Palladium(II)-Catalyzed Enantioselective C($sp^3$)–H Activation

Using a Chiral Hydroxamic Acid Ligand

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General Information

Unless otherwise noted all commercial materials were used without further purification. 1,4-Benzoquinone was purchased from Sigma-Aldrich and sublimed prior to use to give a bright yellow crystalline solid. Solvents were obtained from Acros or Sigma-Aldrich and used directly without further purification. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker AV-400 or Bruker DRX-600 NMR spectrometers. Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for 1H NMR, and chloroform-d(δ 77.00) for 13C NMR unless otherwise noted. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, hept = heptet, m = multiplet, br = broad resonance. The directing group (N-(4-cyano-2,3,5,6-tetra-fluorophenyl)amide) contains four C–F bonds that appear as complex set of short multiplets in the 13C NMR spectra; their ppm values are not assigned in the subsequent experimental section. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and were uncorrected. Optical rotations were obtained on a Perkin-Elmer 341 polarimeter. High resolution mass spectra (HRMS) for new compounds were recorded on an Agilent LC/MSD TOF mass spectrometer. Enantiomeric excesses (ee) were determined on a Hitachi LaChrom Elite HPLC system using commercially available chiral columns. X-ray crystallographic analysis of 2r was done at the X-ray crystallography facility, Department of Chemistry and Biochemistry, University of California, San Diego (UCSD).

Experimental Procedures and Compound Characterizations

General Procedure for the Preparation of Amides 1a-e

A solution of cyclobutanecarboxylic acid S1 (5.0 mmol, 1.0 equiv) in THF (2 mL) was added dropwise to a freshly prepared solution of lithium diisopropylamide (11.0
mmol, 2.2 equiv) in THF/hexanes at −78 °C. The resulting solution was allowed to warm to room temperature and stirred for 1 h. After the addition of alkyl iodide (5.0 mmol, 1.0 equiv) in THF (2 mL) at 0 °C, the reaction mixture was stirred for 12 h at room temperature, then poured into 2 N HCl (10 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give the desired carboxylic acid S₂, which could be used directly in the next step without further purification.

Oxalyl chloride (7.5 mmol, 1.5 equiv) was added slowly to a cold (0 °C) solution of S₂ (5.0 mmol, 1.0 equiv) in DCM (20 mL) and DMF (0.1 mL). After being stirred at room temperature for 45 min, the reaction mixture was concentrated under vacuum to give the corresponding acid chloride. 4-Amino-2,3,5,6-tetrafluorobenzonitrile (6.0 mmol, 1.2 equiv) and toluene (2 mL) was then added. After being refluxed (145 °C) for 12 h, the reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give the corresponding amide.

\[ \text{N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethylclobutanecarboxamide (1a)} \]

White solid; mp: 81-82 °C; \(^1\)H NMR (400 MHz, CDCl₃): \( \delta 7.29 \) (s, 1H), 2.55 – 2.39 (m, 2H), 2.07 – 1.86 (m, 6H), 0.92 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl₃): \( \delta 175.56 , 147.21 \) (dddd, \( J = 260.9, 14.5, 3.9, 3.9 \) Hz), 141.89 (dddd, \( J = 253.3, 13.2, 3.9, 3.9 \) Hz), 123.28 (tt, \( J = 14.3, 2.9 \) Hz), 107.28 (t, \( J = 3.2 \) Hz), 90.80 (t, \( J = 17.3 \) Hz), 49.41, 31.30, 29.40, 15.00, 8.58; HRMS (ESI-TOF) m/z Calcd for C₁₄H₁₃F₄N₂O \([\text{M+H}]^+\) 301.0959, found 301.0958.
N-(4-Cyano-2,3,5,6-tetrafluorophenyl)cyclobutanecarboxamide (1b)

White solid; mp: 91-92 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.22 (s, 1H), 3.31 (p, $J$ = 8.4 Hz, 1H), 2.53 – 2.20 (m, 4H), 2.19 – 1.88 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 173.01, 147.31 (dd, $J$ = 261.3, 15.2, 4.4 Hz), 141.65 (dd, $J$ = 253.0, 13.4, 4.1, 4.1 Hz), 122.95 (tt, $J$ = 14.1, 2.7 Hz), 107.32 (t, $J$ = 4.0 Hz), 90.80 (t, $J$ = 17.2 Hz), 39.55, 25.21, 18.08; HRMS (ESI-TOF) m/z Calcd for C$_{12}$H$_9$F$_4$N$_2$O [M+H]$^+$ 273.0646, found 273.0648.

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-butylcyclobutanecarboxamide (1c)

White solid; mp: 94-95 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.13 (s, 1H), 2.56 – 2.40 (m, 2H), 2.10 – 1.80 (m, 6H), 1.41 – 1.18 (m, 4H), 0.91 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 175.55, 107.29, 48.95, 38.37, 29.92, 26.66, 22.78, 15.18, 13.75; HRMS (ESI-TOF) m/z Calcd for C$_{16}$H$_{17}$F$_4$N$_2$O [M+H]$^+$ 329.1273, found 329.1272.

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-isopropylcyclobutanecarboxamide (1d)

White solid; mp: 108-109 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.01 (s, 1H), 2.50 – 2.39 (m, 2H), 2.22 – 2.03 (m, 3H), 1.96 – 1.84 (m, 2H), 1.02 (d, $J$ = 6.8 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 174.54, 107.33, 53.39, 34.70, 28.33, 17.16, 14.93; HRMS (ESI-TOF) m/z Calcd for C$_{15}$H$_{15}$F$_4$N$_2$O [M+H]$^+$ 315.1115, found 315.1115.

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-cyclopentylcyclobutanecarboxamide (1e)
White solid; mp: 153-154 °C; \(^1\)H NMR (400 MHz, CDCl₃): δ 7.17 (s, 1H), 2.54 –
2.37 (m, 2H), 2.32 – 2.09 (m, 3H), 2.01 – 1.86 (m, 2H), 1.83 – 1.54 (m, 6H), 1.48 –
1.32 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl₃): δ 176.13, 107.28, 51.24, 46.26, 27.67,
27.40, 25.18, 15.13; HRMS (ESI-TOF) m/z Calcd for C\(_{17}\)H\(_{17}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 341.1272,
found 341.1271.

![Chemical structure](image)

**General Procedure for the Preparation of Amides 1f-h\(^3\)**

A solution of LiAl(Or-Bu)₃H (1.0 M, 20.0 mmol, 2.0 equiv) in THF was slowly added
to a cooled (−78 °C) solution of S₃ (10.0 mmol, 1.0 equiv) in THF (10 mL). The
reaction mixture was allowed to warm to room temperature and stirred for 12 h. The
reaction was quenched by careful addition of 2 N HCl (15 mL) and extracted with
EtOAc. The combined organic layers were washed with brine, dried over anhydrous
Na\(_2\)SO₄, filtered and concentrated under vacuum. The residue was purified by column
chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give S₄ as a colorless
oil.

Trifluoromethanesulfonic acid (1.2 mmol, 0.3 equiv) was added dropwise to a cooled
(0 °C) solution of S₄ (4.0 mmol, 1.0 equiv) and benzyl trichloroacetimidate (8.0
mmol, 2.0 equiv) in DCM (30 mL) and hexanes (15 mL). After being stirred at room
temperature for 24 h, the reaction was quenched with saturated NaHCO₃ solution and
extracted with DCM. The combined organic layers were dried over anhydrous
Na\(_2\)SO₄, filtered and concentrated under vacuum. The residue was purified by column
chromatography on silica gel (eluent: EtOAc/hexanes = 1: 10) to give S₅ as a colorless
oil.
Diisopropyl azodicarboxylate (DEAD) (6.0 mmol, 1.5 equiv) was added to a cooled (0 °C) solution of S4 (4 mmol, 1.0 equiv), triphenylphosphine (6.0 mmol, 1.5 equiv) and phthalimide (6.0 mmol, 1.5 equiv) in THF (10 mL) under an argon atmosphere. After being stirred at room temperature for 12 h, the reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give S6 as a white solid.

NaOH (6.0 mmol, 2.0 equiv) was added to a cooled (0 °C) solution of S4-6 (3 mmol, 1.0 equiv) in dioxane (6 mL) and H2O (3 mL). The reaction mixture was stirred for 3 h at room temperature, then poured into 2 N HCl (5 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na2SO4, filtered and concentrated to give the desired carboxylic acid, which could be used directly in the next step without further purification.

An acid chloride, prepared from the corresponding carboxylic acid (2 mmol, 1.0 equiv) and oxalyl chloride (See general procedure for the synthesis of amides 1a-e), was added to a vigorously stirred solution of 4-amino-2,3,5,6-tetrafluorobenzonitrile (2.4 mmol, 1.2 equiv) in toluene (1 mL). After being refluxed for 12 h, the reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give the corresponding amide.

1-(Chloromethyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)cyclobutanecarboxamide (1f)

White solid; mp: 101-102 °C; 1H NMR (400 MHz, CDCl3): δ 7.43 (s, 1H), 3.94 (s, 2H), 2.64 – 2.54 (m, 2H), 2.23 – 1.97 (m, 4H); 13C NMR (100 MHz, CDCl3): δ 172.52, 107.27, 49.84, 49.15, 28.72, 14.75; HRMS (ESI-TOF) m/z Calcd for C13H10ClF4N2O [M+H]+ 321.0412, found 321.0414.
1-((Benzyloxy)methyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)cyclobutanecarboxamide (1g)

White solid; mp: 68-69 °C; ^1H NMR (400 MHz, CDCl3): δ 8.76 (s, 1H), 7.50 – 7.28 (m, 5H), 4.69 (s, 2H), 3.80 (s, 2H), 2.70 – 2.45 (m, 2H), 2.18 – 1.83 (m, 4H); ^13C NMR (100 MHz, CDCl3): δ 173.28, 136.50, 128.66, 128.33, 127.96, 107.47, 74.06, 72.80, 47.47, 27.04, 15.62; HRMS (ESI-TOF) m/z Calcd for C_{20}H_{17}F_{4}N_{2}O_{2} [M+H]^+ 393.1221, found 393.1223.

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-((1,3-dioxoisindolin-2-yl)methyl)-cyclobutanecarboxamide (1h)

White solid; mp: 137-138 °C; ^1H NMR (400 MHz, CDCl3): δ 8.11 (s, 1H), 7.90 – 7.84 (m, 2H), 7.80 – 7.73 (m, 2H), 4.18 (s, 2H), 2.62 – 2.52 (m, 2H), 2.34 – 2.25 (m, 2H), 2.20 – 1.95 (m, 2H); ^13C NMR (100 MHz, CDCl3): δ 173.11, 168.82, 134.52, 131.53, 123.72, 107.42, 49.54, 43.55, 29.53, 15.39; HRMS (ESI-TOF) m/z Calcd for C_{21}H_{14}F_{4}N_{3}O_{3} [M+H]^+ 432.0966, found 432.0967.

**General Procedure for the Preparation of Amides 4a-d**

Oxalyl chloride (3.0 mmol, 1.5 equiv) was added slowly to a cold (0 °C) solution of S7 (2.0 mmol, 1.0 equiv) in DCM (8 mL) and DMF (0.05 mL). After being stirred at room temperature for 45 min, the reaction mixture was concentrated under vacuum to
give the corresponding acid chloride. 4-Amino-2,3,5,6-tetrafluorobenzonitrile (2.4 mmol, 1.2 equiv) and toluene (1 mL) was then added. After being refluxed (145 °C) for 12 h, the reaction mixture was concentrated under vacuum and purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give the corresponding amide.

\[
\begin{align*}
\text{N-}(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})-2,2,3,3\text{-tetramethylbutanamide (4a)}
\end{align*}
\]
White solid; mp: 119-120 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.25 (s, 1H), 1.31 (s, 6H), 1.04 (s, 9H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 174.61, 107.32, 48.90, 35.44, 25.98, 21.41. HRMS (ESI-TOF) m/z Calcd for C\(_{15}\)H\(_{17}\)F\(_{4}\)N\(_2\)O [M+H]\(^+\) 317.1277, found 317.1279.

\[
\begin{align*}
\text{N-}(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})-2,2,3\text{-trimethylbutanamide (4b)}
\end{align*}
\]
White solid; mp: 96-97 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.37 (s, 1H), 2.01 (hept, \(J = 6.8\) Hz, 1H), 1.23 (s, 6H), 0.95 (d, \(J = 6.8\) Hz, 6H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 176.15, 107.31, 46.69, 35.65, 21.49, 17.36. HRMS (ESI-TOF) m/z Calcd for C\(_{14}\)H\(_{15}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 303.1115, found 303.1116.

\[
\begin{align*}
\text{N-}(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})-2,2\text{-dimethylbutanamide (4c)}
\end{align*}
\]
White solid; mp: 73-74 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.29 (s, 1H), 1.68 (q, \(J = 6.8\) Hz, 2H), 1.33 (s, 6H), 0.97 (d, \(J = 6.8\) Hz, 6H). \(^1\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 176.15, 107.31, 46.69, 35.65, 21.49, 17.36. HRMS (ESI-TOF) m/z Calcd for C\(_{14}\)H\(_{15}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 303.1115, found 303.1116.
7.4 Hz, 2H), 1.31 (s, 6H), 0.94 (t, \( J = 7.5 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 175.60, 107.31, 43.71, 33.91, 24.80, 8.94. HRMS (ESI-TOF) m/z Calcd for C\(_{13}\)H\(_{13}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 289.0959, found 289.0957.

\[\text{N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-(2,6-difluorophenyl)-2-methylpropanamide (4d)}\]

White solid; mp: 82-83 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.36 – 7.27 (m, 1H), 7.14 (s, 1H), 6.95 (t, \( J = 9.1 \) Hz, 2H), 1.77 (s, 7H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 174.21, 162.61 (d, \( J = 8.3 \) Hz), 160.12 (d, \( J = 8.5 \) Hz), 129.82 (t, \( J = 11.3 \) Hz), 112.79 (d, \( J = 26.7 \) Hz), 107.25, 45.90, 26.52 (t, \( J = 4.2 \) Hz). HRMS (ESI-TOF) m/z Calcd for C\(_{17}\)H\(_{11}\)F\(_6\)N\(_2\)O [M+H]\(^+\) 373.0770, found 373.0776.

L1-L5 were commercially available. L6 was prepared according to our previously reported procedures.\(^2\) Other ligands were synthesized according to the general procedures shown below.

\[\text{General Procedure for the Preparation of Ligand L7-21}^{4,5}\]

\( O \)-Alkylhydroxylamine hydrochloride salt (1.5 equiv) and \( N,N \)-diisopropylethylamine (DIPEA, 1.5 equiv) were added to a cooled (0 °C) solution of S8 (1.0 equiv), HOBt (1.1 equiv) and EDC (1.1 equiv) in DCM (0.25 M). After being stirred at room temperature for 8 h, the reaction mixture was poured into H\(_2\)O. The organic layer was separated, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: MeOH/DCM =
1: 20) to give the corresponding ligand.

