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Access to 3-Arylindoles through a Tandem One-Pot Protocol Involving Dearomatization, a Regioselective Michael Addition Reaction, and Rearomatization

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A facile, general and rapid protocol for the introduction of oxygenated aryls at the 3-position of indoles is described. This approach consists of a tandem dearomatization, a regioselective Michael addition reaction, and rearomatization in a one-pot three-step sequence to obtain 3-arylindoles in good yields.

Introduction

Indole, a "privileged scaffold" in medicinal chemistry is a common core in numerous natural and synthetic products possessing a remarkable spectrum of biological activity.[1] Owing to the incredible range of pharmacological properties, several useful approaches to the construction of this core structure have been developed and documented in the literature.[2] During one of our projects, we needed 3-arylindoles in which the aryl group had to be a highly oxygenated system. 3-Arylindoles are known to possess numerous biological properties.[3] A literature survey indicated various general procedures for the synthesis of 3-arylindoles from non-indole precursors including Fischer's indole synthesis,[4] and metal-catalyzed reactions.[5] In addition, there is growing research interest in the development of new and efficient methodologies for the direct and regioselective arylation of indole at the 3-position with the aid of metal catalysis.[6] In addition, *p*-benzoquinones and *p*-benzoquinol ethers were employed in the synthesis of requisite 3-arylindoles in metal free procedures.[7] In this context, more than a decade ago, the unique ability of masked *o*-benzoquinones (MOBs) on reaction with indoles to furnish [4+2] cycloaddition reaction products or 3-arylindole under appropriate conditions was reported.[8] These results attracted our attention. However, the study was limited to 2-methoxyphenols bearing an electron-withdrawing substituent ($-CO_2CH_3$, $-COCH_3$ or –CN) at the 4-position. Consequently, on the basis of the above observation and in continuation of our research work focused on the chemistry of MOBs,[9,10] we re-visited this remarkable reaction methodology to exploit the potential of MOBs as an aryl source for the synthesis of oxygenated aryl-substituted indoles. To the best of our knowledge, reaction of indoles with MOBs that do not bear electron-withdrawing substitutions is not known. In this report we disclose our efforts to develop conditions for a tandem one-pot protocol consisting of dearomatization, a regioselective Michael addition reaction and rearomatization to access 3-arylindoles starting from commercially/easily available 2-methoxyphenols and indoles.

Results and Discussion

We began the study by investigating the aforementioned tandem one-pot reaction with creosol (2-methoxy-4-methylphenol, **1**) and indole (**a**; Table 1). At the outset, a methanolic solution of **1** was treated with diacetoxyiodobenzene (DAIB) at room temperature for 15 min. To this reaction mixture indole (**a**) was added and stirring was continued. After 16 h only Diels–Alder dimer **1D**[11] was isolated (Table 1, Entry 1). However, when the reaction temperature was increased to 70 °C, a 1:1.5 mixture of 3-arylindole **1a** and dimer **1D** were produced (Table 1, Entry 2). The structure of compound **1a** was confirmed based on ^{1}H NMR and ^{13}C NMR spectroscopy, DEPT, and HRMS analyses. In the ^{1}H NMR spectra of compound **1a**, peaks at δ = 7.05 ppm (s, H_a) and 6.85 ppm (s, H_b) correspond to pro-

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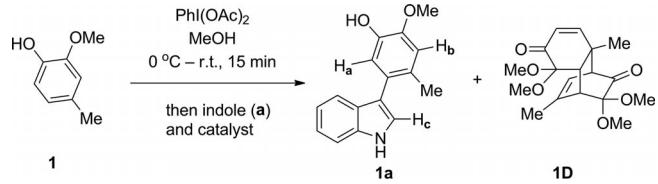
Table 1. Optimization of the reaction conditions for the synthesis of 3-arylindoles.



Entry	Catalyst	Temperature	Time	Product **1a**:**1D**
1[a]	–	r.t.	16 h	only **1D** (85%)[b]
2[c]	–	70 °C	16 h	1.0:1.5[d]
3[e]	$HClO_4/SiO_2$ (5 mol-%)	r.t.	16 h	1.5:1[d]
4[f]	$HClO_4/SiO_2$ (5 mol-%)	70 °C	4 h	only **1a** (86%)[b]
5[g,h]	CH_3SO_3H (25 mol-%)	70 °C	16 h	4:1[d]
6[i]	*p*TSA (25 mol-%)	70 °C	16 h	3:1[d]
7[j]	$HClO_4/SiO_2$ (1 mol-%)	70 °C	16 h	9:1[d]

[a] **1** (1.0 equiv.), $PhI(OAc)_2$ (1.2 equiv.), MeOH, room temp., 15 min followed by addition of indole (**a**, 1.3 equiv.). [b] Yield of isolated product. [c] Same reaction conditions as for Entry 1, after the addition of indole (**a**), the reaction mixture was dipped in a 70 °C pre-heated oil bath for 16 h. [d] Product ratio is obtained from ^1H NMR spectroscopic data integration of the crude reaction mixture. [e] Same reaction conditions as for Entry 1, and along with indole (**a**), 5 mol-% of catalyst $HClO_4/SiO_2$ was added. [f] Same reaction conditions as for Entry 3, the reaction mixture was dipped in a 70 °C pre-heated oil bath for 4 h. [g] Same reaction conditions as for Entry 4, 25 mol-% CH_3SO_3H was used as the catalyst. [h] 20–30% of uncharacterizable product was also obtained. [i] Same reaction conditions as for Entry 4, 25 mol-% *p*-toluenesulfonic acid (*p*TSA) was used as the catalyst. [j] Same reaction conditions as for Entry 4, 1 mol-% of $HClO_4/SiO_2$ was used as the catalyst.

tons of the aryl system indicating the assigned structure. The proton at 2-position of indole in compound **1a** appeared at δ = 7.13 ppm (d, J = 2.4 Hz, H_c) as a doublet owing to the coupling with adjacent indole "-N*H*-". In the deuterium exchange ^1H NMR experiment "H_c" appeared as a singlet owing to decoupling with indole "-N*H*-".[12] It is noteworthy that the regioselectivity of the obtained product (in which indole is attached at the 5-position to 2-methoxyphenol) is completely different from the literature precedent (in which indole is attached at 3-position to 2-methoxyphenol).[8] Although we could not isolate any intermediates from the reaction mixture, a conceivable mechanism for the tandem one-pot protocol leading to 3-arylindole derivative is depicted in Figure 1. Accordingly, 2-methoxyphenol **1** is initially oxidized by DAIB in the presence of methanol to give MOB of **1**. At this stage, indole (**a**) is added to the reaction mixture, which then participates in the Michael addition reaction step with MOB followed by spontaneous aromatization of the intermediate providing observed 3-arylindole **1a**.

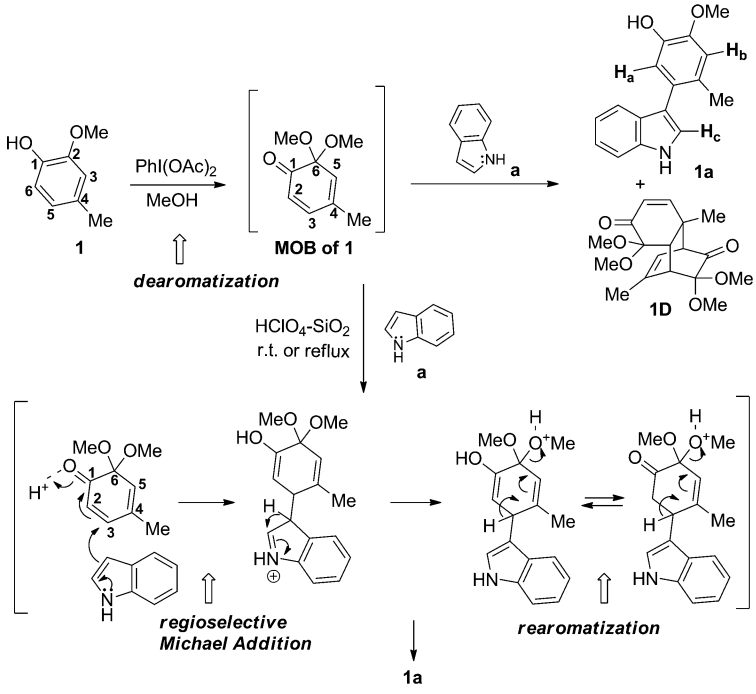
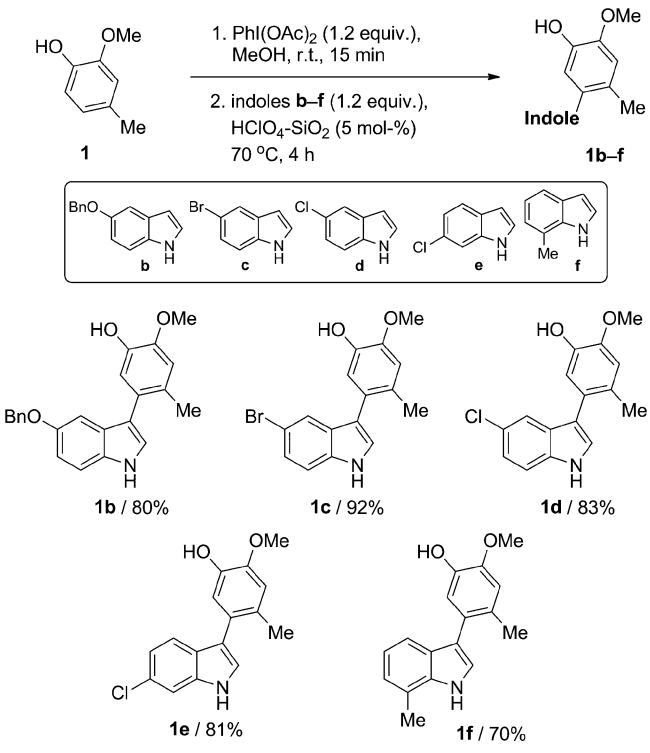


Figure 1. A plausible mechanism for the formation of 3-arylindole **1a**.

