Palladium-Catalyzed Indole and Azaindole Synthesis by Direct Annulation of Electron-Poor *o*-Chloroanilines and *o*-Chloroaminopyridines with Aldehydes

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Received 4 June 2008; revised 4 August 2008

Abstract: A practical process for the synthesis of 2-unsubstituted indoles and azaindoles has been developed by the palladium-catalyzed direct annulation of electron-poor *o*-chloro/bromoanilines and *o*-chloroaminopyridines with aldehydes. Coupled with the previous results of Jia and Zhu, this allows rapid access to a variety of 2-unsubstituted indoles and azaindoles starting from simple and easily accessible precursors.

Key words: indole, azaindole, palladium, annulation, ligand

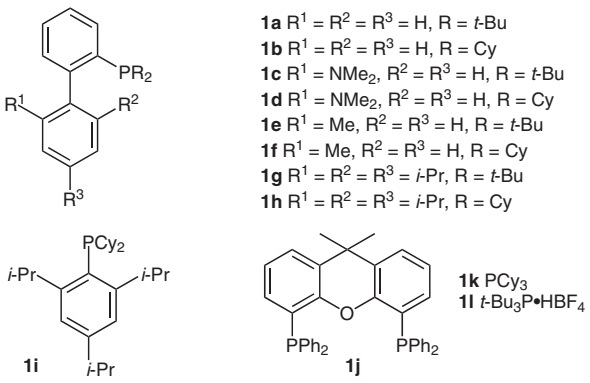
The indole nucleus is a prominent structural motif abundantly found in a wide variety of bioactive natural products and pharmaceuticals.[1] After extensive research over a hundred years, a variety of well-documented methods for the preparation of functionalized indoles are now available.[2] However, the development of general, mild, and efficient methods from simple and easily accessible precursors are of continued interest.[3] In this context, palladium-catalyzed reactions, generally tolerant of many functional groups, are widely applied to the preparation of the indole scaffold and provide alternatives to traditional methods.[4,5]

In 1997, Chen and co-workers at Merck Research Laboratories reported an efficient method for the synthesis of indoles by coupling of *o*-iodoaniline with cyclic ketones; acyclic ketones were found to be less efficient, and surprisingly, aldehydes have not been used as a reaction partner.[6] Recently, Jia and Zhu have extended this method for the synthesis of highly benzofunctionalized 2-unsubstituted indoles, including enantiomerically pure tryptophan derivatives, by using readily available aldehydes as starting materials. This method has been successfully applied to the synthesis of complestatin and suaveolindole[7] and later extended by replacing the *o*-iodoanilines with much cheaper and readily available electron-rich or -neutral *o*-chloro/bromoanilines as the reaction partners by using X-Phos, a bulky electron-rich monophosphine, as the ligand.[8,9] However, under optimized conditions, reaction of electron-poor *o*-chloro/bromoanilines with aldehydes gave the desired products in unsatisfactory yields (around 10–20%), together with significant amounts of the reduced arene compounds.

SYNTHESIS 2008, No. 24, pp 3981–3987
Advanced online publication: 01.12.2008
DOI: 10.1055/s-0028-1083225; Art ID: F12608SS

There are examples in the literature of electron-rich aryl chlorides behaving differently than electron-deficient ones in palladium-catalyzed reactions.[10] Considering the complexity of this palladium-catalyzed process, we thought that by testing combinations of ligands, solvents and bases, we could discover an efficient condition for the annulation of electron-poor *o*-chloro/bromoanilines with aldehydes. Herein, we are pleased to report a general procedure for the synthesis of highly benzofunctionalized 2-unsubstituted indoles and azaindoles by reaction of electron-poor *o*-chloro/bromoanilines and *o*-chloroaminopyridines with a variety of aldehydes.

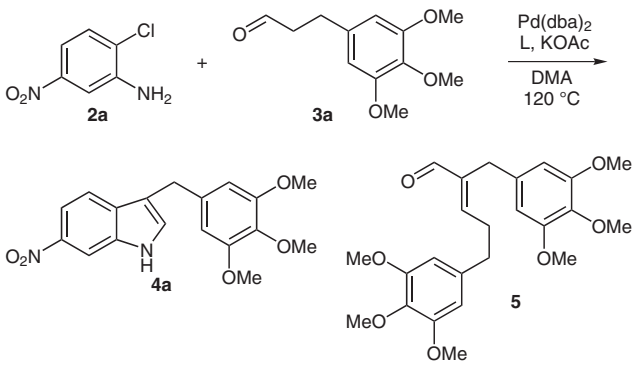
In our initial attempts, ligands **1a–l** (Figure 1) were tested for the reaction of 2-chloro-5-nitroaniline (**2a**) with 3-(3,4,5-trimethoxyphenyl)propanal (**3a**) in the presence of $Pd(dba)_2$ and KOAc in DMA (Scheme 1 and Table 1). Quickly, it was revealed that the choice of the ligand was again critical. Of the ligands tested, t-$Bu_3P{\cdot}HBF_4$ was the most efficient and afforded the desired indole **4a** in 43% yield, albeit with the formation of 12% dechloro product (entry 12). The addition of water, presumably preventing aldol condensation of aldehydes, gave the same yield of the desired product (entry 13). The effects on yield with varying equivalents of aldehyde or aniline were also examined. When 3.0 equivalents of aldehyde were used, the yield increased to 58% (entry 14) contemporaneous with the formation of 2-(3,4,5-trimethoxybenzyl)-5-(3,4,5-trimethoxyphenyl)pent-2-enal (**5**) in 44% (Scheme 1). The use of 5 mol% of commercially available $[Pd(t\text{-}Bu_3P)_2]$ gave result similar to that of $Pd(dba)_2$ and t-$Bu_3P{\cdot}HBF_4$ (entry 16). We also tested this reaction under microwave



