Selective sp^3 C–H Alkylation via Polarity Match Based Cross-Coupling

Chip Le, Yufan Liang, Ryan W. Evans, Ximing Li and David W. C. MacMillan*

Merck Center for Catalysis at Princeton University, Princeton, New Jersey 08544

Supporting Information

Table of Contents

1) General Information

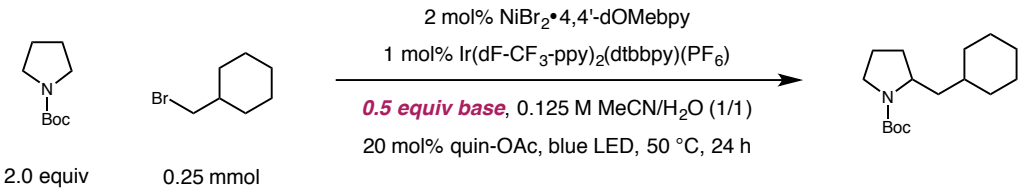
Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] All solvents were purified according to the method of Grubbs.[2] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished by flash chromatography on Silicycle F60 silica gel according to the method of Still.[3] Thin-layer chromatography (TLC) was performed on Analtech 250 micron silica gel plates. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and peaks are reported in terms of frequency of absorption (cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-II 500 (500 and 125 MHz) instrument, and are internally referenced to residual protic solvent signals (note: $CDCl_3$ referenced at δ 7.26 and 77.16 ppm respectively). Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift and no special nomenclature is used for equivalent carbons. High-resolution mass spectra were obtained at Princeton University mass spectrometry facilities. Gas chromatography (GC) was performed on an Agilent 6850 Series chromatograph with splitless capillary injection and FID detection.

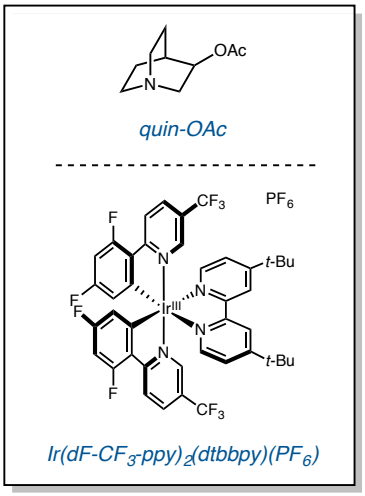
2) Standard reaction setup

In a typical reaction, the reaction mixture is irradiated with 34W Kessil KSH150B from 5 cm away. Regular fans are employed to maintain the temperature at room temperature. For reactions that require elevated temperature, fans are turned off to allow the reaction to reach 50 °C.

3) Reaction optimization

To an oven-dried 8-mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.8 mg, 5.0 μmol, 0.01 equiv.), Ni(II) salt and bipyridyl ligand. MeCN was added and the solution was stirred under nitrogen for 15 minutes to allow for complete complexation. Quinuclidine (as a MeCN solution), inorganic base, amine (2.0 equiv) and alkyl halide (0.25 mmol, 1.0 equiv) were added, followed by addition of water. The reaction was sparged with nitrogen for 15 minutes at 0 °C (ice water bath) before being parafilmed and placed 5 cm away from 34W blue LEDs without fan. The temperature of the reaction is approximately 50 °C. After 12 hours, the reaction was quenched via exposure to air. The organic layer was diluted with EtOAc then biphenyl was added as the internal standard. Aliquot was passed through a plug of celite with EtOAc before samples were submitted for GC analysis.

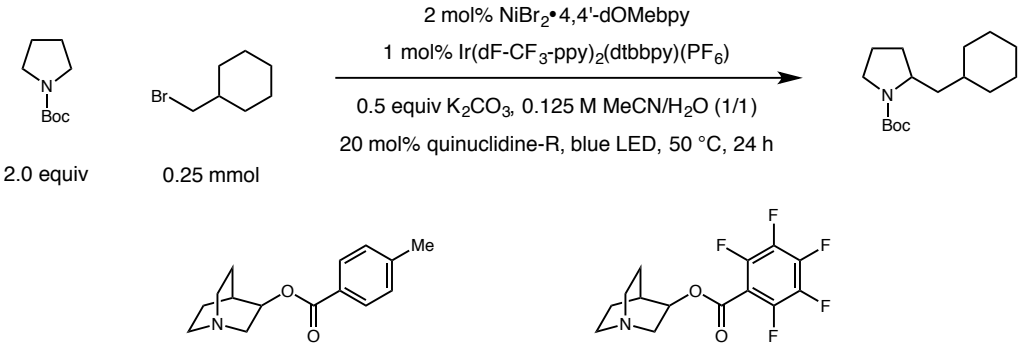




base	Yield
Li_2CO_3	43%
Na_2CO_3	57%
K_2CO_3	57%
Cs_2CO_3	59%
Na_2HPO_4	33%
NaH_2PO_4	3%
$NaHCO_3$	30%
$KHCO_3$	37%

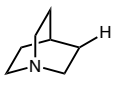
GC yields vs biphenyl

Figure S1: Evaluation of base for HAT-Alkylation Cross-Coupling

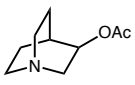


53% yield

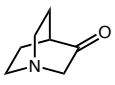
49% yield



57% yield



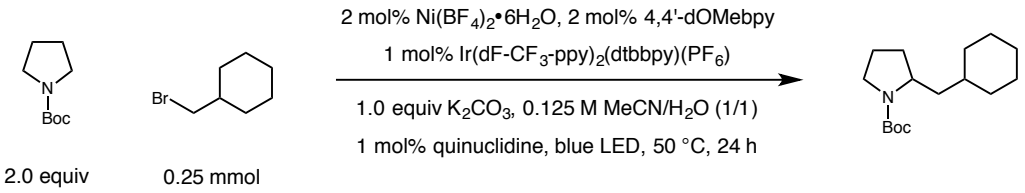
57% yield



57% yield

GC yields vs biphenyl

Figure S2: Evaluation of abstractor for HAT-Alkylation Cross-Coupling



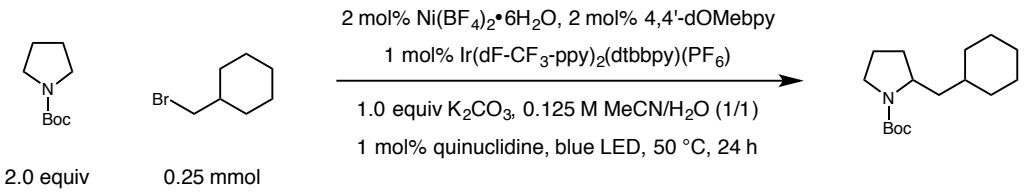
2.0 equiv 0.25 mmol

Deviations from standard	Yield
none	**58%**
2 mol% $NiBr_2$•$3H_2O$	**55%**
2 mol% $Ni(NO_3)_2$•$6H_2O$	**55%**
2 mol% $NiBr_2$•glyme	**58%**
2 mol% $NiCl_2$•glyme	**56%**
2 mol% $Ni(acac)_2$	**59%**

Deviations from standard	Yield
2 mol% 2,2'-bpy	**56%**
2 mol% 4,4'-dMe-2,2'-bpy	**55%**
2 mol% 4,4'-dtbutyl-2,2'-bpy	**58%**
2 mol% 4,4'-dPh-2,2'-bpy	**58%**
2 mol% 1,10-phenanthroline	**56%**
2 mol% 4,7-dOMe-1,10-phen	**51%**

GC yields vs biphenyl

Figure S3: Evaluation of nickel source and ligand



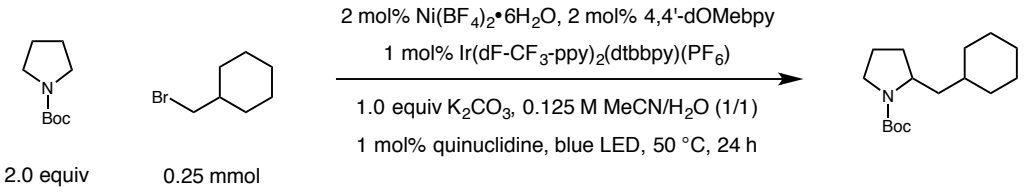
2.0 equiv 0.25 mmol

Deviations from standard	Yield
none	**58%**
5 mol% quinuclidine	**58%**
10 mol% quinuclidine	**57%**

Deviations from standard	Yield
without base	**5%**
0.5 eq K_2CO_3	**46%**
1.0 eq K_2CO_3	**57%**

GC yields vs biphenyl

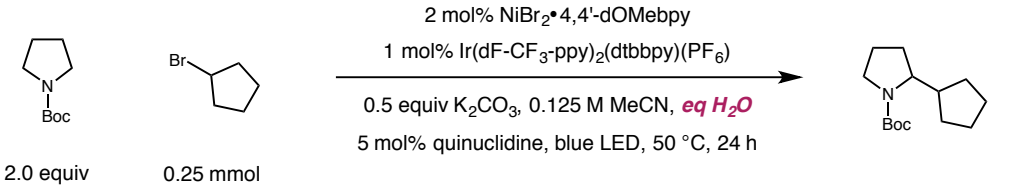
Figure S4: Evaluation of quinuclidine and base equivalent



solvent mixture	Yield
MeCN/H_2O (1/1)	**58%**
MeCN/H_2O (2/1)	**61%**
MeCN/H_2O (3/1)	**60%**
MeCN/H_2O (4/1)	**59%**
MeCN/H_2O (5/1)	**55%**

GC yields vs biphenyl

Figure S5: Effect of solvent mixture with cyclohexylmethyl bromide

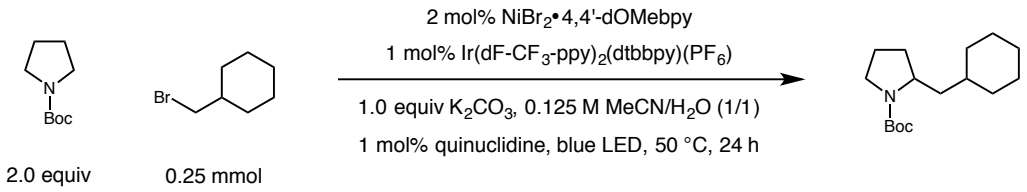


eq Water	Yield
15 eq.	**19%**
25 eq.	**27%**
45 eq.	**42%**
55 eq.	**48%**
65 eq.	**55%**

GC yields vs biphenyl

Figure S6: Effect of solvent mixture with cyclohexylmethyl bromide

4) Control experiments



2.0 equiv 0.25 mmol

Deviations	Yield
None	**64%**
without base	**0%**
without [Ni]	**0%**
without photocat	**0%**
without quinuclidine	**0%**
no light	**0%**

GC yields vs biphenyl

Figure S7: Control experiments for HAT-Alkylation Cross-Coupling

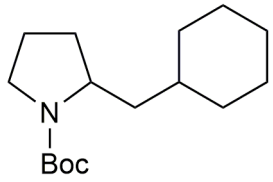
5) General procedure for HAT-Alkylation protocol

To an oven-dried 8-mL vial equipped with a stir bar was added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), Ni(II) salt and bipyridyl ligand. MeCN was added and the solution was stirred under nitrogen for 15 minutes to allow for complete complexation. Quinuclidine (as a MeCN solution), inorganic base, amine (1.00 mmol, 2.0 equiv.) and alkyl halide (0.50 mmol, 1.0 equiv) were added, followed by addition of water. The reaction was sparged with nitrogen for 15 minutes at 0 °C (ice water bath) before being parafilmed and placed 5 cm away from 34W blue LEDs without fan. The temperature of the reaction is approximately 50 °C. After 24 hours, the reaction was quenched via exposure to air. The organic layer was diluted with EtOAc then washed with $NaHCO_3$ (saturated, aq) and brine. The organic layer was then separated, dried with $MgSO_4$ and concentrated to give the crude product. Purification by column chromatography yields the pure product. In all reported examples, the remaining untouched nucleophile can be recovered during purification in good yields.

