Synthesis of meta-substituted [^{18}F]3-fluoro-4-aminopyridine via direct radiofluorination of pyridine N-oxides

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SUPPLEMENTAL METHODS

Complete experimental procedures

SUPPLEMENTAL DATA

Reference NMR data of the used compounds

SUPPLEMENTAL FIGURES

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Sup. Fig. 4. Fluorination of 3-bromopyridine: **A**. UV HPLC trace. **B**. ^{1}H, ^{13}C, ^{19}F NMR.

Sup. Fig. 5. Fluorination of 3-bromopyridine N-oxide: **A**. UV HPLC trace. **B**. ^{1}H, ^{19}F, ^{13}C NMR.

Sup. Fig. 6. Hydrogenation of 3-fluoro-4-nitropyridine N-oxide. UV HPLC before and after.

Sup. Fig. 7. Radioactive and UV HPLC trace of radiofluorination of 3-bromo-4-nitropyridine N-oxide (not spiked with reference standard)

SUPPLEMENTAL METHODS

All radioactivity procedures were approved by the Office of Radiation Safety at the University of Chicago. All chemicals were ordered from Sigma unless otherwise noted.

HPLC conditions (A-F):

A. Nucleodur 5 µm, 4.6 x 250 mm C18ec (Macherey-Nagel). Flow 1.4 mL/min. Solvent A: 50 mM NH_4HCO_3, pH 8.0. Solvent B: 100% MeOH. Method: 0-2 min: 5% B, 2-6 min: 5-50% B, 6-12 min: 50% B, 12-12.5 min: 50-5% B, 12.5-17 min: 5% B.

B. Nucleodur 5 µm, 4.6 x 250 mm C18ec (Macherey-Nagel). Flow 1.4 mL/min. Solvent A: 50 mM NH_4HCO_3, pH 8.0. Solvent B: 100% MeOH. Method: 0-2 min: 1% B, 2-9 min: 1-20% B, 9-11 min: 20% B, 11-11.5 min: 20-1% B, 11.5-14 min: 5% B.

C. Eclipse XDB 5 µm, 9.4 x 250 mm C18 column (Agilent). Flow 4: mL/min. Mobile phase: 50 mM NaH_4PO_4, 10 mM triethylamine, pH 8.0, 5% EtOH. Isocratic: 0-20 min.

D. Eclipse XDB 5 µm, 9.4 x 250 mm C18 column (Agilent). Flow: 4 mL/min. Solvent A: 50 mM NH_4HCO_3, pH 8.0. Solvent B: 100% MeOH. Method: 0-14 min: 5% B, 14-17 min: 5-25% B, 17-19 min: 25% B, 19-20 min: 25-5% B, 20-25 min: 5% B.

E. Eclipse XDB 5 µm, 9.4 x 250 mm C18 column (Agilent). Flow 4: mL/min. Mobile phase: 50 mM NaH_4PO_4, 10 mM triethylamine, pH 8.0, 5% EtOH. Isocratic: 0-10 min.

F. Acclaim 5 µm, 4.6 x 150 mm C18 column (Thermo Scientific). Flow 0.6: mL/min. Mobile phase: H_2O 0.1% TFA, 5% MeOH. Isocratic: 0-6 min.

RadioTLC analysis: The radioactive sample was spotted on a 25 * 75 mm TLC plate (PE SIL G, Whatman) next to the non-radioactive standard (1 mg/mL). The TLC was run in 95:5 methanol:acetic acid. The reference standard was visualized using a handheld UV-lamp and the radioactive stop measured with radio-TLC scanner (Eckert & Ziegler).

Non-radioactive fluorination of 3-bromo-4-nitropyridine (3): 10 µL of 1 M tetrabutylammonium fluoride (TBAF) solution in THF (10 µmol, 0.5 eq.) was added to a solution of 3-bromo-4-nitropyridine (96%, Aurum Pharmatech, LLC) (20 µmol, 1 eq.) in 500 µL of anhydrous dimethylsulfoxide (DMSO) in a 2 mL HPLC vial. The reaction was analyzed by HPLC (conditions A). Retention times: 3-bromo-4-nitropyridine (**3**) = 10.83 min, 3-fluoro-4-nitropyridine = 8.38, 3-bromo-4-fluoropyridine (**6**) = 11.76 min. Retention times for the product matched within 0.05 min the reference standard. Identity of the product was confirmed by HR-MS (*m/z* M^+ exp.: 174.9423, calc: 174.9433) and ^{1}H, ^{13}C and ^{19}F NMR. Product amount was calculated from the area under the curve of the HPLC UV1 trace using a calibration curve.

Non-radioactive fluorination of 3-iodo-4-nitropyridine (4): 10 µL of 1 M TBAF solution in THF (10 µmol, 0.5 eq.) was added to a solution of 3-iodo-4-nitropyridine (96%, Aurum Pharmatech, LLC) (20 µmol, 1 eq.) in 500 µL of anhydrous dimethylsulfoxide (DMSO) in a 2 mL HPLC vial. The reaction was analyzed by HPLC (conditions A). Retention times: 3-iodo-4-aminopyridine (**4**) = 11.02 min, 3-iodo-4-fluoropyridine (**7**) = 13.43 min. Starting material absorbs at 254 and 313 nm. Product does not absorb at 313 nm. The product Identity of the product was confirmed by HR-MS (*m/z* M^+ exp.: 222.9288, calc: 222.9294) and ^{1}H, ^{13}C and ^{19}F NMR.

Non-radioactive fluorination of 3-bromopyridine N-oxide (8): 10 µL of 1 M TBAF solution in THF (10 µmol, 0.5 eq.) was added to a solution of a 3-bromo-4-nitropyridine N-oxide (98+%, Alfa Aesar) (20 µmol, 1 eq.) in 500 µL of anhydrous DMSO in a 2 mL HPLC vial. The reaction was analyzed by HPLC (conditions B). Retention times: 3-bromo-4-nitropyridine N-oxide (**8**) = 11.84 min, 3-fluoro-4-nitropyridine N-oxide (**9**) = 7.93 min. Retention time for the product matched within 0.05 min the reference standard. Identity of the product was confirmed by HR-MS (*m/z* M^+ exp.: 158.0141, calc.: 158.0128) and ^{1}H, ^{13}C and ^{19}F NMR. Product amount was calculated from the area under the curve of the HPLC UV2 trace using a calibration curve.

Reaction of 3-bromopyridine (11) with TBAF: 120 µL of 1 M TBAF solution in THF (120 µmol, 1.2 eq.) was added to a solution of a 3-bromopyridine (97%, Combi-Blocks) (100 µmol, 1 eq.) in

400 µL of anhydrous DMSO in a 2 mL HPLC vial. The reaction was heated to 120 C for 30 min and analyzed by HPLC (conditions F) and ^{1}H, ^{13}C and ^{19}F NMR. Retention times: 3-bromopyridine (**11**) = 4.31 min, 3-fluoropyridine (**12**) = 1.56 min. No product was detected by HPLC or NMR.

Reaction of 3-bromopyridine N-oxide (13) with TBAF: 120 µL of 1 M TBAF solution in THF (120 µmol, 1.2 eq.) was added to a solution of a 3-bromopyridine N-oxide (97%, Alfa-Aesar) (100 µmol, 1 eq.) in 400 µL of anhydrous DMSO in a 2 mL HPLC vial. The reaction was heated to 120 C for 30 min and analyzed by HPLC (conditions F) and ^{1}H, ^{13}C and ^{19}F NMR. Retention times: 3-bromopyridine N-oxide (**13**) = 3.46 min, 3-fluoropyridine N-oxide (**14**) = 1.42 min. Yield was determined based on ^{1}H-NMR and HPLC.

Catalytic hydrogenation of 3-fluoro-4-nitropyridine N-oxide (9): 0.1 mg of 3-fluoro-4-aminopyridine N-oxide (**9**) were dissolved in 4 mL of MeOH in a 50 mL round bottom flask containing a stir bar. While stirring, 3-4 mg of 10% Pd/C (dry basis) was added and the flask sealed with a rubber septum. The vial was evacuated and backfilled with hydrogen gas from a balloon and the mixture was allowed to react for 10 min. After 10 min, the suspension was passed through a 0.4 µm PTFE filter and analyzed by HPLC (conditions C). Reference retention times: 3-fluoro-4-aminopyridine N-oxide (**9**) = 5.80 min, 3-fluoro-4-aminopyridine (**10**) = 7.05 min. Retention time for the product matched within 0.05 min the reference standard. Identity of the product was confirmed by HR-MS (*m/z* M^{+} exp.: 112.0416, calc: 112.0437). Product amount was calculated from the area under the curve of the HPLC UV2 trace using a calibration curve.

Procurement of [^{18}F]fluoride: Cyclotron produced no-carrier-added aqueous [^{18}F]fluoride was obtained from IBA Molecular North America, Inc.

Production of tetrabutyl ammonium [^{18}F]fluoride ([^{18}F]TBAF): Fifty to a hundred mCi (1.85 – 3.7 GBq) of cyclotron produced $^{18}F^{-}$ were trapped in a Sep-Pak Accell Plus QMA Plus Light Cartridge (Waters Corporation) preconditioned with 5 mL of 50 mM of $KHCO_3$ followed by 10 mL of water and 20 mL of air. The cartridge was eluted with a solution containing of 300 µL of 50

mM TBA-HCO_3 in water with 5% EtOH (ABX advanced biochemical compounds GmbH) and 600 µL of acetonitrile (MeCN). The water-MeCN solution was dried azeotropically at 85 ºC under reduced pressure (20 mbar) for 7.5 min. To ensure complete dryness two additional aliquots of MeCN (500 µL) followed by evaporation (3 min) were performed. After drying, the vial was filled with argon gas and cooled down to room temperature in a water beaker. The [^{18}F]TBAF residue was dissolved in 100-400 µL of anhydrous DMSO and used for the reactions.

