HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 920-933. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2016, Accepted, 14th October, 2016, Published online, 29th November, 2016
DOI: 10.3987/COM-16-S(S)60

SIMULTANEOUS FUNCTIONALIZATION AND CYCLIZATION OF 2-ETHYNYLANILINE DERIVATIVES TO INDOLES

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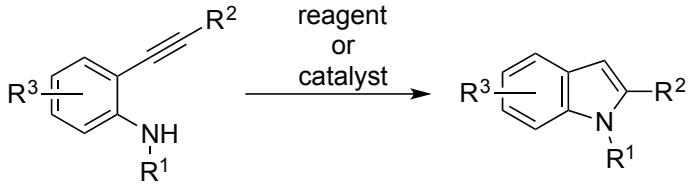
Abstract – Two different kind of sequential cyclization-functionalization are developed. Namely, cyclization-chlorination of 2-ethynylaniline derivatives using $CuCl_2$ gave 3-chloro- and 3,5-dichloroindole derivatives. The plausible mechanism for this reaction is also discussed. On the other hand, the reaction between 2-ethynylaniline derivatives and $Cu(NO_3)_2 \cdot 3H_2O$ in THF provided C4-nitro compound. After being changed the solvent from THF to DMF, followed by heating, 5-nitroindole derivatives was afforded.

INTRODUCTION

Functionalized indoles are frequently found in nature as partial structures of alkaloids, and some have been used as medicines.[1] Many reactions exist for indole ring synthesis, among which the ring closure reactions of 2-ethynylaniline derivatives is preferred due to the ease of starting material preparation (Figure 1).[2,3] Many different methods have been reported for indole syntheses from 2-ethynylaniline derivatives such as ammonium fluoride-mediated reactions,[4] basic reaction conditions,[5] variety of metal-catalyzed reactions,[2,3,6-15] iodine or its equivalent promoted reactions,[16] and others.[17]



Scheme 1. The cyclization reaction of 2-ethynylaniline derivatives to indoles

So far, the regioselective introduction of functional group in indoles have been investigated and many useful methods for synthesizing functionalized indoles have been published.[18] Recent research into indole syntheses from 2-ethynylaniline derivatives has focused on versatility, convenience of reagents and conditions as well as tandem or sequential reactions. Specifically, iodine-promoted cyclization to yield 3-iodoindoles,[16] sequential cyclization-C3 functionalization reactions catalyzed by gold(III) salts,[6b-d,g-i,l,m] zinc compound,[8c-e] platinum(II) chloride,[11a] palladium complexes,[13a-g,i-l,n,p] copper(I)[14b,c] or copper(II)[15b,d,e] have been well investigated.

We have previously reported the copper(II) salt catalyzed synthesis of indoles from 2-ethynylaniline derivatives as applied to sequential cyclization reactions.[15d,e] We have also reported improved reaction conditions for this reaction, including reactions in aqueous media.[15c] Our previous reports indicated that CuX_2 (X = F, Cl, and Br) and $Cu(NO_3)_2 \cdot 3H_2O$ do not catalyze the cyclization reactions of 2-ethynylaniline derivatives.[15d,e] However, $CuCl_2$ and $Cu(NO_3)_2 \cdot 3H_2O$ worked as "reagents" (*not catalysts*) by changing the reaction conditions so that a functional group was introduced onto the indole ring during the cyclization. In this paper, we describe the sequential cyclization-functionalization reaction of 2-ethynylaniline derivatives.

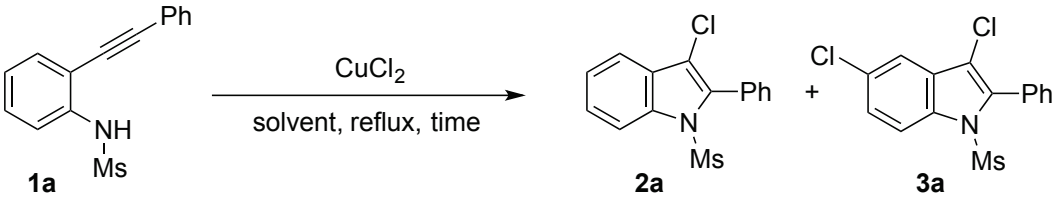
RESULTS AND DISCUSSION

The sequential cyclization-chlorination reactions of 2-ethynylaniline derivatives with $CuCl_2$

To test the feasibility of the sequential cyclization-chlorination reactions with $CuCl_2$ the methanesulfonylamide **1a** was selected to establish the reaction conditions, as sulfonamides possess the highest reactivity among the 2-ethynylaniline derivatives. The solvent was found to strongly influence the sequential cyclization-chlorination reactions, and these results are summarized in Table 1. The reaction was ineffective in toluene, 1,2-dichloroethane, acetone, DMF, and acetonitrile (Table 1, entries 1-5). In the polar and high boiling point solvent, benzonitrile (Table 1, entry 6), the methanesulfonylamide **1a** gave the 3-chlorinated indole **2a** along with the 3,5-dichlorinated indole **3a**. The ratio of **3a** to **2a** was improved by increasing the amount of $CuCl_2$ from 4.0 to 7.0 equivalents but the total yield of **2a** and **3a** decreased. This decrease was presumably due to the decomposition of **1a** or the other reaction products (Table 1, entries 6 and 7).

