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Chemoselective functionalization of α-carbolines at the C-2, C-3, C-4, and C-6 positions using Suzuki–Miyaura reactions

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ABSTRACT

The synthesis of 2-, 3-, 4-, and 6-substituted pyrido[2,3-*b*]indoles (α-carbolines) by palladium-catalyzed cross-coupling reactions from the corresponding halopyrido[2,3-*b*]indoles is described. A sequential and a one-pot chemoselective double Suzuki–Miyaura coupling route is presented for the synthesis of symmetrically and unsymmetrically disubstituted pyrido[2,3-*b*]indoles.

1. Introduction

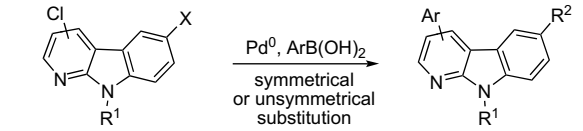
The Suzuki–Miyaura cross-coupling reaction is among the most widely used C_{sp2}–C_{sp2} bond-forming reactions in organic synthesis.[1] Much recent work has been directed toward the development of new catalysts in order to extend the scope of the reaction to aryl chlorides as coupling partners.[2] The properties of the palladium ligands have a significant impact on the outcome of the coupling reaction, as palladium complexes derived from sterically hindered and electron-rich phosphines were found to be effective catalysts for the coupling of aryl chlorides.[3] Some notable examples include the use of bulky trialkylphosphines such as P(*t*Bu$_3$) by Fu,[4] or dialkylbiphenylphosphines such as S-Phos by Buchwald.[5]

Chlorine-substituted heterocycles have been employed less commonly than aryl chlorides as substrates for Suzuki–Miyaura cross-coupling reactions.[6] Reports of C_{sp2}–C_{sp2} bond formation on chloro-substituted nitrogen heterocycles, such as chloropyridines,[6a–c,7] azaindoles,[8] quinolines,[9] and β-carbolines,[10] have been described in the presence of different Pd–L catalysts. In particular, the catalytic Pd/S-Phos system was described for aminoheteroaryl chlorides in several articles.[5a–c,6b] Extending the cross-coupling reaction to other heteroaryl substrates, in particular for sequential double coupling reactions, remains of current interest.

We report herein the functionalization of the C-2, C-3, C-4, and C-6 positions of mono- and dihalogenated pyrido[2,3-*b*]indoles (α-carbolines) through Suzuki–Miyaura cross-coupling reactions (Scheme 1). The α-carboline skeleton is encountered in a variety of biologically active natural products,[11] yet the functionalization of the α-carboline ring system itself remains largely underexploited.[12] In particular, reports of Pd-catalyzed cross-coupling reactions of pyrido[2,3-*b*]indoles are very limited in the literature.[13] We therefore decided to investigate this question, with an eye toward developing chemoselective cross-coupling strategies in order to allow rapid and convenient functionalization of C-2, C-3 or C-4-chlorine-substituted 6-bromopyrido[2,3-*b*]indoles.

2. Results and discussion

We selected the readily accessible chloropyrido[2,3-*b*]indoles as initial starting materials for the study of Suzuki–Miyaura coupling reactions for introducing carbon side chains onto the α-carboline ring system. Thus, 2- and 3-chloropyrido[2,3-*b*]indoles **1** and **2** were synthesized by a Graebe–Ullmann reaction from chloropyridines in two steps.[14] The 4-chloropyrido[2,3-*b*]indole **3** was prepared by Reissert-Henze reaction on pyrido[2,3-*b*]indole *N*-oxide.[15]



R^1 = H, SO_2Ph; X = H, Br — R^1 = H, SO_2Ph; R^2 = H, Ar'

Scheme 1. Functionalization of α-carbolines at the 2-, 3-, 4-, and 6-positions using Suzuki–Miyaura reactions.

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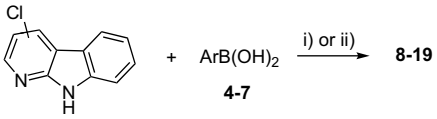
Table 1
Suzuki–Miyaura reactions on chloropyrido[2,3-*b*]indoles **1**–**3**



1: 2-Cl, **2**: 3-Cl, **3**: 4-Cl

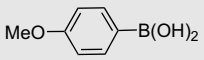
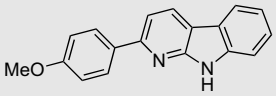
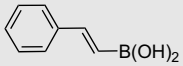
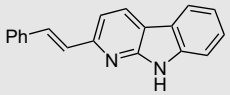
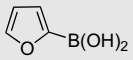
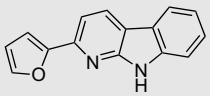
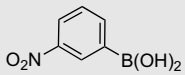
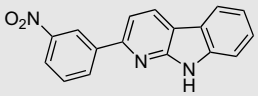
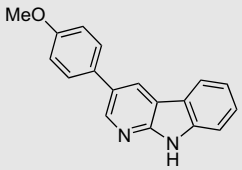
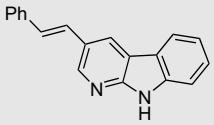
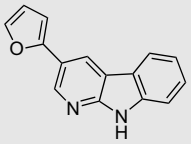
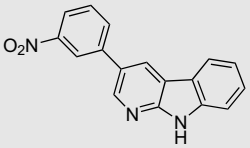
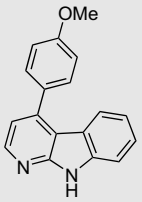
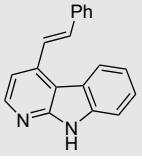
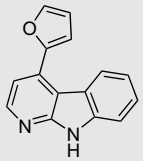
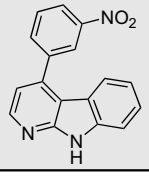
Entry	Catalytic system[a]	Pyridoindoles	$ArB(OH)_2$	Products		Yield (%)
1	$Pd(PPh_3)_4$	**1**	 **4**		**8**	70
2	$Pd(OAc)_2$/S-Phos					68
3	$Pd(OAc)_2$/S-Phos	**1**	 **5**		**9**	68
4	$Pd(OAc)_2$/S-Phos	**1**	 **6**		**10**	81
5	$Pd(PPh_3)_4$	**1**	 **7**		**11**	83
6	$Pd(OAc)_2$/S-Phos	**2**	**4**		**12**	73
7	$Pd(OAc)_2$/S-Phos	**2**	**5**		**13**	68
8	$Pd(OAc)_2$/S-Phos	**2**	**6**		**14**	65
9	$Pd(OAc)_2$/S-Phos	**2**	**7**		**15**	70
10	$Pd(PPh_3)_4$					70
11	$Pd(OAc)_2$/S-Phos	**3**	**4**		**16**	71
12	$Pd(OAc)_2$/S-Phos	**3**	**5**		**17**	72

Table 1 (*continued*)

Entry	Catalytic system[a]	Pyridoindoles	$ArB(OH)_2$	Products		Yield (%)
13	$Pd(OAc)_2$/S-Phos	**3**	**6**		**18**	76
14	$Pd(PPh_3)_4$	**3**	**7**		**19**	77

[a] Reaction conditions: (i) $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), K_3PO_4 (2 equiv), 1,4-dioxane (2.5 mL/mmol), $ArB(OH)_2$ (1.1 equiv), 100 °C, overnight or (ii) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), $ArB(OH)_2$ (1.2 equiv), 1,4-dioxane/H_2O, 100 °C, 12 h.

2.1. Suzuki–Miyaura reactions of 2-, 3-, and 4-chloropyrido[2,3-*b*]indoles

Our initial studies focused on the straightforward functionalization of the α-carboline using palladium-catalyzed coupling reactions on chloropyrido[2,3-*b*]indoles. Two catalytic systems were investigated, the Buchwald (Pd/S-Phos) and a traditional palladium catalyst, $Pd(PPh_3)_4$ (Table 1). The 2-, 3-, and 4-chloro-substituted α-carbolines **1**–**3** each undergoes clean cross-coupling reactions using the Buchwald catalytic system in 65–81% yields. This method allowed the coupling of each substrate with 4-methoxyphenyl-, (*E*)-styryl-, furan-2-yl- or 3-nitrophenylboronic acid **4**–**7** in good yields (entries 2–4, 6–9, and 7–9, Table 1). However, $Pd(PPh_3)_4$ was found to be equally effective for the coupling of 2- and 4-chloropyrido[2,3-*b*]indoles **1** and **3** with the two arylboronic acids tested (entries 1, 5, 10, and 14, Table 1). The cross-coupling reaction of 3-chloropyrido[2,3-*b*]indole **2** using $Pd(PPh_3)_4$ as catalyst failed, as only the $Pd(OAc)_2$/S-Phos catalyst system under non-aqueous conditions was able to produce the 3-substituted compounds in good yield. These results are consistent with literature studies of the reactivity of 2-, 3-, and 4-chloropyridines.[1d]

2.2. Chemoselective Suzuki–Miyaura reactions of 2-, 3-, and 4-chloropyrido[2,3-*b*]indoles bearing a bromine at the C-6 position

Chemoselective cross-coupling reactions of bromine-substituted α-carbolines in the presence of a chlorine substituent on the pyrido ring were investigated, with an eye toward developing a sequential double coupling strategy. Regioselective electrophilic bromination of pyrido[2,3-*b*]indoles **1**–**3** was achieved in the presence of bromine in CH_2Cl_2 to afford the corresponding 6-bromo compounds **20**–**22** in fair yields.[12a]

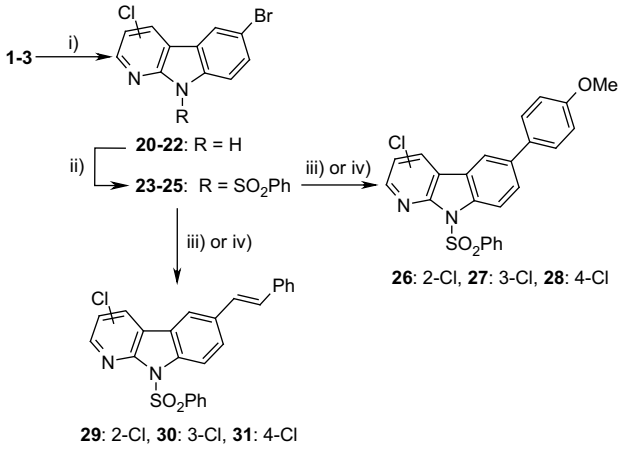
The cross-coupling reaction was first investigated using the less reactive 3-chloro isomer **21**. Unfortunately, neither catalytic system, $Pd(OAc)_2$/S-Phos nor $Pd(PPh_3)_4$, allowed us to obtain a coupling product directly from 6-bromo-3-chloropyrido[2,3-*b*]indole **21**, presumably due to the poor solubility of this substrate under the reaction conditions. In order to overcome this problem, the nitrogen atom was protected using NaH and benzenesulfonyl chloride in THF to give **23**–**25**. The 3-chloro derivative **24** undergoes palladium-catalyzed cross-coupling reaction with $Pd(PPh_3)_4$ and 4-methoxyphenyl- or (*E*)-phenylvinylboronic acids **4** and **5** to afford 3-chloro-6-substituted-α-carbolines **27** and **30** in good yields (entries 4 and 5, Table 2). Given the lower reactivity of the C-3-chlorine bond of **24**, the coupling reactions could be performed successfully at 100 °C in 1,4-dioxane/H_2O (Scheme 2).

