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Development of an Efficient Procedure for Indole Ring Synthesis from 2-Ethynylaniline Derivatives Catalyzed by Cu(II) Salts and Its Application to Natural Product Synthesis

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Received October 16, 2003

The development of efficient methods for the indole synthesis catalyzed by Cu(II) salts and its applications were investigated. $Cu(OAc)_2$ has been proved to be the best catalyst for the synthesis of various 1-*p*-tolylsulfonyl or 1-methylsulfonylindoles, which have both electron-withdrawing and electron-donating groups on the aromatic ring and C2 position of indoles. For the primary aniline derivatives, $Cu(OCOCF_3)_2$ showed good activities, while $Cu(OAc)_2$ was a good catalyst for the cyclization of secondary anilines. This methodology could be applied to the sequential cyclization reaction for the compounds which have the electrophilic part in the same molecule. By prior treatment with KH, the sequential cyclization was realized to provide the tricyclic ring systems, but it was limited to five- and six-membered rings for the second cyclization. Finally, formal and total synthesis of hippadine with the Cu(II)-promoted indole synthesis as the key step was accomplished.

Introduction

Heterocyclic compounds, particularly indoles, are of interest because they widely occur in nature as partial structures of alkaloids and having unique biological activities.[1] As the synthetic procedures for the functionalized 2-ethynylaniline derivatives already have been established,[2] the methods for indole syntheses with these compounds as the starting materials are some of the most efficient procedures. Thus far, many kinds of reagents have been reported for indole syntheses from 2-ethynylaniline derivatives.[2−9] Among these reagents, the most frequently used reagents (catalysts) are the palladium complexes,[2−5] and many applications including both sequential C3 functionalization[9−13] and polymer-supported reactions[14] also have been established recently. However, not only the palladium-mediated reactions, but also other reagents are known to have some disadvantages depending on the nature of the reagents, namely, (i) metal alkoxide mediated reactions cannot be applied to the alkaline-sensitive substrates,[6] (ii) the carbonyl or sulfonyl groups have to be on the nitrogen atom for most procedures (e.g., sulfonamides, amides, and carbamates are usually used),[15] and (iii) there have been no efficient

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(1) (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Gribble, G. W. *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Ed.; Pergamon Press: Oxford, UK, 1996;, Vol. 2, p 207.

(2) (a) Kondo, Y.; Kojima, S.; Sakamoto, T. *J. Org. Chem.* **1997**, *62*, 6507. (b) Ezquerra, J.; Pedregal, C.; Lamas, C.; Barluenga, J.; Pérez, M.; García-Martín, M. A.; González, J. M. *J. Org. Chem.* **1996**, *61*, 5804. (c) Kondo, Y.; Kojima, S.; Sakamoto, T. *Heterocycles* **1996**, *43*, 2741. (d) Rudisill, D. E.; Stille, J. K. *J. Org. Chem.* **1989**, *54*, 5856.

(3) (a) Barluenga, J.; Trincado, M.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406. (b) Arcadi A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 647. (c) McDonald, F. E.; Chatterjee, A. K. *Tetrahedron Lett.* **1997**, *38*, 7687.

(4) Recent review for palladium-catalyzed cyclization reactions, see: Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111.

(5) (a) Kamijo, S.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 4764. (b) Esseveldt, B. C. J.; Delft, F. L.; Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717. (c) Kamijo. S.; Yamamoto Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 3230. (d) Takeda, A.; Kamijo. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (e) Yu, M. S.; Leon, L. L.; McGguire, M. A.; Botha, G. *Tetrahedron Lett.* **1998**, *39*, 9347. (f) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (g) Cacchi, S.; Carnicelli, V.; Marinelli, F. *J. Organomet. Chem.* **1994**, *475*, 289. (h) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Nagano, T.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1305. (i) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett.* **1989**, *30*, 2581.

(6) (a) Sakamoto, T.; Kondo, Y.; Iwashita, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1987**, *35*, 1823. (b) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 1845. (c) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1986**, *24*, 31.

(7) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529.

(8) (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (c) Dai, W. M.; Sun, L. P.; Guo, D. S. *Tetrahedron Lett.* **2002**, *43*, 7699. (d) Dai, W. M.; Guo, D. S.; Sun, L. P. *Tetrahedron Lett.* **2001**, *42*, 5275.

(9) For review, see: Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671.

(10) (a) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (b) Iritani, K.; Matsubara, S.; Uchimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1799.

(11) (a) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (b) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437.

(12) Yasuhara, A.; Kaneko, M.; Sakamoto, T. *Heterocycles* **1998**, *48*, 1793.

(13) (a) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (b) Kondo, Y.; Shiga, F.; Murata, N.; Sakamoto, T.; Yamanaka, H. *Tetrahedron* **1994**, *50*, 11803.

(14) (a) Dai, W.-M.; Guo, D.-S.; Sun, L.-P.; Huang, X.-H. *Org. Lett.* **2003**, *5*, 2919. (b) Yamazaki, K.; Nakamura, Y.; Kondo, Y. *J Org. Chem.* **2003**, *68*, 6011. For review, see: (c) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885.

(15) Only a limited number of examples for unsubstituted aniline cyclization reactions have been reported. See refs 3c, 5b,d−f, 8, and 10b.

10.1021/jo035528b CCC: $27.50
Published on Web 01/16/2004

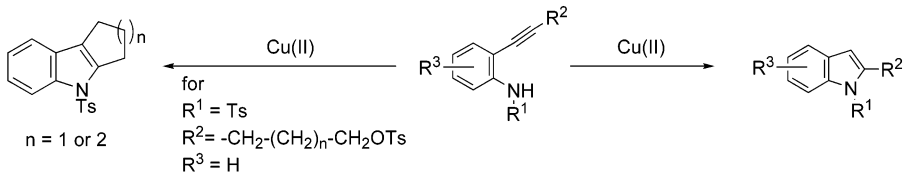


FIGURE 1.

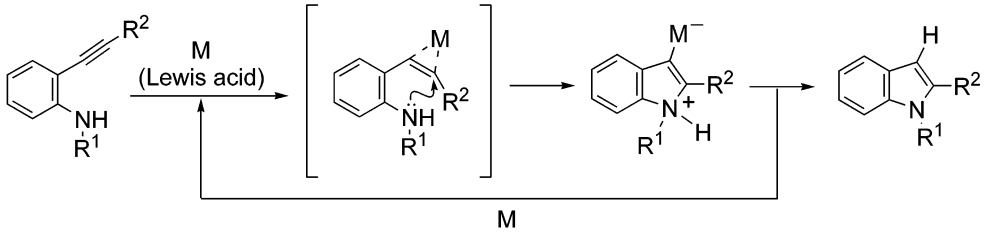


FIGURE 2.

reagents developed for the cyclization reaction of 2-ethynylaniline derivatives which have an electron-withdrawing group on the acetylene terminal. Recently, Knochel et al.[8a,b] reported the efficient indole formation of unsubstituted aniline derivatives mediated by ^{t}BuOK, KH, or ^{t}BuOCs in NMP. Although the cyclization reactions can occur at room temperature based on their conditions and that can be applied for the various substrates which contain hydroxyl groups, acetals, amino groups, and amides (for the linker with resin), it seems to be an unsolved problem as to whether alkaline-sensitive functional groups can be tolerated under the reaction conditions.

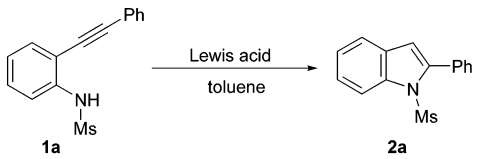
From the background described above, we decided to develop an efficient and general procedure that can be applied to a wide variety of molecules, especially those that have never been cyclized to indoles. Herein, we now report the mild, applicable, and versatile method for indole cyclization catalyzed by Cu(II) salts and its application to the sequential cyclization reaction (Figure 1).[16]

Results and Discussion

The Survey and the Optimization of the Reaction Conditions. For the effective catalytic cyclization reaction starting from 2-ethynylaniline derivatives, the triple bond first has to be activated by Lewis acids, which must not form a strong complex with the nitrogen atom. When the bond between the nitrogen and carbon atoms has been made, the metal−carbon bond at C3 (indole number) will be cleaved by the proton originally bound to the nitrogen atom, then the catalytic cycle will be accomplished (Figure 2).

Therefore, one of the key features to realize this reaction is finding some compound(s) that can selectively activate the triple bond. For this purpose, we decided to start surveying various Lewis acids employing the sulfonamides as the substrate which have the highest reactivity toward these kinds of the cyclization reactions (Table 1). BF_3·OEt_2, $TiCl_4$, $Ti(O^iPr)_4$, and $ZnCl_2$ did not effectively promote the cyclization reaction and **1a** was mainly recovered (entries 1−4). $AlCl_3$ and $Sn(OTf)_2$ induced the decomposition of the substrate (entries 5 and 6). Among the tested Lewis acids, $Cu(OTf)_2$ showed an effective promotion of the cyclization reaction (entry 7). In 1995, Saulnier et al. reported the $Cu(OAc)_2$-promoted indole formation reaction, when they tried to react 2-ethynyltrifluroacetanilide to synthesize the homo coupled product.[17] To the best of our knowledge, there has been no report about Cu(II) salt-mediated indole cyclization reactions except for this report.[18]

TABLE 1. Lewis Acid Promoted Cyclization Reactions of the Sulfonamide 1a



1a **2a**

entry	Lewis acid (equiv)	temp (°C)	time (h)	yield (**2a**) (%)	recovery (**1a**) (%)
1	BF_3·OEt_2 (1.5)	100	17	13	87
2	$TiCl_4$ (3)	100	22	14	69
3	$Ti(O^iPr)_4$ (3)	reflux	24	8	92
4	$ZnCl_2$ (3)	reflux	72	12	86
5	$AlCl_3$ (3)	60	2.5	dec	
6	$Sn(OTf)_2$ (3)	reflux	24	28	13
7	$Cu(OTf)_2$ (3)	reflux	10	89	0

We next investigated the effect of the counteranion and the catalytic version of this reaction (Table 2). In the presence of 20 mol % of $Cu(OTf)_2$, indole **4a** was afforded in 74% yield together with 19% of recovered **3a** (entry 1). Surprisingly, both $Cu(OMs)_2$[19] and $Cu(OTs)_2$[19] did not show any catalytic activities (entries 2 and 3). Arduini et al. reported that the nature of the Cu(II)−oxygen atom bond for Cu(II) sulfate is highly dependent on the acidity of the conjugated acid of the counteranion, which means

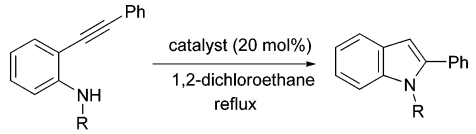
(16) Part of this work has been communicated previously: Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277.