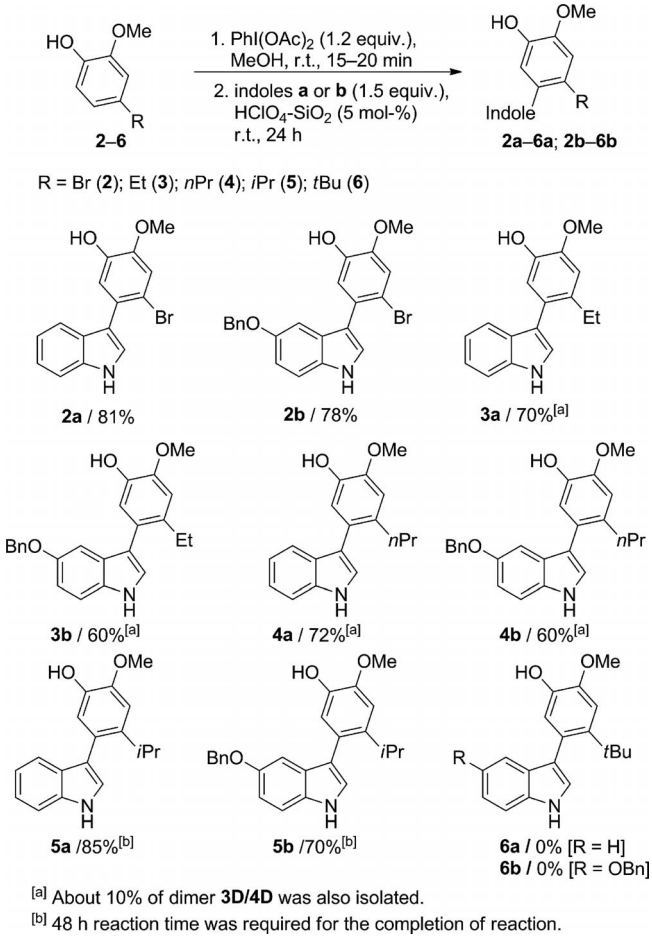
It was predicted that the ratio of 3-arylindole **1a** over dimer **1D** could be enhanced if the rate of the Michael addition reaction step is improved. Interestingly, acetic acid liberated during the MOB generation step was not enough to improve the Michael addition reaction. Thus, catalysts for the above tandem reaction leading to product **1a** were screened. Motivated by our previous work with silica-supported perchloric acid ($HClO_4/SiO_2$),[13] we first decided to investigate the above tandem sequence in the presence of this inexpensive catalyst system. As shown in Table 1, initial optimization studies revealed that efficient 3-arylation of indole occurred in the presence of 5 mol-% of $HClO_4/SiO_2$ at 70 °C (Table 1, Entry 4). Interestingly, 25 mol-% of CH_3SO_3H or *p*TSA was not as effective as 1 mol-% of $HClO_4/SiO_2$ (Table 1, Entries 3–7). Nevertheless, in all the catalyzed reaction procedures the product to dimer ratio was improved.

With the established conditions in hand, we evaluated the reaction of creosol (**1**) with several differently substituted indoles **b**–**f**. To our delight, as delineated in Scheme 1, the tandem procedure was successful with all the indole substrates used to give corresponding 3-arylated indoles **1b**–**1f** in good yields.



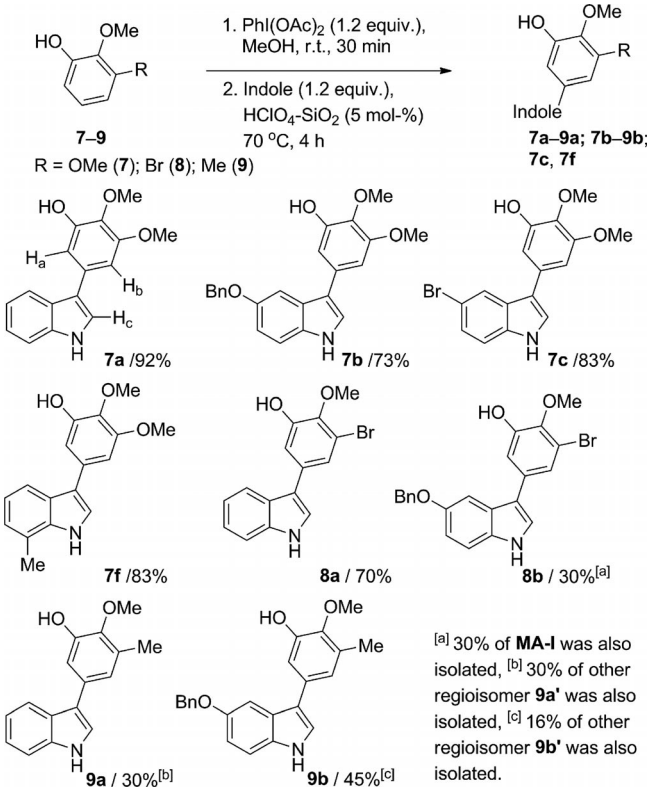
Scheme 1. Creosol (**1**) as aryl source in the synthesis of 3-arylindoles.

In an effort to extend the scope of this methodology, 2-methoxyphenols bearing sterically different substitutions were chosen to be installed at the 3-position of selected indoles **a** and **b**. Thus, when 2-methoxyphenol **2** was subjected to the optimized tandem reaction conditions with indole (**a**), we noticed that purification of the desired product from the reaction mixture was tedious. This difficulty was presumed to be the result of the incompatibility of indoles under the acidic environment and elevated temperatures that led to unidentified impurities and isolation problems. Therefore, subsequent reactions were carried out at room temperature. Gratifyingly, this proved to be the case and products **2a** and **2b** were obtained in 81% and 78% yield, respectively (Scheme 2). As a result, 5 mol-% $HClO_4/SiO_2$ and room temperature were adopted as the new general conditions. Under these reaction conditions, 3-arylindoles **3a**–**3b**, **4a**–**4b** and **5a**–**5b** were produced in satisfactory yields (Scheme 3). It should be noted that in the case of 2-methoxyphenols **3** and **4**, about 10% of dimers **3D** and **4D** were also isolated (Figure 2). Interestingly, the reaction of 2-methoxyphenol **6** with indoles **a** or **b** under the tandem reaction conditions either at room temperature or elevated temperature (70 °C) did not yield any desired product. The only isolated product in these cases was MOB of **6** (Figure 2). This result can be attributed to the presence of the bulky *tert*-butyl group near the reaction center causing severe steric hindrance.



Scheme 2. Effect of sterically different substitutions in the synthesis of 3-arylindoles.

The tandem protocol success with 4-substituted 2-methoxyphenols in Scheme 1 and Scheme 2, led us to examine the substrate scope with a selected set of 3-substituted 2-



Scheme 3. Various 2-methoxyphenols as aryl source in the synthesis of 3-arylindoles.

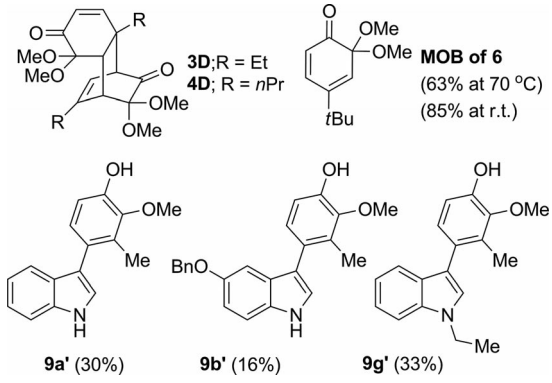
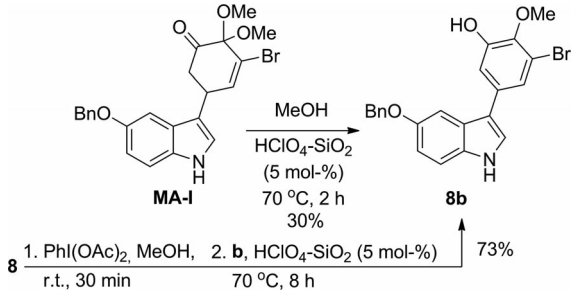


