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Mild and efficient cyclization reaction of 2-ethynylaniline derivatives to indoles in aqueous medium

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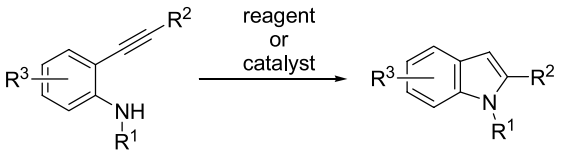
Abstract—Results of the optimized cyclization reaction of 2-ethynylaniline derivatives to indoles catalyzed by copper(II) salts are described. The reactions can be carried out in a mixture of H_2O and MeOH in the presence of 1-ethylpiperidine at room temperature. These conditions can be applied to a bulky substrate, which is difficult to be cyclized efficiently by existing reaction conditions. Furthermore, this reaction condition was applied to a catalyst recycling reaction system.

1. Introduction

Heterocyclic compounds, particularly indoles, occur widely in nature as partial structures of alkaloids and have unique biological activities.[1] Among the many methods for indole ring synthesis, the ring closing reactions of 2-ethynylaniline derivatives are some of the most efficient because methods for synthesizing a variety of functionalized starting materials have already been established (Scheme 1).[2] Thus far, many kinds of reagents and reaction conditions have been reported for indole syntheses from 2-ethynylaniline derivatives, including basic conditions,[2c,3] early transition metal-catalyzed reactions,[4] gold(III),[5] copper(I),[2b,6,10a] copper(II) salt-catalyzed reactions,[7] and ammonium fluoride-mediated reactions.[8] The most frequently used reagents or catalysts for these ring-closing reactions are the palladium complexes,[2d,3a,5b,9,10,11] and many applications together with polymer-supported reactions[12] have also been established.



Scheme 1. Cyclization reaction of 2-ethynylaniline derivatives to indole derivatives.

Recent interest in indole synthesis from 2-ethynylaniline derivatives has focused on versatile applicability, convenient reagents and conditions, and tandem or sequential reactions. For such purposes, iodine-promoted cyclization to yield 3-iodoindoles[13], sequential cyclization-C3 functionalization reactions catalyzed by palladium complexes[5b,11] or gold(III) salt,[14] and carbazoles synthesis[15] were established. We have previously developed both copper(II) salt-catalyzed synthesis of indoles from 2-ethynylaniline derivatives[7a,c] and palladium-complex-catalyzed sequential coupling-cyclization reactions between methyl propiolate and 2-iodoaniline derivatives, with the latter's application to duocarmycin SA synthesis.[10d]

Copper(II) salt-catalyzed reactions can be applied to a variety of 2-ethynylaniline derivatives, including ones with the following features: (1) electron-donating or electron-withdrawing groups on the aromatic ring, (2) an alkyl, aryl, hydroxymethyl, or even methoxycarbonyl group on the acetylene terminal, and (3) sulfonamide, non-substituted aniline derivatives and carbamates (depending on the structure of the substrate). However, problems with efficiency (low solubility of the catalysts in organic media) and high temperature requirements ($>70\,^{\circ}C$) must be solved for copper(II) salt-catalyzed reactions to be useful. Herein, we describe solutions to these problems and improved procedures for copper(II) salt-catalyzed cyclization reactions of 2-ethynylaniline derivatives.

Keywords: Indole; Copper(II) salt; 2-Ethynylaniline; Cyclization reaction.
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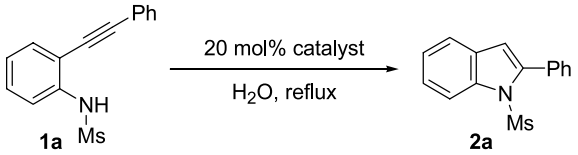
2. Results and discussion

