Organic & Biomolecular Chemistry

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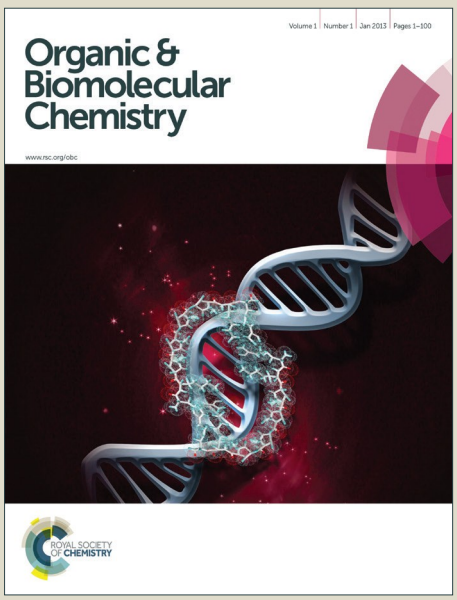

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PAPER

[3+2]-Annulations of *N*-alkyl-3-substituted indoles with quinone monoketals catalysed by Brønsted acids

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Zhuo Chai,*[a,b] Jia-Nan Chen,[a] Zhen Liu,[a] Xue-Fei Li,[a] Pei-Jun Yang,[a] Ji-Ping Hu[a] and Gaosheng Yang[a]

An organocatalytic dearomative [3+2]-annulation of *N*-alkyl-3-alkylindoles with quinone monoketals was developed. The reaction provides a mild and straightforward way to various benzofuro[2,3-b]indolines of potential biological and pharmaceutical interest in moderate to good yields. Moreover, when 3-phenylindole, a problematic substrate in previous relevant studies, was used as the substrate under the otherwise same reaction conditions, a novel 1,2-shift of the phenyl group occurred followed by aromatization to provide 2,3-diaryl indoles useful for cancer therapy studies in moderate yields.

Introduction

Fused indolines are a core structural motif widely present in numerous naturally occurring and synthetic compounds with important biological and pharmaceutical activities. Particularly, benzofuro[2,3-*b*]indolines have recently received much attention from both synthetic chemists and medicinal chemists, as exemplified by the potent anticancer agent diazonamide A,[1] voacalgine A with moderate cell growth inhibitory activity against HL-60 and HCT 116 cells[2] and the advanced intermediate (I) for the synthesis of the natural product haplophytine[3] (Figure 1). Consequently, a number of efforts have been devoted to the development of efficient methods for the construction of such a type of structures.[3-6]

The direct dearomative [3+2] annulation of an indole with an appropriate reaction partner represents a convergent and straightforward way to benzofuro[2,3-*b*]indolines from simple and easily available starting materials. In general, two major strategies have been developed for this annulation. The first strategy involves the intra/intermolecular oxidative coupling of an indole and a phenol component mediated by an oxidant (typically hypervalent iodine (III)), pioneered by Harran in the total synthesis of (-)-diazonamide A.[3,4a] This strategy has been presumed to proceed via the in-situ generation of a quinone intermediate from the phenol component. Very recently, Vincent and co-workers have realized the direct annulation of

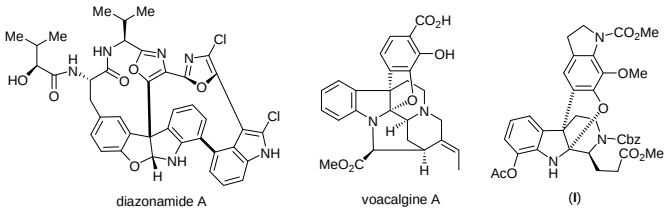


Fig. 1 Examples of naturally occurring and synthetic compounds bearing a benzofuro[2,3-b]indoline core.

N-H indoles with phenols, which was presumed to proceed via NIS-oxidation of the indole followed by trapping of the electrophilic intermediate by phenols promoted by excess $AgBF_4$ and $SnCl_4$.[5]

The other strategy relies on the direct use of quinones or their derivatives as the coupling partner.[6-7] While the direct use of simple quinone with *N*-H indoles reported by Chen is clearly favourable in terms of both substrate availability and atom-economy, the requirement for stoichiometric amount of a superacid catalyst (CF_3SO_3H) at a low reaction temperature (typically -78 to -50 ^{o}C) limits its practical utility.[3c] Very recently, Zhang and co-workers utilized more reactive quinone monoketals as the coupling partner, with which a catalytic amount of $Zn(OTf)_2$ could promote the reaction;[7a] with the even more reactive quinone monoimines, the same group realized highly enantioselective synthesis of benzofuro[2,3-*b*]indolines by using chiral BINOL-derived phosphoric acid catalysts.[7b] The most of the above works have been focused on N-H indoles, while N-alkyl indoles have been rarely studied despite their presence in many biologically active molecules. Therefore, a metal-free procedure tolerable of both *N*-H and *N*-alkyl indoles using cheaply available, easy-to-handle catalyst under mild reaction conditions would still be highly desirable.