1a $R^1 = R^2 = R^3 = H$, R = *t*-Bu
1b $R^1 = R^2 = R^3 = H$, R = Cy
1c $R^1 = NMe_2$, $R^2 = R^3 = H$, R = *t*-Bu
1d $R^1 = NMe_2$, $R^2 = R^3 = H$, R = Cy
1e $R^1 = Me$, $R^2 = R^3 = H$, R = *t*-Bu
1f $R^1 = Me$, $R^2 = R^3 = H$, R = Cy
1g $R^1 = R^2 = R^3 = i$-Pr, R = *t*-Bu
1h $R^1 = R^2 = R^3 = i$-Pr, R = Cy

1k PCy_3
1l t-$Bu_3P{\bullet}HBF_4$

Figure 1 Ligands tested for the annulation of 2-chloro-5-nitroaniline (**2a**) with 3-(3,4,5-trimethoxyphenyl)propanal (**3a**)



Scheme 1 Annulation of 2-chloro-5-nitroaniline (**2a**) with 3-(3,4,5-trimethoxyphenyl)propanal (**3a**)

irradiation at 160 °C for 30 minutes, but it did not show any improvement.

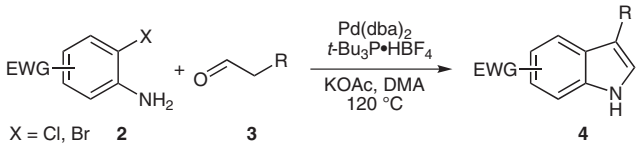
Once reliable conditions to synthesize indoles were established, we proceeded to examine the substrate scope with respect to electron-deficient *o*-chloroanilines (Table 2). The method proved to be effective for a range of electron-deficient *o*-chloroanilines bearing a variety of functional groups, such as nitro (entries 1, 2 and 3), ester (entries 5 and 6), keto (entry 7), and trifluoromethyl (entry 8). The steric hindrance in **2b** could not be suppressed under these conditions, and the yield was not increased even by varying bases, solvents, and equivalents of substrate (entry 4). As expected, the electron-deficient *o*-bromoanilines reacted with similar efficiency (entries 9, 10, and 11). The major side product frequently observed is the dehalogenated starting material, the result of a reductive process. Not surprisingly, this catalyst system proved to be also effective, though inferior relative to X-phos, for the reaction of electron-rich or -neutral *o*-chloroanilines with aldehydes and gave the desired indoles in moderate yields.[9a,6b,11]

Table 1 Optimization of Conditions for the Annulation of 2-Chloro-5-nitroaniline (**2a**) with 3-(3,4,5-Trimethoxyphenyl)propanal (**3a**)[a]

Entry	Ligand	Base	Yield (%)[b]
1	**1a**	KOAc	<1
2	**1b**	KOAc	<1
3	**1c**	KOAc	<1
4	**1d**	KOAc	<5
5	**1e**	KOAc	<1
6	**1f**	KOAc	14
7	**1g**	KOAc	<1
8	**1h**	KOAc	15
9	**1i**	KOAc	<5
10	**1j**	KOAc	<5
11	**1k**	KOAc	<1
12	**1l**	KOAc	43
13[c]	**1l**	KOAc	43
14	**1l**	KOAc	58[d]
15	**1l**	DABCO	22
16	–	KOAc	58[e]

[a] General reaction conditions: concentration = 0.2 M in DMA. $Pd(dba)_2$ (0.05 equiv), ligand (0.10 equiv), 2-chloro-5-nitroaniline (**2a**; 1.0 equiv), 3-(3,4,5-trimethoxyphenyl)propanal (**3a**; 1.0 equiv), and KOAc (3.0 equiv) at 120 °C.
[b] Isolated yield.
[c] H_2O (13%) was used as an additive.
[d] Aldehyde = 3.0 equiv.
[e] $Pd(t\text{-}Bu_3P)_2$ = 0.05 equiv and aldehyde = 3.0 equiv.

