Facile access to benzofuran-fused tetrahydropyridines via catalytic asymmetric [4 + 2] cycloaddition of aurone-derived 1-azadienes with 3-vinylindoles

Wai Lean Koay,ab Guang-Jian Mei,*a and Yixin Lu*abc

a. Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Singapore. E-mail: mgjx1x2x3@163.com; chmlyx@nus.edu.sg.
b. NUS Graduate School for Integrative Sciences & Engineering (NGS), National University of Singapore, University Hall, Tan Chin Tuan Wing #04-02, 21 Lower Kent Ridge Road, Singapore, 119077, Singapore
c. Joint School of National University of Singapore and Tianjin University, International Campus of Tianjin University, Binhai New City, Fuzhou, Fujian, 350207, China
Supporting Information

A. General information S03
B. Representative Procedures S04
C. Analytical Data and HPLC Chromatograms of the Products S06
D. X-Ray Crystallographic Analysis and Determination of the Absolute Configurations of Product 3b S35
E. References S36
F. $^1$H and $^{13}$C NMR Spectra of the Products S37
A. General Information

Unless otherwise specified, all reactions were conducted under an inert atmosphere and anhydrous conditions. All the solvents were purified according to the standard procedures. All chemicals which are commercially available were employed without further purification. Thin-layer chromatography (TLC) was performed on silica gel plates (60F-254) using UV-light (254 and 365 nm). Flash chromatography was conducted on silica gel (200–300 mesh). 

$^1$H and $^{13}$C NMR spectra were recorded at ambient temperature in CDCl$_3$ on a Bruker AMX500 (500 MHz) or AMX400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million (ppm). The data are reported as follows: for $^1$H NMR, chemical shift in ppm from tetramethylsilane with the solvent as internal standard (CDCl$_3$ δ 7.26 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances), integration; for $^{13}$C NMR, chemical shift in ppm from tetramethylsilane with the solvent as internal indicator (CDCl$_3$ δ 77.1 ppm), multiplicity with respect to protons. All high-resolution mass spectra were performed by the MS service at the chemistry department, National University of Singapore, and were obtained on a Finnigan/MAT 95XL-T spectrometer to be given in m/z. Optical rotations were measured using an Anton Paar MCP-100 digital polarimeter using a 1 cm glass cell. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase using CHIRALPAK® columns (IE, ID & IC) eluting with hexane/isopropanol mixtures as indicated. Aurone-derived 1-azadienes 1 and 3-vinylindoles 2 were synthesized according to literature-reported procedures respectively.
B. Representative Procedures

General Procedure for chiral phosphoric acid catalyzed dearomative [3 + 2] cycloaddition reaction of α-naphthols with azoalkenes:

To a stirring anhydrous Et₂O:CH₂Cl₂ (2:1) solution (1 ml) of aurone-derived 1-azadienes 1 (0.1 mmol) and 3-vinylindoles 2 (0.18 mmol) was added 5Å MS (100 mg) and CPA 4b (1 mol%) at rt. The reaction mixture was stirred until completion of reaction (as monitored by TLC). After which, the mixture was filtered and the solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (Hexane:CH₂Cl₂ = 2:1) to afford cycloadducts 3.

Table 1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>dr (%)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>4b</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>95</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>4c</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4d</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>72</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>4e</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>99</td>
<td>34</td>
</tr>
<tr>
<td>6</td>
<td>4f</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>98</td>
<td>46</td>
</tr>
<tr>
<td>7</td>
<td>4g</td>
<td>DCE</td>
<td>&gt;20:1</td>
<td>97</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>4b</td>
<td>CHCl₃</td>
<td>&gt;20:1</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td>9</td>
<td>4b</td>
<td>CH₂Cl₂</td>
<td>&gt;20:1</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>10</td>
<td>4b</td>
<td>toluene</td>
<td>&gt;20:1</td>
<td>90</td>
<td>46</td>
</tr>
<tr>
<td>11</td>
<td>4b</td>
<td>Et₂O</td>
<td>&gt;20:1</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>12*</td>
<td>4b</td>
<td>Et₂O/CH₂Cl₂</td>
<td>&gt;20:1</td>
<td>98</td>
<td>93</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1a (0.1 mmol), 2a (0.18 mmol), and catalyst 4 (1 mol%), 5 Å MS (100 mg) in the solvent specified (1 ml) at RT for 20 h. The diastereomeric ratio (dr) value was determined by crude ¹H NMR. Isolated yield. The ee value was determined by HPLC analysis using a chiral stationary phase.
Synthesis of 3a at a gram-scale:

To a stirring anhydrous Et₂O:CH₂Cl₂ (2:1) solution (15 ml) of aurone-derived 1-azadienes 1a (3 mmol) and 3-vinylindoles 2a (5.4 mmol) was added 5Å MS (3 g) and CPA 4b (1 mol%) at rt. The reaction mixture was stirred until completion of reaction (as monitored by TLC). Then, the reaction mixture was vacuum filtered through Celite and water was added to the filtrate followed by extraction with AcOEt (2 × 20 mL). The combined organic layer was washed with brine, separated, dried over Na₂SO₄ and filtered. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (Hexane: CH₂Cl₂ = 2:1) to afford product 3a (1.3 g) in 87% yield with 92% ee.

Further elaborations of 3a:

For 3a-I: To a stirring anhydrous CH₂Cl₂ solution (1 ml) of 3a (0.1 mmol) was added Et₃N (0.2 mmol) and Boc₂O (0.15 mmol) at rt. The reaction mixture was stirred until completion of reaction (as monitored by TLC). Then, the reaction was quenched by adding the NH₄Cl aqueous solution followed by extraction with AcOEt (2 × 2 mL). The combined organic layer was washed with brine, separated, dried over Na₂SO₄ and filtered. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on silica gel (Hexane: CH₂Cl₂ = 2:1) to afford product 3a-I (58 mg) in 96% yield.
For **3a-II**: To a stirring anhydrous toluene solution (1 ml) of 3a (0.1 mmol) was added Red-Al (1 mmol) at -20 °C. The reaction mixture was stirred until completion of reaction (as monitored by TLC). Then, the reaction was quenched by adding the NH₄Cl aqueous solution followed by extraction with AcOEt (2 × 2 mL). The combined organic layer was washed with brine, separated, dried over Na₂SO₄ and filtered. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography on basic alumina (Hexane: AcOEt = 8:1) to afford product **3a-II** (48 mg) in 93% yield.
C. Analytical Data and HPLC Chromatograms of the Products

