Squaramide-catalyzed asymmetric regioselective allylic alkylation of 4-aminopyrazolones with Morita–Baylis–Hillman carbonates

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1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200~300 mesh). Enantiomeric excesses (ee) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: [α]D (c g/100 mL, solvent). All 1H NMR spectra were recorded on a Bruker Avance II 400 MHz and Bruker Avance III 600 MHz, 13C NMR spectra were recorded on a Bruker Avance II 101 MHz, Bruker Avance II 126 MHz and Bruker Avance III 151 MHz, 19F NMR spectra were recorded on a Bruker Avance II 376 MHz and Bruker Avance III 377 MHz with chemical shifts reported as ppm (in CDCl3, TMS as an internal standard). Data for 1H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with a HRMS/MS instrument (LTQ Orbitrap XL TM). The absolute configuration of 3ao and 5ak were assigned by the X-ray analysis.

4-Aminopyrazolones 1 were prepared according to the literature. MBH carbonates 2 and 4 were prepared according to the literature. Catalyst C8 was synthesized according to the literature procedure. Nitrile oxides 6 and nitrile imine 8a were prepared according to the literature. The racemic products were synthesized using quinine/quinidine = 1:1 as the catalyst.

2. Experimental procedures and characterization of compounds 3, 5, 7 and 9

To a tube were added 4-aminopyrazolone 1 (0.2 mmol), C8 (0.04 mmol), 4 Å MS (200 mg) and toluene (2 mL). MBH carbonate 2 (0.7 mmol) was then added in one portion, and the reaction mixture was stirred at 30 °C. When the substrate 1 was consumed as checked by TLC, the reaction was stopped and purified by column chromatography (petroleum ether/ethyl acetate = 5:1) on silica gel directly to give the product 3.

**Compound 3aa**

Prepared according to the procedure within 48 h as white solid (89.7 mg, 99% yield); [α]D = 9.091 (c 1.32, CH2Cl2); Mp: 148.6 - 149.2 °C; 1H NMR (400 MHz, Chloroform-d) δ 9.15 (s, 1H), 8.09 – 8.01 (m, 4H), 7.90 – 7.87 (m, 2H), 7.51 – 7.41 (m, 5H), 7.39 – 7.35 (m, 3H), 7.25 – 7.20 (m, 1H), 6.41 (s, 1H), 5.69 (s, 1H), 3.80 (s, 3H), 3.36 (d, J = 14.5 Hz, 1H), 2.77 (d, J = 14.4 Hz, 1H); 13C NMR (126 MHz, Chloroform-d) δ 170.9, 166.3, 156.1, 138.3, 133.6, 132.1, 132.0, 131.7, 130.3, 130.2, 128.9, 128.7, 128.6, 127.5, 126.3, 125.3, 119.3, 65.2, 52.9, 37.7. HRMS (ESI) m/z Calcld. for C27H24N3O4 ([M+H]+) 454.1761, Found 454.1755. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, tmajor = 13.0 min, tminor = 28.4 min).
Compound 3ab

Prepared according to the procedure within 48 h as white solid (72.9 mg, 78% yield); 
$[^{13} \alpha ]_{D}^{19} = 7.547$ (c 0.53, CH$_2$Cl$_2$); Mp: 123.5 - 124.6 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.08 (s, 1H), 8.08 – 8.01 (m, 4H), 7.71 – 7.66 (m, 2H), 7.46 – 7.42 (m, 2H), 7.38 – 7.36 (m, 3H), 7.31 – 7.30 (m, 2H), 7.24 – 7.20 (m, 1H), 6.41 (s, 1H), 5.69 (s, 1H), 3.81 (s, 3H), 3.37 (d, $J = 14.7$ Hz, 1H), 2.76 (d, $J = 14.3$ Hz, 1H), 2.36 (s, 3H); $^{13}$C NMR (151 MHz, Chloroform-$d$) $\delta$ 171.0, 169.7, 166.6, 156.1, 138.4, 133.6, 132.9, 132.0, 131.7, 130.3, 128.8, 128.7, 128.5, 126.4, 125.3, 124.4, 119.4, 65.1, 52.9, 37.7, 21.3. HRMS (ESI) m/z Calcd. for C$_{28}$H$_{26}$N$_3$O$_4$ ([M+H]$^+$) 486.1918, Found 486.1924. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 9.0$ min, $t_{\text{minor}} = 14.2$ min).
Compound 3ac

Prepared according to the procedure within 48 h as yellow solid (95.7 mg, 99% yield); [α]_D^26 = 16.083 (c 1.00, CH₂Cl₂); Mp: 104.3 - 105.2 °C; ^1H NMR (400 MHz, Chloroform-d) δ 9.17 (s, 1H), 8.08 – 7.99 (m, 4H), 7.47 – 7.42 (m, 4H), 7.39 – 7.30 (m, 4H), 7.24 – 7.20 (m, 1H), 7.05 – 7.02 (m, 1H), 6.41 (s, 1H), 5.69 (s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.36 (d, J = 14.3 Hz, 1H), 2.76 (d, J = 14.3 Hz, 1H); ^13C NMR (101 MHz, Chloroform-d) δ 171.0, 169.8, 166.3, 159.8, 156.1, 138.3, 133.7, 133.4, 131.6, 130.4, 130.2, 129.6, 128.9, 128.8, 126.3, 125.3, 119.3, 119.2, 112.1, 65.2, 55.4, 52.9, 37.7. HRMS (ESI) m/z Calcd.

for C₂₉H₂₆N₃O₅ ([M+H]^+) 484.1867, Found 484.1875. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 12.4 min, t_minor = 14.9 min).
Compound 3ad

Prepared according to the procedure within 48 h as yellow solid (94.5 mg, 97% yield); [α]_D^16 = 5.603 (c 0.23, CH₂Cl₂); Mp: 147.1 - 148.0 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.30 (s, 1H), 8.08 – 8.01 (m, 4H), 7.91 – 7.90 (m, 1H), 7.79 (d, J = 7.7 Hz, 1H), 7.52 – 7.40 (m, 7H), 7.27 – 7.23 (m, 1H), 6.48 (s, 1H), 5.75 (s, 1H), 3.92 (s, 3H), 3.43 (d, J = 14.5 Hz, 1H), 2.72 (d, J = 14.5 Hz, 1H); ¹³C NMR (101 MHz, Chloroform-d) δ 170.6, 170.4, 165.0, 156.0, 138.3, 134.8, 134.1, 133.8, 132.2, 131.4, 130.5, 130.0, 129.9, 128.9, 128.8, 128.0, 126.3, 125.5, 125.4, 119.3, 65.0, 53.2, 37.8; HRMS (ESI) m/z Calcld. for C₂₇H₂₃ClN₃O₄ ([M+H]⁺) 488.1372, Found 488.1374. Enantiomeric excess was determined to be 95% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 9.6 min, t_minor = 16.4 min).
Compound 3ae

Prepared according to the procedure within 48 h as yellow solid (102.0 mg, 96% yield); [α]$_D^{16}$ = 4.561 (c 0.59, CH$_2$Cl$_2$); Mp: 139.5 - 140.5 °C; $^1$H NMR (400 MHz, Chloroform-$d$) δ 9.18 (s, 1H), 7.96 – 7.90 (m, 5H), 7.72 – 7.69 (m, 1H), 7.54 – 7.52 (m, 1H), 7.37 – 7.28 (m, 5H), 7.22 – 7.11 (m, 2H), 6.35 (s, 1H), 5.61 (s, 1H), 3.77 (s, 3H), 3.30 (d, $J = 14.4$ Hz, 1H), 2.73 – 2.57 (m, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 170.6, 170.3, 164.9, 156.0, 138.3, 135.1, 134.1, 134.0, 131.4, 130.9, 130.5, 130.2, 130.0, 128.9, 128.8, 126.3, 126.0, 125.4, 122.8, 119.3, 65.0, 53.1, 37.7; HRMS (ESI) m/z Calcd. for C$_{27}$H$_{28}$BrN$_3$O$_4$ ([M+H]$^+$) 532.0866, Found 532.0870. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, $t_{\text{major}}$ = 9.0 min, $t_{\text{minor}}$ = 14.7 min).
Prepared according to the procedure within 48 h as white solid (82.3 mg, 88% yield); [α]_D^20 = 15.625 (c 0.21, CH₂Cl₂); Mp: 191.4 - 192.3 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.06 (s, 1H), 8.08 – 8.01 (m, 4H), 7.79 – 7.77 (m, 2H), 7.46 – 7.35 (m, 5H), 7.23 – 7.19 (m, 3H), 7.23 – 7.19 (m, 3H), 5.68 (s, 1H), 3.78 (s, 3H), 3.35 (d, J = 14.3 Hz, 1H), 2.78 (d, J = 14.3 Hz, 1H), 2.37 (s, 3H); ¹³C NMR (151 MHz, Chloroform-d) δ 171.2, 169.7, 166.4, 156.2, 142.6, 138.4, 133.5, 131.7, 130.3, 129.3, 129.1, 128.8, 128.7, 127.6, 126.4, 125.3, 119.4, 65.2, 52.8, 37.6, 21.5. HRMS (ESI) m/z Calcd. for C₂₈H₂₈N₃O₄ ([M+H]⁺) 468.1918, Found 468.1920. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 8.0 min, t_minor = 9.9 min).