In the case of the 2- and 4-chloro derivatives, the 6-substituted-α-carbolines were obtained in lower yields at high temperature, due to a poor chemoselectivity between the more reactive carbon–chlorine bonds and the carbon–bromine bond. For example at 100 °C (entries 1 and 2, Table 2), compound **26** was obtained in only 37% yield, along with 41% of the disubstituted compound **37** and 20% of unreacted starting material. Therefore, milder conditions at 70 °C in THF/H_2O were tested, which allowed for the chemoselective Suzuki–Miyaura reaction at the C-6 position of the 2- and 4-chloro compounds **23** and **25**. These conditions afforded the corresponding mono-coupled products **26**, **28**, **29**, and **31** (entries 1, 3, 6, and 7, Table 2) in good yields with little or none of the disubstituted products or unreacted starting material.

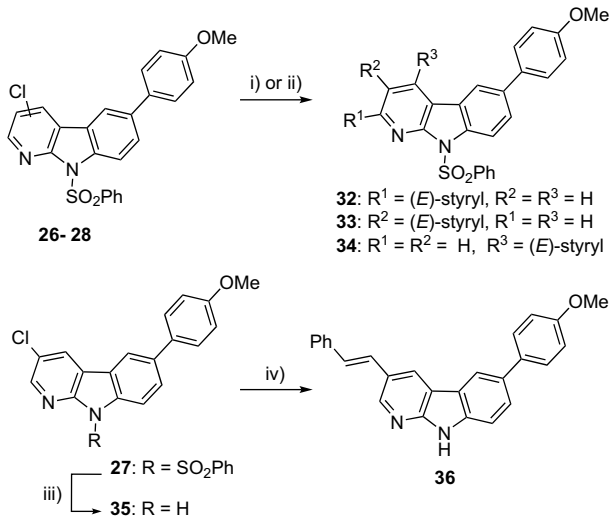
Table 2
Chemoselective Suzuki–Miyaura reactions[a]

Entry	Pyridoindoles	$ArB(OH)_2$	Temperature (°C)	Products	Yield (%)
1	**23**	**4**	70	**26**	58
2	**23**	**4**	100	**26**	37
3	**23**	**5**	70	**29**	64
4	**24**	**4**	100	**27**	83
5	**24**	**5**	100	**30**	71
6	**25**	**4**	70	**28**	70
7	**25**	**5**	70	**31**	68

[a] $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), $ArB(OH)_2$ (1.1 equiv), H_2O/THF or 1,4-dioxane, 12 h.



Scheme 2. (i) Br_2 (1.2 equiv), CH_2Cl_2, rt, 90 min, **20**=75%, **21**=78%, **22**=76%. (ii) 60% NaH (1.1 equiv), $PhSO_2Cl$ (1.2 equiv) THF, 0 °C to rt, 12 h, **23**=90%, **24**=91%, **25**=85%. (iii) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), $ArB(OH)_2$ (1.1 equiv), H_2O/THF, 70 °C, 12 h. (iv) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), $ArB(OH)_2$ (1.1 equiv), 1,4-dioxane/H_2O, 100 °C, 12 h.



Scheme 3. (i) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), (*E*)-phenylvinylboronic acid (**5**) (1.1 equiv), 1,4-dioxane/H_2O, 100 °C, 12 h, **32**=84%, **34**=87%. (ii) $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), K_3PO_4 (3 equiv), (*E*)-phenylvinylboronic acid (**5**) (2.5 equiv), 1,4-dioxane (2.5 mL/mmol), 100 °C, 12 h, **33**=79%. (iii) 1.0 M TBAF in THF (5 equiv), THF, reflux, 4 h, **35**=84%. (iv) $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), K_3PO_4 (2.5 equiv), (*E*)-phenylvinylboronic acid (**5**) (1.5 equiv), 1,4-dioxane/H_2O (2.5 mL/mmol), 100 °C, 12 h, **36**=65%.

2.3. Sequential double Suzuki–Miyaura coupling reactions of 2-, 3-, and 4-chloro-6-(4-methoxyphenyl)pyrido[2,3-*b*]indoles

The ability to substitute halogens sequentially by cross-coupling reactions opens a simple route to diaryl-, aryl-, vinyl-, and divinylsubstituted α-carbolines. Such an approach further allows for a variety of substitution patterns on the aryl and vinyl groups. The unsymmetrically disubstituted pyrido[2,3-*b*]indoles **32**–**34** were therefore synthesized by performing a second palladium coupling reaction at position C-2, C-3, and C-4 (Scheme 3) of the products of the Suzuki–Miyaura reactions at C-6 described above.

Thus, treatment of the 6-aryl-2-chloro product **26** and the 6-aryl-4-chloro coupling product **28** with $Pd(PPh_3)_4$, K_2CO_3, and (*E*)-phenylvinylboronic acid (**5**) (1.1 equiv) in 1,4-dioxane/H_2O at 100 °C afforded 6-(4-methoxyphenyl)-2-styryl-9*H*-pyrido[2,3-*b*]indole **32** and 6-(4-methoxyphenyl)-4-styryl-9*H*-pyrido[2,3-*b*]indole **34**, respectively, in excellent yields. The corresponding 9-benzenesulfonyl-6-(4-methoxyphenyl)-3-styryl-9*H*-pyrido[2,3-*b*]indole (**33**) was synthesized from the less reactive 3-chloro compound **27** in 1,4-dioxane at 100 °C in 79% yield using the $Pd(OAc)_2$/S-Phos catalyst system and a slightly larger excess of (*E*)-phenylvinylboronic acid (**5**) (2.5 equiv). Alternatively, the 3-chloro product **27** was deprotected with 1.0 M TBAF in THF at reflux to furnish 3-chloro-6-(4-methoxyphenyl)-9*H*-pyrido[2,3-*b*]indole (**35**) in 84% yield (Scheme 3); cross-coupling reaction at the C-3 position was then performed on the unprotected α-carboline **35**, using a catalytic amount of $Pd(OAc)_2$/S-Phos, K_3PO_4, and (*E*)-phenylvinylboronic acid (**5**) (1.5 equiv) in 1,4-dioxane at 100 °C, to provide the desired product **36** in 65% yield. The benzenesulfonyl-protected compound **27** gave a lower 48% yield with the same number of equivalents showing that the protecting group interferes somewhat with the coupling reaction.

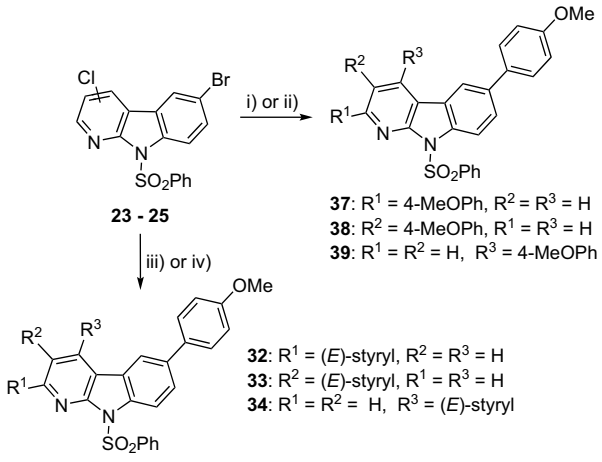
2.3.1. One-pot double Suzuki–Miyaura coupling

Finally, we investigated the possibility of developing more efficient, one-pot sequential coupling conditions for preparation of 2,6-, 3,6-, and 4,6-diaryl-α-carbolines. Indeed, C–C bond formation on two positions is usually realized in two steps, both in the literature and in the route described above (Scheme 3). However, Beletskaya et al.[9a,d] and Mérour et al.[16] have recently developed one-pot double Suzuki–Miyaura reaction conditions. Thus, we applied such conditions to 6-bromo-chloropyrido[2,3-*b*]indoles **23**–**25** (Scheme 4).

The use of 4-methoxyphenylboronic acid (**4**) (2.2 equiv) in the presence $Pd(PPh_3)_4$ in 1,4-dioxane/H_2O at 100 °C according to Mérour's procedure[16] allowed us to obtain the desired symmetrically 2,6- and 4,6-disubstituted compounds **37** and **39** in 90% and 89% yields, respectively. One-pot coupling conditions for the preparation of 3,6-diaryl-α-carbolines using 4-methoxyphenylboronic acid (**4**) (3 equiv) in the presence of $Pd(OAc)_2$/S-Phos in 1,4-dioxane at 100 °C provided the symmetrically disubstituted compound **38** in 81% yield.

We then sought to develop conditions for a regioselective double coupling reaction in one pot to produce unsymmetrically disubstituted compounds. Treatment of the 2,6- or 4,6-dihalogenated starting material **23** or **25** with 4-methoxyphenylboronic acid (**4**) (1.1 equiv) and a catalytic amount of $Pd(PPh_3)_4$ in 1,4-dioxane/H_2O at 70 °C, followed by addition of the second boronic acid **5** at 100 °C afforded products **32** and **34** in 54% and 71% yield, respectively. We further developed a one-pot Suzuki–Miyaura reaction with the Buchwald catalytic system (Pd/S-Phos) for the preparation of unsymmetrically disubstituted 3,6-diaryl compounds. Thus, treatment of the protected 6-bromo-3-chloropyrido[2,3-*b*]indole **24** with 4-methoxyphenylboronic acid (**4**) (1.2 equiv) and a catalytic amount of $Pd(OAc)_2$/S-Phos, K_3PO_4, in 1,4-dioxane at 50 °C, followed after 5 h by addition of the second boronic acid **5** (2.5 equiv) at 100 °C afforded the product **33** in 65% yield. Such conditions can readily be applied to any combination of boronic acids, and thus provides a convenient method for producing a wide range of 2,6-, 3,6-, or 4,6-disubstituted pyrido[2,3-*b*]indoles.

