Enantioselective Intramolecular Cyclization of Alkynyl Esters

Catalyzed by Chiral Brønsted Base

Azusa Kondoh, Hoa Thi Quynh Tran, Kyoko Kimura and Masahiro Terada*

Research and Analytical Center for Giant Molecules, Graduate School of Science, Tohoku University, Aoba-Ku, Sendai 980-8578, Japan
Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-Ku, Sendai 980-8578, Japan

Contents

General Information S1
Experimental Procedure S2
Screening of Chiral Schiff Bases S6
Analytical Data S7
NOE Analysis of 3a and 6 S16
$^1$H NMR and $^{13}$C NMR Spectra of 1 – 7 S18
General Information

Unless otherwise noted, the reactions were carried out with dried glassware under argon atmosphere. $^1$H NMR spectra were recorded on a JEOL JNM-ECA600 (600 MHz) spectrometer. Chemical shifts are reported in ppm from the solvent resonance or tetramethylsilane (TMS) as the internal standard (CDCl$_3$: 7.26 ppm, TMS: 0.00 ppm). Data are reported as follows: chemical shift, integration, multiplicity ($s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $m$ = multiplet), and coupling constants (Hz). $^{13}$C NMR spectra were recorded on a JEOL JNM-ECA600 (150 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from the solvent resonance as the internal standard (CDCl$_3$: 77.0 ppm). Analytical thin layer chromatography (TLC) was performed on Merck precoated TLC plates (silica gel 60 GF$_{254}$, 0.25 mm). Flash column chromatography was performed on silica gel 60N (spherical, neutral, 40-50 µm; Kanto Chemical Co., Inc.). High-performance liquid chromatography (HPLC) was performed on a Jasco equipped with a variable wavelength detector using Daicel chiral column (0.46 × 25 cm). Optical rotations were measured on a Jasco P-1020 digital polarimeter with a sodium lamp and reported as follows; $[\alpha]^\infty_D$ ($c$ = g/100 mL, solvent). High resolution mass spectra analysis was performed on a Bruker Daltonics solariX 9.4T FT-ICR-MS spectrometer at the Instrumental Analysis Center for Chemistry, Graduate School of Science, Tohoku University.

Materials: Unless otherwise noted, materials were purchased from Wako Pure Chemical Industries, Ltd., Tokyo Chemical Industry Co., LTD., Aldrich Inc., and other commercial suppliers and were used without purification. Dichloromethane, tetrahydrofuran and toluene were supplied from Kanto Chemical Co., Inc. as “Dehydrated solvent system”. Other solvents were purchased from commercial suppliers as dehydrated solvents, and used under argon atmosphere.
Experimental Procedure

Procedure for Preparation of Chiral Schiff Base 1

3,5-Di-tert-butylsalicylaldehyde (0.23 g, 1.0 mmol) was added to a solution of L-Valinol (0.11 mL, 1.0 mmol) in EtOH (1.0 mL). The resulting mixture was stirred at 80 °C for overnight. Then, solvent was removed under reduced pressure. After purification by flash column chromatography, the pure Schiff base 1a was obtained (0.30 g, 0.94 mmol, 94%) as a yellow solid.

Procedure for Preparation of Alkynyl Ester 2

Alkynyl esters 2 were synthesized according to the procedure described in the literature.1 Synthesis of 2a is representative.

*Synthesis of S1*

2-iodophenol (2.2 g, 10 mmol) was added portionwise to a suspension of NaH (0.60 g, 15 mmol) in THF (50 mL) at 0 °C. After stirred for 5 min, chloromethyl methyl ether (1.5 mL, 20 mmol) was added. The reaction mixture was then allowed to warm to room temperature, and further stirred for 24 h. The reaction was quenched with H₂O at 0 °C, and the product was extracted with Et₂O. The combined organic layer was washed with H₂O (x2) and brine, dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (AcOEt/Hexane = 1/25) to afford S1 (2.31 g, 87% yield) as a colorless oil.

---

Synthesis of $S_2$

$S_1$ (1.3 g, 5.0 mmol) and phenylacetylene (0.55 mL, 5.0 mmol) in triethylamine (33 mL). The resulting mixture was stirred at 50 °C until the reaction was completed as determined by TLC. Then, the mixture was cooled to room temperature. AcOEt was added to the mixture, and the mixture was filtrated through a pad of celite. After concentrated and purified by flash column chromatography (Et$_2$O / Hexane = 1/10), $S_2$ was obtained (1.1 g, 4.8 mmol, 96%) as a colorless oil.

Synthesis of $S_3$

To a solution of $S_2$ (1.1 g, 4.5 mmol) in a mixture of THF (4.5 mL) and isopropanol (4.5 mL) was added dropwise 2.0 mL of 6N HCl aq. The reaction was stirred for 24 h. The reaction mixture was extracted with Et$_2$O and the combined organic layer was washed with H$_2$O and brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The purification of the crude mixture by flash column chromatography (Et$_2$O / Hexane = 1/10) provided $S_3$ (0.80 g, 4.1 mmol, 92%) as a colorless oil.

Synthesis of $2a$

To a solution of $S_3$ (0.78 g, 4.0 mmol) in acetonitrile (4.0 mL) was added K$_2$CO$_3$ (1.1 g, 8.0 mmol). After stirring for 5 min ethyl 2-bromopropionate (0.60 mL, 4.8 mmol) was added to the reaction mixture. The mixture was further stirred for 24 h and then extracted with Et$_2$O. The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated. The purification by flash column chromatography (Et$_2$O / Hexane = 1/10) followed by recrystallization from hexane afforded $2a$ (0.94 g, 3.2 mmol, 80%) as a white solid.
For the synthesis of 2m and 2n, the corresponding ethyl α-bromoacetate derivatives were prepared as follows.

**Synthesis of S5**

To a solution of potassium tert-butoxide (1.3 g, 10.3 mmol) in THF (25 mL) were added ethyl acetoacetate (1.3 mL, 10 mmol) and tert-butanol (0.10 mL, 1.0 mmol) at 0 °C. After stirring for 30 min, benzyl bromide (1.2 mL, 10 mmol) was added. The resulting mixture was then heated at reflux for 12 h. After cooled to room temperature, the reaction was quenched with H₂O, and sat. aq. NaHCO₃ was added. The mixture was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. After purification by flash column chromatography (AcOEt/Hexane = 1/15), S4 was obtained (1.62 g, 7.4 mmol, 74%) as a colorless oil.

To a solution of sodium ethoxide (0.50 g, 7.4 mmol) in ethanol (12 mL) were slowly added S4 (1.6 g, 7.4 mmol) and N-bromosuccinimide (1.3 g, 7.4 mmol) at −35 °C. The mixture was allowed to warm to room temperature and stirred for 5 h. The reaction was quenched with H₂O, and then the product was extracted with Et₂O. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. After purification by flash column chromatography (Et₂O/Hexane = 1/25), S5 was obtained (1.2 g, 4.5 mmol, 62%) as a colorless oil.