(S)-tert-Butyl 1-(methoxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (L7)

White solid; mp: 59-60 °C; [α]_D^{20} = −56.4 (c = 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃): δ 9.97 (s, 1H), 7.28 (s, 1H), 5.28 (d, J = 8.7 Hz, 1H), 4.07 (ddd, J = 8.7, 8.0, 8.0 Hz, 1H), 3.75 (s, 3H), 1.75 – 1.52 (m, 3H), 0.94 (d, J = 6.5 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H); ^13C NMR (100 MHz, CDCl₃): δ 169.98, 155.99, 80.31, 64.06, 50.37, 40.80, 28.26, 24.59, 22.69, 22.02. HRMS (ESI-TOF) m/z Calcd for C₁₂H₂₃N₂O₄ [M+H]^+ 261.1809, found 261.1813.

(S)-tert-Butyl 1-(isopropoxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (L8)

White solid; mp: 70-71 °C; [α]_D^{20} = −54.1 (c = 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃): δ 9.40 (s, 1H), 5.15 (d, J = 8.6 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.06 (ddd, J = 8.6, 7.9, 7.9 Hz, 1H), 1.71 – 1.49 (m, 3H), 1.43 (s, 9H), 1.24 (d, J = 3.5 Hz, 3H), 1.23 (d, J = 3.5 Hz, 3H), 0.93 (d, J = 6.3 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H); ^13C NMR (100 MHz, CDCl₃): δ 170.14, 155.91, 80.25, 77.86, 50.43, 40.49, 28.27, 24.63, 22.55, 22.25, 20.46, 20.39. HRMS (ESI-TOF) m/z Calcd for C₁₄H₂₉N₂O₄ [M+H]^+ 289.2122, found 289.2120.

(S)-tert-Butyl 1-(tert-butoxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (L9)

White foam; [α]_D^{20} = −55.0 (c = 1.0, CHCl₃); ^1H NMR (400 MHz, CDCl₃): δ 9.40 (s, 1H), 5.39 (d, J = 8.3 Hz, 1H), 4.22 – 4.05 (m, 1H), 1.78 – 1.49 (m, 3H), 1.43 (s, 9H),
1.27 (s, 9H), 0.94 (d, \( J = 6.6 \) Hz, 3H), 0.91 (d, \( J = 6.5 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): 170.99, 155.87, 82.01, 79.93, 50.59, 40.77, 28.23, 26.21, 24.57, 22.45, 22.23. HRMS (ESI-TOF) m/z Calcd for C\(_{15}\)H\(_{31}\)N\(_2\)O\(_4\) [M+H]\(^{+}\) 303.2278, found 303.2273.

\(\text{(S)-Benzyl (1-(methoxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (L10)}\)

White solid; mp: 98-99 °C; [\(\alpha\)]\(_{D}^{20}\) = –43.7 (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.76 (s, 1H), 7.38 – 7.27 (m, 5H), 5.58 (d, \( J = 8.7 \) Hz, 1H), 5.10 (d, \( J = 12.3 \) Hz, 1H), 5.02 (d, \( J = 12.3 \) Hz, 1H), 4.18 – 4.08 (m, 1H), 3.72 (s, 3H), 1.71 – 1.50 (m, 3H), 0.93 (d, \( J = 6.1 \) Hz, 3H), 0.91 (d, \( J = 6.2 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.64, 156.44, 135.90, 128.50, 128.21, 127.93, 67.17, 64.17, 50.86, 40.77, 24.56, 22.63, 22.07. HRMS (ESI-TOF) m/z Calcd for C\(_{15}\)H\(_{23}\)N\(_2\)O\(_4\) [M+H]\(^{+}\) 295.1652, found 295.1656.

\(\text{(S)-[(9H-Fluoren-9-yl)methyl (1-(methoxyamino)-4-methyl-1-oxopentan-2-yl)carbamate (L11)}\)

White solid; mp: 129-130 °C; [\(\alpha\)]\(_{D}^{20}\) = –40.2 (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 10.05 (s, 1H), 7.80 – 7.15 (m, 8H), 5.82 (d, \( J = 8.9 \) Hz, 1H), 4.38 – 4.25 (m, 2H), 4.24 – 4.16 (m, 1H), 4.09 (dd, \( J = 7.1, 7.1 \) Hz, 1H), 3.68 (s, 3H), 1.72 – 1.50 (m, 3H), 0.93 (d, \( J = 6.1 \) Hz, 3H), 0.91 (d, \( J = 6.1 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 169.59, 156.43, 143.55, 143.42, 141.15, 127.67, 127.00, 126.96, 124.94, 119.90, 67.23, 64.08, 50.77, 46.83, 41.05, 24.56, 22.61, 22.11. HRMS (ESI-TOF) m/z Calcd for C\(_{22}\)H\(_{27}\)N\(_2\)O\(_4\) [M+H]\(^{+}\) 383.1965, found 383.1968.
(S)-N-Methoxy-4-methyl-2-(2,2,2-trifluoroacetamido)pentanamide (L12)

White solid; mp: 61-62 °C; $[\alpha]_D^{20} = -58.8$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 10.37 (s, 1H), 8.02 (d, $J = 8.6$ Hz, 1H), 4.62 (ddd, $J = 8.6, 7.9, 7.9$ Hz, 1H), 3.76 (s, 3H), 1.78 – 1.60 (m, 3H), 0.96 (d, $J = 6.3$ Hz, 3H), 0.94 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 167.91, 157.62 (q, $J = 37.8$ Hz), 115.60 (q, $J = 287.4$ Hz), 64.12, 49.65, 40.63, 24.63, 22.35, 22.06. HRMS (ESI-TOF) m/z Calcd for C$_9$H$_{16}$F$_3$N$_2$O$_3$ [M+H]$^+$ 257.1108, found 257.1104.

Formamido-N-methoxy-4-methylpentanamide (L13)

Colorless oil; mp: 192-193 °C; $[\alpha]_D^{20} = -43.8$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 10.60 (s, 1H), 8.16 (s, 1H), 7.31 (d, $J = 7.7$ Hz, 1H), 4.65 – 4.54 (m, 1H), 3.75 (s, 3H), 1.70 – 1.56 (m, 3H), 0.94 (d, $J = 5.8$ Hz, 3H), 0.91 (d, $J = 5.8$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.11, 161.61, 64.07, 47.65, 40.95, 24.61, 22.58, 22.03. HRMS (ESI-TOF) m/z Calcd for C$_8$H$_{17}$N$_2$O$_3$ [M+H]$^+$ 189.1234, found 189.1234.

(1-(Methoxyamino)-4-methyl-1-oxopentan-2-yl)benzamide (L14)

White solid; mp: 103-104 °C; $[\alpha]_D^{20} = -3.9$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): δ 10.74 (s, 1H), 7.87 – 7.33 (m, 6H), 4.77 (ddd, $J = 8.0, 7.9, 7.9$ Hz, 1H), 3.73 (s, 3H), 1.79 – 1.61 (m, 3H), 0.92 (d, $J = 6.0$ Hz, 3H), 0.89 (d, $J = 6.1$ Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 169.47, 167.73, 133.29, 131.88, 128.48, 127.26, 64.04, 49.55, 40.71, 24.80, 22.54, 22.23. HRMS (ESI-TOF) m/z Calcd for
C_{14}H_{21}N_{2}O_{3} [M+H]^+ 265.1547, found 265.1541.

\[
\begin{align*}
\text{Boc-NH} & \quad \text{O} \\
& \quad \text{Me} \\
& \quad \text{NHOMe}
\end{align*}
\]

(S)-**tert-Butyl (1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L15)**

White solid; mp: 58-59 °C; [α]_D^{20} = -74.7 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.89 (s, 1H), 5.34 (d, J = 7.8 Hz, 1H), 4.24 – 4.06 (m, 1H), 3.76 (s, 3H), 1.45 (s, 9H), 1.37 (d, J = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 170.18, 155.69, 80.39, 64.14, 47.51, 28.26, 18.03. HRMS (ESI-TOF) m/z Calcd for C₉H₁₉N₂O₄ [M+H]^+ 219.1339, found 219.1343.

\[
\begin{align*}
\text{Boc-NH} & \quad \text{O} \\
& \quad \text{Me} \\
& \quad \text{NHOMe}
\end{align*}
\]

(S)-**tert-Butyl (1-(methoxyamino)-3-methyl-1-oxobutan-2-yl)carbamate (L16)**

White solid; mp: 78-79 °C; [α]_D^{20} = -38.2 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 10.40 (s, 1H), 5.60 (d, J = 9.0 Hz, 1H), 3.87 (dd, J = 9.0, 8.8 Hz, 1H), 3.76 (s, 3H), 2.11 – 1.95 (m, 1H), 1.45 (s, 9H), 0.98 (d, J = 7.1 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃): δ 168.92, 156.02, 79.95, 63.88, 57.49, 31.02, 28.19, 18.97, 18.42. HRMS (ESI-TOF) m/z Calcd for C₁₁H₂₃N₂O₄ [M+H]^+ 247.1652, found 247.1653.

\[
\begin{align*}
\text{Boc-NH} & \quad \text{O} \\
& \quad \text{Me} \\
& \quad \text{NHOMe}
\end{align*}
\]

(S)-**tert-Butyl (1-(methoxyamino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (L17)**

White solid; mp: 77-78 °C; [α]_D^{20} = -9.9 (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 10.14 (s, 1H), 5.50 (d, J = 9.9 Hz, 1H), 3.87 (d, J = 9.9 Hz, 1H), 3.75 (s, 3H), 1.45 (s, 9H), 1.02 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.04, 156.09, 80.14, 64.00, 59.20, 34.57, 28.26, 26.37. HRMS (ESI-TOF) m/z Calcd for C₁₂H₂₅N₂O₄ [M+H]^+ 261.1809, found 261.1814.
(S)-tert-Butyl (1-(methoxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate (L18)

White solid; mp: 101-102 °C; \([\alpha]_D^{20} = -8.3\) (c = 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 10.01 (s, 1H), 7.31 – 7.14 (m, 5H), 5.61 (d, \(J = 8.6\) Hz, 1H), 4.35 (ddd, \(J = 8.6, 7.4, 7.4\) Hz, 1H), 3.57 (s, 3H), 3.04 (dd, \(J = 13.0, 7.3\) Hz, 1H), 2.98 (dd, \(J = 13.0, 7.4\) Hz, 1H), 1.37 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 168.62, 155.57, 136.29, 129.30, 128.35, 126.73, 80.17, 63.84, 53.25, 38.78, 28.15. HRMS (ESI-TOF) m/z Calcd for \(\text{C}_{15}\text{H}_{23}\text{N}_2\text{O}_4\) [M+H]⁺ 295.1652, found 295.1652.

(S)-tert-Butyl

(3-(4-(tert-butoxy)phenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L19)

White solid; mp: 92-93 °C; \([\alpha]_D^{20} = -6.6\) (c = 1.0, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃): \(\delta\) 9.77 (s, 1H), 7.07 (d, \(J = 8.0\) Hz, 2H), 6.85 (d, \(J = 8.0\) Hz, 2H), 5.50 (d, \(J = 8.2\) Hz, 1H), 4.25 (ddd, \(J = 8.2, 7.9, 7.8\) Hz, 1H), 3.54 (s, 3H), 2.95 (dd, \(J = 13.2, 7.9\) Hz, 1H), 2.92 (dd, \(J = 13.2, 7.8\) Hz, 1H), 1.35 (s, 9H), 1.27 (s, 9H); \(^{13}\)C NMR (100 MHz, CDCl₃): \(\delta\) 168.68, 155.55, 154.09, 131.15, 129.77, 124.10, 80.17, 78.26, 63.92, 53.33, 38.00, 28.69, 28.19. HRMS (ESI-TOF) m/z Calcd for \(\text{C}_{19}\text{H}_{31}\text{N}_2\text{O}_5\) [M+H]⁺ 367.2227, found 367.2223.
(S)-**tert-Butyl**

(1-(methoxyamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)carbamate (L20)

White solid; mp: 144-145 °C; \([\alpha]_D^{20} = -5.4\) (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.69 (s, 1H), 7.80 – 7.27 (m, 7H), 5.50 (d, J = 8.7 Hz, 1H), 4.40 (ddd, J = 8.6, 7.8, 7.7 Hz, 1H), 3.52 (s, 3H), 3.20 (dd, J = 13.6, 7.8 Hz, 1H), 3.13 (dd, J = 13.6, 7.7 Hz, 1H), 1.30 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.67, 155.63, 133.78, 133.35, 132.34, 128.15, 128.07, 127.52, 127.36, 126.02, 125.61, 80.39, 63.98, 53.42, 38.88, 28.12. HRMS (ESI-TOF) m/z Calcd for C₁₉H₂₅N₂O₄ [M+H]⁺ 345.1809, found 345.1812.

(S)-**tert-Butyl**

(3-(2,6-difluorophenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L21)

White solid; mp: 128-129 °C; \([\alpha]_D^{20} = -24.7\) (c = 1.0, CHCl₃); ¹H NMR (400 MHz, CDCl₃): δ 9.50 (s, 1H), 7.24 – 7.15 (m, 1H), 6.91 – 6.82 (m, 2H), 5.26 (d, J = 8.9 Hz, 1H), 4.31 (ddd, J = 8.9, 7.9, 7.6 Hz, 1H), 3.72 (s, 3H), 3.16 (dd, J = 13.8, 7.6 Hz, 1H), 3.07 (dd, J = 13.8, 7.9 Hz, 1H), 1.35 (s, 9H); ¹³C NMR (100 MHz, CDCl₃): δ 168.27, 161.74 (dd, J = 247.7, 8.5 Hz), 155.50, 128.55 (t, J = 10.3 Hz), 112.43 (t, J = 20.0 Hz), 110.97 (dd, J = 20.1, 8.5 Hz), 80.17, 63.85, 51.26, 28.07, 25.55. HRMS (ESI-TOF) m/z Calcd for C₁₃H₂₁F₂N₂O₄ [M+H]⁺ 331.1464, found 331.1469.
4-Nitrobenzenesulfonyl chloride (NsCl, 50 mmol, 1.0 equiv) was added to a cooled (0 °C) solution of L-phenylalanine methyl ester hydrochloride (L-Phe-OMe·HCl, 50 mmol, 1.0 equiv) and triethylamine (TEA, 150 mmol, 3.0 equiv) in DCM (150 mL). After being stirred at room temperature for 12 h, the reaction mixture was poured into H₂O. The organic layer was separated, dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. The residue was purified by trituration with a mixture of 50% DCM/hexanes to give S9.

