A General Approach to Stereospecific Cross-Coupling Reactions of Nitrogen-Containing Stereocenters

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Supporting Information

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1. General Reagent/Analytical Information

BDH brand diethyl ether was purchased from VWR. EMD brand Omnisolv THF (unstabilized) was also purchased from VWR. These solvents were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina. Other anhydrous solvents (Sigma-Aldrich, SureSeal) were purged with argon prior to use. Solvents used for column chromatography were purchased from VWR (BDH brand). Tricyclohexyltin chloride was purchased from Gelest, Inc., and *N*-Boc-pyrrolidine was purchased from Ark Pharm. Reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using Silicycle silica gel (ultra pure grade) and basic or neutral alumina.

All NMR spectra were obtained on a Bruker 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C). All previously unreported compounds were additionally characterized by high resolution MS. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) unless otherwise noted. The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; m = multiplet; br = broad, app = apparent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and were obtained with ^{1}H decoupling. High resolution MS analyses were performed on an Agilent 6520 Q-TOF instrument. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase, or using a 30 m x 0.32 mm chiral column (Rt®-βDEXsm from RESTEK). All GC yields were calibrated using dodecane or tetradecane as an internal standard. Chiral HPLC analyses were performed using a Shimadzu Prominence HPLC system with binary mobile phase pumps and UV-vis detector (LC-20AB, SPD-20A) using an IA3 (dimensions: 4.6 mm x 150 mm; particle size: 3 μm) chiral column (DAICEL CHEMICAL IND., LTD.), an IC3 (dimensions: 4.6 mm x 250 mm; particle size: 3 μm) chiral column (DAICEL CHEMICAL IND., LTD.), OD-RH (dimensions: 4.6 mm x 150 mm; particle size: 5 μm) chiral column (DAICEL CHEMICAL IND., LTD.), or an IA (dimensions: 4.6 mm x 150 mm; particle size: 5 μm) chiral column (DAICEL CHEMICAL IND., LTD.).

2. Additional Reaction Development Information

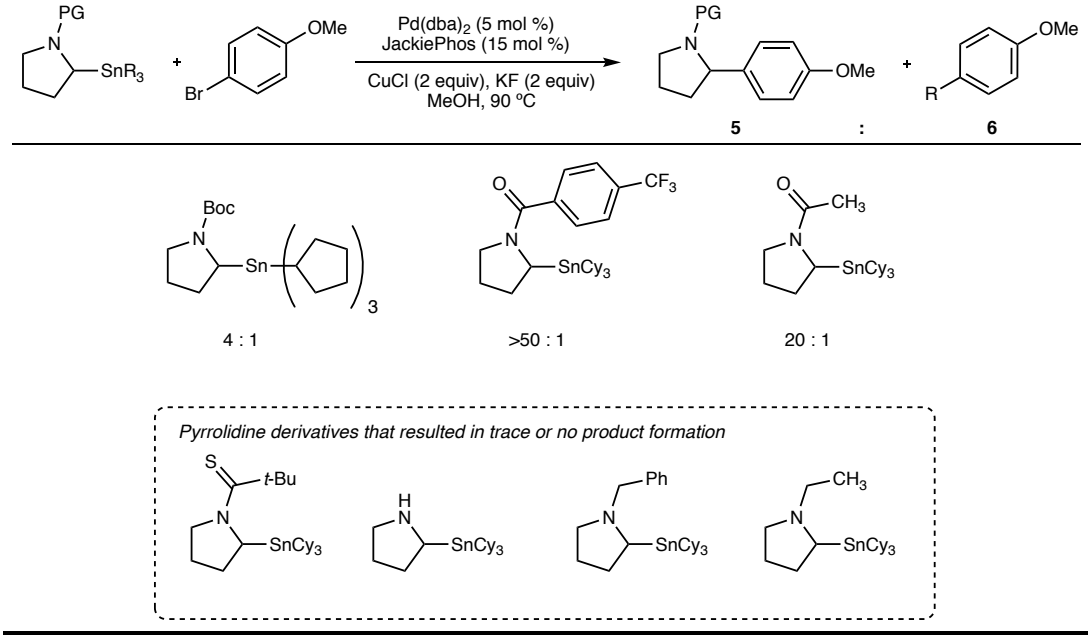


Figure S1. Effect of protecting group and spectator ligand on alkyl transfer.

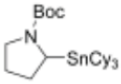
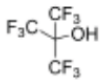
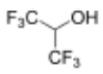
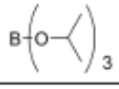
Sn	Solvent	Temperature (℃)	$Pd(dba)_2$ (m%)	CuCl (equiv)		5:6
	DMF	110	5	2		Trace
	tBuOH	75	5	2		1:1
	NMP	85	5	2		No pdt
	DMA	110	5	2		0.5:1
	2-mehyl THF	85	5	2		0.51:1
	MTBE	65	5	2		1:1
	DMSO	75	5	2		0.5:1
	THF	110	5	2		0.2:1
	Dioxane	110	5	2		0.84:1
	Dioxane	110	5	0		0.3:1
	Dioxnae	110	0	2		No pdt
	Ethanol	80	5	2		1.77:1
	Methanol	80	5	2		2.34:1
	Methanol	90	5	2		3.7:1
	Dioxane	110	5	2		0.8:1
	Dioxane	110	5	2		0.8:1
	Dioxane	110	5	2		0.8:1

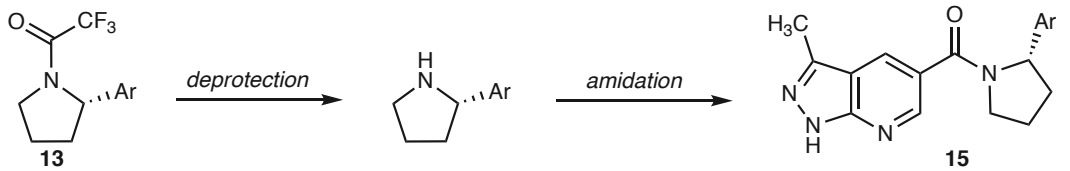
Figure S2. Effect of solvent and additives on alkyl transfer.

3. General Procedural Information

General procedure for cross-coupling reactions

On the benchtop, the electrophile (aryl bromide/triflate, thioester, or acyl chloride, 1.0 equiv), organotin (1.1 to 1.3 equiv), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol % or 15 mol %), CuCl (0.5 or 2.0 equiv), and *anhydrous* KF (for aryl bromide/triflate, 2.0 equiv) were added to an oven-dried 8 mL screw-top test tube equipped with a stirbar. The test tube was sealed with a screw-top septum and electrical tape. The reaction vessel was evacuated (ca. 100 mtorr) and backfilled with argon 3 times. If the electrophile were liquid, it was added to the reaction vessel via syringe at this point. Solvent (CH_3OH, 1,4-dioxane, or toluene, 1.0 or 0.5 mL) was then added via syringe. The septum was covered with electrical tape, and the reaction vessel was heated for 12 h (unoptimized reaction time) using a heating block. The cooled reaction mixture was transferred to a separatory funnel, diluted with water, and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. The organic layer was filtered, concentrated under reduced pressure, and purified by column chromatography.

General procedure for preparation of CDK8 inhibitors[1]

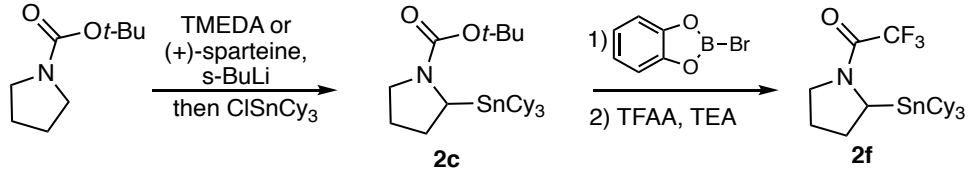


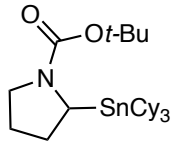
Compound **13** (0.1 mmol, 1 equiv) was added to a screw-top test tube that was equipped with a magnetic stirbar. The test tube was sealed with a screw-top septum and parafilm. The reaction vessel was evacuated (ca. 100 mtorr) and backfilled with argon 3 times. The reaction vessel was cooled to 0 °C. KOH (0.2 mmol, 2 equiv) in MeOH (0.3 mL) was then added via syringe. After 10 min, the reaction was warmed to rt, and was allowed to stir for an additional 12 h. The reaction mixture was diluted with water, and extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, and solvent was removed under reduced pressure to provide the crude deprotected product. To the crude product, 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (14 mg, 0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*′-ethylcarbodiimide (29.4 µl, 0.16 mmol), and 1-hydroxybenzotriazole hydrate (10.8 mg, 0.08 mmol) were added, followed by *N,N*-dimethylformamide (0.4 mL). 4-Methylmorpholine (26.4 µl, 0.24 mmol) was added at rt, and the reaction mixture was allowed to stir for 12 h at rt. The mixture was diluted with ethyl acetate (2 mL), washed with water (3 x 3 mL) followed by brine (2 x 3 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (9:1:0.1 ethyl acetate: MeOH: triethylamine) to afford pure **14**.

4. Compound Characterization Data

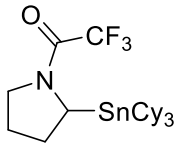
Compounds **2a**[2] and **2b**[3] were prepared following published literature procedures.

Synthetic sequence for preparation of **2f**.



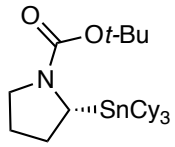


***tert*-Butyl 2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate** (**2c**). To an oven-dried round bottom flask under an atmosphere of argon, tetramethylethlenediamine (TMEDA) (1.3 mmol, 1.3 equiv) was added via syringe. Diethyl ether (6 mL) was then added, and the resulting solution was cooled to -78 ºC. To the cooled solution, s-BuLi (in cyclohexane) (1.3 mmol, 1.3 equiv) was added dropwise, and the resulting mixture was then allowed to stir at -78 ºC for 30 min. Next, *N*-Boc-pyrrolidine (1 mmol, 1.0 equiv) was added dropwise to the cooled solution. The resulting mixture was stirred at -78 ºC for 4 h. A solution of tricyclohexyltin chloride (1.5 mmol, 1.5 equiv) in toluene (1 mL) was added. The mixture was allowed to slowly warm to rt, and stirred overnight at rt. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure, and *tert*-butyl 2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate (**2c**) was isolated by flash column chromatography (10% K_2CO_3/Silica gel, 3:97 ethyl acetate:hexane) as a white solid (479 mg, 88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (m, 0.3H), 3.41 (m, 1.7H), 3.17 (m, 1H), 2.17 (m, 1H), 1.88 (m, 10H), 1.55 (m, 25H), 1.29 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 78.3, 46.2, 46.1, 33.8, 32.5, 32.2, 31.2, 30.9, 29.6, 28.9, 28.7, 28.6, 27.4, 26.9 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 540.2869; Found 540.2885.

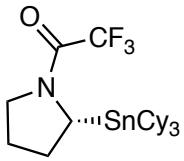


2,2,2-Trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethanone (2f). To a round-bottom flask under argon, **2c** (474 mg, 0.88 mmol) was added, followed by addition of DCM (2 mL). With the reaction mixture at rt, a solution of *B*-bromocatecholborane (349.9 mg, 1.76 mmol, 2.0 equiv) in DCM (2 mL) was added. The mixture was stirred overnight at rt. The reaction was quenched by NaOH (2M aqueous, 2 mL). The mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure to get 2-(tricyclohexylstannyl)pyrrolidine. Triethylamine (0.25 mL, 2.0 equiv) and anhy-

drous DCM (3 mL) were added, and the resulting solution was cooled to 0 ºC. Following the dropwise addition of trifluoroacetic anhydride (0.25 mL, 2.0 equiv), the mixture was stirred for 10 min at 0 ºC. The mixture was then stirred overnight at rt. The resulting solution was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure, and 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethanone was isolated by flash column chromatography (10% K_2CO_3/Silica gel, 5:95 ethyl acetate:hexane) as a white solid (329 mg, 70%) . ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.73 (m, 1H), 3.65 (m, 1H), 3.56 (m, 1H), 2.23 (m, 1H), 1.79 (m, 26H), 1.30 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.7 (q, J = 36.0 Hz, 1C), 116.7 (q, J = 285.3 Hz), 48.3 (major), 47.1 (minor), 33.8 (major), 33.4 (minor), 32.4 (m), 31.5 (minor), 31.2 (major), 29.4 (m), 28.9 (m), 27.3 (m) ppm. ^{19}F NMR (282.2 MHz, $CDCl_3$): δ -71.70 ppm. HRMS (ES^+): Calcd $(M-Na)^+$ 558.1986; Found 558.2004.

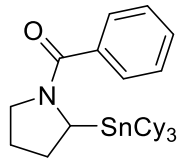


(*R*)-*tert*-Butyl-2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate ((*R*)-2c). To an oven-dried round bottom flask under an atmosphere of argon, (+)-sparteine (2.6 mmol, 1.3 equiv) was added via syringe. Diethyl ether (12 mL) was then added, and the resulting solution was cooled to -78 ºC. To the cooled solution, *s*-BuLi (in cyclohexane) (2.6 mmol, 1.3 equiv) was added dropwise, and the resulting mixture was then allowed to stir at -78 ºC for 30 min. Next, *N*-boc-pyrrolidine (1 mmol, 1.0 equiv) was added dropwise to the cooled solution. The resulting mixture was stirred at -78 ºC for 4 h. A solution of tricyclohexyltin chloride (3 mmol, 1.5 equiv) in toluene (2 mL) was added. The mixture was allowed to slowly warm to rt, and stirred overnight at rt. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure, and **(*R*)-2c** was isolated by flash column chromatography (10% K_2CO_3/Silica gel, 3:97 ethyl acetate:hexane) as a white solid (915.2 mg, 85%). (*S*)-*tert*-butyl 2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate **((*S*)-2c)** was prepared through an analogous route using (–)-sparteine (452 mg, 84%).

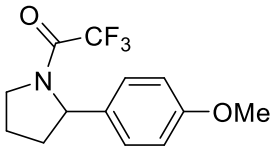


(*R*)-2,2,2-Trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethanone ((*R*)-2f). To a round-bottom flask under argon, **(*R*)-2c** (915.2 mg, 1.7 mmol) was added, followed by addition of DCM (4 mL). With the reaction mixture at rt, a solution of *B*-bromocatecholborane (675.9 mg, 3.4 mmol, 2.0 equiv) in DCM (4 mL) was added. The mixture was stirred overnight at rt. The reaction was quenched by NaOH (2M aqueous, 4 mL). The mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine,

dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure to get (*R*)-2-(tricyclohexylstannyl)pyrrolidine. Triethylamine (0.47 mL, 2.0 equiv) and anhydrous DCM (5 mL) were added, and the resulting solution was cooled to 0 ºC. Following the dropwise addition of trifluoroacetic anhydride (0.48 mL, 2.0 equiv), the mixture was stirred for 10 min at 0 ºC. The mixture was stirred overnight at rt. The resulting solution was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure, and **(*R*)-2f** was isolated by flash column chromatography (10% K_2CO_3/Silica gel, 5:95 ethyl acetate:hexane) as a white solid (614 mg, 68%). The ee value (97% ee) was determined by HPLC analysis of the organic layer.



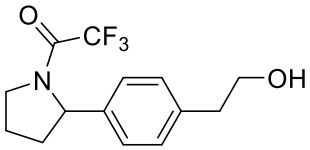
Phenyl-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)methanone (2e). To a round-bottom flask under argon, **2c** (915.2 mg, 1.7 mmol) was added, followed by addition of DCM (1.5 mL). With the reaction mixture at rt, a solution of *B*-bromocatecholborane (0.3 mmol, 2.0 equiv) in DCM (0.5 mL) was added. The mixture was stirred overnight at rt. The reaction was quenched by NaOH (2M aqueous, 4 mL). The mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure to get (*R*)-2-(tricyclohexylstannyl)pyrrolidine. Triethylamine (0.06 mL, 3.0 equiv) and anhydrous DCM (1.5 mL) were added, and the resulting solution was cooled to 0 ºC. Following the dropwise addition of benzoyl chloride (0.03 mL, 2.0 equiv), the mixture was stirred for 10 min at 0 ºC. Then, the mixture was stirred overnight at rt. The resulting solution was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure. A white solid (63 mg, 78%) was isolated by flash column chromatography (10% K_2CO_3/Silica gel, 14:86 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.38 (m, 3H), 3.66 (m, 1H), 3.46 (m, 1H), 3.37 (m, 1H), 2.28 (m, 1H), 1.82 (m, 26H), 1.27 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.0, 137.7, 129.5, 128.3, 127.2, 50.3, 46.8, 32.6, 30.2, 29.6, 28.8, 28.0, 27.5 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 544.2607; Found 544.2620.



2,2,2-Trifluoro-1-(2-(4-methoxyphenyl)pyrrolidin-1-yl)ethan-1-one (7a).
The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-methoxybenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A white solid (51 mg,

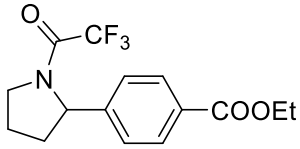
74%) was isolated by flash column chromatography (10:90 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 7.04 (m, 2H), 6.84 (m, 2H), 5.27 (m, 0.28H), 5.17 (m, 0.72H), 3.86 (m,2H), 3.78 (s, 3H), 2.32 (m, 1H), 2.10 (m, 3H) ppm.; ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 155.5 (m), 134.3 (minor), 133.3 (major), 126.7 (major), 126.1 (minor), 116.5 (q, J = 286.2 Hz), 114.2 (major), 114.1 (minor), 62.1 (major), 61.3 (minor), 55.4, 48.5 (minor), 47.6 (major), 36.2 (minor), 33.6 (major), 24.3 (major), 20.2 (minor) ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 296.0874; Found 296.0901.

(*S*)-2,2,2-Trifluoro-1-(2-(4-methoxyphenyl)pyrrolidin-1-yl)ethan-1-one ((*S*)-7a). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-methoxybenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A white solid (45 mg, 66%) was isolated by flash column chromatography (10:90 ethyl acetate:hexane). The ee value (93.3% ee) was determined by chiral GC analysis of the organic layer.



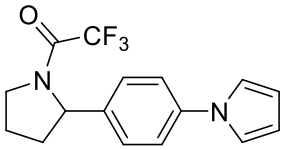
2,2,2-Trifluoro-1-(2-(4-(2-hydroxyethyl)phenyl)pyrrolidin-1-yl)ethan-1-one (7b). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 2-(4-bromophenyl)ethan-1-ol (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (0.5 mL) at 90 ºC. A yellow liquid (20 mg, 70%) was isolated by flash column chromatography (30:70 to 50:50 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (m, 2H), 7.06 (m, 2H), 5.30 (m, 0.3H), 5.20 (m, 0.7H), 3.88 (m, 4H), 2.85 (m, 2H), 2.32 (m, 1H), 2.04 (m, 3H), 1.45 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (m), 140.5 (minor), 139.4 (major), 137.9 (minor), 137.8 (major), 129.5 (major), 129.4 (minor), 125.8 (major), 125.2 (minor), 116.6 (q, J = 286 Hz,), 63.75 (major), 63.70 (minor), 48.6 (minor), 47.7 (major), 38.98 (major), 38.90 (minor), 36.2 (minor), 33.7 (major), 24.3 (major), 20.2 (minor) ppm. HRMS (ES^+): Calcd $(M\text{-}H)^+$ 288.1211; Found 288.1206.

(*S*)-2,2,2-Trifluoro-1-(2-(4-(2-hydroxyethyl)phenyl)pyrrolidin-1-yl)ethan-1-one ((*S*)-7b). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 2-(4-bromophenyl)ethan-1-ol (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A light yellow liquid (17 mg, 60%) was isolated by flash column chromatography (30:70 to 50:50 ethyl acetate:hexane). The ee value (95.6% ee) was determined by HPLC analysis of the organic layer.



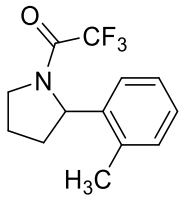
Ethyl 4-(1-(2,2,2-trifluoroacetyl)pyrrolidin-2-yl)benzoate (7c). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), ethyl 4-bromobenzoate (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A pale yellow oil (67.2 mg, 85%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (m, 2H), 7.19 (m, 2H), 5.35 (m, 0.25H), 5.24 (m, 0.75H), 4.36 (m, 2H), 3.90 (m, 2H), 2.39 (m, 1H), 2.01 (m, 3H), 1.37 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 155.8 (m), 147.2 (minor), 146.3 (major), 130.2 (major), 130.1 (minor), 130.0 (minor), 129.8 (major), 125.4 (major), 125.0 (minor), 116.4 (q, J = 286.1 Hz, 1C), 62.5, 61.2 (minor), 61.1 (major), 48.7 (minor), 47.8 (major), 36.0 (minor), 33.6 (major), 24.4 (major), 20.3 (minor), 14.4 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 316.1161; Found 316.1186.

Ethyl (*S*)-4-(1-(2,2,2-trifluoroacetyl)pyrrolidin-2-yl)benzoate ((*S*)-7c). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), ethyl 4-bromobenzoate (0.20 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A pale yellow oil (47 mg, 75%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). The ee value (93.4% ee) was determined by chiral GC analysis of the organic layer.



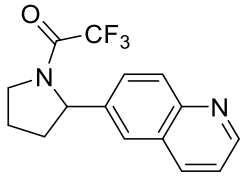
1-(2-(4-(1H-Pyrrol-1-yl)phenyl)pyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (7d). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-(4-bromophenyl)-1H-pyrrole (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A yellow oil (66 mg, 85%) was isolated by flash column chromatography (10:90 to 20:80 ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36 (m, 2H), 7.19 (m, 2H), 7.05 (m, 2H), 6.34 (m, 2H), 5.34 (minor, 0.22H), 5.23 (major, 0.78H), 3.91 (m, 2H), 2.37 (m, 1H), 2.04 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.3 (m), 140.1 (major), 139.6 (minor), 138, 126.8 (major), 126.2 (minor), 121.0 (major), 120.7 (minor), 119.4 (major), 119.4 (minor), 116.5 (q, J = 286.0Hz, 1C), 110.8 (minor), 110.5 (major), 62.2 (major), 61.3 (minor), 48.6 (minor), 47.8 (major), 36.2 (minor), 33.7 (major), 24.4 (major), 20.3 (minor) ppm. HRMS (ES^+): Calcd $(M-H)^+$ 309.1215; Found 309.1219.

(*S*)-1-(2-(4-(1H-Pyrrol-1-yl)phenyl)pyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one ((*S*)-7d). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-(4-bromophenyl)-1H-pyrrole (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A yellow oil (49 mg, 64%) was isolated by flash column chromatography (10:90 to 20:80 ethyl acetate:hexane). The ee value (91% ee) was determined by chiral GC analysis of the organic layer.



2,2,2-Trifluoro-1-(2-(o-tolyl)pyrrolidin-1-yl)ethan-1-one (7e). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-2-methylbenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear liquid (40 mg, 62%) was isolated by flash column chromatography (15:85 to 20:80 diethyl ether:hexane). ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (m, 3H), 6.94 (m, 1H), 5.45 (m, 1H), 4.03 (m, 2H), 2.39 (m, 4H), 2.06 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (m), 140.7 (minor), 139.5 (major), 134.4 (major), 133.3 (minor), 130.99 (major), 130.93 (minor), 127.5 (minor), 127.3 (major), 126.4 (major), 126.3 (minor), 124.3 (minor), 123.4 (major), 116.6 (q, J = 286 Hz, 1C), 59.9 (major), 59.3 (minor), 48.5 (m), 34.2 (minor), 32.1 (major), 24.2, 20.5 (minor), 19.5(major) ppm. HRMS (ES^+): Calcd $(M-H)^+$ 258.1106; Found 258.1125.

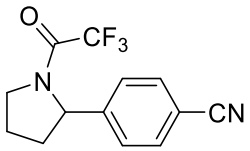
(*S*)-2,2,2-Trifluoro-1-(2-(o-tolyl)pyrrolidin-1-yl)ethan-1-one ((*S*)-7e). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-2-methylbenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear liquid (29 mg, 45%) was isolated by flash column chromatography (15:85 to 20:80 diethyl ether:hexane). The ee value (94% ee) was determined by chiral GC analysis of the organic layer.



2,2,2-Trifluoro-1-(2-(quinolin-6-yl)pyrrolidin-1-yl)ethan-1-one (7f). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), quinolin-6-yl trifluoromethanesulfonate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (0.5 mL) at 90 ºC. A pale yellow solid (16 mg, 55%) was isolate by flash column chromatography (30:70 to 60:40 ethyl acetate: hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 8.1 (m, 1H), 8.11 (m, 2H), 7.45 (m, 3H), 5.50 (m, 0.24H), 5.39 (m, 0.76H), 3.97 (m, 2H), 2.45 (m, 1H), 2.05 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.8 (minor), 150.5 (major), 147.8, 140.4, 139.5, 136.33 (major), 136.26 (minor), 130.42 (minor), 130.38 (major), 128.2 (major), 128.1 (minor), 127.4 (major), 127.0 (minor), 124.1 (major), 123.4 (minor), 121.9 (minor), 121.6 (major), 116.5 (q, J = 185.8 Hz, 1C), 62.6 (major), 61.7 (minor), 48.7 (minor), 47.9 (major), 35.9 (minor), 33.9 (major), 24.5 (major), 20.3 (minor) ppm.

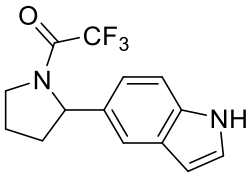
(*S*)-2,2,2-Trifluoro-1-(2-(quinolin-6-yl)pyrrolidin-1-yl)ethanone ((*S*)-7f). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), quinolin-6-yl trifluo-

romethanesulfonate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (0.5 mL) at 90 ºC. A pale yellow solid (17 mg, 58%) was isolated by flash column chromatography (30:70 to 60:40 ethyl acetate: hexane). The ee value (98% ee) was determined by HPLC analysis of the organic layer.



4-(1-(2,2,2-Trifluoroacetyl)pyrrolidin-2-yl)benzonitrile (7g). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 4-bromobenzonitrile (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear oil (46 mg, 69%) was isolated by flash column chromatography (1:2 ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.46 (m, 2H), 7.24 (m, 2H), 5.34 (m, 0.2H), 5.19 (m, 0.8H), 3.91 (m, 2H), 2.40 (m, 1H), 1.97 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0 (m), 147.6 (minor), 146.7 (major), 132.8 (major), 132.7 (minor), 126.3 (major), 125.9 (major), 118.7 (major), 118.5 (minor), 116.3 (q, J = 286.1 Hz, 1C), 111.8 (minor), 111.5 (major), 62.4 (major), 61.4 (major), 48.7 (minor), 48.0 (major), 36.0 (major), 33.6 (major), 24.5 (major), 20.3 (minor) ppm. HRMS (ES^+): Calcd $(M-H)^+$ 269.0902; Found 269.0900.

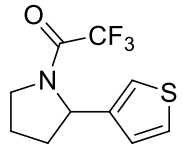
(*S*)-4-(1-(2,2,2-Trifluoroacetyl)pyrrolidin-2-yl)benzonitrile ((*S*)-7g). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 4-bromobenzonitrile (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear solid (36 mg, 54%) was isolated by flash column chromatography (1:2 ethyl acetate:hexane). The ee value (93% ee) was determined by chiral GC analysis of the organic layer.



(2-(1H-Indol-5-yl)pyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (7h). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 5-iodo-1H-indole (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (0.5 mL) at 90 ºC. A pale red solid (14.1 mg, 50%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (b, 1H), 7.36 (m, 2 H), 7.20 (m, 1H), 6.96 (m, 1H), 6.51 (m, 1H), 5.37 (m, 1H), 3.93 (m, 2H), 2.34(m, 1H), 2.03(m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0 (m), 135.3 (major), 135.1 (minor), 133.9 (minor), 132.8 (major), 128.1 (major), 127.9 (minor), 125.2 (minor), 125.0 (major), 120.0 (major), 119.3 (minor), 117.3(major), 116.9 (minor), 111.5 (major), 114.4 (minor), 102.8, 63.1 (major), 62.2

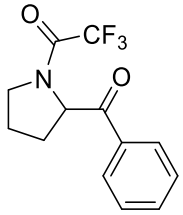
(minor, m), 48.2 (m), 36.6, 34.2, 24.29, 20.2 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 283.1058; Found 283.1059.

(*S*)-1-(2-(1H-Indol-5-yl)pyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one ((*S*)-7h). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 5-iodo-1H-indole (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A pale red solid (37 mg, 53%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). The ee value (97% ee) was determined by HPLC analysis of the organic layer.



2,2,2-Trifluoro-1-(2-(thiophen-3-yl)pyrrolidin-1-yl)ethan-1-one (7i). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 3-bromothiophene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear oil (32 mg, 51%) was isolated by flash column chromatography (20:80 to 30:70 diethyl ether: hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 1H), 6.93 (m, 2H), 5.36 (m, 1H), 3.82 (m, 2H), 2.12 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 143.1 (minor), 141.8 (major), 126.9 (minor), 126.5 (major), 125.8 (major), 125.2 (minor), 120.9 (major), 120.3 (minor), 116.5 (q, J = 286.1Hz, 1C), 58.7, 47.8 (minor), 46.9 (major), 36.5 (minor), 32.4 (major), 24.4 (major), 20.6 (minor) ppm. HRMS (ES^+): Calcd $(M-H)^+$ 250.0513; Found 250.0515.

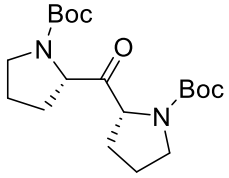
(*S*)-2,2,2-Trifluoro-1-(2-(thiophen-3-yl)pyrrolidin-1-yl)ethan-1-one ((*S*)-7i). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 3-bromothiophene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 ºC. A clear oil (30 mg, 48%) was isolated by flash column chromatography (20:80 to 30:70 diethyl ether:hexane). The ee value (92% ee) was determined by chiral GC analysis of the organic layer.



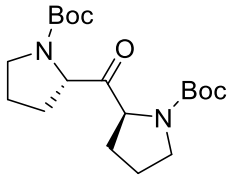
1-(2-Benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one (8a). The general procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), benzoyl chloride (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv) in 1,4-dioxane (1.0 mL) at 110 ºC. A pale yellow solid (48 mg, 70%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). ^1H NMR (300 MHz,

$CDCl_3$): δ 7.97 (m, 2H), 7.62 (m, 1H), 7.49 (m, 2H), 5.65 (m, 0.2H), 5.56 (m, 0.8H), 3.87 (m, 2H), 2.48 (m, 1H), 1.95 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.5, 155.5 (m), 134.6, 134.2 (minor), 133.9 (major), 129.2 (minor, 0.36C), 129.0 (major, 1.64C), 128.7 (major, 1.64C), 128.6 (minor, 0.36 C), 116.5 (q, J = 285.4 Hz, 1C), 62.7 (major), 62.2 (minor), 48.5 (minor), 47.5 (major), 31.4 (minor), 28.7 (major), 25.0 (major), 21.0 (minor) ppm. HRMS (ES^+): Calcd $(M-H)^+$ 272.0898; Found 272.0920.

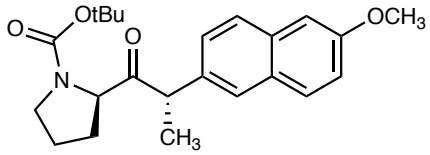
(*S*)-1-(2-Benzoylpyrrolidin-1-yl)-2,2,2-trifluoroethan-1-one ((*S*)-8a). The general procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), benzoyl chloride (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv) in 1,4-dioxane (1.0 mL) at 110 ºC. A pale yellow solid (42 mg, 62%) was isolated by flash column chromatography (25:75 ethyl acetate:hexane). The ee value (95.6% ee) was determined by HPLC analysis of the organic layer.



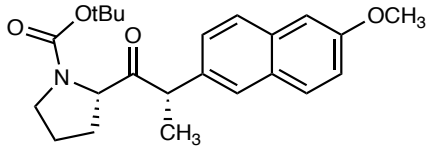
di-*tert*-Butyl 2,2'-carbonyl(*2S*,*2'R*)-*bis*(pyrrolidine-1-carboxylate) (8b) The general procedure for cross-coupling reactions was employed using **(*S*)-2c** (1.3 equiv), *tert*-butyl (*S*)-2-((phenylthio)carbonyl)pyrrolidine-1-carboxylate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv) in 1,4-dioxane (0.5 mL) at 110 ºC. A white solid (27 mg, 72%) was isolated by column chromatography (30:70 ethyl acetate:hexane). The de value (96% de) was determined by GC analysis of the organic layer.



di-*tert*-Butyl 2,2'-carbonyl(*2S*,*2'S*)-*bis*(pyrrolidine-1-carboxylate) (8c).[4] The general procedure for cross-coupling reactions was employed using **(*R*)-2c** (1.3 equiv), *tert*-butyl (*S*)-2-((phenylthio)carbonyl)pyrrolidine-1-carboxylate (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv), in 1,4-dioxane (1.0 mL) at 110 ºC. A white solid (88 mg, 92%) was isolated by column chromatography (30:70 ethyl acetate:hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 4.50 (m, 2H), 3.45 (m, 4H), 2.10 (m, 4H), 1.83 (m, 4H), 1.42 (s, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.3, 206.3, 154.5, 154.0, 80.0, 79.7, 79.5, 62.8, 62.5, 61.8, 61.4, 47.1, 46.9, 46.8, 29.7, 29.3, 28.5, 28.2, 28.1, 24.0, 23.9, 23.0, 22.9 ppm. The de value (96% de) was determined by GC analysis of the organic layer.

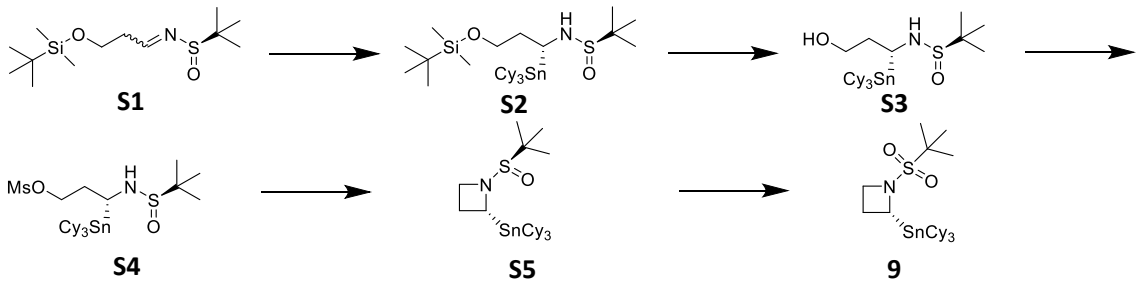


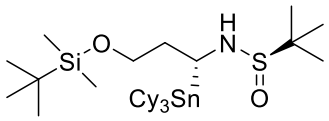
***tert*-Butyl (*R*)-2-((*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl)pyrrolidine-1-carboxylate (8d).** The general procedure for cross-coupling reactions was employed using (*S*)-2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate (1.3 equiv), *S*-phenyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanethioate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv) in 1,4-dioxane (1 mL) at 110 ºC. A white solid (27 mg, 70%) was isolated by flash column chromatography (10:90 to 20:80 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): 7.72 (m, 3H), 7.33 (m, 1H), 7.26 (m, 2H), 4.46 (m, 1H), 4.25 (m, 0.5H), 4.04 (m, 0.5H), 3.92 (s, 3H), 3.48 (m, 2H), 1.79 (m, 2H), 1.48 (m, 12H), 1.28 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 210.4, 157.9, 154.2, 135.0, 133.9, 129.3, 127.5, 126.7, 119.3, 105.8, 79.9, 64.0, 55.5, 52.1, 47.1, 31.1, 28.5, 24.5, 18.0 ppm. The de value (96.7% de) was determined by HPLC analysis of the organic layer.



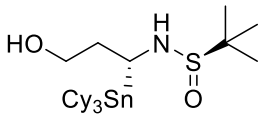
***t*ert-Butyl (*S*)-2-((*S*)-2-(6-methoxynaphthalen-2-yl)propanoyl)pyrrolidine-1-carboxylate (8e).** The general procedure for cross-coupling reactions was employed using (*R*)-2-(tricyclohexylstannyl)pyrrolidine-1-carboxylate (1.3 equiv), *S*-phenyl (*S*)-2-(6-methoxynaphthalen-2-yl)propanethioate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), and CuCl (2.0 equiv) in 1,4-dioxane (1 mL) at 110 ºC. A colorless liquid (34 mg, 88%) was isolated by flash column chromatography (10:90 to 20:80 ethyl acetate: hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 3H), 7.35 (m, 1H), 7.15 (m, 2H), 4.42 (m, 1H), 4.22 (m, 1H), 3.91 (s, 3H), 3.45 (m, 0.7H), 3.20 (m, 1.0H), 2.83 (0.4H), 2.14 (m, 3H), 1.52 (m, 7H), 1.32 (m, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 211.4, 210.4, 157.8, 154.3, 135.5, 133.8, 133.6, 126.9, 119.3, 105.7, 80.1, 65.5, 65.3, 55.4, 49.0, 47.9, 46.8, 30.5, 29.9, 28.7, 28.3, 24.1, 23.3, 18.9 ppm. The de value (97% de) was determined by HPLC analysis of the organic layer.

*Synthetic sequence for preparation of **9**.*

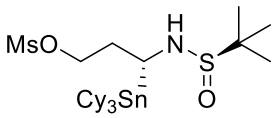




(*R*)-*N*-((*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-1-(tricyclohexylstannyl)propyl)-2-methylpropane-2-sulfinamide (S2).[5] In a round-bottom flask under argon, a solution of tricyclohexyltin chloride (2 mmol, 1.0 equiv), naphthalene (1 mmol, 0.5 equiv) and lithium (20 mmol, 10 equiv) in anhydrous THF (8 mL) were stirred until the solution turned black. Then the solution was stirred for an additional 5 h to generate tricyclohexyltin lithium solution. A solution of **S1** (2.4 mmol, 1.2 equiv) in THF (5 mL) was placed under Ar and cooled to -78 ºC. After 1 h at -78 ºC, the solution was quenched with methanol, followed by water (reaction mixture still at -78 ºC). The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude product was purified by flash column chromatography (10% K_2CO_3/Silica gel, 10:90 ethyl acetate:hexane), providing **S2** as a colorless oil (0.646 g, 49%).

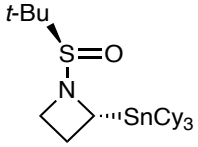


(*R*)-*N*-((*R*)-3-Hydroxy-1-(tricyclohexylstannyl)propyl)-2-methylpropane-2-sulfinamide (S3). To a round-bottom flask, (*R*)-*N*-((*R*)-3-((*tert*-butyldimethylsilyl)oxy)-1-(tricyclohexylstannyl)propyl)-2-methylpropane-2-sulfinamide (**S2**) (0.98 mmol, 1.0 equiv) was added, followed by addition of anhydrous THF (2 mL). The resulting solution was cooled to 0 ºC, tetra-n-butylammonium fluoride (TBAF, 1.03 mmol, 1.05 equiv) was added, the solution was allowed to stir for 1 h at 0 ºC, and finally for 3 h at rt. The reaction was quenched using aqueous sodium bicarbonate. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (10% K_2CO_3/Silica gel, 50:50 ethyl acetate:hexane), providing **S3** as a white solid (0.317 g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.88 (m, 1H), 3.79 (m, 1H), 3.66 (b, 2H), 2.30 (m, 1H), 1.87 (m, 7H), 1.62 (m, 19H), 1.27 (m, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 63.3, 56.1, 47.8, 39.3, 32.7, 29.5, 27.7, 27.3, 23.0 ppm.

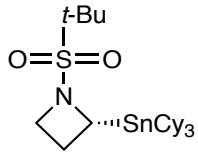


(*R*)-3-(((*R*)-*tert*-Butylsulfinyl)amino)-3-(tricyclohexylstannyl)propyl methanesulfonate (S4). Triethylamine (4.64 mmol, 4 equiv) was added to a solution of (*R*)-*N*-((*R*)-3-hydroxy-1-(tricyclohexylstannyl)propyl)-2-methylpropane-2-sulfinamide (**S3**) (1.16 mmol, 1.0 equiv) dissolved in anhydrous DCM (6 mL). The mixture was cooled to 0 ºC and mesyl chloride (2.32 mmol, 2.0 equiv) was then added under Ar. The mixture was stirred overnight, allowing it to warm to rt. The reaction was quenched with aqueous sodium bicarbonate. The reaction mixture was poured into a separatory fun-

nel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (10% K_2CO_3/Silica gel, 50:50 ethyl acetate:hexane), providing **S4** as a colorless oil (0.615g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.52 (m, 2H), 3.50 (m, 1H), 3.22 (d, J = 10.4 Hz, 1H), 3.14 (s, 0.8H), 3.09 (s, 2.2 H), 2.31 (m, 1H), 2.11 (m, 1H), 1.87 (m, 7H), 1.65 (m, 16H), 1.28 (m, 19H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 69.7, 56.4, 43.5, 37.3, 37.1, 34.0, 32.8, 31.3, 29.4, 29.0, 28.0, 27.2, 26.9, 23.0 ppm.

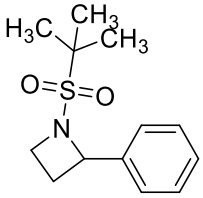


(*R*)-1-((*R*)-*tert*-Butylsulfinyl)-2-(tricyclohexylstannyl)azetidine (S5). A solution of **S4** (0.984 mmol, 1 equiv) in anhydrous THF (3 mL) was prepared under Ar and cooled to 0 ºC. To this mixture, LHMDS (2.95 mmol, 3.0 equiv, 1M in THF) was added dropwise. The mixture was stirred for 1 h at 0 ºC, and then overnight at rt. The reaction was quenched with water. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (10% K_2CO_3/Silica gel, 12:88 ethyl acetate:hexane), providing **S5** as a white solid (0.436 g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.75 (t, J = 9.9 Hz, 1H), 4.58 (m, 1H), 3.40 (m, 1H), 2.62 (m, 1H), 2.33 (m, 1H), 1.91 (m, 6H), 1.64 (m, 18H), 1.25 (m, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 57.1, 56.8, 47.6, 32.6, 29.4, 27.3, 25.1, 23.8 ppm.



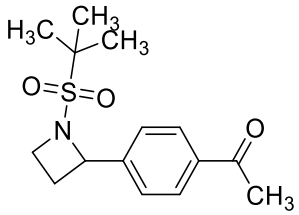
(*R*)-1-(*tert*-Butylsulfonyl)-2-(tricyclohexylstannyl)azetidine ((*R*)-9). A solution of **S5** (0.825 mmol, 1 equiv) in anhydrous DCM (2 mL) was cooled to 0 ºC. *m*CPBA (1.65 mmol, 2 equiv) was added, and the mixture was allowed to warm to rt where it was stirred for 1 h. The reaction was quenched with saturated aqueous solutions of sodium bicarbonate (4 mL) and sodium metabisulfite (3 mL). The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (10% K_2CO_3/Silica gel, 7:93 ethyl acetate:hexane), providing ***R*-9** as a white solid (0.384 g, 85%). The ee value (99.3% ee) was determined by HPLC analysis of the organic layer. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.84 (quintet, J = 8.5 Hz, 1H), 4.26 (m, 1H), 3.92 (q, J = 7.2 Hz, 1H), 2.44 (m, 2H), 1.94 (m, 6H), 1.65 (m, 18H), 1.31 (m, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 59.7, 55.5, 55.2, 32.7, 29.5, 28.0, 27.4, 24.6, 22.0 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 546.2431; Found 546.2453.

(*rac*)-1-(*tert*-Butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (*rac*-9). The procedure for **(*R*)-9** was employed using (*rac*)-*N*-(3-((*tert*-butyldimethylsilyl)oxy)propylidene)-2-methylpropane-2-sulfinamide (2.4 mmol) and tricyclohexyltin chloride (2 mmol). A white solid was obtained (217 mg, 20% for 5 steps).



1-(*tert*-Butylsulfonyl)-2-phenylazetidine (10a). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), bromobenzene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (19.5 mg, 77%) was isolated by flash column chromatography (5:95 to 10:90 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.34 (m, 3H), 5.41 (t, J = 8.34 Hz, 1H), 4.31 (q, *J* = 6.6 Hz, 1H), 3.63 (m, 1H), 2.57 (m, 1H), 2.39 (m, 1H), 1.63 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 128.6, 128.5, 127.7 , 65.1, 59.0, 48.4, 24.7, 23.9 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 254.1214; Found 254.1226.

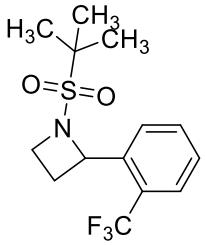
(*S*)-1-(*tert*-butylsulfonyl)-2-phenylazetidine ((*S*)-10a). The general procedure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), bromobenzene (0.05 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC (74% yield). The ee value (97% ee) was determined by HPLC analysis.



1-(4-(1-(*tert*-Butylsulfonyl)azetidin-2-yl)phenyl)ethan-1-one (10b). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 1-(4-iodophenyl)ethanone (0.05 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A pale yellow solid (8.8 mg, 60%) was isolated by flash column chromatography (20:80 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.3Hz, 2H), 5.46 (t, *J* = 8.4 Hz, 1H), 4.33 (q, *J* = 7.8 Hz, 1H), 3.65 (m, 1H), 2.60 (s, 3H), 2.37 (m, 1H), 1.19 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 146.4, 137.2, 128.8, 127.7, 64.2, 59.1, 48.8, 26.8, 24.7, 24.0 ppm. HRMS (ES^+): Calcd $(M-Na)^+$ 318.1140; Found 318.1141.

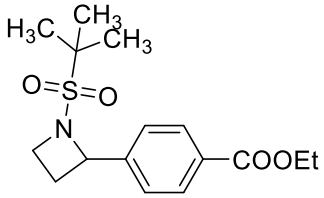
(*S*)-1-(4-(1-(*tert*-Butylsulfonyl)azetidin-2-yl)phenyl)ethan-1-one ((*S*)-10b). The general procedure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 1-(4-bromophenyl)ethanone (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (4.0 mL) at 110 ºC. A pale yellow

solid (21 mg, 72%) was isolated by flash column chromatography (20:80 ethyl acetate:hexane). The ee value (97% ee) was determined by HPLC analysis of the organic layer.



1-(*tert*-Butylsulfonyl)-2-(2-(trifluoromethyl)phenyl)azetidine (10c). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 2-(trifluoromethyl)bromobenzene (0.05 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A light yellow liquid (9.6 mg, 60%) was isolated by flash column chromatography (20:80 to 30:70 diethyl ether:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (d, J = 7.9 Hz, 1H), 7.62 (m, 2H), 7.38 (t, J = 7.8 Hz, 1H), 5.87 (t, J = 8.4Hz, 1H), 4.35 (q, J = 8.5 Hz, 1H), 3.69 (m, 1H), 2.69 (m, 1H), 2.13 (m, 1H), 1.33 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9, 132.3, 127.7, 126.0, 125.8, 27.19, 24.38 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 344.0908; Found 344.0903.

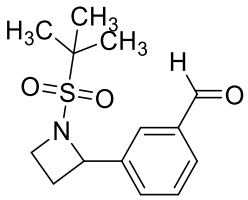
(*S*)-1-(*tert*-butylsulfonyl)-2-(2-(trifluoromethyl)phenyl)azetidine ((*S*)-10c). The general procedure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 2-(trifluoromethyl)bromobenzene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (4.0 mL) at 110 ºC. A light yellow liquid (23 mg, 78%) was isolated by flash column chromatography (20:80 to 30:70 diethyl ether: hexane). The ee value (92% ee) was determined by chiral GC analysis of the organic layer.



Ethyl 4-(1-(*tert*-butylsulfonyl)azetidin-2-yl)benzoate (10d). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), ethyl 4-bromobenzoate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (25 mg, 78%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.04 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5Hz, 2H), 5.46 (t, J = 8.5 Hz, 1H), 4.35 (m, 3H), 3.65 (m, 1H), 2.57 (m, 1H), 2.38 (m, 1H), 1.39 (t, J = 7.1Hz, 3H), 1.18 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 146.1, 130.6, 130.0, 127.5, 64.3, 61.2, 59.1, 24.7, 24.0, 14.5 ppm. HRMS (ES^+): Calcd $(M\text{-}H)^+$ 326.1426; Found 326.1425.

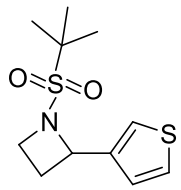
Ethyl (*S*)-4-(1-(*tert*-butylsulfonyl)azetidin-2-yl)benzoate ((*S*)-10d). The general

procedure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 4-bromobenzoate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (23 mg, 72%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). The ee value (98.6% ee) was determined by HPLC analysis of the organic layer.



3-(1-(*tert*-Butylsulfonyl)azetidin-2-yl)benzaldehyde (10e). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 3-bromobenzaldehyde (0.05 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A pale yellow solid (8.7 mg, 62%) was isolated by flash column chromatography (20:80 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.03 (s, 1H), 8.03 (t, *J* = 1.6, 1H), 7.82 (dt, *J* = 7.6, 1.7, 1H), 7.73 (dt, *J* = 7.7, 1.4, 1H), 7.54 (t, *J* = 7.6 , 1H), 5.50 (t, *J* = 8.4, 1H), 4.33 (q, *J* = 7.7 , 1H), 3.67 (m, 1H), 2.58 (m, 1H), 2.40 (m, 1H), 1.19 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 142.5, 136.9, 133.8, 130.0, 129.4, 128.3, 64.0, 59.2, 48.8, 24.6, 24.0 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 304.0983; Found 304.1010.

