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$FeCl_3·6H_2O$-Catalyzed Alkenylation of Indoles with Aldehydes

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Supporting Information

ABSTRACT: $FeCl_3·6H_2O$-catalyzed efficient C3-alkenylation of indoles was realized through the condensation of aldehydes and indole derivatives in the presence of 2 equiv of ethanol at ambient temperature, forming 3-vinylindoles in up to 93% yields. Ethanol promoted formation of the desired products. An obvious solvent effect was observed, and bisindoles were identified as the reaction intermediates.

Indole is an important subunit of many bioactive compounds and natural products, and indole derivatives have become more and more attractive for the construction of agriculturally and pharmaceutically useful molecules.[1] Functionalized indoles[2] such as vinylindoles can be considered as diene equivalents for the synthesis of polyfunctional indole derivatives.[3] Friedel−Crafts alkylation[4] and arylation[5] of indoles have been extensively explored, but their alkenylation has been received much less attention. Although vinylindoles can be obtained by functional group-directed organic synthesis,[6] alkenylation protocols are expected to produce more versatile vinylindoles. Direct alkenylation of the C2-position of indoles bearing a readily removable *N*-pyrimidyl group with alkynes was realized by using a cobalt complex catalyst,[7a] and 3-cyanoindoles reacted with internal alkynes to form 2-vinylindoles under nickel catalysis.[7b] Iron(III)-catalyzed hydroarylation of propynoic acids with indoles afforded the corresponding vinylindoles.[7c] Palladium-catalyzed intramolecular addition of indolyl C−H to alkynes gave fused alkenylated indoles.[7d] Direct oxidative alkenylation of indoles by an alkene has been demonstrated an applicable potential to access vinylindoles.[8] Intramolecular alkenylation was also performed for the same purpose.[9] Both Brønsted[10a] and Lewis[10b] acids catalyzed the direct couplings of indoles with 1,3-dicarbonyls to form 3-alkenylated indoles or 2-vinylindoles.[11] Under microwave irradiation at 140 °C, treatment of indoles with aldehydes (3 equiv) in the presence of trifluoroacetic acid (3 equiv) formed 3-vinylindoles in 18−76% yields.[12]

In view of practical application, iron catalysis is potentially attractive in organic synthesis.[13] Iron compounds have been known to promote the alkenylation of arenes.[14] Recently, we disclosed efficient $FeCl_3$- and $FeCl_3·6H_2O$-mediated intramolecular cyclization of alkynyl acetals and intermolecular reactions of alkynes and aldehyde acetals.[15] In these cases, acetals exhibited much higher reactivity than their mother aldehydes. Keeping this finding in hand, we envisioned that $FeCl_3·xH_2O$ might also promote the reactions of heteroarene C−H bond with aldehyde acetals. Herein, we report $FeCl_3·6H_2O$-catalyzed alkenylation of indoles with the in situ generated acetals, i.e., aldehydes in the presence of ethanol.

Initially, the reaction of 1,2-dimethylindole (**1a**) with phenylacetaldehyde (**2a**) was carried out in the presence of $FeCl_3·xH_2O$ (Table 1). The reaction was completed in toluene within 24 h in the presence of 5 mol % $FeCl_3·6H_2O$ as catalyst, affording the desired product 3-vinylindole (**3a**) in 80% yield (Table 1, entry 1), and in *p*-xylene a similar result was obtained (entry 3). Shortening the reaction time to 3 h led to a lower yield (44%) for **3a** in toluene (entry 2) and resulted in bisindole **4c** (93%) instead of **3a** as the major product in *p*-xylene (entry 4). In CH_3CN and EtOH, the reaction was nearly prohibited (entries 5 and 6). Under the same conditions in CH_2Cl_2, the reaction efficiently proceeded to give **3a** in 85% yield (entry 7), while **3a** was only obtained in 79% yield with 5 mol % anhydrous $FeCl_3$ as catalyst (entry 8). $FeCl_3·6H_2O$ behaved more efficiently than $FeCl_3$ as catalyst, presumably due to the coordination of water molecules to the iron atom to stabilize the metal center during the catalytic reaction. Variation of temperature to 40 and 0 °C deteriorated the reaction (entries 9 and 10). Increasing the catalyst loading to 10 mol % did not improve the formation of **3a**, whereas lowering $FeCl_3·6H_2O$ loading to 2.5 mol % increased the yield of **3a** to 87% (entries 7, 11 and 12). Furthermore, addition of ethanol facilitated formation of the desired product, and **3a** was isolated in 91% yield in the presence of 2 equiv of ethanol (entries 13 and 14), which is presumably attributed to the in situ formation of the more reactive species, i.e., phenylacetaldehyde diethyl acetal (**2a′**). However, further lowering the catalyst loading to 1 mol % led to **3a** in 71% yield (entry 15). By replacing ethanol with water, the reaction only generated a trace amount of **3a** as well as bisindole **4c** (79%) as the major product (entry 16). The separate reaction of **1a** with **2a′** in CH_2Cl_2 and *p*-xylene afforded **3a** in 70 and 64% yields over a period of 2 h, respectively (eq 2), suggesting that the reaction proceeded faster in CH_2Cl_2 than in *p*-xylene. Monitoring by means of TLC

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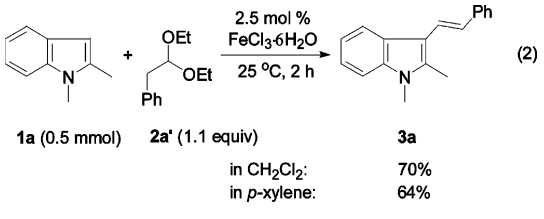
Table 1. Screening of Conditions for the Reaction of 1,2-Dimethylindole (1a) with Phenylacetaldehyde (2a)[a]