It is worth noting that while alkylation of ether moieties is shown to be feasible, these reactions often require large excess of the nucleophile to proceed in good yields.

Consistent with this observation, in cases where amide and ether motifs are both present in the reaction mixture, alkylation was only observed at the α-C–H to the nitrogen. We hypothesize that the difference in hydricity of the α-C–H, coupled with the nucleophilicity of the radical are major contributors to this selectivity.

6) HAT-Alkylation of N-Boc Pyrrolidine



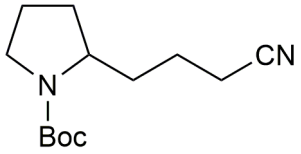
(±)-*tert*-butyl 2-(cyclohexylmethyl)pyrrolidine-1-carboxylate (13)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (78 mg, 0.29 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 – 3.76 (m, 1H), 3.43 – 3.24 (m, 2H), 1.96 – 1.76 (m, 4H), 1.76 – 1.56 (m, 6H), 1.56 – 1.39 (s, 9H), 1.34 – 1.09 (m, 5H), 1.05 – 0.80 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 79.0, 55.2, 46.1, 42.3, 35.5, 34.6, 32.8, 30.7, 28.8, 26.8, 26.6, 26.4, 23.3.

Data are consistent with those reported in the literature: C.P. Johnson, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature,* **535**, 322-325 (2016).



(±)-*tert*-butyl 2-(3-cyanopropyl)pyrrolidine-1-carboxylate (14)

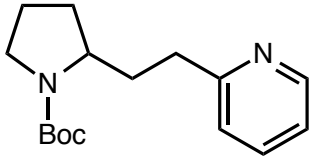
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), 4-bromobutanenitrile (74.0 mg, 49.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 10% to 30% EtOAc in hexanes) yielded the pure product as a clear oil (98 mg, 0.41 mmol, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.00 – 3.64 (m, 1H), 3.64 – 3.19 (m, 2H), 2.56 – 2.24 (m, 2H), 2.08 – 1.74 (m, 4H), 1.74 – 1.55 (m, 4H), 1.55 – 1.35 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 119.6, 79.2, 78.9, 56.1, 46.3, 45.9, 33.8, 33.5, 30.7, 30.1, 28.3, 23.6, 22.9, 22.4, 22.2, 17.1, 16.9.

IR (film) ν_{max} 2970, 2874, 1687, 1478, 1455, 1393, 1365, 1251, 1168, 1124, 1104 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{22}N_2NaO_2$ ($[M+Na]^+$) 261.1574, found 261.1573.



(±)-*tert*-butyl 2-(2-(pyridin-2-yl)ethyl)pyrrolidine-1-carboxylate (15)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-

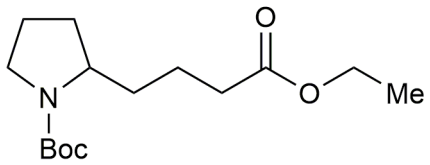
carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 2-(2-bromoethyl)pyridine hydrobromide (133 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (105 mg, 0.75 mmol, 1.5 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 10% to 30% EtOAc in hexanes) yielded the pure product as a clear oil (62 mg, 0.22 mmol, 43% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.19 – 6.96 (m, 2H), 3.79 (m, 1H), 3.45 – 3.12 (m, 2H), 2.84 – 2.56 (m, 2H), 2.19 – 1.96 (m, 1H), 1.94 – 1.78 (m, 2H), 1.71 (m, 3H), 1.37 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 154.7, 149.2, 136.4, 122.6, 121.0, 79.1, 56.9, 46.1, 35.4, 34.8, 30.7, 28.6, 23.8.

IR (film) ν_{max} 2970, 2873, 1688, 1392, 1363, 1168, 1119, 1103 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{25}N_2O_2$ ($[M+H]^+$) 276.1838, found 276.1833.



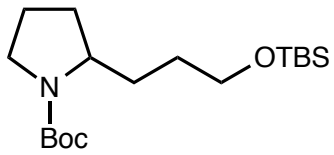
(±)-*tert*-butyl 2-(4-ethoxy-4-oxobutyl)pyrrolidine-1-carboxylate (16)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), ethyl 4-bromobutanoate (97.5 mg, 71.5 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (81 mg, 0.28 mmol, 58% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.20 – 4.08 (q, *J* = 7.0 Hz, 2H), 3.82 – 3.70 (m, 1H), 3.44 – 3.35 (m, 1H), 3.35 – 3.26 (m, 1H), 2.42 – 2.24 (m, 2H), 2.00 – 1.71 (m, 4H), 1.71 – 1.54 (m, 4H), 1.54 – 1.42 (s, 9H), 1.31 – 1.18 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 173.4, 154.6, 79.1, 78.8, 60.2, 56.9, 46.5, 46.0, 34.2, 33.6, 30.7, 29.8, 28.5, 23.8, 23.0, 21.8, 14.2.

Data are consistent with those reported in the literature: F. Abels, C. Lindemann, E. Koch, C. Schneider, *Org. Lett.* **14**(23), 5972-5975 (2012).



(±)-*tert*-butyl 2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)pyrrolidine-1-carboxylate (17)

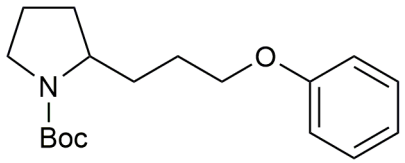
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), (3-bromopropoxy)(*tert*-butyl)dimethylsilane (89 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (105 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 10% to 30% EtOAc in hexanes) yielded the pure product as a clear oil (116 mg, 0.34 mmol, 68% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 – 3.64 (m, 1H), 3.64 – 3.48 (m, 2H), 3.43 – 3.18 (m, 2H), 1.96 – 1.55 (m, 5H), 1.42 (m, 11H), 1.36 – 1.26 (m, 1H), 0.85 (s, 9H), 0.00 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.6, 78.7, 63.2, 57.1, 46.0, 31.2, 29.8, 28.5, 25.9, 23.0, 18.3, 5.3.

IR (film) ν_{max} 2954, 2929, 2858, 1693, 1389, 1364, 1251, 1168, 1096, cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{38}NO_3Si$ ($[M+H]^+$) 343.2543, found 343.2541.



(±)-*tert*-butyl 2-(3-phenoxypropyl)pyrrolidine-1-carboxylate (18)

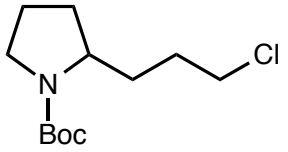
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), (3-bromopropoxy)benzene (107.5 mg, 78.8 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (110 mg, 0.36 mmol, 72% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.19 (m, 2H), 7.00 – 6.83 (m, 3H), 4.05 – 3.89 (m, 2H), 3.89 – 3.69 (m, 1H), 3.48 – 3.35 (m, 1H), 3.35 – 3.21 (m, 1H), 2.10 – 1.72 (m, 6H), 1.72 – 1.56 (m, 2H), 1.55 – 1.39 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 154.8, 129.6, 120.7, 114.6, 79.2, 67.9, 57.6, 57.2, 46.5, 45.9, 31.1, 30.6, 28.9, 28.7, 26.4.

IR (film) ν_{max} 2969, 2872, 1689, 1600, 1497, 1391, 1365, 1244, 1169, 1107 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{27}NNaO_3$ ($[M+Na]^+$) 328.1883, found 328.1884.



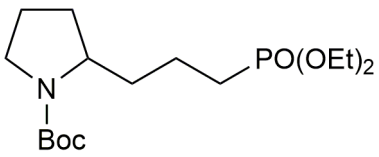
(±)-*tert*-butyl 2-(3-chloropropyl)pyrrolidine-1-carboxylate (19)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 1-bromo-3-chloropropane (79 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (105 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 3% to 5% Ether in Toluene) yielded the pure product as a clear oil (81 mg, 0.33 mmol, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 – 3.64 (m, 1H), 3.55 (m, 2H), 3.36 (m, 2H), 2.02 – 1.70 (m, 6H), 1.63 (m, 1H), 1.46 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 153.8, 79.3, 57.0, 56.6, 46.5, 46.1, 45.0, 32.2, 31.8, 31.5, 30.9, 30.4, 30.1, 30.0, 29.7, 29.6, 27.8, 26.8, 23.8, 23.1.

Data are consistent with those reported in the literature: C.P. Johnson, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature,* **535**, 322-325 (2016).



(±)-*tert*-butyl 2-(3-(diethoxyphosphoryl)propyl)pyrrolidine-1-carboxylate (20)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), diethyl (3-

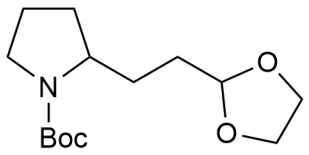
bromopropyl)phosphonate (129.5 mg, 96.1 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 50% to 100% EtOAc in hexanes) yielded the pure product as a clear oil (99 mg, 0.28 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 – 3.85 (m, 4H), 3.84 – 3.54 (m, 1H), 3.54 – 3.04 (m, 2H), 1.96 – 1.67 (m, 6H), 1.67 – 1.51 (m, 4H), 1.49 – 1.41 (s, 9H), 1.34 – 1.25 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 78.5, 78.2, 60.8, 56.2, 45.9, 45.5, 35.4, 34.4, 30.3, 29.3, 28.0, 25.8, 24.5, 23.3, 22.5, 19.0, 16.0.

IR (film) ν_{max} 2974, 2934, 1689, 1392, 1365, 1241, 1167, 1106, 1055, 1028 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{32}NNaO_5P$ ($[M+Na]^+$) 372.1910, found 372.1909.



(±)-*tert*-butyl 2-(2-(1,3-dioxolan-2-yl)ethyl)pyrrolidine-1-carboxylate (21)

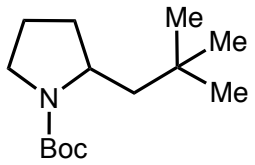
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), 2-(2-bromoethyl)-1,3-dioxolane (90.5 mg, 58.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 3:1 hexane:EtOAc) yielded the pure product as a clear oil (85 mg, 0.31 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 – 4.78 (m, 1H), 3.95 – 3.65 (m, 5H), 3.40 – 3.20 (m, 2H), 1.94 – 1.67 (m, 4H), 1.65 – 1.52 (m, 3H), 1.45 – 1.36 (m, 10H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 104.5, 104.4, 79.1, 78.8, 64.9, 64.9, 57.0, 46.6, 46.1, 30.8, 29.9, 29.1, 28.6, 23.8, 23.1.

IR (film) ν_{max} 2971, 2878, 1690, 1394, 1366, 1167 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{25}NNaO_4$ ($[M+Na]^+$) 294.1676, found 294.1676.



