Supporting Information

Isothiourea-Catalyzed Enantioselective Michael Addition of Malonates to α,β-Unsaturated Aryl Esters.

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1. General Information
Reactions involving moisture sensitive reagents were carried out in flame-dried glassware under an argon or nitrogen atmosphere using standard vacuum line techniques and using anhydrous solvents. Anhydrous solvents (CH\textsubscript{2}Cl\textsubscript{2} and toluene) were obtained from an anhydrous solvent system (purified using an alumina column, Mbraun SPS-800). All other reactions were performed in standard glassware with no precautions
to exclude air or moisture. Solvents and commercial reagents were used as supplied without further purification unless otherwise stated. (2S,3R)-HyperBTM 5 was prepared from a literature procedure. The α,β-unsaturated PNP esters 6 (CF), 16 (CO₂Et), 17 (PhCOR), and the β-trifluoromethyl α,β-unsaturated TCP ester 11 were synthesized as previously reported. All regiomeric ratios were analyzed by the 1H NMR analysis of the crude reaction mixtures.

Room temperature (r.t.) refers to 20−25 °C. Temperatures of 0 °C and −78 °C were obtained using ice/water and CO₂(s)/acetone baths, respectively. Reflux conditions were obtained using a DrySyn, oil bath, or sand bath equipped with a contact thermometer.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F₂₅₄ silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining with a 1% aqueous KMnO₄ solution. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated. Automated chromatography was performed on a Biotage Isolera Four running Biotage OS578 with a UV/Vis detector using the method stated and cartridges filled with Kieselgel 60 silica.

Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected.

Optical rotations [α]D²⁰ were measured on a PerkinElmer Model 341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

HPLC analyses were obtained using either a Shimadzu HPLC consisting of a DGU-20A5 degassing unit, LC-20AT liquid chromatography pump, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven; or a Shimadzu HPLC consisting of a DGU-20A5R degassing unit, LC-20AD liquid chromatography pump, SIL-20AHT autosampler, SPD-20A UV/Vis detector and a CTO-20A column oven. Separation was achieved using DAICEL CHIRALCEL OD-H or DAICEL CHIRALPAK AD-H or AS-H columns. All HPLC traces of enantiomerically-enriched compounds were compared with authentic racemic spectra.

1H, 13C, 19F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (1H 300 MHz), Bruker Avance II 400 (1H 400 MHz; 13C 101 MHz; 19F 376 MHz) or a Bruker Avance II 500 (1H 500 MHz; 13C 126 MHz) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) and referenced to the residual solvent peak. All coupling constants, J, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), and combinations thereof, and m (multiplet). The abbreviation Ar is used to denote aromatic, Ph to denote phenyl, Bn to denote benzyl, br to denote broad, and app to denote apparent.
Infrared spectra \( (\nu_{\text{max}}) \) were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films or solids, with characteristic absorption wave numbers (max) reported in cm\(^{-1}\).

High Resolution Mass spectrometry (HRMS) data were acquired by electrospray ionization time-of-flight (ESI-TOF), either at the University of St Andrews or the University of Edinburgh.

2. General Procedures

**General Procedure 1: Preparation of malonate derivatives.**

\[
\text{HO}_2\text{C} \overset{\text{POCl}_3}{\longrightarrow} \overset{\text{RXH}}{\longrightarrow} \overset{\text{DMAP}}{\longrightarrow} \overset{\text{toluene}}{\longrightarrow} \overset{\text{80 °C}}{\longrightarrow} \overset{\text{X = S, O}}{\longrightarrow} \]

POCl\(_3\) (2.2 equiv) was added dropwise to malonic acid (1.0 equiv), DMAP (0.4 equiv) in anhydrous toluene (0.25 M) at room temperature. The thiol was then added dropwise to the solution and the reaction was heated to 70 °C for 3 h with a condenser. The reaction was then quenched by pouring into ice water. The aqueous solution was then extracted with Et\(_2\)O (3×), washed with brine, dried with MgSO\(_4\), filtered, and the solvent was removed *in vacuo*. The residue was then purified by column chromatography to afford the pure product.

**General Procedure 2: Synthesis of \( \alpha,\beta \)-unsaturated PNP esters**

\[
\text{R} \overset{\text{O}_2\text{N} \overset{\text{(COCl)}_2, \text{Pr}_3\text{NEt}}{\longrightarrow}}{\overset{\text{DMF (cat)}}{\longrightarrow}} \overset{\text{CH}_2\text{Cl}_2, \text{rt}}{\longrightarrow} \text{R} \overset{\text{CO}_2\text{PNP}}{\longrightarrow}
\]

To a solution of corresponding \( \alpha,\beta \)-unsaturated carboxylic acid (1.0 equiv) in anhydrous CH\(_2\)Cl\(_2\) (0.33 M) was added oxalyl chloride (1.0 equiv) and a few drops of DMF at r.t. under a N\(_2\) atmosphere and allowed to stir for 1h. A solution of diisopropylethylamine (2.0 equiv) and the phenol (1.0 equiv) in anhydrous CH\(_2\)Cl\(_2\) (0.33 M) were added dropwise and the mixture was allowed to stir overnight. The solvent was then removed *in vacuo* and the residue was purified by column chromatography to afford the pure product.

**General Procedure 3: Asymmetric Michael addition of malonates to \( \alpha,\beta \)-unsaturated aryl esters**
A mixture of α,β-unsaturated ester (1 equiv) and HyperBTM 5 (20 mol%) in DMF (0.1 M) was cooled to 0 ºC. The malonate (1 equiv.) was added to the pre-cooled mixture, and the resulting mixture was allowed to stir for 16 h at 0 ºC. DMF was removed under vacuum and the crude mixture was purified by column chromatography to afford the product.

3. Synthesis of Starting Materials

3.1 Synthesis of malonate derivatives.

Bis(2-fluorobenzyl) malonate (32)

Following General Procedure 1, malonic acid (0.321 g, 3.08 mmol), DMAP (0.150 g, 1.2 mmol), 2-fluorobenzyl alcohol (0.815 g, 6.5 mmol), and phosphoryl chloride (0.63 mL, 6.8 mmol) in anhydrous toluene (20 mL) gave the title compound as a yellow oil (0.156 g, 0.59 mmol) in a 19% yield. ν<sub>max</sub> (film), 1755 (C=O), 1732 (C=O), 1620, 1589, 1492, 1140, 999, 853; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δH: 3.48 (2H, s), 5.24 (2H, s), 7.04 – 7.13 (4H, m), 7.29 – 7.38 (4H, m); <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>) δF: –117.8 (m); <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δC: 41.4, 61.2 (d, J 4.2), 115.5 (d, J 21.0), 122.5 (d, J 14.5), 124.3 (d, J 3.8), 130.5 (d, J 8.3), 130.71 (d, J 3.6), 161.0, 166.1. HRMS (ESI<sup>+</sup>) C<sub>17</sub>H<sub>15</sub>F<sub>2</sub>O<sub>4</sub> [M]<sup>+</sup> found 321.0929, requires 321.0933 (–1.2 ppm).

S,S-Bis(4-tert-butylnitroxyl)propanebis(thiolate) (35)

Following General Procedure 1, malonic acid (0.500 g, 4.8 mmol), DMAP (0.234 g, 1.9 mmol), 4-tert-butylbenzyl thiol (2.0 mL, 10.6 mmol), and phosphoryl chloride (0.98 mL, 10.6 mmol) in anhydrous toluene (20 mL) gave the title compound as a white solid (1.46 g, 3.41 mmol) in a 71% yield. mp 59–61 ºC; ν<sub>max</sub> (film), 2951 (C–H), 2905 (C–H), 1703 (C=O), 1672, 1516, 1416, 995, 824; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δH: 1.33 (18H, s), 3.83 (2H, s), 4.19 (4H, s), 7.24 (4H, app d, J 8.3), 7.35 (4H, app d, J 8.3); <sup>13</sup>C NMR (126
The title compound was prepared according to General Procedure 2 as a white solid. mp 74–76 °C; ν\text{max} (film), 1526 (N=O), 1736 (C=O); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 6.34 (1H, tdd, J 54.6, 3.9, 1.1), 6.52 (1H, dtd, J 15.9, 2.9, 1.0), 6.97 – 7.18 (1H, m), 7.30 – 7.52 (2H, m), 8.12 – 8.39 (2H, m); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) δ\textsubscript{F} = –116.96 (dd, J 10.1, 3.2), –116.85 (dd, J 10.6, 3.6); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 112.0 (t, J 238.2), 122.4, 125.5, 125.8 (t, J 10.4), 139.6 (t, J 24.2), 145.7, 154.9, 162.2. HRMS (ESI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{7}F\textsubscript{2}NO\textsubscript{4} [M\textsuperscript{+}] found 243.0344, requires 243.0338 (+2.5 ppm).