Radiochemical synthesis of [^{18}F]3-fluoro-4-nitropyridine N-oxide ([^{18}F]**9**) from 3-bromo-4-nitropyridine N-oxide (**8**): 100 µL of 3-bromo-4-nitropyridine N-oxide (**8**) dissolved in DMSO (20 mg/mL) were added to 100 µL of [^{18}F]TBAF solution (~10 mCi, ~370 MBq) in 3 mL microreactor vial and allowed to react for 15 min. 100 µL of this solution with or without reference standard (20 µg) were injected into a semiprep C-18 HPLC column equipped with a variable wavelength UV-Vis detector and a radiation detector (conditions C). The radioactive peaks were collected and the radioactivity of each fraction measured using a Capintec dose calibrator. The radiochemical yield was calculated as radioactivity in the peak corrected for decay over radioactivity injected.

Radiochemical synthesis of [^{18}F]3-fluoro-4-nitropyridine N-oxide ([^{18}F]9) from 3-fluoro-4-nitropyridine N-oxide (9) by ^{19}F/^{18}F exchange: 100 µL of 3-fluoro-4-nitropyridine N-oxide (9) dissolved in DMSO (1 mg/mL) were added to 100 µL of [^{18}F]TBAF solution (~10 mCi, ~370 MBq) in 3 mL microreactor vial and allowed to react for 1 min. 100 µL of this solution were injected into a semiprep C-18 HPLC column equipped with a variable wavelength UV-Vis detector and a radiation detector (conditions E). The radioactive peaks were collected and the radioactivity of each fraction measured using a Capintec dose calibrator. The radiochemical yield was calculated as radioactivity in the peak corrected for decay over radioactivity injected.

Synthesis of [^{18}F]3-fluoro-4-aminopyridine ([^{18}F]10): 1-10 mCi (37-370 MBq) of [^{18}F]3-fluoro-4-aminopyridine N-oxide ([^{18}F]**9**) containing 20-100 µg of cold 3-fluoro-4-aminopyridine N-oxide were dissolved in 4 mL of MeOH and the reaction was carried out as described above. The

presence of cold compound facilitated obtaining reproducible yields. The product was purified by semiprep HPLC (conditons D). The final specific activity was 10-100 mCi/μmol (0.37-3.7 GBq/μmol).

SUPPLEMENTAL DATA

Reference NMR data of the used compounds.

3-bromo-4-nitropyridine (3):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 8.06 (1H, t, J = 1.3 Hz), 8.85 (1H, d, J = 1.3 Hz), 9.11 (1 H, s). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ: (ppm) 110.1 (s), 118.5 (s), 150.8 (s), 150.9 (s), 154.3 (s).

3-iodo-4-nitropyridine (4):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.99 (1H, d, J = 5.2 Hz), 8.80 (1H, d, J = 5.2 Hz), 9.23 (1 H, s). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 83.5 (s), 118.2 (s), 150.0 (s), 158.4 (s), 159.8 (s).

3-fluoro-4-nitropyridine (5):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 8.13 (1H, t, J = 6.2 Hz), 8.75 (1H, d, J = 5.25 Hz), 9.03 (1 H, d, J = 2.9 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 118.4 (d, J = 4.8 Hz), 141.8 (d, J = 23.1 Hz), 141.9 (d, J = 23.1 Hz), 147.5 (d, J = 6.7 Hz), 149.7 (d, J = 269.5 Hz). ^{19}F-NMR (d_6-DMSO, 470 MHz) δ (ppm): -135.13 (dd, J_2 = 8.9 Hz, J_1 = 2.5 Hz).

3-bromo-4-fluoropyridine (6):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.50 (1H, dd, J_2 = 9.0 Hz, J_1 = 5.5 Hz), 8.56 (1H, dd, J_2 = 7.5 Hz, J_1 = 5.5 Hz), 8.81 (1 H, J: 9.5 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 106.0 (s), 112.9 (d, J: 16.2 Hz), 151.1 (d, J: 6.2 Hz), 153.5 (s), 165.0 (d, J: 275.4 Hz). ^{19}F-NMR (d_6-DMSO, 470 MHz) δ (ppm): -99.1 (dd, J_2 = 16.9 Hz, J_1 = 9.1 Hz).

3-bromo-4-nitropyridine N-oxide (8):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 8.15 (1H, d, J = 7.1 Hz), 8.38 (1H, dd, J_2 = 7.1 Hz, J_1 = 2.0 Hz), 8.85 (1 H, d, J = 1.9 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 100? (s), 122.8 (s), 139.2 (s), 142.7 (s), 154.3 (s).

3-fluoro-4-nitropyridine N-oxide (9):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 8.24 (1H, dd, J_2 = 31.6 Hz, J_1 = 0.8 Hz), 8.25 (1H, dd, J_2 = 35.1 Hz, J_1 = 1.8 Hz), 8.91 (1 H, dd, J_2 = 7.1 Hz, J_1 = 1.8 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 122.3 (s), 131.4 (s), 131.7 (s), 137.0 (d, J = 4.3 Hz), 153.3 (d, J = 264.8 Hz). ^{19}F-NMR (d_6-DMSO, 470 MHz) δ (ppm): -126.7 (dd, J_2 = 8.5 Hz, J_1 = 0.8 Hz).

3-bromopyridine (11):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.38 (1H, dd, J_2 = 8.1 Hz, J_1 = 3.5 Hz), 7.85 (1H, dt, J_2 = 8.2 Hz, J_1 = 1.0 Hz), 8.56 (1 H, m), 8.69 (1 H, d, J = 2.3 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 120.3 (s), 124.9 (s), 138.2 (s), 147.6 (s), 150.1 (s).

3-fluoropyridine (12):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.40 (1H, m), 7.60 (1H, dt, J_2 = 7.5 Hz, J_1 = 1.5 Hz), 8.41 (1 H, m), 8.50 (1 H, d, J = 3.0 Hz). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 122.8 (d, J = 17.7 Hz), 124.9 (d, J = 3.9 Hz), 137.7 (d, J = 22.5 Hz), 145.8 (d, J = 4.1 Hz), 159.2 (d, J = 252.8 Hz). ^{19}F-NMR (d_6-DMSO, 470 MHz) δ (ppm): -126.7 (t, J = 5.1 Hz).

3-bromopyridine N-oxide (13):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.37 (1H, t, J = 7.8 Hz), 7.58 (1H, d, J = 7.6 Hz), 8.25 (1 H, d, J = 7.1 Hz), 8.56 (1 H, s). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 120.0 (s), 127.0 (s), 128.3 (s), 138.3 (s), 140.0 (s).

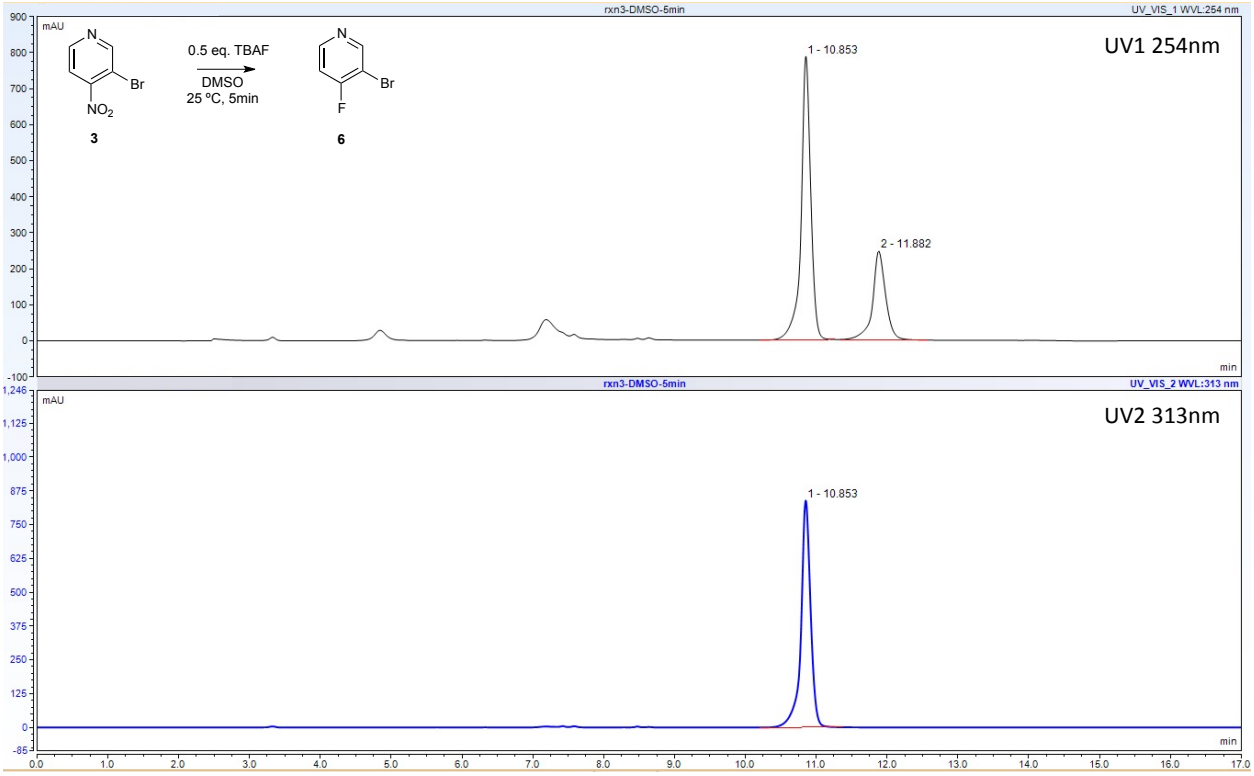
3-fluoropyridine N-oxide (14):

^{1}H-NMR (d_6-DMSO, 500 MHz) δ (ppm): 7.40 (1H, dt, J_2 = 55.4 Hz, J_1 = 7.9 Hz), 7.42 (1H, dd, J_2 = 54.5 Hz, J_1 = 7.2 Hz), 8.13 (1 H, d, J = 6.4 Hz), 8.51 (1 H, s). ^{13}C-NMR (d_6-DMSO, 125 MHz) δ (ppm): 113.2 (d, J = 20.4 Hz), 126.6 (d, J = 10.0 Hz), 129.2 (d, J = 35.5 Hz), 136.2 (s), 160.2 (d, J = 247.9 Hz). ^{19}F-NMR (d_6-DMSO, 470 MHz) δ (ppm): -122.1 (td, J_2 = 5.3 Hz, J_1 = 0.8 Hz).

SUPPLEMENTAL DATA

Sup. Fig. 1. Fluorination of 3-bromo-4-nitropyridine.

