Electronic Supplementary Material (ESI) for Chemical Communications.

Supporting Information

Preparation of Labeled Aromatic Amino Acids via Late-Stage ^{18}F-Fluorination of Chiral Nickel and Copper Complexes

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Organic Synthesis

General Experimental Information

If not otherwise stated, all chemical compounds, including reference compounds and solvents were obtained from Merck (Sigma-Aldrich, Germany), Thermo-Fisher Scientific (Alfa Aesar and Acros, Germany) and Fluorochem (United Kingdom). They were used directly without prior purification. Thin-layer chromatography (TLC) experiments were carried out using pre-coated plates of silica gel 60 F254 (Merck, Darmstadt, Germany), and analyzed under a UV lamp at 254 nm. Moisture sensitive reactions were carried out in pre-heated glassware (2 h at 140 °C) and proceeded under an argon atmosphere. All reactions were stirred magnetically and the organic layers were dried over anhydrous $MgSO_4$. ^1H NMR spectra were collected applying a Bruker Avance II 300 (Bruker Corporation, MA, USA) (300 MHz), Bruker Avance (600 MHz), Bruker Avance 200 (200 MHz), or Varian Inova (400 MHz) spectrometer. ^1H and ^{13}C chemical shifts are reported in ppm relative to residual peaks of deuterated solvents. Higher-order NMR spectra were approximately interpreted as first-order spectra, if possible. The observed signal multiplicities are characterized as follows: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m= multiplet, and br = broad. Coupling constants (*J*) were reported in hertz (Hz). ^{13}C NMR spectra [additional APT (Attached ProtonTest)] were collected via Bruker Avance II 300 (75.5 MHz), Varian Inova (101 MHz), Bruker Avance 200 (50.3 MHz), and Bruker Avance II 600 (125.9 MHz). ^{19}F NMR spectra were collected applying a Bruker Avance II 300 and Bruker Avance II 600 (376 MHz). All chemical shifts (δ, ppm) are provided with respect to the residual deuterated solvent peaks. Low-resolution electron spray ionization mass spectrometry [LRMS (ESI)] analyses of compounds were obtained using a LTQ Orbitrap XL (Thermo Fisher Scientific, Bremen, Germany). High-resolution electron spray ionization mass spectrometry [HRMS (ESI)] analyses of compounds were obtained using a Fourier-transform ion-cyclotron resonance LTQ FT Ultra (Thermo Fisher Scientific, Bremen, Germany). Low resolution electron impact ionization mass spectrometry gas chromatography (LRMS/GC) analyses were carried out using a ISQ GCMS system (Thermo Fisher Scientific, Bremen, Germany) equipped with ISQ (single quadrupole massspectrometer) and Trace 1310 (GC-chromatograph) under the following conditions: ionization potential: 70 eV; detecting ion polarity: positive; scan: m/z 50–500; GC column: Optima 5 Accent 30 m×0.25 mm ID×0.25 µm FD (Macherey-Nagel, Düren, Germany), temperature gradient (°C): 0–5 min: 70; 5–10 min: 70→270; 10–15 min: 270; GC injector + transfer line: isotherm 300 °C; flow rate (carrier gas): 1.2 mL/min (He, splitting: 1:10). High resolution electron impact ionization mass spectrometry gas chromatography (HRMS/GC) analyses were carried out using a Exactive GC

system (Thermo Fisher Scientific, Bremen, Germany) equipped with Orbitrap mass analyzer, Trace 1310 (GC-chromatograph) and TriPlus (RSH autoinjector) under the following conditions: ionization potential: 70 eV; detecting ion polarity: positive; ion source temperature: 250 °C; resolution: 60000; scan: m/z 50–500; GC column: TraceGold-5 SIL MS 30 m×0.25 mm ID×0.25 µm FD (Thermo Fisher Scientific, Bremen, Germany), temperature gradient (°C): 0–1 min: 40; 1–17 min: 40→280; 17–22 min: 280; GC injector + transfer line: isotherm 300 °C; flow rate (carrier gas): 1 mL/min (He, split: 1:20). Elemental analysis (C, H): Vario MICRO Cube (Elementar Analysensysteme GmbH, Langenselbold, Germany). Elemental analysis (C, H, O): Vario EL Cube (Elementar Analysensysteme GmbH, Langenselbold, Germany); analyses were carried out in triplicate.

The C-Bpin signal was unobservable in the ^{13}C NMR spectra.

The preparation of the MOMCl solution (2.1 M, 18% w/w, 0.91 g/mL) in toluene was carried out according to the protocol described by Berliner *et al*.[1]

General procedure for alkylation upon Ni/Cu-BPX-Gly or Ala (GP1)

NaH (60% suspension in mineral oil) (1.6 equiv) was added in small portions to a solution of Cu/Ni-(*S*)-BPX-Gly or -Ala (1 equiv) and the *corresponding alkylating agent* **2a**–**i** (1.6 equiv) in DMF/MeCN (1:2) at 0 °C and the reaction mixture was stirred at 0 °C for 20 min and thereafter, stirred at room temperature for an additional 2 hours. The reaction mixture was poured into an ice-cold 0.5 M pH 5.5 sodium phosphate buffer, the resulting emulsion was extracted thrice with EtOAc, and washed thrice with brine. The organic fraction was dried and concentrated under reduced pressure to give a red residue, which was purified by column chromatography on silica gel using a gradient elution of acetone/$CHCl_3$ to afford the crude product which was further purified by chromatography on C_{18} silica gel using a gradient elution with aqueous MeCN and, finally, triturated with EtOAc/hexane to yield green Cu-BPB-AA or red Ni-BPX-AA solid, respectively. RP Chromatography using aqueous MeCN and subsequent evaporation of the eluent at 40 ºC (under reduced pressure) sometimes caused hydrolysis of the Bpin group furnishing the corresponding boronic acids as side products (e.g., in the case of **3b**, **3h** and **3i**; in these cases we provide NMR-spectra of the respective products before and after RP chromatography; prolonged heating (> 3 h) of solutions of Bpin-substituted Ni-BPB-AAAs in 50% MeCN at 50 ºC caused complete hydrolysis of the Bpin group). As boronic acids are generally better suited substrates for alcohol-enhanced Cu-mediated radiofluorination than the corresponding Bpin esters, no attempts to separate them (or to convert them back into the Bpin

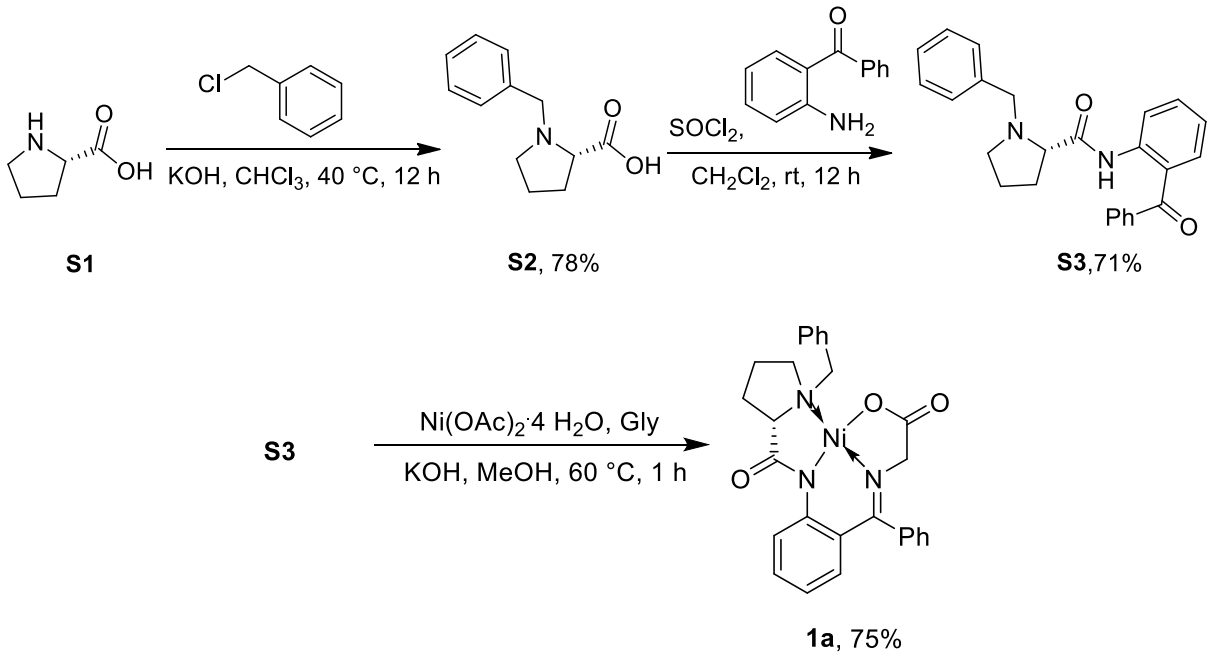
ester) were performed and the mixtures were directly used for the radiolabeling step. Omission of the RP purification step led in some cases to substantially lower ^{18}F-incorporation rates.

General procedure for radical bromination (GP2)

A solution of the corresponding substituted toluene (14.3 mmol), NBS (14.3 mmol) and AIBN (2.25 mmol) in cyclohexane (40 mL) was stirred under Ar under irradiation with a light source (550 W) in a quartz reaction vessel for 3 hours. The reaction mixture was filtered, and the filter cake was washed with hexane. The organic extract was dried and concentrated under reduced pressure to give a yellow oil, which was purified by column chromatography on silica gel using a gradient elution of EtOAc/hexane to give the desired product.

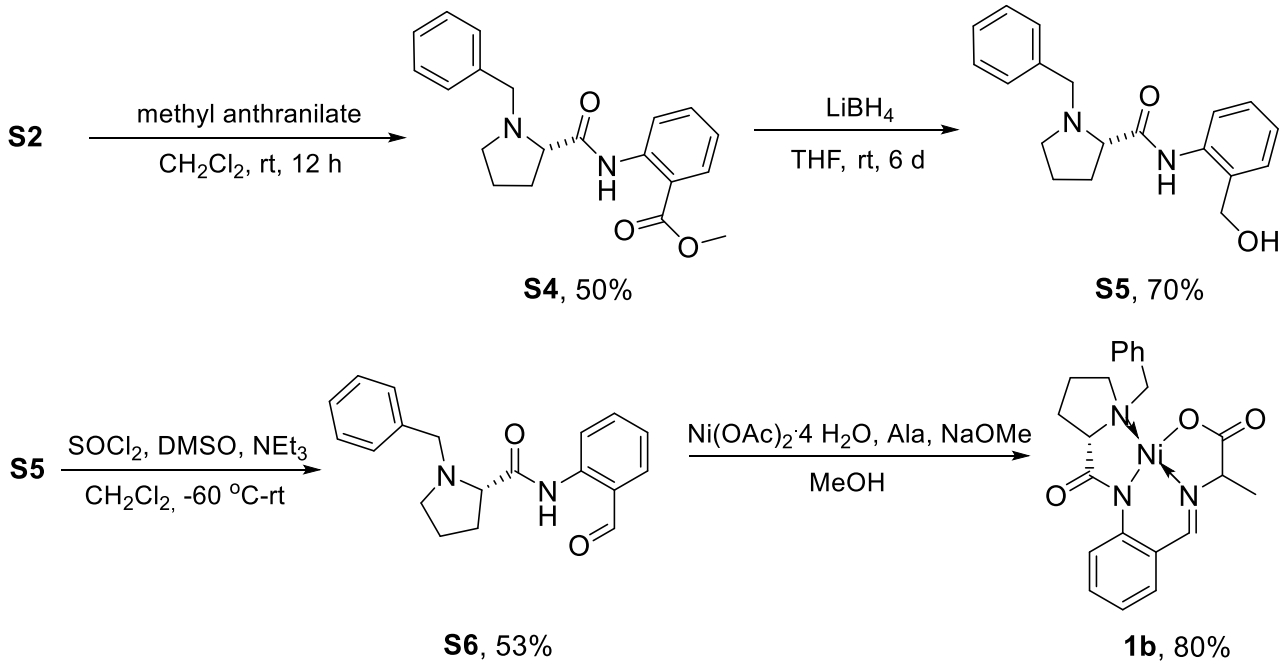
Experimental Procedures and Characterization Data

Synthesis of Ni-/Cu-BPX complexes



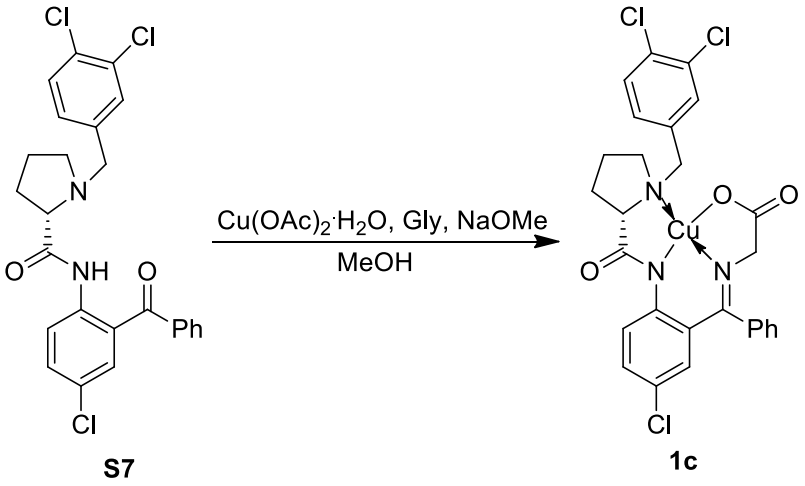
Scheme S1. The preparation of (*S*)-Ni-BPB-Gly (**1a**).[2]

The preparation of (*S*)-Ni-BPB-Gly (**1a**)[3] was carried out according to the protocol described by Belokon *et al*. (Scheme S1)[2]. A similar protocol allowed (*S,S/R*)-Ni-BPX-Ala (**1b**) to be accessed (Scheme S2).[4]



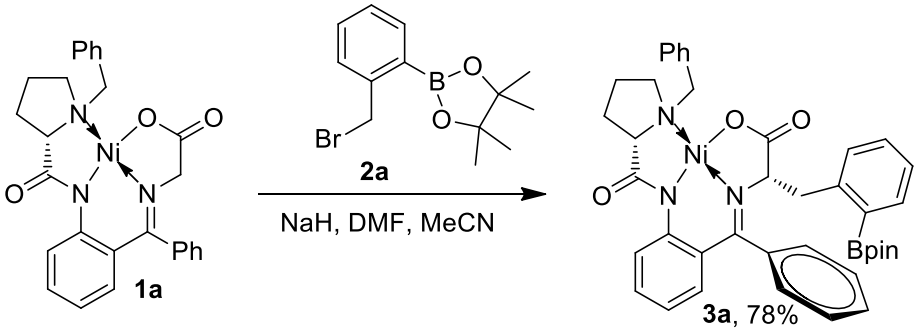
Scheme S2. The preparation of (*S,S/R*)-Ni-BPX-Ala (**1b**).

1c was prepared similarly to the protocol reported by Smith *et al.* (Scheme S3).[5]



Scheme S3. The preparation of chiral Cu complex **1c**.[5]

(*S*,*S*)-Ni-BPB-2-BpinPhe (**3a**)



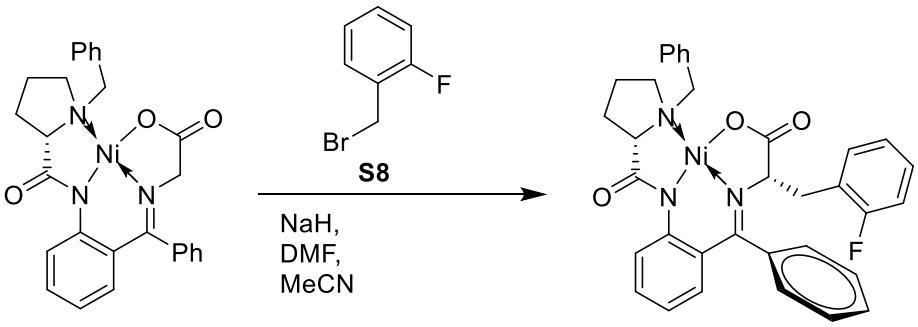
The above compound (**3a**) was prepared according to GP1 whereby, **1a** (0.52 g, 1.05 mmol), **2a** (0.5 g, 1.68 mmol), NaH (60% suspension in mineral oil) (70 mg, 17.5 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 78% (0.59 g, 0.82 mmol).

R_f 0.42, (1:20 acetone/$CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 13.2 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 2H), 7.89 – 7.76 (m, 1H), 7.55 – 7.21 (m, 8H), 7.19 – 7.00 (m, 3H), 6.60 (t, *J* = 7.6 Hz, 1H), 6.54 – 6.47 (m, 1H), 5.95 (d, *J* = 7.6 Hz, 1H), 4.36 (d, *J* = 12.6 Hz, 1H), 4.27 (t, *J* = 5.9 Hz, 1H), 3.87 (d, *J* = 5.9 Hz, 2H), 3.55 – 3.35 (m, 2H), 3.32 – 3.04 (m, 2H), 2.84 – 2.66 (m, 1H), 2.62 – 2.44 (m, 1H), 2.15 – 1.86 (m, 2H), 1.19 (s, 6H), 1.11 (s, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ 180.34, 178.47, 170.73, 142.74, 142.50, 136.92, 134.00, 133.72, 133.34, 132.05, 131.47, 131.36, 131.09, 129.01, 128.76, 128.70, 128.56, 128.35, 127.90, 127.32, 126.44, 126.18, 123.05, 120.38, 83.64, 72.96, 70.80, 62.99, 57.13, 42.35, 31.06, 24.94, 24.34, 23.80. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine fragment were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{40}H_{43}N_3O_5NiB^+$ calcd.714.2644, observed 714.2642; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-2-FPhe (**18a**)



1a **18a**, 69%

The above compound (**18a**)[6] was prepared according to GP1 whereby, **1a** (0.94 g, 1.89 mmol), 1-(bromomethyl)-2-fluorobenzene (**S8**, 0.5 g, 2.65 mmol), NaH (60% suspension in mineral oil) (120 mg, 3.0 mmol) and DMF/MeCN 1:2 (20 mL) were utilized. Yield: 69% (0.83 g, 1.29 mmol; according to the ^{1}H-NMR solvate with 0.5 mol. Et_2O).

R_f 0.35, (1:8 acetone/$CHCl_3$).

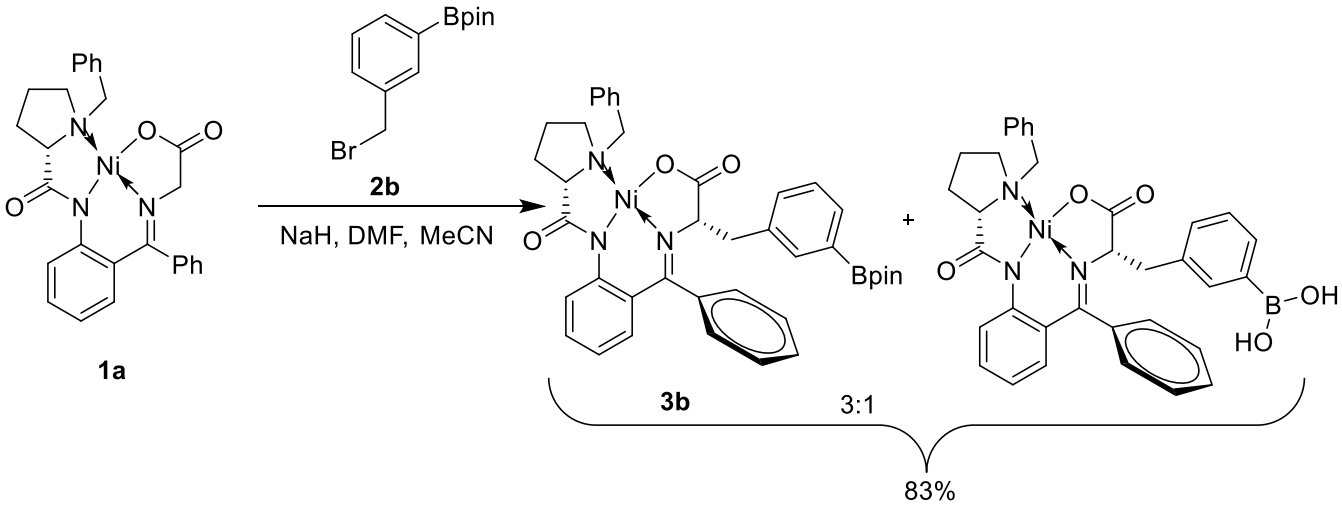
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 7.2 Hz, 2H), 7.61 – 7.47 (m, 2H), 7.46 – 7.40 (m, 1H), 7.40 – 7.09 (m, 9H), 6.98 (d, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 4.1 Hz, 2H), 4.29 (dd, *J* = 9.1, 3.5 Hz, 2H), 3.56 – 3.43 (m, 1H), 3.31 (t, *J* = 8.3 Hz, 1H), 3.22 – 3.06 (m, 2H), 3.02 – 2.89 (m, 1H), 2.47 – 2.23 (m, 3H), 2.01–1.87 (m, 1H), 1.78 – 1.58 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.25, 178.41, 171.98, 162.03 (d, *J* = 246.6 Hz), 142.90, 134.07, 133.56, 133.18, 132.89 (d, *J* = 4.4 Hz), 132.32, 131.53, 129.70, 129.34 (d, *J* = 8.1 Hz), 128.95, 128.91, 128.76, 128.19 (d, *J* = 3.1 Hz), 127.14, 126.21, 124.73 (d, *J* = 3.2 Hz), 123.25, 123.09 (d, *J* = 15.8 Hz), 120.49, 115.74, 115.52, 70.79, 70.34, 63.23, 57.03, 33.28, 30.76, 23.11. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.29.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{34}H_{31}N_3O_3NiF^+$ calcd. 606.1698, observed 606.1698; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-3-BpinPhe (**3b**)



The above compound (**3b**) was prepared according to GP1 whereby, **1a** (0.78 g, 1.56 mmol), **2b** (0.65 g, 2.20 mmol), NaH (60% suspension in mineral oil) (100 mg, 2.50 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 83% (0.90 g; total yield of **3b** and the corresponding boronic acid). In this instance partial hydrolysis of the pinacol boronate moiety to boronic acid was observed during reversed-phase purification. As boronic acids are typically even better substrates for the alcohol-enhanced Cu-mediated radiofluorination than the corresponding Bpin esters, no attempt to separate it (or to convert it back into the Bpin ester) was made and the mixture was directly used for the radiolabeling step. Omission of the RP purification step could lead to lower ^{18}F-incorporation rates.

R_f 0.42, (1:20 acetone/$CHCl_3$).

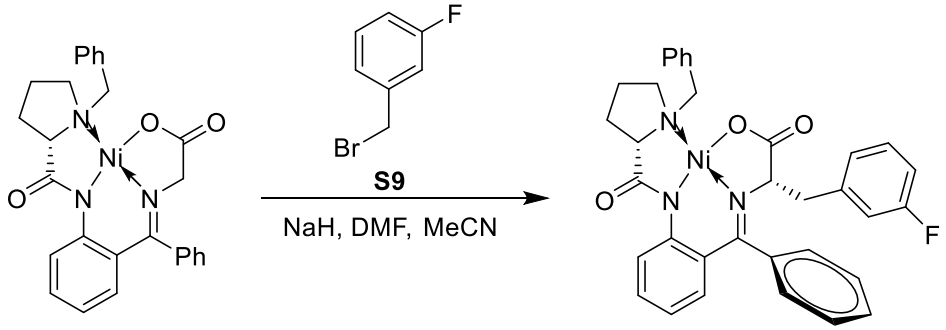
^{1}H NMR (400 MHz, $CDCl_3$; before RP purification) δ 8.33 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 2H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.61 (s, 1H), 7.59 – 7.47 (m, 2H), 7.45 – 7.37 (m, 2H), 7.35 – 7.22 (m, 4H), 7.20 – 7.12 (m, 2H), 6.81 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 3.9 Hz, 2H), 4.32 (d, *J* = 13.5 Hz, 1H), 4.26 (dt, *J* = 13.5, 7.2 Hz, 1H), 3.48 (d, *J* = 12.7 Hz, 1H), 3.30 (dd, *J* = 9.6, 7.6 Hz, 1H), 3.20 (dd, *J* = 13.7, 4.6 Hz, 1H), 3.16 – 3.09 (m, 1H), 2.95 (dd, *J* = 13.7, 6.0 Hz, 1H), 2.60 – 2.42 (m, 1H), 2.40 – 2.26 (m, 2H), 2.02 – 1.90 (m, 1H), 1.83 – 1.71 (m, 1H), 1.31 (s, 6H), 1.29 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$; before RP purification) δ 180.30, 178.60, 171.11, 143.02, 136.82, 135.08, 134.14, 133.71, 133.50, 133.29, 133.18, 132.24, 131.54, 129.67, 128.98, 128.86, 128.76, 128.73, 128.15, 127.91, 127.17, 126.00, 123.40, 120.40, 83.82, 71.51, 70.33, 63.13,

57.15, 40.15, 30.74, 24.86, 24.77, 23.28. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{40}H_{43}N_3O_5NiB^+$ calcd. 714.2644, observed 714.2643; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-3-FPhe (**18b**)



1c **18b**, 88%

The above compound (**18b**)[6] was prepared according to GP1 whereby, **1a** (0.52 g, 1.04 mmol), 1-(bromomethyl)-3-fluorobenzene (**S9**, 0.32 g, 1.68 mmol), NaH (60% suspension in mineral oil) (70 mg, 1.75 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 88% (0.59 g, 0.85 mmol; according to the ^{1}H-NMR solvate with 0.5 mol. Et_2O).

R_f 0.42, (1:20 acetone/$CHCl_3$).

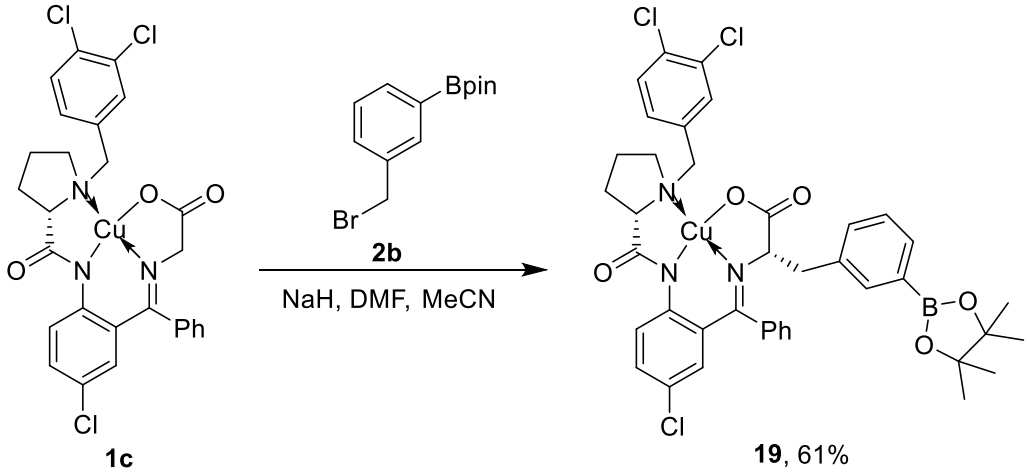
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 6.7 Hz, 2H), 7.65 – 7.49 (m, 2H), 7.48 – 7.38 (m, 1H), 7.39 – 7.22 (m, 4H), 7.21 – 7.00 (m, 3H), 6.98 – 6.78 (m, 3H), 6.73 – 6.59 (m, 2H), 4.38 – 4.12 (m, 2H), 3.58 – 3.40 (m, 2H), 3.32 (t, *J* = 7.9 Hz, 1H), 3.23 – 3.11 (m, 1H), 3.06 (d, *J* = 12.1 Hz, 1H), 2.87 (dd, *J* = 12.1, 4.9 Hz, 1H), 2.62 – 2.43 (m, 1H), 2.43 – 2.28 (m, 2H), 2.08 – 1.89 (m, 1H), 1.86 – 1.69 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.37, 178.22, 171.36, 163.07 (d, *J* = 246.6 Hz), 142.91, 138.32 (d, *J* = 7.4 Hz), 134.07, 133.53, 133.25, 132.49, 131.51, 130.15 (d, *J* = 8.2 Hz), 129.90, 129.08 (d, *J* = 22.6 Hz), 128.83, 128.80, 127.76, 127.17, 126.23, 126.20, 126.06, 123.44, 120.63, 117.34 (d, *J* = 21.0 Hz), 114.37 (d, *J* = 20.9 Hz), 71.13, 65.83, 63.32, 57.23, 39.53, 30.73, 23.20. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.49.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{34}H_{31}N_3O_3NiF^+$ calcd. 606.1698, observed 606.1698; correct isotopic pattern.

(*S*,*S*)-Cu-BPB-3-BpinPhe (**19**)



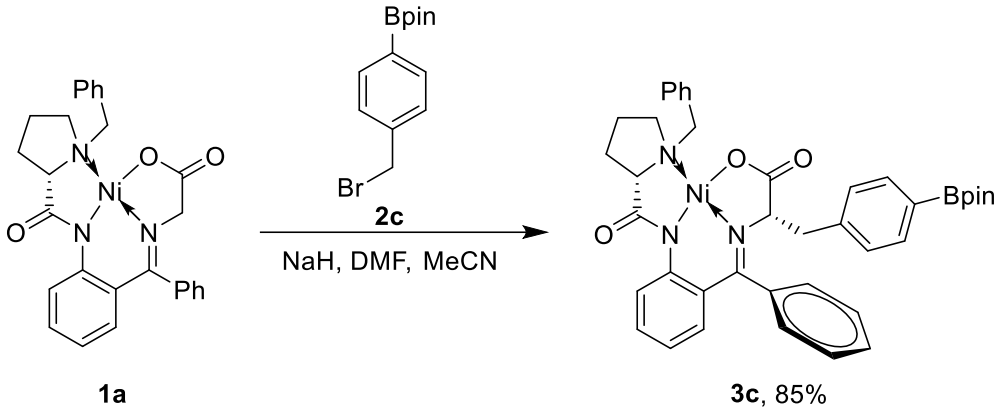
The above compound (**19**) was prepared according to GP1 whereby, **1c** (0.40 g, 0.66 mmol), **2b** (0.314 g, 1.06 mmol), NaH (60% suspension in mineral oil) (42 mg, 1.06 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 61% (0.33 g, 0.40 mmol).

The paramagnetic nature of Cu(II) rendered characterization by NMR spectroscopy inapplicable.

R_f 0.42, (1:20 acetone/$CHCl_3$).

HRMS (ESI) *m/z* $[M + H]^+$, $C_{40}H_{40}N_3O_5CuCl_3B^+$ calcd. 823.1405, observed 823.1386; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-4-BpinPhe (**3c**)



1a **3c**, 85%

The above compound (**3c**) was prepared according to GP1 whereby, **1a** (1.00 g, 2.00 mmol), **2c** (0.95 g, 3.2 mmol), NaH (60% suspension in mineral oil) (130 mg, 3.2 mmol) and DMF/MeCN 1:2 (20 mL) were utilized. Yield: 85% (1.22 g, 1.70 mmol).

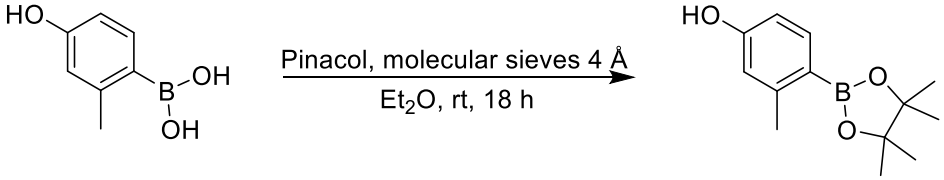
R_f 0.42, (1:20 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 7.1 Hz, 2H), 7.89 (d, *J* = 7.9 Hz, 2H), 7.61 – 7.52 (m, 2H), 7.52 – 7.45 (m, 1H), 7.35 – 7.29 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 2H), 7.20 – 7.14 (m, 2H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 3.9 Hz, 2H), 4.34 – 4.25 (m, 2H), 3.45 (d, *J* = 13.2 Hz, 1H), 3.29 (t, *J* = 8.6 Hz, 1H), 3.12 – 2.97 (m, 2H), 2.83 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.25 (dd, *J* = 15.5, 7.1 Hz, 2H), 2.20 – 2.08 (m, 1H), 2.07 – 1.97 (m, 1H), 1.65 – 1.50 (m, 1H), 1.36 (s, 6H) 1.35 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.42, 178.65, 171.23, 142.94, 138.91, 135.32, 134.19, 133.50, 133.14, 132.37, 131.54, 130.00, 129.80, 129.12, 128.95, 128.77, 128.72, 127.83, 127.12, 126.03, 123.41, 120.57, 83.78, 71.28, 70.34, 63.34, 57.41, 39.54, 30.66, 24.90, 24.67, 23.19. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{40}H_{43}N_3O_5NiB^+$ calcd. 714.2644, observed 714.2643; correct isotopic pattern.

4,4,5,5-Tetramethyl-2-(2-methyl-4-hydroxyphenyl)-1,3,2-dioxaborolane (**S11**)



S10 **S11**, 98%

Following a literature procedure,[7] a suspension of molecular sieves (4 Å) (7 g) in a solution of (2-methyl-4-hydroxyphenyl)boronic acid (**S10**, 5.00 g, 32.9 mmol), and pinacol (4.14 g, 35.0 mmol) in anhydrous Et_2O (100 mL) was stirred under Ar at ambient temperature for 18 hours. The reaction mixture was filtered, and the filter cake was washed with Et_2O. The filtrate was dried and concentrated under reduced pressure to give an oily residue, which was purified by column chromatography using gradient elution with EtOAc/hexane affording the *title compound* in 98% yield (7.61 g, 32.5 mmol) as a colorless solid.[7]

R_f 0.62, (1:10 EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (t, J = 9.9 Hz, 1H), 6.66 – 6.58 (m, 2H), 5.24 (s, 1H), 2.49 (s, 3H), 1.33 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.80, 147.57, 138.02, 116.78, 111.83, 83.25, 24.82, 22.17. *C*-Bpin was not observed.

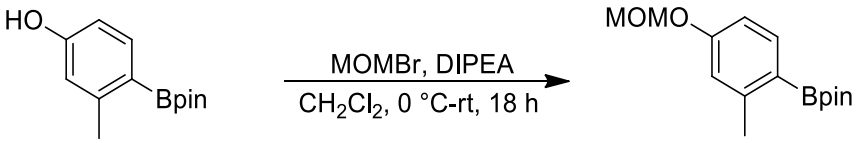
LRMS (ESI) *m/z* $[M + H]^+$, $C_{13}H_{20}O_3B^+$ calcd. 235.15, observed 235.26.

LRMS/GC: R_t 11.82 min, $C_{13}H_{19}O_3B^+$, $[M]^+$ calcd. 234.14, observed 234.16.

HRMS/GC: R_t 12.90 min, $C_{13}H_{19}O_3B^+$, $[M]^+$ calcd. 234.1422, observed 234.1421; correct isotopic pattern.

Elemental analysis calcd (%) for $C_{13}H_{19}O_3B$ (234.4): C 66.70, H 8.18; found C 66.69, H 8.17.

2-(4-(Methoxymethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S12**)



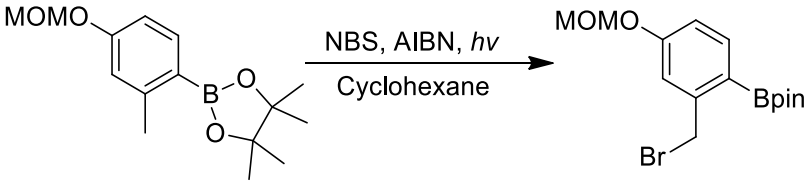
S11 **S12**, 90%

MOMBr (0.7 mL, 1.07 g, 8.56 mmol) was slowly added to a stirred ice-cold solution of 4,4,5,5-tetramethyl-2-(2-methyl-4-hydroxyphenyl)-1,3,2-dioxaborolane (**S11**) (1.00 g, 4.27 mmol) and DIPEA (1.49 mL, 1.11 g, 8.55 mmol) in anhydrous CH_2Cl_2 (40 mL) under Ar. Thereafter, the cooling bath was removed and the reaction mixture was stirred for 18 hours. The reaction mixture was washed with H_2O (2 × 30 mL), washed with brine (2 × 30 mL) and dried and concentrated under reduced pressure to give an oily brown residue, which was purified by column chromatography using gradient elution with EtOAc/hexane (0–20%) affording the *title compound* in 90% yield (1.07 g, 3.85 mmol) as a yellow oil.[8]

R_f 0.31, (1:20 EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 9.0 Hz, 1H), 6.90 – 6.82 (m, 2H), 5.21 (s, 2H), 3.49 (s, 3H), 2.56 (s, 3H), 1.36 (s, 12H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 159.27, 147.27, 137.75, 117.41, 112.32, 93.96, 83.18, 55.98, 24.88, 22.38.
HRMS (ESI) *m/z* $[M + Na]^+$, $C_{15}H_{23}BO_4Na^+$ calcd. 301.1582, observed 301.1584; correct isotopic pattern.

2-(4-(Methoxymethoxy)-2-bromomethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2d**)



S12 **2d**, 85%

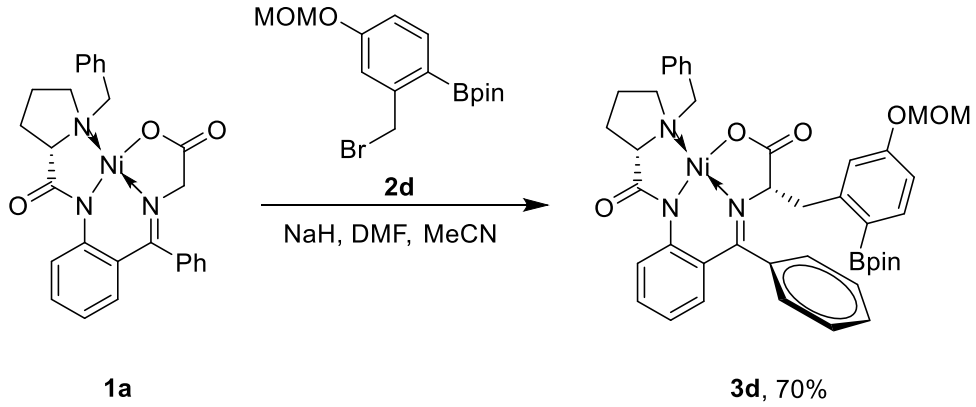
The above compound (**2d**) was prepared according to GP2 whereby, **S12** (4.00 g, 14.4 mmol), NBS (2.55 g, 14.3 mmol), AIBN (0.40 g, 2.44 mmol) and cyclohexane (40 mL) were utilized. Yield: 85% (4.36 g, 1.70 mmol). **2d** was directly used in the next step owing to its instability.

R_f 0.14, (1:10 EtOAc/hexane).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.96 (dd, *J* = 8.3, 2.4 Hz, 1H), 5.20 (s, 2H), 4.89 (s, 2H), 3.47 (s, 3H), 1.36 (s, 12H).

^{13}C NMR (50 MHz, $CDCl_3$) δ 159.56, 146.36, 138.31, 117.81, 115.16, 83.68, 56.15, 56.03, 33.75, 24.89. *C*-Bpin was not observed.

(*S*,*S*)-Ni-BPB-2-Bpin-5-MOMO-Phe (**3d**)



1a **3d**, 70%

The above compound (**3d**) was prepared according to GP1 whereby, **1a** (1.76 g, 3.53 mmol), **2d** (1.89 g, 5.29 mmol), NaH (60% suspension in mineral oil) (142 mg, 3.54 mmol) and DMF/MeCN 1:2 (30 mL) were utilized. Yield: 70% (1.90 g, 2.46 mmol).

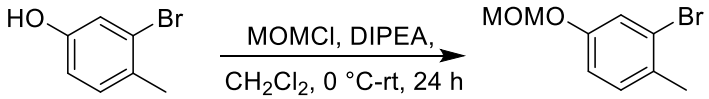
R_f 0.34, (1:8 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 8.7, 1.0 Hz, 1H), 8.06 (d, *J* = 7.0 Hz, 2H), 7.74 (t, *J* = 10.1 Hz, 1H), 7.51 – 7.29 (m, 4H), 7.21 (d, *J* = 2.0 Hz, 1H), 7.19 – 7.04 (m, 4H), 6.92 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.59 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H), 6.51 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.93 (d, *J* = 7.7 Hz, 1H), 4.93 (dd, *J* = 34.0, 6.8 Hz, 2H), 4.38 (d, *J* = 12.6 Hz, 1H), 4.25 (dd, *J* = 7.6, 4.8 Hz, 1H), 4.01 – 3.82 (m, 2H), 3.51 (d, *J* = 12.7 Hz, 1H), 3.41 (dd, *J* = 10.5, 6.8 Hz, 1H), 3.37 – 3.23 (m, 2H), 3.21 (s, 3H), 2.93 – 2.73 (m, 1H), 2.62 – 2.45 (m, 1H), 2.18 – 1.92 (m, 2H), 1.18 (s, 6H), 1.10 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.22, 178.49, 170.62, 159.22, 144.59, 142.92, 138.38, 133.96, 133.74, 133.36, 132.03, 131.51, 129.09, 128.78, 128.69, 128.54, 128.27, 128.16, 126.12, 123.14, 120.25, 118.62, 114.73, 93.88, 83.41, 72.74, 70.83, 62.92, 57.13, 55.87, 42.60, 30.81, 24.89, 24.42, 23.88. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{42}H_{47}N_3O_7NiB^+$ calcd. 774.2856, observed 774.2853; correct isotopic pattern.

2-Bromo-4-(methoxymethoxy)-1-methylbenzene (**S14**)



S13 **S14**, 93%

A solution of 2.1 M MOMCl solution in toluene (20 mL) prepared according to a literary procedure[1] was slowly added to a stirred ice-cold solution of 3-bromo-4-methylphenol (**S13**, 4.6 g, 24.6 mmol) and DIPEA (10 mL, 7.42 g, 57.4 mmol) in anhydrous CH_2Cl_2 (40 mL). Thereafter, the cooling bath was removed and the reaction mixture was stirred for 24 hours. The mixture was washed with H_2O (3 × 30 mL), brine (3 × 30 mL), dried and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc/hexane, gradient elution 20–50%), affording the *title compound*[9] (5.30 g, 23 mmol) in 93% yield.

R_f: 0.75, (1:2 EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, *J* = 2.5 Hz, 1H), 7.15 (dd, *J* = 8.4, 0.5 Hz, 1H), 6.92 (dd, *J* = 8.4, 2.5 Hz, 1H), 5.15 (s, 2H), 3.49 (s, 3H), 2.35 (s, 3H).

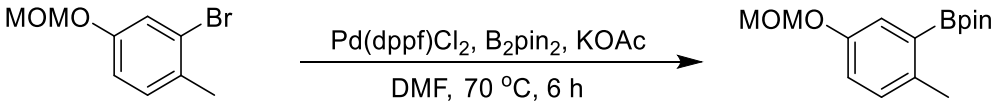
^{13}C NMR (101 MHz, $CDCl_3$) δ 155.76, 131.06, 130.97, 124.76, 120.24, 115.42, 94.65, 55.99, 21.89.

LRMS/GC: R_t 10.44 min, $C_9H_{10}BrO_2^+$, $[M]^+$ calcd. 229.99, observed 229.99.
HRMS/GC: R_t 12.90 min, $C_9H_{10}BrO_2^+$, $[M]^+$ calcd. 229.9937, observed 229.9935; correct isotopic pattern.

Elemental analysis calcd (%) for $C_9H_{10}BrO_2$ (231.09): C 46.78, H 4.80; found C 46.73, H 4.96.

Elemental analysis calcd (%) for $C_9H_{10}BrO_2$ (231.09): C 46.78, H 4.80, O 13.85; found C 46.7 ± < 0.1, H 4.79 ± 0.17, O 14.2 ± < 0.1.

2-[5-(Methoxymethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**S15**)



S14 **S15**, 72%

A suspension of KOAc (0.44 g, 4.54 mmol), 2-bromo-4-(methoxymethoxy)-1-methylbenzene (**S14**) (0.5 g, 2.16 mmol), B_2pin_2 (0.66 g, 2.6 mmol), and $Pd(dppf)Cl_2$ (0.1 g, 0.15 mmol) in anhydrous DMF (10 mL) was stirred at 75 °C for 12 h, followed by 90 °C for 3 h. Thereafter, the solvent was removed under reduced pressure and the residue was taken up in Et_2O (10 mL). The mixture was washed with H_2O (3 × 10 mL), brine (3 × 10 mL), dried and concentrated under reduced pressure. The crude product was purified by column chromatography (1:20 EtOAc/hexane) to furnish the *title compound* (0.43 g, 1.55 mmol) in 72% yield as a light yellow oil.

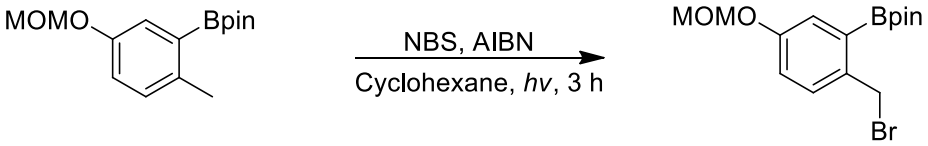
R_f: 0.45, (1:10 EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 2.8 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 7.01 (dd, *J* = 8.3, 2.8 Hz, 1H), 5.17 (s, 2H), 3.48 (s, 3H), 2.48 (s, 3H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.38, 138.18, 130.85, 123.27, 118.84, 94.58, 83.47, 77.00, 55.87, 24.86, 21.23.

HRMS (ESI) *m/z* $[M + Na]^+$, $C_{15}H_{23}O_4BNa^+$ calcd. 301.1582, observed 301.1584; correct isotopic pattern.

2-(2-(Bromomethyl)-5-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**2e**)



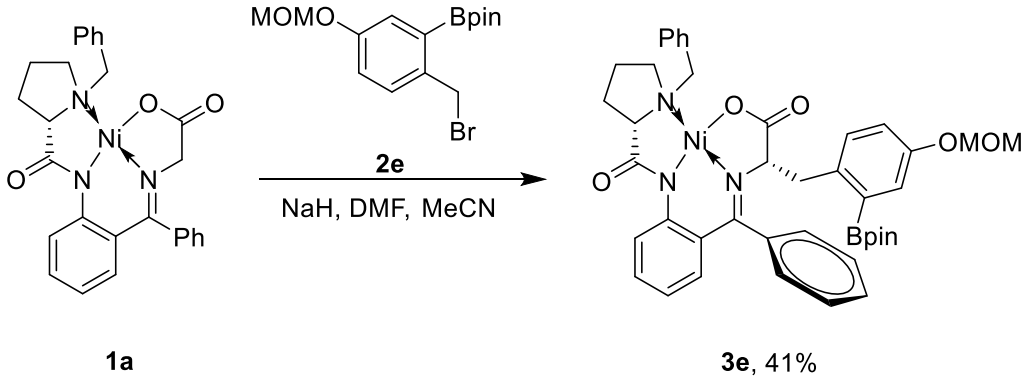
S15 **2e**, 68%

The above compound (**2e**) was prepared according to the general procedure 2 (GP2) whereby, **S15** (0.62 g, 2.25 mmol), NBS (0.40 g, 2.45 mmol), AIBN (44 mg, 0.27 mmol) and cyclohexane (40 mL) were utilized. Yield: 68% (0.55 g, 1.54 mmol). **2e** was directly used for the next step owing to its instability.

R_f: 0.60, (1:3 EtOAc/hexane).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 9.9, 2.6 Hz, 1H), 7.17 – 7.02 (m, 2H), 5.20 (d, *J* = 6.0 Hz, 2H), 3.50 (s, 3H), 2.53 (s, 2H), 1.37, 1.39 (2×s, 12H).

(*S*,*S*)-Ni-BPB-2-Bpin-4-MOMO-Phe (**3e**)



1a **3e**, 41%

The above compound (**3e**) was prepared according to GP1 whereby, **1a** (0.58 g, 1.16 mmol), **2e** (0.5 g, 1.40 mmol), NaH (60% suspension in mineral oil) (56 mg, 1.40 mmol) and DMF/MeCN 1:2 (15 mL) were utilized. Yield: 41% (0.37 g, 0.48 mmol).

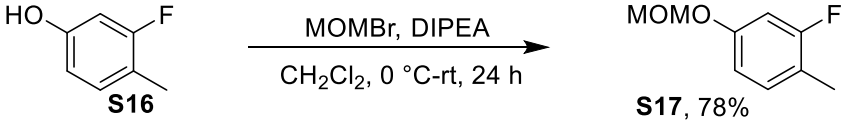
R_f 0.71, (1:10 acetone/ $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.47 – 7.27 (m, 4H), 7.23 – 6.99 (m, 5H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.57 (t, *J* = 7.2 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.90 (d, *J* = 6.9 Hz, 1H), 4.91 (dd, *J* = 32.9, 6.6 Hz, 2H), 4.35 (d, *J* = 12.6 Hz, 1H), 4.28 – 4.19 (m, 1H), 3.96 – 3.78 (m, *J* = 20.8 Hz, 2H), 3.48 (d, *J* = 12.7 Hz, 1H), 3.44 – 3.36 (m, 1H), 3.34 – 3.23 (m, 2H), 3.18 (s, 3H), 2.89 – 2.71 (m, 1H), 2.59 – 2.41 (m, 1H), 2.14 – 1.92 (m, 2H), 1.15 (s, 6H), 1.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.19, 178.49, 170.61, 159.21, 144.55, 142.84, 138.36, 133.91, 133.72, 133.34, 132.00, 131.48, 129.07, 128.75, 128.67, 128.52, 128.25, 128.13, 127.33, 126.10, 123.12, 120.27, 118.59, 114.71, 93.85, 83.38, 72.71, 70.80, 62.90, 57.12, 55.84, 42.56, 30.79, 24.86, 24.39, 23.85. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine fragment were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{42}H_{47}N_3O_7NiB^+$ calcd. 774.2856, observed 774.2853; correct isotopic pattern.

2-Fluoro-4-(methoxymethoxy)-1-methylbenzene (**S17**)



MOMBr (11.2 mL, 17.1 g, 136.8 mol) was slowly added to a stirred ice-cold solution of 3-fluoro-4-methylphenol (**S16**, 8.63 g, 68.42 mmol) and DIPEA (24.4 mL, 18.09 g, 140.0 mmol) in anhydrous CH_2Cl_2 (100 mL). Thereafter, the cooling bath was removed and the reaction mixture was stirred for 24 hours. The reaction mixture was washed with H_2O (3 × 30 mL), brine (3 × 30 mL), dried and concentrated under reduced pressure. The crude orange residue was purified by column chromatography (EtOAc/hexane, gradient elution 10–40%), affording the *title compound*[10] as a colorless oil (9.07 g, 78%).

R_f: 0.32, (1:10 EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.04 (m, 1H), 6.81 – 6.72 (m, 2H), 5.15 (s, 2H), 3.49 (s, 3H), 2.23 (d, *J* = 1.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.44 (d, *J* = 244.3 Hz), 156.33 (d, *J* = 10.8 Hz), 131.42 (d, *J* = 6.8 Hz), 117.85 (d, *J* = 17.4 Hz), 111.64 (d, *J* = 3.2 Hz), 103.86 (d, *J* = 25.5 Hz), 94.63, 55.95, 13.76 (d, *J* = 3.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.15.

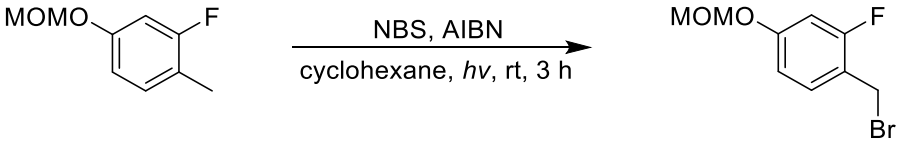
LRMS/GC: R_t 8.38 min, $C_9H_{10}FO_2^+$, $[M]^+$ calcd. 170.07, observed 170.06.

HRMS/GC: R_t 7.91 min, $C_9H_{10}FO_2^+$, $[M]^+$ calcd. 170.0738, observed 170.0737.

Elemental analysis calcd (%) for $C_9H_{10}FO_2$ (170.18): C 63.52, H 6.52; found C 63.67, H 6.49.

Elemental analysis calcd (%) for $C_9H_{10}FO_2$ (170.18): C 63.52, H 6.52, O 18.80; found C 63.7 ± 0.22, H 6.84 ± 0.01, O 21.4 ± 0.22.

1-(Bromomethyl)-2-fluoro-4-(methoxymethoxy)benzene (**S18**)



S17 **S18**, 63%

The above compound (**S18**) was prepared according to the general procedure 2 (GP2) whereby, **S17** (1 g, 5.88 mmol), NBS (1.15 g, 6.46 mmol), AIBN (100 mg, 0.61 mmol) and cyclohexane (40 mL) were utilized. Yield: 63% (0.93 g, 3.73 mmol). **S18** was obtained as a colorless semisolid.

R_f: 0.63, (1:3 EtOAc/hexane).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, 1H), 6.83 – 6.76 (m, 2H), 5.16 (s, 2H), 4.50 (d, *J* = 0.7 Hz, 2H), 3.47 (s, 3H).

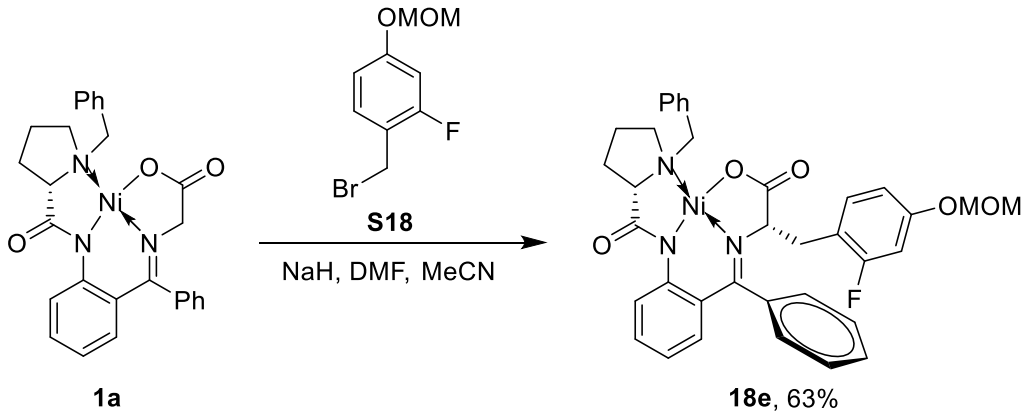
^{13}C NMR (101 MHz, $CDCl_3$) δ 161.20 (d, *J* = 250.1 Hz), 158.89 (d, *J* = 10.9 Hz), 131.67 (d, *J* = 5.0 Hz), 118.28 (d, *J* = 14.6 Hz), 112.33 (d, *J* = 3.1 Hz), 104.19 (d, *J* = 24.8 Hz), 94.42, 56.15, 26.09 (d, *J* = 3.9 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.27.

LRMS/GC: R_t 10.59 min, $C_9H_{10}BrFO_2^+$, $[M]^+$ calcd. 247.98, observed 248.00.

HRMS/GC: R_t 10.97 min, $C_9H_{10}FO_2^+$, $[M]^+$ calcd. 247.9843, observed 247.9840; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-2-F-4-MOMO-Phe (**18e**)



1a **18e**, 63%

The above compound (**18e**) was prepared according to GP1 whereby, **1a** (1.06 g, 2.13 mmol), **S18** (0.85 g, 3.41 mmol), NaH (60% suspension in mineral oil) (136 mg, 3.40 mmol) DMF/MeCN 1:2 (30 mL) were utilized. Yield: 63% (0.89 g, 1.34 mmol).

R_f: 0.57, (1:8 acetone/$CHCl_3$).

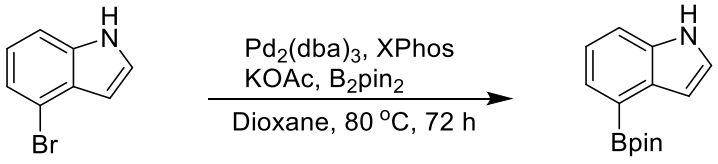
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.7 Hz, 1H), 8.00 (d, *J* = 7.3 Hz, 2H), 7.59 – 7.47 (m, 2H), 7.42 (t, *J* = 6.8 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.20 – 7.10 (m, 2H), 7.08 – 6.98 (m, 2H), 6.94 (d, *J* = 7.4 Hz, 1H), 6.91 – 6.85 (m, *J* = 3.1 Hz, 1H), 6.71 – 6.56 (m, 2H), 5.06 (dd, *J* = 23.4, 6.7 Hz, 2H), 4.30 (d, *J* = 12.7 Hz, 1H), 4.25 (t, *J* = 5.1 Hz, 1H), 3.51 (d, *J* = 12.7 Hz, 1H), 3.42 (s, 3H), 3.37 – 3.29 (m, 1H), 3.16 (d, *J* = 7.5 Hz, 1H), 3.11 (d, *J* = 5.1 Hz, 1H), 3.03 – 2.90 (m, 1H), 2.65 – 2.46 (m, *J* = 9.6 Hz, 1H), 2.46 – 2.27 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.21, 178.36, 171.91, 157.13 (d, *J* = 240.9 Hz), 153.68 (d, *J* = 1.8 Hz), 142.83, 133.97, 133.55, 133.13, 132.31, 131.51, 129.68, 128.88, 128.81, 128.77, 128.20, 128.17, 127.15, 126.20, 123.76 (d, *J* = 17.8 Hz), 123.28, 120.52, 120.25 (d, *J* = 4.1 Hz), 116.95 (d, *J* = 8.0 Hz), 116.06 (d, *J* = 24.3 Hz), 95.00, 70.72, 70.36, 63.18, 57.06, 56.02, 33.55, 30.78, 23.10. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

^{19}F NMR (376 MHz, $CDCl_3$) δ –124.36.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{36}H_{35}N_3O_5NiF^+$ calcd. 666.1909, observed 666.1910; correct isotopic pattern.

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (**S20**)



S19 **S20**, 52 %

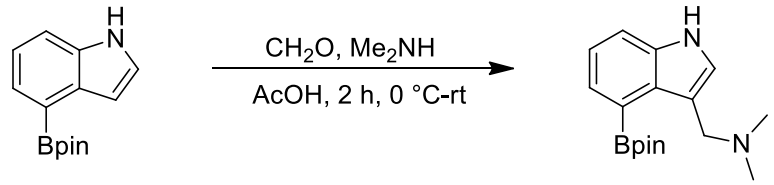
A suspension of KOAc (5.88 g, 60 mmol), 4-bromoindole (**S19**, 4 g, 20 mmol), $Pd_2(dba)_3$ (0.72 g, 0.8 mmol), XPhos (0.76 g, 1.6 mmol), bis(pinacolato)diboron (6 g, 24 mmol) in anhydrous DMSO (120 mL) was stirred at 80 °C for 72 h. The resulting suspension was cooled to ambient temperature and added to H_2O (100 mL) before being extracted with EtOAc (2×100 mL). The combined organic fractions were washed with H_2O (2×100 mL), dried and concentrated under reduced pressure. The crude product was purified by column chromatography to furnish the *title compound*[11] (2.54 g, 10.46 mmol) in 52% yield as a grey solid.

