Supporting Information

for

NHC-catalyzed enantioselective synthesis of β-trifluoromethyl-β-hydroxyamides

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Experimental procedures, product characterization data (mp, NMR, IR, HRMS, [α]D, HPLC), and spectra (1H, 13C, and 19F NMR, HPLC)
General Experimental

Reactions carried out under a nitrogen atmosphere were done so using standard vacuum line
techniques. All reaction glassware was flame-dried and cooled under vacuum prior to use.

Anhydrous THF were obtained and purified by an alumina column (Mbraun SPS-800). Anhydrous
methanol was obtained by distillation over calcium hydride. All commercial reagents were used as
supplied without further purification.

Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60
F_{254} silica). TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining
with a 1% aqueous KMnO_{4} solution. Flash column chromatography was performed on Kieselgel 60
silica in the solvent system stated.

\(^1\)H, \(^{13}\)C and \(^{19}\)F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance
II 400 (\(^1\)H 400 MHz; \(^{13}\)C 101 MHz; \(^{19}\)F 376 MHz), Bruker Avance 500 (\(^1\)H 500 MHz; \(^{13}\)C 126 MHz;
\(^{19}\)F 471 MHz) or a Bruker Avance III 500 (\(^1\)H 500 MHz; \(^{13}\)C 126 MHz; \(^{19}\)F 471 MHz) spectrometer at
ambient temperature in the deuterated solvent stated. All chemical shifts are quoted in parts per
million (ppm) relative to the residual solvent. All coupling constants, \(J\), are quoted in Hz and
determined by analysis using MestReNova v9.0.1 software. Multiplicities are indicated by: s (singlet),
d (doublet), t (triplet) and q (quartet), and combinations of these. The abbreviation Ar is used to
denote aromatic.

Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer
fitted with a Specac Quest ATR accessory (diamond puck). Spectra were recorded of either thin films
or solids, with characteristic absorption wavenumbers (\(\nu_{max}\)) reported in cm\(^{-1}\).

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

HPLC analyses were obtained on a Shimadzu HPLC consisting of a Shimadzu DGU-20A5 degasser,
Shimadzu LC-20AT liquid chromatograph, Shimadzu SIL-20AT auto sampler, Shimadzu CBM-20A
communications bus module, Shimadzu SPD-M20A diode array detector, Shimadzu CTO-20A
column oven and a Shimadzu FRC-10A fraction collector. Analysis was performed using Shimadzu
LabSolutions v5.42 software and separation was achieved using the column described.

GC analyses were obtained on a Shimadzu GC consisting of a Shimadzu AOC-20i auto injector and a
Shimadzu GC-2025 gas chromatograph. Analysis was performed using Shimadzu GCsolution v2.41
software and separation was achieved using the column described.

Mass spectrometry (\(m/z\)) data were acquired by electrospray ionisation (ESI) or atmospheric pressure
chemical ionisation (APCI) at the EPSRC UK National Mass Spectrometry Facility at Swansea
University. 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 PerkinElmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell.

Starting Materials

NHC precatalyst 3\(^{(1)}\) and \(\alpha\)-aryloxyaldehydes 4, S1 and S2\(^{(2)}\) were synthesised as previously reported. Trifluoromethylketones S3–S7 were purchased from the suppliers stated below.
NHC Catalyzed Formal [2+2] Cycloadditions

General procedure A: NHC Catalyzed Formal [2+2] Cycloadditions with trifluoromethylketones, followed by Amine Ring Opening

Following a similar procedure to that described previously,[3] α-aryloxyaldehyde (1.5 eq.), trifluoromethylketone (1.0 eq.) and precatalyst 3 (0.1 eq.) were dissolved in anh. THF (0.05 M) in a flame-dried flask containing molecular sieves (4Å) under an N₂ atmosphere at room temperature. Caesium carbonate (1.1 eq.) was added and the reaction was allowed to stir for 24 h. The mixture was diluted with Et₂O, washed with sat. aq. NH₄Cl and sat. aq. NaHCO₃. The organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo to give a residue which was dissolved in anh. THF (0.1 M). The specified amine nucleophile (5.0 eq.) and NEt₃ (1.1 eq.) were added and the solution was allowed to stir for 24 h. The mixture was diluted with Et₂O, washed with sat. aq. NH₄Cl and brine. The organic layer was dried (Na₂SO₄), filtered and concentrated in vacuo to leave the crude product, which was purified by column chromatography on silica.

Racemic samples of all products were synthesised by the same method using a racemic sample of precatalyst 3.

(2S,3S)-N-Allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (7)

The preparation, characterization data and chiral GC analysis, along with the corresponding NMR and GC traces, for compound 7 can be found in our previous publication.[3]

(2S,3S)-N-Benzyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (8)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), trifluoroacetophenone 5 (140 µL, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24h; followed by benzylamine (0.55 mL, 5.0 mmol), NEt₃ (139 µL, 1.00 mmol) and THF (10 mL) for a further 24 h gave the crude product (75:25 dr), which
was purified by column chromatography on silica (20% Et<sub>2</sub>O in hexane) to give (2S,3S)-N-benzyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide 8 as a pale yellow solid (single diastereoisomer, 161 mg, 0.477 mmol, 48%).