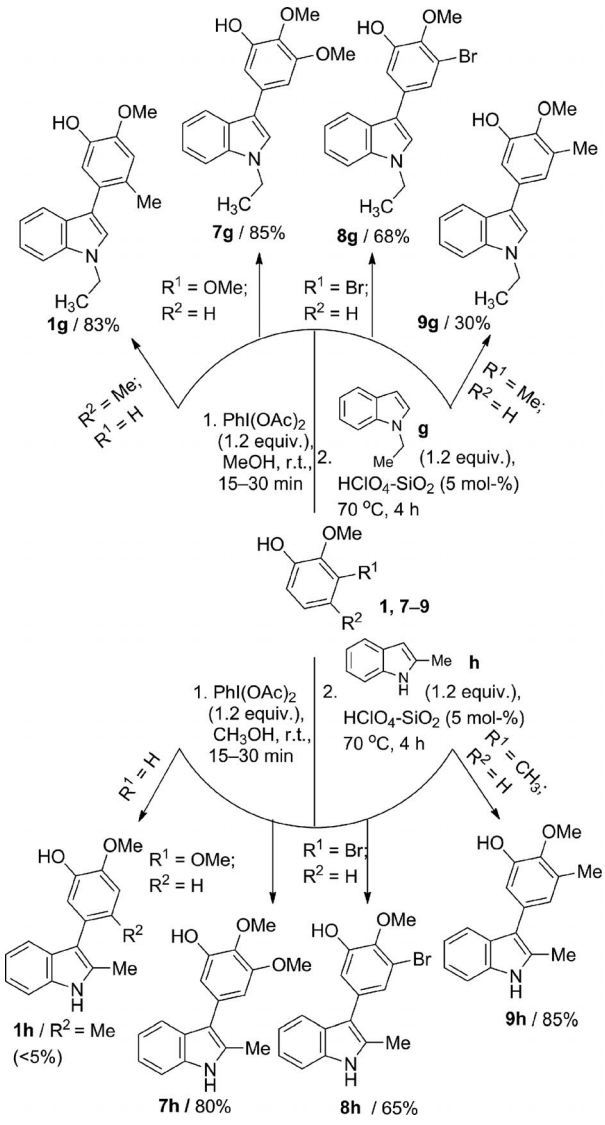
Figure 2. Structures of dimers **3D/4D**, MOB of phenol **6** and regioisomers **9a′ 9b′** and **9g′**.

methoxyphenols **7**–**9**. At the outset, 2,3-dimethoxyphenol (**7**) was treated with DAIB in methanol for 30 min. To this reaction mixture was separately added indoles **a**, **b**, **c** or **f** along with 5 mol-% $HClO_4/SiO_2$ catalyst. The reaction vessel was then dipped in a 70 °C pre-heated oil bath.[14] After the completion of reaction and chromatographic purification, 3-arylindoles **7a** (92%), **7b** (73%), **7c** (83%) and **7f** (83%) were produced in good yields (Scheme 3). For example, in the ^1H NMR spectra of compound **7a**, appearance of aryl protons at δ = 6.90 (d, J = 2.1 Hz, 1 H, H_a), 6.79 (d, J = 2.1 Hz, 1 H, H_b) ppm with *meta* coupling indicated the assigned regioselectivity. Thus, the products obtained were in accordance with the postulated mechanism shown in Figure 1. Similarly, 3-bromo-2-methoxyphenol (**8**) and indole **a** participated in the tandem reaction procedure providing 3-arylindole **8a** in 70% yield. However, compound **8** with indole **b** provided 3-arylindole **8b** in only 30% yield along with the Michael addition reaction product **MA-I** in 30% isolated yield (Scheme 3 and Scheme 4). Interestingly, this is the only case in which the intermediate Michael addition product was isolated. On the other hand, when the reaction time was increased to 8 h, product **8b** could be isolated in 73% yield with no trace of Michael addition reaction product (Scheme 4). Subsequently, to verify our rationale shown in Figure 1, in a separate experiment, a methanolic solution of compound **MA-I** was heated to 70 °C in the presence of 5 mol-% $HClO_4/SiO_2$ catalyst for 2 h. To our satisfaction, 30% of **8b** was produced as expected along with 35% of recovered Michael adduct **MA-I** (Scheme 4). In contrast to 2-methoxyphenols **7** and **8**, when the tandem procedure was applied to 3-methyl-2-methoxyphenol (**9**) and indoles **a** and **b**, a 1:1 mixture of products **9a**:**9a′** and 3:1 mixture of products **9b**:**9b′** were isolated (Scheme 3, Figure 2). Nevertheless, the present tandem protocol was applicable to 2-methoxyphenols bearing different substitution patterns.



Scheme 4. Tandem protocol applied to 2-methoxyphenol **8** and indole **b**.

Next we chose two new indoles, *N*-ethylindole (**g**) and 2-methylindole (**h**) for the tandem protocol with 2-methoxyphenols **1** and **7**–**9**.[15] 2-Methylindole (**h**) was chosen to verify if the substitution at 2-position of indole would affect the reaction course; and *N*-ethylindole (**g**) will provide information on whether free "-NH" is necessary for the reaction to proceed. Initially, 2-methoxyphenols **1** and **7**–**9** were subjected to the tandem protocol with *N*-ethylindole (**g**). Products **1g** (83%), **7g** (85%), and **8g** (68%) were obtained in moderate to good yields (Scheme 5). However product **9g** was obtained in only 30% yield along with its regioisomer **9g′** (Scheme 5, Figure 2). This outcome was in line with the previous results obtained with 2-methoxy-3-methylphenol (**9**). Subsequently, 2-methylindole was used in the tandem protocol with 2-methoxyphenols **1** and **7**–**9**; interestingly, products **7h**–**9h** were only formed. The major product in the tandem reaction involving **1** and indole **h** was MOB dimer **1D** (Scheme 5) with only traces of desired product **1h** according to the ^1H NMR spectroscopic data of the crude reaction mixture.



Scheme 5. Tandem protocol applied to 2-methoxyphenol **1**, **7**–**9** and indoles **g** and **h**.

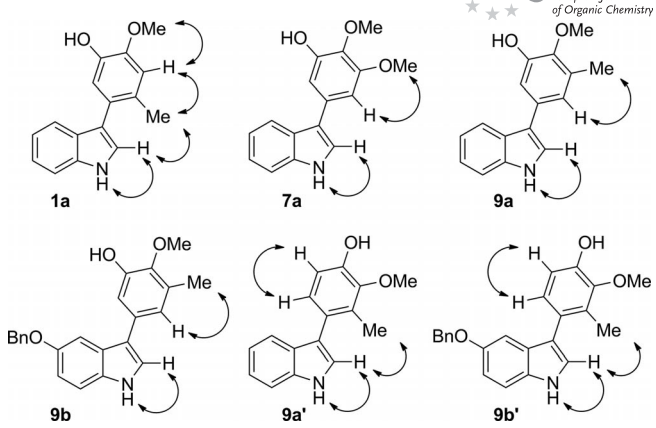


Figure 3. Diagnostic 2D NOESY cross peaks.

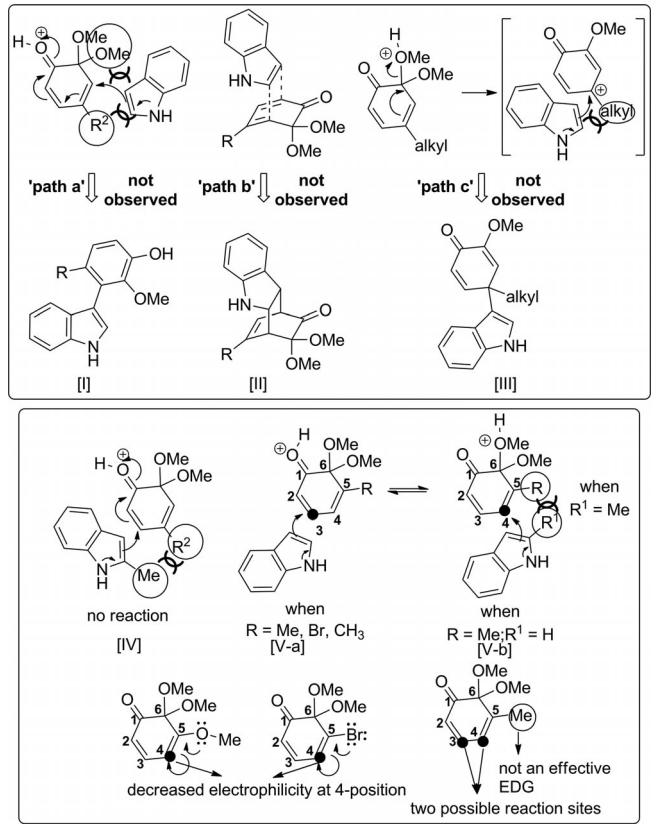


Figure 4. Possible products in the reaction between MOBs and indole, and factors affecting the observed results.

The structures of all of the products were assigned on the basis of ^{1}H NMR and ^{13}C NMR spectroscopy, DEPT and HRMS analyses. In addition, 2D NOESY experiments on a selected set of compounds further confirmed the proposed structural assignment (Figure 3).

Several conclusions can be drawn from the results obtained and are shown in Figure 4. [**I**] In the majority of the cases, the Michael addition reaction of indole to in-situ-generated MOB occurred at the 3-position as opposed to the 5-position reported in the literature.[8] The difference in regioselectivity in the previous work can be attributed to the presence of electron-withdrawing groups (–CO_2CH_3, –$COCH_3$ or –CN) at the 4-position of MOB that directed the Michael addition reaction to the 5-position (Figure 3, Path a). In this work both electronic and steric factors contributed to the Michael addition reaction at the 3-position and thus the observed regioselectivity. [**II**] Indole was reported to take part in inverse electron demand Diels–Alder reactions on several occasions.[16] However, in this study no Diels–Alder adduct (Figure 4, Path b; MOB acting as diene and indole as dienophile) was observed under the reaction conditions employed. Consequently, from the literature precedent[8] and observed experimental results, it can be inferred that MOB should have a strong electron-withdrawing substituent to participate in an inverse electron demand Diels–Alder reaction with indole to furnish the Diels–Alder adduct following Path b. [**III**] Recently it was reported that 4-alkyl-substituted MOBs under acid catalysis provide *p*-quinol ethers through Figure 4, Path c,[17] however, in our study no such products were observed. [**IV**] The failure of

2-methylindole to provide the desired product with 4-substituted MOBs can be attributed to steric hindrance between both the methyl groups as indicated in Figure 4. [**V-a**] 5-Methoxy- and 5-bromo- substituted MOBs on reaction with indoles provided only one kind of product owing to the reaction of indole at the 3-position of MOBs; however, 5-methyl-substituted MOB provided two isomers owing to the reaction of indole at both the 3- and 4-positions, respectively. The difference can be attributed to the electronic factors, in which the Br and OMe substituents decrease the electrophilicity at the 4-position owing to the mesomeric effect, whereas an Me group could not affect such a decrease in the electrophilicity at the 4-position leading to the other possible isomers **9a′**, **9b′**, and **9g′**. [**V-b**] The reaction between 2-methylindole and 5-methyl-substituted MOB gave 85% of isomer **9h**, probably owing to the steric hindrance between both the methyl groups as indicated in Figure 4.