S9 (8.0 mmol, 1.0 equiv), Pd(OAc)₂ (0.075 equiv), Ar-BPin (2.0 equiv), Ac-Val-OH (0.2 equiv), Ag₂CO₃ (2.0 equiv), Na₂CO₃ (2.0 equiv), BQ (0.5 equiv), H₂O (5.0 equiv), and DMSO (0.4 equiv) were weighed in air and placed in a Schlenk tube with a magnetic stir bar. t-AmylOH (50 mL) was added, and the reaction vessel was evacuated and backfilled with nitrogen (x3). The reaction mixture was heated to 80 °C for 24 h under vigorous stirring. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite eluting with EtOAc. The filtrate was concentrated under vacuum and the resulting residue was purified by flash chromatography on silica gel (eluent: EtOAc/hexanes = 1: 3) to
give S10.
4-Methoxybenzenethiol (PMP-SH, 20.0 mmol, 4.0 equiv) and potassium carbonate (20.0 mmol, 4.0 equiv) were added to a solution of S10 (5.0 mmol, 1.0 equiv) in MeCN (40 mL) and DMSO (1.5 mL). After being stirred at room temperature for 12 h, the reaction mixture was diluted with EtOAc, washed with H2O and brine, dried over anhydrous Na2SO4, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 1) to give S11.
Boc2O (8.0 mmol, 2.0 equiv) was added to a solution of S11 (4.0 mmol, 1.0 equiv) and triethylamine (8.0 mmol, 2.0 equiv) in DCM (20 mL). After being stirred at room temperature for 12 h, the reaction mixture was quenched with saturated NH4Cl solution and extracted with DCM. The combined organic layers were dried over anhydrous Na2SO4, filtered and concentrated to give S12, which could be used directly in the next step without further purification.
LiOH (8.0 mmol) was added to a suspension of S12 in THF (8 mL), and H2O (4 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was quenched with 10% aqueous citric acid solution and extracted EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na2SO4, filtered and concentrated to give S13, which could be used directly in the next step without further purification.
O-Methylhydroxylamine hydrochloride salt (3.0 mmol, 1.5 equiv) and DIPEA (3.0 mmol, 1.5 equiv) were added to a cooled (0 °C) solution of S13 (2.0 mmol, 1.0 equiv), HOBt (2.2 mmol, 1.1 equiv) and EDC (2.2 mmol, 1.1 equiv) in DCM (8 mL). After being stirred at room temperature for 8 h, the reaction mixture was poured into H2O. The organic layer was separated, dried over anhydrous Na2SO4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: MeOH/DCM = 1: 20) to give the corresponding ligand.
(S)-tert-Butyl

(3-(2,6-diphenylphenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L22)

White solid; mp: 67-68 °C; [α]_D^{20} = −15.1 (c = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.52 – 7.13 (m, 14H), 4.24 (d, J = 8.9 Hz, 1H), 3.67 – 3.55 (m, 1H), 3.48 (s, 3H), 3.09 (d, J = 14.6 Hz, 1H), 2.92 (dd, J = 14.6, 11.0 Hz, 1H), 1.32 (s, 9H); ^13C NMR (100 MHz, CDCl_3): δ 168.84, 155.12, 143.24, 141.73, 132.24, 129.60, 129.54, 128.48, 127.29, 126.40, 79.70, 64.09, 52.51, 31.78, 28.16. HRMS (ESI-TOF) m/z Calcd for C_{27}H_{31}N_2O_4 [M+H]^+ 447.2278, found 447.2280.

(S)-tert-Butyl

(3-(2,6-di(biphenyl)phenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L23)

Yellow solid; mp: 96-97 °C; [α]_D^{20} = +5.9 (c = 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3): δ 7.77 – 7.25 (m, 22H), 4.34 (d, J = 9.2 Hz, 1H), 3.70 (dd, J =10.8, 9.2 Hz, 1H), 3.40 (s, 3H), 3.22 (d, J = 14.6 Hz, 1H), 3.03 (dd, J = 14.6, 10.8 Hz, 1H), 1.33 (s, 9H); ^13C NMR (100 MHz, CDCl_3): δ 168.94, 155.18, 142.96, 140.67, 140.38, 140.25, 132.45, 130.09, 129.71, 128.83, 127.49, 127.21, 127.05, 126.58, 79.81, 64.14, 52.62, 31.96, 28.21. HRMS (ESI-TOF) m/z Calcd for C_{39}H_{39}N_2O_4 [M+H]^+ 599.2904, found 599.2903.
(S)-tert-Butyl

(3-(2,6-di(4-methoxylphenyl)phenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L24)

White foam; [α]D^{20} = −9.0 (c = 1.0, CHCl₃); $^1$H NMR (400 MHz, CDCl₃): δ 7.71 (br s, 1H), 7.37 – 6.91 (m, 11H), 4.27 (d, $J = 8.8$ Hz, 1H), 3.85 (s, 6H), 3.61 (dd, $J = 11.0$, 8.8 Hz, 1H), 3.50 (s, 3H), 3.11 (d, $J = 14.2$ Hz, 1H), 2.95 (dd, $J = 14.2$, 11.0 Hz, 1H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl₃): δ 168.97, 158.74, 155.16, 142.90, 134.02, 132.77, 130.61, 129.60, 126.32, 113.86, 79.68, 64.02, 55.21, 52.55, 31.54, 28.12. HRMS (ESI-TOF) m/z Calcd for C$_{29}$H$_{35}$N$_2$O$_4$ [M+H]$^+$ 507.2490, found 507.2492.

![Chemical Structure](attachment:image.png)

(3-(2,6-di(4-fluorophenyl)phenyl)-1-(methoxyamino)-1-oxopropan-2-yl)carbamate (L25)

White solid; mp: 72-73 °C; [α]D^{20} = −19.2 (c = 1.0, CHCl₃); $^1$H NMR (400 MHz, CDCl₃): δ 8.22 (s, 1H), 7.45 – 7.03 (m, 11H), 4.24 (d, $J = 9.2$ Hz, 1H), 3.61 (d, $J = 10.6$, 9.2 Hz, 1H), 3.49 (s, 3H), 3.10 (d, $J = 12.9$ Hz, 1H), 2.94 (dd, $J = 12.9$, 10.6 Hz, 1H), 1.31 (s, 9H); $^{13}$C NMR (100 MHz, CDCl₃): δ 168.55, 162.00 (d, $J = 247.0$ Hz), 155.09, 142.45, 137.47, 132.20, 131.08 (d, $J = 7.8$ Hz), 129.88, 126.51, 115.41 (d, $J = 21.6$ Hz), 80.06, 64.02, 52.29, 31.34, 28.10. HRMS (ESI-TOF) m/z Calcd for C$_{27}$H$_{29}$F$_2$N$_2$O$_4$ [M+H]$^+$ 483.2090, found 483.2087.
Optimization of Reaction Conditions

Table S1. Screening of Bases$^{a,b}$

| Base         | Yield | ee   | Base     | Yield | ee   |
|--------------|-------|------|----------|-------|------|
| LiOH.H$_2$O  | 1%    | ---  | KOAc     | 29%   | 69%  |
| Li$_2$CO$_3$ | 35%   | 80%  | CsOAc    | 2%    | ---  |
| Na$_2$CO$_3$ | 67%   | 88%  | NaHCO$_3$| 59%   | 87%  |
| K$_2$CO$_3$  | 2%    | ---  | KHCO$_3$ | 64%   | 88%  |
| Cs$_2$CO$_3$ | 1%    | ---  | Na$_3$PO$_4$| 3%   | ---  |
| LiOAc        | 33%   | 67%  | NaH$_2$PO$_4$| 5%   | ---  |
| NaOAc        | 50%   | 86%  | Na$_2$HPO$_4$| 65% | 88%  |

$^a$ Reaction conditions: substrate 1a (0.1 mmol), Ph-BPin (2.0 equiv), Pd(OAc)$_2$ (10 mol %), [L$_{25}$] (11 mol %), Ag$_2$CO$_3$ (1.5 equiv), base (3.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 70 °C. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_3$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Table S2. Stoichiometry Optimization\textsuperscript{a,b}

![Chemical structure diagram]

| Pd | ligand | Ph-Bpin | Ag\textsubscript{2}CO\textsubscript{3} | Na\textsubscript{2}CO\textsubscript{3} | yield | ee  |
|----|--------|---------|----------------|----------------|-------|-----|
| 0.10 | 0.11 | 2.0 | 1.5 | 1.0 | 62% | 87% |
| 0.10 | 0.11 | 2.0 | 1.5 | 2.0 | 67% | 88% |
| 0.10 | 0.11 | 2.0 | 1.5 | 3.0 | 67% | 88% |
| 0.10 | 0.11 | 2.0 | 2.0 | 2.0 | 73% | 91% |
| **0.10** | **0.11** | **2.0** | **2.5** | **2.0** | **79%** | **92%** |
| 0.10 | 0.11 | 2.0 | 3.0 | 2.0 | 77% | 91% |
| 0.10 | 0.15 | 2.0 | 1.5 | 2.0 | 56% | 90% |
| 0.05 | 0.05 | 2.0 | 1.5 | 2.0 | 44% | 82% |

\textsuperscript{a} Reaction conditions: substrate 1\textsuperscript{a} (0.1 mmol), Ph-BPin, Pd(OAc\textsubscript{2})\textsubscript{2}, L25, Ag\textsubscript{2}CO\textsubscript{3}, Na\textsubscript{2}CO\textsubscript{3}, BQ (0.5 equiv), H\textsubscript{2}O (5.0 equiv), t-AmyLOH (0.5 mL), N\textsubscript{2}, 70 °C. \textsuperscript{b} The yield was determined by \textsuperscript{1}H NMR analysis of the crude product using CH\textsubscript{2}Br\textsubscript{2} as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Table S3. Solvent Effects $^{a,b}$

| solvent        | yield | ee  | solvent         | yield | ee  |
|----------------|-------|-----|-----------------|-------|-----|
| t-AmylOH       | 73%   | 91% | t-AmylOH/DMF (1:1) | 51%   | 77% |
| THF            | 62%   | 88% | t-AmylOH/DMSO (1:1) | 34%   | 80% |
| i-PrOH         | 28%   | 77% | t-AmylOH/THF (1:1) | 21%   | 78% |
| t-BuOH         | 55%   | 83% | t-AmylOH/Hexane (1:1) | 33%   | 84% |
| HFIP           | n.p. | --- | t-AmylOH/CH$_3$CN (1:1) | 35%   | 69% |
| t-AmylOH/DCE (1:1) | 45%   | 85% | t-AmylOH/EtOAc (1:1) | 45%   | 89% |
| t-AmylOH/DME (1:1) | 57%   | 88% | t-AmylOH/Toluene (1:1) | 40%   | 85% |

$^a$ Reaction conditions: substrate 1a (0.1 mmol), Ph-BPin (2.0 equiv), Pd(OAc)$_2$ (10 mol %), L$_{25}$ (11 mol %), Ag$_2$CO$_3$ (2.0 equiv), Na$_2$CO$_3$ (2.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), solvent (0.5 mL), N$_2$, 70 °C. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_2$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Table S4. Screening of Pd Sources$^{a,b}$

| Pd                  | yield  | ee  |
|---------------------|--------|-----|
| Pd(OAc)$_2$         | 79% (75%)$^c$ | 92% |
| PdCl$_2$            | trace  | --- |
| Pd(OPiv)$_2$        | 57%    | 81% |
| Pd(TFA)$_2$         | 19%    | --- |
| Pd(OTf)$_2$(CH$_3$CN)$_4$ | trace | --- |
| Pd(PPh$_3$)$_4$     | trace  | --- |

$^a$ Reaction conditions: substrate 1a (0.1 mmol), Ph-BPin (2.0 equiv), Pd (10 mol %), L25 (11 mol %), Ag$_2$CO$_3$ (2.5 equiv), Na$_2$CO$_3$ (2.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 70 ºC. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_2$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. $^c$ Isolated yield.
**Table S5. Screening of Directing Groups**$^{a,b}$

| R | Reaction conditions | yield | ee  |
|---|---------------------|-------|-----|
| ![NC](image) | substrate (0.1 mmol), Ph-BPin (2.0 equiv), Pd(OAc)$_2$ (10 mol%), L25 (11 mol%), Ag$_2$CO$_3$ (2.5 equiv), Na$_2$CO$_3$ (2.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 70 °C, 24 h. | 79%   | 92% |
| ![F$_3$C](image) | The yield was determined by $^1$H NMR analysis of the crude product using CH$_3$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. | 55%   | 85% |
| ![F$_3$C](image) | n.p. | --  |

$^a$ Reaction conditions: **substrate** (0.1 mmol), Ph–BPin (2.0 equiv), Pd(OAc)$_2$ (10 mol%), L$_{25}$ (11 mol%), Ag$_2$CO$_3$ (2.5 equiv), Na$_2$CO$_3$ (2.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 70 °C, 24 h. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_3$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Table S6. Additional Ligand Screening\textsuperscript{a,b}

| Ligand | Reaction Conditions | Yield | ee (%) |
|--------|---------------------|-------|--------|
| Boc-NH-CONHMe | substrate 1a (0.1 mmol), Ph-BPin (2.0 equiv), Pd(OAc)\textsubscript{2} (10 mol%), ligand (11 mol%), Ag\textsubscript{2}CO\textsubscript{3} (1.5 equiv), Na\textsubscript{2}CO\textsubscript{3} (2.0 equiv), BQ (0.5 equiv), H\textsubscript{2}O (5.0 equiv), t-AmylOH (0.5 mL), N\textsubscript{2}, 70 °C, 24 h. \textsuperscript{b} The yield was determined by \textsuperscript{1}H NMR analysis of the crude product using CH\textsubscript{2}Br\textsubscript{2} as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. | 29% | 79% |
| Boc-NH-CONBOc | | 33% | 78% |
| Boc-NH-CONHOMe | | 25% | 76% |
| Boc-NH-CONHOMe | | 52% | 82% |
| Boc-NH-CONHOMe | | 36% | 75% |
| Boc-NH-CONHOMe | | 42% | 78% |
| Boc-NH-CONHOMe | | 51% | 80% |
| Boc-NH-CONHOMe | | 52% | 81% |
| Boc-NH-CONHOMe | | 38% | 76% |
| Boc-NH-CONHOMe | | 40% | 75% |
| Boc-NH-CONHOMe | | 27% | 17% |
| Boc-NH-CONHOMe | | 38% | 45% |
Enantioselective C\((sp^3)\)–\(H\) Activation of Cyclobutanecarboxylic Acid Derivatives

