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Highly enantioselective amination of η^3-(2-fluorocycloheptenyl)palladium complexes bearing chiral P,P- and P,N-ligands

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1. General information

All reagents were purchased from Acros, Aldrich or ABCR and used without further purification. 2-Methyltatrahydrofuran (2-MeTHF) and THF were distilled over Na-benzophenone ketyl anion-radical and stored over 4Å Linde type molecular sieves. MeCN was distilled over P_2O_5 and stored over 3A Linde type molecular sieves. [(2-Fluorocycloheptenyl)PdCl]$_2$ was prepared by Li_2PdCl_4 reduction with CO in the presence of 2-fluorocyclohept-2-enyl chloride according to the previously published procedure[S1] when the CO bubbling time was extended to 5 hours that allowed us to increase the yields to 80–85%. All reactions were carried out under argon atmosphere using standard Schlenk technique. Silica gel 60 (40–63 μm, Macherey-Nagel) was used for column chromatography. TLC analysis was made on standard Macherey-Nagel plates with F_{254}-inducator using UV or $KMnO_4$ solution for visualization.

GC analysis was performed on Chromatec Crystal 5000.2 gas chromatograph (capillary column Restek Rxi-5Sil MS, 10 m x 0.10 mm, film 0.10 μm of crossbond 5% 1,4-bis(dimethylsiloxy)phenylene 95% dimethylpolysiloxane, carrier gas was helium, FID detector, constant pressure mode 331.738 kPa (corresponds to linear velocity of 30 cm sec^{-1} at 280°C), temperature program from 120° to 280°C with 30 deg min^{-1} rate, manual injection by 10-μl microsyringe, injection volume ca. 1 μl, sample concentration ca. 0.5 mg ml^{-1}, split ratio 300:1). Quantitative GC analysis was performed relative to $C_{19}H_{40}$ used as an internal standard. The GC equipment was calibrated using 3 standard samples with the analyzing compound to $C_{19}H_{40}$ ratio variated and the yield are given to the nearest 5%.

GC/MS analysis was performed on Chromatec Crystal 5000.2 gas chromatograph equipped with Chromatec Quadrupole mass-detector (EI, 70 eV, 200°C) and Chromatec CR-5MS chromatographic column (30 m x 0.25 mm, 5%-phenyl-95%-dimethylpolysiloxane, 0.25 μm).

1D and 2D NMR spectra were recorded on Varian Inova 400 (400.1 MHz for ^{1}H, 376.4 MHz for ^{19}F, 100.6 MHz for ^{13}C, 161.9 MHz for ^{31}P) or Bruker AVANCE II 300 (300.1 MHz for ^{1}H, 282.4 MHz for ^{19}F, 75.5 MHz for ^{13}C, 121.5 MHz for ^{31}P) in $CDCl_3$ containing TMS and C_6F_6 as internal standards. Chemical shifts in $CDCl_3$ were measured relative to TMS (δ = 0 ppm) for ^{1}H, $CDCl_3$ (δ = 77.1 ppm) for ^{13}C, C_6F_6 (δ = –162.2 ppm) for ^{19}F, or relative to external calibration on 85% H_3PO_4 (δ = 0.0 ppm) for ^{31}P.

HPLC analyses on chiral stationary phases were performed under normal phase mode on Shimadzu Prominence-i LC-2030C 3D Plus equipped with Diode-Array Detector or under reverse-phase mode on Thermo-Finnigan Surveyor equipped with 2-channel UV-Vis detector.

HRMS were recorded on Bruker micrOTOF equipment using electro-spray ionization (ESI).

2. Experimental procedures

2.1. Ligand screening and amine scope. General procedure.

Following general strategy was used to set up every series of *N* optimization experiments (each optimization experiment was run on 0.010 mmol scale of [Pd] in 1.0 ml of solvent):

1. Batch solution of [(2-fluoroallyl)Pd]$^{+}$OTf^{-} (already containing $C_{19}H_{40}$ as an internal standard) of total amount for *N*+4 experiments was prepared;
2. An aliquot of this solution of total amount for *N*+2 experiments was transferred to the appropriate ligand affording batch solution of [(2-fluoroallyl)Pd(*L**)]$^{+}$OTf^{-} for *N*+2 experiments;
3. *N* aliquots of the latter solution were added into *N* reaction vials containing appropriate aniline or amine.

Batch solution of [(2-fluoroallyl)Pd]$^{+}$OTf^{-}:

A Schlenk tube was charged with [(2-fluoroallyl)PdCl]$_2$ (0.0050 mmol per 1 experiment), AgOTf (0.011 mmol per 1 experiment, 1.1 equiv.) and $C_{19}H_{40}$ (an internal standard, 1–3 mg per 1 experiment) filled with argon on a Schlenk line. 2-MeTHF (1.0 ml per 1 experiment) was added next, and the suspension was stirred for 30 min at r.t. After this time, stirring was stopped and precipitated AgCl was allowed to settle down. The clear yellow solution was used assuming [Pd] concentration in it to be 0.010 M.

Batch solution of [(2-fluoroallyl)Pd(*L)]$^{+}$OTf^{-}:**

A screw neck 4-ml vial or a Schlenk tube was charged with appropriate Ligand (0.010–0.020 mmol per 1 experiment, 1–2 equiv.) and purged with argon. In a stream of argon the batch solution of [(2-fluoroallyl)Pd]$^{+}$OTf^{-} (0.010 mmol or 1.0 ml per 1 experiment) was added. The solution was stirred for 1 hour at r.t. and then used assuming [Pd] concentration in it to be 0.010 M.

Amination of [(2-fluoroallyl)Pd(*L)]$^{+}$OTf^{-}: General procedure:**

A screw neck 4-ml vial was charged with *p*-anisidine (0.050 mmol, 5 equiv.) or other amine and purged with argon. In a stream of argon the batch solution of [(2-

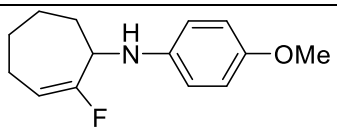
fluoroallyl)Pd(*L**)]$^{+}$OTf^{-} (0.010 mmol, 1.0 ml) was added followed by PhBr (0.050 mmol, 5 equiv.). The reaction mixture was stirred for 5–24 hours and then quenched by dilution with Et_2O (5 ml) and 10% NaOH solution (5 mL). The ether phase was separated, dried over K_2CO_3, and analyzed by GC. Products **3a-g** were identified by comparison of their GC retention times and MS data with authentic samples prepared during our previous works.[S2] For quantification, the gas chromatograph was calibrated using 3 standard samples with the compound to $C_{19}H_{40}$ ratio variated and the yield are given to the nearest 5%.

Samples for chiral HPLC were prepared in the following manner: the crude residue after rotary evaporation was subjected to chromatographic purification on silica column in Pasteur pipette (ca. 0.5 g of silica) collecting fractions of volume around 0.5–1 ml into 2-ml screw-neck vials. After evaporation of appropriate fractions, the residue was analyzed by chiral HPLC (chromatograms are presented below).

Following eluents were used during chromatographic purification: **3a** — benzene/EtOAc (25:1, R_f = 0.32); **3b** — hexane/benzene/EtOAc (30/50/1, R_f = 0.36); **3c** — hexane/benzene/EtOAc (50:50:1, R_f = 0.35); **3f** — benzene/EtOAc (8:1, R_f = 0.29); **3g** — benzene/EtOAc (8:1, R_f = 0.33).

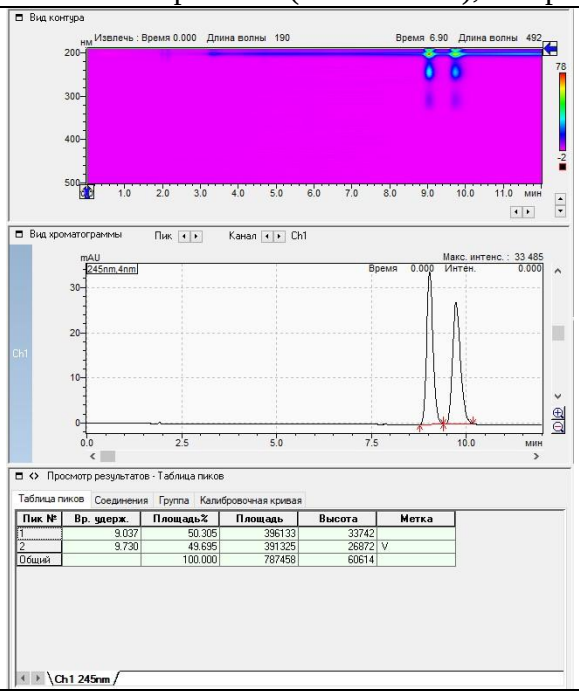
Compounds **3d,e** required preliminary benzoylation to achieve baseline separation of enantiomers. This was carried out in the following way. The crude residue containing **3d,e** after aqueous work-up and evaporation was dissolved in CH_2Cl_2 (1.0 ml) and NEt_3 (50 μl, 0.36 mmol) and benzoyl chloride (29 μl, 0.25 mmol) were added. The solution was stirred for 5 hours, then concentrated and the residue was subjected to the similar chromatographic purification as above eluting with benzene/EtOAc (25:1 for both **3d^{Bz}** and **3e^{Bz}**; R_f(**3d^{Bz}**) = 0.19 and R_f(**3e^{Bz}**) = 0.22). After evaporation of appropriate fractions, the residue was analyzed by chiral HPLC (chromatograms are presented below).

