 2.2 mmol). The resulting mixture was stirred at rt under a constant flow of N_2 for 18 h. The reaction was quenched with H_2O (20 mL), extracted with Et_2O (3×20 mL), and the combined organic layers dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography (20% EtOAc–hexane) to afford **30b** (350 mg, 94%) which was used as soon as possible in the next reaction. δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.38 (3H, s, 2-CH_3), 3.71 (3H, s, NCH_3), 3.87 (3H, s, OCH_3), 6.82 (1H, dd, $J=8.8$, 2.4 Hz, 6-H), 6.91 (1H, d, $J=2.2$ Hz, 4-H) and 7.13 (1H, d, $J=8.8$ Hz, 7-H); δ_C (100 MHz; $CDCl_3$) 11.5 (2-CH_3), 30.3 (NCH_3), 55.8 (OCH_3), 88.5 (3-C), 99.9 (4-C), 109.8 (Ar-CH), 111.9 (Ar-CH), 127.1 (Ar-CH), 131.2 (Ar-C), 134.5 (Ar-C) and 154.5 (5-C).

(c) Boronic acid **31** (260 mg, 1.59 mmol) was dissolved in DMF (2 mL) and O_2 removed from the solution by three freeze-thaw cycles. 3-Bromo-5-methoxy-1,2-dimethyl-1*H*-indole **30b** (200 mg, 0.79 mmol), K_3PO_4 (0.50 g, 2.4 mmol) and $Pd(PPh_3)_4$ (20 mol%, 0.18 g, 0.16 mmol) were added sequentially under an Ar atmosphere. The reaction flask was sealed tightly and heated at 100 °C, for 65 h. After this time the reaction mixture was cooled and followed by the addition of saturated solution of brine (15 mL). The reaction mixture was extracted with Et_2O (4×20 mL), the organic extracts were combined and concentrated under reduced pressure. Purification of the residue by column chromatography (20% EtOAc–hexane) afforded the biaryl compound **20b** as a yellow-brown oil (0.19 g, 80%); IR ν_{max}/cm^{-1} 1684 (C=O), 1597 and 1617 (C=C), 1489 and 1456; δ_H (300 MHz; $CDCl_3$; $MeSi_4$) 1.89 (3H, s, 2-CH_3), 2.24 (3H, s, CH_3CO), 3.71 (3H, s, NCH_3)[a], 3.78 (3H, s, OCH_3)[a], 6.85–6.88 (2H, m, 2×Ar-H), 7.20 (1H, d, J=9.5 Hz, Ar-H), 7.25–7.48 (2H, m, 2×Ar-H) and 7.52–7.57 (1H, m, Ar-H), 7.62–7.65 (1H, m, Ar-H); δ_C (75 MHz; $CDCl_3$) 10.9 (2-CH_3), 29.7 (CH_3CO), 29.8 (NCH_3), 55.8 (OCH_3), 100.4 (Ar-CH), 109.5 (Ar-CH), 111.4 (Ar-CH), 112.6 (Ar-C), 126.6 (Ar-CH), 127.6 (Ar-C), 128.0 (Ar-CH), 130.8 (Ar-CH), 131.9 (Ar-CH), 133.8 (Ar-C), 135.0 (Ar-C), 142.1 (Ar-C), 154.6 (Ar-C) and 205.1 (CH_3CO), (one quaternary not observed, assignments with same superscript may be interchanged); MS *m/z* 294 (M^++1, 21%), 293 (M^+, 100), 279 (7), 278 (35), 263 (8), 250 (6), 247 (5), 234 (5), 207 (6), 206 (8) and 165 (5); HRMS calcd for $C_{19}H_{19}NO_2$: 293.1416, found: M^+293.1407.

