

Supporting Information for

Access to Constrained Fluoropseudopeptides via Ring Closing Metathesis of Fluoroalkenes

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Supporting Information Placeholder

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I. General information

All reactions have been carried out under inert atmosphere in pre-dried glassware. The dry common solvents used were purified by an Innovative Technology PureSolv purification system. Perfluorinated solvent: octafluorotoluene (FluoroChem), was directly used from commercial bottle and kept under argon atmosphere. Commercially available chemicals were obtained from Acros Organics, Aldrich Chemical, Strem Chemicals, Alfa Aesar, TCI, and used as received unless otherwise stated. All commercial chemicals were used without further purification. NMR *spectra* were recorded on a Bruker AC 400 spectrometer. Chemical shifts (δ) are quoted in ppm relative to TMS (^1H) and CFCl_3 (^{19}F). Coupling constants (J) are quoted in Hz. Microwave-assisted reactions were carried out into CEM Microwaves Discover (200 W). High-resolution mass spectra (HRMS) were recorded on Q-TOF Micro WATERS. Infrared spectra were recorded on a Spectrum One Perkin Elmer spectrophotometer. Enantiomeric excesses were determined by chiral HPLC equipped with a photodiode array detector (200–400 nm). See specific conditions detailed for each compound. In all cases, the analysis was calibrated with a sample of the racemate. The wave numbers (ν) of recorded IR-signals are quoted in cm^{-1} . Optical rotations were recorded on an Atago AP - 100 automatic polarimeter at 589 nm. Analytical thin layer chromatography was performed on precoated 200 μm layer thickness silica gel 60 Alumigram® Xtra SIL G/UV₂₅₄. Visualization was accomplished with short wave UV light, potassium permanganate or phosphomolybdic acid staining solution followed by heating. Flash chromatography was either performed on Merck silica gel (40-63 mesh, solid deposit) by standard technique. Yields refer to chromatographically and spectroscopically pure compounds. The products **13**^[1], **14**^[2], **15**^[3] have previously been described and were identified by comparison of their physical and spectroscopic data (^1H , ^{19}F and ^{13}C NMR) with those in the cited references.

^[1] Lemmonier, G.; Zoute, L.; Dupas, G.; Quirion, J.-C.; Jubault, P. *J. Org. Chem.* **2009**, *74*, 4124-4131.

^[2] Zemmouri, R.; Kajjout, M.; Castanet, Y.; Eddarir, S.; Rolando, C. *J. Org. Chem.*, **2011**, *76*, 7691-7698.

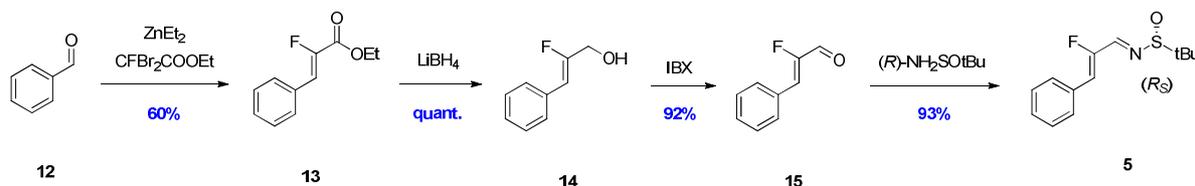
^[3] Wheeler, P.; Vora H. U.; Rovis, T. *Chem. Sci.*, **2013**, *4*, 1674.

II. Synthesis Schemes

1. Synthesis schemes for access to sulfinamides **4**

The synthesis of the various sulfinamides **4** was carried out following a strategy previously described by our laboratory.^[4]

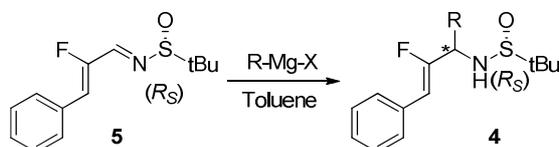
The Ellman sulfinimine **5** was first synthesized through a four steps sequence starting from benzaldehyde **12**.



The primary alcohol **14** was obtained by reduction of the corresponding ethylic ester **13** and was submitted to IBX oxidation to afford aldehyde **15**. Access to the Ellman sulfinimine **5** was possible through condensation of the chiral *tert*-butanesulfinamide to the aldehyde **15**. (*R*)-*tert*-butanesulfinamide auxiliary was chosen in order to obtain major diastereomer with a newly created

stereogenic center in (*S*) configuration, as found in native peptides, by mean of Grignard reagent addition.

The results for the organometallic addition on compound **5** are listed below:



Entry	R	Imine	X	Conditions	Yield of 4 (%) ^a	dr ^b
1	H	(<i>R</i>) _S - 5				
2	Me	(<i>R</i>) _S - 5	Br	0°C, 40 min	93	80/20
3	Ph	(<i>R</i>) _S - 5	Br	-30°C, 2h	96	91/9
4	i-Pr	(<i>R</i>) _S - 5	Cl	0°C, 1h	59	66/33
5	Bn	<i>rac</i> - 5	Br	0°C, 2h	63	50/50

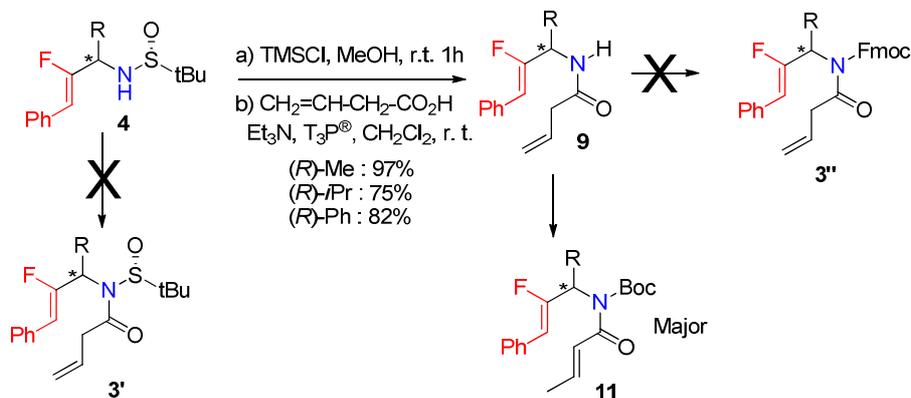
^aYield based on isolated product after flash chromatography. ^bdiastereomeric ratio was determined by ¹⁹F NMR.

Each diastereoisomer was isolated and engaged in the next steps of the sequence.

^[4]Pierry, C.; Cahard, D.; Couve-Bonnaire, S.; Pannecoucke, X. *Org. Biomol. Chem.* **2011**, *9*, 2378.

2. Details for other envisioned strategies

As mentioned in the article, other protecting groups have been envisioned, instead of PMB group, in order to shortcut and/or facilitate the next steps of the synthesis.



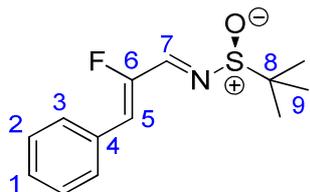
First, keeping the chiral auxiliary seemed to be interesting as it may be hydrolyzed during the last step of the synthesis sequence but unfortunately, various experimental conditions for the amide bond formation remained inefficient (compound **3'**). So after formation of the amide bond (compound **9**), *N*-Fmoc protection in various experimental conditions proved to be unsuccessful (compound **3''**) and the formation of *N*-Boc resulted predominantly in an isomerization of the double bond leading to compound **11**.

III. Synthesis of the various RCM products 2

1. Experimental procedures and data

a. Synthesis of the sulfinimines 5

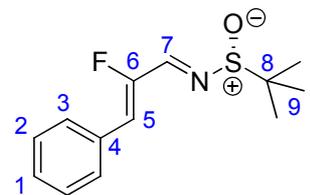
(Ss)-*N*-((*Z*)-2-fluoro-3-phenylallylidene)-2-methylpropane-2-sulfinamide (5)-*S*:



A 100mL round bottom flask was equipped with a stir bar, a reflux condenser and flushed with argon. A solution of aldehyde X (1.2 g, 8 mmol, 1 eq.) in dry THF (36 mL) was prepared. Both $\text{Ti}(\text{OiPr})_4$ (4.78 mL, 16 mmol, 2 eq.) and (*S*)-tertbutylsulfinylamine (1.45 g, 12 mmol, 1.5 eq.) were added. The mixture was heated at reflux for 1h30 and once cooled, poured into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a pad of Celite® and the solid washed with EtOAc. The brine layer was extracted once with EtOAc. The combined organic portions were dried over MgSO_4 , filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (Eluent: Pentane/ Et_2O : 97/03) to afford *(Ss)*-*N*-((*Z*)-2-fluoro-3-phenylallylidene)-2-methylpropane-2-sulfinamide as a light yellow solid (1.99 g, 7.86 mmol, 99%).

^1H NMR (400.13 MHz, CDCl_3): δ (ppm) 8.10 (d, $^3J_{\text{H-F}} = 19\text{Hz}$, 1H, H₇), 7.69 (m, 2H, H₃), 7.42 (m, 3H, H_{1,2}), 6.40 (d, $^3J_{\text{H-F}} = 35\text{Hz}$, 1H, H₅), 1.27 (s, 9H, H₉). **^{19}F NMR (376.50 MHz, CDCl_3):** δ (ppm) -121.36 (dd, $^3J_{\text{F-H}} = 19\text{Hz}$, $^3J_{\text{F-H}} = 35\text{Hz}$, 1F, F₆). **^{13}C NMR (75.47 MHz, CDCl_3):** δ (ppm) 155.4 (d, $^2J_{\text{C-F}} = 21\text{Hz}$, 1C, C₇), 154.2 (d, $^1J_{\text{C-F}} = 264\text{Hz}$, 1C, C₆), 131.7 (d, $^3J_{\text{C-F}} = 4\text{Hz}$, 1C, C₄), 130.2 (s, 2C, C₂), 128.9 (s, 2C, C₃), 129.9 (d, $^6J_{\text{C-F}} = 2\text{Hz}$, 1C, C₁), 122.8 (d, $^2J_{\text{C-F}} = 6\text{Hz}$, 1C, C₅), 58.3 (s, 1C, C₈), 22.5 (s, 3C, C₉). **IR (neat)** ν 2981, 1643, 1571, 1448, 1369, 1180, 1075, 977, 928, 906, 879, 837, 782, 760, 687, 570 cm^{-1} . **HR-MS (ESI⁺):** $m/z = 254.1025$ [$\text{M}+\text{H}$]⁺, calcd. for $\text{C}_{13}\text{H}_{17}\text{FNOS}$: 254.1015. **Anal. calculated for $\text{C}_{13}\text{H}_{16}\text{FNOS}$:** C, 61.63; H, 6.37; N, 5.53; S, 12.66. Found: C, 61.63; H, 6.35; N, 5.52; S, 12.68. $R_f = 0.39$ (5% Et_2O in pentane).

(Rs)-*N*-((*Z*)-2-fluoro-3-phenylallylidene)-2-methylpropane-2-sulfinamide (5)-*R*:



A 100mL round bottom flask was equipped with a stir bar, a reflux condenser and flushed with argon. A solution of aldehyde X (300 mg, 2 mmol, 1 eq.) in dry THF (9 mL) was prepared. Both $\text{Ti}(\text{OiPr})_4$ (1.2 mL, 4 mmol, 2 eq.) and (*R*)-tertbutylsulfinylamine (363 mg, 3 mmol, 1.5 eq.) were added. The mixture was heated at reflux for 1h30 and once cooled, poured

into an equal volume of brine with rapid stirring. The resulting suspension was filtered through a pad of Celite® and the solid washed with EtOAc. The brine layer was extracted once with EtOAc. The combined organic portions were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by chromatography on silica gel (Eluent: Pentane/Et₂O: 97/03) to afford *(Rs)-N-((Z)-2-fluoro-3-phenylallylidene)-2-methylpropane-2-sulfinamide* as a white solid (470 mg, 1.86 mmol, 93%).

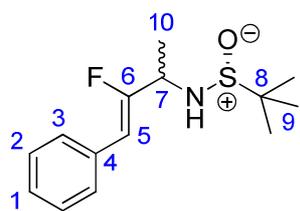
¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 8.11 (d, ³J_{H-F} = 19Hz, 1H, H₇), 7.69 (m, 2H, H₃), 7.42 (m, 3H, H_{1, 2}), 6.40 (d, ³J_{H-F} = 35Hz, 1H, H₅), 1.28 (s, 9H, H₉). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -121.39 (dd, ³J_{F-H} = 19Hz, ³J_{F-H} = 34Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 155.4 (d, ²J_{C-F} = 20Hz, 1C, C₇), 154.2 (d, ¹J_{C-F} = 265Hz, 1C, C₆), 131.7 (d, ³J_{C-F} = 4Hz, 1C, C₄), 130.3 (s, 2C, C₂), 130.0 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 128.9 (s, 2C, C₃), 122.9 (d, ²J_{C-F} = 6Hz, 1C, C₅), 58.2 (s, 1C, C₈), 22.5 (s, 3C, C₉). **IR (neat)** ν 2979, 1715, 1643, 1571, 1449, 1365, 1294, 1256, 1183, 1128, 1077, 980, 928, 906, 828, 762, 758, 687 cm⁻¹. **HR-MS (ESI+):** m/z = 254.1027 [M+H]⁺, calcd. for C₁₃H₁₇FNOS: 254.1015. **Anal. calculated for C₁₃H₁₆FNOS:** C, 61.63; H, 6.37; N, 5.53; S, 12.66. Found: C, 61.67; H, 6.37; N, 5.55; S, 12.66. *Rf* = 0.41 (5% Et₂O in pentane).

b. Synthesis of the sulfinamides **4**

General Procedure for the synthesis of the sulfinamides by nucleophilic addition:

The β-Fluoroenimine (1 eq.) and (depending on the case) a 2M solution of trimethylaluminium (1.1 eq.) were placed in a round-bottom flask under argon atmosphere and dissolved in anhydrous toluene. The solution was cooled down to the reported temperature and a solution of the alkylmagnesium halide was slowly added. The solution was stirred at the reported temperature and the progress of the reaction monitored through ¹⁹F NMR. After completion of the reaction, the solution was quenched with a saturated solution of NH₄Cl and extracted three times with EtOAc. The combined organic layers were then washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue was checked by ¹⁹F NMR for determination of diastereomeric ratio and purified by chromatography on silica gel (eluent: pentane/Et₂O) to afford the desired sulfinamides (*S,Rs*) and (*R,Rs*) separately.

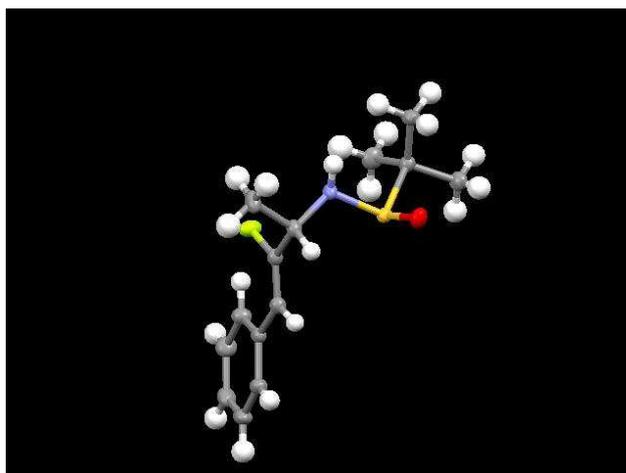
(*R_s*)-*N*-(*Z*)-3-fluoro-4-phenylbut-3-en-2-yl)-2-methylpropane-2-sulfonamide (*4b-c*) :



The general procedure for synthesis of the sulfonamides using (*R_s*)- β -Fluoroenimine (1 eq., 530 mg, 2.1 mmol) and a solution of trimethylaluminium (1.1 eq., 1.15 mL of a 2M solution, 2.3 mmol) in toluene (14 mL) followed by flash chromatography on silica gel (eluent: pentane/Et₂O 80/20) afforded *N*-((*R,Z*)-3-fluoro-4-phenylbut-3-en-2-yl)-2-methylpropane-2-sulfonamide (523 mg, 1.9 mmol, 93 %) as: a white crystalline solid (420 mg, 1.6 mmol, yield 75 %) for diastereomer (*S,R_s*) and a colorless thick oil (103 mg, 0.4 mmol, yield 18 %) for diastereomer (*R,R_s*).

(*S, R_s*) diastereoisomer (*4b*):

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.36 (m, 5H, H_{1,2,3}), 5.74 (d, ³*J*_{H-F} = 39Hz, 1H, H₅), 4.16 (m, 1H, H₇), 3.17 (d, ³*J*_{H-H} = 5Hz, 1H, NH), 1.53 (d, ³*J*_{H-H} = 7Hz, 3H, H₁₀), 1.24 (s, 9H, H₉). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -116.73 (dd, ³*J*_{F-H} = 18Hz, ³*J*_{F-H} = 38Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 159.1 (d, ¹*J*_{C-F} = 270Hz, 1C, C₆), 132.7 (d, ³*J*_{C-F} = 2Hz, 1C, C₄), 128.7 (s, 2C, C₂), 128.5 (s, 2C, C₃), 127.5 (d, ⁶*J*_{C-F} = 2Hz, 1C, C₁), 107.1 (d, ²*J*_{C-F} = 7Hz, 1C, C₅), 55.9 (s, 1C, C₈), 53.3 (d, ²*J*_{C-F} = 28Hz, 1C, C₇), 22.5 (s, 3C, C₉), 20.4 (d, ³*J*_{C-F} = 2Hz, 1C, C₁₀). **IR (neat)** ν 3200, 2980, 1684, 1448, 1366, 1309, 1284, 1172, 1111, 1084, 1053, 1028, 1010, 932, 911, 881, 856, 843, 753, 693 cm⁻¹. **HR-MS (ESI+):** *m/z* = 270.1330 [M+H]⁺, calcd. for C₁₄H₂₁FNOS: 270.1328. **Anal. calculated for C₁₄H₂₀FNOS:** C, 62.42; H, 7.48; N, 5.20; S, 11.90 Found: C, 62.37; H, 7.51; N, 5.17; S, 11.91. [α]_D²⁵ = -99 (*c* 1.5, CH₃Cl). *R_f* = 0.17 (20% Et₂O in pentane).



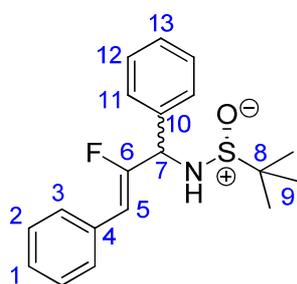
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(*R, R_s*) diastereoisomer (*4c*):

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.32 (m, 5H, H_{1,2,3}), 5.78 (d, ³*J*_{H-F} = 39Hz, 1H, H₅), 4.10 (m, 1H, H₇), 3.55 (d, ³*J*_{H-H} = 5Hz, 1H, NH), 1.48 (d, ³*J*_{H-H} = 7Hz, 3H, H₁₀), 1.23 (s, 9H, H₉). **¹⁹F NMR**

(376.50 MHz, CDCl₃): δ (ppm) -116.05 (dd, $^3J_{F-H} = 14\text{Hz}$, $^3J_{F-H} = 39\text{Hz}$, 1F, F₆). ¹³C NMR (75.47 MHz, CDCl₃): δ (ppm) 159.6 (d, $^1J_{C-F} = 269\text{Hz}$, 1C, C₆), 132.5 (d, $^3J_{C-F} = 2\text{Hz}$, 1C, C₄), 128.6 (s, 2C, C₂), 128.3 (s, 2C, C₃), 127.3 (d, $^6J_{C-F} = 2\text{Hz}$, 1C, C₁), 106.7 (d, $^2J_{C-F} = 7\text{Hz}$, 1C, C₅), 55.8 (s, 1C, C₈), 52.7 (d, $^2J_{C-F} = 28\text{Hz}$, 1C, C₇), 22.3 (s, 3C, C₉), 18.9 (d, $^3J_{C-F} = 2\text{Hz}$, 1C, C₁₀). IR (neat) ν 3198, 2979, 1690, 1494, 1448, 1390, 1363, 1289, 1171, 1111, 1052, 916, 851, 795, 752, 692 cm⁻¹. HR-MS (ESI⁺): $m/z = 270.1330$ [M+H]⁺, calcd. for C₁₄H₂₁FNOS: 270.1328. $[\alpha]_D^{25} = +87$ (c 1.3, CH₃Cl). $R_f = 0.23$ (20% Et₂O in pentane).

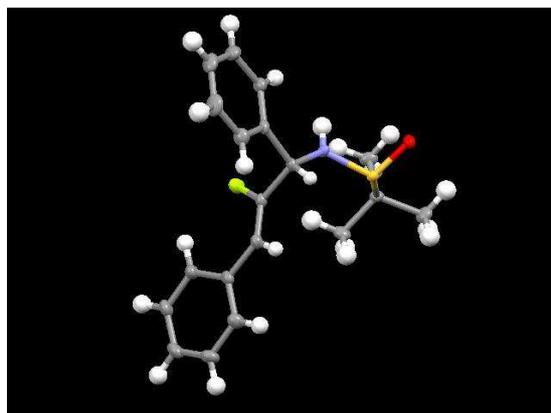
(*R*_S)-*N*-((*Z*)-2-fluoro-1,3-diphenylallyl)-2-methylpropane-2-sulfonamide (4d-e):



The general procedure for synthesis of the sulfonamides using (*R*_S)- β -Fluoroenimine (1 eq., 1 g, 4.0 mmol) in toluene (26 mL) at -30°C during 60 minutes followed by flash chromatography on silica gel (pentane/Et₂O 50/50) afforded *N*-((*R,Z*)-2-fluoro-1,3-diphenylallyl)-2-methylpropane-2-sulfonamide (1.25 g, 3.8 mmol, 96 %) as: a white crystalline solid (900 mg, 2.72 mmol, yield 69%) for diastereomer (*S*)(*R*_S) and a colorless thick oil (350 mg, 1.1 mmol, yield 27 %) for a 50/50 mixture of diastereomers (*R*)(*R*_S) and (*S*)(*R*_S).

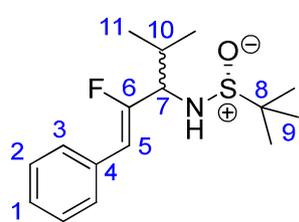
(*S*, *R*_S) diastereoisomer (4d):

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.37 (m, 10H, H_{1, 2, 3, 11, 12, 13}), 5.98 (d, $^3J_{H-F} = 38\text{Hz}$, 1H, H₅), 5.19 (dd, $^3J_{H-F} = 18\text{Hz}$, $^3J_{H-H} = 3\text{Hz}$, 1H, H₇), 3.56 (d, $^3J_{H-H} = 3\text{Hz}$, 1H, NH), 1.30 (s, 9H, H₉). ¹⁹F NMR (376.50 MHz, CDCl₃): δ (ppm) -115.06 (dd, $^3J_{F-H} = 18\text{Hz}$, $^3J_{F-H} = 38\text{Hz}$, 1F, F₆). ¹³C NMR (75.47 MHz, CDCl₃): δ (ppm) 156.9 (d, $^1J_{C-F} = 270\text{Hz}$, 1C, C₆), 138.2 (d, $^3J_{C-F} = 2\text{Hz}$, 1C, C₁₀), 132.6 (d, $^3J_{C-F} = 3\text{Hz}$, 1C, C₄), 128.9-127.6 (10C, C_{1, 2, 3, 11, 12, 13}), 109.3 (d, $^2J_{C-F} = 6\text{Hz}$, 1C, C₅), 60.7 (d, $^2J_{C-F} = 28\text{Hz}$, 1C, C₇), 56.1 (s, 1C, C₈), 22.6 (s, 3C, C₉). IR (neat) ν 3214, 1682, 1598, 1495, 1449, 1406, 1360, 1255, 1153, 1057, 913, 876, 753, 713, 691, 597 cm⁻¹. HR-MS (ESI⁺): $m/z = 332.1498$ [M+H]⁺, calcd. for C₁₉H₂₃FNOS: 332.1484. Anal. calculated for C₁₉H₂₂FNOS: C, 68.85; H, 6.69; N, 4.23; S, 9.67 Found: C, 68.84; H, 6.65; N, 4.22; S, 9.75. $[\alpha]_D^{25} = -87$ (c 1.5, CH₃Cl). $R_f = 0.31$ (40% Et₂O in pentane).



(S, Rs)+(R, Rs) mixture (4d+e):

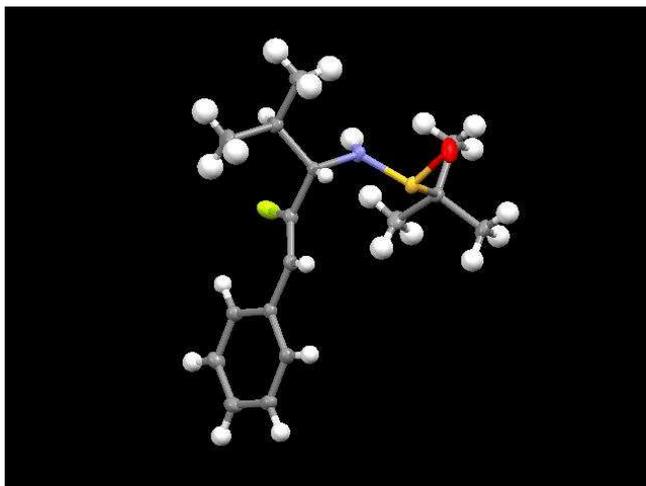
¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.37 (m, 20H, H_{1, 2, 3, 11, 12, 13}, (S, Rs)+(R, Rs)), 5.98 (d, ³J_{H-F} = 38Hz, 1H, H₅, (S, Rs)), 5.85 (d, ³J_{H-F} = 38Hz, 1H, H₅, (R, Rs)), 5.19 (m, 1H, H₇, (S, Rs)), 5.16 (m, 1H, H₇, (R, Rs)), 3.92 (d, ³J_{H-H} = 5Hz, 1H, NH, (R, Rs)), 3.62 (d, ³J_{H-H} = 3Hz, 1H, NH, (S, Rs)), 1.28 (s, 9H, H₉, (S, Rs)), 1.25 (s, 9H, H₉, (R, Rs)). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -113.15 (dd, ³J_{F-H} = 16Hz, ³J_{F-H} = 38Hz, 1F, F₆, (R, Rs)), -115.06 (dd, ³J_{F-H} = 18Hz, ³J_{F-H} = 38Hz, 1F, F₆, (S, Rs)).

(Rs)-N-((Z)-2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-2-methylpropane-2-sulfonamide (4f-g):

The general procedure for synthesis of the sulfonamides using (Rs)-β-Fluoroenimine (1 eq., 1 g, 4.0 mmol) in toluene (26 mL) followed by flash chromatography on silica gel (pentane/Et₂O 70/30) afforded (Rs)-N-((Z)-2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-2-methylpropane-2-sulfonamide (685 mg, 2.3 mmol, 59 %) as: a white crystalline solid (450 mg, 1.5 mmol, yield 39%) for diastereomer (S)(Rs) and a colorless thick oil (225 mg, 0.8 mmol, yield 20 %) for diastereomer (R)(Rs).

(S, Rs) diastereoisomer (4f):

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.50-7.23 (m, 5H, H_{1, 2, 3}), 5.70 (d, ³J_{H-F} = 39Hz, 1H, H₅), 3.68 (ddd, ³J_{H-F} = 23Hz, ³J_{H-H} = 7Hz, ³J_{H-H} = 4Hz, 1H, H₇), 3.33 (d, ³J_{H-H} = 4Hz, 1H, NH), 2.05 (ds, ³J_{H-H} = 7Hz, ³J_{H-H} = 7Hz, 1H, H₁₀), 1.23 (s, 9H, H₉), 1.06 (m, 6H, H₁₁). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -115.61 (dd, ³J_{F-H} = 23Hz, ³J_{F-H} = 39Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 157.6 (d, ¹J_{C-F} = 270Hz, 1C, C₆), 132.9 (d, ³J_{C-F} = 3Hz, 1C, C₄), 128.7 (s, 2C, C₂), 128.5 (2C, C₃), 127.4 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 109.3 (d, ²J_{C-F} = 7Hz, 1C, C₅), 63.7 (d, ²J_{C-F} = 25Hz, 1C, C₇), 55.9 (s, 1C, C₈), 31.5 (s, 1C, C₁₀), 22.5 (s, 3C, C₉), 19.3 (s, 2C, C₁₁). **IR (neat)** ν 3205, 2961, 2870, 1681, 1491, 1466, 1415, 1388, 1361, 1322, 1280, 1163, 1036, 941, 919, 845, 762, 734, 695, 665, 600 cm⁻¹. **HR-MS (ESI+):** m/z = 298.1644 [M+H]⁺, calcd. for C₁₆H₂₅FNOS: 298.1641. **Anal. calculated for C₁₆H₂₄FNOS:** C, 64.61; H, 8.13; N, 4.71; S, 10.78 Found: C, 64.72; H, 8.13; N, 4.74; S, 10.78. [α]_D²⁵ = +15 (c 2.0, CH₃Cl). R_f = 0.30 (50% Et₂O in pentane).

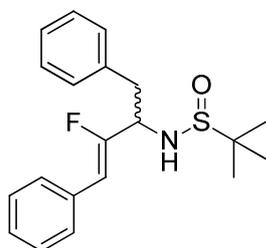


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(R, Rs) diastereoisomer (4g):

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.51-7.20 (m, 5H, H_{1, 2, 3}), 5.77 (d, ³J_{H-F} = 39Hz, 1H, H₅), 3.52 (m, 1H, H₇), 3.52 (br., 1H, NH), 2.04 (ds, ³J_{H-H} = 7Hz, ³J_{H-H} = 7Hz, 1H, H₁₀), 1.25 (s, 9H, H₉), 1.02 (m, 6H, H₁₁). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -116.75 (dd, ³J_{F-H} = 22Hz, ³J_{F-H} = 40Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 158.2 (d, ¹J_{C-F} = 270Hz, 1C, C₆), 132.6 (d, ³J_{C-F} = 2Hz, 1C, C₄), 128.7 (s, 2C, C₂), 128.2 (2C, C₃), 127.1 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 108.3 (d, ²J_{C-F} = 7Hz, 1C, C₅), 64.7 (d, ²J_{C-F} = 26Hz, 1C, C₇), 56.4 (s, 1C, C₈), 31.3 (s, 1C, C₁₀), 22.5 (s, 3C, C₉), 19.3 (s, 1C, C₁₁), 19.0 (s, 1C, C₁₁). **IR (neat)** ν 3203, 2960, 2868, 1687, 1467, 1388, 1363, 1167, 1118, 1054, 876, 754, 693, 594 cm⁻¹. **HR-MS (ESI+):** m/z = 298.1639 [M+H]⁺, calcd. for C₁₆H₂₅FNOS: 298.1641. **Anal. calculated for C₁₆H₂₄FNOS:** C, 64.61; H, 8.13; N, 4.71; S, 10.78 Found: C, 64.72; H, 8.13; N, 4.74; S, 10.78. [α]_D²⁵ = -14.5 (c 4.0, CH₃Cl). R_f = 0.32 (50% Et₂O in pentane).

(Z)-N-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-2-methylpropane-2-sulfinamide (4h):



The general procedure for synthesis of the sulfinamides using a racemic β-Fluoroenimine (1 eq., 400 mg, 1.6 mmol) in toluene (15 mL) followed by flash chromatography on silica gel (pentane/Et₂O 50/50 to 20/80) afforded ***(Z)-N-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-2-methylpropane-2-sulfinamide*** as: a colorless thick oil (340 mg, 1.0 mmol, yield 63 %).

diastereoisomeric mixture (4h):

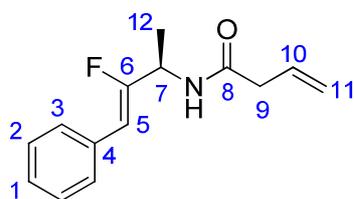
¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.46 (d, ³J_{H-H} = 7Hz, 2H, H₃), 7.28 (m, 8H, H_{1, 2, 12, 13, 14}), 5.64 (d, ³J_{H-F} = 39Hz, 1H, H₅), 4.27 (ddt, ³J_{H-F} = 19Hz, ³J_{H-H} = 7Hz, ³J_{H-H} = 4Hz, 1H, H₇), 3.38 (d, ³J_{H-H} = 4Hz, 1H, NH), 3.16 (m, 2H, H₁₀), 1.20 (s, 9H, H₉). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -118.14 (dd, ³J_{F-H} = 19Hz, ³J_{F-H} = 40Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 156.7 (d, ¹J_{C-F} = 270Hz, 1C, C₆), 135.7 (s, 1C, C₁₁), 132.6 (d, ³J_{C-F} = 2Hz, 1C, C₄), 129.6 (s, 2C, C₂), 128.8 (s, 2C, C₁₃), 128.7 (d, ⁴J_{C-F} = 7Hz, 2C, C₃), 128.5 (2C, C₁₂), 127.5 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 127.2 (s, 1C, C₁₄), 109.4 (d, ²J_{C-F} = 6Hz, 1C, C₅), 58.1 (d, ²J_{C-F} = 27Hz, 1C, C₇), 55.9 (s, 1C, C₈), 39.7 (s, 1C, C₁₀), 22.5 (s, 3C, C₉). **IR (neat)** ν 3180, 3026, 2957, 2873, 1688, 1602, 1495, 1473, 1455, 1363, 1302, 1160, 1050, 947, 914, 882, 847, 748, 712, 692 cm⁻¹. **HR-MS (ESI+):** m/z = 346.1648 [M+H]⁺, calcd. for C₂₀H₂₅FNOS: 346.1641. *R_f* = 0.22 (*like*) (30% Et₂O in pentane). *R_f* = 0.26 (*unlike*) (30% Et₂O in pentane).

c. Synthesis of the bisolefins bearing secondary amide **9**

General procedure:

The starting sulfinamide (1eq.) was placed in a round-bottom flask equipped with a stir bar under argon atmosphere, then dissolved in methanol. The mixture was cooled down to 0°C and trimethylsilyl chloride (4 eq.) was slowly added. The mixture was then placed at room temperature and stirred for 1 hour. The solution was then concentrated under reduced pressure to afford the desired primary amine chlorhydrate salt which was directly involved in the further step. The starting primary amine (1eq.) was placed in a round-bottom flask, equipped with a stir bar under argon atmosphere, and dissolved in dichloromethane. Triethylamine (4 eq.) was added and the mixture was stirred for a few minutes. Then, T3P® (1.5 eq.) and carboxylic acid (1.2 eq.) were added to the mixture. The mixture was stirred at room temperature and the progress of the reaction monitored through ¹⁹F NMR and TLC. After completion, the reaction was stopped by adding water followed by extraction of the aqueous phase with dichloromethane (3x). The organic layers were combined and dried over MgSO₄. After removal of the MgSO₄ and evaporation of the volatile materials under reduced pressure, the crude was purified by flash chromatography on silica gel (Pentane:Et₂O) to afford the expected diene.

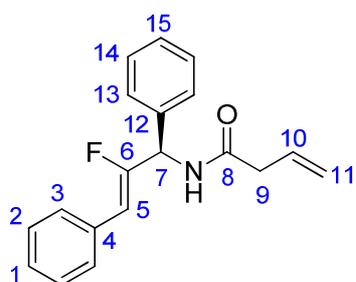
(*R,Z*)-N-(3-fluoro-4-phenylbut-3-en-2-yl)but-3-enamide (9c):



The general two steps procedure for the synthesis of bisolefins bearing secondary amide using sulfinamide **4c** (1 eq., 150 mg, 744 μmol) afforded the (*R,Z*)-N-(3-fluoro-4-phenylbut-3-en-2-yl)but-3-enamide (168 mg, 720 μmol, yield 97 %) as a light yellow oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.49-7.23 (m, 5H, H_{1, 2, 3}), 5.95 (ddt, ³J_{H-H} = 17Hz, ³J_{H-H} = 10Hz, ³J_{H-H} = 7Hz, 1H, H₁₀), 5.81 (d, ³J_{H-H} = 9Hz, 1H, NH), 5.72 (d, ³J_{H-F} = 40Hz, 1H, H₅), 5.26 (m, 2H, H₁₁), 4.84 (ddq, ³J_{H-F} = 20Hz, ³J_{H-H} = 9Hz, ³J_{H-H} = 7Hz, 1H, H₇), 3.05 (d, ³J_{H-H} = 7Hz, 2H, H₉), 1.41 (d, ³J_{H-H} = 7Hz, 3H, H₁₂). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -117.65 (dd, ³J_{F-H} = 19Hz, ³J_{F-H} = 40Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 169.6 (s, 1C, C₈), 158.7 (d, ¹J_{C-F} = 269Hz, 1C, C₆), 132.7 (d, ³J_{C-F} = 2Hz, 1C, C₁), 131.0 (s, 1C, C₁₀), 128.7 (2C, C₂), 128.5 (2C, C₃), 127.5 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 120.2 (s, 1C, C₁₀), 108.5 (d, ²J_{C-F} = 7Hz, 1C, C₅), 46.9 (d, ²J_{C-F} = 28Hz, 1C, C₇), 41.6 (s, 1C, C₉), 18.5 (d, ³J_{C-F} = 2Hz, 1C, C₁₂). **IR (neat)** ν 3278, 3060, 2922, 1685, 1641, 1541, 1492, 1446, 1403, 1346, 1234, 1166, 1099, 1036, 991, 914, 859, 830, 749, 689, 590 cm⁻¹. **HR-MS (ESI+):** m/z = 234.1295 [M+H]⁺, calcd. for C₁₄H₁₇FNO: 234.1294. **Anal. calculated for C₁₄H₁₆FNO:** C, 72.08; H, 6.91; N, 6.00; Found: C, 72.25; H, 7.71; N, 6.19. *R_f* = 0.20 (50% Et₂O in pentane).

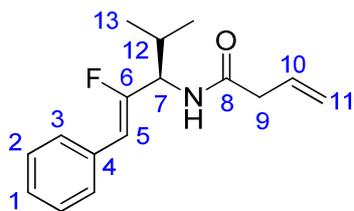
(*R,Z*)-*N*-(2-fluoro-1,3-diphenylallyl)but-3-enamide (9e):



The general two steps procedure for the synthesis of bisolefins bearing secondary amide using sulfinamide **4e** (1 eq., 260 mg, 986 μmol) afforded the (*R,Z*)-*N*-(2-fluoro-1,3-diphenylallyl)but-3-enamide (239 mg, 809 μmol, yield 83 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.38-7.12 (m, 10H, H_{1, 2, 3, 13, 14, 15}), 6.20 (d, ³J_{H-H} = 8Hz, 1H, NH), 5.86 (ddt, ³J_{H-H} = 17Hz, ³J_{H-H} = 10Hz, ³J_{H-H} = 7Hz, 1H, H₁₀), 5.79 (dd, ³J_{H-F} = 20Hz, ³J_{H-H} = 8Hz, 1H, H₇), 5.71 (d, ³J_{H-F} = 39Hz, 1H, H₅), 5.16 (m, 2H, H₁₁), 3.00 (d, ³J_{H-H} = 7Hz, 2H, H₉). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -114.73 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 39Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 169.72 (s, 1C, C₈), 156.8 (d, ¹J_{C-F} = 269Hz, 1C, C₆), 137.6 (s, 1C, C₁₂), 132.5 (d, ³J_{C-F} = 2Hz, 1C, C₄), 130.9 (s, 1C, C₁₀), 128.9-128.2 (8C, C_{2, 3, 13, 14}), 127.7 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 126.9 (s, 1C, C₁₅), 120.4 (s, 1C, C₁₁), 108.7 (d, ²J_{C-F} = 7Hz, 1C, C₅), 54.7 (d, ²J_{C-F} = 28Hz, 1C, C₇), 41.6 (s, 1C, C₉). **IR (neat)** ν 3291, 3030, 1691, 1647, 1527, 1494, 1449, 1404, 1359, 1265, 1214, 1154, 1083, 987, 922, 898, 935, 753, 692 cm⁻¹. **HR-MS (ESI+):** m/z = 296.1452 [M+H]⁺, calcd. for C₁₉H₁₉FNO: 296.1451. **Anal. calculated for C₁₉H₁₈FNO:** C, 77.27; H, 6.14; N, 4.74; S, 9.67 Found: C, 77.25; H, 6.94; N, 5.01. *R_f* = 0.30 (40% Et₂O in pentane).

(*R,Z*)-*N*-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)but-3-enamide (9g):



The general two steps procedure for the synthesis of bisolefins bearing secondary amide using sulfinamide **4g** (1 eq., 100 mg, 435 μmol) afforded the *(R,Z)*-*N*-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)but-3-enamide (85 mg, 330 μmol , yield 75 %) as a light yellow oil.

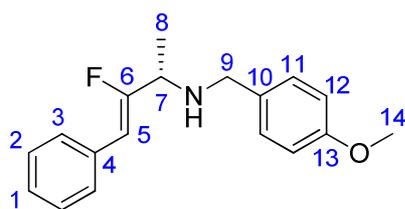
^1H NMR (400.13 MHz, CDCl_3): δ (ppm) 7.49-7.22 (m, 5H, $\text{H}_{1, 2, 3}$), 5.97 (ddt, $^3J_{\text{H-H}} = 17\text{Hz}$, $^3J_{\text{H-H}} = 10\text{Hz}$, $^3J_{\text{H-H}} = 7\text{Hz}$, 1H, H_{10}), 5.88 (d, $^3J_{\text{H-H}} = 10\text{Hz}$, 1H, NH), 5.71 (d, $^3J_{\text{H-F}} = 40\text{Hz}$, 1H, H_5), 5.28 (m, 2H, H_{11}), 4.41 (ddd, $^3J_{\text{H-F}} = 25\text{Hz}$, $^3J_{\text{H-H}} = 9\text{Hz}$, $^3J_{\text{H-H}} = 9\text{Hz}$, 1H, H_7), 3.07 (d, $^3J_{\text{H-H}} = 7\text{Hz}$, 2H, H_9), 2.00 (ds, $^3J_{\text{H-H}} = 7\text{Hz}$, $^3J_{\text{H-H}} = 1\text{Hz}$, 1H, H_{12}), 1.01 (m, 6H, H_{13}). **^{19}F NMR (376.50 MHz, CDCl_3):** δ (ppm) -118.15 (dd, $^3J_{\text{F-H}} = 25\text{Hz}$, $^3J_{\text{F-H}} = 39\text{Hz}$, 1F, F_6). **^{13}C NMR (75.47 MHz, CDCl_3):** δ (ppm) 169.8 (s, 1C, C_8), 157.2 (d, $^1J_{\text{C-F}} = 269\text{Hz}$, 1C, C_6), 132.8 (d, $^3J_{\text{C-F}} = 3\text{Hz}$, 1C, C_4), 131.2 (s, 1C, C_{10}), 128.7 (2C, C_2), 128.5 (2C, C_3), 127.4 (d, $^6J_{\text{C-F}} = 2\text{Hz}$, 1C, C_1), 120.2 (s, 1C, C_{11}), 108.3 (d, $^2J_{\text{C-F}} = 7\text{Hz}$, 1C, C_5), 57.1 (d, $^2J_{\text{C-F}} = 26\text{Hz}$, 1C, C_7), 41.7 (s, 1C, C_9), 30.5 (1C, C_{12}), 19.5 (s, 1C, C_{13}), 18.9 (s, 1C, C_{13}). **IR (neat)** ν 3331, 2963, 1639, 1531, 1353, 1258, 1163, 1074, 996, 912, 840, 762, 693, 595 cm^{-1} . **HR-MS (ESI+):** $m/z = 262.1620$ [$\text{M}+\text{H}$] $^+$, calcd. for $\text{C}_{16}\text{H}_{21}\text{FNO}$: 262.1607. **Anal. calculated for $\text{C}_{16}\text{H}_{20}\text{FNO}$:** C, 73.53; H, 7.71; N, 5.36; Found: C, 73.53; H, 7.75; N, 5.42. $R_f = 0.33$ (40% Et_2O in pentane).

d. Synthesis of the secondary PMB-amines **7**

General procedure:

The starting sulfinamide (1eq.) was placed in a round-bottom flask equipped with a stir bar under argon atmosphere and dissolved in methanol. The mixture was cooled down to 0°C and trimethylsilyl chloride (4 eq.) was slowly added. The mixture was then placed at room temperature and stirred for 1 hour. The solution was then concentrated under reduced pressure to afford the desired primary amine chlorhydrate salt which was directly involved in the further step. The Starting Amine (1eq.) was placed in a two-neck flask, equipped with a reflux condenser and a stir bar under argon atmosphere, and dissolved in acetonitrile. 4-methoxybenzyl chloride (1.2 eq.) and potassium carbonate (5 eq.) were then added in this order. The mixture was heated to 60°C and progress of the reaction monitored through ^{19}F NMR and TLC. After completion, the reaction was stopped by adding water followed by extraction of the aqueous phase with dichloromethane (3x). The organic layers were combined and dried over MgSO_4 . After removal of the MgSO_4 and evaporation of the volatile materials under reduced pressure, the crude was purified by flash chromatography on silica gel (Pentane: Et_2O) to afford the expected PMB protected amine.

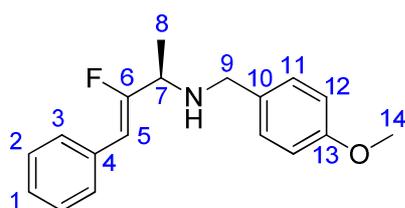
(S,Z)-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine (**7b**):



The general two steps procedure for the synthesis of secondary PMB amines using sulfinamide **4b** (1 eq., 230 mg, 854 μmol) afforded the *(S,Z)*-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine (155 mg, 543 μmol , yield 64 %) as a colorless oil.

$^1\text{H NMR}$ (400.13 MHz, CDCl_3): δ (ppm) 7.44 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H₃), 7.28-7.14 (m, 5H, H_{1,2,11}), 6.78 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H₁₂), 5.59 (d, $^3J_{\text{H-F}} = 39\text{Hz}$, 1H, H₅), 3.70 (s, 3H, H₁₄), 3.77 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H₉), 3.62 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H₉), 3.33 (dquad, $^3J_{\text{H-H}} = 7\text{Hz}$, $^3J_{\text{H-F}} = 22\text{Hz}$, 1H, H₇), 3.16 (br. s, 1H, NH), 1.31 (d, $^3J_{\text{H-H}} = 7\text{Hz}$, 3H, H₈). **$^{19}\text{F NMR}$ (376.50 MHz, CDCl_3):** δ (ppm) -118.43 (dd, $^3J_{\text{F-H}} = 22\text{Hz}$, $^3J_{\text{F-H}} = 39\text{Hz}$, 1F, F₆). **$^{13}\text{C NMR}$ (75.47 MHz, CDCl_3):** δ (ppm) 160.0 (d, $^1J_{\text{C-F}} = 270\text{Hz}$, 1C, C₆), 158.1 (s, 1C, C₁₃), 133.1 (d, $^3J_{\text{C-F}} = 2\text{Hz}$, 1C, C₄), 131.0 (s, 1C, C₁₀), 129.7 (s, 2C, C₁₁), 128.6 (m, 4C, C_{2,3}), 127.3 (d, $^6J_{\text{C-F}} = 2\text{Hz}$, 1C, C₁), 113.9 (s, 2C, C₁₂), 107.2 (d, $^2J_{\text{C-F}} = 8\text{Hz}$, 1C, C₅), 55.3 (s, 1C, C₁₄), 54.6 (d, $^2J_{\text{C-F}} = 27\text{Hz}$, 1C, C₇), 50.3 (s, 1C, C₉), 19.0 (s, 1C, C₈). **IR (neat)** ν 2933, 2855, 1687, 1611, 1585, 1510, 1493, 1463, 1448, 1366, 1300, 1244, 1171, 1109, 1033, 915, 826, 752, 693 cm^{-1} . **HR-MS (ESI+):** $m/z = 286.1616$ [M+H]⁺, calcd. for C₁₈H₂₁FNO: 286.1607. $[\alpha]_{\text{D}}^{25} = -40$ (c 0.5, CH₃Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μm , 1mL/min, 20°C, 95% n-heptane 05% propanol; peak 1: tr = 23.151 min, %Area = 100%. $R_f = 0.19$ (15% Et₂O in pentane).

***(R,Z)*-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine (7c):**



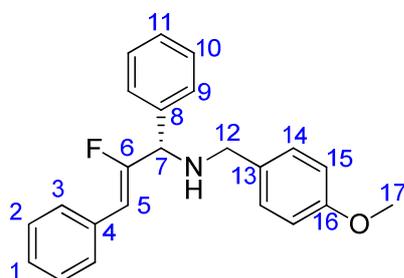
The general two steps procedure for the synthesis of secondary PMB amines using sulfinamide **4c** (1 eq., 180 mg, 668 μmol) afforded the *(R,Z)*-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine (96 mg, 336 μmol , yield 51 %) as a colorless oil.

$^1\text{H NMR}$ (400.13 MHz, CDCl_3): δ (ppm) 7.52 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H₃), 7.37-7.22 (m, 5H, H_{1,2,11}), 6.87 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H₁₂), 5.65 (d, $^3J_{\text{H-F}} = 39\text{Hz}$, 1H, H₅), 3.80 (s, 3H, H₁₄), 3.84 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H₉), 3.68 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H₉), 3.38 (dquad, $^3J_{\text{H-H}} = 7\text{Hz}$, $^3J_{\text{H-F}} = 22\text{Hz}$, 1H, H₇), 1.75 (br. s, 1H, NH), 1.36 (d, $^3J_{\text{H-H}} = 7\text{Hz}$, 3H, H₈). **$^{19}\text{F NMR}$ (376.50 MHz, CDCl_3):** δ (ppm) -118.43 (dd, $^3J_{\text{F-H}} = 22\text{Hz}$, $^3J_{\text{F-H}} = 39\text{Hz}$, 1F, F₆). **$^{13}\text{C NMR}$ (75.47 MHz, CDCl_3):** δ (ppm) 160.8 (d, $^1J_{\text{C-F}} = 270\text{Hz}$, 1C, C₆), 158.8 (s, 1C, C₁₃), 133.3 (d, $^3J_{\text{C-F}} = 2\text{Hz}$, 1C, C₄), 132.0 (s, 1C, C₁₀), 129.4 (s, 2C, C₁₁), 128.6 (m, 4C, C_{2,3}), 127.1 (d, $^6J_{\text{C-F}} = 2\text{Hz}$, 1C, C₁), 113.9 (s, 2C, C₁₂), 106.6 (d, $^2J_{\text{C-F}} = 8\text{Hz}$, 1C, C₅), 55.3 (s, 1C, C₁₄), 54.7 (d, $^2J_{\text{C-F}} = 27\text{Hz}$, 1C, C₇), 50.5 (s, 1C, C₉), 19.4 (s, 1C, C₈). **IR (neat)** ν 2933, 2835, 1687, 1611, 1586, 1511, 1494, 1464, 1448, 1367, 1300, 1245, 1172, 1111, 1034, 916, 828, 736, 694 cm^{-1} . **HR-MS (ESI+):**

$m/z = 286.1617$ $[M+H]^+$, calcd. for $C_{18}H_{21}FNO$: 286.1607. $[\alpha]_D^{25} = +44$ (c 0.8, CH_3Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 95% n-heptane 05% propanol; peak 1: $t_r = 30.735$ min, %Area = 100%. $R_f = 0.19$ (15% Et_2O in pentane).

Mixture of diastereoisomers: **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 95% n-heptane 05% propanol; peak 1: $t_r = 22.458$ min, %Area = 43.63%; peak 2: $t_r = 29.672$ min, %Area = 56.37%.

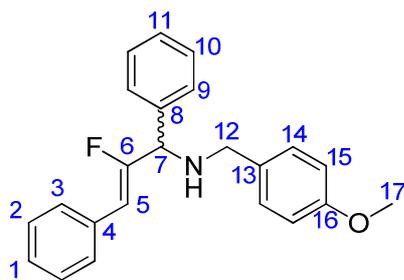
(S,Z)-2-fluoro-N-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine (7d):



The general two steps procedure for the synthesis of secondary PMB amines using sulfonamide **4d** (1 eq., 626 mg, 1.9 mmol) afforded the **(S,Z)-2-fluoro-N-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine** (460 mg, 1.3 mmol, yield 70 %) as a colorless oil.

1H NMR (400.13 MHz, $CDCl_3$): δ (ppm) 7.53 (d, $^3J_{H-H} = 9$ Hz, 2H, H_3), 7.48 (d, $^3J_{H-H} = 8$ Hz, 2H, H_9), 7.39-7.21 (m, 8H, $H_{1,2,10,11,14}$), 6.89 (d, $^3J_{H-H} = 9$ Hz, 2H, H_{15}), 5.90 (d, $^3J_{H-F} = 39$ Hz, 1H, H_5), 4.39 (d, $^3J_{H-F} = 17$ Hz, 1H, H_7), 3.85 (d, $^3J_{H-F} = 13$ Hz, 1H, H_{12}), 3.81 (s, 3H, H_{17}), 3.78 (d, $^3J_{H-F} = 13$ Hz, 1H, H_{12}), 1.82 (br.s, 1H, NH). **^{19}F NMR (376.50 MHz, $CDCl_3$):** δ (ppm) -112.59 (dd, $^3J_{F-H} = 17$ Hz, $^3J_{F-H} = 39$ Hz, 1F, F_6). **^{13}C NMR (75.47 MHz, $CDCl_3$):** δ (ppm) 159.5 (d, $^1J_{C-F} = 269$ Hz, 1C, C_6), 158.8 (C_{16}), 139.7 (1C, C_8), 133.2 (d, $^3J_{C-F} = 2$ Hz, 1C, C_4), 131.9 (1C, C_{13}), 129.4-127.6 (11C, $C_{2,3,9,10,11,14}$), 127.2 (d, $^6J_{C-F} = 2$ Hz, 1C, C_1), 113.9 (2C, C_{15}), 107.3 (d, $^2J_{C-F} = 7$ Hz, 1C, C_5), 63.3 (d, $^2J_{C-F} = 29$ Hz, 1C, C_7), 55.3 (1C, C_{17}), 50.8 (s, 1C, C_{12}). **IR (neat)** ν 3027, 2932, 2835, 1687, 1611, 1585, 1511, 1494, 1448, 1301, 1244, 1173, 1100, 1031, 915, 893, 826, 753, 693 cm^{-1} . **HR-MS (ESI+):** $m/z = 348.1761$ $[M+H]^+$, calcd. for $C_{23}H_{23}FNO$: 348.1764. $[\alpha]_D^{25} = +51$ (c 0.35, CH_3Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 95% n-heptane 05% propanol; peak 1: $t_r = 6.181$ min, %Area = 100%. $R_f = 0.28$ (15% Et_2O in pentane).

