Supporting Information

Remote Oxidation of Aliphatic C—H Bonds in Nitrogen-Containing Molecules

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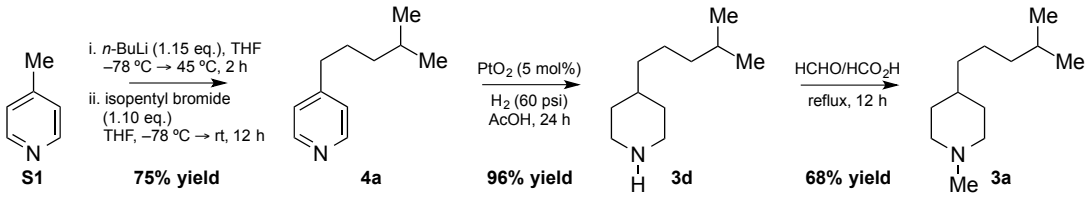
I. General Methods

Experimental. All C—H oxidations were run under air with no precautions taken to exclude moisture. All other reactions were run under an Ar or N_2 atmosphere with dry solvent in flame dried glassware unless otherwise noted. Dry solvents tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), diethyl ether (Et_2O), dimethylsulfoxide (DMSO) and acetonitrile (MeCN) were purified prior to use by passage through a bed of activated alumina (Glass Contour, Laguna Beach, CA). Triethylamine and pyridine were distilled from calcium hydride. Commercially available reagents that were used as received are noted in the individual reaction procedures. (*S,S*)- and (*R,R*)-2,2'-Bispyrrolidine tartrate were prepared according to the literature procedure.[1] The ee of the diamine was checked by conversion to the dibenzoate and analysis by reverse phase HPLC; obtained either enantiomer in >99% ee (Chiralpak AD-RH, 35:60:5 MeCN:H_2O:*i*-PrOH, 0.8 mL/min., 30 ℃, t_R(*S,S*)=10.803 min., t_R(*R,R*)=13.240 min.). (*S,S*)- and (*R,R*)- Fe(PDP) (**1**)[2] and Fe(CF_3PDP) (**2**)[3] were prepared according to literature procedures and stored at 4 °C in a desiccator, prior to use catalysts were warmed to room temperature and weighed out in air. Thin-layer chromatography (TLC) was conducted with E. Merck TLC silica gel 60 F_{254} pre-coated plates (0.25 mm) or E. Merck TLC aluminum oxide 60 F_{254}, basic, pre-coated glass backed plates. Visualization was conducted with UV, ninhydrin and potassium permanganate ($KMnO_4$) stain. Flash chromatography was performed as described by Still[4] using ZEOprep 60 ECO 43-60 micron silica gel (American International Chemical, Inc.) or basic aluminum oxide, Brockmann grade III (6% H_2O added to Brockmann grade I) prepared from Alfa Aesar aluminum oxide, activated, basic, Brockmann grade I, 58 angstroms, 60 mesh power, S.A. 150m^2/g, CAS: 1344-28-1. Medium pressure liquid chromatography was performed on a Teledyne Isco CombiFlash Rf machine using pre-packed RediSep columns (12 g SiO_2).

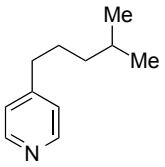
Structural analysis. ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz), Varian Inova-500 (500 MHz), Varian Unity-500 (500 MHz), Varian Unity-600 (600 MHz) and a Varian 750 (750 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CHCl_3$ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, h = hextet, hept = heptet, m = multiplet, br = broad, ap = apparent; coupling constant(s) in Hz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz), Varian Unity-500 (125 MHz) and Varian Inova-500 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.16 ppm). ^{19}F spectra were recorded on Varian Untiy 500 (470 MHz) or Varian VXR 500 (470 MHz) and are reported in ppm using $FCCl_3$ (0 ppm) as an external standard. The ^{13}C NMR spectra will contain the same impurities as the ^{1}H NMR spectra as they were generally obtained from the same sample. Impurities were calculated out when reporting isolated yields. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX FT-IR and are reported in frequency of absorption (cm^{-1}).
High-resolution mass spectrometry (HRMS) performed by Dr. Furong Sun, Dr. Kevin Tucker, Dr. Haijun Yao and Dr. Elizabeth Eves at the University of Illinois Mass Spectrometry Laboratory. X-ray crystallographic analysis carried out by Dr. Jeffery Bertke and Dr. Danielle Gray at the University of Illinois George L. Clark X-Ray Facility. Optical rotations were measured in a 1 mL cell with with 50 mm path length on a Jasco P2000 digital polarimeter, sodium lamp and are reported as follows: $[a]_{\lambda}^{T\,^{\circ}C}$ concentration (c = g / 100 mL, solvent).

II. Synthesis of Substrates and Compound Characterization for Table S1

Scheme S1. Piperidine Synthesis via Pyridine Alkylation and Hydrogenation



General Pyridine Alkylation Procedure



4-(4-Methylpentyl)pyridine (4a) The known compound was prepared following the published procedure and the ^{1}H NMR spectra matched that reported.[5] To a flame dried two-neck round bottom flask equipped with an addition funnel and magnetic stir bar was added 4-picoline (**S1**) (5.4 mL, 55.01 mmol, 1.00 equiv) dissolved in THF (25 mL) and the solution was cooled to –78 ºC via an acetone/dry ice bath. *n*-Butyllithium (39.5 mL, 63.26 mmol, 1.15 equiv, 1.6 M in Hex) was added slowly, upon complete addition the reaction was removed from the –78 ºC bath and warmed to room temperature and stirred at 45 ºC for 2 hours. The resultant 4-picolyllithium salt slurry was dissolved with THF (25 mL) to give a deep red homogeneous solution. The solution was cooled to 0 ºC and slowly transferred via cannula to a solution of isopentyl bromide (9.14 g, 7.3 mL, 60.51 mmol, 1.10 equiv) in THF (10 mL) cooled to –78 ºC. The reaction solution was gradually warmed to room temperature and stirred overnight. Reaction was quenched at room temperature with the addition of H_2O (3 mL). Reaction was filtered through a SiO_2 (250 mL)/sand plug and rinsed with EtOAc (1.5 L, volume = 6 x SiO_2 volume) and the solvent was evaporated. The residue was further purified by flash chromatography (500 mL SiO_2, gradient elution 20→40% EtOAc/Hex) to afford 4-(4-methylpentyl)pyridine (**4a**) as a dark orange oil (6.77 g, 41.47 mmol, 75% yield).

Data for **4a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.47 (d, *J* = 6.0 Hz, 2H), 7.09 (d, *J* = 5.7 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 4H), 1.65 – 1.51 (m, 3H), 1.24 – 1.17 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H);

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.83, 149.77, 124.02, 38.56, 35.60, 28.29, 27.96, 22.66;

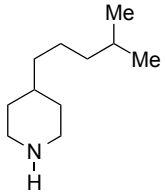
IR: (ATR, neat, cm^{-1})

3068, 3025, 2956, 2869, 1932, 1602, 1558, 1496, 1467, 1415, 1384, 1367, 1218, 1168, 1070, 993, 813, 792, 734;

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}N$ 164.1439; Found 164.1438

General Pyridine Hydrogenation Procedure



4-(4-Methylpentyl)piperidine (3d) To a 100 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine (**4a**) (2.3 g, 14.09 mmol, 1.00 equiv), AcOH (30 mL, 0.47 M) and PtO_2 (159 mg, 0.70 mmol, 5 mol%); rinsed catalyst from side of round bottom flask with AcOH (2 mL). The reaction was placed into a metal pressure reactor, sealed and purged with H_2 (3 x ~70 psi). After purging the metal pressure reactor was pressurized with H_2 (~70 psi) and stirred overnight at room temperature. Upon

completion of the reaction as monitored by TLC analysis the reaction solution color changed from red to colorless. The reaction was filtered through a celite/cotton plug, rinsing with AcOH (100 mL) and concentrated via rotoevaporation. The resultant residue was diluted with H_2O (150 mL) and basified by the addition of 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with H_2O (100 mL) and brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated via rotoevaporation to afford 4-(4-methylpentyl)piperidine (**3d**) as a yellow oil (2.3 g, 13.58 mmol, 96% yield), no further purification required. ***Important Note:*** *4-(4-methylpentyl)piperidine (**3d**) readily forms the carbamic acid upon sitting under an atmosphere of air at room temperature. The carbamic acid is a crystalline sold and was confirmed by ^{1}H NMR. Material was moved forward immediately to the next step or stored under an Ar atmosphere at –20 ºC.*

Data for (**3d**):

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.03 (dt, *J* = 12.5, 3.2 Hz, 2H), 2.56 (td, *J* = 11.9, 2.4 Hz, 2H), 1.64 (br d, *J* = 12.2 Hz, 2H), 1.51 (dp, *J* = 13.2, 6.5 Hz, 1H), 1.44 (br s, 1H), 1.36 – 1.23 (m, 3H), 1.21 – 1.14 (m, 2H), 1.17 – 1.08 (m, 2H), 1.05 (qd, *J* = 11.9, 11.4, 4.0 Hz, 2H), 0.85 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

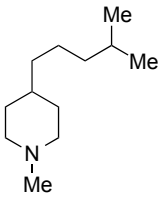
δ 47.11, 39.34, 37.68, 36.47, 33.98, 28.11, 24.38, 22.78;

IR: (ATR, neat, cm^{-1})

3272, 2904, 2805, 2732, 1743, 1650, 1465, 1444, 1384, 1365, 1319, 1255, 1145, 1124, 1101, 1047, 1006, 987, 950, 917, 904, 759

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{24}N$ 170.1909; Found 170.1906



1-Methyl-4-(4-methylpentyl)piperidine (3a) Prepared following the published procedure.[6] To a round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)piperidine (**3d**) (1.54 g, 9.10 mmol, 1.00 equiv), formaldehyde (2.2 g, 2.0 mL, 27.30 mmol, 3.00 equiv, 37% w/w in H_2O) and formic acid (2.5 g, 2 mL, 54.60 mmol, 6.00 equiv). Round bottom was fitted with a condenser and placed in a preheated oil bath (100-110 ºC). Reaction was refluxed overnight. Reaction progress was monitored by TLC analysis. Upon completion the reaction solution was cooled to 0 ºC and basified with 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated via rotoevaporation. The crude material was purified by flash chromatography (170 mL SiO_2, gradient elution 5% MeOH/CH_2Cl_2 doped with 1% NH_4OH→10% MeOH/CH_2Cl_2 doped with 2% NH_4OH). Fractions were combined and concentrated to an oil that was taken up in CH_2Cl_2 and washed with an equal volume of 1M NaOH to remove residual NH_4OH and water. Dried over anhydrous Na_2SO_4, filtered and concentrated to afford 1-methyl-4-(4-methylpentyl)piperidine (**3a**) as a yellow oil (1.13 g, 6.16 mmol, 68% yield).

Data for **3a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.83 (d, *J* = 12.1 Hz, 2H), 2.25 (s, 3H), 1.88 (t, *J* = 11.7 Hz, 2H), 1.66 (d, *J* = 10.4 Hz, 2H), 1.51 (dp, *J* = 13.2, 6.6 Hz, 1H), 1.33 – 1.21 (m, 3H), 1.24 – 1.15 (m, 4H), 1.17 – 1.09 (m, 2H), 0.86 (d, *J* = 6.5 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

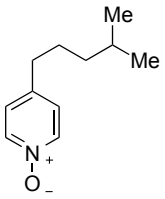
δ 56.24, 46.64, 39.35, 36.98, 35.27, 32.65, 28.13, 24.66, 22.79

IR: (ATR, neat, cm^{-1})

2912, 2778, 2734, 2680, 1712, 1677, 1643, 1573, 1556, 1463, 1378, 1367, 1280, 1199, 1145, 1112, 1072, 981, 767

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{26}N$ 184.2065; Found 184.2063



4-(4-Methylpentyl)pyridine 1-oxide (4b) To a 100 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine **(4a)** (653 mg, 4.00 mmol, 1.0 equiv), *meta*-chloroperoxybenzoic acid (1.18 g, 4.80 mmol, 1.2 equiv, 70 wt.% in H_2O) and CH_2Cl_2 (40 mL). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ (100 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (SiO_2, gradient elution 40% EtOAc/Hex→10% MeOH/CH_2Cl_2) afforded pyridine *N*-oxide (**4b**) as a yellow oil (583.3 mg, 3.25 mmol, 81% yield).

Data for **4b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

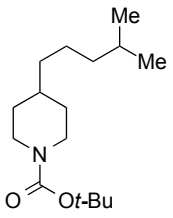
δ 8.12 (d, *J* = 6.9 Hz, 2H), 7.07 (d, *J* = 6.7 Hz, 2H), 2.57 (t, *J* = 7.7 Hz, 2H), 1.65-1.49 (m, 3H), 1.24-1.15 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (100 MHz, $CDCl_3$)

δ 142.76, 138.87, 126.07, 38.33, 34.73, 28.14, 27.91, 22.63

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}NO$ 180.1388; Found 180.1394



***Tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate (3b)** Prepared following the published procedure.[7] To a solution of 4-(4-methylpentyl)piperidine (**3d**) (500 mg, 2.953 mmol, 1.00 equiv) in dioxane-water (1:1 dioxane/H_2O, 1 M) was added Et_3N (415 μL, 2.953 mmol, 1.00 equiv) followed by di-*tert*-butylcarbonate (882 mL, 3.839 mmol, 1.30 equiv) at room temperature and the resulting reaction solution was stirred overnight. The product was then extracted with EtOAc (3 x 5 mL). The combined organic layer was washed with 1 M HCl (1 x 30 mL) and brine (1 x 30 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude material was purified by flash chromatography (60 mL SiO_2, gradient elution 2→5→10% EtOAc/Hex, 1 column volume each) to afford *tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate (**3b**) as a colorless oil (686.0 mg, 2.546 mg, 86% yield).

Data for **3b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

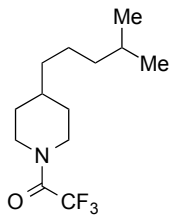
δ 4.06 (br s, 2H), 2.66 (t, *J* = 12.6 Hz, 2H), 1.64 (dd, *J* = 13.4, 3.5 Hz, 2H), 1.52 (tt, *J* = 12.3, 6.1 Hz, 1H), 1.45 (s, 9H), 1.36 (ddq, *J* = 14.9, 7.8, 4.4, 3.9 Hz, 1H), 1.33 – 1.24 (m, 2H), 1.24 – 1.15 (m, 2H), 1.18 – 1.10 (m, 2H), 1.06 (qd, *J* = 12.4, 4.4 Hz, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.06, 79.23, 44.27, 39.28, 36.92, 36.13, 32.39, 28.63, 28.08, 24.49, 22.76

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{16}H_{32}NO_2$ 270.2433; Found 270.2434



2,2,2-Trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one (3c) Prepared following the published procedure.[8] To a flame-dried 50 mL round bottom flask was added 4-(4-methylpentyl)piperidine (**3d**) (500 mg, 2.953 mmol, 1.00 equiv), CH_2Cl_2 (15 mL, 0.2 M) and Et_3N (617 μL, 4.430 mmol, 1.50 equiv), the solution was cooled to 0 ºC and trifluoroacetic anhydride (616 μL, 4.430 mmol, 1.50 equiv) was added. Reaction solution was gradually warmed to room temperature and stirred 12 hours. The reaction solution was poured slowly into aqueous saturated $NaHCO_3$ solution (50 mL) at 0 ºC. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). Combined organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The crude material was purified by flash chromatography (60 mL SiO_2, gradient elution 2→5→10% EtOAc/Hex, 1 column volume each) to afford 2,2,2-trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one (**3c**) as a colorless oil (686.4 mg, 2.587 mmol, 88% yield).

Data for **3c**:

^{1}H NMR: (499 MHz, $CDCl_3$)

δ 4.51 (ddt, *J* = 13.2, 4.4, 2.6 Hz, 1H), 3.99 (dd, *J* = 12.9, 4.0 Hz, 1H), 3.08 (td, *J* = 13.5, 2.6 Hz, 1H), 2.74 (td, *J* = 12.6, 2.8 Hz, 1H), 1.80 (dd, *J* = 13.1, 1.9 Hz, 2H), 1.58 – 1.48 (m, 2H), 1.34 – 1.26 (m, 2H), 1.26 – 1.20 (m, 2H), 1.20 – 1.11 (m, 4H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.29, 116.79 (q, *J* = 286.0 Hz), 46.29 (q, *J* = 3.6 Hz), 44.16 , 39.16 , 36.48 , 35.97 , 32.85 , 31.87 , 28.05 , 24.42 , 22.73

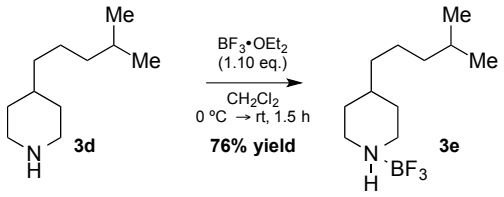
^{19}F NMR: (470 MHz, $CDCl_3$)

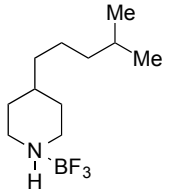
δ -69.27

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{23}NOF_3$ 266.1732; Found 266.1736

Scheme S2. General Synthesis of Amine–BF_3 Complexes





Trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate (3e) To a flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was added 4-(4-methylpentyl)piperidine (**3d**) (637 mg, 3.76 mmol, 1.00 equiv) and CH_2Cl_2. The solution was cooled to 0 ºC and BF_3•OEt_2 (511 μL, 4.13 mmol, 1.10 equiv) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (70 mL SiO_2, gradient elution 15→20→25→50→75→100% EtOAc/Hex, 1 column volume each) to afford trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate (**3e**) as a white crystalline solid (675.8 mg, 2.850 mmol, 76% yield).

Data for **3e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.47 (br s, 1H), 3.41 (d, *J* = 13.4 Hz, 2H), 2.72 (tdd, *J* = 13.7, 11.6, 2.8 Hz, 2H), 1.95 (d, *J* = 14.8 Hz, 2H), 1.56 – 1.43 (m, 2H), 1.33 – 1.10 (m, 8H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 46.05, 39.08, 36.62, 34.65, 31.31, 28.03, 24.25, 22.72

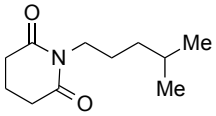
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.29 (q, *J* = 16.0 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{11}H_{22}NBF_3$ 236.1797; Found 236.1800

General Imide Alkylation Procedure 1



1-(4-Methylpentyl)piperidine-2,6-dione (3f) To a flame-dried round bottom flask equipped with a magnetic stir bar, under N_2 atmosphere was added glutarimide (792 mg, 7.00 mmol, 1.0 equiv), DMSO (23 mL, 0.3 M) and NaH (308 mg, 7.70 mmol, 1.1 equiv, 60 wt.% in mineral oil) in one portion. The solution was stirred for 15 minutes and 1-bromo-4-methylpentane (1.09 mL, 7.70 mmol, 1.1 equiv) was added dropwise. The reaction was stirred overnight (12-24 hours) at room temperature. Quenched by the addition of water (100 mL) and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with H_2O (5 x 100 mL) and brine (1 x 100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 30% EtOAc/Hex) afforded 1-(4-methylpentyl)piperidine-2,6-dione (**3f**) as a colorless oil (1.25 g, 6.34 mmol 91% yield).

Data for **3f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.73 – 3.66 (m, 2H), 2.62 (t, *J* = 6.6 Hz, 4H), 1.91 (p, *J* = 6.6 Hz, 2H), 1.57 – 1.42 (m, 3H), 1.19 – 1.12 (m, 2H), 0.84 (d, *J* = 6.6 Hz, 6H)

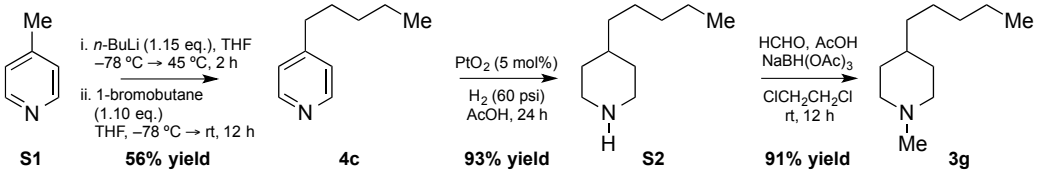
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.6, 39.9, 36.1, 33.0, 27.9, 26.0, 22.6, 17.3

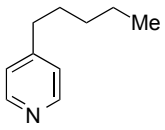
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{19}NO_2$ 198.1494, found 198.1500

Scheme S3. Synthesis of 4-Pentylpyridine and 4-Pentylpiperidine



S1 **56% yield** **4c** **93% yield** **S2** **91% yield** **3g**



4-Pentylpyridine (4c) Following the general pyrdine alkylation procedrue 4-picoline (**S1**) (2.7 mL, 2.56 g, 27.50 mmol, 1.0 equiv) was reacted with 1-bromobutane (3.3 mL, 4.15 g, 30.26 mmol, 1.1 equiv). Purification by flash chromatography (SiO_2, eluting with 20→40% EtOAc/hexanes) afforded 4-pentylpyridine (**4c**) as a yellow oil (2.30 g, 15.4 mmol, 56% yield).

Data for **4c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

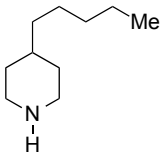
δ 8.47 (d, *J* = 5.3 Hz, 2H), 7.09 (d, *J* = 5.6 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.62 (p, *J* = 7.7 Hz, 2H), 1.40-1.24 (m, 4H), 0.89 (d, *J* = 6.9 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.86, 149.75, 124.02, 35.34, 31.47, 30.10, 22.57, 14.08

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}N$ 150.1283, found 150.1281.



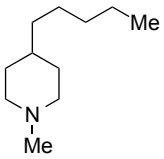
4-Pentylpiperidine (S2) Following the general pyridine hydrogenation procedure 4-pentylpyridine (**4c**) (924.0 mg, 6.19 mmol, 1.0 equiv) was reacted with H_2 (60 psi) and PtO_2 (70.3 mg, 0.310 mmol, 0.05 equiv) in acetic acid (13.2 mL). 4-Pentylpiperidine (**S2**) was obtained as a colorless oil (891.1 mg, 5.74 mmol, 93% yield).

Data for **S2**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.04 (dt, *J* = 12.1, 2.7 Hz, 2H), 2.56 (dt, *J* = 12.1, 2.5 Hz, 2H), 1.65 (d, *J* = 13.7 Hz, 2H), 1.55 (br s, 1H), 1.36-1.16 (m, 9H), 1.05 (qd, *J* = 12.1, 4.0 Hz, 2H), 0.88 (t, *J* = 7.1 Hz, 3H)

General Reductive Amination Procedure for Piperidine Substrates



1-Methyl-4-pentylpiperidine (3g) To a round bottom flask equipped with a magnetic stir bar was added 4-pentylpiperidine (**S2**) (581 mg, 3.74 mmol, 1.0 equiv), 1,2-dichloroethane (37.4 mL, 0.1 M), AcOH (750 μL, 1% v/v) and formaldehyde (1.4 mL, 562 mg, 18.7 mmol, 5.0 equiv, 37% wt. in H_2O), solution was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (1.19 g, 5.61 mmol, 1.5 equiv) was added in one portion and reaction solution was stirred overnight at room temperature. Reaction was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was washed with $NaHCO_3$ solution saturated (100 mL) and brine (100 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (basic Al_2O_3 Brockmann grade III, eluted with 20% EtOAc/Hex) to afford 1-methyl-4-pentylpiperidine (**3g**) as a colorless oil (571.3 mg, 3.38 mmol, 91% yield).

Data for **3g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.81 (d, *J* = 11.6 Hz, 2H), 2.24 (s, 3H), 1.35-1.10 (m, 11H), 0.87 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

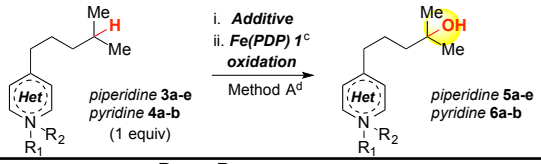
δ 56.32, 46.73, 36.75, 35.32, 32.75, 32.26, 26.61, 22.83, 14.22

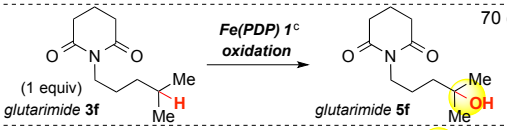
HRMS: (ESI-TOF MS ES+)

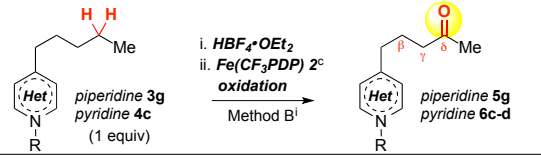
m/z: $[M+H]^+$ Calcd for $C_{11}H_{24}N$ 170.1909; found 170.1912

III. Experimental Procedures and Compound Characterization for Table S1

Table S1. Reaction Optimization[a,b]



Entry	Heterocycle	R_1	R_2	Additive (equiv)	Yield (%) (rsm)[e]
1	**3a**	Me	-	BF_3•OEt_2 (1.1)	46 (28)
2	**4a**	-	-	BF_3•OEt_2 (1.1)	27 (67)
3	**3a**	Me	-	HBF_4•OEt_2 (1.1)	56 (29)
4	**3a**	Me	-	F_3CCO_2H (1.1)	5 (74)
5[f]	**3a**	Me	-	H_2SO_4 (1.1)	0 (76)
6[g]	**3a**	Me	-	HBF_4•H_2O (1.1)	43 (40)
7	**4a**	-	-	HBF_4•OEt_2 (1.1)	57 (23)
8[a]	**4b**	O	-	-	0 (65)
9[a]	**3b**	Boc	-	-	n.d. (37)
10[a]	**3c**	TFA	-	-	n.d. (11)
11	**3d**	H	-	HBF_4•OEt_2 (1.1)	40 (26)
12[a,h]	**3e**	H	BF_3	-	44 (22)
13[a]					70 (8)



Entry	Heterocycle	R	Yield (%) (rsm)[e]	Selectivity[j]
14	**3g**	Me	57 (4)	1:1 δ/mixture
15	**4c**	-	53 (10)	2.6:1 δ/γ

[a]Iterative addition (3x): 5 mol% **1**, AcOH (0.5 equiv), H_2O_2 (1.2 equiv), MeCN (ref 4a). [b]Slow addition: 25 mol% **2**, AcOH (5.0 equiv), H_2O_2 (9.0 equiv), MeCN, syringe pump 6 mL/min (ref 4b,c). [c]Catalyst enantiomers used interchangeably. [d]Method A: (i) Additive (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition, (iii) 1M NaOH. [e]Isolated yields, % recovered starting material (rsm). [f]No product observed with H_2SO_4 (0.55 equiv). [g]In situ addition of HBF_4 (1.1 equiv). [h]2° Piperidine-BF_3 complex **3e** isolated and purifed. Product **5e** isolated/purified as 2° piperidine-BF_3 complex. [i]Method B: (i) HBF_4•OEt_2 (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Slow addition, (iii) 1M NaOH. [j]Based on isolation.

General Procedure (Table S1, entries 1-5, 7, 11 and 14-15). To a flame-dried 40 mL vial equipped with a magnetic stir bar was added heterocycle (0.50 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL, 0.25 M) the vial was flushed with a N_2 stream and then cooled to 0 ºC. Additive (0.55 mmol, 1.1 equiv) was added dropwise via syringe. The reaction mixture was stirred for 30 minutes at 0 ºC and then warmed to room temperature and stirred for an additional hour. The reaction solution was concentrated in vacuo and left on high vacuum overnight (12–24 hours). Resultant heterocycle complexes or salts were then oxidized following an iterative or slow addition protocol.

