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

NHC-Catalyzed Formal [2+2] Cycloadditions

NMR Traces

GC and HPLC Traces

References
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 F₅₂₅₄ 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, ¹³C and ¹⁹F nuclear magnetic resonance (NMR) spectra were acquired on either a Bruker Avance II 400 (¹H 400 MHz; ¹³C 101 MHz; ¹⁹F 376 MHz), Bruker Avance 500 (¹H 500 MHz; ¹³C 126 MHz; ¹⁹F 471 MHz) or a Bruker Avance III 500 (¹H 500 MHz; ¹³C 126 MHz; ¹⁹F 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 (νmax) 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 5 and 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)**

![Structural formula of (2S,3S)-N- Allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (7)](attachment)

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)**

![Structural formula of (2S,3S)-N- Benzyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-phenylbutanamide (8)](attachment)

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% Et₂O 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]²⁰° +38.0 (c 0.5, CHCl₃); **Chiral HPLC analysis**; Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) tᵣ minor (2R,3R): 23.0 min, tᵣ major (2S,3S): 24.8 min, 96:4 er; **¹H NMR** (400 MHz, CDCl₃) δH: 1.00 (3H, d, J 7.0, CH₂CH), 2.96 (1H, q, J 7.0, CH₃CH), 4.33–4.66 (2H, m, NHCH₂), 6.37 (1H, t, J 5.7, NH), 6.74 (1H, s, OH), 7.27–7.44 (8H, m, ArH), 7.56 (1H, d, J 7.3, C(3)ArC(2,6)H); **³¹C [¹H] NMR** (101 MHz, CDCl₃) δC: 13.9 (CH₃CH), 41.8 (CH₂CH), 43.7 (NHCH₂), 75.4 (q, J 27.4, CCF₃), 78.2 (q, J 288.4, CF₃), 126.0 (C(3)ArC(2,6)), 127.9 (CH₂ArC(2,6)H), 128.4 (2 × ArCH), 128.5 (2 × ArCH), 136.0 (C(3)ArC(1)), 137.1 (CH₂ArC(1)), 175.8 (C=O); **IR** νₚₓₜₜ (film)/cm⁻¹: 3397 (O–H), 1647 (C=O); **HRMS** (APCI⁺) C₁₈H₁₉F₉O₂N ([M+H]⁺), 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)**

![Chemical structure of (2S,3S)-4,4,4-Trifluoro-3-hydroxy-2-methyl-3-phenyl-1-(pyrrolidin-1-yl)butan-1-one (9)](image)

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 pyrrolidine (0.42 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 (30% Et₂O 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]²⁰° +45.1 (c 0.5, CHCl₃); **Chiral HPLC analysis**; Chiralcel OD-H (90:10 hexane : 2-propanol, flow rate 1 mLmin⁻¹, 211 nm, 30 °C) tᵣ minor (2R,3R): 5.3 min, tᵣ major (2S,3S): 5.9 min, 96:4 er; **¹H NMR** (500 MHz, CDCl₃) δH: 0.92 (3H, d, J 7.0, CH₂CH), 1.88–1.97 (2H, m, NCH₂CH₂), 1.97–2.12 (2H, m, NCH₂CH₂), 3.29 (1H, q, J 7.0, CH₂CH), 3.46–3.62 (3H, m, NCH₂ and NCH₃H₆), 3.68 (1H, dt, J 9.8, 7.0, NCH₃H₆), 7.33–7.44 (4H, m, ArC(2,3,5,6)H), 7.54–7.64 (2H, m, ArC(4)H and O=H); **³¹C [¹H] NMR** (101 MHz, CDCl₃) δC: 13.2 (CH₃CH), 24.3 (NCH₂CH₂), 26.0 (NCH₂CH₂), 38.0 (CH₂CH), 46.0 (NCH₂), 46.8 (NCH₃), 78.2 (q, J 27.2, CCF₃), 126.0 (q, J 288.7, CF₃), 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);
\[ ^{19}\text{F}[{^1}\text{H}] \text{ NMR} (471 \text{ MHz, CDCl}_3) \delta_F: -77.1 (CF_3); \text{ IR } \nu_{\text{max}} \text{ (film)} / \text{cm}^{-1}: 3063 (O-H), 1617 (C=O); \]

\[ \text{HRMS (APCI') C}_{15}\text{H}_{16}\text{F}_2\text{O}_2\text{N ([M+H]}^+) \], 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), trifluoroacetonaphone 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 ammonia (7 M in MeOH, 0.71 mL, 5.00 mmol), NEt\(_3\) (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 (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}}\]

