Lewis Acid-Catalyzed Friedel-Crafts Alkylations of 3-Hydroxy-2-Oxindole: Approach to the core structure of Azonazine

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Materials and Methods

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa under a nitrogen atmosphere and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred via syringe using standard Schlenk techniques. Tetrahydrofuran (THF) and diethyl ether (Et₂O) were distilled over sodium/benzophenoneketyl. Dichloromethane (CH₂Cl₂), toluene, and benzene were distilled over calcium hydride. All other reagents such as isatins, MeMgBr, lewis acids etc. were used as received, unless otherwise noted. Thin layer chromatography was performed using Merck Silicagel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, anisaldehyde stain and other stains. Silicagel from Merck (particle size 100-200 mesh) was used for flash chromatography. Melting points were recorded on a digital melting point apparatus from Jyoti Scientific (AN ISO 9001:2000) and are uncorrected.

¹H and ¹³C NMR spectra were recorded on Bruker 400, 500 MHz spectrometers with ¹³C operating frequencies of 100, 125 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ¹H NMR and δ = 77.0 for ¹³C NMR). Data for ¹H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). IR spectra were recorded on a FT-IR system (Spectrum BX) from PerkinElmer spectrometer and are reported in frequency of absorption (cm⁻¹). Only selected IR absorbencies are reported. High resolution mass spectral data were obtained from the Central Instrumentation Facility (CIF) at the Indian Institute of Science Education and Research (IISER) Bhopal.

General experimental procedure for the synthesis of 3-hydroxy-2-oxindoles (5a-e): A flame-dried round-bottom flask was charged with isatin [5 mmol,1.0 equiv.] in anhydrous 20 mL of THF and the round bottom flask was placed at 0 ºC. To this reaction mixture, Grignard reagent [12.5 mmol,2.5 equiv.] was added dropwise via a syringe and stirring was continued for 4-5 hours. Upon completion of the reaction (TLC showed complete conversion of starting material), the reaction mixture was quenched at 0 ºC with saturated aqueous NH₄Cl (5 mL). The whole mixture was filtered through a celite-bed and washed with diethylether. The organic layer was
evaporated under reduced pressure and the crude mixture was purified by a silica-gel column chromatography to afford 3-hydroxy-2oxindoles (5a-e) in good to excellent yields.

(±) 3-hydroxy-3-methylindolin-2-one ±(5a): 92% yield, $R_f = 0.42$ (50% EtOAc in hexane), yellowish solid. $^1$H NMR (400 MHz, 0.1 mL DMSO-d$_6$, 0.5 mL CDCl$_3$) $\delta$: 9.86 (s, 1H), 7.29 (d, $J$=7.2 Hz, 1H), 7.14 (t, $J$=7.64 Hz, 1H), 6.95 (m, 1H), 6.86 (d, $J$=7.68 Hz, 1H), 5.65 (m, 1H), 1.49 (br, s, 3H); $^{13}$C NMR (100 MHz, 0.1 mL DMSO-d$_6$, 0.5 mL CDCl$_3$) $\delta$: 181.1, 140.9, 133.3, 129.1, 123.5, 122.4, 110.4, 73.6, 24.7; IR (film) $\nu_{\text{max}}$ 3294, 2924, 1716, 1622, 1472, 1195, 1142, 1019 cm$^{-1}$; HRMS (ESI) m/z 186.0525 [(M+Na)$^+$; calculated for [C$_9$H$_8$NO$_2$ + Na]$^+$: 186.0525]; MP 157–159 °C.

(±) 5-chloro-3-hydroxy-3-methylindolin-2-one ±(5b): 66% yield, $R_f = 0.45$ (50% EtOAc in hexane), yellowish solid. $^1$H NMR (400 MHz, 0.1 mL DMSO-d$_6$, 0.5 mL CDCl$_3$) $\delta$: 10.02 (s, 1H), 7.14 (br, s, 1H), 7.07 (dd, $J$= 8.24, 2.12 Hz, 1H), 6.72 (d, $J$= 8.24 Hz, 1H), 5.83 (s, 1H), 1.41 (s, 3H); $^{13}$C NMR (100 MHz, 0.1 mL DMSO-d$_6$, 0.5 mL CDCl$_3$) $\delta$: 180.1, 139.9, 135.5, 128.6, 126.8, 123.9, 111.2, 73.4, 24.7; IR (film) $\nu_{\text{max}}$ 3172, 2920, 2852, 1698, 1456, 1185 cm$^{-1}$; HRMS (ESI) m/z 220.0143 [(M+Na)$^+$; calculated for [C$_9$H$_8$NO$_2$ + Na]$^+$: 220.0136]; MP 230–235 °C.

(±) 5-bromo-3-hydroxy-3-methylindolin-2-one ±(5c): 65% yield, $R_f = 0.47$ (50% EtOAc in hexane), yellowish solid. $^1$H NMR (400 MHz, 0.1 mL DMSO-d$_6$, 0.5 mL CDCl$_3$) $\delta$: 10.12 (s,
1H), 7.33 (br, s, 1H), 7.23 (dd, J=8.2, 2.04 Hz, 1H), 6.70 (dd, J=8.24, 2.8 Hz, 1H), 5.89 (br, s, 1H), 1.40 (s, 3H);\(^1\)\(^3\)C NMR (100 MHz, 0.1 mL DMSO-\(d_6\), in 0.5 mL CDCl\(_3\)) \(\delta\): 179.9, 140.6, 136.0, 131.5, 126.6, 114.1, 111.8, 73.3, 24.7; IR (film) \(\nu_{\text{max}}\) 3173, 2923, 2853, 1698, 1470, 1185 cm\(^{-1}\); HRMS (ESI) m/z 263.9622 [(M+Na)\(^+\); calculated for [C\(_9\)H\(_8\)BrN\(_2\)O\(_2\) + Na\(^+\): 263.9636]; MP 231–234 °C.