**Synthesis of S7**

To a solution of α-bromo-γ-butyrolactone (1.8 mL, 16 mmol) in ethanol (16 mL) at 0 °C was added dropwise 4.0 mL of conc. H₂SO₄. After stirring at room temperature for 5 min, the resulted mixture was allowed to be heated at reflux for 24 h. Then, the reaction mixture was cooled to room temperature and brought to pH 3 with sat. aq. NaHCO₃, followed by extraction with AcOEt. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. After purification by a short-pass column chromatography (AcOEt/Hexane = 1/4), a mixture of S6 and α-bromo-γ-butyrolactone was obtained (ratio = ca. 3 : 1). The mixture thus obtained was dissolved in CH₂Cl₂ (30 mL). Then, triethylamine (2.9 mL, 40 mmol) and tert-butyl(chloro)dimethylsilane (4.8 g, 32 mmol) were added to the solution at 0 °C. After stirring for 24 h at room temperature, the mixture was extracted with CH₂Cl₂. The combined organic layer was washed with brine, dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash column chromatography (AcOEt/Hexane = 1/15) to provide S7 (2.2 g, 6.8 mmol, 43% over 2 steps) as a colorless oil.

---


S4
Typical Procedure for Enantioselective Intramolecular Cyclization

The reaction of 2a is representative (Table 1, entry 17). To a solution of 1 (6.4 mg, 0.020 mmol) and 1,1-diphenylethanol (4b, 4.0 mg, 0.020 mmol) in toluene (0.60 mL) was added a solution of t-BuOK in THF (1.0 M, 60 μL, 0.060 mmol). The mixture was stirred for 10 min at room temperature. Then, the mixture was cooled to −40 °C. After stirring for 5 min, a solution of 2a (59 mg, 0.20 mmol) in toluene (0.40 mL) was added. The resulting mixture was stirred at −40 °C for 24 h. The reaction was quenched with sat. aq. NH₄Cl, and then extracted with AcOEt. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was purified by flash column chromatography (Et₂O/Hexane = 1/25) to afford 3a (53 mg, 0.18 mmol, 90%) as a colorless oil. The E/Z ratio was determined by ¹H NMR analysis after purification by flash column chromatography. The enantiomeric excess was calculated by HPLC analysis for Z isomer.

Procedure for Transformation of 3 into 5 (Scheme 2a)

The reaction of 3a is representative. NaBH₄ (0.11 g, 3.0 mmol) was added portionwise to a solution of 3a (90% ee, 59 mg, 0.20 mmol) in a mixture of THF (0.50 mL) and methanol (0.50 mL) at 0 °C. The mixture was allowed to warm to room temperature, and then stirred for additional 3 h. The reaction was quenched with sat. aq. NH₄Cl, and then the product was extracted with AcOEt. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. Purification of the crude mixture by flash column chromatography (AcOEt/Hexane = 1/10) provided 5a (46 mg, 0.18 mmol, 90%, 90% ee) as a white solid.

Procedure for Hydrogenation of 3a into 6 (Scheme 2b)

A mixture of 3a (90% ee, 59 mg, 0.20 mmol), 10% Pd/C (10 wt %, 11 mg) in MeOH (1.0 mL) was vigorously stirred at room temperature under hydrogen atmosphere (balloon, 1 atm) for 2.5 h. The reaction mixture was filtered through a thick pad of Celite, and the filtrate was concentrated. After purification by flash column chromatography (Et₂O/Hexane = 1/25), 6 was obtained (54 mg, 91%, dr = >95:5, 90% ee) as a white solid. The ratio of diastereomers was determined by ¹H NMR analysis after flash column chromatography and the enantiomeric excess was calculated by HPLC analysis for the major diastereomer.
Procedure for Hydrogenation of 3n into 7 (Scheme 2c)

To a solution of 3n (78% ee, 73 mg, 0.15 mmol) in THF (0.75 mL) was added a solution of tetrabutylammonium fluoride in THF (1.0 M, 0.45 mL, 0.45 mmol). The mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NaHCO₃, and then the product was extracted with AcOEt. The combined organic layer was dried over Na₂SO₄, filtered, and concentrated. The residue was purified by flash column chromatography (Et₂O /Hexane = 1/8) to afford 7 (37 mg, 0.13 mmol, 90%, 77% ee) as a white solid.

Screening of Chiral Schiff Bases

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Yield (%)ᵃ</th>
<th>Z/Eᵃ</th>
<th>%ee (Z)ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i-Pr</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>H</td>
<td>84</td>
<td>95/5</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>H</td>
<td>82</td>
<td>&gt;95/5</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>H</td>
<td>t-Bu</td>
<td>H</td>
<td>90</td>
<td>&gt;95/5</td>
<td>59</td>
</tr>
<tr>
<td>4</td>
<td>i-Pr</td>
<td>H</td>
<td>i-Pr</td>
<td>H</td>
<td>88</td>
<td>94/6</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>i-Pr</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>92</td>
<td>&gt;95/5</td>
<td>6</td>
</tr>
<tr>
<td>6</td>
<td>i-Pr</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>86</td>
<td>95/5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr</td>
<td>H</td>
<td>Ph₃Si</td>
<td>H</td>
<td>83</td>
<td>93/7</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>i-Pr</td>
<td>H</td>
<td>i-Pr₃Si</td>
<td>H</td>
<td>81</td>
<td>&gt;95/5</td>
<td>49</td>
</tr>
<tr>
<td>9ᶜ</td>
<td>i-Pr</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>Ph</td>
<td>75</td>
<td>&gt;95/5</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr</td>
<td>t-Bu</td>
<td>t-Bu</td>
<td>Ph</td>
<td>89</td>
<td>94/6</td>
<td>9</td>
</tr>
</tbody>
</table>

ᵃ Determined by ¹H NMR analysis after column chromatography.
ᵇ Enantiomeric excess was determined by chiral stationary phase HPLC analysis for Z isomer.
ᶜ The reaction was conducted for 6 h.
Analytical Data

(S)-2,4-di-tert-butyl-6-{(1-hydroxy-3-methylbutan-2-ylamino)methyl}phenol (1): yellow solid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 0.95 (3H, d, $J = 6.6$ Hz), 0.97 (3H, d, $J = 6.6$ Hz), 1.31 (9H, s), 1.45 (9H, s), 1.94 (1H, dq, $J = 6.6, 6.6, 6.6$ Hz), 3.03 (1H, ddd, $J = 9.0, 6.6, 3.6$ Hz), 3.76-3.78 (1H, m), 3.82-3.85 (1H, m), 7.13 (1H, d, $J = 2.4$ Hz), 7.40 (1H, d, $J = 2.4$ Hz), 8.38 (1H, s); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 18.8, 19.8, 29.4, 30.1, 31.5, 34.1, 35.0, 64.7, 77.9, 117.7, 126.1, 127.1, 136.7, 140.2, 158.1, 167.1.