**mp 102−104 °C; [α]<sup>20</sup><sub>D</sub> +38.0 (c 0.5, CHCl<sub>3</sub>): Chiral HPLC analysis**; Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mL min<sup>−1</sup>, 211 nm, 30 °C) t<sub>R</sub> minor (2R,3R): 23.0 min, t<sub>R</sub> major (2S,3S): 24.8 min, 96:4 er; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ<sub>CH</sub> 1.00 (3H, d, J 7.0, CH<sub>2</sub>CH), 2.96 (1H, q, J 7.0, CH<sub>3</sub>CH), 4.33−4.66 (2H, m, NHCH<sub>2</sub>), 6.37 (1H, t, J 5.7, NH), 6.74 (1H, s, OH), 7.27−7.44 (8H, m, ArH); 13C<sup>1</sup>H NMR (101 MHz, CDCl<sub>3</sub>) δ C: 13.9 (CH<sub>3</sub>CH), 41.8 (CH<sub>2</sub>CH), 43.7 (NHCH<sub>2</sub>), 78.4 (q, J 27.4, CFC<sub>3</sub>), 125.8 (q, J 288.4, CF<sub>3</sub>), 126.0 (C(3)ArC(2,6)), 127.9 (CH<sub>2</sub>ArC(2,6)H), 127.9 (ArCH), 128.4 (2 × ArCH), 128.5 (ArCH), 136.0 (C(3)ArC(1)), 137.1 (CH<sub>2</sub>ArC(1)), 175.8 (C=O); <sup>19</sup>F<sup>1</sup>H NMR (376 MHz, CDCl<sub>3</sub>) δ F: −76.7 (CF<sub>3</sub>); IR ν<sub>max</sub> (film)/cm<sup>−1</sup>: 3397 (O−H), 1647 (C=O); HRMS (APCI<sup>+</sup>) C<sub>18</sub>H<sub>19</sub>F<sub>3</sub>O<sub>2</sub>N ([M+H]<sup>+</sup>), found 338.1362, requires 338.1362 (−0.1 ppm).

(2S,3S)-4,4,4-Trifluoro-3-hydroxy-2-methyl-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (9)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), trifluorooctethophenone 5 (140 µL, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24 h; followed by pyrrolidine (0.42 mL, 5.0 mmol), NEt<sub>3</sub> (139 µL, 1.00 mmol) and THF (10 mL) for a further 24 h gave the crude product (75:25 dr), which was purified by column chromatography on silica (30% Et<sub>2</sub>O in hexane) to give (2S,3S)-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one 9 as a colourless crystalline solid (single diastereoisomer, 166 mg, 0.551 mmol, 55%).

**mp 122−125 °C; [α]<sup>20</sup><sub>D</sub> +45.1 (c 0.5, CHCl<sub>3</sub>): Chiral HPLC analysis**; Chiralcel OD-H (90:10 hexane : 2-propanol, flow rate 1 mL min<sup>−1</sup>, 211 nm, 30 °C) t<sub>R</sub> minor (2R,3R): 5.3 min, t<sub>R</sub> major (2S,3S): 5.9 min, 96:4 er; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ<sub>CH</sub> 0.92 (3H, d, J 7.0, CH<sub>2</sub>CH), 1.88−1.97 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 1.97−2.12 (2H, m, NCH<sub>2</sub>CH<sub>2</sub>), 3.29 (1H, q, J 7.0, CH<sub>2</sub>CH), 3.46−3.62 (3H, m, NCH<sub>2</sub> and NCH<sub>2</sub>H<sub>2</sub>), 3.68 (1H, dt, J 9.8, 7.0, NCH<sub>2</sub>H<sub>2</sub>), 7.33−7.44 (4H, m, ArC(2,3,5,6)H), 7.54−7.64 (2H, m, ArC(4)H and OH); 13C<sup>1</sup>H NMR (101 MHz, CDCl<sub>3</sub>) δ C: 13.2 (CH<sub>2</sub>CH), 24.3 (NCH<sub>2</sub>CH<sub>2</sub>), 26.0 (NCH<sub>2</sub>CH<sub>2</sub>), 38.0 (CH<sub>2</sub>CH), 46.0 (NCH<sub>2</sub>), 46.8 (NCH<sub>2</sub>), 78.2 (q, J 27.2, CFC<sub>3</sub>), 126.0 (q, J 288.7, CF<sub>3</sub>), 126.2 (ArC(2,6)H), 128.28 (ArC(3,5)H), 128.34 (ArC(4)H), 136.5 (ArC(1)), 174.3 (C=O);
\(^{19}\text{F}\{^{1}\text{H}\}\text{ NMR}\) (471 MHz, CDCl\(_{3}\)) \(\delta_{F}: -77.1\) (CF\(_{3}\)); \(\text{IR} \ \nu_{\text{max}}\) (film)/cm\(^{-1}\): 3063 (O–H), 1617 (C=O); \(\text{HRMS}\) (APCI\(^{+}\)) \(\text{C}_{13}\text{H}_{16}\text{F}_{3}\text{O}_{2}\text{N}\) ([M+H]\(^{+}\)), found 302.1362, requires 302.1362 (–0.1 ppm).