4-Nitrophenyl (E)-4,4-difluorobut-2-enoate (12)

HF\textsubscript{2}C\(\equiv\)\text{CO}\textsubscript{2}PNP

The title compound was prepared according to General Procedure 2 as a yellow oil (75% yield, ν\text{max} (film), 1526 (N=O), 1755 (C=O); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 6.78 (1H, dt, J 15.8, 2.1), 7.05 (1H, dt, J 15.8, 11.5), 7.34 – 7.41 (2H, m), 8.28 – 8.36 (2H, m); \textsuperscript{19}F NMR (470 Hz, CDCl\textsubscript{3}) δ\textsubscript{F} = –117.4 (q, J 2.3), –84.4 (t, J 2.2); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 111.4 (tq, J 253.0, 39.7), 118.5 (qt, J 285.6, 36.2), 122.3, 125.6, 129.6 (t, J 8.4), 133.5 (t, J 24.3), 145.9, 154.6, 161.3. HRMS (ESI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{7}F\textsubscript{3}NO\textsubscript{4} [M\textsuperscript{+}] found 311.0206, requires 311.0211 (–0.1 ppm).

4-Nitrophenyl (E)-4,4,5,5,5-pentafluoropent-2-enoate (13)

C\textsubscript{2}F\textsubscript{5}\(\equiv\)\text{CO}\textsubscript{2}PNP

The title compound was prepared according to General Procedure 2 as a white solid. mp 99–100 °C; ν\text{max} (film), 1522 (N=O), 1751 (C=O); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 6.60 (1H, dt, J 15.6, 1.8), 7.16 (1H, dt, J 15.6, 9.0), 7.35 – 7.38 (2H, m), 8.29 – 8.32 (2H, m); \textsuperscript{19}F NMR (470 MHz, CDCl\textsubscript{3}) δ\textsubscript{F} = –54.46; \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 122.4, 123.2 (t, J 287.9), 124.2 (t, J 6.5), 125.5, 139.6 (t, J = 29.1 Hz), 145.8, 154.7, 161.8. HRMS (ESI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{8}F\textsubscript{5}ClNO\textsubscript{4} [M\textsuperscript{+}] found 276.9943, requires 276.9948 (–1.8 ppm).

4-Nitrophenyl (E)-4-bromo-4,4-difluorobut-2-enoate (15)
Following General Procedure 2, (E)-4-bromo-4,4-difluorobut-2-enoic acid (0.50 g, 2.49 mmol), oxalyl chloride (0.32 g, 3.73 mmol), diisopropylethylamine (0.87 mL, 4.98 mmol), and p-nitrophenol (0.35 g, 2.49 mmol) gave the title compound as a yellow solid (0.30 g, 0.93 mmol) in a 37% yield. mp 79–80 °C; ν\textsubscript{max} (film), 1522 (N–O), 1749 (C=O); \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ\textsubscript{H}: 6.52 (1H, dt, J 15.6, 1.7), 7.22 (1H, dt, J 15.6, 10.0), 7.36 (2H, app d, J 8.7), 8.31 (2H, app d, J 8.7); \textsuperscript{19}F NMR (376 MHz, CDCl\textsubscript{3}) δ\textsubscript{F}: −50.6; \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ\textsubscript{C}: 114.7 (t, J 301.8), 122.4, 122.6 (t, J 6.8), 125.6, 141.0 (t, J 25.9), 145.7, 154.8, 161.9. HRMS (ESI\textsuperscript{+}) C\textsubscript{10}H\textsubscript{6}BrF\textsubscript{2}NO\textsubscript{4} [M]\textsuperscript{+} found 320.9437, requires 320.9443 (−1.9 ppm).
4. Synthesis of Michael Addition Products.

(S)-1,1-Dimethyl 3-(4-nitrophenyl) 2-(trifluoromethyl)propane-1,1,3-tricarboxylate (8a)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (26.0 mg, 0.1 mmol), (2S,3R)-HyperBTM 5 (6.2 mg, 0.02 mmol) and dimethylmalonate 7 (0.011 mL, 0.1 mmol) in DMF (1.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (5:3 CH$_2$Cl$_2$:Petrol) to give the title compound (26.1 mg, 66%) as white solid. mp 74–76 °C. ν$_{max}$ (film) / cm$^{-1}$ 3035 (C–H), 1751 (C=O); $[\alpha]_D^{20}$ +18.3 (c 0.1 in CHCl$_3$); Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min$^{-1}$, 211 nm, 30 °C) t$_R$ (minor): 31.6 min, t$_R$ (major): 19.3 min, >99:1 er; $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.01 (1H, dd, J 17.7, 7.2), 3.23 (1H, dd, J 17.6, 4.8), 3.66–3.76 (1H, m), 3.78 (6H, s), 3.88 (1H, d, J 5.3), 7.27–7.34 (2H, m), 8.23–8.30 (2H, m); $^{19}$F NMR (470 MHz, CDCl$_3$) δ: −70.6 (d, J 8.9); $^{13}$C {$^1$H} NMR (126 MHz, CDCl$_3$) δ: 30.9 (q, J 2.2), 39.9 (q, J 27.9), 48.9 (q, J 2.6), 53.3 (CO$_2$CH$_3$), 53.5, 122.5, 125.4, 126.3 (q, J 280.2), 145.6, 155.2, 167.2, 168.5. HRMS (ESI$^+$) C$_{15}$H$_{14}$F$_3$NO$_8$Na [M+Na]$^+$ found 416.0555, requires 416.0564 (−2.2 ppm).

Gram Scale

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (1.00 g, 3.82 mmol), (2S,3R)-HyperBTM 5 (236.0 mg, 0.77 mmol) and dimethylmalonate 7 (0.44 mL, 3.82 mmol) in DMF (38.0 mL) at 0 °C for 16 h. The reaction was then quenched with benzylamine (0.029 mL, 0.24 mmol) at 0 °C and allowed to warm to room temperature
over 1 h. The reaction was then diluted with ether, washed with 1 M HCl, sat Na2CO3 (3×), brine, dried with MgSO4, and filtered. The organics were then concentrated under reduced pressure and purified by column chromatography 30% EtOAc: Hexane) to give the title compound (46 mg, 54%) as white solid. mp 83–85 °C. v_max (film) / cm⁻¹ 3302 (N–H), 1749 (C=O), 1742 (C=O), 1647, 1560, 1269, 1148, 978, 901; [α]_D²⁰ +18.8 (c 1.0 in CHCl₃); **Chiral HPLC analysis**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) t_R (minor): 16.5 min, t_R (major): 11.3 min, 99:1 er; ¹H NMR (500 MHz, CDCl₃) δ H: 2.61 (1H, dd, J 15.9, 6.7), 2.81 (1H, dd, J 15.8, 5.7), 3.69 – 3.77 (1H, m), 3.74 (3H, s), 3.75 (3H, s), 3.86 (1H, d, J 4.7), 4.34 (1 H, dd, J 14.8, 5.4), 4.46 (1 H, dd, J 14.7, 6.0), 6.20 – 6.30 (1 H, m), 7.18 – 7.38 (5 H, m); ¹⁹F NMR (470 MHz, CDCl₃) δ F: −70.1 (CF₃, d, J 9.3); ¹³C ¹H NMR (126 MHz, CDCl₃) δ C: 32.2 (q, J 2.2), 40.2 (q, J 27.9), 43.8, 49.1 (q, J 2.3), 53.0 (CO₂CH₃), 53.3 (CO₂CH₃), 126.6 (q, J 280.4), 127.6, 127.9, 128.8, 129.9, 138.0, 167.4, 167.6, 169.0. HRMS (ESI⁺) C₁₆H₁₉F₃NO₅Na [M+Na]⁺ found 384.1018, requires 384.1030 (–3.1 ppm).

