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Efficient Synthesis of α- and δ-Carbolines by Sequential Pd-Catalyzed Site-Selective C-C and Twofold C-N Coupling Reactions

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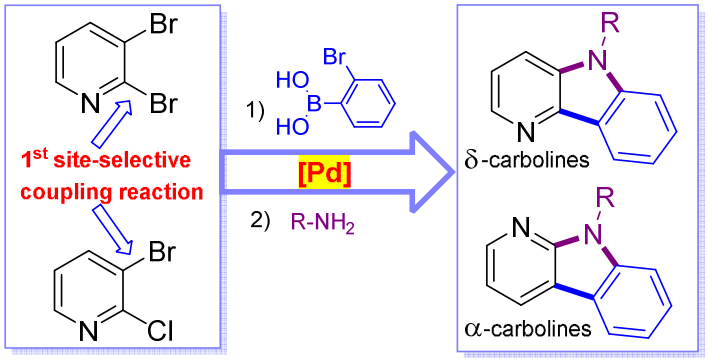
ABSTRACT

Two concise and efficient approaches were developed for the synthesis of α- and δ-carboline derivatives. The success of the synthesis relies on site-selective Suzuki-Miyaura reaction of 1-chloro-2-bromopyridine or 2,3-dibromopyridine with 2-bromophenylboronic acid and subsequent cyclization with amines which proceeds by twofold Pd-catalyzed C-N coupling.

Graphical abstract:



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INTRODUCTION

Carbolines (pyridoindoles) are present in many natural products and synthetic bioactive molecules.[1] Among the class of carbolines, especially *β*-carbolines and *γ*-carbolines are widely spread in nature. A smaller number of *α*-carbolines were also isolated as natural alkaloids. Examples include the *α*-carbolines grossularine 1 and 2, anticancer compounds isolated from *Dendrodoa grossularia*,[2] and mescengricin which represents an inhibitor of *L*-glutamate excitotoxicity isolated from *Streptomyces griseoflavu*.[3] A few *δ*-carbolines have also been isolated, for example, quindoline, cryptolepine, cryptoquindoline, cryptomisrine, and jusbetonin.[4] All of these alkaloids were isolated from *Cryptolepis sanguinolenta* and *Justica bentonica,* which have been traditionally used for the treatment of malaria and several infectious diseases in Central and West Africa.[5] In the light of recent research in medicinal chemistry, *α*- and *δ*-carboline derivatives have shown important biological properties, such as antitumor,[6] antimalarial,[7] antimicrobial,[8] antiviral,[9] and anti-inflammatory[10] activities. In the context of drug discovery, implitapide, a potential drug containing an *α*-carboline moiety, was used in clinical trials for the treatment of atherosclerosis.[11]

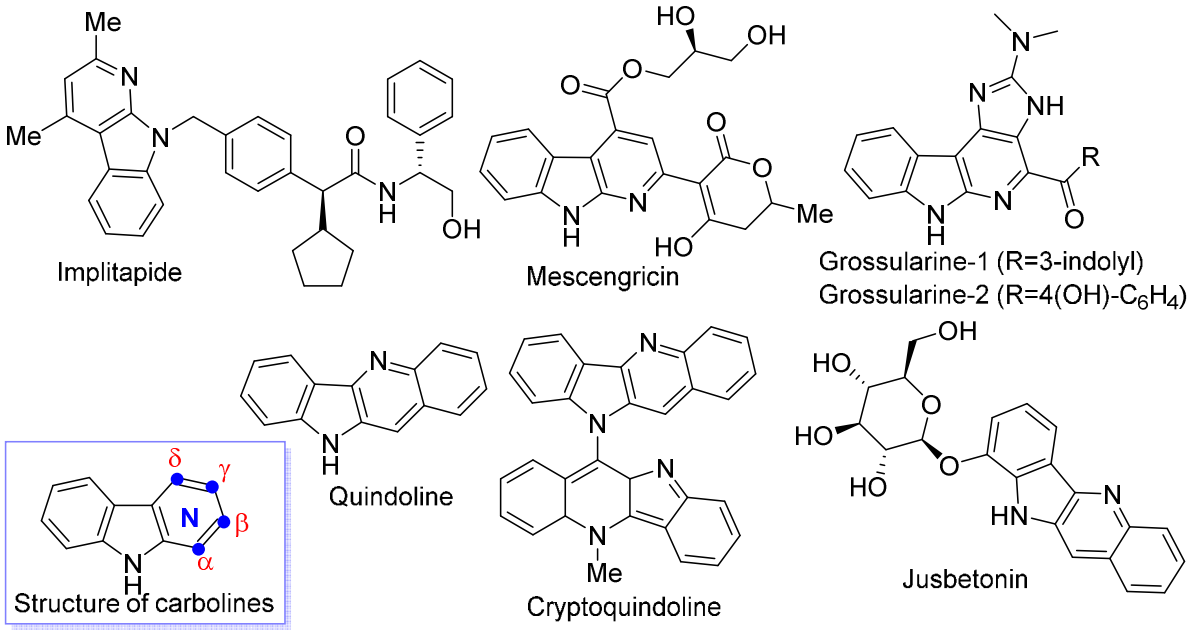

Figure 1. Some bioactive compounds containing *α*- and *δ*-carboline substructures.

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Carbolines not only find many important applications in medicinal chemistry, but also in material sciences. For example, carbolines and their derivatives were commonly used as electron transport unit in bipolar host materials.[12] The replacement of the carbazole by a carboline unit improved the electron carrier mobility.[12] In 2013, Lee *et al.* synthesized **CzBPCb** and **CbBPCb** which showed above 30% external quantum efficiency in blue phosphorescence organic light emitting diodes.[13] The trimer **TATA** showed a 200 times longer life-time than the analogue carrying three carbazole units.[14]

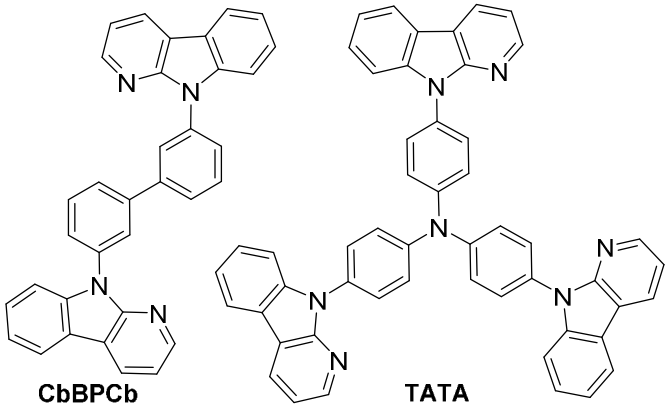

Figure 2. Some organic materials contain *α*-carbolines structure.

Because of the importance of carbolines in both medicinal chemistry and material sciences, many synthetic methods have been developed for the synthesis of carbolines. Classic methods to prepare *α*-carbolines have been reported, for examples, intramolecular Diels-Alder reactions,[15] Graebe-Ullmann reactions of triazoles,[16] annulations of azaindoles[17] and multi-component reactions.[18] In 2011, Kumar and Nagarajan reported a two-step synthesis of *α*-carbolines based on the Pd-catalyzed amidation of 3-acetyl-2-chloroindoles followed by a Vilsmeier-Haack reaction.[19] Recently, some one-pot syntheses based on Pd-catalyzed aryl aminations and subsequent intramolecular arylations were reported.[20] In 2013, Moody *et al.* described a new method for the synthesis of *α*-carbolines by 6π-electrocyclizations of indole-3-alkenyl oximes.[21]

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Very recently, Yang *et al.* developed a convenient approach to *α*-carbolines by a one-pot tandem reaction of *α,β*-unsaturated ketones with 2-nitrophenylacetonitriles in the presence of zinc dust.[22]

In contrast to *α-, β-,* and *γ*-carbolines, only a few methods have been developed so far for the synthesis of *δ*-carbolines. In 1997, Yang *et al.* converted *α*-(*o*-bromoanilino)alkenenitriles to *δ*-carboline derivatives by domino Pd-catalyzed cyclizations.[23] In their effort to access functionalized *δ*-carbolines, Dupas *et al.* carried out cyclizations of indole amines with 1,3-dicarbonyl compounds to afford 3,4-disubtituted *δ*-carbolines.[24] During the synthesis of bioactive analogues of Eudistomin D, Kobayashi and coworkers reported photocyclizations of *N*-(4-methoxy-3,5-dimethylphenyl)pyridin-3-amine which gave mixtures of regioisomeric *β*- and *δ*–carbolines.[25] In 2011, Ablordeppey *et al.* developed a short method for the formation of *δ*-carboline derivatives in moderate yields by another Pd-catalyzed intramolecular arylation of *N*-aryl-3-aminopyridine.[26] Recently, Kundu *et al.* reported an efficient one-pot multicomponent reation using *N*-Boc-3-amido indoles, aryl aldehydes and terminal alkynes under microwave conditions which gave *δ*-carbolines in good yields.[27] *δ*-Carbolines could also be synthesized by intramolecular reductive ring closure of 3-nitro-2-phenylpyridines using phosphine reagents.[28] In 2012, Detert's group prepared *δ*-carboline in 6 steps starting from 2-chloro-3-nitropyridine.[29] Very recently, Cao *et al.* described an interesting synthesis of *δ*-carbolines by a Pd-catalyzed cascade reaction of 2-iodoanilines and N-tosyl-enynamines.[30] General methods, which allow to access all four types of carbolines, have been reported, but still have limitations. Sakamoto and coworkers developed the first Pd-catalyzed intramolecular arylation of *ortho*-bromo-substituted anilinopyridines which provided a very convenient and general method to prepare all four regioisomeric carbolines in 31-61% yield.[31] Recently, Cuny and coworkers reported a general pathway to prepare selectively *α-, β-, γ-,* and *δ*–carbolines in good yields by photostimulated cyclization of anilinohalopyridines.[32]

In fact, the reported synthetic methods are often complicated, low yielding or require many synthetic steps to prepare the starting materials. Baumgartner and Lammertsma and their coworkers reported the synthesis of phospholes by reaction of 2,3-dibromobenzothiophene with *o*-bromophenylboronic acid and subsequent base mediated cyclization with dichlorophosphanes.[33a,b] Nozaki and Chida and their coworkers reported the cyclization of

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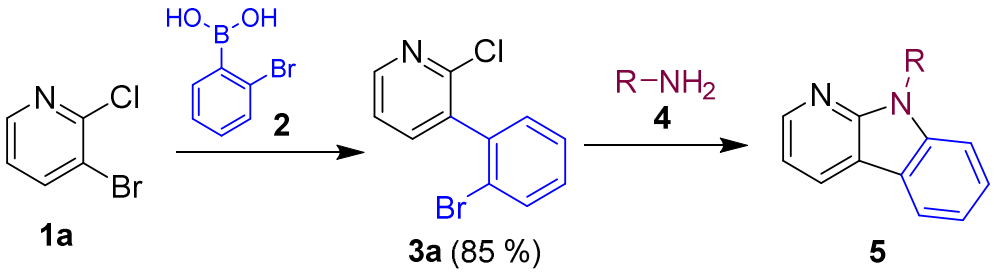
dibromobiphenyls and related compounds with amines.[33c,d] Related transformations have also been reported.[33e-h] We have previously reported the synthesis of diindolo[3,2-b:4,5-*b'*]thiophenes,[33i] indolo[2,3-*b*]quinoxalines,[33j] and 5-methyl-5,10-dihydroindolo[3,2-*b*]indoles[33k] based on the cyclization of *o*-bromophenylboronic acid with tetrabromothiophene and 2,3-dibromoquinoxaline, and 2,3-dibromo-1-methyl-1*H*-indole, respectively. Herein, we wish to report a new and efficient two-step strategy for the chemoselective synthesis of *α*- and *δ*-carbolines from readily available starting materials. Our synthesis is based on what are, to the best of our knowledge, the first site-selective Suzuki reactions of *o*-bromophenylboronic acid with 2,3-dihalopyridines (1-chloro-2-bromopyridine or 2,3-dibromopyridine) and subsequent two-fold C-N coupling reactions.