(±) 3-allyl-3-hydroxyindolin-2-one ±(5d): 69% yield, \(R_f = 0.48\) (50% EtOAc in hexane), yellowish solid.\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 8.89 (s, 1H), 7.36 (d, J=7.24 Hz, 1H), 7.07 (t, \(J=7.4\) Hz, 1H), 6.89 (d, J=7.64 Hz, 1H), 5.65 (m, 1H), 5.65 (m, 1H), 5.10 (m, 2H), 4.02 (s, 1H), 2.75 (m, 1H), 2.63 (m, 1H);\(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\): 180.7, 140.4, 130.4, 130.3, 129.6, 124.4, 123.1, 120.4, 110.5, 76.5, 42.7; IR (film) \(\nu_{\text{max}}\) 3321, 1716, 1274, 1187, 1110, 921, 747 cm\(^{-1}\); HRMS (ESI) m/z 188.0703 [(M–H)\(^+\); calculated for [C\(_{11}\)H\(_{10}\)NO\(_2\)]\(^+\): 188.706]; MP 109–113 °C.

(±) 3-ethynyl-3-hydroxyindolin-2-one ±(5e): 69% yield, \(R_f = 0.49\) (50% EtOAc in hexane), yellowish solid.\(^1\)H NMR (400 MHz, 0.1 mL DMSO-\(d_6\), 0.5 mL CDCl\(_3\)) \(\delta\): 9.90 (s, 1H), 7.38 (d, \(J=7.4\) Hz, 1H), 7.14 (td, \(J=7.72, 1.24\) Hz, 1H), 6.94 (td, \(J=7.56, 0.84\) Hz, 1H), 6.80 (d, \(J=7.72\) Hz, 1H), 6.47 (s, 1H), 2.56 (br, s, 1H);\(^1\)\(^3\)C NMR (100 MHz, 0.1 mL DMSO-\(d_6\), in 0.5 mL CDCl\(_3\)) \(\delta\): 170.6, 136.4, 125.5, 125.2, 119.7, 117.9, 105.8, 76.8, 69.1, 64.2; IR (film) \(\nu_{\text{max}}\) 3290, 2925, 2856, 1698, 1622, 1470, 1183, 1019 cm\(^{-1}\); HRMS (ESI) m/z 196.0355 [(M+Na)\(^+\); calculated for [C\(_{10}\)H\(_7\)NO\(_2\) + Na\(^+\): 196.0369]; MP 185–190 °C.
Experimental procedure for the preparation of (±) 2-(2-(3-hydroxy-2-oxindolin-3-yl)ethyl)isoindoline-1,3-dione:

A round-bottom flask was charged with N-phthalimido protected tryptamine (5 mmol, 1.0 equiv.) in MeCN and H₂O (9:1) then it was placed at 0 °C. IBX (12.5 mmol, 2.5 equiv.) was added in one portion followed by the addition of cerious(III)chloride heptahydrate and then stirring was continued for 1 h. Upon completion of the reaction (judged by TLC), the reaction mixture was quenched at 0 °C with saturated aqueous NaHCO₃ (15 mL for 5 mmol). Then the reaction mixture was diluted with 100 mL of CH₂Cl₂. The whole reaction mixture was taken in a separatory funnel and extracted with CH₂Cl₂ (50 mL x 2). The organic filtrate was dried over Na₂SO₄ and concentrated in a rotary evaporator under reduced pressure. The crude products were purified by flash chromatography (2:1-1:1 hexanes/EtOAc) to afford compound (±)5f in 58% yield.

(±) 2-(2-(3-hydroxy-2-oxindolin-3-yl)ethyl)isoindoline-1,3-dione (5f): 58% yield, Rf = 0.39 (75% EtOAc in hexane), colorless solid. ¹H NMR (400 MHz, 0.1 mL DMSO-d₆, 0.5 mL CDCl₃) δ: 10.05 (br, s, 1H), 7.68 (m, 4H), 7.26 (m, 1H), 7.03 (m, 1H), 6.80 (m, 1H), 6.73 (m, 1H), 5.88 (br, s, 1H), 3.74 (m, 1H), 3.66 (m, 1H), 2.25 (m, 1H), 2.13 (m, 1H); ¹³C NMR (100 MHz, 0.1 mL DMSO-d₆, 0.5 mL CDCl₃) δ: 179.2, 167.7, 141.8, 134.0, 132.0, 131.5, 129.1, 124.0, 122.9, 121.9, 110.2, 74.7, 35.7, 33.0; IR (film) ν_max 3348, 1713, 1678, 1620, 1470, 1404, 1281, 1196, 1115, 1022, 899,710 cm⁻¹; HRMS (ESI) m/z 345.0845 [(M+Na)⁺; calculated for [C₁₈H₁₄N₂O₄ + Na]⁺: 345.0851]; MP 165–167 °C.
General experimental procedure for Friedel-Craft’s alkylation using 3-hydroxy-2-oxindoles in presence of Lewis acids:

A flame-dried round-bottom flask was charged with 3-alkyl-3-hydroxy-2-oxindole (0.5 mmol, 1.0 equiv.) in dichloromethane. To this Lewis acid (10-50 mol%) was added and stirred at rt for 5 minutes. Then 4-substituted phenol (1.5 mmol, 3.0 equiv.) was added to the reaction mixture. The reaction mixture was then stirred at rt for 5 minutes and then it was heated under refluxed at 45 ºC for indicated time. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was cooled to room temperature. Most of the volatile components were evaporated under reduced pressure and the crude materials were purified by flash chromatography using EtOAc and petroleum ether as eluents to afford Friedel-Craft’s alkylated products (4).

Table 1: Optimization with Lewis acids as catalyst.