### 1,1-Dimethyl 3-(2,4,6-trichlorophenyl) (S)-2-((trifluoromethyl)propane-1,1,3-tricarboxylate (18)

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{F}_3\text{C} & \quad \text{CO}_2\text{TCP}
\end{align*}
\]

The title compound was prepared according to General Procedure 3 from 2,4,6-trichlorophenyl (E)-4,4,4-trifluorobut-2-enoate 11 (31.9 mg, 0.1 mmol), (2S,3R)-HyperBTM 5 (6.2 mg, 0.02 mmol) and dimethylmalonate 7 (0.011 mL, 0.1 mmol) in DMF (1.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:1 CH₂Cl₂:Petrol) to give the title compound (28.4 mg, 63%) as white solid. mp 67–68 °C. v_max (film) / cm⁻¹ 3091 (C–H), 3010 (C–H), 2960 (C–H), 1776 (C=O), 1735 (C=O); [α]_D²⁰ +15.3 (c 0.1 in CHCl₃); **Chiral HPLC analysis**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) t_R (minor): 7.8 min, t_R (major): 6.5 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ H: 3.13 (1H, dd, J 18.3, 7.9), 3.33 (1H, dd, J 18.3, 3.5), 3.67 – 3.78 (1H, m), 3.80 (6H, s), 3.91 (1H, d, J 5.0), 7.38 (2H, s); ¹⁹F NMR (376 MHz, CDCl₃) δ F: −70.32; ¹³C ¹H NMR (126 MHz, CDCl₃) δ C: 30.1 (q, J 1.9), 39.6 (q, J 28.1), 49.0 (m), 53.3, 53.5, 126.23 (q, J 280.3), 128.8, 129.7, 132.4, 142.8, 167.1, 167.2. HRMS (ESI⁺) C₁₅H₁₂F₃Cl₃O₆Na [M+Na]⁺ found 472.9532, requires 472.9544 (–2.5 ppm).
1,1-Dimethyl 3-(4-nitrophenyl) (S)-2-(difluoromethyl)propane-1,1,3-tricarboxylate (19)

\[
\text{MeO}_2\text{C} - \text{CO}_2\text{Me} \\
\text{HF}_2\text{C} \quad \text{CO}_2\text{PNP}
\]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4-difluorobut-2-enoate 12 (76.0 mg, 0.3 mmol), (2R,3S)-HyperBTM 5 (19.0 mg, 0.064 mmol) and dimethylmalonate 7 (0.036 mL, 0.3 mmol) in DMF (3.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:1 CH₂Cl₂:Pentol) to give the title compound (70.0 mg, 60%) as colourless oil. νₘₐₓ (film) / cm⁻¹ 3091 (C–H), 2960 (C–H), 1776 (C=O), 1755 (C=O), 1734 (C=O); [α]_D^{20}+21.3 (c 0.1 in CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (85:15 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 18.7 min, tᵣ (major): 17.2 min, 85:15 er; ¹H NMR (400 MHz, CDCl₃) δH: 3.00 (2H, d, J 6.3), 3.27 (1H, ddqd, J 17.8, 12.1, 6.2, 3.8), 3.78 – 3.80 (7H, m), 6.17 (1H, td, J 56.2, 3.8), 7.27 – 7.33 (2H, m), 8.24 – 8.31 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δF: −124.57 (ddd, J 286.5, 56.3, 17.2), −121.34 (ddd, J 286.9, 56.1, 11.8); ¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 30.4 (t, J 4.2), 39.3 (t, J 21.1), 49.4 (t, J 4.2), 53.2, 53.3, 115.9 (t, J 243.3), 122.6, 125.4, 145.6, 155.2, 167.9, 168.0, 169.2; HRMS (ESI⁺) C₁₅H₁₅F₂N₂O₈Na [M+Na]⁺ found 398.0648, requires 398.0658 (−2.5 ppm).

(S)-1,1-Dimethyl 3-(4-nitrophenyl) 2-(perfluoroethyl)propane-1,1,3-tricarboxylate (20)

\[
\text{MeO}_2\text{C} - \text{CO}_2\text{Me} \\
\text{C}_₂\text{F}_₆ \quad \text{CO}_2\text{PNP}
\]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,5,5,5-pentafluoropent-2-enoate 13 (31.1 mg, 0.1 mmol), (2S,3R)-HyperBTM 5 (6.2 mg, 0.02 mmol) and dimethylmalonate 7 (0.011 mL, 0.1 mmol) in DMF (1.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:1 CH₂Cl₂: Petrol) to give the title compound (16.2 mg, 37%) as white solid. mp 86–87 °C. νₘₐₓ (film) / cm⁻¹ 2960 (C–H), 2918 (C–H), 2848 (C–H), 1739 (C=O), 1703 (C=O); [α]_D^{20}+17.6 (c 0.1 in CHCl₃); Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 24.2 min, tᵣ (major): 11.9 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δH: 3.12 (1H, dd, J 18.4, 6.8), 3.33 (1H, dd, J 18.5, 4.4), 3.76 – 3.85 (1H, m), 3.79 (3H, s), 3.80 (3H, s), 3.97 (1H, d, J 4.0), 7.27 – 7.33 (2H, m), 8.24 – 8.30 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δF: −118.23 (app dd, J 275.4, 16.8), −117.48 (app dd, 275.6, 14.2), −82.30 (app s); ¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 30.4 (t, J 4.1), 37.2 (t, J 20.8), 48.3 (t, J 4.0), 53.3, 53.6, 115.2 (tq, J
258.2, 37.6), 119.0 (qt, J 286.7, 36.3), 122.5, 125.4, 145.7, 155.2, 167.4, 168.7. HRMS (ESI') C_{16}H_{15}F_{2}NO_{8}Na [M+Na]^+ found 466.0527, requires 466.0532 (−1.1 ppm).

1,1-Dimethyl 3-(4-nitrophenyl) (S)-2-(chlorodifluoromethyl)propane-1,1,3-tricarboxylate (21)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4-chloro-4,4-difluorobut-2-enoate 14 (27.8 mg, 0.1 mmol), (2S,3R)-HyperBTM 5 (6.2 mg, 0.02 mmol) and dimethylmalonate 7 (0.011 mL, 0.1 mmol) in DMF (1.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (4:1 CH$_2$Cl$_2$: Petrol) to give the title compound (27.3 mg, 67%) as white solid.

mp 78–80 °C. v$_{max}$ (film) / cm$^{-1}$ 3118 (C–H), 2958 (C–H), 2852 (C–H), 1759 (C=O), 1738 (C=O); [α]$_D^{20}$ +14.0 (c 0.1 in CHCl$_3$);

Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min$^{-1}$, 211 nm, 30 °C) tf (minor): 24.2 min, tf (major): 11.9 min, >99:1 er.

$^1$H NMR (500 MHz, CDCl$_3$) δH: 3.07 (1H, dd, J 17.7, 6.5), 3.29 (1H, dd, J 17.7, 5.1), 3.79 (6H, s), 3.82 – 3.93 (1H, m), 3.99 (1H, d, J 4.9), 7.29 – 7.35 (2H, m), 8.25 – 8.31 (2H, m); $^1$F NMR (470 MHz, CDCl$_3$) δF: −55.43 (dd, J 167.6, 4.0), −55.18 (dd, J 167.6, 4.0); $^{13}$C $^1$H NMR (126 MHz, CDCl$_3$) δC: 32.1 (t, J 2.3), 46.2 (t, J 23.7), 50.0 (t, J 2.0), 53.3, 53.6, 122.6, 125.4, 130.0 (t, J 295.5), 145.7, 155.3, 167.3, 167.4, 168.6. HRMS (ESI') C$_{15}$H$_{14}$Cl$_2$NO$_8$Na [M+Na]^+ found 432.0259, requires 432.0268 (−2.1 ppm).

1,1-Dimethyl 3-(4-nitrophenyl) (S)-2-(bromodifluoromethyl)propane-1,1,3-tricarboxylate (22)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4-bromo-4,4-difluorobut-2-enoate 15 (32.2 mg, 0.1 mmol), (2S,3R)-HyperBTM 5 (6.2 mg, 0.02 mmol) and dimethylmalonate 7 (0.011 mL, 0.1 mmol) in DMF (1.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (4:1 CH$_2$Cl$_2$:Petrol) to give the title compound (27.9 mg, 61%) as white solid.

mp 82–83 °C. v$_{max}$ (film) / cm$^{-1}$ 3082 (C–H), 2956 (C–H), 2850 (C–H), 1762 (C=O), 1737 (C=O); [α]$_D^{20}$ +3.0 (c 0.1 in CHCl$_3$);

Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min$^{-1}$, 211 nm, 30 °C) tf (minor): 30.9 min, tf (major): 24.2 min, >99:1 er;

$^1$H NMR (400 MHz, CDCl$_3$) δH: 3.07 (1H, dd, J 17.8, 6.3), 3.27 (1H, dd, J 17.8, 5.2), 3.79 (6H, s), 3.86 (1H, t, J 11.1, 5.4), 4.00 (1H, d, J 5.0), 7.29 – 7.37 (2H, m), 8.24 – 8.32 (2H, m); $^{19}$F NMR (471 MHz, CDCl$_3$) δF: −48.84 (t, J 11.0); $^{13}$C $^1$H NMR (101 MHz, CDCl$_3$) δC: 32.6 (t, J 2.5), 47.8 (t, J 21.3),...
50.4 (t, J 2.3), 53.3, 53.6, 122.6, 123.4 (t, J 308.6), 125.4, 145.6, 155.3, 167.3, 168.5. **HRMS** (ESI⁺) C₁₅H₁₀BrF₂NO₈Na [M+Na]⁺ found 475.9754, requires 475.9763 (−1.9 ppm).

