Supporting Information

Fast, solvent-free and highly enantioselective fluorination of β-keto esters catalyzed by chiral copper complexes in a ball mill

Yifeng Wang, a,† Haojiang Wang, a,† Yidong Jiang, a Cheng Zhang, a Juanjuan Shao a and Danqian Xu a,*

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology, Key Laboratory of Green Pesticides and Cleaner Production Technology of Zhejiang Province, Zhejiang University of Technology, Hangzhou 310014, P. R. China
Fax: (+86) 0571 88320066; E-mail: chrc@zjut.edu.cn

Table of Contents

1. General method S2
2. General procedure for the asymmetric fluorination of β-Ketoesters: S2
3. Characterization results S3
4. NMR spectra S23
5. HPLC analysis S68
6. Reference S113
1. General methods

Flash chromatography (FC) was carried out using silica gel (200-300 mesh). Monitoring of reactions was performed by TLC on silica gel precoated on glass plates, and spots were visualized with UV light at 254 nm. $^1$H and $^{13}$C NMR were recorded in CDCl$_3$ on Bruker AVANCE III (500 MHz for $^1$H NMR and 125 MHz for $^{13}$C NMR). TMS served as internal standard ($\delta = 0$ ppm) for $^1$H NMR and CDCl$_3$ was used as internal standard ($\delta = 77.0$ ppm) for $^{13}$C NMR; $^1$H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constants (Hz) and integration. HPLC experiments were carried out using a JASCO LC-2000 Plus system with MD-2010 HPLC diode array detector. Electrospray ionization (ESI) mass experiments were performed on a Thermo LCQ fleet. All experiments were carried out under air. Reactions in the ball mill were conducted using a Fritsch Planetary Micro Mill model “Pulverisette 7”. The milling instrument consists of a main disk which can rotate at a speed of 100-800 rpm and accommodates two grinding bowls (45 mL). Both bowls and balls (2 mm diameter) are made of stainless steel. GC analyses were performed on Supelco $\beta$-DEX 120 (30 m) columns; carrier gas: N$_2$; flow rate, 1 ml min$^{-1}$; injector, 200°C; FID detector, air/H$_2$ 400/40 ml min$^{-1}$, 250°C.

Ligands I, substrates 1 and 3 were synthesized according to the reported procedures.$^{[1]}$ Commercially available fluorination reagent (NFSI), ligands I, 7a-e and solvents were used without further purification or drying. All reactions were carried out in oven-dried stainless steel milling vessel. The absolute configurations of 2f$^{[2]}$ and 4j$^{[3]}$ were assigned by comparing the retention times of the HPLC analysis reported in the literature.

2. General procedure for the asymmetric fluorination of $\beta$-Ketoesters:

A clean, dry ball milling vessel was charged with 60 stainless steel grinding balls (2 mm diameter), the Lewis acid and the chiral ligands was grinded firstly for 5 minute to form the metal complexes, and then 1,3-dicarbonyl compounds 1a (1 mol) and NFSI (1.2 equiv.) were added sequentially. After 4 min milling at 200 rpm and monitoring by TLC, the mixture was obtained by washing the vessel and the balls
with 3 × 30 mL ethyl acetate. The organic solution was concentrated and purified by Flash chromatography to afford the fluorinated product (gradient: pentane: ethyl acetate=5:1). The enantiomeric excess was determined by chiral-phase HPLC analysis.

3. Characterization results

methyl (R)-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2a)

![2a]

White solid; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.85 (d, $J = 7.7$ Hz, 1H), 7.72 (t, $J = 8.0$ Hz, 1H), 7.53-7.46 (m, 2H), 3.82 (s, 3H), 3.81 (dd, $J = 11.7, 17.7$ Hz, 1H), 3.45 (dd, $J = 23.3, 17.6$ Hz, 1H); $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 195.02 (d, $J_{CF} = 18.2$ Hz), 167.74 (d, $J_{CF} = 27.9$ Hz), 150.80 (d, $J_{CF} = 3.6$ Hz), 136.72, 133.32, 128.67, 126.61, 125.68, 94.64 (d, $J_{CF} = 201.8$ Hz), 53.17, 38.29 (d, $J_{CF} = 24.0$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm) tᵣ = 11.2 min (major), tᵣ = 13.3 min (minor). MS (ES$^+$): m/z = 209.15 ([M+H$^+$])

ethyl (R)-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2b)

![2b]

Yellow oil; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.79 (d, $J = 7.7$ Hz, 1H), 7.68 (t, $J = 7.5$ Hz, 1H), 7.49 (d, $J = 7.7$ Hz, 1H), 7.43 (t, $J = 7.5$ Hz, 1H), 4.24 (q, $J = 7.1$ Hz, 2H), 3.77 (dd, $J = 17.7, 11.6$ Hz, 1H), 3.40 (dd, $J = 23.4, 17.7$ Hz, 1H), 1.22 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 195.13 (d, $J_{CF} = 18.1$ Hz), 167.16 (d, $J_{CF} = 27.8$ Hz), 150.80 (d, $J_{CF} = 3.5$ Hz), 136.59, 133.19, 128.50, 126.54, 125.37, 94.42 (d, $J_{CF} = 201.3$ Hz), 62.38, 38.16 (d, $J_{CF} = 23.9$ Hz), 13.85. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): tᵣ = 9.4 min (major), tᵣ = 10.9 min (minor). MS (ES$^-$): m/z
isopropyl (R)-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2c)

White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.84 (d, $J = 7.7$ Hz, 1H), 7.71 (t, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 5.13-5.18 (m, 1H), 3.77 (dd, $J = 17.6$, 11.8 Hz, 1H), 3.43 (dd, $J = 23.3$, 17.6 Hz, 1H), 1.25 (dd, $J = 12.0$, 6.3 Hz, 6H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.29 (d, $J_{CF} = 18.4$ Hz), 166.88 (d, $J_{CF} = 27.4$ Hz), 150.92 (d, $J_{CF} = 3.5$ Hz), 136.55, 133.47, 128.56, 126.55, 125.57, 94.47 (d, $J_{CF} = 201.7$ Hz), 70.66, 38.30 (d, $J_{CF} = 24.0$ Hz), 21.51 (d, $J_{CF} = 13.3$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, Hexane: iPrOH= 99: 1, flow rate 0.5ml/min, 254nm): $t_R = 34.8$ min (minor), $t_R = 43.7$ min (major). MS (ES$^+$): m/z =237.85 ([M+H]$^+$)

cyclohexyl (R)-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2d)

