Electronic Supplementary Material (ESI) for ChemComm. This journal is © The Royal Society of Chemistry 2017

# Supplementary Information for Diastereo- and enantioselective phase-transfer alkylation of 3-substituted oxindoles with racemic secondary alkyl halides

Kohsuke Ohmatsu,<sup>a</sup> Yukino Furukawa,<sup>a</sup> Mari Kiyokawa,<sup>a</sup> and Takashi Ooi<sup>\*,a,b</sup>

<sup>a</sup> Institute of Transformative Bio-Molecules (WPI-ITbM), and Department of Molecular and Macromolecular

Chemistry, Graduate School of Engineering, Nagoya University, Nagoya, 464-8601, Japan.

<sup>b</sup> CREST, Japan Science and Technology Agency (JST), Nagoya, 464-8601, Japan.

tooi@chembio.nagoya-u.ac.jp

**General information:** Infrared spectra were recorded on a Shimadzu IRAffinity-1 spectrometer. <sup>1</sup>H NMR spectra were recorded on a JEOL JNM-ECS400 (400 MHz) or JNM-ECZ400S (400 MHz). Chemical shifts are reported in ppm from the tetramethylsilane (0.0 ppm) resonance as the internal standard (CDCl<sub>3</sub>) spectrometer. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, and br = broad) and coupling constants (Hz). <sup>13</sup>C NMR spectra were recorded on a JEOL JNM-ECS400 (101 MHz), JNM-ECZ400S (101 MHz) or JNM-ECA 600II (151 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard (CDCl<sub>3</sub>; 77.16 ppm). Optical rotations were measured on a HORIBA SEPA-500 polarimeter. The high resolution mass spectra were conducted on Thermo Fisher Scientific Exactive. Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Flash column chromatography was performed on Silica gel 60 (spherical, 40-50 µm) from Kanto Chemical Co., Inc. Enantiomeric excesses were determined by HPLC analysis using chiral columns [ $\varphi$  4.6 mm x 250 mm, DAICEL CHIRALCEL OD-3 (OD3), CHIRALPAK AD-3 (AD3), CHIRALPAK IE-3 (IE3), CHIRALPAK AZ-3 (AZ3), and CHIRALPAK OZ-3 (OZ3)] with hexane (H) and isopropyl alcohol (IPA) as eluent.

All air- and moisture-sensitive reactions were performed under an atmosphere of argon (Ar) in dried glassware. Toluene, dichloromethane (CH<sub>2</sub>Cl<sub>2</sub>), diethyl ether (Et<sub>2</sub>O), and tetrahydrofuran (THF) were supplied from Kanto Chemical Co., Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. 1,2,3-Triazolium salts **1·Br** were synthesised by following the literature methods.<sup>1</sup> Other simple chemicals were purchased and used as such.

<sup>&</sup>lt;sup>1</sup> Ohmatsu, K.; Kiyokawa, M.; Ooi, T. J. Am. Chem. Soc. 2011, 133, 1307.

#### Characterization of 1,2,3-triazolium bromide 1.Br:



**1a·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.3 (1H, br), 9.14 (1H, br), 8.41 (2H, d, J = 8.2 Hz), 7.88 (2H, d, J = 8.0 Hz), 7.84 (1H, q, J = 6.9 Hz), 7.75-7.63 (3H, m), 7.55-7.47 (2H, m), 7.47-7.41 (3H, m), 7.38 (2H, t, J = 7.8 Hz), 7.30 (1H, d, J = 7.8 Hz), 7.25-7.17 (2H, m), 7.14-6.86 (8H, m), 6.71 (2H, d, J = 8.0 Hz), 4.99 (1H, d, J = 14.9 Hz), 4.91 (1H, d, J = 14.9 Hz), 1.65 (3H, d, J = 6.9 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.3, 142.8, 140.7,

139.5, 138.3, 136.7, 134.7, 133.6, 133.3 (q,  $J_{C-F}$ = 32.9 Hz), 132.8, 132.7, 132.1 (q,  $J_{C-F}$ = 33.7 Hz), 131.9, 131.3, 129.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.2, 128.0, 127.6, 127.2, 126.1 (q,  $J_{C-F}$ = 3.9 Hz), 125.4 (q,  $J_{C-F}$ = 3.9 Hz), 123.9 (q,  $J_{C-F}$ = 276.7 Hz), 123.5 (q,  $J_{C-F}$ = 276.5 Hz), 119.9, 69.6, 65.9, 54.5, 15.8; IR 3032, 1680, 1526, 1476, 1325, 1267, 1167, 1115, 1067, 758, 704 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>45</sub>H<sub>35</sub>F<sub>6</sub>N<sub>4</sub>O<sup>+</sup> ([M–Br]<sup>+</sup>) 761.2710. Found 761.2699.; [ $\alpha$ ]<sub>D</sub><sup>22</sup> = -39.6 (c = 1.0, MeOH).