### 2-Ethyl 1,1-dimethyl 3-(4-nitrophenyl) (S)-propane-1,1,2,3-tetraacarboxylate (23)

The title compound was prepared according to General Procedure 3 from ethyl (4-nitrophenyl) fumarate 16 (53.0 mg, 0.2 mmol), (2S,3R)-HyperBTM 5 (12.4 mg, 0.02 mmol) and dimethylmalonate 7 (0.022 mL, 0.2 mmol) in DMF (2.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (100% CH₂Cl₂) to give the title compound (51.3 mg, 65%) as colorless oil. \( \nu_{\text{max}} \) (film) / cm⁻¹ 2968 (C–H), 1765 (C=O), 1749 (C=O); [\( \alpha \)] \( _D ^{20} \) −19.3 (c 0.1 in CHCl₃); **Chiral HPLC analysis**: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) \( t_R \) (major): 53.8 min, \( t_R \) (minor): 41.5 min, 98:2 er; \(^1\text{H NMR} \) (400 MHz, CDCl₃) \( \delta_h \): 1.28 (3H, t, J 7.1), 3.00 (1H, dd, J 17.1, 4.8), 3.14 (1H, dd, J 17.1, 8.2), 3.67 (1H, ddd, J 8.2, 6.4, 4.8), 3.77 (3H, s), 3.78 (3H, s), 4.03 (1H, d, J 6.4), 4.16 – 4.24 (2H, m), 7.27 – 7.33 (2H, m), 8.23 – 8.30 (2H, m); \(^{13}\text{C} \) \(^{1}\text{H NMR} \) (101 MHz, CDCl₃) \( \delta_c \): 14.1, 33.5, 40.6, 51.8, 53.1, 62.0, 122.5, 125.3, 145.6, 155.4, 168.0, 168.3, 169.4, 171.3; **HRMS** (ESI⁺) C₁₇H₁₉NO₁₆Na [M+Na]⁺ found 420.0897, requires 420.0901 (−1.0 ppm).

### 1,1-Dimethyl 3-(4-nitrophenyl) (S)-2-benzoylpropane-1,1,3-tricarboxylate (24)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4-oxo-4-phenylbut-2-enoate 17 (59.4 mg, 0.2 mmol), (2S,3R)-HyperBTM 5 (12.4 mg, 0.04 mmol) and dimethylmalonate 7 (0.022 mL, 0.2 mmol) in DMF (2.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:2 EtOAc:Petrol) to give the title compound (42.1 mg, 49%) as orange oil. \( \nu_{\text{max}} \) (film) / cm⁻¹ 3086 (C=O), 2956 (C–H), 2956 (C–H), 1751 (C=O), 1732 (C=O), 1683 (C=O); [\( \alpha \)] \( _D ^{20} \) −29.6 (c 0.1 in CHCl₃); **Chiral HPLC analysis**: Chiralpak AS-H (95:5 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 40 °C) \( t_R \) (minor): 24.7 min, \( t_R \) (major): 27.5 min, 97:3 er; \(^1\text{H NMR} \) (500 MHz, CDCl₃) \( \delta_h \): 3.03 (1H, dd, J 16.9, 5.8), 3.09 (1H, dd, J 16.9, 7.0), 3.64 (3H, s), 3.76 (3H, s), 4.04 (1H, d, J 8.8), 4.69 (1H, ddd, J 8.9, 7.0, 5.8), 7.15 – 7.19 (2H, m), 7.47 – 7.53 (2H, m), 7.57 – 7.63 (1H, m), 8.00 – 8.04 (2H, m), 8.19 – 8.23 (2H, m); \(^{13}\text{C} \) \(^{1}\text{H NMR} \) (126 MHz, CDCl₃) \( \delta_c \): 34.6, 41.8,
52.8, 53.1, 53.2, 122.5, 125.3, 128.8, 129.1, 133.9, 135.5, 145.5, 155.1, 168.2, 168.4, 169.1, 199.3 (C(O)Ph). HRMS (ESI⁺) C₂₃H₂₀NO₅ [M+H]+ found 430.1127, requires 430.1132 (−1.2 ppm).

1,1-Dimethyl 3-(4-nitrophenyl) (S)-1-fluoro-2-(trifluoromethyl)propane-1,1,3-tricarboxylate (37)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (52.2 mg, 0.2 mmol), (2S,3R)-HyperBTM 5 (12.4 mg, 0.04 mmol) and dimethyl 2-fluoromalonate 29 (30.0 mg, 0.2 mmol) in DMF (2.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (4:1 CH₂Cl₂:Petrol) to give the title compound (67.4 mg, 82%) as white solid. mp 54–56 °C, νmax (film) / cm⁻¹ 2968 (C–H), 1768 (C=O), 1749 (C=O); [α]D²₀ +36.0 (c 0.1 in CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tₘ (minor): 22.8 min, tₘ (major): 15.6 min, 98:2 er;¹H NMR (400 MHz, CDCl₃) δH: 3.01 (2H, d, J 5.9), 3.87 (3H, s), 3.90 (3H, s), 4.03 – 4.19 (1H, m), 7.29 – 7.33 (2H, m), 8.25 – 8.29 (2H, m); ¹⁹F NMR (376 MHz, CDCl₃) δF: −173.85 (qd, J 9.8, 2.7), −66.88 (d, J 9.9);¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 30.2 (t, J 2.5), 44.4 (qd, J 27.8, 20.0), 54.3, 54.5, 92.5 (d, J 210.5), 122.5, 125.1 (q, J 281.4), 125.5, 145.8, 155.0, 164.2 (d, J 25.9), 164.5 (d, J 24.4), 167.7. HRMS (ESI⁺) C₁₃H₁₃F₂NO₅Na [M+Na]+ found 434.0459, requires 434.0470 (−2.5 ppm).

1,1-Diethyl 3-(4-nitrophenyl) (S)-2-(trifluoromethyl)propane-1,1,3-tricarboxylate (38)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (52.2 mg, 0.2 mmol), (2S,3R)-HyperBTM 5 (12.4 mg, 0.02 mmol) and diethylmalonate 30 (0.030 mL, 0.2 mmol) in DMF (2.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (2:1 CH₂Cl₂:Petrol) to give the title compound (36.2 mg, 43%) as colourless oil. νmax (film) / cm⁻¹ 3088 (C–H), 2985 (C–H), 2899 (C–H), 1732 (C=O); [α]D²₀ +33.6 (c 0.1 in CHCl₃); Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tₘ (minor): 24.8 min, tₘ (major): 15.4 min, >99:1 er;¹H NMR (500 MHz, CDCl₃) δH: 1.29 (6H, q, J 7.0), 3.01 (1H, dd, J 17.6, 7.4), 3.24 (1H, dd, J 17.6, 4.5), 3.66–3.77 (1H, m), 3.84 (1H, d, J 5.2), 4.25 (4H, qd, J 7.1, 1.6), 7.28 – 7.34 (2H, m), 8.24 – 8.31 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δF: −70.4 (d, J 8.7);¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 14.0, 31.0 (m), 39.9 (q, J 27.8), 471.

S12
The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (100.0 mg, 0.4 mmol), (2R,3S)-HyperBTM 5 (23.5 mg, 0.08 mmol) and diisopropylmalonate 31 (0.072 mL, 0.4 mmol) in DMF (4.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (100% CH₂Cl₂) to give the title compound (54.2 mg, 32%) as colorless oil. νmax (neat) / cm⁻¹: 2984 (C–H), 1768 (C=O), 1730 (C=O), 1346, 1097, 910, 862; [α]D²⁰ −18.8 (c 1.5 in CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (99:1 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 18.6 min, tᵣ (major): 15.1 min, >99:1 er; ¹H NMR (500 MHz, CDCl₃) δ n: 1.23 – 1.30 (12H, m), 3.00 (1H, dd, J 17.6, 7.6), 3.22 (1H, dd, J 17.6, 4.2), 3.65 – 3.75 (1H, m), 3.77 (1H, d, J 5.3), 5.06 – 5.12 (2H, m), 7.27 – 7.34 (2H, m), 8.24 – 8.31 (2H, m); ¹⁹F NMR (376 MHz, CDCl₃) δ c: −70.26; ¹³C {¹H} NMR (126 MHz, CDCl₃) δ c: 21.6, 31.1 (m), 39.8 (q, J 27.7, 49.8 – 49.9 (m), 70.2, 70.6, 122.6, 126.5 (q, J 280.1), 125.4, 145.6, 155.3, 166.3, 166.4, 168.6. HRMS (EI⁺) C₁₀H₁₂F₃NO₃Na [M+Na]⁺ found 472.1197, requires 472.1190 (−1.4 ppm).