2.1. Improvement of the reaction conditions

Copper(II) salt-catalyzed indole formation reactions appear as suspensions due to low solubility of the salts in organic solvents such as 1,2-dichloroethane. We have previously described how the ionic character of the copper–oxygen bond in copper(II) sulfonate is required for effective catalyst of the cyclization, which makes suspension in an organic solvent unavoidable.[7a] However, the bulky counter-anion in copper(II) carbonate (e.g., stearic acid) does not improve solubility or catalytic activity.[16] Therefore, we changed the solvent to H_2O. The results are summarized in Table 1. It was known that sulfonamides possess the highest reactivity among 2-ethynylaniline derivatives, so the mesylamide **1a** was selected as the substrate for establishing the new reaction conditions. Most of the copper(II) salts tested dissolved into H_2O except for $Cu(OBz)_2$, but the reaction medium was again a suspension because of the low solubility of **1a** in H_2O. The copper(II) salts that catalyze the reactions in organic solvent [$Cu(OAc)_2$, $Cu(OTf)_2$, $Cu(OBz)_2$, and $Cu(OCHO)_2\cdot xH_2O$] did not provide satisfactory results (Table 1, entries 1–4). Surprisingly, only $Cu(OCOCF_3)_2\cdot xH_2O$ catalyzed the reaction, even though it forms a suspension in the reaction mixture (Table 1, entry 5). Why only this copper(II) salt works is not yet clear. However, it is apparent that CF_3COOH is not a catalyst for this reaction (Table 1, entry 6). We selected $Cu(OCOCF_3)_2\cdot xH_2O$ as the catalyst for further improvement of the reaction conditions.

Table 1. Copper(II) salt-catalyzed cyclization reactions of **1a** in H_2O



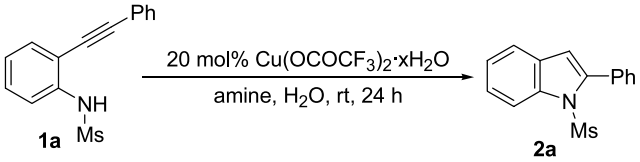
Entry	Catalyst	Time (h)	Yield of **2a** (%)
1	$Cu(OAc)_2$	23	Trace
2	$Cu(OTf)_2$	24	7 (76)[a]
3	$Cu(OBz)_2$	24	18 (66)[a]
4	$Cu(OCHO)_2\cdot xH_2O$	24	22 (75)[a]
5	$Cu(OCOCF_3)_2\cdot xH_2O$	24	96
6	CF_3COOH	23	No reaction

[a] The numbers in parentheses are the yields of recovered **1a**.

High temperature is essential for the cyclization reactions of 2-ehtynylaniline derivatives catalyzed by copper(II) salts and the substrates can be recovered perfectly at room temperature. However, we have previously reported that the rate of copper(II) salt-catalyzed cyclization reactions is accelerated in the presence of 1-ethylpiperidine and realized the reaction at room temperature (room temperature for 72 h with 2.0 equiv of 1-ethylpiperidine, 76% yield).[7a] We now apply the $Cu(OCOCF_3)_2\cdot xH_2O$-catalyzed cyclization reaction of **1a** with various amines in H_2O. The results are summarized in Table 2.

The rate acceleration effect of the amine in H_2O was less than in 1,2-dichloroethane. The addition of a tertiary aliphatic amine slightly accelerated the reaction, but the yield of **2a** was less than the amount of added catalyst and more than 80% of **1a** was recovered (Table 2, entries 1–3). Addition of a tertiary aromatic amine or pyridine did not accelerate the reaction (Table 2, entries 4 and 5). The addition of secondary amines (piperidine or *N*,*N*-diisopropylamine) or primary amines (butylamine, aniline, or ethylenediamine) also did not promote the reaction, and the starting material **1a** was completely recovered (data not shown). Since the reactions in H_2O appear as a suspension, we speculated that the reason for the reactivity difference between H_2O and 1,2-dichloroethane might be the low solubility of **1a** in H_2O. Therefore, we attempted the reaction in a mixed solvent system, with and without 1-ethylpiperidine (Table 3).