<table>
<thead>
<tr>
<th>entry</th>
<th>Lewis acid</th>
<th>equiv.</th>
<th>temp.</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Sc(O Tf)3</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>24 h</td>
<td>10%</td>
</tr>
<tr>
<td>2.</td>
<td>In(O Tf)3</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>24 h</td>
<td>46%</td>
</tr>
<tr>
<td>3.</td>
<td>Zn(O Tf)2</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>24 h</td>
<td>traces</td>
</tr>
<tr>
<td>4.</td>
<td>Zn(O Tf)2</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>traces</td>
</tr>
<tr>
<td>5.</td>
<td>Cu(O Tf)2</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>24 h</td>
<td>24%</td>
</tr>
<tr>
<td>6.</td>
<td>Sn(O Tf)2</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>18 h</td>
<td>42%</td>
</tr>
<tr>
<td>7.</td>
<td>FeCl3</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>24 h</td>
<td>40%</td>
</tr>
<tr>
<td>8.</td>
<td>In(O Tf)3</td>
<td>50 mol%</td>
<td>45 °C</td>
<td>4 h</td>
<td>95%</td>
</tr>
<tr>
<td>9.</td>
<td>In(O Tf)3</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>5 h</td>
<td>92%</td>
</tr>
<tr>
<td>10.</td>
<td>In(O Tf)3</td>
<td>10 mol%</td>
<td>45 °C</td>
<td>7 h</td>
<td>92%</td>
</tr>
<tr>
<td>11.</td>
<td>FeCl3</td>
<td>50 mol%</td>
<td>45 °C</td>
<td>18 h</td>
<td>56%</td>
</tr>
<tr>
<td>13.</td>
<td>Ce(O Tf)3</td>
<td>50 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>90%</td>
</tr>
<tr>
<td>14.</td>
<td>Ce(O Tf)3</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>82%</td>
</tr>
<tr>
<td>15.</td>
<td>Cu(O Tf)2</td>
<td>50 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>92%</td>
</tr>
<tr>
<td>16.</td>
<td>Cu(O Tf)2</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>14 h</td>
<td>91%</td>
</tr>
<tr>
<td>17.</td>
<td>Cu(O Tf)2</td>
<td>10 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>91%</td>
</tr>
<tr>
<td>18.</td>
<td>Bi(O Tf)3</td>
<td>50 mol%</td>
<td>25 °C</td>
<td>12 h</td>
<td>94%</td>
</tr>
<tr>
<td>19.</td>
<td>Bi(O Tf)3</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>12 h</td>
<td>93%</td>
</tr>
<tr>
<td>20.</td>
<td>Bi(O Tf)3</td>
<td>10 mol%</td>
<td>45 °C</td>
<td>10 h</td>
<td>94%</td>
</tr>
<tr>
<td>21.</td>
<td>Sn(O Tf)2</td>
<td>50 mol%</td>
<td>45 °C</td>
<td>14 h</td>
<td>86%</td>
</tr>
<tr>
<td>22.</td>
<td>Sn(O Tf)2</td>
<td>25 mol%</td>
<td>45 °C</td>
<td>14 h</td>
<td>79%</td>
</tr>
<tr>
<td>23.</td>
<td>Sn(O Tf)2</td>
<td>10 mol%</td>
<td>45 °C</td>
<td>15 h</td>
<td>65%</td>
</tr>
</tbody>
</table>
Reactions were carried out on a 0.50 mmol of 4 with 1.50 mmol of cresol in 6 mL of dichloromethane at rt or 45 °C, unless noted otherwise. Isolated yields after column chromatography.

(±) 3-(2-hydroxy-5-methylphenyl)-3-methylindolin-2-one ±(4a): Colorless solid, Rf = 0.64 (50% EtOAc in hexane). $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.09 (s, 1H), 8.80 (s, 1H), 7.28 (m, 2H), 7.17 (m, 1H), 6.98 (m, 2H), 6.93 (m, 1H), 6.85 (d, J=8.08 Hz, 1H), 2.22 (s, 3H), 1.89 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 184.9, 153.6, 139.8, 133.7, 129.8, 129.4, 128.4, 128.3, 125.4, 125.2, 123.1, 119.1, 110.7, 52.9, 22.7, 20.7; IR (film) $\nu_{max}$ 3290, 2970, 2924, 1685, 1682, 1620, 1512, 1454, 1419, 1373, 1334, 1269, 1196, 1130, 818, 752 cm$^{-1}$; HRMS (ESI) m/z 254.1172 [(M+H)$^+$]; calculated for [C$_{16}$H$_{16}$NO$_2$]$^+$: 254.1176; MP 108–112 °C.

Figure 2: Substrates Scope.

Reactions were carried out on a 0.50 mmol of 3-alkyl-3-hydroxy-2-oxindole derivatives with 1.50 mmol of cresol or 4-tert-butylphenol in 6 mL of dichloromethane at 45 °C, unless noted otherwise. Isolated yields after column chromatography.
(±) 3-(5-(tert-butyl)-2-hydroxyphenyl)-3-methylindolin-2-one ±(4b): Colorless gel, R_f = 0.52 (30% EtOAc in hexane). \(^1\)H NMR (400 MHz, 0.1 mL of DMSO-d_6, 0.5 mL of CDCl_3) δ: 9.88 (s, 1H), 9.47 (s, 1H), 7.15 (d, \(J = 2.12\) Hz, 1H), 7.09 (t, \(J = 7.64\) Hz, 1H), 7.03 (m, 2H), 6.93 (t, \(J = 7.44\) Hz, 1H), 6.84 (d, \(J = 7.72\) Hz, 1H), 6.67 (d, \(J = 8.36\) Hz, 1H), 1.7 (s, 3H), 1.13 (s, 9H); \(^{13}\)C NMR (100 MHz, 0.1 mL of DMSO-d_6, 0.5 mL of CDCl_3) δ: 184.2, 153.4, 141.9, 141.0, 134.7, 127.6, 125.5, 125.1, 124.6, 124.3, 122.0, 117.4, 110.2, 52.4, 34.1, 31.5, 23.0; IR (film) \(\nu_{\text{max}}\) 3460, 3348, 2256, 1647, 1010, 999, 825, 764 cm\(^{-1}\); HRMS (ESI) m/z 318.1462 [(M+H)\(^+\); calculated for [C_{16}H_{14}ClNO_2]\(^+\): 318.1465]; MP 215–218 °C.

(±) 5-chloro-3-(2-hydroxy-5-methylphenyl)-3-methylindolin-2-one±(4c): Colorless gel, R_f = 0.52 (30% EtOAc in hexane). \(^1\)H NMR (400 MHz, CDCl_3) δ: 8.80 (s, 1H), 8.15 (s, 1H), 7.09-7.12 (m, 2H), 7.03 (d, \(J = 1.64\) Hz, 1H), 6.95 (dd, \(J = 8.08, 1.52\) Hz, 1H), 6.73 (d, \(J = 8.16\) Hz, 1H), 6.68 (d, \(J = 8.08\) Hz, 1H), 2.29 (s, 3H), 1.82 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl_3) δ: 184.7, 152.5, 138.4, 136.2, 129.9, 129.7, 128.3, 128.1, 128.0, 125.0, 124.8, 118.1, 111.4, 52.4, 22.9, 20.8; IR (film) \(\nu_{\text{max}}\) 3283, 2924, 2854, 2357, 1693, 1620, 1477, 1192, 995, 814, 737 cm\(^{-1}\); HRMS (ESI) m/z 310.0601 [(M+Na)\(^+\); calculated for [C_{16}H_{14}ClNO_2 + Na]\(^+\): 310.0605].