White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 7.7$ Hz, 1H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 1H), 4.94-4.89 (m, 1H), 3.76 (dd, $J = 17.5$, 10.9 Hz, 1H), 3.43 (dd, $J = 22.9$, 17.5 Hz, 1H), 1.76 (dd, $J = 10.9$, 7.9 Hz, 2H), 1.53 (dd, $J = 14.0$, 9.1 Hz, 2H), 1.47-1.38 (m, 3H), 1.36-1.28 (m, 2H), 1.24-1.18 (m, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.33 (d, $J_{CF} = 18.3$ Hz), 166.60 (d, $J_{CF} = 27.8$ Hz), 150.79 (d, $J_{CF} = 3.8$ Hz), 136.49, 133.51, 128.51, 126.50, 125.42, 94.55 (d, $J_{CF} = 201.7$ Hz), 74.94, 38.34 (d, $J_{CF} = 24.0$ Hz), 31.00 (d, $J_{CF} = 15.5$ Hz), 25.09, 23.08 (d, $J_{CF} = 6.0$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 98: 2, flow rate 1.0ml/min, 254nm): $t_R = 15.6$ min (major), $t_R = 17.4$ min (minor). MS (ES$^+$): m/z =277.15 ([M+H]$^+$)
benzyl \((R)\)-2-fluoro-1-oxo-2,3-dihydro-1\(H\)-indene-2-carboxylate \((2e)\)

![2e](image)

White solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.04 (d, \(J = 7.4\) Hz, 1H), 7.86 (d, \(J = 7.7\) Hz, 1H), 7.72 (d, \(J = 7.7\) Hz, 1H), 7.62 (t, \(J = 8.0\) Hz, 1H), 7.51-7.48 (m, 2H), 7.34 (d, \(J = 6.9\) Hz, 3H), 5.27 (dd, \(J = 30.5\) Hz, 12 Hz 2H), 3.79 (dd, \(J = 17.6, 11.5\) Hz, 1H), 3.49-3.41 (m, 1H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 194.96 (d, \(J_{CF} = 17.5\) Hz), 167.17 (d, \(J_{CF} = 28.0\) Hz), 150.78 (d, \(J_{CF} = 3.8\) Hz), 136.67, 135.80, 134.77, 133.41, 128.67, 128.46, 128.02, 126.59, 125.70, 94.66 (d, \(J_{CF} = 202.4\) Hz), 67.85, 38.29 (d, \(J_{CF} = 23.8\) Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: \(i\)PrOH= 90: 10, flow rate 1.0ml/min, 254nm): \(t_R = 18.3\) min (major), \(t_R = 24.1\) min (minor). MS (ES\(^+\)): \(m/z = 285.37\) ([M+H]\(^+\))

tert-butyl \((R)\)-2-fluoro-1-oxo-2,3-dihydro-1\(H\)-indene-2-carboxylate \((2f)\)

![2f](image)

White solid; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.83 (d, \(J = 7.7\) Hz, 1H), 7.69 (t, \(J = 7.5\) Hz, 1H), 7.50 (d, \(J = 7.7\) Hz, 1H), 7.46 (t, \(J = 7.5\) Hz, 1H), 3.74 (dd, \(J = 17.5, 10.8\) Hz, 1H), 3.41 (dd, \(J = 22.9, 17.5\) Hz, 1H), 1.44 (s, 9H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 195.70 (d, \(J_{CF} = 18.4\) Hz), 166.26 (d, \(J_{CF} = 27.6\) Hz), 150.94 (d, \(J_{CF} = 3.7\) Hz), 136.39, 133.68, 128.46, 126.47, 125.43, 94.41 (d, \(J_{CF} = 201.9\) Hz), 84.08, 38.37 (d, \(J_{CF} = 24.1\) Hz), 27.85. The enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, Hexane: \(i\)PrOH= 99: 1, flow rate 0.5ml/min, 254nm): \(t_R = 29.0\) min (minor), \(t_R = 40.6\) min (major). MS (ES\(^+\)): \(m/z = 272.95\) ([M+Na]\(^+\))

\((3r)\)-adamantan-1-yl \((R)\)-2-fluoro-1-oxo-2,3-dihydro-1\(H\)-indene-2-carboxylate \((2g)\)
White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.83 (d, $J = 7.7$ Hz, 1H), 7.69 (t, $J = 7.5$ Hz, 1H), 7.50 (d, $J = 7.7$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 1H), 3.74 (dd, $J = 17.5$, 10.5 Hz, 1H), 3.40 (dd, $J = 22.8$, 17.5 Hz, 1H), 2.15 (s, 3H), 2.05 (d, $J = 2.9$ Hz, 6H), 1.63 (t, $J = 2.7$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 195.75 (d, $J_{CF} = 18.4$ Hz), 165.82 (d, $J_{CF} = 27.8$ Hz), 150.95 (d, $J_{CF} = 3.9$ Hz), 136.32, 133.75, 128.41, 126.44, 125.39, 94.34 (d, $J_{CF} = 201.9$ Hz), 84.10, 41.12, 38.47 (d, $J_{CF} = 24.2$ Hz), 35.95, 30.93. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): t$_R$ = 7.6 min (major), t$_R$ = 10.5 min (minor). MS (ES$^+$): m/z =329.17 ([M+H]$^+$)

methyl (R)-2,5-difluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2h)

White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.81-7.75 (m, 1H), 7.61 (t, $J = 8.0$ Hz, 1H), 7.18 (dd, $J = 13.2$, 5.3 Hz, 1H), 3.83 (s, 3H), 3.81 (dd, $J = 17.8$, 10.9 Hz, 1H), 3.44 (dd, $J = 22.9$, 17.9 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.08 (d, $J_{CF} = 18.3$ Hz), 169.23, 167.53, 167.23 (d, $J_{CF} = 17.9$ Hz), 153.79 (dd, $J_{CF} = 10.6$, 3.8 Hz), 128.18 (d, $J_{CF} = 10.7$ Hz), 117.17 (d, $J_{CF} = 23.9$ Hz), 113.54 (d, $J_{CF} = 23.0$ Hz), 94.61 (d, $J_{CF} = 202.6$ Hz), 53.26, 38.11 (dd, $J_{CF} = 24.3$, 1.9 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): t$_R$ = 14.9 min (major), t$_R$ = 18.3 min (minor). MS (ES$^+$): m/z =227.04 ([M+H]$^+$)

methyl (R)-5-chloro-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2i)
White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.78 (d, $J = 8.2$ Hz, 1H), 7.52 (s, 1H), 7.47-7.45 (m, 1H), 3.83 (s, 3H), 3.79 (dd, $J = 17.9$, 11.1 Hz, 1H), 3.43 (dd, $J = 22.9$, 17.8 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.58 (d, $J_{CF} = 18.4$ Hz), 167.36 (d, $J_{CF} = 27.7$ Hz), 152.13 (d, $J_{CF} = 3.8$ Hz), 143.52, 131.73, 129.60, 126.90, 126.72, 94.53 (d, $J_{CF} = 202.9$ Hz), 53.30, 37.98 (d, $J_{CF} = 24.3$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 99:1, flow rate 1.0ml/min, 254nm): $t_R =$ 35.2 min (major), $t_R =$ 49.9 min (minor). MS (ES$^+$): m/z = 243.75 ([M+H$^+$]).