\[ \text{mp } 149-151 \text{ °C; } [\alpha]_D^{20} +17.4 (c 0.5, \text{CHCl}_3); \text{ Chiral GC analysis Restek Rt®bDEXcst (length: 30 m, thickness: 0.250 mm, film thickness: 0.25 µm), carrier gas: He, linear velocity: 60 cm/sec, temperature: 160 °C, } t_b \text{ minor (2R,3R) 44.0 min, } t_b \text{ major (2S,3S) 45.6 min, } > 99:1 \text{ er; } ^1\text{H NMR} (400 MHz, CDCl}_3) \delta_H: 1.00 (3H, d, J 7.0, CH\text{3CH}), 3.01 (1H q, J 7.0, CH\text{3CH}), 5.96 (1H, s, NH), 6.14 (1H, s, NH), 6.53 (1H, s, OH), 7.32-7.46 (3H, m, ArC(3,4,5)\text{H}), 7.56 (2H, dd, J 7.3, 1.8, ArC(2,6)\text{H}); \]

\[ ^{13}\text{C}[{^1}\text{H}] \text{ NMR} (101 MHz, CDCl}_3) \delta_C: 13.8 (CH\text{3CH}), 40.9 (CH\text{3CH}), 78.3 (q, J 27.4, CCF\text{3}), 125.7 (q, J 288.2, CF\text{3}), 126.0 (ArC(2,6)\text{H}), 128.4 (ArC(3,5)\text{H}), 128.5 (ArC(4)\text{H}), 135.9 (ArC(1)), 178.7 (C=O); \text{ IR } \nu_{\text{max}} \text{ (film)} / \text{cm}^{-1}: 3200 (O-H), 1668 (C=O); \text{ HRMS (APCI') C}_{15}\text{H}_{16}\text{F}_2\text{O}_2\text{N ([M+H]}^+) \], 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 modification of general procedure A, 1-oxopropan-2-yl 4-nitrobenzoate 4 (335 mg, 1.50 mmol), trifluoroacetonaphone 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. 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 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% EtO 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%).

[α]D²⁰ –39.4 (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: 30 cm/sec, temperature: 135 °C, tR minor (2S,3R) 50.8 min, tR major (2R,3S) 51.8 min, 96:4 er; 1H NMR (400 MHz, CDCl₃) δH: 0.90 (3H, d, J 7.2, CH₃CH), 2.11 (1H, s, CH₂OH), 2.35–2.53 (1H, m, CH₃CH), 3.83 (1H, dt, J 10.8, 1.8, CH₂OH), 4.41 (1H, d, J 10.7, CH₂OH), 5.20 (1H, s, F₃CCOH), 7.31–7.43 (3H, m, ArC(3,4,5)H), 7.55 (2H, d, J 7.7, ArC(2,6)H); 13C{¹H} NMR (101 MHz, CDCl₃) δC: 12.6 (CH₂CH), 37.8 (CH₃CH), 66.0 (CH₂OH), 80.4 (q, J 27.1, CCF₃), 125.6 (ArC(2,6)H), 126.2 (q, J 287.9, CF₃), 128.0 (ArC(4)H), 128.2 (ArC(3,5)H), 138.2 (ArC(1)); 19F{¹H} NMR (376 MHz, CDCl₃) δF: −74.7 (CF₃); IR νmax (film)/cm⁻¹: 3372 (O–H); HRMS (APCI⁺) C₁₃H₁₄F₃O₂ ([M+H]⁺), found 235.0934, requires 235.0940 (−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 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 (75:25 dr), which was purified by column chromatography on silica (30% EtO 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; [α]D²⁰ +22.6 (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: 60 cm/sec, temperature: 190 °C, tR minor (2R,3R) 29.9 min, tR major (2S,3S) 30.6 min, 99:1 er; 1H NMR (400 MHz, CDCl₃) δH: 0.97 (3H, d, J 7.0, CH₃), 2.88 (1H, q, J 7.0, CH₃CH), 3.74–4.12 (2H, m, NHCH₂), 5.06–5.37 (2H, m, HC=CH₂), 5.85 (1H, ddt, J 17.2, 10.2, 5.7, HC=CH₂), 6.10 (1H, t, J 5.8, 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, CCH$_3$), 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$_2$), 135.2 (ArC(1)), 175.5 (C=O); $^{19}$F$^{1}$H NMR (376 MHz, CDCl$_3$) δF: −76.9 (CF$_3$); IR $\nu_{max}$ (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 (+0.3 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; $[\alpha]_{D}^{20}$ +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, CCH$_3$), 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 $\nu_{max}$ (film)/cm$^{-1}$: 3306 (O–H), 1622 (C=O); HRMS (ESI$^+$) C$_{14}$H$_{16}$F$_3$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 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 (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 Cycsil-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, CH₂(CH), 2.94 (1H, q, J 7.0, CH₃(CH), 3.85–4.09 (2H, m, NHCH₂), 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 (CH₃CH), 41.6 (CH₂CH), 42.0 (NHCH₂), 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⁺) C₁₅H₁₃F₆O₂N ([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 24h; 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% EtO in hexane) to give (2S,3S)-N-allyl-4,4,4-trifluoro-3-hydroxy-2-methyl-3-(p-toly)butanamide 15 as a colourless crystalline solid (single diastereoisomer, 139 mg, 0.460 mmol, 46%)