Next we investigated application of the tandem protocol of 2-methoxyphenols **10**–**12**. To our surprise, the tandem reaction at room temperature or 70 °C furnished only dimers **10D**–**12D** (Figure 5). Presumably, after the oxidation step, the competing MOB dimerization is preferred over the Michael addition reaction in these cases.

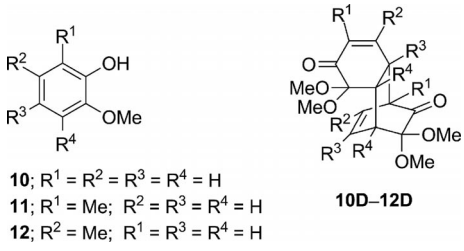


Figure 5. 2-Methoxyphenols **10**–**12** and dimers **10D**–**12D**.

Conclusions

In conclusion, the ability of unactivated MOBs to undergo a tandem one-pot three-step reaction facilitates a useful, direct and efficient approach for the preparation of 3-arylindoles. This strategy is amenable for the introduction of diverse oxygenated aryls at C-3 of the indole and generally the yields are good. However, a few 2-methoxyphenols did not provide expected results under the reaction conditions and investigations are in progress to obtain 3-arylindoles from such 2-methoxyphenols.

Experimental Section

Preparation of $HClO_4/SiO_2$ Catalyst System: To a suspension of SiO_2 (230–400 mesh, 50 g) in CH_2Cl_2 (150 mL) at room temperature was added 70% aqueous $HClO_4$ (3.60 g, 2.2 mL, 25.0 mmol). After stirring for 30 min, the mixture was concentrated and the residue was heated to 60 °C under vacuum for 2 h to furnish perchloric acid adsorbed on silica gel ($HClO_4/SiO_2$, 0.05 mmol/100 mg) as a free flowing powder.

General Procedure for the Synthesis of 3-Arylindoles: To a solution of 2-methoxyphenol (1.0 mmol) in methanol (4 mL) was added DAIB (1.2 mmol) and the resulting mixture was stirred for 15–30 min at room temperature (generation of MOB). After this time, indole (1.2 mmol) and $HClO_4/SiO_2$ (0.05 mmol, 100 mg) were added at ambient temperature and the reaction vessel was dipped in a 70 °C pre-heated oil bath or left stirring at room temperature until the reaction was complete. The reaction mixture was concentrated and the residue was purified by column chromatography on silica gel by using a mixture of ethyl acetate and hexanes as eluent to obtain 3-arylindoles.

5-(1*H*-Indol-3-yl)-2-methoxy-4-methylphenol (1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br. s, 1 H), 7.56 (d, J = 8.0 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.27–7.23 (m, 1 H), 7.18–7.16 (m, 1 H), 7.13 (d, J = 2.4 Hz, 1 H), 7.05 (s, 1 H), 6.85 (s, 1 H), 5.55 (s, 1 H), 3.95 (s, 3 H), 2.27 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3 (C), 143.1 (C), 135.8 (C), 128.4 (C), 127.2 (C), 127.1 (C), 122.7 (CH), 122.0 (CH), 120.1 (CH), 119.8 (CH), 117.1 (C), 116.9 (CH), 112.8 (CH), 111.1 (CH), 55.9 (CH_3), 20.2 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{15}NNaO_2$ [M + Na] 276.0995; found 276.0991.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-2-methoxy-4-methylphenol (1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (br. s, 1 H), 7.45–7.42 (m, 2 H), 7.38–7.32 (m, 2 H), 7.32–7.25 (m, 2 H), 7.06 (d, J = 2.4 Hz, 2 H), 7.03 (d, J = 2.4 Hz, 1 H), 6.97 (s, 1 H), 6.95 (dd, J = 2.4, 8.8 Hz, 1 H), 6.80 (s, 1 H), 5.49 (s, 1 H), 5.03 (s, 2 H), 3.91 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (C), 145.3 (C), 143.2 (C), 137.6 (C), 131.1 (C), 128.43 (CH ×2), 128.40 (C), 127.7 (CH), 127.6 (CH ×2), 127.58 (C), 127.2 (C), 123.5 (CH), 117.0 (C), 116.8 (CH), 113.2 (CH), 112.8 (CH), 111.8 (CH), 103.3 (CH), 70.9 (CH_2), 56.0 (CH_3), 20.2 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{22}NO_3$ [M + H] 360.1594; found 360.1596.

5-(5-Bromo-1*H*-indol-3-yl)-2-methoxy-4-methylphenol (1c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (br. s, 1 H), 7.61 (s, 1 H), 7.22–7.30 (m, 2 H), 7.11 (d, J = 2.0 Hz, 1 H), 6.93 (s, 1 H), 6.81 (s, 1 H), 5.52 (s, 1 H), 3.92 (s, 3 H), 2.20 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5 (C), 143.2 (C), 134.4 (C), 129.0 (C), 128.4 (C), 126.3 (C), 124.9 (CH), 123.8 (CH), 122.5 (CH), 116.9 (CH), 116.8 (C), 113.2 (C), 112.8 (CH), 112.5 (CH), 56.0 (CH_3), 29.6 (C), 20.1 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{14}BrNNaO_2$ [M + Na] 354.0100; found 354.0115.

5-(5-Chloro-1*H*-indol-3-yl)-2-methoxy-4-methylphenol (1d): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br. s, 1 H), 7.48 (app. s, 1 H), 7.32 (app. d, J = 8.7 Hz, 1 H), 7.19–7.14 (m, 2 H), 6.96 (s, 1 H), 6.83 (s, 1 H), 5.53 (s, 1 H), 3.94 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.5 (C), 143.2 (C), 134.2 (C), 128.43 (C), 128.39 (C), 126.4 (C), 125.7 (C), 124.0 (CH), 122.4 (CH), 119.5 (CH), 117.0 (C), 116.8 (CH), 112.8 (CH), 112.1 (CH), 56.0 (CH_3), 20.2 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{15}ClNO_2$ [M + H] 288.0786; found 288.0798.

5-(6-Chloro-1*H*-indol-3-yl)-2-methoxy-4-methylphenol (1e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.18 (br. s, 1 H), 7.42–7.40 (m, 2 H), 7.12–7.08 (m, 2 H), 6.97 (s, 1 H), 6.82 (s, 1 H), 5.50 (s, 1 H), 3.94 (s, 3 H), 2.22 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.5 (C), 143.2 (C), 136.2 (C), 128.4 (C), 128.0 (C), 126.5 (C), 125.9 (C), 123.2 (CH), 121.0 (CH), 120.6 (CH), 117.4 (C), 116.8 (CH), 112.8 (CH), 111.0 (CH), 56.0 (CH_3), 20.1 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{15}ClNO_2$ [M + H] 288.0786; found 288.0787.

2-Methoxy-4-methyl-5-(7-methyl-1*H*-indol-3-yl)phenol (1f): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11 (br. s, 1 H), 7.42–7.31 (m, 1

H), 7.15 (d, J = 2.4 Hz, 1 H), 7.09–6.97 (m, 3 H), 6.82 (s, 1 H), 5.47 (s, 1 H), 3.94 (s, 3 H), 2.54 (s, 3 H), 2.25 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.3 (C), 143.2 (C), 135.4 (C), 128.4 (C), 127.4 (C), 126.8 (C), 122.6 (CH), 122.4 (CH), 120.2 (CH), 120.0 (C), 117.9 (CH), 117.7 (C), 116.9 (CH), 112.8 (CH), 56.0 (CH_3), 20.3 (CH_3), 16.6 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{18}NO_2$ [M + H] 268.1332; found 268.1325.

4-Bromo-5-(1*H*-indol-3-yl)-2-methoxyphenol (2a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (br. s, 1 H), 7.60 (d, J = 7.8 Hz, 1 H), 7.41 (d, J = 7.8 Hz, 1 H), 7.34 (d, J = 2.4 Hz, 1 H), 7.24–7.13 (m, 3 H), 7.12 (s, 1 H), 5.56 (s, 1 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 145.9 (C), 144.8 (C), 135.6 (C), 128.8 (C), 126.7 (C), 123.8 (CH), 122.2 (CH), 120.1 (CH), 120.0 (CH), 117.7 (CH), 116.5 (C), 115.5 (CH), 113.0 (C), 111.2 (CH), 56.3 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{15}H_{12}BrNNaO_2$ [M + Na] 339.9944; found 339.9943.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-4-bromo-2-methoxyphenol (2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (br. s, 1 H), 7.46–7.44 (m, 2 H), 7.39–7.28 (m, 5 H), 7.16 (s, 1 H), 7.13 (d, J = 2.4 Hz, 1 H), 7.07 (s, 1 H), 6.95 (dd, J = 2.4, 8.7 Hz, 1 H), 5.58 (s, 1 H), 5.05 (s, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$): δ = 153.6 (C), 145.9 (C), 144.8 (C), 137.6 (C), 131.0 (C), 128.8 (C), 128.5 (CH ×2), 127.73 (CH ×2), 127.71 (CH), 127.0 (C), 124.6 (CH), 117.6 (CH), 116.3 (C), 115.5 (CH), 113.3 (CH), 112.9 (C), 111.9 (CH), 103.5 (CH), 71.0 (CH_2), 56.3 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{22}H_{18}BrNNaO_3$ [M + Na] 446.0362; found 446.0367.