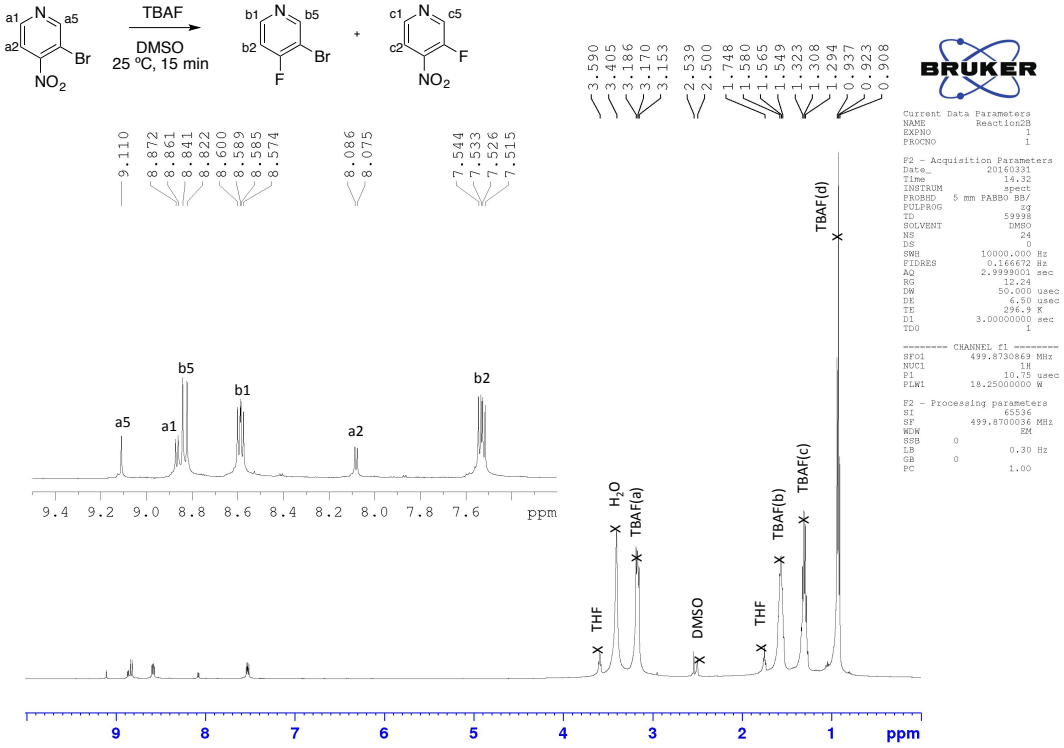
1A. UV HPLC trace



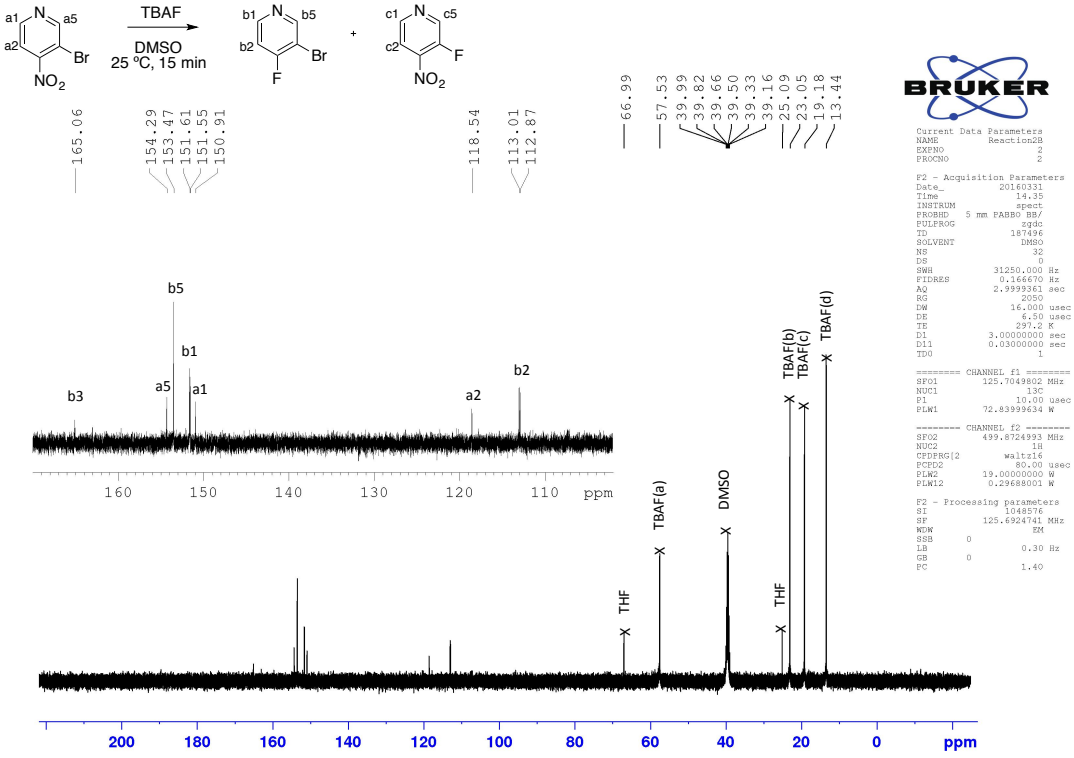
Elution times:
3-bromo-4-nitropyridine (**3**): 10.85 min – absorbs at 254 and 313 nm
3-bromo-4-fluoropyridine (**6**): 11.88 min – absorbs only at 254 nm

1B. NMR

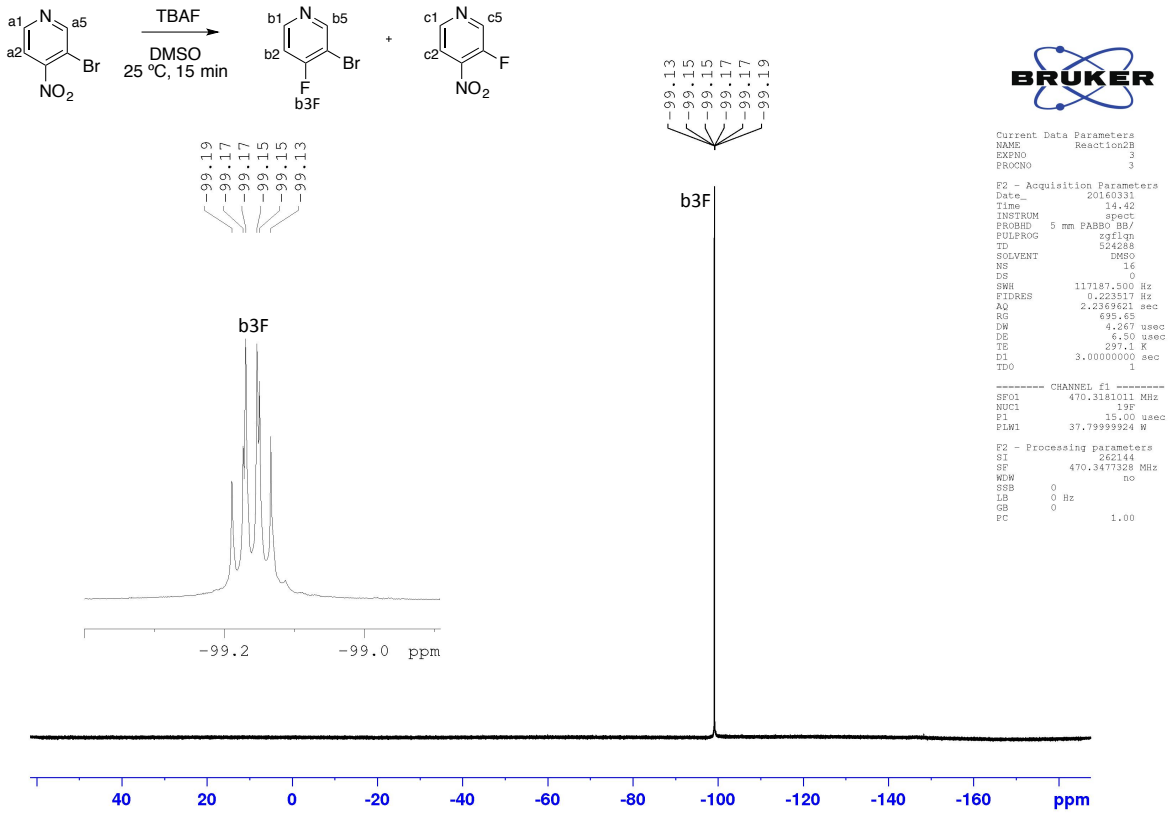
^{1}H NMR



^{13}C NMR



^{19}F NMR



BRUKER

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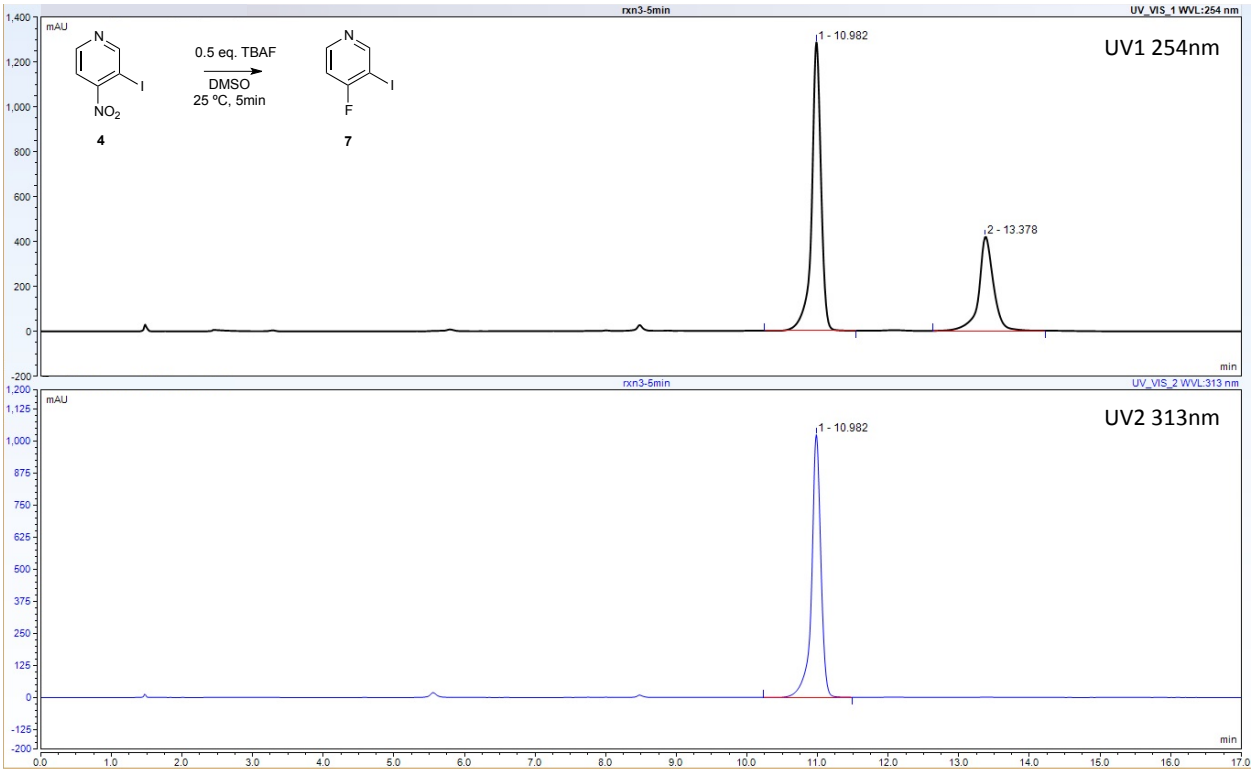
Sup. Fig. 2. Fluorination of 3-iodo-4-nitropyridine