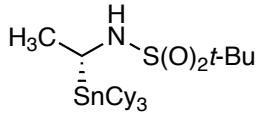
(*S*)-3-(1-(*tert*-Butylsulfonyl)azetidin-2-yl)benzaldehyde ((*S*)-10e). The general procedure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 3-bromobenzaldehyde (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (4.0 mL) at 110 ºC. A pale yellow solid (14.5 mg, 51%) was isolated by flash column chromatography (20:80 ethyl acetate:hexane). The ee value (97.7% ee) was determined by HPLC analysis of the organic layer.



1-(*tert*-Butylsulfonyl)-2-(thiophen-3-yl)azetidine (10f). The general procedure for cross-coupling reactions was employed using 1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 3-bromothiophene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (14 mg, 54%) was isolated by flash column chromatography (20:80 diethyl ether:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (m, 3H), 5.50 (t, *J* = 8.4 Hz, 1H), 4.28 (q, *J* = 7.7 Hz, 1H), 3.59 (m, 1H), 2.56 (m, 2H), 1.12 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.8, 126.7, 126.4, 123.8, 60.3, 59.1, 48.2, 24.0, 23.8 ppm. HRMS (ES^+): Calcd $(M\text{-}H)^+$ 260.0778; Found 260.0728.

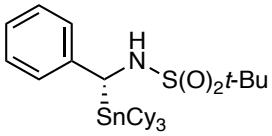
(*S*)-1-(tert-butylsulfonyl)-2-(thiophen-3-yl)azetidine ((*S*)-10f). The general proce-

dure for cross-coupling reactions was employed using (*R*)-1-(*tert*-butylsulfonyl)-2-(tricyclohexylstannyl)azetidine (1.1 equiv), 3-bromothiophene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (0.5 equiv), and KF (2.0 equiv) in toluene (4.0 mL) at 110 ºC. A pale yellow solid (9.5 mg, 37%) was isolated by flash column chromatography (20:80 diethyl ether:hexane). The ee value (89% ee) was determined by chiral GC analysis.



(*R*)-2-Methyl-N-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide ((*R*)-11a). In a round-bottom flask under argon, a solution of tricyclohexyltin chloride (2 mmol, 1.0 equiv), naphthalene (1.0 mmol, 0.5 equiv) and lithium (20 mmol, 10 equiv) in anhydrous THF (8 mL) were stirred until the solution turned black. Then the solution was stirred for an additional 5 h to generate tricyclohexyltin lithium solution. To a solution of (*R*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (2.6 mmol, 1.3 equiv) in THF (6 mL) which was under Ar and cooled to -78 ºC, tricyclohexyltin lithium solution (2 mmol, 1.0 equiv) was added. The mixture was allowed to stir at -78 ºC for 1 h. The solution was quenched with methanol followed by water at -78 ºC. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product, (*R*)-2-methyl-*N*-((*R*)-1-(tricyclohexylstannyl)ethyl)propane-2-sulfinamide. *m*CPBA (4 mmol, 2 equiv) was added to (*R*)-2-methyl-*N*-((*R*)-1-(tricyclohexylstannyl)ethyl)propane-2-sulfinamide dissolved in anhydrous DCM (1.5 mL) at 0 ºC. The mixture was stirred for 1 h at rt. The reaction was quenched with saturated aqueous solutions of sodium bicarbonate (4 mL) and sodium metabisulfite (3 mL). The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 4:96 to 6:94 ethyl acetate:hexane), providing **(*R*)-11a** as a white solid (0.605 g, 57% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68 (d, J = 10.2 Hz, 1H), 3.52 (m, 1H), 1.90 (m, 6H), 1.62 (m, 21H), 1.39 (s, 9H) 1.7 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 59.6, 39.6, 32.6, 29.4, 27.5, 27.2, 24.6, 24.4 ppm. HRMS (ES^+): Calcd $(M-H)^+$ 534.2431; Found 534.2438 The ee value (99.8 % ee) was determined by HPLC analysis.

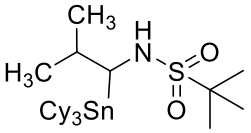
(*rac*)-2-Methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (11a). The procedure for **(*R*)-11a** was applied using (*rac*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (2.6 mmol). A white solid (0.565 g, 53%) was isolated.



(*R*)-2-Methyl-*N*-(phenyl(tricyclohexylstannyl)methyl)propane-2-sulfonamide ((*R*)-11b). In a round-bottom flask under argon, a solution of tricyclohexyltin chlo-

ride (3 mmol, 1.0 equiv), naphthalene (1.5 mmol, 0.5 equiv) and lithium (30 mmol, 10 equiv) in anhydrous THF (12 mL) were stirred until the solution turned black. Then the solution was stirred for an additional 5 h to generate tricyclohexyltin lithium solution. To a solution of (*R*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (3.6 mmol, 1.2 equiv) in THF (10 mL) which was under Ar and cooled to -78 ºC, tricyclohexyltin lithium solution (3 mmol, 1.0 equiv) was added. The mixture was allowed to stir at -78 ºC for 1 h. The solution was quenched with methanol followed by water at -78 ºC. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 20:80 ethyl acetate:hexane), providing crude (*R*)-2-methyl-*N*-((*R*)-phenyl(tricyclohexylstannyl)methyl)propane-2-sulfinamide. *m*CPBA (6 mmol, 2 equiv) was added to (*R*)-2-methyl-*N*-((*R*)-phenyl(tricyclohexylstannyl)methyl)propane-2-sulfinamide dissolved in anhydrous DCM (3 mL) at 0 ºC. The mixture was stirred for 1 h at rt. The reaction was quenched with saturated aqueous solutions of sodium bicarbonate (4 mL) and sodium metabisulfite (3 mL). The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (10% K_2CO_3/silica gel, 5:95 ethyl acetate: hexane) to afford **(*R*)-11b** as a white solid (482 mg, 27% for 2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26 (m, 2H),7.07 (m, 3H), 4.96 (d, *J* = 8.9 Hz, 1H), 4.47 (d, *J* = 8.9 Hz, 1H), 1.71 (m, 12H), 1.5 (m, 6H), 1.22 (m, 14H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.9, 128.7, 124.8, 59.6, 47.6, 32.3, 29.3, 28.6, 27.1, 24.3 ppm. HRMS (ES$^+$): Calcd $(M-H)^+$ 596.2588; Found 596.2582. The ee value (98% ee) was determined by chiral HPLC analysis.

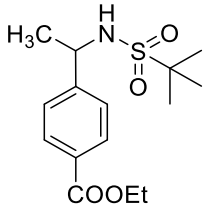
(*rac*)-2-Methyl-*N*-(phenyl(tricyclohexylstannyl)methyl)propane-2-sulfonamide (11b). The procedure for **(*R*)-11b** was employed using (*rac*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (4.8 mmol, 1.2 equiv). After oxidation by *m*CPBA, a white solid was isolated (515 mg, 28%).



(*R*)-2-methyl-N-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide ((*R*)-11c). At room temperature, the solution of tricyclohexyltin chloride (1 mmol, 1.0 equiv), naphthalene (0.5 mmol, 0.5 equiv) and lithium (10 mmol, 10 equiv.) in anhydrous THF (9 mL) was stirred until the solution turned black under Ar. The solution was further stirred for 5 h to generate the tricyclohexyltin lithium solution. At -78 ºC, the tricyclohexyltin lithium solution (1 mmol, 1.0 equiv) was then added to the solution of (R)-2-methyl-N-(2-methylpropylidene)propane-2-sulfinamide (1.3 mmol, 1.3 equiv) in THF (5 mL) under Ar and allowed to stir at -78 ºC for 1 h. The solution was quenched with methanol followed by water at -78 ºC. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Sol-

vent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 15:85 to 20:80 ethyl acetate: hexane) to get (*R*)-2-methyl-*N*-((*R*)-2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfinamide. The white solid (0.288 g, 52.8%) was isolated. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.50 (m, 1H), 3.36 (m, 1H), 2.36 (m, 1H), 1.64 (m, 32H), 1.21 (s, 9H), 1.16 (m, 2H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 58.2, 56.1, 34.2, 32.5, 29.6, 28.3, 27.3, 22.8, 21.8, 20.9 ppm. mCPBA (1.9 mmol, 2 equiv) was added to (*R*)-2-methyl-*N*-((*R*)-2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfinamide (0.975 mmol) dissolved in anhydrous DCM (6 mL) at 0 ºC. The mixture was stirred for 1 h at room temperature and subsequently quenched with a aqueous solution containing both sodium bicarbonate and sodium metabisulfite. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 10:90 ethyl acetate:hexane) to get (*R*)-2-methyl-*N*-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide. The white solid (437 mg, 80%) was isolated. The overall yield for the 2 steps is 41%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.72 (m, 2H), 2.25 (m, 1H), 1.75 (m, 24H), ppm. 1.40 (s, 9H), 1.24 (m, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ 59.7, 53.9, 34.2 32.6, 29.6, 28.7, 27.3, 24.5, 21.5, 20.8 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 584.2564; Found 584.2590. The ee value (98 % ee) was determined by HPLC analysis.

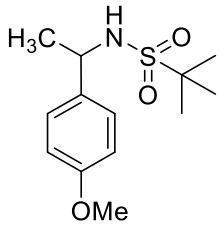
(*rac*)-2-methyl-N-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide (11c). The procedure for (*R*)-2-methyl-*N*-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide was applied using tricyclohexyltin lithium solution (1 mmol) and (*rac*)-*N*-ethylidene-2-methylpropane-2-sulfinamide (1.3 mmol). A white solid (0.235 g, 42%) was isolated.



Ethyl 4-(1-((1,1-dimethylethyl)sulfonamido)ethyl)benzoate (12a). The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (1.2 equiv), ethyl 4-bromobenzoate (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (53.3 mg, 85%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.4 Hz, 2H), 4.73 (m, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 4.18 (d, *J* = 8.9 Hz, 1H), 1.58 (d, *J* = 6.9 Hz, 3H), 1.39 (t, J = 7.1 Hz, 3H), 1.31 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 148.9, 130.2, 129.7, 126.1, 61.1, 59.9, 54.4, 25.6, 24.3, 14.4 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 336.1245; Found 336.1257.

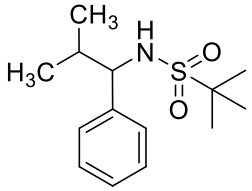
Ethyl (*S*)-4-(1-((1,1-dimethylethyl)sulfonamido)ethyl)benzoate ((*S*)-12a). The

general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl) propane-2-sulfonamide (1.2 equiv), 4-bromobenzoate (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (46.3 mg, 74%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). The ee value (99% ee) was determined by chiral HPLC analysis.



***N*-(1-(4-Methoxyphenyl)ethyl)-2-methylpropane-2-sulfonamide (12b).** The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (1.2 equiv), 4-bromoanisole (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (34 mg, 64%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (m, 2H), 6.88 (m, 2H), 4.63 (m, 1H), 4.04 (d, J = 4.8 Hz, 1H), 3.80 (s, 3H), 1.56 (d, J = 6.8Hz, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.0, 136.0, 127.3, 114.2, 59.8, 55.4, 54.1, 25.6, 24.3 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 294.1140; Found 294.1149.

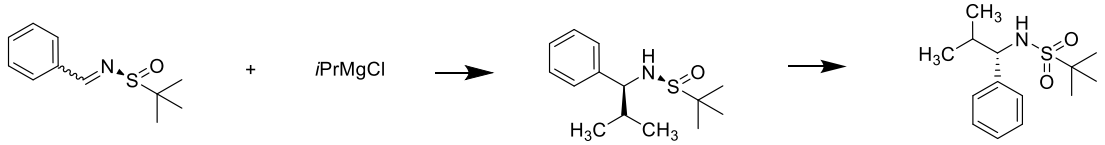
(*S*)-*N*-(1-(4-Methoxyphenyl)ethyl)-2-methylpropane-2-sulfonamide ((*S*)-12b). The general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl) propane-2-sulfonamide (1.2 equiv), 4-bromoanisole (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (31 mg, 58%) was isolated by flash column chromatography (15:85 ethyl acetate:hexane). The ee value (95.5% ee) was determined by chiral HPLC analysis.



2-Methyl-*N*-(2-methyl-1-phenylpropyl)propane-2-sulfonamide (12c). The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide (1.2 equiv), bromobenzene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A white solid (16.7 mg, 62%) was isolated by flash column chromatography (5:95 to 15:85 ethyl acetate:hexane) . ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 3H), 7.16 (m, 2H), 4.26 (m, 2H), 1.95 (m, 1H), 1.22 (s, 9H), 0.99 (d, J = 6.7Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.9, 128.5, 127.4, 127.0, 64.6, 59.9, 35.9, 33.9, 31.2, 28.9, 26.9, 24.3, 19.7, 18.9

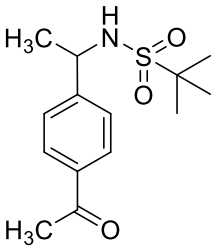
ppm. Calcd $(M-H)^+$ 270.1528; Found 270.1501.

(*S*)-2-Methyl-*N*-(2-methyl-1-phenylpropyl)propane-2-sulfonamide ((*S*)-12c). The general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(2-methyl-1-(tricyclohexylstannyl)propyl)propane-2-sulfonamide (1.2 equiv), bromobenzene (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A white solid (18.3 mg, 68%) was isolated. The ee value (80% ee) was determined by specific rotation. $[\alpha]_D^{20}$ = -24.49 (*c* 0.245 $CHCl_3$) [preparation of reference compound below].



At -78 ºC, *i*PrMgCl (2 equiv, in THF) was added dropwise to a solution of (*S*)-*N*-benzylidene-2-methylpropane-2-sulfinamide (0.5 mmol, 1 equiv) in anhydrous diethyl ether (1 mL) under Ar. The reaction mixture was stirred for 1.5 h at -78 ºC, followed by the addition of methanol (0.2 mL). The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure to provide the crude product. The crude reaction product was purified by flash column chromatography (1:2 ethyl acetate:hexane) to get (*S*)-2-methyl-*N*-((*S*)-2-methyl-1-phenylpropyl)propane-2-sulfinamide. A white solid (0.108 g, 85%) was isolated. The ^1H NMR was identical to the literature.[4] The product was determined to be 61.3% ee by HPLC (IA, *i*PrOH/hexane 5/95, 0.6 mL/min, t = (*R*) 10.9 min, (*S*) 16.2 min).

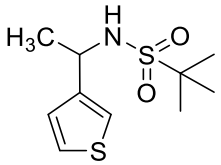
mCPBA (0.4 mmol, 2 equiv) was added to (*S*)-2-methyl-*N*-((*S*)-2-methyl-1-phenylpropyl)propane-2-sulfinamide (0.2 mmol) dissolved in anhydrous DCM (1.5 mL) at 0 ºC. The mixture was stirred for 1 h at rt and subsequently quenched with a aqueous solution containing both sodium bicarbonate and sodium metabisulfite. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction product was purified by flash column chromatography (15:85 ethyl acetate:hexane) to get (*S*)-2-methyl-*N*-(2-methyl-1-phenylpropyl)propane-2-sulfonamide. A white solid (52.7 mg, 95%) was isolated. $[\alpha]_D^{20}$ = -18.8 (*c* 0.25 $CHCl_3$) corresponds to 61% ee from previous reaction.



***N*-(1-(4-Acetylphenyl)ethyl)-2-methylpropane-2-sulfonamide (12d).** The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (1.2 equiv), 1-(4-

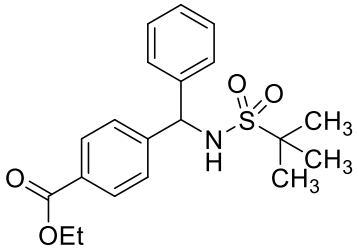
iodophenyl)ethan-1-one (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale white solid (36.8 mg, 65%) was isolated by flash column chromatography (20:80 ethyl acetate: hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (d, J = 8.4Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.73 (m, 1H), 4.24 (br, 1H), 2.60 (s, 3H), 1.58 (d, J = 6.9Hz, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 149.2, 136.4, 129.1, 126.3, 60.0, 54.4, 26.8, 25.5, 24.3 ppm. HRMS (ES^+): HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 306.1140; Found 306.1159.

(*S*)-*N*-(1-(4-acetylphenyl)ethyl)-2-methylpropane-2-sulfonamide ((*S*)-12d). The general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (1.2 equiv), 1-(4-bromophenyl)ethan-1-one (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (0.5 mL) at 110 ºC. A white solid (18.3 mg, 64.5%) was isolated. The ee value (99% ee) was determined by chiral HPLC analysis.



2-Methyl-*N*-(1-(thiophen-3-yl)ethyl)propane-2-sulfonamide (12e). The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (1.2 equiv), 3-bromothiophene (0.2 mmol) $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (24 mg, 48%) was isolated by flash column chromatography (35:65 diethyl ether:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 1H), 7.17 (m, 1H), 7.08 (m, 1H), 4.74 (m, 1H), 3.96 (d, J = 9.6 Hz, 1H), 1.61 (d, J = 6.8 Hz, 3H), 1.37 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.9, 126.7, 126.2, 120.9, 60.0, 50.7, 24.7, 24.3 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 270.0598; Found 270.0618.

(*S*)-2-Methyl-*N*-(1-(thiophen-3-yl)ethyl)propane-2-sulfonamide ((*S*)-12e). The general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl) propane-2-sulfonamide (1.2 equiv), 3-bromothiophene (0.2 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A pale yellow solid (22 mg, 44%) was isolated by flash column chromatography (35:65 diethyl ether:hexane). The ee value (98.5% ee) was determined by chiral HPLC analysis.

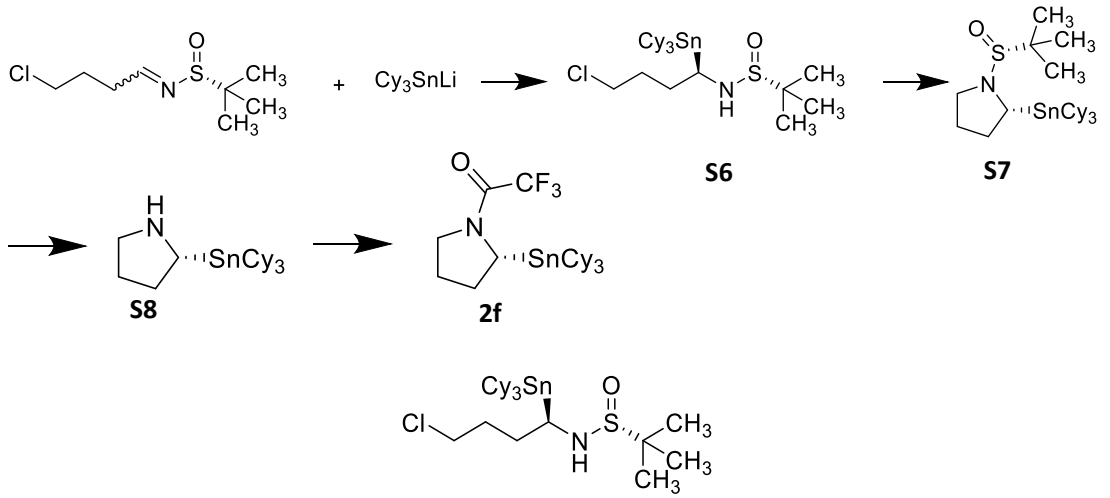


Ethyl 4-(((1,1-dimethylethyl)sulfonamido)(phenyl)methyl)benzoate (12f). The general procedure for cross-coupling reactions was employed using 2-methyl-*N*-

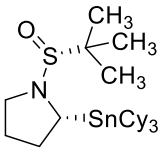
(phenyl(tricyclohexylstannyl)methyl)propane-2-sulfonamide (1.2 equiv), ethyl 4-bromobenzoate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A white solid (28 mg, 75%) was isolated by flash column chromatography (5:95 to 15:85 ethyl acetate:hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (m, 2H), 7.36 (m, 2H), 7.24 (m, 2H), 5.83 (d, J = 9.2 Hz, 1H), 4.56 (d, J = 9.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H), 1.32 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 146.9, 141.4, 130.2, 129.1, 128.1, 127.6, 127.5, 61.6, 61.2, 60.3, 24.3, 14.5 ppm. HRMS (ES^+): Calcd $(M\text{-}Na)^+$ 398.1402; Found 398.1414.

Ethyl (*S*)-4-(((1,1-dimethylethyl)sulfonamido)(phenyl)methyl)benzoate ((*S*)-12f). The general procedure for cross-coupling reactions was employed using (*R*)-2-methyl-*N*-(phenyl(tricyclohexylstannyl)methyl)propane-2-sulfonamide (1.2 equiv), ethyl 4-bromobenzoate (0.1 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (10 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in toluene (1.0 mL) at 110 ºC. A white solid (32.3 mg, 86%) was isolated. The ee value (98% ee) was determined by chiral HPLC analysis.

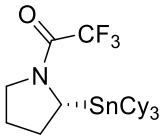
*Preparation of (R)-**2f** using Ellman auxiliary strategy:*



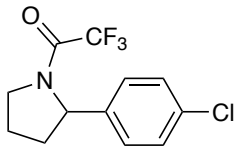
(*R*)-*N*-((*R*)-4-Chloro-1-(tricyclohexylstannyl)butyl)-2-methylpropane-2-sulfinamide (S6). In a round-bottom flask under argon, a solution of tricyclohexyltin chloride (2.2 mmol, 1.0 equiv), naphthalene (1.1 mmol, 0.5 equiv) and lithium (22 mmol, 10 equiv) in anhydrous THF (8 mL) were stirred until the solution turned black. Then the solution was stirred for an additional 5 h to generate tricyclohexyltin lithium solution. To a solution of (*R*)-*N*-(4-chlorobutylidene)-2-methylpropane-2-sulfinamide (2.86 mmol, 1.3 equiv) in THF (6 mL) which was under Ar and cooled to -78 ºC, the tricyclohexyltin lithium solution was added. The mixture was allowed to stir at -78 ºC for 1 h. The solution was quenched with methanol followed by water at -78 ºC. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 5:95 to 10:90 ethyl acetate:hexane), providing **S6** (0.496 g, 39%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.57 (t, J = 6.6 Hz, 2H), 3.45 (m, 1H), 2.23 (d, J = 10.6 Hz, 1H), 1.68 (m, 29H), 1.23 (m, 17H) ppm. ^{13}C NMR δ 55.8, 48.6, 44.8, 36.9, 32.4, 29.3, 27.7, 27.1, 25.6, 22.6 ppm.



(*R*)-1-((*R*)-*tert*-Butylsulfinyl)-2-(tricyclohexylstannyl)pyrrolidine (S7). A solution of **S6** (428 mg, 0.74 mmol) in anhydrous THF (1 mL) was prepared under Ar and cooled to 0 ºC. To this mixture, LHMDS (2.22 mmol, 3.0 equiv, 1M in THF) was added dropwise. The mixture was stirred for 1 h at 0 ºC, and then overnight at rt. The reaction was quenched with water. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. The reaction mixture was poured into a separatory funnel containing a mixture of water and diethyl ether. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 15:85 to 20:80 ethyl acetate:hexane), providing **S7** (0.272 g, 68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (m, 1H), 3.59 (m, 1H), 3.27 (m, 1H), 2.23 (m, 1H), 1.92 (m, 9H), 1.67 (m, 17H), 1.28 (m, 19H) ppm. ^{13}C NMR δ 57.6, 56.0, 41.8, 32.6, 31.1, 29.6, 29.0, 27.9, 27.3, 26.9, 25.5, 24.5 ppm. (1-*tert*-butylsulfonylpyrrolidin-2-yl)-tricyclohexyl-stannane **(2d)** was prepared using **S7** (1.0 equiv) and *m*CPBA (1.5 equiv) in anhydrous DCM). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (m, 1H), 3.59 (m, 1H), 3.27 (m, 1H), 2.23 (m, 1H), 1.92 (m, 9H), 1.67 (m, 17H), 1.28 (m, 19H) ppm.

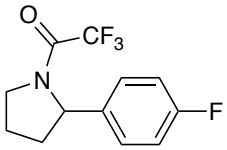


(*R*)-2,2,2-Trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethanone (2f). (*R*)-1-((*R*)-*tert*-butylsulfinyl)-2-(tricyclohexylstannyl)pyrrolidine (**S7**) (0.16 mmol, 1 equiv) and anhydrous $ZnCl_2$ (0.064 mmol, 0.4 equiv) were added to a round-bottom flask. After the flask was evacuated and backfilled with argon, anhydrous DCM (1 mL) was added. Thiophenol (0.48 mmol, 3 equiv) was then added to the solution at rt. After the solution was stirred for 24 h, it was quenched by NaOH (2 mL, 2M, aq.) and extracted by diether ether (1 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure to get the crude product, (R)-2-(tricyclohexylstannyl)pyrrolidine (**S8**). To the crude product, triethylamine (0.8 mmol, 5.0 equiv) and anhydrous DCM (1 mL) were added. The reaction mixture was cooled to 0 ºC, and trifluoroacetic anhydride (TFAA, 0.64 mmol, 4 equiv) was added. The reaction mixture was stirred for 10 min at 0 ºC, and then overnight at rt. The reaction mixture was poured into a separatory funnel containing a mixture of water and DCM. The organic layer was separated, washed with brine, dried over Na_2SO_4, and filtered. Solvent was removed under reduced pressure and dried *in vacuo* to provide the crude product. The crude reaction products were purified by flash column chromatography (10% K_2CO_3/Silica gel, 5:95 ethyl acetate:hexane), providing **2f** as a white solid (14.6 mg, 18% for 2 steps). The ee value (98% ee) was determined by chiral HPLC analysis. The (*R*)-enantiomer was generated, which is consistent with the anticipated stereoinduction from the (*R*)-enantiomer of Ellman's sulfonamide, and based upon the crystal structure below.



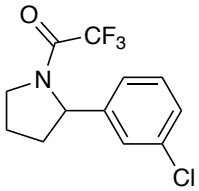
1-[2-(4-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-chlorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow oil (44.3 mg, 64%) was isolated. ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.11 (m, 2H), 5.31 (m, 0.25H), 5.18 (m, 0.75H), 3.91 (m, 2H), 2.40 (m, 1H), 2.07 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (m), 140.67(minor), 139.7 (major), 133.0 (major), 128.8 (major), 126.8 (major), 126.2 (minor), 122.0 (minor), 118.2 (major), 114.3 (major), 110.5 (minor), 62.0 (major), 61.1 (minor), 48.7 (major), 47.6 (major), 35.9 (major), 33.5 (major), 24.1 (major), 20.0 (major) ppm.

(*S*)-1-[2-(4-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-chlorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow oil (42.0 mg, 61%) was isolated. The ee value (95.4% ee) was determined by HPLC analysis of the organic layer.



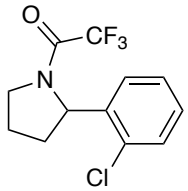
1-[2-(4-fluorophenyl)-1-pyrrolidinyl]- 2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-fluorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow viscous oil (40.8 mg, 63%) was isolated. ^1H NMR (300 MHz, $CDCl_3$): δ 7.14 (m, 1.50H), 7.11 (m, 2.31H), 5.32 (m, 0.25H), 5.22 (m, 0.75H), 3.93 (m, 2H), 2.41 (m, 1H), 2.08 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.7, 160.4, 155.9 (m), 138.0(minor), 137.0 (major), 127.2 (major), 126.5 (minor), 122.1 (minor), 118.3 (minor), 115.8 (major), 114.5 (minor), 110.7 (minor), 62.0 (major), 61.1 (minor), 48.5 (minor), 47.6 (major), 36.2 (minor), 33.7 (major), 24.3 (major), 20.1 (major) ppm.

(*S*)-1-[2-(4-fluorophenyl)-1-pyrrolidinyl]- 2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-4-fluorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow oil (38.5 mg, 59%) was isolated. The ee value (94.8% ee) was determined by HPLC analysis of the organic layer.



1-[2-(3-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-chloro-3-iodobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A dark brown solid (42.9 mg, 62%) was isolated. ^1H NMR (300 MHz, $CDCl_3$): δ 7.31 (m, 0.8H), 7.24 (m, 1H), 7.13 (m, 1.7H), 5.30 (m, 0.27H), 5.19 (m, 0.73H), 3.93 (m, 2H), 2.42 (m, 1H), 2.12 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.3 (minor), 143.3 (major), 134.7 (major), 130.1 (major), 125.7 (major), 125.2 (minor), 123.7 (major), 123.1 (minor), 62.1 (major), 61.2 (minor), 47.8 (minor), 47.7 (major), 36.0 (minor), 33.6 (major), 24.3 (major), 20.2 (major) ppm.

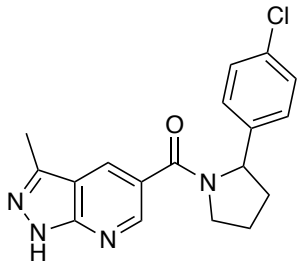
(*S*)-1-[2-(3-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-chloro-3-iodobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow solid (41.5 mg, 60%) was isolated. The ee value (91% ee) was determined by HPLC analysis of the organic layer.



1-[2-(2-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using 2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-2-chlorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow oil (51.2 mg, 74%) was isolated. ^1H NMR (300 MHz, $CDCl_3$): δ 7.41 (m, 1.0H), 7.24 (m, 1.86H), 6.99(m, 1.0H), 5.63 (m, 0.31H), 5.53 (m, 0.69H), 4.01 (m, 2H), 2.46 (m, 1H), 2.06 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7 (m), 139.6 (minor), 138.3 (major), 132.2 (major), 131.2 (minor), 130.2 (major), 130.1 (minor), 128.8 (minor), 128.6 (major), 127.1 (major), 127.0 (minor), 126.0 (minor), 125.4 (major), 122.1 (minor), 118.3 (major), 118.0 (minor), 114.5 (major), 114.2 (minor), 110.7 (minor), 60.3 (major), 59.5 (minor), 48.0 (minor), 47.9 (major), 34.0 (minor), 31.8 (major), 24.08 (major), 20.1 (major) ppm.

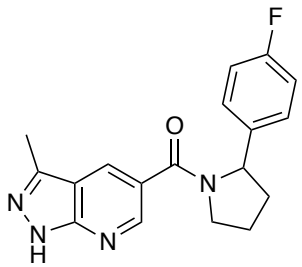
(*S*)-1-[2-(3-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone. General procedure for cross-coupling reactions was employed using (*R*)-2,2,2-trifluoro-1-(2-(tricyclohexylstannyl)pyrrolidin-1-yl)ethan-1-one (1.3 equiv), 1-bromo-2-chlorobenzene (0.25 mmol), $Pd(dba)_2$ (5 mol %), JackiePhos (15 mol %), CuCl (2.0 equiv), and KF (2.0 equiv) in CH_3OH (1.0 mL) at 90 °C. A light yellow oil (45.7 mg, 66%) was isolated. The ee value (91% ee) was determined by HPLC analysis of the

organic layer.



[2-(4-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone.[1] General procedure for the synthesis of CDK8 inhibitors was employed using 1-[2-(4-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-methylmorpholine (26.4 µl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow solid (22 mg) was isolated. The overall yield for 2 steps is 81%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.51-13.19 (m, 1.0H), 8.76-6.96 (m, 6H), 5.25-4.95 (m, 1H), 4.03-3.51 (m, 2H), 2.62-2.28 (m, 4H), 2.00-1.68 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 152.4, 148.1, 146.9, 143.0, 142.1, 130.9, 129.1, 128.1, 127.6, 124.9, 112.8, 60.4, 50.7, 34.8, 24.9, 12.2 ppm.[5]

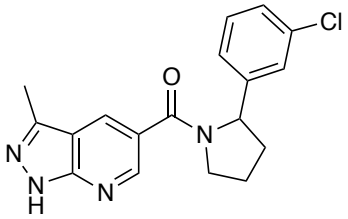
[(2*S*)-2-(4-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using (*S*)-1-[2-(4-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 µl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow solid (20 mg) was isolated. The overall yield for 2 steps is 59%. The ee value (96.2% ee) was determined by HPLC analysis of the organic layer.



[2-(4-fluorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using 1-[2-(4-fluorophenyl)-1-pyrrolidinyl]- 2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 µl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (10.8 mg) was isolated. The overall yield for 2 steps is 42%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.43 (m, 1.0H), 8.70 (s, 0.73H), 8.53 (s, 0.76H), 8.23 (0.34H), 7.89 (0.33H), 7.44 (1.53H), 7.17-7.04 (m, 2.91H), 5.20 (m, 0.77H), 5.03 (s, 0.33H), 3.99 (m, 0.77H), 3.81 (s, 0.63H), 3.58 (m, 0.93H), 2.55 (s, 2.10H), 2.39-2.35H (m, 2.09H), 1.91-1.73 (m,

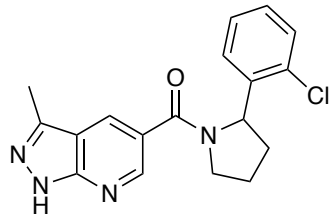
3.37H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0, 167.3, 162.5, 159.3, 152.4, 148.2, 142.2, 140.1, 129.1, 127.6, 125.0, 115.0, 114.7, 112.9, 60.3, 50.7, 36.0, 34.9, 24.9, 21.6, 12.2 ppm.

[(2*S*)-2-(4-fluorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using (*S*)-1-[2-(4-fluorophenyl)-1-pyrrolidinyl]- 2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 μl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (12.9 mg) was isolated. The overall yield for 2 steps is 50%. The ee value (96% ee) was determined by HPLC analysis of the organic layer.



[2-(3-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using 1-[2-(3-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 μl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (19.4 mg) was isolated. The overall yield for 2 steps is 71%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.44 (m, 1.0H), 8.73 (s, 0.73H), 8.57 (s, 0.73H), 8.25 (0.26H), 7.88 (0.26H), 7.47-7.04 (m, 4H), 5.18 (m, 0.78H), 5.04 (s, 0.29H), 4.04 (m, 0.84H), 3.83 (s, 0.56H), 3.59 (m, 0.82H), 2.56 (s, 2.03H), 2.42 (m, 1.75H), 1.95 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 152.4, 148.2, 146.7, 142.3, 133.0, 130.2, 129.3, 126.5, 125.7, 124.8, 124.4, 112.9, 79.2, 60.7, 50.8, 34.9, 25.0, 12.2 ppm.

[(2*S*)-2-(3-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using (*S*)-1-[2-(3-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 μl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (15.5 mg) was isolated. The overall yield for 2 steps is 57%. The ee value (94% ee) was determined by HPLC analysis of the organic layer.

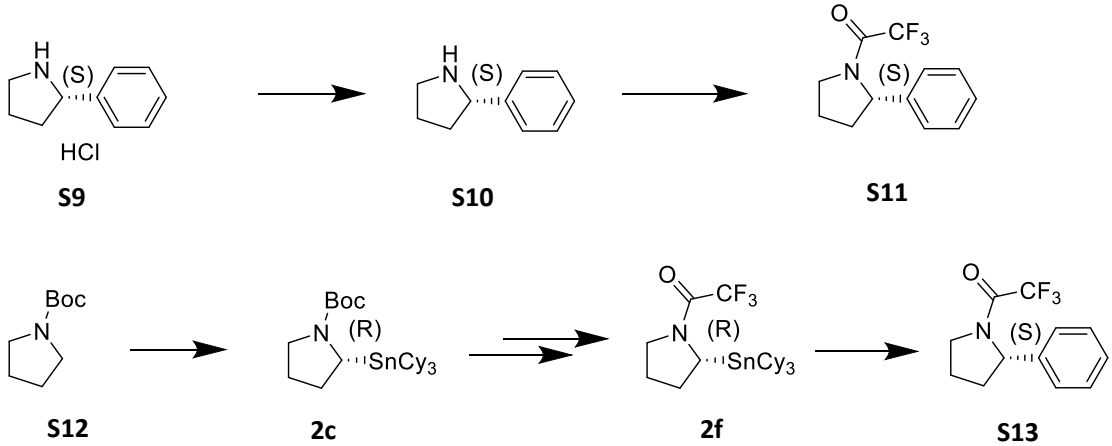


[2-(2-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using 1-[2-(2-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 μl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (18.7 mg) was isolated. The overall yield for 2 steps is 69%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.44 (m, 1.0H), 8.72 (s, 0.67H), 8.58 (s, 0.65H), 8.24 (0.29H), 7.90 (0.30H), 7.57-7.44 (m, 1.37), 7.37-7.22 (m, 2.23H), 5.48-5.43 (m, 0.71H), 5.30 (m, 0.29H), 4.04 (m, 0.72H), 3.87 (m, 0.54H), 3.65 (m, 0.73H), 2.56 (s, 1.85H), 2.47-2.28 (m, 1.58H), 2.04-1.84 (m, 2H), 1.75-1.66 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 152.4, 148.2, 142.3, 141.0, 131.2, 128.3, 127.6, 127.5, 126.5, 124.9, 112.9, 79.2, 60.4, 58.6, 50.7, 47.7, 34.0, 32.8, 24.7, 12.3 ppm.

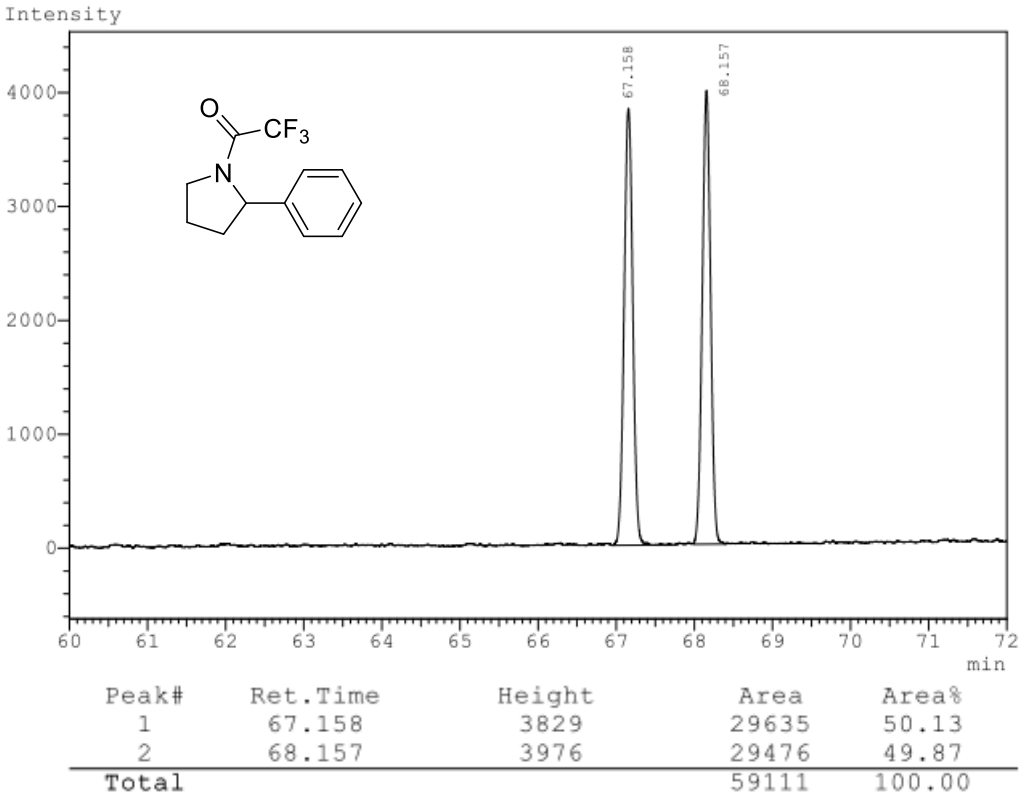
[(2*S*)-2-(2-chlorophenyl)-1-pyrrolidinyl](3-methyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)-methanone. General procedure for the synthesis of CDK8 inhibitors was employed using (*S*)-1-[2-(2-chlorophenyl)-1-pyrrolidinyl]-2,2,2-trifluoro-ethanone (1 equiv.), KOH (0.2 mmol); as well as 3-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid (0.08 mmol), *N*-(3-(dimethylamino)propyl)-*N*'-ethylcarbodiimide (0.16 mmol), and 1-hydroxybenzotriazole hydrate (0.08 mmol), 4-Methylmorpholine (26.4 μl, 0.24 mmol) in *N,N*-dimethylformamide (0.4 mL) at rt. A light yellow oil (17.6 mg) was isolated. The overall yield for 2 steps is 65%. The ee value (92% ee) was determined by HPLC analysis of the organic layer.

4. Mechanistic Investigations

Investigation of stereochemistry of transmetallation.

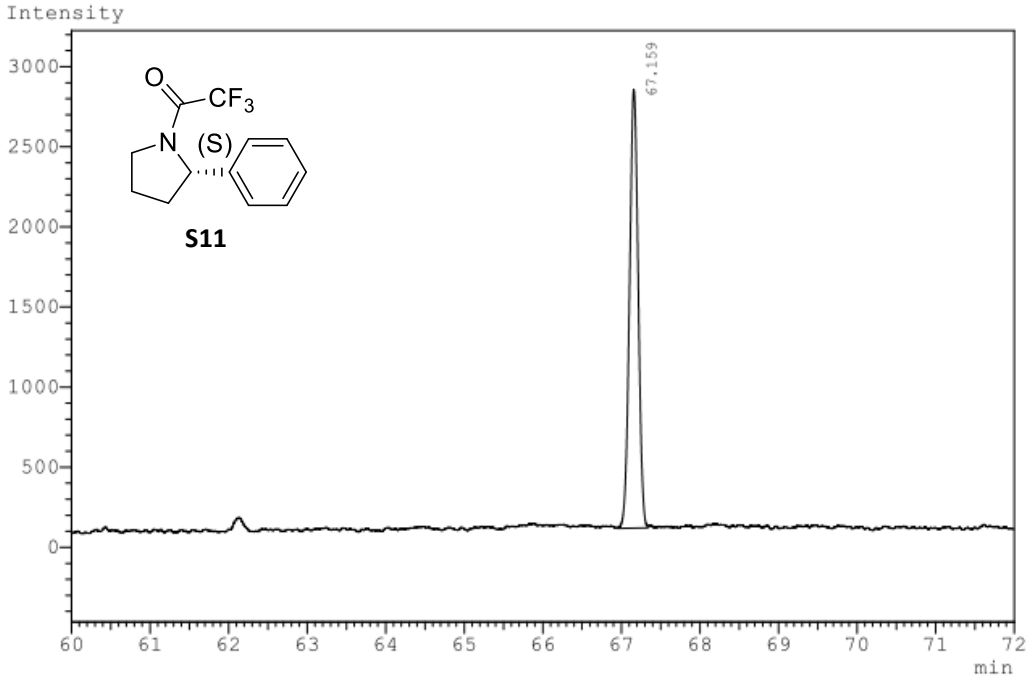


An aqueous solution of (*S*)-2-phenylpyrrolidine hydrochloride (**S9**) (15.5 mg, 0.08 mmol) and $NaHCO_3$ (0.32 mmol, 4 equiv) was stirred for 4 h at rt. The reaction mixture was extracted with diethyl ether (1 mL x 3). The combined organic layers were washed with brine (10 mL), and dried over Na_2SO_4. The organic layer was filtered, and concentrated under reduced pressure providing free base (*S*)-2-phenylpyrrolidine (**S10**). To the flask containing **S10**, dry DCM (1 mL) and triethylamine (0.24 mmol, 3 equiv) were added. The reaction flask was cooled to 0 ºC, and TFAA (0.16 mmol, 2 equiv) was added dropwise. The reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture (**S11**) was washed with water, and chiral GC was used to analyze the organic layer. Compound **S13** was also prepared using the general procedure for cross-coupling reactions, with bromobenzene and **2f**.

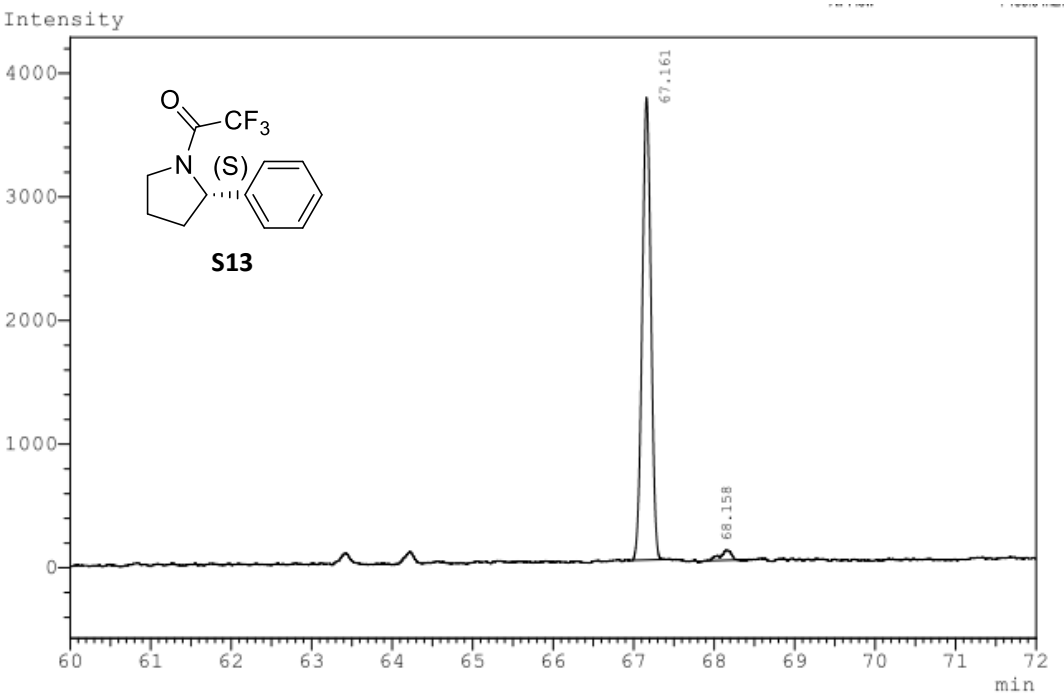


Peak#	Ret.Time	Height	Area	Area%
1	67.158	3829	29635	50.13
2	68.157	3976	29476	49.87
Total			59111	100.00

Figure S3. GC trace of racemic **S11**.

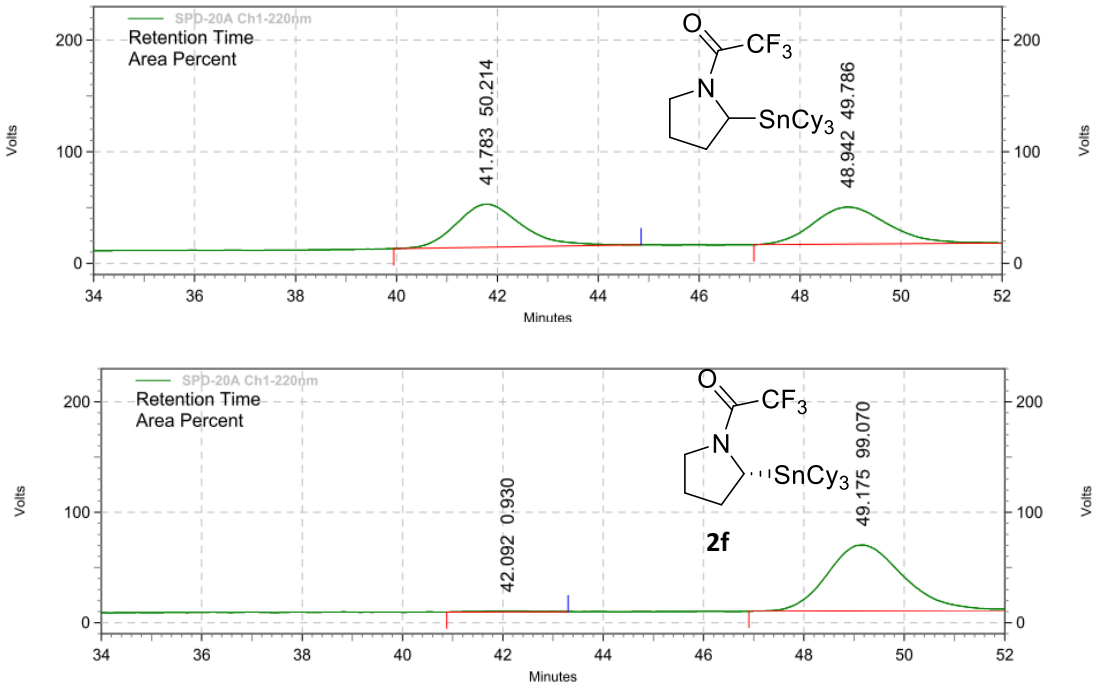


Peak#	Ret.Time	Height	Area	Area%
1	67.159	2732	20984	100.00
Total			20984	100.00



Peak#	Ret.Time	Height	Area	Area%
1	67.161	3738	28155	97.53
2	68.158	78	714	2.47
Total			28869	100.00

Figure S4. GC traces of enantioenriched **S11** and **S13**.

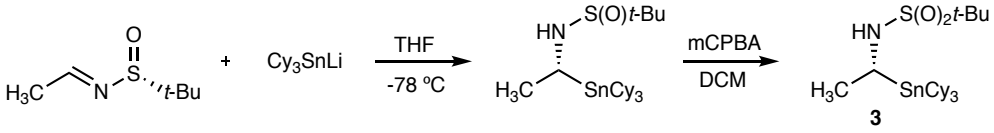


Condition and results:

Column	IC3
Mobile Phase	100 : 0.1= (5%CH_3CN/CH_3OH) : H_2O
Flow	0.6 mL/min
Detector	220nm
Temp	25°C

Figure S5. HPLC traces of racemic and enantioenriched **2f**.