4-Ethyl-2-methoxyphenol (3):[18] A solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone (2.0 g, 12.0 mmol) in glacial acetic acid (50 mL) was heated to 70 °C with stirring. To this solution was added zinc dust (7.8 g, 120 mmol) portion-wise for 15 min. The resulting heterogeneous mixture was then heated to reflux and stirred for 6 h. The reaction mixture was filtered through a pad of Celite followed by solvent evaporation. The residue was basified with saturated aqueous sodium hydrogen carbonate solution. The resulting aqueous layer was then extracted with ethyl acetate (5× 30 mL), dried with sodium sulfate, filtered and concentrated under vacuum to afford 4-ethyl-2-methoxyphenol (**3**, 1.65 g, 90% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.86 (m, 1 H), 6.66–6.73 (m, 2 H), 5.45 (br. s, 1 H), 3.89 (s, 3 H), 2.59 (q, J = 10.0 Hz, 2 H), 1.22 (t, J = 10.0 Hz, 3 H) ppm.

4-Ethyl-5-(1*H*-indol-3-yl)-2-methoxyphenol (3a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br. s, 1 H), 7.48 (dd, J = 0.8, 8.0 Hz, 1 H), 7.39–7.44 (m, 1 H), 7.19–7.24 (m, 1 H), 7.09–7.15 (m, 2 H), 6.96 (s, 1 H), 6.85 (s, 1 H), 5.47 (s, 1 H), 3.95 (s, 3 H), 2.58 (q, J = 7.6 Hz, 2 H), 1.07 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7 (C), 143.1 (C), 135.8 (C), 135.2 (C), 127.7 (C), 126.5 (C), 122.5 (CH), 122.1 (CH), 120.0 (CH), 119.8 (CH), 117.3 (CH), 117.0 (C), 111.0 (CH), 111.0 (CH), 56.0 (CH_3), 26.2 (CH_2), 16.2 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{17}NNaO_2$ [M + Na] 290.1151; found 290.1160.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-4-ethyl-2-methoxyphenol (3b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (br. s, 1 H), 7.40–7.47 (m, 2 H), 7.26–7.29 (m, 4 H), 7.09 (d, J = 2.1 Hz, 1 H), 6.94–7.03 (m, 2 H), 6.93 (s, 1 H), 6.84 (s, 1 H), 5.47 (s, 1 H), 5.02 (s, 2 H), 3.94 (s, 3 H), 2.55 (q, J = 7.5 Hz, 2 H), 1.05 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6 (C), 145.7 (C), 143.2 (C), 137.6 (C), 135.2 (C), 131.1 (C), 128.4 (CH ×2), 128.0 (C), 127.7 (CH), 127.6 (CH ×2), 126.6 (C), 123.3 (CH), 117.2 (CH), 116.9 (C), 113.2 (CH), 111.8 (CH), 111.0 (CH), 103.2 (CH), 70.9 (CH_2), 56.0 (CH_3), 26.2 (CH_2), 16.2 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{24}H_{24}NO_3$ [M + H] 374.1751; found 374.1756.

2-Methoxy-4-propylphenol (4):[19] A solution of 4-allyl-2-methoxyphenol (1.0 g, 6.1 mmol) in ethanol (50 mL) and 10% Pd/C (200 mg) was stirred at room temperature under a hydrogen atmosphere by using a hydrogen filled balloon for 16 h. The reaction mixture was filtered through a pad of Celite and the filtrate was evaporated to provide 2-methoxy-4-propylphenol (0.94 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81–6.85 (m, 1 H), 6.65–6.71 (m, 2 H), 5.47 (br. s, 1 H), 3.88 (s, 3 H), 2.52 (dd, J = 7.2, 7.6 Hz, 2 H), 1.56–1.67 (m, 2 H), 0.94 (t, J = 7.6 Hz, 3 H) ppm.

5-(1*H*-Indol-3-yl)-2-methoxy-4-propylphenol (4a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H), 7.48 (d, J = 8.1 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 1 H), 7.21 (t, J = 7.2 Hz, 1 H), 7.07–7.15 (m, 2 H), 6.95 (s, 1 H), 6.83 (s, 1 H), 5.45 (s, 1 H), 3.94 (s, 3 H), 2.48–2.58 (m, 2 H), 1.41–1.51 (m, 2 H), 0.78 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 145.5 (C), 143.1 (C), 135.8 (C), 133.6 (C), 127.7 (C), 126.8 (C), 122.4 (CH), 122.1 (CH), 120.0 (CH), 119.8 (CH), 117.3 (CH), 117.1 (C), 111.6 (CH), 111.0 (CH), 56.0 (CH_3), 35.2 (CH_2), 24.9 (CH_2), 13.9 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{20}NO_2$ [M + H] 282.1489; found 282.1488.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-2-methoxy-4-propylphenol (4b): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (br. s, 1 H), 7.39–7.41 (m, 2 H), 7.25–7.39 (m, 4 H), 7.08 (d, J = 2.7 Hz, 1 H), 7.02–6.94 (m, 2 H), 6.93 (s, 1 H), 6.82 (s, 1 H), 5.46 (s, 1 H), 5.02 (s, 2 H), 3.94 (s, 3 H), 2.45–2.55 (m, 2 H), 1.43–1.54 (m, 2 H), 0.77 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6 (C), 145.5 (C), 143.2 (C), 137.7 (C), 133.7 (C), 131.1 (C), 128.4 (CH ×2), 128.1 (C), 127.7 (CH), 127.6 (CH ×2), 126.8 (C), 123.3 (CH), 117.2 (CH), 117.0 (C), 113.2 (CH), 111.7 (CH), 111.6 (CH), 103.1 (CH), 70.9 (CH_2), 56.0 (CH_3), 35.2 (CH_2), 24.9 (CH_2), 14.0 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{26}ClNO_3$ [M + H] 388.1907; found 388.1913.

4-Isopropyl-2-methoxyphenol (5):[20] A solution of 1-(4-hydroxy-3-methoxyphenyl)ethanone (3.0 g, 18.1 mmol) in dry tetrahydrofuran (30 mL) at 0 °C was added methylmagnesiumbromide (13.3 mL, 39.8 mmol, 3.0 M in diethyl ether). The reaction mixture was allowed to stir for 3 h at room temperature. Aqueous 1 N HCl was added to the reaction and it was extracted with ethyl acetate. Organic extracts were collected and dried with sodium sulfate, filtered and concentrated to give a residue. The obtained residue was dissolved in ethanol (40 mL) and 10% wet Pd/C (500 mg) was added to it and subjected to hydrogenation on a Parr shaker at 45 psi for 8 h. The reaction mixture was filtered through a pad of Celite followed by solvent evaporation to provide a residue that was purified by column chromatography with silica gel by using a mixture of ethyl acetate and hexanes as eluent to give 4-isopropyl-2-methoxyphenol (**5**, 2.2 g, 73% for two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.84 (d, J = 8.8 Hz, 1 H), 6.69–6.74 (m, 2 H), 5.44 (s, 1 H), 3.89 (s, 3 H), 2.78–2.90 (m, 1 H), 1.22 (d, J = 6.8 Hz, 6 H) ppm.

5-(1*H*-Indol-3-yl)-4-isopropyl-2-methoxyphenol (5a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H), 7.47 (d, J = 8.1 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.25–7.17 (m, 1 H), 7.14–7.06 (m, 2 H), 6.91 (s, 1 H), 6.89 (s, 1 H), 5.49 (s, 1 H), 3.95 (s, 3 H), 3.17–3.08 (m, 1 H), 1.12 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0 (C), 143.0 (C), 140.2 (C), 135.8 (C), 128.0 (C), 125.9 (C), 122.6 (CH), 122.0 (CH), 119.8 (CH), 119.7 (CH), 117.2 (CH), 117.0 (C), 111.0 (CH), 107.8 (CH), 56.0 (CH_3), 29.5 (CH), 24.6 (CH_3 ×2) ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{20}NO_2$ [M + H] 282.1489; found 282.1485.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-4-isopropyl-2-methoxyphenol (5b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (br. s, 1 H), 7.45–7.42 (m, 2 H), 7.38–7.27 (m, 4 H), 7.08 (d, J = 2.4 Hz, 1 H), 7.00–6.99 (m,

1 H), 6.96 (app. dd, J = 2.4, 8.8 Hz, 1 H), 6.89 (app. d, J = 2.0 Hz, 1 H), 5.48 (s, 1 H), 5.02 (s, 2 H), 3.96 (s, 3 H), 3.15–3.08 (m, 1 H), 1.07 (d, J = 6.8 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6 (C), 146.0 (C), 143.0 (C), 140.2 (C), 137.6 (C), 131.0 (C), 128.4 (CH ×2), 128.3 (C), 127.7 (CH), 127.6 (CH ×2), 125.9 (C), 123.4 (CH), 117.1 (CH), 116.9 (C), 113.3 (CH), 111.8 (CH), 107.8 (CH), 102.7 (CH), 70.8 (CH_2), 56.0 (CH_3), 29.5 (CH), 24.6 (CH_3 ×2) ppm. HRMS (ESI$^+$): calcd. for $C_{25}H_{25}NNaO_3$ [M + Na] 410.1727; found 410.1722.