(17) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841.

(18) Cyclization reactions of 2,3-allenoic acid and allenamide promoted by CuX_2 (X = Cl or Br) have been reported: (a) Ma, S.; Xie, H. *Org. Lett.* **2000**, 2, 3801. (b) Ma, S.; Wu, S. *J. Org. Chem.* **1999**, *64*, 9314.

(19) Arduini, A. L.; Garnett, M.; Thompson, R. C.; Wong, T. C. T. *Can. J. Chem.* **1975**, *53*, 3812.

TABLE 2. Cyclization Reaction of 1a or 3a Catalyzed by Various Cu(II) Salts



1a: R=Ms
3a: R=Ts

2a: R=Ms
4a: R=Ts

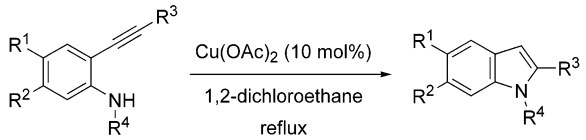
entry	substrate	catalyst	time (h)	yield (%)	recovery (%)
1	**3a**	$Cu(OTf)_2$	48	74 (**4a**)	19 (**3a**)
2	**3a**	$Cu(OMs)_2$	48	0	quant. (**3a**)
3	**3a**	$Cu(OTs)_2$	48	0	quant. (**3a**)
4	**3a**	$Cu(OBz)_2$	48	33 (**4a**)	67 (**3a**)
5	**3a**	$Cu(OAc)_2$	27	98 (**4a**)	0
6	**3a**	$Cu(OCOCF_3)_2 \cdot xH_2O$	48	56 (**4a**)	44 (**3a**)
7	**3a**	$Cu(OCHO)_2 \cdot xH_2O$	40	94 (**4a**)	0
8	**3a**	$Cu[CH(OH)COO]_2 \cdot xH_2O$	46	0	quant. (**3a**)
9	**3a**	$Cu(ClO_4)_2 \cdot 6H_2O$	48	trace	61 (**3a**)
10	**3a**	$Cu(BF_4)_2 \cdot xH_2O$	48	8 (**4a**)	92 (**3a**)
11	**3a**	$Cu(NO_3)_2 \cdot 3H_2O$	48	trace	85 (**3a**)
12	**3a**	$Cu[Et_2NCSS]_2$	48	0	quant. (**3a**)
13	**3a**	Cu bis(8-hydroxyquinolinate)	48	0	quant. (**3a**)
14	**1a**	$CuBr_2$ (10 mol %)	48	0	quant. (**1a**)
15	**1a**	CuF_2 (10 mol %)	72	7 (**2a**)	93 (**1a**)
16	**1a**	$CuCl_2$ (400 mol %)	48	0	quant. (**1a**)

that the Cu(II)−oxygen bond will have a more ionic character when the oxygen comes from the conjugated base of a stronger sulfonic acid.[19] According to their argument, the Cu(II)−O character of $Cu(OMs)_2$ and $Cu(OTs)_2$ will be more covalent than that of $Cu(OTf)_2$ and it seems likely that the trifluoromethanesulfonic anion can easily be eliminated when the Cu(II) atom coordinates to the acetylene. Therefore, we speculated that the elimination of the counteranion must be essential for these reactions.

On the other hand, Cu(II) carboxylates tended to show higher catalytic activities than $Cu(OTf)_2$. $Cu(OAc)_2$ is the best catalyst for this substrate among the tested Cu(II) salts (entry 5). However, a lower reaction rate was observed when $Cu(OBz)_2$ was used as the catalyst (entry 6). The reason for the difference between $Cu(OAc)_2$ and $Cu(OBz)_2$ has not yet been clarified, but one possibility is the difference in the solubility in 1,2-dichloroethane. Before starting the reactions, we expected the salts, which contain crystalline water, will have either lower or no catalytic activities. Although Cu(II) tartrate hydrate did not show any activities, $Cu(OCOCF_3)_2 \cdot xH_2O$ and $Cu(OCHO)_2 \cdot xH_2O$ catalyzed the reaction, especially the latter showed an almost comparable activity as $Cu(OAc)_2$ (entries 6, 7, and 8). These results suggest that this reaction was not sensitive for moisture to the solvent, which will be a great advantage for practical uses. As the structures of the Cu(II) carboxylates are known to be dimeric,[20] it seems likely that one copper atom assists in the elimination of the carboxylate residue from the other copper atom. Again, it is also suggested that the elimination of the counteranion from the copper atom is crucial for these cyclization reactions to occur.

(20) (a) Cotton, F. A.; Wilkinson, G.; Murillo, C. A.; Bochmann, M. *Advanced Inorganic Chemistry*, 6th ed.; John Wiley & Sons: NewYork, 1999; p 870. (b) Crystal structure of $Cu(OCOCF_3)_2 \cdot xH_2O$: Karpova, E. V.; Boltalin, A. I.; Zakharov, M. A.; Sorokina, N. I.; Korenev, Y. M. *Z. Anorg. Allg. Chem.* **1998**, *624*, 741. (c) Crystal structure of $Cu(OCHO)_2 \cdot xH_2O$: Kiriyama, R.; Ibamoto, H.; Matsuo, K. *Acta Crystallogr.* **1954**, *7*, 482.

TABLE 3. Cyclization Reaction of the Various Substrates Catalyzed by $Cu(OAc)_2$



1a-k **2a-k**

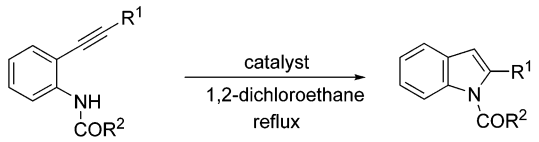
entry	substrate	R^1	R^2	R^3	R^4	time (h)	yield (%)	recovery (%)
1	**1a**	H	H	Ph	Ms	18	94 (**2a**)	0
2	**1b**	H	H	Bu	Ms	20	91 (**2b**)	0
3	**1c**	H	H	H	Ms	1.5	87 (**2c**)	0
4[a]	**1d**	H	H	CH_2OH	Ts	2	76 (**2d**)	0
5	**1e**	H	H	CO_2Me	Ms	24	79 (**2e**)	0
6	**1f**	H	H	^{t}Bu	Ms	72	22 (**2f**)	74 (**1f**)
7	**1g**	H	H	TMS	Ms	72	9 (**2g**)	64 (**1g**)
8	**1h**	Br	H	Ph	Ms	7	76 (**2h**)	0
9	**1i**	CN	H	Ph	Ms	50	74 (**2i**)	0
10	**1j**	H	OMe	Ph	Ms	38	95 (**2j**)	0
11	**1k**	Me	H	Ph	Ms	6	97 (**2k**)	0

[a] 20 mol % of $Cu(OAc)_2$ was used.

The other Cu(II) salts, which include the inorganic and halogen counteranions, did not afford satisfactory results (entries 9−16).

At this stage, we concluded that $Cu(OAc)_2$ is the best catalyst for the sulfonamide. We next applied this condition to the functionalized substrates and these results are summarized in Table 3. The chemical properties of substituents on the acetylene terminal (R^3) did not affect the yields of the indoles, even if the hydroxyl group is present in the molecule (entries 1−5). However, the balkiness of the substituents has significant effect on the yield of the indoles. Namely, when the substituents are too big to inhibit the approach of the catalyst and/or nitrogen atom such as ^{t}Bu and TMS, the yields significantly decreased (entries 6 and 7). The remarkable feature of the Cu(II) salt-catalyzed reaction is the ability to synthesize the indole, which has an electron-with-

TABLE 4. Cyclization Reaction of the Carbamates Catalyzed by Cu(II) Salts



5a-d, 5g, 7a **6a-c, 9a**

entry	substrate	R^1	R^2	catalyst (mol %)	time (h)	yield (%)	recovery (%)
1	**5a**	Ph	OEt	$Cu(OAc)_2$ (10)	72	20 (**6a**)	65 (**5a**)
2	**5a**	Ph	OEt	$Cu(OBz)_2$ (20)	48	0	quant. (**5a**)
3	**5a**	Ph	OEt	$Cu(OCHO)_2 \cdot xH_2O$ (20)	48	0	quant. (**5a**)
4	**5a**	Ph	OEt	$Cu(OCOCF_3)_2 \cdot xH_2O$ (20)	48	33 (**6a**), 28 (**9a**)[a]	38 (**5a**)
5	**5a**	Ph	OEt	$Cu(OTf)_2$ (10)	28	88 (**6a**)	0
6	**5b**	Bu	OEt	$Cu(OTf)_2$ (10)	48	81 (**6b**)	0
7	**5c**	H	OEt	$Cu(OTf)_2$ (10)	48	35 (**6c**)	4 (**5c**)
8	**5d**	CH_2OH	OEt	$Cu(OTf)_2$ (20)	19	dec	0
9	**5g**	TMS	OEt	$Cu(OTf)_2$ (20)	21	28 (R^1 = H) (**6c**)	0
10	**7a**	Ph	Me	$Cu(OAc)_2$ (20)	48	0	quant. (**7a**)
11	**7a**	Ph	Me	$Cu(OTf)_2$ (20)	48	dec	0

[a] **9a**: 2-phenylindole.

drawing group at C-2 (indole number) (entry 5). In this case, the dimeric product was not observed at all and only 2-carbomethoxylindole **2e** was isolated. To the best of our knowledge, the cyclization reactions of such substrates have not been reported with use of any other reagents.