Substrate 1 (0.1 mmol, 1.0 equiv), Pd(OAc)\(_2\) (0.1 equiv), Ar-BPin (2.0 equiv), L25 (0.11 equiv), Ag\(_2\)CO\(_3\) (2.5 equiv), Na\(_2\)CO\(_3\) (2.0 equiv), BQ (0.5 equiv), H\(_2\)O (5.0 equiv) and \(\tau\)-AmylOH (0.5 mL) were added into a 10 ml sealed tube. The reaction vessel was evacuated and backfilled with nitrogen (\(\times 3\)). The reaction mixture was heated to 70 °C for 24 h under vigorous stirring. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite, eluting with EtOAc. The filtrate was concentrated under vacuum and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product. The \(ee\) value was determined on a Hitachi LaChrom HPLC system using commercially available chiral columns as described below.

\[
\text{N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-phenylcyclobutanecarboxamide (2a, enantioenriched)}
\]

Colorless oil; \([\alpha]_{D}^{20} = -3.7\) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.41 – 7.20 (m, 5H), 6.25 (s, 1H), 3.59 (dd, \(J = 8.8, 8.8\) Hz, 1H), 2.79 (ddd, \(J = 11.6, 9.7, 4.7\) Hz, 1H), 2.41 – 2.21 (m, 2H), 2.15 – 1.97 (m, 2H), 1.92 (ddd, \(J = 11.6, 8.7, 8.7\) Hz, 1H), 0.96 (t, \(J = 7.4\) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \(\delta\) 171.75, 139.85, 129.30, 127.73, 127.19, 107.37, 57.60, 50.24, 34.11, 25.82, 21.76, 8.73; HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{17}\)F\(_4\)N\(_2\)O [M+H\(^+\)]\(^+\) 377.1272, found 377.1272. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.6 mL/min) \(t_r\) 42.813 min (major), 50.080 min (minor): 92\% \(ee\).
N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(p-tolyl)cyclobutanecarboxamide (2b, enantioenriched)

Colorless oil; \( \alpha \) \(_{\text{D}}^{20} = -15.8 \) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.16 (d, \( J = 8.7 \) Hz, 2H), 7.13 (d, \( J = 8.7 \) Hz, 2H), 6.24 (s, 1H), 3.55 (dd, \( J = 8.8, 8.8 \) Hz, 1H), 2.77 (ddd, \( J = 11.7, 9.6, 4.7 \) Hz, 1H), 2.33 (d, 3H), 2.37 – 2.20 (m, 2H), 2.11 – 1.95 (m, 2H), 1.90 (ddd, \( J = 11.7, 8.7, 8.7 \) Hz, 1H), 0.95 (t, \( J = 7.4 \) Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 171.96, 137.52, 136.76, 129.95, 127.07, 107.41, 57.72, 49.92, 34.16, 25.85, 21.83, 21.00, 8.75; HRMS (ESI-TOF) m/z Calcd for C\(_{21}\)H\(_{19}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 391.1428, found 391.1429. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.5 mL/min) \( t_\text{R} \) 39.633 min (major), 48.167 min (minor): 92% ee.

N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-(p-tolyl)cyclobutanecarboxamide (2c, enantioenriched)

White solid; mp: 140-141 °C; \( \alpha \) \(_{\text{D}}^{20} = -37.5 \) (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 7.15 (d, \( J = 8.2 \) Hz, 2H), 7.11 (d, \( J = 8.2 \) Hz, 2H), 6.49 (br s, 1H), 4.03 (ddd, \( J = 8.8, 8.8, 8.8 \) Hz, 1H), 3.68 – 3.59 (m, 1H), 2.66 – 2.49 (m, 2H), 2.41 – 2.26 (m, 2H), 2.31 (s, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): \( \delta \) 170.28, 137.52, 136.76, 129.95, 127.07, 107.36, 46.62, 42.82, 25.10, 20.99, 20.45. HRMS (ESI-TOF) m/z Calcd for C\(_{19}\)H\(_{15}\)F\(_4\)N\(_2\)O [M+H]\(^+\) 363.1115, found 363.1117. HPLC, Chiralcel AD-H column (5% isopropanol in hexanes, 0.5 mL/min) \( t_\text{R} \) = 41.080 min (minor), 46.893 min.
(major): 54% ee.

\[
N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(4-phenylphenyl)cyclobutanecarboxamide (2d, enantioenriched)
\]
Yellow foam; \([\alpha]_D^{20} = -48.9\) (c = 1.0, CHCl\(_3\)); \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.60 - 7.28\) (m, 9H), 6.30 (s, 1H), 3.63 (dd, \(J = 8.8, 8.8\) Hz, 1H), 2.82 (ddd, \(J = 11.7, 9.7, 4.6\) Hz, 1H), 2.45 – 2.25 (m, 2H), 2.16 – 2.00 (m, 2H), 1.94 (ddd, \(J = 11.7, 8.7, 8.7\) Hz, 1H), 0.98 (t, \(J = 7.4\) Hz, 3H); \(^13C\) NMR (150 MHz, CDCl\(_3\)): \(\delta 171.71, 140.82, 140.63, 138.84, 128.03, 127.64, 127.43, 127.01, 107.36, 57.76, 50.01, 34.10, 25.83, 21.86, 8.77\); HRMS (ESI-TOF) \(m/z\) Calcd for C\(_{26}\)H\(_{21}\)F\(_4\)N\(_2\)O \([M+H]^+\) 453.1585, found 453.1587. HPLC, Chiralcel OD-H column (10% isopropanol in hexanes, 0.3 mL/min) \(t_r = 63.960\) min (major), 70.813 min (minor): 91% ee.

\[
N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(4-(trifluoromethyl)phenyl)cyclobutanecarboxamide (2e, enantioenriched)
\]
White foam; \([\alpha]_D^{20} = -14.5\) (c = 1.0, CHCl\(_3\)); \(^1H\) NMR (400 MHz, CDCl\(_3\)): \(\delta 7.59\) (d, \(J = 8.0\) Hz, 2H), 7.36 (d, \(J = 8.0\) Hz, 2H), 6.35 (s, 1H), 3.63 (dd, \(J = 8.7, 8.7\) Hz, 1H), 2.82 (ddd, \(J = 11.7, 8.7, 6.4\) Hz, 1H), 2.44 – 2.30 (m, 2H), 2.15 – 2.03 (m, 2H), 1.98 (ddd, \(J = 11.7, 8.7, 8.7\) Hz, 1H), 0.98 (t, \(J = 7.3\) Hz, 3H); \(^13C\) NMR (150 MHz, CDCl\(_3\)): \(\delta 171.00, 143.99, 129.82\) (q, \(J = 32.4\) Hz), 127.65, 125.96 (q, \(J = 3.9\) Hz),
122.18 (q, $J = 272$ Hz), 107.24, 57.41, 50.04, 33.72, 25.67, 21.76, 8.73; HRMS (ESI-TOF) $m/z$ Calcd for C$_{21}$H$_{16}$F$_4$N$_2$O [M+H]$^+$ 455.1145, found 455.1144. HPLC Chiralcel AD-H column (5% isopropanol in hexanes, 0.3 mL/min) $t_r = 17.180$ min (major), 22.073 min (minor): 89% ee.

\[
\begin{align*}
N&(\text{-}(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})\text{-}1\text{-ethyl-2(4-fluorophenyl)cyclobutanecarboxamide (2f, enantioenriched)}) \\
\text{White foam; } &\{\alpha\}_D^{20} = -15.5 (c = 1.0, \text{CHCl}_3); \quad \text{H NMR (400 MHz, CDCl}_3); \quad \delta 7.25 – 7.17 (m, 2H), 7.08 – 6.99 (m, 2H), 6.28 (s, 1H), 3.56 (dd, $J = 8.8, 8.8$ Hz, 1H), 2.78 (ddd, $J = 11.7, 7.0, 7.0$ Hz, 1H), 2.35-2.26 (m, 2H), 2.10 – 1.98 (m, 2H), 1.92 (ddd, $J = 11.7, 8.8, 8.8$ Hz, 1H), 0.96 (t, $J = 7.3$ Hz, 3H); \quad ^{13}C \text{ NMR (150 MHz, CDCl}_3); \quad \delta 171.42, 162.21 (d, J = 246.6 Hz), 135.65 (d, J = 3.2 Hz), 128.83 (d, J = 7.9 Hz), 116.00 (d, J = 21.3 Hz), 107.30, 57.52, 49.61, 33.89, 25.66, 22.17, 8.75; \quad \text{HRMS (ESI-TOF) } m/z \text{ Calcd for C}_{20}\text{H}_{16}\text{F}_{5}\text{N}_2\text{O [M+H]}^+ 395.1177, \text{ found 395.1179. HPLC, Chiralcel OD-H column (10% isopropanol in hexanes, 0.8 mL/min) } t_r = 17.913 \text{ min (major), 25.680 min (minor): 90% ee.} \\
\end{align*}
\]

\[
\begin{align*}
N&(\text{-}(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})\text{-}1\text{-ethyl-2(3-fluorophenyl)cyclobutanecarboxamide (2g, enantioenriched)}) \\
\text{White foam; } &\{\alpha\}_D^{20} = -15.9 (c = 1.0, \text{CHCl}_3); \quad \text{H NMR (400 MHz, CDCl}_3); \quad \delta 7.35 –
\end{align*}
\]
7.26 (m, 1H), 7.03 (d, J = 7.6 Hz, 1H), 7.01 – 6.92 (m, 2H), 6.35 (s, 1H), 3.58 (dd, J = 8.7, 8.7 Hz, 1H), 2.79 (ddd, J = 11.7, 7.4, 7.4 Hz, 1H), 2.31 (m, 2H), 2.12 – 2.01 (m, 2H), 1.93 (ddd, J = 11.6, 8.6, 8.6 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): δ 171.25, 163.34 (d, J = 247.7 Hz), 142.54 (d, J = 6.8 Hz), 130.80 (d, J = 8.4 Hz), 122.88 (d, J = 2.8 Hz), 114.54 (d, J = 21.8 Hz), 114.21 (d, J = 21.3 Hz), 107.32, 57.53, 49.93, 33.91, 25.73, 21.80, 8.71; HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{16}\)F\(_5\)N\(_2\)O [M+H]\(^+\) 395.1177, found 395.1184. HPLC, Chiralcel OD-H column (10% isopropanol in hexanes, 0.5 mL/min) t\(_r\) = 31.473 min (major), 38.453 min (minor): 87% ee.

![Chemical Structure](image)

**N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(4-chlorophenyl)cyclobutanecarboxamide (2h, enantioenriched)**

Colorless oil; [\(\alpha\)]\(_D\)\(^{20}\) = -30.7 (c = 1.0, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.30 (d, J = 8.3 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.35 (s, 1H), 3.55 (dd, J = 8.7, 8.7 Hz, 1H), 2.78 (ddd, J = 11.7, 7.1, 7.1 Hz, 1H), 2.35 – 2.27 (m, 2H), 2.11 – 1.98 (m, 2H), 1.93 (ddd, J = 11.7, 8.7, 8.7 Hz, 1H), 0.96 (t, J = 7.4 Hz, 3H); \(^{13}\)C NMR (150 MHz, CDCl\(_3\)): δ 171.26, 138.37, 133.44, 129.20, 128.60, 107.30, 57.49, 49.72, 33.85, 25.70, 21.97, 8.74; HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{16}\)F\(_4\)ClN\(_2\)O [M+H]\(^+\) 411.0882, found 411.0881. HPLC, Chiralcel OD-H column (10% isopropanol in hexanes, 0.4 mL/min) t\(_r\) = 41.947 min (major), 47.347 min (minor): 89% ee.
\(N-(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})-1\text{-ethyl-2-}(4\text{-bromophenyl})\text{cyclobutanecarboxamide (2i, enantioenriched)}\)

Yellow oil; \([\alpha]_{D}^{20} = -37.7 \; (c = 1.0, \text{CHCl}_3); \) \(^1\text{H NMR (400 MHz, CDCl}_3\): \(\delta \) 7.45 (d, \(J = 8.3 \text{ Hz, 2H})), 7.12 (d, \(J = 8.3 \text{ Hz, 2H})), 6.35 (s, 1H), 3.53 (dd, \(J = 8.8, 8.8 \text{ Hz, 1H})), 2.78 (ddd, \(J = 11.7, 7.1, 7.1 \text{ Hz, 1H})), 2.36 – 2.26 (m, 2H), 2.12 – 1.98 (m, 2H), 1.93 (ddd, \(J = 11.7, 8.6, 8.6 \text{ Hz, 1H})), 0.96 (t, \(J = 7.4 \text{ Hz, 3H}); \) \(^{13}\text{C NMR (150 MHz, CDCl}_3\): \(\delta \) 171.23, 138.88, 132.15, 128.94, 121.50, 107.31, 57.43, 49.78, 33.83, 25.69, 21.91, 8.74; HRMS (ESI-TOF) m/z Calcd for C\(_{20}\)H\(_{16}\)BrF\(_4\)N\(_2\)O \([\text{M+H}]^+\) 455.0377, found 455.0375. HPLC, Chiralcel AD-H column (5% isopropanol in hexanes, 0.6 mL/min) \(t_r = 38.027 \text{ min (minor), 42.253 min (major): 86}\% ee.\)

\(N-(4\text{-Cyano-2,3,5,6-tetrafluorophenyl})-1\text{-ethyl-2-}(4\text{-methoxycarbonylphenyl})\text{cyclobutanecarboxamide (2j, enantioenriched)}\)

Colorless oil; \([\alpha]_{D}^{20} = -69.5 \; (c = 1.0, \text{CHCl}_3); \) \(^1\text{H NMR (400 MHz, CDCl}_3\): \(\delta \) 7.99 (d, \(J = 8.3 \text{ Hz, 2H})), 7.32 (d, \(J = 8.1 \text{ Hz, 2H})), 6.41 (s, 1H), 3.91 (s, 3H), 3.63 (dd, \(J = 8.7, 8.7 \text{ Hz, 1H})), 2.82 (ddd, \(J = 11.8, 8.8, 5.6 \text{ Hz, 1H})), 2.44 – 2.29 (m, 2H), 2.17 – 2.02 (m, 2H), 1.97 (ddd, \(J = 11.8, 8.6, 8.6 \text{ Hz, 1H})), 0.97 (t, \(J = 7.4 \text{ Hz, 3H}); \) \(^{13}\text{C NMR (150 MHz, CDCl}_3\): \(\delta \) 171.12, 166.72, 145.25, 130.27, 129.27, 127.32, 107.26, 57.44, 52.16, 50.20, 33.80, 25.78, 21.79, 8.71; HRMS (ESI-TOF) m/z Calcd for C\(_{22}\)H\(_{19}\)F\(_4\)N\(_2\)O\(_3\) \([\text{M+H}]^+\) 435.1326, found 435.1327. HPLC, Chiralpak IC column (10% isopropanol in
hexanes, 1.0 mL/min) $t_r = 16.973$ min (major), 39.087 min (minor): 89% ee.