**Compound 3af**
Compound 3ag

Prepared according to the procedure within 48 h as yellow solid (95.7 mg, 99% yield); [α]$_D^{17}$ = 7.547 (c 0.53, CH$_2$Cl$_2$); Mp: 123.5 - 124.6 °C; $^1$H NMR (400 MHz, Chloroform-d) δ 9.01 (s, 1H), 8.07 – 8.00 (m, 4H), 7.84 – 7.81 (m, 2H), 7.44 – 7.35 (m, 5H), 7.22 – 7.18 (m, 1H), 6.87 – 6.85 (m, 2H), 6.37 (s, 1H), 5.66 (s, 1H), 3.79 – 3.77 (m, 6H), 3.32 (d, $J = 14.3$ Hz, 1H), 2.77 (d, $J = 14.3$ Hz, 1H);

$^{13}$C NMR (151 MHz, Chloroform-d) δ 170.2, 168.6, 165.0, 161.6, 155.2, 137.3, 132.4, 130.7, 129.3, 129.2, 128.4, 127.8, 127.6, 125.3, 124.2, 123.4, 118.3, 112.7, 64.1, 54.3, 51.8, 36.6. HRMS (ESI) m/z Calcd. for C$_{29}$H$_{38}$N$_3$O$_5$ ([M+H]$^+$) 484.1867, Found 484.1878. Enantiomeric excess was determined to be 91% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 10.4$ min, $t_{\text{minor}} = 14.0$ min).
**Compound 3ah**

Prepared according to the procedure within 48 h as white solid (95.3 mg, 99% yield); \([\alpha]_D^{17} = 11.101 (c 1.00, CH_2Cl_2); \text{Mp: 152.7 - 153.3} \degree C; ^1H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.07 (s, 1H), 8.08 – 8.01 (m, 4H), 7.82 – 7.80 (m, 2H), 7.45 – 7.41 (m, 2H), 7.38 – 7.36 (m, 3H), 7.25 – 7.19 (m, 3H), 6.40 (s, 1H), 5.68 (s, 1H), 3.79 (s, 3H), 3.35 (d, \(J = 14.3\) Hz, 1H), 2.77 (d, \(J = 14.3\) Hz, 1H), 2.67 (q, \(J = 7.6\) Hz, 2H), 1.24 (t, \(J = 7.6\) Hz, 3H); \(^{13}C\) NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.1, 169.7, 166.4, 156.2, 148.9, 138.4, 133.6, 131.7, 130.3, 130.3, 129.5, 128.8, 128.7, 128.1, 127.7, 126.4, 125.3, 119.4, 65.1, 52.9, 37.7, 28.9, 15.3. HRMS (ESI) m/z Calcd. for C_{29}H_{28}N_3O_4 ([M+H]+) 482.2074, Found 482.2072.

Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 \degree C, 0.8 mL/min, \(t_{\text{major}} = 7.2\) min, \(t_{\text{minor}} = 8.8\) min).
Compound 3ai

Prepared according to the procedure within 48 h as yellow solid (95.8 mg, 94% yield); $[\alpha]_D^{18} = 8.781$ (c 0.91, CH$_2$Cl$_2$); Mp: 229.3 - 229.9 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.08 (s, 1H), 8.08 – 8.02 (m, 4H), 7.86 – 7.83 (m, 2H), 7.46 – 7.37 (m, 7H), 7.23 – 7.19 (m, 1H), 6.40 (s, 1H), 5.69 (s, 1H), 3.82 (s, 3H), 3.37 (d, $J = 14.3$ Hz, 1H), 2.76 (d, $J = 14.3$ Hz, 1H), 1.33 (s, 9H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 171.1, 169.8, 166.3, 156.3, 155.7, 138.4, 133.6, 131.7, 130.3, 130.3, 129.3, 128.8, 128.7, 127.4, 126.4, 125.6, 125.3, 119.3, 65.1, 53.0, 37.7, 35.0, 31.2. HRMS (ESI) m/z Calcd. for C$_{31}$H$_{32}$N$_3$O$_4$ ([M+H]$^+$) 510.2387, Found 510.2389; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 5.7$ min, $t_{\text{minor}} = 9.0$ min).
Compound 3aj

Prepared according to the procedure within 48 h as yellow solid (96.5 mg, 99% yield); \([\alpha]_D^{16} = 4.864 (c 0.51, \text{CH}_2\text{Cl}_2)\); Mp: 145.4 - 146.3 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.24 (s, 1H), 8.03 – 8.01 (m, 2H), 7.99 – 7.97 (m, 2H), 7.81 – 7.76 (m, 2H), 7.43 – 7.35 (m, 7H), 7.22 – 7.18 (m, 1H), 6.39 (s, 1H), 5.67 (s, 1H), 3.81 (s, 3H), 3.34 (d, \(J = 14.4\) Hz, 1H), 2.71 (d, \(J = 14.4\) Hz, 1H); \(^{13}\)C NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 170.7, 170.3, 165.3, 156.1, 138.5, 138.3, 134.0, 131.5, 130.5, 130.1, 128.9, 128.9, 128.8, 126.3, 125.4, 119.3, 65.0, 53.1, 37.8; HRMS (ESI) \(m/z\) Calcd. for C\(_{27}\)H\(_{23}\)ClN\(_3\)O\(_4\) ([M+H]\(^+\)) 488.1372, Found 488.1377. Enantiomeric excess was determined to be 98% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{\text{major}} = 9.6\) min, \(t_{\text{minor}} = 34.9\) min).
Compound 3ak

Prepared according to the procedure within 48 h as yellow solid (98.8 mg, 93% yield); \([\alpha]_D^{16} = 4.184 \text{ (c 0.47, CH}_2\text{Cl}_2\); Mp: 150.3 - 151.4 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.19 (s, 1H), 7.97 – 7.90 (m, 4H), 7.68 – 7.66 (m, 2H), 7.49 – 7.47 (m, 2H), 7.37 – 7.29 (m, 5H), 7.18 – 7.12 (m, 1H), 6.34 (s, 1H), 5.62 (s, 1H), 3.77 (s, 3H), 3.29 (d, \(J = 14.4 \text{ Hz, 1H})\), 2.63 (d, \(J = 14.4 \text{ Hz, 1H})\); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 170.7, 170.2, 165.4, 156.0, 138.3, 134.0, 131.9, 131.5, 130.9, 130.5, 130.1, 129.1, 128.9, 128.8, 127.1, 126.3, 125.4, 119.3, 65.1, 53.1, 37.8; HRMS (ESI) m/z Calcd. for C\(_{27}\)H\(_{23}\)BrN\(_3\)O\(_4\) ([M+H]+) 532.0866, Found 532.0861. Enantiomeric excess was determined to be 91% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, \(\lambda = 254 \text{ nm, 30 °C, 0.8 mL/min, } t_{\text{major}} = 10.5 \text{ min, } t_{\text{minor}} = 41.6 \text{ min})

Prepared according to the procedure within 48 h as red solid (81.9 mg, 85% yield);
$[\alpha]_D^{15} = 9.910$ (c 1.10, CH$_2$Cl$_2$); Mp: 163.6 - 164.2 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 9.00 (s, 1H), 8.07 – 8.00 (m, 4H), 7.49 – 7.42 (m, 4H), 7.38 – 7.35 (m, 3H), 7.24 – 7.20 (m, 1H), 7.13 (s, 1H), 6.41 (s, 1H), 5.69 (s, 1H), 3.81 (s, 3H), 3.37 (d, $J = 14.2$ Hz, 1H), 2.77 (d, $J = 14.3$ Hz, 1H), 2.33 (s, 6H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 171.0, 169.7, 166.8, 156.2, 138.4, 138.2, 133.8, 133.7, 131.9, 131.8, 130.29, 130.25, 128.8, 128.7, 126.4, 125.4, 125.3, 119.4, 65.1, 52.8, 37.6, 21.2. HRMS (ESI) m/z Calcd. for C$_{29}$H$_{28}$N$_3$O$_4$ ([M+H]$^+$) 482.2074, Found 482.2079. Enantiomeric excess was determined to be 95% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{major} = 11.3$ min, $t_{minor} = 8.1$ min).

Compound 3al
Compound 3am

Prepared according to the procedure within 48 h as white solid (27.2 mg, 27% yield); 
\([\alpha]_{D}^{18} = 1.754 \text{ (c 0.57, CH}_2\text{Cl}_2); \) Mp: 158.7 - 159.8 °C; 
\(^1\)H NMR (600 MHz, Chloroform-d) \(\delta\) 8.55 (s, 1H), 8.21 (d, \(J = 8.5\) Hz, 1H), 8.12 - 8.04 (m, 4H), 7.91 (d, \(J = 8.3\) Hz, 1H), 7.81 (d, \(J = 8.1\) Hz, 1H), 7.68 - 7.66 (m, 1H), 7.47 - 7.40 (m, 8H), 7.26 - 7.23 (m, 1H), 6.41 (s, 1H), 5.70 (s, 1H), 3.65 (s, 3H), 3.34 (d, \(J = 14.3\) Hz, 1H), 2.82 (d, \(J = 14.3\) Hz, 1H); 
\(^13\)C NMR (101 MHz, Chloroform-d) \(\delta\) 171.0, 169.1, 168.9, 156.1, 138.3, 133.6, 133.3, 131.9, 131.7, 131.3, 130.4, 130.4, 130.2, 128.9, 128.8, 128.1, 127.2, 126.4, 126.4, 125.7, 125.5, 125.4, 124.6, 119.5, 65.4, 52.7, 37.6. HRMS (ESI) m/z Calcd. for C\(_{31}\)H\(_{26}\)N\(_3\)O\(_4\) ([M+H]+) 504.1918, Found 504.1925. Enantiomeric excess was determined to be 75% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{major} = 9.4\) min, \(t_{minor} = 13.5\) min).
Prepared according to the procedure within 48 h as yellow solid (99.7 mg, 99% yield); [α]_D^20 = 18.422 (c 0.76, CH₂Cl₂); Mp: 218.5 - 219.3 °C; ¹H NMR (400 MHz, Chloroform-­d) δ 9.34 (s, 1H), 8.40 (s, 1H), 8.13 – 8.05 (m, 4H), 7.91 – 7.78 (m, 4H), 7.55 – 7.43 (m, 4H), 7.39 – 7.35 (m, 3H), 7.25 – 7.21 (m, 1H), 6.40 (s, 1H), 5.69 (s, 1H), 3.79 (s, 3H), 3.41 (d, J = 14.2 Hz, 1H), 2.84 (d, J = 14.3 Hz, 1H); ¹³C NMR (151 MHz, Chloroform-d) δ 171.1, 169.7, 166.6, 156.2, 138.4, 135.0, 133.6, 132.5, 131.7, 130.4, 130.3, 129.2, 128.9, 128.8, 128.7, 128.4, 127.9, 127.7, 126.7, 126.4, 125.4, 123.6, 119.4, 65.4, 52.8, 37.7. HRMS (ESI) m/z Calcd. for C₃₁H₂₆N₃O₄ ([M+H⁺]⁺) 504.1918, Found 504.1917. Enantiomeric excess was determined to be 91% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 12.1 min, t_minor = 10.1 min).
Compound 3ao

