Supporting Information
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Thieme
meta-Selective Substitution of Phenols with Indoles via One-pot Oxidative Dearomatization-Michael Addition-Rearomatization

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Supporting Information

1. General experimental method (S2)
2. General Experimental procedure (S2)
3. Characterization data of compounds 3a and 5 (S2-S6)
General experimental method:

All reactions were performed in test tubes under nitrogen atmosphere at 80 °C. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated at ~20 Torr (house vacuum) at 25–35 °C. Solvents were re-distilled prior to use in the reactions. Other commercial reagents were used as received.

General Procedure for Oxidative Coupling Reaction of 4-Substituted Phenols with Indoles: PhI(OAc)₂ (177 mg, 0.55 mmol) was added into the solution of 4-Substituted Phenols (0.5 mmol) in MeOH (2 mL) at 0 °C. After 10 min, the reaction mixture was treated with indole (59 mg, 0.5 mmol) and TsOH (4 mg, 0.025 mmol), and then was allowed to warm up to 70 °C. Upon completion by TLC, the reaction was quenched with saturated NaHCO₃, and extracted by ethyl acetate (100 mL x 3). The organic layer was dried over anhydrated Na₂SO₄, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (15% ethyl acetate in hexanes) to give the corresponding product 5.

3-(1H-indol-3-yl)-4-methylphenol 3a: yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.18 (br, 1 H), 7.53 (d, J = 7.8 Hz, 1 H), 7.40 (d, J = 8.2 Hz, 1 H), 7.11-7.25 (m, 4 H), 6.89 (d, J = 2.8 Hz, 1 H), 6.74 (dd, J = 8.2, 2.8 Hz, 1 H), 4.92 (br, 1 H), 2.22 (s, 3 H).

3-(5-methoxy-2-methylphenyl)-1H-indole 5a: yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 8.17 (br, 1 H), 7.55 (d, J = 8.2 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.19-7.23 (m, 2 H), 7.11-7.16 (m, 2 H), 7.01 (d, J = 2.7 Hz, 1 H), 6.83 (dd, J = 8.2, 2.8 Hz, 1 H), 3.79 (s, 3 H), 2.24 (s, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 136.0, 135.6, 131.4, 129.0, 127.1, 123.1, 122.3, 120.2, 120.1, 117.5, 116.1, 112.6, 111.4, 55.5, 20.0; HRMS m/z calcd for C₁₆H₁₅NNaO ([M+Na]+): 260.1046, found 260.1059.
5-fluoro-3-(5-methoxy-2-methylphenyl)-1H-indole 5b: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.23 (br, 1 H), 7.32 (dd, $J = 8.8$, 4.4 Hz, 1 H), 7.20-7.24 (m, 2 H), 7.18 (dd, $J = 9.6$, 2.4 Hz, 1 H), 6.94-7.00 (m, 2 H), 6.84 (dd, $J = 8.0$, 2.8 Hz, 1 H), 3.81 (s, 3 H), 2.23 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 159.3, 157.5, 157.0, 134.9, 132.3, 131.2, 128.7, 127.5, 127.4, 124.5, 117.7, 117.6, 115.9, 112.6, 111.9, 111.8, 110.8, 110.5, 105.0, 104.8, 55.3, 19.7; HRMS m/z calcd for C$_{16}$H$_{14}$FNNaO ([M+H]$^+$): 278.0952, found 278.0942.

5-chloro-3-(5-methoxy-2-methylphenyl)-1H-indole 5c: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.25 (br, 1 H), 7.49 (d, $J = 2.0$ Hz, 1 H), 7.30 (d, $J = 8.4$ Hz, 1 H), 7.22 (d, $J = 8.4$ Hz, 1 H), 7.15-7.18 (m, 2 H), 6.94 (d, $J = 2.8$ Hz, 1 H), 6.84 (dd, $J = 8.4$, 2.8 Hz, 1 H), 3.81 (s, 3 H), 2.21 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.5, 134.6, 134.1, 131.2, 128.8, 128.1, 125.8, 124.0, 122.5, 119.4, 117.2, 116.0, 112.6, 112.2, 55.3, 19.7; HRMS m/z calcd for C$_{16}$H$_{14}$ClNNaO ([M+Na]$^+$): 294.0656, found 294.0667.