Assignment of absolute configuration of α-aminostannane formed from reaction of Cy_3SnLi and Ellman sulfonamides[5]



(*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (**3**) was prepared from (*R*)-*N*-ethylidene-2-methylpropane-2-sulfinamide as described on page S19. The crystal of (*R*)-2-methyl-*N*-(1-(tricyclohexylstannyl)ethyl)propane-2-sulfonamide (**3**) was grown by from diethyl ether by slow evaporation.

5. Single Crystal X-Ray Structure Determination

Experimental Description

Geometry and intensity data collection with a Bruker SMART APEXII CCD area detector on a D8 goniometer at 100 K. The temperature during the data collection was controlled with an Oxford Cryosystems Series 700+ instrument. Preliminary lattice parameters and orientation matrices were obtained from three sets of frames. Data

were collected using graphite- monochromated and 0.5 mm-MonoCap-collimated Mo-K⟨ radiation (λ = 0.71073 Å) with the ω scan method. Data were processed with the INTEGRATE program of the APEX2 software for reduction and cell refinement. Multi-scan absorption corrections were applied by using the SCALE program for the area detector. The structure was solved by the direct method and refined on F^2 (SHELXTL). Non-hydrogen atoms were refined with anisotropic displacement parameters, and hydrogen atoms on carbons were placed in idealized positions (C-H = 0.95-1.00 Å) and included as riding with U_{iso}(H) = 1.2 or 1.5 U_{eq}(non-H), and the hydrogen atom on the nitrogen atom was refined with a restrained distance of N-H 0.86 Å.

*Crystal structure of **3***

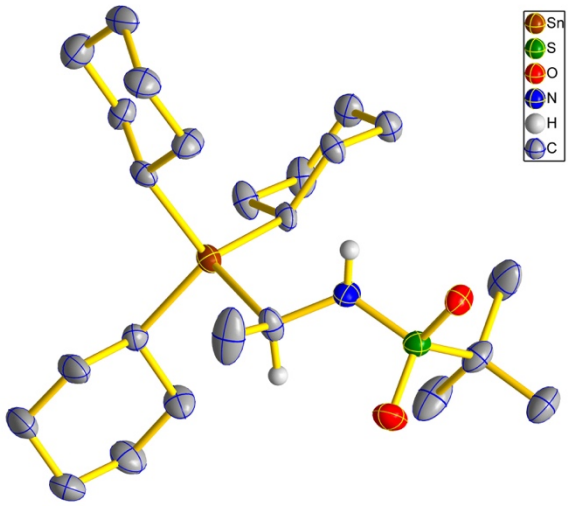


Figure S6. X-ray crystal structure of **3**.

6. References

[1] Czodrowski, P., Mallinger, A., Wienke, D., Esdar, C., Poschke, O., Busch, M., Rohdich, F., Eccles, S. A., Ortiz-Ruiz, M.J., Schneider, R., Raynaud, F. I., Clarke, P. A., Musil, D., Schwarz, D., Dale, T., Urbahns, K., Blagg, J., & Schiemann. K. *J. Med. Chem.* **59,** 9337-9349 (2016).

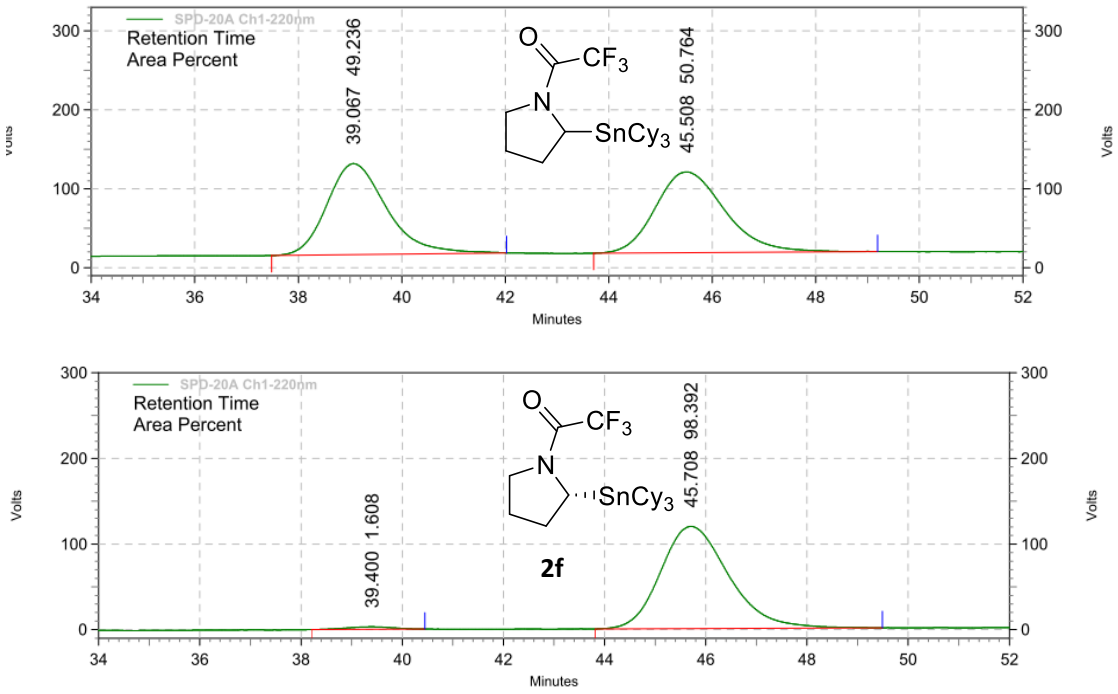
[2] Li, L., Wang, C., Huang, R.& Biscoe, M. R. *Nature Chem.* **5**, 607-612 (2013).

[3] Rayner, P. J., Gelardi, G., O'Brien, P., Horan, R. A. J. & Blakemore, D. C. *Org. Biomol. Chem.* **12**, 3499-3512 (2014).

[4] Le, C. C. & MacMillan, D. W. C. *J. Am. Chem. Soc*. **137**, 11938−11941 (2015).

[5] Liu, G., Cogan, D. A., & Ellman, J. A. *J. Am. Chem. Soc.* **119**, 9913-9914 (1997).

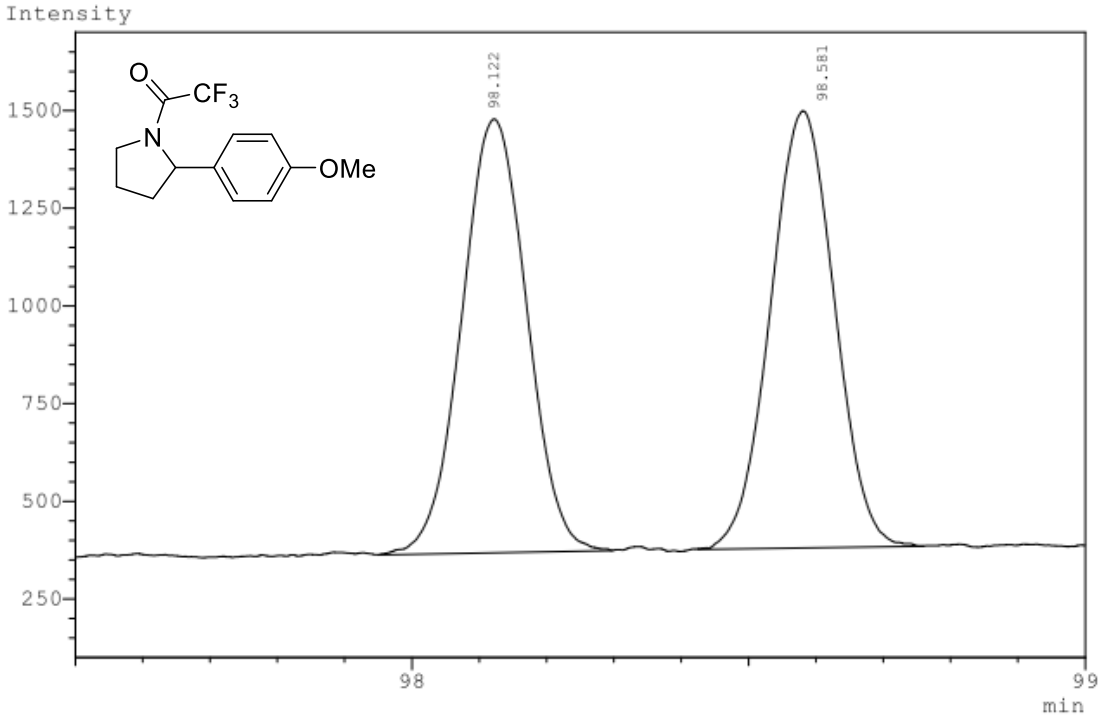
7. Chiral HPLC and GC spectra



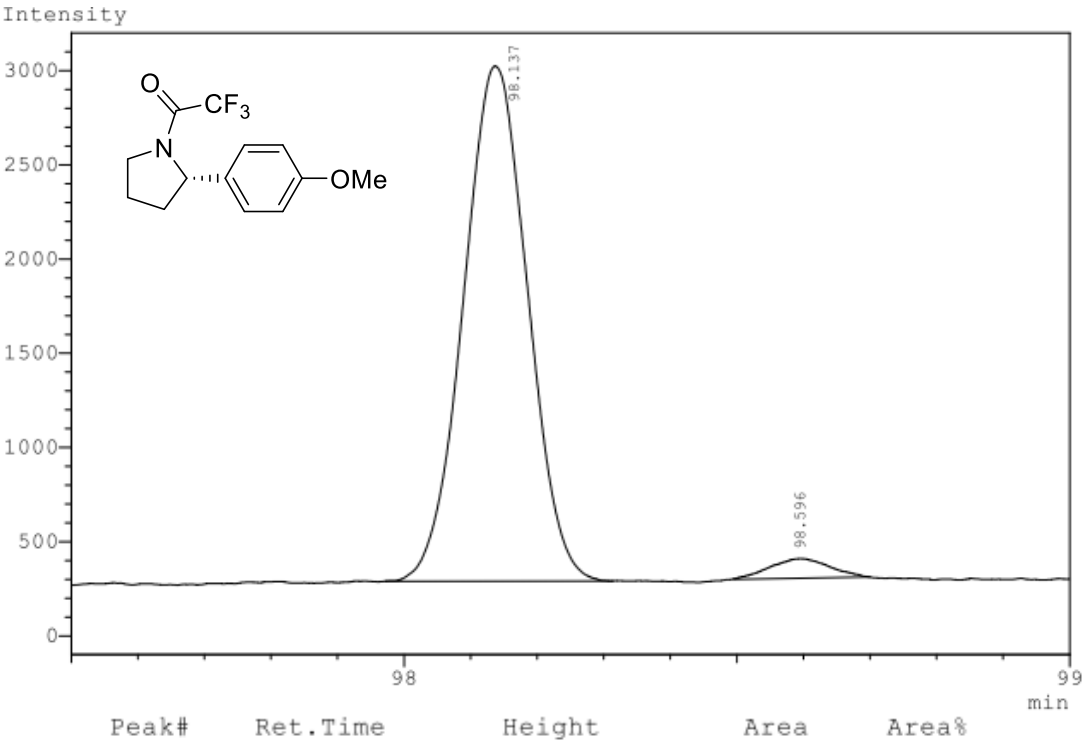
Conditions and results:

Column	IC3
Mobile Phase	85 : 15 = (5%CH_3CN/CH_3OH) : H_2O
Flow	0.6 mL/min
Detector	220nm
Temp	25°C

Figure S7. HPLC traces of racemic and enantioenriched **2f**.

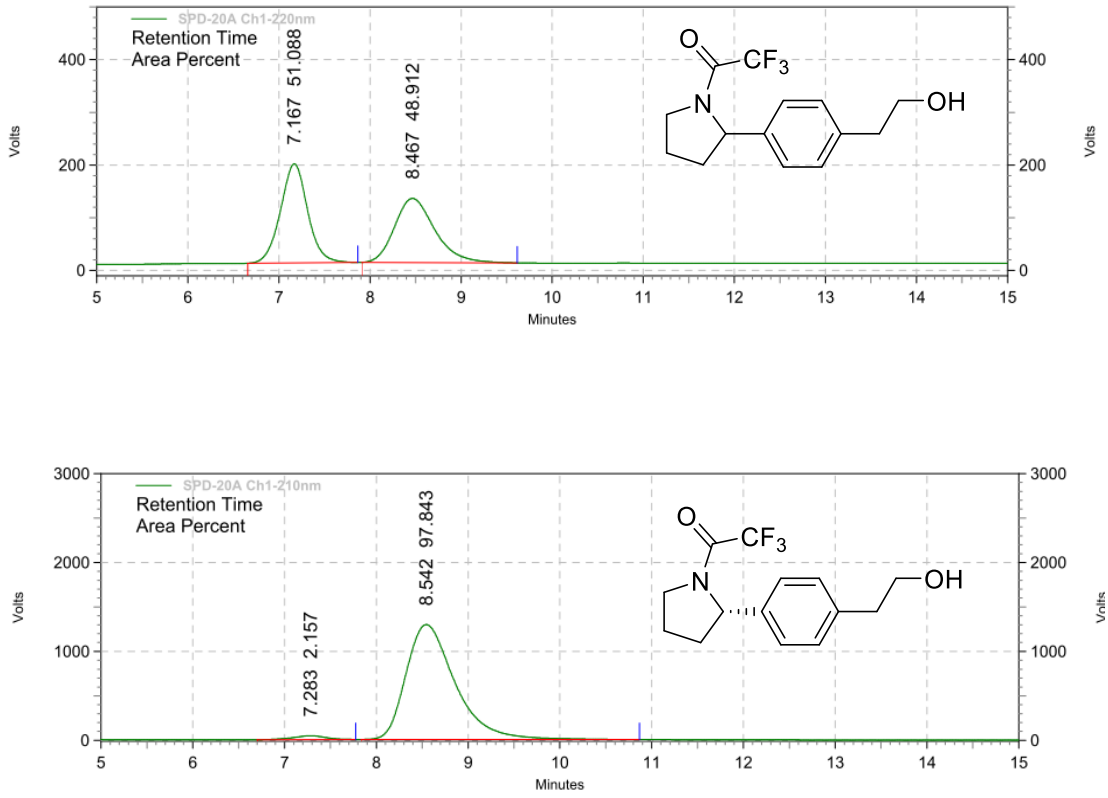


Peak#	Ret.Time	Height	Area	Area%
1	98.122	1107	7451	50.17
2	98.581	1117	7400	49.83
Total			14851	100.00



Peak#	Ret.Time	Height	Area	Area%
1	98.137	2732	18322	96.62
2	98.596	103	641	3.38
Total			18963	100.00

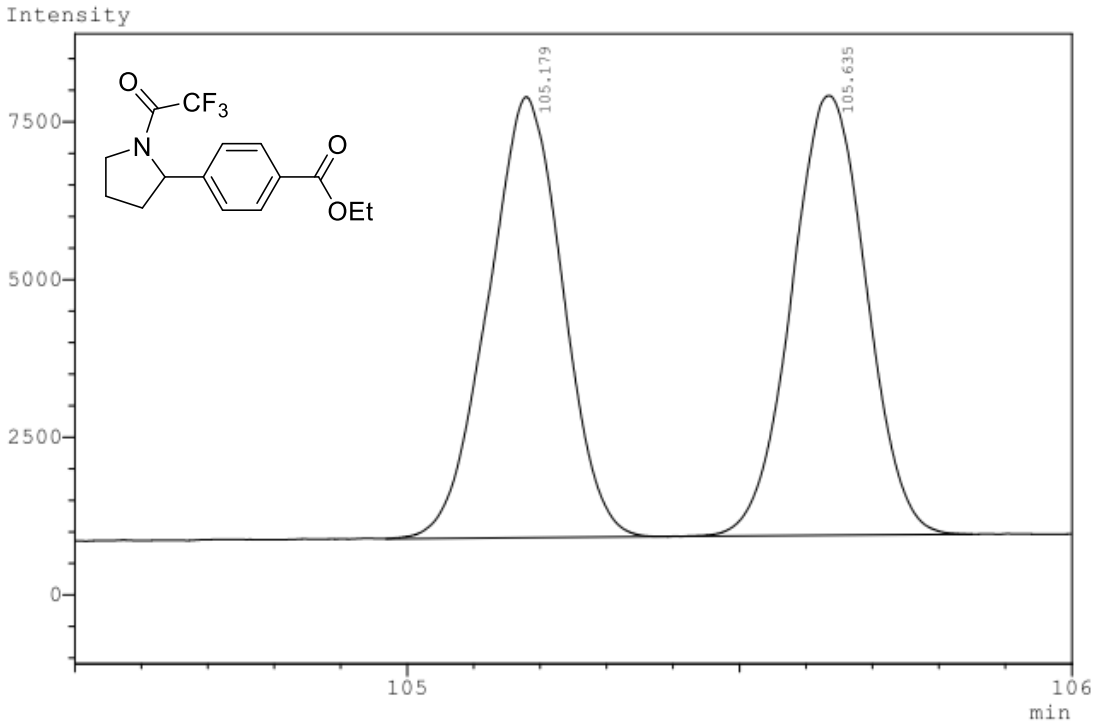
Figure S8. GC traces of racemic and enantioenriched **7a**.



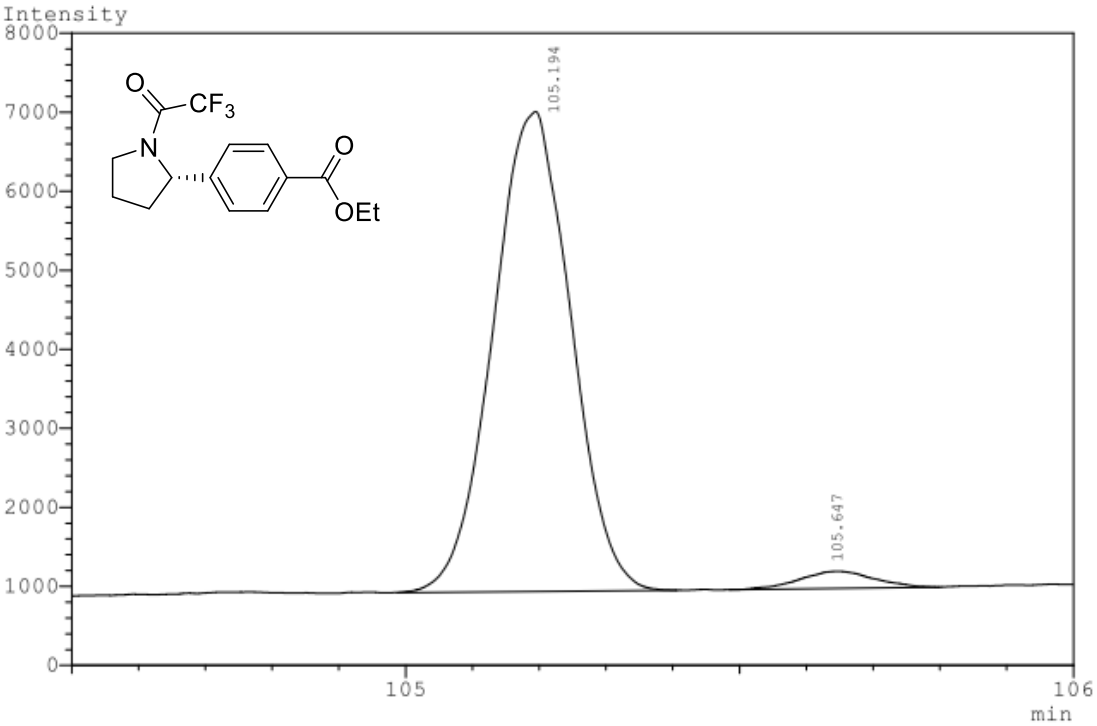
Conditions and results:

Column	IA
Mobile Phase	75 : 25 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	220 nm
Temp	25°C

Figure S9. HPLC traces of racemic and enantioenriched **7b**.

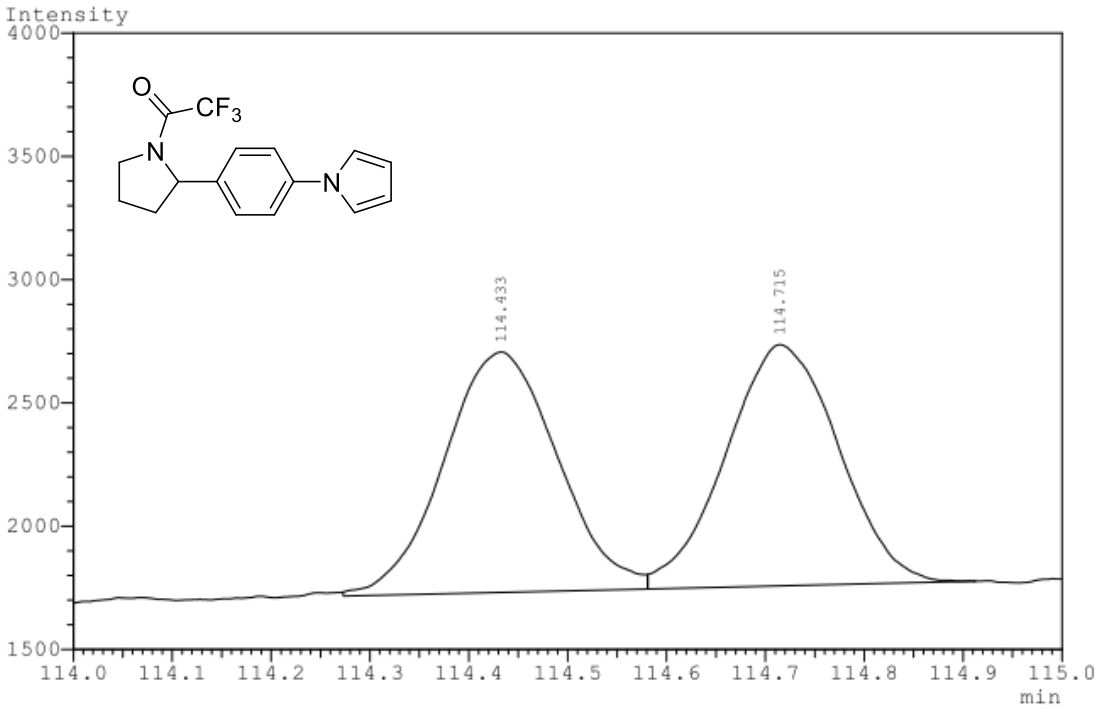


Peak#	Ret.Time	Height	Area	Area%
1	105.179	6981	54743	50.02
2	105.635	6964	54699	49.98
Total			109442	100.00

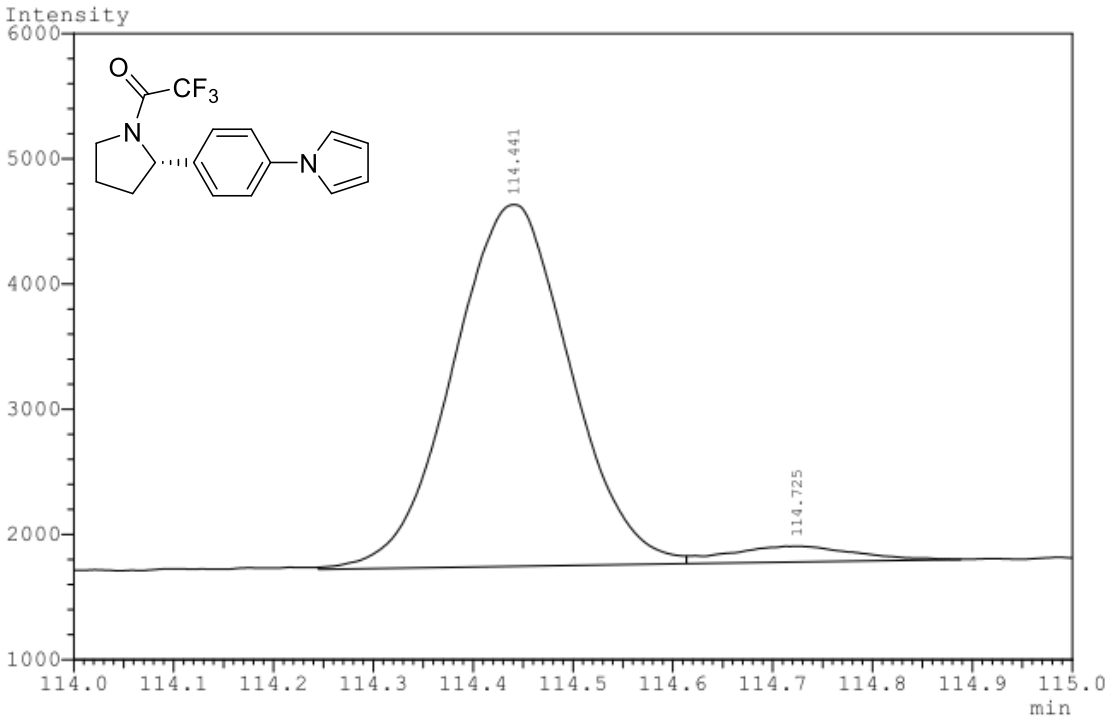


Peak#	Ret.Time	Height	Area	Area%
1	105.194	6071	49274	96.72
2	105.647	216	1671	3.28
Total			50945	100.00

Figure S10. GC traces of racemic and enantioenriched **7c**.

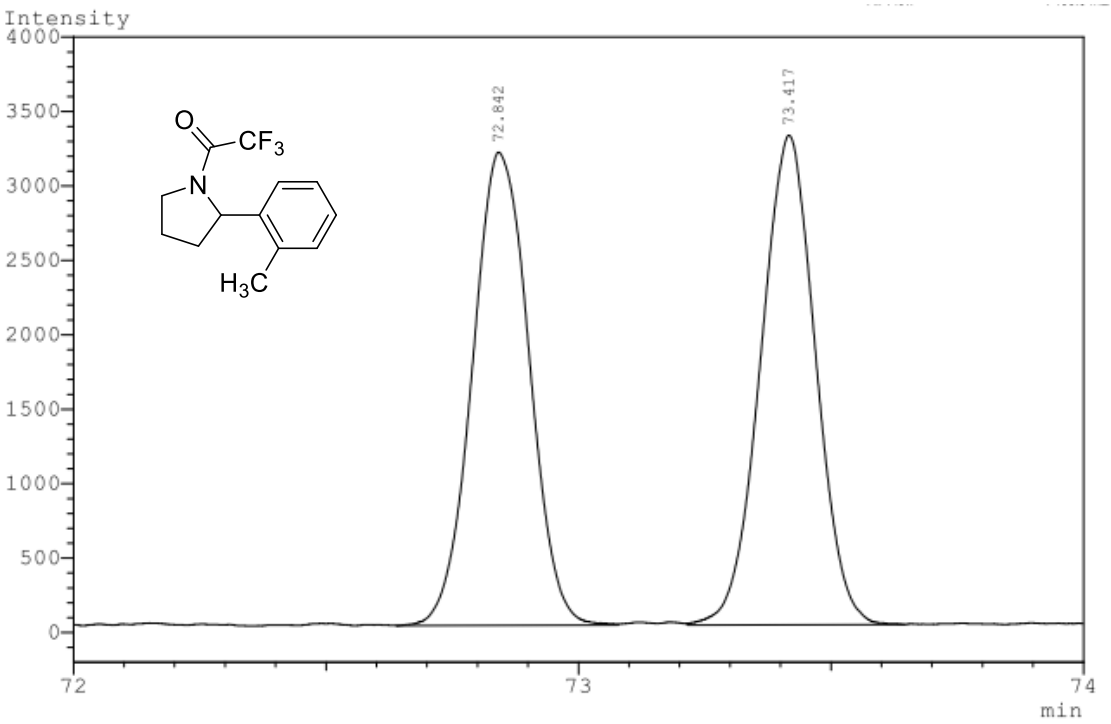


Peak#	Ret.Time	Height	Area	Area%
1	114.433	973	7780	50.06
2	114.715	977	7760	49.94
Total			15540	100.00

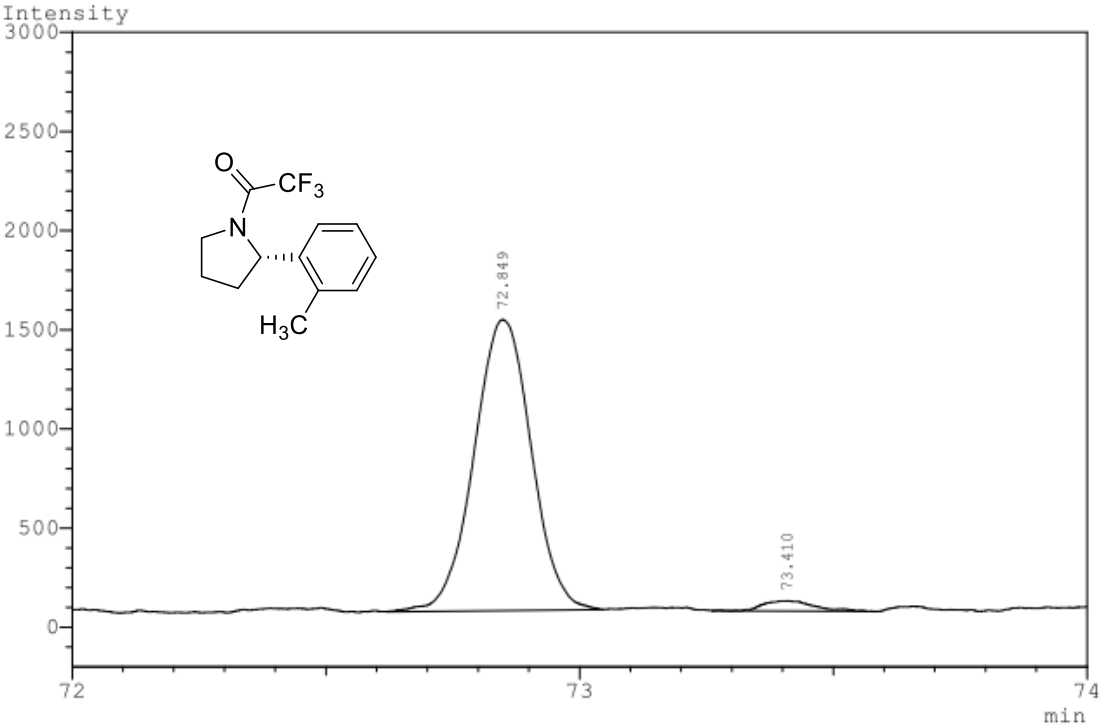


Peak#	Ret.Time	Height	Area	Area%
1	114.441	2886	23612	95.52
2	114.725	124	1107	4.48
Total			24719	100.00

Figure S11. GC traces of racemic and enantioenriched **7d**.

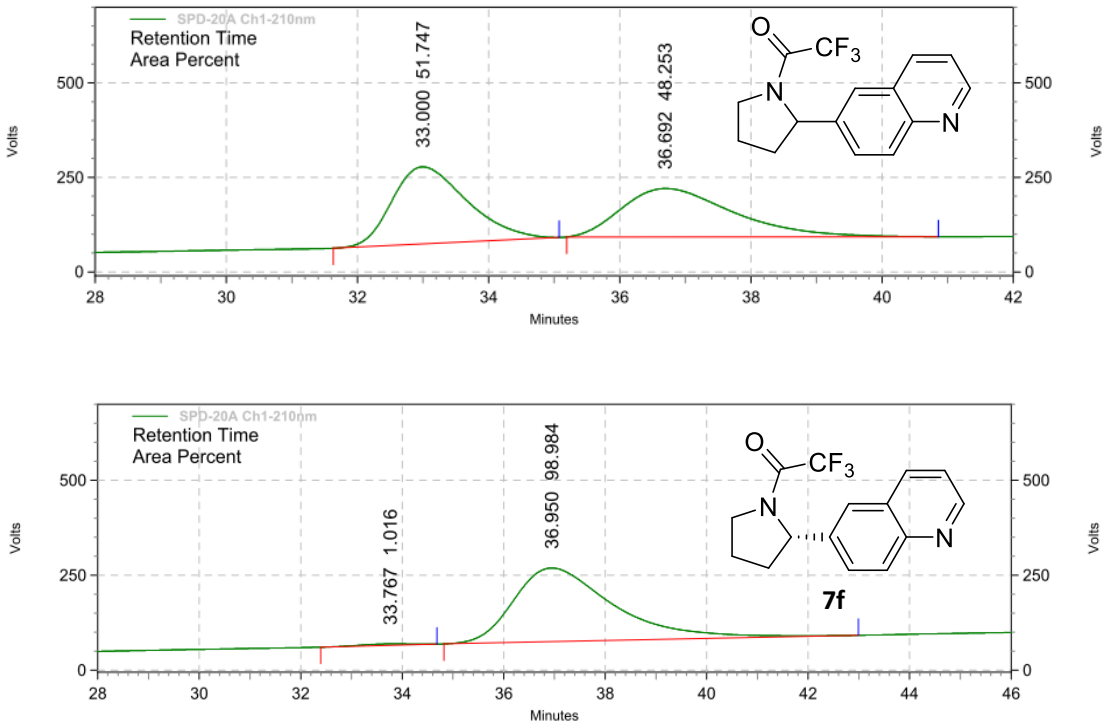


Peak#	Ret.Time	Height	Area	Area%
1	72.842	3174	24835	49.99
2	73.417	3283	24843	50.01
Total			49678	100.00



Peak#	Ret.Time	Height	Area	Area%
1	72.849	1466	11495	97.10
2	73.410	50	343	2.90
Total			11838	100.00

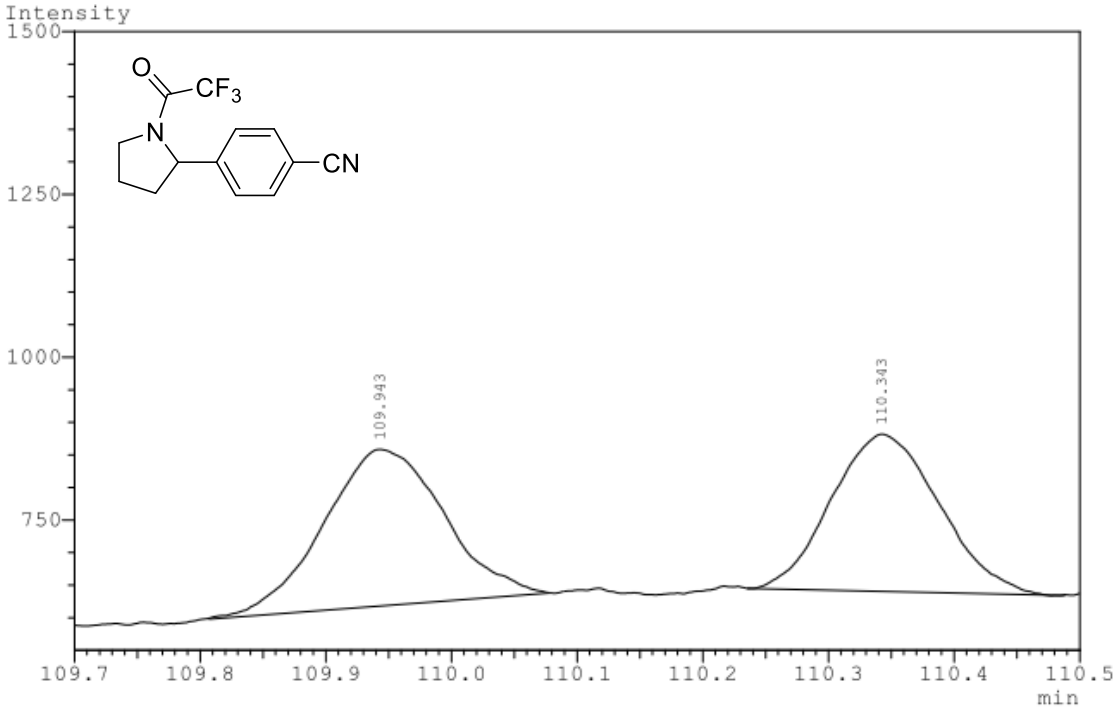
Figure S12. GC traces of racemic and enantioenriched **7e**.



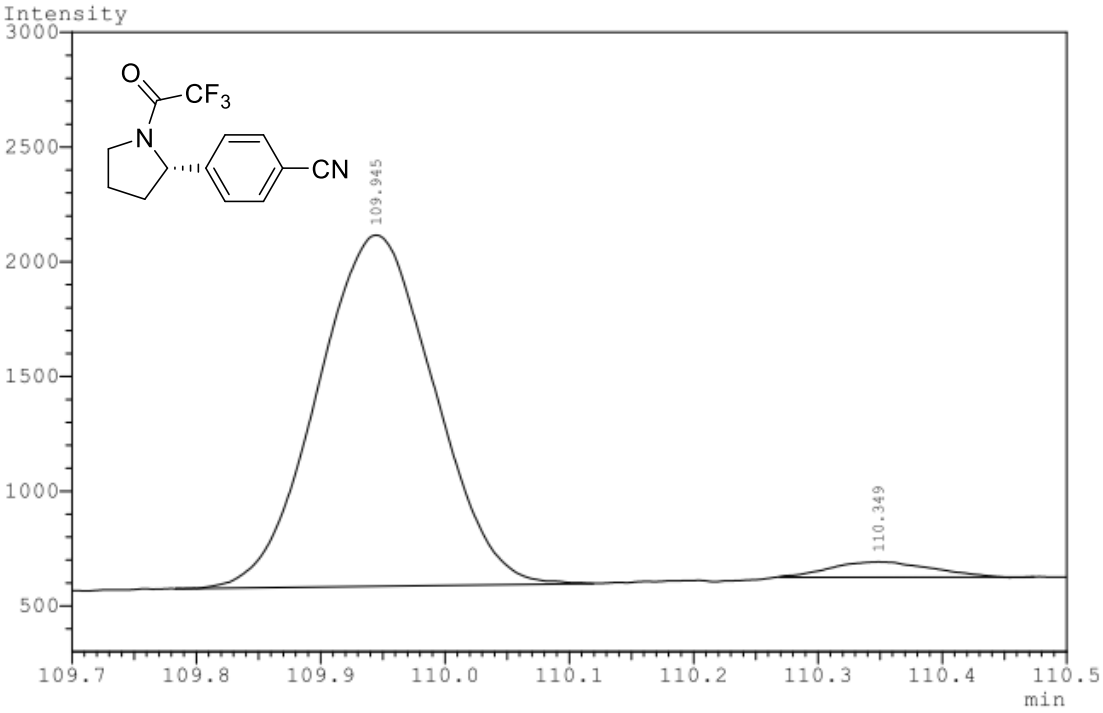
Conditions and results:

Column	IA
Mobile Phase	50 : 50 = (5% CH_3CN/CH_3OH) : H_2O
Flow	1.0 mL/min
Detector	220 nm
Temp	25°C

Figure S13. HPLC traces of racemic and enantioenriched **7f**.

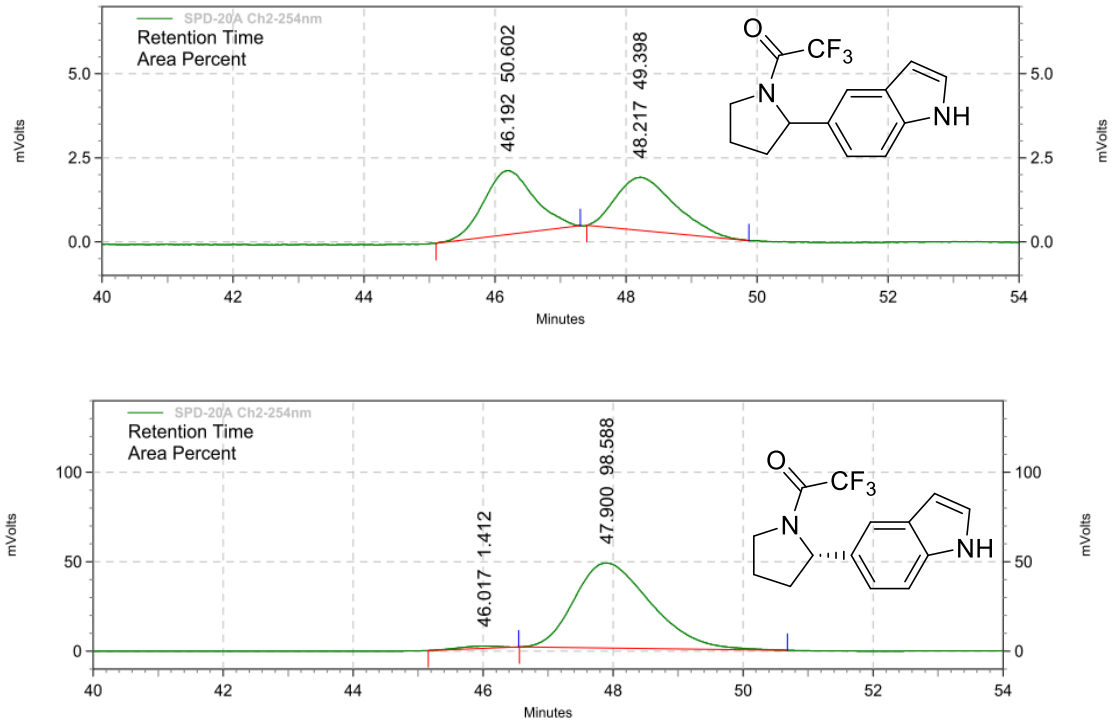


Peak#	Ret.Time	Height	Area	Area%
1	109.943	239	1583	52.50
2	110.343	241	1432	47.50
Total			3015	100.00



Peak#	Ret.Time	Height	Area	Area%
1	109.945	1529	9969	96.45
2	110.349	65	367	3.55
Total			10336	100.00

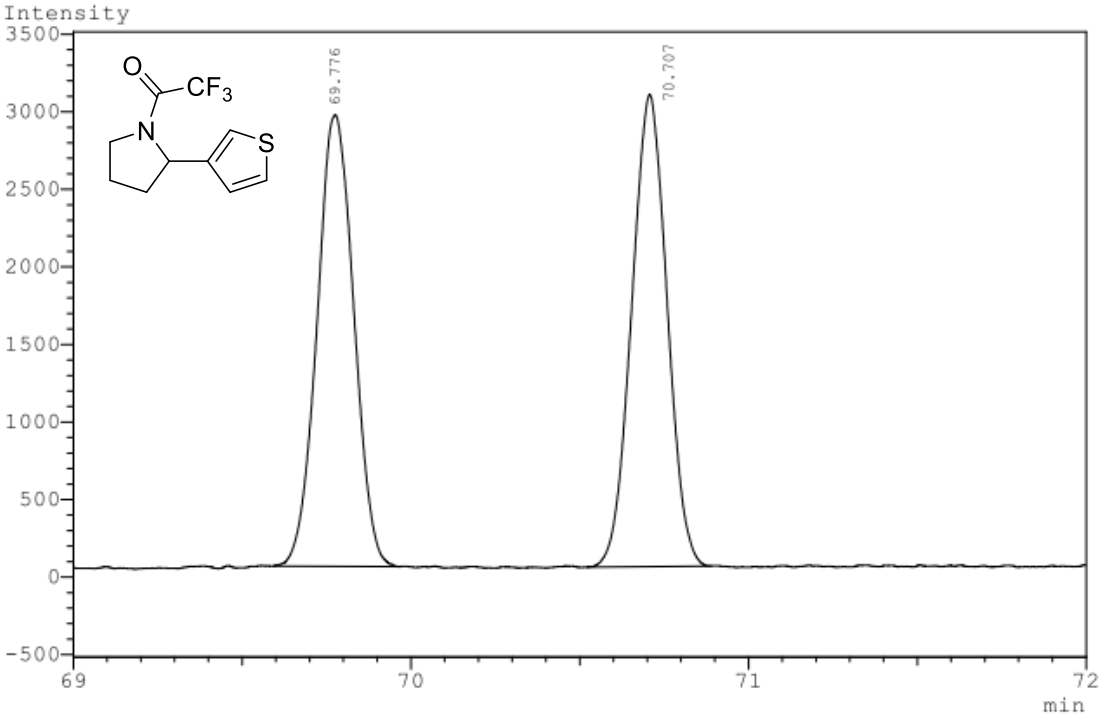
Figure S14. GC traces of racemic and enantioenriched **7g**.



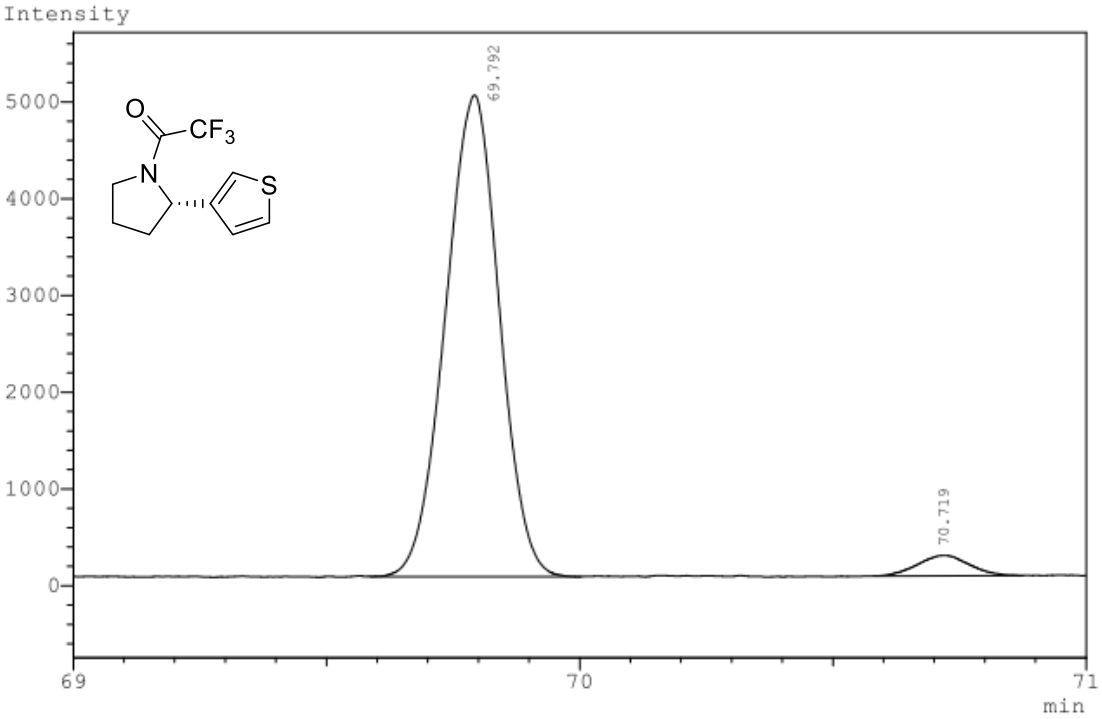
Conditions and results:

Column	IA
Mobile Phase	25 : 75 = (CH_3CN : H_2O) for 15 min, gradually to 40: 60 (CH_3CN : H_2O) at 40 min.
Flow	1.2 mL/min
Detector	220 nm
Temp	25°C

Figure S15. GC traces of racemic and enantioenriched **7h**.

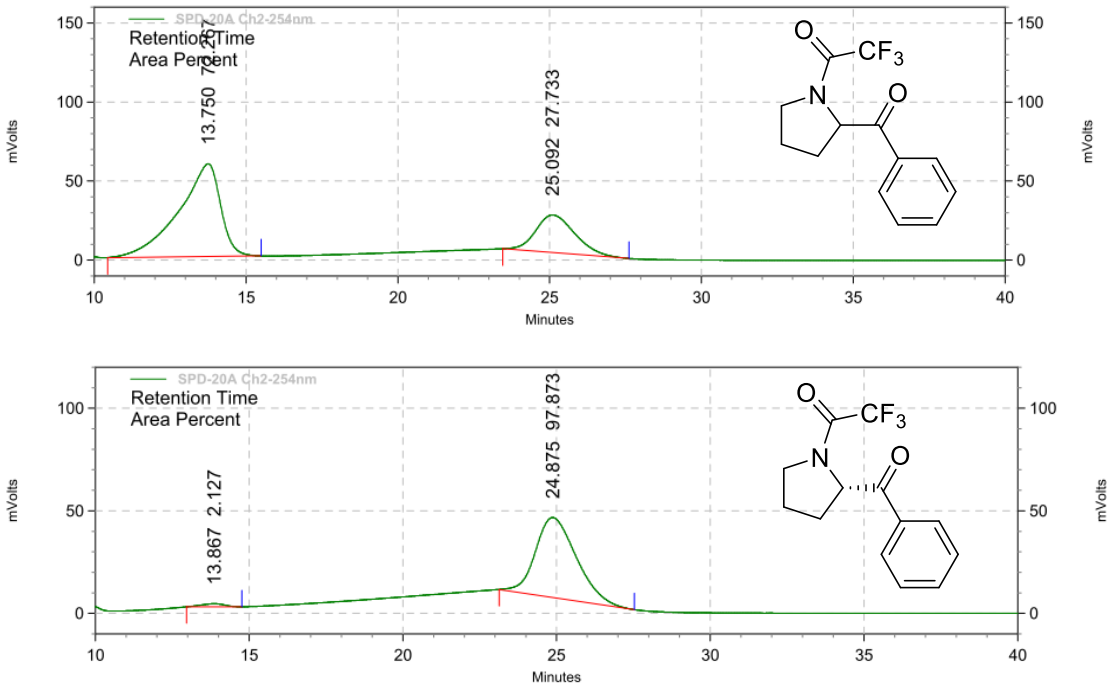


Peak#	Ret.Time	Height	Area	Area%
1	69.776	2908	22012	49.83
2	70.707	3041	22160	50.17
Total			44172	100.00



Peak#	Ret.Time	Height	Area	Area%
1	69.792	4974	36880	96.11
2	70.719	210	1493	3.89
Total			38373	100.00

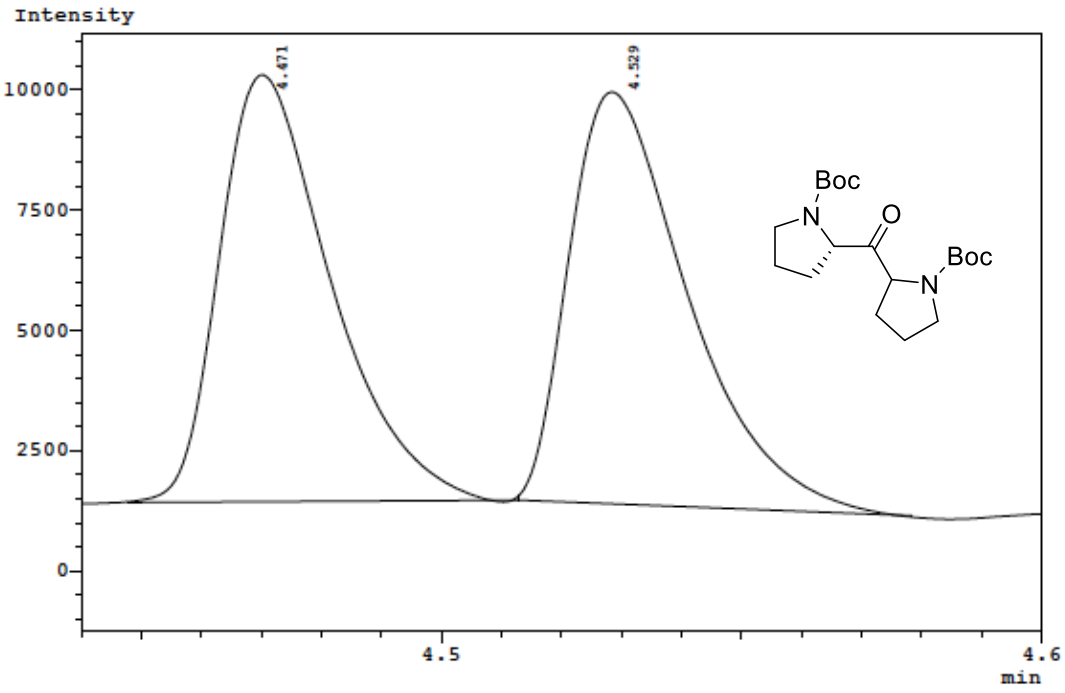
Figure S16. GC traces of racemic and enantioenriched **7i**.