Ethyl 2-(2-phenylethylnaphthoxy)propanoate (2a): white solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.25 (3H, dd, $J = 7.2, 7.2$ Hz), 1.70 (3H, d, $J = 6.6$ Hz), 4.20 (1H, dq, $J = 10.8, 7.2$ Hz), 4.23 (1H, dq, $J = 10.8, 7.2$ Hz), 4.86 (1H, q, $J = 6.6$ Hz), 6.87 (1H, ddd, $J = 8.4, 1.2$ Hz), 6.99 (1H, ddd, $J = 7.8, 7.2, 1.2$ Hz), 7.23-7.26 (1H, m), 7.31-7.36 (3H, m), 7.50 (1H, dd, $J = 7.2, 1.8$ Hz), 7.53-7.55 (2H, m); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 18.6, 61.2, 74.5, 85.6, 93.8, 114.3, 115.2, 122.0, 123.6, 128.1, 128.2, 129.4, 131.5, 133.5, 158.4, 171.9; IR (ATR) 2985, 2219, 1750, 1733, 1497, 1482, 1444, 1275, 1236, 1194, 1131, 1094, 1046, 948, 860 cm$^{-1}$; HRMS (ESI) Calcd for C$_{16}$H$_{13}$NaO$_3$ [M+Na]$^+$ 317.1148, Found 317.1148.

Ethyl 2-(2-(4-ethoxycarbonylphenylethynaphthoxy)propanoate (2b): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.25 (3H, dd, $J = 7.2, 7.2$ Hz), 1.70 (3H, d, $J = 6.6$ Hz), 4.21 (1H, dq, $J = 10.8, 7.2$ Hz), 4.24 (1H, dq, $J = 10.8, 7.2$ Hz), 4.38 (2H, q, $J = 7.2$ Hz), 4.84 (1H, q, $J = 6.6$ Hz), 6.85 (1H, d, $J = 9.0$ Hz), 6.99 (1H, ddd, $J = 7.8, 7.2, 0.6$ Hz), 7.26-7.29 (1H, m), 7.51 (1H, ddd, $J = 7.8, 1.8$ Hz), 7.59 (2H, d, $J = 8.4$ Hz), 8.02 (2H, d, $J = 8.4$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 14.3, 18.5, 61.1, 61.3, 74.1, 88.6, 93.0, 113.5, 114.5, 121.8, 128.2, 129.4, 129.6, 130.0, 131.3, 133.6, 158.5, 166.1, 171.8; IR (ATR) 2983, 2938, 2218, 1752, 1714, 1605, 1595, 1485, 1446, 1367, 1268, 1240, 1195, 1175, 1095, 1018, 948, 858 cm$^{-1}$; HRMS (ESI) Calcd for C$_{22}$H$_{22}$NaO$_3$ [M+Na]$^+$ 389.1359, Found 389.1359.

Ethyl 2-(2-(4-trifluoromethylphenylethynapthoxy)propanoate (2c): white solid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.25 (3H, dd, $J = 7.2, 7.2$ Hz), 1.70 (3H, d, $J = 6.6$ Hz), 4.21 (1H, dq, $J = 10.8, 7.2$ Hz), 4.24 (1H, dq, $J = 10.8, 7.2$ Hz), 4.84 (1H, q, $J = 6.6$ Hz), 6.84 (1H, d, $J = 8.4$ Hz), 6.99 (1H, ddd, $J = 7.8, 7.2, 0.6$ Hz), 7.28 (1H, ddd, $J = 8.4, 7.8, 1.8$ Hz), 7.51 (1H, dd, $J = 7.2, 1.8$ Hz), 7.59 (2H, d, $J = 7.8$ Hz), 7.63 (2H, d, $J = 7.8$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.0, 18.5, 61.3, 74.2, 88.2, 92.3, 113.4, 114.5, 121.8, 124.0 (q, $J = 270$ Hz), 125.2 (q, $J = 3$ Hz), 127.5, 129.7 (q, $J = 32$ Hz), 130.1, 131.7, 133.6, 158.6, 171.8; IR (ATR) 2989, 2939, 2221, 1752, 1732, 1614, 1487, 1448, 1321, 1277, 1197, 1166, 1125, 1105, 1065, 1015, 949, 842 cm$^{-1}$; HRMS (ESI) Calcd for C$_{20}$H$_{17}$F$_3$NaO$_3$ [M+Na]$^+$ 385.1022, Found 385.1022.
Ethyl 2-(2-(4-methoxyphenyl)ethynylphenoxy)propanoate (2d): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

1.24 (3H, dd, $J = 7.2, 6.6$ Hz), 1.69 (3H, d, $J = 6.6$ Hz), 3.82 (3H, s), 4.20 (1H, dq, $J = 10.8, 7.2$ Hz), 4.22 (1H, dq, $J = 10.8, 7.2$ Hz), 4.85 (1H, q, $J = 6.6$ Hz), 6.86-6.88 (3H, m), 6.98 (1H, dd, $J = 7.2, 7.2$ Hz), 7.20-7.23 (1H, m), 7.46-7.48 (3H, m); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 18.6, 55.3, 61.2, 74.5, 84.2, 93.8, 113.9, 114.7, 115.4, 115.8, 122.0, 129.1, 133.0, 133.3, 158.3, 159.5, 172.0; IR (neat) 2985, 2938, 2838, 2216, 1720, 1606, 1733, 1510, 1487, 1446, 1286, 1246, 1195, 1131, 1106, 1028, 948, 832 cm$^{-1}$; HRMS (ESI) Calcd for C$_{21}$H$_{20}$NaO$_4$ [M+Na]$^+$ 347.1254, Found 347.1254.

Ethyl 2-(2-(4-bromophenyl)ethynylphenoxy)propanoate (2e): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

1.25 (3H, dd, $J = 7.2, 7.2$ Hz), 1.69 (3H, d, $J = 6.6$ Hz), 4.19 (1H, dq, $J = 10.8, 7.2$ Hz), 4.22 (1H, dq, $J = 10.8, 7.2$ Hz), 4.83 (1H, q, $J = 6.6$ Hz), 6.84 (1H, d, $J = 9.0$ Hz), 6.99 (1H, dd, $J = 7.8, 7.2$ Hz), 7.26 (1H, ddd, $J = 7.8, 7.8, 1.8$ Hz), 7.40 (2H, d, $J = 9.0$ Hz), 7.46 (2H, d, $J = 9.0$ Hz), 7.48 (1H, dd, $J = 7.8, 1.8$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 18.5, 61.2, 74.2, 86.8, 92.6, 113.8, 114.7, 121.9, 122.3, 122.6, 129.7, 131.5, 132.9, 133.4, 154.8, 171.8; IR (ATR) 2985, 2938, 2220, 1751, 1733, 1496, 1481, 1446, 1278, 1238, 1196, 1132, 1095, 1069, 1010, 948, 824 cm$^{-1}$; HRMS (ESI) Calcd for C$_{19}$H$_{17}$BrNaO$_4$ [M+Na]$^+$ 395.0253, Found 395.0253.