**1b·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.3 (1H, br), 9.37 (1H, br), 8.45 (2H, d, J = 8.2 Hz), 8.30-7.89 (3H, m), 7.70 (2H, d, J = 8.2 Hz), 7.64 (1H, t, J = 8.0 Hz), 7.51-7.41 (3H, m), 7.41-7.28 (5H, m), 7.28-7.09 (9H, m), 7.09-6.98 (4H, m), 6.98-6.81 (2H, m), 6.47 (2H, d, J = 7.3 Hz), 4.81 (2H, br), 3.59 (1H, brd, J = 14.2 Hz), 3.02 (1H, brdd, J = 14.2, 14.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  166.8, 142.4, 141.0, 139.8, 138.2, 136.7, 135.5,

 $(Ar = 4 - CF_{3} - C_{6} - H_{4}) = 134.6, 134.1, 133.5 (q, J_{C-F} = 32.9 Hz), 133.2, 132.8, 132.2, 131.9 (q, J_{C-F} = 32.9 Hz), 131.2, 129.4, 129.3, 129.2, 129.0, 128.8, 128.7, 128.6, 128.5, 128.2, 128.0, 127.4, 126.0 (q, J_{C-F} = 3.9 Hz), 125.6 (q, J_{C-F} = 3.9 Hz), 123.9 (q, J_{C-F} = 276.7 Hz), 123.5 (q, J_{C-F} = 276.7 Hz), 119.6, 70.2, 69.5, 54.4, 35.5, four peaks for aromatic carbons were not found probably due to broadening or overlapping; IR 3030, 1682, 1531, 1497, 1323, 1294, 1163, 1130, 1067, 756, 706 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>51</sub>H<sub>39</sub>F<sub>6</sub>N<sub>4</sub>O<sup>+</sup> ([M-Br]<sup>+</sup>) 837.3023. Found 837.3016; [\alpha]<sub>D</sub><sup>21</sup> = -35.5 (c = 1.1, MeOH).$ 



**1c·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.33 (1H, br), 8.63 (1H, br), 8.13 (2H, d, J = 8.2 Hz), 7.78 (1H, d, J = 7.8 Hz), 7.70 (2H, d, J = 8.7 Hz), 7.67 (1H, t, J = 7.8 Hz), 7.50-7.42 (4H, m), 7.41 (2H, d, J = 8.2 Hz), 7.23 (1H, dd, J = 7.8, 7.3 Hz), 7.20-6.95 (10H, m), 6.91 (1H, br), 6.82 (2H, d, J = 7.3 Hz), 6.78 (2H, d, J = 8.2 Hz), 5.46 (1H, d, J = 14.7 Hz), 5.13

 $(Ar^{1} = 4-CF_{3}-C_{6}H_{4})$  (1H, d, J = 14.7 Hz), 5.05 (1H, br), 4.19 (2H, br); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.7, 142.5, 141.4, 138.9, 138.5, 136.9, 136.4, 134.0, 133.7 (q,  $J_{C-F} = 33.1$  Hz), 132.9, 132.4, 132.3, 131.8 (q,  $J_{C-F} = 32.9$  Hz), 131.2, 130.1, 129.0, 128.9, 128.4, 128.2, 128.1, 128.1, 128.0, 125.9 (q,  $J_{C-F} = 2.9$  Hz), 125.8 (q,  $J_{C-F} = 3.9$  Hz), 123.8 (q,  $J_{C-F} = 276.7$  Hz), 123.7 (q,  $J_{C-F} = 275.8$  Hz), 120.3, 73.4, 68.2, 60.6, 55.0, four peaks for aromatic carbons were not found probably due to broadening or overlapping; IR 3223, 1682, 1526, 1489, 1323, 1296, 1169, 1130, 1067, 758, 704 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>45</sub>H<sub>35</sub>F<sub>6</sub>N<sub>4</sub>O<sub>2</sub><sup>+</sup> ([M–Br]<sup>+</sup>) 777.2659. Found 777.2651.;  $[\alpha]_{D}^{21} = -25.7$  (c = 1.1, MeOH).