$N$-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(4-methoxyphenyl)cyclobutanecarboxamide (2k, enantioenriched)

Colorless oil; $[\alpha]_{D}^{20} = –12.1$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.17 (d, $J$ = 8.6 Hz, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H), 6.25 (s, 1H), 3.80 (s, 3H), 3.54 (dd, $J$ = 8.9, 8.9 Hz, 1H), 2.76 (ddd, $J$ = 11.7, 9.0, 5.0 Hz, 1H), 2.37 – 2.21 (m, 2H), 2.10 – 1.95 (m, 2H), 1.89 (ddd, $J$ = 11.7, 8.8, 8.8 Hz, 1H), 0.95 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 171.98, 159.18, 131.79, 128.32, 114.69, 107.42, 57.73, 55.38, 49.63, 34.11, 25.78, 22.12, 8.77; HRMS (ESI-TOF) m/z Calcd for C$_{21}$H$_{19}$F$_4$N$_2$O$_2$ [M+H]$^+$ 407.1377, found 407.1375. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.8 mL/min) $t_r = 41.873$ min (minor), 51.467 min (major): 90% ee.

$N$-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(4-acetamidophenyl)cyclobutanecarboxamide (2l, enantioenriched)

White solid; $[\alpha]_D^{20} = –36.8$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, Acetone-d6): $\delta$ 9.22 (s, 1H), 8.61 (s, 1H), 7.57 (d, $J$ = 8.5 Hz, 2H), 7.24 (d, $J$ = 8.5 Hz, 2H), 3.57 (dd, $J$ = 8.2, 8.2 Hz, 1H), 2.85 (ddd, $J$ = 10.6, 10.6, 5.8 Hz, 1H), 2.49 – 2.33 (m, 2H), 2.30 – 2.18 (m, 1H), 2.09 (s, 3H), 2.13 – 2.02 (m, 1H), 1.98 – 1.89 (m, 1H), 0.96 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (150 MHz, Acetone-d6): $\delta$ 171.91, 168.36, 138.90, 136.11, 128.47,
119.37, 108.11, 57.31, 50.45, 33.03, 25.60, 23.92, 22.75, 8.80; HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{20}$F$_4$N$_3$O$_2$ [M+H]$^+$ 434.1486, found 434.1486. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.3 mL/min) $t_r = 36.153$ min (major), 44.247 min (minor): 93% ee.

$N$-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-ethyl-2-(naphthalen-1-yl)cyclobutanecarboxamide (2m, enantioenriched)

White foam; $[\alpha]_D^{20} = -200.7$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.19 (d, $J = 8.3$ Hz, 1H), 7.92 (d, $J = 8.3$ Hz, 1H), 7.85 – 7.70 (m, 1H), 7.64 – 7.42 (m, 4H), 5.88 (s, 1H), 4.48 (dd, $J = 8.9$, 8.9 Hz, 1H), 2.84 (ddd, $J = 11.6$, 9.6, 3.0 Hz, 1H), 2.72 – 2.60 (m, 1H), 2.35 – 2.20 (m, 3H), 1.99 (ddd, $J = 11.2$, 9.3, 9.3 Hz, 1H), 0.97 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 171.40, 134.97, 134.27, 131.60, 129.48, 128.09, 126.69, 126.08, 125.88, 124.90, 122.51, 107.32, 59.22, 45.33, 34.87, 25.44, 20.83, 8.93; HRMS (ESI-TOF) m/z Calcd for C$_{24}$H$_{19}$F$_4$N$_2$O [M+H]$^+$ 427.1428, found 427.1427. HPLC, Chiralcel OD-H column (10% isopropanol in hexanes, 0.6 mL/min) $t_r = 30.687$ min (minor), 43.700 min (major): 90% ee.

1-Ethyl-$N$-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (2n, enantioenriched)

White foam; $[\alpha]_D^{20} = + 8.2$ (c = 1.0, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 –
(m, 5H), 6.22 (s, 1H), 3.60 (dd, $J = 8.9, 8.9$ Hz, 1H), 2.80 (ddd, $J = 11.6, 9.6, 4.2$ Hz, 1H), 2.42 – 2.22 (m, 2H), 2.06 – 1.87 (m, 3H), 1.45 – 1.16 (m, 4H), 0.92 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 171.81, 139.74, 129.31, 127.76, 127.22, 107.39, 57.16, 50.62, 41.11, 26.66, 26.46, 22.89, 21.90, 13.91; HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{21}$F$_4$N$_2$O $[M+H]^+$ 405.1585, found 405.1584. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.2 mL/min) $t_r$ = 74.593 min (minor), 78.100 min (major): 88% ee.

$N$-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-isopropyl-2-phenylcyclobutanecarboxamide (2o, enantioenriched)

White foam: [$\alpha$]$^D_{20}$ = + 4.1 ($c = 1.0$, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.39 – 7.24 (m, 5H), 6.17 (s, 1H), 3.77 (dd, $J = 8.7, 8.7$ Hz, 1H), 2.68 (ddd, $J = 11.8, 7.3, 7.3$ Hz, 1H), 2.30 – 2.16 (m, 3H), 2.02 (ddd, $J = 11.8, 8.5, 8.5$ Hz, 1H), 1.19 (d, $J = 6.8$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (150 MHz, CDCl$_3$): $\delta$ 171.71, 140.59, 129.40, 127.71, 127.42, 107.38, 61.03, 46.60, 35.39, 23.16, 21.71, 17.81, 17.75; HRMS (ESI-TOF) m/z Calcd for C$_{21}$H$_{19}$F$_4$N$_2$O $[M+H]^+$ 391.1428, found 391.1430. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.5 mL/min) $t_r$ = 17.507 min (major), 23.873 min (minor): 95% ee.
amide (2p, enantioenriched)

White foam; [α]_D<sup>20</sup> = +15.6 (c = 1.0, CHCl₃); <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 7.39 – 7.22 (m, 5H), 6.21 (s, 1H), 3.76 (dd, J = 8.9, 8.9 Hz, 1H), 2.66 (ddd, J = 11.9, 9.9, 4.3 Hz, 1H), 2.42 – 1.98 (m, 5H), 1.84 – 1.60 (m, 7H); <sup>13</sup>C NMR (150 MHz, CDCl₃): δ 172.41, 140.22, 129.41, 127.71, 127.23, 107.42, 59.62, 47.35, 46.65, 28.40, 27.64, 25.41, 25.38, 21.67, 21.66; HRMS (ESI-TOF) m/z Calcd for C<sub>23</sub>H<sub>21</sub>F₄N₂O [M+H]<sup>+</sup> 417.1585, found 417.1583. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.3 mL/min) t<sub>r</sub> = 22.393 min (major), 27.173 min (minor): 92% ee.

![amide (2p, enantioenriched)](image)

1-(Chloromethyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (2q, enantioenriched)

White solid; mp: 157-158 °C; <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 7.36 – 7.20 (m, 5H), 3.99 (d, J = 6.7 Hz, 1H), 3.95 (d, J = 6.7 Hz, 1H), 3.88 (dd, J = 9.8, 9.8 Hz, 1H), 2.79 – 2.66 (m, 1H), 2.55 – 2.47 (m, 1H), 2.46 – 2.35 (m, 1H), 2.32 – 2.22 (m, 1H); <sup>13</sup>C NMR (150 MHz, CDCl₃): δ 167.48, 138.60, 128.56, 127.31, 127.06, 107.34, 64.77, 53.26, 46.45, 24.82, 22.89; HRMS (ESI-TOF) m/z Calcd for C<sub>19</sub>H<sub>12</sub>ClF₄N₂O [M-H]<sup>−</sup> 395.0574, found 395.0586. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.5 mL/min) t<sub>r</sub> = 21.787 min (major), 24.760 min (minor): 84% ee.

![1-(Chloromethyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (2q, enantioenriched)](image)

1-((Benzyloxy)methyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (3s, enantioenriched)

White foam; [α]_D<sup>20</sup> = +15.6 (c = 1.0, CHCl₃); <sup>1</sup>H NMR (400 MHz, CDCl₃): δ 7.39 – 7.22 (m, 5H), 6.21 (s, 1H), 3.76 (dd, J = 8.9, 8.9 Hz, 1H), 2.66 (ddd, J = 11.9, 9.9, 4.3 Hz, 1H), 2.42 – 1.98 (m, 5H), 1.84 – 1.60 (m, 7H); <sup>13</sup>C NMR (150 MHz, CDCl₃): δ 172.41, 140.22, 129.41, 127.71, 127.23, 107.42, 59.62, 47.35, 46.65, 28.40, 27.64, 25.41, 25.38, 21.67, 21.66; HRMS (ESI-TOF) m/z Calcd for C<sub>23</sub>H<sub>21</sub>F₄N₂O [M+H]<sup>+</sup> 417.1585, found 417.1583. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.3 mL/min) t<sub>r</sub> = 22.393 min (major), 27.173 min (minor): 92% ee.

![1-((Benzyloxy)methyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (3s, enantioenriched)](image)

1-((Benzyloxy)methyl)-N-(4-cyano-2,3,5,6-tetrafluorophenyl)-2-phenylcyclobutanecarboxamide (3s, enantioenriched)
ecarboxamide (2r, enantioenriched)
White solid; mp: 94-95 °C; [α]D20 = −28.7 (c = 1.0, CHCl3); 1H NMR (400 MHz, CDCl3): δ 8.64 (s, 1H), 7.53 – 7.14 (m, 10H), 4.75 (d, J = 11.8 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 3.95 (d, J = 9.5 Hz, 1H), 3.90 (d, J = 9.5 Hz, 1H), 3.85 (dd, J = 9.1, 9.1 Hz, 1H), 2.76 (ddd, J = 11.6, 9.9, 4.4 Hz, 1H), 2.63 – 2.51 (m, 1H), 2.35 – 2.25 (m, 1H), 1.77 (ddd, J = 11.6, 8.8, 8.8 Hz, 1H); 13C NMR (150 MHz, CDCl3): δ 170.22, 139.45, 136.37, 128.75, 128.41, 128.26, 127.84, 127.82, 127.03, 107.51, 75.70, 74.12, 54.40, 48.10, 23.51, 21.87. HRMS (ESI-TOF) m/z Calcd for C26H21F4N2O2 [M+H]+ 469.1534, found 469.1533. HPLC, Chiralcel OD-H column (5% isopropanol in hexanes, 0.5 mL/min) tR = 52.267 min (minor), 57.653 min (major): 95% ee.

\[ \text{N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-1-((1,3-dioxoisoindolin-2-yl)methyl-2-phe nylcyclobutanecarboxamide (2s, enantioenriched)} \]
White solid; mp: 179-180 °C; 1H NMR (400 MHz, CDCl3): δ 7.91 – 7.85 (m, 2H), 7.81 – 7.75 (m, 2H), 7.38 – 7.24 (m, 6H), 4.33 (d, J = 14.8 Hz, 1H), 4.20 (d, J = 14.8 Hz, 1H), 3.82 (dd, J = 9.1, 9.1 Hz, 1H), 2.82 – 2.75 (m, 1H), 2.55 – 2.37 (m, 2H), 2.31 – 2.21 (m, 1H); 13C NMR (150 MHz, CDCl3): δ 169.77, 168.78, 138.51, 134.59, 131.56, 129.15, 127.92, 127.43, 123.74, 107.37, 56.98, 47.07, 44.74, 27.20, 21.85; HRMS (ESI-TOF) m/z Calcd for C27H18F4N3O3 [M+H]+ 508.1279, found 508.1280. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.8 mL/min) tR = 40.233 min (major), 57.360 min (minor): 81% ee.
Auxiliary Cleavage

Substrate 2o (39.0 mg, 0.1 mmol) and concentrated HCl (1 mL) were added into a 10 ml sealed tube. The reaction mixture was heated to 110 °C for 8 h. After being cooled to room temperature, the reaction mixture was diluted with H2O (2 mL) and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na2SO4, filtered and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluent: EtOAc/hexanes = 1: 5) to give 3 (20.4 mg, 94%) as a colorless oil. 1H NMR (400 MHz, CDCl3): δ 7.29 – 7.11 (m, 5H), 3.68 (t, J = 8.8 Hz, 1H), 2.52 – 2.03 (m, 4H), 1.93 – 1.83 (m, 1H), 1.06 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); 13C NMR (150 MHz, CDCl3): δ 179.65, 141.13, 128.04, 127.49, 126.50, 59.98, 46.60, 33.64, 22.38, 21.40, 18.07, 17.57; HRMS (ESI-TOF) m/z Calcd for C14H19O2 [M+H]+ 219.1379, found 219.1380. HPLC, Chiralcel OJ column (10% isopropanol in hexanes, 0.1 mL/min) tₗ = 51.047 min (minor), 54.167 min (major): 95% ee.
Desymmetrization of Prochiral Methyl Groups

Table S7. Screening of Directing Groups$^{a,b}$

| Ar   | yield | ee  | Ar   | yield | ee  |
|------|-------|-----|------|-------|-----|
| NC   | 68%   | 80% | F    | 25%   | 63% |
| F$_3$C | 61%   | 77% | NO$_2$ | n.p. | --- |
| O$_2$N | 72%   | 78% | Cl   | n.p. | --- |

$^a$ Reaction conditions: substrate (0.1 mmol), 4-(MeO)Ph-BF$_3$K (1.2 equiv), Pd(OAc)$_2$ (10 mol%), L7 (11 mol%), Ag$_2$CO$_3$ (1.0 equiv), NaHCO$_3$ (3.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 50 °C, 72 h. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_2$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Table S8. Screening of O-Methylhydroxamic Acid Ligands.\textsuperscript{a,b}

\begin{table}
\centering
\begin{tabular}{|c|c|c|}
\hline
Ligand & Yield & ee\textsuperscript{c} \\
\hline
Boc-NH\_O\_NHMe & 34\%, 58\% & 32\%, 51\% \\
Boc-NH\_O\_NHMe & 29\%, 54\% & 29\% yield, 26\% ee \\
Cbz-NH\_O\_NHMe & 47\%, 59\% & 53\% yield, 66\% ee \\
Cbz-NH\_O\_NHMe & 56\% yield, 68\% ee & \\
TFA-NH\_O\_NHMe & 16\% yield, 36\% ee & \\
TFA-NH\_O\_NHMe & 9\% yield, 10\% ee & \\
Boc-NH\_O\_NHMe & 59\% yield, 71\% ee & \\
Boc-NH\_O\_NHMe & 59\% yield, 72\% ee & \\
Boc-NH\_O\_NHMe & 53\% yield, 70\% ee & \\
Boc-NH\_O\_NHMe & 53\% yield, 70\% ee & \\
Boc-NH\_O\_NHMe & 53\% yield, 35\% ee & \\
\hline
\end{tabular}
\end{table}