Table 2. $Cu(OCOCF_3)_2\cdot xH_2O$-catalyzed cyclization reaction of **1a** in the presence of various amines



Entry	Amine (2.0 equiv)	Yield of **2a** (%)
1	1-Ethylpiperidine	14 (85)[a]
2	Triethylamine	10 (88)[a]
3	*N*,*N*-diisopropylethylamine	17 (83)[a]
4	*N*,*N*-dimethylaniline	No reaction
5	Pyridine	No reaction

[a] The numbers in parentheses are the yields of recovered **1a**.

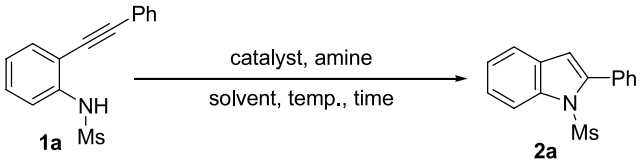
We wanted to dissolve both the catalyst and the substrate, so we chose an alcohol as the second solvent. Surprisingly, we discovered that the efficiency of the reaction is closely related to the carbon number of employed alcohol: as the carbon number of the alcohol solvent increased, the yield decreased (Table 3, entries 1–3). It is apparent from the above results that the reactivity is controlled by the balance of the solubility of the catalyst and the substrate. However, even with the second alcohol solvent, the reaction did not proceed at room temperature (Table 3, entry 4). The effect of 1-ethylpiperidine was remarkable, and the amount of catalyst could be reduced from 20 to 5 mol% (Table 3, entries 6 and 7). Note that less expensive $Cu(OAc)_2$, which did not show catalytic activities in H_2O alone (Table 1, entry 1), can be used as the catalyst under optimized reaction conditions (Table 3, entry 8). While the reaction could be promoted with 1-ethylpiperidine in the absence of a copper(II) salt, the low yield can be disregarded (Table 3, entry 5).

2.2. Application to various kinds of substrates

Having established the cyclization reaction in aqueous solvent at room temperature, we applied it to other substrates. To avoid too long reaction time, we used same reaction condition shown in Table 3 entry 6 [20 mol% of $Cu(OCOCF_3)_2\cdot H_2O$] and the results are summarized in Table 4.

For the substituents at the alkyne terminal, this condition

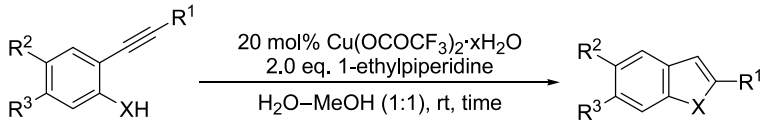
Table 3. Copper(II) salt-catalyzed cyclization reaction of **1a** in a mixed solvent system



Entry	Catalyst (mol%)	Amine (2.0 equiv)	Solvent	Temperature	Time (h)	Yield (%)
1	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–^{t}BuOH (1/1)	~90 °C	24	10 (86)[a]
2	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–EtOH (1/1)	~90 °C	24	85 (7)[a]
3	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–MeOH (1/1)	~90 °C	21	93
4	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	—	H_2O–MeOH (1/1)	Room temperature	23	No reaction
5	—	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	14 (85)[a]
6	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	92
7	$Cu(OCOCF_3)_2 \cdot xH_2O$ (5)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	24	95
8	$Cu(OAc)_2$ (10)	1-Ethylpiperidine	H_2O–MeOH (1/1)	Room temperature	17	96

[a] The numbers in parentheses are the yields of recovered **1a**.