**1d·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.68 (1H, br), 8.72 (1H, br), 8.35 (2H, d, J = 8.2Hz), 7.84-7.61 (6H, m), 7.53 (1H, t, J = 7.8 Hz), 7.50 (1H, d, J = 7.8 Hz), 7.46-7.34 (4H, m), 7.34-7.06 (10H, m), 6.89 (2H, d, *J* = 7.4 Hz), 6.80 (2H, d, *J* = 8.2 Hz), 5.42-5.06 (2H, m), 2.22 (1H, ddq, J = 14.6, 7.2, 7.2 Hz), 1.89-1.74 (1H, m), 0.71 (3H, dd, J = 7.2, 7.2 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 166.8, 142.5, 141.1, 140.6, 138.4, 136.7, 135.9, 133.9,

133.3 (q, *J*<sub>C-F</sub> = 32.9 Hz), 132.8, 132.7, 132.2, 132.0 (q, *J*<sub>C-F</sub> = 33.9 Hz), 131.0, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 128.8, 128.6, 128.3, 128.0, 127.5, 126.1 (q, JC-F = 3.9 Hz), 125.5 (q, JC-F = 2.9 Hz), 123.8 (q, JC-F = 276.7 Hz), 123.4 (q, JC-F = 276.7 Hz), 119.8, 72.1, 69.3, 55.1, 23.6, 10.3, one peak for aromatic carbon was not found probably due to broadening or overlapping; IR 3044, 1680, 1530, 1495, 1323, 1275, 1167, 1128, 1067, 758, 708 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{46}H_{37}F_6N_4O^+$  ([M–Br]<sup>+</sup>) 775.2866. Found 775.2853.;  $[\alpha]_D^{22} = -23.7$  (c = 1.5, MeOH).

![](_page_2_Picture_3.jpeg)

**1e·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  10.2 (1H, br), 9.06 (1H, br), 8.38 (2H, d, J = 8.2Hz), 7.83-7.66 (5H, m), 7.61 (1H, br), 7.59-7.42 (5H, m), 7.36 (2H, d, J = 8.7 Hz), 7.30-7.20 (2H, m), 7.20-6.97 (5H, m), 6.92 (2H, d, *J* = 7.3 Hz), 6.77 (2H, d, *J* = 8.2 Hz), 5.11 (2H, br), 2.13 (1H, ddq, *J* = 13.7, 7.5, 7.5 Hz), 1.91-1.71 (1H, m), 0.72 (3H, dd, *J* = 7.5,  $Ar^{2} = 4 - CI - C_{6}H_{4}$ 6.7 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 167.0, 142.7, 141.4, 138.5, 138.4, 136.2, 134.3, 134.2, 133.8 (q, *J*<sub>C-F</sub> = 33.5 Hz), 133.6, 133.5, 133.0, 132.4 (q, *J*<sub>C-F</sub> = 33.9 Hz), 132.0, 131.2, 130.7, 130.5, 129.3, 129.2, 129.1, 128.9, 128.8, 128.8, 128.7, 127.7, 126.3 (q, *J*<sub>C-F</sub> = 3.9 Hz), 125.6 (q, *J*<sub>C-F</sub> = 3.9 Hz), 123.8 (q, *J*<sub>C-F</sub>) = 276.7 Hz), 123.4 (q,  $J_{C-F} = 276.7$  Hz), 119.7, 71.8, 68.9, 55.1, 23.2, 10.3, one peak for aromatic carbon was not found probably due to broadening or overlapping; IR 3021, 1680, 1530, 1493, 1323, 1277, 1165, 1126, 1067, 752, 706 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{46}H_{35}Cl_2F_6N_4O^+$  ([M–Br]<sup>+</sup>) 843.2087. Found 843.2080.;  $[\alpha]_D^{22} = -29.2$  (c = 1.0, MeOH).

![](_page_2_Figure_5.jpeg)

$$\left[\begin{array}{c} \mathsf{Ar}^1 = \mathsf{4}\text{-}\mathsf{CF}_3\text{-}\mathsf{C}_6\mathsf{H}_4\\ \mathsf{Ar}^2 = \mathsf{4}\text{-}\mathsf{CI}\text{-}\mathsf{C}_6\mathsf{H}_4 \end{array}\right]$$

MeOH).