\((2S,3S)-4,4,4\text{-Trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (10)}\)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), trifluoroacetophenone 5 (140 \(\mu\)L, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24h; followed by ammonia (7 \(\text{M}\) in MeOH, 0.71 mL, 5.00 mmol), NEt\(_{3}\) (139 \(\mu\)L, 1.00 mmol) and THF (10 mL) for a further 24 h gave the crude product (735:25 dr), which was purified by column chromatography on silica (40\% Et\(_{2}\)O in hexane) to give \((2S,3S)-4,4,4\text{-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide 10}\) as a colourless solid (single diastereoisomer, 104 mg, 0.419 mmol, 42\%).

\(\text{mp} \ 149–151\ ^{\circ}\text{C}; \ [\alpha]^{20}_{D} +17.4\ (c\ 0.5, \text{CHCl}_{3})\); \(\text{Chiral GC analysis}\) Restek Rt\(^{\circ}\)bDEXcst (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 \(\mu\)m), carrier gas: He, linear velocity: 60 cm/sec, temperature: 160 \(^{\circ}\text{C} \ t_{R}\) minor \((2R,3R)\) 44.0 min, \(t_{R}\) major \((2S,3S)\) 45.6 min, > 99:1 er; \(^{1}\text{H NMR}\) (400 MHz, CDCl\(_{3}\)) \(\delta_{H}: 1.00\) (3H, d, \(J\ 7.0\), CH\(_{3}\)CH), 3.01 (1H q, \(J\ 7.0\), CH\(_{3}\)CH), 5.96 (1H, s, NH), 6.14 (1H, s, NH), 6.53 (1H, s, OH), 7.32–7.46 (3H, m, ArC(3,4,5)\(H\)), 7.56 (2H, dd, \(J\ 7.3, 1.8\), ArC(2,6)\(H\)); \(^{13}\text{C}\{^{1}\text{H}\}\text{ NMR}\) (101 MHz, CDCl\(_{3}\)) \(\delta_{C}: 13.8\) (CH\(_{3}\)CH), 40.9 (CH\(_{2}\)CH), 78.3 (q, \(J\ 27.4\), CCF\(_{3}\)), 125.7 (q, \(J\ 288.2\), CF\(_{3}\)), 126.0 (ArC(2,6)\(H\)), 128.4 (ArC(3,5)\(H\)), 128.5 (ArC(4)\(H\)), 135.9 (ArC(1)), 178.7 (C=O); \(^{19}\text{F}\{^{1}\text{H}\}\text{ NMR}\) (376 MHz, CDCl\(_{3}\)) \(\delta_{F}: -76.9\) (CF\(_{3}\)); \(\text{IR} \ \nu_{\text{max}}\) (film)/cm\(^{-1}\): 3200 (O–H), 1668 (C=O); \(\text{HRMS}\) (APCI\(^{+}\)) \(\text{C}_{13}\text{H}_{16}\text{F}_{3}\text{O}_{2}\text{N}\) ([M+H]\(^{+}\)), found 248.0893, requires 248.0893 (+0.0 ppm).

\((2R,3S)-4,4,4\text{-Trifluoro-2-methyl-3-phenylbutane-1,3-diol (11)}\)

Following a \textit{modification of general procedure A}, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), trifluoroacetophenone 5 (140 \(\mu\)L, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24h. The crude product was then dissolved in MeOH (10 mL), DMAP (24 mg, 0.20 mmol) was added, and the reaction allowed to stir for 24 h. The solvent was removed \textit{in vacuo} and the crude product was treated with lithium aluminium hydride (2 \text{M}
in PhMe, 2 mL, 4.00 mmol) under a N₂ atmosphere, and allowed to stir for a further 24 h. The reaction was quenched by slow addition of 1 m KOH, and the mixture extracted using EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried (Na₂SO₄), filtered and concentrated in vacuo to give the crude product (75:25 dr), which was purified by column chromatography on silica (15% Et₂O in hexane) to give (2R,3S)-4,4,4-trifluoro-2-methyl-3-phenylbutane-1,3-diol 11 as an orange oil (single diastereoisomer, 113 mg, 0.483 mmol, 48%).