Iterative Addition Protocol: Iterative addition protocol previously described in the literature was followed.[2] The heterocycle complex or salt was dissolved in MeCN (746 µL, 0.67 M to substrate). A solution of Fe(PDP) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 µL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 µL, 0.05 M to Fe(PDP)) was added. A solution of H_2O_2 (34.1 µL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to

the stirring solution over 1.5–2 minutes. ***Significant decreases in yield were noted when the peroxide solution was added rapidly.*** After 10 min, a second portion of Fe(PDP) and AcOH dissolved in MeCN was added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last addition, for a total reaction time of approximately 36 minutes.

Slow Addition Protocol: The heterocycle complex or salt was dissolved in MeCN (0.75 mL, 0.67 M). A 1 mL syringe was charged with a solution of Fe(CF_3PDP) (0.125 mmol, 0.25 equiv), MeCN (0.55 mL, 0.23 M to Fe catalyst) and AcOH (143 μL, 2.50 mmol, 5.0 equiv). A 10 mL syringe was charged with a solution of H_2O_2 (256 μL, 4.50 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (6.0 mL, 0.75 M). Both syringes were fitted with 25G needles and solutions were added simultaneously into the stirring reaction mixture via a syringe pump at 6 mL/h.

Reaction Workup: MeCN volume was reduced to approximately 1–2 mL via rotoevaporation and diluted with CH_2Cl_2 (10 mL). Reaction was basified with 1 M NaOH (10 mL) and stirred vigorously for 10 minutes. Solution was poured into 1 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (1 x 60 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated via rotoevaporation. Purification by flash chromatography (25 mL, basic Al_2O_3 Brockmann grade III, gradient elution 10→20→40→80→100% EtOAc/Hex, 1 column volume of each) afforded 2-methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (**5a**) as a colorless oil.

Entry 1. According to the general procedure, 1-methyl-4-(4-methylpentyl)piperidine (**3a**) (91.7 mg, 0.500 mmol, 1.0 equiv) was complexed with BF_3•OEt_2 (67.9 μL, 0.550 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **BF_3-3a** complex. The oxidation was carried out in iterative fashion with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (**5a**) was isolated according to the reaction workup and purification described.

Run 1 (49.2 mg, 0.247 mmol, 49% yield; 35.9 mg, 0.196 mmol; 39% rsm)

Run 1 (42.9 mg, 0.215 mmol, 43% yield; 15.0 mg, 0.082 mmol; 16% rsm)

Average yield: 46% (28% rsm)

Entry 2. According to the general procedure, 4-(4-methylpentyl)pyridine (**4a**) (81.6 mg, 0.500 mmol, 1.0 equiv) was complexed with BF_3•OEt_2 (67.9 μL, 0.550 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **BF_3-4a** complex. The oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. MeCN volume was reduced to approximately 1–2 mL via rotoevaporation and diluted with Et_2O (10 mL). Reaction was basified with 20 wt.% NaOH (10 mL) and stirred vigorously for 2 hours to hydrolyze. The organic layer was separated, and the aqueous layer was filtered through a Celite® plug and extracted with Et_2O (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated via

rotoevaporation. Purification by flash chromatography (50 mL SiO_2, gradient elution 2→5→10% MeOH/CH_2Cl_2) afforded 2-methyl-5-(pyridin-4-yl)pentan-2-ol (**6a**) as a colorless oil.

Run 1 (21.0 mg, 0.117 mmol, 23% yield; 51.4 mg, 0.315 mmol, 63% rsm)

Run 2 (26.9 mg, 0.150 mmol, 30% yield; 56.9 mg, 0.349 mmol, 70% rsm)

Average yield: 27% (67% rsm)

Entry 3. According to the general procedure, 1-methyl-4-(4-methylpentyl)piperidine (**3a**) (91.7 mg, 0.500 mmol, 1.0 equiv) was protonated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-3a** salt. The oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (**5a**) was isolated according to the reaction workup and purification described.

Run 1 (56.0 mg, 0.281 mmol, 56% yield; 15.5 mg, 0.085 mmol, 40% rsm)

Run 2 (54.8 mg, 0.275 mmol, 55% yield; 37.0 mg, 0.202 mmol, 17% rsm)

Average yield: 56% (29% rsm)

Entry 4. According to the general procedure, 1-methyl-4-(4-methylpentyl)piperidine (**3a**) (91.7 mg, 0.500 mmol, 1.0 equiv) was protonated with F_3CCO_2H (550 μL, 0.550 mmol, 1.1 equiv, 1 M F_3CCO_2H in CH_2Cl_2) in CH_2Cl_2 (1.5 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **F_3CCO_2H-3a** salt. The oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (**5a**) was isolated according to the reaction workup and purification described.

Run 1 (4.8 mg, 0.0242 mmol, **5% yield**; 67.6 mg, 0.369 mmol, **74% rsm**)

Entry 5. According to the general procedure, 1-methyl-4-(4-methylpentyl)piperidine (**3a**) (91.7 mg, 0.500 mmol, 1.0 equiv) was protonated with concentrated H_2SO_4 (30.6 μL, 0.550 mmol, 1.1 equiv, 18 M) in CH_2Cl_2 (2.0 mL, 0.25 M). Solvent was removed and the **H_2SO_4-3a** salt was placed on a high vacuum for 1-12 hours. MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **H_2SO_4-3a** salt. The oxidation was carried out in iterative fashion with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 1-Methyl-4-(4-methylpentyl)piperidine (**3a**) was recovered according to the reaction workup and purification described.

Run 1 (74.3 mg, 0.405 mmol, 81% rsm)

Run 2 (66.2 mg, 0.361 mmol, 72% rsm)

Average: 76% rsm

Entry 6. In situ protection/oxidation procedure. To a 40 mL vial equipped with a magnetic stir bar was added 1-methyl-4-(4-methylpentyl)piperidine (**3a**) (91.7 mg, 0.500 mmol, 1.0 equiv) and MeCN (746 μL, 0.67 M to substrate) the solution was cooled to 0 ºC and HBF_4 (71.9 μL, 0.550 mmol, 1.1 equiv, 48 wt.% in H_2O) was added. The solution was stirred for 10 minutes at 0 ºC then at room temperature for 30 minutes. Oxidation via the iterative addition protocol was then carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (**5a**) was isolated according to the reaction workup and purification described.

Run 1 (42.9 mg, 0.215 mmol, 43% yield; 41.8 mg, 0.228 mmol; 46% rsm)

Run 2 (42.3 mg, 0.212 mmol, 42% yield; 31.0 mg, 0.169 mmol; 34% rsm)

Average overall yield: 43% (40% rsm)

Entry 7. According to the general procedure, 4-(4-methylpentyl)pyridine (**4a**) (81.6 mg, 0.500 mmol, 1.0 equiv) was protonated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-4a** salt. The oxidation was carried out in iterative fashion with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. 2-Methyl-5-(pyridin-4-yl)pentan-2-ol (**6a**) was isolated according to the reaction workup and purification by flash chromatography (50 mL SiO_2, gradient elution 2→5→10% MeOH/CH_2Cl_2).

Run 1 (50.1 mg, 0.280 mmol, 56% yield; 19.9 mg, 0.120 mmol, 24% rsm)

Run 2 (51.3 mg, 0.286 mmol, 57% yield; 18.0 mg, 0.110 mmol, 22% rsm)

Average yield: 57% (23% rsm)

Entry 8. To a 40 mL vial equipped with a magnetic stir bar was added 4-(4-methylpentyl)pyridine 1-oxide (**4b**) (53.8 mg, 0.300 mmol, 1.0 equiv) and MeCN (450 μL, 0.67 M to substrate). Oxidation via the iterative addition protocol was then carried out with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.6 μL, 0.15 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.7 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. By TLC analysis there was no evidence of desired product. The MeCN volume was concentrated and purified directly by flash chromatography (50 mL SiO_2, gradient elution with 5→10% MeOH/CH_2Cl_2) to recover 4-(4-methylpentyl)pyridine 1-oxide (**4b**).

Run 1 (33.6 mg, 0.187 mmol, 62% rsm)

Run 2 (36.3 mg, 0.202 mmol, 67% rsm)

Average recovered starting material: 65% rsm

Entry 9. To a 40 mL vial equipped with a magnetic stir bar was added *tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate (**3b**) (80.8 mg, 0.300 mmol, 1.0 equiv) and MeCN (448 μL, 0.67 M to substrate). Oxidation via the iterative addition protocol was then carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.9 μL, 0.15 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv, 50 wt.% in H_2O) in

MeCN (2.8 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. It was evident by TLC that there was over oxidation. The reaction was directly concentrated onto SiO_2 and purified by flash chromatography (20 mL SiO_2, gradient elution 10→20→40→80→100% EtOAc/Hex, 1 column volume each, approximately 30 mL) to recover *tert*-butyl 4-(4-methylpentyl)piperidine-1-carboxylate (**3b**) and an intractable mixture of over oxidized products.

Run 1 (29.8 mg, 0.111 mmol, **37% rsm**)

Entry 10. To a 40 mL vial equipped with a magnetic stir bar was added 2,2,2-trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one (**3c**) (79.6 mg, 0.300 mmol, 1.0 equiv) and MeCN (447 μL, 0.67 M to substrate). Oxidation via the iterative addition protocol was then carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.9 μL, 0.15 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. It was evident by TLC that there was over oxidation. The reaction was directly concentrated onto SiO_2 and purified by flash chromatography (100:1 SiO_2/theoretical yield, 20 mL SiO_2, gradient elution 10→20→30→40→50→60→70→80→90→100% EtOAc/Hex, 1 column volume each, approximately 30 mL) to recover 2,2,2-trifluoro-1-(4-(4-methylpentyl)piperidin-1-yl)ethan-1-one (**3c**) and an intractable mixture of over oxidized products.

Run 1 (8.8 mg, 0.033 mmol, **11% rsm**)

Entry 11. According to the general procedure, 4-(4-methylpentyl)piperidine (**3d**) (84.7 mg, 0.500 mmol, 1.0 equiv) was protonated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-3d** salt. The oxidation was carried out in iterative fashion with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The reaction was worked up as described and purification by flash chromatography (25 mL, basic Al_2O_3 Brockmann grade III, gradient elution 0→2→5→10% MeOH/DCM, 2 column volume of each) afforded 2-methyl-5-(piperidin-4-yl)pentan-2-ol (**5d**) as a colorless oil.

Run 1 (37.6 mg, 0.203 mmol, 41% yield; 21.0 mg, 0.124 mmol, 25% rsm)

Run 2 (36.0 mg, 0.194 mmol, 39% yield; 23.9 mg, 0.141 mmol, 28% rsm)

Average yield: 40% (26% rsm)

Entry 12. To a 40 mL vial equipped with a magnetic stir bar was added trifluoro(4-(4-methylpentyl)piperidine-1-ium-1-yl)borate (**3e**) (118.6 mg, 0.500 mmol, 1.0 equiv) and MeCN (746 μL, 0.67 M to substrate). Oxidation via the iterative addition protocol was then carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The MeCN volume was concentrated to approximately 0.5–1 mL and purified directly by flash chromatography (25 mL SiO_2, gradient elution 25→35→45→55→65→75→85→100% EtOAc/Hex, 1 column volume each, approximately 35 mL) to afford tertiary alcohol **5e** as a crystalline white solid.

Run 1 (54.5 mg, 0.215 mmol, 43% yield; 26.7 mg, 0.113 mmol, 23% rsm)

Run 2 (56.3 mg, 0.222 mmol, 44% yield; 24.1 mg, 0.102 mmol, 20% rsm)

Average yield: 44% (22% rsm)

Entry 13. According to the iterative addition protocol, 1-(4-methylpentyl)piperidine-2,6-dione (**3f**) (99 mg, 0.50 mmol, 1 equiv) was dissolved in MeCN (0.750 mL, 0.67 M). [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. Reaction was concentrated to minimal volume and directly purified by flash chromatography (SiO_2, gradient elution 10% up to 70% EtOAc/Hex) afforded 1-(4-hydroxy-4-methylpentyl)piperidine-2,6-dione (**5f**) as a white solid.

Run 1 (77 mg, 0.361 mmol, 72% yield, 12 mg, 0.061 mmol, 12% rsm)

Run 2 (71 mg, 0.333 mmol, 67% yield, 4 mg, 0.020 mmol, 4% rsm)

Average yield: 70% (8% rsm)

Entry 14. According to the general procedure, 1-methyl-4-pentylpiperidine **(3g)** (0.300 mmol, 50.8 mg) was protonated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μl, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-3g** salt. Oxidation was carried out following the slow addition protocol. H_2O_2 (153 μL, 2.7 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.0 mL) in 10 mL syringe and AcOH (86 μL, 90 mg, 1.5 mmol, 5.0 equiv) mixed together with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (14.0 mg, 0.015 mmol, 0.05 equiv) in MeCN (0.3 mL) and filled in 1 mL syringe were added simultaneously via a syringe pump to the substrate/MeCN solution (6.0 mL/min). Reaction was worked up as described and purification by flash chromatography (20 mL, basic Al_2O_3 Brockmann grade III, gradient elution 0→25→50→75→100% Et_2O/Pentane, 1.5 column volume of each) afforded pure 5-(1-methylpiperidin-4-yl)pentan-2-one **(5g)** and a mixture of minor ketones.

Run 1 (16.9 mg, 0.092 mmol, 31% yield **5g**; 2.8 mg, 0.017 mmol, 6% rsm; 17.2 mg, 0.094 mmol, 31% yield combined minor ketones)

Run 2 (13.8 mg, 0.075 mmol, 25% yield **5g**; 1.2 mg, 0.007 mmol, 2% rsm; 14.9 mg, 0.081 mmol, 27% yield combined minor ketones)

Average overall yield: 28% yield 5g, 29% yield combined minor ketones (4% rsm)

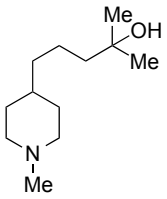
Entry 15. According to the general procedure, 4-pentylpyridine (**4c**) (0.3 mmol, 44.8 mg) was protonated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μl, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-4c** salt. Oxidation was carried out following the slow addition protocol. H_2O_2 (153 μL, 2.7 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.0 mL) in 10 mL syringe and AcOH (86 μL, 90 mg, 1.5 mmol, 5.0 equiv) mixed together with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (14.0 mg, 0.015 mmol, 0.05 equiv) in MeCN (0.3 mL) and filled in 1 mL syringe were added simultaneously via a syringe pump to the substrate/MeCN solution (6.0 mL/min). Reaction was worked up as described and purified by flash chromatography (50 mL, SiO_2, eluting with 80% EtOAc/hexanes) to afford 5-(pyridin-4-yl)pentan-2-one (**6c**) and 1-(pyridin-4-yl)pentan-3-one **(6d)** both as colorless oils.

Run 1 (18.9 mg, 0.116 mmol, 39% yield **6c**; 7.2 mg, 0.044 mmol, 15% yield **6d**; 4.3 mg, 0.029 mmol, 10% rsm)

Run 2 (18.3 mg, 0.112 mmol, 37% yield **6c**; 7.0 mg, 0.043 mmol, 14% yield **6d**; 5.0 mg, 0.034 mmol, 11% rsm)

Average overall: 38% yield 6c and 15% yield 6d (10% rsm)

2-Methyl-5-(1-methylpiperidin-4-yl)pentan-2-ol (5a)



Data for **5a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.82 (dd, *J* = 11.7, 3.8 Hz, 2H), 2.23 (s, 3H), 1.87 (t, *J* = 11.4 Hz, 2H), 1.66 (d, *J* = 9.8 Hz, 2H), 1.45 – 1.39 (m, 2H), 1.34 (ddd, *J* = 12.8, 9.2, 5.7 Hz, 2H), 1.28 – 1.20 (m, 5H), 1.19 (s, 6H)

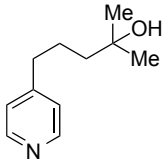
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.10, 56.16, 46.59, 44.25, 37.16, 35.23, 32.54, 29.38, 21.64

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{26}NO$ 200.2014, found 200.2016

2-Methyl-5-(pyridin-4-yl)pentan-2-ol (6a)



Data for **6a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.43 (dd, *J* = 4.6, 1.3 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.16 (br s, 1H), 1.74-1.69 (m, 2H), 1.49-1.45 (m, 2H), 1.19 (s, 6H)

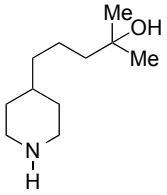
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.57, 149.55, 124.02, 70.58, 43.30, 35.65, 29.40, 25.10

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}NO$ 180.1388, found 180.1393

2-Methyl-5-(piperidin-4-yl)pentan-2-ol (5d)



Data for **5d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.05 (dt, *J* = 12.4, 3.2 Hz, 2H), 2.57 (td, *J* = 12.3, 2.6 Hz, 2H), 1.82 (br s, 1H), 1.67 (d, *J* = 13.1 Hz, 2H), 1.47 – 1.38 (m, 3H), 1.41 – 1.29 (m, 3H), 1.20 (s, 6H), 1.14 – 1.04 (m, 2H)

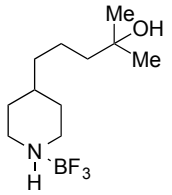
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.09, 46.89, 44.26, 37.82, 36.35, 33.69, 29.41, 21.37

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{23}NO$ 186.1858, found 186.1863

Tertiary Alcohol (5e)



Data for **5e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.63 (br s, 1H), 3.40 (ddd, *J* = 13.8, 4.3, 2.2 Hz, 2H), 2.72 (tdd, *J* = 13.5, 11.3, 2.8 Hz, 2H), 1.95 (d, *J* = 13.5 Hz, 2H), 1.50 (dddd, *J* = 15.1, 8.5, 6.9, 3.3 Hz, 1H), 1.46 – 1.34 (m, 5H), 1.31 – 1.23 (m, 4H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.10, 45.96, 43.89, 36.84, 34.66, 31.19, 29.46, 21.23

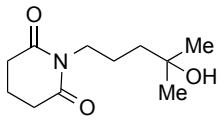
^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.20 (q, *J* = 16.6 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{11}H_{22}NOF_3B$ 252.1747, found 252.1749

1-(4-Hydroxy-4-methylpentyl)piperidine-2,6-dione (5f)



Data for **5f**:

^{1}H NMR: (500 MHz, Chloroform-*d*)

δ 3.74 – 3.68 (m, 2H), 2.60 (t, *J* = 6.6 Hz, 4H), 1.98 (s, 1H), 1.89 (p, *J* = 6.6 Hz, 2H), 1.59 – 1.49 (m, 2H), 1.45 – 1.38 (m, 2H), 1.15 (s, 6H)

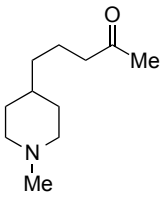
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.6, 70.6, 40.6, 40.0, 32.9, 29.3, 23.1, 17.2

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{11}H_{19}NO_3Na$ 236.1263, found 236.1265

5-(1-Methylpiperidin-4-yl)pentan-2-one (5g)



Data for **5g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.82 (d, *J* = 11.6 Hz, 2H), 2.45-2.37 (m, 2H), 2.24 (s, 3H), 2.13 (s, 3H), 1.86 (t, *J* = 11.2 Hz, 2H), 1.67 (d, *J* = 11.2 Hz, 2H), 1.63-1.49 (m, 2H), 1.27-1.15 (m, 5H)

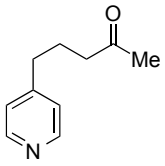
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 209.27, 55.90, 46.20, 44.00, 35.97, 34.96, 31.98, 30.08, 21.19

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{22}NO$ 184.1701, found 184.1705

5-(Pyridin-4-yl)pentan-2-one (6c)



Data for **6c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.46 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.58 (t, *J* = 7.7 Hz, 2H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.88 (p, *J* = 7.4 Hz, 2H)

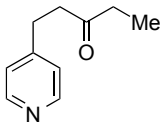
^{13}C NMR: (101 MHz, $CDCl_3$)

δ 208.20, 150.60, 149.84, 123.94, 42.56, 34.31, 30.12, 24.00

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ calculated for 164.1075, found 164.1082

1-(Pyridin-4-yl)pentan-3-one (6d)



Data for **6d**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 8.48 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.11 (d, *J* = 5.9 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.75 (t, *J* = 7.4 Hz, 2H), 2.42 (q, *J* = 7.3 Hz, 2H), 1.05 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (101 MHz, $CDCl_3$)

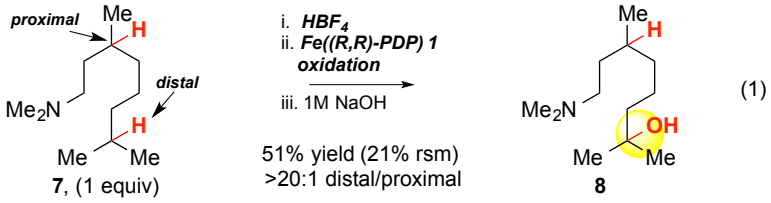
δ 209.74, 150.30, 149.96, 123.92, 42.47, 36.24, 28.98, 7.84

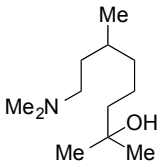
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{14}NO$ 164.1075, found 164.1080

IV. Experimental Procedures and Compound Characterization for Equation S1

Equation S1. HBF_4 Protonation/Fe(PDP) Oxidation of Linear Tertiary Amine





8-(dimethylamino)-2,6-dimethyloctan-2-ol (8) According to the general procedure, the known tertiary amine, *N,N*,3,7-Tetramethyloctan-1-amine[9] (**7**) (92.7, 0.50 mmol, 1.0 equiv) was protonated with HBF_4•OEt_2 (75.8 µL, 0.55 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 µL, 0.67 M to substrate) was used to dissolve the resultant **HBF_4-7** salt. The oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 µL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 µL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 µL, 0.60 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. Purification by flash chromatography (25 mL basic Al_2O_3 Brockmann grade III, gradient elution 10→20→40→80→100% EtOAc/Hex, 2 column volumes each) afforded 8-(dimethylamino)-2,6-dimethyloctan-2-ol (**8**) as a colorless oil.

Run 1 (50.1 mg, 0.249 mmol, 50% yield; 19.3 mg, 0.104 mmol, 21% rsm)

Run 2 (51.6 mg, 0.256 mmol, 51% yield; 18.8 mg, 0.101 mmol, 20% rsm)

Average yield: 51% (21% rsm)

Data for **8**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.26 (t, *J* = 7.6 Hz, 2H), 2.22 (s, 6H), 1.54 – 1.23 (m, 9H), 1.20 (s, 6H), 1.18 – 1.09 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

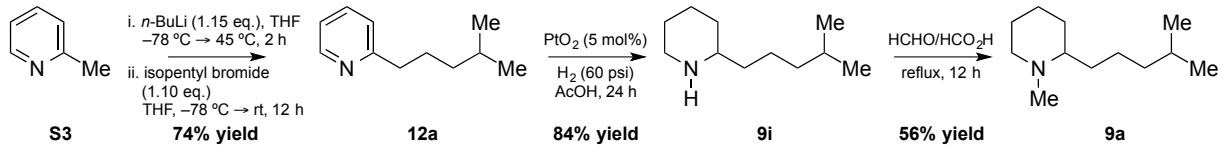
δ 71.14, 58.01, 45.69, 44.35, 37.83, 34.98, 31.38, 29.47, 29.37, 21.85, 19.90

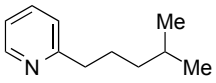
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{28}NO$ 202.2171, found 202.2165

V. Synthesis of Substrates and Compound Characterization for Table S2

Scheme S4. Synthesis of 2-Alkylpyridine and Piperidine Substrates





2-(4-Methylpentyl)pyridine (12a) Following the general pyridine alkylation procedure, 2-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv) (**S3**) was reacted with isopentyl bromide (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv). Purification by flash chromatography (SiO_2, eluting with 10→25% EtOAc/Hex) afforded 2-(4-methylpentyl)pyridine (**13a**) as a light yellow oil (1.77 g, 10.80 mmol, 74% yield).

Data for **12a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

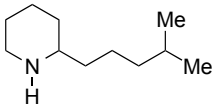
δ 8.51 (d, *J* = 4.2 Hz, 1H), 7.56 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.12 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.1, 5.1 Hz, 1H), 2.75 (t, *J* = 7.8 Hz, 2H), 1.76-1.66 (m, 2H), 1.56 (hept, *J* = 6.6 Hz, 2H), 1.27-1.19 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.68, 149.33, 136.31, 122.77, 120.95, 38.86, 28.06, 27.95, 22.72

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{18}N$ 164.1439, found 164.1445



2-(4-Methylpentyl)piperidine (9i) Following the general pyridine hydrogenation procedure, 2-(4-methylpentyl)pyridine (**12a**) (863.0 mg, 5.29 mmol, 1.0 equiv) was reacted with hydrogen gas (60 psi) and platinum dioxide (60.0 mg, 0.264 mmol, 0.05 equiv) in acetic acid (11.3 mL). 2-(4-methylpentyl)piperidine (**9i**) was obtained as a colorless oil (750.8 mg, 4.43 mmol, 84% yield).

Data for **9i**:

^{1}H NMR: (500 MHz, $CDCl_3$)

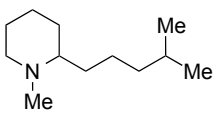
δ 3.05 (ddt, *J* = 12.0, 4.1, 2.1 Hz, 1H), 2.61 (td, *J* = 11.7, 2.7 Hz, 1H), 2.47-2.36 (m, 1H), 1.81-1.72 (m, 1H), 1.69-1.46 (m, 4H), 1.46-1.22 (m, 6H), 1.21-1.11 (m, 2H), 1.10-0.98 (m, 1H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 57.10, 47.43, 39.32, 37.93, 33.18, 28.06, 26.83, 25.09, 23.81, 22.76

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{24}N$ 170.1909, found 170.1906



1-Methyl-2-(4-methylpentyl)piperidine (9a) Prepared following the published procedure.[6] To a round bottom flask equipped with a magnetic stir bar was added 2-(4-methylpentyl)piperidine (**9i**) (535 mg, 3.16 mmol, 1.00 equiv), formaldehyde (3.0 mL, 40.00 mmol, 13.0 equiv, 37% w/w in H_2O) and formic acid (3 mL, 79.51 mmol, 25.16 equiv). Round bottom was fitted with a condenser and placed in a preheated oil bath (100-110

ºC). Reaction was refluxed overnight. Reaction progress was monitored by TLC analysis. Upon completion the reaction solution was cooled to 0 ºC and basified with 50% aq. NaOH (pH = 10-11). The basic aqueous layer was extracted with Et_2O (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated via rotoevaporation. The crude material was purified by flash chromatography (Brockmann grade III basic Al_2O_3, gradient elution 2→5→10% EtOAc/Hex) to afford 1-methyl-2-(4-methylpentyl)piperidine (**9a**) as a yellow oil (325.2 mg, 1.77 mmol, 56% yield).