RESULTS AND DISCUSSION

The chemoselective Suzuki-Miyaura reaction of commercially available 2-chloro-3-bromopyridine (**1a**) with 1.2 equivalents of *o*-bromophenylboronic acid (**2**) in the presence of 5% mol of $Pd(PPh_3)_4$ gave product **3a** in 85% isolated yield. The reaction proceeded chemoselectively at position 3 which is attached to the bromide atom which is a better leaving group than chloride. The subsequent cyclization of **3a** with various amines **4**, by two-fold Pd-catalyzed C-N coupling, resulted in formation of the desired *α*-carbolines **5** (Scheme 1).



Scheme 1. Synthesis of of *α*-carbolines. *Conditions*: (*i*) 1.2 equiv. of **2**, 5.0 mol% of $Pd(PPh_3)_4$ catalyst, 3 equiv. of NaOH, THF, H_2O, 70 ºC, 4h. (*ii*) 1.5 equiv. of **4**, 3 equiv. of NaO*t*-Bu, 5 mol% of $Pd_2(dba)_3$, ligand (method A: 10% of dppf, method B: 10% of dpePhos), toluene, 100 ºC, 7h.

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Our initial optimizations started with Pd-catalyzed cyclization of **3a** with *tert*-butylaniline **5c** using 4-nitroacetophenone as an internal standard (Table 1). Important factors including palladium source, ligand, solvent and temperature were examined in detail. The screening of different monodentate phosphine ligands, for example, Xphos, Xphos(tBu)$_2$, SPhos, DavePhos, PCy_3, P(tBu)$_3$ gave **5c** in up to 93% yield (Entries 6-11). In order to investigate the effect of bidentate ligands in this cyclization, we carried out some further optimizations using bidentate phosphine ligands, such as XantPhos, DpePhos, Dppf. In fact, the yield was improved to up to 97% using the dppf ligand in combination with Pd_2dba_3 (method A). The use of $Pd(OAc)_2$ as palladium resulted in lower yield (85%). During the optimizations, we also realized that toluene was the most suitable solvent for this cyclization.

Table 1. Optimizations for the synthesis of 5c

Entry	Catalyst	Ligand	Solvent	Time (h)	Temperature (°C)	Yield (%)[a]
1	$Pd_2(dba)_3$	BINAP	Tol	7	100	56
2	$Pd_2(dba)_3$	XantPhos	Tol	7	100	93
3	$Pd_2(dba)_3$	DpePhos	Tol	7	100	95
4	$Pd_2(dba)_3$	Dppe	Tol	7	100	81
5	$Pd_2(dba)_3$	Dppf	Tol	7	100	97
6	$Pd_2(dba)_3$	$PCy_3 \cdot HBF_4$	Tol	7	100	64
7	$Pd_2(dba)_3$	P(t-Bu)$_3 \cdot HBF_4$	Tol	7	100	79
8	$Pd_2(dba)_3$	XPhos	Tol	7	100	87
9	$Pd_2(dba)_3$	XPhos$\cdot t$Bu$_2$	Tol	7	100	35
10	$Pd_2(dba)_3$	SPhos	Tol	7	100	93
11	$Pd_2(dba)_3$	DavePhos	Tol	7	100	88
12	$Pd(OAc)_2$	Dppf	Tol	7	100	85[b]
13	$Pd_2(dba)_3$	Dppf	Dioxane	7	100	87
14	$Pd_2(dba)_3$	Dppf	DMF	7	100	53
15	$Pd_2(dba)_3$	Dppf	Tol	7	110	82

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16	$Pd_2(dba)_3$	Dppf	Tol	7	80	77

[a] Yield was calculated by ^{1}H-NMR of crude product using 4-nitroacetophenone as an internal standard. [b] 10 mol% of $Pd(OAc)_2$ was used.

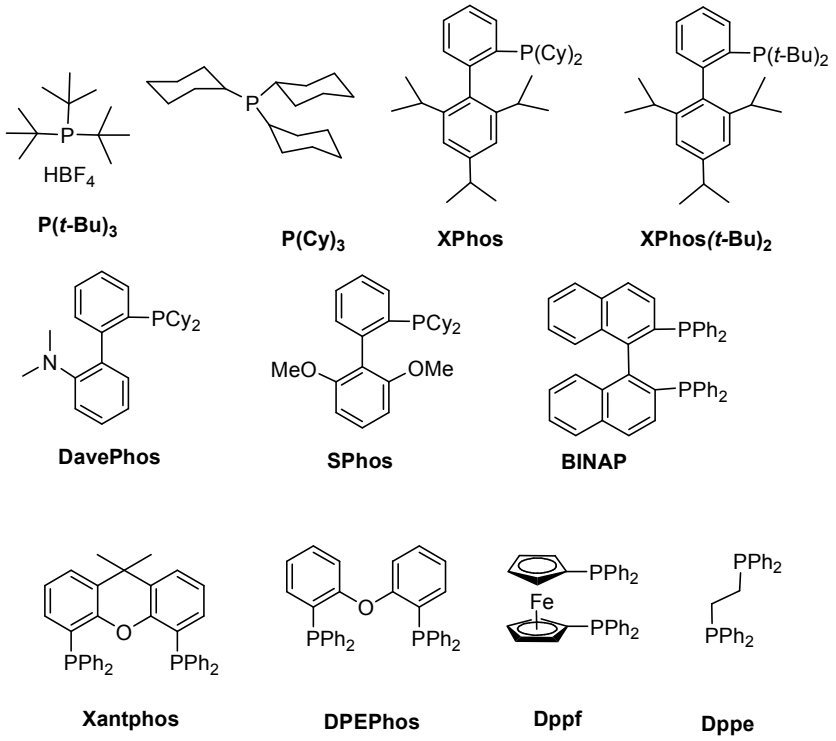

Figure 3. Struture of monodentate and bidentate ligands.

With our optimized conditions in hand (method A), we were interested to explore the substrate scope of the cyclization of **3a** with a series of different amines. The cyclization products **5a-h**, which are depicted in Table 2, were isolated in 83-98% yields. The reaction was compatible with a variety of functional groups. The structure of **5d** was independently confirmed by single-crystal X-ray diffraction (Figure 4). Unfortunately, the Pd-catalyzed cyclization of **3a** with aliphatic amines using method A did not result in satisfactory yields, due to the formation of side products. After some optimization studies using different conditions, we found that employment

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of dpePhos as the ligand (method B) allowed to improve the yield of the reaction. Up to 90% isolated yields of the cyclization products were achieved (products **5i-l**).

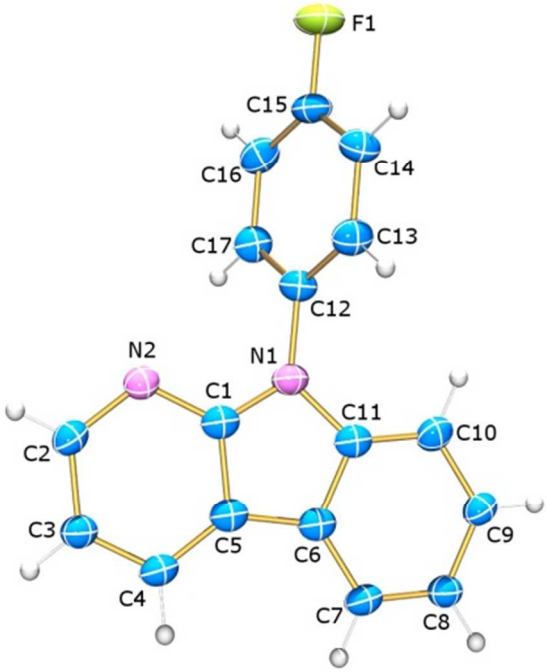

Figure 4. X-ray structure of **5d**

Table 2. Synthesis of α-carbolines **5a-l**

5	R	Method [a]	Yield (%)[b]
a	Ph	A	92
b	4-MeC_6H_4	A	95
c	4-(*t*-Bu)C_6H_4	A	94
d	4-FC_6H_4	A	89
e	3-(CF_3)C_6H_4	A	88
f	4-(MeO)C_6H_4	A	98
g	4-(MeS)C_6H_4	A	92
h	4-(CN)C_6H_4	A	83
i	Bn	B	88

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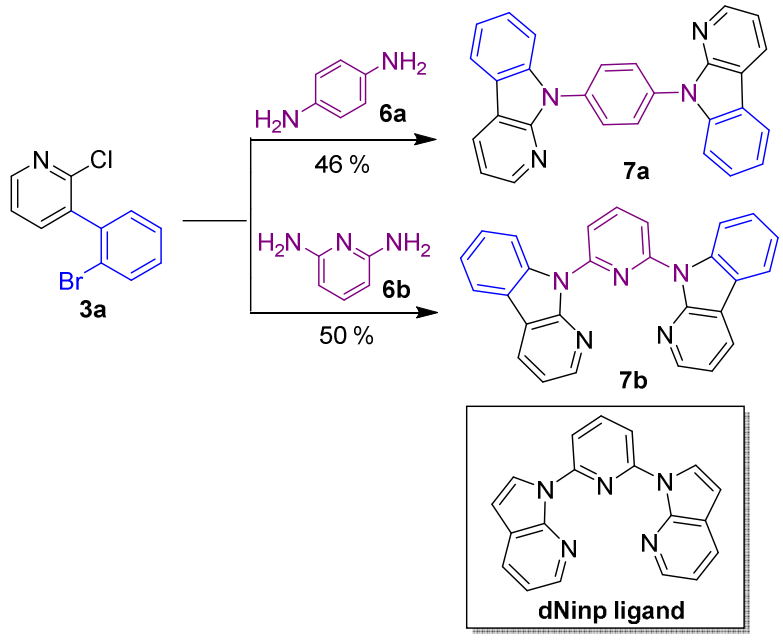
j	(4-FC_6H_4)CH_2	B	87
k	3-(CF_3)$C_6H_4CH_2$	B	90
l	*n*-C_3H_7	B	91

[a] Conditions: 3 equiv. of **4**, 6 equiv. of NaO*t*Bu, 5% mol of $Pd_2(dba)_3$, ligand (method A: 10 mol% of Dppf, method B: 10 mol% of DpePhos), toluene, 100 ºC, 7 h. [b] Isolated yields

We were interested to extend to the synthesis of bis(carbolines). The Pd-catalyzed cyclization of **3a** with diamines **6a** and **6b** afforded, following our optimized procedure, products **7a** and **7b** in 46 and 50% yields, respectively. It is worth to mention that product **7b** represents an analogue of the recently developed ligand dNinp ligand.[34] This, our methodology allows for a convenient access to this type of molecule.