\[ \alpha \]D \text{ } 20 \text{ } -39.4 \text{ } (c \text{ } 0.5, \text{ } CHCl₃); \text{ Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 30 cm/sec, temperature: 135 °C, } t_r \text{ minor } (2S,3R) 50.8 \text{ min, } t_r \text{ major } (2R,3S) 51.8 \text{ min, 96:4 er; } ^{1}H \text{ NMR (400 MHz, CDCl₃) } \delta_H: 0.90 \text{ (3H, d, } J 7.2, \text{ } CH₂CH), 2.11 \text{ (1H, s, CH₂OH), 2.35–2.53 (1H, m, CH₃CH), 3.83 (1H, dt, } J 10.8, 1.8, \text{ } CH₂H₃OH), 4.41 (1H, d, } J 10.7, \text{ } CH₂H₃OH), 5.20 (1H, s, F₃CCO), 7.31–7.43 (3H, m, ArC(3,4,5)H), 7.55 (2H, d, } J 7.7, \text{ } ArC(2,6)H); ^{13}C \text{ NMR (101 MHz, CDCl₃) } \delta_C: 12.6 \text{ (CH₂CH), 37.8 (CH₃CH), 66.0 (CH₂OH), 80.4 (q, } J 27.1, \text{ } CCF₃), 125.6 \text{ (ArC(2,6)H), 126.2 (q, } J 287.9, \text{ } CF₃), 128.0 \text{ (ArC(4)H), 128.2 (ArC(3,5)H), 138.2 (ArC(1)); } ^{19}F \text{ NMR (376 MHz, CDCl₃) } \delta_F: -74.7 \text{ (CF₃); IR } \nu_{\text{max}} \text{ (film)/cm}^{-1}: 3372 \text{ (O–H); HRMS (APCI⁺) } C_{11}H_{14}F_3O_2 [(M+H)⁺], \text{ found } 235.0934, \text{ requires } 235.0940 \text{ (–2.7 ppm).}

(2S,3S)-N-Allyl-3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxy-2-methylbutanamide (12)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (167 mg, 0.750 mmol), 1-(4-bromophenyl)-2,2,2-trifluoroethan-1-one S3 (127 mg, 0.500 mmol), precatalyst 3 (18 mg, 50 µmol), caesium carbonate (179 mg, 0.550 mmol) and THF (10 mL) for 24 h; followed by allylamine (188 µL, 2.50 mmol), NEt₃ (70 µL, 0.50 mmol) and THF (5 mL) for a further 24 h gave the crude product (75:25 dr), which was purified by column chromatography on silica (30% Et₂O in hexane) to give (2S,3S)-N-allyl-3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxy-2-methylbutanamide 12 as a colourless crystalline solid (single diastereoisomer, 111 mg, 0.304 mmol, 61%).

mp 107–108 °C; \[ \alpha \]D \text{ } 20 \text{ } +22.6 \text{ } (c \text{ } 0.5, \text{ } CHCl₃); \text{ Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 190 °C, } t_r \text{ minor } (2R,3R) 29.9 \text{ min, } t_r \text{ major } (2S,3S) 30.6 \text{ min, 99:1 er; } ^{1}H \text{ NMR (400 MHz, CDCl₃) } \delta_H: 0.97 \text{ (3H, d, } J 7.0, \text{ } CH₃), 2.88 \text{ (1H, q, } J 7.0, \text{ } CH₃CH), 3.74–4.12 \text{ (2H, m, NHCH₂), 5.06–5.37 (2H, m, HC=CH₂), 5.85 (1H, dt, } J 17.2, 10.2, 5.7, \text{ } HC=CH₂), 6.10 (1H, t, } J 5.8, \text{ } NH), 6.75
(1H, s, OH), 7.43 (2H, d, J 8.4, ArC(3,5)H), 7.53 (2H, d, J 8.8, ArC(2,6)H); $^{13}$C$^1$H NMR (126 MHz, CDCl$_3$) δc: 13.9 (CH$_3$), 41.6 (CH$_2$CH), 42.0 (NHCH$_2$), 78.2 (q, J 27.6, CCF$_3$), 117.4 (HC=CH$_2$), 122.9 (ArC(4)), 125.5 (q, J 288.4, CF$_3$), 127.9 (ArC(3,5)H), 131.6 (ArC(2,6)H), 132.9 (HC=CH$_3$), 135.2 (ArC(1)), 175.5 (C=O); $^{19}$F$^1$H NMR (376 MHz, CDCl$_3$) δf: −76.9 (CF$_3$); IR ν$_{max}$ (film)/cm$^{-1}$: 3302 (O–H), 1634 (C=O); HRMS (ESI$^+$) C$_{14}$H$_{16}$BrF$_3$NO$_2$ ([M+H]$^+$), found 366.0314, requires 366.0311 (+0.8 ppm).

(2S,3S)-N-allyl-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-2-methylbutanamide (13)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (167 mg, 0.750 mmol), 2,2,2-trifluoro-1-(4-fluorophenyl)ethan-1-one S4 (70 µL, 0.50 mmol), precatalyst 3 (18 mg, 50 µmol), caesium carbonate (179 mg, 0.550 mmol) and THF (10 mL) for 24h; followed by allylamine (188 µL, 2.50 mmol), NEt$_3$ (70 µL, 0.50 mmol) and THF (5 mL) for a further 24 h gave the crude product (75:25 dr), which was purified by column chromatography on silica (30% Et$_2$O in hexane) to give (2S,3S)-N-allyl-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-2-methylbutanamide 13 as a colourless crystalline solid (single diastereoisomer, 109 mg, 0.357 mmol, 71%).