1,1-Bis(2-fluorobenzyl) 3-(4-nitrophenyl) (S)-2-(trifluoromethyl)propane-1,1,3-tricarboxylate (40)

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (130.5 mg, 0.5 mmol), (2S,3R)-HyperBTM 5 (31.0 mg, 0.1 mmol) and bis(2-fluorobenzyl) malonate 32 (160.5 mg, 0.5 mmol) in DMF (5.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:4 EtOAc:Petrol) to give the title compound (235.7 mg, 81%) as colourless oil. νmax (film) / cm⁻¹: 3078 (C–H), 2951 (C–H), 1759 (C=O), 1737 (C=O); [α]D²⁰ +14.0 (c 0.1 in CHCl₃); Chiral HPLC analysis: Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 35.1 min, tᵣ (major): 24.0 min, 99:1 er; ¹H NMR (500 MHz, CDCl₃) δ n: 3.02 (1H, dd, J 17.7, 7.4), 3.22 (1H, dd, J 17.7, 4.6), 3.75 (1H, m), 3.97

S13
(1H, d, J 5.1), 5.20 – 5.30 (4H, m), 7.02 – 7.15 (4H, m), 7.25 – 7.38 (6H, m), 8.23 – 8.30 (2H, m); \(^{19}\text{F NMR}\) (471 MHz, CDCl\(_3\)) \(\delta\): −117.8 (dt, \(J\) 11.7, 6.4), −117.7 (dt, \(J\) 11.8, 6.2), −70.4 (d, \(J\) 8.7); \(^{13}\text{C} \{^1\text{H}\} \text{NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\): 30.9, 39.9 (q, \(J\) 27.9), 49.2, 62.1 (d, \(J\) 4.4), 62.4 (d, \(J\) 4.2), 115.6 (d, \(J\) 4.5), 115.8 (d, \(J\) 4.4), 121.8 (d, \(J\) 5.5), 121.9 (d, \(J\) 5.5), 122.5, 124.4 (app t, \(J\) 3.7), 125.4, 126.3 (q, \(J\) 280.4) 130.8 – 131.0 (m) 145.6, 155.2, 161.10 (dd, \(J\) 249.1, 2.5), 166.3, 166.4, 168.4; HRMS (ESI\(^+\)) \(C_{27}H_{20}F_3NO_4Na\) [M+Na\(^+\)]\(^\dagger\) found 604.0993, requires 604.1001 (−1.3 ppm).

1,1-Dibenzyl 3-(4-nitrophenyl) (S)-2-(trifluoromethyl)propane-1,1,3-tricarboxylate (41)

\[
\text{F}_3\text{C} \quad \text{CO}_2\text{Bn} \quad \text{CO}_2\text{BN}
\]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (52.2 mg, 0.2 mmol), (2S,3R)-HyperBTM 5 (12.4 mg, 0.04 mmol) and dibenzyl malonate 33 (0.022 mL, 0.2 mmol) in DMF (2.0 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:4 EtOAc:Petrol) to give the title compound (78.5 mg, 72%) as white solid. mp 60–62 °C. \(\nu_{\text{max}}\) (film) / cm\(^{-1}\) 3086 (C–H), 3064 (C–H), 3035 (C–H), 2956 (C–H), 1759 (C=O), 1734 (C=O); [\(\alpha\)]\(D\)^{20} +22.6 (c 0.1 in CHCl\(_3\)); Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min\(^{-1}\), 211 nm, 30 °C) \(t_r\) (minor): 30.3 min, \(t_r\) (major): 34.3 min, >99:1 er; \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\): 3.01 (1H, dd, \(J\) 17.7, 7.4), 3.21 (1H, dd, \(J\) 17.6, 4.6), 3.70 – 3.82 (1H, m), 3.97 (1H, d, \(J\) 5.1), 5.09 – 5.30 (4H, m), 7.19 – 7.41 (12H, m), 8.21 – 8.32 (2H, m); \(^{19}\text{F NMR}\) (376 MHz, CDCl\(_3\)) \(\delta\): −70.3; \(^{13}\text{C} \{^1\text{H}\} \text{NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\): 30.9 (m), 39.9 (q, \(J\) 28.0), 49.4 (m), 68.2, 68.4, 122.5, 125.4, 126.4 (q, \(J\) 280.3), 128.5 – 128.8, 134.7, 145.6, 155.2, 166.5, 166.6, 168.4. HRMS (ESI\(^+\)) \(C_{27}H_{22}F_3NO_4Na\) [M+Na\(^+\)]\(^\dagger\) found 568.1181, requires 568.1190 (−1.6 ppm).

4-Nitrophenyl (S)-3-(dicyanomethyl)-4,4,4-trifluorobutanoate (42)

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{CO}_2\text{P}_\text{NP} \\
\end{align*}
\]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (79.0 mg, 0.3 mmol), (2R,3S)-HyperBTM 5 (18.5 mg, 0.06 mmol) and malononitrile 34 (20.0 mg, 0.3 mmol) diisopropylethylamine (0.005 mL, 0.03 mmol) in MeCN (3.0 mL) at 0 °C for 5 h. The reaction was concentrated under reduced pressure and purified by column chromatography (4:1 CH\(_2\)Cl\(_2\):Petrol) to give the title compound (47 mg, 48%) as colourless oil. \(\nu_{\text{max}}\) (film) / cm\(^{-1}\) 2968 (C–H), 2899 (C–H), 1749 (C=O), 1220 (C=N); [\(\alpha\)]\(D\)^{20} +37.2 (c 0.06 in CHCl\(_3\)); Chiral HPLC analysis: Chiralpak
AD-H (95:5 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 29.4 min, tᵣ (major): 89.5 min, >99:1 er. ¹H NMR (500 MHz, CDCl₃) δH: 3.15 (1H, dd, J 18.0, 7.7), 3.30 (1H, dd, J 18.0, 5.1), 3.51 – 3.60 (1H, m), 4.46 (1H, d, J 4.6), 7.30 – 7.38 (2H, m), 8.28 – 8.36 (2H, m); ¹⁹F NMR (471 MHz, CDCl₃) δF: −69.36 (d, J 7.6); ¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 22.3 (q, J 3.0), 30.9 (m), 41.3 (q, J 29.4), 109.4, 109.7, 122.3, 124.3 (q, J 281.3), 125.6, 146.1, 154.4, 166.8. HRMS (ESI⁺) C₁₃H₃F₃NO₃S₂ [M+Na]⁺ found 350.0355, requires 350.0360 (−1.4 ppm).

4-Nitrophenyl (S)-5-((4-(tert-butyl)benzyl)thio)-4-(((4-(tert-butyl)benzyl)thio)carbonyl)-5-oxo-3-(trifluoromethyl)pentanoate (43)

![Chemical Structure]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (200.0 mg, 0.77 mmol), (2S,3R)-HyperBTM 5 (47.0 mg, 0.15 mmol) and S,S-bis(4-(tert-butyl)benzyl) propanebis(thioate) 3 (328.0 mg, 0.77 mmol) diisopropylethylamine (0.013 mL, 0.08 mmol) in MeCN (7.0 mL) at 0 °C for 3 h. The crude reaction mixture was concentrated under reduced pressure and recrystallized from MeCN to give the title compound (398 mg, 58%) as white solid. mp 107–108 °C. νmax (film) / cm⁻¹: 2958 (C–H), 1770 (C=O), 1346, 1201, 1161, 983; [α]D⁰ +54.7 (c 1.0 in CHCl₃). Chiral HPLC analysis: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tᵣ (minor): 24.1 min, tᵣ (major): 12.9 min, >99:1 er; ¹H NMR (400 MHz, CDCl₃) δH: 1.30 (18H), 2.94 (1H, dd, J 17.5, 7.2), 3.22 (1H, dd, J 17.5, 4.3), 3.79 – 3.94 (1H, m), 4.11 – 4.32 (5H, m), 7.18 – 7.21 (4H, m), 7.29 – 7.31 (6H, m), 8.25 – 8.31 (2H, m); ¹⁹F NMR (376 MHz, CDCl₃) δF: −69.08; ¹³C {¹H} NMR (126 MHz, CDCl₃) δC: 31.1 (m), 31.4, 34.2, 34.3, 34.7, 41.0 (q, J 27.6), 122.6, 125.4, 125.9, 126.2 (q, J 280.7), 128.7, 132.6, 145.6, 151.0, 155.2, 168.2, 190.6, 190.9. HRMS (ESI⁺) C₁₃H₃F₃NO₃S₂ [M–H]⁻ found 688.2020, requires 688.2020 (0.0 ppm).