(±)3-(5-(tert-butyl)-2-hydroxyphenyl)-5-chloro-3-methylindolin-2-one ±(4d): Colorless gel, R_f = 0.50 (30% EtOAc in hexane). \(^1\)H NMR (400 MHz, CDCl_3) δ: 8.61 (s, 1H), 8.42 (s, 1H), 7.20 (s, 2H), 7.17 (m, 2H), 6.82 (d, \(J = 8.24\) Hz, 1H), 6.79 (d, \(J = 7.68\) Hz, 1H), 1.87 (s, 3H), 1.28 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl_3) δ: 184.6, 152.8, 143.1, 138.3, 135.9, 128.3, 128.2, 126.4,
125.3, 124.5, 124.1, 118.2, 111.5, 53.0, 34.3, 31.5, 22.9; IR (film) \( \nu_{\text{max}} \) 3314, 2924, 2858, 2322, 1697, 1612, 1473, 1273, 1199, 1123, 903, 818, 748 cm\(^{-1}\); HRMS (ESI) m/z 352.1071 [(M+Na)+; calculated for [C\(_{20}\)H\(_{22}\)ClNO\(_2\) + Na\(^+\): 352.1075].

(\pm\(^)\) 5-bromo-3-(2-hydroxy-5-methylphenyl)-3-methylindolin-2-one (4e): Colorless gel, \( R_f = 0.55 \) (40% EtOAc in hexane). \(^1\)H NMR (400 MHz, 0.5 mL CDCl\(_3\), 0.1 mL DMSO-d\(_6\)) \( \delta \): 10.45 (s, 1H), 9.10 (s, 1H), 2.27-7.30 (m, 2H), 6.91-6.94 (m, 2H), 6.80 (d, \( J = 8.20 \) Hz, 1H), 6.54 (d, \( J = 8.04 \) Hz, 1H), 2.29 (s, 3H), 1.56 (s, 3H), [3.37 (br, DMSO)]; \(^13\)C NMR (100 MHz, 0.5 mL CDCl\(_3\), 0.1 mL DMSO-d\(_6\)) \( \delta \): 181.6, 152.9, 142.0, 139.4, 130.0, 129.1, 128.8, 127.5, 127.0, 125.5, 115.4, 113.1, 111.2, 50.4, 23.7, 20.9; IR (film) \( \nu_{\text{max}} \) 3525, 2897, 2360, 2252, 1647, 1001, 995, 825, 763 cm\(^{-1}\); HRMS (ESI) m/z 354.0088 [(M+Na)+; calculated for [C\(_{16}\)H\(_{14}\)BrNO\(_2\) + Na\(^+\): 354.0100].

(\pm\(^)\) 5-bromo-3-(5-(tert-butyl)-2-hydroxyphenyl)-3-methylindolin-2-one (4f): Colorless gel, \( R_f = 0.56 \) (40% EtOAc in hexane). \(^1\)H NMR (400 MHz, 0.5 mL CDCl\(_3\), 0.1 mL DMSO-d\(_6\)) \( \delta \): 9.87 (s, 1H), 8.84 (s, 1H), 7.22 (m, 1H), 7.12-7.15 (m, 1H), 7.00-7.04 (m, 1H), 6.94 (m, 1H), 6.66-6.70 (m, 1H), 6.56-6.58 (m, 1H), 1.63 (s, 3H), 1.18 (s, 9H); \(^13\)C NMR (100 MHz, 0.5 mL CDCl\(_3\), 0.1 mL DMSO-d\(_6\)) \( \delta \): 183.1, 152.7, 141.7, 140.6, 138.1, 130.0, 126.4, 125.6, 125.0, 124.3, 116.2, 114.1, 111.2, 51.6, 34.1, 31.6, 23.2; IR (film) \( \nu_{\text{max}} \) 3426, 2126, 1643, 1269, 1010, 991, 891, 756 cm\(^{-1}\); HRMS (ESI) m/z 396.0589 [(M+Na)+; calculated for [C\(_{19}\)H\(_{20}\)BrNO\(_2\) + Na\(^+\): 396.0570].
Figure 3: Substrates Scope.

\[ R = \text{Me (4g)}, 60\%, 18\h (A: 25\text{ mol\% cat.}) \]
\[ R = \text{Me (4g)}, 93\%, 18\h (B: 25\text{ mol\% cat.}) \]
\[ R = \text{Me (4g)}, 82\%, 18\h (C: 25\text{ mol\% cat.}) \]
\[ R = \text{Me (4g)}, 90\%, 12\h (D: 50\text{ mol\% cat.}) \]
\[ R = \text{\textsuperscript{t}Bu (4h)}, 50\%, 16\h (A: 40\text{ mol\% cat.}) \]
\[ R = \text{\textsuperscript{t}Bu (4h)}, 84\%, 16\h (C: 40\text{ mol\% cat.}) \]
\[ R = \text{\textsuperscript{t}Bu (4h)}, 92\%, 16\h (C: 40\text{ mol\% cat.}) \]
\[ R = \text{\textsuperscript{t}Bu (4h)}, 94\%, 12\h (D: 50\text{ mol\% cat.}) \]

\^Reactions were carried out on a 0.50 mmol of 5 with 1.50 mmol of cresol in 6 mL of dichloromethane at 45 °C, unless noted otherwise. \*Isolated yields after column chromatography.