Table 2 Pd-Catalyzed Indole Synthesis by Annulation of Electron-Poor *o*-Chloro/bromoanilines with Aldehydes[a]



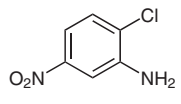
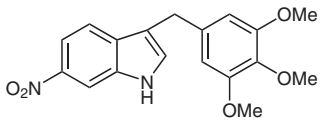
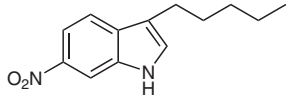
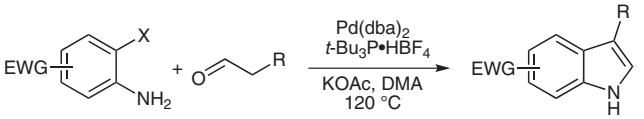
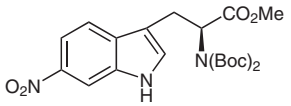
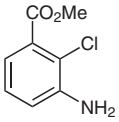
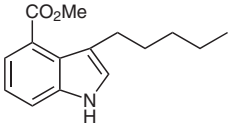
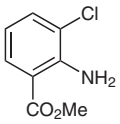
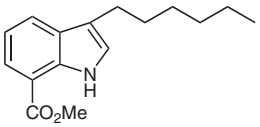
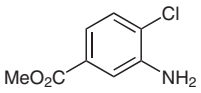
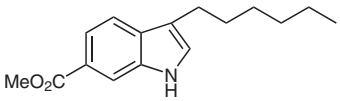
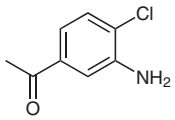
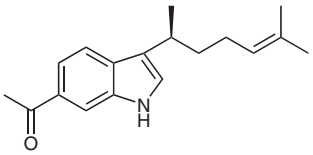
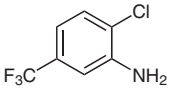
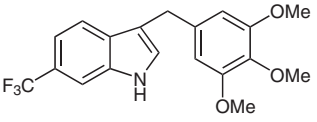
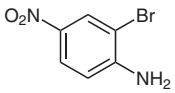
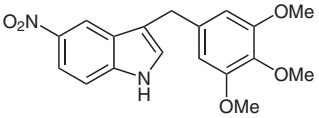
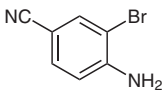
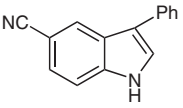
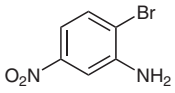
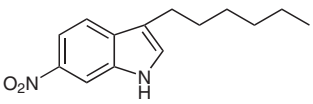
Entry	*o*-Chloro/bromoaniline	Product	Yield (%)[b]
1	 **2a**	 **4a**	58
2	**2a**	 **4b**	65

Table 2 Pd-Catalyzed Indole Synthesis by Annulation of Electron-Poor *o*-Chloro/bromoanilines with Aldehydes[a] (continued)



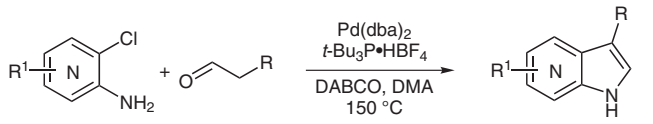
X = Cl, Br **2** **3** **4**

Entry	*o*-Chloro/bromoaniline	Product	Yield (%)[b]
3	**2a**	 **4c**	65
4	 **2b**	 **4d**	25
5	 **2c**	 **4e**	71
6	 **2d**	 **4f**	71
7	 **2e**	 **4g**	41
8	 **2f**	 **4h**	51
9	 **2g**	 **4i**	41
10	 **2h**	 **4j**	61
11	 **2i**	 **4k**	68

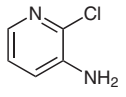
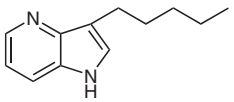
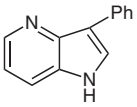
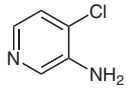
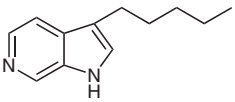
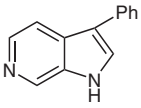
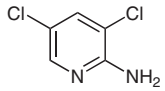
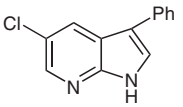
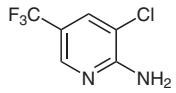
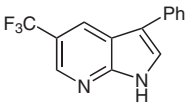
[a] General reaction conditions: concentration = 0.2 M in DMA. $Pd(dba)_2$ (0.05 equiv), *t*-$Bu_3P{\cdot}HBF_4$ (0.10 equiv), *o*-chloro/bromoaniline (1.0 equiv), aldehyde (3.0 equiv), KOAc (3.0 equiv) at 120 °C.
[b] Isolated yield.