Prepared according to the procedure within 48 h as yellow white (91.0 mg, 99% yield); \([\alpha]^{15}_D = 14.875\) (c 1.60, CH\(_2\)Cl\(_2\)); Mp: 116.3 - 117.4 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.08 (s, 1H), 8.05 – 8.01 (m, 4H), 7.67 – 7.66 (m, 1H), 7.45 – 7.37 (m, 6H), 7.23 – 7.19 (m, 1H), 7.04 – 7.02 (m, 1H), 6.39 (s, 1H), 5.66 (s, 1H), 3.77 (s, 3H), 3.32 (d, \(J = 14.3\) Hz, 1H), 2.76 (d, \(J = 14.3\) Hz, 1H); \(^13\)C NMR (151 MHz, Chloroform-\(d\)) \(\delta\) 170.9, 169.7, 161.4, 156.0, 138.3, 137.1, 133.7, 131.6, 131.3, 130.4, 130.2, 129.4, 128.8, 128.8, 127.8, 126.4, 125.4, 119.4, 65.1, 52.9, 37.7. HRMS (ESI) m/z Calcd. for C\(_{25}\)H\(_{22}\)N\(\text{O}_3\)S ([M+H]\(^+\)) 460.1326, Found 460.1332. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-OD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.5 mL/min, \(t_{\text{major}} = 31.8\) min, \(t_{\text{minor}} = 10.3\) min).
Compound 3ap

Prepared according to the procedure within 48 h as red white (84.1 mg, 87% yield); [α]$^D_{16}$ = -56.034 (c 1.10, CH$_2$Cl$_2$); Mp: 105.7 - 106.4 °C; $^1$H NMR (400 MHz, Chloroform-$d$) δ 8.75 (s, 1H), 8.04 – 8.02 (m, 2H), 7.86 – 7.76 (m, 3H), 7.50 – 7.32 (m, 6H), 7.21 – 7.16 (m, 1H), 6.97 – 6.90 (m, 2H), 6.43 (s, 1H), 5.73 (s, 1H), 3.80 – 3.79 (m, 6H), 3.50 (d, $J$ = 14.4 Hz, 1H), 2.69 (d, $J$ = 14.4 Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 170.5, 169.9, 166.0, 157.3, 157.0, 138.5, 133.5, 132.5, 131.9, 131.6, 131.5, 130.8, 128.8, 128.5, 127.4, 125.1, 121.0, 119.9, 119.3, 111.7, 66.1, 55.5, 52.8, 36.3. HRMS (ESI) m/z Calcd. for C$_{28}$H$_{26}$N$_3$O$_5$ ([M+H]$^+$) 484.1867, Found 484.1875. Enantiomeric excess was determined to be 98% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, $\lambda$ = 254 nm, 30 °C, 0.8 mL/min, $t_{major}$ = 13.8 min, $t_{minor}$ = 18.2 min).
Prepared according to the procedure within 48 h as white solid (92.6 mg, 99% yield); [α]<sub>D</sub> = -18.182 (c 0.11, CH<sub>2</sub>Cl<sub>2</sub>); Mp: 140.5 - 141.5 °C; <sup>1</sup>H NMR (600 MHz, Chloroform-<d>) δ 9.10 (s, 1H), 8.07 – 8.06 (m, 2H), 7.93 – 7.88 (m, 4H), 7.51 – 7.40 (m, 5H), 7.22 – 7.18 (m, 3H), 6.42 (s, 1H), 5.70 (s, 1H), 3.83 (s, 3H), 3.38 (d, <i>J</i> = 14.4 Hz, 1H), 2.73 (d, <i>J</i> = 14.4 Hz, 1H), 2.35 (s, 3H); <sup>13</sup>C NMR (101 MHz, Chloroform-<d>) δ 170.9, 170.0, 166.3, 156.3, 140.7, 138.4, 133.7, 132.1, 131.7, 129.5, 128.8, 128.6, 127.5, 127.4, 126.3, 125.2, 119.3, 65.1, 53.0, 37.8, 21.5.

HRMS (ESI) m/z Calcd. for C<sub>22</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub> ([M+H]<sup>+</sup>) 468.1918, Found 468.1923. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.8 mL/min, <i>t</i><sub>major</sub> = 36.4 min, <i>t</i><sub>minor</sub> = 35.0 min).
Compound 3ar

Prepared according to the procedure within 48 h as white solid (85.1 mg, 88% yield); 

$[\alpha]_D^{13}$ = -12.500 (c 0.72, CH$_2$Cl$_2$); Mp: 150.4 - 151.3 °C; $^1$H NMR (400 MHz, Chloroform-$d$) δ 9.12 (s, 1H), 8.07 – 8.05 (m, 2H), 7.98 – 7.96 (m, 2H), 7.89 – 7.86 (m, 2H), 7.50 – 7.38 (m, 5H), 7.22 – 7.18 (m, 1H), 6.89 – 6.87 (m, 2H), 6.41 (s, 1H), 5.69 (s, 1H), 3.80 – 3.78 (m, 6H), 3.35 (d, $J$ = 14.3 Hz, 1H), 2.75 (d, $J$ = 14.3 Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$d$) δ 170.9, 169.8, 166.3, 161.2, 156.1, 138.4, 133.6, 132.1, 131.7, 128.8, 128.6, 128.0, 127.5, 125.2, 122.8, 119.3, 114.2, 65.2, 55.4, 52.9, 37.8. HRMS (ESI) m/z Calcd. for C$_{28}$H$_{26}$N$_3$O$_5$ ([M+H]$^+$) 484.1867, Found 484.1878.

Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 8/2, $\lambda$ = 254 nm, 30 °C, 0.8 mL/min, t$_{major}$ = 13.3 min, t$_{minor}$ = 11.6 min).
Compound 3as

Prepared according to the procedure within 48 h as white solid (89.6 mg, 95% yield); [α]$_D^{17}$ = -10.891 (c 3.30, CH$_2$Cl$_2$); Mp: 110.9 - 111.5 °C; $^1$H NMR (400 MHz, Chloroform-d) δ 9.14 (s, 1H), 8.05 – 8.00 (m, 4H), 7.89 – 7.85 (m, 2H), 7.52 – 7.39 (m, 5H), 7.24 – 7.20 (m, 1H), 7.09 – 7.03 (m, 2H), 6.40 (s, 1H), 5.68 (s, 1H), 3.81 (s, 3H), 3.30 (d, J = 14.3 Hz, 1H), 2.76 (d, J = 14.3 Hz, 1H); $^{19}$F NMR (377 MHz, Chloroform-d) δ -107.02 – -110.08 (m); $^{13}$C NMR (101 MHz, Chloroform-d) δ 170.8, 169.8, 166.5, 163.9 (d, J = 252.5 Hz), 155.3, 138.3, 133.7, 132.3, 131.9, 131.6, 128.9, 128.7, 128.4 (d, J = 9.1 Hz), 127.5, 126.5 (d, J = 3.0 Hz), 125.4, 119.3, 115.9 (d, J = 22.2 Hz), 65.1, 53.0, 37.7. HRMS (ESI) m/z Calcd. for C$_{27}$H$_{23}$F$_3$N$_3$O$_4$ ([M+H]$^+$) 472.1667, Found 472.1673. Enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t$_{major}$ = 10.9 min, t$_{minor}$ = 15.5 min).

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Compound 3at

Prepared according to the procedure within 48 h as white solid (80.6 mg, 80% yield; \([\alpha]_D^{17} = -47.101 \ (c \ 1.30, \ \text{CH}_2\text{Cl}_2)\); Mp: 105.8 - 106.7 ºC; \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta 9.24 \ (s, 1H), 8.39 \ (s, 1H), 8.23 - 8.21 \ (m, 1H), 8.11 - 8.10 \ (m, 2H), 7.93 - 7.92 \ (m, 2H), 7.86 - 7.80 \ (m, 3H), 7.51 - 7.43 \ (m, 7H), 7.25 - 7.23 \ (m, 1H), 6.42 \ (s, 1H), 5.73 \ (s, 1H), 3.86 \ (s, 3H), 3.48 \ (d, J = 14.5 Hz, 1H), 2.81 \ (d, J = 14.6 Hz, 1H); \(^13\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta 171.0, 170.1, 166.4, 156.2, 138.4, 134.1, 133.8, 132.9, 132.2, 132.1, 131.8, 128.9, 128.8, 128.6, 128.6, 127.8, 127.7, 127.5, 127.3, 126.6, 126.5, 125.4, 123.3, 119.4, 65.2, 53.0, 38.0. HRMS (ESI) m/z Calcd. for C\(_{31}\)H\(_{26}\)N\(_3\)O\(_4\) ([M+H]\(^+\)) 504.1918, Found 504.1923. Enantiomeric excess was determined to be 98% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \(\lambda = 254 \ nm, 30 \ ^\circ C, 0.8 \ mL/min, t_{\text{major}} = 11.4 \ min, t_{\text{minor}} = 21.2 \ min\).
Compound 3au