Table 4. Applications of the copper(II) salt-catalyzed cyclization reaction in aqueous solvent



1b-h, 3-5 **2b-h, 6**

Entry	Substrate					Time (h)	Yield of **2** and **6** (%)
	Number	X	R^1	R^2	R^3		
1	**1b**	NMs	Bu	H	H	13	**2b**:98
2	**1c**	NMs	TMS	H	H	14	**2i**:91 (R^2=H)
3	**1d**	NMs	^{t}Bu	H	H	10	**2d**:90
4	**1e**	NMs	Ph	NO_2	H	14	**2e**:85
5	**1f**	NMs	Ph	Br	H	72	**2f**:99
6	**1g**	NMs	Ph	Me	H	27	**2g**:99
7	**1h**	NMs	Ph	H	OMe	21	**2h**:99
8	**3**	NH	Ph	H	H	24	No reaction
9	**4**	NBoc	Ph	H	H	24	No reaction
10	**5**	O	Ph	H	H	11	**6**:87 (7)[a]

[a] The number in parentheses is the yield of recovered **5**.

can be applied not only to the alkyl group (Table 4, entry 1) and hydrogen (Table 4, entry 2; TMS group eliminated before cyclization reaction), but also in the presence of a bulky ^{t}Bu group (Table 4, entry 3). To our knowledge, only one report[5b] had been published for a high yield of an indole from 2-ethynylaniline derivatives with a quaternary center at the C-3′ position.[7a] Substituents on the aromatic ring generally did not affect the efficiency of the reaction (Table 4, entries 4–7). Disappointingly, this reaction has the limitation about the substituents on the nitrogen atom: the

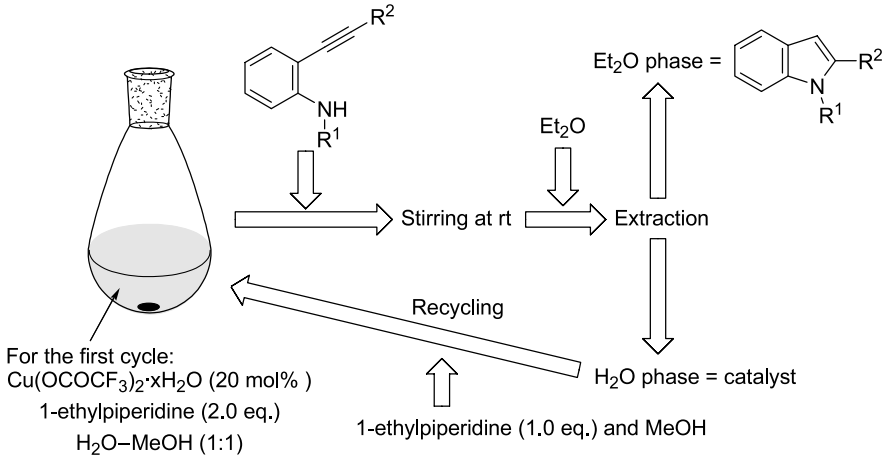
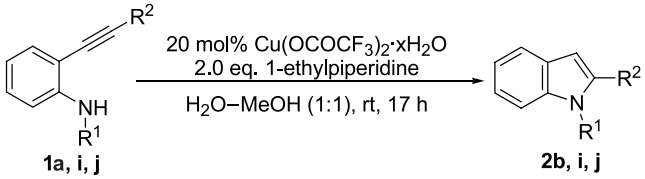


Figure 1. The general form of the catalyst recycling reaction.

Table 5. The catalyst recycling reaction for 2-ethynylaniline derivatives



1a, i, j **2b, i, j**

Entry	Substrate			Yield of **2** (%)		
	Number	R^1	R^2	First cycle	Second cycle	Third cycle
1	**1a**	Ms	Ph	99	94	97
2	**1i**	Ms	H	73	84	89
3	**1j**	Ts	CH_2OH	96	99	98

sulfonamides could be cyclized, but not the aniline derivative or the carbamate (Table 4, entries 8 and 9). However, this reaction condition could be applied to the synthesis of the benzofuran derivative **6** (Table 4, entry 10).