mp 90–92 °C; [α]$_D^{20}$ +19.2 (c 0.5, CHCl$_3$); Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 157 °C, t$_r$ minor (2R,3R) 40.1 min, t$_r$ major (2S,3S) 41.1 min, 97:3 er; $^1$H NMR (400 MHz, CDCl$_3$) δH: 0.97 (3H, d, J 7.0, CH$_3$CH), 2.89 (1H, q, J 7.0, CH$_2$CH), 5.12–5.32 (2H, m, HC=CH$_2$), 5.85 (1H, ddt, J 17.2, 10.2, 5.7, HC=CH$_2$), 6.05 (1H, s, NH), 6.71 (1H, s, OH), 7.08 (2H, dd, J 9.1, 8.4, ArC(3,5)H), 7.54 (2H, dd, J 8.6, 5.3, ArC(2,6)H); $^{13}$C$^1$H NMR (101 MHz, CDCl$_3$) δC: 13.8 (CH$_3$CH), 41.8 (CH$_2$CH), 42.0 (NHCH$_2$), 78.1 (q, J 27.6, CCF$_3$), 115.3 (d, J 21.5, ArC(3,5)H), 117.4 (HC=CH$_2$), 125.6 (q, J 288.3, CF$_3$), 128.0 (d, J 8.1, ArC(2,6)H), 131.8 (d, J 3.2, ArC(1)), 133.0 (HC=CH$_2$), 162.7 (d, J 247.7, ArC(4)), 175.5 (C=O); $^{19}$F$^1$H NMR (377 MHz, CDCl$_3$) δF: −113.7 (ArC(4)F), −77.1 (CF$_3$); IR ν$_{max}$ (film)/cm$^{-1}$: 3306 (O–H), 1622 (C=O); HRMS (ESI$^+$) C$_{14}$H$_{16}$BrF$_3$NO$_2$Na ([M+Na]$^+$), found 328.0932, requires 328.0931 (+0.3 ppm).
(2S,3S)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(4-(trifluoromethyl)phenyl)butanamide (14)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (167 mg, 0.750 mmol), 2,2,2-trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-one S5 (84 µL, 0.50 mmol), precatalyst 3 (18 mg, 50 µmol), caesium carbonate (179 mg, 0.550 mmol) and THF (10 mL) for 24 h; followed by allylamine (188 µL, 2.50 mmol), NEt3 (70 µL, 0.50 mmol) and THF (5 mL) for a further 24 h gave the crude product (75:25 dr), which was purified by column chromatography on silica (30% Et2O in hexane) to give (2S,3S)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(4-(trifluoromethyl)phenyl)butanamide 14 as a colourless crystalline solid (single diastereoisomer, 105 mg, 0.295 mmol, 59%).

mp 86–87 °C; [α]D20 +14.6 (c 0.5, CHCl3); Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 40 cm/sec, temperature: 165 °C, tr minor (2R,3R) 40.0 min, tr major (2S,3S) 40.7 min, 95:5 er; 1H NMR (500 MHz, CDCl3) δH: 0.97 (3H, d, J 7.0, CH3(CH)), 2.94 (1H, q, J 7.0, CH3(CH)), 3.85–4.09 (2H, m, NHCH3), 5.15–5.34 (2H, m, HC=CH2), 5.86 (1H, ddt, J 17.2, 10.3, 5.7, HC=CH2), 6.08 (1H, t, J 5.9, NH), 6.83 (1H, s, OH), 7.59–7.80 (4H, m, ArH); 13C{1H} NMR (126 MHz, CDCl3) δC: 13.9 (CH3(CH)), 41.6 (CH3(CH)), 42.0 (NHCH3), 78.3 (q, J 27.6, CCF3), 117.4 (HC=CH2), 123.9 (q, J 272.2, CF3), 125.4 (q, J 3.3, ArC(3,5)H), 125.5 (q, J 288.6, CF3), 126.6 (ArC(2,6)H), 130.8 (q, J 32.6, ArC(4)), 132.9 (HC=CH2), 140.1 (ArC(1)), 175.3 (C=O); 19F{1H} NMR (471 MHz, CDCl3) δF: –76.8 (CF3), –62.7 (ArCF3); IR νmax (film)/cm⁻¹: 3323 (O–H), 1641 (C=O); HRMS (APCI') C15H16F6O2N ([M+H]+), found 356.1079, requires 356.1080 (±0.2 ppm).

(2S,3S)-N-Allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(p-tolyl)butanamide (15)

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), 2,2,2-trifluoro-1-(p-tolyl)ethan-1-one S6 (152 µL, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24 h; followed by allylamine (0.38 mL, 5.0 mmol), NEt3 (139 µL, 1.00 mmol) and THF (10 mL) for a further 24 h gave the crude product (75:25
dr), which was purified by column chromatography on silica (25% Et₂O in hexane) to give (2S,3S)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(p-tolyl)butanamide 15 as a colourless crystalline solid (single diastereoisomer, 139 mg, 0.460 mmol, 46%).

