Direct Catalytic Asymmetric Mannich–Type Reaction of an \( \alpha\text{-CF}_3 \) Amide to Isatin Imines

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1. General information

1-1. Reactions and purifications

Unless otherwise noted, all reactions were carried out in an oven-dried glassware fitted with a 3-way glass stopcock under an argon atmosphere and were stirred with Teflon-coated magnetically stirred bars. All work-up and purification procedures were carried out with reagent-grade solvents under ambient atmosphere. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with ninhydrin or KMnO4. Flash column chromatography was performed on a Biotage Isolera Spektra One.

1-2. Characterizations

Infrared (IR) spectra were recorded on a HORIBA FT210 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a Bruker AVANCE III HD400 or 600 NMR spectrometers. Chemical shifts (δ) are given in ppm relative to residual solvent peaks. Data for 1H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), q (quartet), m (multiplet), br (broad). Single-crystal X-ray data were collected on a Rigaku R-AXIS RAPID II imaging plate area detector with graphite-monochromated Cu-Ka radiation. Optical rotation was measured using a 1 mL cell with a 1.0 dm path length on a JASCO polarimeter P-1030. High-resolution mass spectra (ESI TOF (+)) were measured on a Thermo Fisher Scientific LTQ Orbitrap XL. Normal phase HPLC analysis was conducted on a JASCO HPLC system equipped with Daicel chiral-stationary-phase columns (ø 0.46 cm x 25 cm).

1-3. Solvents and reagents

Unless otherwise noted, materials were purchased from commercial suppliers and were used without further purification. Anhydrous THF, and toluene was purified by passing through a solvent purification system (Glass Contour). [Cu(CH3CN)4]PF6 was purchased from Sigma-Aldrich, and used as received. Chiral phosphine ligands were purchased from Sigma-Aldrich or Strem, and used as received. Isatin derived ketimines 1 and 7-azaindoline α-CF3 amide 2 were prepare according to the reported procedures.

1-4. List of abbreviations

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<th>Entry</th>
<th>Chemical name</th>
<th>Abbreviation</th>
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<tr>
<td>1</td>
<td>2-tert-Butyl-1,1,3,3-tetramethylguanidine</td>
<td>Barton’s base</td>
</tr>
<tr>
<td>2</td>
<td>Diisobutylaluminium hydride</td>
<td>DIBAL-H</td>
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2. Direct catalytic asymmetric Mannich-type reaction

2-1. Substrate scope

![Diagram of the reaction](image)

General procedure A for the preparation of chiral Cu(I) catalyst solution:

A flame-dried 10 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock were charged with [Cu(MeCN)₃]PF₆ (3.7 mg, 0.01 mmol), (R, R)-Ph-BPE L₈ (6.1 mg, 0.012 mmol) and THF (0.5 mL). The resultant mixture was stirred for 30 minutes at room temperature (RT) to form the chiral Cu(I) catalyst solution (0.02 M in THF), which was stored at RT and used within one hour.

General procedure B for direct catalytic asymmetric Mannich-type reaction:

A flame-dried 10 mL test tube equipped with a magnetic stirring bar and 3-way glass stopcock were charged with isatin imines 1 (0.2 mmol, 1.0 equiv), and α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), followed by the addition of anhydrous THF (0.2 M) via syringe with a stainless steel needle under an Ar atmosphere. After being stirred at RT for 5 min, the chiral copper (I) catalyst solution (0.02 M in THF, 1 mol% or 3 mol%) prepared by the general procedure A and a solution of Barton’s base (0.04 M in THF, 2 or 3 mol%) were sequentially added via syringe with a stainless steel needle. After being stirred at RT for 12 h, the reaction mixture was filtered through a short pad of silica gel and washed with EtOAc, then concentrated in vacuo to afford the crude residue. To determine the diastereoselectivity of the product, the residue was first dissolved in CDCl₃, and 1H NMR was recorded. Then the sample for analysis and the rest of crude residue were recombined and purified by silica gel column chromatography (5% to 80% EtOAc in hexane) to afford products 3.

