Isothiourea-mediated asymmetric Michael-lactonisation of trifluoromethylenones: a synthetic and mechanistic study

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SUPPORTING INFORMATION

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Appendix I: ¹H and ¹³C NMR Spectra for Novel Compounds and HPLC data
1.1 General information

Reactions involving moisture sensitive reagents were carried out under an argon atmosphere using standard vacuum line techniques in addition to freshly distilled solvents. All glassware used was flame dried and cooled under vacuum.

Solvents (THF, CH₂Cl₂, toluene, hexane and Et₂O) were obtained anhydrous and purified by an alumina column (Mbraun SPS-800). Petrol is defined as petroleum ether 40-60 °C. All other solvents and commercial reagents were used as supplied without further purification unless stated otherwise.

Room temperature (rt) refers to 20-25 °C. Temperatures of 0 °C and -78 °C were obtained using ice/water and CO₂(s)/acetone baths respectively. Temperatures of 0 °C to -50 °C for overnight reactions were obtained using an immersion cooler (HAAKE EK 90). Reflux conditions were obtained using an oil bath equipped with a contact thermometer. In vacuo refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC₂ vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller.

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. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated.

¹H and ¹³C nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance 300 (300 MHz, ¹H, 75 MHz ¹³C), Bruker Avance II 400 (400 MHz, ¹H, 100 MHz ¹³C) or a Bruker Avance II 400 (500 MHz, ¹H, 125 MHz ¹³C) spectrometer at ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent as the internal standard. All coupling constants, J, are quoted in Hz. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), ABq (AB quartet), sept (septet), oct (octet), m (multiplet), dd (doublet of doublets), ddd (doublet of doublet of doublets, dt (doublet of triplets) and td (triplet of doublets). The abbreviation Ar is used to denote aromatic, br to denote broad and app. to denote apparent.

Infrared spectra (ν max) were recorded on a Perkin-Elmer Spectrum GX FT-IR spectrometer using either thin films on NaCl plates or KBr discs. Only the characteristic peaks are quoted. Melting points were recorded on an Electrothermal apparatus and are uncorrected.

HPLC analyses were obtained on two separate machines; a Gilson HPLC consisting of a Gilson 305 pump, Gilson 306 pump, Gilson 811C dynamic mixer, Gilson 805 manometric module, Gilson 401C dilutor, Gilson 213XL sample injector and sample detection was performed with a Gilson 118 UV/vis detector while the temperature was assumed to be 20 °C; a Shimadzu HPLC consisting of a DGU-20A5 degasser, LC-20AT liquid chromatograph, SIL-20AHT autosampler, CMB-20A communications bus module, SPD-M20A diode array detector and a CTO-20A column oven which allowed the temperature to be set from 25-40 °C. Separation was achieved using Chiralcel OD-H and OJ-H columns or Chiralpak AD-H, AS-H, IA, IB, IC and ID columns.

Mass spectrometry (m/z) data were acquired by electrospray ionisation (ES), electron impact (EI) or nanospray ionisation (NSI) either at the University of St Andrews or the EPSRC National Mass Spectrometry Service Centre, Swansea. At the University of St Andrews, low and high resolution ESI MS were carried out on a
Micromass LCT spectrometer. At the EPSRC National Mass Spectrometry Service Centre, low resolution NSI MS was carried out on a Micromass Quattro II spectrometer and high resolution NSI MS on a Thermofisher LTQ Orbitrap XL spectrometer.

Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell.

1.2 General Experimental procedures

**General procedure A: Formation of trifluoromethyl enones.**

Following the procedure outlined by Zhang et al., to a solution of diisopropylamine (2 equiv.) in THF was added nBuLi (2.5M in hexanes, 2 equiv.) at -78 °C and the solution was allowed to stir for 20 minutes. Diethyl methylphosphonate (1 equiv.) was added at -78 °C followed by a further 30 minutes of stirring. (Z)-2,2,2-trifluoro-N-phenylacetimidoyl chloride (1 equiv) was then added slowly followed by stirring at -78 °C for 1 h.

A solution of the requisite aldehyde (1 equiv) in THF was then added dropwise at -78 °C. The reaction mixture was then warmed to rt over 2 h and stirred for 16 h. 2 M HCl (4 equiv.) was added and the reaction mixture was stirred for a further 4 h before being extracted with diethyl ether (x 3). The combined organic extracts were washed with sat. aq. NaHCO₃, brine, dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude reaction mixture.

**General procedure B: Michael addition-lactonization with DHPB (Racemic Protocol).**

To a solution of acid (1 equiv.) in DCM (~1 mL per 0.2 mmol of acid) were added DIPEA (1.5 equiv.) and pivaloyl chloride (1.5 equiv.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 20 minutes. The requisite Michael acceptor (1 equiv.), Lewis base (1-20 mol%) and DIPEA (2.5 equiv.) were then added in that order at the required temperature. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of 1M HCl. Once warmed to rt, the reaction mixture was poured into water and extracted twice with CH₂Cl₂. The combined organics were dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude reaction mixture.

**General procedure C: Michael addition-lactonization with chiral isothioureas (Asymmetric Protocol).**

To a solution of acid (1 equiv.) in DCM (~1 mL per 0.2 mmol of acid) were added DIPEA (1.5 equiv.) and pivaloyl chloride (1.5 equiv.) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 20 minutes. The requisite Lewis base (1-20 mol%), Michael acceptor (1 equiv.) and DIPEA (2.5 equiv.) were then added in that order at the required temperature. The reaction mixture was stirred at the required temperature until complete by TLC and was subsequently quenched by addition of 1M HCl. Once warmed to rt, the reaction mixture was poured into water and extracted twice with CH₂Cl₂. The combined organics were dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude reaction mixture.
**General procedure D: LiAlH₄ Mediated Rearrangements.**

To a solution of lactone (1 equiv.) in THF at rt was added 2M LiAlH₄ in THF (4 equiv.) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. NaHCO₃ and extracted with diethyl ether (x 3). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give crude the crude reaction mixture.

**1.3 Reaction Optimisation**

Optimisation studies on compound 3

3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenyl acetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 30 minutes at rt gave crude lactone (±)-3 (86:14 dr).

Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (±)-3 (96:4 dr) as a white solid (41.9 mg, 66%); mp 90-92 °C; νmax (KBr) 3084, 3032, 2962 (C-H), 1774 (C=O), 1702, 1606, δH (300 MHz, CDCl₃) 3.89 (1H, d, J=8.8, C(3)H), 3.92-3.98 (1H, m, C(4)H), 6.06 (1H, d, J=3.5, C(5)H), 6.94-6.96 (2H, m, ArH), 6.99-7.03 (2H, m, ArH); δC (100 MHz, CDCl₃) 44.8 (C(4)), 52.8 (C(3)), 110.7 (q, J=3.5, C(5)), 118.5 (q, J=270, CF₃), 127.4 (ArC), 128.1 (ArC), 128.2 (ArC), 128.3 (ArC), 128.9 (ArC), 129.2 (ArC), 135.1 (4ry ArC), 138.8 (4ry ArC), 140.9 (q, J=38, C(6)), 165.8 (C(2)); δF (282 MHz, CDCl₃) -72.6; m/z (NSI⁺) 336 ([M+NH₄⁺]+, 100%); HRMS (NSI⁺) C₁₈H₁₇F₃NO₂⁺ ([M+NH₄⁺]) requires 336.1206; found 336.1205 (-0.3 ppm).

**Asymmetric Catalyst Screen:**

All reactions for 15 minutes at rt.

(-)-Tetramisole hydrochloride 4 (4.82 mg, 0.02 mmol, 10 mol%) gave crude lactone (3S,4S)-3 (87:13 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3S,4S)-3 (97:3 dr) as a white solid (38.6 mg, 61%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) τₘ(3R,4R): 10.6 min, τₘ(3S,4S): 12.0 min, 89% ee.

Benzotetramisole (2R)-5 (5.04 mg, 0.02 mmol, 10 mol%) gave crude lactone (3S,4S)-3 (82:18 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3S,4S)-3 (95:5 dr) as a white solid.
(48.5 mg, 76%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 10.5 min, t_R(3S,4S): 11.7 min, 77% ee.

Ph/i-Pr isothiourea catalyst (2S,3R)-6 (6.17 mg, 0.02 mmol, 10 mol%) gave crude lactone (3R,4R)-3 (85:15 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (97:3 dr) as a white solid (46.3 mg, 73%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 10.6 min, t_R(3S,4S): 11.8 min, 95% ee.

Temperature Screen:
All reactions with Ph/i-Pr isothiourea catalyst (2S,3R)-6 (6.17 mg, 0.02 mmol, 10 mol%) 

Reaction for 3 h at -30 °C gave crude lactone (3R,4R)-3 (86:14 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (97:3 dr) as a white solid (50.1 mg, 79%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 11.0 min, t_R(3S,4S): 12.4 min, 96% ee.

Reaction for 4 h at -78 °C gave crude lactone (3R,4R)-3 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (98:2 dr) as a white solid (52.5 mg, 83%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 10.8 min, t_R(3S,4S): 12.1 min, 99% ee.

Catalyst Loading Screen:
All reactions at -78 °C for 16 h.

Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%) gave crude lactone (3R,4R)-3 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (98:2 dr) as a white solid (50.8 mg, 80%); [α]_D^20 -227.2 (c 0.25, CH₂Cl₂); Major diastereoisomer: Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 11.0 min, t_R(3S,4S): 12.3 min, 99% ee. Minor diastereoisomer: Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm, 30 °C) t_R(3S,4R): 6.4 min, t_R(3R,4S): 9.0 min, 99% ee.

Ph/i-Pr isothiourea catalyst (2S,3R)-6 (1.23 mg, 0.004 mmol, 2 mol%) gave crude lactone (3R,4R)-3 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (98:2 dr) as a white solid (50.5 mg, 79%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(3R,4R): 11.5 min, t_R(3S,4S): 12.9 min, 99% ee.

Ph/i-Pr isothiourea catalyst (2S,3R)-6 (0.62 mg, 0.002 mmol, 1 mol%) gave crude lactone (3R,4R)-3 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-3 (98:2 dr) as a white solid...
(50.2 mg, 79%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min\(^{-1}\), 211 nm) \(t_R(3R,4R)\): 11.3 min, \(t_R(3S,4S)\): 12.6 min, 99\% ee.

1.4 Improved synthesis of HBTM-2.1

**tert-butyl (phenyl(phenylsulfonyl)methyl)carbamate**

Following the method described by List et al.,\(^9\) to a stirred solution of *tert*-butyl carbamate (60.0 g, 0.51 mol) in THF (225 mL) in a 2 L three neck round bottom flask equipped with an overhead stirrer was added water (450 mL), sodium benzenesulfinate (92.3 g, 0.52 mol), benzaldehyde (53.2 mL, 0.52 mmol) and formic acid (110 mL, 2.92 mol). The reaction mixture was stirred for 24 h at rt. The resulting precipitate was filtered and washed with water (200 mL) followed by hexane/CH\(_2\)Cl\(_2\) (91/9) (2 × 200 mL). Stirring the combined liquors from filtration and the water wash for a further 24 h provided a second, smaller quantity of solid. The combined solids were dried in an oven at 90 °C until a constant weight was obtained, giving sulfone (±)-68 as a white solid (138 g, 78%); mp 164-165 °C (hexane/CH\(_2\)Cl\(_2\)) \{lit.\(^9\) mp 153-154 °C (hexane/CH\(_2\)Cl\(_2\))\}; \(\delta_H\) (300 MHz, \(d_6\)-DMSO) 1.18 (9H, s, C(CH\(_3\))\(_3\)), 6.02 (1H, d, \(J\) 10.7, CH), 7.39-7.43 (3H, m, ArH), 7.61-7.66 (4H, m, ArH), 7.73 (1H, t, \(J\) 7.4, ArH), 7.85-7.87 (2H, m, ArH) 8.73 (1H, d, \(J\) 10.7, NH).

**tert-butyl benzylidencarbamate**

To a stirred solution of potassium carbonate (397 g, 2.88 mol) in water (2.06 L) in a 5 L three neck round bottom flask equipped with an overhead stirrer was added a slurry of sulfone (±)-68a in CH\(_2\)Cl\(_2\) (1.20 L). The biphasic reaction mixture was stirred at rt for 2.5 h then separated. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2× 200 mL), the organic portions combined, dried with MgSO\(_4\), filtered and concentrated \textit{in vacuo}. Further drying at 2 mbar for 2 h provided imine 7 as a colorless oil (58.0 g, 98%); \(\delta_H\) (300 MHz, (CD\(_3\))\(_2\)CO) 1.54 (9H, s, C(CH\(_3\))\(_3\)), 7.54-7.57 (2H, m, ArH), 7.62-7.64 (1H, m, ArH), 7.94-7.97 (2H, m, ArH) 8.73 (1H, d, \(J\) 10.7, NH).

**tert-butyl ((1S,2S)-2-formyl-3-methyl-1-phenylbutyl)carbamate**
Following the method described by List et al.,\textsuperscript{9} to a stirred solution of imine 7 (58.0 g, 0.28 mol) in CH\textsubscript{3}CN (2.50 L) in a flame dried 5 L three neck round bottom flask equipped with an overhead stirrer under argon was added isovaleraldehyde (59.3 mL, 0.57 mol). The resulting solution was cooled to 0 °C in an ice/brine bath. (S)-proline (6.51 g, 565 mmol) was added and the reaction mixture was stirred for 14 h at 0 °C before warming to rt. Water (800 mL), Et\textsubscript{2}O (500 mL) and brine (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et\textsubscript{2}O (2 × 200 mL). The organic extracts were combined, dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo}. Trituration of the resulting solid with hexane (2 × 300 mL) gave aldehyde (1S,2S)-9 (>99:1 dr) as a white solid (77.9 g, 94%); mp 142-146 °C (hexane); \[\alpha\]\textsuperscript{20}D \textendash 66.7 (c 1.0 in CHCl\textsubscript{3}); \[\alpha\]\textsuperscript{20}D \textendash 70.9 (c 0.81 in CHCl\textsubscript{3}); δ\textsubscript{H} (300 MHz, CDCl\textsubscript{3}) 1.03 (3H, d, J\textsubscript{CH} 6.9, C\textsubscript{H}\textsubscript{3}), 1.14 (3H, d, J\textsubscript{CH} 6.9, C\textsubscript{H}\textsubscript{3}), 1.41 (9H, s, C(C\textsubscript{H}\textsubscript{3})\textsubscript{3}), 2.08-2.13 (1H, m, C(3)H), 2.47-2.51 (1H, m, C(2)H), 4.91-5.11 (2H, m, C(1)H and N\textsubscript{H}), 7.23-7.35 (5H, m, Ar\textsubscript{H}), 9.50 (1H, d, J 4.3, C(O)H); Chiral HPLC Chiralcel OD-H (2% IPA:hexane, flow rate 1 mL min\textsuperscript{-1}, 220 nm, 30 °C) \textit{t}\textsubscript{R}(3R,4R): 8.19 min, \textit{t}\textsubscript{R}(3S,4S): 9.43 min, >99% ee.

tert-butyl ((1S,2S)-2-(hydroxymethyl)-3-methyl-1-phenylbutyl)carbamate

Following a slightly modified method of that described by Smith et al.,\textsuperscript{10} to a slurry of aldehyde (1S,2S)-9 (77.0g, 0.26 mmol) in methanol (1.50 L) at 2 °C in a 3 L three neck round bottom flask equipped with an overhead stirrer was added NaBH\textsubscript{4} (15.0 g 0.40 mol) portion wise over 30 mins and the reaction mixture was left to stir for 1 h at rt. Saturated aqueous NaHCO\textsubscript{3} was added (100 mL) drop wise over 10 mins forming a white precipitate. The methanol was removed \textit{in vacuo} and water (1.00 L) and CH\textsubscript{2}Cl\textsubscript{2} (750 mL) was added. The layers were separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 × 250 mL). The organic extracts were combined, dried (MgSO\textsubscript{4}), filtered and concentrated \textit{in vacuo} and dried for 2 h at 2 mbar to give alcohol (1S,2S)-69 as a white solid (67.3 g, 87%); mp 92-94 °C; \{lit.\textsuperscript{10} mp 106-108 °C\}; \[\alpha\]\textsuperscript{20}D 26.4 (c 1.0 in CHCl\textsubscript{3}); \{lit.\textsuperscript{10} \[\alpha\]\textsuperscript{20}D \textendash 26.7 (c 0.7 in CHCl\textsubscript{3})\}; δ\textsubscript{H} (400 MHz, CDCl\textsubscript{3}) 0.85 (3H, d, J 6.9, CH\textsubscript{3}), 1.00 (3H, d, J 6.4, CH\textsubscript{3}), 1.42 (9H, s, C(C\textsubscript{H}\textsubscript{3})\textsubscript{3}), 1.71-1.87 (3H, m, C(2)H, C(3)H), 3.51 (1H, dd, J 11.5, 8.7 CHH), 3.67-3.69 (1H, m, CHH), 5.00 (1H, br s, C(1)H), 5.51-5.53 (1H, d, J 8.7, NH), 7.24-7.37 (5H, m, Ar\textsubscript{H}).

(S)-2-((S)-amino(phenyl)methyl)-3-methylbutan-1-ol hydrochloride

(S)-2-((S)-amino(phenyl)methyl)-3-methylbutan-1-ol hydrochloride
To a slurry of alcohol (1S,2S)-69 (67.0 g, 0.23 mol) in dioxane (200 mL) was added 4M HCl in dioxane (285 mL, 1.14 mol) drop wise over 30 mins and the reaction mixture was left to stir for 12 h at rt. 150 mL of dioxane was removed in vacuo and the solution cooled to 15 °C to precipitate a white solid. Et₂O (100 mL) was added and the precipitate was filtered, washed with Et₂O (2×200 mL) and the resulting white solid dried (15 mbar, 45 °C) for 2 h to give amino alcohol (1S,2S)-10 as a white solid (41.5 g, 79%); mp 142-144 °C; {lit.10 mp 168-170 °C}; \(\alpha\)\textsubscript{20} D –25.0 (c 1.0 in CH₃OH); {lit.10 \(\alpha\)\textsubscript{20} D –22.9 (c 0.98 in CH₃OH)}; \(\delta\)\textsubscript{H} (300 MHz, CD₃OD) 0.83 (3H, d, J₆.8, C₃H₃), 1.14 (3H, d, J₆.7, C₃H₃), 1.54 (1H, dq, J₁₃.7, 6.8, C(3)H), 2.00-2.09 (1H, m, C(2)H), 3.48 (1H, app. td, J₉.5, 9.8, C₃H), 3.75 (1H, dd, J₁₀.7, 4.6, C₃H), 4.58 (1H, d, J₄.2 C₅H, 7.40-7.55 (5H, m, ArH). (S)-2-((S)-(benzo[d]thiazol-2-ylamino)(phenyl)methyl)-3-methylbutan-1-ol

To a slurry of (1S,2S)-10 (41.0 g, 0.178 mol) in chlorobenzene (250 mL) was added iPr₂NEt (121 mL, 0.696 mol), 2-chlorobenzothiazole (24.6 mL, 0.189 mol) and the mixture heated to reflux for 70 h. The reaction mixture was cooled to rt, washed with water (2×200 mL), dried (MgSO₄), filtered and concentrated in vacuo. The resulting solid was stirred in hexane (250 mL) for 15 mins, filtered and dried at 2 mbar for 2 h to provide alcohol (1S,2S)-12 as a white solid (51.8 g, 89%); mp 136-139 °C; {lit. 10 mp 137-139 °C}; \(\alpha\)\textsubscript{20} D –52.3 (c 1.0 in CHCl₃); {lit. 10 \(\alpha\)\textsubscript{20} D –54.8 (c 0.5 in CHCl₃)}; \(\delta\)\textsubscript{H} (300 MHz, CDCl₃) 0.84 (3H, d, J₆.8, C₃H₃), 1.16 (3H, d, J₆.8, C₃H₃), 1.65-1.72 (1H, m, C(3)H), 2.17-2.23 (1H, m, C(2)H), 3.70 (1H, app. t, J₁₀.8, C₃H), 3.96 (1H, dd, J₁₀.8, 3.9, C₃H), 4.96 (1H, d, J₃.76 CHN), 7.03-7.09 (1H, m, ArH), 7.25-7.39 (4H, m, ArH), 7.45 (1H, app d, J₈.0, ArH), 7.53-7.55 (3H, m, ArH).