\textsuperscript{a} Reaction conditions: substrate 4a (0.1 mmol), 4-(MeO)Ph-BF\textsubscript{3}K (1.2 equiv), Pd(OAc)\textsubscript{2} (10 mol\%), \textbf{Ligand} (11 mol\%), Ag\textsubscript{2}CO\textsubscript{3} (1.0 equiv), NaHCO\textsubscript{3} (3.0 equiv), BQ (0.5 equiv), H\textsubscript{2}O (5.0 equiv), \textit{t}-AmylOH (0.5 mL), N\textsubscript{2}, 50 °C, 24 h. \textsuperscript{b} The yield was determined by \textsuperscript{1}H NMR analysis of the crude product using CH\textsubscript{2}Br\textsubscript{2} as an internal standard. The \textit{ee} values were determined by HPLC analysis on a chiral stationary phase. \textsuperscript{c} 4-(MeO)Ph-BPin was used in place of 4-(MeO)Ph-BF\textsubscript{3}K.
Table S9.  Screening of ligand equiv, temperature, and reaction time $^{a,b}$

| Ag$_2$CO$_3$ | 4-MeOPhBF$_3$K | L7 | $T$ ($^\circ$C) | $t$ (h) | yield | ee  |
|-------------|---------------|----|--------------|--------|-------|-----|
| 1.0         | 1.2           | 0.11 | 70         | 24     | 61%   | 70% |
| 1.0         | 1.2           | 0.15 | 70         | 24     | 38%   | 72% |
| 1.0         | 1.2           | 0.20 | 70         | 24     | 27%   | 72% |
| 1.0         | 1.2           | 0.11 | 50         | 24     | 36%   | 80% |
| **2.0**     | **2.0**       | **0.11** | **50**     | **72** | **68%(61)%** | **80%** |
| **2.0**     | **2.0**       | **0.11** | **40**     | **72** | **47%** | **82%** |

$^{a}$ Reaction conditions: substrate 4a (0.1 mmol), 4-(MeO)Ph-BF$_3$K, Pd(OAc)$_2$ (10 mol%), L7, Ag$_2$CO$_3$, NaHCO$_3$, BQ, t-AmylOH, H$_2$O, N$_2$, $T$ $^\circ$C, $t$ h. $^{b}$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_3$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase. $^{c}$ Isolated yield.
Table S10. Screening of Bases$^{a,b}$

| base          | yield | ee  | base          | yield | ee  |
|---------------|-------|-----|---------------|-------|-----|
| Li$_2$CO$_3$  | 33%   | 76% | Na$_3$PO$_4$  | 23%   | 79% |
| Na$_2$CO$_3$  | 29%   | 78% | K$_3$PO$_4$   | trace | --- |
| K$_2$CO$_3$   | 0%    | --- | LiH$_2$PO$_4$ | 0%    | --- |
| Cs$_2$CO$_3$  | 0%    | --- | NaH$_2$PO$_4$ | 0%    | --- |
| LiOAc         | 17%   | 60% | KH$_2$PO$_4$  | 18%   | 76% |
| KOAc          | 29%   | 69% | Na$_2$HPO$_4$ | 0%    | --- |
| NaOAc         | 29%   | 69% | K$_2$HPO$_4$  | 16%   | 75% |
| CsOAc         | 13%   | 66% | t-BuOK        | 21%   | 75% |
| NaHCO$_3$     | 36%   | 80% | t-BuCO$_2$Na  | 8%    | --- |
| KHCO$_3$      | 30%   | 74% | CF$_3$CO$_2$Na| 0%    | --- |

$^a$ Reaction conditions: substrate 4a (0.1 mmol), 4-(MeO)Ph-BF$_3$K (1.2 equiv), Pd(OAc)$_2$ (10 mol%), L7 (11 mol%), Ag$_2$CO$_3$ (1.0 equiv), base (3.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv), t-AmylOH (0.5 mL), N$_2$, 50 °C, 20 h. $^b$ The yield was determined by $^1$H NMR analysis of the crude product using CH$_2$Br$_2$ as an internal standard. The ee values were determined by HPLC analysis on a chiral stationary phase.
Enantioselective Desymmetrization of Prochiral Methyl Groups

Substrate 4 (0.1 mmol, 1.0 equiv), Pd(OAc)$_2$ (0.1 equiv), Ar-BF$_3$K (2.0 equiv), L7 (0.11 equiv), Ag$_2$CO$_3$ (2.0 equiv), NaHCO$_3$ (3.0 equiv), BQ (0.5 equiv), H$_2$O (5.0 equiv) and t-AmylOH (0.5 mL) were added into a 50 ml sealed tube. The reaction vessel was evacuated and backfilled with nitrogen (×3). The reaction mixture was heated to 50 °C for 72 h under vigorous stirring. After being cooled to room temperature, the reaction mixture was diluted with EtOAc and filtered through a pad of Celite eluting with EtOAc. The filtrate was concentrated under vacuum and the resulting residue was purified by preparative TLC using EtOAc/hexanes as the eluent to give the desired product. The ee value was determined on a Hitachi LaChrom HPLC system using commercially available chiral columns as described below.

\[ N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-(4-methoxybenzyl)-2,3,3-trimethylbutanamide \ (5a, \text{enantioenriched}) \]

White foam; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.05 (d, $J = 8.6$ Hz, 2H), 6.96 (s, 1H), 6.79 (d, $J = 8.6$ Hz, 2H), 3.78 (s, 3H), 3.56 (d, $J = 13.2$ Hz, 1H), 2.44 (d, $J = 13.2$ Hz, 1H), 1.14 (s, 3H), 1.11 (s, 9H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 173.79, 158.27, 131.17, 129.95, 113.55, 107.30, 55.19, 53.67, 38.80, 36.78, 26.13, 17.86. HRMS (ESI-TOF) m/z Calcd for C$_{22}$H$_{23}$F$_4$N$_2$O$_2$ [M+H]$^+$ 423.1696, found 423.1699. HPLC, Chiralcel AS-H column (10% isopropanol in hexanes, 0.1 mL/min) $t_r = 59.147$ min (minor), 73.340 min (major): 80% ee.
**N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-benzyl-2,3-dimethylbutanamide**  (5b, enantioenriched)

White foam; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.31 – 7.21 (m, 3H), 7.17 – 7.08 (m, 2H), 6.84 (s, 1H), 3.18 (d, $J = 13.2$ Hz, 1H), 2.69 (d, $J = 13.1$ Hz, 1H), 2.27 (hept, $J = 6.8$ Hz, 1H), 1.15 (s, 3H), 1.06 (d, $J = 6.9$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 174.63, 137.06, 130.10, 128.28, 126.81, 107.30, 52.19, 44.09, 35.93, 18.31, 16.95, 14.80. HRMS (ESI-TOF) m/z Calcd for C$_{20}$H$_{19}$F$_4$N$_2$O [M+H]$^+$ 379.1428, found 379.1416. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.2 mL/min) $t_r = 39.367$ min (minor), 44.113 min (major): 35% ee.

**N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-benzyl-2,3-dimethylbutanamide**  (5c, enantioenriched)

White foam; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.32 – 7.23 (m, 3H), 7.18 – 7.13 (m, 2H), 6.90 (s, 1H), 3.16 (d, $J = 13.4$ Hz, 1H), 2.71 (d, $J = 13.4$ Hz, 1H), 1.62 – 1.50 (m, 2H), 1.26 (s, 3H), 0.99 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 174.37, 136.72, 130.12, 128.32, 126.90, 107.29, 48.90, 45.99, 33.16, 20.11, 8.85. HRMS (ESI-TOF) m/z Calcd for C$_{19}$H$_{17}$F$_4$N$_2$O [M+H]$^+$ 365.1272, found 365.1260. HPLC, Chiralcel AD-H column (7% isopropanol in hexanes, 0.5 mL/min) $t_r = 28.360$ min (major), 31.480 min (minor): 29% ee.
N-(4-Cyano-2,3,5,6-tetrafluorophenyl)-2-(2,6-difluorophenyl)-3-(4-methoxyphenyl)-2-methylpropanamide (5d, enantioenriched)

White foam; $^1$H NMR (400 MHz, CDCl$_3$): δ 7.38 – 7.28 (m, 1H), 6.95 (s, 1H), 6.90 (t, $J = 9.3$ Hz, 2H), 6.70 (d, $J = 9.5$ Hz, 2H), 6.67 (d, $J = 9.5$ Hz, 2H), 3.75 (s, 3H), 3.37 (d, $J = 13.9$ Hz, 1H), 3.26 (d, $J = 13.9$ Hz, 1H), 1.83 (s, 3H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ 173.76, 162.70 (d, $J = 8.3$ Hz), 161.04 (d, $J = 8.3$ Hz), 158.50, 131.36, 130.33 (t, $J = 11.2$ Hz), 128.06, 113.30, 112.68 (d, $J = 27.3$ Hz), 107.29, 55.13, 50.88, 42.09, 24.21. HRMS (ESI-TOF) m/z Calcd for C$_{24}$H$_{17}$F$_6$N$_2$O$_2$ [M+H]$^+$ 479.1189, found 479.1177. HPLC, Chiralcel AD-H column (10% isopropanol in hexanes, 0.3 mL/min) $t_r$ = 39.027 min (major), 44.200 min (minor): 61% ee.

References

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2s

2a
HPLC Spectra

![HPLC Spectra Image]

**Area % Report**

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj3-144-ee-5%-0.6mL-75min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/2/2013 10:38:37 PM
Printed: 12/13/2013 3:28:56 PM

| Retention Time | Area       | Area % | Height   | Height % |
|----------------|------------|--------|----------|----------|
| 42.813         | 99583407   | 96.20  | 1028719  | 96.07    |
| 50.080         | 3931542    | 3.80   | 42050    | 3.93     |

**Totals**

|                |            |      |          |          |
|----------------|------------|------|----------|----------|
|                | 103514949  | 100.00 | 1070769  | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj3-141-1-ee-5%-0.5mL-60min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/27/2013 9:06:25 PM
Printed: 12/13/2013 3:35:02 PM

DAD-CH1
250 nm Results

| Retention Time | Area    | Area % | Height  | Height % |
|----------------|---------|--------|---------|----------|
| 39.633         | 121150470 | 96.06  | 1482196 | 96.28    |
| 48.167         | 4968642  | 3.94   | 57281   | 3.72     |
| Totals         | 126119112 | 100.00 | 1539477 | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj-4\xkj4-7-1-ee-5%-0.5mL-60min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 40 min without fc 0.2 ml per min.met
Acquired: 9/13/2013 4:30:58 PM
Printed: 1/29/2014 9:43:36 AM

DAD-CH1
250 nm Results

| Retention Time | Area     | Area % | Height | Height % |
|----------------|----------|--------|--------|----------|
| 41.080         | 1371738  | 22.90  | 19795  | 25.20    |
| 46.893         | 4617886  | 77.10  | 58768  | 74.80    |
| Totals         | 5989624  | 100.00 | 78563  | 100.00   |
Area % Report

Data File: \C:\EZChrom\Elite\Enterprise\Projects\Default\Data\KJ\xkj4-23-8-ee-10%-0.3mL-120min-ODH
Method: \C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/2/2013 12:39:54 PM
Printed: 12/13/2013 4:43:43 PM

| Retention Time | Area    | Area % | Height  | Height % |
|----------------|---------|--------|---------|----------|
| 63.960         | 10974165| 4.48   | 78925   | 5.18     |
| 70.813         | 233826181| 95.52  | 1444405 | 94.82    |
| **Totals**     | **244800346** | **100.00** | **1523330** | **100.00** |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xk4-23-2-ee-5%-1.0mL-30min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/27/2013 4:39:52 PM
Printed: 12/13/2013 4:08:03 PM

DAD-CH1 250 nm Results

| Retention Time | Area     | Area % | Height  | Height % |
|----------------|----------|--------|---------|----------|
| 17.180         | 3994756  | 5.44   | 115569  | 10.60    |
| 22.073         | 69386246 | 94.56  | 974586  | 89.40    |
| Totals         | 73381002 | 100.00 | 1090155 | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-14-1-ee-10%-0.8mL-40min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/20/2013 4:55:24 PM
Printed: 12/13/2013 3:37:43 PM

DAD-CH1 250 nm Results

| Retention Time | Area   | Area % | Height   | Height % |
|----------------|--------|--------|----------|----------|
| 17.913         | 193921709 | 94.88  | 3556520  | 95.78    |
| 25.680         | 10471129  | 5.12   | 156724   | 4.22     |
| Totals         | 204392838 | 100.00 | 3713244  | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\KJ\xkj4-14-2-ee-10%-0.5mL-60min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/21/2013 3:06:36 PM
Printed: 12/13/2013 3:39:46 PM

DAD-CH1
250 nm Results

| Retention Time | Area       | Area % | Height   | Height % |
|----------------|------------|--------|----------|----------|
| 31.473         | 275166328  | 93.68  | 3566013  | 94.10    |
| 38.453         | 18549833   | 6.32   | 223715   | 5.90     |
| Totals         | 293716161  | 100.00 | 3789728  | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-14-4-ee-10%-0.4mL-60min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/20/2013 10:21:31 PM
Printed: 12/13/2013 3:47:41 PM

**DAD-CH1 250 nm Results**

| Retention Time | Area   | Area % | Height  | Height % |
|----------------|--------|--------|---------|----------|
| 41.947         | 62044244 | 94.38  | 639286  | 94.89    |
| 47.347         | 3695000 | 5.62   | 34418   | 5.11     |
| **Totals**     | **65739244** | **100.00** | **673704** | **100.00** |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xk\j4-14-5-ee-5%-0.6mL-60min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/21/2013 8:46:13 PM
Printed: 12/13/2013 6:37:07 PM

DAD-CH1
250 nm Results

| Retention Time | Area     | Area % | Height    | Height % |
|----------------|----------|--------|-----------|----------|
| 38.027         | 14432537 | 7.11   | 211181    | 14.54    |
| 42.253         | 188501740| 92.89  | 1241411   | 85.46    |
| Totals         | 202934277| 100.00 | 1452592   | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-41-1-ee-10%-1.0mL-45min-IC
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/17/2013 3:00:51 PM
Printed: 12/13/2013 6:09:45 PM

![Graph of retention times and areas]