Azaindole ring systems have attracted considerable interest due to their applications in medicinal relevance, material synthesis, coordination chemistry, and they are frequently exploited as indole bioisosteres in the design of biologically interesting molecules.[12,13] Synthetic routes to azaindole using classical indole formation methods are often not efficient or even fail because of the electron-deficient nature of the pyridine ring. More recently, most practical and mild methods for the synthesis of azaindoles are based on transition metal catalysis. Therefore, we sought to extend our palladium-catalyzed methodology to the synthesis of azaindoles.

Table 3 Pd-Catalyzed Azaindole Synthesis by Annulation of *o*-Chloroaminopyridines with Aldehydes[a]



6 **3** **7**

Entry	*o*-Chloroaminopyridine	Product	Yield (%)[b]
1	 **6a**	 **7a**	44
2	**6a**	 **7b**	68
3	 **6b**	 **7c**	76[c]
4	**6b**	 **7d**	50[c]
5	 **6c**	 **7e**	42
6	 **6d**	 **7f**	31 56[d]

[a] General reaction conditions: concentration = 0.2 M in DMA. $Pd(dba)_2$ (0.05 equiv), t-$Bu_3P{\cdot}HBF_4$ (0.10 equiv), *o*-chloroaminopyridine (1.0 equiv), aldehyde (3.0 equiv), and DABCO (3.0 equiv) at 150 °C.
[b] Isolated yield.
[c] At 120 °C.
[d] KOAc = 3.0 equiv at 120 °C.

We next examined the reaction of electron-deficient *o*-chloroaminopyridines under the aforementioned conditions. Soon it was proved that these substrates are more challenging. Only 2-amino-3-chloro-5-trifluoromethylpyridine (**6d**) afforded the desired product in 56% yield (Table 3, entry 6), while other substrates did not react efficiently and gave the azaindoles in low yields.

We envisioned that the inefficiency of the reaction maybe due to electronic effects of pyridine ring or to coordination of Pd by the lone pair of electrons on the pyridine nitrogen at some point of the catalytic cycle. Thus, this effect would be reduced by increasing the temperature or choosing the proper base. As anticipated, eventually, it was found that this problem could be alleviated by using DABCO as a base and using a higher temperature (150 °C). It should be emphasized that the yield was lower under microwave irradiation conditions than thermal heating conditions in this one-pot azaindole synthesis.[14]

To illustrate the scope of this methodology, a variety of azaindoles were synthesized under our standard conditions (Table 3). Both 3-amino-2-chloropyridine (**6a**) and 3-amino-4-chloropyridine (**6b**) could react with aliphatic aldehyde and phenylacetaldehyde to give the desired products (entries 1–4). However, 2-amino-3,5-dichloropyridine (**6c**) and 2-amino-3-chloro-5-trifluoromethylpyridine (**6d**) only reacted with phenylacetaldehyde, but not with aliphatic aldehydes (entries 5 and 6). Unfortunately, to date, all attempts to perform this reaction with 4-amino-3-bromopyridine have been unsuccessful.

In summary, we have developed a practical one-pot procedure for the synthesis of highly benzofunctionalized 2-unsubstituted indoles and azaindoles by the reaction of electron-poor *o*-chloro/bromoanilines and *o*-chloroaminopyridines with a variety of aldehydes. Coupled with the previous results of Jia and Zhu, this allows rapid access to a variety of 2-unsubstituted indoles and azaindoles starting from simple and easily accessible precursors. Further applications of this chemistry to the synthesis of natural products are currently in progress and will be reported in due course.

Melting points were recorded using XT-4A digital micro-melting apparatus. IR spectra were recorded on a NEXUS-470 FRIR (Nicolet) spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker AC-300 spectrometer, JEOL JNM-AL 300 spectrometer, and Varian INOVA-500 spectrometer. High resolution mass spectra (HRMS) were obtained using a Bruker APEX IV FT-MS (ESI) instrument. Flash chromatography was performed using silica gel from Qingdao Mar. Chem. Ind. Co. Ltd. (200–300 mesh). Anilines **2a**,**f–i** and *o*-chloroaminopyridines **6a–d** are commercially available. Anilines **2c–e** were prepared following known procedures.

Methyl 3-Amino-2-chlorobenzoate (2b)

To a solution of 2-chloro-3-nitrobenzoic acid (403 mg, 2.0 mmol) in anhyd MeOH (8 mL) was added dropwise $SOCl_2$ at 0 °C (ice bath). After the addition was over, the mixture was warmed to 40 °C and stirred overnight until the starting material had disappeared (monitored by TLC). The mixture was then evaporated to dryness. The product was used directly for the next step without purification. The above methyl 2-chloro-3-nitrobenzoate and $SnCl_2{\cdot}2H_2O$ (2.26

g, 10.0 mmol, 5.0 equiv) was dissolved in anhyd EtOH (5 mL) and the mixture was stirred at 70 °C for 30 min under argon. The mixture was cooled to r.t. and made slightly basic (pH 7–8) by aq sat. $NaHCO_3$. The mixture was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with brine (3 × 15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by silica gel eluting with 60% CH_2Cl_2 in petroleum ether (bp 60–90 °C); yield: 362 mg (98%); yellowish oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, *J* = 7.5 Hz, 1 H), 7.00 (t, *J* = 7.5 Hz, 1 H), 6.79 (d, *J* = 7.5 Hz, 1 H), 4.16 (br s, 2 H), 3.83 (s, 3H).