The functional group(s) on the aromatic ring also did not affect the reaction efficiency, namely, in the presence of either electron-withdrawing groups (bromine and nitrile; entries 8 and 9) or electron-donating groups (methoxyl and methyl; entries 10 and 11), the yield of the indoles were within 70−95%.

To investigate the scope and limitations of the Cu(II)-catalyzed indole syntheses, we next tried to use a series of carbamates and acetate as the substrates (Table 4). In contrast to the sulfonamides, the Cu(II)-carboxylates did not give satisfactory results, only recovery of the starting material (entries 2 and 3) or a yield only twice the amount of the catalyst (entry 1). Only $Cu(OCOCF_3)_2 \cdot xH_2O$ gave the indole in 61% yield, but almost half of the product was decarboethoxylated **9a** (entry 4). The best catalyst for the carbamates **5a** and **5b** was $Cu(OTf)_2$, which catalyzed the cyclization reaction in 81−88% yield (entries 5 and 6), but it is apparent that even this salt did not show general application properties for the other substrates (e.g., entries 8 and 9). Furthermore, the corresponding acetamide **7a** was negative toward this cyclization reaction by any tested Cu(II) salts and only the recovered starting materials were observed (entries 10 and 11).[21]

We next investigated the application of the Cu(II)-catalyzed cyclization reactions to the unsubstituted aniline derivatives. In general, the cyclization of the unsubstituted aniline derivatives seems to be useful because the substituents on the nitrogen atom do not have to be added and there have been only a few reports about the cyclization of such substrates.[15] However, before starting the investigation, we had doubts about the possibility of these reactions, because the Cu(II) salt could bind tightly to the lone pair of the nitrogen atom and the acidity of the hydrogen atom on the nitrogen seems to be not high enough. Thus, we tested the reaction using the five different Cu(II) salts and 2-phenylethynylaniline **8a** as the substrates (Table 5). As a result, $Cu(OTf)_2$, $Cu(OBz)_2$, and the $Cu(OCOCF_3)_2 \cdot xH_2O$ catalyzed the cyclization reactions, especially, the third compound produced the fastest and cleanest reaction (entries 2, 3, and 5). This compound can also be applied to other substrates which have various substituents on the aromatic ring (entries 6−9). The secondary amines **10a**,**c**,**m** also could be cyclized into the corresponding indole rings by $Cu(OAc)_2$ catalysis in good yield (entries 10, 11, and 12).

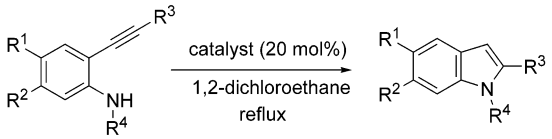
Reaction Mechanism. From the results described above, it is likely that the reactivity of the substrates was highly dependent on the acidity of the proton on the nitrogen atom. This hypothesis was confirmed by the reactions in the presence of an extra base (Scheme 1). When the cyclization reaction was performed in the presence of 2 equiv of 1-ethylpiperidine, the reaction rate was highly accelerated and the corresponding indole was afforded even at room temperature. As we have already confirmed that the reaction did not progress at all in the absence of $Cu(OAc)_2$, it is apparent that the amine base might facilitate the reaction by assistance with the deprotonation from the nitrogen atom.

Therefore, we speculate that the mechanism of the Cu-(II)-catalyzed cyclization reaction for the sulfonamides and carbamates is as shown in Figure 3.

The catalytic process starts from the ligation of the acetylene moiety to the copper atom (**A** → **B**). From intermediate **B**, two different pathways can be considered depending on the counteranion (X^-). If the counteranion is not a strong enough base to remove the proton on the nitrogen atom, the lone pair may attack the activated acetylene to produce **D**, next the proton will be eliminated by the counteranion (**B** → **C** → **D**). On the other hand, if the counteranion is strong enough to remove the proton on the nitrogen atom, deprotonation will occur first, followed by cyclization (**B** → **E** → **F**). Finally, the C3 position of the indole is protonated and the catalyst is regenerated (**F** → **G**). For this reaction, more electrophilic

(21) The same observation has been reported for the solid-phase reaction. See ref 14a.

TABLE 5. Cyclization Reaction of Unsubstituted Anilines Catalyzed by Cu(II) Salts



8a,h, j-l,10a,c,m **9a,h,j-l,11a,c,m**

entry	substrate	catalyst	R^1	R^2	R^3	R^4	time (h)	yield (%)
1	**8a**	$Cu(OAc)_2$	H	H	Ph	H	48	32 (**9a**)[a]
2	**8a**	$Cu(OTf)_2$	H	H	Ph	H	1.5	63 (**9a**)
3	**8a**	$Cu(OBz)_2$	H	H	Ph	H	48	79 (**9a**)
4	**8a**	$Cu(OCHO)_2 \cdot xH_2O$	H	H	Ph	H	48	32 (**9a**)[b]
5	**8a**	$Cu(OCOCF_3)_2 \cdot xH_2O$	H	H	Ph	H	2	72 (**9a**)
6	**8h**	$Cu(OCOCF_3)_2 \cdot xH_2O$	Br	H	Ph	H	4	83 (**9h**)
7	**8j**	$Cu(OCOCF_3)_2 \cdot xH_2O$	H	OMe	Ph	H	6	58 (**9j**)
8	**8k**	$Cu(OCOCF_3)_2 \cdot xH_2O$	Me	H	Ph	H	2.5	71 (**9k**)
9	**8*l***	$Cu(OCOCF_3)_2 \cdot xH_2O$	H	CN	Ph	H	24	84 (**9*l***)
10	**10a**	$Cu(OAc)_2$[c]	H	H	Ph	PMB[d]	48	92 (**11a**)
11	**10c**	$Cu(OAc)_2$	H	H	H	PMB[d]	48	89 (**11c**)
12	**10m**	$Cu(OAc)_2$	H	H	$(CH_2)_4OTBS$	^{i}Pr	48	100 (**11m**)

[a] 67% of **8a** was recovered. [b] 64% of **8a** was recovered (yields were calculated from ^{1}H NMR). [c] 40 mol % of $Cu(OAc)_2$ was used. [d] PMB: *p*-methoxybenzyl

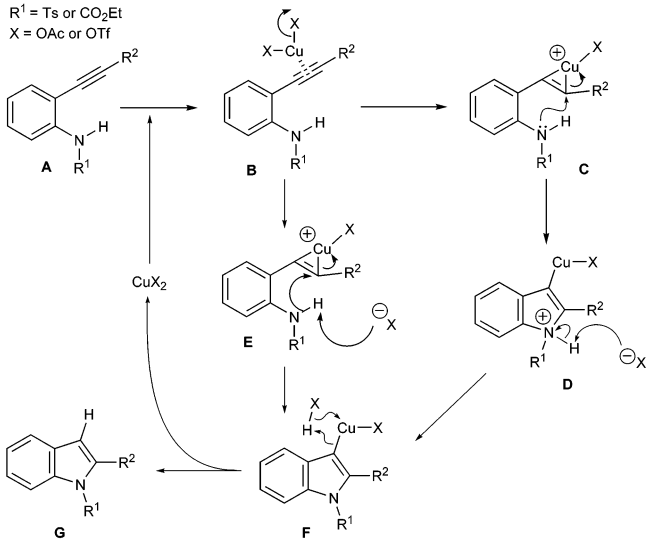
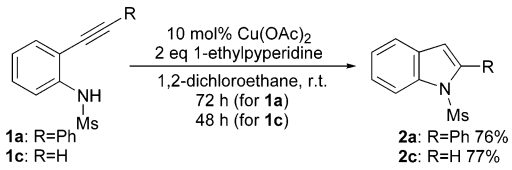


FIGURE 3.

SCHEME 1



copper might favor the activation of the acetylene moiety toward nucleophilic attack, but a stronger base could be more efficient in the cyclization step on the pathway **B** → **F** → **G**. The different reactivity depending on the copper salts and the nature of R^1 might depend on a different balance between these two effects. For the unsubstituted and secondary anilines, the coordination of the copper atom between acetylene moiety and nitrogen atom cannot be ruled out.