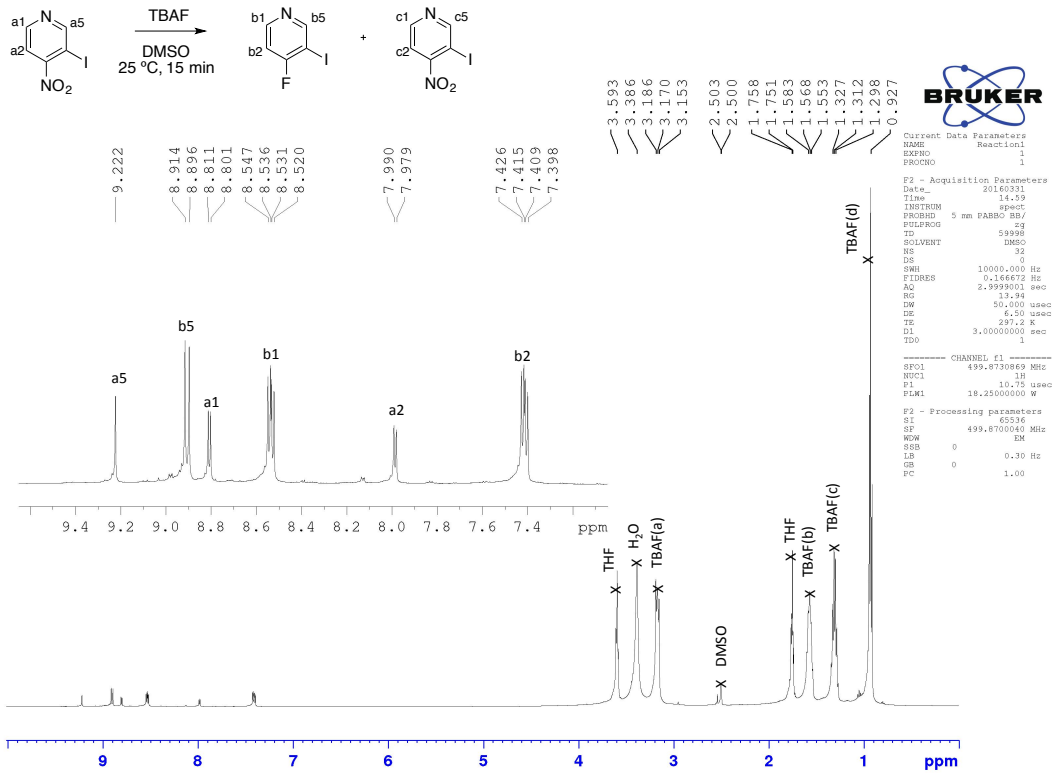
2A. UV HPLC trace



Elution times:
3-iodo-4-nitropyridine (**4**): 10.98 min – absorbs at 254 and 313 nm
3-iodo-4-fluoropyridine (**7**): 13.38 min – absorbs only at 254 nm

2B. NMR

^{1}H NMR



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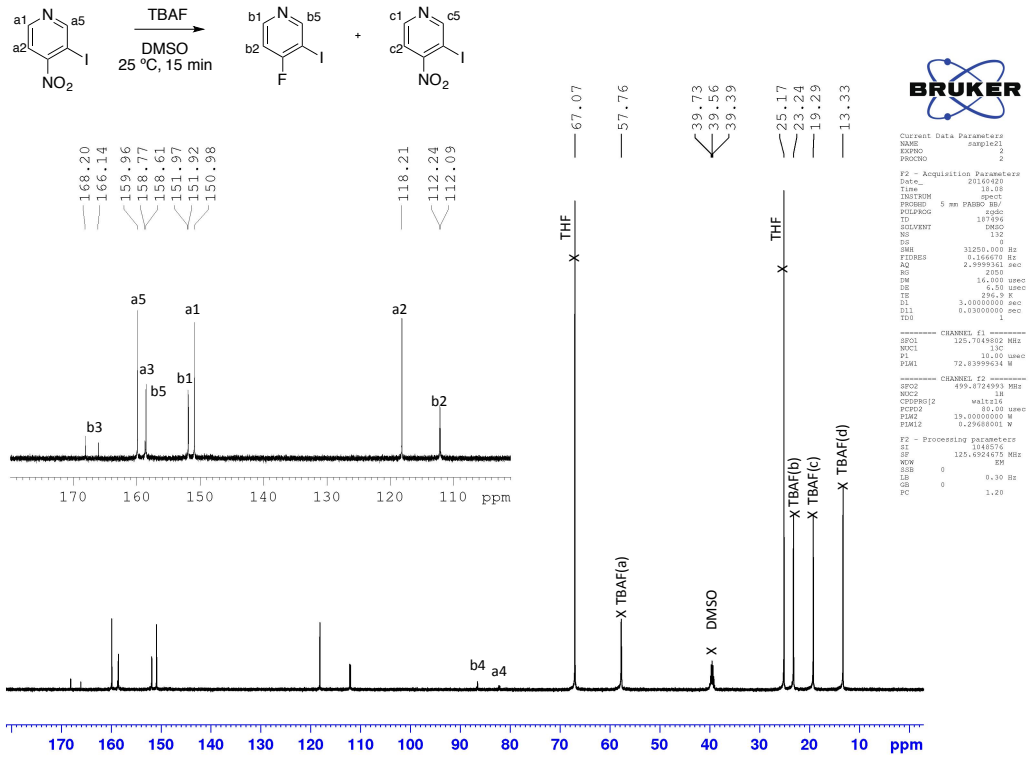

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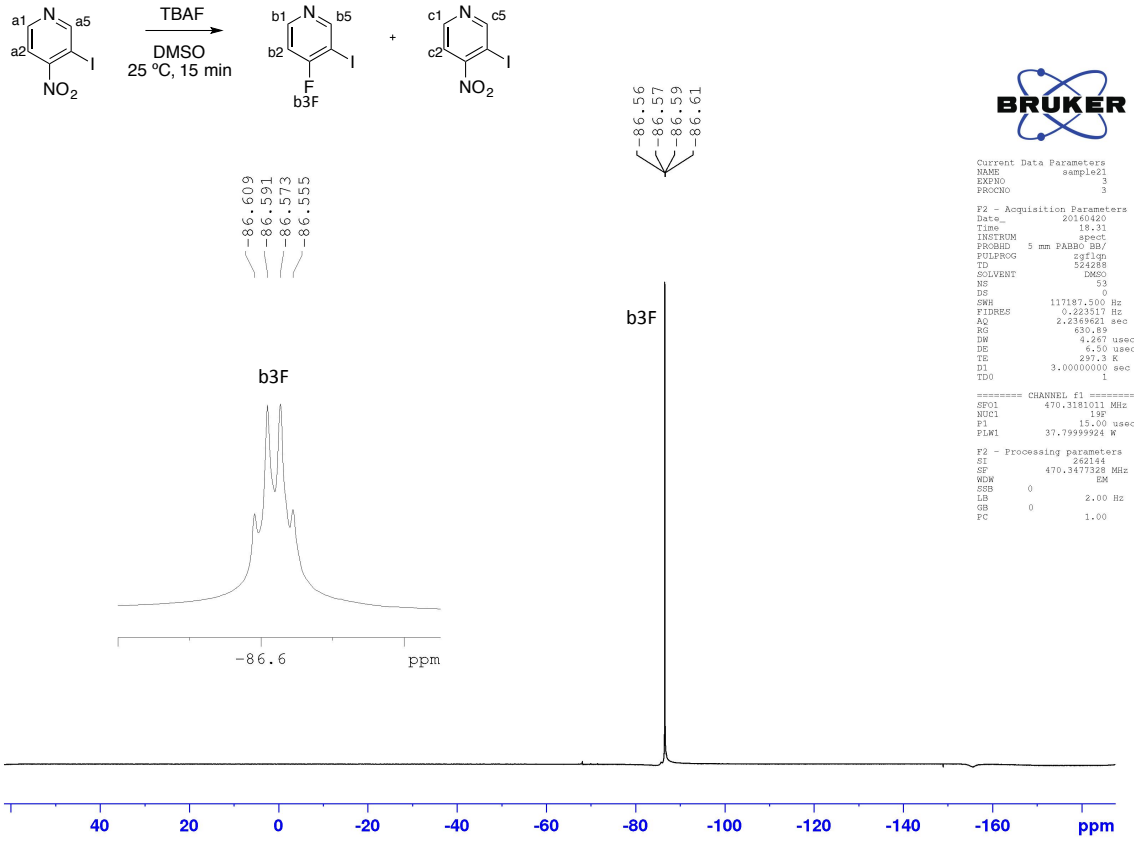
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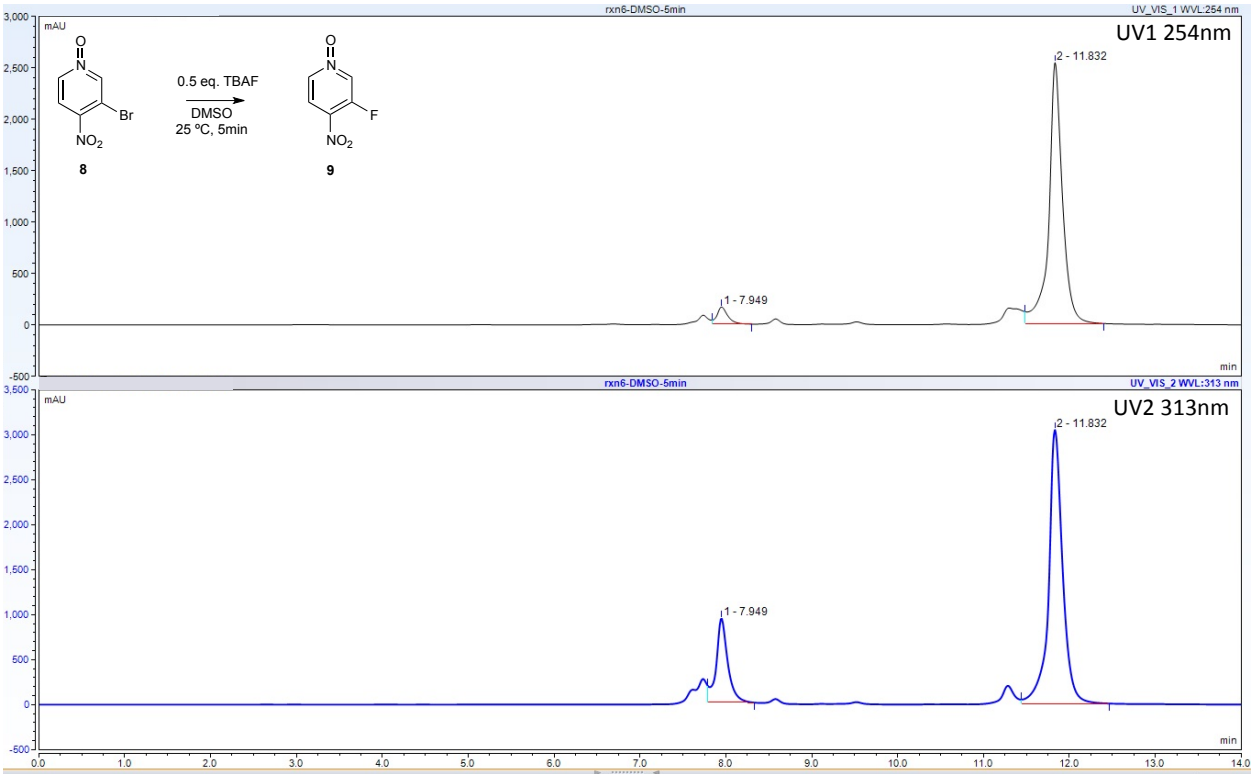
Sup. Fig. 3. Fluorination of 3-bromo-4-nitropyridine N-oxide

