PdX_2/CuX_2-Catalyzed Annulation of 2-Ethynylbenzeneamines: Selective Synthesis of 2-Substituted 3-Halo-1*H*-indoles

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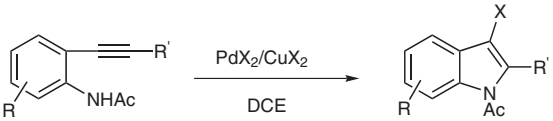
Received 6 March 2007; revised 10 April 2007

Abstract: A novel and effective protocol for the synthesis of 2-substituted 3-halo-1*H*-indoles by PdX_2/CuX_2-catalyzed annulations of 2-ethynylbenzeneamines has been developed. In the presence of PdX_2 and CuX_2, the annulation reactions of a variety of 2-ethynylbenzeneamines were conducted in moderate to good yields. It is noteworthy that only *N*-acetyl-protected 2-ethynylbenzeneamines can undergo the reaction successfully.

Key words: palladium(II) halide, copper(II) halide, annulation, 2-ethynylbenzeneamine, 2-substituted 3-halo-1*H*-indoles

Indoles, in particular 3-halo-substituted ones, have attracted considerable interest on their synthesis because this structural motif is common to a variety of biologically active alkaloids and important pharmaceuticals and valuable intermediates for organic synthesis.[1–7] The most common synthetic approach to 3-haloindoles is direct halogenation of indoles with *N*-halosuccinimides,[3] halogen,[4] POX_3/imidazole,[5] and others.[6] However, the reaction conditions of these methods generally involve highly acidic or basic media. Other drawbacks of these methods include poor selectivity, overhalogenation, sensitivity to air/water, and limited functional group tolerance. Recently, the electrophilic cyclizations of 2-ethynylbenzeneamines proved especially efficient for the synthesis of 3-haloindoles.[7] However, only 3-iodoindoles were prepared from the reaction of the corresponding 2-ethynylbenzeneamines with I_2 or IPy_2BF_4. Therefore, the development of a new and general approach for forming 3-haloindoles is still significant. Very recently, we have reported a novel and selective palladium-catalyzed annulation of 2-alkynylphenols for the synthesis of 2-substituted 3-halobenzo[*b*]furans.[8] In the presence of PdX_2 and CuX_2 (X = Br, Cl), 2-substituted 3-halobenzo[*b*]furans were selectively obtained as the major products using HEt_3NX as the promoter. Herein, we wish to report that the PdX_2/CuX_2 system was extended to the annulation of 2-ethynylbenzeneamines successfully to synthesize 2-substituted 3-haloindoles in moderate to good yields. This process represents a novel approach for the synthesis of 2-substituted 3-haloindoles (Scheme 1).



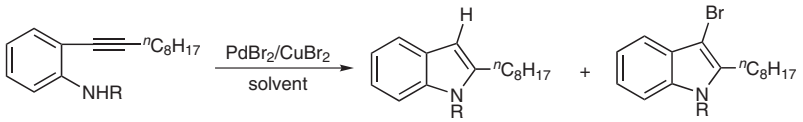
X = Cl, Br R = H, F, Cl, NO_2
R' = $^n C_8H_{17}$, Ph, ^{t}Bu, CH_2CH_2OAc