Prepared according to the procedure within 48 h as yellow solid (77.6 mg, 83% yield); $[\alpha]_D^{21} = -30.488$ (c 1.60, CH$_2$Cl$_2$); Mp: 130.4 - 131.5 °C; $^1$H NMR (400 MHz, Chloroform-$_d$) $\delta$ 8.67 (s, 1H), 7.95 – 7.92 (m, 2H), 7.78 – 7.76 (m, 2H), 7.52 – 7.48 (m, 1H), 7.42 – 7.34 (m, 6H), 7.25 – 7.12 (m, 4H), 6.46 (s, 1H), 5.72 (s, 1H), 3.85 (s, 3H), 3.77 (dd, $J = 24.3, 15.3$ Hz, 2H), 2.85 (d, $J = 14.2$ Hz, 1H), 2.45 (d, $J = 14.3$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-$_d$) $\delta$ 170.6, 169.7, 166.1, 160.5, 138.4, 134.8, 133.6, 132.0, 130.1, 128.8, 128.4, 127.4, 127.0, 125.0, 119.2, 65.6, 53.0, 36.7, 35.1. HRMS (ESI) m/z Calcd. for C$_{25}$H$_{23}$N$_3$O$_4$ ([M+H]$^+$) 468.1918, Found 468.1925. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 10.5$ min, $t_{\text{minor}} = 11.8$ min).
Prepared according to the procedure within 48 h as yellow solid (89.1 mg, 97% yield); \( \left[ \alpha \right]_{D}^{15} = 20.930 \) (c 0.86, CH\(_2\)Cl\(_2\)); Mp: 152.7 - 153.3 °C; \(^1\)H NMR (400 MHz, Chloroform-d) \( \delta \): 9.15 (s, 1H), 8.03 – 8.01 (m, 2H), 7.90 – 7.88 (m, 2H), 7.58 – 7.57 (m, 1H), 7.53 – 7.48 (m, 1H), 7.45 – 7.41 (m, 4H), 7.38 – 7.37 (m, 1H), 7.23 – 7.19 (m, 1H), 7.03 – 7.01 (m, 1H), 6.43 (s, 1H), 5.72 (s, 1H), 3.85 (s, 3H), 3.32 (d, \( J = 14.3 \) Hz, 1H), 2.76 (d, \( J = 14.5 \) Hz, 1H); \(^{13}\)C NMR (101 MHz, Chloroform-d) \( \delta \): 170.4, 170.0, 166.3, 153.2, 138.2, 133.8, 133.0, 132.2, 132.0, 131.6, 128.9, 128.6, 128.4, 127.7, 127.6, 127.5, 125.4, 119.4, 65.1, 53.1, 37.9. HRMS (ESI) m/z Calcd. for C\(_{25}\)H\(_{22}\)N\(_3\)O\(_4\)S ([M+H]\(^+\)) 460.1326, Found 460.1329. Enantiomeric excess was determined to be 96% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, \( \lambda = 254 \) nm, 30 °C, 0.8 mL/min, \( t_{\text{major}} = 56.6 \) min, \( t_{\text{minor}} = 64.7 \) min).
Compound 3aw

Prepared according to the procedure within 48 h as yellow solid (80.5 mg, 96% yield); $[\alpha]_D^{16} = -31.528$ (c 0.52, CH$_2$Cl$_2$); Mp: 130.3 - 131.2 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.73 (s, 1H), 7.88 - 7.85 (m, 2H), 7.79 - 7.77 (m, 2H), 7.44 - 7.40 (m, 1H), 7.36 - 7.28 (m, 4H), 7.09 - 7.06 (m, 1H), 6.41 (s, 1H), 5.69 (s, 1H), 3.79 (s, 3H), 3.07 (d, $J = 14.1$ Hz, 1H), 2.68-2.58 (m, 1H), 2.50 (d, $J = 14.2$ Hz, 1H), 1.24 (d, $J = 6.8$ Hz, 3H), 1.12 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 170.6, 169.9, 166.3, 166.1, 138.6, 133.6, 132.2, 131.7, 128.7, 128.6, 127.5, 124.9, 119.1, 65.7, 53.1, 36.8, 28.3, 21.3, 20.5. HRMS (ESI) m/z Calcd. for C$_{24}$H$_{26}$N$_3$O$_4$ ([M+H]$^+$) 420.1918, Found 420.1921. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{major} = 7.6$ min, $t_{minor} = 10.0$ min).
Compound 3ax

Prepared according to the procedure within 48 h as yellow solid (75.1 mg, 90% yield); \([\alpha]_D^{16} = 6.875 \, (c \, 1.60, \text{CH}_2\text{Cl}_2)\); Mp: 127.9 - 128.3 °C; \(^1H\) NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 8.82 (s, 1H), 7.92 – 7.88 (m, 4H), 7.52 – 7.49 (m, 1H), 7.44 – 7.42 (m, 2H), 7.38 – 7.35 (m, 2H), 7.16 – 7.13 (m, 1H), 6.50 (s, 1H), 5.84 (s, 1H), 3.88 (s, 3H), 3.05 (d, \(J = 14.3\) Hz, 1H), 2.79 (d, \(J = 14.2\) Hz, 1H), 1.50 – 1.47 (m, 1H), 1.14 – 1.10 (m, 2H), 0.91 – 0.86 (m, 2H); \(^13C\) NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.1, 169.6, 166.1, 164.2, 138.6, 133.4, 132.3, 132.1, 132.0, 128.7, 128.6, 127.5, 124.8, 119.0, 66.0, 53.0, 37.1, 9.1, 8.7, 8.1. HRMS (ESI) m/z Calcd. for C_{24}H_{24}N_{3}O_{4} ([M+H]+=) 418.1761, Found 418.1766.

Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{\text{major}} = 7.5\) min, \(t_{\text{minor}} = 8.7\) min).
Compound 3ay

Prepared according to the procedure within 48 h as yellow solid (69.4 mg, 80% yield); $[\alpha]_D^{16} = 25.455$ (c 0.55, CH$_2$Cl$_2$); Mp: 133.7 - 134.2 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.80 (s, 1H), 7.91 – 7.87 (m, 4H), 7.53 – 7.41 (m, 3H), 7.36 – 7.31 (m, 3H), 6.38 (s, 1H), 5.64 (s, 1H), 3.80 (s, 3H), 3.24 (d, $J = 14.1$ Hz, 1H), 2.66 (d, $J = 14.1$ Hz, 1H), 1.66 (s, 9H); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 172.9, 169.6, 166.3, 153.8, 146.9, 132.9, 132.6, 132.0, 131.9, 130.9, 129.5, 128.5, 127.5, 125.8, 65.0, 58.4, 52.8, 37.7, 28.2. HRMS (ESI) m/z Calcd. for C$_{25}$H$_{28}$N$_3$O$_4$ ([M+H]$^+$) 434.2074, Found 434.2071.

Enantiomeric excess was determined to be 21% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 7.4$ min, $t_{\text{minor}} = 5.8$ min).
Prepared according to the procedure within 72 h as white solid (60.3 mg, 57% yield); \([\alpha]_D^{16} = 47.782\) (c 0.29, CH₂Cl₂); Mp: 128.1 – 129.0 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.48 (s, 1H), 8.10 – 8.08 (m, 2H), 8.04 – 8.00 (m, 4H), 7.59 – 7.43 (m, 6H), 7.37 – 7.21 (m, 8H), 7.08 – 7.06 (m, 2H), 6.86 (s, 1H), 3.60 (s, 3H), 3.24 (d, \(J = 14.3\) Hz, 1H), 3.00 (d, \(J = 14.3\) Hz, 1H); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.8, 171.5, 166.5, 156.0, 145.5, 135.3, 132.3, 132.2, 130.6, 130.2, 128.8, 128.7, 128.6, 128.4, 127.9, 127.7, 126.4, 125.3, 123.2, 119.4, 65.5, 52.4, 40.4. HRMS (ESI) m/z Calcd. for \(\text{C}_{33}\text{H}_{28}\text{N}_3\text{O}_4\) ([M+H]⁺) 530.2074, Found 530.2067. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{\text{major}} = 12.8\) min, \(t_{\text{minor}} = 25.6\) min).
(E)-Compound 3az

Prepared according to the procedure within 72 h as white solid (28.6 mg, 27% yield); $[\alpha]_{D}^{16} = -55.783$ (c 0.12, CH$_2$Cl$_2$);Mp: 132.4 - 133.2 °C; $^1$H NMR (400 MHz, Chloroform-d) $\delta$ 9.37 (s, 1H), 8.03 (s, 1H), 8.00 – 7.98 (m, 2H), 7.88 – 7.83 (m, 4H), 7.53 – 7.49 (m, 1H), 7.46 – 7.34 (m, 7H), 7.21 – 7.15 (m, 6H), 3.96 (s, 3H), 3.54 (d, $J = 15.1$ Hz, 1H), 3.18 (d, $J = 15.0$ Hz, 1H); $^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 171.2, 170.7, 166.2, 156.5, 146.6, 138.2, 134.2, 132.2, 132.1, 130.3, 130.0, 129.1, 128.8, 128.7, 128.7, 128.6, 128.6, 127.5, 126.3, 125.1, 125.0, 119.3, 65.2, 53.2, 32.2. HRMS (ESI) m/z Calcd. for C$_{33}$H$_{28}$N$_3$O$_4$ ($[M+H]^+$) 530.2074, Found 530.2075. Enantiomeric excess was determined to be 89% (determined by HPLC using chiral IF-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{major} = 14.4$ min, $t_{minor} = 52.0$ min).
Gram scale synthesis of the product 3aa

To a tube were added 4-aminopyrazolone 1a (782 mg, 2.2 mmol, 1.0 eq.), C₈ (258 mg, 0.4 mmol, 0.2 eq.), 4 Å MS (2200 mg) and toluene (22 mL). MBH carbonate 2a (1665 mg, 7.7 mmol, 3.5 eq.) was then added in one portion, and the reaction mixture was stirred at 30 °C. When the substrate 1a was consumed as checked by TLC, the reaction was stopped and purified by column chromatography on silica gel directly to give the product 3aa 1.00 g as white solid (yield 99%, ee 97%).

The procedure for the synthesis of compounds 5

To a tube were added 4-aminopyrazolone 1 (0.2 mmol), C₈ (0.04 mmol), 4Å MS (200 mg) and DCM (2 mL). MBH carbonate 4 (0.3 mmol) was then added in one portion and the reaction mixture was stirred at 30 °C. When the substrate 1 was consumed as checked by TLC, the reaction was stopped and purified by column chromatography (petroleum ether/ethyl acetate = 5:1) on silica gel directly to give the product 5.

Compound 5aa

Prepared according to the procedure within 72 h as yellow solid (111.0 mg, 95% yield); [α]ᵢ⁰ = -182.86 (c 0.70, CH₂Cl₂); Mp: 149.6 - 150.3 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.72 (s, 1H), 8.11 – 8.09 (m, 2H), 8.00 – 7.98 (m, 2H), 7.82 – 7.80 (m, 2H), 7.66 – 7.64 (m, 1H), 7.38 – 7.21 (m, 9H), 7.14 – 7.10 (m, 1H), 6.95 – 6.91 (m, 1H), 6.73 (d, J = 7.8 Hz, 1H), 4.49 (d, J = 13.9 Hz, 1H), 3.74 (s, 3H), 3.35 (d, J = 13.9 Hz, 1H), 3.22 (s, 3H); ¹³C NMR (101 MHz, Chloroform-d) δ 171.0, 169.1, 168.0, 166.4, 155.6, 143.6, 138.6, 135.0, 134.7, 132.3, 131.9, 131.7, 130.3, 129.8, 128.8, 128.8, 128.4,
127.7, 126.5, 126.1, 125.1, 123.2, 120.6, 119.2, 108.7, 66.9, 53.0, 33.8, 26.4. HRMS (ESI) m/z Caled.
for C_{35}H_{29}N_{4}O_{5} ([M+H]^+) 585.2132, Found 585.2125. Enantiomeric excess was determined to be 95%
(determined by HPLC using chiral AS-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8
mL/min, t_{major} = 10.2 min, t_{minor} = 17.3 min).