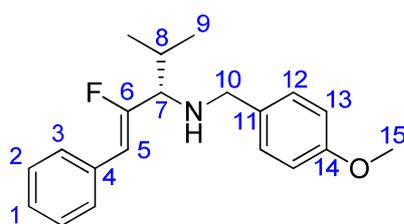
(Z)-2-fluoro-N-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine (7d+e):



The general two steps procedure for the synthesis of secondary PMB amines using sulfinamides **4d+e** (1 eq., 850 mg, 2.6 mmol) afforded the *(Z)*-2-fluoro-*N*-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine (614 mg, 1.8 mmol, yield 69 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.55 (d, ³J_{H-H} = 9Hz, 2H, H₃), 7.50 (d, ³J_{H-H} = 8Hz, 2H, H₉), 7.40-7.21 (m, 8H, H_{1, 2, 10, 11, 14}), 6.91 (d, ³J_{H-H} = 9Hz, 2H, H₁₅), 5.92 (d, ³J_{H-F} = 39Hz, 1H, H₅), 4.41 (d, ³J_{H-F} = 17Hz, 1H, H₇), 3.86 (d, ³J_{H-F} = 13Hz, 1H, H₁₂), 3.81 (s, 3H, H₁₇), 3.79 (d, ³J_{H-F} = 13Hz, 1H, H₁₂), 1.92 (br.s, 1H, NH). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -112.42 (dd, ³J_{F-H} = 17Hz, ³J_{F-H} = 39Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 159.4 (d, ¹J_{C-F} = 269Hz, 1C, C₆), 158.8 (C₁₆), 139.7 (1C, C₈), 133.2 (d, ³J_{C-F} = 2Hz, 1C, C₄), 131.9 (1C, C₁₃), 129.4-127.6 (11C, C_{2, 3, 9, 10, 11, 14}), 127.2 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 113.9 (2C, C₁₅), 107.3 (d, ²J_{C-F} = 7Hz, 1C, C₅), 63.3 (d, ²J_{C-F} = 29Hz, 1C, C₇), 55.3 (1C, C₁₇), 50.8 (s, 1C, C₁₂). **IR (neat)** ν 3027, 2933, 2835, 1687, 1611, 1585, 1511, 1494, 1449, 1300, 1245, 1173, 1101, 1032, 916, 826, 753, 694 cm⁻¹. **HR-MS (ESI+):** m/z = 348.1765 [M+H]⁺, calcd. for C₂₃H₂₃FNO: 348.1764. **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 95% n-heptane 05% propanol; peak 1: tr = 6.071 min, %Area = 50.04%; peak 2: tr = 7.042 min, %Area = 49.96%. R_f = 0.28 (15% Et₂O in pentane).

***(S,Z)*-2-fluoro-*N*-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine (7f):**

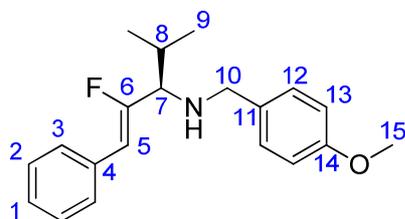


The general two steps procedure for the synthesis of secondary PMB amines using sulfinamide **4f** (1 eq., 210 mg, 706 μmol) afforded the *(S,Z)*-2-fluoro-*N*-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine (148 mg, 472 μmol, yield 66 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.56 (d, ³J_{H-H} = 8Hz, 2H, H₃), 7.36 (m, ³J_{H-H} = 8Hz, 2H, H₂), 7.30 (d, ³J_{H-H} = 9Hz, 2H, H₁₂), 7.25 (m, 1H, H₁), 6.89 (d, ³J_{H-H} = 9Hz, 2H, H₁₃), 5.59 (d, ³J_{H-F} = 39Hz, 1H, H₅), 3.90 (d, ³J_{H-H} = 13Hz, 1H, H₁₀), 3.81 (s, 3H, H₁₅), 3.67 (d, ³J_{H-H} = 13Hz, 1H, H₁₀), 2.83 (dd, ³J_{H-H} = 7Hz, ³J_{H-F} = 25Hz, 1H, H₇), 1.91 (m, 1H, H₈), 1.55 (br. s, 1H, NH), 1.08 (d, ³J_{H-H} = 7Hz, 3H, H₉), 0.99 (d, ³J_{H-H} = 7Hz, 3H, H₉). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -116.08 (dd, ³J_{F-H} = 25Hz, ³J_{F-H} = 39Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 159.3 (d, ¹J_{C-F} = 271Hz, 1C, C₆), 158.6 (s, 1C, C₁₄), 133.4 (d, ³J_{C-F} = 2Hz, 1C, C₄), 132.5 (s, 1C, C₁₁), 129.4-128.5 (s, 6C, C_{2, 3, 12}), 127.0 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 113.8 (s, 2C, C₁₃), 108.4 (d, ²J_{C-F} = 7Hz, 1C, C₅), 65.7 (d, ²J_{C-F} = 25Hz, 1C, C₇), 55.2 (s, 1C, C₁₅), 50.6 (s, 1C, C₁₀), 31.1 (s, 1C, C₈), 19.8 (s, 1C, C₉), 19.7 (s, 1C, C₉). **IR (neat)** ν 2958, 2835, 1683, 1611, 1586, 1511, 1463, 1448, 1385, 1365, 1300, 1243, 1171, 1100, 1034, 960, 915, 824, 752,

693 cm^{-1} . **HR-MS (ESI+)**: $m/z = 314.1933$ $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{20}\text{H}_{25}\text{FNO}$: 314.1920. $[\alpha]_{\text{D}}^{25} = +102$ (c 1.05, CH_3Cl). $R_f = 0.17$ (15% Et_2O in pentane).

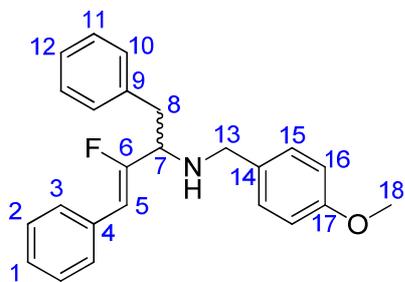
(R,Z)-2-fluoro-N-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine (7g):



The general two steps procedure for the synthesis of secondary PMB amines using sulfinamide **4g** (1 eq., 140 mg, 471 μmol) afforded the **(R,Z)-2-fluoro-N-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine** (85 mg, 272 μmol , yield 58 %) as a colorless oil.

^1H NMR (400.13 MHz, CDCl_3): δ (ppm) 7.55 (d, $^3J_{\text{H-H}} = 8\text{Hz}$, 2H, H_3), 7.37 (t, $^3J_{\text{H-H}} = 8\text{Hz}$, 2H, H_2), 7.29 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H_{12}), 7.25 (m, 1H, H_1), 6.88 (d, $^3J_{\text{H-H}} = 9\text{Hz}$, 2H, H_{13}), 5.59 (d, $^3J_{\text{H-F}} = 39\text{Hz}$, 1H, H_5), 3.90 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H_{10}), 3.81 (s, 3H, H_{15}), 3.66 (d, $^3J_{\text{H-H}} = 13\text{Hz}$, 1H, H_{10}), 2.83 (dd, $^3J_{\text{H-H}} = 7\text{Hz}$, $^3J_{\text{H-F}} = 25\text{Hz}$, 1H, H_7), 1.91 (m, 1H, H_8), 1.72 (br. s, 1H, NH), 1.07 (d, $^3J_{\text{H-H}} = 7\text{Hz}$, 3H, H_9), 0.98 (d, $^3J_{\text{H-H}} = 7\text{Hz}$, 3H, H_9). **^{19}F NMR (376.50 MHz, CDCl_3)**: δ (ppm) -116.08 (dd, $^3J_{\text{F-H}} = 25\text{Hz}$, $^3J_{\text{F-H}} = 39\text{Hz}$, 1F, F_6). **^{13}C NMR (75.47 MHz, CDCl_3)**: δ (ppm) 159.3 (d, $^1J_{\text{C-F}} = 271\text{Hz}$, 1C, C_6), 158.6 (s, 1C, C_{14}), 133.4 (d, $^3J_{\text{C-F}} = 2\text{Hz}$, 1C, C_4), 132.4 (s, 1C, C_{11}), 129.4-128.5 (s, 6C, $\text{C}_{2,3,12}$), 127.0 (d, $^6J_{\text{C-F}} = 2\text{Hz}$, 1C, C_1), 113.7 (s, 2C, C_{13}), 108.5 (d, $^2J_{\text{C-F}} = 7\text{Hz}$, 1C, C_5), 65.7 (d, $^2J_{\text{C-F}} = 25\text{Hz}$, 1C, C_7), 55.3 (s, 1C, C_{15}), 50.6 (s, 1C, C_{10}), 31.1 (s, 1C, C_8), 19.8 (s, 1C, C_9), 19.7 (s, 1C, C_9). **IR (neat)** ν 2957, 2835, 1683, 1611, 1585, 1510, 1463, 1448, 1385, 1365, 1300, 1243, 1171, 1100, 1034, 915, 825, 753, 693, 663 cm^{-1} . **HR-MS (ESI+)**: $m/z = 314.1935$ $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{20}\text{H}_{25}\text{FNO}$: 314.1920. $[\alpha]_{\text{D}}^{25} = -116.8$ (c 0.95, CH_3Cl). $R_f = 0.17$ (15% Et_2O in pentane).

(Z)-3-fluoro-N-(4-methoxybenzyl)-1,4-diphenylbut-3-en-2-amine (7h):



The general two steps procedure for the synthesis of secondary PMB amines using sulfinamide **4h** (1 eq., 244 mg, 706 μmol) afforded the **(Z)-3-fluoro-N-(4-methoxybenzyl)-1,4-diphenylbut-3-en-2-amine** (250 mg, 692 μmol , yield 98 %) as a colorless oil.

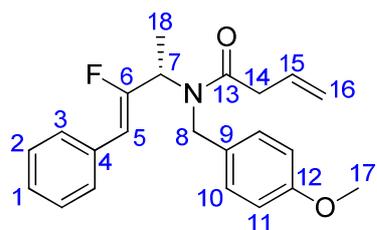
¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.51 (d, ³J_{H-H} = 8Hz, 2H, H₃), 7.36 (t, ³J_{H-H} = 8Hz, 2H, H₂), 7.26 (m, 8H, H_{1, 10, 11, 12}), 7.13 (d, ³J_{H-H} = 9Hz, 2H, H₁₅), 6.84 (d, ³J_{H-H} = 9Hz, 2H, H₁₆), 5.57 (d, ³J_{H-F} = 40Hz, 1H, H₅), 3.88 (d, ³J_{H-H} = 13Hz, 1H, H₁₃), 3.81 (s, 3H, H₁₈), 3.66 (d, ³J_{H-H} = 13Hz, 1H, H₁₃), 3.42 (dt, ³J_{H-H} = 7Hz, ³J_{H-F} = 22Hz, 1H, H₇), 3.07 (dd, ³J_{H-H} = 7Hz, ²J_{H-H} = 13Hz, 1H, H₈), 2.93 (dd, ³J_{H-H} = 7Hz, ²J_{H-H} = 13Hz, 1H, H₈), 1.63 (br. s, 1H, NH). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -117.85 (dd, ³J_{F-H} = 22Hz, ³J_{F-H} = 40Hz, 1F, F₆). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 159.0 (d, ¹J_{C-F} = 270Hz, 1C, C₆), 158.7 (s, 1C, C₁₇), 138.0 (s, 1C, C₉), 133.2 (d, ³J_{C-F} = 2Hz, 1C, C₄), 132.0 (s, 1C, C₁₄), 129.3-128.5 (s, 10C, C_{2, 3, 10, 11, 15}), 126.6 (d, ⁶J_{C-F} = 2Hz, 1C, C₁), 126.6 (s, 1C, C₁₂), 113.8 (s, 2C, C₁₆), 108.0 (d, ²J_{C-F} = 7Hz, 1C, C₅), 61.0 (d, ²J_{C-F} = 27Hz, 1C, C₇), 55.3 (s, 1C, C₁₈), 50.5 (s, 1C, C₁₃), 39.8 (s, 1C, C₈). **IR (neat)** ν 3060, 3027, 2932, 2835, 1713, 1687, 1611, 1585, 1510, 1495, 1453, 1362, 1300, 1244, 1173, 1104, 1032, 915, 827, 736, 693 cm⁻¹. **HR-MS (ESI+):** m/z = 362.1904 [M+H]⁺, calcd. for C₂₄H₂₅FNO: 362.1920. *R*_f = 0.28 (15% Et₂O in pentane).

e. Synthesis of the PMB-protected bisolefins **3**

General procedure:

In an oven dried round-bottom flask equipped with a stir bar and flushed with argon, a solution of the starting secondary amine (1 eq.), triethylamine (2 eq.) and a solution (50% in EtOAc) of T3P® (1.5 eq.) in DCM was prepared. Carboxylic acid (1.2 eq.) was finally added to the mixture. The mixture was stirred at room temperature and the reaction was controlled by TLC and ¹⁹F NMR. When full consumption of starting material was observed, the reaction was stopped by adding water and the aqueous layer extracted with DCM. The organic layers were combined and dried over MgSO₄. After filtration and evaporation of the volatile materials under reduced pressure, the crude was purified by flash chromatography on silica gel (Pentane:Et₂O) to afford the desired PMB protected bisolefin.

(*S,Z*)-*N*-(3-fluoro-4-phenylbut-3-en-2-yl)-*N*-(4-methoxybenzyl)but-3-enamide (3b**):**

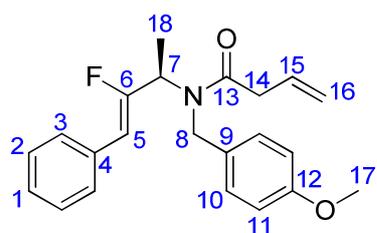


yield 82 %) as a light yellow oil.

The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7b** (1 eq., 53 mg, 186 μmol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 50:50) afforded the (*S,Z*)-*N*-(3-fluoro-4-phenylbut-3-en-2-yl)-*N*-(4-methoxybenzyl)but-3-enamide (65 mg, 151 μmol,

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.30 (m, 7H, H_{1, 2, 3, 10} both rotamers), 6.87 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 2), 6.79 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 1), 6.08 (m, 1H, H₁₅ rotamer 1), 5.99 (m, 1H, H₁₅ rotamer 2), 5.75 (m, 1H, H₇ rotamer 2), 5.71 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.67 (d, ³J_{H-F} = 38 Hz, 1H, H₅ rotamer 1), 5.23 (m, 2H, H₁₆ rotamer 1), 5.11 (m, 2H, H₁₆ rotamer 2), 4.80 (m, 1H, H₇ rotamer 1), 4.54 (m, 2H, H₈ both rotamers), 3.80 (s, 3H, H₁₇ rotamer 2), 3.76 (s, 3H, H₁₇ rotamer 1), 3.37 (d, ³J_{H-H} = 6Hz, 2H, H₁₄ rotamer 1), 3.11 (m, H₁₄ rotamer 2), 1.37 (d, ³J_{H-H} = 7Hz, 3H, H₁₄ rotamer 1), 1.32 (d, ³J_{H-H} = 7Hz, 3H, H₁₈ rotamer 2). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -106.71 (dd, ³J_{F-H} = 5Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 1), -107.90 (dd, ³J_{F-H} = 12Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.2 (C₁₃ rotamer 2), 171.7 (C₁₃ rotamer 1), 158.8 (C₁₂ rotamer 2), 158.6 (d, ¹J_{C-F} = 269Hz, C₆ rotamer 2), 158.5 (C₁₂ rotamer 1), 157.6 (d, ¹J_{C-F} = 269Hz, C₆ rotamer 1), 132.7 (d, ³J_{C-F} = 2Hz, C₄ rotamer 2), 132.3 (d, ³J_{C-F} = 3Hz, C₄ rotamer 1), 131.6 (C₁₅ rotamer 2), 131.1 (C₁₅ rotamer 1), 129.8 - 127.1 (C_{1, 2, 3, 9, 10} both rotamers), 118.1 (C₁₆ rotamer 1), 117.8 (C₁₆ rotamer 2), 114.2 (C₁₁ rotamer 2), 113.7 (C₁₁ rotamer 1), 108.5 (d, ²J_{C-F} = 8Hz, C₅ rotamer 2), 108.2 (d, ²J_{C-F} = 8Hz, C₅ rotamer 1), 55.3 (C₁₇ rotamer 2), 55.2 (C₁₇ rotamer 1), 54.2 (d, ²J_{C-F} = 28Hz, C₇ rotamer 1), 50.5 (d, ²J_{C-F} = 26Hz, C₇ rotamer 2), 46.8 (C₈ rotamer 2), 44.9 (C₈ rotamer 1), 39.2 (C₁₄ both rotamers), 17.0 (d, ³J_{C-F} = 6Hz, C₁₈ rotamer 1), 15.6 (d, ³J_{C-F} = 6Hz, C₁₈ rotamer 2). **IR (neat)** ν 2935, 2836, 1685, 1646, 1612, 1586, 1511, 1495, 1447, 1405, 1360, 1332, 1290, 1244, 1174, 1108, 1032, 994, 915, 856, 820, 753, 693 cm⁻¹. **HR-MS (ESI+):** m/z = 354.1874 [M+H]⁺, calcd. for C₂₂H₂₅FNO₂: 354.1869. [α]_D²⁵ = -68 (c 0.5, CH₃Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 6.924 min, %Area = 0.82%; peak 2: tr = 7.678 min, %Area = 99.15%. R_f = 0.24 (40% Et₂O in pentane).

(R,Z)-N-(3-fluoro-4-phenylbut-3-en-2-yl)-N-(4-methoxybenzyl)but-3-enamide (3c):



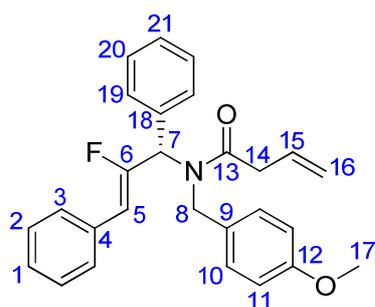
yield 74 %) as a light yellow oil.

The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7c** (1 eq., 35 mg, 123 μmol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 50:50) afforded the **(R,Z)-N-(3-fluoro-4-phenylbut-3-en-2-yl)-N-(4-methoxybenzyl)but-3-enamide** (39 mg, 91 μmol,

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.30 (m, 7H, H_{1, 2, 3, 10} both rotamers), 6.87 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 2), 6.79 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 1), 6.05 (m, 1H, H₁₅ rotamer 1), 5.98 (m, 1H, H₁₅ rotamer 2), 5.75 (m, 1H, H₇ rotamer 2), 5.70 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.67 (d, ³J_{H-F} = 38 Hz, 1H, H₅ rotamer 1), 5.22 (m, 2H, H₁₆ rotamer 1), 5.10 (m, 2H, H₁₆ rotamer 2), 4.80 (m, 1H, H₇ rotamer 1), 4.54 (m, 2H, H₈ both rotamers), 3.79 (s, 3H, H₁₇ rotamer 2), 3.75 (s, 3H, H₁₇ rotamer 1), 3.35 (d, ³J_{H-H} = 6Hz, 2H, H₁₄ rotamer 1), 3.10 (m, H₁₄ rotamer 2), 1.35 (d, ³J_{H-H} = 7Hz, 3H, H₁₄ rotamer 1), 1.31 (d, ³J_{H-H} = 7Hz, 3H, H₁₈ rotamer 2). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -106.71 (dd, ³J_{F-H} = 5Hz, ³J_{F-H} = 40Hz, 1F, F₆ rotamer 1), -107.90 (dd, ³J_{F-H} = 12Hz, ³J_{F-H} = 40Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.2 (C₁₃ rotamer 2), 171.7 (C₁₃ rotamer 1), 158.8 (C₁₂ rotamer 2), 158.6 (d, ¹J_{C-F} = 269Hz, C₆ rotamer 2), 158.5 (C₁₂ rotamer 1), 157.6 (d, ¹J_{C-F} = 269Hz, C₆ rotamer 1), 132.7 (d, ³J_{C-F} = 2Hz, C₄ rotamer 2), 132.3 (d, ³J_{C-F} = 3Hz, C₄ rotamer 1), 131.6 (C₁₅ rotamer 2), 131.1 (C₁₅ rotamer 1), 129.8 - 127.1 (C_{1, 2, 3, 9, 10} both rotamers), 118.1 (C₁₆ rotamer 1), 117.8 (C₁₆ rotamer 2), 114.2 (C₁₁ rotamer 2), 113.7 (C₁₁ rotamer 1), 108.5 (d, ²J_{C-F} = 8Hz, C₅ rotamer 2), 108.2 (d, ²J_{C-F} = 8Hz, C₅ rotamer 1), 55.3 (C₁₇ rotamer 2), 55.2 (C₁₇ rotamer 1), 54.2 (d, ²J_{C-F} = 28Hz, C₇ rotamer 1), 50.5 (d, ²J_{C-F} = 26Hz, C₇ rotamer 2), 46.8 (C₈ rotamer 2), 44.9 (C₈ rotamer 1), 39.2 (C₁₄ both rotamers), 17.0 (d, ³J_{C-F} = 6Hz, C₁₈ rotamer 1), 15.6 (d, ³J_{C-F} = 6Hz, C₁₈ rotamer 2). **IR (neat)** ν 2934, 2836, 1685, 1646, 1612, 1586, 1511, 1495, 1447, 1405, 1360, 1332, 1290, 1244, 1174, 1108, 1032, 994, 915, 856, 821, 753, 735, 693 cm⁻¹. **HR-MS (ESI+):** m/z = 354.1882 [M+H]⁺, calcd. for C₂₂H₂₅FNO₂: 354.1869. **[α]_D²⁵** = +58 (c 0.5, CH₃Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 6.910 min, %Area = 100%. R_f = 0.24 (40% Et₂O in pentane).

Mixture of diastereoisomers: **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 6.908 min, %Area = 47.92%; peak 2: tr = 7.669 min, %Area = 52.08%.

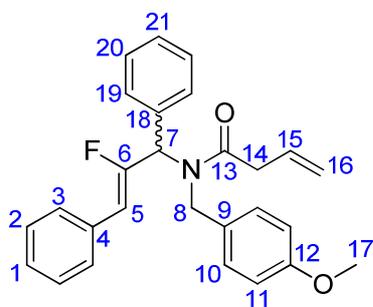
(S,Z)-N-(2-fluoro-1,3-diphenylallyl)-N-(4-methoxybenzyl)but-3-enamide (3d):



The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7d** (1 eq., 300 mg, 864 μmol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 60:40) afforded the **(S,Z)-N-(2-fluoro-1,3-diphenylallyl)-N-(4-methoxybenzyl)but-3-enamide** (360 mg, 838 μmol, yield 97 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.32 (m, 10H, H_{1, 2, 3, 19, 20, 21} both rotamers), 7.02 (d, ³J_{H-H} = 9 Hz, 2H, H₁₀ rotamer 2), 6.99 (d, ³J_{H-H} = 9 Hz, 2H, H₁₀ rotamer 1), 6.79 (m, 1H, H₇ rotamer 2), 6.78 (d, ³J_{H-H} = 8 Hz, 2H, H₁₁ rotamer 2), 6.67 (d, ³J_{H-H} = 8 Hz, 2H, H₁₁ rotamer 1), 6.01 (m, 1H, H₁₅ both rotamers), 5.90 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.82 (m, 1H, H₇ rotamer 1), 5.67 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 1), 5.13 (m, 2H, H₁₆ both rotamers), 4.63 (m, 2H, H₈ both rotamers), 3.76 (s, 3H, H₁₇ rotamer 2), 3.74 (s, 3H, H₁₇ rotamer 1), 3.26 (d, ³J_{H-H} = 6Hz, 2H, H₁₄ rotamer 1), 3.13 (m, H₁₄ rotamer 2). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -104.57 (dd, ³J_{F-H} = 1Hz, ³J_{F-H} = 38Hz, 1F, F₆ rotamer 1), -108.55 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 38Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.5 (C₁₃ rotamer 2), 172.2 (C₁₃ rotamer 1), 158.5 (C₁₂ both rotamers), 156.5 (d, ¹J_{C-F} = 270Hz, C₆ both rotamers), 135.9 (s, C₁₈ rotamer 2), 135.3 (s, C₁₈ rotamer 1), 132.5 (s, C₄ rotamer 2), 132.0 (s, C₄ rotamer 1), 131.4 (C₁₅ both rotamers), 129.3 - 126.8 (C_{1, 2, 3, 9, 10, 19, 20, 21} both rotamers), 118.1 (C₁₆ both rotamers), 113.9 (C₁₁ rotamer 2), 113.3 (C₁₁ rotamer 1), 111.3 (d, ²J_{C-F} = 6Hz, C₅ rotamer 2), 111.1 (m, C₅ rotamer 1), 63.0 (d, ²J_{C-F} = 29Hz, C₇ rotamer 1), 59.1 (d, ²J_{C-F} = 25Hz, C₇ rotamer 2), 55.1 (C₁₇ both rotamers), 48.6 (C₈ rotamer 2), 47.2 (C₈ rotamer 1), 39.0 (C₁₄ both rotamers). **IR (neat)** ν 3028, 2934, 2836, 1650, 1612, 1585, 1511, 1495, 1449, 1401, 1355, 1288, 1245, 1199, 1174, 1132, 1108, 1078, 1031, 992, 955, 915, 809, 752, 693, 660 cm⁻¹. **HR-MS (ESI+):** m/z = 416.2014 [M+H]⁺, calcd. for C₂₇H₂₇FNO₂: 416.2026. [α]_D²⁵ = -92 (c 1.0, CH₃Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 12.564 min, %Area = 99.20%; peak 2: tr = 14.250 min, %Area = 0.8%. R_f = 0.31 (50% Et₂O in pentane).

Racemic (Z)-N-(2-fluoro-1,3-diphenylallyl)-N-(4-methoxybenzyl)but-3-enamide (3d+e):



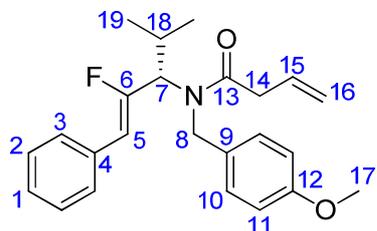
The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7d+e** (1 eq., 100 mg, 288 μmol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 60:40) afforded the **Racemic (Z)-N-(2-fluoro-1,3-diphenylallyl)-N-(4-methoxybenzyl)but-3-enamide** (115 mg, 268 μmol, yield 93 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.32 (m, 10H, H_{1, 2, 3, 19, 20, 21} both rotamers), 7.02 (d, ³J_{H-H} = 9 Hz, 2H, H₁₀ both rotamers), 6.78 (d, ³J_{H-H} = 8 Hz, 2H, H₁₁ rotamer 2), 6.78 (m, 1H, H₇ rotamer 2), 6.70

(m, 2H, H₁₁ rotamer 1), 6.01 (m, 1H, H₁₅ both rotamers), 5.90 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.82 (m, 1H, H₇ rotamer 1), 5.68 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 1), 5.13 (m, 2H, H₁₆ both rotamers), 4.64 (m, 2H, H₈ both rotamers), 3.76 (s, 3H, H₁₇ both rotamers), 3.19 (m, H₁₄ both rotamers). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -104.60 (dd, ³J_{F-H} = 1Hz, ³J_{F-H} = 38Hz, 1F, F₆ rotamer 1), -108.60 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.5 (C₁₃ both rotamers), 158.5 (C₁₂ both rotamers), 156.5 (d, ¹J_{C-F} = 270Hz, C₆ both rotamers), 135.9 (s, C₁₈ both rotamers), 132.5 (s, C₄ both rotamers), 131.4 (C₁₅ both rotamers), 129.3 - 126.8 (C_{1, 2, 3, 9, 10, 19, 20, 21} both rotamers), 118.1 (C₁₆ both rotamers), 113.9 (C₁₁ rotamer 2), 113.3 (C₁₁ rotamer 1), 111.3 (d, ²J_{C-F} = 6Hz, C₅ both rotamers), 63.0 (m, C₇ rotamer 1), 59.1 (d, ²J_{C-F} = 25Hz, C₇ rotamer 2), 55.1 (C₁₇ both rotamers), 48.6 (C₈ rotamer 2), 47.2 (C₈ rotamer 1), 39.0 (C₁₄ both rotamers). **IR (neat)** ν 3028, 2934, 2836, 1650, 1612, 1585, 1511, 1495, 1448, 1401, 1355, 1288, 1245, 1199, 1174, 1131, 1108, 1078, 1031, 993, 955, 916, 809, 752, 693 cm⁻¹. **HR-MS (ESI+):** m/z = 416.2008 [M+H]⁺, calcd. for C₂₇H₂₇FNO₂: 416.2026. **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 12.603 min, %Area = 49.29%; peak 2: tr = 14.261 min, %Area = 50.71%. R_f = 0.31 (50% Et₂O in pentane).

(S,Z)-N-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-N-(4-methoxybenzyl)but-3-enamide (3f):

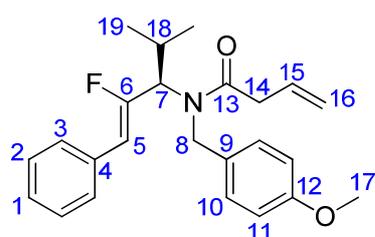
The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7f** (1 eq., 130 mg, 415 μmol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 60:40) afforded the **(S,Z)-N-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-N-(4-methoxybenzyl)but-3-enamide** (95 mg, 221 μmol, yield 54 %) as a light yellow oil.



¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.25 (m, 5H, H_{1, 2, 3} both rotamers), 7.12 (d, ³J_{H-H} = 9 Hz, 2H, H₁₀ both rotamers), 6.78 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 2), 6.72 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 1), 6.08 (m, 1H, H₁₅ rotamer 1), 5.95 (m, 1H, H₁₅ rotamer 2), 5.88 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.69 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 1), 5.23 (m, 2H, H₁₆ rotamer 1), 5.22 (m, 1H, H₇ rotamer 2), 5.07 (m, 2H, H₁₆ rotamer 2), 4.61 (m, 2H, H₈ both rotamers), 4.09 (dd, ³J_{H-H} = 11Hz, ³J_{H-F} = 20Hz, 1H, H₇ rotamer 1), 3.73 (s, 3H, H₁₇ rotamer 2), 3.71 (s, 3H, H₁₇ rotamer 1), 3.35 (m, 2H, H₁₄ rotamer 1), 3.05 (m, H₁₄ rotamer 2), 2.22 (m, 1H, H₁₈ both rotamers), 1.00 (m, 6H, H₁₉ both rotamers). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -107.78 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 1), -111.61 (dd, ³J_{F-H} = 27Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.5 (C₁₃ rotamer 2), 171.6 (C₁₃ rotamer 1), 158.6 (C₁₂ rotamer 2), 158.3 (C₁₂ rotamer 1), 157.4 (d, ¹J_{C-F} = 272Hz, C₆ both rotamers), 132.7 (d, ³J_{C-F} = 2Hz, C₄ rotamer 2), 132.2 (d, ³J_{C-F} = 3Hz, C₄ rotamer 1), 131.9 (C₁₅ rotamer 1), 131.7 (C₁₅ rotamer 2), 129.8 - 127.1 (C_{1, 2, 3, 9, 10} both rotamers), 118.1 (C₁₆ rotamer 1), 117.9 (C₁₆ rotamer 2),

114.1 (C₁₁ rotamer 2), 113.5 (C₁₁ rotamer 1), 110.7 (d, ²J_{C-F} = 7Hz, C₅ rotamer 2), 110.4 (d, ²J_{C-F} = 8Hz, C₅ rotamer 1), 66.1 (d, ²J_{C-F} = 24Hz, C₇ rotamer 1), 61.3 (d, ²J_{C-F} = 25Hz, C₇ rotamer 2), 55.2 (C₁₇ rotamer 2), 55.1 (C₁₇ rotamer 1), 47.1 (d, ⁴J_{C-F} = 3Hz, C₈ rotamer 2), 45.7 (d, ⁴J_{C-F} = 3Hz, C₈ rotamer 1), 39.4 (C₁₄ rotamer 1), 39.1 (C₁₄ rotamer 2), 27.7 (d, ³J_{C-F} = 3Hz, C₁₈ rotamer 1), 26.9 (d, ³J_{C-F} = 2Hz, C₁₈ rotamer 2), 20.6 (3C, C₁₉ rotamer 1), 20.0 (3C, C₁₉ rotamer 2), 19.5 (3C, C₁₉ rotamer 1), 19.1 (3C, C₁₉ rotamer 2). **IR (neat)** ν 2964, 1648, 1613, 1513, 1465, 1247, 1176, 1109, 1034, 968, 916, 810, 753, 695 cm⁻¹. **HR-MS (ESI+)**: m/z = 382.2189 [M+H]⁺, calcd. for C₂₄H₂₉FNO₂: 382.2182. $[\alpha]_D^{25}$ = -168 (c 1.3, CH₃Cl). **Chiral HPLC**: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 60% n-heptane 40% propanol; peak 1: tr = 3.773 min, %Area = 100%. R_f = 0.27 (40% Et₂O in pentane).

(R,Z)-N-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-N-(4-methoxybenzyl)but-3-enamide (3g):



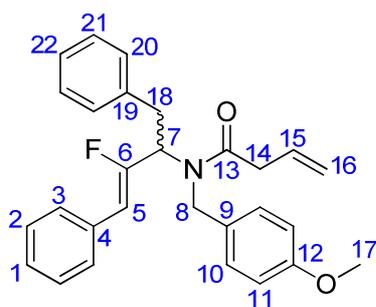
The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7g** (1 eq., 130 mg, 415 μ mol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 60:40) afforded the **(R,Z)-N-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-N-(4-methoxybenzyl)but-3-enamide** (43 mg, 100 μ mol, yield 37 %) as a light yellow oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.25 (m, 5H, H_{1,2,3} both rotamers), 7.13 (d, ³J_{H-H} = 9 Hz, 2H, H₁₀ both rotamers), 6.79 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 2), 6.73 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 1), 6.08 (m, 1H, H₁₅ rotamer 1), 5.95 (m, 1H, H₁₅ rotamer 2), 5.88 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 2), 5.70 (d, ³J_{H-F} = 39 Hz, 1H, H₅ rotamer 1), 5.23 (m, 2H, H₁₆ rotamer 1), 5.22 (m, 1H, H₇ rotamer 2), 5.07 (m, 2H, H₁₆ rotamer 2), 4.62 (m, 2H, H₈ both rotamers), 4.10 (dd, ³J_{H-H} = 11Hz, ³J_{H-F} = 20Hz, 1H, H₇ rotamer 1), 3.74 (s, 3H, H₁₇ rotamer 2), 3.72 (s, 3H, H₁₇ rotamer 1), 3.35 (m, 2H, H₁₄ rotamer 1), 3.06 (m, H₁₄ rotamer 2), 2.22 (m, 1H, H₁₈ both rotamers), 1.01 (m, 6H, H₁₉ both rotamers). **¹⁹F NMR (376.50 MHz, CDCl₃)**: δ (ppm) -107.77 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 1), -111.61 (dd, ³J_{F-H} = 27Hz, ³J_{F-H} = 39Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃)**: δ (ppm) 172.5 (C₁₃ both rotamers), 158.7 (C₁₂ rotamer 2), 158.4 (C₁₂ rotamer 1), 157.4 (d, ¹J_{C-F} = 272Hz, C₆ both rotamers), 132.8 (d, ³J_{C-F} = 2Hz, C₄ rotamer 2), 132.2 (d, ³J_{C-F} = 3Hz, C₄ rotamer 1), 131.7 (C₁₅ both rotamers), 129.6 - 126.9 (C_{1,2,3,9,10} both rotamers), 118.2 (C₁₆ rotamer 1), 117.9 (C₁₆ rotamer 2), 114.1 (C₁₁ rotamer 2), 113.5 (C₁₁ rotamer 1), 110.7 (d, ²J_{C-F} = 7Hz, C₅ rotamer 2), 110.4 (d, ²J_{C-F} = 6Hz, C₅ rotamer 1), 61.3 (d, ²J_{C-F} = 25Hz, C₇ both rotamers), 55.3 (C₁₇ rotamer 2), 55.2 (C₁₇ rotamer 1), 47.2 (d, ⁴J_{C-F} = 3Hz, C₈ rotamer 2), 45.7 (d, ⁴J_{C-F} = 3Hz, C₈ rotamer 1), 39.4 (C₁₄ rotamer 1), 39.1 (C₁₄ rotamer 2), 26.9 (d, ³J_{C-F} = 2Hz, C₁₈

both rotamers), 20.6 (3C, C₁₉ rotamer 1), 20.0 (3C, C₁₉ rotamer 2), 19.5 (3C, C₁₉ rotamer 1), 19.1 (3C, C₁₉ rotamer 2). **IR (neat)** ν 2964, 1646, 1613, 1586, 1512, 1464, 1449, 1405, 1389, 1289, 1245, 1174, 1108, 1033, 993, 968, 915, 883, 808, 737, 693, 664 cm⁻¹. **HR-MS (ESI+)**: $m/z = 382.2197$ [M+H]⁺, calcd. for C₂₄H₂₉FNO₂: 382.2182. $[\alpha]_D^{25} = +181$ (c 1.42, CH₃Cl). **Chiral HPLC**: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 60% n-heptane 40% propanol; peak 1: $t_r = 6.169$ min, %Area = 100%. $R_f = 0.27$ (40% Et₂O in pentane).

Mixture of diastereoisomers: **Chiral HPLC**: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 60% n-heptane 40% propanol; peak 1: $t_r = 3.762$ min, %Area = 26.51%; peak 2: $t_r = 6.150$ min, %Area = 73.49%.

(S,Z)-N-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-N-(4-methoxybenzyl)but-3-enamide (3h):



The general procedure for the synthesis of the PMB protected bisolefins using secondary amine **7h** (1 eq., 250 mg, 692 μ mol) followed by a purification by chromatography over silica gel (eluent: pentane:Et₂O = 60:40) afforded the *(S,Z)-N-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-N-(4-methoxybenzyl)but-3-enamide* (230 mg, 536 μ mol, yield 78 %) as a colorless oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.24 (m, 12H, H_{1, 2, 3, 10, 20, 21, 22} both rotamers), 6.82 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 2), 6.77 (d, ³J_{H-H} = 9 Hz, 2H, H₁₁ rotamer 1), 5.83 (m, 1H, H₁₅ both rotamers), 5.75 (d, ³J_{H-F} = 39 Hz, 1H, H₅ both rotamers), 5.08 (m, 2H, H₁₆ rotamer 1), 5.02 (m, 2H, H₁₆ rotamer 2), 4.67 (m, 2H, H₈ rotamer 1), 4.58 (m, 2H, H₈ rotamer 2), 5.79 (m, 1H, H₇ rotamer 2), 4.80 (m, 1H, H₇ rotamer 1), 3.77 (s, 3H, H₁₇ rotamer 2), 3.75 (s, 3H, H₁₇ rotamer 1), 3.09 (m, 2H, H₁₈ both rotamers), 3.03 (d, ³J_{H-H} = 7Hz, 2H, H₁₄ rotamer 2), 2.78 (m, H₁₄ rotamer 1). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -105.41 (dd, ³J_{F-H} = 12Hz, ³J_{F-H} = 38Hz, 1F, F₆ rotamer 1), -109.37 (dd, ³J_{F-H} = 20Hz, ³J_{F-H} = 38Hz, 1F, F₆ rotamer 2). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 172.2 (C₁₃ rotamer 2), 171.9 (C₁₃ rotamer 1), 158.9 (C₁₂ rotamer 2), 158.6 (C₁₂ rotamer 1), 156.9 (d, ¹J_{C-F} = 269Hz, C₆ rotamer 2), 155.4 (d, ¹J_{C-F} = 270Hz, C₆ rotamer 1), 136.9 (C₁₅ rotamer 2), 136.7 (C₁₅ rotamer 1), 132.7 (d, ³J_{C-F} = 2Hz, C₄ rotamer 2), 132.1 (d, ³J_{C-F} = 3Hz, C₄ rotamer 1), 131.6 (C₁₉ rotamer 1), 131.5 (C₁₉ rotamer 2), 129.7 - 126.8 (C_{1, 2, 3, 9, 10, 20, 21, 22} both rotamers), 118.0 (C₁₆ rotamer 1), 117.9 (C₁₆ rotamer 2), 114.2 (C₁₁ rotamer 2), 113.7 (C₁₁ rotamer 1), 110.5 (d, ²J_{C-F} = 7Hz, C₅ rotamer 2), 109.9 (d, ²J_{C-F} = 7Hz, C₅ rotamer 1), 58.5 (d, ²J_{C-F} = 25Hz, C₇ rotamer 1), 56.7 (d, ²J_{C-F} = 25Hz, C₇ rotamer 2), 55.3 (C₁₇ rotamer 2), 55.2 (C₁₇

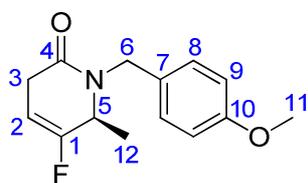
rotamer 1), 47.8 (C₈ rotamer 2), 45.4 (C₈ rotamer 1), 39.2 (C₁₄ rotamer 2), 38.6 (C₁₄ rotamer 1), 36.4 (d, ³J_{C-F} = 3Hz, C₁₈ rotamer 1), 35.8 (d, ³J_{C-F} = 3Hz, C₁₈ rotamer 2). **IR (neat)** ν 3062, 3028, 2933, 2836, 1686, 1646, 1612, 1585, 1511, 1495, 1449, 1404, 1357, 1328, 1302, 1291, 1245, 1175, 1108, 1079, 1031, 993, 959, 915, 822, 749, 733, 693 cm⁻¹. **HR-MS (ESI+)**: m/z = 430.2194 [M+H]⁺, calcd. for C₂₈H₂₉FNO₂: 430.2182. R_f = 0.35 (50% Et₂O in pentane).

f. Synthesis of the cyclic lactams **2** through ring-closing-metathesis

General procedure:

An oven-dried microwave flask equipped with a stir bar was filled under argon with diene (1eq.) and perfluorotoluene (0.02M) before the addition of the pre-catalyst **M2** (reported number of eq.). The mixture was heated at the reported temperature during 15 minutes into a microwave reactor at 200W. The vial content was then transferred into a round-bottom flask from the which the solvent was evaporated. The conversion was calculated by both ¹H and ¹⁹F NMR integrations. A purification was then carried out by flash chromatography on silica gel (Pentane:Et₂O) to reach the desired cyclic lactam.

(S)-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3H)-one (2b):

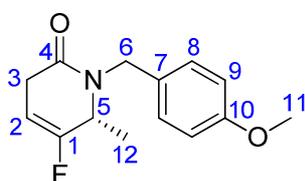


The general procedure for the synthesis of the cyclic lactams through ring-closing-metathesis using PMB-protected bisolefin **3b** (1 eq., 26 mg, 74 μmol) and M2 catalyst (2 eq.) at 70°C followed by purification by chromatography on silica gel (Pentane:Et₂O = 60:40) afforded the **(S)-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3H)-one** (14.3 mg, 66 μmol, yield 95 %) as a thick light brown oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.18 (d, ³J_{H-H} = 9Hz, 2H, H₈), 6.86 (d, ³J_{H-H} = 9Hz, 2H, H₉), 5.39 (d, ²J_{H-H} = 15Hz, 1H, H₆), 5.22 (m, 1H, H₂), 3.90 (d, ²J_{H-H} = 15Hz, 1H, H₆), 3.83 (m, 1H, H₅), 3.79 (s, 3H, H₁₁), 3.10 (m, 2H, H₃), 1.39 (d, ³J_{H-H} = 7Hz, 3H, H₁₂). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -116.88 (m, 1F, F₁). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 166.8 (s, 1C, C₄), 159.2 (s, 1C, C₁₀), 156.2 (d, ¹J_{C-F} = 254Hz, 1C, C₁), 129.4 (s, 2C, C₈), 128.4 (1C, C₇), 114.2 (s, 2C, C₉), 96.9 (d, ²J_{C-F} = 17Hz, 1C,

C₂), 55.3 (s, 1C, C₁₁), 51.0 (d, ²J_{C-F} = 36Hz, 1C, C₅), 45.9 (s, 1C, C₆), 29.9 (d, ³J_{C-F} = 9Hz, 1C, C₃), 18.3 (d, ²J_{C-F} = 2Hz, 1C, C₁₂). **IR (neat)** ν 2934, 2837, 1729, 1644, 1613, 1585, 1512, 1462, 1414, 1379, 1357, 1303, 1282, 1241, 1171, 1083, 1113, 1067, 1027, 983, 905, 813, 752, 721, 693 cm⁻¹. **HR-MS (ESI+)**: m/z = 250.1254 [M+H]⁺, calcd. for C₁₄H₁₇FNO₂: 250.1243. [α]_D²⁵ = -106 (c 1.5, CH₃Cl). **Chiral HPLC**: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 8.360 min, % Area = 98.97%; peak 2: tr = 9.962 min, % Area = 1.03%. R_f = 0.23 (50% Et₂O in pentane).

(R)-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3H)-one (2c):

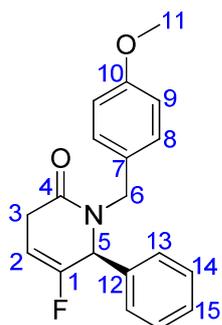


The general procedure for the synthesis of the cyclic lactams through ring-closing-metathesis using PMB-protected bisolefin **3c** (1 eq., 18 mg, 51 μmol) and M2 catalyst (2 eq.) at 70°C followed by purification by chromatography on silica gel (Pentane:Et₂O = 60:40) afforded the **(R)-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3H)-one** (9.9 mg, 46 μmol, yield 91 %) as a thick light brown oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.18 (d, ³J_{H-H} = 9Hz, 2H, H₈), 6.86 (d, ³J_{H-H} = 9Hz, 2H, H₉), 5.39 (d, ²J_{H-H} = 15Hz, 1H, H₆), 5.23 (m, 1H, H₂), 3.90 (d, ²J_{H-H} = 15Hz, 1H, H₆), 3.83 (m, 1H, H₅), 3.80 (s, 3H, H₁₁), 3.10 (m, 2H, H₃), 1.39 (d, ³J_{H-H} = 7Hz, 3H, H₁₂). **¹⁹F NMR (376.50 MHz, CDCl₃)**: δ (ppm) -116.88 (m, 1F, F₁). **¹³C NMR (75.47 MHz, CDCl₃)**: δ (ppm) 166.8 (s, 1C, C₄), 159.2 (s, 1C, C₁₀), 156.2 (d, ¹J_{C-F} = 254Hz, 1C, C₁), 129.4 (s, 2C, C₈), 128.4 (1C, C₇), 114.2 (s, 2C, C₉), 96.9 (d, ²J_{C-F} = 17Hz, 1C, C₂), 55.3 (s, 1C, C₁₁), 51.0 (d, ²J_{C-F} = 36Hz, 1C, C₅), 45.9 (s, 1C, C₆), 29.9 (d, ³J_{C-F} = 9Hz, 1C, C₃), 18.3 (d, ²J_{C-F} = 2Hz, 1C, C₁₂). **IR (neat)** ν 2936, 2837, 1729, 1644, 1613, 1585, 1512, 1463, 1414, 1379, 1357, 1304, 1283, 1243, 1172, 1113, 1067, 1028, 983, 906, 814, 752, 721, 693 cm⁻¹. **HR-MS (ESI+)**: m/z = 250.1255 [M+H]⁺, calcd. for C₁₄H₁₇FNO₂: 250.1243. [α]_D²⁵ = +97 (c 1.3, CH₃Cl). **Chiral HPLC**: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 8.370 min, % Area = 0.57%; peak 2: tr = 9.929 min, % Area = 99.43%. R_f = 0.23 (50% Et₂O in pentane).

Racemic mixture: Chiral HPLC: Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5μm, 1mL/min, 20°C, 80% n-heptane 20% propanol; peak 1: tr = 8.349 min, % Area = 47.88%; peak 2: tr = 9.928 min, % Area = 52.12%.

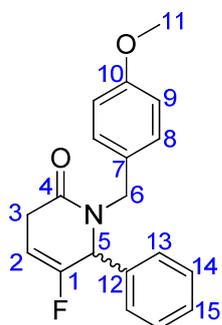
(S)-5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one (2d):



The general procedure for the synthesis of the cyclic lactams through ring-closing-metathesis using PMB-protected bisolefin **3d** (1 eq., 215 mg, 518 μmol) and M2 catalyst (2 eq.) at 70°C followed by purification by chromatography on silica gel (Pentane:Et₂O = 60:40) afforded the *(S)*-5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one (110 mg, 511 μmol , yield 98 %) as a thick light brown oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.41 (m, 3H, H_{14, 15}), 7.25 (m, 2H, H₁₃), 7.12 (d, ³J_{H-H} = 8Hz, 2H, H₈), 6.87 (d, ³J_{H-H} = 8Hz, 2H, H₉), 5.50 (dd, ⁴J_{H-H} = 2Hz, ²J_{H-H} = 14Hz, 1H, H₆), 5.27 (m, 1H, H₂), 4.73 (d, ³J_{H-F} = 7Hz, 1H, H₅), 3.81 (s, 3H, H₁₁), 3.29 (m, 2H, H₃), 3.29 (d, ²J_{H-H} = 14Hz, 1H, H₆). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -115.13 (m, 1F, F₁). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 166.6 (s, 1C, C₄), 159.3 (s, 1C, C₁₀), 154.1 (d, ¹J_{C-F} = 253Hz, 1C, C₁), 137.2 (d, ³J_{C-F} = 2Hz, 1C, C₁₂), 129.9 (s, 2C, C₈), 129.2 (s, 2C, C₁₄), 129.0 (s, 1C, C₁₅), 128.0 (1C, C₇), 127.6 (s, 2C, C₁₃), 114.2 (s, 2C, C₉), 97.3 (d, ²J_{C-F} = 17Hz, 1C, C₂), 59.6 (d, ²J_{C-F} = 36Hz, 1C, C₅), 55.3 (s, 1C, C₁₁), 45.7 (s, 1C, C₆), 30.0 (d, ³J_{C-F} = 8Hz, 1C, C₃). **IR (neat)** ν 2933, 2837, 2299, 1728, 1646, 1611, 1585, 1511, 1493, 1450, 1411, 1357, 1323, 1302, 1282, 1237, 1171, 1110, 1066, 1030, 950, 926, 834, 817, 752, 729, 698, 664 cm⁻¹. **HR-MS (ESI+):** m/z = 312.1414 [M+H]⁺, calcd. for C₁₉H₁₉FNO₂: 312.1400. [α]_D²⁵ = +153 (*c* 0.85, CH₃Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μm , 1mL/min, 20°C, 60% n-heptane 40% propanol; peak 1: t_r = 23.146 min, % Area = 100%. *Rf* = 0.26 (50% Et₂O in pentane).

Racemic 5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one (2d+e):

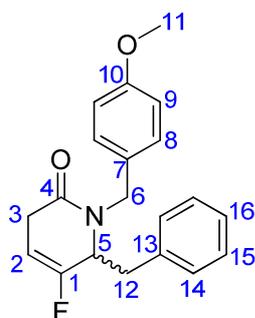


The general procedure for the synthesis of the cyclic lactams through ring-closing-metathesis using PMB-protected bisolefin **3d+e** (1 eq., 55 mg, 132 μmol) and M2 catalyst (2 eq.) at 70°C followed by purification by chromatography on silica gel (Pentane:Et₂O = 60:40) afforded the *Racemic* 5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one (26 mg, 121 μmol , yield 93 %) as a thick light brown oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.40 (m, 3H, H_{14, 15}), 7.25 (m, 2H, H₁₃), 7.12 (d, ³J_{H-H} = 8Hz, 2H, H₈), 6.87 (d, ³J_{H-H} = 8Hz, 2H, H₉), 5.49 (dd, ⁴J_{H-H} = 2Hz, ²J_{H-H} = 14Hz, 1H, H₆), 5.27 (m, 1H, H₂), 4.73 (d, ³J_{H-F} = 7Hz, 1H, H₅), 3.81 (s, 3H, H₁₁), 3.30 (m, 2H, H₃), 3.30 (d, ²J_{H-H} = 14Hz, 1H, H₆). **¹⁹F NMR**

NMR (376.50 MHz, CDCl₃): δ (ppm) -115.12 (m, 1F, F₁). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 166.5 (s, 1C, C₄), 159.2 (s, 1C, C₁₀), 154.0 (d, ¹J_{C-F} = 253Hz, 1C, C₁), 137.1 (d, ³J_{C-F} = 2Hz, 1C, C₁₂), 129.9 (s, 2C, C₈), 129.2 (s, 2C, C₁₄), 129.0 (s, 1C, C₁₅), 128.0 (1C, C₇), 127.6 (s, 2C, C₁₃), 114.1 (s, 2C, C₉), 97.2 (d, ²J_{C-F} = 17Hz, 1C, C₂), 59.6 (d, ²J_{C-F} = 36Hz, 1C, C₅), 55.3 (s, 1C, C₁₁), 45.7 (s, 1C, C₆), 30.0 (d, ³J_{C-F} = 8Hz, 1C, C₃). **IR (neat)** ν 2935, 2837, 2311, 1729, 1645, 1611, 1586, 1511, 1493, 1451, 1411, 1357, 1323, 1302, 1281, 1238, 1172, 1110, 1066, 1031, 950, 927, 834, 817, 752, 729, 698, 664 cm⁻¹. **HR-MS (ESI+):** m/z = 312.1413 [M+H]⁺, calcd. for C₁₉H₁₉FNO₂: 312.1400. **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20°C, 60% n-heptane 40% propanol; peak 1: tr = 11.805 min, %Area = 50.18%; peak 2: tr = 23.138 min, %Area = 49.82%. R_f = 0.26 (50% Et₂O in pentane).

6-benzyl-5-fluoro-1-(4-methoxybenzyl)-1,6-dihydropyridin-2(3H)-one (2h):



The general procedure for the synthesis of the cyclic lactams through ring-closing-metathesis using PMB-protected bisolefin **3h** (1 eq., 35 mg, 82 μ mol) and M2 catalyst (4 eq.) at 120°C followed by purification by chromatography on silica gel (Pentane:Et₂O = 70:30) afforded the **6-benzyl-5-fluoro-1-(4-methoxybenzyl)-1,6-dihydropyridin-2(3H)-one** (20 mg, 62 μ mol, yield 86 %) as a thick light brown oil.

¹H NMR (400.13 MHz, CDCl₃): δ (ppm) 7.27 (m, 3H, H_{15, 16}), 7.21 (d, ³J_{H-H} = 8Hz, 2H, H₈), 7.09 (m, 2H, H₁₄), 6.88 (d, ³J_{H-H} = 8Hz, 2H, H₉), 5.60 (d, ²J_{H-H} = 15Hz, 1H, H₆), 5.12 (m, 1H, H₂), 4.09 (m, 1H, H₅), 3.88 (d, ²J_{H-H} = 14Hz, 1H, H₆), 3.81 (s, 3H, H₁₁), 3.18 (dd, ³J_{H-H} = 4Hz, ²J_{H-H} = 14Hz, 1H, H₁₂), 2.88 (dd, ³J_{H-H} = 3Hz, ²J_{H-H} = 14Hz, 1H, H₁₂), 2.64 (m, 1H, H₃), 1.88 (m, 1H, H₃). **¹⁹F NMR (376.50 MHz, CDCl₃):** δ (ppm) -116.52 (m, 1F, F₁). **¹³C NMR (75.47 MHz, CDCl₃):** δ (ppm) 167.9 (s, 1C, C₄), 159.3 (s, 1C, C₁₀), 153.5 (d, ¹J_{C-F} = 254Hz, 1C, C₁), 134.3 (s, 1C, C₁₃), 130.2 (s, 2C, C₈), 129.6 (s, 2C, C₁₅), 128.3 (s, 2C, C₁₄), 128.2 (1C, C₇), 127.3 (s, 1C, C₁₆), 114.3 (s, 2C, C₉), 99.8 (d, ²J_{C-F} = 16Hz, 1C, C₂), 56.0 (d, ²J_{C-F} = 36Hz, 1C, C₅), 55.3 (s, 1C, C₁₁), 46.0 (s, 1C, C₆), 35.5 (s, 1C, C₁₂), 29.5 (d, ³J_{C-F} = 9Hz, 1C, C₃). **IR (neat)** ν 3063, 3030, 2934, 2837, 1727, 1645, 1612, 1585, 1511, 1496, 1455, 1413, 1384, 1357, 1318, 1303, 1284, 1243, 1172, 1110, 1070, 1032, 970, 904, 815, 753, 725, 702, 666 cm⁻¹. **HR-MS (ESI+):** m/z = 326.1550 [M+H]⁺, calcd. for C₂₀H₂₁FNO₂: 326.1556. R_f = 0.20 (50% Et₂O in pentane).