Scheme 1

In an earlier report,[8] we demonstrated that with the aid of HEt_3NX, 2-substituted 3-halobenzo[*b*]furans were prepared selectively from the annulation of 2-alkynylphenols using PdX_2 and CuX_2 as the catalytic system. We have since extended the application of the $PdX_2/CuX_2/HEt_3NX$ system to the annulation of 2-ethynylbenzeneamines (Table 1). As expected, the $PdX_2/CuX_2/HEt_3NX$ system was effective for the annulation of *N*-[2-(dec-1-ynyl)phenyl]acetamide (**1a**) using DCE (1,2-dichloroethane) as the solvent. In the presence of $PdBr_2$ (5 mol%), $CuBr_2$ (3 equiv) and HEt_3NI (0.2 equiv), 91% GC yield of 1-(3-bromo-2-octyl-1*H*-indol-1-yl)ethanone (**3a**) was obtained along with 8% GC yield of a by-product, 1-(2-octyl-1*H*-indol-1-yl)ethanone (**2a**), from the reaction of substrate **1a** (entry 1). The yield of the target product **3a** was decreased to some extent when HEt_3NBr, NaOH, or AcOH was used to instead HEt_3NI (entries 2–4). *N*-[2-(Dec-1-ynyl)phenyl]acetamide (**1a**) could undergo the annulation reaction smoothly without HEt_3NI (entry 5). Subsequently, other solvents including MeCN, CH_2Cl_2 and THF were examined, and they were less effective for the annulation reaction than DCE (entries 5–8). Screening results showed that three equivalents of $CuBr_2$ provided the best results (entries 5 and 9–11). Without $CuBr_2$, 1-(2-octyl-1*H*-indol-1-yl)ethanone (**2a**) was isolated as the major product together with 5% GC yield of the target product **3a** (entry 9), whereas the yield of the target product **3a** was enhanced sharply when $CuBr_2$ was added (32% yield/2 equiv of $CuBr_2$, 96% yield/3 equiv of $CuBr_2$ and 90% yield/5 equiv of $CuBr_2$; entries 5, 10 and 11).[9] The other blank experiments indicated that both $PdBr_2$ and $CuBr_2$ played a curial role in the reactions. Without a Pd source, a messy result was observed in the presence of $CuBr_2$ alone (entry 12), but in the absence of $CuBr_2$ 1-(2-octyl-1*H*-indol-1-yl)ethanone (**2a**) was obtained as the major product using 5 mol% of $PdBr_2$ (entry 9). Note that good isolated yield of **3a** is still achieved at room temperature after prolonging

SYNTHESIS 2007, No. 12, pp 1841–1847
Advanced online publication: 08.06.2007
DOI: 10.1055/s-2007-983717; Art ID: F04907SS

Table 1 Palladium-Catalyzed Annulation Reactions of 2-(Dec-1-ynyl)benzeneamines[a]



1 2 3

Entry	R	Additive (equiv)	Time (h)	GC yield (%)[b]	
				2a	**3a**
1	Ac (**1a**)	Et_3NHI (0.2)	DCE	8 (6)	91 (88)
2	Ac (**1a**)	Et_3NHBr (0.2)	DCE	35	17
3	Ac (**1a**)	NaOH (2.0)	DCE	64	21
4	Ac (**1a**)	AcOH (2.0)	DCE	21	64
5	Ac (**1a**)	–	DCE	0	96(92)
6	Ac (**1a**)	–	MeCN	21	12
7	Ac (**1a**)	–	CH_2Cl_2	34	23
8[c]	Ac (**1a**)	–	THF	nd	nd
9[d]	Ac (**1a**)	–	DCE	95 (94)	5 (3)
10[e]	Ac (**1a**)	–	DCE	30	32
11[f]	Ac (**1a**)	–	DCE	10 (8)	90 (88)
12[c,g]	Ac (**1a**)	–	DCE	nd	nd
13[h]	Ac (**1a**)	–	DCE	(7)	(89)
14[c]	H (**1b**)	–	DCE	nd	nd
15[c]	PhCO (**1c**)	–	DCE	nd	nd
16[c]	Bn (**1d**)	–	DCE	nd	nd

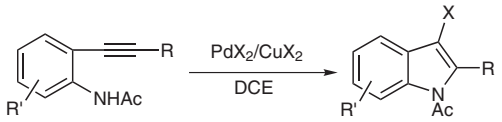
[a] Unless otherwise indicated, the reaction conditions were as follows: **1** (0.3 mmol), $PdBr_2$ (5 mol%) and $CuBr_2$ (3 equiv) in DCE (5 mL) under argon at 40 °C for 5 h.
[b] Yield was determined by GC-MS analysis. Isolated yield is given in the parenthesis.
[c] No determined.
[d] Without $CuBr_2$.
[e] $CuBr_2$ (2 equiv).
[f] $CuBr_2$ (5 equiv).
[g] Without $PdBr_2$.
[h] For 24 h at r.t.