Data for **9a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.83 (dtd, *J* = 11.6, 3.6, 1.5 Hz, 1H), 2.24 (s, 3H), 2.09 – 2.00 (m, 1H), 1.79 (tt, *J* = 7.5, 3.2 Hz, 1H), 1.71 (dtd, *J* = 8.7, 3.6, 1.6 Hz, 1H), 1.68 – 1.60 (m, 1H), 1.61 – 1.47 (m, 4H), 1.34 (m, 2H), 1.31 – 1.16 (m, 3H), 1.19 – 1.11 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H)

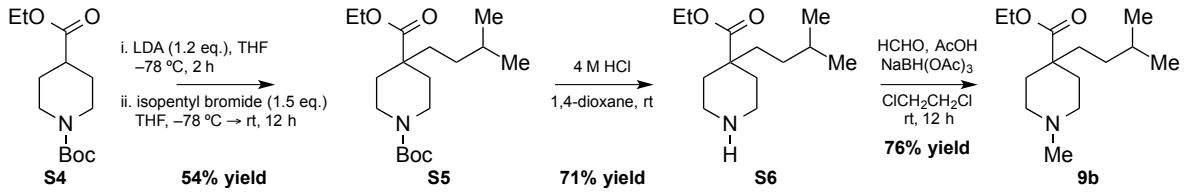
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 64.14, 57.48, 43.14, 39.69, 33.37, 30.96, 28.13, 26.06, 24.63, 23.15, 22.91, 22.68

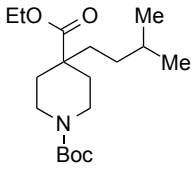
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{26}N$ 184.2065; found 184.2069

Scheme S5. Synthesis of Ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate



General Piperidine Alkylation Procedure



1-(*Tert*-butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate (S5) To a flame dried 500 mL round bottom flask equipped with a magnetic stir bar was added diisopropylamine (6.1 mL, 43.85 mmol) and THF (48 mL, 0.5 M to *n*-BuLi), the solution was cooled to –78 ºC and *n*-BuLi was added; stirred 1 hour at –78 ºC. A solution of 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate[7] (**S4**) (8.55g, 33.22 mmol, 1.00 equiv) in THF (20 mL, 1.7 M to substrate) was added to the LDA solution via cannula at –78 ºC, solution was stirred at –78 ºC for 2 hours. Isopentyl bromide (6 mL, 49.83 mmol, 1.5 equiv) was added in one portion, dropwise (moderate rate) at –78 ºC. The reaction solution was warmed slowly to room temperature and stirred overnight. Reaction was cooled to 0 ºC and quenched with 10% aqueous citric acid solution (50 mL). The quenched reaction solution was poured into brine (200 mL) and extracted with EtOAc (3 x 100 mL). Combined organic layer was washed with brine (300 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 0→2→5→10→15→20→25% EtOAc/Hex, 1 column volume each) to afford 1-(*tert*-butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate (**S5**) as a viscous colorless oil (5.88 g, 17.96 mmol, 54% yield).

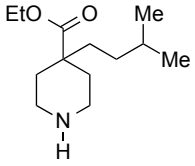
Data for **S5**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (br s, 2H), 2.87 (br s, 2H), 2.08 (d, *J* = 13.3 Hz, 2H), 1.52 – 1.44 (m, 2H), 1.44 (s, 9H), 1.44 – 1.38 (m, 1H), 1.38 – 1.28 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.02 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.77, 155.03, 79.48, 60.51, 45.60, 38.23, 33.54, 32.93, 28.60, 28.57, 28.45, 22.63, 14.50



Ethyl 4-isopentylpiperidine-4-carboxylate (S6) To a 100 mL round bottom flask equipped with a magnetic stir bar was added 1-(*tert*-butyl) 4-ethyl 4-isopentylpiperidine-1,4-dicarboxylate (**S5**) (1.96 g, 6.00 mmol, 1.00 equiv), 1,4-dioxane (24 mL, 0.25 M) and 4 M HCl (15 mL, 60.00 mmol, 10.00 equiv). Reaction was stirred at room temperature and TLC was employed to monitor conversion. Upon completion 1,4-dioxane was removed via rotoevaporation. Solution was basified with 1 M NaOH (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford ethyl 4-isopentylpiperidine-4-carboxylate (**S6**) as a yellow oil (975 mg, 4.29 mmol, 71% yield).

Data for **S6**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.13 (q, *J* = 7.3 Hz, 2H), 2.89 (dt, *J* = 12.8, 4.0 Hz, 2H), 2.67 – 2.57 (m, 2H), 2.06 (d, *J* = 13.1 Hz, 2H), 1.59 (s, 1H), 1.48 – 1.37 (m, 3H), 1.30 (ddd, *J* = 13.0, 11.3, 4.1 Hz, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.06 – 1.00 (m, 2H), 0.82 (d, *J* = 6.9 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.29, 60.22, 45.75, 44.08, 38.79, 34.86, 32.73, 28.41, 22.59, 14.45

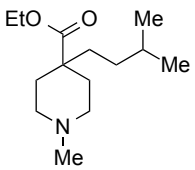
IR: (ATR, neat, cm^{-1})

2953, 2870, 1722, 1467, 1451, 1386, 1367, 1321, 1281, 1201, 1178, 1146, 1096, 1081, 1026, 981, 860, 761

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{26}NO_2$ 228.1964; found 228.1968

General Procedure for Reductive Amination of Piperidine Substrates



Ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate (9b) To a round bottom flask equipped with a magnetic stir bar was added ethyl 4-isopentylpiperidine-4-carboxylate (**S6**) (560 mg, 2.46 mmol, 1.00 equiv), 1,2-dichloroethane (25 mL, 0.1 M), AcOH (250 μL, 1% v/v) and formaldehyde (366 μL, 4.92 mmol, 2.00 equiv, 37% wt. in H_2O), solution was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (782 mg, 3.69 mmol, 1.5 equiv) was added in one portion and reaction solution was stirred overnight at room temperature. Reaction was quenched with saturated $NaHCO_3$ solution (50 mL) and extracted with CH_2Cl_2 (3 x 25 mL). Combined organic layer was washed with $NaHCO_3$ solution saturated (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (Brockmann grade III basic Al_2O_3, eluted with 10% EtOAc/Hex) to afford ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate (**9b**) (449 mg, 1.86 mmol, 76% yield).

Data for **9b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.11 (q, *J* = 7.1 Hz, 2H), 2.61 (d, *J* = 12.1 Hz, 2H), 2.19 (s, 3H), 2.09 (ddd, *J* = 13.8, 4.6, 2.4 Hz, 2H), 1.99 – 1.91 (m, 2H), 1.46 – 1.34 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.04 – 0.98 (m, 2H), 0.80 (d, *J* = 6.6 Hz, 6H)

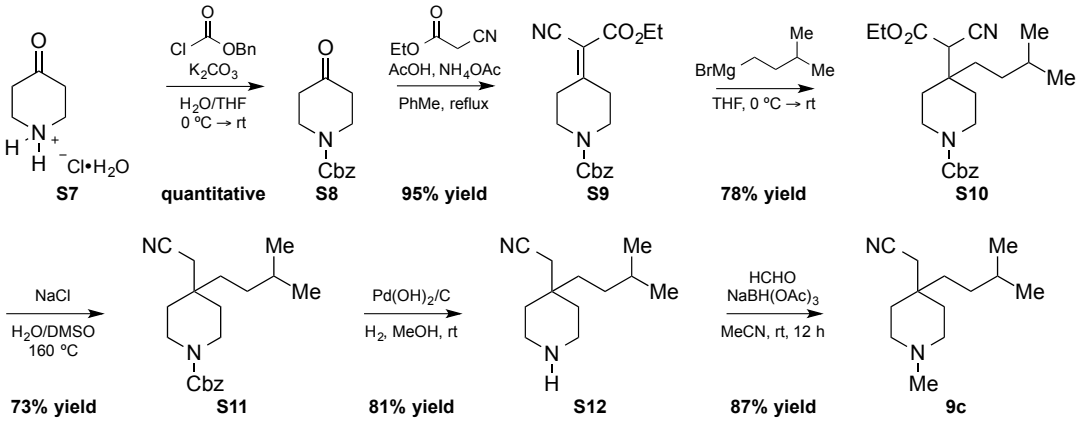
^{13}C NMR: (126 MHz, $CDCl_3$)

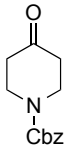
δ 176.10, 60.19, 53.39, 46.46, 44.69, 38.44, 33.80, 32.97, 28.40, 22.58, 14.44

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{28}NO_2$ 242.2120; found 242.2115

Scheme S6. Synthesis of 2-(4-Isopentyl-1-methylpiperidin-4-yl)acetonitrile



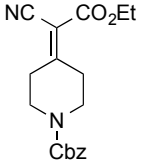


Benzyl 4-oxopiperidine-1-carboxylate (S8) To a solution of piperidine-4-one hydrochloride (**S7**) (5.00 g, 32.55 mmol, 1.00 equiv) in THF (33 mL, 1 M) was added K_2CO_3 (9.00 g, 65.10 mmol, 2.00 equiv) dissolved in water (22 mL, 3 M) at room temperature. The mixture was cooled to 0 ºC and benzyl chloroformate (5.1 mL, 35.80 mmol, 1.10 equiv) was added dropwise. The reaction mixture was warmed to room temperature and allowed to stir. TLC was used to monitor reaction progress. Upon disappearance of the starting material the mixture was filtered and the layers separated. The aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford benzyl 4-oxopiperidine-1-carboxylate (**S8**) (7.59 g, 32.55 mmol, quantitative) as a viscous colorless oil. Material was used without further purification.

Data for **S8**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39 – 7.35 (m, 5H), 5.18 (s 2H), 3.80 (t, *J* = 6.3 Hz, 4H), 2.52 – 2.36 (m, 4H)

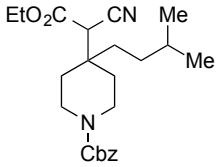


Benzyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (S9) To a round bottom flask equipped with a magnetic stir was added benzyl 4-oxopiperidine-1-carboxylate (**S8**) (1.75 g, 7.46 mmol, 1.00 equiv), PhMe (50 mL), ethyl cyanoacetate (2.0 mL, 18.65 mmol, 2.50 equiv), NH_4OAc (575 mg, 7.46 mmol, 1.00) and AcOH (0.3 mL). The round bottom was fitted with a Dean-Stark trap with a condenser and heated to reflux for 48 hours. Reaction was cooled to room temperature and concentrated. Crude material was purified by flash chromatography (25:1 SiO2/theoretical yield, gradient elution 25→50% EtOAc/Hex, 3 column volumes each) to afford benzyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (**S9**) as a white solid (2.32 g, 7.07 mmol, 95% yield).

Data for **S9**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.31 (m, 5H), 5.16 (s, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.69 (t, *J* = 5.9 Hz, 2H), 3.62 (t, *J* = 5.9 Hz, 2H), 3.15 (s, 2H), 2.79 (s, 2H), 1.35 (t, *J* = 7.2 Hz, 3H)

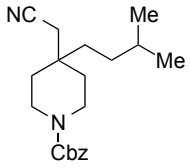


Benzyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-isopentylpiperidine-1-carboxylate (S10) Preparation of isopentylmagnesium bromide: Magnesium turnings (681 mg, 28.00 mmol, 1.12 equiv) were flame dried under vacuum with stirring in a 3-neck flask equipped with a condenser. Magnesium was suspended in THF (1.2 mL) under N_2. Several drops of isopently bromide solution (3.0 mL, 25.00 mmol, 1.00 equiv) in THF (8 mL, 3 M) was added to initiate the reaction. Remaining solution was added over 20 minutes via syringe pump. After 2 hours stirring, magnesium turnings were consumed and mild refluxing state had been achieved, reaction was a thick grey solution. Diluted with THF (5.5 mL, 1.7 M). To a flame dried round bottom flask equipped with a magnetic stir bar was added benzyl 4-(1-cyano-2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (**S9**) (1.14 g, 3.47 mmol, 1.00 equiv) and THF (16 mL, 0.22 M). The solution was cooled to 0 ºC and isopentylmagnesium bromide was added via cannula. Solution was slowly warmed to room temperature and stirred overnight. Reaction was quenched with saturated NH_4Cl solution (200 mL) and extracted with EtOAc (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, gradient elution 2→10→20→30→40→% EtOAc/Hex, 2 column volumes each) to afford benzyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-isopentylpiperidine-1-carboxylate (**S10**) (1.09 g, 2.72 mmol, 78% yield).

Data for **S10**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.28 (m, 5H), 5.13 (s, 2H), 4.32 – 4.19 (m, 2H), 3.78 (br s, 2H), 3.61 (s, 1H), 3.26 (ddd, *J* = 13.8, 10.0, 3.3 Hz, 2H), 1.76 (tdd, *J* = 13.9, 9.9, 4.4 Hz, 2H), 1.71 – 1.59 (m, 3H), 1.59 – 1.44 (m, 2H), 1.32 (t, *J* = 7.1 Hz, 2H), 1.17 (dt, *J* = 9.0, 6.9 Hz, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H) – *Contains EtOAc*

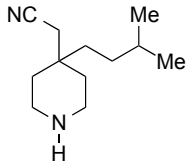


Benzyl 4-(cyanomethyl)-4-isopentylpiperidine-1-carboxylate (S11) To a round bottom flask equipped with magnetic stir bar was added benzyl 4-(1-cyano-2-ethoxy-2-oxoethyl)-4-isopentylpiperidine-1-carboxylate (**S10**) (1.09 g, 2.72 mmol, 1.00 equiv), DMSO (9 mL, 0.30 M), H_2O (130 μL, 7.07 mmol, 2.60 equiv), NaCl (64 mg, 1.09 mmol, 0.4 equiv). Reaction was fitted with a condenser and heated to 160 ºC for 7 hours. TLC was used to monitor reaction progress. Reaction was cooled to room temperature and diluted with H_2O (30 mL) and extracted with Et_2O (3 x 15 mL). Combined organic layer was washed with H_2O (100 mL) and brine (100 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, gradient elution 10→20→30% EtOAc/Hex) to afford benzyl 4-(cyanomethyl)-4-isopentylpiperidine-1-carboxylate (**S11**) (648.9 mg, 1.98 mmol, 73% yield).

Data for **S11**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39 – 7.29 (m, 5H), 5.13 (s, 2H), 3.47 (m, 4H), 2.34 (s, 2H), 1.59 – 1.45 (m, 7H), 1.14 – 1.08 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H)



2-(4-Isopentylpiperidin-4-yl)acetonitrile (S12) To a round bottom flask equipped with a magnetic stir bar was added benzyl 4-(cyanomethyl)-4-isopentylpiperidine-1-carboxylate (**S11**) (648.9 mg, 1.976 mmol, 1.00 equiv) and MeOH (10 mL, 0.2 M). The solution was purged with Ar (balloon x 3) then $Pd(OH)_2$ (130 mg, 20 wt.%) was added followed by purging with H_2 (balloon x 3). Reaction was stirred at room temperature. TLC was used to monitor reaction progress. Reaction was filtered through celite, rinsing with MeOH and concentrated. Crude material was purified by flash chromatography (50:1 Brockmann grade III basic Al_2O_3/theoretical yield, gradient elution 0→1→2→3→4→5% MeOH/DCM, 3 column volumes each) to afford 2-(4-isopentylpiperidin-4-yl)acetonitrile (**S12**) (310.3 mg, 1.60 mmol, 81% yield).

Data for **S12**:

^{1}H NMR: (500 MHz, $CDCl_3$)

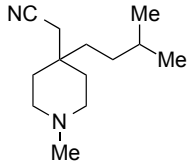
δ 2.85 (ddd, *J* = 12.9, 7.2, 4.0 Hz, 2H), 2.77 (ddd, *J* = 12.9, 7.3, 4.0 Hz, 2H), 2.34 (s, 2H), 2.02 (s, 1H), 1.49 (m, 7H), 1.10 (ddd, *J* = 11.9, 8.1, 5.7 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 118.04, 41.97, 35.54, 35.26, 34.23, 31.78, 28.57, 26.34, 22.70

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{23}N_2$ 195.1861, found 195.1861



2-(4-Isopentyl-1-methylpiperidin-4-yl)acetonitrile (9c) To a round bottom flask equipped with a magnetic stir bar was added 2-(4-isopentylpiperidin-4-yl)acetonitrile (**S12**) (207 mg, 1.07 mmol, 1.00 equiv), MeCN (2.7 mL, 0.4 M) and formaldehyde (159 μL, 2.13 mmol, 2.00 equiv, 37% wt. in H_2O), solution was stirred at room temperature for 30 minutes. $NaBH(OAc)_3$ (339.1 mg, 1.60 mmol, 1.5 equiv) was added in one portion and reaction solution was stirred overnight at room temperature. Reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layer was washed with $NaHCO_3$ solution saturated (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by column chromatography (basic Al_2O_3 Brockmann grade III, eluted with 10% EtOAc/Hex) to afford 2-(4-isopentyl-1-methylpiperidin-4-yl)acetonitrile (**9c**) (194.0 mg, 0.931 mmol, 87% yield).

Data for **9c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 2.46 – 2.37 (m, 2H), 2.30 (s, 2H), 2.27 (br m, 2H), 2.25 (s, 3H), 1.63 – 1.41 (m, 7H), 1.12 – 1.05 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

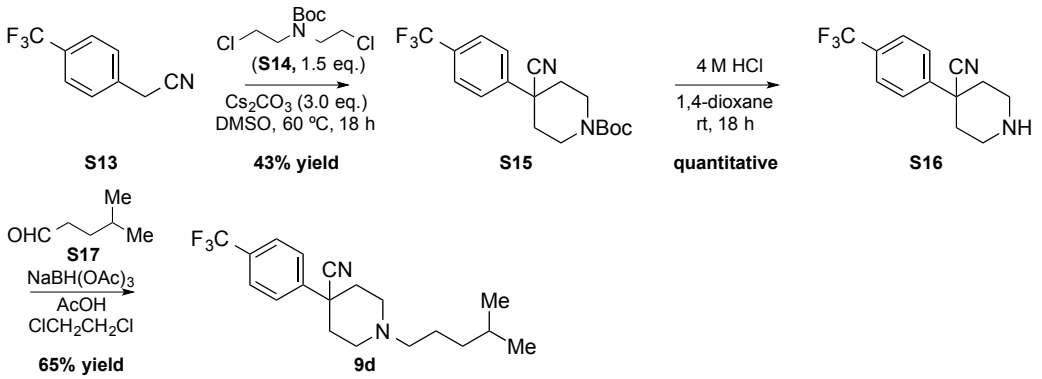
^{13}C NMR: (126 MHz, $CDCl_3$)

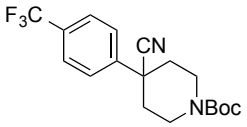
δ 118.04, 51.28, 46.36, 34.80, 33.18, 31.87, 28.55, 25.68, 22.69

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{25}N_2$ 209.2018; found 209.2019

Scheme S7. Synthesis of 1-(4-Methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile





***Tert*-Butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (S15)** To a flame-dried two neck round bottom flask equipped with a magnetic stir bar was added Cs_2CO_3 (17.9 g, 55.09 mmol, 3.00 equiv) and DMSO (40 mL) to this heterogeneous solution was added 4-(trifluoromethyl)phenyl acetonitrile (**S13**) (3.4 g, 18.36 mmol, 1.00 equiv) dissolved in DMSO (20 mL) via cannula (rinsed with 10 mL of DMSO to ensure complete material transfer); reaction solution turned yellow. Bis-(2-chloroethyl)carbamic acid *tert*-butyl ester[10] (**S14**) (6.7 g, 27.55 mmol, 1.50 equiv) dissolved in DMSO (10 mL) via cannula (rinsed with 10 mL of DMSO). The reaction solution was transferred to a 60 ºC oil bath and stirred for 18 hours. The reaction solution turned dark purple. TLC analysis and GC were employed to monitor reaction progress. Reaction solution was cooled to room temperature, diluted with Et_2O (200 mL) and H_2O (200 mL). Upon sitting in separatory funnel emulsion separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layer was washed with H_2O (2 x 300 mL) and brine (1 x 300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification by flash chromatography (400 mL SiO_2, gradient elution 100% Hex→2→5→10→15% EtOAc/Hex) afforded *tert*-butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (**S15**) as a viscous orange oil (2.79 g, 7.87 mmol, 43% yield).

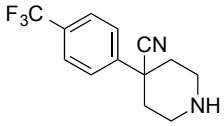
Data for **S15**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H), 4.31 (br s, 2H), 3.21 (br s, 2H), 2.10 (d, J = 13.2 Hz, 2H), 1.96 (dt, J = 12.8, 6.3 Hz, 2H), 1.48 (s, 9H)

HRMS: (ESI-TOF MS ES+)

m/z: $[(M–Boc)+2H]^+$ Calcd for $C_{13}H_{14}N_2F_3$ 255.1109; Found 255.1112



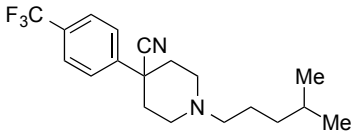
4-(4-(Trifluoromethyl)phenyl)piperidine-4-carbonitrile (S16) To a round bottom flask equipped with a magnetic stir bar was added *tert*-butyl 4-cyano-4-(4-(trifluoromethyl)phenyl)piperidine-1-carboxylate (**S15**) (636 mg, 1.795 mmol, 1.0 equiv), 1,4-dioxane (2 mL, 0.9 M) and 4 M HCl in 1,4-dioxane (3.6 mL, 14.360 mmol, 8.0 equiv). Reaction solution was stirred at room temperature over night (18 h). Reaction solution was concentrated and basified with 1 M NaOH (50 mL) to pH = 10-11. The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to

afford 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**S16**) as a pink crystalline solid. No further purification was required and material was taken directly on to reductive amination (457 mg, 1.80 mmol, quantitative).

Data for **S16**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 2H), 3.24 – 3.11 (m, 4H), 2.10 (dt, *J* = 13.4, 2.5 Hz, 2H), 2.00 (ddd, *J* = 13.3, 11.5, 4.5 Hz, 2H), 1.68 (s, 1H)



1-(4-Methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (9d) To a round bottom flask equipped with a magnetic stir bar was added 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**S16**) (499 mg, 1.963 mmol, 1.0 equiv), 1,2-dichloroethane (20 mL, 0.1 M), 4-methylpentanal[11] (**S17**) (295 mg, 2.945 mmol, 1.5 equiv) and acetic acid (0.2 mL, 1% v/v). The reaction solution was stirred for 30 minutes at room temperature. $NaBH(OAc)_3$ (624.2 mg, 2.945 mmol, 1.5 equiv) was added in one portion and the interior of the flask rinsed with 1,2-dichloroethane (2 mL). The reaction solution was stirred overnight (18 h) at room temperature. The reaction was quenched at room temperature by the addition of sat. $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with sat. $NaHCO_3$ solution (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, 80 mL SiO_2, gradient elution Hex→2→4→6→8→10→20→30% EtOAc/Hex) afforded 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**9d**) as a light orange oil (433 mg, 1.28 mmol, 65% yield)

Data for **9d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.9 Hz, 2H), 3.06 (d, *J* = 12.5 Hz, 2H), 2.48 (ddd, *J* = 12.3, 10.0, 4.5 Hz, 2H), 2.47 – 2.39 (m, 2H), 2.16 – 2.09 (m, 4H), 1.62 – 1.47 (m, 3H), 1.20 (dd, *J* = 15.9, 6.8 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

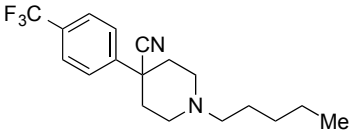
δ 144.29, 130.60 (q, *J* = 32.8 Hz), 126.34, 126.18 (q, *J* = 3.6 Hz), 125.01 (q, *J* = 275.6), 121.55, 59.00, 50.82, 43.23, 36.88, 36.70, 28.12, 24.97, 22.75

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.11

HRMS: (ESI-TOF MS ES+)

m/z:$[M+H]^+$ Calcd for $C_{19}H_{26}N_2F_3$ 339.2048; found 339.2047



1-Pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (9e) To a round bottom flask equipped with a magnetic stir bar was added 4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**S16**) (713.2 mg, 2.805 mmol, 1.0 equiv), 1,2-dichloroethane (56 mL, 0.05 M), valeraldehyde (1.5 mL, 14.025 mmol, 5.0 equiv) and acetic acid (0.56 mL, 1% v/v). The reaction solution was stirred for 30 minutes at room temperature. $NaBH(OAc)_3$ (892 mg, 4.208 mmol, 1.5 equiv) was added in one portion and the interior of the flask rinsed with 1,2-dichloroethane (2 mL). The reaction solution was stirred overnight (18

h) at room temperature. The reaction was quenched at room temperature by the addition of saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (50 mL) and brine (50 mL). Dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, 100 mL SiO_2, gradient elution CH_2Cl_2→5% MeOH/CH_2Cl_2) afforded 1-pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**9e**) as a light orange oil (493 mg, 1.52 mmol, 54% yield).

Data for **9e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.8 Hz, 2H), 3.09 – 3.03 (m, 2H), 2.51 – 2.41 (m, 4H), 2.18 – 2.07 (m, 4H), 1.57 – 1.47 (m, 2H), 1.39 – 1.26 (m, 4H), 0.91 (t, *J* = 7.0 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.31, 130.59 (q, *J* = 32.8 Hz), 126.34, 126.17 (q, *J* = 3.7 Hz), 123.93 (q, *J* = 272.2 Hz), 121.55, 58.71, 50.79, 43.23, 36.70, 29.89, 26.81, 22.75, 14.20

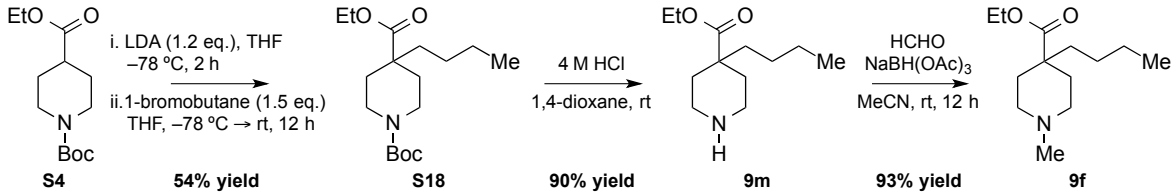
^{19}F NMR: (470 MHz, $CDCl_3$)

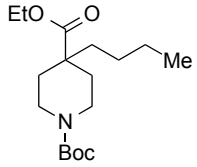
δ -63.11

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{18}H_{24}N_2F_3$ 325.1892; found 325.1894

Scheme S8. Synthesis of Ethyl 4-butyl-1-methylpiperidine-4-carboxylate



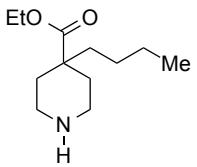


1-(*Tert*-butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate (S18) According to the general piperidine alkylation procedure 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate[7] (**S4**) (10.3 g, 33.2 mmol, 1.00 equiv) and 1-bromobutane (5.4 mL, 49.83 mmol, 1.5 equiv) were reacted. Crude material was purified by flash chromatography (SiO_2, eluting with 15% EtOAc/Hex) to afford 1-(*tert*-butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate (**S18**) (5.63 g, 18.0 mmol, 54% yield) as a colorless oil.

Data for **S18**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.17 (q, *J* = 7.1 Hz, 2H), 3.85 (br s, 2H), 2.87 (br s, 2H), 2.13 – 2.04 (m, 2H), 1.48 (dt, *J* = 12.0, 4.2 Hz, 2H), 1.46 (s, 9H), 1.38 – 1.28 (m, 2H), 1.29 – 1.22 (m, 5H), 1.22 – 1.11 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H)



Ethyl 4-butylpiperidine-4-carboxylate (9m) To round bottom flask was added 1-(*tert*-butyl) 4-ethyl 4-butylpiperidine-1,4-dicarboxylate (**S18**) (1.9 g, 6.06 mmol, 1.00 equiv) and 4 M HCl in dioxane (15 mL, 60.62 mmol, 10.00 equiv) and reaction solution was stirred at room temperature. TLC was used to monitor

reaction progress. Upon complete conversion of starting material reaction was concentrated via rotoevaporation. Residue was basified with 1 M NaOH (100 mL) and extracted with CH_2CL_2 (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated. Crude material was purified by flash chromatography (Brockmann grade III basic Al_2O_3, eluted with 10% MeOH/DCM) to afford ethyl 4-butylpiperidine-4-carboxylate (**9m**) as a colorless oil (1.16 g, 5.44 mmol, 90% yield).

Data for **9m**:

^{1}H NMR: (500 MHz, $CDCl_3$)

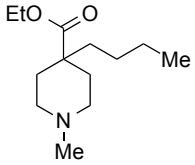
δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.92 (dt, *J* = 12.9, 3.8 Hz, 2H), 2.69-2.59 (m, 2H), 2.10 (d, *J* = 13.2 Hz, 2H), 1.64 (br s, 1H), 1.52-1.45 (m, 2H), 1.33 (ddd, *J* = 13.6, 11.5, 4.0 Hz, 2H), 1.29-1.21 (m, 5H), 1.21-1.12 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 176.39, 60.33, 45.87, 44.12, 40.87, 34.87, 26.05, 23.21, 14.51, 14.08

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{24}NO_2$ 214.1807; found 214.1806.