3-(3,4,5-Trimethoxybenzyl)-6-nitro-1*H*-indole (4a); Typical Procedure

A solution of 2-chloro-5-nitroaniline (**2a**; 52 mg, 0.3 mmol), 3-(3,4,5-trimethoxyphenyl)propanal (**3a**; 202 mg, 0.9 mmol), and KOAc (88 mg, 0.9 mmol) in anhyd DMA (1.5 mL) was degassed for 20 min. $Pd(dba)_2$ (8.6 mg, 0.015 mmol) and *t*-$Bu_3P{\cdot}HBF_4$ (8.7 mg, 0.03 mmol) were added, and the resulting mixture was heated at 120 °C for 9 h. The mixture was cooled to r.t. and diluted with H_2O (15 mL) and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine (3 × 15 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of the crude product by flash column chromatography (FCC) (PE–EtOAc, 7:3) provided the desired product **4a**; yield: 59.5 mg (58%); mp 166–167 °C (Table 2).

IR ($CHCl_3$): 3361, 2936, 1590, 1505, 1456, 1418, 1311, 1240, 1123, 1057, 1001, 963, 895, 822 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.90 (br s, 1 H), 8.33 (d, *J* = 2.1 Hz, 1 H), 7.98 (dd, *J* = 2.1, 8.7 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1 H), 7.25 (d, *J* = 2.7 Hz, 1 H), 6.49 (s, 2 H), 4.07 (s, 2 H), 3.84 (s, 3 H), 3.80 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.2, 143.3, 136.3, 136.0, 134.9, 132.0, 128.5, 118.9, 116.5, 114.9, 108.2, 105.6, 60.9, 56.1, 31.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_2O_5$ + Na (M + Na)$^+$: 365.1113; found: 365.1130.

2-(3,4,5-Trimethoxybenzyl)-5-(3,4,5-trimethoxyphenyl)pent-2-enal (5)

This product was formed along with **4a** in the above reaction. Product **5** was isolated by FCC (PE–EtOAc, 7:3); yield: 85 mg (44%); yellowish oil.

IR ($CHCl_3$): 2938, 1681, 1588, 1506, 1456, 1420, 1328, 1236, 1123, 1005, 907, 821 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.46 (s, 1 H), 6.63 (t, *J* = 7.0 Hz, 1 H), 6.35 (s, 2 H), 6.33 (s, 2 H), 3.81 (s, 9 H), 3.77 (s, 9 H), 3.53 (s, 2 H), 2.69–2.73 (m, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.3, 154.6, 153.1, 153.0, 142.4, 136.4, 136.3, 135.9, 134.5, 105.2, 105.1, 60.64, 60.62, 55.93, 55.90, 34.6, 30.9, 29.7.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{30}O_7$ + Na (M + Na)$^+$: 453.1889; found: 453.1909.

6-Nitro-3-pentyl-1*H*-indole (4b)

Purified by FCC (PE–EtOAc, 8:1); mp 114–116 °C.

IR ($CHCl_3$): 3336, 2922, 2852, 1501, 1457, 1321, 1301, 1287, 1107, 1058, 887, 821 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.54 (br s, 1 H), 8.34 (d, *J* = 2.1 Hz, 1 H), 8.01 (dd, *J* = 2.1, 9.0 Hz, 1 H), 7.63 (d, *J* = 9.0 Hz, 1 H), 7.29 (s, 1 H), 2.76 (t, *J* = 7.2 Hz, 2 H), 1.71 (m, 2 H), 1.40–1.25 (m, 4 H), 0.91 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 134.7, 132.3, 127.2, 118.8, 118.3, 114.6, 108.0, 31.7, 29.8, 24.8, 22.5, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{16}N_2O_2$ + Na (M + Na)$^+$: 255.1109; found: 255.1122.

Methyl 3-Pentyl-1*H*-indole-4-carboxylate (4d)

Purified by FCC (PE–EtOAc, 5:1); oil.

IR (KBr): 3367, 2954, 2928, 2857, 1702, 1615, 1435, 1345, 1277, 1200, 1143, 922, 806, 777, 750 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21 (br s, 1 H), 7.56 (dd, *J* = 0.6, 7.5 Hz, 1 H), 7.46 (dd, *J* = 0.6, 7.5 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 7.07 (d, *J* = 2.4 Hz, 1 H), 3.95 (s, 3 H), 2.83 (t, *J* = 6.9 Hz, 2 H), 1.50–1.58 (m, 2 H), 1.24–1.33 (m, 4 H), 0.87 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.4, 137.7, 124.3, 124.2, 124.1, 122.1, 120.7, 117.6, 115.0, 51.9, 31.9, 30.2, 27.2, 22.7, 14.1.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{20}NO_2$ (M + H)$^+$: 246.14886; found: 246.14839.