the reaction time in the presence of $PdBr_2$ (5 mol%) and $CuBr_2$ (3 equiv) (entry 13). Finally, N-protected groups were also tested under the $PdBr_2/CuBr_2$ catalytic system. Unfortunately, 2-(dec-1-ynyl)benzeneamine (**1b**), *N*-[2-(dec-1-ynyl)phenyl]benzamide (**1c**) and *N*-benzyl-2-(dec-1-ynyl)benzeneamine (**1d**) were not suitable substrates for the annulation reaction (entries 14–16).

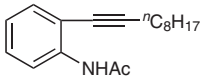
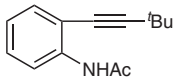
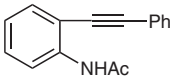
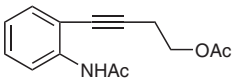
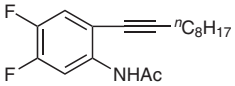
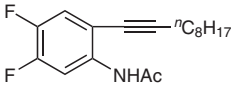
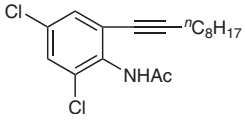
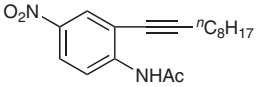
We then investigated the reaction scope of this PdX_2/CuX_2 catalytic system and its tolerance of functional groups both at the terminal of alkynes and on the aromatic rings (Table 2). We rapidly noticed the broad field of application of the process and its remarkable functional group compatibility on both parts. We were pleased to observe that *N*-[2-(dec-1-ynyl)phenyl]acetamide (**1a**) could also react with $PdCl_2$ and $CuCl_2$ smoothly to afford the corresponding 1-(3-chloro-2-octyl-1*H*-indol-1-yl)ethanone (**4a**) in a 56% yield (entry 1). Unfortunately, the reaction of *N*-[2-(3,3-dimethylbut-1-ynyl)phenyl]acetamide (**1e**), a substrate bearing a bulky group at the terminal of alkyne, with $PdBr_2$ and $CuBr_2$ was unsuccessful providing a low yield of the target product **3e** even at 70 °C (entry 2). However, treatment of substrate **1e** with $PdCl_2$ and $CuCl_2$ were conducted smoothly to afford 2-*tert*-butyl-3-chloro-1*H*-indole (**4e′**), an N-deprotected product, in an 88% yield (entry 3). To our delight, the other substrates **1f** and **1g** bearing a phenyl and an ester groups at the terminal of alkyne also worked well with PdX_2 and CuX_2 to give the corresponding products **3f**, **4f**

and **3g** in 64%, 59% and 57% yields, respectively (entries 4–6). The results also indicated that substituents, such as fluoride, chloride and nitro, on the aromatic rings were tolerated well under the standard reaction conditions (entries 7–12). Noteworthy is that MeCN is required to improve the annulation reactions of substrates **1h** and **1i** (entries 7–10). Substrate **1h** bearing two fluoro groups, for example, was annulated to produce the corresponding products **3h** and **4h** in moderate yields using a mixture of DCE and MeCN as the solvent (entries 7 and 8).

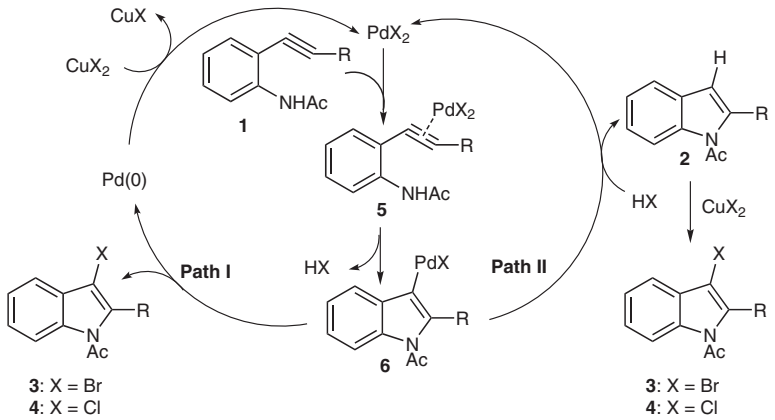
Table 2 Annulation Reactions of 2-Ethynylbenzeneamines **1** in the Presence of PdX_2 and CuX_2[a]