**tert-Butyl**

\[(S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3a):\] Prepared by the general procedure B from imine 1a (52.0 mg, 0.22 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.1 mL, 2 μmol, 1 mol%) and Barton’s base (0.04 M in THF, 0.1 mL, 4 μmol, 2 mol%), stirred for 12 h at RT, and isolated as a white foam (96.5 mg, 98% yield). 1H NMR analysis revealed that the dr was >95:5. IR (thin film): ν 3371, 2943, 1746, 1634, 1548, 1538, 1452, 1343, 1293, 1272, 1268, 1254 (d, J = 2.5 Hz), 1243 (q, J = 281.1 Hz), 122.2, 119.0, 108.1, 80.0, 61.2, 48.9 (q, J = 26.1 Hz), 46.0, 27.9, 26.1, 23.7; 13C NMR (100 MHz, CDCl₃): δ 174.6, 163.4, 154.8, 153.8, 145.2, 134.3, 129.3, 127.2, 126.8, 125.4 (d, J = 2.5 Hz), 124.3 (q, J = 281.1 Hz), 122.2, 119.0, 108.1, 80.0, 61.2, 48.9 (q, J = 26.1 Hz), 46.0, 27.9, 26.1, 23.7; 19F NMR (376 MHz, CDCl₃): δ –57.98 (d, J = 8.5 Hz). HRMS (ESI): m/z calc’d for C₃₃H₂₇O₆NaF₃Na [M + Na]+: 513.1720, found: 513.1724. [α]D²⁴ = -48.0 (c = 1.00, CHCl₃): Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tR = 5.8 min (major), 13.0 min (minor)).
Racemic sample

Reaction sample

Benzyl ((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxindolin-3-yl)carbamate (3b): Prepared by following the general procedure B from imine 1b (58.9 mg, 0.2 mmol), \( \alpha \)-CF\(_3\) amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.1 mL, 2 \( \mu \)mol, 1 mol%) and Barton’s base (0.04 M in THF, 0.1 mL, 4 \( \mu \)mol, 2 mol%), stirred for 12 h, and isolated as a white solid (95.5 mg, 91% yield). \(^1\)H NMR analysis revealed that the dr was >95:5. m.p. 70–72 °C; IR (thin film): \( \nu \) 3356, 2942, 1725, 1427, 1256, 1124, 754 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.85 (d, \( J = 4.8 \) Hz, 1H), 7.44–7.38 (m, 3H), 7.30–7.15 (m, 6H), 7.02 (td, \( J = 7.6, 0.8 \) Hz, 1H), 6.84 (dd, \( J = 7.6, 5.2 \) Hz, 1H), 6.76 (brs, 1H), 6.28 (q, \( J = 8.4 \) Hz, 1H), 4.90–4.79 (m, 2H), 4.21–4.10 (m, 2H), 3.07–2.88 (m, 5H); \(^1\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 174.3, 163.5, 154.8, 154.6, 145.2, 143.4, 135.8, 134.3, 129.6, 128.3, 128.0, 127.9, 126.8, 126.4, 125.6 (d, \( J = 2.6 \) Hz), 124.2 (q, \( J = 281.1 \) Hz), 122.4, 119.1, 108.2, 66.9, 61.2, 48.8 (q, \( J = 26.6 \) Hz), 46.0, 26.2, 23.8; \(^1\)F NMR (376 MHz, CDCl\(_3\)): \( \delta \) –58.03 (d, \( J = 8.5 \) Hz). HRMS (ESI): \( m/z \) calc’d for C\(_{27}\)H\(_{23}\)O\(_4\)N\(_4\)F\(_3\)Na [M + Na]\(^+\): 547.1564, found: 547.1558. \([\alpha]\)\(^D\) = –39.5 (c = 0.53, CHCl\(_3\)); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (\( \phi \) 0.46 cm x 25 cm), 2-propanol/\( n \)-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, \( t_R \) = 16.9 min (major), 13.0 min (minor)).
**tert-Butyl**

((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-5-fluoro-1-methyl-2-oxoindolin-3-yl)carbamate (3c): Prepared by the general procedure B from imine 1c (55.7 mg, 0.2 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.1 mL, 2 μmol, 1 mol%) and Barton’s base (0.04 M in THF, 0.1 mL, 4 μmol, 2 mol%), stirred for 12 h at RT, and isolated as a white solid (88.0 mg, 86% yield). ¹H NMR analysis revealed that the dr was 94:6. **m.p.** 136–138 °C; IR (thin film): ν 3367, 2939, 1721, 1654, 1497, 1426, 1256, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.95–7.94 (m, 1H), 7.53–7.51 (m, 1H), 7.22–7.20 (m, 1H), 7.09 (brs, 1H), 7.04 (td, J = 8.8, 2.6 Hz, 1H), 6.93 (dd, J = 7.2, 4.8 Hz, 1H), 6.76 (dd, J = 8.4, 4.0 Hz, 1H), 6.32 (q, J = 8.4 Hz, 1H), 4.32–4.16 (m, 2H), 3.17–3.02 (m, 2H), 2.96 (s, 3H), 1.25 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 174.4, 163.2, 158.9 (d, J = 239.1 Hz), 154.8, 153.9, 145.2, 139.22 (d, J = 1.9 Hz), 134.4, 128.8, 126.8, 124.2 (q, J = 281.0 Hz), 119.1, 115.6 (d, J = 23.5 Hz), 113.7 (d, J = 25.5 Hz), 108.5 (d, J = 8.0 Hz), 80.4, 61.4, 48.8 (q, J = 26.7 Hz), 46.1, 28.0, 26.3, 23.8; ¹⁹F NMR (376 MHz, CDCl₃): δ –58.06 (d, J = 8.0 Hz), –120.75 (s). HRMS (ESI): m/z calc’d for CaH₂O₅N₂F₄Na [M + Na]⁺: 531.1626, found: 531.1625. [α]D²⁴ = –50.9 (c = 0.77, CHCl₃); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/i-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tₑ = 5.1 min (major), 6.6 min (minor)).