Methyl 3-Hexyl-1*H*-indole-7-carboxylate (4e)

Purified by FCC (PE–EtOAc, 60:1); mp 47–48 °C.

IR ($CHCl_3$): 3422, 2948, 2924, 2853, 1686, 1587, 1439, 1267, 1200, 1142, 1075, 1059, 990, 898, 807 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.59 (br s, 1 H), 7.89 (d, *J* = 7.5 Hz, 1 H), 7.83 (d, *J* = 7.5 Hz, 1 H), 7.14 (t, *J* = 7.5 Hz, 1 H), 7.08 (br s, 1 H), 3.99 (s, 3 H), 2.77 (t, *J* = 8.0 Hz, 2 H), 1.69–1.75 (m, 2 H), 1.40–1.42 (m, 2 H), 1.32–1.35 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 136.2, 128.9, 124.6, 124.1, 122.0, 118.2, 117.1, 112.3, 51.8, 31.7, 30.2, 29.3, 25.0, 22.7, 14.1.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{22}NO_2$ (M + H)$^+$: 260.1651; found: 260.1658.

Methyl 3-Hexyl-1*H*-indole-6-carboxylate (4f)

Purified by FCC (PE–EtOAc, 10:1); mp 83–84 °C.

IR ($CHCl_3$): 3322, 2948, 2922, 2854, 1689, 1623, 1563, 1503, 1458, 1434, 1356, 1302, 1272, 1210, 1086, 984, 879, 827 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.40 (br s, 1 H), 8.13 (d, *J* = 1.5 Hz, 1 H), 7.82 (dd, *J* = 1.5 8.4 Hz, 1 H), 7.63 (d, *J* = 8.4 Hz, 1 H), 7.13 (d, *J* = 2.4 Hz, 1 H), 3.95 (s, 3 H), 2.76 (t, *J* = 7.5 Hz, 2 H), 1.73 (m, 2 H), 1.42 (m, 2 H), 1.30–1.43 (m, 4 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4, 135.6, 131.2, 124.7, 123.3, 120.0, 118.5, 117.5, 113.5, 51.9, 31.7, 30.1, 29.2, 25.0, 22.6, 14.1.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{21}NO_2$ + Na (M + Na)$^+$: 282.1470; found: 282.1461.

1-{3-[(*S*)-6-Methylhept-5-en-2-yl]-1*H*-indol-6-yl}ethanone (4g)

Purified by FCC (PE–EtOAc, 8:1); mp 60–62 °C; $[\alpha]_D^{23}$ +16 (*c* 0.50, $CHCl_3$).

IR ($CHCl_3$): 3322, 2959, 2919, 2852, 1656, 1614, 1536, 1495, 1454, 1356, 1312, 1270, 1206, 1106, 816 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (br s, 1 H), 8.07 (s, 1 H), 7.73 (dd, *J* = 1.2, 8.4 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 1 H), 7.17 (d, *J* = 2.4 Hz, 1 H), 5.14 (t, *J* = 6.9 Hz, 1 H), 3.01 (m, 1 H), 2.66 (s, 3 H), 1.88–2.04 (m, 2 H), 1.68–1.76 (m, 1 H), 1.60 (s, 3 H), 1.57–1.61 (m, 1 H), 1.52 (s, 3 H), 1.35 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.6, 136.0, 131.5, 131.1, 130.7, 124.5, 124.2, 123.0, 119.3, 119.0, 112.2, 37.7, 30.3, 26.8, 26.1, 25.7, 21.4, 17.6.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{24}NO$ (M + H)$^+$: 270.1858; found: 270.1860.

3-(3,4,5-Trimethoxybenzyl)-6-(trifluoromethyl)-1*H*-indole (4h)
Purified by FCC (PE–EtOAc, 4:1); mp 138–139 °C.

IR ($CHCl_3$): 3348, 1933, 1590, 1504, 1457, 1421, 1332, 1233, 1157, 1103, 1051, 1001, 915, 813 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.53 (br s, 1 H), 7.64 (s, 1 H), 7.61 (d, *J* = 8.5 Hz, 1 H), 7.33 (dd, *J* = 1.0, 8.5 Hz, 1 H), 7.09 (d, *J* = 2.0 Hz, 1 H), 6.52 (s, 2 H), 4.08 (s, 2 H), 3.85 (s, 3 H), 3.80 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.1, 136.5, 136.1, 135.3, 129.6, 125.2 (q, *J* = 271.5 Hz), 125.2, 124.0 (q, *J* = 31.8 Hz), 119.3, 115.9 (q, *J* = 3.5 Hz), 115.7, 108.7 (q, *J* = 4.4 Hz), 105.6, 60.8, 56.0, 31.8.