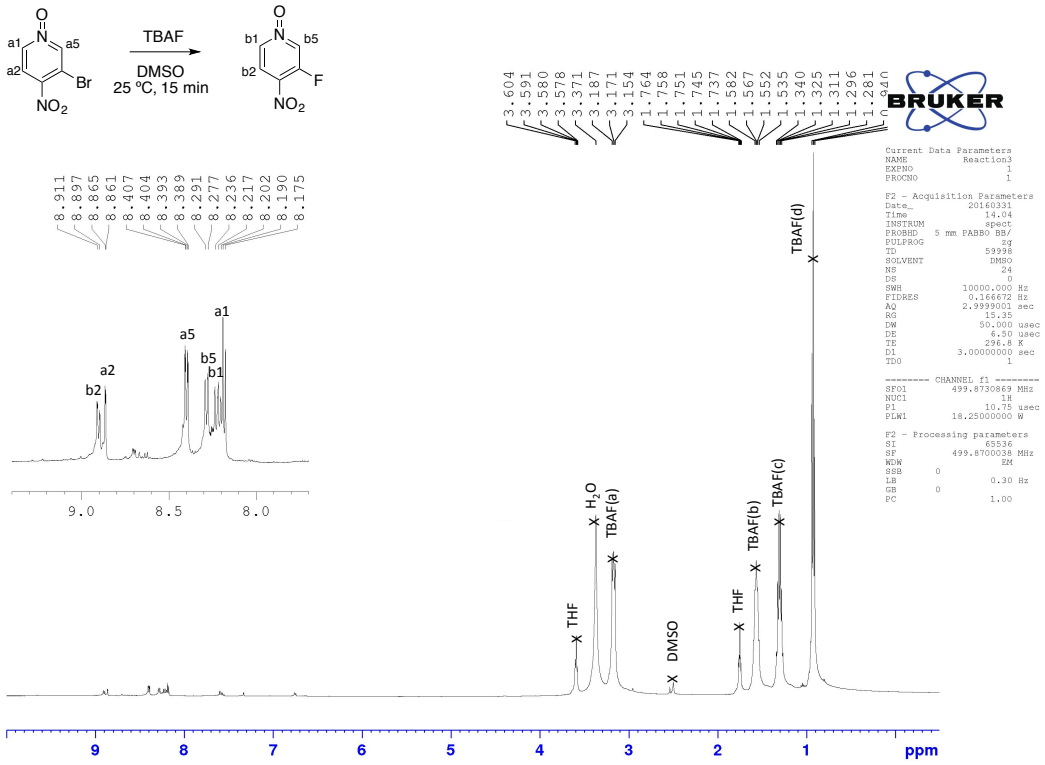
3A. UV HPLC trace



Elution times:
3-bromo-4-nitropyridine N-oxide (**8**): 11.83 min – absorbs at 254 and 313 nm
3-fluoro-4-nitropyridine N-oxide (**9**): 7.95 min – absorbs only at 254 and 313 nm

3B. NMR

^{1}H NMR



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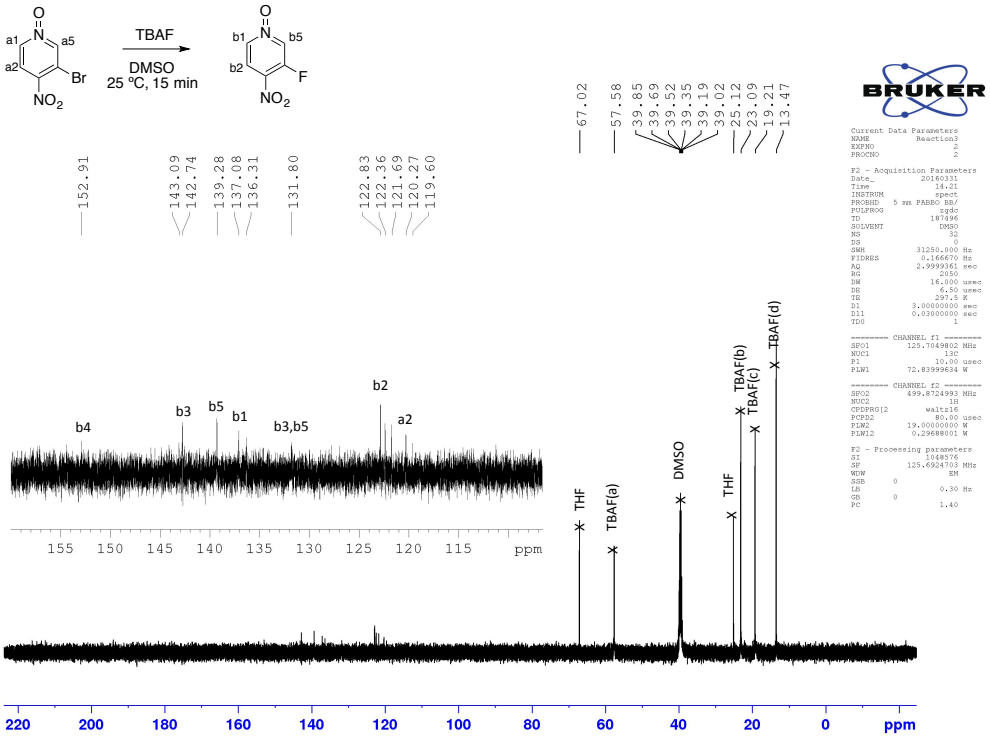