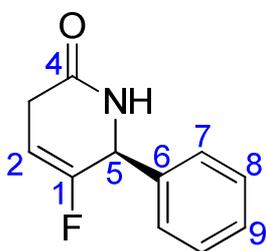
IV. Synthesis of the various fluoropseudopeptides **1**

1. Experimental procedures and datas

a. Synthesis of the deprotected lactams **10**

General procedure for the PMB-deprotection of the lactams:

In an oven dried round-bottom flask equipped with a stir bar and flushed with argon, a solution of the starting lactam (1 eq.), in MeCN:H₂O (5:1 v/v) mixture was prepared. The CAN (5 eq.) powder was added portionwise to the mixture. The resulting solution was stirred at room temperature and the progress of the reaction was controlled by TLC and ¹⁹F NMR. When full consumption of starting material was observed, the reaction was stopped by adding a saturated solution of NaHCO₃ and the

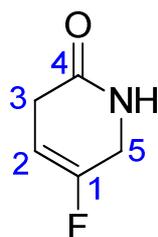


aqueous layer extracted with diethylether. The organic layers were combined and dried over Na₂SO₄. After filtration and evaporation of the volatile materials under reduced pressure, the crude was purified by flash chromatography on silica gel (Pentane:Et₂O) to afford the desired PMB-protected lactam.

5-fluoro-1,6-dihydropyridin-2(3H)-one (10a):

The general procedure for the PMB-deprotection of the lactams using PMB-protected bisolefin **2a** (1 eq., 100 mg, 425 μmol) at room temperature during 7 hours followed by purification by chromatography on silica gel (Pentane:Et₂O = 80:20) afforded the **5-fluoro-1,6-dihydropyridin-2(3H)-one** (40 mg, 348 μmol, yield 81 %) as a white solid.

¹H NMR (400.13 MHz, MeOD-*d*6): δ (ppm) 5.32 (m, 1H, H₂), 3.99 (dd, ²J_{H-H} = 1Hz, ³J_{H-F} = 5Hz, 2H, H₅), 2.97 (m, 2H, H₃). **¹⁹F NMR (282.40 MHz, MeOD-*d*6):** δ (ppm) -119.93 (dt, ³J_{H-F} = 5Hz, ³J_{H-F} = 15Hz, 1F, F₁). **¹³C NMR (75.47 MHz, MeOD-*d*6):** δ (ppm) 174.0 (s, C₄), 156.6 (d, ¹J_{C-F} = 250Hz, C₁), 101.1 (d, ²J_{C-F} = 16Hz, C₂), 44.9 (d, ²J_{C-F} = 40Hz, C₅), 32.2 (d, ³J_{C-F} = 9Hz, C₃). **IR (neat)** ν 3208, 1732, 1668, 1372, 1275, 1159, 1018, 818, 750 cm⁻¹. **HR-MS (ESI+):** m/z = 138.0332 [M+H]⁺, calcd. for C₅H₆FNONa: 138.0331. *R*_f = 0.17 (20% Et₂O in pentane).



(S)-5-fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one (10d):

The general procedure for the PMB-deprotection of the lactams using PMB-protected bisolefin **2d** (1 eq., 30 mg, 96 μmol) at room temperature during 14 hours followed by purification by chromatography on silica gel (Pentane:Et₂O = 80:20) afforded the **(S)-5-**

fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one (14 mg, 73 μ mol, yield 76 %) as a white solid.

^1H NMR (400.13 MHz, CDCl_3): δ (ppm) 7.39 (m, 5H, $\text{H}_{7,8,9}$), 6.00 (br., 1H, NH), 5.36 (ddt, $^3J_{\text{H-H}} = 1\text{Hz}$, $^3J_{\text{H-H}} = 4\text{Hz}$, $^3J_{\text{H-F}} = 14\text{Hz}$, 1H, H_2), 5.10 (m, 1H, H_5), 3.15 (m, 2H, H_3). **^{19}F NMR (282.40 MHz, CDCl_3):** δ (ppm) -117.69 (m, 1F, F_1). **^{13}C NMR (75.47 MHz, CDCl_3):** δ (ppm) 167.9 (s, C_4), 153.9 (d, $^1J_{\text{C-F}} = 251\text{Hz}$, C_1), 138.0 (s, 1C, C_7), 129.1 (s, 2C, C_7), 127.2 (s, 2C, C_8), 98.0 (d, $^2J_{\text{C-F}} = 17\text{Hz}$, C_2), 57.4 (d, $^2J_{\text{C-F}} = 37\text{Hz}$, C_3), 29.1 (d, $^3J_{\text{C-F}} = 8\text{Hz}$, C_3). **IR (neat)** ν 1754, 1663, 1627, 1530, 1491, 1476, 1399, 1376, 1313, 1274, 1193, 1163, 1119, 1021, 838, 742, 697 cm^{-1} . **HR-MS (ESI+):** $m/z = 192.0818$ $[\text{M}+\text{H}]^+$, calcd. for $\text{C}_{11}\text{H}_{11}\text{FNO}$: 192.0825. $[\alpha]_{\text{D}}^{25} = +112.7$ (c 1.1, CH_3Cl). **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20 $^\circ\text{C}$, 80% n-heptane 20% propanol; peak 1: $t_r = 9.300$ min, %Area = 99.10%; peak 2: $t_r = 11.104$ min, %Area = 0.90%. $R_f = 0.15$ (20% Et_2O in pentane).

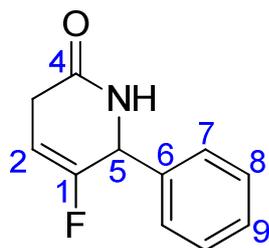
5-fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one (rac-10d):

The general procedure for the PMB-deprotection of the lactams using PMB-protected bisolefin **2d+e** (1 eq., 21 mg, 68 μ mol) at room temperature during 14 hours followed by purification by chromatography on silica gel (Pentane: $\text{Et}_2\text{O} = 80:20$) afforded the **5-fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one** (7 mg, 37 μ mol, yield 55 %) as a white solid.

^1H NMR (400.13 MHz, CDCl_3): δ (ppm) 7.38 (m, 5H, $\text{H}_{7,8,9}$), 6.00 (br., 1H, NH), 5.36 (ddt, $^3J_{\text{H-H}} = 1\text{Hz}$, $^3J_{\text{H-H}} = 4\text{Hz}$, $^3J_{\text{H-F}} = 14\text{Hz}$, 1H, H_2), 5.10 (m, 1H, H_5), 3.16 (m, 2H, H_3). **^{19}F NMR (282.40 MHz, CDCl_3):** δ (ppm) -117.68 (m, 1F, F_1). **Racemic mixture:** **Chiral HPLC:** Method conditions: Col. Daicel Chiralpak ASH 4.6mmx250mm 5 μ m, 1mL/min, 20 $^\circ\text{C}$, 80% n-heptane 20% propanol; peak 1: $t_r = 9.283$ min, %Area = 50.36%; peak 2: $t_r = 11.070$ min, %Area = 49.64%.

b. Synthesis of the fluoropseudopeptides **1**

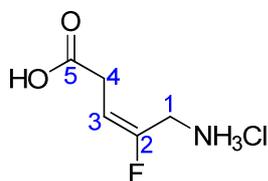
General procedure for the hydrolysis of lactams:



In an oven dried Schlenk flask equipped with a stir bar and flushed with argon, a solution of the starting lactam (1 eq.), in HCl 6N (30 eq.) was prepared. The resulting solution was stirred at 100 $^\circ\text{C}$ and the progress of the reaction was controlled by TLC and ^{19}F NMR. When full consumption of starting material was observed, the vial content was evaporated under reduced pressure. The crude

was washed with dichloromethane to afford the pure desired fluoropseudopeptide.

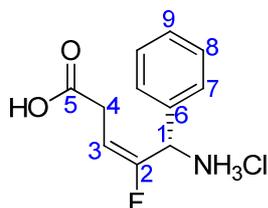
(E)-5-amino-4-fluoropent-3-enoic acid chlorhydrate (1a):



The general procedure for the hydrolysis of the lactams using PMB-deprotected lactam **10a** (1 eq., 8 mg, 70 μ mol) afforded the **(E)-5-amino-4-fluoropent-3-enoic acid chlorhydrate** quantitatively as a white solid.

^1H NMR (400.13 MHz, D_2O): δ (ppm) 5.62 (dt, $^3J_{\text{H-H}} = 8\text{Hz}$, $^3J_{\text{H-F}} = 19\text{Hz}$, 1H, H₃), 3.84 (d, $^3J_{\text{H-F}} = 19\text{Hz}$, 2H, H₁), 3.15 (d, $^3J_{\text{H-H}} = 8\text{Hz}$, 2H, H₄). **^{19}F NMR (282.40 MHz, D_2O):** δ (ppm) -110.11 (dt, $^3J_{\text{H-F}} = 19\text{Hz}$, $^3J_{\text{H-F}} = 19\text{Hz}$, 1F, F₂). **^{13}C NMR (75.47 MHz, D_2O):** δ (ppm) 175.1 (d, $^4J_{\text{C-F}} = 3\text{Hz}$, C₅), 154.5 (d, $^1J_{\text{C-F}} = 247\text{Hz}$, C₂), 105.9 (d, $^2J_{\text{C-F}} = 25\text{Hz}$, C₃), 35.8 (d, $^2J_{\text{C-F}} = 29\text{Hz}$, C₁), 30.2 (d, $^3J_{\text{C-F}} = 10\text{Hz}$, C₄). **IR (neat)** ν 3370, 3011, 2620, 2510, 1713, 1634, 1506, 1396, 1306, 1206, 1162, 1076, 989, 937, 851 cm^{-1} . **HR-MS (ESI+):** $m/z = 134.0612$ [M+H]⁺, calcd. for C₅H₉FNO₂: 134.0617.

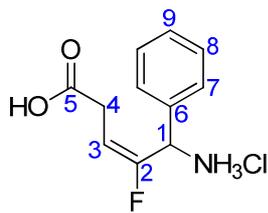
(S)-(E)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate (1d):



The general procedure for the hydrolysis of the lactams using PMB-deprotected lactam **10d** (1 eq., 8 mg, 42 μ mol) afforded the **(S)-(E)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate** quantitatively as a white solid.

^1H NMR (400.13 MHz, D_2O): δ (ppm) 7.45 (s, 5H, H_{7,8,9}), 5.65 (dt, $^3J_{\text{H-H}} = 8\text{Hz}$, $^3J_{\text{H-F}} = 21\text{Hz}$, 1H, H₃), 5.49 (d, $^3J_{\text{H-F}} = 25\text{Hz}$, 1H, H₁), 3.17 (m, 2H, H₄). **^{19}F NMR (282.40 MHz, D_2O):** δ (ppm) -117.2 (dd, $^3J_{\text{H-F}} = 21\text{Hz}$, $^3J_{\text{H-F}} = 25\text{Hz}$, 1F, F₂). **^{13}C NMR (75.47 MHz, D_2O):** δ (ppm) 175.0 (d, $^4J_{\text{C-F}} = 4\text{Hz}$, C₅), 154.6 (d, $^1J_{\text{C-F}} = 253\text{Hz}$, C₂), 132.5 (d, $^3J_{\text{C-F}} = 2\text{Hz}$, C₆), 129.8 (s, C₉), 129.5 (s, 2C, C₈), 127.0 (d, $^4J_{\text{C-F}} = 2\text{Hz}$, 2C, C₇), 105.1 (d, $^2J_{\text{C-F}} = 24\text{Hz}$, C₃), 51.0 (d, $^2J_{\text{C-F}} = 25\text{Hz}$, C₁), 30.1 (d, $^3J_{\text{C-F}} = 10\text{Hz}$, C₄). **IR (neat)** ν 3395, 3136, 2865, 1721, 1638, 1594, 1567, 1515, 1495, 1400, 1377, 1297, 1191, 1185, 1160, 1110, 1093, 991, 934, 906, 836, 753, 696 cm^{-1} . **HR-MS (ESI+):** $m/z = 210.0937$ [M+H]⁺, calcd. for C₁₁H₁₃FNO₂: 210.0930. $[\alpha]_{\text{D}}^{25} = -107$ (c 0.75, D_2O).

(E)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate (*rac-1d*):

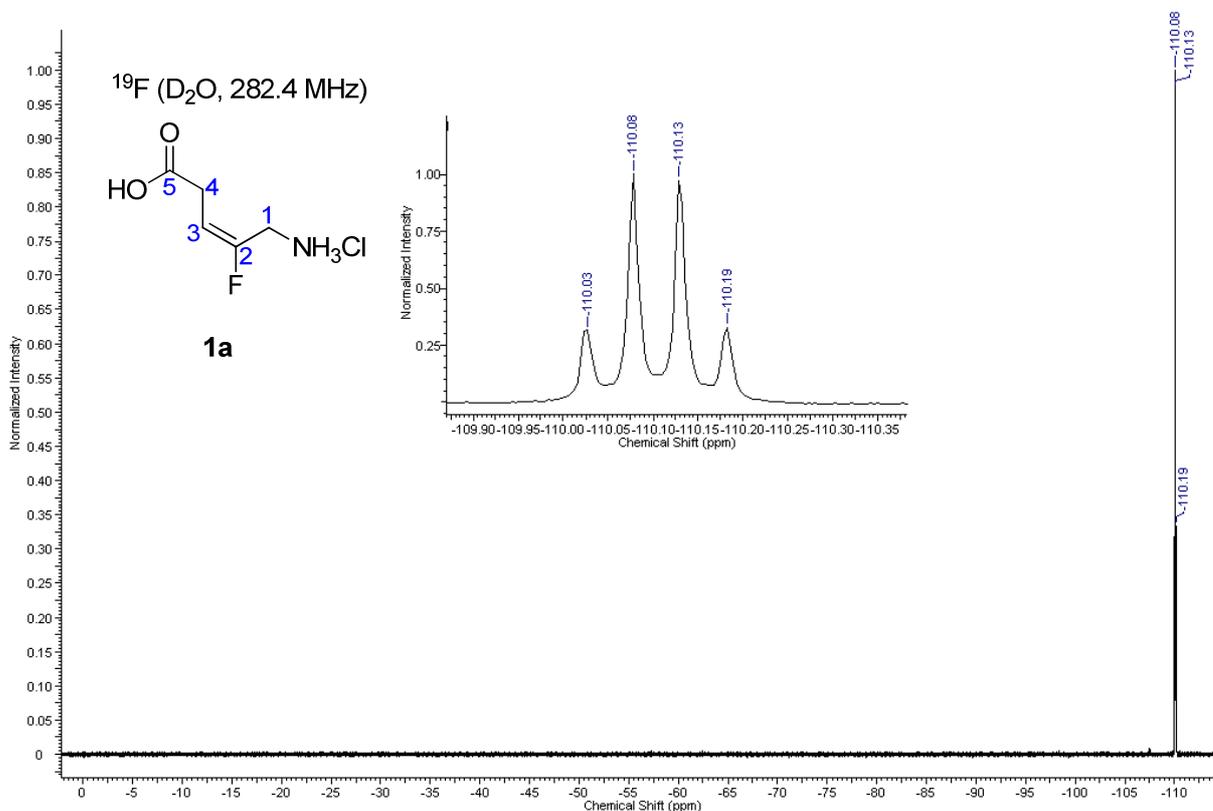
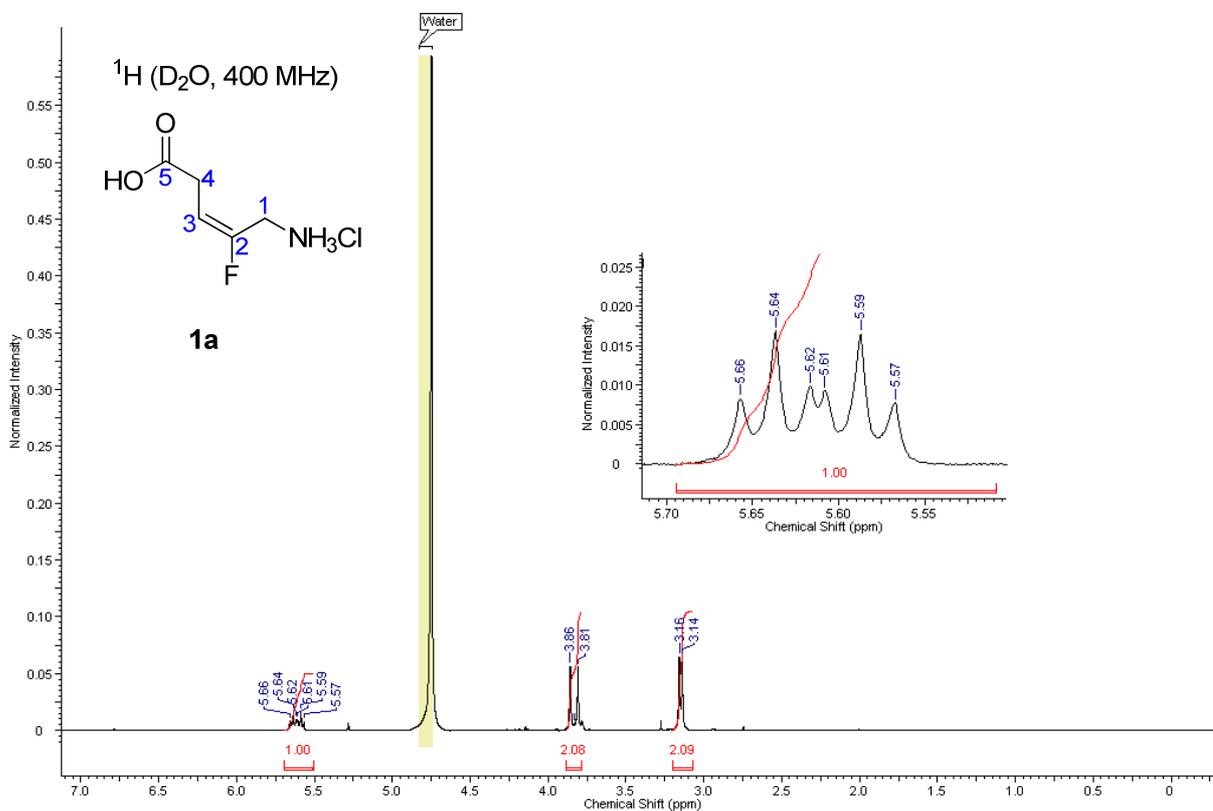


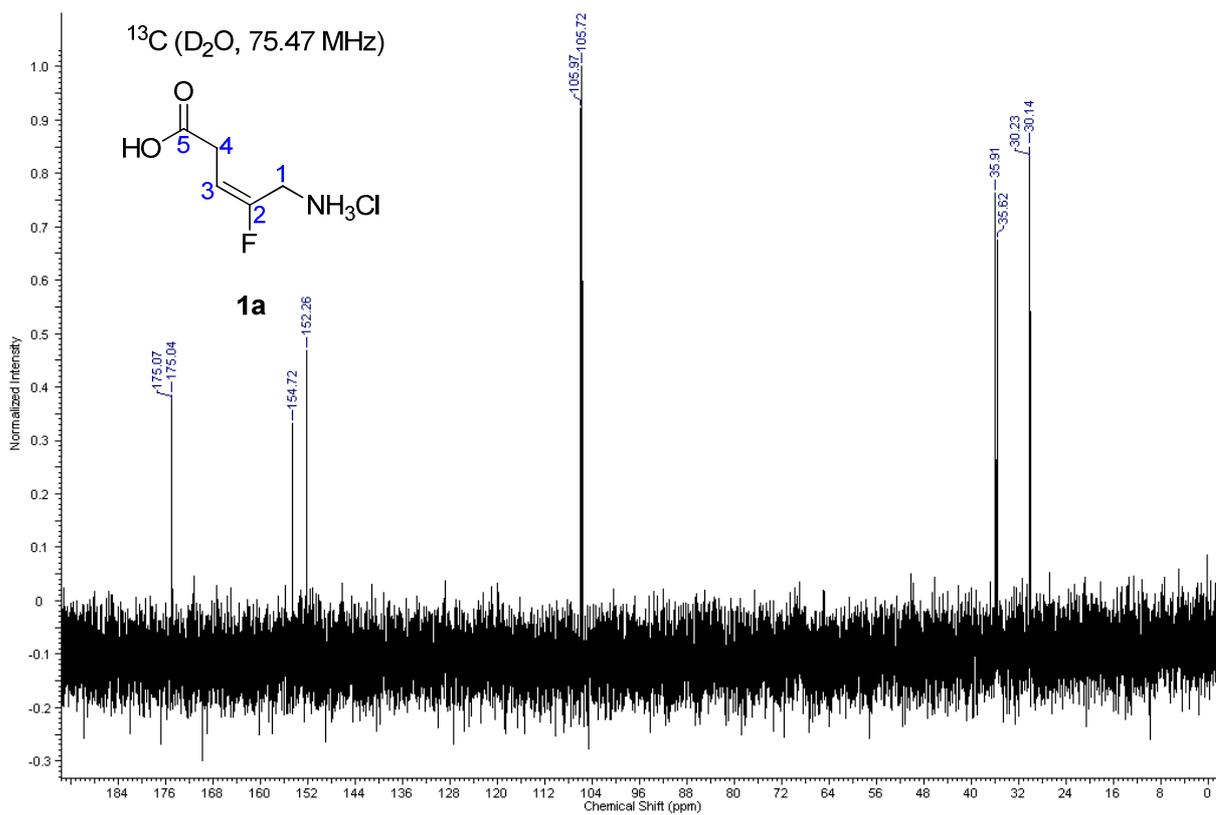
The general procedure for the hydrolysis of the lactams using PMB-protected lactam **rac-10d** (1 eq., 8 mg, 42 μmol) afforded the **(E)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate** quantitatively as a white solid.

^1H NMR (400.13 MHz, D_2O): δ (ppm) 7.45 (s, 5H, $\text{H}_{7,8,9}$), 5.65 (dt, $^3J_{\text{H-H}} = 8\text{Hz}$, $^3J_{\text{H-F}} = 21\text{Hz}$, 1H, H_3), 5.49 (d, $^3J_{\text{H-F}} = 25\text{Hz}$, 1H, H_1), 3.05 (m, 2H, H_4). **^{19}F NMR (282.40 MHz, D_2O):** δ (ppm) -117.2 (dd, $^3J_{\text{H-F}} = 21\text{Hz}$, $^3J_{\text{H-F}} = 25\text{Hz}$, 1F, F_2).

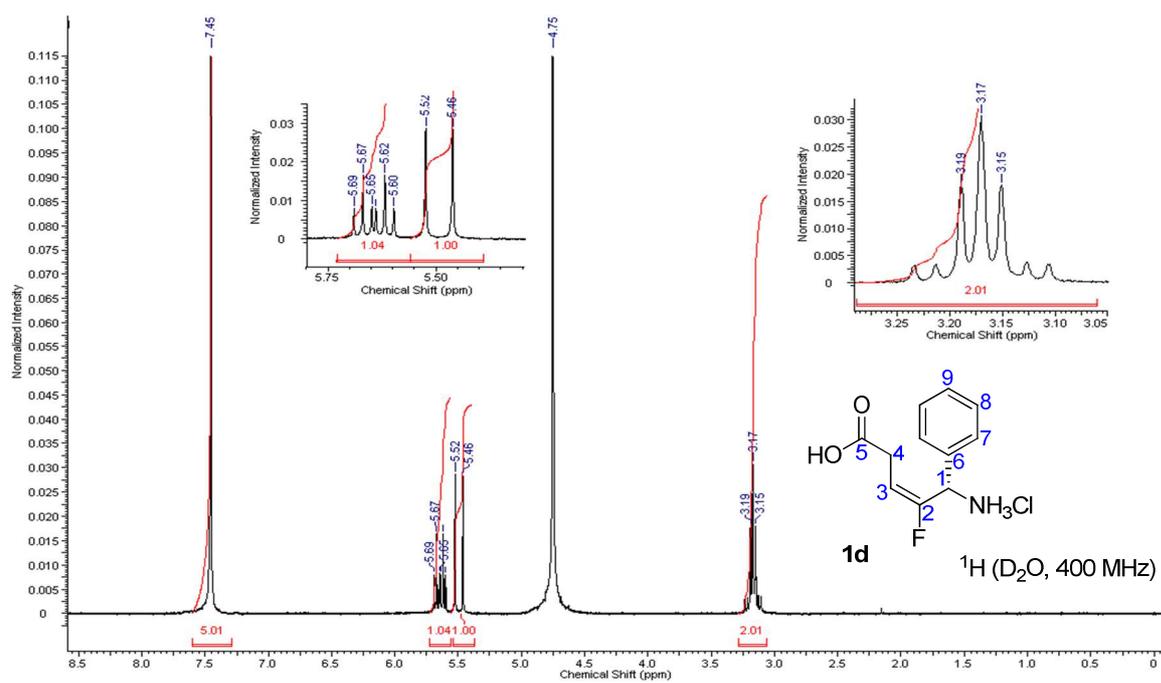
V. ^1H , ^{19}F and ^{13}C Spectra for compounds **1a,d**, **2b-e,h**, **3a-h**, **4a-c**, **5**, **7 a-h**, **9c,e,g**, **10a,d**

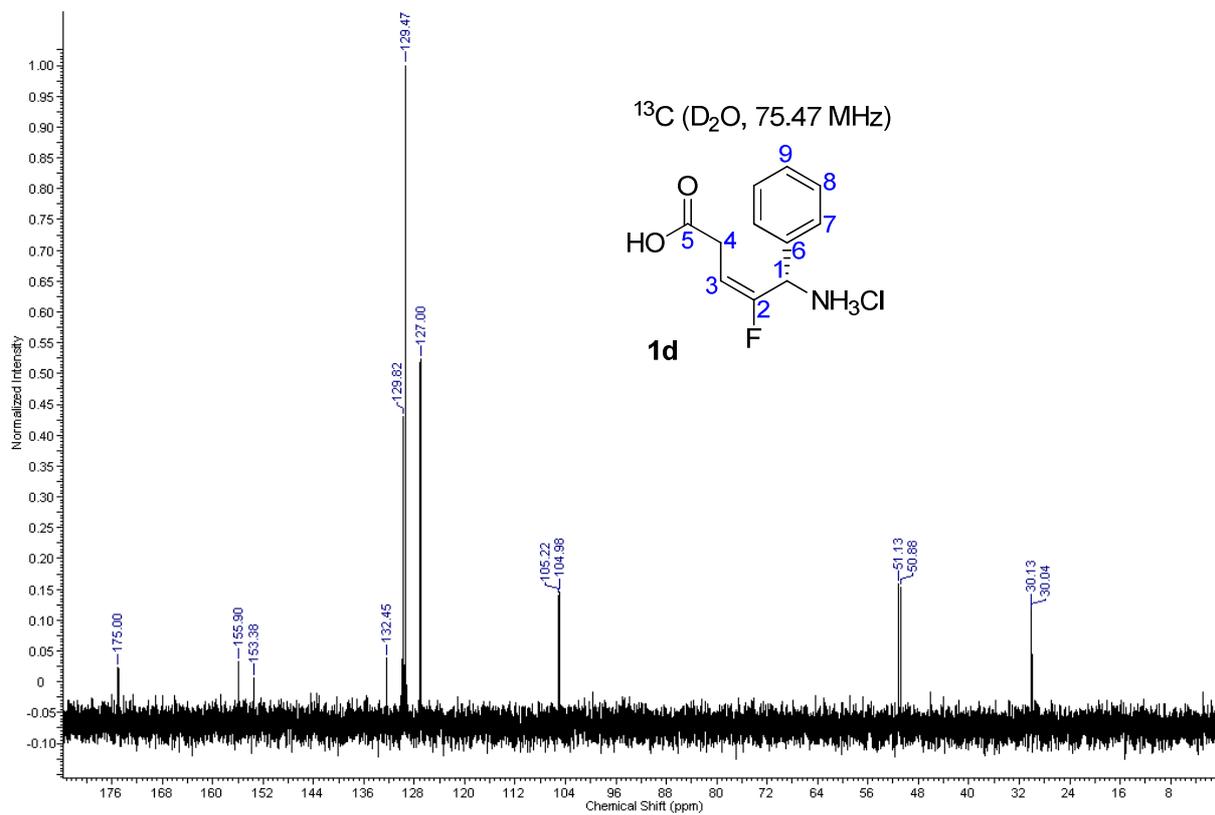
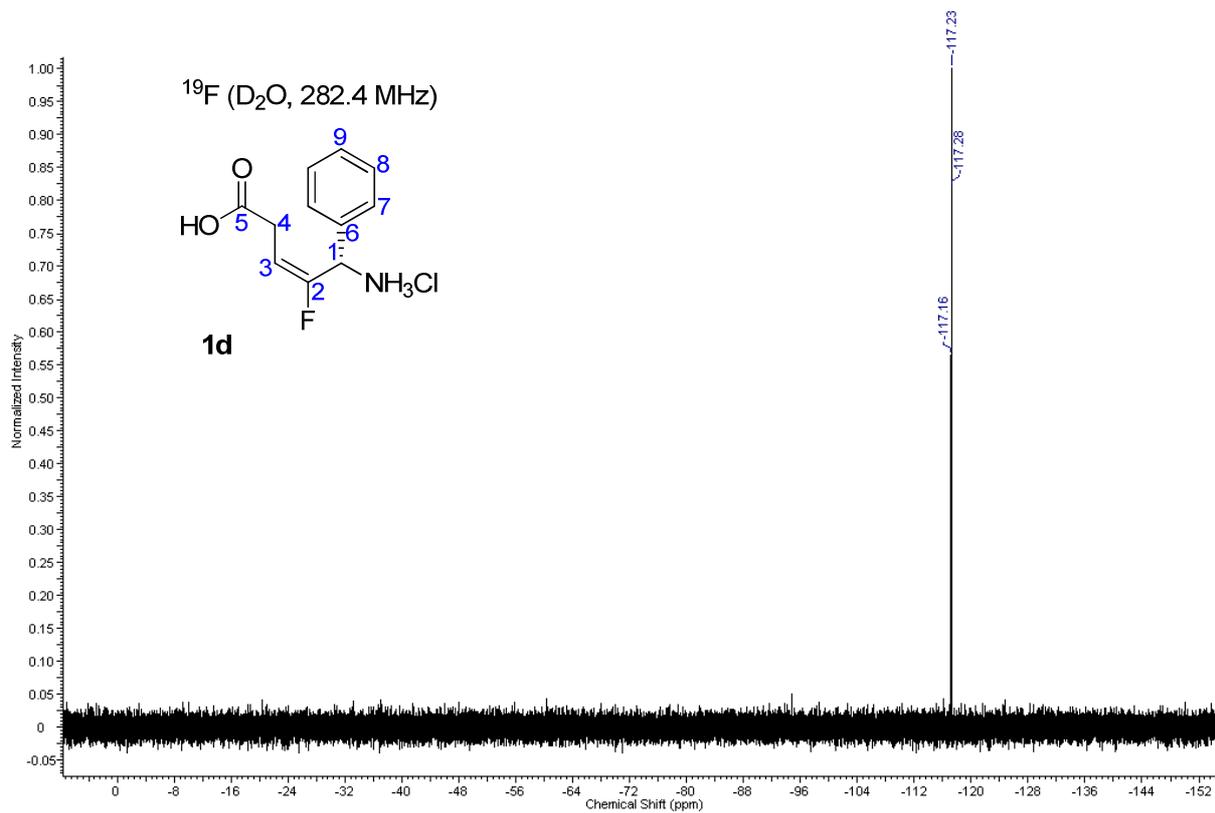
Compound **1a**: (*E*)-5-amino-4-fluoropent-3-enoic acid chlorhydrate



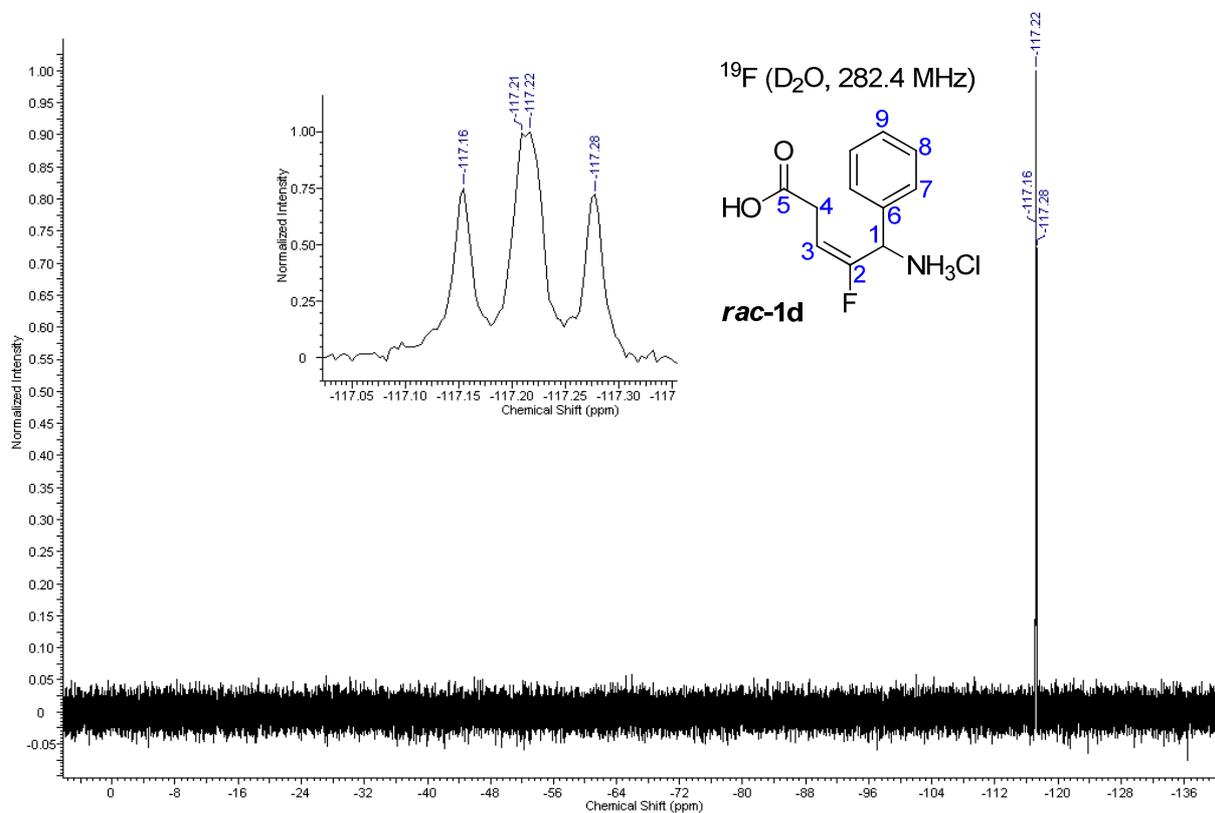
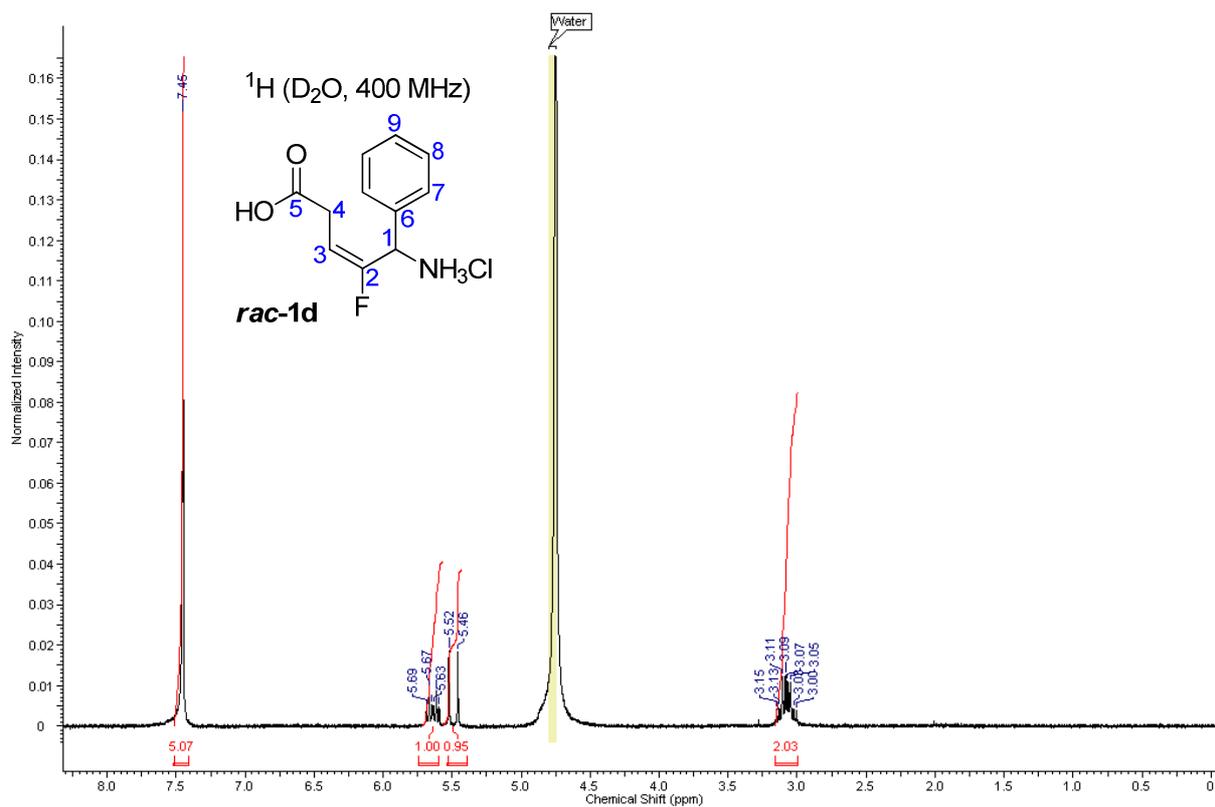


Compound **1d**: (*S*)-(*E*)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate (*1d*)

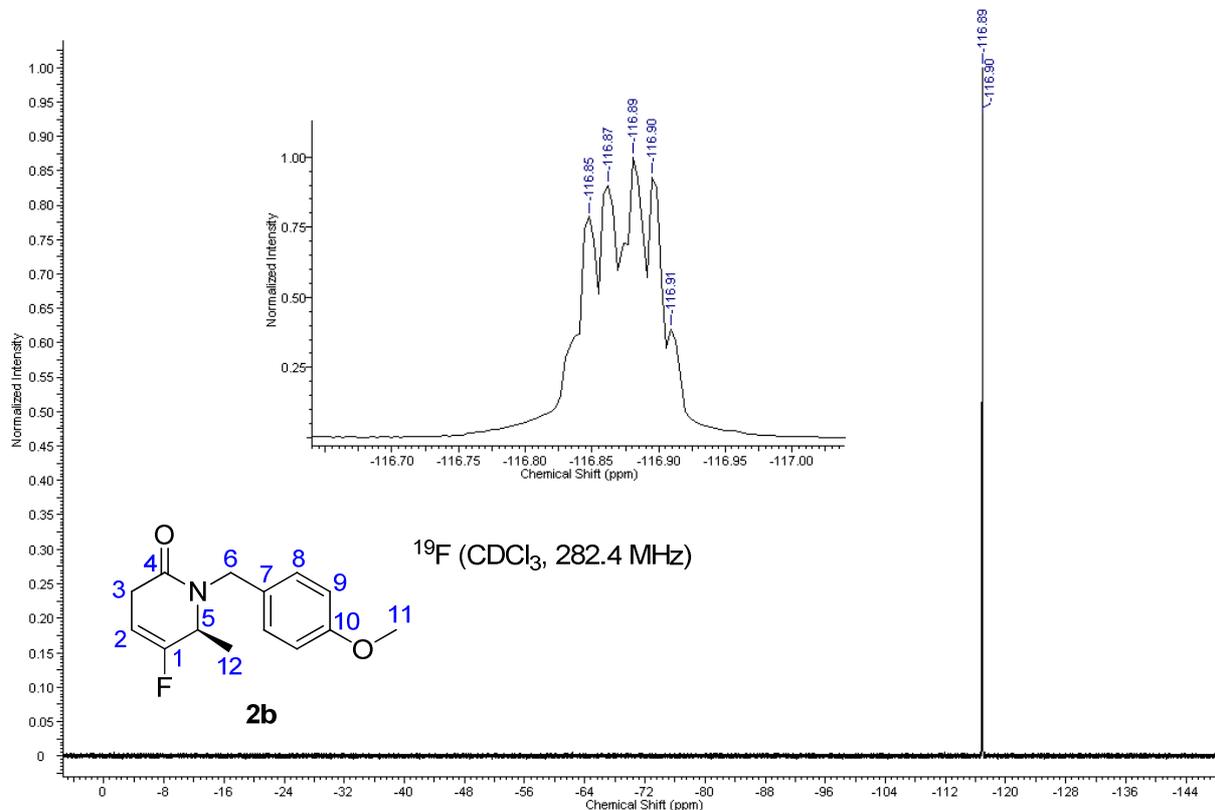
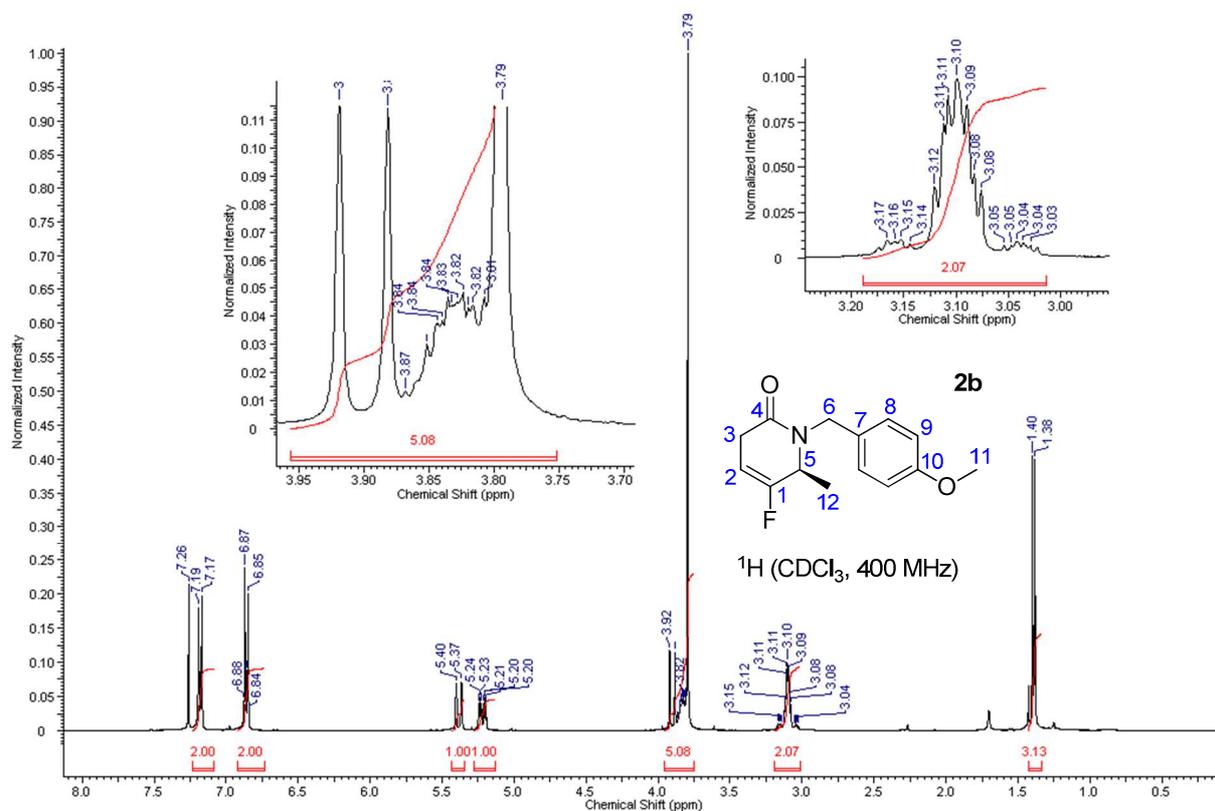


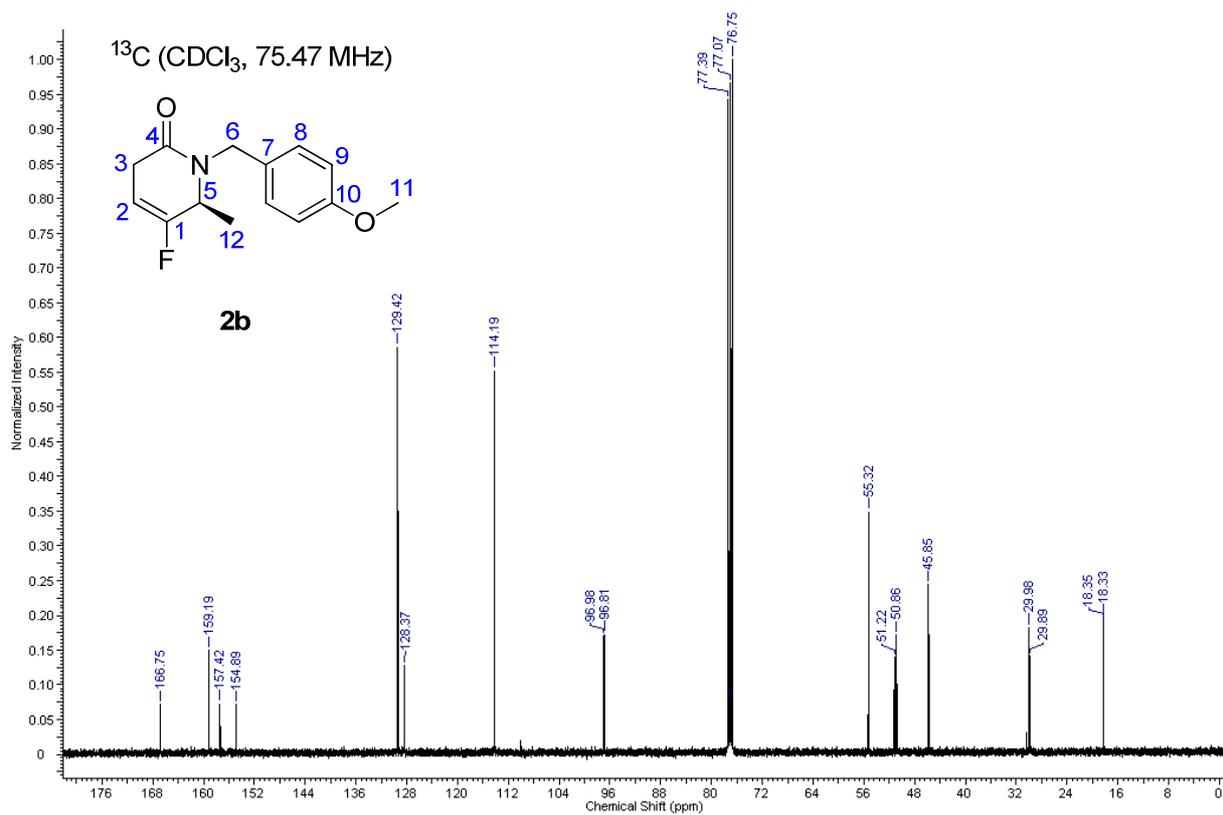


Compound *rac*-1d: (*E*)-5-amino-4-fluoro-5-phenylpent-3-enoic acid chlorhydrate

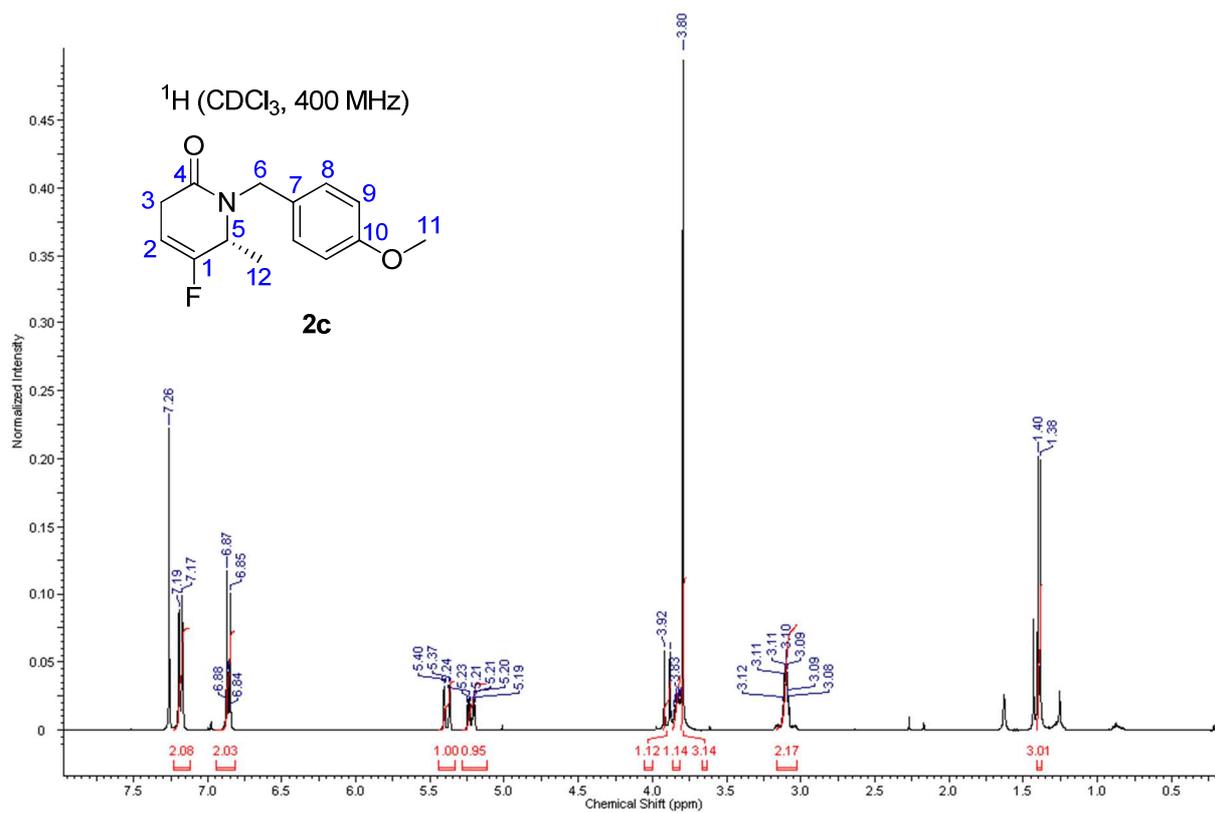


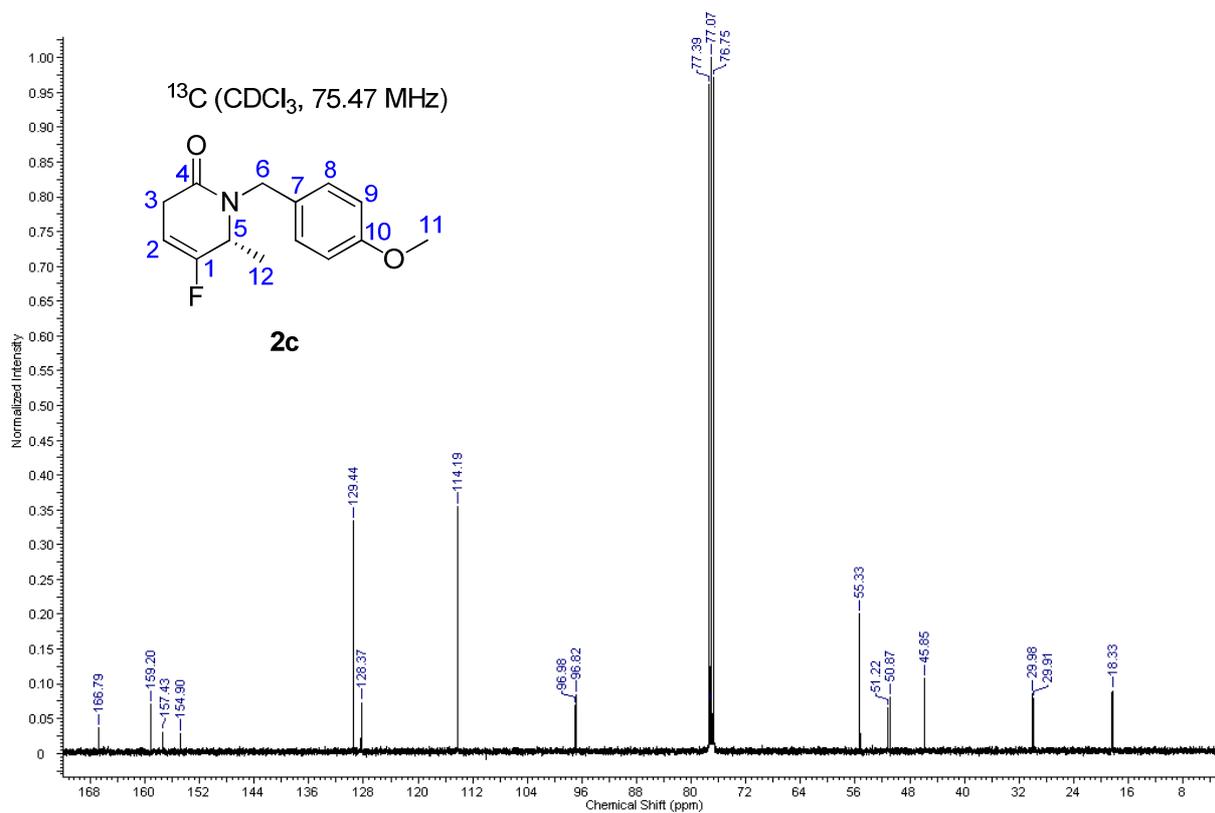
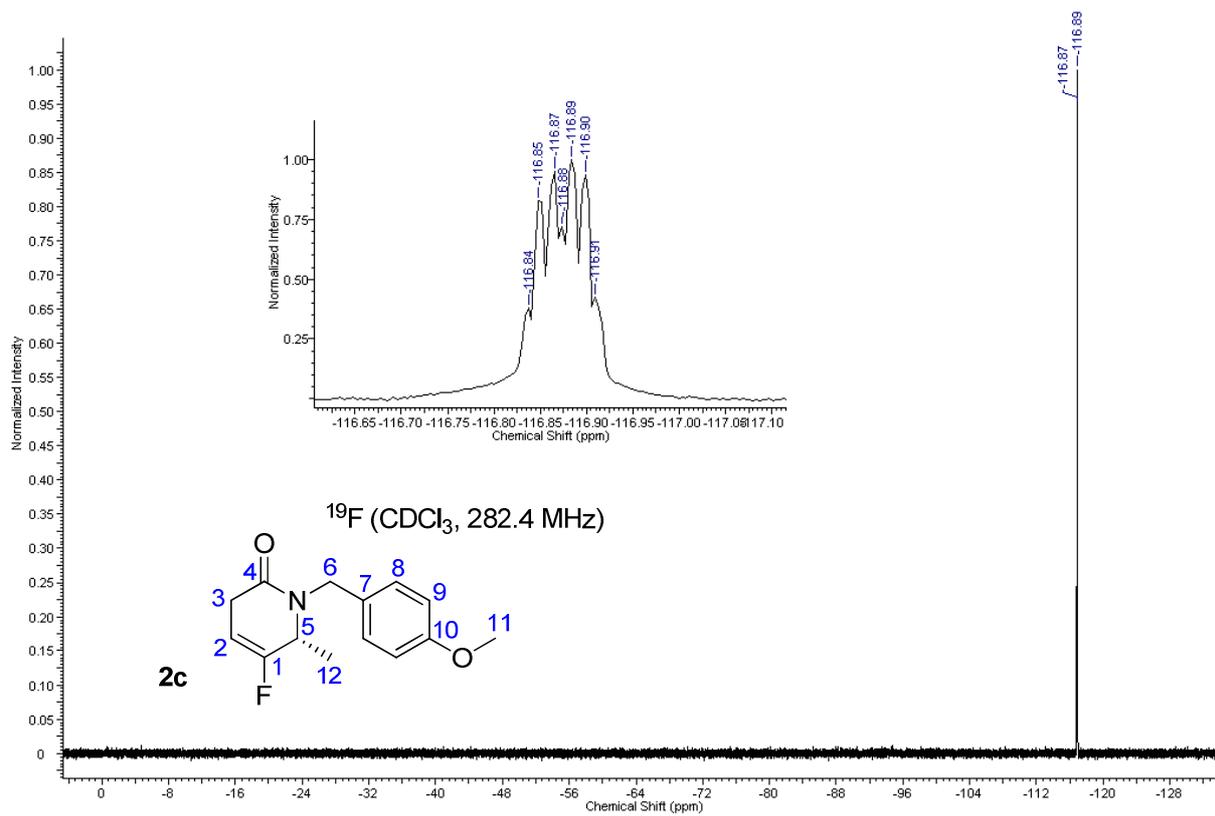
Compound **2b**: *(S)*-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3H)-one