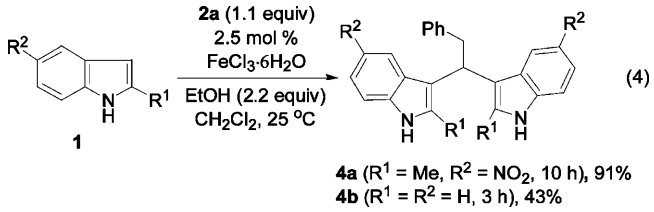
entry	catalyst (mol %)	solvent	additive (equiv)	temp (°C)	time (h)	yield[b] (%)
1	$FeCl_3·6H_2O$ (5)	toluene		25	24	80
2	$FeCl_3·6H_2O$ (5)	toluene		25	3	44
3	$FeCl_3·6H_2O$ (2.5)	*p*-xylene		25	24	70
4	$FeCl_3·6H_2O$ (2.5)	*p*-xylene		25	3	trace[c]
5	$FeCl_3·6H_2O$ (5)	CH_3CN		25	3	trace
6	$FeCl_3·6H_2O$ (5)	EtOH		25	3	trace
7	$FeCl_3·6H_2O$ (5)	CH_2Cl_2		25	3	85
8	$FeCl_3$ (5)	CH_2Cl_2		25	3	79
9	$FeCl_3·6H_2O$ (5)	CH_2Cl_2		40	3	80
10	$FeCl_3·6H_2O$ (5)	CH_2Cl_2		0	3	58
11	$FeCl_3·6H_2O$ (10)	CH_2Cl_2		25	3	79
12	$FeCl_3·6H_2O$ (2.5)	CH_2Cl_2		25	3	87
13	$FeCl_3·6H_2O$ (2.5)	CH_2Cl_2	EtOH (0.2)	25	3	88
14	**$FeCl_3·6H_2O$ (2.5)**	**CH_2Cl_2**	**EtOH (2.2)**	**25**	**3**	**91**
15	$FeCl_3·6H_2O$ (1.0)	CH_2Cl_2	EtOH (2.2)	25	3	71
16	$FeCl_3·6H_2O$ (2.5)	CH_2Cl_2	H_2O (2.2)	25	3	trace[d]

[a]Conditions: 1,2-dimethylindole (**1a**), 0.5 mmol; phenylacetaldehyde (**2a**), 0.55 mmol; solvent, 3 mL. [b]Average yield of two or three experiments. [c]The major product was bisindole **4c** (93%). [d]The major product was bisindole **4c** (79%).



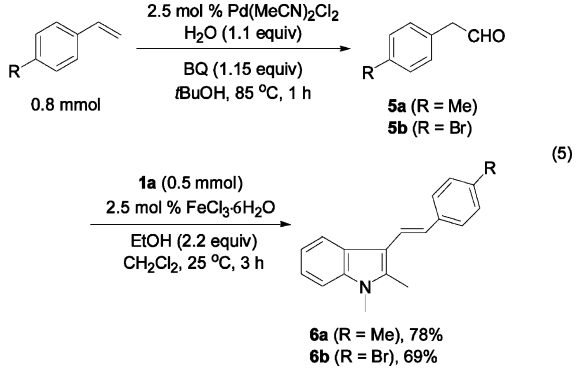
analysis revealed that the reaction in CH_2Cl_2 was finished within 2 h and accompanied by unidentified side reactions, while the reaction in *p*-xylene was slower, and **3a** could be obtained in 85% yield by extending the reaction time to 3 h, showing an obvious solvent effect (Table 1 and eq 2). It is noteworthy that diethyl acetal **2a′** is not very stable and difficult to be isolated in high purity. Although **2a′** reacted with **1a** more efficiently in *p*-xylene due to the undesired reactions occurring in CH_2Cl_2 (eq 2), CH_2Cl_2 was still chosen as the reaction medium because the reaction of **2a** and **1a** proceeded much faster in CH_2Cl_2 than in *p*-xylene (entries 3, 4 and 14). In all the cases, compound **3a** was obtained in the exclusive (*E*)-configuration.

Next, the substrate scope was explored under the optimized conditions (Table 2). With 2-substituted *N*-unprotected indoles as substrates, the desired products **3b–l** were obtained in 43–91% yields, and treatment of *N*-alkyl-2-substituted indoles with **2a** produced **3n–t** in 66–93% yields. Substituent effects of the *N*-, 2-, and 5-substituents on the reaction efficiency were observed (Table 2). On the basis of the proposed mechanism (Scheme 1), when the 2-position of an indole substrate is substituent-free, nucleophilic attack of the 2-C of such an indole at species **B** in path *a* or species **A′** in path *b* can not result in relatively stable intermediates of type **C** or **B′**, leading to the 2-alkenylation product in a poor yield. Thus, with a 1,3-disubstituted indole as substrate, **3u** was only obtained in 7% yield over a period of 36 h. Unexpectedly, the reaction of 2-methyl-5-nitroindole with **2a** afforded compound **4a** in 91% yield (eq 4), revealing a remarkable electronic effect of 5-NO_2

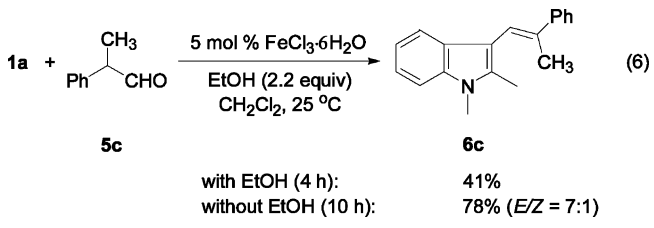


group. Bisindole **4a** was gradually formed as an insoluble solid in CH_2Cl_2 during the reaction, but it could not undergo further reaction with **2a** to form the desired product. The reaction of simple indole with **2a** also produced the product of type **4**, i.e., **4b** (43%), giving no desired product under the same conditions due to the substituent effect as discussed above (eq 4).

Substituted arylacetaldehydes cannot be easily prepared in high purity that crude arylacetaldehydes[16] were directly used for the synthesis of alkenylated indoles. Such a two-step procedure was developed to give the desired products **6a** and **6b** in 69–78% yields (eq 5), which extended the substrate scope. 2-



Substituted phenylacetaldehyde (**5c**) also reacted with **1a** to form the desired product **6c** in moderate to good yields (eq 6).