**mp** 108–110 °C; [α]_D^20 +23.0 (c 0.5, CHCl$_3$); $^1$H NMR (500 MHz, CDCl$_3$) δ_H: 0.98 (3H, d, J 7.0, CH$_3$(CH), 2.36 (3H, s, ArC(4)CH$_3$), 2.90 (1H, q, J 7.0, CH$_3$CH), 3.78–4.10 (2H, m, NHCH$_2$), 5.07–5.38 (2H, m, HC=CH$_2$), 5.86 (1H, ddt, J 16.3, 10.8, 5.7, HC=CH$_2$), 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); $^{19}$F$[^1]$H NMR (471 MHz, CDCl$_3$) δ_F: –77.0; $^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) δ_C: 13.9 (CH$_3$(CH), 21.2 (ArC(4)CH$_3$), 41.9 (CH$_3$CH), 42.0 (NHCH$_2$), 78.3 (q, J 27.3, CCF$_3$), 117.2 (HC=CH$_2$), 125.8 (q, J 288.3, CF$_3$), 125.9 (ArC(2,6)H), 129.1 (ArC(3,5)H), 133.0 (ArC(1)), 133.1 (HC=CH$_2$), 138.2 (ArC(4)), 175.8 (C=O); IR ν$_{\text{max}}$ (film)/cm$^{-1}$: 3356 (O–H), 1647 (C=O); HRMS (APCI) $^{1}$C$_{15}$H$_{19}$F$_3$O$_2$N ([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)

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), NEt$_3$ (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% EtO 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%).

**mp** 108–109 °C; [α]_D^20 +14.6 (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: 160 °C, t$_r$ minor (2R,3R) 33.6 min, t$_r$ major (2S,3S) 34.5 min, 96:4 er; $^1$H NMR (400 MHz, CDCl$_3$) δ_H: 1.09 (3H, d, J 7.0, CH$_3$), 2.81 (1H, q, J 7.0, CH$_3$CH), 3.78–4.12 (2H, m, NHCH$_2$), 5.11–5.34 (2H, m, HC=CH$_2$), 5.84 (1H, ddt, J 17.2, 10.3, 5.8, HC=CH$_2$), 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); $^{13}$C$[^1]$H NMR (126 MHz, CDCl$_3$) δ_C: 14.0 (CH$_3$), 42.0 (NHCH$_2$), 43.1 (CH$_3$CH), 78.4 (q, J 28.9, CCF$_3$), 117.4 (HC=CH$_2$), 124.5 (ArC(3)H or ArC(5)H), 125.2 (q, J 287.8, CF$_3$), 125.9 (ArC(4)H), 127.2 (ArC(3)H or ArC(5)H),
133.0 (HC=CH₂), 140.3 (Ar(C(2)), 175.4 (C=O); ¹⁹F{¹H} NMR (376 MHz, CDCl₃) δF: −78.5 (CF₃);
IR νmax (film)/cm⁻¹: 3341 (O–H), 1638 (C=O); HRMS (ESI⁺) C₁₂H₁₅F₂NO₂S ([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 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 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 (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]₁₀^D +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; ¹H NMR (400 MHz, CDCl₃) δH: 2.39 (1H, dd, J 12.9, 2.8, CH₂H₆CH), 2.80–2.90 (1H,
m, CH₂H₆CH), 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=CH₃), 5.00 (1H, dd, J 10.3, 1.3, HC=CH₃), 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); ¹³C{¹H} NMR
(126 MHz, CDCl₃) δC: 34.3 (CH₂CH₃), 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); ¹⁹F{¹H} 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).
(2S,3S)-N-Allyl-2-(2-(benzyloxy)ethyl)-4,4,4-trifluoro-3-hydroxy-3-phenylbutanamide (18)

Following general procedure A, 4-(benzyloxy)-1-oxobutan-2-yl 4-nitrobenzoate S2 (258 mg, 0.750 mmol), trifluoroacetophenone 5 (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), NEt₃ (70 µL, 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% Et₂O 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%).