(±)-*tert*-butyl 2-neopentylpyrrolidine-1-carboxylate (22)

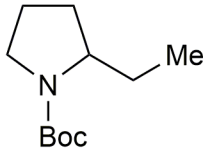
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (11.0 mg, 50.0 μmol, 0.10 equiv.), MeCN (3.2 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), 1-bromo-2,2-dimethylpropane (75.5 mg, 63.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.8 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (54 mg, 0.23 mmol, 46% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 – 3.74 (m, 1H), 3.38 – 3.22 (m, 2H), 2.00 – 1.89 (m, 1H), 1.89 – 1.73 (m, 2H), 1.73 – 1.65 (m, 1H), 1.65 – 1.59 (m, 1H), 1.52 – 1.41 (s, 9H), 1.30 – 1.17 (m, 1H), 1.03 – 0.90 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.55, 79.2, 54.6, 48.6, 45.9, 32.9, 30.4, 28.9, 23.4.

IR (film) ν_{max} 2957, 2872, 1694, 1477, 1392, 1364, 1247, 1171, 1114, 1096 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{27}NNaO_2$ ($[M+Na]^+$) 264.1934, found 264.1932.



(±)-*tert*-butyl 2-ethylpyrrolidine-1-carboxylate (23)

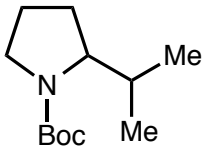
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (11.0 mg, 50.0 μmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.2 mg, 175.2 μL, 1.00 mmol, 2.0 equiv.), bromoethane (54.0 mg, 36.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (0.4 mL). Purification by column chromatography (silica gel, gradient 3% to 10% ether in hexanes) yielded the pure product as a clear oil (55 mg, 0.28 mmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.95 – 3.56 (m, 1H), 3.55 – 3.12 (m, 2H), 2.15 – 1.74 (m, 4H), 1.74 – 1.9 (m, 2H), 1.59 – 1.40 (s, 9H), 0.80 (t, J = 7.7 Hz, 3H)

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 78.8, 58.7, 46.6, 46.2, 30.2, 29.3, 28.6, 27.5, 26.8, 23.8, 23.1, 10.6.

IR (film) ν_{max} 2968, 2932, 2876, 1694, 1478, 1456, 1392, 1364, 1255, 1171, 1139, 1107 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{21}NNaO_2$ ($[M+Na]^+$) 222.1465, found 222.1459.



(±)-*tert*-butyl 2-isopropylpyrrolidine-1-carboxylate (24)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (6.8 mg, 20.0 μmol, 0.04 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (4.32 mg, 20.0 μmol, 0.04

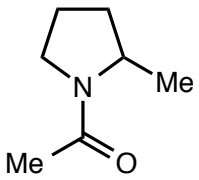
equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 2-bromopropane (61.5 mg, 47.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (95 eq, 0.86 mL). Purification by column chromatography (silica gel, gradient 5% to 20% ether in hexanes) yielded the pure product as a clear oil (56 mg, 0.26 mmol, 53% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.69 (m, 1H), 3.57 – 3.46 (m, 1H), 3.23 (m, 1H), 2.12 (m, 1H), 1.91 – 1.65 (m, 4H), 1.47 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 1H), 0.81 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 78.9, 62.3, 46.9, 30.5, 26.2, 24.0, 19.6, 16.9.

IR (film) ν_{max} 2965, 2874, 1689, 1455, 1383, 1164, 1102 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_8H_{16}NO_2$ ($[M–tBu+H]^+$) 157.1103, found 157.1106



(±)-1-(2-methylpyrrolidin-1-yl)ethan-1-one (25)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiBr_2$•diglyme (3.25 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), Acetone (4.0 mL), methyl tosylate (93 mg, 0.50 mmol, 1.00 equiv.), 1-(pyrrolidin-1-yl)ethan-1-one (113.0 mg, 1.00 mmol, 2.0 equiv.), CsBr (128 mg, 0.60 mmol, 1.2 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.). Purification by column chromatography (silica gel, gradient 5% to 30% ether in pentanes) yielded the pure product as a clear oil (39 mg, 0.31 mmol, 61% yield).

We found the inclusion of quinuclidine was slightly detrimental to the reaction. Under these conditions, slightly diminished yield was observed upon addition of quinuclidine, presumably due to consumption of the methyl tosylate via an SN2 process. During the course of our studies, this is the only case where

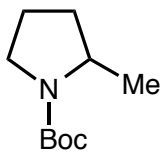
quinuclidine proved unproductive for the desired transformation. As the control experiment has shown, absence of quinuclidine resulted in zero reactivity. We believe that for the methylation case, an alternate mechanism involving C–H abstraction via a bromide radical can be operative. For recent examples of such a mechanism see: (1) *J. Am. Chem. Soc.*, **2016**, *138*, 8084, (2) *J. Am. Chem. Soc.* **2016**, *138*, 12719 ,and (3) *J. Am. Chem. Soc.*, **2016**, *138* (39), 12715. In addition, while methyl iodide fails to furnish any of the desired product, methyl bromide gives similar yields. Ultimately, methyl tosylate, which undergoes an *in-situ* SN2 with bromide anion to give methyl bromide, was chosen due the ease of operation.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18, 3.95 (m, 1H), 3.95, 3.52 – 3.30 (m, 2H), 2.08, 2.01 (s, 3H) 2.10 – 1.82 (m, 3H), 1.71 – 1.53 (m, 1H), 1.18 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 53.9, 52.6, 47.6, 45.5, 33.2, 32.0, 23.8, 22.9, 22.1, 22.0, 21.0, 19.5.

IR (film) ν_{max} 2968, 2876, 1615, 1417, 1349, 1198, 1172 cm^{-1}.

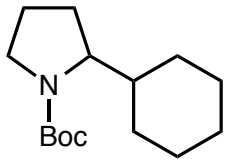
HRMS (ESI-TOF) m/z calcd. for $C_7H_{13}NO$ ($[M+H]^+$) 127.0997, found 127.0997.



(±)-*tert*-butyl 2-methylpyrrolidine-1-carboxylate (26)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiBr_2$•diglyme (3.25 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), Acetonitrile (4.0 mL), methyl tosylate (93 mg, 0.50 mmol, 1.00 equiv.), 1-(pyrrolidin-1-yl)ethan-1-one (113.0 mg, 1.00 mmol, 2.0 equiv.), CsBr (128 mg, 0.60 mmol, 1.2 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.). This yielded an inseperable mixture of product

and starting material, and 41% yield (average of three reactions: 42% yield, 39% yield, and 41% yield) was calculated from a calibrated GC assay after the addition of a standard (biphenyl). (average of three reactions: 42% yield, 39% yield, and 41% yield) (Authentic product was synthesized following the procedure from C. P. Johnston, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature*. **536**, 322–325 (2016)).



(±)-*tert*-butyl 2-cyclohexylpyrrolidine-1-carboxylate (27)

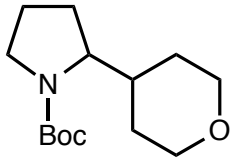
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclohexane (82 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (60 eq, 0.54 mL). Purification by column chromatography (silica gel, gradient 2% to 5% EtOAc in hexanes) yielded the pure product as a clear oil (66 mg, 0.26 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (m, 1H), 3.52 – 3.37 (m, 1H), 3.27 – 3.14 (m, 1H), 1.84 – 1.53 (m, 10H), 1.46 (s, 9H), 1.27 – 0.85 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 78.8, 61.8, 46.7, 41.1, 30.1, 28.6, 28.0, 26.6, 26.6, 26.3.

IR (film) ν_{max} 2972, 2924, 2852, 1689, 1388, 1363, 1376, 1164, 1105 cm^{-1}

HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{20}NO_2$ ($[M–tBu+H]^+$) 197.1416, found 197.1412.



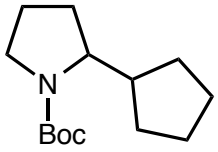
(±)-*tert*-butyl 2-(tetrahydro-2*H*-pyran-4-yl)pyrrolidine-1-carboxylate (28)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 4-bromotetrahydro-2H-pyran (83 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 5% to 15% EtOAc in hexanes) yielded the pure product as a clear oil (89 mg, 0.35 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.08 – 3.94 (m, 2H), 3.74 (s, 1H), 3.48 (s, 1H), 3.35 (m, 2H), 3.23 (m, 1H), 1.89 – 1.73 (m, 5H), 1.47 (s, 12H), 1.42 – 1.29 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 79.2, 68.2, 68.0, 61.2, 47.0, 46.4, 39.0, 38.2, 30.1, 28.6, 27.8, 26.5, 24.3, 23.4.

Data are consistent with those reported in the literature: C.P. Johnson, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature,* **535**, 322-325 (2016).



(±)-*tert*-butyl 2-cyclopentylpyrrolidine-1-carboxylate (29)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclopentane (62 mg, 0.50 mmol, 1.0 equiv.),

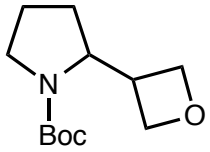
K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 2% to 5% EtOAc in hexanes) yielded the pure product as a clear oil (66 mg, 0.26 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 – 3.77 (m, 1H), 3.46 (m, 1H), 3.33 – 3.16 (m, 1H), 2.05 (m, 1H), 1.92 – 1.75 (m, 3H), 1.73 – 1.57 (m, 5H), 1.56 – 1.48 (m, 2H), 1.46 (s, 9H), 1.42 – 1.33 (m, 1H), 1.23 – 1.12 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 78.8, 60.7, 46.3, 44.3, 30.0, 28.8, 28.5, 25.3, 25.1.

IR (film) ν_{max} 2953, 2869, 1689, 1385, 1363, 1167, 1103 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{25}NNaO_2$ ($[M+Na]^+$) 239.1885, found 239.1881.



(±)-*tert*-butyl 2-(oxetan-3-yl)pyrrolidine-1-carboxylate (30)

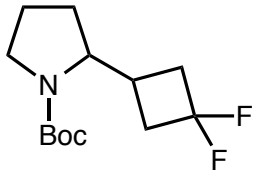
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 3-bromooxetane (68.5 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (60 eq, 0.54 mL). Purification by column chromatography (silica gel, gradient 5% to 15% EtOAc in hexanes) yielded the pure product as a clear oil (81 mg, 0.36 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.81 (m, 1H), 4.68 (dd, J = 8.1, 6.2 Hz, 1H), 4.64 (dd, J = 8.4, 6.1 Hz, 1H), 4.50 (t, J = 6.7 Hz, 1H), 4.14 (tt, J = 7.3, 3.7 Hz, 1H), 3.56 – 3.34 (m, 1H), 3.36 – 3.13 (m, 2H), 2.00 (m, 1H), 1.82 (m, 2H), 1.59 (m, 1H), 1.47 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 80.0, 76.2, 73.9, 58.8, 46.6, 40.1, 28.5, 22.9.

IR (film) ν_{max} 2971, 2874, 1688, 1386, 1342, 1250, 1164, 1104, cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{21}NO_3Na$ ($[M+Na]^+$) 227.1521, found 227.1518.



(±)-*tert*-butyl 2-(3,3-difluorocyclobutyl)pyrrolidine-1-carboxylate (31)

Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (2.9 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), 3-bromo-1,1-difluorocyclobutane (85 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.68 mL). Purification by column chromatography (silica gel, gradient 5% to 10% ether in hexanes) yielded the pure product as a clear oil (85.5 mg, 0.33 mmol, 65% yield).