(2S,3R,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3a

Yellowish oil; isolated yield = 98%; \([\alpha]_D^{25} = -55.2 (c 1.0, \text{CHCl}_3)\); \(^1^H\) NMR (500 MHz, CDCl\(_3\)) \(\delta 8.07 – 8.01 (m, 1H), 7.90 (s, 1H), 7.58 – 7.31 (m, 4H), 7.25 – 7.13 (m, 5H), 7.11 – 6.88 (m, 5H), 6.85 – 6.73 (m, 3H), 5.86 (d, J = 7.1 Hz, 1H), 4.58 (d, J = 5.6 Hz, 1H), 4.43 – 4.40 (m, 1H), 2.35 (s, 3H); \(^1^C\) NMR (125 MHz, CDCl\(_3\)) \(\delta 154.0, 146.3, 141.8, 139.3, 135.9, 128.6, 128.0, 127.9, 127.8, 127.1, 126.3, 126.1, 124.9, 124.6, 123.3, 123.1, 122.1, 121.4, 120.0, 119.9, 118.5, 112.0, 111.8, 111.3, 61.4, 51.5, 45.7, 41.6. HRMS (ESI) m/z calcd for C\(_{32}\)H\(_{26}\)N\(_2\)O\(_3\)S [M - H] = 517.1591, found = 517.1589; HRMS (ESI) m/z calcd for C\(_{32}\)H\(_{25}\)FN\(_2\)O\(_3\)S [M - H] = 535.1497, found = 535.1502; the ee value was 93%, \(t_R\) (major) = 10.6 min, \(t_R\) (minor) = 20.8 min (Chiralpak IE, \(\lambda = 254 \text{ nm, 20\%} \ i-\text{PrOH/Hexane, flow rate} = 1.0 \text{ mL/min}).

![HPLC Chromatogram](image)

**Racemic 3a**

![HPLC Chromatogram](image)

**Enatioenriched 3a**
(2S,3R,4R)-2-(5-fluoro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2- 

b]pyridine 3b

Yellowish oil; isolated yield = 93%; $[\alpha]_{D}^{25} = -156$ (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.17 – 8.04 (m, 1H), 7.88 (s, 1H), 7.51 – 7.43 (m, 1H), 7.41 – 7.30 (m, 2H), 7.30 – 7.17 (m, 5H), 7.15 – 7.12 (m, 1H), 7.07 – 7.04 (m, 1H), 6.94 – 6.81 (m, 3H), 6.81 – 6.78 (m, 1H), 6.73 – 6.66 (m, 2H), 5.84 (d, $J = 6.2$ Hz, 1H), 4.62 (d, $J = 4.8$ Hz, 1H), 4.37 – 4.34 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 157.7 (d, $J = 234$ Hz), 154.1, 145.4, 141.7, 139.4, 132.5, 128.8, 128.0, 127.8, 127.7, 127.4, 126.4, 126.2, 124.8, 123.3, 122.9, 121.6, 119.8, 112.0, 111.9, 111.8, 110.5 (d, $J = 26$ Hz), 103.7 (d, $J = 24$ Hz), 61.3, 50.9, 44.6, 41.2; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$FN$_2$O$_3$S [M - H] $^-$ = 535.1497, found = 535.1502; the ee value was 99%, $t_R$ (major) = 8.0 min, $t_R$ (minor) = 18.9 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3b

Enantioenriched 3b
(2S,3R,4R)-2-(5-chloro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3c

Yellowish oil; isolated yield = 92%; \([\alpha]_{D}^{25} = -171 \text{ (c 0.5, CHCl}_3\); \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta 8.19 - 8.13 \text{ (m, 1H), 7.93 (s, 1H), 7.52 - 7.43 \text{ (m, 1H), 7.43 (s, 1H), 7.41 - 7.27 \text{ (m, 2H), 7.30 - 7.15 \text{ (m, 4H), 7.07 - 6.96 \text{ (m, 2H), 6.93 - 6.80 \text{ (m, 4H), 6.71 - 6.64 \text{ (m, 2H), 5.86 (d, J = 6.2 Hz, 1H), 4.64 (d, J = 4.6 Hz, 1H), 4.39 - 4.36 \text{ (m, 1H), 2.30 (s, 3H); \(^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3\)) \(\delta 154.1, 145.2, 141.6, 139.4, 134.4, 128.8, 128.0, 127.7, 127.6, 127.4, 126.9, 126.1, 125.9, 125.4, 124.7, 123.2, 122.7, 122.3, 121.6, 119.7, 118.1, 112.4, 112.2, 111.8, 61.2, 50.7, 44.3, 41.1; HRMS (ESI) m/z calcd for C\(_{32}\)H\(_{25}\)ClN\(_2\)O\(_3\)S [M - H] = 551.1202, found = 551.1204; the ee value was 99\%, \(t_R \text{ (major) = 6.9 min, } t_R \text{ (minor) = 8.8 min (Chiralpak IE, } \lambda = 254 \text{ nm, 20\% i-PrOH/Hexane, flow rate = 1.0 mL/min).}

Racemic 3c

Enantioenriched 3c
(2S,3R,4R)-2-(5-bromo-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3d

Yellowish oil; isolated yield = 84%; $\left[\alpha\right]_{D}^{25} = -188$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.22 – 8.16 (m, 1H), 7.98 (s, 1H), 7.61 (s, 1H), 7.53 – 7.48 (m, 1H), 7.43 – 7.34 (m, 2H), 7.33 – 7.21 (m, 3H), 7.16 – 7.14 (m, 1H), 7.02 (d, $J = 8.6$ Hz, 1H), 6.95 – 6.83 (m, 5H), 6.71 (d, $J = 7.0$ Hz, 2H), 5.89 (d, $J = 6.0$ Hz, 1H), 4.67 (d, $J = 4.6$ Hz, 1H), 4.43 – 4.37 (m, 1H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 145.3, 141.6, 139.4, 134.7, 128.8, 128.0, 127.8, 127.7, 127.6, 127.4, 126.2, 125.8, 124.9, 124.8, 123.3, 122.8, 121.6, 121.2, 119.7, 113.1, 112.7, 112.3, 111.9, 61.3, 50.7, 44.4, 41.1; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$BrN$_2$O$_3$S [M - H]$^-$ = 595.0696, found = 595.0682; the ee value was 91%, $t_{R}$ (major) = 6.8 min, $t_{R}$ (minor) = 7.7 min (Chiralpak IE, $\lambda$ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-2-(6-fluoro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-\textit{b}]pyridine 3e