2.3. Catalyst recycling reaction

This reaction, in which the copper(II) salts dissolve into H_2O while the indole products dissolve into the organic solvent, allows constructions of a catalyst recycling reaction, depicted in Figure 1.

The reaction was started by adding the 2-ethynylaniline derivatives to a solution of $Cu(OCOCF_3)_2 \cdot xH_2O$ (20 mol%) and 1-ethylpiperidine (2.0 equiv) in H_2O–MeOH (1/1). After being stirred at room temperature, the mixture was extracted with Et_2O. The desired indole derivatives were extracted in essentially pure form from the Et_2O phase, and the catalyst-containing H_2O phase could be recycled after adding more 1-ethylpiperidine (1.0 equiv) and MeOH. The results of three cycles for three 2-ethynylaniline derivatives are listed in Table 5. The catalytic activity of $Cu(OCOCF_3)_2 \cdot xH_2O$ did not change over the three cycles.

3. Conclusion

We improved the cyclization reaction of 2-ethynylaniline derivatives to indoles. While the original conditions require heating, the optimized reaction can be carried out at room temperature in a mixture of H_2O and MeOH in the presence of 1-ethylpiperidine. Further, the reaction does not require an argon atmosphere and can be done as open-flask reaction. This reaction condition was applied to a catalyst recycling reaction system. Although the substrates for this reaction condition are limited to sulfonamides, the reaction conditions will be useful for versatile synthesis of indole derivatives, especially in large-scale reactions.

4. Experimental

4.1. General

All melting points were determined with a Yazawa Micro Melting Point BY-2 and are 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 from 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. Standard and high-resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively. IR spectra were recorded on a Shimadzu FTIR-8400.

4.2. General procedure for the selected entries for Tables 1, 3, and 4.

Copper(II) salt was added to a suspension of 2-ethynylaniline derivatives **1a**–**h** or 2-(2-phenylethynyl)phenol **5** in H_2O or in mixed solution of H_2O and alcohol, then the mixture was stirred under reflux or at room temperature for the reaction time listed in Tables 1, 3, and 4. The reaction mixture was extracted with AcOEt (three times). The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure.

4.2.1. 1-Methylsulfonyl-2-phenylindole (2a) (Table 3, entry 7). A suspension of **1a** (89.6 mg, 0.33 mmol), $Cu(OCOCF_3)_2 \cdot xH_2O$ (4.9 mg, 0.017 mmol) and 1-ethylpiperidine (0.090 mL, 0.65 mmol) in mixed solution of H_2O (5 mL) and MeOH (5 mL) was stirred for 24 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2a**[7a,8] (85.0 mg, 95%) as a colorless solid; mp 115–117 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 115–117 °C, lit.[8] mp 115–116 °C); 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), 190 (100), 165 (52); HRMS calcd for $C_{15}H_{13}NO_2S$ 271.0667, found 271.0673.

4.2.2. 1-Methylsulfonyl-2-butylindole (2b) (Table 4, entry 1). A suspension of **1b** (102.5 mg, 0.41 mmol), $Cu(OCOCF_3)_2 \cdot xH_2O$ (21.2 mg, 0.073 mmol), and 1-ethylpiperidine (0.113 mL, 0.82 mmol) in mixed solution of H_2O (5.5 mL) and MeOH (5.5 mL) was stirred for 13 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2b**[7a,8] (100.8 mg, 98%) as a colorless solid; mp 80–81 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 80–81 °C, lit.[8] mp 81–82 °C); IR (film, cm^{-1}) 1366, 1171; ^{1}H NMR (400 MHz, $CDCl_3$) δ

0.97 (3H, t, J=7.5 Hz), 1.46 (2H, sex, J=7.5 Hz), 1.75 (2H, sex, J=7.5 Hz), 2.95 (2H, t, J=7.5 Hz), 3.00 (3H, s), 6.45 (1H, s), 7.21–7.29 (2H, m), 7.48 (1H, dd, J=7.7, 2.7 Hz), 7.99 (1H, dd, J=7.9, 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.5, 28.6, 31.0, 40.3, 108.3, 114.0, 120.1, 123.5, 123.8, 129.7, 136.7, 142.3; MS m/z 251 (M^+, 37), 209 (40), 130 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.1012.