Scheme 2. Synthesis of bis(carbolines) **7a,b**. *Conditions*: 2.2 equiv. of **3a**, 1 equiv. of **6a,b**, 6 equiv. of NaO*t*Bu, 5% mol of $Pd_2(dba)_3$, 10% of dppf, toluene, 110 ºC, 10 h.

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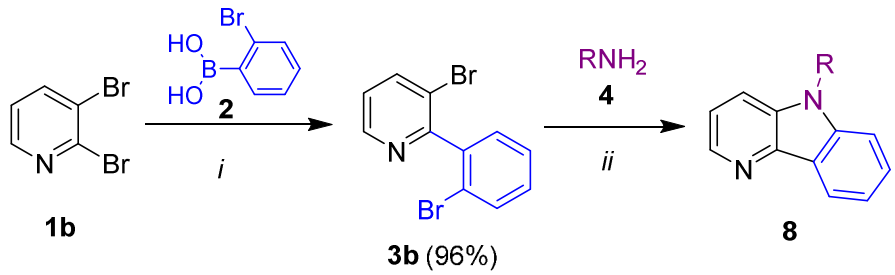
Our next goal was to apply our methodology to the synthesis of *δ*-carbolines. The Suzuki-Miyaura coupling of *o*-bromophenylboronic acid (**2**) with 2,3-dibromopyridine (**1b**) proceeded, following our optimized procedure, with very good regioselectivity at the more electron-deficient 2-position of the pyridine ring and afforded product **3b** in 96% isolated yield. With intermediate **3b** in hand, we prepared a series of *δ*-carbolines **8a-j,** using either method A or method B, in moderate to excellent yields. The yields were moderate in case of less nucleophilic amines carrying an electron withdrawing substituent located at the aryl group. The structure of **8b** was independently confirmed by X-ray crystal structure analysis (Figure 5).[35]

Scheme 3. Synthesis of *δ*-carbolines **8a-i**



Conditions: (*i*) 1.2 equiv. of **2**, 5% of $Pd(Ph_3)_4$ catalyst, 3 equiv. of NaOH, THF, H_2O, 70 ºC, 4 h. (*ii*) 3 equiv. of **4**, 6 equiv. of NaO*t*Bu, 5% mol of $Pd_2(dba)_3$, ligand (method A: 10 mol% of Dppf, method B: 10 mol% of DpePhos), toluene, 100 ºC, 7 h.

Table 3. Synthesis of *δ*-carbolines **8a-i**

8	**R**	**Conditions**	**Yield (%)**
a	Ph	A	83
b	4-FC_6H_4	A	73
c	3-$(F_3C)C_6H_4$	A	64
d	4-$(MeO)C_6H_4$	A	94
e	3,5-$(MeO)_2C_6H_4$	A	75
f	4-$(NC)C_6H_4$	B	42

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g	Bn	B	92
h	4-(MeO)$C_6H_4CH_2$	B	65
i	$PhCH_2CH_2$	B	77

Conditions: 3 equiv. of **4**, 6 equiv. of NaO*t*Bu, 5% mol of $Pd_2(dba)_3$, ligand (method A: 10 mol% of Dppf, method B: 10 mol% of DpePhos), toluene, 100 ºC, 7 h.

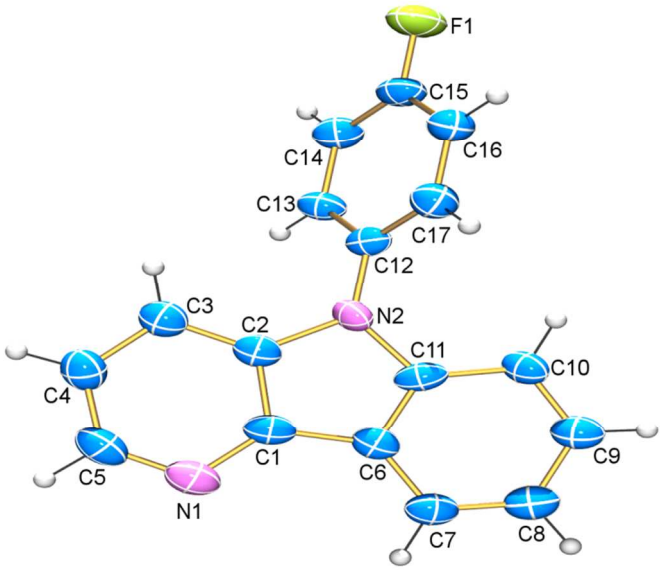
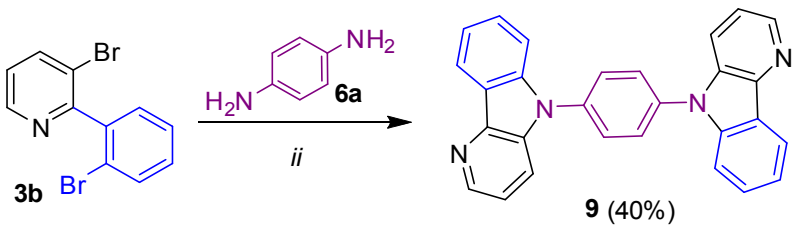


Figure 5. X-ray structure of 8**b**.

The cyclization of **3b** with diamine **6a** afforded bis(carboline) **9** in 40% isolated yield (Scheme 4).



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Scheme 4. Synthesis of bis(carboline) **9**. *Conditions*: 2.5 equiv. of **3**, 1 equiv. of **6a**, 6 equiv. of NaO*t*Bu, 5% mol of $Pd_2(dba)_3$, 10% of dppf, toluene, 100 ºC, 10 h.

CONCLUSION

In conclusion, we have successfully developed an efficient two-step synthesis of α- and δ-carbolines from readily available chemicals. The reactions rely on site-selective Suzuki-Miyaura reaction and subsequent two-fold C-N coupling reactions. The synthesis of β- and γ-carbolines are currently carrying out in our laboratory. Our results reported herein would be interesting for further applications in both medicinal chemistry and materials science.

Experimental Section

General. Chemicals were purchased from alfa aesar, sigma Aldrich and were used without further purification. NMR spectra were recorded on a Brucker AV 300 and 250 MHz instruments. IR spectra were recorded on a Perkin Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained on a Hewlett-Packard HPGC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63e200 mesh, Merck) and silica gel Merck 60F254 plates were used for TLC. Commercially available solvents were distilled for column chromatography. All other solvents were purified and dried by standard methods.

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General procedure for prepared of *3-(2-bromophenyl)-2-chloropyridine* 3a. 3-bromo-2-chloropyridine **1a** (1 g, 5.2 mmol), 2-bromophenyl boronic acid **2** (1.25 g, 6.2 mmol), $Pd(PPh_3)_4$ (300 mg, 260 µmol) and sodium hydroxide (624 mg, 15.6 mmol) were added to 500 mL Schlenk flask. The mixture was back-filled several times with argon. To the mixture 70 mL THF and 10 mL distilled water were added, then, back-filled several times. The reaction was heated at 70 ºC for 4h. The solvent was evaporated *in vacuo*. The residue was extracted with dichloromethane and water. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The yellow residue was purified by column chromatography (silica gel, heptane/ethylacetate 4:1) to yield 3-(2-bromophenyl)-2-chloropyridine **3a** (1.19 g, 85 %) as colorless syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.66 – 7.59 (m, 1H), 7.54 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.33 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 – 7.13 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.36, 149.18, 139.84, 138.41, 136.39, 132.88, 130.95, 130.07, 127.42, 123.40, 122.16; IR (ATR, cm^{-1}): ν = 3051 (w), 1576 (m), 1558 (m), 1479 (w), 1441 (m), 1427 (m), 1390 (vs), 1300 (w), 1255 (w), 1242 (w), 1207 (m), 1122 (m), 1103 (s), 1063 (s), 1053 (m), 1026 (m), 997 (s), 945 (w), 802 (m), 781 (m), 748 (vs), 723 (s), 694 (s), 654 (s), 615 (m), 569 (m), 553 (m); GC-MS (EI, 70 eV): m/z (%) = 269 (59), 188 (100), 153 (58), 126(29); HRMS (EI): calcd. for $C_{11}H_7N_1Br_1Cl_1$ ($[M]^+$): 266.94449; found: 266.94495; calcd. for $C_{11}H_7N_1{}^{81}Br_1Cl_1$ ($[M]^+$): 268.94244; found: 268.94288; calcd. for $C_{11}H_7N_1Br_1{}^{37}Cl_1$ ($[M]^+$): 270.93949; found: 270.94012.

General procedure A for double C-N coupling with aniline derivatives, exemplified by: *9-phenyl-9H-pyrido[2,3-b]indole* 8a. Aniline (52 µL, 0.56 mmol) was added to pressure tube charged with **3a** (100 mg, 0.37 mmol), $Pd_2(dba)_3$ (17 mg, 19 µmol), ligand dppf (21 mg, 37

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μmol) and sodium tert-butoxide (107 mg, 1.12 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL) and heated at 110 ºC for 7 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield 9-phenyl-9*H*-pyrido[2,3-*b*]indole **5a** (84 mg, 92%) as a white solid; m.p. 110-111 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.42 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.31 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.05 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.63 – 7.48 (m, 4H), 7.47 – 7.33 (m, 3H), 7.33 – 7.22 (m, 1H), 7.20 – 7.10 (m, 1H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 151.93, 146.47, 140.11, 136.26, 129.65, 128.28, 127.64, 127.38, 126.93, 120.91, 120.81, 120.71, 116.36, 116.04, 110.41; IR (ATR, cm^{-1}): ν = 3037 (m), 1591 (s), 1568 (m), 1504 (s), 1473 (s), 1452 (s), 1414 (vs), 1377 (m), 1354 (m), 1335 (s), 1309 (m), 1290 (s), 1228 (s), 1176 (m), 1167 (m), 1115 (s), 1074 (m), 1051 (m), 1026 (m), 997 (m), 970 (m), 958 (m), 951 (m), 937 (m), 766 (s), 756 (s), 748 (s), 735 (vs), 715 (m), 692 (vs), 636 (s), 617 (s), 579 (s), 569 (m); GC-MS (EI, 70 eV): m/z (%) = 243 (100), 122 (17); HRMS (ESI): calcd. for $C_{17}H_{12}N_2$ ($[M + H]^+$): 245.10732; found: 245.10756.

9-(p-Tolyl)-9H-pyrido[2,3-b]indole **5b** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-toluidine (60 mg, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5b** (91 mg, 95 %) as a white solid; m.p. 102-103 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.29 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.29 (m, 6H), 7.28 – 7.19 (m, 1H), 7.18 – 7.09 (m, 1H), 2.39 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 152.10, 146.50, 140.28, 137.60, 133.56, 130.30, 128.21, 127.25, 126.85, 120.87, 120.71, 120.54, 116.24, 115.87, 110.39, 21.26; IR (ATR, cm^{-1}):

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ν = 3039 (w), 2920 (w), 1589 (m), 1568 (m), 1514 (s), 1475 (m), 1456 (s), 1412 (vs), 1377 (m), 1354 (m), 1336 (s), 1311 (m), 1290 (s), 1228 (s), 1219 (s), 1200 (m), 1182 (m), 1169 (m), 1155 (w), 1120 (m), 1109 (m), 1051 (w), 1038 (w), 1018 (m), 997 (m), 966 (w), 951 (w), 941 (w), 924 (m), 841 (w), 812 (s), 798 (m), 771 (vs), 744 (s), 735 (vs), 714 (s), 702 (s), 646 (m), 633 (s), 617 (m), 577 (s), 571 (s); GC-MS (EI, 70 eV): m/z (%) = 258 (100), 242 (17), 128 (9); HRMS (ESI): calcd. for $C_{18}H_{14}N_2$ ($[M + H]^+$): 259.12297; found: 259.12331.