Ethyl (S)-2-oxo-6-phenyl-4-(trifluoromethyl)-3,4-dihydro-2H-pyran-5-carboxylate (44)

![Chemical Structure]

The title compound was prepared according to General Procedure 3 from (E)-4-nitrophenyl 4,4,4-trifluorobut-2-enoate 6 (100 mg, 0.4 mmol), (2S,3R)-HyperBTM 5 (23.5 mg, 0.08 mmol) and ethyl
benzoylacetate 36 (0.07 mL, 0.4 mmol) in DMF (3.5 mL) at 0 °C for 16 h. The reaction was concentrated under reduced pressure and purified by column chromatography (1:1 CH₂Cl₂:Hexane) to give the title compound (80 mg, 66%) as a white solid. mp 66–67 °C. νmax (film) / cm⁻¹ 2981 (C–H), 1788 (C=O), 1701 (C=O), 1225, 1153, 1039, 995; [α]D²⁰ +5.0 (c 1.0 in CHCl₃); **Chiral HPLC analysis:** Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tR (minor): 8.4 min, tR (major): 7.7 min, >99:1 er; **¹H NMR** (400 MHz, CDCl₃) δH: 0.97 (3H, t, J 7.1), 2.91 (1H, dd, J 17.1, 7.9), 3.11 (1H, dd, J 17.1, 1.4), 3.94 – 4.10 (3H, m), 7.33 – 7.55 (5H, m); **¹⁹F NMR** (376 MHz, CDCl₃) δF: –72.4; **¹³C {¹H} NMR** (126 MHz, CDCl₃) δC: 13.6, 27.6 (q, J 2.3), 37.9 (q, J 29.9), 61.7, 103.1, 125.8 (q, J 281.4), 128.2, 128.7, 130.8, 132.6, 162.2, 163.7, 165.6. **HRMS** (ESI⁺) C₁₅H₁₅F₃O₄Na [M+Na]⁺ found 337.0657, requires 337.0658 (−0.3 ppm).
5. Determination of Product Configuration by X-Ray Crystallography

X-ray diffraction data were collected at 148 K using a Rigaku XtaLAB P200 diffractometer [Cu Kα radiation (λ = 1.54184 Å)]. Data were collected using CrystalClear and processed (including correction for Lorentz, polarization and absorption) using CrysAlisPro. Structures were solved by dual-space (SHELXT), direct (SIR2011) or charge-flipping (Superflip) methods and refined by full-matrix least-squares against F2 (SHELXL-2018). Non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were refined using a riding model. All calculations were performed using the CrystalStructure interface. Crystals suitable for X-ray diffraction analysis were obtained using the vapor diffusion technique with ethyl acetate and petroleum ether at room temperature. ORTEP plot of the crystal structure of 22, and thermal ellipsoid is set at 50% probability.

| CCDC compound number | 6 empirical formula | fw | crystal description | crystal size [mm] | space group | a [Å] | b [Å] | c [Å] | vol [Å³] | α [°] | β [°] | γ [°] | Z | ρ (calc) [g/cm³] | μ [mm⁻¹] | F(000) | reflections collected | independent reflections (Rint) | data/parameters | GOF on F2 | R1 [I > 2σ(I)] | wR2 (all data) | largest diff. peak/hole [e/Å³] | Flack parameter |
|----------------------|---------------------|----|---------------------|------------------|-------------|-------|-------|-------|---------|-------|-------|-------|---|-----------------|---------|--------|------------------|----------------|--------------|--------|----------|------------|-------------|----------------------|------------------|
| 2145495              | C₁₅H₁₄BrF₂NO₈       | 454.18 | colourless plate    | 0.10x0.04x0.02   | C₂          | 15.4843(6) | 8.0244(3) | 14.6382(6) | 1755.12(12) | 105.210(4) | 4     | 1.719          | 3.819   | 912.0  | 9017             | 3392 (0.0247)   | 3392/244   | 1.09   | 0.0409   | 0.1160     | 0.43, −0.95     | 0.09(3)            |
6. Computational Details

6.1 Methodology

All calculations were performed in Gaussian 09 suite of programs. Where applicable, the initial geometries for the calculations were adapted from the optimised geometries in the study from Wang et al. Optimisation were performed at the M06-2X/6-31G(d,p)/IEFPCM<sub>THF</sub> level, using a polarisable continuum model in the integrated equation formalism (IEFPCM) together with the parameters for THF, followed by evaluation of the harmonic vibrational frequencies at the same level. Structures were characterised as either true energy minima (all real frequencies) or a first order saddle point i.e. a transition state (a single imaginary frequency). Visual inspection of the single imaginary vibrational modes ensured the desired transition states had been found. Energies were refined by single point energy calculations at the M06-2X-D3/6-311++G(2df, 2dp)//IEFPCM<sub>THF</sub> level. Subsequently, the potential energies from this level were combined with the thermal corrections at the M06-2X/6-31G(d,p)//IEFPCM<sub>THF</sub> level to give Gibbs free energies and enthalpies at 298.15 K and 1 atm. The reaction profile was calculated at 273.15 K as follows:

\[ \Delta G^{273} = \Delta H^{298} - (273.15 \text{ K}) \Delta S^{298} \]  

(eq 1)

The enantiomeric ratio (er) was calculated from a Boltzmann equilibrium at that temperature.

6.2 Results and Discussion

Our target system bears considerable resemblance to that from Wang et al. for the synthesis of pyridones and pyranones. Both systems are catalysed by isothiourea HyperBTM (5) and include Michael addition reactions to fluorinated α,β-unsaturated esters. The key differences are that we use a different aryl alcohol ester (para-nitrophenol, OPNP, instead of 2,4,6-trichlorophenolate) and a different nucleophile for Michael addition (dimethyl malonate ester 7 instead of 2-acetylbenzazole). In the system of Wang et al., catalytic turnover is achieved from an intramolecular cyclisation step, whereas in our system, catalytic turnover is driven by the free aryl oxide. Because of this close similarity of both systems, it is reasonable to assume that they would have similar transition state and intermediate geometries in the initial steps. We therefore used the study from Wang et al. as inspiration for our own calculations, which were performed at the same level of theory. The resulting profile including the key steps is summarised in Figure S1.
Figure S1: Reaction profile for Michael addition of dimethyl malonate (7') to α,β-unsaturated ester (6) catalysed by HyperBTM (5) at 273.15 K, M06-2X-D3/6-311++G(2df,2dp)/IEFPCM_{THF}/M06-2X/6-31G(d,p)/IEFPCM_{THF} level.

Following the procedure from Wang et al. the free energies are reported relative to an encounter complex between catalyst 5 and our model reactant 6 (R = CF₃ in Scheme 4 in the main paper), denoted 5•6. This is to minimise artifacts from entropies of associative steps that are evaluated from standard thermodynamic expressions based on ideal-gas approximation. At 0°C, formation of 5•6 is computed endergonic by ΔG = 23.2 kJ mol⁻¹. The first key intermediate, M1, is obtained as contact ion pair between a cationic isothiouronium complex and the OPNP leaving group. Depending on which face of the prochiral enone moiety the phenolate is located, two diastereomeric forms are possible, of which the si form is less stable despite a potentially favourable π−π interaction (see Figure S2), presumably because the steric clash between the two aromatic moieties leads to an unfavourably large charge separation in the zwitterion.
Two transition states were located leading from 5-6 to re-M1 and si-M1, labelled re-TS1 and si-TS1, respectively, in Figure S1. It turned out that one of them, si-TS1, does not connect to the reactant complex directly, but to a shallow minimum, a tetrahedral intermediate (si-M1'). The barrier connecting this intermediate to 5-6 is so low on the potential energy surface, however, that after the single-point energy and thermodynamic corrections the corresponding transition state (si-TS1') is lower in free energy than si-M1', indicating that both exist only as points along the reaction pathway, not as stationary points proper. The lowest barrier leading to one of the diastereomeric M1 intermediates (the more stable of the two, actually), is found via re-TS1 at $\Delta G^\dagger = 52.8$ kJ mol$^{-1}$.

Again following the protocol of Wang et al.$^{13}$ we assume facile exchange between the phenolate and the Michael nucleophile, the deprotonated malonate ester ($7'$), and have located the transition states for attack of the latter at the $\beta$-carbon of the $\alpha$, $\beta$-unsaturated ketone moiety in M1, as well as the resulting zwitterionic intermediates, M2. This is the point where the stereochemistry of the final product, ($R$ or $S$) is determined.

Figure S2: (a) Schematic sketch of formation of re- and si-M1; (b) three-dimensional plot of re- and si-M1, the latter is less stable despite the highlighted $\pi$–$\pi$ interaction.
In addition to the stereochemistry in the product, there is some conformational flexibility about the newly formed C-C single bond. We have trialled several such conformations (for both R and S intermediates M2 and transition states, TS2) and report only the results for the most stable of each in Figure S1.

It turns out that S-M2 is more stable than R-M2, but only by $\Delta\Delta G = 3.6$ kJ mol$^{-1}$. The steric clash that, arguably, favours S-M2 over R-M2 is illustrated in Figure S3.

![Figure S3](image)

**Figure S3**: (a) Schematic sketch of formation of R- and S-M2; (b) three-dimensional plot of R- and S-M2, the latter is slightly more stable because of the steric clash highlighted.

There is also some conformational flexibility in the malonate moiety itself. In the M2 products, like in the free neutral malonate ester 7, the two carbonyl groups adopt a gauche conformation (as opposed to an anti orientation with $C_2$- or pseudo $C_2$-symmetry). These conformations would connect to the deprotonated malonate 7' in its cis configuration ($C_{2v}$-symmetry), however for the free anion 7', the trans configuration ($C_s$-symmetry) turned out to be slightly more stable (by $\Delta G = -4.9$ kJ mol$^{-1}$). We located a total of 10 transition states for TS2 involving both cis-7' and trans-7'; the relative free energies of these TSs are collected in Table S1. Those leading to $S$ products tend to be more stable than those leading to $R$. The free energy difference between the lowest of each, S-TS2 and R-TS2 (both involving trans-7'), is $\Delta\Delta G^\ddagger = 17.5$ kJ mol$^{-1}$. 