HRMS (ESI): *m*/*z* calcd for $C_{19}H_{18}F_3NO_3$ + Na (M + Na)$^+$: 388.1136; found: 388.1128.

3-(3,4,5-Trimethoxybenzyl)-5-nitro-1*H*-indole (4i)
Purified by FCC (PE–EtOAc, 5:2); mp 167–168 °C.

IR ($CHCl_3$): 3338, 2927, 1591, 1506, 1458, 1421, 1327, 1239, 1125, 1002, 812 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.76 (br s, 1 H), 8.54 (d, *J* = 2.0 Hz, 1 H), 8.08 (dd, *J* = 2.0, 9.0 Hz, 1 H), 7.38 (d, *J* = 9.0 Hz, 1 H), 7.09 (s, 1 H), 6.52 (s, 2 H), 4.08 (s, 2 H), 3.84 (s, 3 H), 3.81 (s, 6 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.3, 141.6, 139.4, 136.4, 135.8, 126.8, 125.4, 118.3, 117.8, 116.4, 111.1, 105.7, 60.9, 56.1, 31.7.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{18}N_2O_5$ + Na (M + Na)$^+$: 365.1113; found: 365.1097.

3-Phenyl-1*H*-indole-5-carbonitrile (4j)
Purified by FCC (PE–EtOAc, 5:1); mp 158–159 °C.

IR ($CHCl_3$): 3287, 2221, 1600, 1544, 1468, 1450, 1427, 1359, 1265, 1246, 1113, 970, 912, 876 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.83 (br s, 1 H), 8.27 (s, 1 H), 7.61 (d, *J* = 7.2 Hz, 2 H), 7.46–7.52 (m, 5 H), 7.36 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 134.0, 129.0, 127.5, 126.7, 125.7, 125.6, 125.1, 123.8, 120.8, 119.1, 112.4, 103.1.

HRMS (ESI): *m*/*z* calcd for $C_{16}H_{14}N_2O$ + Na (M + MeOH + Na)$^+$: 273.1004; found: 273.1009.

3-Hexyl-6-nitro-1*H*-indole (4k)
Purified by FCC (PE–EtOAc, 16:1); mp 102–103 °C.

IR ($CHCl_3$): 3360, 2921, 2856, 1501, 1463, 1325, 1103, 1057, 877, 831 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (br s, 1 H), 8.36 (d, *J* = 2.1 Hz, 1 H), 8.01 (dd, *J* = 2.1, 9.0 Hz, 1 H), 7.63 (d, *J* = 9.0 Hz, 1 H), 7.29 (d, *J* = 2.4 Hz, 1 H), 2.76 (t, *J* = 7.2 Hz, 2 H), 1.70 (m, 2 H), 1.28–1.42 (m, 6 H), 0.89 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 143.1, 134.7, 132.4, 127.3, 118.8, 118.3, 114.6, 108.1, 31.7, 30.0, 29.2, 24.8, 22.6, 14.1.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{18}N_2O_2$ + Na (M + Na)$^+$: 269.1266; found: 269.1268.

3-Pentyl-1*H*-pyrrolo[3,2-*b*]pyridine (7a); Typical Procedure
A solution of 3-amino-2-chloropyridine (**6a**; 39 mg, 0.3 mmol), heptanal (103 mg, 0.9 mmol), and DABCO (101 mg, 0.9 mmol) in anhyd DMA (1.5 mL) was degassed for 20 min. $Pd(dba)_2$ (8.6 mg, 0.015 mmol) and *t*-$Bu_3P{\cdot}HBF_4$ (8.7 mg, 0.03 mmol) were added, and the resulting mixture was heated at 150 °C for 9 h. The mixture was cooled to r.t. and diluted with H_2O (15 mL). The aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine (3 × 15 mL), dried (Na_2SO_4), and evaporated to dryness under reduced pressure. Purification of the crude product by FCC (PE–EtOAc, 4:1) provided the desired product **7a**; yield: 25 mg (44%); oil (Table 3).

IR (KBr): 3132, 3094, 3045, 2921, 2854, 2812, 1724, 1620, 1493, 1462, 1415, 1371, 1292, 1122, 1101, 897, 817, 784, 769, 727 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.87 (br s, 1 H), 8.48 (dd, *J* = 1.2, 4.5 Hz, 1 H), 7.63 (dd, *J* = 1.2, 8.1 Hz, 1 H), 7.25 (d, *J* = 2.7 Hz, 1 H), 7.09 (dd, *J* = 4.5, 8.1 Hz, 1 H), 2.87 (t, *J* = 7.2 Hz, 2 H), 1.76 (m, 2 H), 1.36 (m, 4 H), 0.88 (t, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, CD_3OD): δ = 145.6, 141.9, 131.3, 127.5, 120.3, 117.2, 116.8, 32.9, 31.2, 24.8, 23.7, 14.5.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}N_2$ (M + H)$^+$: 189.13863; found: 189.13787.