1 **3**: X = Br; **4**: X = Cl

Entry	Substrate	X	Time (h)	Yield (%)[b]	
				2	**3** or **4**
1	 (**1a**)	Cl	5	25 (**2a**)	56 (**4a**)
2[c]	 (**1e**)	Br	15	<5 (**2e**)	<5 (**3e**)
3[c]	(**1e**)	Cl	15	<5 (**2e**)	88 (**4e′**)
4	 (**1f**)	Br	12	18 (**2f**)	64 (**3f**)
5	(**1f**)	Cl	12	20 (**2f**)	59 (**4f**)
6	 (**1g**)	Br	5	<5 (**2g**)	57 (**3g**)
7[d]	 (**1h**)	Br	11	30 (**2h**)	62 (**3h**)
8[d]	 (**1h**)	Cl	11	40 (**2h**)	45 (**4h**)
9[d]	 (**1i**)	Br	5	50 (**2i**)	41 (**3i**)
10[d]	(**1i**)	Cl	5	41 (**2i**)	54 (**4i**)
11	 (**1j**)	Br	5	18 (**2j**)	58 (**3j**)
12	(**1j**)	Cl	5	13 (**2j**)	65 (**4j**)

[a] Reaction conditions: **1** (0.3 mmol), PdX_2 (5 mol%) and CuX_2 (3 equiv) in DCE (5 mL) under argon at 40 °C.
[b] Isolated yield.
[c] At 70 °C.
[d] 1 mL of MeCN was added and 20–30% of substrate **1i** was recovered.



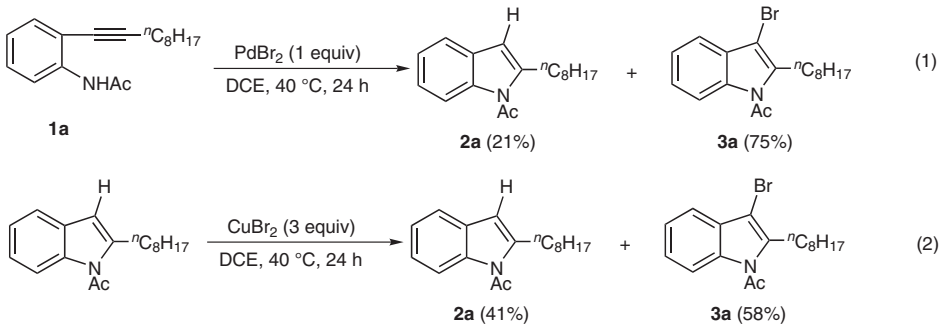
Scheme 2

A working mechanism for the present annulation reaction is proposed as shown in Scheme 2.[1,7–12] Firstly, attack of the active palladium species with ethynylbenzeneamine **1** provides intermediate **5**, followed by the addition of the nitrogen nucleophile to the PdX_2-activated intermediate **5** affording intermediate **6** and HX.[9] With the aid of CuX_2, the cleavage of the C–Pd σ-bond of intermediate **6** occurs readily to form 2-substituted 3-haloindole **3/4** and the Pd(0) species.[10] The active Pd(II) species is regenerated by the oxidation reaction of Pd(0) with CuX_2 to start a new catalytic cycle. During the process, protonolysis of intermediate **6** also takes place to form 2-substituted indole **2** and regenerates the active Pd(II) species.[11] 2-Substituted indole **2** can also undergo the halogenation reaction to afford the product **3/4** in the presence of CuX_2.