5-bromo-3-(5-methoxy-2-methylphenyl)-1H-indole 5d: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.32 (br, 1 H), 7.65 (s, 1 H), 7.21-7.33 (m, 3 H), 7.17 (d, $J = 2.3$ Hz, 1 H), 6.94 (d, $J = 2.7$ Hz, 1 H), 6.84 (dd, $J = 8.3$, 2.7 Hz, 1 H), 3.81 (s, 3 H), 2.21 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.5, 152.0, 134.6, 134.4, 131.2, 130.4, 128.8, 128.7, 125.1, 123.9, 122.5, 117.1, 116.1, 113.3, 112.6, 112.5, 55.3, 19.7; HRMS m/z calcd for C$_{16}$H$_{14}$BrNNaO ([M+Na]$^+$): 338.0151, found 338.0136.

3-(5-methoxy-2-methylphenyl)-2-methyl-1H-indole 5e: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.93 (br, 1 H), 7.21-7.32 (m, 3 H), 7.14 (td, $J = 7.3$, 0.9 Hz, 1 H), 7.03-7.08 (m, 1 H), 6.83-6.87 (m, 2 H), 3.79 (s, 3 H), 2.28 (s, 3 H), 2.09 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4, 135.6, 135.2, 131.8, 131.0, 130.1, 128.7, 121.3, 119.7, 119.3, 116.7, 114.5, 112.8, 110.3, 55.4, 19.3, 12.4; HRMS m/z calcd for C$_{17}$H$_{17}$NO ([M+Na]$^+$): 274.1202, found 274.1210.

3-(5-methoxy-2-methylphenyl)-5-methyl-1H-indole 5f: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.08 (br, 1 H), 7.33 (d, $J = 1.2$ Hz, 1 H), 7.29 (d, $J = 8.4$ Hz, 1 H), 7.22 (d, $J = 8.4$ Hz, 1 H), 7.11 (d, $J = 2.4$ Hz, 1 H), 7.05 (dd, $J = 8.4$, 1.2 Hz, 1 H), 7.00 (d, $J = 2.8$ Hz, 1 H), 6.83 (dd, $J = 8.4$, 2.8 Hz, 1 H), 3.80 (s, 3 H), 2.42 (s, 3 H), 2.24 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4, 135.6, 134.1, 131.1, 129.2, 128.9, 127.2, 123.8, 122.9, 119.6, 116.9, 116.0, 112.3, 110.8, 55.3, 21.5, 19.8; HRMS m/z calcd for C$_{17}$H$_{17}$NNaO ([M+Na]$^+$): 274.1202, found 274.1197.
4-methoxy-3-(5-methoxy-2-methylphenyl)-1H-indole 5g: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.15 (br, 1 H), 7.10-7.15 (m, 2 H), 6.99 (d, $J$ = 8.0 Hz, 1 H), 6.93 (d, $J$ = 2.8 Hz, 1 H), 6.91 (d, $J$ = 2.8 Hz, 1 H), 6.80 (dd, $J$ = 8.4, 2.8 Hz, 1 H), 6.51 (d, $J$ = 8.0 Hz, 1 H), 3.78 (s, 3 H), 3.69 (s, 3 H), 2.16 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.7, 154.4, 137.5, 137.0, 130.1, 129.9, 122.9, 121.8, 117.2, 117.1, 116.5, 112.2, 104.5, 100.3, 55.2, 55.1, 19.5; HRMS m/z calcd for C$_{17}$H$_{17}$NNaO$_2$ ([M+H]$^+$): 290.1151, found 290.1149.