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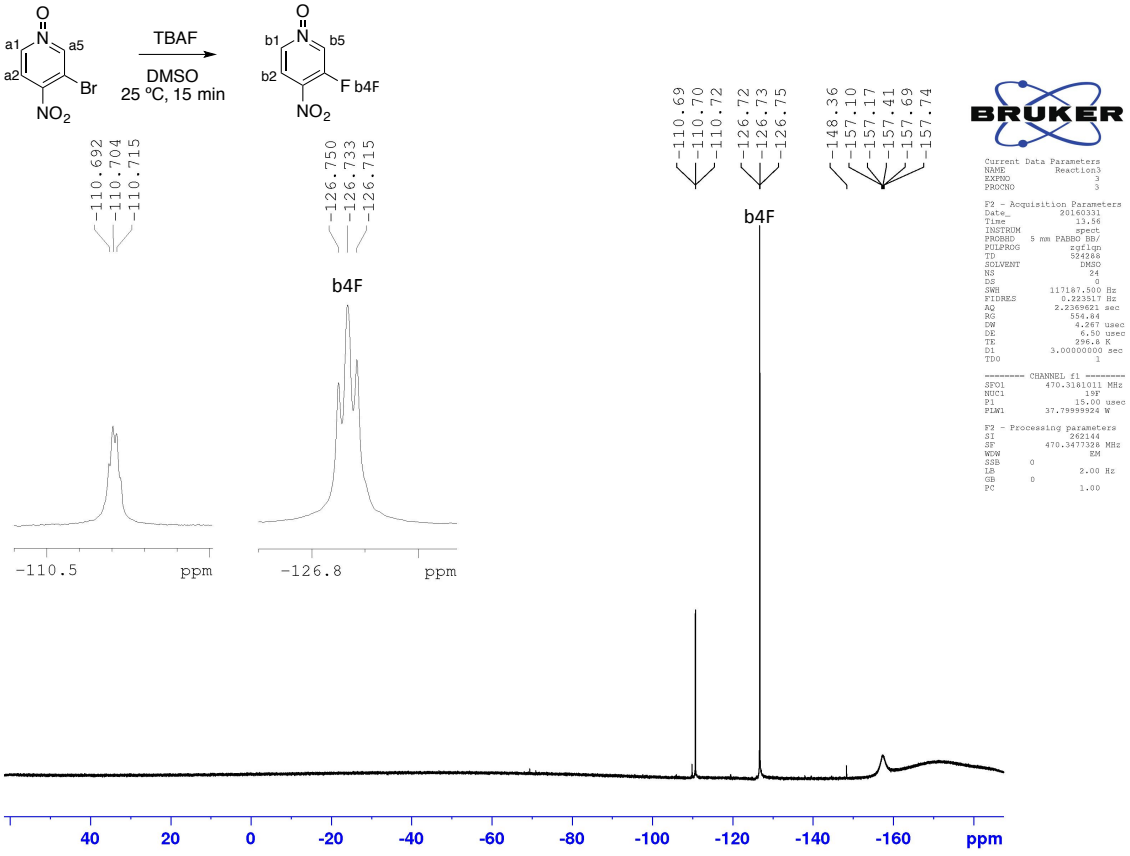
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b5
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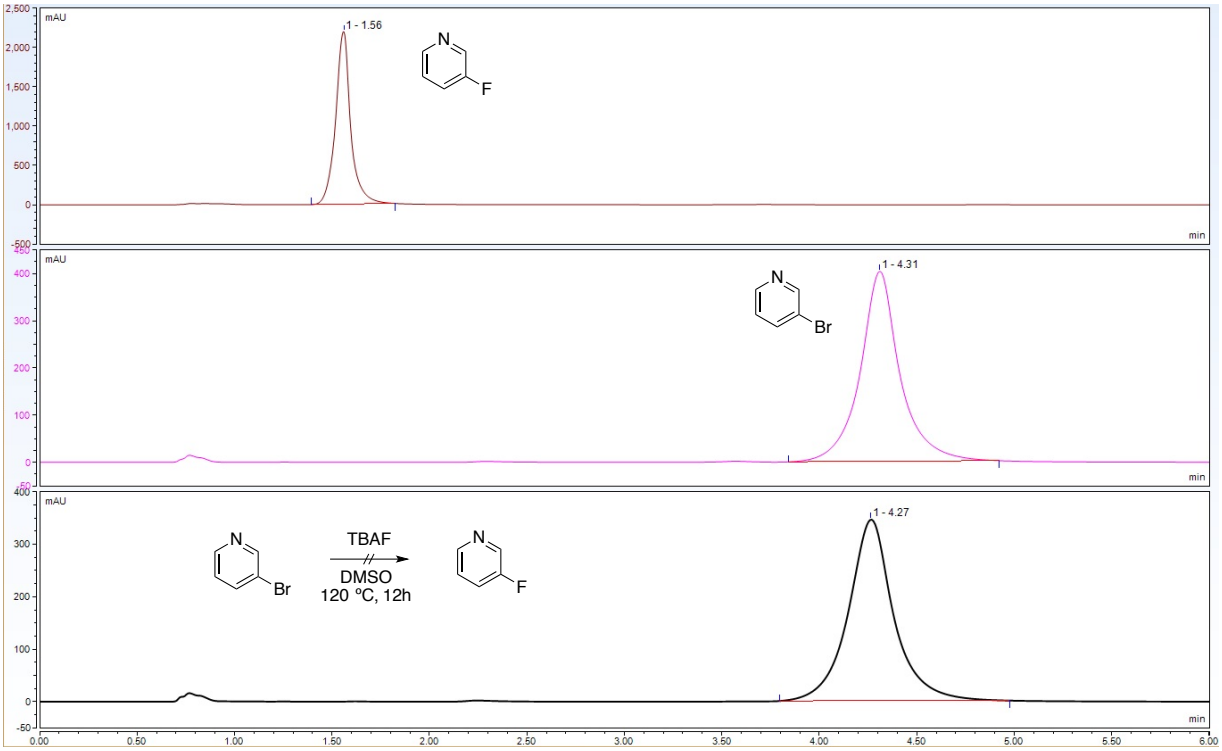
-157.74
b4F
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
ppm

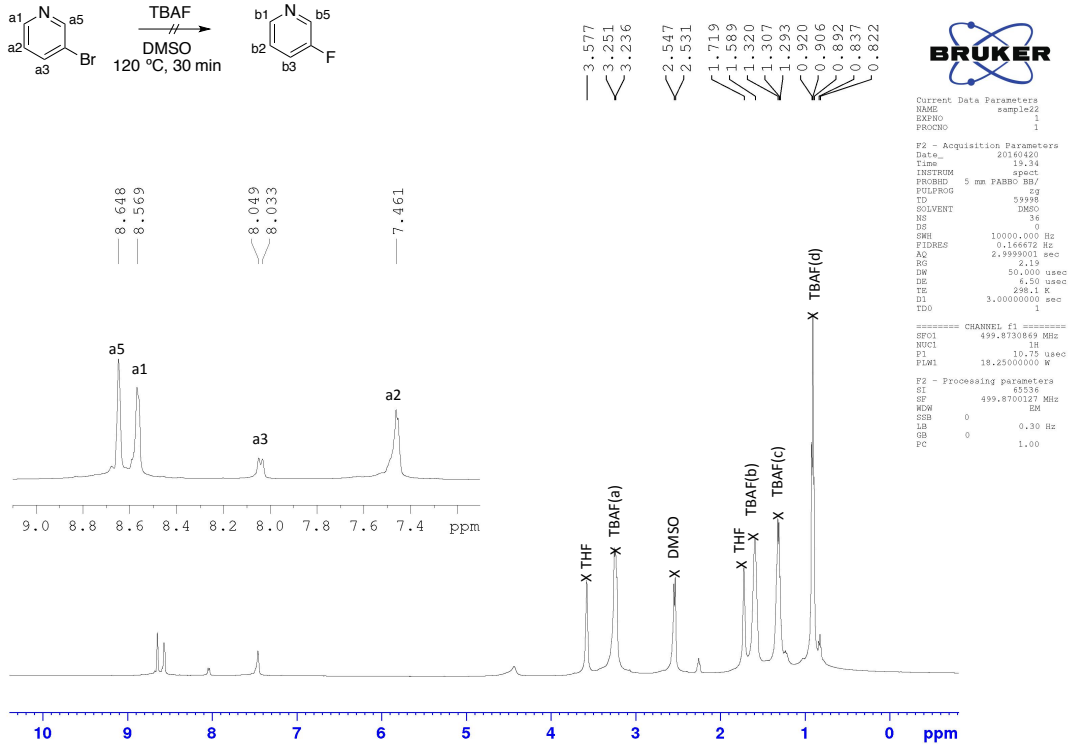
Sup. Fig. 4. Fluorination of 3-bromopyridine:

4A. UV HPLC trace.