methyl (R)-5-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2j)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.69 (m, 2H), 7.62 (dd, $J = 8.2$, 0.7 Hz, 1H), 3.82 (s, 3H), 3.78 (dd, $J = 10.5$, 17.5 Hz 1H), 3.43 (dd, $J = 22.9$, 17.7 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.82 (d, $J_{CF} = 18.3$ Hz), 167.28 (d, $J_{CF} = 27.8$ Hz), 152.15 (d, $J_{CF} = 3.7$ Hz), 132.42, 132.38, 132.08, 129.97, 126.68, 94.41 (d, $J_{CF} = 202.9$ Hz), 53.28, 37.86 (d, $J_{CF} = 24.2$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 90:10, flow rate 1.0ml/min, 254nm): $t_R =$ 36.9 min (major), $t_R =$ 50.9 min (minor). MS (ES$^+$): m/z = 287.45 ([M+H$^+$]).

methyl (R)-4-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2k)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.88 (d, $J = 7.8$ Hz, 1H), 7.81 (d, $J = 7.6$ Hz, 1H), 7.47-7.45 (m, 1H), 3.83 (s, 3H), 3.79 (dd, $J = 17.9$, 11.1 Hz, 1H), 3.43 (dd, $J = 22.9$, 17.8 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 193.82 (d, $J_{CF} = 18.3$ Hz), 167.28 (d, $J_{CF} = 27.8$ Hz), 152.15 (d, $J_{CF} = 3.7$ Hz), 132.42, 132.38, 132.08, 129.97, 126.68, 94.41 (d, $J_{CF} = 202.9$ Hz), 53.28, 37.86 (d, $J_{CF} = 24.2$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 90:10, flow rate 1.0ml/min, 254nm): $t_R =$ 36.9 min (major), $t_R =$ 50.9 min (minor). MS (ES$^+$): m/z = 287.45 ([M+H$^+$]).
Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 3.84 (s, 3H), 3.75 (dd, J = 18.1, 11.6 Hz, 1H), 3.38 (dd, J = 23.2, 18.2 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 194.48 (d, J$_{CF}$ = 18.5 Hz), 167.27 (d, J$_{CF}$ = 27.8 Hz), 150.65 (d, J$_{CF}$ = 3.7 Hz), 139.39, 135.15, 130.37, 124.39, 121.86, 94.07 (d, J$_{CF}$ = 202.7 Hz), 53.38, 39.32 (d, J$_{CF}$ = 24.8 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH = 90: 10, flow rate 1.0ml/min, 254nm): $t_R$ = 17.0 min (major), $t_R$ = 20.1 min (minor). MS (ES$^+$): m/z = 287.49 ([M+H$^+$]).

methyl (R)-6-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2l)

![Image](image)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.87 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 3.83 (s, 3H), 3.74 (dd, J = 18.1, 11.6 Hz, 1H), 3.37 (dd, J = 23.2, 18.2 Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 194.39 (d, J$_{CF}$ = 18.3 Hz), 167.24 (d, J$_{CF}$ = 27.8 Hz), 150.60 (d, J$_{CF}$ = 3.8 Hz), 139.34, 135.19, 130.35, 124.34, 121.85, 94.07 (d, J$_{CF}$ = 202.7 Hz), 53.29, 39.32 (d, J$_{CF}$ = 24.8 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH = 90: 10, flow rate 1.0ml/min, 254nm): $t_R$ = 11.9 min (major), $t_R$ = 14.5 min (minor). MS (ES$^+$): m/z = 287.46 ([M+H$^+$]).

methyl (R)-2-fluoro-6-methyl-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2m)

![Image](image)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): δ 7.61 (s, 1H), 7.52 (dd, J = 7.9, 1.1 Hz, 1H), 7.39 (d, J = 7.9 Hz, 1H), 3.79 (s, 3H), 3.74 (dd, J = 17.5, 11.1 Hz, 1H), 3.37 (dd, J = 23.3, 17.5 Hz, 1H), 2.41 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 195.03 (d, J$_{CF}$ = 18.2 Hz), 167.75 (d, J$_{CF}$ = 28.0 Hz), 148.19 (d, J$_{CF}$ = 3.7 Hz), 138.80, 137.98, 133.36, 126.24, 125.36, 94.94 (d, J$_{CF}$ = 201.4 Hz), 53.02, 37.89 (d, J$_{CF}$ = 23.8 Hz), 20.95. The
enantiomeric excess was determined by HPLC (Daicel Chiralpak AD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): t_R = 9.3 min (major), t_R = 10.7 min (minor). MS (ES^+): m/z =223.20 ([M+H]^+)

methyl (R)-2-fluoro-5,6-dimethoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2n)

White solid; ^1H NMR (500 MHz, CDCl3): 6 7.18 (s, 1H), 6.89 (s, 1H), 3.98 (s, 3H), 3.79 (s, 3H), 3.69 (dd, J = 17.4, 10.4 Hz, 1H), 3.32 (dd, J = 22.5, 17.4 Hz, 1H). ^13C NMR (125 MHz, CDCl3): 6 193.25 (d, J_{CF} = 18.5 Hz), 167.97 (d, J_{CF} = 28.1 Hz), 157.27, 150.39, 146.79 (d, J_{CF} = 4.1 Hz), 125.95, 107.36, 105.49, 95.05 (d, J_{CF} = 201.2 Hz), 56.41, 56.13, 53.04, 37.92 (d, J_{CF} = 24.1 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): t_R = 44.7 min (major), t_R = 59.6 min (minor). MS (ES^+): m/z =269.21 ([M+H]^+)

methyl (R)-2-fluoro-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2o)