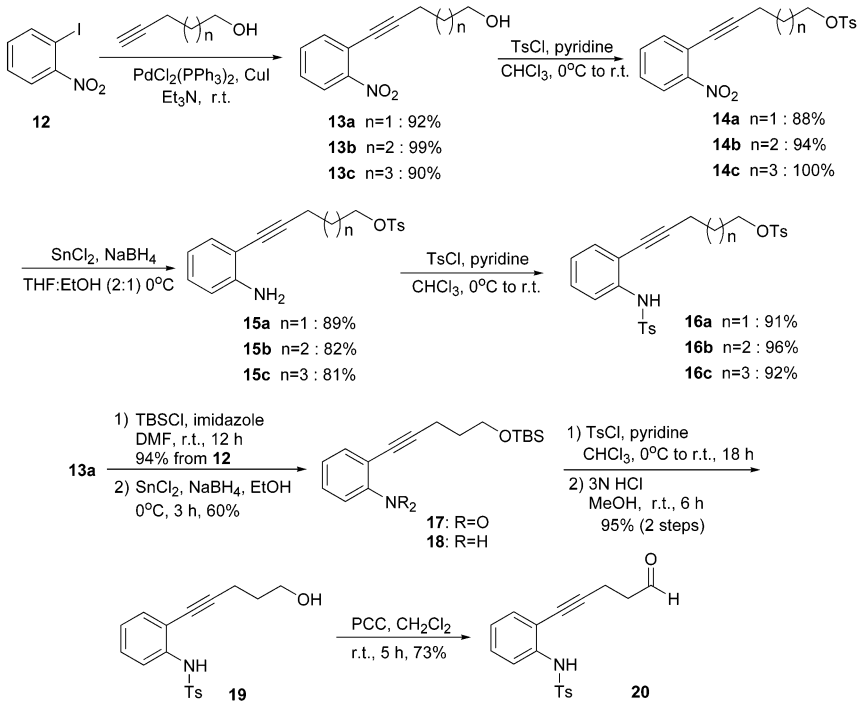
Sequential Cyclization Reactions. The spontaneous indole cyclization and C-3 functionalization reactions have been developed with use of Pd(II) catalysts.[9] However, the reactants for this reaction were limited to the allyl halides,[10] aryl halides,[11] vinyl triflates,[11b] olefin (Heck reaction),[12] and carbon monoxide (carbonylation).[13] In the Cu(II)-catalyzed reaction, the catalyst was regenerated by quenching of the C3−CuX species by the proton that was originally bound on the nitrogen atom. Therefore, we tried to examine our cyclization reaction of the compounds having the electrophilic part in the same molecule that was treated with base to remove the proton on the nitrogen group to realize the sequential cyclization reaction that cannot be done by the Pd catalysis.

Three kinds of substrates were synthesized from **12** in the same way by the standard 4-step sequences (Scheme 2). The aldehyde **20** was synthesized from **13a** in 5 steps and in good overall yield.

For developing the optimum conditions, we chose **16a** as the substrate and surveyed the reaction conditions (Table 6). For the reaction without the base treatment, the monocyclized indole was obtained almost quantitatively as the sole product (entry 1). The base-promoted cyclization reaction can be neglected (entry 2). The combination of KH and $Cu(OAc)_2$ seems to be essential for this reaction, but the amount of $Cu(OAc)_2$ is important, namely, the excess amount of copper salts produced a lower yield, but a smaller amount of the reagent needed a longer reaction time and the yield was also disappointing (entries 4, 5, and 6). The high reaction temperature also caused the low yield (entry 7). The solvent is another important factor for this reaction and 1,2-dichloroethane was the best solvent among those tested (entries 5, 8, and 9).

To clarify the scope and limitation of this reaction, we tested both substrates which have longer carbon chains than **16a** and a carbonyl group instead of a tosyloxy group. The yields of the tricyclic compounds were depressed corresponding to the length of the carbon chain and only the monocyclized compound **22c** was isolated when **16c** was reacted. As a consequence, it appeared that the second cyclization reaction can be applied for only five- and six-membered-ring syntheses (Scheme 3).

SCHEME 2



12

13a n=1 : 92%
13b n=2 : 99%
13c n=3 : 90%

14a n=1 : 88%
14b n=2 : 94%
14c n=3 : 100%

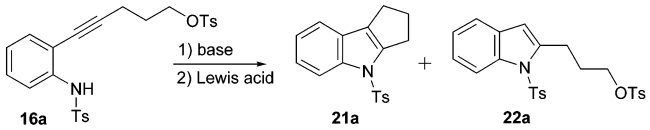
15a n=1 : 89%
15b n=2 : 82%
15c n=3 : 81%

16a n=1 : 91%
16b n=2 : 96%
16c n=3 : 92%

17: R=O
18: R=H

19 **20**

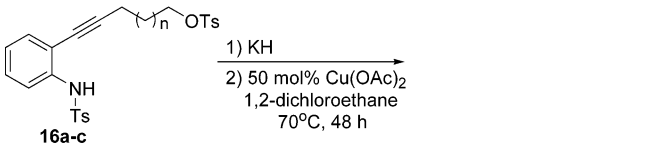
TABLE 6. The Sequential Cyclization Reactions



16a **21a** **22a**

						yield (%)	
entry	Lewis acid (mol %)	base	solvent	temp. (°C)	time (h)	**21a**	**22a**
1	$Cu(OAc)_2$ (50)		toluene	70	48		100
2		KH	toluene	70	48	7	
3	$Cu(OTf)_2$ (50)	KH	toluene	70	48	46	9
4	$Cu(OAc)_2$ (120)	KH	toluene	70	48	26	
5	$Cu(OAc)_2$ (50)	KH	toluene	70	48	51	
6	$Cu(OAc)_2$ (20)	KH	toluene	70	72	20	trace
7	$Cu(OAc)_2$ (50)	KH	toluene	reflux	20	40	
8	$Cu(OAc)_2$ (50)	KH	trifluorotoluene	70	48	28	
9	$Cu(OAc)_2$ (50)	KH	1,2-dichloroethane	70	48	67	

SCHEME 3



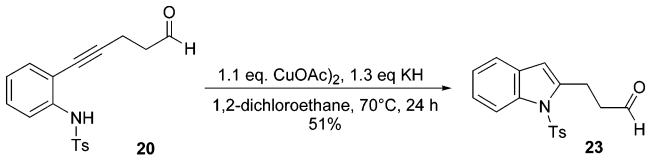
16a-c

21a (n=1): 67%
21b (n=2): 64%
21c (n=3): 0%

22a (n=1): 0%
22b (n=2): 13%
22c (n=3): 59%

Not only the application to larger ring formations but also the trapping reaction by the carbonyl was disappointing. The only indole aldehyde **23** was isolated when even a stoichiometric amount of $Cu(OAc)_2$ was used

SCHEME 4



20 **23**

(Scheme 4). Further studies on the other kind of sequential reactions are now in progress.

Synthesis of Hippadine. Hippadine **24** was one of the lycorine alkaloids isolated from various species of *Amaryllidaceae* and known to have inhabitation effects on fertility in male rats.[22] Due to its unique structure, hippadine **24** had been synthesized by many organic chemists using independent approaches.[23] As we wanted to synthesize the indole part of hippadine **24** at the later

(22) Ghosal, S.; Rao, P. H.; Jaiswal, D. K.; Kumar, Y.; Frahm, A. W. *Phytochemistry* **1981**, *20*, 2003.

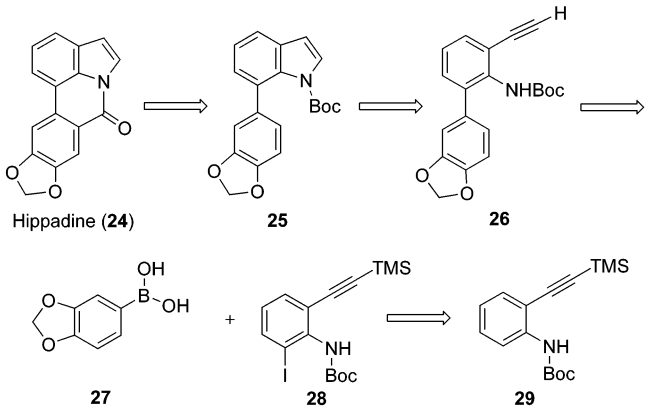


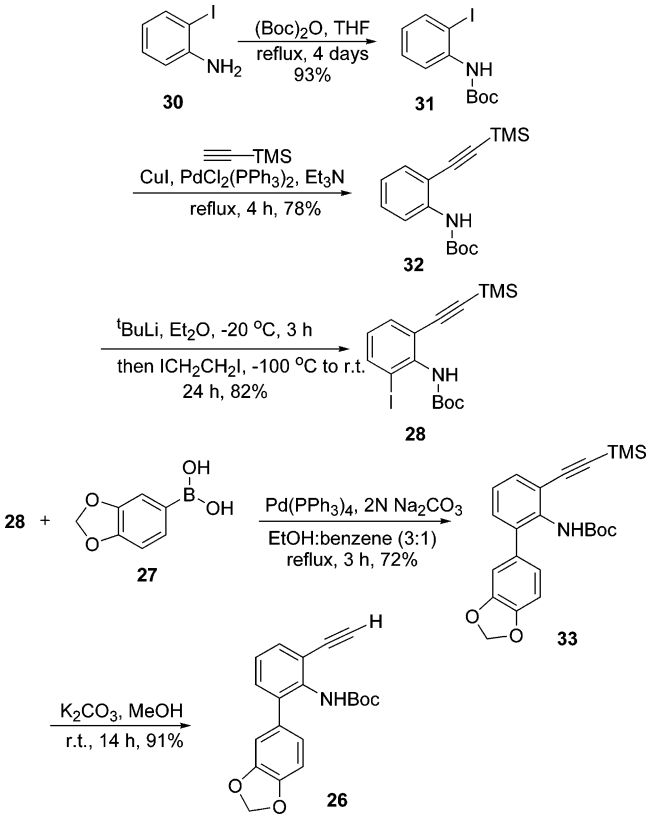
FIGURE 4.

stage of the synthesis, we have to first construct the bisaromatic compound. To realize this basic idea, we considered synthesizing **26** by the palladium-catalyzed Suzuki−Miyaura coupling reaction between the boronic ester **27** and iodide **28**. The iodine atom of **28** could be introduced to the ortho position of the nitrogen function of **29** by using a regioselective lithiation reaction[2b,c] (Figure 4).

N-Boc-2-iodoaniline **31**, which was synthesized from commercially available 2-iodoaniline **30** with a standard procedure, was subjected to the Sonogashira coupling reaction with TMS−acetylene to afford **32** in a good overall yield. The regioselective lithiation reaction of **32** was successful by reacting with ^{t}BuLi in Et_2O at −20 °C and the resulting lithium salt was trapped by the iodine atom at −100 °C using 1,2-diiodoethane to afford **28**[2c] in 82% yield. The palladium-catalyzed Suzuki−Miyaura coupling reaction between the iodide **28** and easily available **27** (which contains some amounts of anhydride) was carried out under standard conditions to produce the bisaromatic compound **33** in 72% yield, followed by the TMS group that was eliminated under solvolysis conditions (Scheme 5).