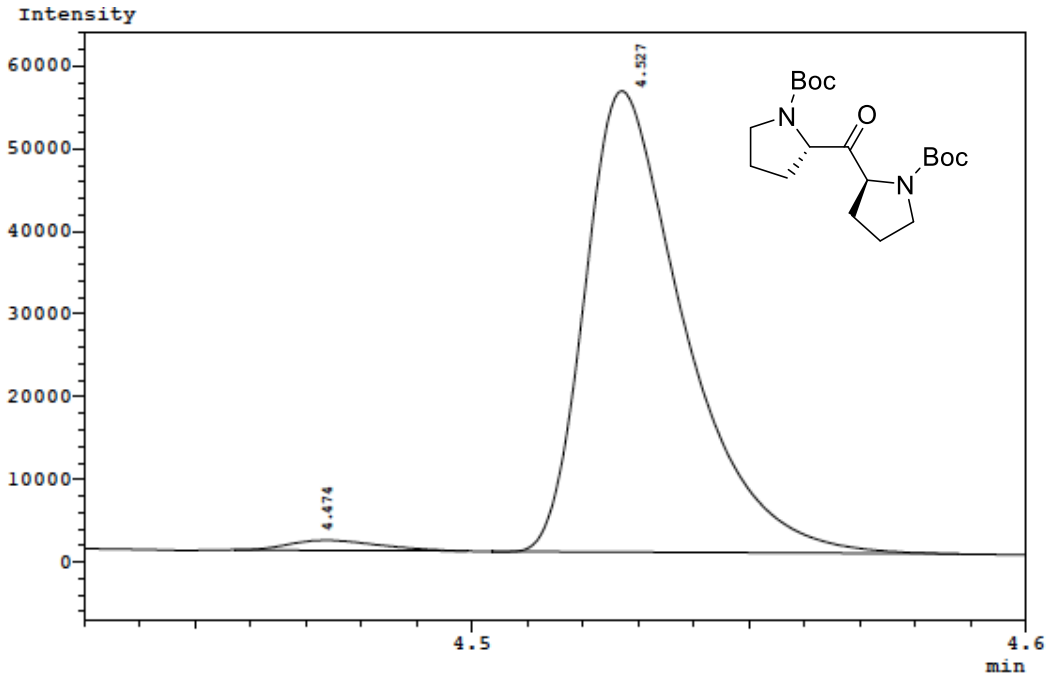
Conditions and results:

Column	IA
Mobile Phase	65 : 35 = (5%CH_3CN/CH_3OH) : H_2O
Flow	1.0 mL/min
Detector	220 nm
Temp	25°C

Figure S17. HPLC traces of racemic and enantioenriched **8a**.

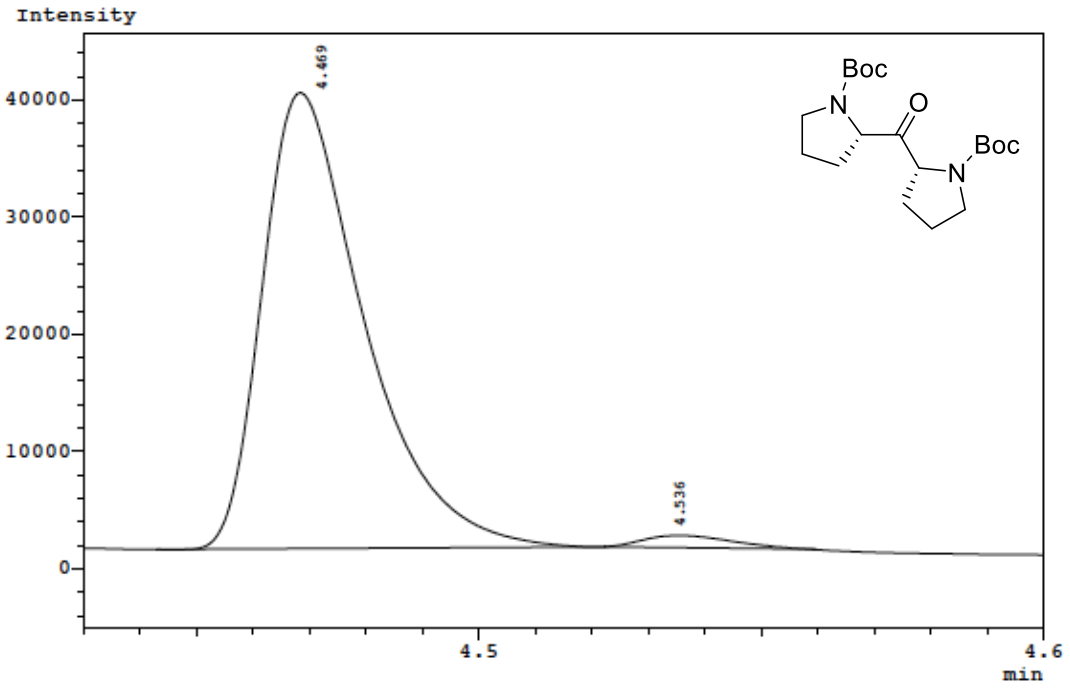


Peak#	Ret.Time	Height	Area	Area%
1	4.471	8638	11408	49.22
2	4.529	8385	11769	50.78
Total			23177	100.00



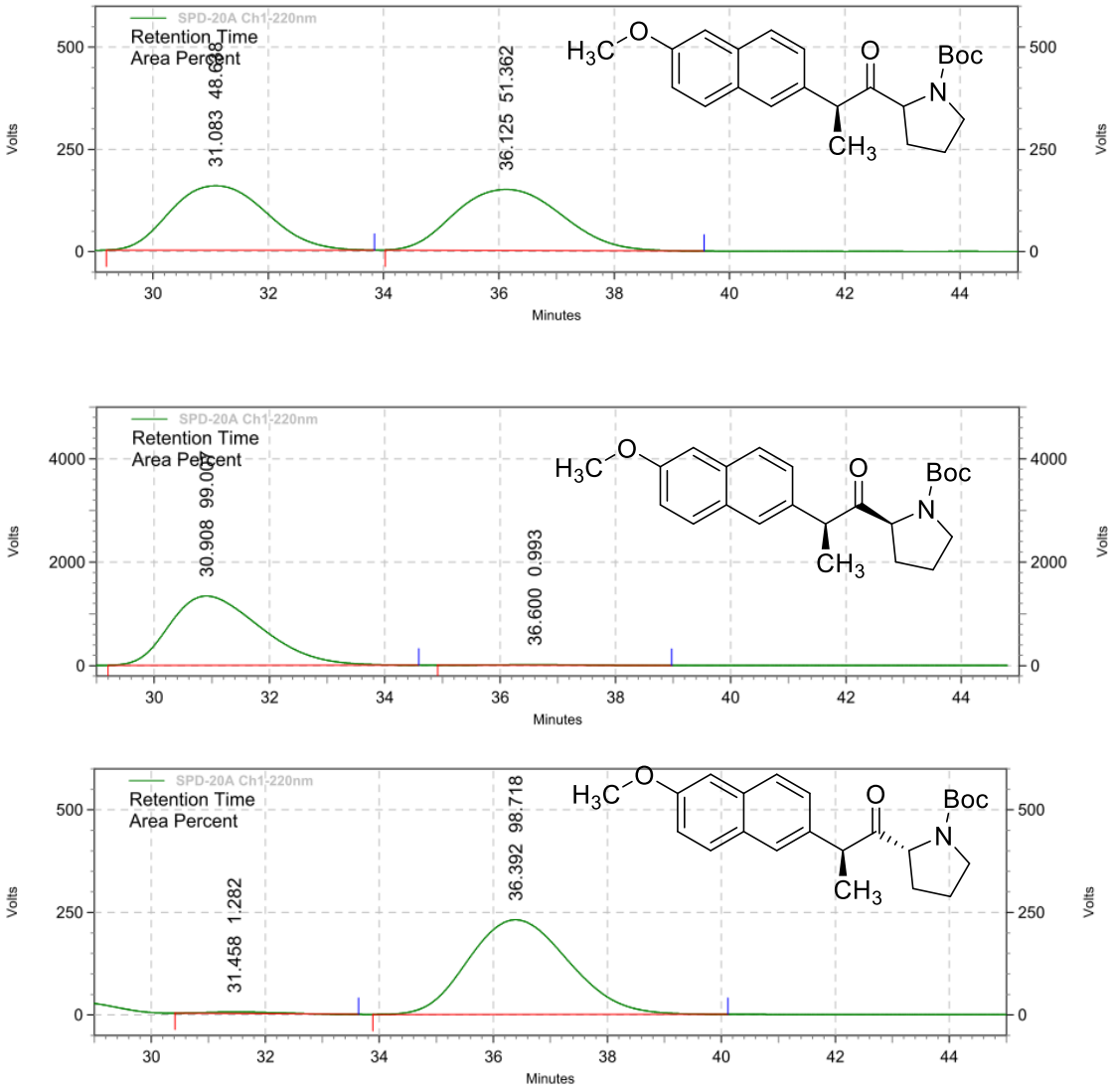
Peak#	Ret.Time	Height	Area	Area%
1	4.474	1190	1335	1.88
2	4.527	52616	69756	98.12
Total			71091	100.00

Figure S18. GC traces of diastereomer mixture **8bc** and single-diastereomer **8c**.



Peak#	Ret.Time	Height	Area	Area%
1	4.469	38195	48800	97.75
2	4.536	1019	1125	2.25
Total			49925	100.00

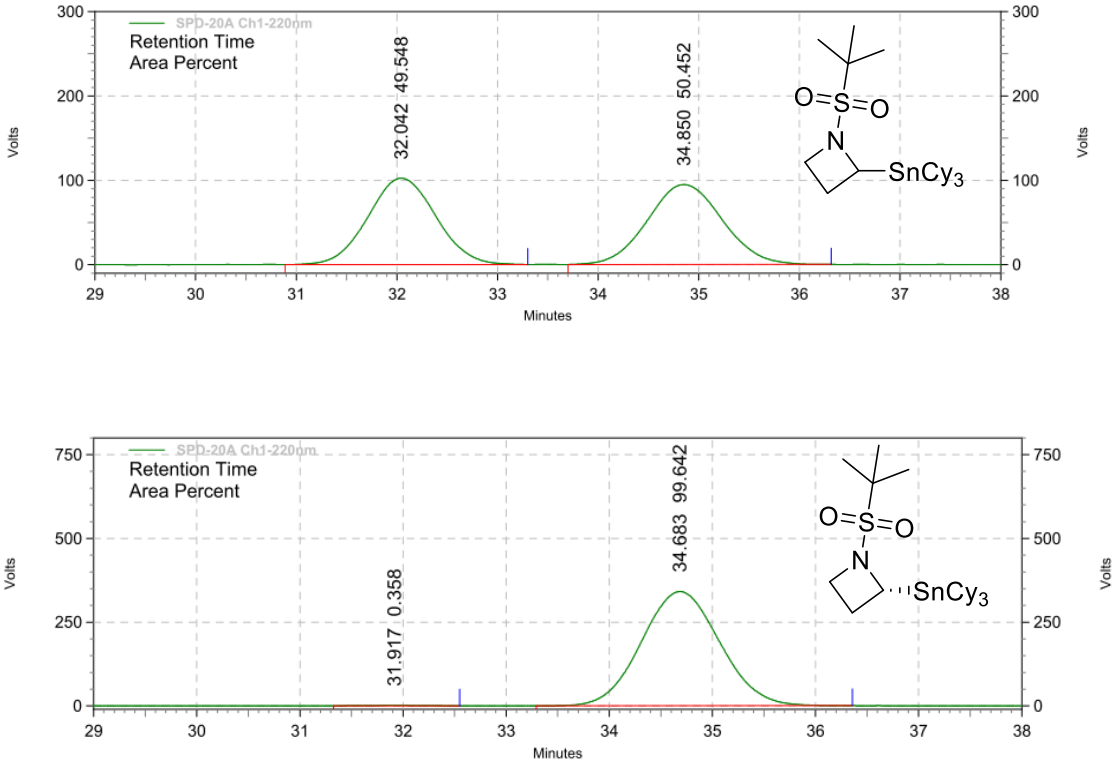
Figure S19. GC trace of single-diastereomer **8b**.



Conditions and results:

Column	ODRH
Mobile Phase	75 : 25 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.6 mL/min
Detector	220 nm
Temp	25°C

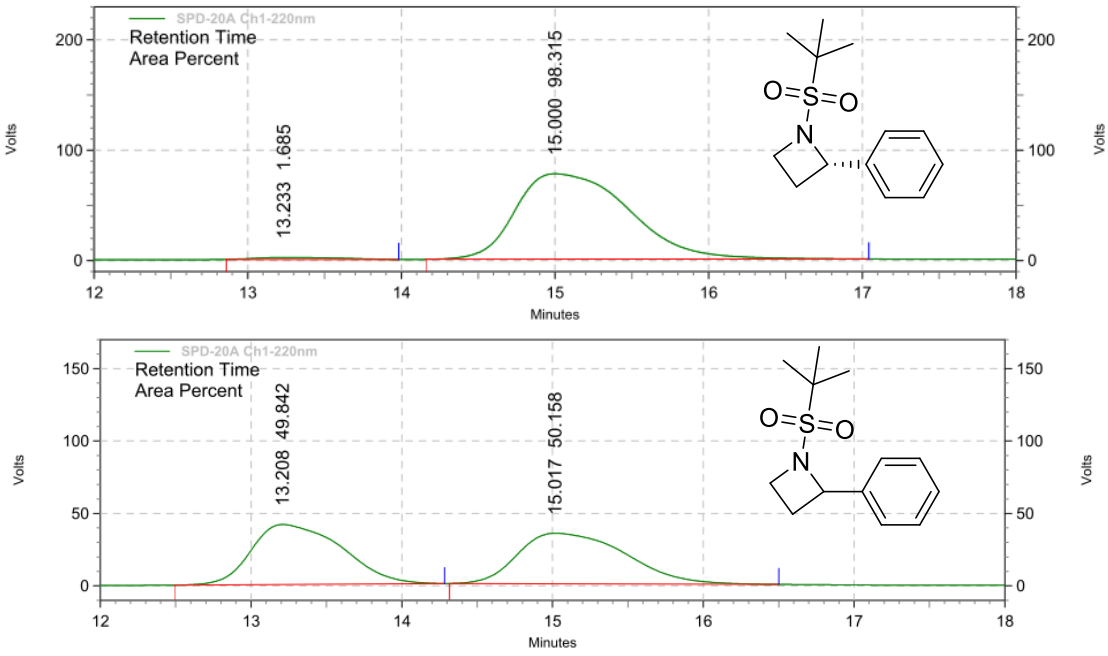
Figure S20. HPLC traces of diastereomer mixture **8de** and single-diastereomers **8d** and **8e**.



Conditions and results:

Column	IC3
Mobile Phase	90 : 10 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.5 mL/min
Detector	220 nm
Temp	25°C

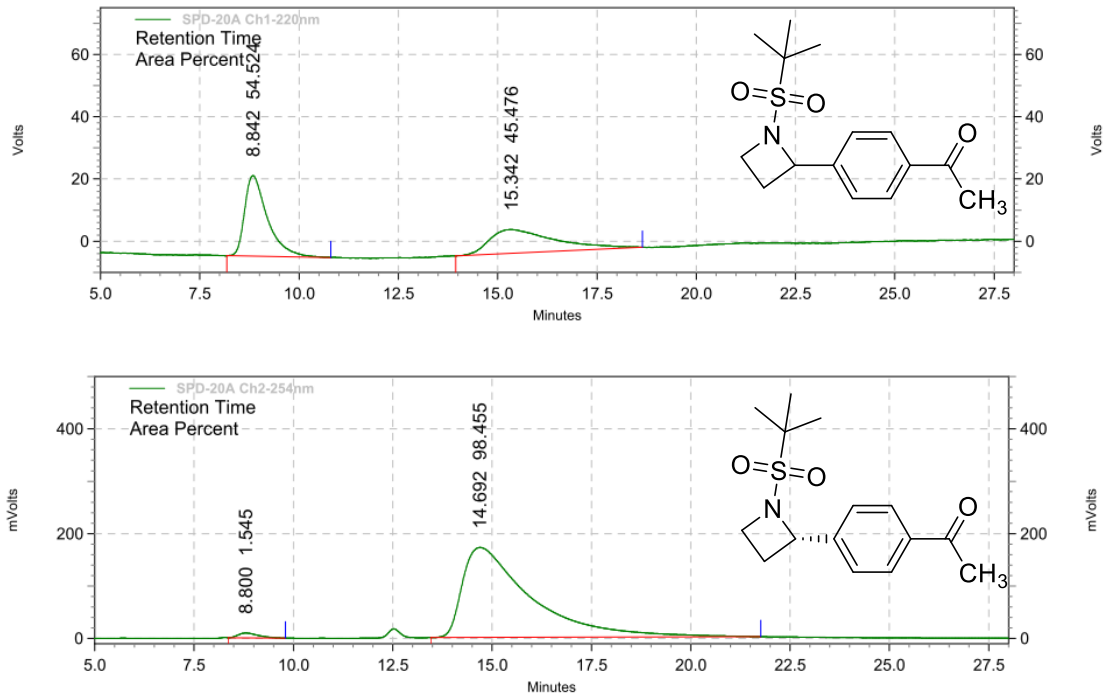
Figure S21. HPLC traces of racemic and enantioenriched **9**.



Conditions and results:

Column	IA
Mobile Phase	75 : 25 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.6 mL/min
Detector	220 nm
Temp	25°C

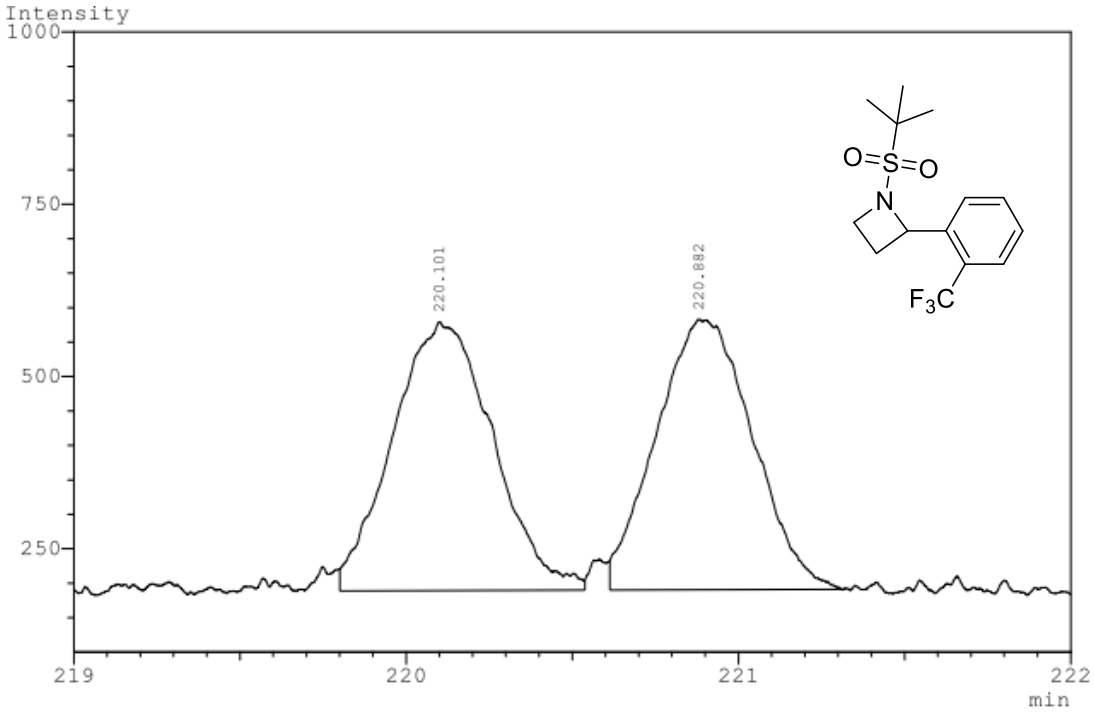
Figure S22. HPLC traces of racemic and enantioenriched **10a**.



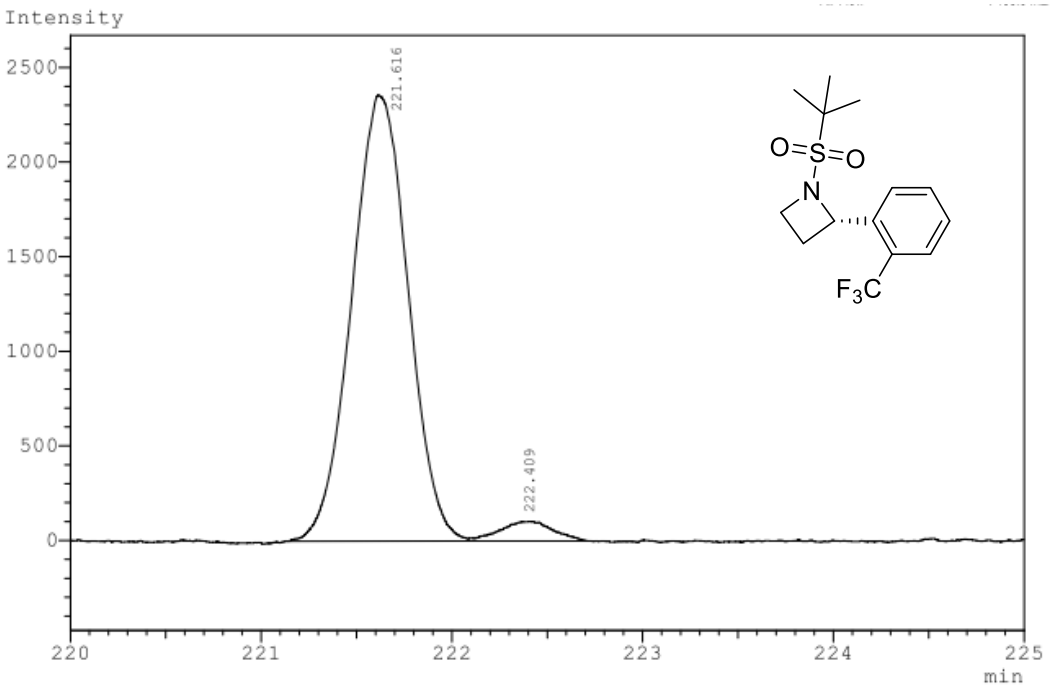
Conditions and results:

Column	IA
Mobile Phase	85 : 15 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	254 nm
Temp	25°C

Figure S23. HPLC traces of racemic and enantioenriched **10b**.

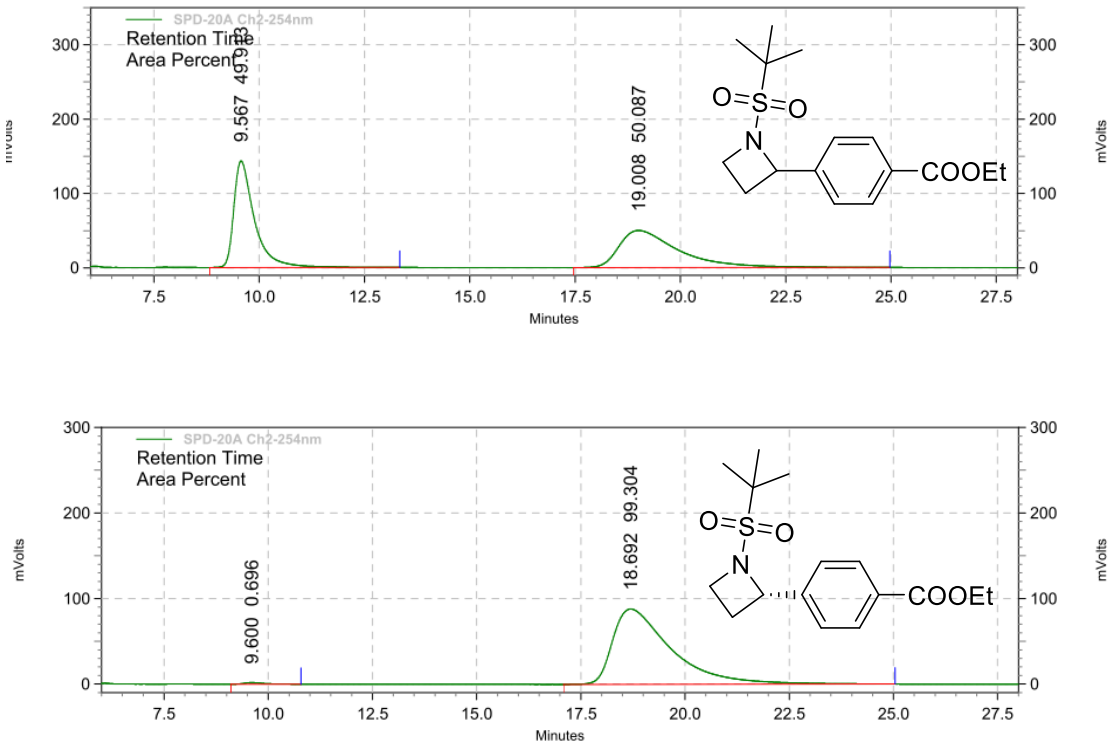


Peak#	Ret.Time	Height	Area	Area%
1	220.101	389	8149	50.74
2	220.882	392	7913	49.26
Total			16062	100.00



Peak#	Ret.Time	Height	Area	Area%
1	221.616	2358	48557	95.98
2	222.409	103	2035	4.02
Total			50592	100.00

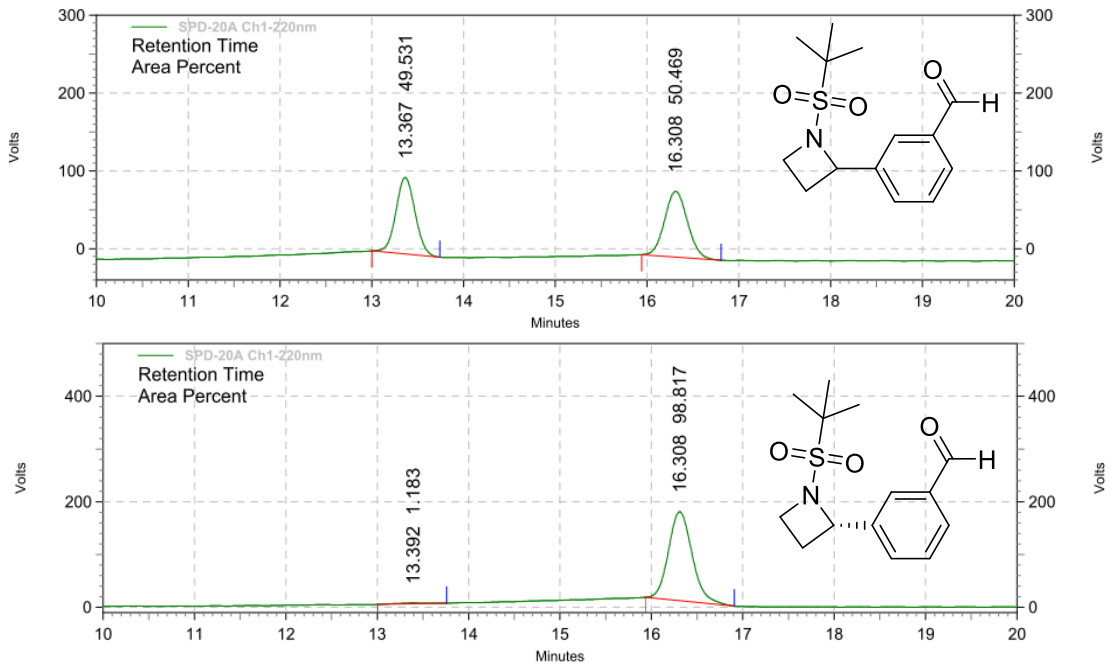
Figure S24. GC traces of racemic and enantioenriched **10c**.



Conditions and results:

Column	IA
Mobile Phase	85 : 15 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	254 nm
Temp	25°C

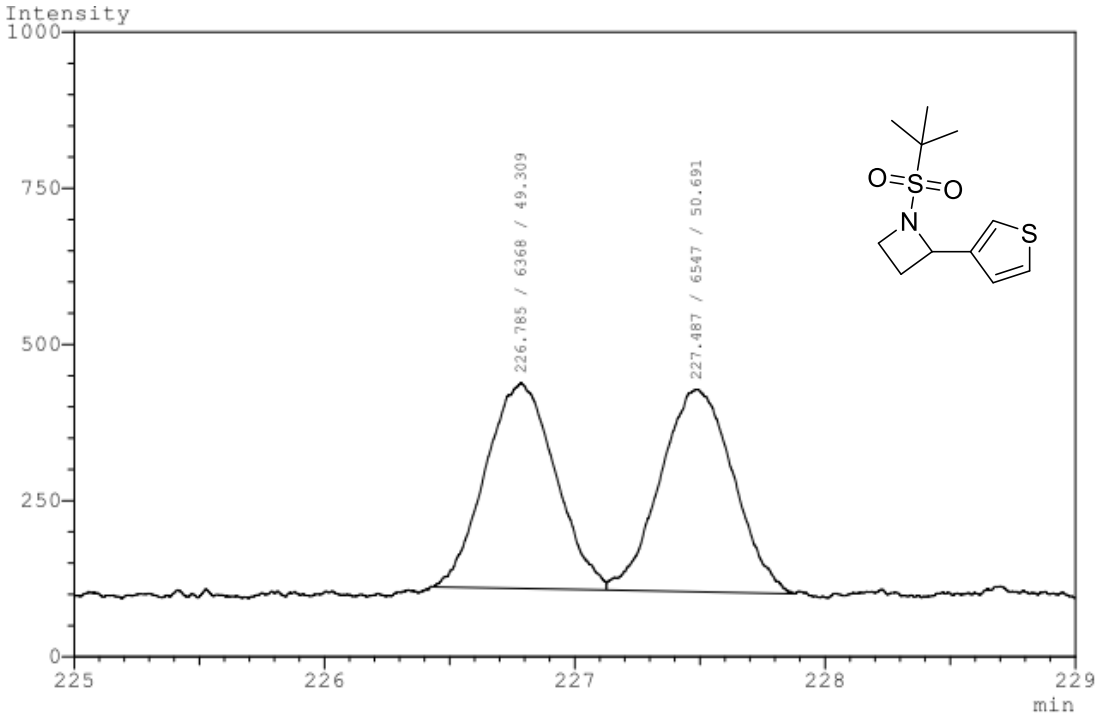
Figure S25. HPLC traces of racemic and enantioenriched **10d**.



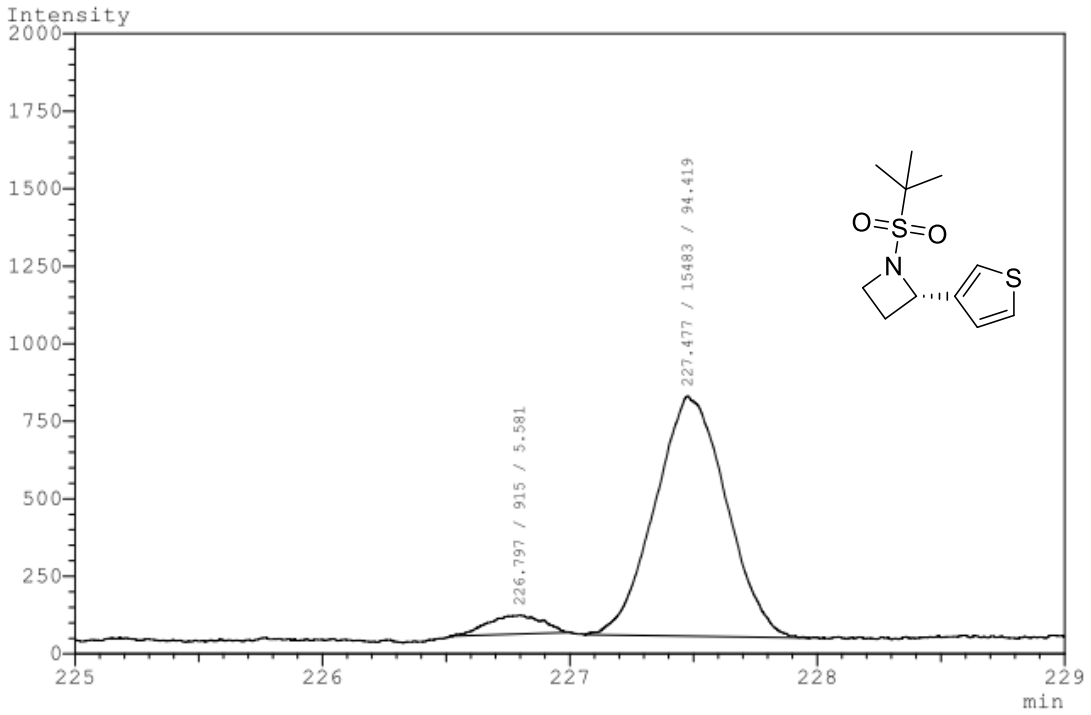
Conditions and results:

Column	IC3
Mobile Phase	90 : 10 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.5 mL/min
Detector	220 nm
Temp	25°C

Figure S26. HPLC traces of racemic and enantioenriched **10e**.

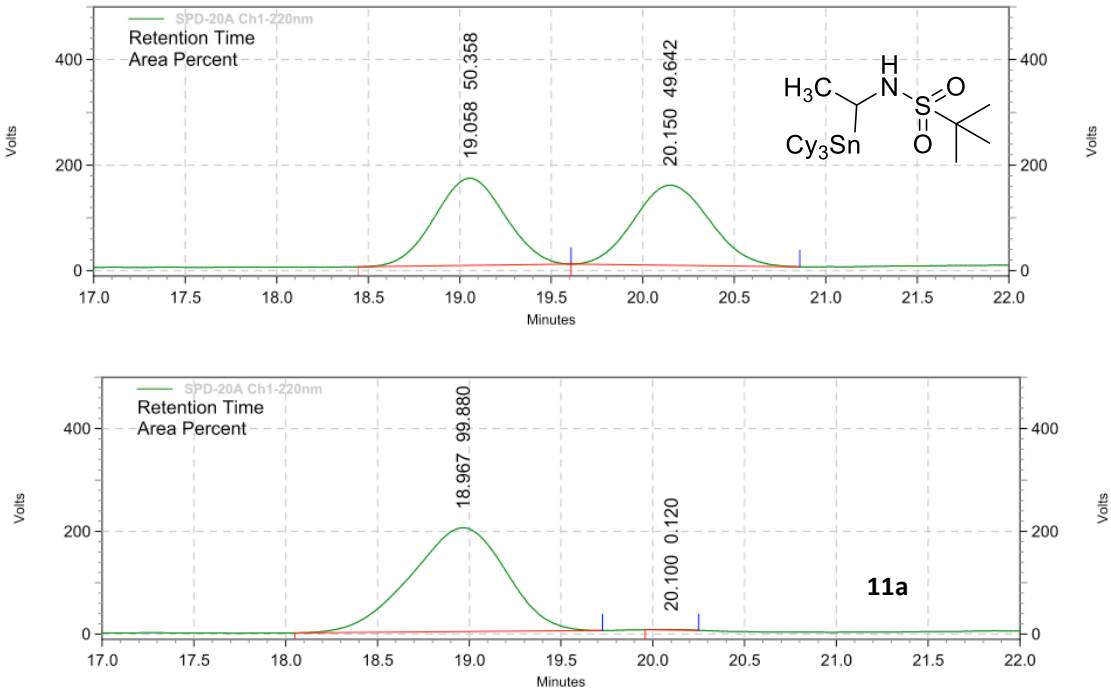


Peak#	Ret.Time	Height	Area	Area%
1	226.785	328	6368	49.31
2	227.487	323	6547	50.69
Total			12915	100.00



Peak#	Ret.Time	Height	Area	Area%
1	226.797	60	915	5.58
2	227.477	774	15483	94.42
Total			16398	100.00

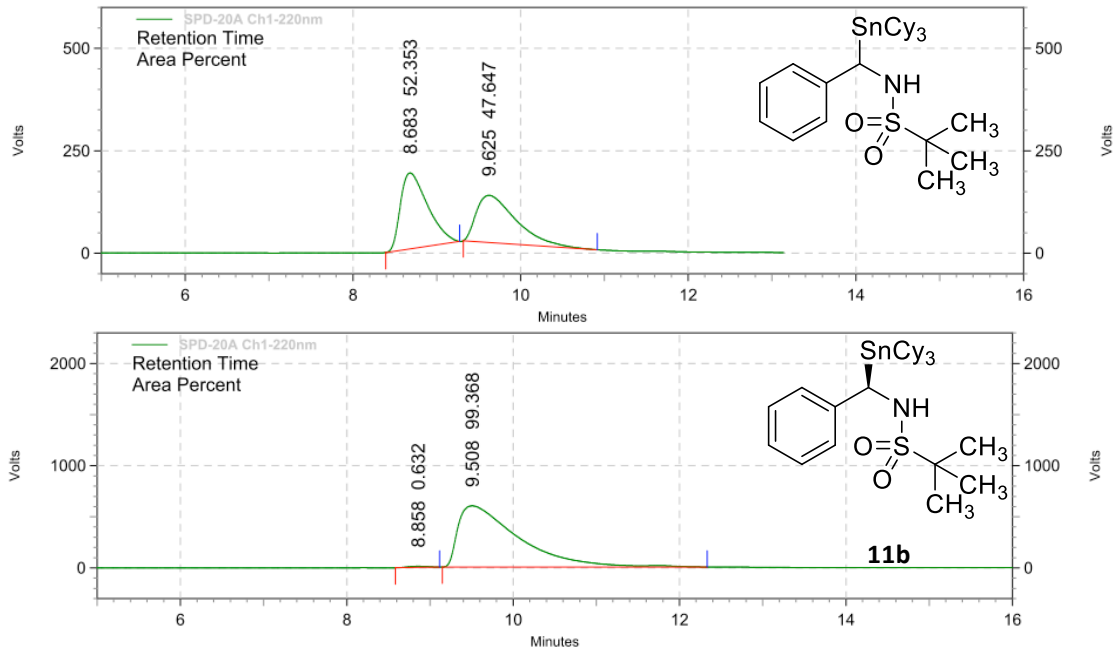
Figure S27. GC traces of racemic and enantioenriched **10f.**



Conditions and results:

Column	IC3
Mobile Phase	90 : 10 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.6 mL/min
Detector	220 nm
Temp	25°C

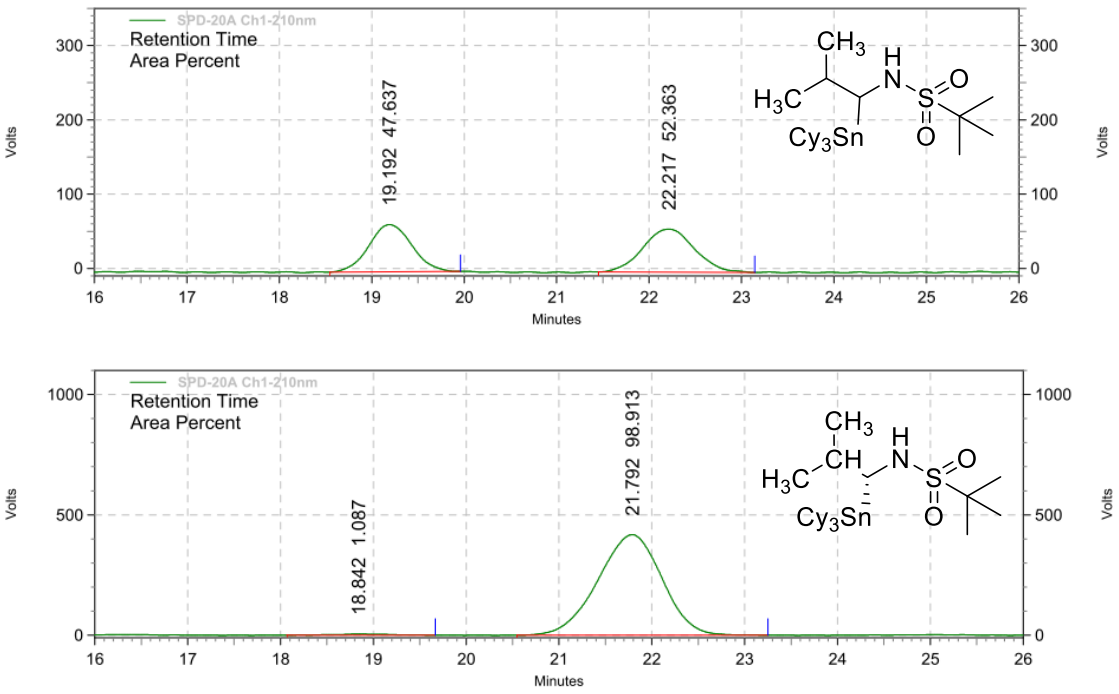
Figure S28. HPLC traces of racemic and enantioenriched **11a**.



Conditions and results:

Column	IA
Mobile Phase	0.5 : 99.5 = isopropanol : hexane
Flow	1.0 mL/min
Detector	220 nm
Temp	25°C

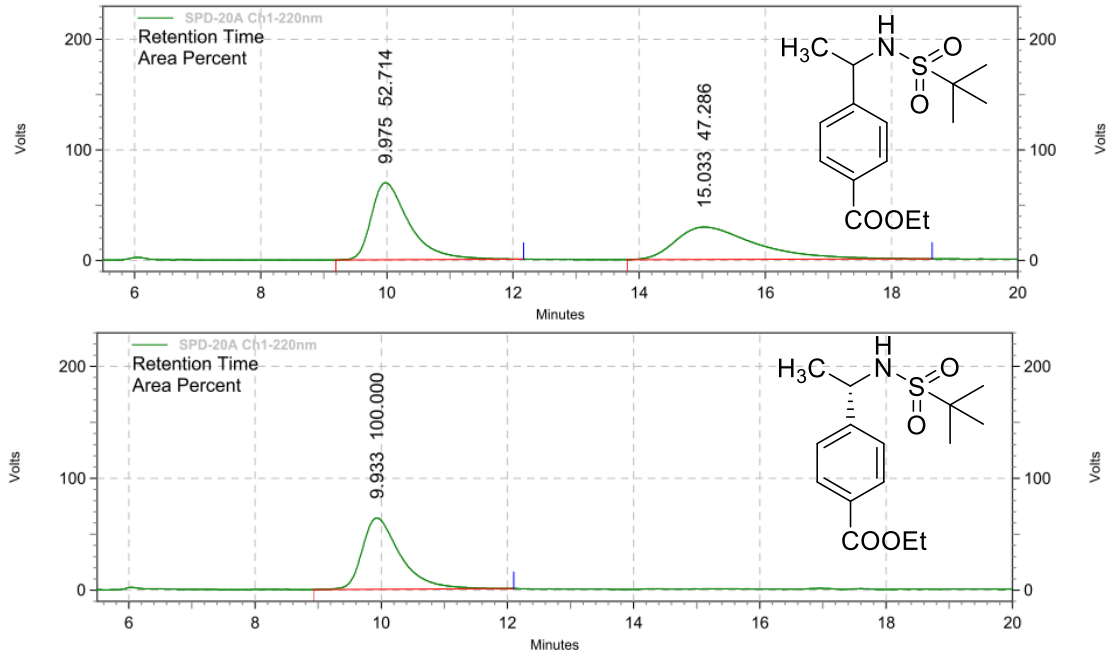
Figure S29. HPLC traces of racemic and enantioenriched **11b**.



Condition and results:

Column	IC3
Mobile Phase	90 : 10= CH_3OH : H_2O
Flow	0.6 mL/min
Detector	220nm
Temp	25°C

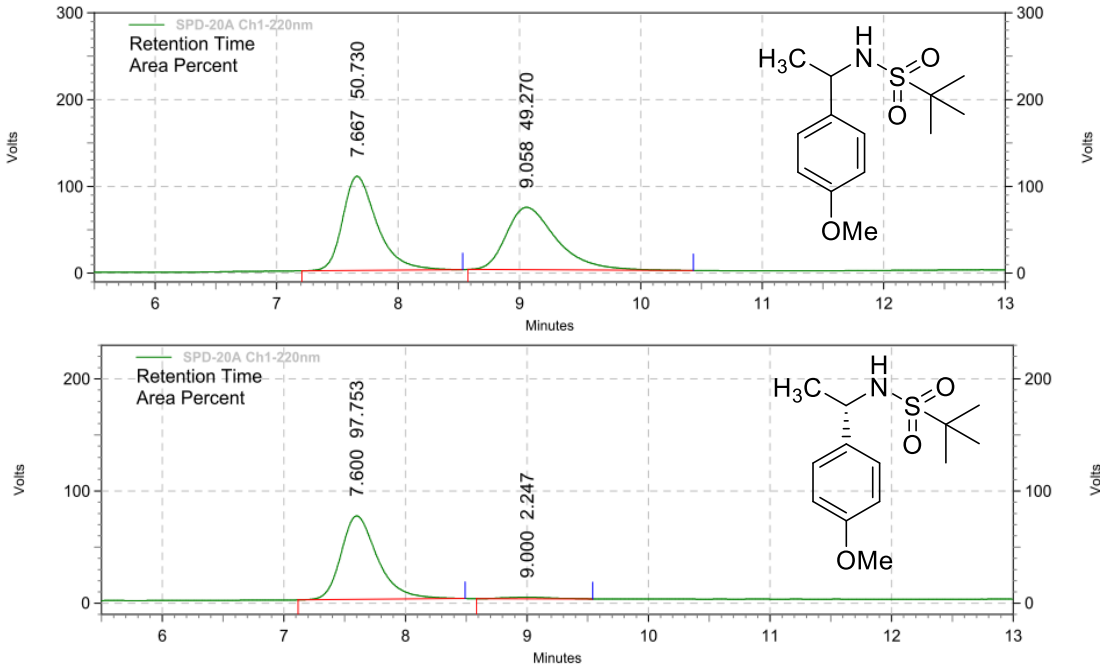
Figure S30. HPLC traces of racemic and enantioenriched **11c**.