It should be noted that in the presence of EtOH the reaction proceeded to completion within 4 h to give **6c** (41%) as well as

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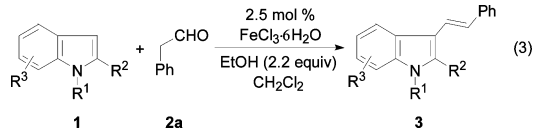
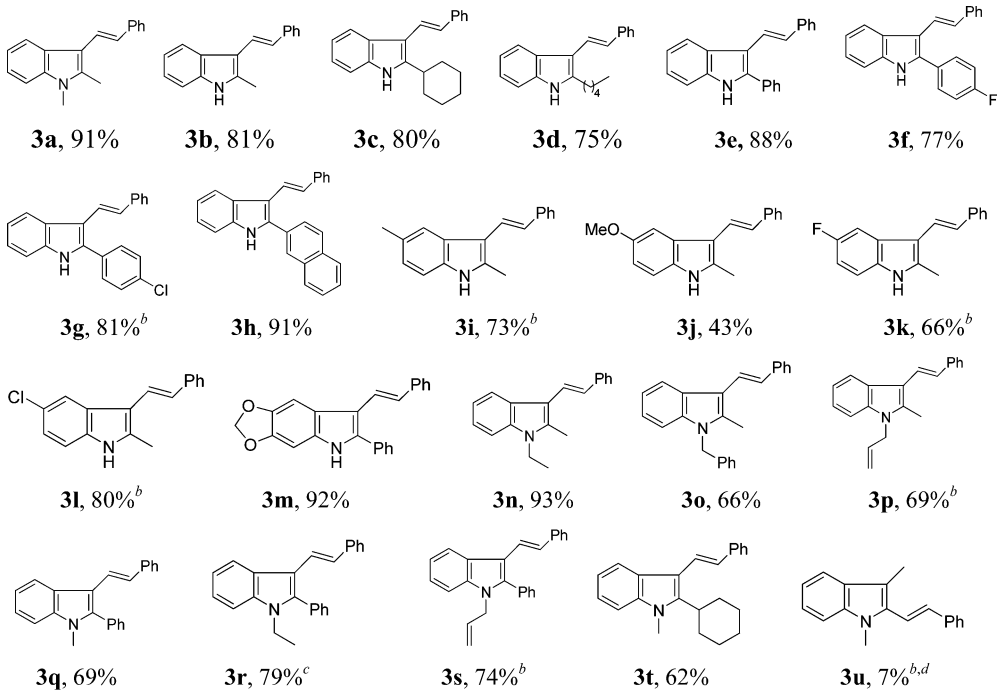
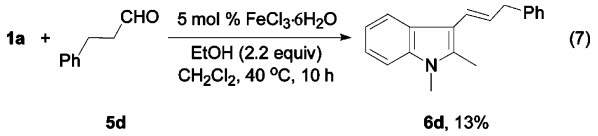
Table 2. Alkenylation of Indoles (1) with Phenylacetaldehyde (2a)[a]



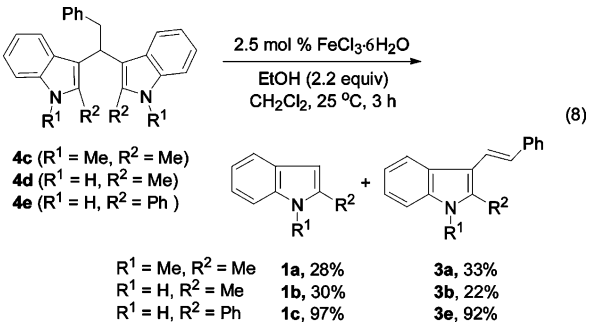


[a]Conditions: indole (**1**), 0.5 mmol; aldehyde (**2a**), 0.55 mmol; EtOH, 1.1 mmol; CH_2Cl_2, 3 mL; 25 °C, 3 h. [b]Using 5 mol % $FeCl_3·6H_2O$. [c]10 h. [d]36 h, *E*:*Z* > 20:1.

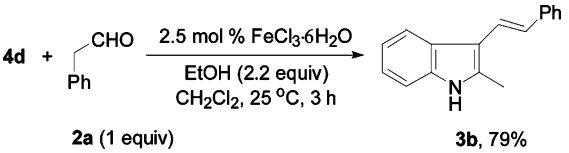
a considerable amount of unidentified byproduct, while in the absence of EtOH the reaction initially generated bisindole **4c** as the major product within the first 4 h, which was then gradually transformed to **6c** (78%) over a period of 10 h. The diethyl acetal intermediate generated in situ from the interaction of sterically hindered aldehyde **5c** and ethanol may be susceptible to the reaction condition to undergo side reactions and form undesired products. These results suggest the possible role of ethanol during the reaction of **1** with **2**: (1) as an additive to form the more reactive diethyl acetal intermediate in situ and thus accelerate the reaction; (2) as a medium to help dissolving the bisindole intermediate to promote the reaction; (3) the in situ generated diethyl acetal species may undergo side reactions to form undesired products under the reaction conditions. However, both 3-phenylpropionaldehyde (**5d**) and butyraldehyde (**5e**) only exhibited a poor reactivity. By means of 5 mol % catalyst at 40 °C, the reaction of **5d** with **1a** formed the alkenylation product **6d** in 13% yield (eq 7).



Bisindoles **4c** and **4d** were separately synthesized as the reaction intermediates by quenching the corresponding reactions of **1** and **2** in CH_2Cl_2 at 10 min with saturated aqueous $NaHCO_3$, and **4e** was prepared by carrying out the reaction in *p*-xylene for 3 h. Monitoring the reaction of **1a** and **2a** by ^1H NMR and TLC analysis revealed that the reaction initially formed bisindole **4c**, which was then gradually transformed to vinylindole **3a**. However, these bisindoles (**4c**–**e**) could not tolerate the reaction conditions in CH_2Cl_2, decomposing into the corresponding free indoles **1a**–**c** and vinylindoles **3a**, **3b** and **3e**, respectively, as the reaction proceeded (eq 8). Furthermore, in the presence of a



phenylacetaldehyde substrate such as **2a**, bisindole **4d** was efficiently transformed to the alkenylation product **3b** (eq 9), further suggesting that bisindole of type **4** is the reaction intermediate in the catalytic cycle.