4-*tert*-Butyl-2-methoxyphenol (6): A two-step literature protocol utilizing 4-*tert*-butylphenol as starting material was employed for the synthesis of 4-*tert*-butyl-2-methoxyphenol.[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80–6.95 (m, 3 H), 5.53 (br. s, 1 H), 3.88 (s, 3 H), 1.30 (9 H) ppm.

4-*tert*-Butyl-6,6-dimethoxycyclohexa-2,4-dienone (MOB of 6): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (dd, J = 2.4, 10.0 Hz, 1 H), 6.08 (d, J = 2.4 Hz, 1 H), 6.01 (d, J = 10.0 Hz, 1 H), 3.36 (s, 6 H), 1.16 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 195.5 (C), 145.8 (C), 140.5 (CH), 126.3 (CH), 125.5 (CH), 91.6 (C), 50.0 (2× CH_3), 34.4 (C), 28.4 (3× CH_3) ppm. HRMS (ESI$^+$): calcd. for [M + Na] 233.1148; found 233.1154.

5-(1*H*-Indol-3-yl)-2,3-dimethoxyphenol (7a): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (br. s, 1 H), 7.93 (d, J = 7.8 Hz, 1 H), 7.42 (app. d, J = 7.8 Hz, 1 H), 7.33 (d, J = 2.4 Hz, 1 H), 7.14–7.29 (m, 2 H), 6.90 (d, J = 2.1 Hz, 1 H), 6.79 (d, J = 2.1 Hz, 1 H), 5.80 (s, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5 (C), 149.5 (C), 136.6 (C), 134.1 (C), 131.8 (C), 125.6 (C), 122.4 (CH), 121.7 (CH), 120.3 (CH), 119.7 (CH), 118.1 (C), 111.4 (CH), 107.1 (CH), 103.7 (CH), 61.1 (CH_3), 55.9 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{16}NO_3$ [M + H] 270.1125; found 270.1122.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-2,3-dimethoxyphenol (7b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br. s, 1 H), 7.42–7.49 (m, 3 H), 7.35–7.41 (m, 2 H), 7.27–7.33 (m, 3 H), 6.99 (dd, J = 2.4, 8.8 Hz, 1 H), 6.85 (d, J = 2.0 Hz, 1 H), 6.70 (d, J = 2.0 Hz, 1 H), 5.80 (s, 1 H), 5.12 (s, 2 H), 3.94 (s, 3 H), 3.86 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDC1_3$ + CD_3OD): δ = 153.4 (C), 152.7 (C), 150.0 (C), 137.4 (C), 134.1 (C), 132.0 (C), 128.4 (CH ×2), 127.6 (CH), 127.4 (CH ×2), 125.7 (C), 122.7 (CH), 117.2 (C), 112.9 (CH), 112.1 (CH), 107.3 (CH), 104.4 (C), 103.2 (CH), 103.1 (CH), 71.0 (CH_2), 60.8 (CH_3), 55.7 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{23}H_{21}NNaO_4$ [M + Na] 398.1363; found 398.1368.

5-(5-Bromo-1*H*-indol-3-yl)-2,3-dimethoxyphenol (7c): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (br. s, 1 H), 8.02 (d, J = 1.6 Hz, 1 H), 7.22–7.37 (m, 3 H), 6.85 (d, J = 1.6 Hz, 1 H), 6.70 (d, J = 1.6 Hz, 1 H), 5.86 (s, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.6 (C), 149.6 (C), 135.2 (C), 134.3 (C), 130.9 (C), 127.4 (C), 125.3 (CH), 122.7 (CH), 122.3 (CH), 117.9 (C), 113.7 (C), 112.8 (CH), 107.2 (CH), 103.8 (CH), 61.1 (CH_3), 56.0 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{16}H_{14}BrNNaO_3$ [M + Na] 370.0049; found 370.0063.

2,3-Dimethoxy-5-(7-methyl-1*H*-indol-3-yl)phenol (7f): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (br. s, 1 H), 7.82 (d, J = 8.0 Hz, 1 H), 7.30 (d, J = 2.4 Hz, 1 H), 7.14 (app. t, J = 7.2 Hz, 1 H), 7.07 (d, J = 7.2 Hz, 1 H), 6.93 (d, J = 1.6 Hz, 1 H), 6.82 (d, J = 1.6 Hz, 1 H), 5.91 (br. s, 1 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 2.52 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.5 (C), 149.5 (C), 136.1 (C), 134.0 (C), 131.9 (C), 125.2 (C), 122.9 (CH), 121.5 (CH), 120.5 (CH), 120.48 (C), 118.5 (C), 117.5 (CH), 107.1 (CH), 103.7 (CH), 61.0 (CH_3), 55.9 (CH_3), 16.5 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{17}NNaO_3$ [M + Na] 306.1101; found 306.1108.

5-(1-Ethyl-1*H*-indol-3-yl)-2,3-dimethoxyphenol (7g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 7.8 Hz, 1 H), 7.38 (app. d, J = 8.1 Hz, 1 H), 7.22–7.28 (m, 2 H), 7.12–7.21 (m, 1 H), 6.89 (d, J = 1.8 Hz, 1 H), 6.77 (d, J = 1.8 Hz, 1 H), 5.79 (s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.94 (s, 3 H), 3.93 (s, 3 H), 1.50 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 152.5 (C), 149.5 (C), 136.4 (C), 133.9 (C), 131.9 (C), 126.1 (C), 124.7 (CH), 121.8 (CH), 119.9 (CH), 119.8 (CH), 116.5 (C), 109.6 (CH), 106.9 (CH), 103.5 (CH), 61.0 (CH_3), 55.9 (CH_3), 40.9 (CH_2), 15.4 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{20}NO_3$ [M + H] 298.1438; found 298.1449.

2,3-Dimethoxy-5-(2-methyl-1*H*-indol-3-yl)phenol (7h): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.95 (br. s, 1 H), 7.67 (d, J = 7.5 Hz, 1 H), 7.29–7.39 (m, 1 H), 7.06–7.21 (m, 2 H), 6.72 (d, J = 2.1 Hz, 1 H), 6.64 (d, J = 2.1 Hz, 1 H), 5.80 (s, 1 H), 3.96 (s, 3 H), 3.89 (s, 3 H), 2.51 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3 (C), 149.2 (C), 135.1 (C), 133.7 (C), 131.6 (C), 131.4 (C), 127.7 (C), 121.4 (CH), 119.9 (CH), 118.7 (CH), 114.1 (C), 110.3 (CH), 109.0 (CH), 105.6 (CH), 61.0 (CH_3), 55.9 (CH_3), 12.4 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{17}NNaO_3$ [M + Na] 306.1101; found 306.1108.

3-Bromo-2-methoxyphenol (8):[22] A four-step protocol was utilized for the synthesis of aforementioned 3-bromo-2-methoxyphenol starting from 1,2-dihydroxybenzene. A solution of 1,2-dihydroxybenzene (5.0 g, 45.5 mmol) in acetone (150 mL) was treated with K_2CO_3 (9.4 g, 68.3 mmol) and stirred for 20 min. To mixture this was added MOMCl (3.85 g, 3.6 mL, 47.8 mmol) and stirred for 8 h at room temperature. The reaction mixture was filtered through a pad of Celite and the solvents were evaporated followed by aqueous NH_4Cl and ethyl acetate extraction. The organic extracts were collected and concentrated to give a residue that was purified by column chromatography to give mono-MOM-protected catechol[23] (3.9 g, 56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.08 (d, J = 8.1 Hz, 1 H), 6.91–6.99 (m, 2 H), 6.77–6.87 (m, 1 H), 5.96 (br. s, 1 H), 5.19 (s, 2 H), 3.52 (s, 3 H) ppm.

To a solution of *tert*-butylamine (2.8 g, 4.1 mL, 39 mmol) in toluene (35 mL) at –30 °C was added bromine (3.1 g, 1.0 mL, 19.5 mmol) dropwise and stirred for 30 min. The reaction mixture was further cooled to –60 °C to which a solution of mono-MOM-protected catechol (3.0 g, 19.5 mmol) in dichloromethane (–5 mL) was added. The reaction was brought to room temperature over a period of 4–5 h then treated with 10% sodium thiosulfate, washed with brine and extracted with ethyl acetate. The organic extracts were dried with sodium sulfate, filtered and concentrated to give a residue. ^{1}H NMR (300 MHz, $CDCl_3$) (peaks assigned from ^{1}H NMR spectroscopic data obtained for the crude residue): δ = 7.16 (dd, J = 1.5, 8.1 Hz, 1 H), 7.04 (dd, J = 1.5, 8.1 Hz, 1 H), 6.72 (app. t, J = 8.1 Hz, 1 H), 5.21 (s, 2 H), 3.52 (s, 3 H) ppm. The obtained residue was dissolved in dimethylformamide (DMF, 40 mL) and was treated with K_2CO_3 (5.5 g, 40 mmol) and methyl iodide (4.16 g, 1.8 mL, 29.3 mmol). The reaction mixture was stirred at room temperature for 8 h and after usual workup provided a crude residue. ^{1}H NMR (300 MHz, $CDCl_3$) (peaks assigned from ^{1}H NMR spectroscopic data obtained for the crude residue): δ = 7.19 (dd, J = 1.5, 8.1 Hz, 1 H), 7.09 (dd, J = 1.5, 8.1 Hz, 1 H), 6.90 (app. t, J = 8.1 Hz, 1 H), 5.21 (s, 2 H), 3.88 (s, 3 H), 3.51 (s, 3 H) ppm. The obtained crude product was treated with 4 N HCl in dioxane (15 mL) and stirred for 5 h. The solvents were evaporated and the obtained residue was purified by column chromatography with silica gel by using a mixture of ethyl acetate and hexanes as eluent to give 3-bromo-2-methoxyphenol (**8**, 1.9 g, 49% over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (dd, J = 1.6, 8.0 Hz, 1 H), 6.83–6.97 (m, 2 H), 6.30 (s, 1 H), 3.88 (s, 3 H) ppm.