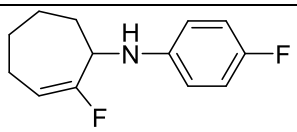
2.2. Chiral HPLC data



3a — *ee* 87%

Diacel Chiralpak-IA3 (150x4.6 mm), *n*-heptane/IPA 99/1 (1.0 ml/min)





3b — *ee* 84%

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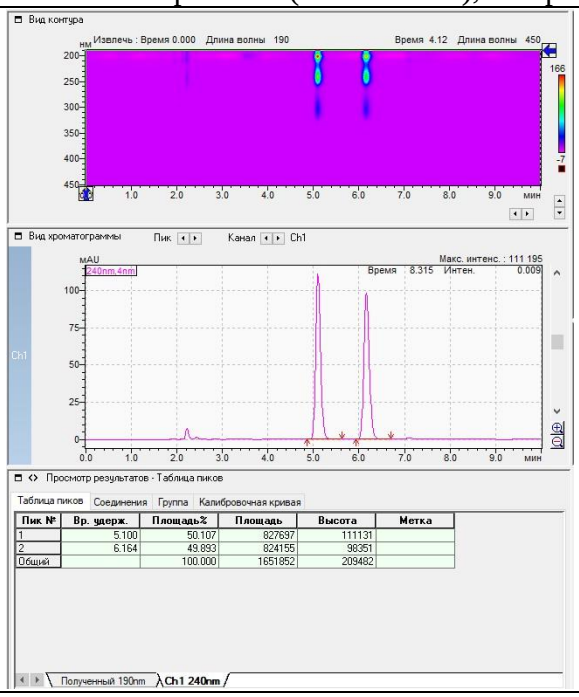

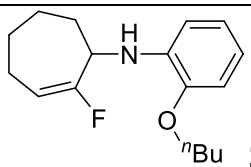

3c — *ee* 78%

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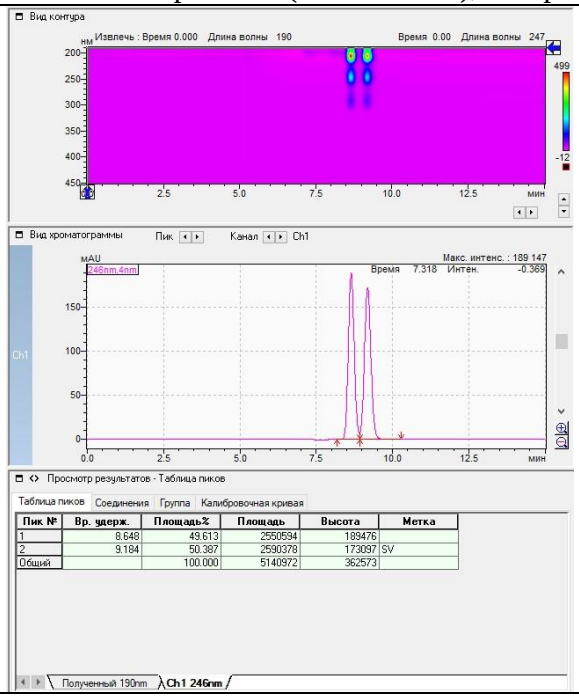
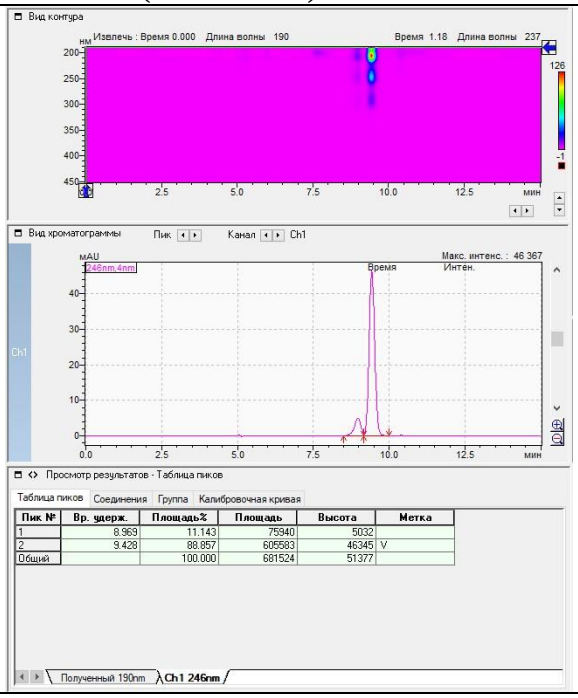
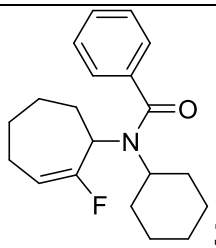
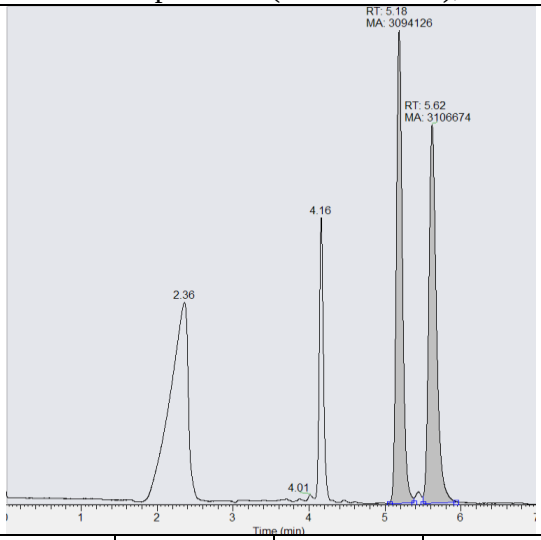


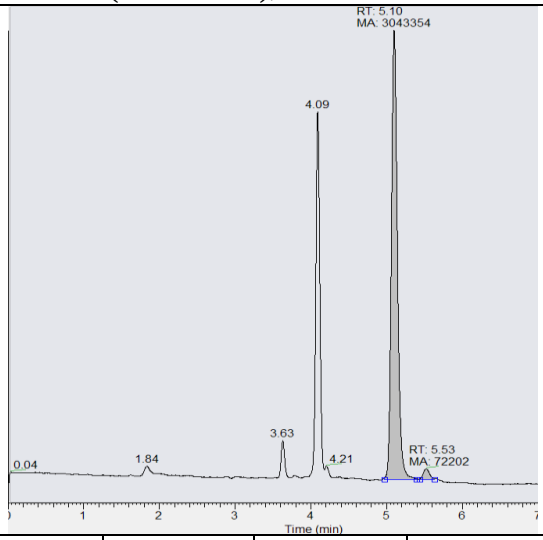




3d^{Bz} — *ee* 95%

Diacel Chiralpak-IA3 (250x4.6 mm), H_2O/MeCN 15/85 (1.0 ml/min), 210 nm





Peak #	R_t (min)	Area %	Area	Peak #	R_t (min)	Area %	Area
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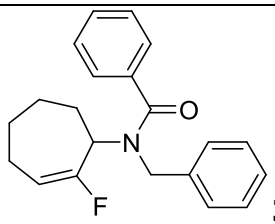
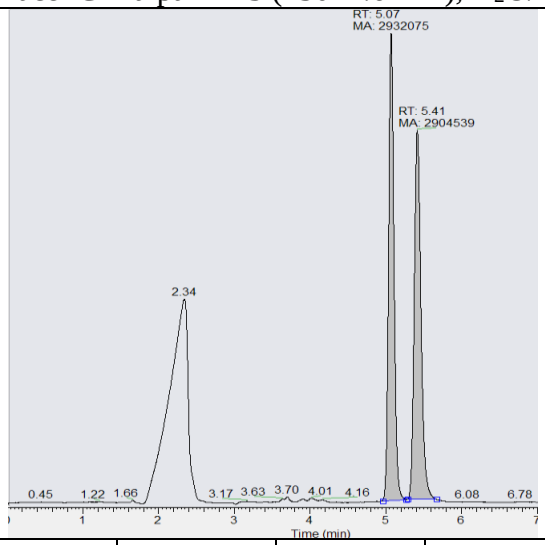
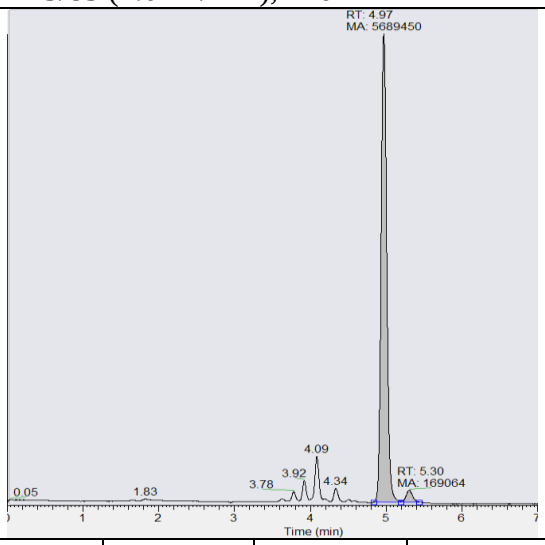