In conclusion, we have developed new routes to functionalize α-carbolines through palladium-catalyzed Suzuki–Miyaura reactions. This methodology provides a powerful tool for the preparation of a wide range of 2-, 3-, 4-, and 6-substituted pyrido[2,3-*b*]indoles and allows a rapid increase in molecular complexity. The sequential or one-pot Suzuki–Miyaura synthetic routes thus provide access to unsymmetrically disubstituted products such as **32**, **33**, **34**, and **36** in 33–47% overall yield in 3–5 steps from the readily available mono-substituted chloro-9*H*-pyrido[2,3-*b*]indoles **1**–**3**.



Scheme 4. (i) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), 4-methoxyphenylboronic acid (**4**) (2.2 equiv), 1,4-dioxane/H_2O, 100 °C, 12 h, **37**=90%, **39**=89%. (ii) $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), K_3PO_4 (3.0 equiv), 4-methoxyphenylboronic acid (**4**) (3 equiv), 1,4-dioxane (2.5 mL/mmol), 100 °C, 12 h, **38**=81%. (iii) $Pd(PPh_3)_4$ (8 mol %), K_2CO_3 (3 equiv), 4-methoxyphenylboronic acid (**4**) (1.1 equiv), 1,4-dioxane/H_2O, 70 °C, 4 h then (*E*)-phenylvinylboronic acid (**5**) (1.1 equiv), 100 °C, 2 h, **32**=54%, **34**=71%. (iv) $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), K_3PO_4 (3.5 equiv), 4-methoxyphenylboronic acid (**4**) (1.2 equiv), 1,4-dioxane (2.5 mL/mmol), 50 °C, 5 h, then (*E*)-phenylvinylboronic acid (**5**) (2.5 equiv), 100 °C, 12 h, **33**=65%.

3. Experimental

3.1. General

All reactions were carried out under an argon atmosphere. Solvents (THF, 1,4-dioxane) were distilled and dried by standard methods 4-Methoxyphenylboronic acid (**4**) was purchased from Maybridge. $Pd(OAc)_2$ and furan-2-ylboronic acid (**6**) were purchased from Acros. $Pd(PPh_3)_4$, S-Phos, (*E*)-phenylvinylboronic acid (**5**), and 3-nitrophenylboronic acid (**7**) were purchased from Aldrich. Reactions were routinely monitored by thin-layer chromatography (TLC) on silica gel 60 F_{254}. Purifications on flash silica gel column chromatography were performed with Geduran® silica gel Si 60 (40–63 μm). ^1H and ^{13}C NMR spectra were recorded at 23 °C. The following abbreviations are used to describe the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; td, triplet of doublets; m, multiplet; br s, broad singlet. ^{13}C NMR multiplicities are based on DEPT experiments. MS (EI, ESI and CI) and HRMS were recorded in positive ion mode. Unless otherwise indicated, peaks corresponding only to the major ^{35}Cl isotope are given in the LRMS and the HRMS, while the bromine isotopes are indicated in the LRMS (in the case of HRMS, only ^{79}Br isotope is given). Melting points are uncorrected. IR spectra were recorded by attenuated-total-reflection (ATR) spectroscopy using a ZnSe crystal.

3.2. General procedure for Suzuki reactions

Procedure A for Suzuki–Miyaura coupling with $Pd(OAc)_2$/S-Phos. A sealed pressure tube with a stir bar was charged with $Pd(OAc)_2$ (8 mol %), S-Phos (16 mol %), α-carboline (100 mg, 0.498 mmol), boronic acid (1.2 equiv), and K_3PO_4 (2 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (2.5 mL/mmol) was added and the reaction mixture was stirred at 100 °C overnight. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvent was removed under reduced pressure. The product was purified as described below and an analytical sample for mp was obtained by trituration with MeOH.

Procedure B for Suzuki–Miyaura coupling with $Pd(PPh_3)_4$. At rt under an inert atmosphere, $Pd(PPh_3)_4$ (8 mol %), boronic acid (1.1 equiv), and 0.3 M aqueous K_2CO_3 solution (3 equiv) in H_2O were added to a 0.1 M solution of **1** or **3** (100 mg, 0.498 mmol) in 1,4-dioxane. This solution was stirred at 100 °C for 12 h. After cooling to rt, the solution was filtered through Celite and solvents were removed under reduced pressure. The product was purified as described below and an analytical sample for mp was obtained by trituration with MeOH.

3.2.1. 2-(4-Methoxyphenyl)-9H-pyrido[2,3-b]indole (**8**)

Procedure A or B. The product was purified by flash chromatography (CH_2Cl_2) to afford **8** as a white solid (*procedure A*: 93 mg, 0.339 mmol, 68% yield; *procedure B*: 96 mg, 0.350 mmol, 70% yield); mp>220 °C; IR 3136, 3083, 2958, 1596, 1583, 1572, 1457, 1415, 1028, 818 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 8.52 (d, 1H, *J*=8.1 Hz), 8.14 (d, 2H, *J*=8.9 Hz), 8.13 (br d, 1H, *J*=6.8 Hz), 7.74 (d, 1H, *J*=8.1 Hz), 7.48 (br d, 1H, *J*=7.3 Hz), 7.42 (td, 1H, *J*=1.0 and 6.8 Hz), 7.21 (td, 1H, *J*=1.3 and 7.9 Hz), 7.07 (d, 2H, *J*=8.9 Hz), 3.83 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.8 (C), 152.8 (C), 152.0 (C), 139.1 (C), 131.9 (C), 129.1 (CH), 128.0 (2 CH), 126.2 (CH), 120.9 (CH), 120.5 (C), 119.4 (CH), 114.1 (2 CH), 113.5 (C), 111.2 (CH), 111.1 (CH), 55.2 (CH_3); MS (ESI) *m*/*z* 275.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{18}H_{15}N_2O$ $[M+H]^+$: 275.1184. Found: 275.1186.

3.2.2. 2-(Styryl)-9H-pyrido[2,3-b]indole (**9**)

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **9** (92 mg, 0.340 mmol) in 68% yield as a white solid; mp>220 °C; IR 3159, 3089, 3041, 2888, 1601, 1579, 1458, 1413, 1227, 954, 726, 685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.75 (br s, 1H), 8.48 (d, 1H, *J*=7.9 Hz), 8.12 (d, 1H, *J*=7.9 Hz), 7.72 (d, 1H, *J*=16.0 Hz), 7.69 (d, 2H, *J*=7.2 Hz), 7.46–7.40 (m, 6H), 7.34–7.29 (m, 1H), 7.21 (td, 1H, *J*=1.3 and 8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.0 (C), 151.8 (C), 139.4 (C), 136.5 (C), 131.0 (CH), 128.9 (CH), 128.8 (2 CH), 128.8 (CH), 128.1 (CH), 126.9 (2 CH), 126.5 (CH), 120.9 (CH), 120.5 (C), 119.5 (CH), 114.9 (CH), 114.6 (C), 111.1 (CH); MS (ESI) *m*/*z* 271.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235. Found: 271.1236.

3.2.3. 2-(Furan-2-yl)-9H-pyrido[2,3-b]indole (***10***)

Procedure A. The product was purified by flash chromatography (CH_2Cl_2) to afford **10** (95 mg, 0.405 mmol) in 81% yield as a brown solid; mp 208–210 °C; IR 3235, 2923, 1626, 1593, 1490, 1458, 1412, 1229, 1087, 884, 734 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.85 (br s, 1H), 8.54 (d, 1H, *J*=7.8 Hz), 8.13 (d, 1H, *J*=7.8 Hz), 7.85 (d, 1H, *J*=1.7 Hz), 7.62 (d, 1H, *J*=8.1 Hz), 7.48–7.41 (m, 2H), 7.22 (ddd, 1H, *J*=1.9, 6.8, and 8.1 Hz), 7.13 (d, 1H, *J*=3.4 Hz), 6.68 (dd, 1H, *J*=1.7 and 3.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.0 (C), 151.8 (C), 145.3 (CH), 143.8 (C), 139.3 (C), 129.1 (CH), 126.5 (CH), 120.9 (CH), 120.4 (C), 119.6 (CH), 114.3 (C), 112.3 (CH), 111.2 (CH), 110.2 (CH), 108.3 (CH); MS (CI isobutane) *m*/*z* 235 $[M+H]^+$; HRMS (CI isobutane): Calcd for $C_{15}H_{11}N_2O$ $[M+H]^+$: 235.0871. Found: 235.0873.

3.2.4. 2-(3-Nitrophenyl)-9H-pyrido[2,3-b]indole (***11***)

Procedure B. The product was purified by flash chromatography (CH_2Cl_2/PE 9:1) to afford **11** (120 mg, 0.415 mmol) in 83% yield as a yellow solid; mp 185–187 °C; IR 3165, 3091, 1625, 1596, 1585, 1518, 1455, 1414, 1346, 1286, 789, 755, 684 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 12.01 (br s, 1H), 9.03 (t, 1H, *J*=1.7 Hz), 8.62 (d, 1H, *J*=8.0 Hz), 8.60 (d, 1H *J*=8.1 Hz), 8.25 (dd, 1H, *J*=1.7 and 8.1 Hz), 8.19 (d, 1H, *J*=7.7 Hz), 7.96 (d, 1H, *J*=8.0 Hz), 7.79 (t, 1H, *J*=8.1 Hz), 7.51 (d, 1H, *J*=8.9 Hz), 7.47 (td, 1H, *J*=0.8 and 8.9 Hz), 7.25 (td, 1H, *J*=1.5 and 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.0 (C), 150.0 (C), 148.5 (C), 141.0 (C), 139.6 (C), 132.7 (CH), 130.3 (CH), 129.5 (CH), 127.0 (CH), 123.1 (CH), 121.4 (CH), 120.9 (CH), 120.1 (C), 119.7 (CH), 115.4 (C), 112.2 (C), 111.3 (CH); MS (ESI) *m*/*z* 290.2 $[M+H]^+$, 244.3 $[M-NO_2+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{12}N_3O_2$ $[M+H]^+$: 290.0930. Found: 290.0931.