Ethyl 4-butyl-1-methylpiperidine-4-carboxylate (9f) Following general piperidine reductive amination procedure ethyl 4-butylpiperidine-4-carboxylate (**9m**) (456.8 mg, 2.14 mmol, 1.0 equiv) was reacted with formaldehyde (797 µL, 321.5 mg, 10.7 mmol, 5.0 eq, 37 wt% in water) and $NaBH(OAc)_3$ (680 mg, 3.21 mmol, 1.5 equiv) in acetic acid (0.43 mL) and 1,2-dichloroethane (42.4 mL). Purification by flash chromatography (20 mL Brockmann grade III basic Al_2O_3, eluting with 80% EtOAc/Hex) yielded ethyl 4-butyl-1-methylpiperidine-4-carboxylate (**9f**) as a colorless oil (452.3 mg, 1.99 mmol, 93% yield).

Data for **9f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

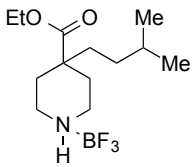
δ 4.15 (q, *J* = 7.1 Hz, 2H), 2.64 (d, *J* = 11.9 Hz, 2H), 2.22 (s, 3H), 2.14 (d, *J* = 13.2 Hz, 2H), 1.98 (t, *J* = 11.5 Hz, 2H), 1.51-1.42 (m, 4H), 1.30-1.10 (m, 7H), 0.86 (t, *J* = 7.2 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.22, 60.28, 53.48, 46.53, 44.84, 40.53, 33.87, 26.31, 23.21, 14.48, 14.08

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{26}NO_2$ 228.1964; found 228.1962



Trifluoro(ethyl 4-isopentylpiperidine-4-carboxylate-1-ium-yl)borate (9g) Following the general BF_3 protection procedure ethyl 4-isopentylpiperidine-4-carboxylate (**S6**) (974.9 mg, 4.29 mmol, 1.00 equiv) in CH_2Cl_2 (17 mL, 0.25 M) was cooled to 0 ºC and BF_3•OEt_2 (582 µL, 4.72 mmol, 1.10 equiv) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 20→40→60% EtOAc/Hex, 1 column volume of each) to afford trifluoro(ethyl 4-isopentylpiperidine-4-carboxylate-1-ium-yl)borate (**9g**) as a white crystalline solid (933.3 mg, 3.16 mmol, 74% yield).

Data for **9g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.55 (br s, 1H), 3.32 (ddd, *J* = 14.1, 4.3, 2.2 Hz, 2H), 2.77 (tdd, *J* = 14.1, 11.8, 2.6 Hz, 2H), 2.41 (d, *J* = 15.1 Hz, 2H), 1.55 – 1.48 (m, 2H), 1.50 – 1.35 (m, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.10 – 1.04 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.46, 61.21, 44.75, 43.65, 39.09, 32.65, 32.47, 28.29, 22.53, 14.41, 14.37

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.12 (q, *J* = 15.5 Hz)

^{11}B NMR: (128 MHz, $CDCl_3$)

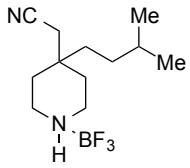
δ -0.36 (br q, *J* = 15.9 Hz)

IR: (ATR, neat, cm^{-1})

3244, 2959, 2933, 2871, 1726, 1473, 1457, 1404, 1368, 1348, 1320, 1301, 1290, 1248, 1204, 1158, 1122, 1096, 1063, 1031, 1006, 990, 979, 963, 946, 929, 874, 804, 777, 746

HRMS: (ESI-TOF MS ES+)

m/z: $[(M–H)+Na]^+$ Calcd for $C_{13}H_{25}BNO_2F_3Na$ 318.1828; found 318.1830



2-(4-Isopentylpiperidin-4-yl)acetonitrile-BF_3 (9h) Following the general BF_3 protection procedure 2-(4-isopentylpiperidin-4-yl)acetonitrile (**S12**) (310 mg, 1.60 mmol, 1.00 equiv) in CH_2Cl_2 (6.4 mL, 0.25 M) was cooled to 0 ºC and BF_3•OEt_2 (217 µL, 1.76 mmol, 1.10 equiv) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 50% EtOAc/Hex) to afford 2-(4-isopentylpiperidin-4-yl)acetonitrile-BF_3 (**9h**) as a white crystalline solid (289.5 mg, 1.10 mmol, 69% yield).

Data for **9h**: *Isolated an inseparable ~1:1 mixture of trans/cis isomers by ^{19}F NMR.*

^{1}H NMR: (500 MHz, CD_3CN)

δ 4.71 (s, 2H), 3.17 – 3.07 (m, 3H), 2.84 – 2.67 (m, 3H), 2.57 (s, 1H), 2.40 (s, 2H), 1.74 – 1.57 (m, 7H), 1.56 – 1.47 (m, 4H), 1.46 – 1.40 (m, 2H), 1.23 – 1.14 (m, 2H), 1.13 – 1.06 (m, 2H), 0.91 (dd, *J* = 6.7, 1.9 Hz, 10H)

^{13}C NMR: (126 MHz, CD_3CN)

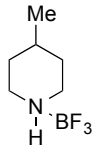
δ 118.87, 118.81, 41.71, 41.53, 39.90, 33.74, 33.70, 32.88, 32.60, 32.42, 32.11, 30.75, 29.33, 29.23, 29.19, 22.89, 22.77, 22.75

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.27 (q, *J* = 15.5 Hz), -157.66 (q, *J* = 15.8 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{12}H_{21}N_2F_3B$ 261.1750, found 261.1755



Trifluoro(4-methylpiperidine-1-ium-yl)borate (9j) Following the general BF_3 protection procedure 4-methylpiperidine (1.2 mL, 10.00 mmol, 1.00 equiv) was reacted with BF_3•OEt_2 (1.4 mL, 11.00 mmol, 1.10 equiv) in CH_2Cl_2 (40 mL, 0.25 M). Crude material was purified by flash chromatography (25:1 SiO_2/theoretical yield, gradient elution 10→20% EtOAc/Hex) to afford trifluoro(4-methylpiperidine-1-ium-yl)borate (**9j**) a white solid (1.40 g, 8.38 mmol, 84% yield).

Data for **9j**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.44 (br s, 1H), 3.40 (ddd, *J* = 13.9, 4.4, 2.1 Hz, 2H), 2.73 (tdd, *J* = 13.7, 11.6, 2.8 Hz, 2H), 1.95 – 1.83 (m, 2H), 1.62 (dddd, *J* = 15.4, 12.4, 7.0, 3.6 Hz, 1H), 1.29 – 1.17 (m, 2H), 0.99 (d, *J* = 6.5 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

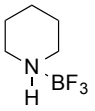
δ 45.90, 32.75, 29.69, 21.72

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.99 (q, *J* = 16.6 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_6H_{12}BNF_3$ 166.1015, found 166.1014



Trifluoro(piperidine-ium-yl)borate (9k) Following the general BF_3 protection procedure piperidine (494 µL, 425.8 mg, 5.00 mmol, 1.0 equiv) was reacted with BF_3•OEt_2 (678 µL, 5.50 mmol, 1.1 equiv). Purification by flash chromatography (25:1 SiO_2/theoretical yield, eluting with 40% EtOAc/Hex) yielded trifluoro(piperidine-ium-yl)borate (**9k**) as a white solid (592.1 mg, 3.87 mmol, 77% yield).

Data for **9k**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 3.82 (br s, 1H), 3.34 (d, *J* = 12.9 Hz, 2H), 2.68 (q, *J* = 11.4 Hz, 2H), 1.85 (t, *J* = 16.6 Hz, 3H), 1.67-1.52 (m, 2H), 1.42 (qt, *J* = 12.8, 3.5 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

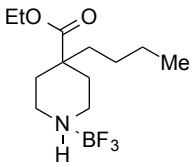
δ 46.13, 24.51, 22.77

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.22 (app t, *J* = 15.4)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_5H_{10}NF_3B$ 152.0858; found 152.0856



Trifluoro(ethyl 4-butylpiperidine-4-carboxylate-ium-yl)borate (9l) Following the general BF_3 protection procedure piperidine (**9m**) (426.6 mg, 2.00 mmol, 1.0 equiv) was reacted with BF_3•OEt_2 (272 µL, 2.20 mmol, 1.1 equiv). Purification by flash chromatography (20 mL SiO_2, eluting with 40% EtOAc/Hex) yielded trifluoro(ethyl 4-butylpiperidine-4-carboxylate-ium-yl)borate (**9l**) as a white solid (328.6 mg, 1.17 mmol, 58% yield).

Data for **9l**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.21 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 1H), 3.30 (d, *J* = 15.5 Hz, 2H), 2.80 – 2.68 (m, 2H), 2.40 (d, *J* = 15.3 Hz, 2H), 1.55 – 1.47 (m, 2H), 1.42 (td, *J* = 14.2, 4.2 Hz, 2H), 1.34 – 1.22 (m, 6H), 1.17 (ddd, *J* = 13.4, 6.9, 3.5 Hz, 2H), 0.87 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

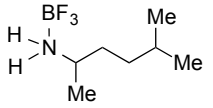
δ 174.45, 61.29, 44.82, 43.65, 41.03, 32.54, 25.95, 22.99, 14.40, 14.00

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.83 (q, *J* = 16.0 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{12}H_{22}NO_2F_3B$ 280.1696; found 280.1698



Trifluoro(1,4-dimethylpentylamino)borate (9n) Following the general BF_3 protection procedure 2-amino-5-methylhexane (2.5 g, 3.3 mL, 21.70 mmol, 1.00 equiv) in CH_2Cl_2 (25 mL, 0.9 M) was cooled to 0 ºC and BF_3•OEt_2 (2.3 mL, 23.87 mmol, 1.10 equiv) was added. The solution was stirred at 0 ºC for 30 minutes followed by 1 hour room temperature. Solvent was removed via rotoevaporation. The crude material was purified by flash chromatography (150 mL SiO_2, gradient elution 25→50 % EtOAc/Hex, 2 column volumes of each) to afford trifluoro(1,4-dimethylpentylamino)borate (**9n**) as a white solid (2.52 g, 13.77 mmol, 63% yield).

Data for **9n**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 3.98 (br s, 1H), 3.87 (br s, 1H), 3.25 (dq, *J* = 12.4, 6.4 Hz, 1H), 1.72-1.62 (m, 1H), 1.61-1.52 (m, 1H), 1.48 (ddd, *J* = 16.1, 13.0, 6.7 Hz, 1H), 1.29 (d, *J* = 6.5 Hz, 3H), 1.21 (ddd, *J* = 10.0, 7.9, 6.4 Hz, 2H), 0.90 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 49.68, 34.34, 34.23, 27.94, 22.62, 22.37, 19.30

^{19}F NMR: (470 MHz, $CDCl_3$)

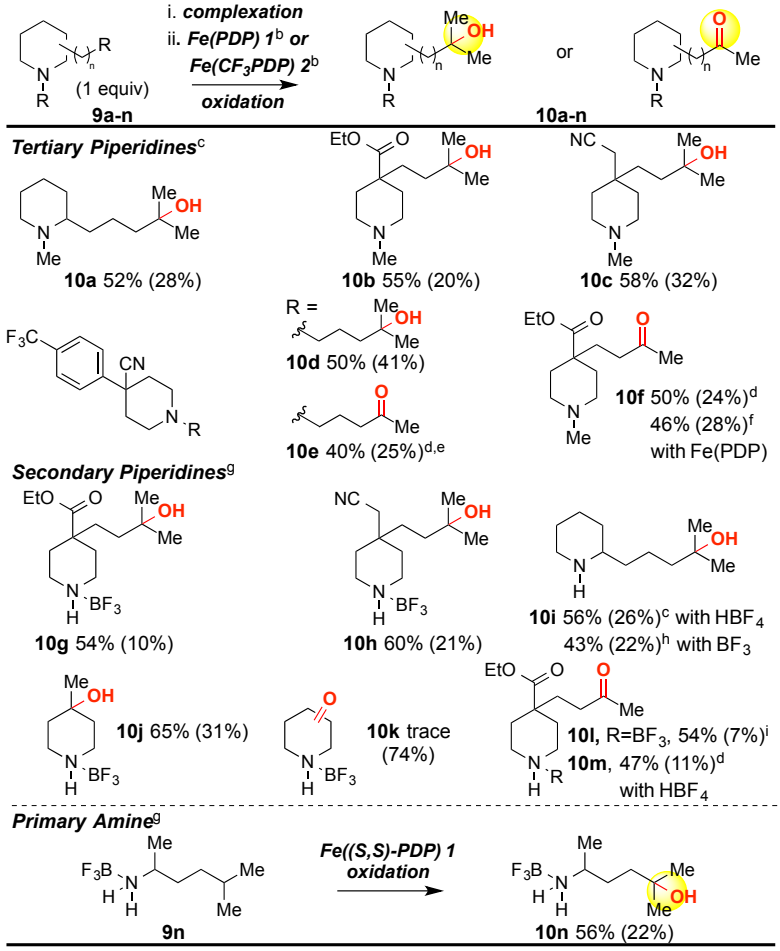
δ -147.66 (q, *J* = 16.7 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_7H_{16}BNF_3$ 182.1328; found 182.1328

VI. Experimental Procedures and Compound Characterization for Table S2

Table S2. Basic Amines[a]



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B. [e]Starting material recycled 1x. [f]Method B with **1**. [g]Method A with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. Isolated as BF_3-complex, no NaOH workup. [h]Method A with BF_3•Et_2O (1.1 equiv). [i]Method B with BF_3•Et_2O (1.1 equiv) concd and purified prior to use. Isolated as BF_3-complex, no NaOH workup.

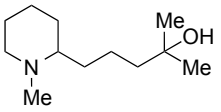
General Procedure for Amines (1º, 2º, 3º) and Pyridines (Table S2 and Table S3): To a flame-dried 40 mL vial equipped with a stir bar was added amine or pyridine (0.50 mmol, 1.0 equiv) and CH_2Cl_2 (2.0 mL, 0.25 M) the vial was flushed with a N_2 stream and then cooled to 0 ºC. HBF_4•OEt_2 (75.8 µL, 0.55 mmol, 1.1 equiv) was added dropwise via syringe. The reaction solution was stirred at 0 ºC for 30 minutes followed by warming to room temperature and stirring for 1 hour. The reaction solution was concentrated in vacuo and left on high vacuum overnight (12–24 hours). The resultant amine- or pyridine-HBF_4 salts were then oxidized following an iterative or slow addition protocol.

Iterative Addition Protocol: The amine- or pyridine-HBF_4 salt (0.50 mmol, 1.0 equiv) was dissolved in MeCN (746 µL, 0.67 M to substrate). A solution of Fe(PDP) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 µL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 µL, 0.05 M to Fe(PDP)) was added. A solution of H_2O_2 (34.1 µL, 0.6 mmol, 1.2 equiv, 50

wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. ***Significant decreases in yield were noted when the peroxide solution was added rapidly.*** After 10 min, a second portion of Fe(PDP) and AcOH dissolved in MeCN was added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes.

Slow Addition Protocol: The amine- or pyridine-HBF_4 salt (0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.75 mL, 0.67 M). A 1 mL syringe was charged with a solution of Fe(CF_3PDP) (0.125 mmol, 0.25 equiv), MeCN (0.55 mL, 0.23 M to Fe catalyst) and AcOH (143 μL, 2.50 mmol, 5.0 equiv). A 10 mL syringe was charged with a solution of H_2O_2 (256 μL, 4.50 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (6.0 mL, 0.75 M). Both syringes were fitted with 25G needles and solutions were added simultaneously into the stirring reaction mixture via a syringe pump at 6 mL/h.

Reaction Workup: MeCN volume was reduced to approximately 1–2 mL via rotary evaporation and diluted with CH_2Cl_2 (10 mL). Aqueous 1 M NaOH solution (10 mL) was added to basify and stirred vigorously for 10 minutes. The hydrolysis was poured into aqueous 1 M NaOH (30 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layer was washed with brine (1 x 60 mL), dried over anhydrous Na_2SO_4, filtered and concentrated via rotary evaporation. The crude material was purified by flash chromatography to affords the oxidation product.



2-Methyl-5-(1-methylpiperidin-2-yl)pentan-2-ol (10a) According to the general procedure, 1-methyl-2-(4-methylpentyl)piperidine **(9a)** (91.7 mg, 0.500 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (15 mL basic Al_2O_3 Brockmann grade III, gradient elution 10→20→40→80→100% EtOAc/Hex, 1 column volume each) afforded 2-methyl-5-(1-methylpiperidin-2-yl)pentan-2-ol (**10a**) as a colorless oil.

Run 1 (49.5 mg, 0.248 mmol, 50% yield; 24.1 mg, 0.131 mmol, 26% rsm)

Run 2 (52.7 mg, 0.264 mmol, 53% yield; 27.7 mg, 0.151 mmol, 30% rsm)

Average yield: 52% (28% rsm)

Data for **10a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

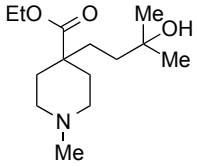
δ 2.84 (dtd, *J* = 11.8, 3.7, 1.5 Hz, 1H), 2.24 (s, 3H), 2.10 – 2.02 (m, 1H), 1.89 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.68 – 1.62 (m, 1H), 1.56 (ddt, *J* = 11.0, 8.0, 4.1 Hz, 3H), 1.49 – 1.35 (m, 4H), 1.34 – 1.22 (m, 4H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.08, 63.95, 57.43, 44.52, 43.05, 33.61, 30.86, 29.41, 25.93, 24.59, 20.02

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{26}NO$ 200.2014, found 200.2009



Ethyl 4-(3-hydroxy-3-methylbutyl)-1-methylpiperidine-4-carboxylate (10b) According to the general procedure, ethyl 4-isopentyl-1-methylpiperidine-4-carboxylate **(9b)** (120.7 mg, 0.500 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL basic Al_2O_3 Brockmann grade III, gradient elution 40→80% EtOAc/Hex→100% EtOAc→1% MeOH/EtOAc→10% MeOH/EtOAc, 1 column volume each) afforded ethyl 4-(3-hydroxy-3-methylbutyl)-1-methylpiperidine-4-carboxylate (**10b**) as a colorless oil.

Run 1 (70.4 mg, 0.274 mmol, 55% yield; 25.2 mg, 0.104 mmol, 21% rsm)

Run 2 (70.9 mg, 0.275 mmol, 55% yield; 22.7 mg, 0.094 mmol, 19% rsm)

Average yield: 55% (20% rsm)

Data for **10b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

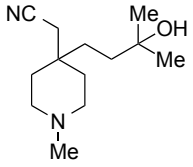
δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.65 (d, *J* = 11.6 Hz, 2H), 2.23 (s, 3H), 2.14 (d, *J* = 13.3 Hz, 2H), 2.02 (t, *J* = 10.3 Hz, 2H), 1.82 (br s, 1H), 1.62 – 1.54 (m, 2H), 1.49 (ddd, *J* = 13.6, 11.5, 3.9 Hz, 2H), 1.39 – 1.32 (m, 2H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.18 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.99, 70.68, 60.44, 53.33, 46.47, 44.48, 37.85, 35.24, 33.78, 29.32, 14.53

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{28}NO_3$ 258.2069, found 258.2017



2-(4-Isopentyl-1-methylpiperidin-4-yl)acetonitrile (10c) According to the general procedure, 2-(4-isopentyl-1-methylpiperidin-4-yl)acetonitrile (**9c**) (62.5 mg, 0.300 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.6 μL, 0.150 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.360 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (10 mL basic Al_2O_3 Brockmann grade III, gradient elution 20→40→80% EtOAc/Hex→100% EtOAc→1% MeOH/EtOAc, 2 column volumes of each) afforded 2-(4-isopentyl-1-methylpiperidin-4-yl)acetonitrile (**10c**) as a colorless oil.

Run 1 (40.4 mg, 0.180 mmol, 60% yield; 20.8 mg, 0.100 mmol, 33% rsm)

Run 2 (36.8 mg, 0.164 mmol, 55% yield; 18.6 mg, 0.089 mmol, 30% rsm)

Average yield: 58% (32% rsm)

Data for **10c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

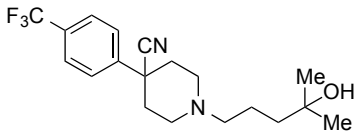
δ 2.51 – 2.42 (m, 2H), 2.33 (s, 2H), 2.29 (s, 3H), 2.27 (br m, 2H) 1.67 – 1.53 (m, 6H), 1.44 – 1.38 (m, 2H), 1.24 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 117.92, 70.76, 51.24, 46.31, 36.69, 34.77, 33.06, 29.44

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{25}N_2O$ 225.1967, found 225.1973



1-(4-Methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (10d)

According to the general procedure, 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**9d**) (101.5 mg, 0.3 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.6 μL, 0.150 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.360 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL SiO_2, eluting with 2→5→10% MeOH/CH_2Cl_2) afforded as a 1-(4-methylpentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**10d**) light yellow oil.

Run 1 (55.7 mg, 0.16 mmol, 52% yield; 39.8 mg, 0.12 mmol, 39% rsm)

Run 2 (50.3 mg, 0.14 mmol, 47% yield; 42.9 mg, 0.13 mmol, 42% rsm)

Average overall yield: 50% (41% rsm)

Data for **10d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.65 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.7 Hz, 2H), 3.13 (d, *J* = 12.4 Hz, 2H), 2.59-2.46 (m, 4H), 2.12 (dd, *J* = 7.3, 3.0 Hz, 4H), 1.72-1.60 (m, 4H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

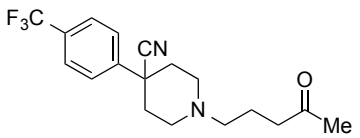
δ 143.65, 130.71 (q, *J* = 32.9 Hz), 126.38, 126.13 (q, *J* = 3.8 Hz), 123.86 (q, *J* = 272.3 Hz), 121.27, 69.08, 59.21, 50.64, 43.25, 42.97, 36.21, 29.84, 21.68

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.24 (s, 3F)

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{19}H_{26}N_2OF_3$ 355.1997, found 355.1990



1-(4-Oxopentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (10e)

According to the general procedure, 1-pentyl-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**9e**) (97.3 mg, 0.3 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Following the slow addition protocol, oxidation was carried out with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (101.7 mg, 0.075 mmol, 0.25 equiv) and AcOH (85.9 μL, 1.50 mmol, 5.0 equiv) dissolved in MeCN (336 μL, 0.23 M to Fe(PDP)). H_2O_2 (153.4 μL, 2.70 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL SiO_2, eluting with 2% MeOH/CH_2Cl_2) to afford 1-(4-oxopentyl)-4-(4-(trifluoromethyl)phenyl)piperidine-4-carbonitrile (**10e**) as a colorless oil.

Run 1 (*cycle 1*: 24% yield, 24.3 mg, 0.072 mmol; 56% rsm, 54.6 mg, 0.17 mmol; *cycle 2*: 28% yield, 16.0 mg, 0.047 mmol; 45% rsm, 24.3 mg, 0.075 mmol; ***overall**:* 40% yield, 40.3 mg, 0.12 mmol; 25% rsm, 24.3 mg, 0.075 mmol)

Run 2 (*cycle 1*: 26% yield, 26.7 mg, 0.079 mmol; 57% rsm, 55.7 mg, 0.17 mmol; *cycle 2*: 25% yield, 14.7 mg, 0.043 mmol; 45% rsm, 25.3 mg, 0.078 mmol; ***overall***: 41% yield, 41.4 mg, 0.12 mmol; 26% rsm, 25.3 mg, 0.078 mmol)

Average overall yield: 40% (25% rsm).

Data for **10e**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.66 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 3.01 (d, *J* = 12.5 Hz, 2H), 2.55-2.37 (m, 6H), 2.16 (s, 3H), 2.14-2.00 (m, 4H), 1.80 (p, *J* = 7.1 Hz, 2H)

^{13}C NMR: (126 MHz, $CDCl_3$)

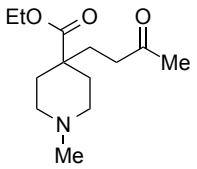
δ 208.52, 144.14, 130.59 (q, *J* = 32.9 Hz), 126.31, 126.16 (q, *J* = 3.6 Hz), 123.89 (q, *J* = 272.3 Hz), 121.42, 57.58, 50.63, 43.03, 41.40, 36.51, 30.31, 21.15

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.21

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{18}H_{22}N_2OF_3$ 339.1684, found 339.1684



Ethyl 1-methyl-4-(3-oxobutyl)piperidine-4-carboxylate (10f) According to the general procedure, ethyl 4-butyl-1-methylpiperidine-4-carboxylate (**9f**) (0.3 mmol, 68.2 mg) treated with HBF_4•OEt_2 (45.5 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (1.2 mL, 0.25 M). MeCN (447 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Following the addition protocol, oxidation was carried out with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (101.7 mg, 0.075 mmol, 0.25 equiv) and AcOH (85.9 μL, 1.50 mmol, 5.0 equiv) dissolved in MeCN (336 μL, 0.23 M to Fe(PDP)). H_2O_2 (153.4 μL, 2.70 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2). Following work up crude material was purified by flash chromatography (20 mL basic Al_2O_3 Brockmann III, eluting with 40%→80% EtOAc/Hex→100% EtOAc→10% MeOH/EtOAc) to afford ethyl 1-methyl-4-(3-oxobutyl)piperidine-4-carboxylate (**10f**) as a colorless oil.

Run 1 (50% yield, 35.9 mg, 0.15 mmol; 25% rsm, 17.0 mg, 0.075 mmol)

Run 2 (49% yield, 35.7 mg, 0.15 mmol; 23% rsm, 15.7 mg, 0.069 mmol)

Average overall yield: 50% (24% rsm)

*Oxidation with [Fe((R,R)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) same procedure as above:* (46% yield, 33.3 mg, 0.14 mmol; 28% rsm, 19.4 mg, 0.085 mmol)

Data for **10f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

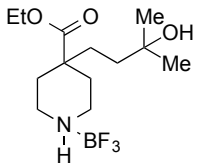
δ 4.12 (q, *J* = 7.1, 2H), 2.63 (d, *J* = 11.9 Hz, 2H), 2.38-2.32 (m, 2H), 2.20 (s, 3H), 2.15-2.07 (m, 5H), 1.96 (t, *J* = 11.4 Hz, 2H), 1.79-1.73 (m, 2H), 1.48-1.40 (m, 2H), 1.23 (t, *J* = 7.1 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 207.97, 175.54, 60.61, 53.20, 46.39, 44.01, 38.36, 33.57, 30.12, 14.40, 14.38

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{24}NO_3$ 242.1756, found 242.1753



Alcohol (10g) According to the iterative oxidation protocol, trifluoro(ethyl 4-isopentylpiperidine-4-carboxylate-1-ium-yl)borate **(9g)** (147.6 mg, 0.500 mmol, 1.0 equiv) was oxidized with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (50 mL SiO_2, gradient elution 30→40→50→60% EtOAc/Hex) to afford alcohol (**10g**) as a white solid.

Run 1 (81.5 mg, 0.262 mmol, 52% yield; 17.6 mg, 0.060 mmol, 12% rsm)

Run 2 on 0.3 mmol scale (52.3 mg, 0.168 mmol, 56% yield; 6.6 mg, 0.224 mmol, 7% rsm)

Average overall yield: 54% (10% rsm)

Data for **10g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.22 (q, *J* = 7.1 Hz, 2H), 3.50 (br s, 1H), 3.34 (ddd, *J* = 14.2, 4.4, 2.3 Hz, 2H), 2.79 (tdd, *J* = 14.0, 11.7, 2.6 Hz, 2H), 2.43 (d, *J* = 14.0 Hz, 2H), 1.66 – 1.61 (m, 2H), 1.59 (br s, 1H), 1.43 (td, *J* = 14.2, 4.2 Hz, 2H), 1.39 – 1.34 (m, 2H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

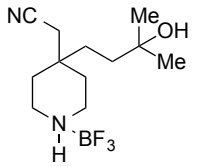
δ 174.13, 70.52, 61.45, 44.46, 43.63, 37.27, 35.67, 32.66, 29.42, 14.45.