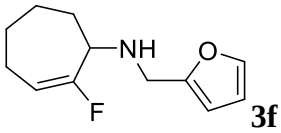
3e^{Bz} — *ee* 94%

Diacel Chiralpak-IA3 (250x4.6 mm), H_2O/MeCN 15/85 (1.0 ml/min), 210 nm



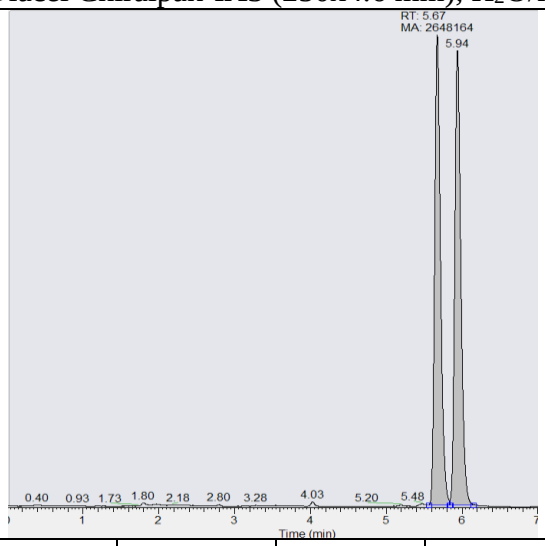


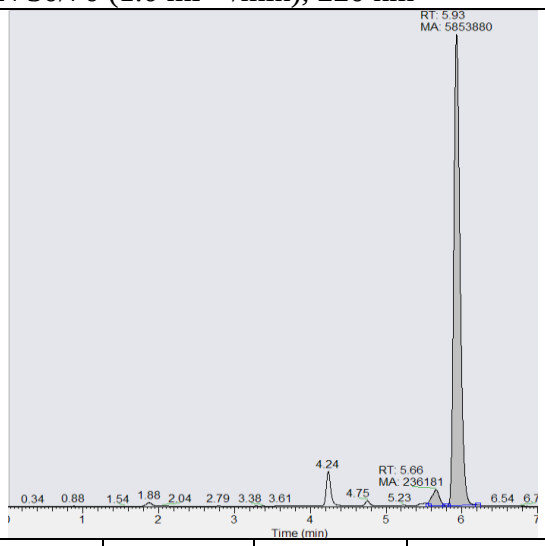
Peak #	R_t (min)	Area %	Area	Peak #	R_t (min)	Area %	Area
1	5.07	50.2	2932075	1	4.97	97.1	5689450
2	5.41	49.8	2904539	2	5.30	2.9	169064



3f — *ee* 92%

Diacel Chiralpak-IA3 (250x4.6 mm), H_2O/MeCN 30/70 (1.0 ml /min), 220 nm





Peak #	R_t (min)	Area %	Area	Peak #	R_t (min)	Area %	Area
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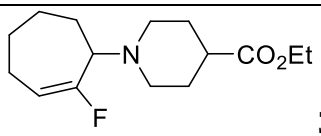
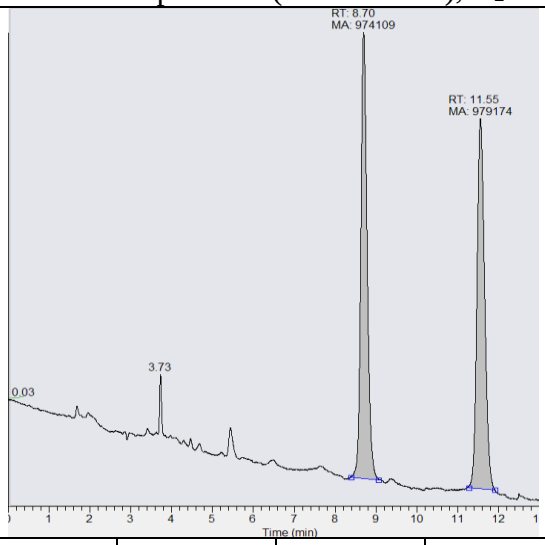
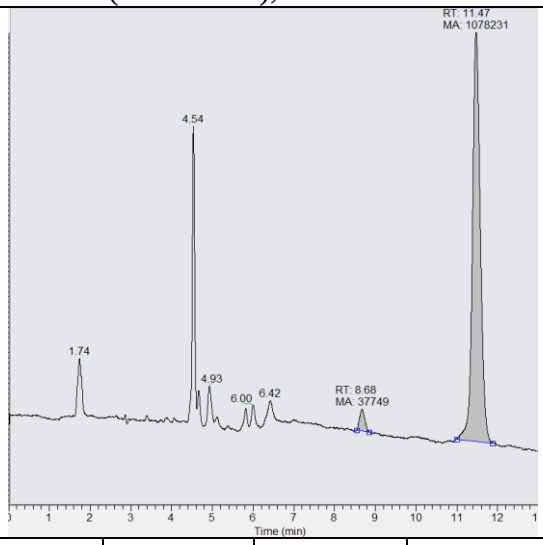
2	5.94	50.1	2657515	2	5.93	96.1	5853880



3g — *ee* 93%

Diacel Chiralpak-IA3 (250x4.6 mm), H_2O/MeCN 20/80 (1.0 ml/min), 220 nm





Peak #	R_t (min)	Area %	Area
1	8.70	49.9	974109
2	11.55	50.1	979174

Peak #	R_t (min)	Area %	Area
1	8.68	3.4	37749
2	11.47	96.6	1078231

2.3. [(2-Fluorocycloheptenyl)Pd((*S*)-Bu^{t}PHOX)]$^+$[BARF]$^-$: preparative synthesis

A flame-dried 10-ml Schlenk tube was charged with [(2-fluorocycloheptenyl)PdCl]$_2$ (25.7 mg, 0.050 mmol), (*S*)-Bu^{t}PHOX (29.1 mg, 0.10 mmol) and Na[BARF] (89.2 mg, 0.10 mmol, BAFR = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate and filled with argon on a Schlenk line. Dry MeCN (2.0 ml) was added, and the reaction mixture was stirred at r.t. for 1 hour. After that it was filtered through 0.45 μm Teflon syringe filter which was then washed with 1.0 ml more of dry MeCN. The filtrate was concentrated on a rotary evaporator resulting in a brown oil which was redissolved in CH_2Cl_2, concentrated again and dried under high vacuum affording **1·[BARF]** as a grey solid (142.0 mg, 97% yield, $[\alpha]_D^{24}$ = +76° (*c* = 0.300, CH_2Cl_2)).

In $CDCl_3$ solution, **1·[BARF]** persists as a mixture of 2 diastereomers with d.r. 94/6.

Crystals suitable for X-Ray analysis were grown by slow vapor diffusion of *n*-hexane into dilute solution of **1·[BARF]** in CH_2Cl_2 at 2°C.