3.2.5. 3-(4-Methoxyphenyl)-9H-pyrido[2,3-b]indole (***12***)

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **12** (99 mg, 0.363 mmol) in 73% yield as a yellow solid; mp>220 °C (lit. mp 265–266 °C (EtOH)[17]); IR 3125, 2979, 1607, 1587, 1570, 1519, 1455, 1244, 1231, 1034, 742 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.80 (br s, 1H), 8.75 (d, 1H, *J*=2.1 Hz), 8.67 (d, 1H, *J*=2.1 Hz), 8.23 (d, 1H, *J*=7.9 Hz), 7.72 (d, 2H, *J*=8.6 Hz), 7.51–7.43 (m, 2H), 7.23 (td, 1H, *J*=1.5 and 8.1 Hz), 7.07 (d, 2H, *J*=8.6 Hz), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6 (C), 151.1 (C), 144.4 (CH), 139.4 (C), 130.9 (C), 127.9 (2 CH), 127.4 (C), 126.7 (CH), 126.0 (CH), 121.4 (CH), 120.5 (C), 119.3 (CH), 115.3 (C), 114.5 (2 CH), 111.3 (CH), 55.2 (CH_3); MS (ESI) *m*/*z* 275.2 $[M+H]^+$; Anal. Calcd for $C_{18}H_{14}N_2O$: C, 78.81; H, 5.14; N, 10.21. Found: C, 78.46; H, 4.98; N, 10.44.

3.2.6. 3-(Styryl)-9H-pyrido[2,3-b]indole (***13***)

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **13** (91 mg, 0.338 mmol) in 68% yield as a white solid; mp>220 °C; IR 2973, 1604, 1496, 1456, 1403, 1243, 1109, 961, 741, 685 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 11.85 (br s, 1H), 8.84 (d, 1H, *J*=2.1 Hz), 8.62 (d, 1H, *J*=2.1 Hz), 8.19 (d, 1H, *J*=7.7 Hz), 7.63 (d, 2H, *J*=7.4 Hz), 7.51–7.34 (m, 6H), 7.30–7.22 (m,

2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.6 (C), 146.2 (CH), 139.4 (C), 137.4 (C), 128.7 (2 CH), 127.3 (CH), 126.9 (CH), 126.8 (CH), 126.4 (CH), 126.2 (2 CH), 124.8 (CH), 124.7 (C), 121.3 (CH), 120.4 (C), 119.7 (CH), 115.5 (C), 111.4 (CH); MS (ESI) m/z 271.2 $[M+H]^+$; HRMS (ESI): Calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235. Found: 271.1236.

*3.2.7. 3-(Furan-2-yl)-9H-pyrido[2,3-b]indole (**14**)*

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **14** (75 mg, 0.320 mmol) in 65% yield as a yellow solid; mp>220 °C; IR 3124, 3079, 1628, 1604, 1445, 1234, 1005, 731, 722 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.91 (br s, 1H), 8.80 (s, 2H), 8.23 (d, 1H, J=7.9 Hz), 7.79 (dd, 1H, J=0.8 and 1.8 Hz), 7.51 (d, 1H, J=8.1 Hz), 7.47 (td, 1H, J=1.1 and 8.1 Hz), 7.24 (ddd, 1H, J=1.9 and 7.2 Hz), 6.99 (dd, 1H, J=0.7 and 3.4 Hz), 6.64 (dd, 1H, J=1.8 and 3.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.2 (C), 151.1 (C), 142.5 (CH), 142.4 (CH), 139.4 (C), 126.9 (CH), 123.3 (CH), 121.5 (CH), 120.4 (C), 119.7 (CH), 118.7 (C), 115.1 (C), 112.0 (CH), 111.4 (CH), 104.6 (CH); MS (EI) m/z 234.0 $[M]^{+\bullet}$; HRMS (EI): Calcd for $C_{15}H_{10}N_2O$ $[M]^{+\bullet}$: 234.0793. Found: 234.0792.

*3.2.8. 3-(3-Nitrophenyl)-9H-pyrido[2,3-b]indole (**15**)*

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 8:2) to afford **15** (100 mg, 0.346 mmol) in 70% yield as a yellow solid; mp>220 °C; IR 3127, 3069, 1606, 1523, 1343, 1231, 871, 733, 674 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.99 (br s, 1H), 9.02 (d, 1H, J=2.3 Hz), 8.85 (d, 1H, J=2.3 Hz), 8.62 (t, 1H, J=2.1 Hz), 8.32–8.27 (m, 2H), 8.23 (ddd, 1H, J=1.0, 2.1, and 8.2 Hz), 7.81 (t, 1H, J=8.2 Hz), 7.55–7.46 (m, 2H), 7.27 (td, 1H, J=1.5 and 7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.2 (C), 148.8 (C), 145.3 (CH), 140.7 (C), 139.8 (C), 133.6 (CH), 130.8 (CH), 127.3 (2 CH), 125.6 (C), 122.0 (CH), 121.9 (CH), 121.4 (CH), 120.8 (C), 120.1 (CH), 115.8 (C), 111.8 (CH); MS (ESI) m/z 290.1 $[M+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{12}N_3O_2$ $[M+H]^+$: 290.0930. Found: 290.0934.

*3.2.9. 4-(4-Methoxyphenyl)-9H-pyrido[2,3-b]indole (**16**)*

Procedure A or B. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **16** as a yellow solid (*procedure A*: 97 mg, 0.350 mmol, 71% yield, *procedure B*: 96 mg, 0.350 mmol, 70% yield); mp 208–210 °C; IR 3062, 2968, 2835, 1599, 1560, 1515, 1456, 1252, 1176, 1029, 809, 745, 724 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (br s, 1H), 8.41 (d, 1H, J=5.0 Hz), 7.63 (d, 2H, J=8.7 Hz), 7.60 (d, 1H, J=9.0 Hz), 7.50 (d, 1H, J=8.1 Hz), 7.40 (td, 1H, J=0.9 and 7.2 Hz), 7.17 (d, 2H, J=8.7 Hz), 7.06 (d, 1H, J=5.0 Hz), 7.04 (td, 1H, J=1.1 and 7.5 Hz), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.6 (C), 149.2 (C), 145.9 (CH), 144.1 (C), 138.9 (C), 130.6 (C), 129.8 (2 CH), 126.4 (CH), 121.9 (CH), 119.9 (C), 119.0 (CH), 115.9 (CH), 114.2 (2 CH), 112.1 (C), 111.3 (CH), 55.3 (CH_3); MS (ESI) m/z 275.2 $[M+H]^+$; HRMS (EI): Calcd for $C_{18}H_{14}N_2O$ $[M]^{+\bullet}$: 274.1106. Found: 274.1105.

*3.2.10. 4-(Styryl)-9H-pyrido[2,3-b]indole (**17**)*

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **17** (96 mg, 0.355 mmol) in 72% yield as a yellow solid; mp>220 °C; IR 3059, 2972, 1633, 1599, 1580, 1561, 1455, 1397, 1255, 957, 730, 690 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (br s, 1H), 8.39 (d, 1H, J=5.3 Hz), 8.32 (d, 1H, J=8.0 Hz), 8.07 (d, 1H, J=16.3 Hz), 7.85 (d, 2H, J=7.2 Hz), 7.65 (d, 1H, J=16.3 Hz), 7.53 (d, 1H, J=5.3 Hz), 7.51–7.45 (m, 4H), 7.41–7.36 (m, 1H), 7.27 (td, 1H, J=1.5 and 8.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.7 (C), 145.9 (CH), 139.8 (C), 139.0 (C), 136.3 (C), 134.5 (CH), 128.9 (2 CH), 128.8 (CH), 127.4 (2 CH), 126.3 (CH), 123.7 (CH), 123.4 (CH), 120.4 (C), 119.7 (CH), 112.3 (C), 111.2 (CH), 110.9 (CH); MS (EI) m/z 270 $[M]^+$; HRMS (ESI): Calcd for $C_{19}H_{15}N_2$ $[M+H]^+$: 271.1235. Found: 271.1235.

*3.2.11. 4-(Furan-2-yl)-9H-pyrido[2,3-b]indole (**18**)*

Procedure A. The product was purified by flash chromatography (CH_2Cl_2/EtOAc 8:2) to afford **18** (88 mg, 0.376 mmol) in 76% yield as a green solid; mp>220 °C; IR 3135, 3062, 1617, 1590, 1546, 1454, 1264, 1026, 996, 733, 670 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.00 (br s, 1H), 8.50 (d, 1H, J=8.5 Hz), 8.42 (d, 1H, J=5.3 Hz), 8.13 (dd, 1H, J=0.7 and 1.7 Hz), 7.54–7.51 (m, 1H), 7.48 (td, 1H, J=1.1 and 6.9 Hz), 7.43 (d, 1H, J=5.1 Hz), 7.31 (dd, 1H, J=0.7 and 3.4 Hz), 7.21 (ddd, 1H, J=1.5, 6.8, and 8.2 Hz), 6.82 (dd, 1H, J=1.7 and 3.4 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.0 (C), 151.7 (C), 145.8 (CH), 144.5 (CH), 139.2 (C), 131.7 (C), 126.7 (CH), 123.7 (CH), 119.7 (C), 119.5 (CH), 112.5 (2 CH), 111.2 (CH), 111.1 (CH), 109.8 (C); MS (CI, isobutane) m/z 235 $[M+H]^+$; HRMS (CI isobutane): Calcd for $C_{15}H_{11}N_2O$ $[M+H]^+$: 235.0871. Found: 235.0872.