(±) 3-allyl-3-(2-hydroxy-5-methylphenyl)indolin-2-one ±(4g): Colorless gel, R\_f = 0.48 (20\% EtOAc in hexane). \textsuperscript{1}H NMR (400 MHz, CDCl\_3) \( \delta \): 9.86 (s, 1H), 8.83 (s, 1H), 7.38 (d, \( J = 7.44 \) Hz, 1H), 7.35 (td, \( J = 7.72, 1.02 \) Hz, 1H), 7.24 (td, \( J = 7.6, 0.96 \) Hz, 1H), 7.02 (m, 2H), 6.94 (m, 1H), 6.87 (d, \( J = 1.76 \) Hz, 1H), 5.33-5.42 (m, 1H), 5.06 (dd, \( J = 16.92, 1.24 \) Hz, 1H), 4.95 (m, 1H), 3.43 (dd, \( J = 13.76, 8.2 \) Hz, 1H), 2.99 (dd, \( J = 13.72, 6.32 \) Hz, 1H), 2.20 (s, 3H) [EtOAc: 4.16 (q, \( J = 7.16 \) Hz, 2H), 2.08 (s, 3H), 1.29 (t, \( J = 13.72, 6.28 \) Hz, 1H), 2.19 (s, 3H)]; \textsuperscript{13}C NMR (100 MHz, CDCl\_3) \( \delta \): 183.6, 154.2, 140.2, 131.8, 130.7, 130.1, 129.4, 128.9, 128.6, 126.6, 123.5, 123.0, 119.9, 119.7, 110.8, 58.1, 39.4, 20.7; IR (film) \( \nu_{\text{max}} \): 3260, 2959, 2666, 2360, 2334, 1681, 1620, 1473, 1342, 1269, 1238, 1192, 1130, 918 cm\(^{-1}\); HRMS (ESI) m/z 302.1154 [((M+Na)\(^{+}\); calculated for [C\(_{18}\)H\(_{17}\)NO\(_{2}\) + Na\(^{+}\): 302.1151].
(±) 3-allyl-3-(5-(tert-butyl)-2-hydroxyphenyl)indolin-2-one ±(4h): Colorless gel, Rf = 0.60 (25% EtOAc in hexane). $^1$H NMR (400 MHz, CDCl$_3$) δ: 10.00 (s, 1H), 9.08 (s, 1H), 7.39 (d, $J = 7.44$ Hz, 1H), 7.34 (dt, $J = 7.72, 1.16$ Hz, 1H), 7.22-7.26 (m, 2H), 7.14 (br, 1H), 7.03 (d, $J = 7.60$ Hz, 1H), 6.99 (d, $J = 8.36$ Hz, 1H), 5.34-5.41 (m, 1H), 5.06 (dd, $J = 16.96, 1.24$ Hz, 1H), 4.95 (dd, $J = 10.12, 1.76$ Hz, 1H), 3.48 (dd, $J = 13.80, 8.16$ Hz, 1H), 2.97 (dd, $J = 13.76, 6.28$ Hz, 1H), 1.20 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 183.7, 154.0, 142.8, 140.3, 131.9, 130.7, 128.6, 126.5, 126.4, 125.5, 122.84, 122.83, 119.7, 119.5, 110.9, 58.6, 39.5, 34.3, 31.5; IR (film) $\nu_{max}$ 3267, 3210, 2959, 2866, 1678, 1620, 1485, 1469, 1269, 1188, 1103, 910, 822, 737 cm$^{-1}$; HRMS (ESI) m/z 344.1622 [(M+Na)$^+$]; calculated for [C$_{21}$H$_{23}$NO$_2$ + Na]$^+$: 344.1621.

(±) 2-(2-(3-(2-hydroxy-5-methylphenyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione ±(4i): Colorless gel, Rf = 0.62 (25% EtOAc in hexane). $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.69 (s, 1H), 9.05 (s, 1H), 7.70 (m, 2H), 7.59 (m, 2H), 7.38 (d, $J = 7.4$ Hz, 1H), 7.14 (td, $J = 7.68, 1.12$ Hz, 1H), 7.05 (td, $J = 7.56, 0.92$ Hz, 1H), 6.94-6.98 (m, 2H), 6.87 (m, 1H), 6.80 (d, $J = 1.64$ Hz, 1H), 3.60-3.73 (m, 2H), 3.24 (dt, $J = 14.32, 5.72$ Hz, 1H), 2.74 (m, 1H), 2.16 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 183.3, 168.0, 154.1, 140.5, 133.8, 131.8, 130.2, 130.0, 129.4, 128.6, 128.5, 126.0, 123.6, 123.1, 123.0, 119.8, 111.3, 60.5, 56.4 (CH$_2$Cl$_2$), 34.5, 32.2, 20.6; IR (film) $\nu_{max}$ 3560, 3271, 2924, 1767, 1713, 1612, 1470, 1400, 1261, 1029, 752, 717 cm$^{-1}$; HRMS (ESI) m/z 435.1316 [(M+Na)$^+$]; calculated for [C$_{25}$H$_{20}$N$_2$O$_4$ + Na]$^+$: 435.1315.
(±) 2-(2-(3-(5-(tert-butyl)-2-hydroxyphenyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione

Colorless gel, Rf = 0.41 (20% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃) δ: 9.82 (s, 1H), 9.19 (s, 1H), 7.69 (dd, J = 5.48, 3.04 Hz, 2H), 7.53 (dd, J = 5.44, 3.04 Hz, 2H), 7.40 (d, J = 7.4 Hz, 1H), 7.4-7.19 (m, 2H), 7.07 (dd, J = 7.56, 1.08 Hz, 1H), 7.05(d, J = 2.4 Hz, 1H), 6.98 (m, 1H), 6.91 (d, J = 8.40 Hz, 1H), 3.61-3.75 (m, 2H), 3.25-3.32 (dt, J = 14.44, 5.88 Hz, 1H), 2.70 (m, 1H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ: 183.3, 167.9, 154.1, 142.8, 140.5, 133.8, 131.8, 130.1, 128.7, 126.4, 126.1, 125.1, 123.0, 122.9, 122.8, 119.5, 111.5, 56.9, 34.5, 34.3, 32.3, 31.4; IR (film) νmax 3284, 2959, 1770, 1708, 1616, 1400, 1369, 1269, 1192, 1030, 910, 752 cm⁻¹; HRMS (ESI) m/z 477.1786 [(M+Na)⁺; calculated for [C₂₈H₂₆N₂O₄ + Na]⁺: 477.1785].

Figure 4: Substrates scope of F-C alkylations with phenol.