To a solution of alcohol (1S,2S)-12 (50.0 g, 0.15 mol) and Et₃N (64.0 mL, 0.46 mol) in anhydrous CH₂Cl₂ (1.00 L) at 5 °C under argon was added methanesulfonylchloride (17.8 mL, 0.23 mol) over 10 mins and the solution allowed to warm to rt. The solution was stirred for 1.5 h at which time NMR spectroscopic analysis indicated the consumption of alcohol (1S,2S)-53. Methanol (50 mL) was added followed by Et₃N (64.0 mL, 0.46 mol) and the solution heated to reflux for 1.5 h at which time NMR spectroscopic analysis indicated the formation of isothiourea (2S,3R)-6. The solution was cooled to rt, washed with water (2×400 mL) dried (MgSO₄), filtered and concentrated in vacuo. The crude light brown solid was suspended in EtOAc (250 mL) and heated to reflux for 5 mins causing partial dissolution of the crude solid. Upon cooling to rt and stirring for 1 h, the slurry was...
cooled to 0 °C in a ice/water bath for a further 15 mins then filtered to provide a white solid. The solid was
dried at 2 mbar for 5 h to give isothiourea (2S,3R)-6 as a colorless crystalline solid (40.2 g, 85%); C_{19}H_{20}N_{2}S
requires C, 74.07; H, 6.68; N, 9.03%; found C, 74.13; H, 6.61; N, 9.02%; mp 189-190 °C; \{\text{lit.}^{10}\ \text{mp 136-138 ° C}\}; [\alpha]_{D}^{20} +355.0 (c 1.0 in CHCl_{3}); \{\text{lit.10 } [\alpha]_{D}^{20} +288.4 (c 0.5 in CHCl_{3})\}; δ_{H} (300 MHz, CDCl_{3}) 0.89 (3H, d, J 6.6, CH_{3}), 1.18 (3H, d, J 6.4, CH_{3}), 1.30-1.42 (1H, m, CH(CH_{3})_{2}), 1.95-2.05 (1H, m, C(2)H), 3.40 (1H, app. t, J 11.5, CHH), 3.93 (1H, dd, J 11.6, 5.2, 1.7, CHH), 4.97 (1H, dd, J 4.4, 1.5, C(3)H), 6.86 (1H, d, J 7.9, ArH), 7.08 (1H, td, J 7.6, 1.0, ArH), 7.24-7.40 (7H, m, ArH); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min\(^{-1}\), 254 nm) \(t_{R}(2S,3R):\) 17.6 min >99% ee.

1.5 Synthesis of starting materials – DHPB and trifluoromethylenones

3-(benzo[d]thiazol-2-ylamino)propan-1-ol

Following the procedure described by Birman \textit{et al.},\(^{1}\) to a sealed pressure tube was charged 2-
chlorobenzothiazole (1.02 mL, 8.00 mmol), \(iPr_{2}NEt\) (2.11 mL, 12.0 mmol) and 3-amino-1-propanol (0.61 mL, 8.00 mmol). The tubes were purged with argon and then sealed and heated at 110 °C for 24 h. The reaction
mixture was allowed to cool to rt. Chromatographic purification (eluent \(iPrOH:CH_{2}Cl_{2} 10:90\)) gave alcohol 70
as a white solid (1.24 g, 80%); mp 120-122 °C; \{\text{lit.}\ \text{mp 123-124 °C}\}; δ_{H} (400 MHz, CD_{3}OD) 1.89 (2H, quintet, J 6.6, CH_{2}), 3.54 (2H, t, J 6.9, CH_{2}), 3.69 (2H, t, J 6.2 CH_{2}), 7.06 (1H, td, J 7.6, 1.0, ArH), 7.22-7.28 (1H, m, ArH), 7.42 (1H, dd, J 8.1, 0.6, ArH), 7.57 (1H, dd, J 7.9, 0.6, ArH).


Following the procedure described by Birman \textit{et al.},\(^{1}\) to a solution of 70 (4.97 g, 25.6 mmol) in dry \(CH_{2}Cl_{2}\) (250 mL) at 0 °C under argon was added triethylamine (10.7 mL, 76.8 mmol) and MsCl (2.99 mL, 38.4 mmol). The reaction
mixture was allowed to stir at 0 °C for 1 h. The solution was then warmed to rt and methanol (6 mL) was added to quench any remaining MsCl. A further portion of triethylamine (42.0 mL, 302 mmol) was added
to the solution and it was stirred at reflux overnight. The cooled reaction mixture was washed with water, dried
(MgSO_{4}), filtered and concentrated \textit{in vacuo}. Chromatographic purification (eluent Et_{3}N:\(iPrOH:CH_{2}Cl_{2} 1:9:89\))
gave DHPB 71 as a white solid (4.41 g, 91%); mp 120-121 °C; \{\text{lit.}\ \text{mp 122-123 °C}\}; δ_{H} (400 MHz, CDCl_{3}) 1.95 (2H, quintet, J 5.7, CH_{2}), 3.50 (2H, t, J 5.6, CH_{2}), 3.70 (2H, t, J 6.1 CH_{2}), 6.66 (1H, dd, J 8.0, 0.7, ArH), 6.91 (1H, td, J 7.6, 1.1, ArH), 7.11 (1H, td, J 7.6, 1.1, ArH), 7.19-7.22 (1H, m, ArH).
(Z)-2,2,2-trifluoro-N-phenylacetimidoyl chloride

Following the procedure outlined by Tamura et al., a solution of triphenylphosphine (34.6 g, 132 mmol), triethylamine (7.39 mL, 53.0 mmol), trifluoroacetic acid (3.37 mL, 44.0 mmol) and CCl₄ (21 mL) was stirred for 10 minutes before aniline (4.83 mL, 53.0 mmol) was added and the reaction mixture was stirred at reflux for 3 h. The reaction mixture was then concentrated in vacuo and the residue taken up in hexane. The precipitate was filtered and washed several times with hexane. The filtered was concentrated in vacuo and the residual oil was purified by distillation to give imine 72 as a yellow oil (3.08 g, 34%); bp 50-52 °C (5 mmHg); \( \delta_H \) (300 MHz, CDCl₃) 6.98-7.02 (2H, m, ArH), 7.18-7.24 (1H, m, ArH), 7.31-7.38 (2H, m, ArH); \( \delta_F \) (282 MHz, CDCl₃) -72.1 (C₃F₃).

(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one

Following general procedure A, diisopropylamine (5.44 mL, 40 mmol) and nBuLi (2.5M in hexanes, 16 mL, 40 mmol) in THF (80 mL), diethyl methylphosphonate (2.96 mL, 20 mmol), imine 72 (4.16 g, 20 mmol) and benzaldehyde (2.04 mL, 20 mmol) in THF (20 mL) followed by 2 M HCl (40 mL, 80 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 2 as a light yellow oil (3.63 g, 91%); \( \delta_H \) (500 MHz, CDCl₃) 6.96 (1H, d, \( J_{16.0} \) C(3)H), 7.37-7.45 (3H, m, ArH), 7.57-7.59 (2H, m, ArH), 7.91 (1H, d, \( J_{16.0} \) C(4)H); \( \delta_F \) (470 MHz, CDCl₃) -77.6 (C₃F₃).

(E)-4-(4-bromophenyl)-1,1,1-trifluorobut-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-bromobenzaldehyde (463 mg, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 3:97) gave enone 73 as a light yellow solid (521 mg, 75%); mp 40-42 °C; \{lit. \( \delta_F \) (300 MHz, CDCl₃) 6.94 (1H, dd, \( J_{16.0} \), 0.8 C(3)H), 7.41-7.45 (2H, m, ArH), 7.51-7.55 (2H, m, ArH), 7.83 (1H, d, J 16.0, C(4)H); \( \delta_F \) (470 MHz, CDCl₃) -78.1 (C₃F₃).
(E)-4-(3-bromophenyl)-1,1,1-trifluorobut-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 3-bromobenzaldehyde (463 mg, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 3:97) gave enone 74 as a light yellow oil (433 mg, 62%); ν_{max} (film) 3067, 2921 (C-H), 1722 (C=O), 1611, 1561; δ_{H} (400 MHz, CDCl₃) 6.93 (1H, dd, J 16.0, 0.8, C(3)H), 7.26 (1H, t, J 7.9, ArH), 7.48 (1H, d, J 7.8, ArH), 7.55 (1H, ddd, J 8.0, 1.9, 1.0, ArH), 7.71 (1H, t, J 1.8, ArH), 7.80 (1H, d, J 16.0, C(4)H); δ_{C} (100 MHz, CDCl₃) 116.3 (q, J 289, CF₃), 117.9 (C(3)), 123.4 (4ry ArC), 127.9 (ArC), 130.7 (ArC), 131.7 (ArC), 135.0 (ArC), 135.3 (4ry ArC), 148.2 (C(4)), 179.8 (q, J 35, C(2)); δ_{F} (376 MHz, CDCl₃) -78.2 (CF₃); m/z (NSI⁺) 279 ([M+H⁺], 100%); HRMS (NSI⁺) C₁₀H₇⁷⁹BrF₃O⁺ ([M+H⁺]⁺) requires 278.9627; found 278.9626 (-0.3 ppm).

(E)-4-(2-bromophenyl)-1,1,1-trifluorobut-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 2-bromobenzaldehyde (0.29 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 75 as a light yellow oil (453 mg, 65%); ν_{max} (film) 3070, 2923 (C-H), 1724 (C=O), 1603, 1564; δ_{H} (300 MHz, CDCl₃) 6.89 (1H, dd, J 16.0, 0.7, C(3)H), 7.18-7.34 (2H, m, ArH), 7.62 (2H, ddd, J 15.9, 7.7, 1.7, ArH), 8.29 (1H, d, J 16.0, C(4)H); δ_{C} (125 MHz, CDCl₃) 116.3 (q, J 289, CF₃), 119.1 (C(3)), 127.0 (4ry ArC), 128.0 (ArC), 128.2 (ArC), 133.0 (ArC), 133.3 (4ry ArC), 133.9 (ArC), 148.3 (C(4)), 179.8 (q, J 36, C(2)); δ_{F} (282 MHz, CDCl₃) -78.2 (CF₃); m/z (NSI⁺) 279 ([M+H⁺], 100%); HRMS (NSI⁺) C₁₀H₇⁷⁹BrF₃O⁺ ([M+H⁺]⁺) requires 278.9627; found 278.9626 (-0.3 ppm).

(E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-
methoxybenzaldehyde (0.31 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 30:70) gave enone 76 as a yellow solid (455 mg, 79%); mp 30-32 °C; {lit. mp 35-37 °C}; δH (400 MHz, CDCl₃) 3.81 (3H, s, OCH₃), 6.82 (1H, dd, J 15.8, 0.8, C(3)H), 6.87-6.90 (2H, m, ArH), 7.52-7.56 (2H, m, ArH), 7.87 (1H, d, J 15.8, C(4)H); δF (376 MHz, CDCl₃) -78.0 (CF₃).

(E)-1,1,1-trifluoro-4-(4-nitrophenyl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-nitrobenzaldehyde (378 mg, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 30:70) gave enone 77 as a yellow solid (428 mg, 70%); mp 80-82 °C; {lit. mp 98-99 °C}; δH (400 MHz, CDCl₃) 7.05 (1H, dd, J 16.1, 0.7, C(3)H), 7.72-7.76 (2H, m, ArH), 7.91 (1H, d, J 16.1, C(4)H), 8.23-8.26 (2H, m, ArH); δF (376 MHz, CDCl₃) -78.2 (CF₃).

(E)-1,1,1-trifluoro-4-(p-tolyl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-methylbenzaldehyde (0.30 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 78 as a light yellow solid (476 mg, 89%); mp 30-32 °C; {lit. mp 35 °C}; δH (400 MHz, CDCl₃) 2.44 (3H, s, CH₃), 7.00 (1H, dd, J 15.9, 0.7, C(3)H), 7.28-7.30 (2H, m, ArH), 7.57 (2H, d, J 8.2, ArH), 7.98 (1H, d, J 15.9, C(4)H); δF (376 MHz, CDCl₃) -78.0 (CF₃).

(E)-4-(4-chlorophenyl)-1,1,1-trifluorobut-3-en-2-one

S12
Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-chlorobenzaldehyde (351 mg, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 79 as a white solid (444 mg, 76%); mp 42-44 °C; \( \delta \)H (300 MHz, CDCl₃) 6.92 (1H, dd, \( J \) 16.0, 0.8, C(3)H), 7.34-7.39 (2H, m, ArH), 7.49-7.54 (2H, m, ArH), 7.85 (1H, d, \( J \) 16.0, C(4)H); \( \delta \)F (282 MHz, CDCl₃) -78.1 (CF₃).

**\((E)-1,1,1\text{-trifluoro-4-(4-fluorophenyl)but-3-en-2-one}\)**

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 4-fluorobenzaldehyde (0.27 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 80 as a white solid (412 mg, 76%); mp 26-28 °C; \( \delta \)H (400 MHz, CDCl₃) 6.97 (1H, d, \( J \) 16.0, C(3)H), 7.16-7.20 (2H, m, ArH), 7.67-7.70 (2H, m, ArH), 7.96 (1H, d, \( J \) 16.0, C(4)H); \( \delta \)F (376 MHz, CDCl₃) -78.1 (CF₃), -106.0 (ArF).

**\((E)-1,1,1\text{-trifluoro-4-(naphthalen-2-yl)but-3-en-2-one}\)**

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 2-naphthaldehyde (391 mg, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 81 as a light yellow solid (476 mg, 76%); mp 65-67 °C; \( \delta \)H (400 MHz, CDCl₃) 7.06 (1H, dd, \( J \) 15.9, 0.7, C(3)H), 7.47-7.54 (2H, m, ArH), 7.68 (1H, dd, \( J \) 8.6, 1.7, ArH), 7.79-7.85 (3H, m, ArH), 8.01 (1H, s, ArH), 8.07 (1H, d, \( J \) 15.9, C(4)H); \( \delta \)F (376 MHz, CDCl₃) -78.0 (CF₃).
(E)-1,1,1-trifluoro-4-(naphthalen-1-yl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5 M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and 1-naphthaldehyde (0.34 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 5:95) gave enone 82 as a yellow oil (555 mg, 82%); δH (400 MHz, CDCl₃) 7.08 (1H, d, J 15.7, C(3)H), 7.45-7.60 (3H, m, ArH), 7.84-7.88 (2H, m, ArH), 7.94 (1H, d, J 8.2, ArH), 8.15 (1H, d, J 8.5, ArH), 8.80 (1H, d, J 15.7, C(4)H); δF (376 MHz, CDCl₃) -78.0 (CF₃).

(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5 M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and furfuraldehyde (0.21 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 10:90) gave enone 83 as a yellow oil (273 mg, 57%); δH (300 MHz, CDCl₃) 6.51 (1H, dd, J 3.5, 1.8, ArH), 6.80-6.85 (2H, m, C(3)H and ArH), 7.54-7.55 (1H, m, ArH), 7.62 (1H, d, J 15.6, C(4)H); δF (282 MHz, CDCl₃) -78.1 (CF₃).

(E)-1,1,1-trifluoro-4-(thiophen-2-yl)but-3-en-2-one

Following general procedure A, diisopropylamine (0.68 mL, 5 mmol) and nBuLi (2.5 M in hexanes, 2 mL, 5 mmol) in THF (10 mL), diethyl methylphosphonate (0.37 mL, 2.5 mmol), imine 72 (0.52 g, 2.5 mmol) and thiophene-2-carbaldehyde (0.23 mL, 2.5 mmol) in THF (2.5 mL) followed by 2 M HCl (5 mL, 10 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 10:90) gave enone 84 as a light yellow oil (460 mg, 89%); δH (500 MHz, CDCl₃) 6.71 (1H, d, J 15.6, C(3)H), 7.08 (1H, dd, J 5.0, 3.8, ArH), 7.41 (1H, d, J 3.6, ArH), 7.51 (1H, d, J 5.0, ArH), 8.00 (1H, d, J 15.6, C(4)H); δF (282 MHz, CDCl₃) -78.0 (CF₃).
(E)-1,1,1-trifluoronon-3-en-2-one

Following general procedure A, diisopropylamine (1.36 mL, 10.0 mmol) and nBuLi (2.5M in hexanes, 4 mL, 10.0 mmol) in THF (20 mL), diethyl methylphosphonate (0.74 mL, 5.00 mmol), imine 72 (1.04 g, 5.00 mmol) and hexanal (0.61 mL, 5.00 mmol) in THF (10 mL) followed by 2 M HCl (10 mL, 20 mmol) gave crude reaction mixture. Chromatographic purification (eluent CH₂Cl₂:petrol 10:90) gave enone 87 as a light yellow oil (740 mg, 76%); δ_H (500 MHz, CDCl₃) 0.93 (3H, t, J₇.₁, CH₃), 1.33-1.37 (4H, m, 2CH₂), 1.53-1.58 (2H, m, CH₂), 2.36 (2H, qd, J₇.₄, 1.₂, CH₂C=), 6.44 (1H, dd, J₁₅.₈, 0.₉, C(3)H), 7.36 (1H, dt, J₁₅.₃, 7.₄, C(4)H).

1,1,1-trifluoro-4-phenylbut-3-en-2-one

To a solution of phenylacetylene (1.00 mL, 9.12 mmol) in THF (25 mL) at -78 °C was added n-BuLi (3.65 mL, 9.12 mmol) and the reaction mixture was stirred at -78 °C for 20 minutes. A solution of ethyl trifluoroacetate (1.09 mL, 9.12 mmol) in THF (15 mL) was added followed by boron trifluoride diethyl etherate (1.37 mL, 10.9 mmol) and the reaction mixture was stirred at -78 °C for 2 h. The reaction mixture was quenched by dropwise addition of sat. aq. NaCl and extracted with Et₂O (x 3). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give the crude reaction mixture. Chromatographic purification (eluent Et₂O:petrol 20:80) gave alkyne 85 as a yellow oil (1.80 g, quant.); δ_H (300 MHz, CDCl₃) 7.36-7.41 (2H, m, Ar(3)H), 7.48-7.54 (1H, m, Ar(4)H), 7.60-7.64 (2H, m, Ar(2)H); δ_F (282 MHz, CDCl₃) -78.3 (C_F₃).

(Z)-1,1,1-trifluoro-4-phenylbut-3-en-2-one

To a solution of alkyne 85 (1.80 g, 9.10 mmol) in THF (50 mL) at rt was added 5% Palladium on calcium carbonate (968 mg, 0.46 mmol) and hydrogen gas was bubbled through the solution using an appended balloon for 4 h at rt. The reaction mixture was filtered through celite and the filtrate was concentrated in vacuo to give the crude reaction mixture. Chromatographic purification (eluent 100% petrol) gave enone 86 as a light yellow oil (730 mg, 40%); ν_max (film) 3067, 2965 (C-H), 1719 (C=O), 1593, 1568; δ_H (300 MHz, CDCl₃) 6.52 (1H, dd, J₁₂.₉, 0.₇, C(3)H), 7.29 (1H, d, J₁₂.₉, C(4)H), 7.42-7.50 (3H, m, ArH), 7.87-7.91 (2H, m, Ar(2)H); δ_C (100 MHz, CDCl₃) 116.3 (q, J290, CF₃), 116.7 (C(3)), 128.4 (ArC), 131.2 (ArC), 131.6 (ArC(4)), 133.7 (4ry...
ArC(1)), 151.9 (C(4)), 179.1 (q, J 34.3, C(2)); δF (282 MHz, CDCl3) -79.0 (C F3); m/z (APCI+) 201 ([M+H]+, 100%); HRMS (APCI+) C10H8F3O+ ([M+H]+) requires 201.0522; found 201.0520 (-0.9 ppm).

1.6 Examples – acid and enone variation

3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-13 (83:17 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (±)-13 (>99:1 dr) as a white solid (53.6 mg, 80%); mp 79-81 °C; νmax (KBr) 3088, 2928 (C-H), 1772 (C=O), 1702, 1611, 1518; δH (300 MHz, CDCl3) 3.83-3.94 (2H, m, C(3)H and C(4)H), 6.07 (1H, d, J 2.9, C(5)H), 6.87-6.97 (6H, m, ArH), 7.17-7.24 (3H, m, ArH); δC (100 MHz, CDCl3) 44.9 (C(4)), 52.1 (C(3)), 111.0 (q, J 3.5, C(5)), 115.9 (d, J 21.5, ArC), 118.4 (q, J 270, CF3), 127.4 (ArC), 128.2 (ArC), 129.2 (ArC), 130.2 (d, J 8.2, ArC), 130.7 (d, J 3.4, 4ry ArC), 138.5 (4ry ArC), 140.9 (q, J 38.0, C(6)), 162.3 (d, J 246, 4ry ArC), 165.7 (C(2)); δF (282 MHz, CDCl3) -72.6 (C F3), -114.2 (ArF); m/z (NSI+) 354 ([M+NH4]+, 100%); HRMS (NSI+) C18H16F4NO2+ ([M+NH4]+) requires 354.1112; found 354.1115 (+0.9 ppm).