*3.2.12. 4-(3-Nitrophenyl)-9H-pyrido[2,3-b]indole (**19**)*

Procedure B. The product was purified by chromatography (CH_2Cl_2/EtOAc 8:2) to afford **19** (110 mg, 0.380 mmol) in 77% yield as a yellow solid; mp>220 °C; IR 3063, 1622, 1599, 1561, 1523, 1456, 1344, 1292, 815, 734 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.11 (br s, 1H), 8.52 (d, 1H, J=5.0 Hz), 8.48 (t, 1H, J=1.8 Hz), 8.43 (ddd, 1H, J=1.0, 1.8, and 8.0 Hz), 8.18 (ddd, 1H, J=1.0, 1.8, and 8.0 Hz), 7.93 (t, 1H, J=8.0 Hz), 7.55 (d, 1H, J=7.9 Hz), 7.46 (d, 1H, J=7.9 Hz), 7.45 (td, 1H, J=1.0 and 7.9 Hz), 7.21 (d, 1H, J=5.0 Hz), 7.04 (td, 1H, J=1.0 and 7.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.3 (C), 148.1 (C), 146.2 (CH), 141.6 (C), 139.9 (C), 139.2 (C), 135.2 (CH), 130.6 (CH), 126.8 (CH), 123.5 (CH), 123.1 (CH), 121.7 (CH), 119.4 (CH), 119.2 (C), 115.8 (CH), 111.9 (C), 111.6 (CH); MS (ESI) m/z 290.2 $[M+H]^+$, 244.3 $[M-NO_2+H]^+$; HRMS (ESI): Calcd for $C_{17}H_{12}N_3O_2$ $[M+H]^+$: 290.0930. Found: 290.0925; Anal. Calcd for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.83; N, 14.52. Found: C, 70.30; H, 3.85; N, 14.20.

3.3. General procedure for the bromation reaction

At rt and under an inert atmosphere, a solution of bromine (1.2 equiv, 0.7 M) in CH_2Cl_2 was added to a 0.45 M suspension of **1** or **2** or **3** (1 equiv) in anhydrous CH_2Cl_2. The mixture was stirred for 1 h at rt. Excess bromine was reduced by addition of saturated aqueous $Na_2S_2O_3$ solution. The resulting mixture was extracted with EtOAc/DMF (99:1). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The product was purified by trituration with MeOH.

*3.3.1. 6-Bromo-2-chloro-9H-pyrido[2,3-b]indole (**20**)*

Starting material **1**: 500 mg, 2.49 mmol. Compound **20** was obtained by trituration with MeOH (522 mg, 1.87 mmol, 75% yield); mp>220 °C; IR 3135, 3053, 2956, 1626, 1597, 1574, 1404, 1273, 1202, 1128, 794, 771 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.21 (br s, 1H), 8.62 (d, 1H, J=8.1 Hz), 8.46 (d, 1H, J=1.7 Hz), 7.61 (dd, 1H, J=1.7 and 8.7 Hz), 7.48 (d, 1H, J=8.7 Hz), 7.31 (d, 1H, J=8.1 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.2 (C), 147.1 (C), 137.5 (C), 132.2 (CH), 129.3 (CH), 123.9 (CH), 121.8 (C), 115.0 (CH), 113.6 (CH), 113.4 (C), 112.1 (C); MS (ESI) m/z 279 $[M-H, {}^{79}Br]^{-\bullet}$, 281 $[M-H, {}^{81}Br]^{-\bullet}$; HRMS (EI): Calcd for $C_{11}H_6BrClN_2$ $[M]^{+\bullet}$: 279.9403. Found: 279.9405.

*3.3.2. 6-Bromo-3-chloro-9H-pyrido[2,3-b]indole (**21**)*

Starting material **2**: 200 mg, 0.990 mmol. The compound **21** was obtained by trituration with MeOH (217 mg, 0.775 mmol, 78% yield); mp>220 °C; IR 3031, 3005, 2957, 1577, 1604, 1486, 1269, 1232, 1089, 803, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.19 (br s, 1H), 8.75 (d, 1H, J=2.5 Hz), 8.48 (d, 1H, J=1.9 Hz), 8.46 (d, 1H, J=2.5 Hz), 7.62 (dd, 1H, J=1.9 and 8.6 Hz), 7.48 (d, 1H, J=8.6 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.3 (C), 145.0 (CH), 138.4 (C), 129.9 (CH), 128.8 (CH), 124.4 (CH), 122.1 (C), 121.5 (C), 115.4 (C),

113.6 (CH), 111.8 (C); MS (ESI) *m/z* 281 [M+H, ^{79}Br]$^{+\bullet}$, 283 [M+H, ^{81}Br]$^{+\bullet}$; HRMS (EI): Calcd for $C_{11}H_6BrClN_2$ [M]$^{+\bullet}$: 279.9403. Found: 279.9405.

*3.3.3. 6-Bromo-4-chloro-9H-pyrido[2,3-b]indole (**22**)*

Starting material **3**: 500 mg, 2.49 mmol. Compound **22** was obtained by trituration with MeOH (530 mg, 1.89 mmol, 76% yield); mp>220 °C; IR 3123, 2950, 1603, 1569, 1442, 1276, 870, 795 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.40 (br s, 1H), 8.43 (d, 1H, *J*=1.5 Hz), 8.42 (d, 1H, *J*=5.3 Hz), 7.69 (dd, 1H, *J*=1.5 and 8.6 Hz), 7.54 (d, 1H, *J*=8.6 Hz), 7.38 (d, 1H, *J*=5.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.8 (C), 147.6 (CH), 137.6 (C), 136.9 (C), 129.9 (CH), 124.4 (CH), 120.7 (C), 115.9 (CH), 113.7 (CH), 111.9 (C), 111.7 (C); MS (ESI) *m/z* 281.1 [M+H, ^{79}Br]$^{+\bullet}$, 283.1 [M+H, ^{81}Br]$^{+\bullet}$; HRMS (ESI): Calcd for $C_{11}H_7BrClN_2$ [M+H]$^+$: 280.9481. Found: 280.9485.

3.4. General procedure for the benzenesulfonyl protection

To a 0.15 M suspension of **20** or **21** or **22** in THF at 0 °C was added NaH (60% in oil, 1.1 equiv) in small portions and the resulting solution mixture was stirred at 0 °C for 20 min. A solution of benzenesulfonyl chloride (1.2 equiv) was added dropwise at 0 °C. The final solution was stirred for 12 h and was slowly quenched with a 5% aqueous $NaHCO_3$ solution and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered, and the solvent was removed under reduced pressure. The product was purified as described below and an analytical sample for mp was obtained by trituration with MeOH.

*3.4.1. 9-Benzenesulfonyl-6-bromo-2-chloro-9H-pyrido[2,3-b]-indole (**23**)*

Starting material **20**: 200 mg, 0.716 mmol. The crude product was purified by flash chromatography (CH_2Cl_2) to afford **23** (272 mg, 0.647 mmol) in 90% yield as a white solid; mp 204–206 °C (CH_2Cl_2/PE); IR 3060, 1614, 1573, 1448, 1380, 1371, 1187, 1173, 1128, 1088, 979, 813, 727, 682 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, 1H, *J*=8.9 Hz), 8.21–8.18 (m, 2H), 8.08 (d, 1H, *J*=8.1 Hz), 8.02 (d, 1H, *J*=1.8 Hz), 7.68 (dd, 1H, *J*=1.8 and 8.9 Hz), 7.58–7.56 (m, 1H), 7.50–7.45 (m, 2H), 7.31 (d, 1H, *J*=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6 (C), 149.2 (C), 138.1 (C), 136.5 (C), 134.5 (CH), 131.4 (CH), 130.7 (CH), 129.1 (2 CH), 128.2 (2 CH), 123.8 (C), 123.6 (CH), 119.8 (CH), 117.5 (C), 116.6 (CH), 115.9 (C); MS (ESI) *m/z* 421.0 [M+H, ^{79}Br]$^+$, 422.9 [M+H, ^{81}Br]$^+$; HRMS (ESI): Calcd for $C_{17}H_{10}BrClN_2O_2SNa$ [M+Na]$^+$: 442.9233. Found: 442.9229.

*3.4.2. 9-Benzenesulfonyl-6-bromo-3-chloro-9H-pyrido[2,3-b]-indole (**24**)*

Starting material **21**: 400 mg, 1.42 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **24** (543 mg, 1.29 mmol) in 91% yield as a white solid; mp>220 °C; IR 3061, 1584, 1569, 1447, 1384, 1356, 1184, 1091, 970, 847, 815, 724 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (d, 1H, *J*=2.5 Hz), 8.62 (d, 1H, *J*=2.5 Hz), 8.56 (d, 1H, *J*=2.1 Hz), 8.30 (d, 1H, *J*=9.0 Hz), 8.05–8.02 (m, 2H), 7.85 (dd, 1H, *J*=2.1 and 9.0 Hz), 7.70 (tt, 1H, *J*=1.1 and 7.4 Hz), 7.59–7.54 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 148.2 (C), 145.6 (CH), 137.2 (C), 136.3 (C), 134.6 (CH), 131.8 (CH), 129.6 (CH), 129.3 (2 CH), 126.9 (C), 126.7 (2 CH), 124.6 (CH), 123.3 (C), 116.1 (C); 116.5 (C) 116.2 (CH); MS (ESI) *m/z* 421.0 [M+H, ^{79}Br]$^+$, 443.1 [M+Na, ^{79}Br]$^+$; HRMS (ESI): Calcd for $C_{17}H_{10}BrClN_2O_2SNa$ [M+Na]$^+$: 442.9233. Found: 442.9229.

*3.4.3. 9-Benzenesulfonyl-6-bromo-4-chloro-9H-pyrido[2,3-b]indole (**25**)*

Starting material **22**: 445 mg, 1.59 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **25** (571 mg, 1.35 mmol) in 85% yield as a white solid; mp 212–214 °C (CH_2Cl_2/PE); IR 3122, 3059, 1607, 1579, 1558, 1432, 1384, 1349, 1193, 1183, 995, 806, 722 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 1H, *J*=2.1 Hz), 8.45 (d, 1H, *J*=5.3 Hz), 8.40 (d, 1H, *J*=8.9 Hz), 8.14–8.11 (m, 2H), 7.71 (dd, 1H, *J*=2.1 and 8.9 Hz), 7.55 (tt, 1H, *J*=1.3 and 7.3 Hz), 7.45–7.40 (m, 2H), 7.29 (d, 1H, *J*=5.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6 (C), 147.5 (CH), 138.8 (C), 138.3 (C), 136.4 (C), 134.5 (CH), 131.9 (CH), 129.2 (2 CH), 127.8 (2 CH), 125.9 (CH), 123.4 (C), 120.5 (CH), 117.4 (C), 116.4 (CH); 115.6 (C); MS (ESI) *m/z* 420.9 [M+H, ^{79}Br]$^+$, 422.9 [M+H, ^{81}Br]$^+$, 442.9 [M+Na, ^{79}Br]$^+$, 444.9 [M+Na, ^{81}Br]$^+$; Anal. Calcd for $C_{17}H_{10}BrClN_2O_2S$: C, 48.42; H, 2.39; N, 6.64. Found: C, 48.43; H, 2.29; N, 7.07.