As part of our ongoing project on the utilization of indoles in annulation reactions for the construction of various useful azaheterocyclic compounds,[8] we became interested in the

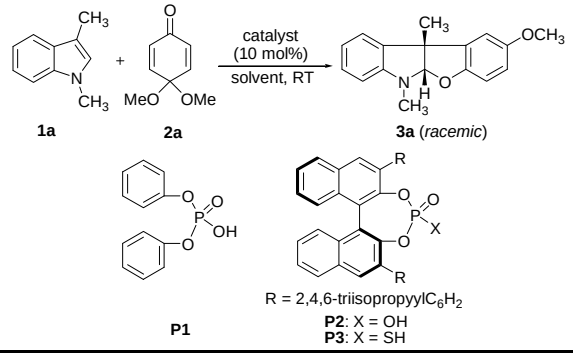
[a] Key Laboratory of Functional Molecular Solids, Ministry of Education, Anhui Laboratory of Molecule-Based Materials, Institute of Organic Chemistry, School of Chemistry and Materials Science, Anhui Normal University, Wuhu, Anhui 241000, China. chaizhuo@mail.ahnu.edu.cn; gshyang@mail.ahnu.edu.cn
[b] Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.
Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of all products **3** and **4**. See DOI: 10.1039/x0xx00000x

realization of an organocatalysed [3+2]-annulation of *N*-alkyl substituted indoles with quinone monoketals. Herein we report the details of our research featuring the use of cheaply available L-CSA as catalyst.

Results and discussion

Our study commenced with the screen of catalysts using the model reaction between 1,3-dimethyl indole **1a** and quinone monoketal **2a** (Table 1). For the Lewis acid catalysts $Sc(OTf)_3$ and $Cu(OTf)_2$, full conversion of **2a** could be achieved, but the yield of the desired product **3a** was low, together with the recovery of unconsumed **1a** and some unidentified side products (entries 1-2). Then several Brønsted acids were screened, and the cheap and commercially available L-CSA was identified as the optimum catalyst for the reaction (entry 5), while benzoic acid was not effective probably due to its much weaker acidity (entry 3). The short reaction time (2 h) represents another advantage of the current organocatalytic system. Unfortunately, similar to the observation by Zhang with the corresponding *N*-H indole, although chiral phosphoric acids **P2** and **P3** also catalysed the reaction with moderate yields, no appreciable enantioselectivity was observed (entries8-9). Examination of different solvents pinpointed

Table 1 Screen of reaction conditions[a]



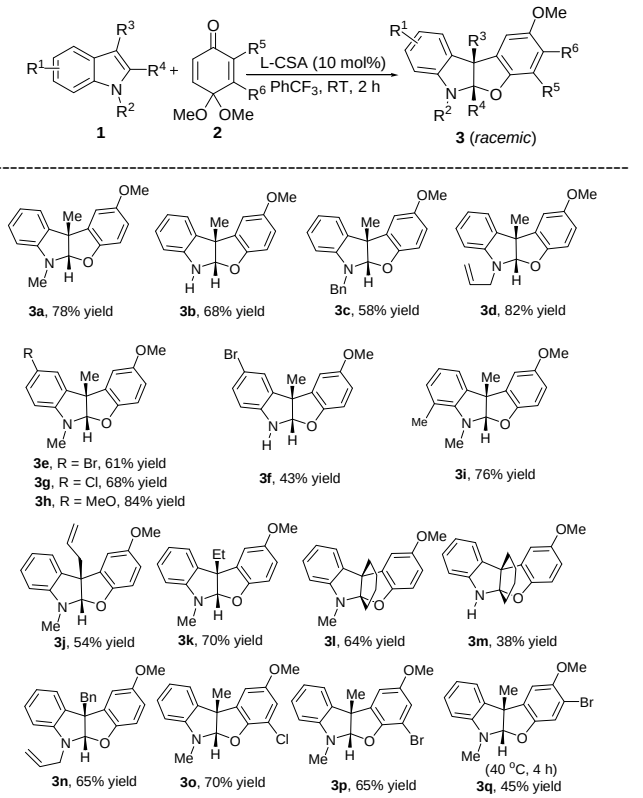
Entry	Catalyst	Solvent	Time (h)	Yield (%)[b]
1	$Sc(OTf)_3$	Toluene	2	27
2	$Cu(OTf)_2$	Toluene	12	trace
3	Benzoic acid	Toluene	12	NR
4	*p*-TSA	Toluene	2	31
5	L-CSA	Toluene	2	61
6[c]	L-CSA	Toluene	2	36
7	**P1**	Toluene	4	56
8	**P2**	Toluene	4	51
9	**P3**	Toluene	4	47
10	L-CSA	$PhCF_3$	2	78
11	L-CSA	DCM	2	48
12	L-CSA	Et_2O	2	32
13[d]	L-CSA	$PhCF_3$	2	65