(3R,4R)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-13 (90:10 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3R,4R)-13 (>99:1 dr) as a white solid (54.3 mg, 81%); [α]D20 -256.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R): 19.2 min, tR(3S,4S): 39.4 min, 99% ee.

3-(4-chlorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
Following general procedure B, 4-chlorophenyl acetic acid (34.1 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-14 (84:16 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (±)-14 (>99:1 dr) as a white solid (56.0 mg, 79%); mp 91-93 °C; νₘₐₓ (KBr) 3086, 3031 (C-H), 1771 (C=O), 1701, 1602; δ H (400 MHz, CDCl₃) 3.84 (1H, d, J 10.2, C(3)H), 3.89-3.93 (1H, m, C(4)H), 6.06 (1H, d, J 2.8, C(5)H), 6.89-6.93 (4H, m, ArH), 7.17-7.23 (5H, m, ArH); δ C (100 MHz, CDCl₃) 44.7 (C(4)), 52.3 (C(3)), 111.1 (q, J 3.4, C(5)), 118.4 (q, J 270, CF₃), 127.4 (ArC), 128.2 (ArC), 129.1 (ArC), 129.2 (ArC), 129.9 (ArC), 133.3 (4ry ArC), 134.1 (4ry ArC), 138.4 (4ry ArC), 140.9 (q, J 38.0, C(6)), 165.5 (C(2)); δ F (376 MHz, CDCl₃) -72.6 (C₃F₃); m/z (NSI⁺) 353 ([M+H]⁺, 100%); HRMS (NSI⁺) C₁₈H₁₃ClF₃O₂⁺ ([M+H]⁺) requires 353.0551; found 353.0551 (+0.1 ppm).

(3R,4R)-3-(4-chlorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 4-chlorophenylacetic acid (34.1 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-14 (91:9 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-14 (>99:1 dr) as a white solid (58.2 mg, 83%); [α] D₂₀ -226.0 (c 0.25, CH₂Cl₂); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tₘₖ(3R,4R): 25.4 min, tₘₖ(3S,4S): 40.3 min, 96% ee.

3-(4-bromophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 30 minutes at rt gave crude lactone (±)-15 (84:16 dr).
Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (±)-15 (>99:1 dr) as a white solid (56.2 mg, 71%); mp 66-68 °C; ν max (KBr) 3089, 3030, 2961 (C-H), 1784 (C=O), 1700; δ H (300 MHz, CDCl₃) 3.83 (1H, d, J 10.2, C(3)H), 3.88-3.95 (1H, m, C(4)H), 6.06 (1H, d, J 2.6, C(5)H), 6.83-6.87 (2H, m, ArH), 6.90-6.94 (2H, m, ArH), 7.17-7.24 (3H, m, ArH), 7.32-7.36 (2H, m, ArH); δC (100 MHz, CDCl₃) 44.7 (C(4)), 52.3 (C(3)), 111.0 (q, J 3.3, C(5)), 118.4 (q, J 270, C(F)), 122.3 (4ry ArC), 127.4 (ArC), 128.2 (ArC), 129.3 (ArC), 130.2 (ArC), 132.0 (ArC), 133.9 (4ry ArC), 140.7 (q, J 37.9, C(6)), 156.4 (C(2)); δ F (282 MHz, CDCl₃) -72.6 (C F₃); m/z (NSI+) 414 ([M+NH₄]+, 61%); HRMS (NSI +) C₁₈H₁₆BrF₃NO₂⁺ ([M+NH₄]+) requires 414.0311; found 414.0310 (-0.2 ppm).

(3R,4R)-3-(4-bromophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 4-bromophenylacetic acid (43.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-15 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 3.5:96.5) gave lactone (3R,4R)-15 (>99:1 dr) as a white solid (56.9 mg, 72%); [α] D₂₀ -198.5 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3S,4S): 23.5 min, tR(3R,4R): 25.5 min, 95% ee.

3-(3,4-dimethoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 3,4-dimethoxyphenylacetic acid (39.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-16 (80:20 dr). Chromatographic purification (eluent Et₂O:petrol 30:70) gave lactone (±)-16 (84:16 dr) as a colourless oil (60.0 mg, 79%); ν max (thin film) 3088, 3006, 2934 (C-H), 1790 (C=O), 1698, 1594, 1516; δ H (300 MHz, CDCl₃) 3.71 (3H, s, OC₃H₃), 3.78 (3H, s, OC₃H₃), 3.84 (1H, d, J 8.8, C(3)H), 3.89-3.94 (1H, m, C(4)H), 6.07 (1H, d, J 3.5, C(5)H), 6.48 (1H, d, J 2.1, ArH), 6.57 (1H, dd, J 8.3, 2.1, ArH), 6.70 (1H, d, J 8.3, ArH), 6.94-6.98 (2H, m, ArH), 7.17-7.25 (3H, m, ArH); δC (75 MHz, CDCl₃) 45.0 (C(4)), 52.4 (C(3)), 55.9 (OCH₃), 55.9 (OCH₃), 110.7 (q, J 3.5, C(5)), 112.8 (ArC), 111.3 (ArC), 118.5 (q, J 270, CF₃), 120.6 (ArC), 127.4 (ArC) 127.4 (4ry ArC), 130.2 (ArC), 133.9 (4ry ArC), 140.7 (q, J 37.9, C(6)), 156.4 (C(2)); δ F (282 MHz, CDCl₃) -72.6 (C F₃); m/z (NSI+) 414 ([M+NH₄]+, 61%); HRMS (NSI +) C₁₈H₁₆BrF₃NO₂⁺ ([M+NH₄]+) requires 414.0311; found 414.0310 (-0.2 ppm).
128.1 (ArC), 129.2 (ArC), 138.9 (4ry ArC), 140.9 (q, J 38.0, C(6)), 148.8 (4ry ArC), 149.1 (4ry ArC), 165.9 (C(2)); $\delta_F$ (282 MHz, CDCl$_3$) -72.6 (C$_3$F$_3$); $m/z$ (NSI$^+$) 379 ([M+H$^+$], 100%); HRMS (NSI$^+$) C$_{20}$H$_{18}$F$_3$O$_4^+$ ([M+H$^+$]) requires 379.1152; found 379.1149 (-0.7 ppm).

(3R,4R)-3-(3,4-dimethoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 3,4-dimethoxyphenylacetic acid (39.4 mg, 0.20 mmol), DIPEA (51.9 $\mu$L, 0.30 mmol) and pivaloyl chloride (37.0 $\mu$L, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 $\mu$L, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-16 (90:10 dr). Chromatographic purification (eluent Et$_2$O:petrol 30:70) gave lactone (3R,4R)-16 (92:8 dr) as a white solid (66.1 mg, 87%); $[\alpha]_D^{20}$ -268.0 (c 0.1, CH$_2$Cl$_2$); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min$^{-1}$, 211 nm) $t_R$(3S,4S): 19.6 min, $t_R$(3R,4R): 21.1 min, 98% ee.

3-(4-methoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, p-methoxyphenylacetic acid (33.2 mg, 0.20 mmol), DIPEA (51.9 $\mu$L, 0.30 mmol) and pivaloyl chloride (37.0 $\mu$L, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 $\mu$L, 0.5 mmol) for 1 h at rt gave crude lactone (+)-17 (82:18 dr). Chromatographic purification (eluent Et$_2$O:petrol 10:90) gave lactone (+)-17 (>99:1 dr) as a white solid (52.0 mg, 75%); mp 90-92 °C; $\nu_{\max}$ (KBr) 3033, 2961 (C-H), 2840, 1784 (C=O), 1700, 1614, 1586, 1516; $\delta H$ (400 MHz, CDCl$_3$) 3.69 (3H, s, C$_3$H$_3$), 3.84 (1H, d, J 9.0, C(3)H), 3.89-3.93 (1H, m, C(4)H), 6.05 (1H, d, J 3.5, C(5)H), 6.73-6.76 (2H, m, ArH), 6.91-6.96 (4H, m, ArH), 7.17-7.23 (3H, m, ArH); $\delta C$ (100 MHz, CDCl$_3$) 44.8 (C(4)), 52.0 (C(3)), 55.3 (CH$_3$), 110.8 (q, J 3.5, C(5)), 114.3 (ArC), 118.5 (q, J 270, CF$_3$), 127.0 (4ry ArC), 127.4 (ArC), 128.0 (ArC), 129.2 (ArC), 129.4 (ArC), 138.9 (4ry ArC), 140.8 (q, J 37.9, C(6)), 159.3 (4ry ArC), 166.1 (C(2)); $\delta_F$ (376 MHz, CDCl$_3$) -72.6 (CF$_3$); $m/z$ (NSI$^+$) 366 ([M+NH$_4^+$], 100%); HRMS (NSI$^+$) C$_{19}$H$_{16}$F$_3$NO$_5^+$ ([M+NH$_4^+$]) requires 366.1312; found 366.1318 (+1.8 ppm).

(3R,4R)-3-(4-methoxyphenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
Following general procedure C, p-methoxyphenylacetic acid (33.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-17 (92:8 dr). Chromatographic purification (eluent Et₂O:petrol 10:90) gave lactone (3R,4R)-17 (98:2 dr) as a white solid (58.9 mg, 85%); [α]D 20 -199.5 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tᵦ(3R,4R): 28.7 min, tᵦ(3S,4S): 31.2 min, 98% ee.

3-(4-(dimethylamino)phenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 2-(4-(dimethylamino)phenyl)acetic acid (35.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-18 (80:20 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave lactone (±)-18 (85:15 dr) as a yellow oil (64.6 mg, 89%); νmax (thin film) 3088, 3031, 2922 (C-H), 1790 (C=O), 1698, 1615, 1525; δH (300 MHz, CDCl₃) 2.85 (6H, s, 2 NC₃H₃), 3.83 (1H, d, J 7.6, C(3)H), 3.88-3.93 (1H, m, C(4)H), 6.04 (1H, d, J 4.1, C(5)H), 6.53-6.58 (2H, m, ArH), 6.87-6.91 (2H, m, ArH), 6.98-7.01 (3H, m, ArH); δC (100 MHz, CDCl₃) 40.4 (2 NCH₃), 44.8 (C(4)), 51.8 (C(3)), 110.4 (q, J 3.4, C(5)), 112.6 (ArC), 118.6 (q, J 270, CF₃), 122.4 (4ry ArC), 127.4 (ArC), 127.9 (ArC), 128.7 (ArC), 129.2 (ArC), 139.3 (4ry ArC), 140.8 (q, J 37.8, C(6)), 150.2 (4ry ArC), 166.3 (C(2)); δF (282 MHz, CDCl₃) -72.6 (CF₃); m/z (NSI⁺) 362 ([M+H]+, 100%); HRMS (NSI⁺) C₂₀H₁₉F₃NO₂⁺ ([M+H]⁺) requires 362.1362; found 362.1362 (-0.1 ppm).

(3R,4R)-3-(4-(dimethylamino)phenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 2-(4-(dimethylamino)phenyl)acetic acid (35.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16
h at -78 °C gave crude lactone (3R,4R)-18 (95:5 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave lactone (3R,4R)-18 (95:5 dr) as a colourless oil (57.5 mg, 80%); [α]D 20° -286.5 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tₘ(3R,4R): 14.9 min, tₘ(3S,4S): 16.8 min, 99% ee.

3-[[1,1'-biphenyl]-4-yl]-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, biphenylacetic acid (42.4 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-19 (85:15 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (±)-19 (98:2 dr) as a white solid (57.5 mg, 73%); νmax (KBr) 3085, 3031 (C-H), 1771 (C=O), 1705, 1600; δH (300 MHz, CDCl₃) 3.92-4.01 (2H, s, C(3)H and C(4)H), 6.08 (1H, d, J 3.4, C(5)H), 6.96-6.99 (2H, m, ArH), 7.06-7.09 (2H, m, ArH), 7.15-7.37 (6H, m, ArH), 7.42-7.49 (4H, m, ArH); δC (100 MHz, CDCl₃) 44.8 (C(4)), 52.5 (C(3)), 110.8 (q, J 3.4, C(5)), 118.5 (q, J 270, CF₃), 127.1 (ArC), 127.4 (ArC), 127.6 (ArC), 128.1 (ArC), 128.7 (ArC), 128.8 (ArC), 129.2 (ArC), 134.0 (4ry ArC), 138.8 (4ry ArC), 140.3 (4ry ArC), 140.9 (q, J 380, C(6)), 141.0 (4ry ArC), 165.8 (C(2)); δF (282 MHz, CDCl₃) -72.6 (C₃F₃); m/z (NSI⁺) 395 ([M+H⁺], 100%); HRMS (NSI⁺) C₂₄H₁₈F₃O₂⁺ ([M+H⁺]) requires 395.1253; found 395.1246 (-1.9 ppm).

(3R,4R)-3-[[1,1'-biphenyl]-4-yl]-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, biphenylacetic acid (42.4 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-19 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-19 (98:2 dr) as a white solid (70.4 mg, 89%); [α]D 20° -297.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tₘ(3R,4R): 14.0 min, tₘ(3S,4S): 16.8 min, 98% ee.
4-phenyl-3-(m-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, m-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-20 (84:16 dr). Chromatographic purification (eluent Et2O:petrol 3:97) gave lactone (±)-20 (97:3 dr) as a white solid (49.9 mg, 75%); mp 52-54 °C; νmax (KBr) 3079, 3031 (C-H), 2921, 1779 (C=O), 1698, 1611; δH (300 MHz, CDCl3) 2.23 (3H, s, CH3), 3.87 (1H, d, J 8.1, CH(3)), 3.92-3.96 (1H, m, CH(4)), 6.05 (1H, d, J 3.8, CH(5)), 6.81-6.84 (2H, m, ArH), 6.97-7.02 (3H, m, ArH), 7.11 (1H, t, J 7.6, ArH); δC (100 MHz, CDCl3) 21.4 (CH3), 44.8 (CH(4)), 52.7 (CH(3)), 110.5 (q, J 3.5, CH(5)), 118.5 (q, J 270, CF3), 125.1 (ArC), 127.4 (ArC), 128.1 (ArC), 128.8 (ArC), 128.9 (ArC), 129.2 (ArC), 135.1 (4ry ArC), 138.7 (4ry ArC), 138.9 (4ry ArC), 140.8 (q, J 38.0, C(6)), 165.8 (C(2)); δF (376 MHz, CDCl3) -72.7 (CF3); m/z (NSI+) 350 ([M+NH4]+, 100%); HRMS (NSI+) C19H19F3NO2+ ([M+NH4]+) requires 350.1362; found 350.1367 (+1.3 ppm).

(3R,4R)-4-phenyl-3-(m-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, m-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-20 (94:6 dr). Chromatographic purification (eluent Et2O:petrol 3:97) gave lactone (3R,4R)-20 (99:1 dr) as a white solid (60.1 mg, 91%); [α]D20 -219.5 (c 0.2, CH2Cl2); Chiral HPLC Chiralcel OD-H (2% IPA:hexane, flow rate 1 mL min-1, 211 nm) tr(3R,4R): 18.4 min, tr(3S,4S): 27.7 min, >99% ee.

Scale-up:

Following general procedure C, m-tolylacetic acid (1.13 g, 7.50 mmol), DIPEA (1.96 mL, 11.3 mmol) and pivaloyl chloride (1.39 mL, 11.3 mmol) in DCM (75 mL), Ph/i-Pr isothiourea catalyst (25.3R)-6 (23.1 mg, 0.075 mmol, 1 mol%), enone 2 (1.50 g, 7.5 mmol) and DIPEA (3.27 mL, 18.8 mmol) for 40 h at -78 °C gave crude lactone (3R,4R)-20 (94:6 dr). Chromatographic purification (eluent Et2O:petrol 2:98) gave lactone (3R,4R)-20 (96:4 dr) as a white solid (2.12 g, 85%); 98% ee.
4-phenyl-3-(p-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, p-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 µL, 0.30 mmol) and pivaloyl chloride (37.0 µL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 µL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-21 (84:16 dr). Chromatographic purification (eluent Et₂O:petrol 3:97) gave lactone (±)-21 (94:6 dr) as a white solid (55.6 mg, 84%); mp 88-90 °C; ν max (KBr) 3083, 3030 (C-H), 1773 (C=O), 1700, 1519; δ H (300 MHz, CDCl 3) 2.23 (3H, s, C₆H₃), 3.87 (1H, d, J 8.6, C(3)H), 3.92-3.95 (1H, m, C(4)H), 6.04 (1H, d, J 3.7, C(5)H), 6.90-6.92 (2H, m, ArH), 6.95-6.98 (2H, m, ArH), 7.02-7.04 (2H, m, ArH), 7.15-7.23 (3H, m, ArH); δC (100 MHz, CDCl 3) 21.1 (C₆H₃), 44.7 (C(4)), 52.4 (C(3)), 110.7 (q, J 3.5, C(5)), 118.5 (q, J 270, CF₃), 127.4 (ArC), 128.0 (ArC), 128.0 (ArC), 129.2 (ArC), 129.7 (ArC), 132.0 (4ry ArC), 138.0 (4ry ArC), 138.9 (4ry ArC), 140.8 (q, J 38.0, C(6)), 166.0 (C(2)); δF (282 MHz, CDCl 3) -72.6 (CF₃); m/z (NSI+) 350 ([M+NH₄]+, 100%); HRMS (NSI+) C₁₉H₁₉F₃NO₂⁺ ([M+NH₄]⁺) requires 350.1362; found 350.1366 (+1.0 ppm).

(3R,4R)-4-phenyl-3-(p-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, p-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 µL, 0.30 mmol) and pivaloyl chloride (37.0 µL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 µL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-21 (93:7 dr). Chromatographic purification (eluent Et₂O:petrol 3:97) gave lactone (3R,4R)-21 (98:2 dr) as a white solid (49.8 mg, 75%); [α]D²⁰ -219.0 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tₚ(3S,4S): 14.0 min, tₚ(3R,4R): 16.4 min, 98% ee.

3-(naphthalen-2-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 2-naphthylacetic acid (37.2 mg, 0.20 mmol), DIPEA (51.9 µL, 0.30 mmol) and pivaloyl chloride (37.0 µL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg,
0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-22 (86:14 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (±)-22 (95:5 dr) as a colourless oil (55.9 mg, 76%); ν max (thin film) 3088, 2962 (C-H), 1791 (C=O), 1701, 1602, 1509; δ H (400 MHz, CDCl₃) 4.05 (2H, s, C(3)H and C(4)H), 6.07 (1H, s, C(5)H), 6.96-6.98 (2H, m, ArH), 7.13-7.19 (4H, m, ArH), 7.36-7.40 (3H, m, ArH), 7.61-7.64 (1H, m, ArH), 7.71-7.74 (2H, m, ArH); δ F (282 MHz, CDCl₃) -72.6 (C₂F₃); m/z (NSI +) 386 ([M+NH₄]+, 56%); HRMS (NSI +) C₂₂H₁₉F₃NO₂+ ([M+NH₄]+) requires 386.1362; found 386.1364 (+0.4 ppm).

(3R,4R)-3-(naphthalen-2-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 2-naphthylacetic acid (37.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-22 (94:6 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-22 (98:2 dr) as a colourless oil (64.5 mg, 88%); [α] D 20 -289.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralcel OD-H (20% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R): 18.0 min, tR(3S,4S): 27.6 min, 97% ee.