3.5. Typical procedure for Suzuki coupling at C-6

At rt and under inert atmosphere, a solution of $Pd(PPh_3)_4$ (0.08 equiv), boronic acid (1.1 equiv), and 0.3 M aqueous K_2CO_3 (3 equiv) was added to a 0.1 M suspension of **24** in 1,4-dioxane (or **23**, or **25** in THF). This solution was stirred at 100 °C or 70 °C, respectively, for 12 h. After cooling to rt, the solution was filtered through Celite and solvents were removed under reduced pressure. The product was purified as described below and an analytical sample for mp was obtained by trituration with MeOH.

*3.5.1. 9-Benzenesulfonyl-2-chloro-6-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**26**)*

Starting material **23**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 3:7) to afford **26** (62 mg, 0.138 mmol) in 58% yield as a white solid; mp 176–178 °C (CH_2Cl_2/PE); IR 2932, 1606, 1587, 1567, 1519, 1465, 1450, 1369, 1172, 1039, 813, 732, 683 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.48 (d, 1H, *J*=8.7 Hz), 8.24–8.21 (m, 2H), 8.14 (d, 1H, *J*=8.1 Hz), 8.01 (d, 1H, *J*=1.5 Hz), 7.74 (dd, 1H, *J*=1.5 and 8.7 Hz), 7.57 (d, 2H, *J*=8.7 Hz), 7.56 (td, 1H, *J*=1.1 and 8.1 Hz), 7.48–7.43 (m, 2H), 7.28 (d, 1H, *J*=8.1 Hz), 6.98 (d, 2H, *J*=8.7 Hz), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C), 159.4 (C), 148.4 (C), 138.4 (C), 137.3 (C), 136.7 (C), 134.3 (CH), 133.0 (C), 130.5 (CH), 129.1 (2 CH), 128.4 (2 CH), 128.1 (2 CH), 127.6 (CH), 122.7 (C), 119.5 (CH), 118.5 (CH), 117.3 (C), 115.3 (CH), 114.5 (2 CH), 55.5 (CH_3); MS (ESI) *m/z* 448.9 [M+H]$^+$, 471 [M+Na]$^+$; Anal. Calcd for $C_{24}H_{17}ClN_2O_3S$: C, 64.21; H, 3.82; N, 6.24. Found: C, 64.25; H, 3.95; N, 6.55.

*3.5.2. 9-Benzenesulfonyl-3-chloro-6-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**27**)*

Starting material **24**: 150 mg, 0.355 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 7:3) to afford **27** (132 mg, 0.294 mmol) in 83% yield as a yellow solid; mp>220 °C (CH_2Cl_2/PE); IR 3016, 1607, 1683, 1520, 1473, 1361, 1216, 1182, 1091, 978, 822, 725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 1H, *J*=8.9 Hz), 8.50 (d, 1H, *J*=2.3 Hz), 8.19 (d, 1H, *J*=2.3 Hz), 8.15–8.12 (m, 2H), 8.02 (d, 1H, *J*=1.5 Hz), 7.78 (dd, 1H, *J*=1.5 and 8.9 Hz), 7.57 (d, 2H, *J*=8.8 Hz), 7.55–7.51 (m, 1H), 7.45–7.40 (td, 2H, *J*=2.8 and 8.9 Hz), 7.01 (d, 2H, *J*=8.8 Hz), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6 (C), 159.5 (C), 159.0 (C), 149.2 (C), 145.7 (CH), 138.6 (C), 137.5 (C), 134.3 (CH), 132.9 (C) 129.2 (2 CH), 128.4 (2 CH), 128.3 (CH), 128.1 (CH), 127.6 (2 CH), 122.4 (C), 120.1 (C), 118.8 (CH), 115.5 (CH), 114.6 (2 CH), 54.5 (CH_3); MS (ESI) *m/z* 449.0 [M+H]$^+$, 471.0 [M+Na]$^+$, 918.8 [2M+Na]$^+$; Anal. Calcd for $C_{24}H_{17}ClN_2O_3S$: C, 64.21; H, 3.82; N, 6.24. Found: C, 64.77; H, 3.87; N, 6.63.

*3.5.3. 9-Benzenesulfonyl-4-chloro-6-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**28**)*

Starting material **25**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **28** (75 mg, 0.167 mmol) in 70% yield as a white solid; mp 209–211 °C (CH_2Cl_2/PE); IR 3020, 2835, 1607, 1583, 1521, 1467, 1441, 1375, 1234,

1172, 1020, 834, 770, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (d, 1H, J=1.8 Hz), 8.55 (d, 1H, J=8.8 Hz), 8.43 (d, 1H, J=5.5 Hz), 8.18–8.15 (m, 2H), 7.80 (dd, 1H, J=1.8 and 8.8 Hz), 7.61 (d, 2H, J=8.7 Hz), 7.54 (tt, 1H, J=1.3 and 7.4 Hz), 7.45–7.40 (m, 2H), 7.29 (d, 1H, J=5.5 Hz), 7.03 (d, 2H, J=8.7 Hz), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 151.9 (C), 146.8 (CH), 138.6 (C), 138.5 (C), 137.3 (C), 136.7 (C), 134.3 (CH), 133.2 (C), 129.1 (2 CH), 128.5 (2 CH), 128.0 (CH), 127.8 (2 CH), 122.5 (C), 121.2 (CH), 120.4 (CH), 116.8 (C), 115.0 (CH), 114.5 (2 CH); 55.5 (CH_3); MS (ESI) m/z 449.0 $[M+H]^+$, 471.0 $[M+Na]^+$, 918.8 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{24}H_{17}ClN_2O_3SNa$ $[M+Na]^+$: 471.0546. Found: 471.0545.

3.5.4. 9-Benzenesulfonyl-2-chloro-6-(styryl)-9H-pyrido[2,3-b]-indole (**29**)

Starting material **23**: 200 mg, 0.476 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 3:7) to afford **29** (134 mg, 0.301 mmol) in 64% yield as a white solid; mp 180–182 °C (CH_2Cl_2/PE); IR 3022, 1587, 1571, 1470, 1447, 1380, 1172, 980, 807, 753, 728, 682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, 1H, J=8.9 Hz), 8.23–8.20 (m, 2H), 8.11 (d, 1H, J=8.1 Hz), 8.00 (d, 1H, J=1.8 Hz), 7.75 (dd, 1H, J=1.8 and 9.0 Hz), 7.57–7.54 (m, 3H), 7.49–7.47 (m, 2H), 7.39 (t, 2H, J=7.1 Hz), 7.31 (d, 1H, J=8.1 Hz), 7.31 (td, 1H, J=1.1 and 7.2 Hz), 7.23 (d, 1H, J=16.3 Hz), 7.17 (d, 1H, J=16.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C), 148.5 (C), 138.3 (C), 137.2 (C), 137.1 (C), 134.3 (CH), 133.8 (C), 130.5 (CH), 129.2 (CH), 129.1 (2 CH), 128.9 (2 CH), 128.2 (2 CH), 127.9 (CH), 127.8 (CH), 127.1 (CH), 126.6 (2 CH), 122.6 (C), 119.6 (CH), 118.4 (CH), 117.1 (C), 115.3 (CH); MS (ESI) m/z 445.0 $[M+H]^+$, 467.0 $[M+Na]^+$, 910.6 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{25}H_{17}ClN_2O_2SNa$ $[M+Na]^+$: 467.0597. Found: 467.0597.

3.5.5. 9-Benzenesulfonyl-3-chloro-6-(styryl)-9H-pyrido[2,3-b]-indole (**30**)

Starting material **24**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 6:4) to afford **30** in (75 mg, 0.168 mmol) 71% yield as a yellow solid; mp 190–192 °C (MeOH); IR 3025, 1568, 1474, 1433, 1366, 1176, 1090, 972, 727, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, 1H, J=2.4 Hz), 8.45 (d, 1H, J=8.9 Hz), 8.18 (d, 1H, J=2.4 Hz), 8.14–8.11 (m, 2H), 8.00 (d, 1H, J=1.7 Hz), 7.76 (dd, 1H, J=1.7 and 8.9 Hz), 7.57–7.52 (m, 3H), 7.45–7.36 (m, 4H), 7.29 (tt, 1H, J=1.2 and 7.4 Hz), 7.23 (d, 1H, J=16.4 Hz), 7.16 (d, 1H, J=16.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C), 145.7 (CH), 138.5 (C), 137.8 (C), 137.1 (C), 134.3 (CH), 133.9 (C), 129.3 (CH), 129.2 (2 CH), 128.9 (2 CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 127.7 (CH), 127.6 (C), 127.6 (2 CH), 126.7 (2 CH), 122.4 (C), 119.9 (C), 118.6 (CH), 115.5 (CH); MS (ESI) m/z 445.0 $[M+H]^+$, 466.9 $[M+Na]^+$, 910.9 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{25}H_{17}ClN_2O_2SNa$ $[M+Na]^+$: 467.0597. Found: 467.0598.