Yellowish oil; isolated yield = 84\%; [\alpha]_D^{25} = -128 (c 0.5, CHCl\_3); \textsuperscript{1}H NMR (400 MHz, CDCl\_3) \delta 8.18 – 8.11 (m, 1H), 7.83 (s, 1H), 7.50 – 7.45 (m, 1H), 7.43 – 7.30 (m, 3H), 7.25 – 7.21 (m, 4H), 6.90 – 6.63 (m, 8H), 5.89 (d, J = 6.0 Hz, 1H), 4.64 (d, J = 4.6 Hz, 1H), 4.40 – 4.33 (m, 1H), 2.34 (s, 3H); \textsuperscript{13}C NMR (125 MHz, CDCl\_3) \delta 159.8 (d, J = 237 Hz), 154.1, 145.2, 141.8, 139.5, 136.2, 136.1, 128.8, 128.0, 127.8, 127.7, 127.4, 126.2, 124.8, 124.7, 123.3, 122.8, 122.4, 121.6, 119.8, 119.4, 119.3, 113.0, 111.9, 108.6 (d, J = 25 Hz), 97.5 (d, J = 26 Hz), 61.4, 51.2, 44.3, 41.1; HRMS (ESI) m/z calcd for C\textsubscript{32}H\textsubscript{25}FN\textsubscript{2}O\textsubscript{3}S [M - H] = 535.1497, found = 535.1496; the ee value was 88\%, t\textsubscript{R} (major) = 8.7 min, t\textsubscript{R} (minor) = 16.2 min (Chiralpak IE, \lambda = 254 nm, 20\% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3e

Enantioenriched 3e
(2S,3R,4R)-2-(6-chloro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3f

Yellowish oil; isolated yield = 92%; $[\alpha]_D^{25} = -100$ (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.16 – 8.10 (m, 1H), 7.87 (s, 1H), 7.52 – 7.43 (m, 1H), 7.41 – 7.30 (m, 3H), 7.30 – 7.16 (m, 4H), 7.14 – 7.13 (m, 1H), 6.96 – 6.94 (m, 1H), 6.89 – 6.88 (m, 3H), 6.81 – 6.80 (m, 1H), 6.69 – 6.67 (m, 2H), 5.87 (d, $J = 5.5$ Hz, 1H), 4.63 (d, $J = 4.8$ Hz, 1H), 4.38 – 4.31 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 154.1, 145.3, 141.6, 139.3, 136.4, 128.8, 128.0, 127.8, 127.4, 126.3, 125.1, 124.8, 124.4, 123.3, 122.8, 121.6, 120.6, 119.7, 119.5, 113.0, 111.9, 111.2, 61.3, 51.2, 44.4, 41.1; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$ClN$_2$O$_3$S [M - H] = 551.1202, found = 551.1197; the ee value was 92%, $t_R$ (major) = 8.7 min, $t_R$ (minor) = 17.6 min (Chiralpak IE, $\lambda = 254$ nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3f

Enantioenriched 3f
(2S,3R,4R)-2-(7-fluoro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-

b]pyridine 3g

Yellowish oil; isolated yield = 97%; [α]D 25 = −131 (c 2, CHCl₃); 1H NMR (500 MHz, CDCl₃) δ 8.17 – 8.15 (m, 1H), 8.05 (s, 1H), 7.52 – 7.45 (m, 1H), 7.41 – 7.32 (m, 2H), 7.32 – 7.18 (m, 5H), 6.94 – 6.83 (m, 5H), 6.80 – 6.76 (m, 1H), 6.70 – 6.67 (m, 2H), 5.91 (d, J = 6.1 Hz, 1H), 4.65 (d, J = 4.6 Hz, 1H), 4.42 – 4.36 (m, 1H), 2.35 (s, 3H);

13C NMR (125 MHz, CDCl₃) δ 154.1, 149.3 (d, J = 243 Hz), 145.2, 141.7, 139.4, 129.4 (d, J = 5 Hz), 128.8, 128.0, 127.8, 127.6, 127.4, 126.2, 125.0, 124.8, 124.5 (d, J = 14 Hz), 123.2, 122.7, 121.6, 120.2, 120.1, 119.7, 114.5 (d, J = 4 Hz), 113.7, 111.9, 106.9 (d, J = 16 Hz), 61.3, 51.0, 44.3, 41.1; HRMS (ESI) m/z calcld for C₃₂H₂₅FN₂O₃S [M - H]⁻ = 535.1497, found = 535.1500; the ee value was 95%, tR (major) = 8.6 min, tR (minor) = 12.4 min (Chiralpak IE, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3g

Enantioenriched 3g
(2S,3R,4R)-2-(5,6-dichloro-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-
b]pyridine 3h

Yellowish oil; isolated yield = 98%; $[\alpha]_D^{25} = -158$ (c 2.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.24 – 8.23 (m, 1H), 7.91 (s, 1H), 7.52 – 7.42 (m, 2H), 7.41 – 7.18 (m, 7H), 6.88 – 6.77 (m, 4H), 6.64 – 6.58 (m, 2H), 5.87 (d, $J$ = 6.2 Hz, 1H), 4.68 (d, $J$ = 3.8 Hz, 1H), 4.36 – 4.29 (m, 1H), 2.28 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.2, 144.5, 141.5, 139.5, 135.0, 129.0, 128.0, 127.7, 127.6, 126.1, 125.8, 125.3, 125.0, 123.7, 123.4, 122.4, 121.7, 119.8, 119.5, 113.1, 112.6, 111.9, 61.3, 50.5, 43.3, 40.7; HRMS (ESI) m/z calc'd for C$_{32}$H$_{24}$Cl$_2$N$_2$O$_3$S [M - H]$^-$ = 585.0812, found = 585.0811; the ee value was 94%, $t_R$ (major) = 6.6 min, $t_R$ (minor) = 7.5 min (Chiralpak IE, $\lambda$ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3h

Enantioenriched 3h
(2S,3R,4R)-2-(2-methyl-1H-indol-3-yl)-1-(methylsulfonyl)-3,4-diphenyl-1,2,3,4-tetrahydrobenzofuro[3,2-
b]pyridine 3i

Brownish oil; isolated yield = 97%; $[\alpha]_{D}^{25} = -12$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.74 – 7.69 (m, 1H), 7.62 (s, 1H), 7.46 – 7.35 (m, 2H), 7.34 – 7.21 (m, 2H), 7.20 – 6.94 (m, 10H), 6.82 – 6.77 (m, 2H), 5.60 (d, $J$ = 11.0 Hz, 1H), 4.69 (d, $J$ = 11.0 Hz, 1H), 3.89 – 3.84 (m, 1H), 2.61 (s, 3H), 1.77 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.0, 146.6, 139.0, 136.8, 135.3, 134.2, 129.1, 128.7, 128.3, 128.1, 127.2, 127.0, 126.3, 124.1, 123.7, 122.9, 121.3, 121.1, 120.0, 118.9, 118.7, 111.9, 110.8, 108.8, 61.1, 57.7, 46.1, 41.9, 11.2; HRMS (ESI) m/z calcd for C$_{33}$H$_{28}$N$_2$O$_3$S [M – H]$^-$ = 531.1748, found = 531.1751; the ee value was 63%, $t_R$ (major) = 7.1 min, $t_R$ (minor) = 14.0 min (Chiralpak IE, $\lambda$ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-3-(2-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-1,2,3,4-
tetrahydrobenzofuro[3,2-b]pyridine 3j