4-phenyl-3-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 2-(thiophen-2-yl)acetic acid (28.4 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at -78 °C gave crude lactone (±)-23 (82:18 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (±)-23 (95:5 dr) as a white solid (45.7 mg, 71%); mp 51-53 °C; ν max (KBr) 3084, 2921 (C-H), 1775 (C=O), 1702; δ H (400 MHz, CDCl₃) 3.98-4.01 (1H, m, C(4)H), 4.24 (1H, d, J 6.8, C(3)H), 6.09 (1H, d, J 4.5, C(5)H), 6.78 (1H, dt, J 3.5, 0.9, ArH), 6.85 (1H, dd, J 5.1, 3.6, ArH), 7.03-7.06 (2H, m, ArH), 7.18-7.29 (4H, m, ArH); δ C (100 MHz, CDCl₃) 45.3 (C(4)), 48.1 (C(3)), 109.9 (q, J 3.5, C(5)), 118.4 (q, J 270, CF₃), 125.9 (ArC), 127.0 (ArC), 127.1 (ArC), 127.2 (ArC), 128.4 (ArC), 129.4 (ArC), 136.5 (4ry ArC), 138.2 (4ry ArC), 141.1 (q, J 38.2, C(6)), 164.4 (C(2)); δ F (282 MHz, CDCl₃) -72.6 (C₂F₃); m/z (NSI +) 386 ([M+NH₄]+, 56%); HRMS (NSI +) C₂₂H₁₉F₃NO₂+ ([M+NH₄]+) requires 386.1362; found 386.1364 (+0.4 ppm).
72.7 (C<sub>F3</sub>); m/z (NSI<sup>+</sup>) 342 ([M+NH<sub>4</sub>]<sup>+</sup>, 100%); HRMS (NSI<sup>+</sup>) C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>NO<sub>2</sub>S<sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>) requires 342.0770; found 342.0775 (+1.4 ppm).

**(3S,4R)-4-phenyl-3-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one**

Following general procedure C, 2-(thiophen-2-yl)acetic acid (28.4 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-23 (87:13 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 5:95) gave lactone (3R,4R)-23 (96:4 dr) as a white solid (48.4 mg, 75%); [α]<sub>D</sub> <sup>20</sup> -248.0 (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min<sup>-1</sup>, 211 nm) t<sub>R</sub>(3S,4R): 5.8 min, t<sub>R</sub>(3R,4S): 8.4 min, 89% ee.

**(4R,4R)-4-phenyl-6-(trifluoromethyl)-3-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-pyran-2-one**

Following general procedure B, 2-(4-(trifluoromethyl)phenyl)acetic acid (40.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at rt gave crude lactone (±)-24 (81:19 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 5:95) gave lactone (±)-24 (>99:1 dr) as a white solid (35.0 mg, 45%); m.p 80-82 °C; ν<sub>max</sub> (KBr) 3030, 2926 (C-H), 1780 (C=O), 1621; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.94-3.96 (2H, m, C(3)H and C(4)H), 6.09 (1H, d, J 2.3, C(5)H), 6.91-6.93 (2H, m, ArH), 7.10 (2H, d, J 8.1, ArH), 7.19-7.22 (3H, m, ArH), 7.48 (2H, d, J 8.1, ArH); δ<sub>C</sub> (100 MHz, CDCl<sub>3</sub>) 44.7 (C(4)), 52.6 (C(3)), 111.1 (q, J 3.3, C(5)), 118.4 (q, J 270, CF<sub>3</sub>), 123.8 (q, J 271, CF<sub>3</sub>), 125.8 (q, J 3.6, ArC), 127.4 (ArC), 128.3 (ArC), 129.0 (ArC), 129.3 (ArC), 130.4 (q, J 32.4, 4ry ArC), 138.1 (4ry ArC), 138.8 (4ry ArC), 141.0 (q, J 38.2, C(6)), 165.2 (C(2)); δ<sub>F</sub> (376 MHz, CDCl<sub>3</sub>) -63.2 (C<sub>6</sub>H<sub>4</sub>C<sub>F</sub><sub>3</sub>), -72.6 (C<sub>F</sub><sub>3</sub>); m/z (NSI<sup>+</sup>) 404 ([M+NH<sub>4</sub>]<sup>+</sup>, 82%); HRMS (NSI<sup>+</sup>) C<sub>19</sub>H<sub>16</sub>F<sub>6</sub>NO<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub>]<sup>+</sup>) requires 404.1080; found 404.1080 (+0.1 ppm).
Following general procedure C, 2-(4-(trifluoromethyl)phenyl) acetic acid (40.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 72 h at -30 °C gave crude lactone (3R,4R)-24 (86:14 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-24 (99:1 dr) as a white solid (46.2 mg, 60%); [α]D 20 -153.6 (c 0.125, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3S,4S): 16.2 min, tR(3R,4R): 18.8 min, 64% ee.

3-(naphthalen-1-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 1-naphthylacetic acid (37.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-25 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 4:96) gave lactone (±)-25 (91:9 dr) as a colourless oil (66.2 mg, 90%); vmax (thin film) 3087, 2962 (C-H), 1780 (C=O), 1702, 1600, 1512; δH (300 MHz, CDCl₃) 4.09-4.13 (1H, m, C(4)H), 4.64 (1H, d, J 6.7, C(3)H), 6.03 (1H, d, J 4.5, C(5)H), 6.98-7.01 (2H, m, ArH), 7.12 (1H, d, J 6.8, ArH), 7.16-7.23 (3H, m, ArH), 7.29 (1H, t, J 7.7, ArH), 7.40-7.49 (2H, m, ArH), 7.72-7.82 (3H, m, ArH); δC (75 MHz, CDCl₃) 44.3 (C(4)), 49.6 (C(3)), 110.4 (q, J 3.5, C(5)), 118.6 (q, J 270, CF₃), 122.8 (ArC), 125.3 (ArC), 125.8 (ArC), 126.0 (ArC), 126.9 (ArC), 127.2 (ArC), 128.2 (ArC), 129.2 (ArC), 129.4 (ArC), 129.6 (ArC), 130.5 (4ry ArC), 131.5 (4ry ArC), 134.3 (4ry ArC), 139.2 (4ry ArC), 140.8 (q, J 38.0, C(6)), 165.6 (C(2)); δF (282 MHz, CDCl₃) -72.6 (CF₃); m/z (NSI⁺) 369 ([M+H⁺], 100%); HRMS (NSI⁺) C₂₂H₁₉F₃O₂⁺ ([M+H⁺]) requires 369.1097; found 369.1087 (-2.7 ppm).

(3R,4R)-3-(naphthalen-1-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
Following general procedure C, 1-naphthylacetic acid (37.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-25 (67:33 dr). Chromatographic purification (eluent Et2O:petrol 4:96) gave lactone (3R,4R)-25 (71:29 dr) as a colourless oil (65.0 mg, 88%); [α] D 20 -303.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3S,4S): 18.5 min, tR(3R,4R): 26.0 min, 97% ee.

3-(1-methyl-1H-indol-3-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, 2-(1-methyl-1H-indol-3-yl)acetic acid (37.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-26 and (±)-27 (68:32 dr). Major (anti) Diastereoisomer: Chromatographic purification (eluent Et2O:petrol 10:90) gave lactone (±)-26 (96:4 dr) as a white solid (50.1 mg, 68%); mp 126-128 °C; ν max (KBr) 3033, 2939 (C-H), 1780 (C=O), 1699, 1616, 1544; δ H (400 MHz, CDCl3) 3.66 (3H, s, C3H3), 4.06-4.08 (1H, m, C(4)H), 4.26 (1H, d, J 4.8, C(3)H), 6.05 (1H, d, J 5.1, C(5)H), 6.78 (1H, s, ArH), 7.07-7.12 (3H, m, ArH), 7.18-7.28 (5H, m, ArH), 7.52 (1H, d, J 7.9, ArH); δ C (100 MHz, CDCl3) 32.9 (CH3), 44.0 (C(4)), 44.7 (C(3)), 108.4 (4ry ArC), 109.6 (q, J 3.4, C(5)), 109.8 (ArC), 118.6 (ArC), 118.6 (q, J 270, CF3), 119.9 (ArC), 122.4 (ArC), 126.1 (4ry ArC), 126.6 (ArC), 127.1 (ArC), 128.1 (ArC), 129.4 (ArC), 137.0 (4ry ArC), 139.1 (4ry ArC), 141.1 (q, J 37.7, C(6)), 156.2 (C(2)); δ F (376 MHz, CDCl3) -72.6 (CF3); m/z (NSI⁺) 389 ([M+NH4]⁺, 100%); HRMS (NSI⁺) C21H19F3N2O2⁺ ([M+NH4]⁺) requires 389.1471; found 389.1474 (+0.7 ppm).

Minor (syn) Diastereoisomer: Chromatographic purification (eluent Et2O:petrol 10:90) gave lactone (±)-27 (>99:1 dr) as a yellow oil (15.0 mg, 20%); ν max (KBr) 3032, 2934 (C-H), 1791 (C=O), 1700, 1616, 1550; δ H (400 MHz, CDCl3) 3.55 (3H, s, C3H3), 4.00 (1H, td, J 6.4, 1.4, C(4)H), 4.64 (1H, d, J 6.7, C(3)H), 6.23 (1H, d, J
6.0, C(5)H, 6.40 (1H, s, ArH), 6.86-6.71 (2H, m, ArH); δC (100 MHz, CDCl3) 32.8 (CH3), 42.7 (C(4)), 42.9 (C(3)), 104.8 (4ry ArC), 109.5 (ArC), 111.5 (q, J 3.4, C(5)), 117.7 (ArC), 118.7 (q, J 270, CF3), 119.4 (ArC), 121.8 (ArC), 127.2 (4ry ArC), 128.2 (ArC), 128.6 (ArC), 128.8 (ArC), 135.6 (4ry ArC), 136.2 (4ry ArC), 141.8 (q, J 37.7, C(6)), 166.0 (C(2)); δF (376 MHz, CDCl3) -72.4 (CF3); m/z (NSI+) 372 ([M+H]+, 18%); HRMS (NSI+) C21H17F3NO2+ ([M+H]+) requires 372.1206; found 372.1211 (+1.4 ppm).

(3R,4R)-3-(1-methyl-1H-indol-3-yl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 2-(1-methyl-1H-indol-3-yl)acetic acid (37.8 mg, 0.20 mmol), DIPEA (51.9 µL, 0.30 mmol) and pivaloyl chloride (37.0 µL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-5 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 µL, 0.5 mmol) for 16 h at -30 °C gave crude lactone (3R,4R)-26 and 27 (74:26 dr).

Major (anti) Diastereoisomer: Chromatographic purification (eluent Et2O:petrol 10:90) gave lactone (3R,4R)-26 (98:2 dr) as a yellow solid (50.2 mg, 68%); [α]D20 -164.0 (c 0.225, CH2Cl2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R): 21.1 min, tR(3S,4S): 34.9 min, 96% ee.

Minor (syn) Diastereoisomer: Chromatographic purification (eluent Et2O:petrol 10:90) gave lactone 27 (>99:1 dr) as a yellow oil (19.1 mg, 26%); [α]D20 +47.5 (c 0.2, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR: 16.0 min, tR: 20.0 min, 28% ee.

4-(4-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 µL, 0.30 mmol) and pivaloyl chloride (37.0 µL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 73 (55.8 mg, 0.20 mmol) and DIPEA (87 µL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-28 (86:14 dr). Chromatographic purification (eluent Et2O:petrol 4.5:95.5) gave lactone (±)-28 (>99:1 dr) as a white solid (46.4 mg, 58%); mp 58-60 °C; νmax (KBr) 3088, 3033, 2926 (C-H), 1780 (C=O), 1703; δH (400 MHz, CDCl3) 3.82 (1H, d, J 9.6,
(3R,4R)-4-(4-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 73 (55.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-28 (88:12 dr). Chromatographic purification (eluent Et2O:petrol 4.5:95.5) gave lactone (3R,4R)-28 (99:1 dr) as a white solid (54.0 mg, 68%); [α]D20 -252.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min-1, 211 nm) tR(3R,4R): 26.9 min, tR(3S,4S): 30.8 min, 98% ee.

4-(3-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 74 (55.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-29 (88:12 dr). Chromatographic purification (eluent Et2O:petrol 4.5:95.5) gave lactone (±)-29 (>99:1 dr) as a white solid (57.6 mg, 73%); mp 70-72 °C; νmax (KBr) 3083, 2960 (C-H), 1774 (C=O), 1702, 1592, 1570; δH (300 MHz, CDCl3) 3.85 (1H, d, J 9.3, C(3)H), 3.96 (1H, m, C(4)H), 6.02 (1H, dd, J 3.2, C(5)H), 6.84 (1H, dd, J 6.6, J 1.2, ArH), 6.90-7.12 (4H, m, ArH), 7.21-7.33 (4H, m, ArH); δC (100 MHz, CDCl3) 44.4 (C(4)), 52.6 (C(3)), 109.9 (q, J 3.5, C(5)), 118.4 (q, J 270, CF3), 123.1 (4ry ArC), 126.1 (ArC), 128.3 (ArC), 128.4 (ArC), 129.1 (ArC), 130.5 (ArC), 130.7 (ArC), 131.3 (ArC), 134.5 (4ry ArC), 141.0 (4ry ArC), 141.3 (q, J 38.2, C(6)), 165.3 (C(2)); δF (282 MHz, CDCl3) -72.7 (CF3); m/z (NSI+1) 414 ([M+NH4]+, 68%); HRMS (NSI+) C19H1679BrF3NO2+ ([M+NH4]+) requires 414.0311; found 414.0313 (+0.5 ppm).
(3R,4R)-4-(3-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 74 (55.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-29 (80:20 dr). Chromatographic purification (eluent Et2O:petrol 4.5:95.5) gave lactone (3R,4R)-29 (99:1 dr) as a white solid (51.0 mg, 64%); [α] D 20 -227.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min -1, 211 nm) tR(3R,4R): 24.3 min, tR(3S,4S): 47.5 min, 97% ee.

4-(3-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 75 (55.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-30 (85:15 dr). Chromatographic purification (eluent Et2O:petrol 4:96) gave lactone (±)-30 (96:4 dr) as a white solid (64.0 mg, 81%); mp 78-80 °C; νmax (KBr) 3083, 3037, 2926 (C-H), 1778 (C=O), 1709, 1567; δH (400 MHz, CDCl3) 4.12 (1H, d, J 5.6, C(3)H), 4.49-4.52 (1H, m, C(4)H), 5.99 (1H, d, J 5.1, C(5)H), 7.07-7.11 (2H, m, ArH), 7.20-7.29 (6H, m, ArH), 7.51 (1H, dd, J 8.1, 1.1, ArH); δC (125 MHz, CDCl3) 43.6 (C(4)), 50.9 (C(3)), 109.0 (q, J 3.4, C(5)), 118.4 (q, J 270, CF3), 124.1 (4ry ArC), 127.7 (ArC), 128.3 (ArC), 128.4 (ArC), 128.5 (ArC), 129.1 (ArC), 129.9 (ArC), 133.9 (ArC), 134.8 (4ry ArC), 136.9 (4ry ArC), 141.8 (q, J 38.0, C(6)), 165.2 (C(2)); δF (376 MHz, CDCl3) -72.6 (CF3); m/z (NSI+) 414 ([M+NH4]+, 85%); HRMS (NSI+) C19H1679BrF3NO2+ ([M+NH4]+) requires 414.0311; found 414.0314 (+0.7 ppm).

(3R,4R)-4-(2-bromophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 75 (55.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-30 (87:13 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 3:97) gave lactone (3R,4R)-30 (95:5 dr) as a white solid (68.0 mg, 86%); [α]<sub>D</sub><sup>20</sup> -214.0 (c 0.25, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralcel OD-H (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm) t<sub>R</sub>(3R,4R): 8.8 min, t<sub>R</sub>(3S,4S): 18.5 min, 97% ee.

4-(4-fluorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 76 (43.6 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-31 (85:15 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 5:95) gave lactone (±)-31 (99:1 dr) as a white solid (52.0 mg, 73%); mp 80-82 °C; ν<sub>max</sub> (KBr) 3086, 3037, 2926 (C-H), 1774 (C=O), 1703, 1605, 1512; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.82 (1H, d, J 9.5, C(3)H), 3.93-3.97 (1H, m, C(4)H), 6.04 (1H, dd, J 3.5, 0.5, C(5)H), 6.86-6.93 (4H, m, ArH), 6.97-7.00 (2H, m, ArH), 7.20-7.25 (3H, m, ArH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 44.1 (C(4)), 53.0 (C(3)), 110.6 (q, J 3.3, C(5)), 116.1 (d, J 21.4, ArC), 118.4 (q, J 270, CF<sub>3</sub>), 128.2 (ArC), 128.3 (ArC), 129.0 (ArC), 129.1 (d, J 8.3, ArC), 134.5 (d, J 3.0, 4ry ArC), 134.7 (4ry ArC), 141.1 (q, J 38.0, C(6)), 162.3 (d, J 246, 4ry ArC), 165.6 (C(2)); δ<sub>F</sub> (470 MHz, CDCl<sub>3</sub>) -72.2 (CF<sub>3</sub>), -113.7 (ArF); m/z (NSI<sup>+</sup>) 354 ([M+NH<sub>4</sub><sup>+</sup>], 100%); HRMS (NSI<sup>+</sup>) C<sub>18</sub>H<sub>16</sub>F<sub>4</sub>NO<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub><sup>+</sup>]) requires 354.1112; found 354.1115 (+0.9 ppm).

(3R,4R)-4-(4-fluorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 76 (43.6 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-31 (85:15 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 5:95) gave lactone (±)-31 (99:1 dr) as a white solid (52.0 mg, 73%); mp 80-82 °C; ν<sub>max</sub> (KBr) 3086, 3037, 2926 (C-H), 1774 (C=O), 1703, 1605, 1512; δ<sub>H</sub> (400 MHz, CDCl<sub>3</sub>) 3.82 (1H, d, J 9.5, C(3)H), 3.93-3.97 (1H, m, C(4)H), 6.04 (1H, dd, J 3.5, 0.5, C(5)H), 6.86-6.93 (4H, m, ArH), 6.97-7.00 (2H, m, ArH), 7.20-7.25 (3H, m, ArH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 44.1 (C(4)), 53.0 (C(3)), 110.6 (q, J 3.3, C(5)), 116.1 (d, J 21.4, ArC), 118.4 (q, J 270, CF<sub>3</sub>), 128.2 (ArC), 128.3 (ArC), 129.0 (ArC), 129.1 (d, J 8.3, ArC), 134.5 (d, J 3.0, 4ry ArC), 134.7 (4ry ArC), 141.1 (q, J 38.0, C(6)), 162.3 (d, J 246, 4ry ArC), 165.6 (C(2)); δ<sub>F</sub> (470 MHz, CDCl<sub>3</sub>) -72.2 (CF<sub>3</sub>), -113.7 (ArF); m/z (NSI<sup>+</sup>) 354 ([M+NH<sub>4</sub><sup>+</sup>], 100%); HRMS (NSI<sup>+</sup>) C<sub>18</sub>H<sub>16</sub>F<sub>4</sub>NO<sub>2</sub><sup>+</sup> ([M+NH<sub>4</sub><sup>+</sup>]) requires 354.1112; found 354.1115 (+0.9 ppm).
Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 76 (43.6 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-31 (86:14 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3R,4R)-31 (>99:1 dr) as a white solid (57.2 mg, 85%); [α]D20 -302.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tR(3R,4R): 10.9 min, tR(3S,4S): 22.3 min, 98% ee.

4-(4-chlorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 77 (46.9 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-32 (87:12 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (±)-32 (>99:1 dr) as a white solid (51.2 mg, 73%); mp 64-66 °C; νmax (KBr) 3086, 3034 (C-H), 1774 (C=O), 1702, 1597; δ H (400 MHz, CDCl3) 3.82 (1H, d, J 9.6, C(3)H), 3.93-3.96 (1H, m, C(4)H), 6.02 (1H, d, J 3.3, C(5)H), 6.86-6.88 (2H, m, ArH), 6.97-7.00 (2H, m, ArH), 7.15-7.26 (5H, m, ArH); δC (100 MHz, CDCl3) 44.2 (C(4)), 52.7 (C(3)), 110.3 (q, J 3.3, C(5)), 118.4 (q, J 270, CF3), 128.3 (ArC), 128.3 (ArC), 128.8 (ArC), 129.0 (ArC), 129.3 (ArC), 134.0 (4ry ArC), 134.6 (4ry ArC), 137.2 (4ry ArC), 141.2 (q, J 38.2, C(6)), 165.5 (C(2)); δF (376 MHz, CDCl3) -72.7 (C F3); m/z (NSI⁺) 370 ([M+NH4]+, 95%); HRMS (NSI⁺) C18H16Cl3F3NO2⁺ ([M+NH4]+) requires 370.0816; found 370.0818 (+0.5 ppm).