**1f·Br**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  9.54 (1H, br), 8.68 (1H, br), 8.33 (2H, d, J = 8.2Hz), 8.14 (1H, br), 7.82 (1H, d, J = 8.2 Hz), 7.76 (1H, s), 7.69 (2H, d, J = 8.2 Hz), 7.65-7.53 (2H, m), 7.50 (2H, d, J = 8.2 Hz), 7.40-7.24 (4H, m), 7.24-7.08 (6H, m), 6.89 (2H, d, J = 8.2 Hz), 6.86 (2H, d, J = 8.2 Hz), 5.40 (1H, br), 5.23 (1H, d, J = 15.1 Hz), 2.23-2.07 (1H, m), 1.78-1.60 (1H, m), 0.68 (3H, t, J = 6.9 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ167.4, 143.6, 140.3, 138.9, 137.1, 136.2, 135.0 (q, *J*<sub>C-F</sub> = 33.9 Hz), 134.7, 134.4, 134.3, 133.9 (q, *J*<sub>C-F</sub> = 32.9 Hz), 133.3, 133.0, 132.5 (q, *J*<sub>C-F</sub> = 33.9 Hz), 130.9, 130.1, 129.5, 129.4, 129.0, 128.7, 128.0, 127.8, 126.3 (q, *J*<sub>C-F</sub> = 3.9 Hz), 125.7 (q, *J*<sub>C-F</sub> = 2.9 Hz), 123.8 (q, *J*<sub>C-F</sub> = 276.7 Hz), 123.4 (q, *J*<sub>C-F</sub> = 276.7 Hz), 123.4, 123.1 (q, J<sub>C-F</sub> = 277.7 Hz), 71.5, 68.7, 55.9, 23.9, 10.3, four peaks for aromatic carbon was not found probably due to broadening or overlapping; IR 3032, 2359, 1680, 1530, 1493, 1325, 1285, 1175, 1125, 826, 752 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{47}H_{34}Cl_2F_9N_4O^+$  ([M–Br]<sup>+</sup>) 911.1960. Found 911.1950.;  $[\alpha]_D^{22} = -21.5$  (c = 1.0, General procedure for 1f·Br-catalysed asymmetric alkylation of 3-substituted oxindoles with racemic secondary alkyl halides:

![](_page_3_Figure_1.jpeg)

A solution of **1f·Br** (1.99 mg, 0.002 mmol), *N*-Boc oxindole **2a** (27.7 mg, 0.10 mmol), and alkyl bromide **3a** (27.3 µL, 0.20 mmol) in Et<sub>2</sub>O (300 µL) was cooled to -78 °C and degassed by alternating vacuum evacuation/Ar backfill. To this solution was added K<sub>2</sub>CO<sub>3</sub> (34.6 mg, 0.25 mmol), and the degassing with Ar was conducted again. The whole reaction mixture was cooled to 0 °C and stirred for 48 h. The reaction was quenched with a saturated aqueous solution of NH<sub>4</sub>Cl, and the extractive workup was performed with EtOAc. After drying over Na<sub>2</sub>SO<sub>4</sub>, filtration, and removal of solvents, the resulting crude residue was purified by column chromatography on silica gel (H/EtOAc = 20:1 as eluent) to afford **4a** (37.9 mg, 0.099 mmol, 99% yield) as a colorless oil. **4a**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.66 (1H, d, *J* = 9.0 Hz), 7.30-7.21 (3H, m), 7.13-7.07 (2H, m), 6.77 (1H, dd, *J* = 9.0, 2.7 Hz), 6.33 (1H, d, *J* = 2.7 Hz), 3.72 (3H, s), 3.27 (1H, q, *J* = 7.3 Hz), 1.63 (9H, s), 1.35 (3H, s), 1.18 (3H, d, *J* = 7.3 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.5, 156.3, 149.3, 140.6, 132.9, 132.4, 129.5, 127.7, 127.2, 115.5, 113.1, 110.6, 84.1, 55.6, 52.5, 47.4, 28.3, 23.1, 15.3; IR 2974, 1786, 1765, 1726, 1483, 1454, 1298, 1279, 1246, 1152, 1034, 806 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>23</sub>H<sub>27</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 404.1832. Found 404.1826.; HPLC OD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 10.4 min (minor isomer of minor diastereomer), 11.0 min (*R*,*R*), 12.3 min (*S*,*S*), 14.9 min (major isomer of minor diastereomer).

MeC

1.17 (3H, d, J = 7.1 Hz), 0.49 (3H, dd, J = 7.8, 7.3 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.0, 156.3, 149.2, 140.9, 134.1, 130.2, 129.6, 127.6, 127.2, 115.4, 113.1, 110.6, 84.0, 58.3, 55.6, 47.6, 30.0, 28.3, 15.4, 9.2; IR 2970, 1788, 1755, 1724, 1485, 1454, 1271, 1244, 1152, 1076, 818 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>24</sub>H<sub>29</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 418.1989. Found 418.1985.; HPLC OZ3, H/IPA = 99:1, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 11.7 min (major isomer of minor diastereomer), 12.7 min (minor isomer of major diastereomer), 13.5 min (major isomer of major diastereomer).

![](_page_3_Figure_5.jpeg)

1726, 1483, 1246, 1150, 1076 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>29</sub>H<sub>31</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 480.2145. Found

480.2137; HPLC AD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 13.9 min (minor isomer of major diastereomer), 16.9 min (major isomer of major diastereomer), 18.2 min (major isomer of minor diastereomer), 23.1 min (minor isomer of minor diastereomer).