Yellowish oil; isolated yield = 94%; \([\alpha]_{D}^{25} = -142 \) (c 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) \( \delta \) 8.01 (s, 1H), 7.92 (s, 1H), 7.69 – 7.67 (m, 1H), 7.48 – 7.46 (m, 1H), 7.37 – 7.35 (m, 3H), 7.17 – 7.06 (m, 4H), 7.01 – 6.90 (m, 5H), 6.73 (s, 2H), 6.73 (s, 1H), 4.97 (s, 1H), 4.58 (s, 1H), 2.50 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) \( \delta \) 154.1, 139.2, 135.9, 134.4, 130.0, 128.5, 127.9, 127.3, 126.4, 124.7, 123.2, 122.2, 121.4, 120.5, 120.0, 119.1, 111.9, 111.1, 59.4, 45.7, 42.1, 29.8; HRMS (ESI) m/z calcd for C₃₂H₂₅ClN₂O₃S [M - H] = 551.1202, found = 551.1191; the ee value was 90%, \( t_R \) (major) = 8.6 min, \( t_R \) (minor) = 28.8 min (Chiralpak IE, \( \lambda = 254 \) nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3j

Enantioenriched 3j
(2S,3R,4R)-3-(3-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-1,2,3,4-

tetrahydrobenzofuro[3,2-b]pyridine 3k

Yellowish oil; isolated yield = 92%; $[\alpha]_D^{25} = -105$ (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.99 – 7.91 (m, 2H), 7.56 – 7.54 (m, 1H), 7.46 – 7.44 (m, 1H), 7.36 – 7.33 (m, 2H), 7.23 – 7.22 (m, 1H), 7.14 – 6.97 (m, 9H), 6.86 – 6.80 (m, 2H), 5.75 (d, $J = 7.9$ Hz, 1H), 4.48 (d, $J = 6.6$ Hz, 1H), 4.40 – 4.33 (m, 1H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 143.9, 138.9, 135.8, 134.4, 130.0, 128.2, 128.1, 127.4, 126.8, 126.3, 125.4, 124.7, 123.6, 123.2, 122.5, 121.2, 120.2, 118.5, 111.9, 111.5, 111.3, 60.9, 52.1, 46.8, 42.1; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$ClN$_2$O$_3$S [M-H]$^{-}$ = 551.1202, found = 551.1199; the ee value was 91%, $t_R$ (major) = 10.7 min, $t_R$ (minor) = 12.8 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-3-(4-fluorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 31

Yellowish oil; isolated yield = 99%; \([\alpha]_D^{25} = -152\) (c 0.5, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 7.99 – 7.88 (m, 2H), 7.56 – 7.54 (m, 1H), 7.45 – 7.43 (m, 1H), 7.35 – 7.32 (m, 2H), 7.24 – 7.22 (m, 1H), 7.14 – 7.11 (m, 1H), 7.09 – 6.97 (m, 5H), 6.89 – 6.79 (m, 5H), 5.73 (d, \(J = 8.1\) Hz, 1H), 4.46 (d, \(J = 6.8\) Hz, 1H), 4.38 – 4.35 (m, 1H), 2.43 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl₃) \(\delta\) 161.7 (d, \(J = 245\) Hz), 154.1, 146.9, 139.0, 137.4, 137.4, 135.7, 129.5 (d, \(J = 7\) Hz), 128.2, (d, \(J = 13\) Hz), 126.8, 126.3, 125.6, 124.7, 123.6, 123.1, 122.4, 121.2, 120.2, 118.5, 115.5 (d, \(J = 21\) Hz), 111.9, 111.5, 111.3, 61.2, 51.7, 47.2, 42.2; HRMS (ESI) m/z calcd for C₃₂H₂₅FN₂O₃S [M - H]° = 535.1497, found = 535.1500; the ee value was 92%, \(t_R\) (major) = 8.1 min, \(t_R\) (minor) = 13.5 min (Chiralpak IE, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-3-(4-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3m

Yellowish oil; isolated yield = 96%; \([\alpha]^{25}_D = -152\) (c 0.5, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) δ 8.00 (s, 1H), 7.89 – 7.87 (m, 1H), 7.57 – 7.55 (m, 1H), 7.44 – 7.42 (m, 1H), 7.35 – 7.31 (m, 2H), 7.25 – 7.23 (m, 1H), 7.18 – 6.93 (m, 8H), 6.85 – 6.83 (m, 3H), 5.71 (d, \(J = 8.4\) Hz, 1H), 4.44 (d, \(J = 7.1\) Hz, 1H), 4.38 – 4.35 (m, 1H), 2.42 (s, 3H); \(^13\)C NMR (125 MHz, CDCl₃) δ 154.1, 147.1, 140.1, 138.8, 135.7, 132.8, 129.4, 128.8, 128.3, 128.2, 126.9, 126.4, 125.8, 124.7, 123.8, 123.1, 122.5, 121.1, 120.3, 120.2, 118.5, 111.9, 111.5, 111.0, 61.0, 51.9, 47.4, 42.3; HRMS (ESI) m/z calcd for C₃₂H₂₅ClN₂O₃S [M - H] = 551.1202, found = 551.1192; the ee value was 96%, \(t_R\) (major) = 9.0 min, \(t_R\) (minor) = 15.1 min (Chiralpak IE, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](image1.png)

**Racemic 3m**

![Chromatogram](image2.png)

**Enantioenriched 3m**
(2S,3R,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-3-(4-(trifluoromethyl)phenyl)-1,2,3,4-
tetrahydrobenzofuro[3,2-b]pyridine 3n

Yellowish oil; isolated yield = 98%; [α]$_D^{25}$ = -132 (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.05 (s, 1H), 7.86 – 7.84 (m, 1H), 7.60 – 7.58 (m, 1H), 7.48 – 7.38 (m, 3H), 7.35 – 7.32 (m, 2H), 7.25 (s, 1H), 7.19 – 7.03 (m, 7H), 6.90 – 6.80 (m, 2H), 5.75 (d, $J$ = 8.1 Hz, 1H), 4.51 – 4.39 (m, 2H), 2.41 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.1, 147.2, 145.7, 138.6, 135.6, 129.4, 129.1, 128.4, 128.3, 128.3, 127.1, 126.5, 126.0, 125.5, 125.5, 124.7, 124.0 (q, $J$ = 271 Hz), 123.8, 123.2, 122.6, 121.1, 120.4, 120.3, 118.4, 111.9, 111.6, 110.6, 60.7, 52.4, 47.7, 42.4; HRMS (ESI) m/z calcd for C$_{33}$H$_{25}$F$_3$N$_2$O$_3$S [M - H]$^-$ = 585.1465, found = 585.1446; the ee value was 96%, $t_R$ (major) = 6.3 min, $t_R$ (minor) = 11.3 min (Chiralpak IE, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-3-(p-tolyl)-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3o