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst (0.1 mmol) in 1.0 mL of solvent. [b] Isolated yield. [c] Run with 5 mol% of L-CSA. L-CSA: L-camphorsulfonic acid.

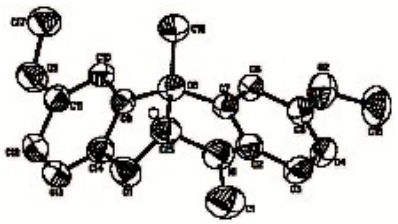
$PhCF_3$ as the best one while reducing the catalyst loading from 10 mol% to 5 mol% led to an apparent drop in the yield (entry 13). Therefore, the reaction was best performed with 10 mol% of L-CSA in $PhCF_3$ at RT for 2 h (entry 10).

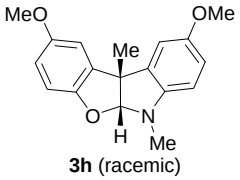
With the optimized reaction conditions in hand, we then probed the reaction scope with differently substituted indoles (Table 2). In general, moderate to good yields were obtained. Pleasingly, the reaction also tolerated corresponding *N*-H indoles, albeit with somewhat lower yields (**3b**, **3m**, and **3f**). The reaction tolerates both benzyl and allyl groups on the nitrogen atom of the indole (**3c** and **3d**), though a relatively lower yield was observed in the case of **3c** with a benzyl group. However, probably due to the reduced nucleophilicity, *N*-Boc and *N*-Ts protected 3-methyl indoles were inert to the reaction conditions. For the effects of substituents on the benzene ring of the indole on the reaction, the presence of an electron-donating group seemed to be favoured over an electron-withdrawing one (cf. **3e**, **3g** and **3h**), which might be ascribed to the better nucleophilicity of the corresponding indoles. The results with **3k**-**3n** demonstrated the good tolerance of the reaction with regard to the different substitution types at the 2 and/or 3 positions of the indole. Moreover, substituted quinone monoketals also underwent the reaction smoothly to give comparable yields of the desired products **3o**-**3p**. For 3-Br quinone monoketal **2d** (R^5 =H, R^6 = Br), which was unreactive in the $Zn(OTf)_2$ system,[7a] a moderate yield of **3q** was obtainable at an elevated reaction temperature.

Table 2 Reaction scope study[a]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), L-CSA (10 mol%) in 1.0 mL of $PhCF_3$.



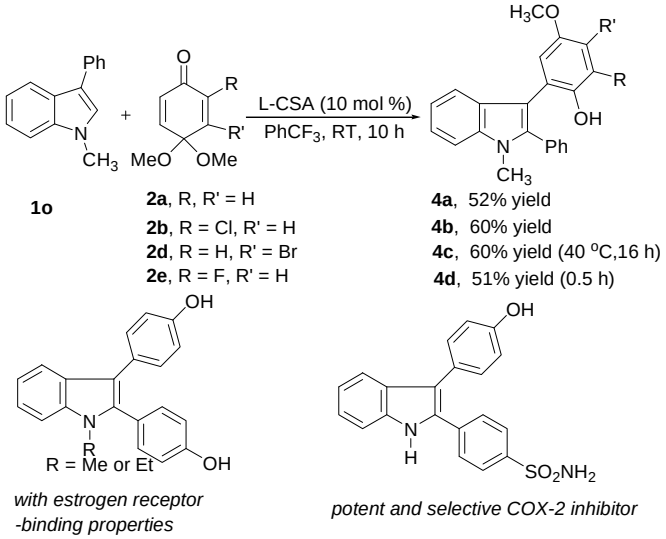


3h (racemic)