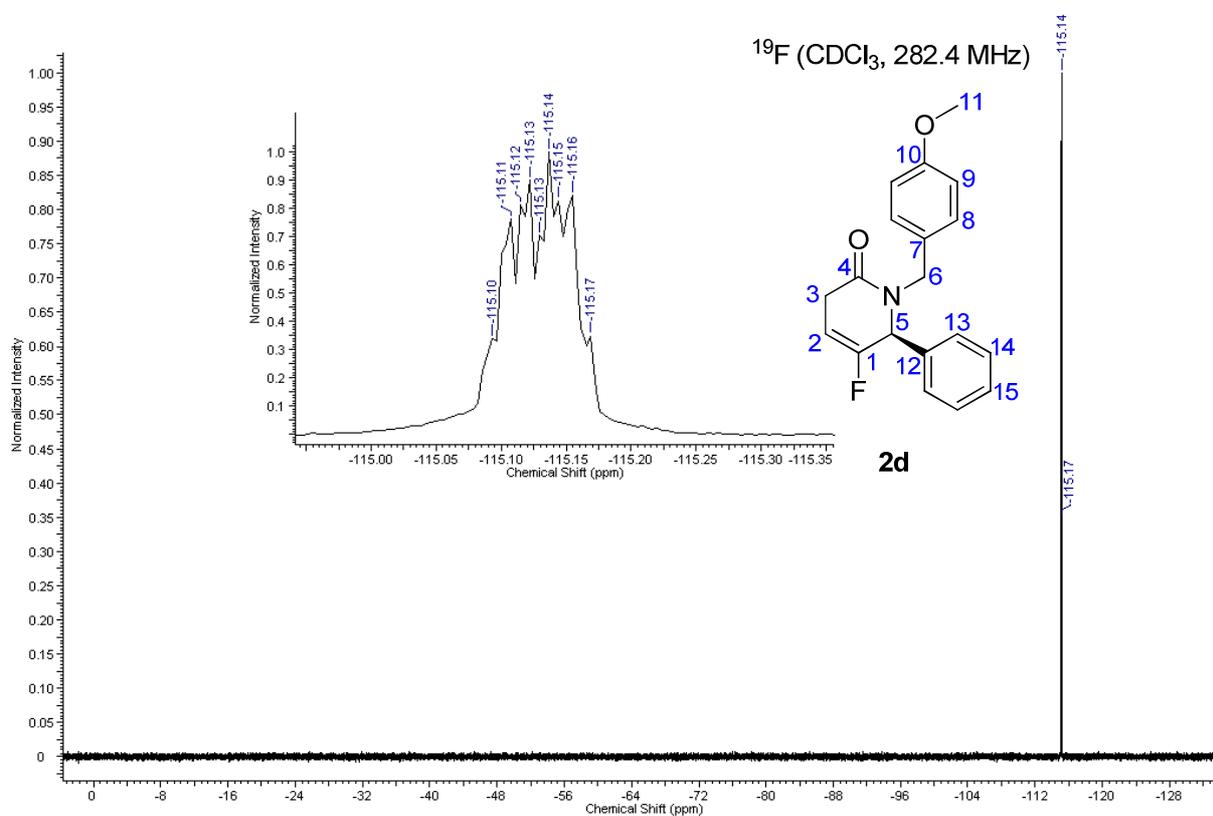
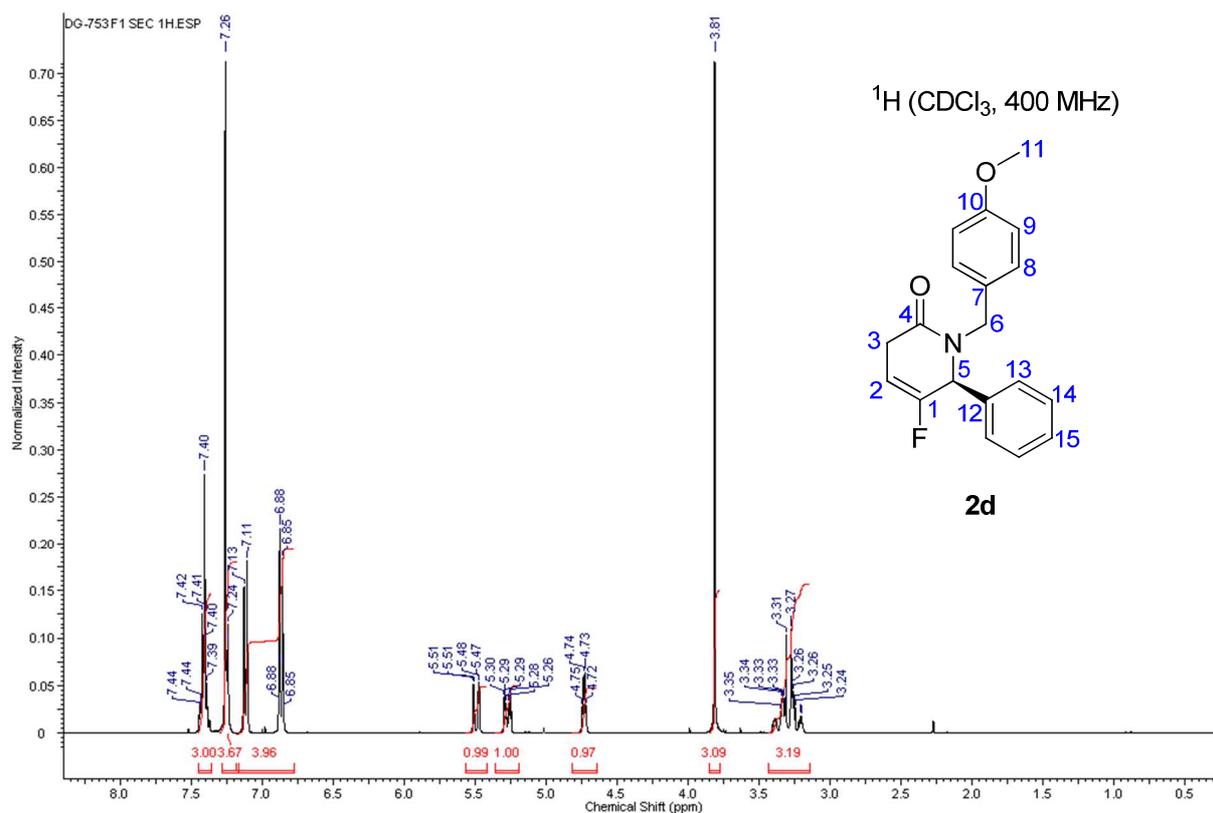


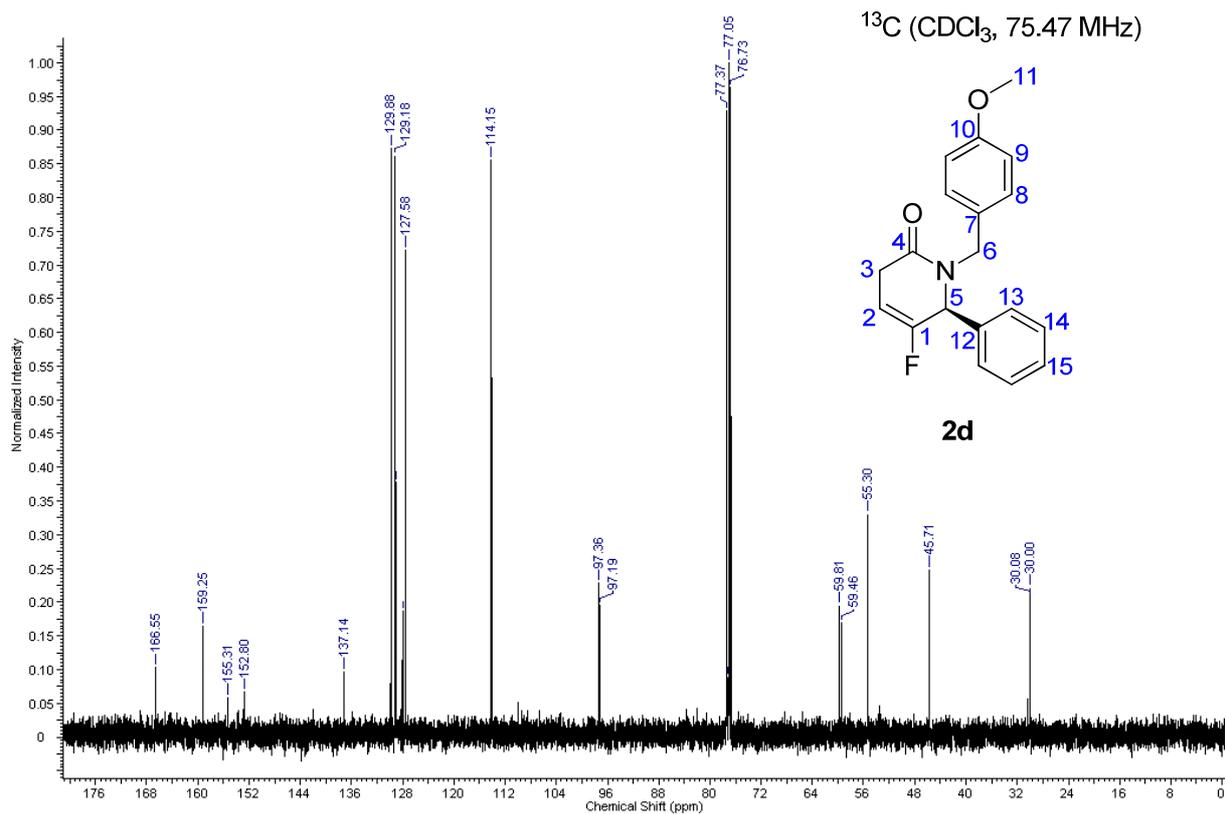
Compound **2c**: (*R*)-5-fluoro-1-(4-methoxybenzyl)-6-methyl-1,6-dihydropyridin-2(3*H*)-one



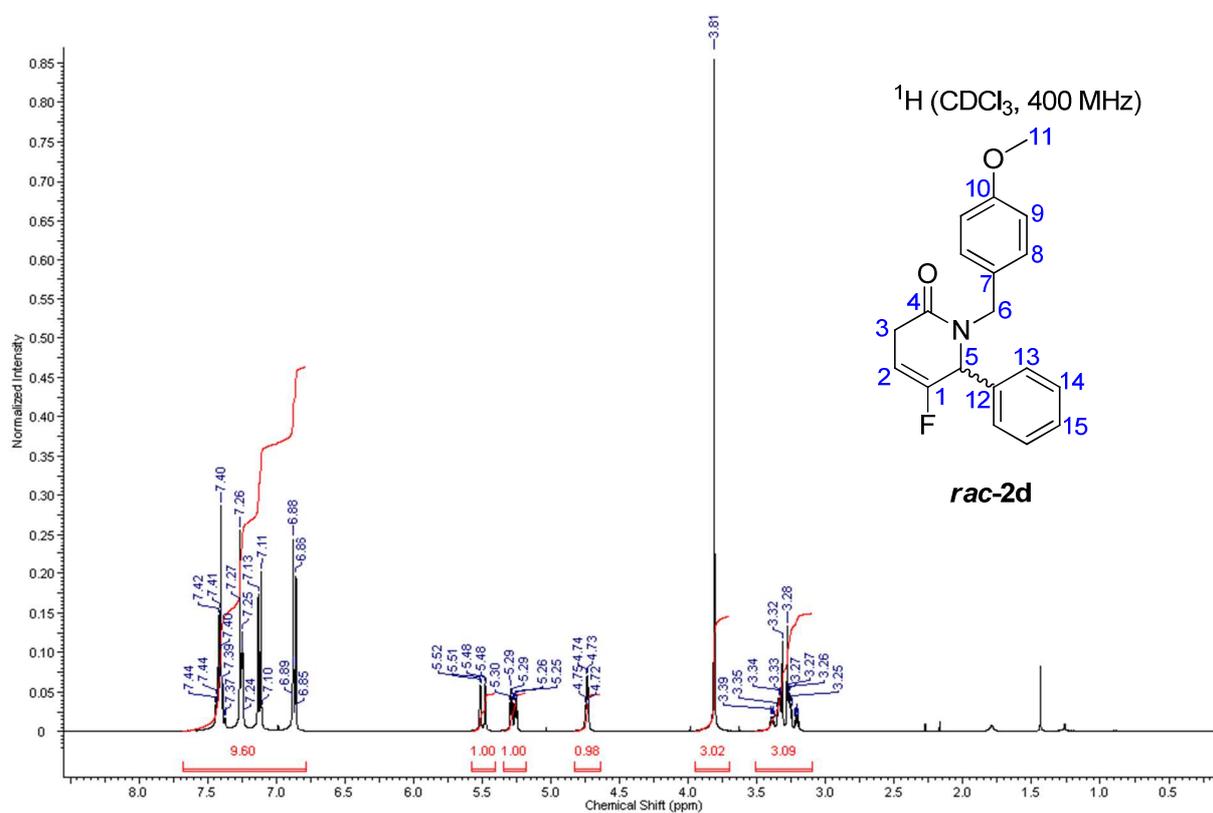


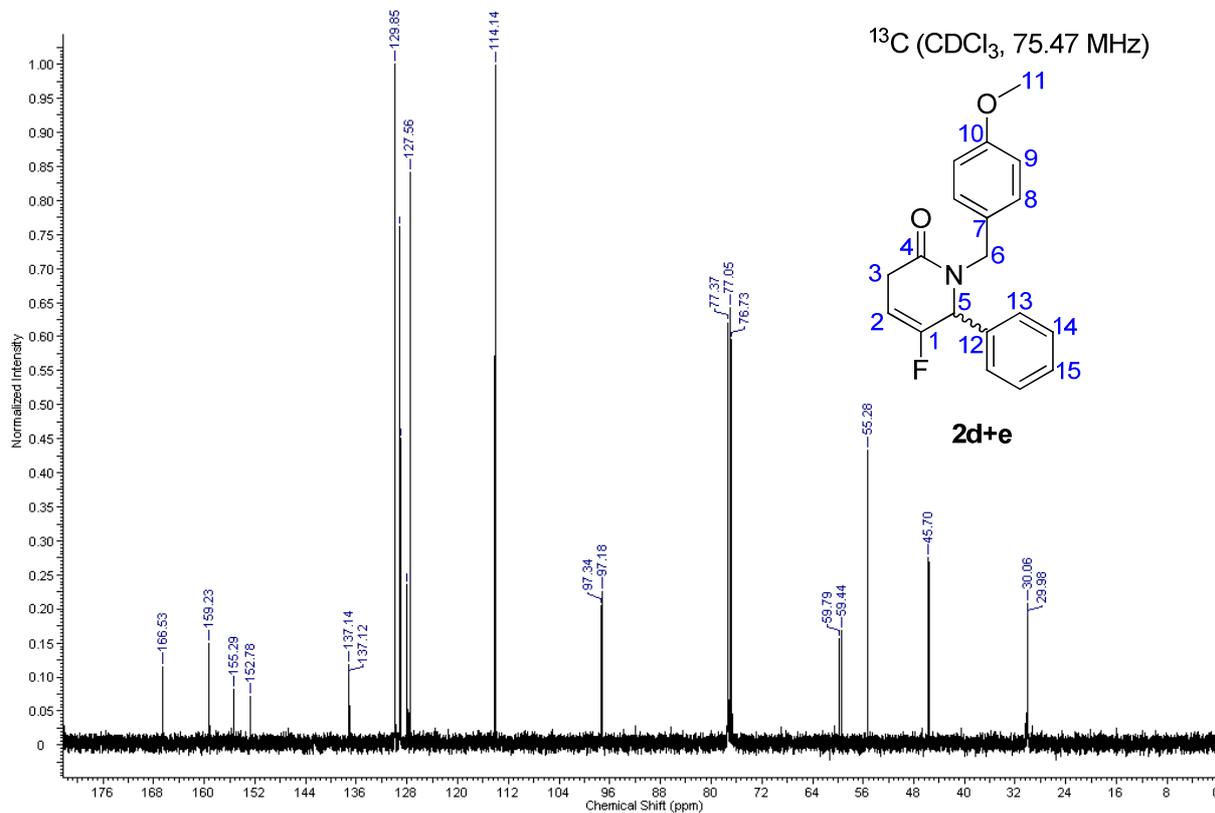
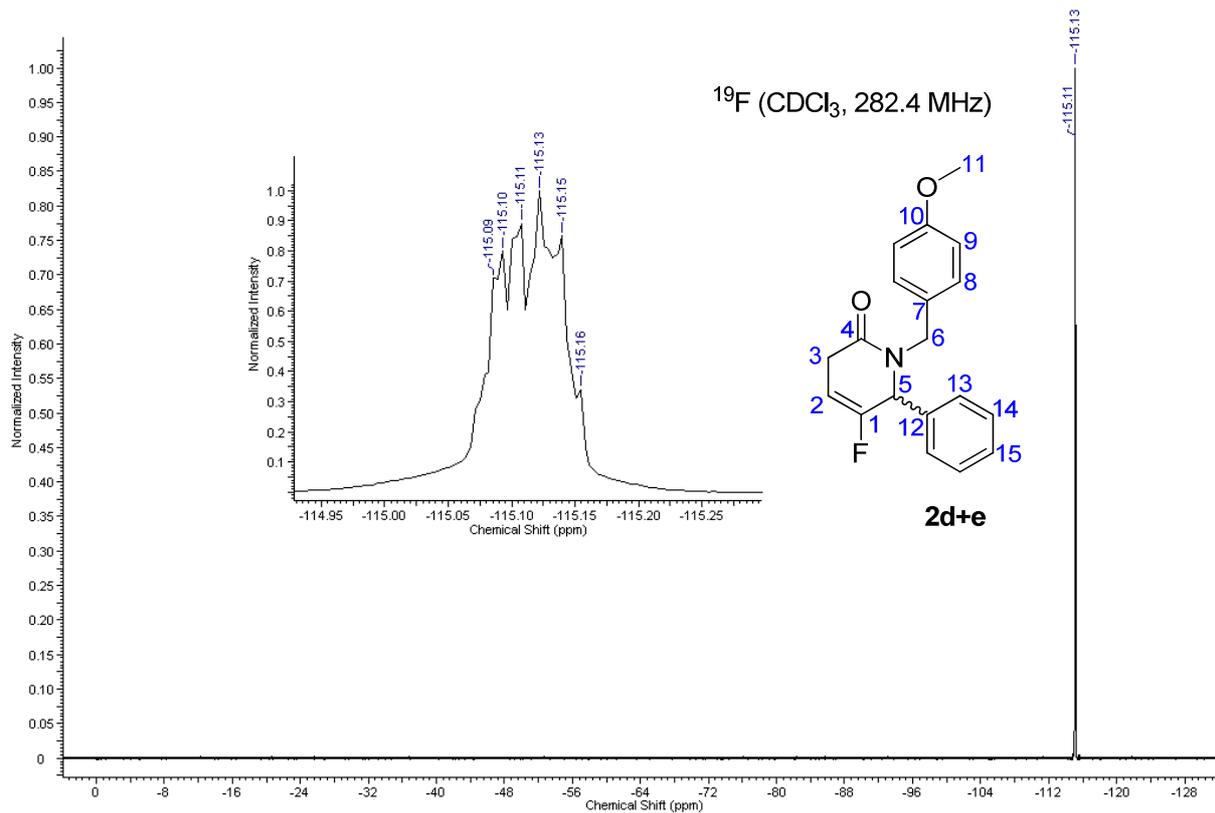
Compound **2d**: *(S)*-5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one



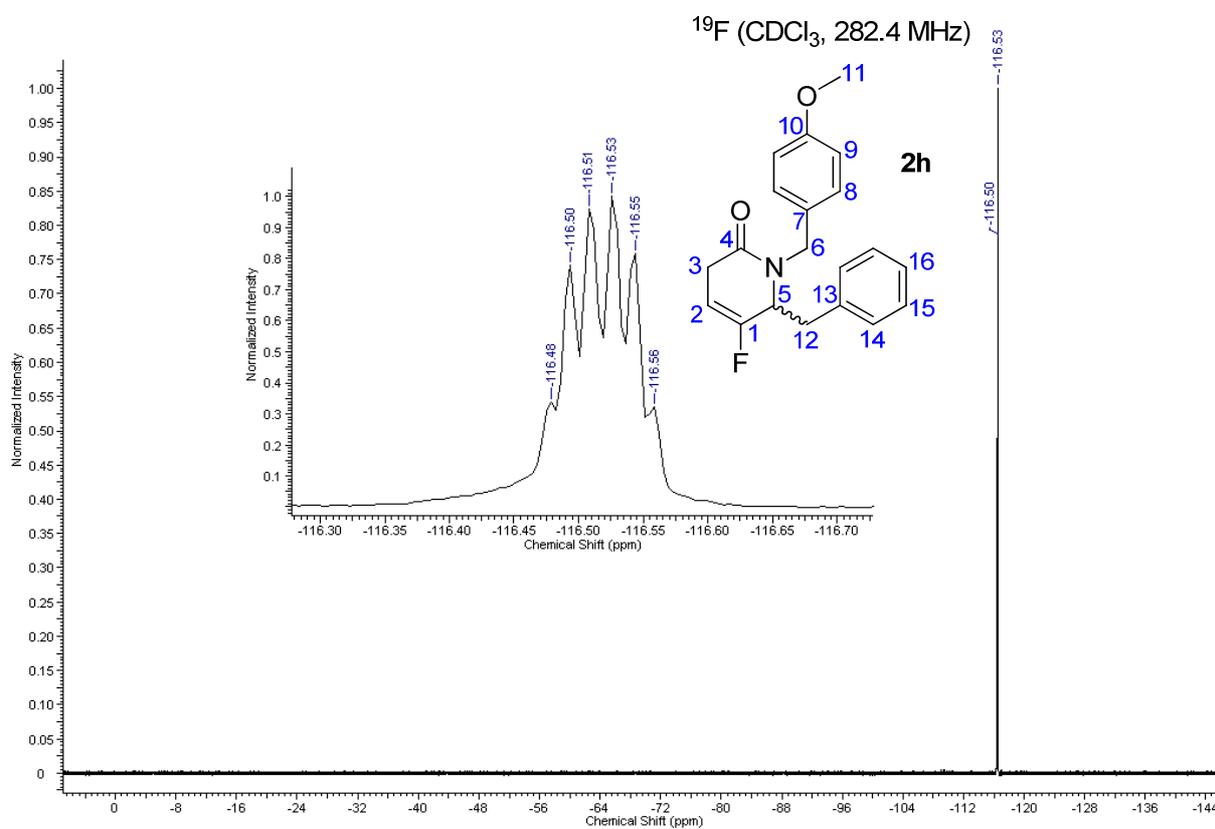
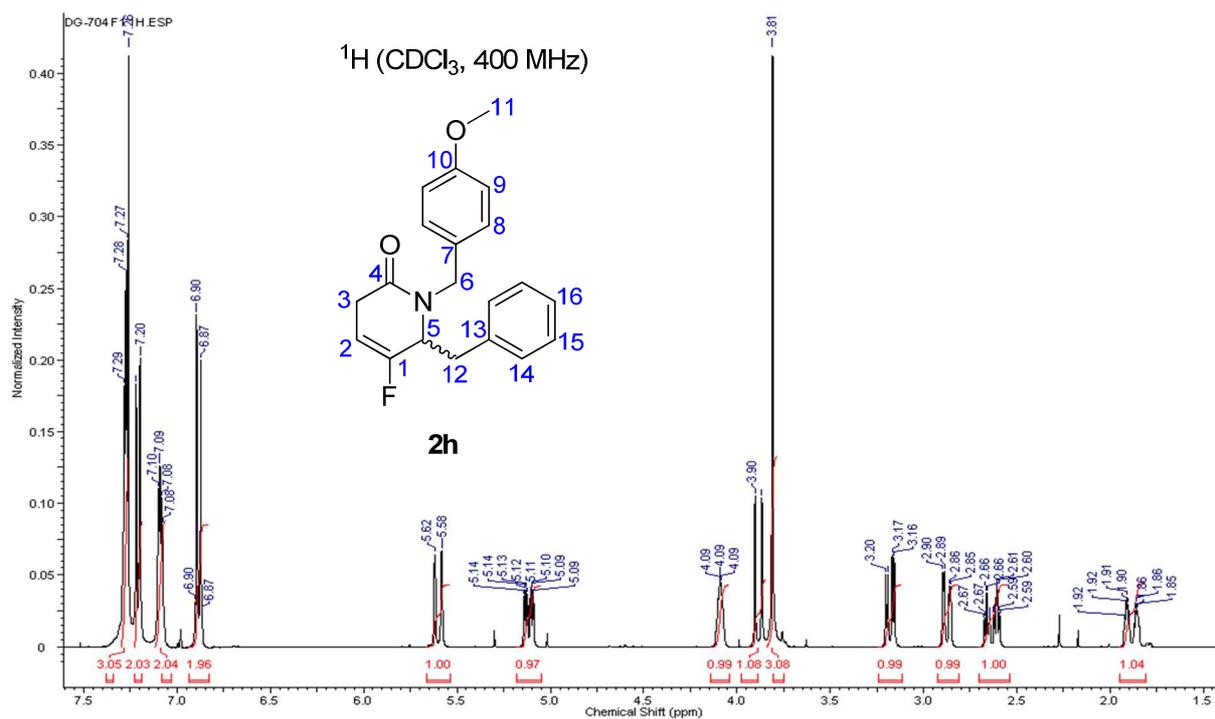


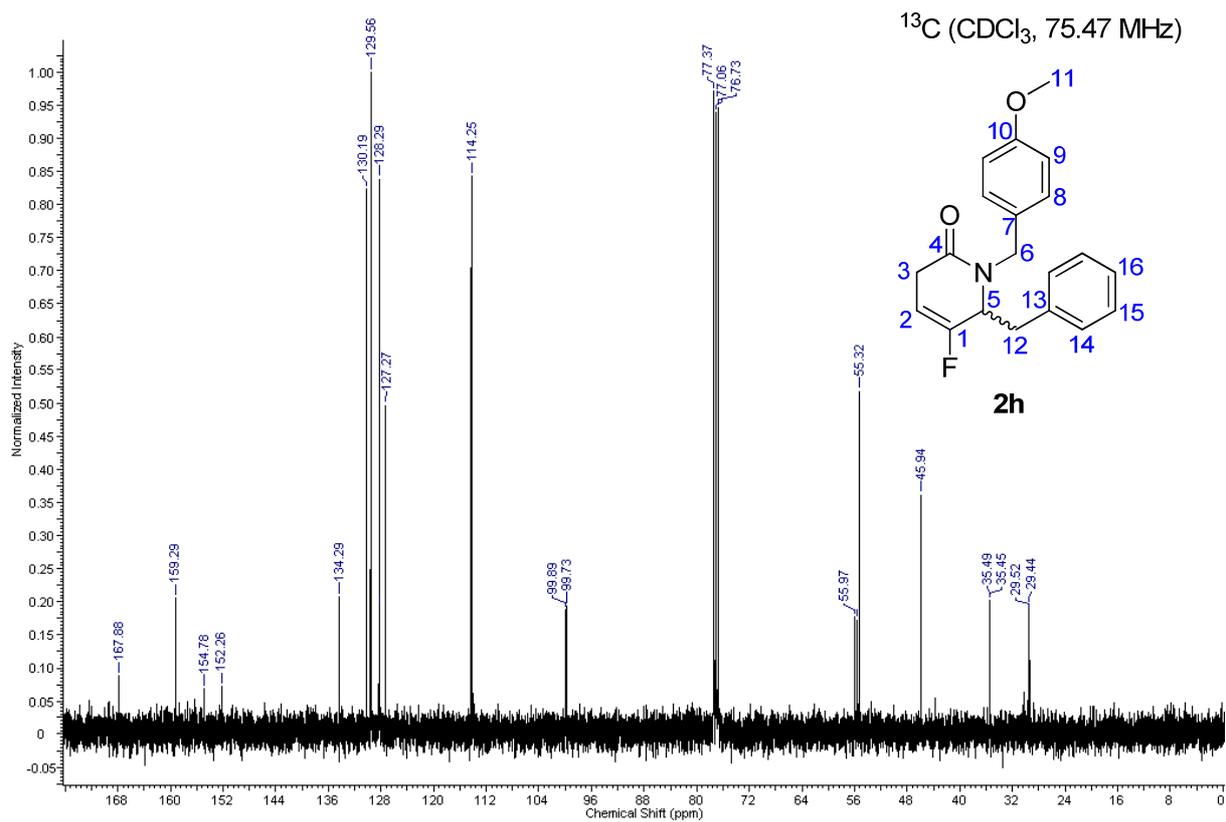
Compound **2d+e**: *Racemic 5-fluoro-1-(4-methoxybenzyl)-6-phenyl-1,6-dihydropyridin-2(3H)-one*



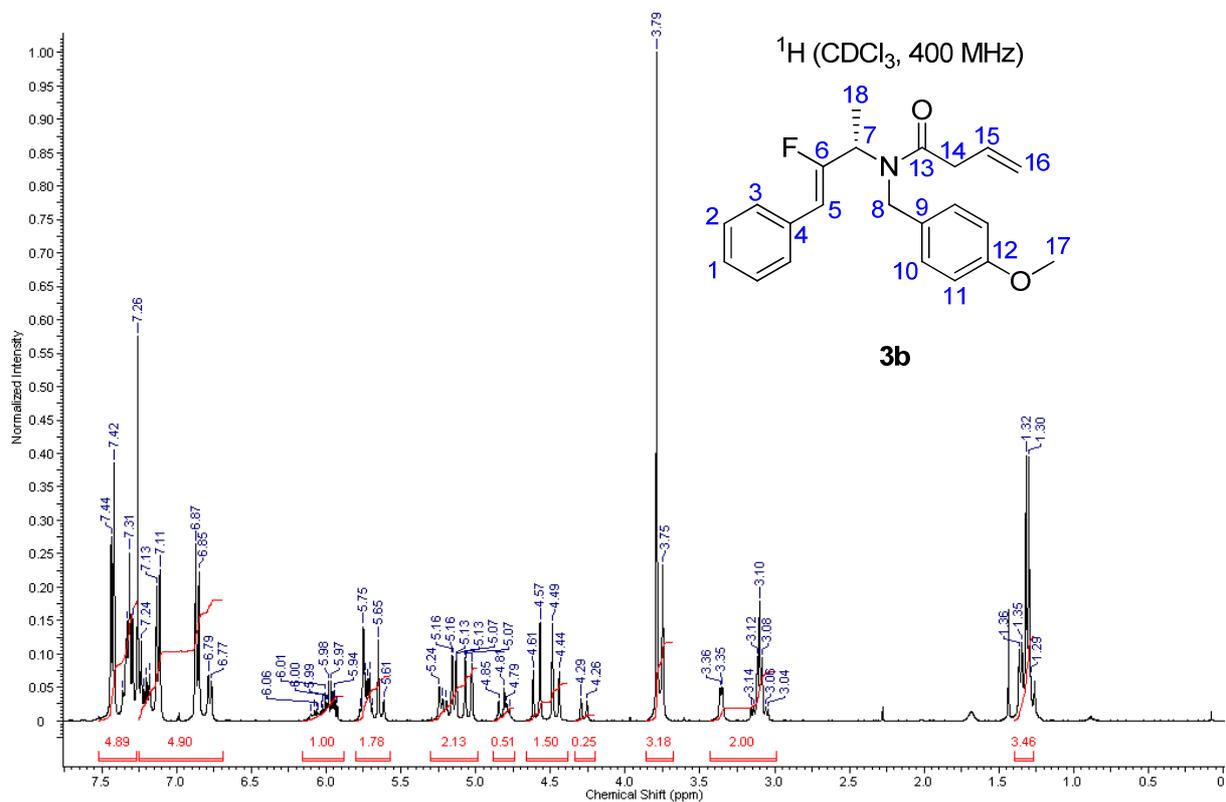


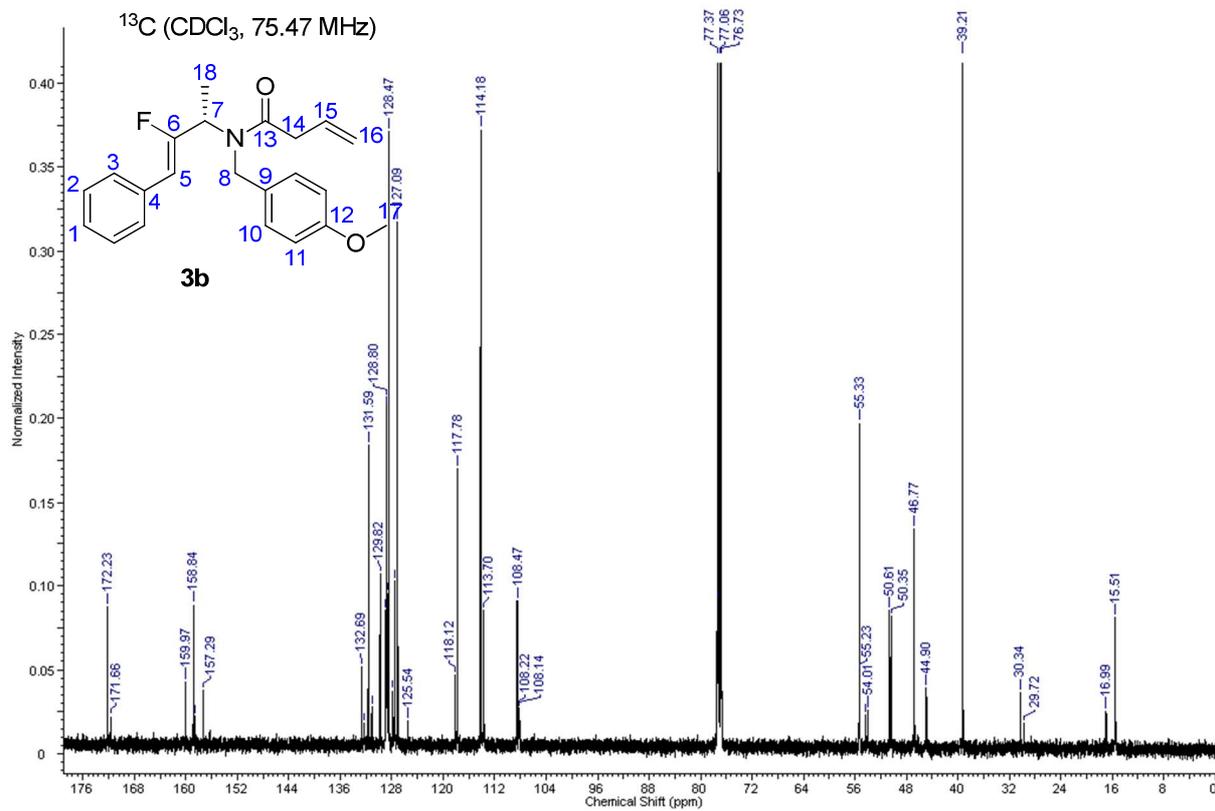
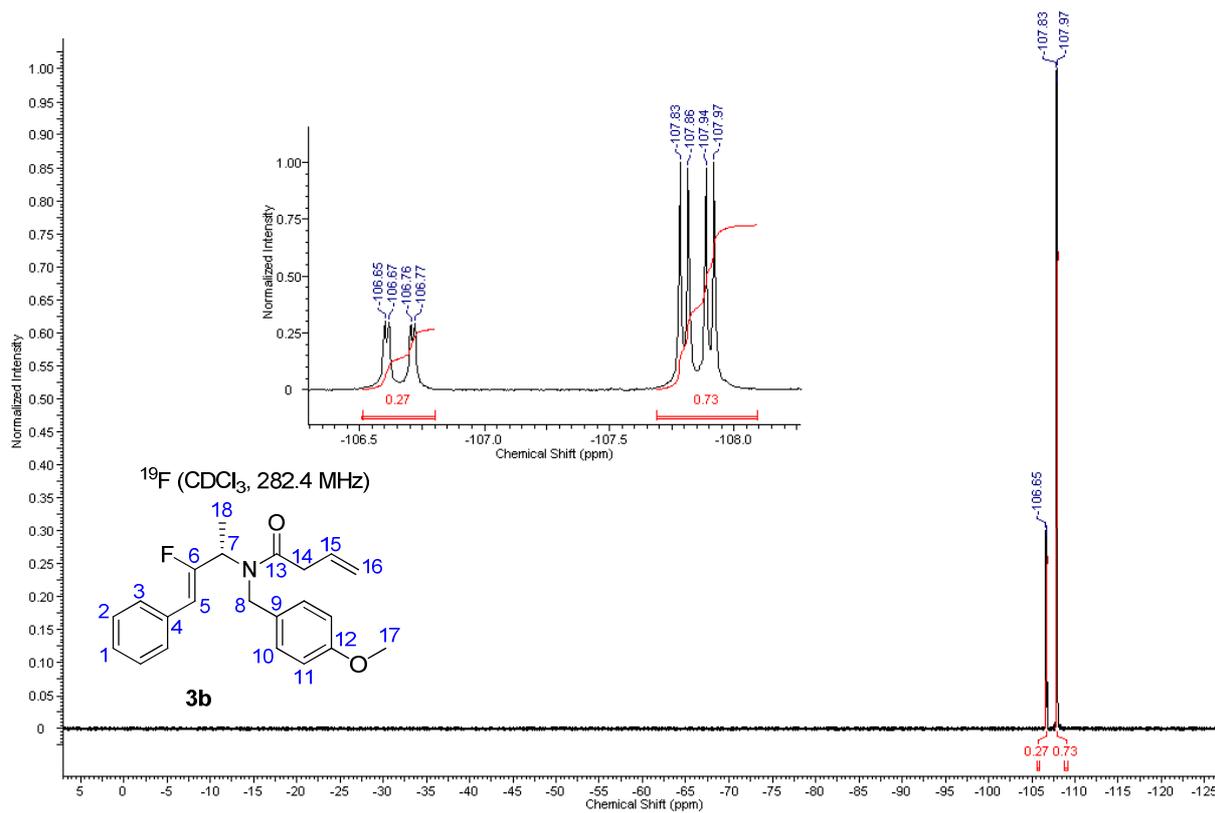
Compound **2h**: 6-benzyl-5-fluoro-1-(4-methoxybenzyl)-1,6-dihydropyridin-2(3H)-one



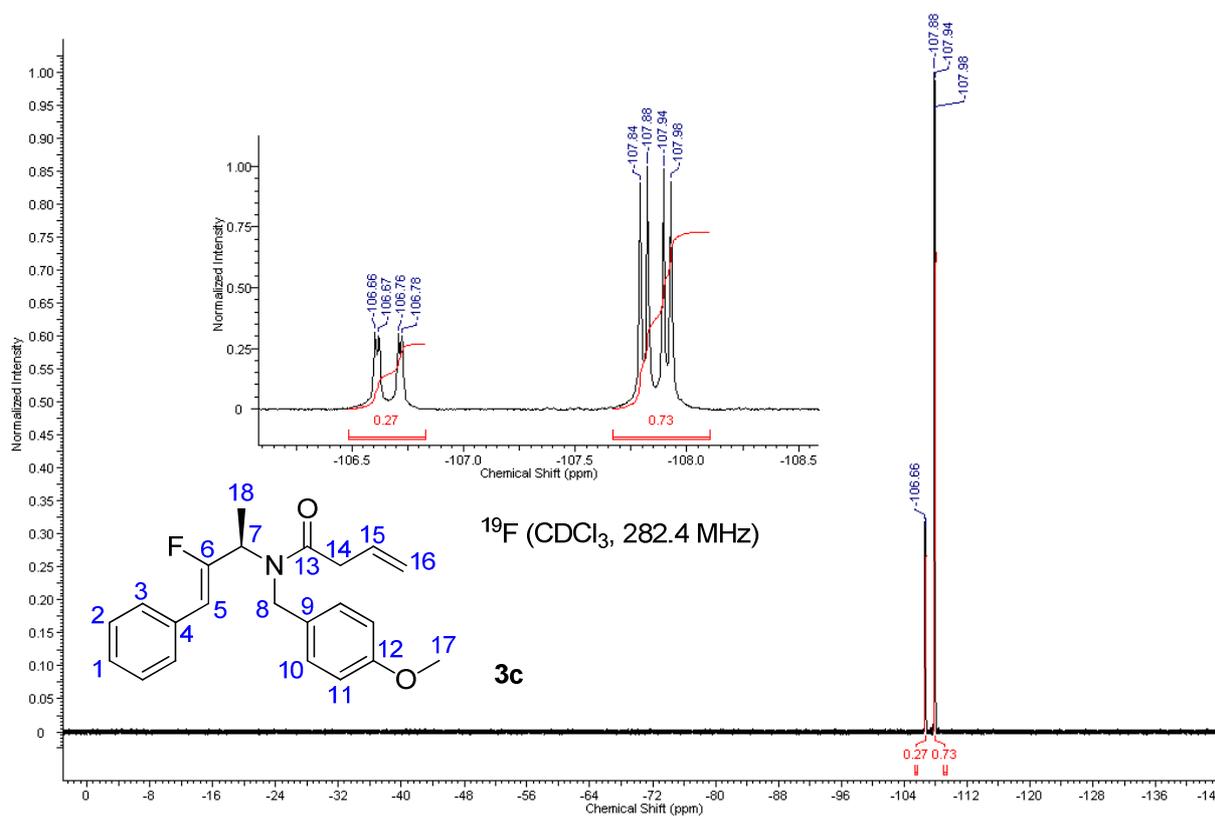
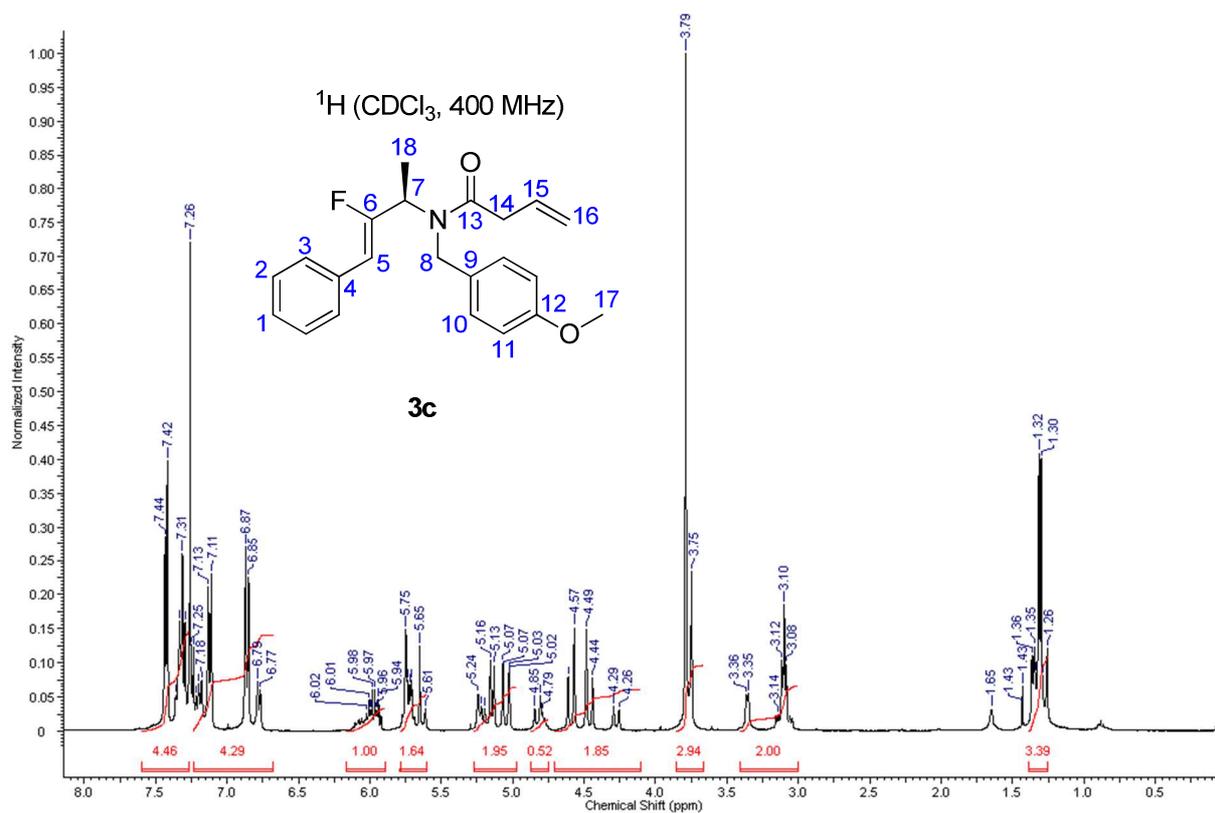


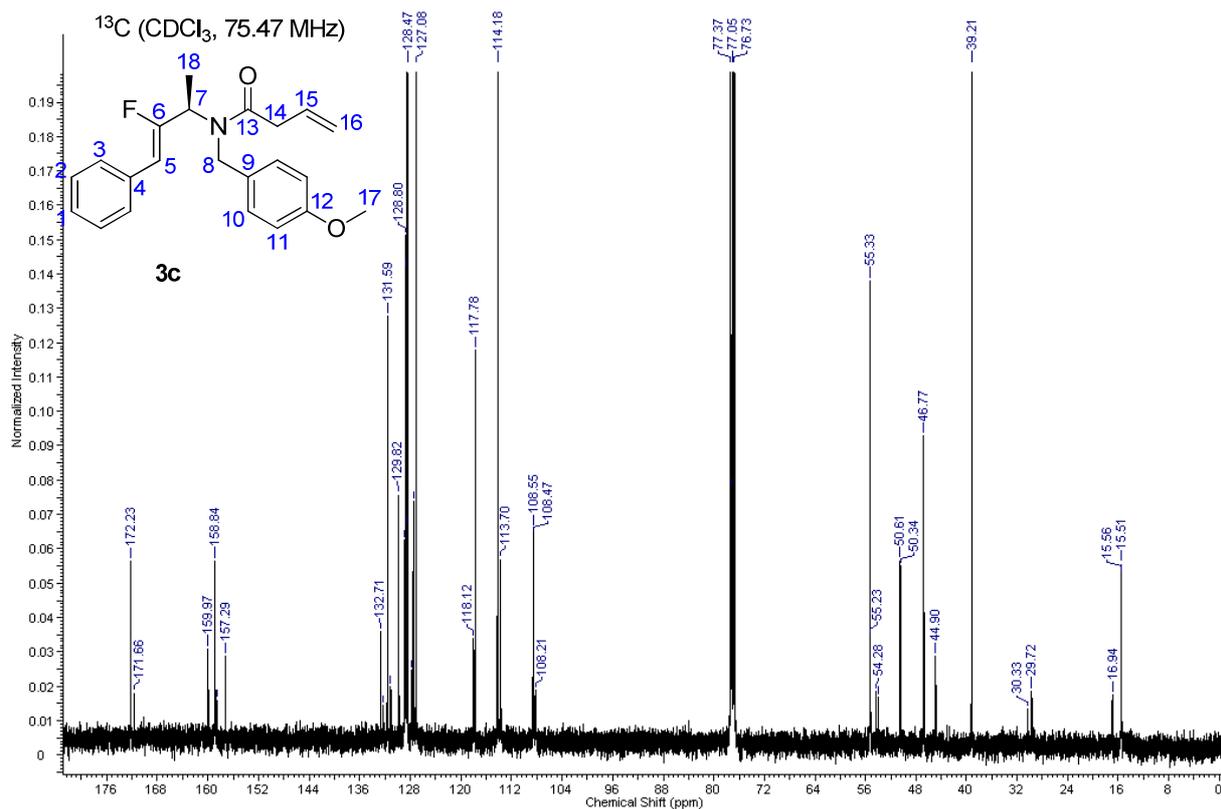
Compound **3b**: *(S,Z)*-*N*-(3-fluoro-4-phenylbut-3-en-2-yl)-*N*-(4-methoxybenzyl)but-3-enamide



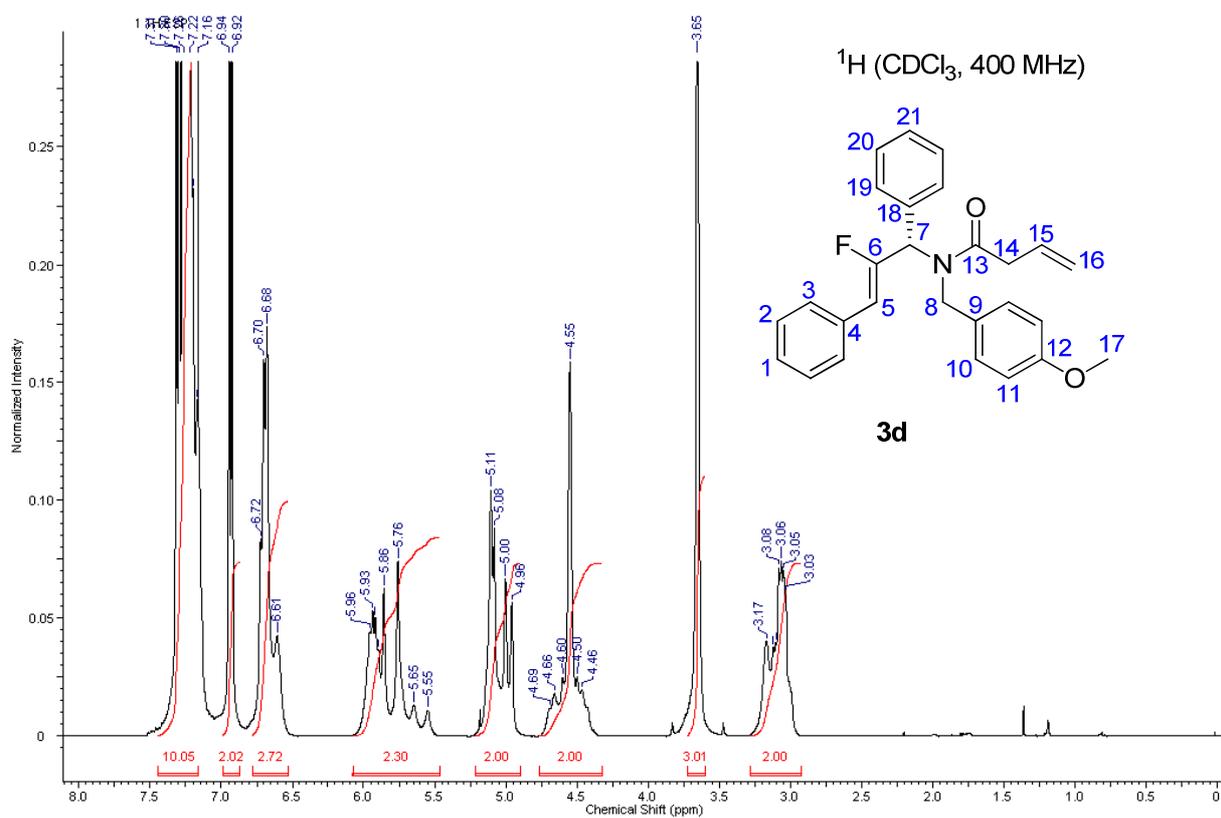


Compound **3c**: (*R,Z*)-*N*-(3-fluoro-4-phenylbut-3-en-2-yl)-*N*-(4-methoxybenzyl)but-3-enamide