Yellowish oil; isolated yield = 98%; \([\alpha]_D^{25} = -112\) (c 1.0, CHCl\(_3\)); \(\text{^1}{\text{H}}\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 – 8.05 (m, 1H), 7.89 (s, 1H), 7.55 – 7.53 (m, 1H), 7.47 – 7.44 (m, 1H), 7.36 – 7.32 (m, 2H), 7.18 – 7.15 (m, 1H), 7.12 – 6.97 (m, 6H), 6.97 – 6.86 (m, 2H), 6.83 – 6.82 (m, 1H), 6.78 – 6.71 (m, 2H), 5.84 (d, \(J = 7.0\) Hz, 1H), 4.56 (d, \(J = 5.5\) Hz, 1H), 4.41 – 4.34 (m, 1H), 2.35 (s, 3H), 2.27 (s, 3H); \(\text{^13}{\text{C}}\) NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.1, 146.3, 139.5, 138.8, 136.8, 135.9, 129.4, 128.0, 127.9, 127.8, 126.3, 126.1, 124.9, 124.6, 123.3, 123.1, 122.1, 121.5, 119.9, 118.6, 112.2, 111.8, 111.3, 61.5, 51.1, 45.6, 41.5; HRMS (ESI) m/z calcld for C\(_{33}\)H\(_{28}\)N\(_2\)O\(_3\)S [M - H] = 531.1748, found = 531.1759; the ee value was 92%, \(t_R\) (major) = 15.2 min, \(t_R\) (minor) = 28.1 min (Chiralpak IE, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-3-(3,4-dichlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3p

Yellowish oil; isolated yield = 98%; \([\alpha]_{D}^{25} = -138 (c 1.0, \text{CHCl}_3)\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 8.05 (s, 1H), 7.84 - 7.82 (m, 1H), 7.57 - 7.55 (m, 1H), 7.44 - 7.42 (m, 1H), 7.37 - 7.26 (m, 2H), 7.23 - 7.13 (m, 2H), 7.13 - 7.05 (m, 5H), 6.91 - 6.81 (m, 4H), 5.66 (d, \(J = 8.6 \text{ Hz}, 1H\)), 4.43 - 4.29 (m, 2H), 2.46 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 154.2, 147.1, 141.9, 138.5, 135.6, 132.5, 131.0, 130.6, 130.0, 128.4, 128.3, 127.4, 127.2, 126.4, 125.9, 124.7, 123.8, 123.2, 122.7, 121.0, 120.5, 120.3, 118.4, 111.9, 111.6, 110.5, 60.6, 52.1, 47.9, 42.5; HRMS (ESI) m/z calcld for C\(_{32}\)H\(_{24}\)Cl\(_2\)N\(_2\)O\(_3\)S [M - H] \(= 585.0812\), found = 585.0804; the ee value was 95%, \(t_R\) (major) = 11.7 min, \(t_R\) (minor) = 12.7 min (Chiralpak ID, \(\lambda = 254 \text{ nm}, 20\% \text{i-PrOH/Hexane, flow rate = 1.0 mL/min}).
(2S,3R,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-(naphthalen-2-yl)-4-phenyl-1,2,3,4-
tetrahydrobenzofuro[3,2-b]pyridine 3q

Brownish oil; isolated yield = 99%; \([\alpha]_{D}^{25} = -139\) (c 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.99 – 7.92 (m, 1H), 7.90 – 7.85 (m, 1H), 7.78 – 7.65 (m, 2H), 7.64 – 7.61 (m, 2H), 7.51 – 7.31 (m, 5H), 7.35 – 7.25 (m, 1H), 7.22 – 7.15 (m, 1H), 7.15 – 7.03 (m, 2H), 7.02 – 6.94 (m, 3H), 6.87 – 6.77 (m, 3H), 5.92 (d, \(J = 8.0\) Hz, 1H), 4.65 (d, \(J = 6.6\) Hz, 1H), 4.59 – 4.55 (m, 1H), 2.29 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 154.1, 147.3, 139.3, 139.0, 135.7, 133.2, 132.4, 128.6, 128.2, 128.1, 127.8, 127.6, 127.1, 126.7, 126.5, 126.2, 125.9, 125.7, 124.6, 123.8, 123.1, 122.3, 121.3, 120.2, 120.1, 118.6, 111.9, 111.4, 61.2, 52.3, 46.9, 42.0; HRMS (ESI) m/z calcd for C\(_{36}\)H\(_{28}\)N\(_2\)O\(_3\)S [M - H]\(^-\) = 567.1748, found = 567.1752; the ee value was 97%, \(t_R\) (major) = 19.6 min, \(t_R\) (minor) = 25.6 min (Chiralpak IE, \(\lambda = 254\) nm, 20% \(i\)-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3S,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-phenyl-3-(thiophen-2-yl)-1,2,3,4-tetrahydrobenzofuro[3,2-
b]pyridine 3r

Brownish oil; isolated yield = 98%; [α]$_D^{25}$ = −60 (c 0.5, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.21 – 8.14 (m, 1H), 7.85 (s, 1H), 7.52 – 7.43 (m, 2H), 7.40 – 7.30 (m, 2H), 7.19 – 6.93 (m, 4H), 6.92 – 6.79 (m, 5H), 6.78 – 6.67 (m, 2H), 5.98 (d, $J$ = 5.3 Hz, 1H), 4.71 – 4.68 (m, 2H), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.2, 145.4, 139.2, 136.2, 127.6, 126.9, 126.2, 125.6, 124.8, 124.4, 124.1, 123.2, 122.7, 122.1, 121.7, 119.8, 119.3, 118.6, 112.4, 111.9, 111.2, 61.8, 46.7, 45.9, 41.1; HRMS (ESI) m/z calcd for C$_{30}$H$_{24}$N$_2$O$_3$S$_2$ [M - H]$^-$ = 523.1156, found = 523.1144; the ee value was 65%, $t_R$ (major) = 12.9 min, $t_R$ (minor) = 35.9 min (Chiralpak IE, $\lambda$ = 254 nm, 20% i-ProOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(2-fluorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3s