![](_page_4_Figure_1.jpeg)

Me Me <sup>Me</sup> 4e: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.72 (1H, d, J = 8.0 Hz), 7.25-7.18 (4H, m), 7.08-7.02 (3H, m), 6.81 (1H, d, J = 7.6 Hz), 3.26 (1H, q, J = 7.0 Hz), 1.64 (9H, s), 1.38 (3H, s), 1.20 (3H, d, J = 7.0 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 179.3, 149.3, 140.7, 139.5, 131.3, 129.4, 128.1, 127.7, 127.1, 124.3, 123.8, 114.6, 84.2, 52.2, 47.7, 28.3, 23.0, 15.3; IR 2978, 1763, 1728, 1479, 1288, 1250, 1150, 773, 754 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>22</sub>H<sub>25</sub>NNaO<sub>3</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 374.1727. Found 374.1721.; Enantiomeric excess was determined after *N*-Boc deprotection, yielding oxindole **S2**. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.78 (1H, brs), 7.31-7.23 (3H, m), 7.21-7.13 (3H, m), 6.95 (1H, t, J = 7.8 Hz), 6.84 (1H, d, J = 7.8 Hz), 6.77 (1H, d, J = 7.3 Hz), 3.28 (1H, q, J = 7.3 Hz), 1.32 (3H, s), 1.18 (3H, d, J = 7.3 Hz); HPLC AD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda = 210$  nm, 24.8 min (minor isomer of major diastereomer), 26.3 min (minor isomer of minor diastereomer), 28.3 min (major isomer of major diastereomer), 35.6 min (major isomer of minor diastereomer).

![](_page_4_Picture_3.jpeg)

**4f**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.75 (1H, d, *J* = 7.9 Hz), 7.29 (1H, t, *J* = 7.9 Hz), 7.24-7.21 (3H, m), 7.12 (1H, t, *J* = 7.9 Hz), 7.05-7.01 (2H, m), 6.80 (1H, d, *J* = 7.9 Hz), 3.27 (1H, q, *J* = 7.3 Hz), 2.84 (2H, dd, *J* = 8.2, 6.6 Hz), 2.48 (1H, dt, *J* = 13.8, 8.2 Hz), 1.89 (1H, dt, *J* = 13.8, 6.6 Hz), 1.64 (9H, s), 1.18 (3H, d, *J* = 7.3 Hz); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  177.9, 149.0,

140.4, 140.3, 129.4, 128.7, 127.9, 127.5, 127.4, 124.5, 124.0, 115.0, 84.4, 55.2, 48.1, 47.8, 35.4, 28.3, 15.0; IR 2978, 2097, 1728, 1479, 1456, 1288, 1248, 1148, 754 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{23}H_{26}N_4NaO_3^+$  ([M+Na]<sup>+</sup>) 429.1897. Found 429.1889.; HPLC OZ3, H/IPA = 99:1, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 13.2 min (minor isomer of major diastereomer), 15.4 min (major isomer of minor diastereomer), 18.5 min (minor isomer of minor diastereomer), 20.0 min (major isomer of major diastereomer).

**4g**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.63 (1H, d, J = 9.0 Hz), 7.20 (2H, d, J = 8.5 Hz), 7.01 Me Me MeC (2H, d, *J* = 8.5 Hz), 6.77 (1H, dd, *J* = 9.0, 2.7 Hz), 6.37 (1H, d, *J* = 2.7 Hz), 3.75 (3H, s),  $3.22 (1H, q, J = 7.1 Hz), 1.62 (9H, s), 1.36 (3H, s), 1.20 (3H, d, J = 7.1 Hz); {}^{13}C NMR (101)$ Boc  $(Ar = 4-CI-C_6H_4)$ MHz, CDCl<sub>3</sub>) δ179.0, 156.4, 149.2, 139.3, 133.0, 132.9, 132.4, 130.6, 127.8, 115.7, 112.9, 110.5, 84.2, 55.7, 52.4, 47.0, 28.3, 22.8, 15.3; IR 2978, 1726, 1483, 1279, 1246, 1153, 1040, 831 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{23}H_{26}CINNaO_4^+$  ([M+Na]<sup>+</sup>) 438.1443. Found 438.1438.; HPLC OD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 10.2 min (minor isomer of major diastereomer), 11.0 min (minor isomer of minor diastereomer), 12.9 min (major isomer of major diastereomer), 16.5 min (major isomer of minor diastereomer).