3-Bromo-5-(1*H*-indol-3-yl)-2-methoxyphenol (8a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (br. s, 1 H), 7.88 (d, J = 7.6 Hz, 1 H), 7.38–7.40 (m, 2 H), 7.10–7.28 (m, 4 H), 5.92 (br. s, 1 H), 3.92 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C), 142.6 (C), 136.5 (C), 133.8 (C), 125.3 (C), 123.2 (CH), 122.5 (CH), 122.1 (CH), 120.5 (CH), 119.5 (CH), 116.3 (C), 116.1 (C), 113.8 (CH), 111.5 (CH), 61.2 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{15}H_{12}BrNNaO_2$ [M + Na] 339.9944; found 339.9942.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-3-bromo-2-methoxyphenol (8b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (br. s, 1 H), 7.47–7.51 (m, 2 H), 7.37–7.43 (m, 3 H), 7.28–7.35 (m, 4 H), 7.16 (d, J = 2.0 Hz, 1 H), 6.99 (dd, J = 2.4, 8.8 Hz, 1 H), 5.72 (s, 1 H), 5.13 (s, 2 H), 3.96 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9 (C), 150.0 (C), 142.6 (C), 137.5 (C), 133.9 (C), 131.8 (C), 128.6 (CH ×2), 127.8 (CH), 127.7 (CH ×2), 125.7 (C), 123.1 (CH), 122.9 (CH), 116.3 (C), 116.0 (C), 113.6 (CH), 113.4 (CH), 112.1 (CH), 103.2 (CH), 71.0 (CH_2), 61.2 (CH_3) ppm. HRMS (EI^+): calcd. for $C_{22}H_{18}BrNNaO_3$ [M + Na] 446.0362; found 446.0350.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-3-bromo-2,2-dimethoxycyclohex-3-enone (MA-I): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (br. s, 1 H), 7.51–7.44 (m, 2 H), 7.43–7.36 (m, 2 H), 7.35–7.25 (m, 2 H), 7.11 (d, J = 2.4 Hz, 1 H), 6.98 (d, J = 2.4 Hz, 1 H), 6.96 (app. d, J = 2.4 Hz, 1 H), 6.80 (d, J = 3.6 Hz, 1 H), 5.11 (s, 2 H), 4.13–4.02 (m, 1 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 3.13–3.02 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.5 (C), 153.4 (C), 140.5 (CH), 137.4 (C), 131.8 (C), 128.5 (CH ×2), 127.9 (CH), 127.6 (CH ×2), 125.9 (C), 122.8 (C), 121.8 (CH), 115.6 (C), 113.6 (CH), 112.3 (CH), 102.0 (CH), 96.9 (C), 71.0 (CH_2), 52.1 (CH_3), 51.9 (CH_3), 43.4 (CH_2), 36.1 (CH) ppm. HRMS (ESI^+): calcd. for $C_{23}H_{22}BrNNaO_4$ [M + Na] 478.0624; found 478.0613.

3-Bromo-5-(1-ethyl-1*H*-indol-3-yl)-2-methoxyphenol (8g): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, J = 7.6 Hz, 1 H), 7.32–7.39 (m, 2 H), 7.21–7.29 (m, 3 H), 7.12–7.20 (m, 1 H), 5.87 (br. s, 1 H), 4.14 (q, J = 7.2 Hz, 2 H), 3.92 (s, 3 H), 1.45 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9 (C), 142.3 (C), 136.4 (C), 134.0 (C), 125.9 (C), 125.0 (CH), 123.0 (CH), 122.0 (CH), 120.1 (CH), 119.7 (CH), 115.9 (C), 114.8 (C), 113.6 (CH), 109.6 (CH), 61.2 (CH_3), 41.0 (CH_2), 15.3 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{17}H_{16}BrNNaO_2$ [M + Na] 368.0257; found 363.0259.

3-Bromo-2-methoxy-5-(2-methyl-1*H*-indol-3-yl)phenol (8h): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (br. s, 1 H), 7.63 (d, J = 7.6 Hz, 1 H), 7.17–7.26 (m, 2 H), 7.07–7.16 (m, 2 H), 7.03 (d, J = 1.6 Hz, 1 H), 5.95 (br. s, 1 H), 3.93 (s, 3 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7 (C), 142.4 (C), 135.0 (C), 133.7 (C), 131.8 (C), 127.4 (C), 125.2 (CH), 121.6 (CH), 120.1 (CH), 118.4 (CH), 115.8 (CH), 115.7 (C), 112.5 (C), 110.4 (CH), 61.1 (CH_3), 12.4 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{16}H_{14}BrNNaO_2$ [M + Na] 354.0100; found 354.0107.

2-Methoxy-3-methylphenol (9):[18] To a solution of 2,3-dihydroxybenzaldehyde (2.0 g, 14.5 mmol) in DMF (25 mL) was added K_2CO_3 (2.2 g, 15.9 mmol). After stirring the mixture for 30 min, methyliodide (0.99 mL, 15.9 mmol) was added dropwise and the reaction was continued for 16 h. The reaction was quenched with water and extracted with ethyl acetate (4× 30 mL). The organic layers were dried with sodium sulfate and concentrated under vacuum. The residue was purified by column chromatography to afford 3-hydroxy-2-methoxybenzaldehyde (1.3 g, 60% yield).[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.27 (s, 1 H), 7.38 (dd, J = 1.8, 7.8 Hz, 1 H), 7.24 (dd, J = 1.8, 7.8 Hz, 1 H), 7.16 (app. t, J = 7.8 Hz, 1 H), 5.85 (br. s, 1 H), 3.98 (s, 3 H) ppm. A mixture of 3-hydroxy-2-methoxybenzaldehyde (1.0 g, 6.6 mmol) and 10% Pd/C (150 mg) in ethanol (25 mL) was taken in a pressure reaction vessel. The reaction mixture was subjected to hydrogenation at 45 psi at room temperature on a Parr shaker. After 8 h, the reaction mixture was filtered through a pad of Celite and the filtrate was concentrated. The residue was purified by column chromatography by using ethyl acetate/hexanes as eluents to provide 2-methoxy-3-methylphenol (0.82 g, 91% yield) as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (t, J = 8.0 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 5.60 (br. s, 1 H), 3.79 (s, 3 H), 2.30 (s, 3 H) ppm.

5-(1*H*-Indol-3-yl)-2-methoxy-3-methylphenol (9a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br. s, 1 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.37 (app. d, J = 8.0 Hz, 1 H), 7.26 (d, J = 2.8 Hz, 1 H), 7.15–7.25 (m, 2 H), 7.11 (d, J = 2.0 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H), 5.71 (br. s, 1 H), 3.83 (s, 3 H), 2.36 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (C), 143.9 (C), 136.6 (C), 132.1 (C), 130.9 (C), 125.7 (C), 122.3 (CH), 121.6 (CH), 121.6 (CH), 120.2 (CH), 119.8 (CH), 117.8 (C), 112.1 (CH), 111.3 (CH), 60.8 (CH_3), 16.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{16}H_{15}NNaO_2$ [M + Na] 276.0995; found 276.1004.

4-(1*H*-Indol-3-yl)-2-methoxy-3-methylphenol (9a′): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.20 (br. s, 1 H), 7.46 (d, J = 8.0 Hz, 1 H), 7.41 (app. d, J = 8.0 Hz, 1 H), 7.19–7.26 (m, 2 H), 7.10–7.16 (m, 2 H), 7.08 (d, J = 8.0 Hz, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 3.85 (s, 3 H), 2.23 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.7 (C), 145.7 (C), 135.8 (C), 130.2 (C), 127.7 (C), 127.4 (C), 127.2 (CH), 122.7 (CH), 122.1 (CH), 120.0 (CH), 119.8 (CH), 117.2 (C), 112.5 (CH), 111.2 (CH), 60.6 (CH_3), 13.9 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{16}H_{15}NNaO_2$ [M + Na] 276.0995; found 276.0992.

5-[5-(Benzyloxy)-1*H*-indol-3-yl]-2-methoxy-3-methylphenol (9b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (br. s, 1 H), 7.42–7.52 (m, 3 H), 7.35–7.41 (m, 2 H), 7.22–7.34 (m, 3 H), 7.05 (d, J = 1.6 Hz, 1 H), 6.97 (dd, J = 2.4, 8.8 Hz, 1 H), 6.93 (d, J = 1.6 Hz, 1 H), 5.68 (s, 1 H), 5.11 (s, 2 H), 3.84 (s, 3 H), 2.35 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7 (C), 148.9 (C), 143.8 (C), 137.7 (C), 132.1 (C), 131.9 (C), 130.9 (C), 128.5 (CH ×2), 127.8 (CH), 127.6 (CH ×2), 126.1 (C), 122.5 (CH), 121.4 (CH), 117.7 (C), 113.2 (CH), 112.0 (CH ×2), 103.6 (CH), 71.1 (CH_2), 60.8 (CH_3), 16.0 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{23}H_{21}NNaO_3$ [M + Na] 382.1414; found 382.1412.