4.2.3. 1-Methylsulfonylindole (2i) (Table 4, entry 2). A suspension of **1c** (33.5 mg, 0.13 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (8.0 mg, 0.028 mmol), and 1-ethylpiperidine (0.034 mL, 0.25 mmol) in mixed solution of H_2O (1.5 mL) and MeOH (1.5 mL) was stirred for 14 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2i**[7a,8] (22.2 mg, 91%) as a colorless oil; IR (neat, cm^{-1}) 1361, 1170; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (3H, s), 6.69 (1H, d, J=3.7 Hz), 7.28 (1H, d, J=7.7 Hz), 7.35 (1H, t, J=7.7 Hz), 7.42 (1H, d, J=3.7 Hz), 7.61 (1H, d, J=7.7 Hz), 7.90 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6, 108.7, 112.8, 121.5, 123.4, 124.7, 125.9, 130.5, 134.7; MS m/z 195 (M^+, 55), 116 (100); HRMS calcd for $C_9H_9NO_2S$ 195.0354, found 195.0359.

4.2.4. 1-Methylsulfonyl-2-(1,1-dimethylethyl)indole (2d) (Table 4, entry 3). A suspension of **1d** (52.0 mg, 0.21 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (12.1 mg, 0.042 mmol), and 1-ethylpiperidine (0.057 mL, 0.41 mmol) in mixed solution of H_2O (2.5 mL) and MeOH (2.5 mL) was stirred for 10 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2d**[5b,7a] (46.9 mg, 90%) as a colorless oil; IR (neat, cm^{-1}) 1371, 1176; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.93 (3H, s), 6.61 (1H, s), 7.24 (1H, td, J=7.4, 1.9 Hz), 7.28 (1H, td, J=7.4, 1.9 Hz), 7.48 (1H, dd, J=7.4, 1.9 Hz), 8.07 (1H, br d, J=7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.9, 34.8, 39.5, 110.1, 115.3, 120.5, 123.8, 124.5, 129.4, 138.5, 151.8; MS m/z 251 (M^+, 42), 236 (51), 172 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0966.

4.2.5. 1-Methylsulfonyl-5-nitro-2-phenylindole (2e) (Table 4, entry 4). A suspension of **1e** (56.7 mg, 0.18 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (9.1 mg, 0.031 mmol), and 1-ethylpiperidine (0.049 mL, 0.35 mmol) in mixed solution of H_2O (2.5 mL) and MeOH (2.5 mL) was stirred for 14 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2e** (48.4 mg, 85%) 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), 7.25 (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, 129.62, 129.63, 130.3, 130.6, 140.4, 144.3, 144.7; MS m/z 316 (M^+, 91), 237 (100); HRMS calcd for $C_{15}H_{12}N_2O_4S$ 316.0518, found 316.0500.

4.2.6. 5-Bromo-1-methylsulfonyl-2-phenylindole (2f) (Table 4, entry 5). A suspension of **1f** (104.0 mg, 0.30 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (17.0 mg, 0.059 mmol), and 1-ethylpiperidine (0.082 mL, 0.59 mmol) in mixed solution of H_2O (4 mL) and MeOH (4 mL) was stirred for 72 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2f**[7a] (103.4 mg, 99%) as a colorless solid; mp 186–187 °C (colorless needles from AcOEt–hexane, lit[7a] mp 186–187 °C); IR (film, cm^{-1}) 1361, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.73 (3H, s), 6.62 (1H, s), 7.40–7.47 (4H, m), 7.51–7.56 (2H, m), 7.71 (1H, d, J=1.7 Hz), 7.98 (1H, d, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 111.8, 117.1, 117.8, 123.5, 127.67, 127.73, 129.1, 130.1, 131.2, 131.8, 136.5, 143.0; MS m/z 351 (M^++2, 66), 349 (M^+, 65), 272 (99), 270 (100); HRMS calcd for $C_{15}H_{12}BrNO_2S$ 348.8772, found 348.9763.