**tert-Butyl**

((S)-5-chloro-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3d): Prepared by the general procedure B from imine 1d (58.9 mg, 0.2 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.1 mL, 2 μmol, 1 mol%) and Barton’s base (0.04 M in THF, 0.1 mL, 4 μmol, 2 mol%), stirred for 12 h at RT, and isolated as a white solid (93.7 mg, 89% yield). ¹H NMR analysis revealed that the dr was 92:8. **m.p.** 195–197 °C; IR (thin film): ν 3367, 2939, 1733, 1655, 1427, 1256, 1166, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.94–7.93 (m, 1H), 7.53–7.51 (m, 1H), 7.42–7.41 (m, 1H), 7.31 (dd, J = 8.4, 2.0 Hz, 1H), 7.07 (brs, 1H), 6.92 (dd, J = 7.2, 5.2 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 6.31 (q, J = 8.8 Hz, 1H), 4.31–4.15 (m, 2H), 3.16–3.02 (m, 2H), 2.96 (s, 3H), 1.26 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 174.2, 163.1, 154.8, 153.9, 145.2, 141.8, 134.4, 129.3, 128.8, 127.8, 126.8, 125.8 (d, J = 2.6 Hz), 124.1 (q, J = 281.1 Hz), 119.2, 109.1, 80.5, 61.2, 48.8 (q, J = 26.7 Hz), 46.1, 28.0, 26.3, 23.8; ¹⁹F NMR (376 MHz, CDCl₃): δ –58.05 (d, J = 8.0 Hz). HRMS (ESI): m/z calc’d for CaH₂O₅N₂ClF₃Na [M + Na]⁺: 547.1330, found: 547.1336. [α]D³⁴ = –36.8 (c = 1.00, CHCl₃); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46
cm x 25 cm). 2-propanol/\(n\)-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, \(t_R = 5.2\) min (major), 5.9 min (minor).

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**Racemic sample**

**Reaction sample**

**tert-Butyl**

((S)-5-bromo-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1- methyl-2-oxindolin-3-yl)carbamate (3e): Prepared by the general procedure B from imine 1e (67.8 mg, 0.2 mmol), \(\alpha\)-CF\(_3\) amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 µmol, 3 mol%), and Barton’s base (0.04 M in THF, 0.15 mL, 6 µmol, 3 mol%), stirred for 12 h at RT, and isolated as a white solid (102.4 mg, 90% yield). \(^1\)H NMR analysis revealed that the dr was >95:5. m.p. 209–211 °C; IR (thin film): \(v = 3371, 2936, 1733, 1655, 1426, 1256, 1164, 755\) cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 7.94–7.92\) (m, 1H), 7.54–7.51 (m, 2H), 7.45 (dd, \(J = 8.4, 2.0\) Hz, 1H), 7.06 (brs, 1H), 6.92 (dd, \(J = 7.6, 5.2\) Hz, 1H), 6.72 (d, \(J = 8.4\) Hz, 1H), 6.31 (q, \(J = 8.8\) Hz, 1H), 4.29–4.14 (m, 2H), 3.16–3.01 (m, 2H), 2.95 (s, 3H), 1.25 (s, 9H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 174.1, 163.1, 154.8, 153.9, 145.2, 142.3, 134.4, 132.2, 129.1, 128.5\) (d, \(J = 2.5\) Hz), 126.8, 124.1 (q, \(J = 281.1\) Hz), 119.2, 114.9, 109.6, 80.5, 61.1, 48.8 (q, \(J = 26.6\) Hz), 46.1, 28.0, 26.3, 23.8; \(^19\)F NMR (376 MHz, CDCl\(_3\)): \(\delta = -58.03\) (d, \(J = 7.9\) Hz). HRMS (ESI): \(m/z\) calcd for C\(_{24}\)H\(_{24}\)O\(_4\)N\(_4\)Br\(_3\)F\(_3\)Na [M + Na]: 591.0825, found: 591.0825. \([\alpha]_{D}^{24} = -27.9\) (c = 0.85, CHCl\(_3\)); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK ID (\(\phi 0.46\) cm x 25 cm), 2-propanol/\(n\)-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, \(t_R = 10.9\) min (major), 14.2 min (minor)).
tert-Butyl