S21
**Table S1:** Optimised C···C distances (M06-2X/6-31G(d,p)/IEFPCM<sub>THF</sub> level) and relative free energies (M06-2X-D3/6-311++G(2df,2dp)/ IEFPCM<sub>THF</sub>/M06-2X/6-31G(d,p)/IEFPCM<sub>THF</sub> level, 273.15 K)

| Nucleophile | TS     | \( r_{\text{C···C}} \) [Å] | \( \Delta \Delta G^\dagger_{\text{rel}} \) [kJ mol\(^{-1}\)] |
|-------------|--------|-----------------------------|-----------------------------|
| **trans-7'**| S-TS2  | 2.40                         | 0.0                         |
| "          | S-TS2a | 2.43                         | 1.2                         |
| "          | S-TS2b | 2.51                         | 5.2                         |
| "          | S-TS2c | 2.56                         | 24.3                        |
| "          | R-TS2  | 2.57                         | 17.5                        |
| "          | R-TS2a | 2.62                         | 19.4                        |
| **cis-7'**  | S-TS2d | 2.54                         | 10.3                        |
| "          | S-TS2e | 2.60                         | 18.5                        |
| "          | R-TS2b | 2.62                         | 19.2                        |
| "          | R-TS2c | 2.63                         | 23.4                        |

The structures of S-TS2 and R-TS2 are shown in Figure S4 (which is a stereo version of Figure 1 in the main paper). A similar steric clash as in the product R-M2 (Figure S3) is seen in R-TS2 (Figures 1 and S4). It is arguably this clash that causes an elongated C···C distance in that TS (2.57 Å at the M06-2X level), compared to the same distance in S-TS2 (2.40 Å). In fact, there appears to be a loose correlation between that distance and the barrier height, the latter tending to increase with the former (see \( r_{\text{C···C}} \) values in Table S1).
Figure S4: Stereoplot of S- and R-TS2 (M06-2X/6-31G(d,p)/IEFPCM optimized, malonate rendered as ball-and-stick, HyperBTM as tube).

Note that S- and R-TS2 do not connect directly to S- and R-M2, but to slightly higher-lying rotamers (S-M2’ and R-M2’, not shown), which can convert to the more stable intermediates S-M2 and R-M2 via simple rotation about C-C single bonds. This step, addition of the malonate, is computed so exergonic (e.g. ΔG = -78.9 kJ mol⁻¹ from re-M1 to S-M2) that the barriers for the reverse reaction are essentially unsurmountable under the mild reaction conditions (e.g. ΔG° = 91.9. kJ mol⁻¹ from S-M2 to S-TS2). This addition is therefore irreversible and under kinetic control. The stereochemistry of the final product should thus be determined by the free-energy difference between the (selectivity-determining) transition states S-TS2 and R-TS2. This aforementioned difference of ΔΔG° = 17.5 kJ mol⁻¹ corresponds to a computed er of 99.95:0.05 at 273.15 K, in excellent agreement with the experimental values exceeding 99:1 (see Table 1 in the main paper). For a full prediction of the stereocontrol one could calculate the amount of S- and R-product from appropriate Boltzmann averages over all relative barriers leading to these products (ΔΔG°,rel values in Table S1, weighted by the Boltzmann equilibrium of nucleophiles cis-7’ and trans-7’), which would afford a very similar outcome, namely essentially exclusive formation of S-product.¹⁹
The reaction is completed by the protonation of the enolate moiety in M2 and substitution of the HyperBTM moiety with the aryl enolate, affording the final product (8) and regenerating the organocatalyst (5). Starting from the lowest intermediate S-M2, the intermediate of the first step of this sequence was modelled via reaction with free aryl phenol, HOPNP affording a contact ion pair S-M3 (again following the procedure of Wang et al.,\textsuperscript{13} in order to avoid artifacts from charge separation with the simple solvation model). The energetics of this step include the driving force for formation of the phenol via deprotonation of the neutral malonate ester (7), according to

\[
\text{O}_2\text{N} - \text{OPNP}^- + \text{MeO} - \text{O} - \text{Me} \rightarrow \text{O}_2\text{N} - \text{HOPNP}^- + \text{MeO} - \text{O} - \text{Me}, \quad \Delta G = 54.4 \text{ kJ mol}^{-1} \quad (\text{eq } 2),
\]

which produces the Michael nucleophile 7' needed earlier. Formation of S-M3 and its decay into the final products, S-8 and 5, are computed to be so favourable (with driving forces for each elementary step between \(\Delta G \approx -26\) to \(-33\) kJ mol\(^{-1}\), see the last two steps on the profile in Figure S1) that no kinetic hindrance and, thus, no bearing on the stereocontrol is to be expected. Therefore, no other stereoisomers were considered for M3 and no transition states connecting to it were located at this stage.
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The cis and trans configurations of the deprotonated malonate ester are expected to be close in energy, as both have been characterized by X-ray crystallography, e.g.: (a) Huang, Z.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2012**, *51*, 1028 –1032 (b) Zhang, Y.; Schmitt, M.; Falivene, L.; Caporaso, L.; Cavallo, L.; Chen, E. Y.-X. *J. Am. Chem. Soc.* **2013**, *135*, 17925–17942.

Note that if only the slightly less stable form of the nucleophile (*cis*-7') would have been considered, the corresponding lowest *S*- and *R*-TSs (*S-TS2d* and *R-TS2b*, respectively, in Table S1) would have afforded \(\Delta \Delta G^\ddagger = 8.9\) kJ mol\(^{-1}\), corresponding to a computed *er* of 98:2 at 273.15 K in favour of the observed *S*-enantiomer, still in very good (albeit slightly worse) agreement with experiment.
8. Appendix 1: NMR Spectra

$^{1}H$, CDCl$_3$, 500 MHz

32

$^{13}C$ ($^{1}H$), CDCl$_3$, 126 MHz

S27
$^{19}$F, CDCl$_3$, 470 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$ {$^1H$}, CDCl$_3$, 126 MHz
$\text{HF}_2C\xrightarrow{\phantom{\text{CO}_2\text{PNP}}} \text{CO}_2\text{PNP}$

$^{1}H$, CDCl$_3$, 500 MHz

$\text{HF}_2C\xrightarrow{\phantom{\text{CO}_2\text{PNP}}} \text{CO}_2\text{PNP}$

$^{13}C\{^{1}H\}$, CDCl$_3$, 126 MHz
$^{19}\text{F}, \text{CDCl}_3, 470 \text{ MHz}$
$\text{C}_2\text{F}_5\text{CO}_2\text{PNP}$

13

$^1\text{H}$, CDCl$_3$, 500 MHz

$\text{C}_2\text{F}_5\text{CO}_2\text{PNP}$

13

$^{13}\text{C}$ ($^1\text{H}$), CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 376 MHz

C$_2$F$_5$\(\rightarrow\)CO$_2$PNP

13
$\text{ClF}_2\text{C} = \text{CO}_2\text{PNP}$

13C {$^1$H}, CDCl$_3$, 126 MHz
$\text{ClF}_2\text{C} = \text{CO}_2\text{PNP}$

$^{19}\text{F}, \text{CDCl}_3, 470 \text{ MHz}$
BrF₂C=CO₂PNP

1H, CDCl₃, 500 MHz

13C {1H}, CDCl₃, 126 MHz
$^{19}$F, CDCl$_3$, 470 MHz
MeO₂C—CO₂Me
F₃C—CO₂PNP

8a

¹H, CDCl₃, 500 MHz

MeO₂C—CO₂Me
F₃C—CO₂PNP

8a

¹³C{¹H}, CDCl₃, 126 MHz
$^1\text{H}$, CDCl$_3$, 377 MHz
$\text{MeO}_2\text{C} \rightleftharpoons \text{CO}_2\text{Me}$

$\text{F}_3\text{C} \rightleftharpoons \text{CONHBn}$

8b

$^1\text{H}, \text{CDCl}_3, 500 \text{ MHz}$

$\text{MeO}_2\text{C} \rightleftharpoons \text{CO}_2\text{Me}$

$\text{F}_3\text{C} \rightleftharpoons \text{CONHBn}$

8b

$^{13}\text{C}\{^1\text{H}\}, \text{CDCl}_3, 126 \text{ MHz}$
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C{$^1$H}, CDCl$_3$, 126 MHz
$^{19}\text{F, CDCl}_3$, 376 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C-$^1$H, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 471 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C$^{[1]}$H, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 471 MHz
$\text{MeO}_2\text{C}-\text{CO}_2\text{Me}$

ClF$_2$C-\text{CO}_2\text{PNP}  

$^{1}H$, CDCl$_3$, 500 MHz

$\text{MeO}_2\text{C}-\text{CO}_2\text{Me}$

ClF$_2$C-\text{CO}_2\text{PNP}  

$^{13}C\{^{1}H\}$, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 470 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C\{^1H\}$, CDCl$_3$, 126 MHz
$^{19}\text{F}, \text{CDCl}_3, 471 \text{ MHz}$
$\text{MeO}_2\text{C} \rightleftharpoons \text{CO}_2\text{Me}$