**Compound 5ab**

Prepared according to the procedure within 72 h as white solid (43.0 mg, 35% yield); [α]_{D}^{23} = -93.231 (c 0.52, CH_{2}Cl_{2}); Mp: 108.5 - 109.3 °C; ¹H NMR (600 MHz, Chloroform-d) δ 9.50 (s, 1H), 8.10 – 8.02 (m, 2H), 7.89 – 7.87 (m, 2H), 7.74 – 7.69 (m, 2H), 7.49 – 7.45 (m, 2H), 7.42 – 7.36 (m, 4H), 7.35 – 7.31 (m, 1H), 7.19 – 7.17 (m, 1H), 7.03 – 6.92 (m, 3H), 6.81 (d, J = 7.9 Hz, 1H), 4.45 (d, J = 14.1 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.51 (d, J = 14.0 Hz, 1H), 3.26 (s, 3H); ¹³C NMR (101 MHz, Chloroform-d) δ 170.7, 168.8, 168.4, 166.4, 157.7, 143.6, 138.6, 135.6, 134.0, 133.6, 132.7, 131.6, 131.4, 131.3, 130.2, 128.6, 128.4, 128.3, 127.7, 125.8, 124.9, 122.9, 120.9, 120.7, 119.9, 119.3, 111.5, 68.1, 55.6, 52.8, 33.0, 26.2. HRMS (ESI) m/z Caled. for C_{36}H_{31}N_{4}O_{5} ([M+H]^+) 615.2238, Found 615.2232. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 11.7 min, t_{minor} =
Prepared according to the procedure within 72 h as red solid (112.0 mg, 93% yield); [α]_D<sup>18</sup> = -175.71 (c 0.70, CH₂Cl₂); Mp: 123.8 - 124.5 °C; <sup>1</sup>H NMR (600 MHz, Chloroform-d) δ 9.82 (s, 1H), 8.22 – 8.20 (m, 2H), 8.09 – 8.07 (m, 2H), 7.91 – 7.89 (m, 2H), 7.76 – 7.73 (m, 1H), 7.50 – 7.43 (m, 2H), 7.34 – 7.31 (m, 1H), 7.24 – 7.21 (m, 1H), 7.13 – 7.10 (m, 2H), 7.03 – 7.00 (m, 1H), 6.83 – 6.82 (m, 1H), 4.54 (d, J = 11.3 Hz, 1H), 3.84 (s, 3H), 3.44 (d, J = 11.2 Hz, 1H), 3.30 (s, 3H); <sup>19</sup>F NMR (376 MHz, Chloroform-d) δ -109.30 – -109.44 (m); <sup>13</sup>C NMR (101 MHz, Chloroform-d) δ 170.8, 169.1, 168.0, 166.4, 163.9 (d, J = 252.5 Hz), 154.7, 143.6, 138.5, 134.8, 134.8, 132.2, 132.0, 131.8, 128.9, 128.8, 128.6 (d, J = 8.1 Hz), 128.5, 127.6, 126.1 (d, J = 13.8 Hz), 125.2, 123.2, 120.5, 119.1, 116.0 (d, J = 21.2 Hz), 108.8, 66.8, 52.9, 33.8, 26.4. HRMS (ESI) m/z Calcd. for C₂₃H₂₈FN₄O₅ ([M+H]<sup>+</sup>) <sup>603.2038</sup>, Found <sup>603.2036</sup>; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t<sub>major</sub> = 38.5 min, t<sub>minor</sub> = 50.6 min).
Prepared according to the procedure within 72 h as white solid (96.4 mg, 76% yield); \([\alpha]_D^{18}\) = -243.59 (c 0.78, CH₂Cl₂); Mp: 114.8 - 115.6 °C; \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 9.78 (s, 1H), 8.56 (s, 1H), 8.22 – 8.20 (m, 1H), 8.04 – 8.02 (m, 2H), 7.81 – 7.76 (m, 3H), 7.72 (d, \(J = 8.7\) Hz, 1H), 7.66 – 7.58 (m, 2H), 7.36 – 7.31 (m, 5H), 7.28 – 7.25 (m, 2H), 7.16 – 7.12 (m, 2H), 6.87 – 6.84 (m, 1H), 6.60 (d, \(J = 7.8\) Hz, 1H), 4.62 (d, \(J = 14.0\) Hz, 1H), 3.73 (s, 3H), 3.32 (d, \(J = 14.1\) Hz, 1H), 3.14 (s, 3H); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.2, 169.0, 168.1, 166.4, 155.7, 143.5, 138.7, 135.0, 134.7, 134.0, 133.0, 132.4, 131.9, 131.7, 130.1, 129.0, 128.8, 128.5, 128.5, 127.7, 127.6, 127.3, 126.9, 126.5, 125.9, 125.2, 123.4, 123.1, 120.5, 119.3, 108.7, 66.9, 52.9, 34.1, 26.3. HRMS (ESI) m/z Calcd. for C\(_{39}\)H\(_{31}\)N\(_4\)O\(_5\) ([M+H\(^+\)]) 635.2289, Found 635.2288. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{major} = 52.8\) min, \(t_{minor} = 45.4\) min).
Compound 5ae

Prepared according to the procedure within 72 h as yellow solid (35.9 mg, 30% yield); [α]_D = -89.474 (c 0.38, CH₂Cl₂); Mp: 145.8 - 146.2 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.30 (s, 1H), 7.96 – 7.94 (m, 2H), 7.76 – 7.74 (m, 2H), 7.69 (d, J = 7.9 Hz, 1H), 7.48 – 7.30 (m, 8H), 7.25 – 7.21 (m, 2H), 7.19 – 7.15 (m, 1H), 7.12 – 7.08 (m, 1H), 7.03 – 6.98 (m, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.02 (d, J = 13.6 Hz, 1H), 3.92 – 3.79 (m, 5H), 3.30 (s, 3H), 3.12 (d, J = 13.6 Hz, 1H); ¹³C NMR (101 MHz, Chloroform-d) δ 170.7, 169.0, 167.9, 166.2, 159.6, 143.5, 138.6, 135.2, 134.9, 134.1, 132.1, 131.8, 131.5, 129.5, 128.7, 128.6, 128.2, 127.6, 126.9, 125.9, 124.8, 123.1, 120.6, 119.1, 108.6, 67.3, 52.8, 34.8, 32.9, 26.3. HRMS (ESI) m/z Calcd. for C₃₆H₃₁N₄O₅ ([M+H]+) 599.2289, Found 599.2287. Enantiomeric excess was determined to be 98% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 95/5, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 83.5 min, t_minor = 79.4 min).
**Compound 5af**

Prepared according to the procedure within 72 h as red solid (93.3 mg, 78% yield); [α]_D^18 = -116.67 (c 0.30, CH₂Cl₂); Mp: 121.8 - 122.2 °C; ¹H NMR (600 MHz, Chloroform-d) δ 9.82 (s, 1H), 8.21 – 8.20 (m, 2H), 8.10 – 8.09 (m, 2H), 7.76 – 7.71 (m, 3H), 7.46 – 7.37 (m, 5H), 7.34 – 7.31 (m, 1H), 7.30 – 7.27 (m, 2H), 7.24 – 7.21 (m, 1H), 7.03 – 7.00 (m, 1H), 6.83 (d, J = 7.8 Hz, 1H), 4.62 (d, J = 12.0 Hz, 1H), 3.83 (s, 3H), 3.43 (d, J = 14.0 Hz, 1H), 3.32 (s, 3H), 2.36 (s, 3H), ¹³C NMR (101 MHz, Chloroform-d) δ 171.0, 169.1, 167.9, 166.5, 155.7, 143.6, 138.6, 138.1, 135.3, 134.6, 132.6, 132.2, 131.7, 130.2, 129.9, 128.8, 128.8, 128.5, 128.3, 126.5, 126.1, 125.1, 124.7, 123.2, 120.6, 119.2, 108.7, 66.9, 52.9, 33.8, 26.3, 21.4. HRMS (ESI) m/z Calcd. for C₃₆H₃₁N₄O₅ ([M+H]+) 599.2289, Found 599.2288. Enantiomeric excess was determined to be 84% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 39.4 min, t_minor = 35.7 min).
Prepared according to the procedure within 72 h as white solid (74.9 mg, 61% yield); [α]_D = -206.45 (c 0.31, CH₂Cl₂); Mp: 129.7 - 130.5 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.83 (s, 1H), 8.21 – 8.18 (m, 2H), 8.11 – 8.08 (m, 2H), 7.76 – 7.74 (m, 1H), 7.51 – 7.49 (m, 1H), 7.47 – 7.38 (m, 6H), 7.35 – 7.29 (m, 2H), 7.24 – 7.20 (m, 1H), 7.04 – 7.00 (m, 2H), 6.83 – 6.81 (m, 1H), 4.59 (d, J = 13.9 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.44 (d, J = 13.9 Hz, 1H), 3.31 (s, 3H); ¹³C NMR (101 MHz, Chloroform-d) δ 170.9, 169.1, 168.0, 166.2, 159.7, 155.5, 143.6, 138.6, 135.0, 134.7, 133.7, 131.7, 130.3, 129.8, 129.4, 128.8, 128.8, 126.5, 126.1, 125.1, 123.2, 120.6, 119.6, 119.1, 118.9, 112.3, 108.7, 66.9, 55.4, 53.0, 33.8, 26.4. HRMS (ESI) m/z Calcd. for C₃₆H₃₁N₄O₆ ([M+H]+) 615.2238, Found 615.2233. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t<sub>major</sub> = 56.4 min, t<sub>minor</sub> = 47.5 min).
Compound 5a