Yellowish oil; isolated yield = 90%; [α]D\(^{25}\) = -117 (c 1.0, CHCl₃); \(^1\)H NMR (500 MHz, CDCl₃) δ 8.24 – 8.23 (m, 1H), 7.84 (s, 1H), 7.55 – 7.46 (m, 2H), 7.41 – 7.20 (m, 6H), 7.13 – 6.93 (m, 3H), 6.83 – 6.71 (m, 2H), 6.68 – 6.60 (m, 1H), 6.48 – 6.45 (m, 1H), 6.25 (s, 1H), 5.98 (d, J = 5.3 Hz, 1H), 4.93 (d, J = 3.9 Hz, 1H), 4.53 – 4.48 (m, 1H), 2.35 (s, 3H); \(^1\)C NMR (125 MHz, CDCl₃) δ 160.5 (d, J = 244 Hz), 154.1, 141.6, 136.5, 129.2 (d, J = 4 Hz), 128.8, 127.9, 127.7, 127.4, 126.2 (d, J = 13 Hz), 125.4, 124.8, 123.6, 123.0, 122.8, 122.5, 122.0, 121.8, 120.1, 119.7, 118.6, 114.7 (d, J = 22 Hz), 113.3, 111.9, 111.2, 61.7, 48.6, 40.9, 37.6; HRMS (ESI) m/z calcd for C\(_{32}\)H\(_{25}\)FN\(_2\)O\(_3\)S [M - H] = 535.1497, found = 535.1487; the ee value was 92%, t\(_R\) (major) = 10.1 min, t\(_R\) (minor) = 18.0 min (Chiralpak IE, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(2-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3t

Yellowish oil; isolated yield = 82%; $\left[\alpha\right]_D^{25} = -26$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.38 (s, 1H), 7.80 (s, 1H), 7.53 – 7.21 (m, 9H), 7.10 – 6.83 (m, 5H), 6.60 – 6.41 (m, 2H), 6.05 – 6.00 (m, 1H), 5.02 (s, 1H), 4.62 (s, 1H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 142.0, 136.7, 133.1, 131.6, 129.2, 128.9, 127.9, 127.6, 127.0, 125.2, 125.1, 125.0, 123.4, 123.0, 122.1, 121.9, 120.3, 119.6, 118.5, 114.0, 112.4, 111.9, 111.0, 61.9, 47.1, 40.6, 39.6; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$ClN$_2$O$_3$S [M - H$^-$] = 551.1202, found = 551.1191; the ee value was 89%, $t_R$ (major) = 8.7 min, $t_R$ (minor) = 18.5 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(3-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-
tetrahydrobenzofuro[3,2-b]pyridine 3u

![Chemical Structure](image)

Yellowish oil; isolated yield = 84%; [α]_{D}^{25} = -51 (c 1.0, CHCl₃); H NMR (500 MHz, CDCl₃) δ 8.23 – 8.18 (m, 1H), 7.86 (s, 1H), 7.52 – 7.24 (m, 8H), 7.15 – 6.91 (m, 3H), 6.82 – 6.58 (m, 4H), 6.36 (s, 1H), 5.94 (d, J = 5.1 Hz, 1H), 4.59 (d, J = 3.6 Hz, 1H), 4.39 – 4.37 (m, 1H), 2.30 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl₃) δ 154.3, 143.4, 141.8, 136.4, 133.2, 129.5, 129.0, 128.9, 128.0, 127.8, 127.7, 126.2, 126.1, 125.5, 125.1, 124.1, 123.4, 122.4, 122.2, 122.0, 120.2, 119.9, 118.6, 112.8, 112.1, 111.3, 61.5, 50.3, 43.2, 41.2; HRMS (ESI) m/z calcd for C_{32}H_{25}ClN_{2}O_{3}S [M - H] = 551.1202, found = 551.1197; the ee value was 83%, t_R (major) = 12.0 min, t_R (minor) = 30.4 min (Chiralpak IE, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(3-bromophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3v

Yellowish oil; isolated yield = 80%; $[\alpha]_{D}^{25} = -116$ (c 0.4, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.27 – 8.25 (m, 1H), 7.89 (s, 1H), 7.55 – 7.29 (m, 8H), 7.19 – 6.93 (m, 3H), 6.84 (s, 2H), 6.70 – 6.67 (m, 2H), 6.51 (s, 1H), 5.99 (d, $J = 4.6$ Hz, 1H), 4.63 (s, 1H), 4.42 (s, 1H), 2.34 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.2, 142.0, 141.7, 136.3, 130.5, 129.1, 129.0, 127.9, 127.6, 126.4, 125.3, 125.0, 123.8, 123.4, 122.1, 122.0, 121.4, 120.0, 119.8, 118.5, 112.0, 111.2, 61.4, 50.0, 42.8, 41.1; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$BrN$_2$O$_3$S [M - H]$^- = 595.0696$, found = 595.0698; the ee value was 89%, $t_R$ (major) = 12.4 min, $t_R$ (minor) = 34.5 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3v

Enantioenriched 3v
(2S,3R,4R)-2-((1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-4-(3-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3w

Yellowish oil; isolated yield = 92%; $[\alpha]_D^{25} = -93$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.29 – 8.28 (m, 1H), 7.84 (s, 1H), 7.55 – 7.24 (m, 8H), 7.09 – 6.70 (m, 8H), 6.02 (d, $J = 4.7$ Hz, 1H), 4.72 (d, $J = 2.8$ Hz, 1H), 4.48 – 4.43 (m, 1H), 2.33 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.2, 141.6, 140.8, 136.3, 130.8, 129.6, 129.3, 129.0, 127.9, 127.9, 127.7, 125.1, 124.1, 123.9 (q, $J = 271$ Hz), 123.5, 123.4, 122.7, 122.1, 122.0, 120.2, 119.7, 118.4, 112.8, 111.9, 111.3, 61.4, 49.9, 42.7, 41.0; HRMS (ESI) m/z calcd for C$_{33}$H$_{25}$F$_3$N$_2$O$_3$S [M - H]$^-$ = 585.1465, found = 585.1470; the ee value was 90%, $t_R$ (major) = 8.1 min, $t_R$ (minor) = 19.2 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

**Racemic 3w**

**Enantioenriched 3w**
(2S,3R,4R)-4-(4-fluorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3x

Yellowish oil; isolated yield = 93%; [α]D^25 = −113 (c 1.0, CHCl₃); ^1H NMR (500 MHz, CDCl₃) δ 8.10 – 8.04 (m, 1H), 7.93 (s, 1H), 7.56 – 7.32 (m, 6H), 7.25 – 7.14 (m, 9H), 7.14 – 7.00 (m, 4H), 6.82 – 6.81 (m, 1H), 6.72 – 6.56 (m, 5H), 5.88 (d, J = 6.8 Hz, 1H), 4.57 (d, J = 5.4 Hz, 1H), 4.41 – 4.35 (m, 1H), 2.33 (s, 3H); ^13C NMR (125 MHz, CDCl₃) δ 161.3 (d, J = 244 Hz), 154.1, 145.7, 141.6, 136.0, 135.2 (d, J = 3 Hz), 129.4 (d, J = 8 Hz), 128.8, 128.0, 127.3, 126.0, 124.8, 123.2, 123.1, 122.3, 121.6, 120.1, 112.0, 118.5, 114.6 (d, J = 22 Hz), 112.0, 111.8, 111.4, 61.4, 51.4, 44.7, 41.5; HRMS (ESI) m/z calcd for C_{32}H_{25}FN_{2}O_{3}S [M - H]^- = 535.1497, found = 535.1492; the ee value was 95%, t_R (major) = 10.4 min, t_R (minor) = 20.3 min (Chiralpak IE, λ = 254 nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(4-chlorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3y