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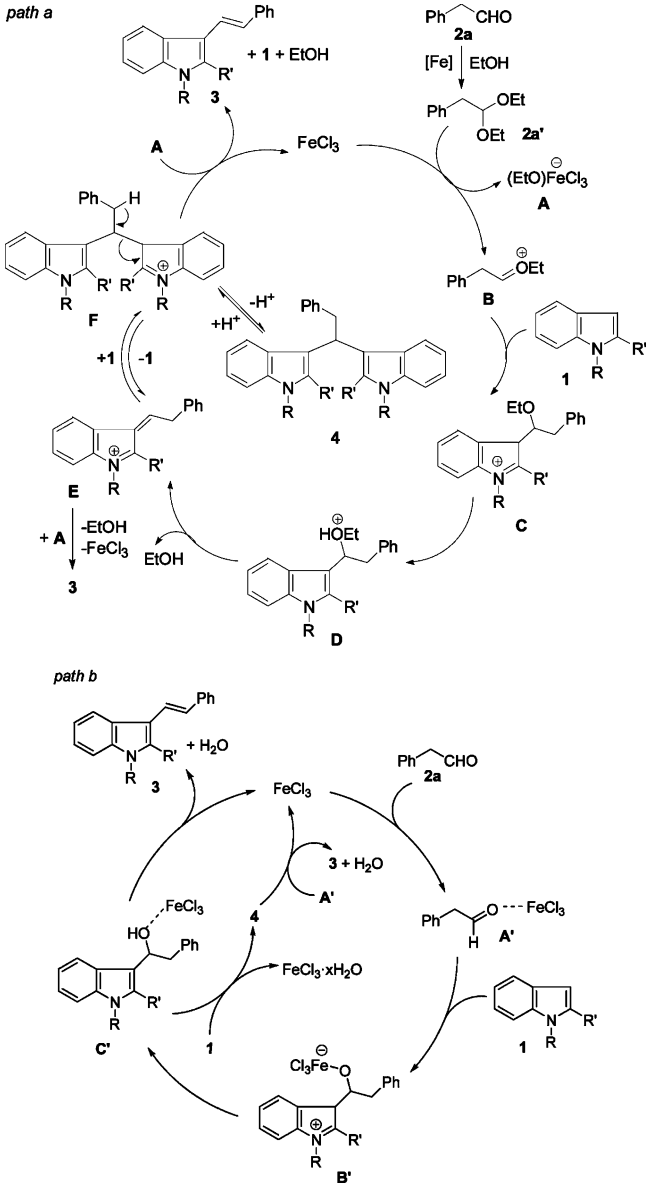
A plausible mechanism is proposed in Scheme 1. In the presence of ethanol (*path a*), the Lewis acid iron catalyst

Scheme 1. Proposed Mechanism



promotes in situ generation of phenylacetaldehyde diethyl acetal (**2a′**),[17] which then interacts with $FeCl_3$ to form oxocarbenium cation **B** and anion **A**.[15c] Species **B** reacts with indole **1** to form iminium cation **C**, which is considered as a relatively stable intermediate in the catalytic cycle due to the substituent effect from the 2-position of the indole backbone. **C** is tautomerized to **D**, which loses EtOH to form **E**. Species **E** reacts with **1** to produce bisindole sepecies **F**/**4**, which interact with anion **A** to afford the desired product **3** and **1** and regenerate the catalyst.[12] The released **1** can be used in the next catalytic cycle through a convergent way. It is also possible for **E** to interact with **A** to form **3**. Without ethanol as additive (*path b*), Lewis acid $FeCl_3$ activates the aldehyde substrate (**2a**) through coordination of the carbonyl oxygen to the iron(III) center to form adduct **A′**, i.e., the activated form of **2a**. Species **A′** reacts with indole **1** to generate inonic intermediate **B′**, which can be further transformed to adduct **C′**. Dehydration of **C′** affords product **3** and regenerates the catalyst. Adduct **C′** may also interact with **1** to form bisindole **4**, which reacts with **A′** to afford **3** and regenerate the catalyst. It is noteworthy that 1 equiv of BHT (butylated hydroxytoluene) was added as a radical scavenger to the reaction of **1a** and **2a**, leading to **3a** in 71% yield, which excludes a radical pathway.[4f]

In conclusion, efficient $FeCl_3·6H_2O$-catalyzed C3-alkenylation of 2-substituted indoles has been successfully realized by using phenylacetaldehydes as alkenylating reagents in the presence of ethanol. Formation of diethyl acetal of the aldehyde substrate and/or adduct of aldehyde with the catalyst is proposed to initiate the catalytic cycle, and the reaction proceeds via the bisindole intermediate. The present protocol provides a convenient route to vinylindole derivatives under mild conditions.

EXPERIMENTAL SECTION

General Considerations. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a 400 and 100 MHz FT-NMR spectrometer, and all chemical shift values refer to δ_{TMS} = 0.00 ppm or $CDCl_3$ ($\delta(^1H)$, 7.26 ppm; $\delta(^{13}C)$, 77.16 ppm). The HRMS analysis was obtained on a GC-TOF mass spectrometer. $FeCl_3·6H_2O$ and $FeCl_3$ (>99.0%) were purchased from the Fifth Shengyang Reagent Factory, China. All the other chemical reagents were purchased from commercial sources and used as received unless otherwise indicated. *N*-Substituted indoles, i.e., 1,2-dimethylindole, 1-ethyl-2-methylindole, 1-benzyl-2-methylindole, and 1-methyl-2-phenylindole,[18] 1-allyl-2-methyl-indole,[19] 1-allyl-2-phenyl-1*H*-indole,[20] 2-cyclohexylindole and 2-pentylindole,[21] 1-methyl-2-cyclohexylindole,[22] and 1,3-dimethylindole[23] were prepared as reported.

Typical Procedure for $FeCl_3·6H_2O$-Catalyzed Alkenylation of Indoles 1 with Aldehyde 2a: Synthesis of 3a. To a 25-mL round-bottom flask were successively added $FeCl_3·6H_2O$ (3.4 mg, 0.0125 mmol), CH_2Cl_2 (3 mL), EtOH (51.0 mg, 1.1 mmol), phenylacetaldehyde (**2a**) (66.0 mg, 0.55 mmol) and 1,2-dimethylindole (**1a**) (72.5 mg, 0.5 mmol). The mixture was stirred at ambient temperature for 3 h. All the volatiles were removed under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/CH_2Cl_2 = 8:1, v/v) to afford the target product **3a**[24] (112.0 mg, 91%): mp 130−132 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 6.9 Hz, 1 H), 7.55 (d, J = 7.5 Hz, 2 H), 7.40−7.31 (m, 4 H), 7.27−7.21 (m, 3 H), 7.13 (d, J = 16.4 Hz, 1 H), 3.70 and 2.54 (s each, 3:3 H).

(*E*)-2-Methyl-3-styryl-1*H*-indole ((*E*)-3b).[6c] 95 mg, yield 81%. Yellow solid: mp 187−188 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 6.9 Hz, 1 H), 7.83 (s, 1 H), 7.64 (d, J = 7.5 Hz, 2 H), 7.47 (t, J = 7.5 Hz, 2 H), 7.39 and 7.21 (d each, J = 16.4 Hz, 1:1 H), 7.34−7.27 (m, 4 H), 2.55 (s, 3 H).