9-(4-(tert-Butyl)phenyl)-9H-pyrido[2,3-b]indole **5c** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-*tert*-butylaniline (83 mg, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5c** (105 mg, 94 %) as a white solid; m.p. 147-148 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.29 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.06 – 7.99 (m, 1H), 7.58 – 7.32 (m, 6H), 7.23 (ddd, *J* = 8.1, 6.7, 1.6 Hz, 1H), 7.19 – 7.08 (m, 1H), 1.32 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 152.01, 150.43, 146.50, 140.26, 133.51, 128.22, 126.84, 126.77, 126.63, 120.84, 120.72, 120.56, 116.31, 115.87, 110.55, 34.76, 31.42; IR (ATR, cm^{-1}): ν = 2960 (m), 2902 (w), 2868 (w), 1587 (m), 1568 (m), 1520 (s), 1475 (m), 1454 (s), 1414 (vs), 1360 (m), 1335 (s), 1288 (s), 1269 (m), 1228 (s), 1186 (m), 1169 (m), 1153 (w), 1119 (m), 1097 (w), 1018 (m), 997 (m), 930 (m), 833 (m), 825 (m), 800 (w), 769 (vs), 748 (s), 739 (vs), 687 (m), 638 (s), 617 (m), 580 (m), 569 (m), 552 (s); GC-MS (EI, 70 eV): m/z (%) = 300 (45), 285 (100), 128 (13); HRMS (EI): calcd. for $C_{21}H_{20}N_2$ ($[M]^+$): 300.16210; found: 300.16183.

9-(4-Fluorophenyl)-9H-pyrido[2,3-b]indole **5d** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-fluoroaniline (53 µL, 0.56 mmol). The product was purified

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by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5d** (87 mg, 89 %) as a white solid; m.p. 156-157 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.27 (dt, *J* = 5.0, 2.5 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.42 – 7.29 (m, 2H), 7.28 – 7.10 (m, 4H) ; ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.83 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.79 (d, *J* = 247.2 Hz), 152.02, 146.54, 140.17, 132.23 (d, *J* = 3.1 Hz), 129.23 (d, *J* = 8.6 Hz), 128.39, 127.08, 121.04, 120.89, 120.83, 116.66 (d, *J* = 22.8 Hz), 116.35, 116.22, 110.19; IR (ATR, cm^{-1}): ν = 3061 (w), 1589 (m), 1570 (m), 1510 (s), 1475 (s), 1456 (s), 1416 (s), 1356 (m), 1336 (s), 1294 (s), 1228 (s), 1213 (s), 1173 (s), 1151 (s), 1119 (s), 1092 (s), 1053 (m), 1020 (m), 1012 (m), 997 (m), 964 (m), 953 (m), 941 (m), 931 (m), 924 (m), 899 (w), 870 (w), 856 (w), 833 (s), 816 (s), 798 (m), 769 (vs), 762 (s), 746 (s), 737 (vs), 715 (s), 704 (s), 665 (m), 644 (m), 629 (m), 617 (m), 579 (s), 569 (s); GC-MS (EI, 70 eV): m/z (%) = 261 (100), 131 (9); HRMS (ESI): calcd. for $C_{17}H_{11}F_1N_2$ ($[M + H]^+$): 263.0979; found: 263.09813.

9-(3-(Trifluoromethyl)phenyl)-9H-pyrido[2,3-b]indole **5e** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-fluoroaniline (53 µL, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5e** (87 mg, 89 %) as a white solid; m.p. 71-72 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.28 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.02 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.87 (s, 1H), 7.84 – 7.76 (m, 1H), 7.68 – 7.59 (m, 2H), 7.41 – 7.35 (m, 2H), 7.26 (ddd, *J* = 8.2, 5.4, 2.9 Hz, 1H), 7.20 – 7.13 (m, 1H) ; ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.70 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.71, 146.56, 139.59, 136.99, 132.14 (q, *J* = 32.8 Hz), 130.73 (d, *J* = 1.0 Hz), 130.25, 128.49, 127.28, 124.47 – 123.68 (m, 2xC), 123.83 (q, *J* = 272.6 Hz), 121.31, 121.17, 121.14, 116.66, 116.57, 110.10; IR (ATR, cm^{-1}): ν = 3051 (w), 1612 (w), 1591 (m), 1574 (m), 1497 (m), 1477 (m), 1458

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(s), 1410 (s), 1358 (m), 1338 (m), 1321 (s), 1306 (s), 1290 (s), 1275 (s), 1228 (s), 1178 (m), 1167 (s), 1155 (s), 1119 (vs), 1103 (s), 1093 (s), 1068 (s), 1020 (m), 999 (m), 972 (s), 937 (m), 931 (m), 914 (m), 889 (m), 852 (m), 810 (s), 796 (s), 771 (s), 760 (m), 744 (s), 737 (vs), 715 (m), 694 (vs), 661 (s), 642 (s), 619 (s), 582 (m), 565 (m), 528 (s); GC-MS (EI, 70 eV): m/z (%) = 311 (100), 243 (11); HRMS (ESI): calcd. for $C_{18}H_{11}F_3N_2$ ($[M + H]^+$): 313.09471; found: 313.09460.

9-(4-Methoxyphenyl)-9H-pyrido[2,3-b]indole **5f** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and *p*-anisidine (69 mg, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 2:1) to yield **5f** (100 mg, 98 %) as a white solid; m.p. 137-138 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.04 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.40 – 7.30 (m, 2H), 7.29 – 7.19 (m, 1H), 7.18 – 7.09 (m, 1H), 7.09 – 7.01 (m, 2H), 3.82 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.00, 152.24, 146.51, 140.55, 128.90, 128.73, 128.22, 126.86, 120.86, 120.60, 120.49, 116.17, 115.81, 115.00, 110.30, 55.58; IR (ATR, cm^{-1}): ν = 3057 (w), 2960 (w), 2935 (w), 2908 (w), 2835 (w), 1589 (m), 1570 (m), 1512 (s), 1477 (m), 1456 (s), 1441 (m), 1416 (s), 1358 (m), 1336 (m), 1298 (m), 1288 (s), 1230 (vs), 1190 (m), 1174 (s), 1149 (m), 1117 (s), 1103 (s), 1053 (w), 1028 (s), 999 (m), 962 (m), 951 (m), 939 (m), 930 (m), 918 (m), 847 (w), 827 (s), 814 (m), 798 (m), 769 (vs), 744 (s), 735 (vs), 721 (s), 702 (m), 646 (s), 631 (s), 617 (m), 586 (s), 579 (s), 571 (m), 530 (vs); GC-MS (EI, 70 eV): m/z (%) = 274 (100), 259 (55), 231 (25), 168 (10), 115 (9); HRMS (EI): calcd. for $C_{18}H_{14}O_1N_2$ ($[M]^+$): 274.11006; found: 274.10996.

9-(4-(Methylthio)phenyl)-9H-pyrido[2,3-b]indole **5g** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-(methylthio)aniline (69 µL, 0.56 mmol). The product

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was purified by flash chromatography (silica gel, heptanes/ethylacetate 2:1) to yield **5g** (99 mg, 92 %) as a white solid; m.p. 136-137 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.30 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.04 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.52 – 7.36 (m, 6H), 7.31 – 7.21 (m, 1H), 7.15 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.92, 145.46, 139.03, 137.06, 132.25, 127.27, 126.70, 125.94, 119.92, 119.78, 119.73, 115.32, 115.05, 109.30, 15.00; IR (ATR, cm^{-1}): ν = 3039 (w), 2960 (m), 2920 (m), 1626 (w), 1589 (m), 1568 (m), 1500 (s), 1475 (m), 1452 (m), 1437 (m), 1414 (s), 1356 (m), 1335 (m), 1309 (m), 1300 (m), 1290 (s), 1259 (m), 1228 (s), 1182 (m), 1169 (m), 1151 (m), 1117 (m), 1103 (m), 1090 (s), 1049 (m), 1014 (s), 997 (s), 980 (m), 970 (m), 953 (m), 933 (m), 924 (m), 858 (m), 814 (s), 798 (s), 769 (vs), 735 (vs), 714 (s), 679 (m), 642 (s), 629 (s), 617 (m), 580 (m), 569 (m); GC-MS (EI, 70 eV): m/z (%) = 290 (100), 275 (50), 243 (24); HRMS (EI): calcd. for $C_{18}H_{14}N_2S_1$ ($[M]^+$): 290.08722; found: 290.08702.

9-(4-Cyanophenyl)-9H-pyrido[2,3-b]indole **5h** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-aminobenzonitrile (66 mg, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 1.5:1) to yield **5h** (83 mg, 83 %) as a white solid; m.p. 179-180 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.29 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.51 – 7.36 (m, 2H), 7.33 – 7.24 (m, 1H), 7.19 (dd, *J* = 7.8, 4.9 Hz, 1H) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 151.32, 146.45, 140.52, 138.85, 133.45, 128.58, 127.37, 127.28, 121.74, 121.45, 121.28, 118.52, 117.11, 116.85, 110.41, 110.23; IR (ATR, cm^{-1}): ν = 3057 (w), 2227 (m), 1603 (m), 1591 (m), 1574 (m), 1512 (m), 1487 (w), 1475 (w), 1450 (m), 1410 (s), 1356 (m), 1336 (m), 1311 (w), 1286 (m), 1228 (m), 1217 (m), 1184 (w), 1169 (m), 1155 (w), 1119 (m), 1103 (w), 1057 (w), 1020 (w), 1001 (w), 960 (w), 953

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(w), 945 (w), 928 (w), 856 (m), 833 (m), 823 (m), 800 (w), 789 (w), 773 (m), 766 (s), 744 (m), 735 (vs), 694 (m), 656 (w), 631 (m), 619 (w), 577 (m), 569 (m), 550 (s), 532 (m); GC-MS (EI, 70 eV): m/z (%) = 268 (100), 134 (7); HRMS (EI): calcd. for $C_{18}H_{10}N_3$ ($[M]^+$): 268.08692; found: 268.08700.

General procedure B for double C-N coupling with chain amine derivatives, exemplified by: ***5-benzyl-5H-pyrido[3,2-b]indole*** **5i.** To pressure tube charged with **3a** (100 mg, 0.37 mmol), $Pd_2(dba)_3$ (17 mg, 19 µmol), ligand DPEPhos (21 mg, 37 µmol) and sodium tert-butoxide (107 mg, 0.12 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL). benzylamine (61 µL, 0.56 mmol) was added to the mixture and heated at 100 ºC for 7 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5i** (85 mg, 88 %) as a white solid; m.p. 98-99 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.41 (dd, J = 4.9, 1.6 Hz, 1H), 8.20 (dd, J = 7.7, 1.6 Hz, 1H), 7.99 – 7.92 (m, 1H), 7.36 – 7.20 (m, 2H), 7.19 – 7.01 (m, 7H), 5.58 (s, 2H) ; ^{13}C NMR (63 MHz, $CDCl_3$) δ 150.65, 145.10, 138.49, 136.25, 127.55, 127.08, 126.26, 125.88, 125.68, 119.92, 119.56, 118.93, 114.79, 114.24, 108.80, 43.87; IR (ATR, cm^{-1}): ν = 3028 (w), 2960 (w), 2918 (w), 1626 (w), 1589 (m), 1568 (m), 1483 (s), 1466 (s), 1452 (m), 1431 (s), 1412 (s), 1356 (m), 1348 (m), 1333 (m), 1315 (w), 1292 (m), 1259 (s), 1211 (s), 1194 (m), 1155 (m), 1128 (m), 1119 (m), 1092 (m), 1078 (m), 1065 (m), 1053 (m), 1030 (s), 1020 (s), 995 (s), 970 (m), 947 (m), 928 (w), 906 (w), 870 (w), 850 (m), 839 (m), 800 (s), 791 (s), 773 (vs), 748 (s), 729 (vs), 694 (s), 652 (s), 619 (m), 606 (m), 582 (m), 569 (m), 555 (s), 528 (s); GC-MS (EI, 70 eV): m/z (%) = 257

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(100), 181 (34), 91 (45); HRMS (ESI): calcd. for $C_{18}H_{14}N_2$ ($[M + H]^+$): 259.12297; found: 259.12298.