Yellowish oil; isolated yield = 83%; $[\alpha]_{D}^{25} = -50$ (c 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.10 – 8.08 (m, 1H), 7.90 (s, 1H), 7.59 – 7.31 (m, 4H), 7.28 – 6.99 (m, 7H), 6.86 – 6.84 (m, 3H), 6.64 – 6.62 (m, 2H), 5.89 (d, $J = 6.5$ Hz, 1H), 4.57 (d, $J = 4.9$ Hz, 1H), 4.40 – 4.37 (m, 1H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 141.6, 138.0, 136.0, 132.1, 129.1, 128.8, 128.3, 128.0, 127.9, 127.4, 125.9, 125.4, 124.9, 124.7, 123.3, 123.0, 122.4, 121.7, 120.2, 120.0, 118.6, 111.8, 111.4, 61.4, 53.5, 51.0, 41.5; HRMS (ESI) m/z calcd for C$_{32}$H$_{25}$ClN$_2$O$_3$S [M - H]$^- = 551.1202$, found = 551.1204; the ee value was 91%, $t_{R}$ (major) = 11.7 min, $t_{R}$ (minor) = 22.0 min (Chiralpak IE, $\lambda = 254$ nm, 20% $i$-PrOH/Hexane, flow rate = 1.0 mL/min).
(2S,3R,4R)-4-(4-bromophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3z

Yellowish oil; isolated yield = 80%; $[\alpha]_D^{25} = -160$ (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.11 – 8.09 (m, 1H), 7.88 (s, 1H), 7.54 – 7.44 (m, 2H), 7.40 – 7.31 (m, 2H), 7.31 – 7.15 (m, 5H), 7.13 – 7.10 (m, 1H), 7.05 – 6.95 (m, 3H), 6.84 – 6.80 (m, 1H), 6.57 – 6.55 (m, 2H), 5.90 (d, $J = 6.6$ Hz, 1H), 4.55 (d, $J = 5.0$ Hz, 1H), 4.40 – 4.38 (m, 1H), 2.31 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.1, 141.5, 138.6, 136.1, 130.8, 129.5, 128.9, 128.0, 127.4, 124.9, 124.6, 123.3, 122.9, 122.4, 121.7, 120.2, 120.0, 118.5, 112.2, 111.8, 111.5, 61.4, 50.8, 44.4, 41.5; HRMS (ESI) m/z calced for C$_{32}$H$_{25}$BrN$_2$O$_3$S [M - H]$^-$ = 595.0696, found = 595.0685; the ee value was 89%, $t_R$ (major) = 11.5 min, $t_R$ (minor) = 20.8 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

![Chromatogram](image1.png)

![Peak Table](image2.png)

Racemic 3z

![Chromatogram](image3.png)

![Peak Table](image4.png)

Enantioenriched 3z

S32
(2S,3R,4R)-4-(3-chloro-2-fluorophenyl)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3a’

Yellowish oil; isolated yield = 90%; \( [\alpha]_D^{25} = -75 \) (c 0.5, CHCl\(_3\)); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 8.34 – 8.28 (m, 1H), 7.81 (s, 1H), 7.53 – 7.47 (m, 2H), 7.43 – 7.20 (m, 6H), 7.12 – 6.97 (m, 3H), 6.85 – 6.68 (m, 2H), 6.31 – 6.28 (m, 1H), 6.06 – 5.90 (m, 2H), 4.92 (d, \( J = 3.1 \) Hz, 1H), 4.58 – 4.53 (m, 1H), 2.31 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 155.8 (d, \( J = 247 \) Hz), 154.2, 141.4, 136.7, 129.0, 128.1, 128.0, 127.8, 127.6 (d, \( J = 4 \) Hz), 125.2, 123.6, 123.4, 123.0 (d, \( J = 5 \) Hz), 122.2 (d, \( J = 8 \) Hz), 120.3, 119.9, 118.6, 113.7, 112.0, 111.2, 61.8, 47.5, 40.8, 37.2; HRMS (ESI) m/z calcld for C\(_{32}\)H\(_{24}\)ClFN\(_2\)O\(_3\)S [M - H]\(^-\) = 569.1107, found = 569.1105; the ee value was 97%, \( t_R \) (major) = 10.1 min, \( t_R \) (minor) = 23.8 min (Chiralpak IE, \( \lambda = 254 \) nm, 20% \( i\)-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3a’  Enantioenriched 3a’
(2S,3R,4R)-2-(1H-indol-3-yl)-1-(methylsulfonyl)-4-(naphthalen-2-yl)-3-phenyl-1,2,3,4-tetrahydrobenzofuro[3,2-b]pyridine 3b’

Yellowish oil; isolated yield = 85%; $\left[\alpha\right]_D^{25} = -135$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.10 – 8.04 (m, 1H), 7.81 (s, 1H), 7.64 – 7.51 (m, 2H), 7.48 – 7.29 (m, 6H), 7.21 – 7.17 (m, 5H), 7.07 (s, 1H), 7.03 – 6.85 (m, 5H), 5.90 (d, $J = 7.1$ Hz, 1H), 4.74 (d, $J = 5.6$ Hz, 1H), 4.56 – 4.50 (m, 1H), 2.37 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.1, 141.8, 136.8, 135.8, 133.0, 132.2, 128.7, 128.1, 127.8, 127.6, 127.4, 127.2, 127.2, 126.1, 125.9, 125.7, 125.4, 125.1, 124.6, 123.4, 123.2, 122.14 121.5, 120.1, 119.9, 118.5, 111.9, 111.1, 61.5, 51.1, 46.0, 41.7; HRMS (ESI) m/z calcd for C$_{36}$H$_{28}$N$_2$O$_3$S [M - H] = 567.1748, found = 567.1754; the ee value was 87%, $t_R$ (major) = 15.3 min, $t_R$ (minor) = 34.1 min (Chiralpak IE, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 3b’

Enantioenriched 3b’
(E)-N-(2-(phenyl(2-styryl-1H-indol-3-yl)methyl)benzofuran-3-yl)methanesulfonamide 5