\[ \text{mp 108–110 °C; } [\alpha]_D^{10} +23.0 (c 0.5, CHCl}_3; \] ¹H NMR (500 MHz, CDCl₃) δH: 0.98 (3H, d, J 7.0, CH₃(CH), 2.36 (3H, s, ArC(4)H), 2.90 (1H, q, J 7.0, CH₂CH), 3.78–4.10 (2H, m, NHCH₃), 5.07–5.38 (2H, m, HC=CH₂), 5.86 (1H, ddt, J 16.3, 10.8, 5.7, HC=CH₂), 6.04 (1H, t, J 6.0, NH), 6.58 (1H, s, OH), 7.20 (2H, d, J 8.0, ArC(3,5)H), 7.43 (2H, d, J 7.9, ArC(2,6)H); ¹³C[¹H] NMR (471 MHz, CDCl₃) δC: −77.0; ¹⁹F[¹H] NMR (101 MHz, CDCl₃) δF: 0.98 (3H, d, J 7.0, CH₃(CH), 2.36 (3H, s, ArC(4)H), 2.90 (1H, q, J 7.0, CH₂CH), 3.78–4.10 (2H, m, NHCH₃), 5.07–5.38 (2H, m, HC=CH₂), 5.86 (1H, ddt, J 16.3, 10.8, 5.7, HC=CH₂), 6.04 (1H, t, J 6.0, NH), 6.58 (1H, s, OH), 7.20 (2H, d, J 8.0, ArC(3,5)H), 7.43 (2H, d, J 7.9, ArC(2,6)H); IR νmax (film)/cm⁻¹: 3356 (O=H), 1647 (C=O); HRMS (APCI⁺) C₁₅H₁₉F₃O₂N [M+H⁺], found 302.1365, requires 302.1362 (+0.9 ppm).

*No separation of the enantiomers could be obtained using Chiral GC or HPLC.*

(2S,3R)-N- Allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(thiophen-2-yl)butanamide (16)

\[
\begin{align*}
\text{MeC₆H₄} & \text{N} \text{H} \\
\text{S} & \text{C} \text{F}_3 \\
\text{OH} & \text{CH} \\
\text{MeC₆H₄} \text{N} & \text{H} \text{C} \text{F}_3 \\
\end{align*}
\]

Following general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (167 mg, 0.750 mmol), 2,2,2-trifluoro-1-(thiophen-2-yl)ethan-1-one S7 (64 µL, 0.50 mmol), precatalyst 3 (18 mg, 50 µmol), caesium carbonate (179 mg, 0.550 mmol) and THF (10 mL) for 24h; followed by allylamine (188 µL, 2.50 mmol), NEt₃ (70 µL, 0.50 mmol) and THF (5 mL) for a further 24 h gave the crude product (80:20 dr), which was purified by column chromatography on silica (20% Et₂O in hexane) to give (2S,3R)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(thiophen-2-yl)butanamide 16 as a colourless crystalline solid (single diastereoisomer, 76 mg, 0.26 mmol, 51%).

\[ \text{mp 108–109 °C; } [\alpha]_D^{10} +14.6 (c 0.5, CHCl}_3; \text{ Chiral GC analysis Agilent Cyclosil-B (length: 30 m, } \\
\text{thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 60 cm/sec, } \\
\text{temperature: 160 °C, } \text{tR minor (2R,3R) 33.6 min, } \text{tR major (2S,3S) 34.5 min, 96:4 dr; } \text{¹H NMR (400 MHz, CDCl}_3) \deltaH: 1.09 (3H, d, J 7.0, CH₃(CH), 2.81 (1H, q, J 7.0, CH₂CH), 3.78–4.12 (2H, m, NHCH₃), 5.11–5.34 (2H, m, HC=CH₂), 5.84 (1H, ddt, J 17.2, 10.3, 5.8, HC=CH₂), 5.97 (1H, s, NH), 6.84 (1H, s, OH), 7.00–7.07 (2H, m, ArC(3,5)H), 7.30–7.37 (1H, m, ArC(4)H); ¹³C[¹H] NMR (126 MHz, CDCl₃) δC: 14.0 (CH₃), 42.0 (NHCH₂), 43.1 (CH₂CH), 78.4 (q, J 28.9, CCF₃), 117.4 (HC=CH₂), 124.5 (ArC(3)H or ArC(5)H), 125.2 (q, J 287.8, CCF₃), 125.9 (ArC(4)H), 127.2 (ArC(3)H or ArC(5)H), \]

S10
133.0 (HC=CH₂), 140.3 (Ar(C(2))), 175.4 (C=O); \[^{19}F\text{(H)}\] NMR (376 MHz, CDCl₃) δF: −78.5 (CF₃); IR νmax (film)/cm⁻¹: 3341 (O–H), 1638 (C=O); HRMS (ESI⁺) C₁₂H₁₅F₃NO₂S ([M+H]⁺), found 294.0773, requires 294.0770 (+1.0 ppm).