### DAD-CH1 250 nm Results

| Retention Time | Area   | Area % | Height  | Height % |
|----------------|--------|--------|---------|----------|
| 16.973         | 66630061 | 94.59  | 1985391 | 97.79    |
| 39.087         | 3807576  | 5.41   | 44858   | 2.21     |

| Totals         |        | 100.00 | 2030249 | 100.00   |
Area % Report

Data File:  C:\EZChrom
Elite\Enterprise\Projects\Default\Data\KJ\xj4-23-3-ee-5%-0.8mL-60min-ODH
Method:  C:\EZChrom  Elite\Enterprise\Projects\Default\Method\A  60 min without fc 0.2 ml per min.met
Acquired:  10/1/2013 1:23:03 AM
Printed:  12/13/2013 4:11:31 PM

DAD-CH1
250 nm Results

| Retention Time | Area   | Area % | Height  | Height % |
|----------------|--------|--------|---------|----------|
| 41.873         | 97146558 | 94.73  | 872342  | 94.97    |
| 51.467         | 5406346  | 5.27   | 46176   | 5.03     |

| Totals         | 102552904 | 100.00 | 918518  | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-41-2-3-ee-10%-0.3mL-60min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/15/2013 8:56:32 PM
Printed: 12/13/2013 6:12:02 PM

| Retention Time | Area       | Area %  | Height    | Height % |
|----------------|------------|---------|-----------|----------|
| 36.153         | 293032872 | 96.30   | 2834213   | 96.21    |
| 44.247         | 11274462  | 3.70    | 111777    | 3.79     |
| Totals         | 304307334 | 100.00  | 2945990   | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-14-6-ee-10%-0.6mL-60min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 9/22/2013 8:12:50 PM
Printed: 12/13/2013 6:13:41 PM

DAD-CH1
250 nm Results

| Retention Time | Area    | Area % | Height | Height % |
|----------------|---------|--------|--------|----------|
| 30.687         | 894521  | 4.83   | 12050  | 9.20     |
| 43.700         | 17622071| 95.17  | 118959 | 90.80    |
| **Totals**     | **18516592** | **100.00** | **131009** | **100.00** |
Area % Report

Data File:  C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-44-1-ee-5%-0.2mL-90min-ODH
Method:   C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/23/2013 2:05:23 PM
Printed:  12/13/2013 6:03:24 PM

DAD-CH1 250 nm Results

| Retention Time | Area    | Area % | Height   | Height % |
|----------------|---------|--------|----------|----------|
| 74.593         | 12606891| 6.08   | 122017   | 7.86     |
| 78.100         | 194743196| 93.92  | 1431044  | 92.14    |

| Totals         | 207350087| 100.00 | 1553061  | 100.00   |
Area % Report

Data File:   C:\EZChrom
Elite\Enterprise\Projects\Default\Data\KJ\xkj4-12-2-ee-10%-0.5mL-45min-ADH
Method:     C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min
without fc 0.2 ml per min.met
Acquired:   10/16/2013 3:19:44 PM
Printed:    12/13/2013 3:49:53 PM

| Retention Time | Area       | Area % | Height      | Height % |
|----------------|------------|--------|-------------|----------|
| 17.507         | 125894254  | 97.51  | 2444784     | 96.80    |
| 23.873         | 3214340    | 2.49   | 80747       | 3.20     |
| Totals         | 129108594  | 100.00 | 2525531     | 100.00   |
**Area % Report**

Data File: \C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-44-3-ee-10%-0.3mL-45min-ADH

Method: \C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met

Acquired: 10/14/2013 1:54:45 PM

Printed: 12/13/2013 6:01:23 PM

![Graph of DAD-CH1 250 nm Results](image)

### DAD-CH1 250 nm Results

| Retention Time | Area     | Area % | Height    | Height % |
|----------------|----------|--------|-----------|----------|
| 22.393         | 91584097 | 96.12  | 1679302   | 95.59    |
| 27.173         | 3694730  | 3.88   | 77421     | 4.41     |

| Totals         | 95278827 | 100.00 | 1756723   | 100.00   |
Area % Report

Data File:   C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-44-11-ee-10%-0.5mL-60min-ADH
Method:     C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired:   10/23/2013 6:24:04 AM
Printed:    12/13/2013 6:05:47 PM

DAD-CH1
250 nm Results

| Retention Time | Area      | Area % | Height    | Height % |
|----------------|-----------|--------|-----------|----------|
| 21.787         | 43315299  | 91.76  | 1118547   | 90.73    |
| 24.760         | 3890382   | 8.24   | 114232    | 9.27     |

| Totals         | 47205681  | 100.00 | 1232779   | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj4-24-3-ee-5%-0.5mL-75min-ODH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired: 10/1/2013 3:46:53 PM
Printed: 12/13/2013 3:56:21 PM

DAD-CH1 250 nm Results

| Retention Time | Area    | Area % | Height  | Height % |
|---------------|---------|--------|---------|----------|
| 52.267        | 4376190 | 2.40   | 50261   | 3.34     |
| 57.653        | 178195292 | 97.60 | 1453555 | 96.66    |

Totals        | 182571482 | 100.00 | 1503816 | 100.00   |
Area % Report

Data File:    C:\EZChrom
Elite\Enterprise\Projects\Default\Data\kJ\xkj4-57-2-ee-10%-0.8mL-60min-ADH
Method:    C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.2 ml per min.met
Acquired:    10/22/2013 11:26:51 PM
Printed:    12/13/2013 3:53:16 PM

### DAD-CH1
#### 250 nm Results

| Retention Time | Area    | Area % | Height | Height % |
|----------------|---------|--------|--------|----------|
| 40.233         | 256456212 | 90.34  | 1779027 | 90.07    |
| 57.360         | 27414979  | 9.66   | 196168  | 9.93     |

| Totals         | 283871191 | 100.00 | 1975195 | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj5-31-ee-10%-0.1mL-75min-OJ
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.4 ml per min.met
Acquired: 4/6/2014 2:56:41 PM
Printed: 4/6/2014 7:56:42 PM

DAD-CH2 205 nm Results

| Retention Time | Area   | Area % | Height | Height % |
|----------------|--------|--------|--------|----------|
| 51.047         | 1175458| 2.21   | 17900  | 3.37     |
| 54.167         | 51976978| 97.79  | 512503 | 96.63    |

Totals | 53152436 | 100.00 | 530403 | 100.00 |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj1-150-3-ee-10%-0.1mL-90min-ASH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 120 min without fc 0.5 ml per min.met
Acquired: 1/17/2014 4:52:36 PM
Printed: 1/17/2014 8:10:26 PM

DAD-CH1
250 nm Results

| Retention Time | Area     | Area % | Height  | Height % |
|----------------|----------|--------|---------|----------|
| 59.147         | 68569529 | 10.15  | 684838  | 15.08    |
| 73.340         | 606819489| 89.85  | 3856405 | 84.92    |
| Totals         | 675389018| 100.00 | 4541243 | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJxkj5-20-2-ee-10%-0.2mL-60min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.4 ml per min.met
Acquired: 3/24/2014 1:43:25 AM
Printed: 3/24/2014 10:02:59 AM

DAD-CH1 250 nm Results

| Retention Time | Area   | Area %  | Height  | Height % |
|----------------|--------|---------|---------|----------|
| 39.367         | 29211297 | 32.29   | 447157  | 37.65    |
| 44.113         | 61251781 | 67.71   | 740553  | 62.35    |
| Totals         | 90463078 | 100.00  | 1187710 | 100.00   |
Area % Report

Data File: C:\EZChrom Elite\Enterprise\Projects\Default\Data\KJ\xkj5-20-1-ee-7%-0.5mL-60min-ADH
Method: C:\EZChrom Elite\Enterprise\Projects\Default\Method\A 60 min without fc 0.4 ml per min.met
Acquired: 3/23/2014 6:28:39 PM
Printed: 3/23/2014 8:29:37 PM

DAD-CH1 250 nm Results

| Retention Time | Area       | Area % | Height  | Height % |
|----------------|------------|--------|---------|----------|
| 28.360         | 24668009   | 64.39  | 490988  | 65.24    |
| 31.480         | 13642256   | 35.61  | 261584  | 34.76    |
| Totals         | 38310265   | 100.00 | 752572  | 100.00   |
Area % Report

Data File:  C:\EZChrom
Elite\Enterprise\Projects\Default\Data\KJ\xkj5-20-6-ee-10%-0.3mL-45min-ADH
Method:  C:\EZChrom  Elite\Enterprise\Projects\Default\Method\A  60 min without fc 0.4 ml per min.met
Acquired:  3/22/2014 9:51:42 PM
Printed:  3/23/2014 8:26:53 PM

| Retention Time | Area   | Area % | Height  | Height % |
|----------------|--------|--------|---------|----------|
| 39.027         | 111915021 | 80.48  | 1432987 | 80.70    |
| 44.200         | 27142610  | 19.52  | 342707  | 19.30    |

| Totals         | 139057631 | 100.00 | 1775694 | 100.00   |
X-ray Crystallographic Data of 2r

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa APEX-II CCD diffractometer equipped with Cu Kα radiation (λ = 1.5478). A 0.115 x 0.091 x 0.053 mm colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using φ and θ scans. Crystal-to-detector distance was 45 mm using variable exposure time (1s-5s) depending on θ with a scan width of 1.0°. Data collection was 99.4% complete to 68.00° in θ. A total of 15223 reflections were collected covering the indices, -9<=h<=10, -10<=k<=10, -19<=l<=18. 4110 reflections were found to be symmetry independent, with a Rint of 0.0267. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P21. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All nonhydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. Crystallographic data are summarized in Table 1.
Table 1. Crystal data and structure refinement for Yu35.

| Property                              | Value                                      |
|---------------------------------------|--------------------------------------------|
| Report date                           | 2014-04-02                                 |
| Identification code                   | Yu35                                       |
| Empirical formula                     | C26 H20 F4 N2 O2                            |
| Molecular formula                     | C26 H20 F4 N2 O2                            |
| Formula weight                        | 468.44                                     |
| Temperature                           | 100.0 K                                    |
| Wavelength                            | 1.54178 Å                                  |
| Crystal system                        | Monoclinic                                 |
| Space group                           | P 1 2 1                                    |
| Unit cell dimensions                  | a = 8.5521(2) Å                           α= 90°. |
|                                      | b = 8.5649(3) Å                           β= 103.6840(14)°. |
|                                      | c = 15.8893(5) Å                          γ = 90°. |
| Volume                                | 1130.82(6) Å                               |
| Z                                     | 2                                          |
| Density (calculated)                  | 1.376 Mg/m³                                |
| Absorption coefficient                | 0.937 mm⁻¹                                 |
| F(000)                                | 484                                        |
| Crystal size                          | 0.115 x 0.091 x 0.053 mm³                  |
| Crystal color, habit                  | Colorless Block                            |
| Theta range for data collection       | 2.862 to 68.959°.                         |
| Index ranges                          | -9≤h≤10, -10≤k≤10, -19≤l≤18                |
| Reflections collected                 | 15223                                      |
| Independent reflections               | 4110 [R(int) = 0.0267]                     |
| Completeness to theta = 68.000°       | 99.4 %                                     |
| Absorption correction                 | Semi-empirical from equivalents            |
| Max. and min. transmission            | 0.7531 and 0.7070                          |
| Refinement method                     | Full-matrix least-squares on F²            |
| Data / restraints / parameters         | 4110 / 2 / 311                             |
| Goodness-of-fit on F²                  | 1.019                                      |
| Final R indices [I>2σ(I)]             | R1 = 0.0253, wR2 = 0.0637                  |
| R indices (all data)                  | R1 = 0.0265, wR2 = 0.0645                  |
| Absolute structure parameter          | 0.08(4)                                    |
| Extinction coefficient                | n/a                                        |
| Largest diff. peak and hole           | 0.141 and -0.119 e Å⁻³                    |
Table 2. Atomic coordinates ($x \times 10^4$) and equivalent isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for Yu35. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized $U^{ij}$ tensor.

| Atom | $x$   | $y$   | $z$   | $U(\text{eq})$ |
|------|-------|-------|-------|----------------|
| F(1) | 4395(2) | 2729(2) | 5973(1) | 49(1) |
| F(2) | 2052(2) | 4398(3) | 4964(1) | 72(1) |
| F(3) | 4898(2) | 9037(2) | 5902(1) | 60(1) |
| F(4) | 7201(2) | 7368(1) | 6961(1) | 39(1) |
| O(1) | 5556(2) | 2720(2) | 7747(1) | 33(1) |
| O(2) | 10312(1) | 4174(2) | 7772(1) | 28(1) |
| N(1) | 7086(2) | 4194(2) | 7060(1) | 27(1) |
| N(2) | 1180(3) | 8408(5) | 4430(2) | 95(1) |
| C(1) | 6878(2) | 3091(2) | 7654(1) | 26(1) |
| C(2) | 8435(2) | 2402(2) | 8199(1) | 29(1) |
| C(3) | 8162(2) | 690(2) | 8447(2) | 35(1) |
| C(4) | 7934(2) | 1236(2) | 9335(2) | 33(1) |
| C(5) | 8670(2) | 2835(2) | 9187(1) | 28(1) |
| C(6) | 7977(2) | 4308(2) | 9462(1) | 26(1) |
| C(7) | 7172(2) | 4290(3) | 10128(1) | 32(1) |
| C(8) | 6561(2) | 5654(3) | 10396(1) | 35(1) |
| C(9) | 6722(2) | 7061(2) | 9994(1) | 33(1) |
| C(10) | 7531(2) | 7086(2) | 9336(1) | 32(1) |
| C(11) | 8168(2) | 5736(2) | 9077(1) | 28(1) |
| C(12) | 9904(2) | 2572(2) | 7825(1) | 31(1) |
| C(13) | 5833(2) | 5017(2) | 6523(1) | 29(1) |
| C(14) | 4497(2) | 4291(3) | 5999(1) | 37(1) |
| C(15) | 3303(3) | 5154(4) | 5469(1) | 50(1) |
| C(16) | 3394(3) | 6759(4) | 5424(2) | 50(1) |
| C(17) | 4747(3) | 7491(3) | 5929(1) | 44(1) |
| C(18) | 5930(2) | 6630(3) | 6466(1) | 34(1) |
| C(19) | 2156(3) | 7672(5) | 4875(2) | 71(1) |
| C(20) | 11747(2) | 4359(2) | 7458(1) | 31(1) |
| C(21) | 12079(2) | 6074(2) | 7404(1) | 26(1) |
| C(22) | 13499(2) | 6713(2) | 7896(1) | 28(1) |
| C(23) | 13817(2) | 8295(2) | 7831(1) | 32(1) |
| C(24) | 12719(3) | 9255(3) | 7290(1) | 35(1) |
|   |      |      |      |      |
|---|------|------|------|------|
| C(25) | 11297(3) | 8624(3) | 6804(1) | 36(1) |
| C(26) | 10986(2) | 7041(2) | 6854(1) | 31(1) |
Table 3. Bond lengths [Å] and angles [°] for Yu35.