(Major diastereomer):

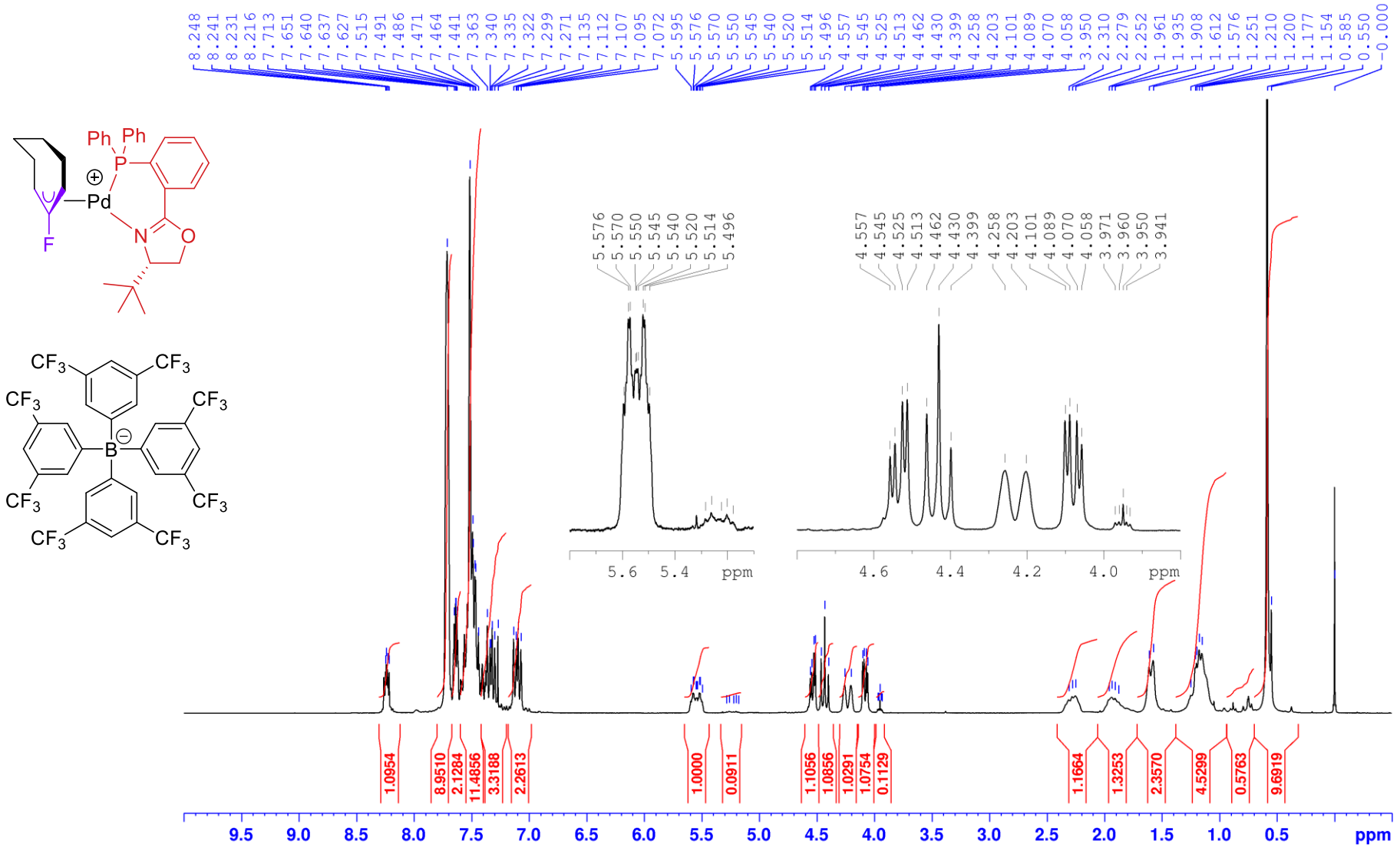
^{1}H NMR (300.1 MHz, $CDCl_3$, 273 K) δ: 8.29 – 8.19 (m, 1H, 1 CH in ^{t}Bu-PHOX), 7.76 – 7.67 (m, 8H, 8 CH in $BAr^F{}_4$), 7.67 – 7.61 (m, 2H, 2 CH in ^{t}Bu-PHOX), 7.61 – 7.42 (m, 11H,

7 CH in ^{t}Bu-PHOX + 4 CH in BAr^F_4), 7.42 – 7.28 (m, 2H, 2 CH in ^{t}Bu-PHOX), 7.17 – 7.04 (m, 2H, 2 CH in ^{t}Bu-PHOX), 5.62 – 5.47 (m, 1H, CH in η^3-allyl *anti*- to P), 4.54 (dd, J = 9.6, 3.8 Hz, 1H, CH_2 in ^{t}Bu-PHOX), 4.43 (t, J = 9.5 Hz, 1H, CH^tBu in ^{t}Bu-PHOX), 4.23 (d, J = 16.4 Hz, 1H, CH in η^3-allyl *anti*- to P), 4.08 (dd, J = 9.3, 3.8 Hz, 1H, CH_2 in ^{t}Bu-PHOX), 2.38 – 2.17 (m, 1H, CH_2 in η^3-cycloheptenyl), 2.03 – 1.77 (m, 1H, CH_2 in η^3-cycloheptenyl), 1.68 – 1.49 (m, 2H, CH_2 in η^3-cycloheptenyl), 1.32 – 1.01 (m, 4H, CH_2 in η^3-cycloheptenyl), 0.59 (s, 9H, ^{t}Bu). **^{19}F NMR (282.4 MHz, $CDCl_3$, 273 K) δ:** –63.0 (s, 12F, CF_3), –92.2 (t, J = 17.1 Hz, 1F, CF in η^3-allyl). **^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$, 273 K) δ:** 23.0 (d, $J_{P\text{-}F}$ = 1.7 Hz). **^{11}B{^{1}H} NMR (96.3 MHz, $CDCl_3$, 273 K) δ:** –6.7 (sept, $J_{B\text{-}F}$ = 2.7 Hz). **^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 273 K) δ:** 165.5 (d, J = 2.8 Hz, N=C–O in ^{t}Bu-PHOX), 161.7 (4 lines, J = 49.7 Hz on ^{11}B, B-<u>*C*</u>< in BAr^F_4), 145.9 (dd, J = 281.8, 7.0 Hz, CF in η^3-allyl), 135.8 (s, CH), 134.8 (broad, CH in BAr^F_4), 134.4 (d, J = 14.6 Hz, CH), 134.2 (d, J = 8.6 Hz, CH), 133.9 (d, J = 6.2 Hz, CH), 132.8 (m, CH), 131.9 (s, CH), 131.6 (d, J = 11.9 Hz, CH), 129.9 (d, J = 11.0 Hz, CH), 129.5 (d, J = 10.9 Hz, CH), 128.8 (br. q, J = 31.3 Hz, <u>*C*</u>-CF_3 in BAr^F_4), 124.5 (q, J = 272.5 Hz, CF_3), 117.5 (broad, CH in BAr^F_4), 89.8 (dd, J = 31.4, 15.6 Hz, CH in η^3-allyl *anti*- to P), 81.5 (s, CH in ^{t}Bu-PHOX), 69.4 (s, CH_2 in ^{t}Bu-PHOX), 62.1 (dd, J = 14.6, 4.5 Hz, CH in η^3-allyl *syn*- to P), 34.9 (s, C in ^{t}Bu), 29.3 (t, J = 4.8 Hz, CH_2), 28.7 (d, J = 4.1 Hz, CH_2), 26.0 (s, CH_2), 25.7 (d, J = 4.0 Hz, CH_2), 25.2 (s, CH_3 in ^{t}Bu). **HRMS (ESI), *m/z*:** $[M]^+$, Calcd. for $C_{32}H_{36}FNOPPd^+$ 606.1560; Found 606.1550.