**4h**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (1H, d, J = 9.0 Hz), 7.07 (2H, d, J = 8.2 Hz), 7.00 Мe Me MeC (2H, d, *J* = 8.2 Hz), 6.78 (1H, dd, *J* = 9.0, 2.8 Hz), 6.35 (1H, d, *J* = 2.8 Hz), 3.73 (3H, s), 3.24 (1H, q, J = 7.4 Hz), 2.32 (3H, s), 1.61 (9H, s), 1.33 (3H, s), 1.13 (3H, d, J = 7.4 Hz); Boc  $(Ar = 4-Me-C_6H_4)$ <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ179.6, 156.3, 149.3, 137.6, 136.8, 133.0, 132.5, 129.5, 128.4, 115.5, 113.0, 110.7, 84.0, 55.7, 52.6, 46.9, 28.1, 23.2, 21.2, 15.5; IR 2978, 1724, 1481, 1279, 1246, 1153,

1040, 820 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>24</sub>H<sub>29</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 418.1989. Found 418.1982.; HPLC OZ3, H/IPA = 99:1, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 15.1 min (minor isomer of major diastereomer), 16.7 min (major isomer of major diastereomer), 19.0 min (major isomer of minor diastereomer), 21.9 min (minor isomer of minor diastereomer).

**4i**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.70 (1H, d, J = 9.2 Hz), 7.17-7.07 (4H, m), 6.78 (1H, Мe Me MeO dd, J = 9.2, 2.8 Hz), 6.52 (1H, d, J = 2.8 Hz), 3.75 (3H, s), 3.66 (1H, q, J = 7.0 Hz), 2.40  $(3H, s), 1.65 (9H, s), 1.32 (3H, s), 1.13 (3H, d, J = 7.0 Hz); {}^{13}C NMR (101 MHz, CDCl_3)$ Boc  $(Ar = 2-Me-C_6H_4)$ δ179.8, 156.2, 149.4, 139.8, 137.0, 132.9, 132.6, 130.6, 128.3, 126.9, 125.4, 115.5, 113.2, 111.2, 84.1, 55.7, 53.3, 41.8, 28.3, 22.3, 20.7, 16.7; IR 2976, 1724, 1483, 1277, 1246, 1152, 1070, 1040, 727 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>24</sub>H<sub>29</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 418.1989. Found 418.1985.; HPLC OD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 9.7 min (minor isomer of minor diastereomer), 11.2 min (major isomer of major diastereomer), 13.2 min (major isomer of minor diastereomer), 20.0 min (minor isomer of major diastereomer).

**4**j: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.84-7.75 (2H, m), 7.72 (1H, d, J = 8.4 Hz), 7.64 (1H, d, J = 9.0 Hz), 7.59 (1H, s), 7.50-7.42 (2H, m), 7.24 (1H, dd, J = 8.6, 1.6 Hz), 6.78 (1H, Boc dd, J = 9.0, 2.8 Hz), 6.36 (1H, d, J = 2.8 Hz), 3.65 (3H, s), 3.44 (1H, q, J = 7.0 Hz), 1.60 (Ar = 2-Naph)(9H, s), 1.39 (3H, s), 1.27 (3H, d, J = 7.0 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.4, 156.4, 149.3, 138.3, 133.0, 133.0, 132.7, 132.3, 128.2, 128.0, 127.9, 127.6, 127.0, 126.1, 125.9, 115.6, 113.4, 110.4, 84.1, 55.6, 52.7, 47.5, 28.2, 23.2, 15.6; IR 2976, 1761, 1724, 1481, 1277, 1246, 1152, 1038, 818, 735 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{27}H_{29}NNaO_4^+$  ([M+Na]<sup>+</sup>) 454.1989. Found 454.1981.; HPLC OD3, H/IPA = 99:1, flow rate = 0.5 mL/min,  $\lambda$ = 210 nm, 15.0 min (minor isomer of major diastereomer), 16.1 min (minor isomer of minor diastereomer), 20.0 min (major isomer of minor diastereomer), 22.6 min (major isomer of major diastereomer).

![](_page_6_Figure_0.jpeg)

**4k**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.41 (1H, d, *J* = 8.4 Hz), 7.85 (1H, d, *J* = 8.0 Hz), 7.78 (1H, d, *J* = 8.4 Hz), 7.72 (1H, d, *J* = 9.0 Hz), 7.59-7.41 (3H, m), 7.31 (1H, d, *J* = 7.2 Hz), 6.77 (1H, dd, *J* = 9.0, 2.6 Hz), 6.45 (1H, d, *J* = 2.6 Hz), 4.41 (1H, q, *J* = 7.0 Hz), 3.71 (3H, s), 1.67 (9H, s), 1.23 (3H, s), 1.23 (3H, d, *J* = 7.0 Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  180.0,

156.2, 149.5, 137.7, 133.8, 133.2, 133.0, 132.2, 129.0, 128.0, 126.3, 126.0, 125.5, 124.7, 124.3, 115.6, 113.4, 111.0, 84.2, 55.6, 53.6, 39.7, 28.3, 23.4, 17.0; IR 2976, 1759, 1724, 1481, 1277, 1246, 1152, 1038, 775 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>27</sub>H<sub>29</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 454.1989. Found 454.1982.; HPLC AD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 10.3 min (major isomer of minor diastereomer), 10.9 min (minor isomer of major diastereomer), 19.0 min (major isomer of major diastereomer).