Yellowish oil; isolated yield = 95%; $[\alpha]_D^{25} = +75$ (c 1.0, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.34 (s, 1H), 7.58 – 7.56 (m, 1H), 7.49 – 7.34 (m, 4H), 7.34 – 7.14 (m, 13H), 7.02 – 6.99 (m, 1H), 6.83 (d, $J = 16.3$ Hz, 1H), 6.49 (s, 1H), 6.09 (d, $J = 13.3$ Hz, 1H), 2.87 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 156.2, 153.3, 139.9, 136.7, 136.6, 133.8, 128.9, 128.6, 128.5, 128.3, 127.9, 127.9, 127.0, 126.5, 125.8, 124.8, 123.6, 123.4, 120.6, 120.2, 118.7, 117.0, 114.2, 113.5, 112.2, 110.7, 40.3, 38.9; HRMS (ESI) m/z calcd for C$_{32}$H$_{26}$N$_2$O$_3$S $[\text{M - H}]^-$ = 517.1591, found = 517.1590; the ee value was 92%, $t_R$ (major) = 5.2 min, $t_R$ (minor) = 6.0 min (Chiralpak IC, $\lambda = 254$ nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).

Racemic 5

Enantioenriched 5

![Chromatogram](image1)

![Chromatogram](image2)

![Peak Table](image3)

![Peak Table](image4)
Off white oil; isolated yield = 96%; \([\alpha]_D^{25} = -35.5\) (c 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.30 – 8.20 (m, 1H), 7.88 – 7.86 (m, 1H), 7.57 – 7.06 (m, 12H), 6.82 – 6.79 (m, 3H), 6.71 – 6.61 (m, 2H), 5.92 – 5.91 (m, 1H), 4.71 (d, \(J = 3.6\) Hz, 1H), 4.35 – 4.32 (m, 1H), 2.41 (s, 3H), 1.53 (s, 9H); \(^13\)C NMR (126 MHz, CDCl₃) \(\delta\) 154.10, 149.27, 143.98, 141.49, 139.22, 135.47, 128.94, 128.37, 128.02, 127.99, 127.69, 127.63, 127.41, 126.12, 126.08, 125.15, 124.88, 124.77, 124.21, 123.34, 122.40, 122.21, 121.80, 119.60, 118.75, 117.55, 115.19, 111.77, 83.61, 60.83, 50.27, 42.69, 40.71, 28.03, 27.95, 27.72; HRMS (ESI) m/z calcd for C₃₇H₅₅N₂O₅S [M + H]⁺ = 619.2261, found = 619.2278; the ee value was 90%, \(t_R\) (major) = 20.5 min, \(t_R\) (minor) = 34.4 min (Chiralpak IE, \(\lambda = 254\) nm, 20% i-PrOH/Hexane, flow rate = 0.5 mL/min).
Pale yellow oil; isolated yield = 93%; \([\alpha]^{25}_D = -33.8\) (c 1.0, MeOH); \(^1^H\) NMR (400 MHz, CD\(_3\)CN) \(\delta\) 8.68 (s, 1H), 7.63 – 7.53 (m, 2H), 7.36 (d, \(J = 7.8\) Hz, 1H), 7.32 – 7.21 (m, 5H), 7.19 – 7.14 (m, 1H), 7.04 – 6.90 (m, 9H), 6.40 (d, \(J = 2.2\) Hz, 1H), 4.81 (d, \(J = 11.4\) Hz, 1H), 3.92 (td, \(J = 11.4, 3.3\) Hz, 1H), 3.02 (dd, \(J = 14.5, 11.4\) Hz, 1H), 2.90 – 2.82 (m, 4H); \(^{13}\)C NMR (100 MHz, CD\(_3\)CN) \(\delta\) 156.9, 153.8, 143.4, 140.7, 136.7, 129.4, 129.3, 128.6, 128.3, 127.9, 127.1, 126.6, 125.3, 124.0, 123.2, 121.7, 119.9, 119.2, 118.8, 115.2, 113.6, 112.0, 111.7, 51.3, 49.0, 40.5, 31.1; HRMS (ESI) m/z calcd for C\(_{32}\)H\(_{27}\)N\(_2\)O\(_3\)S [M - H] = 519.1748, found = 519.1760; the ee value was 89%, \(t_R\) (major) = 16.4 min, \(t_R\) (minor) = 11.1 min (Chiralpak AD-H, \(\lambda = 254\) nm, 20% i-PrOH/Hexane, flow rate = 1.0 mL/min).
D. X-Ray Crystallographic Analysis and Determination of the Absolute Configurations of Product 3b

![X-ray structure of 3b](image)

Table 1. Crystal data and structure refinement for K255.

<table>
<thead>
<tr>
<th>Identification code</th>
<th>K255</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C35 H32 F N2 O3 S</td>
</tr>
<tr>
<td>Formula weight</td>
<td>579.68</td>
</tr>
<tr>
<td>Temperature</td>
<td>100(2) K</td>
</tr>
<tr>
<td>Wavelength</td>
<td>0.71073 Å</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Orthorhombic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁2₁2₁</td>
</tr>
<tr>
<td>Unit cell dimensions</td>
<td>a = 10.8396(7) Å (= 90°)</td>
</tr>
<tr>
<td></td>
<td>b = 14.8000(10) Å (= 90°)</td>
</tr>
<tr>
<td></td>
<td>c = 20.0419(13) Å (= 90°)</td>
</tr>
<tr>
<td>Volume</td>
<td>3215.2(4) Å³</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
</tr>
<tr>
<td>Density (calculated)</td>
<td>1.198 Mg/m³</td>
</tr>
<tr>
<td>Absorption coefficient</td>
<td>0.142 mm$^{-1}$</td>
</tr>
</tbody>
</table>
F(000) 1220
Crystal size 0.340 x 0.272 x 0.051 mm³
Theta range for data collection 2.753 to 29.756°.
Index ranges -15<=h<=15, -20<=k<=20, -25<=l<=27
Reflections collected 46293
Independent reflections 9075 [R(int) = 0.0911]
Completeness to theta = 25.242° 99.7 %
Absorption correction Semi-empirical from equivalents
Max. and min. transmission 0.7459 and 0.5968
Refinement method Full-matrix least-squares on F²
Data / restraints / parameters 9075 / 49 / 409
Goodness-of-fit on F² 1.066
Final R indices [I>2sigma(I)] R1 = 0.0703, wR2 = 0.1644
R indices (all data) R1 = 0.1416, wR2 = 0.2051
Absolute structure parameter -0.03(5)
Extinction coefficient 0.025(3)
Largest diff. peak and hole 0.730 and -0.534 e.Å⁻³

**E. References**


F. $^1$H and $^{13}$C NMR Spectra of Products
HSQC