Yellow solid. ^1H NMR (500 MHz, CDCl3) 6 7.75 (d, J = 8.6 Hz, 1H), 6.97 (dd, J = 8.6, 2.2 Hz, 1H), 6.92 (s, 1H), 3.91 (s, 3H), 3.80 (s, 3H), 3.74 (dd, J = 17.6, 11.1 Hz, 1H), 3.36 (dd, J = 23.1, 17.7 Hz, 1H). ^13C NMR (125 MHz, CDCl3) 6 192.82 (d, J = 18.3 Hz), 168.03, 166.92, 153.94 (d, J = 3.8 Hz), 127.41, 126.30, 116.73, 109.81, 95.04 (d, J = 201.1 Hz), 55.87, 53.05, 38.21 (d, J = 24.1 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): t_R = 21.3 min (major), t_R = 24.9 min (minor). MS (ES^+): m/z =239.08 ([M+H]^+)
methyl (R)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (2p)

White solid; ¹H NMR (500 MHz, CDCl₃): δ 8.06 (d, J = 7.9 Hz, 1H), 7.56-7.53 (m, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 3.82 (s, 3H), 3.22-3.14 (m, 1H), 3.10-3.04 (m, 1H), 2.77-2.67 (m, 1H), 2.58-2.49 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 188.40 (d, JₐCF = 18.7 Hz), 167.76 (d, JₐCF = 26.1 Hz), 143.12, 134.55, 130.46, 128.74, 128.38, 127.22, 93.25 (d, JₐCF = 194.0 Hz), 52.90, 31.84 (d, JₐCF = 22.2 Hz), 24.77 (d, JₐCF = 7.3 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): tᵣ = 12.4 min (major), tᵣ = 13.7 min (minor). MS (ES⁺): m/z =223.25 ([M+H]+)

methyl (R)-6-fluoro-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate (2q)

Yellow oil; ¹H NMR (500 MHz, CDCl₃): δ 7.54 (dd, J = 7.7, 1.2 Hz, 1H), 7.43 (td, J = 7.5, 1.3 Hz, 1H), 7.30 (dd, J = 14.3, 7.0 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 3.82 (s, 3H), 3.14-3.07 (m, 1H), 2.96-2.90 (m, 1H), 2.68-2.56 (m, 1H), 2.33-2.24 (m, 1H), 2.18-2.10 (m, 1H), 1.95-1.87 (m, 1H). ¹³C NMR (125 MHz, CDCl₃): δ 198.59 (d, JₐCF = 26.7 Hz), 167.60 (d, JₐCF = 25.2 Hz), 140.60, 136.44, 132.26, 129.54, 129.26, 126.62, 99.10 (d, JₐCF = 195.9 Hz), 52.93, 33.40 (d, JₐCF = 1.3 Hz), 32.66 (d, JₐCF = 21.25 Hz), 22.38 (d, JₐCF = 2.1 Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): tᵣ = 12.2 min (minor), tᵣ = 13.6 min (major). MS (ES⁺): m/z =237.15 ([M+H]+)

(3r)-adamantan-1-yl (R)-2-fluoro-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate
White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.06 (d, $J = 7.9$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.27 (d, $J = 7.6$ Hz, 1H), 3.19-3.04 (m, 2H), 2.72-2.63 (m, 1H), 2.53-2.43 (m, 1H), 2.13 (s, 3H), 2.04 (d, $J = 2.8$ Hz, 6H), 1.61 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.25 (d, $J_{CF} = 18.4$ Hz), 165.72 (d, $J_{CF} = 26.4$ Hz), 142.84, 134.14, 131.14, 128.59, 128.03 (d, $J_{CF} = 0.8$ Hz), 127.04, 93.03 (d, $J_{CF} = 194.0$ Hz), 83.96, 41.02, 35.86, 31.97 (d, $J_{CF} = 22.3$ Hz), 30.81, 25.29 (d, $J_{CF} = 8.1$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): $t_R$ = 7.8 min (major), $t_R$ = 13.1 min (minor). MS (ES$^+$): $m/z = 343.20$ ([M+H$^+$])

(3r)-adamantan-1-yl

(R)-6-fluoro-5-oxo-6,7,8,9-tetrahydro-5H-benzo[7]annulene-6-carboxylate (2s)

White solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.53 (dd, $J = 7.6, 1.2$ Hz, 1H), 7.43 (td, $J = 7.5, 1.3$ Hz, 1H), 7.32 (t, $J = 7.2$ Hz, 1H), 7.20 (d, $J = 7.6$ Hz, 1H), 3.09-3.03 (m, 1H), 2.96-2.91 (m, 1H), 2.69-2.47 (m, 2H), 2.23 (d, $J = 3.9$ Hz, 2H), 2.16 (s, 3H), 2.06 (dd, $J = 5.0, 3.1$ Hz, 6H), 1.65 (t, $J = 2.7$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 199.21 (d, $J_{CF} = 24.1$ Hz), 165.64 (d, $J_{CF} = 25.1$ Hz), 140.06, 137.30, 132.04, 129.46, 129.21, 126.61, 98.32 (d, $J_{CF} = 195.0$ Hz), 83.67, 41.02, 36.03, 33.29, 32.62 (d, $J_{CF} = 22.4$ Hz), 30.92, 22.29 (d, $J_{CF} = 3.9$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): $t_R$ = 11.9 min (minor), $t_R$ = 14.3 min (major). MS (ES$^+$): $m/z = 357.25$ ([M+H$^+$])
(R)-2-fluoro-1-oxo-N-phenyl-2,3-dihydro-1H-indene-2-carboxamide (2t)