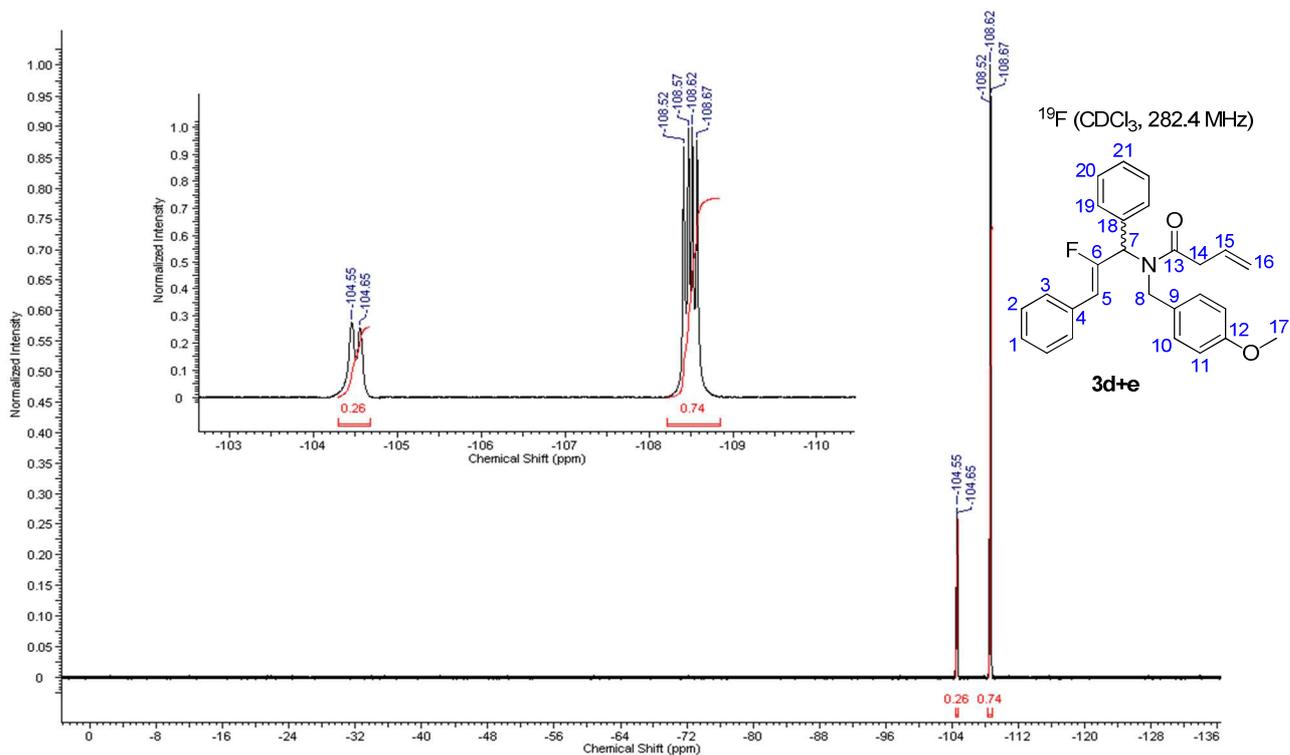
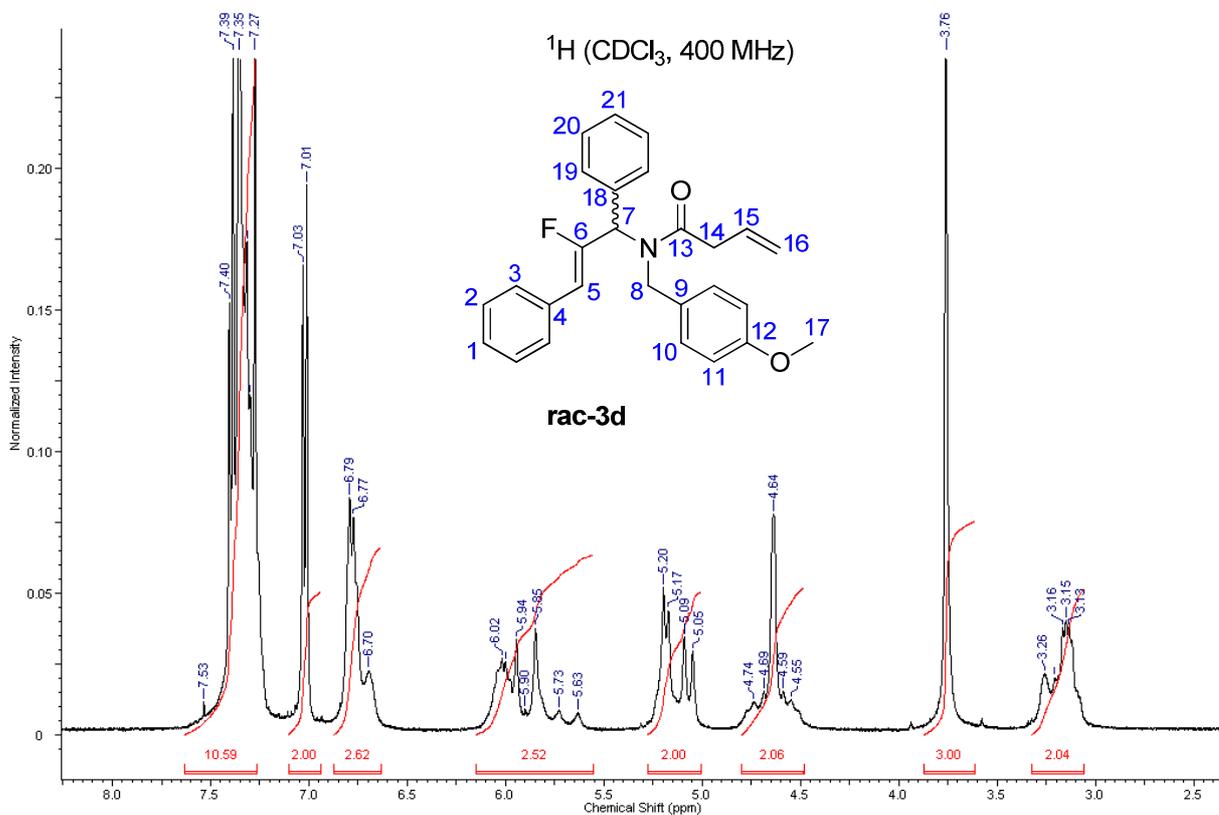


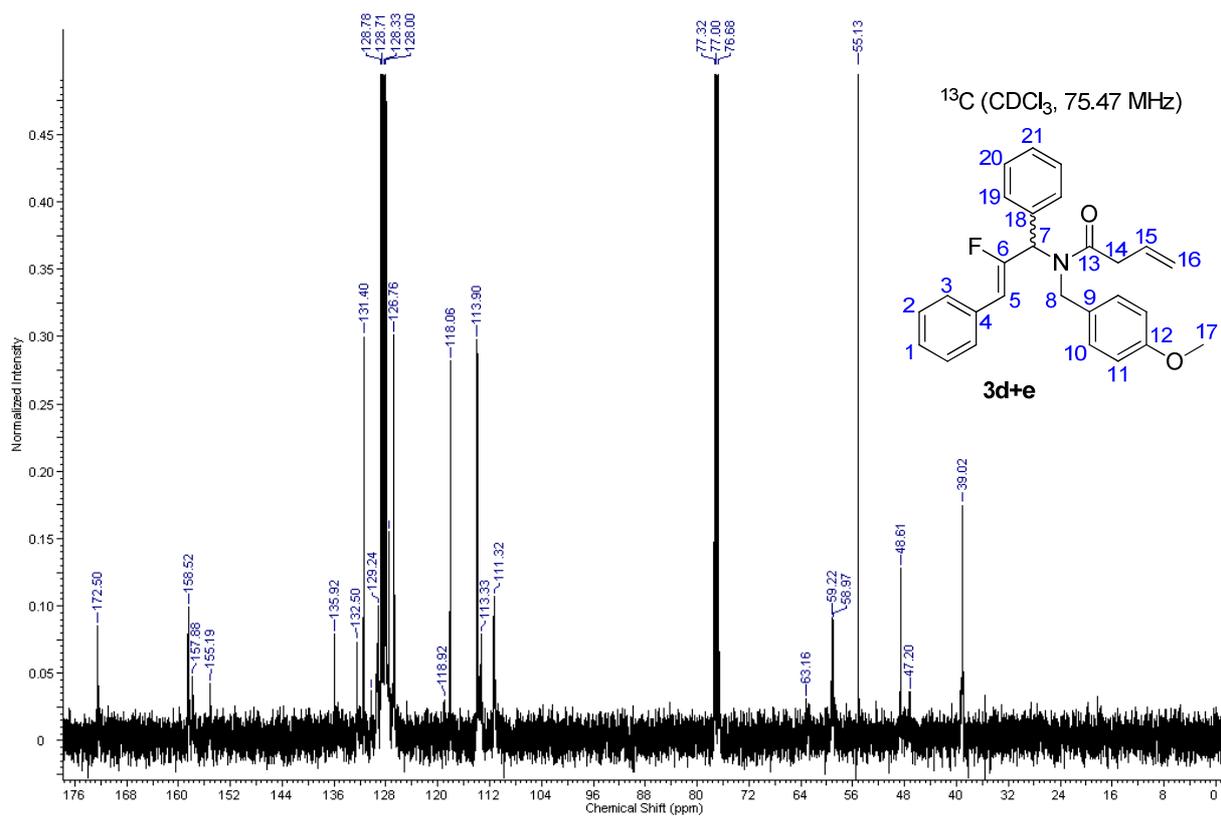


Compound **3d**: (*S,Z*)-*N*-(2-fluoro-1,3-diphenylallyl)-*N*-(4-methoxybenzyl)but-3-enamide

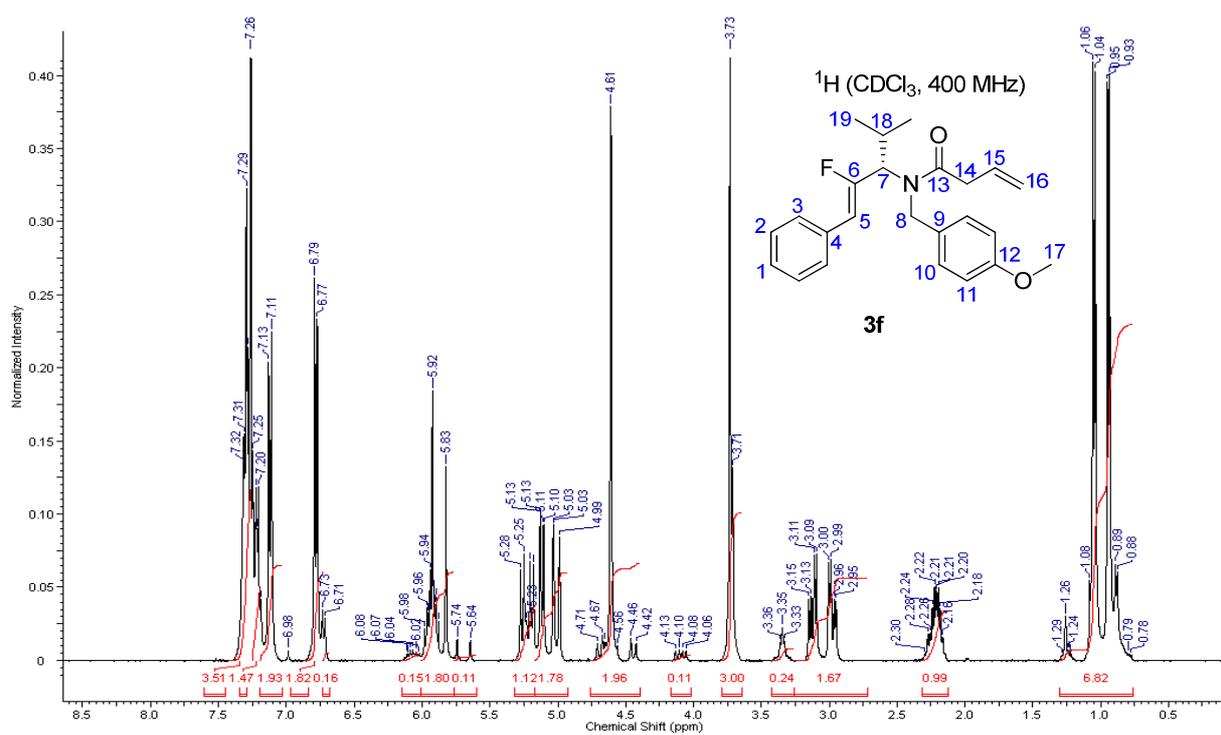


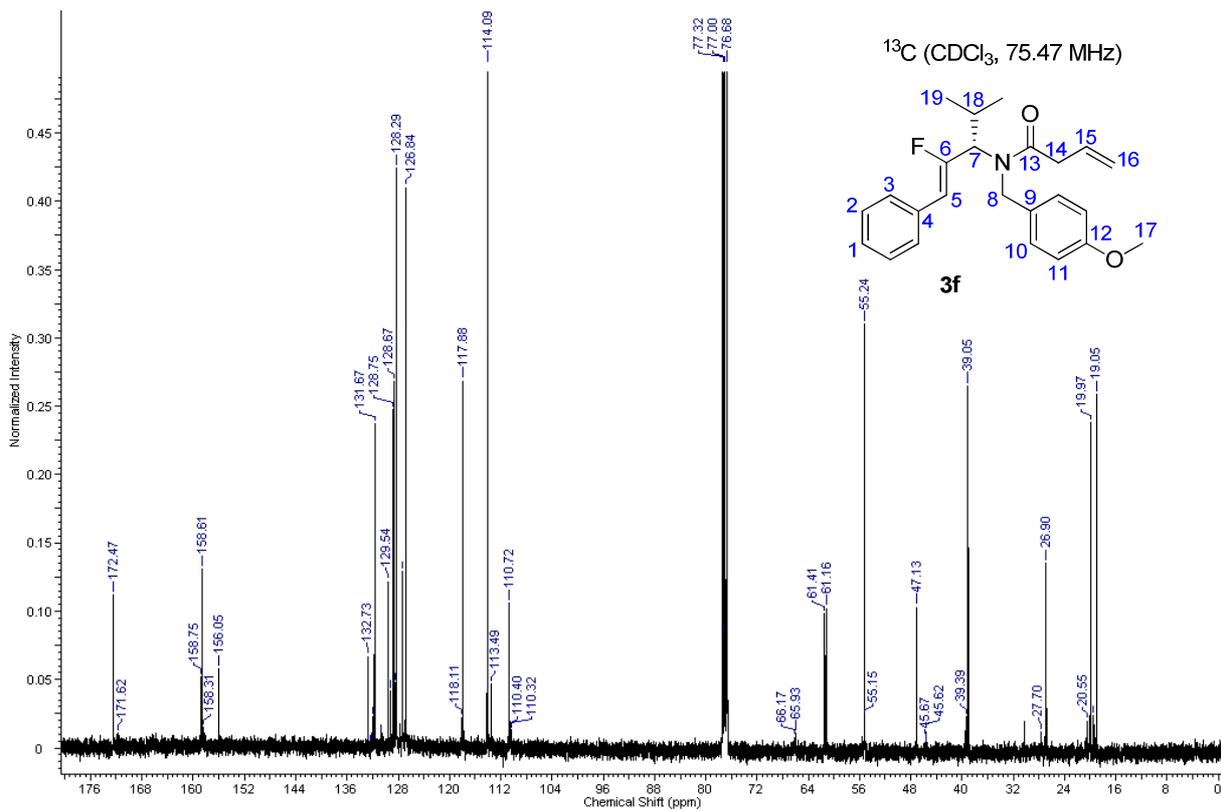
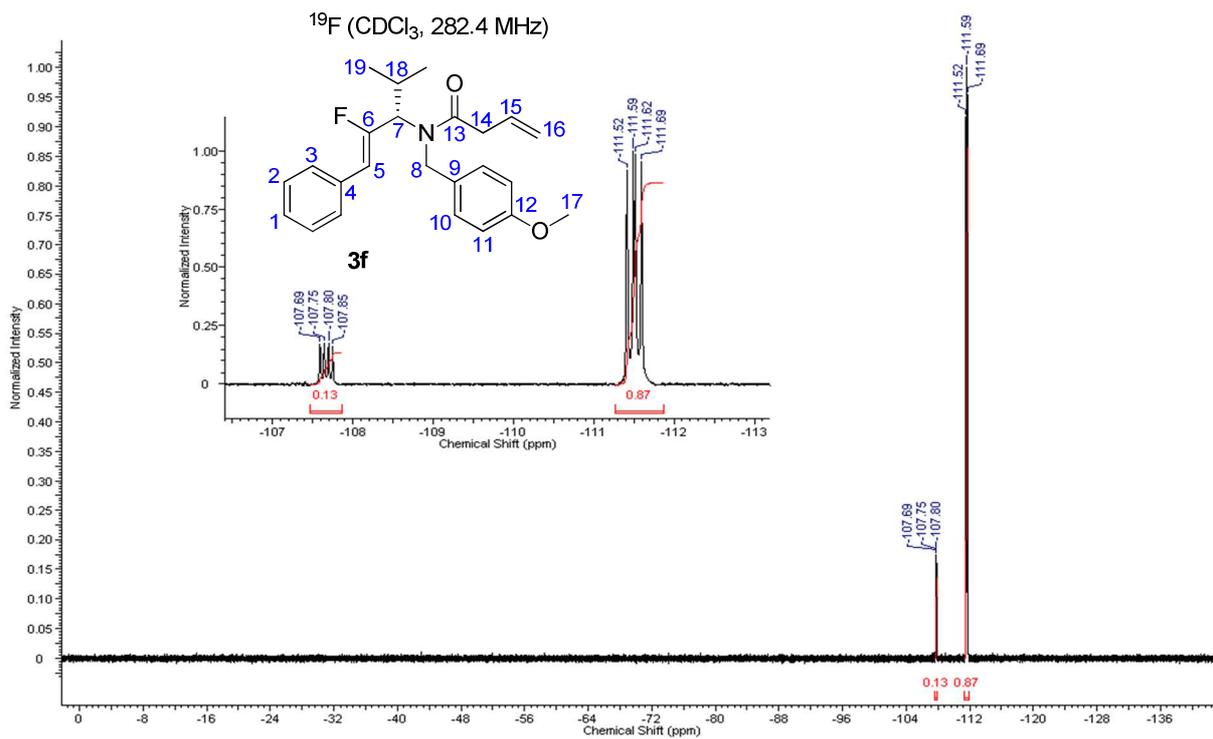
Compound 3d+e: *Racemic (Z)-N-(2-fluoro-1,3-diphenylallyl)-N-(4-methoxybenzyl)but-3-enamide*



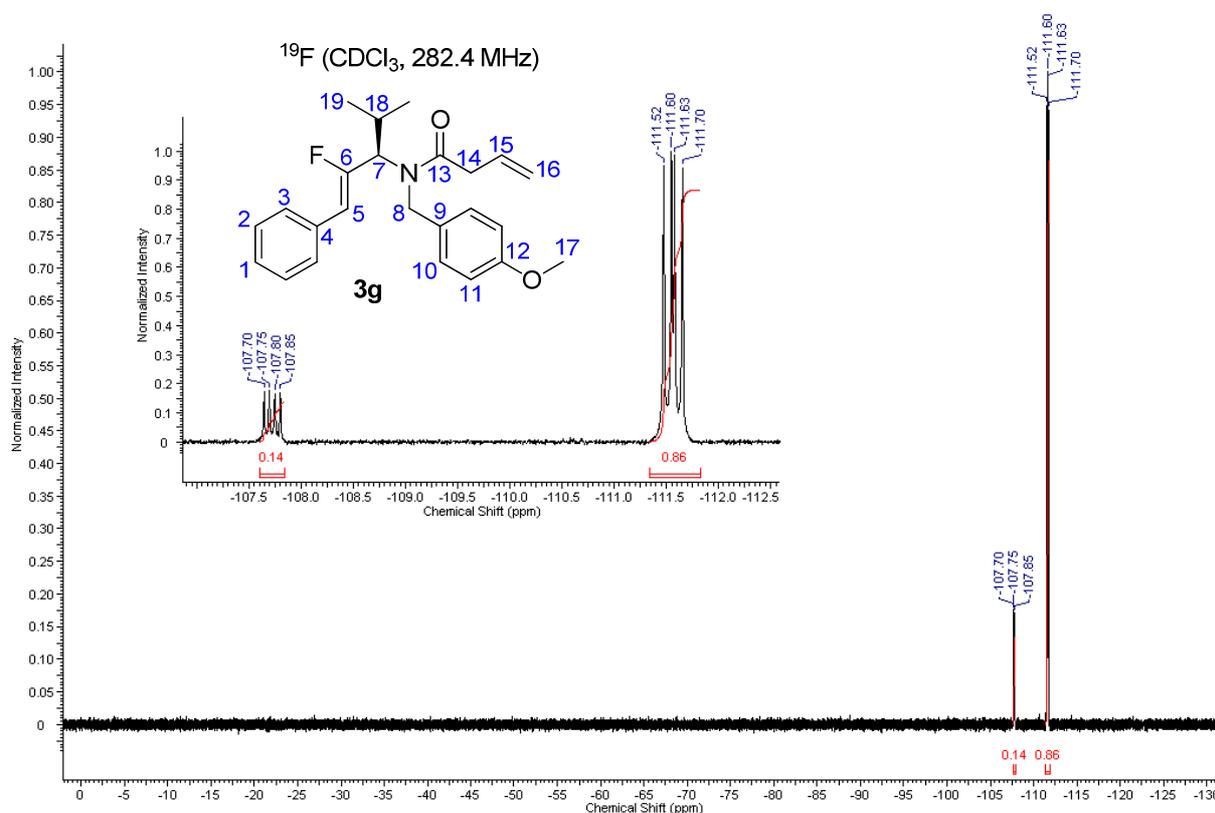
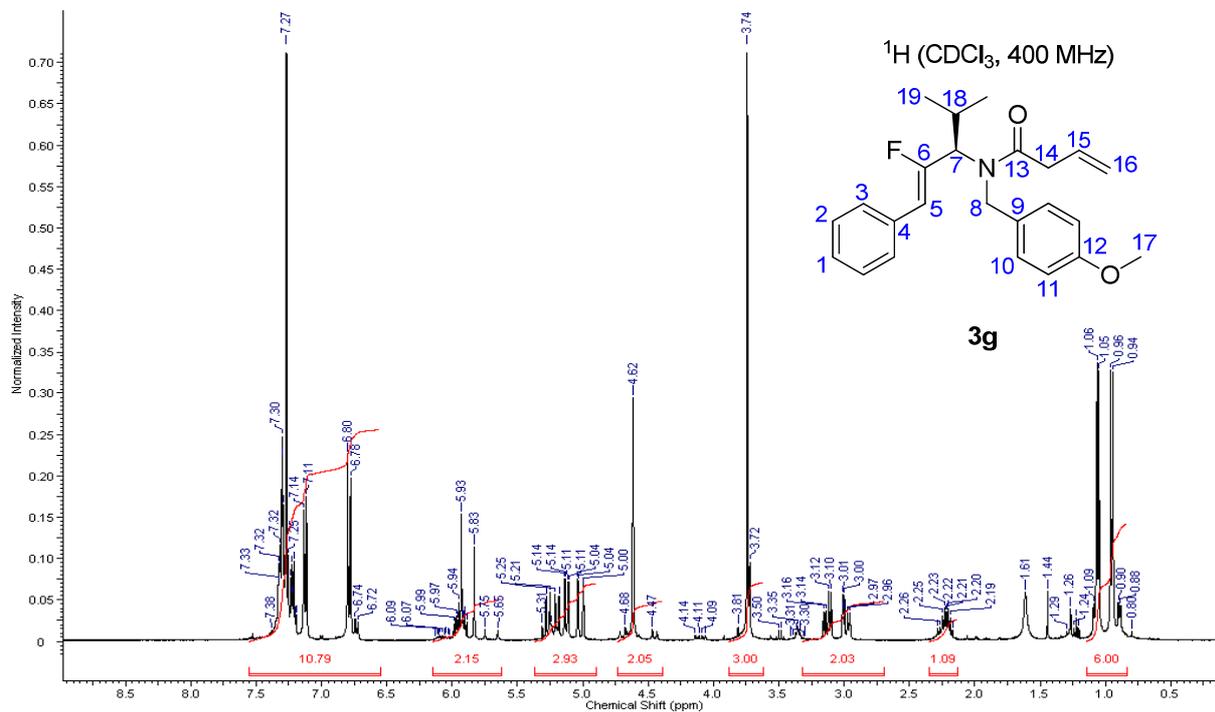


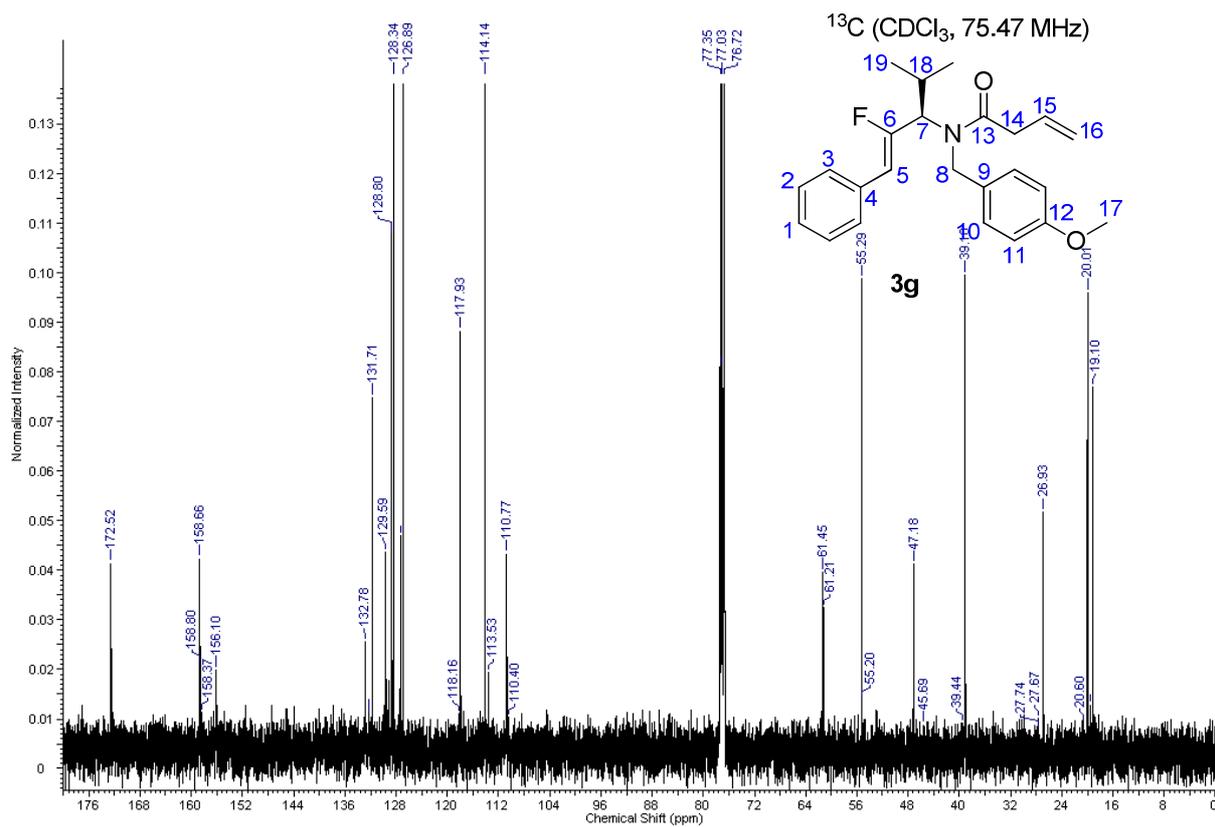
Compound **3f**: *(S,Z)*-*N*-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-*N*-(4-methoxybenzyl)but-3-enamide



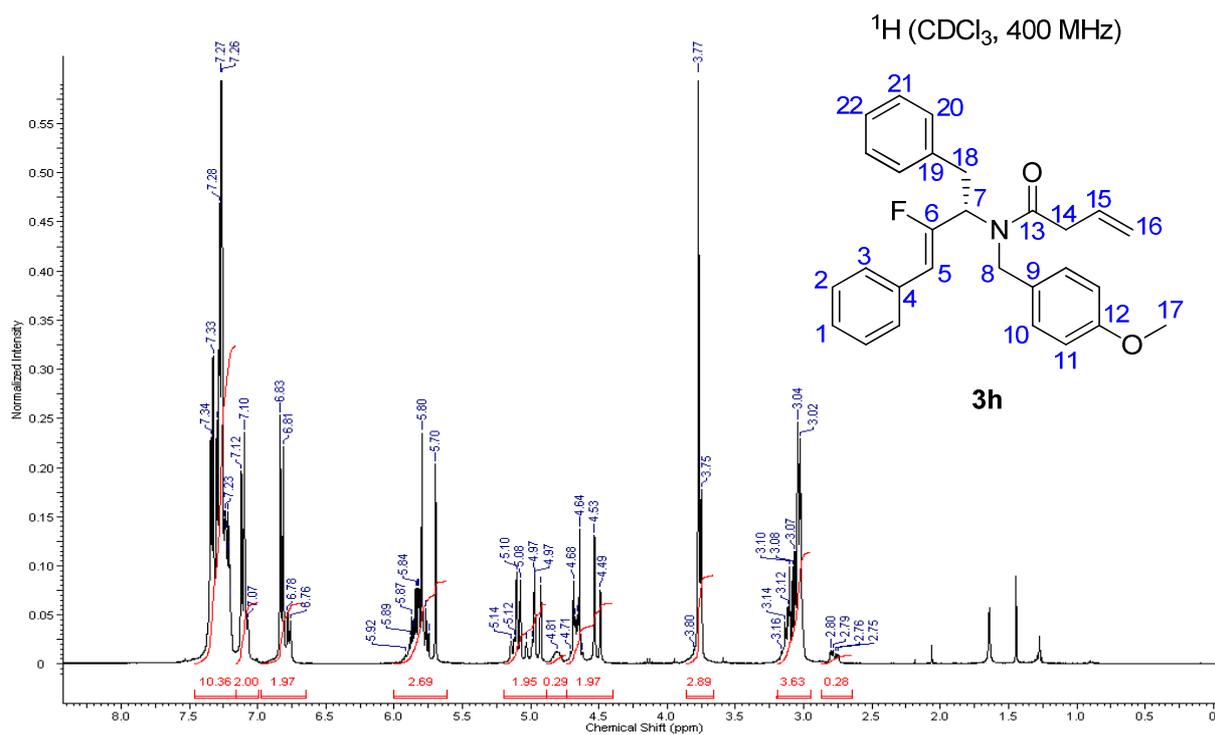


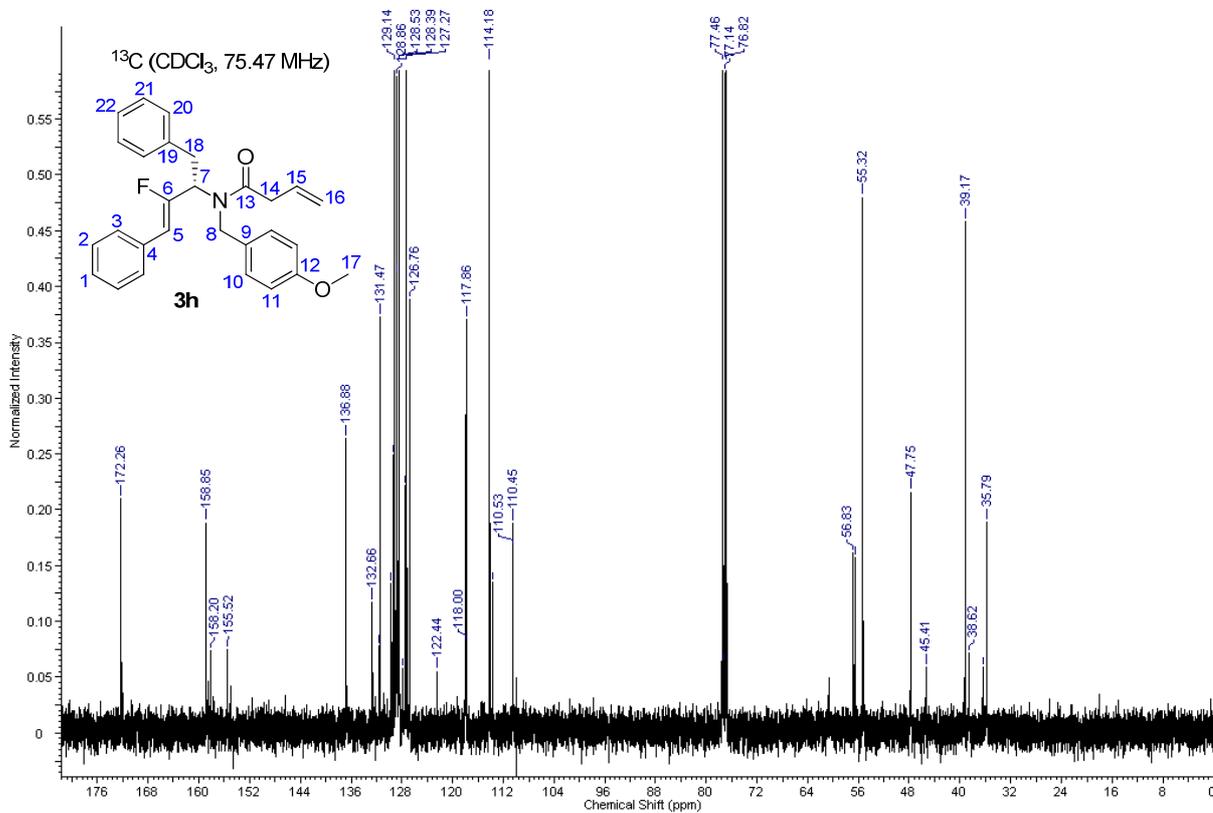
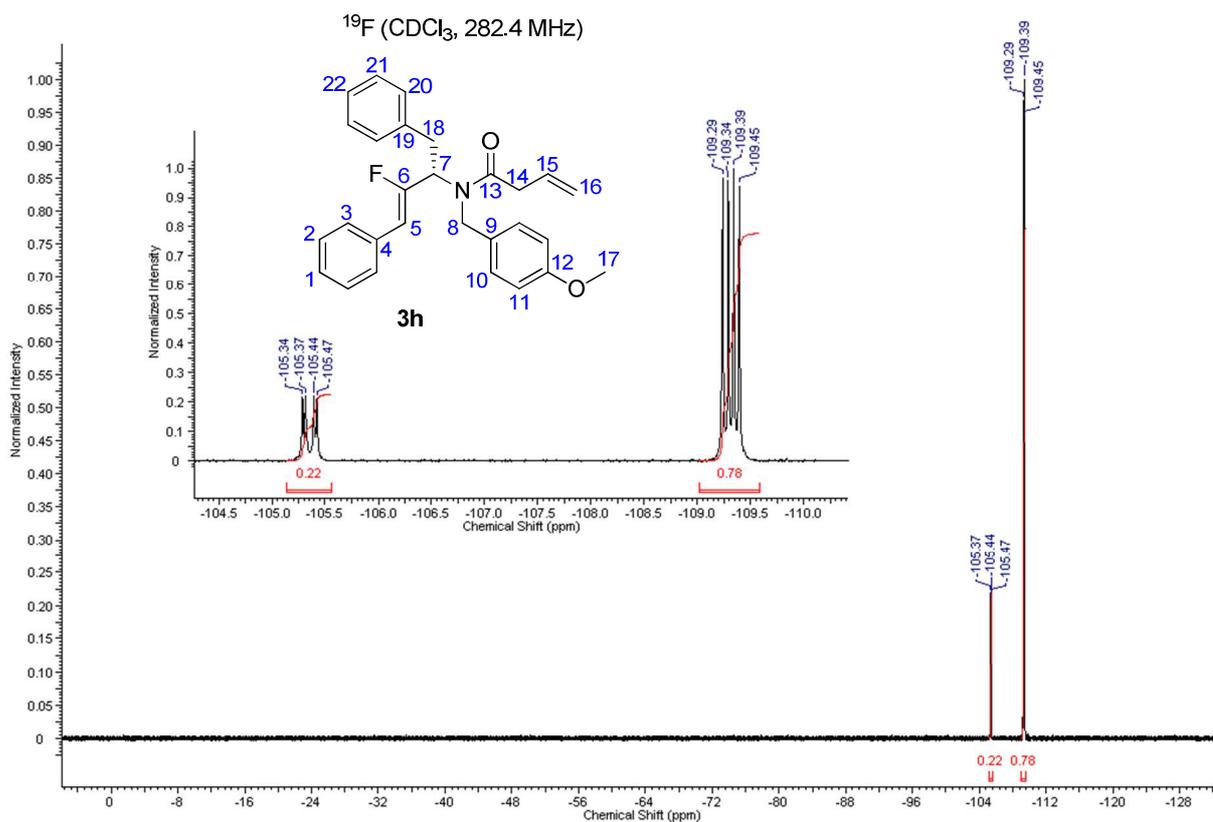
Compound **3g**: *(R,Z)*-*N*-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-*N*-(4-methoxybenzyl)but-3-enamide



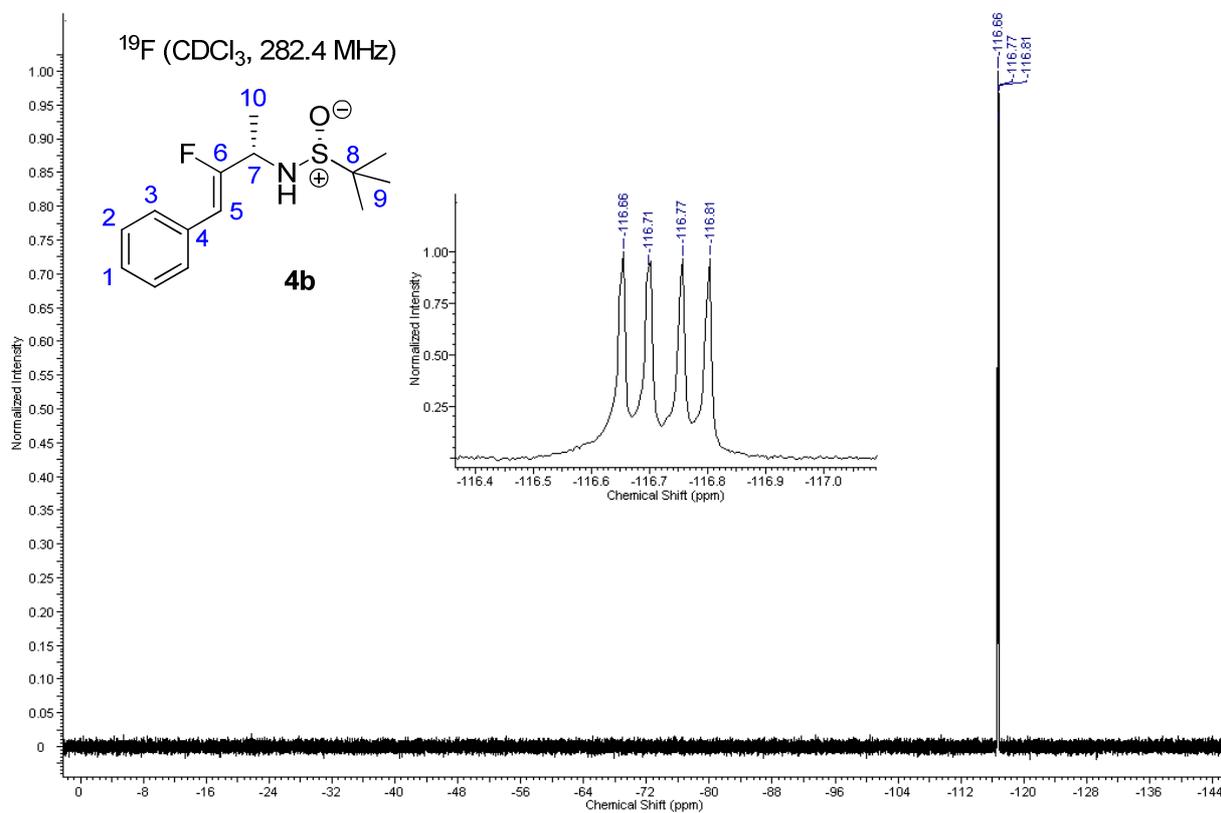
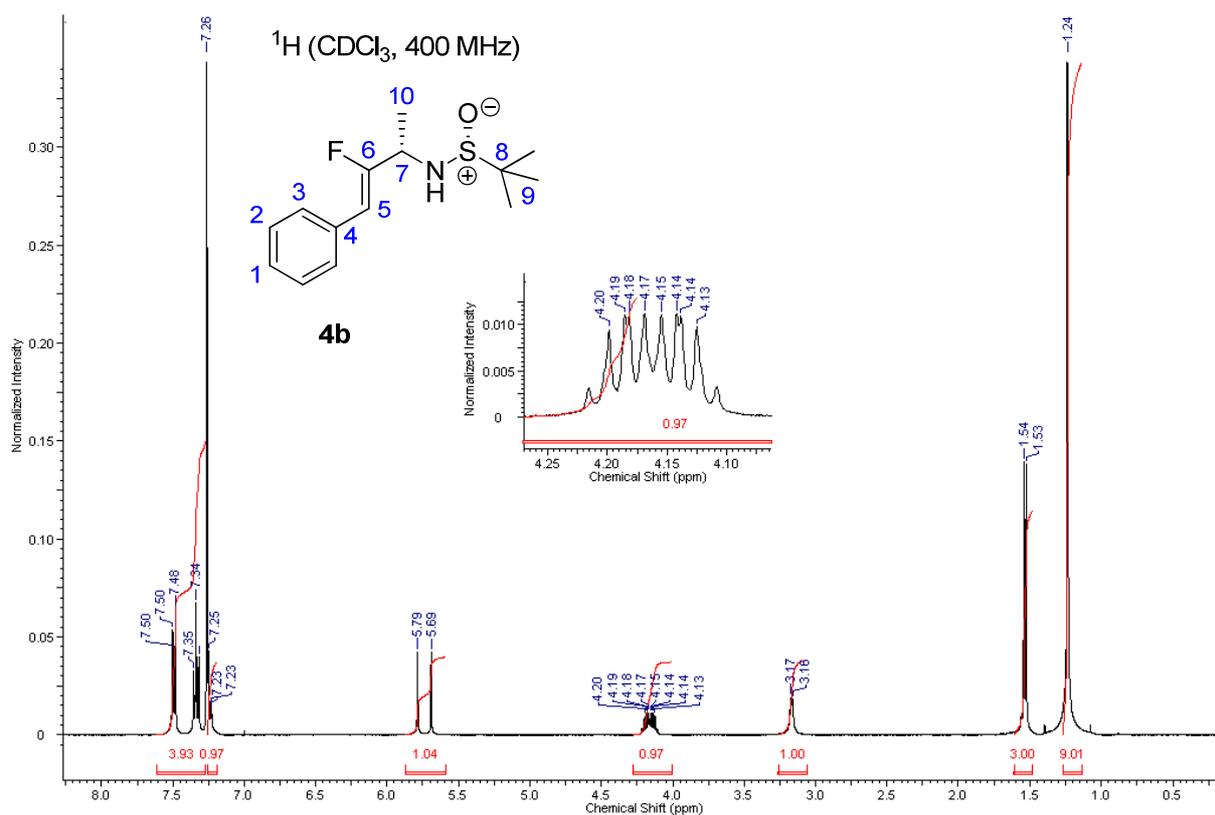


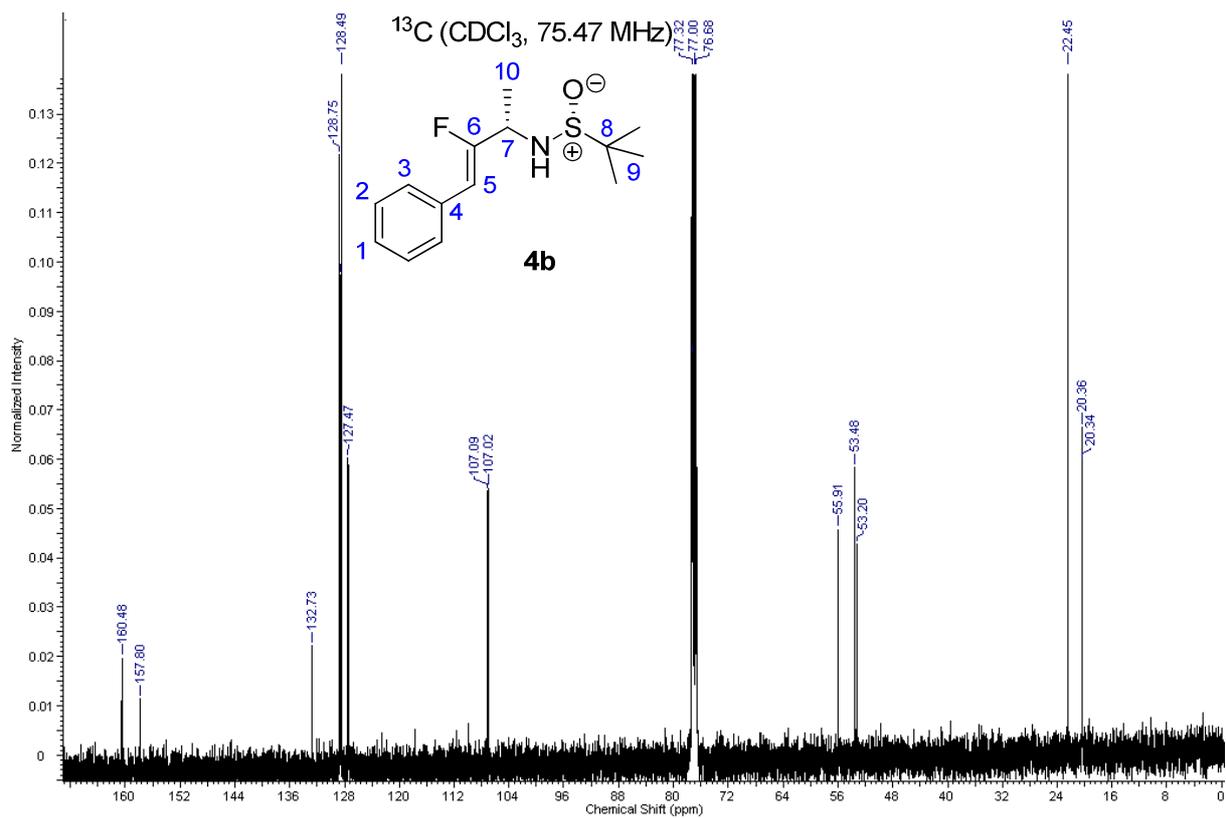
Compound **3h**: *(S,Z)*-*N*-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-*N*-(4-methoxybenzyl)but-3-enamide



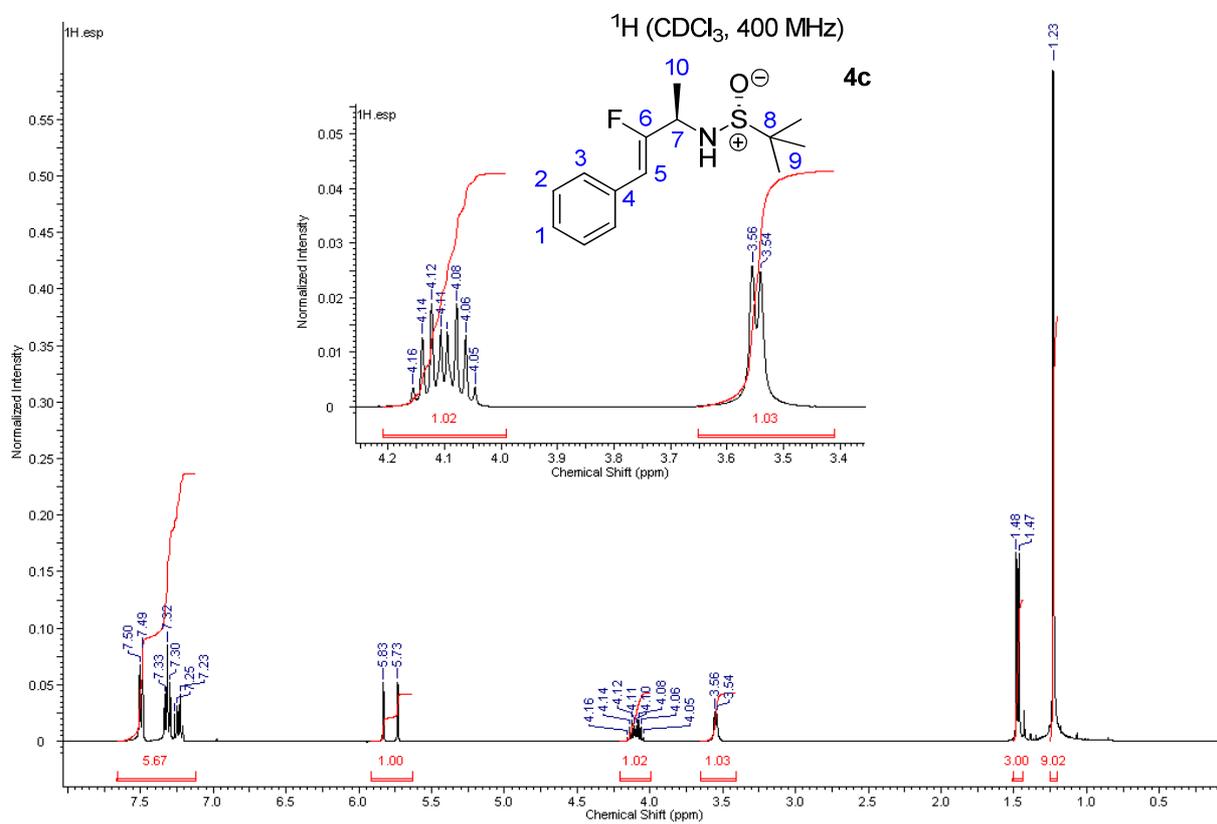


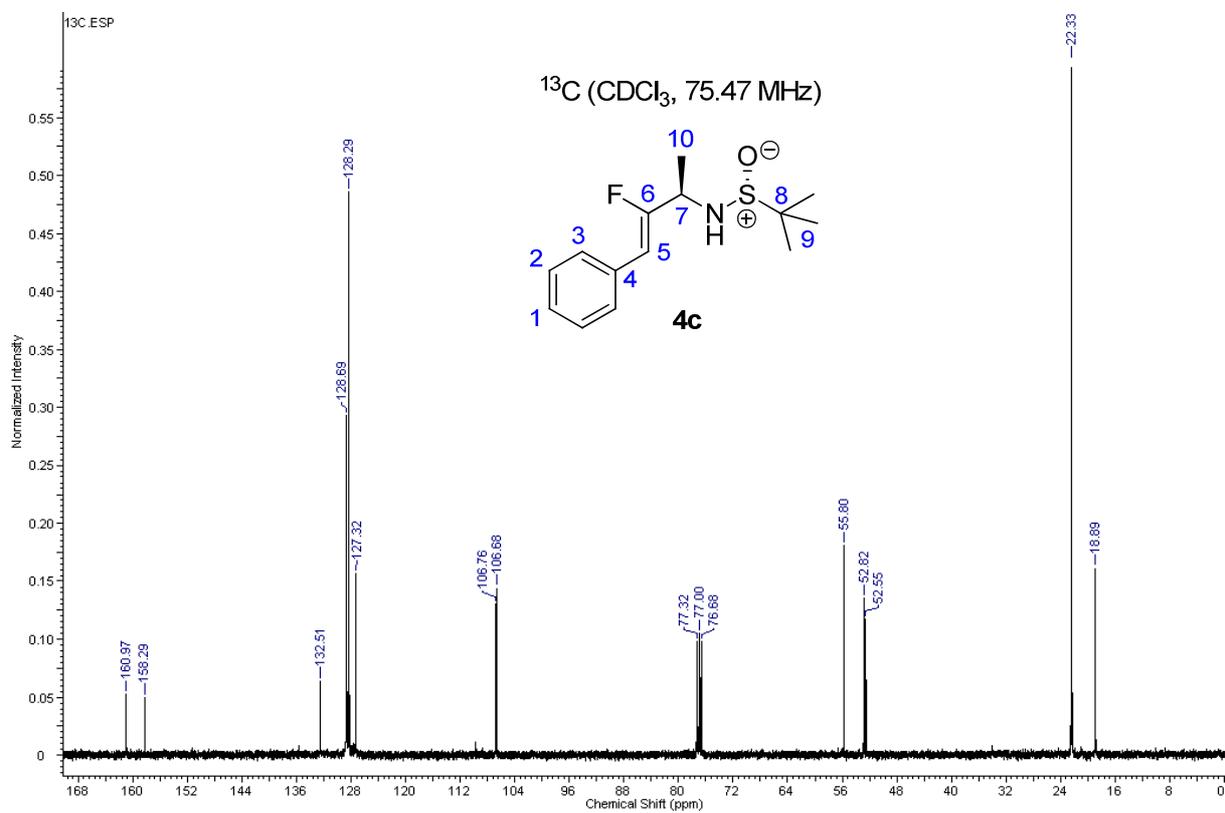
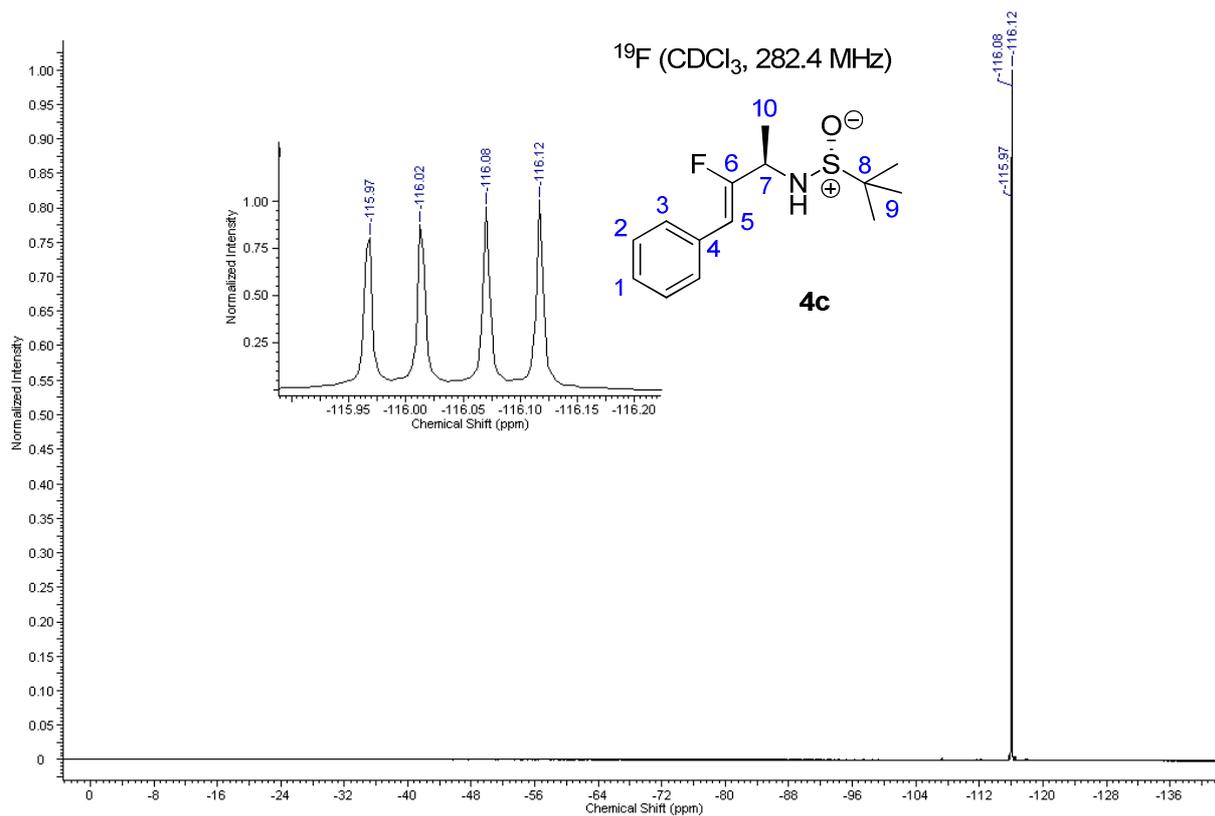
Compound **4b**: (*R*)-*N*-((*S,Z*)-3-fluoro-4-phenylbut-3-en-2-yl)-2-methylpropane-2-sulfonamide