Two control reactions were carried out to further elucidate the mechanism of the annulation reaction (Scheme 3). The results showed that both $PdBr_2$ and $CuBr_2$ have a fundamental influence on the reaction. It was found that treatment of *N*-[2-(dec-1-ynyl)phenyl]acetamide (**1a**) with one equivalent of $PdBr_2$ for 24 hours afforded two products, **2a** and **3a**, in 21% and 75% yields, respectively (Scheme 3, eq 1). On the other hand, the reaction of 1-(2-octyl-1*H*-indol-1-yl)ethanone (**2a**) with three equivalents of $CuBr_2$ directly at 40 °C was also tested, and only 58% yield of **3a** was observed by GC-MS analysis after 24 hours (Scheme 3 eq 2).[6e,f] Hiroya and co-workers[12] have reported that a catalytic amount of $CuBr_2$ was inert for the cyclization of 2-ethynylbenzeneamine. Indeed, we found that in the presence of three equivalents of $CuBr_2$ the cyclization of 2-ethynylbenzeneamine provided messy results (entry 12 in Table 1). It is worth noting that 3% yield of **3a** is observed form the cyclization of 2-ethynylbenzeneamine only in the presence of 5 mol% of $PdBr_2$ (entry 9 in Table 1). Furthermore, the results of entry 11 in Table 1 demonstrated that the unhalogenated product **2a** was still isolated in an 8% yield even in the presence of five equivalents of $CuBr_2$. The above results suggested that the products **3** or **4** were generated mainly via pathway 1 in Scheme 2. Further studies are in progress to elucidate the exact mechanism.

In summary, we have developed a novel and selective method for the synthesis of 2-substituted 3-halo-1*H*-indoles by PdX_2/CuX_2-catalyzed annulation of 2-ethynylbenzeneamines. In the presence of PdX_2 and CuX_2, the annulation reactions of a variety of 2-ethynylbenzeneamines were conducted in moderate to good yields. Noteworthy is that only *N*-acetyl protected 2-ethynylbenzeneamines can undergo the reaction successfully. Further efforts to extend the application of the catalytic system and the products in organic synthesis are underway in our laboratory.

NMR spectroscopy was performed on an Inova-400 (Varian) spectrometer operating at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). TMS was used an internal standard and $CDCl_3$ was used as



Scheme 3

the solvent. Mass spectrometric analyses were performed on GC-MS analysis (Shimadzu GCMS-QP2010). All melting points are uncorrected.

2-Substituted Indoles 2a, 2h and 2i, and 2-Substituted 3-Haloindoles 3 and 4; General Procedure

A mixture of ethynylbenzeneamine **1** (0.3 mmol), PdX_2 (5 mol%), CuX_2 (3 equiv) and DCE (5 mL) was stirred at 40 or 70 °C (see Tables 1 and 2 for the reaction temperature) for 5–15 h until complete consumption of starting material as monitored by TLC and GC-MS analysis. Then the mixture was filtered and evaporated, and the residue was purified by flash column chromatography to afford **2**, **3**, or **4** (hexane–EtOAc).

1-(2-Octyl-1*H*-indol-1-yl)ethanone (2a)

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 8.8 Hz, 1 H), 7.48 (d, *J* = 8.8 Hz, 1 H), 7.26–7.21 (m, 2 H), 6.41 (s, 1 H), 2.99 (t, *J* = 7.2 Hz, 2 H), 2.76 (s, 3 H), 1.72–1.68 (m, 2 H), 1.43–1.25 (m, 10 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 143.0, 136.3, 129.9, 123.4, 122.9, 120.1, 114.8, 108.1, 31.9, 30.5, 29.5 (2 C), 29.3, 28.9, 27.7, 22.7, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 271 (M^+, 11), 229 (5), 173 (12), 144 (23), 130, (92), 103 (32), 77 (28), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{25}NO$ (M^+): 271.1936; found: 271.1936.