(3R,4R)-4-(4-chlorophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 77 (46.9 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-32 (88:12 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3R,4R)-32 (>99:1 dr) as a white solid (52.4 mg, 74%); [α]D20 0 -353.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tR(3R,4R): 10.2 min, tR(3S,4S): 23.3 min, >99% ee.
3-phenyl-4-(p-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 78 (42.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-33 (85:15 dr). Chromatographic purification (eluent Et2O:petrol 4:96) gave lactone (±)-33 (93:7 dr) as a white solid (43.0 mg, 65%); mp 60-62 °C; νmax (KBr) 3098, 3033, 2940 (C-H), 1778 (C=O), 1701, 1635, 1516; δH (400 MHz, CDCl3) 2.22 (3H, s, CH3), 3.86-3.93 (2H, m, C(3)H and C(4)H), 6.03 (1H, d, J 3.3, C(5)H), 6.84 (2H, d, J 8.1, ArH), 6.99-7.04 (4H, m, ArH); δC (125 MHz, CDCl3) 21.1 (CH3), 44.4 (C(4)), 52.8 (C(3)), 110.9 (q, J 3.3, C(5)), 118.5 (q, J 270, CF3), 127.2 (ArC), 128.2 (ArC), 128.9 (ArC), 129.8 (ArC), 135.2 (4ry ArC), 135.7 (4ry ArC), 137.9 (4ry ArC), 140.7 (q, J 38.0, C(6)), 165.9 (C(2)); δF (376 MHz, CDCl3) -72.6 (CF3); m/z (NSI+) 350 ([M+NH4]+, 95%); HRMS (NSI+) C19H19F3NO2+ ([M+NH4]+) requires 350.1362; found 350.1368 (+1.6 ppm).

(3R,4R)-3-phenyl-4-(p-tolyl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 78 (42.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-33 (95:5 dr). Chromatographic purification (eluent Et2O:petrol 3:97) gave lactone (3R,4R)-33 (98:2 dr) as a white solid (61.8 mg, 93%); [α]D20 -256.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tR(3R,4R): 7.2 min, tR(3S,4S): 11.5 min, 97% ee.

4-(4-methoxyphenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

(±)-34

S33
Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 \( \mu \)L, 0.30 mmol) and pivaloyl chloride (37.0 \( \mu \)L, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 79 (46.0 mg, 0.20 mmol) and DIPEA (87 \( \mu \)L, 0.5 mmol) for 1 h at rt gave crude lactone (±)-34 (85:15 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave lactone (±)-34 (87:13 dr) as a colourless oil (57.8 mg, 83%); \( \nu_{\text{max}} \) (KBr) 3090, 3033, 2938 (C-H), 1780 (C=O), 1700, 1612, 1585, 1514; \( \delta \) H (400 MHz, CDCl_3) 3.68 (3H, s, OCH_3), 3.85 (1H, d, J 8.8, C(3)H), 3.88-3.91 (1H, m, C(4)H), 6.03 (1H, d, J 3.4, C(5)H), 6.71-6.73 (2H, m, ArH), 6.85-6.87 (2H, m, ArH), 7.00-7.02 (2H, m, ArH), 7.18-7.24 (3H, m, ArH); \( \delta \)C (100 MHz, CDCl_3) 44.0 (C(4)), 53.0 (C(3)), 55.3 (OCH_3), 111.1 (q, J 3.4, C(5)), 114.5 (ArC), 118.5 (q, J 270, ArC), 128.1 (4ry ArC), 128.3 (ArC), 128.5 (ArC), 128.9 (ArC), 130.7 (4ry ArC), 135.2 (4ry ArC), 140.7 (q, J 38.0, C(6)), 159.2 (4ry ArC), 165.9 (C(2)); \( \delta \) F (376 MHz, CDCl_3) -72.6 (CF_3); m/z (NSI+) 366 ([M+NH_4]^+, 100%); HRMS (NSI+) C_{19}H_{19}F_3NO_3 + ([M+NH_4]^+) requires 366.1312; found 366.1316 (+1.2 ppm).

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(3R,4R)-4-(4-methoxyphenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
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Following general procedure C phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 \( \mu \)L, 0.30 mmol) and pivaloyl chloride (37.0 \( \mu \)L, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 79 (46.0 mg, 0.20 mmol) and DIPEA (87 \( \mu \)L, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-34 (94:6 dr). Chromatographic purification (eluent Et_2O:petrol 7.5:92.5) gave lactone (3R,4R)-34 (96:4 dr) as a white solid (65.0 mg, 93%); \([\alpha]_D^{20} -345.0 \ (c 0.1, CH_2Cl_2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min^{-1}, 211 nm) t_R(3R,4R): 19.4 min, t_R(3S,4S): 24.4 min, 98% ee.

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4-(4-nitrophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one
\]

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 \( \mu \)L, 0.30 mmol) and pivaloyl chloride (37.0 \( \mu \)L, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 80 (49.0 mg, 0.20 mmol) and DIPEA (87 \( \mu \)L, 0.5 mmol) for 10 min at -78 °C gave crude lactone (±)-35 (84:16 dr). Chromatographic purification (eluent Et_2O:petrol 10:90) gave lactone (±)-35 (>99:1 dr) as a white solid (41.0 mg, 56%); mp 102-104 °C; \( \nu_{\text{max}} \) (KBr) 3089, 2925, 2854 (C-H), 1778 (C=O), 1707, 1608, 1518; \( \delta \)H (400 MHz, CDCl_3) 3.84 (1H, d, J 10.4, C(3)H), 4.09-4.14 (1H, m, C(4)H), 6.05 (1H, d, J 3.0, C(5)H), 6.96-6.98 (2H, m,
ArH), 7.10-7.13 (2H, m, ArH), 7.21-7.25 (3H, m, ArH), 8.03-8.07 (2H, m, ArH); δC (100 MHz, CDCl 3) 44.6 (C(4)), 52.4 (C(3)), 109.4 (q, J 3.4, C(5)), 118.3 (q, J 270, CF₃), 124.3 (ArC), 128.4 (ArC), 128.6 (ArC), 129.2 (ArC), 133.9 (4ry ArC), 141.9 (q, J 38.3, C(6)), 145.9 (4ry ArC), 147.6 (4ry ArC); δF (376 MHz, CDCl 3) -72.7 (CF₃); m/z (NSI⁺) 386 ([M+NH₄⁺], 57%); HRMS (NSI⁺) C22H19F3NO2⁺ ([M+NH₄⁺]) requires 386.1362; found 386.1366 (+0.9 ppm).

(3R,4R)-4-(4-nitrophenyl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 80 (49.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-35 (73:27 dr). Chromatographic purification (eluent Et₂O:petrol 25:75) gave lactone (3R,4R)-35 (>99:1 dr) as a white solid (47.4 mg, 65%); [α]D²₀ -216.2 (c 0.5, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (20% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R): 15.0 min, tR(3S,4S): 29.9 min, 86% ee.

4-(naphthalen-1-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 81 (50.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-36 (89:11 dr). Chromatographic purification (eluent Et₂O:petrol 4:96) gave lactone (±)-36 (97:3 dr) as a white solid (63.3 mg, 88%); mp 118-120 °C; νmax (KBr) 3094, 3038, 2875 (C-H), 1774 (C=O), 1708, 1596, 1513; δH (400 MHz, CDCl 3) 4.20 (1H, d, J 5.3, C(3)H), 4.75-4.77 (1H, m, C(4)H), 6.15 (1H, d, J 5.0, C(5)H), 7.16-7.28 (6H, m, ArH), 7.35 (1H, t, J 7.7, ArH), 7.42-7.48 (2H, m, ArH), 7.73 (1H, d, J 8.2, ArH), 7.77-7.83 (2H, m, ArH); δC (100 MHz, CDCl 3) 40.0 (C(4)), 51.5 (C(3)), 109.8 (q, J 3.3, C(5)), 118.5 (q, J 270, CF₃), 122.1 (ArC), 124.7 (ArC), 126.1 (ArC), 127.0 (ArC), 127.6 (ArC), 128.4 (ArC), 129.0 (ArC), 129.3 (ArC), 129.6 (ArC), 130.4 (4ry ArC), 133.7 (4ry ArC), 134.4 (4ry ArC), 135.6 (4ry ArC), 141.5 (q, J 37.9, C(6)), 165.4 (C(2)); δF (376 MHz, CDCl 3) -72.5 (CF₃); m/z (NSI⁺) 386 ([M+NH₄⁺], 57%); HRMS (NSI⁺) C22H19F3NO2⁺ ([M+NH₄⁺]) requires 386.1362; found 386.1366 (+0.9 ppm).
(3R,4R)-4-(naphthalen-1-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 81 (50.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-36 (94:6 dr). Chromatographic purification (eluent Et2O:petrol 4:96) gave lactone (3R,4R)-36 (99:1 dr) as a white solid (66.7 mg, 91%); [α]D20 -284.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min-1, 211 nm) tR(3R,4R): 8.5 min, tR(3S,4S): 10.3 min, 98% ee.

4-(naphthalen-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 82 (50.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-37 (88:12 dr). Chromatographic purification (eluent Et2O:petrol 4:96) gave lactone (±)-37 (97:3 dr) as a white solid (61.0 mg, 83%); mp 60-62 °C; νmax (KBr) 3062, 2927 (C-H), 1771 (C=O), 1700, 1634, 1601, 1509; δH (300 MHz, CDCl3) 4.00 (1H, d, J 8.9, C(3)H), 4.08-4.14 (1H, m, C(4)H), 6.12 (1H, d, J 3.3, C(5)H), 7.01-7.07 (3H, m, ArH), 7.17-7.22 (3H, m, ArH), 7.37-7.43 (3H, m, ArH), 7.64-7.73 (3H, m, ArH); δC (125 MHz, CDCl3) 44.9 (C(4)), 52.6 (C(3)), 110.7 (q, J 3.4, C(5)), 118.5 (q, J 270, CF3), 124.9 (ArC), 126.5 (ArC), 126.5 (ArC), 126.7 (ArC), 127.7 (ArC), 127.8 (ArC), 128.2 (ArC), 128.3 (ArC), 129.0 (ArC), 129.2 (ArC), 132.8 (4r ArC), 133.3 (4r ArC), 135.0 (4r ArC), 136.0 (4r ArC), 140.8 (q, J 37.9, C(6)), 165.8 (C(2)); δF (282 MHz, CDCl3) -72.5 (CF3); m/z (NSI+)+ 386 ([M+NH4]+, 75%); HRMS (NSI+) C22H19F3NO2+[M+NH4]+ requires 386.1362; found 386.1365 (+0.7 ppm).

(3R,4R)-4-(naphthalen-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

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Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 82 (50.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-37 (90:10 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3R,4R)-37 (98:2 dr) as a white solid (59.8 mg, 81%); [α]D 20 -294.4 (c 0.25, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min -1, 211 nm) tR(3R,4R): 11.1 min, tR(3S,4S): 26.8 min, >99% ee.

4-(furan-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 83 (38.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-38 (88:12 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (±)-38 (>99:1 dr) as a white solid (54.0 mg, 88%); mp 61-63 °C; νmax (KBr) 3033, 2940, 2879 (C-H), 1780 (C=O), 1703, 1635, 1510; δ H (300 MHz, CDCl3) 4.04-4.09 (1H, m, C(4)H), 4.16 (1H, d, J 7.1, C(3)H), 5.94 (1H, d, J 3.3, C(5)H), 6.03 (1H, d, J 4.4, ArH), 6.18 (1H, dd, J 3.3, 1.9, ArH), 7.09-7.12 (2H, m, ArH), 7.24-7.31 (4H, m, ArH); δc (100 MHz, CDCl3) 38.3 (C(4)), 49.5 (C(3)), 107.6 (ArC), 107.8 (q, J 3.5, C(5)), 110.5 (ArC), 118.4 (q, J 270, CF3), 127.8 (ArC), 128.4 (ArC), 129.1 (ArC), 134.7 (4r ArC), 141.2 (q, J 38.1, C(6)), 143.0 (ArC), 150.4 (4r ArC), 165.4 (C(2)); δF (282 MHz, CDCl3) -72.9 (CF3); m/z (NIS+) 326 ([M+NH4]+, 100%); HRMS (NIS+) C16H15F3NO3+ ([M+NH4]+) requires 326.0999; found 326.1003 (+1.4 ppm).

(3R,4R)-4-(furan-2-yl)-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 83 (38.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-38 (89:11 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (±)-38 (>99:1 dr) as a white solid (47.3 mg, 77%); [α]D 20 -267.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min -1, 211 nm) tR(3R,4R): 7.4 min, 98% ee.
3-phenyl-4-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 84 (41.2 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (±)-39 (84:16 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (±)-39 (99:1 dr) as a white solid (50.1 mg, 77%); mp 58-60 °C; ν max (KBr) 3088, 3034, 2923, 2865 (C-H), 1774 (C=O), 1703; δ H (400 MHz, CDCl₃) 4.00 (1H, d, J 8.1, C(3)H), 4.24-4.27 (1H, m, C(4)H), 6.11 (1H, d, J 4.1, C(5)H), 6.65-6.66 (1H, m, ArH), 6.81 (1H, dd, J 5.1, 3.5, ArH), 7.06-7.09 (2H, m, ArH), 7.13 (1H, dd, J 5.1, 1.1, ArH), 7.23-7.29 (3H, m, ArH); δ C (100 MHz, CDCl₃) 39.8 (C(4)), 53.3 (C(3)), 110.2 (q, J 3.5, C(5)), 118.4 (q, J 270, CF₃), 125.4 (ArC), 125.7 (ArC), 127.3 (ArC), 128.1 (ArC), 128.4 (ArC), 129.1 (ArC), 134.7 (4ry ArC), 140.8 (q, J 38.2, C(6)), 141.1 (4ry ArC), 165.3 (C(2)); δ F (376 MHz, CDCl₃) -72.8 (C F₃); m/z (NSI⁺) 342 ([M+NH₄]+, 97%); HRMS (NSI⁺) C₁₆H₁₅F₃NO₂S⁺ ([M+NH₄]+) requires 342.0770; found 342.0775 (+1.4 ppm).

(3R,4R)-3-phenyl-4-(thiophen-2-yl)-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 84 (41.2 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-39 (88:12 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-39 (98:2 dr) as a white solid (55.6 mg, 86%); [α]D 20 -258.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tR(3S,4S): 6.8 min, tR(3R,4R): 9.1 min, 95% ee.

4-pentyl-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 84 (41.2 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-39 (88:12 dr). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-39 (98:2 dr) as a white solid (55.6 mg, 86%); [α]D 20 -258.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (2% IPA:hexane, flow rate 2 mL min⁻¹, 211 nm) tR(3S,4S): 6.8 min, tR(3R,4R): 9.1 min, 95% ee.
Following general procedure B, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 87 (38.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt gave crude lactone (+)-40 (77:23 dr). Chromatographic purification (eluent Et₂O:petrol 2:98) gave lactone (+)-40 (90:10 dr) as a colourless oil (36.0 mg, 58%); ν max (Diamond Cell) 2957, 2932 (C-H), 1786 (C=O), 1713; Data for major diastereoisomer: δ H (500 MHz, CDCl 3) 0.89 (3H, J 7.0, C H₃), 1.21-1.50 (8H, m, 4C H₂), 2.85-2.87 (1H, m, C(4)H), 3.72 (1H, d, J 8.6, C(3)H), 6.03 (1H, d, J 3.8, C(5)H), 7.21-7.22 (2H, m, ArH), 7.35-7.43 (3H, m, ArH); Selected data for minor diastereoisomer δ H (500 MHz, CDCl 3) 4.08 (1H, d, J 6.5, C(3)H), 6.12 (1H, d, J 5.0, C(5)H); Data for major diastereoisomer: δ C (100 MHz, CDCl 3) 13.9 (C H₃), 22.4 (CH₂), 25.6 (CH₂), 31.4 (CH₂), 32.6 (CH₂), 37.6 (C(4)), 50.1 (C(3)), 111.2 (q, J 3.3, C(5)), 118.5 (q, J 270, CF₃), 128.1 (ArC), 128.2 (C(3)-ArC(4)), 129.1 (ArC), 135.4 (4ry C(3)-ArC(1)), 140.1 (q, J 37.9, C(6)), 166.9 (C(2)); Selected data for minor diastereoisomer: δ C (100 MHz, CDCl 3) 26.4 (CH₂), 29.5 (CH₂), 31.6 (CH₂), 36.9 (C(4)), 48.9 (C(3)), 112.4 (q, J 3.3, C(5)), 128.7 (ArC), 129.4 (ArC), 166.4 (C(2)); m/z (APCI⁺) 313 ([M+H]⁺, 100%); HRMS (APCI⁺) C₁₇H₂₀F₃O₂⁺ ([M+H]⁺) requires 313.1410; found 313.1408 (-0.6 ppm).

(3R,4R)-4-pentyl-3-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 87 (38.8 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-40 (78:22 dr). Chromatographic purification (eluent Et₂O:petrol 2:98) gave lactone (3R,4R)-40 (86:14 dr) as a colourless oil (45.7 mg, 73%); [α] D₂₀ -73.0 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak IB (2% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R): 7.0 min, tR(3S,4S): 7.7 min, 98% ee.

1.7 Product Derivatisations

Methanolation

methyl 6,6,6-trifluoro-5-oxo-3-phenyl-2-(m-tolyl)hexanoate

Following general procedure B, m-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), DHPB 71 (7.60 mg, 0.04 mmol), enone 2 (40.0 mg,
0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at rt followed by addition of MeOH (2 mL) and stirring at rt overnight gave crude ester (±)-41 (80:20 dr). Chromatographic purification (eluents Et₂O:petrol 10:90) gave ester (±)-41 (82:18 dr) as a white solid (62.0 mg, 85%); mp 58-60 °C; νₘₐₓ (KBr) 3031, 2958, 1761 (C=O), 1732 (C=O), 1605; δₜ (300 MHz, CDCl₃) 2.15 (3H, s, C₃H₃), 3.08 (1H, dd, J₁₈.₃, 3.8, C(4)H), 3.29 (1H, dd, J 18.4, 9.4, C(4)H), 3.60 (3H, s, CO₂C₃H₃), 3.76 (1H, d, J 10.3, C(2)H), 3.82-3.90 (1H, m, C(3)H), 6.80-6.84 (3H, m, ArH), 6.93-7.09 (6H, m, ArH); δₖ (100 MHz, CDCl₃) 21.3 (C₃H₃), 40.6 (C(4)), 43.4 (C(3)), 52.3 (CO₂C₃H₃), 56.9 (C(2)), 115.3 (q, J C₉F₃), 125.5 (ArC), 127.1 (ArC), 128.0 (ArC), 128.3 (ArC), 128.4 (ArC), 129.1 (ArC), 136.0 (4raj ArC), 138.1 (4raj ArC), 139.6 (4raj ArC), 173.2 (C(1)), 189.2 (q, J 35.2, C(5)); δₖ (282 MHz, CDCl₃) -80.0 (CF₃); m/z (NSI⁺) 382 ([M+NH₄]+, 50%); HRMS (NSI⁺) C₂₀H₂₅F₃NO₃⁺ ([M+NH₄]⁺) requires 382.1625; found 382.1627 (+0.6 ppm).

(2R,3R)-methyl 6,6,6-trifluoro-5-oxo-3-phenyl-2-(m-tolyl)hexanoate

Following general procedure C, m-tolylacetic acid (30.0 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C, followed by addition of MeOH (2 mL) and stirring at rt overnight gave crude ester (2R,3R)-41 (92:8 dr). Chromatographic purification (eluents Et₂O:petrol 10:90) gave ester (2R,3R)-41 (92:8 dr) as a white solid (52.6 mg, 72%); [α] D₂₀ -130.4 (c 0.25, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (5 % IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tₘ(2S,3S): 4.4 min, tₘ(2R,3R): 5.1 min, 97% ee.