4.2.7. 1-Methylsulfonyl-5-methyl-2-phenylindole (2g) (Table 4, entry 6). A suspension of **1g** (69.0 mg, 0.24 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (12.5 mg, 0.043 mmol), and 1-ethylpiperidine (0.067 mL, 0.49 mmol) in mixed solution of H_2O (3 mL) and MeOH (3 mL) was stirred for 27 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/3)] to afford **2g**[7a] (68.4 mg, 99%) as a colorless solid; mp 137–138 °C (colorless needles from AcOEt–hexane, lit.[7a] mp 137–138 °C); IR (film, cm^{-1}) 1366, 1173; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (3H, s), 2.70 (3H, s), 6.65 (1H, s), 7.19 (1H, d, J=8.5 Hz), 7.37–7.45 (4H, m), 7.53–7.57 (2H, m), 7.98 (1H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 39.0, 113.0, 115.5, 120.9, 126.4, 127.6, 128.7, 130.0, 130.5, 132.0, 134.2, 136.2, 142.1; MS m/z 285 (M^+, 48), 206 (100). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.35; H, 5.43; N, 4.52.

4.2.8. 1-Methylsulfonyl-6-methoxy-2-phenylindole (2h) (Table 4, entry 7). A suspension of **1h** (71.7 mg, 0.24 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (13.8 mg, 0.048 mmol), and 1-ethylpiperidine (0.066 mL, 0.48 mmol) in mixed solution of H_2O (3 mL) and MeOH (3 mL) was stirred for 21 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/5)] to afford **2h**[7a] (70.7 mg, 99%) as a colorless solid; mp 134–135 °C (colorless prisms from AcOEt–hexane, lit.[7a] mp 134–135 °C); IR (film, cm^{-1}) 1612, 1367, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (3H, s), 3.88 (3H, s), 6.62 (1H, s), 6.96 (1H, dd, J=8.5, 2.2 Hz), 7.36–7.40 (3H, m), 7.44 (1H, d, J=8.5 Hz), 7.50–7.55 (2H, m), 7.67 (1H, d, J=2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.0, 55.7, 110.1, 113.0, 113.5, 121.3, 123.9, 127.5, 128.4, 129.8, 132.0, 139.1, 140.6, 158.0; MS m/z 301 (M^+, 41), 222 (100). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.73; H, 4.95; N, 4.60.

4.2.9. 2-Phenylbenzofuran (6) (Table 4, entry 10). A suspension of **5** (94.7 mg, 0.49 mmol), $Cu(OCOCF_3)_2\cdot xH_2O$ (24.9 mg, 0.086 mmol), and 1-ethylpiperidine (0.135 mL, 0.98 mmol) in mixed solution of H_2O (5 mL) and MeOH (5 mL) was stirred for 11 h at room temperature. The residue was chromatographed on silica gel [AcOEt–hexane (1/20)] to afford **6**[17] (82.4 mg, 87%) as a colorless solid. From the later fraction, **5** (7.0 mg, 7%) was recovered; **6**; mp 117–118 °C (colorless scales from hexane, lit.[17] mp 118–120 °C); IR (film, cm^{-1}) 1215, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (1H, d, J=0.7 Hz), 7.22 (1H, td, J=7.5, 1.3 Hz), 7.28 (1H, td, J=7.5, 1.3 Hz), 7.35 (1H, t, J=7.5 Hz), 7.45 (2H, d, J=7.5 Hz), 7.52 (1H, d, J=7.5 Hz),

7.58 (1H, d, J=7.5 Hz), 7.86 (2H, d, J=7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 101.3, 111.1, 120.8, 122.9, 124.2, 124.9, 128.5, 128.7, 129.1, 130.4, 154.8, 155.8; MS *m/z* 194 (M^+, 100); HRMS calcd for $C_{14}H_{10}O$ 194.0732, found 194.0727.