(2S,3S)-N-Allyl-2-benzyl-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide (17)

Following general procedure A, 1-oxo-3-phenylpropan-2-yl 4-nitrobenzoate S₁ (449 mg, 1.50 mmol), trifluoroacetophenone S (140 µL, 1.00 mmol), precatalyst 3 (37 mg, 0.10 mmol), caesium carbonate (358 mg, 1.10 mmol) and THF (20 mL) for 24h; followed by allylamine (0.38 mL, 5.0 mmol), NEt₃ (139 µL, 1.00 mmol) and THF (10 mL) for a further 24h gave the crude product (70:30 dr), which was purified by column chromatography on silica (20% Et₂O in hexane) to give (2S,3S)-N-allyl-2-benzyl-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide 17 as a colourless crystalline solid (single diastereoisomer, 125 mg, 0.343 mmol, 34%).

mp 126–128 °C; [α]D²⁰ +31.1 (c 0.5, CHCl₃); Chiral HPLC analysis; Chiralcel OD-(H): 95:5 hexane : 2-propanol, flow rate 1 mL/min, 211 nm, 30 °C) tᵣ minor (2R,3R): 5.7 min, tᵣ major (2S,3S): 7.1 min, 99:1 er; \[^{1}H\] NMR (400 MHz, CDCl₃) δH: 2.39 (1H, dd, J 12.9, 2.8, CH₃H₆CH), 2.80–2.90 (1H, m, CH₃H₆CH), 2.94 (1H, dd, J 11.9, 2.8, CH₂CH₂), 3.72 (2H, tt, J 5.6, 1.4, NHCH₂), 4.89 (1H, dd, J 17.1, 1.4, HC=CH₃H₆H), 5.00 (1H, dd, J 10.3, 1.3, HC=CH₃H₆H), 5.35 (1H, t, J 4.7, NH), 5.49 (1H, ddt, J 17.2, 10.3, 5.8, HC=CH₂), 6.69 (1H, s, OH), 6.96–7.03 (2H, m, ArH), 7.15–7.26 (3H, m, ArH), 7.38–7.44 (1H, m, ArH), 7.45–7.53 (2H, m, ArH), 7.68 (2H, d, J 7.6, C(3)ArC(2,6)H); \[^{13}C\text{(H)}\] NMR (126 MHz, CDCl₃) δC: 34.3 (CH₃CH₂), 41.8 (NHCH₂), 51.3 (CH₂CH₂), 78.4 (q, J 27.3, CCF₃), 117.1 (HC=CH₂), 125.5 (q, J 288.6, CF₃), 125.9 (C(3)ArC(2,6)H), 126.8 (ArCH), 128.63 (2 × ArCH), 128.65 (2 × ArCH), 128.68 (ArCH), 128.8 (2 × ArCH), 132.8 (HC=CH₂), 136.2 (C(3)ArC(1)), 138.2 (CH₂ArC(1)), 173.6 (C=O); \[^{19}F\text{(H)}\] NMR (376 MHz, CDCl₃) δF: −76.5 (CF₃); IR νmax (film)/cm⁻¹: 3312 (O–H), 1628 (C=O); HRMS (ESI⁺) C₂₀H₂₁F₃NO₂ ([M+H]⁺), found 364.1518, requires 364.1519 (−0.2 ppm).
Following general procedure A, 4-(benzyloxy)-1-oxobutan-2-yl 4-nitrobenzoate \( S_2 \) (258 mg, 0.750 mmol), trifluoroacetophenone \( 5 \) (70 \( \mu \)L, 0.50 mmol), precatalyst \( 3 \) (18 mg, 50 \( \mu \)mol), caesium carbonate (179 mg, 0.550 mmol) and THF (10 mL) for 24h; followed by allylamine (188 \( \mu \)L, 2.50 mmol), \( \text{NEt}_3 \) (70 \( \mu \)L, 0.50 mmol) and THF (5 mL) for a further 24 h gave the crude product (70:30 dr), which was purified by column chromatography on silica (20\% \( \text{Et}_2 \text{O} \) in hexane) to give \((2S,3S)\)-N-allyl-2-(2-(benzyloxy)ethyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide \( 18 \) as a colourless oil (single diastereoisomer, 70 mg, 0.17 mmol, 34\%).

\[ [\alpha]^{20}_D +26.5 \text{ (c 0.5, CHCl}_3) \] Chiral HPLC analysis: Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mLmin\(^{-1}\), 211 nm, 30 °C) \( t_\text{R} \) minor (2R,3R): 6.8 min, \( t_\text{R} \) major (2S,3S): 10.0 min, 96:4 er;