Ethyl 2-(2-(3-methoxyphenyl)ethynylphenoxy)propanoate (2f): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

1.25 (3H, dd, $J = 7.2, 6.6$ Hz), 1.69 (3H, d, $J = 6.6$ Hz), 3.83 (3H, s), 4.20 (1H, dq, $J = 10.8, 7.2$ Hz), 4.23 (1H, dq, $J = 10.8, 7.2$ Hz), 4.85 (1H, q, $J = 6.6$ Hz), 6.86 (1H, d, $J = 8.4$ Hz), 6.89 (1H, ddd, $J = 8.4, 2.4, 0.6$ Hz), 6.99 (1H, ddd, $J = 7.8, 7.2, 0.6$ Hz), 7.08 (1H, dd, $J = 2.4, 1.2$ Hz), 7.14 (1H, dt, $J = 7.2, 0.6$ Hz), 7.23-7.27 (2H, m), 7.50 (1H, dd, $J = 7.8, 1.8$ Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 18.6, 55.2, 61.2, 74.4, 85.4, 93.7, 114.2, 114.7, 115.1, 116.4, 121.9, 124.1, 124.6, 129.3, 129.5, 133.5, 158.4, 159.3, 171.9; IR (ATR) 2985, 2938, 2210, 1750, 1733, 1594, 1574, 1495, 1447, 1282, 1242, 1195, 1138, 1094, 1045, 949, 930, 856, 810 cm$^{-1}$; HRMS (ESI) Calcd for C$_{20}$H$_{22}$O$_4$ [M+Na]$^+$ 347.1254, Found 347.1254.

Ethyl 2-(2-(2-methylphenylethynyl)phenoxy)propanoate (2g): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

1.24 (3H, dd, $J = 7.2, 6.6$ Hz), 1.68 (3H, d, $J = 7.2$ Hz), 2.55 (3H, s), 7.20 (1H, dq, $J = 10.8, 7.2$ Hz), 7.23 (1H, dq, $J = 10.8, 7.2$ Hz), 4.86 (1H, q, $J = 6.6$ Hz), 6.82 (1H, d, $J = 7.8$ Hz), 6.98 (1H, ddd, $J = 7.2, 7.2, 0.6$ Hz), 7.14-7.19 (1H, m), 7.22-7.24 (3H, m), 7.50-7.52 (2H, m); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.1, 18.6, 20.8, 61.2, 73.8, 89.6, 92.7, 113.8, 114.1, 121.6, 123.4, 125.4, 128.1, 129.29, 129.34, 131.7, 133.4, 140.2, 158.1, 171.9; IR (ATR) 2985, 2938, 2214, 1752, 1732, 1495, 1479, 1446, 1274, 1236, 1192, 1132, 1098, 1045, 946, 861 cm$^{-1}$; HRMS (ESI) Calcd for C$_{20}$H$_{21}$NaO$_3$ [M+Na]$^+$ 331.1305, Found 331.1305.
Ethyl 2-(2-(phenylethynyl)-5-(trifluoromethyl)phenoxy)propanoate (2h): colorless liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.24 (3H, t, $J$ = 7.2 Hz), 1.72 (3H, d, $J$ = 6.6 Hz), 4.22 (1H, q, $J$ = 7.2 Hz), 4.89 (1H, q, $J$ = 6.6 Hz), 7.07 (1H, s), 7.23 (1H, dd, $J$ = 7.8, 0.6 Hz), 7.34-7.36 (3H, m), 7.54-7.56 (2H, m), 7.58 (1H, d, $J$ = 7.8 Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 14.0, 18.4, 61.5, 74.4, 84.3, 96.0, 111.5, 118.0, 118.5, 122.9, 123.6 (q, $J$ = 270 Hz), 128.4, 128.7, 130.9 (q, $J$ = 32 Hz), 131.7, 133.7, 158.3, 171.2; IR (ATR) 2988, 2940, 2220, 1752, 1423, 1326, 1269, 1236, 1196, 1170, 1123, 964, 859, 829 cm$^{-1}$; HRMS (ESI) Calcd for C$_{20}$H$_{17}$F$_{3}$NaO$_3$ [M+Na]$^+$ 385.1022, Found 385.1022.

Ethyl 2-(5-methoxy-2-(phenylethynyl)phenoxy)propanoate (2i): yellowish liquid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

Ethyl 2-(2-((4-bromophenylethynyl)-5-methoxyphenoxy)propanoate (2j): white solid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

Ethyl 2-((1-(phenylethynyl)naphthalen-2-yl)oxy)propanoate (2k): white solid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$

Ethyl 2-phenyl-2-(2-phenylethynlyphenoxy)acetate (2l): white solid; $^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 1.18 (3H, dd, $J$ = 7.2, 7.2 Hz), 4.16 (1H, dq, $J$ = 10.8, 7.2 Hz), 4.19 (1H, dq, $J$ = 10.8, 7.2 Hz), 5.75 (1H, s), 6.87 (1H, d, $J$ = 7.8 Hz), 7.00 (1H, ddd, $J$ = 7.8, 7.2, 1.2 Hz), 7.23 (1H, ddd, $J$ = 8.4, 7.8, 1.8 Hz), 7.31-7.41 (6H, m), 7.50-7.53 (3H, m), 7.70 (2H, m); $^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 13.9, 61.5,
(Z)-Ethyl 3-benzylidene-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3a): colorless liquid; HPLC analysis
Chiralpak IC-3 (hexane/-i-PrOH = 95/5, 1.0 mL/min, 254 nm, 30 °C); 6.0 (minor), 6.9 (major)
min; 92% ee, [d]_{D}^{25} = +411 (c = 0.99, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 1.15 (3H, dd, J = 7.2, 7.2 Hz),
1.70 (3H, s), 4.14 (1H, dq, J = 10.8, 7.2 Hz), 4.20 (1H, dq, J = 10.8, 7.2 Hz), 6.87
(1H, d, J = 8.4 Hz), 6.98 (1H, ddd, J = 7.8, 7.2, 0.6 Hz), 7.00 (1H, s), 7.22-7.28 (4H, m), 7.34 (2H, dd, J = 7.2, 7.2 Hz),
7.48 (1H, dd, J = 7.8, 0.6 Hz); ¹³C NMR (150 MHz, CDCl₃) δ 13.8, 20.7, 62.0, 89.3, 110.5, 119.8, 120.3,
121.3, 127.1, 127.4, 128.4, 128.6, 130.3, 135.5, 140.5, 160.3, 169.8; IR (ATR) 2983, 2938, 1735, 1595, 1464, 1252,

