Combined Experimental/theoretical Study on D-Glucosamine
Promoted Regioselective Sulfenylation of Indoles Catalyzed by Copper

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General methods

Melting points were determined on an X4-Data microscopic melting point apparatus and were uncorrected. Nuclear magnetic resonance (NMR) spectra were measured at 400 MHz ($^1$H) or at 100 MHz ($^{13}$C) on a Bruker Avance DRX-400 spectrometer. All reactions were monitored by analytical thin-layer chromatography (TLC) from Merck with detection by UV. The products were purified by column chromatography through silica gel (300-400 mesh). All reagents and solvents were general reagent grade unless otherwise stated.

**General procedure of Cu(OAc)$_2$/D-Glucosamine catalyzed regioselective sulfenylation of indoles with sodium benzenesulfinate.**

To a stirred solution of DMSO (5 ml) were added Cu(OAc)$_2$ (0.1 mmol, 20 mg), indole (1.0 mmol), sodium benzenesulfinate (1.2 mmol), NH$_4$I (3 mmol, 435 mg) and D-Glucosamine (0.1 mmol) were added to the solution, subsequently the mixture was heated to 110 °C under air and stirred for 6 h. When the reaction was finished, the mixture was cooled and partitioned by adding the ethyl acetate (20 ml) and water (20 ml). Then, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (20 ml) twice. The combined organic phases were washed with saturated brine, dried over Na$_2$SO$_4$, and concentrated in vacuo. Then the crude product was purified by column chromatography through silica gel, eluting with ethyl acetate/petroleum ether solvent mixture, to give the pure product.

**Table S1. Optimization of C3-iodization of indoles$^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Copper Source</th>
<th>Solvent</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$</td>
<td>DMSO</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>CuSO$_4$·5H$_2$O</td>
<td>DMSO</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$</td>
<td>toluene</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$</td>
<td>hexane</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: 1a (1 mmol), catalyst (0.1 mmol), NH$_4$I (3 mmol), Solvent (5 mL), 110 °C, 6 h. $^b$ Isolated yield.

**General procedure of the reduction of sodium benzenesulfinate to diphenyldisulfide.**

To a stirred solution of DMSO (5 ml) were added Cu(OAc)$_2$ (0.1 mmol, 20 mg), sodium benzenesulfinate (1.2 mmol), NH$_4$I (3 mmol, 435 mg) were added to the solution, subsequently the mixture was heated to 110 °C under air and stirred for 6 h. When the reaction was finished, the mixture was cooled and partitioned by adding the ethyl acetate (20 ml) and water (20 ml). Then, the organic
phase was separated and the aqueous phase was extracted with ethyl acetate (20 ml) twice. The combined organic phases were washed with saturated brine, dried over Na₂SO₄, and concentrated in vacuo. Then the crude product was purified by column chromatography through silica gel, eluting with ethyl acetate/petroleum ether solvent mixture, to give the pure diphenyldisulfide (89% yield).
The spectral data of the products

3-Iodoindole. Light yellow solid, m.p.: 72-73 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.40 (s, 1H), 7.50 (dd, $J = 8.3, 0.7$ Hz, 1H), 7.39 (dd, $J = 7.2, 1.1$ Hz, 1H), 7.31 (t, $J = 2.4$ Hz, 1H), 7.28 (s, 1H), 7.27 – 7.23 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 135.63, 129.81, 128.41, 123.20, 121.02, 120.82, 111.27, 57.58. MS (EI): m/z = 243 [M]+.

3-(Phenylthio)-1H-indole. White solid, m.p.: 149-150 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.36 (s, 1H), 7.54 (d, $J = 7.9$ Hz, 1H), 7.40 (d, $J = 2.6$ Hz, 1H), 7.36 (d, $J = 8.2$ Hz, 1H), 7.22 - 7.14 (m, 1H), 7.13 - 7.05 (m, 3H), 7.03 (t, $J = 4.2$ Hz, 2H), 6.97 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 138.19, 135.47, 129.66, 128.07, 127.66, 124.82, 123.74, 122.01, 119.87, 118.64, 110.55, 101.78. MS (EI): m/z = 225 [M]+.

N-methyl-3-phenylthio-1H-indole. White solid, m.p.: 86-87 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J = 7.9$ Hz, 1H), 7.45 – 7.35 (m, 2H), 7.33 (t, $J = 7.6$ Hz, 1H), 7.19 (dd, $J = 14.2, 7.1$ Hz, 3H), 7.14 – 7.10 (m, 2H), 7.08 (d, $J = 7.1$ Hz, 1H), 3.88 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.68, 137.56, 135.05, 129.85, 128.65, 125.74, 124.67, 122.57, 120.50, 119.76, 109.71, 100.57, 33.15. MS (EI): m/z = 239 [M]+.