((S)-(S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (3f): Prepared by the general procedure B from imine 1f (54.9 mg, 0.2 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 μmol, 3 mol%) and Barton’s base (0.04 M in THF, 0.15 mL, 6 μmol, 3 mol%), stirred for 12 h at RT, and isolated as a white solid (100.8 mg, 99% yield). ¹H NMR analysis revealed that the dr was >95:5. m.p. 170–172 °C; IR (thin film): ν 3378, 2939, 1720, 1651, 1426, 1265, 1156, 756 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.92 (d, J = 4.0 Hz, 1H), 7.49 (dd, J = 7.2, 1.2 Hz, 1H), 7.25 (s, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.04 (brs, 1H), 6.90 (dd, J = 7.2, 5.2 Hz, 1H), 6.72 (d, J = 7.6 Hz, 1H), 6.30 (q, J = 8.8 Hz, 1H), 4.31–4.13 (m, 2H), 3.14–3.01 (m, 2H), 2.93 (s, 3H), 2.33 (s, 3H), 1.22 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 174.4, 163.5, 154.9, 153.8, 145.2, 146.0, 138.4, 131.6, 129.5, 127.1, 126.7, 126.2 (d, J = 2.6 Hz), 124.3 (q, J = 281.2 Hz), 118.9, 107.8, 80.0, 61.3, 49.0 (q, J = 26.4 Hz), 46.0, 28.0, 26.1, 23.7, 21.1; ¹⁹F NMR (376 MHz, CDCl₃): δ −57.91 (d, J = 8.4 Hz). HRMS (ESI): m/z calc’d for C₂₉H₂₅N₃F₅Na [M + Na⁺]: 527.1877, found: 527.1873. [α]D²⁴ = −29.9 (c = 1.40, CHCl₃); Enantiomeric excess of the product was determined to be 98% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tR = 12.2 min (major), 14.7 min (minor)).

Racemic sample

Reaction sample

tert-Butyl

((S)-(S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (3g): Prepared by following the general procedure B from imine 1g (58.1 mg, 0.2 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 μmol, 3 mol%) and Barton’s base (0.04 M in THF, 0.15 mL, 6 μmol, 3 mol%), stirred for 12 h, and isolated as a white solid (84.3 mg, 81% yield). ¹H NMR analysis revealed that the dr was >95:5. m.p. 155–157 °C; IR (thin film): ν 3378, 2939, 1720, 1651, 1426, 1256, 1159, 755 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.93 (d, J = 4.8 Hz, 1H), 7.50 (dd, J = 7.2, 1.2 Hz, 1H), 7.07 (s, 2H), 6.92–6.86 (m, 2H), 6.74 (d, J = 8.4 Hz, 1H), 6.32 (q, J = 8.8 Hz, 1H), 4.31–4.14 (m, 2H), 3.78 (s, 3H), 3.16–3.00 (m, 2H), 2.93 (s, 3H), 1.23 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 174.2, 163.5, 155.7, 154.9, 153.9, 145.2, 136.7, 134.3, 128.5, 126.8, 124.3 (q, J = 281.1 Hz), 119.0, 114.2, 112.6, 108.4, 80.1, 61.6, 55.9, 48.9 (q, J = 26.5 Hz), 46.0, 28.0, 26.2, 23.8; ¹⁹F NMR (376 MHz, CDCl₃): δ −57.82 (d, J = 8.4 Hz). HRMS (ESI): m/z calc’d for C₂₉H₂₅N₃F₅Na [M + Na⁺]: 543.1826, found: 543.1819. [α]D²⁴ = −44.0 (c = 0.62, CHCl₃); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tR = 12.2 min (major), 14.7 min (minor)).
2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, $t_R = 6.9$ min (major), 10.8 min (minor)).