(*E*)-2-Cyclohexyl-3-styryl-1*H*-indole ((*E*)-3c). 121 mg, yield 80%. White solid: mp 64−66 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04 (br, 2 H), 7.60 (d, J = 6.8 Hz, 2 H), 7.45−7.37 (m, 4 H), 7.26 (m, 3 H), 7.20 (d, J = 16.4 Hz, 1 H), 3.15 (m, 1 H), 2.04 (m, 2 H), 1.94 (m, 2 H), 1.87 (d, J = 13.9 Hz, 1 H), 1.52 (m, 4 H), 1.35 (m, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.8, 139.2, 135.6, 126.55, 109.5, 128.7, 126.51, 125.8, 125.4, 121.8, 121.7, 120.5, 120.2, 110.9, 36.0, 33.1, 26.7, 26.1; HRMS (EI) Calcd for $C_{22}H_{23}N$ 301.1830, found 301.1842.

(*E*)-2-Pentyl-3-styryl-1*H*-indole ((*E*)-3d). 108 mg, yield 75%. Yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 6.9 Hz, 1 H), 7.90 (s, 1 H), 7.60 (d, J = 7.7 Hz, 2 H), 7.43 (t, 2 H), 7.34 (m, 2 H), 7.29−7.24 (m, 3 H), 7.20 (d, J = 16.4 Hz, 1 H), 2.89 (t, J = 7.7 Hz, 2 H), 1.74 (m, 2 H), 1.42 (m, 4 H), 0.96 (t, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.5, 139.2, 135.7, 126.6, 110.7, 128.7, 126.5, 125.8, 125.3, 121.9, 121.8, 120.5, 120.1, 110.8, 31.6, 29.6, 26.6, 22.6, 14.1; HRMS (EI) Calcd for $C_{21}H_{23}N$ 289.1830, found 289.1823.

(*E*)-2-Phenyl-3-styryl-1*H*-indole ((*E*)-3e). 130 mg, yield 88%. White solid: mp 90−91 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (m, 1 H), 8.12 (s, 1 H), 7.62 (m, 2 H), 7.59−7.54 (m, 4 H), 7.51−7.30 (m, 9

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H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.9, 137.5, 136.5, 132.5, 126.9, 111.9, 129.0, 128.9, 128.7, 128.3, 127.5, 126.7, 126.0, 123.0, 122.4, 120.91, 120.89, 111.3; HRMS (EI) Calcd for $C_{22}H_{17}N$ 295.1361, found 295.1366.

(*E*)-2-(4-Fluorophenyl)-3-styryl-1*H*-indole ((*E*)-3f). 121 mg, yield 77%. White solid: mp 104−107 °C; ^1H NMR (400 MHz, acetone-d_6) δ 10.69 (s, 1 H), 8.16 (d, J = 7.4 Hz, 1 H), 7.75 (m, 2 H), 7.56 (d, J = 7.5 Hz, 2 H), 7.52 (d, J = 7.5 Hz, 1 H), 7.46 (d, J = 16.5 Hz, 1 H), 7.33 (m, 5 H), 7.23 (m, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 163.4 (d, J = 244.9 Hz), 139.7, 137.8, 137.7, 127.5, 111.9, 129.9 (d, J = 3.2 Hz), 131.8 (d, J = 8.6 Hz), 116.5 (d, J = 21.6 Hz), 129.4, 126.5, 127.4, 127.3, 123.4, 123.1, 121.4, 121.2, 112.4; HRMS (EI) Calcd for $C_{22}H_{16}FN$ 313.1267, found 313.1277.

(*E*)-2-(4-Chlorophenyl)-3-styryl-1*H*-indole ((*E*)-3g). 134 mg, yield 81%. White solid: mp 129−130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (m, 2 H), 7.54−7.48 (m, 6 H), 7.40 (t, 3 H), 7.34−7.26 (m, 5 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.6, 136.5, 136.0, 134.3, 131.0, 126.9, 112.4, 130.0, 129.3, 128.8, 128.1, 127.0, 126.0, 123.3, 121.8, 121.1, 121.0, 111.4; HRMS (EI) Calcd for $C_{22}H_{16}ClN$ 329.0971, found 329.0970.

(*E*)-2-(Naphthalen-2-yl)-3-styryl-1*H*-indole ((*E*)-3h). 157 mg, yield 91%. White solid: mp 85−88 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (m, 2 H), 8.03 (s, 1 H), 7.96−7.89 (m, 3 H), 7.72 (d, J = 8.4 Hz, 1 H), 7.59−7.48 (m, 5 H), 7.41−7.26 (m, 6 H), 7.28 (t, 1 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.9, 137.5, 136.7, 133.5, 132.9, 130.0, 127.0, 112.3, 128.8, 128.7, 128.3, 128.0, 127.9, 127.7, 126.84, 126.78, 126.7, 126.5, 126.0, 123.1, 122.3, 121.0, 120.9, 111.4; HRMS (EI) Calcd for $C_{26}H_{19}N$ 345.1517, found 345.1528.

(*E*)-2,5-Dimethyl-3-styryl-1*H*-indole ((*E*)-3i). 91 mg, yield 73%. White solid: mp 165−167 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1 H), 7.71 (br, 1 H), 7.59 (d, J = 7.4 Hz, 2 H), 7.41 and 7.26 (t each, 2:1 H), 7.32 (d, J = 16.4 Hz, 1 H), 7.18−7.11 (m, 2 H), 7.05 (d, J = 8.1 Hz, 1 H), 2.55 and 2.49 (s each, 3:3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 134.9, 133.9, 129.8, 126.9, 110.7, 128.7, 126.5, 125.8, 125.0, 123.3, 122.0, 119.6, 110.3, 21.8, 12.5; HRMS (EI) Calcd for $C_{18}H_{17}N$ 247.1361, found 247.1363.