Prepared according to the procedure within 72 h as white solid (52.6 mg, 44% yield); [α]$_D$ = -127.42 (c 0.76, CH$_2$Cl$_2$); Mp: 135.1 - 136.5 °C; $^1$H NMR (400 MHz, Chloroform-d) δ 9.86 (s, 1H), 8.21 – 8.18 (m, 2H), 8.10 – 8.06 (m, 2H), 7.92 – 7.90 (m, 2H), 7.55 (d, $J$ = 1.6 Hz, 1H), 7.50 – 7.37 (m, 8H), 7.24 – 7.19 (m, 1H), 7.15 – 7.13 (m, 1H), 6.72 (d, $J$ = 7.9 Hz, 1H), 4.58 (d, $J$ = 14.0 Hz, 1H), 3.84 (s, 3H), 3.43 (d, $J$ = 13.9 Hz, 1H), 3.30 (s, 3H), 2.31 (s, 3H); $^{13}$C NMR (101 MHz, Chloroform-d) δ 171.0, 169.1, 168.1, 166.4, 155.6, 141.4, 138.6, 134.9, 134.6, 132.5, 132.3, 132.0, 131.9, 130.3, 130.2, 129.8, 128.8, 128.4, 127.7, 126.9, 126.5, 125.1, 120.6, 119.2, 108.4, 66.9, 52.8, 33.8, 26.4, 21.4. HRMS (ESI) m/z Calcd. for C$_{36}$H$_{31}$N$_4$O$_5$ ([M+H]$^+$) 599.2289, Found 599.2284. Enantiomeric excess was determined to be 73% (determined by HPLC using chiral OD-AD-H column, hexane/2-propanol = 7/3, $\lambda$ = 254 nm, 30 °C, 0.5 mL/min, $t_{major}$ = 61.4 min, $t_{minor}$ = 114.4 min).
Compound 5ai

Prepared according to the procedure within 72 h as yellow solid (93.9 mg, 78% yield); \([\alpha]_D^{21} = -210.53\) (c 0.76, CH₂Cl₂); Mp: 140.9 - 141.5 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.77 (s, 1H), 8.19 – 8.16 (m, 2H), 8.09 – 8.05 (m, 2H), 7.90 – 7.87 (m, 2H), 7.60 – 7.57 (m, 1H), 7.49 – 7.43 (m, 3H), 7.42 – 7.35 (m, 5H), 7.24 – 7.19 (m, 1H), 7.06 – 7.01 (m, 1H), 6.76 – 6.73 (m, 1H), 4.62 (d, \(J = 13.9\) Hz, 1H), 3.82 (s, 3H), 3.43 (d, \(J = 13.9\) Hz, 1H), 3.30 (s, 3H); \(^{19}\)F NMR (376 MHz, Chloroform-\(d\)) \(\delta\) -119.15 – -119.21 (m); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 170.9, 168.9, 167.3, 166.3, 159.1 (d, \(J = 239.7\) Hz), 155.5, 139.7, 138.5, 136.8, 134.4, 132.4, 131.9, 130.3, 129.8, 128.8, 128.4, 127.6, 126.5, 125.1, 121.6 (d, \(J = 9.1\) Hz), 119.1, 118.0 (d, \(J = 24.2\) Hz), 114.4, 109.0 (d, \(J = 8.1\) Hz), 66.9, 53.0, 33.8, 26.5. HRMS (ESI) \(m/z\) Calcd. for C\(_{35}\)H\(_{28}\)FN\(_4\)O\(_5\) ([M+H]\(^{+}\)) 603.2038, Found 603.2030. Enantiomeric excess was determined to be 65% (determined by HPLC using chiral OD-AD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 30 °C, 0.5 mL/min, \(t_{major} = 47.9\) min, \(t_{minor} = 87.3\) min).
Compound 5aj

Prepared according to the procedure within 72 h as yellow solid (131.1 mg, 99% yield); [α]_D^25 = -96.400 (c 0.60, CH₂Cl₂); Mp: 136.2 - 137.0 °C; ¹H NMR (400 MHz, Chloroform-d) δ 9.70 (s, 1H), 8.17 – 8.15 (m, 2H), 8.08 – 8.06 (m, 2H), 7.88 – 7.86 (m, 2H), 7.62 (d, J = 8.5 Hz, 1H), 7.44 – 7.34 (m, 8H), 7.22 – 7.17 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.93 (s, 1H), 4.51 (d, J = 13.9 Hz, 1H), 3.77 (s, 3H), 3.43 (d, J = 13.9 Hz, 1H), 3.23 (s, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 170.9, 169.0, 167.7, 166.3, 155.6, 144.7, 138.6, 135.6, 134.0, 132.3, 132.1, 130.4, 129.8, 128.9, 128.8, 128.5, 127.6, 127.5, 126.5, 126.0, 125.7, 125.2, 119.4, 119.1, 112.2, 66.8, 53.1, 33.8, 26.5. HRMS (ESI) m/z Calcd. for C₃₅H₂₈BrN₄O₅ ([M+H]+) 663.1238, Found 663.1240. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral IB-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 17.3 min, t_minor = 28.1 min).
Compound 5ak

Prepared according to the procedure within 72 h as yellow solid (75.0 mg, 54% yield); \([\alpha]_D^{25} = -92.000 \) (c 0.50, CH₂Cl₂); Mp: 134.9 - 135.5 °C; ¹H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 9.73 (s, 1H), 8.24 - 8.22 (m, 2H), 8.11 - 8.09 (m, 2H), 7.90 - 7.88 (m, 2H), 7.78 (d, \(J = 8.4\) Hz, 1H), 7.48 - 7.41 (m, 6H), 7.39 - 7.37 (m, 3H), 7.34 - 7.30 (m, 4H), 7.25 - 7.21 (m, 1H), 7.02 - 7.00 (m, 1H), 6.76 (s, 1H), 5.18 (d, \(J = 15.9\) Hz, 1H), 4.93 (d, \(J = 15.9\) Hz, 1H), 4.59 (d, \(J = 13.8\) Hz, 1H), 3.87 (s, 3H), 3.56 (d, \(J = 13.8\) Hz, 1H). ¹³C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 170.9, 169.3, 167.8, 166.3, 155.5, 143.9, 138.5, 137.5, 135.9, 134.4, 133.7, 132.2, 131.9, 130.4, 129.7, 129.2, 128.9, 128.8, 128.5, 128.2, 127.6, 127.4, 126.9, 126.5, 125.2, 123.2, 121.8, 119.2, 110.1, 66.8, 53.2, 44.0, 33.8. HRMS (ESI) m/z Calcd. for C₄₁H₃₂ClN₄O₅ ([M+H]+) 695.2056, Found 695.2053. Enantiomeric excess was determined to be 94% (determined by HPLC using chiral IB-H column, hexane/2-propanol = 9/1, \(\lambda = 254\) nm, 30 °C, 0.8 mL/min, \(t_{\text{major}} = 45.9\) min, \(t_{\text{minor}} = 60.4\) min).
Gram scale synthesis of the product 5aj

To a tube were added 4-aminopyrazolone 1a (639 mg, 1.50 mmol, 1.0 eq.), C8 (193 mg, 0.30 mmol, 0.2 eq.), 4 Å MS (1500 mg) and DCM (15 mL). MBH carbonate 4d (978 mg, 2.30 mmol, 1.5 eq.) was then added in one portion, and the reaction mixture was stirred at 30 °C. When the substrate 1a was consumed as checked by TLC, the reaction was stopped and purified by column chromatography on silica gel directly to give the product 5aj 0.98 g as yellow solid (yield 99%, ee 97%).
The procedure for the synthesis of compounds 7

To a solution of nitrile oxide 6 (0.6 mmol) and Cs₂CO₃ (0.6 mmol) in DCM (2.0 mL) was added the product 3 (0.2 mmol). The reaction mixture was stirred at rt for 12 h, and then the reaction was detected by TLC. When the reaction finished, the crude mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound 7.

**Compound 7aa**

Prepared according to the procedure within 12 h as yellow solid (113.4 mg, 99% yield, dr = 4:1); [α]₁⁰⁰ᵣ = 97.500 (c 0.40, CH₂Cl₂); Mp: 126.7 - 127.5 °C; ¹H NMR (400 MHz, Chloroform-d) δ 8.80 (s, 1H), 8.04 – 8.00 (m, 4H), 7.95 – 7.92 (m, 2H), 7.62 – 7.59 (m, 2H), 7.45 – 7.40 (m, 6H), 7.38 – 7.36 (m, 5H), 7.24 – 7.19 (m, 1H), 3.85 – 3.81 (m, 4H), 3.35 (d, J = 17.5 Hz, 1H), 2.93 (d, J = 15.2 Hz, 1H), 2.69 (d, J = 15.2 Hz, 1H); ¹³C NMR (101 MHz, Chloroform-d) δ 171.6, 170.9, 166.9, 156.8, 156.0, 138.2, 132.3, 132.2, 131.1, 130.6, 129.5, 128.9, 128.8, 127.6, 127.0, 126.4, 125.5, 119.3, 86.7, 64.1, 53.7, 47.9, 40.7, 29.7. HRMS (ESI) m/z Calcd. for C₃₄H₂₉N₄O₅ ([M+H]⁺) 573.2132, Found 573.2130. Enantiomeric excess was determined to be 98% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 25.8 min, t_minor = 49.0 min).
Compound 7ab

Prepared according to the procedure within 12 h as yellow solid (116.9 mg, 97% yield, dr = 5:1); [α]D = 150.00 (c 0.10, CH2Cl2); Mp: 108.5 - 109.6 °C; 1H NMR (400 MHz, Chloroform-d) δ 8.82 (s, 1H), 8.04 – 8.00 (m, 4H), 7.63 – 7.60 (m, 2H), 7.56 – 7.53 (m, 1H), 7.48 – 7.40 (m, 10H), 7.10 – 7.07 (m, 1H), 3.89 – 3.84 (m, 4H), 3.83 (s, 3H), 3.36 (d, J = 17.5 Hz, 1H), 2.94 (d, J = 15.3 Hz, 1H), 2.68 (d, J = 15.2 Hz, 1H); 13C NMR (101 MHz, Chloroform-d) δ 171.6, 170.9, 166.8, 159.9, 156.7, 155.9, 147.1, 138.1, 133.5, 131.1, 130.6, 129.8, 129.5, 129.0, 128.9, 127.8, 127.2, 127.0, 126.4, 125.5, 119.3, 112.2, 86.7, 64.0, 55.4, 53.7, 47.8, 40.7, 29.7. HRMS (ESI) m/z Calcd. for C35H31N4O6 ([M+H]+) 603.2238, Found 603.2238. Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 23.3 min, t_minor = 36.5 min).
**Compound 7ac**