**41**: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  7.67 (1H, d, J = 9.0 Hz), 7.21 (1H, dd, J = 5.2, 2.8 Hz), Me Me MeO 6.92 (1H, d, J = 2.8 Hz), 6.86 (1H, d, J = 5.2 Hz), 6.78 (1H, dd, J = 9.0, 2.8 Hz), 6.32 (1 H, d, J = 2.8 Hz), 3.73 (3H, s), 3.39 (1H, q, J = 7.2 Hz), 1.63 (9H, s), 1.39 (3H, s), 1.16 Boc (Ar = 3-thienyl) (3H, d, J = 7.2 Hz); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  179.3, 156.5, 149.3, 141.7, 133.0, 132.6, 128.8, 124.3, 122.8, 115.6, 113.0, 110.3, 84.1, 55.7, 52.4, 43.0, 28.3, 23.1, 15.9; IR 2977, 1788, 1759, 1723, 1480, 1456, 1297, 1278, 1245, 1151, 1038, 847, 807 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>21</sub>H<sub>25</sub>NNaO<sub>4</sub>S<sup>+</sup> ([M+Na]<sup>+</sup>) 410.1397. Found 410.1389.; Enantiomeric excess was determined after N-Boc deprotection, yielding oxindole S3. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (1H, brs), 7.29-7.21 (1H, m), 7.00-6.93 (2H, m), 6.78-6.69 (2H, m), 6.33 (1H, s), 3.72 (3H, s), 3.40 (1H, q, *J* = 7.0 Hz), 1.35 (3H, s), 1.13 (3H, d, *J* = 7.0 Hz); HPLC OD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 230 nm, 22.6 min (minor isomer of minor diastereomer), 24.1 min (major isomer of major diastereomer), 29.2 min (major isomer of minor diastereomer), 32.5 min (minor isomer of major diastereomer).

Hz); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  179.8, 156.4, 149.3, 138.1, 133.0, 132.7, 130.3, 127.8, 127.2, 115.6, 112.9, 110.7, 84.1, 55.7, 55.6, 52.7, 28.3, 23.5, 21.8, 12.3; IR 2968, 1759, 1724, 1483, 1279, 1246, 1152, 1042, 731 cm<sup>-1</sup>; HRMS (ESI) Calcd for C<sub>24</sub>H<sub>29</sub>NNaO<sub>4</sub><sup>+</sup> ([M+Na]<sup>+</sup>) 418.1989. Found 418.1985.; HPLC IE3, H/IPA = 99:1, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 43.5 min (major isomer of major diastereomer), 48.6 min (minor isomer of major diastereomer), 51.1 min (major isomer of minor diastereomer), 56.7 min (minor isomer of minor diastereomer).

 $\begin{array}{ccc} & & & & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & &$ 

171.7, 156.7, 148.8, 133.4, 132.9, 131.2, 129.4, 128.4, 128.0, 115.5, 113.7, 111.8, 83.9, 58.3, 55.8, 52.3, 52.3,

28.2, 22.4; IR 2980, 1728, 1485, 1302, 1279, 1246, 1152, 1036, 1005, 704 cm<sup>-1</sup>; HRMS (ESI) Calcd for  $C_{24}H_{27}NNaO_6^+$  ([M+Na]<sup>+</sup>) 448.1731. Found 448.1725.; HPLC AD3, H/IPA = 97:3, flow rate = 0.5 mL/min,  $\lambda$  = 210 nm, 13.9 min (major isomer of major diastereomer), 16.2 min (minor isomer of major diastereomer), 26.3 min (minor isomer of minor diastereomer), 39.0 min (major isomer of minor diastereomer).

Synthesis of *N*-Nos derivative 5:

![](_page_7_Figure_2.jpeg)

The alkylation product **4a** (80.1 mg, 0.21 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and TFA (46 uL, 0.63 mmol) was added at room temperature. After stirring for 5 h, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and a saturated aqueous solution of Na<sub>2</sub>CO<sub>3</sub>, and then the extractive work-up was conducted with CH<sub>2</sub>Cl<sub>2</sub>. After drying over Na<sub>2</sub>SO<sub>4</sub>, filtration, and concentration, the crude residue was used for the next step without further purification. To a suspension of NaH (8 mg, 0.324 mmol) in THF (3 mL) was successively added a solution of crude material in THF (2 mL) and NosCl (69.8 mg, 0.315 mmol) at 0 °C. After stirring for 6 h, the reaction was quenched with water (0.5 mL), and the extractive work-up was performed with EtOAc (5 mL). The organic extracts were washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation to remove the solvents and purification of the crude residue by column chromatography on silica gel (H/EtOAc = 10:1 as eluent) afforded **5** (78.4 mg, 0.17 mmol, 80% yield for 2 steps, dr = >20:1, 99% ee) as a white solid.