As the substrate for the indole synthesis had been furnished in good overall yield, we next examined the cyclization reaction of **26**. When a solution of **26** in 1,2-dichloroethane in the presence of a stoichiometric amount of $Cu(OAc)_2$ was refluxed for 5 h, the 1-Boc-indole **25** was produced in 80% yield. The Boc group of **25** was eliminated under acidic conditions to provide indole **34**, which was converted to hippadine **24** by Banwell et al.[23g] in 4 steps, thus formal synthesis of hippadine **24** was accomplished. On the other hand, **34** was converted to formamide **35** by the reaction between the sodium salt of **34** and acetic formic anhydride.[24] Finally, **35** was

SCHEME 5



subjected to the Bischler−Napieralski reaction with $(TfO)_2O$ and DMAP[23f,25] that directly provided hippadine **24** via the cyclic acetal **36**, followed by an air oxidation reaction, although the yield has to be improved (Scheme 6).

Conclusion

We have developed a relatively general and efficient method for indole cyclization reactions from 2-ethynyl aniline derivatives. The distinctive features of our reactions are the following:

(1) The Cu(II)-catalyzed reaction can be applied to not only the sulfonamides, but also the unsubstituted primary and secondary aniline derivatives. The yield of the Cu(II)-promoted cyclization reaction is not affected by the chemical properties of the substituted groups on both the aromatic ring and acetylene terminal. However, the yields of the indoles are dependent on the bulkiness of the substituents on the acetylene terminal.

(2) It is possible to realize the sequential cyclization reaction of the 2-ethynyl aniline derivatives which have a leaving group in the same molecule. However, the product for this reaction is limited to the five- and six-membered rings for the second cyclization.

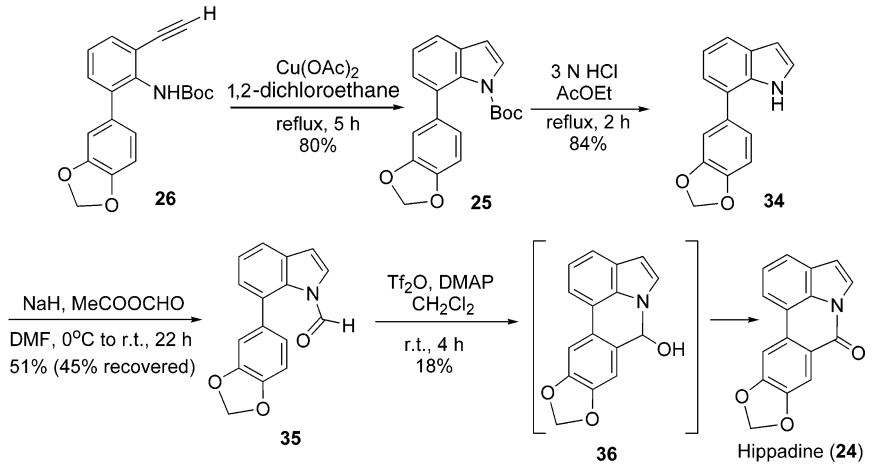
Thus, we could demonstrate the application of the Cu(II)-promoted cyclization reaction for the hippadine synthesis. Further studies including the synthesis of the

(23) (a) Hartung, C. G.; Fecher, A.; Chapell, B.; Snieckus, V. *Org. Lett.* **2003**, *5*, 1899. (b) Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120. (c) Padwa, A.; Brodney, M. A.; Liu, B.; Satake, K.; Wu, T. *J. Org. Chem.* **1999**, *64*, 3595. (d) Harrowven, D. C.; Lai, D.; Lucas, M. C. *Synthesis* **1999**, 1300. (e) Miki, Y.; Shirokoshi, H.; Matushita, K. *Tetrahedron Lett.* **1999**, *40*, 4347. (f) Hutchings, R. H.; Meyers, I. A. *J. Org. Chem.* **1996**, *61*, 1004. (g) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. R.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551. (h) Sakamoto, T.; Yasuhara, A.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1993**, *36*, 2597. (i) Grigg, R.; Teasdale, A.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 3859. (j) Siddiqui, M. A.; Snieckus, V. *Tetrahedron Lett.* **1990**, *31*, 1523. (k) Hayakawa, K.; Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1987**, *28*, 5895.

(24) Krimen, L. I. *Organic Syntheses*; Wiley: New York, 1988; Collect Vol. VI, p 8.

(25) (a) Banwell, M. G.; Havey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241. (b) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3515.

SCHEME 6



biologically active compounds with our methodology are now in progress in our laboratory.

Experimental Section

General Procedure for the Selected Entries for Tables 3 and 5. A solution of 2-ethynylaniline derivatives in anhydrous toluene or 1,2-dichloroethane was added to a suspension of Lewis acid in anhydrous toluene or 1,2-dichloroethane, then the mixture was heated at the temperature and for the reaction time listed in the tables. Water was added to the mixture and 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.

1-Methylsulfonyl-2-phenylindole (2a) (Table 3, entry 1). A solution of **1a** (100.2 mg, 0.37 mmol) and $Cu(OAc)_2$ (6.7 mg, 0.037 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 18 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:10)] to afford **2a** (94.1 mg, 94%) as a colorless solid; mp 115−117 °C (colorless needles from AcOEt−hexane, lit.[7] mp 115−116 °C); IR (film, cm^{-1}) 1367, 1171; ^1H NMR (300 MHz, $CDCl_3$) δ 2.74 (3H, s), 6.72 (1H, s), 7.35−7.45 (5H, m), 7.56−7.62 (3H, m), 8.13 (1H, d, J = 7.1 Hz); MS m/z 271 (M^+, 51.3), 192 (100), 165 (51.8); HRMS calcd for $C_{15}H_{13}NO_2S$ 271.0667, found 271.0673.

1-Methylsulfonyl-2-butylindole (2b) (Table 3, entry 2). A solution of **1b** (103.2 mg, 0.41 mmol) and $Cu(OAc)_2$ (7.4 mg, 0.041 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 20 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:10)] to afford **2b** (94.4 mg, 91%) as a colorless solid; mp 80−81 °C (colorless needles from AcOEt−hexane, lit.[7] mp 81−82 °C); IR (film, cm^{-1}) 1366, 1171; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.7 Hz), 1.46 (2H, sex, J = 7.7 Hz), 1.75 (2H, quint, J = 7.7 Hz), 2.96 (2H, t, J = 7.7 Hz), 3.00 (3H, s), 6.46 (1H, s), 7.23−7.30 (2H, m), 7.47−7.52 (1H, m), 8.00 (1H, d, J = 8.1 Hz); MS m/z 251 (M^+, 36.8), 209 (39.5), 130 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.1012.

1-Methylsulfonylindole (2c) (Table 3, entry 3). A solution of **1c** (90.6 mg, 0.47 mmol) and $Cu(OAc)_2$ (8.6 mg, 0.047 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 1.5 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **2c**[7] (79.1 mg, 87%) as a yellow oil; IR (neat, cm^{-1}) 1361, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 3.09 (1H, s), 6.72 (1H, d, J = 3.7 Hz), 7.30 (1H, td, J = 7.8, 1.2 Hz), 7.37 (1H, td, J = 7.8, 1.2 Hz), 7.44 (1H, d, J = 3.7 Hz), 7.63 (1H, br d, J = 7.8 Hz), 7.92 (1H, dd, J = 7.8, 0.7 Hz); MS m/z 195 (M^+, 54.6), 116 (100); HRMS calcd for $C_9H_9NO_2S$ 195.0354, found 195.0359.

1-*p*-Tolylsulfonyl-2-hydroxymethylindole (2d) (Table 3, entry 4). A solution of **1d** (100.7 mg, 0.33 mmol) and $Cu(OAc)_2$ (12.5 mg, 0.069 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 2 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:3)] to afford **2d** (76.2 mg, 76%) as a colorless solid; mp 91−92 °C (colorless needles from AcOEt−hexane); IR (film, cm^{-1}) 3566, 3425, 1367, 1173; ^1H 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), 7.04 (1H, d, J = 7.7 Hz); MS m/z 301 (M^+, 68.4), 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.

Methyl1-Methylsulfonyl-2-indolecarboxylate (2e) (Table 3, entry 5). A solution of **1e** (43.6 mg, 0.17 mmol) and $Cu(OAc)_2$ (3.0 mg, 0.017 mmol) in anhydrous 1,2-dichloroethane (8 mL) was refluxed for 24 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **2e** (34.5 mg, 79%) as a colorless solid; mp 89−91 °C (colorless prisms from AcOEt−hexane); IR (film, cm^{-1}) 1728, 1435, 1367, 1352, 1205; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71 (3H, s), 3.96 (3H, s), 7.30 (1H, s), 7.31 (1H, br t, J = 8.0 Hz), 7.45 (1H, td, J = 8.0, 1.1 Hz), 7.65 (1H, br d, J = 8.0 Hz), 8.05 (1H, br d, J = 8.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 43.5, 52.7, 115.0, 117.2, 122.7, 123.8, 127.18, 127.22, 130.4, 138.5, 161.3; MS m/z 253 (M^+, 49.2), 175 (100), 141 (92.1); HRMS calcd for $C_{11}H_{11}NO_4S$ 253.0409, found 253.0406.

1-Methylsulfonyl-2-(1,1-dimethylethyl)indole (2f) (Table 3, entry 6). A solution of **1f** (99.7 mg, 0.40 mmol) and $Cu(OAc)_2$ (7.6 mg, 0.042 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 72 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:10)] to afford **2f** (22.1 mg, 22%) as a yellow oil. From the later fraction, **1f** (73.3 mg, 74%) was recovered. **2f**: IR (neat, cm^{-1}) 1371, 1176; ^1H NMR (300 MHz, $CDCl_3$) δ 1.56 (9H, s), 2.94 (3H, s), 6.62 (1H, s), 7.23−7.32 (2H, m), 7.49 (1H, d, J = 6.9 Hz), 8.08 (1H, d, J = 7.1 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^+, 42.4), 236 (50.7), 172 (100); HRMS calcd for $C_{13}H_{17}NO_2S$ 251.0980, found 251.0966.