1-(5,6-Difluoro-2-octyl-1*H*-indol-1-yl)ethanone (2h)

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 8.0 Hz, 1 H), 6.75 (t, *J* = 8.8 Hz, 1 H), 6.33 (s, 1 H), 2.86 (t, *J* = 8.0 Hz, 2 H), 2.61 (s, 3 H), 1.72–1.64 (m, 2 H), 1.40–1.28 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

LRMS (EI, 70 eV): *m*/*z* (%) = 307 (M^+, 1), 264 (26), 180 (3), 166 (64), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}F_2NO$ (M^+): 307.1748; found: 307.1747.

1-(5,7-Dichloro-2-octyl-1*H*-indol-1-yl)ethanone (2i)

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (s, 1 H), 7.20 (s, 1 H), 6.28 (s, 1 H), 2.74 (t, *J* = 8.0 Hz, 2 H), 2.58 (s, 3 H), 1.71–1.65 (m, 2 H), 1.39–1.28 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

LRMS (EI, 70 eV): *m*/*z* (%) = 341 (M^+, 5), 339 (7), 299 (6), 297 (9), 214 (4), 212 (7), 201 (15), 200 (13), 199 (24), 198 (19), 179 (1), 177 (M^+ – Cl, 3), 142 (M^+ – 2 Cl, 1), 56 (16), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}Cl_2NO$ (M^+): 339.1157; found: 339.1156.

1-(3-Bromo-2-octyl-1*H*-indol-1-yl)ethanone (3a)[6f]

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 8.8 Hz, 1 H), 7.50 (d, *J* = 8.8 Hz, 1 H), 7.33–7.21 (m, 2 H), 3.11 (t, *J* = 7.6 Hz, 2 H), 2.76 (s, 3 H), 1.69–1.58 (m, 2 H), 1.40–1.27 (m, 10 H), 0.87 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 139.7, 135.0, 129.1, 124.8, 123.6, 119.5, 114.6, 101.7, 31.9, 29.5, 29.4, 29.3, 29.2, 28.2, 27.5, 22.7, 14.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 351 (M^+ + 2, 18), 349 (M^+, 18), 309 (24), 307 (26), 228 (82), 130 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}{}^{79}BrNO$ (M^+): 349.1041;, found: 349.1040.

1-(3-Bromo-2-phenyl-1*H*-indol-1-yl)ethanone (3f)

Pale yellow solid; mp 101.8–102.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 8.0 Hz, 1 H), 7.60–7.31 (m, 8 H), 1.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 136.2, 136.0, 132.2, 130.4, 129.4, 128.9, 128.5, 126.5, 124.3, 119.5, 116.3, 102.6, 27.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 315 (M^+ + 2, 20), 313 (M^+, 20), 273 (96), 271 (100), 190 (26), 189 (27), 165 (41).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}{}^{79}BrNO$ (M^+): 313.0102; found: 313.0102.

2-(1-Acetyl-3-bromo-1*H*-indol-2-yl)ethyl Acetate (3g)

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.68 (d, *J* = 8.4 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.38–7.32 (m, 2 H), 4.40 (t, *J* = 6.4 Hz, 2 H), 3.51 (t, *J* = 6.4 Hz, 2 H), 2.83 (s, 3 H), 2.01 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 169.7, 135.4, 134.8, 129.1, 125.2, 123.7, 120.0, 114.3, 103.8, 62.7, 29.7, 28.2, 27.7, 21.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 325 (M^+ + 2, 0.1), 323 (M^+, 0.1), 283 (1), 281 (1), 265 (2), 263 (2), 223 (13), 221 (13), 115 (11), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{14}{}^{79}BrNO_3$ (M^+): 323.0157; found: 323.0155.

1-(3-Bromo-5,6-difluoro-2-octyl-1*H*-indol-1-yl)ethanone (3h)

White solid; mp 91.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 8.8 Hz, 1 H), 2.96 (t, *J* = 7.8 Hz, 2 H), 2.62 (d, *J* = 6.4 Hz, 3 H), 1.63–1.59 (m, 2 H), 1.38–1.27 (m, 10 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 160.1 (d, *J* = 10.7 Hz, 1 C), 157.7 (d, *J* = 10.7 Hz, 1 C), 149.9 (d, *J* = 13.8 Hz, 1 C), 147.4 (d, *J* = 13.0 Hz, 1 C), 142.8, 132.6, 118.7, 101.2 (dd, *J* = 3.8 Hz, 3.9 Hz, 1 C), 100.2 (dd, *J* = 24.4 Hz, 24.5 Hz, 1 C), 98.1, 31.8, 29.4, 29.3, 29.2, 27.2, 26.7, 26.5, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 387 (M^+ + 2, 7), 385 (M^+, 6), 345 (13), 343 (14), 264 (20), 166 (46), 43 (100).