(*E*)-5-Methoxy-2-methyl-3-styryl-1*H*-indole ((*E*)-3j). 57 mg, yield 43%. White solid: mp 115−117 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (br, 1 H), 7.54 (d, J = 7.5 Hz, 2 H), 7.44 (s, 1 H), 7.38 and 7.23 (t each, 2:1 H), 7.29 (d, J = 16.4 Hz, 1), 7.04 (d, J = 16.4 Hz, 1 H), 7.19 (d, J = 8.7 Hz, 1 H), 6.85 (dd, J = 8.7 and 2.3 Hz, 1 H), 3.92 and 2.51 (s each, 3:3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 139.1, 135.5, 130.7, 127.3, 111.0, 128.6, 126.5, 125.8, 125.1, 121.9, 111.2, 110.9, 102.9, 56.2, 12.7; HRMS (EI) Calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1320.

(*E*)-5-Fluoro-2-methyl-3-styryl-1*H*-indole ((*E*)-3k). 82 mg, yield 66%. White solid: mp 126−129 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (br, 1 H), 7.66 (d, J = 8.6 Hz, 1 H), 7.57 (d, J = 7.7 Hz, 2 H), 7.42 (t, 2 H), 7.30−7.25 (m, 2 H), 7.16 (dd, J = 8.7 and 4.5 Hz, 1 H), 7.05 (d, J = 16.5 Hz, 1 H), 6.96 (dt, J = 9.0 and 2.2 Hz, 1 H), 2.48 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.5, 138.8, 136.5, 132.0, 127.0, 111.3, 128.8, 125.8, 126.7, 125.4, 121.3, 111.1, 109.7 (d, J = 25.8 Hz), 105.1 (d, J = 24.1 Hz), 12.5; HRMS (EI) Calcd for $C_{17}H_{14}NF$ 251.1110, found 251.1119.

(*E*)-5-Chloro-2-methyl-3-styryl-1*H*-indole ((*E*)-3l). 107 mg, yield 80%. White solid: mp 128−130 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1 H), 7.93 (br, 1 H), 7.63 (d, J = 7.4 Hz, 2 H), 7.47 (t, 2 H), 7.35−7.28 (m, 2 H), 7.23 (m, 2 H), 7.11 (d, J = 16.5 Hz, 1 H), 2.55 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz,$CDCl_3$) δ 138.7, 136.0, 133.9, 127.7, 126.1, 110.9, 128.8, 126.8, 125.9, 125.8, 121.9, 121.0, 119.3, 111.6, 12.5; HRMS (EI) Calcd for $C_{17}H_{14}NCl$ 267.0815, found 267.0822.

(*E*)-6-Phenyl-7-styryl-5*H*-[1,3]dioxolo[4,5-f]indole ((*E*)-3m). 156 mg, yield 92%. White solid: mp 149−150 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1 H), 7.63−7.54 (m, 7 H), 7.50−7.40 (m, 4 H), 7.34 (t, 1 H), 7.23 (d, J = 16.5 Hz, 1 H), 6.90 (s, 1 H), 6.07 (s, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.3, 143.7, 138.8, 136.3, 132.6, 131.5, 120.8, 112.2, 129.0, 128.7, 128.5, 127.8, 127.0, 126.7, 125.9, 122.4, 100.9, 99.6, 92.2; HRMS (EI) Calcd for $C_{23}H_{17}NO_2$ 339.1259, found 339.1267.

(*E*)-1-Ethyl-2-methyl-3-styryl-1*H*-indole ((*E*)-3n). 121 mg, yield 93%. White solid: mp 105−107 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (br, 1 H), 7.66, 7.48−7.43, 7.34, and 7.26−7.20 (m each, 2:4:3:1 H), 4.24 (q, 2 H), 2.63 (s, 3 H), 1.46 (t, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 139.4, 136.2, 135.8, 126.1, 110.6, 128.7, 126.4, 125.7, 124.9, 122.2, 121.5, 120.2, 120.0, 109.1, 38.0, 15.3, 10.6; HRMS (EI) Calcd for $C_{19}H_{19}N$ 261.1517, found 261.1525.

(*E*)-1-Benzyl-2-methyl-3-styryl-1*H*-indole ((*E*)-3o). 107 mg, yield 66%. White solid: mp 123−125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.6 Hz, 1 H), 7.60 (d, J = 7.4 Hz, 2 H), 7.42 and 7.32−7.25 (m each, 3:8 H), 7.03 (d, J = 7.0 Hz, 2 H), 5.35 (s, 2 H), 2.50 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 137.4, 137.2, 136.4, 126.1, 111.1, 128.9, 128.7, 127.5, 126.5, 126.0, 125.8, 125.4, 122.0, 121.8, 120.5, 120.0, 109.5, 46.7, 10.9; HRMS (EI) Calcd for $C_{24}H_{21}N$ 323.1674, found 323.1678.

(*E*)-1-Allyl-2-methyl-3-styryl-1*H*-indole ((*E*)-3p). 95 mg, yield 69%. White solid: mp 76−78 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (br, 1 H), 7.62 (d, J = 7.2 Hz, 2 H), 7.42 and 7.27 (m each, 3:4 H), 7.21 (d, J = 16.4 Hz, 1 H), 5.97 (m, 1 H), 5.19 (d, J = 10.2 Hz, 1 H), 4.90 (d, J = 17.1 Hz, 1 H), 4.71 (t, 2 H), 2.53 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.2, 136.8, 136.3, 126.0, 110.8, 132.9, 128.7, 126.4, 125.7, 125.1, 122.1, 121.6, 120.4, 119.9, 116.5, 109.4, 45.4, 10.6; HRMS (EI) Calcd for $C_{20}H_{19}N$ 273.1517, found 273.1520.

(*E*)-1-Methyl-2-phenyl-3-styryl-1*H*-indole ((*E*)-3q). 107 mg, yield 69%. White solid: mp 142−144 °C.^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.1 Hz, 1 H), 7.48, 7.35, and 7.19 (m each, 7:5:3 H), 3.62 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 141.0, 139.1, 138.0, 131.4, 125.7, 112.1, 131.2, 128.64, 128.59, 126.4, 125.8, 122.8, 122.6, 120.8, 109.9, 31.1; HRMS (EI) Calcd for $C_{23}H_{19}N$ 309.1517, found 309.1518.

(*E*)-1-Ethyl-2-phenyl-3-styryl-1*H*-indole ((*E*)-3r). 127 mg, yield 79%. White solid: mp 113−115 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (m, 1 H), 7.65, 7.57, 7.47, and 7.30 (m each, 5:3:4:2 H), 7.38 (d, J = 16.5 Hz, 1 H), 4.21 (q, 2 H), 1.39 (t, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.5, 139.1, 136.7, 131.6, 126.0, 112.3, 131.0, 128.64, 128.59, 128.58, 126.3, 125.7, 125.5, 122.8, 122.4, 120.8, 120.7, 110.6, 38.8, 15.3; HRMS (EI) Calcd for $C_{24}H_{21}N$ 323.1674, found 323.1676.