Hydrogenation

4-phenyl-3-(m-tolyl)-6-(trifluoromethyl)tetrahydro-2H-pyran-2-one

To a solution of lactone (±)-20 (100 mg, 0.30 mmol) (90:10 dr) in EtOAc (5 mL) was added 10% Pd/C (31.9 mg, 0.03 mmol). Hydrogen gas (1 balloon) was bubbled through the solution and the reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through Celite and washed several times with CH₂Cl₂. Concentration in vacuo gave crude lactones (±)-42 and (±)-43 (47:53 dr). Chromatographic purification (eluents Et₂O:petrol 20:80) gave:
Lactone (±)-42 (87:13 dr) as a colourless oil (47.1 mg, 47%); ν<sub>max</sub> (thin film) 3031, 2923 (C-H), 1756 (C=O), 1606; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.16-2.26 (4H, s, CH<sub>3</sub> and C(5)H), 2.37-2.46 (1H, m, C(5)H), 3.46 (1H, q, J 6.6, C(4)H), 3.93 (1H, d, J 8.0, C(3)H), 4.70-4.76 (1H, m, C(6)H), 6.77-6.80 (2H, m, ArH), 6.91-7.25 (7H, m, ArH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 21.4 (CH<sub>3</sub>), 27.3 (C(5)), 42.5 (C(4)), 52.5 (C(3)), 74.1 (q, J 33.0, (C(6)), 123.3 (q, J 279, CF<sub>3</sub>), 125.5 (ArC), 126.9 (ArC), 128.4 (ArC), 128.6 (ArC), 129.1 (ArC), 129.2 (ArC), 137.0 (4ry ArC), 138.4 (4ry ArC), 140.6 (4ry ArC), 169.6 (C(2)); δ<sub>F</sub> (282 MHz, CDCl<sub>3</sub>) -77.7 (CF<sub>3</sub>); m/z (ES+) 357 ([M+Na]+, 100%); HRMS (ES +) C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>NaO<sub>2</sub> + ([M+Na] +) requires 357.1078; found 357.1076 (-0.6 ppm).

Lactone (±)-43 (>99:1 dr) as a white solid (53.4 mg, 53%); mp 96-98 °C; ν<sub>max</sub> (KBr) 3071, 3031, 2921 (C-H), 1743 (C=O), 1612; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 2.16 (3H, s, CH<sub>3</sub>), 2.23-2.37 (2H, m, C(5)H<sub>2</sub>), 3.26 (1H, td, J 11.8, 3.9, C(4)H), 4.83-4.94 (1H, m, C(6)H), 6.65-6.70 (2H, m, ArH), 6.91-6.94 (3H, m, ArH), 7.01 (1H, t, J 7.5, ArH), 7.10-7.20 (3H, m, ArH); δ<sub>C</sub> (125 MHz, CDCl<sub>3</sub>) 21.4 (CH<sub>3</sub>), 29.4 (C(5)), 45.1 (C(4)), 55.5 (C(3)), 76.0 (q, J 33.8, C(6)), 122.6 (q, J 278, CF<sub>3</sub>), 125.7 (ArC), 127.1 (ArC), 127.6 (ArC), 128.5 (ArC), 128.9 (ArC), 129.3 (ArC), 136.7 (4ry ArC), 138.4 (4ry ArC), 140.0 (4ry ArC), 169.4 (C(2)); δ<sub>F</sub> (282 MHz, CDCl<sub>3</sub>) -79.8 (CF<sub>3</sub>); m/z (ES') 357 ([M+Na]+, 100%); HRMS (ES') C<sub>19</sub>H<sub>17</sub>F<sub>3</sub>NaO<sub>2</sub> + ([M+Na] +) requires 357.1078; found 357.1087 (+2.5 ppm).

(3R,4R,6S)-4-phenyl-3-(m-tolyl)-6-(trifluoromethyl)tetrahydro-2H-pyran-2-one and (3R,4R,6R)-4-phenyl-3-(m-tolyl)-6-(trifluoromethyl)tetrahydro-2H-pyran-2-one

To a solution of lactone (3R,4R)-20 (96:4 dr) (100 mg, 0.30 mmol) in EtOAc (5 mL) was added 10% Pd/C (31.9 mg, 0.03 mmol). Hydrogen gas (1 balloon) was bubbled through the solution and the reaction mixture was stirred at rt for 16 h. The reaction mixture was filtered through Celite and washed several times with CH<sub>2</sub>Cl<sub>2</sub>. Concentration in vacuo gave crude lactones (3R,4R,6S)-42 and (3R,4R,6R)-43 (47:53 dr). Chromatographic purification (eluent Et<sub>2</sub>O:petrol 20:80) gave:

Lactone (3R,4R,6S)-42 (>99:1 dr) as a colourless oil (45.6 mg, 45%); [α]<sub>D</sub><sup>20</sup> -100.0 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min<sup>-1</sup>, 211 nm) t<sub>R</sub>(3R,4R,6S): 17.8 min, t<sub>R</sub>(3S,4S,6R): 36.4 min, 97% ee.
Lactone (3R,4R,6R)-43 (>99:1 dr) as a white solid (51.6 mg, 51%); [α]D20 -252.7 (c 0.15, CH2Cl2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R,6R): 14.6 min, tR(3S,4S,6S): 41.8 min, 98% ee.

(3R,4R,6R)-4-phenyl-3-((m-tolyl)-6-(trifluoromethyl)tetrahydro-2H-pyran-2-one

To a solution of lactone (3R,4R)-20 (96:4 dr) (100 mg, 0.30 mmol) in EtOAc (3 mL) was added 5% Rh(PPh3)3Cl (14.0 mg, 0.015 mmol). The reaction mixture was heated at 80 °C under a 50 bar pressure of Hydrogen gas for 16 h. The reaction mixture was filtered through Celite and washed several times with CH2Cl2. Concentration in vacuo gave crude lactone (3R,4R,6R)-43 (96:4 dr). Chromatographic purification (eluent Et2O:petrol 20:80) gave lactone (3R,4R,6R)-43 (>99:1 dr) as a white solid (96.3 mg, 96%); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(3R,4R,6R): 14.6 min, tR(3S,4S,6S): 41.8 min, 98% ee.

Reductive Ring Opening

6,6,6-trifluoro-3-phenyl-2-((m-tolyl)hexane-1,5-diol

To a solution of lactone (±)-42 (50.0 mg, 0.15 mmol) (87:13 dr) in THF (1 mL) at 0 °C was added 2M LiAlH4 in THF (0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. NaHCO3 and extracted with diethyl ether (x 3). The combined organic extracted were dried (MgSO4), filtered and concentrated in vacuo to give crude diol (±)-44 (87:13 dr). Chromatographic purification (eluent Et2O:petrol 60:40) gave diol (±)-44 (>99:1 dr) as a white solid (43.6 mg, 86%); mp 102-104 °C; νmax (KBr) 3412 (O-H), 2924 (C-H), 2854; δH (400 MHz, CDCl3) 1.92-2.00 (1H, m, C(4)H), 2.13-2.20 (4H, m, C(4)H and C(4)H3), 3.11 (1H, q, J 6.9, C(3)H), 3.29 (1H, q, J 7.1, C(2)H), 3.78 (1H, dd, J 10.7, 6.7, C(1)H), 3.84-3.94 (2H, m, C(1)H and C(5)H), 6.57-6.59 (2H, m, ArH), 6.86-6.90 (3H, m, ArH), 6.97-7.00 (1H, m, ArH), 7.05-7.13 (3H, m, ArH); δC (125 MHz, CDCl3) 21.4 (C(4)H3), 33.8 (C(4)), 43.5 (C(3)), 51.7 (C(2)), 64.9 (C(1)), 69.1 (q, J 30.5, C(5)), 125.3 (q, J 281,CF3), 126.1 (ArC), 126.8 (ArC), 127.7 (ArC), 128.0 (ArC), 128.1 (ArC), 129.0 (ArC), 129.9 (ArC), 137.7 (4ry ArC), 138.8 (4ry ArC), 140.7 (4ry ArC); δF (376 MHz, CDCl3) -80.0 (CF3); m/z (ES⁺) 361 ([M+Na]+, 100%); HRMS (ES⁺) C19H21F3NaO2⁺ ([M+Na]+) requires 361.1391; found 361.1380 (-3.2 ppm).
(2R,3R,5S)-6,6,6-trifluoro-3-phenyl-2-(m-tolyl)hexane-1,5-diol

To a solution of lactone (3R,4R,6S)-42 (50.0 mg, 0.15 mmol) (>99:1 dr) in THF (1 mL) at 0 °C was added 2M LiAlH₄ in THF (0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. NaHCO₃ and extracted with diethyl ether (× 3). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give crude diol (2R,3R,5S)-44 (>99:1 dr). Chromatographic purification (eluent Et₂O:petrol 60:40) gave diol (2R,3R,5R)-44 (>99:1 dr) as a white solid (42.3 mg, 83%); [α]D²⁰ -19.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(2S,3S,5R): 8.2 min, tR(2R,3R,5S): 9.3 min, 96% ee.

6,6,6-trifluoro-3-phenyl-2-(m-tolyl)hexane-1,5-diol

To a solution of lactone (+)-43 (50.0 mg, 0.15 mmol) (>99:1 dr) in THF (1 mL) at 0 °C was added 2M LiAlH₄ in THF (0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. NaHCO₃ and extracted with diethyl ether (× 3). The combined organic extracts were dried (MgSO₄), filtered and concentrated in vacuo to give crude diol (+)-45 (>99:1 dr). Chromatographic purification (eluent Et₂O) gave diol (+)-45 (>99:1 dr) as a colourless oil (44.4 mg, 88%); νmax (thin film) 3334 (O-H), 3030, 2925 (C-H), 1606, 1589; δH (300 MHz, CDCl₃) 1.67 (1H, br s, O-H), 1.84-1.93 (1H, m, C(4)H), 2.06 (1H, ddd, J 14.2, 10.9, 3.5, C(4)H), 2.15 (3H, s, CH₃), 2.83 (1H, br s, O-H), 2.93-3.00 (1H, m, C(2)H), 3.32-3.43 (2H, m, C(3)H and C(5)H), 3.83 (2H, d, J 6.3, C(1)H₂), 6.54-6.67 (2H, m, ArH), 6.83-6.87 (3H, m, ArH), 6.98 (1H, t, J 7.7, ArH), 7.01-7.12 (3H, m, ArH); δC (125 MHz, CDCl₃) 21.4 (CH₃), 33.1 (C(4)), 42.2 (C(3)), 53.4 (C(2)), 64.6 (C(1)), 68.3 (q, J 31.0, C(5)), 125.3 (q, J 280,CF₃), 126.1 (ArC), 126.7 (ArC), 127.6 (ArC), 128.0 (ArC), 128.2 (ArC), 128.9 (ArC), 129.8 (ArC), 137.7 (4ry ArC), 139.5 (4ry ArC), 140.1 (4ry ArC); δF (282 MHz, CDCl₃) -80.5 (CF₃); m/z (ES⁺) 361 ([M+Na]⁺, 100%); HRMS (ES⁺) C₁₉H₂₁F₃NaO₂⁺ ([M+Na]⁺) requires 361.1391; found 361.1398 (+1.9 ppm).

(2R,3R,5R)-6,6,6-trifluoro-3-phenyl-2-(m-tolyl)hexane-1,5-diol

S43
To a solution of lactone (3R,4R,6R)-43 (50.0 mg, 0.15 mmol) (>99:1 dr) in THF (1 mL) at 0 °C was added 2M LiAlH₄ in THF (0.23 mL, 0.45 mmol) and the reaction mixture was allowed to stir for 10 minutes at rt. The reaction mixture was quenched by addition of sat. aq. NaHCO₃ and extracted with diethyl ether (x 3). The combined organic extracted were dried (MgSO₄), filtered and concentrated in vacuo to give crude diol (2R,3R,5R)-45 (>99:1 dr). Chromatographic purification (eluent Et₂O) gave diol (2R,3R,5R)-45 (>99:1 dr) as a colourless oil (41.5 mg, 82%); [α]_D²⁰ -17.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(2R,3R,5R): 6.1 min, t_R(2S,3S,5S): 7.5 min, 98% ee.

Methanol Ring Opening

methyl 6,6,6-trifluoro-5-hydroxy-3-phenyl-2-(m-toly)hexanoate

To a solution of lactone (±)-43 (50.0 mg, 0.15 mmol) (>99:1 dr) in methanol (5 mL) was added DMAP (3.66 mg, 0.03 mmol). The reaction mixture was stirred at 40 °C for 5 h before being concentrated in vacuo to give crude alcohol (±)-46 (>99:1 dr). Chromatographic purification (eluent Et₂O:petrol 20:80) gave alcohol (±)-46 (>99:1 dr) as a white solid (49.3 mg, 90%); [α]_D²⁰ -169.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(2R,3R,5R): 6.1 min, t_R(2S,3S,5S): 7.5 min, 98% ee.

(2R,3R,5R)-methyl 6,6,6-trifluoro-5-hydroxy-3-phenyl-2-(m-toly)hexanoate

To a solution of lactone (3R,4R,6R)-43 (50.0 mg, 0.15 mmol) (>99:1 dr) in methanol (5 mL) was added DMAP (3.66 mg, 0.03 mmol). The reaction mixture was stirred at 40 °C for 5 h before being concentrated in vacuo to give crude alcohol (2R,3R,5R)-46 (>99:1 dr). Chromatographic purification (eluent Et₂O:petrol 20:80) gave alcohol (2R,3R,5R)-46 (>99:1 dr) as a white solid (49.3 mg, 90%); [α]_D²⁰ -169.0 (c 0.1, CH₂Cl₂); Chiral HPLC
Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) \( t_R(2S,3S,5S): 7.4 \) min, \( t_R(2R,3R,5R): 12.8 \) min, 98% ee.

**LiAlH₄ Reduction / Cyclisations**

4-phenyl-5-(\(m\)-tolyl)-2-(trifluoromethyl)tetrahydro-2\(H\)-pyran-2-ol

Following general procedure D, lactone (\(\pm\)-20 (100 mg, 0.30 mmol) (90:10 dr) and 2M LiAlH₄ in THF (0.60 mL, 1.2 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (\(\pm\)-47 (90:10 dr). Chromatographic purification (eluent Et₂O:petrol 10:90) gave pyran (\(\pm\)-47 (>99:1 dr) as a colourless oil (77.3 mg, 81%); \( \nu_{\text{max}} \) (thin film) 3418 (O-H), 3030, 2941 (C-H), 1705, 1608. 1591; \( \delta_H \) (500 MHz, CDCl₃) 1.94 (1H, t, \( J_{13.1} \) C(3)H), 2.12-2.15 (4H, m, C(3)H and C(3)H), 2.74 (1H, br s, O-H), 3.08 (1H, td, \( J_{11.7, 4.6} \) C(5)H), 3.43 (1H, td, \( J_{12.2, 3.8} \) C(4)H), 3.86 (1H, dd, \( J_{11.4, 4.7} \) C(6)H), 4.00 (1H, t, \( J_{11.5, 6.1} \) C(6)H), 6.81-6.83 (3H, m, ArH), 6.96-7.03 (4H, m, ArH), 7.07-7.10 (2H, m, ArH); \( \delta_C \) (125 MHz, CDCl₃) 21.4 (\( \text{CH}_3 \)), 35.3 (C(3)), 40.7 (C(4)), 47.2 (C(5)), 67.2 (C(6), 94.5 (q, \( J_{32.0} \) C(2)), 122.7 (q, \( J_{284,C(2)} \)), 125.2 (ArC), 126.6 (ArC), 127.6 (ArC), 127.8 (ArC), 128.3 (ArC), 128.5 (ArC), 138.0 (ArC), 138.5 (ArC), 142.0 (ArC); \( \delta_F \) (470 MHz, CDCl₃) -87.1 (C(3)F₃); \( m/z \) (ES⁺) 359 ([M+Na⁺], 100%); HRMS (ES⁺) C₁₉H₁₈F₃O₂⁺ ([M-H]⁺) requires 335.1259; found 335.1258 (-0.4 ppm).

\((2R,4R,5R)-4\text{-phenyl-5-(m-tolyl)-2-((trifluoromethyl)tetrahydro-2H-pyran-2-ol}

Following general procedure D, lactone (3\(R,4R\))-20 (100 mg, 0.30 mmol) (96:4 dr) and 2M LiAlH₄ in THF (0.60 mL, 1.2 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (\(2R,4R,5R\)-47 (96:4 dr). Chromatographic purification (eluent Et₂O:petrol 10:90) gave pyran (\(2R,4R,5R\)-47 (>99:1 dr) as a colourless oil (77.1 mg, 80%); [\(\alpha\)]\text{D}\text{20} -38.3 (c 1.0, CH₂Cl₂); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) \( t_R(2R,4R,5R): 5.8 \) min, \( t_R(2S,4S,5S): 7.3 \) min, 97% ee.

5-(naphthalen-2-yl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2\(H\)-pyran-2-ol

Following general procedure D, lactone (3\(R,4R\))-20 (100 mg, 0.30 mmol) (96:4 dr) and 2M LiAlH₄ in THF (0.60 mL, 1.2 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (\(2R,4R,5R\)-47 (96:4 dr). Chromatographic purification (eluent Et₂O:petrol 10:90) gave pyran (\(2R,4R,5R\)-47 (>99:1 dr) as a colourless oil (77.1 mg, 80%); [\(\alpha\)]\text{D}\text{20} -38.3 (c 1.0, CH₂Cl₂); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) \( t_R(2R,4R,5R): 5.8 \) min, \( t_R(2S,4S,5S): 7.3 \) min, 97% ee.
Following general procedure D, lactone (±)-22 (42.8 mg, 0.12 mmol) (95:5 dr) and 2M LiAlH₄ in THF (0.23 mL, 0.47 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-48 (95:5 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (±)-48 (>99:1 dr) as a white solid (38.3 mg, 89%); mp 111-113 °C; ν_max (KBr) 3490 (O-H), 3031, 2941 (C-H); δ H (400 MHz, CDCl₃) 2.00 (1H, td, J 13.0, 2.6, C(3)H), 2.20 (1H, dd, J 13.6, 4.0, C(3)H), 2.75 (1H, d, J 2.7, OH), 3.30 (1H, td, J 11.7, 4.7, C(5)H), 3.58 (1H, td, 12.1, 4.0, C(4)H), 3.94 (1H, dd, J 11.4, 4.7, C(6)H), 4.12 (1H, t, J 11.5, C(6)H), 6.94-6.98 (1H, m, ArH), 7.03-7.08 (4H, m, ArH), 7.17-7.19 (1H, m, ArH), 7.29-7.35 (2H, m, ArH), 7.49 (1H, s, ArH), 7.58-7.65 (3H, m, ArH); δC (100 MHz, CDCl₃) 35.4 (C(3)), 40.8 (C(4)), 47.4 (C(5)), 67.1 (C(6)), 94.5 (q, J 32.0, C(2)), 122.7 (q, J 284.0, C(2)), 125.7 (ArC), 126.0 (ArC), 126.2 (ArC), 126.7 (ArC), 127.2 (ArC), 127.5 (ArC), 127.6 (ArC), 128.2 (ArC), 128.6 (ArC), 132.5 (4ry ArC), 133.4 (4ry ArC), 136.1 (4ry ArC), 141.8 (4ry ArC); δF (376 MHz, CDCl₃) -87.6 (C(3)F); m/z (ES⁻) 371 ([M-H]⁺, 100%); HRMS (ES⁻) C₂₂H₁₈F₃O₂⁺ ([M-H]⁺) requires 371.1259; found 371.1272 (+3.6 ppm).

(2R,4R,5R)-5-(naphthalen-2-yl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (3R,4R)-22 (39.8 mg, 0.11 mmol) (98:2 dr) and 2M LiAlH₄ in THF (0.23 mL, 0.47 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2R,4R,5R)-48 (98:2 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (2R,4R,5R)-48 (>99:1 dr) as a white solid (38.7 mg, 90%); [α]_D²⁰ -98.7 (c 0.15, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) t_R(2R,4R,5R): 11.9 min, t_R(2S,4S,5S): 17.6 min, 97% ee.

5-(4-chlorophenyl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (±)-14 (42.2 mg, 0.12 mmol) (>99:1 dr) and 2M LiAlH₄ in THF (0.23 mL, 0.47 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-49 (>99:1 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (±)-49 (>99:1 dr) as a colourless oil (39.3 mg, 93%); ν_max (thin film) 3399 (O-H), 3031, 2940 (C-H); δ H (400 MHz, CDCl₃) 1.95 (1H, td, J 13.0, 2.1, C(3)H), 2.15 (1H, dd, J 13.5, 3.8, C(3)H), 2.72 (1H, d, J 2.2, OH), 3.09 (1H, td, J 11.7, 4.7, C(5)H), 3.38 (1H, td, 12.1, 3.9, C(4)H), 3.85 (1H, dd, J 11.4, 4.6, C(6)H), 4.00 (1H, t, J 11.5, C(6)H), 6.95-7.13 (9H, m, ArH); δC (100 MHz, CDCl₃) 35.2 (C(3)), 41.0 (C(4)), 46.9 (C(5)), 66.8 (C(6)), 94.4 (q, J 31.9, C(2)), 122.6 (q, J 283.0, C(3)), 126.9...
(ArC), 127.5 (ArC), 128.6 (ArC), 128.7 (ArC), 132.7 (4ry ArC), 137.1 (4ry ArC), 141.4 (4ry ArC); δF (376 MHz, CDCl3) -87.6 (CF3); m/z (ES-) 355 ([M-H]+, 100%); HRMS (ES-) C18H1535ClF3O2+ ([M-H]+) requires 355.0713; found 355.0716 (+0.8 ppm).