5-(4-Fluorobenzyl)-5H-pyrido[3,2-b]indole **5j** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 4-fluorobenzylamine (61 µL, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5j** (90 mg, 87 %) as a white solid; m.p. 103-104 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.25 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.02 – 7.96 (m, 1H), 7.36 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 7.28 – 7.07 (m, 5H), 6.89 – 6.79 (m, 2H), 5.57 (s, 2H) ; ^{19}F NMR (282 MHz, $CDCl_3$) δ -115.23 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.07 (d, *J* = 245.4 Hz), 150.56, 145.15, 138.33, 132.02 (d, *J* = 3.2 Hz), 127.62 (d, *J* = 8.1 Hz), 127.20, 125.77, 120.05, 119.63, 119.09, 114.85, 114.47 (d, *J* = 21.6 Hz), 114.39, 108.65, 43.24; IR (ATR, cm^{-1}): ν = 3053 (w), 3034 (w), 2935 (w), 1624 (w), 1587 (m), 1572 (m), 1508 (s), 1481 (m), 1464 (s), 1439 (m), 1416 (s), 1383 (w), 1354 (m), 1335 (m), 1294 (m), 1252 (m), 1217 (s), 1207 (s), 1163 (m), 1128 (m), 1119 (m), 1101 (m), 1061 (m), 1049 (m), 1030 (w), 1020 (m), 1001 (w), 987 (m), 966 (w), 928 (w), 862 (m), 849 (m), 823 (m), 800 (m), 791 (m), 777 (vs), 762 (s), 746 (s), 735 (vs), 704 (m), 665 (w), 638 (m), 629 (s), 619 (m), 609 (m), 580 (m), 565 (m); GC-MS (EI, 70 eV): m/z (%) = 276 (100), 181 (30), 109 (73); HRMS (ESI): calcd. for $C_{18}H_{13}F_1N_2$ ($[M + H]^+$): 277.11355; found: 277.11394.

5-(3-(Trifluoromethyl)benzyl)-5H-pyrido[3,2-b]indole **5k** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and 3-(trifluoromethyl)benzylamine (80 µL, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5k** (109 mg, 90 %) as a white solid; m.p. 81-82 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39

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(dd, J = 4.9, 1.6 Hz, 1H), 8.21 (dd, J = 7.7, 1.6 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.49 (s, 1H), 7.39 – 7.30 (m, 2H), 7.17 (ddd, J = 11.9, 6.6, 0.9 Hz, 4H), 7.12 – 7.03 (m, 1H), 5.60 (s, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.51 (s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.65, 146.29, 139.36, 138.47, 131.04 (q, J = 32.3 Hz), 130.30, 129.26, 128.36, 126.99, 124.38 (q, J = 3.8 Hz), 124.06 (q, J = 272.4 Hz), 123.89 (q, J = 3.8 Hz), 121.23, 120.81, 120.37, 115.99, 115.68, 109.55, 44.61; IR (ATR, cm^{-1}): ν = 3053 (w), 1628 (w), 1591 (m), 1572 (m), 1483 (m), 1466 (m), 1450 (w), 1433 (m), 1416 (s), 1325 (vs), 1296 (m), 1281 (m), 1261 (m), 1217 (m), 1205 (m), 1186 (m), 1157 (s), 1117 (vs), 1097 (s), 1072 (vs), 1022 (m), 1011 (m), 993 (m), 966 (m), 937 (m), 922 (m), 903 (m), 868 (m), 852 (m), 800 (s), 791 (s), 771 (s), 744 (s), 735 (s), 702 (vs), 671 (m), 646 (s), 619 (m), 600 (m), 575 (m), 559 (m); GC-MS (EI, 70 eV): m/z (%) = 326 (100), 181 (62), 159 (20), 140 (13), 109 (13); HRMS (ESI): calcd. for $C_{19}H_{13}F_3N_2$ ($[M + H]^+$): 327.11036; found: 327.11066.

5-Propyl-5H-pyrido[3,2-b]indole **5l** was prepared following general procedure A using **3a** (100 mg, 0.37 mmol) and n-propylamine (46 µL, 0.56 mmol). The product was purified by flash chromatography (silica gel, heptanes/ethylacetate 3:1) to yield **5l** (71 mg, 91 %) as a white liquid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, J = 4.9, 1.6 Hz, 1H), 8.16 (dd, J = 7.6, 1.6 Hz, 1H), 7.97 – 7.89 (m, 1H), 7.43 – 7.29 (m, 2H), 7.14 (ddd, J = 8.0, 6.9, 1.4 Hz, 1H), 7.01 (dd, J = 7.6, 4.9 Hz, 1H), 4.37 – 4.26 (m, 2H), 1.90 – 1.73 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.61, 145.94, 139.71, 128.03, 126.61, 121.03, 120.44, 119.62, 115.83, 114.86, 109.38, 43.16, 22.32, 11.65; IR (ATR, cm^{-1}): ν = 3049 (w), 2962 (m), 2929 (m), 2874 (w), 1626 (w), 1589 (m), 1570 (m), 1481 (s), 1466 (s), 1443 (m), 1414 (vs), 1381 (m), 1371 (m), 1360 (m), 1342 (s), 1333 (s), 1313 (w), 1290 (s), 1255 (m), 1219 (s), 1157 (m), 1138 (m), 1128

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(m), 1119 (s), 1090 (w), 1068 (m), 1049 (w), 1018 (w), 997 (m), 960 (w), 926 (w), 893 (w), 845 (w), 800 (w), 771 (vs), 748 (s), 733 (vs), 712 (m), 633 (m), 619 (m), 580 (m), 561 (m); GC-MS (EI, 70 eV): m/z (%) = 210 (32), 181 (100), 168 (82), 140 (12), 127 (14); HRMS (EI): calcd. for $C_{14}H_{14}N_2$ ($[M]^+$): 210.11515; found: 210.11500.

General procedure C for double C-N coupling with diamine derivatives, exemplified by: ***1,4-bis(9H-pyrido[2,3-b]indol-9-yl)benzene*** **7a.** To pressure tube was charged with **3a** (200 mg, 0.75 mmol), 1,4-diaminobenzen (37 mg, 0.34 mmol), $Pd_2(dba)_3$ (15 mg, 17 µmol), ligand dppf (19 mg, 34 µmol) and sodium tert-butoxide (195 mg, 2.0 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL) and heated at 110 ºC for 10 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 1:1:1) to yield 1,4-bis(9*H*-pyrido[2,3-*b*]indol-9-yl)benzene **7a** (64 mg, 46 %) as a white solid; m.p. 307-308 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.8, 1.4 Hz, 2H), 8.34 (dt, *J* = 9.4, 4.7 Hz, 2H), 8.09 (d, *J* = 7.7 Hz, 2H), 7.87 (s, 4H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.50 – 7.37 (m, 3H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.25 – 7.16 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 151.90, 146.48, 139.94, 135.34, 128.42, 128.32, 127.14, 121.02, 116.61, 116.37, 110.73; IR (ATR, cm^{-1}): ν = 3045 (m), 2922 (m), 1591 (m), 1572 (m), 1518 (s), 1481 (m), 1450 (s), 1406 (s), 1356 (m), 1338 (s), 1317 (m), 1290 (s), 1228 (s), 1173 (m), 1128 (m), 1120 (m), 1111 (m), 1051 (m), 1018 (m), 999 (m), 928 (m), 918 (m), 827 (m), 762 (s), 742 (s), 727 (vs), 700 (s), 642 (s), 619 (m), 579 (m), 567 (m), 534 (s); GC-MS (EI, 70 eV): m/z (%) =

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410 (100), 242 (24), 205 (23), 191 (12); HRMS (EI): calcd. for $C_{28}H_{18}N_4$ ($[M]^+$): 410.15260; found: 410.15147.

9-(6-(9H-Indeno[2,1-b]pyridin-9-yl)pyridin-2-yl)-9H-pyrido[2,3-b]indole **7b** was prepared following general procedure C using **3a** (200 mg, 0.75 mmol) and 2,6-diaminopyridine (37 mg, 0.34 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 1:1:1) to yield **7b** (70 mg, 50 %) as a white solid; m.p. 236-237 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 4.8, 1.5 Hz, 2H), 8.43 – 8.29 (m, 4H), 8.29 – 8.21 (m, 2H), 8.13 (dd, *J* = 8.8, 7.1 Hz, 1H), 8.00 (t, *J* = 9.9 Hz, 2H), 7.38 – 7.14 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.36, 149.76, 146.01, 140.02, 139.02, 128.26, 127.54, 121.79, 121.57, 120.37, 117.76, 117.15, 116.61, 114.34; IR (ATR, cm^{-1}): ν = 3047 (w), 2922 (w), 1599 (m), 1591 (s), 1570 (m), 1485 (w), 1450 (vs), 1414 (m), 1400 (vs), 1362 (m), 1340 (m), 1331 (s), 1286 (s), 1242 (m), 1223 (m), 1209 (m), 1180 (s), 1165 (m), 1155 (m), 1120 (m), 1105 (m), 1095 (m), 1057 (m), 1039 (m), 1026 (m), 999 (m), 985 (w), 974 (w), 968 (w), 957 (w), 943 (m), 933 (m), 922 (m), 849 (w), 796 (m), 764 (vs), 744 (s), 727 (vs), 700 (m), 683 (m), 658 (m), 634 (m), 619 (m), 611 (m), 579 (m), 567 (w), 559 (m); GC-MS (EI, 70 eV): m/z (%) = 410 (100), 244 (28), 206 (89); HRMS (EI): calcd. for $C_{27}H_{16}N_5$ ($[M]^+$): 410.14002; found: 410.13958.