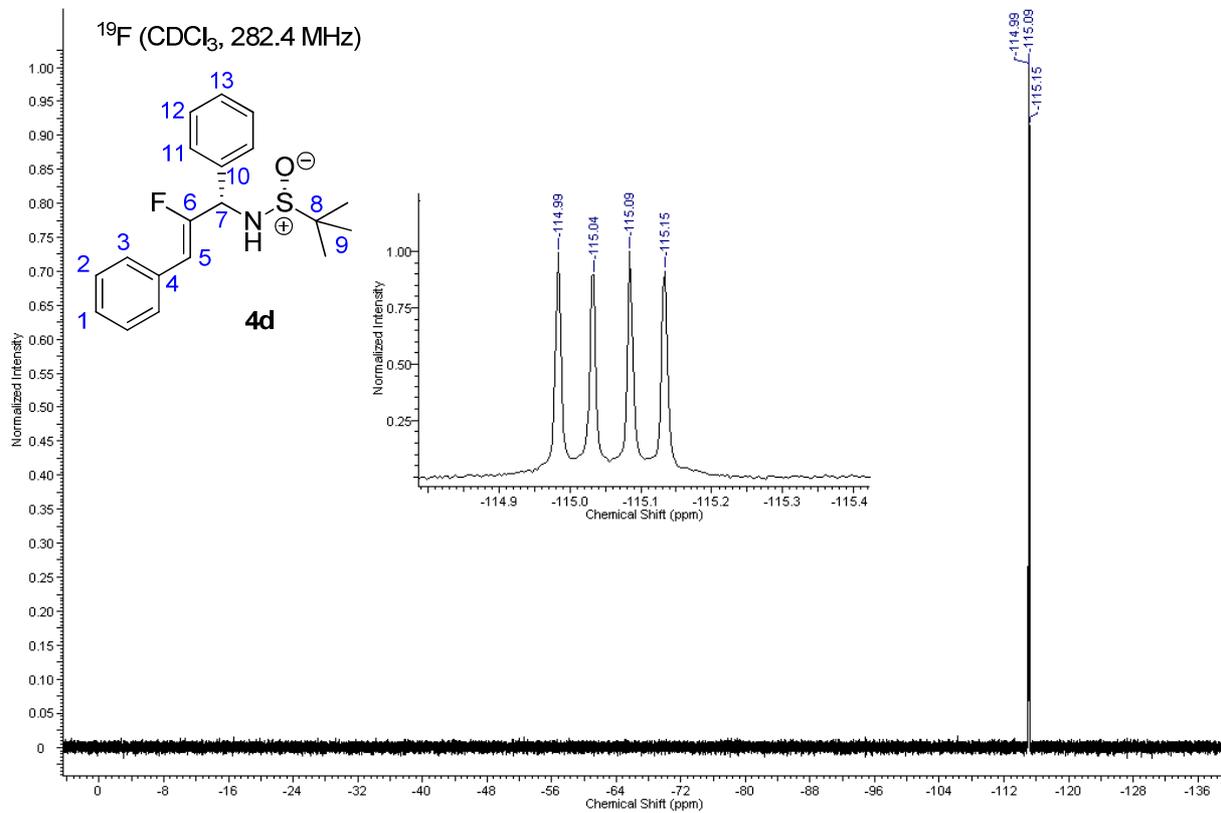
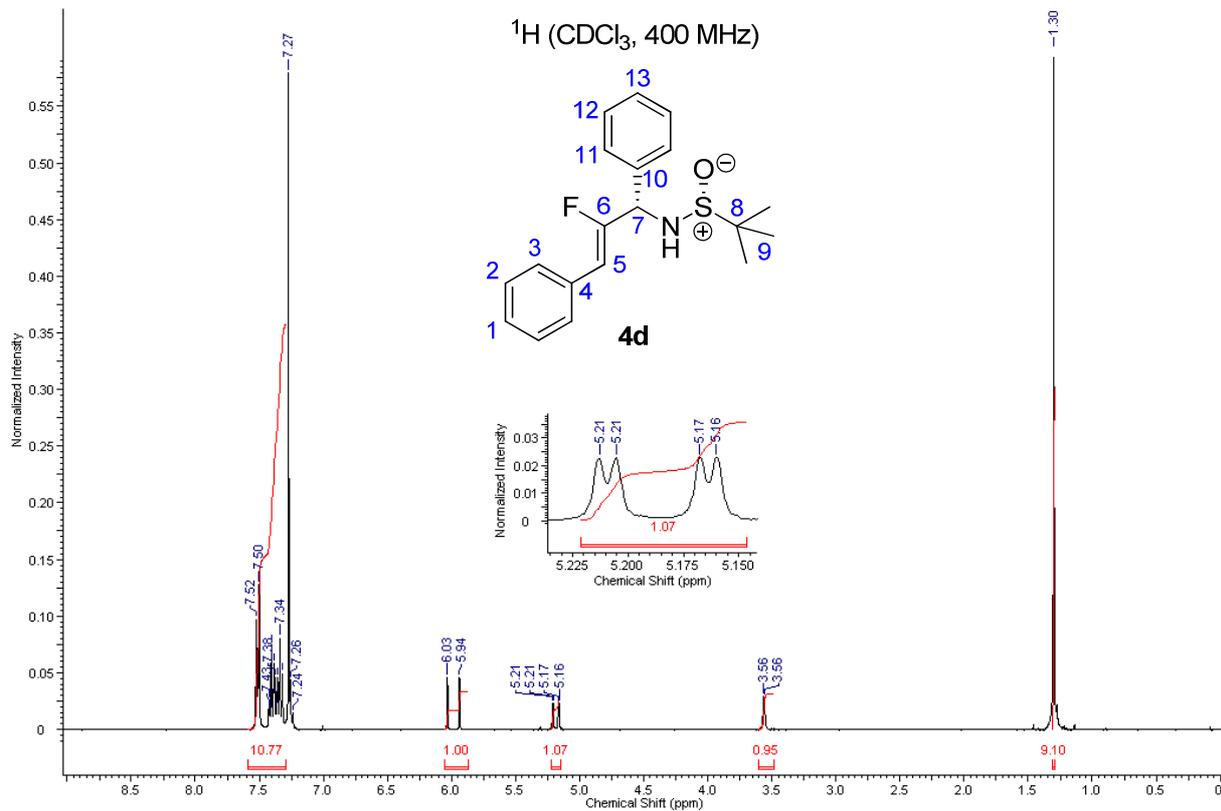


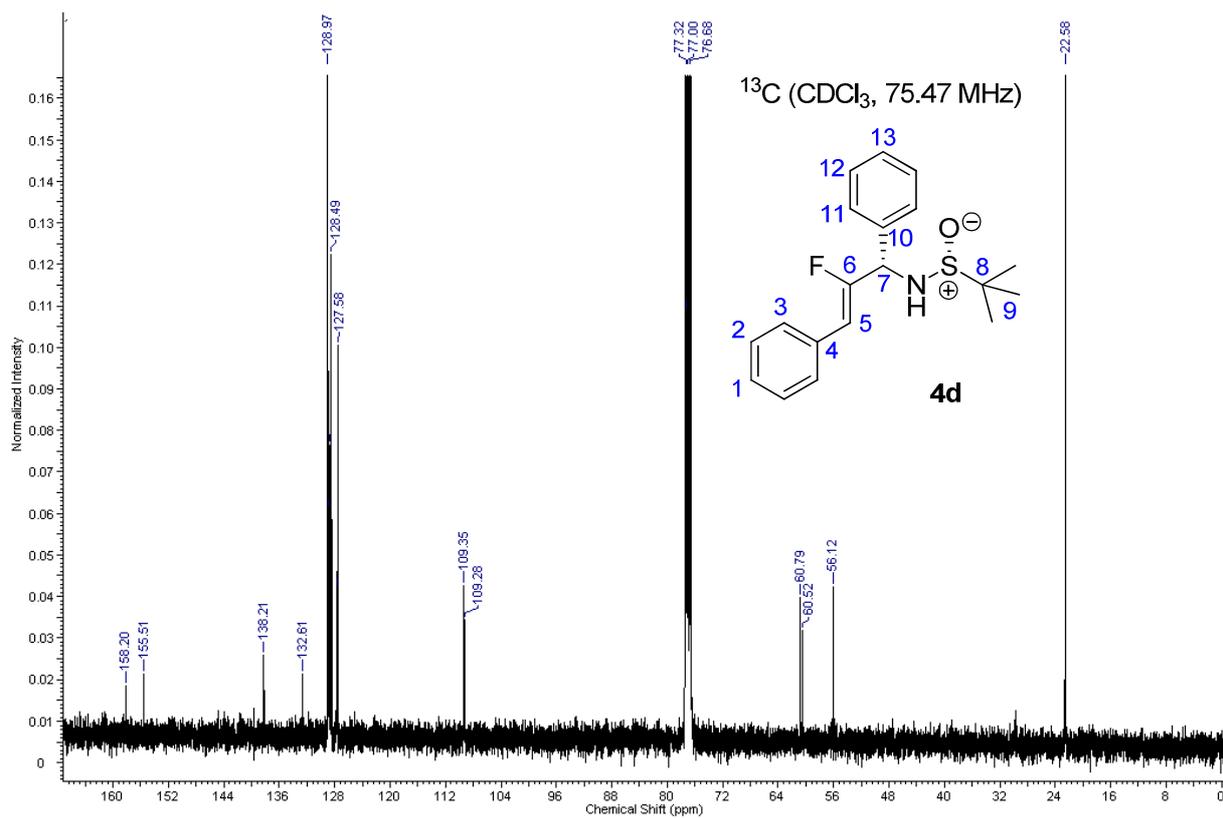
Compound **4c**: *(R)*-*N*-((*R,Z*)-3-fluoro-4-phenylbut-3-en-2-yl)-2-methylpropane-2-sulfonamide



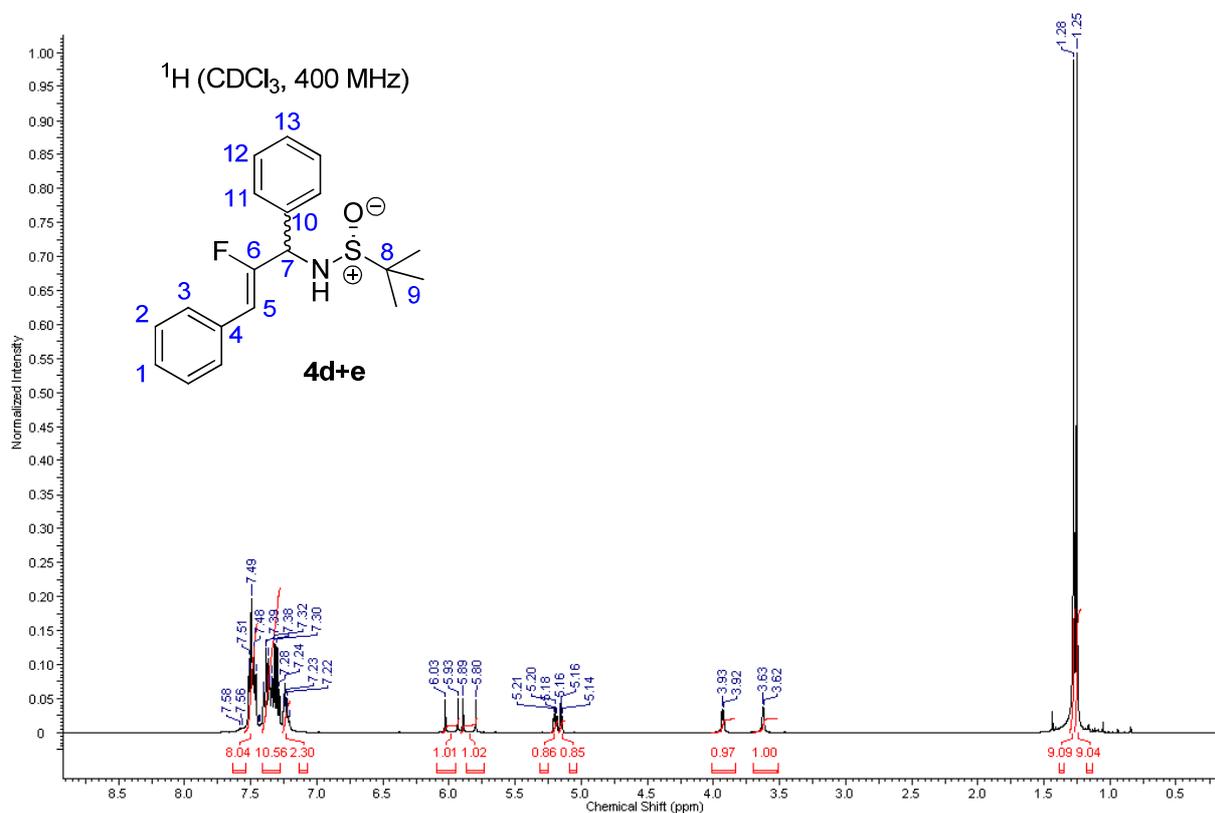


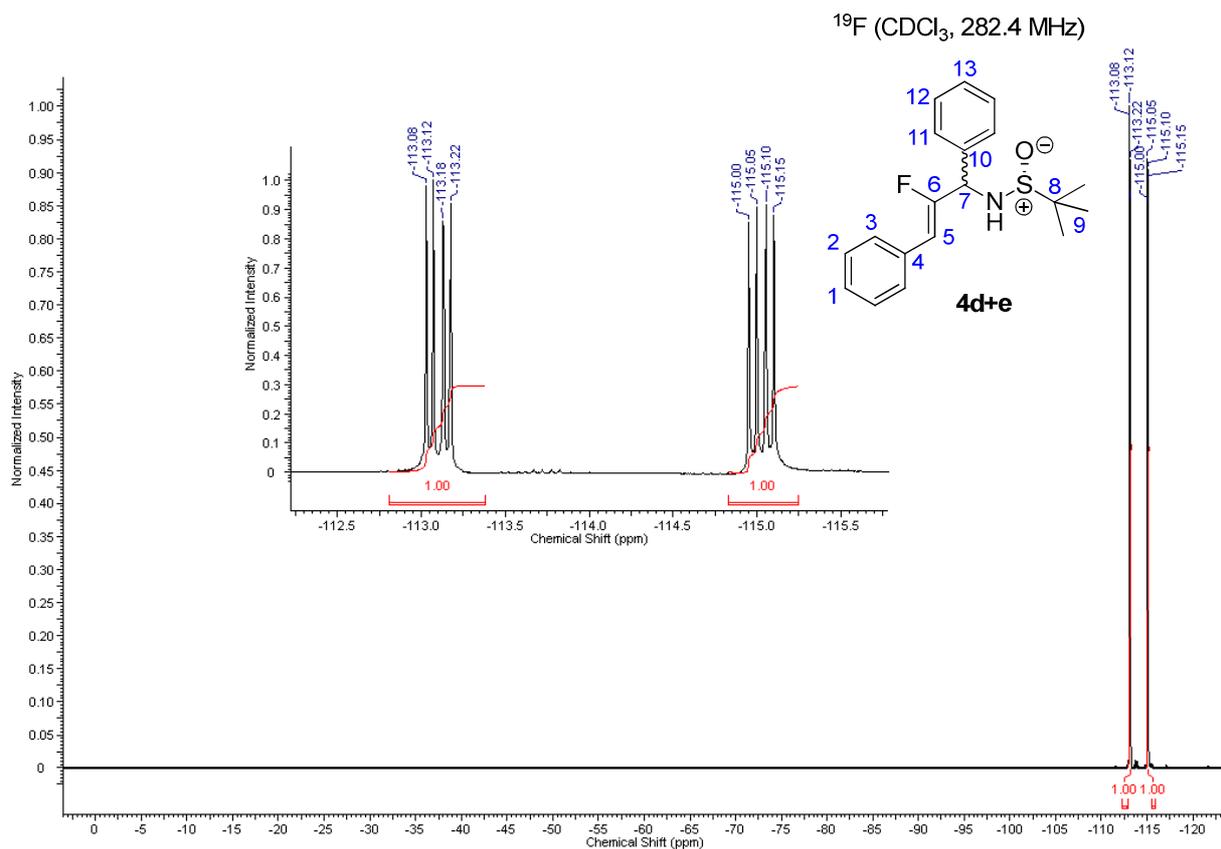
Compound **4d**: *(R)*-*N*-((*S,Z*)-2-fluoro-1,3-diphenylallyl)-2-methylpropane-2-sulfonamide



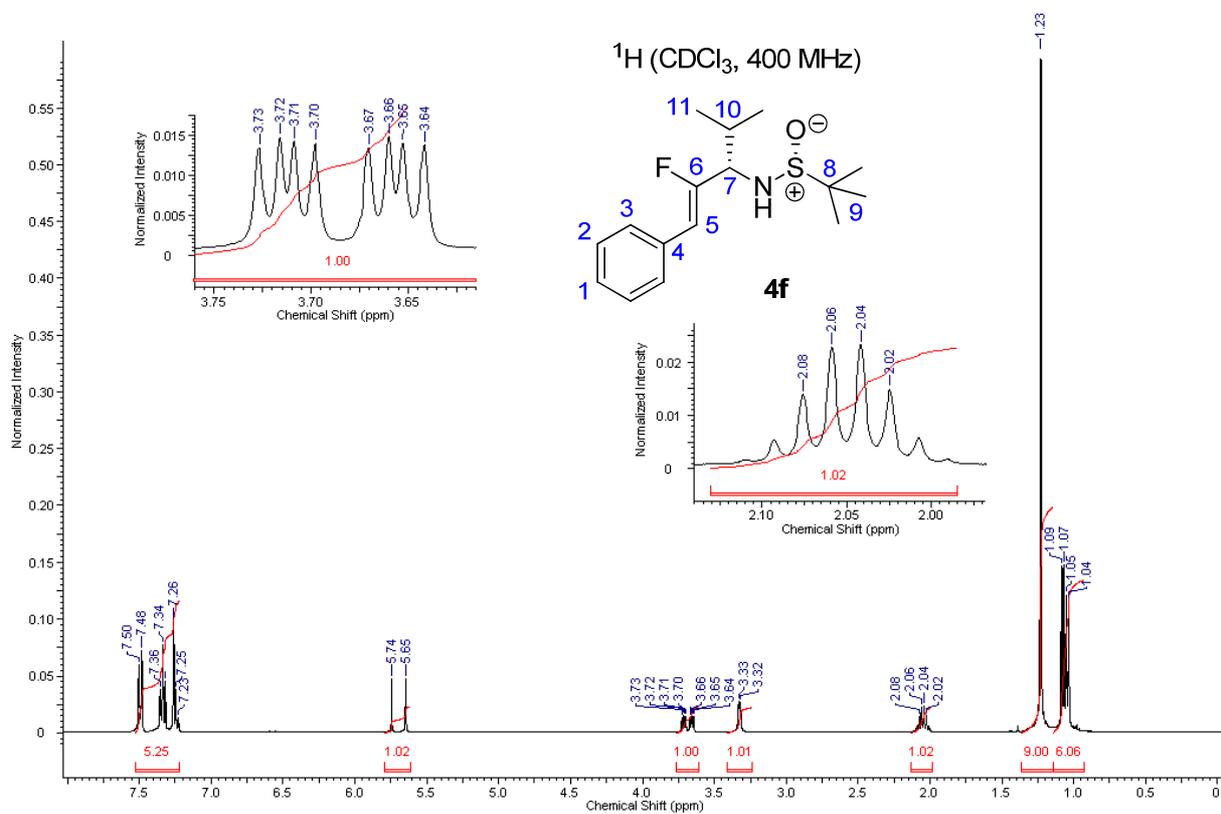


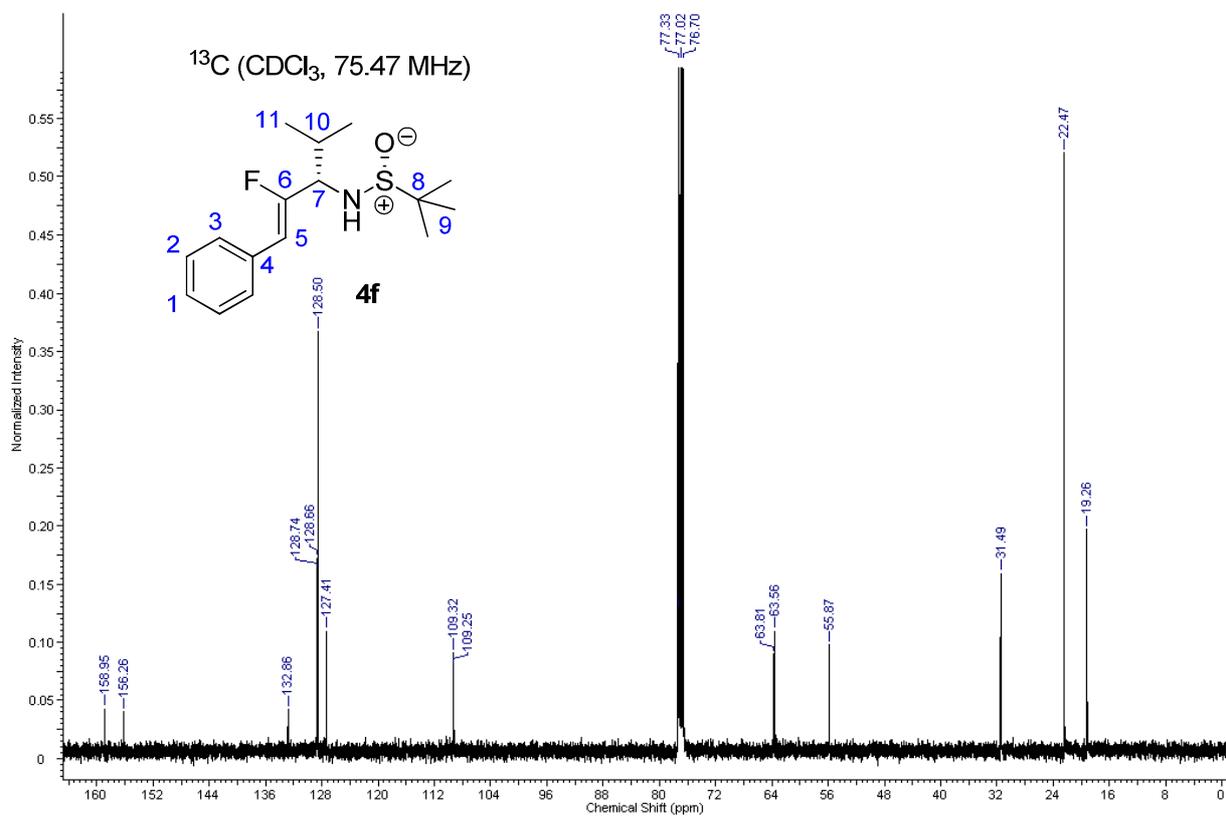
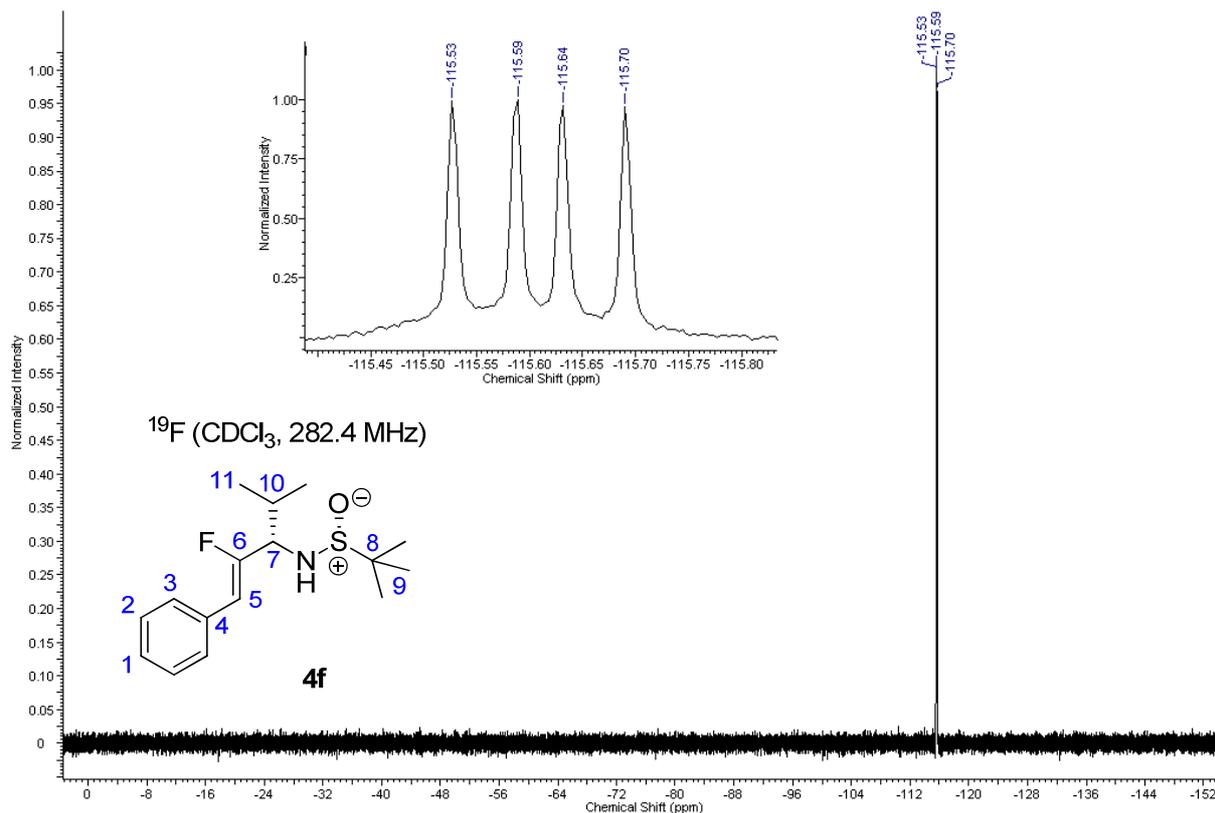
Compound **4d+e**: *N*-((*R,Z*)-2-fluoro-1,3-diphenylallyl)-2-methylpropane-2-sulfonamide



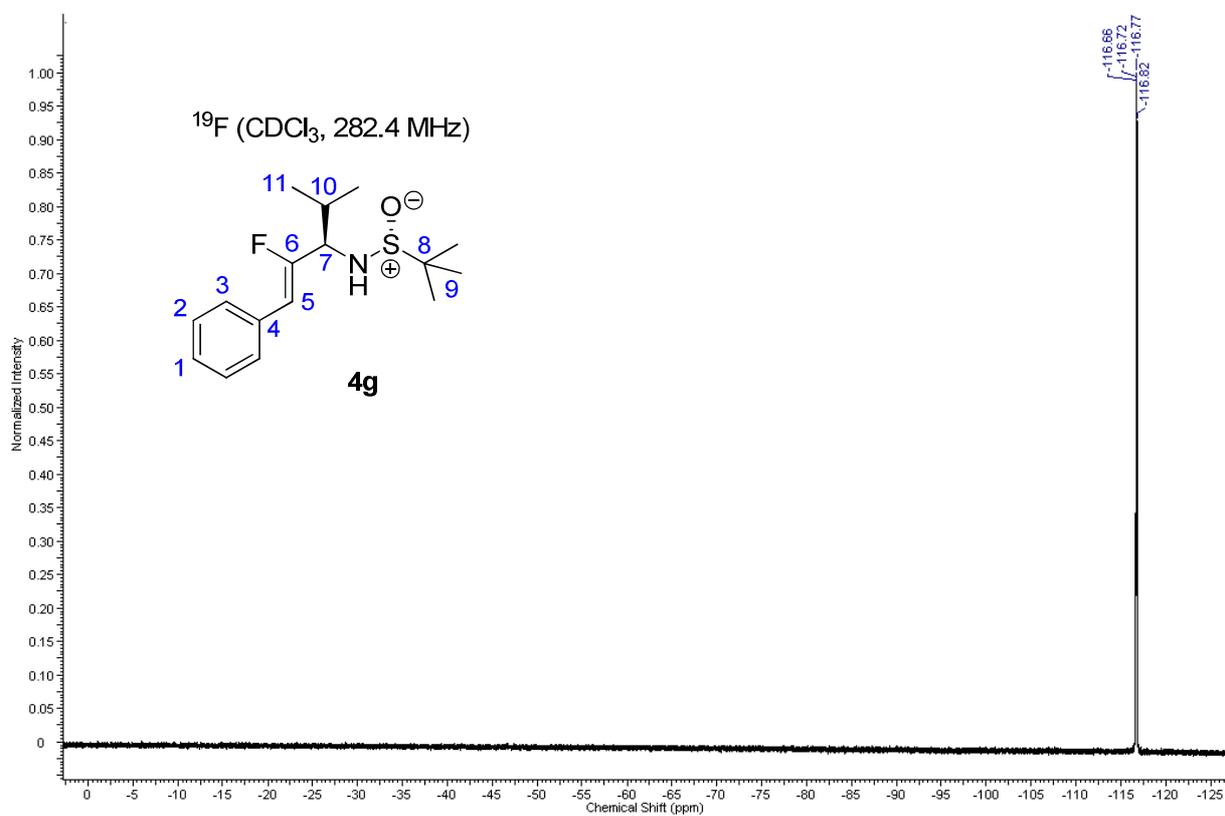
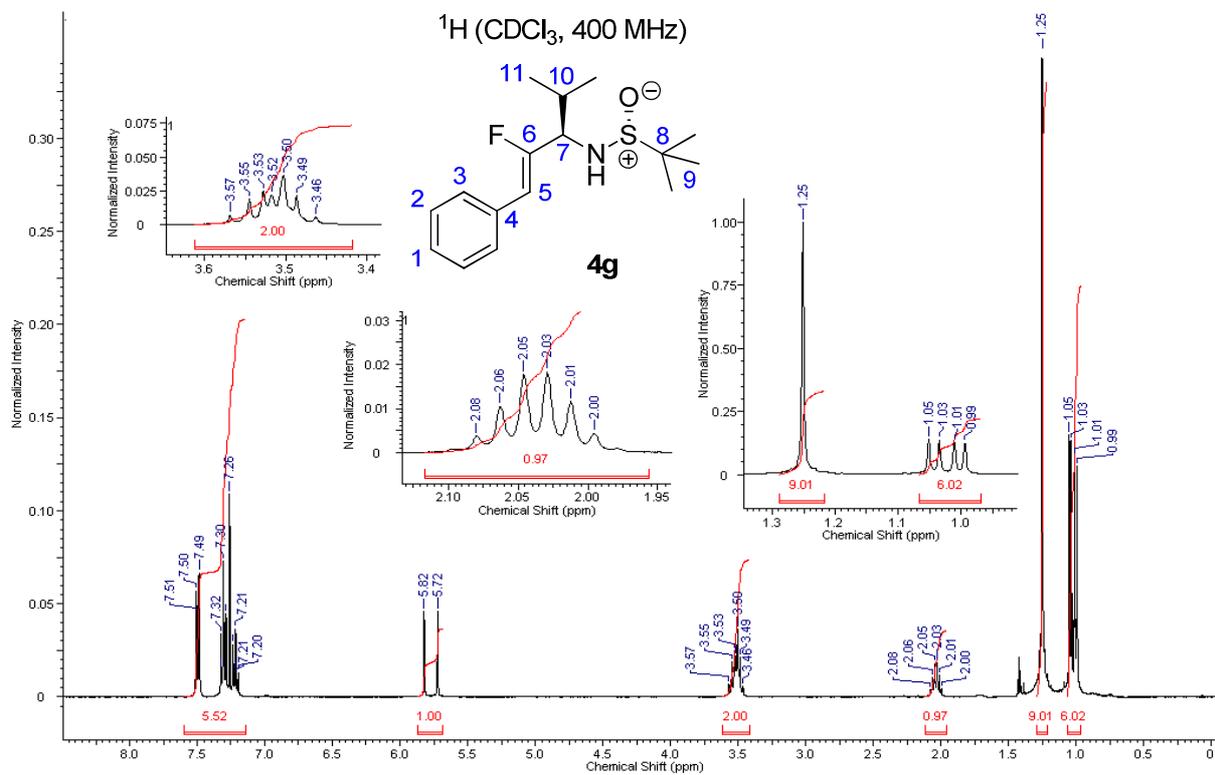


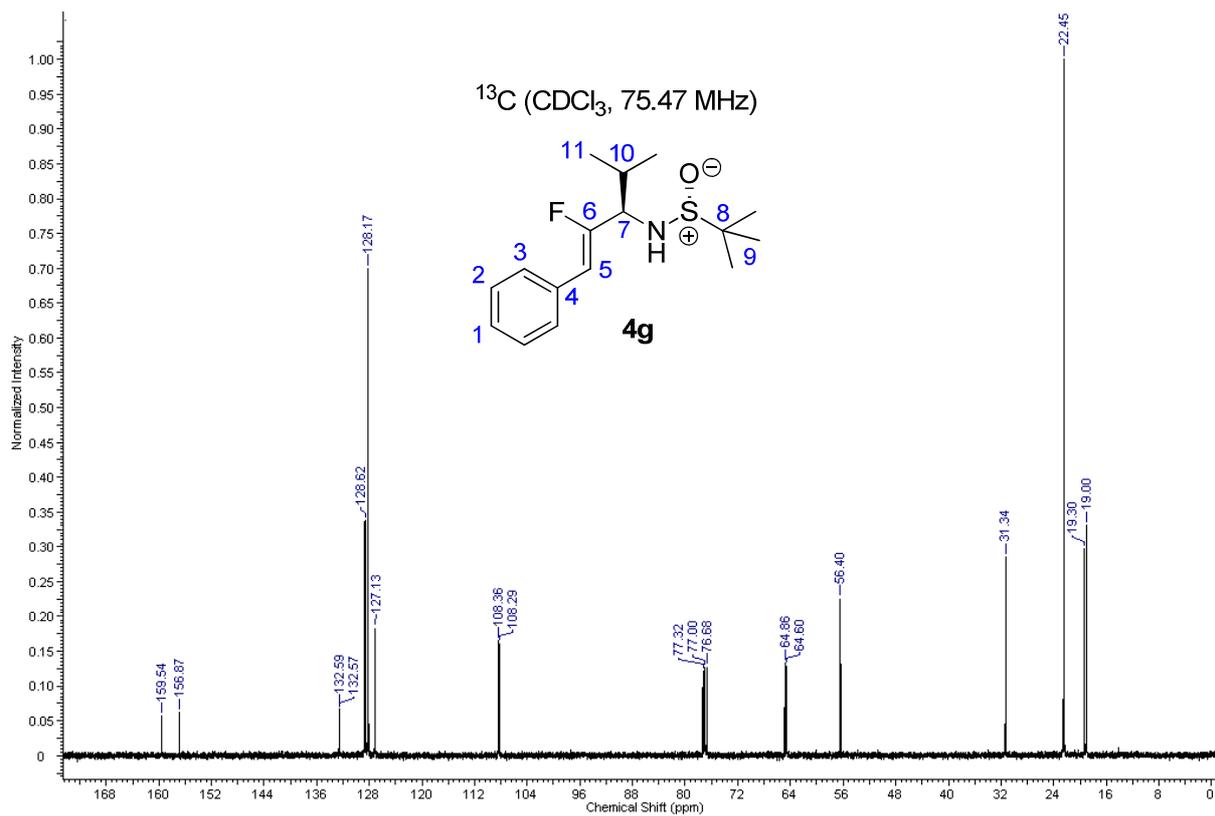
Compound **4f**: (*R*)-*N*-((*S,Z*)-2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-2-methylpropane-2-sulfonamide



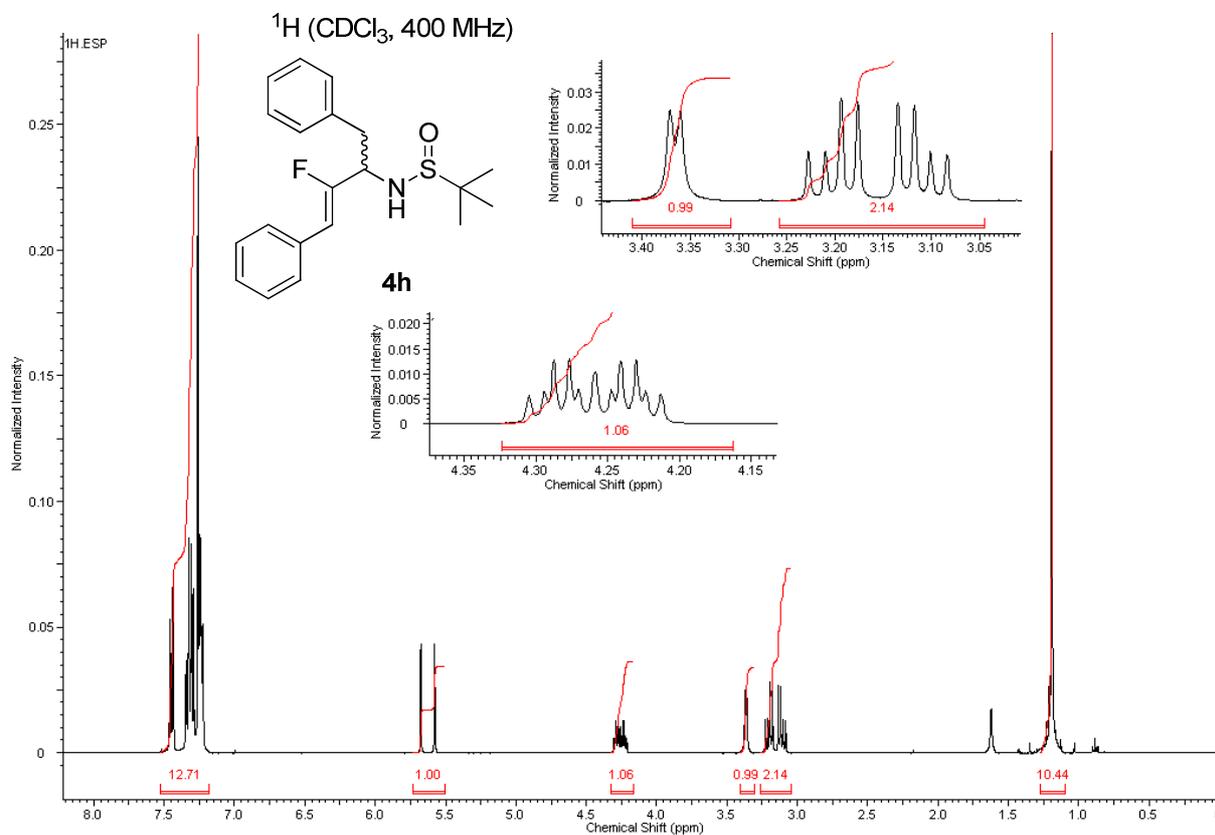


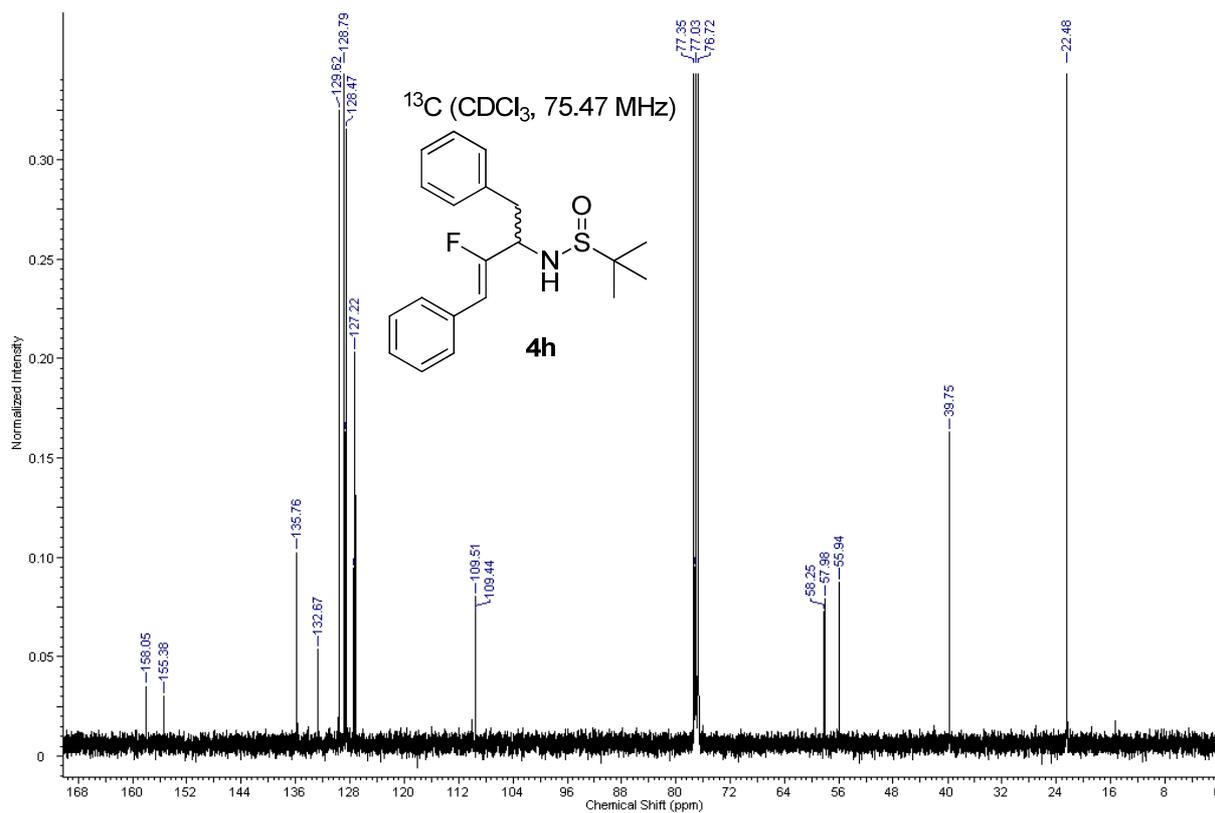
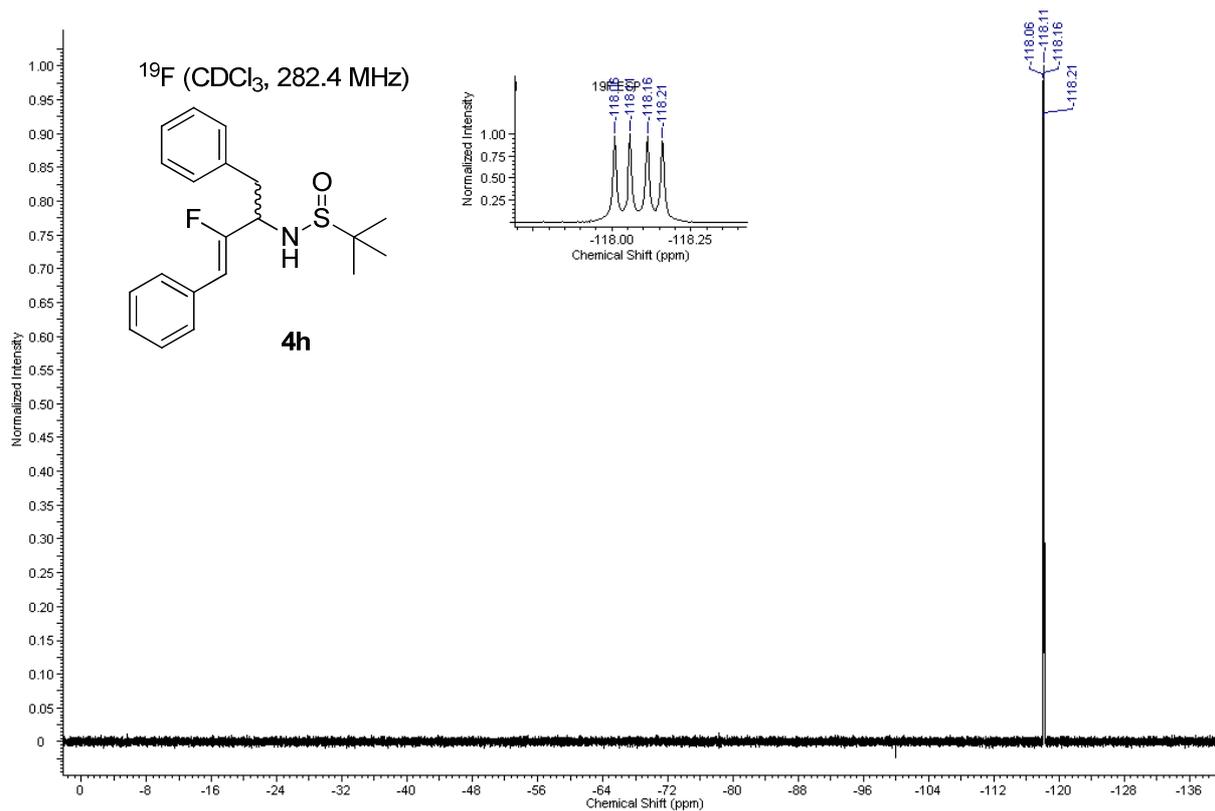
Compound **4g**: (*Rs*)-*N*-((*Z*)-2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)-2-methylpropane-2-sulfonamide



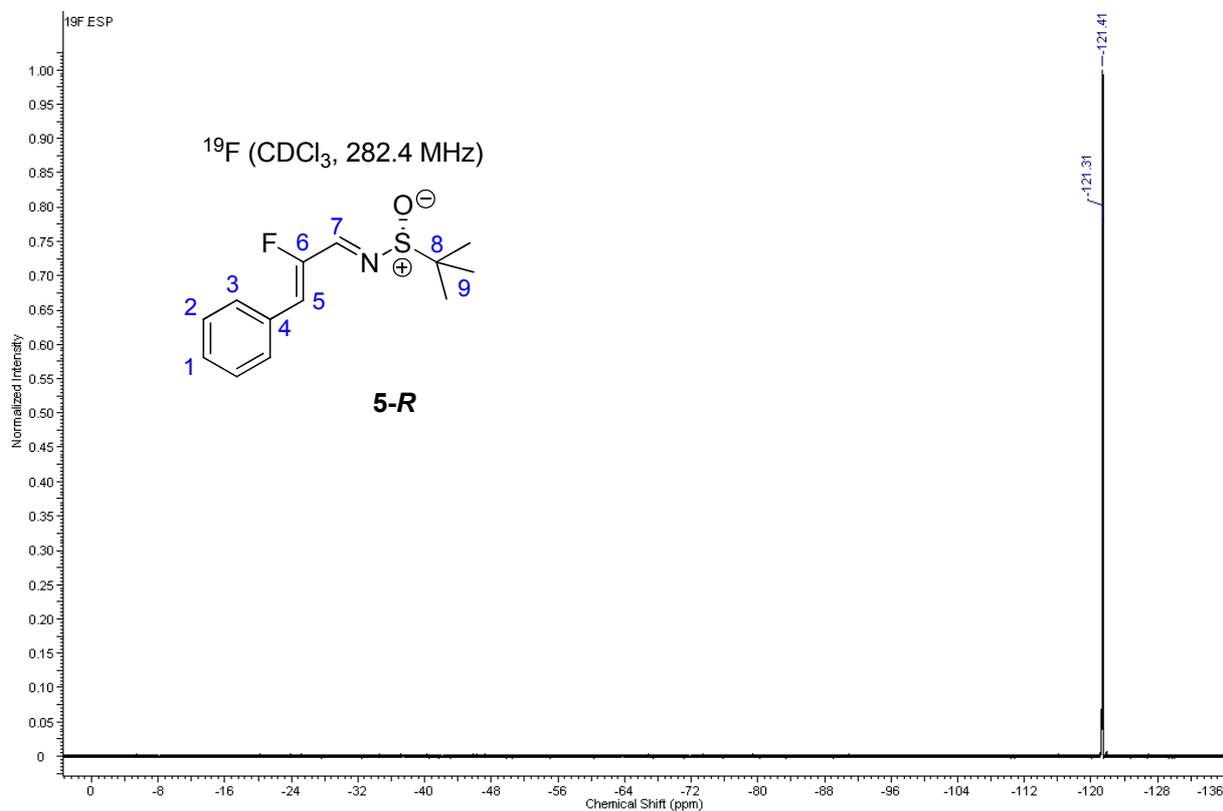
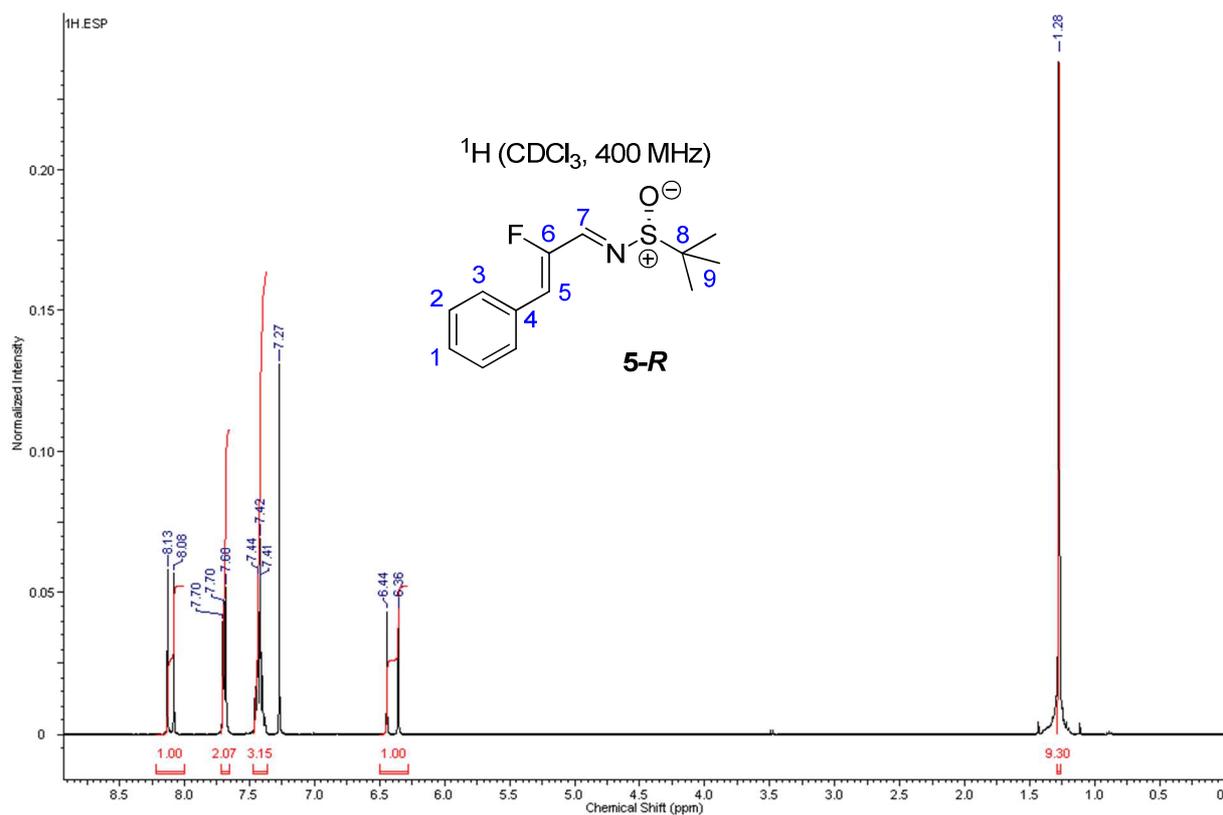


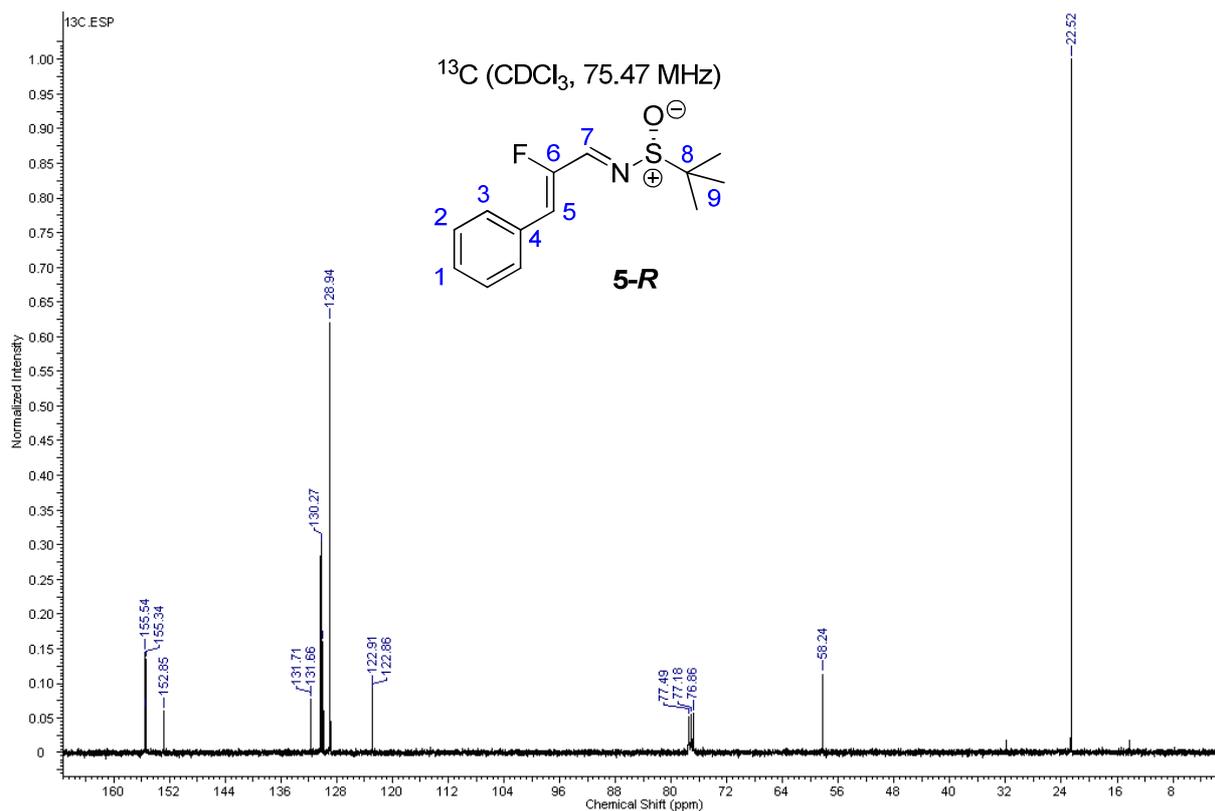
Compound **4h**: (*Z*)-*N*-(3-fluoro-1,4-diphenylbut-3-en-2-yl)-2-methylpropane-2-sulfonamide