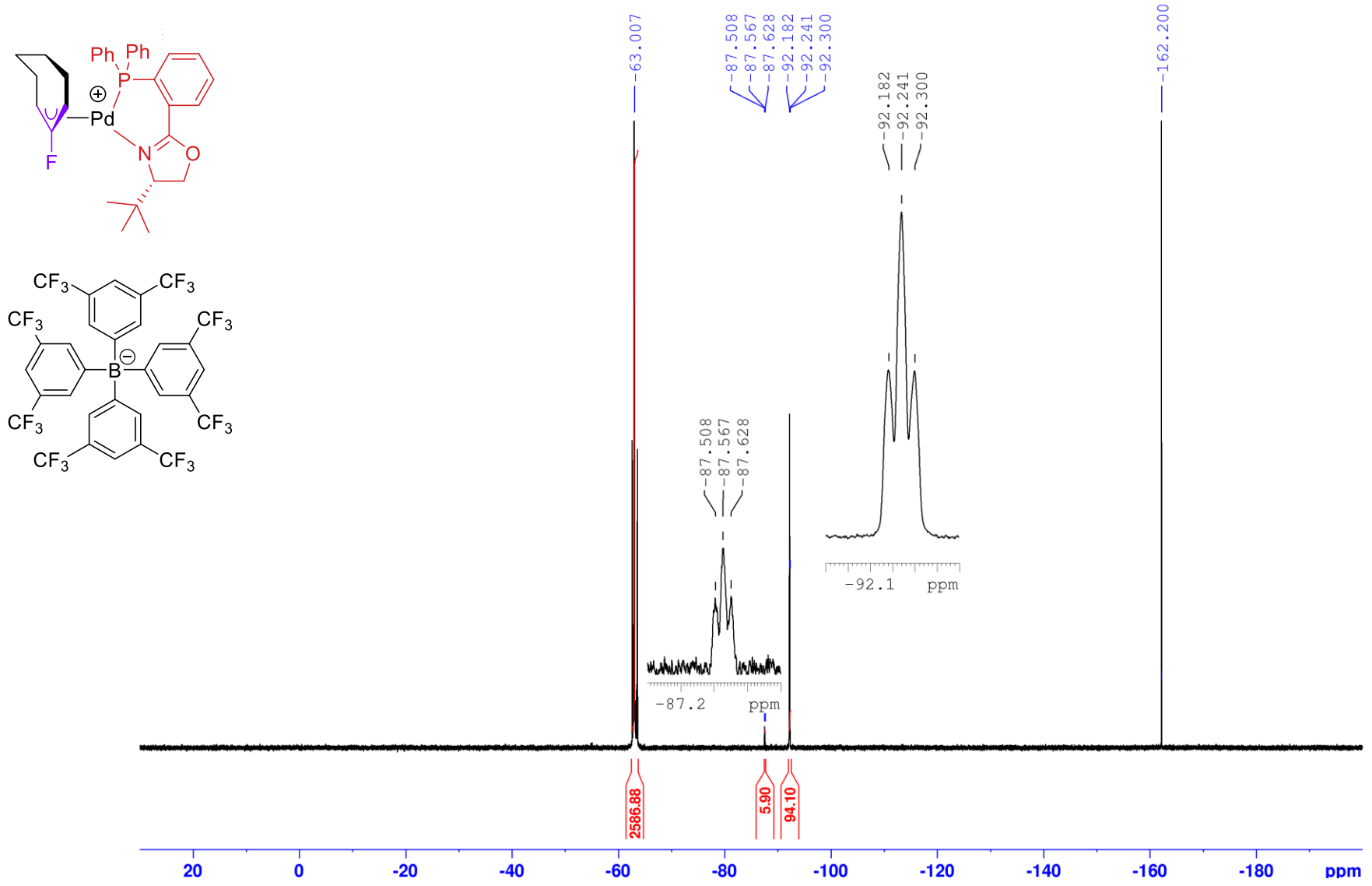
<u>*(Minor diastereomer):*</u>

^{1}H NMR (300.1 MHz, $CDCl_3$, 273 K) δ: (selected signals): 5.29 – 5.16 (m, 1H, CH in η^3-allyl *anti*- to P), 4.08 (CH in η^3-allyl *syn*- to P, from {^{1}H,^{13}C}-HSQC) 3.95 (dd, J = 8.7, 2.9 Hz, 1H, CH in ^{t}Bu-PHOX). **^{19}F NMR (282.4 MHz, $CDCl_3$, 273 K) δ:** –87.6 (t, J = 17.4 Hz, 1F, CF in η^3-allyl). **^{31}P{^{1}H} NMR (121.5 MHz, $CDCl_3$, 273 K) δ:** 20.5 (s).

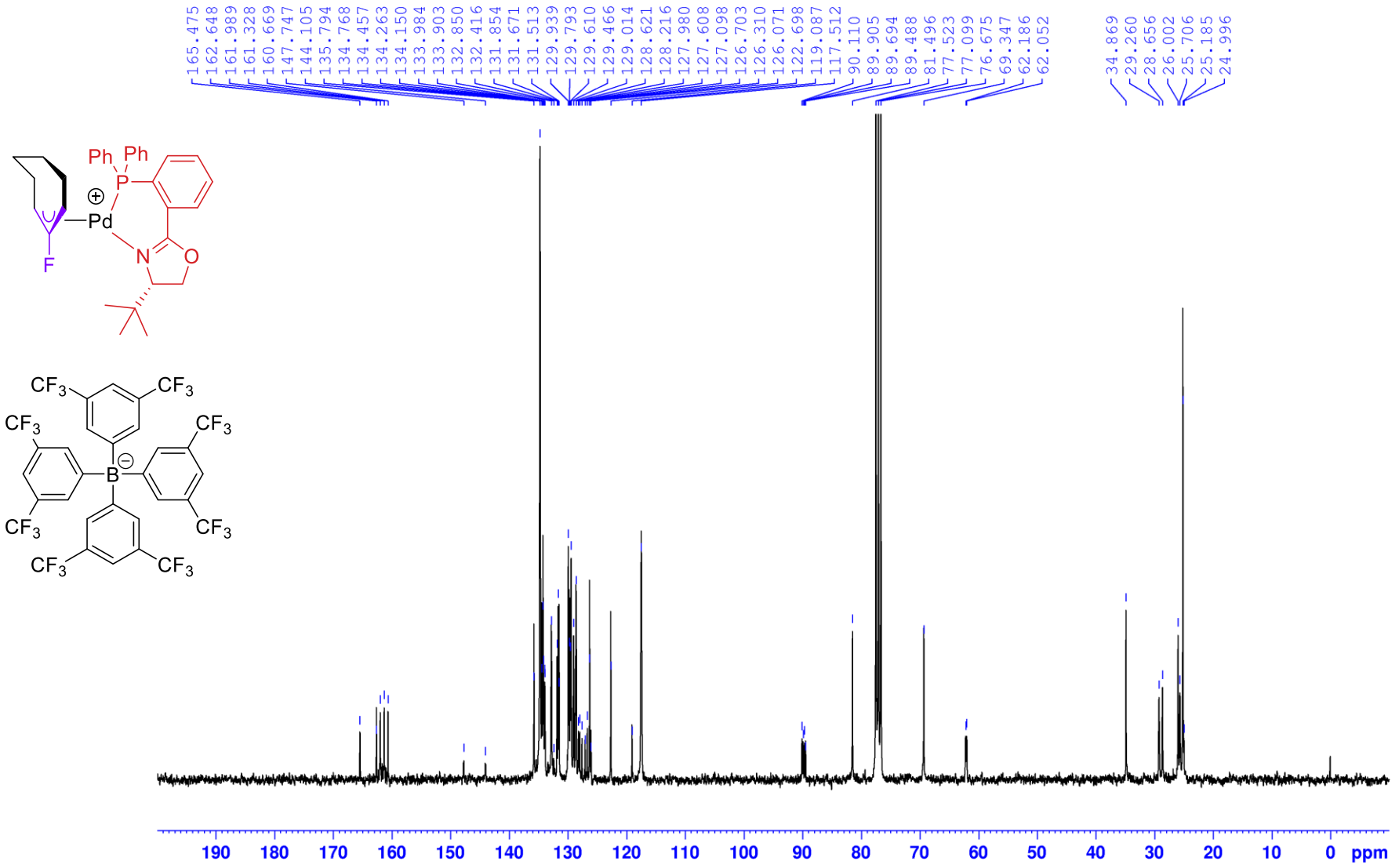
^{1}H NMR (300.1 MHz, $CDCl_3$, 273 K)



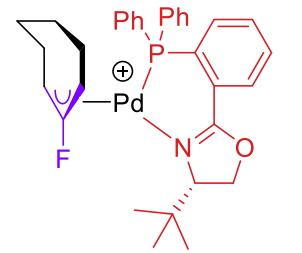
^{19}F NMR (282.4 MHz, $CDCl_3$, 273 K)