White solid; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.31 (s, 1H), 7.84 (d, $J = 7.7$ Hz, 1H), 7.72 (t, $J = 7.5$ Hz, 1H), 7.59 (d, $J = 7.9$ Hz, 2H), 7.55 (d, $J = 7.7$ Hz, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.9$ Hz, 2H), 7.18 (t, $J = 7.4$ Hz, 1H), 4.08 (dd, $J = 17.4, 11.3$ Hz, 1H), 3.42 (dd, $J = 24.0, 17.4$ Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 196.30 (d, $J_{CF} = 18.1$ Hz), 164.75 (d, $J_{CF} = 21.8$ Hz), 151.83 (d, $J_{CF} = 4.0$ Hz), 136.84, 136.63, 133.25, 129.11, 128.54, 126.56, 125.58, 125.22, 120.13, 97.03 (d, $J_{CF} = 204.7$ Hz), 37.39 (d, $J_{CF} = 22.6$ Hz). The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: iPrOH= 90: 10, flow rate 1.0ml/min, 254nm): $t_R = 17.3$ min (major), $t_R = 25.0$ min (minor). MS (ES$^+$): m/z = 270.16 ([M+H$^+$])

methyl (R)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5a)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.77-7.72 (m, 2H), 7.30-7.20 (m, 2H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.63 (d, $J_{CF} = 18.1$ Hz), 171.14 (d, $J_{CF} = 1.2$ Hz), 162.64 (d, $J_{CF} = 36.7$ Hz), 139.70, 125.88, 124.47, 117.46, 113.61, 103.36 (d, $J_{CF} = 249.3$ Hz), 53.81. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, column at Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 18.3$ min (minor), $t_R = 20.7$ min (major). MS (ES$^+$): m/z = 211.15 ([M+H$^+$])

ethyl (R)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5b)
Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.76-7.72 (m, 2H), 7.28-7.21 (m, 2H), 4.35 (dd, $J = 7.1$, 3.9 Hz, 2H), 1.31 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.83 (d, $J_{CF} = 18.2$ Hz), 171.20 (d, $J_{CF} = 1.3$ Hz), 162.22 (d, $J_{CF} = 36.4$ Hz), 139.66, 125.83, 124.40, 117.46, 113.58, 103.28 (d, $J_{CF} = 249.5$ Hz), 63.51, 13.87. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R =15.6$ min (minor), $t_R =18.8$ min (major). MS (ES$^+$): $m/z =225.05$ ([M+H$^+$])

isopropyl (R)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5c)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.77-7.72 (m, 2H), 7.28-7.22 (m, 2H), 5.24-5.16 (m, 1H), 1.30 (t, $J = 5.9$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.98 (d, $J_{CF} = 18.4$ Hz), 171.27 (d, $J_{CF} = 1.4$ Hz), 161.80 (d, $J_{CF} = 35.9$ Hz), 139.57, 125.83, 124.33, 117.54, 113.58, 103.24 (d, $J_{CF} = 249.9$ Hz), 72.03, 21.45. The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: $i$PrOH= 95:5, flow rate 1.0 mL/min, 254nm): $t_R =8.7$ (minor), $t_R = 9.1$ min (major). MS (ES$^+$): $m/z =239.08$ ([M+H$^+$])

tert-butyl (R)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5d)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.74-7.70 (m, 2H), 7.25-7.19 (m, 2H), 1.49 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 190.32 (d, $J_{CF} = 18.4$ Hz), 171.27 (d, $J_{CF} = 1.6$ Hz), 161.08 (d, $J_{CF} = 35.9$ Hz), 139.42, 125.66, 124.18, 117.64, 113.48, 103.19 (d, $J_{CF} = 250.4$ Hz), 85.60, 27.70. The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R =5.6$ min (minor), $t_R =5.9$ min (major). MS (ES$^+$): $m/z =253.15$ ([M+H$^+$])
benzyl (R)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5e)

![5e](image)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.76-7.71 (m, 2H), 7.39-7.35 (m, 3H), 7.34-7.31 (m, 2H), 7.28-7.21 (m, 2H), 5.33 (d, $J = 3.0$ Hz, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.65 (d, $J_{CF} = 18.3$ Hz), 171.19 (d, $J_{CF} = 1.5$ Hz), 162.18 (d, $J_{CF} = 36.6$ Hz), 139.69, 134.07, 128.76, 128.68, 128.16, 125.91, 124.46, 117.47, 113.60, 103.35 (d, $J_{CF} = 250.1$ Hz), 68.70. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 99:1, flow rate 1.0 mL/min, 254nm): $t_R = 12.0$ min (major), $t_R = 13.3$ min (minor). MS (ES$^+$): m/z =287.07 ([M+H]$^+$)

methyl (R)-2-fluoro-5-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5f)

![5f](image)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.54 (dd, $J = 8.5$, 1.9 Hz, 1H), 7.50 (s, 1H), 7.10 (d, $J = 8.4$ Hz, 1H), 3.86 (s, 3H), 2.38 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.68 (d, $J_{CF} = 18.2$ Hz), 169.56 (d, $J_{CF} = 1.2$ Hz), 162.72 (d, $J_{CF} = 37.3$ Hz), 140.80, 134.45, 125.23, 117.29, 113.12, 103.66 (d, $J_{CF} = 248.5$ Hz), 53.69, 20.52. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 15.3$ min (minor), $t_R = 19.7$ min (major). MS (ES$^+$): m/z =225.17 ([M+H]$^+$)

methyl (R)-2-fluoro-6-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5g)
Yellow oil; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.62 (d, $J$ = 7.9 Hz, 1H), 7.07 (d, $J$ = 7.9 Hz, 1H), 7.02 (s, 1H), 3.88 (s, 3H), 2.49 (s, 3H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 188.90 (d, $J_{CF}$ = 18.4 Hz), 171.66 (d, $J_{CF}$ = 1.4 Hz), 162.79 (d, $J_{CF}$ = 37.0 Hz), 152.53, 125.84, 125.49, 115.09, 113.74, 103.83 (d, $J_{CF}$ = 249.0 Hz), 53.75, 22.78. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH = 90:10, flow rate 1.0 mL/min, 254 nm): $t_R$ = 17.1 min (minor), $t_R$ = 24.3 min (major). MS (ES$^+$): m/z = 225.15 ([M+H]+)

methyl (R)-2-fluoro-7-methyl-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5h)

Yellow oil; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.55 (m, 2H), 7.15 (t, $J$ = 7.5 Hz, 1H), 3.89 (s, 3H), 2.36 (s, 3H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 190.18 (d, $J_{CF}$ = 18.1 Hz), 169.85 (d, $J_{CF}$ = 1.6 Hz), 162.86 (d, $J_{CF}$ = 37.0 Hz), 140.58, 124.28, 123.91, 123.04, 116.94, 103.36 (d, $J$ = 248.6 Hz), 53.76, 13.99. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH = 95:5, flow rate 1.0 mL/min, 254 nm): $t_R$ = 11.5 min (major), $t_R$ = 12.0 min (minor). MS (ES$^+$): m/z = 225.16 ([M+H]+)

methyl (R)-2-fluoro-5-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5i)