Prepared according to the procedure within 12 h as white solid (97.4 mg, 83% yield, \( \text{dr} = 5:1 \)); \([\alpha]_{D}^{18}\) = 141.66 (c 0.24, \( \text{CH}_2\text{Cl}_2 \)); Mp: 111.7 - 112.5 °C; \(^1\)H NMR (400 MHz, Chloroform-\( d \)) \( \delta \) 8.80 (s, 1H), 8.04 – 8.02 (m, 2H), 7.96 – 7.91 (m, 4H), 7.63 – 7.60 (m, 2H), 7.54 – 7.52 (m, 1H), 7.49 – 7.38 (m, 8H), 7.20 – 7.18 (m, 2H), 3.87 – 3.83 (m, 4H), 3.35 (d, \( J = 17.5 \) Hz, 1H), 2.94 (d, \( J = 15.3 \) Hz, 1H), 2.68 (d, \( J = 15.2 \) Hz, 1H), 2.33 (s, 3H); \(^{13}\)C NMR (151 MHz, Chloroform-\( d \)) \( \delta \) 171.6, 170.9, 166.8, 165.8, 156.8, 156.1, 141.0, 138.2, 132.3, 131.1, 129.7, 129.0, 128.9, 128.7, 127.9, 127.6, 127.0, 126.8, 126.3, 125.4, 119.3, 86.7, 64.1, 53.7, 47.8, 40.8, 29.7, 21.5. HRMS (ESI) m/z Caled. for \( \text{C}_{35}\text{H}_{31}\text{N}_{4}\text{O}_{5} \) ([M+H]\(^+\)) 587.2286, Found 587.2286; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \( \lambda = 254 \) nm, 30 °C, 0.8 mL/min, \( t_{\text{major}} = 21.2 \) min, \( t_{\text{minor}} = 42.8 \) min).

**Compound 7ad**

Prepared according to the procedure within 12 h as yellow solid (121.7 mg, 93% yield, \( \text{dr} = 3:1 \)); \([\alpha]_{D}^{18}\) = 93.684 (c 1.90, \( \text{CH}_2\text{Cl}_2 \)); Mp: 119.8 - 120.6 °C; \(^1\)H NMR (400 MHz, Chloroform-\( d \)) \( \delta \) 8.93 – 8.88 (m, 1H), 8.08 – 7.93 (m, 6H), 7.56 – 7.41 (m, 9H), 7.24 – 7.20 (m, 1H), 6.89 (s, 1H), 3.91 (s, 3H), 3.68 – 3.61 (m, 1H), 3.15 (d, \( J = 18.1 \) Hz, 1H), 3.17 – 3.10 (m, 1H), 3.09 – 3.03 (m, 1H), 2.29 – 2.26 (m, 3H), 1.7127.
2.20 – 2.17 (m, 6H); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.6, 170.8, 166.9, 158.2, 156.0, 147.1, 139.6, 138.2, 136.5, 132.3, 132.2, 130.7, 129.5, 129.0, 128.9, 128.8, 128.8, 127.6, 126.3, 125.5, 124.1, 119.3, 86.1, 64.0, 53.6, 51.4, 40.5, 21.1, 19.7, 17.8. HRMS (ESI) m/z Calcd. for C\(_{37}\)H\(_{35}\)N\(_4\)O\(_5\) ([M+H]\(^+\)) 615.2602, Found 615.2596. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \(\lambda = 254\) nm, 0.8 mL/min, \(t_{\text{major}} = 9.7\) min, \(t_{\text{minor}} = 18.8\) min).

**Compound 7ae**

Prepared according to the procedure within 12 h as yellow solid (127.7 mg, 99% yield, \(\text{dr} = 4:1\)); \([\alpha]_D^20 = 97.619\) (c 0.42, CH\(_2\)Cl\(_2\)); Mp: 126.9 - 127.5 °C; \(^1\)H NMR (400 MHz, Chloroform-\(d\)) \(\delta\) 8.92 – 8.86 (m, 1H), 8.08 – 7.98 (m, 4H), 7.55 – 7.53 (m, 1H), 7.48 – 7.46 (m, 1H), 7.45 – 7.35 (m, 6H), 7.23 – 7.19 (m, 1H), 7.08 – 7.05 (m, 1H), 6.88 – 6.85 (m, 2H), 3.90 (s, 3H), 3.80 (s, 3H), 3.67 – 3.62 (m, 1H), 3.15 – 3.10 (m, 2H), 2.65 (d, \(J = 15.3\) Hz, 1H), 2.28 – 2.25 (m, 3H), 2.19 – 2.15 (m, 6H); \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 171.6, 170.8, 166.8, 159.9, 158.2, 156.0, 139.6, 138.1, 136.5, 133.5, 130.7, 129.8, 129.4, 129.0, 128.9, 128.8, 128.6, 126.3, 125.5, 124.1, 119.3, 112.2, 86.1, 64.0, 53.6, 51.3, 40.6, 29.7, 21.1, 19.7, 17.8. HRMS (ESI) m/z Calcd.
for C_{38}H_{37}N_{4}O_{6} ([M+H]^+) 645.2708, Found 645.2710. Enantiomeric excess was determined to be 92% (determined by HPLC using chiral AS-H column, hexane/2-propanol = 9/1, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 20.3 min, t_{minor} = 17.5 min).

Prepared according to the procedure within 12 h as white solid (118.2 mg, 94% yield, dr = 4:1); [α]_{D}^{18} = 80.597 (c 0.67, CH_{2}Cl_{2}); Mp: 116.4 - 117.3 °C; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.90 – 8.84 (m, 1H), 8.02 – 7.93 (m, 6H), 7.55 – 7.40 (m, 5H), 7.25 – 7.21 (m, 3H), 6.90 – 6.78 (m, 2H), 3.91 (s, 3H), 3.68 – 3.63 (m, 1H), 3.16 – 3.03 (m, 2H), 2.68 (d, J = 15.2 Hz, 1H), 2.38 – 2.36 (m, 3H), 2.29 – 2.27 (m, 3H), 2.22 – 2.16 (m, 6H); ^{13}C NMR (101 MHz, Chloroform-d) δ 171.6, 170.9, 166.8, 158.2, 156.1, 141.0, 139.6, 138.2, 136.5, 132.2, 130.3, 129.7, 128.8, 128.7, 127.6, 126.7, 126.3, 125.4, 124.1, 121.9, 119.3, 86.2, 64.0, 53.6, 51.4, 40.7, 21.5, 21.1, 19.6, 17.6. HRMS (ESI) m/z Calcd. for C_{38}H_{37}N_{4}O_{6} ([M+H]^+) 629.2758, Found 629.2756. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 10.7 min, t_{minor} = 8.3 min).
Prepared according to the procedure within 12 h as white solid (104.3 mg, 82% yield, $\text{dr} = 4:1$); $[\alpha]_D^{18} = 118.75$ ($c = 0.16$, CH$_2$Cl$_2$); Mp: 116.2 - 117.5 °C; $^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 8.93 – 8.87 (m, 1H), 8.08 – 8.03 (m, 2H), 7.99 – 7.92 (m, 4H), 7.55 – 7.51 (m, 1H), 7.47 – 7.39 (m, 4H), 7.23 – 7.19 (m, 1H), 7.13 – 7.07 (m, 2H), 6.88 – 6.86 (m, 2H), 3.90 (s, 3H), 3.67 – 3.61 (m, 1H), 3.16 – 3.09 (m, 1H), 2.65 (d, $J = 15.2$ Hz, 1H), 2.28 – 2.25 (m, 3H), 2.19 – 2.16 (m, 6H); $^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -108.31 – -108.57 (m); $^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 171.4, 170.8, 167.0, 164.1 (d, $J = 252.3$ Hz), 158.3, 155.2, 139.7, 138.0, 136.4, 135.9, 132.4, 132.0, 128.9, 128.8, 128.7, 128.4 (d, $J = 8.1$ Hz), 127.6, 125.8 (d, $J = 3.0$ Hz), 125.6, 124.0, 119.3, 116.2 (d, $J = 21.2$ Hz), 86.1, 63.9, 53.7, 51.5, 40.5, 21.1, 19.6, 17.8. HRMS (ESI) m/z Calcd. for C$_{37}$H$_{34}$FN$_4$O$_5$ ([M+H]$^+$) 633.2508, Found 633.2503. Enantiomeric excess was determined to be 95% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 11.9$ min, $t_{\text{minor}} = 9.0$ min).
Compound 7ah

Prepared according to the procedure within 12 h as white solid (131.6 mg, 99% yield, dr = 4:1); [α]_D^{18} = 104.76 (c 0.21, CH₂Cl₂); Mp: 122.3 - 123.4 °C; ¹H NMR (600 MHz, Chloroform-d) δ 9.04 – 8.98 (m, 1H), 8.44 (s, 1H), 8.27 – 8.25 (m, 1H), 8.06 – 8.05 (m, 2H), 7.98 – 7.96 (m, 2H), 7.91 – 7.83 (m, 3H), 7.54 – 7.44 (m, 7H), 7.22 (d, J = 7.7 Hz, 1H), 6.96 – 6.88 (m, 2H), 3.92 (s, 3H), 3.69 – 3.65 (m, 1H), 3.21 – 3.11 (m, 2H), 2.72 (d, J = 12.4 Hz, 1H), 2.28 – 2.25 (m, 3H), 2.19 – 2.15 (m, 6H); ¹³C NMR (101 MHz, Chloroform-d) δ 171.7, 170.8, 167.1, 158.3, 156.0, 139.6, 138.2, 136.4, 134.2, 132.9, 132.3, 132.2, 130.3, 128.9, 128.9, 128.8, 128.8, 127.8, 127.6, 127.5, 126.9, 126.7, 126.3, 125.5, 124.1, 123.3, 119.4, 86.2, 64.1, 53.6, 51.5, 40.8, 21.1, 19.6, 17.8. HRMS (ESI) m/z Caled. for C₄₁H₃₇N₄O₅ ([M+H]⁺) 665.2758, Found 665.2760. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral OD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_major = 14.0 min, t_minor = 10.2 min).
The procedure for the synthesis of compounds 9

To a solution of nitrile imine 8a (0.6 mmol) and Cs$_2$CO$_3$ (0.6 mmol) in DCM (2.0 mL) was added the product 3 (0.2 mmol). The reaction mixture was stirred at rt for 12 h, and then the reaction was detected by TLC. When the reaction finished, the crude mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10:1) to give compound 9.