(*E*)-1-Allyl-2-phenyl-3-styryl-1*H*-indole ((*E*)-3s). 125 mg, yield 74%. Yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (br, 1 H), 7.48, 7.41, 7.29, and 7.15 (m each, 5:2:5:3 H), 5.89 (m, 1 H), 5.15 (d, J = 10.3 Hz, 1 H), 4.94 (d, J = 17.1 Hz, 1 H), 4.59 (br, 2 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 140.9, 139.1, 137.4, 131.3, 112.4, 133.5, 131.0, 128.7, 128.6, 128.5, 126.4, 125.9, 125.8, 122.8, 122.6, 120.9, 120.8, 116.7, 110.7, 46.6; HRMS (EI) Calcd for $C_{25}H_{21}N$ 335.1674, found 335.1678.

(*E*)-2-Cyclohexyl-1-methyl-3-styryl-1*H*-indole ((*E*)-3t). 97 mg, yield 62%. White solid: mp 117−120 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.5 Hz, 1 H), 7.70 (m, 3 H), 7.55 (t, 2 H), 7.40 (m, 4 H), 7.26 (d, J = 16.3 Hz, 1 H), 3.91 (s, 3 H), 3.23 (m, 1 H), 2.10, 2.01, 1.64−1.46 (m each, 6:1:3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 143.9, 139.2, 137.4, 126.2, 110.1, 128.7, 126.5, 126.2, 125.8, 122.7, 121.6, 120.2, 120.1, 109.2, 37.2, 32.1, 27.3, 26.2, 30.7; HRMS (EI) Calcd for $C_{23}H_{25}N$ 315.1987, found 315.1990.

(*E*)-1,3-Dimethyl-2-styryl-1*H*-indole ((*E*)-3u). E/Z = 30:1. 8 mg, yield 7%. White solid: mp 79−82 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 1 H), 7.68 (d, J = 7.3 Hz, 2 H), 7.53 (t, 2 H), 7.38 (m, 4 H), 7.28 (m, 1 H), 7.08 (d, J = 16.4 Hz, 1 H), 3.90 (s, 3 H), 2.63 (s, 3 H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 137.7, 137.6, 134.3, 128.7, 110.2, 132.2, 128.9, 127.8, 126.4, 122.3, 119.2, 118.9, 117.9, 109.0, 30.7, 10.4; HRMS (EI) Calcd for $C_{18}H_{17}N$ 247.1361, found 247.1370.

3,3′-(2-Phenylethane-1,1-diyl)bis(2-methyl-5-nitro-1*H*-indole) (4a). 150 mg, yield 91%. Yellow solid: mp 265−268 °C; ^1H NMR (400 MHz, acetone-d_6) δ 10.59 (s, 2 H), 8.47 (s, 2 H), 7.90 and 7.39 (d each, J = 8.9 Hz, 2:2 H), 7.16 (m, 3 H), 7.04 (d, J = 7.4 Hz, 2 H), 4.85 (t, 1 H), 3.81 (d, J = 7.9 Hz, 2 H), 2.35 (s, 6 H); $^{13}C\{^1H\}$ NMR (100 MHz, acetone-d_6) δ 141.9, 141.7, 139.8, 136.7, 128.2, 116.2, 130.0, 128.8, 126.8, 116.6, 116.3, 111.4, 41.4, 38.0, 12.6; HRMS (EI) Calcd for $C_{19}H_{15}N_4O_4$ $[M - C_7H_7]^+$ 363.1093, found 363.1087.

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3,3′-(2-Phenylethane-1,1-diyl)bis(1*H*-indole) (4b).[25] 36 mg, yield 43%. Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 2 H), 7.58 (d, J = 7.9 Hz, 2 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.14 (m, 7 H), 7.03 (t, 2 H), 6.94 (s, 2 H), 4.81 (t, 1 H), 3.55 (d, J = 7.4 Hz, 2 H).

3,3′-(2-Phenylethane-1,1-diyl)bis(1,2-dimethyl-1*H*-indole) (4c). Compound **1a** (363 mg, 2.5 mmol) was added to a stirred solution of $FeCl_3{\cdot}6H_2O$ (17 mg, 0.0625 mmol), EtOH (255 mg, 5.5 mmol), and **2a** (330 mg, 2.75 mmol) in CH_2Cl_2 (15 mL), and stirring was continued for 10 min. To the resultant mixture was added 15 mL of saturated aqueous $NaHCO_3$, and extraction was performed with CH_2Cl_2 (3 × 15 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4, and all the volatiles were evaporated under reduced pressure. Purification of the resulting residue by flash silica gel column chromatography (petroleum ether (60−90 °C)/CH_2Cl_2 = 10:1, v/v) afforded **4c** as a white solid (363 mg, 37%): mp 268−270 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.72, 7.20, 7.08, 6.98, 6.88 (m each, 2:2:3:2:4 H), 4.63 and 3.76 (m each, 1:2 H), 3.50 and 2.05 (s each, 6:6 H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ 142.9, 137.7, 133.9, 128.1, 114.3, 129.9, 128.5, 126.4, 120.6, 120.3, 119.1, 109.5, 42.1, 39.4, 29.5, 10.5; HRMS (EI) Calcd for $C_{21}H_{21}N_2$ [M − C_7H_7]$^+$ 301.1704, found 301.1690.

3,3′-(2-Phenylethane-1,1-diyl)bis(2-methyl-1*H*-indole) (4d). In a fashion similar to the preparation of **4c**, bisindole **4d** was obtained from the reaction of **1b** and **2a** as a yellow solid (402 mg, 44%): mp >264 °C, sublimated; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.67 (s, 2 H), 7.62 (d, J = 7.9 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2 H), 7.11 (m, 3 H), 6.96−6.91 (m, 4 H), 6.84 (t, 2 H), 4.63 (t, 1 H), 3.75 (d, J = 7.8 Hz, 2 H), 2.15 (s, 6 H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ 142.1, 135.8, 131.3, 128.3, 113.5, 129.1, 127.6, 125.4, 119.7, 119.1, 118.2, 110.2, 40.9, 37.8, 11.5; HRMS (EI) Calcd for $C_{19}H_{17}N_2$ [M − C_7H_7]$^+$ 273.1391, found 273.1380.