Having established a suitable solvent for the sequential reaction, the other functionalized aromatic substrates were studied (Table 2). The functional groups on the aromatic ring (R^1) generally did not affect the yield of **3a**, **3c-e**. Regardless of whether electron-withdrawing groups (chlorine, bromine, or nitrate; Table 2, entries 1, 2, and 4) or the electron-donating group (methyl; Table 2, entry 3) was present the product yield was more than 88%. The choice of R^2 terminal group on the acetylene is evidently limited in this reaction as the methanesulfonylamide **1f** (R^2 = Bu) did not produce the cyclized product. Many unidentifiable products were, however, observed (Table 2, entry 5).

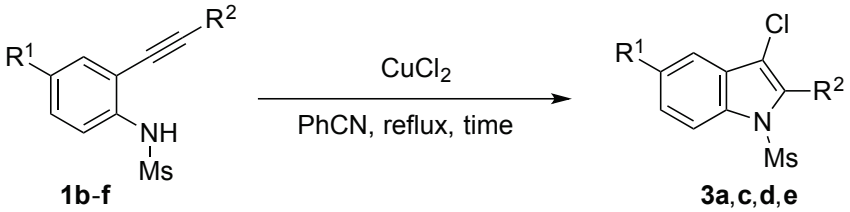
Table 1. The sequential cyclization-chlorination reaction of **1a**



entry	$CuCl_2$ (equivalents)	solvent	time (h)	yield (%)	
				2a	**3a**
1	4.0	toluene	48	-	-
2	4.0	1,2-dichloroethane	48	-	-
3	4.0	acetone	48	-	-
4	4.0	DMF	72	-	-
5[a]	4.0	acetonitrile	72	trace	trace
6[a]	4.0	benzonitrile	1	37	63
7	7.0	benzonitrile	1	20	62

[a] The yields of **2a** and **3a** were estimated by their ^{1}H-NMR spectroscopy.

Table 2. The sequential cyclization-chlorination reaction of **1b**-**f**

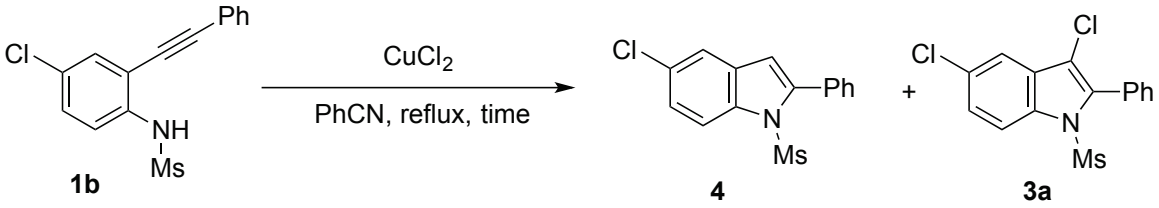


entry	compound number	R^1	R^2	$CuCl_2$ (equivalents)	time (h)	yield (%)
1	**1b**	Cl	Ph	4.0	1.0	93 (**3a**)
2	**1c**	Br	Ph	4.0	1.5	96 (**3c**)
3	**1d**	Me	Ph	4.0	1.5	88 (**3d**)
4	**1e**	NO_2	Ph	7.0	1.0	88 (**3e**)
5	**1f**	H	Bu	7.0	1.0	-

To investigate a possible mechanism for this reaction we examined the influence of the amount of $CuCl_2$ on the yield of **3a** using **1b** as the substrate and the results are listed in Table 3. When 4.0 equivalents of $CuCl_2$ was used, **3a** was obtained as the only product in 93% yield (Table 3, entry 1). The amount of $CuCl_2$ used determined the reaction rate; when reduced to 1 equivalent and refluxed for 1 h the indole **4**, which cyclized without chlorination, and **3a** were afforded in 5% and 22% yield respectively; 73% of the original **1b** was also recovered (Table 3, entry 2). The yield of **3a** was greatly improved by a longer reaction time (12 h, 85% yield, Table 3, entry 3). It is clear that the yield of **3a** depends on the quantity of $CuCl_2$ [Table 3, entry 3 (1.0 equivalent $CuCl_2$, **4**: 13%, **3a**: 85%) vs. entry 4 (0.5 equivalent $CuCl_2$, **4**: 51%, **3a**: 36%)]. From these results, two possibilities were considered for chlorination at the C3 position; the

first possibility is that chlorination occurred simultaneously with cyclization; the other is that chlorination occurred after indole ring formation.