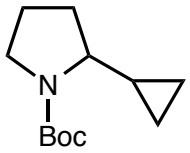
^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 – 3.83 (m, 1H), 3.42 (s, 1H), 3.36 – 3.25 (m, 2H), 2.70 – 2.45 (m, 3H), 2.36 – 2.14 (m, 2H), 1.98 – 1.77 (m, 4H), 1.62 – 1.54 (m, 1H), 1.46 (d, J = 1.9 Hz, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 119.6 (dd, J = 286.0, 270.1 Hz), 79.6, 60.4, 46.7, 38.8 (dd, J = 23.7, 21.6 Hz), 38.0 (dd, J = 23.7, 21.6 Hz), 28.4, 28.2, 25.4.

^{19}F NMR (282 MHz, $CDCl_3$) δ -81.48 – -82.87 (m, 1F), -98.68 – -99.90 (m, 0.78F), -102.16 (dp, J = 191.9, 17.1 Hz, 0.13F).

IR (film) ν_{max} 2973, 2882, 1689, 1384, 1365, 1293, 1163, 1105 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_9H_{14}NO_2F_2$ ($[M–tBu+H]^+$) 205.0914, found 205.0913.



(±)-*tert*-butyl 2-cyclopropylpyrrolidine-1-carboxylate (32)

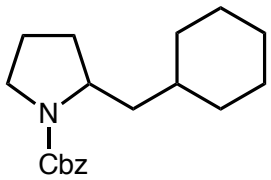
Prepared following the general procedure outlined above using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $NiBr_2$•diglyme (3.5 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (2.2 mg, 10.0 μmol, 0.02 equiv.), MeCN (4.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl pyrrolidine-1-carboxylate (171.0 mg, 1.00 mmol, 2.0 equiv.), bromocyclopropane (61 mg, 0.50 mmol, 1.0 equiv.), K_2CO_3 (70 mg, 0.50 mmol, 1.0 equiv.) and water (75 eq, 0.67 mL). Purification by column chromatography (silica gel, gradient 5% to 20% ether in hexanes) yielded the pure product as a clear oil (48 mg, 0.23 mmol, 43% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 – 3.26 (m, 3H), 2.00 – 1.67 (m, 4H), 1.46 (s, 9H), 0.86 (m, 1H), 0.53 (m, 1H), 0.47 (m, 1H), 0.35 (m, 1H), 0.12 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 79.1, 60.9, 46.7, 31.5, 28.7, 23.6, 16.0, 4.5, 1.8.

Data are consistent with those reported in the literature: C.P. Johnson, R. T. Smith, S. Allmendinger, D. W. C. MacMillan, *Nature,* **535**, 322-325 (2016).

7) HAT-Alkylation with cyclohexylmethyl bromide



(±)-benzyl 2-(cyclohexylmethyl)pyrrolidine-1-carboxylate (33)

Prepared following the general procedure outlined above (with fan cooling) using

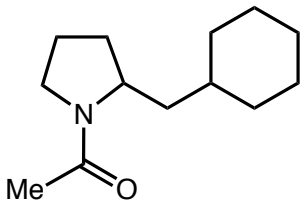
$Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-di-*tert*-butyl-2,2'-bipyridine (2.7 mg, 10.0 μmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), benzyl pyrrolidine-1-carboxylate (205.3 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc) yielded the pure product as a clear oil (85 mg, 0.28 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.17 – 5.07 (m, 2H), 4.03 – 3.84 (m, 1H), 3.50 – 3.33 (m, 2H), 1.97 – 1.43 (m, 10H), 1.36 – 1.06 (m, 5H), 1.04 – 0.66 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 154.5, 137.1, 136.8, 128.2, 127.8, 127.64, 127.57, 127.54, 66.5, 66.1, 55.6, 55.0, 46.1, 45.8, 42.2, 41.4, 35.1, 35.0, 34.2, 32.4, 30.8, 30.0, 26.5, 26.40, 26.3, 26.0, 25.9, 23.6, 22.7.

IR (film) ν_{max} 2921, 2850, 1698, 1447, 1408,1357,1100 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{27}NNaO_2$ ($[M+Na]^+$) 324.1934, found 324.1936.



(±)-1-(2-(cyclohexylmethyl)pyrrolidin-1-yl)ethan-1-one (34)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), 1-acetylpyrrolidine (113 mg, 110 μL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and

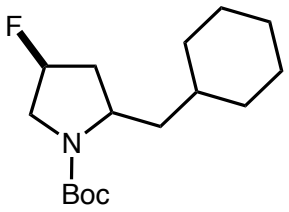
water (2 mL). Reaction time: 12 h. Purification by column chromatography (silica gel, 1:2 hexane:EtOAc) yielded the pure product as a clear oil (77 mg, 0.37 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 – 4.12 and 3.84 – 3.79 (m, 1H, rotamer), 3.48 – 3.28 (m, 2H), 2.03 and 1.97 (s, 3H, rotamer), 1.95 – 1.73 (m, 4H), 1.71 – 1.55 (m, 5H), 1.33 – 1.29 (m, 1H), 1.26 – 0.84 (m, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.84, 168.81, 56.4, 55.0, 47.4, 45.2, 42.5, 40.9, 35.5, 35.3, 34.5, 34.4, 32.4, 32.4, 30.5, 29.6, 26.6, 26.5, 26.4, 26.3, 26.2, 26.1, 24.0, 23.1, 22.2, 22.1.

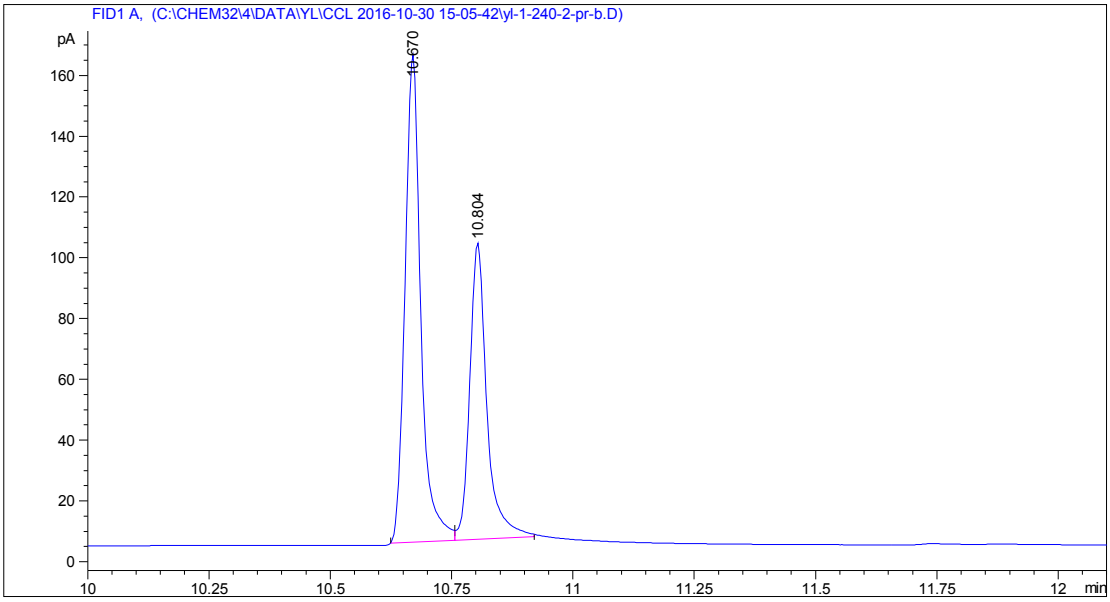
IR (film) ν_{max} 2922, 2851, 1637, 1447, 1415 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{13}H_{24}NO$ ($[M+H]^+$) 210.1852, found 210.1853.



***tert*-butyl (4*S*)-2-(cyclohexylmethyl)-4-fluoropyrrolidine-1-carboxylate (35)**

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (3.4 mg, 10.0 μmol, 0.02 equiv.), 4,4'-dimethyl-2,2'-bipyridine (1.8 mg, 10.0 μmol, 0.02 equiv.), MeCN (2.4 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), (S)-*tert*-butyl 3-fluoropyrrolidine-1-carboxylate (189.2 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (88.5 mg, 69.7 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.) and water (1.6 mL). Reaction time: 24 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc) yielded the pure product as a clear oil (105 mg, 0.37 mmol, 74% yield, 1.5:1 d.r. by ^{19}F NMR and GC).



Signal 1: FID1 A,

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	10.670	BV	0.0342	360.98373	160.49733	60.17228
2	10.804	VB	0.0366	238.93327	97.51319	39.82772
Totals :				599.91701	258.01052	

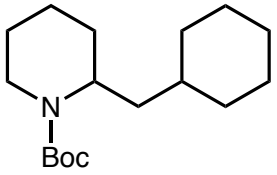
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.25 – 5.00 (m, 1H), 4.14 – 3.20 (m, 3H), 2.45 – 1.55 (m, 8H), 1.44 (s, 9H), 1.26 – 1.05 (m, 5H), 1.00 – 0.82 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 154.3, 94.4, 93.6, 93.0, 92.7, 92.4, 92.2, 91.3, 91.0, 79.6, 54.8, 53.9, 53.1, 53.0, 52.8, 52.5, 52.3, 43.7, 42.4, 41.7, 39.8, 39.6, 38.9, 37.2, 37.1, 36.2, 36.0, 35.2, 35.0, 34.6, 34.2, 32.8, 32.6, 28.6, 26.7, 26.6, 26.5, 26.31, 26.25.

^{19}F NMR (282 MHz, $CDCl_3$) δ -168.4 – -170.0 (m, 0.4F), -176.7 – -178.0 (m, 0.6F).

IR (film) ν_{max} 2975, 2923, 2852, 1694, 1449, 1395, 1365, 1275, 1258, 1163, 1113 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{28}FNNaO_2$ ($[M+Na]^+$) 308.1996, found 308.1996.



(±)-*tert*-butyl 2-(cyclohexylmethyl)piperidine-1-carboxylate (36)

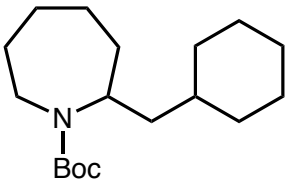
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.8 mg, 2.5 μmol, 0.005 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50 μmol, 0.10 equiv.), *N*-Boc piperidine (463 mg, 0.48 mL, 2.50 mmol, 5.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 18 h. Purification by column chromatography (silica gel, 30:1 hexane:EtOAc) yielded the pure product as a clear oil (59 mg, 0.21 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.30 (br s, 1H), 3.96 (br s, 1H), 2.80 – 2.66 (m, 1H), 1.91 – 1.83 (m, 1H), 1.71 – 1.50 (m, 10H), 1.44 (s, 9H), 1.40 – 1.30 (m, 1H), 1.23 – 1.08 (m, 5H), 0.98 – 0.78 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 79.1, 48.0, 38.4, 37.6, 34.4, 34.0, 33.5, 29.1, 28.6, 26.8, 26.6, 26.5, 25.9, 19.2.

IR (film) ν_{max} 2922, 2852, 1689, 1448, 1415, 1364, 1269, 1252, 1182, 1161, 1150 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{31}NNaO_2$ ($[M+Na]^+$) 304.2247, found 304.2249.