R_f: 0.56, (1:10 acetone/$CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (br, 1H), 7.68 (dd, *J* = 7.0, 1.0 Hz, 1H), 7.58 – 7.47 (m, 1H), 7.34 – 7.18 (m, 2H), 7.13 – 7.05 (m, *J* = 1.0 Hz, 1H), 1.43 (s, 12H).

HRMS (ESI) *m/z* $[M + H]^+$, $C_{14}H_{19}BNO_2^+$ calcd. 244.1503, observed 244.1507; correct isotopic pattern.

N,*N*-Dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)methanamine (**S21**)



S20 **S21**, 49 %

40% Dimethylamine (1.42 mL) was added to an ice-cold solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**S20**) (2.0 g, 8.22 mmol), an aqueous solution of formaldehyde (37%) and AcOH (8.4 mL). Thereafter, the cooling bath was removed and the reaction mixture was stirred for 2 hours. The resulting reaction mixture was cooled with an ice-bath and the pH value was adjusted to 10 using 3 M NaOH. The mixture was extracted with EtOAc (4 × 50 mL), dried, and concentrated under reduced pressure. The crude product was purified by aluminum oxide chromatography on aluminum oxide to furnish the *title compound* (1.20 g, 3.99 mmol) in 49% yield as a colorless solid.

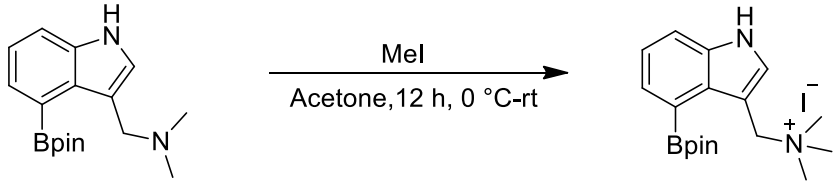
R_f: 0.34, (95:5 CH_2Cl_2/MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (br, 1 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.73 (d, *J* = 8.0 Hz, 1 H), 7.21 – 7.11 (m, 2H) 3.98 (s, 2 H), 2.66 (s, 6 H), 1.43 (s, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 143.36, 134.89, 127.49, 124.10, 121.13, 114.12, 113.40, 83.25, 55.90, 45.34, 25.34. *C*-Bpin was not observed.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{17}H_{26}BN_2O_2^+$ calcd. 301.2082, observed 301.2085; correct isotopic pattern.

N,*N*,*N*-Trimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)methanaminium iodide (**2f**)



S21 **2f**, 75%

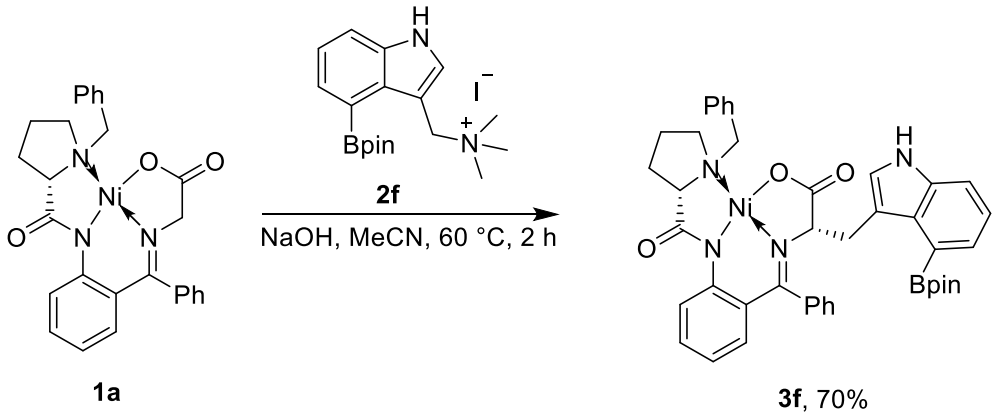
MeI (0.81 g, 5.75 mmol) was added to an ice-cold solution of *N*,*N*-dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-indol-3-yl)methanamine (**S21**) (0.36 g, 1.15 mmol) in acetone (20 mL) under the protection from light. Thereafter, the cooling bath was removed and stirring was continued for 12 hours at ambient temperature. The reaction mixture was placed in a fridge (4 °C) for 2 hours and the precipitate was filtered and washed with cold Et_2O (50 mL) to furnish the *title compound* (0.38 g, 0.86 mmol) in 75% yield as a colorless solid.

^{1}H NMR (300 MHz, DMSO) δ 11.84 (br, 1 H), 7.95 – 7.77 (m, 1 H), 7.74–7.66 (m, 2 H), 7.21 (t, *J* = 8.0, 1 H), 3.3 (s, 2 H), 3.00 (s, 9 H), 1.44 (s, 12 H).

^{13}C NMR (75 MHz, DMSO) δ 136.74, 132.19, 131.60, 130.96, 121.46, 116.62, 103.33, 84.39, 61.81, 51.63, 25.24. *C*-Bpin was not observed.

HRMS (ESI) *m/z* $[M - I]^+$, $C_{18}H_{28}BN_2O_2^+$ calcd. 315.2239, observed 315.2243; correct isotopic pattern.

(*S*,*S*)-Ni-BPB-4-Bpin-Trp (**3f**)



NaOH (0.08 g, 2.03 mmol) powder was added to a solution of *N*,*N*,*N*-trimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)methane-aminium iodide (**2f**) (0.36 g, 0.81 mmol) and **1a** (0.41 g, 0.81 mmol) in anhydrous MeCN (20 mL) under Ar and the reaction mixture was stirred for 2 hours. Sat. NH_4Cl (60 mL) was added and the mixture was extracted with EtOAc (3 × 60 mL). The combined organic fractions were dried and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to furnish the *title compound* (0.43 g, 0.57 mmol) in 70% yield as a red solid.

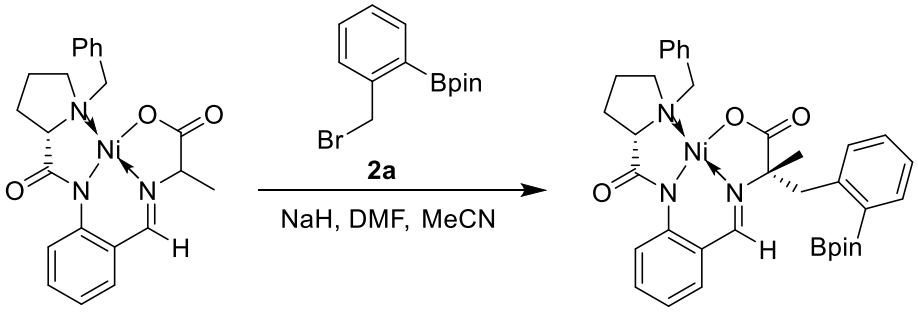
R_f: 0.60, (1:2 acetone/ CH_2Cl_2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 – 8.06 (m, 4H), 7.51 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.38 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.24 – 7.16 (m, 2H), 7.15 – 7.06 (m, 2H), 7.05 – 6.94 (m, 3H), 6.56 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 6.40 (dd, *J* = 8.2, 1.6 Hz, 1H), 6.00 (t, *J* = 7.5 Hz, 1H), 4.79 (d, *J* = 7.8 Hz, 1H), 4.50 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.38 (d, *J* = 12.6 Hz, 1H), 4.32 – 4.23 (m, 2H), 3.89 – 3.61 (m, 1H), 3.58 – 3.48 (m, 2H), 2.96 – 2.78 (m, 1H), 2.73 – 2.53 (m, 1H), 2.30 – 2.14 (m, 1H), 2.14 – 2.00 (m, 1H), 1.30 (s, 6H), 1.28 (s, 6H). N-*H* of the indole ring was not observed.

^{13}C NMR (75 MHz, $CDCl_3$) δ 180.31, 179.23, 170.08, 142.14, 136.05, 133.50, 132.95, 131.67, 131.37, 130.80, 129.53, 128.82, 128.73, 128.51, 127.95, 127.46, 126.93, 126.66, 125.63, 122.94, 121.06, 120.58, 114.23, 111.89, 83.71, 71.33, 70.89, 63.11, 57.19, 35.74, 31.10, 24.65, 24.18, 24.06. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{42}H_{44}BN_4NiO_5^+$ calcd. 753.2753, observed 753.2758; correct isotopic pattern.

α-Methyl-2-[^{18}F]FPhe precursor (**3g**)



1b **3g**, 72%

The above compound (**3g**) was prepared according to GP1 whereby, **1b** (0.40 g, 0.92 mmol), **2a** (0.44 g, 1.48 mmol), NaH (60% suspension in mineral oil) (70 mg, 1.75 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 72% (0.50 g, 0.77 mmol).

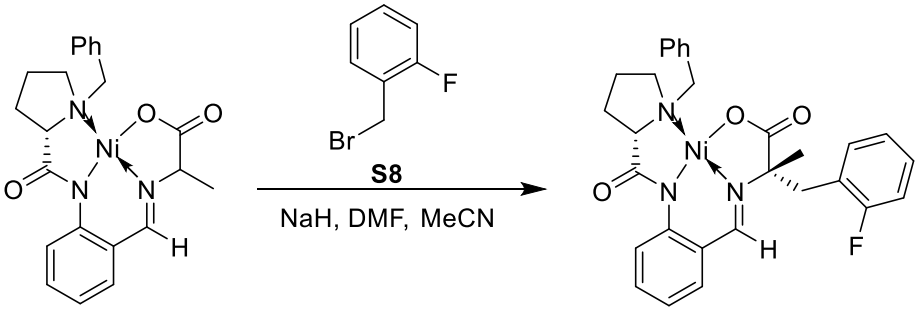
R_f: 0.42, (1:10 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.7 Hz, 1H), 7.97 (d, *J* = 7.2 Hz, 2H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.37 – 7.30 (m, 4H), 7.28 – 7.20 (m, 2H), 7.13 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.92 – 6.86 (m, *J* = 7.9 Hz, 1H), 4.36 (d, *J* = 12.6 Hz, 1H), 3.73 (d, *J* = 13.4 Hz, 1H), 3.55 (dd, *J* = 13.4, 3.5 Hz, 2H), 3.43 (ddt, *J* = 14.8, 7.5, 3.5 Hz, 1H), 3.30 (t, *J* = 8.3 Hz, 1H), 2.83 – 2.67 (m, 1H), 2.36 – 2.24 (m, 2H), 2.12 – 2.00 (m, 1H), 1.91 – 1.77 (m, 1H), 1.60 (s, 3H), 1.26 (s, 6H), 1.20 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 182.00, 181.45, 161.94, 142.57, 141.88, 136.84, 133.68, 133.33, 133.24, 131.65, 130.95, 130.93, 128.88, 128.68, 126.52, 123.53, 123.34, 120.88, 83.69, 74.69, 70.17, 62.92, 57.29, 44.70, 30.85, 25.65, 25.25, 24.24, 23.36. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{35}H_{41}N_3O_5NiB^+$ calcd. 652.2488, observed 652.2484; correct isotopic pattern.

Ni-BPB α-methyl-2-FPhe reference compound (**18g**)



1b **18g**, 73%

The above compound (**18g**) was prepared according to GP1 whereby, **1b** (0.29 g, 0.66 mmol), 1-(bromomethyl)-2-fluorobenzene (**S8**, 0.17 g, 0.90 mmol), NaH (60% suspension in mineral oil) (36 mg, 0.90 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 73% (263 mg, 0.48 mmol).

R_f: 0.61, (1:10 acetone/$CHCl_3$).

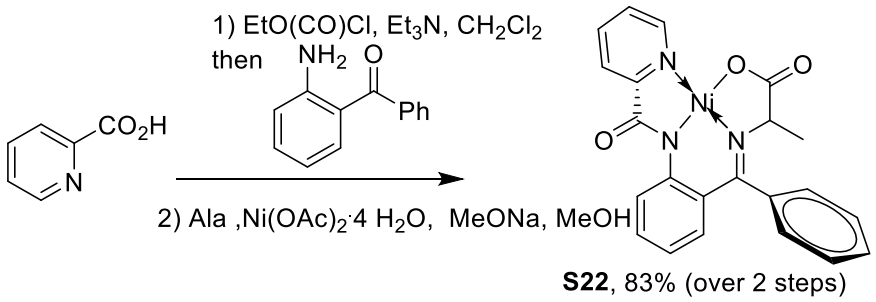
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 2H), 7.54 (d, *J* = 2.4 Hz, 1H), 7.45 – 7.29 (m, 5H), 7.26 – 7.23 (m, 2H), 7.19 (td, *J* = 7.5, 1.1 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.96 – 6.90 (m, 1H), 4.30 (d, *J* = 12.7 Hz, 1H), 3.56 (d, *J* = 12.7 Hz, 1H), 3.34 – 3.16 (m, 4H), 2.53 – 2.35 (m, 1H), 2.30 – 2.13 (m, 2H), 1.92 (td, *J* = 10.8, 6.4 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.47, 181.16, 161.99 (d, $J_{F,\ C=NH}$ = 2.6 Hz,), 161.13 (d, *J* = 248.5 Hz), 142.81, 133.84, 133.62, 133.07, 132.46 (d, *J* = 4.1 Hz), 131.64, 129.31 (d, *J* = 8.3 Hz), 128.98, 128.74, 124.54 (d, *J* = 3.4 Hz), 123.60, 123.42, 122.68 (d, *J* = 15.2 Hz), 121.21, 115.53 (d, *J* = 22.7 Hz), 74.13, 70.04, 62.81, 57.02, 39.60, 30.73, 25.61, 22.93.

^{19}F NMR (376 MHz, $CDCl_3$) δ –116.72.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{29}H_{29}N_3O_3NiF^+$ calcd. 544.1541, observed 544.1542; correct isotopic pattern.

Ni-PBP-(*RS*)-Ala (**S22**)



Ethyl chloroformate (7.7 mL, 8.75 g, 80.63 mmol) was added to an ice-cold solution of picolinic acid (9.97 g, 80.98 mmol) and Et_3N (11.3 mL, 8.2 g, 81.04 mmol) in CH_2Cl_2 (130 mL) and the reaction mixture was stirred for 20 min at ambient temperature. Afterwards, 2-aminobenzophenone (13.4 g, 67.94 mmol) was added and the reaction mixture was stirred at 40 °C for 16 h. Thereafter, the mixture was cooled to ambient temperature washed with H_2O (3×100 mL), brine (2×50 mL), dried and concentrated under reduced pressure. The residue was triturated with Et_2O, the formed precipitate was filtered, washed with Et_2O and dried to give *N*-(2-benzoylphenyl)pyridine-2-carboxamide (**S23**)[12] as a colorless solid (17.5 g, 85%), which was used for the next step without any characterization and purification.

5.4 N MeONa in MeOH (120 mL) was added to a suspension of **S23** (17.5 g, 57.88 mmol), (*RS*)-Ala (11.04 g, 123.92 mmol) and $Ni(OAc)_2$×4 H_2O (30.84 g, 123.94 mmol) in MeOH (150 mL) and the reaction mixture was stirred at 55 °C for 90 min. The resulting deep-red solution was cooled to ambient temperature and poured to an ice-cold solution of AcOH (40 mL in 1.5 L H_2O) and the resulting suspension was allowed to stay at ambient temperature for 16 h and filtered. The precipitate was washed with H_2O (1 L), hexane (3×100 mL), dried, washed with Et_2O (5×100 mL) and dried affording the title compound[13] (24.3 g, 98%).

R_f: 0.33, (1:8 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1H), 8.26 (s, 1H), 7.97 (d, *J* = 33.4 Hz, 2H), 7.61 – 7.06 (m, 7H), 6.79 (s, 2H), 4.04 (s, 1H), 1.59 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 180.60, 171.97, 169.99, 153.35, 146.90, 143.00, 140.52, 134.46, 133.73, 133.37, 129.78, 129.17, 128.74, 127.90, 127.03, 126.93, 126.62, 124.03, 123.53, 121.38, 67.29, 21.58. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

LRMS (ESI) *m/z* $[M + H]^+$ $C_{22}H_{18}N_3O_3Ni^+$ calcd. 430.15, observed 430.07; correct isotopic pattern.

HRMS (ESI) *m/z* $[M + Na]^+$, $C_{22}H_{17}N_3O_3NaNi^+$ calcd. 452.05136, observed 452.05156; $[M + H]^+$, $C_{22}H_{18}N_3O_3Ni^+$ calcd. 430.06962, observed 430.06938; correct isotopic pattern.

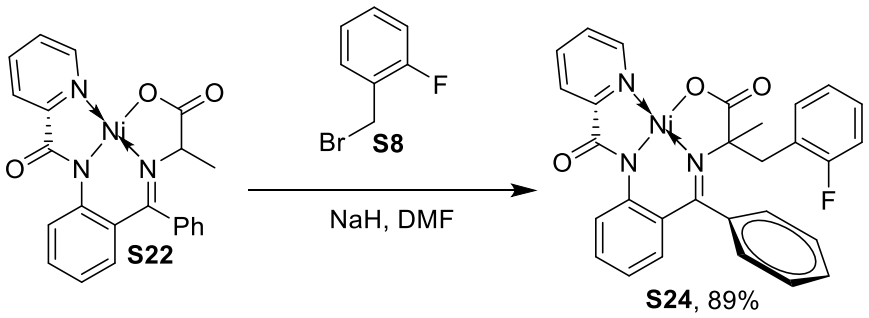
General procedure for alkylation upon Ni-PBP-(*RS*)-Ala (GP3)

NaH (0.37 g, 9.3 mmol; 60% suspension in mineral oil) was added to a suspension of **S22** (2 g, 4.65 mmol) in DMF (20 mL) and the mixture was stirred for 5 min. The corresponding fluorobenzyl bromide (1.41 g, 7.44 mmol) was added to the resulting black solution and the mixture was stirred for further 60 min. Thereafter, the deep red reaction mixture was poured into an ice-cold solution of AcOH (0.6 mL in 300 mL H_2O) and the resulting suspension was stirred at ambient temperature for 3 h and filtered. The precipitate was washed with H_2O (300 mL), hexane (3×50 mL), dried, washed with Et_2O (3×40 mL) and dried affording the corresponding Ni-PBP-αMe-n-FPhe complex (n = 2–4) as a red solid.

General procedure for decomposition of Ni-PBP-αMe-n-FPhe complexes (n = 2–4) (GP4)

4 M HCl was added dropwise to a boiling red suspension of the corresponding Ni-PBP-n-αMe-FPhe complex (n = 2–4) (1.0 g, 1.86 mmol) in 80% MeOH (15 mL) until a light green solution formed. The solution was concentrated under reduced pressure, the solid residue was dried at 50 °C and 2 mbar under dynamic vaccum, taken up in MeOH (30 mL) and the resulting solution was concentrated under reduced pressure (×3). The residue was taken up with a cold water (10 mL), the precipitate of **S23**×HCl was filtered, and the filtrate was concentrated under reduced pressure. The rest was taken up with H_2O (40 mL), the pH of the resulting solution was carefully adjusted to 7–8 with 25% NH_3 and the precipitated **S23** was extracted with CH_2Cl_2 (3×5 mL; αMe-2-FPhe partially co-precipitated with **S23**; it was however insoluble in CH_2Cl_2). Preswollen Amberlite IRA-120 in the H^+ form [30 mL; the resin was preliminary washed with 1 M HCl (150 mL) and thereafter with H_2O until pH 5] was added to the water fraction, and the mixture was shaken for 45 min at 40–50 °C. The ion-exchange resin was filtered off, washed with water until the eluent reached pH 5 and treated with 7 % NH_3 (2×100 mL) for 1 h. The combined filtrates were concentrated under reduced pressure to give a colorless to offwhite solid, which was triturated acetone. The formed precipitate was filtered off to give the appropriate αMe-n-FPhe as a colorless solid.

Ni-PBP-αMe-2-FPhe (**S24**)



The title compound (2.23 g, 89%) was prepared according to GP3.

R_f: 0.39, (1:8 acetone/$CHCl_3$).

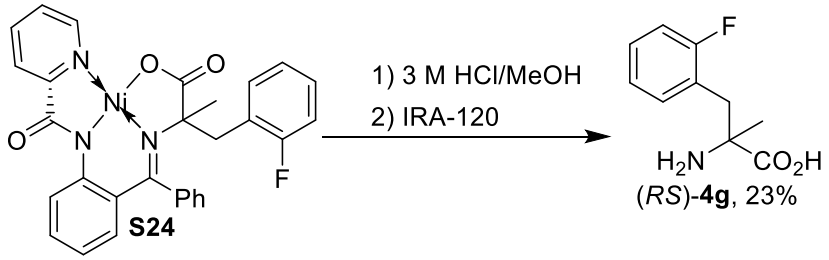
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 8.6 Hz, 1H), 7.86 (td, *J* = 7.7, 1.4 Hz, 1H), 7.77 (d, *J* = 5.4 Hz, 1H), 7.75 – 7.69 (m, 1H), 7.54 – 7.42 (m, 5H), 7.26 (s, 3H), 7.05 – 6.97 (m, 1H), 6.81 (dd, *J* = 8.4, 1.4 Hz, 1H), 6.79 – 6.73 (m, 2H), 6.73 – 6.67 (m, 1H), 3.48 (d, *J* = 13.6 Hz, 1H), 2.87 (d, *J* = 13.6 Hz, 1H), 1.04 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.71, 173.37, 168.98, 162.85 (d, *J* = 245.6 Hz), 153.38, 146.93, 142.60, 139.83, 136.99, 134.83, 133.05 (d, *J* = 4.5 Hz), 132.86, 130.44, 129.57, 129.32, 129.15 (d, *J* = 8.5 Hz), 128.93, 127.46, 126.88, 126.80, 126.23, 124.41 (d, *J* = 15.1 Hz), 124.06 (d, *J* = 3.2 Hz), 123.35 (d, *J* = 5.3 Hz), 121.27, 115.43 (d, *J* = 23.0 Hz), 81.01, 41.61, 28.74. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent. The signal of one of the *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue has C-F splitting.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.58.

LRMS (ESI) *m/z* $[M + H]^+$ $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.20, observed 538.20; correct isotopic pattern.
HRMS (ESI) *m/z* $[M + Na]^+$, $C_{29}H_{22}FN_3O_3NaNi^+$ calcd. 560.08909, observed 560.08907; $[M + H]^+$, $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.10714, observed 538.10729; correct isotopic pattern.

(*RS*)-α-Methyl-2-fluorophenylalanine [(*RS*)-**4g**]



The title compound[14] (85 mg, 23%) was prepared according to GP4.

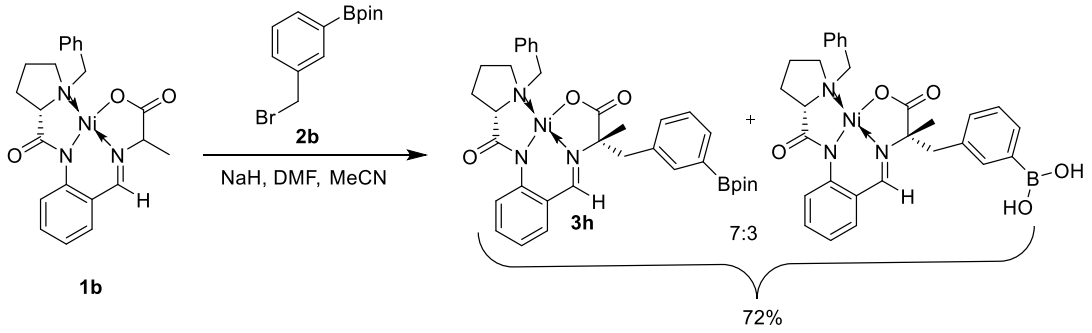
^{1}H NMR (400 MHz, MeOD + 20% DCl) δ 7.44 – 7.31 (m, 2H), 7.17 (ddd, *J* = 20.7, 13.1, 4.7 Hz, 2H), 3.30 (q, *J* = 13.7 Hz, 2H), 1.63 (s, 3H).

^{13}C NMR (101 MHz, MeOD + 20% DCl) δ 173.15, 162.76 (d, *J* = 244.8 Hz), 133.77 (d, *J* = 3.8 Hz), 131.37 (d, *J* = 8.3 Hz), 125.76 (d, *J* = 3.5 Hz), 121.44 (d, *J* = 15.9 Hz), 116.64 (d, *J* = 22.2 Hz), 61.45, 37.01, 22.13.

^{19}F NMR (376 MHz, MeOD + 20% DCl) δ –116.88.

LRMS (ESI) *m/z* $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09, observed 198.29.
HRMS (ESI) *m/z* $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09248, observed 198.09246.

α-Methyl-3-[^{18}F]FPhe precursor (**3h**)



The above compound (**3h**) was prepared according to GP1 whereby, **1b** (0.55 g, 1.26 mmol), **2b** (0.50 g, 1.68 mmol), NaH (60% suspension in mineral oil) (74 mg, 1.85 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 72% (0.57 g, 0.91 mmol; total yield of **3h** and the corresponding boronic acid). RP Chromatography using aqueous MeCN and subsequent evaporation of the eluent at 40 ºC caused hydrolysis of Bpin ester to give the corresponding boronic acid as side product. As boronic acids are typically even better substrates for the alcohol-enhanced Cu-mediated radiofluorination than Bpin esters, no attempt to separate it (or to convert it back into the Bpin ester) was performed and the mixture was directly used for the radiolabeling step. Omission of the RP purification step could lead to lower ^{18}F-incorporation rates.

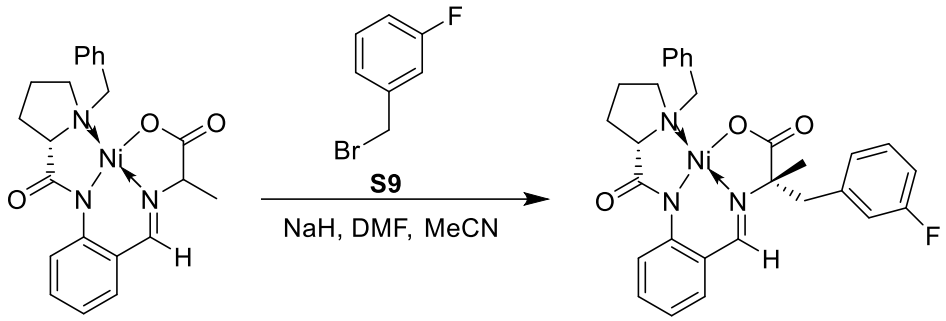
R_f: 0.45, (1:10 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$; before RP purification) δ 8.60 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.80 (d, *J* = 6.5 Hz, 1H), 7.50 (s, 1H), 7.40 – 7.22 (m, 8H), 6.93 (t, *J* = 7.3 Hz, 1H), 4.33 (d, *J* = 12.6 Hz, 1H), 3.55 (d, *J* = 12.6 Hz, 1H), 3.39 (d, *J* = 13.3 Hz, 1H), 3.31 – 3.18 (m, 2H), 2.94 – 2.86 (m, 1H), 2.51 – 2.36 (m, 1H), 2.30 – 2.16 (m, 2H), 2.00 – 1.89 (m, 1H), 1.76 – 1.66 (m, 1H), 1.62 (s, 3H), 1.22 (s, 6H), 1.18 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$; before RP purification) δ 181.51, 181.12, 161.19, 143.08, 137.32, 134.53, 133.88, 133.61, 133.55, 133.43, 133.08, 131.66, 128.90, 128.67, 128.09, 123.65, 123.00, 120.96, 83.75, 74.23, 70.00, 62.70, 57.11, 47.53, 30.77, 24.84, 24.80, 24.61, 23.04. *C*-Bpin was not observed. Pairs of methyl groups of the Bpin residue were inequivalent.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{35}H_{41}N_3O_5NiB^+$ calcd. 652.2488, observed 652.2484; correct isotopic pattern.

Ni-BPB α-methyl 3-FPhe (**18h**)



1b **18h**, 77%

The above compound (**18h**) was prepared according to GP1 whereby, **1b** (0.20 g, 0.46 mmol), 1-(bromomethyl)-3-fluorobenzene (**S9**, 0.15 g, 0.79 mmol), NaH (60% suspension in mineral oil) (33 mg, 0.83 mmol) and DMF/MeCN 1:2 (7 mL) were utilized. Yield: 77% (0.194 g, 0.35 mmol).

R_f: 0.55, (1:10 acetone/$CHCl_3$).

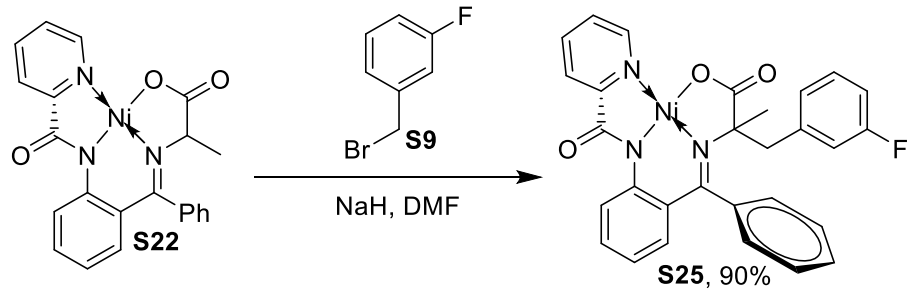
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.7 Hz, 1H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.51 (s, 1H), 7.40 – 7.29 (m, 4H), 7.26 – 7.20 (m, 2H), 7.07 (td, *J* = 8.4, 1.8 Hz, 1H), 7.01 – 6.91 (m, *J* = 7.2 Hz, 2H), 6.86 (d, *J* = 7.6 Hz, 1H), 4.29 (d, *J* = 12.7 Hz, 1H), 3.54 (d, *J* = 12.7 Hz, 1H), 3.34 (d, *J* = 13.5 Hz, 1H), 3.29 – 3.19 (m, 2H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.52 – 2.33 (m, 1H), 2.33 – 2.13 (m, 2H), 2.00 – 1.87 (m, 1H), 1.80 – 1.69 (m, 1H), 1.62 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.61, 180.81, 162.93 (d, *J* = 246.8 Hz), 161.13, 143.01, 137.89 (d, *J* = 7.3 Hz), 133.92, 133.82, 133.11, 131.63, 130.01 (d, *J* = 8.1 Hz), 129.00, 128.75, 126.45 (d, *J* = 2.7 Hz), 123.76, 123.06, 121.29, 117.38 (d, *J* = 21.2 Hz), 114.38 (d, *J* = 21.0 Hz), 74.28, 70.06, 62.91, 57.20, 47.21, 30.78, 25.64, 22.91.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.42.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{29}H_{29}N_3O_3NiF^+$ calcd. 544.1541, observed 544.1541; correct isotopic pattern.

Ni-PBP-αMe-3-FPhe (**S25**)



The title compound (2.25 g, 90%) was prepared according to GP3.

R_f: 0.48, (1:8 acetone/$CHCl_3$).

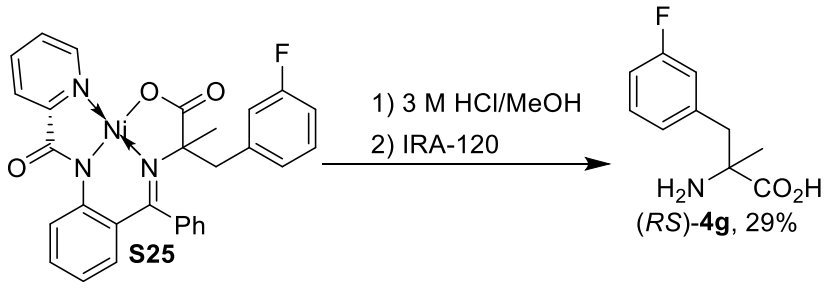
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.90 (td, *J* = 7.7, 1.5 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.76 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.58 – 7.47 (m, 3H), 7.36 – 7.13 (m, 7H), 6.81 (dd, *J* = 8.4, 1.6 Hz, 1H), 6.72 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 6.52 (dq, *J* = 8.4, 1.2 Hz, 1H), 3.09 (q, *J* = 13.6 Hz, 2H), 1.09 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.52, 172.45, 169.03, 162.91 (d, *J* = 246.5 Hz), 153.01, 146.76, 142.45, 139.88, 139.24 (d, *J* = 7.3 Hz), 136.59, 134.61, 132.90, 130.45, 129.63, 129.62 (d, *J* = 8.0 Hz), 128.84, 128.46, 127.60, 126.81 (d, *J* = 2.8 Hz), 126.55, 126.42, 123.45 (d, *J* = 19.1 Hz), 121.26, 118.00, 117.79, 113.99 (d, *J* = 21.0 Hz), 80.82, 47.59 (d, *J* = 1.0 Hz), 28.82. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

^{19}F NMR (376 MHz, $CDCl_3$) δ –112.72.

LRMS (ESI) *m/z* $[M + H]^+$ $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.20, observed 538.20; correct isotopic pattern.
HRMS (ESI) *m/z* $[M + Na]^+$, $C_{29}H_{22}FN_3O_3NaNi^+$ calcd. 560.08909, observed 560.08907; $[M + H]^+$, $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.10714, observed 538.10728; correct isotopic pattern.

(*RS*)-α-Methyl-3-fluorophenylalanine [(*RS*)-**4h**]



The title compound[15] (106 mg, 29%) was prepared according to GP4.

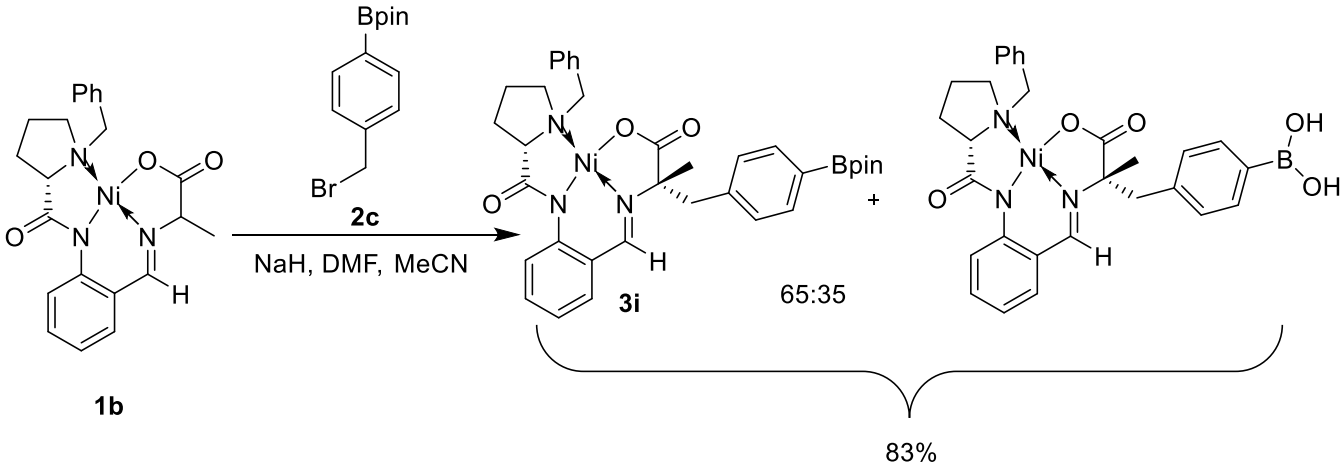
^{1}H NMR (400 MHz, MeOD + 20% DCl) δ 7.42 – 7.35 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 7.10 – 7.02 (m, *J* = 8.1, 7.5, 1.7 Hz, 2H), 3.26 (dd, *J* = 56.9, 14.1 Hz, 2H), 1.65 (s, 3H).

^{13}C NMR (101 MHz, MeOD + 20% DCl) δ 173.15, 164.20 (d, *J* = 245.2 Hz), 137.18 (d, *J* = 7.3 Hz), 131.82 (d, *J* = 8.3 Hz), 127.29 (d, *J* = 2.8 Hz), 118.01 (d, *J* = 21.8 Hz), 115.88 (d, *J* = 21.2 Hz), 61.62, 43.26, 22.84.

^{19}F NMR (376 MHz, MeOD + 20% DCl) δ –114.46.

LRMS (ESI) *m/z* $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09, observed 198.31.
HRMS (ESI) *m/z* $[M + Na]^+$, $C_{10}H_{12}FNO_2NaNi^+$ calcd. 220.07443, observed 220.07455; $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09248, observed 198.09245.

α-Methyl-4-[^{18}F]FPhe precursor (**3i**)



The above compound (**3i**) was prepared according to GP1 whereby, **1b** (0.50 g, 1.15 mmol), **2c** (0.55 g, 1.85 mmol), NaH (60% suspension in mineral oil) (74 mg, 1.85 mmol) and DMF/MeCN 1:2 (10 mL) were utilized. Yield: 83% (0.59 g, 0.95 mmol; total yield of **3i** and the corresponding boronic acid). RP Chromatography using aqueous MeCN and subsequent evaporation of MeCN at 40 ºC under reduced pressure caused partial hydrolysis of Bpin ester to give the corresponding boronic acid as side product. As boronic acids are typically even better substrates for the alcohol-enhanced Cu-mediated radiofluorination than Bpin esters, no attempt to separate it (or to convert it back into the Bpin ester) was performed and the mixture was directly used for the radiolabeling step. Omission of the RP purification step could lead to substantially lower ^{18}F-incorporation rates.

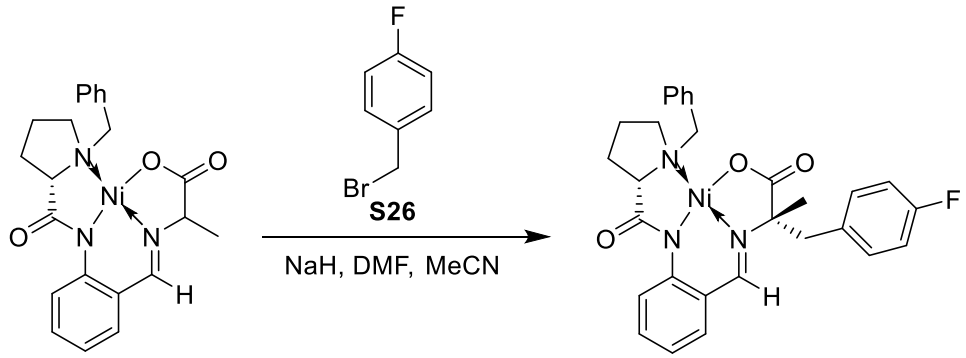
R_f: 0.49, (1:10 acetone/$CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$; before RP purification) δ 8.54 (d, *J* = 8.6 Hz, 1H), 7.97 – 7.91 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.56 (s, 1H), 7.37 – 7.26 (m, 5H), 7.16 (d, *J* = 8.0 Hz, 2H), 6.96 (t, *J* = 7.0 Hz, 1H), 4.30 (d, *J* = 12.7 Hz, 1H), 3.51 (d, *J* = 12.7 Hz, 1H), 3.39 (d, *J* = 13.3 Hz, 1H), 3.27 – 3.14 (m, 2H), 2.83 (d, *J* = 13.3 Hz, 1H), 2.27 – 2.10 (m, 3H), 2.01 – 1.89 (m, 1H), 1.64 (s, 3H), 1.62 – 1.54 (m, 1H), 1.33 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$; before RP purification) δ 181.55, 180.88, 161.00, 142.97, 138.55, 135.08, 133.82, 133.72, 133.10, 131.63, 130.02, 128.90, 128.67, 123.70, 123.13, 121.18, 83.72, 74.52, 70.04, 62.87, 57.30, 48.05, 30.73, 25.43, 24.79, 24.72, 22.94.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{35}H_{41}N_3O_5NiB^+$ calcd. 652.2488, observed 652.2485; correct isotopic pattern.

Ni-BPB α-methyl-4FPhe Reference Compound (**18i**)



1b **18i**, 82%

The above compound (**18i**) was prepared according to GP1 whereby, **1b** (0.235 g, 0.54 mmol), 1-(bromomethyl)-4-fluorobenzene (**S26**, 0.165 g, 0.87 mmol), NaH (60% suspension in mineral oil) (36 mg, 0.90 mmol) and DMF/MeCN 1:2 (7 mL) were utilized. Yield: 82% (0.26 g, 0.48 mmol).

R_f: 0.53, (1:10 acetone/$CHCl_3$).

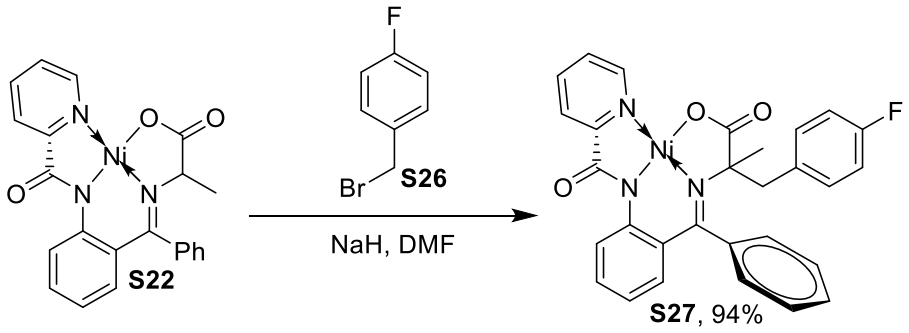
^{1}H NMR (400 MHz, $CDCl_3$) 8.53 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.52 (s, 1H), 7.42 – 7.21 (m, 5H), 7.16 – 7.04 (m, 4H), 6.97 (t, *J* = 7.9 Hz, 1H), 4.30 (d, *J* = 12.7 Hz, 1H), 3.54 (d, *J* = 12.7 Hz, 1H), 3.33 (d, *J* = 13.6 Hz, 1H), 3.29 – 3.20 (m, 2H), 2.81 (d, *J* = 13.6 Hz, 1H), 2.48 – 2.32 (m, 1H), 2.32 – 2.15 (m, 2H), 1.95 (td, *J* = 10.7, 6.4 Hz, 1H), 1.76 (dtd, *J* = 8.8, 6.4, 3.2 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 181.64, 180.89, 162.53 (d, *J* = 246.2 Hz), 161.07, 143.00, 133.91, 133.89 (d, *J* = 4.8 Hz), 132.24, 132.16, 131.65, 131.21 (d, *J* = 3.4 Hz), 129.03, 128.78, 123.79, 123.12, 121.33, 115.49 (d, *J* = 21.2 Hz), 74.58, 70.03, 62.97, 57.26, 46.93, 30.83, 25.36, 22.87.

^{19}F NMR (376 MHz, $CDCl_3$) δ –115.23.

HRMS (ESI) *m/z* $[M + H]^+$, $C_{29}H_{29}N_3O_3NiF^+$ calcd. 544.1541, observed 544.1541; correct isotopic pattern.

Ni-PBP-αMe-4-FPhe (**S27**)



The title compound (2.36 g, 94%) was prepared according to GP3.

R_f: 0.22, (1:8 acetone/$CHCl_3$).

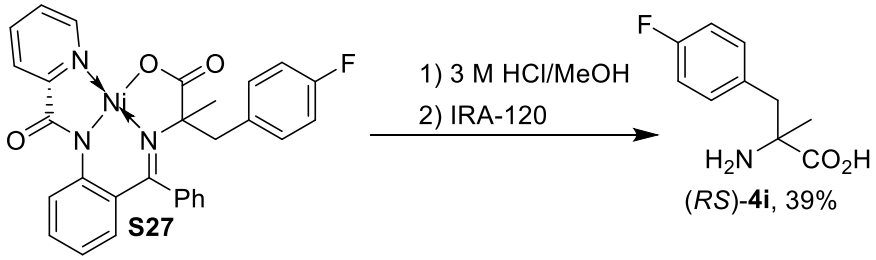
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 8.1 Hz, 1H), 7.91 (td, *J* = 7.7, 1.3 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 5.1 Hz, 1H), 7.55 – 7.46 (m, 5H), 7.37 – 7.20 (m, 4H), 6.81 (ddd, *J* = 14.4, 9.2, 5.0 Hz, 3H), 6.75 – 6.69 (m, 1H), 3.08 (dd, *J* = 30.0, 13.6 Hz, 2H), 1.07 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 179.46, 172.28, 168.95, 162.15 (d, *J* = 246.6 Hz), 153.01, 146.73, 142.33, 140.01, 136.61, 134.57, 132.81, 132.70, 132.63 (d, *J* = 8.0 Hz), 130.47, 129.60, 129.02, 128.48, 127.59, 126.48, 126.18, 123.50 (d, *J* = 10.2 Hz), 121.29, 114.91 (d, *J* = 21.2 Hz), 81.16, 47.34, 28.67. *o*- and *m*-Carbons of the phenyl group of the [(2-amido)phenyl]phenylmethanimine residue were inequivalent.

^{19}F NMR (376 MHz, $CDCl_3$) δ –114.53.

LRMS (ESI) *m/z* $[M + H]^+$ $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.20, observed 538.20; correct isotopic pattern.
HRMS (ESI) *m/z* $[M + Na]^+$, $C_{29}H_{22}FN_3O_3NaNi^+$ calcd. 560.08909, observed 560.08908; $[M + H]^+$, $C_{29}H_{23}FN_3O_3Ni^+$ calcd. 538.10714, observed 538.10726; correct isotopic pattern.

(*RS*)-α-Methyl-4-fluorophenylalanine [(*RS*)-**4i**]



The title compound[14] (142 mg, 39%) was prepared according to GP4.

^{1}H NMR (400 MHz, MeOD + 20% DCl) δ δ 7.34 – 7.28 (m, 2H), 7.13 – 7.05 (m, 2H), 3.23 (dd, *J* = 53.7, 14.2 Hz, 2H), 1.65 (s, 3H).

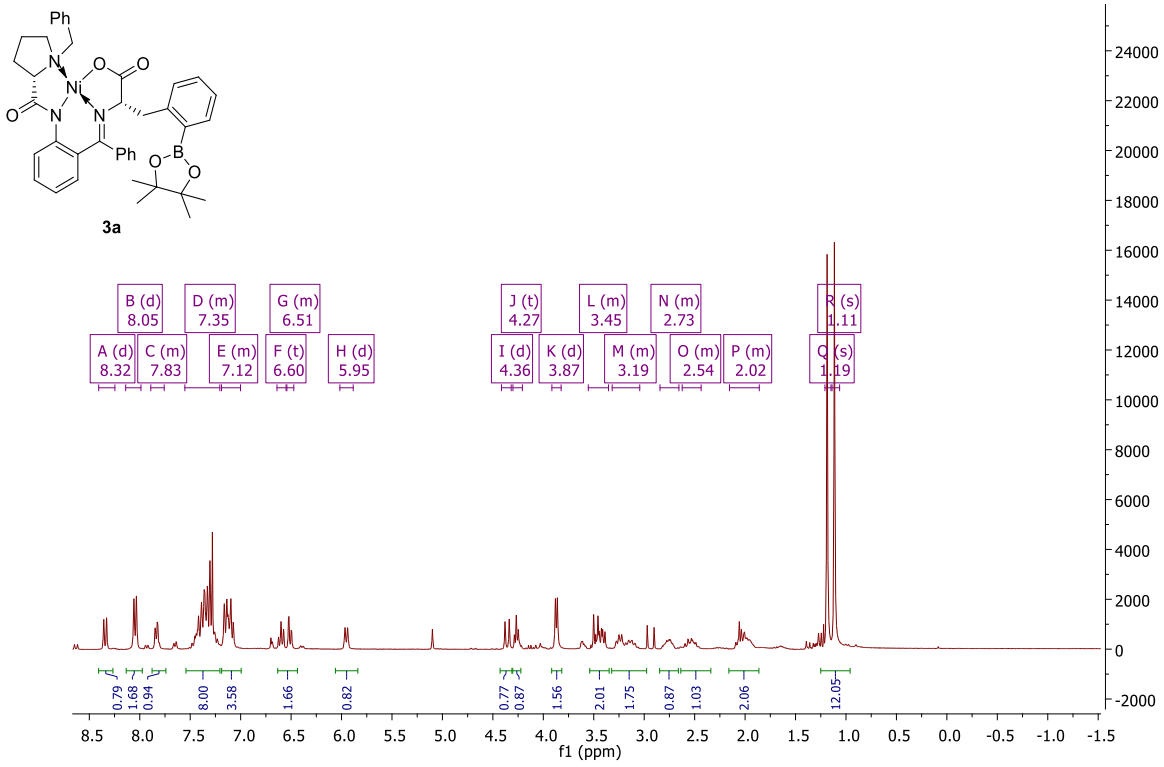
^{13}C NMR (101 MHz, MeOD + 20% DCl) δ 173.26, 163.90 (d, *J* = 245.2 Hz), 133.21 (d, *J* = 8.3 Hz), 130.58 (d, *J* = 3.4 Hz), 116.65 (d, *J* = 21.7 Hz), 61.70, 42.82, 22.70.

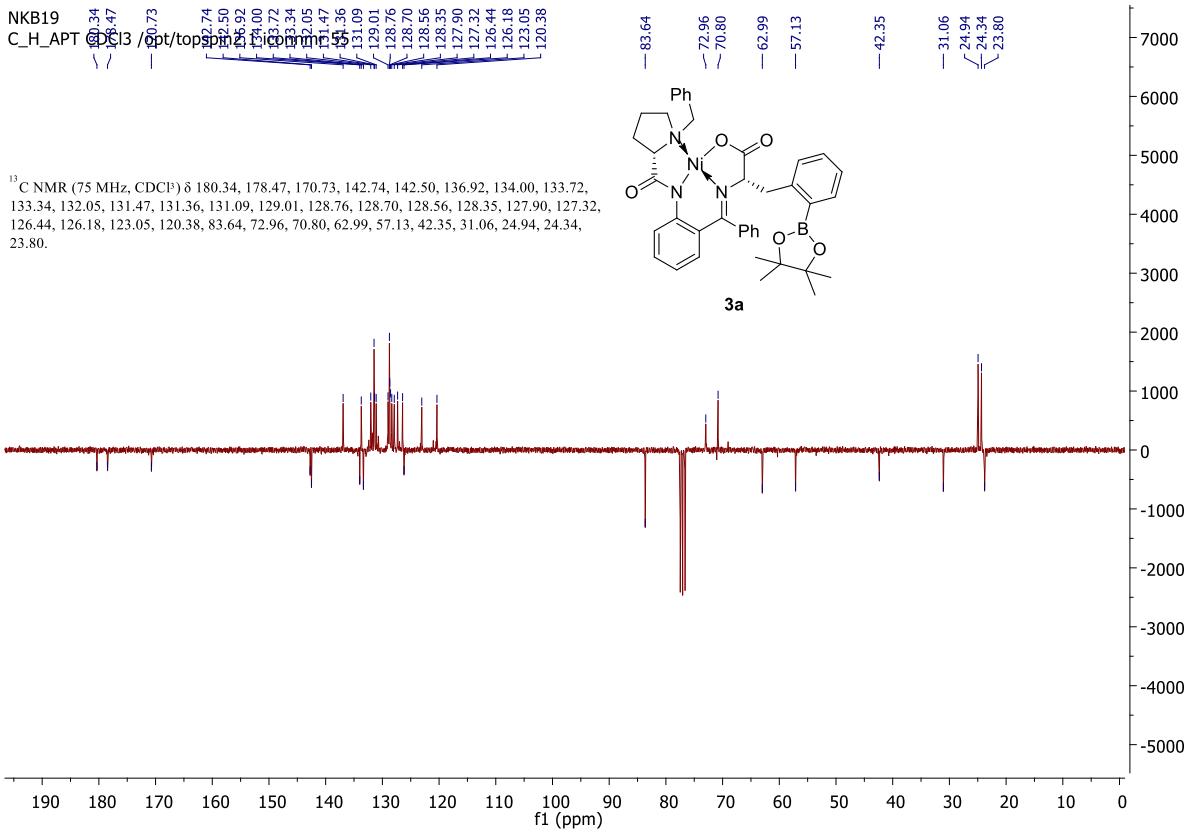
^{19}F NMR (376 MHz, MeOD + 20% DCl) δ –114.45.

LRMS (ESI) *m/z* $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09, observed 198.27.
HRMS (ESI) *m/z* $[M + H]^+$, $C_{10}H_{13}FNO_2Ni^+$ calcd. 198.09248, observed 198.09251.