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -158.16 (q, *J* = 15.1 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M-H]^-$ Calcd for $C_{13}H_{24}BNO_3F_3$ 310.1801, found 310.1800



Alcohol (10h) According to the iterative oxidation protocol, 2-(4-isopentylpiperidin-4-yl)acetonitrile•BF_3 (**9h**) (122.4 mg, 0.467 mmol, 1.0 equiv) in (700 μL MeCN, 0.67 M to substrate) was oxidized with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (21.4 mg, 0.023 mmol, 0.05 equiv) and AcOH (31.4 μL, 0.234 mmol, 0.5 equiv) dissolved in MeCN (460 μL, 0.05 M to Fe(PDP)). H_2O_2 (31.8 μL, 0.560 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.3 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (50 mL SiO_2, gradient elution 30→40→50→60→70→80→90→100% EtOAc/Hex) to afford alcohol (**10h**) as a white solid.

Run 1 (75.9 mg, 0.273 mmol, 58% yield; 27.5 mg, 0.104 mmol, 22% rsm)

Run 2 (79.5 mg, 0.286 mmol, 61% yield; 22.8 mg, 0.087 mmol, 19% rsm)

Average overall yield: 60% (21% rsm)

Data for **10h**: *Isolated as an inseparable ~1:1 mixture of trans/cis isomers.*

^{1}H NMR: (500 MHz, CD_3CN)

δ 4.74 (s, 2H), 3.19 – 3.03 (m, 3H), 2.85 – 2.68 (m, 3H), 2.57 (s, 1H), 2.49 (d, *J* = 10.6 Hz, 2H), 2.39 (s, 3H), 2.24 (s, 3H), 1.76 – 1.56 (m, 9H), 1.53 – 1.48 (m, 1H), 1.43 – 1.38 (m, 1H), 1.34 – 1.28 (m, 2H), 1.15 (s, 9H)

^{13}C NMR: (126 MHz, CD_3CN)

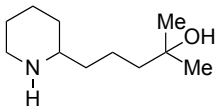
δ 118.81, 118.73, 70.32, 70.30, 41.70, 41.49, 37.07, 36.83, 36.36, 33.57, 33.51, 32.82, 32.58, 29.42, 29.25, 27.22, 22.97

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -157.26 (q, *J* = 16.2 Hz), -157.64 (q, *J* = 15.6 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{12}H_{21}BN_2OF_3$ 277.1699, found 277.1704



2-methyl-5-(piperidin-2-yl)pentan-2-ol (10i) According to the iterative oxidation protocol, 2-(4-methylpentyl)piperidine (**9i**) (84.7 mg, 0.500 mmol, 1.0 equiv) treated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out in iterative fashion with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Following work up crude material was purified by flash chromatography (25 mL basic Al_2O_3 Brockmann grade III, gradient elution 100% CH_2Cl_2→2→5→10% MeOH/CH_2Cl_2, 2 column volume each) afforded 2-methyl-5-(piperidin-2-yl)pentan-2-ol (**10i**) as a colorless oil.

Run 1 (54.1 mg, 0.292 mmol, 58% yield; 22.9 mg, 0.135 mmol, 27% rsm)

Run 2 (49.9 mg, 0.269 mmol, 54% yield, 21.8 mg, 0.129 mmol, 26% rsm)

Average yield: 56% (26% rsm)

Same procedure as above used BF_3•OEt_2 (67.9 mL, 0.550 mmol, 1.1 equiv) for complexation.

Run 1 (39.2 mg, 0.212 mmol, 42% yield; 16.1 mg, 0.095 mmol, 19% rsm)

Run 2 (40.8 mg, 0.220 mmol, 44% yield, 21.5 mg, 0.127 mmol, 25% rsm)

Average yield: 43% (22% rsm)

Data for **10i**:

^{1}H NMR: (500 MHz, $CDCl_3$)

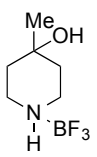
δ 3.03 (ddt, *J* = 12.2, 4.1, 2.1 Hz, 1H), 2.59 (td, *J* = 11.8, 2.9 Hz, 1H), 2.43 (dtd, *J* = 12.9, 6.2, 2.6 Hz, 1H), 1.86 – 1.65 (m, 2H), 1.67 – 1.58 (m, 1H), 1.60 – 1.51 (m, 1H), 1.50 – 1.24 (m, 9H), 1.18 (s, 6H), 1.04 (tdd, *J* = 12.5, 10.7, 3.8 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 70.88, 56.87, 47.27, 44.08, 38.02, 33.15, 29.49, 29.32, 26.77, 24.98, 20.69

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{11}H_{24}NO$ 186.1858, found 186.1857



Trifluoro(4-methylpiperidin-4-ol-1-ium-yl)borate (10j) According to the iterative oxidation protocol, trifluoro(4-methylpiperidine-1-ium-yl)borate (**9j**) (100.2 mg, 0.500 mmol, 1.0 equiv) was oxidized with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (15 mL SiO_2, gradient elution 25→50→75% EtOAc/Hex, 2 column volumes each) to afford alcohol (**10j**) as a white solid.

Run 1 (55.5 mg, 0.303 mmol, 61% yield; 31.0 mg, 0.186 mmol, 37% rsm)

Run 2 (62.2 mg, 0.340 mmol, 68% yield; 20.9 mg, 0.125 mmol, 25% rsm)

Average overall yield: 65% (31% rsm)

Data for **10j**:

^{1}H NMR: (500 MHz, CD_3CN)

δ 4.52 (br s, 1H), 3.05 (d, *J* = 12.8 Hz, 2H), 2.94 (qd, *J* = 12.4, 11.7, 6.5 Hz, 2H), 2.67 (br s, 1H), 1.64 (dd, *J* = 9.7, 4.1 Hz, 4H), 1.22 (s, 3H)

^{13}C NMR: (126 MHz, CD_3CN)

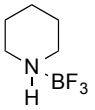
δ 66.02, 41.87, 36.71, 30.63.

^{19}F NMR: (470 MHz, CD_3CN)

δ -158.74 (q, *J* = 16.5 Hz).

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_6H_{12}BNOF_3$ 182.0964, found 182.0969



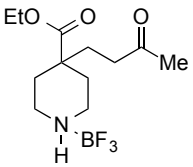
Trifluoro(piperidine-ium-yl)borate (9k) According to the iterative oxidation protocol, trifluoro(piperidine-ium-yl)borate (**9k**) (76.5 mg, 0.500 mmol, 1.0 equiv) was oxidized with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and the crude material was purified by flash chromatography (20 mL SiO_2, gradient elution 30→40→50→60→80% EtOAc/Hex) to afford recovered trifluoro(piperidine-ium-yl)borate (**9k**).

Trace ketones were observed as an intractable mixture.

Run 1 (57.1 mg, 0.373 mmol, 75% rsm)

Run 2 (56.5 mg, 0.369 mmol, 74% rsm)

Average overall rsm: 74%



Ketone (10l) Following the slow addition protocol, oxidation of trifluoro(ethyl 4-butylpiperidine-4-carboxylate-ium-yl)borate (**9l**) (89.2 mg, 0.300 mmol, 1.0 equiv) was dissolved in MeCN (447 μL, 0.67 M to substrate). Oxidation was carried out with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (107.5 mg, 0.079 mmol, 0.25 equiv) and AcOH (90.7 μL, 1.56 mmol, 5.0 equiv) dissolved in MeCN (345 μL, 0.23 M to Fe(CF_3PDP)). H_2O_2 (162.1 μL, 2.85 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.8 mL, 0.75 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (25 mL SiO_2, eluting with 20→40→50→60→70→80→90→100% EtOAc/Hex) to afford ketone (**10l**) as a white solid.

Run 1 (45.8 mg, 0.155 mmol, 52% yield; 7.4 mg, 0.026 mmol, 9% rsm)

Run 2 (48.5 mg, 0.164 mmol, 55% yield; 3.7 mg, 0.013 mmol, 4% rsm)

Average overall yield: 54% (7% rsm)

Data for **10l**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.19 (q, *J* = 7.1 Hz, 2H), 4.07 (br s, 1H), 3.33 – 3.25 (m, 2H), 2.75 – 2.64 (m, 2H), 2.44 – 2.28 (m, 4H), 2.13 (s, 3H), 1.81 (t, *J* = 7.8 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

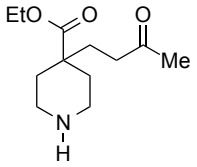
δ 207.85, 173.95, 61.63, 44.03, 43.40, 37.76, 33.91, 32.10, 30.20, 14.31.

^{19}F NMR (470 MHz, $CDCl_3$)

δ -157.83 (q, J = 15.8 Hz)

HRMS: (ESI-TOF MS ES–)

m/z: $[M–H]^-$ Calcd for $C_{12}H_{20}NO_3F_3B$ 294.1488, found 294.1493



Ethyl 4-(3-oxobutyl)piperidine-4-carboxylate (10m) According to the general procedure, ethyl 4-butylpiperidine-4-carboxylate (**9m**) (64.0 mg, 0.300 mmol, 1.0 equiv) was treated with HBF_4•OEt_2 (44.9 μL, 0.330 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2 mL, 0.25 M). MeCN (447 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Oxidation was carried out according to the slow addition protocol with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (101.7 mg, 0.075 mmol, 0.25 equiv) and AcOH (86 μL, 1.5 mmol, 5.0 equiv) dissolved in MeCN (345 μL, 0.22 M to Fe(CF_3PDP)). H_2O_2 (153 μL, 2.70 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (3.8 mL, 0.71 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (20 mL basic Al_2O_3 Brockmann grade III, eluting with 2→5→10% MeOH/CH_2Cl_2) to afford ketone (**10m**) as an inseperable mixture with the starting material as a colorless oil.

Run 1 (33.6 mg, 0.148 mmol, 49% yield; 6.9 mg, 0.032 mmol, 11% rsm)

Run 2 (30.3 mg, 0.133 mmol, 44% yield; 7.7 mg, 0.036 mmol, 12% rsm)

Average overall yield: 47% (11% rsm)

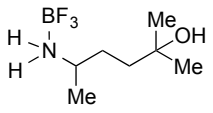
Data for **10m**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 4.16 (q, J = 7.1 Hz, 2H), 2.94 (dt, J = 12.6, 4.1 Hz, 2H), 2.63 (td, J = 12.5, 2.5 Hz, 2H), 2.38 (app t, J = 8.0 Hz, 2H), 2.13 (s, 3H), 2.10 (app d, J = 15.6 Hz, 2H), 1.80 (app t, J = 8.0 Hz, 2H), 1.38 – 1.29 (m, 2H), 1.27 (app t, J = 7.1 Hz, 4H)

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{22}NO_3$ 228.1600, found 228.1598



Alcohol (10n) According to the iterative oxidation protocol, trifluoro(1,4-dimethylpentylamino)borate **(9n)** (91.5 mg, 0.5 mmol) was oxidized with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2). Reaction was concentrated and purified by flash chromatography (20 mL SiO_2 eluting with 20→40→60→80% EtOAc/Hex) to afford alcohol (**10n**) as a white solid.

Run 1 (57.6 mg, 0.29 mmol, 58% yield; 19.7 mg, 0.11 mmol, 22% rsm)

Run 2 (54.2 mg, 0.27 mmol, 54% yield; 19.6 mg, 0.11 mmol, 21% rsm)

Average overall yield: 56% (22% rsm)

Data for **10n**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.47 (br s, 1H), 3.92 (br s, 1H), 3.24 (br s, 1H), 2.35 (br s, 1H), 1.76-1.67 (m, 2H), 1.67-1.50 (m, 2H), 1.30 (d, J = 6.6 Hz, 3H), 1.26 (s, 3H), 1.24 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 71.14, 49.51, 38.76, 30.84, 30.03, 29.08, 19.80

^{19}F NMR: (470 MHz, $CDCl_3$)

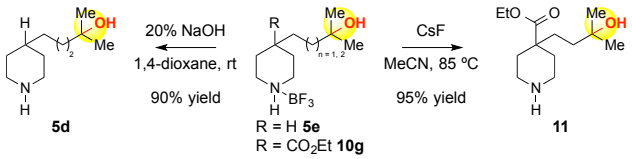
δ -147.71 (q, J = 16.5 Hz)

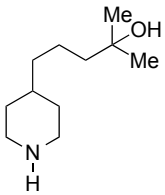
HRMS: (ESI-TOF MS ES–)

m/z: $[M-H]^-$ Calcd for $C_7H_{16}BNOF_3$ 198.1277, found 198.1278

VII. Experimental Procedures and Compound Characterization for Scheme S9

Scheme S9. Amine Deprotection Strategies





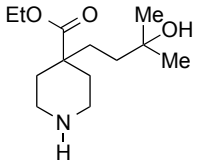
2-methyl-5-(piperidin-4-yl)pentan-2-ol (5d) To a 2 dram vial equipped with a magnetic stir bar was added alcohol **5e** (50.9 mg, 0.201 mmol, 1.00 equiv) and 1,4-dioxane (1 mL). 20% NaOH (2 mL) was added and the reaction soution was stirred vigorously at room temperature. TLC was used to monitor reaction progess. Reaction was diluted with 1 M NaOH (20 mL and extracted with CH_2Cl_2 (3 x 10 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford 2-methyl-5-(piperidin-4-yl)pentan-2-ol (**5d**). No futher purification required. Spectra matched that reported *vide supra*.

Run 1 – 0.3 mmol scale (45.2 mg, 0.244 mmol, 81% yield); *Note: with Et_2O instead of 1,4-dioxane and CH_2Cl_2*

Run 2 (36.9 mg, 0.199 mmol, 99% yield)

Average overall yield: 90%

See Table S1 for characterization of ***5d.***



Ethyl 4-(3-hydroxy-3-methylbutyl)piperidine-4-carboxylate (11) Following the procedure of Dieter and Watson.[12] To a 2 dram vial equipped with a magnetic stir bar was added alcohol **10g** (93.3 mg, 0.300 mmol, 1.0 equiv), cesium fluoride (227.9 mg, 1.500 mmol, 5.0 equiv) and MeCN (1.5 mL, 0.25 M). Vial was sealed and heated to 85 ºC. Reaction was monitored by TLC. All starting material was consumed after 12 hours. Reaction was basified with 1 M NaOH (20 mL) an extracted with CH_2Cl_2 (3 x 10 mL). Combined org. layer was dried over anhydrous Na_2SO_4, filtered and concentrated to afford ethyl 4-(3-hydroxy-3-methylbutyl)piperidine-4-carboxylate (**11**). No further purification required.

Run 1 (69.6 mg, 0.286 mmol, 95% yield)

Run 2 (68.4 mg, 0.281 mmol, 94% yield)

Average overall yield: 95%

Data for **11**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 4.16 (q, *J* = 7.1 Hz, 2H), 2.93 (dt, *J* = 12.8, 4.0 Hz, 2H), 2.65 (ddd, *J* = 13.1, 11.2, 2.7 Hz, 2H), 2.10 (dq, *J* = 11.4, 2.3 Hz, 2H), 1.76 (br s, 1H), 1.61 – 1.54 (m, 2H), 1.35 (qd, *J* = 7.5, 4.2 Hz, 4H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.17 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 176.12, 70.59, 60.45, 45.48, 43.96, 37.59, 35.29, 34.78, 29.31, 14.52.

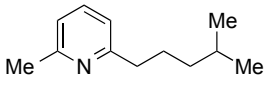
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{13}H_{26}NO_3$ 244.1913, found 244.1921

VIII. Synthesis of Substrates and Compound Characterization for Table S3

Pyridine Alkylation Procedure (**Method A)**: A flame-dried 100 mL round bottom flask was charged with methylpyridine (13.75 mmol, 1.0 equiv), tetrahydrofuran (THF) (6.3 mL) and a magnetic stir bar. The mixture was stirred and cooled down to -78 °C, and *n*-butyllithium (1.6 M, 9.9 mL, 15.81 mmol, 1.15 equiv) was added dropwise via syringe. Upon completion of addition the flask was allowed to warm to ambient temperature and placed in 45 °C oil bath and stirred for 2 h. Another portion of THF (6.3 mL) was then added to fully dissolve the orange organolithium salt formed. The solution was then placed in an ice bath. In a separate flame-dried 200 mL round bottom flask was charged alkyl bromide (15.13 mmol, 1.10 equiv), THF (2.5 mL) and a magnetic stir bar. The mixture was stirred and cooled down to -78 °C, and the organolithium solution was transferred via cannula into the reaction mixture containing the alkyl bromide. The reaction mixture was then allowed to warm to ambient temperature and stirred overnight. Water (0.5 mL) was added to quench the reaction, and the mixture was passed through a silica plug (50 mL), and flushed with EtOAc (300 mL). The filtrate was concentrated in vacuo. Purification by flash chromatography provided the pure product.

Negishi Cross-Coupling for Alkyl Pyridine Preparation (Method B): A flame-dried 50 mL flask was charged with zinc powder (1.51 g, 23.09 mmol, 1.5 equiv) and a magnetic stir bar. The flask was stirred and heated to 70 °C in oil bath in vacuo for 0.5 h. The mixture was then taken out of oil bath, and dimethylacetamide (DMA) (15 mL, freshly distilled over CaH_2) and iodine (97.7 mg, 0.38 mmol, 0.025 equiv) were added. The mixture was stirred until the brown color disappeared. Alkyl bromide (15.39 mmol, 1.0 equiv) was then added via syringe, and the flask was placed back in the 70 °C oil bath and stirred overnight. The mixture was filtered through a Schlenk filter into a flame-dried 50 mL three neck flask, and the zinc reagent was stored under nitrogen. A separate flame-dried 100 mL flask was charged with $Pd_2(dba)_3$ (91.6 mg, 0.10 mmol, 0.02 equiv), RuPhos (186.7 mg, 0.40 mmol, 0.08 equiv) and a magnetic stir bar. DMA (23.5 mL, freshly distilled over CaH_2) was added via syringe, followed by 3-bromopyridine (790 mg, 5.0 mmol, 1.0 equiv) and the zinc reagent (10 mL, 10 mmol, 2.0 equiv). The reaction mixture was placed in a 70 °C oil bath and stirred overnight. The reaction mixture was quenched with 100 mL saturated NH_4Cl solution and extracted with diethyl ether (3x50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography provided the pure product.



2-Methyl-6-(4-methylpentyl)pyridine (12b) 2,6-lutidine (1.6 mL, 1.47 g, 13.75 mmol, 1.0 equiv) was reacted with 1-bromo-3-methylbutane (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv) following method A. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (1.90 g, 10.7 mmol, 78% yield).

Data for **12b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

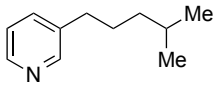
δ 7.46 (t, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.6, 4.0 Hz, 2H), 2.71 (t, *J* = 7.9 Hz, 2H), 2.52 (s, 3H), 1.72-1.64 (m, 2H), 1.56 (hept, *J* = 6.7 Hz, 1H), 1.27-1.21 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.07, 157.77, 136.56, 120.45, 119.54, 39.01, 38.92, 28.30, 28.10, 24.70, 22.74

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596, found 178.1601.



3-(4-Methylpentyl)pyridine (12c) Prepared from 3-bromopyridine (0.48 mL, 790 mg, 5.0 mmol, 1.0 equiv) and 1-bromo-4-methylpentane (2.54 g, 15.39 mmol) following method B. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (662.8 mg, 4.1 mmol, 81% yield).

Data for **12c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

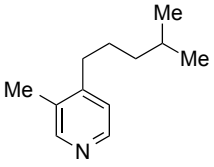
δ 8.46-8.40 (m, 2H), 7.48 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.8 Hz, 1H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.66-1.50 (m, 3H), 1.26-1.17 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.09, 147.30, 138.11, 135.91, 123.36, 38.55, 33.40, 29.14, 27.97, 22.69

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439, found 164.1445.



3-Methyl-4-(4-methylpentyl)pyridine (12d) 3,4-lutidine (1.5 mL, 1.47 g, 13.75 mmol, 1.0 equiv) was reacted with 1-bromo-3-methylbutane (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as a yellow oil (1.80 g, 10.1 mmol, 74% yield).

Data for **12d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

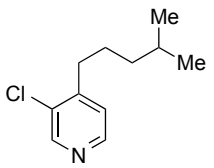
δ 8.34-8.28 (m, 2H), 7.02 (d, *J* = 5.0 Hz, 1H), 2.53 (t, *J* = 7.9 Hz, 2H), 2.25 (s, 3H), 1.63-1.49 (m, 3H), 1.29-1.19 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.66, 149.89, 147.55, 131.56, 123.46, 38.85, 32.78, 27.95, 27.07, 22.64, 16.16

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}N$ $[M+H]^+$: 178.1596, found 178.1601.



3-Chloro-4-(4-methylpentyl)pyridine (12e) Prepared following a modified version of general method A. In a flame-dried 100 mL round bottom flask was charged with diisopropylamine (2.3 mL, 1.61 g, 15.91 mmol, 1.16 equiv), THF (6.3 mL) and a magnetic stir bar. The mixture was cooled down to -78 °C upon stirring, and *n*-butyllithium (1.6 M, 9.9 mL, 15.81 mmol, 1.15 equiv) was added dropwise via syringe. The reaction mixture was stirred at -78 °C for 15 min and 0 °C for 5 min. The mixture was cooled back down to -78 °C, upon which 3-chloro-4-methylpyridine (1.5 mL, 1.75 g, 13.75 mmol, 1.0 equiv) was added dropwise. The mixture was further stirred for 1 h, at which time 1-bromo-3-methylbutane (1.9 mL, 2.33 g, 15.13 mmol, 1.1 equiv) was added. The mixture was stirred for an additional 5 min at -78°C and was then allowed to warm up to ambient temperature, stirred overnight, and quenched with water (0.5 mL). Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a colorless oil (2.12 g, 10.7 mmol, 78% yield).

Data for **12e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

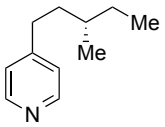
δ 8.50 (s, 1H), 8.36 (d, *J* = 4.9, 1H), 7.13 (d, *J* = 4.9 Hz, 1H), 2.69 (t, *J* = 7.7 Hz, 2H), 1.67-1.52 (m, 3H), 1.29-1.21 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.41, 149.22, 147.72, 132.21, 124.90, 38.64, 33.14, 27.91, 26.73, 22.64

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{17}NCl$ $[M+H]^+$: 198.1050, found 198.1051



(*S*)-4-(3-methylpentyl)pyridine (12f) 4-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv) was reacted with (S)-1-bromo-2-methylbutane (1.9 mL, 2.29 g, 15.13 mmol, 1.1 equiv) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as an orange oil (1.96 g, 12.0 mmol, 87% yield).

Data for **12f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

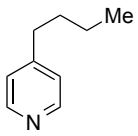
δ 8.45 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.08 (d, *J* = 5.8 Hz, 2H), 2.57 (dddd, *J* = 41.3, 13.9, 10.4, 5.7 Hz, 2H), 1.67-1.56 (m, 1H), 1.46-1.30 (m, 3H), 1.18 (oct, *J* = 8.3 Hz, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.86 (d, *J* = 7.3 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.17, 149.75, 123.97, 37.38, 34.14, 32.96, 29.38, 19.14, 11.39

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}N$ $[M+H]^+$: 164.1439, found 164.1442.



4-Butylpyridine (12g) 4-picoline (1.4 mL, 1.28 g, 13.75 mmol, 1.0 equiv) was reacted with 1-bromopropane (1.4 mL, 1.86 g, 15.13 mmol, 1.1 equiv) following method A. Purification by flash chromatography on silica eluting with 20→40% EtOAc/hexanes yielded the product as a light yellow oil (953 mg, 7.05 mmol, 66% yield).

Data for **12g**:

^{1}H NMR: (400 MHz, $CDCl_3$)

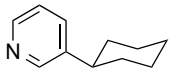
δ 8.48 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.11 (dd, *J* = 4.4, 1.5 Hz, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.66-1.59 (m, 2H), 1.36 (h, *J* = 7.3 Hz, 2H), 0.93 (d, *J* = 7.6 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 151.84, 149.75, 124.03, 35.08, 32.55, 22.40, 13.98

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_9H_{14}N$ $[M+H]^+$: 136.1126, found 136.1126.



3-Cyclohexylpyridine (12h) Prepared from 3-bromopyridine (0.48 mL, 790 mg, 5.0 mmol, 1.0 equiv) and bromocyclohexane (2.50 g, 15.39 mmol) following method B. Purification by flash chromatography on silica eluting with 10→25% EtOAc/hexanes yielded the product as a light yellow oil (803.5 mg, 5.0 mmol, quantitative yield).

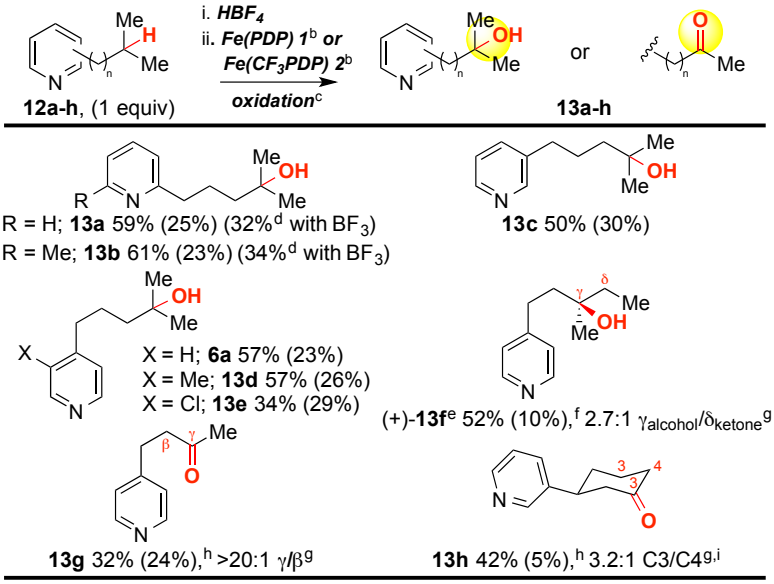
Data for **12h**:

^{1}H NMR: (400 MHz, $CDCl_3$) These spectral data matched those reported.[13]

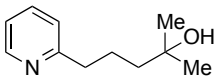
δ 8.45 (d, *J* = 2.0 Hz, 1H), 8.40 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.48 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.18 (dd, *J* = 7.8, 4.8 Hz, 1H), 2.59-2.44 (m, 1H), 1.93-1.77 (m, 4H), 1.77-1.66 (m, 1H), 1.45-1.32 (m, 4H), 1.30-1.16 (m, 1H)

IX. Experimental Procedures and Compound Characterization for Table S3

Table S3. Pyridines[a]



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Catalyst enantiomers used interchangeably. [c]Method A with HBF_4•Et_2O (1.1 equiv). [d]Method B with BF_3•OEt_2 (1.1 equiv), catalyst **1** and 20% NaOH workup. [e](+)-**13f** Refers to pure alcohol. [f]Starting material recycled 1x. [g]Based on isolation. [h]Method B. [i]1.6:1 C3/C4 adjusted for number of hydrogens.



2-methyl-5-(pyridin-2-yl)pentan-2-ol (13a) 2-(4-Methylpentyl)pyridine (**12a**) (0.5 mmol, 81.6 mg) was reacted with [Fe((*S,S*)-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a light yellow oil.