Conditions and results:

Column	IA
Mobile Phase	85 : 15 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	220 nm
Temp	25°C

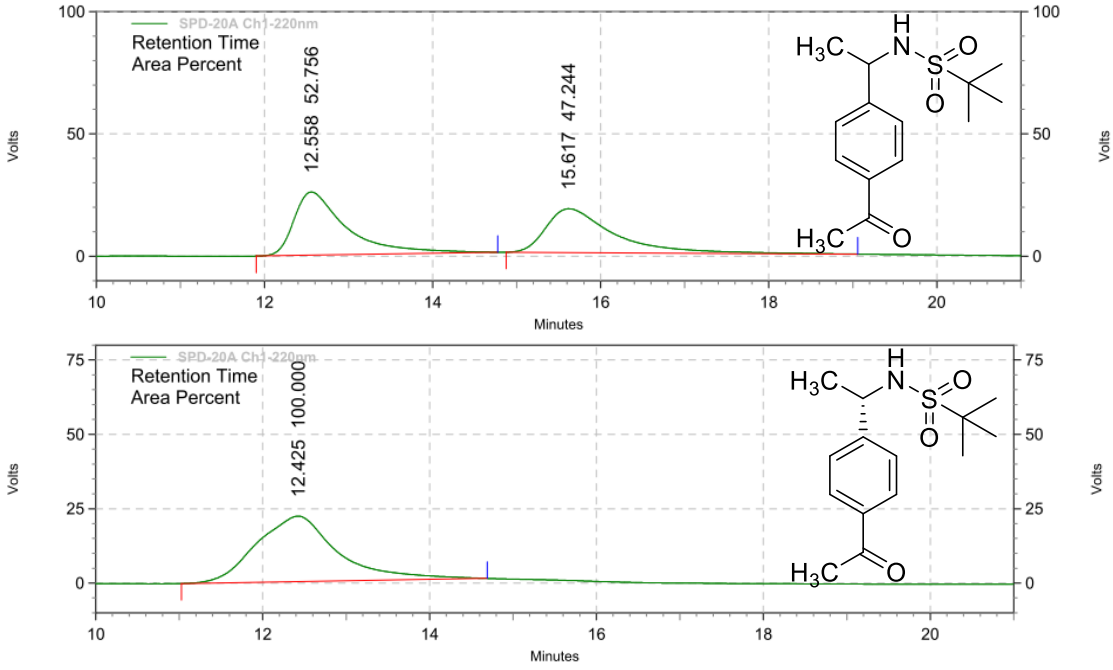
Figure S31. HPLC traces of racemic and enantioenriched **12a**.



Conditions and results:

Column	IA
Mobile Phase	80 : 20 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	220 nm
Temp	25°C

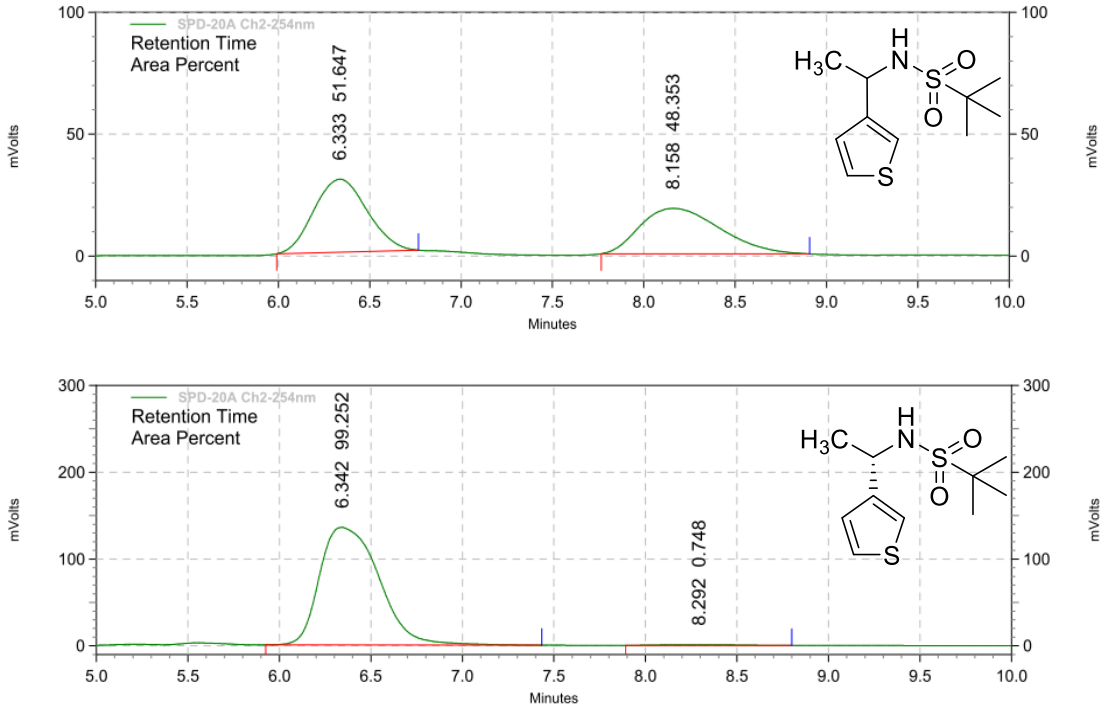
Figure S32. HPLC traces of racemic and enantioenriched **12b**.



Conditions and results:

Column	IA3
Mobile Phase	40 : 60 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.5 mL/min
Detector	220 nm
Temp	25°C

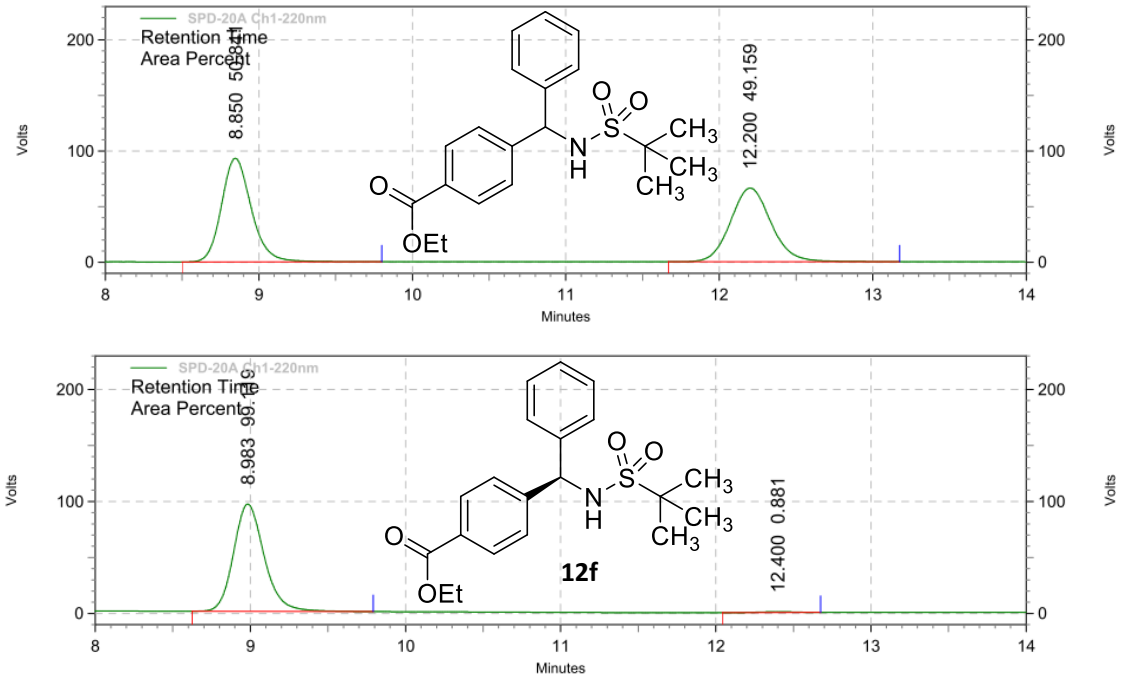
Figure S33. HPLC traces of racemic and enantioenriched **12d**.



Conditions and results:

Column	IA
Mobile Phase	85 : 15 = (5% CH_3CN/CH_3OH) : H_2O
Flow	0.8 mL/min
Detector	220 nm
Temp	25°C

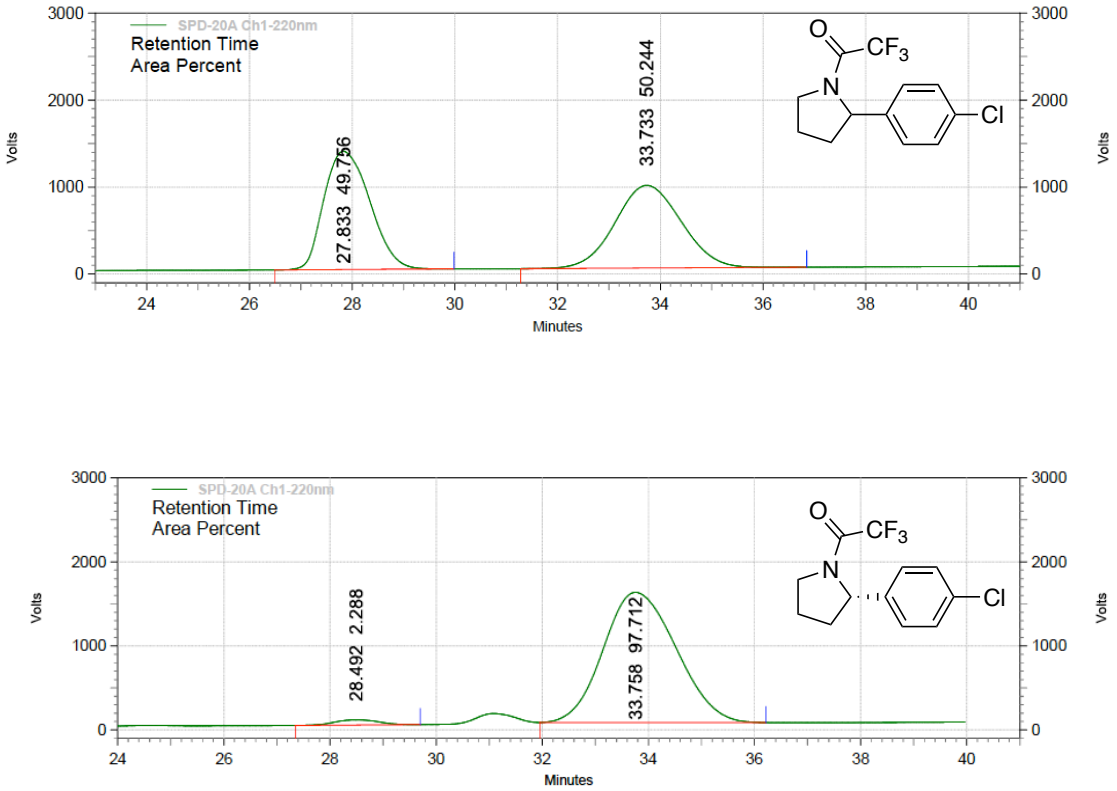
Figure S34. HPLC traces of racemic and enantioenriched **12e**.



Conditions and results:

Column	IA
Mobile Phase	1 : 99 = isopropanol : hexane
Flow	0.8 mL/min
Detector	220 nm
Temp	25°C

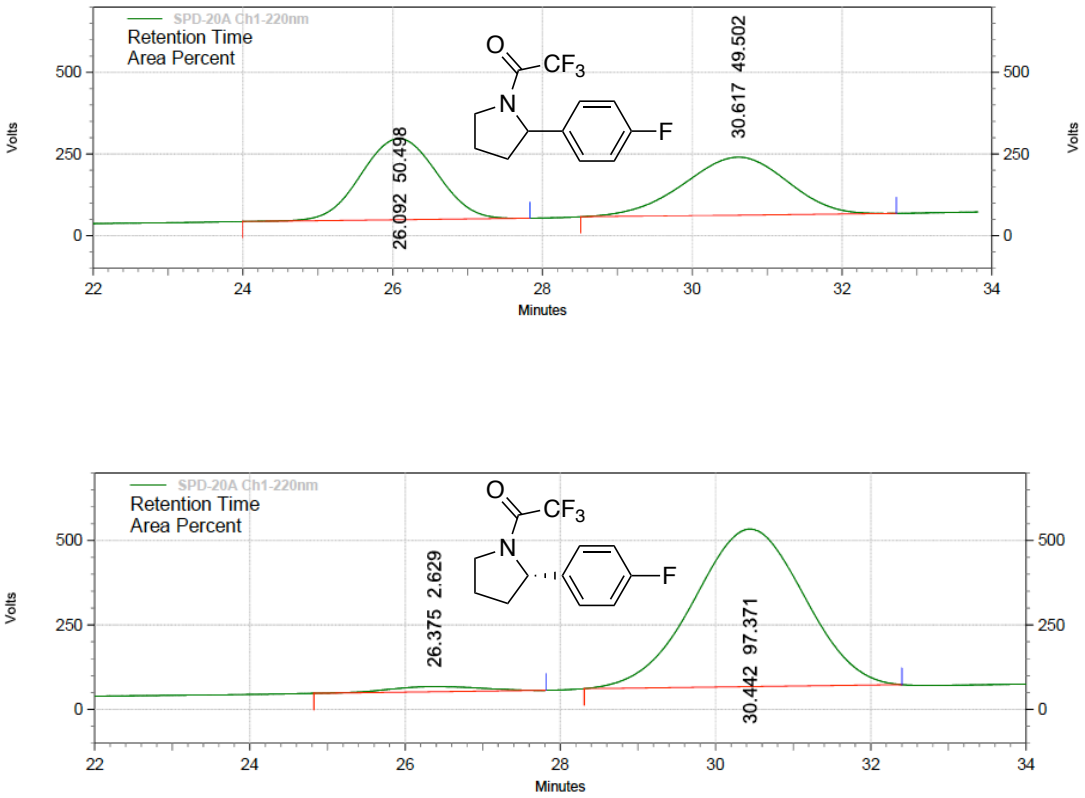
Figure S35. HPLC traces of racemic and enantioenriched **12f**.



Conditions and results:

Column	OJ-RH
Mobile Phase	50 : 50 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 40 min.
Flow	1.4 ml/min
Detector	220 nm
Temp	25 °C

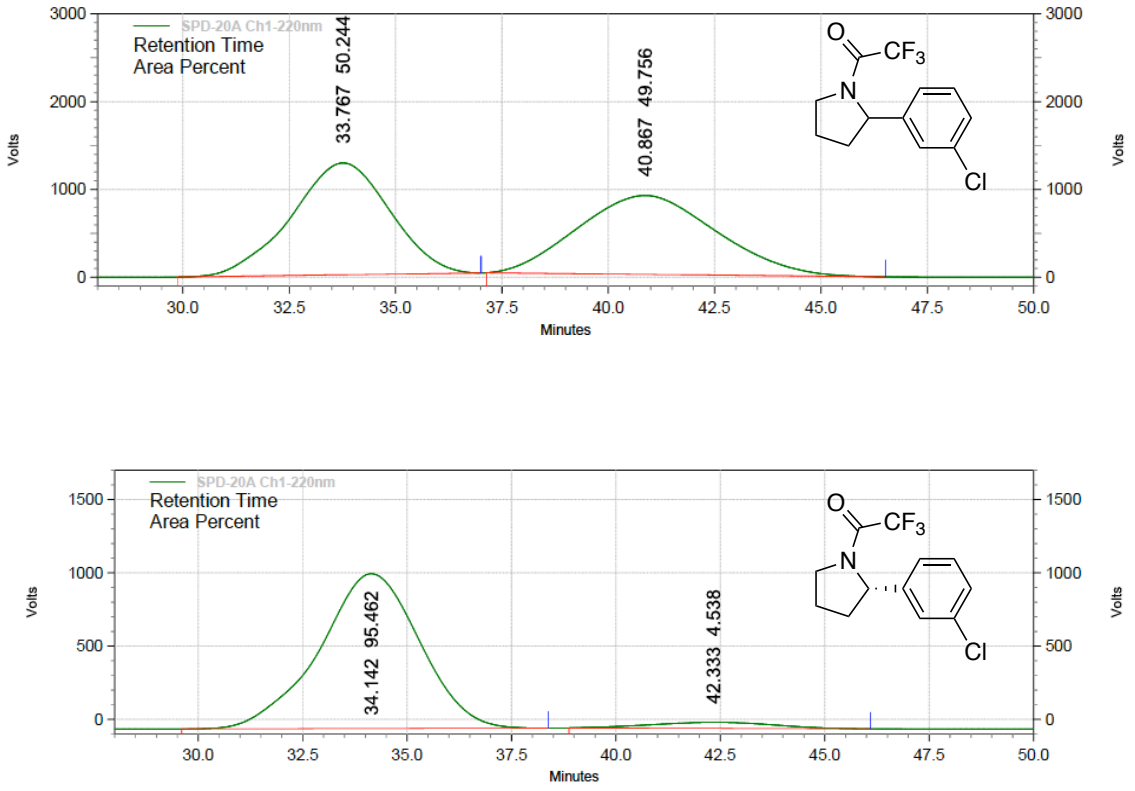
Figure S36. HPLC traces of racemic and enantioenriched **13a**.



Conditions and results:

Column	OJ-RH
Mobile Phase	50 : 50 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 40 min.
Flow	1.4 ml/min
Detector	220 nm
Temp	25 °C

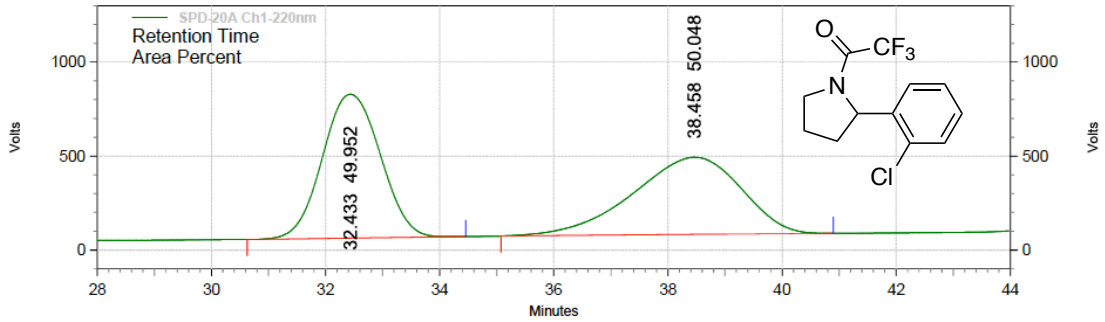
Figure S37. HPLC traces of racemic and enantioenriched **13b**.

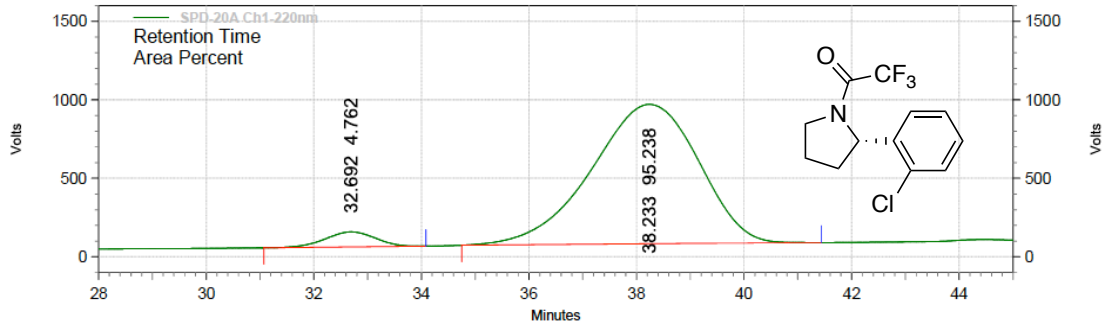


Conditions and results:

Column	OJ-RH
Mobile Phase	35 : 65 = (H_2O : 5% CH_3CN/CH_3OH)
Flow	0.5 ml/min
Detector	220 nm
Temp	25 °C

Figure S38. HPLC traces of racemic and enantioenriched **13c**.

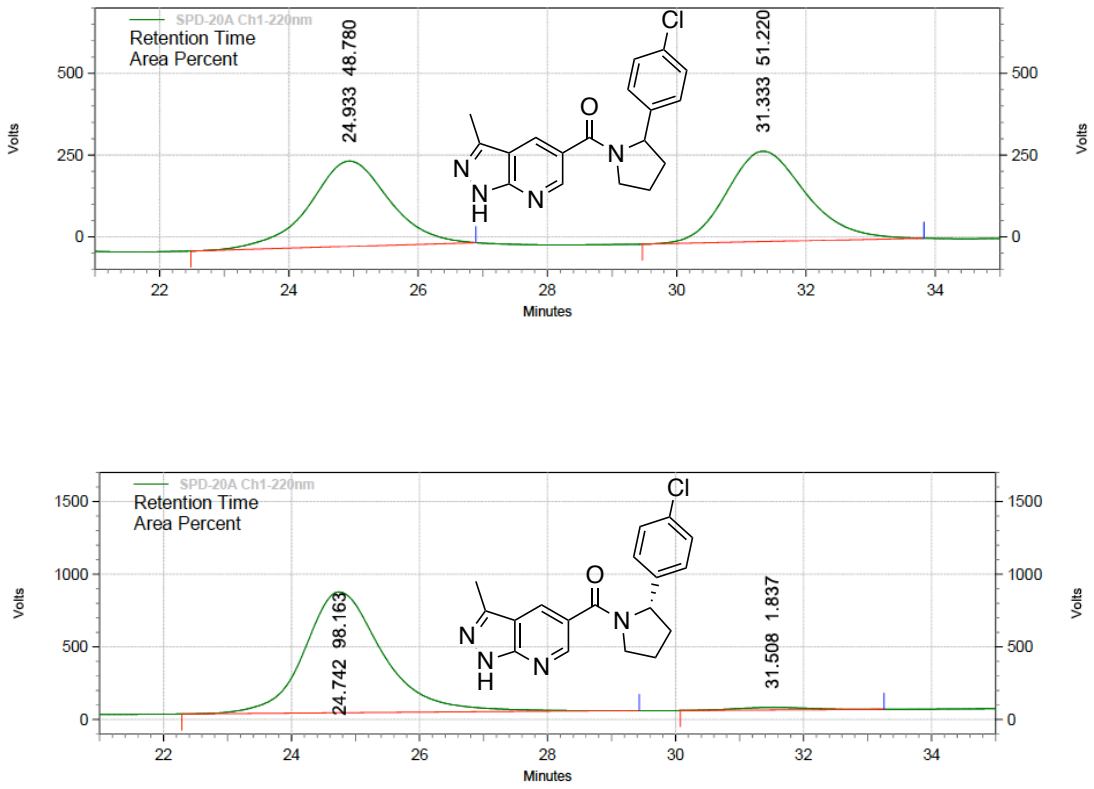




Conditions and results:

Column	OJ-RH
Mobile Phase	55 : 45 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 45 min.
Flow	1.4 ml/min
Detector	220 nm
Temp	25 °C

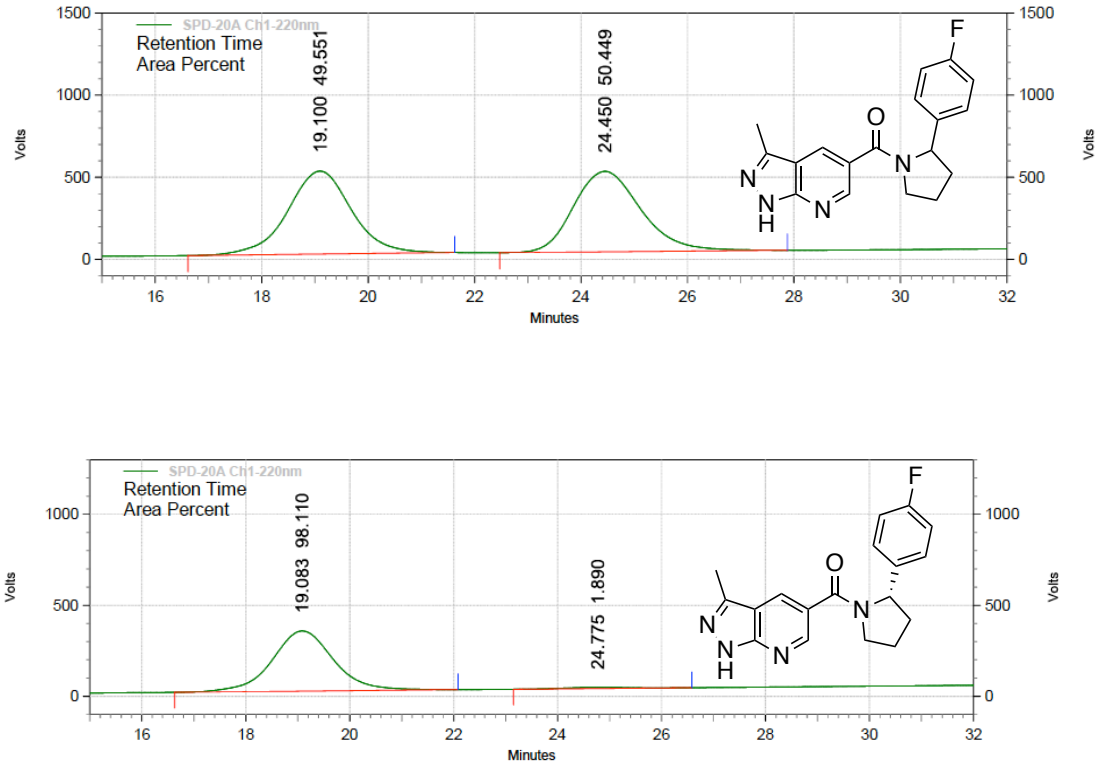
Figure S39. HPLC traces of racemic and enantioenriched **13d**.



Conditions and results:

Column	OJ-RH
Mobile Phase	55 : 45 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 45 min.
Flow	1.2 ml/min
Detector	220 nm
Temp	25 °C

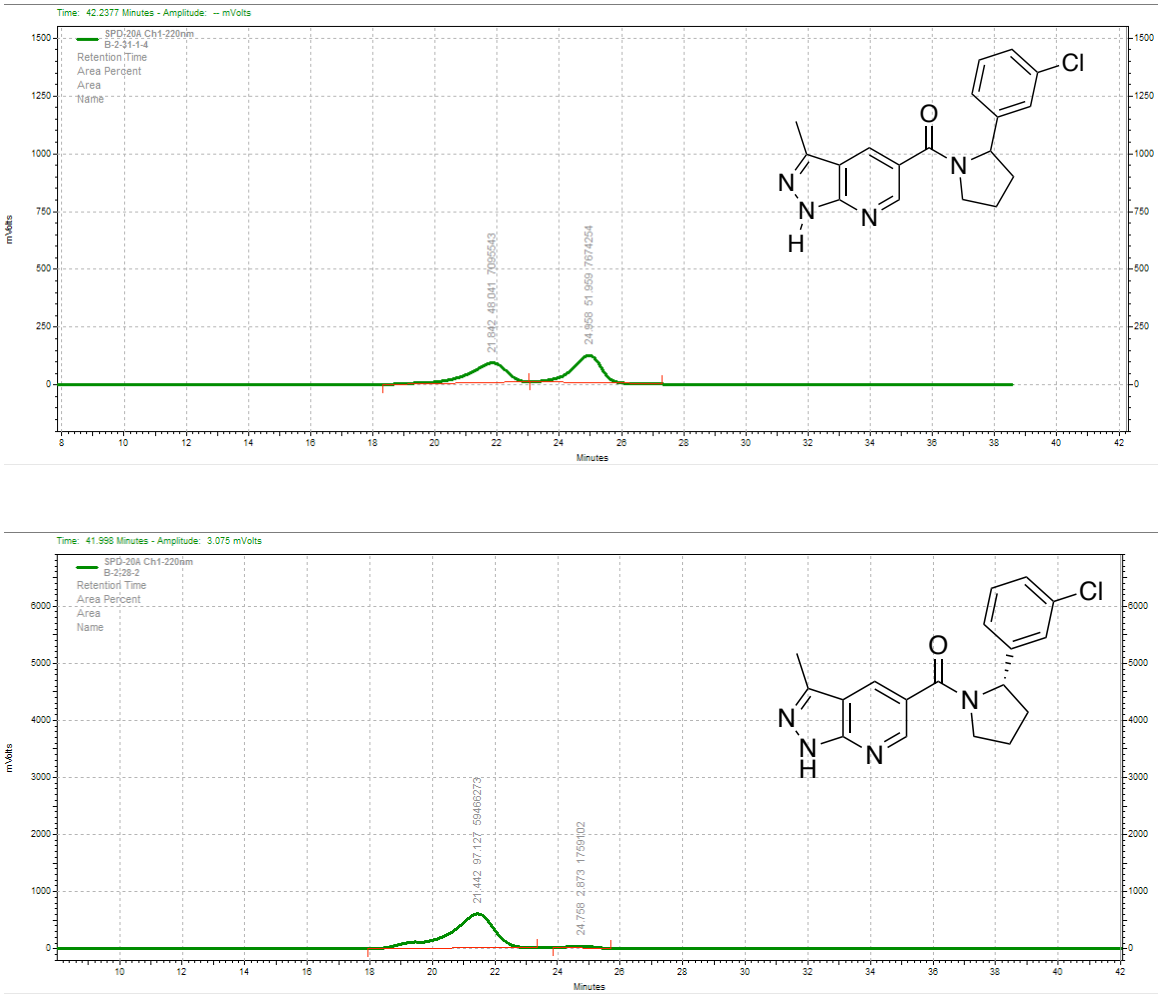
Figure S40. HPLC traces of racemic and enantioenriched **15a**.



Conditions and results:

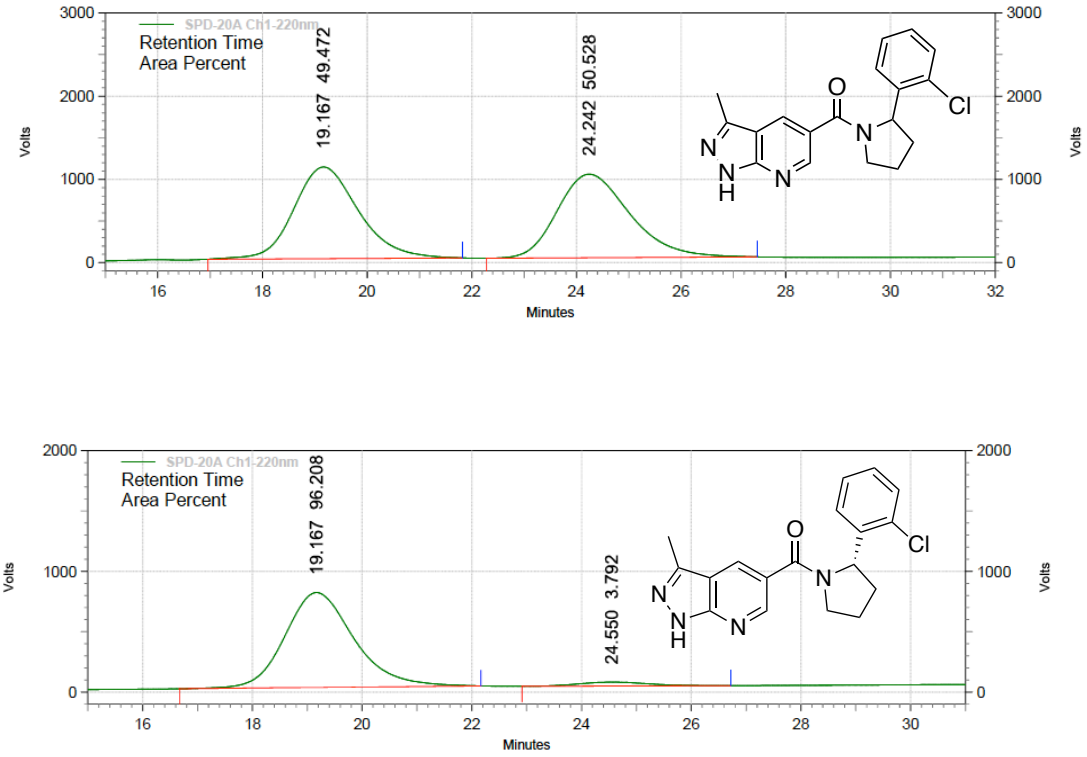
Column	OJ-RH
Mobile Phase	55 : 45 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 45 min.
Flow	1.2 ml/min
Detector	220 nm
Temp	25 °C

Figure S41. HPLC traces of racemic and enantioenriched **15b**.



Column	OJ-RH
Mobile Phase	80 : 20 = (H_2O : CH_3CN) for 10 min, gradient to 60 : 40 (H_2O : CH_3CN) for 40 min.
Flow	1.0 ml/min
Detector	220 nm
Temp	25 °C

Figure S42. HPLC traces of racemic and enantioenriched **15c**.



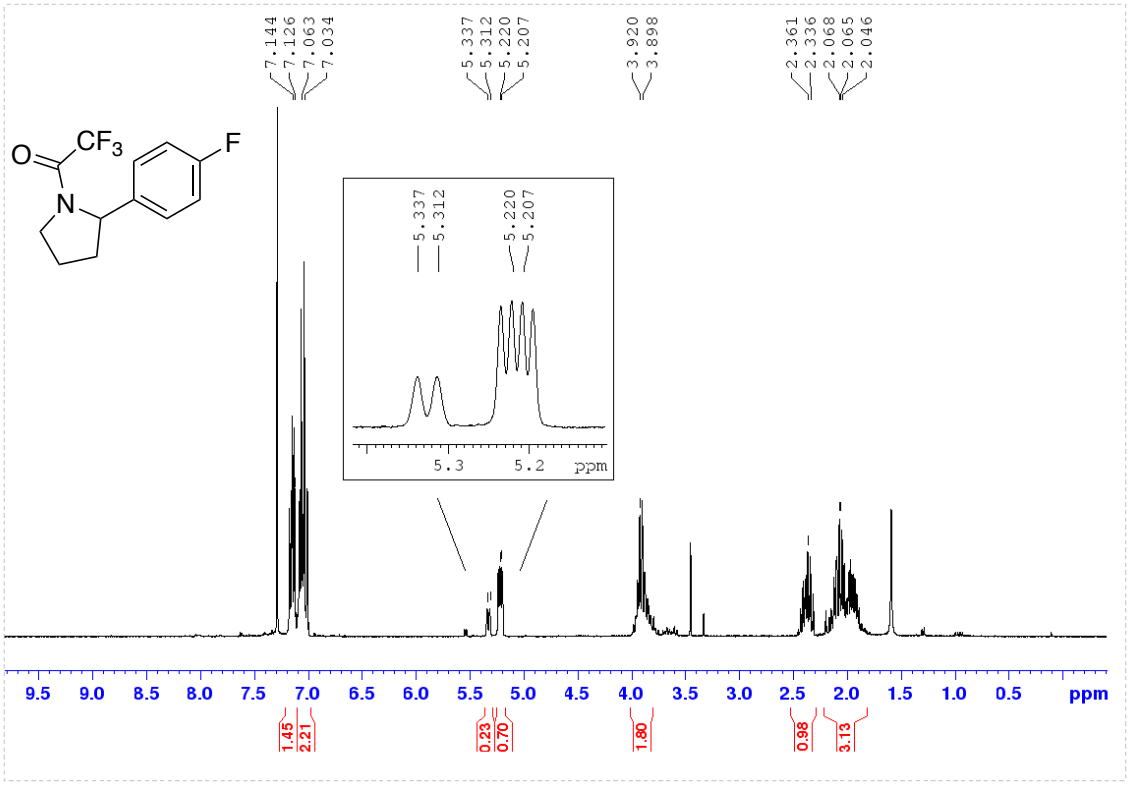
Conditions and results:

Column	OJ-RH
Mobile Phase	55 : 45 = (H_2O : 5% CH_3CN/CH_3OH) for 5 min, gradient to 20 : 80 (H_2O : 5% CH_3CN/CH_3OH) for 45 min.
Flow	1.4 ml/min
Detector	220 nm
Temp	25 °C

Figure S43. HPLC traces of racemic and enantioenriched **15d**.

8. ^{1}H and ^{13}C NMR spectra

Crude, protected cross-coupling product



Deprotected cross-coupling product

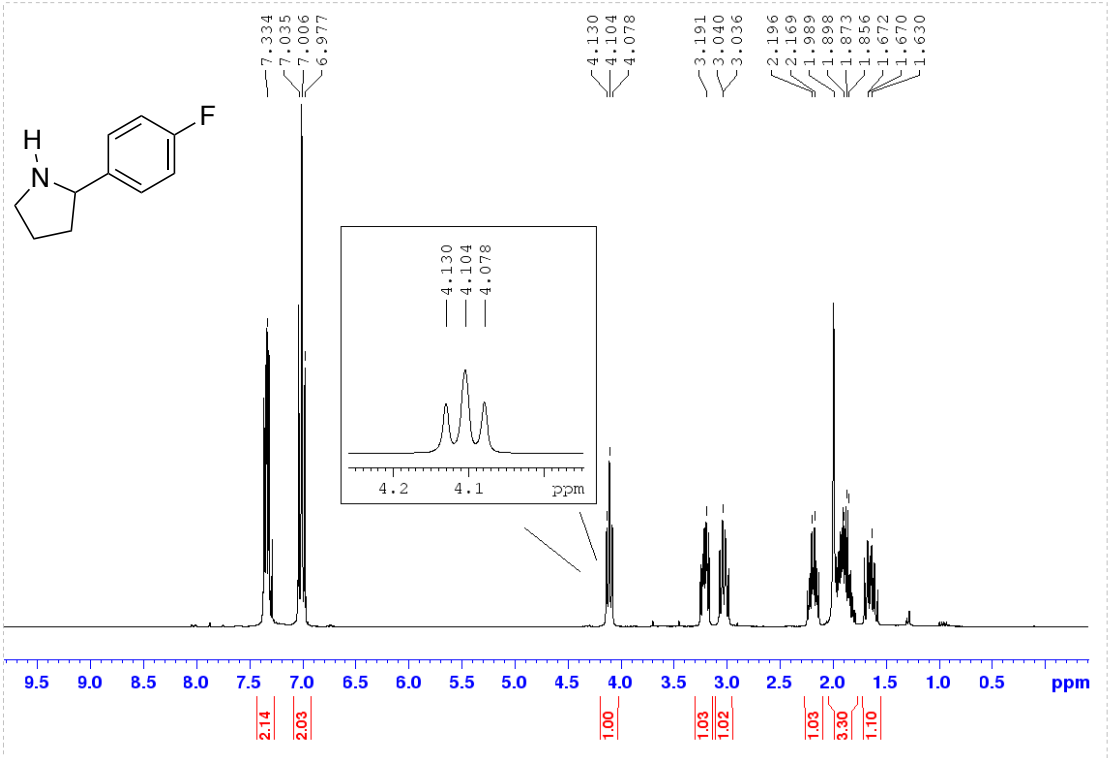


Figure S44. Comparison of ^{1}H NMR spectra from protected (**13b**) and deprotected (**S14**) cross-coupling products to illustrate complexity resulting from amide rotamers.

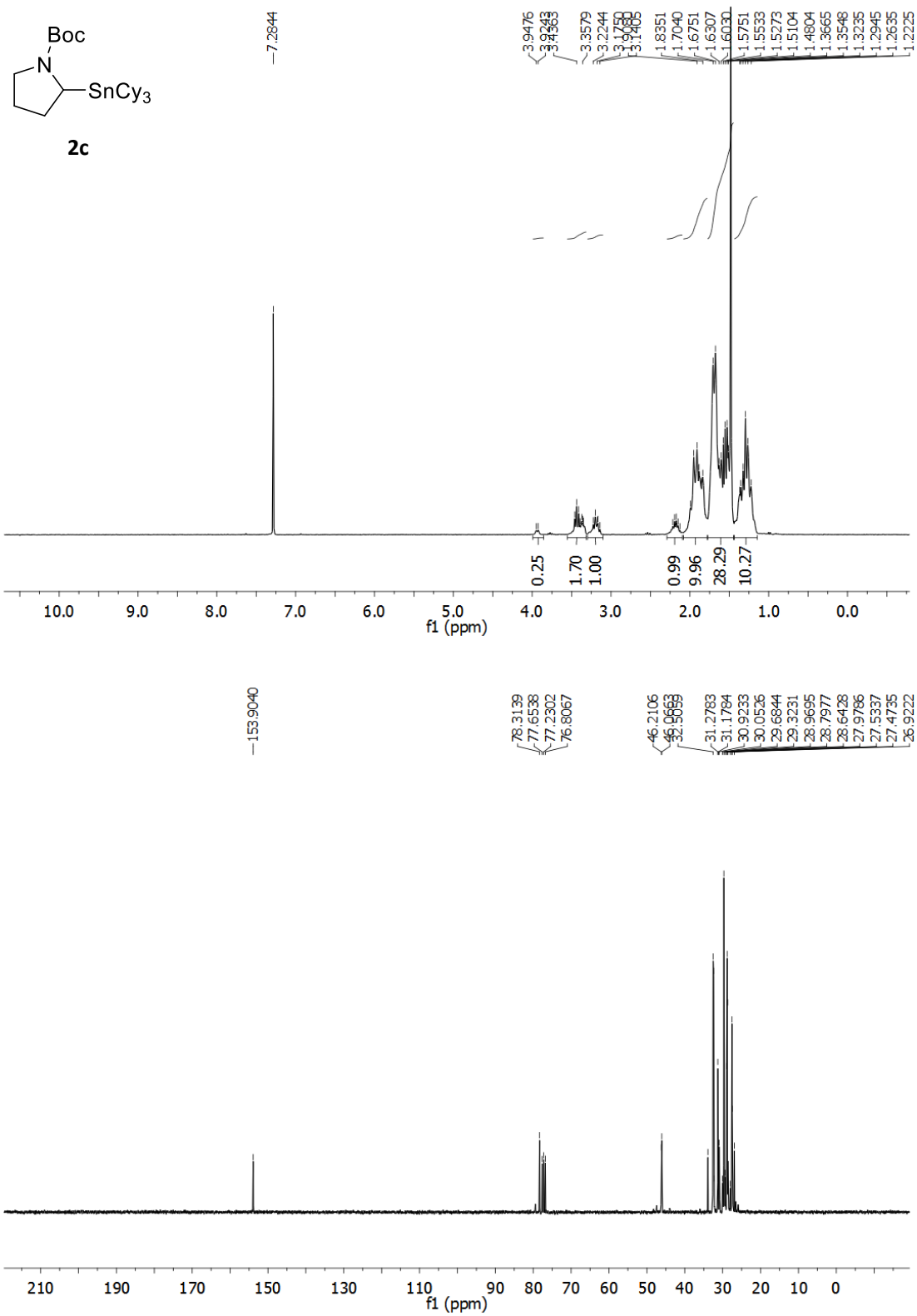


Figure S45. ^{1}H and ^{13}C NMR spectra of **2c**.

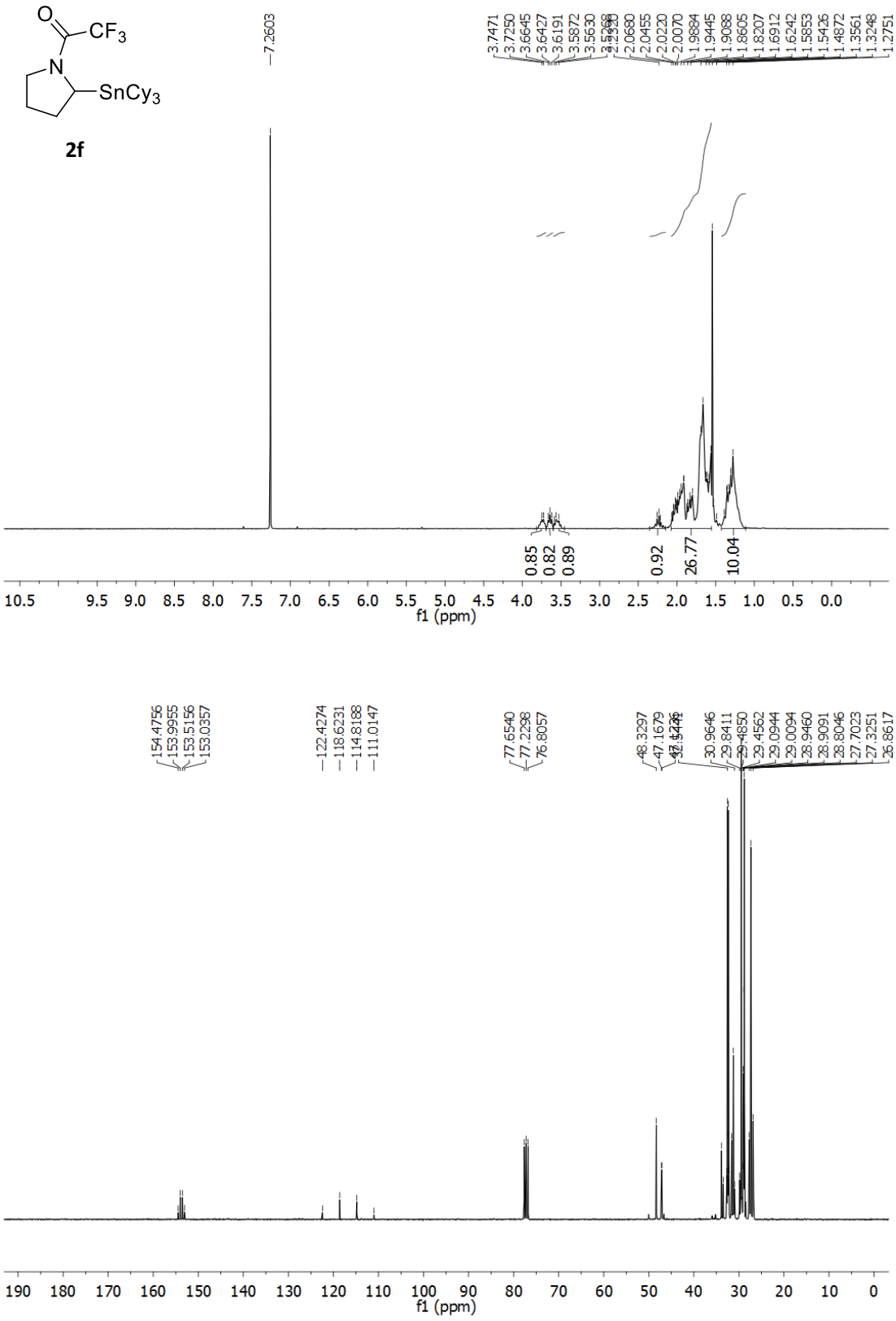


Figure S46. ^{1}H and ^{13}C NMR spectra of **2f**.

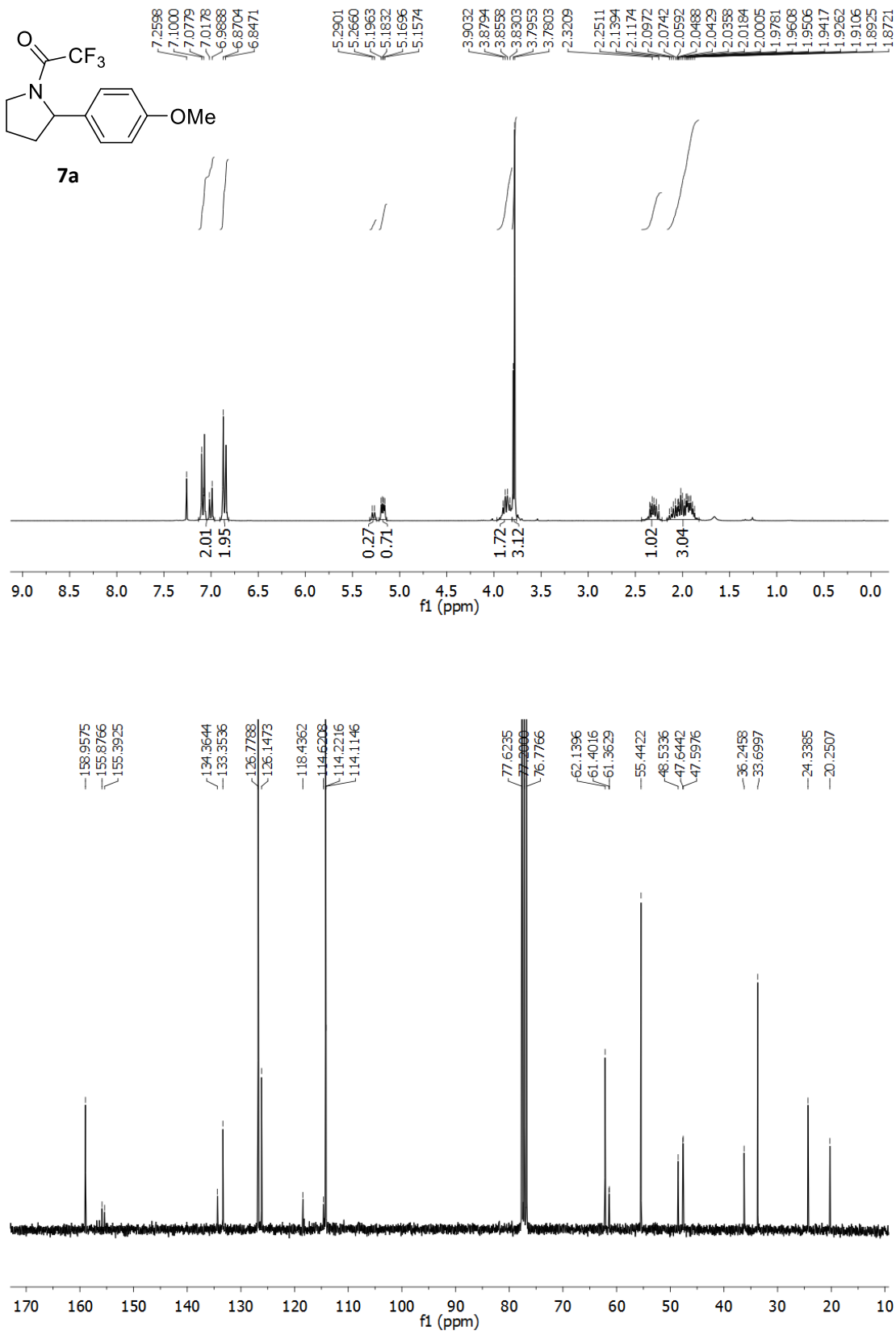


Figure S47. ^{1}H and ^{13}C NMR spectra of **7a**.