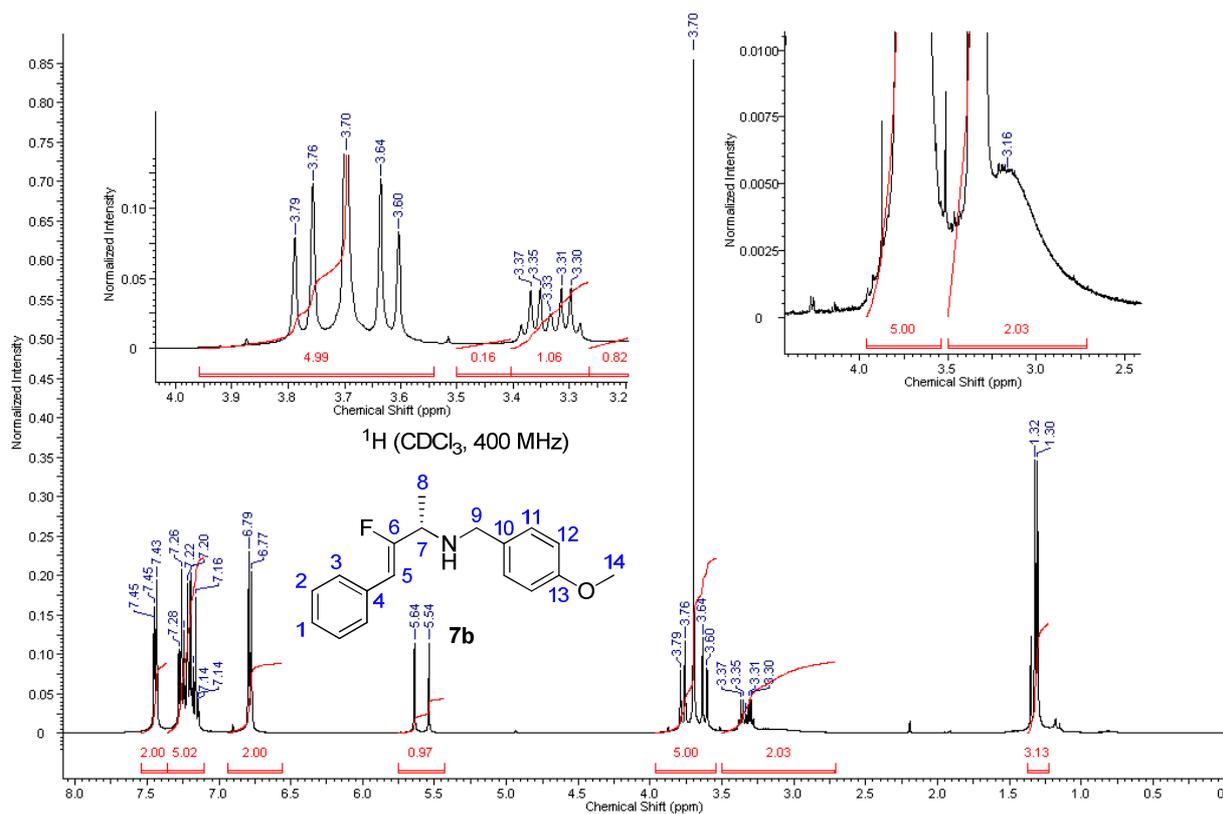


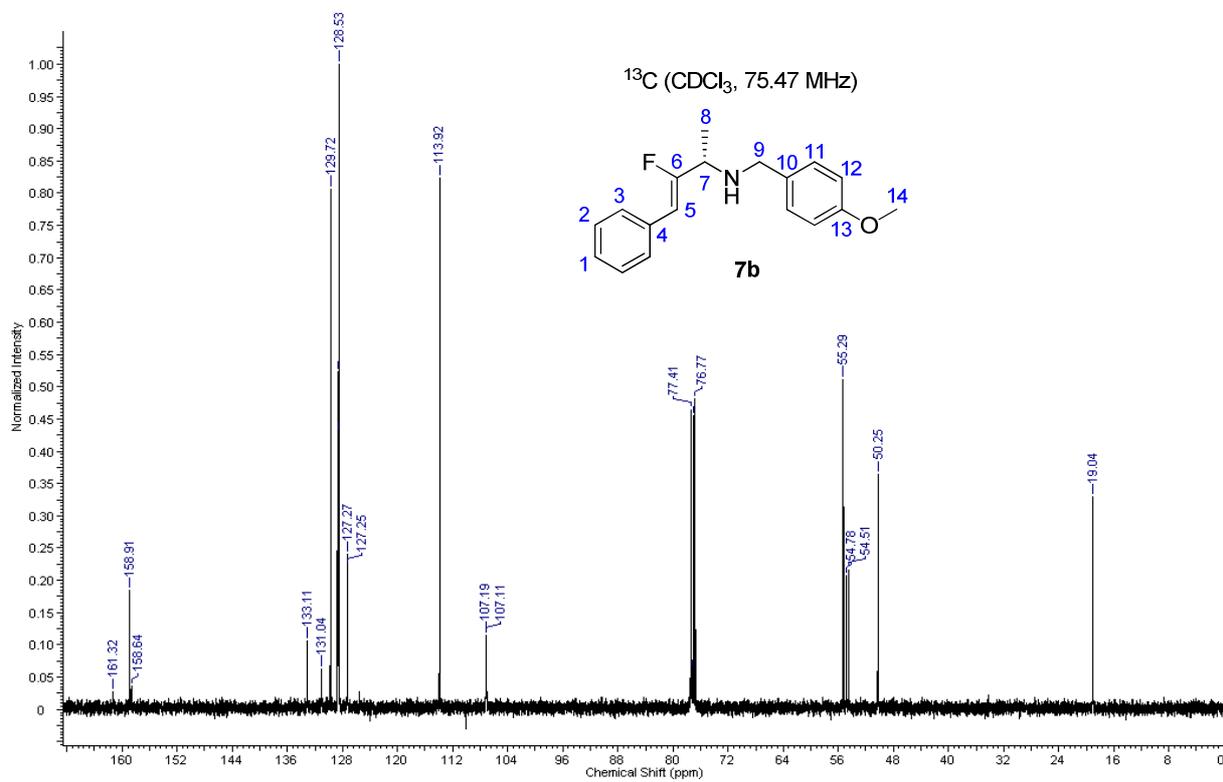
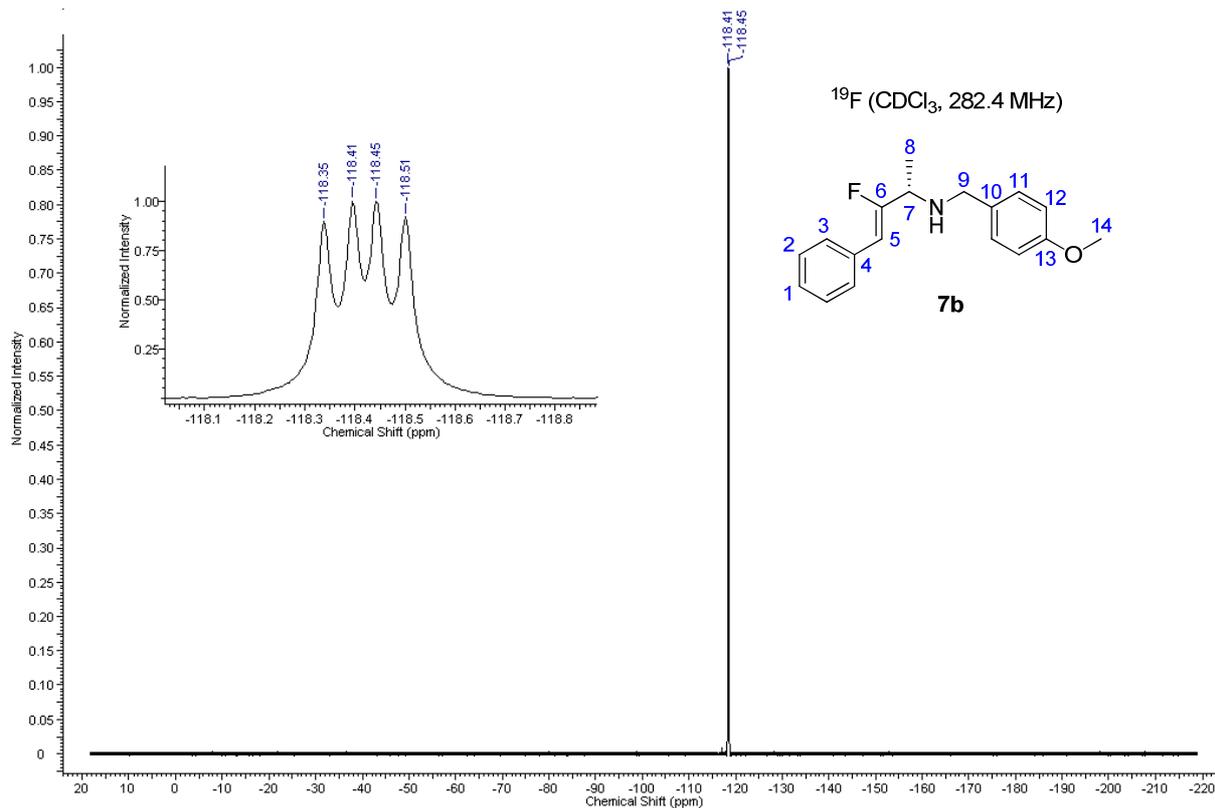
Compound **5-R**: (*R,E*)-*N*-((*Z*)-2-fluoro-3-phenylallylidene)-2-methylpropane-2-sulfinamide



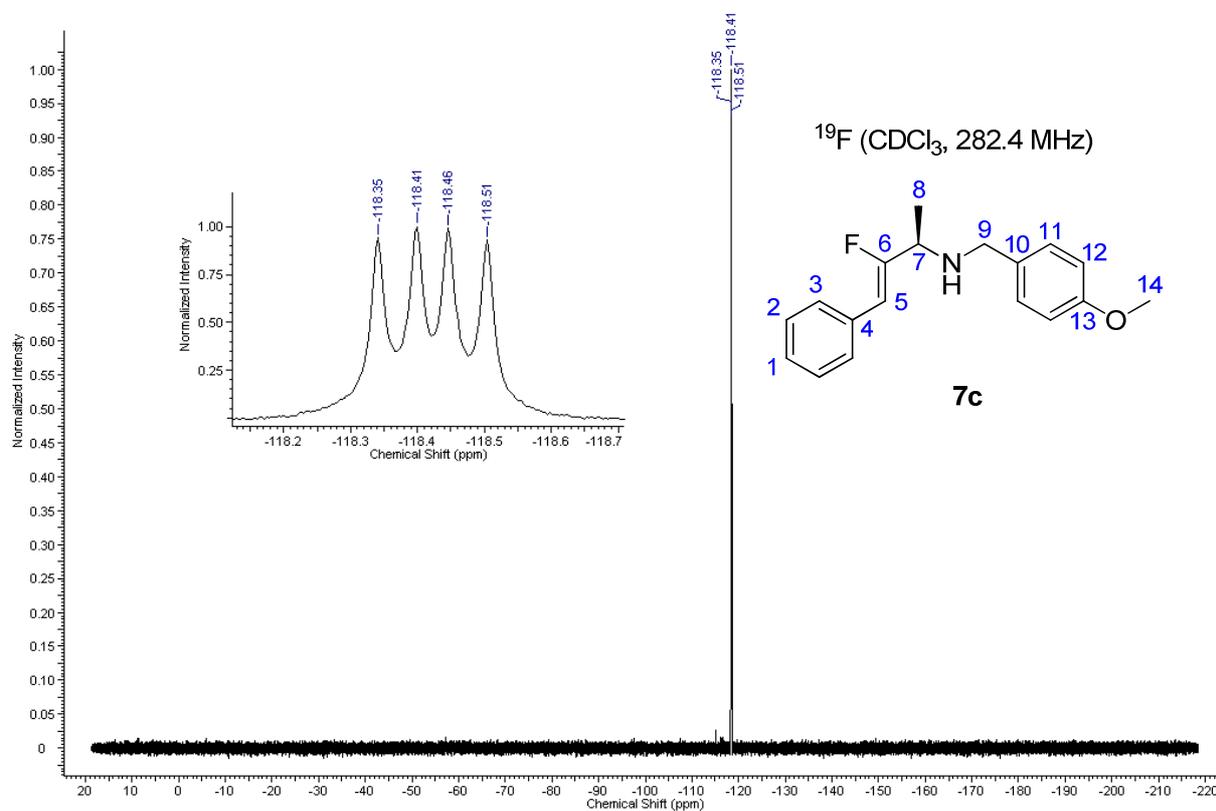
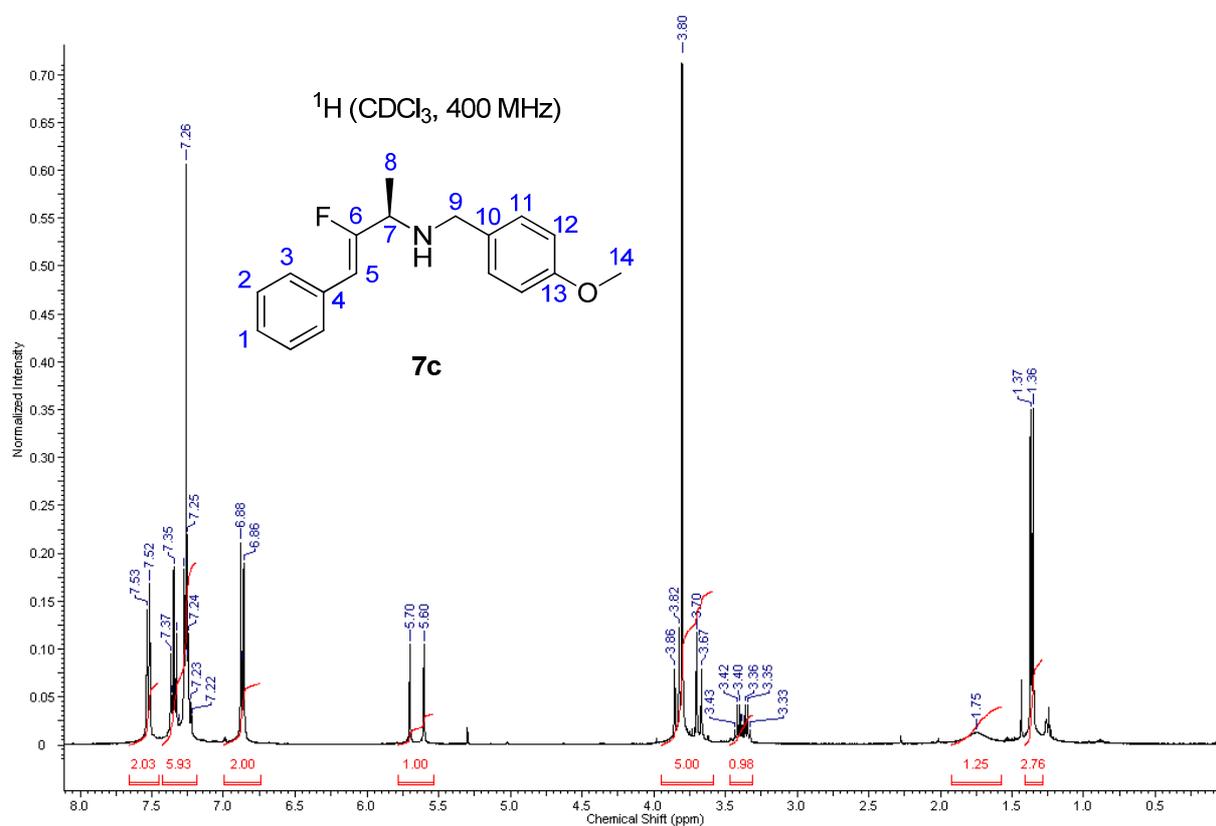


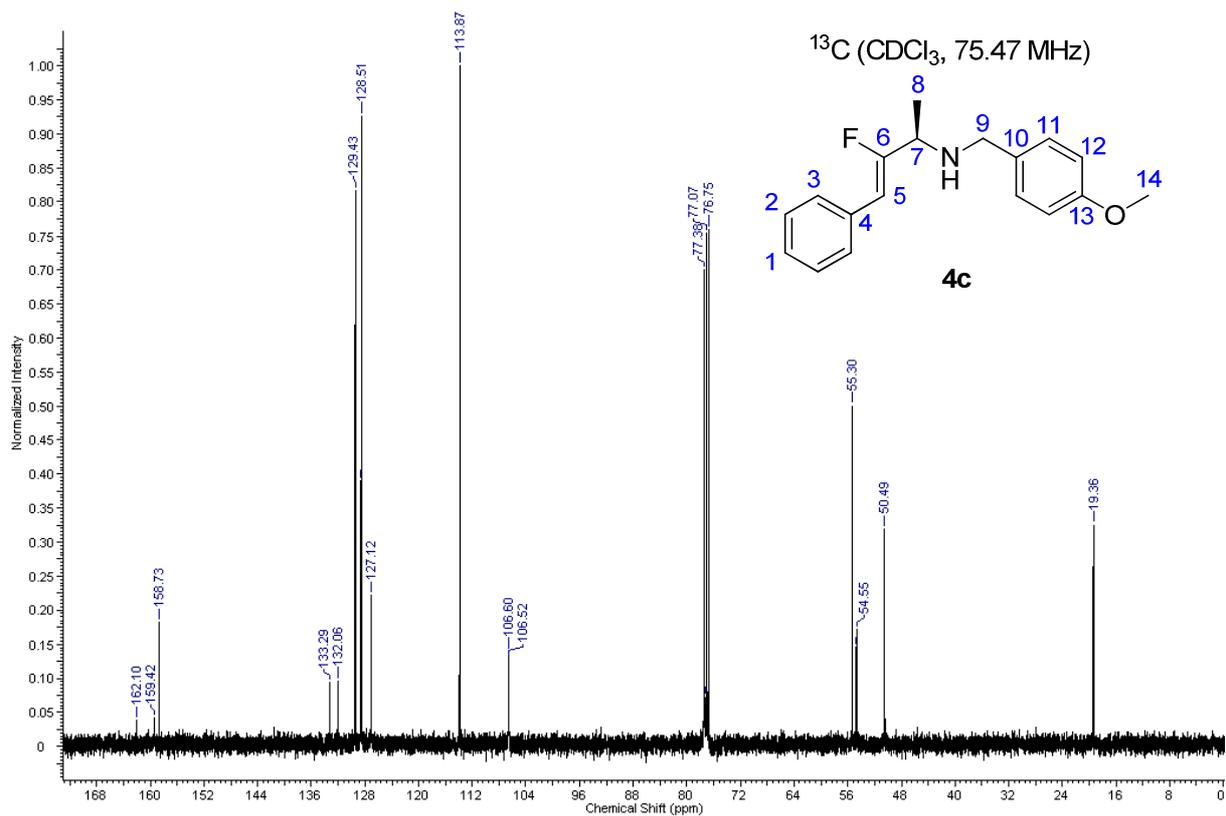
Compound **7b**: *(S,Z)*-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine



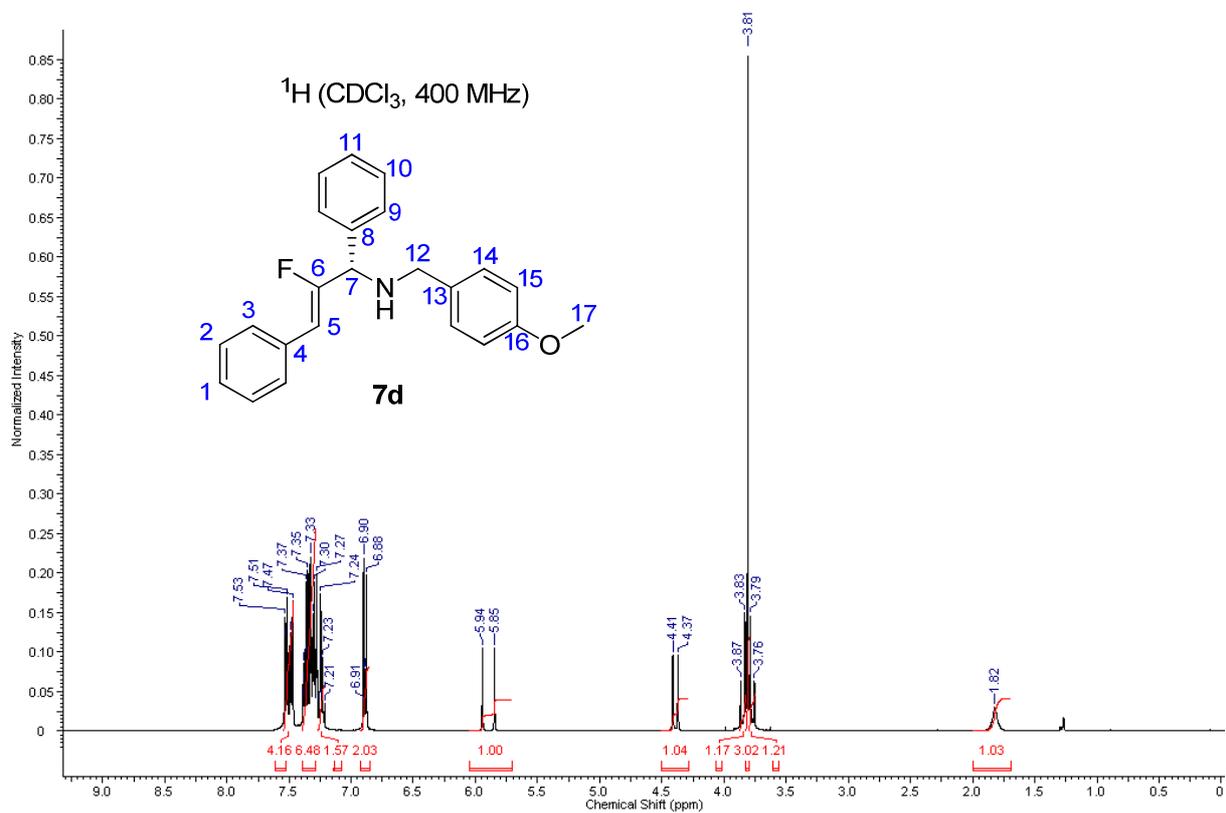


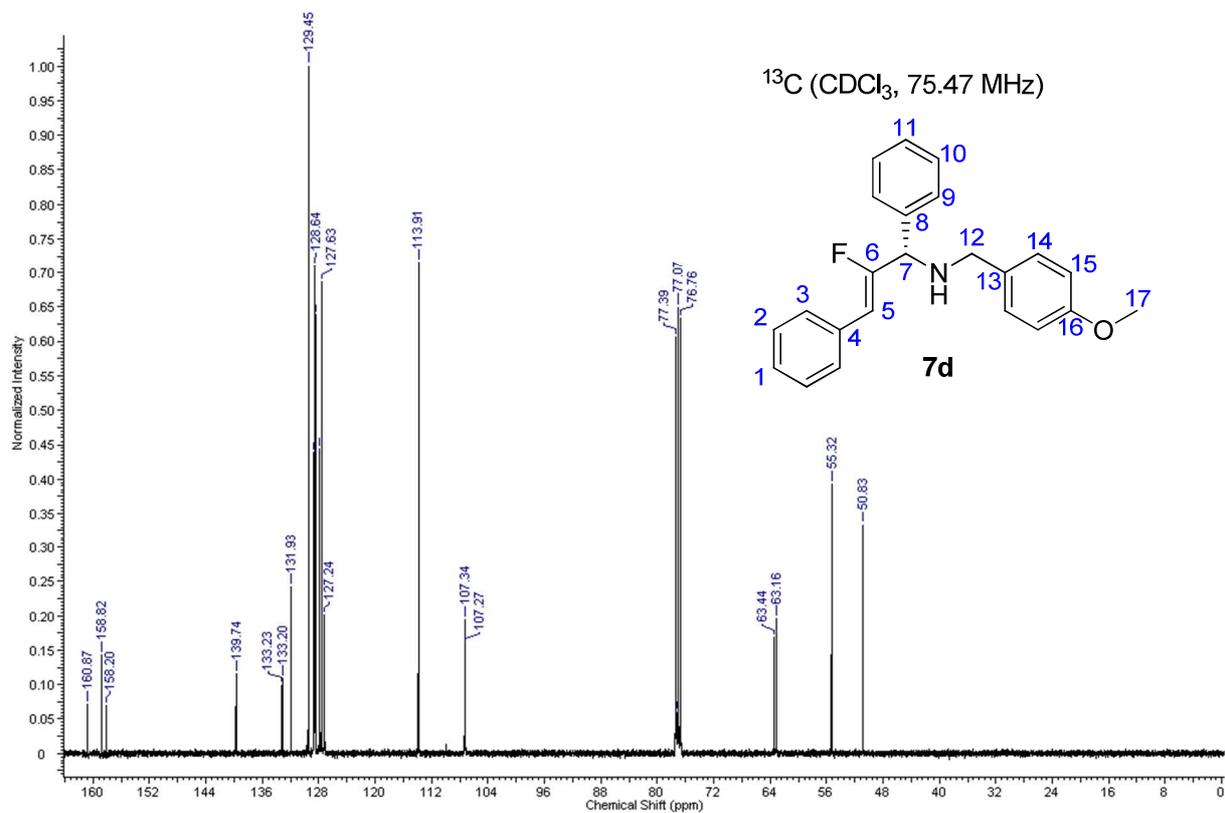
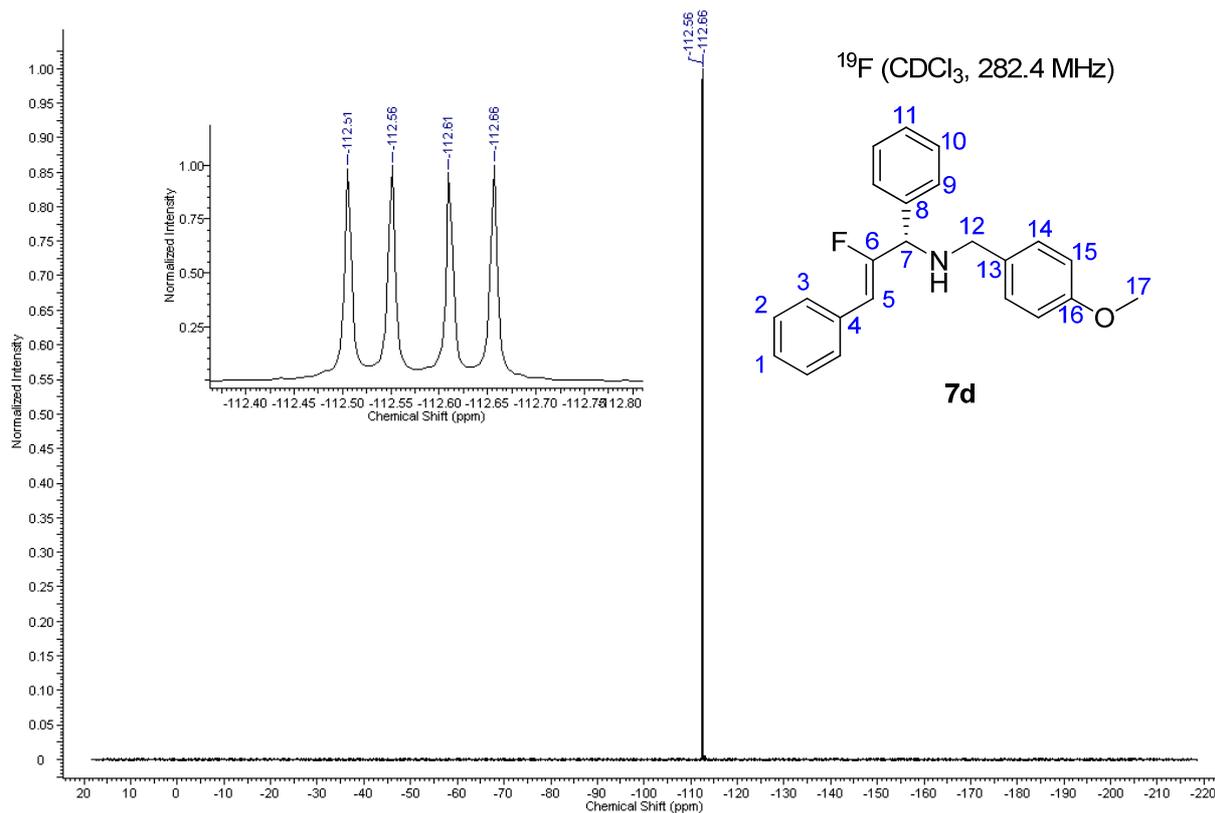
Compound **7c**: (*R,Z*)-3-fluoro-*N*-(4-methoxybenzyl)-4-phenylbut-3-en-2-amine



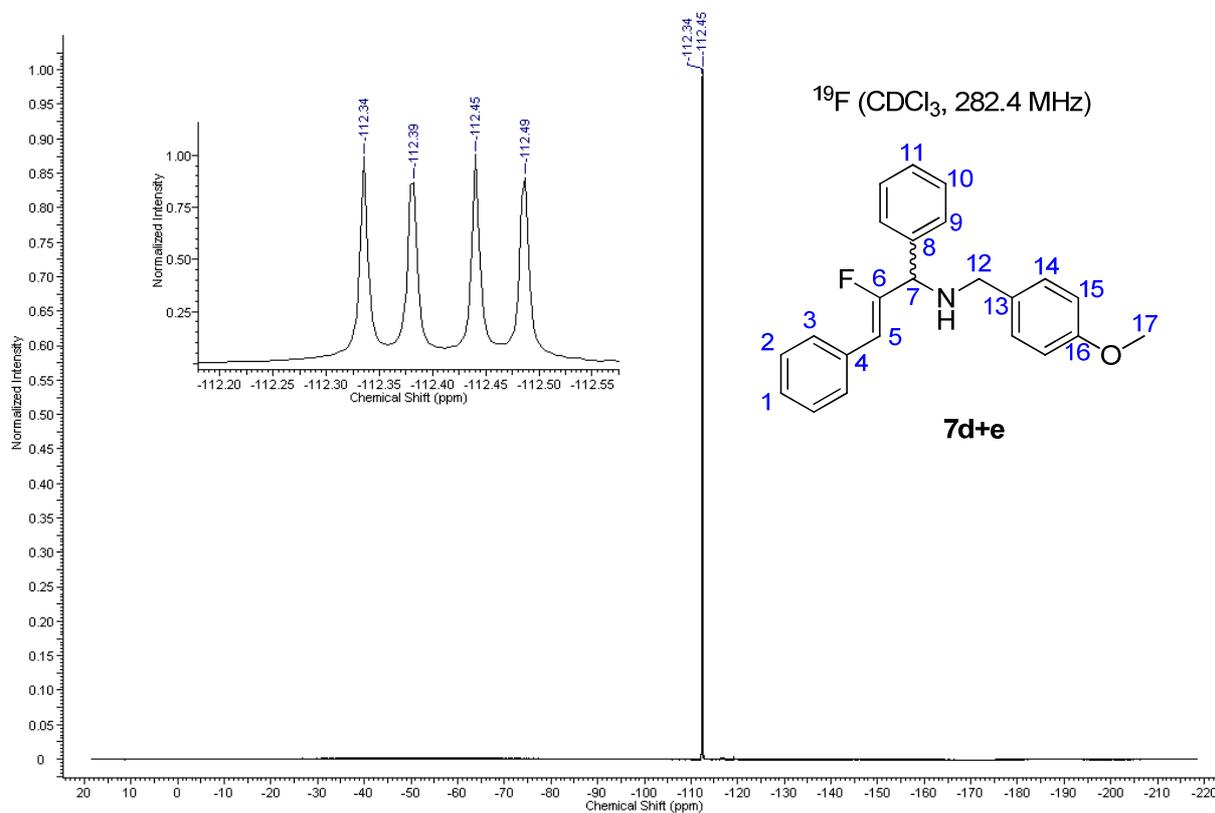
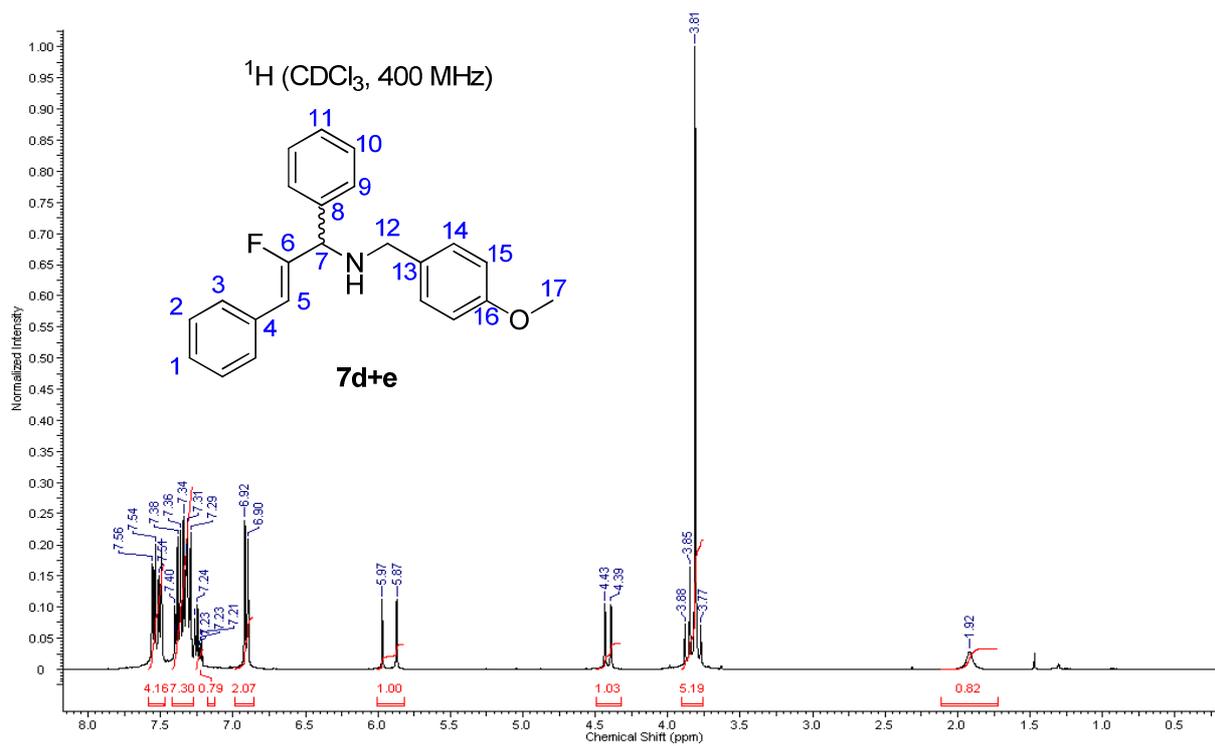


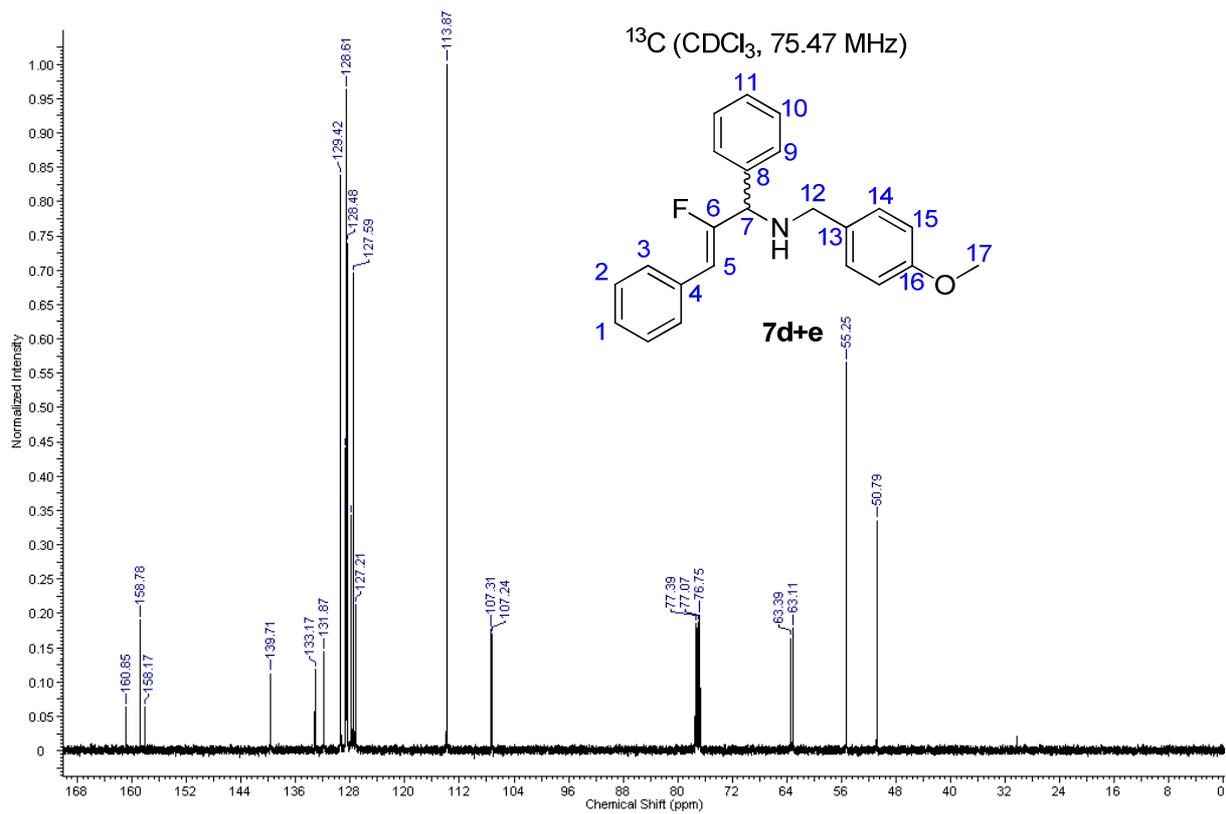
Compound **7d**: *(S,Z)*-2-fluoro-*N*-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine



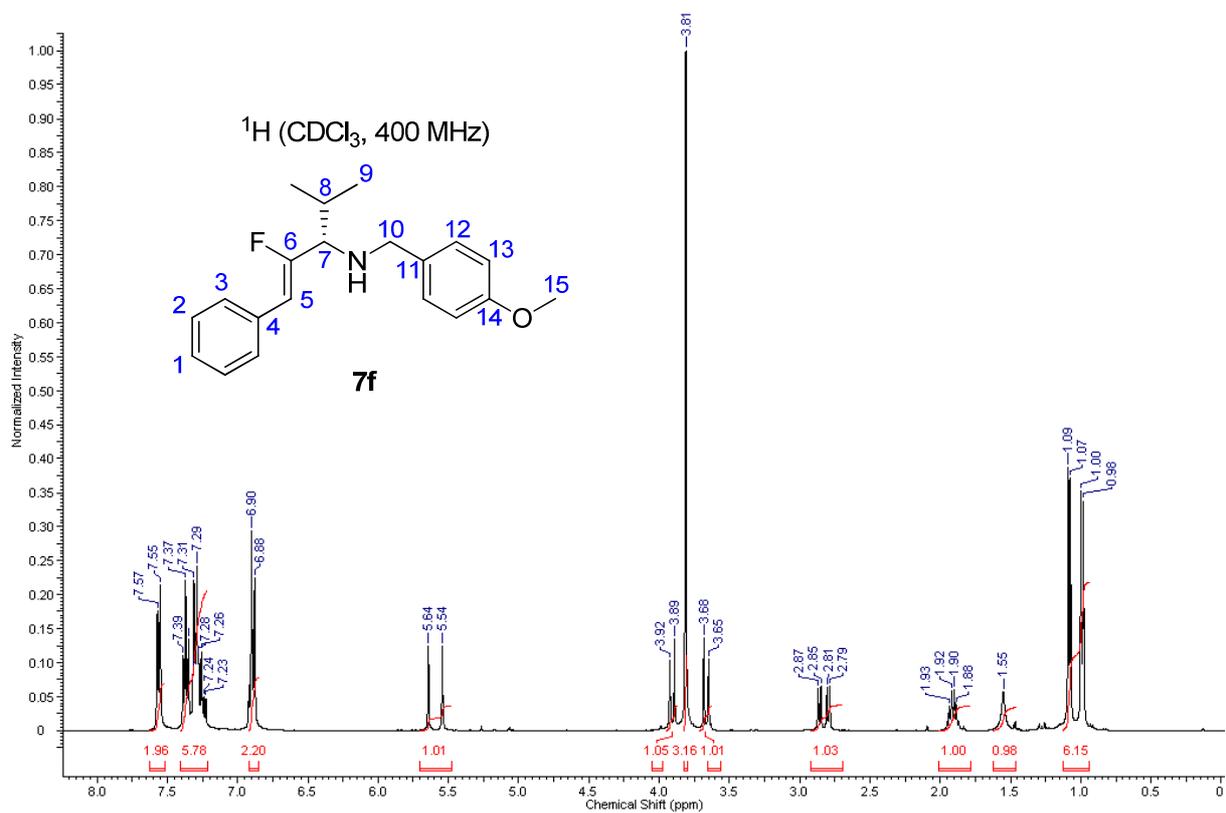


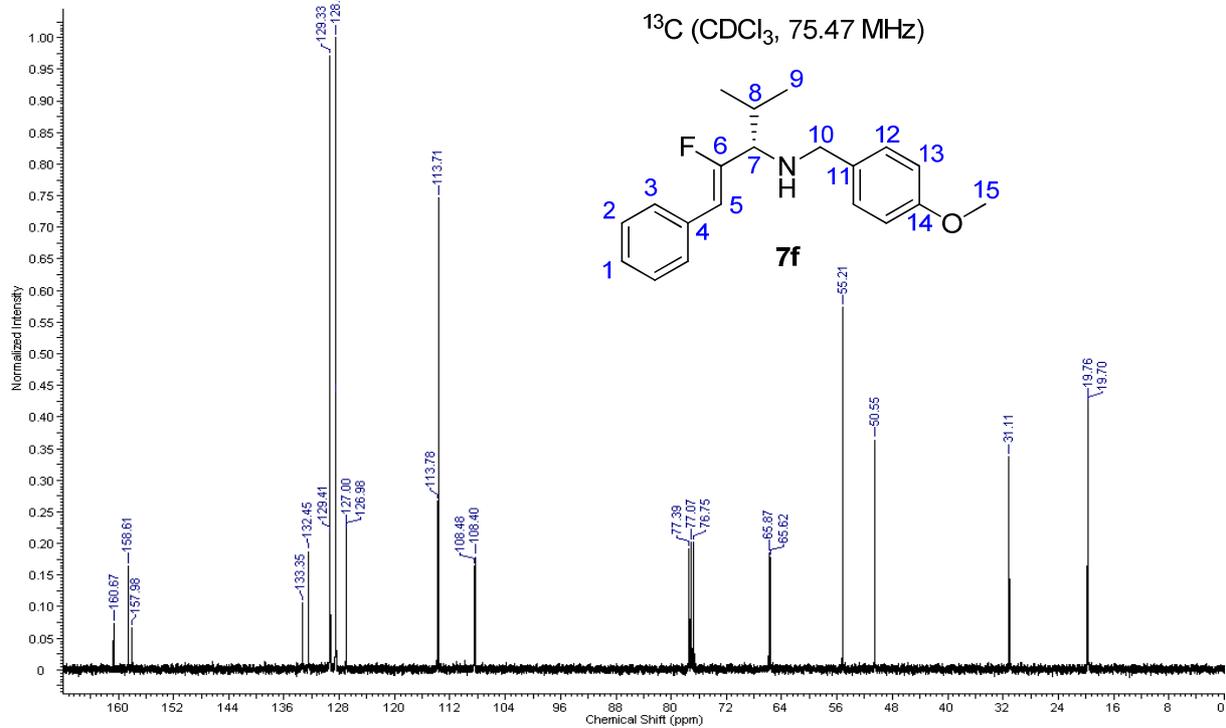
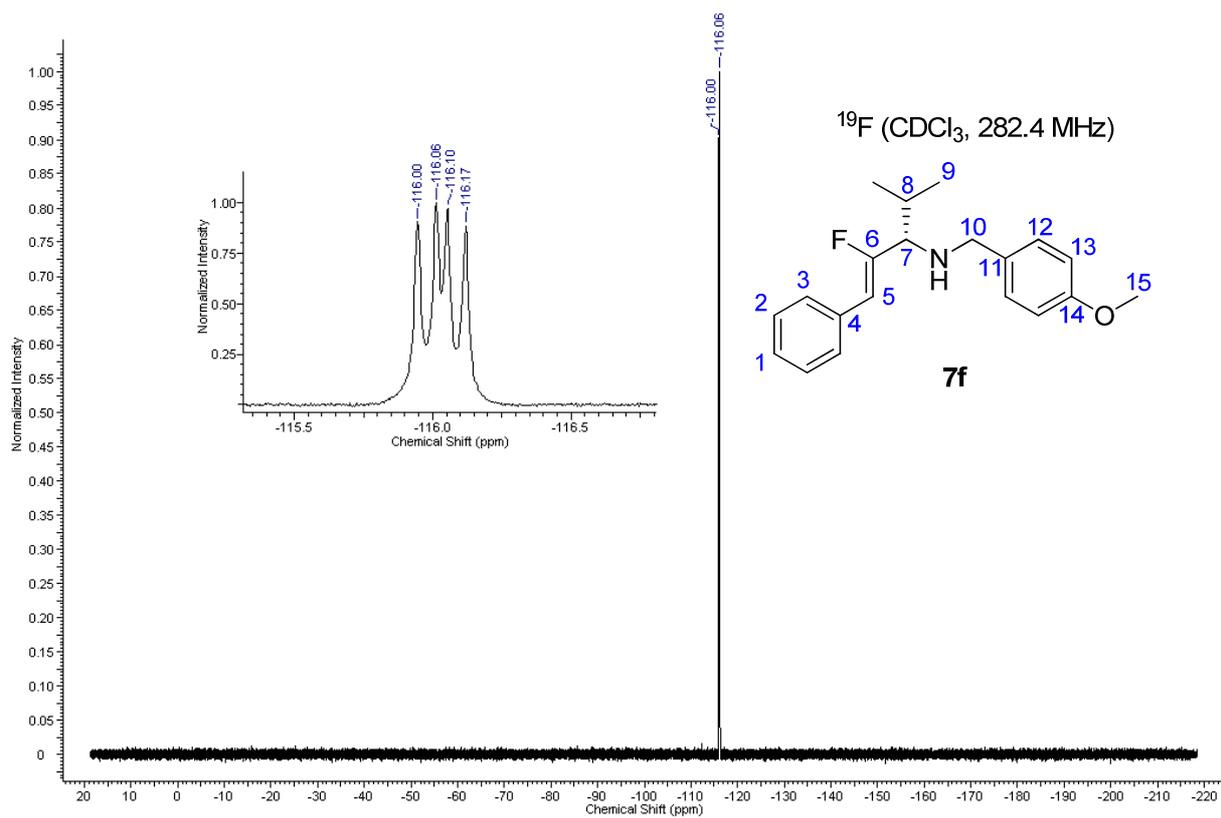
Compound **7d+e**: *(Z)*-2-fluoro-*N*-(4-methoxybenzyl)-1,3-diphenylprop-2-en-1-amine



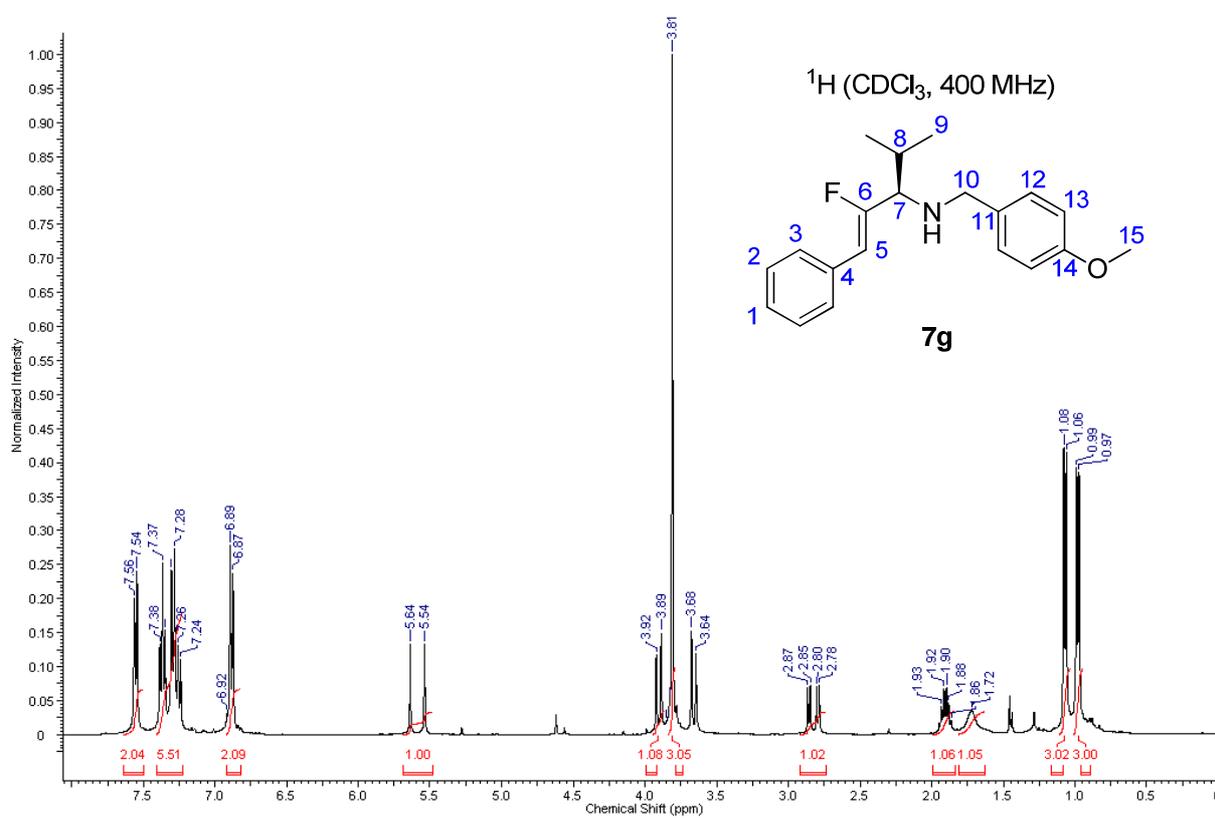
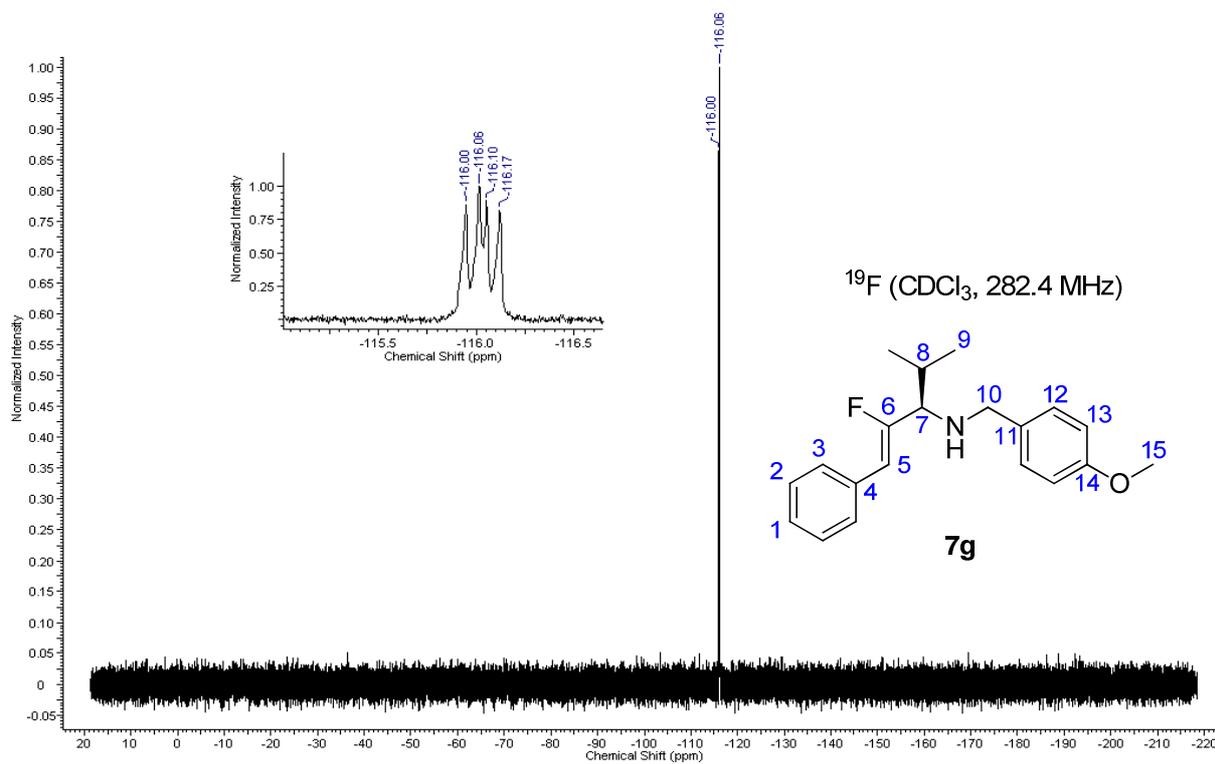


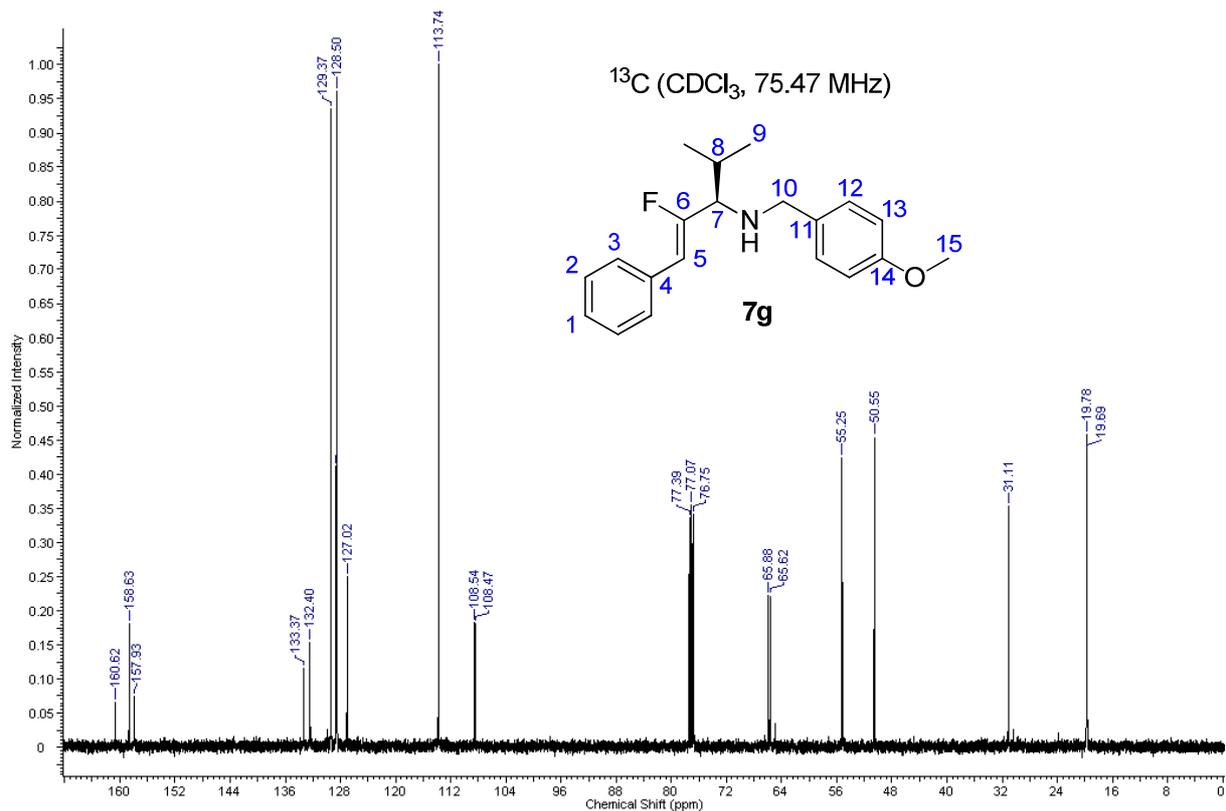
Compound **7f**: (*S,Z*)-2-fluoro-*N*-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine



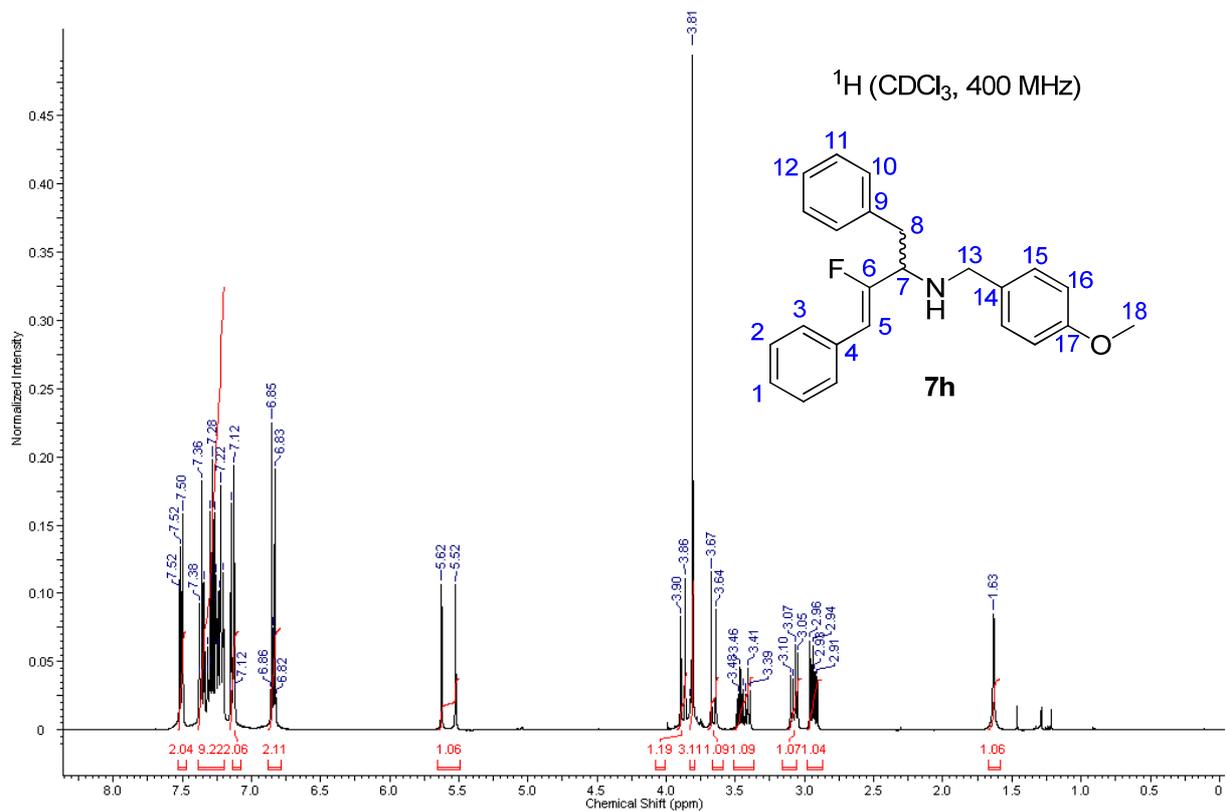


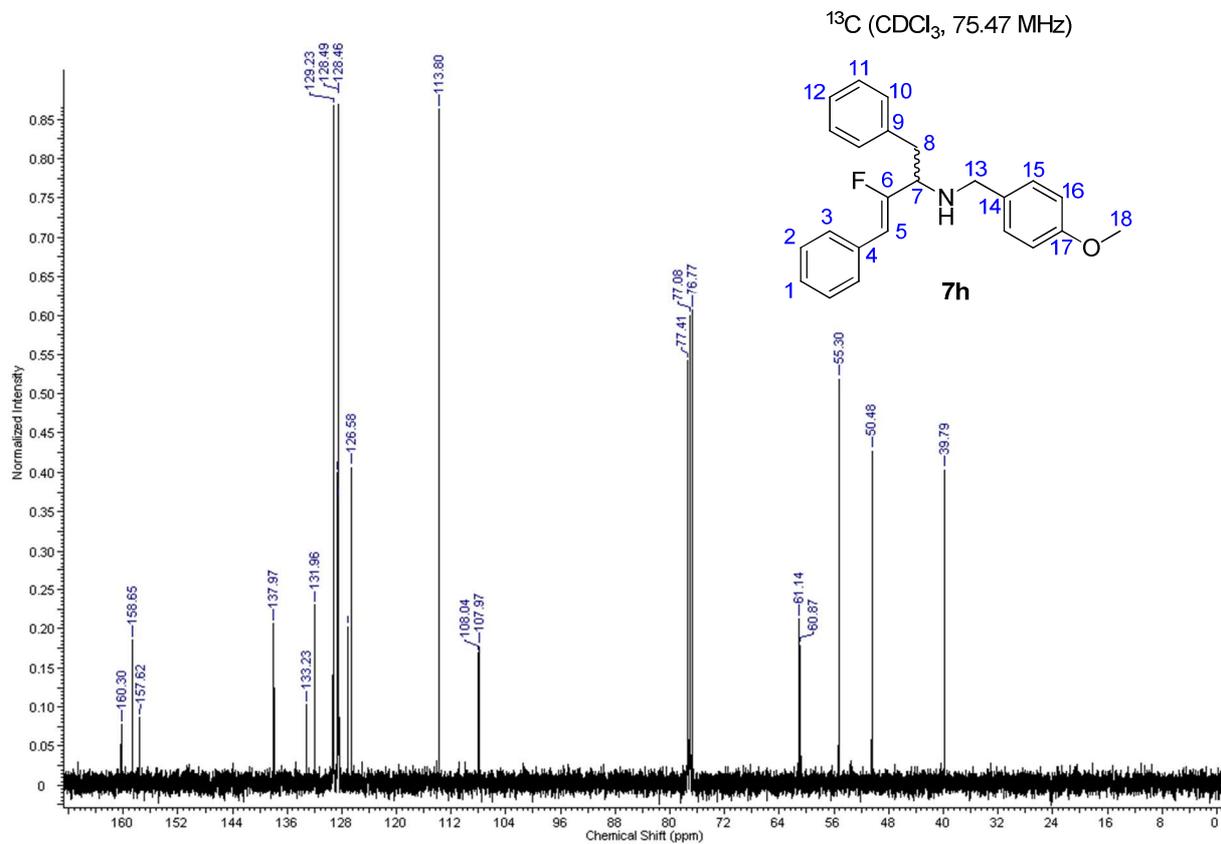
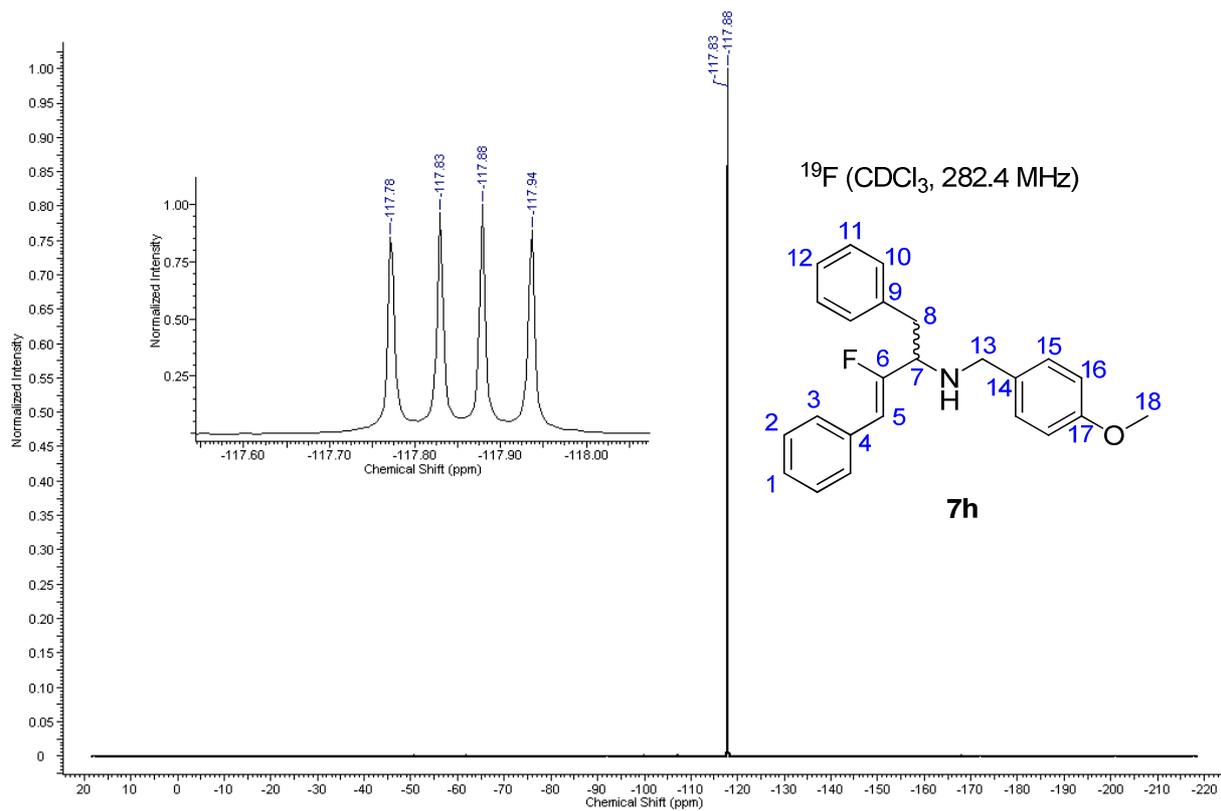
Compound **7g**: (*R,Z*)-2-fluoro-*N*-(4-methoxybenzyl)-4-methyl-1-phenylpent-1-en-3-amine



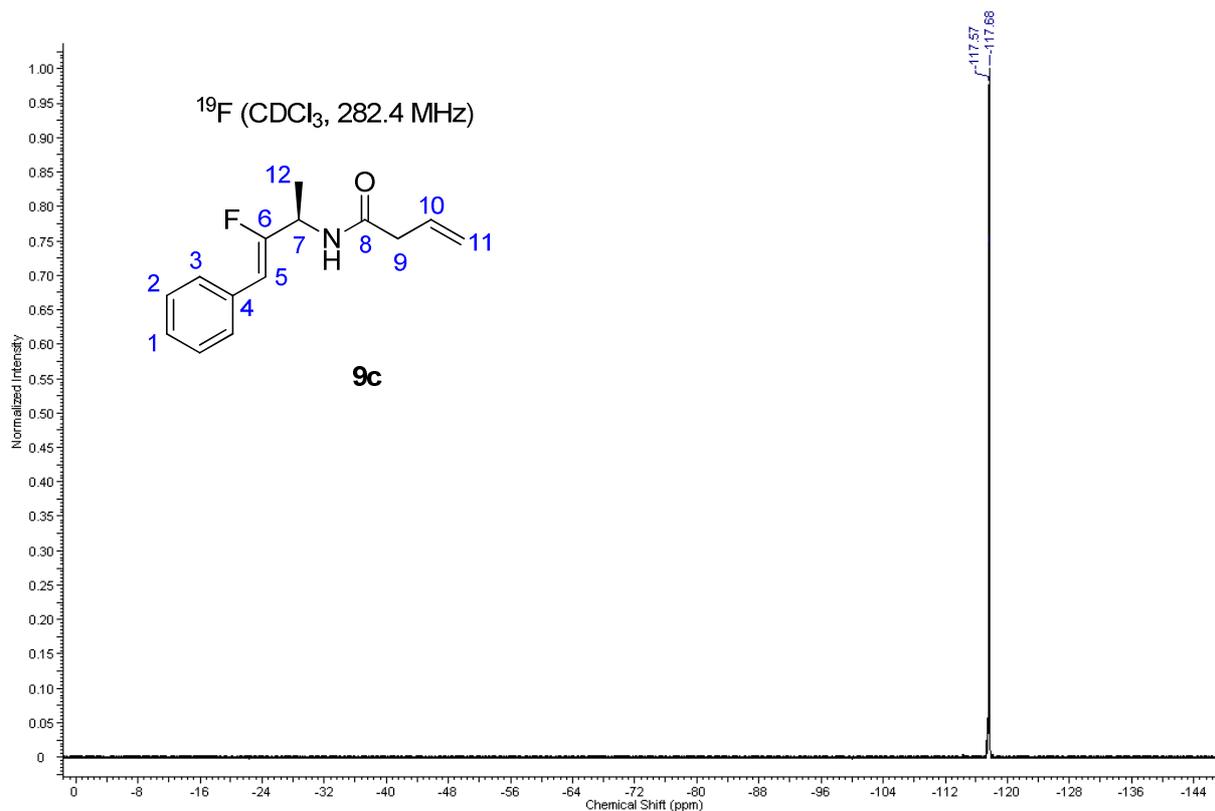
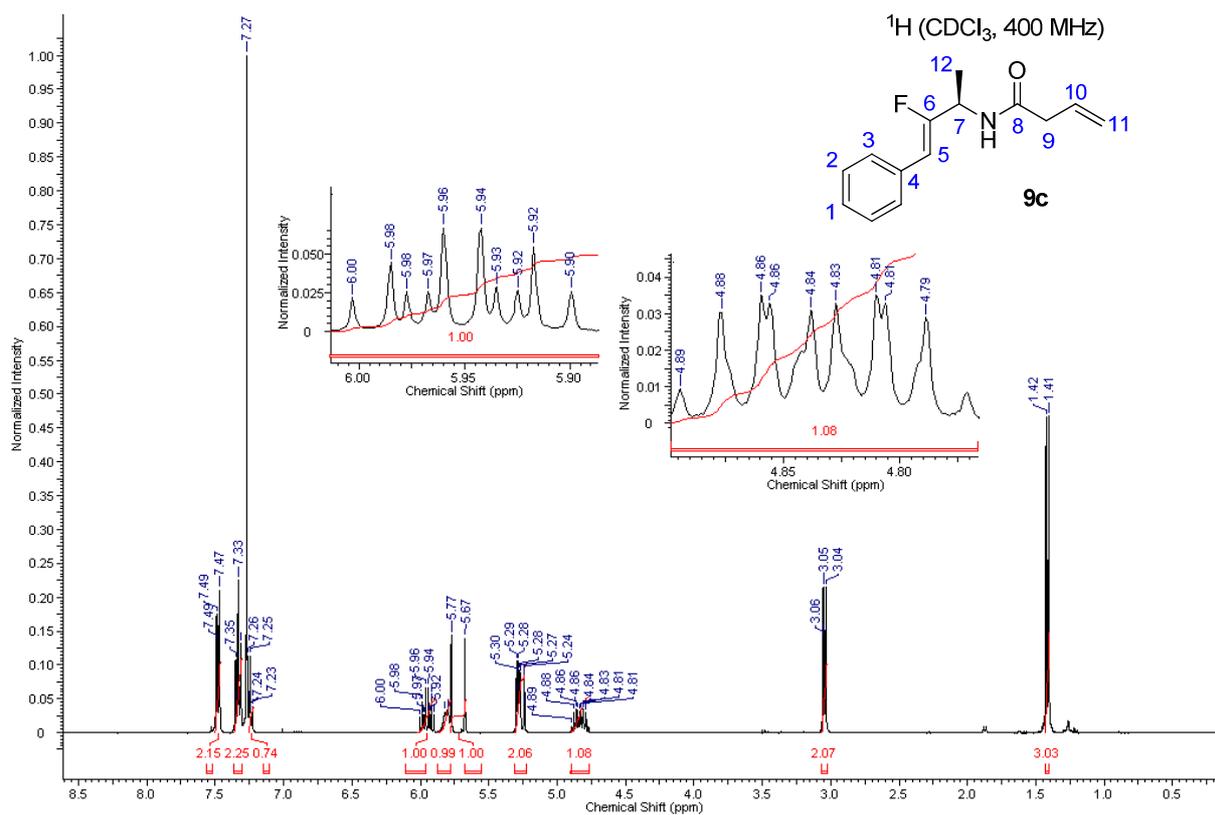


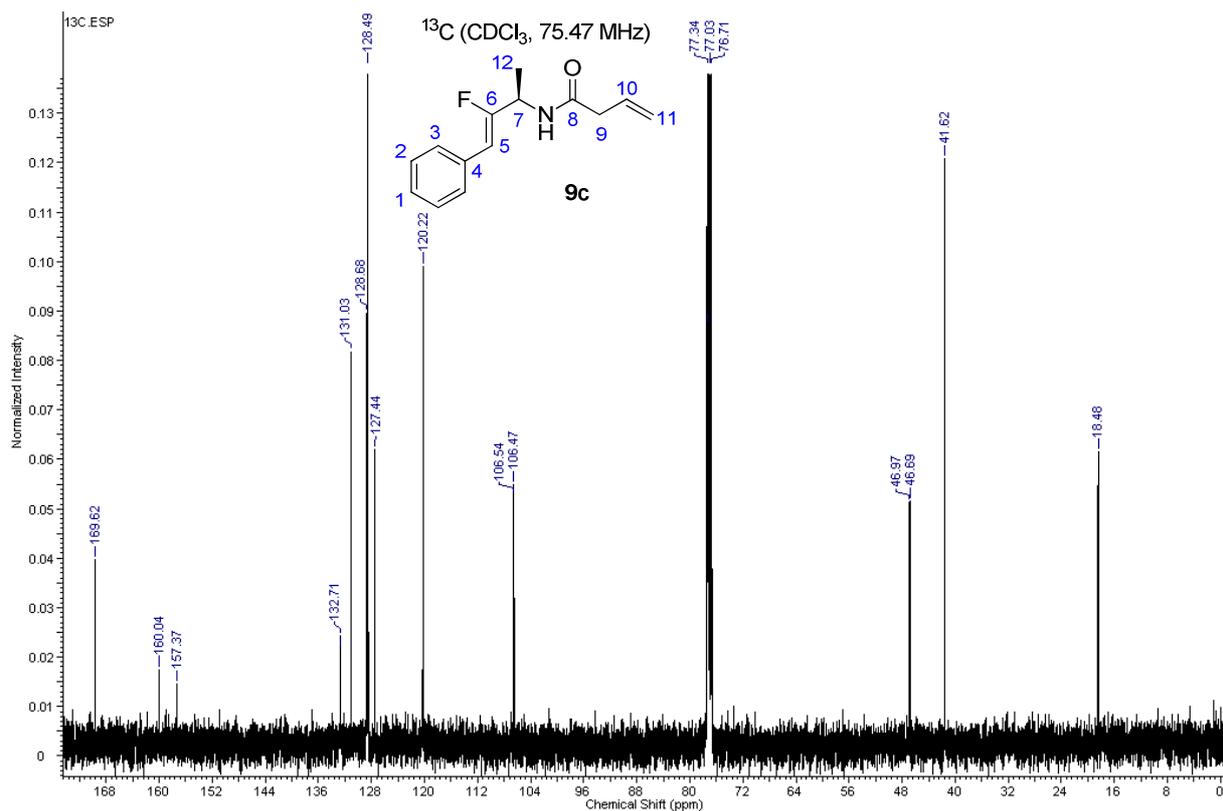
Compound **7h**: *(Z)*-3-fluoro-*N*-(4-methoxybenzyl)-1,4-diphenylbut-3-en-2-amine



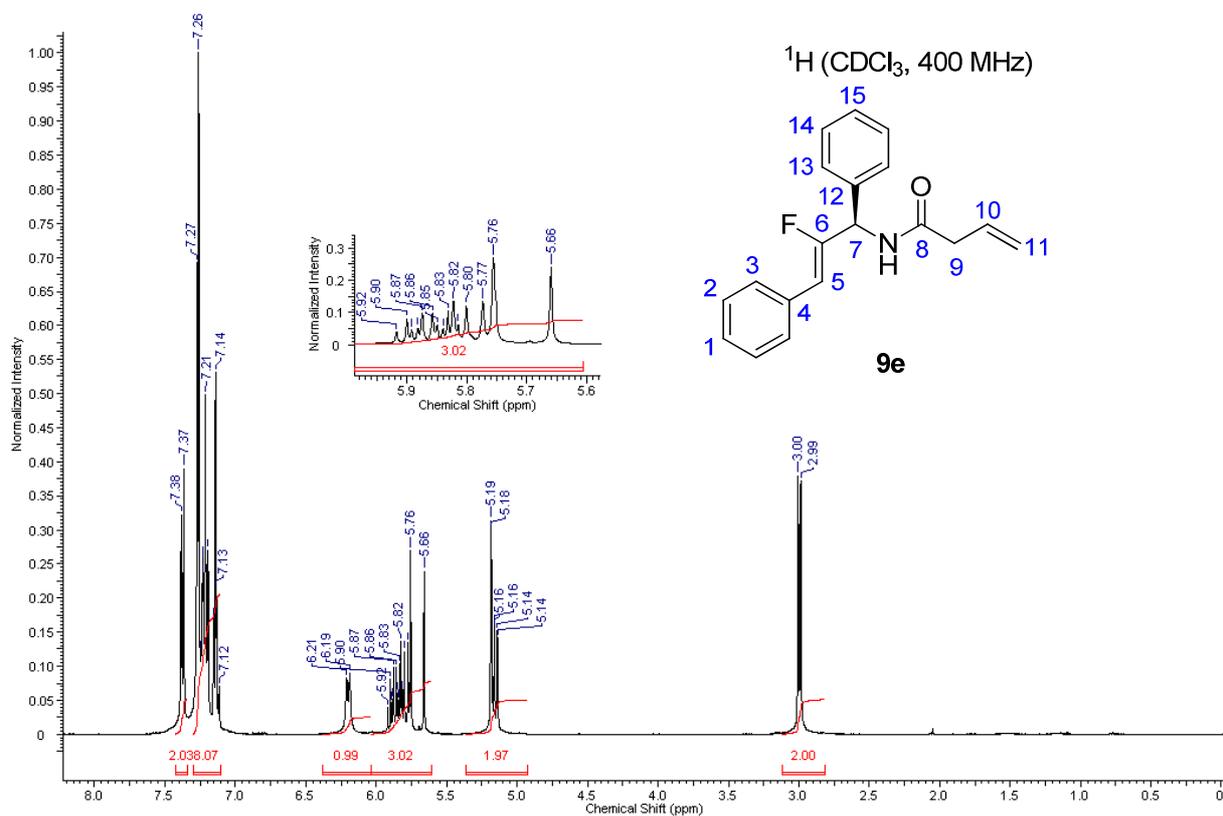


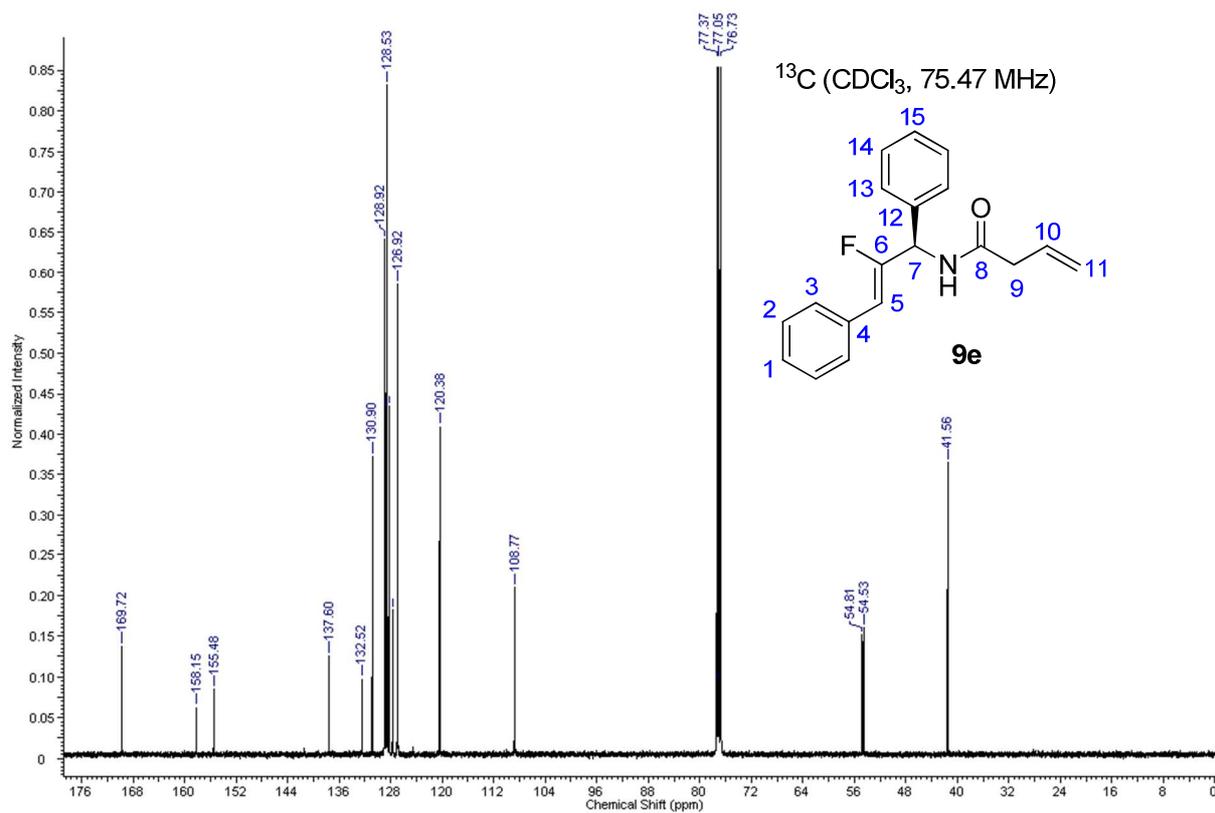
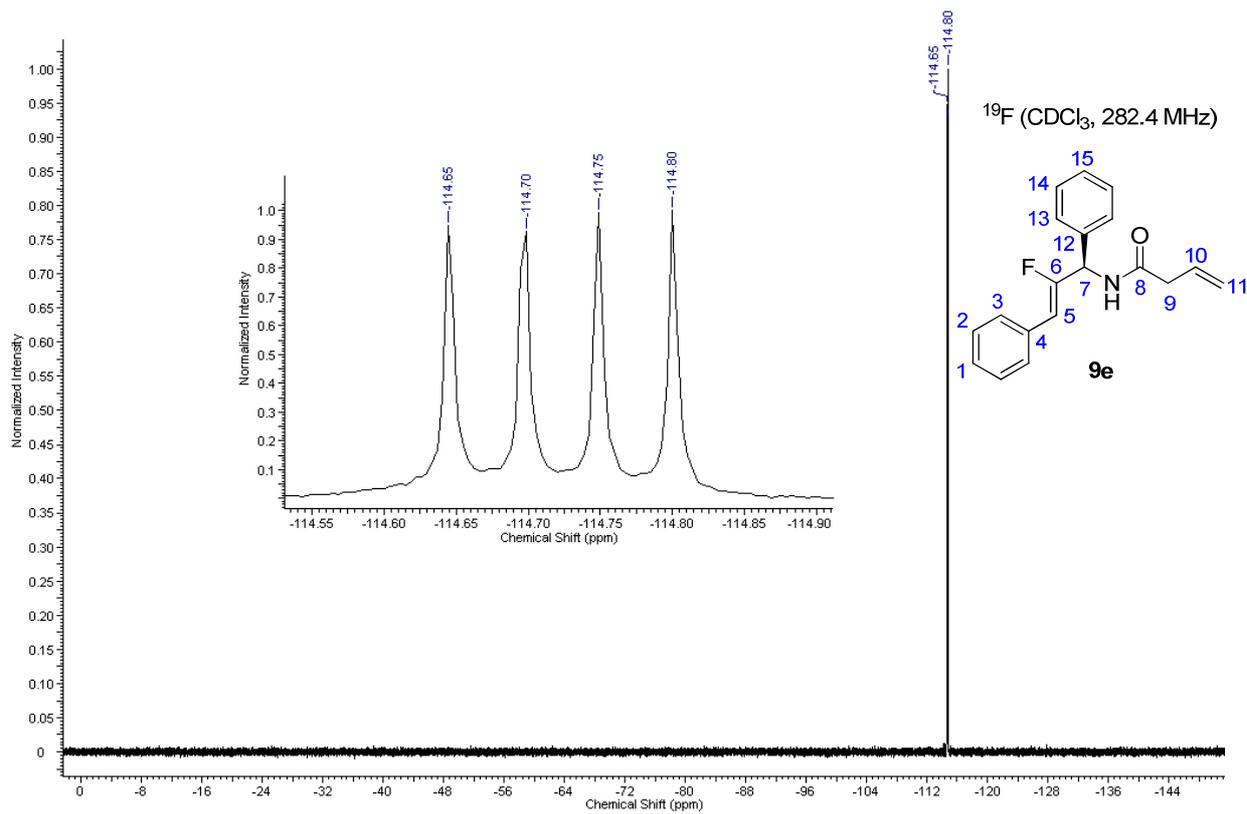
Compound **9c**: (*R,Z*)-*N*-(3-fluoro-4-phenylbut-3-en-2-yl)but-3-enamide



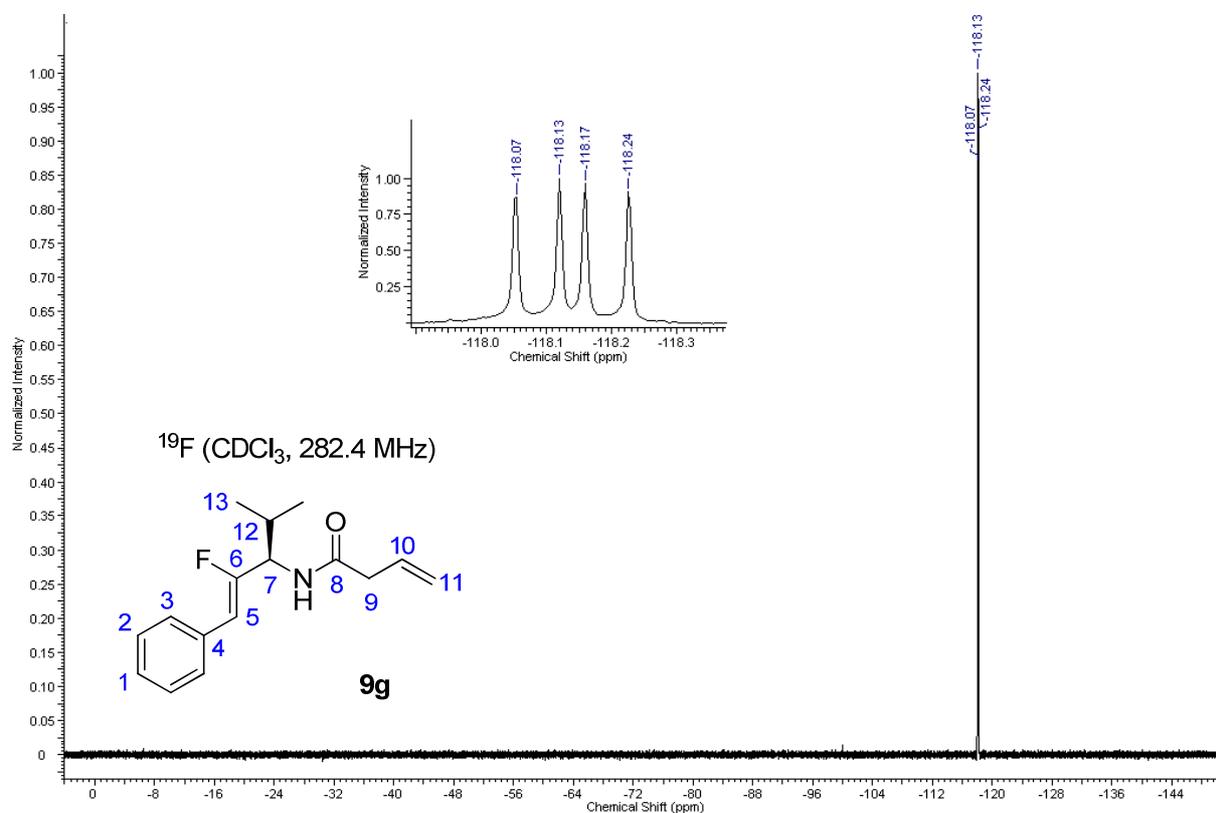
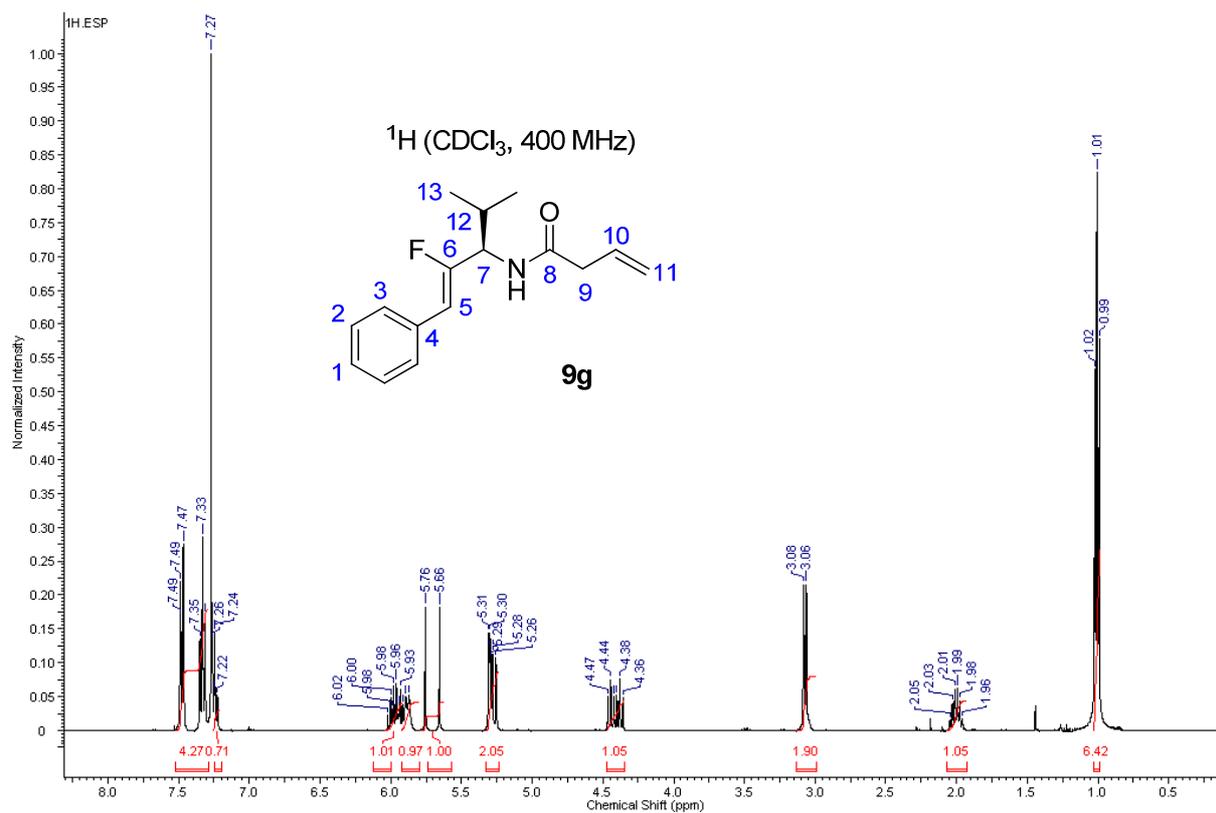


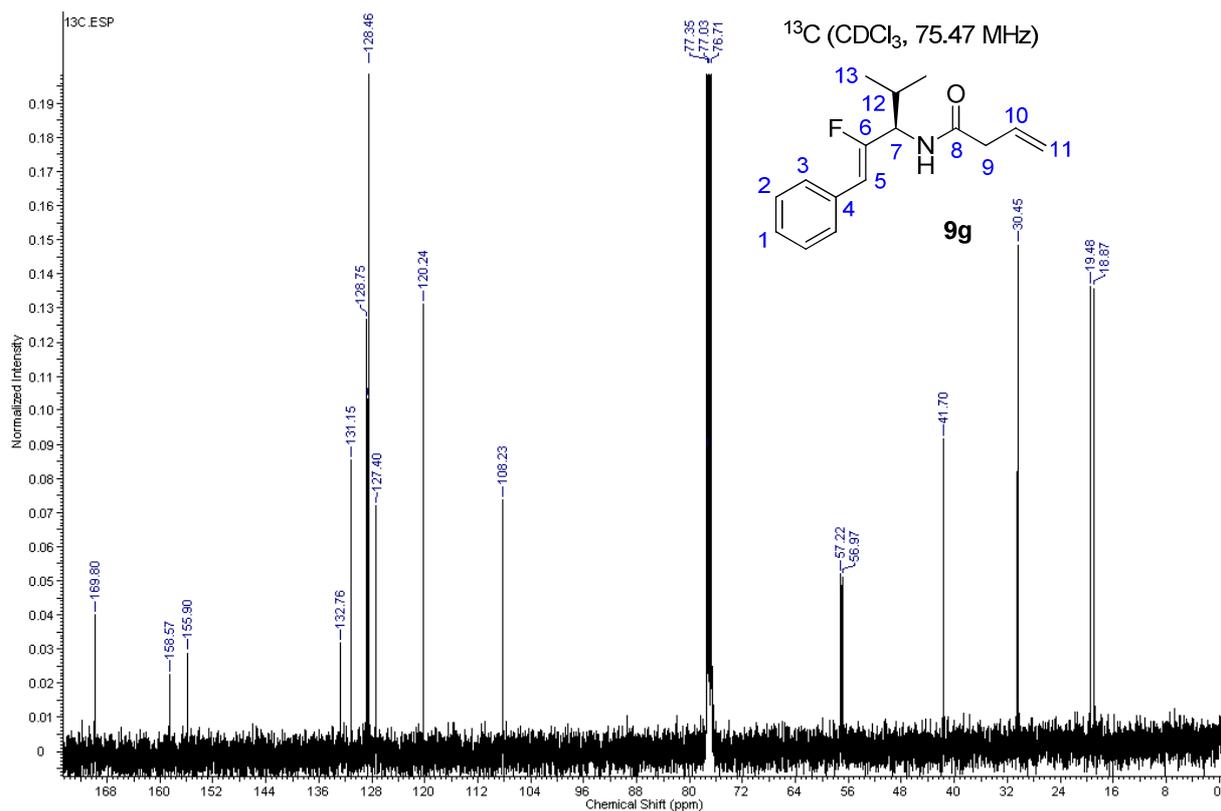
Compound **9e**: (*R,Z*)-*N*-(2-fluoro-1,3-diphenylallyl)but-3-enamide



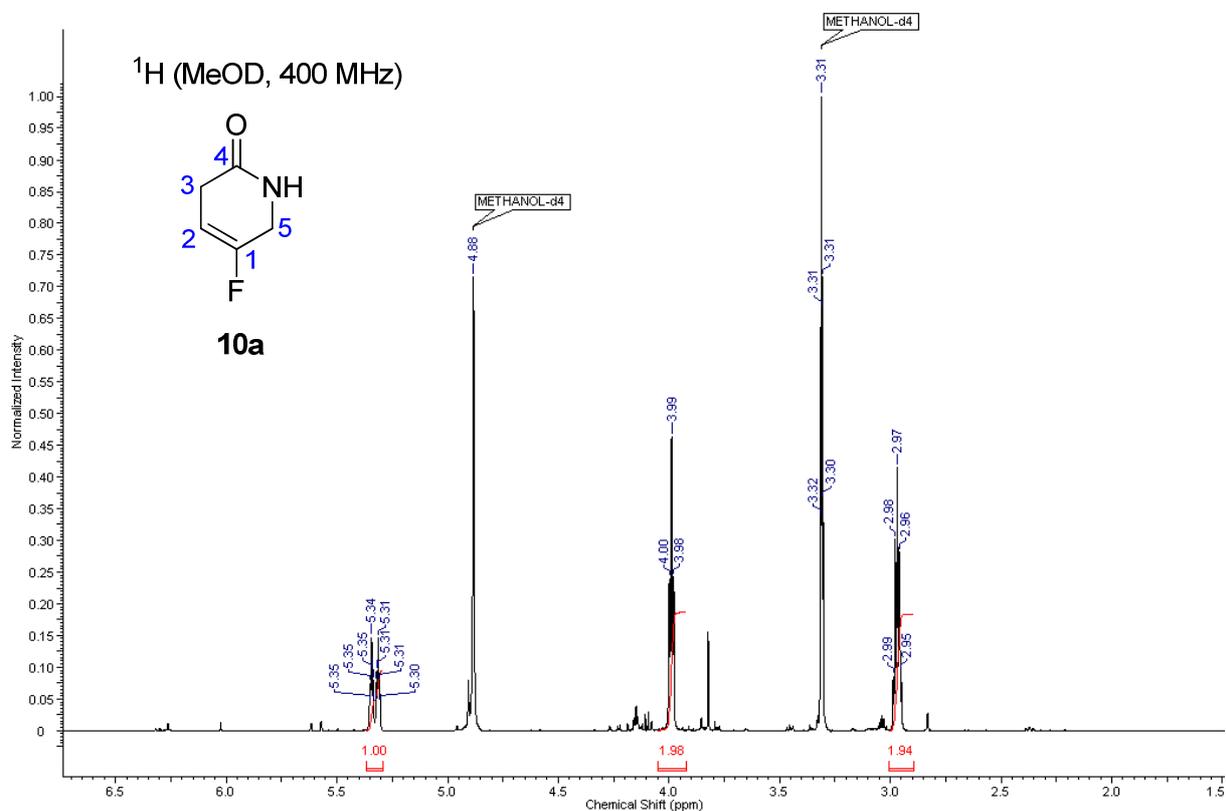


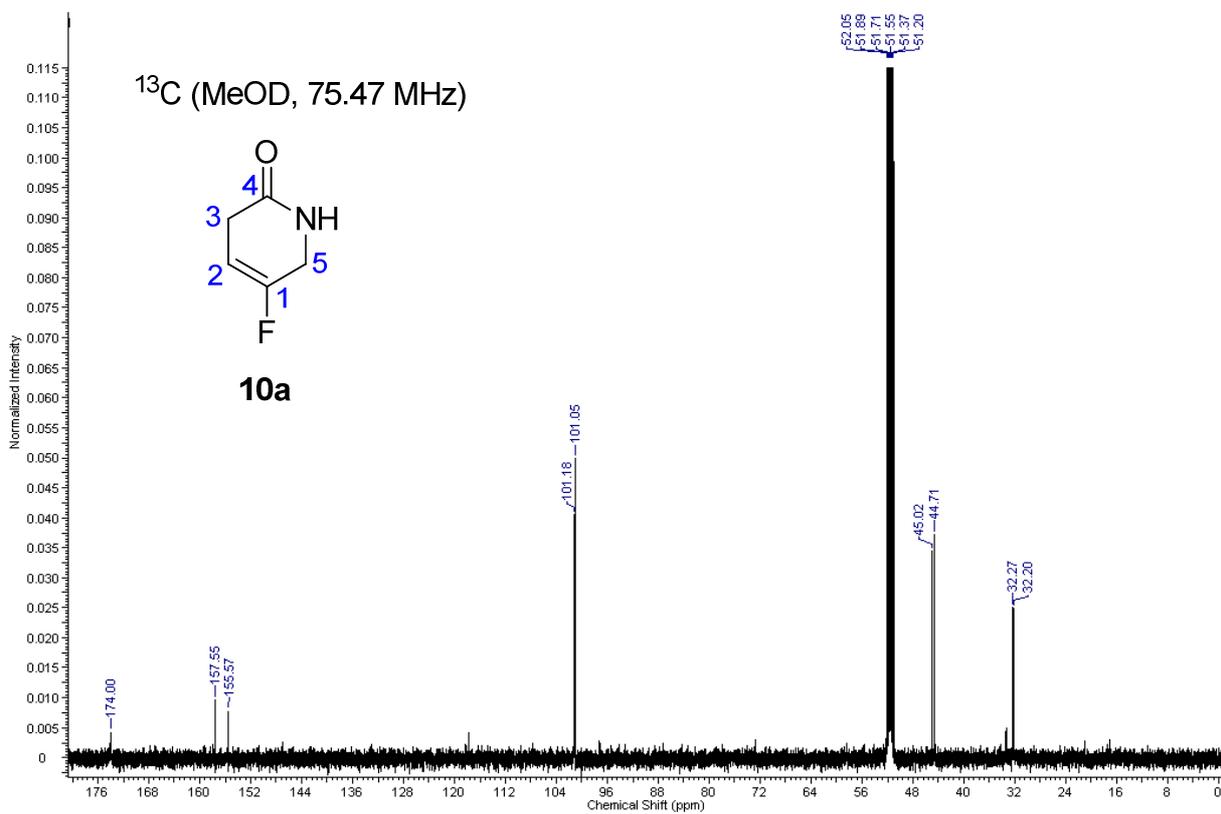
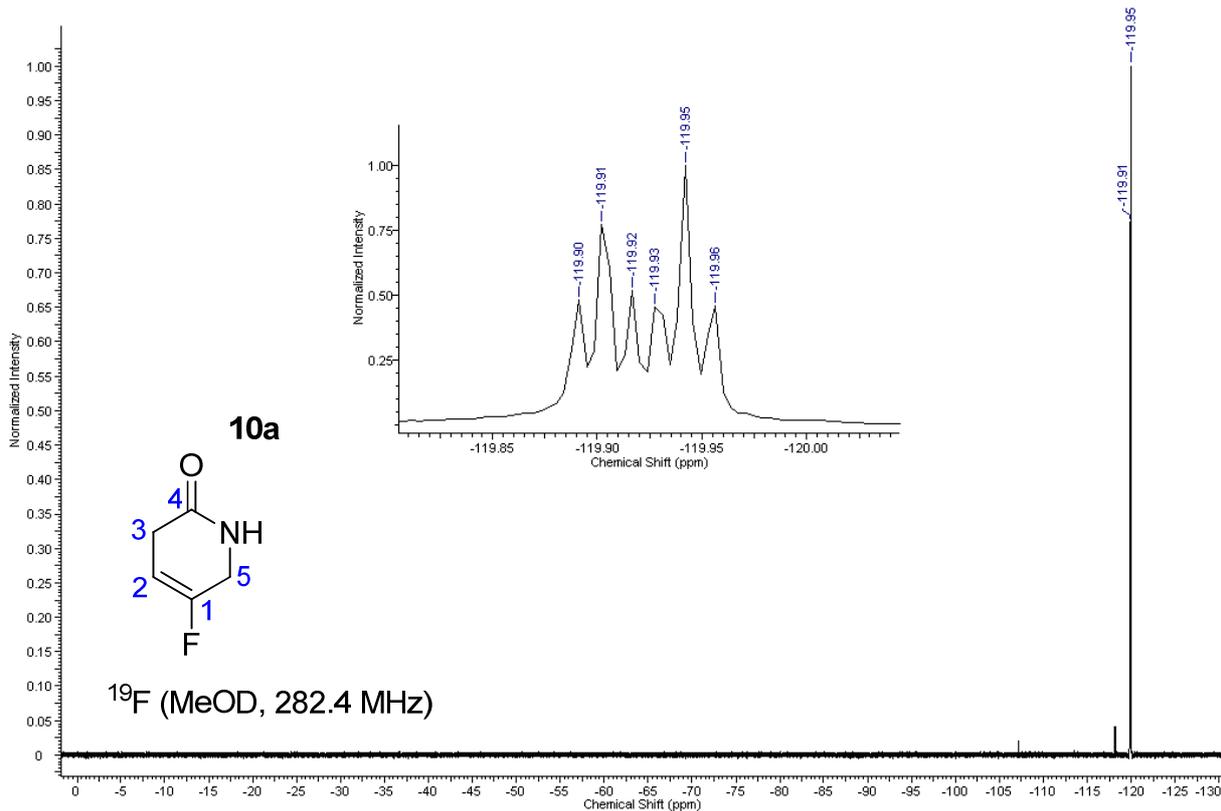
Compound **9g**: (*R,Z*)-*N*-(2-fluoro-4-methyl-1-phenylpent-1-en-3-yl)but-3-enamide



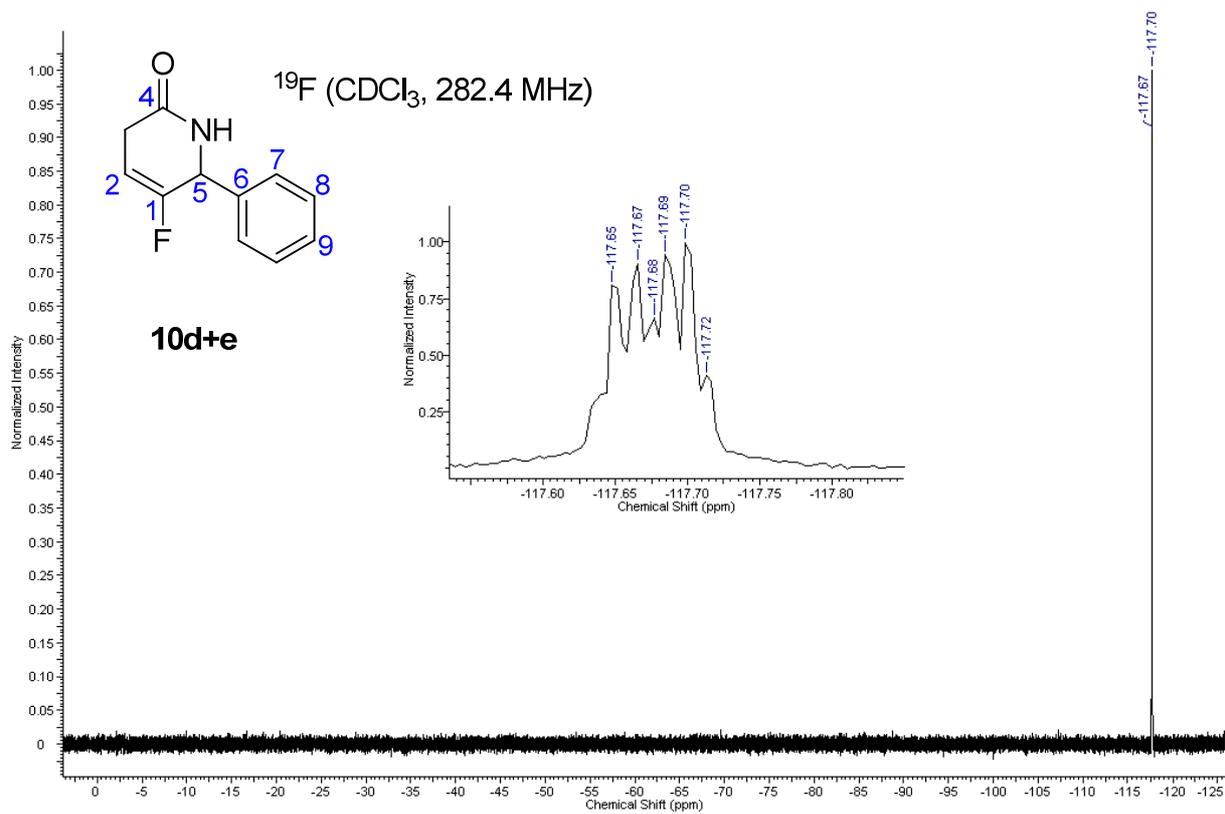
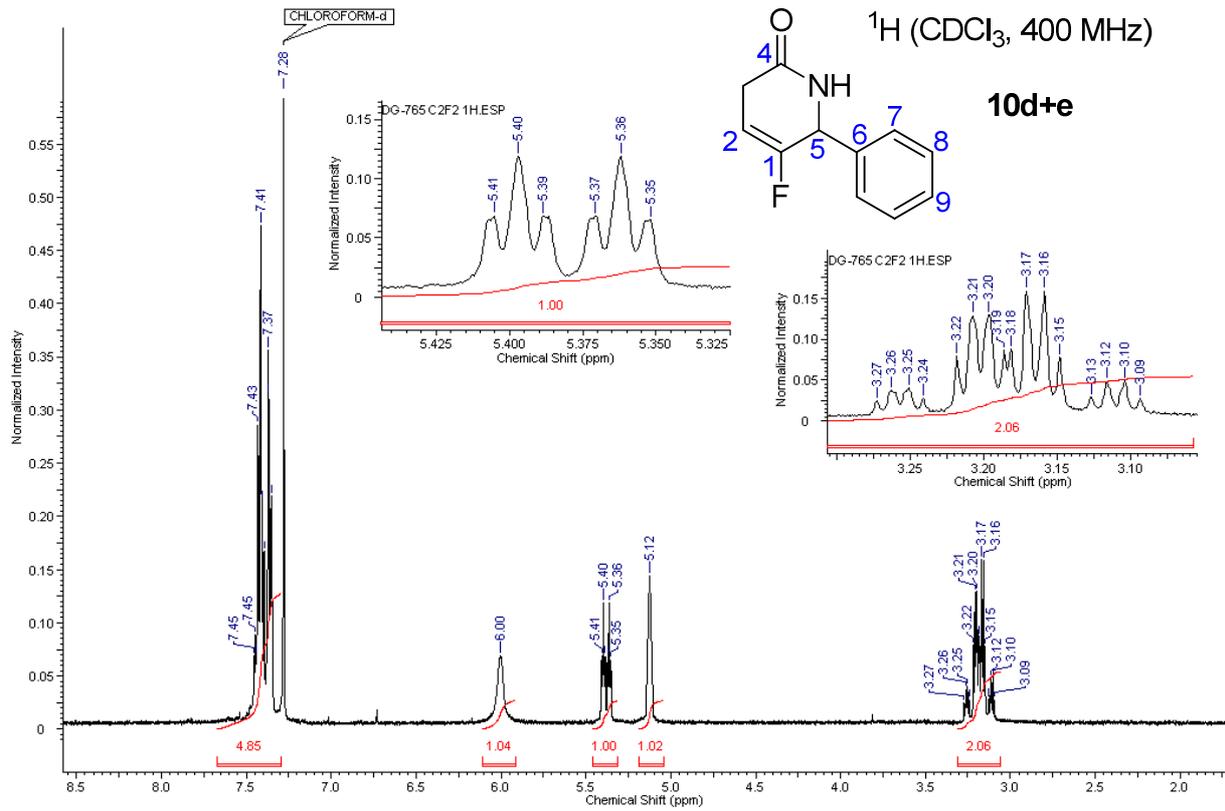


Compound 10a: 5-fluoro-1,6-dihydropyridin-2(3H)-one





Compound **10d+e**: 5-fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one



Compound **10d**: (*S*)-5-fluoro-6-phenyl-1,6-dihydropyridin-2(3H)-one