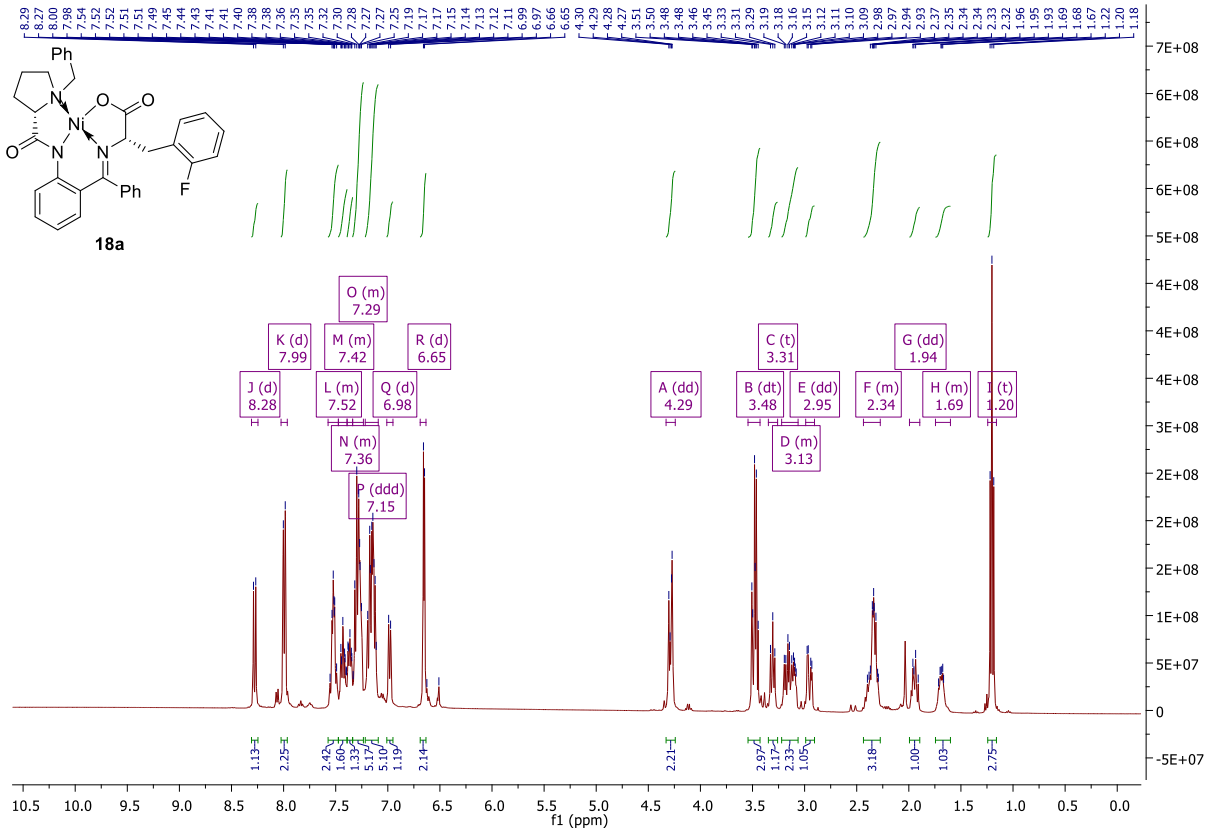
NMR Spectra

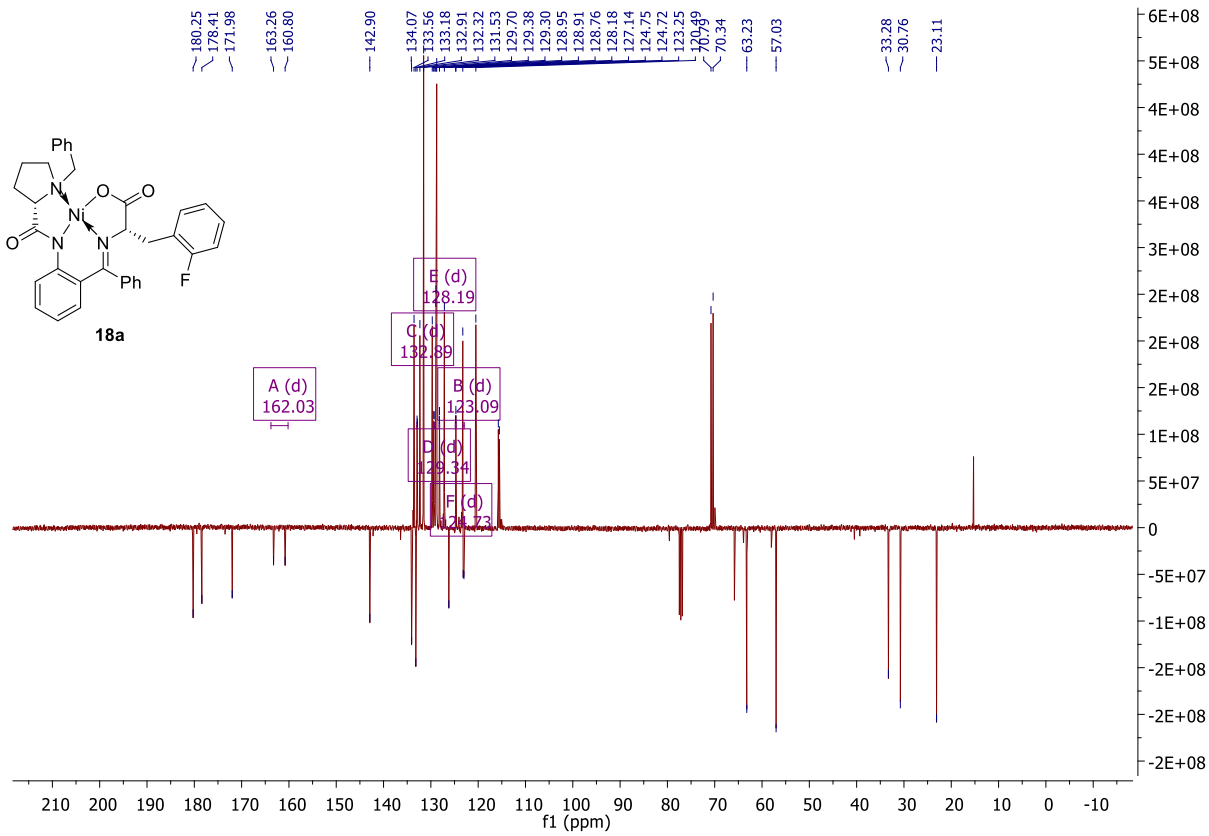
(*S*,*S*)-Ni-BPB-2-BpinPhe (3a) ($CDCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz)

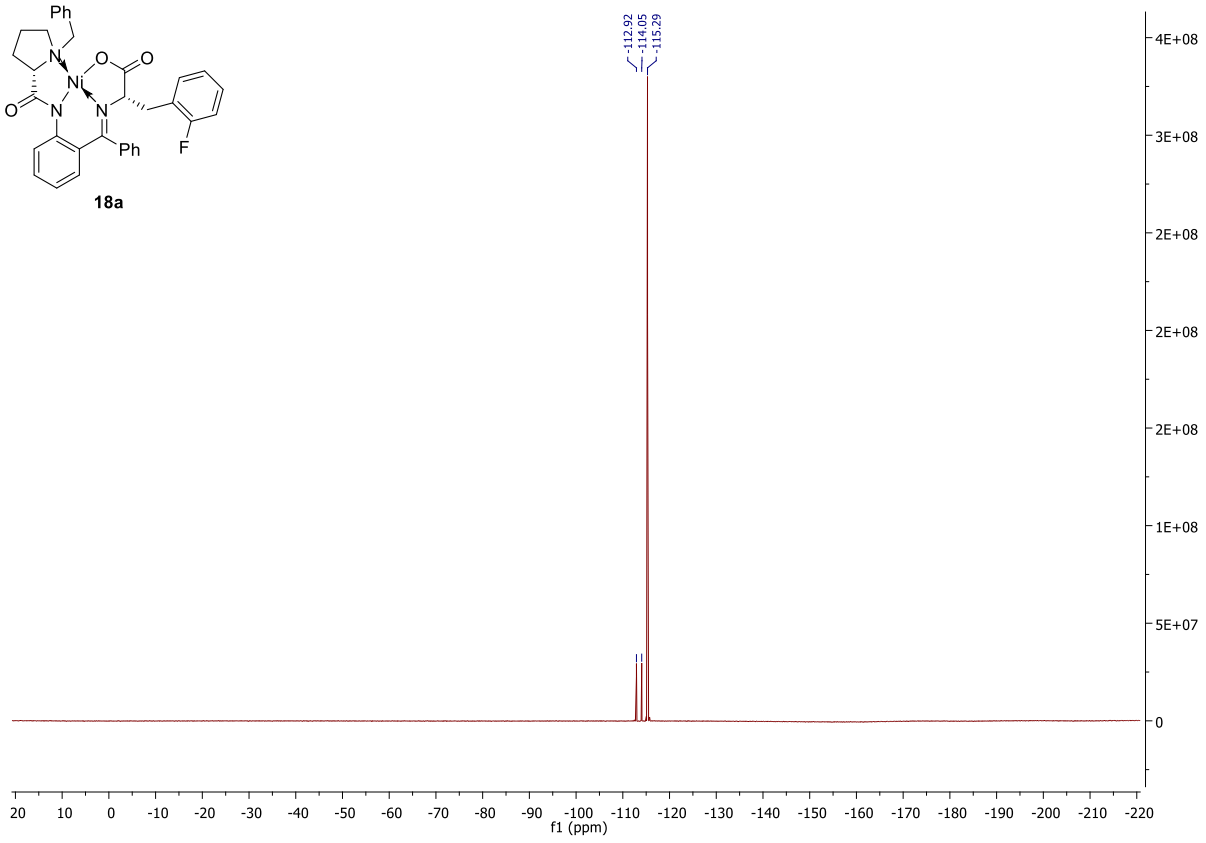




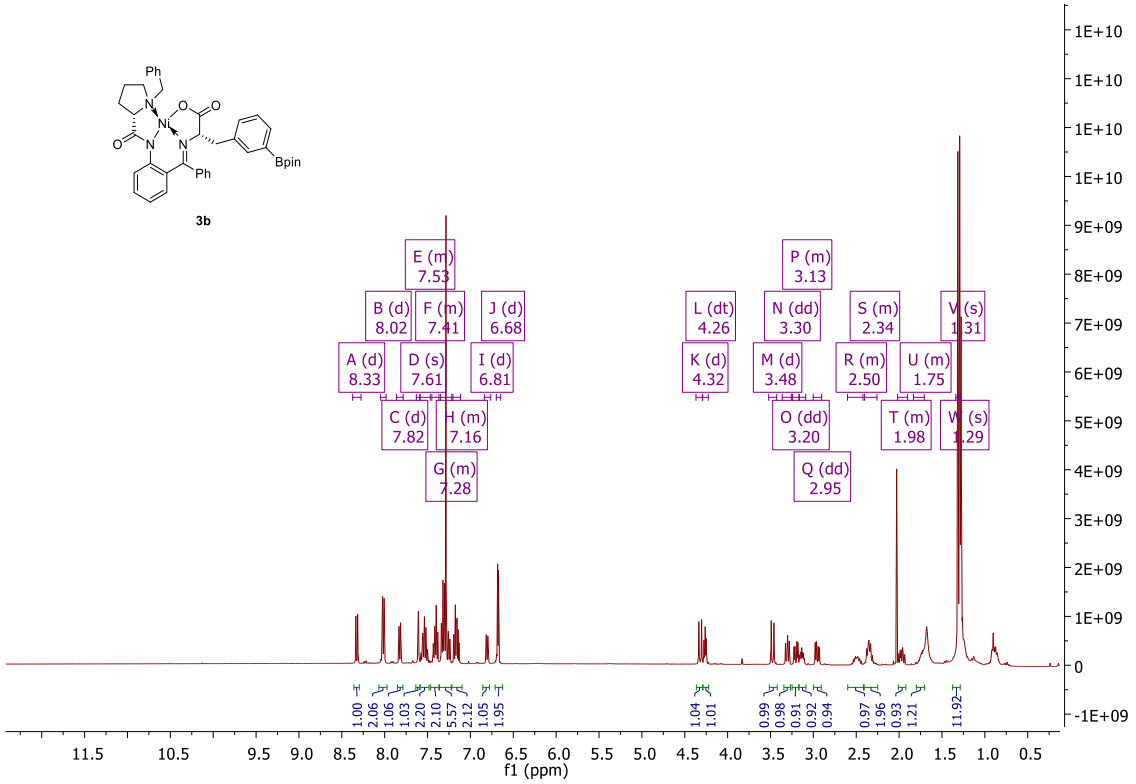
(*S*,*S*)-Ni-BPB-2-FPhe (18a) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)

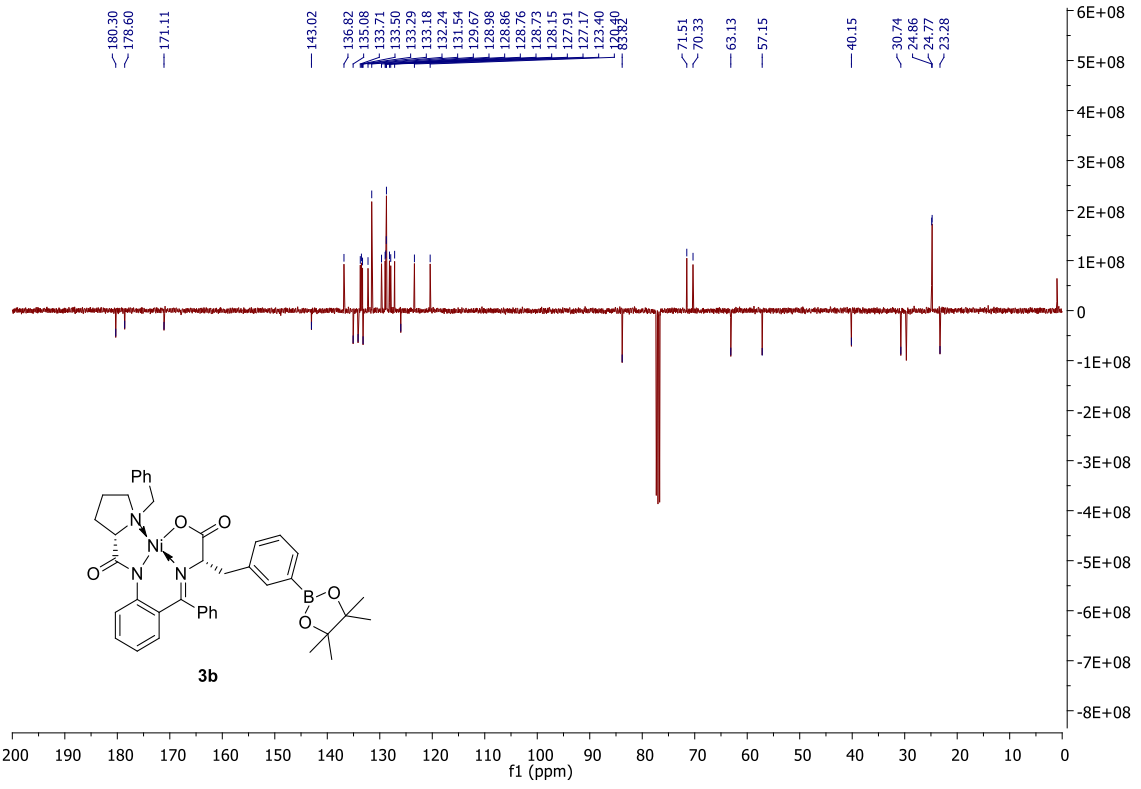




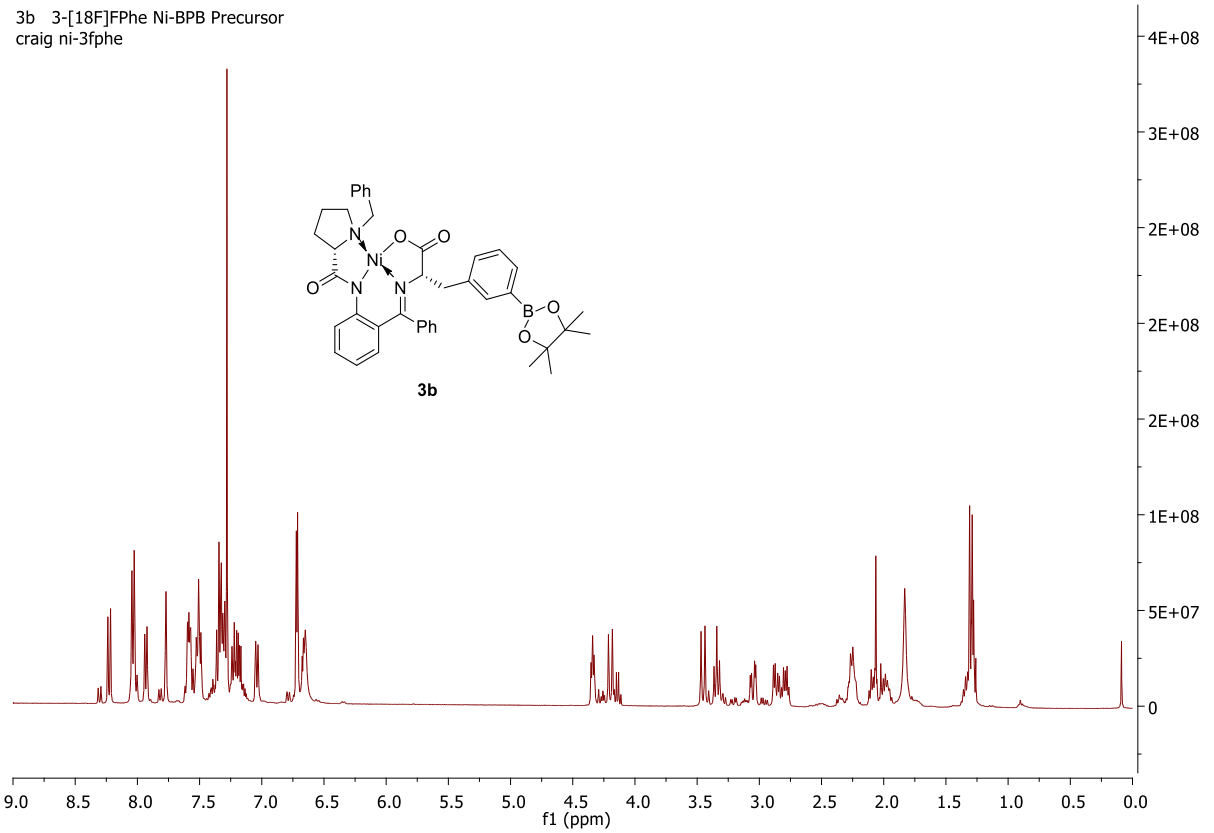

Ph
N
O
O
Ni
O
N
N
Ph
F
18a
-112.92
-114.05
-115.29
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

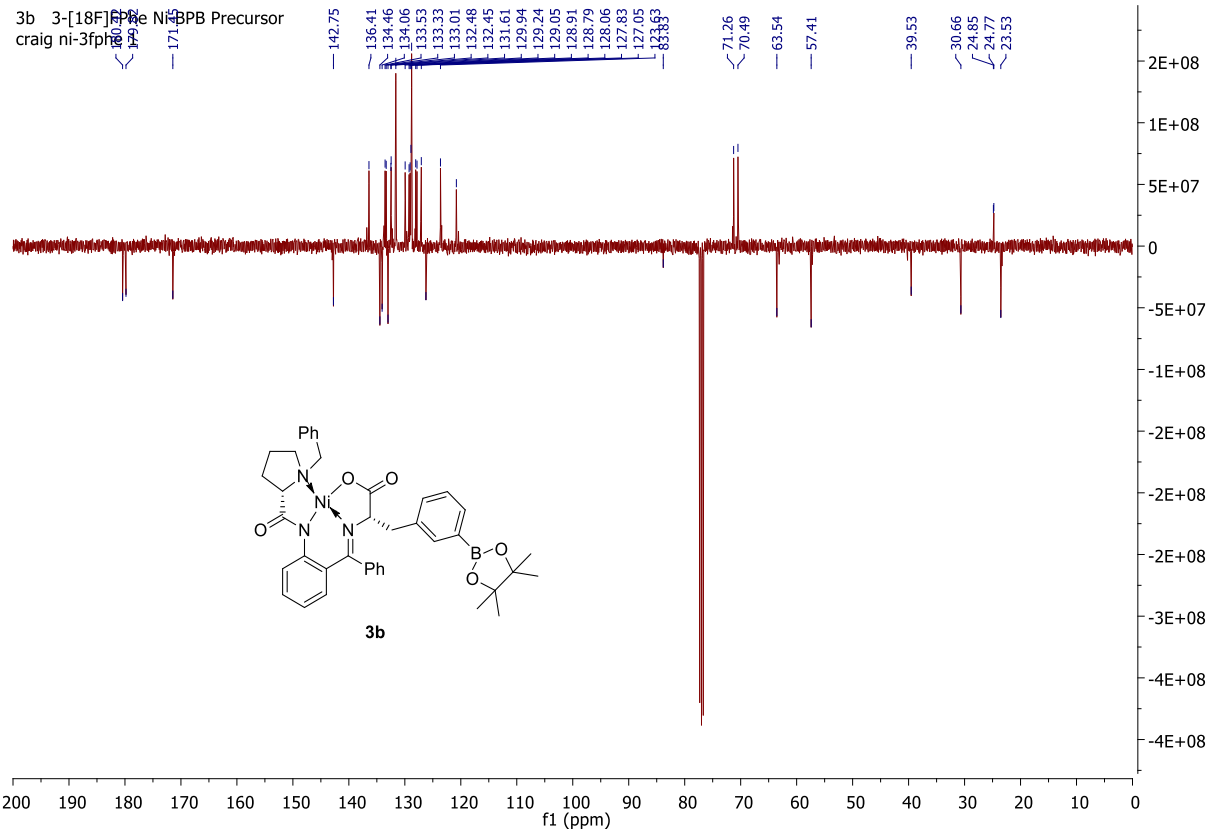
(*S*,*S*)-Ni-BPB-3-BpinPhe (3b) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (before RP purification)



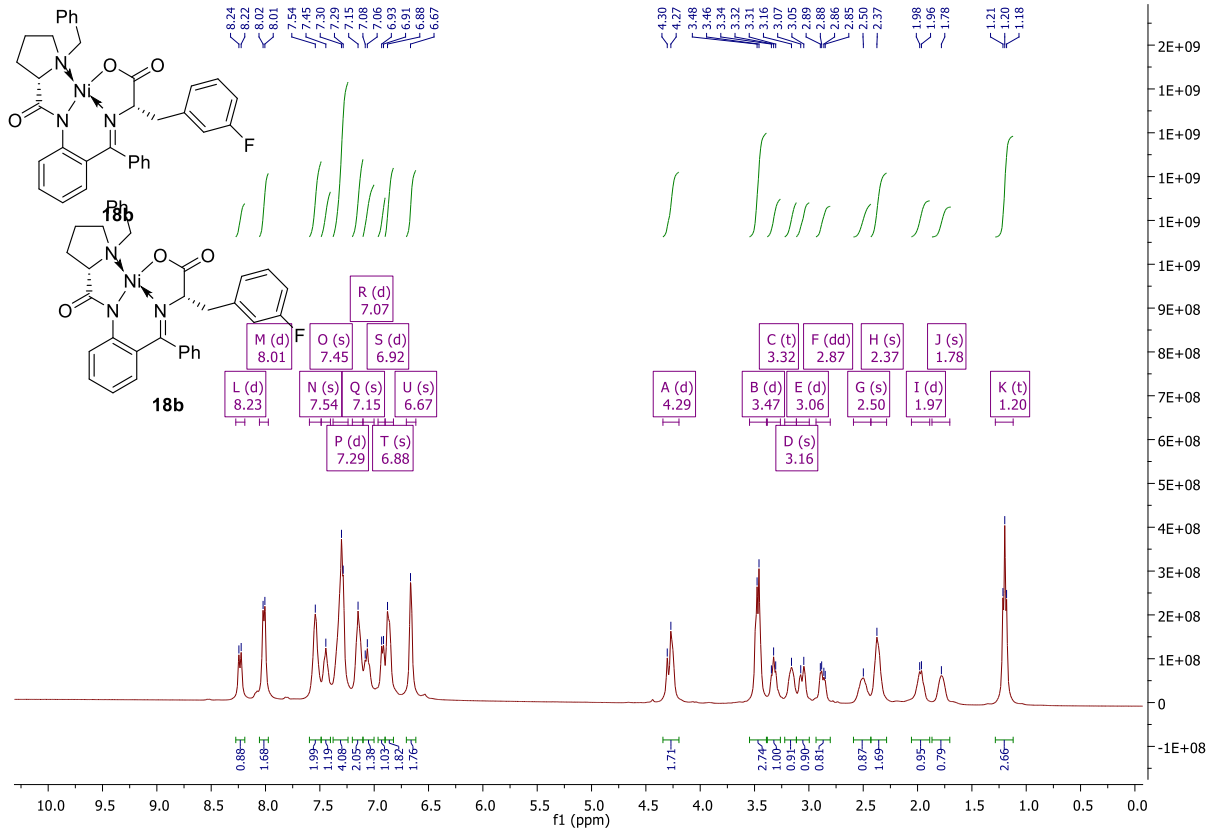


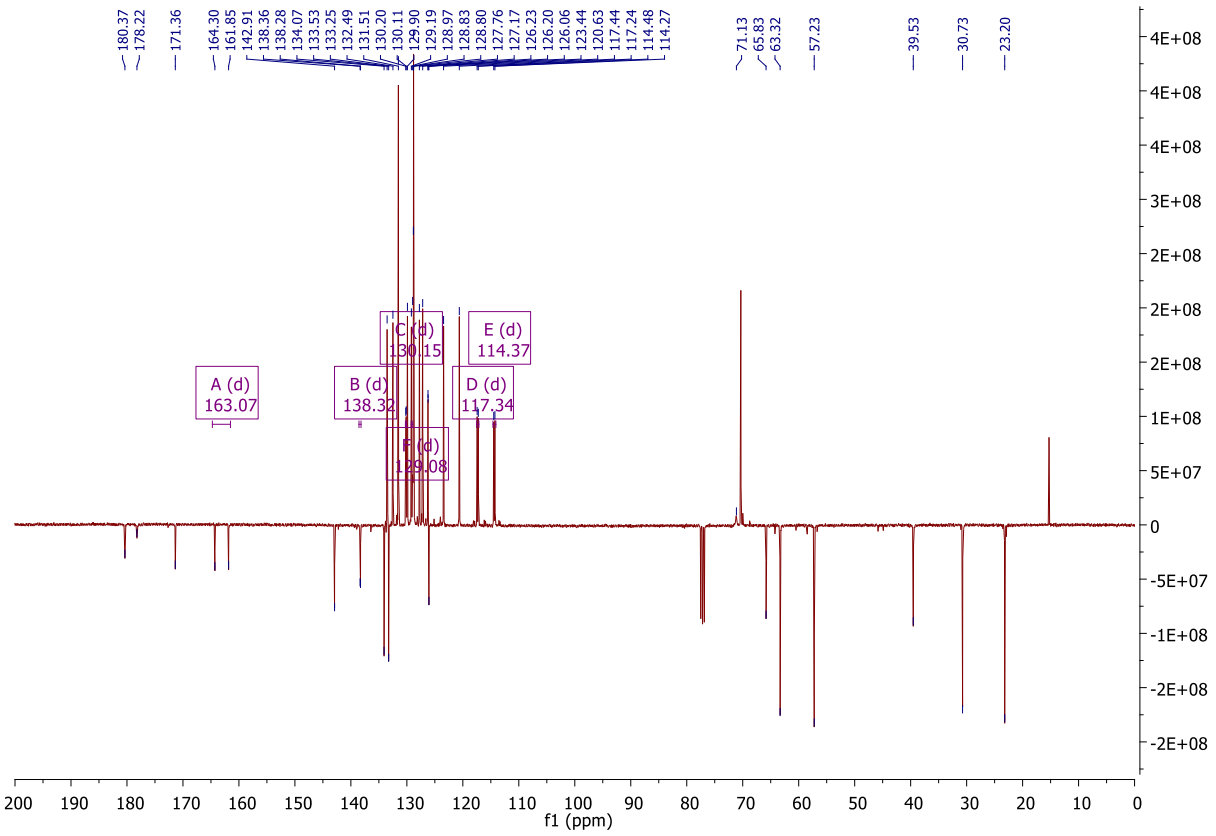
(*S*,*S*)-Ni-BPB-3-BpinPhe (3b) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (after RP purification)

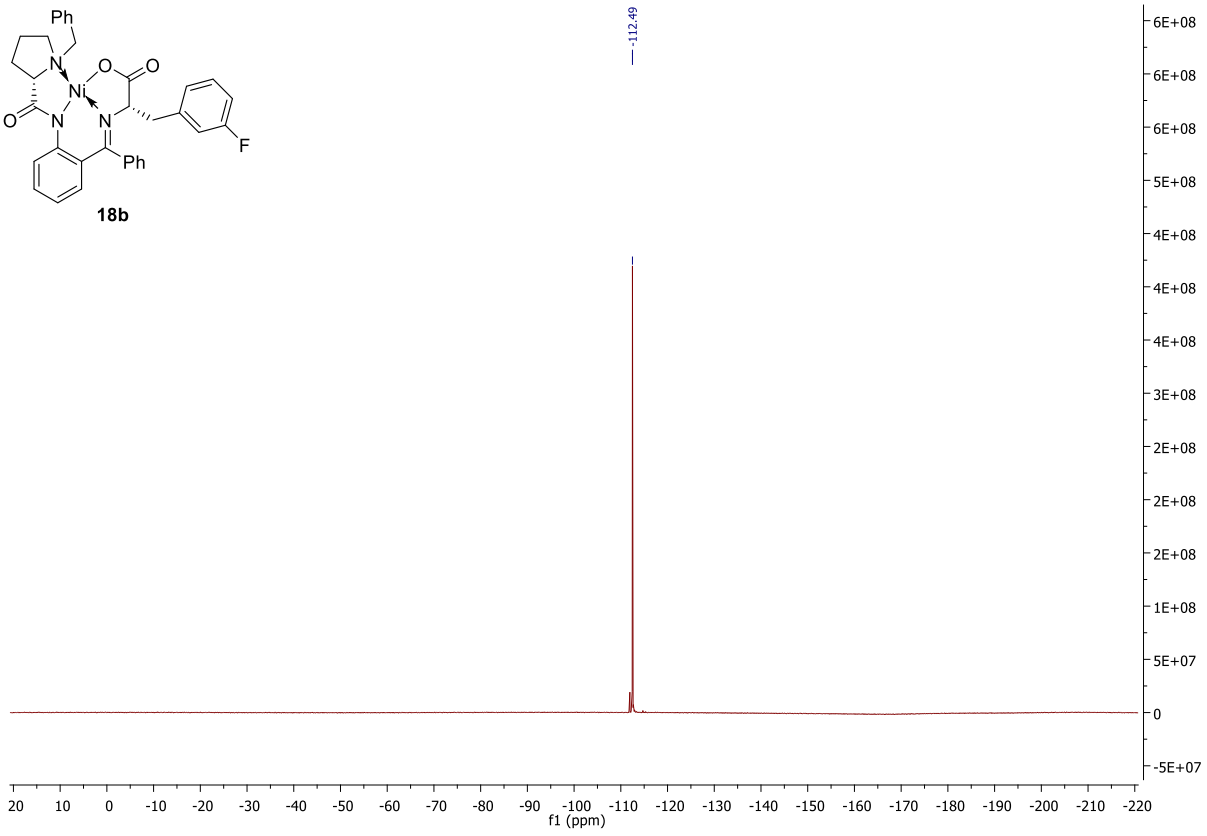




(*S*,*S*)-Ni-BPB-3-FPhe (18b) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)






Ph
N
Ni
O
O
O
N
N
Ph
F
18b
-112.49
6E+08
6E+08
6E+08
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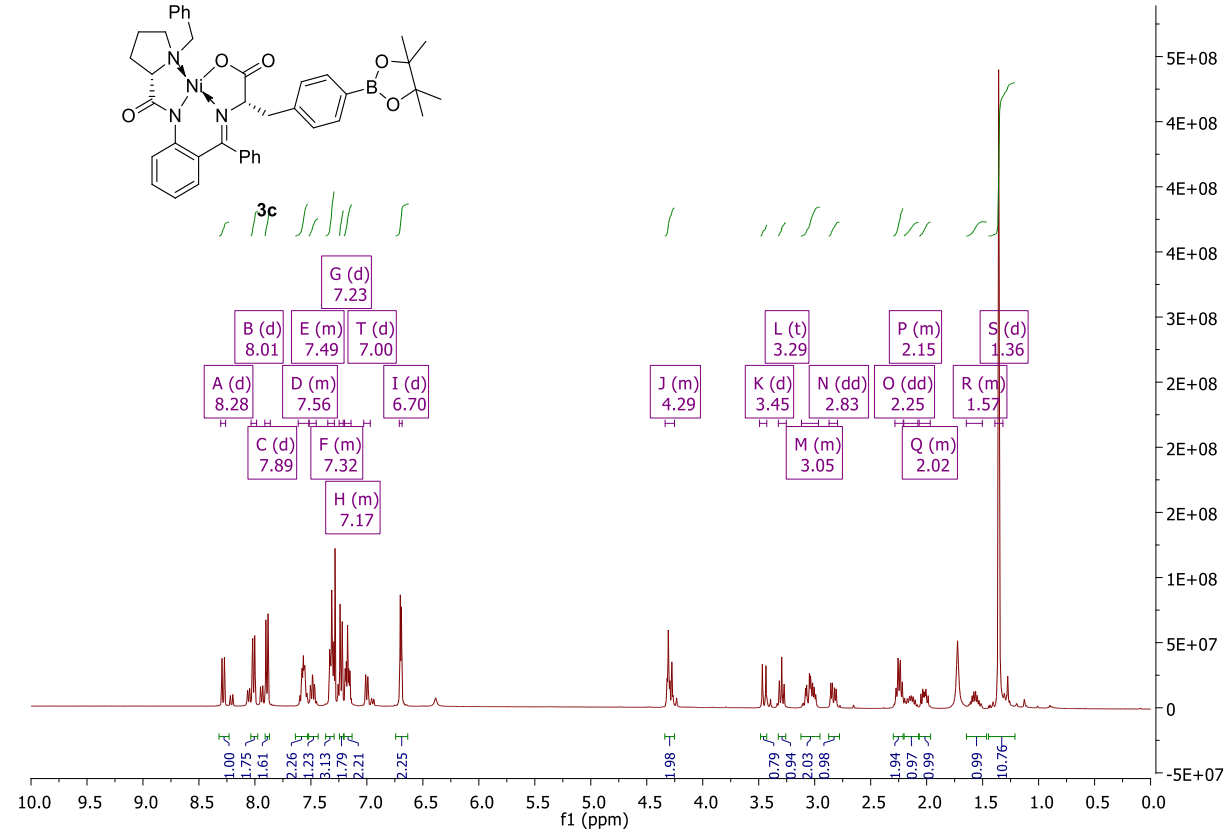
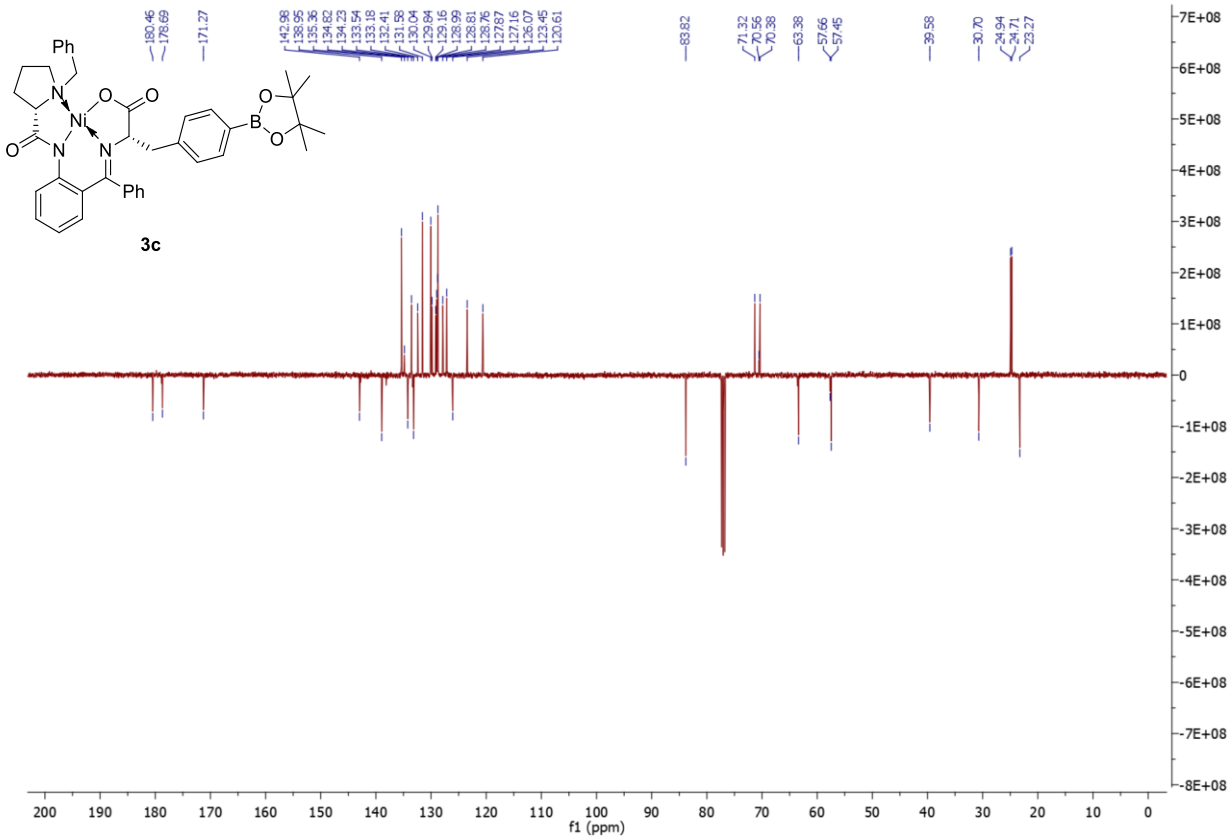
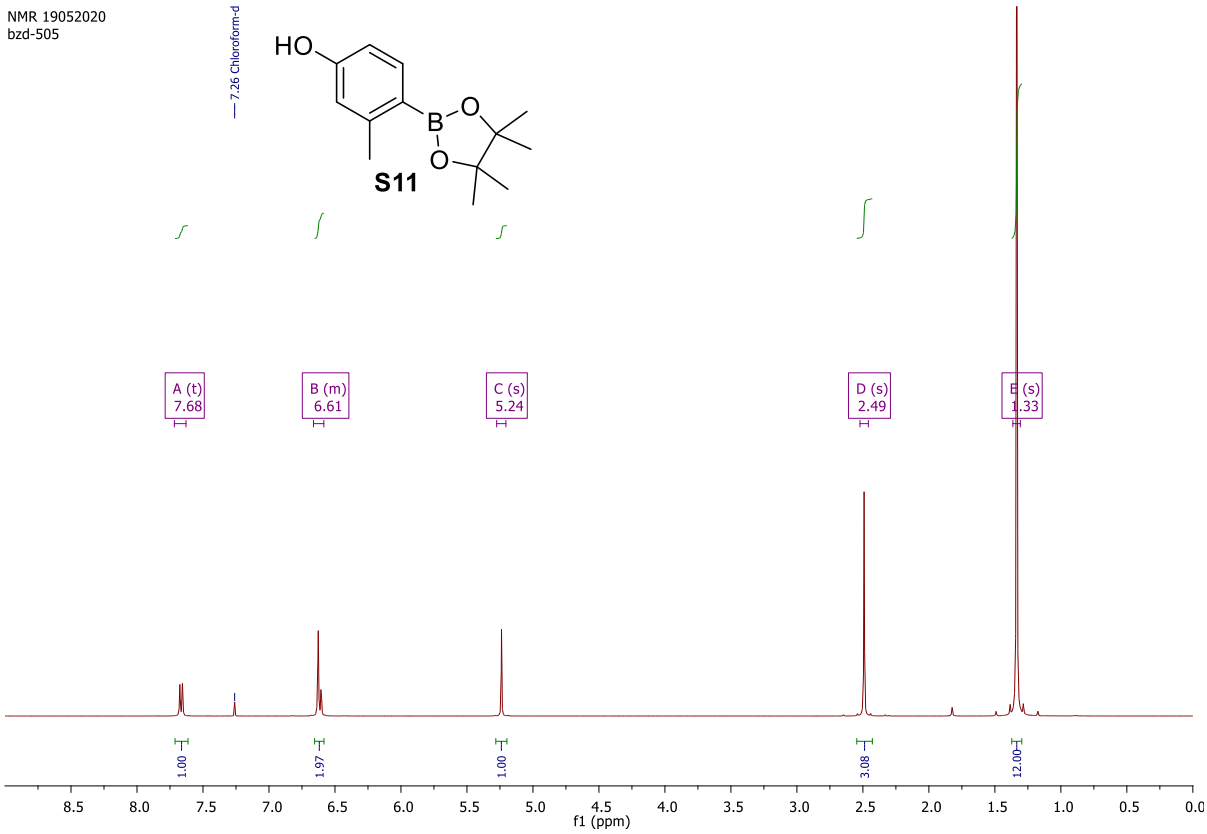
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

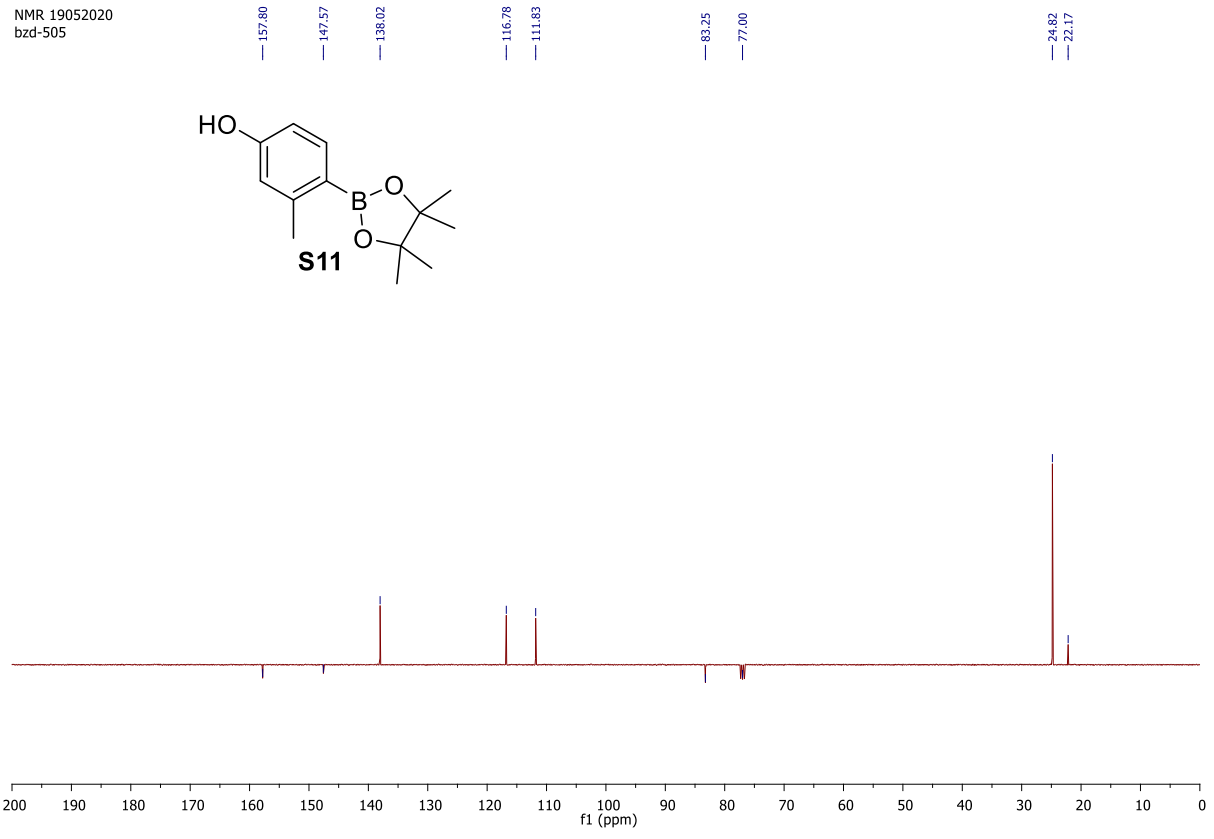
(*S*,*S*)-Ni-BPB-4-BpinPhe (3c) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)





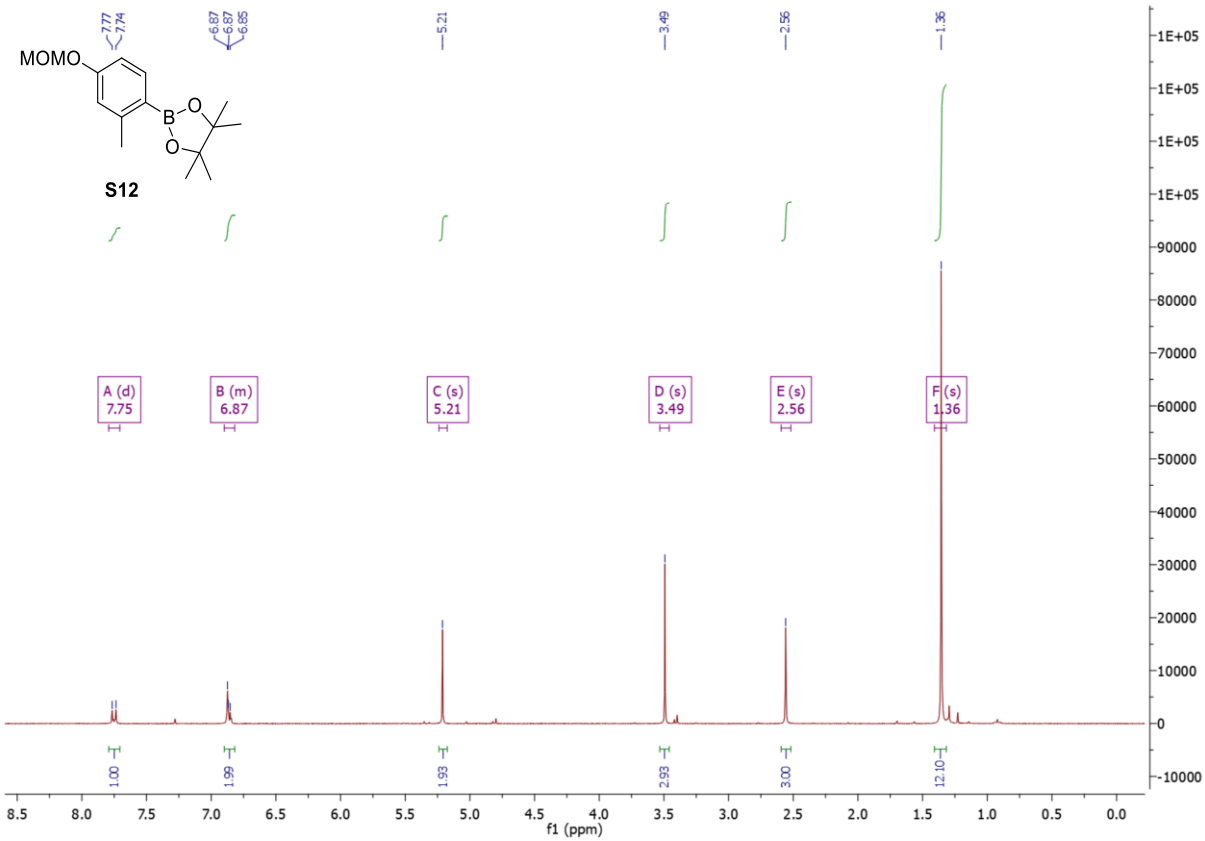
4,4,5,5-Tetramethyl-2-(2-methyl-4-hydroxyphenyl)-1,3,2-dioxaborolane (S11) ($CDCl_3$) ^1H NMR (400 MHz) ^{13}C NMR (101 MHz)

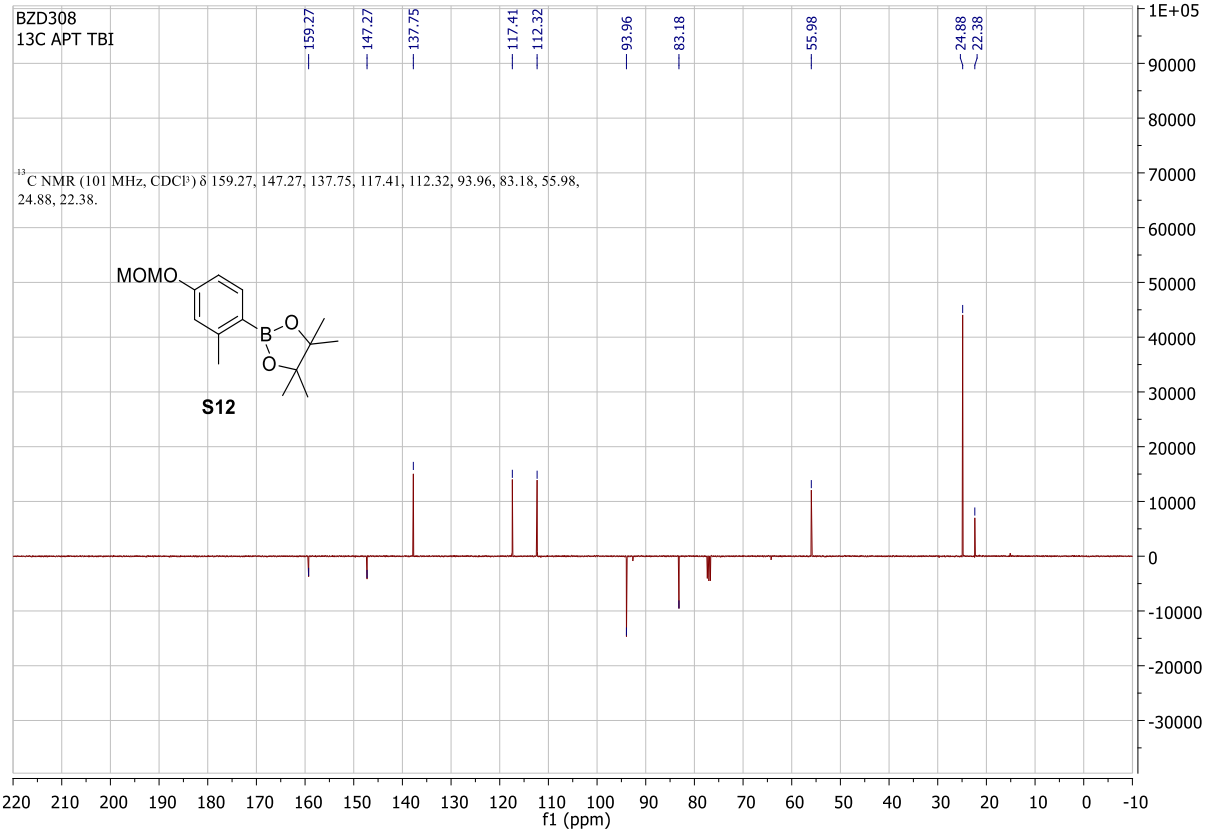




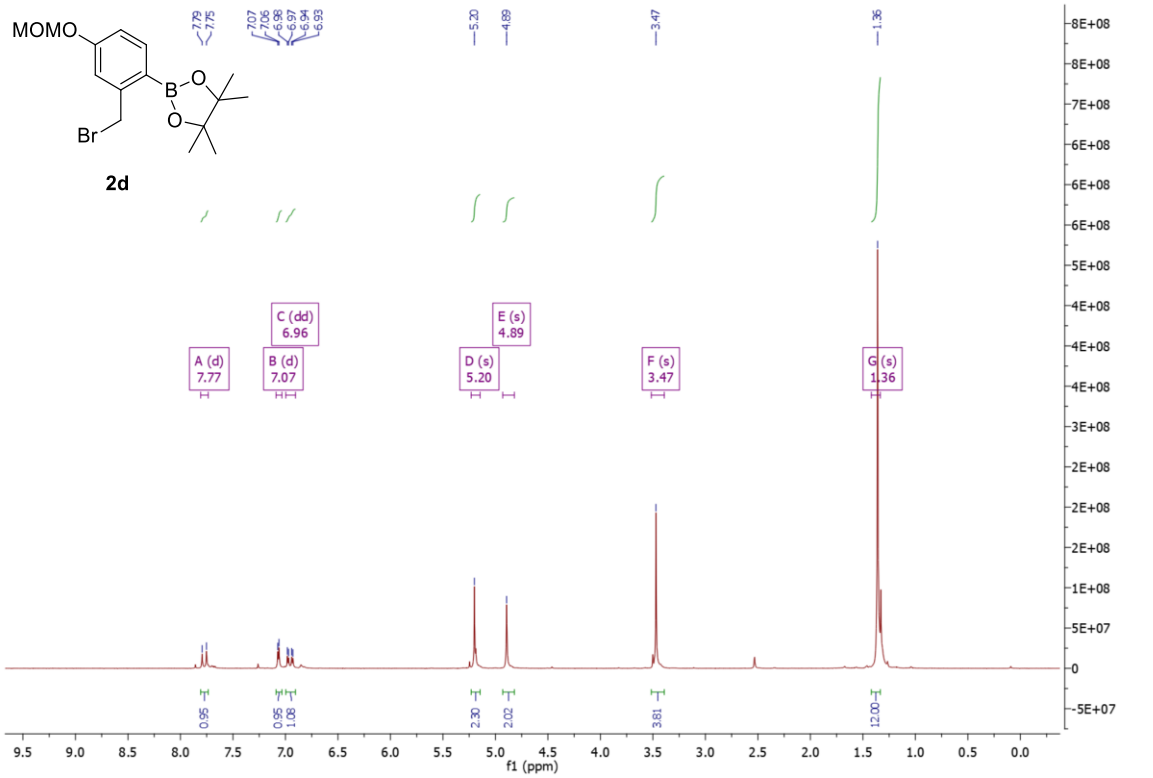
2-(4-(Methoxymethoxy)-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S12)

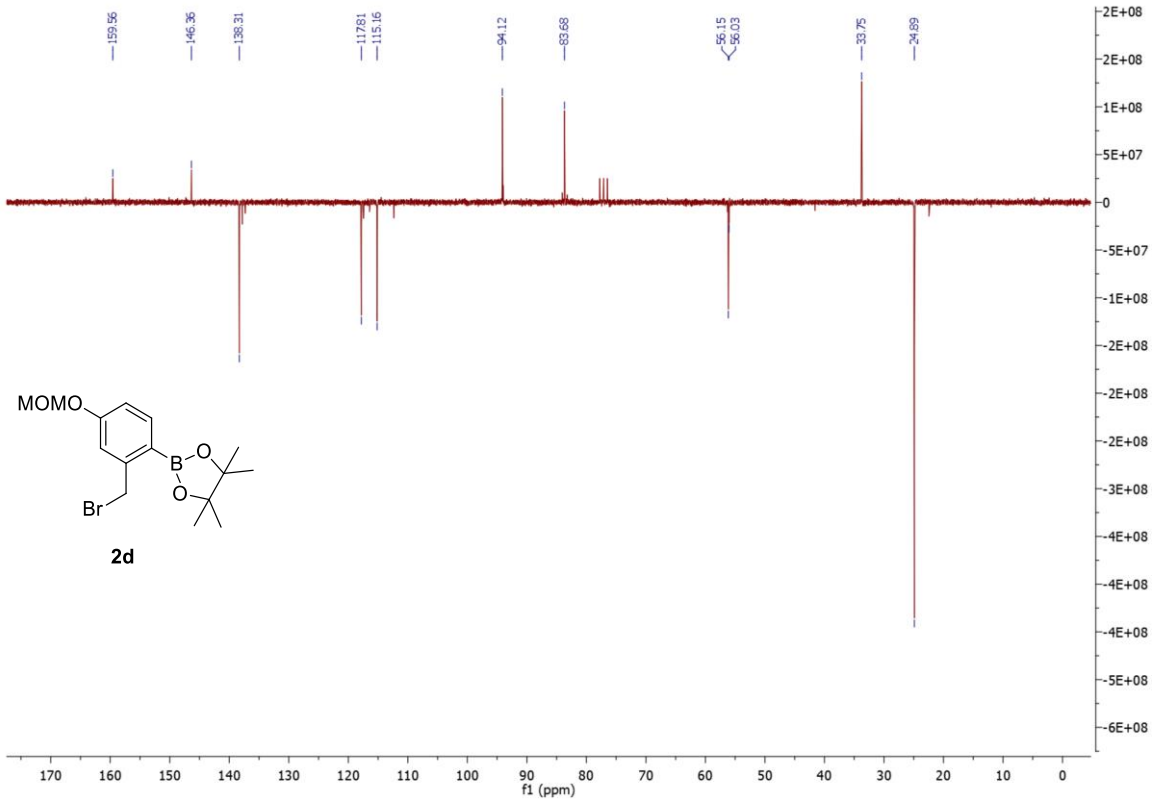
($CDCl_3$) ^1H NMR (400 MHz) ^{13}C NMR (101 MHz)



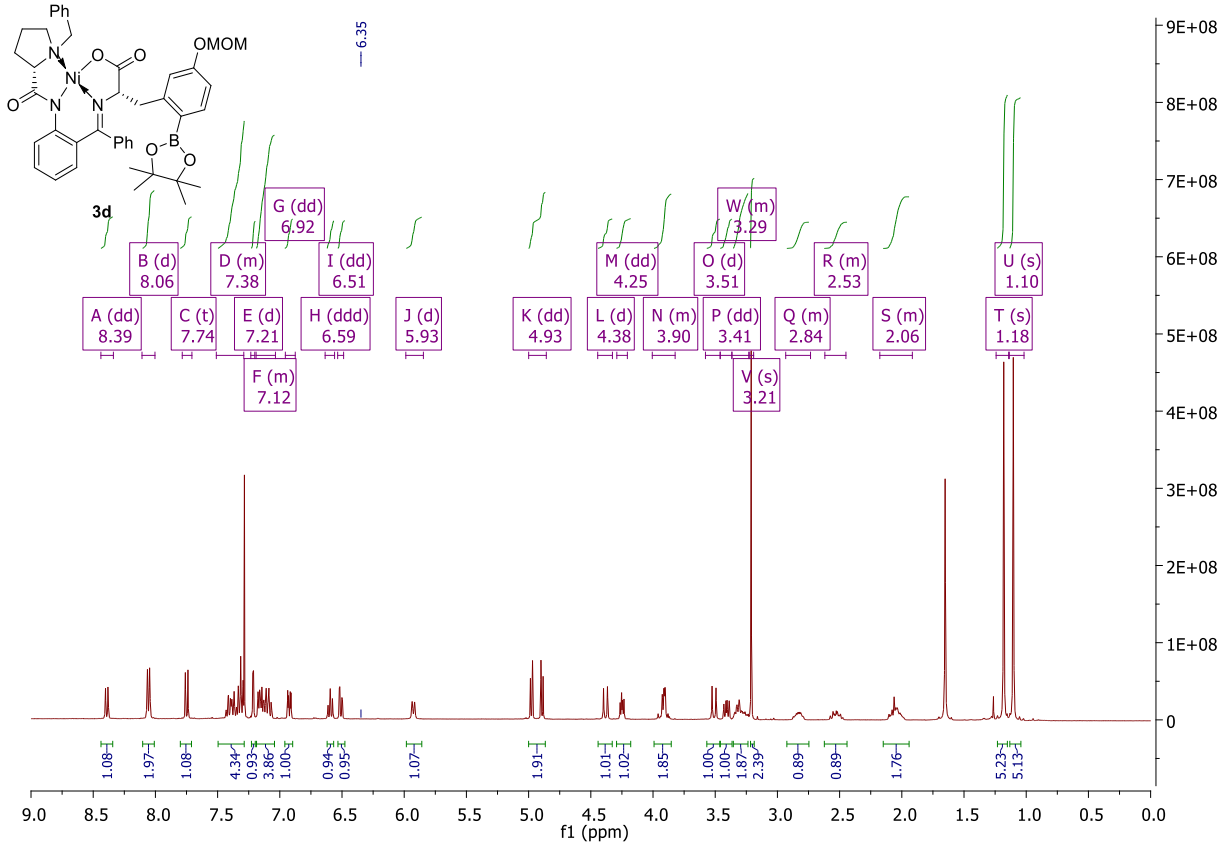


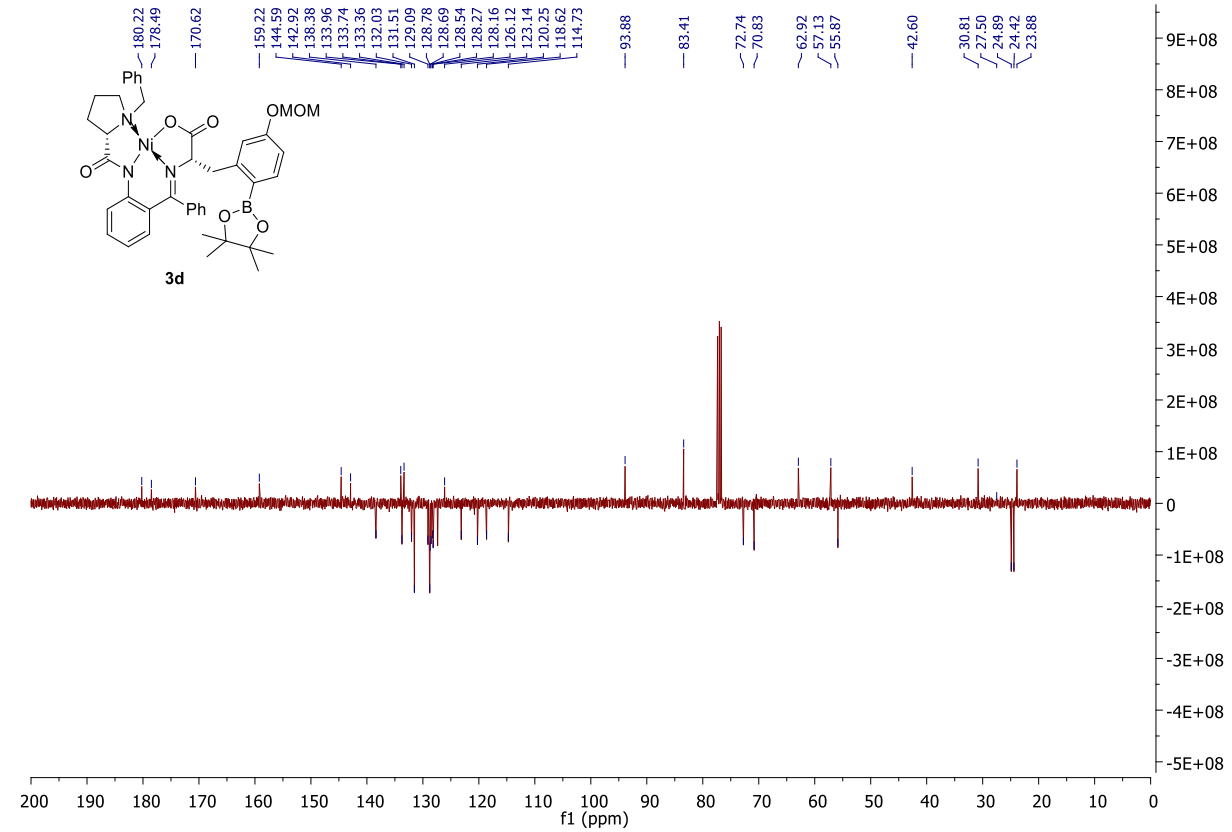
2-(2-(Bromomethyl)-4-(methoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (2d) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)