General experimental procedure for Friedel-Craef’t’salkylations using 3-hydroxy-2-oxindoles in presence of Lewis acids:

A flame-dried round-bottom flask was charged with 3-alkyl-3-hydroxy-2-oxindole (0.5 mmol, 1.0 equiv.) and phenol (1.50 mmol, 3.0 equiv.) in dichloromethane. To this reaction mixture was 25 mol% of catalyst and then it was heated under refluxed at 45 °C for 12-16 h. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was cooled to room temperature. Most of the volatile components were evaporated under reduced pressure and the crude materials were purified by flash chromatography using EtOAc and petroleum ether as eluents to afford compound (6).
(±) 3-(4-hydroxyphenyl)-3-methylindolin-2-one ±(6a): Colorless gel, Rf = 0.50 (40% EtOAc in hexane). $^1$H NMR (400 MHz, 1:1 CDCl$_3$ and DMSO-d$_6$) δ: 7.26 (m, 1H), 7.16-7.19 (m, 3H), 7.08 (m, 1H), 6.95 (d, $J = 7.76$ Hz, 1H), 6.78 (m, 2H), 1.79 (s, 3H); IR (film) $\nu_{\text{max}}$ 3410, 3367, 1709, 1512, 1050, 1002, 825, 764 cm$^{-1}$; HRMS (ESI) m/z 262.0839 [(M+Na)$^+$; calculated for [C$_{13}$H$_{13}$NO$_2$ + Na]$^+$: 262.0832].

(±) 3-ethynyl-3-(4-hydroxyphenyl)indolin-2-one ±(6b): Colorless gel, Rf = 0.51 (40% EtOAc in hexane). $^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) δ: 10.25 (s, 1H), 8.95 (br, 1H), 7.11-7.20 (m, 4H), 6.88-7.00 (m, 2H), 6.68-6.73 (m, 2H), 2.56 (br, s, 1H); $^{13}$C NMR (100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) δ: 176.0, 157.2, 141.6, 132.5, 128.9, 128.5, 127.8, 124.8, 122.8, 115.6, 110.4, 81.9, 72.7, 51.9; IR (film) $\nu_{\text{max}}$ 3537, 2349, 2252, 1720, 1632, 1258, 1010, 1007, 829, 759 cm$^{-1}$; HRMS (ESI) m/z 272.0744 [(M+Na)$^+$; calculated for [C$_{16}$H$_{11}$NO$_2$ + Na]$^+$: 272.0744].

(±) 3-allyl-3-(4-hydroxyphenyl)indolin-2-one ±(6c): Colorless gel, Rf = 0.50 (40% EtOAc in hexane). $^1$H NMR (400 MHz, CDCl$_3$) δ: 9.91 (s, 1H), 8.88 (s, 1H), 7.16-7.23 (m, 4H), 7.02 (m, 1H), 6.93 (d, $J = 7.48$ Hz, 1H), 6.76 (d, $J = 8.64$ Hz, 2H), 5.41-5.51 (m, 1H), 5.03 (d, $J = 17.04$ Hz, 1H), 4.91 (d, $J = 10.12$ Hz, 1H), 2.96 (d, $J = 6.88$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ: 180.3, 156.5, 142.0, 132.9, 132.8, 130.4, 128.0, 127.8, 125.1, 121.7, 118.7, 115.4, 109.9, 56.0, 41.7; IR (film) $\nu_{\text{max}}$ 3580, 3495, 3414, 2252, 2129, 1647, 1516, 1473, 999, 825, 771, 706 cm$^{-1}$; HRMS (ESI) m/z 288.0964 [(M+Na)$^+$; calculated for [C$_{17}$H$_{15}$NO$_2$ + Na]$^+$: 288.0995].
(±) 2-(2-(3-(4-hydroxyphenyl)-2-oxoindolin-3-yl)ethyl)isoindoline-1,3-dione±(6d): Colorless gel, 
Rf = 0.53 (40% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃) δ: 10.08 (s, 1H), 8.88 (s, 1H), 
7.70-7.76 (m, 4H), 7.16-7.22 (m, 3H), 7.11 (m, 1H), 6.89-6.92 (m, 2H), 6.72-6.74 (m, 2H), 3.59- 
3.62 (m, 2H), 2.58-2.65 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ: 179.9, 167.7, 156.6, 142.0, 
133.9, 132.2, 131.9, 130.2, 128.0, 127.7, 124.7, 122.9, 121.9, 115.5, 110.3, 54.6, 34.8, 34.4; IR 
(film) νmax 3348, 2924, 2357, 2337, 1766, 1708, 1616, 1400, 1184, 1030, 752, 718 cm⁻¹; HRMS 
(ESI) m/z 421.1182 [(M+Na)⁺; calculated for [C₂₄H₁₈N₂O₄ + Na]⁺: 421.1159].

Procedure for TBS protection of phenol:

A flame-dried round-bottom flask was charged with phenol derivative 6a (0.2 mmol, 1.0 
equiv.) in DMF (1.5 mL) and 3 equiv. of imidazole (0.6 mmol, 3.0 equiv.). To this reaction 
mixture was added TBSCI (0.26 mmol, 1.3 equiv.) at room temperature and the reaction mixture 
was stirred at room temperature for 12 h. Upon completion of the reaction (TLC showed 
complete formation of product), the reaction mixture was diluted with diethylether (5 mL) and 
water (5 mL). The whole reaction mixture was taken in a separatory funnel and extracted with 
ether (5 mL x 2). The organic filtrate was dried over Na₂SO₄ and concentrated in a rotary 
evaporator under reduced pressure. The crude products were purified by flash chromatography 
(10:1 hexanes/EtOAc) to afford compound ±(6e).

(±) 3-(4-(tert-butylidimethylsilyl)oxy)phenyl)-3-methylindolin-2-one ±(6e): Colorless gel, Rf = 0.70 
(20% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃) δ: 8.63 (s, 1H), 7.25 (dt, ¹J = 7.64, 1.32 
Hz, 1H), 7.18-7.21 (m, 2H), 7.15 (m, 1H), 7.07 (dt, ¹J = 7.52, 1.00 Hz, 1H), 6.98 (d, ¹J = 7.68 Hz,
1H), 6.76-6.80 (m, 2H), 1.80 (s, 3H), 0.99 (s, 9H), 0.20 (s, 3H), 0.19 (s, 3H); \(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\): 182.3, 154.9, 140.3, 135.8, 133.1, 128.0, 127.7, 124.4, 122.7, 120.0, 110.1, 52.1, 29.7, 25.7, 23.7, 18.2, -0.44; \(\text{IR (film)}\) \(\nu_{\text{max}}\): 3217, 2928, 2856, 2357, 2333, 1717, 1612, 1508, 1469, 1323, 918, 837, 748 cm\(^{-1}\); \(\text{HRMS (ESI)}\) m/z 354.1896 [(M+H)\(^+\); calculated for [C\(_{21}\)H\(_{27}\)NO\(_2\)Si + H]\(^+\): 354.1884].