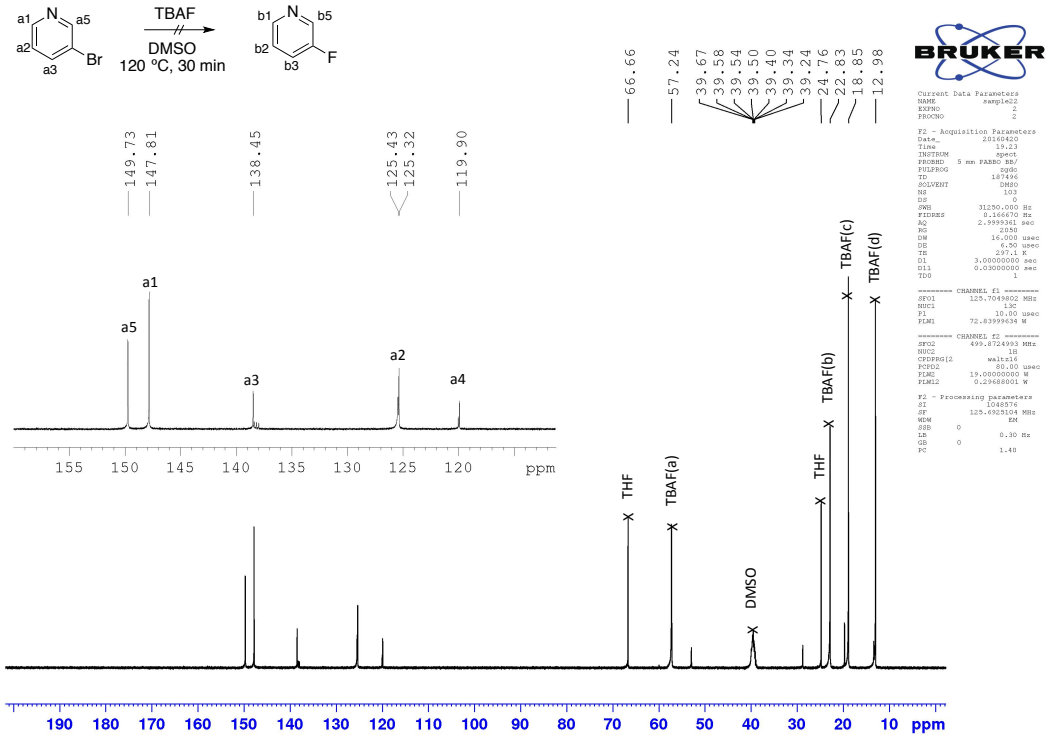


4B. NMR

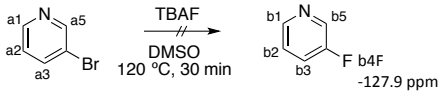
^{1}H NMR



^{13}C NMR



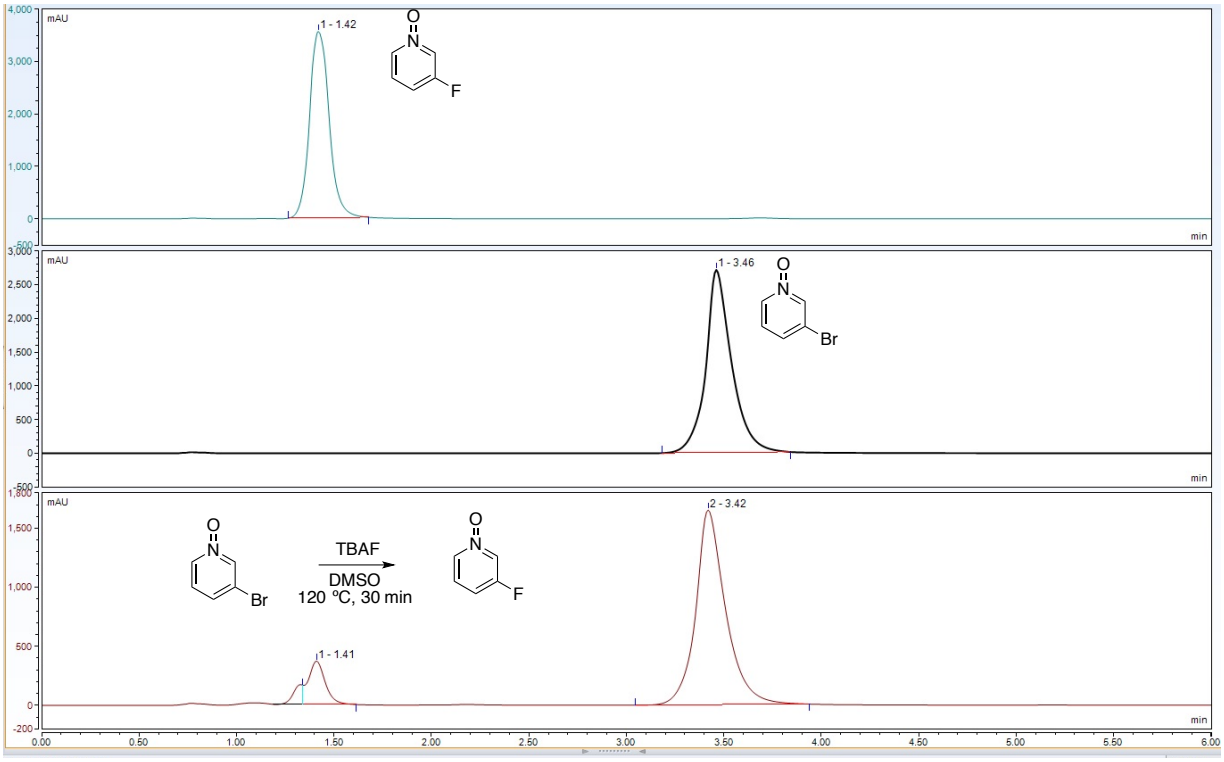
^{19}F NMR


a1
a5
a2
Br
a3
TBAF
DMSO
120 °C, 30 min
b1
b5
b2
F b4F
b3
-127.9 ppm

-110.4
-111.3
BRUKER
Current Data Parameters
NAME sample22
EXPNO 3
PROCNO 3
F2 - Acquisition Parameters
Date_ 20160420
Time 19.41
INSTRUM spect
PROBHD 5 mm PABBO BB/
PULPROG zgflqn
TD 524288
SOLVENT DMSO
NS 23
DS 0
SWH 117187.500 Hz
FIDRES 0.223517 Hz
AQ 2.2369621 sec
RG 499.75
DW 4.267 usec
DE 6.50 usec
TE 297.4 K
D1 3.00000000 sec
TD0 1
======== CHANNEL f1 ========
SFO1 470.3181011 MHz
NUC1 19F
P1 15.00 usec
PLW1 37.79999924 W
F2 - Processing parameters
SI 262144
SF 470.3477328 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.00
40
20
0
-20
-40
-60
-80
-100
-120
-140
-160
ppm

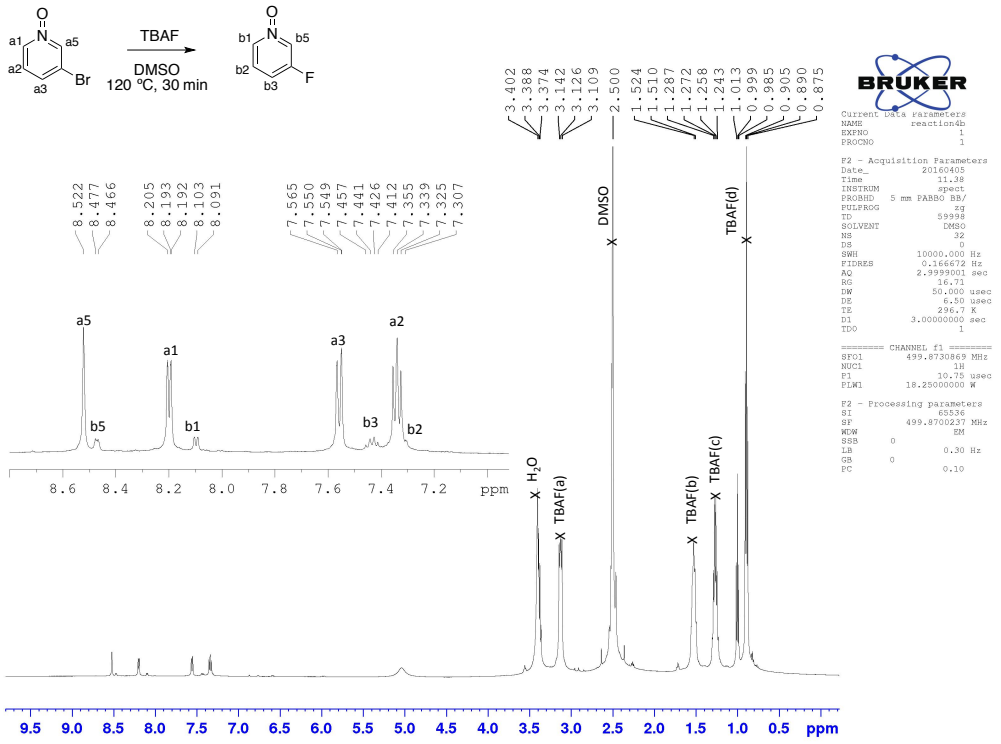
Sup. Fig. 5. Fluorination of 3-bromopyridine N-oxide:

5A. UV HPLC trace.