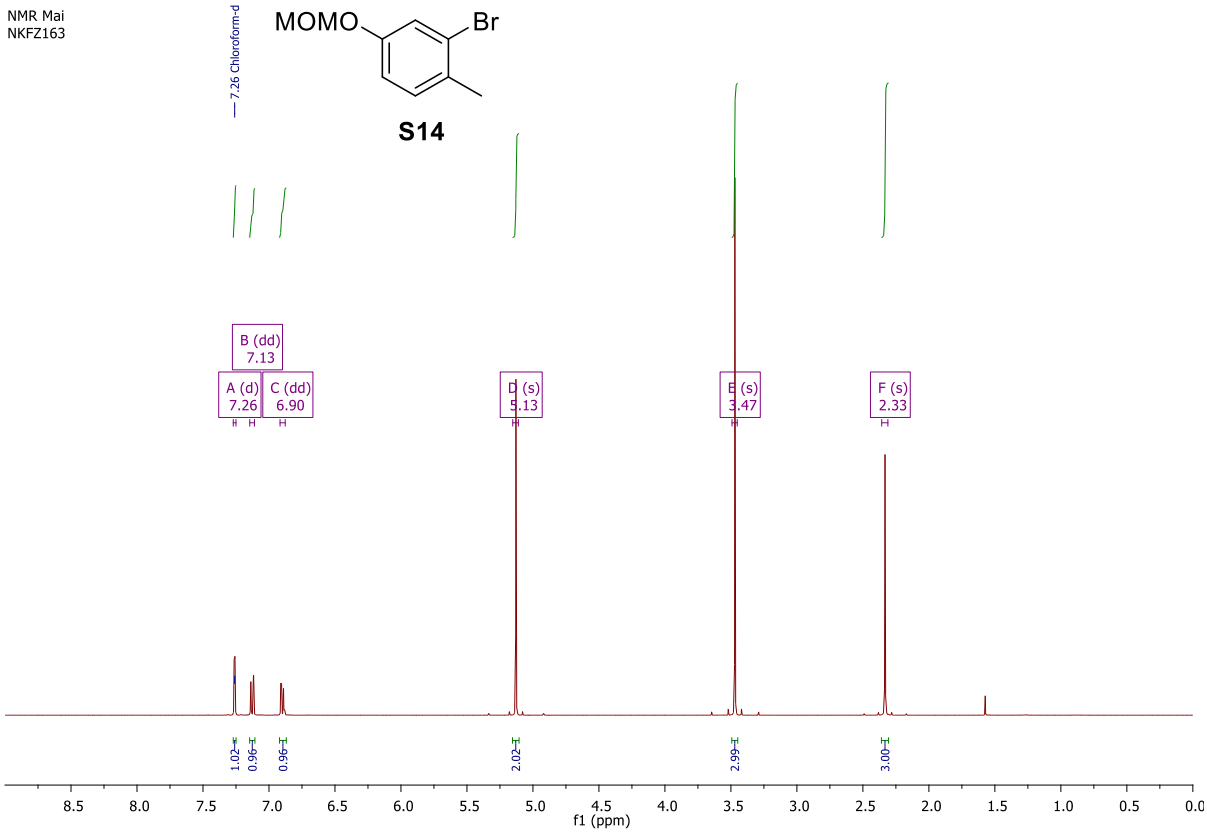


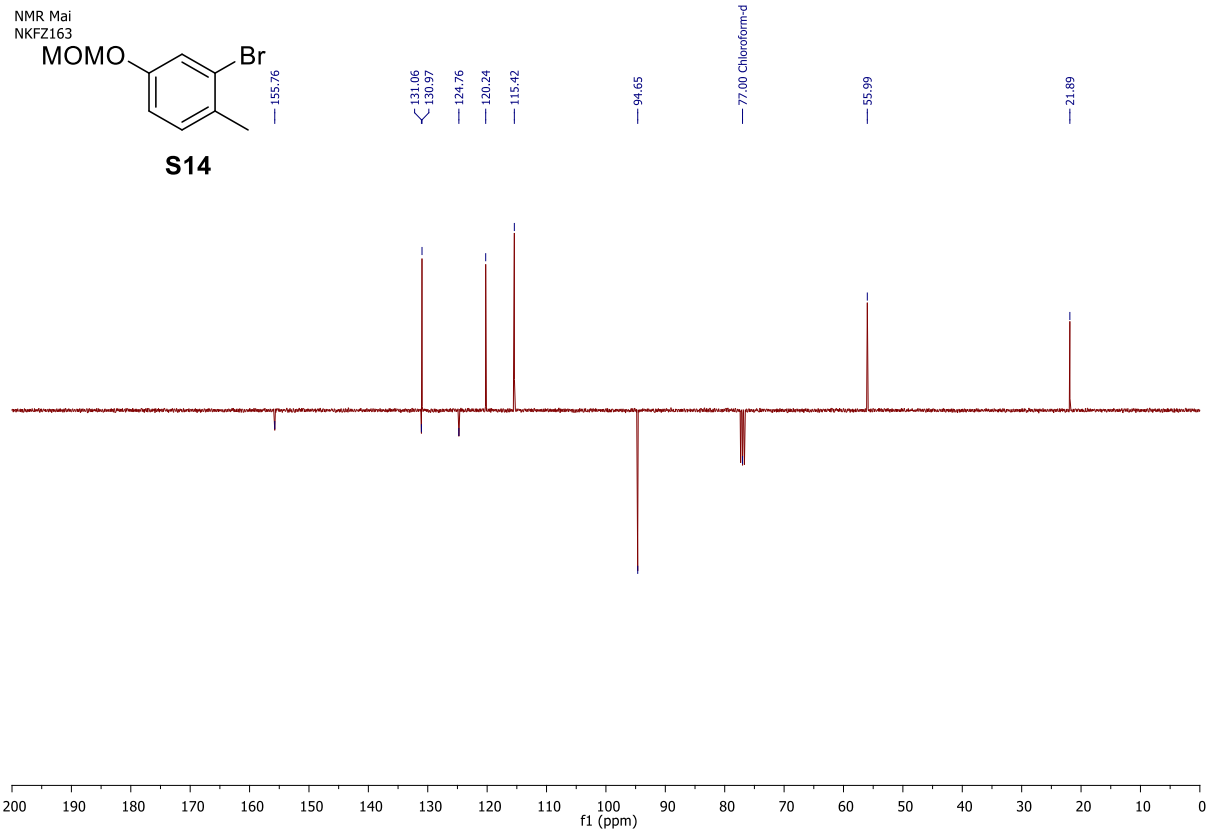
(*S*,*S*)-Ni-BPB-2-Bpin-5-MOMO-Phe (3d) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)





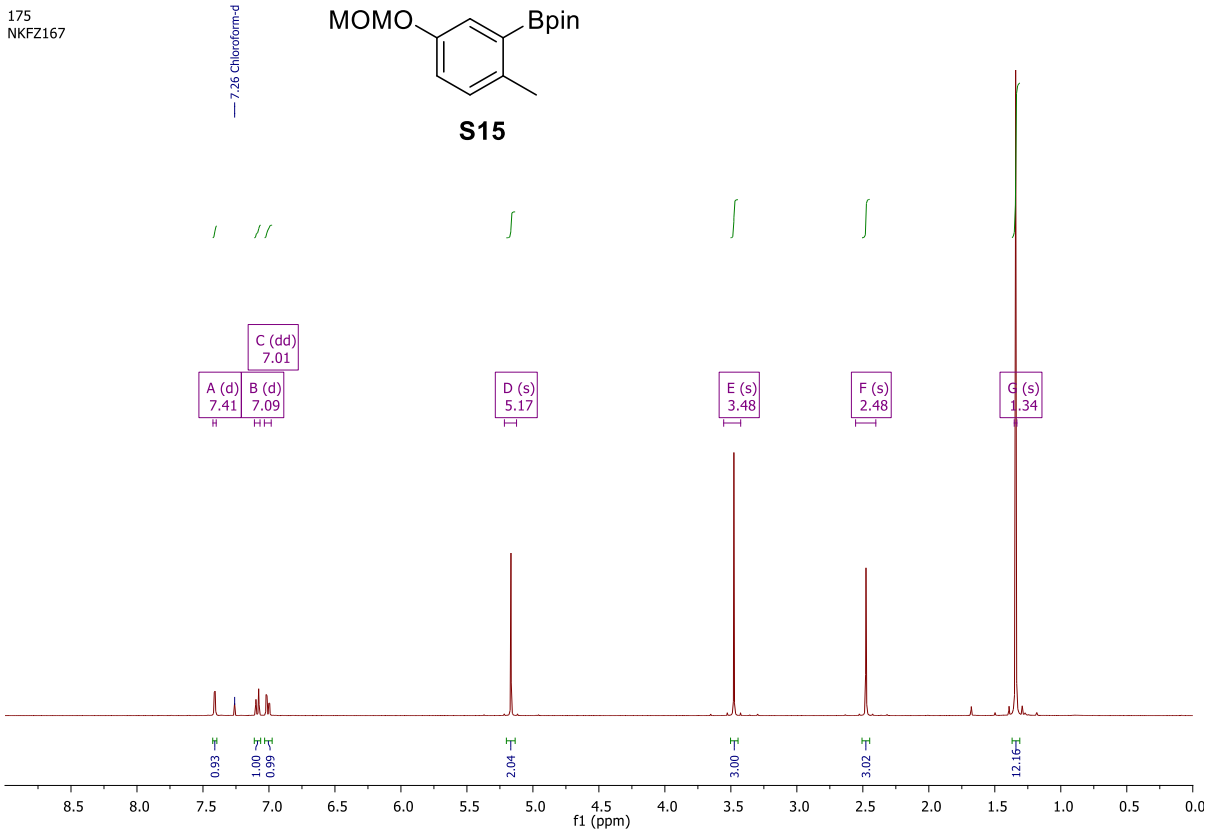
2-Bromo-4-(methoxymethoxy)-1-methylbenzene (S14) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz)

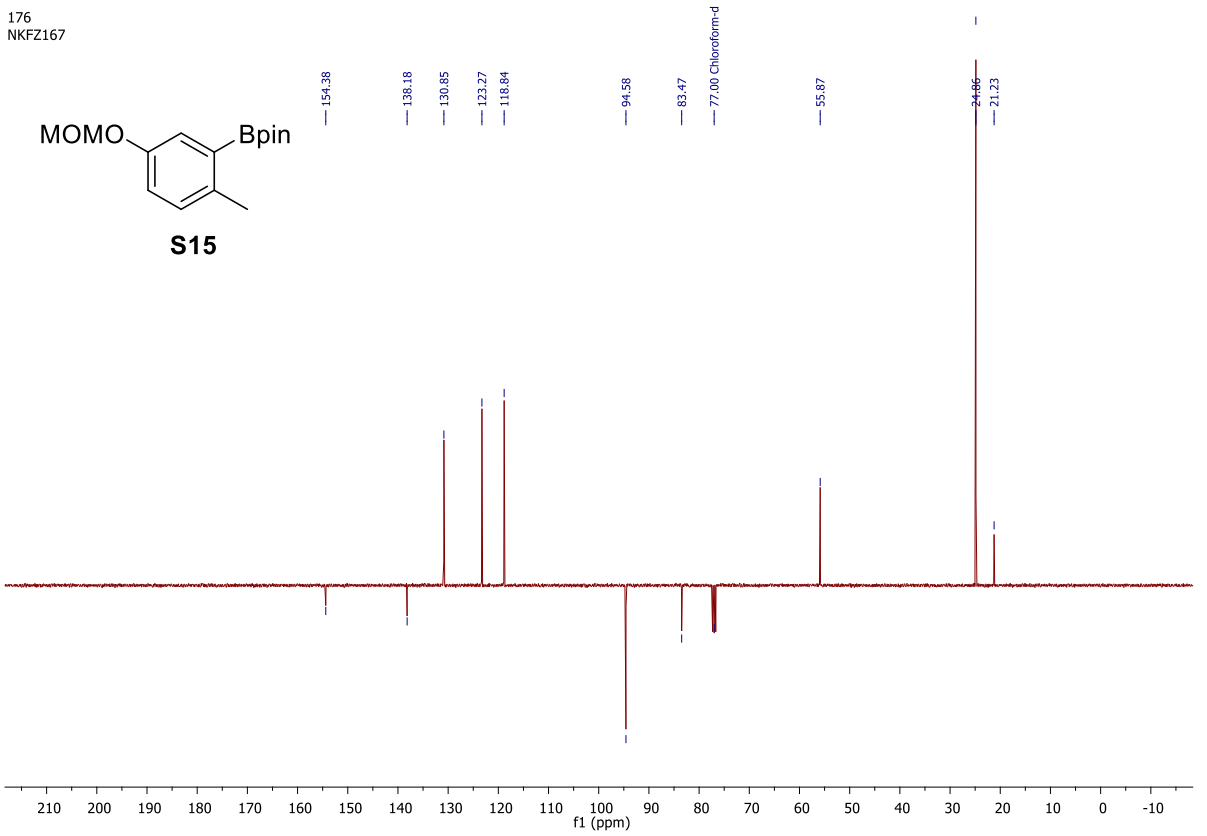




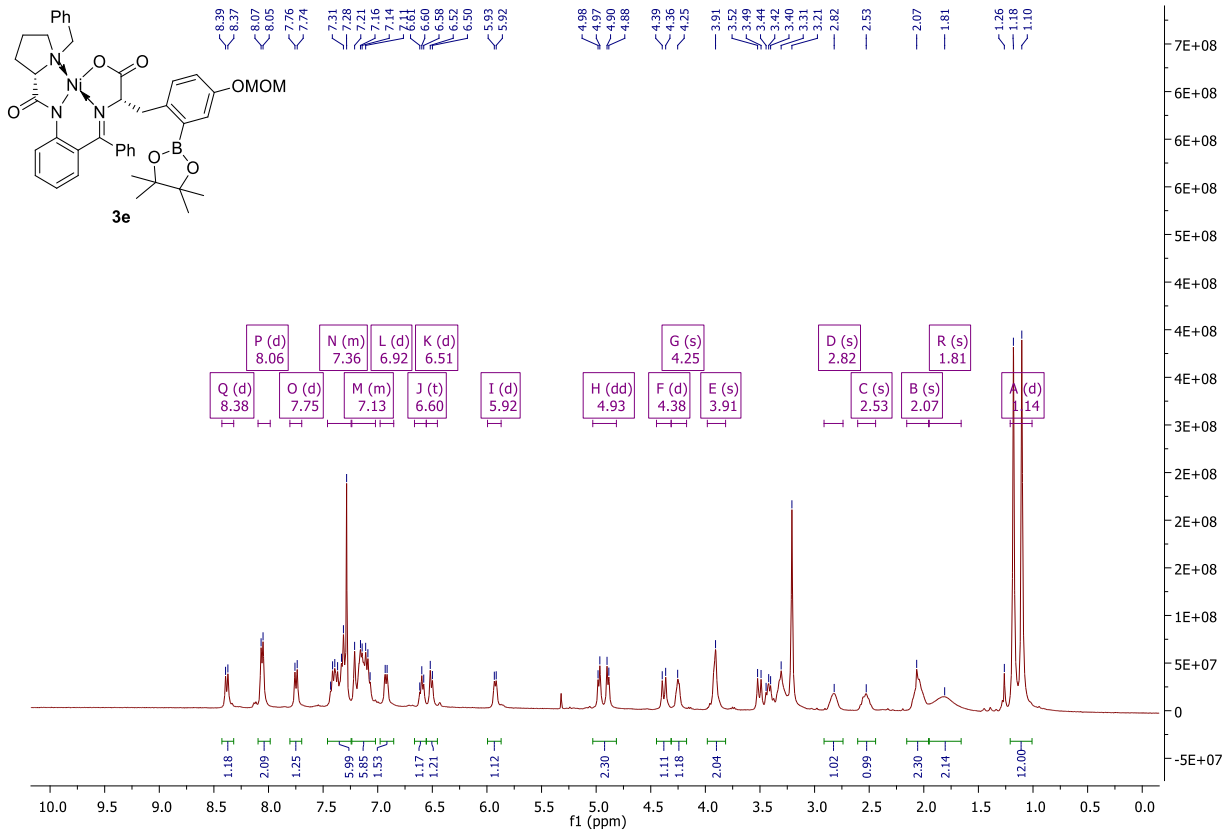
2-[5-(Methoxymethoxy)-2-methylphenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (S15)

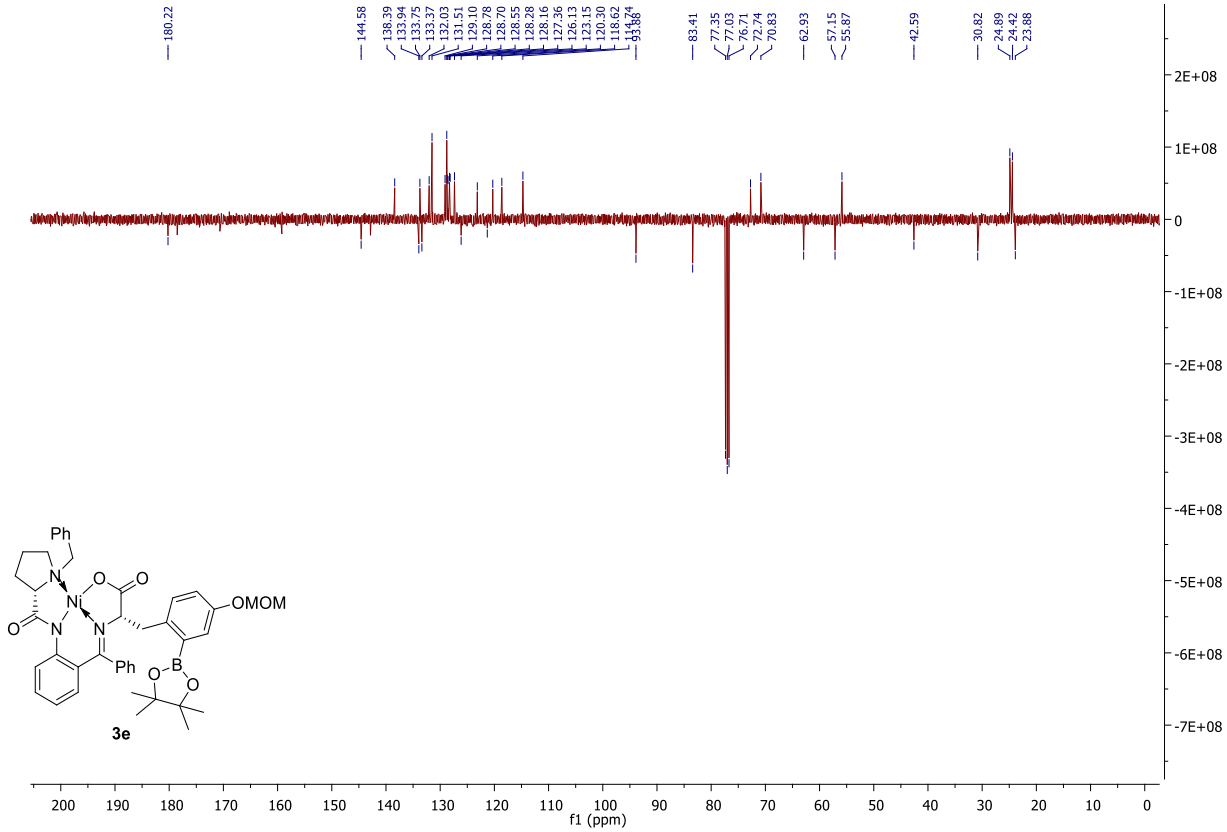
($CDCl_3$) ^1H NMR (400 MHz) ^{13}C NMR (101 MHz)



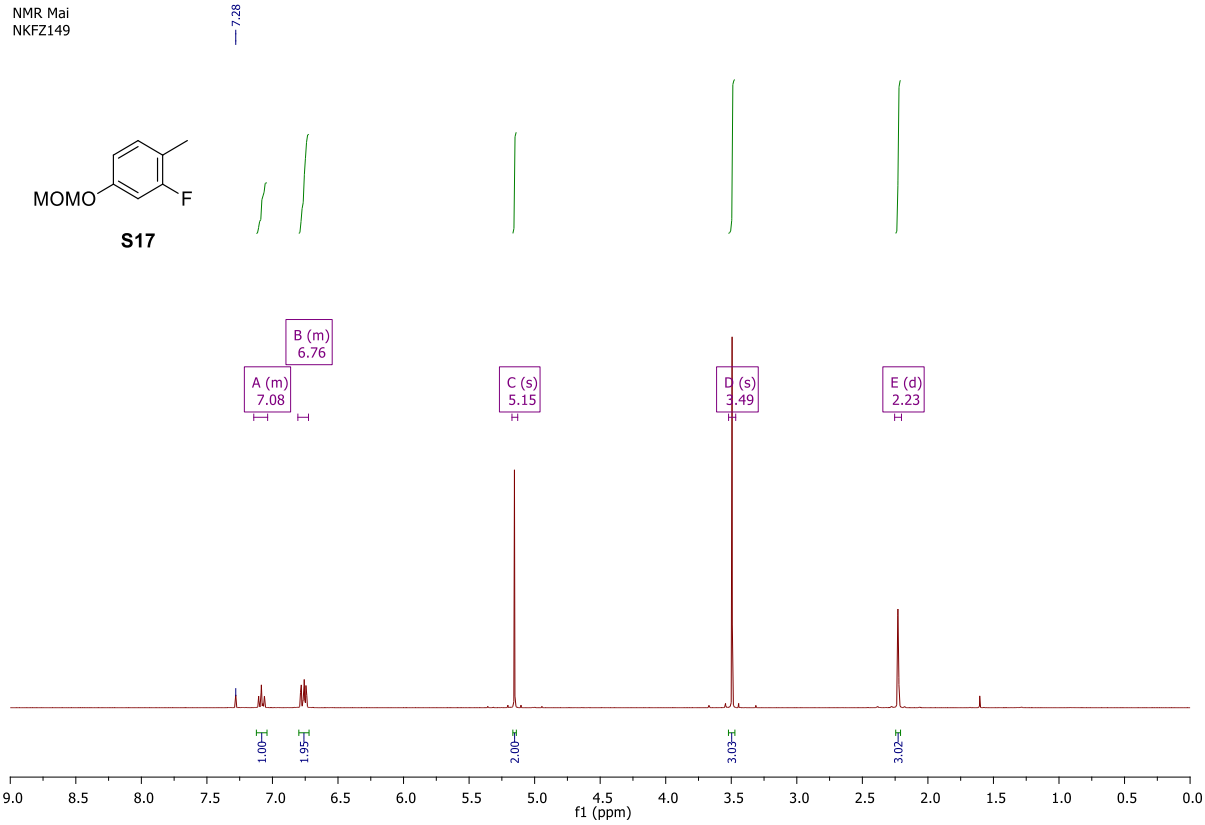


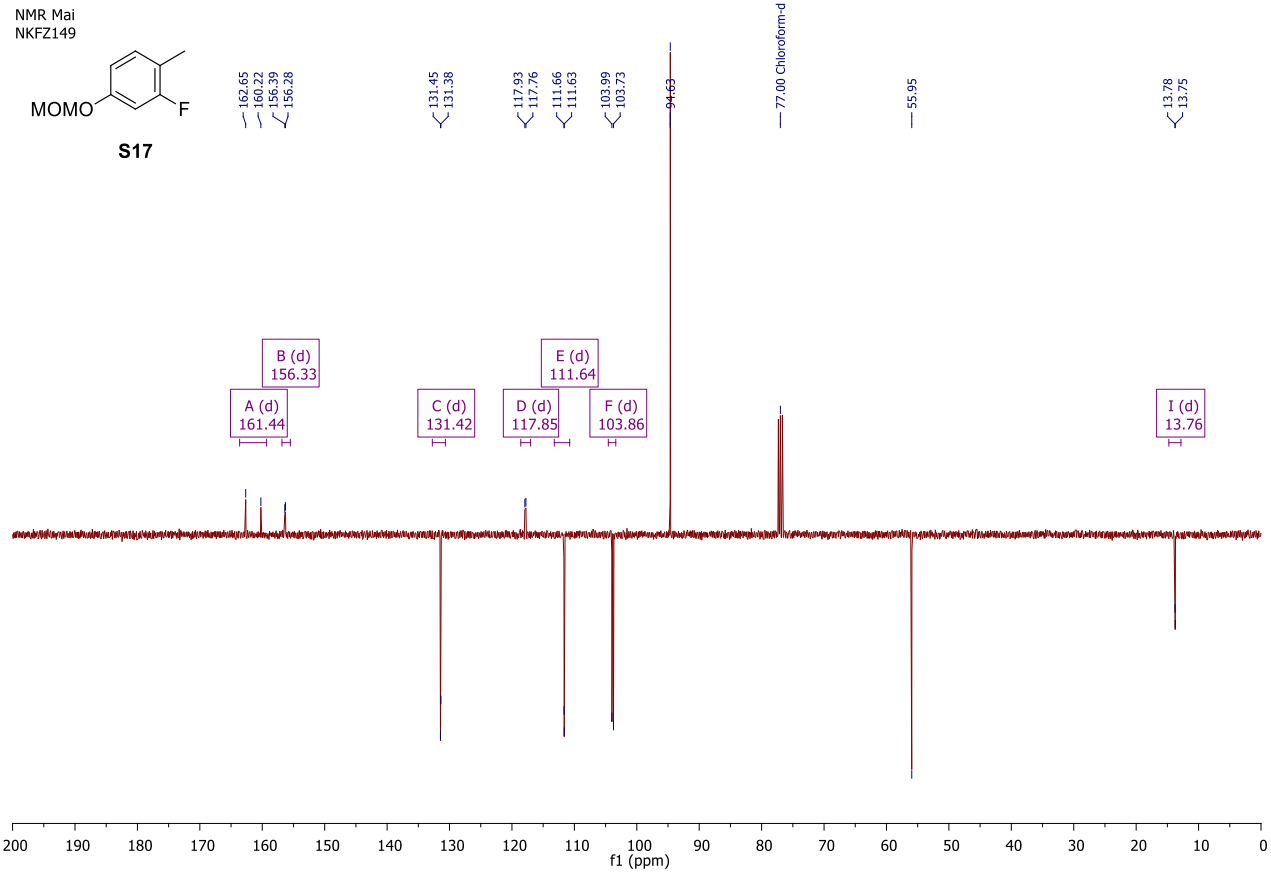
(*S*,*S*)-Ni-BPB-2-Bpin-OMOM-Tyr (3e) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)



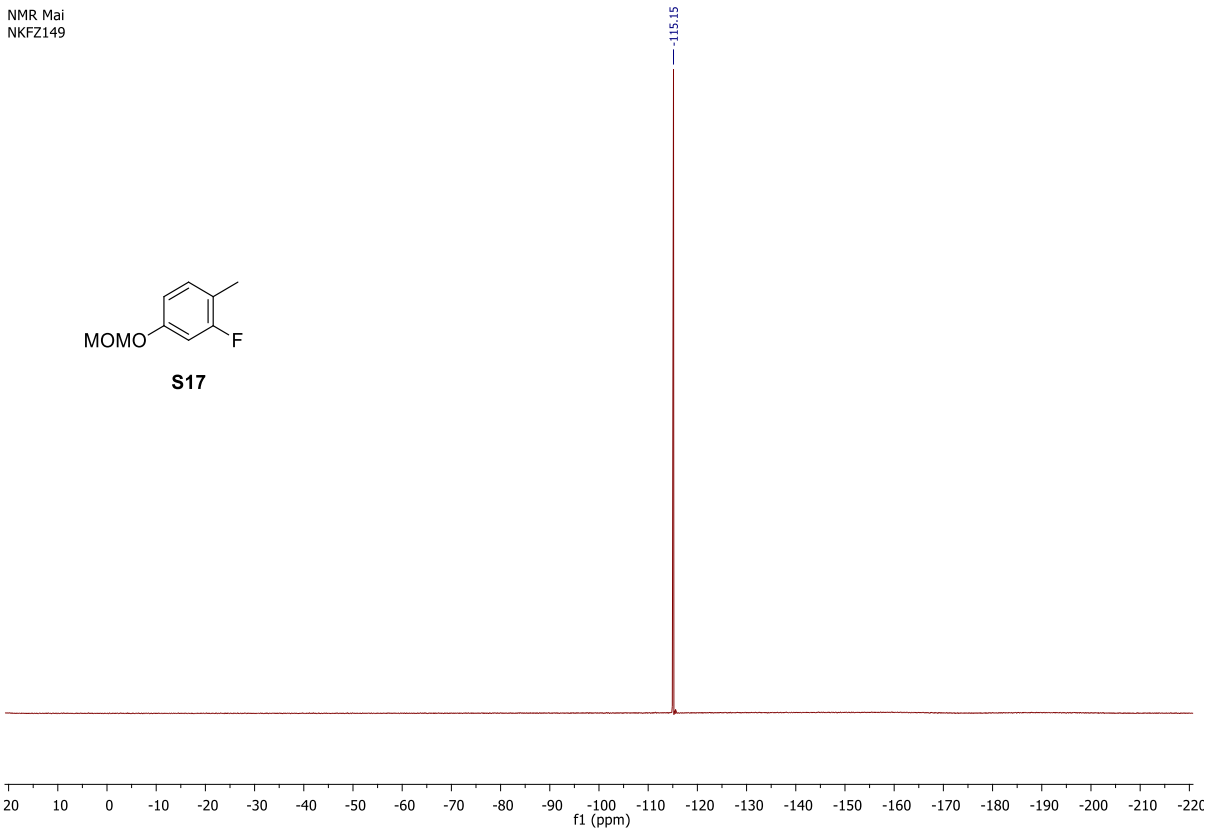


1-Fluoro-4-(methoxymethoxy)-2-methylbenzene (S17) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)



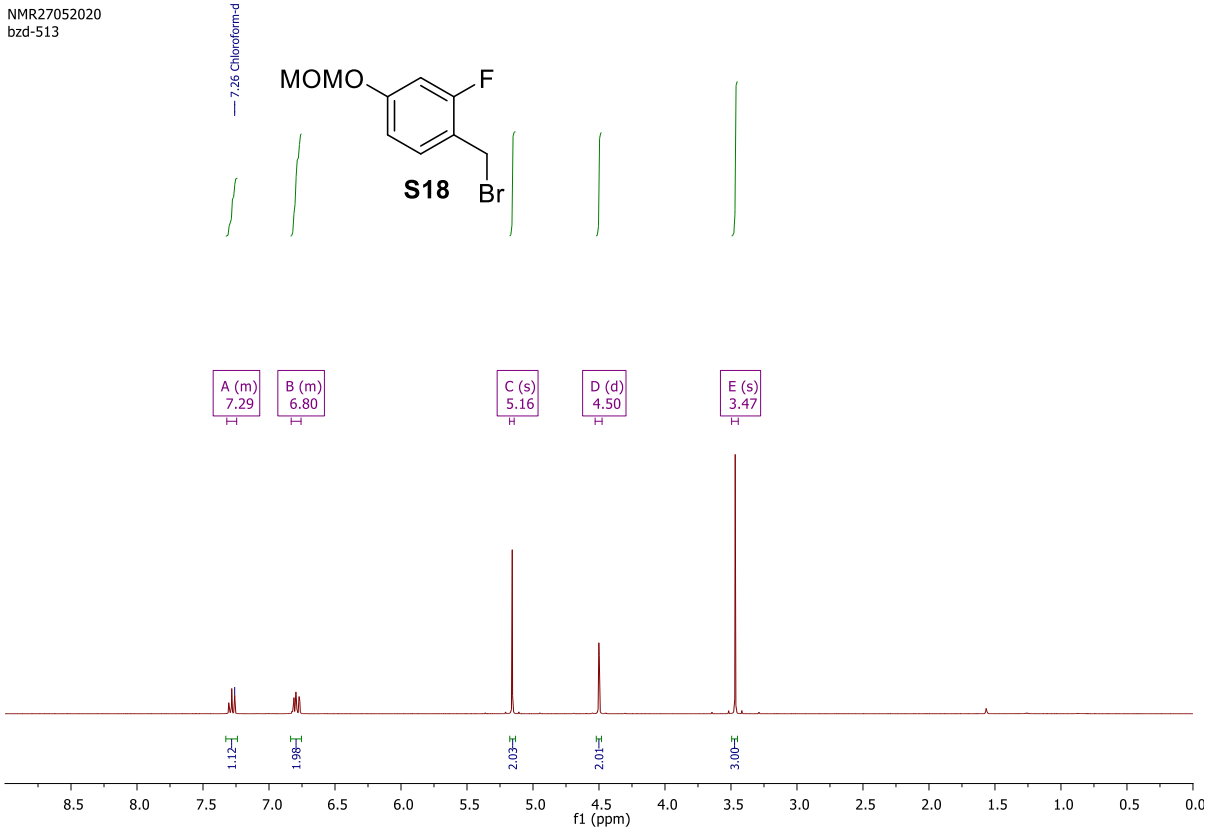


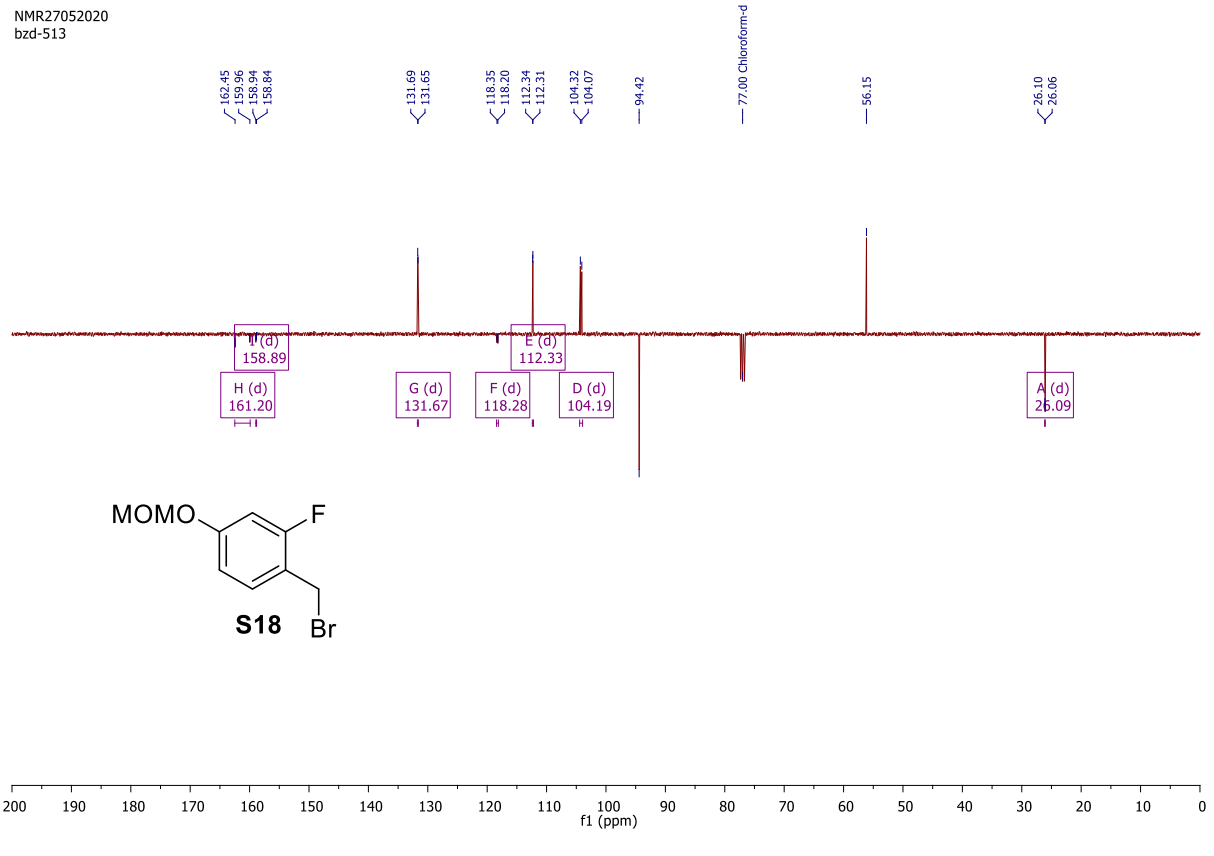
NMR Mai
NKFZ149



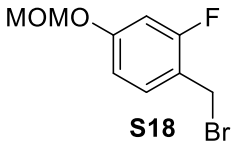
S17

1-(Bromomethyl)-2-fluoro-4-(methoxymethoxy)benzene (S18) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)



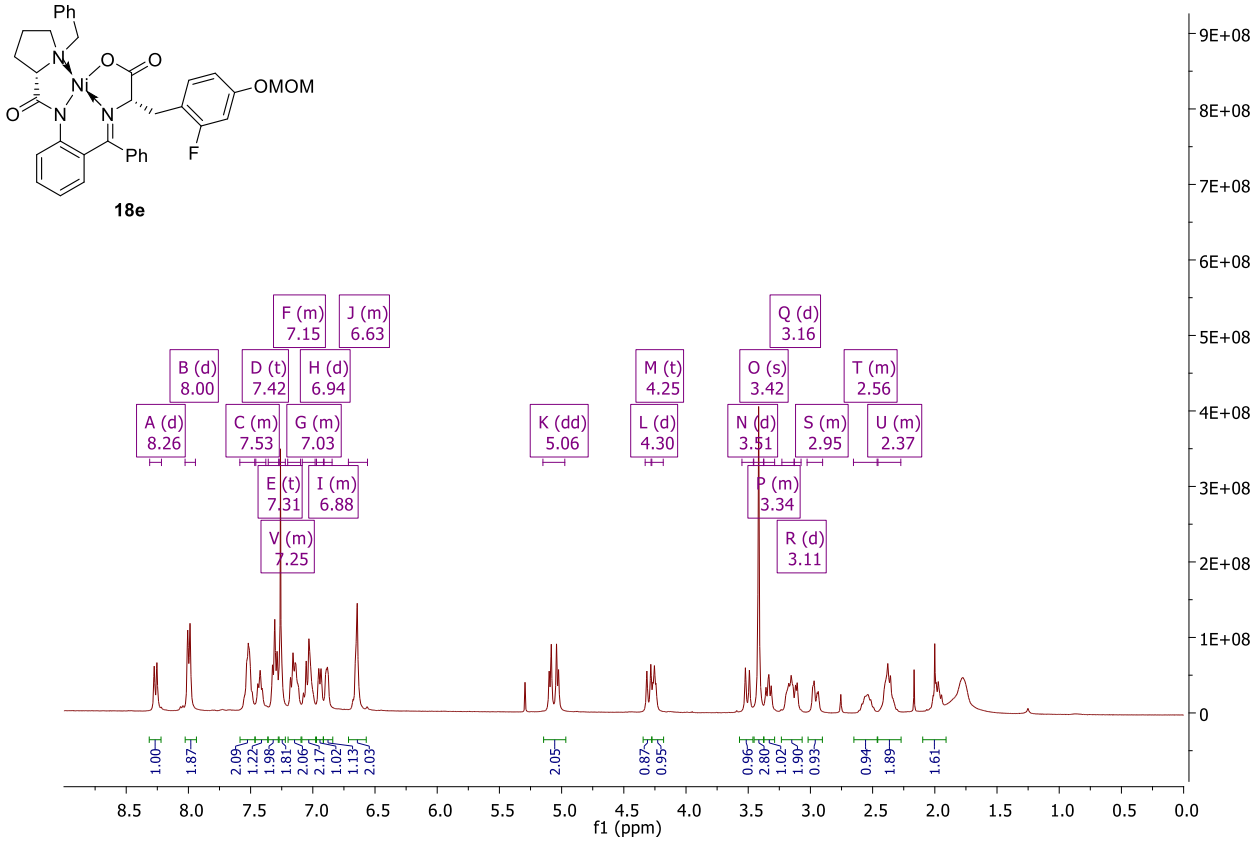


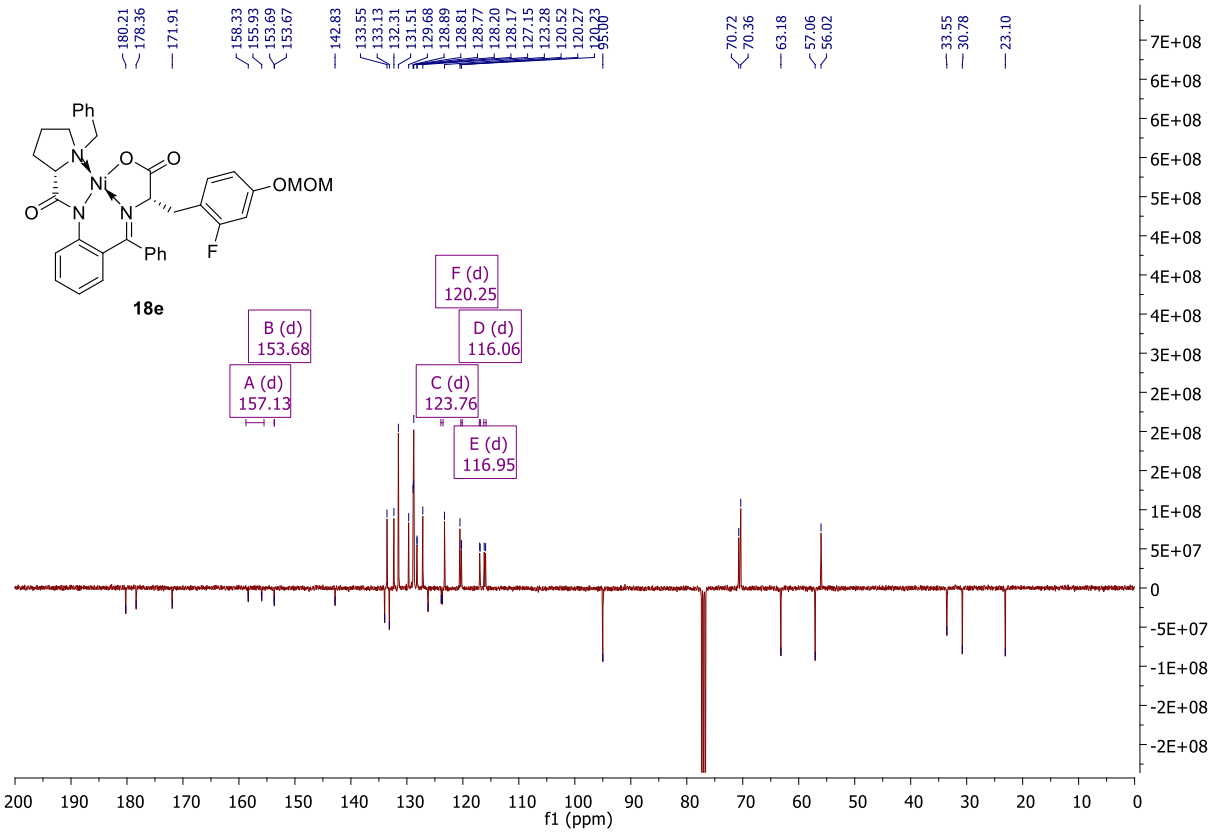
NMR27052020
bzd-513

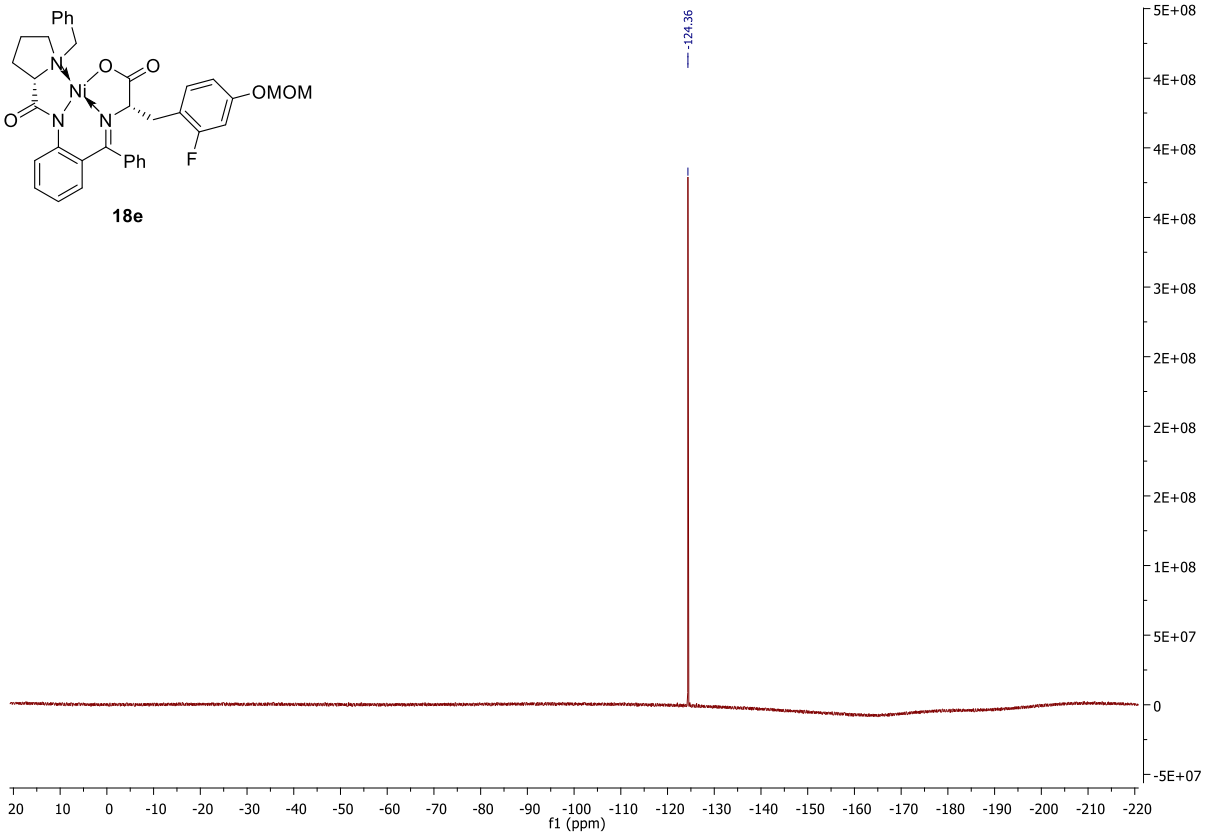


S18

(*S*,*S*)-Ni-BPB-2-F-OMOM-Tyr (18e) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)






Ph
N
O
O
Ni
O
N
N
Ph
F
OMOM
18e
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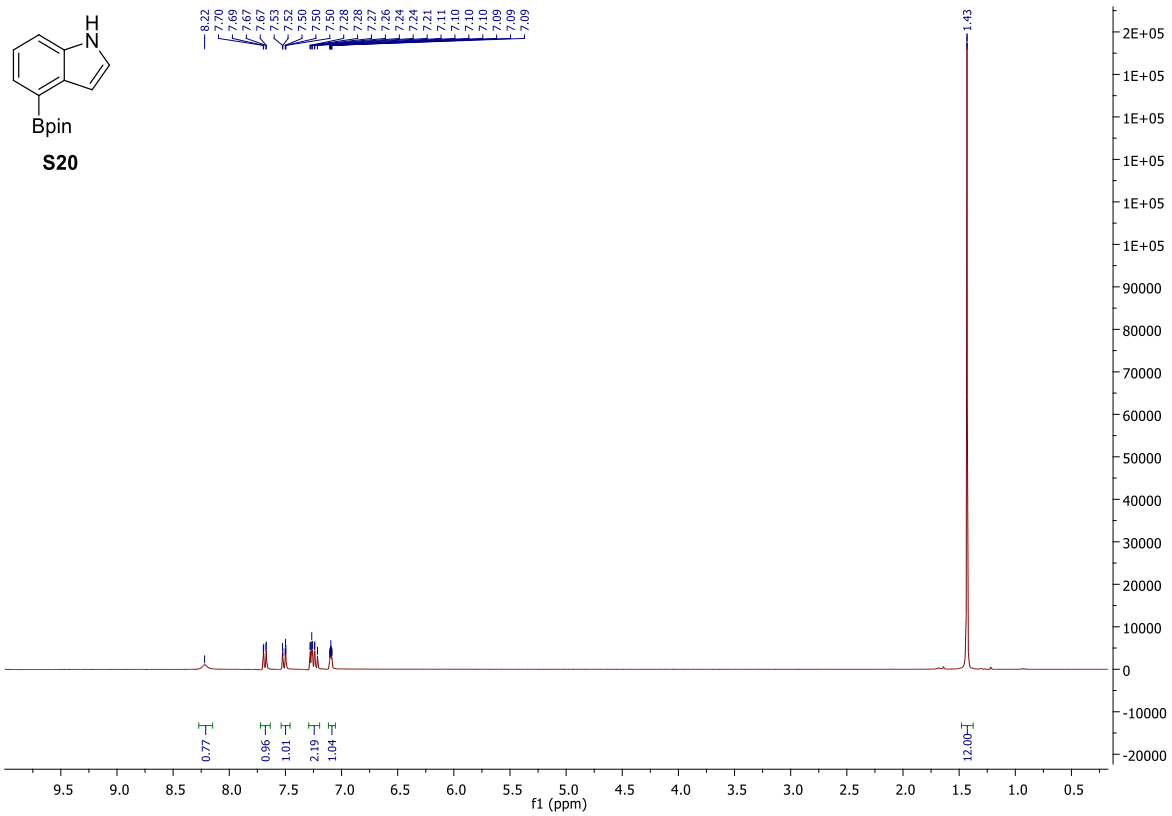
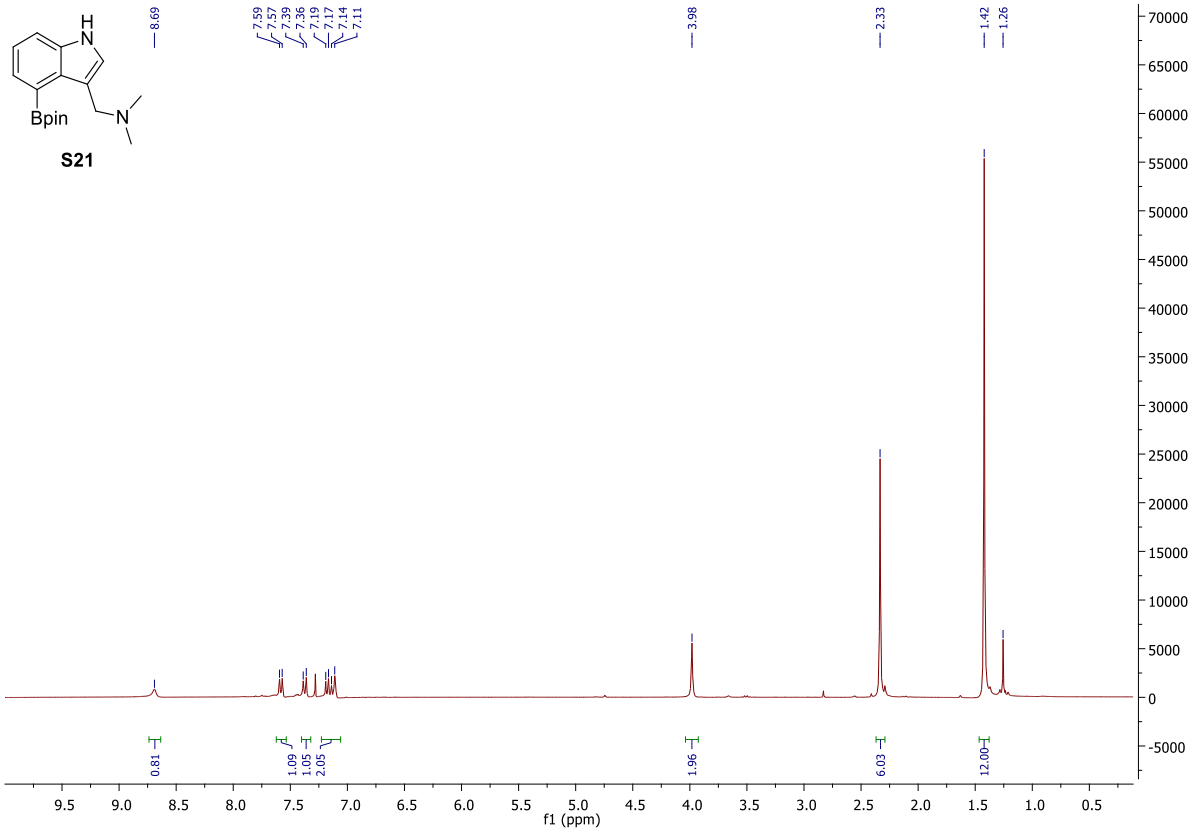
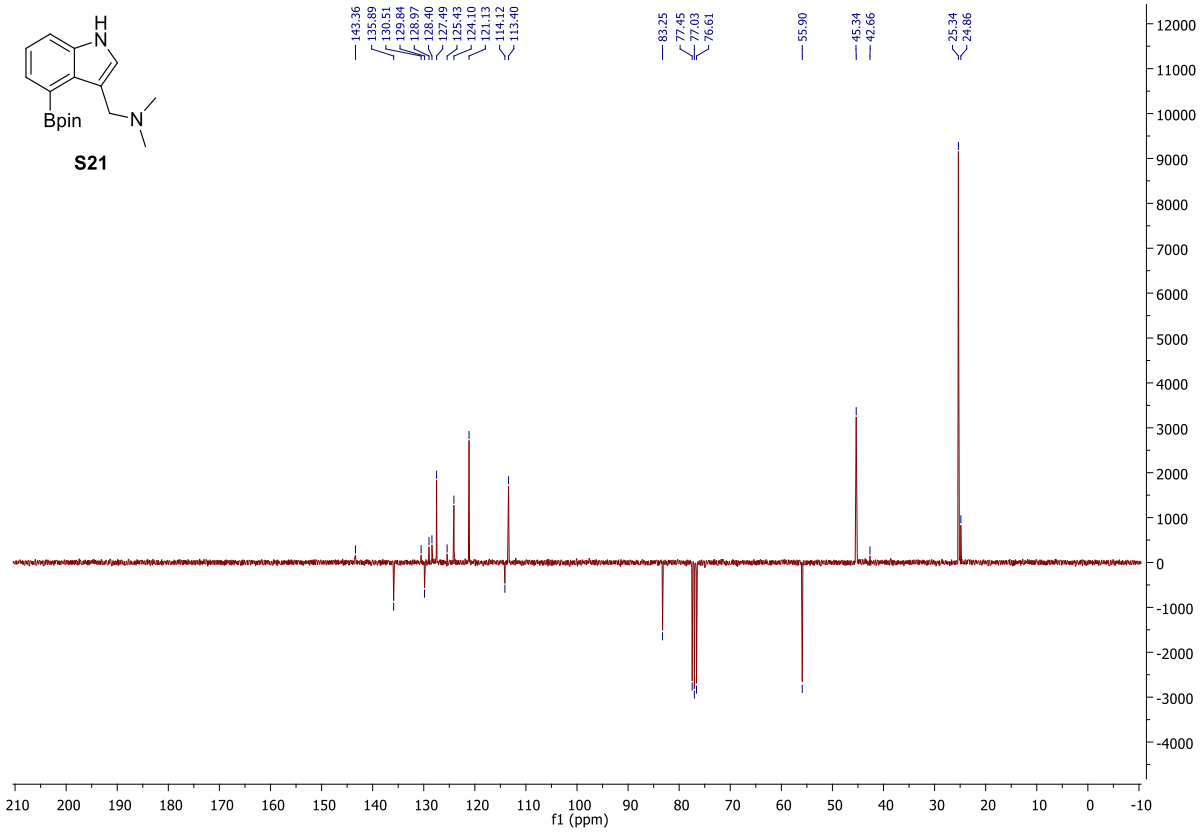
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indole (S20) ^{1}H NMR (400 MHz, $CDCl_3$),

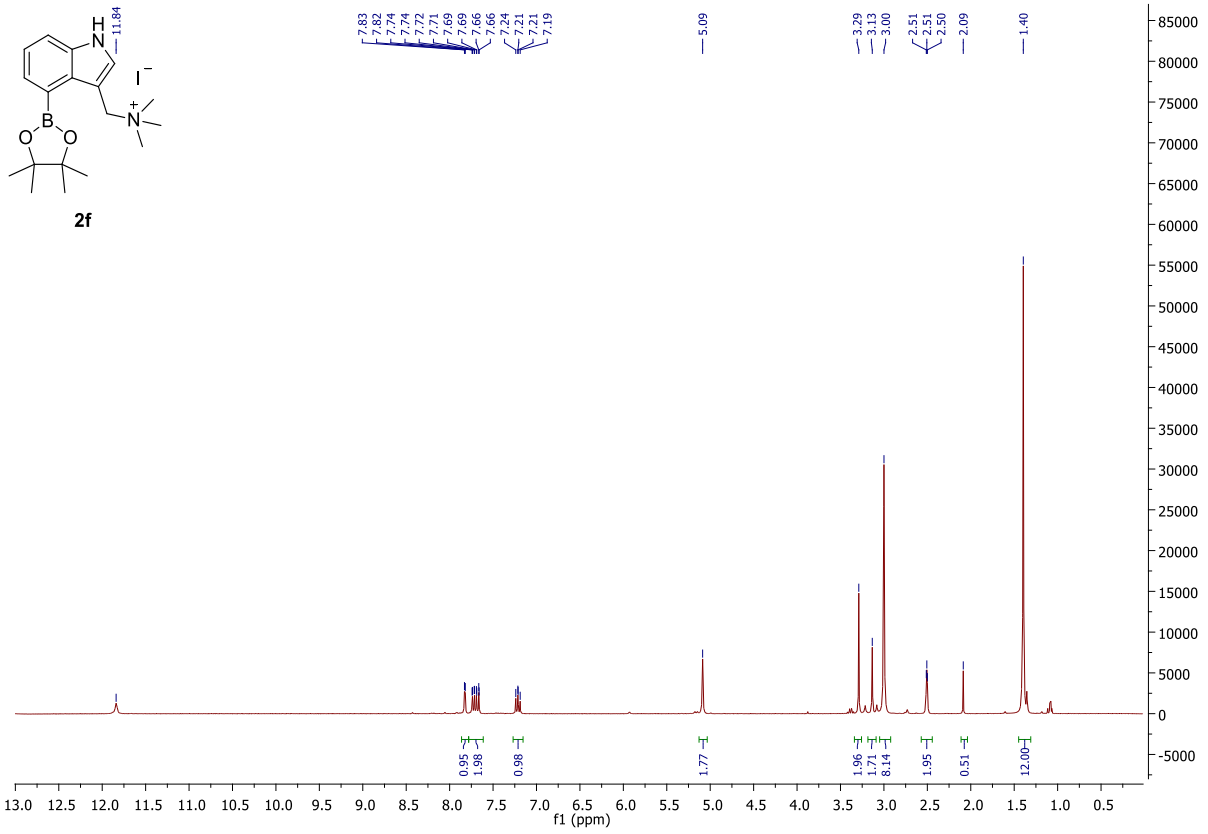


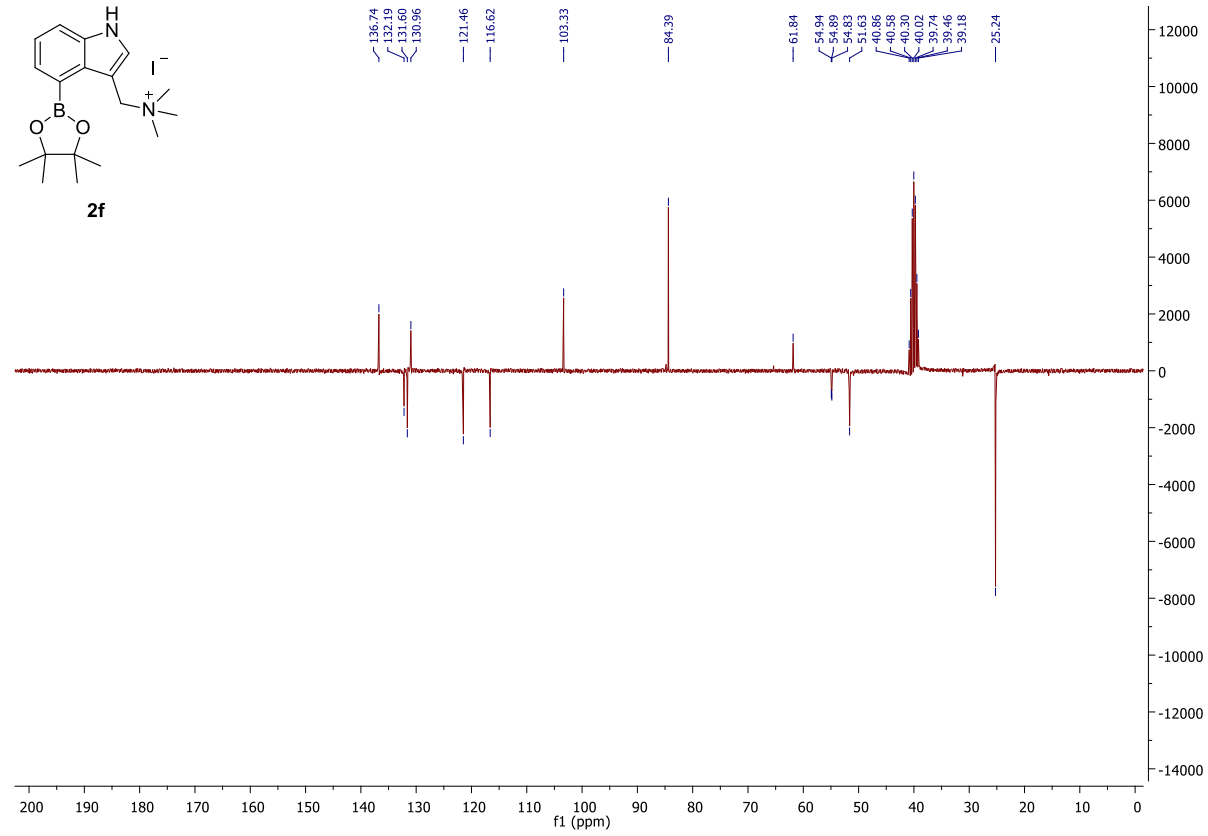
***N*,*N*-Dimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)methanamine (S21)** ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)