Run 1 (53.3 mg, 0.30 mmol, 59% yield; 23.8 mg, 0.15 mmol. 29% rsm)

Run 2 (53.3 mg, 0.30 mmol, 59% yield; 17.1 mg, 0.10 mmol, 21% rsm)

Average overall yield: 59% (25% rsm)

Oxidation with BF_3 protection under slow addition protocol:

Run 1 (32.4 mg, 0.18 mmol, 36% yield; 33.6 mg, 0.21 mmol. 41% rsm)

Run 2 (24.3 mg, 0.14 mmol, 27% yield; 39.0 mg, 0.24 mmol, 48% rsm)

Average overall yield: 32% (45% rsm)

Data for **13a**:

^{1}H NMR: (400 MHz, $CDCl_3$)

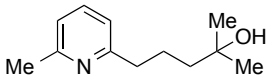
δ 8.51 (d, *J* = 4.1 Hz, 1H), 7.58 (dt, *J* = 7.7, 1.7 Hz, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10 (dd, *J* = 6.8, 5.3 Hz, 1H), 2.80 (t, *J* = 7.6 Hz, 2H), 1.94 (br s, 1H), 1.86-1.76 (m, 2H), 1.57-1.50 (m, 2H), 1.20 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.12, 149.22, 136.51, 122.98, 121.14, 70.97, 43.32, 38.55, 29.46, 24.71

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1394.



2-methyl-5-(6-methylpyridin-2-yl)pentan-2-ol (13b) 2-Methyl-6-(4-methylpentyl)pyridine (**12b**) (0.5 mmol, 88.6 mg) was reacted with $[Fe((S,S)\text{-PDP})(MeCN)_2](SbF_6)_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% $MeOH/CH_2Cl_2$ yielded the product as a light yellow oil.

Run 1 (57.0 mg, 0.29 mmol, 59% yield; 20.8 mg, 0.12 mmol, 23% rsm)

Run 2 (60.8 mg, 0.31 mmol, 63% yield; 19.4 mg, 0.11 mmol, 22% rsm)

Average overall yield: 61% (23% rsm)

Oxidation with BF_3 protection under slow addition protocol:

Run 1 (35.4 mg, 0.18 mmol, 37% yield; 35.7 mg, 0.20 mmol. 40% rsm)

Run 2 (30.7 mg, 0.16 mmol, 32% yield; 41.2 mg, 0.23 mmol, 47% rsm)

Average overall yield: 34% (43% rsm)

Data for **13b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

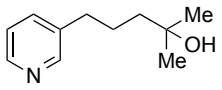
δ 7.46 (d, *J* = 7.6 Hz, 1H), 6.94 (dd, *J* = 7.6, 3.0 Hz, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.51 (s, 3H), 2.19 (br s, 1H), 1.82-1.73 (m, 2H), 1.56-1.49 (m, 2H), 1.19 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 161.45, 157.70, 136.73, 120.61, 119.78, 70.94, 43.17, 38.47, 29.45, 24.90, 24.54

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}NO$ $[M+H]^+$: 194.1545, found 194,1550.



2-Methyl-5-(pyridin-3-yl)pentan-2-ol (13c) 3-(4-Methylpentyl)pyridine (**12c**) (0.5 mmol, 81.6 mg) was reacted with $[Fe((S,S)\text{-PDP})(MeCN)_2](SbF_6)_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% $MeOH/CH_2Cl_2$ yielded the product as a light yellow oil.

Run 1 (44.1 mg, 0.25 mmol, 49% yield; 23.4 mg, 0.14 mmol, 29% rsm)

Run 2 (46.0 mg, 0.26 mmol, 51% yield; 25.2 mg, 0.15 mmol, 31% rsm)

Average overall yield: 50% (30% rsm)

Data for **13c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

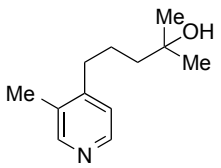
δ 8.43-8.36 (m, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.6, 4.9 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.10 (br s, 1H), 1.73-1.64 (m, 2H), 1.51-1.45 (m, 2H), 1.18 (s, 6H)

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 149.91, 147.32, 137.75, 136.04, 123.47, 70.88, 43.34, 33.50, 29.44, 26.01

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1388



2-methyl-5-(3-methylpyridin-4-yl)pentan-2-ol (13d) 3-Methyl-4-(4-methylpentyl)pyridine (**12d**) (0.5 mmol, 88.6 mg) was reacted with [Fe((*R,R*)-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (56.8 mg, 0.29 mmol, 59% yield; 23.3 mg, 0.13 mmol, 26% rsm)

Run 2 (54.0 mg, 0.28 mmol, 56% yield; 23.1 mg, 0.13 mmol, 26% rsm)

Average overall yield: 57% (26% rsm)

Data for **13d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

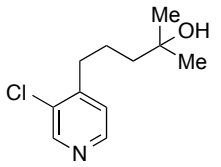
δ 8.29-8.24 (m, 2H), 7.01 (d, *J* = 5.0 Hz, 1H), 2.56 (t, *J* = 7.7 Hz, 2H), 2.36 (br s, 1H), 2.23 (s, 3H), 1.70-1.62 (m, 2H), 1.54-1.48 (m, 2H), 1.19 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.46, 149.66, 147.33, 131.65, 123.47, 70.54, 43.57, 32.84, 29.41, 23.92, 16.16

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{12}H_{20}NO$ $[M+H]^+$: 194.1545, found 194.1552



5-(3-chloropyridin-4-yl)-2-methylpentan-2-ol (13e) 3-Chloro-4-(4-methylpentyl)pyridine (**12e**) (0.5 mmol, 98.8 mg) was reacted with [Fe((*S,S*)-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (50 mL) eluting with 2→5→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (33.8 mg, 0.16 mmol, 32% yield; 28.1 mg, 0.14 mmol, 28% rsm)

Run 2 (38.0 mg, 0.18 mmol, 36% yield; 28.8 mg, 0.15 mmol, 29% rsm)

Average overall yield: 34% (29% rsm)

Data for **13e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

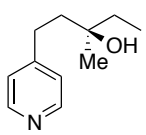
δ 8.49 (s, 1H), 8.34 (d, *J* = 4.9, 1H), 7.14 (d, *J* = 4.9 Hz, 1H), 2.72 (t, *J* = 7.7 Hz, 2H), 1.76-1.67 (m, 2H), 1.66 (br s, 1H), 1.56-1.50 (m, 2H), 1.21 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.33, 148.88, 147.66, 132.21, 124.90, 70.74, 43.32, 33.20, 29.44, 23.65

HRMS: (ESI-TOF MS ES+)

m/z calculated for C11H17NOCl [M+H]+: 214.0999, found 214.1004



(*R*)-3-methyl-1-(pyridin-4-yl)pentan-3-ol (13f) (*S*)-4-(3-Methylpentyl)pyridine (**12f**) (0.5 mmol, 81.6 mg) was reacted with [Fe((*R,R*)-PDP)(MeCN)$_2$](SbF$_6$)$_2$ (**1**) following the general procedure and the iterative addition protocol. Purification by flash chromatography on silica (20 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil.

Run 1 (*cycle 1*: 26.6 mg, 0.15 mmol, 30% yield; 26.4 mg, 0.16 mmol, 32% rsm; *cycle 2*: 7.6 mg, 0.042 mmol, 26% yield; 5.9 mg, 0.036 mmol, 22% rsm; ***overall***: 34.2 mg, 0.19 mmol, 38% yield; 5.9 mg, 0.036 mmol, 7% rsm)

Run 2 (*cycle 1*: 26.6 mg, 0.15 mmol, 30% yield; 27.1 mg, 0.17 mmol, 33% rsm; *cycle 2*: 6.7 mg, 0.038 mmol, 23% yield; 10.8 mg, 0.066 mmol, 40% rsm; ***overall***: 33.3 mg, 0.19 mmol, 37% yield; 10.8 mg, 0.066 mmol, 13% rsm)

Average overall yield: 38% (10% rsm)

Data for **13f**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.46 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.11 (d, *J* = 5.8 Hz, 2H), 2.68 (dd, *J* = 11.2, 5.7 Hz, 2H), 1.81 (br s, 1H), 1.73 (dd, *J* = 11.1, 5.3 Hz, 2H), 1.56 (q, *J* = 7.5 Hz, 2H), 1.22 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H)

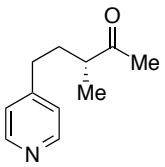
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.05, 149.69, 123.98, 72.55, 42.08, 34.65, 29.80, 26.42, 8.40

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{18}NO$ $[M+H]^+$: 180.1388, found 180.1389

$[\alpha]_D^{25}$ = +4.3° (c=1.37, CH_2Cl_2)



(*R*)-3-methyl-5-(pyridin-4-yl)pentan-2-one (S19) Purification by flash chromatography on silica (20 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil.

Run 1 (*cycle 1*: 11% yield, 9.3 mg, 0.052 mmol; *cycle 2*: 10% yield, 2.9 mg, 0.016 mmol; ***overall***: 14% yield, 12.2 mg, 0.069 mmol)

Run 2 (*cycle 1*: 12% yield, 10.8 mg, 0.061 mmol; *cycle 2*: 7% yield, 2.1 mg, 0.012 mmol; ***overall***: 15% yield, 12.9 mg, 0.073 mmol)

Average overall yield: 14%

Data for **S19**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.49 (dd, *J* = 4.5, 1.4 Hz, 2H), 7.09 (d, *J* = 5.9 Hz, 2H), 2.57 (t, *J* = 8.0 Hz, 2H), 2.52 (h, *J* = 7.0 Hz), 2.14 (s, 3H), 2.05-1.92 (m, 1H), 1.68-1.60 (m, 1H), 1.15 (d, *J* = 7.1 Hz, 3H)

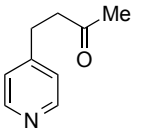
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 211.87, 150.85, 149.79, 123.90, 46.39, 33.05, 32.76, 28.32, 16.56

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{11}H_{16}NO$ $[M+H]^+$: 178.1232, found 178.1237

$[\alpha]_D^{25}$ = -0.8° (c=1.38, CH_2Cl_2).



4-(Pyridin-4-yl)butan-2-one (13g) Following the general procedure and the slow addition protocol, 4-butylpyridine (**12g**) (0.3 mmol, 40.6 mg) was reacted with $[Fe((R,R)\text{-}CF_3PDP)(MeCN)_2](SbF_6)_2$ (**2**) (101.7 mg, 0.125 mmol, 0.25 equiv) and AcOH (86 μL, 90.2 mg, 1.5 mmol, 5.0 equiv) in MeCN (3.0 mL, 0.50 M to AcOH), and H_2O_2 (153 μL, 2.7 mmol, 9.0 equiv, 50 wt. % in H_2O) in MeCN (3.6 mL, 0.75 M to H_2O_2). Purification by flash chromatography on silica (50 mL) eluting with 80% EtOAc/hexanes yielded the product as a colorless oil.

Run 1 (14.0 mg, 0.094 mmol, 31% yield; 10.1 mg, 0.075 mmol, 25% rsm);

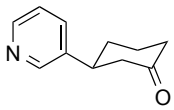
Run 2 (14.4 mg, 0.097 mmol, 32% yield; 9.5 mg, 0.070 mmol, 23% rsm).

Average overall yield: 32% (24% rsm)

Data for **13g**: Spectra matched those reported in the literature.[14]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.47 (d, *J* = 5.4 Hz, 2H), 7.10 (d, *J* = 5.4 Hz, 2H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.77 (t, *J* = 7.3 Hz, 2H), 2.15 (s, 3H)



3-(pyridin-3-yl)cyclohexan-1-one (13h) 3-Cyclohexylpyridine (**12h**) (0.3 mmol, 48.4 mg) was protected according to the general procedure an oxidized following the slow addition protocol. The resultant salt and AcOH (8.6 μL, 9.0 mg, 0.15 mmol, 0.5 equiv) were dissolved in acetonitrile (0.45 mL, 0.67 M to **12h**). [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (101.7 mg, 0.125 mmol, 0.25 equiv) was dissolved in MeCN (3.0 mL, 0.42 M) and loaded in a 1 mL syringe. Another 10 mL syringe was charged with H_2O_2 (86.5 μL, 1.5 mmol, 5.0 equiv, 50 wt. % in H_2O) in MeCN (3.6 mL, 0.42 M). Both syringes were fitted with 25G needles and were added simultaneously into the stirring reaction mixture via a syringe pump at 4 mL/h over approximately 1 h. Purification by MPLC on silica (12 g) eluting with 0→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (18.4 mg, 0.11 mmol, 35% yield; 2.3 mg, 0.014 mmol, 5% rsm)

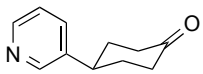
Run 2 (15.2 mg, 0.087 mmol, 29% yield; 2.4 mg, 0.015 mmol, 5% rsm)

Average overall yield: 32% (5% rsm)

Data for **13h**: These spectral data matched those reported.[15]

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.51 (d, *J* = 2.2 Hz, 1H), 8.49 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.53 (dt, *J* = 7.8, 1.9 Hz, 1H), 7.26 (dd, *J* = 7.8, 4.8 Hz, 1H), 3.04 (tq, *J* = 11.6, 3.7 Hz, 1H), 2.60 (ddt, *J* = 14.0, 4.2, 1.9 Hz, 1H), 2.56-2.51 (m, 1H), 2.51-2.45 (m, 1H), 2.39 (dt, *J* = 13.5, 6.3 Hz, 1H), 2.18 (ddt, *J* = 12.9, 6.6, 3.2 Hz, 1H), 2.10 (ddt, *J* = 11.3, 3.2, 1.7 Hz, 1H), 1.93-1.75 (m, 2H)



4-(pyridin-3-yl)cyclohexan-1-one (S20) Purification by MPLC on silica (12 g) eluting with 0→10% MeOH/CH_2Cl_2 yielded the product as a colorless oil.

Run 1 (4.8 mg, 0.027 mmol, 9% yield)

Run 2 (5.5 mg, 0.031 mmol, 10% yield)

Average overall yield: 10%

Data for **S20**: These spectral data matched those reported.[16]

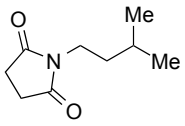
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.55 (d, *J* = 2.0 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.55 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.26 (dd, *J* = 6.6, 6.0 Hz, 1H), 3.07 (tt, *J* = 12.2, 3.3 Hz, 1H), 2.54 (dd, *J* = 9.6, 5.0 Hz, 4H), 2.24 (ddt, *J* = 10.3, 5.2, 3.1 Hz, 2H), 1.96 (dq, *J* = 12.4, 8.6 Hz, 2H)

X. Synthesis of Substrates and Compound Characterization for Table S4

Imide alkylation procedure 1: To a flame-dried round bottom flask equipped with a magnetic stir bar, under N_2 atmosphere was added imide (1.0 equiv), DMSO (0.3 M to substrate) and NaH (1.1 equiv, 60 wt.% in mineral oil) in one portion. The solution was stirred for 15 minutes and the corresponding alkyl bromide (1.1 equiv) was added dropwise. The reaction was stirred overnight (12-24 hours) at room temperature. The reaction was quenched by the addition of water (50 mL). The aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with H_2O (5 x 50 mL) and brine (1 x 50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude mixture was purified by flash chromatography.

Imide alkylation procedure 2: To a flame-dried round bottom flask equipped with a magnetic stir bar, under a N_2 atmosphere, was added imide (2.0 equiv), alcohol (1.0 equiv), triphenylphosphine (2.0 equiv) and Et_2O (0.4 M to imide). The reaction solution was cooled to 0 °C and diethylazodicarboxylate (1.7 equiv, 40 wt.% in PhMe) was added over 10 minutes. The reaction was gradually warmed to room temperature and stirred overnight (12-24 hours). Upon completion reaction was concentrated and the crude mixture was purified by flash chromatography.



1-isopentylpyrrolidine-2,5-dione (14a) According to the imide alkylation procedure 1, succinimide (396 mg, 4.00 mmol, 1.0 equiv), NaH (106 mg, 4.40 mmol, 1.1 equiv, 60 wt.% in mineral oil), DMSO (13 mL, 0.3 M) and 1-bromo-3-methylbutane (0.528 mL, 4.40 mmol, 1.1 equiv) were reacted. Flash chromatography with gradient elution (10% up to 50% EtOAc/Hex) afforded 1-isopentylpyrrolidine (**14a**) as a colorless oil (657 mg, 3.88 mmol, 97% yield).

Data for **14a**:

^{1}H NMR: (500 MHz, $CDCl_3$)

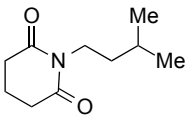
δ 3.46 – 3.40 (m, 2H), 2.62 (s, 4H), 1.48 (n, *J* = 6.7 Hz, 1H), 1.39 – 1.33 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 177.2, 37.3, 36.4, 28.2, 26.0, 22.3

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_9H_{15}NO_2$ 170.1181; found 170.1186



1-Isopentylpiperidine-2,6-dione (14b) According to the imide alkylation procedure 1, glutarimide (1.00 g, 8.84 mmol, 1.0 equiv), NaH (389 mg, 9.72 mmol, 1.1 equiv, 60 wt.% in mineral oil), DMSO (30 mL, 0.3 M to substrate) and 1-bromo-3-methylbutane (1.17 mL, 9.72 mmol, 1.1 equiv) were reacted. Flash chromatography with gradient elution (10% up to 50% EtOAc/Hex) afforded 1-isopentylpiperidine-2,6-dione (**14b**) as a colorless oil (1.60 g, 8.73 mmol, 99% yield).

Data for **14b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

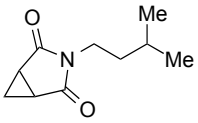
δ 3.73 – 3.66 (m, 2H), 2.58 (t, *J* = 6.6 Hz, 4H), 1.87 (p, *J* = 6.6 Hz, 2H), 1.52 (n, *J* = 6.7 Hz, 1H), 1.35 – 1.27 (m, 2H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 172.6, 38.4, 37.0, 33.1, 26.5, 22.7, 17.4

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1338



3-Isopentyl-3-azabicyclo[3.1.0]hexane-2,4-dione (14c) According to the imide alkylation procedure 1, 3-azabicyclo[3.1.0]hexane-2,4-dione (321 mg, 2.89 mmol, 1.0 equiv), NaH (76 mg, 3.18 mmol, 1.1 equiv, 60 wt.% in mineral oil), DMSO (9.6 mL, 0.3M) and 1-bromo-3-methylbutane (0.381 mL, 3.18 mmol, 1.1 equiv) were reacted. Flash chromatography using gradient elution (25% up to 50% EtOAc/Hex) afforded 3-isopentyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**14c**) as a colorless oil (350 mg, 1.93 mmol, 67% yield).

Data for **14c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

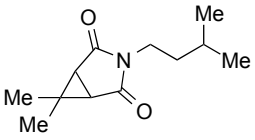
δ 3.40 – 3.30 (m, 2H), 2.44 (dd, *J* = 8.1, 3.5 Hz, 2H), 1.54 – 1.43 (m, 2H), 1.38 – 1.29 (m, 3H), 0.89 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.3, 36.6, 36.6, 26.0, 22.4, 21.0, 20.3

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_2$ 182.1181, found 182.1182



3-isopentyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (14d) Following imide alkylation procedure 1, 6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (300 mg, 2.16 mmol, 1.0 equiv), NaH (96 mg, 2.40 mmol, 1.1 equiv, 60 wt% in mineral oil), DMSO (7 mL, 0.3M), and 1-bromo-3-methylbutane (0.288 mL, 2.40 mmol, 1.1 equiv) were reacted. Crude material was purified by flash chromatography (SiO_2, gradient elution 10% up to 20% EtOAc/Hex) afforded 3-isopentyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**14d**) (340 mg, 1.62 mmol, 75% yield) as a colorless oil.

Data for **14d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

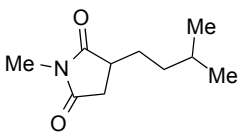
δ 3.36 – 3.29 (m, 2H), 2.26 (s, 2H), 1.50 (n, *J* = 6.7 Hz, 1H), 1.39 – 1.31 (m, 2H), 1.17 (d, *J* = 15.3 Hz, 6H), 0.87 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.0, 36.8, 36.6, 35.4, 33.6, 26.3, 26.2, 22.4, 15.7

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{12}H_{20}NO_2$ 210.1494, found 210.1498



3-Isopentyl-1-methylpyrrolidine-2,5-dione (14e) To a flame-dried 100 mL round bottom equipped with a magnetic stir bar, under a N_2 atmosphere, was added N-methylsuccinimide (2.0 g, 17.7 mmol, 1 equiv) and THF (15 mL). The solution was cooled to 0 °C and a solution of LiHMDS (3.55 g, 21.2 mmol, 1.2 equiv) dissolved in THF (20 mL) was added dropwise via syringe over 5 minutes. After stirring for 30 minutes at 0 °C, 1-bromo-3-methylbutane (3.18 mL, 26.6 mmol, 1.5 equiv) was added. The reaction was brought

to room temperature and allowed to stir overnight. The reaction was quenched with brine (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and the solvent evaporated. The crude material was purified via flash chromatography (SiO2, gradient elution 100% Hex up to 20% EtOAc/Hex) to afford 3-isopentyl-1-methylpyrrolidine-2,5-dione (**14e**) as a white solid (273 mg, 8% yield).

Data for **14e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

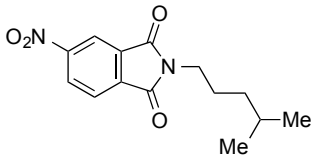
δ 2.96 (s, 3H), 2.85 – 2.71 (m, 2H), 2.35 (dd, *J* = 17.7, 4.0 Hz, 1H), 1.96 – 1.85 (m, 1H), 1.59 – 1.41 (m, 2H), 1.30 – 1.12 (m, 2H), 0.88 (dd, *J* = 6.6, 3.9 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 180.3, 176.9, 40.3, 35.9, 34.5, 29.3, 28.0, 24.9, 22.6, 22.5

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{18}NO_2$ 184.1338, found 184.1338



2-(4-Methylpentyl)-5-nitroisoindoline-1,3-dione (14g) Following imide alkylation procedure 2, 4-nitrophthalimide (2.0 g, 10.4 mmol, 2 equiv), 4-methyl-1-pentanol (0.656 mL, 5.2 mmol, 1 equiv), triphenylphosphine (2.73 g, 10.4 mmol, 2 equiv) diethyl ether (0.4 M to the 4-nitrophthalimide, 26 mL), and diethyl azodicarboxylate 40 wt.% in toluene (4.03 mL, 8.84 mmol, 1.7 equiv) were reacted. The crude material was purified by flash chromatography (SiO_2, gradient elution 100% Hex up to 10% EtOAc/Hex) afforded 2-(4-methylpentyl)-5-nitroisoindoline-1,3-dione (**14g**) as a yellow solid (2.30 g, 8.32 mmol 80% yield).

Data for **14g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

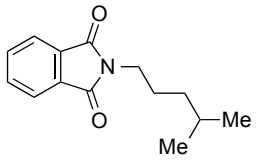
δ 8.66 (d, *J* = 1.9 Hz, 1H), 8.60 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 3.71 (t, *J* = 7.4 Hz, 2H), 1.74 – 1.64 (m, 2H), 1.58 (n, *J* = 6.7 Hz, 1H), 1.27 – 1.19 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 166.5, 166.2, 151.9, 136.8, 133.8, 129.4, 124.6, 118.8, 39.2, 36.0, 27.9, 26.6, 22.7

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}NO_4$ 277.1188, found 211.1190



2-(4-Methylpentyl)isoindoline-1,3-dione (14h) Following imide alkylation procedure 2, phthalimide (1.47 g, 10.0 mmol, 2 equiv), 4-methyl-1-pentanol (0.630 mL, 5.0 mmol, 1 equiv), triphenylphosphine (2.62 g, 10.0 mmol, 2 equiv) diethyl ether (0.4 M to the phthalimide, 25 mL), and diethyl azodicarboxylate 40 wt.% in toluene (3.87 mL, 8.5 mmol, 1.7 equiv) were reacted. The crude material was purified by flash chromatography (SiO_2, gradient elution 100% Hex up to 10% EtOAc/Hex) to afford 2-(4-methylpentyl)isoindoline-1,3-dione (**14h**) as a white solid (971 mg, 4.20 mmol, 84% yield)

Data for **14h**:

^{1}H NMR: (500 MHz, $CDCl_3$)

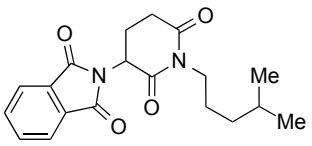
δ 7.82 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.0 Hz, 2H), 3.64 (t, *J* = 7.4 Hz, 2H), 1.71 – 1.61 (m, 2H), 1.55 (n, *J* = 6.7 Hz, 1H), 1.25 – 1.14 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 168.5, 133.9, 132.3, 123.2, 38.4, 36.0, 27.8, 26.6, 22.6

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{18}NO_2$ 232.1338, found 232.1338



2-(1-(4-methylpentyl)-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (14i) Following imide alkylation procedure 1, thalidomide (250 mg, 0.97 mmol, 1.0 equiv), NaH (43 mg, 1.06 mmol, 1.1 equiv, 60 wt.% in mineral oil), DMSO (3.2 mL, 0.3 M) and 1-bromo-3-methylbutane (0.150 mL, 1.06 mmol, 1.1 equiv) were reacted. The crude material was purified by flash chromatography (SiO_2 gradient elution 10% up to 30% EtOAc/Hex) to afford 2-(1-(4-methylpentyl)-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**14i**) as a white solid (280 mg, 0.818 mmol 84% yield).

Data for **14i**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.85 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.1 Hz, 2H), 5.01 – 4.92 (m, 1H), 3.74 (tq, *J* = 9.9, 5.9, 5.2 Hz, 2H), 3.01 – 2.88 (m, 1H), 2.86 – 2.69 (m, 2H), 2.15 – 2.02 (m, 1H), 1.60 – 1.44 (m, 3H), 1.21 – 1.09 (m, 2H), 0.83 (d, *J* = 6.6 Hz, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

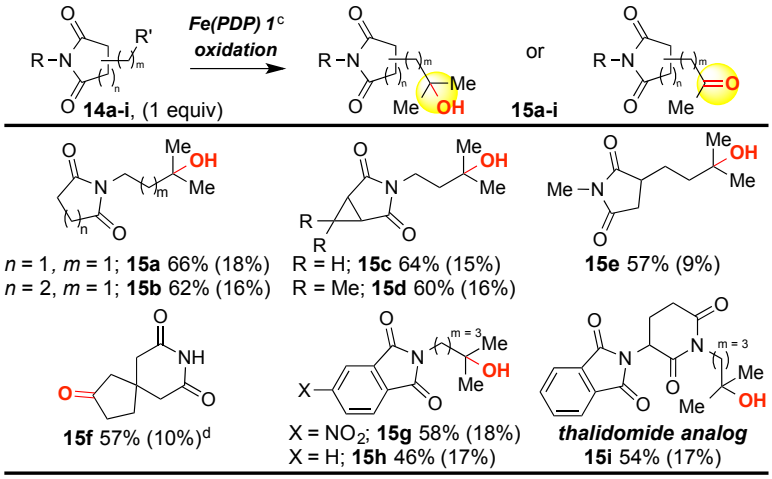
δ 170.9, 168.5, 167.5, 134.5, 131.8, 123.8, 50.2, 41.0, 35.9, 32.1, 27.7, 25.7, 22.6, 22.5, 22.1

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}N_2O_4$ 343.1658, found 343.1662

XI. Experimental Procedures and Compound Characterization for Table S4

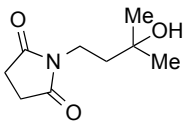
Table S4. Imides[a,b]



[a]Isolated yield is average of two runs, % rsm in parentheses. [b]Iterative addition. [c]Catalyst enantiomers used interchangeably. [d]Starting material recycled 1x.

Iterative Addition Protocol (Table S4): Imide substrate (0.500 mmol, 1.0 equiv) was dissolved in MeCN (746 μL, 0.67 M to substrate). A solution of Fe(PDP) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 15.0 mg, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)) was added. A solution of H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.5 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. ***Significant decreases in yield were noted when the peroxide solution was added rapidly.*** After 10 min, a second portion of Fe(PDP) and AcOH dissolved in MeCN was added to the reaction mixture, followed by the dropwise addition of a second portion of H_2O_2 solution in MeCN as described above. After an additional 10 minutes, a third portion of Fe(PDP) and AcOH dissolved in MeCN were added followed by the dropwise addition of a third portion of H_2O_2 solution in MeCN as described above. The reaction solution was stirred for 10 minutes after the last iterative addition, for a total reaction time of approximately 36 minutes.