3.5.6. 9-Benzenesulfonyl-4-chloro-6-(styryl)-9H-pyrido[2,3-b]-indole (**31**)

Starting material **25**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 6:4) to afford **31** (72 mg, 0.161 mmol) in 68% yield as a white solid; mp 216–218 °C (CH_2Cl_2/PE); IR 3063, 2924, 1614, 1583, 1562, 1442, 1371, 1170, 1006, 995, 814, 684 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, 1H, J=8.6 Hz), 8.51 (d, 1H, J=1.5 Hz), 8.43 (d, 1H, J=5.5 Hz), 8.16–8.15 (m, 2H), 7.81 (dd, 1H, J=1.5 and 8.6 Hz), 7.58–7.52 (m, 3H), 7.45–7.36 (m, 4H), 7.31–7.28 (m, 1H), 7.30 (d, 1H, J=5.5 Hz), 7.27 (d, 1H, J=16.4 Hz), 7.18 (d, 1H, J=16.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (C), 149.8 (C), 146.9 (CH), 138.5 (C), 137.2 (C), 137.1 (C), 134.3 (CH), 133.8 (C), 129.2 (CH), 129.1 (2 CH), 128.9 (2 CH), 128.1 (CH), 127.9 (CH), 127.8 (2 CH), 127.3 (CH), 126.7 (2 CH), 122.4 (C), 121.2 (CH), 120.4 (CH), 116.7 (C), 115.0 (CH); MS (ESI) m/z 445.0 $[M+H]^+$, 466.9 $[M+Na]^+$, 910.8 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{25}H_{17}ClN_2O_2SNa$ $[M+Na]^+$: 467.0597. Found: 467.0598.

3.6. Typical procedure Suzuki–Miyaura on 2- and 4-chloro-6-substituted pyrido[2,3-*b*]indoles

At rt and under an inert atmosphere, a solution of $Pd(PPh_3)_4$, (0.08 equiv), (*E*)-phenylvinylboronic acid (**5**) (1.1 equiv), and 0.3 M K_2CO_3 (3 equiv) in H_2O was added to a 0.1 M solution of **26** or **28** in 1,4-dioxane. This solution was stirred at 100 °C for 12 h. After cooling to rt, solution was filtered through Celite and solvents were removed under reduced pressure.

3.6.1. 9-Benzenesulfonyl-6-(4-methoxyphenyl)-2-(styryl)-9H-pyrido[2,3-b]indole (**32**)

Starting material **26**: 104 mg, 0.231 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **32** (100 mg, 0.194 mmol), in 84% yield as a yellow solid; mp 193–195 °C (CH_2Cl_2/PE); IR 2926, 1607, 1586, 1518, 1465, 1382, 1172, 1090, 967, 812 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, 1H, J=8.9 Hz), 8.34–8.31 (m, 2H), 8.14 (d, 1H, J=7.9 Hz), 8.06 (d, 1H, J=1.8 Hz), 7.91 (d, 1H, J=16.0 Hz), 7.78 (dd, 1H, J=1.8 and 8.6 Hz), 7.71 (d, 2H, J=7.4 Hz), 7.66 (d, 2H, J=8.6 Hz), 7.60–7.36 (m, 6H), 7.34 (d, 1H, J=2.6 Hz), 7.28 (d, 1H, J=16.0 Hz), 7.09 (d, 2H, J=8.6 Hz), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (C), 153.5 (C), 151.2 (C), 139.0 (C), 137.1 (C), 136.9 (C), 136.8 (C), 134.0 (CH), 133.4 (CH), 133.2 (C), 128.9 (4 CH), 128.6 (CH), 128.5 (CH); 128.3 (2 CH), 127.9 (3 CH), 127.3 (2 CH), 127.0 (CH), 123.6 (C), 118.5 (CH), 118.3 (CH), 117.4 (C), 115.2 (CH), 114.4 (2 CH); 55.4 (CH_3); MS (ESI) m/z 517.1 $[M+H]^+$, 539 $[M+Na]^+$; Anal. Calcd for $C_{32}H_{24}N_2O_3S$: C, 74.40; H, 4.68; N, 5.42. Found: C, 74.58; H, 4.82; N, 5.45.

3.6.2. 9-Benzenesulfonyl-6-(4-methoxyphenyl)-4-(styryl)-9H-pyrido[2,3-b]indole (**34**)

Starting material **28**: 60 mg, 0.134 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 7:3) to afford **34** (61 mg, 0.118 mmol) in 87% yield as a yellow solid; mp 190–192 °C (CH_2Cl_2/PE); IR 3073, 2838, 1633, 1607, 1587, 1517, 1462, 1443, 1377, 1179, 1047, 810, 728, 688 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.59 (d, 1H, J=8.7 Hz), 8.52 (d, 1H, J=5.1 Hz), 8.23 (d, 1H, J=1.8 Hz), 8.20–8.17 (m, 2H), 7.84 (d, 1H, J=16.2 Hz), 7.75 (dd, 1H, J=1.8 and 8.7 Hz), 7.62–7.58 (m, 2H), 7.58 (d, 2H, J=8.8 Hz), 7.52–7.50 (m, 1H), 7.45 (d, 1H, J=5.1 Hz), 7.43–7.36 (m, 5H), 7.35 (d, 1H, J=16.2 Hz), 7.02 (d, 2H, J=8.8 Hz), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 146.7 (CH), 141.6 (C), 138.9 (C), 137.1 (C), 136.8 (C), 136.2 (C), 135.8 (CH), 134.0 (CH), 133.5 (C), 129.2 (3 CH), 129.0 (2 CH), 128.4 (2 CH), 127.7 (2 CH), 127.3 (2 CH), 127.1 (CH), 124.0 (C), 123.4 (CH), 121.2 (CH), 116.0 (CH), 115.9 (C), 115.3 (CH), 114.6 (2 CH), 55.5 (CH_3); MS (ESI) m/z 517.1 $[M+H]^+$, 1055.0 $[2M+Na]^+$; Anal. Calcd $C_{32}H_{24}N_2O_3S$: C, 74.40; H, 4.68; N, 5.42. Found: C, 74.39; H, 4.68; N, 5.62.

3.7. 9-Benzenesulfonyl-6-(4-methoxyphenyl)-3-(styryl)-9*H*-pyrido[2,3-*b*]indole (33)

A sealed pressure tube with a stir bar was charged with $Pd(OAc)_2$ (4 mg, 0.018 mmol, 0.04 equiv), S-Phos (15 mg, 0.036 mmol, 0.08 equiv), α-carboline **27** (100 mg, 0.222 mmol), (*E*)-phenylvinylboronic acid (**5**) (82 mg, 0.556 mmol, 2.5 equiv), and K_3PO_4 (141 mg, 0.666 mmol, 3 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (600 μL) was added and the reaction mixture was stirred at 100 °C overnight. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/PE 3:1) to afford **33** (90 mg, 0.174 mmol) in 79% yield as a yellow solid; mp 176–178 °C (CH_2Cl_2/PE); IR 3036, 2934, 1609, 1481, 1462, 1442, 1369, 1255, 1178, 1038, 980, 810 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, 1H, J=2.1 Hz), 8.50 (d, 1H, J=8.6 Hz), 8.39 (d, 1H, J=2.1 Hz), 8.18–8.15 (m, 2H), 8.11 (d, 1H, J=1.8 Hz), 7.76 (dd, 1H, J=1.8 and 8.6 Hz), 7.61 (d, 2H, J=8.7 Hz), 7.56–7.50 (m, 3H), 7.43 (d, 2H, J=7.9 Hz), 7.38 (d, 2H, J=7.9 Hz), 7.31 (d, 1H, J=7.4 Hz), 7.24 (s, 2H), 7.03 (d, 2H, J=8.7 Hz), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4 (C), 150.5 (C), 146.6 (CH), 138.7 (C), 137.2 (C), 137.1 (C), 136.8 (C), 134.0 (CH), 133.1 (C), 130.1 (CH), 129.3 (C), 129.0 (2 CH), 128.9 (2 CH), 128.3 (2 CH), 128.2 (CH), 127.6 (3 CH), 126.6 (2 CH), 124.8 (CH), 124.7 (CH), 123.4 (C), 119.2 (C), 118.7 (CH), 115.4 (CH), 114.5 (2 CH), 55.5 (CH_3); MS (ESI) m/z 517.0 $[M+H]^+$, 539.0 $[M+Na]^+$, 1054.8 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{32}H_{25}N_2O_3S$ $[M+H]^+$: 517.1586. Found: 517.1587.

3.8. 3-Chloro-6-(4-methoxyphenyl)-9*H*-pyrido[2,3-*b*]-indole (35)

At rt and under inert atmosphere, a 1.0 M TBAF solution in THF (1.8 mL, 1.88 mmol, 5 equiv) was added to a solution of **27** (169 mg, 0.376 mmol) in THF (17 mL). The solution was refluxed for 2 h. The resulting mixture was then cautiously quenched at 0 °C with H_2O. The mixture was extracted with EtOAc (3×10 mL). The resulting organic layers were dried over $MgSO_4$, then filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1 to EtOAc) to afford **35** (97 mg, 0.313 mmol) in 84% yield as a yellow solid; mp>220 °C (MeOH); IR 3109, 3035, 2935, 2848, 1630, 1603, 1578, 1483, 1232, 1090, 1033, 800, 778, 700 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.02 (br s, 1H), 8.74 (d, 1H, J=2.4 Hz), 8.49 (d, 1H, J=1.8 Hz), 8.42 (d, 1H, J=2.4 Hz), 7.76 (dd, 1H, J=1.8 and 8.6 Hz), 7.67 (d, 2H, J=8.6 Hz), 7.55 (d, 1H, J=8.6 Hz), 7.06 (d, 2H, J=8.6 Hz), 3.81 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4 (C), 150.7 (C), 144.1 (CH), 138.8 (C), 133.2 (C), 132.1 (C), 128.3 (CH), 127.7 (2 CH), 126.2 (CH), 121.7 (C), 120.2 (C), 119.3 (CH), 126.6 (C), 114.4 (2 CH), 111.8 (CH), 55.2 (CH_3); MS (ESI) m/z 309.1 $[M+H]^+$; HRMS (EI): Calcd for $C_{18}H_{13}ClN_2O$ $[M]^{+\bullet}$: 308.0716. Found: 308.0714.