**Racemic sample**

**Reaction sample**

**tert-Butyl**

((S)-6-chloro-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3h): Prepared by following the general procedure B from imine 1h (58.9 mg, 0.2 mmol), $\alpha$-CF$_3$ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 µmol, 3 mol%), and Barton’s base (0.04 M in THF, 0.15 mL, 6 µmol, 3 mol%), stirred for 12 h, and isolated as a white solid (90.3 mg, 86% yield). $^1$H NMR analysis revealed that the dr was >95:5. m.p. 173–175 °C; IR (thin film): $\nu$ 3367, 2936, 1735, 1656, 1426, 1255, 1163, 756 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.94 (d, $J = 4.4$ Hz, 1H), 7.52 (d, $J = 7.2$ Hz, 1H), 7.35 (d, $J = 7.6$ Hz, 1H), 7.08–7.03 (m, 2H), 6.93 (dd, $J = 7.2$, 5.2 Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H), 6.28 (q, $J = 8.8$ Hz, 1H), 4.31–4.15 (m, 2H), 3.13–3.06 (m, 2H), 2.96 (s, 3H), 1.25 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.6, 163.2, 154.8, 153.9, 145.2, 144.4, 143.1, 134.4, 126.8, 126.4 (d, $J = 2.4$ Hz), 125.6, 124.2 (q, $J = 281.0$ Hz), 122.1, 119.2, 108.9, 80.4, 60.9, 48.8 (q, $J = 26.5$ Hz), 46.1, 28.0, 26.3, 23.8; $^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -58.06 (d, $J = 8.0$ Hz). HRMS (ESI): m/z calc’d for C$_{24}$H$_{24}$O$_4$N$_4$ClF$_3$Na $[M + Na]^+$: 547.1330, found: 547.1331. $[\alpha]_{D}^{24} = -19.4$ (c = 0.82, CHCl$_3$); Enantiomeric excess of the product was determined to be 99% by chiral stationary phase HPLC analysis (CHIRALPAK ID ($\phi$ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, $t_R = 10.5$ min (major), 9.4 min (minor)).
tert-Butyl

\((S)-7\text{-chloro}-3-((S)-3-(2,3\text{-dihydro-1H-} \text{pyrrolo}[2,3-b] \text{pyridin}-1\text{-yl})-1,1,1\text{-trifluoro-3-oxopropan-2-yl})-1\text{-methyl-2-oxoindolin-3-yl} \text{carbamate} \ (3i)\): Prepared by following the general procedure B from imine \(2i\) (58.9 mg, 0.2 mmol), \(\alpha\text{-CF}_3\) amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 \text{ \mu mol}, 3 mol\%) and Barton’s base (0.04 M in THF, 0.15 mL, 6 \text{ \mu mol}, 3 mol\%), stirred for 12 h, and isolated as a white solid (94.5 mg, 90% yield).

\(^1\text{H} \text{NMR analysis revealed that the dr was >95:5.} \text{ m.p. 195–197 °C; IR (thin film): } \nu \text{ 3363, 2936, 1734, 1656, 1426, 1258, 1166, 756 \text{ cm}^{-1}; ^1\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3):} \delta \ 8.00–7.99 (m, 1H), 7.52 (dd, \( J = 7.6, 1.2 \text{ Hz, 1H}), 7.34 \text{ (d, } J = 7.6 \text{ Hz, 1H}), 7.26–7.24 \text{ (m, 1H), 7.11 \text{ (brs, 1H), 7.00–6.93 (m, 2H), 6.29 (q, } J = 8.4 \text{ Hz, 1H})}, 4.32–4.15 \text{ (m, 2H), 3.31 (s, 3H), 3.17–3.02 \text{ (m, 2H), 1.24 (s, 9H);} ^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3):} \delta 175.0, 163.1, 154.8, 153.8, 145.3, 139.1, 134.4, 131.6, 130.0, 126.8, 124.1 (q, \( J = 281.1 \text{ Hz}), 123.9, 122.9, 119.2, 115.5, 80.4, 60.9, 48.9 (q, \( J = 26.6 \text{ Hz}), 46.1, 29.7, 28.0, 23.8; ^{19}\text{F} \text{ NMR} (376 MHz, CDCl}_3): \delta \text{ –57.81 (d, } J = 7.5 \text{ Hz). HRMS (ESI): m/z calc’d for } \text{CaH}_3\text{O}_5\text{N}_2\text{F}_3\text{Na [M + Na]}}: 547.1330, \text{ found: 547.1326. [c]_D^{24} = –47.2 (c = 0.82, CHCl}_3): \text{ Enantiomeric excess of the product was determined to be 96% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/\text{hexane} = 1/4, flow rate 1.0 mL/min, detection at 254 nm, t_r = 5.7 min (major), 8.1 min (minor)).}