2-Methyl-3-(phenylthio)-1H-indole. White solid, m.p.: 109-110 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (s, 1H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.27 (d, $J = 8.1$ Hz, 1H), 7.15 – 7.09 (m, 1H), 7.08 – 7.03 (m, 3H), 6.94-6.99 (m, 3H), 2.44 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 139.68, 137.56, 135.05, 129.85, 128.65, 125.74, 124.67, 122.57, 120.50, 119.76, 109.71, 100.57, 33.15. MS (EI): m/z = 239 [M]+.
4-chloro-3-(phenylthio)-1H-indole. White solid, m.p.: 107-108 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.44 (s, 1H), 7.38 (d, J = 2.7 Hz, 1H), 7.24 (m, 1H), 7.14 - 7.06 (m, 3H), 7.04 (m, 3H), 6.99 (dt, J = 9.0, 4.2 Hz, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 139.76, 136.96, 131.65, 127.64, 125.91, 124.84, 124.17, 123.73, 122.60, 121.25, 109.44, 101.87. MS (EI): m/z = 259 [M]$^+$.

5-chloro-3-(phenylthio)-1H-indole. White solid, m.p.: 111-112 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.49 (s, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.52 (d, J = 2.6 Hz, 1H), 7.37 (d, J = 8.6 Hz, 1H), 7.26 (dd, J = 10.9, 8.9 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.14 – 7.09 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.71, 134.84, 131.99, 130.42, 128.82, 126.95, 125.97, 125.06, 123.56, 119.17, 112.67, 102.97. MS (EI): m/z = 259 [M]$^+$.

5-Bromo-3-(phenylthio)-1H-indole. White solid, m.p.: 120-121 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.47 (s, 1H), 7.78 (s, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.38 (dd, J = 8.6, 1.7 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 9.7, 5.4 Hz, 2H), 7.15 – 7.08 (m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.70, 135.14, 131.82, 131.02, 128.83, 126.15, 125.94, 125.06, 122.29, 114.52, 113.05, 102.93. MS (EI): m/z = 303 [M]$^+$.

4-Methyl-3-(phenylthio)-1H-indole. Brown oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.63 (s, 1H), 7.49 (dd, J = 6.4, 2.8 Hz, 1H), 7.44 (d, J = 2.7 Hz, 1H), 7.29 (d, J = 7.1 Hz, 1H), 7.19 - 7.12 (m, 2H), 7.11 - 7.06 (m, 3H), 6.92 (d, J = 7.1 Hz, 1H), 2.67 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 141.56, 137.07, 132.11, 131.86, 128.76, 127.01, 125.25, 124.51, 123.11, 122.48, 109.49, 102.33, 18.57. MS (EI): m/z = 239 [M]$^+$.
5-Methyl-3-(phenylthio)-1H-indole. White solid, m.p.: 136-137 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.22 (s, 1H), 7.38-7.31 (m, 2H), 7.24 (d, \(J = 8.3\) Hz, 1H), 7.12-7.05 (m, 2H), 7.04-6.98 (m, 3H), 6.99-6.93 (m, 1H), 2.33 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.47, 133.74, 129.87, 129.38, 128.37, 127.66, 124.60, 123.68, 123.62, 118.12, 110.20, 100.91, 20.41. MS (EI): m/z = 239 [M]+.

6-Methyl-3-(phenylthio)-1H-indole. White solid, m.p.: 156-157 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.17 (s, 1H), 7.40 (d, \(J = 8.1\) Hz, 1H), 7.31 (d, \(J = 2.6\) Hz, 1H), 7.14 (s, 1H), 7.07 (dd, \(J = 10.1, 4.9\) Hz, 2H), 7.02 (dd, \(J = 5.4, 3.2\) Hz, 2H), 6.99 - 6.94 (m, 1H), 6.92 (d, \(J = 8.1\) Hz, 1H), 2.39 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 138.33, 135.91, 131.98, 129.02, 127.64, 125.88, 124.73, 123.65, 121.66, 118.26, 110.48, 101.51, 20.67. MS (EI): m/z = 239 [M]+.

7-Methyl-3-(phenylthio)-1H-indole. White solid, m.p.: 142-143 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.40 (s, 1H), 7.56 – 7.46 (m, 2H), 7.25 – 7.00 (m, 7H), 2.56 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.35, 136.10, 130.42, 128.74, 128.71, 125.87, 124.76, 123.61, 121.09, 120.80, 117.39, 103.23, 16.46. MS (EI): m/z = 239 [M]+.