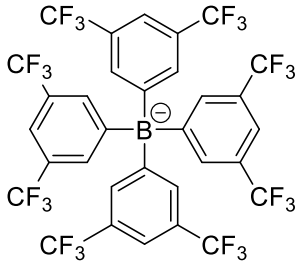


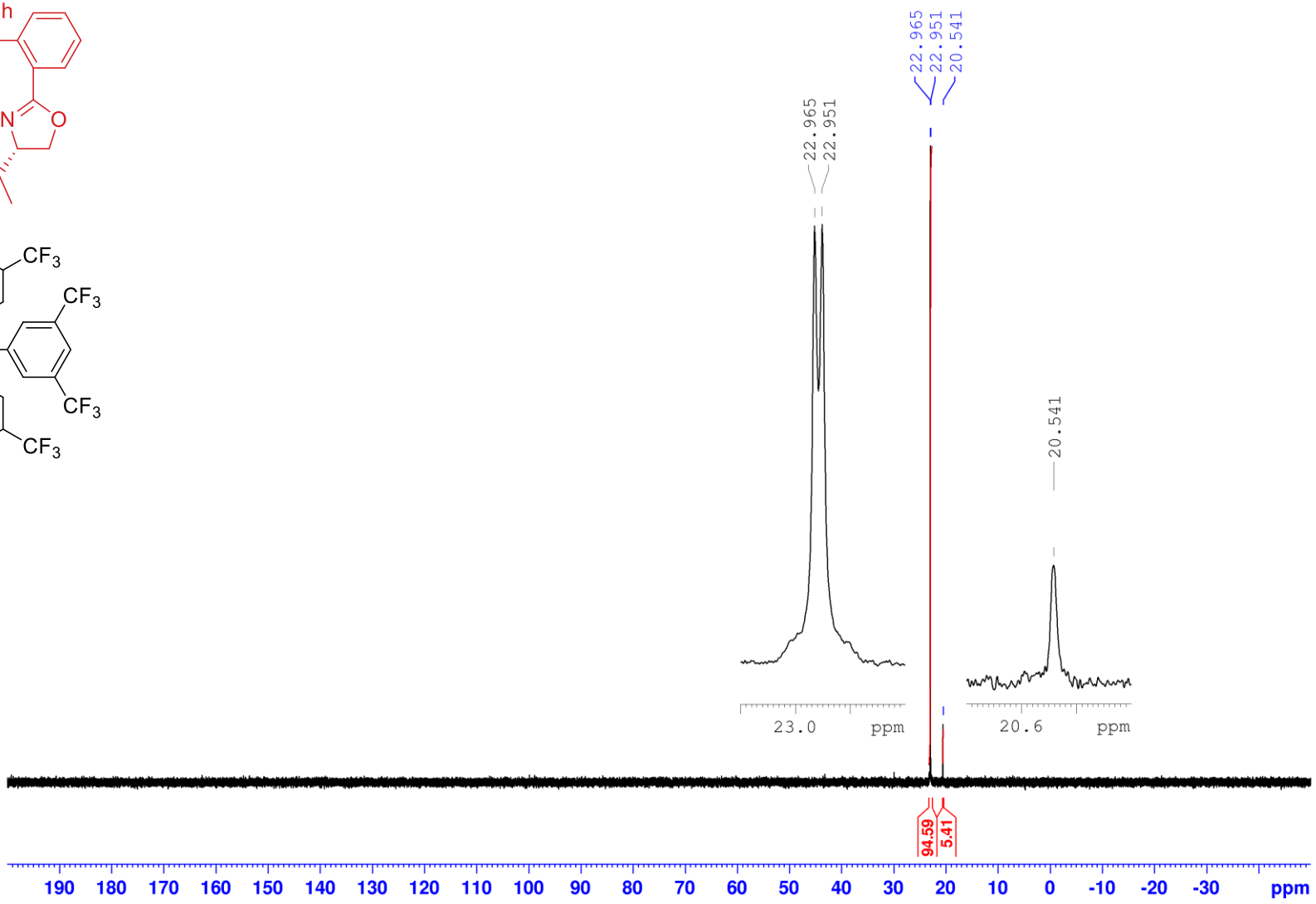
$^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, 273 K)



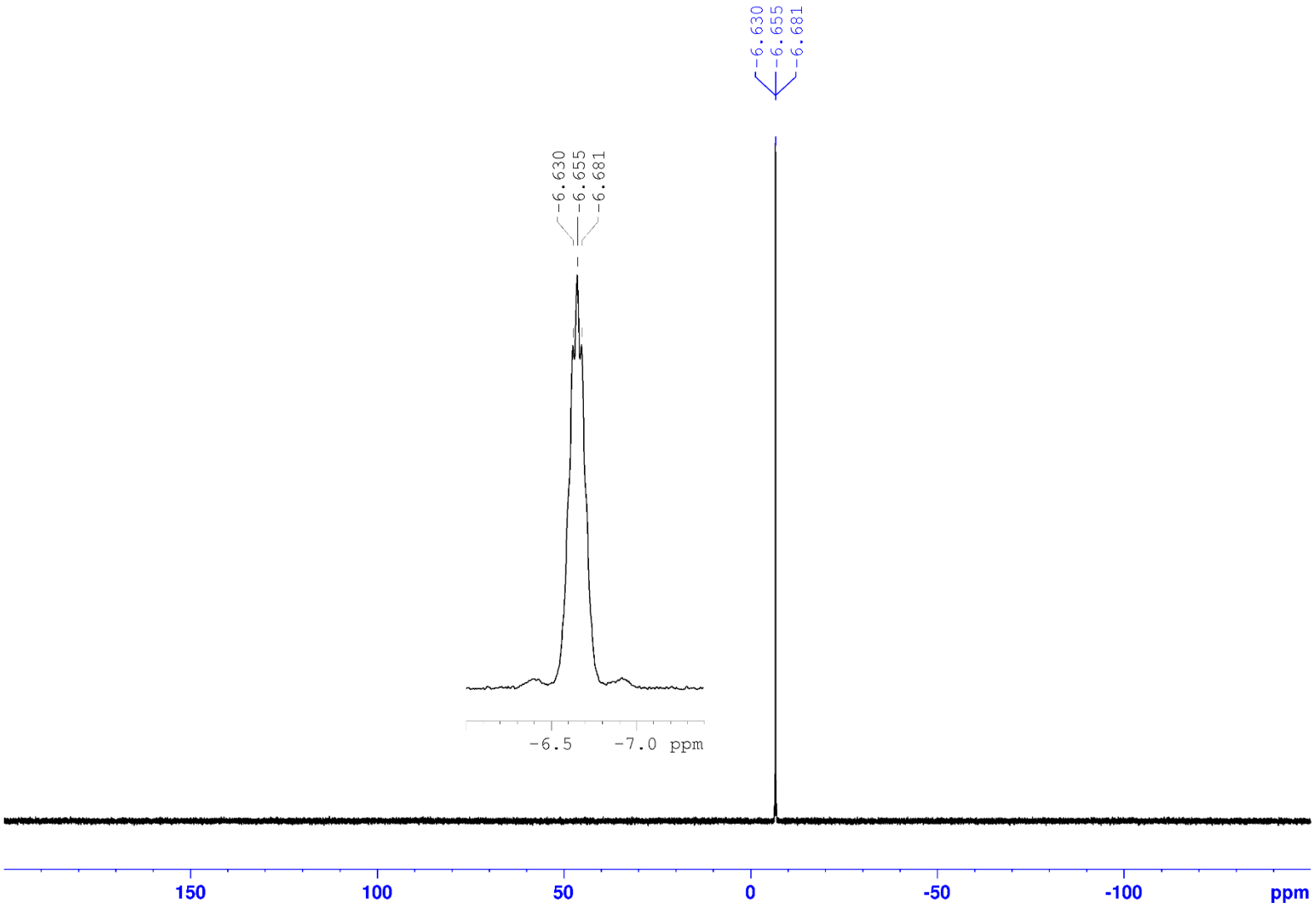
$^{31}P\{^{1}H\}$ NMR (121.5 MHz, $CDCl_3$, 273 K)



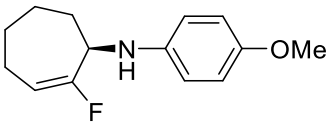




$^{11}B\{^{1}H\}$ NMR (96.3 MHz, $CDCl_3$, 273 K)