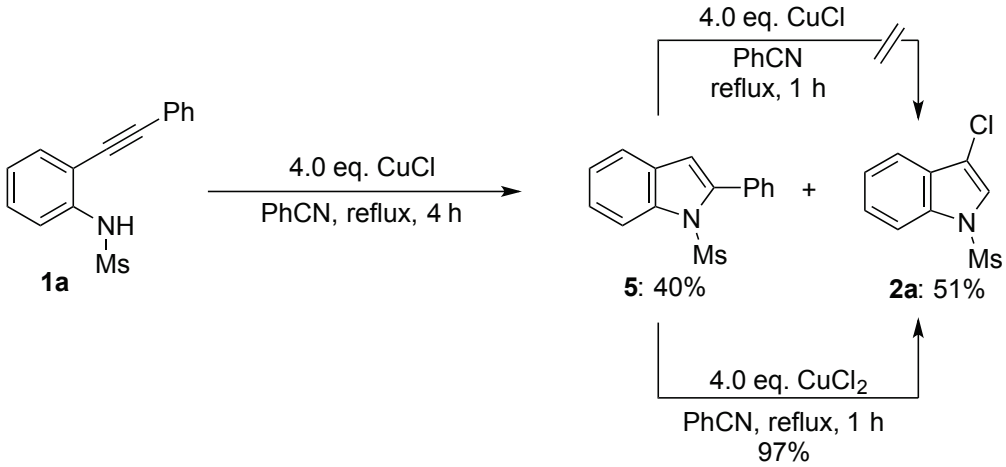
Table 3. The sequential cyclization-chlorination reaction of **1b**



entry	$CuCl_2$ (equivalents)	time (h)	yield (%)		
			4	**3a**	recovered **1b**
1	4.0	1	0	93	0
2[a]	1.0	1	5	22	73
3[a]	1.0	12	13	85	0
4[a]	0.5	12	51	36	0

[a] The yields of **4** and **3a** were estimated by their ^{1}H-NMR spectroscopy.

The reduction of $CuCl_2$ to CuCl could possibly be responsible for the chlorination of the reactant. The reaction was also mediated by CuCl as **1a** transformed into **5** and **2a** in 40% and 51% yields, respectively (Scheme 2). The chlorination reaction did not proceed from **5** by CuCl mediation. This suggests that the cyclization and chlorination by CuCl may proceed simultaneously. The reaction of **5** with $CuCl_2$ gave **2a** almost quantitatively and **3a** was not detected (Scheme 2).



Scheme 2. The sequential cyclization-chlorination reaction of **1a** mediated by CuCl

Possible mechanism for sequential cyclization-chlorination reaction

To explain the results above, the following observations [(A) – (D)] are considered in the $CuCl_2$-mediated sequential cyclization-chlorination reactions:

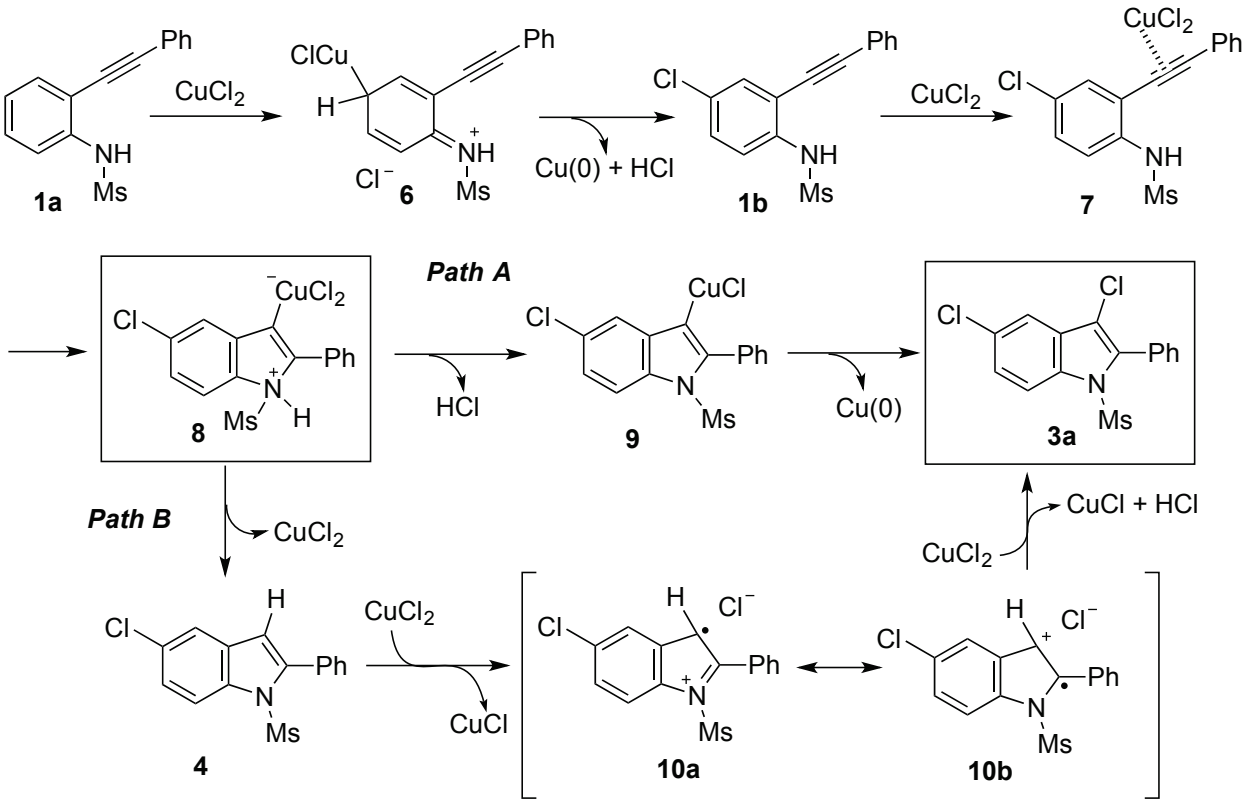
(A) The chlorination reaction at C5 (indole number) proceeds ***before*** cyclization by $CuCl_2$.

(B) The chlorination at C5 (indole number) was not due to CuCl (Scheme 2).

(C) The chlorination at C3 (indole number) by $CuCl_2$ occurs after indole cyclization (Scheme 3: ***Path B***) or simultaneously with indole cyclization (Scheme 3: ***Path A***).

(D) The chlorination at C3 (indole number) by CuCl occurred simultaneously with indole cyclization and not after cyclization (Scheme 2).

A possible mechanism for the $CuCl_2$-mediated sequential cyclization-chlorination reactions of **1a** is shown in Scheme 3 and may proceed according to the reaction sequence listed below.



Scheme 3. Proposed reaction mechanism for the transformation of **1a** to **3a**

From **1a** to the intermediate **8**

(1) **1a** reacts with $CuCl_2$ to produce the ionic intermediate **6**, followed by a reductive elimination of Cu(II) to afford **1b** and Cu(0).

(2) The interaction of the acetylene moiety of **1b** with $CuCl_2$ forms the Cu(II)-coordinated complex **7**.

(3) The intramolecular nucleophilic attack of a nitrogen atom to the activated acetylene moiety leads to the zwitter ionic intermediate **8**.

From **8** to **3a** via **9** (***Path A***)

(1) One possible mechanism contains the elimination of a chloride anion from C3-$CuCl_2^-$ of **8**, which removes the proton on the nitrogen atom to produce the neutral intermediate **9**.

(2) Reductive elimination from C3–CuCl of **9** produces **3a** and Cu(0).

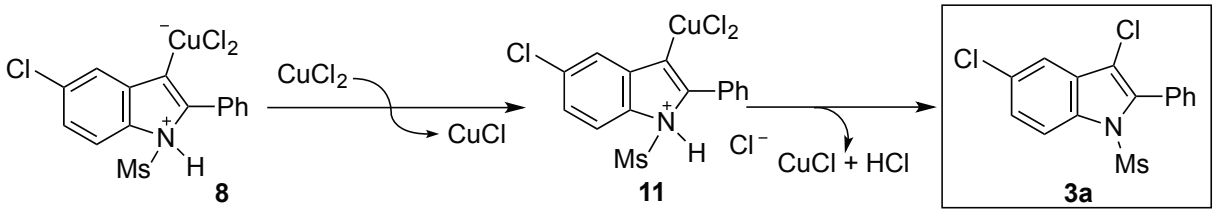
From **8** to **3a** via **4** (***Path B***)

(1) Protonolysis of the C3–Cu bond or an intramolecular [1,3]-proton migration from the nitrogen atom to C3 leads to **4** and $CuCl_2$.

(2) Single electron transfer (SET) from **4** to another molecule of $CuCl_2$ forms intermediate **10a**,**b** (where **10b** is another resonant form of **10a**), CuCl and a counter Cl^- anion. Because the chlorination reaction from **5** to **2a** in the presence of CuCl did not proceed (Scheme 2) this SET reaction has to occur from **4** to $CuCl_2$.