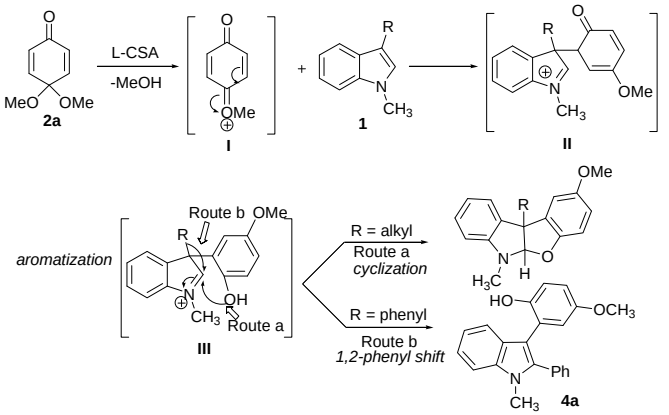
Fig. 2 ORTEP diagram of **3h**.

The relative configuration of the product **3h** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2), and those of others were assigned by analogy.[9]

In previous studies, indoles with a phenyl group at the 3-position have usually been problematic and thus they have been rarely studied in dearomative annulation reactions under Lewis or Brønsted acid catalysis.[8c-8e] For example, in the $Zn(OTf)_2$-catalysed system developed by Zhang, the corresponding 3-phenyl indole was inert toward quinone monoketals.[7a] In our system, the reaction of *N*-methyl-3-phenyl indole **1o** with several quinone monoketals provided the 2,3-diaryl indoles **4a**-**4d** as the major products in moderate yields, instead of the corresponding [3+2]-annulation product (Scheme 1).[10] The better migratory power of the phenyl group via a bridged phenonium intermediate might be accountable for this reactivity difference. It's worth mentioning that 2,3-diaryl indoles have showed some important biological activities, such as estrogen receptor affinity for the development of fluorescent probe useful in the cell-by-cell assay of the content of estrogen in breast cancer cells to provide useful information for hormonal therapy,[11a] and the cyclooxygenase-2 (COX-2) inhibitors[11b-f]. Previously, accesses to these compounds have usually required multi-step synthesis and/or transition metal-catalysis under relatively harsh conditions.[11b-c, 12] Thus, the readiness, mildness and transition metal-free properties of this reaction render it an attractive complement to the arsenal of synthetic methods to such important compounds.



Scheme 1 Reactions of 3-phenyl indole **1o** leading to 2,3-diaryl indoles.



Scheme 2 A plausible reaction mechanism.

Based on the above results and previous relevant studies,[7a] a plausible mechanism for this reaction was proposed (Scheme 2). First, the Brønsted acid catalyst L-CSA converted the quinone monoketals to the highly electrophilic quinone oxonium **I** with the loss of a methanol molecule, followed by the nucleophilic attack of an indole **1** to form the intermediate **II**. After an aromatization process, **II** would be transformed to the iminium intermediate **III**, which may undergo a cyclization process (when R = alkyl groups) via the nucleophilic attack of the phenolic hydroxyl group to form the [3+2]-annulation products (Route a). When R is a phenyl group, a 1,2-phenyl migration (probably via a bridged phenonium intermediate) followed by deprotonative aromatization sequence may predominate to provide the product **4a** (Route b).

Conclusions

In conclusion, we have developed an organocatalytic dearomative [3+2]-annulation of 3-alkylindoles and quinone monoketals to provide benzofuro[2,3-b]indolines in a highly convergent and atom-economic way under mild conditions. Moreover, the reaction of *N*-methyl-3-phenylindole with quinone monoketals has been found to undergo a novel 1,2-phenyl shift process to constitute a new and facile way to 2,3-diarylindoles, which are an important class of molecules with potential pharmaceutical interest.

Experimental

General remarks

Commercial reagents and solvents were purified prior to use following the guidelines of Perrin and Armarego. ^{1}H NMR spectra (300 or 500 MHz) and ^{13}C NMR (75 or 125 MHz) spectra were recorded on Bruker DPX 300 or AVANCE-500 spectrometers in $CDCl_3$ and are internally referenced to residual protio solvent signals (δ7.26 and δ77.16, respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz) and integration. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Shimadzu

IRPrestige-21 spectrometer as thin films on a KBr plate and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained on a Bruker Apex IV RTMS.

Typical procedure for the [3+2] annulations

Under argon atmosphere, to a solution of **1a** (0.1 mmol) and **2a** (0.15 mmol) in 1.0 mL of $PhCF_3$ was added L-CSA (0.01 mmol). The resulting solution was stirred at RT for 2 h, and then 5 mL of each saturated aqueous $NaHCO_3$ and EtOAc were added. After separation of the phases, the organic phase was extracted with EtOAc (5 mL×2) and the combined organic phases were dried over anhydrous Na_2SO_4. Removal of the solvent via rotary evaporation gave the crude product mixture, which was purified by flash column chromatography to provide the pure product **3a**.