| Bond          | Distance [Å] |
|---------------|--------------|
| F(1)-C(14)    | 1.340(3)     |
| F(2)-C(15)    | 1.342(3)     |
| F(3)-C(17)    | 1.332(3)     |
| F(4)-C(18)    | 1.340(3)     |
| O(1)-C(1)     | 1.216(2)     |
| O(2)-C(12)    | 1.423(2)     |
| O(2)-C(20)    | 1.439(2)     |
| N(1)-H(1)     | 0.88(2)      |
| N(1)-C(1)     | 1.376(2)     |
| N(1)-C(13)    | 1.394(3)     |
| N(2)-C(19)    | 1.147(4)     |
| C(1)-C(2)     | 1.525(3)     |
| C(2)-C(3)     | 1.551(3)     |
| C(2)-C(5)     | 1.580(3)     |
| C(2)-C(12)    | 1.519(3)     |
| C(3)-H(3A)    | 0.9900       |
| C(3)-H(3B)    | 0.9900       |
| C(3)-C(4)     | 1.541(3)     |
| C(4)-H(4A)    | 0.9900       |
| C(4)-H(4B)    | 0.9900       |
| C(4)-C(5)     | 1.549(3)     |
| C(5)-H(5)     | 1.0000       |
| C(5)-C(6)     | 1.502(3)     |
| C(6)-C(7)     | 1.393(3)     |
| C(6)-C(11)    | 1.394(3)     |
| C(7)-H(7)     | 0.9500       |
| C(7)-C(8)     | 1.387(3)     |
| C(8)-H(8)     | 0.9500       |
| C(8)-C(9)     | 1.386(3)     |
| C(9)-H(9)     | 0.9500       |
| C(9)-C(10)    | 1.383(3)     |
| C(10)-H(10)   | 0.9500       |
| C(10)-C(11)   | 1.382(3)     |
| C(11)-H(11)   | 0.9500       |
| C(12)-H(12A)  | 0.9900       |
| C(12)-H(12B)  | 0.9900       |
| Bond                  | Length  |
|----------------------|---------|
| C(13)-C(14)          | 1.391(3) |
| C(13)-C(18)          | 1.388(3) |
| C(14)-C(15)          | 1.376(3) |
| C(15)-C(16)          | 1.380(4) |
| C(16)-C(17)          | 1.392(4) |
| C(16)-C(19)          | 1.434(4) |
| C(17)-C(18)          | 1.373(3) |
| C(20)-H(20A)         | 0.9900  |
| C(20)-H(20B)         | 0.9900  |
| C(20)-C(21)          | 1.502(3) |
| C(21)-C(22)          | 1.391(3) |
| C(21)-C(26)          | 1.391(3) |
| C(22)-H(22)          | 0.9500  |
| C(22)-C(23)          | 1.391(3) |
| C(23)-H(23)          | 0.9500  |
| C(23)-C(24)          | 1.383(3) |
| C(24)-H(24)          | 0.9500  |
| C(24)-C(25)          | 1.387(3) |
| C(25)-H(25)          | 0.9500  |
| C(25)-C(26)          | 1.388(3) |
| C(26)-H(26)          | 0.9500  |
| C(12)-O(2)-C(20)     | 111.55(14) |
| C(1)-N(1)-H(1)       | 116.1(16)  |
| C(1)-N(1)-C(13)      | 124.22(16) |
| C(13)-N(1)-H(1)      | 118.6(17)  |
| O(1)-C(1)-N(1)       | 122.49(18) |
| O(1)-C(1)-C(2)       | 122.81(17) |
| N(1)-C(1)-C(2)       | 114.68(15) |
| C(1)-C(2)-C(3)       | 110.26(15) |
| C(1)-C(2)-C(5)       | 111.25(14) |
| C(3)-C(2)-C(5)       | 87.74(14)  |
| C(12)-C(2)-C(1)      | 115.67(16) |
| C(12)-C(2)-C(3)      | 112.25(15) |
| C(12)-C(2)-C(5)      | 116.34(16) |
| C(2)-C(3)-H(3A)      | 113.6     |
| C(2)-C(3)-H(3B)      | 113.6     |
| H(3A)-C(3)-H(3B)     | 110.9     |
C(4)-C(3)-C(2)    90.30(15)
C(4)-C(3)-H(3A)   113.6
C(4)-C(3)-H(3B)   113.6
C(3)-C(4)-H(4A)   113.8
C(3)-C(4)-H(4B)   113.8
C(3)-C(4)-C(5)    89.20(15)
H(4A)-C(4)-H(4B)  111.0
C(5)-C(4)-H(4A)   113.8
C(5)-C(4)-H(4B)   113.8
C(2)-C(5)-H(5)    108.4
C(4)-C(5)-C(2)    88.97(15)
C(4)-C(5)-H(5)    108.4
C(6)-C(5)-C(2)    121.33(15)
C(6)-C(5)-C(4)    119.76(15)
C(6)-C(5)-H(5)    108.4
C(7)-C(6)-C(5)    120.80(17)
C(7)-C(6)-C(11)   118.25(19)
C(11)-C(6)-C(5)   120.92(17)
C(6)-C(7)-H(7)    119.5
C(8)-C(7)-C(6)    120.94(19)
C(8)-C(7)-H(7)    119.5
C(7)-C(8)-H(8)    119.8
C(9)-C(8)-C(7)    120.32(19)
C(9)-C(8)-H(8)    119.8
C(8)-C(9)-H(9)    120.5
C(10)-C(9)-C(8)   118.93(19)
C(10)-C(9)-H(9)   120.5
C(9)-C(10)-H(10)  119.5
C(11)-C(10)-C(9)  121.01(18)
C(11)-C(10)-H(10) 119.5
C(6)-C(11)-H(11)  119.7
C(10)-C(11)-C(6)  120.52(18)
C(10)-C(11)-H(11) 119.7
O(2)-C(12)-C(2)   110.64(15)
O(2)-C(12)-H(12A) 109.5
O(2)-C(12)-H(12B) 109.5
C(2)-C(12)-H(12A) 109.5
C(2)-C(12)-H(12B) 109.5
H(12A)-C(12)-H(12B) 108.1
C(14)-C(13)-N(1) 123.0(2)
C(18)-C(13)-N(1) 119.6(2)
C(18)-C(13)-C(14) 117.3(2)
F(1)-C(14)-C(13) 120.19(19)
F(1)-C(14)-C(15) 119.0(2)
C(15)-C(14)-C(13) 120.8(2)
F(2)-C(15)-C(14) 118.5(3)
F(2)-C(15)-C(16) 119.8(2)
C(14)-C(15)-C(16) 121.6(2)
C(15)-C(16)-C(17) 117.9(2)
C(15)-C(16)-C(19) 122.2(3)
C(17)-C(16)-C(19) 119.9(3)
F(3)-C(17)-C(16) 120.2(2)
F(3)-C(17)-C(18) 119.4(2)
C(18)-C(17)-C(16) 120.4(2)
F(4)-C(18)-C(13) 118.92(18)
F(4)-C(18)-C(17) 119.2(2)
C(17)-C(18)-C(13) 121.9(2)
N(2)-C(19)-C(16) 179.2(3)
O(2)-C(20)-H(20A) 110.0
O(2)-C(20)-H(20B) 110.0
O(2)-C(20)-C(21) 108.39(14)
H(20A)-C(20)-H(20B) 108.4
C(21)-C(20)-H(20A) 110.0
C(21)-C(20)-H(20B) 110.0
C(22)-C(21)-C(20) 120.26(17)
C(22)-C(21)-C(26) 119.08(18)
C(26)-C(21)-C(20) 120.66(17)
C(21)-C(22)-H(22) 119.9
C(23)-C(22)-C(21) 120.11(19)
C(23)-C(22)-H(22) 119.9
C(22)-C(23)-H(23) 119.7
C(24)-C(23)-C(22) 120.6(2)
C(24)-C(23)-H(23) 119.7
C(23)-C(24)-H(24) 120.3
C(23)-C(24)-C(25) 119.4(2)
C(25)-C(24)-H(24) 120.3
| Bond                  | Angle (°) |
|-----------------------|-----------|
| C(24)-C(25)-H(25)     | 119.9     |
| C(24)-C(25)-C(26)     | 120.2(2)  |
| C(26)-C(25)-H(25)     | 119.9     |
| C(21)-C(26)-H(26)     | 119.7     |
| C(25)-C(26)-C(21)     | 120.54(19)|
| C(25)-C(26)-H(26)     | 119.7     |
Table 4. Anisotropic displacement parameters ($\text{Å}^2 \times 10^3$) for Yu35. The anisotropic displacement factor exponent takes the form: 

$$-2\pi^2 [h^2 a^* U_{11}^* + \ldots + 2hk a^* b^* U_{12}^*]$$

|       | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|-------|----------|----------|----------|----------|----------|----------|
| F(1)  | 35(1)    | 67(1)    | 42(1)    | -20(1)   | 7(1)     | -7(1)    |
| F(2)  | 30(1)    | 146(2)   | 35(1)    | -5(1)    | -3(1)    | -4(1)    |
| F(3)  | 62(1)    | 64(1)    | 65(1)    | 42(1)    | 39(1)    | 33(1)    |
| F(4)  | 38(1)    | 36(1)    | 44(1)    | 10(1)    | 13(1)    | 4(1)     |
| O(1)  | 19(1)    | 40(1)    | 41(1)    | 3(1)     | 8(1)     | -2(1)    |
| O(2)  | 18(1)    | 29(1)    | 40(1)    | 5(1)     | 12(1)    | 1(1)     |
| N(1)  | 18(1)    | 33(1)    | 31(1)    | 3(1)     | 6(1)     | 4(1)     |
| N(2)  | 56(2)    | 186(4)   | 50(1)    | 60(2)    | 24(1)    | 61(2)    |
| C(1)  | 19(1)    | 27(1)    | 34(1)    | -2(1)    | 7(1)     | 1(1)     |
| C(2)  | 21(1)    | 23(1)    | 42(1)    | 7(1)     | 9(1)     | 2(1)     |
| C(3)  | 28(1)    | 26(1)    | 53(1)    | 7(1)     | 13(1)    | -1(1)    |
| C(4)  | 27(1)    | 28(1)    | 47(1)    | 13(1)    | 11(1)    | 0(1)     |
| C(5)  | 18(1)    | 29(1)    | 38(1)    | 11(1)    | 4(1)     | -1(1)    |
| C(6)  | 17(1)    | 28(1)    | 32(1)    | 8(1)     | 0(1)     | -2(1)    |
| C(7)  | 24(1)    | 31(1)    | 40(1)    | 12(1)    | 7(1)     | 0(1)     |
| C(8)  | 24(1)    | 42(1)    | 38(1)    | 5(1)     | 6(1)     | 1(1)     |
| C(9)  | 26(1)    | 31(1)    | 37(1)    | -1(1)    | -2(1)    | 3(1)     |
| C(10) | 32(1)    | 26(1)    | 33(1)    | 7(1)     | -3(1)    | -4(1)    |
| C(11) | 25(1)    | 28(1)    | 28(1)    | 4(1)     | 0(1)     | -7(1)    |
| C(12) | 22(1)    | 28(1)    | 45(1)    | 7(1)     | 10(1)    | 4(1)     |
| C(13) | 22(1)    | 46(1)    | 22(1)    | 3(1)     | 10(1)    | 9(1)     |
| C(14) | 26(1)    | 60(1)    | 27(1)    | -5(1)    | 9(1)     | 5(1)     |
| C(15) | 22(1)    | 106(2)   | 21(1)    | 1(1)     | 5(1)     | 6(1)     |
| C(16) | 31(1)    | 93(2)    | 29(1)    | 24(1)    | 16(1)    | 26(1)    |
| C(17) | 39(1)    | 64(2)    | 36(1)    | 24(1)    | 24(1)    | 23(1)    |
| C(18) | 30(1)    | 47(1)    | 27(1)    | 9(1)     | 13(1)    | 10(1)    |
| C(19) | 43(1)    | 138(3)   | 37(1)    | 39(2)    | 21(1)    | 38(2)    |
| C(20) | 18(1)    | 36(1)    | 41(1)    | -1(1)    | 13(1)    | -1(1)    |
| C(21) | 20(1)    | 34(1)    | 28(1)    | -2(1)    | 12(1)    | -2(1)    |
| C(22) | 22(1)    | 38(1)    | 26(1)    | -2(1)    | 10(1)    | -1(1)    |
| C(23) | 26(1)    | 40(1)    | 34(1)    | -7(1)    | 12(1)    | -6(1)    |
| C(24) | 37(1)    | 31(1)    | 40(1)    | -4(1)    | 18(1)    | -3(1)    |
| C(25) | 33(1)    | 39(1)    | 36(1)    | 5(1)     | 11(1)    | 6(1)     |
| C(26) | 23(1) | 40(1) | 31(1) | -2(1) | 7(1)  | -2(1) |
|-------|-------|-------|-------|-------|-------|-------|

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Table 5. Hydrogen coordinates (x $10^4$) and isotropic displacement parameters ($\AA^2 x 10^3$) for Yu35.

|     | x         | y         | z         | U(eq)  |
|-----|-----------|-----------|-----------|--------|
| H(1)| 8080(20)  | 4510(30)  | 7102(15)  | 34(6)  |
| H(3A)| 7187     | 207       | 8076      | 42     |
| H(3B)| 9113     | 11        | 8486      | 42     |
| H(4A)| 8584     | 642       | 9830      | 40     |
| H(4B)| 6794     | 1295      | 9368      | 40     |
| H(5)| 9848     | 2809      | 9467      | 34     |
| H(7)| 7039     | 3330      | 10402     | 38     |
| H(8)| 6030     | 5623      | 10858     | 42     |
| H(9)| 6285     | 7993      | 10167     | 39     |
| H(10)| 7651    | 8045      | 9058      | 39     |
| H(11)| 8740    | 5781      | 8633      | 34     |
| H(12A)| 10824   | 2009      | 8196      | 37     |
| H(12B)| 9681    | 2100      | 7240      | 37     |
| H(20A)| 11597   | 3873      | 6879      | 37     |
| H(20B)| 12666   | 3842      | 7857      | 37     |
| H(22)| 14253    | 6067      | 8276      | 34     |
| H(23)| 14797    | 8721      | 8161      | 39     |
| H(24)| 12937    | 10337     | 7252      | 42     |
| H(25)| 10533    | 9278      | 6436      | 43     |
| H(26)| 10019    | 6613      | 6510      | 38     |
Table 6. Hydrogen bonds for Yu35 [Å and °].

| D-H...A       | d(D-H) | d(H...A) | d(D...A) | <(DHA) |
|---------------|--------|----------|----------|--------|
| N(1)-H(1)...O(2) | 0.88(2) | 1.98(2)  | 2.722(2) | 142(2) |