General procedure for prepared of *3-bromo-2-(2-bromophenyl)pyridine* 3b. 2,3-dibromopyridine **1b** (1 g, 4.2 mmol), 2-bromophenyl boronic acid **2** (1.0 g, 5.1 mmol), $Pd(PPh_3)_4$ (244 mg, 211 μmol) and sodium hydroxide (507 mg, 12.7 mmol) were added to 500 mL Schlenk flask. The mixture was back-filled several times with argon. To the mixture 70 mL THF and 10 mL distilled water were added, then, back-filled several times. The reaction was heated at 70 ºC

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for 4h. The solvent was evaporated *in vacuo*. The residue was extracted with dichloromethane and water. The organic layer was dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The yellow residue was purified by column chromatography (silica gel, Heptane/dichloromethane/ethylacetate 4:1:1) to yield 3-bromo-2-(2-bromophenyl)pyridine **3b** (1.27 g, 96 %) as colorless syrup; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (dd, J = 4.7, 1.5 Hz, 1H), 7.93 (dd, J = 8.1, 1.5 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.39 – 7.32 (m, 1H), 7.29 – 7.13 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.84, 140.99, 140.46, 132.69, 130.23, 130.08, 127.34, 124.13, 122.46, 121.35; IR (ATR, cm^{-1}): ν = 3053 (w), 2920 (w), 2850 (w), 1593 (m), 1568 (m), 1549 (m), 1479 (m), 1437 (m), 1412 (s), 1298 (w), 1269 (w), 1252 (m), 1230 (w), 1211 (w), 1201 (w), 1159 (w), 1124 (m), 1093 (m), 1055 (m), 1024 (s), 1011 (vs), 943 (m), 793 (s), 777 (m), 748 (vs), 723 (s), 694 (m), 681 (s), 650 (m), 615 (s), 561 (m); GC-MS (EI, 70 eV): m/z (%) = 313 (37), 234 (99), 233 (100), 153 (82), 126 (28), 99 (10), 75 (14), 63 (10), 50 (12); HRMS (EI): calcd. for $C_{11}H_7N_1Br_2$ ($[M]^+$): 310.89398; found: 310.89479; calcd. for $C_{11}H_7N_1Br_1{}^{81}Br_1$ ($[M]^+$): 312.89193; found: 312.89233; calcd. for $C_{11}H_7N_1{}^{81}Br_2$ ($[M]^+$): 314.88988; found: 314.89073.

General procedure D for double C-N coupling with aniline derivatives, exemplified by: *5-phenyl-5H-pyrido[3,2-b]indole* 8a. Aniline (44 µL, 479 µmol) was added to pressure tube charged with **3b** (100 mg, 0.32 mmol), $Pd_2(dba)_3$ (15 mg, 16 µmol), ligand dppf (18 mg, 32 µmol) and sodium tert-butoxide (92 mg, 0.96 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL) and heated at 100 ºC for 4 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel,

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heptanes/dichloromethane/ethylacetate 10:1:1) to yield 5-phenyl-5*H*-pyrido[3,2-*b*]indole **8a** (65 mg, 83%) as a white solid; m.p. 99-101 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.50 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.40 – 8.30 (m, 1H), 7.60 – 7.12 (m, 11H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 142.54, 142.26, 141.54, 136.84, 134.31, 130.04, 127.95, 127.80, 126.79, 122.45, 120.87, 120.83, 120.18, 116.72, 110.04; IR (ATR, cm^{-1}): ν = 3053 (m), 1622 (m), 1593 (s), 1574 (m), 1502 (s), 1481 (s), 1452 (s), 1412 (vs), 1371 (m), 1340 (m), 1315 (m), 1304 (s), 1282 (m), 1234 (m), 1209 (s), 1178 (m), 1167 (m), 1147 (m), 1119 (m), 1107 (m), 1072 (m), 1026 (m), 1011 (m), 931 (m), 906 (m), 787 (m), 777 (s), 762 (s), 744 (vs), 727 (vs), 698 (vs), 665 (m), 642 (m), 633 (s), 615 (s), 582 (m), 567 (m), 534 (m); GC-MS (EI, 70 eV): m/z (%) = 244 (100), 216 (4), 189 (3), 167 (3), 152 (3), 140 (4), 122 (9), 88 (3), 77 (4), 63 (3), 51 (5), 39 (4); HRMS (EI): calcd. for $C_{17}H_{12}N_2$ ($[M]^+$): 244.09950; found: 244.09922;

5-(4-Fluorophenyl)-5H-pyrido[3,2-b]indole **8b** was prepared following general procedure D using **3b** (100 mg, 0.32 mmol) and 4-fluoroaniline (45 µL, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 8:1:1) to yield **8b** (61 mg, 73 %) as a white solid; m.p. 115-117 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.39 – 8.29 (m, 1H), 7.53 – 7.32 (m, 4H), 7.31 – 7.11 (m, 3H), 6.78 – 6.65 (m, 1H), 6.48 (ddd, *J* = 6.7, 5.2, 2.9 Hz, 1H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -112.83 (s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.79 (d, *J* = 248.2 Hz), 142.62, 141.69, 134.45, 132.77, 128.73 (d, *J* = 8.6 Hz), 128.06, 122.38, 120.94, 120.27, 117.24, 116.88, 116.50, 115.61 (d, *J* = 22.4 Hz), 109.80; IR (ATR, cm^{-1}): ν = 3055 (m), 3037 (m), 1620 (m), 1587 (m), 1506 (vs), 1477 (s), 1452 (s), 1412 (s), 1354 (m), 1342 (m), 1311 (s), 1294 (m), 1281 (m), 1215 (s), 1207 (s), 1169 (s), 1151 (s), 1119 (m), 1105 (m), 1093 (s), 1049 (m), 1034 (m), 1028 (m), 1011 (m), 937 (m), 912 (s), 845

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(s), 833 (s), 816 (s), 781 (s), 764 (m), 742 (vs), 727 (vs), 715 (s), 700 (s), 646 (m), 627 (m), 617 (s), 575 (s), 534 (s); GC-MS (EI, 70 eV): m/z (%) = 262 (100), 261 (29), 131 (10); HRMS (EI): calcd. for $C_{17}H_{11}F_1N_2$ ($[M]^+$): 262.09008; found: 262.08948.

5-(3-(Trifluoromethyl)phenyl)-5H-pyrido[3,2-b]indole **8c** was prepared following general procedure D using **3b** (100 mg, 0.32 mmol) and 3-(trifluoromethyl)aniline (60 µL, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 8:1:1) to yield **8c** (64 mg, 64 %) as a white solid; m.p. 144-146 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.47 – 8.29 (m, 1H), 7.84 – 7.53 (m, 4H), 7.52 – 7.14 (m, 4H); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.70 (s); ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.08, 142.52, 141.17, 137.65, 133.96, 132.76 (q, *J* = 33.2 Hz), 130.80, 130.03, 128.26, 124.44 (q, *J* = 3.6 Hz), 123.61 (q, *J* = 3.6 Hz), 122.75, 121.41, 121.09, 120.39, 116.43, 109.66; IR (ATR, cm^{-1}): ν = 3055 (w), 3041 (w), 1622 (m), 1606 (w), 1595 (m), 1579 (w), 1498 (m), 1481 (m), 1456 (s), 1412 (s), 1362 (m), 1356 (m), 1333 (m), 1309 (s), 1292 (m), 1275 (m), 1232 (m), 1217 (m), 1207 (m), 1182 (s), 1163 (s), 1155 (s), 1117 (vs), 1095 (s), 1074 (s), 1028 (m), 1014 (m), 1001 (m), 966 (m), 945 (m), 935 (m), 928 (m), 918 (m), 906 (m), 854 (w), 810 (m), 802 (s), 791 (m), 781 (s), 760 (w), 744 (vs), 727 (s), 715 (s), 706 (vs), 673 (m), 663 (s), 638 (m), 621 (m), 607 (m), 582 (w), 563 (w), 536 (m); GC-MS (EI, 70 eV): m/z (%) = 312 (100), 242 (8); HRMS (EI): calcd. for $C_{18}H_{11}F_3N_2$ ($[M]^+$): 312.08688; found: 312.08662.

5-(4-Methoxyphenyl)-5H-pyrido[3,2-b]indole **8d** was prepared following general procedure D using **3b** (100 mg, 0.32 mmol) and *p*-anisidine (59 mg, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 5:1:1) to yield **8d** (88

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mg, 94 %) as a white solid; m.p. 128-130 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.53 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.43 – 8.30 (m, 1H), 7.55 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.50 – 7.21 (m, 6H), 7.11 – 6.99 (m, 2H), 3.85 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 159.13, 142.22, 142.06, 134.81, 129.36, 128.30, 127.90, 122.13, 120.85, 120.59, 120.12, 116.68, 115.22, 109.97, 55.62; IR (ATR, cm^{-1}): ν = 2955 (w), 2929 (w), 2837 (w), 1620 (m), 1510 (vs), 1479 (m), 1454 (s), 1441 (m), 1414 (s), 1385 (w), 1342 (m), 1313 (s), 1300 (m), 1286 (m), 1242 (s), 1209 (s), 1176 (s), 1149 (m), 1120 (m), 1107 (s), 1066 (m), 1028 (s), 1012 (m), 937 (m), 912 (m), 860 (w), 829 (s), 812 (m), 791 (s), 748 (vs), 729 (vs), 700 (s), 667 (m), 646 (m), 629 (m), 617 (s), 584 (s), 536 (s); GC-MS (EI, 70 eV): m/z (%) = 274 (100), 259 (55), 231 (13), 230 (15), 229 (14), 115 (9); HRMS (EI): calcd. for $C_{18}H_{14}O_1N_2$ ($[M]^+$): 274.11006; found: 274.11009.

5-(3,5-Dimethoxyphenyl)-5H-pyrido[3,2-b]indole **8e** was prepared following general procedure D using **3b** (100 mg, 0.32 mmol) and 3,5-dimethoxyaniline (73 mg, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 3:1:1) to yield **8d** (88 mg, 94 %) as a white solid; m.p. 150-152 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.58 – 8.41 (m, 1H), 8.33 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.64 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.53 – 7.12 (m, 4H), 6.57 (d, *J* = 2.2 Hz, 2H), 6.45 (t, *J* = 2.2 Hz, 1H), 3.71 (s, *J* = 9.9 Hz, 6H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 161.82, 142.55, 142.26, 141.37, 138.46, 134.17, 127.95, 122.48, 120.82, 120.20, 116.99, 110.33, 104.96, 99.76, 93.72, 55.59; IR (ATR, cm^{-1}): ν = 3051 (m), 3007 (m), 2970 (m), 2945 (m), 2916 (m), 2841 (m), 1620 (m), 1605 (s), 1583 (s), 1495 (m), 1475 (m), 1452 (s), 1425 (s), 1416 (s), 1367 (m), 1342 (m), 1331 (m), 1313 (s), 1296 (s), 1282 (s), 1252 (m), 1223 (m), 1194 (s), 1147 (vs), 1057 (s), 1009 (s), 991 (m), 928 (m), 906 (m), 868 (m), 852 (m), 833 (s), 823 (s), 783 (s), 773 (s), 741 (s), 723 (vs), 696 (s), 690 (s), 675 (s), 660 (s), 621 (s), 607 (s), 573 (s),

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557 (m), 532 (m); GC-MS (EI, 70 eV): m/z (%) = 304 (100), 261 (8), 245 (10), 218 (7); HRMS (EI): calcd. for $C_{19}H_{16}O_2N_2$ ($[M]^+$): 304.12063; found: 304.12015.