5-Hydroxy-3-(phenylthio)-1H-indole. Brown oil. \(^1\)H NMR (400 MHz, DMSO) \(\delta\) 11.41 (s, 1H), 8.89 (s, 1H), 7.64 (d, \(J = 2.7\) Hz, 1H), 7.32 (d, \(J = 8.6\) Hz, 1H), 7.23 - 7.15 (m, 2H), 7.08 - 6.96 (m, 3H), 6.77 - 6.69 (m, 2H). \(^{13}\)C NMR (100 MHz, DMSO) \(\delta\) 152.12, 139.85, 132.99, 131.49, 130.16, 129.26, 125.59, 125.10, 113.34, 112.98, 102.65, 98.45. MS (EI): m/z = 241 [M]+.

5-Cyano-3-(phenylthio)-1H-indole. White solid, m.p.: 183-184 °C. \(^1\)H NMR (400 MHz, DMSO) \(\delta\)
12.25 (s, 1H), 8.00 (s, 1H), 7.82 (d, J = 0.9 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.54 (dd, J = 8.5, 1.5 Hz, 1H), 7.21 (t, J = 7.6 Hz, 2H), 7.09 (s, 1H), 7.07 – 7.01 (m, 2H). \(^{13}C\) NMR (101 MHz, DMSO) \(\delta\) 139.08, 138.59, 135.60, 129.47, 129.03, 126.34, 125.76, 125.47, 124.04, 120.61, 114.32, 102.90, 101.76. MS (EI): m/z = 250 [M]^+.

- **5-Nitro-3-(phenylthio)-1H-indole.** Yellow solid, m.p.: 155-1156 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.21 (s, 1H), 8.59 (d, J = 2.2 Hz, 1H), 8.18 (dd, J = 9.0, 2.2 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.24 – 7.18 (m, 2H), 7.16 – 7.11 (m, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 139.58, 137.91, 133.74, 128.95, 126.45, 125.53, 124.77, 124.04, 118.63, 116.85, 111.97, 106.45. MS (EI): m/z = 270 [M]^+.

- **3-(4-Tolylthio)-1H-indole.** White solid, m.p.: 125-127 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.39 (s, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.34-7.26 (m, 1H), 7.24-7.17 (m, 1H), 7.12-7.05 (m, 2H), 7.02 (d, J = 8.1 Hz, 2H), 2.29 (s, 3H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 136.51, 135.51, 134.70, 130.44, 129.51, 129.14, 126.35, 122.98, 120.84, 119.70, 111.56, 103.55, 20.86. MS (EI): m/z = 239 [M]^+.

- **3-((4-Fluorophenyl)thio)-1H-indole.** White solid, m.p.: 137-138 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.47 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.31 (m, 1H), 7.24-7.17 (m, 1H), 7.16-7.08 (m, 2H), 6.94-6.85 (m, 2H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 136.52, 134.05, 134.02, 130.50, 128.88, 127.95, 127.87, 123.14, 120.98, 119.53, 115.86, 115.64, 111.65, 103.42. MS (EI): m/z = 243 [M]^+.

- **3-((4-Chlorophenyl)thio)-1H-indole.** White solid, m.p.: 127-128 °C. \(^1H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.49 (s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.35 – 7.26 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 137.84, 136.53, 130.72, 130.56, 128.82, 128.76, 127.13, 123.22, 121.07, 119.52, 111.68, 102.46. MS (EI): m/z = 259 [M]^+.
NMR Spectra of All Products
Computational details

The theoretical work was performed using the Gaussian 09 program. For geometry optimization and frequency analysis, the cc-pVDZ-pp basis set were used for the I and Cu atoms, and the 6-31g(d) all-electron basis was used for all the other atoms (BSI); for sing-point energy calculation, the aug-cc-pVTZ(PP) basis set (BSII) was used for all atoms. The Polarizable Continuum Model using the integral equation formalism variant (IEFPCM) was employed to evaluate the solvation energies. The B97-1 functional was employed, and this functional has been proven to be reliable for calculating Cu complex-containing systems. Stationary points were optimized without symmetry constraint, and their nature confirmed by vibrational frequency analysis. Intrinsic reaction coordinate calculations were performed to link transition structures with the respective intermediates. Unscaled vibrational frequencies were used to correct the relative energies for zero-point energy (ZPE) contributions.

Figure 1. Simplified PESs for the generation of 2-I-indole and 3-I-indole starting from the encounter complex EC2 as calculated at the B97-1/BSII//B97-1/BSI level of theory. Zero-point corrected, relative energies are given in kJ mol\(^{-1}\) and bond lengths in Å; charges are omitted for the sake of clarity.
References