5-Methoxy-1,6b-dimethyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3a). Pale purple oil; 20.8 mg, 78% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.3 Hz, 1H), 7.12 (m, 1H), 6.90 (d, *J* = 2.2 Hz, 1H), 6.75-6.72 (m, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.63 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.47 (d, *J* = 7.7 Hz, 1H), 5.82 (s, 1H), 3.77 (s, 3H), 3.07 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.6, 148.9, 134.2, 133.6, 128.4, 122.3, 118.4, 112.9, 110.0, 109.9, 109.6, 106.2, 56.2, 55.1, 31.7, 24.1; IR (CH_2Cl_2): 2922, 1603, 1493, 1196, 1020, 874 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{17}H_{18}NO_2$ ($[M+H]^+$): 268.1332, found: 268.1340.

5-Methoxy-6b-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3b).[7a] Pale yellow oil; 17.2 mg, 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.1 Hz, 1H), 7.06 (m, 1H), 6.93 (m, 1H), 6.71-6.63 (m, 3H), 6.06 (s, 1H), 5.02 (brs, 1H), 3.78 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.6, 147.1, 134.0, 133.4, 128.3, 122.7, 119.9, 112.8, 109.7, 109.5, 109.3, 104.6, 56.5, 56.2, 24.3; IR (CH_2Cl_2): 3391, 2959, 2924, 1607, 1489, 1207 cm^{-1}.

1-Benzyl-5-methoxy-6b-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b] indole (3c). Pale yellow oil; 19.9 mg, 58% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.29 (m, 1H), 7.26-7.20 (m, 1H), 7.02-6.99 (m, 1H), 6.90 (m, 1H), 6.71 (m, 2H), 6.62 (m, 1H), 6.35 (d, *J* = 7.7 Hz, 1H), 5.90 (s, 1H), 3.75 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.6, 148.3, 137.9, 134.3, 133.7, 128.7, 128.3, 127.5, 127.3, 122.4, 118.6, 112.9, 109.9, 109.6, 108.4, 106.6, 56.2, 55.2, 49.2, 24.2; IR (CH_2Cl_2): 2922, 1601, 1493, 1273, 1204, 1163 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{23}H_{22}NO_2$ ($[M+H]^+$): 344.1645, found: 344.1649.

1-Allyl-5-methoxy-6b-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3d). Pale yellow oil; 24.0 mg, 82% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (d, *J* = 7.1 Hz, 1H), 7.06 (pseudo t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.73-6.68 (m, 2H), 6.61 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.45 (d, *J* = 7.7 Hz, 1H), 5.97-5.91 (m, 1H), 5.90 (s, 1H), 5.29 (d, *J* = 17.0 Hz, 1H), 5.20 (d, *J* = 10.4 Hz, 1H), 4.04 (m, 2H), 3.74 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.6, 148.0, 134.2, 133.7, 133.6, 128.2, 122.3, 118.5, 117.3, 112.9, 109.9, 109.6, 108.4, 106.7, 56.2, 55.1, 47.9, 24.3; IR (CH_2Cl_2): 2922, 1603, 1493, 1273, 1206, 1169 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{19}H_{20}NO_2$ ($[M+H]^+$): 294.1489, found: 294.1493.

8-Bromo-5-methoxy-1,6b-dimethyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3e). Pale yellow oil; 21.1 mg, 61% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.69 (d, *J* = 8.9 Hz, 1H), 6.64 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.30 (d, *J* = 8.3 Hz, 1H), 5.77 (s, 1H), 3.77 (s, 3H), 3.02 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 152.5, 148.0, 135.8, 133.4, 131.0, 125.4, 113.2, 110.0, 109.7, 109.5, 107.6, 106.7, 56.2, 55.1, 47.9, 24.3; IR (CH_2Cl_2): 2922, 1597, 1491, 1194, 880 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{17}H_{17}BrNO_2$ ($[M+H]^+$): 346.0437, found: 346.0445.

8-Bromo-5-methoxy-6b-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b] indole (3f).[7a] Pale yellow oil; 14.3 mg, 43% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, *J* = 2.2 Hz, 1H), 7.13 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.72-6.63 (m, 2H), 6.51 (d, *J* = 8.0 Hz, 1H), 6.03 (s, 1H), 5.02 (brs, 1H), 3.79 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 152.5, 146.2, 135.6 133.1, 130.9, 125.9, 113.1, 111.4, 110.7, 109.9, 109.5, 104.6, 56.6, 56.2, 24.1; IR (CH_2Cl_2): 3393, 2961, 1601, 1489, 1207, 1030 cm^{-1}.