Compound 9aa

Prepared according to the procedure within 12 h as white solid (127.4 mg, 99% yield, dr = 3:1); [α]$_D^{18}$ = -93.333 (c 0.30, CH$_2$Cl$_2$); Mp: 125.8 - 126.5 °C; $^1$H NMR (600 MHz, Chloroform-$_d$) δ 8.60 (s, 1H), 8.04 – 8.02 (m, 2H), 7.92 – 7.91 (m, 2H), 7.81 – 7.79 (m, 2H), 7.52 – 7.28 (m, 9H), 7.25 – 7.23 (m, 2H), 7.11 – 7.05 (m, 3H), 4.24 – 4.14 (m, 2H), 3.86 (d, $J = 18.7$ Hz, 1H), 3.79 (s, 3H), 3.44 (d, $J = 18.6$ Hz, 1H), 3.37 (d, $J = 15.6$ Hz, 1H), 2.59 (d, $J = 15.6$ Hz, 1H), 1.25 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (101 MHz, Chloroform-$_d$) δ 172.7, 172.2, 166.8, 161.4, 156.8, 141.7, 140.4, 137.9,
132.3, 132.2, 130.5, 129.6, 129.3, 128.9, 128.7, 127.4, 126.2, 125.7, 124.1, 119.4, 118.6, 73.6, 63.7, 61.4, 53.9, 44.8, 41.6, 14.1. HRMS (ESI) m/z Calcd. for C_{37}H_{34}N_{5}O_{6} ([M+H]^+) 644.2504, Found 644.2503. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 7.1 min, t_{minor} = 23.8 min).

 Compound 9ab

Prepared according to the procedure within 12 h as white solid (129.4 mg, 96% yield, dr = 4:1); [α]_{D}^{25} = -169.23 (c 0.13, CH_{2}Cl_{2}); Mp: 113.8 - 114.5 °C; ^1H NMR (400 MHz, Chloroform-d) δ 8.54 (s, 1H), 7.96 – 7.94 (m, 2H), 7.85 – 7.81 (m, 2H), 7.38 – 7.32 (m, 2H), 7.30 – 7.25 (m, 3H), 7.23 – 7.19 (m, 3H), 7.15 – 7.12 (m, 3H), 7.00 – 6.93 (m, 4H), 4.14 – 4.02 (m, 2H), 3.77 (d, J = 18.7 Hz, 1H), 3.68 (s, 6H), 3.38 (d, J = 18.7 Hz, 1H), 3.30 (d, J = 15.4 Hz, 1H), 2.53 (d, J = 15.5 Hz, 1H), 1.16 (t, J = 7.2 Hz, 3H); ^13C NMR (101 MHz, Chloroform-d) δ 171.7, 171.1, 165.6, 160.4, 158.8, 155.7, 140.6, 139.3, 136.8, 132.5, 129.4, 128.6, 128.4, 128.2, 127.9, 127.8, 125.2, 124.7, 123.0, 118.3, 118.1, 118.0, 117.4, 111.4, 72.5, 62.6, 60.4, 54.4, 52.9, 43.7, 40.4, 13.1. HRMS (ESI) m/z Calcd. for C_{18}H_{20}N_{5}O_{7} ([M+H]^+) 674.2609, Found 674.2606. Enantiomeric excess was determined to be 91%
(determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, \( t_{\text{major}} = 6.8 \text{ min} \), \( t_{\text{minor}} = 17.8 \text{ min} \)).

**Compound 9ac**

Prepared according to the procedure within 12 h as yellow solid (114.4 mg, 87% yield, dr = 3:1); \([\alpha]_{D}^{25} = -72.727 (c 0.33, \text{CH}_2\text{Cl}_2)\); Mp: 119.6 - 120.3 °C; \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \( \delta \) 8.49 (s, 1H), 7.95 – 7.94 (m, 2H), 7.72 – 7.70 (m, 4H), 7.43 – 7.40 (m, 1H), 7.37 – 7.31 (m, 4H), 7.17 – 7.14 (m, 3H), 7.01 – 6.96 (m, 5H), 4.14 – 4.04 (m, 2H), 3.76 (d, \( J = 18.7 \text{ Hz} \), 1H), 3.69 (s, 3H), 3.36 (d, \( J = 18.6 \text{ Hz} \), 1H), 3.30 (d, \( J = 15.6 \text{ Hz} \), 1H), 2.53 (d, \( J = 15.6 \text{ Hz} \), 1H), 2.21 (s, 3H), 1.16 (t, \( J = 7.2 \text{ Hz} \), 3H); \(^13\)C NMR (101 MHz, Chloroform-\(d\)) \( \delta \) 171.7, 171.1, 165.7, 160.3, 155.8, 140.6, 139.8, 139.3, 136.9, 131.2, 131.2, 128.5, 128.2, 127.9, 127.6, 126.4, 125.7, 125.1, 124.6, 122.9, 118.4, 117.4, 72.5, 62.7, 60.3, 52.8, 43.7, 40.6, 20.4, 13.1. HRMS (ESI) \( m/z \) Calcd. for C\(_{38}\)H\(_{36}\)N\(_5\)O\(_6\) ([M+H]\(^+\)) 658.2660, Found 658.2659. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, \( \lambda = 254 \text{ nm} \), 30 °C, 0.8 mL/min, \( t_{\text{major}} = 9.1 \text{ min} \), \( t_{\text{minor}} = 24.6 \text{ min} \)).
Compound 9ad

Prepared according to the procedure within 12 h as yellow solid (124.4 mg, 94% yield, dr = 3:1); [α]_D^17 = -123.08 (c 0.13, CH₂Cl₂); Mp: 125.4 - 126.7 °C; 

$^1$H NMR (400 MHz, Chloroform-d) δ 8.43 (s, 1H), 8.02 – 8.00 (m, 2H), 7.90 – 7.85 (m, 2H), 7.80 – 7.76 (m, 2H), 7.54 – 7.50 (m, 1H), 7.46 – 7.40 (m, 4H), 7.24 – 7.22 (m, 3H), 7.07 – 7.04 (m, 3H), 6.97 – 6.93 (m, 2H), 4.23 – 4.08 (m, 2H), 3.82 (d, J = 18.7 Hz, 1H), 3.78 (s, 3H), 3.43 (d, J = 18.8 Hz, 1H), 3.30 (d, J = 15.5 Hz, 1H), 2.65 (d, J = 15.5 Hz, 1H), 1.25 – 1.21 (m, 3H);

$^{13}$F NMR (377 MHz, Chloroform-d) δ -108.80 – -108.99 (m);

$^{13}$C NMR (101 MHz, Chloroform-d) δ 172.7, 172.1, 166.8, 163.9 (d, J = 252.0 Hz), 161.3, 155.6, 141.6, 140.1, 137.8, 132.4, 131.9, 129.3, 128.9, 128.7, 128.3 (d, J = 8.5 Hz), 127.4, 125.9 (d, J = 3.2 Hz), 125.8, 123.8, 119.3, 117.9, 116.0 (d, J = 22.0 Hz), 73.0, 63.6, 61.4, 53.5, 44.7, 41.4, 14.1. HRMS (ESI) m/z Calcd. for C$_{37}$H$_{33}$FNO$_5$ ([M+H]$^+$) 662.2409, Found 662.2413. Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t$_{major}$ = 7.4 min, t$_{minor}$ = 19.8 min).
Prepared according to the procedure within 12 h as red solid (137.4 mg, 97% yield, dr = 3:1); [α]$_D$ = 126.31 (c 0.19, CH$_2$Cl$_2$); Mp: 116.1 - 117.5 °C; ¹H NMR (400 MHz, Chloroform-d) δ 8.50 (s, 1H), 8.22 (d, J = 1.8 Hz, 1H), 8.13 – 8.09 (m, 3H), 7.79 – 7.69 (m, 5H), 7.51 – 7.38 (m, 8H), 7.12 – 7.08 (m, 2H), 6.87 – 6.83 (m, 1H), 4.15 – 4.01 (m, 2H), 3.80 – 3.75 (m, 4H), 3.54 (d, J = 18.8 Hz, 1H), 3.45 (d, J = 15.5 Hz, 1H), 2.87 (d, J = 15.5 Hz, 1H), 1.20 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, Chloroform-d) δ 172.8, 172.4, 166.7, 161.3, 156.4, 141.6, 140.0, 138.0, 134.1, 132.7, 132.3, 132.1, 129.1, 128.9, 128.8, 128.7, 128.7, 127.7, 127.4, 127.3, 127.1, 126.42, 126.39, 125.7, 123.6, 123.1, 119.4, 117.6, 72.9, 63.8, 61.3, 53.9, 44.6, 41.5, 14.1. HRMS (ESI) m/z Calcd. for C$_{41}$H$_{36}$N$_5$O$_6$ ([M+H]+) 694.2660, Found 694.2661. Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 7/3, λ = 254 nm, 30 °C, 0.8 mL/min, t$_{major}$ = 10.1 min, t$_{minor}$ = 21.1 min).
3. Experimental procedures of intermediates A1 and C1

To a tube were added MBH carbonate 2a (0.1 mmol), C8 (0.01 mmol), 4 Å MS (100 mg) and toluene (1 mL). The reaction mixture was stirred at 30 °C for 12 h, and the mixture solution was directly detected by HRMS.
To a tube were added MBH carbonate 4a (0.1 mmol), C8 (0.01 mmol), 4Å MS (100 mg) and DCM (1 mL). The reaction mixture was stirred at 30 °C for 24 h, and the mixture solution was directly detected by HRMS.
4. References


5. NMR spectra for compounds
S 143
6. X-ray crystal structure of 3ao

![Image of molecule]

**CCDC: 2181593**

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X-ray crystal structure of 5ak

**CCDC: 2234675**

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