Yellow solid; $^1$H NMR (500 MHz, CDCl₃): $\delta$ 7.50-7.45 (m, 1H), 7.39 (dd, $J$ = 6.3, 2.8 Hz, 1H), 7.22 (dd, $J$ = 9.0, 3.5 Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, CDCl₃): $\delta$ 189.15 (dd, $J_{CF}$ = 18.4, 3.0 Hz), 167.20, 162.27 (d, $J_{CF}$ = 36.7 Hz), 158.99 (d, $J_{CF}$ =
245 Hz), 127.16 (d, $J_{CF} = 25.7$ Hz), 118.18 (d, $J_{CF} = 8.3$ Hz), 114.92 (d, $J_{CF} = 7.8$ Hz), 111.25 (d, $J_{CF} = 24.8$ Hz), 104.07 (d, $J_{CF} = 250.3$ Hz), 53.92. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 99:1, flow rate 1.0 mL/min, 254nm): $t_R = 36.5$ min (major). MS (ES$^+$): m/z = 251.03 ([M+Na$^+$])

methyl ($R$)-2-fluoro-5-chloro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5j)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.70-7.67 (m, 2H), 7.20 (d, $J = 9.5$ Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.49 (d, $J_{CF} = 18.4$ Hz), 169.38 (d, $J_{CF} = 1.4$ Hz), 162.14 (d, $J_{CF} = 36.6$ Hz), 139.44, 130.14, 125.18, 118.63, 114.95, 103.74 (d, $J_{CF} = 250.9$ Hz), 53.93. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 7.6$ min (major), $t_R = 8.9$ min (minor). MS (ES$^+$): m/z = 245.04 ([M+H$^+$])

methyl ($R$)-2-fluoro-5-bromo-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5k)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.86 (d, $J = 2.0$ Hz, 1H), 7.83 (dd, $J = 8.7$, 2.2 Hz, 1H), 7.15 (d, $J = 8.7$ Hz, 1H), 3.90 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.31 (d, $J_{CF} = 18.1$ Hz), 169.85 (d, $J_{CF} = 1.2$ Hz), 162.14 (d, $J_{CF} = 36.6$ Hz), 142.18, 128.34, 119.17, 117.12, 115.35, 103.58 (d, $J_{CF} = 251.2$ Hz), 53.97. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OD-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 17.6$ min (major), $t_R = 19.3$ min (minor). MS (ES$^+$): m/z = 288.95 ([M+H$^+$])

methyl ($R$)-2-fluoro-5-iodo-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5l)
Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 8.05 (d, $J$ = 1.8 Hz, 1H), 8.00 (dd, $J$ = 8.7, 1.9 Hz, 1H), 7.05 (d, $J$ = 8.6 Hz, 1H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.02 (d, $J_{CF}$ = 18.3 Hz), 170.56 (d, $J_{CF}$ = 1.1 Hz), 162.14 (d, $J_{CF}$ = 36.5 Hz), 147.83, 134.42, 119.71, 115.75, 103.24 (d, $J_{CF}$ = 251.0 Hz), 86.71, 53.96. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R$ =21.3 min (major), $t_R$ = 27.1 min (minor). MS (ES$^+$): m/z =336.93 ([M+H]$^+$)

methyl (R)-2-fluoro-6-iodo-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5m)

Yellow solid; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.67 (d, $J$ = 1.1 Hz, 1H), 7.63 (dd, $J$ = 8.0, 1.2 Hz, 1H), 7.43 (d, $J$ = 8.0 Hz, 1H), 3.88 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 188.64 (d, $J_{CF}$ = 18.2 Hz), 170.50 (d, $J_{CF}$ = 1.1 Hz), 162.12 (d, $J_{CF}$ = 36.7 Hz), 134.18, 126.27, 123.22, 116.95, 107.82, 103.34 (d, $J_{CF}$ = 251.1 Hz), 53.91. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: $i$PrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R$ =17.2 min (minor), $t_R$ = 28.8 min (major). MS (ES$^+$): m/z =337.03 ([M+H]$^+$)

methyl (R)-2-fluoro-5-methoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5n)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31 (dd, $J$ = 9.0, 2.8 Hz, 1H), 7.13 (d, $J$ = 9.0 Hz, 1H), 7.10 (d, $J$ = 2.8 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.87 (d, $J_{CF}$ = 18.1 Hz), 166.28 (d, $J_{CF}$ = 1.7 Hz), 162.65 (d, $J_{CF}$ = 37.4 Hz)
Hz), 156.57, 128.92, 117.51, 114.39, 105.94, 104.06 (d, $J_{CF} = 248.5$ Hz), 55.98, 53.72.

The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 27.4$ min (minor), $t_R = 30.7$ min (major). MS (ES$^+$): m/z = 263.04 ([M+Na$^+$ ])

methyl (R)-2-fluoro-6-methoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5o)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 8.7$ Hz, 1H), 6.77 (dd, $J = 8.6$, 2.1 Hz, 1H), 6.65 (d, $J = 2.1$ Hz, 1H), 3.94 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 187.07 (d, $J_{CF} = 18.0$ Hz), 173.82, 169.60, 162.84 (d, $J_{CF} = 36.9$ Hz), 127.07, 113.34, 110.34, 104.46 (d, $J_{CF} = 249.6$ Hz), 97.21, 56.31, 53.76. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 28.9$ min (minor), $t_R = 41.3$ min (major). MS (ES$^+$): m/z =263.05 ([M+Na$^+$ ])

methyl (R)-2-fluoro-7-methoxy-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (5p)

Yellow oil; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.30 (dd, $J = 7.6$, 1.2 Hz, 1H), 7.26 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.18 (t, $J = 7.8$ Hz, 1H), 3.98 (s, 3H), 3.87 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 189.81 (d, $J_{CF} = 18.0$ Hz), 162.43 (d, $J_{CF} = 36.9$ Hz), 160.79 (d, $J_{CF} = 1.7$ Hz), 146.16, 125.09, 121.24, 118.57, 116.59, 103.36 (d, $J_{CF} = 250.2$ Hz), 56.50, 53.78. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm): $t_R = 46.3$ min (minor), $t_R = 60.4$ min (major). MS (ES$^+$): m/z =263.08 ([M+Na$^+$ ])

s18
methyl \((R)-2\text{-fluoro-1-oxo-1,2-dihydrornaphtho}[2,1-b]\text{furan-2-carboxylate (5q)}\)

\[
\begin{align*}
\text{5q}
\end{align*}
\]