5-(4-Cyanophenyl)-5H-pyrido[3,2-b]indole **8f** was prepared following general procedure D using **3b** (100 mg, 0.32 mmol) and 4-aminobenzonitrile (56 mg, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 4:1:1) to yield **8f** (36 mg, 42 %) as a white solid; m.p. 162-164 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.41 – 8.33 (m, 1H), 7.90 – 7.81 (m, 2H), 7.71 – 7.60 (m, 3H), 7.52 – 7.23 (m, 4H), ^{13}C NMR (63 MHz, $CDCl_3$) δ 143.51, 141.21, 134.10, 133.45, 128.42, 126.86, 123.12, 121.88, 121.23, 120.49, 116.59, 111.02, 109.77; IR (ATR, cm^{-1}): ν = 3051 (w), 3007 (w), 2226 (m), 1616 (w), 1601 (s), 1587 (m), 1558 (w), 1506 (s), 1489 (w), 1479 (m), 1454 (m), 1412 (s), 1373 (w), 1354 (m), 1340 (m), 1315 (s), 1290 (m), 1246 (w), 1234 (m), 1221 (m), 1207 (s), 1182 (m), 1169 (m), 1153 (m), 1136 (m), 1128 (m), 1117 (m), 1107 (m), 1053 (w), 1028 (w), 1014 (m), 978 (w), 968 (w), 953 (w), 935 (w), 916 (m), 885 (w), 841 (s), 783 (s), 748 (vs), 731 (vs), 723 (s), 667 (m), 656 (m), 631 (m), 619 (s), 582 (w), 567 (m), 552 (s), 528 (m); GC-MS (EI, 70 eV): m/z (%) = 269 (100), 270 (25), 75 (7), 39 (7); HRMS (EI): calcd. for $C_{18}H_{11}N_3$ ($[M]^+$): 269.09475; found: 269.09432.

General procedure E for double C-N coupling with chain amine derivatives, exemplified by: ***5-benzyl-5H-pyrido[3,2-b]indole*** **8g.** To pressure tube charged with **3b** (100 mg, 0.32 mmol), $Pd_2(dba)_3$ (15 mg, 16 µmol), ligand DPEPhos (17 mg, 32 µmol) and sodium tert-butoxide (92 mg, 0.96 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL). benzylamine **4i** (52 µL, 0.48 mmol)

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was added to the mixture and heated at 100 ºC for 7 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 5:1:1) to yield **8g** (76 mg, 92 %) as a white solid; m.p. 137-139 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.2 Hz, 1H), 8.32 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.30 (m, 2H), 7.28 – 7.01 (m, 6H), 6.93 (dd, *J* = 6.7, 2.6 Hz, 2H), 5.26 (s, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 140.82, 140.75, 140.27, 135.40, 132.91, 127.78, 126.80, 126.62, 125.25, 121.08, 119.82, 119.07, 118.93, 114.75, 108.14, 45.35; IR (ATR, cm^{-1}): ν = 3051 (w), 3028 (w), 2926 (w), 1622 (m), 1603 (w), 1589 (m), 1576 (w), 1558 (w), 1495 (m), 1483 (m), 1458 (s), 1450 (s), 1414 (s), 1373 (m), 1356 (w), 1335 (s), 1319 (s), 1281 (w), 1263 (w), 1242 (m), 1211 (m), 1194 (s), 1178 (m), 1149 (m), 1132 (m), 1117 (m), 1080 (m), 1057 (w), 1047 (w), 1028 (m), 1012 (m), 999 (w), 972 (w), 962 (w), 937 (w), 912 (w), 845 (m), 802 (w), 789 (m), 781 (s), 742 (vs), 731 (vs), 721 (vs), 694 (s), 644 (m), 621 (m), 600 (m), 584 (m), 567 (m), 557 (m), 536 (m); GC-MS (EI, 70 eV): m/z (%) = 258 (88), 181 (5), 167 (8), 91 (100), 39 (9); HRMS (EI): calcd. for $C_{18}H_{14}N_2$ ($[M]^+$): 258.11515; found: 258.11534.

5-(4-Methoxybenzyl)-5H-pyrido[3,2-b]indole **8h** was prepared following general procedure E using compound **3b** (100 mg, 0.32 mmol) and 4-methoxybenzylamine (63 µL, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 3:1:1) to yield **8h** (60 mg, 65 %) as a white solid; m.p. 124-126 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (dt, *J* = 5.7, 2.9 Hz, 1H), 8.36 – 8.28 (m, 1H), 7.48 – 7.31 (m, 2H), 7.30 – 7.07 (m, 3H), 6.88 (t, *J* = 5.8 Hz, 2H), 6.68 – 6.58 (m, 2H), 5.22 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.15, 141.92, 141.77, 141.37, 134.01, 128.51, 127.90, 127.71, 122.17, 120.94,

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120.12, 120.02, 115.94, 114.27, 109.30, 55.24, 46.00; IR (ATR, cm^{-1}): ν = 2931 (w), 2835 (w), 1624 (m), 1610 (m), 1583 (m), 1512 (s), 1485 (s), 1460 (s), 1443 (m), 1412 (s), 1377 (m), 1354 (w), 1323 (s), 1308 (s), 1246 (vs), 1211 (m), 1203 (m), 1194 (s), 1178 (s), 1155 (m), 1134 (m), 1113 (s), 1059 (w), 1034 (s), 1009 (m), 984 (m), 962 (m), 939 (w), 864 (w), 845 (s), 837 (m), 820 (m), 791 (s), 775 (s), 746 (vs), 727 (vs), 708 (s), 665 (m), 640 (m), 625 (s), 600 (s), 582 (m), 565 (m), 540 (s); GC-MS (EI, 70 eV): m/z (%) = 288 (29), 242 (3), 167 (8), 140 (5), 121 (100), 91 (7), 78 (10), 77 (9); HRMS (EI): calcd. for $C_{19}H_{16}N_2O_1$ ($[M]^+$): 288.12571; found: 288.12541.

5-Phenethyl-5H-pyrido[3,2-b]indole **8i** was prepared following general procedure E using compound **3b** (100 mg, 0.32 mmol) and 2-phenylethylamine (60 µL, 0.48 mmol). The product was purified by flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 5:1:1) to yield **8j** (67 mg, 77 %) as a white solid; m.p. 61-63 ºC; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (dd, *J* = 4.7, 1.3 Hz, 1H), 8.29 (d, *J* = 7.7 Hz, 1H), 7.38 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.28 – 7.13 (m, 3H), 7.13 – 6.96 (m, 4H), 6.96 – 6.82 (m, 2H), 4.30 (t, *J* = 7.2 Hz, 2H), 2.93 (t, *J* = 7.2 Hz, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.61, 141.46, 140.80, 138.37, 133.73, 128.73, 128.66, 127.66, 126.76, 122.05, 120.91, 119.88, 119.75, 115.45, 108.91, 44.82, 35.27; IR (ATR, cm^{-1}): ν = 3051 (w), 3041 (w), 3026 (w), 3001 (w), 2964 (w), 2939 (w), 2922 (w), 1622 (m), 1603 (w), 1587 (m), 1562 (w), 1483 (s), 1462 (s), 1452 (s), 1414 (vs), 1377 (m), 1360 (m), 1342 (s), 1319 (s), 1248 (w), 1223 (s), 1200 (m), 1186 (s), 1151 (m), 1132 (m), 1122 (m), 1080 (m), 1065 (w), 1049 (w), 1028 (m), 1009 (m), 974 (w), 962 (w), 939 (w), 926 (w), 881 (w), 856 (w), 839 (w), 791 (m), 777 (m), 764 (w), 742 (vs), 727 (vs), 696 (vs), 642 (w), 623 (m), 613 (m), 606 (m), 590 (m), 582 (w), 565 (w), 548 (m), 540 (m); GC-MS (EI, 70 eV): m/z (%) = 272 (23), 181 (100),

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154 (5), 127 (12), 91 (5), 78 (5); HRMS (EI): calcd. for $C_{19}H_{16}N_2$ ($[M]^+$): 272.13080; found: 272.13063.

Synthesis of *1,4-bis(5H-pyrido[3,2-b]indol-5-yl)benzene* 9. To pressure tube was charged with **3b** (200 mg, 0.64 mmol), 1,4-diaminobenzen (34 mg, 0.32 mmol), $Pd_2(dba)_3$ (12 mg, 13 µmol), ligand dppf (14 mg, 26 µmol) and sodium tert-butoxide (147 mg, 1.53 mmol) under argon. The mixture was back-filled with argon several times. The mixture was dissolved in anhydrous toluene (10 mL) and heated at 100 ºC for 10 h. After cooling, the reaction mixture was diluted with dichloromethane (20 mL) and filtered through a celite pad, washing with dichloromethane (40 mL). The filtrate was reduced *in vacuo*. The product was separated via flash chromatography (silica gel, heptanes/dichloromethane/ethylacetate 1:1:1) to yield 1,4-bis(5*H*-pyrido[3,2-*b*]indol-5-yl)benzene **9** (52 mg, 40 %) as a white solid; m.p. 277-279 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.76 – 8.33 (m, 4H), 7.96 – 7.06 (m, 14H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 142.02, 141.51, 140.20, 137.74, 132.99, 130.64, 127.24, 124.84, 123.60, 121.75, 120.36, 120.12, 119.37, 115.61, 108.83; IR (ATR, cm^{-1}): ν = 3053 (w), 1620 (w), 1595 (m), 1585 (m), 1576 (m), 1497 (s), 1475 (m), 1450 (s), 1408 (s), 1373 (w), 1362 (w), 1340 (m), 1315 (s), 1306 (s), 1288 (m), 1263 (m), 1238 (w), 1215 (m), 1203 (s), 1178 (m), 1155 (m), 1120 (m), 1111 (m), 1101 (m), 1090 (m), 1049 (m), 1026 (m), 1012 (m), 968 (w), 922 (m), 903 (w), 877 (w), 850 (w), 810 (m), 800 (m), 779 (s), 742 (vs), 727 (vs), 700 (s), 671 (m), 648 (m), 631 (m), 619 (s), 584 (m), 567 (m), 536 (m); GC-MS (EI, 70 eV): m/z (%) = 410 (100), 242 (28), 205 (11); HRMS (ESI): calcd. for $C_{28}H_{18}N_4$ ($[M + H]^+$): 411.16042; found: 411.15977.

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Supporting Information

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge *via* the Internet:

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REFERENCES

(1) (a) Cao, R.; Peng,W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (b) Alekseyev, R. S.; Kurkin, A. V.; Yurovskaya, M. A. *Chem. Heterocycl. Compd*. **2009**, *45*, 889. (c) Kumar, E. V. K. Suresh; Etukala, J. R.; Ablordeppey, S. Y. *Mini Rev. Med. Chem.* **2008**, *8*, 538.

(2) (a) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *Synlett* **1995**, 147. (b) Choshi, T.; Yamada, S.; Sugino, E.; Kuwada, T.; Hibino, S. *J. Org. Chem.* **1995**, *60*, 5899. (c) Achab, S.; Guyot, M.; Potier, P. *Tetrahedron Lett.* **1995**, *36*, 2615. (d) Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3280.

View Article Online
DOI: 10.1039/C4OB02226B

(3) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431.

(4) (a) Subbaraju, G. V.; Kavitha, J.; Rajasekhar, D.; Jimenez, J.I. *J. Nat. Prod.* **2004**, *67*, 461. (b) Paulo, A.; Gomes, E. T.; Steele, J.; Warhurst, D. C.; Houghton, P. J. *Planta Med.* **2000**, *66*, 30. (c) Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N.; Phoebe, C. H.; Johnson, R. L. *J. Heterocycl. Chem.* **1996**, *33*, 789. (d) Yang, S.-W.; Maged, A.-K.; Malone, S.; Werkhoven, M. C. M.; Wisse, J. H.; Bursuker, I.; Neddermann, K.; Fairchild, C.; Raventos-Suarez, C.; Menendez, A. T.; Lane, K.; Kingston, D. G. I. *J. Nat. Prod.* **1999**, *62*, 976.