(3) Finally, a nucleophilic attack of the chloride anion on C3 followed by SET to $CuCl_2$ proceeds to afford **3a**, CuCl and HCl. The difference in the redox potentials of Cu(II) and Cu(I) is much smaller than that between Cu(I) and Cu(0).[19] SET from **10a**,**b** may thus occur from $CuCl_2$ → CuCl but not from CuCl → Cu.

As there is no evidence for the reaction mechanism described above at present, the following mechanism containing SET from **8** is suggested; **8** is oxidized by $CuCl_2$ to produce a Cu(III) species **11** followed by a proton removal on the nitrogen atom of **11** by the Cl^- anion. A reductive elimination of the Cu(III) species leads to **3a**, CuCl, and HCl (Scheme 4).[20]



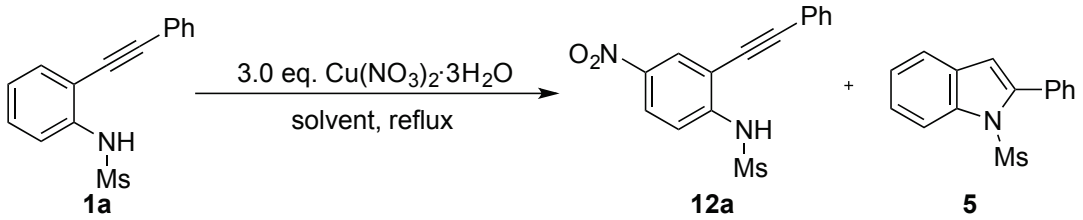
Scheme 4. Another possible mechanism for the transformation of **8** to **3a**

Nitration reaction and cyclization reaction of 2-ethynylaniline derivatives with $Cu(NO_3)_2{\cdot}3H_2O$

Our previous studies, concerned with the cyclization reaction of 2-ethynylaniline derivatives to indoles catalyzed by various Cu(II) salts, found that the methanesulfonylamide **1a** gave a small amount of **12a** in the presence of a catalytic amount of $Cu(NO_3)_2{\cdot}3H_2O$. The solvent effect of this reaction was examined and the results are summarized in Table 4. The methanesulfonylamide **1a** gave **12a** in relatively non-polar solvents such as toluene, acetonitrile, 1,2-dichloroethane and THF in good yield (Table 4, entries 1-4). Surprisingly, in DMF, **1a** gave the indole **5**, which cyclized without nitration (Table 4, entry 5). These results indicate that the cyclization or nitration can be controlled by solvent selection. The difference in

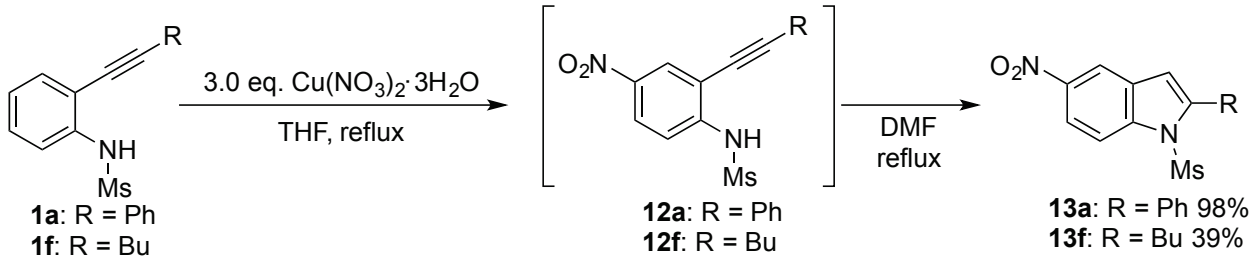
polarities and boiling points of the solvents possibly leads to different reaction pathways. At a lower temperature, the nitration reaction is dominant over the cyclization reaction. On the other hand, the reactions in a polar solvent at higher temperature gave **5** as the sole product and the cyclization reaction occurred much faster than the nitration reaction. The different roles of $Cu(NO_3)_2 \cdot 3H_2O$ may be attributed to the varied ligation abilities of the solvents. However, the exact reason is not clear yet.

Table 4. Reaction of **1a** in the presence of $Cu(NO_3)_2 \cdot 3H_2O$



entry	solvent	time (h)	yield (%)	
			12a	**5**
1	toluene	2	95	0
2	acetonitrile	0.5	79	0
3	1,2-dichloroethane	24	86	0
4	THF	17	86	0
5	DMF	2	0	93

Using the difference in reactivity as described above we could establish a unique reaction system in which different products could be obtained from the same starting materials and reagents. The reaction of **1a** with 3.0 equivalents $Cu(NO_3)_2 \cdot 3H_2O$ in DMF gave indole **5** without the nitro group in good yield (Table 4, entry 5). The same reagents in refluxing THF gave **12a**, which was converted into **13a** in almost quantitative yield by refluxing for 4 h in DMF, in the same flask (Scheme 5). This reaction is, however, limited by the reacting substrates as **1f** gave the corresponding indole **13f** in only 39% yield. Further improvements of the reaction conditions are in progress in our laboratory.