4-[5-(Benzyloxy)-1*H*-indol-3-yl]-2-methoxy-3-methylphenol (9b′): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (br. s, 1 H), 7.41–7.49 (m, 2 H), 7.28–7.40 (m, 4 H), 7.10 (d, J = 2.4 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 1 H), 6.95–7.02 (m, 2 H), 6.89 (d, J = 8.4 Hz, 1 H), 5.71 (br. s, 1 H), 5.06 (s, 2 H), 3.86 (s, 3 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 (C), 147.7 (C), 145.7 (C), 137.6 (C), 131.1 (C), 130.2 (C), 128.4 (2 X CH), 127.75 (C), 127.7 (CH), 127.5 (2 X CH), 127.1 (CH), 123.5 (CH), 117.0 (C), 113.2 (CH), 112.5 (CH), 111.9 (CH), 103.4 (CH), 70.9 (CH_2), 60.7 (CH_3), 13.9 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{23}H_{22}NO_3$ [M + H] 360.1594; found 360.1605.

5-(1-Ethyl-1*H*-indol-3-yl)-2-methoxy-3-methylphenol (9g): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.95 (m, 1 H), 7.35–7.38 (m, 1 H), 7.22–7.27 (m, 2 H), 7.16 (ddd, J = 1.2, 7.2, 8.0 Hz, 1 H), 7.11 (d, J = 2.0 Hz, 1 H), 7.00 (dd, J = 0.4, 2.0 Hz, 1 H), 5.67 (br. s, 1 H), 4.19 (q, J = 7.6 Hz, 2 H), 3.84 (s, 3 H), 2.36 (s, 3 H), 1.49 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9 (C), 143.6 (C), 136.4 (C), 132.3 (C), 130.9 (C), 126.2 (C), 124.6 (CH), 121.7 (CH), 121.4 (CH), 120.0 (CH), 119.7 (CH), 116.3 (C), 111.9 (CH), 109.5 (CH), 60.7 (CH_3), 40.9 (CH_2), 16.0 (CH_3), 15.4 (CH_3) ppm. HRMS (ESI^+): calcd. for $C_{18}H_{20}NO_2$ [M + H] 282.1489; found 282.1484.

4-(1-Ethyl-1*H*-indol-3-yl)-2-methoxy-3-methylphenol (9g′): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (app. d, J = 8.0 Hz, 1 H), 7.37 (app. d, J = 8.0 Hz, 1 H), 7.20–7.27 (m, 1 H), 7.06–7.13 (m, 2 H), 7.05 (s, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 5.71 (br. s, 1 H), 4.20 (q, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 2.25 (s, 3 H), 1.50 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.5 (C), 145.7 (C), 135.7 (C), 130.0 (C), 127.89 (C), 127.87 (C), 127.2 (CH), 125.7 (CH), 121.5 (CH), 120.2 (CH), 119.3 (CH), 115.7 (C), 112.5 (CH), 109.3 (CH), 60.6 (CH_3), 40.9 (CH_2), 15.5 (CH_3), 14.0 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{18}H_{19}NNaO_2$ [M + Na] 304.1308; found 304.1321.

2-Methoxy-3-methyl-5-(2-methyl-1*H*-indol-3-yl)phenol (9h): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (br. s, 1 H), 7.73 (d, J = 7.6 Hz, 1 H), 7.30 (app. d, J = 7.6 Hz, 1 H), 7.12–7.23 (m, 2 H), 7.01 (d, J = 2.0 Hz, 1 H), 6.91 (d, J = 2.0 Hz, 1 H), 5.85 (s, 1 H), 3.90 (s, 3 H), 2.47 (s, 3 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (C), 143.5 (C), 135.1 (C), 131.9 (C), 131.3 (C), 130.6 (C), 127.7 (C), 123.5 (CH), 121.3 (CH), 119.8 (CH), 118.8 (CH), 114.0 (CH), 113.8 (C), 110.3 (CH), 60.6 (CH_3), 15.9 (CH_3), 12.4 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{17}H_{18}NO_2$ [M + H] 268.1332; found 268.1328.

2-Methoxy-6-methylphenol (11):[25] A mixture of 2-hydroxy-3-methoxybenzaldehyde (2.0 g, 13.2 mmol) and 10% Pd/C (300 mg) in ethanol (50 mL) was taken in a pressure reaction vessel. The reaction mixture was subjected to hydrogenation at 40 psi at room temperature on a Parr shaker. After 8 h, the reaction mixture was filtered through a pad of Celite and the filtrate was evaporated. The residue was purified by column chromatography by using ethyl acetate/hexanes as eluents to provide 2-methoxy-6-methylphenol (1.45 g, 82% yield) as an off-white low-melting solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70–6.80 (m, 3 H), 5.71 (s, 1 H), 3.89 (s, 3 H), 2.28 (s, 3 H) ppm.

Dimer 1D:[26] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.14 (d, J = 10.0 Hz, 1 H), 5.94 (d, J = 10.0 Hz, 1 H), 5.48–5.53 (m, 1 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.31 (s, 3 H), 3.07 (s, 3 H), 2.83–2.89 (m, 2 H), 2.77 (d, J = 6.4 Hz, 1 H), 1.75 (d, J = 1.6 Hz, 3 H), 1.36 (s, 3 H) ppm.

Dimer 3D: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.28 (d, J = 10.4 Hz, 1 H), 5.98 (d, J = 10.4 Hz, 1 H), 5.39–5.46 (m, 1 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.30 (s, 3 H), 3.04 (s, 3 H), 2.96 (d, J = 6.8 Hz, 1 H), 2.87 (t, J = 2.0 Hz, 1 H), 2.82 (d, J = 2.0 Hz, 1 H), 2.05–2.13 (m, 2 H), 1.71–1.84 (m, 1 H), 1.60–1.70 (m, 1 H), 1.02 (t, J = 7.6 Hz, 3 H), 0.92 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1 (C), 193.2 (C), 150.4 (CH), 149.2 (C), 127.5 (CH), 119.3 (CH), 98.3 (C), 94.7 (C), 57.8 (CH), 50.3 (CH_3), 50.2 (CH_3), 49.9 (CH_3), 48.8 (CH_3), 48.5 (C), 45.6 (CH), 44.9 (CH), 32.8 (CH_2), 27.5 (CH_2), 10.0 (CH_3), 9.3 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{20}H_{28}NaO_6$ [M + Na] 387.1778; found 387.1792.

Dimer 4D: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (d, J = 10.4 Hz, 1 H), 5.97 (d, J = 10.4 Hz, 1 H), 5.40–5.45 (m, 1 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 3.05 (s, 3 H), 2.94 (d, J = 6.4 Hz, 1 H), 2.82–2.88 (m, 2 H), 1.98–2.06 (m, 2 H), 1.48–1.75 (m, 3 H), 1.24–1.48 (m, 3 H), 0.92 (t, J = 6.8 Hz, 3 H), 0.89 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.1 (C), 193.1 (C), 151.0 (CH), 147.9 (C), 127.2 (CH), 119.9 (CH), 98.3 (C), 94.7 (C), 58.3 (CH), 50.4 (CH_3), 50.1 (CH_3), 49.9 (CH_3), 48.7 (CH_3), 48.2 (C), 45.6 (CH), 45.0 (CH), 42.6 (CH_2), 36.7 (CH_2), 19.0 (CH_2), 18.1 (CH_2), 14.7 (CH_3), 13.7 (CH_3) ppm. HRMS (ESI$^+$): calcd. for $C_{22}H_{32}NaO_6$ [M + Na] 415.2097, 415.2091; found 415.2100.

Dimer 10D:[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.42 (dd, J = 4.0, 10.0 Hz, 1 H), 6.27 (ddd, J = 1.2, 7.6, 8.8 Hz, 1 H), 6.05 (dd, J = 1.6, 10.0 Hz, 1 H), 5.92 (ddd, J = 1.6, 6.4, 8.0 Hz, 1 H), 3.45 (s, 3 H), 3.41 (s, 3 H), 3.35–3.40 (m, 1 H), 3.27–3.31 (m, 1 H), 3.24 (s, 3 H), 3.21–3.23 (m, 1 H), 3.11–3.14 (m, 1 H), 3.08 (s, 3 H) ppm.

Dimer 11D:[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (d, J = 3.2 Hz, 1 H), 6.19 (t, J = 7.2 Hz, 1 H), 5.53 (d, J = 8.0 Hz, 1 H), 3.46 (s, 3 H), 3.39 (s, 3 H), 3.26 (d, J = 8.4 Hz, 1 H), 3.22 (s, 3 H), 3.09 (d, J = 6.8 Hz, 1 H), 3.04 (s, 3 H), 2.86–2.94 (m, 1 H), 1.85 (s, 3 H), 1.33 (s, 3 H) ppm.

Dimer 12D:[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (s, 1 H), 5.81 (d, J = 6.8 Hz, 1 H), 3.42 (s, 3 H), 3.38 (s, 3 H), 3.22 (s, 3 H), 3.12–3.20 (m, 3 H), 3.04 (s, 3 H), 3.00 (app. d, J = 6.8 Hz, 1 H), 1.95 (s, 3 H), 1.60 (s, 3 H) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra.

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Heterocycles

A non-metal mediated detour method for installing oxygenated aryls at the 3-position of indoles is described.

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