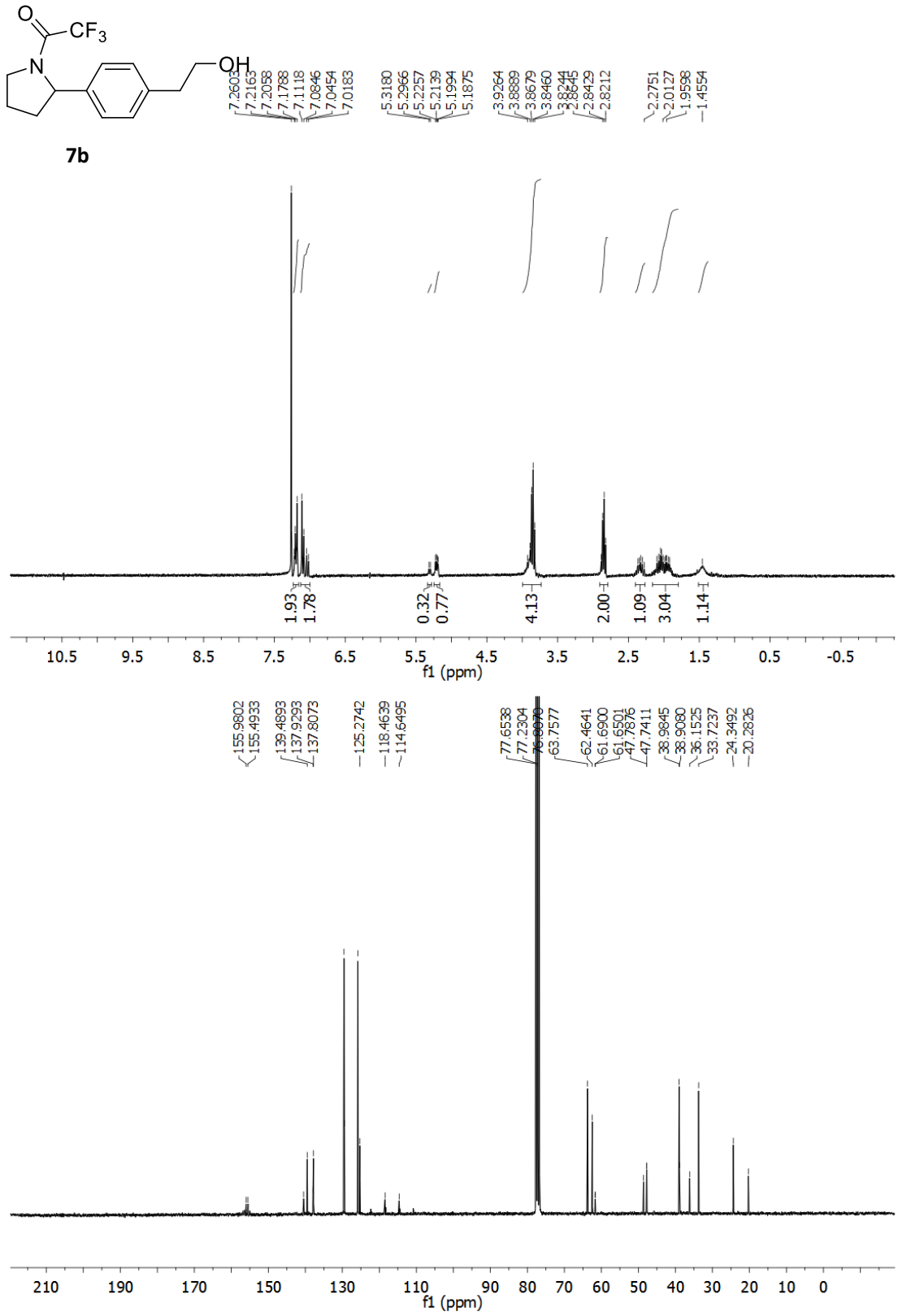


Figure S48. ^{1}H and ^{13}C NMR spectra of **7b**.

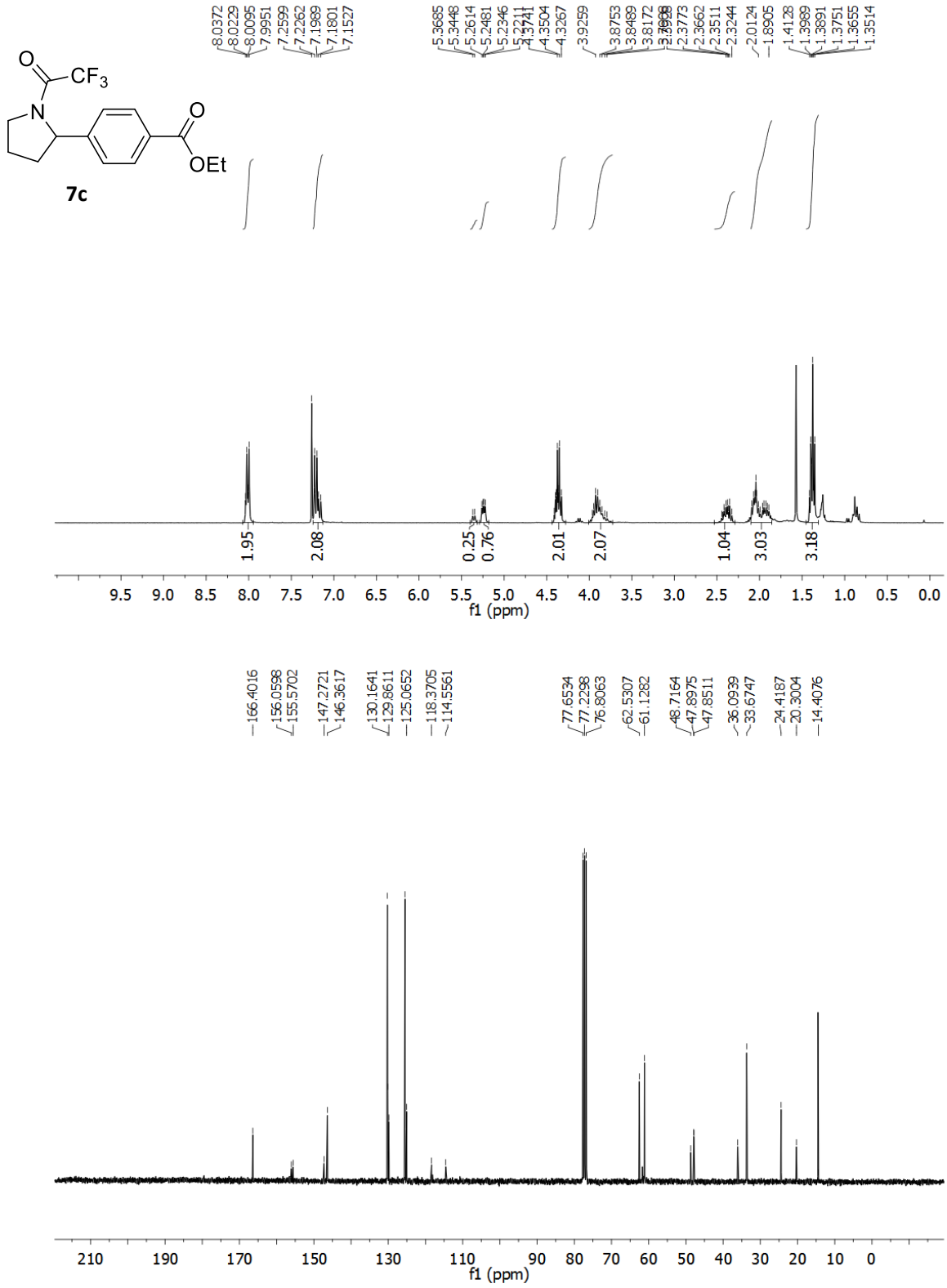


Figure S49. ^{1}H and ^{13}C NMR spectra of **7c**.

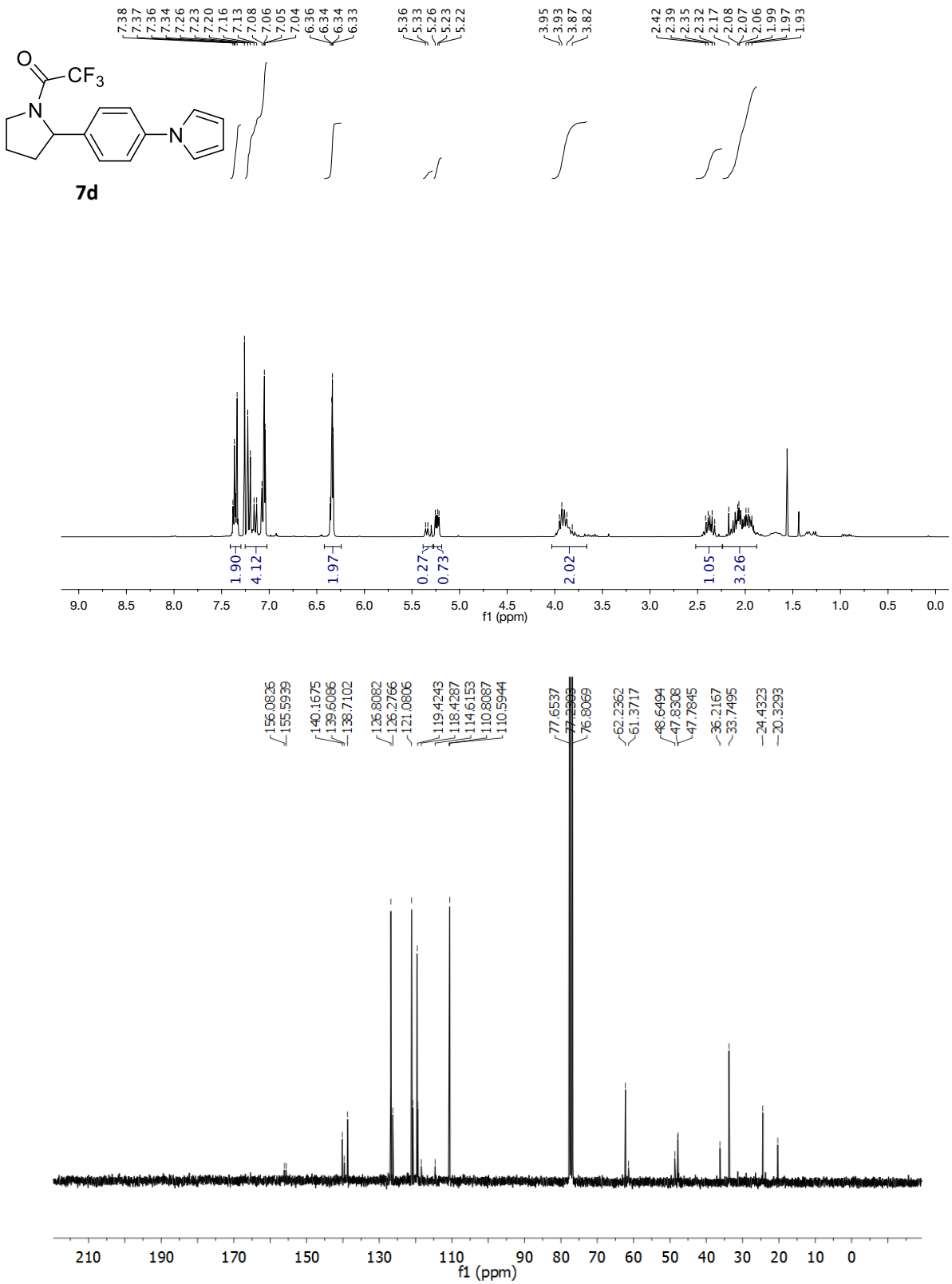


Figure S50. ^{1}H and ^{13}C NMR spectra of **7d**.

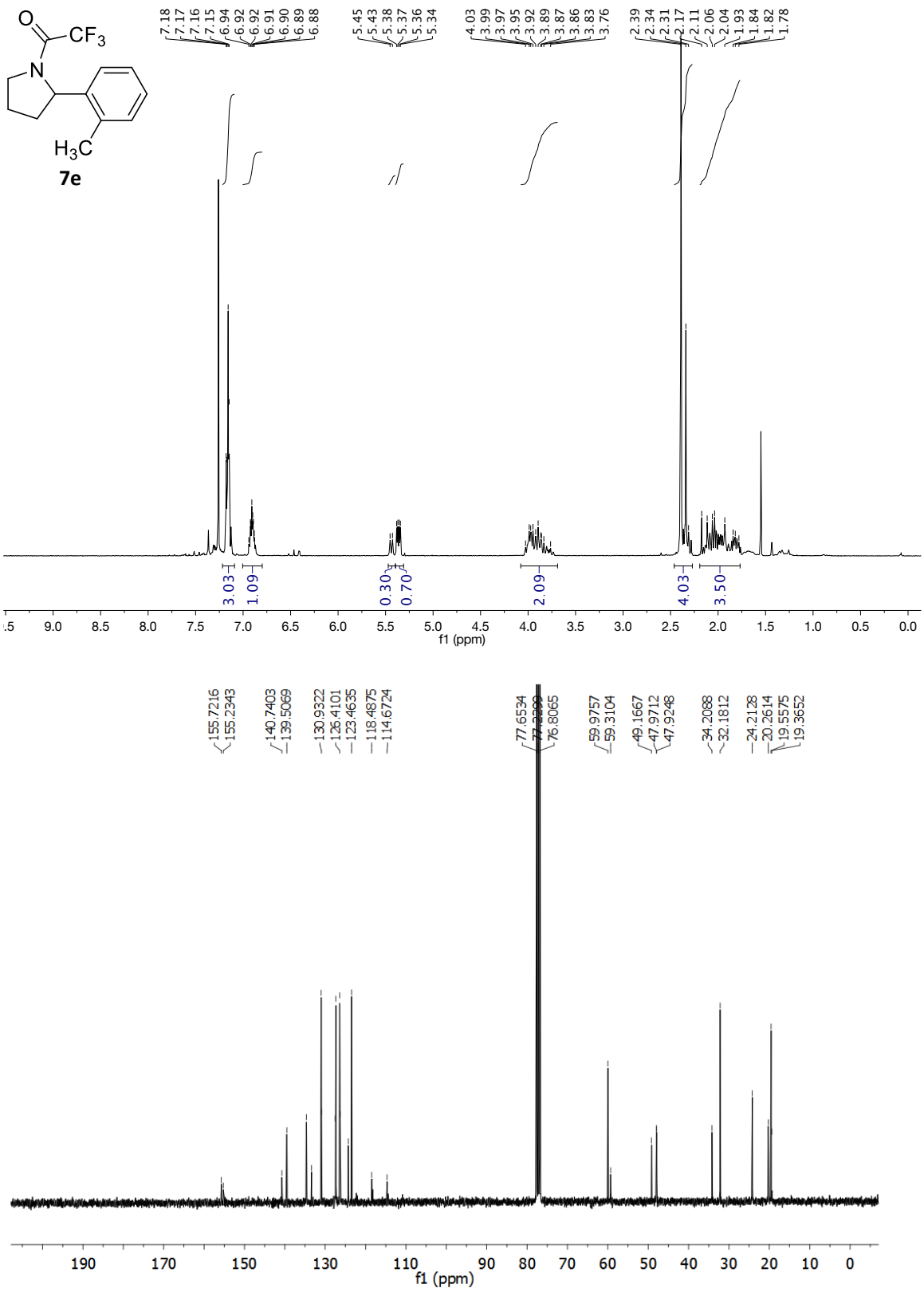


Figure S51. ^{1}H and ^{13}C NMR spectra of **7e**.

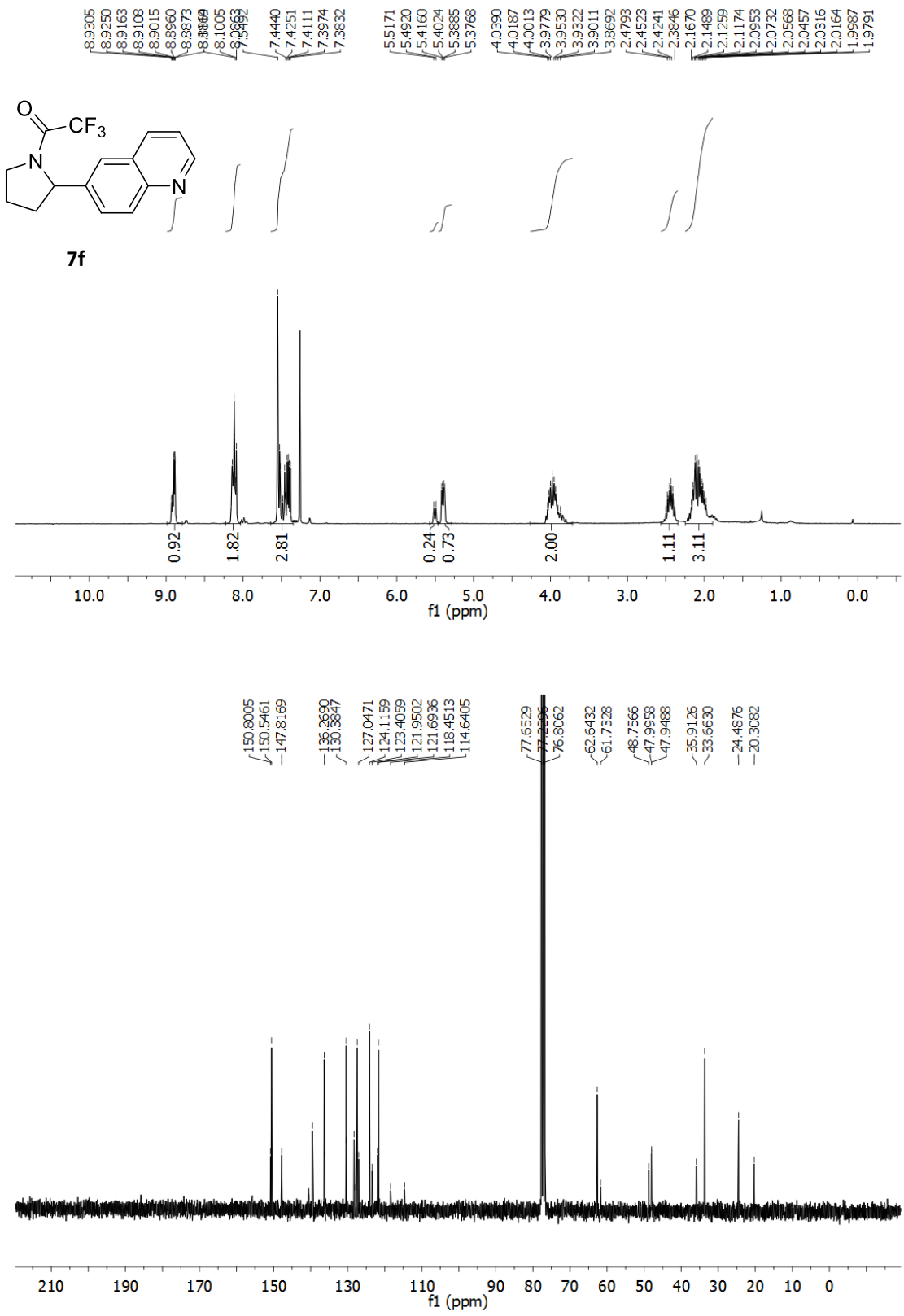


Figure S52. ^{1}H and ^{13}C NMR spectra of **7f**.

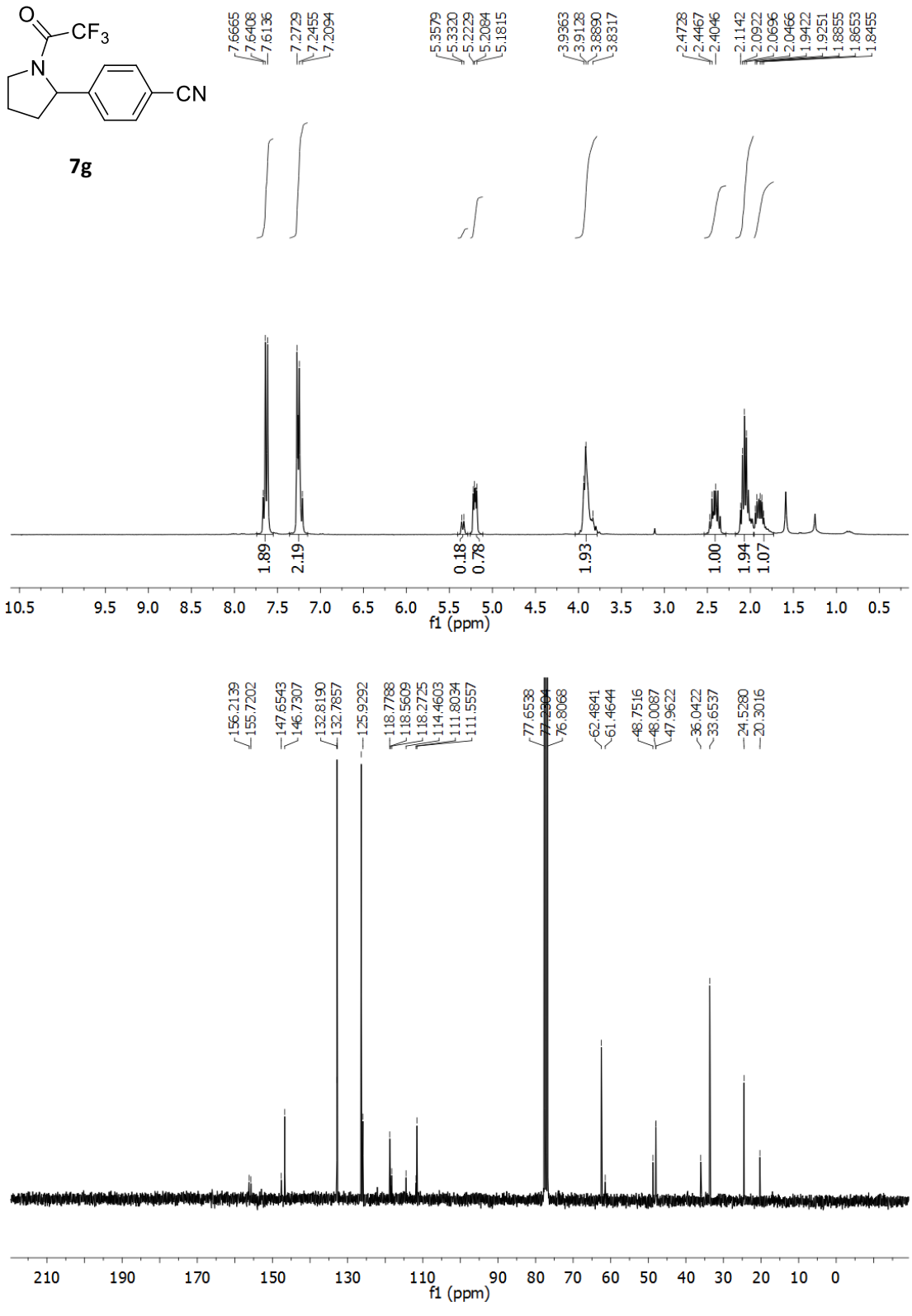


Figure S53. ^{1}H and ^{13}C NMR spectra of **7g**.

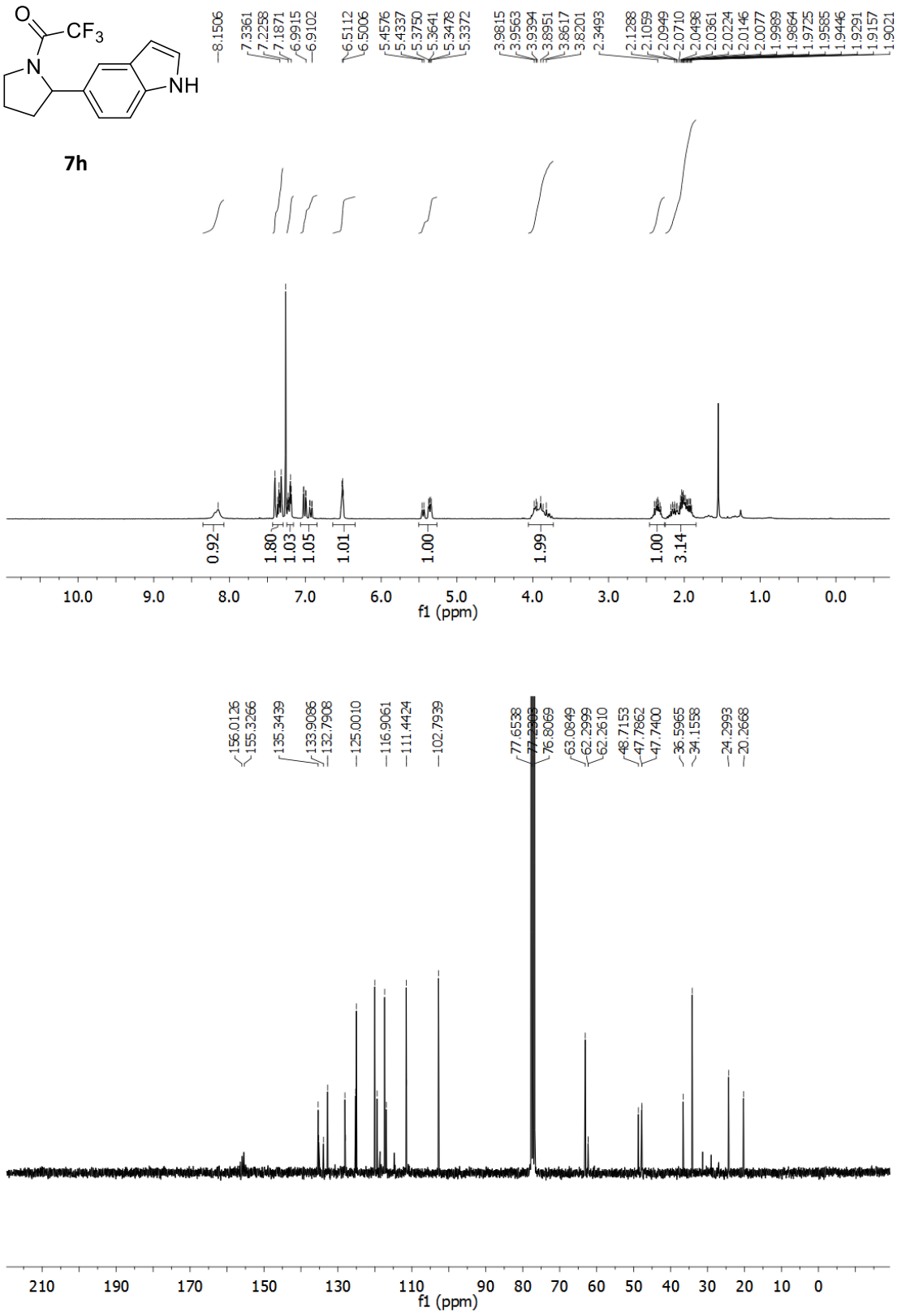


Figure S54. ^{1}H and ^{13}C NMR spectra of **7h**.

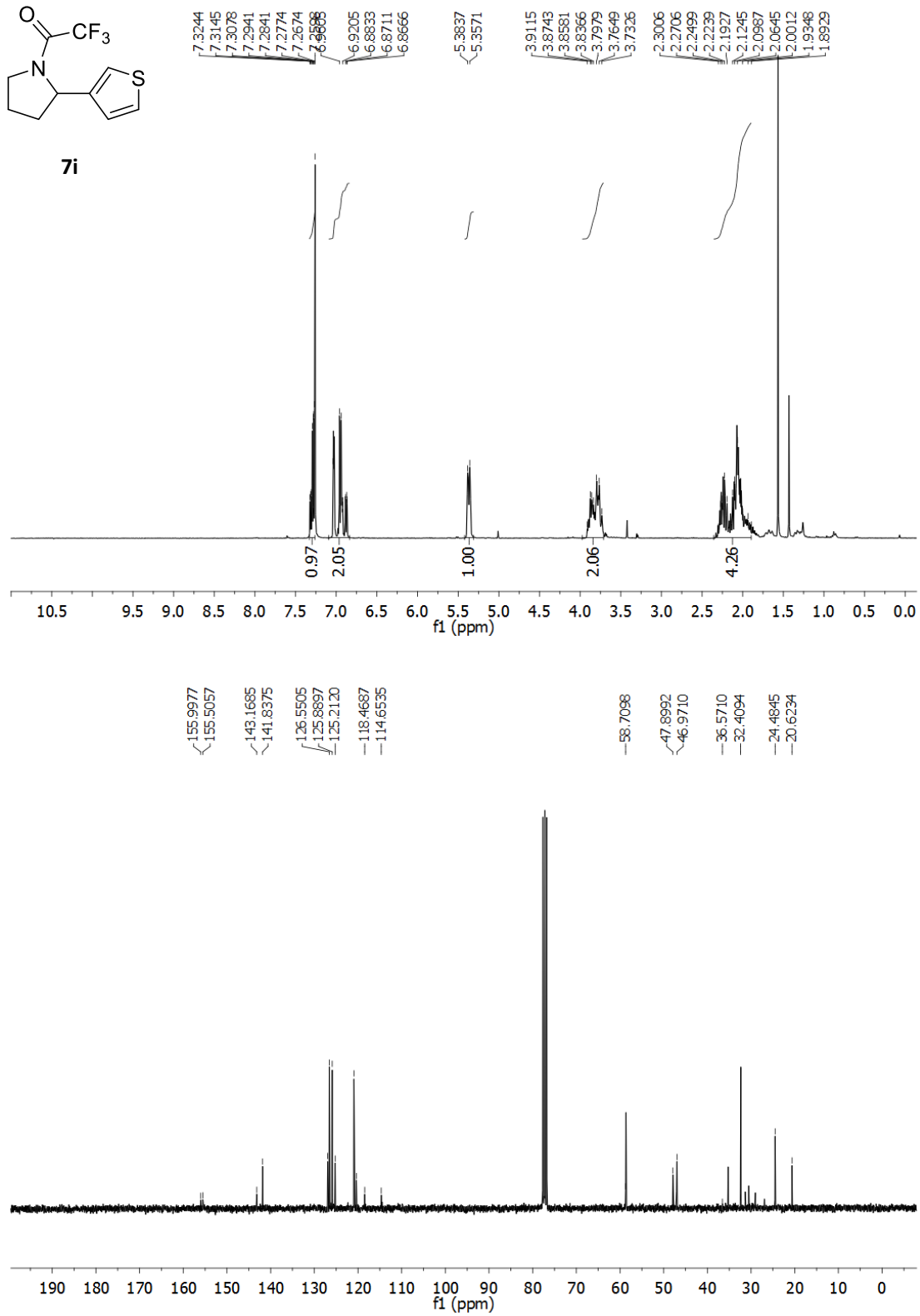


Figure S55. ^{1}H and ^{13}C NMR spectra of **7i**.

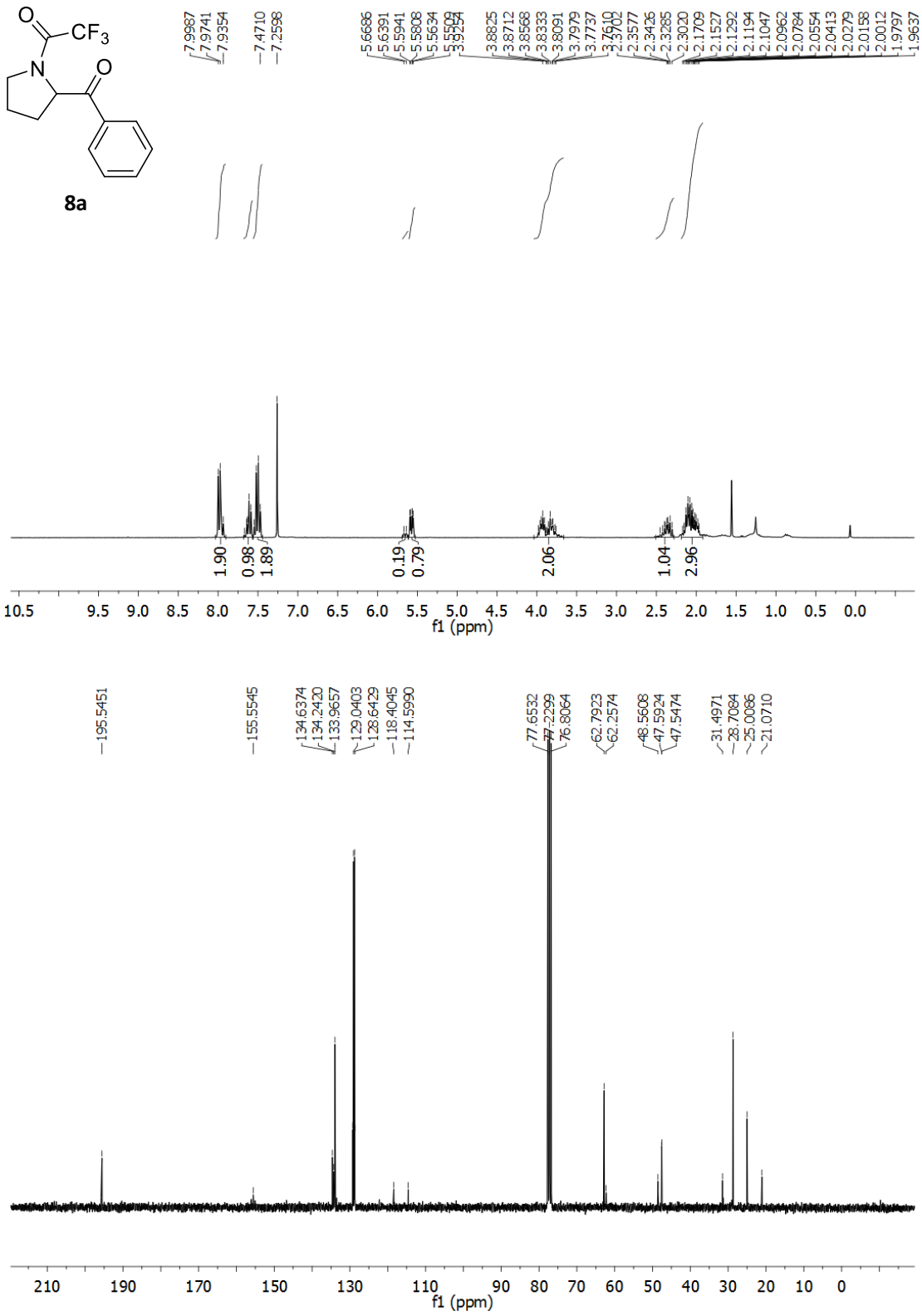


Figure S56. ^{1}H and ^{13}C NMR spectra of **8a**.

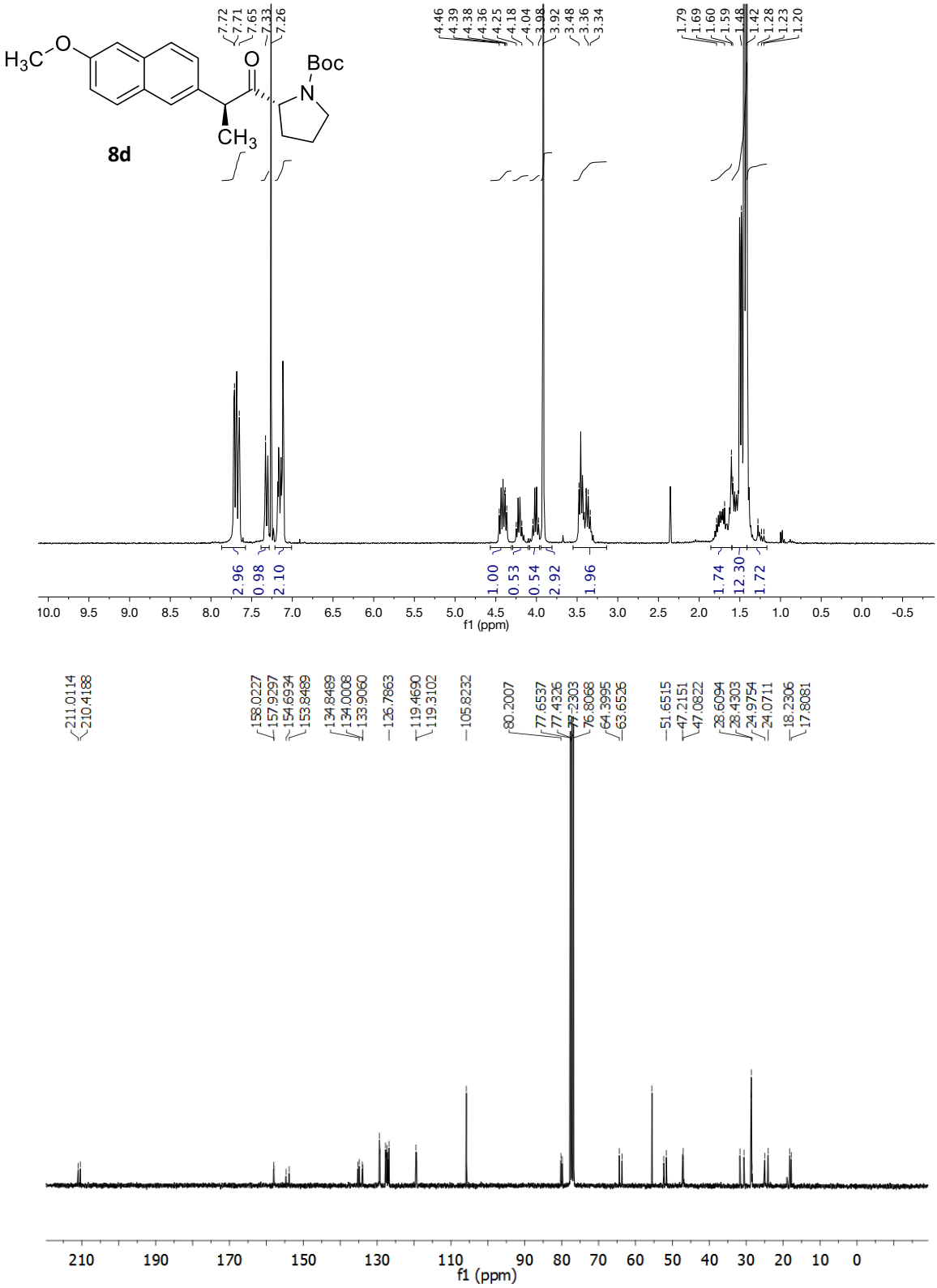


Figure S57. ^{1}H and ^{13}C NMR spectra of **8d**.

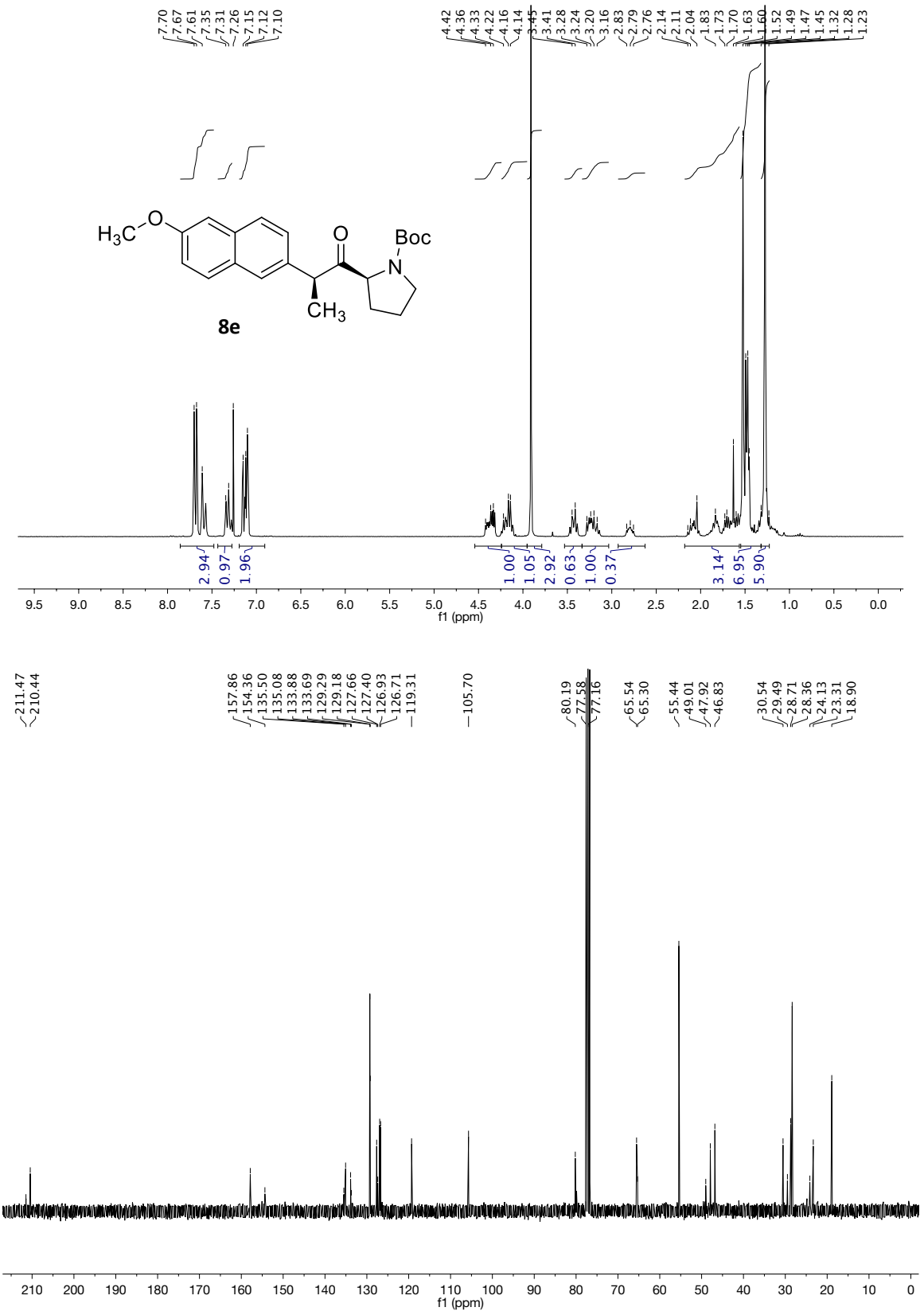


Figure S58. ^{1}H and ^{13}C NMR spectra of **8e**.

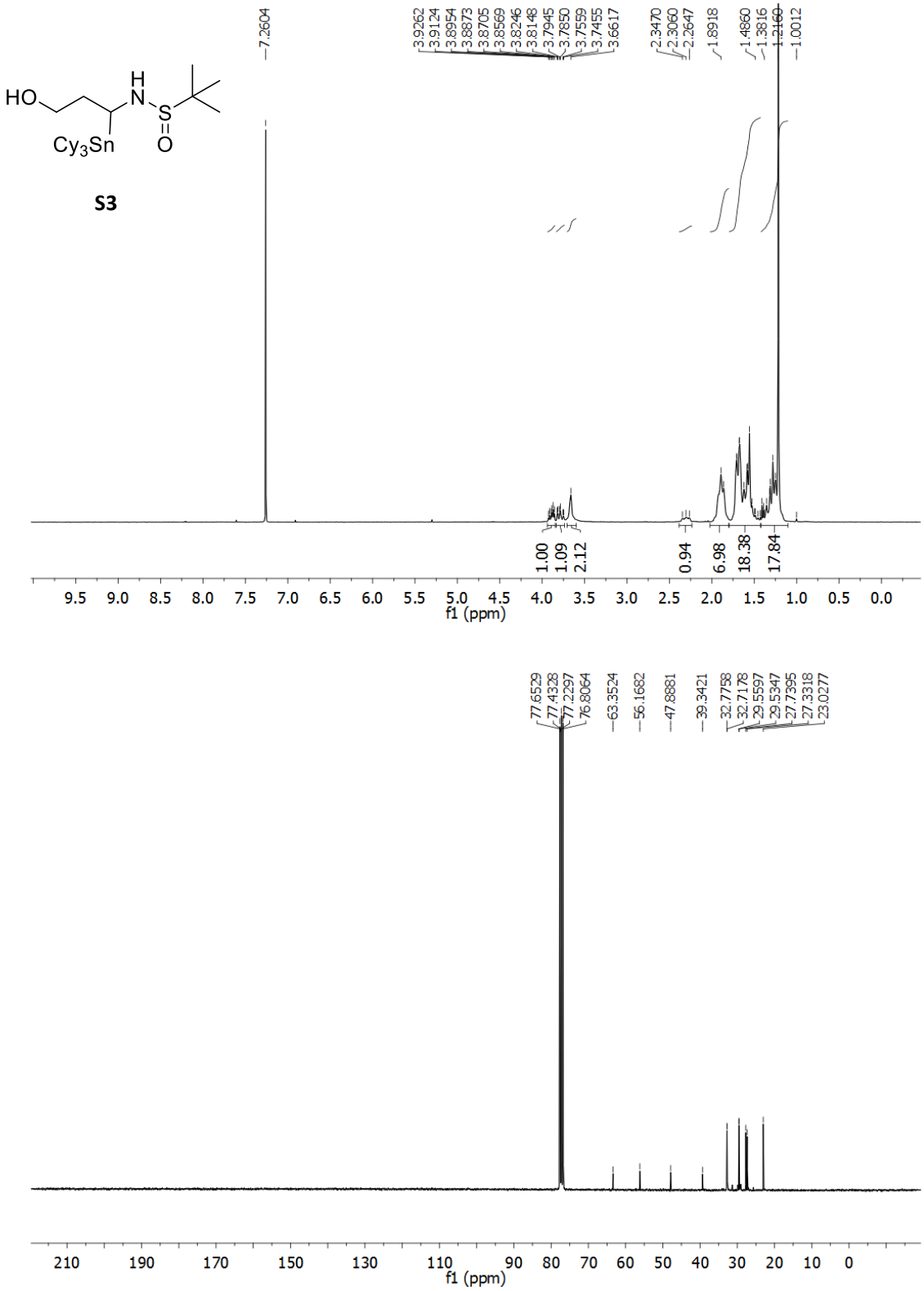


Figure S59. ^{1}H and ^{13}C NMR spectra of **S3**.

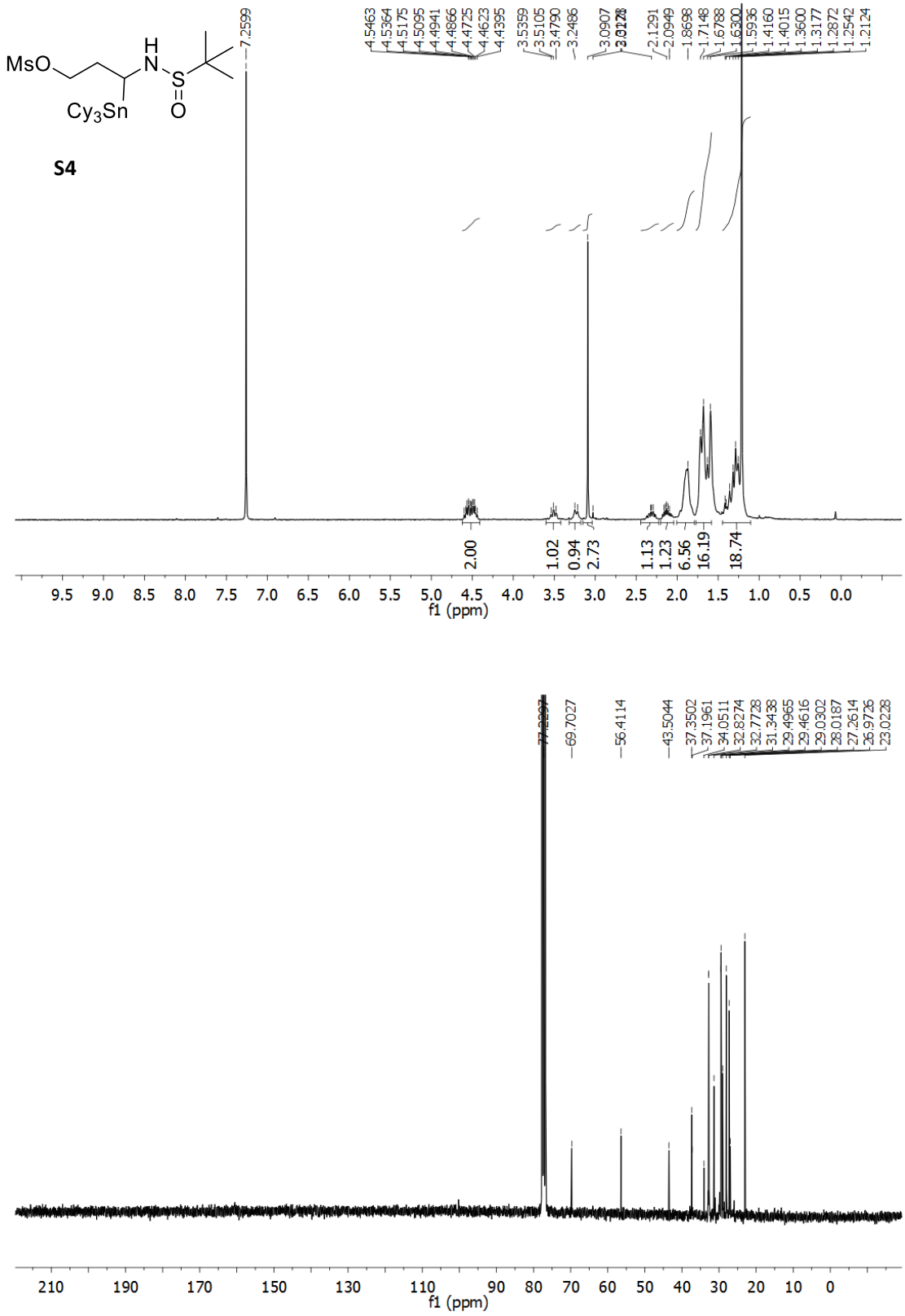


Figure S60. ^{1}H and ^{13}C NMR spectra of **S4**.