(2R,4R,5R)-5-(4-chlorophenyl)-4-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (3R,4R)-14 (42.2 mg, 0.12 mmol) (> 99:1 dr) and 2M LiAlH4 in THF (0.22 mL, 0.44 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2R,4R,5R)-49 (>99:1 dr). Chromatographic purification (eluent Et2O:petrol 15:85) gave pyran (2R,4R,5R)-49 (>99:1 dr) as a colourless oil (40.3 mg, 94%); [α]D 20 -67.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min\(^{-1}\), 211 nm) \(t_R(2R,4R,5R)\): 10.7 min, \(t_R(2S,4S,5S)\): 18.5 min, 92% ee.

4-(4-methoxyphenyl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (±)-34 (49.7 mg, 0.14 mmol) (87:13 dr) and 2M LiAlH4 in THF (0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-50 (87:13 dr). Chromatographic purification (eluent Et2O:petrol 15:85) gave pyran (±)-50 (>99:1 dr) as a colourless oil (41.3 mg, 82%); ν\(_{\text{max}}\) (thin film) 3391 (O-H), 3031, 2939 (C-H), 1612, 1515; δH (300 MHz, CDCl3) 1.92 (1H, td, \(J = 13.0, 2.5\), C(3)H), 2.12 (1H, dd, \(J = 13.5, 4.0\), C(3)H), 2.77 (1H, d, \(J = 2.6\), OH), 3.06 (1H, td, \(J = 11.7, 4.7\), C(5)H), 3.34-3.43 (1H, m, C(4)H), 3.62 (3H, s, OCH3), 3.87 (1H, dd, \(J = 11.4, 4.8\), C(6)H), 4.02 (1H, t, \(J = 11.5\), C(6)H), 6.60-6.65 (2H, m, ArH), 6.91-6.96 (2H, m, ArH), 7.01-7.14 (5H, m, ArH); δC (125 MHz, CDCl3) 35.4 (C(3)), 40.0 (C(4)), 47.7 (C(5)), 55.1 (OCH3), 67.1 (C(6)), 94.4 (q, \(J = 32.0\), C(2)), 113.8 (ArC), 122.7 (q, \(J = 284,\) CF3), 126.9 (ArC), 128.2 (ArC), 128.4 (ArC), 128.5 (ArC), 134.0 (4ry ArC), 138.7 (4ry ArC), 158.1 (4ry ArC); δF (282 MHz, CDCl3) -87.6 (CF3), -116.6 (ArF); m/z (ES+) 351 ([M-H]+, 100%); HRMS (ES+) C19H18F3O3+ ([M-H]+) requires 351.1208; found 351.1204 (-1.1 ppm).
Following general procedure D, lactone (3R,4R)-34 (49.7 mg, 0.14 mmol) (96:4 dr) and 2M LiAlH₄ in THF (0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2R,4R,5R)-50 (96:4 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (2R,4R,5R)-50 (>99:1 dr) as a colourless oil (46.8 mg, 93%); [α]D₂₀ -39.0 (c 0.1, CH₂Cl₂); Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tR(2R,4R,5R): 12.7 min, tR(2S,4S,5S): 44.4 min, 98% ee.

4-(naphthalen-1-yl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (±)-36 (52.8 mg, 0.14 mmol) (97:3 dr) and 2M LiAlH₄ in THF (0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-51 (97:3 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (±)-51 (>99:1 dr) as a white solid (49.0 mg, 92%); mp 132-134 °C; νmax (KBr) 3517 (O-H), 3065, 2948 (C-H), 1599; δH (500 MHz, CDCl₃) 1.85 (1H, t, J 12.9, C(3)H), 2.36 (1H, dd, J 13.7, 3.3, C(3)H), 2.81 (1H, s, OH), 3.54 (1H, td, J 11.4, 4.5, C(5)H), 4.00 (1H, dd, J 11.5, 4.6, C(6)H), 4.10 (1H, t, J 11.4, C(6)H), 4.48 (1H, td, 12.0, 3.3, C(4)H), 6.96 (1H, t, J 7.3, ArH), 7.03 (2H, t, J 7.5, ArH) 7.11 (2H, d, J 7.3, ArH), 7.22 (1H, t, J 7.6, ArH), 7.27 (1H, d, J 6.9 ArH), 7.38 (1H, t, J 7.5, ArH), 7.47-7.50 (1H, m, ArH), 7.54 (1H, d, J 7.9, ArH), 7.72 (1H, d, J 8.1, ArH), 8.17 (1H, d, J 8.6, ArH); δC (100 MHz, CDCl₃) 33.9 (C(4)), 36.0 (C(3)), 45.9 (C(5)), 68.1 (C(6)), 94.6 (q, J 32.1, C(2)), 122.3 (ArH), 122.6 (q, J 283,CF₃), 128.3 (ArC), 125.5 (ArC), 125.5 (ArC), 126.4 (ArC), 127.0 (ArC), 127.1 (ArC), 128.0 (ArC), 128.6 (ArC), 129.1 (ArC), 131.4 (4ry ArC), 134.0 (4ry ArC), 137.7 (4ry ArC) 138.4 (4ry ArC); δF (470 MHz, CDCl₃) -87.0 (CF₃), -116.6 (ArF); m/z (ES⁺) 371 ([M-H]⁺, 100%); HRMS (ES⁺) C₂₂H₁₈F₃O₂⁺ ([M-H]⁺) requires 371.1259; found 371.1258 (-0.3 ppm).

(2R,4R,5R)-4-(naphthalen-1-yl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (3R,4R)-36 (52.8 mg, 0.14 mmol) (99:1 dr) and 2M LiAlH₄ in THF (0.29 mL, 0.57 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2R,4R,5R)-51 (99:1 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (2R,4R,5R)-51 (>99:1 dr) as a white solid.
(50.7 mg, 95%); \([\alpha]_D^{20} +159.6 \ (c \ 0.25, \ CH_2Cl_2); \) Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min\(^{-1}\), 211 nm) \(t_R(2'S,4'S,5'S): \) 9.7 min, \(t_R(2'R,4'R,5'R): \) 13.0 min, 98% ee.

4-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (±)-31 (40.3 mg, 0.12 mmol) (99:1 dr) and 2M LiAlH\(_4\) in THF (0.24 mL, 0.48 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-52 (99:1 dr). Chromatographic purification (eluent Et\(_2\)O:petrol 15:85) gave pyran (±)-52 (>99:1 dr) as a colourless oil (38.3 mg, 94%); \(\nu_{\text{max}}\) (thin film) 3419 (O-H), 3032, 2941 (C-H), 1704, 1606; \(\delta_H\) (400 MHz, CDCl\(_3\)) 1.93 (1H, td, \(J\) 13.0, 2.4, C(3)H), 2.13 (1H, dd, \(J\) 13.4, 3.9, C(3)H), 2.72 (1H, d, \(J\) 2.5, OH), 3.04 (1H, td, \(J\) 11.7, 4.7, C(5)H), 3.42 (1H, ddd, 14.5, 9.8, 4.4, C(4)H), 3.88 (1H, dd, \(J\) 11.4, 4.7, C(6)H), 4.04 (1H, t, \(J\) 11.5, C(6)H), 6.77-6.79 (2H, m, ArH), 6.96-7.13 (7H, m, ArH); \(\delta_C\) (100 MHz, CDCl\(_3\)) 35.2 (C(3)), 40.3 (C(4)), 47.8 (C(5)), 66.9 (C(6)), 94.4 (q, \(J\) 32.1, C(2)), 115.3 (d, \(J\) 21.1, ArC), 122.6 (q, \(J\) 283,CF\(_3\)), 127.1 (ArC), 128.1 (ArC), 128.6 (ArC), 128.9 (d, \(J\) 7.8, ArC), 137.5 (d, \(J\) 3.0, ArC), 138.3 (ArC), 161.5 (d, \(J\) 243, 4ry ArC); \(\delta_F\) (376 MHz, CDCl\(_3\)) -87.6 (C\(_{\text{CF}}\)), -116.6 (ArF); \(m/z\) (ES\(^{-}\)) 339 ([M-H]\(^+\), 100%); HRMS (ES\(^{-}\)) C\(_{13}H_{15}F_{4}O_{2}\)+ ([M-H]\(^+\)) requires 339.1008; found 339.1014 (+1.8 ppm).

(2\(R\),4\(R\),5\(R\))-4-(4-fluorophenyl)-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (3\(R\),4\(R\))-31 (40.3 mg, 0.12 mmol) (>99:1 dr) and 2M LiAlH\(_4\) in THF (0.22 mL, 0.44 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2\(R\),4\(R\),5\(R\))-52 (>99:1 dr). Chromatographic purification (eluent Et\(_2\)O:petrol 15:85) gave pyran (2\(R\),4\(R\),5\(R\))-52 (>99:1 dr) as a colourless oil (37.9 mg, 93%); \([\alpha]_D^{20} -52.0 \ (c\ 0.1, \ CH_2Cl_2); \) Chiral HPLC Chiralpak AD-H (5% IPA:hexane, flow rate 1 mL min\(^{-1}\), 211 nm) \(t_R(2'R,4'R,5'R): \) 8.4 min, \(t_R(2'S,4'S,5'S): \) 26.0 min, 98% ee.

4-pentyl-5-phenyl-2-(trifluoromethyl)tetrahydro-2H-pyran-2-ol

Following general procedure D, lactone (±)-40 (50.0 mg, 0.27 mmol) (90:10 dr) and 2M LiAlH\(_4\) in THF (0.54 mL, 1.1 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-53 (90:10 dr). Chromatographic
purification (eluent Et₂O:petrol 10:90) gave pyran (±)-53 (>99:1 dr) as a colourless oil (41.0 mg, 80%); ν\textsubscript{max} (Diamond Cell) 3408 (O-H), 2957, 2932 (C-H), 1602; δ H (500 MHz, CDCl\textsubscript{3}) 0.84 (3H, t, J 7.11, CH₃), 0.96-1.31 (8H, m, 4CH₂), 1.51 (1H, app t, J 12.7, C(3)H), 2.18 (1H, dd, J 13.3, 3.9, C(3)H), 2.22-2.29 (1H, m, C(4)H), 2.61 (1H, td, J 11.6, 4.7, C(5)H), 2.68 (1H, br s, OH), 3.80 (1H, dd, J 11.3, 4.7, C(6)H), 3.95 (1H, t, J 11.6, C(6)H), 7.22 (2H, d, J 7.2, C(5)Ar(2,6)H), 7.29 (1H, t, J 7.3, C(5)Ar(4)H), 7.36 (2H, t, J 7.5, C(5)Ar(3,5)H); δC (125 MHz, CDCl\textsubscript{3}) 14.0 (C(CH₃)₃), 22.5 (C(CH₂)₂), 25.5 (C(CH₂)₂), 31.8 (C(CH₂)₂), 32.0 (C(CH₂)₂), 33.0 (C(4)), 33.5 (C(5)), 66.9 (C(6)), 94.5 (q, J 31.8, C(2)), 122.8 (q, J 284, CF₃), 127.1 (C(5)-ArC(4)), 128.2 (ArC), 128.7 (ArC), 139.5 (C(5)-4ry ArC(1)); m/z (APCI⁺) 316 ([M⁺]⁺, 100%); HRMS (APCI⁺) C\textsubscript{17}H\textsubscript{27}F\textsubscript{3}NO\textsubscript{2}⁺ ([M+NH₄]⁺) requires 334.1988; found 334.1986 (-0.7 ppm).

2-(4-fluorophenyl)acetic pivalic anhydride

To a solution of 4-fluorophenylacetic acid (100 mg, 0.65 mmol) in CH₂Cl₂ (3 mL) at rt was added DIPEA (0.17 mL, 0.98 mmol) and pivaloyl chloride (0.12 mL, 0.98 mmol). The reaction mixture was allowed to stir for 15 minutes before being concentrated in vacuo. The crude reaction mixture was treated with petrol (10 mL) and then filtered to remove inorganic salts. The filtrate was concentrated in vacuo to give mixed anhydride 54 as a yellow oil (150 mg, 97%) which was used crude without further purification. δ H (400 MHz, CD₂Cl₂) 1.09 (9H, s, C(CH₃)₃), 3.66 (2H, s, CH₂), 6.93-6.99 (2H, m, Ar(3,5)H), 7.15-7.20 (2H, m, Ar(2,6)H); δ F (376 MHz, CD₂Cl₂) -116.2 (ArF).

(2S,3R)-1-(2-(4-fluorophenyl)acetyl)-3-isopropyl-2-phenyl-1,2,3,4-tetrahydrobenzo[4,5]thiazolo[3,2-a]pyrimidin-5-ium chloride

To a solution of 4-fluorophenylacetyl chloride (100 mg, 0.58 mmol) in CH₂Cl₂ (2 mL) was added isothiourea (2S,3R)-6 (178 mg, 0.58 mmol) and the reaction mixture was allowed to stir at rt for 10 minutes before being filtered to give salt (2S,3R)-60 as a light yellow solid (257 mg, 92%); mp 102-104 °C (dec); ν\textsubscript{max} (KBr) 2925 (C-H), 1712 (C=O), 1603, 1535, 1511; δ H (400 MHz, CD₂Cl₂) 0.95 (3H, d, J 6.7, CH₃), 1.42 (3H, d, J 6.6, CH₃), 1.65-1.74 (1H, m, CH(CH₃)₂), 3.13-3.21 (1H, m, C(3)H), 3.66 (1H, d, J 17.7, CHH), 3.95 (1H, app. t, J 13.0, C(4)H), 4.79 (1H, dd, J 13.3, 4.4, C(4)H), 5.51 (1H, d, J 17.8, CHH), 6.60 (1H, d, J 4.2, C(2)H), 6.95-6.99 (2H, m, 4-FAr(3,5)H), 7.15-7.18 (2H, m, ArH), 7.19-7.23 (2H, m, 4-FAr(2,6)H), 7.42-7.48 (3H, m, ArH), 7.66-
7.70 (1H, m, ArH), 7.81 (1H, td, J 7.9, 1.0), 8.02 (1H, d, J 8.4, ArH), 8.10 (1H, d, J 7.6, ArH); δC (125 MHz, CD2Cl2) 19.6 (CH3), 21.9 (CH3), 26.8 (CH(CH3)2), 39.8 (C(3)), 40.6 (CH2), 44.8 (C(4)), 61.5 (C(2)), 114.2 (ArC), 115.4 (d, J 21.3, 4-FArC(3,5)), 123.4 (ArC), 126.2 (ArC), 127.1 (ArC), 127.7 (d, J 3.0, 4-FArC(1)), 127.9 (ArC), 129.6 (ArC), 129.9 (ArC), 131.9 (d, J 8.0, 4-FArC(2,6)), 134.6 (ArC), 136.1 (ArC), 160.7 (C=N), 162.2 (d, J 245, 4-FArC(4)), 173.7 (C=O); δF (376 MHz, CD2Cl2) -116.3 (ArF);

7.70 (1H, m, ArH), 7.81 (1H, td, J 7.9, 1.0), 8.02 (1H, d, J 8.4, ArH), 8.10 (1H, d, J 7.6, ArH); δC (125 MHz, CD2Cl2) 19.6 (CH3), 21.9 (CH3), 26.8 (CH(CH3)2), 39.8 (C(3)), 40.6 (CH2), 44.8 (C(4)), 61.5 (C(2)), 114.2 (ArC), 115.4 (d, J 21.3, 4-FArC(3,5)), 123.4 (ArC), 126.2 (ArC), 127.1 (ArC), 127.7 (d, J 3.0, 4-FArC(1)), 127.9 (ArC), 129.6 (ArC), 129.9 (ArC), 131.9 (d, J 8.0, 4-FArC(2,6)), 134.6 (ArC), 136.1 (ArC), 160.7 (C=N), 162.2 (d, J 245, 4-FArC(4)), 173.7 (C=O); δF (376 MHz, CD2Cl2) -116.3 (ArF);

Following general procedure C, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), acyl ammonium (2'S,3'R)-60 (4.81 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3'R,4'R)-13 (90:10 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3'R,4'R)-13 (>99:1 dr) as a white solid (59.3 mg, 88%); [α]D20 -256.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min-1, 211 nm) tR(3'R,4'R): 19.2 min, tR(3'S,4'S): 39.4 min, 99% ee.

2-d2-(4-fluorophenyl)acetic acid

To a solution of 4-fluorophenylacetic acid (1.00 g, 6.49 mmol) in D2O (6 mL) was added K2CO3 (3.59 g, 26.0 mmol) and the reaction mixture was heated at reflux for 16 h. The crude reaction mixture was acidified by careful addition of 8M HCl and extracted with CH2Cl2. The organic layer was separated, dried (MgSO4), filtered and concentrated in vacuo. The whole process was repeated a further 3 times to give acid 62 as a white solid (570 mg, 56%) which was 99% deuterated according to 1H NMR; mp 83-84 °C; νmax (Diamond Cell) 3200-2520 (CO 2H), 2922 (C-H), 1692 (C=O), 1608, 1512; δ H (300 MHz, CDCl3) 7.02-7.10 (2H, m, Ar(3,5)H), 7.25-7.32 (2H, m, Ar(2,6)H), 11.9 (1H, s, OH); δC (75 MHz, CDCl3) 116.0 (d, J 21.4, ArC(3,5)), 129.3 (ArC(1)), 131.4 (d, J 8.0, ArC(2,6)), 163.0 (d, J 244, ArC(4)), 178.7 (C=O); m/z (ES') 445 ([M]+, 100%); HRMS (ES') C27H26FN2OS+ ([M]+) requires 445.1750; found 445.1743 (-1.4 ppm).

(3R,4R)-3-(4-fluorophenyl)-4-phenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one

Following general procedure C, 4-fluorophenylacetic acid (30.8 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), acyl ammonium (2'S,3'R)-60 (4.81 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3'R,4'R)-13 (90:10 dr). Chromatographic purification (eluent Et2O:petrol 5:95) gave lactone (3'R,4'R)-13 (>99:1 dr) as a white solid (59.3 mg, 88%); [α]D20 -256.0 (c 0.1, CH2Cl2); Chiral HPLC Chiralcel OD-H (10% IPA:hexane, flow rate 1 mL min-1, 211 nm) tR(3'R,4'R): 19.2 min, tR(3'S,4'S): 39.4 min, 99% ee.

2-d2-(4-fluorophenyl)acetic acid

To a solution of 4-fluorophenylacetic acid (1.00 g, 6.49 mmol) in D2O (6 mL) was added K2CO3 (3.59 g, 26.0 mmol) and the reaction mixture was heated at reflux for 16 h. The crude reaction mixture was acidified by careful addition of 8M HCl and extracted with CH2Cl2. The organic layer was separated, dried (MgSO4), filtered and concentrated in vacuo. The whole process was repeated a further 3 times to give acid 62 as a white solid (570 mg, 56%) which was 99% deuterated according to 1H NMR; mp 83-84 °C; νmax (Diamond Cell) 3200-2520 (CO 2H), 2922 (C-H), 1692 (C=O), 1608, 1512; δ H (300 MHz, CDCl3) 7.02-7.10 (2H, m, Ar(3,5)H), 7.25-7.32 (2H, m, Ar(2,6)H), 11.9 (1H, s, OH); δC (75 MHz, CDCl3) 116.0 (d, J 21.4, ArC(3,5)), 129.3 (ArC(1)), 131.4 (d, J 8.0, ArC(2,6)), 163.0 (d, J 244, ArC(4)), 178.7 (C=O); m/z (ES') 445 ([M]+, 100%); HRMS (ES') C27H26FN2OS+ ([M]+) requires 445.1750; found 445.1743 (-1.4 ppm).

Reaction using 2-d2-(4-fluorophenyl)acetic acid
Following general procedure D, acetic acid 62 (31.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.08 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 16 h at -78 °C gave crude lactone (3R,4R)-61 (90:10 dr) with 30% proton incorporation observed at C(3). Chromatographic purification (eluent Et₂O:petrol 5:95) gave lactone (3R,4R)-63 (>99:1 dr) as a white solid (49.0 mg, 73%).