(E)-Ethyl 3-benzylidene-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3a): white solid; ¹H NMR (500 MHz,
CDCl₃) δ 1.27 (3H, t, J = 7.2 Hz), 1.84 (3H, s), 4.25 (2H, q, J = 7.2 Hz), 6.67 (1H, s), 6.70 (1H, ddd, J = 7.8, 7.8,
0.6 Hz), 6.94 (1H, d, J = 7.8 Hz), 7.19 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.22 (1H, d, J = 7.8 Hz), 7.30-7.33 (1H, m),
7.37-7.42 (4H, m); ¹³C NMR (150 MHz, CDCl₃) δ 14.0, 25.1, 61.9, 89.2, 110.7, 120.7, 121.7, 122.9, 123.9, 127.6,
128.4, 128.5, 130.9, 136.4, 140.4, 162.3, 171.2; IR (ATR) 2982, 2935, 1734, 1462, 1252, 1117, 1092, 1021, 982,
(Z)-Ethyl 3-(4-ethoxycarbonylbenzylidene)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3b): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 98/2, 1.0 mL/min, 254 nm, 30 °C); 13.3 (major), 29.6 (minor) min; 33% ee, [α]D25 = +135 (c = 1.06, CDCl3); 1H NMR (600 MHz, CDCl3) δ 1.16 (3H, dd, J = 7.2, 7.2 Hz), 1.40 (3H, t, J = 7.2 Hz), 1.71 (3H, s), 4.16 (1H, dq, J = 10.8, 7.2 Hz), 4.21 (1H, dq, J = 10.8, 7.2 Hz), 4.38 (2H, q, J = 7.2 Hz), 6.89 (1H, d, J = 7.8 Hz), 6.99 (1H, dd, J = 7.2, 7.2 Hz), 6.99 (1H, s), 7.26 (1H, dd, J = 7.2, 7.2 Hz), 7.35 (2H, d, J = 8.4 Hz), 7.49 (1H, d, J = 7.2 Hz), 8.01 (2H, d, J = 8.4 Hz); 13C NMR (150 MHz, CDCl3) δ 13.9, 14.3, 20.7, 61.0, 62.1, 89.4, 110.7, 118.7, 120.6, 121.5, 126.8, 128.5, 129.7, 130.9, 140.0, 142.5, 160.6, 166.2, 169.6; IR (ATR) 2982, 2938, 1738, 1713, 1465, 1269, 1101, 1018, 913, 889, 854 cm⁻¹; HRMS (ESI) Calcd for C25H22NaO5 [M+Na]+ 389.1359, Found 389.1359.

(Z)-Ethyl 2-methyl-3-(4-trifluoromethylbenzylidene)-2,3-dihydrobenzofuran-2-carboxylate (3c): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 30 °C); 4.5 (major), 6.6 (minor) min; 53% ee, [α]D25 = +223 (c = 1.01, CDCl3); 1H NMR (600 MHz, CDCl3) δ 1.15 (3H, dd, J = 7.2, 7.2 Hz), 1.69 (3H, s), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 4.21 (1H, dq, J = 10.8, 7.2 Hz), 6.90 (1H, d, J = 8.4 Hz), 6.99 (1H, s), 7.00 (1H, ddd, J = 7.2, 7.2, 0.6 Hz), 7.27 (1H, dd, J = 8.4, 7.2, 1.2 Hz), 7.40 (2H, d, J = 8.4 Hz), 7.49 (1H, dd, J = 7.8, 1.2 Hz), 7.50 (2H, d, J = 8.4 Hz); 13C NMR (150 MHz, CDCl3) δ 13.8, 20.7, 62.2, 89.2, 110.7, 118.1, 124.0 (q, J = 270 Hz), 125.3, (q, J = 4 Hz), 125.3, 125.4, 126.6, 128.8, 129.1 (q, J = 32 Hz), 131.0, 142.6, 160.6, 166.9; IR (ATR) 2986, 2940, 1378, 1466, 1320, 1254, 1165, 1118, 1066, 1017, 914, 858 cm⁻¹; HRMS (ESI) Calcd for C20H15F2NaO3 [M+Na]+ 385.1022, Found 385.1022.

(Z)-Ethyl 3-(4-methoxybenzylidene)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3d): yellowish liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 30 °C); 9.2 (major), 10.2 (minor) min; 85% ee, [α]D20 = +375 (c = 1.02, CHCl3); 1H NMR (600 MHz, CDCl3) δ 1.14 (3H, dd, J = 7.2, 7.2 Hz), 1.73 (3H, s), 3.81 (3H, s), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 4.20 (1H, dq, J = 10.8, 7.2 Hz), 6.85 (1H, d, J = 8.4 Hz), 6.87 (2H, d, J = 9.0 Hz), 6.92 (1H, s), 6.95 (1H, ddd, J = 7.8, 7.2, 0.6 Hz), 7.20 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.44 (1H, dd, J = 7.2, 0.6 Hz); 13C NMR (150 MHz, CDCl3) δ 13.9, 20.5, 55.2, 62.9, 89.3, 110.3, 113.9, 119.6, 120.0, 121.2, 127.6, 128.0, 129.9, 130.0, 138.6, 158.9, 160.0, 170.0; IR (ATR) 2982, 2937, 2837, 1733, 1510, 1464, 1249, 1180, 1127, 1031, 912, 883, 863, 826 cm⁻¹; HRMS (ESI) Calcd for C20H15O3Na [M+Na]+ 347.1254, Found 347.1254.

(Z)-Ethyl 3-(4-bromobenzylidene)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3e): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 95/05, 1.0 mL/min, 254 nm, 30 °C); 8.0 (major), 10.2 (minor) min; 85% ee, [α]D20 = +363 (c = 1.08, CDCl3); 1H NMR (600 MHz, CDCl3) δ 1.15 (3H, dd, J = 7.2, 7.2 Hz), 1.69 (3H, s), 4.14 (1H, dq, J = 10.8, 7.2 Hz), 4.19 (1H, dq, J = 10.8, 7.2 Hz), 6.87 (1H, d, J = 9.0 Hz), 6.90 (1H, s), 6.97 (1H, ddd, J = 7.8, 7.2, 0.6 Hz), 7.16 (2H, d, J = 9.0 Hz), 7.24 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.44-7.47 (3H, m); 13C NMR (150 MHz, CDCl3) δ 13.9, 20.7, 62.1, 89.3, 110.6, 118.5, 120.4, 121.3, 121.4, 126.9, 130.2, 130.7, 131.6, 134.4, 141.2, 160.4, 169.7; IR (ATR) 2982, 2938, 1735, 1488, 1464, 1253, 1126, 1076, 1009, 913, 858, 813 cm⁻¹; HRMS (ESI) Calcd for C19H13BrNaO3