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Racemic sample

Reaction sample

tert-Butyl

\((S)-3-((S)-3-(2,3\text{-dihydro-1H-} \text{pyrrolo}[2,3-b] \text{pyridin}-1\text{-yl})-1,1,1\text{-trifluoro-3-oxopropan-2-yl})-1\text{-}3\text{-methoxy benzy}-2\text{-oxoindolin-3-yl} \text{carbamate} \ (3j)\): Prepared by following the general procedure B from imine \(2j\) (73.3 mg, 0.2 mmol), \(\alpha\text{-CF}_3\) amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 \text{ \mu mol}, 3 mol\%) and Barton’s base (0.04 M in THF, 0.15 mL, 6 \text{ \mu mol}, 3 mol\%), stirred for 12 h, and isolated as a white foam (78.7 mg, 66% yield). \(^1\text{H} \text{NMR analysis revealed that the dr was 86:14.} \text{ IR (thin film): } \nu \text{ 3360, 2937, 1719, 1651, 1426, 1251, 1163, 753 \text{ cm}^{-1}; ^1\text{H} \text{ NMR} (400 \text{ MHz, CDCl}_3):} \delta 7.91 (d, \( J = 4.0 \text{ Hz, 1H}), 7.51–7.45 (m, 2H), 7.34 \text{ (brs, 1H), 7.23–7.17 (m, 3H), 7.05–7.01 (m, 1H), 6.91 (dd, \( J = 7.6, 5.2 \text{ Hz, 1H}), 6.77–6.74 (m, 2H), 6.71 (d, \( J = 8.0 \text{ Hz, 1H}), 6.37 (q, \( J = 8.4 \text{ Hz, 1H}), 4.66 \text{ (d, } J = 16.0 \text{ Hz, 1H}), 4.57 \text{ (d, } J = 16.0 \text{ Hz, 1H})}, 4.31–4.20 \text{ (m, 2H), 3.76 (s, 3H), 3.17–3.01 (m, 2H), 1.24 (s, 9H);} ^{13}\text{C} \text{ NMR} (100 \text{ MHz, CDCl}_3):} \delta 175.2, 163.7, 158.9, 154.8, 154.0, 145.5, 142.7, 134.3, 129.2, 128.7, 127.4, 127.1, 126.7, 125.7, 124.2 (q, \( J = 281.1 \text{ Hz}), 122.3, 119.0, 114.0, 109.3, 80.1, 61.3, 55.2, 48.8 (q, \( J = 26.4 \text{ Hz}), 46.1, 43.7, 28.0, 23.8; ^{19}\text{F} \text{ NMR} (376 MHz, CDCl}_3): \delta \text{ –57.93 (d, } J = 7.9 \text{ Hz). HRMS (ESI): m/z calc’d for } \text{CaH}_3\text{O}_5\text{N}_2\text{F}_3\text{Na [M + Na]}}: 619.2139, \text{ found: 619.2127. [c]_D^{24} = –3.7 (c = 0.61, CHCl}_3): \text{ Enantiomeric excess of the product was determined to be 92% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/\text{hexane} = 1/4, flow rate 1.0 mL/min, detection at 254 nm, t_r = 5.7 min (major), 8.1 min (minor)).}
2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tR = 12.9 min (major), 8.8 min (minor)).

**tert-Butyl ((S)-1-allyl-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-2-oxoindolin-3-yl)carbamate (3k):** Prepared by following the general procedure B from imine 1k (57.3 mg, 0.2 mmol), α-CF₃ amide 2 (50.6 mg, 0.22 mmol, 1.1 equiv), chiral copper (I) catalyst solution (0.3 mL, 6 µmol, 3 mol%), and Barton’s base (0.04 M in THF, 0.15 mL, 6 µmol, 3 mol%), stirred for 12 h, and isolated as a white foam (100.2 mg, 97% yield).

**1H NMR analysis revealed that the dr was >95:5.** IR (thin film): ν 3363, 2939, 1720, 1654, 1426, 1257, 1164, 755 cm⁻¹; **1H NMR** (400 MHz, CDCl₃): δ 7.94–7.93 (m, 1H), 7.51–7.45 (m, 2H), 7.29 (td, J = 7.6, 1.1 Hz, 1H), 7.26 (s, 1H), 7.06 (td, J = 7.6, 0.6 Hz, 1H), 6.91 (dd, J = 7.4, 5.1 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 6.36 (q, J = 8.6 Hz, 1H), 5.68–5.61 (m, 1H), 5.30–5.26 (m, 1H), 5.14–5.11 (m, 1H), 4.30–4.18 (m, 3H), 3.93 (dd, J = 16.1, 4.2 Hz, 1H), 3.16–3.00 (m, 2H), 1.23 (s, 9H); **13C NMR** (100 MHz, CDCl₃): δ 174.6, 163.5, 154.8, 153.9, 145.4, 142.6, 134.3, 150.9, 129.2, 127.1, 126.7, 125.5 (d, J = 2.5 Hz), 124.3 (q, J = 281.1 Hz), 122.2, 119.0, 117.7, 109.0, 80.0, 61.1, 48.8 (q, J = 26.4 Hz), 46.1, 42.7, 28.0, 23.7; **19F NMR** (376 MHz, CDCl₃): δ −57.98 (d, J = 8.3 Hz). HRMS (ESI): m/z calc’d for C₂₆H₂₇O₄N₄F₃Na [M + Na]⁺: 539.1877, found: 539.1868. [α]D²⁴ = −18.2 (c = 0.59, CHCl₃); Enantiomeric excess of the product was determined to be 97% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/n-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, tR = 5.5 min (major), 8.1 min (minor)).
2-2. Gram-scale reaction