3,3′-(2-Phenylethane-1,1-diyl)bis(2-phenyl-1*H*-indole) ((*E*)-4e). The mixture of 2-phenyl-1*H*- indole (483 mg, 2.5 mmol), $FeCl_3{\cdot}6H_2O$ (17 mg, 0.0625 mmol) and **2a** (330 mg, 2.75 mmol) in *p*-xylene (15 mL) was stirred at room temperature for 3 h. All the volatiles were evaporated under reduced pressure, and the resultant residue was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/ethyl acetate =2:1, v/v) to afford **4e** as a white solid (311 mg, 51%): mp 241−245 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.10 (br, 2 H), 7.71 and 7.36 (d each, J = 8.1 Hz, 2:2 H), 7.25−7.22 (m, 10 H), 7.04 (t, 2 H), 7.01−6.93 (m, 3 H), 6.91−6.79 (m, 4 H), 5.26 (t, 1 H), 3.73 (d, J = 7.9 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, acetone-d_6) δ 142.3, 137.4, 136.5, 135.1, 129.3, 115.8, 129.9, 129.7, 129.0, 128.5, 128.2, 126.4, 122.2, 121.9, 119.5, 111.9, 37.7; HRMS (EI) Calcd for $C_{29}H_{21}N_2$ [M − C_7H_7]$^+$ 397.1704, found 397.1703.

(*E*)-1,2-Dimethyl-3-(4-methylstyryl)-1*H*-indole ((*E*)-6a). Pre-heated-to-85 °C *t*BuOH (5 mL) was added to a mixture of $Pd(MeCN)_2Cl_2$ (5.2 mg, 0.02 mg) and *p*-benzoquinone (100 mg, 0.92 mmol). Water (16 μL, 0.88 mmol) and 1-methyl-4-vinylbenzene (95 mg, 0.8 mmol) were then added with stirring. After being stirred at 85 °C for 60 min, the mixture was allowed to cool to room temperature. The resulting mixture was filtered through a short path of Celite, eluting with ethyl acetate. All the volatiles were removed under reduced pressure to give crude 2-*p*-tolylacetaldehyde,[16] and its solution in 3 mL of CH_2Cl_2 was added to the mixture of $FeCl_3{\cdot}6H_2O$ (3.4 mg, 0.0125 mmol), EtOH (51.0 mg, 1.1 mmol) and **1a** (72.5 mg, 0.5 mmol) and was stirred at ambient temperature for 3 h. All the volatiles were removed under reduced pressure, and the resultant mixture was purified by silica gel column chromatography (eluent: petroleum ether (60−90 °C)/CH_2Cl_2 = 8:1, v/v) to afford **6a** as a white solid (102 mg, 78%): mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.5 Hz, 1 H), 7.48 (d, J = 7.8 Hz, 2 H), 7.34−7.24 (m, 4 H), 7.21 (d, J = 7.9 Hz, 2 H), 7.13 (d, J = 16.4 Hz, 1 H), 3.68, 2.53, and 2.41 (s each, 3:3:3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.3, 136.5, 136.3, 136.1, 125.9, 110.6, 129.4, 125.6, 125.0, 121.4, 121.2, 120.2, 119.9, 109.0, 29.7, 21.3, 10.8; HRMS (EI) Calcd for $C_{19}H_{19}N$ 261.1517, found 261.1514.

(*E*)-3-(4-Bromostyryl)-1,2-dimethyl-1*H*-indole ((*E*)-6b). In a fashion similar to the preparation of **6a**, **6b** was obtained as a yellow solid (113 mg, yield 69%): mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.98 (m, 1 H), 7.48 (d, J = 8.4 Hz, 2 H), 7.40 (d, J = 8.4 Hz, 2 H), 7.34−7.22 (m, 4 H), 7.05 (d, J = 16.3 Hz, 1 H), 3.67 and 2.51 (s each, 3:3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.3, 137.4, 137.0, 125.8, 119.7, 110.3, 131.7, 127.1, 123.4, 122.9, 121.6, 120.4, 119.8, 109.2), 29.8, 10.8; HRMS (EI) Calcd for $C_{18}H_{16}BrN$ 325.0466, found 325.0463.

(*E*)-1,2-Dimethyl-3-(2-phenylprop-1-enyl)-1*H*-indole ((*E*/*Z*)-6c). *E*/*Z* = 7:1, 101 mg, yield 78%. White solid: mp 98−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ for (*E*/*Z*)-**6c** 7.69 (d, J = 7.2 Hz, 2 H), 7.56 (d, J = 7.7 Hz, 1 H), 7.46 (t, 2 H), 7.35, 7.26, and 7.19 (m each, 2:1:1 H), 7.03 (s, 1 H); for (*E*)-**6c** 3.75, 2.42, and 2.20 (s each, 3:3:3 H); for (*Z*)-**6c** 3.59, 2.40, and 1.95 (s each, 3:3:3 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ for (*E*/*Z*)-**6c** 143.5, 136.8, 136.7, 134.4, 119.2, 110.7; for (*E*)-**6c** 128.4, 126.9, 125.9, 120.9, 120.0, 119.4, 119.3, 108.8, 29.7, 18.1, 11.7; for (*Z*)-**6c** 128.2, 127.3, 126.2, 120.6, 119.2, 119.0, 108.4, 29.6, 25.6, 11.1; HRMS (EI) Calcd for $C_{19}H_{19}N$ 261.1517, found 261.1532.

(*E*)-1,2-Dimethyl-3-(3-phenylprop-1-enyl)-1*H*-indole ((*E*)-6d). 17 mg, yield 13%. Yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 7.9 Hz, 1 H), 7.32 and 7.24 (m each, 4:2 H), 7.17 (d, J = 7.2 Hz, 1 H), 7.12 (t, 1 H), 6.67 (d, J = 15.8 Hz, 1 H), 6.30 (dt, J = 15.8 and 6.9 Hz, 1 H), 3.66 and 2.45 (s each, 3:3 H), 3.64 (d, J = 6.7 Hz, 2 H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.5, 137.2, 135.0, 126.1, 110.2, 128.7, 128.5, 126.0, 125.8, 124.0, 121.2, 119.8, 119.6, 108.8, 40.5, 29.6, 10.7; HRMS (EI) Calcd for $C_{19}H_{19}N$ 261.1517, found 261.1526.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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