\[ ^1H \text{ NMR (400 MHz, CDCl}_3) \] \( \delta_H \): 1.42–1.52 (1H, m, \( CH_\text{H}_a CH \)), 1.79 (1H, ddt, \( J \) 14.7, 11.4, 3.4, \( CH_\text{H}_a CH \)), 3.12 (1H, dd, \( J \) 11.4, 3.4, \( CH_2 CH \)), 3.26–3.40 (2H, m, \( OC_\text{H}_2 CH \)), 3.65–3.76 (1H, m, \( NHC_\text{H}_a CH \)), 3.89–3.99 (1H, m, \( NHCH_\text{H}_a CH \)), 4.29 (1H, d, \( J \) 11.9, \( OCH_3 CH \)), 4.44 (1H, d, \( J \) 11.9, \( OCH_3 CH \)), 5.13–5.29 (2H, m, \( HC=CH \)), 5.77 (1H, ddt, \( J \) 17.1, 10.2, 5.8, \( HC=CH_2 \)), 5.90 (1H, t, \( J \) 6.0, \( NH \)), 6.65 (1H, s, \( OH \)), 7.24–7.45 (8H, m, \( ArH \)), 7.57 (2H, d, \( J \) 7.5, \( C(3)Ar CH(C(2,6)H) \)); \[ ^13C\{^1H\} \text{ NMR (126 MHz, CDCl}_3) \] \( \delta_C \): 27.8 (\( CH_2 CH \)), 42.0 (\( NHCH \)), 44.1 (\( CH_2 CH \)), 66.5 (\( OCH_3 CH \)), 72.8 (\( OCH_2 CH \)), 78.5 (q, \( J \) 27.4, \( CCF_3 \)), 117.4 (\( HC=CH_2 \)), 125.6 (q, \( J \) 288.5, \( CF_3 \)), 126.1 (\( C(3)Ar CH(C(2,6)H) \)), 127.9 (2 \( \times \) \( Ar CH \)), 128.0 (\( Ar CH \)), 128.4 (2 \( \times \) \( Ar CH \)), 128.5 (\( Ar CH \)), 128.6 (2 \( \times \) \( Ar CH \)), 133.2 (\( HC=CH_2 \)), 136.1 (\( C(3)Ar CH(C(1)) \)), 138.0 (\( OCH_2 Ar CH(C(1)) \)), 174.4 (\( C=O \)); \[ ^19F\{^1H\} \text{ NMR (376 MHz, CDCl}_3) \] \( \delta_F \): −76.7 (\( CF_3 \)); IR \( \nu_{\text{max}} \) (film)/cm\(^{-1}\): 3319 (O–H), 1628 (C=O); HRMS (APCI\(^+\)) \( C_{22}H_{25}F_3O_3N ([M+H]^+) \), found 408.1781, requires 408.1781 (+0.0 ppm).
$^1$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^1$H, 500 MHz, CDCl$_3$
$^{13}$C, 126 MHz, CDCl$_3$
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\[ ^1H, 400 \text{ MHz, CDCl}_3 \]
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}\text{F}, 376 \text{ MHz, CDCl}_3$
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$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
$^{1}$H, 400 MHz, CDCl$_3$
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$^{19}$F, 376 MHz, CDCl$_3$
$^1$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
BnO
\[\text{Ph}^2\text{OH} \quad \text{CF}_3\]

18

$^1$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
(2S,3S)-N-Benzyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (8)

Chiral HPLC analysis: Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tᵣ minor (2R,3R): 23.0 min, tᵣ major (2S,3S): 24.8 min, 96:4 er.
(2S,3S)-4,4,4-Trifluoro-3-hydroxy-2-methyl-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (9)

Chiral HPLC analysis: Chiralcel OD-H (90:10 hexane : 2-propanol, flow rate 1 mL min$^{-1}$, 211 nm, 30 °C) $t_R$ minor (2R,3R): 5.3 min, $t_R$ major (2S,3S): 5.9 min, 96:4 er.
(2S,3S)-4,4,4-Trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (10)

**Chiral GC analysis**
Restek Rt®bDEXcst (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 160 °C, $t_R$ minor (2\text{R},3\text{R}) 44.0 min, $t_R$ major (2\text{S},3\text{S}) 45.6 min, > 99:1 er.

*Peaks at 46.5 and 49.1 min in racemic trace belong to minor diastereoisomer*
(2R,3S)-4,4,4-Trifluoro-2-methyl-3-phenylbutane-1,3-diol (11)

**Chiral GC analysis** Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 30 cm/sec, temperature: 135 °C, $t_R$ minor (2S,3R) 50.8 min, $t_R$ major (2R,3S) 51.8 min, 96:4 er.
(2S,3S)-N-allyl-3-(4-bromophenyl)-4,4,4-trifluoro-3-hydroxy-2-methylbutanamide (12)

**Chiral GC analysis** Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 190 °C, $t_R$ minor (2R,3R) 29.9 min, $t_R$ major (2S,3S) 30.6 min, 99:1 er.
(2S,3S)-N-Allyl-4,4,4-trifluoro-3-(4-fluorophenyl)-3-hydroxy-2-methylbutanamide (13)

Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 157 °C, $t_R$ minor (2R,3R) 40.1 min, $t_R$ major (2S,3S) 41.1 min, 97:3 er.
(2S,3S)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(4-(trifluoromethyl)phenyl)butanamide (14)

Chiral GC analysis Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 40 cm/sec, temperature: 165 °C, t<sub>R</sub> minor (2R,3R) 40.0 min, t<sub>R</sub> major (2S,3S) 40.7 min, 95:5 er.
(2S,3R)-N-Allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(thiophen-2-yl)butanamide (16)

**Chiral GC analysis** Agilent Cyclosil-B (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 μm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 160 °C, t_r minor (2R,3R) 33.6 min, t_r major (2S,3S) 34.5 min, 96:4 er.
(2S,3S)-N-Allyl-2-benzyl-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide (17)

Chiral HPLC analysis: Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tᵣ minor (2R,3R): 5.7 min, tᵣ major (2S,3S): 7.1 min, 99:1 er.
(2S,3S)-N-Allyl-2-(2-(benzyloxy)ethyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide (18)

Chiral HPLC analysis: Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tᵣ minor (2R,3R): 6.8 min, tᵣ major (2S,3S): 10.0 min, 96:4 er.

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