**Scheme 3:** Unsuccessful reductive approach to tetracyclic core.

**Reaction of (4a) with LiAlH\(_4\) followed by acetylation:**

Compound 4a (0.5 mmol, 1.0 equiv.) was taken in anhydrous THF (5 mL) and cooled the reaction mixture at 0 °C. To this reaction mixture was added LiAlH\(_4\) (1.5 mmol, 3.0 equiv.) portion wise and the reaction mixture was placed in a pre-heated oil-bath maintaining the temperature at 75 °C for 5 h. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was cooled to room temperature and then placed on an ice-bath. The reaction mixture was quenched with EtOAc (1 mL), water (1 mL), followed by 2(N) NaOH (1 mL), successively. The whole mixture was filtered through a celite-bed and washed with EtOAc (5 mL). The organic layer was evaporated under reduced pressure and the crude product (11) was directly used for acylation reaction.

Compound 11 (0.5 mmol, 1.0 equiv.) was taken in anhydrous dichloromethane (3 mL) and triethylamine (3.0 mmol, 6.0 equiv.) was added to this mixture. Ac\(_2\)O (2.5 mmol, 5.0 equiv.) was added to this reaction mixture and it was stirred at rt for overnight. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was
evaporated under reduced pressure and the crude materials were purified by flash chromatography using EtOAc and petroleum ether to afford bis-acetylated compound (12) in 79% overall yield.

(±) 2-(1-acetyl-3-methylindolin-3-yl)-4-methylphenyl acetate (12): Colorless gel, Rf 0.38 (20% EtOAc in hexane). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 8.28 (d, $J = 8.00$ Hz, 1H), 7.35 (d, $J = 1.52$ Hz, 1H), 7.23 (dt, $J = 8.08$, 1.28 Hz, 1H), 7.15 (dd, $J = 8.16$, 1.48 Hz, 1H), 6.99 (dt, $J = 7.48$, 1.04 Hz, 1H), 6.91 (d, $J = 8.12$ Hz, 1H), 6.82 (dd, $J = 7.52$, 0.76 Hz, 1H), 5.31 (s, 1H, CH$_2$Cl$_2$), 4.33 (d, $J = 10.32$ Hz, 1H), 3.91 (d, $J = 10.32$ Hz, 1H), 2.41 (s, 3H), 2.24 (s, 3H), 1.73 (s, 3H), 1.69 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$: 168.78, 168.71, 146.55, 141.56, 139.39, 136.21, 135.20, 128.95, 128.26, 127.74, 124.24, 124.09, 123.13, 116.78, 64.09, 53.45 (CH$_2$Cl$_2$), 45.81, 28.91, 24.25, 21.21, 20.16; HRMS (ESI) m/z 346.1416 [(M+ Na)$^+$; calculated for [C$_{20}$H$_{21}$NO$_3$ + Na]$^+$: 346.1414].

**Scheme 4:** Crafting the tetracyclic core *via* oxidative coupling.
Synthesis of tetracyclic core by reduction of (4a) with LiAlH₄ followed by MnO₂ treatment:

Compound 4a (0.5 mmol, 1.0 equiv.) was taken in anhydrous THF (5 mL) and cooled the reaction mixture at 0 °C. To this reaction mixture was added LiAlH₄ (1.5 mmol, 3.0 equiv.) portion wise and the reaction mixture was placed in a pre-heated oil-bath maintaining the temperature at 75 °C for 5 h. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was cooled to room temperature and then placed on an ice-bath. The reaction mixture was quenched with EtOAc (1 mL), water (1 mL), followed by 2(N) NaOH (1 mL), successively. The whole mixture was filtered through a celite-bed and washed with EtOAc (5 mL). The organic layer was evaporated under reduced pressure and the crude product (11) was directly used for MnO₂-oxidation.

In a flame-dried round-bottom flask, compound 11 (0.5 mmol, 1.0 equiv.) was taken in anhydrous benzene (3 mL). To this solution was added MnO₂ (5.0 mmol, 10.0 equiv.) and the reaction mixture was heated under reflux (80 °C) for an hour. Upon completion of the reaction (TLC showed complete consumption of starting material), the reaction mixture was filtered through celite-bed and washed with 30% EtOAc in hexane. Most of the organic volatiles was evaporated under reduced pressure and the crude materials were purified by flash chromatography using EtOAc and petroleum ether to afford tetracyclic core (3a) in 70% overall yield.

(±)-2,10b-dimethyl-6,10b-dihydro-5aH-benzofuro[2,3-b]indole±(3a): 70% yield, Colorless gel, Rf = 0.40 (20% EtOAc in hexane). ¹H NMR (400 MHz, CDCl₃) δ: 7.28 (dd, J = 7.56, 0.76 Hz, 1H), 7.17 (m, 1H), 7.07 (dt, J = 7.60, 1.20 Hz, 1H), 6.90-6.92 (m, 1H), 6.81 (dt, J = 7.44, 0.96 Hz, 1H), 6.69 (t, J = 8.24 Hz, 1H), 6.08 (d, J = 2.20 Hz, 1H), 5.01 (br, s, 1H), 2.32 (s, 3H), 1.72 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ:156.3, 147.0, 133.6, 132.9, 130.4, 128.6, 128.0, 123.3, 122.6, 119.7, 109.3, 109.2, 104.4, 56.1, 24.3, 20.9; IR(film) vmax 3402, 2927, 2854, 1724, 1612, 1481, 1261, 1196, 1064, 810, 736 cm⁻¹; HRMS (ESI) m/z 260.1038 [(M+ Na)⁺; calculated for [C₁₆H₁₅NO + Na]⁺: 260.1046].
**Synthesis of acetylated tetracyclic core (3b):**

Compound 3a (0.3mmol, 1.0 equiv.) was taken in anhydrous dichloromethane (2 mL) and triethylamine (0.9mmol, 3.0 equiv.) was added to this mixture. Ac₂O (0.9mmol, 3.0 equiv.) was added to this reaction mixture and it was stirred at rt for overnight. After 12 h (TLC showed product formation), the reaction mixture was evaporated under reduced pressure and the crude materials were purified by flash chromatography using EtOAc and petroleum ether to afford acetylated tetracyclic compound (3b) in 72% yield.