3.9. 6-(4-Methoxyphenyl)-3-(styryl)-9*H*-pyrido[2,3-*b*]-indole (36)

A sealed pressure tube with a stir bar was charged with $Pd(OAc)_2$ (5 mg, 0.02 mmol, 0.08 equiv), S-Phos (18 mg, 0.04 mmol, 0.16 equiv), α-carboline **35** (83 mg, 0.267 mmol), (*E*)-phenylvinylboronic acid (**5**) (59 mg, 0.400 mmol, 1.5 equiv), and K_3PO_4 (142 mg, 0.667 mmol, 2.5 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (700 μL) was added and the reaction mixture was stirred at 100 °C overnight. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/EtOAc 9:1) to afford **36** (65 mg, 0.172 mmol) in 65% yield as a white solid; mp>220 °C (MeOH); IR 3060, 2994, 2833, 1606, 1517, 1485, 1460, 1232, 957, 813, 740, 692 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.86 (br s, 1H), 8.95 (d, 1H, J=2.1 Hz), 8.61 (d, 1H, J=2.1 Hz), 8.47 (d, 1H, J=1.6 Hz), 7.74 (dd, 1H, J=1.6 and 8.5 Hz), 7.71 (d, 2H, J=8.9 Hz), 7.63 (d, 2H, J=7.3 Hz), 7.54 (d, 1H, J=8.5 Hz), 7.46 (d, 1H, J=16.4 Hz), 7.43–7.39 (m, 2H), 7.37 (d, 1H, J=16.4 Hz), 7.27 (t, 1H, J=7.4 Hz), 7.07 (d, 2H, J=8.9 Hz), 3.82 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.4 (C), 152.0 (C), 146.5 (CH), 138.5 (C), 137.4 (C), 133.4 (C), 131.9 (C), 128.8 (2 CH), 127.7 (2 CH), 127.4 (CH), 126.8 (CH), 126.3 (CH), 126.2 (2 CH), 125.6 (CH), 124.9 (CH), 127.8 (C), 121.1 (C), 118.9 (CH), 115.8 (C), 114.4 (2 CH), 111.7 (CH), 55.2 (CH_3); MS (ESI) m/z 377.3 $[M+H]^+$; HRMS (ESI): Calcd for $C_{26}H_{21}N_2O$ $[M+H]^+$: 377.1654. Found: 377.1653.

3.10. Typical procedure for Suzuki reactions with 2 equiv of boronic acid from compounds 23 and 25

At rt and under inert atmosphere, a solution of $Pd(PPh_3)_4$ (0.08 equiv), 4-methoxyphenylboronic acid (**4**) (2.2 equiv), and a 0.3 M K_2CO_3 solution (3 equiv) was added to 0.1 M solution of **23** or **25** in 1,4-dioxane. This solution was stirred at reflux for 12 h. After cooling to rt, solution was filtered through Celite and solvents were removed under reduced pressure.

*3.10.1. 9-Benzenesulfonyl-2,6-di-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**37**)*

Starting material **23**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **37** (112 mg, 0.215 mmol) in 90% yield as white solid; mp 206–208 °C (CH_2Cl_2/PE); IR 2993, 1607, 1591, 1518, 1464, 1167, 1039, 978, 807 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (d, 1H, J=8.7 Hz), 8.23–8.20 (m, 2H), 8.16 (d, 1H, J=7.7 Hz), 8.15 (d, 2H, J=8.79 Hz), 8.02 (d, 1H, J=1.5 Hz), 7.72 (dd, 1H, J=1.5 and 8.7 Hz), 7.66 (d, 1H, J=8.1 Hz), 7.60 (d, 2H, J=8.7 Hz), 7.50–7.46 (m, 1H), 7.41–7.36 (m, 2H), 7.04 (d, 2H, J=8.7 Hz), 7.02 (d, 2H, J=8.7 Hz), 3.89 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.8 (C), 159.3 (C), 154.6 (C), 151.3 (C), 139.9 (C), 136.9 (2 C), 133.9 (CH), 133.4 (C), 131.6 (C), 128.9 (2 CH), 128.5 (2 CH), 128.4 (2 CH), 127.8 (2 CH), 126.9 (CH), 123.7 (C), 118.4 (CH), 116.6 (C), 115.2 (CH), 115.1 (CH), 114.5 (3 CH), 114.3 (2 CH); 55.5 (2 CH_3); MS (ESI) m/z 521.1 $[M+H]^+$, 543.0 $[M+Na]^+$; HRMS (ESI): Calcd for $C_{31}H_{24}N_2O_4SNa$ $[M+Na]^+$: 543.1354. Found: 543.1355.

*3.10.2. 9-Benzenesulfonyl-4,6-di-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**39**)*

Starting material **25**: 100 mg, 0.237 mmol. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1) to afford **39** (110 mg, 0.211 mmol) in 89% yield as a white solid; mp 162–164 °C (CH_2Cl_2/PE); IR 3010, 2965, 1608, 1515, 1464, 1232, 1170, 822 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (d, 1H, J=5.0 Hz), 8.53 (dd, 1H, J=0.8 and 8.5 Hz), 8.22–8.20 (m, 2H), 7.72 (d, 1H, J=1.9 Hz), 7.70 (dd 1H, J=1.9 and 8.5 Hz), 7.54–7.41 (m, 3H), 7.51 (d, 2H, J=8.7 Hz), 7.38 (d, 2H, J=8.7 Hz), 7.14 (d, 1H, J=5.0 Hz), 7.07 (d, 2H, J=8.7 Hz), 6.94 (d, 2H, J=8.7 Hz), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5 (C), 159.2 (C), 151.7 (C), 149.5 (2 C), 146.6 (CH), 145.7 (C), 138.9 (C), 136.7 (C), 136.3 (C), 134.0 (CH), 133.2 (C), 130.0 (2 CH), 129.0 (2 CH), 128.1 (2 CH), 127.8 (2 CH), 126.9 (CH), 123.5 (C), 120.7 (CH), 120.5 (CH), 115.0 (CH), 114.5 (2 CH), 114.3 (2 CH), 55.6 (CH_3), 55.5 (CH_3); MS (ESI) m/z 521.1 $[M+H]^+$, 1062.9 $[2M+Na]^+$; Anal. Calcd $C_{31}H_{24}N_2O_4S$: C, 71.52; H, 4.65; N, 5.38. Found: C, 71.12; H, 4.70; N, 5.52.

*3.10.3. 9-Benzenesulfonyl-3,6-di-(4-methoxyphenyl)-9H-pyrido[2,3-b]indole (**38**)*

A sealed pressure tube with a stir bar was charged with $Pd(OAc)_2$ (5 mg, 0.02 mmol, 0.08 equiv), S-Phos (17 mg, 0.04 mmol, 0.16 equiv), 6-bromo-3-chloropyrido[2,3-*b*]indole **24** (100 mg, 0.238 mmol), 4-methoxyphenylboronic acid (**4**) (109 mg, 0.71 mmol, 3 equiv), and K_3PO_4 (177 mg, 0.833 mmol, 3.5 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (650 μL) was added and the reaction mixture was stirred at 100 °C overnight. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×30 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2) to afford **38** in 81% yield as a white solid; mp 110–112 °C (CH_2Cl_2/PE); IR 2933, 1608, 1518, 1475, 1438, 1362, 1362, 1174, 1245, 1089, 1038, 976, 816 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.77 (d, 1H, J=2.1 Hz), 8.51 (d, 1H, J=8.8 Hz), 8.34 (d, 1H, J=2.1 Hz), 8.20–8.17 (m, 2H), 8.11 (d, 1H, J=1.7 Hz), 7.76 (dd, 1H, J=1.7 and

8.8 Hz), 7.60 (d, 2H, *J*=8.9 Hz), 7.56 (d, 2H, *J*=8.9 Hz), 7.52 (tt, 1H, *J*=1.3 and 6.0 Hz), 7.45–7.39 (m, 2H), 7.02 (d, 2H, *J*=8.9 Hz), 7.03 (d, 2H, *J*=8.9 Hz), 3.88 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7 (C), 159.3 (C), 150.2 (C), 145.8 (CH), 138.8 (C), 137.1 (2 C), 134.0 (CH), 133.1 (C), 132.7 (C), 130.3 (C), 129.0 (2 CH), 128.4 (2 CH), 128.3 (2 CH), 127.5 (2 CH), 127.4 (CH), 126.3 (CH), 123.5 (C), 119.0 (C), 118.6 (CH), 115.3 (CH), 114.7 (2 CH), 114.4 (2 CH), 55.4 (2 CH_3); MS (ESI) *m*/*z* 521.0 $[M+H]^+$, 543.0 $[M+Na]^+$, 1062.8 $[2M+Na]^+$; HRMS (ESI): Calcd for $C_{31}H_{25}N_2O_4S$ $[M+H]^+$: 521.1535. Found: 521.1534.

3.11. Typical procedure for Suzuki reactions with two different boronic acids from 2-chloro or 4-chloro 6-bromopyrido[2,3-*b*]indole

At rt and under an inert atmosphere, a solution of $Pd(PPh_3)_4$ (22 mg, 0.019 mmol, 0.08 equiv), 4-methoxyphenylboronic acid (**4**) (40 mg, 0.261 mmol, 1.1 equiv), and K_2CO_3 (99 mg, 0.714 mmol, 3 equiv) in H_2O (2.5 mL) was added to a solution of **23** or **25** (100 mg, 0.238 mmol) in 1,4-dioxane (10 mL). This solution was stirred at 70 °C for 4 h. After cooling to rt, (*E*)-phenylvinylboronic acid (**5**) (39 mg, 0.262 mmol, 1.1 equiv) was added to the solution. This solution was stirred at 100 °C for 2 h. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/PE 1:1 or CH_2Cl_2/PE 7:3) to afford **32** or **34** in 54% or 71% yield.

3.12. Typical procedure for Suzuki reactions with two different boronic acids from 6-bromo-3-chloropyrido[2,3-*b*]indole

A sealed pressure tube with a stir bar was charged with $Pd(OAc)_2$ (5 mg, 0.02 mmol, 0.08 equiv), S-Phos (17 mg, 0.04 mmol, 0.16 equiv), 6-bromo-3-chloropyrido[2,3-*b*]indole **24** (100 mg, 0.238 mmol), 4-methoxyphenylboronic acid (**4**) (44 mg, 0.286 mmol, 1.2 equiv), and K_3PO_4 (151 mg, 0.71 mmol, 3 equiv). The tube was evacuated and back-filled with argon (this was repeated three additional times). Freshly degassed 1,4-dioxane (650 μL) was added and the reaction mixture was stirred at 50 °C for 5 h. After cooling to rt, (*E*)-phenylvinylboronic acid (**5**) (88 mg, 0.595 mmol, 2.5 equiv) was added to the solution. This solution was stirred at 100 °C for 12 h. After cooling to rt, the solution was diluted with H_2O and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, then filtered through Celite, and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography (CH_2Cl_2/PE 3:1) to afford **33** in 65% yield.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.04.032.

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