(Z)-Ethyl 3-(3-methoxybenzylidene)-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (3f): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 30 °C); 7.2 Hz (minor), 14.1 (major) min; 87% ee, [α]$^D_{25}$ = +333 (c = 1.00, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.15 (3H, dd, J = 7.2, 7.2 Hz), 1.73 (3H, s), 3.81 (3H, s), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 4.20 (1H, dq, J = 10.8, 7.2 Hz), 6.81 (1H, dd, J = 8.4, 1.2 Hz), 6.84 (1H, s), 6.87 (1H, d, J = 8.4 Hz), 6.96 (1H, s), 6.97 (1H, ddd, J = 7.8, 7.8, 0.6 Hz) 7.23 (1H, ddd, J = 7.2, 7.2, 1.2 Hz), 7.24 (1H, dd, J = 7.8, 7.8 Hz), 7.46 (1H, d, J = 8.4 Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 13.8, 20.6, 55.2, 62.0, 89.3, 110.5, 113.4, 113.5, 119.7, 120.3, 121.29, 121.34, 127.1, 129.4, 130.4, 136.7, 140.5, 159.6, 160.3, 169.8; IR (neat) 2991, 2938, 2835, 1735, 1594, 1464, 1247, 1127, 1078, 1017, 908, 854 cm$^{-1}$; HRMS (ESI) Caled for C$_{20}$H$_{20}$NaO$_4$ [M+Na]$^+$ 347.1254, Found 347.1254.

(Z)-Ethyl 2-methyl-3-(2-methylbenzylidene)-2,3-dihydrobenzofuran-2-carboxylate (3g): colorless liquid; HPLC analysis Chiralpak IA-3 (hexane/i-PrOH = 98/2, 1.0 mL/min, 254 nm, 30 °C); 6.0 (minor), 7.2 (major) min; 81% ee, [α]$^D_{25}$ = +275 (c = 1.00, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.17 (3H, dd, J = 7.2, 7.2 Hz), 1.50 (3H, s), 2.27 (3H, s), 4.08 (1H, dq, J = 10.8, 7.2 Hz), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 6.89 (1H, d, J = 8.4 Hz), 6.99 (1H, dd, J = 7.8, 7.2 Hz), 7.01 (1H, s), 7.08 (1H, d, J = 7.8 Hz), 7.14 (1H, ddd, J = 7.2, 7.2, 1.2 Hz), 7.18-7.26 (3H, m), 7.50 (1H, d, J = 7.8 Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 13.8, 20.2, 21.3, 61.8, 89.0, 110.5, 119.1, 120.5, 121.2, 125.5, 126.5, 127.8, 128.2, 129.7, 130.3, 135.1, 136.8, 141.2, 160.5, 169.9; IR (ATR) 2983, 2938, 1464, 1251, 1127, 1112, 1079, 1018, 913, 858 cm$^{-1}$; HRMS (ESI) Caled for C$_{20}$H$_{20}$NaO$_4$ [M+Na]$^+$ 331.1305. Found 331.1304.

(Z)-Ethyl 3-benzylidene-2-methyl-6-(trifluoromethyl)-2,3-dihydrobenzofuran-2-carboxylate (3h): colorless liquid; HPLC analysis Chiralpak IA-3 (hexane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 30 °C); 4.3 (major), 10.3 (minor) min; 79% ee, [α]$^D_{25}$ = +291 (c = 0.98, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.16 (3H, dd, J = 7.2, 7.2 Hz), 1.72 (3H, s), 4.16 (1H, dq, J = 10.8, 7.2 Hz), 4.21 (1H, dq, J = 10.8, 7.2 Hz), 7.10 (1Hx2, s), 7.24 (1H, dd, J = 7.8, 0.6 Hz), 7.28 (2H, d, J = 7.8 Hz), 7.29 (1H, t, J = 6.6 Hz), 7.36 (2H, dd, J = 7.8, 6.6 Hz), 7.54 (1H, d, J = 7.8 Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 13.8, 20.6, 62.2, 90.3, 107.7 (q, J = 4 Hz), 118.4, 118.5, 120.5, 122.6, 123.9 (q, J = 270 Hz), 128.0, 128.5, 128.7, 130.8, 132.1 (q, J = 33 Hz), 134.8, 138.9, 160.1; IR (ATR) 2987, 2941, 1739, 1437, 1322, 1264, 1165, 1119, 1053, 934, 868, 820 cm$^{-1}$; HRMS (ESI) Caled for C$_{20}$H$_{17}$F$_3$NaO$_3$ [M+Na]$^+$ 385.1022, Found 385.1022.

(Z)-Ethyl 3-benzylidene-2-methyl-6-methoxy-2,3-dihydrobenzofuran-2-carboxylate (3i): yellowish liquid; HPLC analysis Chiralpak IC-3 (hexane/i-PrOH = 98/2, 1.0 mL/min, 254 nm, 30 °C); 15.5 (minor), 19.4 (major) min; 89% ee, [α]$^D_{24}$ = +308 (c = 0.71, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.16 (3H, dd, J = 7.2, 7.2 Hz), 1.70 (3H, s), 3.82 (3H, s), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 4.21 (1H, dq, J = 10.8, 7.2 Hz), 6.44 (1H, d, J = 2.4 Hz), 6.56 (1H, dd, J = 8.4, 2.4 Hz), 6.82 (1H, s), 7.23 (1H, t, J = 7.2 Hz), 7.25 (2H, d, J = 7.8 Hz), 7.32 (1H, dd, J = 7.8, 7.2 Hz), 7.36 (1H, d, J = 8.4 Hz); $^{13}$C NMR (150
(Z)-Ethyl 3-(4-bromobenzylidene)-6-methoxy-2-methyl-2,3-dihydropyran-2-carboxylate (3j): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 96/4, 1.0 mL/min, 254 nm, 30 °C); 11.3 (minor), 14.4 (major) min; 92% ee, [\alpha]_{D}^{25} = +333 (c = 1.03, CHCl_3); \^1H NMR (600 MHz, CDCl_3) δ 1.17 (3H, dd, J = 7.2, 7.2 Hz), 1.68 (3H, s), 3.81 (3H, s), 4.15 (1H, dq, J = 10.8, 7.2 Hz), 4.21 (1H, dq, J = 10.8, 7.2 Hz), 6.43 (1H, d, J = 8.4 Hz), 6.55 (1H, dd, J = 8.4, 1.8 Hz), 6.72 (1H, s), 7.13 (2H, d, J = 8.4 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.44 (2H, d, J = 8.4 Hz); \(^1^3^C\) NMR (150 MHz, CDCl_3) δ 13.9, 20.7, 55.5, 62.0, 90.2, 95.9, 108.4, 117.3, 119.9, 120.9, 127.0, 128.3, 128.5, 135.8, 140.0, 161.7, 162.3, 169.8; IR (ATR) 2982, 2939, 2837, 1736, 1616, 1593, 1498, 1445, 1285, 1158, 1127, 1080, 1027, 957, 826 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{23}\)H\(_{20}\)NaO\(_4\) [M+Na]^+ 347.1254, Found 347.1254.