## Crystallographic structure determination:

#### **Recrystallization of 5 (CCDC 1573942):**

A single crystal of **5** was obtained from hexane/toluene solvent system at 0 °C. The single crystal thus obtained was mounted on CryoLoop. Data of X-ray diffraction were collected at 123 K on a Brucker SMART APEX CCD diffractometer with graphite-monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). An absorption correction was made using SADABS. The structure was solved by direct methods and Fourier syntheses, and refined by full-matrix least squares on  $F^2$  by using SHELXTL.<sup>2</sup> All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in calculated positions. The crystallographic data were summarised in Tables S1.

Table S1.	Crystal data and structu	are refinement for 5
Identificatio	on code	shelxs

	Shemb
Empirical formula	$C_{24}H_{22}N_2O_6S$
Formula weight	466.49

<sup>&</sup>lt;sup>2</sup> Sheldrick, G. M. SHELXTL 5.1, Bruker AXS Inc., Madison, Wisconsin, 1997.

Temperature	103(2) K		
Wavelength	0.71075 Å		
Crystal system	Monoclinic		
Space group	P 2 <sub>1</sub>		
Unit cell dimensions	a = 12.800(3)  Å	$\alpha = 90^{\circ}.$	
	b = 7.0766(13) Å	$\beta = 116.294(3)^{\circ}.$	
	c = 13.621(3)  Å	$\gamma = 90^{\circ}.$	
Volume	1106.1(4) Å <sup>3</sup>		
Z	2		
Density (calculated)	1.401 Mg/m <sup>3</sup>		
Absorption coefficient	0.191 mm <sup>-1</sup>		
F(000)	488		
Crystal size	0.250 x 0.050 x 0.050 mm <sup>3</sup>		
Theta range for data collection	3.006 to 27.478°.		
Index ranges	-16<=h<=14, -9<=k<=9, -17<=l<=15		
Reflections collected	8990		
Independent reflections	4985 [R(int) = 0.0296]		
Completeness to theta = $25.242^{\circ}$	99.3 %		
Absorption correction	Empirical		
Refinement method	Full-matrix least-squares on F <sup>2</sup>		
Data / restraints / parameters	4985 / 1 / 301		
Goodness-of-fit on F <sup>2</sup>	0.926		
Final R indices [I>2sigma(I)]	R1 = 0.0287, wR2 = 0.0627		
R indices (all data)	R1 = 0.0380, wR2 = 0.0650		
Absolute structure parameter	0.05(4)		
Extinction coefficient	n/a		
Largest diff. peak and hole	0.261 and -0.199 e.Å <sup>-3</sup>		
		•	

Figure S1. Molecular structure of 5. Calculated hydrogen atoms are omitted for clarity. Yellow = sulfer, red = oxygen, blue = nitrogen, black = carbon.

# Copies of 1H and 13 C NMR Spectra:

![](_page_9_Figure_1.jpeg)

![](_page_10_Figure_0.jpeg)

![](_page_11_Figure_0.jpeg)

![](_page_12_Figure_0.jpeg)

![](_page_13_Figure_0.jpeg)

![](_page_14_Figure_0.jpeg)

![](_page_15_Figure_0.jpeg)

![](_page_16_Figure_0.jpeg)

![](_page_17_Figure_0.jpeg)

![](_page_18_Figure_0.jpeg)

![](_page_19_Figure_0.jpeg)

![](_page_20_Figure_0.jpeg)

![](_page_21_Figure_0.jpeg)

![](_page_22_Figure_0.jpeg)

![](_page_23_Figure_0.jpeg)

![](_page_24_Figure_0.jpeg)

![](_page_25_Figure_0.jpeg)

![](_page_26_Figure_0.jpeg)

210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.020.0

![](_page_27_Figure_0.jpeg)

![](_page_28_Figure_0.jpeg)

## **HPLC Chromatograms:**

![](_page_29_Figure_1.jpeg)

![](_page_30_Figure_0.jpeg)

![](_page_31_Figure_0.jpeg)

![](_page_31_Figure_1.jpeg)

![](_page_31_Figure_2.jpeg)

PDA Multi 1 210nm,4nm

25.0 mir

25.0

min

22.761

![](_page_32_Figure_0.jpeg)

![](_page_32_Figure_2.jpeg)