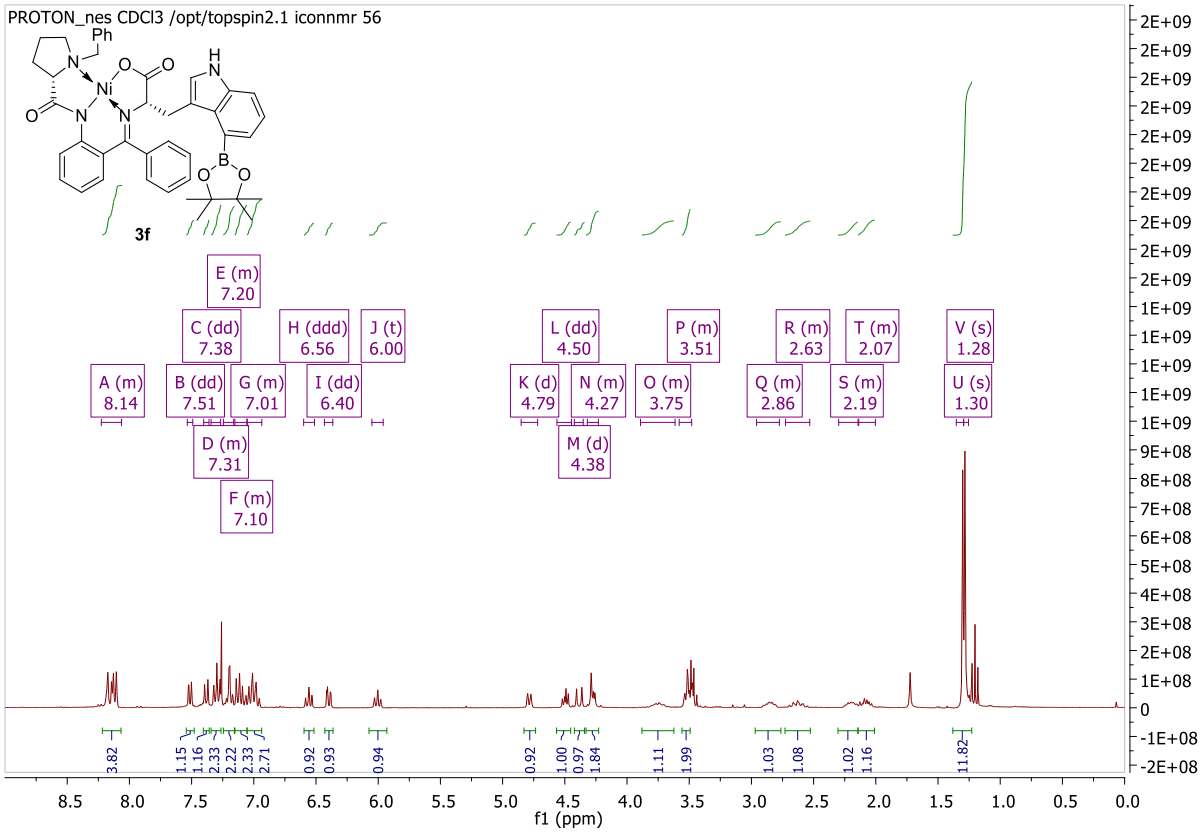


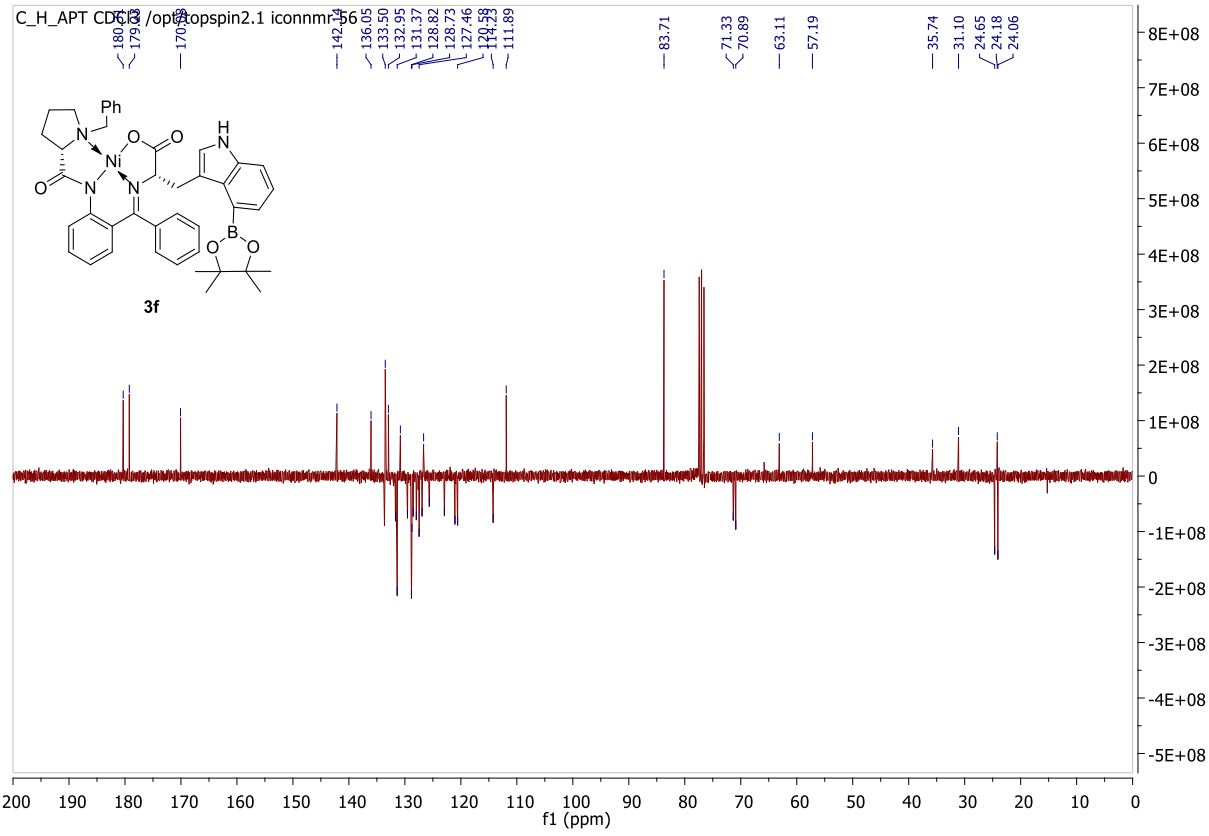
***N*,*N*,*N*-Trimethyl-1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)methanaminium iodide (2f)** (DMSO, d_6) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz)



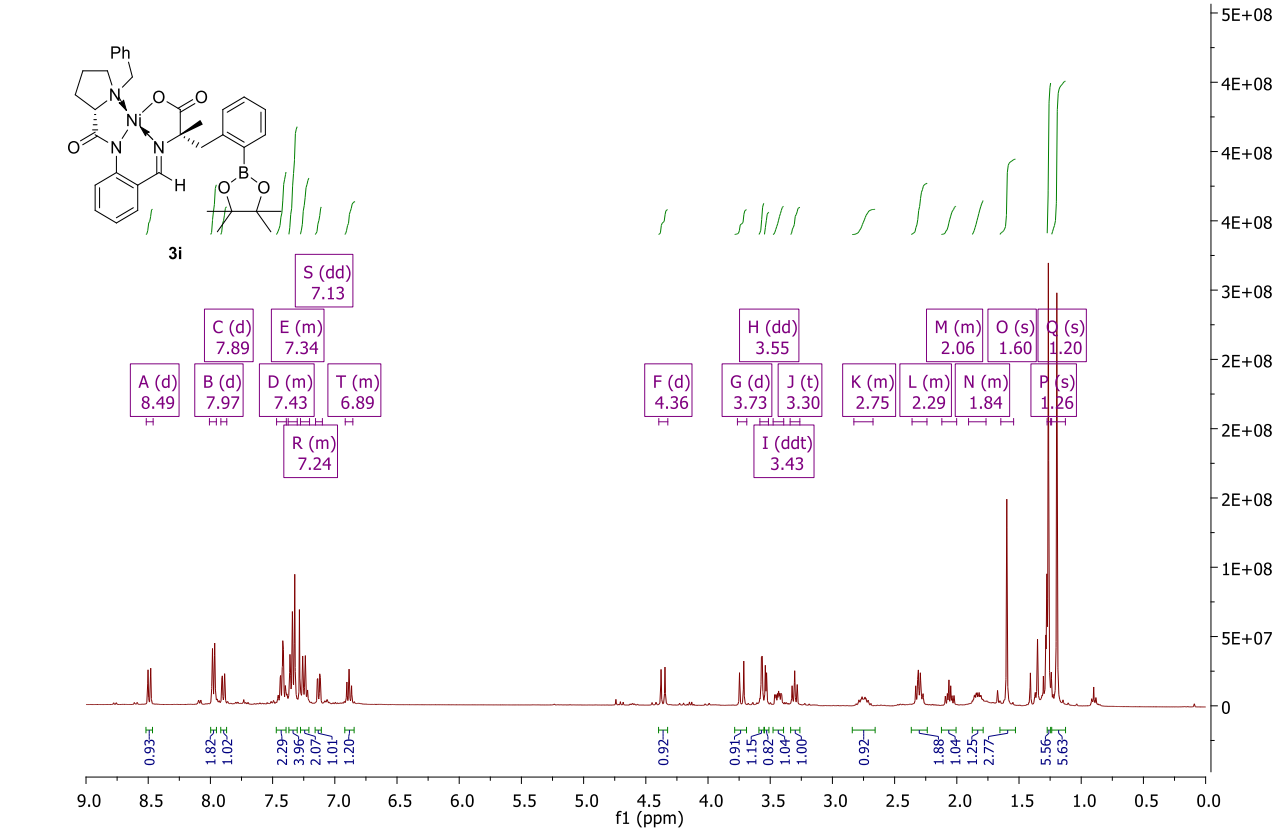


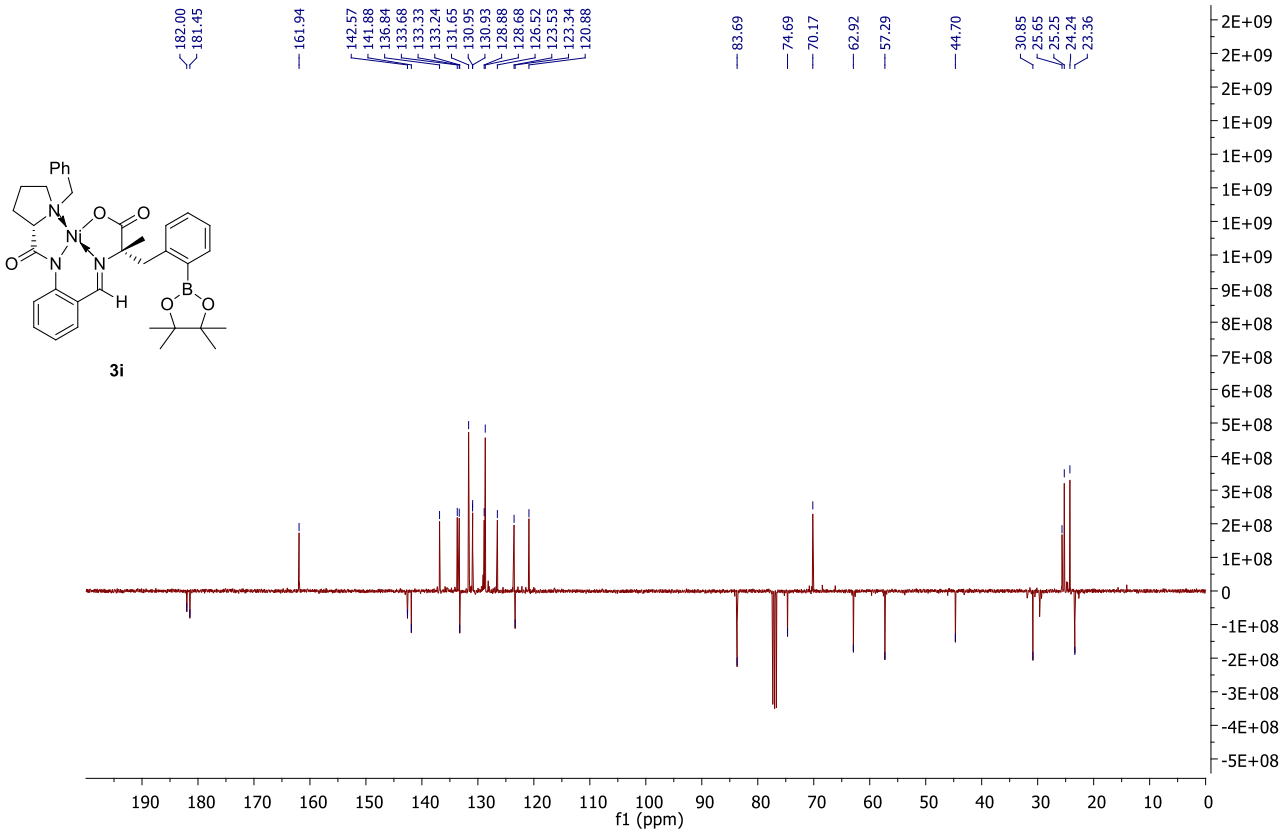
(*S*,*S*)-Ni-BPB-4-Bpin-Trp (3f) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)



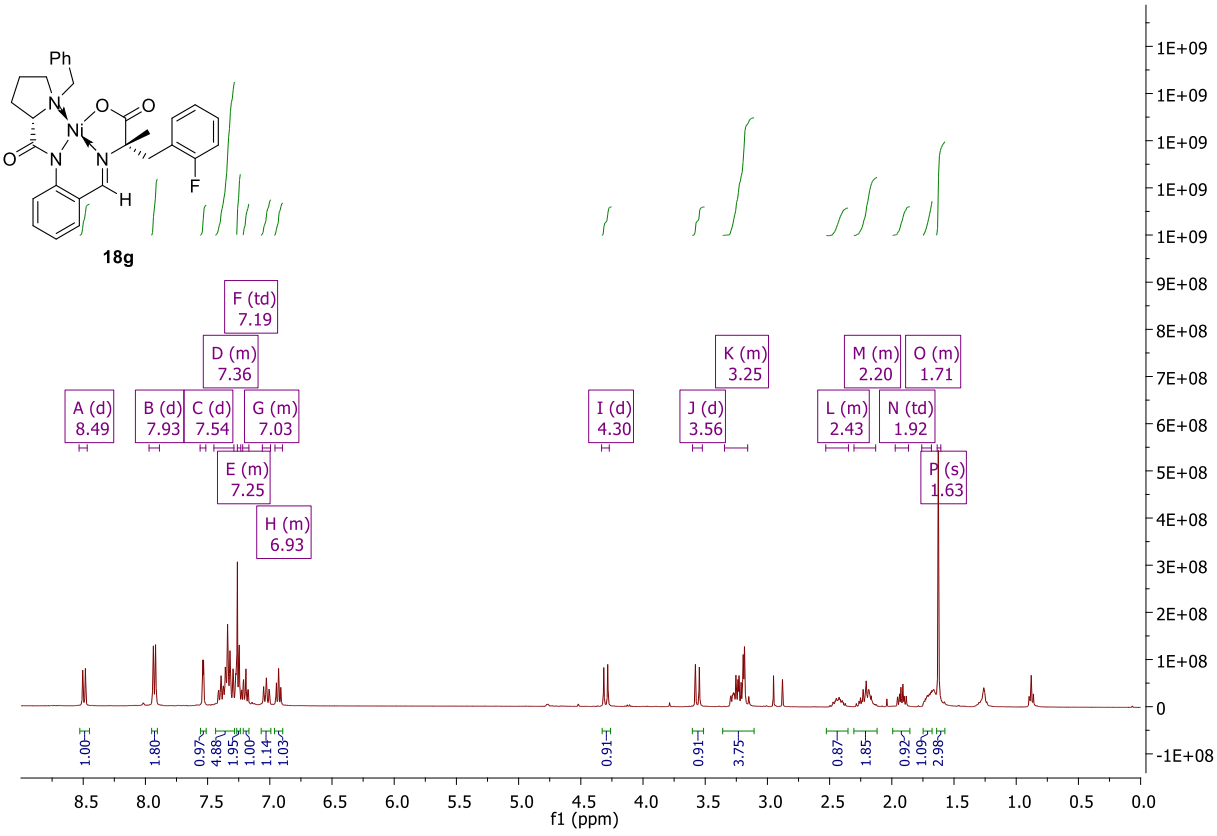


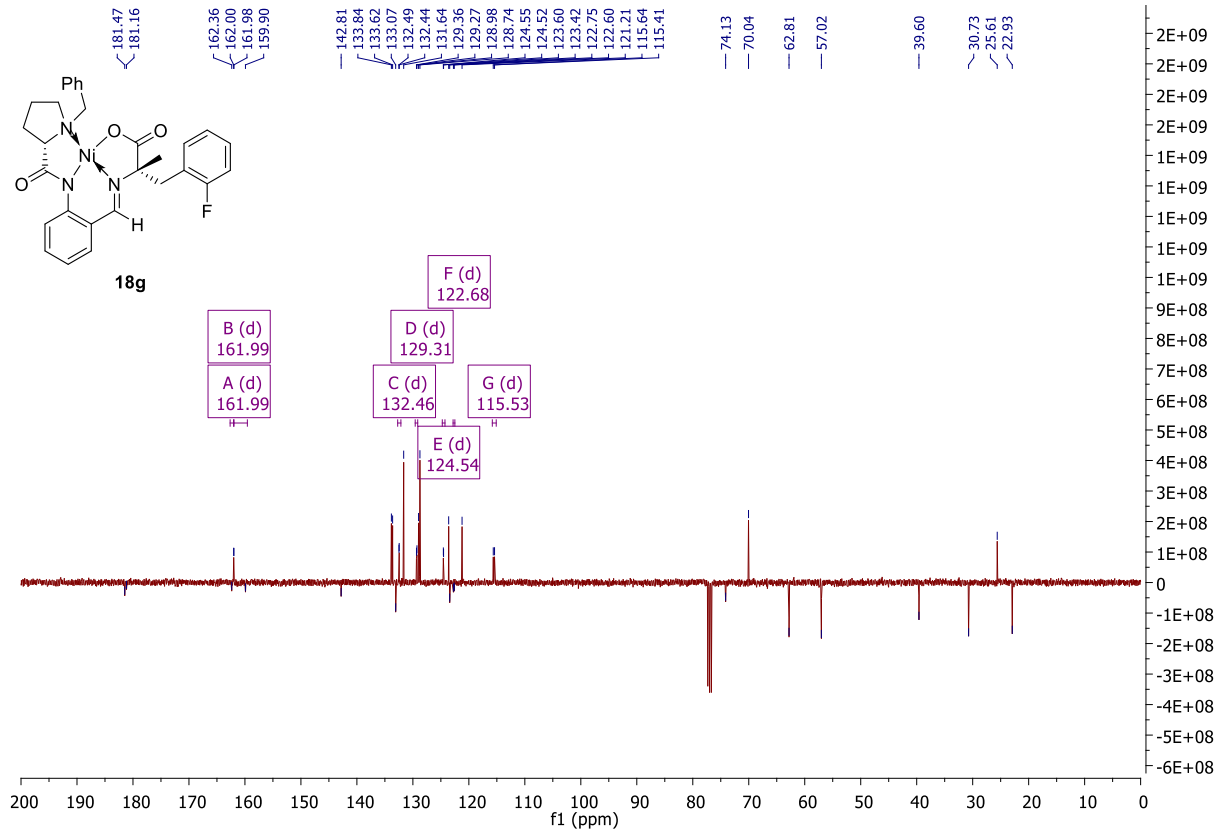
Ni-BPB-AAA α-methyl-2-[^{18}F]FPhe Precursor (3i) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)

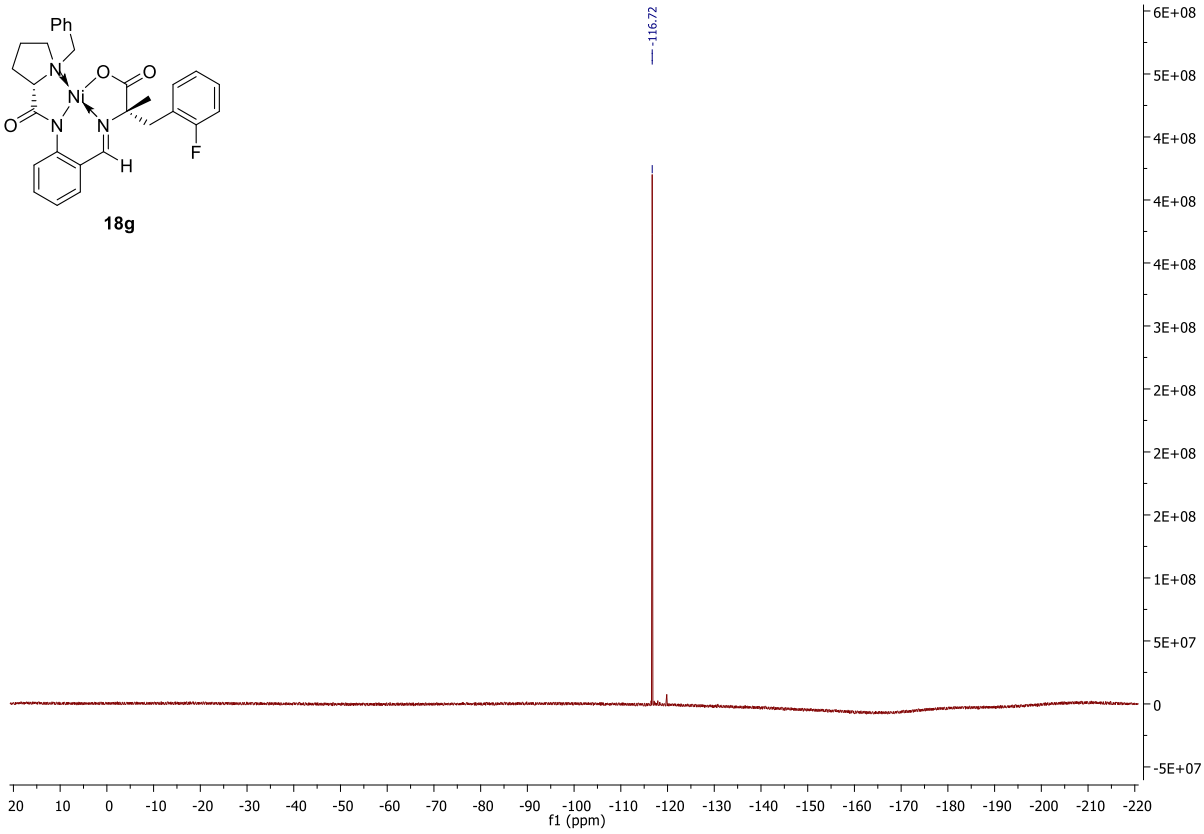




α-Methyl-2-FPhe reference compound (18g) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)






Ph
N
O
O
Ni
O
N
N
H
F
18g
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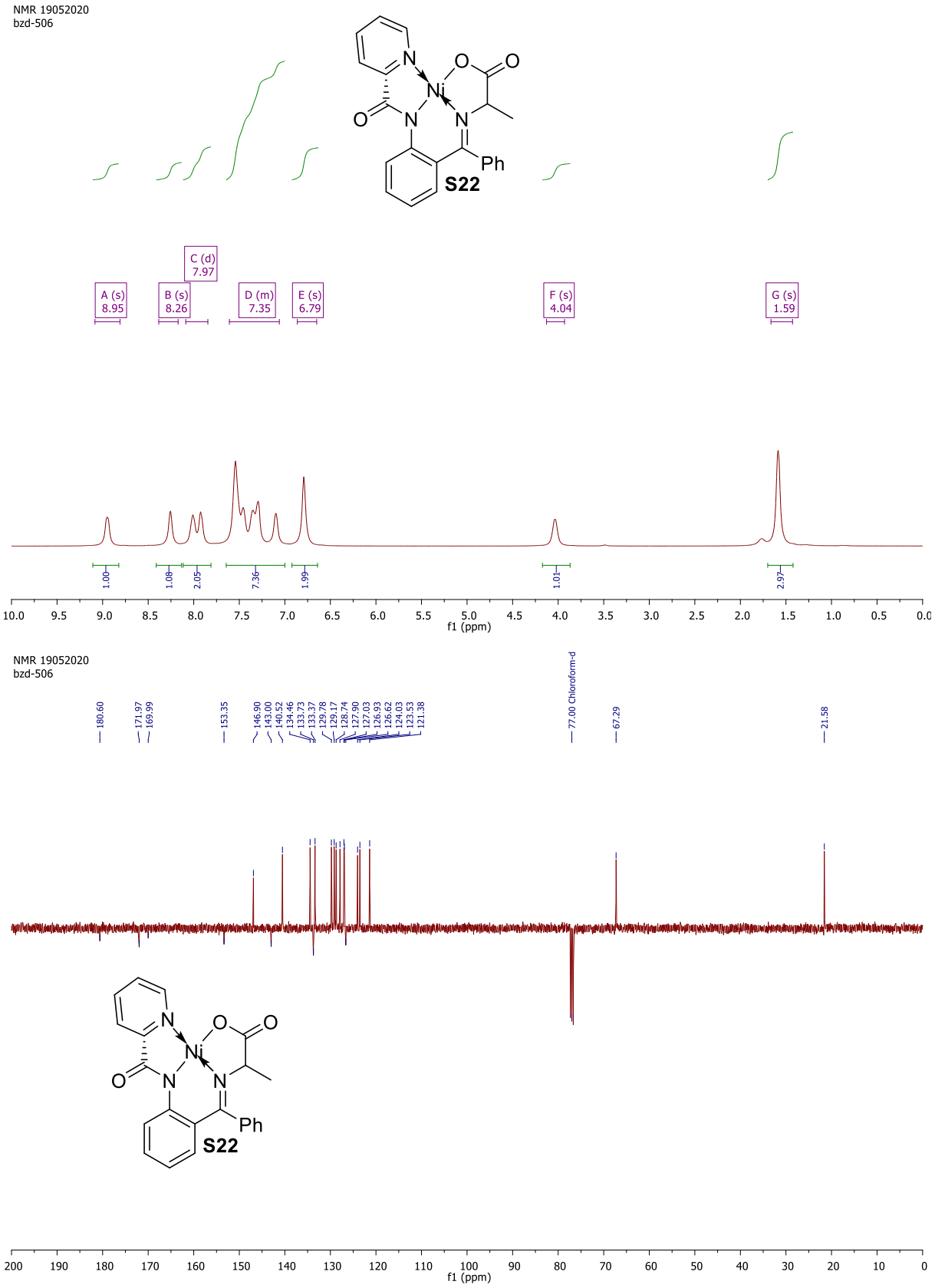
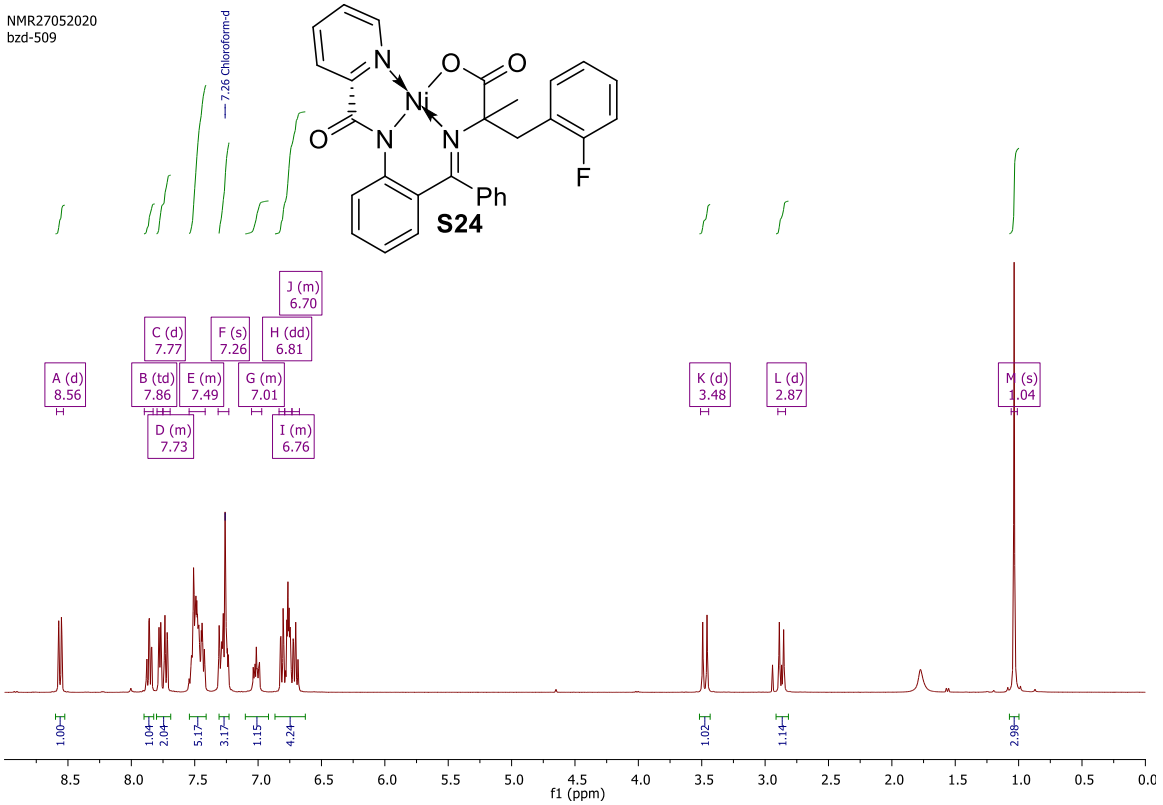
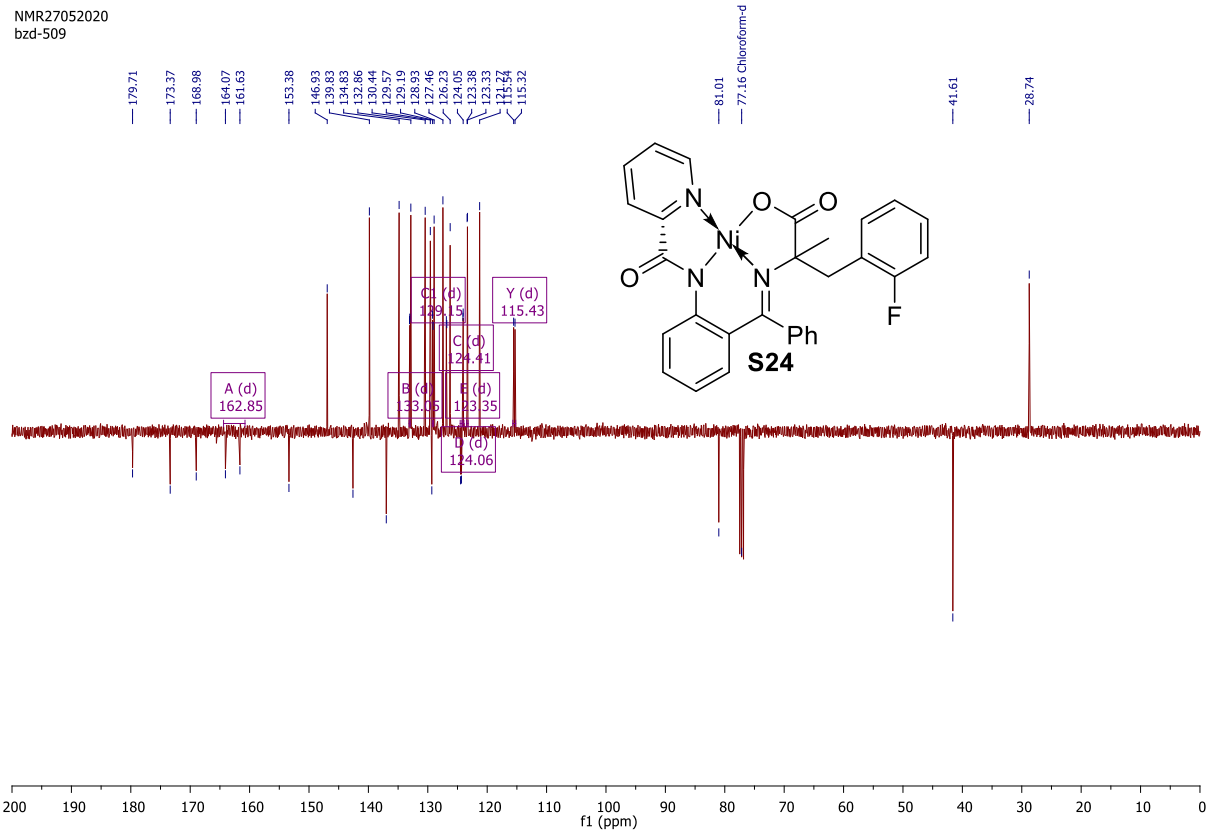
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

Ni-PBP-(*RS*)-Ala (S22) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz)

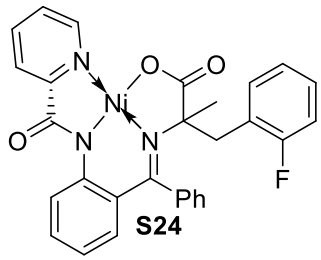


Ni-PBP-αMe-2-FPhe (S24) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)



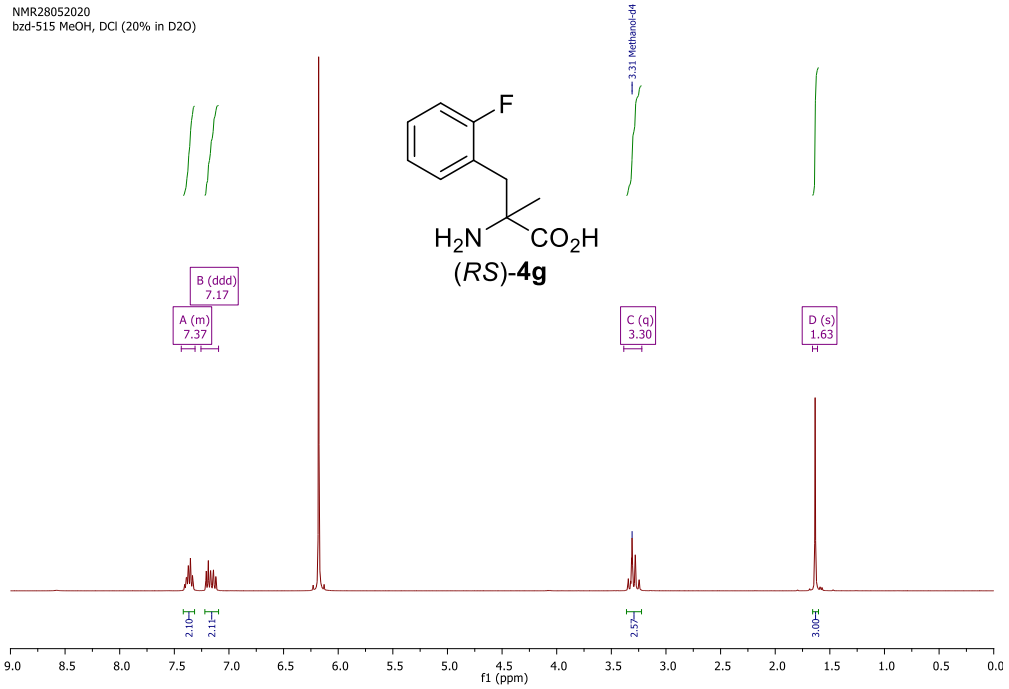


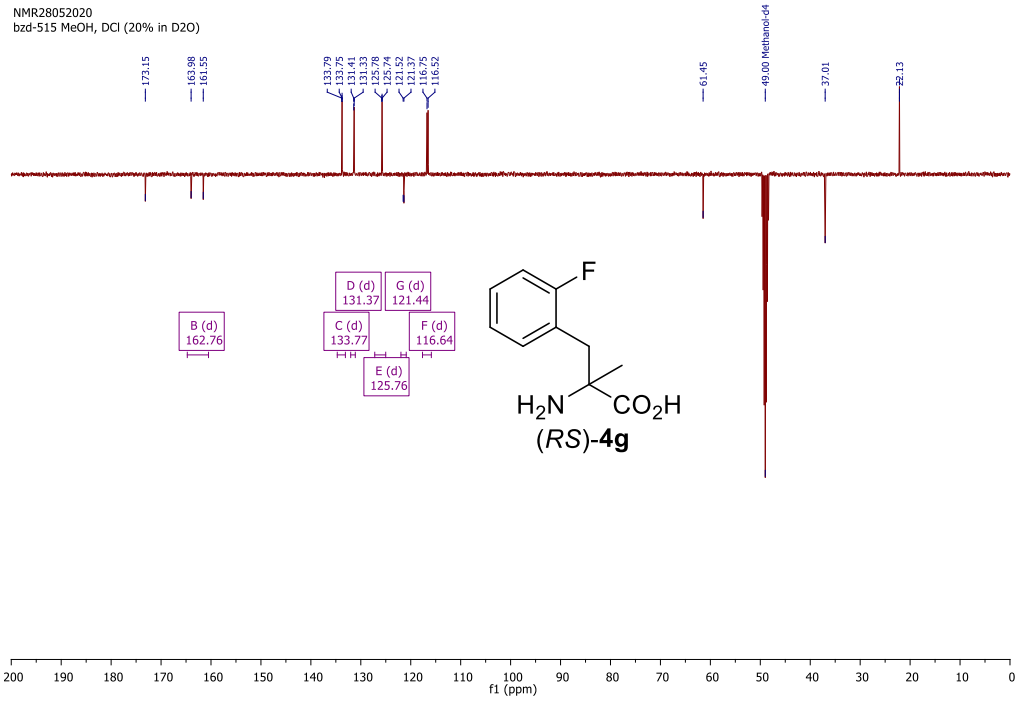
NMR27052020
bzd-509



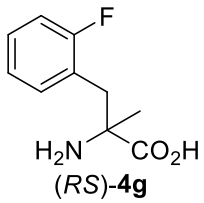
S24

(*RS*)-α-Methyl-2-fluorophenylalanine [(*RS*)-4g] (CD_3OD + 20% DCl) ^1H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)



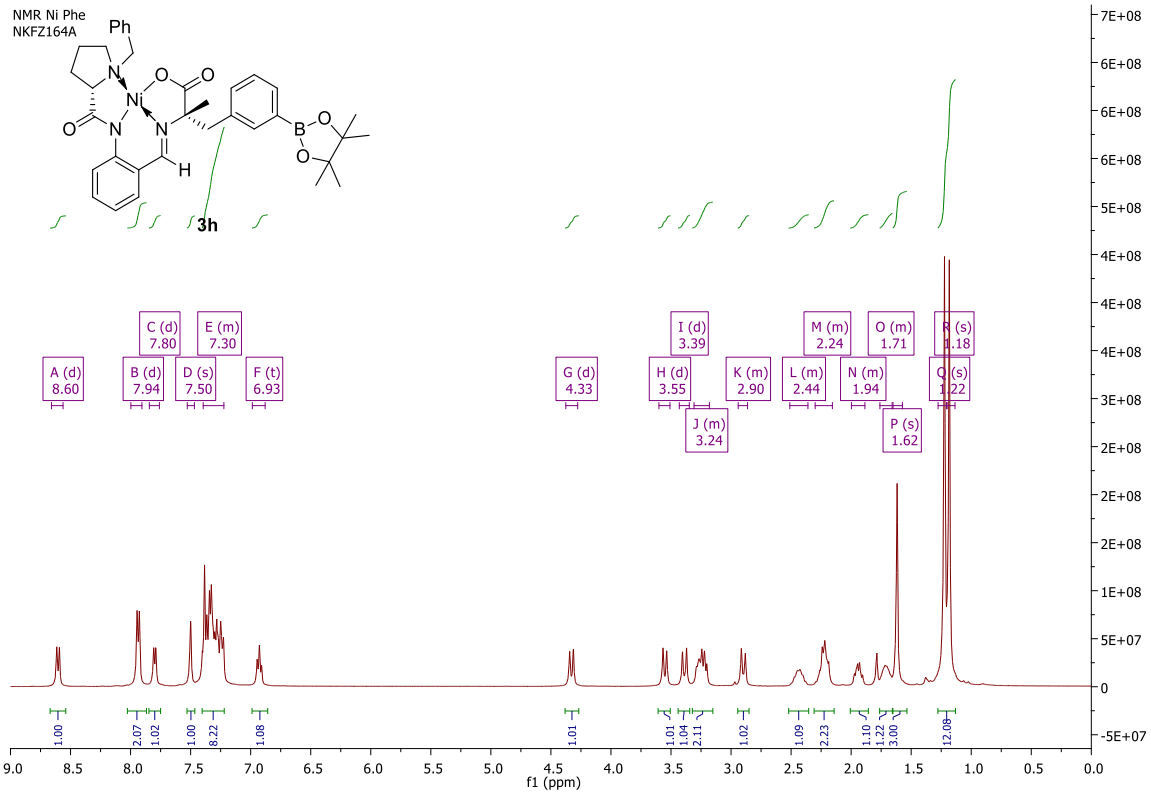


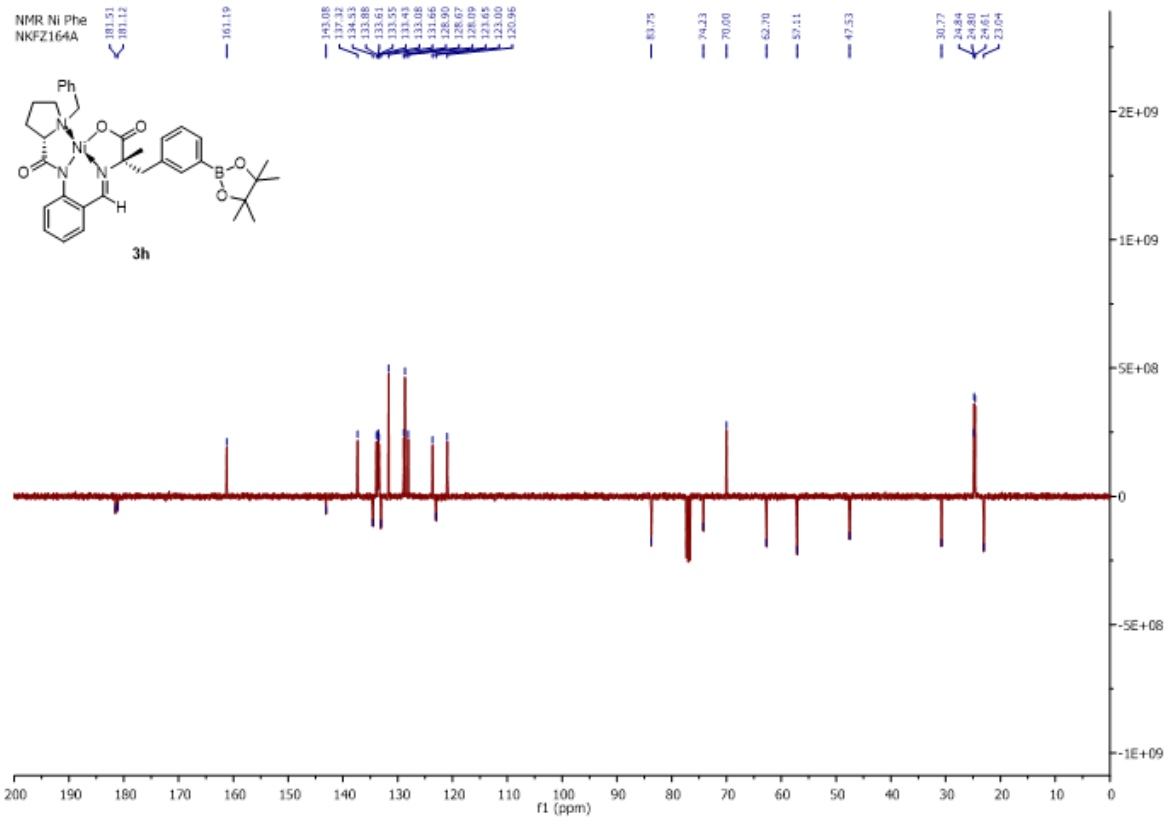
NMR28052020
bzd-515 MeOH, DCl (20% in D2O)



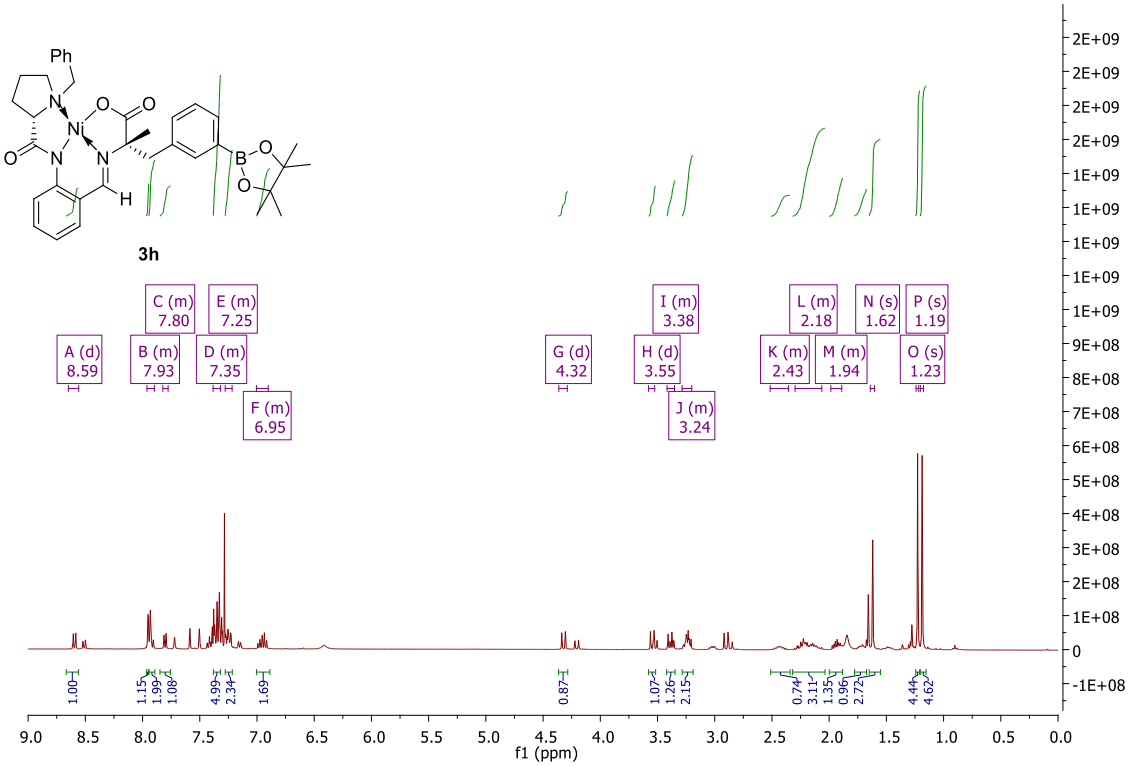
(*RS*)-**4g**

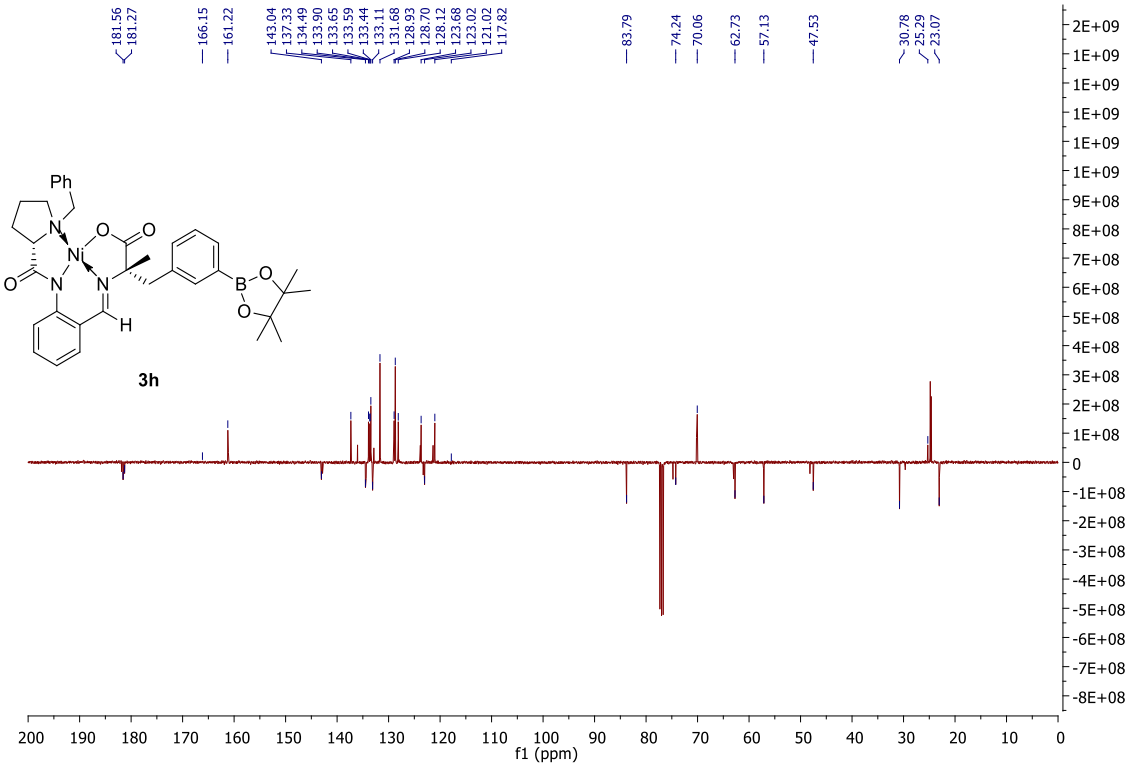
α-Methyl-3-[^{18}F]FPhe Precursor (3h) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (before RP chromatography)



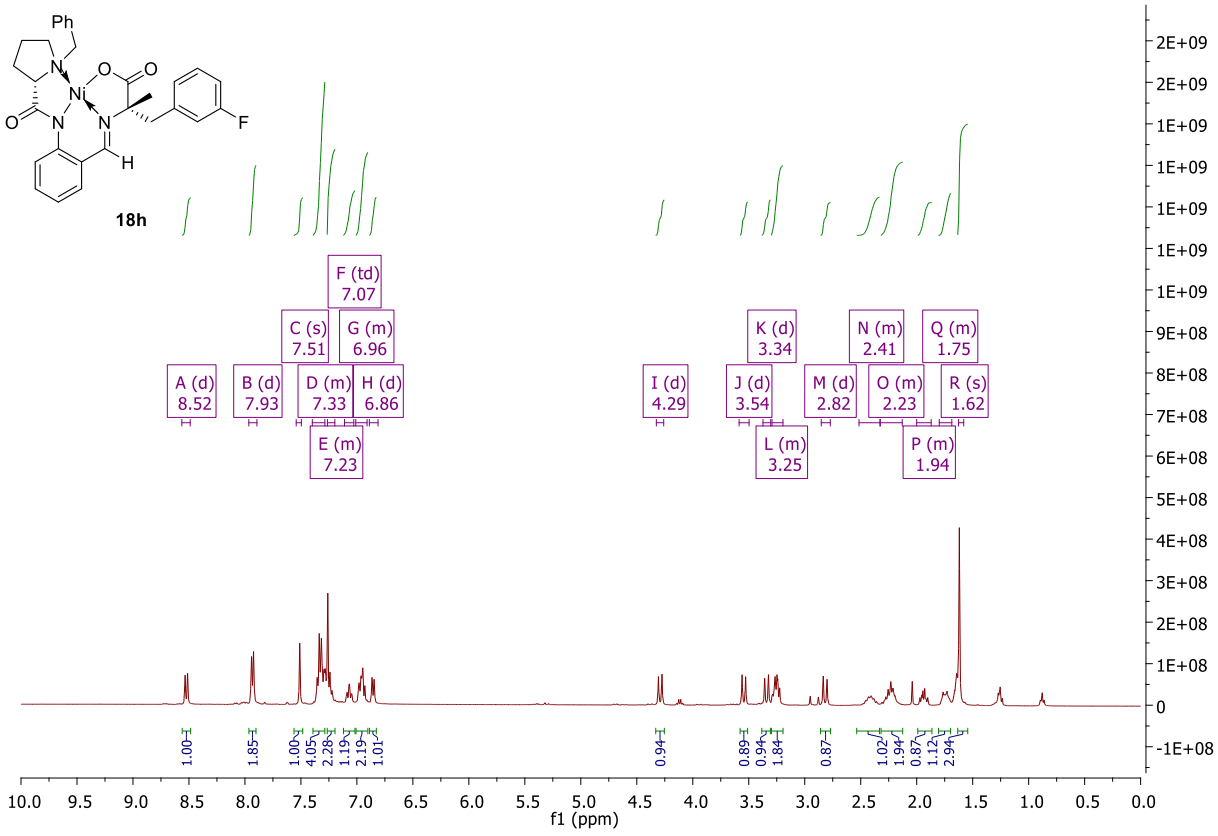


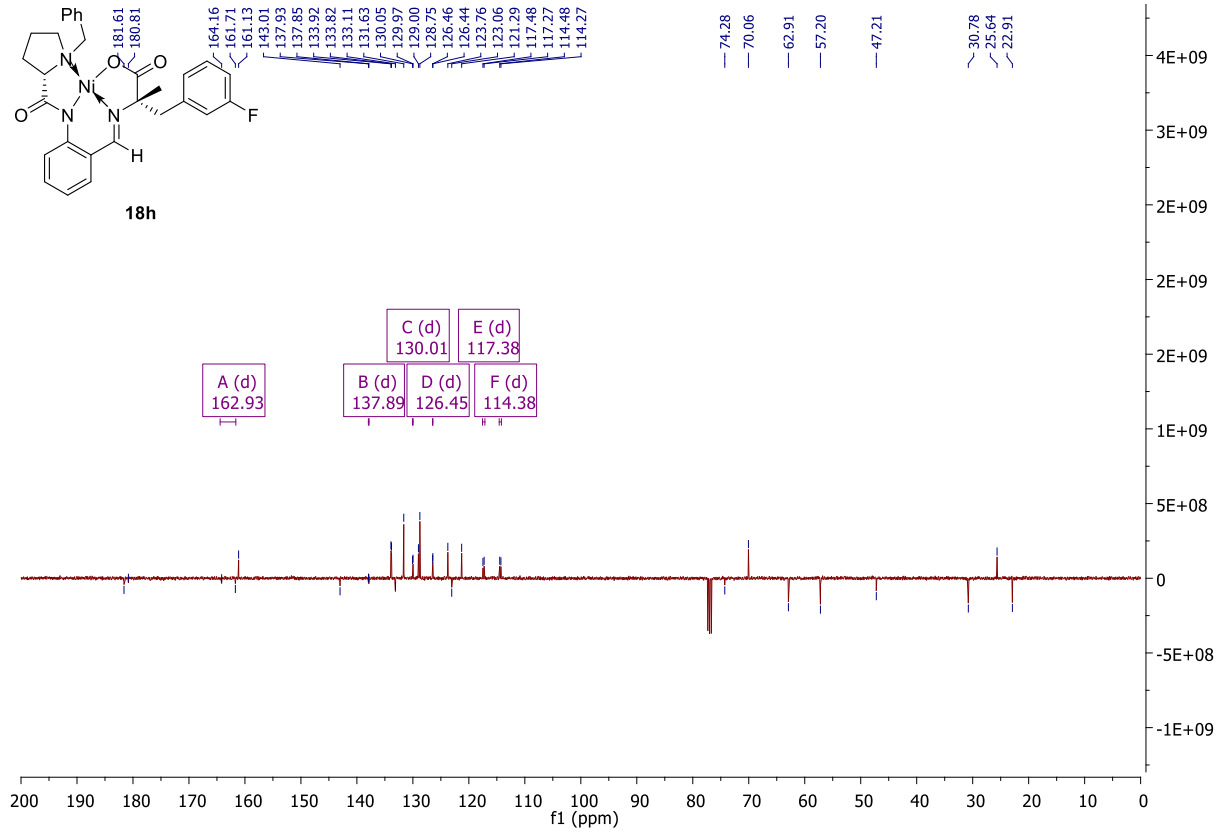
α-Methyl-3-[^{18}F]FPhe Precursor (3h) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (after RP chromatography)