**General procedure C for gram-scale reaction:** A flame-dried 30 mL flask equipped with a magnetic stirring bar and 3-way glass stopcock were charged with imine 1a (780.5 mg, 3.0 mmol, 1.0 equiv), and \(\alpha\)-CF\(_3\) amide 2 (760.0 mg, 3.3 mmol, 1.1 equiv), followed by the addition of anhydrous THF (9.6 mL, 0.2 M) via syringe with a stainless steel needle under an Ar atmosphere. After being stirred at RT for 5 min, the catalyst solution in THF (4.5 mL) containing chiral copper (I) complex (0.09 mmol, 3.0 mol%), which was prepared from \([\text{Cu(MeCN)}_4]\text{PF}_6\) (33.5 mg, 0.09 mmol) and \((R, R)-\text{Ph-BPE L8}\) (54.7 mg, 0.108 mmol, 3.6 mol%) using general procedure A, and a solution of Barton’s base (0.1 M in THF, 0.9 mL, 0.09 mmol, 3.0 mol%) were sequentially added via a syringe with a stainless steel needle. After stirring at RT for 12 h, the reaction mixture was filtered through a short pad of silica gel and washed with EtOAc, then concentrated in vacuo to afford the crude residue. \(^1\)H NMR analysis of the crude residue showed that the dr was >20:1. The combined crude residue was then purified by silica gel column chromatography (5% to 80% EtOAc in hexane) to afford product 3a (1.46 g, 99% yield). Enantiomeric excess of the product was determined to be 98% by chiral stationary phase HPLC analysis (CHIRALPAK AD-H (φ 0.46 cm x 25 cm), 2-propanol/\(n\)-hexane = 1/4, flow rate 1.0 mL/min, detection at 254 nm, \(t_R = 5.9\) min (major), 13.2 min (minor)).
3. Synthesis of CF₃-containing tricycle 4

**tert-Butyl**

\((2R, 3S, 3aS, 8aR)-2-hydroxy-8-methyl-3-(trifluoromethyl)-2,3,8,8a-tetrahydro-3aH-furo[2,3-b]indol-3a-yl)carbamate (4): To a solution of \(3a\) (98.0 mg, 0.20 mmol, 1.0 equiv) in toluene (3.2 mL) was added DIBAL-H (0.8 mL, 1.0 M in toluene, 4.0 equiv) at \(-40^\circ\text{C}\). The reaction solution was stirred at \(-40^\circ\text{C}\) until full consumption of \(3a\) by TLC analysis (about 4 h). After diluting with EtOAc (3 mL), MeOH (1 mL) was added slowly at \(-40^\circ\text{C}\). The resulting mixture continued to be stirred for 15 min at the same temperature, then moved to room temperature (RT), and added potassium sodium tartrate aqueous solution. After being stirred at RT for 2 h, the mixture was extracted with EtOAc (3x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to give the crude residue, which was purified by silica gel column chromatography (5% to 80% EtOAc in hexane) to afford product 4 as white solid (34.6 mg, 46% yield). The diastereomer ratio of 4 gradually increased from ca. 3:1 to 94:6 upon standing at a bench-top. The configuration of product 4 was determined by NOE analysis. **m.p.** 126–128 °C; \([\alpha]_D^{24} = -79.3\) (c = 0.62, CHCl₃); **IR** (thin film): \(\nu\) 3298, 2977, 1687, 1499, 1284, 1158, 1124, 751 cm\(^{-1}\); **¹H NMR** (400 MHz, CDCl₃): \(\delta\) 7.27–7.22 (m, 2H), 7.00 (d, \(J = 13.2\) Hz, 1H), 6.78–6.74 (m, 1H), 6.49 (d, \(J = 8.0\) Hz, 1H), 6.01 (s, 1H), 5.48 (dd, \(J = 13.2, 5.6\) Hz, 1H), 5.08 (s, 1H), 3.24–3.15 (m, 1H), 3.00 (s, 3H), 1.45 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃): \(\delta\) 155.5, 148.6, 130.8, 130.3, 124.3 (q, \(J = 275.9\) Hz), 122.5 (d, \(J = 1.5\) Hz), 118.4, 106.9, 99.6, 95.2 (d, \(J = 2.4\) Hz), 82.4, 66.9, 57.5 (d, \(J = 25.5\) Hz), 31.2, 28.1; **¹⁹F NMR** (376 MHz, CDCl₃): \(\delta\) -62.57 (d, \(J = 9.4\) Hz). **HRMS** (ESI): \(m/z\) calc’d for \(C_{17}H_{21}O_2N_2F_3Na\) [M + Na]⁺: 397.1346, found: 397.1346.
4. Determination of the relative and absolute configurations of 3e