1-Methylsulfonyl-2-trimethylsilylindole (2g) (Table 3, entry 7). A solution of **1g** (101.3 mg, 0.38 mmol) and $Cu(OAc)_2$ (7.2 mg, 0.040 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 72 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:10)] to afford **2g**[5h] (9.0 mg, 9%) as a yellow oil. From the later fraction, **1g** (64.5 mg, 64%) was recovered. **2g**: IR (neat, cm^{-1}) 1366, 1170; ^1H NMR (300 MHz, $CDCl_3$) δ 0.41 (9H, s), 3.01 (3H, s), 6.95 (1H, s), 7.28 (1H, td, J = 8.1, 0.9 Hz), 7.36 (1H, td, J = 8.1, 0.9 Hz), 7.59 (1H, br d, J = 8.1 Hz), 8.00 (1H, br d, J = 8.1 Hz); MS m/z 267 (M^+,

27.7), 252 (100), 189 (55.3); HRMS calcd for $C_{12}H_{17}NO_2SSi$ 267.0749, found 267.0710.

5-Bromo-1-methylsulfonyl-2-phenylindole (2h) (Table 3, entry 8). A solution of **1h** (35.0 mg, 0.10 mmol) and $Cu(OAc)_2$ (1.8 mg, 0.010 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 7 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **2h** (26.7 mg, 76%) as a colorless solid; mp 186−187 °C (colorless needle from AcOEt−hexane); IR (film, cm^{-1}) 1361, 1177; ^1H NMR (300 MHz, $CDCl_3$) δ 2.76 (3H, s), 6.65 (1H, s), 7.40−7.50 (4H, m), 7.50−7.58 (2H, m), 7.74 (1H, d, J = 1.4 Hz), 8.01 (1H, d, J = 8.8 Hz); MS m/z 351 ($M^+ + 2$, 66.4), 349 (M^+, 65.3), 272 (98.8), 270 (100), 191 (94.3). Anal. Calcd for $C_{15}H_{12}NO_2BrS$: C, 51.44; H, 3.45; N, 4.00. Found: C, 51.39; H, 3.47; N, 3.86.

5-Cyano-1-methylsulfonyl-2-phenylindole (2i) (Table 3, entry 9). A solution of **1i** (34.9 mg, 0.12 mmol) and $Cu(OAc)_2$ (2.4 mg, 0.013 mmol) in anhydrous 1,2-dichloroethane (7 mL) was refluxed for 50 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **2i** (25.9 mg, 74%) as a colorless solid; mp 213−214 °C (colorless needle from AcOEt−hexane); IR (film, cm^{-1}) 2226, 1371, 1175; ^1H NMR (300 MHz, $CDCl_3$) δ 2.87 (3H, s), 6.74 (1H, s), 7.41−7.59 (5H, m), 7.64 (1H, d, J = 8.5 Hz), 7.95 (1H, s), 8.25 (1H, d, J = 8.5 Hz); MS m/z 296 (M^+, 58.4), 217 (100), 190 (62.5). Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 64.85; H, 4.08; N, 9.45. Found: C, 64.94; H, 4.26; N, 9.28.

1-Methylsulfonyl-6-methoxy-2-phenylindole (2j) (Table 3, entry 10). A solution of **1j** (103.6 mg, 0.34 mmol) and $Cu(OAc)_2$ (5.7 mg, 0.031 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 38 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **2j** (98.8 mg, 95%) as a colorless solid; mp 134−135 °C (colorless prisms from AcOEt−hexane); IR (film, cm^{-1}) 1612, 1367, 1180; ^1H NMR (300 MHz, $CDCl_3$) δ 2.72 (3H, s), 3.91 (3H, s), 6.64 (1H, s), 6.98 (1H, dd, J = 8.5, 2.2 Hz), 7.38−7.44 (3H, m), 7.47 (1H, d, J = 8.6 Hz), 7.52−7.60 (2H, m), 7.69 (1H, d, J = 2.2 Hz); MS m/z 301 (M^+, 40.6), 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.

1-Methylsulfonyl-5-methyl-2-phenylindole (2k) (Table 3, entry 11). A solution of **1k** (71.6 mg, 0.25 mmol) and $Cu(OAc)_2$ (4.8 mg, 0.026 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 6 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **2k** (69.1 mg, 97%) as a colorless solid; mp 137−138 °C (colorless needles from AcOEt−hexane); IR (film, cm^{-1}) 1366, 1173; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (3H, s), 2.70 (3H, s), 6.66 (1H, s), 7.20 (1H, d, J = 8.6 Hz), 7.38−7.46 (4H, m), 7.54−7.60 (2H, m), 7.99 (1H, d, J = 8.5 Hz); ^{13}C NMR (100 MHz, CDCl3) δ 21.3, 39.0, 113.0, 115.5, 120.9, 126.4, 127.6, 128.7, 130.0, 130.5, 132.0, 142.2, 136.2, 142.1; MS m/z 285 (M^+, 47.5), 206 (100); HRMS calcd for $C_{16}H_{15}NO_2S$ 285.0824, found 285.0848. 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.

5-Bromo-2-phenylindole (9h) (Table 5, entry 6). A solution of **8h** (108.3 mg, 0.40 mmol) and $Cu(OCOCF_3)_2 \cdot xH_2O$ (23.0 mg, 0.079 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 4 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **9h** (89.5 mg, 83%) as a pale yellow solid; mp 194−195 °C (colorless plates from Et_2O−hexane, lit.[7] mp 196−198 °C); IR (film, cm^{-1}) 3435; ^1H NMR (400 MHz, $CDCl_3$) δ 6.75 (1H, s), 7.24−7.29 (2H, m), 7.34 (1H, t, J = 7.5 Hz), 7.44 (2H, t, J = 7.7 Hz), 7.64 (2H, d, J = 7.8 Hz), 7.74 (1H, s), 8.38 (1H, br); MS m/z 273 ($M^+ + 2$, 95.7), 271 (M^+, 100); HRMS calcd for $C_{14}H_{10}NBr$ 270.9997, found 270.9994.

6-Methoxy-2-phenylindole (9j) (Table 5, entry 7). A solution of **8j** (98.2 mg, 0.44 mmol) and $Cu(OCOCF_3)_2 \cdot xH_2O$ (24.1 mg, 0.083 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 6 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **9j** (56.8 mg, 58%) as a pale yellow solid; mp 169−171 °C (colorless plates from acetone−hexane, lit.[7] mp 171−172 °C); IR (KBr, cm^{-1}) 3394; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (3H, s), 6.74 (1H, d, J = 2.0 Hz), 6.79 (1H, dd, J = 8.5, 2.0 Hz), 6.88 (1H, d, J = 2.0 Hz), 7.28 (1H, t, J = 7.7 Hz), 7.41 (2H, t, J = 7.7 Hz), 7.48 (1H, br d, J = 8.5 Hz), 7.60 (2H, d, J = 7.7 Hz), 8.25 (1H, br); MS m/z 223 (M^+, 91.7), 208 (100); HRMS calcd for $C_{15}H_{13}NO$ 223.0997, found 223.1004.

5-Methyl-2-phenylindole (9k) (Table 5, entry 8). A solution of **8k** (97.3 mg, 0.47 mmol) and $Cu(OCOCF_3)_2 \cdot xH_2O$ (6.2 mg, 0.021 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 2.5 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **9k** (68.7 mg, 71%) as a pale yellow solid; mp 217 °C (colorless needles from Et_2O−hexane, lit.[26] mp 218−219 °C); IR (film, cm^{-1}) 3435; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (3H, s), 6.74 (1H, s), 7.01 (1H, d, J = 8.2 Hz), 7.26−7.33 (2H, m), 7.39−7.45 (3H, m), 7.64 (2H, d, J = 7.2 Hz), 8.24 (1H, br); MS m/z 207 (M^+, 100); HRMS calcd for $C_{15}H_{13}N_2$ 207.10480, found 207.1014.

6-Cyano-2-phenylindole (9*l*) (Table 5, entry 9). A solution of **8*l*** (109.9 mg, 0.50 mmol) and $Cu(OCOCF_3)_2 \cdot xH_2O$ (29.2 mg, 0.101 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 24 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:5)] to afford **9*l*** (92.1 mg, 84%) as a pale yellow solid; mp 226−227 °C (colorless needle from hexane); IR (KBr, cm^{-1}) 3368, 2210; ^1H NMR (400 MHz, $CDCl_3$) δ 6.88 (1H, d, J = 2.2 Hz), 7.30−7.51 (4H, m), 7.65−7.74 (4H, m), 8.69 (1H, br); MS m/z 218 (M^+, 100). Anal. Calcd for $C_{15}H_{10}N_2$: C, 82.55; H, 4.62; N, 12.84. Found: C, 82.26; H, 4.86; N, 12.59.

1-(*p*-Methoxybenzyl)-2-phenylindole (11a) (Table 5, entry 10). A solution of **10a** (95.7 mg, 0.31 mmol) and $Cu(OAc)_2$ (22.1 mg, 0.12 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 48 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:9)] to afford **11c** (88.4 mg, 92%) as a yellow solid; mp 156−157 °C (yellow prisms from Et_2O−AcOEt); IR (film, cm^{-1}) 1510, 1460, 1246; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (3H, s), 5.31 (2H, s), 6.63 (1H, s), 6.79 (2H, d, J = 8.7 Hz), 6.94 (2H, d, J = 8.7 Hz), 7.10−7.22 (3H, m), 7.34−7.46 (5H, m), 7.63−7.67 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.2, 55.2, 102.2, 110.5, 114.0, 120.0, 120.4, 121.8, 127.1, 127.9, 128.2, 128.4, 129.1, 130.1, 132.7, 137.8, 141.7, 158.6; MS m/z 313 (M^+, 44.5), 121 (100); HRMS calcd for $C_{22}H_{19}NO$ 313.1467, found 313.1449.