HRMS (EI): *m*/*z* for $C_{18}H_{22}{}^{79}BrF_2NO$ (M^+): 385.0853; found: 385.0852.

1-(3-Bromo-5,7-dichloro-2-octyl-1*H*-indol-1-yl)ethanone (3i)

Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1 H), 7.27 (s, 1 H), 2.83 (t, *J* = 8.0 Hz, 2 H), 2.58 (s, 3 H), 1.64–1.59 (m, 2 H), 1.37–1.27 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 141.4, 132.0, 130.3, 128.9, 124.7, 118.8, 117.7, 95.2, 31.8, 29.4, 29.3, 29.2 (2 C), 26.4, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 417 (M^+, 0.5), 379 (5), 377 (11), 375 (3), 298 (7), 296 (11), 280 (11), 278 (18), 200 (31), 198 (41), 69 (26), 55 (41), 41 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{22}{}^{79}Br^{35}Cl_2NO$ (M^+): 417.0262; found: 417.0261.

1-(3-Bromo-6-nitro-2-octyl-1*H*-indol-1-yl)ethanone (3j)

Yellow solid; mp 75.9–76.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.38 (s, 1 H), 8.19 (d, *J* = 9.6 Hz, 1 H), 7.99 (d, *J* = 9.2 Hz, 1 H), 3.12 (t, *J* = 7.6 Hz, 2 H), 2.83 (s, 3 H), 1.66–1.62 (m, 2 H), 1.32–1.25 (m, 10 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 144.0, 142.3, 138.0, 129.1, 119.8, 115.4, 115.1, 101.2, 31.8, 29.3, 29.2, 29.1 (2 C), 28.1, 27.2, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 396 (M^+ + 2, 14), 394 (M^+, 14), 366 (10), 364 (11), 354 (33), 352 (35), 324 (11), 322 (11), 273 (63), 175 (98), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}{}^{79}BrN_2O_3$ (M^+): 394.0892; found: 394.0892.

1-(3-Chloro-2-octyl-1*H*-indol-1-yl)ethanone (4a)
Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.32 (t, *J* = 3.6 Hz, 2 H), 3.10 (t, *J* = 7.2 Hz, 2 H), 2.78 (s, 3 H), 1.64–1.59 (m, 2 H), 1.39–1.26 (m, 10 H), 0.87 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 137.8, 134.5, 127.8, 123.5, 118.3, 114.7, 113.1, 31.9, 29.4, 29.3 (2C), 29.2, 27.5, 22.7, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 307 (M^+ + 2, 2.4), 305 (M^+, 7.1), 265 (5), 263 (13), 228 (8), 166 (11), 164 (31), 130 (26), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{24}{}^{35}ClNO$ (M^+): 305.1546; found: 305.1546.

2-*tert*-Butyl-3-chloro-1*H*-indole (4e′)
Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (br s, 1 H), 7.56 (d, *J* = 8.8 Hz, 1 H), 7.31–7.24 (m, 1 H), 7.19–7.13 (m, 2 H), 1.51 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 132.5, 127.3, 122.1, 120.2, 117.4, 110.7, 101.5, 32.5, 28.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 209 (M^+ + 2, 15), 207 (M^+, 45), 194 (33), 192 (100), 157 (34).

HRMS (EI): *m*/*z* for $C_{12}H_{14}{}^{35}ClN$ (M^+): 207.0815; found: 207.0814.