Single crystals of 3e were obtained by slow diffusion of the solution of 3e in hexane/EtOAc at RT. A suitable crystal was selected and the sample was measured on a Rigaku R-AXIS RAPID diffractometer using graphite monochromated Cu-Ka radiation. The data were collected at 93 K. Refined structure and crystallographic parameters are summarized in Figure S1 and Table S1. CCDC 1874483 contains the supplementary crystallographic data for 3e. The absolute configuration of other products was deduced by analogy.

Table S1 Selected crystal data of 3e.

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<tr>
<td>c</td>
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<td>V</td>
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</table>

Figure S1 ORTEP diagram of 3e.
5. References


6. NMR Spectra

tert-Butyl ((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3a):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
Benzyl ((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3b):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
**Supporting Information**

**tert-Butyl**

((S)-(S)-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-5-fluoro-1-methyl-2-oxoindolin-3-yl)carbamate (**3c**):  

$^1$H NMR (400 MHz, CDCl$_3$)

![1H NMR Spectrum](image)

$^{13}$C NMR (100 MHz, CDCl$_3$)

![13C NMR Spectrum](image)
$^{19}\text{F NMR}$ (376 MHz, CDCl$_3$)
tert-Butyl

((S)-5-chloro-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3d):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
**Supporting Information**

**tert-Butyl**

((S)-5-bromo-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3e):

$^1$H NMR (400 MHz, CDCl$_3$)

![1H NMR spectrum](image)

$^{13}$C NMR (100 MHz, CDCl$_3$)

![$^{13}$C NMR spectrum](image)
$^{19}\text{F NMR}$ (376 MHz, CDCl$_3$)
**tert-Butyl**

\(((S)-(S)-(S)-3,3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1,5-dimethyl-2-oxoindolin-3-yl)carbamate (3f):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
tert-Butyl

((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-5-methoxy-1-methyl-2-oxoindolin-3-yl)carbamate (3g):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)
**Supporting Information**

**tert-Butyl**

\[\text{((S)-6-chloro-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3h):} \]

\[^{1}H\text{ NMR (400 MHz, CDCl}_3\text{)}\]

\[^{13}C\text{ NMR (100 MHz, CDCl}_3\text{)}\]
$^{19}$F NMR (376 MHz, CDCl$_3$)
**tert-Butyl**

((S)-7-chloro-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-methyl-2-oxoindolin-3-yl)carbamate (3i):

$^{1}$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}\text{F NMR}$ (376 MHz, CDCl$_3$)
**tert-Butyl**

((S)-3-((S)-3-(2,3-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)-1,1,1-trifluoro-3-oxopropan-2-yl)-1-(4-methoxy benzyl)-2-oxoindolin-3-yl)carbamate (3j):

**H NMR (400 MHz, CDCl₃)**

![H NMR spectrum](image)

**C NMR (100 MHz, CDCl₃)**

![C NMR spectrum](image)
$^{19}F$ NMR (376 MHz, CDCl$_3$)
 tert-Butyl

\((S)-1\text{-allyl-3-}((S)-3\text{-}(2,3\text{-dihydro-1H-pyrrolo}[2,3-b]pyridin-1-yl)\text{-}1,1,1\text{-trifluoro-3-oxopropan-2-yl})\text{-}2\text{-oxo indolin-3-yl})\text{carbamate (3k):}

\(^1\text{H NMR (400 MHz, CDCl}_3\))

\(^{13}\text{C NMR (100 MHz, CDCl}_3\))
$^{19}$F NMR (376 MHz, CDCl$_3$)
tert-Butyl
((2R,3S,3aS,8aR)-2-hydroxy-8-methyl-3-(trifluoromethyl)-2,3,8a-tetrahydro-3aH-furo[2,3-b]indol-3a-yl)carbamate (4):

$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{19}$F NMR (376 MHz, CDCl$_3$)

COSY (400 MHz, CDCl$_3$)
**DEPT135** (600 MHz, CDCl₃)

**HSQC** (600 MHz, CDCl₃)
HMBC (400 MHz, CDCl₃)

NOESY (600 MHz, CDCl₃)