4.3. General procedure for Table 5

1-Ethylpiperidine (2.0 equiv), 2-ethynylaniline derivatives and $Cu(OCOCF_3)\cdot xH_2O$ in mixed solution of H_2O and MeOH was stirred for 17 h at room temperature. Et_2O (7 mL) was added to the reaction mixture and stirred for 10 min, and then Et_2O phase were separated. This operation was repeated again. The combined Et_2O phase was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and the solvent was evaporated. The residue was purified by silica gel chromatography [AcOEt–hexane (1/5) for **2b**, (1/3) for **2i**, and (1/2) for **2j**]. For the second and third cycles, a solution of 1-ethylpiperidine (1.0 equiv) and 2-ethynylaniline derivatives in MeOH was added to a catalyst solution in H_2O, and then the mixture was stirred for 17 h at room temperature and worked up and purified as above.

4.3.1. 1-Methylsulfonyl-2-phenylindole (2a) (Table 5, entry 1).

Substrate and reagents	First cycle	Second cycle	Third cycle
1a	98.7 mg, 0.36 mmol	96.5 mg, 0.36 mmol	94.4 mg, 0.35 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.7 mg, 0.075 mmol	—	—
1-Ethylpiperidine	0.099 mL, 0.72 mmol	0.049 mL, 0.35 mmol	0.049 mL, 0.35 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	97.6 mg, 99%	90.6 mg, 94%	91.4 mg, 97%

4.3.2. 1-Methylsulfonylindole (2i) (Table 5, entry 2).

Substrate and reagents	First cycle	Second cycle	Third cycle
1i	71.9 mg, 0.37 mmol	73.8 mg, 0.38 mmol	70.4 mg, 0.36 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.2 mg, 0.073 mmol	—	—
1-Ethylpiperidine	0.102 mL, 0.74 mmol	0.051 mL, 0.37 mmol	0.050 mL, 0.36 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	52.5 mg, 73%	61.8 mg, 84%	62.8 mg, 89%

4.3.3. 1-*p*-Tolylsulfonyl-2-hydroxymethylindole (2j) (Table 5, entry 3).

Substrate and reagents	First cycle	Second cycle	Third cycle
1j	111.1 mg, 0.37 mmol	113.3 mg, 0.38 mmol	116.7 mg, 0.39 mmol
$Cu(OCOCF_3)_2\cdot xH_2O$	21.4 mg, 0.074 mmol	—	—
1-Ethylpiperidine	0.107 mL, 0.78 mmol	0.053 mL, 0.38 mmol	0.053 mL, 0.38 mmol
H_2O	5 mL	—	—
MeOH	5 mL	3 mL	3 mL
Yield	106.8 mg, 96%	112.7 mg, 99%	114.9 mg, 98%

Mp 91–92 °C (colorless scales from AcOEt–hexane, lit.[7a] mp 91–92 °C); IR (film, cm^{-1}) 3566, 3425, 1367, 1173; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 3.11 (1H, t, J=7.4 Hz), 4.90 (2H, d, J=7.4 Hz), 6.64 (1H, s), 7.20 (2H, d, J=8.6 Hz), 7.22 (1H, t, J=7.7 Hz), 7.29 (1H, t, J=7.7 Hz), 7.48 (1H, d, J=7.7 Hz), 7.71 (2H, d, J=8.6 Hz), 8.04 (1H, d, J=7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 58.6, 111.2, 114.3, 121.1, 123.7, 124.9, 126.3, 129.0, 129.9, 135.5, 136.9, 140.0, 145.0; MS *m/z* 301 (M^+, 68), 129 (100). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.82; H, 5.02; N, 4.46.

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