6-methoxy-3-(5-methoxy-2-methylphenyl)-1H-indole 5h: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.14 (br, 1 H), 7.42 (d, $J$ = 8.7 Hz, 1 H), 7.21 (d, $J$ = 8.2 Hz, 1 H), 7.03 (d, $J$ = 1.8 Hz, 1 H), 7.00 (d, $J$ = 2.8 Hz, 1 H), 6.86 (d, $J$ = 2.3 Hz, 1 H), 6.79-6.84 (m, 2 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 2.25 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4, 156.5, 136.5, 135.5, 131.1, 128.7, 121.7, 121.4, 120.7, 115.8, 112.3, 109.9, 94.6, 55.6, 55.3, 19.8; HRMS m/z calcd for C$_{17}$H$_{17}$NNaO$_2$ ([M+Na]$^+$): 290.1151, found 290.1152.

3-(5-methoxy-2-methylphenyl)-1-methyl-1H-indole 5j: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (d, $J$ = 7.6 Hz, 1 H), 7.36 (d, $J$ = 7.6 Hz, 1 H), 7.26 (td, $J$ = 7.6, 0.8 Hz, 1 H), 7.21 (d, $J$ = 8.4 Hz, 1 H), 7.13 (td, $J$ = 7.6, 0.8 Hz, 1 H), 7.04 (d, $J$ = 2.6 Hz, 1 H), 6.81 (dd, $J$ = 8.4, 2.6 Hz, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.26 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4, 136.6, 135.5, 131.1, 128.6, 127.5, 127.4, 121.7, 120.2, 119.5, 115.9, 112.2, 109.3, 55.3, 32.8, 19.9; HRMS m/z calcd for C$_{17}$H$_{17}$NNaO ([M+Na]$^+$): 274.1202, found 274.1209.

1-benzyl-3-(5-methoxy-2-methylphenyl)-1H-indole 5k: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.58 (d, $J$ = 7.8 Hz, 1 H), 7.10-7.32 (m, 10 H), 7.02 (d, $J$ = 2.8 Hz, 1 H), 6.80 (dd, $J$ = 8.7, 3.2Hz, 1 H), 5.33 (s, 2 H), 3.79 (s, 3 H), 2.26 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.5, 137.3, 135.3, 131.2, 128.8, 128.6, 127.7, 127.6, 127.0, 126.8, 121.9, 120.3, 119.7, 116.5, 115.9, 112.3, 109.8, 55.3, 50.0, 19.9; IR (KBr) 3028, 2933, 2832, 1606, 1495, 1466, 1355, 1279, 1246 cm$^{-1}$; HRMS m/z calcd for C$_{23}$H$_{21}$NNaO ([M+Na]$^+$): 350.1521, found 350.1514.

1-allyl-3-(5-methoxy-2-methylphenyl)-1H-indole 5l: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (d, $J$ = 7.8 Hz, 1 H), 7.35 (d, $J$ = 8.2 Hz, 1 H), 7.17-7.25 (m, 2 H), 7.07-7.14 (m, 2 H), 7.01 (d, $J$ = 2.8 Hz, 1 H), 6.80 (dd, $J$ = 8.2, 2.7Hz, 1 H), 5.98-6.05 (m, 1 H), 5.20 (d, $J$ = 10.0 Hz, 1 H),
5.09-5.14 (m, 1 H), 4.74 (d, $J = 5.5$ Hz, 2 H), 3.78 (s, 3 H), 2.25 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.4, 136.0, 135.4, 133.4, 131.1, 128.6, 127.6, 126.5, 121.7, 120.3, 119.6, 117.3, 116.3, 115.9, 112.3, 109.6, 55.3, 48.7, 19.8; IR (KBr) 2926, 2824, 1606, 1494, 1466, 1330, 1279 cm$^{-1}$; HRMS m/z calcd for C$_{19}$H$_{19}$NNaO ([M+Na]$^+$): 300.1364, found 300.1358.