3.3.19. 5,7-Dimethyl-7*H*-benzo[*c*]carbazole 18a. 1-[2-(1,2-Dimethyl-1*H*-indol-3-yl)phenyl]ethanone **20a** (96 mg, 0.36 mmol) was dissolved in DMF (4 mL) at 80 °C. To the resulting solution was added ^{t}BuOK (0.164 mg, 1.46 mmol). The resulting reaction mixture was stirred at 80 °C and irradiated with a high pressure mercury lamp through a quartz filter for 10 min. After this time, the reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×20 mL) before the organic fractions were combined. The fractions were dried with $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (20% EtOAc–hexane) to afford **18a** as yellow crystals (63 mg, 71%). Mp 112 °C; IR ν_{max}/cm^{-1} 1617 and 1591 (ArC=C), 1523, 1465, 1416, 1378; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.79 (3H, d, J=0.9 Hz, $ArCH_3$), 3.79 (3H, s, NCH_3), 7.31–7.38 (2H, m, 2×Ar-H), 7.41–7.48 (3H, m, 3×Ar-H), 7.65–7.69 (1H, m, Ar-H), 8.08 (1H, d, J=8.4 Hz, Ar-H), 8.50 (1H, d, J=8.0 Hz, Ar-H) and 8.77 (1H, d, J=8.2 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.6 ($ArCH_3$), 29.0 (NCH_3), 108.9 (Ar-CH), 111.2 (Ar-CH), 113.4 (Ar-C), 119.6 (Ar-CH), 121.6 (Ar-CH), 122.5 (Ar-CH), 123.5 (Ar-CH), 123.6 (Ar-CH), 125.2 (Ar-CH), 125.5 (Ar-CH), 126.5 (Ar-CH), 128.2 (Ar-C), 130.2 (Ar-C), 133.4 (Ar-C), 138.2 (Ar-C) and 139.6 (Ar-C); MS *m/z* (M^++1, 21%) 245 (M^+, 100), 244 (26), 230 (7), 229 (6), 228 (5), 202 (5) and 122 (9); HRMS calcd for $C_{18}H_{15}N$: 245.1205, found: M^+245.1198.[23]

3.3.20. 10-Methoxy-5,7-dimethyl-7*H*-benzo[*c*]carbazole 18b. 1-[2-(5-Methoxy-1,2-dimethyl-1*H*-indol-3-yl)phenyl]-ethanone **20b** (114 mg, 0.389 mmol) was dissolved in DMF (4 mL) at 80 °C. To the resulting solution was added ^{t}BuOK (0.21 g, 1.9 mmol). The resulting reaction mixture was stirred at 80 °C and irradiated with a high pressure mercury lamp through a quartz filter for 10 min. The reaction was quenched with H_2O (15 mL), extracted with Et_2O (3×20 mL) and the organic fractions were combined. The organic fractions were dried with $MgSO_4$, concentrated under reduced pressure and the residue purified by column chromatography (20% EtOAc–hexane) to afford **18b** as yellow crystals (92 mg, 70%). Mp 120 °C; IR ν_{max}/cm^{-1} 1671, 1608 (ArC=C), 1566, 1532 and 1428; δ_H (400 MHz; $CDCl_3$; $MeSi_4$) 2.84 (3H, s, $ArCH_3$), 3.88 (3H, s, NCH_3)[a], 4.01 (3H, s, OCH_3)[a], 7.11 (1H, dd, J=8.8, 2.2 Hz, 9-H), 7.37–7.51 (3H, m, 3×Ar-H), 7.68–7.72 (1H, m, Ar-H), 8.00 (1H, d, J=2.2 Hz, 11-H), 8.12 (1H, d, J=8.3 Hz, Ar-H) and 8.71 (1H, d, J=8.2 Hz, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.7 ($ArCH_3$), 28.9 (NCH_3), 56.3 (OCH_3), 105.1 (Ar-CH), 109.4 (Ar-CH), 111.4 (Ar-CH), 112.5 (Ar-CH), 113.1 (Ar-C), 122.4 (Ar-CH), 123.3 (Ar-CH), 123.7 (Ar-C), 125.3 (Ar-CH), 126.5 (Ar-CH), 128.1 (Ar-C), 130.2 (Ar-C), 133.4 (Ar-C), 134.9 (Ar-C), 138.8 (Ar-C) and 154.1 (10-C), (assignments with same superscript may be interchanged); MS *m/z* (M^++1, 24%) 275 (M^+, 100), 261 (10), 260 (39), 233 (6), 232 (30), 217 (9), 216 (6), 137 (12), 116 (8) and 115 (7); HRMS calcd for $C_{19}H_{17}NO$: 275.1310, found: M^+275.1308.

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