1-(*p*-Methoxybenzyl)indole (11c) (Table 5, entry 11). A solution of **10c** (134.8 mg, 0.57 mmol) and $Cu(OAc)_2$ (22.1 mg, 0.12 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 48 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:9)] to afford **11c** (119.9 mg, 89%) as a yellow oil; IR (neat, cm^{-1}) 1512, 1248; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (3H, s), 5.26 (2H, s), 6.52 (1H, d, J = 3.2 Hz), 6.82 (2H, d, J = 8.7 Hz), 7.06 (2H, d, J = 8.7 Hz), 7.08−7.12 (2H, m), 7.16 (1H, td, J = 8.0, 1.2 Hz), 7.29 (1H, d, J = 8.0 Hz), 7.63 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 49.6, 55.3, 101.5, 109.6, 114.0, 119.4, 120.9, 121.5, 128.0, 128.1, 128.6, 129.4, 136.1, 158.9; MS m/z 237 (M^+, 42.4), 121 (100); HRMS calcd for $C_{16}H_{15}NO$ 237.1154, found 237.1120.

2-(4-*tert*-Butyldimethylsilyloxybutyl)-1-isopropylindole (11m) (Table 5, entry 12). A solution of **10m** (134.3 mg, 0.39 mmol) and $Cu(OAc)_2$ (14.5 mg, 0.080 mmol) in anhydrous 1,2-dichloroethane (10 mL) was refluxed for 48 h. The residue was chromatographed on silica gel [AcOEt−hexane (1:9)] to afford **11m** (134.0 mg, 100%) as a yellow oil; IR (neat, cm^{-1}) 1312, 1105; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.90 (9H, s), 1.62 (6H, d, J = 7.1 Hz), 1.58−1.60 (2H, m), 1.60−1.83 (2H, m), 2.75 (2H, t, J = 7.7 Hz), 3.67 (2H, t, J = 6.0 Hz), 4.62 (1H, septet, J = 7.1 Hz), 6.21 (1H, s), 7.02 (1H, td, J = 7.7, 1.4 Hz), 7.08 (1H, td, J = 7.7, 1.4 Hz), 7.48 (1H, br d, J = 7.7 Hz), 7. 52 (1H, br d, J = 7.7 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ −5.2, 18.4, 21.5, 25.5, 26.0, 27.5, 32.6, 46.8, 62.8, 99.2, 111.4,

(26) Smith, A. B.; Visnick, M.; Haseltine, J. N.; Sprengeler, P. L. *Tetrahedron* **1986**, *42*, 2957.

118.7, 119.8, 119.9, 128.8, 134.9, 140.5; MS *m*/*z* 345 (M^+, 100); HRMS calcd for $C_{21}H_{35}NOSi$ 345.2488, found 345.2458.

The Cyclization Reaction in the Presence of 1-Ethylpiperidine (Scheme 1). For 2a: A suspension of **1a** (98.6 mg, 0.36 mmol), $Cu(OAc)_2$ (6.4 mg, 0.035 mmol), and 1-ethylpiperidine (0.10 mL, 0.73 mmol) in anhydrous 1,2-dichloroethane (10 mL) was stirred for 72 h at room temperature. H_2O was added to the mixture and extracted with AcOEt (3 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 purified by silica gel column chromatography [AcOEt−hexane (1:9)] to afford **2a** (75.3 mg, 76%) as a colorless solid.

For 2c: A suspension of **1c** (105.3 mg, 0.54 mmol), $Cu(OAc)_2$ (10.0 mg, 0.055 mmol), and 1-ethylpiperidine (0.15 mL, 1.09 mmol) in anhydrous 1,2-dichloroethane (10 mL) was stirred for 48 h at room temperature. H_2O was added to the mixture and extracted with AcOEt (3 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 purified by silica gel column chromatography [AcOEt−hexane (1:5)] to afford **2c** (81.0 mg, 77%) as a yellow oil.

General Procedure for Scheme 3. A solution of 2-ethynylaniline derivatives in anhydrous 1,2-dichloroethane was added to a suspension of KH in anhydrous 1,2-dichloroethane at 0 °C and the mixture was stirred for 1 h at the same temperature and for another 1 h at room temperature. The mixture was added to a suspension of $Cu(OAc)_2$ (50 mol %) in anhydrous 1,2-dichloroethane and then the mixture was heated at 70 °C. After the mixture was stirred for 48 h, saturated aqueous ammonium chloride solution was added to the mixture and extracted with AcOEt (3 times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$, and the solvent was evaporated.

4-(*p*-Toluenesulfonyl)-1,2,3,4-tetrahydrocyclopenta[*b*]indole (21a). A solution of **16a** (169.2 mg, 0.35 mmol), KH (23.6 mg, 0.59 mmol), and $Cu(OAc)_2$ (32.0 mg, 0.18 mmol) in anhydrous 1,2-dichloroethane (13 mL) was reacted. The crude product was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **21a** (73.3 mg, 67%); mp 165−166 °C (colorless needles from Et_2O−hexane); IR (film, cm^{-1}) 1366, 1178; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (2H, quint, J = 6.7 Hz), 2.31 (3H, s), 2.71 (2H, t, J = 6.7 Hz), 3.13 (2H, t, J = 6.7 Hz), 7.14−7.24 (4H, m), 7.30 (1H, dd, J = 8.0, 1.6 Hz), 7.70 (2H, d, J = 8.5 Hz), 8.01 (1H, dd, J = 7.2, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 24.1, 27.5, 28.1, 114.3, 118.9, 123.1, 123.2, 126.4, 126.5, 127.1, 129.7, 135.7, 140.1, 143.5, 144.5; MS *m*/*z* 311 (M^+, 58.5), 156 (100). Anal. Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.51; H, 5.69; N, 4.31.

***N*-*p*-Tolylsulfonyl-1,2,3,4-tetrahydrocarbazole (21b) and 1-(*p*-Tolylsulfonyl)-2-[3-(*p*-tolylsulfonyloxy)butyl]indole (22b).** A solution of **16b** (150.8 mg, 0.30 mmol), KH (18.1 mg, 0.45 mmol), and $Cu(OAc)_2$ (29.0 mg, 0.16 mmol) in anhydrous 1,2-dichloroethane (13 mL) was reacted. The crude product was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **21b** (63.4 mg, 64%) and **22b** (20.3 mg, 13%), both as a yellow solid. **21b**: mp 116−117 °C (pale yellow prisms from Et_2O−hexane, lit.[27] mp 93−96 °C); IR (film, cm^{-1}) 1369, 1178; ^1H NMR (300 MHz, $CDCl_3$) δ 1.70−1.95 (4H, m), 2.30 (3H, s), 2.57 (2H, d, J = 6.0 Hz), 3.00 (2H, t, J = 6.0 Hz), 7.15 (2H, d, J = 8.4 Hz), 7.18−7.29 (2H, m), 7.32 (1H, d, J = 7.1 Hz), 7.64 (2H, d, J = 8.4 Hz), 8.15 (1H, d, J = 8.2 Hz); MS *m*/*z* 325 (M^+, 54.3), 170 (100); HRMS calcd for $C_{19}H_{19}NO_2S$ 325.1137, found 325.1140. **22b**: mp 126−127 °C (colorless prisms from Et_2O−hexane); IR (film, cm^{-1}) 1362, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70−1.80 (4H, m), 2.33 (3H, s), 2.43 (3H, s), 2.95 (2H, t, J = 6.4 Hz), 4.07 (2H, t, J = 6.4 Hz), 6.32 (1H, s), 7.17 (2H, d, J = 8.2 Hz), 7.18−7.30 (2H, m), 7.32 (2H, d, J = 8.2 Hz), 7.39 (1H, d, J = 8.3 Hz), 7.57 (2H, d, J = 8.2 Hz), 7.78 (2H, d, J = 8.2 Hz), 8.13 (1H, d, J = 8.1 Hz); MS *m*/*z* 497 (M^+, 9.0), 170 (100). Anal. Calcd for $C_{26}H_{27}NO_5S_2$: C, 62.75; H, 5.47; N, 2.81. Found: C, 62.90; H, 5.61; N, 2.57.

1-(*p*-Tolylsulfonyl)-2-[3-(*p*-tolylsulfonyloxy)pentyl]indole (22c). A solution of **16c** (151.9 mg, 0.30 mmol), KH (18.4 mg, 0.46 mmol), and $Cu(OAc)_2$ (17.6 mg, 0.10 mmol) in anhydrous 1,2-dichloroethane (13 mL) was reacted. The crude product was chromatographed on silica gel [AcOEt−hexane (1:7)] to afford **22c** (88.9 mg, 59%) as a yellow solid; mp 122−123 °C (colorless needles from AcOEt−hexane); IR (film, cm^{-1}) 1362, 1175; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40−1.49 (2H, m), 1.65−1.74 (4H, m), 2.33 (3H, s), 2.42 (3H, s), 2.93 (2H, t, J = 7.4 Hz), 4.03 (2H, t, J = 6.3 Hz), 6.33 (1H, s), 7.17 (2H, d, J = 8.2 Hz), 7.19−7.29 (2H, m), 7.32 (2H, d, J = 8.2 Hz), 7.39 (1H, d, J = 7.7 Hz), 7.58 (2H, d, J = 8.2 Hz), 7.78 (2H, d, J = 8.2 Hz), 8.14 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 21.7, 25.1, 28.4, 28.6, 28.9, 70.4, 108.9, 114.8, 120.0, 123.5, 123.8, 126.1, 127.8, 129.6, 129.72, 129.74, 133.0, 136.0, 137.1, 141.6, 144.59, 144.62; MS *m*/*z* 511 (M^+, 44.7), 356 (100); HRMS calcd for $C_{27}H_{29}NO_5S_2$ 511.1487, found 511.1492.