Reaction workup: MeCN was removed in vacuo. The crude reaction was purified by flash chromatography to afford the desired oxidation product.



1-(3-hydroxy-3-methylbutyl)pyrrolidine-2,5-dione (15a) According to the iterative oxidation protocol, 1-isopentylpyrrolidine (**14a**) (85.0 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.750 mL, 0.67 M). Oxidation was carried out with [Fe((*R*,*R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The crude reaction mixture was purified by flash chromatography (SiO_2, 10% up to 70% EtOAc/Hex) to afford 1-(3-hydroxy-3-methylbutyl)pyrrolidine-2,5-dione (**15a**) as a white solid.

Run 1 (62 mg, 0.335 mmol, 67% yield, 16 mg, 0.095 mmol, 19% rsm)

Run 2 (59 mg, 0.320 mmol, 64% yield, 14 mg, 0.085 mmol, 17% rsm)

Average yield: 66% (18% rsm)

Data for **15a**:

^{1}H NMR: (500 MHz, DMSO-d_6)

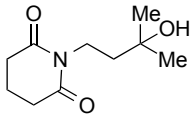
δ 4.33 (s, 1H), 3.47 – 3.38 (m, 2H), 2.59 (s, 4H), 1.56 – 1.48 (m, 2H), 1.10 (s, 6H)

^{13}C NMR: (126 MHz, DMSO-d_6)

δ 177.64, 67.88, 40.47, 34.30, 29.21, 28.04

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_9H_{15}NO_3$ 186.1130, found 186.1137



1-(3-hydroxy-3-methylbutyl)piperidine-2,6-dione (15b) According to the iterative oxidation protocol, 1-isopentylpiperidine-2,6-dione (**14b**) (92 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.750 mL, 0.67 M). Oxidation was carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. Flash chromatography using gradient elution (10% up to 70% EtOAc/Hex) afforded 1-(3-hydroxy-3-methylbutyl)piperidine-2,6-dione (**15b**) as a white solid.

Run 1 (61 mg, 0.305 mmol, 61% yield, 15 mg, 0.080 mmol, 16% rsm)

Run 2 (62 mg, 0.310 mmol, 62% yield, 15 mg, 0.080 mmol, 16% rsm)

Average yield: 62% (16% rsm)

Data for **15b**:

^{1}H NMR: (500 MHz, DMSO-d_6)

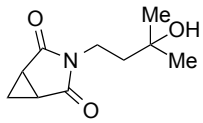
δ 4.26 (s, 1H), 3.73 – 3.65 (m, 2H), 2.56 (t, J = 6.5 Hz, 4H), 1.79 (p, J = 6.5 Hz, 2H), 1.50 – 1.43 (m, 2H), 1.10 (s, 6H)

^{13}C NMR: (126 MHz, DMSO-d_6)

δ 173.2, 68.8, 41.7, 35.9, 32.9, 29.9, 17.3

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{10}H_{17}NO_3Na$ 222.1106, found 222.1108



3-(3-hydroxy-3-methylbutyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (15c) According to the iterative oxidation procedure, 3-isopentyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**14c**) (91 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.750 mL, 0.67 M). Oxidation was carried with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The reaction mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 70% EtOAc/Hex) to afford 3-(3-hydroxy-3-methylbutyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (**15c**) as a white solid.

Run 1 (63 mg, 0.320 mmol, 64% yield, 11 mg, 0.060 mmol, 12% rsm)

Run 2 (62 mg, 0.314 mmol, 63% yield, 17 mg, 0.094 mmol, 19% rsm)

Average yield: 64% (15% rsm)

Data for **15c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

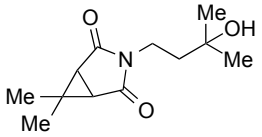
δ 3.54 – 3.46 (t, *J* = 7.5 Hz, 2H), 2.44 (dd, *J* = 8.0, 3.6 Hz, 2H), 1.75 – 1.57 (m, 3H), 1.48 (td, *J* = 8.0, 4.7 Hz, 1H), 1.42 (q, *J* = 3.7 Hz, 1H), 1.23 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 175.4, 70.0, 40.6, 34.2, 29.5, 20.7, 20.4

HRMS: (ESI-TOf MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{10}H_{16}NO_3$ 198.1130, found 198.1136



3-(3-hydroxy-3-methylbutyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (15d) According to the iterative oxidation procedure, 3-isopentyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**14d**) (105 mg, 0.50 mmol, 1.0 equiv) in MeCN (0.750 mL, 0.67 M). Oxidation was carried with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The reaction mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 70% EtOAc/Hex) to afford 3-(3-hydroxy-3-methylbutyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,4-dione (**15d**) as a white solid.

Run 1 (66 mg, 0.295 mmol, 59% yield, 16 mg, 0.075 mmol, 15% rsm)

Run 2 (69 mg, 0.305 mmol, 61% yield, 17 mg, 0.080 mmol, 16% rsm)

Average yield: 60% (16% rsm)

Data for **15d**:

^{1}H NMR: (500 MHz, $CDCl_3$)

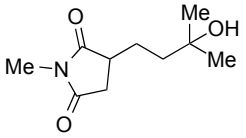
δ 3.56 – 3.50 (m, 2H), 2.32 (s, 2H), 1.73 (s, 1H), 1.71 – 1.66 (m, 2H), 1.25 (s, 6H), 1.23 (s, 3H), 1.20 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 174.2, 69.8, 41.0, 35.8, 34.3, 33.7, 29.4, 26.4, 15.8

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{12}H_{19}NO_3Na$ 248.1263, found 248.1264



3-(3-hydroxy-3-methylbutyl)-1-methylpyrrolidine-2,5-dione (15e) According to the iterative oxidation procedure, 3-isopentyl-1-methylpyrrolidine-2,5-dione (**14e**) (92 mg, 0.50 mmol, 1 equiv) was dissolved in MeCN (0.750 mL, 0.67M). Oxidation was carried with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The reaction mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 70% EtOAc/Hex) to afford 3-(3-hydroxy-3-methylbutyl)-1-methylpyrrolidine-2,5-dione (**15e**) as a white solid.

Run 1 (57 mg, 0.285 mmol, 57% yield, 8 mg, 0.045 mmol, 9% rsm)

Run 2 (57 mg, 0.285 mmol, 57% yield, 8 mg, 0.045 mmol, 9% rsm)

Average yield: 57% (9% rsm)

Data for **15e**:

^{1}H NMR: (500 MHz, $CDCl_3$)

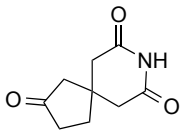
δ 2.94 (s, 3H), 2.87 – 2.74 (m, 2H), 2.36 (d, *J* = 13.9 Hz, 1H), 2.04 – 1.92 (m, 1H), 1.87 (br s, 1H), 1.67 – 1.50 (m, 2H), 1.49 – 1.40 (m, 1H), 1.20 (s, 3H), 1.19 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 180.2, 176.8, 70.6, 40.5, 40.1, 34.5, 29.6, 29.3, 26.3, 24.9

HRMS: (ESI-TOF MS ES+)

*m/*z: $[M+H]^+$ Calcd for $C_{10}H_{18}NO_3$ 200.1287, found 200.1296



8-Azaspiro[4.5]decane-2,7,9-trione (15f) According to the iterative oxidation protocol, 3,3-tetramethyleneglutarimide (84 mg, 0.50 mmol, 1 equiv) was dissolved in MeCN (0.750 mL). Oxidation was carried with [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (0.0143 mL, 0.25 mmol, 0.5 equiv) in MeCN (0.50 mL), H_2O_2 (0.0341 mL, 0.60 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL) were reacted. The reaction mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 70% EtOAc/Hex) to afford 8-azaspiro[4.5]decane-2,7,9-trione (**15f**) as a white solid and recovered 3,3-tetramethyleneglutarimide.

Run 1: recycled one time for an overall product yield (51 mg, 0.281 mmol, 56% yield) recovered starting material (7 mg, 0.042 mmol, 8%); cycle 1 product (36 mg, 0.215 mmol, 40% yield) recovered starting material (30 mg, 0.179 mmol, 36%); cycle 2 product (15 mg, 0.083 mmol, 46% yield), recovered starting material (7 mg, 0.042 mmol, 23%)

Run 2: recycled one time for an overall product yield (52 mg, 0.287 mmol, 57% yield) recovered starting material (9 mg, 0.054 mmol, 11%); product (40 mg, 0.221 mmol, 44% yield) recovered starting material (24 mg, 0.144 mmol, 29%); cycle 2 product (12 mg, 0.066 mmol, 46% yield), recovered starting material (9 mg, 0.054 mmol, 29%)

Average yield: 57% (10%)

Data for **15f**:

^{1}H NMR: (500 MHz, CD_3CN)

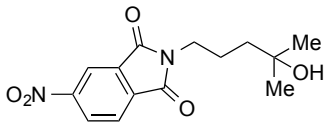
δ 8.85 (s, 1H), 2.60 (s, 4H), 2.30 (t, *J* = 7.9 Hz, 2H), 2.16 (s, 2H), 1.92 (t, *J* = 7.8 Hz, 2H)

^{13}C NMR: (126 MHz, CD_3CN)

δ 216.8, 172.7, 49.7, 43.2, 38.6, 36.9, 33.8

HRMS: (ESI-TOF MS ES+)

*m/*z: $[M+H]^+$ Calcd for $C_9H_{12}NO_3$ 182.0817, found 182.0819



2-(4-Hydroxy-4-methylpentyl)-5-nitroisoindoline-1,3-dione (15g) According to the iterative oxidation protocol, 2-(4-methylpentyl)-5-nitroisoindoline-1,3-dione (**14g**) (138 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.750 mL, 0.67 M). Oxidation was carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. The reaction mixture was purified by flash chromatography (SiO_2, gradient elution 10% up to 60% EtOAc/Hex) to afford 2-(4-hydroxy-4-methylpentyl)-5-nitroisoindoline-1,3-dione (**15g**) as a white solid.

Run 1 (85 mg, 0.293 mmol, 59% yield, 25 mg, 0.090 mmol, 18% rsm)

Run 2 (82 mg, 0.280 mmol, 56% yield, 23 mg, 0.083 mmol, 17% rsm)

Average yield: 58% (18% rsm)

Data for **15g**:

^{1}H NMR: (500 MHz, $CDCl_3$)

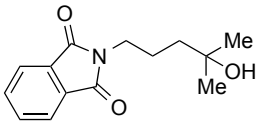
δ 8.62 (d, *J* = 1.7 Hz, 1H), 8.58 (dd, *J* = 8.1, 1.9 Hz, 1H), 8.03 (d, *J* = 8.1 Hz, 1H), 3.74 (t, *J* = 7.3 Hz, 2H), 1.83 – 1.72 (m, 2H), 1.64 (s, 1H), 1.55 – 1.42 (m, 2H), 1.18 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 166.4, 166.1, 151.8, 136.6, 133.5, 129.3, 124.5, 118.7, 70.6, 40.5, 39.1, 29.4, 23.6

HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{17}N_2O_5$ 293.1137, found 293.1135



2-(4-hydroxy-4-methylpentyl)isoindoline-1,3-dione (15h) According to the iterative oxidation protocol, 2-(4-methylpentyl)isoindoline-1,3-dione (**14h**) (116 mg, 0.50 mmol, 1.0 equiv) was dissolved in MeCN (0.750 mL, 0.67M). Oxidation was carried with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (23.3 mg, 0.025 mmol, 0.05 equiv) and AcOH (14.3 μL, 0.25 mmol, 0.5 equiv) dissolved in MeCN (500 μL, 0.05 M to Fe(PDP)). H_2O_2 (34.1 μL, 0.6 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (4.6 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. Flash chromatography (SiO_2, gradient elution 10% up to 60% EtOAc/Hex) to afford 2-(4-hydroxy-4-methylpentyl)isoindoline-1,3-dione (**15h**) as a white solid.

Run 1 (57 mg, 0.230 mmol, 46% yield, 19 mg, 0.082 mmol, 16% rsm)

Run 2 (57 mg, 0.230 mmol, 46% yield, 20 mg, 0.086 mmol, 17% rsm)

Average yield: 46% (17% rsm)

Data for **15h**:

^{1}H NMR: (500 MHz, Chloroform-*d*)

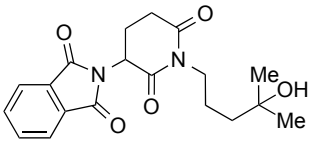
δ 7.81 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.69 (dd, *J* = 5.4, 3.0 Hz, 2H), 3.69 (t, *J* = 7.2 Hz, 2H), 1.86 (s, 1H), 1.81 – 1.69 (m, 2H), 1.57 – 1.44 (m, 2H), 1.19 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 168.6, 134.0, 132.2, 123.3, 70.7, 40.6, 38.4, 29.4, 23.8

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{14}H_{17}NO_3Na$ 270.1106, found 270.1108



2-(1-(4-hydroxy-4-methylpentyl)-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (15i) According to the iterative oxidation protocol, 2-(1-(4-methylpentyl)-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**14i**) (102.7 mg, 0.30 mmol, 1.0 equiv) was dissolved in MeCN (0.450 mL, 0.67 M). Oxidation was carried out with [Fe((*R,R*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14.0 mg, 0.015 mmol, 0.05 equiv) and AcOH (8.6 μL, 0.15 mmol, 0.5 equiv) dissolved in MeCN (300 μL, 0.05 M to Fe(PDP)). H_2O_2 (20.5 μL, 0.36 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.8 mL, 0.13 M to H_2O_2) was added dropwise to the stirring solution over 1.5–2 minutes. Flash chromatography using gradient elution (100% CH_2Cl_2 up to 5% MeOH/CH_2Cl_2) afforded 2-(1-(4-hydroxy-4-methylpentyl)-2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione (**15i**) as a white solid.

Run 1 (55 mg, 0.153 mmol, 51% yield, 12 mg, 0.035 mmol, 12% rsm)

Run 2 (60 mg, 0.167 mmol, 56% yield, 23 mg, 0.067 mmol, 22% rsm)

Average yield: 54% (17% rsm)

Data for **15i**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 4.98 (dd, *J* = 12.3, 5.6 Hz, 1H), 3.84 – 3.71 (m, *J* = 7.7 Hz, 2H), 3.01 – 2.86 (m, 1H), 2.83 – 2.65 (m, 2H), 2.26 – 1.75 (m, 2H), 1.69 – 1.51 (m, 2H), 1.50 – 1.38 (m, 2H), 1.15 (s, 6H)

^{13}C NMR: (126 MHz, $CDCl_3$)

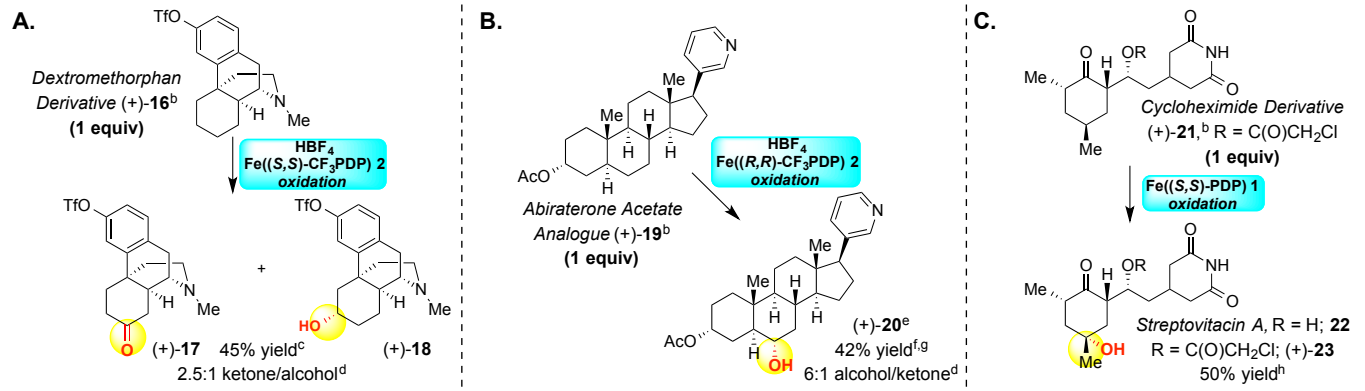
δ 171.1, 168.7, 167.5, 134.5, 131.8, 123.8, 70.6, 50.2, 41.0, 40.5, 32.0, 29.4, 29.1, 22.8, 22.0

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{19}H_{22}N_2O_5Na$ 381.1426, found 381.1426

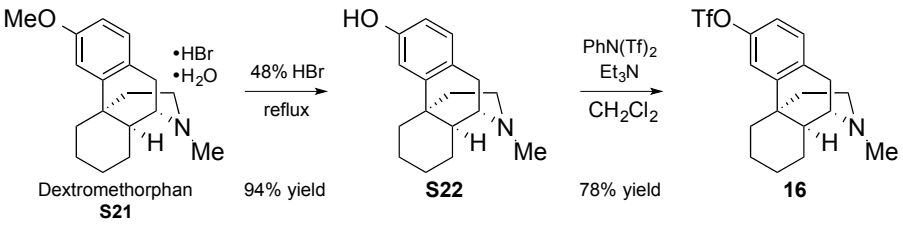
XII. Synthesis of Substrates, Experimental Procedures and Characterization for Scheme S10

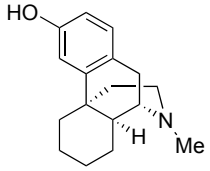
Scheme S10. Late-Stage Functionalization of Nitrogen-Containing Molecules[a]



[a]Isolated yield is average of two runs. [b]Substrates containing chirality demonstrated matched/mis-matched reactivity with catalyst enantiomers. [c](i) HBF_4•Et_2O (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Slow addition with **2**, (iii) 1M NaOH. [d]Based on isolation. [e](+)-**20** Refers to pure alcohol. [f](i) HBF_4•Et_2O (1.1 equiv), CH_2Cl_2, concd in vacuo, (ii) Iterative addition with **2**, (iii) $NaHCO_3$. [g]Starting material recycled 2x. [h]Iterative addition with **1**.

Scheme S11. Preparation of 3-(OTf) Dextromethorphan



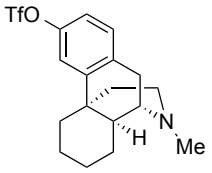


3-(O-Desmethyl) dextromethorphan (S22) Following the procedure of Senderoff and coworkers,[17] dextromethorphan hydrobromide hydrate (**S21**) (2.7 g, 7.29 mmol, 1.00 equiv) was added to a round bottom flask equipped with a magnetic stir bar. HBr (16 mL, 48 wt.% in H_2O) was added the reaction was refluxed for 24 hours. Upon cooling to room temperature the reaction solution was poured onto ice and the resultant solution was basified with saturated K_2CO_3 to pH = 10. The aqueous layer was extracted with $CHCl_3$ (3 x 50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered ad concentrated to afford 3-(O-desmethyl) dextromethorphan (**S22**) (1.77 g, 6.88 mmol, 94% yield). No purification required material was taken directly onto triflation.

Data for **S22**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 6.96 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 2.6 Hz, 1H), 6.60 (dd, *J* = 8.2, 2.6 Hz, 1H), 2.97 (d, *J* = 18.1 Hz, 1H), 2.84 (dd, *J* = 5.9, 3.1 Hz, 1H), 2.62 (dd, *J* = 18.1, 5.8 Hz, 1H), 2.48 (dd, *J* = 11.1, 3.8 Hz, 1H), 2.40 (s, 3H), 2.32 – 2.25 (m, 1H), 2.15 (td, *J* = 12.4, 3.3 Hz, 1H), 1.86 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.76 (td, *J* = 12.8, 4.8 Hz, 1H), 1.67 – 1.59 (m, 1H), 1.53 – 1.46 (m, 1H), 1.41 (dt, *J* = 14.2, 2.6 Hz, 1H), 1.38 – 1.23 (m, 4H), 1.15 (qd, *J* = 12.4, 3.8 Hz, 1H)



3-(OTf) dextromethorphan (16) Following the procedure of Neumeyer and Zhang,[18] 3-(O-desmethyl) dextromethorphan (**S22**) (1.77 g, 6.88 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (46 ml, 0.15 M) and Et_3N (19 mL, 137.54 mmol, 20.00 equiv). The mixture was cooled to 0 ºC and then $PhNTf_2$ (3.7 g, 10.32 mmol, 1.50 equiv) was added in one portion. The reaction was allowed to warm to room temperature overnight. The solution was diluted with CH_2Cl_2 (100 mL) and washed with 1 M NaOH (3 x 100 mL) followed by brine (100 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Crude material was purified by flash chromatography (50:1 SiO_2/theoretical yield, gradient elution 2→5→10% MeOH/CH_2Cl_2, doped with 2%NH_4OH). Column fractions were collected and washed with 1 M NaOH to remove residual NH_4OH and H_2O. Fractions were dried over anhydrous Na_2SO_4, filtered and concentrated to afford 3-(OTf) dextromethorphan (**16**) (2.10 g, 5.39 mmol, 78% yield) as a viscous purple oil.

Data for **16**:

^{1}H NMR: (750 MHz, $CDCl_3$)

δ 7.17 (d, *J* = 8.4 Hz, 1H), 7.11 (d, *J* = 2.7 Hz, 1H), 7.01 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.04 (d, *J* = 18.5 Hz, 1H), 2.83 (dd, *J* = 5.8, 3.1 Hz, 1H), 2.62 (dd, *J* = 18.5, 5.8 Hz, 1H), 2.45 (dd, *J* = 12.3, 3.1 Hz, 1H), 2.38 (s, 3H), 2.29 (dd, *J* = 14.2, 2.1 Hz, 1H), 1.99 (td, *J* = 12.5, 3.2 Hz, 1H), 1.86 (dt, *J* = 12.6, 3.3 Hz, 1H), 1.78 (td, *J* = 12.8, 4.9 Hz, 1H), 1.65 (d, *J* = 13.9 Hz, 1H), 1.55 (dt, *J* = 14.0, 3.5 Hz, 1H), 1.46 – 1.32 (m, 3H), 1.30 (dt, *J* = 13.0, 2.5 Hz, 1H), 1.19 (qt, *J* = 13.5, 3.5 Hz, 1H), 1.03 (qd, *J* = 12.9, 3.9 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 148.53, 143.56, 138.50, 129.51, 118.91 (q, *J* = 321.0 Hz), 118.36, 118.30, 57.63, 47.05, 45.01, 42.91, 41.95, 37.67, 36.61, 26.75, 26.51, 23.86, 21.99

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -73.22

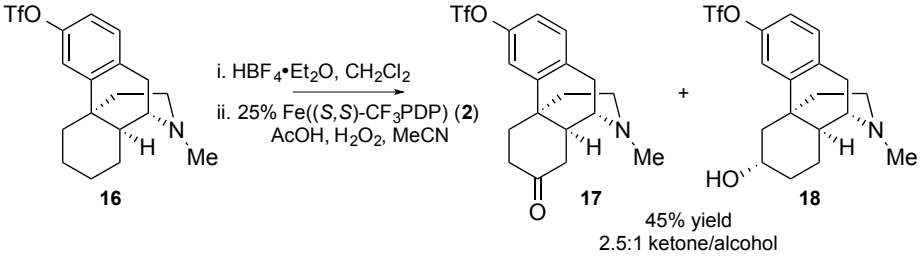
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}NO_3SF_3$ 390.1351, found 390.1350

$[\alpha]_D^{25}$ = +47.9° (c = 1.05, $CHCl_3$)

For COSY and HSQC see Supporting Information: Spectral Data

Scheme S12. Oxidation of 3-(OTf) Dextromethorphan



According to the general procedure, 3-(OTf) dextromethorphan (**16**) (194.7 mg, 0.500 mmol, 1.0 equiv) was treated with HBF_4•OEt_2 (75.8 μL, 0.550 mmol, 1.1 equiv, 54 wt.%) in CH_2Cl_2 (2.0 mL, 0.25 M) followed by the removal of solvent and excess acid. MeCN (746 μL, 0.67 M to substrate) was used to dissolve the resultant salt. Following the slow addition protocol, oxidation was carried out with [Fe((*S,S)*-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) (169.5 mg, 0.125 mmol, 0.25 equiv) and AcOH (143

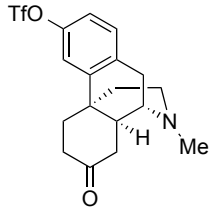
μL, 2.50 mmol, 5.0 equiv) dissolved in MeCN (543 μL, 0.23 M to Fe(PDP)). H_2O_2 (256 μL, 4.50 mmol, 9.0 equiv, 50 wt.% in H_2O) in MeCN (6.0 mL, 0.75 M to H_2O_2). Following work up crude material was purified by flash chromatography (50 mL basic Al_2O_3 Brockmann grade III, gradient elution with 10→20→30→40→50→60→70→80→90→100% EtOAc/Hex→10% MeOH/EtOAc, 1 column volume of each EtOAc/Hex solvent system followed by 2 column volumes of MeOH/EtOAc solvent system) to afford 3-(OTf) dextromethorphan ketone (**17**) and 3-(OTf) dextromethorphan alcohol (**18**) both as light yellow oils.

Run 1 (66.1 mg, 0.164 mmol, 33% yield ketone (**17**); 22.9 mg, 0.056 mmol, 11% yield alcohol (**18**); 21.6 mg, 0.056 mmol, 11% rsm)

Run 2 (63.4 mg, 0.157 mmol, 31% yield ketone (**17**); 28.8 mg, 0.071 mmol, 14 % yield alcohol (**18**); 16.0 mg, 0.041 mmol, 8% rsm)

Average yield: 32% ketone (17); 13% alcohol (18) (10% rsm) – ***45% yield (2.5:1 ketone/alcohol) (10% rsm)***

3-(OTf) Dextromethorphan *C*-7 Ketone (17)



Data for **17**:

^{1}H NMR: (750 MHz, $CDCl_3$)

δ 7.28 (d, *J* = 8.5 Hz, 1H), 7.22 (d, *J* = 2.6 Hz, 1H), 7.11 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.15 (d, *J* = 18.9 Hz, 1H), 2.92 – 2.89 (m, 1H), 2.69 (dd, *J* = 18.9, 5.9 Hz, 1H), 2.62 (ddd, *J* = 14.5, 5.6, 2.5 Hz, 1H), 2.52 (ddd, *J* = 12.5, 4.9, 1.9 Hz, 1H), 2.41 (s, 3H), 2.37 – 2.31 (m, 1H), 2.30 – 2.19 (m, 3H), 2.07 – 2.00 (m, 2H), 1.87 – 1.78 (m, 2H), 1.49 (dt, *J* = 12.9, 2.4 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 209.61, 148.75, 140.87, 137.98, 130.22, 119.42, 118.88 (q, *J* = 320.9 Hz), 118.25, 56.73, 46.53, 44.44, 42.81, 42.52, 40.64, 38.10, 36.93, 35.92, 23.23

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -73.14

HRMS: (ESI-TOF MS ES+)

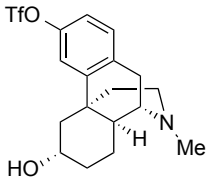
m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}NO_4SF_3$ 404.1143, found 404.1139

$[\alpha]_D^{25}$ = +39.4° (c = 1.14, $CHCl_3$)

For DQCOSY, HSQC and TOCSY see Supporting Information: Spectral Data

Site of oxidation was assigned based on a combination of ^{1}H, DQCOSY, HSQC and TOCSY NMR methods.