8-Chloro-5-methoxy-1,6b-dimethyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3g). Pale yellow oil; 20.4 mg, 68% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (d, *J* = 2.2 Hz, 1H), 7.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.35 (d, *J* = 8.2 Hz, 1H), 5.80 (s, 1H), 3.78 (s, 3H), 3.04 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 152.5, 147.5, 135.4, 133.4, 128.1, 123.1, 122.7, 113.1, 110.0, 109.8, 109.5, 106.9, 56.2, 55.0, 31.7, 23.8; IR (CH_2Cl_2): 2924, 1601, 1493, 1273, 1194, 880 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{17}H_{17}ClNO_2$ ($[M+H]^+$): 302.0942, found: 302.0947.

5,8-Dimethoxy-1,6b-dimethyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3h). Pale yellow solid; 24.7 mg, 84% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (s, 1H), 6.84 (s, 1H), 6.71-6.63 (m, 3H), 6.39 (d, *J* = 8.2 Hz, 1H), 5.78 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.04 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.4, 152.7, 143.2, 134.9, 133.9, 112.9, 112.3, 110.7, 110.4, 109.8, 109.5, 106.5, 56.18, 56.16, 32.4, 23.8; IR (CH_2Cl_2): 2934, 1499, 1285, 1217, 1196, 1057 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{18}H_{20}NO_3$ ($[M+H]^+$): 298.1438, found: 298.1447.

5-Methoxy-1,6b,10-trimethyl-1a,6b-dihydro-1H-benzofuro[2,3-b]indole (3i). Pale yellow oil; 21.4 mg, 76% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07 (d, *J* = 8.2 Hz, 1H), 6.87 (d, *J* = 2.7 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 6.71-6.69 (m, 2H), 6.62 (dd, *J* = 8.2, 2.2 Hz, 1H), 5.71 (s, 1H), 3.76 (s, 3H), 3.32 (s, 3H), 2.42 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 152.4, 147.1, 134.8, 134.5, 131.7, 120.4, 119.8, 119.4, 112.8, 112.4, 109.73, 109.69, 56.2, 54.4, 37.1, 24.8, 19.3; IR (CH_2Cl_2): 2959, 2922, 1593, 1489, 1202, 1028 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{18}H_{20}NO_2$ ($[M+H]^+$): 282.1489, found: 282.1497.

6b-Allyl-5-methoxy-1-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3j). Pale yellow oil; 15.8 mg, 54% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 7.7 Hz, 1H), 7.10 (pseudo t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.73-6.68 (m, 2H), 6.62 (dd, *J* = 8.2, 2.8 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 1H), 5.60-5.51 (m, 1H), 5.11 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.5 Hz, 1H), 3.76 (s, 3H), 3.04 (s, 3H), 2.79 (ABX, *J* = 14.3, 7.1 Hz, 2H), 1.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.2, 149.5, 133.3, 132.6, 132.0, 128.5, 122.5, 118.9, 118.4, 113.1, 109.9, 109.8, 107.3, 106.2, 58.9, 56.2, 41.6, 31.8; IR (CH_2Cl_2): 2961, 2920,

1603, 1491, 1261, 1094 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{19}H_{20}NO_2$ ($[M+H]^+$): 294.1489, found: 294.1485.

6b-Ethyl-5-methoxy-1-methyl-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3k). Pale yellow oil; 19.7 mg, 70% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J* = 7.1 Hz, 1H), 7.11 (pseudo t, *J* = 7.7 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.74-6.69 (m, 2H), 6.63 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.44 (d, *J* = 8.3 Hz, 1H), 5.92 (s, 1H), 3.76 (s, 3H), 3.06 (s, 3H), 2.15-2.01 (m, 2H), 0.83 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 153.1, 149.4, 133.0, 132.4, 128.3, 122.4, 118.3, 112.8, 109.7, 107.3, 106.0, 59.9, 56.2, 31.8, 29.9, 8.9; IR (CH_2Cl_2): 2934, 1603, 1495, 1267, 1196, 743 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{18}H_{20}NO_2$ ($[M+H]^+$): 282.1489, found: 282.1487.