***tert*-Butyl 6-(3,4-Methylenedioxyphenyl)-2-(trimethylsilylethynyl)phenylcarbamate (33).** 4-Bromo-1,2-(methylenedioxy)benzene (3.0 mL, 24.9 mmol) was added to a mixture of Mg (0.67 g, 27.5 mmol) in anhydrous THF (20 mL) at room temperature and refluxed for 19 h. $B(OMe)_3$ (3.3 mL, 28.0 mmol) was added to the mixture at −78 °C. After the solution was stirred for 3 h at the same temperature, 3 N HCl was added at room temperature and stirred for 15 h. H_2O was added and extracted with AcOEt (3 times). The combined organic solution was washed with saturated aqueous NaCl solution and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford **27** (2.40 g) as a pale yellow solid, which was used in the next reaction without purification.

$Pd(PPh_3)_4$ (95.5 mg, 0.08 mmol) and a solution of **27** (1.26 g, 2.8 mmol) in EtOH (6 mL) were added to a solution of **28** (1.20 g, 2.9 mmol) in a mixed solution of aqueous 2 N Na_2CO_3 (5.8 mL) and benzene (18 mL) at room temperature and refluxed for 3 h. H_2O was added to the mixture and extracted with AcOEt. 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 purified by silica gel column chromatography eluting with AcOEt−hexane(1:9) to afford **33** (0.85 g, 72%) as a yellow viscous oil; IR (neat, cm^{-1}) 2154, 1719, 1491, 1227, 1163; ^1H NMR (400 MHz, $CDCl_3$) δ 0.26 (9H, s), 1.36 (9H, s), 5.96 (2H, s), 6.19 (1H, br), 6.80−6.93 (3H, m), 7.18 (1H, t, J = 7.7 Hz), 7.26 (1H, dd, J = 7.3, 2.0 Hz), 7.42 (1H, dd, J = 7.6, 1.7 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ 0.0, 28.1, 80.0, 99.6, 100.8, 101.6, 108.1, 108.9, 121.2, 121.8, 126.0, 130.9, 131.2, 133.2, 135.9, 138.6, 146.6, 147.3, 152.9; MS *m*/*z* 409 (M^+, 5.7), 57 (100); HRMS calcd for $C_{23}H_{27}NO_4Si$ 409.1709, found 409.1736.

***tert*-Butyl 6-(3,4-Methylenedioxyphenyl)-2-ethynylphenylcarbamate (26).** A suspension of **33** (753.9 mg, 1.84 mmol) and K_2CO_3 (392.1 mg, 2.84 mmol) in MeOH (15 mL) was stirred at room temperature for 14 h. H_2O was added to the mixture and extracted with AcOEt. 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 a silica gel column [AcOEt−hexane (1:5)] to afford **26** (566.3 mg, 91%) as a pale red solid; mp 110−112 °C (pale red prisms from Et_2O−hexane); IR (film, cm^{-1}) 3391, 3292, 1717, 1491; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (9H, s), 3.30 (1H,s), 5.96 (2H, s), 6.14 (1H, br), 6.84−6.95 (3H, m), 7.21 (1H, t, J = 7.7 Hz), 7.28 (1H, td, J = 7.7, 1.2 Hz), 7.47 (1H, dd, J = 7.7, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 80.3, 80.5, 82.1, 101.0, 108.3, 109.1, 120.6, 122.0, 126.2, 131.1, 131.9, 133.0, 136.1, 138.9, 146.8, 147.5, 153.1; MS *m*/*z* 337 (M^+, 13.6), 237 (100); HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1338.

(27) Fleming, I.; Farckenpohl, J.; Ila, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1229.

1-*tert*-Butoxycarbonyl-7-(3,4-methylenedioxyphenyl)-indole (25). A solution of **26** (566.3 mg, 1.68 mmol) in anhydrous 1,2-dichloroethane (20 mL) was added to a suspension of $Cu(OAc)_2$ (310.3 mg, 1.71 mmol) in anhydrous 1,2-dichloroethane at room temperature and the mixture was refluxed for 5 h. H_2O was added to the mixture and extracted with AcOEt. 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 a silica gel column [AcOEt−hexane (1:9)] to afford **25** (452.7 mg, 80%) as a colorless viscous oil; IR (neat, cm^{-1}) 1751, 1728, 1153; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36 (9H, s), 5.96 (2H, s), 6.60 (1H, d, J = 3.7 Hz), 6.85 (1H, d, J = 7.8 Hz), 6.94−6.99 (2H, m), 7.22 (1H, d, J = 7.6 Hz), 7.28 (1H, d, J = 7.6 Hz), 7.51 (1H, d, J = 7.6 Hz), 7.53 (1H, d, J = 3.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 83.5, 100.9, 107.0, 108.2, 108.3, 119.7, 120.7, 123.1, 126.5, 128.6, 129.4, 132.4, 132.6, 136.1, 146.2, 147.5, 149.0; MS *m*/*z* 337 (M^+, 26.2), 237 (100); HRMS calcd for $C_{20}H_{19}NO_4$ 337.1314, found 337.1329.

7-(3,4-Methylenedioxyphenyl)indole (34). A solution of **25** (671.1 mg, 1.99 mmol) and 3 N HCl (4 mL) in AcOEt (15 mL) was refluxed for 2 h. H_2O was added to the mixture and extracted with AcOEt. 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 a silica gel column [AcOEt−hexane (1:5)] to afford **34** (397.2 mg, 84%) as a yellow solid; mp 118−119 °C (colorless prisms from Et_2O−hexane, lit.[23f] mp 119−121 °C); IR (film, cm^{-1}) 3423, 1229; ^1H NMR (400 MHz, $CDCl_3$) δ 6.02 (2H, d, J = 2.4 Hz), 6.61 (1H, s), 6.93 (1H, d, J = 8.3 Hz), 7.05−7.25 (5H, m), 7.61 (1H, d, J = 6.6 Hz), 8.39 (1H, br); MS *m*/*z* 237 (M^+, 100); HRMS calcd for $C_{15}H_{11}NO_2$ 237.0790, found 237.0814.

1-Formyl-7-(3,4-methylenedioxyphenyl)indole (35). 34 (47.1 mg, 0.20 mmol) was added to a suspension of NaH (60% in oil, 15.6 mg, 0.39 mmol) in anhydrous DMF (5 mL) at 0 °C and the solution was stirred for 30 min at the same temperature and for another 30 min at room temperature. The mixture was cooled at 0 °C, then acetic formic anhydride[24] (35.1 mg, 0.66 mmol) was added. After the solution was stirred for 22 h at room temperature, H_2O was added to the mixture and extracted with AcOEt. 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 a silica gel column [AcOEt−hexane (1:9)] to afford **35** (26.7 mg, 51%) as a yellow viscous oil; IR (neat, cm^{-1}) 1701; ^1H NMR (400 MHz, $CDCl_3$) δ 6.04 (2H, s), 6.76 (1H, d, J = 3.4 Hz), 6.84−6.93 (2H, m), 7.13 (1H, d, J = 7.3 Hz), 7.20−7.30 (2H, m), 7.57 (1H, d, J = 7.8 Hz), 7.83 (1H, d, J = 3.4 Hz), 8.82 (1H, s); ^{13}C NMR (100 MHz $CDCl_3$) δ 101.4, 109.0, 109.2, 110.3, 120.7, 122.1, 123.0, 123.2, 127.0, 127.3, 131.8, 132.8, 133.2, 147.5, 148.2, 158.3; MS *m*/*z* 265 (M^+, 100); HRMS calcd for $C_{16}H_{11}NO_3$ 265.0739, found 265.0743. **34** (21.1 mg, 45%) was recovered from the later fraction.

Hippadine (24). Tf_2O (0.15 mL, 0.89 mmol) was added to a solution of **35** (47.2 mg, 0.18 mmol) and DMAP (56.9 mg, 0.47 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred for 4 h at room temperature. Saturated aqueous $NaHCO_3$ solution was added to the mixture and extracted with AcOEt. The combined organic solution was washed with saturated aqueous NaCl solution, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by preparative TLC [AcOEt−hexane (1:2)] to provide hippadine (**24**) (8.4 mg, 18%) as a pale yellow solid; mp 213−215 °C (pale red needles from $CHCl_3$, lit.[23g] mp 215−217 °C); IR (film, cm^{-1}) 1670, 1310; ^1H NMR (400 MHz, $CDCl_3$) δ 6.15 (2H, s), 6.89 (1H, d, J = 2.3 Hz), 7.46 (1H, t, J = 7.4 Hz), 7.64 (1H, s), 7.74 (1H, d, J = 7.4 Hz), 7.90 (1H, d, J = 7.4 Hz), 7.97 (1H, s), 8.03 (1H, d, J = 2.3 Hz); MS *m*/*z* 263 (M^+, 100); HRMS calcd for $C_{16}H_9NO_3$ 263.0582, found 263.0555.

Acknowledgment. This work was supported by Grants-in Aid for Scientific Research (No. 13672206 and No. 14044007) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supporting Information Available: The experimental procedures and compound characterization data for **1a**−**k**, **2a**, **3a**, **4a**, **5a**−**d**,**g**, **6a**−**c**, **7a**, **8a**,**b**, **e**−***l***, **10a**,**c**,**m**, **13a**−**c**, **14a**−**c**, **15a**−**c**, **16a**−**c**, **17**−**20**, **22a**, **23**, **28**, **31**, **32**, Table 1 (entries 1−4, 6, 7), Table 2 (entries 1, 4−7), Table 4 (entries 1, 4−7, 9), Table 5 (entries 1−4), and Table 6 (entries 1−8). This material is available free of charge via the Internet at http://pubs.acs.org.

JO035528B