(±)-*tert*-butyl 2-(cyclohexylmethyl)azepane-1-carboxylate (37)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg,

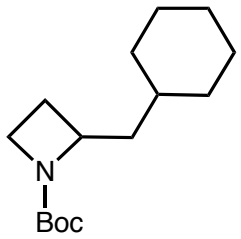
50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), *N*-Boc azepane (199 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 20:1 hexane:EtOAc) yielded the pure product as a clear oil (123 mg, 0.42 mmol, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.16 – 4.09 and 3.97 – 3.90 (m, 1H, rotamer), 3.65 – 3.59 and 3.52 – 3.46 (m, 1H, rotamer), 2.61 – 2.54 (m, 1H), 2.00 – 1.88 (m, 1H), 1.84 – 1.48 (m, 9H), 1.40 and 1.39 (s, 9H, rotamer), 1.25 – 0.97 (m, 9H), 0.92 – 0.70 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 155.7, 78.9, 78.5, 52.4, 51.6, 46.9, 46.5, 43.1, 42.7, 41.4, 41.1, 35.3, 34.7, 34.5, 34.2, 33.8, 33.7, 33.6, 33.4, 30.0, 30.0, 28.9, 28.6, 28.5, 28.2, 26.69, 26.65, 26.5, 26.4, 25.0, 24.8.

IR (film) ν_{max} 2920, 2852, 1687, 1411, 1364, 1172, 1157, 982 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{18}H_{33}NNaO_2$ ($[M+Na]^+$) 318.2404, found 318.2401.



(±)-*tert*-butyl 2-(cyclohexylmethyl)azetidine-1-carboxylate (38)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), *N*-Boc azetidine (157 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 17 h. Purification by column chromatography (silica gel, 15:1 hexane:EtOAc)

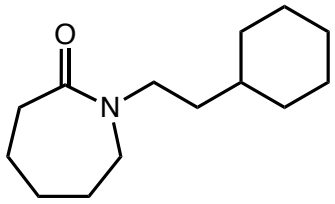
yielded the pure product as a clear oil (70 mg, 0.276 mmol, 55% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 – 4.18 (m, 1H), 3.81 – 3.72 (m, 2H), 2.26 – 2.19 (m, 1H), 1.90 – 1.72 (m, 2H), 1.68 – 1.56 (m, 5H), 1.45 – 1.35 (m, 10H), 1.32 – 1.07 (m, 4H), 0.97 – 0.83 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 156.8, 79.1, 60.8, 46.5, 43.7, 34.4, 33.9, 33.4, 28.6, 26.6, 26.4, 26.3, 23.2.

IR (film) ν_{max} 2922, 2852, 1700, 1449, 1364, 1254, 1182, 1134 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{27}NNaO_2$ ($[M+Na]^+$) 276.1934, found 276.1932.



1-(2-cyclohexylethyl)azepan-2-one (39)

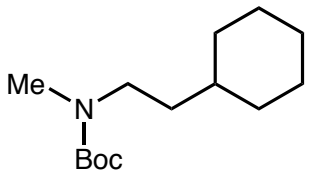
Prepared following the general procedure outlined above (*with* fan) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethyl-2,2'-bipyridine (9.2 mg, 50.0 μmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50 μmol, 0.10 equiv.), *N*-methylcaprolactam (191 mg, 192 μL, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (0.4 mL). After stirring for 12 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs with a fan. Continue stirring for another 24 h. Purification by column chromatography (silica gel, 1:1 hexane:EtOAc) yielded the pure product as a clear oil (56 mg, 0.25 mmol, 50% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.34 – 3.29 (m, 2H), 3.28 – 3.23 (m, 2H), 2.46 – 2.40 (m, 2H), 1.73 – 1.54 (m, 11H), 1.35 – 1.30 (m, 2H), 1.25 – 1.02 (m, 4H), 0.90 – 0.81 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 49.4, 46.2, 37.4, 35.6, 35.5, 33.3, 30.0, 28.8, 26.6, 26.3, 23.5.

IR (film) ν_{max} 2920, 2850, 1638, 1484, 1446, 1423, 1198, 975 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{25}NNaO$ ($[M+Na]^+$) 246.1828, found 246.1829.



***tert*-butyl (2-cyclohexylethyl)(methyl)carbamate (40)**

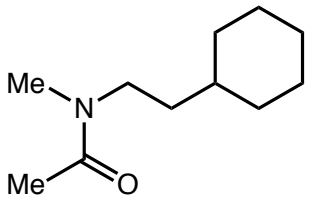
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (4.0 mg, 15.0 μmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), *tert*-butyl dimethylcarbamate (145.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), Li_2CO_3 (37 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (77 mg, 0.32 mmol, 64% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.26 – 3.16 (m, 2H), 2.81 (s, 3H), 1.77 – 1.60 (m, 5H), 1.45 (s, 9H), 1.37 (q, *J* = 7.1 Hz, 2H), 1.27 – 1.08 (m, 4H), 0.91 (qd, *J* = 13.9, 13.0, 3.8 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 79.1, 46.6, 35.2, 33.9, 33.3, 28.5, 26.6, 26.3.

IR (film) ν_{max} 2975, 2921, 2851, 1693, 1393, 1364, 1155 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{14}H_{27}NNaO_2$ ($[M+Na]^+$) 264.1934, found 264.1938.



***N*-(2-cyclohexylethyl)-*N*-methylacetamide (41)**

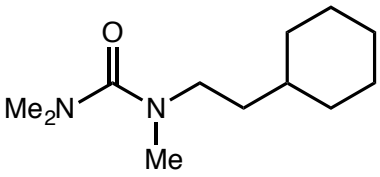
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethyl-2,2'-bipyridine (9.2 mg, 50.0 μmol, 0.10 equiv.), MeCN (3.6 mL), quinuclidine (5.6 mg, 50 μmol, 0.10 equiv.), DMA (131 mg, 139 μL, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (0.4 mL). After stirring for 16 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs *with* a fan. Continue stirring for another 22 h. Purification by column chromatography (silica gel, 1:3 hexane:EtOAc) yielded the pure product as a light yellow oil (48 mg, 0.26 mmol, 52% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.28 – 3.22 and 3.18 – 3.12 (m, 2H, rotamer), 2.85 and 2.78 (s, 3H, rotamer), 1.96 and 1.94 (s, 3H, rotamer), 1.63 – 1.50 (m, 5H), 1.38 – 1.24 (m, 2H), 1.19 – 1.02 (m, 4H), 0.89 – 0.74 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 170.0, 48.7, 45.3, 35.8, 35.7, 35.4, 35.2, 34.5, 33.1, 33.0, 26.4, 26.3, 26.1, 26.0, 21.8, 21.0.

IR (film) ν_{max} 2921, 2851, 1638, 1487, 1448, 1405, 1034, 1010 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{11}H_{22}NO$ ($[M+H]^+$) 184.1696, found 184.1694.



1-(2-cyclohexylethyl)-1,3,3-trimethylurea (42)

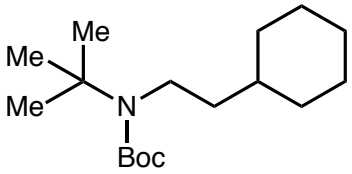
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (4.0 mg, 15.0 μmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (2.8 mg, 25.0 μmol, 0.05 equiv.), tetramethylurea (174.0 mg, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 5% to 20% EtOAc in hexanes) yielded the pure product as a clear oil (62 mg, 0.29 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.20 – 3.11 (m, 2H), 2.79 (s, 6H), 2.77 (s, 3H), 1.74 – 1.58 (m, 5H), 1.47 – 1.38 (m, 2H), 1.27 – 1.08 (m, 4H), 0.91 (qd, *J* = 13.4, 12.6, 3.6 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 48.5, 38.8, 36.4, 35.6, 35.0, 33.3, 26.6, 26.3.

IR (film) ν_{max} 2919, 2850, 1642, 1493, 1379, 1143, 1110 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{12}H_{25}N_2O$ ($[M+H]^+$) 213.1961, found 213.1962.



***tert*-butyl *tert*-butyl(2-cyclohexylethyl)carbamate (43)**

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (4.0 mg, 15.0 μmol, 0.03

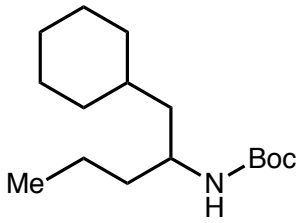
equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), Di-*t*ert-butyl dicarbonate (32.7 mg, 0.15 mmol, 0.3 equiv.), *tert*-butyl *tert*-butyl(methyl)carbamate (187.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 10% EtOAc in hexanes) yielded the pure product as a clear oil (105 mg, 0.37 mmol, 75% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.27 – 3.24 (m, 2H), 1.75 – 1.56 (m, 6H), 1.46 (s, 9H), 1.42 – 1.32 (m, 2H), 1.38 (s, 9H), 1.25 – 1.12 (m, 5H), 0.96 – 0.88 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 78.8, 55.2, 43.3, 38.6, 36.2, 33.4, 29.7, 28.6, 26.6, 26.3.

IR (film) ν_{max} 2974, 2922, 2852, 1694, 1477, 1449, 1388, 1362, 1167, 1138 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{33}NNaO_2$ ($[M+Na]^+$) 306.2403, found 306.2404.



(±)-*tert*-butyl (1-cyclohexylpentan-2-yl)carbamate (44)

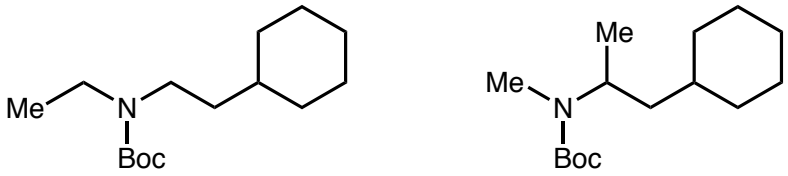
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 1,10-phenanthroline (2.7 mg, 15.0 μmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), Di-*t*ert-butyl dicarbonate (21.8 mg, 0.10 mmol, 0.2 equiv.), *tert*-butyl butylcarbamate (173.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), Li_2CO_3 (37 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 2% to 10% EtOAc in hexanes) yielded the pure product as a white solid (83 mg, 0.31 mmol, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.15 (d, *J* = 7.1 Hz, 0.7H), 3.90 (s, 0.15H), 3.90 (s, 0.8H), 3.56 (s, 0.2H), 1.83 (d, *J* = 12.9 Hz, 1H), 1.74 – 1.61 (m, 4H), 1.44 (s, 9H), 1.41 – 1.08 (m, 5H), 0.99 – 0.88 (m, 1H), 0.9 (t, *J* = 6.7 Hz, 3H), 0.86 – 0.75 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 78.7, 47.9, 43.7, 38.5, 34.4, 33.9, 33.0, 28.4, 26.6, 26.4, 26.3, 19.0, 14.1.

IR (film) ν_{max} 3341, 2957, 1921, 1851, 1689, 1523, 1364, 1172 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{31}NNaO_2$ ($[M+Na]^+$) 292.2247, found 292.2252.



***tert*-butyl (2-cyclohexylethyl)(ethyl)carbamate (major isomer) and (±)-*tert*-butyl (1-cyclohexylpropan-2-yl)(methyl)carbamate (minor isomer) (45)**

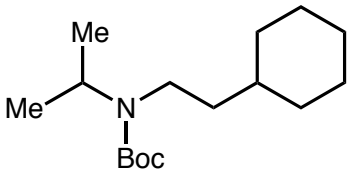
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (4.0 mg, 15.0 μmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), Di-*t*ert-butyl dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), *tert*-butyl ethyl(methyl)carbamate (159.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 8% EtOAc in hexanes) yielded a mixture of regioisomers as a clear oil (82 mg, 0.32 mmol, 64% yield, 5:1 r.r by NMR).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.25 – 3.14 (m, 3.25H), 2.64 (s, 0.5H, minor isomer), 1.76 – 1.56 (m, 5H), 1.45 (s, 9H), 1.42 – 1.34 (m, 2H), 1.26 – 1.13 (m, 4H), 1.08 (t, *J* = 7.1 Hz, 2.82H, major isomer), 1.04 (d, *J* = 6.8 Hz, 0.55H, minor isomer), 0.99 – 0.85 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 78.9, 44.5, 41.5, 36.1, 35.5, 33.3, 28.5, 26.62, 26.60, 26.5, 26.3, 13.7.