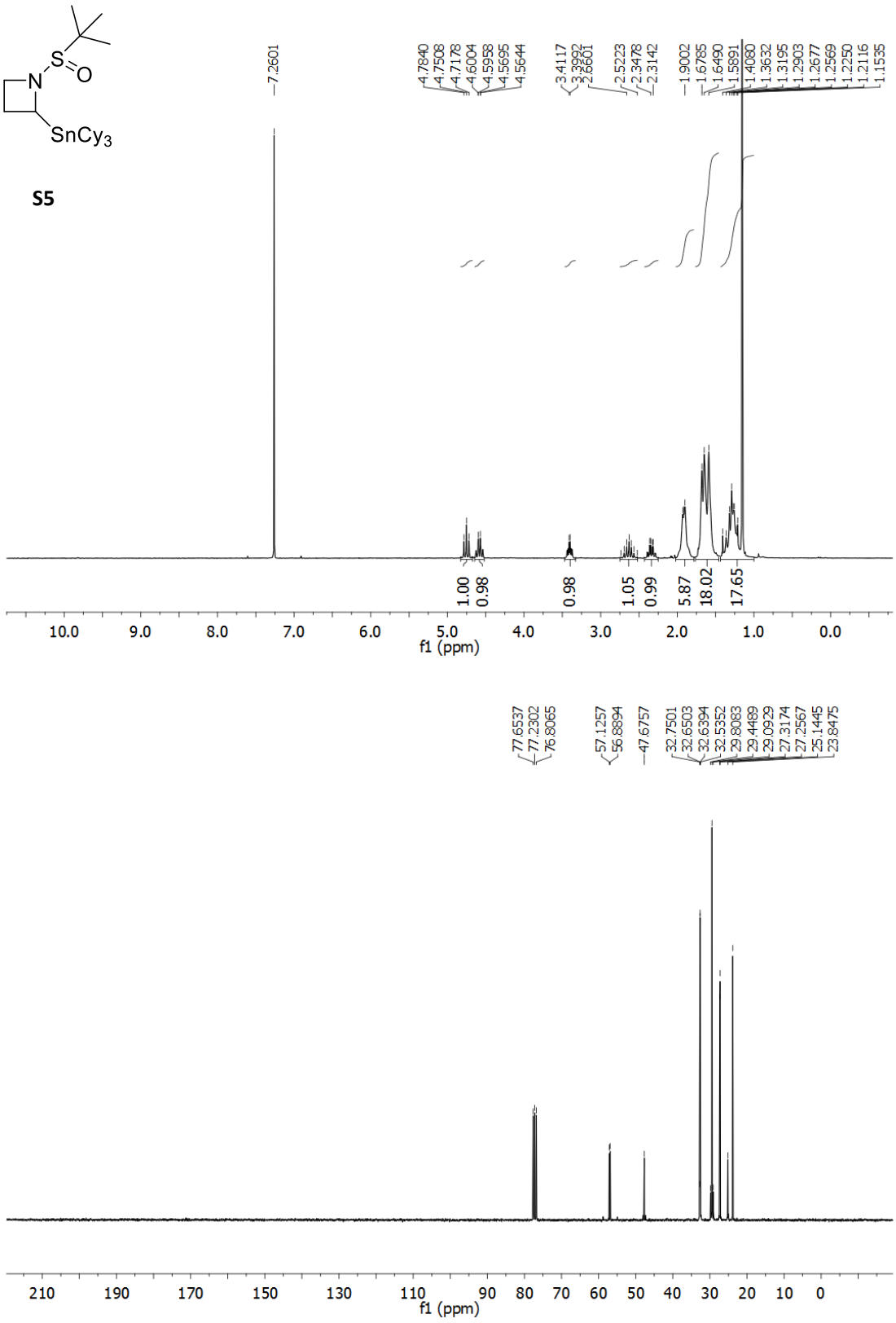


Figure S60. ^{1}H and ^{13}C NMR spectra of **S5**.

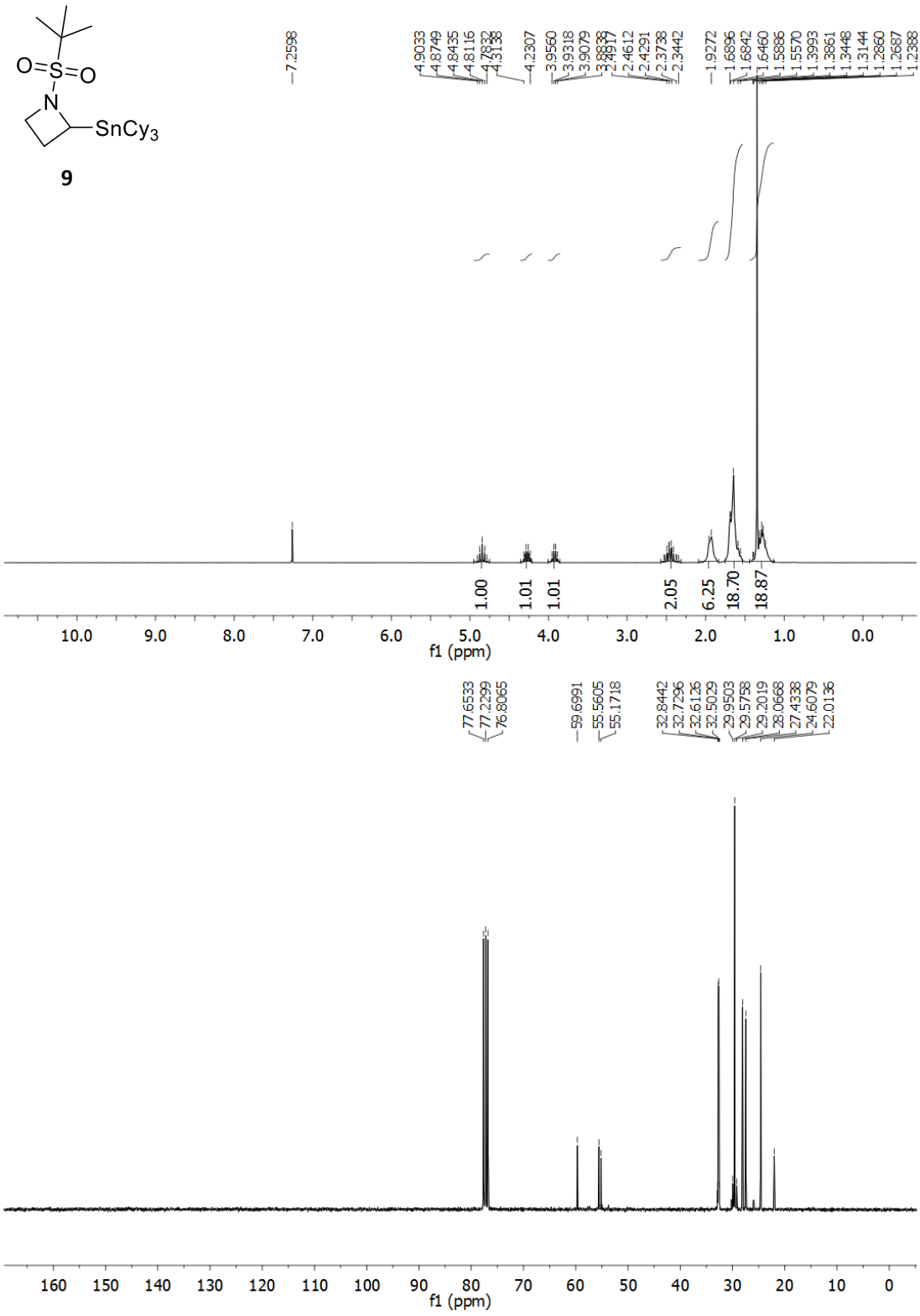


Figure S61. ^{1}H and ^{13}C NMR spectra of **9**.

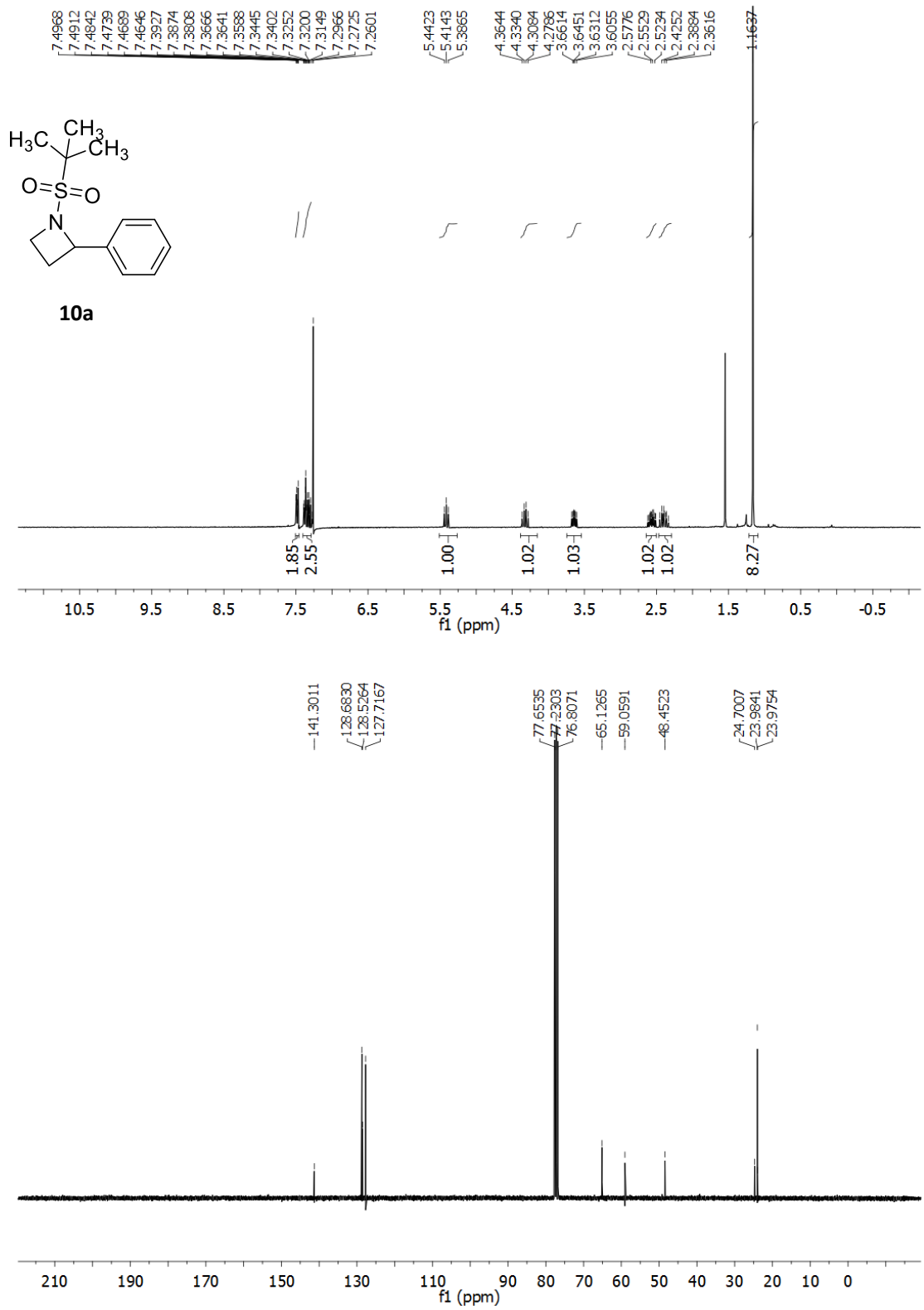


Figure S62. ^{1}H and ^{13}C NMR spectra of **10a**.

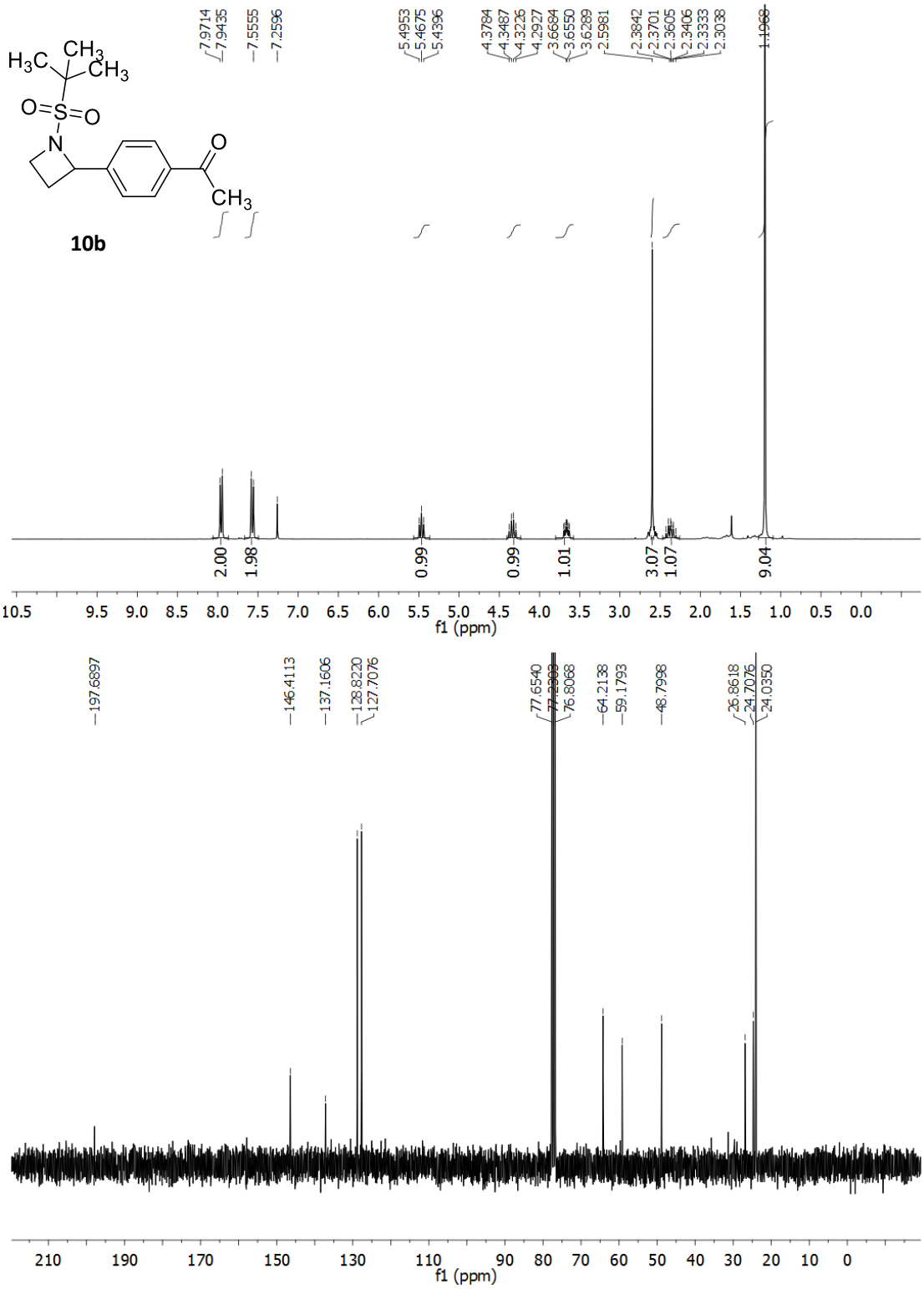


Figure S63. ^{1}H and ^{13}C NMR spectra of **10b**.

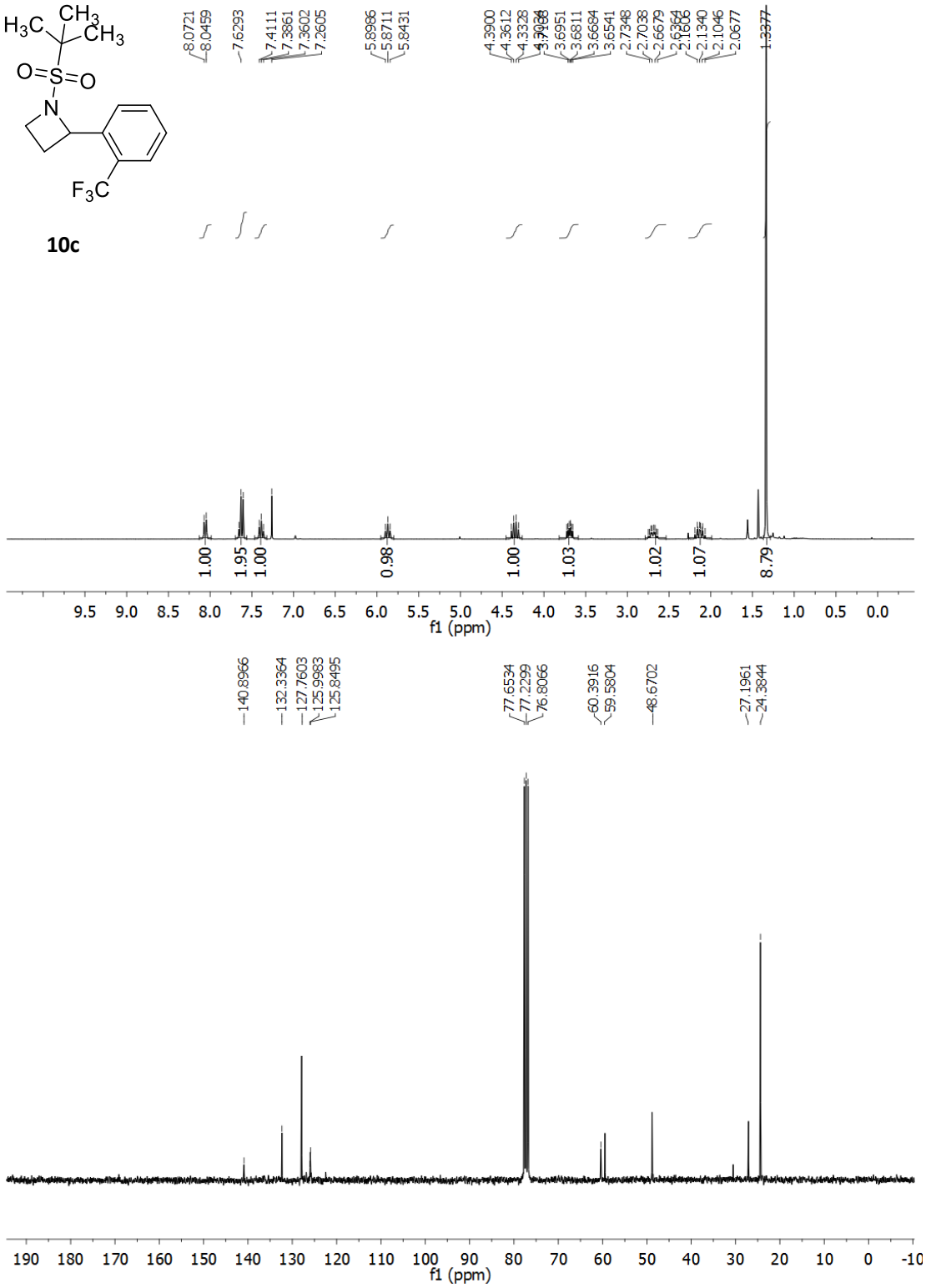


Figure S64. ^{1}H and ^{13}C NMR spectra of **10c**.

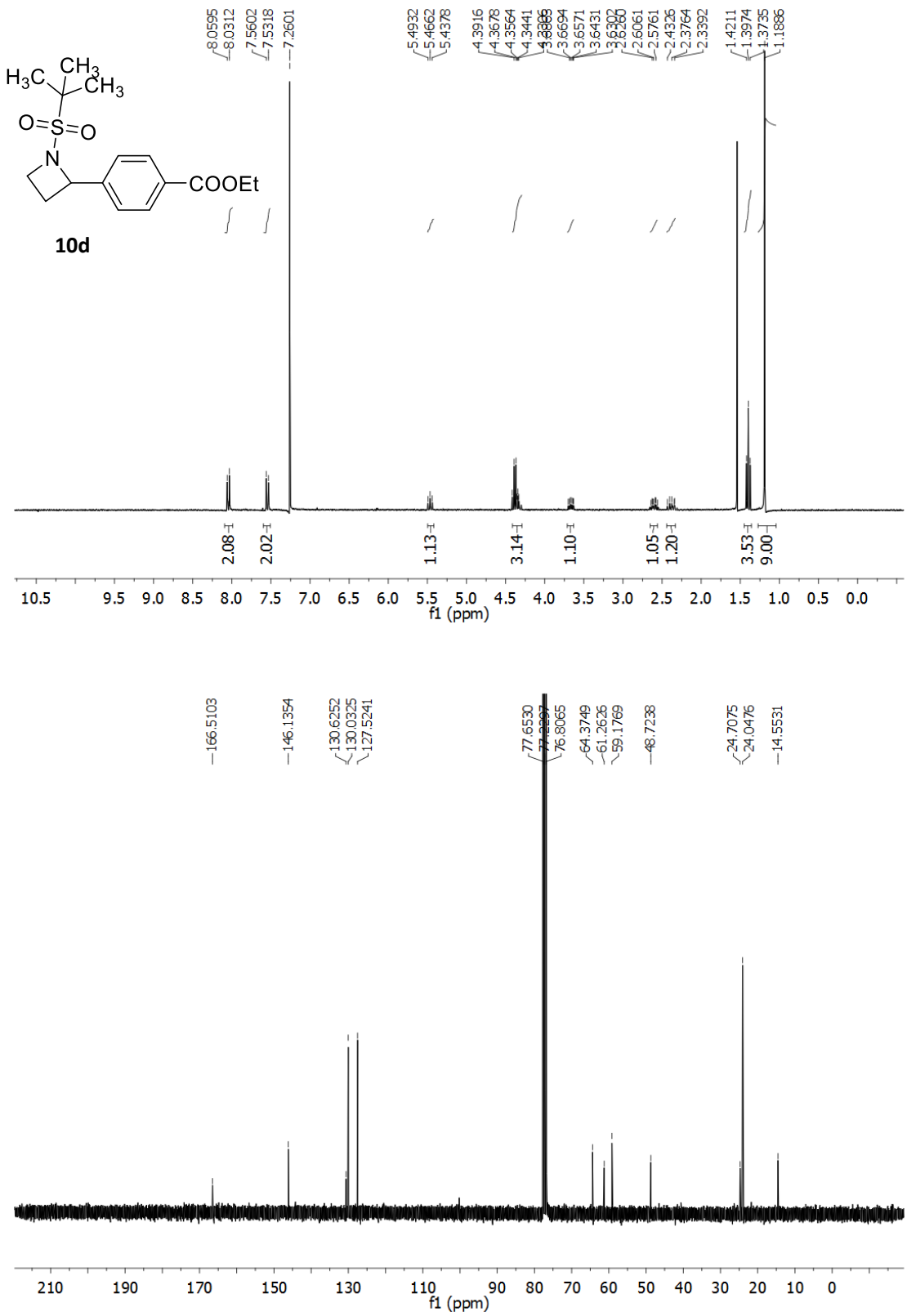


Figure S65. ^{1}H and ^{13}C NMR spectra of **10d**.

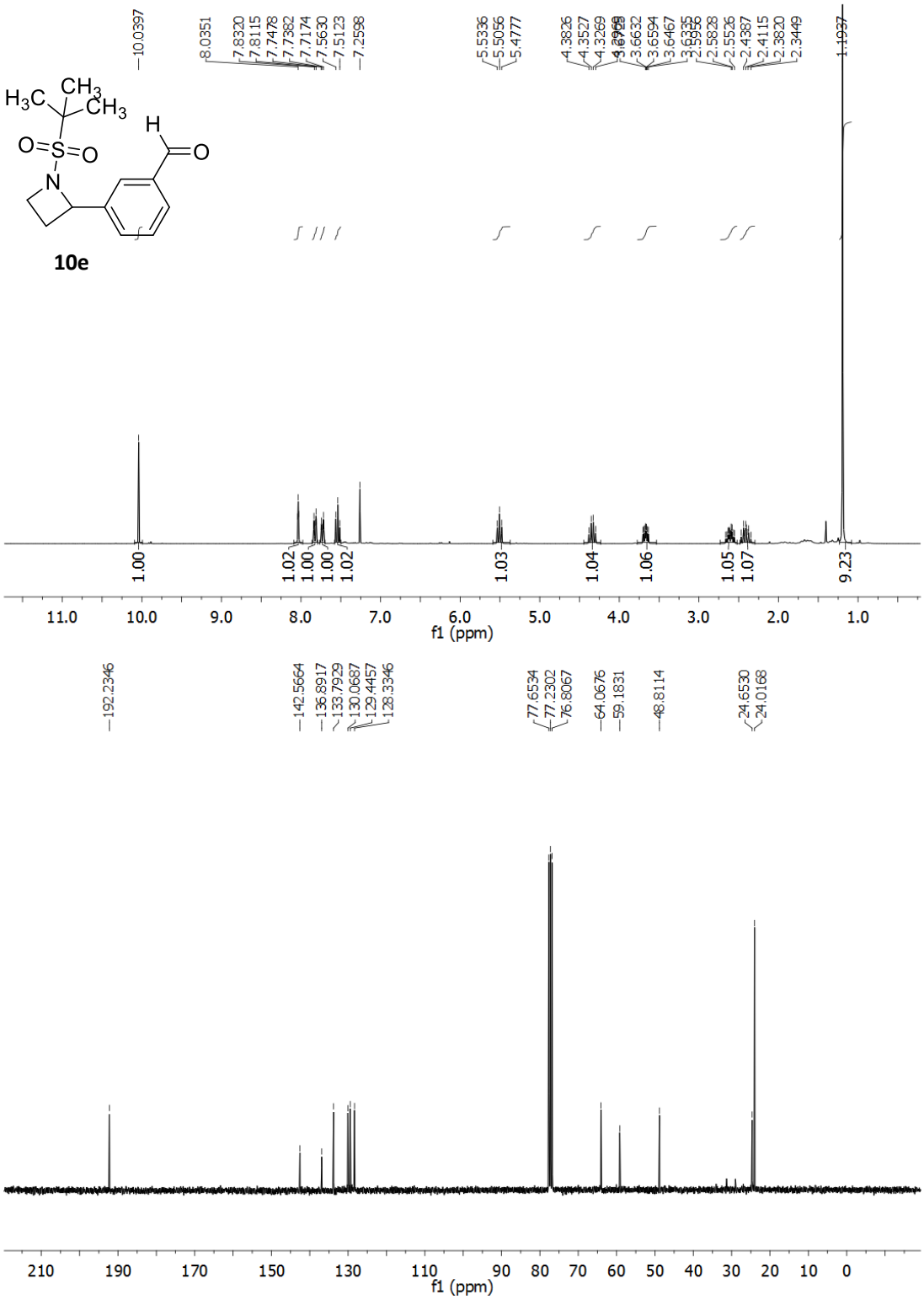


Figure S66. ^{1}H and ^{13}C NMR spectra of **10e**.

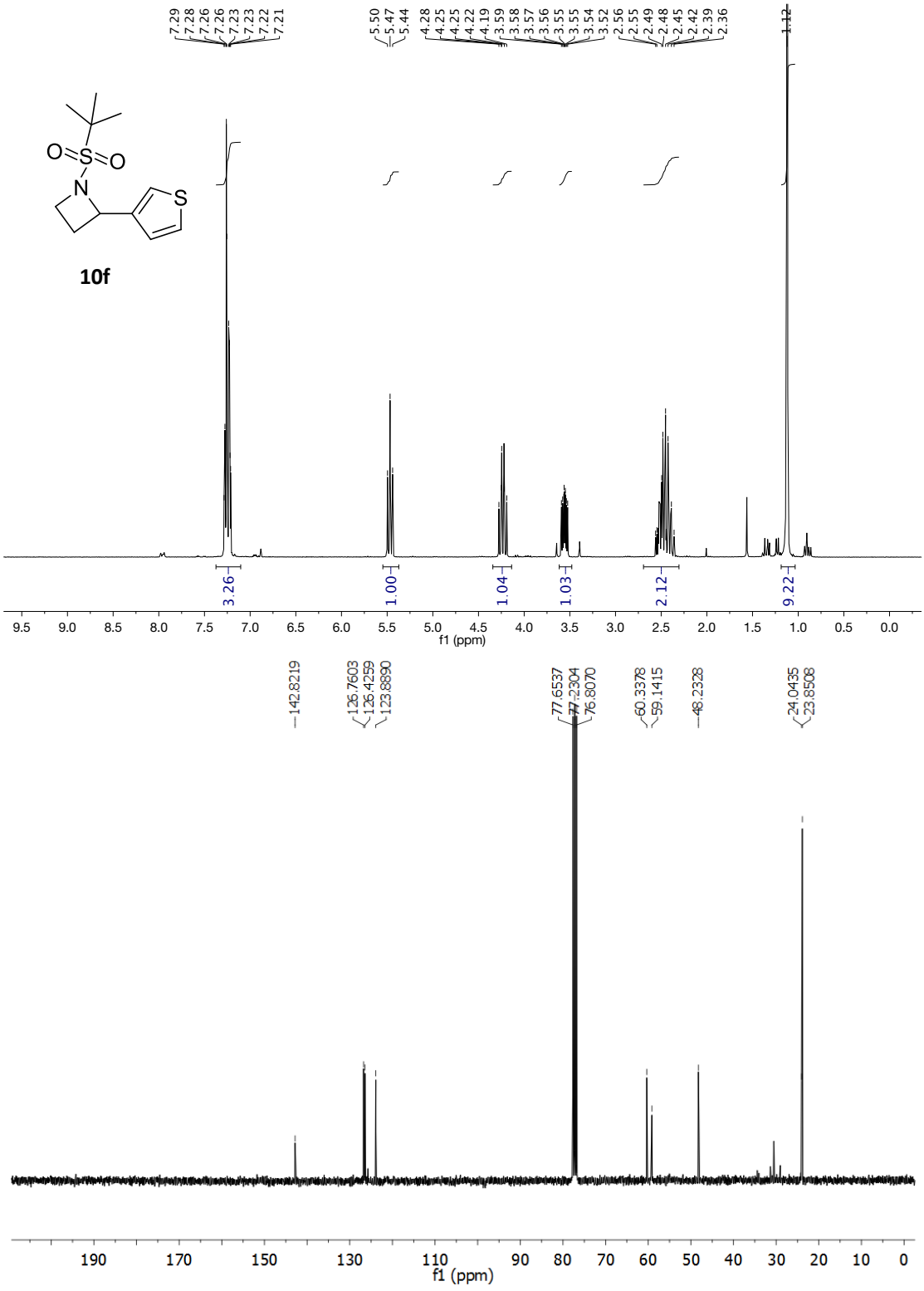


Figure S67. ^{1}H and ^{13}C NMR spectra of **10f**.

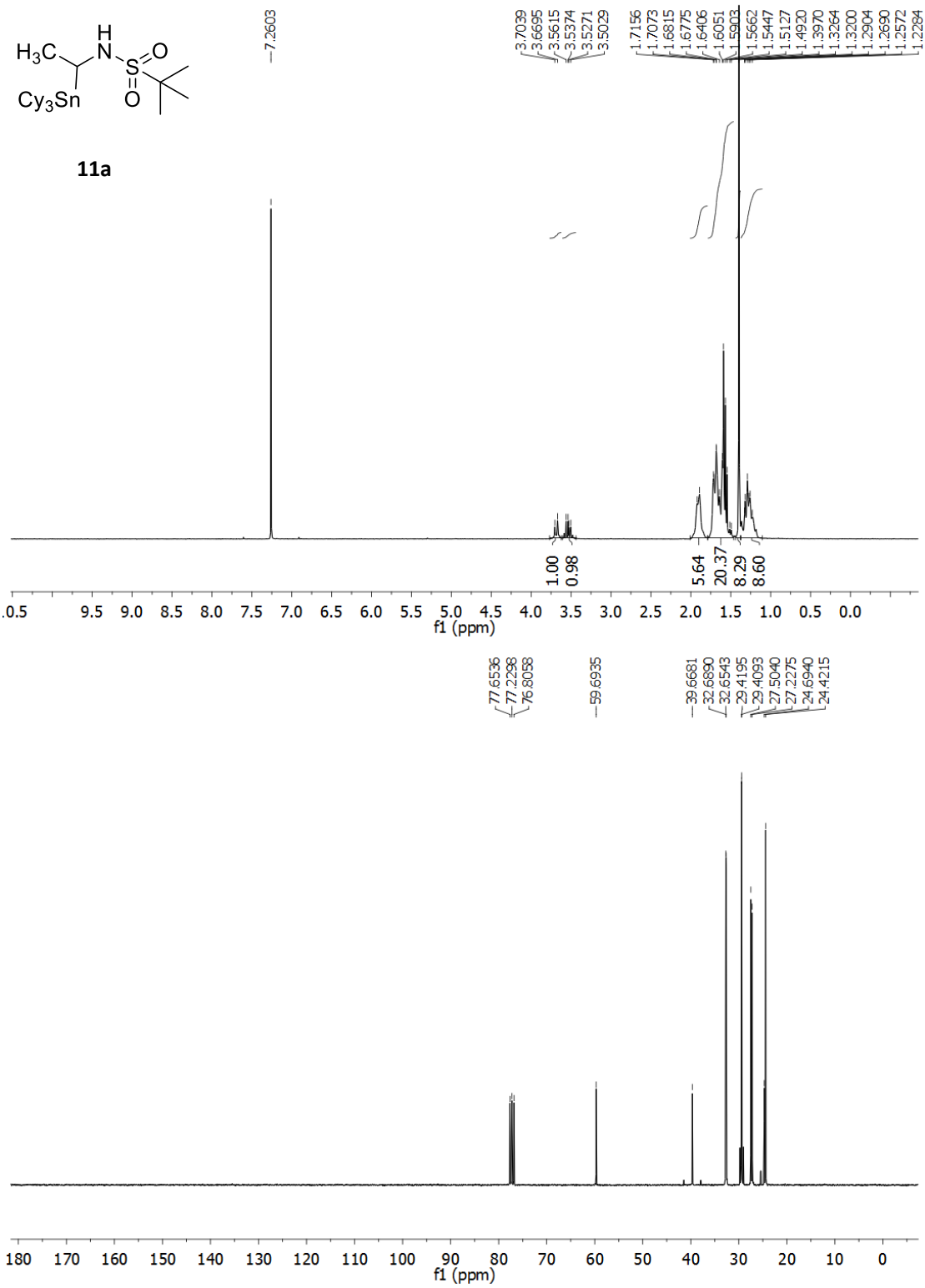


Figure S68. ^{1}H and ^{13}C NMR spectra of **11a**.

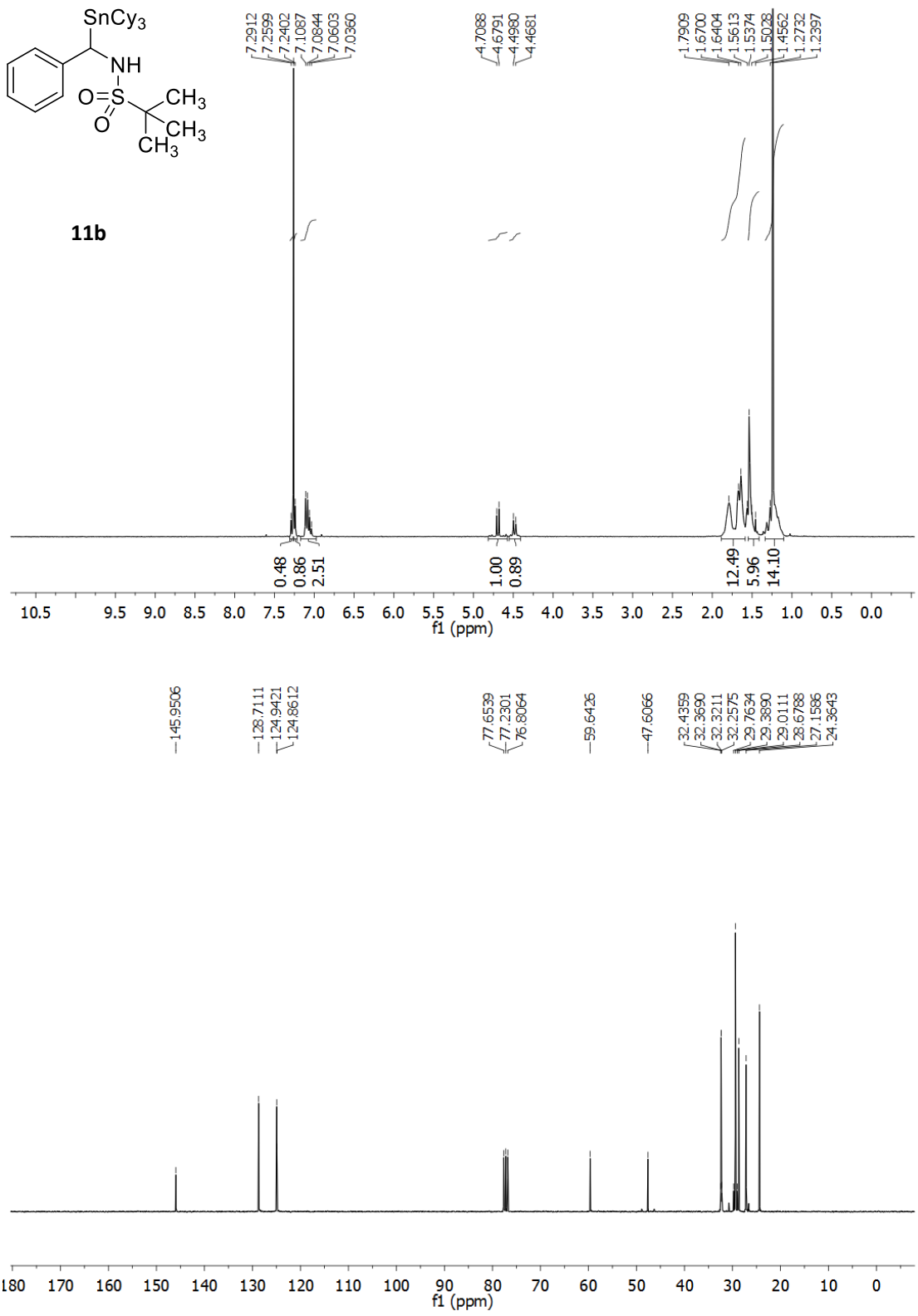


Figure S69. ^{1}H and ^{13}C NMR spectra of **11b**.

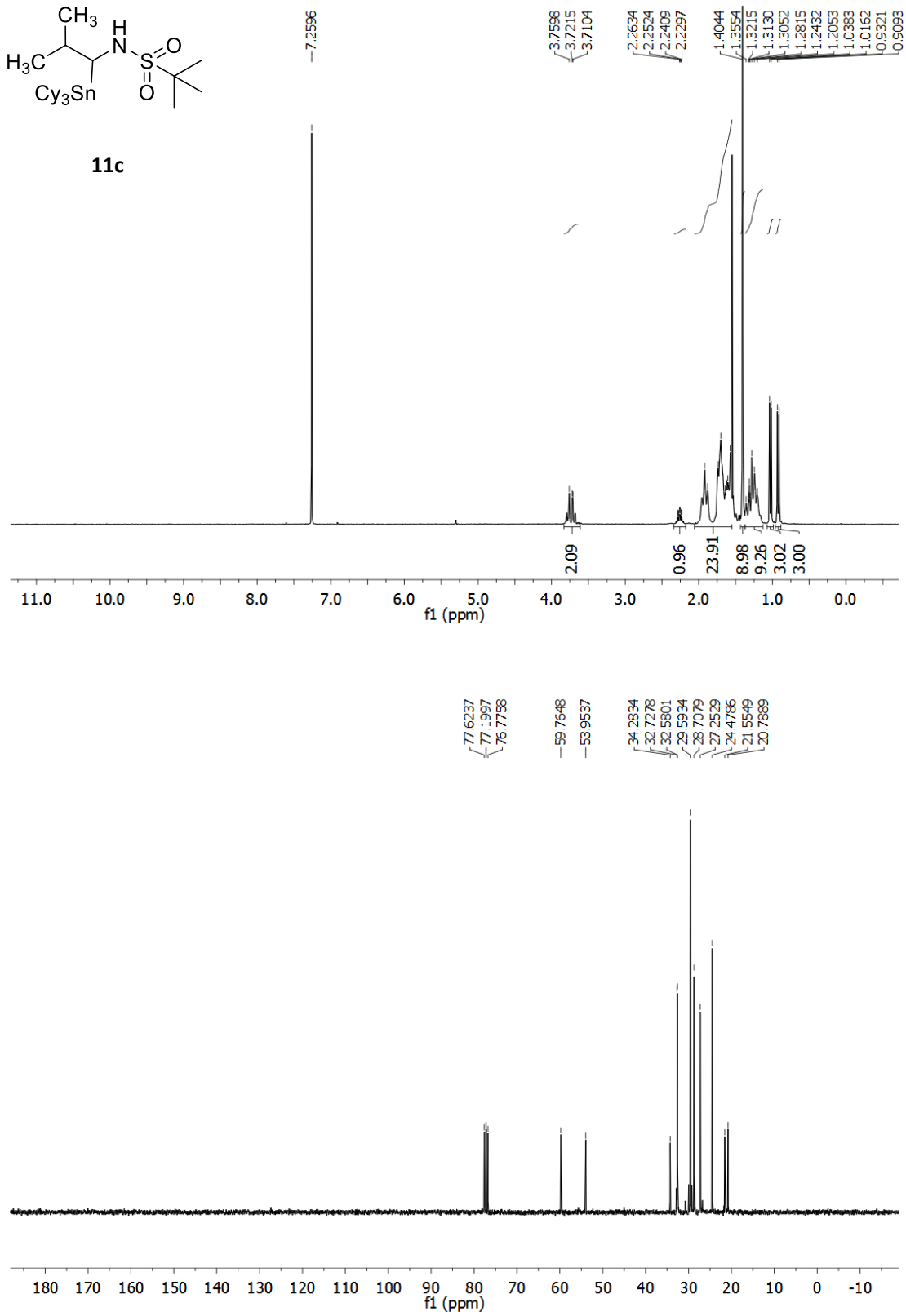


Figure S70. ^{1}H and ^{13}C NMR spectra of **11c**.

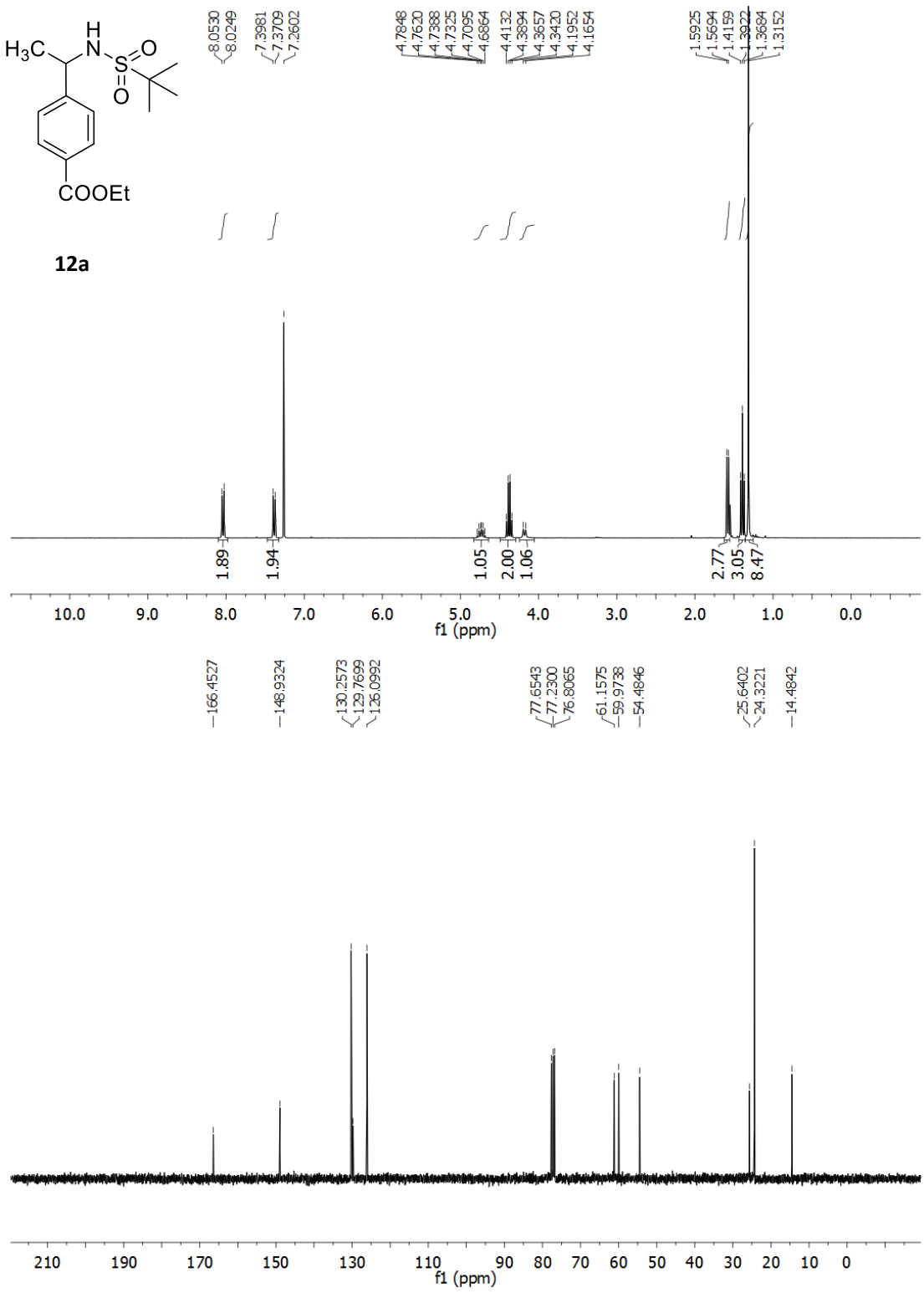


Figure S71. ^{1}H and ^{13}C NMR spectra of **12a**.

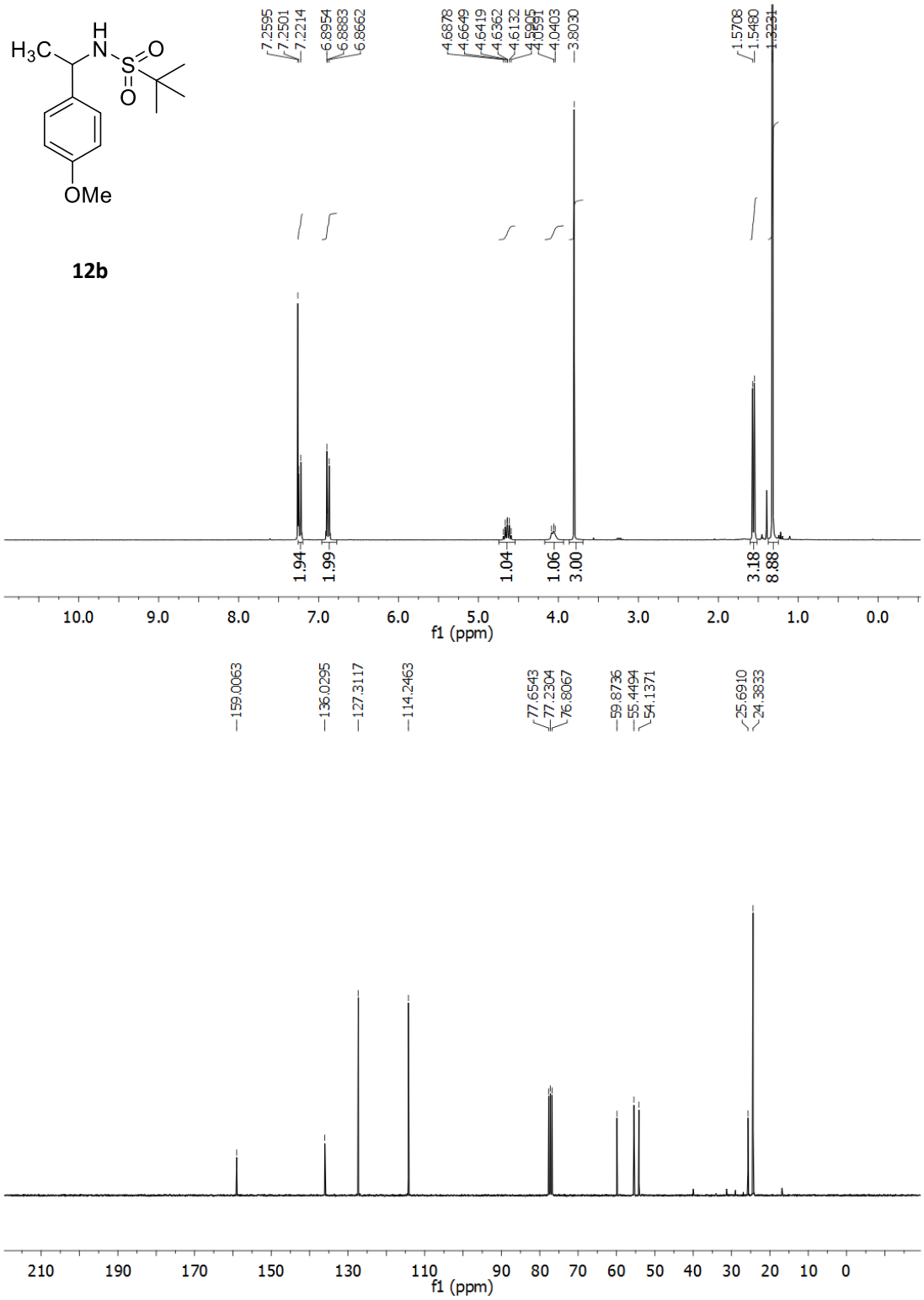


Figure S72. ^{1}H and ^{13}C NMR spectra of **12b**.