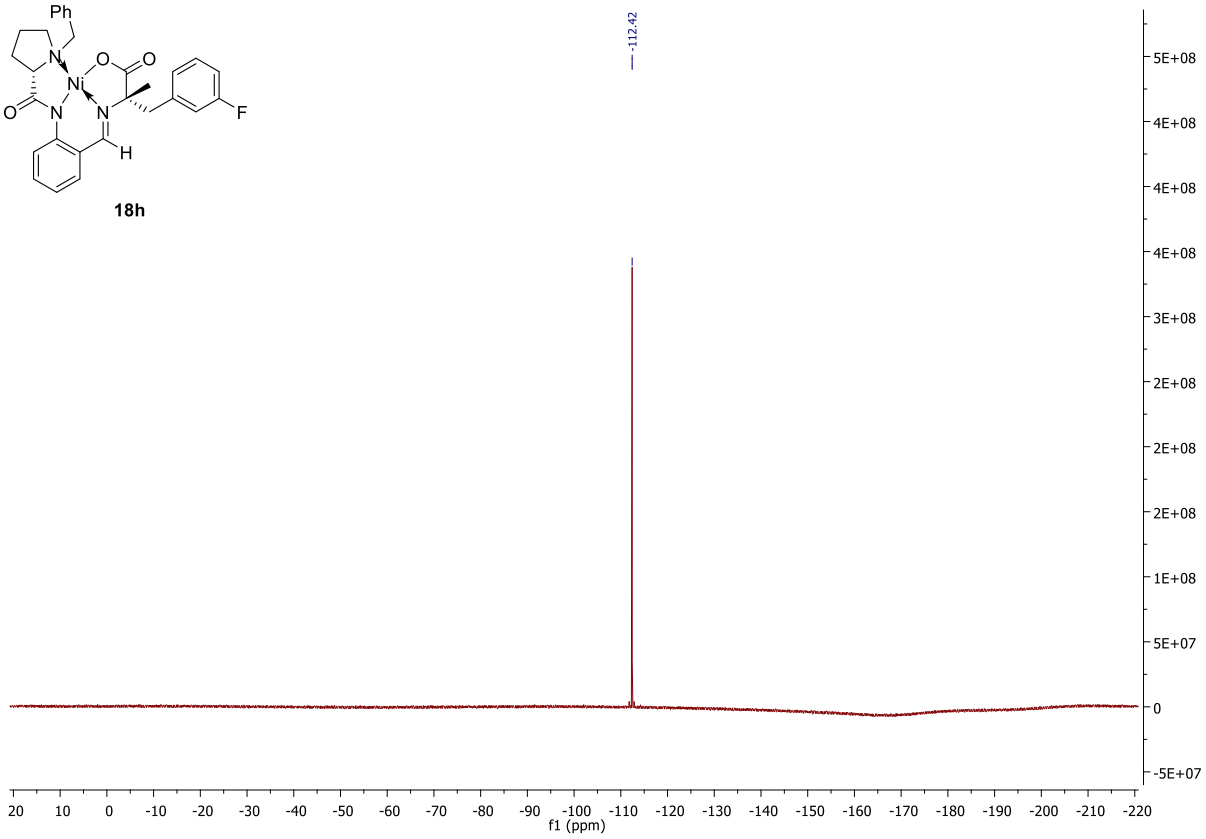




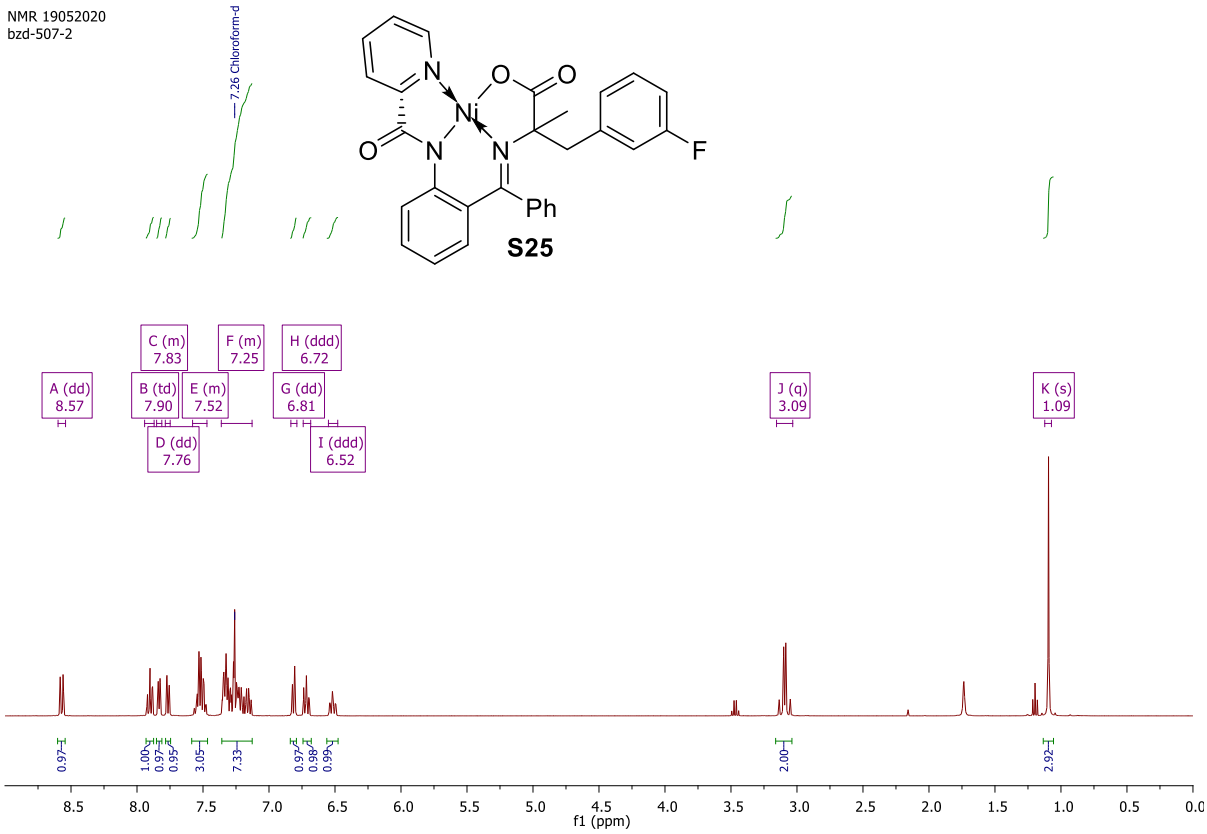
α-Methyl-3-FPhe reference compound (18h) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)

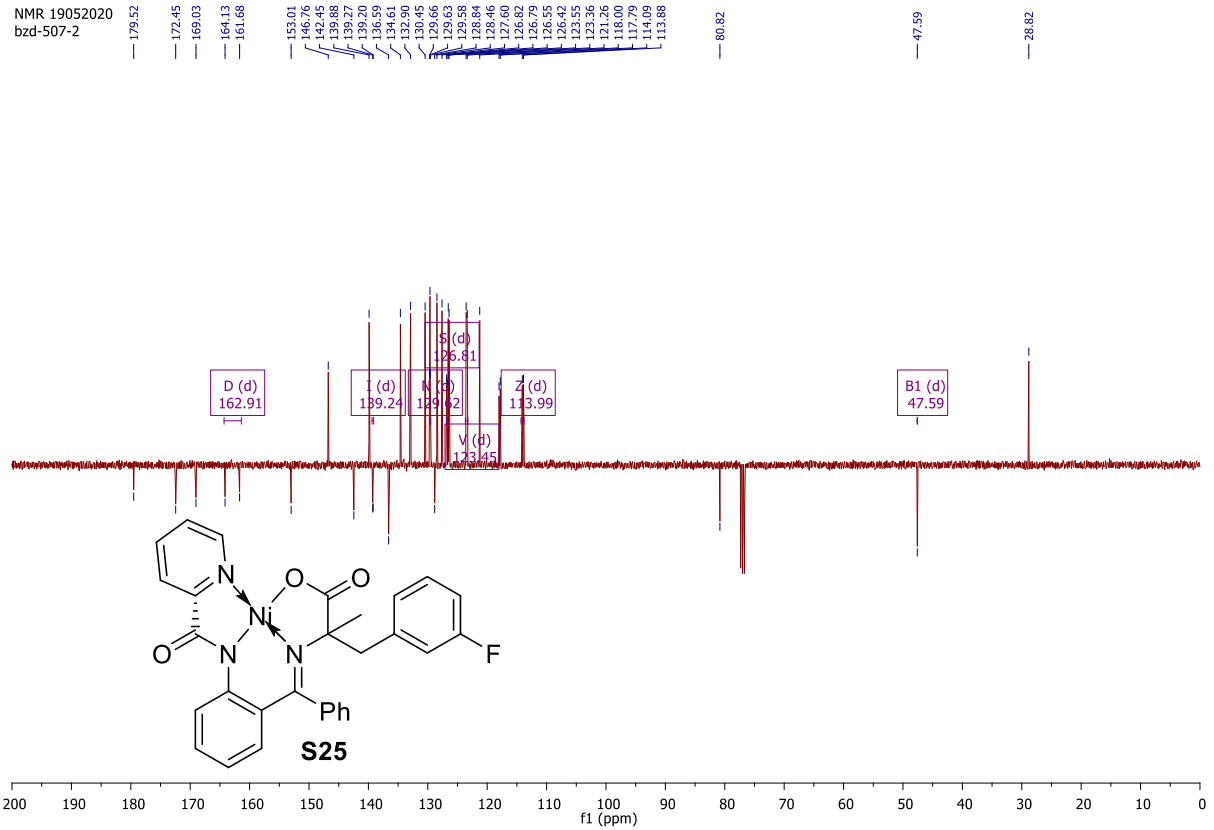


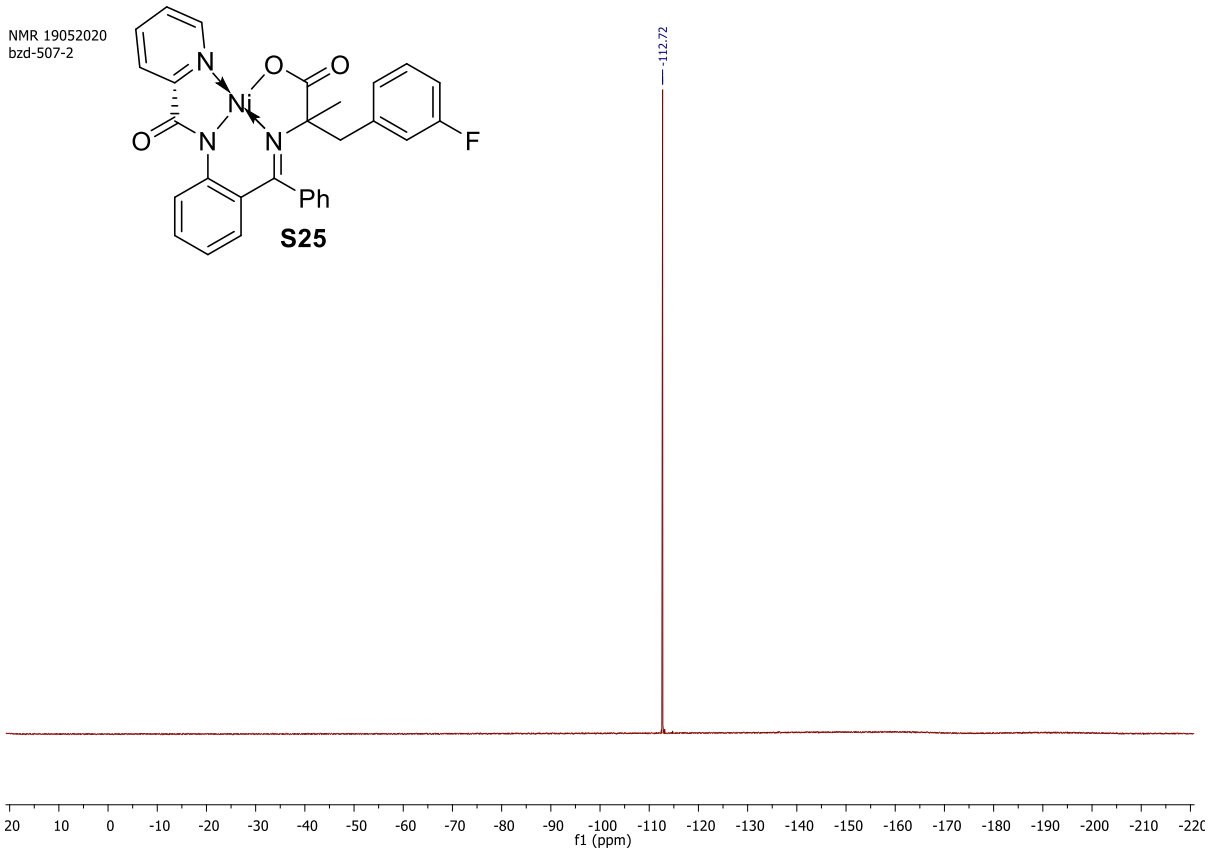



Ph
N
Ni
O
O
O
N
N
F
H
18h
-112.42
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

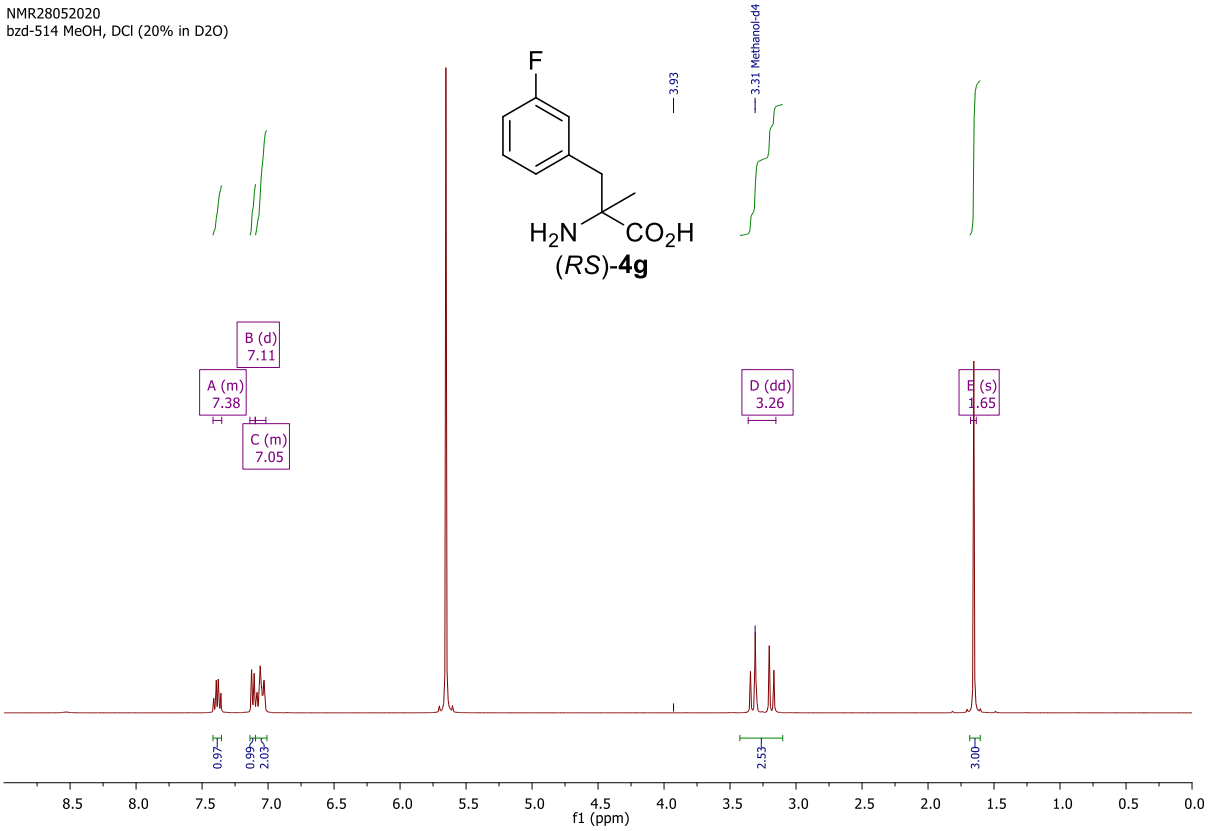
Ni-PBP-αMe-3-FPhe (S25) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)

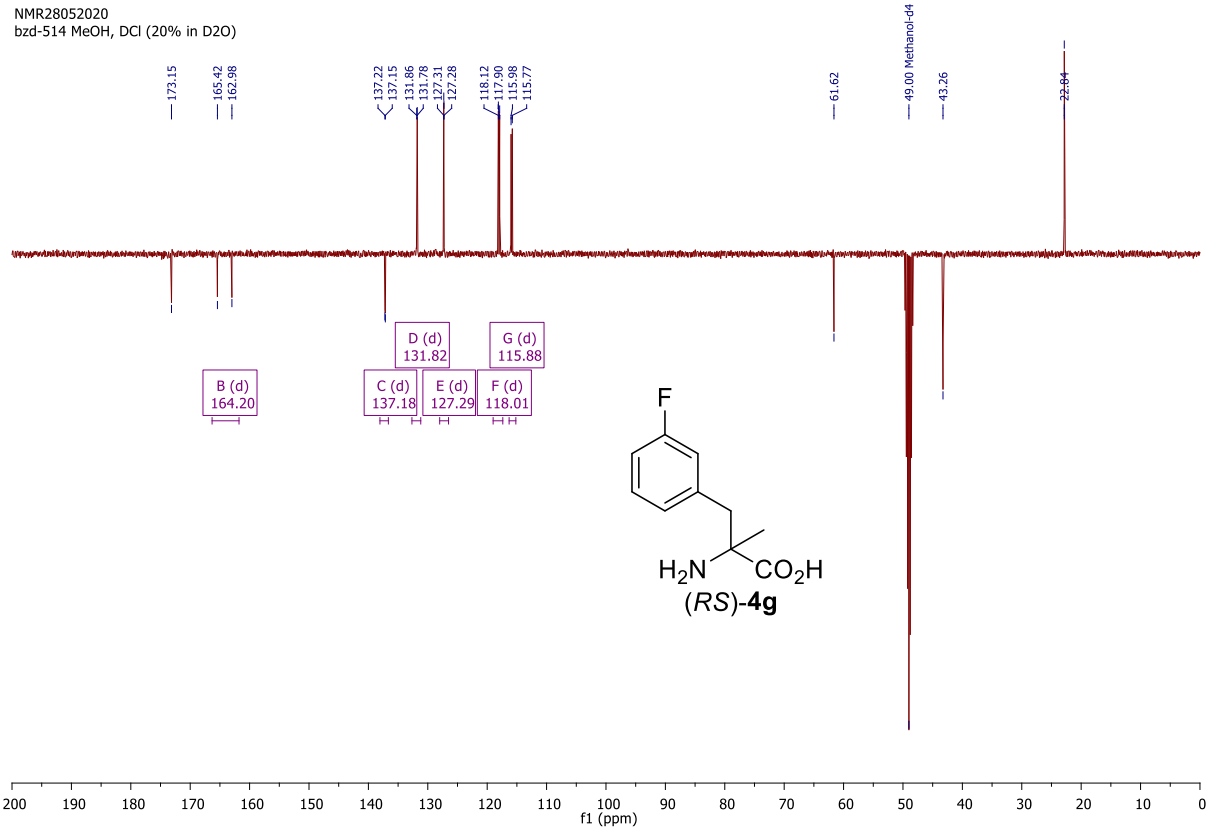




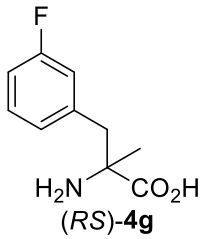

NMR 19052020
bzd-507-2
N
O
O
Ni
O
N
N
F
Ph
S25
-112.72
20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

(*RS*)-α-Methyl-3-fluorophenylalanine [(*RS*)-4h] (CD_3OD + 20% DCl) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)



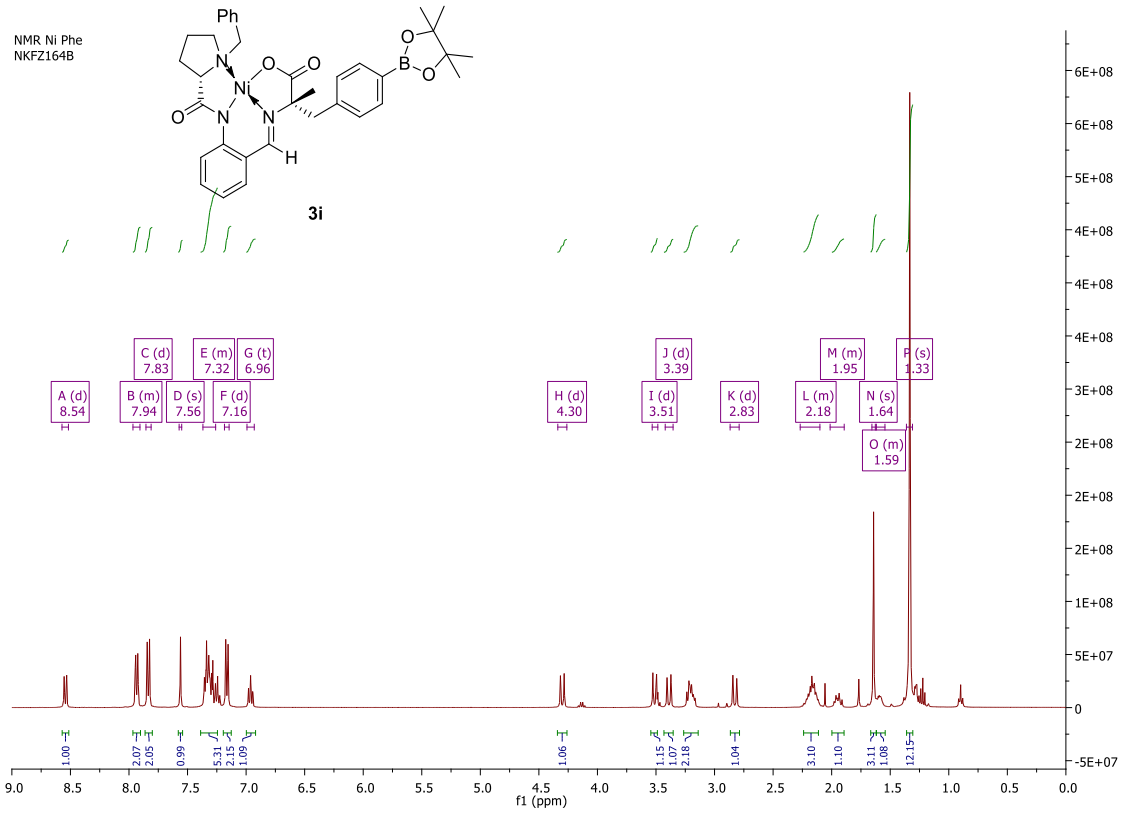


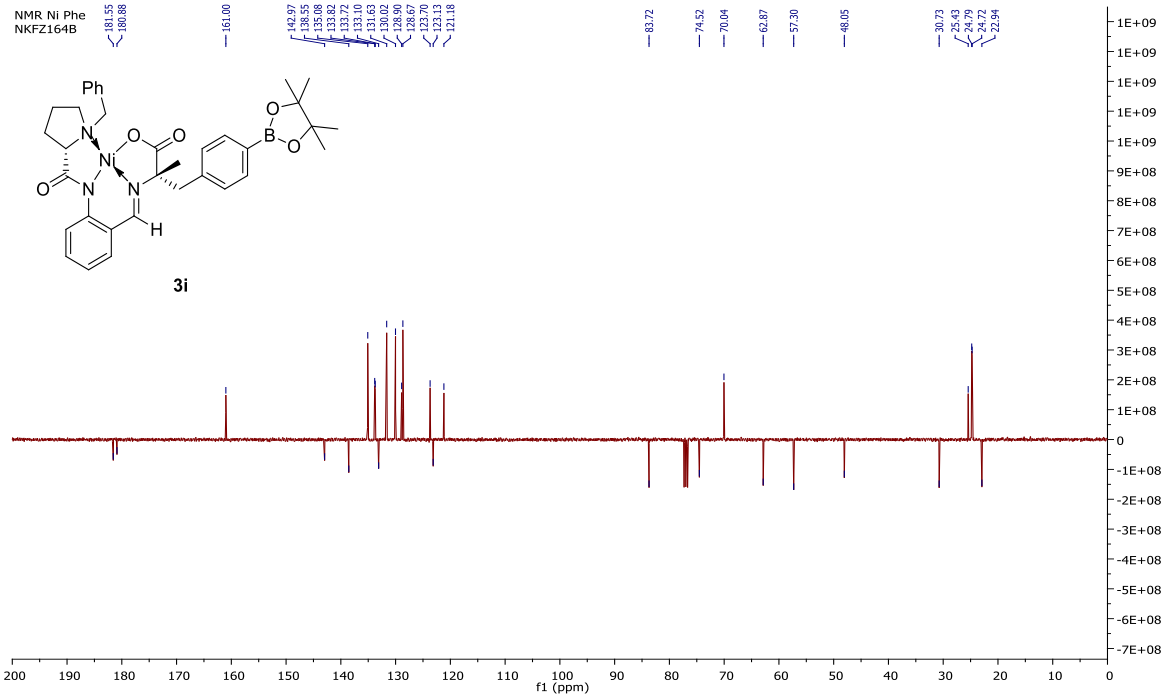
NMR28052020
bzd-514 MeOH, DCl (20% in D2O)



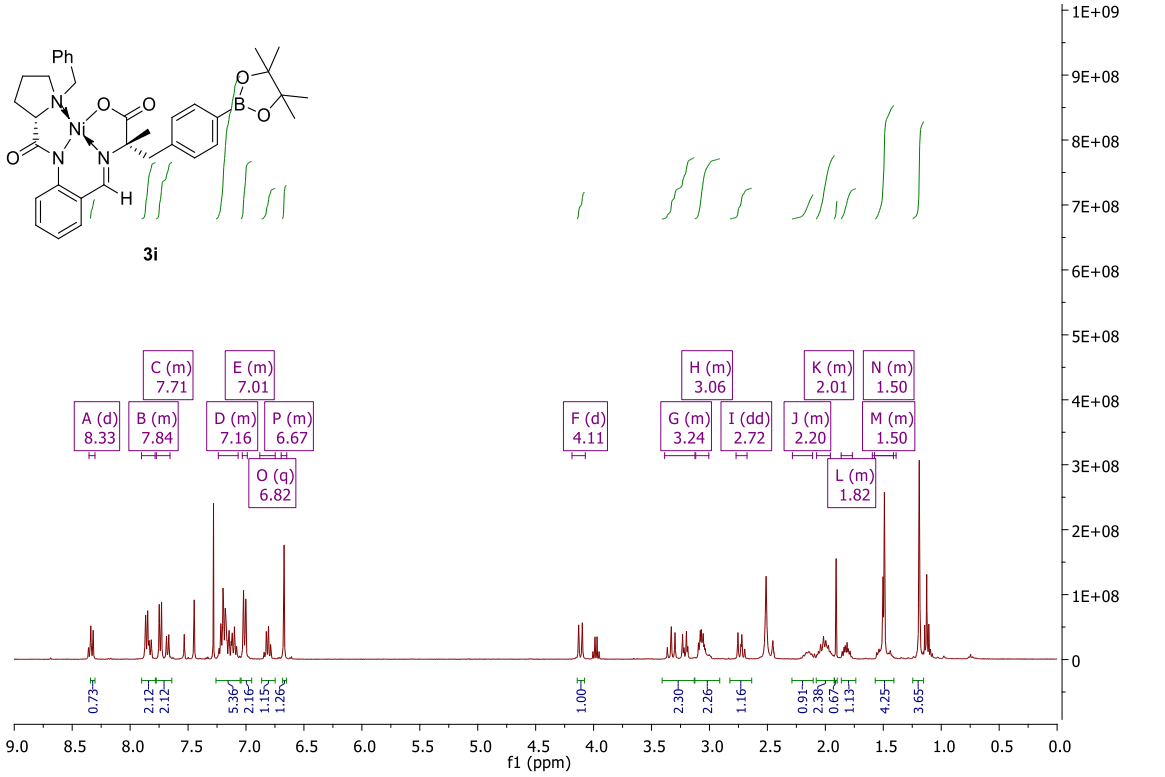
(*RS*)-**4g**

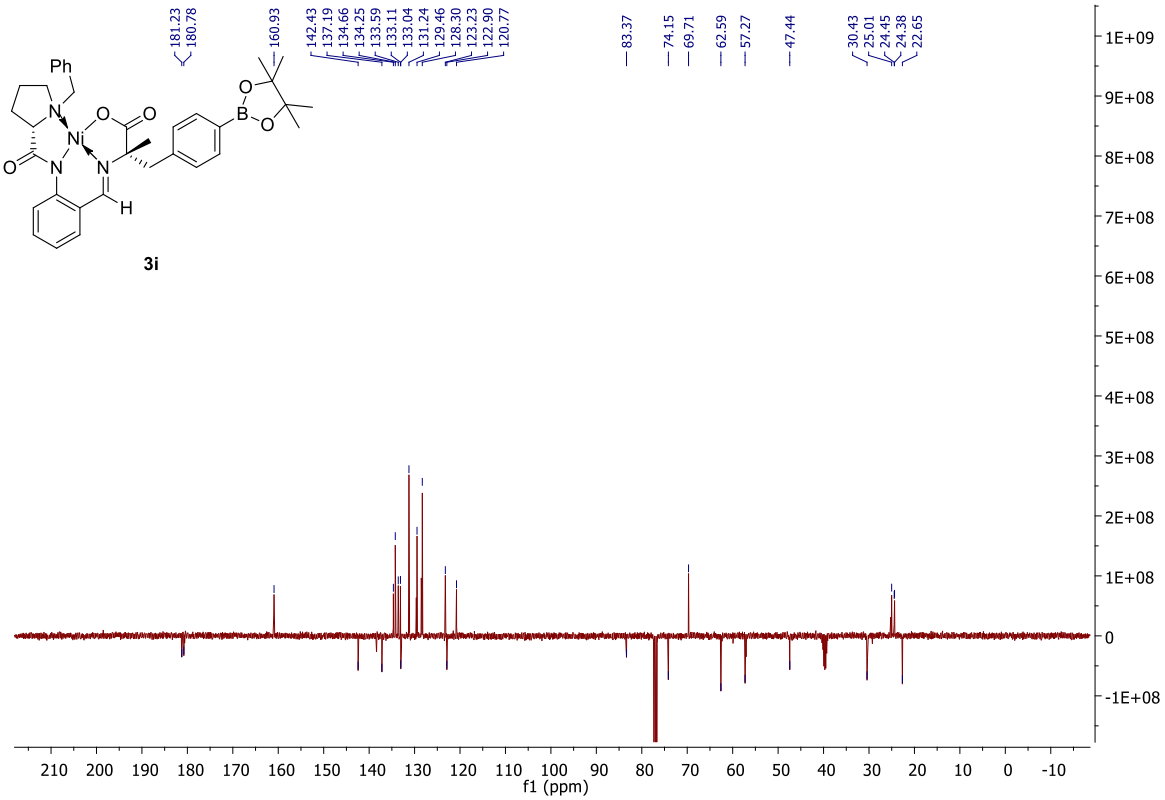
α-Methyl-4-[^{18}F]FPhe Precursor (3i) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (before RP chromatography)



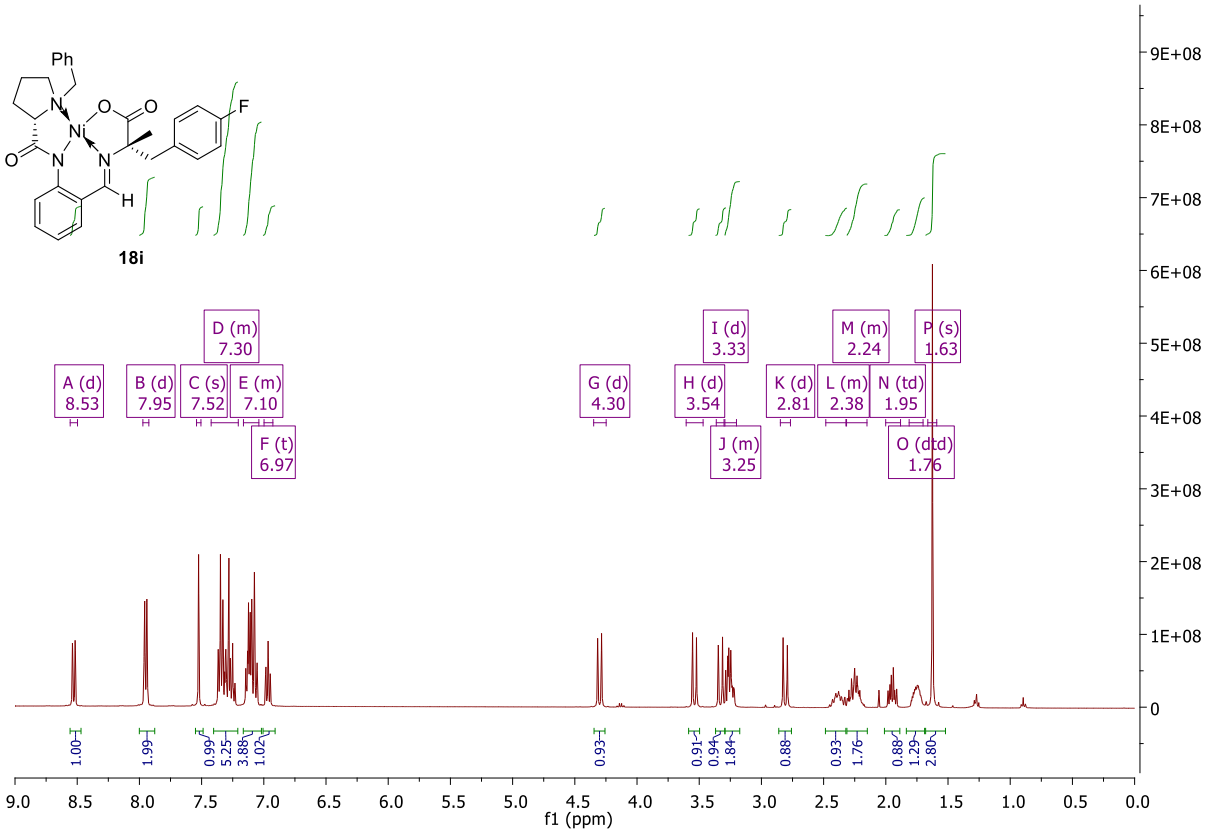


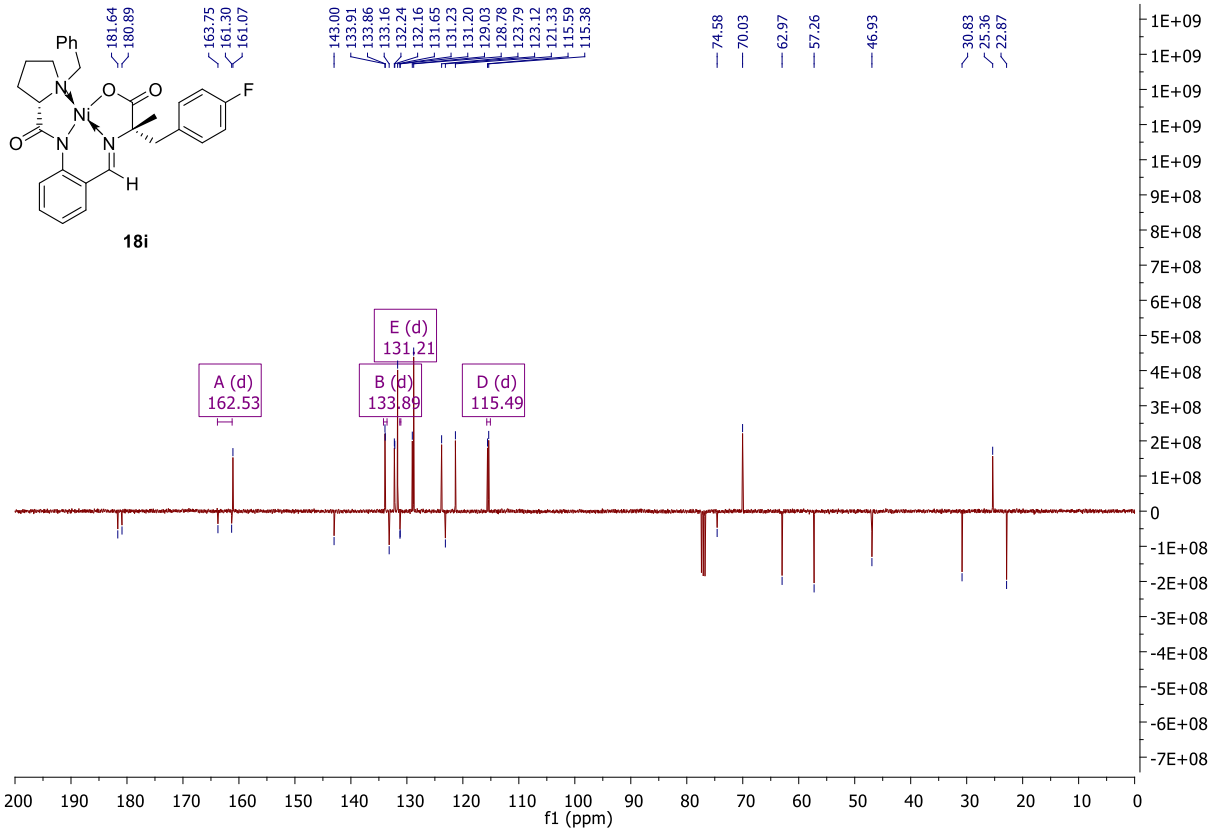
α-Methyl-4-[^{18}F]FPhe Precursor (3i) ($CDCl_3$) ^{1}H NMR (400 MHz) ^{13}C NMR (101 MHz) (after RP chromatography)

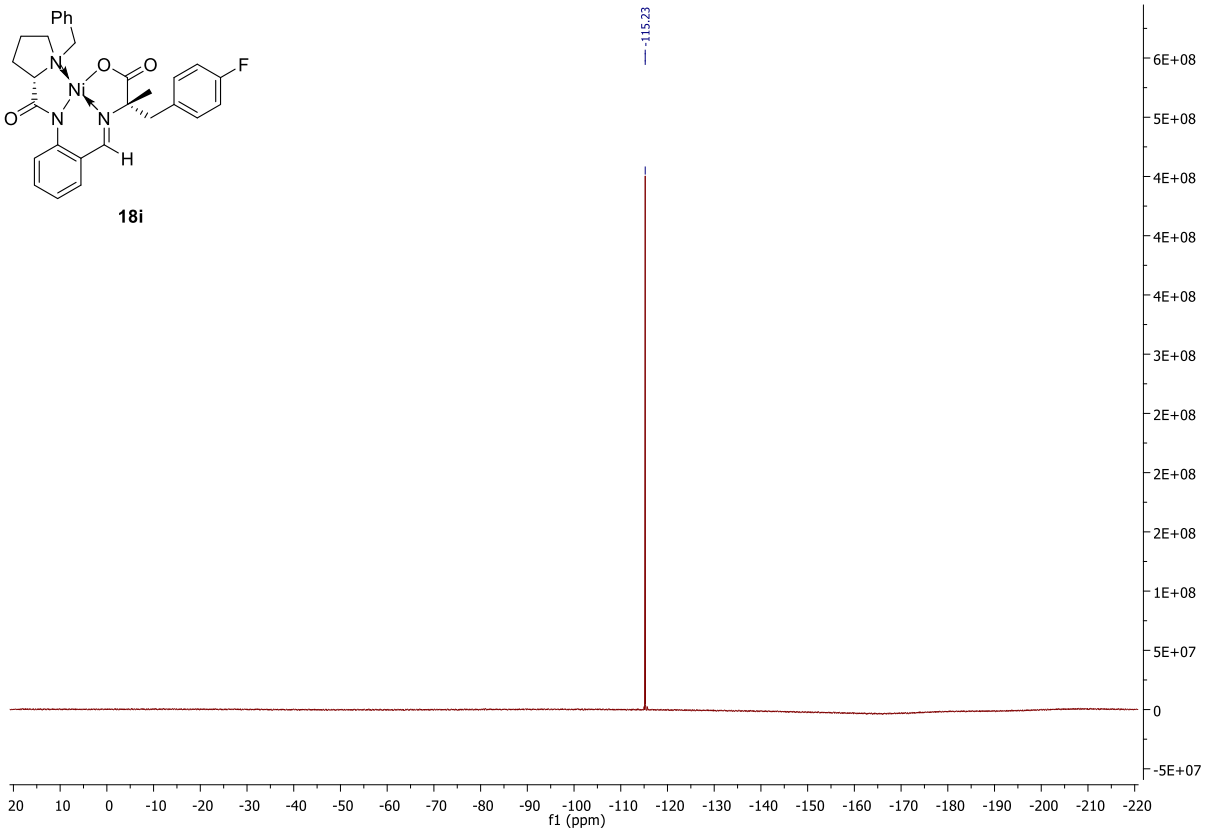




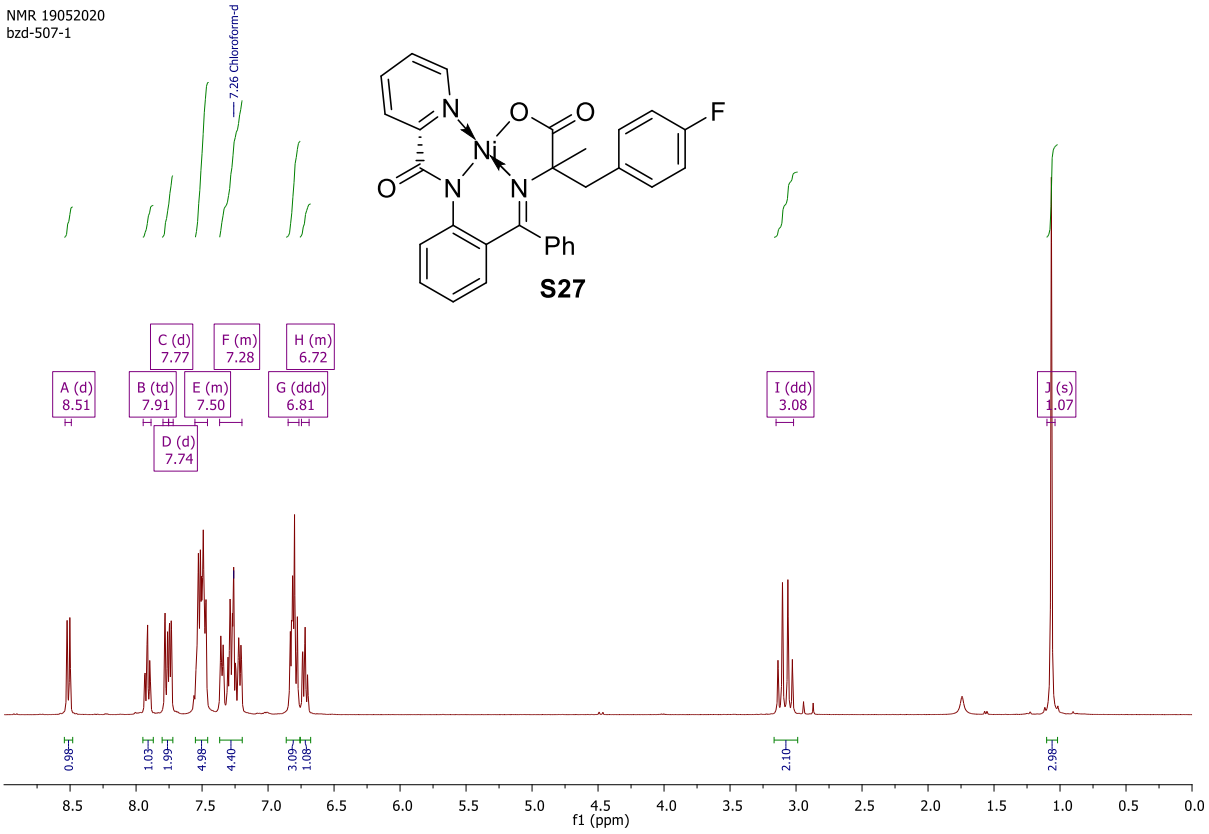
α-Methyl-4-FPhe reference compound (18i) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)

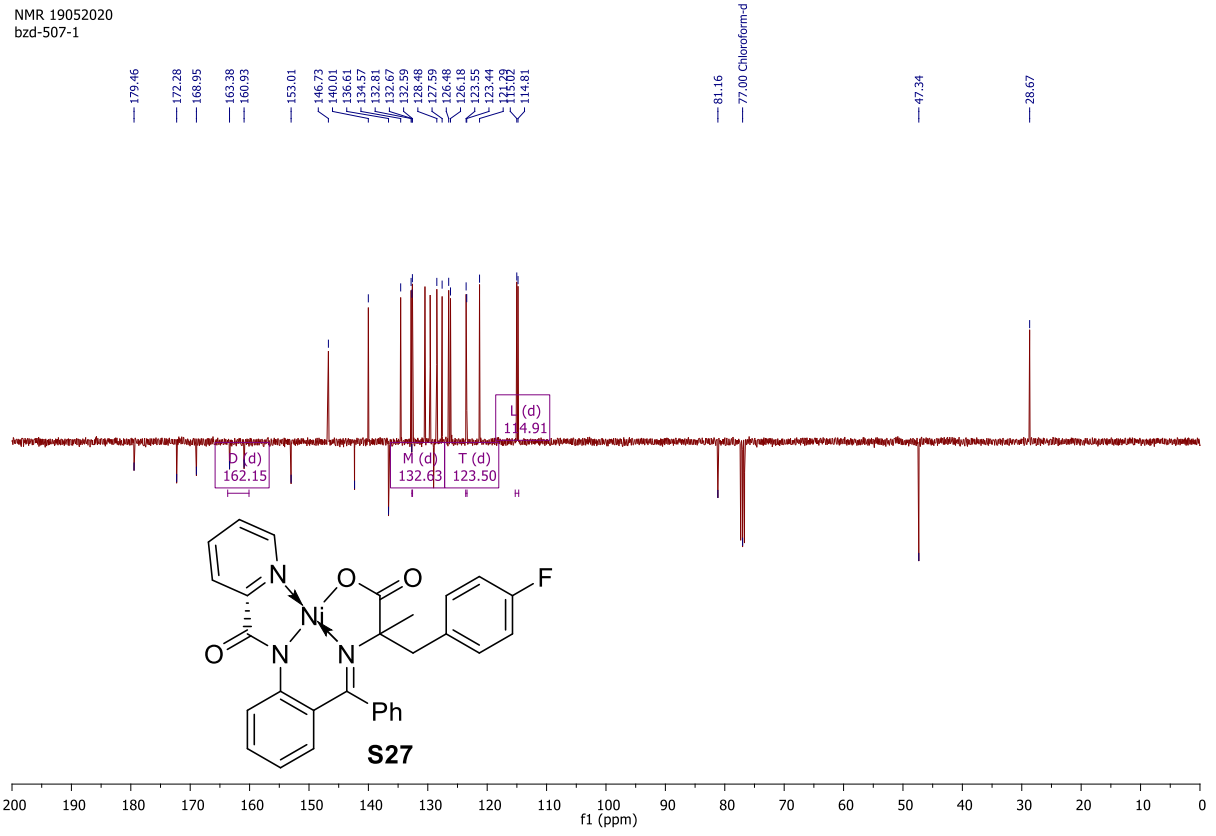




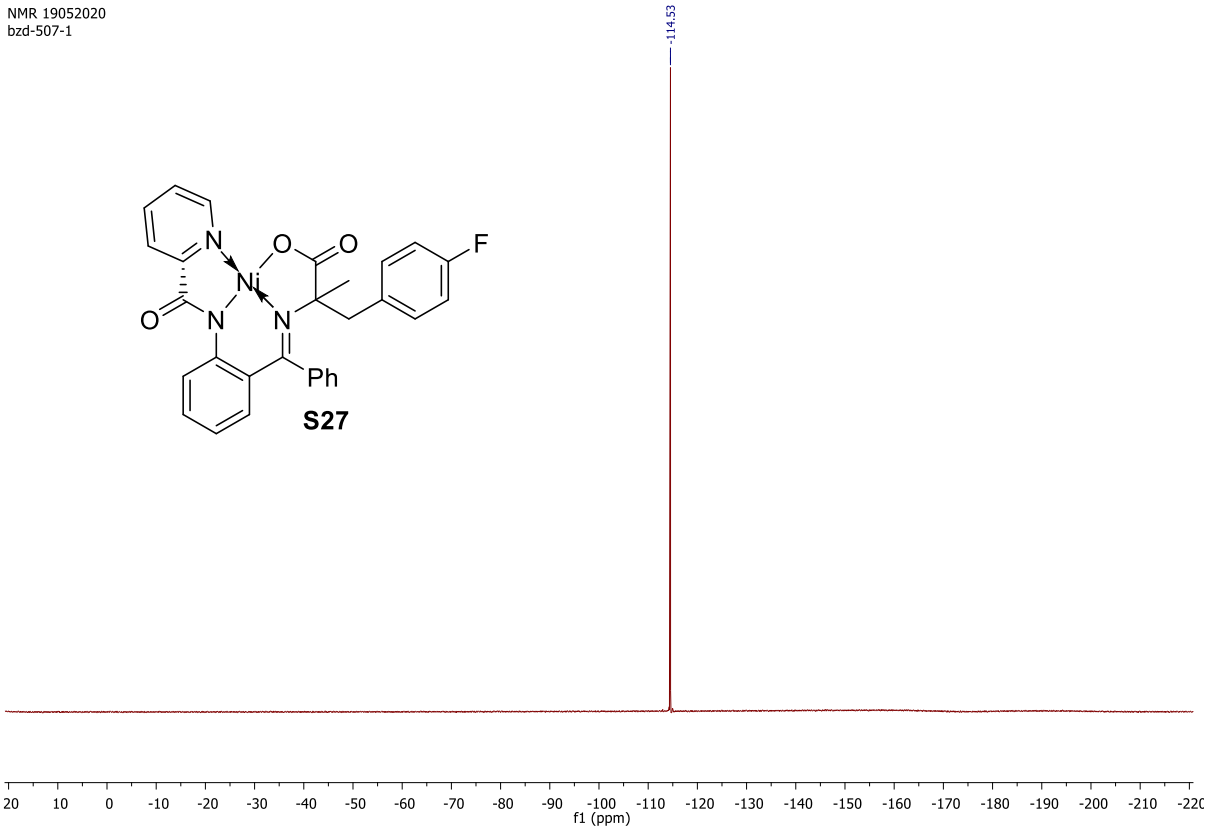

Ph
N
O
O
Ni
O
N
N
H
F
18i
-115.23
6E+08
5E+08
4E+08
4E+08
4E+08
3E+08
2E+08
2E+08
2E+08
1E+08
5E+07
0
-5E+07
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

Ni-PBP-αMe-4-FPhe (S27) ($CDCl_3$) ^{1}H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)

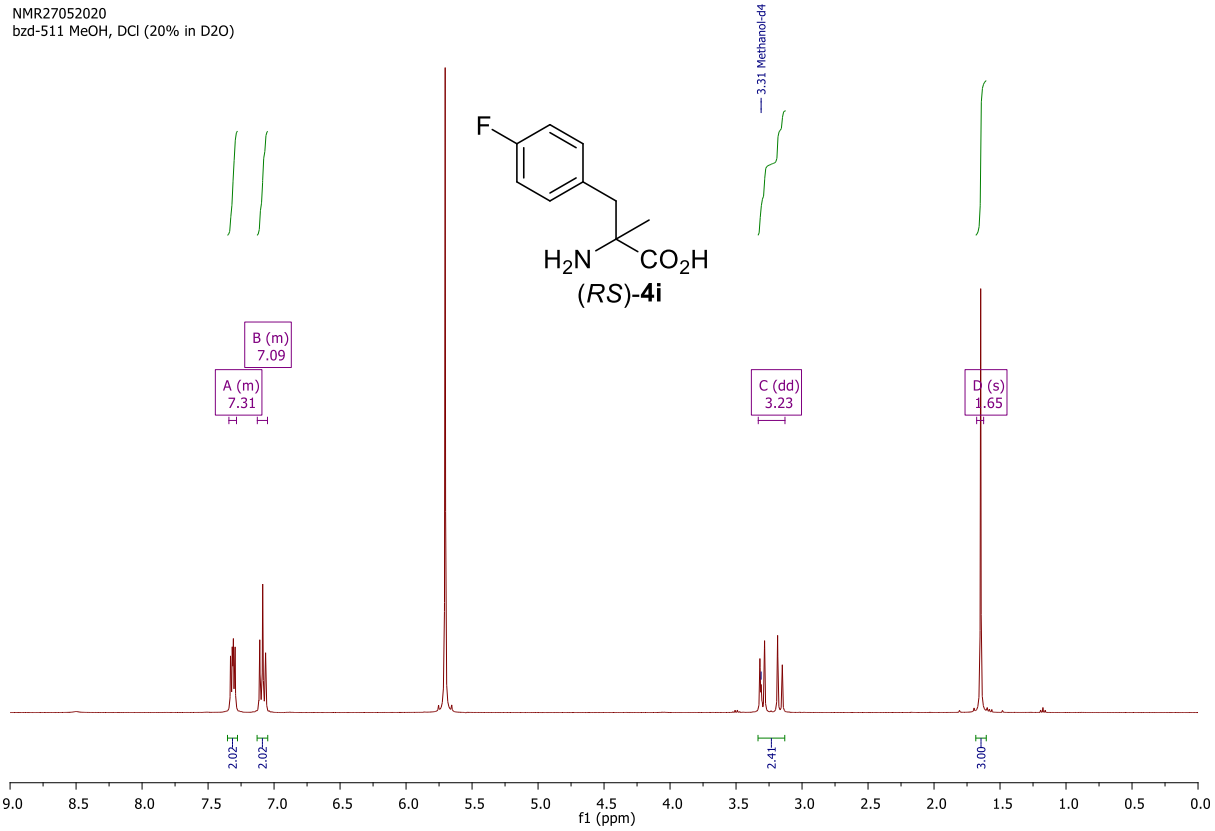


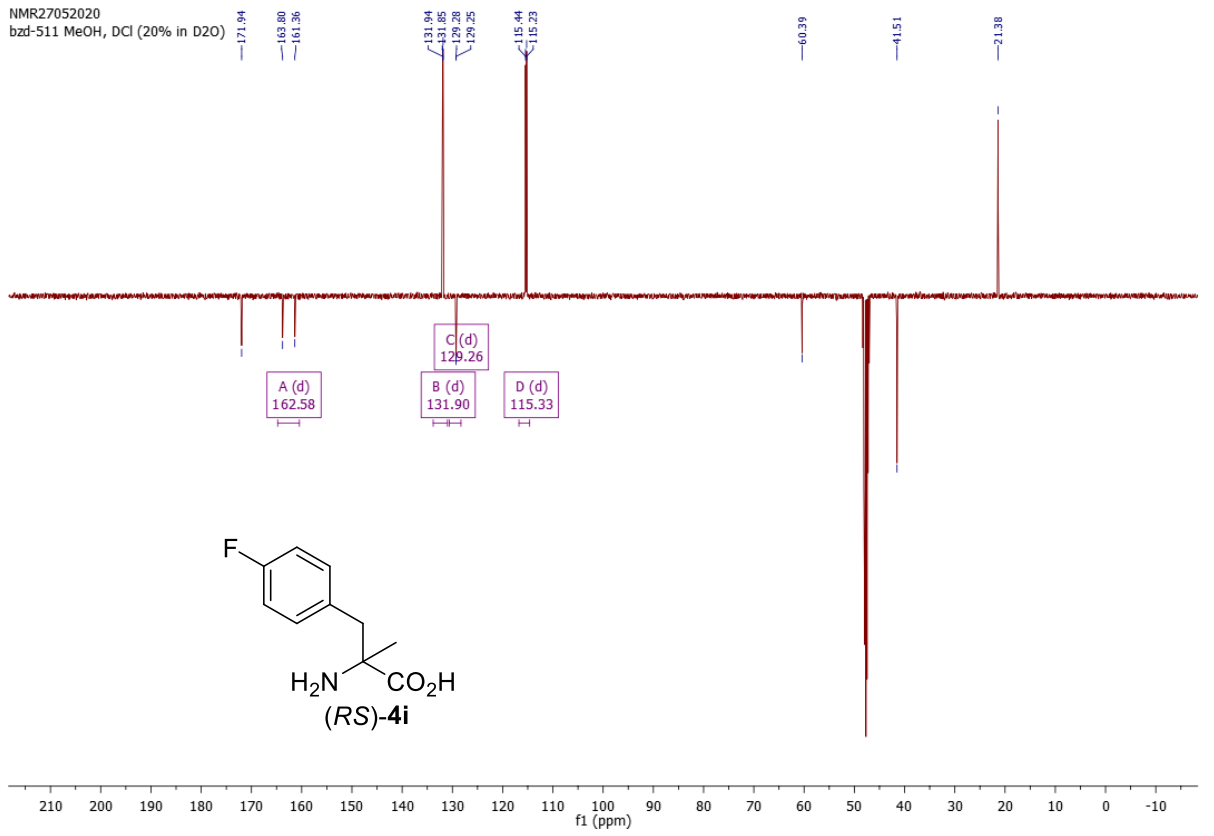


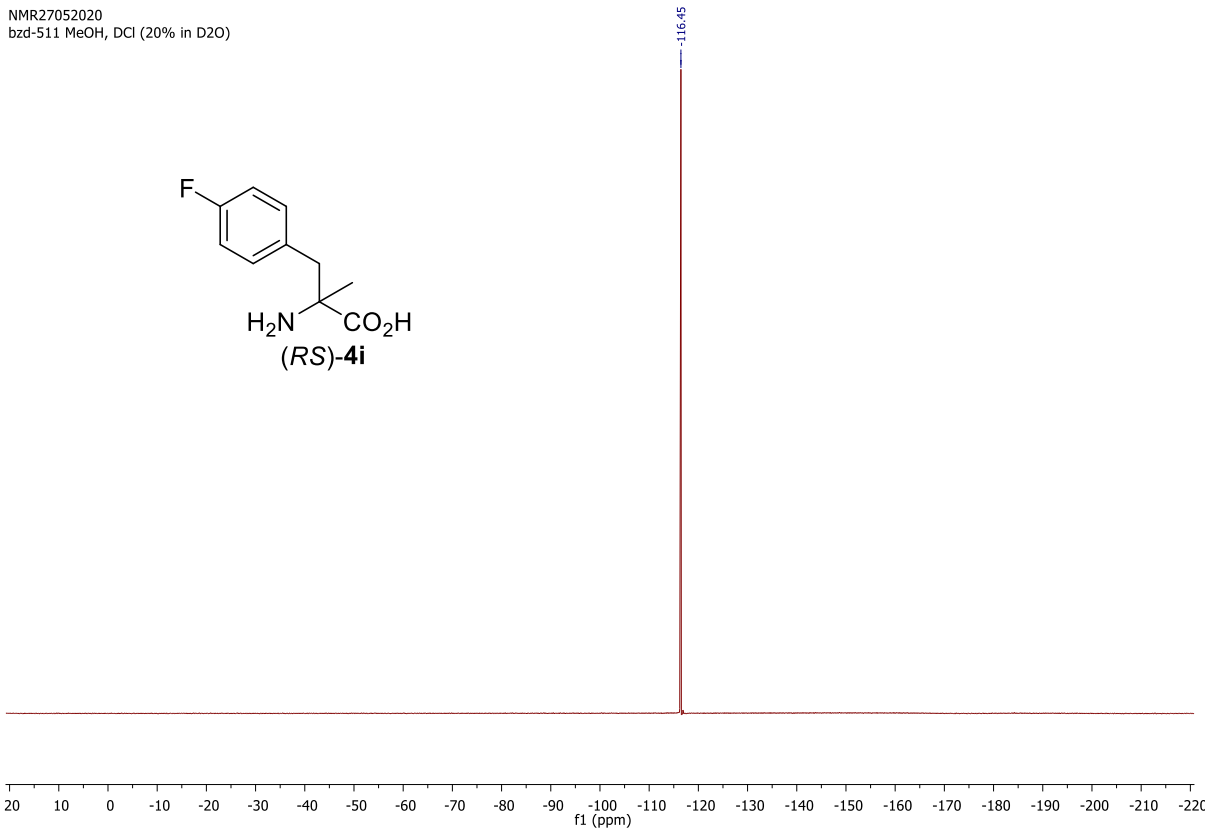
NMR 19052020
bzd-507-1



(*RS*)-α-Methyl-4-fluorophenylalanine [(*RS*)-4i] (CD_3OD + 20% DCl) ^1H NMR (400 MHz), ^{13}C NMR (101 MHz), ^{19}F NMR (376 MHz)






NMR27052020
bzd-511 MeOH, DCl (20% in D2O)
-116.45
F
H2N
CO2H
(RS)-4i
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

Radiochemistry

General Information and Procedures

[^{18}F]Fluoride was produced by bombardment of enriched [^{18}O]H_2O by 16.5 MeV protons *via* $^{18}O(p,n)^{18}F$ reaction at the BC1710 cyclotron (The Japan Steel Works Ltd., Shinagawa, Japan) at the INM-5 (Forschungszentrum Jülich).