Yellow oil; \(\text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}):}\ delta 8.64 (d, J = 8.3 Hz, 1H), 8.23 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.76-7.72 (m, 1H), 7.59-7.55 (m, 1H), 7.35 (d, J = 8.9 Hz, 1H), 3.91 (s, 3H). \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}):}\ delta 189.27 (d, J\text{_{CF}} = 17.9 Hz), 174.38 (d, J\text{_{CF}} = 0.9 Hz), 162.72 (d, J\text{_{CF}} = 36.6 Hz), 141.95, 130.92, 130.26, 128.96, 128.94, 126.55, 123.39, 113.10, 110.25, 103.73 (d, J\text{_{CF}} = 249.7 Hz), 53.84. \text{The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm):} t\text{R} = 21.4 \text{ min (major), } t\text{R} = 31.4 \text{ min (minor). MS (ES\textsuperscript{+}): m/z =261.06 ([M+H])} \end{align*}

methyl \((R)-2\text{-fluoro-3-oxo-2,3-dihydrornaphtho}[2,3-b]\text{furan-2-carboxylate (5r)}\)

\[
\begin{align*}
\text{5r}
\end{align*}
\]

Yellow solid; \(\text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}):}\ delta 8.37 (s, 1H), 7.97 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.68-7.65 (m, 1H), 7.52-7.48 (m, 2H), 3.91 (s, 3H). \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}):}\ delta 189.60 (d, J\text{_{CF}} = 19.1 Hz), 174.38 (d, J\text{_{CF}} = 0.9 Hz), 162.93 (d, J\text{_{CF}} = 39.2 Hz), 139.55, 131.10, 130.95, 130.12, 128.58, 127.85, 126.00, 117.36, 108.42, 104.03 (d, J\text{_{CF}} = 248.7 Hz), 53.82. \text{The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH= 90:10, flow rate 1.0 mL/min, 254nm):} t\text{R} = 29.3 \text{ min (minor), } t\text{R} = 42.2 \text{ min (major). MS (ES\textsuperscript{+}): m/z =261.05 ([M+H])} \end{align*}

methyl 2-fluoro-3-oxo-2,3-dihydrobenzo[b]thiophene-2-carboxylate (6a)
The product was synthesized according to the general procedure as yellow oil in 80\% overall yield. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 8.01 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 8.3$ Hz, 1H), 7.67-7.63 (m, 1H), 7.54 (t, $J = 7.6$ Hz, 1H), 3.93 (s, 3H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 181.47 (d, $J_{CF} = 19.0$ Hz), 178.24, 161.98 (d, $J_{CF} = 35.0$ Hz), 149.23, 131.30, 125.98, 124.91, 123.22, 109.68 (d, $J_{CF} = 258.1$ Hz), 54.02. The enantiomeric excess was determined by HPLC with an IC-H column at 254nm (2-propanol:hexane=5: 95), 1.0 mL/min; $t_R =11.0$ min (major), 12.3 min (minor). 99\% ee.

tert-butyl 2-fluoro-3-oxo-2,3-dihydrobenzo[b]thiophene-2-carboxylate (6b)

The product was synthesized according to the general procedure as yellow oil in 88\% overall yield. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.85 – 7.79 (m, 1H), 7.67 – 7.61 (m, 1H), 7.38 (d, $J = 8.0$ Hz, 1H), 7.34-7.28 (m, 1H), 1.47 (s, 9H). $^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 192.18 (d, $J_{CF} = 16.0$ Hz), 163.73 (d, $J_{CF} = 32.2$ Hz), 149.00, 137.25, 128.06, 126.35, 124.33, 124.31, 98.31 (d, $J_{CF} = 240.8$ Hz), 85.32, 27.71. The enantiomeric excess was determined by HPLC with an OJ-H column at 254nm (2-propanol: hexane=10: 90), 1.0 mL/min; $t_R =$17.9 min (minor), 19.8 min (major). 93\% ee.

ethyl 1-fluoro-2-oxocyclopentane-1-carboxylate (8a)

Coloreless oil. $^1$H NMR (500 MHz, Chloroform-d) $\delta$ = 4.26-4.19 (m, 2H), 2.53 – 2.45 (m, 1H), 2.44-2.40 (m, 2H), 2.30-2.20 (m, 1H), 2.14-2.03 (m, 2H), 1.24 (t, $J = 7.1$ Hz,
ethyl 1-fluoro-2-oxocyclohexane-1-carboxylate (8b)

White solid; $^1$H NMR (500 MHz, CDCl$_3$): $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.32-4.27 (m, 2H), 2.75-2.57 (m, 2H), 2.52-2.42 (m, 1H), 2.20-2.09 (m, 1H), 1.99-1.79 (m, 4H), 1.32 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 201.79 (d, $J_{CF}$ = 20.0 Hz), 166.89 (d, $J_{CF}$ = 24.8 Hz), 96.30 (d, $J_{CF}$ = 196.6 Hz), 62.31, 39.58, 35.98 (d, $J_{CF}$ = 21.7 Hz), 26.50, 20.91 (d, $J_{CF}$ = 5.9 Hz), 13.95. The enantiomeric excess was determined by HPLC (Daicel Chiralpak AS-H, Hexane: iPrOH= 98:2, flow rate 0.5ml/min, 220nm): $t_R$ = 68.4 min (minor), $t_R$ = 142.4 min (major). MS (ES$^+$): m/z = 189.07 ([M+H]$^+$)

3-acetyl-3-fluorodihydrofuran-2(3H)-one (8c)

Coloreless oil. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ = 4.44-4.29 (m, 2H), 2.77-2.70 (m, 1H), 2.55-2.44 (m, 1H), 2.33 (d, $J$ = 4.9 Hz, 3H). $^{13}$C NMR (125 MHz, Chloroform-$d$) $\delta$ = 203.08 (d, $J_{CF}$ = 31.2 Hz), 169.14 (d, $J_{CF}$ = 24.2 Hz), 96.15 (d, $J_{CF}$ = 204.0 Hz), 65.59 (d, $J_{CF}$ = 4.6 Hz), 31.78 (d, $J_{CF}$ = 21.3 Hz), 25.45. The enantiomeric excess was determined by HPLC (Daicel Chiralpak IC-H, Hexane: iPrOH= 95:5, flow rate 1.0 mL/min, 210nm): $t_R$ =14.1 min (minor), $t_R$ = 15.0 min (major).

ethyl 2-fluoro-2-methyl-3-oxo-3-phenylpropanoate (8d)
Coloreless oil. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta = 8.07$-$8.04$ (m, 2H), $7.62$-$7.58$ (m, 1H), $7.49$-$7.46$ (m, 2H), $4.30$-$4.23$ (m, 2H), $1.88$ (d, $J = 22.5$ Hz, 3H), $1.20$ (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (125 MHz, Chloroform-$d$) $\delta = 191.68$ (d, $J_{CF} = 25.3$ Hz), $168.43$ (d, $J_{CF} = 25.5$ Hz), $133.89$, $133.37$, $133.35$, $129.72$, $129.67$, $128.61$, $96.99$ (d, $J_{CF} = 194.7$ Hz), $62.56$, $20.96$ (d, $J_{CF} = 23.5$ Hz), $13.86$. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OB-H, Hexane: iPrOH = 96:4, flow rate 0.7 mL/min, 254nm): $t_R =$ 14.4 min (minor), $t_R =$ 17.0 min (major).