Scheme 5. The nitration-cyclization reaction of **1a** and **1f** mediated by $Cu(NO_3)_2 \cdot 3H_2O$

CONCLUSION

Two different kinds of sequential functionalization-cyclization reactions of 2-ethynylaniline derivatives to indoles were developed. The first reaction is a cyclization-chlorination promoted by $CuCl_2$ which involves the reduction of a Cu(II) species to Cu(I) and a chlorination of the indole ring. Several possible pathways are proposed. The second reaction is a nitration-cyclization by $Cu(NO_3)_2 \cdot 3H_2O$. A unique, solvent-dependent reaction system which gave different products was also developed.

EXPERIMENTAL

General

All melting points were determined with a Yazawa Micro Melting Point BY-2 and were uncorrected. ^{1}H-NMR spectra (400 MHz) and ^{13}C-NMR spectra (100 MHz) were recorded on a JEOL JMN AL-400 spectrometer. Chemical shifts (δ) are given relative to TMS (0 ppm) as the internal standard for ^{1}H-NMR and $^{13}CDCl_3$ (77.0 ppm) as the internal standard for ^{13}C-NMR. Low-resolution and high-resolution mass spectra were measured on a JEOL JMS-DX303 instrument and a MS-AX500 instrument, respectively. IR spectra were recorded on a Shimadzu FTIR-8400.

General procedure for cyclization-chlorination reactions shown in Tables 1-3

CuCl or $CuCl_2$ was added to a solution of 2-ethynylaniline derivatives in benzonitrile or the relevant solvent listed in the Tables. These mixtures were then refluxed for the reaction time listed in the Tables. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$. The solvent was then evaporated off.

3-Chloro-1-methylsulfonyl-2-phenylindole (2a) and 3,5-Dichloro-1-methylsulfonyl-2-phenylindole (3a) (Table 1, entry 7). According to the general procedure, a suspension of **1a**[15c,d] (47.5 mg, 0.18 mmol) and $CuCl_2$ (166.5 mg, 1.24 mmol) in benzonitrile (3 mL) was reacted for 1 h. The residue was chromatographed on silica gel [AcOEt–hexane–Et_3N (1:20:20)] to afford 3-chloro-1-methylsulfonyl-2-phenylindole (**2a**) (10.7 mg, 20%) as a colorless solid and 3,5-dichloro-1-methylsulfonyl-2-phenylindole (**3a**) (36.8 mg, 62%) as a colorless solid. **2a**: mp 109–110 °C (colorless prisms from AcOEt–hexane). IR (film) cm^{-1}: 1371, 1177. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.79 (3H, s), 7.42–7.56 (7H, m), 7.66 (1H, dd, *J* = 7.4, 2.4 Hz), 8.14 (1H, dd, *J* = 7.4, 2.4 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 40.1, 115.4, 115.6, 119.0, 124.9, 126.4, 127.8, 128.3, 128.9, 129.4, 131.0, 135.7, 135.9. MS *m/z*: 307 (M^++2, 23.1), 305 (M^+, 56.1), 228 (38.7), 226 (100). HRMS *m/z*: 305.0290 (Calcd for $C_{15}H_{12}{}^{35}ClNO_2S$: 305.0277). **3a**: mp 136–137 °C (colorless needles from acetone–hexane). IR (film) cm^{-1}: 1448, 1358, 1171. ^{1}H-NMR (400 MHz, $CDCl_3$)

δ: 2.80 (3H, s) 7.40 (1H, dd, *J* = 8.9, 2.2 Hz), 7.47–7.55 (5H, m), 7.64 (1H, d, *J* = 2.2 Hz), 8.07 (1H, d, *J* = 8.9 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 40.4, 114.4, 116.8, 118.7, 126.5, 127.9, 128.3, 129.4, 129.7, 130.9, 131.0, 134.1, 137.0. MS *m*/*z*: 343 (M^++4, 9.2), 341 (M^++2, 41.6), 339 (M^+, 57.6), 262 (69.2), 260 (100). HRMS *m*/*z*: 338.9863 (Calcd for $C_{15}H_{11}{}^{35}Cl_2NO_2S$: 338.9888).