All radiosyntheses were carried out using anhydrous *n*-BuOH and DMA stored over molecular sieves in Acroseal© flasks (Thermo-Fisher Scientific, Acros, Germany) and under ambient air. $Cu(py)_4(OTf)_2$ was prepared according to the literature procedure[16] and stored under ambient conditions. Sep-Pak Accell Plus QMA light carbonate cartridges (46 mg) were purchased from Waters GmBH (Eschborn, Germany).

Preprocessing of [^{18}F]fluoride

[^{18}F]Fluoride was processed prior to radiosynthesis as follows: A solution of aqueous [^{18}F]fluoride was loaded onto a QMA light carbonate (anion-exchange cartridge) from the male side. Washing and flushing was also carried out from the male side. The [^{18}F]fluoride was eluted from the female to the male side.

Synthesis of FET

[^{18}F]FET was prepared at the cyclotron and GMP facility of the INM-5 (Forschungszentrum, Jülich GmbH) as previously reported[17].

HPLC

Gradient A1: column: Chromolith SpeedROD®, 50 × 4.6 mm (Merck Millipore, Germany); gradient: 0–2 min: 5% MeCN, 2–2.5 min 5→20% MeCN, 2.5–6 min: 20% MeCN, 6–7 min 20→70% MeCN, 7–9 min: 70% MeCN, 9–12 min 70→5% MeCN, flow rate: 2 mL/min.

Gradient A2: column: Chromolith SpeedROD®, 50 × 4.6 mm (Merck Millipore, Germany); gradient: 0–2 min: 5% MeCN, 2–2.5 min: 5→70% MeCN, 2.5–7 min: 70% MeCN, 7–8 min: 70→5% MeCN, 8–9 min: 5% MeCN, flow rate: 3 mL/min.

Gradient B1: Synergi Hydro-RP, 4 µm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 6% EtOH (0.2% H_3PO_4), flow rate: 1.3 mL/min. These conditions were used for the isolation of 2-[^{18}F]FPhe ([^{18}F]**4a**)

Gradient B2: Synergi Hydro-RP, 4 μm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 4% EtOH (0.2% H_3PO_4), flow rate: 1.3 mL/min. These conditions were used for the isolation of 6-[^{18}F]FMT ([^{18}F]**4d**).

Gradient B3: Synergi Hydro-RP, 4 μm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 10% EtOH (0.2% H_3PO_4), flow rate: 1.0 mL/min.

Gradient B4: Synergi Hydro-RP, 4 μm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 7% EtOH, flow rate: 1.0 mL/min. These conditions were used for the isolation of 4-[^{18}F]FTrp ([^{18}F]**4f**) for animal experiments.

Gradient B5: Hydro RP Synergi 250 mm × 10 mm Synergi Hydro-RP, 4 μm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 10% EtOH (0.1% TFA), flow rate: 6 mL/min. These conditions were used for the isolation of 3–4-[^{18}F]Phes ([^{18}F]**4a**–**c**), 2–4-αMe-[^{18}F]Phes ([^{18}F]**4a**–**c**), and 2-[^{18}F]FTyr ([^{18}F]**4e**).

Gradient B6: Synergi Hydro-RP, 4 μm, 80 Å, 250 mm × 4.6 mm (Phenomenex, Aschaffenburg, Germany), eluent: 7% EtOH, flow rate: 1.0 mL/min. Gradient C: 1 mL/min 60% EtOH Chirobiotic T column (Astec®), 5 μm, 100 Å isocratic 1–12 min. A precolumn protector was not utilized in this case.

HPLC analyses were carried out on a Dionex Ultimate 3000 HPLC system and a DAD UV detector coupled in series with a Berthold NaI detector or on a homemade HPLC system consisting of a Knauer 80-P pump, a Knauer K-2500 UV/vis detector (Knauer, Berlin, Germany), and a Rheodyne manual injector coupled in series with a NaI(Tl) well-type scintillation detector model 276 photomultiplier base with an ACE mate amplifier and BIAS supply (EG&G Ortec Ametek, Meerbusch, Germany). Semipreparative HPLC separations were carried out using the same HPLC systems or a homemade HPLC system equipped with a Hitachi L-6000 pump (Merck, Darmstadt), a Knauer K-2500 UV/vis detector (Knauer, Berlin, Germany), and a Rheodyne manual injector (5 mL loop) coupled in series with a NaI(Tl) well-type scintillation detector model 276 photomultiplier base with an ACE mate amplifier and BIAS supply (EG&G Ortec Ametek, Meerbusch, Germany). The unselective adsorption of ^{18}F onto HPLC columns was determined to be < 10% in each case. The UV and radioactivity detectors were connected in sequence, giving a time delay of 0.1–0.9 min between the corresponding responses, depending on the flow rate. The identity of the ^{18}F-labeled products was confirmed by the co-injection of the respective non-radioactive reference compound. All

radiosyntheses were carried out at least three times. In most cases, the standard deviation (SD) of RCCs did not exceed 10% of the mean values.

Gradient	Compound	Retention time (min)
A1	[^{18}F]**18a**	8.1
A1	[^{18}F]**18b**	8.0
A1	[^{18}F]**18c**	8.0
A1	[^{18}F]**18d**	8.1
A1	[^{18}F]**18e**	8.4
A2	[^{18}F]**18f**	3.2
A2	[^{18}F]**18g**	4.4
A2	[^{18}F]**18h**	4.6
A2	[^{18}F]**18i**	4.5
A1	Cu-BPB-3-[^{18}F]FPhe	8.7

*Table S1. Retention times of radiolabeled intermediates [^{18}F]**18a–i** and Cu-BPB-3-[^{18}F]FPhe.*

Gradient	Compound	Retention time (min)
B1	[^{18}F]**4a**	4.2
B1	[^{18}F]**4b**	4.1
B1	[^{18}F]**4c**	5.0
B2	[^{18}F]**4d**	4.0
B2	[^{18}F]**4e**	4.8
B4	[^{18}F]**4f**	12.2
B1	[^{18}F]**4g**	5.4
B1	[^{18}F]**4h**	5.8
B1	[^{18}F]**4i**	6.5

*Table S2. Retention times of radiolabeled amino acids [^{18}F]**4a–i** (analytic HPLC).*

Gradient	Compound	Retention time (min)
B1	[^{18}F]**4a**	4.2
B5	[^{18}F]**4b**	8.2
B5	[^{18}F]**4c**	8.3
B2	[^{18}F]**4d**	4.0
B5	[^{18}F]**4e**	6.9
B4	[^{18}F]**4f**	12.2
B5	[^{18}F]**4g**	9.7
B5	[^{18}F]**4h**	11.7
B5	[^{18}F]**4i**	12.5

*Table S3. Approximate retention times of radiolabeled amino acids [^{18}F]**4a–i** (semi-preparative HPLC separations).*

General procedure for the preparation of ^{18}F-labeled aromatic amino acids from Ni-BPX-(Bpin)AAA complexes (GP5)

The radiosynthesis commenced with the loading of [^{18}F]fluoride (500–5000 MBq) onto a QMA® light carbonate cartridge (preconditioned with 1 mL H_2O) followed by subsequent elution with Et_4NHCO_3 (3 mg, 15.7 µmol) in MeOH (0.75 mL). Thereafter, all volatiles were removed under reduced pressure at 80 °C for 5 minutes, a solution of the corresponding precursor (10 µmol) and $Cu(py)_4(OTf)_2$ (20 µmol) in DMA/*n*BuOH 2:1 (0.75 mL) added, and the reaction mixture was stirred at 110 °C for 15 min. The mixture was then concentrated under reduced pressure at 110 °C for 10 min. 12 M HCl (0.3 mL) was added, the reaction mixture was stirred at 110 °C for 15 min and concentrated at the same temperature under reduced pressure. Thereafter, the residue was taken up in the suitable eluent (1 mL; please refer to Table S3) and purified using high-performance liquid chromatography (HPLC). Unless otherwise stated, all columns were fitted with a precolumn protector (Phenomenex, SecurityGuard Cartridge System). If the produced tracer should be used for the *in vivo* studies the product fraction was concentrated under reduced pressure and the flow of argon, and the residue was taken up into saline or in PBS {in the case of 6-[^{18}F]FMT ([^{18}F]**4d**)}. Some of ^{18}F-labeled amino acids, especially 3-[^{18}F]FPhe ([^{18}F]**4b**), were sensitive to radiolysis. If tracer was not intended to be used immediately, it was stabilized by the addition of sodium ascorbate (10 mg) into the product vial.

Automated Radiosyntheses

All automated radiosyntheses were carried out in a home-made synthesis module. FFKM valves (Christian Bürkert GmbH&Co. KG, Ingelfingen, Germany) were applied. All connections between the valves were made using PTFE tubes and PEEK fittings. The flow scheme for the preparation of radiolabeled amino acids is depicted in Figure S3. Synthetic air and He (Westfalen AG, Muenster, Germany) were used as operating gases.

Optimization of Radiofluorination Conditions

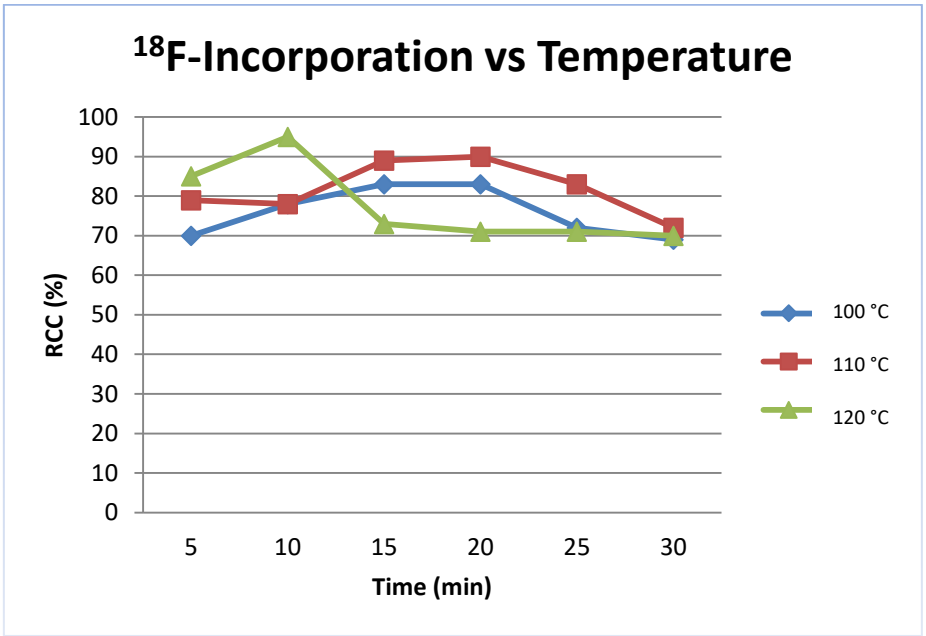


*Figure S1. The dependency of ^{18}F-incorporation on temperature. Conditions: [^{18}F]Fluoride (~50 MBq) was loaded onto a QMA-CO_3^- cartridge from the male side. The cartridge was washed with water (1 mL) in the same direction and flushed with air (5 mL). Thereafter, $^{18}F^-$ was eluted from the female side with a solution of Et_4NHCO_3 (3 mg) in MeOH (0.7 mL). The MeOH was evaporated under a flow of air within 5 min. A solution of **3b** (7.1 mg, 10 µmol) and $Cu(py)_4(OTf)_2$ (13.6 mg, 20 µmol) in nBuOH/DMA (1:2, 750 µL) was added, the reaction mixture was heated at the corresponding temperature for the specified time under air, diluted with water (1 mL) and analyzed by HPLC. All experiments were carried out in triplicate.*

Optimization with respect to reaction temperature was carried out with precursor **3b** at 100 °C, 110 °C, and 120 °C. It was found that 110 °C for 15 minutes afforded the highest ^{18}F-incorporation of the three temperatures.

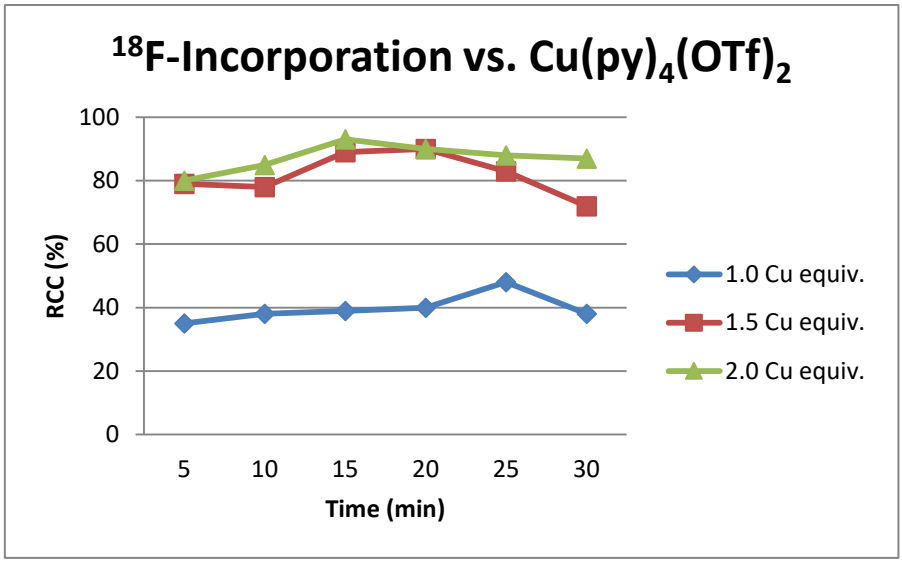


Figure S2. The dependency of ^{18}F-incorporation on Cu mediator concentration. Conditions: [^{18}F]Fluoride (~50 MBq) was loaded onto a QMA-CO_3^- cartridge from the male side. The cartridge was washed with water (1 mL) in the same direction and flushed with air (5 mL). Thereafter, $^{18}F^-$ was eluted from the female side with a solution of Et_4NHCO_3 (3 mg) in MeOH (0.7 mL). The MeOH was evaporated under a flow of air within 5 min. A solution of ***3b*** *(7.1 mg, 10 µmol) and the corresponding $Cu(py)_4(OTf)_2$ amount in nBuOH/DMA (1:2, 750 µL) was added, the reaction mixture was heated at the 110 °C for 15 min under air, diluted with water (1 mL) and analyzed by HPLC. All experiments were carried out in triplicate.*

Optimization with respect to the equivalents of $Cu(py)_4(OTf)_2$ was carried out with precursor **3b** at 110 °C. It was found that the application of 2 molar equivalents of $Cu(py)_4(OTf)_2$ at 110 °C for 15 minutes afforded the highest ^{18}F-incorporation among the tested conditions.

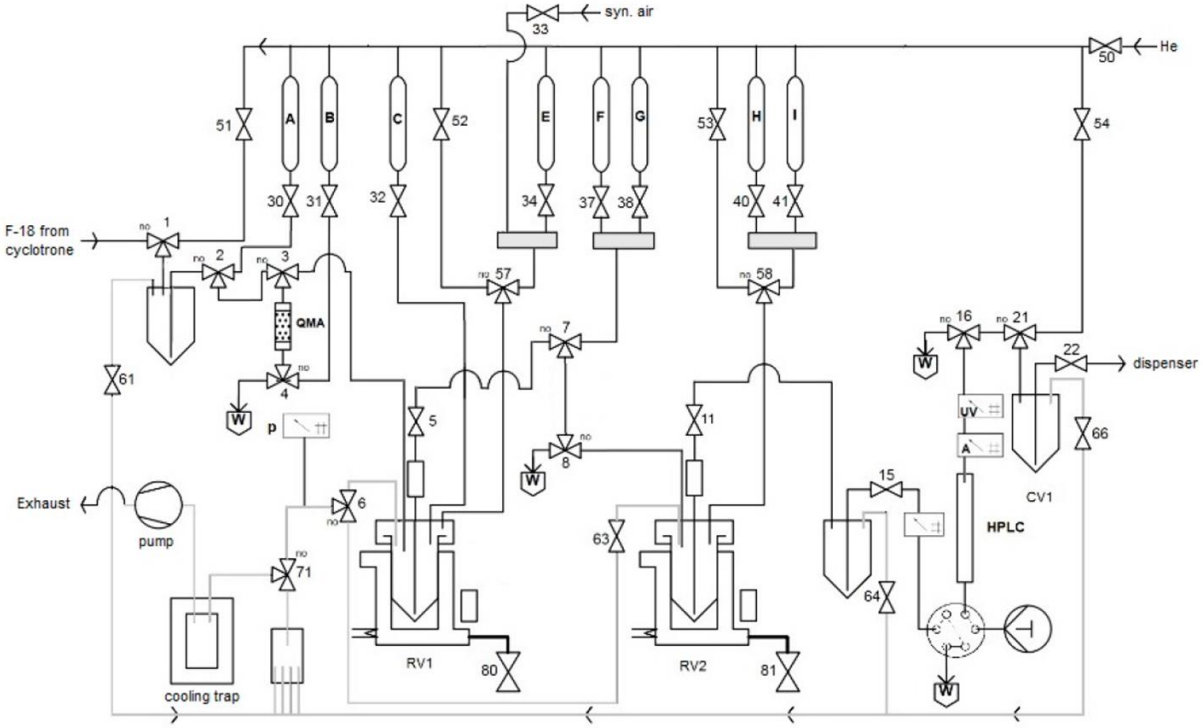


Figure S3. Process flow diagram (PFD) for the automated radiosynthesis of ^{18}F-labeled AAAs. A: MeOH (2 mL); B: Et_4NHCO_3 (3 mg, 15.7 µmol) in MeOH (0.75 mL); C: $Cu(py)_4(OTf)_2$ (13.6 mg, 20 µmol) and radiolabeling precursor (10 µmol) in DMA/nBuOH (2:1) (0.75 mL); E: 37% HCl (1 mL); F: 6% $EtOH_{aq}$ (1 mL).

1. Loading of [^{18}F]fluoride onto an QMA ion exchange cartridge;

2. Washing of the QMA with MeOH (2 mL);

3. Closing air valve (50), and system venting;

4. Elution of [^{18}F]fluoride from the ion-exchange cartridge with a methanolic solution of Et_4NHCO_3 into RV 1;

5. Open air valve (50) to completely transfer methanolic solution from QMA to RV 1;

6. Evaporation of MeOH in RV1 at 80 °C for 3–5 min using a flow of synthetic air under reduced pressure;

7. Addition of a solution of the radiolabeling precursor (10 µmol) and $Cu(py)_4(OTf)_2$ (20 µmol) in *n*BuOH/DMA 1:2 (0.75 mL);

8. Heating of the reaction mixture in RV1 at 110 °C for 15 min;

9. Evaporation of reaction mixture in RV1 at 110 °C for 10 min;

10. Addition of 37% HCl (1 mL) and heating at 110 °C for 15 min;

11. Evaporation of reaction mixture in RV1 at 130 °C for 10 min;

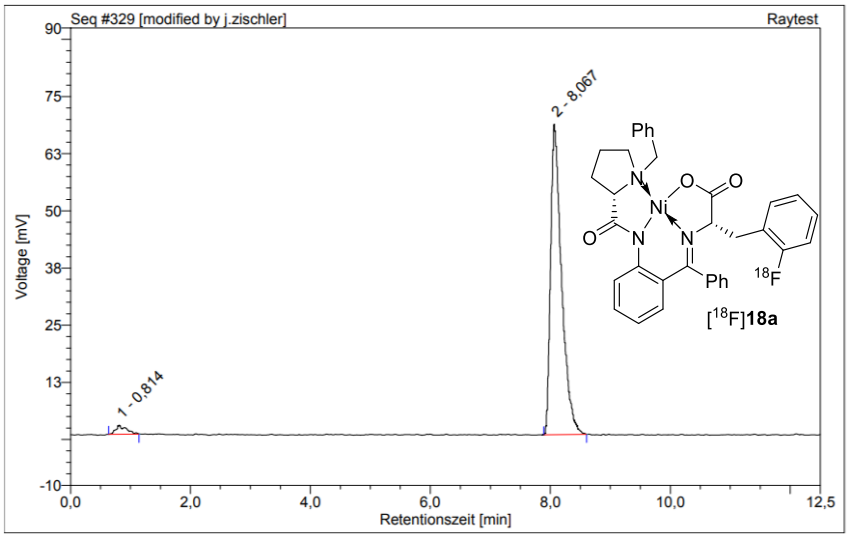
12. Addition of the appropriate eluent (please, refer to Table S3) in RV1;

13. Injection of the loop content onto the HPLC column and elution of the tracer with the appropriate eluent (please, refer to Table S3);

14. Manual collection of the product fraction in a collection vial (CV1).

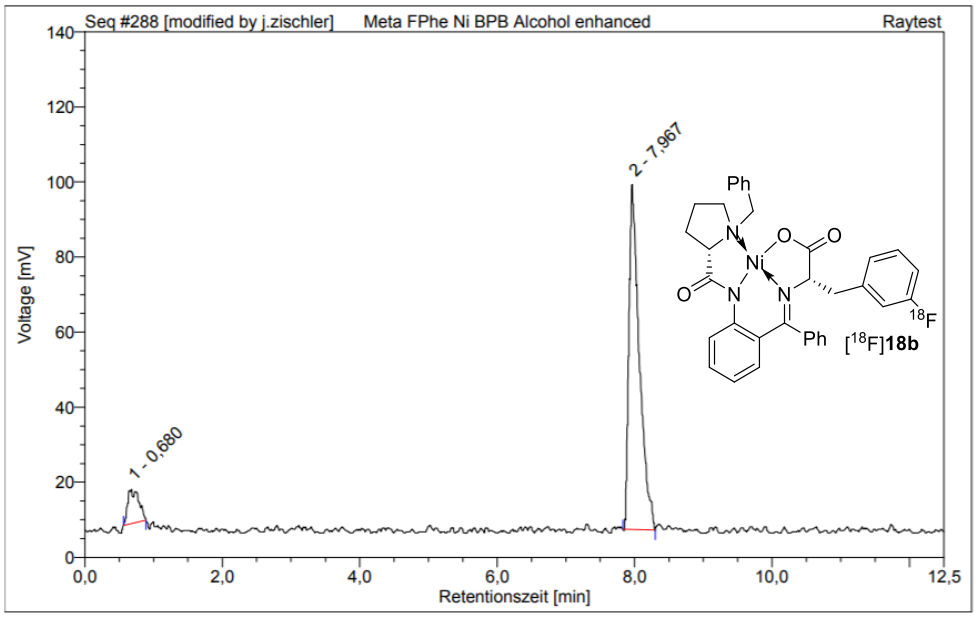
Radio HPLC traces and RCC data for ^{18}F-labeled Products

[^{18}F]18a (Gradient A1)



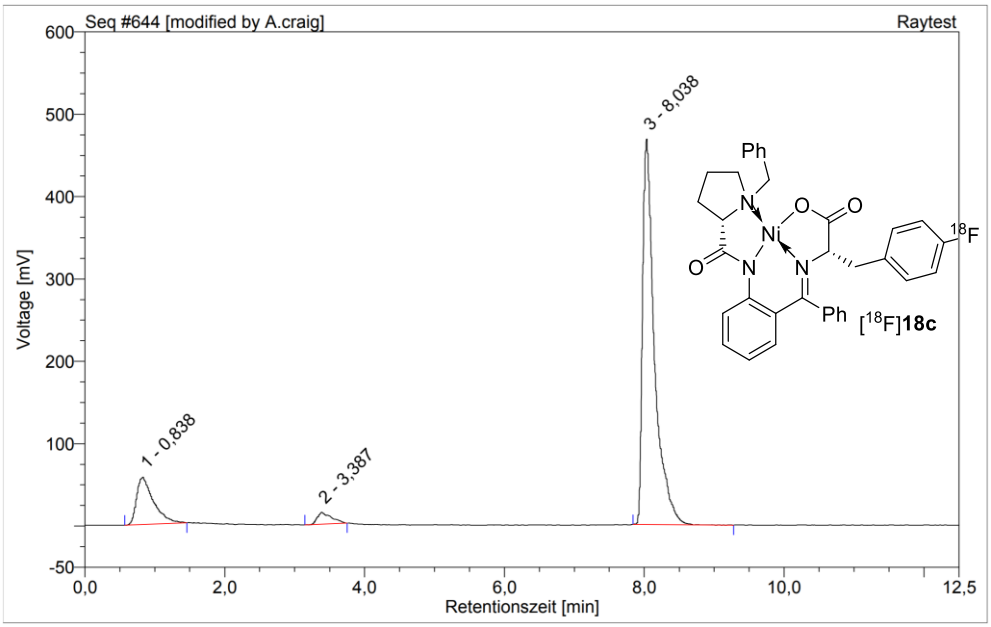
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,81	1,965	2,76
2	8,07	67,890	97,24
Total:		69,855	100,00

[^{18}F]18b (Gradient A1)



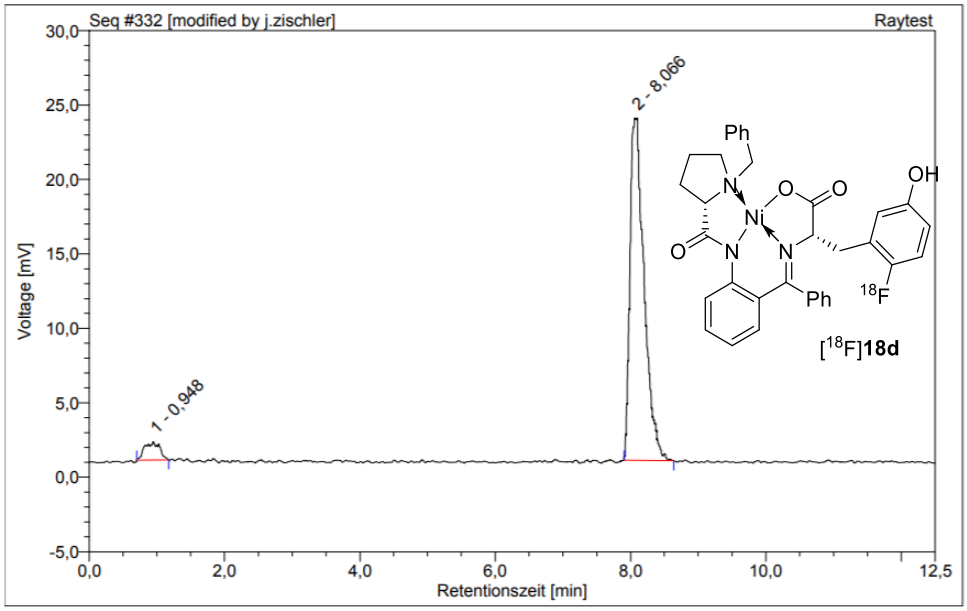
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,68	9,128	9,45
2	7,97	91,921	90,55
Total:		101,048	100,00

[^{18}F]18c (Gradient A1)



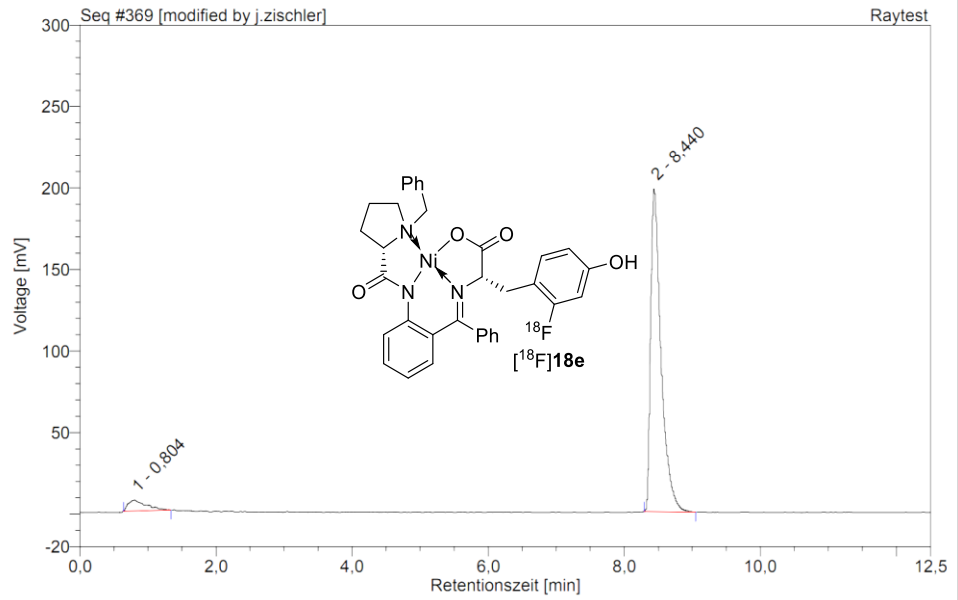
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,84	57,485	14,38
2	3,39	14,358	2,94
3	8,04	468,332	82,68
Total:		540,175	100,00

[^{18}F]18d (Gradient A1)



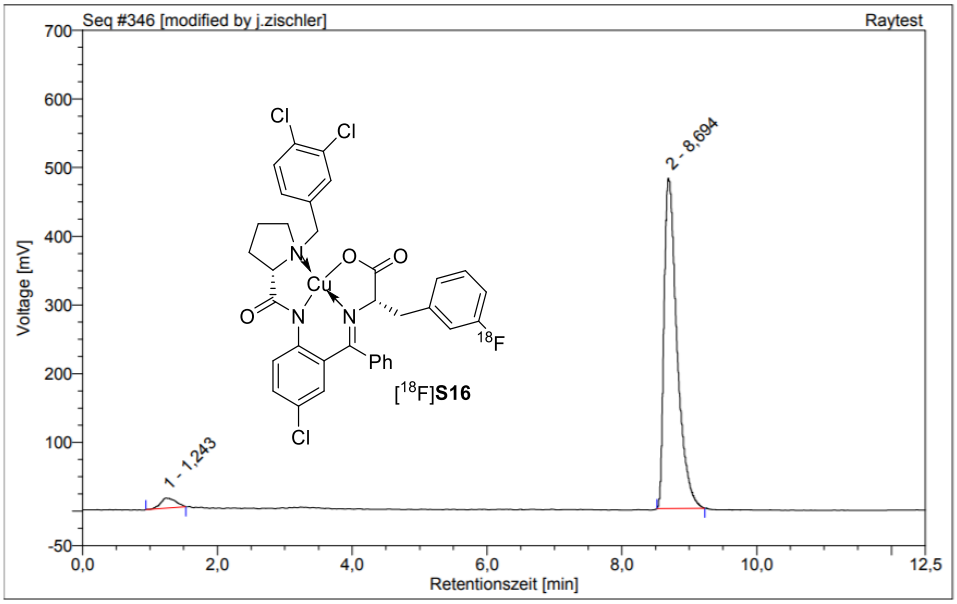
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,95	1,222	5,28
2	8,07	22,987	94,72
Total:		24,209	100,00

[^{18}F]18e (Gradient A1)



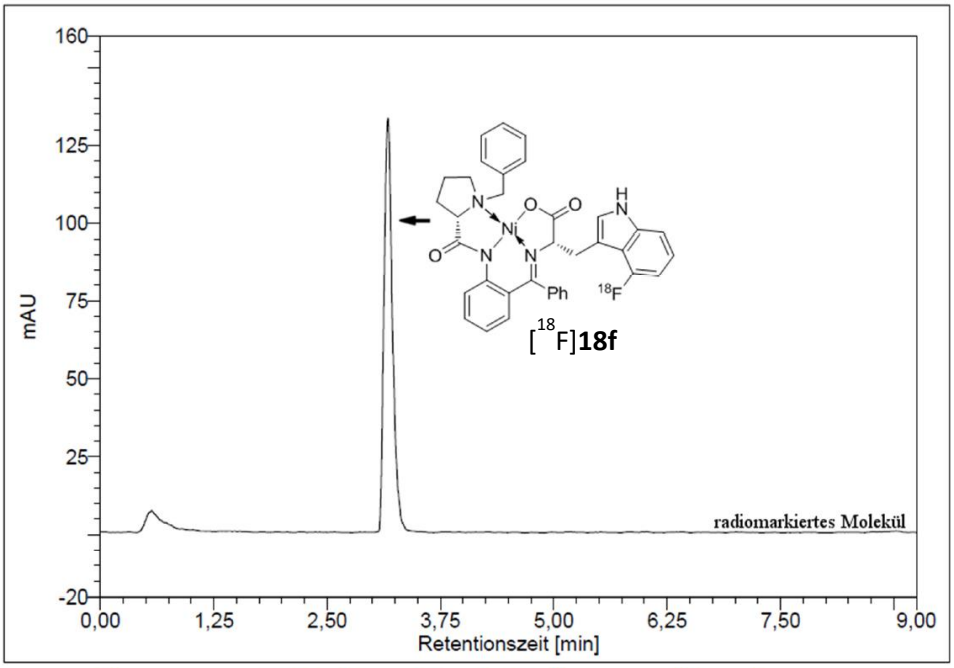
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,80	6,724	5,48
2	8,44	198,105	94,52
Total:		204,829	100,00

[^{18}F]S16 (Gradient A1)



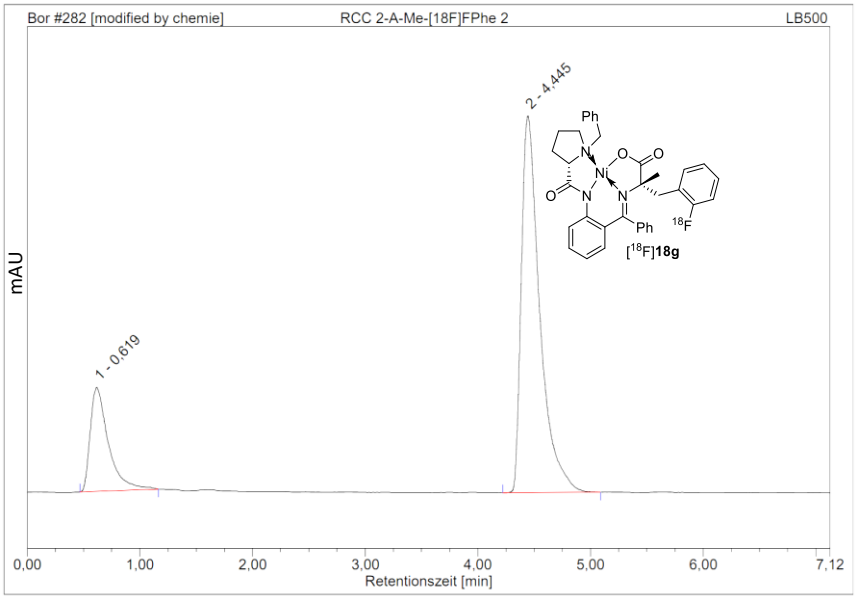
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	1,24	14,748	3,41
2	8,69	480,914	96,59
Total:		495,662	100,00

[^{18}F]18f (Gradient A2)



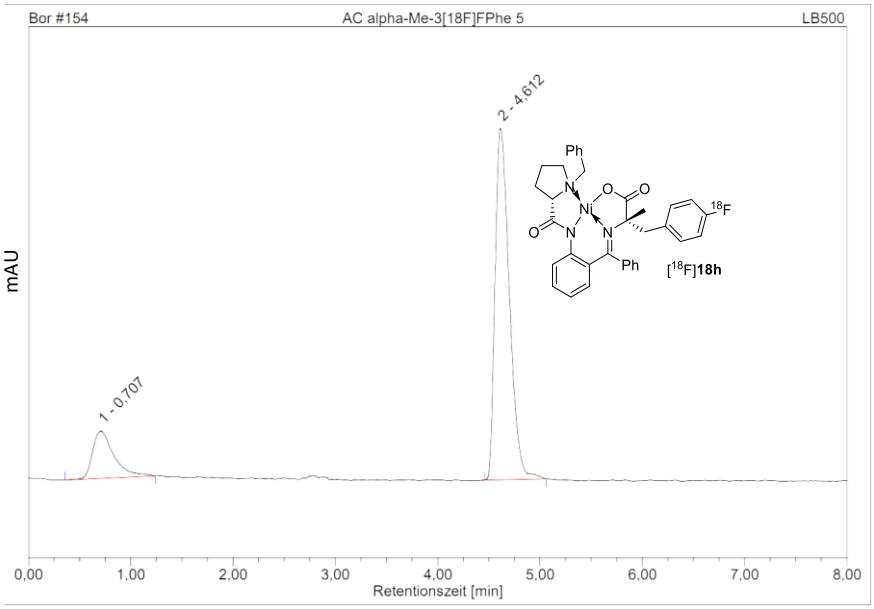
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,57	5,813	6,39
2	3,17	132,733	93,61
Total:		138,546	100,00

[^{18}F]18g (Gradient A1)



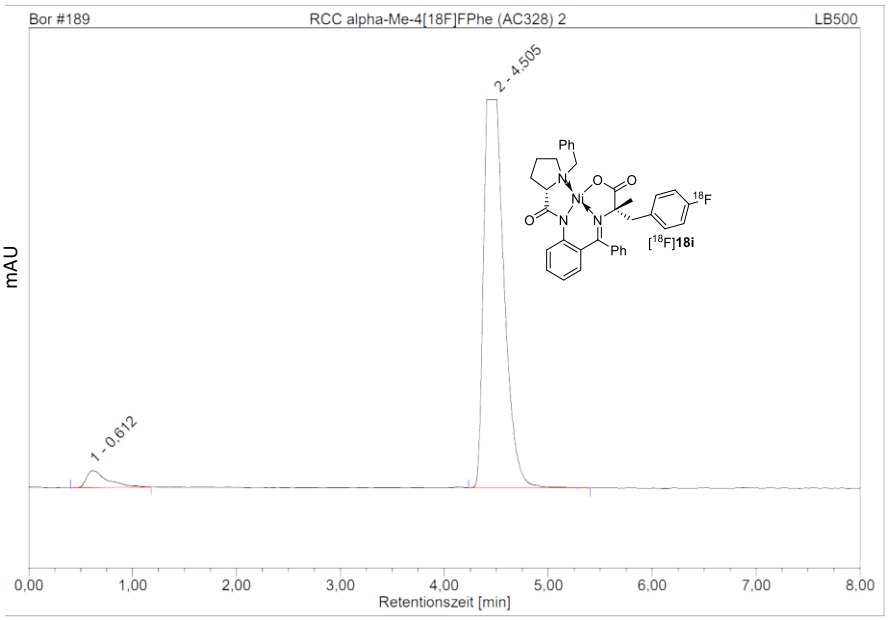
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,62	198,870	21,28
2	4,45	722,458	78,72
Total:		921,328	100,00

[^{18}F]18h (Gradient A1)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,71	71,571	16,76
2	4,61	529,945	83,24
Total:		601,516	100,00

[^{18}F]18i (Gradient A1)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	0,61	44,688	4,31
2	4,50	1006,396	95,69
Total:		1051,084	100,00

Deprotection Optimization

The deprotection step was optimized with respect to time, temperature and HCl concentration. It was found that 12 M HCl (1 mL) at 110 °C for 15 min provided the highest deprotection yield (Figure S4). Exceeding any of these parameters usually resulted in the loss of product or infeasibility of the procedure towards automated module implementation.

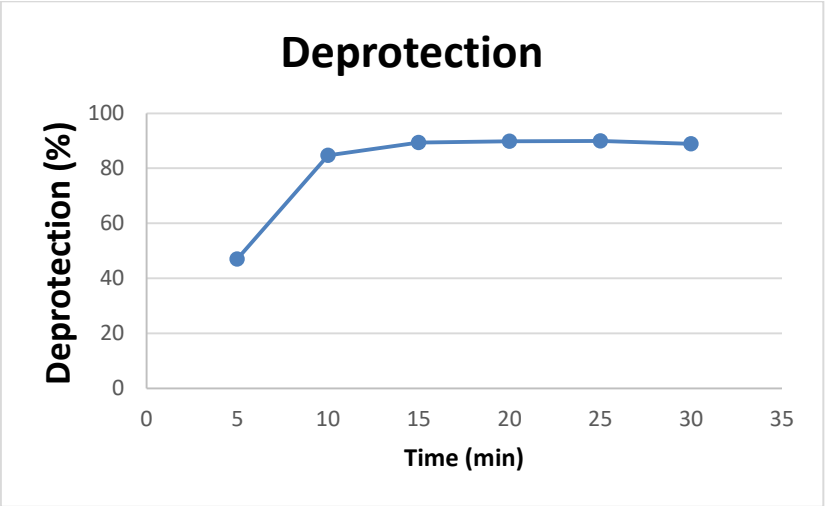
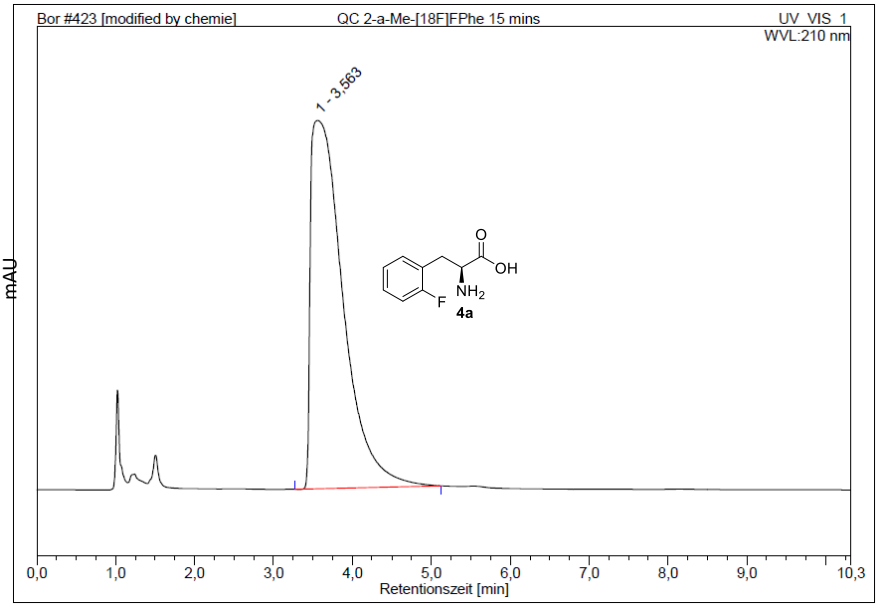


Figure S4. Deprotection of Cu/Ni-BPB-AAA at 110 °C.

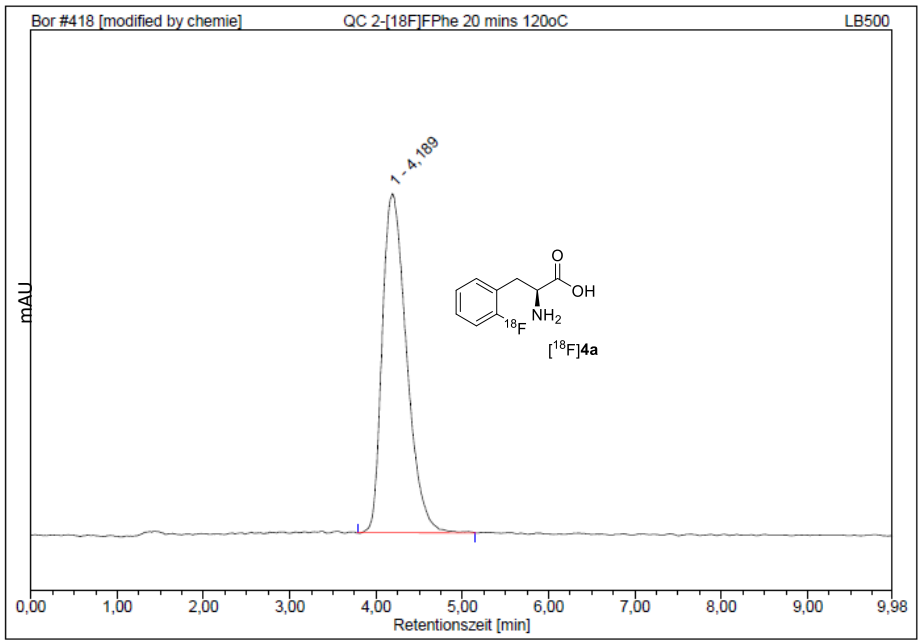
Quality Control of Products

2-FPhe (4a) (Gradient B1)



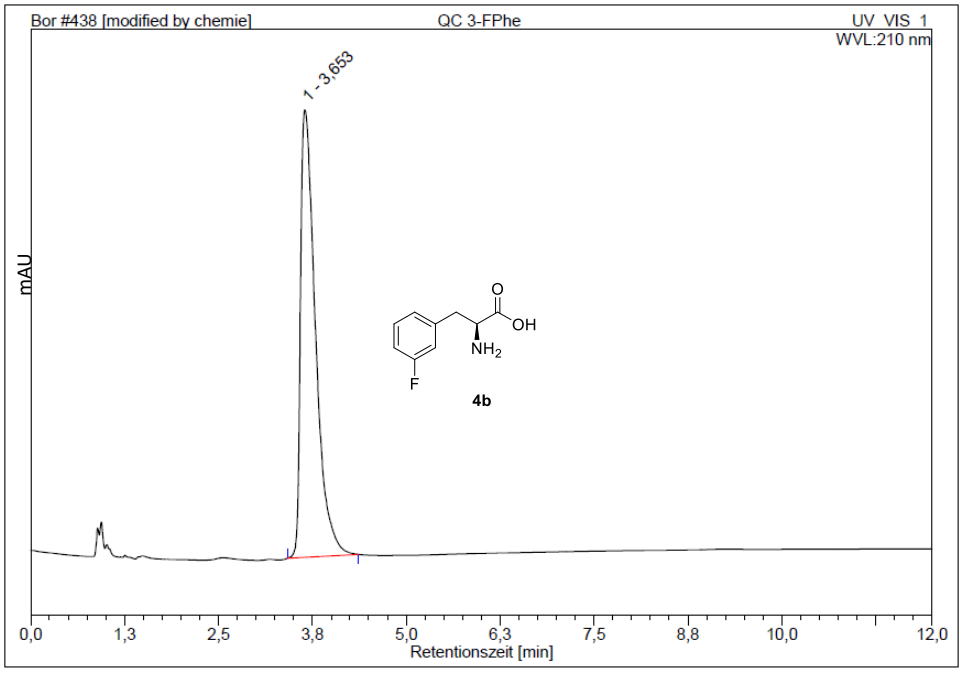
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	3,56	2782,507	100,00
Total:		2782,507	100,00

2-[^{18}F]FPhe ([^{18}F]4a) (Gradient B1)



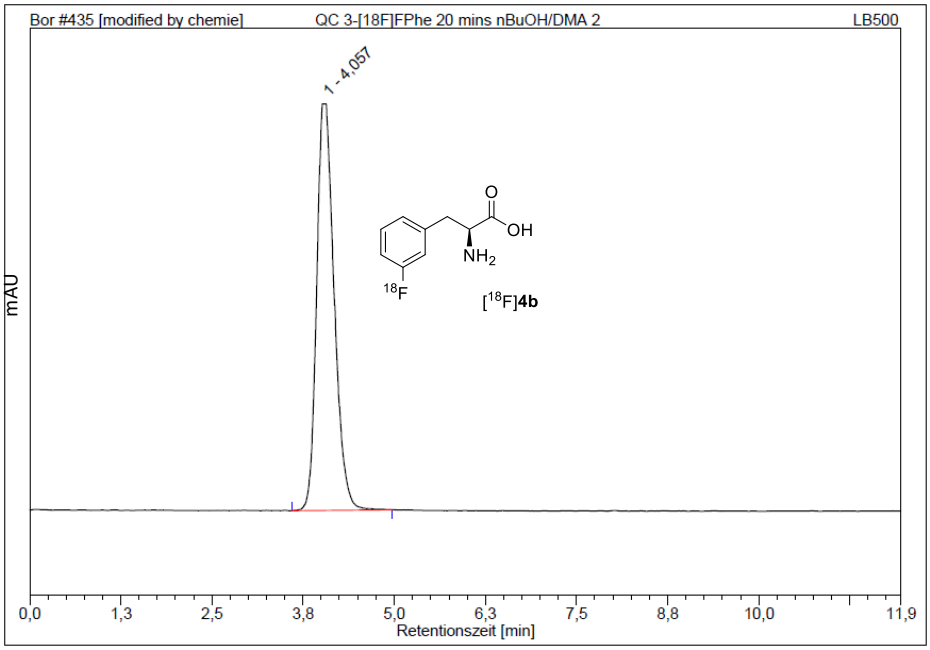
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,19	163,696	100,00
Total:		163,696	100,00

3-FPhe (4b) (Gradient B1)



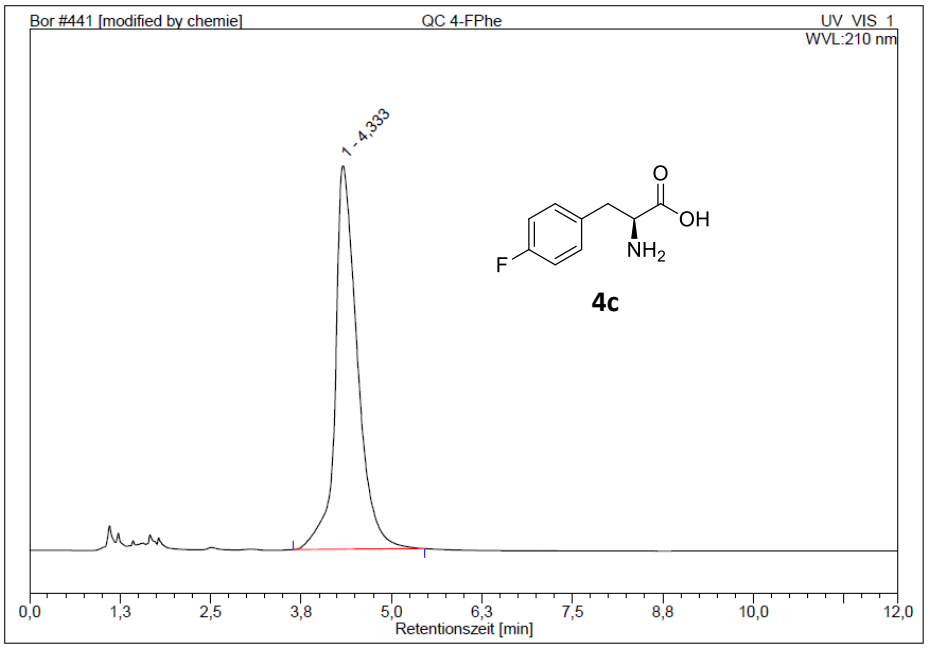
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	3,65	687,692	100,00
Total:		687,692	100,00

3-[^{18}F]FPhe ([^{18}F]4b) (Gradient B1)



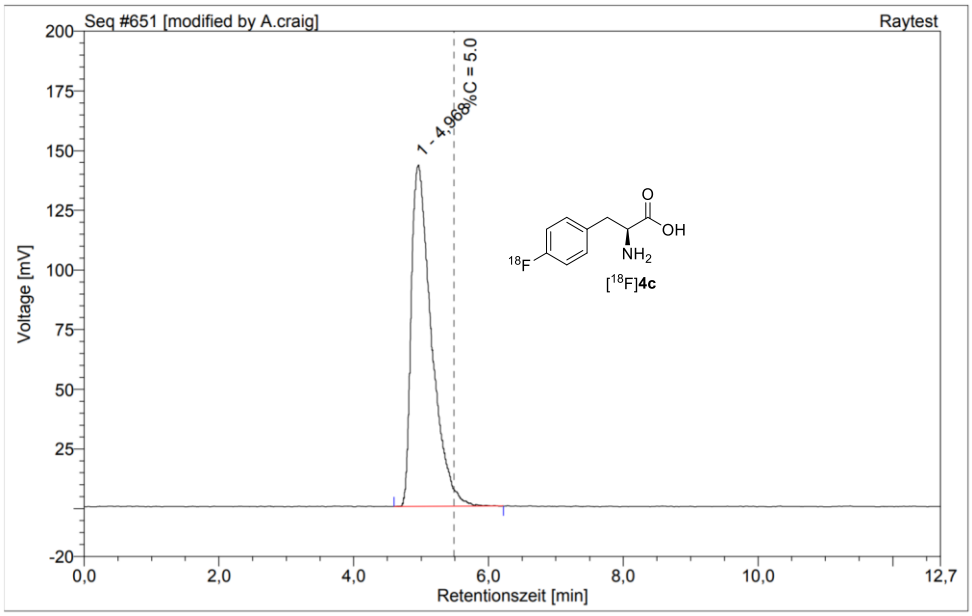
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,06	1004,256	100,00
Total:		1004,256	100,00

4-FPhe (4c) (Gradient B1)



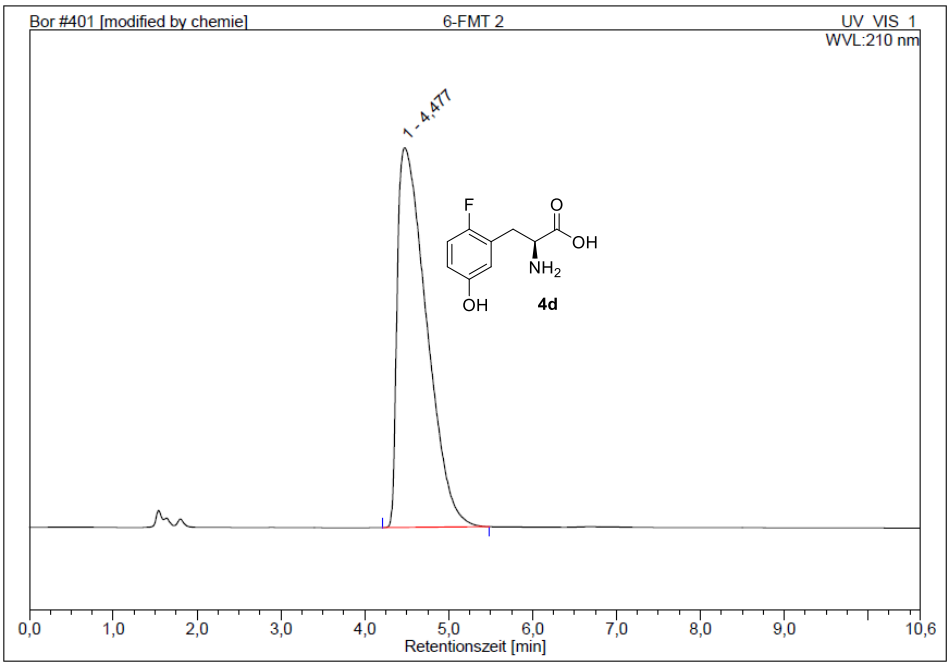
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,33	441,810	100,00
Total:		441,810	100,00

4-[^{18}F]FPhe ([^{18}F]4c) (Gradient B1)



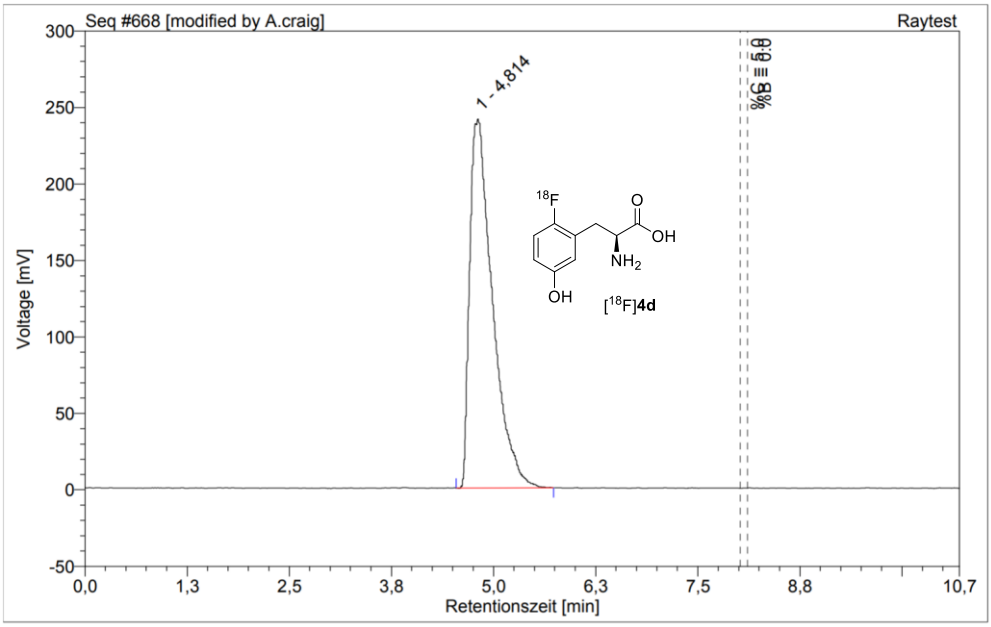
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,97	143,092	100,00
Total:		143,092	100,00

6-FMT (4d) (Gradient B2)



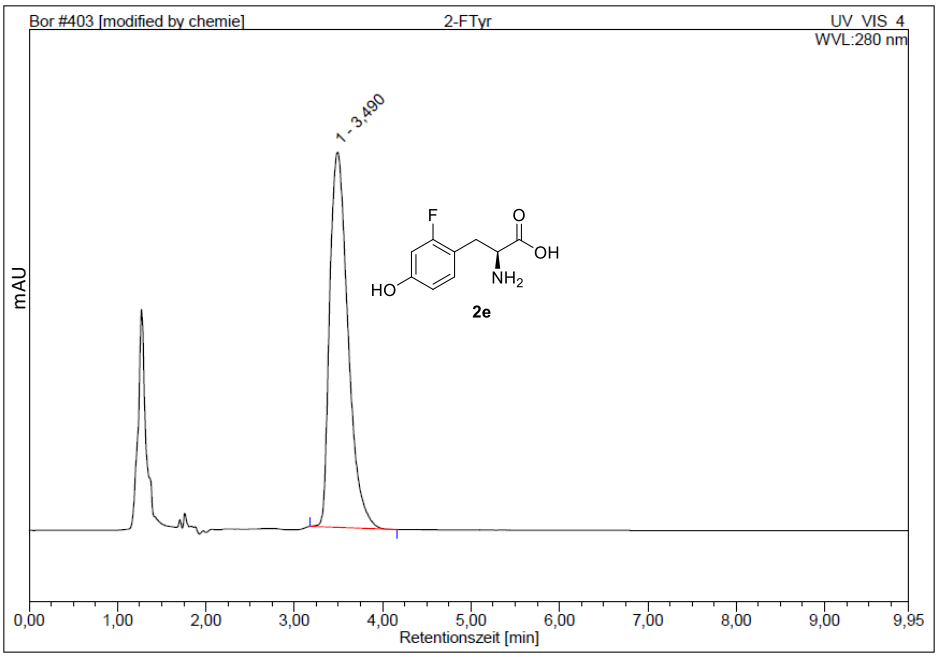
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,48	2291,784	100,00
Total:		2291,784	100,00

6-[^{18}F]FMT ([^{18}F]4d) (Gradient B2)