5-methoxy-3-(5-methoxy-2,3-dimethylphenyl)-1H-indole 5n: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.19 (br, 1 H), 7.27 (d, $J = 8.7$ Hz, 1 H), 7.09 (d, $J = 2.3$ Hz, 1 H), 6.92 (d, $J = 2.3$ Hz, 1 H), 6.88 (dd, $J = 8.7$, 2.7 Hz, 1 H), 6.83 (d, $J = 2.7$ Hz, 1 H), 6.78 (d, $J = 2.7$ Hz, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.34 (s, 3 H), 2.14 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 156.9, 154.3, 138.4, 135.6, 130.9, 127.7, 127.6, 123.6, 118.0, 114.6, 113.4, 112.5, 111.9, 101.6, 55.8, 55.2, 21.1, 16.3; IR (KBr) 3407, 2934, 2829, 1601, 1484, 1438, 1324, 1277, 1210 cm$^{-1}$; HRMS m/z calcd for C$_{18}$H$_{20}$NO$_2$ ([M+H]$^+$): 282.1489, found 282.1483.

3-(4-methoxybiphenyl-2-yl)-1H-indole 5o: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.92 (br, 1 H), 7.65 (d, $J = 8.2$ Hz, 1 H), 7.37 (d, $J = 8.3$ Hz, 1 H), 7.30 (d, $J = 7.8$ Hz, 1 H), 7.11-7.23 (m, 7 H), 7.08 (td, $J = 7.3$, 0.9 Hz, 1 H), 6.94 (dd, $J = 8.2$, 2.7 Hz, 1 H), 6.60 (d, $J = 2.3$ Hz, 1 H), 3.87 (s, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.8, 142.0, 135.7, 134.5, 133.9, 131.7, 129.6, 127.7, 126.7, 126.0, 124.1, 122.0, 119.9, 119.8, 116.5, 115.9, 112.3, 111.0, 55.4; HRMS m/z calcd for C$_{21}$H$_{17}$NNaO ([M+Na]$^+$): 322.1202, found 322.1195.

3-(2-butyl-5-methoxyphenyl)-1H-indole 5p: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.21 (br, 1 H), 7.52 (d, $J = 7.8$ Hz, 1 H), 7.41 (d, $J = 8.2$ Hz, 1 H), 7.20-7.25 (m, 2 H), 7.10-7.17 (m, 2 H), 6.95 (d, $J = 2.8$ Hz, 1 H), 6.87 (dd, $J = 8.7$, 2.8 Hz, 1 H), 3.80 (s, 3 H), 2.58 (t, $J = 7.8$ Hz, 2 H), 1.38-1.47 (m, 2 H), 1.13-1.23 (m, 2 H), 0.75 (t, $J = 7.3$ Hz, 3 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.2, 135.8, 135.0, 134.1, 130.1, 127.4, 122.5, 122.1, 119.9, 119.8, 117.4, 116.2, 112.8, 111.1, 55.3, 33.9, 32.2, 22.4, 13.9; HRMS m/z calcd for C$_{19}$H$_{21}$NNaO ([M+Na]$^+$): 302.1515, found 302.1523.

2-(2-(1H-indol-3-yl)-4-methoxyphenyl)ethanol 5r: yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.38 (br, 1 H), 7.48 (d, $J = 8.2$ Hz, 1 H), 7.37 (d, $J = 7.8$ Hz, 1 H), 7.19-7.28 (m, 2 H), 7.09-7.15
(m, 2 H), 6.96 (d, $J = 2.8$ Hz, 1 H), 6.88 (dd, $J = 8.2$, 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.60 (t, $J = 6.9$ Hz, 2 H), 2.86 (t, $J = 6.9$ Hz, 2 H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.9, 135.9, 135.8, 130.8, 129.3, 127.2, 122.8, 122.2, 120.0, 119.7, 116.7, 116.6, 112.9, 111.2, 63.7, 55.2, 35.8; HRMS m/z calcd for C$_{17}$H$_{17}$NNaO$_2$ ([M+Na]$^+$): 290.1151, found 290.1155.