[α]D° +26.5 (c 0.5, CHCl₃); **Chiral HPLC analysis**: Chiralcel OD-H (95:5 hexane : 2-propanol, flow rate 1 mL min⁻¹, 211 nm, 30 °C) tₘₜₘₙₜ minor (2R,3R): 6.8 min, tₘₜₘₙₜ major (2S,3S): 10.0 min, 96:4 er; **¹H NMR** (400 MHz, CDCl₃) δH: 1.42–1.52 (1H, m, C₂H₂CH), 1.79 (1H, ddt, J 14.7, 11.4, 3.4, CH₂H₂CH), 3.12 (1H, dd, J 11.4, 3.4, CH₂CH), 3.26–3.40 (2H, m, OC₂H₂CH₂), 3.65–3.76 (1H, m, NHC₂H₂CH), 3.89–3.99 (1H, m, NHCH₂H₂CH), 4.29 (1H, d, J 11.9, OCH₂H₂CH), 4.44 (1H, d, J 11.9, OCH₂H₂Ar), 5.13–5.29 (2H, m, HC=CH₂), 5.77 (1H, ddt, J 17.1, 10.2, 5.8, HC=CH₂), 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)ArC(2,6)H); **¹³C{¹H} NMR** (126 MHz, CDCl₃) δC: 27.8 (CH₂CH), 42.0 (NHCH₂), 44.1 (CH₂CH), 66.5 (OCH₂CH₂), 72.8 (OCH₂Ar), 78.5 (q, J 27.4, CCF₂), 117.4 (HC=CH₂), 125.6 (q, J 288.5, CCF₂), 126.1 (C(3)ArC(2,6)H), 127.9 (2 × ArCH), 128.0 (ArCH), 128.4 (2 × ArCH), 128.5 (ArCH), 128.6 (2 × ArCH), 133.2 (HC=CH₂), 136.1 (C(3)ArC(1)), 138.0 (OCH₂ArC(1)), 174.4 (C=O); **¹⁹F{¹H} NMR** (376 MHz, CDCl₃) δF: −76.7 (CF₃); **IR νmax** (film)/cm⁻¹: 3319 (O=H), 1628 (C=O); **HRMS** (APCI⁺) C₂₂H₂₃F₃O₃N ([M+H]⁺), found 408.1781, requires 408.1781 (+0.0 ppm).
$^{1}H$, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz. CDCl₃
$^1$H, 500 MHz, CDCl$_3$
$^{13}$C, 126 MHz, CDCl$_3$
$^{19}\text{F}, 471 \text{ MHz, CDCl}_3$
$^1$H, 400 MHz, CDCl$_3$
$^13$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
^1H, 400 MHz, CDCl₃
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
\( ^1\text{H}, 400\text{ MHz}, \text{CDCl}_3 \)
$^{19}$F, 376 MHz, CDCl$_3$
$^{1}H$, 400 MHz, CDCl$_3$
$^{13}\text{C}, 101 \text{ MHz, CDCl}_3$
$^{19}$F, 376 MHz, CDCl$_3$
$^1$H, 500 MHz, CDCl$_3$
$^{13}$C, 126 MHz, CDCl$_3$
$^1$H, 500 MHz, CDCl$_3$
$^{13}$C, 126 MHz, CDCl$_3$
$^{19}$F, 471 MHz, CDCl₃
$^1$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
$^{1}$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl$_3$
$^1$H, 400 MHz, CDCl$_3$
$^{13}$C, 101 MHz, CDCl$_3$
$^{19}$F, 376 MHz, CDCl₃
(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.

![Chiral HPLC chromatogram]

**<Peak Table>**

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 22.795    | 49.822 |
| 2     | 25.208    | 50.178 |
| Total |           | 100.000|

![Another Chiral HPLC chromatogram]

**<Peak Table>**

| Peak# | Ret. Time | Area%  |
|-------|-----------|--------|
| 1     | 22.984    | 4.496  |
| 2     | 24.813    | 95.504 |
| Total |           | 100.000|
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 (2R,3R) 44.0 min, $t_R$ major (2S,3S) 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, \( t_R \) minor (2R,3R) 40.0 min, \( t_R \) 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<sub>R</sub> minor (2R,3R) 33.6 min, t<sub>R</sub> 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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