3-Phenyl-1*H*-pyrrolo[3,2-*b*]pyridine (7b)
Purified by FCC (PE–EtOAc, 4:1); oil.

^1H NMR (300 MHz, CD_3OD): δ = 8.36 (dd, *J* = 1.5, 4.8 Hz, 1 H), 7.93 (dt, *J* = 2.0, 8.1 Hz, 2 H), 7.83 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.82 (s, 1 H), 7.39 (m, 2 H), 7.25–7.17 (m, 2 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 144.4, 143.5, 135.7, 131.7, 129.5, 128.3, 127.6, 126.9, 120.6, 117.8, 117.5.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}N_2$ (M + H)$^+$: 195.09168; found: 195.09231.

3-Pentyl-1*H*-pyrrolo[2,3-*c*]pyridine (7c)
Purified by FCC (CH_2Cl_2–MeOH, 15:1); oil.

IR (KBr): 3141, 3091, 2956, 2924, 2854, 2766, 1615, 1501, 1459, 1219, 1123, 1037, 1025, 888, 809, 790 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.93 (br s, 1 H), 8.80 (s, 1 H), 8.22 (d, *J* = 5.4 Hz, 1 H), 7.54 (d, *J* = 5.4 Hz, 1 H), 7.24 (s, 1 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 1.70 (m, 2 H), 1.36 (m, 4 H), 1.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.5, 133.9, 133.6, 132.6, 126.6, 116.3, 113.9, 31.7, 29.9, 24.7, 22.5, 14.0.

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{17}N_2$ (M + H)$^+$: 189.13863; found: 189.13785.

3-Phenyl-1*H*-pyrrolo[2,3-*c*]pyridine (7d)
Purified by FCC (CH_2Cl_2–MeOH, 12:1); oil.

^1H NMR (300 MHz, CD_3OD): δ = 8.72 (s, 1 H), 8.12 (d, *J* = 5.4 Hz, 1 H), 7.86 (dd, *J* = 0.9, 5.4 Hz, 1 H), 7.79 (br s, 1 H), 7.65 (dt, *J* = 1.5, 8.7 Hz, 2 H), 7.24 (dt, *J* = 1.5, 8.7 Hz, 2 H), 7.26 (tt, *J* = 1.5, 8.7 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 138.4, 136.0, 135.6, 135.1, 131.9, 129.9, 128.7, 128.1, 127.2, 118.2, 115.6.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{11}N_2$ (M + H)$^+$: 195.09168; found: 195.09213.

5-Chloro-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (7e)
Purified by FCC (PE–EtOAc, 4:1); oil.

IR (KBr): 3451, 3120, 3023, 2879, 1599, 1565, 1531, 1478, 1410, 1275, 1126, 910, 758, 699, 664 cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 12.22 (s, 1 H), 8.34 (d, *J* = 2.1 Hz, 1 H), 8.30 (d, *J* = 2.1 Hz, 1 H), 8.01 (d, *J* = 2.7 Hz, 1 H), 7.74 (dt, *J* = 1.5, 8.4 Hz, 2 H), 7.46 (dt, *J* = 1.5, 8.4 Hz, 2 H), 7.28 (tt, *J* = 1.5, 8.4 Hz, 1 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 147.4, 141.0, 134.3, 128.9, 126.6, 126.3, 126.0, 125.8, 123.0, 118.1, 114.2.

5-(Trifluoromethyl)-3-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (7f)
Purified by FCC (PE–EtOAc, 4:1); mp 209–211 °C.

IR ($CHCl_3$): 3129, 2883, 1591, 1536, 1348, 1307, 1281, 1114, 1070, 973, 916, 902, 829 cm^{-1}.

^{1}H NMR (300 MHz, acetone-d_6): δ = 11.46 (br s, 1 H), 8.63 (d, *J* = 1.8 Hz, 1 H), 8.57 (d, *J* = 1.8 Hz, 1 H), 8.00 (s, 1 H), 7.76 (dt, *J* = 1.5, 7.5 Hz, 2 H), 7.48 (t, *J* = 1.5, 7.5 Hz, 2 H), 7.32 (tt, *J* = 1.5, 7.5 Hz, 1 H).

^{13}C NMR (75 MHz, acetone-d_6): δ = 151.6, 141.0 (q, *J* = 3.8 Hz), 135.1, 129.9, 127.9, 127.4, 126.3, 126.2 (q, *J* = 271.0 Hz), 125.9 (q, *J* = 3.8 Hz), 119.7 (q, *J* = 31.6 Hz), 117.8, 117.6.

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{10}F_3N_2$ $(M + H)^+$: 263.0785; found: 263.0796.

Acknowledgment

We are grateful to Peking University Health Science Center and the National Natural Science Foundation of China (20842004) for their generous financial support of this research. We also thank Prof. Jieping Zhu (ICSN, Gif) for helpful discussions and generous gift of ligands.

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