2.4. Catalytic amination procedure: preparation of (*R*)-*N*-(4-methoxyphenyl)-2-fluorocyclohept-2-en-1-amine ((*R*)-3a)

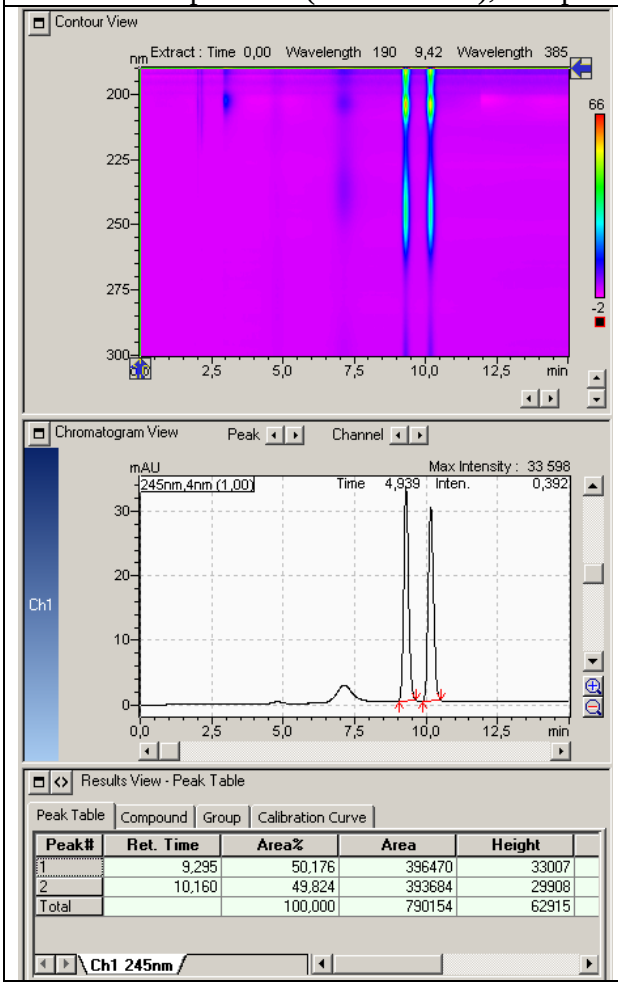


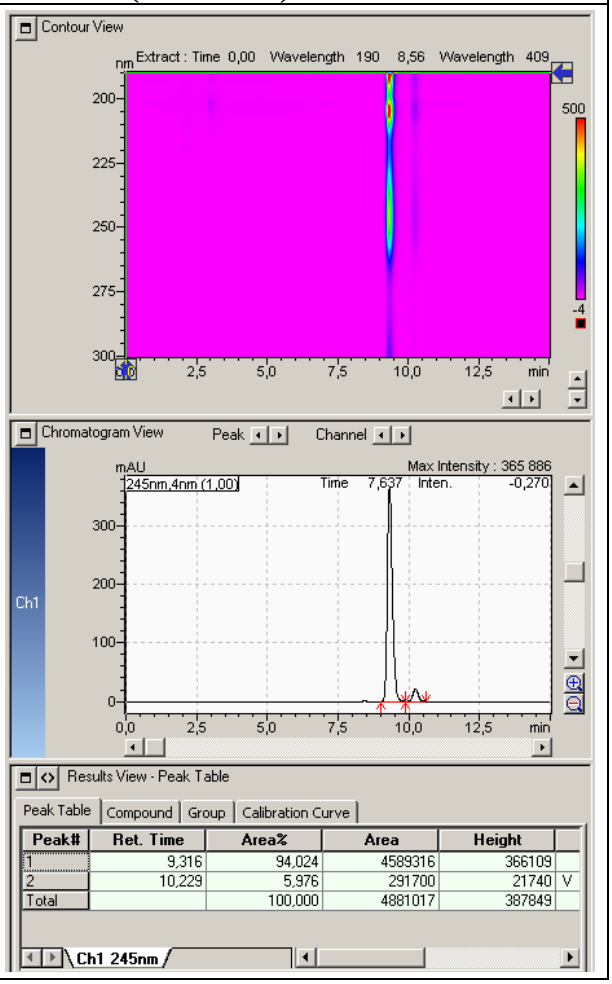
A 10-ml Schlenk flask was charged with (2-fluorocyclohept-2-enyl)pyridinium tetrafluoroborate (139.5 mg, 0.50 mmol), *p*-anisidine (184.9 mg, 1.5 mmol) and Na_3PO_4 (258.0 mg, 1.6 mmol), then connected to a Schlenk line, and evacuated/backfilled with argon three times. 2-MeTHF (2.5 ml) was added followed by freshly prepared batch solution of [(2-methallyl)Pd((*S*)-Bu^{t}PHOX)]$^+$OTf$^-$ (2.5 ml, *C* = 0.010 M, 5 mol. % of Pd, the ratio Pd/Bu^{t}PHOX upon preparation was 1 to 0.9). The reaction mixture was stirred at r.t. for 7 days. Then, it was diluted with EtOAc and 10% aqueous NaOH. Organic layer was separated, dried over Na_2SO_4, concentrated on a rotary evaporator. The residue was triturated with *n*-heptane, concentrated on a rotary evaporator once again to remove formed pyridine as azeotrope with *n*-heptane and dried under high vacuum. The residue was subjected to column chromatography using 50:1 g/g of silica passivated with NEt_3 (5 μl on 1 g of silica, added to a suspension of silica in an eluent prior to column packing) and eluting with benzene/EtOAc 25:1 (R_f = 0.32). The title compound was obtained as an orange oil (98.7 mg, 76%, *ee* = 88%, For **(*R*)-3a·HCl**: $[\alpha]_D^{22}$ = +56° (C = 0.218, MeOH)). NMR data are fully agreed with previously published.[2]

Crystals suitable for X-Ray analysis were grown for hydrobromide salt **1·HBr** by slow cooling of hot solution in 95% EtOH.

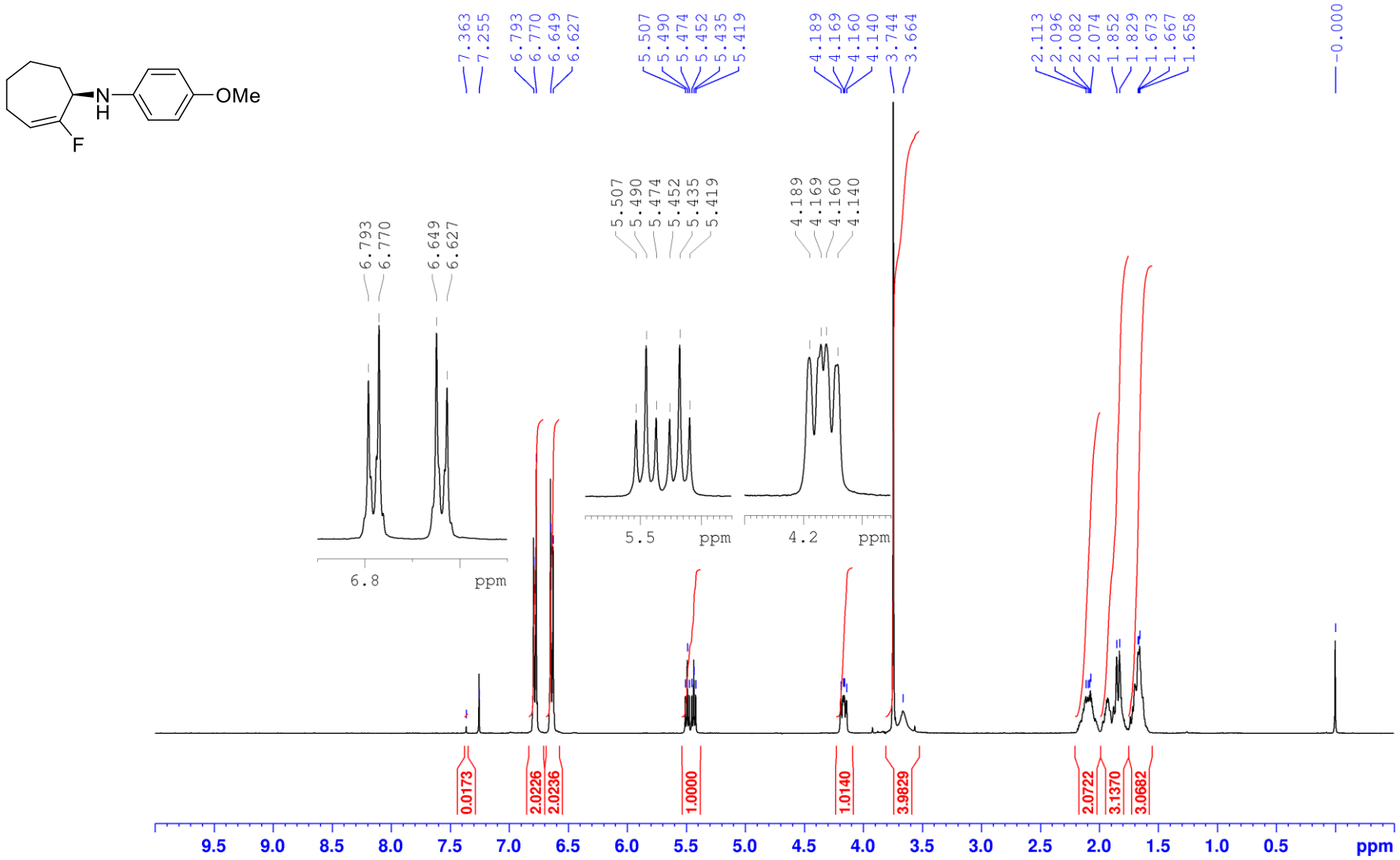
^{1}H NMR (400.0 MHz, $CDCl_3$) δ: 6.80 – 6.75 (m, 2H), 6.65 – 6.60 (m, 2H), 5.46 (dt, *J* = 22.0, 6.6 Hz, 1H), 4.20 – 4.12 (m, 1H), 3.74 (s, 2H), 3.66 (br. s, 1H), 2.18 – 1.99 (m, 2H), 1.98 – 1.76 (m, 3H), 1.75 – 1.58 (m, 3H). **^{19}F NMR (376.4 MHz, $CDCl_3$) δ:** –102.8 (dd, *J* = 22.0, 11.9 Hz). **^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$) δ:** 162.8 (d, *J* = 253.6 Hz, =CF–), 152.5 (s, C-arom.), 141.2 (s, C-arom.), 115.1 (s, CH-arom.), 114.9 (s, CH-arom.), 107.8 (d, *J* = 21.6 Hz, *CH*=CF), 55.8 (s, OCH_3), 55.4 (d, *J* = 27.4 Hz, >CH-N), 29.6 (d, *J* = 6.9 Hz, CH_2), 27.1 (s, CH_2), 24.4 (s, CH_2), 22.5 (d, *J* = 10.8 Hz, CH_2). **MS (EI) *m/z*** 235 ([*M*]$^+$, 100), 220 (19), 206 (31), 123 (52), 122 (60), 108 (62), 95 (20). **HRMS (ESI), *m/z*:** [*M*+H]$^+$, Calcd. for $C_{14}H_{19}FNO^+$ 236.1445; Found 236.1449.