(Z)-Ethyl 1-benzylidene-2-methyl-1,2-dihydronaphtho[2,1-b]furan-2-carboxylate (3k): bright yellow liquid; HPLC analysis Chiralpak IC-3 (hexane/i-PrOH = 95/5, 1.0 mL/min, 254 nm, 30 °C); 7.4 (major), 13.5 (minor) min; 93% ee, [\alpha]_{D}^{25} = +313 (c = 1.03, CHCl_3); \^1H NMR (600 MHz, CDCl_3) δ 1.10 (3H, dd, J = 7.2, 7.2 Hz), 1.72 (3H, s), 4.04 (1H, dq, J = 11.4, 7.2 Hz), 4.07 (1H, dq, J = 11.4, 7.2 Hz), 7.14 (1H, d, J = 9.0 Hz), 7.27 (1H, t, J = 7.2 Hz), 7.30 (2H, d, J = 7.2 Hz), 7.35 (2H, dd, J = 7.2, 7.2 Hz), 7.39 (1H, ddd, J = 7.2, 7.2, 1.2 Hz), 7.57 (1H, s), 7.58 (1H, ddd, J = 7.2, 7.2, 1.2 Hz), 7.76 (1H, d, J = 9.0 Hz), 7.86 (1H, d, J = 7.8 Hz), 8.37 (1H, d, J = 7.8 Hz); \(^1^3^C\) NMR (150 MHz, CDCl_3) δ 13.7, 22.2, 61.9, 89.6, 112.5, 117.1, 122.2, 122.4, 123.5, 127.2, 127.9, 128.2, 128.7, 129.4, 129.7, 130.3, 132.3, 136.7, 143.1, 160.1, 169.8; IR (ATR) 3058, 2984, 2937, 1739, 1702, 1631, 1581, 1522, 1462, 1447, 1374, 1258, 1125, 1082, 1007, 932, 859, 822 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{29}\)H\(_{19}\)BrNaO\(_3\) [M+Na]^+ 425.0359, Found 425.0359.

(Z)-Ethyl 3-benzylidene-2-phenyl-2,3-dihydropyran-2-carboxylate (3l): white solid; HPLC analysis Chiralpak IA-3 (hexane/i-PrOH = 90/10, 1.0 mL/min, 254 nm, 30 °C); 10.4 (major), 12.1 (minor) min; 48% ee, [\alpha]_{D}^{25} = -167 (c = 1.02, CHCl_3); \^1H NMR (600 MHz, CDCl_3) δ 0.96 (3H, dd, J = 7.2, 7.2 Hz), 4.05 (1H, dq, J = 10.8, 7.2 Hz), 4.14 (1H, dq, J = 10.8, 7.2 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.00 (1H, dd, J = 7.8, 7.2 Hz), 7.12-7.16 (3H, m), 7.19-7.24 (3H, m), 7.27 (1H, s), 7.30-7.35 (3H, m), 7.57-7.60 (3H, m); \(^1^3^C\) NMR (150 MHz, CDCl_3) δ 13.6, 62.2, 93.2, 110.6, 120.1, 121.5, 123.1, 127.4, 127.5, 127.9, 128.2, 128.6, 129.0, 129.6, 130.4, 134.7, 15.7, 136.9, 159.6, 168.4; IR (ATR) 3059, 3027, 2980, 1735, 1460, 1447, 1234, 1019, 971, 928, 861 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{23}\)H\(_{20}\)NaO\(_3\) [M+Na]^+ 379.1305, Found 379.1304.

(Z)-Ethyl 2-benzyl-3-benzylidene-2,3-dihydropyran-2-carboxylate (3m): colorless liquid; HPLC analysis Chiralpak IC-3 (hexane/i-PrOH = 98/2, 1.0 mL/min, 254 nm, 30 °C); 7.6 (minor), 8.2 (major) min; 84% ee, [\alpha]_{D}^{25} = +80 (c = 0.87, CHCl_3); \^1H NMR (600 MHz, CDCl_3) δ 1.16 (3H, dd, J = 7.2, 7.2 Hz), 3.37 (1H, d, J = 14.4 Hz), 3.59 (1H, d, J = 14.4 Hz), 4.18 (1H, dq, J = 10.8, 7.2 Hz), 7.24 (2H, d, J = 7.2, 7.2 Hz), 7.27 (1H, d, J = 7.2, 7.2 Hz), 7.19-7.45 (5H, m), 7.58 (1H, s), 7.67-7.73 (3H, m), 7.79-7.85 (3H, m), 7.85-7.90 (3H, m); \(^1^3^C\) NMR (150 MHz, CDCl_3) δ 13.6, 62.2, 93.2, 110.6, 120.1, 121.5, 123.1, 127.4, 127.5, 127.9, 128.2, 128.6, 129.0, 129.6, 130.4, 134.7, 15.7, 136.9, 159.6, 168.4; IR (ATR) 3059, 3027, 2980, 1735, 1460, 1447, 1234, 1019, 971, 928, 861 cm\(^{-1}\); HRMS (ESI) Calcd for C\(_{23}\)H\(_{20}\)NaO\(_3\) [M+Na]^+ 379.1305, Found 379.1304.
(Z)-Ethyl 3-benzylidene-2-(2-((tert-butyldimethylsilyl)oxy)ethyl)-2,3-dihydrobenzofuran-2-carboxylate (3n): colorless liquid; HPLC analysis Chiralpak IA-3 (hexane/i-ProOH = 98.5/1.5, 1.0 mL/min, 254 nm, 30 °C); 5.6 (major) min; 80% ee, [α]25°D = +172 (c = 1.13, CHCl3); 1H NMR (600 MHz, CDCl3) δ = -0.17 (3H, s), 0.76 (9H, s), 1.15 (3H, dd, J = 7.2, 7.2 Hz), 2.37 (1H, ddd, J = 15.0, 9.6, 6.0 Hz), 2.49 (1H, ddd, J = 15.0, 9.0, 5.4 Hz), 3.59 (1H, ddd, J = 10.2, 9.0, 6.0 Hz), 3.64 (1H, ddd, J = 10.2, 9.6, 5.4 Hz), 4.12 (1H, dq, J = 10.8, 7.2 Hz), 4.19 (1H, d, J = 10.8, 7.2 Hz), 6.87 (1H, d, J = 8.4 Hz), 6.96 (1H, ddd, J = 7.2, 7.2, 0.6 Hz), 7.04 (1H, s) 7.22 (2H, ddd, J = 7.2, 7.2, 1.8 Hz) 7.24-7.27 (m, 2H), 7.30-7.35 (4H, m), 7.45 (1H, d, J = 7.8, 0.6 Hz); 13C NMR (150 MHz, CDCl3) δ = -5.62, -5.58, 13.8, 18.1, 25.8, 36.1, 58.4, 61.9, 90.3, 110.2, 120.2, 120.4, 121.2, 127.4 (2C), 128.3, 128.7, 130.3, 135.5, 138.4, 160.9, 169.6; IR (ATR) 2954, 2928, 2856, 1464, 1249, 1218, 1084, 1028, 940, 834 cm⁻¹; HRMS (ESI) Calcd for C25H32NaO3 [M+Na]+ 393.1461, Found 393.1461.