5-Bromo-3-chloro-1-methylsulfonyl-2-phenylindole (3c) (Table 2, entry 2). According to the general procedure, a suspension of **1c**[15c,d] (56.1 mg, 0.16 mmol) and $CuCl_2$ (88.1 mg, 0.66 mmol) in benzonitrile (3 mL) was reacted for 1.5 h. The residue was chromatographed on silica gel [AcOEt–hexane (1:9)] to afford **3c** (58.9 mg, 96%) as a pale yellow solid. mp 171–172 °C (colorless prisms from AcOEt–hexane); IR (film) cm^{-1}: 1373, 1175. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.81 (3H, s), 7.48–7.56 (6H, m), 7.80 (1H, d, *J* = 2.2 Hz), 8.02 (1H, d, *J* = 9.0 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 40.5, 116.8, 117.1, 118.4, 121.7, 127.91, 127.93, 128.3, 129.2, 129.7, 129.8, 131.0, 134.5. MS *m*/*z*: 387 (M^++4, 24.1), 385 (M^++2, 75.8), 383 (M^+, 57.9), 308 (29.3), 306 (100), 304 (78.9). HRMS *m*/*z*: 382.9392 (Calcd for $C_{15}H_{11}{}^{79}Br^{35}ClNO_2S$: 382.9382).

3-Chloro-5-methyl-1-methylsulfonyl-2-phenylindole (3d) (Table 2, entry 3). According to the general procedure, a suspension of **1d**[15c,d] (50.2 mg, 0.18 mmol) and $CuCl_2$ (90.8 mg, 0.68 mmol) in benzonitrile (3 mL) was reacted for 1.5 h. The residue was chromatographed on silica gel [AcOEt–hexane (1:9)] to afford 3-chloro-5-methyl-1-methylsulfonyl-2-phenylindole (**3d**) (49.4 mg, 88%) as an orange solid. mp 150–151 °C (pale orange needles from AcOEt–hexane). IR (film) cm^{-1}: 1371, 1173. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.51 (3H, s), 2.75 (3H, s), 7.26 (1H, d, *J* = 8.5 Hz), 7.40–7.56 (6H, m), 8.00 (1H, d, *J* = 8.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 21.4, 39.6, 115.4, 118.8, 127.75, 127.77, 127.8, 128.5, 129.0, 129.3, 130.9, 134.2, 134.9, 135.8. MS *m*/*z*: 321 (M^++2, 21.5), 319 (M^+, 52.7), 242 (37.3), 240 (100). HRMS *m*/*z*: 319.0440 (Calcd for $C_{16}H_{14}{}^{35}ClNO_2S$: 319.0434).

3-Chloro-5-nitro-1-methylsulfonyl-2-phenylindole (3e) (Table 2, entry 4). According to the general procedure, a suspension of **1e**[15c] (48.4 mg, 0.16 mmol) and $CuCl_2$ (147.2 mg, 1.09 mmol) in benzonitrile (3 mL) was refluxed for 1 h. The residue was chromatographed on silica gel [AcOEt–hexane (1:2)] to afford 3-chloro-5-nitro-1-methylsulfonyl-2-phenylindole (**3e**) (47.3 mg, 88%) as an orange solid. mp 180 °C (pale orange prisms from acetone–hexane). IR (film) cm^{-1}: 1522, 1377, 1346, 1177. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.96 (3H, s), 7.50–7.67 (5H, m), 8.26–8.35 (2H, m), 8.53 (1H, br). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 41.9, 114.9, 115.2, 115.9, 121.0, 127.6, 127.9, 128.1, 130.1, 131.0, 138.3, 138.4, 144.9. MS *m*/*z*: 352 (M^++2, 36.9), 350 (M^+, 87.0), 273 (40.3), 271 (100). HRMS *m*/*z*: 350.0126 (Calcd for $C_{15}H_{11}{}^{35}ClN_2O_4S$: 350.0128).

General Procedure for the Selected Entries in Table 4

$Cu(NO_3)_2 \cdot 3H_2O$ was added to a solution of **1a** in solvent listed in Table 4, then the mixture was refluxed for the reaction time listed in Table 4. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was evaporated.

***N*-[4-Nitro-2-(phenylethynyl)phenyl]methanesulfonamide (12a)[15c] (Table 4, entry 1).** According to the general procedure, a suspension of **1a**[15c,d] (47.3 mg, 0.17 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (131.5 mg, 0.54 mmol) in toluene (5 mL) was reacted for 2 h. The residue was chromatographed on silica gel [AcOEt–hexane (1:3)] to afford *N*-[4-nitro-2-(phenylethynyl)phenyl]methanesulfonamide (**12a**) (52.4 mg, 95%) as a yellow solid. mp 153–155 °C (colorless needles from acetone–hexane). IR (film) cm^{-1}: 1520, 1339, 1151. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.19 (3H, s), 7.40–7.47 (3H, m), 7.48 (1H, br), 7.55–7.59 (2H, m), 7.75 (1H, d, *J* = 9.0, Hz), 8.23 (1H, dd, *J* = 9.0, 2.7 Hz), 8.42 (1H, d, *J* = 2.7 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 40.8, 81.2, 99.2, 113.3, 116.4, 120.7, 125.1, 127.8, 128.7, 129.9, 131.8, 142.9, 143.2. MS *m*/*z*: 316 (M^+, 100), 237 (85.7). HRMS *m*/*z*: 316.0517 (Calcd for $C_{15}H_{12}N_2O_4S$: 316.0518).