5-Methoxy-1-methyl-1a,6b-butano-1*H*-benzofuro[2,3-b]indole (3l). Pale yellow oil; 19.6 mg, 64% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.11 (pseudo t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 2.7 Hz, 1H), 6.72 (m, 1H), 6.64-6.60 (m, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 3.78 (s, 3H), 2.98 (s, 3H), 2.35 (m, 2H), 1.88-1.82 (m, 1H), 1.79-1.74 (m, 1H), 1.62-1.57 (m, 1H), 1.48-1.42 (m, 1H), 1.39-1.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.0, 149.3, 133.9, 133.6, 128.1, 122.3, 118.9, 112.4, 112.0, 109.8, 109.7, 107.1, 56.4, 56.2, 32.4, 28.5, 28.2, 20.2, 20.0; IR (CH_2Cl_2): 2936, 1603, 1483, 1304, 1263, 1206 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{20}H_{26}NO_2$ ($[M+H]^+$): 308.1645, found: 308.1653.

5-Methoxy-1a,6b-butano-1*H*-benzofuro[2,3-b]indole (3m). Pale yellow oil; 11.1 mg, 38% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.08-7.04 (m, 2H), 6.94 (d, *J* = 1.6 Hz, 1H), 6.77 (pseudo t, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.65-6.61 (m, 2H), 4.76 (brs, 1H), 3.79 (s, 1H), 2.42 (dt, *J* = 13.8, 4.4 Hz, 1H), 2.21 (dt, *J* = 14.3, 4.4 Hz, 1H), 1.94-1.88 (m, 1H), 1.72-1.62 (m, 2H), 1.54-1.48 (m, 1H), 1.44-1.36 (m, 1H), 1.30-1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.1, 146.7, 134.4, 133.3, 127.9, 123.0, 120.1, 112.4, 109.8, 109.7, 109.6, 56.6, 56.2, 32.5, 32.0, 20.8, 20.0; IR (CH_2Cl_2): 3372, 2936, 1607, 1485, 1213, 1165 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{19}H_{20}NO_2$ ($[M+H]^+$): 294.1489, found: 294.1495.

1-Allyl-6b-benzyl-5-methoxy-1a,6b-dihydro-1*H*-benzofuro[2,3-b]indole (3n). Pale yellow oil; 24.0 mg, 65% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.16-7.14 (m, 3H), 7.08-7.05 (m, 1H), 6.98 (m, 1H), 6.92-6.90 (m, 2H), 6.76 (m, 1H), 6.66-6.62 (m, 2H), 6.34 (d, *J* = 8.2 Hz, 1H), 6.01 (s, 1H), 5.61-5.53 (m, 1H), 5.01 (dd, *J* = 10.4, 1.6 Hz, 1H), 4.92 (dd, *J* = 17.0, 1.6 Hz, 1H), 3.85 (m, 2H), 3.78 (s, 3H), 3.36 (AB, *J* = 13.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.0, 148.7, 136.4, 133.1, 132.2, 130.1, 128.4, 128.2, 126.9, 122.9, 118.4, 116.9, 113.1, 110.0, 106.8, 105.1, 59.9, 56.2, 47.7, 43.3; IR (CH_2Cl_2): 2918, 1689, 1600, 1491, 1273, 1171 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{25}H_{24}NO_2$ ($[M+H]^+$): 370.1802, found: 370.1801.

6b-Benzyl-3-chloro-5-methoxy-1-methyl-1a,6b-dihydro-1*H*-benzofuro [2,3-b]indole (3o). Pale yellow oil; 21.1 mg, 70% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.18 (d, *J* = 7.1 Hz, 1H), 7.15-7.12 (m, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 6.76-6.73 (m, 1H), 6.65 (d, *J* = 2.7 Hz, 1H), 6.49 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 1H), 3.75 (s, 3H), 3.12 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 149.0, 148.7, 135.5, 133.1, 128.6, 122.2, 118.6, 114.8, 113.0, 110.3, 108.6, 106.4, 56.3, 55.9, 31.7, 23.9; IR (CH_2Cl_2): 2961, 2926, 1605, 1491, 1437, 1120 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{17}H_{17}ClNO_2$ ($[M+H]^+$): 302.0942, found: 302.0953.

3-Bromo-5-methoxy-1,6b-dimethyl-1a,6b-dihydro-1H-benzofuro[2,3-b]indole (3p). Pale yellow solid; 22.4 mg, 65% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 6.73 (t, *J* = 7.4 Hz, 1H), 6.48 (d, *J* = 7.9 Hz, 1H), 5.89 (s, 1H), 3.74 (s, 3H), 3.10 (s, 3H); 1.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 150.4, 148.8, 135.2, 133.1, 128.6, 122.3, 118.7, 115.6, 110.1, 109.4, 106.4, 102.3, 56.4, 56.1, 31.7, 24.0; HRMS (ESI-TOF) Calculated for $C_{17}H_{17}BrNO_2$ ($[M+H]^+$): 346.0437, found: 346.0436.