Diacel Chiralpak-IA3 (150x4.6 mm), *n*-heptane/IPA 99/1 (1.0 ml/min)

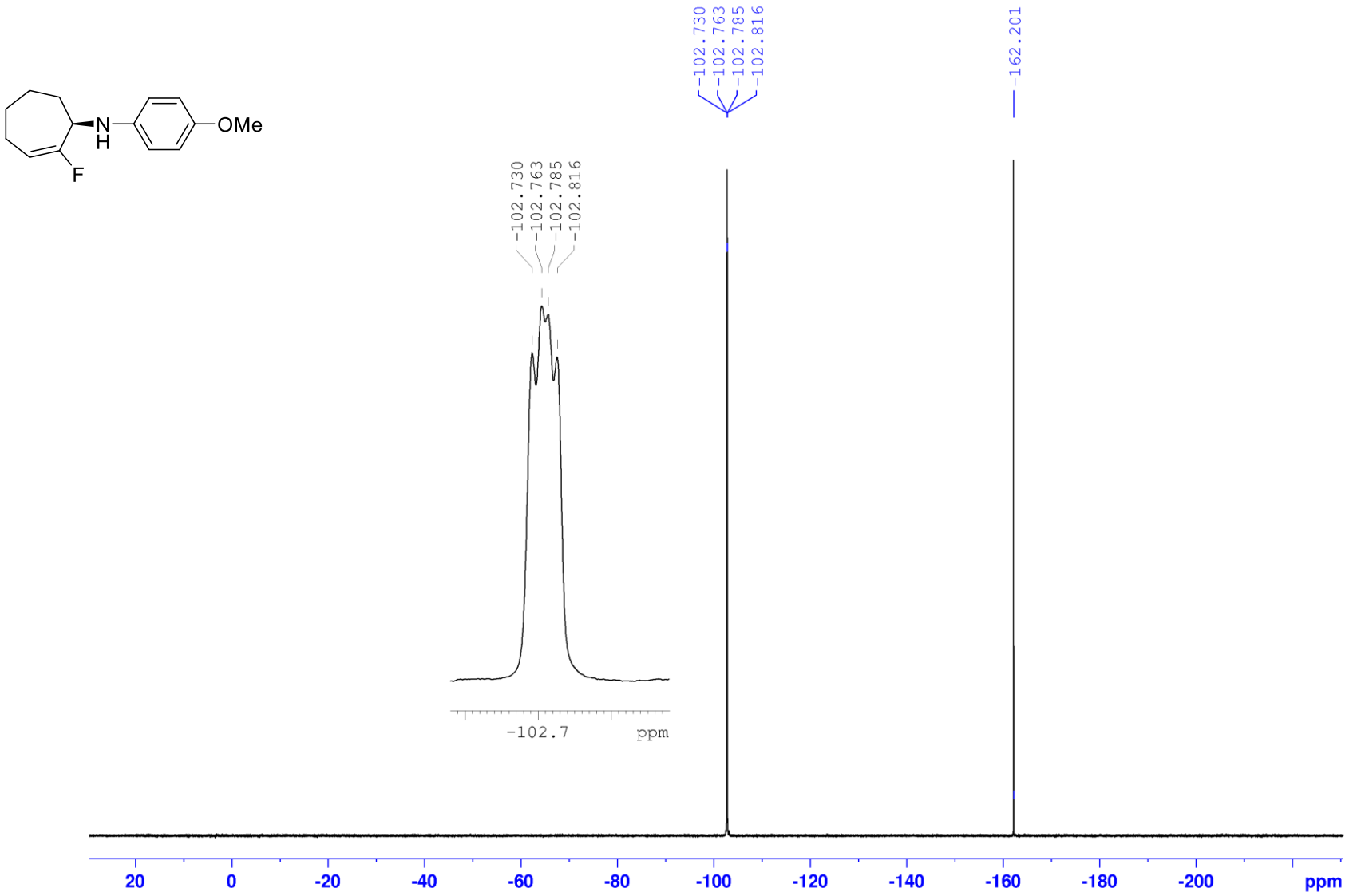




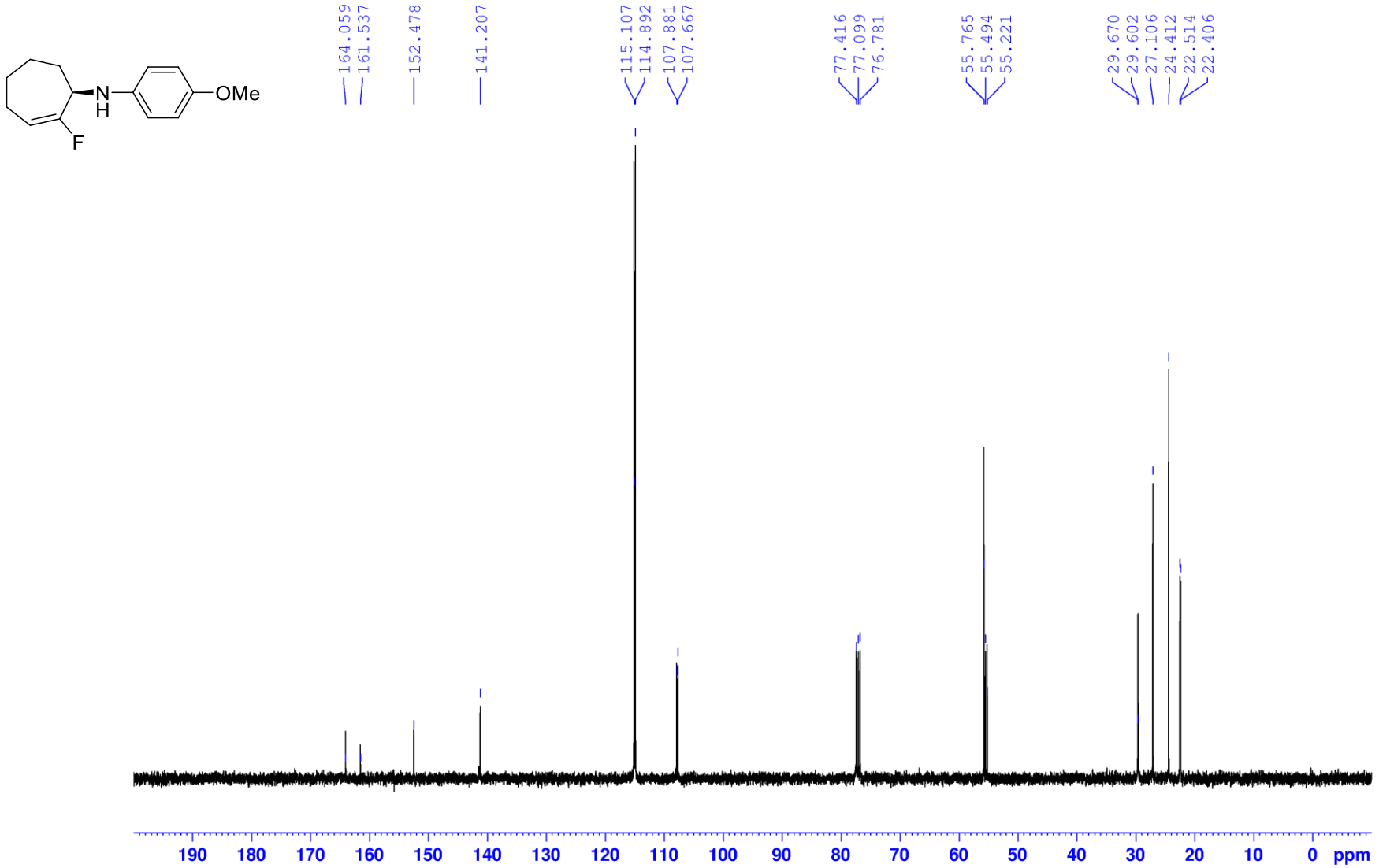
^{1}H NMR (400.0 MHz, $CDCl_3$)



^{19}F NMR (376.4 MHz, $CDCl_3$)



$^{13}C\{^{1}H\}$ NMR (100.6 MHz, $CDCl_3$)



3. References

S1 A. Yu. Bobrova, M. A. Novikov, I. A. Mezentsev and Y. V. Tomilov, *J. Fluor. Chem.*, 2020, **236**, 109553.
S2 A. Y. Bobrova, M. A. Novikov and Y. Tomilov, *Org. Biomol. Chem.*, 2021, **19**, 4678–4684.