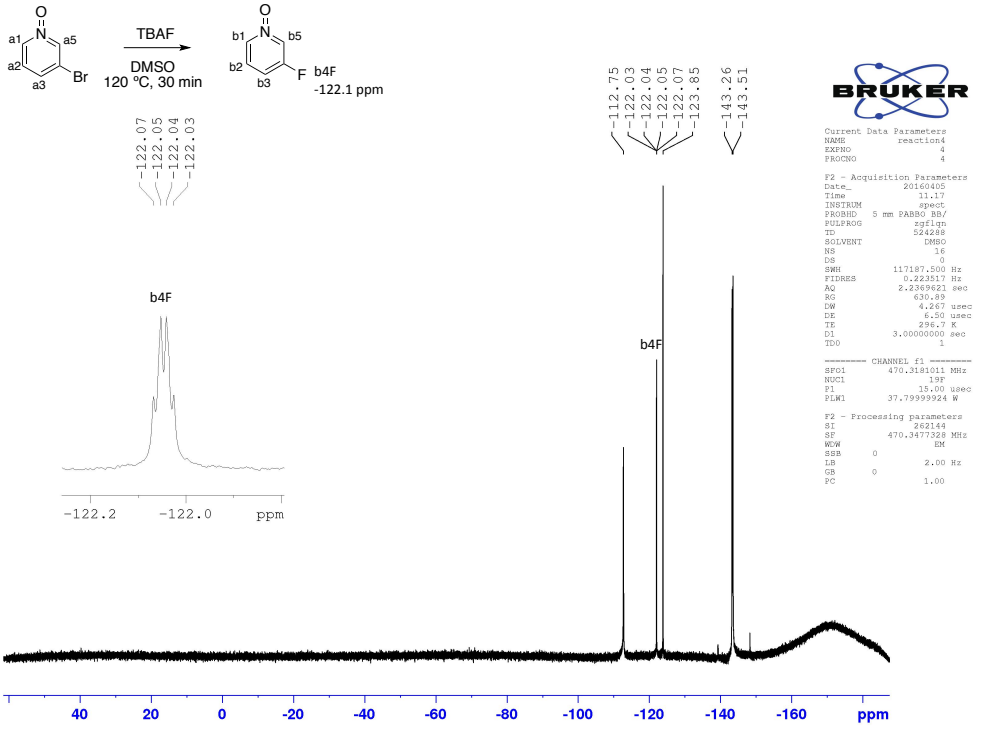


5B. NMR

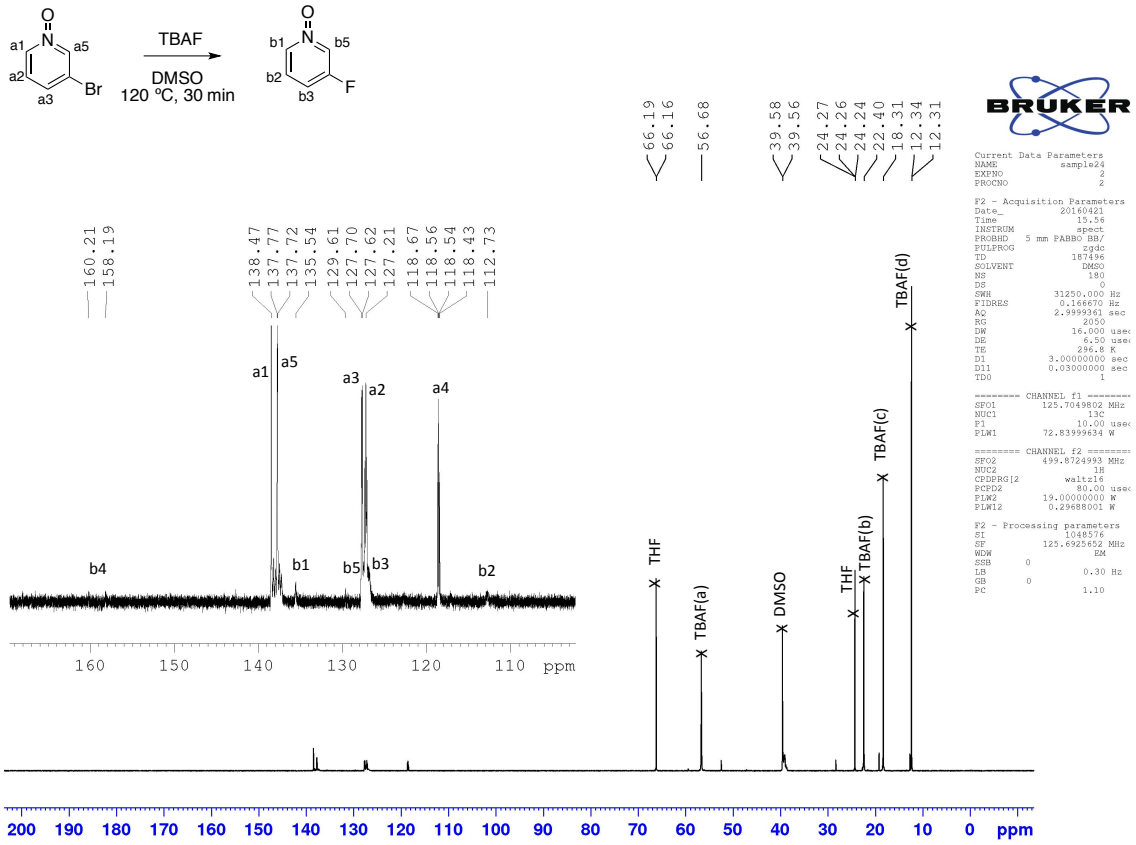
^{1}H NMR



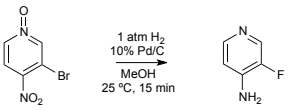
^{19}F NMR



^{13}C NMR (replicate reaction sample)

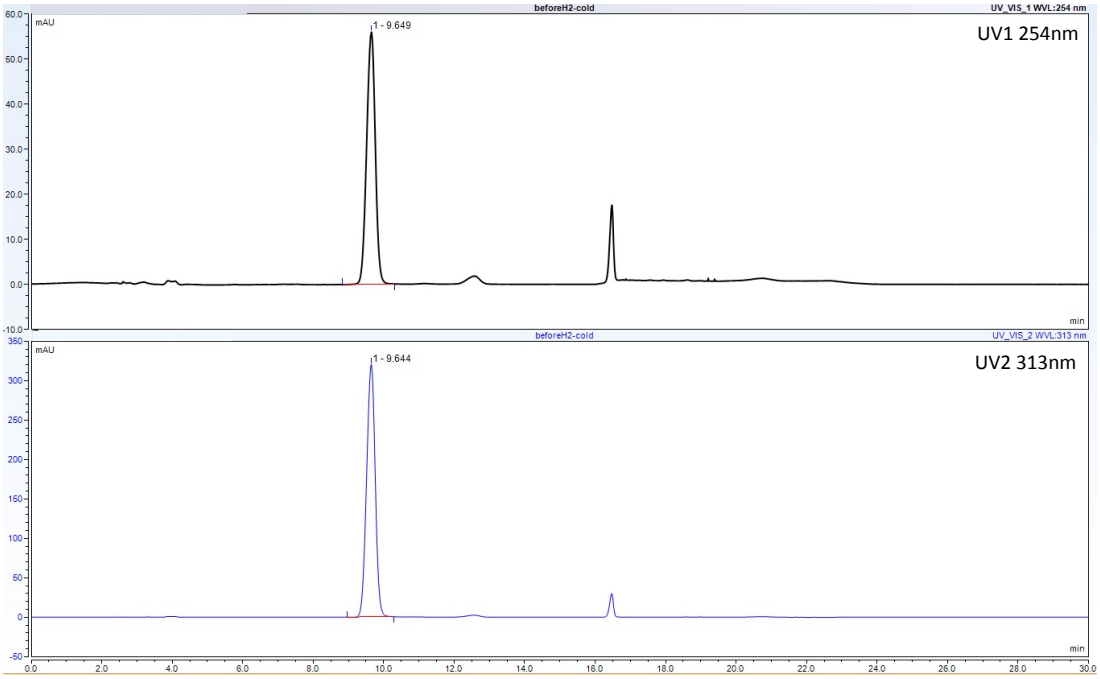


Sup. Fig. 6. UV HPLC traces hydrogenation of 3-fluoro-4-nitropyridine N-oxide (before and after)

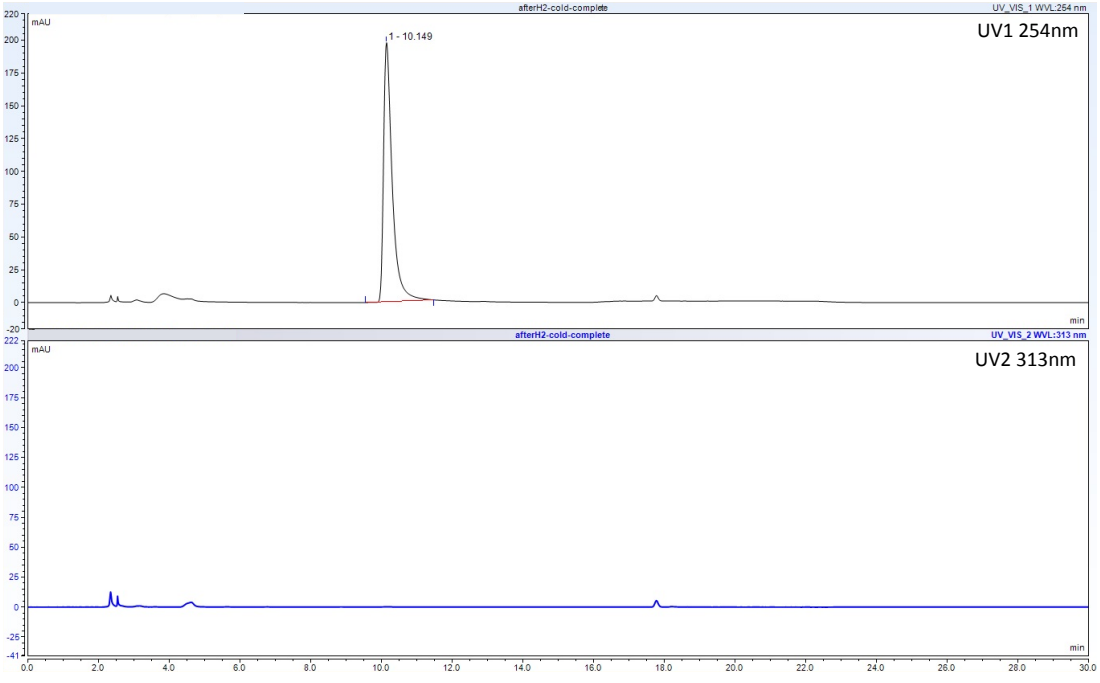


9 10

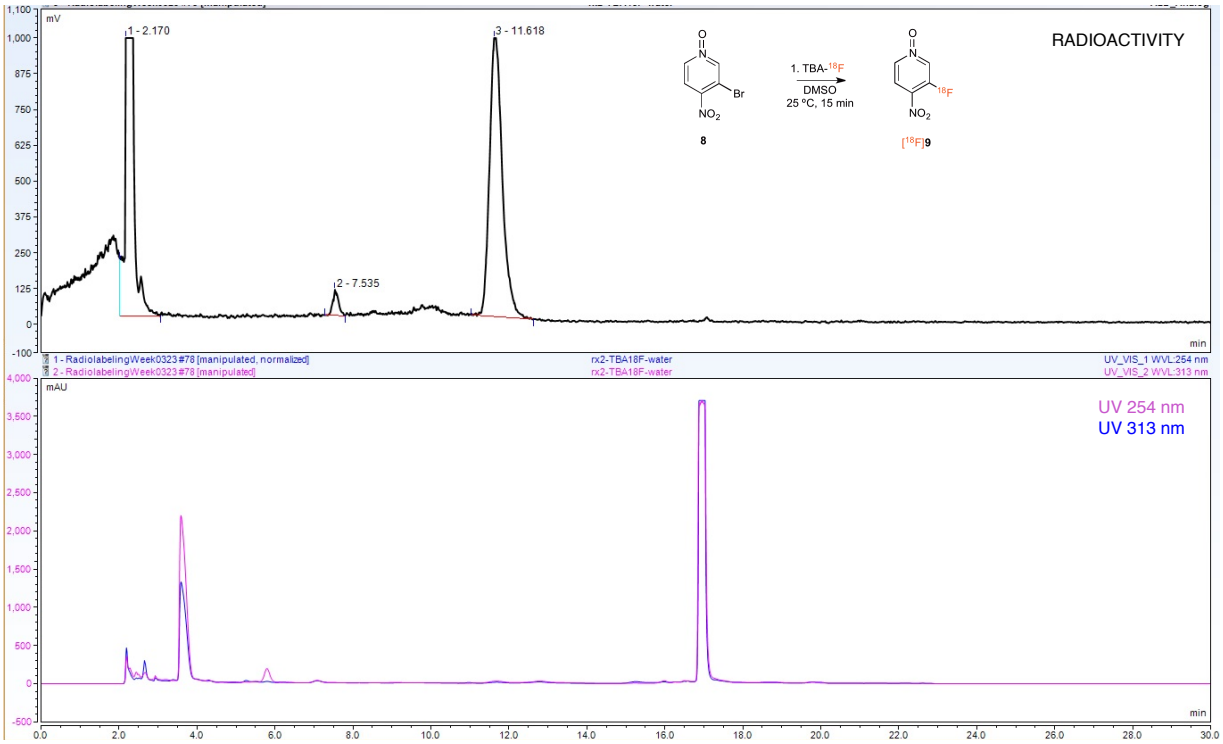
BEFORE



AFTER



Sup. Fig. 7. Radioactive and UV HPLC trace of radiofluorination of 3-bromo-4-nitropyridine N-oxide (not spiked with reference standard)



Product elutes at 11.6 min and precursor elutes at 17.2 min.

HPLC conditions: Eclipse XDB 5 µm, 9.4 x 250 mm C18 column (Agilent). Flow: 4 mL/min. Solvent A: 50 mM NH_4HCO_3, pH 8.0. Solvent B: 100% MeOH. Method: 0-13 min: 5% B, 13-14 min: 5-25% B, 14-20 min: 25% B, 20-21 min: 25-5% B, 21-30 min: 5% B.