IR (film) ν_{max} 2974, 2922, 2851, 1691, 1416, 1159 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{15}H_{29}NNaO_2$ ($[M+Na]^+$) 278.2091, found 278.2097.



***tert*-butyl (2-cyclohexylethyl)(isopropyl)carbamate (46)**

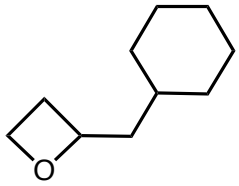
Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (5.1 mg, 15.0 μmol, 0.03 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (4.0 mg, 15.0 μmol, 0.03 equiv.), MeCN (2.0 mL), quinuclidine (5.6 mg, 50.0 μmol, 0.10 equiv.), Di-*t*ert-butyl dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), *tert*-butyl isopropyl(methyl)carbamate (173.0 mg, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (70 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Purification by column chromatography (silica gel, gradient 1% to 8% EtOAc in hexanes) yielded the pure product as a clear oil (76 mg, 0.28 mmol, 56% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.17 (bs, 1H), 3.08 – 3.00 (m, 2H), 1.80 – 1.57 (m, 5H), 1.45 (s, 9H), 1.42 – 1.37 (m, 2H), 1.26 – 1.14 (m, 4H), 1.11 (d, *J* = 6.8 Hz, 6H), 0.97 – 0.89 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.4, 78.9, 36.2, 33.4, 28.6, 26.6, 26.3, 20.9.

IR (film) ν_{max} 2973, 2923, 2851, 1689, 1449, 1364, 1163, 1142 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{16}H_{31}NNaO_2$ ($[M+Na]^+$) 292.2247, found 292.2253.



(±)-2-(cyclohexylmethyl)oxetane (47)

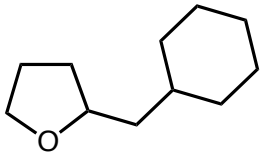
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), oxetane (1.45 g, 1.63 mL, 25.0 mmol, 50.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 17 h. Purification by column chromatography (silica gel, 1:3 pentane:DCM) yielded the pure product as a clear oil (54 mg, 0.35 mmol, 70% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 – 4.90 (m, 1H), 4.68 – 4.61 (m, 1H), 4.50 – 4.45 (m, 1H), 2.68 – 2.59 (m, 1H), 2.35 – 2.27 (m, 1H), 1.80 – 1.73 (m, 1H), 1.70 – 1.62 (m, 4H), 1.53 – 1.47 (m, 1H), 1.40 – 1.29 (m, 1H), 1.27 – 1.09 (m, 4H), 0.98 – 0.85 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 81.4, 68.2, 46.1, 34.1, 33.9, 33.2, 28.7, 26.6, 26.4, 26.3.

IR (film) ν_{max} 2920, 2851, 1448, 973 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{10}H_{18}O$ (M^+) 154.1352, found 154.1351.



(±)-2-(cyclohexylmethyl)tetrahydrofuran (48)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethyl-2,2'-bipyridine (9.2 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), THF (1.80 g, 2.02 mL,

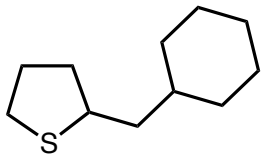
25.0 mmol, 50.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 20 h. Purification by column chromatography (silica gel, 1:2 hexane:DCM) yielded the pure product as a clear oil (51 mg, 0.30 mmol, 60% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.90 – 3.80 (m, 2H), 3.70 – 3.64 (m, 1H), 1.97 – 1.91 (m, 1H), 1.89 – 1.75 (m, 3H), 1.71 – 1.58 (m, 4H), 1.51 – 1.32 (m, 3H), 1.30 – 1.06 (m, 4H), 0.94 – 0.81 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 77.2, 67.6, 43.7, 35.3, 34.1, 33.3, 32.1, 26.7, 26.4, 26.4, 25.8.

IR (film) ν_{max} 2919, 2850, 1448, 1068, 1057 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{11}H_{20}O$ (M^+) 168.1509, found 168.1507.



(±)-2-(cyclohexylmethyl)tetrahydrothiophene (49)

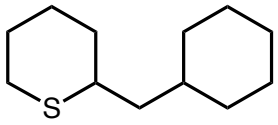
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), tetrahydrothiophene (88 mg, 88 μL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 12:1 hexane:DCM) yielded the pure product as a clear oil (58 mg, 0.315 mmol, 63% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.44 (ddd, *J* = 14.1, 8.5, 5.5 Hz, 1H), 2.90 – 2.77 (m, 2H), 2.10 – 2.02 (m, 2H), 1.90 – 1.79 (m, 1H), 1.77 – 1.58 (m, 5H) 1.55 – 1.38 (m, 3H), 1.35 – 1.06 (m, 4H), 0.92 – 0.78 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 46.7, 45.6, 37.9, 37.4, 33.9, 33.0, 32.2, 30.4, 26.7, 26.4, 26.3.

IR (film) ν_{max} 2920, 2851, 1446 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{11}H_{20}S$ (M^+) 184.1280, found 184.1282.



(±)-2-(cyclohexylmethyl)tetrahydro-2*H*-thiopyran (50)

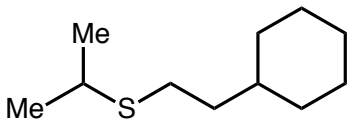
Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2$•$6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (22.2 mg, 200 μmol, 0.40 equiv.), tetrahydrothiopyran (102 mg, 103 μL, 1.00 mmol, 2.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 10:1 hexane:DCM) yielded the pure product as a clear oil (61 mg, 0.307 mmol, 61% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 – 2.73 (m, 1H), 2.64 (td, *J* = 12.7, 11.8, 2.8 Hz, 1H), 2.57 – 2.53 (m, 1H), 1.95 – 1.87 (m, 2H), 1.86 – 1.80 (m, 1H), 1.78 – 1.74 (m, 1H), 1.68 – 1.59 (m, 4H), 1.58 – 1.51 (m, 1H), 1.49 – 1.39 (m, 1H), 1.38 – 1.07 (m, 7H), 0.91 – 0.77 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 44.2, 40.0, 35.4, 34.4, 33.9, 33.1, 29.3, 27.6, 26.7, 26.44, 26.38, 26.3.

IR (film) ν_{max} 2919, 2848, 1447 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{12}H_{22}S$ (M^+) 198.1437, found 198.1442.



(2-cyclohexylethyl)(isopropyl)sulfane (51)

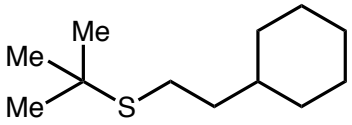
Prepared following the general procedure outlined above (*with* fan) using $Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethyl-2,2'-bipyridine (9.2 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), isopropyl methyl sulfide (0.45 g, 0.54 mL, 5.00 mmol, 10.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 8:1 hexane:DCM) yielded the pure product as a clear oil (66 mg, 0.354 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 2.93 – 2.84 (m, 1H), 2.54 – 2.50 (m, 2H), 1.73 – 1.60 (m, 5H), 1.48 – 1.42 (m, 2H), 1.36 – 1.29 (m, 1H), 1.24 (d, *J* = 6.8 Hz, 6H), 1.21 – 1.07 (m, 3H), 0.92 – 0.83 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 37.5, 37.2, 34.8, 33.2, 28.2, 26.7, 26.4, 23.5.

IR (film) ν_{max} 2921, 2851, 1448, 1241 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{11}H_{22}S$ (M^+) 186.1437, found 186.1440.



***tert*-butyl(2-cyclohexylethyl)sulfane (52)**

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), *tert*-butyl methyl sulfide (0.52 g, 0.63 mL, 5.00 mmol, 10.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 21 h. Purification by column chromatography (silica gel, 10:1 hexane:DCM) yielded the pure product as a clear oil (66 mg, 0.33 mmol, 66% yield).

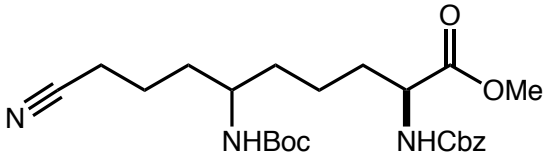
^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 – 2.49 (m, 2H), 1.74 – 1.59 (m, 5H), 1.46 – 1.41 (m, 2H), 1.37 – 1.31 (m, 1H), 1.30 (s, 9H), 1.26 – 1.09 (m, 3H), 0.92 – 0.84 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 41.9, 37.4, 37.4, 33.2, 31.1, 26.7, 26.4, 25.9.

IR (film) ν_{max} 2922, 2852, 1449, 1363, 1165 cm^{-1}.

HRMS (EI-TOF) m/z calcd. for $C_{12}H_{24}S$ (M^+) 200.1593, found 200.1597.

7) HAT-Alkylation of amino acids and peptides



methyl (2*S*)-2-(((benzyloxy)carbonyl)amino)-6-((*tert*-butoxycarbonyl)amino)-9-cyan-ononanoate (53)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg,

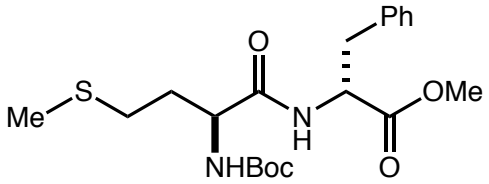
50.0 μmol, 0.10 equiv.), 1,10-phenanthroline (9.0 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.2 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), di-*tert*-butyl dicarbonate (22 mg, 0.10 mmol, 0.20 equiv.), methyl N^2-((benzyloxy)carbonyl)-N^6-(*tert*-butoxycarbonyl)-*L*-lysinate (592 mg, 1.50 mmol, 3.0 equiv.), 4-bromobutyronitrile (74 mg, 50.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2 mL). Reaction time: 33 h. Purification by column chromatography (silica gel, 2:1 hexane:EtOAc) yielded the pure product as a clear oil (95 mg, 0.205 mmol, 41% yield, 1:1 d.r.).

^{1}H NMR (500 MHz, C_6D_6) δ 7.26 – 7.21 (m, 2H), 7.14 – 7.04 (m, 3H), 5.35 (d, *J* = 8.1 Hz, 0.42H), 5.28 (d, *J* = 8.1 Hz, 0.49H), 5.16 – 5.04 (m, 2H), 4.51 – 4.40 (m, 1H), 3.85 (d, *J* = 9.2 Hz, 0.37H), 3.66 (d, *J* = 9.5 Hz, 0.43H), 3.38 – 3.26 (m, 4H), 1.69 – 1.54 (m, 1H), 1.49 – 1.39 (m, 11H), 1.38 – 1.28 (m, 1H), 1.21 – 0.72 (m, 8H).

^{13}C NMR (125 MHz, C_6D_6) δ 172.9, 172.8, 156.4, 156.3, 156.0, 155.8, 137.2, 137.1, 128.7, 128.6, 128.5, 128.4, 119.32, 119.31, 78.8, 67.1, 67.0, 54.01, 53.94, 51.84, 51.77, 49.2, 49.0, 35.1, 34.8, 34.7, 34.4, 32.2, 28.53, 28.51, 22.14, 22.11, 21.84, 21.75, 16.43, 16.41.