(5) (a) Arzel, E.; Rocca, P.; Grellier, P.; Labaeid, M.; Frappier, F.; Gueritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949. (b) Wright, C. W.; Addae-Kyereme, J.; Breen, A. G.; Brown, J. E.; Cox, M. F.; Croft, S. L.; Goekcek, Y.; Kendrick, H.; Phillips, R. M.; Pollet, P. L. *J. Med. Chem.* **2001**, *44*, 3187. (c) Caprio, V.; Guyen, B.; Opoku-Boahen, Y.; Mann, J.; Gowan, S. M.; Kelland, L. M.; Read, M. A.; Neidle, S. *Bioorg. Med. Chem.Lett.* **2000**, *10*, 2063. (d) Cimanga, K.; Li, Y.; De Bruyne, T.; Apers, S.; Cos, P.; Bakana, P.; Kambu, K.; Tona, L.; Pieters, L.; Berghe, D. V.; Vlietinck, A. J. *Pharm. Pharmacol.Commun.* **2000**, *6*, 321.

(6) (a) Seville, S.; Phillips, R. M.; Shnyder, S. D.; Wright, C. W. *Bioorg. Med. Chem.***2007**, *15*, 6353. (b) Riechert-Krause, F.; Eick, A.; Grünert, R.; Bednarski, P. J.; Weisz, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2380. (c) Li, B.; Yue, Z.-Z.; Feng, J.-M.; He, Q.; Miao, Z.-H.; Yang, C.-H. *Eur. J. Med. Chem.* **2013**, *66*, 531. (d) Rajanarendar, E.; Reddy, K. G.; Ramakrishna, S.; Nagi Reddy, M.; Shireesha, B.; Durgaiah, G.; Reddy, Y. N. *Bioorg. Med. Chem. Lett.***2012**, *22*, 6677. (e) Yin, R.; Zhang, M.; Hao, C.; Wang, W.; Qiu, P.; Wan, S.; Zhang, L.; Jiang, T. *Chem. Commun.* **2013**, *49*, 8516. (f) Boddupally, P. V. L.; Hahn, S.; Beman, C.; De, B.; Brooks, T. a; Gokhale, V.; Hurley, L. H. *J. Med. Chem.***2012**, *55*, 6076. (g) Beauchard, A.; Jaunet, A.; Murillo, L.; Baldeyrou, B.; Lansiaux, A.; Chérouvrier, J.-R.; Domon, L.; Picot, L.; Bailly, C.; Besson, T.; Thiéry, V. *Eur. J. Med. Chem.***2009**, *44*, 3858.

(7) (a) Rocha e Silva, L. F.; Montoia, A; Amorim, R. C. N.; Melo, M. R.; Henrique, M. C.; Nunomura, S. M.; Costa, M. R. F.; Andrade Neto, V. F.; Costa, D. S.; Dantas, G.; Lavrado, J.; Moreira, R.; Paulo, A; Pinto, A. C.; Tadei, W. P.; Zacardi, R. S.; Eberlin, M. N.; Pohlit,

View Article Online
DOI: 10.1039/C4OB02226B

A. M. *Phytomedicine* **2012**, *20*, 71. (b) Van Baelen, G.; Hostyn, S.; Dhooghe, L.; Tapolcsányi, P.; Mátyus, P.; Lemière, G.; Dommisse, R.; Kaiser, M.; Brun, R.; Cos, P.; Maes, L.; Hajós, G.; Riedl, Z.; Nagy, I.; Maes, B. U. W.; Pieters, L. *Bioorg. Med. Chem.* **2009**, *17*, 7209.

(8) Queiroz, M.-J. R. P.; Ferreira, I. C. F. R.; De Gaetano, Y.; Kirsch, G.; Calhelha, R. C.; Estevinho, L. M. *Bioorg. Med. Chem.* **2006**, *14*, 6827.

(9) (a) Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.***2008**, *16*, 3780. (b) Peczynska-Czoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J.; *J. Med. Chem*. **1994**, *37*, 3503.

(10) (a) Okamoto, T.; Akase, T.; Izumi, T.; Inaba; S.; Yamamoto, H.; Japanese Patent, 7220196. (b) Winters G.; Mola, N. D.; German Patent, 2442513.

(11) (a) Shiomi, M.; Ito, T. *Eur. J. Pharm.* **2001**, *431*, 127. (b) Ueshima, K.; Akihisa-Umeno, H.; Nagayoshi, A.; Takakura, S.; Matsuo, M.; Mutoh, S. *Biol. Pharm. Bull.* **2005**, *28*, 247.

(12) (a) Lee, C. W.; Im, Y.; Seo, J.-A.; Lee, J. Y. *Org. Electron.* **2013**, *14*, 2687. (b) Lee, C. W.; Im, Y.; Seo, J.-A.; Lee, J. Y. *Chem. Commun.* **2013**, *49*, 9860. (c) Kim, S. J.; Kim, Y. J.; Son, Y. H.; Hur, J. a; Um, H. A.; Shin, J.; Lee, T. W.; Cho, M. J.; Kim, J. K.; Joo, S.; Yang, J. H.; Chae, G. S.; Choi, K.; Kwon, J. H.; Choi, D. H. *Chem. Commun.* **2013**, *49*, 6788. (d) Im, Y.; Lee, J. Y. *Chem. Commun.***2013**, *49*, 5948.

(13) Lee, C. W.; Lee, J. Y. *Adv. Mater.* **2013**, *25*, 5450.

(14) Son, Y. H.; Kim, Y. J.; Park, M. J.; Oh, H.-Y.; Park, J. S.; Yang, J. H.; Suh, M. C.; Kwon, J. H. *J. Mater. Chem. C* **2013**, *1*, 5008.

(15) (a) Tahri, A.; Buysens, K. J.; Van der Eycken, E. V.; Vandenberghe, D. M.; Hoornaert, G. J. *Tetrahedron* **1998**, *54*, 13211. (b) Molina, P.; Alajarin, M.; Vidal A.; Sanchez-Andrada, P. *J. Org. Chem.* **1992**, *57*, 929.

(16) (a) Vera-Luque, P.; Alajarín, R.; Alvarez-Builla J.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 415. (b) Goekjian, P.; Schneider, C.; Gueyrard, D.; Popowycz F.; Joseph, B. *Synlett* **2007**, 2237.

View Article Online
DOI: 10.1039/C4OB02226B

(17) (a) Okuda S.; Robinson, M. M. *J. Am. Chem. Soc.* **1959**, *81*, 740. (b) Portela-Cubillo, F.; Surgenor, B. A.; Aitken R. A.; Walton, J. C. *J. Org. Chem.* **2008**, *73*, 8124.

(18) Ghahremanzadeh, R.; Ahadi, S.; Bazgir, A.*Tetrahedron Lett.* **2009**, *50*, 7379. (b) Gupta, S.; Kumar B.; Kundu, B. *J. Org. Chem.* **2011**, *76*, 10154. (c) Sharma, S. K.; Gupta, S.; Saifuddin, M.; Mandadapu, A. K.; Agarwal, P. K.; Gauniyal H. M.; Kundu, B. *Tetrahedron Lett*. **2011**, *52,* 65.

(19) Kumar, A. S.; Rao, P. V. A.; Nagarajan, R. *Org. Biomol. Chem.* **2012**, *10*, 5084.

(20) (a) Hostyn, S. Baelen, G. V.; Lemiere, G. L. F.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 2653. (b) Laha, J. K. Petron, P. Cuny, G. D. *J. Org. Chem.* **2009**, *74*, 3152.

(21) Markey, S. J.; Lewis, W.; Moody, C. J. *Org. Lett.* **2013**, *15*, 6306.

(22) Zhang, X.; He, Q.; Xiang, H.; Song, S.; Miao, Z.; Yang, C. *Org. Biomol. Chem.* **2014**, *12*, 355.

(23) Yang, C.-C.; Tai, H.-M.; Sun, P.-J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2843.

(24) Papamicael, C.; Queguiner, G.; Bourguignon, J.; Dupas, G. *Tetrahedron* **2001**, *57*, 5385.

(25) Ishiyama, H.; Ohshita, K.; Abe, T.; Nakata, H.; Kobayashi, J. *Bioorg. Med. Chem.* **2008**, *16*, 3825.

(26) Mazu, T. K.; Etukala, J. R.; Jacob, M. R.; Khan, S. I.; Walker, L. A. Ablordeppey, S. Y. *Eur. J. Med. Chem.* **2011**, *46*, 2378.

(27) Sharma, S. K. Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 6022.

(28) Peng, H.; Chen, X.; Chen, Y. He, Q.; Xie, Y.; Yang, C. *Tetrahedron* **2011**, *67*, 5725.

(29) Letessier, J.; Detert, H. *Synthesis* **2012**, *44*, 290.

(30) Cao, J.; Xu, Y.; Kong, Y.; Cui, Y.; Hu, Z.; Wang, G.; Deng, Y.; Lai, G. *Org. Lett.* **2012**, *14*, 38.

View Article Online
DOI: 10.1039/C4OB02226B

(31) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505.

(32) Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421.

(33) (a) Ren, Y.; Baumgartner, T. *J. Am. Chem. Soc.* **2011**, *133*, 1328–1340. (b) Weymiens, W.; Zaal, M.; Slootweg, J. C.; Ehlers, A. W.; Lammertsma, K., *Inorg. Chem.* **2011**, *50*, 8516–8523. (c) Kitawaki, T.; Hayashi, Y.; Ueno, A.; Chida, N. *Tetrahedron* **2006**, *62*, 6792–6801. (d) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem. Int. Ed.* **2003**, *42*, 2051 – 2053. € Dahl, T.; Tornoe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jorgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1726-1728. (f) Mitsudo, K.; Shimohara, S.; Mizoguchi, J.; Mandai, H.; Suga, S. *Org. Lett.* **2012**, *14*, 2702-2705. (g) Odom, S. A.; Lancaster, K.; Beverina, L.; Lefler, K. M.; Thompson, N. J.; Coropceanu, V.; Bredas, J. L.; Marder, S. R.; Barlow, S. *Chem. Eur. J.* **2007**, *13*, 9637-9646. (h) Ackermann, L. *Org. Lett.* **2005**, *7*, 439-442. (i) Hung, T. Q.; Dang, T. T.; Villinger, A.; Sung, T. V.; Langer, P. *Org. Biomol. Chem.* **2012**, *10*, 9041 - 9044. (j) Hung, T. Q.; Hoang, D. H.; Thang, N. N.; Dang, T. T.; Ayub, K.; Villinger, A.; Lochbrunner, S.; Flechsig, G.-U.; Langer, P. *Org. Biomol. Chem.* **2014**, 12, 6151–6166. (k) Hung, T. Q.; Hancker, S.; Villinger, A.; Lochbrunner, S.; Dang, T. T.; Friedrich, A.; Breitsprecher, W.; Langer, P. *Org. Biomol. Chem.* **2014**, in print DOI: 10.1039/C4OB01723D.

(34) (a) Garner, K. L.; Parkes, L. F.; Piper, J. D.; Williams, J. A. G. *Inorg. Chem.* **2010**, *49*, 476. (b) G. A. Parada, L. A. Fredin, M.-P. Santoni, M. Jäger, R. Lomoth, L. Hammarström, O. Johansson, P. Persson, S. Ott. *Inorg. Chem.* **2013**, *52*, 5128.

(35) X-Ray Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 1009792-1009793 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or via www.ccdc.cam.ac.uk/data_request/cif

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