4-Bromo-5-methoxy-1,6b-dimethyl-1a,6b-dihydro-1H-benzofuro[2,3-b]indole (3q). Pale yellow solid; 15.5 mg, 45% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.19 (d, *J* = 7.3 Hz, 1H), 7.14-7.11 (m, 1H), 6.99 (s, 1H), 6.90 (s, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 7.9 Hz, 1H), 5.83 (s, 1H), 3.87 (s, 3H), 3.06 (s, 3H); 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 151.0, 148.8, 133.3, 133.1, 128.6, 122.1, 118.6, 114.7, 110.9, 110.4, 107.8, 106.4, 57.5, 55.1, 31.7, 23.9; HRMS (ESI-TOF) Calculated for $C_{17}H_{17}BrNO_2$ ($[M+H]^+$): 346.0437, found: 346.0435.

4-Methoxy-2-(1-methyl-2-phenyl-1*H*-indol-3-yl)phenol (4a). Pale yellow oil; 17.1 mg, 52% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.7 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.40-7.30 (m, 5H), 7.26-7.22 (m, 2H), 6.93-6.87 (m, 2H), 6.82 (d, *J* = 2.7 Hz, 1H), 4.91 (brs, 1H, disappeared when shaken with D_2O), 3.77 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 148.3, 138.1, 134.2, 131.8, 129.1, 128.7, 126.8, 126.4, 122.9, 120.7, 120.0, 118.4, 117.0, 116.7, 116.6, 116.5, 110.0, 55.9, 30.8; IR (CH_2Cl_2): 3505, 2938, 1603, 1489, 1466, 1209 cm^{-1}; HRMS (ESI-TOF) Calculated for $C_{22}H_{20}NO_2$ ($[M+H]^+$): 330.1489, found: 330.1492.

2-Chloro-4-methoxy-6-(1-methyl-2-phenyl-1*H*-indol-3-yl)phenol (4b). Pale yellow oil (turned to a black solid after refrigeration at -10 °C); 21.8 mg, 60% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 7.9 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 7.37-7.29 (m, 5H), 7.22 (m, 2H), 6.99 (d, *J* = 3.0 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 5.34 (s, 1H, disappeared when shaken with D_2O), 3.67 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 144.7, 137.8, 134.6, 132.1, 129.4, 128.6, 126.9, 126.2, 122.8, 121.1, 120.5, 120.3, 120.1, 117.1, 116.6, 116.1, 109.8, 56.0, 30.8; HRMS (ESI-TOF) Calculated for $C_{22}H_{19}ClNO_2$ ($[M+H]^+$): 364.1099, found: 364.1110.

3-Bromo-4-methoxy-6-(1-methyl-2-phenyl-1*H*-indol-3-yl)phenol (4c). Pale white foam; 24.5 mg, 60% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37-7.31 (m, 5H), 7.25-7.21 (m, 2H), 7.19 (s, 1H), 6.77 (s, 1H), 4.98 (s, 1H), 3.78 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 148.6, 138.2, 133.9, 131.0, 129.1, 128.9, 126.7, 126.6, 123.2, 121.3, 120.8, 120.1, 117.5, 116.9, 114.9, 113.7, 110.0, 57.0, 30.9; HRMS (ESI-TOF) Calculated for $C_{22}H_{19}BrNO_2$ ($[M+H]^+$): 408.0594, found: 408.0593.

2-Fluoro-4-methoxy-6-(1-methyl-2-phenyl-1*H*-indol-3-yl)phenol (4d). Pale white foam; 14.7 mg, 51% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 7.9 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.37-7.30 (m, 5H), 7.22 (t, *J* = 7.9 Hz,2H), 6.77 (dd, J_{H-F} = 12.2, J_{H-H} = 3.0 Hz, 1H), 6.55 (s, 1H), 4.89 (s, 1H, disappeared when shaken

with D_2O), 3.69 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0 (d, J_{C-F} = 10.9 Hz), 151.6 (d, J_{C-F} = 241.6 Hz), 137.9, 136.7 (d, J_{C-F} = 10.9 Hz), 134.4, 131.3, 129.2, 128.7, 126.8 (d, J_{C-F} = 3.6 Hz), 126.3, 122.9, 120.7, 120.6, 120.0, 116.6 (d, J_{C-F} = 3.6 Hz), 112.3, 109.9, 103.9 (d, J_{C-F} = 21.8 Hz), 56.0, 30.8; HRMS (ESI-TOF) Calculated for $C_{22}H_{19}FNO_2$ ([M+H]$^+$): 348.1394, found: 348.1399.

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