3-(OTf) Dextromethorphan *C*-6 α-Alcohol (18)



Data for **18**:

^{1}H NMR: (750 MHz, $CDCl_3$)

δ 7.21 (d, *J* = 2.6 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.52 (tt, *J* = 11.2, 4.2 Hz, 1H), 3.05 (d, *J* = 18.6 Hz, 1H), 2.95 – 2.91 (m, 1H), 2.65 – 2.57 (m, 2H), 2.46 (ddd, *J* = 12.1, 4.8, 1.8 Hz, 1H), 2.40 (s, 3H), 1.97 (m, 2H), 1.88 – 1.81 (m, 2H), 1.73 – 1.58 (br s, 1H), 1.55 (dd, *J* = 13.5, 3.6 Hz, 1H), 1.43 (d, *J* = 11.6 Hz, 1H), 1.40 – 1.34 (m, 2H), 1.14 (qd, *J* = 13.3, 3.8 Hz, 1H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 148.58, 142.89, 137.78, 129.71, 118.91 (q, *J* = 320.1 Hz), 118.75, 118.12, 66.79, 57.02, 46.30, 45.45, 44.03, 42.86, 41.77, 38.08, 35.86, 25.42, 23.74

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -73.19

HRMS: (ESI-TOF MS ES+)

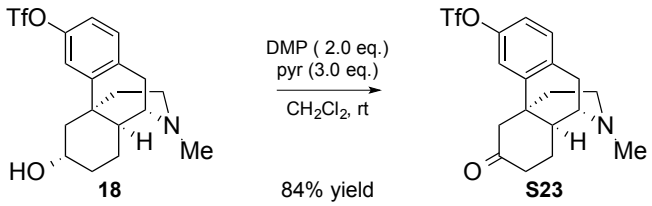
m/z: $[M+H]^+$ Calcd for $C_{18}H_{23}NO_4SF_3$ 406.1300, found 406.1299

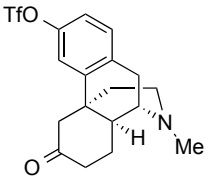
$[\alpha]_D^{25}$ = +36.8° (c = 0.96, $CHCl_3$)

For DQCOSY, HSQC and NOESY see Supporting Information: Spectral Data

Site of oxidation was assigned based on a combination of ^{1}H, DQCOSY, HSQC and 1D NOESY NMR methods.

Scheme S13. Oxidation of Alcohol 18





3-(OTf) Dextromethorphan *C*-6 Ketone (S23) To vial was added 3-(OTf) dextromethorphan *C*-6 α-alcohol (**18**), CH_2Cl_2 (500 μL, 0.06 M), pyridine (7 μL, 0.087 mmol, 3.00 equiv) and DMP (25.0 mg, 0.058 mmol, 2.00 equiv). Reaction was stirred at room temperature for 7 hours. TLC was used to monitor reaction progress. Reaction was diluted with CH_2Cl_2 (1 mL) and basified with 1 M NaOH (2 mL). Extracted basic aqueous layer with CH_2Cl_2 (1 x 1 mL). Combined organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated. Purified by flash chromatography (~2-5 mL basic Al_2O_3 Brockmann grade III, gradient elution 50→70→90→100% EtOAc/Hex, 2 column volumes each) to afford 3-(OTf) dextromethorphan *C*-6 ketone (**S23**) as a yellow oil (9.8 mg, 0.024 mmol, 83% yield).

Data for **S23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.19 (d, *J* = 8.4 Hz, 1H), 7.15 (d, *J* = 2.6 Hz, 1H), 7.06 (dd, *J* = 8.4, 2.6 Hz, 1H), 3.11 (d, *J* = 18.8 Hz, 1H), 3.10 – 3.02 (m, 2H), 2.65 (dd, *J* = 18.9, 6.0 Hz, 1H), 2.54 – 2.44 (m, 2H), 2.45 (s, 3H), 2.41 (dd, *J* = 14.1, 6.9 Hz, 1H), 2.35 (dt, *J* = 13.1, 3.6 Hz, 1H), 2.28 (ddt, *J* = 14.3, 4.6, 2.2 Hz, 1H), 2.00 (td, *J* = 12.5, 3.7 Hz, 2H), 1.88 (dddd, *J* = 13.0, 6.3, 3.7, 2.2 Hz, 1H), 1.51 (td, *J* = 13.3, 4.8 Hz, 1H), 1.47 – 1.41 (m, 1H)

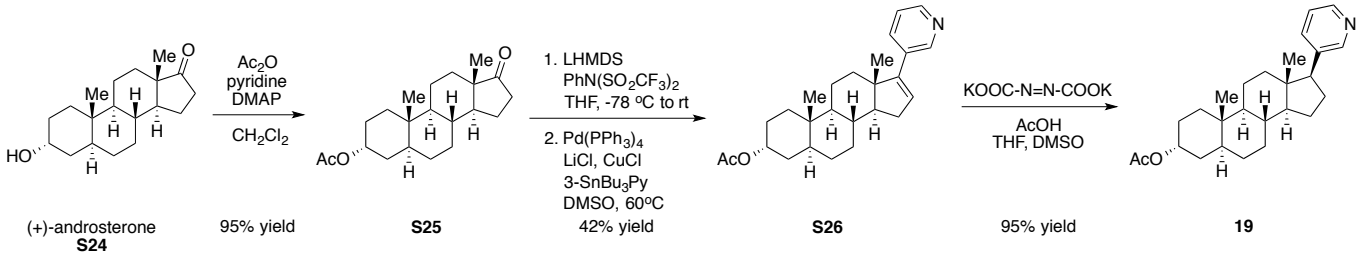
^{13}C NMR: (126 MHz, $CDCl_3$)

δ 208.24, 148.52, 140.71, 137.31, 129.81, 119.67, 119.13, 118.97 (q, *J* = 320.9 Hz), 56.91, 51.41, 45.93, 42.97, 41.96, 41.50, 41.17, 29.95, 26.90, 23.80

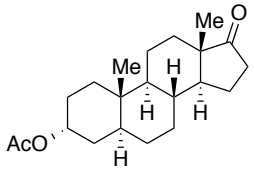
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{18}H_{21}NO_4SF_3$ 404.1143, found 404.1143

Scheme S14. Synthesis of Abiraterone Acetate Analogue



(+)-androsterone **S24** — 95% yield — **S25** — 42% yield — **S26** — 95% yield — **19**

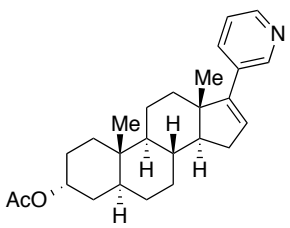


(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-oxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (S25): In a flame-dried 100 mL round bottom flask equipped with a stir bar was charged (+)-androsterone (**S24**) (5.0 g, 17.2 mmol, 1.0 equiv), pyridine (7.0 mL, 6.8 g, 86.1 mmol, 5.0 equiv), 4-dimethylaminopyridine (DMAP) (210.1 mg, 1.72 mmol, 0.10 equiv) and CH_2Cl_2 (34.4 mL). The reaction mixture was placed in ice bath upon stirring, and acetic anhydride (4.9 mL, 5.27 g, 51.6 mmol, 3.0 equiv) was added dropwise via syringe. The reaction mixture was stirred at 0 °C for 5 min and was then allowed to warm to ambient temperature and stirred overnight. The reaction was washed with water (20 mL), 1 M HCl (4x20 mL) and brine (20 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 10%→25% EtOAc/hexanes yielded **S25** as a white powder (5.57 g, 16.7 mmol, 97% yield).

Data for **S25**:

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 5.04-4.99 (m, 1H), 2.44 (dd, *J* = 19.2, 8.7 Hz, 1H), 2.14-2.00 (m, 4H), 1.94 (ddd, *J* = 12.6, 8.7, 5.9 Hz, 1H), 1.80 (dt, *J* = 11.8, 3.0 Hz, 2H), 1.76-1.69 (m, 1H), 1.69-1.59 (m, 2H), 1.59-1.54 (m, 1H), 1.54-1.51 (m, 1H), 1.54-1.43 (m, 4H), 1.35-1.18 (m, 6H), 1.01 (dq, *J* = 12.4, 4.7 Hz, 1H), 0.86 (s, 3H), 0.82 (s, 3H), 0.85-0.77 (m, 1H)



(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (S26) In a flame-dried 250 mL round bottom flask equipped with a stir bar was added **S25** (3.62 g, 10.89 mmol, 1.0 equiv) and THF (72 mL). The reaction mixture was cooled down to -78 °C

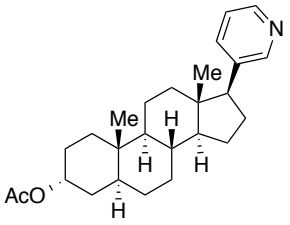
with stirring. LHMDS (2.00g, 11.98 mmol, 1.1 equiv) was dissolved in THF (80 mL), and was slowly transferred via cannula into the reaction mixture. The reaction was stirred for 1 h. $PhN(SO_2CF_3)_2$ (4.28 g, 11.98 mmol, 1.1 equiv) was then dissolved in THF (13.6 mL) and was added dropwise into the reaction mixture via syringe. The reaction was stirred for an additional 20 min and then allowed to warm up to ambient temperature and stirred for an additional hour. Water (10 mL) was then added to quench the reaction and THF was removed in vacuo. Diethyl ether (50 mL) was added to extract the product, and the organic layer was washed with saturated NH_4Cl (20 mL) and brine (20 mL). The organic layer was then separated, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 2→5% EtOAc/hexanes yielded the product as a white solid (2.75 g, 5.92 mmol, 54% yield) with minor $PhN(SO_2CF_3)_2$ as impurity, which was removed in the subsequent step.

The product (2.61 g, 5.62 mmol, 1.0 equiv) was dissolved in DMSO (70 mL) at 60 °C and cannulated into a flame-dried 500 mL Schlenk flask charged with LiCl (1.43 g, 33.7 mmol, 6.0 equiv), $Pd(PPh_3)_4$ (649.4 mg, 0.562 mmol, 0.10 equiv), CuCl (2.78 g, 28.1 mmol, 5.0 equiv), DMSO (150 mL) and a magnetic stir bar. 3-(tributylstannyl)pyridine (3.6 mL, 4.14 g, 11.2 mmol, 2.0 equiv) was then added via syringe. The mixture was degassed through freeze-pump-thaw (-78 °C→0 °C) three times, and was stirred for 1 h at room temperature. The reaction flask was then placed into 60 °C oil bath and stirred vigorously for 20 h. The reaction was then quenched with the mixed solution of concentrated NH_4OH (5.5 mL) and brine (200 mL), extracted with diethyl ether (4x50 mL). The organic layers were then combined, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography on silica eluting with 40% EtOAc/hexanes yielded **S26** as a white powder (1.69 g, 4.30 mmol, 77% yield). Overall yield: 42%.

Data for **S26**:

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 8.61 (s, 1H), 8.45 (d, *J* = 3.0 Hz, 1H), 7.63 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.97 (dd, *J* = 3.2, 1.6 Hz, 1H), 5.04-5.00 (m, 1H), 2.24 (ddd, *J* = 15.7, 6.4, 3.3 Hz, 1H), 2.05 (s, 3H), 2.04-1.98 (m, 1H), 1.81-1.69 (m, 3H), 1.69-1.63 (m, 3H), 1.58 (td, *J* = 11.3, 6.4 Hz, 1H), 1.54-1.46 (m, 4H), 1.46-1.32 (m, 2H), 1.30-1.20 (m, 3H), 1.11-1.02 (m, 1H), 1.00 (s, 3H), 0.94-0.86 (m, 1H), 0.84 (s, 3H)



(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (19): In a flame-dried 200 mL round bottom flask equipped with a stir bar was added (3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*)-10,13-dimethyl-17-(pyridin-3-yl)-2,3,4,5,6,7,8,9,10,11,12,13,14,15-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (**S26**) (1.64 g, 4.17 mmol, 1.0 equiv), THF (39 mL) and DMSO (39 mL). The mixture was cooled down to 0 °C upon stirring, and potassium azodicarboxylate (KOOC—N=N—COOK) (3x5.4 g, 83.3 mmol, 20 equiv) was added in three equal portion over the course of 2 h, each followed by the addition of AcOH (3x3.2 mL, 3x3.33 g, 166.7 mmol, 40 equiv). After adding the last portion of potassium azodicarboxylate, the reaction was allowed to warm to ambient temperature and stirred overnight. The reaction was quenched with brine (100 mL) and extracted with diethyl ether (3x50 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography on silica eluting with 20%→30%→40%→80% EtOAc/hexanes yielded the **19** as a white powder (1.55 g, 3.93 mmol, 94% yield).

Data for **19**:

^{1}H NMR: (500 MHz; $CDCl_3$)

δ 8.49-8.40 (m, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.20 (dd, *J* = 7.1, 5.1 Hz, 1H), 5.03-4.98 (m, 1H), 2.65 (t, *J* = 9.8 Hz, 1H), 2.10-2.01 (m, 4H), 2.01-1.91 (m, 1H), 1.85-1.76 (m, 1H), 1.76-1.68 (m, 2H), 1.68-1.58 (m, 1H), 1.58-1.51 (m, 2H), 1.51-1.44 (m, 4H), 1.44-1.39 (m, 1H), 1.39-1.30 (m, 1H), 1.29-1.23 (m, 2H), 1.23-1.11 (m, 4H), 0.99 (dq, *J* = 12.5, 4.9 Hz, 1H), 0.86-0.79 (m, 1H), 0.78 (s, 3H), 0.46 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.81, 150.52, 147.60, 136.60, 135.72, 122.86, 70.21, 56.47, 54.70, 54.51, 44.63, 40.25, 37.72, 36.05, 33.02, 32.11, 28.47, 26.23, 26.00, 24.54, 21.71, 20.53, 12.90, 11.51

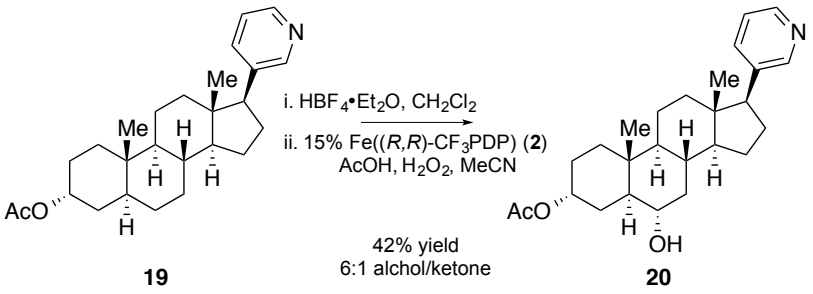
HRMS: (ESI-TOF MS ES+)

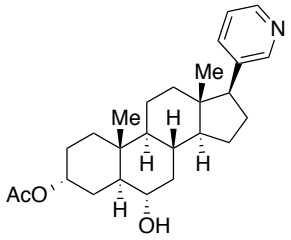
m/z calculated for $C_{26}H_{38}NO_2$ $[M+H]^+$: 396.2903, found 396.2894.

$[\alpha]_D^{25}$ = +17.9° (c = 1.03, CH_2Cl_2).

For HSQC and COSY see Supporting Information: Spectral Data

Scheme S15. Oxidation of Abiraterone Acetate Analog





(3*R*,5*S*,6*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-6-hydroxy-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (20)

(3*R*,5*S*,8*R*,9*S*,10*S*,13*S*,14*S*,17*S*)-10,13-dimethyl-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (**19**) (0.3 mmol, 118.7 mg) was reacted with [Fe((*R,R*)-CF_3PDP)$(MeCN)_2$]$(SbF_6)_2$ (**2**) following the general procedure and the iterative addition protocol. After oxidation MeCN was removed and the crude mixture was dissolved in CH_2Cl_2 (3 mL), saturated $NaHCO_3$ solution (10 mL) was then added and the mixture was stirred vigorously overnight. Purification by MPLC on silica (12 g) eluting with 0→70% EtOAc/hexanes yielded the product as a white crystalline solid. Recovered starting material was recycled twice.

Cycle 1 (21% yield, 25.9 mg, 0.063 mmol; 50% rsm, 59.4 mg, 0.15 mmol)

Cycle 2 (20% yield, 12.4 mg, 0.030 mmol; 50% rsm, 29.8 mg, 0.075 mmol)

Cycle 3 (20% yield, 6.1 mg, 0.015 mmol; 48% rsm, 14.4 mg, 0.036 mmol)

Overall Mass (44.4 mg, 0.11 mmol)

Overall yield: 36% (12% rsm)

Protection with excess HBF_4 (2.0 eq) was also attempted and similar yield was obtained (20% alcohol yield, 24.5 mg, 0.060 mmol; 4% ketone yield, 5.1 mg, 0.012 mmol; 46% rsm, 54.6 mg, 0.14 mmol).

Data for **20**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.50-8.46 (m, 2H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.25 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.17-5.13 (m, 1H), 3.49-3.41 (m, 1H), 2.72 (t, *J* = 9.8 Hz, 1H), 2.17-2.10 (m, 2H), 2.09 (s, 3H), 2.08-1.99 (m, 1H), 1.92-1.84 (m, 1H), 1.83-1.74 (m, 1H), 1.72-1.62 (m, 2H), 1.62-1.57 (m, 2H), 1.57-1.49 (m, 2H), 1.49-1.44 (m, 2H), 1.44-1.39 (m, 1H), 1.39-1.30 (m, 2H), 1.30-1.24 (m, 2H), 1.20 (dq, *J* = 13.4, 3.7 Hz, 1H), 1.04 (q, *J* = 11.9 Hz, 1H), 0.91 (dt, *J* = 11.9, 3.9 Hz, 1H), 0.84 (s, 3H), 0.51 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.75, 150.37, 147.56, 136.44, 135.82, 122.92, 69.67, 69.32, 56.13, 54.57, 53.93, 47.21, 44.59, 41.76, 37.49, 36.72, 34.80, 33.18, 27.43, 25.92, 25.86, 24.50, 21.70, 20.41, 12.87, 12.68

HRMS: (ESI-TOF MS ES+)

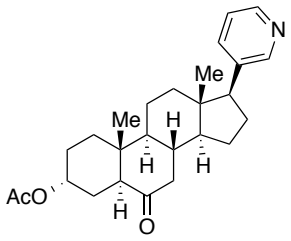
m/z calculated for $C_{26}H_{38}NO_3$ $[M+H]^+$: 412.2852, found 412.2843

$[\alpha]_D^{25}$ = +17.4° (c = 0.78, CH_2Cl_2)

For HSQC, COSY and NOESY see Supporting Information: Spectral Data

Stereochemistry was assigned based on ^{1}H NMR, COSY, HSQC and NOESY 1D NMR methods.

*The site of oxidation was confirmed by oxidizing the product to **20-ketone** using DMP and matching the spectra reported below. The stereochemistry was assigned based on a combination of ^{1}H NMR, COSY, HSQC and NOESY 1D NMR methods.*



(3*R*,5*S*,8*S*,9*S*,10*R*,13*S*,14*S*,17*S*)-10,13-dimethyl-6-oxo-17-(pyridin-3-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl acetate (20-Ketone) Purification by MPLC on silica (12 g) eluting with 0→70% EtOAc/hexanes followed by flash chromatography on silica (10 mL) eluting with 40% EtOAc/hexanes yielded the product as a white crystal.

Cycle 1 (3% yield, 4.3 mg, 0.010 mmol)

Cycle 2 (3% yield, 2.1 mg, 0.0051 mmol)

Cycle 3 (2% yield, 0.6 mg, 0.001 mmol)

Overall Mass (7.0 mg, 0.017 mmol)

Average overall yield: 6%

Data for **20-Ketone**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.45 (s, 2H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.22 (dd, *J* = 7.6, 4.9 Hz, 1H), 5.15-5.09 (m, 1H), 2.72 (t, *J* = 9.8 Hz, 1H), 2.60 (dd, *J* = 12.1, 2.3 Hz, 1H), 2.39 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.16-1.96 (m, 6H), 1.93-1.83 (m, 1H), 1.83-1.75 (m, 3H), 1.75-1.66 (m, 2H), 1.65-1.56 (m, 2H), 1.56-1.49 (m, 2H), 1.49-1.41 (m, 1H), 1.44-1.36 (m, 1H), 1.36-1.26 (m, 2H), 1.26-1.18 (m, 1H), 0.74 (s, 3H), 0.48 (s, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 211.62, 170.39, 150.50, 147.83, 136.01, 135.66, 122.95, 68.90, 56.64, 54.42, 54.02, 52.77, 46.84, 44.92, 41.39, 38.42, 37.18, 32.52, 25.80, 25.39, 25.16, 24.28, 21.58, 20.81, 12.86, 12.61

HRMS: (ESI-TOF MS ES+)

m/z calculated for $C_{26}H_{36}NO_3$ $[M+H]^+$: 410.2695, found 410.2690

$[\alpha]_D^{25}$ = –19.8° (c = 0.51, CH_2Cl_2)

For HSQC and COSY see Supporting Information: Spectral Data

Site of oxidation was confirmed by X-ray crystallography.

Scheme S16. Crystal Structure of 20-Ketone

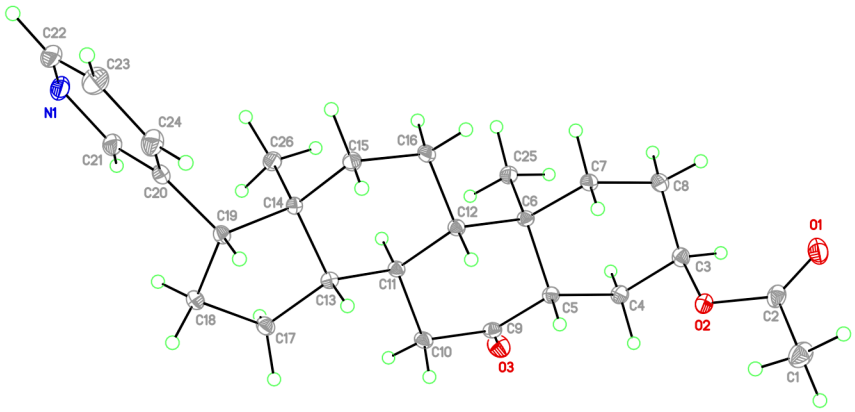
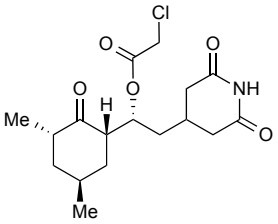


Table S5. Crystal data and structure refinement for cd66ssa (20-Ketone)

Identification code	cd66ssa
Empirical formula	C26 H35 N O3
Formula weight	409.55
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.4928(18) Å a= 90°.
	b = 7.5529(13) Å b= 98.217(4)°.
	c = 13.883(2) Å g = 90°.
Volume	1089.0(3) $Å^3$
Z	2
Density (calculated)	1.249 Mg/m^3
Absorption coefficient	0.633 mm^{-1}
F(000)	444
Crystal size	0.364 x 0.166 x 0.078 mm^3
Theta range for data collection	3.216 to 72.014°.
Index ranges	-12<=h<=12, -8<=k<=9, -17<=l<=15
Reflections collected	14626
Independent reflections	4205 [R(int) = 0.0246]
Completeness to theta = 67.679°	99.9 %
Absorption correction	Integration

Max. and min. transmission	0.96348 and 0.87764
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4205 / 1 / 275
Goodness-of-fit on F^2	1.137
Final R indices [I>2sigma(I)]	R1 = 0.0339, wR2 = 0.0847
R indices (all data)	R1 = 0.0342, wR2 = 0.0850
Absolute structure parameter	0.06(5)
Extinction coefficient	0.066(3)
Largest diff. peak and hole	0.320 and -0.333 e.Å^{-3}



(*R*)-1-((1*S*,3*S*,5*S*)-3,5-dimethyl-2-oxocyclohexyl)-2-(2,6-dioxopiperidin-4-yl)ethyl 2-chloroacetate (21) Prepared according to the literature procedure and spectral data matched that reported.[19]

^{1}H NMR: (400 MHz, Chloroform-*d*)

δ 7.98 (s, 1H), 5.45 – 5.38 (m, 1H), 4.05 (s, 2H), 2.92 (dd, *J* = 17.3, 2.7 Hz, 1H), 2.76 – 2.67 (m, 1H), 2.67 – 2.53 (m, 2H), 2.40 (dd, *J* = 17.4, 10.0 Hz, 1H), 2.28 (dd, *J* = 16.8, 10.3 Hz, 1H), 2.24 – 2.12 (m, 2H), 1.97 – 1.83 (m, 2H), 1.81 – 1.55 (m, 4H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

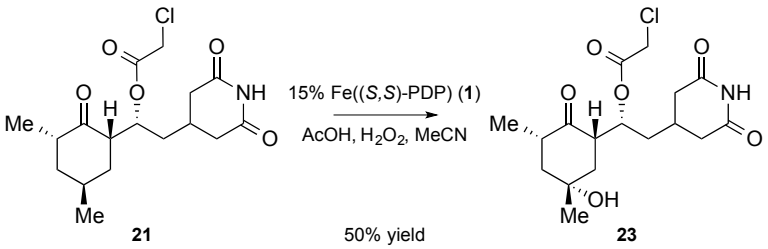
δ 212.0, 171.9, 171.8, 167.1, 71.8, 49.1, 42.7, 40.9, 40.8, 38.6, 38.4, 37.0, 36.1, 27.3, 26.9, 18.2, 14.3

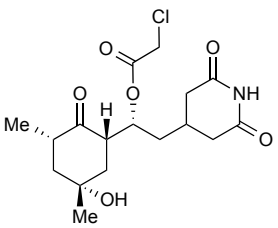
HRMS: (ESI-TOF MS ES+)

m/z: $[M+H]^+$ Calcd for $C_{17}H_{25}NO_5Cl$ 358.1421, found 358.1430

$[\alpha]_D^{25}$ = +9.4° (c = 1.0, $CHCl_3$)

Scheme S17. Oxidation of Cycloheximide Derivative





(*R*)-2-(2,6-dioxopiperidin-4-yl)-1-((1*S*, 3*S*, 5*R*)-5-hydroxy-3,5-dimethyl-2-oxocyclohexyl)ethyl-2-chloroacetate (23) According to the iterative oxidation procedure, cycloheximide-OAcCl (**21**) (107.3 mg, 0.30 mmol, 1 equiv) in MeCN (0.450 mL), [Fe((*S,S*)-PDP)$(MeCN)_2$]$(SbF_6)_2$ (**1**) (14 mg, 0.015 mmol, 0.05 equiv) and AcOH (0.0086 mL, 0.15 mmol,

0.5 equiv) MeCN (0.30 mL), H_2O_2 (0.0205 mL, 0.36 mmol, 1.2 equiv, 50 wt.% in H_2O) in MeCN (2.76 mL) were reacted. Flash chromatography using gradient elution (100% CH_2Cl_2 up to 5% MeOH in CH_2Cl_2) yielded the pure product as an off-white solid.

Run 1 (56 mg, 0.150 mmol, 50% yield; 8 mg, 0.022 mmol, 7% rsm)

Run 2 (56 mg, 0.150 mmol, 50% yield; 12 mg, 0.034 mmol, 11% rsm)

Average yield: 50% (9% rsm)

Data for **23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.78 (s, 1H), 5.40 (t, *J* = 6.8 Hz, 1H), 4.06 (s, 2H), 2.86 (dd, *J* = 17.2, 3.1 Hz, 1H), 2.68 – 2.53 (m, 2H), 2.51 – 2.40 (m, 1H), 2.36 (dd, *J* = 17.2, 10.1 Hz, 1H), 2.26 (dd, *J* = 16.8, 10.5 Hz, 1H), 2.21 – 1.99 (m, 4H), 1.81 – 1.69 (m, 2H), 1.69 – 1.57 (m, 2H), 1.55 (s, 3H), 0.98 (d, *J* = 6.4 Hz, 3H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 210.3, 172.4, 167.2, 71.1, 69.6, 50.0, 48.8, 42.0, 41.9, 41.0, 38.3, 38.3, 36.9, 27.1, 26.2, 14.3

HRMS: (ESI-TOF MS ES+)

m/z: $[M+Na]^+$ Calcd for $C_{17}H_{24}NO_6NaCl$ 396.1190, found 396.1182

$[\alpha]_D^{25}$ = +21.0° (c = 1.0, MeOH)

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