**ethyl 2-benzyl-2-fluoro-3-oxobutanoate (8e)**

Coloreless oil. $^1$H NMR (500 MHz, Chloroform-$d$) $\delta = 7.31$-$7.21$ (m, 5H), $4.23$ (q, $J = 7.1$, 2H), $3.41$ (dd, $J = 25.8$, $7.6$ Hz, 2H), $2.13$ (d, $J = 5.1$ Hz, 3H), $1.25$ (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (125 MHz, Chloroform-$d$) $\delta = 202.27$ (d, $J_{CF} = 29.5$ Hz), $165.63$ (d, $J_{CF} = 25.4$ Hz), $133.02$, $130.30$, $128.33$, $127.35$, $99.91$ (d, $J_{CF} = 200.1$ Hz), $62.57$, $39.66$ (d, $J_{CF} = 20.2$ Hz), $26.15$, $13.86$. The enantiomeric excess was determined by HPLC (Daicel Chiralpak OJ-H, Hexane: iPrOH = 95:5, flow rate 1.0 mL/min, 210nm): $t_R =$ 23.0 min (minor), $t_R =$ 37.1 min (major).
3. NMR spectra
4. HPLC analysis

![HPLC analysis graph]

<table>
<thead>
<tr>
<th></th>
<th>Name</th>
<th>Time [min]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1H N/O/N</td>
<td>11.230</td>
<td>35.709</td>
</tr>
<tr>
<td>2</td>
<td>1H N/O/N</td>
<td>13.390</td>
<td>4.20%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.00%</td>
</tr>
</tbody>
</table>
2c
### Table 1: Different Y Units

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time [Min]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>26.036</td>
<td>47.735</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>40.764</td>
<td>52.185</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>

---

### Table 2: GAUSSIAN 16

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time [Min]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>26.036</td>
<td>2.126</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>40.764</td>
<td>97.874</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
<tr>
<td>#</td>
<td>Name</td>
<td>Time (Min)</td>
<td>Area [%]</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>1.560</td>
<td>53.71%</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>10.860</td>
<td>49.78%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>100.00%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (Min)</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>7.098</td>
<td>98.21%</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>10.558</td>
<td>1.79%</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>100.00%</td>
</tr>
<tr>
<td>#</td>
<td>Name</td>
<td>Time (min)</td>
<td>Area (%)</td>
</tr>
<tr>
<td>---</td>
<td>-----------</td>
<td>------------</td>
<td>----------</td>
</tr>
<tr>
<td>1</td>
<td>UNKNOWN1</td>
<td>44.22</td>
<td>10.557</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN2</td>
<td>59.019</td>
<td>7.443</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>18.000</td>
</tr>
</tbody>
</table>

**Diagram 1:**

- Graph showing peak areas with retention times.

**Diagram 2:**

- Graph showing peak areas with retention times.

S81
<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (min)</th>
<th>Area % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unknown</td>
<td>20.412</td>
<td>50.750</td>
</tr>
<tr>
<td>2</td>
<td>unknown</td>
<td>24.112</td>
<td>49.248</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (min)</th>
<th>Area % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>unknown</td>
<td>21.805</td>
<td>56.892</td>
</tr>
<tr>
<td>2</td>
<td>unknown</td>
<td>24.978</td>
<td>43.108</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.000</td>
</tr>
<tr>
<td>#</td>
<td>Name</td>
<td>Time (min)</td>
<td>Area % (%)</td>
</tr>
<tr>
<td>---</td>
<td>-------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>1</td>
<td>UNK1050</td>
<td>12.988</td>
<td>49.082</td>
</tr>
<tr>
<td>2</td>
<td>UNK1050</td>
<td>13.892</td>
<td>50.913</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.000</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (min)</th>
<th>Area % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNK1050</td>
<td>12.999</td>
<td>77.622</td>
</tr>
<tr>
<td>2</td>
<td>UNK1050</td>
<td>13.752</td>
<td>22.378</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>100.000</td>
</tr>
</tbody>
</table>
5a

---

Table 1: Summary of Analysis Results

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (min)</th>
<th>Area % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>18.345</td>
<td>99.763</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>19.345</td>
<td>99.763</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>100.000</td>
</tr>
</tbody>
</table>

---

Table 2: Summary of Analysis Results

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time (min)</th>
<th>Area % (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UNKNOWN</td>
<td>18.345</td>
<td>99.763</td>
</tr>
<tr>
<td>2</td>
<td>UNKNOWN</td>
<td>19.345</td>
<td>99.763</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td></td>
<td>100.000</td>
</tr>
</tbody>
</table>

---

**Chemical Structure Image:**

![Chemical Structure](image)
![Chemical Structure](attachment:image.png)

### 5d

**Table 1:**

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time [Min]</th>
<th>Area % [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unnamed</td>
<td>5.63</td>
<td>43.756</td>
</tr>
<tr>
<td>2</td>
<td>Unnamed</td>
<td>5.903</td>
<td>56.244</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>

**Table 2:**

<table>
<thead>
<tr>
<th>#</th>
<th>Name</th>
<th>Time [Min]</th>
<th>Area % [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unnamed</td>
<td>5.867</td>
<td>99.943</td>
</tr>
<tr>
<td>2</td>
<td>Unnamed</td>
<td>5.903</td>
<td>0.057</td>
</tr>
<tr>
<td></td>
<td><strong>Total</strong></td>
<td></td>
<td><strong>100.000</strong></td>
</tr>
</tbody>
</table>

---

S91
5f
5k
50
$5p$
6a
8b