(Z)-(3-Benzylidene-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol (5a): white solid; HPLC analysis Chiralpak IC-3 (hexane/i-ProOH = 96/4, 1.0 mL/min, 254 nm, 30 °C); 14.0 (major), 17.8 (minor) min; 90% ee, [α]25°D = +64 (c = 1.20, CHCl3); 1H NMR (600 MHz, CDCl3) δ = 1.49 (3H, s), 1.85 (1H, br), 3.63 (1H, dd, J = 12.0, 6.6 Hz), 3.67 (1H, dd, J = 12.0, 7.8 Hz), 6.84 (1H, d, J = 7.8 Hz), 6.94 (1H, ddd, J = 7.2, 7.2, 1.2 Hz), 7.13 (1H, s), 7.22 (1H, ddd, J = 7.2, 7.2, 0.6 Hz), 7.28 (1H, t, J = 7.2 Hz), 7.29 (2H, d, J = 7.8 Hz), 7.34 (1H, dd, J = 7.8, 7.2 Hz), 7.45 (1H, dd, J = 7.8, 0.6 Hz); 13C NMR (150 MHz, CDCl3) δ = 22.2, 67.7, 91.8, 110.4, 118.9, 120.5, 130.8, 127.2, 128.1, 128.8, 130.3, 136.1, 141.4, 160.1; IR (ATR) 3449, 3052, 2983, 2932, 2869, 1596, 1491, 1466, 1322, 1261, 1053, 926, 905, 867 cm⁻¹; HRMS (ESI) Calcd for C17H18NaO2 [M+Na]+ 275.1042, Found 275.1043.

(Z)-(3-(4-Bromobenzylidene)-2-methyl-2,3-dihydrobenzofuran-2-yl)methanol (5e): white solid; HPLC analysis Chiralpak IA-3 (hexane/i-ProOH = 96/4, 1.0 mL/min, 254 nm, 30 °C); 23.7 (major), 28.5 (minor) min; 85% ee, [α]25°D = +52 (c = 1.01, CHCl3); 1H NMR (600 MHz, CDCl3) δ = 1.41 (3H, s), 1.80-1.95 (1H, br), 3.60 (dd, J = 12.0, 6.0 Hz, 1H), 3.66 (dd, J = 12.0, 7.2 Hz, 1H), 6.85 (1H, d, J = 7.8 Hz), 6.94 (1H, dd, J = 7.8, 7.2 Hz), 7.01 (1H, s), 7.17 (2H, d, J = 8.4 Hz), 7.23 (1H, ddd, J = 7.8, 7.2 Hz), 7.44 (1H, d, J = 7.2 Hz), 7.47 (2H, d, J = 8.4 Hz); 13C NMR (150 MHz, CDCl3) δ = 22.2, 67.7, 91.7, 110.5, 117.5, 120.6, 120.9, 121.3, 126.9, 130.55, 130.62, 131.3, 135.1, 142.2, 160.2; IR (neat) 3421, 2982, 2932, 2869, 1595, 1486, 1465, 1321, 1261, 1070, 1054, 1011, 912, 869 cm⁻¹; HRMS (ESI) Calcd for C17H18BrNaO2 [M+Na]+ 353.0148. Found 353. 0148; CCDC No. 1431742.
Figure S1. ORTEP diagram of 5e.

Ethyl 3-benzyl-2-methyl-2,3-dihydrobenzofuran-2-carboxylate (6a): white solid, dr = 21 : 1; HPLC analysis Chiralpak IB-3 (hexane/i-PrOH = 98/02, 1.0 mL/min, 254 nm, 30 °C); 5.5 (major), 7.5 (minor) min; 90% ee, [α]$_D^{25}$ = -133 (c = 1.13, CHCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 1.31 (3H, s), 2.58 (1H, dd, J = 7.2, 7.2 Hz), 1.66 (3H, s), 3.07 (1H, dd, J = 13.2, 4.8 Hz), 3.53 (1H, dd, J = 11.4, 4.8 Hz), 4.23 (1H, dq, J = 10.8, 7.2 Hz), 6.66 (1H, d, J = 7.2 Hz), 7.10 (2H, d, J = 8.4 Hz), 7.12 (1H, ddd, J = 7.8, 7.8, 1.2 Hz), 7.23-7.26 (1H, m), 7.30 (2H, dd, J = 7.2, 7.2 Hz); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 14.2, 24.5, 37.4, 53.0, 61.5, 90.4, 110.1, 120.3, 125.5, 126.5, 128.3, 128.4, 128.6, 129.5, 138.3, 157.9, 171.4; IR (ATR) 3029, 2981, 1733, 1478, 1461, 1244, 1123, 1084, 930, 859 cm$^{-1}$; HRMS (ESI) Calcd for C$_{19}$H$_{20}$NaO$_3$ [M+Na]$^+$ 319.1305, Found 319.1305.

(Z)-3-Benzyldiene-4',5'-dihydro-2'H,3H-spiro[benzofuran-2,3'-furan]-2'-one (7): colorless liquid; HPLC analysis Chiralpak AD-3 (hexane/i-PrOH = 85/15, 1.0 mL/min, 254 nm, 30 °C); 10.1 (minor), 17.7 (major) min; 77% ee, [α]$_D^{25}$ = +535 (c = 1.01, CDCl$_3$); $^1$H NMR (600 MHz, CDCl$_3$) δ 2.37 (1H, ddd, J = 14.4, 7.2, 2.4 Hz), 2.60 (1H, ddd, J = 14.4, 9.0, 9.0 Hz), 4.01 (1H, ddd, J = 14.4, 9.0, 9.0 Hz), 4.42 (1H, ddd, J = 9.0, 9.0, 7.2 Hz), 6.87 (1H, d, J = 7.8 Hz), 7.00 (1H, ddd, J = 7.8, 7.2, 0.6 Hz), 7.19 (1H, s), 7.23-7.27 (3H, m), 7.29 (1H, t, J = 7.2 Hz), 7.37 (2H, dd, J = 7.8, 7.2 Hz), 7.48-7.50 (1H, m); $^{13}$C NMR (150 MHz, CDCl$_3$) δ 32.3, 66.0, 88.0, 110.5, 120.4, 121.0, 121.9, 126.4, 127.8, 128.4, 128.8, 130.8, 135.4, 137.5, 159.8, 173.1; IR (ATR) 3054, 3024, 2922, 1775, 1464, 1173, 1020, 957, 932, 859 cm$^{-1}$; HRMS (ESI) Calcd for C$_{18}$H$_{18}$NaO$_3$ [M+Na]$^+$ 301.0835, Found 301.0835.
NOE Analysis of 3a
NOE Analysis of 6a
S23