1-Methylsulfonyl-2-phenylindole (5)[4b,15c,d] (Table 4, entry 5). According to the general procedure, a solution of **1a**[15c,d] (51.5 mg, 0.19 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (148.0 mg, 0.61 mmol) in DMF (5 mL) was reacted for 2 h. The residue was chromatographed on silica gel [AcOEt–hexane (1:2)] to afford 1-methylsulfonyl-2-phenylindole (**5**) (47.7 mg, 93%) as a colorless solid. mp 115–117 °C (colorless needles from AcOEt–hexane). IR (film) cm^{-1}: 1367, 1171. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.73 (3H, s), 6.70 (1H, s), 7.34 (1H, td, *J* = 7.4, 1.5 Hz), 7.37 (1H, td, *J* = 7.4, 1.5 Hz), 7.40–7.46 (3H, m), 7.52–7.61 (3H, m), 8.12 (1H, d, *J* = 7.8 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 39.5, 113.0, 115.7, 120.9, 124.5, 125.0, 127.6, 128.8, 130.0, 130.2, 131.9, 137.9, 141.8. MS *m*/*z* 271 (M^+, 51.3), 190 (100), 165 (51.8). HRMS *m*/*z*: 271.0673 (Calcd for $C_{15}H_{13}NO_2S$: 271.0667).

5-Nitro-1-methylsulfonyl-2-phenylindole (13a)[15c] (Scheme 5). A solution of **1a**[15c,d] (94.5 mg, 0.35 mmol) and $Cu(NO_3)_2 \cdot 3H_2O$ (275.1 mg, 1.14 mmol) in THF (10 mL) was reacted for 24 h. THF was evaporated to afford a solid, which was dissolved into DMF (10 mL) and the mixture was refluxed for 4 h. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1:2)] to afford 5-nitro-1-methylsulfonyl-2-phenylindole (**13a**) (108.0 mg, 98%) as a pale yellow solid. mp 187–188 °C (pale yellow needles from acetone–hexane). IR (film) cm^{-1}: 1518, 1344, 1165. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.90 (3H, s), 6.81

(1H, s), 7.44–7.50 (3H, m), 7.53–7.58 (2H, m), 8.25 (2H, d, *J* = 1.5 Hz), 8.51 (1H, t, *J* = 1.5 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 41.4, 112.2, 115.7, 116.9, 119.9, 127.9, 129.61, 129.63, 130.3, 130.6, 140.4, 144.3, 144.7. MS *m*/*z*: 316 (M^+, 90.7), 237 (100). HRMS *m*/*z*: 316.0500 (Calcd for $C_{15}H_{12}N_2O_4S$: 316.0518).

2-Butyl-1-methylsulfonyl-5-nitroindole (13f) (Scheme 5). A solution of **1f**[15c,d] (103.0 mg, 0.41 mmol) and $Cu(NO_3)_2{\cdot}3H_2O$ (316.6 mg, 1.31 mmol) in THF (10 mL) was refluxed for 27 h. THF was evaporated to afford a solid, which was dissolved into DMF (10 mL) and the mixture was refluxed for 2 h. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel [AcOEt–hexane (1:5)] to afford 2-butyl-1-methylsulfonyl-5-nitroindole (**13f**) (47.8 mg, 39%) as a pale yellow solid. mp 111–112 °C (pale yellow needles from Et_2O–hexane). IR (film) cm^{-1}: 3932, 1520, 1369, 1346, 1173. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, t, *J* = 7.6 Hz), 1.49 (2H, sex, *J* = 7.6 Hz), 1.78 (2H, quint, *J* = 7.6 Hz), 2.99 (2H, t, *J* = 7.6 Hz), 3.13 (3H, s), 8.11 (1H, d, *J* = 9.1 Hz), 8.16 (1H, dd, *J* = 9.1, 2.2 Hz), 8.40 (1H, d, *J* = 2.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 13.9, 22.5, 28.6, 30.8, 41.6, 108.2, 114.1, 116.2, 119.9, 129.5, 139.5, 144.3, 145.7. MS *m*/*z*: 296 (M^+, 48.4), 254 (89.3), 175 (100). HRMS *m*/*z*: 296.0844 (Calcd for $C_{13}H_{16}N_2O_4S$: 296.0831).

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