**3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (±)-6 (3.09 mg, 0.01 mmol), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at -78 °C gave crude lactone (±)-64 (81:19 dr). Chromatographic purification (eluent Et₂O:petrol 3:97) gave lactone (±)-64 (92:8 dr) as a white solid (46.2 mg, 73%); mp 100-102 °C; ν max (KBr) 3094, 2922 (C-H), 1790 (C=O), 1705; Data for major diastereoisomer: δ H (300 MHz, CDCl₃) 3.86-3.91 (1H, m, C(4)H), 4.23 (1H, d, J 7.1, C(3)H), 6.23 (1H, dd, J 5.9, 0.6, C(5)H), 6.63-6.66 (2H, m, ArH), 6.69-6.72 (2H, m, ArH), 7.05-7.23 (6H, m, ArH); δ C (100 MHz, CDCl₃) 44.4 (C(4)), 51.0 (C(3)), 111.3 (q, J 3.4, C(5)), 118.6 (q, J 270, CF₃), 128.0 (ArC), 128.1 (ArC), 128.4 (ArC), 128.5 (ArC), 128.8 (ArC), 129.6 (ArC), 132.6 (4ry ArC), 134.7 (4ry ArC), 141.6 (q, J 38, C(6)), 165.5 (C(2)); δ F (282 MHz, CDCl₃) -72.5 (CF₃); m/z (APCI⁺) 319 ([M+H]+, 100%); HRMS (APCI⁺) C₁₈H₁₄F₃O₂⁺ ([M+H]+) requires 319.0940; found 319.0944 (+1.1 ppm).

**3(R,4S)-3,4-diphenyl-6-(trifluoromethyl)-3,4-dihydro-2H-pyran-2-one**

Following general procedure C, phenylacetic acid (27.2 mg, 0.20 mmol), DIPEA (51.9 μL, 0.30 mmol) and pivaloyl chloride (37.0 μL, 0.30 mmol) in DCM (1 mL), Ph/i-Pr isothiourea catalyst (2S,3R)-6 (3.09 mg, 0.01 mmol, 5 mol%), enone 2 (40.0 mg, 0.20 mmol) and DIPEA (87 μL, 0.5 mmol) for 1 h at -78 °C gave crude...
lactone (3R,4S)-64 (85:15 dr). Chromatographic purification (eluent Et₂O:petrol 3:97) gave lactone (3R,4S)-64 (91:9 dr) as a white solid (47.3 mg, 74%); [α]²⁰ D +370.0 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tₚ(3S,4R): 6.5 min, tₚ(3R,4S): 9.2 min, 99% ee.

4,5-diphenyl-2-(trifluoromethyl)tetrahydro-2H-pyrano-2-ol

Following general procedure D, lactone (±)-64 (37 mg, 0.12 mmol) (92:8 dr) and 2M LiAlH₄ in THF (0.23 mL, 0.46 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (±)-65 (92:8 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (±)-65 (93:7 dr) as a white solid (30.2 mg, 81%); mp 130-132 °C; ν max (Diamond Cell) 3526 (O-H), 3029, 2944 (C-H), 1700, 1618; Data for major diastereoisomer: δ H (400 MHz, CDCl₃) 1.82 (1H, dd, J 13.2, 3.3, C(3)H), 2.21 (1H, t, J 13.5, C(3)H), 2.73 (1H, br s, OH), 2.94 (1H, t, J 4.0, C(5)H), 3.73 (1H, dt, 14.0, 4.0, C(4)H), 4.21 (1H, d, J 11.5, C(6)H), 6.68-6.71 (2H, m, ArH), 6.87-6.89 (2H, m, ArH), 7.00-7.10 (6H, m, ArH); δC (125 MHz, CDCl₃) 26.4 (C(3)), 38.6 (C(4)), 45.2 (C(5)), 66.8 (C(6)), 94.7 (q, J 32.1, C(2)), 122.9 (q, J 284,CF₃), 126.6 (ArC), 126.7 (ArC), 127.9 (ArC), 128.1 (ArC), 138.8 (4ry ArC), 141.3 (4ry ArC); δF (376 MHz, CDCl₃) -87.8 (CF₃); m/z (APCI⁺) 340 ([M+NH₄]+, 100%); HRMS (APCI⁺) C₁₈H₂₁F₃NO₂⁺ ([M+NH₄]⁺) requires 340.1519; found 340.1517 (-0.6 ppm).

(2R,4S,5R)-4,5-diphenyl-2-(trifluoromethyl)tetrahydro-2H-pyrano-2-ol

Following general procedure D, lactone (3R,4S)-64 (84 mg, 0.26 mmol) (92:8 dr) and 2M LiAlH₄ in THF (0.53 mL, 1.06 mmol) in THF (1 mL) for 10 minutes at rt gave crude pyran (2R,4S,5R)-65 (92:8 dr). Chromatographic purification (eluent Et₂O:petrol 15:85) gave pyran (2R,4S,5R)-65 (94:6 dr) as a white solid (65.0 mg, 76%); [α]²⁰ D -232 (c 0.2, CH₂Cl₂); Chiral HPLC Chiralcel OJ-H (5% IPA:hexane, flow rate 1 mL min⁻¹, 211 nm) tₚ(2S,4R,5S): 13.2 min, tₚ(2R,4S,5R): 15.5 min, 99% ee.

1.8 NMR Analysis

The stereochemistry of lactone 42 was assigned on the basis of the NOE observed between H5 and H3 (Figure 1). In the case of the diastereomeric lactone 43, a surprisingly strong NOE between H5 and H2 was observed. This can be explained by the presence of a boat conformation, which according to DFT calculations at the B3LYP/6-31G** level of theory, is only about 6 kJmol⁻¹ higher in energy than the more stable chair conformation (Figure 2). Further evidence about the stereochemistry of 43 was provided by analysis of the
coupling pattern of the H5 resonance (Figure 3). Simulation of the ddq coupling pattern by Bruker Topspin DAISY module shows a $^{3}J_{HH}$ coupling constant of 12.2 Hz which is in accordance with an axial position of H5 in the minimum energy chair conformation of 43. The structure of 43, obtained by MM conformational search and geometry optimisation at B3LYP/6-31G** level of theory, is shown in Figure 3c. The H4a-C-C-H5 dihedral angle of 170.8° corresponds to coupling constant of 11.7 Hz, calculated by the Althona equation, which is in good agreement with the experimental data.

\[
\begin{align*}
\text{Figure 1} & \quad \text{1H NMR of 43 (a) and 42 (c) and corresponding 1D gs-NOESY spectra (b, d) acquired upon selective irradiation of H5. NOEs observed for H3 and H2 enables stereochemical assignment of 43 and 42 respectively.}
\end{align*}
\]
\[ E_{\text{rel}} = 0.0 \text{kJ.mol}^{-1}, \quad d(H_2,H_5) = 4.163 \text{Å} \]
\[ E_{\text{rel}} = 6.4 \text{kJ.mol}^{-1}, \quad d(H_2,H_5) = 2.319 \text{Å} \]

\[ d(H_3,H_5) = 3.812 \text{Å} \]
\[ d(H_3,H_5) = 3.834 \text{Å} \]

**Figure 2** Geometries of both chair and boat conformations of 42 calculated at the B3LYP/6-31G** level of theory, corresponding relative energies and distances between H2, H3 and H5 protons.

**Figure 3** Experimental (a) and simulated (b) ddq coupling pattern of the H5 resonance of compound 43 which enables us to derive coupling constants 12.2, 5.5 and 3.18 Hz. c) The structure of minimum energy conformation of 43 obtained by MM conformational search and geometry optimisation at the B3LYP/6-31G** level of theory.

The 1D gs-NOESY spectra of 47 shows NOEs between OH, H3 and H1a resonances (Figure 4). This implies a R-configuration at C5 which places the hydroxyl group in an axial position along with protons H3 and H1a as shown by the structure of minimum energy conformation of 47 obtained by MM conformational search and geometry optimisation at B3LYP/6-31G** level of theory.
Figure 4 $^1$H NMR of 47 (a) and corresponding 1D gs-NOESY spectra acquired upon selective irradiation of H3 (b) and OH (c). NOEs observed between OH, H3 and H1a enables the stereochemical assignment of 47. d) The structure of minimum energy conformation of 47 obtained by MM conformational search and geometry optimisation at B3LYP/6-31G** level of theory.

1.9 Mechanistic and kinetic studies

Determination of all stereoisomers

Racemic sample of both diastereoisomers

Chiral HPLC Chiralpak IB (5% IPA:hexane, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C) Syn Diastereoisomer: $t_R(3S,4R)$: 6.5 min, $t_R(3R,4S)$: 9.2 min; Anti Diastereoisomer: $t_R(3R,4R)$: 10.3 min, $t_R(3S,4S)$: 14.4 min
Reaction using (E)-enone

Reaction using (Z)-enone
Kinetic Studies

To complement these synthetic studies, kinetic investigations aimed to establish the catalytic cycle were performed. 4-Fluorophenylacetic acid (preactivated with pivaloyl chloride and Hunig’s base to prepare the mixed anhydride 54 \textit{in situ}) and trifluoromethylenone 2 were used as model substrates in order to measure reaction progress \textit{by in situ} $^{19}$F NMR spectroscopic analysis. The reactions were performed in CD$_2$Cl$_2$ at -78 °C using HBTM 2.1 6.

General Experimental Procedure For Kinetic Studies

To an NMR tube was added the required amount of 4-fluorophenylacetic acid, 1-fluoro-4-nitrobenzene, DIPEA, pivaloyl chloride and CD$_2$Cl$_2$. Subsequently, at -78 °C was added the required amount of isothiourea (2S,3R)-6, enone 2 and DIPEA. The reaction was followed dynamically by $^{19}$F NMR at -78 °C.

A typical $^{19}$F NMR spectrum is shown below in which the key species are clearly visible and highlighted, including both diastereoisomers of the forming lactone 3 and 64, 4-fluoronitrobenzene (standard), trifluoromethylenone 2 and mixed anhydride 54.

A typical kinetic profile is shown below for the reaction with reactant concentrations: 100 mM Acid, 100 mM Acceptor, 20 mM Standard, 0.5 mM catalyst. It is clearly visible that both the major and minor diastereoisomers of lactone 3 and 64 increase in concentration over time while the concentration of both the mixed anhydride 54 and enone 2 decrease over time. Typically the reactions were approximately 20% complete by the time of the first obtained data point.
Kinetic runs for eight combinations of initial concentrations of anhydride, acceptor and catalyst were performed (see table). Data for the concentrations of both the mixed anhydride and the enone acceptor are given below. Data were fitted (using MATLAB® R2011a) using plots of log concentrations (of either anhydride or enone) vs time. Only data either the anhydride or enone has not fallen to zero is presented and fitted. While plots of the natural log of the concentration of the anhydride vs time are linear in all cases, the plots of the natural log of the enone acceptor vs time are only (coincidentally) linear when anhydride and enone concentration are equal throughout the reaction. The fitted “t = 0” intercept concentrations of the anhydride and observed rate constants $k_{obs}$ are shown in the table.
**Data from NMR experiments.** Concentrations are calculated based on 20 nM internal standard. See table above for initial conditions. Plots of ln([anhydride]/mM) and ln([enone]/mM) vs time are included for each run.

### Run 1

<table>
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![Graphs showing kinetic data for Run 2](image-url)
Run 3

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Run 4

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Run 6

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Run 8

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1.10 References and Notes


HPLC Data

HPLC data compound 3: Chiralpak AD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 99% ee

![HPLC Chart]

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![HPLC Chart]

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<th>Area %</th>
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![HPLC Chart]
HPLC data compound 13: Chiralcel OD-H 10% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 99% ee
HPLC data compound 14: Chiralcel OD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 96% ee
HPLC data compound 15: Chiralpak AD-H 2% IPA:hexane, 1 mL min⁻¹, 211 nm, 95% ee
HPLC data compound 16: Chiralpak AD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 98% ee
HPLC data compound 17: Chiralpak AD-H 2% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 98% ee
HPLC data compound 18: Chiralpak AD-H 2% IPA:hexane, 2 mL min\(^{-1}\), 211 nm, 99% ee

![Chemical Structure](image)

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![Graph](image)
HPLC data compound 19: Chiralpak AD-H 2% IPA:hexane, 2 mL min⁻¹, 211 nm, 98% ee
HPLC data compound 20: Chiralcel OD-H 2% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, >99% ee
HPLC data compound 21: Chiralpak AD-H 2% IPA:hexane, 1 mL min⁻¹, 211 nm, 98% ee
HPLC data compound 22: Chiralcel OD-H 20% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 97% ee
HPLC data compound 23: Chiralpak AD-H 2% IPA:hexane, 2 mL min$^{-1}$, 211 nm, 89% ee

![HPLC graph]

### Table 1

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</table>

![Second HPLC graph]

### Table 2

<table>
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</table>
HPLC data compound 24: Chiralpak AD-H 2% IPA:hexane, 1 mL min⁻¹, 211 nm, 64% ee

<table>
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<th>Area</th>
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<th>Area</th>
<th>Area %</th>
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</table>
HPLC data compound 25: Chiralcel OD-H 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 97% ee

![Chemical structure image]

<table>
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<tr>
<th>Seq. Number</th>
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<th>R. Time</th>
<th>Area</th>
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<td>7127 (12.75)</td>
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</table>

![Graph image]
HPLC data compound 26: Chiralpak AD-H 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 96% ee
HPLC data compound 27: Chiralpak AD-H 2% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 28% ee
HPLC data compound 28: Chiralcel OD-H 5% IPA: hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee
HPLC data compound 29: Chiralcel OD-H 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 97% ee
HPLC data compound 30: Chiralcel OD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 97% ee
HPLC data compound 31: Chiralpak AD-H 2% IPA:hexane, 2 mL min\(^{-1}\), 211 nm, 98% ee
HPLC data compound 32: Chiralpak AD-H 2% IPA:hexane, 2 mL min\(^{-1}\), 211 nm, >99% ee
HPLC data compound 33: Chiralpak AD-H 2% IPA:hexane, 2 mL min$^{-1}$, 211 nm, 97% ee
HPLC data compound 34: Chiralpak AD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee
HPLC data compound 35: Chiralpak AD-H 20% IPA:hexane, 1 mL min⁻¹, 211 nm, 86% ee
HPLC data compound 36: Chiralpak AD-H 2% IPA:hexane, 2 mL min⁻¹, 211 nm, 98% ee
HPLC data compound 37: Chiralpak AD-H 2% IPA:hexane, 2 mL min⁻¹, 211 nm, >99% ee
HPLC data compound 38: Chiralpak AD-H 2% IPA:hexane, 2 mL min\(^{-1}\), 211 nm, 98% ee

![HPLC chromatogram](image-url)
HPLC data compound 39: Chiralpak AD-H 2% IPA:hexane, 2 mL min\(^{-1}\), 211 nm, 95% ee
HPLC data compound 40: Chiralpak IB 2% IPA:hexane, 1 mL min⁻¹, 211 nm, 30 °C, 98% ee
HPLC data compound 41: Chiralpak AD-H 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 97% ee

![Molecular Structure](image)

<table>
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![Graph](image)

<table>
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<th>Peak</th>
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<th>Area</th>
<th>Area %</th>
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</table>
HPLC data compound 42: Chiralpak AD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 97% ee

![Chemical Structure of Compound 42](image)

<table>
<thead>
<tr>
<th>Inj Number</th>
<th>Peak Name</th>
<th>R. Time</th>
<th>Area</th>
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</tbody>
</table>

![Graph of HPLC Results](image)
HPLC data compound 43: Chiralpak AD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee

![HPLC graph]

<table>
<thead>
<tr>
<th>Inj. Number</th>
<th>Peak Name</th>
<th>R. Time</th>
<th>Area</th>
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</table>

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HPLC data compound 44: Chiralpak IB 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 96% ee
HPLC data compound 45: Chiralcel OD-H 10% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 98% ee
HPLC data compound 46: Chiralpak AD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee

![HPLC Chromatogram](image-url)
HPLC data compound 47: Chiralpak IB 5% IPA:hexane, 1 mL min$^{-1}$, 211 nm, 97% ee
HPLC data compound 48: Chiralpak AD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 97% ee

![Graph of HPLC data for compound 48]
HPLC data compound 49: Chiralpak AD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 92% ee
HPLC data compound 50: Chiralpak AD-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 98% ee
HPLC data compound 51: Chiralpak IB 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee
HPLC data compound 52: Chiralpak AD-H 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 98% ee
HPLC data compound 64: Chiralpak IB 5% IPA:hexane, 1 mL min\(^{-1}\), 211 nm, 30 °C, 99% ee
HPLC data compound 65: Chiralcel OJ-H 5% IPA:hexane, 1 mL min⁻¹, 211 nm, 30 °C, 99% ee
$^1$H, CDCl$_3$, 300 MHz
$^{13}$C, CDCl$_3$, 100 MHz
$^{1}H, CDCl_{3}, 400 MHz$
13C, CDCl3, 100 MHz
**1H, CDCl₃, 300 MHz**

**15**

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Electronic Supplementary Material (ESI) for Chemical Science

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$^{1}H$, CDCl$_3$, 300 MHz

$^{1}H$, CDCl$_3$, 300 MHz

[Chemical structure and NMR spectrum with peak assignments]
$^1$H, CDCl$_3$, 300 MHz
$^{1}H$, CDCl$_3$, 300 MHz

Electronic Supplementary Material (ESI) for Chemical Science
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$^1$H, CDCl$_3$, 400 MHz
$^{1}$H, CDCl$_3$, 400 MHz
$^1$H, CDCl$_3$, 400 MHz
$^1$H, CDCl$_3$, 400 MHz
1H, CDCl₃, 400 MHz

Electronic Supplementary Material (ESI) for Chemical Science
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$^{13}$C, CDCl$_3$, 75 MHz

Electronic Supplementary Material (ESI) for Chemical Science
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$^{13}$C, CDCl$_3$, 100 MHz
$^{1}H$, CDCl$_3$, 400 MHz
$^1$H, CDCl$_3$, 400 MHz
$^{13}$C, CDCl$_3$, 125 MHz
$^{1}$H, CDCl$_3$, 300 MHz
$^{1}H$, CDCl$_3$, 400 MHz

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$\text{Ph}$ $\text{O}$ $\text{CF}_3$

$^{1}H, \text{CDCl}_3, 400 \text{ MHz}$
$^1$H, CDCl$_3$, 400 MHz
\[ ^{1}H, CDCl_3, 500 \text{ MHz} \]
$\text{OMe}$

$\text{O}$

$\text{Ph}$

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

$\text{O}$

$\text{Me}$

$^{1}\text{H}, \text{CDCl}_3, 300 \text{ MHz}$

Electronic Supplementary Material (ESI) for Chemical Science

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$^1$H, CDCl$_3$, 300 MHz

3.01
2.02
1.05
2
2.99
1
0.997
1
3.15
2.02
3.01
Electronic Supplementary Material (ESI) for Chemical Science
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$^1$H, CDCl$_3$, 300 MHz
$^{13}$C, CDCl$_3$, 100 MHz
$^1$H, CDCl$_3$, 400 MHz
Electronic Supplementary Material (ESI) for Chemical Science

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$^1$H, CDCl$_3$, 400 MHz
Electronic Supplementary Material (ESI) for Chemical Science
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$^1$H, CDCl$_3$, 300 MHz
$^1$H, CDCl$_3$, 500 MHz
$^{1}$H, CDCl$_3$, 500 MHz

Ph$_3$CF$_3$
Electronic Supplementary Material (ESI) for Chemical Science

1H, CDCl3, 400 MHz
$^1$H, CDCl$_3$, 75 MHz

$^{13}$C, CDCl$_3$, 75 MHz
$^{1}H$, CDCl$_3$, 300 MHz
Electronic Supplementary Material (ESI) for Chemical Science
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1H, CDCl₃, 400 MHz

Ph, Ph' OH

O

CF₃Ph

65
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The image shows a 13C NMR spectrum of a compound with the formula shown below. The spectrum was recorded in CDCl₃ at 125 MHz. The chemical shifts are indicated at ppm, and the peaks correspond to the various carbon atoms in the molecule.

The structural formula of the compound includes a bromine (Br) atom and a trifluoromethyl (CF₃) group. The spectrum contains several peaks, with chemical shifts ranging from 75 ppm to approximately 180 ppm.