1-(3-Chloro-2-phenyl-1*H*-indol-1-yl)ethanone (4f)
Pale yellow solid; mp 83.1 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.55–7.36 (m, 7 H), 2.00 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 136.8, 134.0, 131.3, 130.2, 129.3, 128.9, 127.1, 126.5, 124.2, 118.4, 116.3, 114.3, 27.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 271 (M^+ + 2, 3), 269 (M^+, 10), 229 (13), 227 (46), 201 (2), 199 (6), 165 (11), 89 (70), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{12}{}^{35}ClNO$ (M^+): 269.0607; found: 269.0607.

1-(3-Chloro-5,6-difluoro-2-octyl-1*H*-indol-1-yl)ethanone (4h)
Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, *J* = 8.8 Hz, 1 H), 6.77–6.71 (m, 1 H), 6.33 (s, 1 H), 2.86 (t, *J* = 7.8 Hz, 2 H), 2.62 (d, *J* = 6.0 Hz, 3 H), 1.70–1.64 (m, 2 H), 1.40–1.28 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 160.0 (d, *J* = 11.3 Hz, 1 C), 157.6 (d, *J* = 11.3 Hz, 1 C), 149.9 (d, *J* = 14.2 Hz, 1 C), 147.6 (d, *J* = 14.2 Hz, 1 C), 146.2, 133.7, 119.9, 105.9, 101.6 (dd, *J* = 3.6 Hz, 2.8 Hz, 1 C), 98.9 (dd, *J* = 25.1 Hz, 25.1 Hz, 1 C), 31.9, 29.4, 29.3, 29.1, 28.7, 26.9, 26.8, 22.7, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 343 (M^+ + 2, 5), 341 (M^+, 15), 301 (9), 299 (28), 264 (18), 165 (15), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{22}{}^{35}ClF_2NO$ (M^+): 341.1358; found: 341.1357.

1-(3,5,7-Trichloro-2-octyl-1*H*-indol-1-yl)ethanone (4i)
Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (s, 1 H), 7.27 (s, 1 H), 2.83 (t, *J* = 7.6 Hz, 2 H), 2.58 (s, 3 H), 1.64–1.60 (m, 2 H), 1.38–1.29 (m, 10 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 139.8, 130.6, 129.7, 128.9, 124.7, 119.0, 116.7, 108.0, 31.8, 29.4, 29.3, 29.2 (2C), 29.1, 25.3, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 375 (M^+ + 2, 12), 373 (M^+, 12), 332 (9), 330 (9), 276 (14), 274 (13), 242 (6), 240 (8), 216 (6), 214 (9), 111 (4), 109 (12), 74 (8), 55 (29), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{22}{}^{79}Br^{35}Cl_2NO$ (M^+): 373.0767; found: 373.0766.

1-(3-Chloro-6-nitro-2-octyl-1*H*-indol-1-yl)ethanone (4j)
Yellow solid; mp 62.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (s, 1 H), 8.22 (d, *J* = 9.6 Hz, 1 H), 8.04 (d, *J* = 9.2 Hz, 1 H), 3.11 (t, *J* = 7.6 Hz, 2 H), 2.82 (s, 3 H), 1.66–1.61 (m, 2 H), 1.32–1.25 (m, 10 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 144.0, 140.5, 137.4, 127.7, 120.0, 115.2, 114.4, 104.3, 31.8, 29.4, 29.2 (2C), 29.1, 27.3, 26.8, 22.6, 14.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 352 (M^+ + 2, 7), 350 (M^+, 21), 310 (30), 308 (92), 280 (7), 278 (17), 273 (33), 209 (41), 163 (26), 43 (100).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{23}{}^{35}ClN_2O_3$ (M^+): 350.1397; found: 350.1397.

Acknowledgment

The authors thank Specialized Research Fund for the Doctoral Program of Higher Education (No. 20060542007), the National Natural Science Foundation of China (No 20572020 and 20472090), Fok Ying Tung Education Foundation (No. 101012), the Key Project of Chinese Ministry of Education (No. 206102), and Hunan Provincial Natural Science Foundation of China (No. 05JJ1002) for financial support.

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