$\text{EtO}_2\text{C} \rightleftharpoons \text{CO}_2\text{PNP}$

$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C\{^{1}H\}$, CDCl$_3$, 101 MHz
\[ \text{MeO}_2\text{C}\overbrace{\text{CO}_2\text{Me}} \]

\[ \text{Ph} \overbrace{\text{CO}_2\text{PNP}} \quad \text{24} \]

\[^1\text{H}, \text{CDCl}_3, \text{500 MHz}\]

\[ \text{MeO}_2\text{C}\overbrace{\text{CO}_2\text{Me}} \]

\[ \text{Ph} \overbrace{\text{CO}_2\text{PNP}} \quad \text{24} \]

\[^{13}\text{C}[^1\text{H}], \text{CDCl}_3, \text{126 MHz}\]
$\text{MeO}_2\text{C}_\text{F}$$\text{CO}_2\text{Me}_\text{F}_\text{CO}_2\text{PNP}$

$^1\text{H}$, CDCl$_3$, 500 MHz

$\text{MeO}_2\text{C}_\text{F}$$\text{CO}_2\text{Me}_\text{F}_\text{CO}_2\text{PNP}$

$^{13}\text{C}[^{1}\text{H}]$, CDCl$_3$, 126 MHz
$^{19}\text{F, CDCl$_3$, 376 MHz}$
^1^H, CDCl\textsubscript{3}, 500 MHz

\[ \text{EtO}_2\text{C} \text{CO}_2\text{Et} \]
\[ \text{F}_3\text{C} \text{CO}_2\text{PNP} \]

$^1^H$, CDCl\textsubscript{3}, 500 MHz

\[ \text{EtO}_2\text{C} \text{CO}_2\text{Et} \]
\[ \text{F}_3\text{C} \text{CO}_2\text{PNP} \]

$^{13}^C\{^1^H\}$, CDCl\textsubscript{3}, 126 MHz

\[ \text{EtO}_2\text{C} \text{CO}_2\text{Et} \]
\[ \text{F}_3\text{C} \text{CO}_2\text{PNP} \]

$^{13}^C\{^1^H\}$, CDCl\textsubscript{3}, 126 MHz
$^{19}\text{F}$, CDCl$_3$, 471 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$($^{1}H$), CDCl$_3$, 126 MHz
$\text{iPrO}_2\text{C} - \text{CO}_2\text{Pr}$

\[ \text{F}_3\text{C} - \text{CO}_2\text{PNP} \]

$^{19}\text{F, CDCl}_3, 376 \text{ MHz}$
$^{1}H$, CDCl$_{3}$, 500 MHz

$^{13}C\{^1H\}$, CDCl$_{3}$, 126 MHz
$^{19}$F, CDCl$_3$, 471 MHz
$\text{BnO}_2\text{C}_\text{\(\cdots\)CO}_2\text{Bn}$

$\text{F}_3\text{C}_\text{\(\cdots\)CO}_2\text{PNP}$

$^1\text{H}$, CDCl$_3$, 500 MHz

$^{13}\text{C}[^1\text{H}]$, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 376 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$-$^1H$, CDCl$_3$, 126 MHz
$^{19}\text{F, CDCl}_3$, 471 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C{$^1$H}, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 376 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C{$^1$H}, CDCl$_3$, 126 MHz
$^{19}$F, CDCl$_3$, 376 MHz
9. Appendix 2: HPLC Spectra

HPLC Data for 8a: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min⁻¹, 211 nm, 30 °C) t_R (minor): 31.6 min, t_R (major): 19.3 min, >99:1 er.
HPLC Data for 8b: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min$^{-1}$, 211 nm, 30 °C) $t_R$ (minor): 16.5 min, $t_R$ (major): 11.3 min, 99:1 er.
HPLC Data for 18: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min\(^{-1}\), 211 nm, 30 °C) \(t_R\) (minor): 7.8 min, \(t_R\) (major): 6.5 min, >99:1 er.

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 6.554     | 49.469|
| 2     | 7.932     | 50.531|
| Total |           | 100.000|

PDA Ch1 211nm

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 6.472     | 99.491|
| 2     | 7.849     | 0.509 |
| Total |           | 100.000|
HPLC Data for 19: Chiralcel OD-H (85:15 hexane:IPA, flow rate 1.00 mL.min\(^{-1}\), 211 nm, 30 °C) \(t_R\) (minor): 18.7 min, \(t_R\) (major): 17.2 min, 85:15 er.

\[
\begin{array}{c|c|c}
\text{Peak#} & \text{Ret. Time} & \text{Area%} \\
1 & 17.196 & 49.843 \\
2 & 18.597 & 50.157 \\
\hline
\text{Total} & 18.597 & 100.000 \\
\end{array}
\]

\[
\begin{array}{c|c|c}
\text{Peak#} & \text{Ret. Time} & \text{Area%} \\
1 & 17.166 & 84.597 \\
2 & 18.396 & 15.403 \\
\hline
\text{Total} & 18.396 & 100.000 \\
\end{array}
\]
HPLC Data for 20: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL,min⁻¹, 211 nm, 30 °C) tᵣ (minor): 24.2 min, tᵣ (major): 11.9 min, >99:1 er.

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 11.858    | 50.069|
| 2     | 23.980    | 49.931|
| Total |           | 100.000|

PDA Ch1 211nm

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 11.877    | 99.902|
| 2     | 24.245    | 0.098 |
| Total |           | 100.000|
HPLC Data for 21: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) tₚ (minor): 21.0 min, tₚ (major): 29.8 min, >99:1 er.
HPLC Data for 22: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min⁻¹, 211 nm, 30 °C) $t_R$ (minor): 30.9 min, $t_R$ (major): 23.8 min, >99:1 er.
HPLC Data for 23: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min⁻¹, 211 nm, 30 °C) $t_R$ (minor): 53.8 min, $t_R$ (major): 41.5 min, 98:2 er.
HPLC Data for 24: Chiralpak AS-H (95:5 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 40 °C) tₘ (major): 27.5 min, tₘ (minor): 24.7 min, 97:3 er.

![HPLC Chromatogram](image)

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 25.469    | 50.232|
| 2     | 28.752    | 49.768|
| Total |           | 100.000|

![HPLC Chromatogram](image)

| Peak# | Ret. Time | Area% |
|-------|-----------|-------|
| 1     | 24.676    | 3.399 |
| 2     | 27.464    | 96.601|
| Total |           | 100.000|
HPLC Data for 37: Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.00 mL min⁻¹, 211 nm, 30 °C) $t_R$ (minor): 22.8 min, $t_R$ (major): 15.6 min, 98:2 er.
HPLC Data for 38: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL min⁻¹, 211 nm, 30 °C) t_R (minor): 24.8 min, t_R (major): 15.4 min, >99:1 er.
HPLC Data for 39: Chiralcel OD-H (99:1 hexane:IPA, flow rate 1.00 mL.min⁻¹, 211 nm, 30 °C) \( t_R \) (minor): 18.6 min, \( t_R \) (major): 15.1 min, >99:1 er.

![HPLC graph](image)

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 15.092    | 50.368 |
| 2     | 18.241    | 49.632 |
| Total |           | 100.000|

![HPLC graph](image)

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 15.140    | 99.227 |
| 2     | 18.587    | 0.773  |
| Total |           | 100.000|
HPLC Data for 40: Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.00 mL.min$^{-1}$, 211 nm, 30 °C) $t_R$ (minor): 35.1 min, $t_R$ (major): 24.0 min, 99:1 er.
HPLC Data for 41: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min\(^{-1}\), 211 nm, 30 °C) \( t_R \) (minor): 30.3 min, \( t_R \) (major): 34.3 min, >99:1 er.
HPLC Data for 42: Chiralpak AD-H (95:5 hexane:IPA, flow rate 1.00 mL min$^{-1}$, 211 nm, 30 °C) $t_R$ (minor): 29.4 min, $t_R$ (major): 89.5 min, >99:1 er.
HPLC Data for 43: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min\(^{-1}\), 211 nm, 30 °C) \( t_R \) (minor): 24.1 min, \( t_R \) (major): 12.9 min, >99:1 er.
HPLC Data for 44: Chiralpak AD-H (90:10 hexane:IPA, flow rate 1.00 mL.min\(^{-1}\), 211 nm, 30 °C) \(t_R\) (minor): 8.4 min, \(t_R\) (major): 7.7 min, >99:1 er.

![HPLC Chromatogram](image)

**PDA Ch1 211nm**

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 7.721     | 50.666 |
| 2     | 8.424     | 49.334 |
| Total |           | 100.000|

![HPLC Chromatogram](image)

**PDA Ch1 211nm**

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 7.718     | 99.963 |
| 2     | 8.368     | 0.037  |
| Total |           | 100.000|