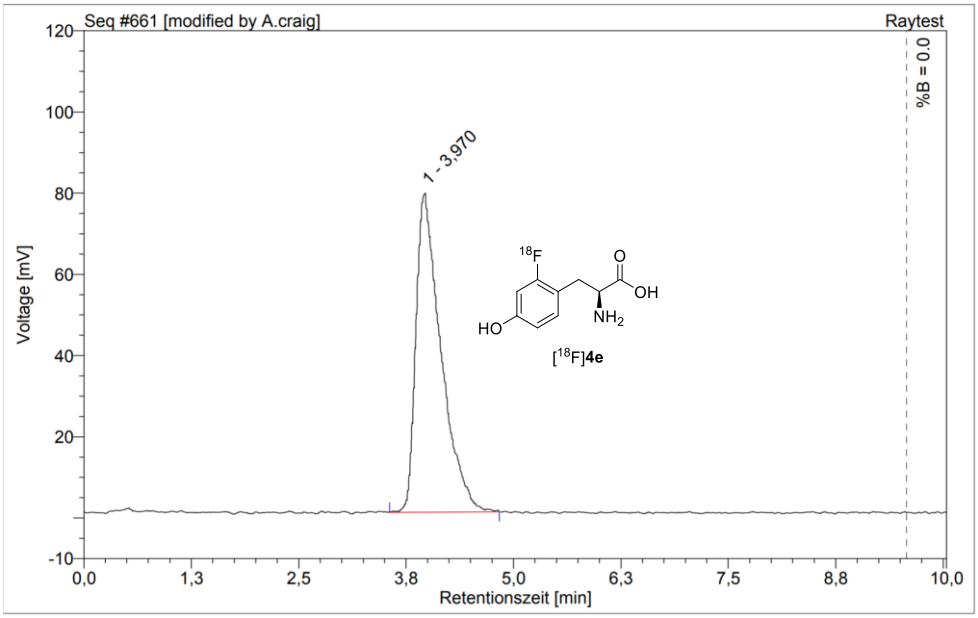
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,81	241,305	100,00
Total:		241,305	100,00

2-FTyr (2e) (Gradient B2)



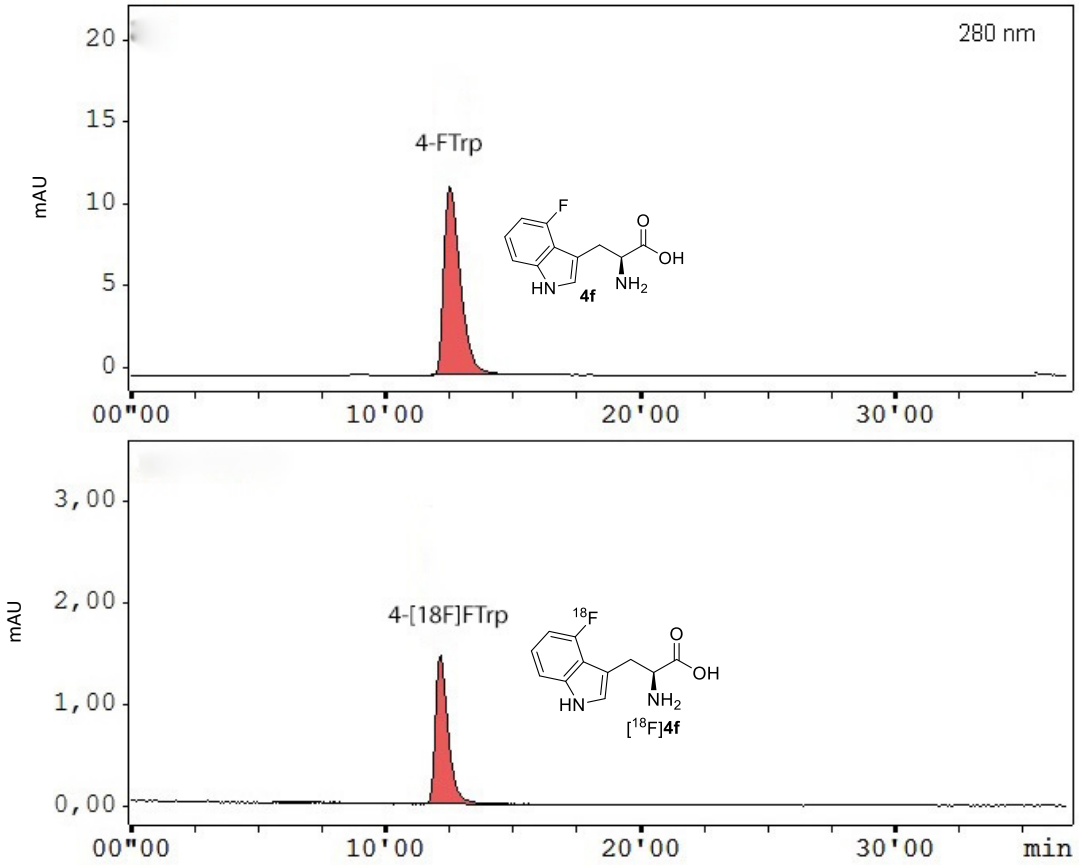
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	3,49	104,956	100,00
Total:		104,956	100,00

2-[^{18}F]FTyr ([^{18}F]4e) (Gradient B2)

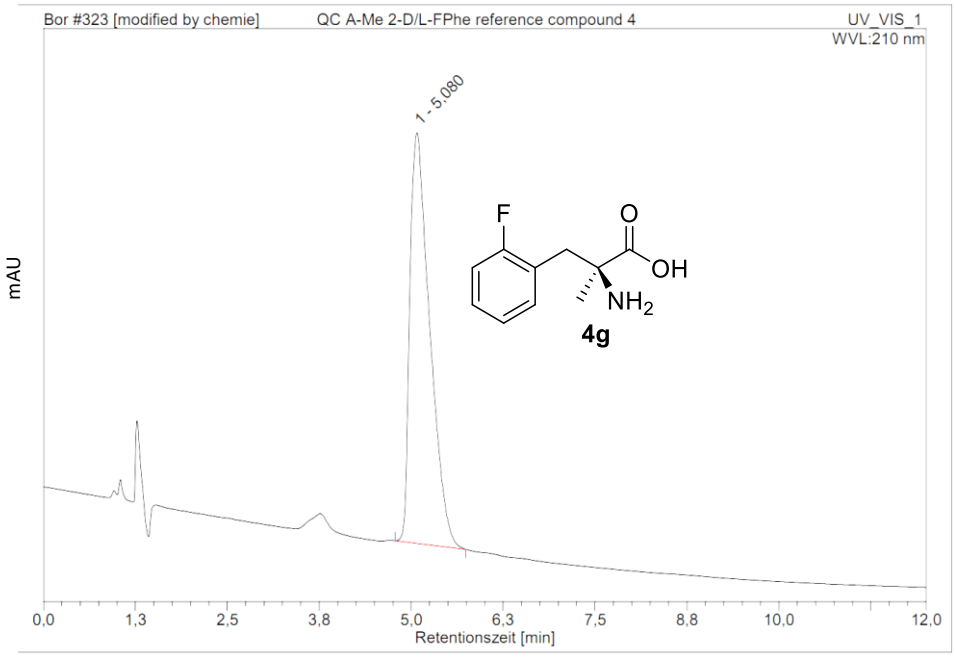


Nr.	Retentionszeit min	Intensität mAU	Integral %
1	3,97	78,543	100,00
Total:		78,543	100,00

4-FTrp (4f) and 4-[^{18}F]FTrp ([^{18}F]4f) (Gradient B3)

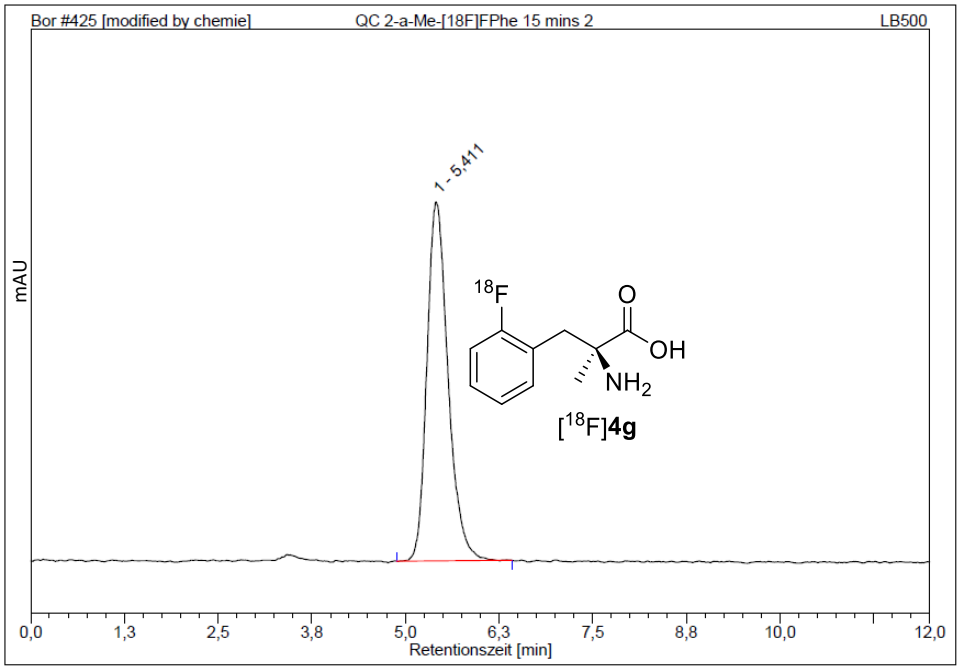


α-Methyl-2-FPhe (4g) (Gradient B1)



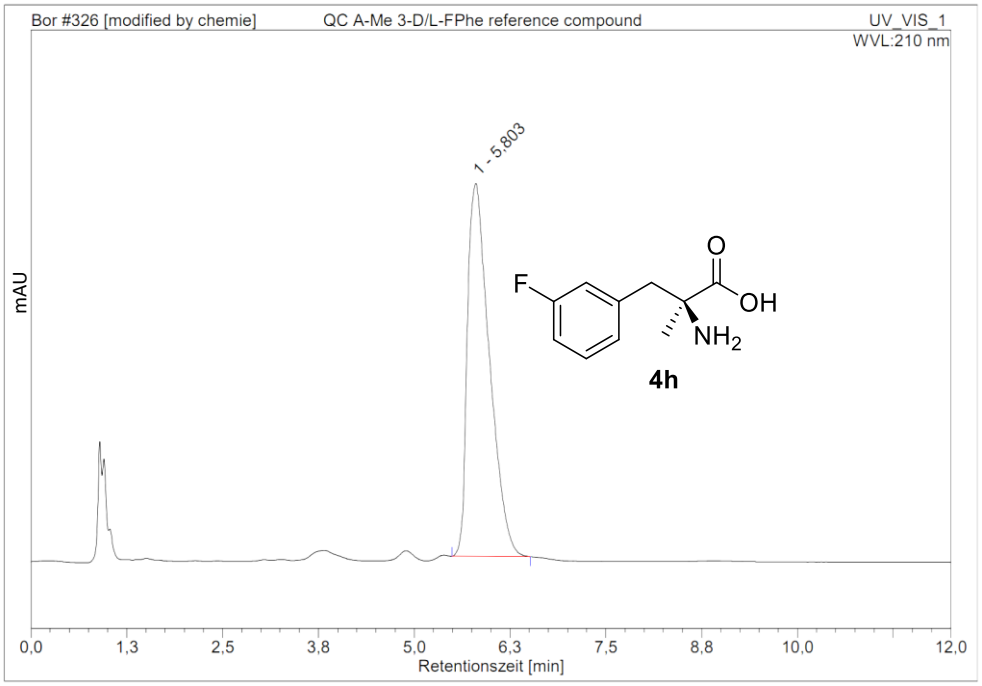
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,08	358,252	100,00
Total:		358,252	100,00

α-Methyl-2-[^{18}F]FPhe ([^{18}F]4g) (Gradient B1)



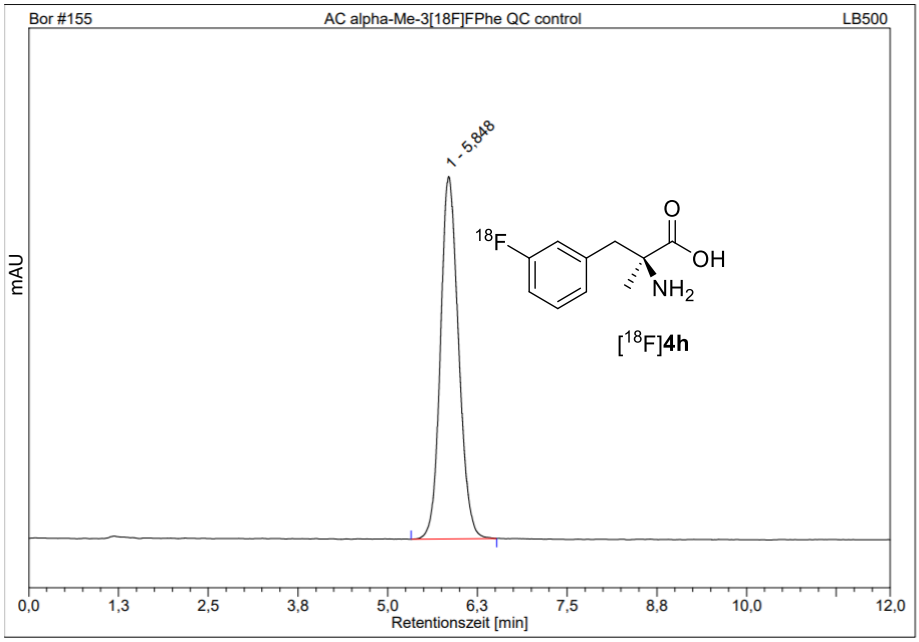
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,41	196,987	100,00
Total:		196,987	100,00

α-Methyl-3-FPhe (4h) (Gradient B1)



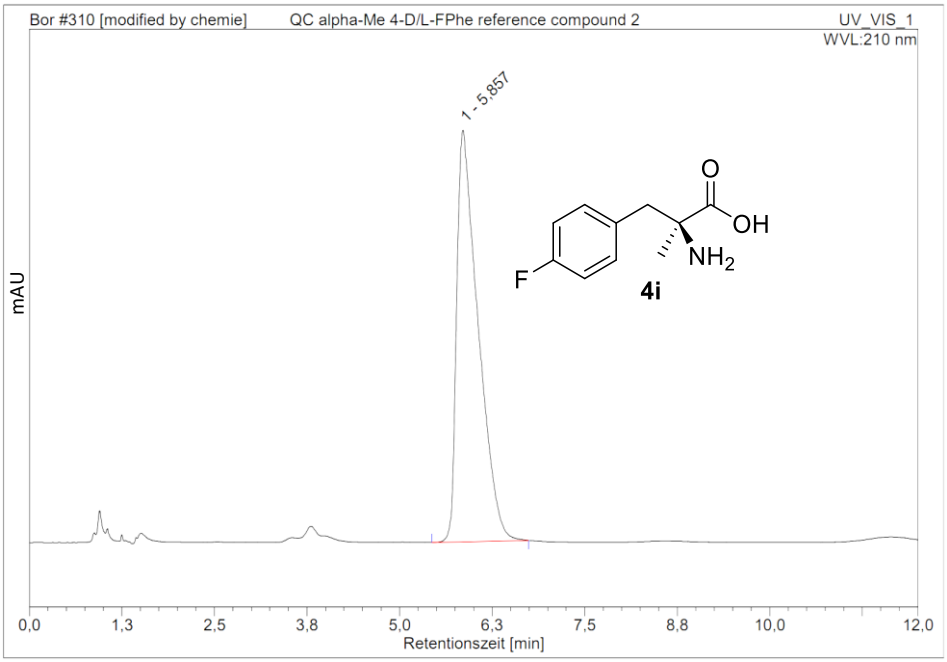
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,80	280,639	100,00
Total:		280,639	100,00

α-Methyl-3-[^{18}F]FPhe ([^{18}F]4h) (Gradient B1)



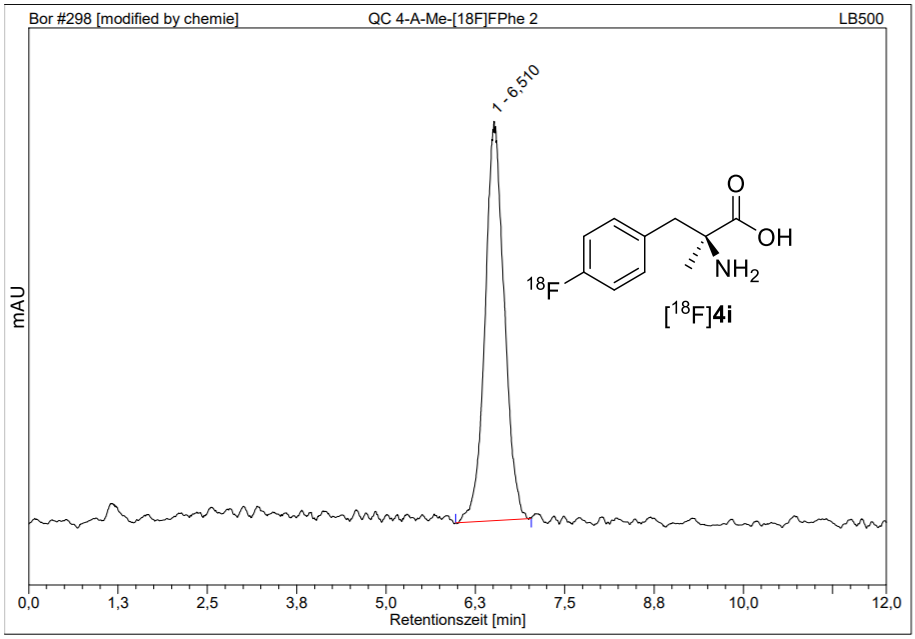
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,85	842,027	100,00
Total:		842,027	100,00

α-Methyl-4-FPhe (4i) (Gradient B1)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,86	320,770	100,00
Total:		320,770	100,00

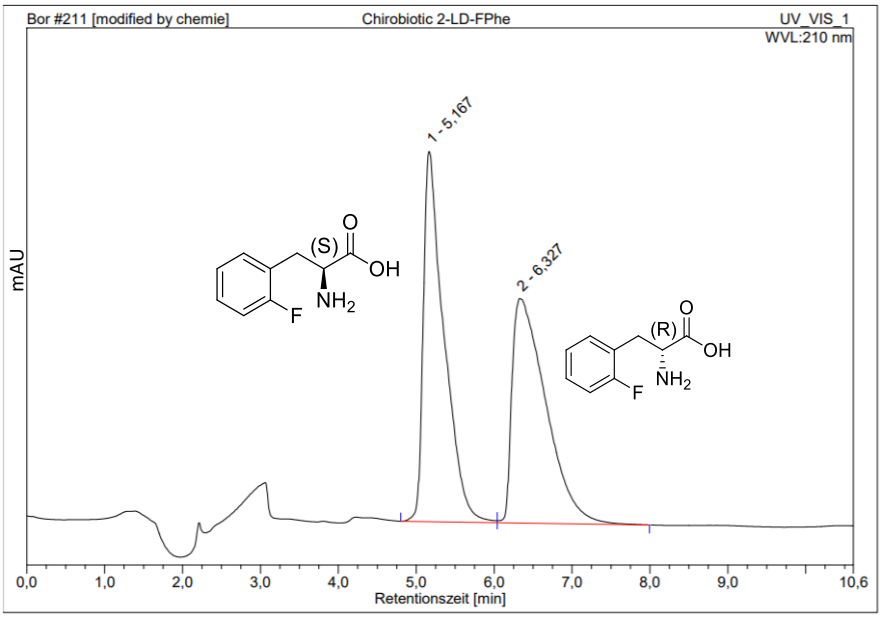
α-Methyl-4-[^{18}F]FPhe ([^{18}F]4i) (Gradient B1)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	6,51	35,846	100,00
Total:		35,846	100,00

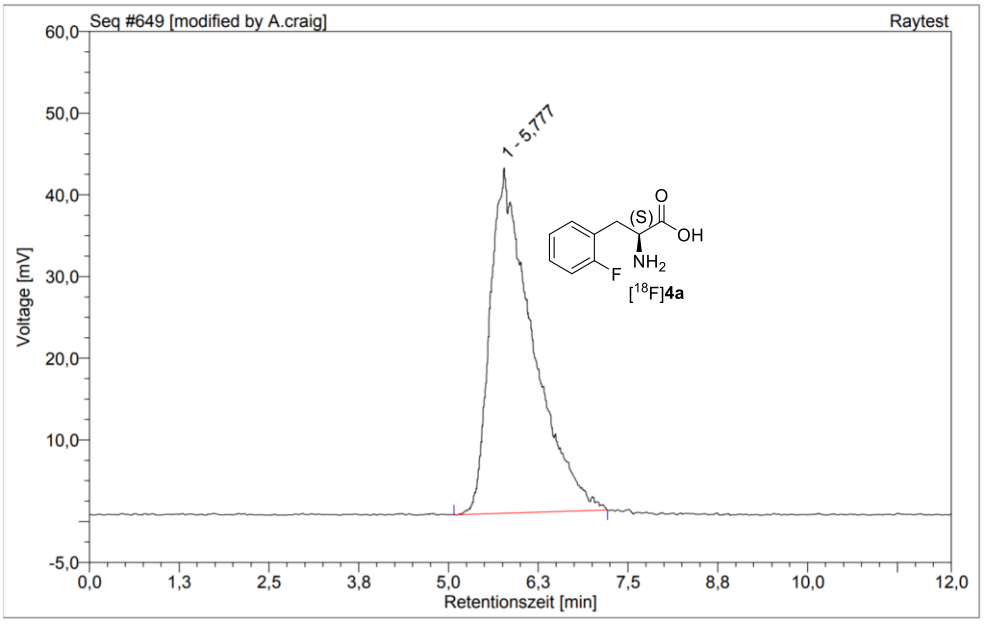
Determination of Enantiomeric Excess for AAA PET tracers

rac-2-FPhe (Gradient C)



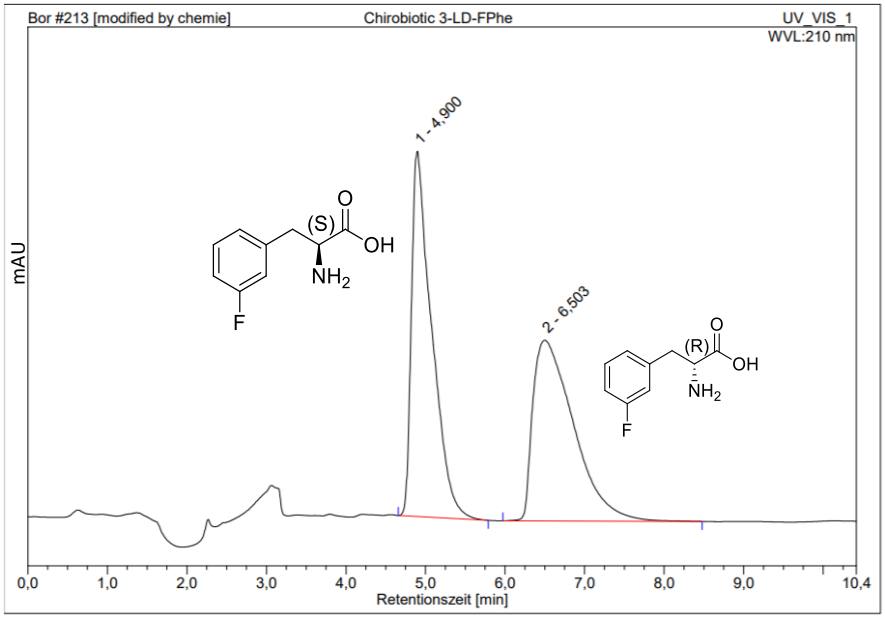
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,17	379,213	50,19
2	6,33	230,063	49,81
Total:		609,276	100,00

2-[^{18}F]FPhe ([^{18}F]4a) (Gradient C)



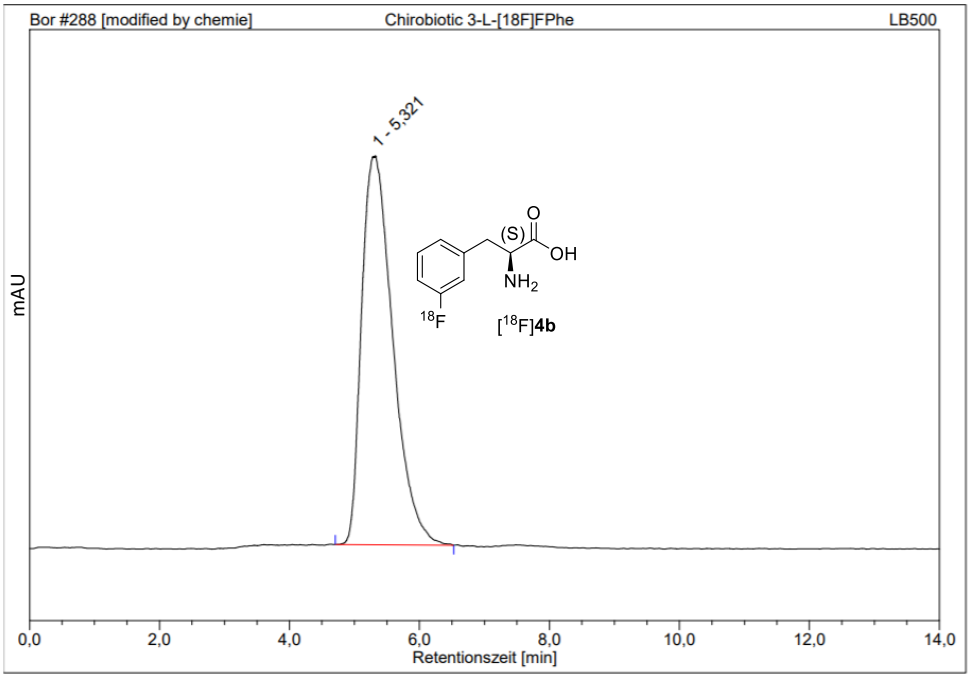
Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,78	42,251	100,00
Total:		42,251	100,00

rac-3-FPhe (Gradient C)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	4,90	373,068	50,00
2	6,50	184,506	50,00
Total:		557,574	100,00

3-[^{18}F]FPhe ([^{18}F]4b) (Gradient C)



Nr.	Retentionszeit min	Intensität mAU	Integral %
1	5,32	592,219	100,00
Total:		592,219	100,00

General Procedure for determination of carrier amount and molar activity (GP 6)

An aliquot of the tracer obtained after HPLC purification was set aside for 24 h and thereafter concentrated under reduced pressure. The residue was re-dissolved in 10% MeOH (0.1% TFA) and completely injected into the HPLC system. The peak area was determined and the carrier amount[18] as well as the molar activity were calculated according to the calibration curves (λ=210 nm, Fig. S5–S9).

Tracer	Carrier amount (nmol/batch)	Molar activity (GBq/µmol)	Tracer amount (GBq)
3-[^{18}F]FPhe	27.3	4.6	0.127
3-[^{18}F]FPhe	14.4	76.3	1.1
3-[^{18}F]FPhe	7.5	252.1	1.9
4-[^{18}F]FPhe	6.2	29.1	0.179
2-αMe-[^{18}F]FPhe	43.7	3.23	0.14
3-αMe-[^{18}F]FPhe	8.2	61.2	0.5
3-αMe-[^{18}F]FPhe	42.3	33.1	1.4
4-αMe-[^{18}F]FPhe	164.2	2.0	0.33

*Table S4. Carrier amounts and molar activities for [^{18}F]**4b,c** and [^{18}F]**4g–i**.*

Determination of specific activity and carrier amount for 3-[^{18}F]FPhe ([^{18}F]**4b**).

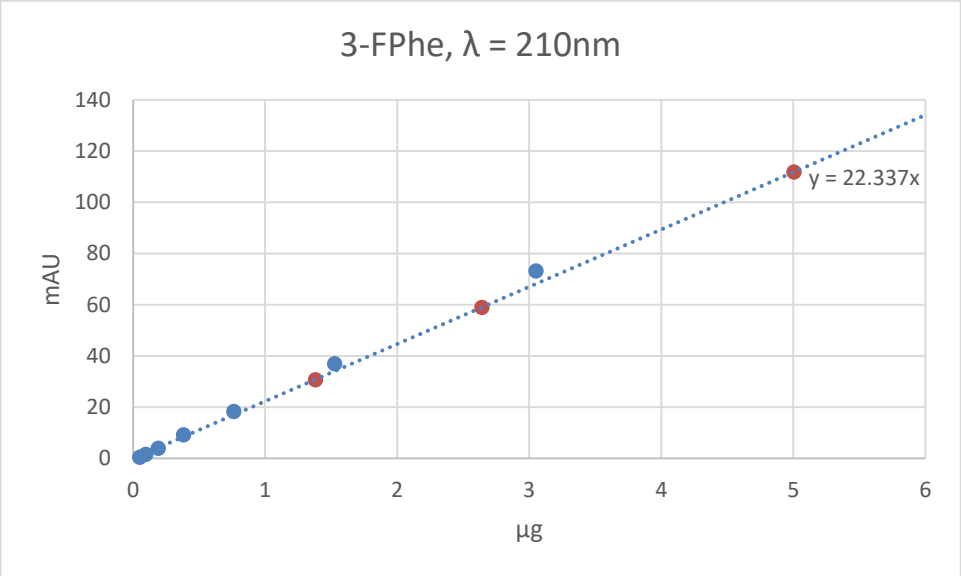


*Figure S5. Calibration curve for 3-FPhe (**4b**). Blue points: calibration points; peak areas in mAU which correspond to definite masses of 3-FPhe (Y and X values, respectively), red points; peak areas in mAU which correspond to masses of 3-FPhe in the whole batches.*

Sample 1: 42 MBq aliquot was taken from 127 MBq batch of the tracer.

Peak area of the 3-FPhe peak in the injected aliquot: 37.27 mAU.

Mass of injected 3-FPhe: 1.67 µg.

3-FPhe in the whole batch: 5.01 µg.

Mr(3-FPhe) = 183.18 Da.

Carrier amount: 27.3 nmol/batch

Molar activity: 4.6 GBq/µmol.

Sample 2: 0.2 GBq aliquot was taken from 1.1 GBq batch of the tracer.

Peak area of the 3-FPhe peak in the injected aliquot: 10.7 mAU.

Mass of injected 3-FPhe: 0.48 µg.

3-FPhe in the whole batch: 2.64 µg.

Carrier amount: 14.4 nmol/batch

Molar activity: 76.3 GBq/µmol.

Sample 3: 0.25 GBq aliquot was taken from 1.9 GBq batch of the tracer.

Peak area of the 3-FPhe peak in the injected aliquot: 4.1 mAU.

Mass of injected 3-FPhe: 0.18 µg.

3-FPhe in the whole batch: 1.38 µg.

Carrier amount: 7.5 nmol/batch

Molar activity: 252.1 GBq/µmol.

Determination of specific activity and carrier amount for 4-[^{18}F]FPhe ([^{18}F]**4c**).

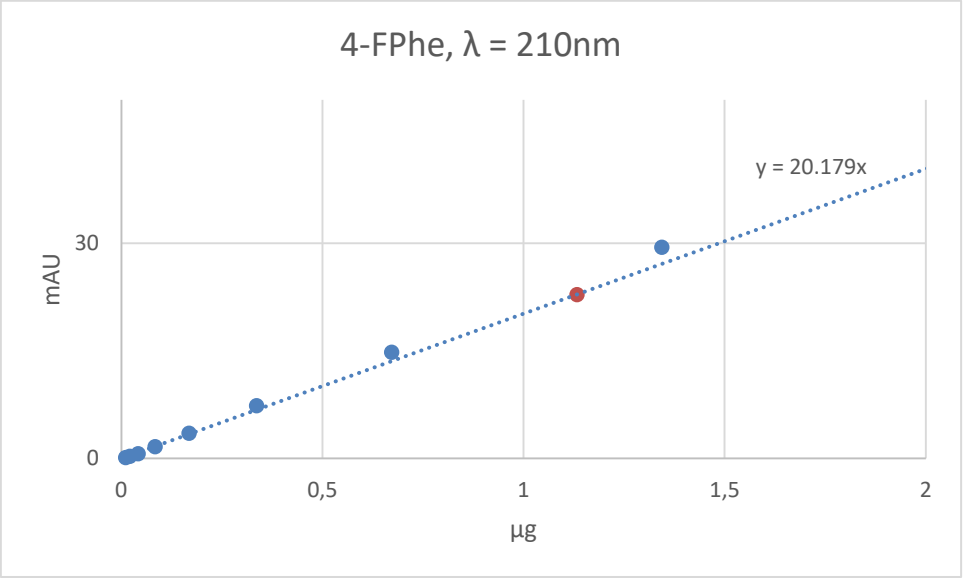


*Figure S6. Calibration curve for 4-FPhe (**4b**). Blue points: calibration points; peak areas in mAU which correspond to definite masses of 4-FPhe (Y and X values, respectively), red points; peak areas in mAU which correspond to mass of 4-FPhe in the whole batch.*

Sample: 60 MBq aliquot was taken from 179 MBq batch of the tracer.

Peak area of the 4-FPhe peak in the injected aliquot: 7.62 mAU.

Mass of injected 4-FPhe: 0.38 µg.

4-FPhe in the whole batch: 1.13 µg.

Mr(4-FPhe) = 183.18 Da.

Carrier amount: 6.2 nmol/batch

Molar activity: 29.1 GBq/µmol.

Determination of specific activity and carrier amount for αMe-2-[^{18}F]FPhe ([^{18}F]**4g**).

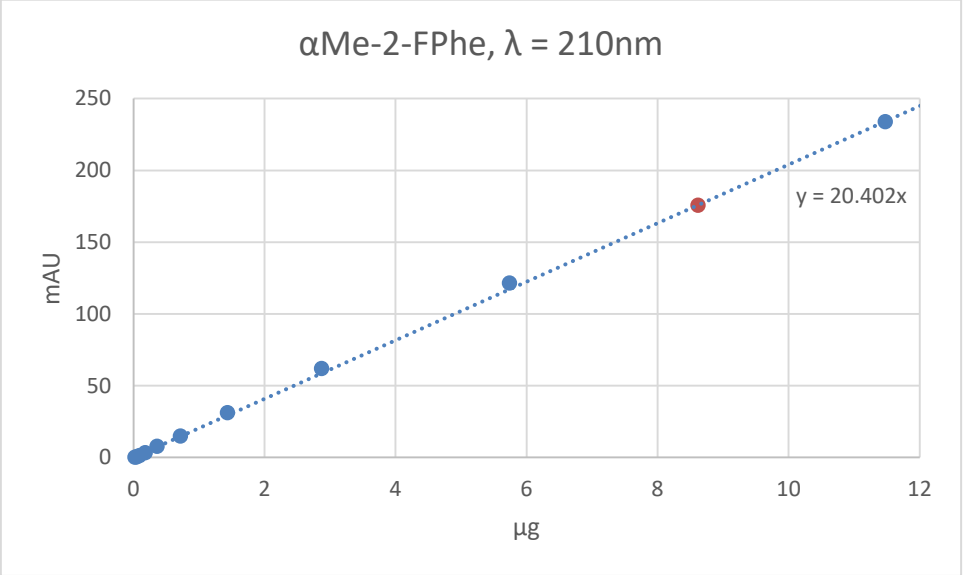


Figure S7. Calibration curve for αMe-2-FPhe ***(4g)****. Blue points: calibration points; peak areas in mAU which correspond to definite masses of αMe-2-FPhe (Y and X values, respectively), red points; peak areas in mAU which correspond to mass of αMe-2-FPhe in the whole batch.*

Sample: 47 MBq aliquot was taken from 140 MBq batch of the tracer.

Peak area of the αMe-2-FPhe peak in the injected aliquot: 58.6 mAU.

Mass of injected αMe-2-FPhe: 2.87 µg.

αMe-2-FPhe in the whole batch: 8.62 µg.

Mr(αMe-2-FPhe) = 197.21 Da.

Carrier amount: 43.7 nmol/batch

Molar activity: 3.23 GBq/µmol.

Determination of specific activity and carrier amount for αMe-3-[^{18}F]FPhe ([^{18}F]**4h**).

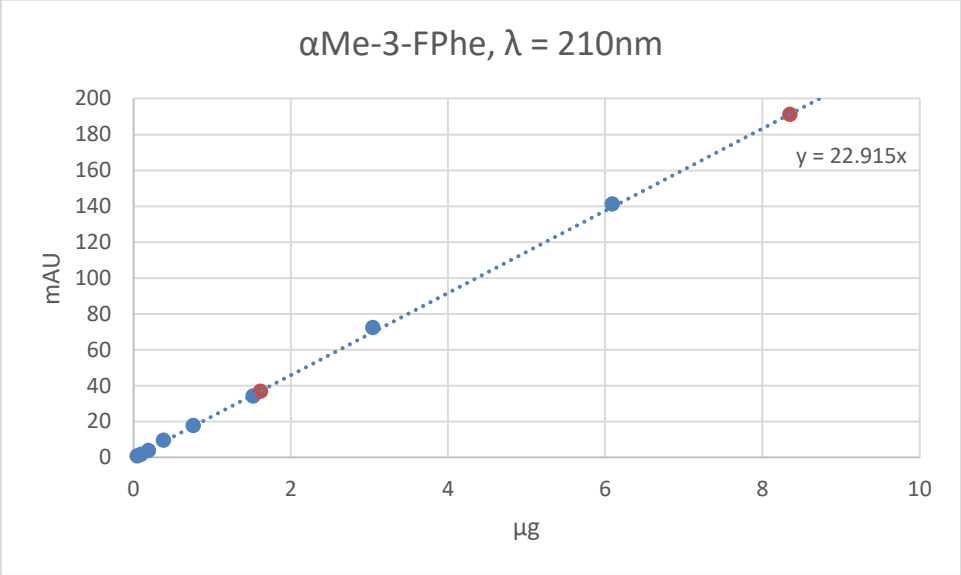


Figure S8. Calibration curve for αMe-3-FPhe ***(4h)****. Blue points: calibration points; peak areas in mAU which correspond to definite masses of αMe-3-FPhe (Y and X values, respectively), red points; peak areas in mAU which correspond to masses of αMe-3-FPhe in the whole batches.*

Sample 1: 167 MBq aliquot was taken from 500 MBq batch of the tracer.

Peak area of the αMe-3-FPhe peak in the injected aliquot: 12.3 mAU.

Mass of injected αMe-3-FPhe: 0.54 μg.

αMe-3-FPhe in the whole batch: 1.61 μg.

Mr(αMe-3-FPhe) = 197.21 Da.

Carrier amount: 8.2 nmol/batch

Molar activity: 61.2 GBq/μmol.

Sample 2: 0.2 GBq aliquot was taken from 1.4 GBq batch of the tracer.

Peak area of the αMe-3-FPhe peak in the injected aliquot: 27.3 mAU.

Mass of injected αMe-3-FPhe: 1.16 μg.

αMe-3-FPhe in the whole batch: 8.35 μg.

Carrier amount: 42.3 nmol/batch

Molar activity: 33.1 GBq/μmol.

Determination of specific activity and carrier amount for αMe-4-[^{18}F]FPhe ([^{18}F]**4i**).

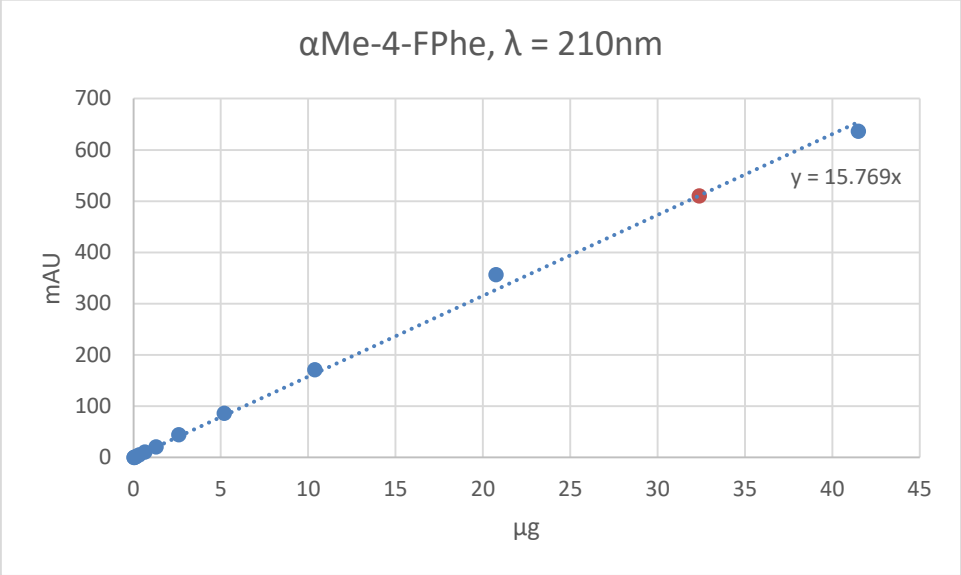


Figure S9. Calibration curve for αMe-4-FPhe ***(4i)****. Blue points: calibration points; peak areas in mAU which correspond to definite masses of αMe-4-FPhe (Y and X values, respectively), red points; peak areas in mAU which correspond to mass of αMe-3-FPhe in the whole batch.*

Sample 1: 110 MBq aliquot was taken from 330 MBq batch of the tracer.

Peak area of the αMe-4-FPhe peak in the injected aliquot: 170.2 mAU.

Mass of injected αMe-4-FPhe: 10.79 µg.

αMe-4-FPhe in the whole batch: 32.38 µg.

Mr(αMe-4-FPhe) = 197.21 Da.

Carrier amount: 164.2 nmol/batch

Molar activity: 2.0 GBq/µmol.

Induced-Coupled Plasma Mass Spectrometry Results

Sample	Ni		Cu	
	Mean [mg/L]	Amount per product batch (mg)	Mean [mg/L]	Amount per product batch (mg)
2-[^{18}F]FPhe	0.125	0.004	0.703	0.021
3-[^{18}F]FPhe	0.215	0.006	1.803	0.054
4-[^{18}F]FPhe	0.041	0.001	0.82	0.024
2-[^{18}F]FTyr	2.016	0.060	4.413	0.013
6-[^{18}F]FMT	27.4	0.082	84.6	0.2538
αMe-2-[^{18}F]FPhe	0.845	0.025	1.213	0.036
αMe-3-[^{18}F]FPhe	9.42	0.028	15	0.045
αMe-4-[^{18}F]FPhe	58.3	0.1749	124	0.372
3-[^{18}F]FPhe*	-	-	0.248	0.007

***Prepared via **19**.

Table S5. Induced-Coupled Plasma Mass Spectrometry results.

In vitro experiments

General Information

MDA-MB-231

MDA-MB-231 cells were purchased from the Leibniz-Institute DSMZ (German Collection of Microorganisms and Cell Cultures GmbH) and cultured in a mixture Dulbecco's modified Eagle's medium (DMEM)/Ham's F12 medium (1:1) supplemented with L-glutamine (2 mM), FBS (10%), and penicillin/streptomycin (1%).

MCF-7

Human breast adenocarcinoma MCF-7 cells were purchased from the Leibniz-Institute DSMZ (German Collection of Microorganisms and Cell Cultures GmbH) and cultured in minimum essential medium (Gibco, 41090028) supplemented with 10% fetal bovine serum (Sigma Aldrich F 2442), 100 U/ml penicillin/streptomycin (Gibco 15140122), 1% sodium pyruvate (Gibco 11360070), 1% non-essential amino acid and 10 µg/mL human insulin at 37°C in a humidified atmosphere of 5% CO_2 in air.

PC-3

Human prostate carcinoma PC-3 cells were purchased from the Leibniz-Institute DSMZ (German Collection of Microorganisms and Cell Cultures GmbH) and cultured in F-12 K Nutrit Mix Medium (Gibco, 21127022) supplemented with 10% fetal bovine serum (Sigma Aldrich F 2442) and 100 U/ml penicillin/streptomycin (Gibco 15140122) at 37 °C in a humidified atmosphere of 5% CO_2 in air.

HD-MB03

Human medulloblastoma HD-MB03 cells were purchased from the Leibniz-Institute DSMZ (German Collection of Microorganisms and Cell Cultures GmbH) and cultured in RPMI 1640 Medium (Gibco, 6187010) supplemented with 10% fetal bovine serum (Sigma Aldrich F 2442), 100 U/ml penicillin/streptomycin (Gibco 15140122) and 1 % non-essential amino acid at 37 °C in a humidified atmosphere of 5% CO_2 in air.

Cellular uptake studies

Cells were used in their exponential growth phase. 48 hours prior to the start of the uptake studies the cells were seeded to obtain a cell density of 2.5×10^5 cells per vial. The culture medium was then replaced by an incubation medium. Cell viability assays were performed

according to a standard protocol using trypan blue (95% of cells vital). The incubation medium was aspirated and cells were incubated with 1 mL of radiotracer containing medium (150 µCi radiotracer/mL medium) each for 20, 40, 60, 80, 100 and 120 minutes at 37 °C in a humidified atmosphere of 5% CO_2 in air.

At the respective time points, the supernatant medium was aspirated, cells were washed three times with 1 mL ice-cold PBS each, detached with trypsin and suspended in medium. Radiotracer uptake was determined by counting in a gamma counter. Radioactivity was referenced to a 1 mL sample of medium containing 150 µCi of the radiotracer (100% value). All determinations were performed in triplicate. For direct comparison, all given percentages have been normalized to 250,000 cells.

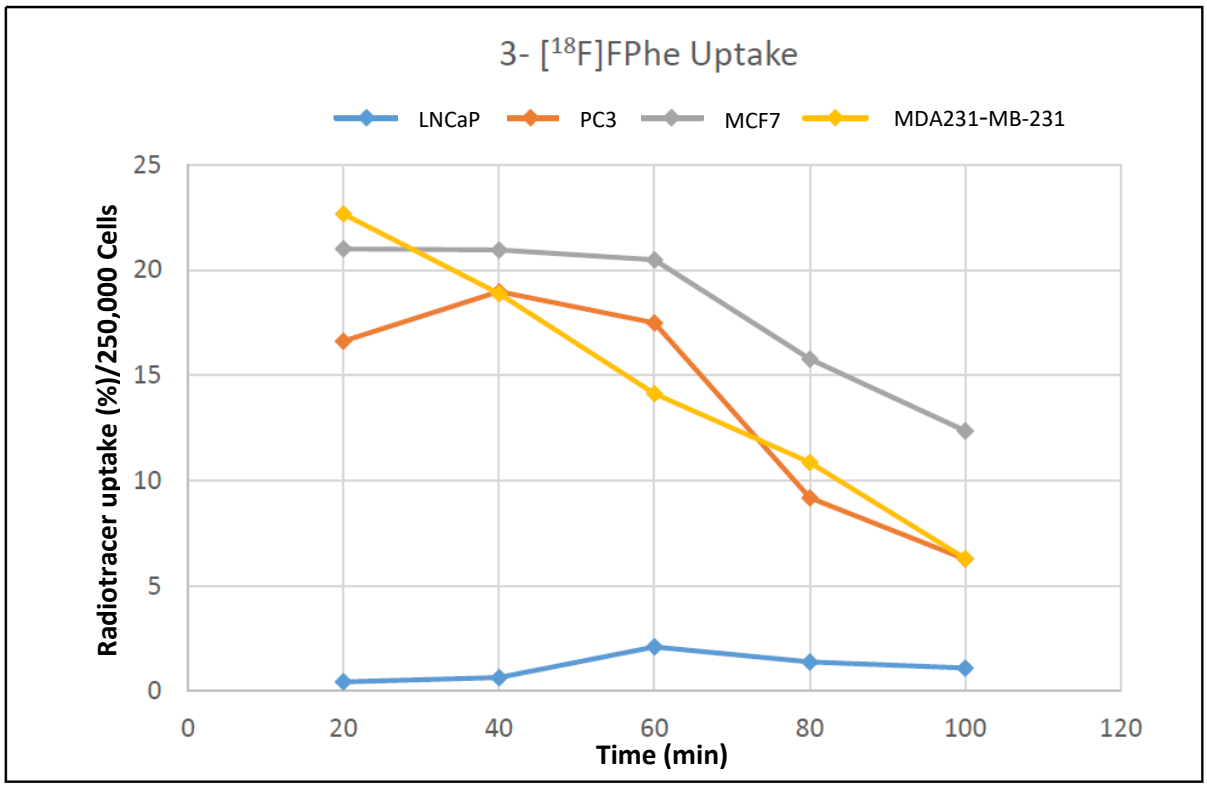


*Figure S10. 3-[^{18}F]FPhe (**4b**) uptake in various cell lines.*

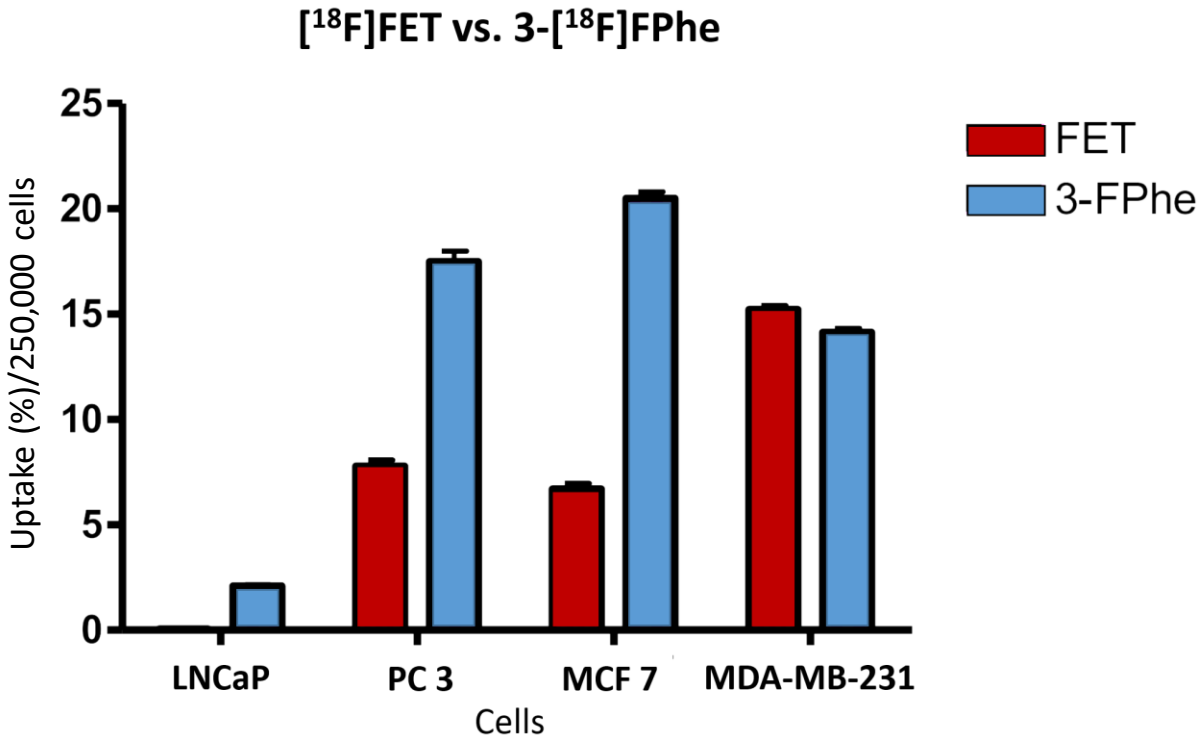


*Chart S1. Uptake of [^{18}F]FET and 3-[^{18}F]FPhe ([^{18}F]**4b**) in different tumor cell lines after 1 h incubation.*

PET Evaluation

General

Animals

Experiments were carried out in accordance with the EU directive 2010/63/EU for animal experiments and the German Animal Welfare Act (TierSchG, 2006) and were approved by regional authorities (LANUV NRW, 84-02.04.2017.A288). Six healthy male Long Evans rats (243–534 g body weight) were used for this study. Rats were housed in pairs in individually ventilated cages (NexGen Ecoflo, cages RAT1800 with 1805 cm^2 floor space and 41 cm height; Allentown Inc., Allentown, NJ, USA) under controlled ambient conditions (22 ± 1 °C and 55 ± 5% relative humidity) on an inversed 12 h light/dark schedule (lights on 9:00 p.m. to 9:00 a.m.). Food and water were available at all times.

PET Imaging

The six rats were assigned to two groups (n=3 each): With and without AADC inhibition. In the AADC inhibition group, rats received an intraperitoneal injection of 15 mg/kg benserazide in 0.5 mL NaCl 1 h before tracer injection. Prior to PET measurements, animals were anesthetized (initial dosage, 5% isoflurane in O_2/air (3:7), then reduction to 2%), and a catheter for tracer injection was inserted into the lateral tail vein. Rats were placed on an animal holder (Minerve, Esternay, France) and fixed with a tooth bar in a respiratory mask. Dynamic PET scans in list mode were performed using a Focus 220 micro-PET scanner (CTI-Siemens, Germany) with a resolution at center of field of view of 1.4 mm. Data acquisition started with tracer injection (65.5 ± 2.6 MBq of 3-[^{18}F]FPhe ([^{18}F]**4b**) in 0.5 mL, i.v.), continued for 120 min, and was followed by a 10 min transmission scan using a [^{57}Co] point source. The breathing rate was monitored and kept around 60/min by adjusting isoflurane concentration (1.5–2.5%). Body temperature was maintained at 37 °C by warm airflow through the animal bed. Following Fourier rebinning, data were reconstructed using an iterative OSEM3D/MAP procedure including attenuation and decay correction in two different ways: (1) 28 frames (2 × 1 min, 2 × 2 min, 6 × 4 min, 18 × 5 min) for a compilation of time-activity curves; (2) 4 frames (4 × 30 min) for visual display. Resulting voxel sizes were always 0.38 mm × 0.38 mm × 0.79 mm.

Image analysis and statistics

Data analysis was performed using the software VINCI 4.72. Images were manually co-registered with a structural MR image template, Gauss filtered (1 mm FWHM), and SUV_{bw} was determined by dividing each image by the injected dose and multiplying the result by bodyweight times 100. To obtain bone TACs, an elliptical 4 mm^3 (36 voxels) volume of interest (VOI) was placed over the lambdoidal crest of the skull. For brain TACs, a 620 mm^2 (5400 voxels) VOI was used, which was carefully placed to avoid areas with radioactivity spillover from bones. VOI mean SUV_{bw} values were extracted from each of the 28 frames and plotted over time.

Differences in 3-[^{18}F]FPhe brain uptake were evaluated using a two-way ANOVA (Graphpad Prism 6.0) with the factors AADC inhibition (no repeated measures) and timepoint (repeated measures), followed by Sidak's multiple comparison test.

Comparison of brain uptake of 3-[^{18}F]FPhe in healthy rats with/without benserazide

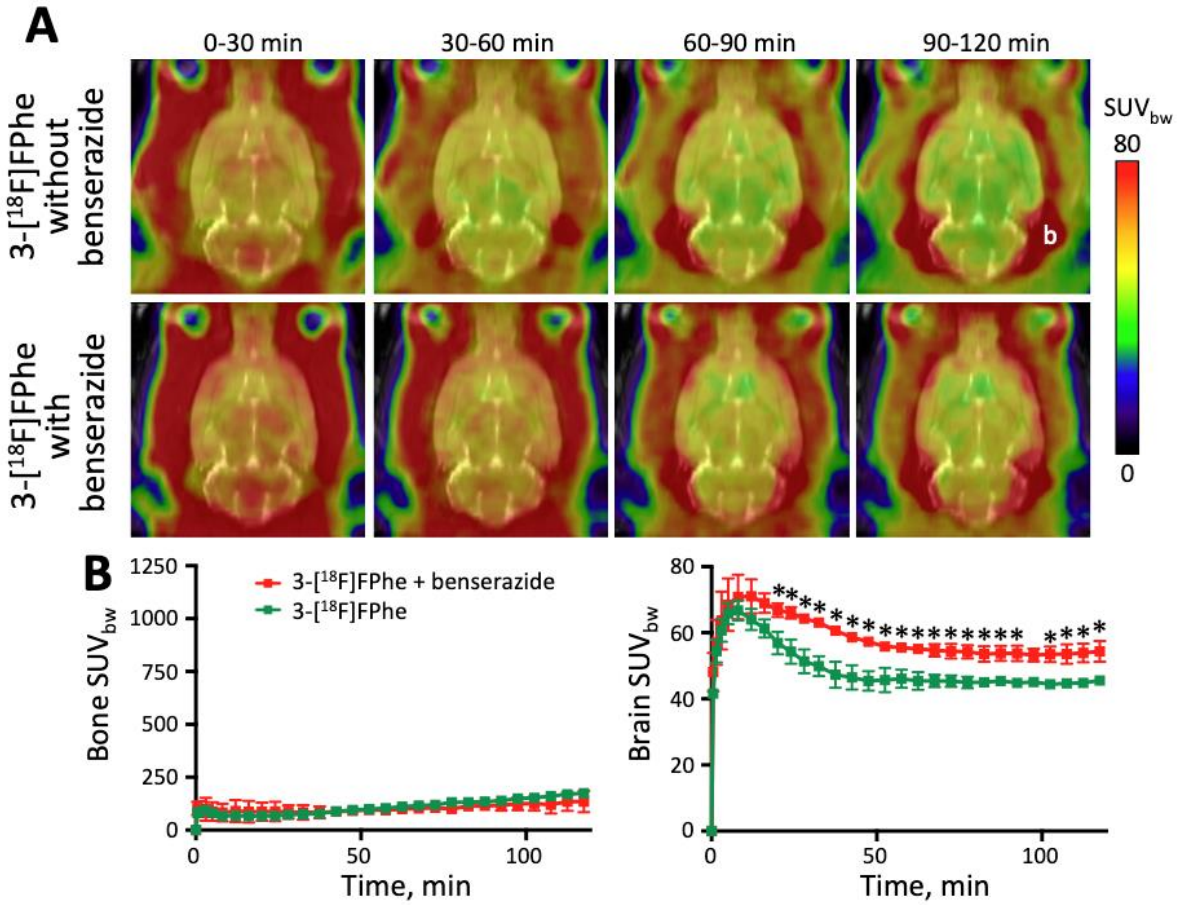


*Figure S11: Biodistribution of 3-[^{18}F]FPhe in healthy rat brains with and without the peripheral amino acid decarboxylase (AADC) inhibitor benserazide. A: Horizontal PET images displayed in frames of 30 min and projected onto an MRI template. b: Lambdoidal crest where bone uptake was measured for time-activity curves (TACs). B: TACs (n=3 each) for bone (left) and whole brain (right). Asterisks: significantly different 3-[^{18}F]FPhe ([^{18}F]**4b**) uptake at the respective time points.*

While bone uptake of 3-[^{18}F]FPhe ([^{18}F]**4b**) was similar in the two groups, brain uptake was significantly higher when peripheral AADC was blocked with benserazide. Two-way ANOVA revealed a significant main effect of factor AADC inhibition: $F(1,4)=26.4$; $p=0.0068$. Sidak's post-hoc comparison showed significant differences in 3-[^{18}F]FPhe uptake ($p<0.05$) from 20 min p.i. through 120 min p.i. (except 95 min p.i.).

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