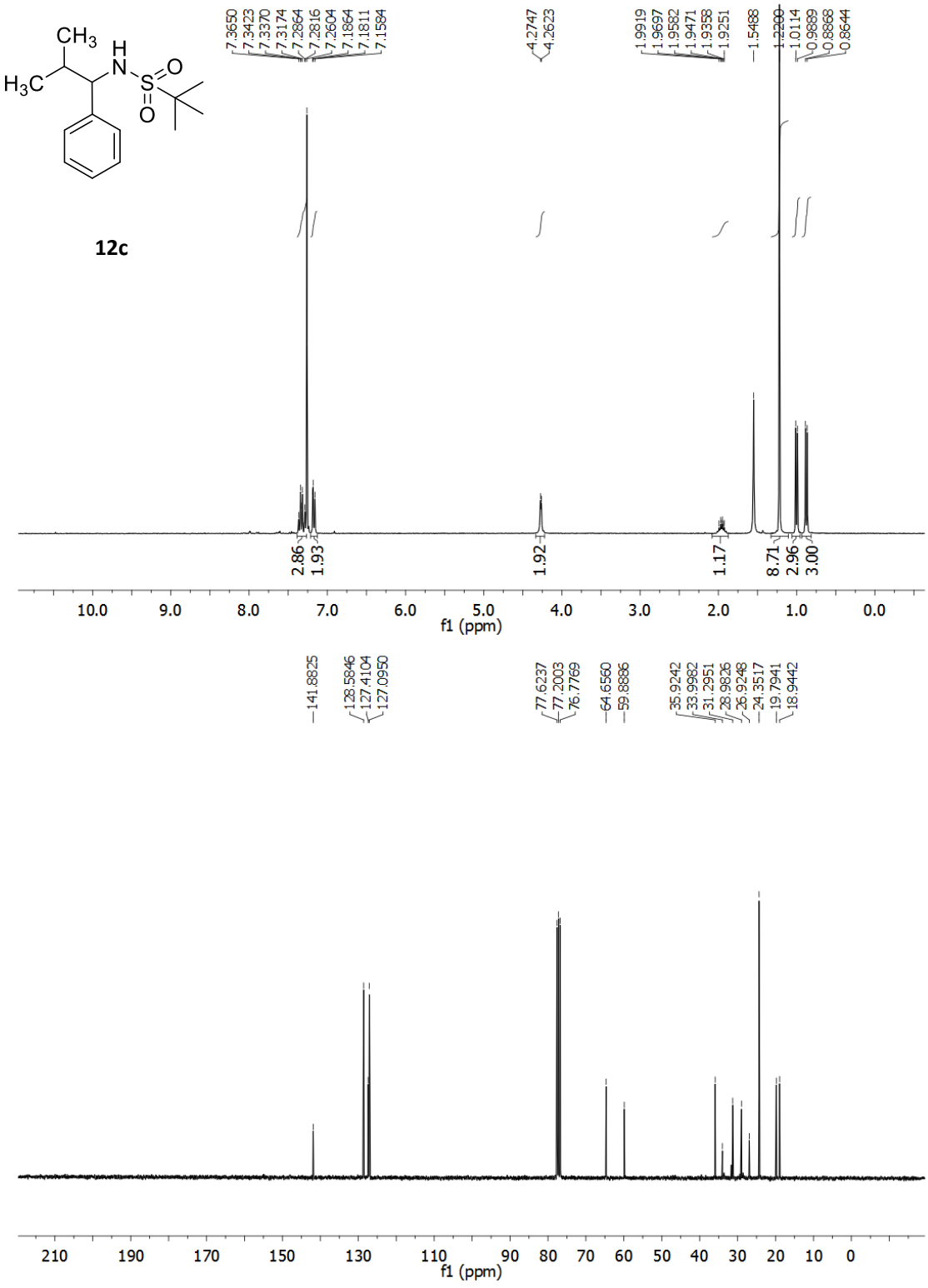


Figure S73. ^{1}H and ^{13}C NMR spectra of **12c**.

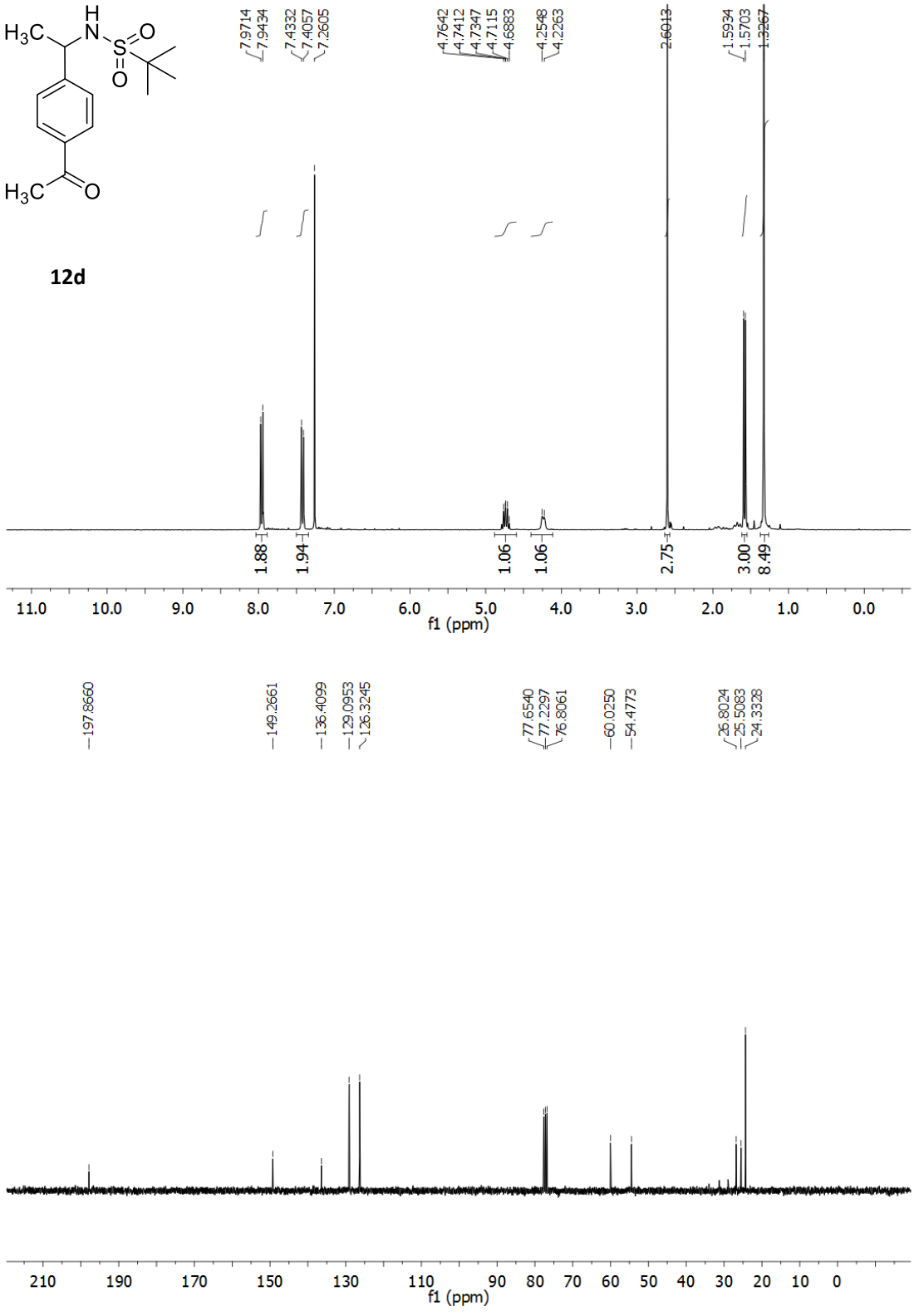


Figure S74. ^{1}H and ^{13}C NMR spectra of **12d**.

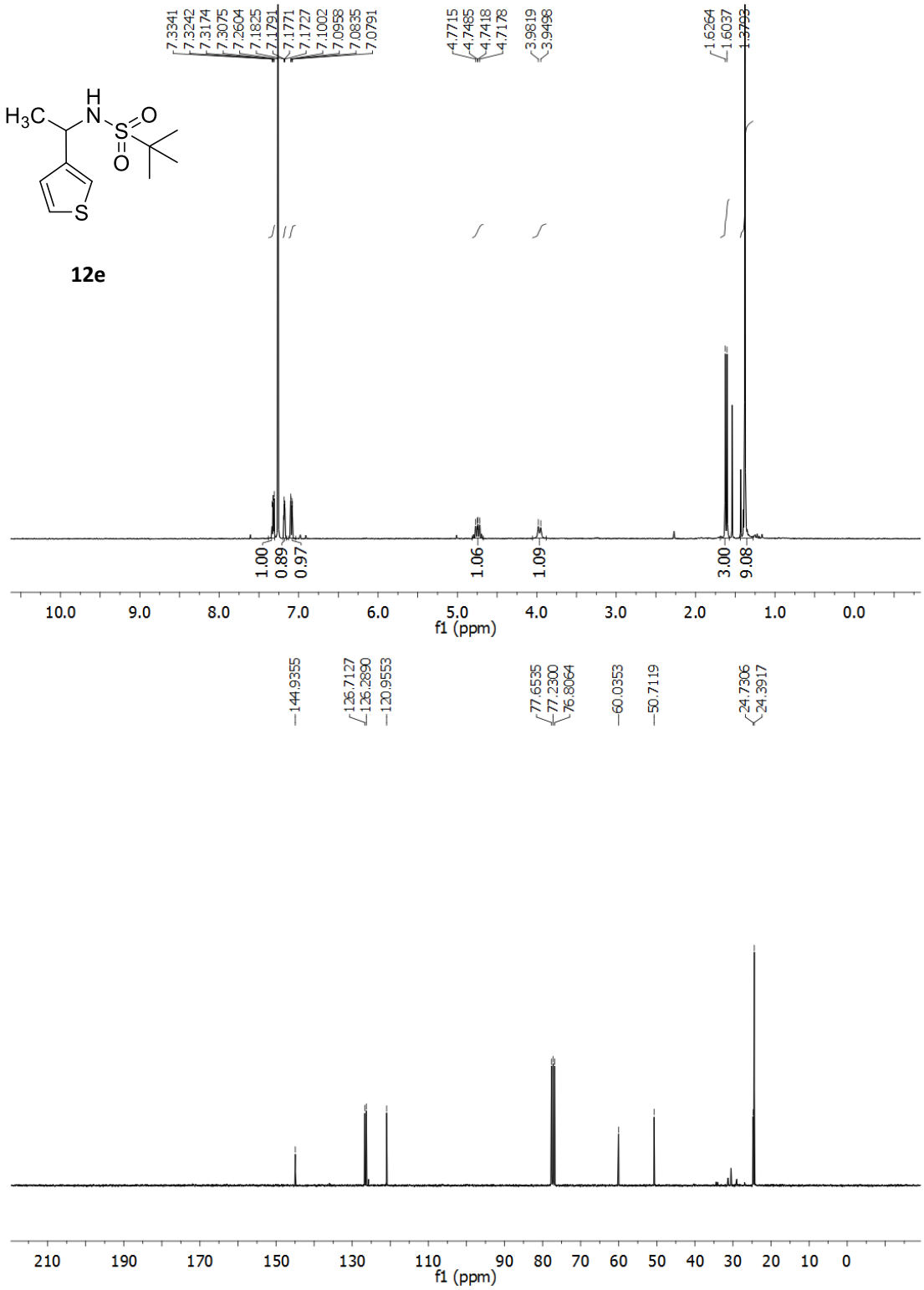


Figure S75. ^{1}H and ^{13}C NMR spectra of **12e**.

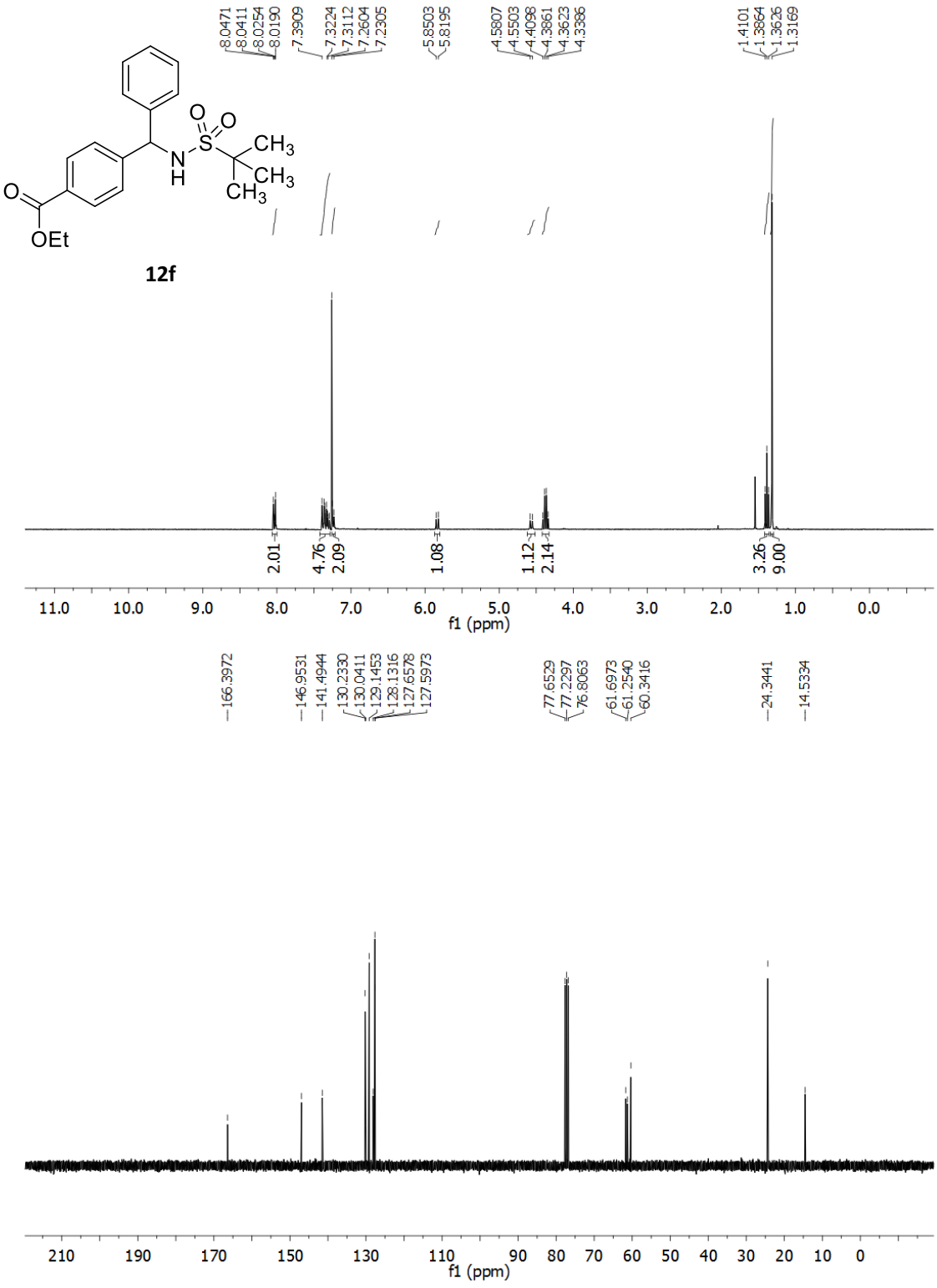


Figure S76. ^{1}H and ^{13}C NMR spectra of **12f**.

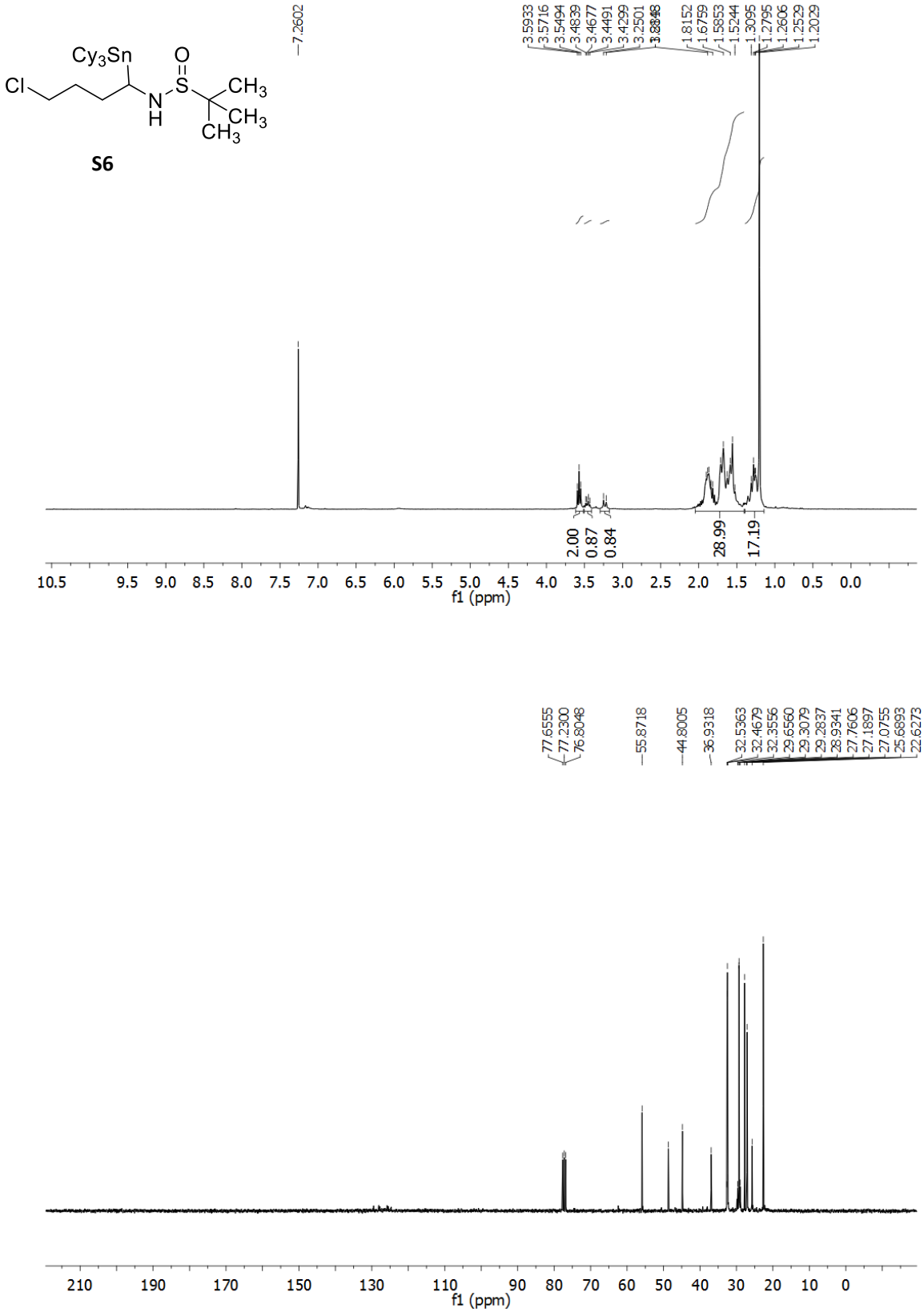


Figure S77. ^{1}H and ^{13}C NMR spectra of **S6**.

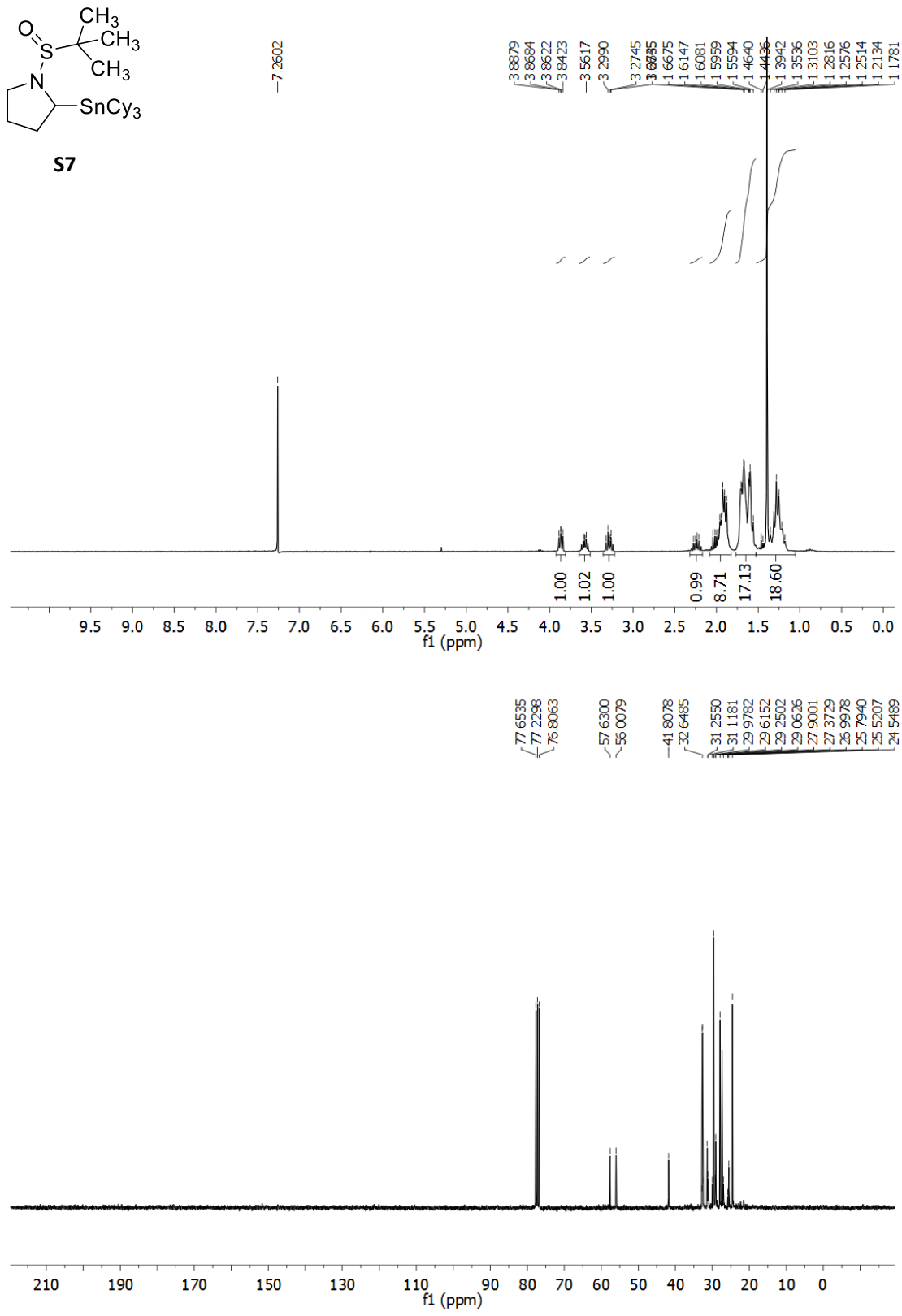


Figure S78. ^{1}H and ^{13}C NMR spectra of **S7**.

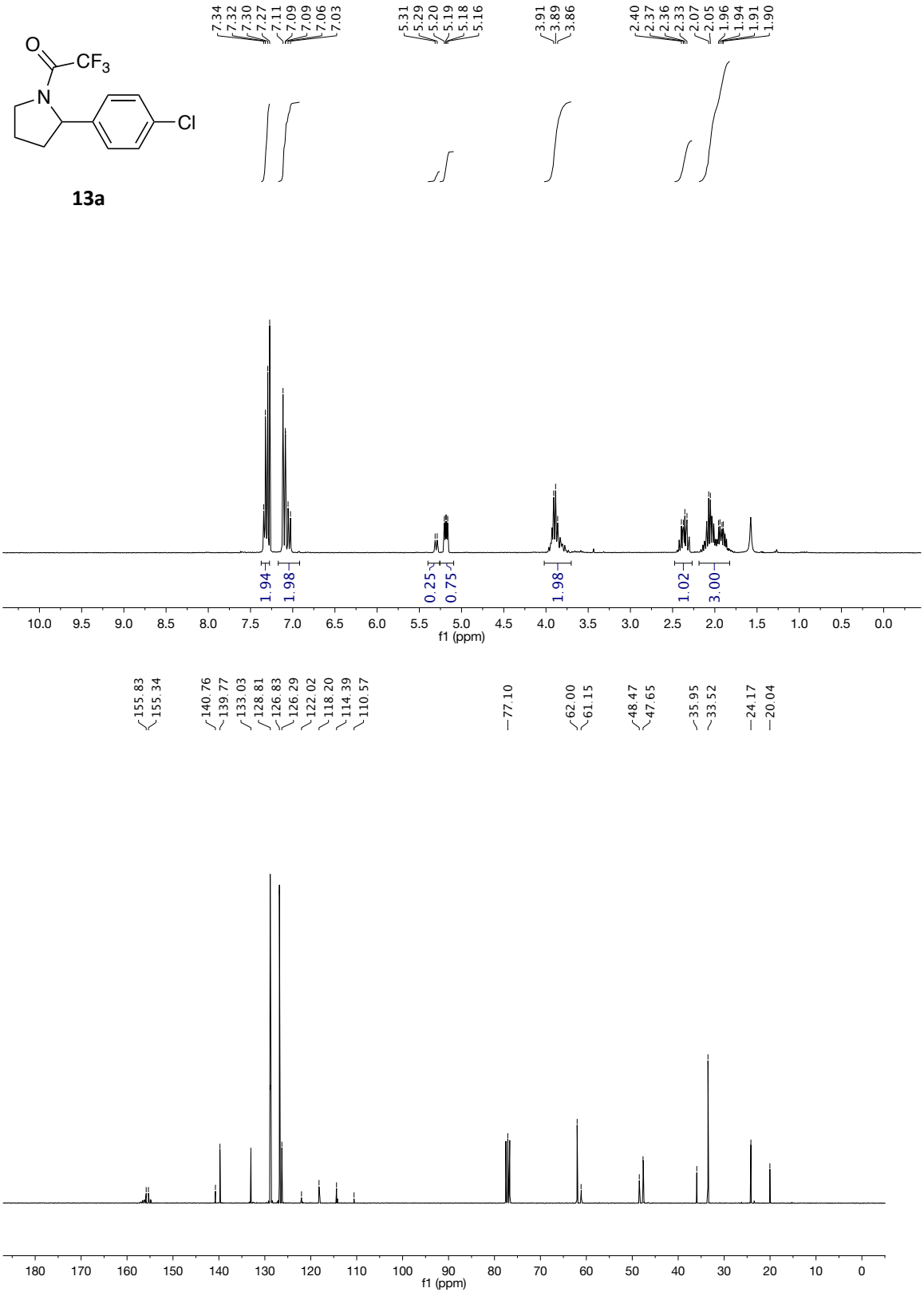


Figure S79. ^{1}H and ^{13}C NMR spectra of **13a**.

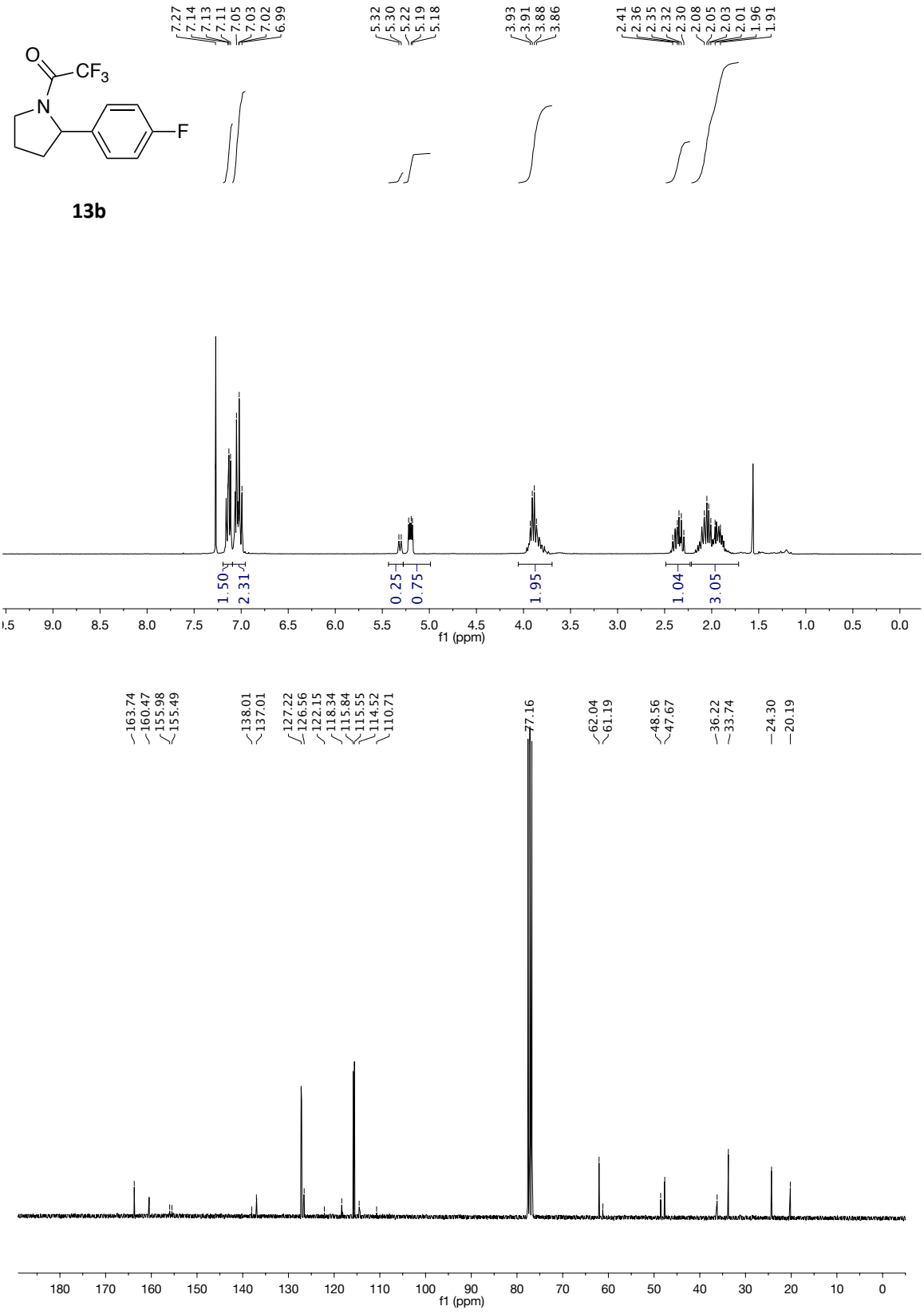


Figure S80. ^{1}H and ^{13}C NMR spectra of **13b**.

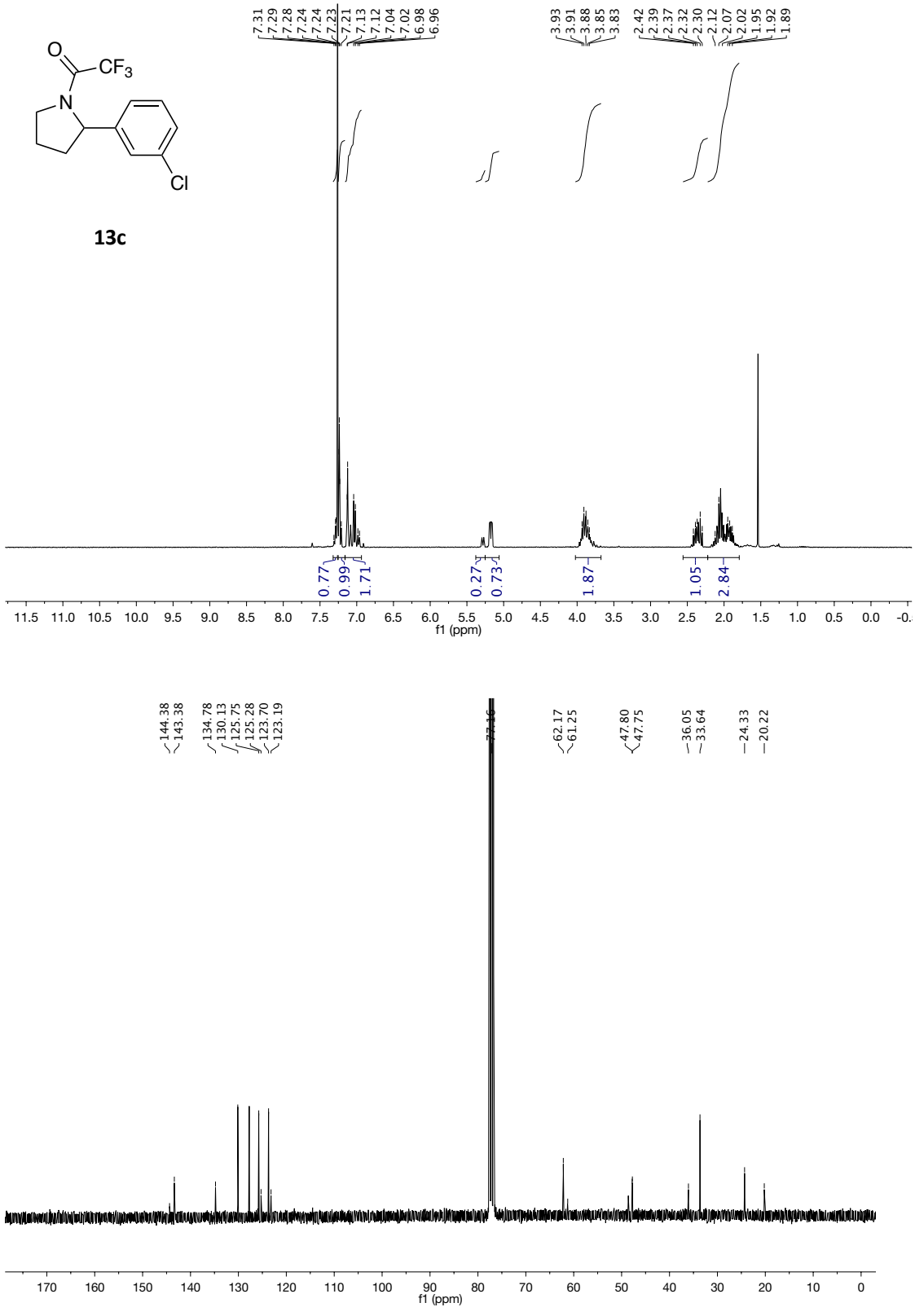


Figure S81. ^{1}H and ^{13}C NMR spectra of **13c**.

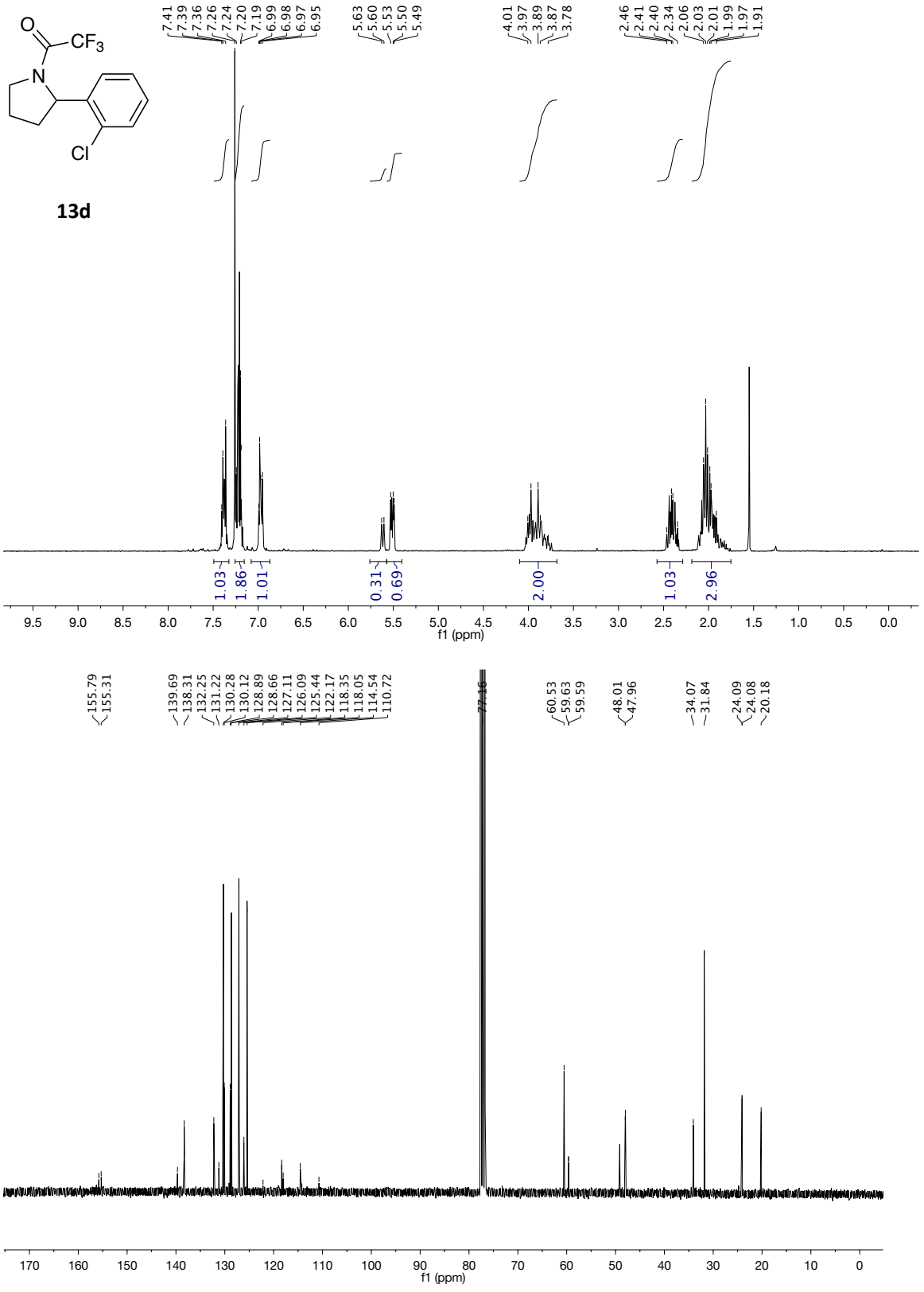


Figure S82. ^{1}H and ^{13}C NMR spectra of **13d**.

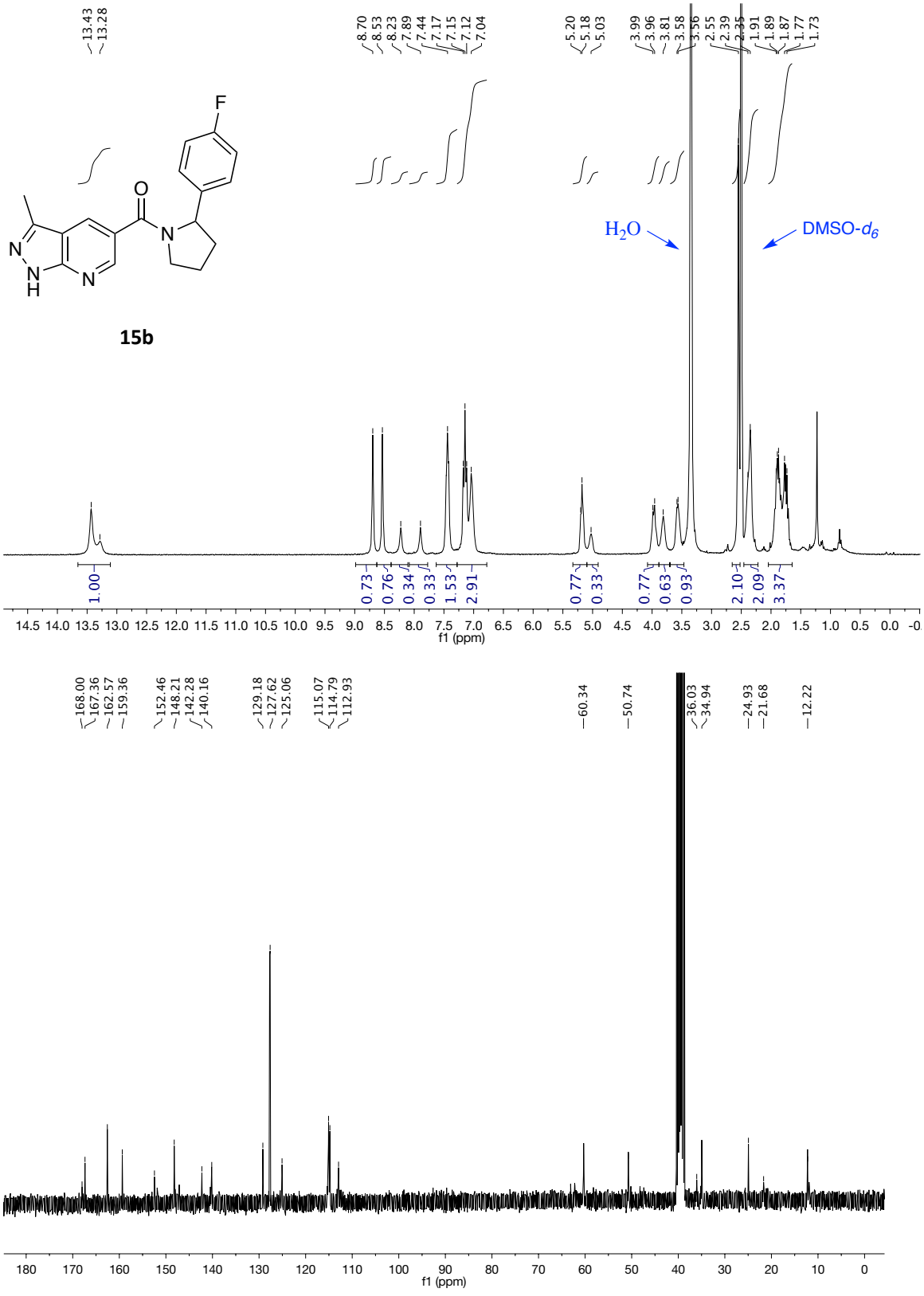


Figure S83. ^{1}H and ^{13}C NMR spectra of **15b**.

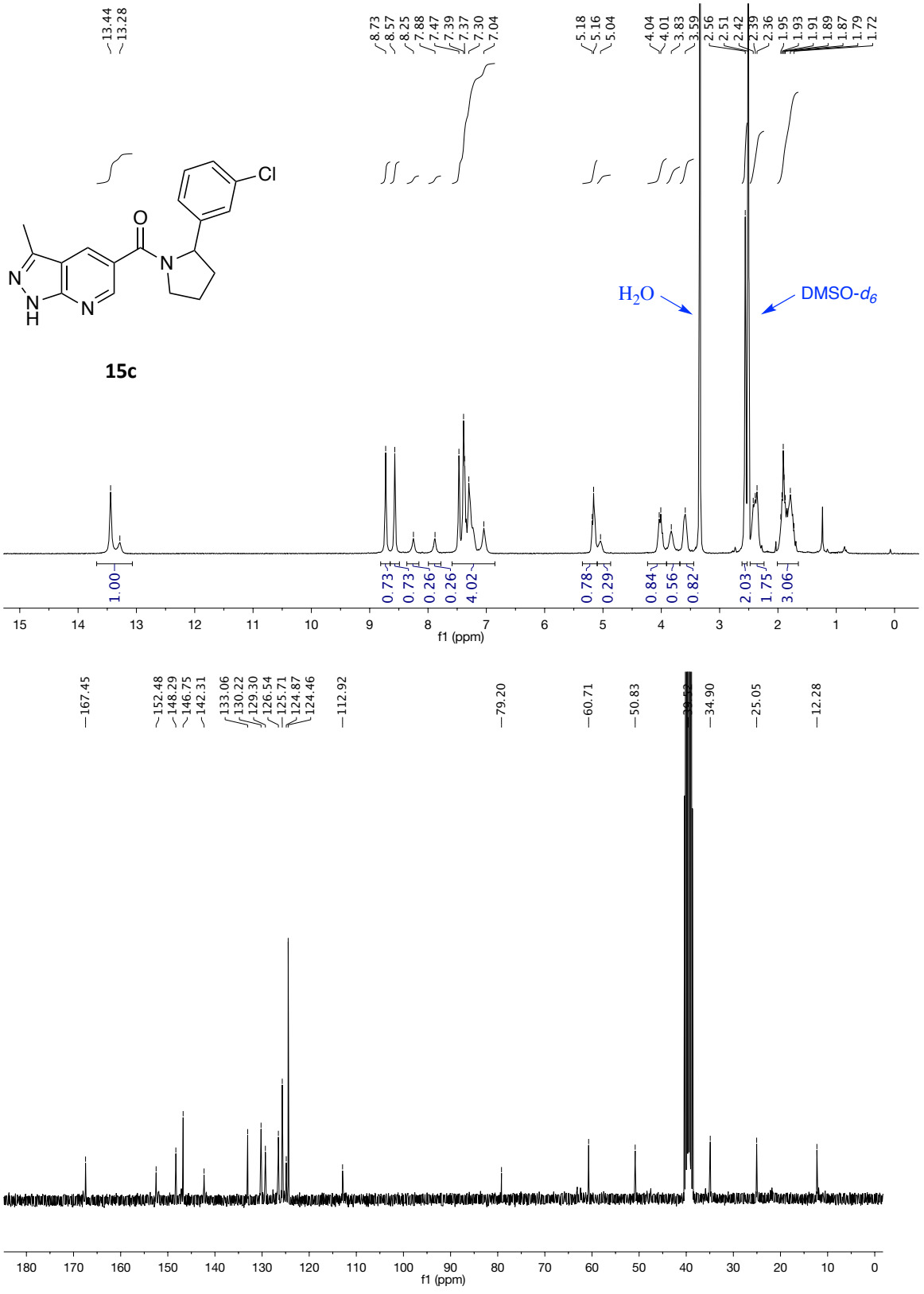


Figure S84. ^{1}H and ^{13}C NMR spectra of **15c**.

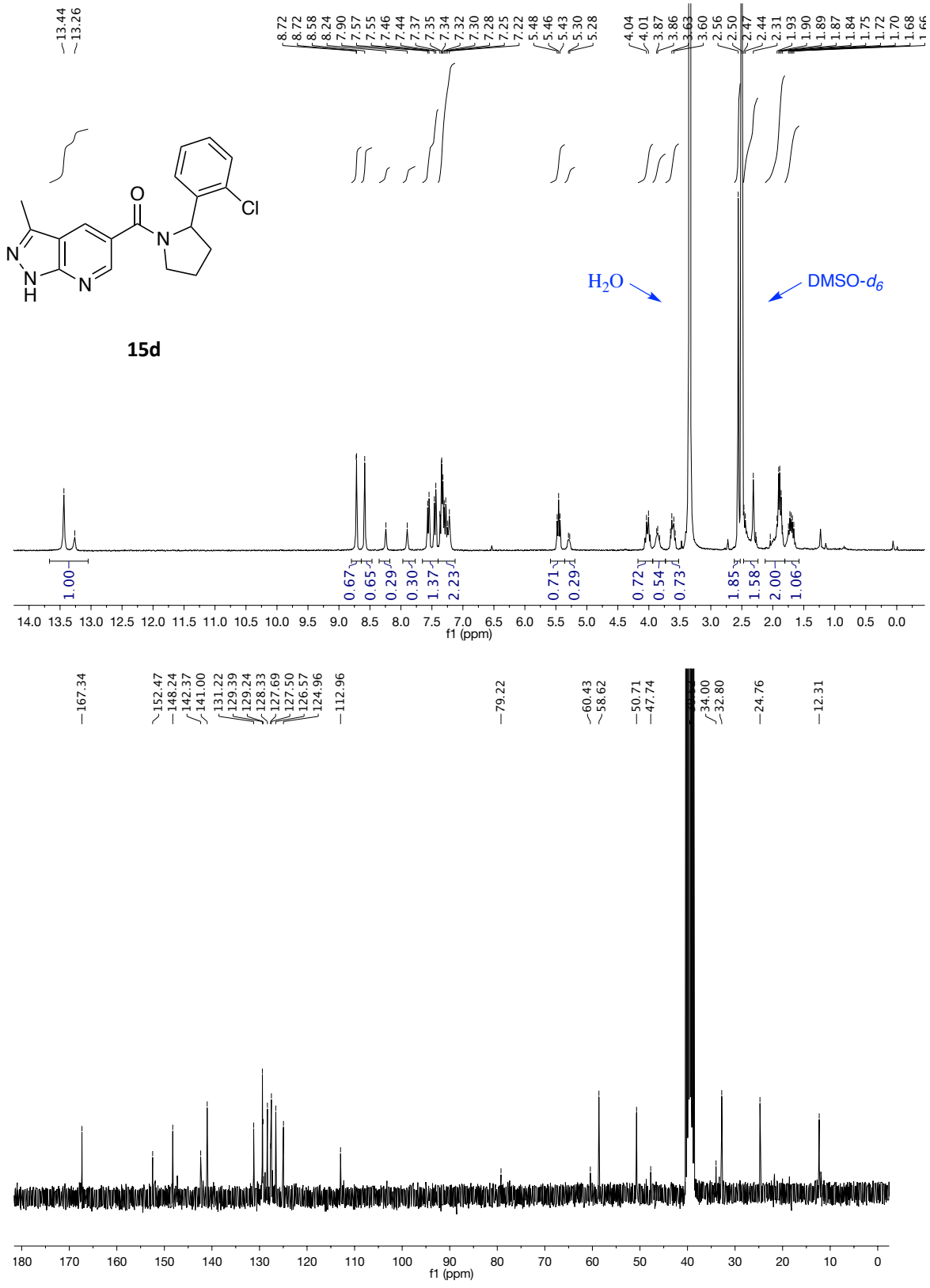


Figure S85. ^{1}H and ^{13}C NMR spectra of **15d**.