![Structure of 3b](image)

1-((±)-2,10b-dimethyl-5H-benzofuro[2,3-b]indol-6(10bH)-yl)ethanone (3b): 72% yield, Rₚ= 0.50 (30% EtOAc in hexane).

**¹H NMR** (400 MHz, CDCl₃)  δ: 8.20 (d,  J = 8.04 Hz, 1H), 7.36 (d,  J = 7.56 Hz, 1H), 7.23 (dt,  J = 8.12, 1.32 Hz, 1H), 7.18 (m, 1H), 7.10 (dt,  J = 7.44, 1.04 Hz, 1H), 6.94 (m, 1H), 6.71 (d,  J = 8.12 Hz, 1H), 6.34 (s, 1H), 2.54 (s, 3H), 2.33 (s, 3H), 1.79 (s, 3H);

**¹³C NMR** (100 MHz, CDCl₃) δ: 170.2, 155.5, 141.0, 135.6, 131.9, 131.3, 129.2, 128.4, 124.5, 123.2, 122.2, 117.0, 109.5, 103.0, 55.0, 24.9, 23.9, 20.9; **IR** (film) νmax 2963, 2924, 2858, 2384, 1681, 1605, 1485, 1392, 1288, 1192, 968, 810, 752 cm⁻¹; **HRMS** (ESI) m/z 302.1160 [(M+ Na)⁺; calculated for [C₁₈H₁₇NO₂ + Na]⁺: 302.1151].
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5a)
$^{13}$CNMR (100 MHz, 0.5 mL CDCl₃, 0.1 mL DMSO-d$_6$) of compound ±(5a)
Scanned copy of mass spectrum of compound±(5a)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound $\pm$(5b)
$^{13}$C NMR (100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5b)
Scanned copy of mass spectrum of compound±(5b)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5c)
$^{13}$CNMR (100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-$d_6$) of compound $\pm$(5c)
Scanned copy of mass spectrum of compound±(5c)
$^1$H NMR (400 MHz, CDCl$_3$) of compound ±(5d)
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound ±(5d)
Scanned copy of mass spectrum of compound±(5d)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5e)
$^{13}$CNMR(100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5e)
Scanned copy of mass spectrum of compound±(5e)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5f)
$^{13}$CNMR (100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(5f)
Scanned copy of mass spectrum of compound ±(5f)
$^{1}$H NMR (400 MHz, CDCl$_3$) of compound $\pm$(4a)
$^{13}{\text{CNMR}}(100\ \text{MHz, CDCl}_3)$ of compound ±(4a)
Scanned copy of mass spectrum of compound±(4a)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound $\pm(4b)$
$^{13}$CNMR(100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(4b)
Scanned copy of mass spectrum of compound±(4b)
$^1$H NMR (400 MHz, CDCl$_3$) of compound ±(4c)
$^{13}$CNMR (100 MHz, CDCl$_3$) of compound ±(4e)
Scanned copy of mass spectrum of compound (4c)
$^1$H NMR (400 MHz, CDCl$_3$) of compound $\pm 4d$
$^{13}$CNMR (100 MHz, CDCl$_3$) of compound ±(4d)
Scanned copy of mass spectrum of compound±(4d)
$^1$H NMR (400 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(4e)
$^{13}$CNMR (100 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(4e)
Scanned copy of mass spectrum of compound±(4e)
$^1$H NMR (400 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound ±(4f)
$^{13}$CNMR (100 MHz, 0.5 mL CDCl$_3$, 0.1 mL DMSO-d$_6$) of compound $\pm$(4f)
Scanned copy of mass spectrum of compound±(4f)
$\text{H NMR}(400 \text{ MHz, CDCl}_3)$ of compound ±(4g)

S56
$^{13}$CNMR(100 MHz, CDCl$_3$) of compound ±(4g)
Scanned copy of mass spectrum of compound±(4g)
$^{1}$H NMR (400 MHz, CDCl$_3$) of compound ±(4h)
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound ±(4h)
Scanned copy of mass spectrum of compound±(4h)

S61
$^1$H NMR (400 MHz, CDCl$_3$) of compound ±(4i)
$^{13}$CNMR(100 MHz, CDCl$_3$) of compound ±(4i)
Scanned copy of mass spectrum of compound±(4i)
$^1$H NMR (400 MHz, CDCl$_3$) of compound ±(4j)
$^{13}$CNMR(100 MHz, CDCl$_3$) of compound ±(4j)
Scanned copy of mass spectrum of compound $\pm(4j)$
$^1$H NMR (400 MHz, 1:1 CDCl$_3$ and DMSO-d$_6$) of compound ±(6a)
Scanned copy of mass spectrum of compound±(6a)
$^1$H NMR (400 MHz, CDCl$_3$) of compound ±(6e)
$^{13}$CNMR (100 MHz, CDCl$_3$) of compound ±(6e)
Scanned copy of mass spectrum of compound $\pm(6e)$
$^1$H NMR (400 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(6b)
$^{13}$C NMR (100 MHz, CDCl$_3$ and DMSO-d$_6$) of compound $\pm$(6b)
Scanned copy of mass spectrum of compound±(6b)
$^1$H NMR (400 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(6c)
$^{13}$CNMR(100 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(6c)
Scanned copy of mass spectrum of compound±(6c)
$^1$H NMR (400 MHz, CDCl$_3$ and DMSO-d$_6$) of compound ±(6d)
$^{13}$CNMR (100 MHz, CDCl$_3$ and DMSO-d$_6$) of compound $\pm(6d)$
Scanned copy of mass spectrum of compound±(6d)
\(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) of compound ±(12)
$^{13}$C NMR (100 MHz, CDCl$_3$) of compound ±(12)
Scanned copy of mass spectrum of compound±(12)
$^1$H NMR(400 MHz, CDCl$_3$) of compound ±(3a)
$^{13}$CNMR (100 MHz, CDCl$_3$) of compound $\pm$(3a)
Scanned copy of mass spectrum of compound±(3a)
$^1$H NMR (400 MHz, CDCl$_3$) of compound $\pm$(3b)
$^{13}$CNMR (100 MHz, CDCl$_3$) of compound ±(3b)
Scanned copy of mass spectrum of compound±(3b)