IR (film) ν_{max} 3342, 2947, 1696, 1521, 1455, 1366, 1248, 1214, 1169, 1054, 1029, 741, 699 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{35}N_3NaO_6$ ($[M+Na]^+$) 484.2418, found 484.2419.



methyl (*tert*-butoxycarbonyl)-*L*-methionyl-*D*-phenylalaninate (S1)

To a 250 mL round bottom flask containing (*tert*-butoxycarbonyl)-*L*-methionine (5.0 g, 20 mmol, 1 equiv.) and methyl *D*-phenylalaninate hydrochloride (4.3 g, 20 mmol, 1 equiv.) in 60 mL CH_2Cl_2 at 0 ºC was added Et_3N (2.8 mL, 20 mmol, 1 equiv.). After stirring at 0 ºC for 5 min, *N*,*N*′-dicyclohexylcarbodiimide (4.1 g, 20 mmol, 1 equiv.) was

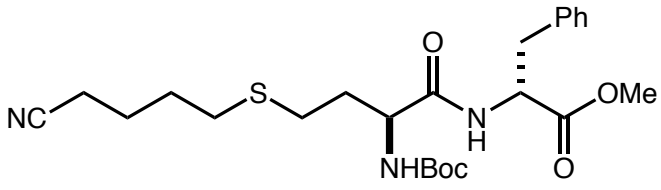
added. The reaction mixture was warmed to room temperature and stirred for 12 hours. Next, 100 mL deionized water was added to the same flask. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, 4:1 hexane:EtOAc). The title compound was isolated as a white solid (4.8 g, 11.7 mmol, 59% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.26 – 7.22 (m, 1H), 7.14 (d, *J* = 7.0 Hz, 2H), 6.99 (d, *J* = 7.5 Hz, 1H), 5.44 (d, *J* = 7.9 Hz, 1H), 4.88 (q, *J* = 7.4 Hz, 1H), 4.39 – 4.24 (m, 1H), 3.71 (s, 3H), 3.17 (dd, *J* = 13.9, 5.5 Hz, 1H), 3.04 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.48 – 2.29 (m, 2H), 2.05 (s, 3H), 2.03 – 1.97 (m, 1H), 1.87 – 1.77 (m, 1H), 1.43 (s, 9H).

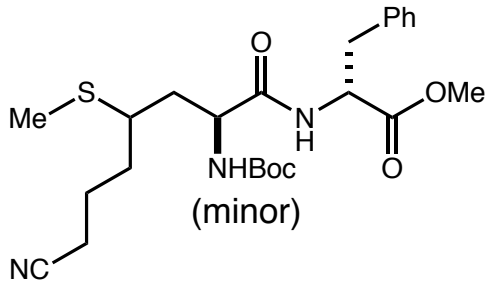
^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.3, 155.5, 135.8, 129.2, 128.6, 127.1, 79.9, 53.3, 53.1, 52.3, 37.8, 31.8, 29.8, 28.3, 15.2.

IR (film) ν_{max} 3306, 2977, 2920, 1739, 1656, 1507, 1437, 1366, 1282, 1246, 1215, 1164, 1048, 1024, 744, 700 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{20}H_{30}N_2NaO_5$ ($[M+Na]^+$) 433.1768, found 433.1764.



(major)



(minor)

methyl *N*-(*tert*-butoxycarbonyl)-*S*-(4-cyanobutyl)-*L*-homocysteinyl-*D*-phenylalaninate (major isomer) (54)

Prepared following the general procedure outlined above (*with* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), methyl (*tert*-butoxycarbonyl)-*L*-methionyl-*D*-phenylalaninate (411 mg, 1.00 mmol, 2.0 equiv.), 4-bromobutyronitrile (74 mg, 50.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 23 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs with a fan. Continue stirring for another 21 h. Purification by column chromatography (silica gel, 2:1 to 1:1 hexane:EtOAc) yielded the product as a clear oil (124 mg, 0.26 mmol, 52% yield, mixture of regioisomers, rr = 5:1).

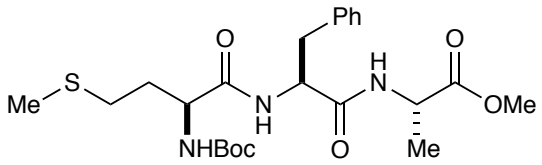
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 3H), 7.15 – 7.08 (m, 2H), 6.85 (d, *J* = 6.9 Hz, 0.12H, minor isomer), 6.65 (d, *J* = 6.7 Hz, 0.71H, major isomer), 5.40 (d, *J* = 7.7 Hz, 0.13H, minor isomer), 5.14 (d, *J* = 6.9 Hz, 0.72H, major isomer), 4.85 (q, *J* = 6.6 Hz, 1H), 4.31 – 4.19 (m, 1H), 3.72 (s, 2.58H, major isomer), 3.70 (s, 0.46H, minor isomer), 3.16 (dd, *J* = 14.0, 5.5 Hz, 1H), 3.06 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.64 – 2.39 (m, 4H), 2.36 (t, *J* = 6.8 Hz, 2H), 2.06 – 1.67 (m, 6H), 1.42 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 171.4, 171.2, 155.5, 135.9, 135.8, 129.2, 128.7, 127.2, 119.5, 119.2, 80.2, 53.3, 53.2, 52.4, 37.9, 37.8, 32.2, 30.8, 30.3, 28.3, 28.1, 27.9, 27.7, 25.0, 24.3, 16.8, 16.0.

IR (film) ν_{max} 3317, 2936, 1741, 1710, 1661, 1510, 1455, 1441, 1366, 1247, 1217, 1167, 1047, 1024, 756, 702 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{35}N_3NaO_5S$ ($[M+Na]^+$) 500.2190, found

500.2191.



methyl (*tert*-butoxycarbonyl)-*L*-methionyl-*L*-phenylalanyl-*L*-alaninate (S2)

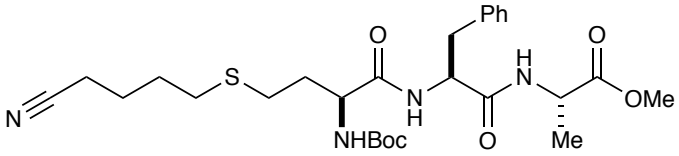
To a 250 mL round bottom flask containing (*tert*-butoxycarbonyl)-*L*-methionine (2.8 g, 11.2 mmol, 1 equiv.) and methyl *D*-phenylalanyl-*L*-alaninate (2.8 g, 11.2 mmol, 1 equiv., prepared based on a published procedure) in 50 mL DMF at 0 ºC was added *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (2.6 g, 13.4 mmol, 1.2 equiv.), 1-hydroxybenzotriazole hydrate (2.1 g, 13.4 mmol, 1.2 equiv.) and Et_3N (3.4 mL, 24.6 mmol, 1 equiv.). After stirring at 0 ºC for 1 hour, the reaction mixture was warmed to room temperature and stirred for 24 hours. Next, the solution was extracted with ethyl acetate (150 mL) and washed with deionized water (4 × 50 mL). The organic layer was collected and the aqueous layer was combined and extracted with ethyl acetate (3 × 70 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, 1:1 hexane:EtOAc). The title compound was isolated as a white solid (1.7 g, 3.53 mmol, 32% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 2H), 7.24 – 7.18 (m, 3H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.97 (d, *J* = 6.1 Hz, 1H), 5.50 (d, *J* = 7.1 Hz, 1H), 4.80 (q, *J* = 6.9 Hz, 1H), 4.51 (p, *J* = 7.2 Hz, 1H), 4.41 – 4.23 (m, 1H), 3.72 (s, 3H), 3.09 (d, *J* = 6.6 Hz, 2H), 2.54 – 2.46 (m, 2H), 2.07 (s, 3H), 2.05 – 1.97 (m, 1H), 1.94 – 1.84 (m, 1H), 1.43 (s, 9H), 1.35 (d, *J* = 7.2 Hz, 3H).

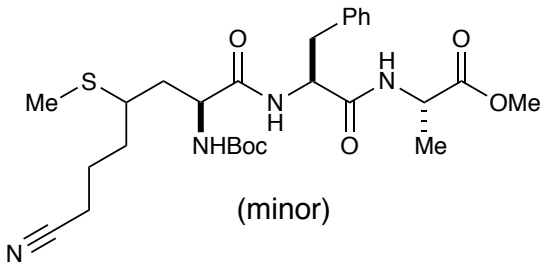
^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.6, 170.3, 155.6, 136.3, 129.4, 128.6, 127.0, 80.2, 54.2, 53.9, 52.5, 48.2, 38.3, 31.8, 30.1, 28.4, 18.1, 15.3.

IR (film) ν_{max} 3280, 2979, 2921, 1748, 1694, 1641, 1548, 1520, 1366, 1241, 1209, 1161, 1052, 740, 699 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{35}N_3NaO_6$ ($[M+Na]^+$) 504.2139, found 504.2141.



(major)



(minor)

methyl *N*-(*tert*-butoxycarbonyl)-*S*-(4-cyanobutyl)-*L*-homocysteinyl-*L*-phenylalanyl-*L*-alaninate (55) and methyl ((2*S*)-2-((*tert*-butoxycarbonyl)amino)-7-cyano-4-(methylthio)heptanoyl)-*D*-phenylalanyl-*L*-alaninate (minor isomer)

Prepared following the general procedure outlined above (with fan cooling) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), methyl (*tert*-butoxycarbonyl)-*L*-methionyl-*D*-phenylalanyl-*L*-alaninate (482 mg, 1.00 mmol, 2.0 equiv.), 4-bromobutyronitrile (74 mg, 50.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). Reaction time: 40 h. Purification by column chromatography (silica gel, 1:1 to 1:2 hexane:EtOAc) yielded the product as a yellow oil (163 mg, 0.297 mmol, 59% yield, mixture of regioisomers, rr = 8:1).

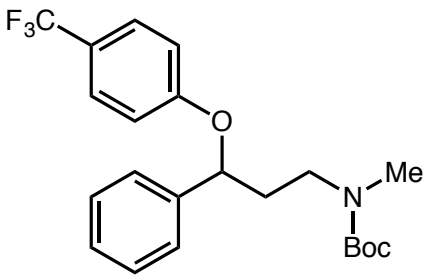
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 7.26 – 7.17 (m, 3H), 6.80 – 6.70 (m, 1H), 6.50 – 6.35 (m, 1H), 5.46 – 5.05 (m, 1H), 4.76 (q, *J* = 7.2 Hz, 0.09H, minor isomer), 4.66 (q, *J* = 6.9 Hz, 0.88H, major isomer), 4.47 (p, *J* = 7.2 Hz, 1H), 4.41 – 4.15 (m, 1H), 3.71 (s, 2.61H, major isomer), 3.70 (s, 0.33H, minor isomer), 3.14 – 3.03 (m, 2H), 2.71 – 2.41 (m, 4H), 2.38 (t, *J* = 6.7 Hz, 2H), 2.08 – 1.67 (m, 6H), 1.41 (s, 9H), 1.33 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.9, 171.4, 170.2, 155.6, 155.6, 136.4, 136.3, 129.4, 129.2, 128.7, 128.5, 127.1, 119.6, 119.3, 80.3, 54.2, 53.8, 52.5, 48.2, 38.2, 32.24, 32.19, 30.8, 30.4, 30.2, 29.7, 28.3, 28.1, 28.0, 27.9, 25.0, 24.3, 22.7, 18.1, 16.9, 16.0.

IR (film) ν_{max} 3295, 2932, 1744, 1646, 1526, 1454, 1367, 1246, 1212, 1163, 1052, 700 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{40}N_4NaO_6S$ ($[M+Na]^+$) 571.2561, found 576.2560.

8) HAT-Alkylation with N-Boc Prozac



(±)-*tert*-butyl Methyl(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (S3)

To a 250 mL round bottom flask containing Fluoxetine hydrochloride (6.9 g, 20 mmol, 1.0 equiv.) in 100 mL CH_2Cl_2 at 0 ºC was added Et_3N (5.9 mL, 42 mmol, 2.1 equiv.). The solution was stirred for 5 min at 0 ºC, then a solution of Boc_2O (4.8 g, 22 mmol, 1.1 equiv.) in 20 mL CH_2Cl_2 was added in one portion. The reaction mixture was warmed to room temperature and stirred for 2 hours. Next, 100 mL deionized water was added to quench the reaction. The resulting mixture was extracted with CH_2Cl_2 (3 × 70 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (silica gel, 10:1 hexane:EtOAc). The title compound was isolated as a viscous clear oil (8.0 g, 19.5 mmol, 98% yield).

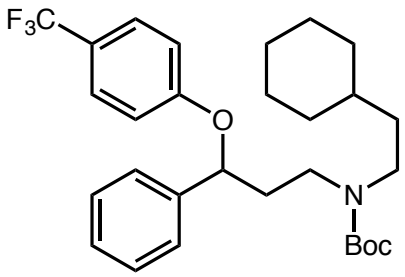
^{1}H NMR (500 MHz, CD_3CN) δ 7.49 (d, *J* = 8.6 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.24 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 5.33 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.55 – 3.23 (m, 2H), 2.81 (s, 3H), 2.19 – 1.99 (m, 2H), 1.45 – 1.23 (m, 9H).

^{13}C NMR (125 MHz, CD_3CN) δ 161.7, 151.3, 142.0, 129.7, 128.8, 127.7 (q, *J* = 3.7 Hz), 127.0, 125.6 (q, *J* = 268.4 Hz), 122.3 (q, *J* = 32.4 Hz), 117.1, 79.6, 78.7, 78.2, 46.2, 46.0, 37.5, 37.1, 34.7, 34.4, 28.5.

^{19}F NMR (282 MHz, CD_3CN) δ –62.0 (s, 3F).

IR (film) ν_{max} 2977, 2931, 1691, 1614, 1517, 1454, 1393, 1366, 1323, 1246, 1154, 1109, 1067, 1049, 1009, 835, 762, 701 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{26}F_3NNaO$ ($[M+Na]^+$) 432.1757, found 432.175



(±)-*tert*-butyl (2-cyclohexylethyl)(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (56)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), *N*-Boc fluoxetine (614 mg, 1.50 mmol, 3.0 equiv.), (bromomethyl)cyclohexane (89 mg, 70.0 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 23 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs. Continue stirring for another 27 h. Purification by column chromatography (silica gel, 25:1 hexane:EtOAc) yielded the product as a clear oil (131 mg, 0.26 mmol, 52% yield, rr

>20:1). The remaining untouched *N*-Boc Prozac can be recovered during purification in good yields.

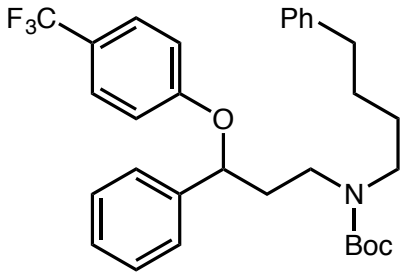
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.37 – 7.30 (m, 4H), 7.29 – 7.23 (m, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.22 – 5.12 (m, 1H), 3.50 – 3.06 (m, 4H), 2.34 – 2.06 (m, 2H), 1.70 – 1.60 (m, 5H), 1.50 – 1.35 (m, 11H), 1.24 – 1.09 (m, 4H), 0.93 – 0.83 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 155.6, 141.0, 128.9, 128.0, 126.9 (q, *J* = 3.5 Hz), 125.8, 124.5 (q, *J* = 269.3 Hz), 123.9 (q, *J* = 33.7 Hz), 115.8, 79.4, 78.5, 77.8, 45.5, 44.1, 43.8, 38.0, 37.5, 36.3, 35.7, 35.3, 33.4, 33.3, 28.5, 26.6, 26.37, 26.36.

^{19}F NMR (282 MHz, $CDCl_3$) δ –61.6 (s, 3F).

IR (film) ν_{max} 2925, 2853, 1691, 1615, 1518, 1452, 1417, 1366, 1327, 1250, 1162, 1117, 1069, 835, 756, 701 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{38}F_3NNaO_3$ ($[M+Na]^+$) 528.2696, found 528.2692.



(±)-*tert*-butyl (3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)(4-phenylbutyl)carbamate (57)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2•6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-di(*tert*-butyl)-2,2'-bipyridine (13.4 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.2 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), di-*tert*-butyl

dicarbonate (22.0 mg, 0.10 mmol, 0.2 equiv.), *N*-Boc fluoxetine (1.02 g, 2.50 mmol, 5.0 equiv.), 1-bromo-3-phenylpropane (100 mg, 76 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 19 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs. Continue stirring for another 21 h. Purification by column chromatography (silica gel, 25:1 hexane:EtOAc) yielded the product as a clear oil (119 mg, 0.225 mmol, 45% yield, rr >20:1). The remaining untouched *N*-Boc Prozac can be recovered during purification in good yields.

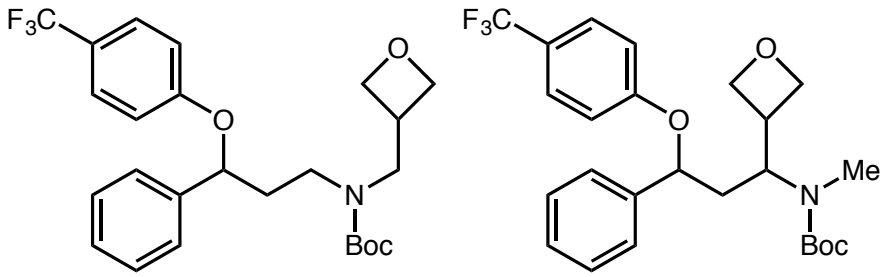
^{1}H NMR (500 MHz, CD_3CN) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.40 – 7.32 (m, 4H), 7.29 – 7.23 (m, 3H), 7.18 – 7.14 (m, 3H), 6.99 (d, *J* = 8.5 Hz, 2H), 5.31 (dd, *J* = 8.3, 4.2 Hz, 1H), 3.40 – 3.28 (m, 2H), 3.26 – 3.08 (m, 2H), 2.58 (t, *J* = 7.2 Hz, 2H), 2.17 – 2.00 (m, 2H), 1.58 – 1.45 (m, 4H), 1.34 (s, 9H).

^{13}C NMR (125 MHz, CD_3CN) δ 161.7, 156.2, 143.5, 142.0, 129.7, 129.3, 129.2, 128.8, 127.7 (q, *J* = 3.6 Hz), 127.0, 126.6, 125.6 (q, *J* = 268.8 Hz), 123.0 (q, *J* = 32.4 Hz), 117.1, 79.6, 78.7, 78.5, 47.9, 47.4, 44.5, 38.2, 37.9, 36.0, 29.4, 28.6.

^{19}F NMR (282 MHz, CD_3CN) δ –61.9 (s, 3F).

IR (film) ν_{max} 2931, 1690, 1615, 1517, 1454, 1416, 1366, 1326, 1249, 1160, 1115, 1068, 836, 700 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{31}H_{36}F_3NNaO_3$ ($[M+Na]^+$) 550.2540, found 55.2535.



(major) (minor)

(±)-*tert*-butyl (oxetan-3-ylmethyl)(3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (major isomer) and *tert*-butyl methyl(1-(oxetan-3-yl)-3-phenyl-3-(4-(trifluoromethyl)phenoxy)propyl)carbamate (minor isomer) (58)

Prepared following the general procedure outlined above (*without* fan) using $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (5.6 mg, 5.0 μmol, 0.01 equiv.), $Ni(BF_4)_2 \bullet 6H_2O$ (17.0 mg, 50.0 μmol, 0.10 equiv.), 4,4'-dimethoxy-2,2'-bipyridine (10.8 mg, 50.0 μmol, 0.10 equiv.), MeCN (2.0 mL), quinuclidine (11.1 mg, 100 μmol, 0.20 equiv.), *N*-Boc fluoxetine (614 mg, 1.50 mmol, 3.0 equiv.), 3-bromooxetane (68 mg, 41 μL, 0.50 mmol, 1.0 equiv.), K_2CO_3 (69 mg, 0.50 mmol, 1.0 equiv.) and water (2.0 mL). After stirring for 21 h, the vial was removed from the light source and a solution of quinuclidine (5.6 mg, 50 μmol, 0.10 equiv) in MeCN (0.2 mL) was added to the reaction vial. The reaction mixture was degassed via two cycles of freeze-pump-backfill-thaw again before being parafilmed and placed 4 cm away from 34W blue LEDs. Continue stirring for another 23 h. Purification by column chromatography (silica gel, 3:1 hexane:EtOAc) yielded the product as a clear oil (105 mg, 0.225 mmol, 45% yield, mixture of regioisomers, rr = 5:1). The remaining untouched *N*-Boc Prozac can be recovered during purification in good yields.

^{1}H NMR (500 MHz, CD_3CN) δ 7.50 (d, *J* = 8.7 Hz, 2H), 7.41 – 7.32 (m, 4H), 7.30 – 7.25 (m, 1H), 7.00 (d, *J* = 8.6 Hz, 2H), 5.42 – 5.28 (m, 1H), 5.00 – 4.56 (m, 2H), 4.38 – 4.17 (m, 2H), 3.56 – 3.13 (m, 4.36H, major isomer + minor isomer), 2.81 (s, 0.48H, minor isomer), 2.19 – 1.99 (m, 2H), 1.36 (s, 9H).

^{13}C NMR (125 MHz, CD_3CN) δ 161.7, 156.3, 143.7, 142.8, 142.5, 141.9, 135.2, 134.8, 130.0, 129.7, 128.9, 128.1, 127.7 (q, *J* = 3.7 Hz), 127.4, 127.3, 127.0, 125.5, 125.4, 125.6

(q, J = 268.4 Hz), 123.0 (q, J = 32.4 Hz), 117.1, 80.0, 79.6, 79.02, 79.00, 78.97, 78.6, 75.79, 75.77, 50.4, 45.0, 40.8, 40.6, 37.8, 35.6, 28.5, 28.4.

^{19}F NMR (282 MHz, CD_3CN) δ –62.0 (s, 3F).

IR (film) ν_{max} 2972, 2931, 2874, 1691, 1614, 1517, 1416, 1367, 1326, 1249, 1160, 1112, 1068, 836, 702 cm^{-1}.

HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{30}F_3NNaO_4$ ($[M+Na]^+$) 488.2019, found 488.2020.

13) References Cited

1) D. D. Perrin, W. L. F.Armarego, *Purification of Laboratory Chemicals* (Pergamon Press, Oxford, 1988) ed 3.

2) A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **15**, 1518-1520 (1996).

3) W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* **43**, 2923-2925 (1978).