Supplementary Materials for

Alkyl-Alkyl Cross-Coupling Enabled by Redox-Active Esters and Alkylzinc Reagents

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Compound **71** ^{13}C NMR ……page S444
Compound **72** ^{1}H NMR ……page S445
Compound **72** ^{13}C NMR ……page S446
Compound **73** ^{1}H NMR ……page S447
Compound **73** ^{13}C NMR ……page S448
Compound **74** ^{1}H NMR ……page S449
Compound **74** ^{13}C NMR ……page S450
Compound **75** ^{1}H NMR ……page S451
Compound **75** ^{13}C NMR ……page S452
Compound **76** ^{1}H NMR ……page S453
Compound **76** ^{13}C NMR ……page S454
Compound **77** ^{1}H NMR ……page S455
Compound **77** ^{13}C NMR ……page S456
Compound **78** ^{1}H NMR ……page S457
Compound **78** ^{13}C NMR ……page S458

References……page S459

General Experimental. Tetrahydrofuran (THF), *N*,*N*-dimethylformamide (DMF), and dichloromethane (CH_2Cl_2) were obtained by passing the previously degassed solvents through an activated alumina column. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. $NiCl_2$•glyme was purchased from Strem. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by GC/MS, LC/MS, and thin layer chromatography (TLC). TLC was performed using 0.25 mm E. Merck silica plates (60F-254), using short-wave UV light as the visualizing agent, and phosphomolybdic acid and $Ce(SO_4)_2$ or $KMnO_4$ and heat as developing agents. NMR spectra were recorded on Bruker DRX-600, DRX-500, and AMX-400 instruments and are calibrated using residual undeuterated solvent ($CHCl_3$ at 7.26 ppm ^{1}H NMR, 77.16 ppm ^{13}C NMR, internal calibration for ^{19}F NMR). The following abbreviations were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was performed using E. Merck silica gel (60, particle size 0.043–0.063 mm), and preparative TLC was performed on Merck silica plates (60F-254). High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected. The UCSD small molecule X-ray facility collected and analyzed all X-ray diffraction data.

Handling of [Ni] catalysts.

All Ni catalysts were handled open to air on the bench top, and the bottles were not stored under inert atmosphere.

Mechanistic investigations.

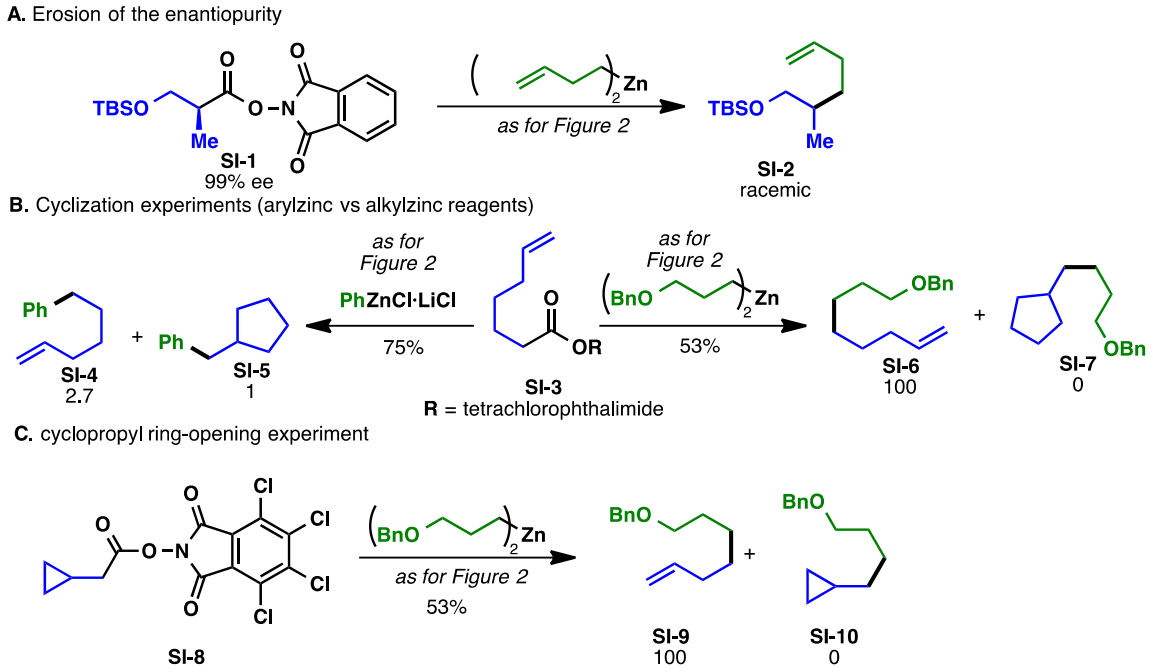


Figure S1. Mechanistic experiments.

Discussion:

The fact that an enantioenriched redox-active ester loses chiral information (Figure S1A) and a cyclopropylacetic acid derivative ring-opens under the reaction conditions (Figure S1C) suggest the intermediacy of radical species during the catalytic cycle. Similar to the protocol for the arylation of redox-active esters,(*21*) we suggest a possible mechanism in which the Ni catalyst is responsible for the generation of such radicals.

As outlined in Figure S1B, a pendant olefin substrate was designed and tested under the reaction conditions with arylzinc reagents and alkylzinc reagents in separate experiments. As a result, *5-exo-trig* cyclization product was observed when phenylzinc chloride was used as coupling partner (**SI-4**:**SI-5**, 2.7:1). However, when an alkylzinc reagent was used instead, the acyclic product was obtained exclusively. Based on the distinct outcomes with arylzinc versus alkylzinc reagents, it is hypothesized that with alkylzinc reagents the radical generation and subsequent radical trapping occurs within the solvent cage. It is believed that the cationic Ni(II)-Ph species would be far more stable than the Ni(II)-alkyl species, thereby allowing some of the carbon-centered radical to escape and

cyclize in a *5-exo-trig* fashion. On the other hand, when the cationic Ni(II)-alkyl complex is formed, the carbon-centered radical reacts at much faster rates with the Ni(II)-alkyl complex, preventing the radical from cyclizing. The fact that the cyclopropyl radical can rearrange but a *5-exo-trig* cyclization does not occur is explained by the kinetics associated with the opening of a cyclopropyl ring (8.6 x 10^7 s^{-1}) (*35*) and *5-exo-trig* cyclizations (2 x 10^5 s^{-1}). (*36*)

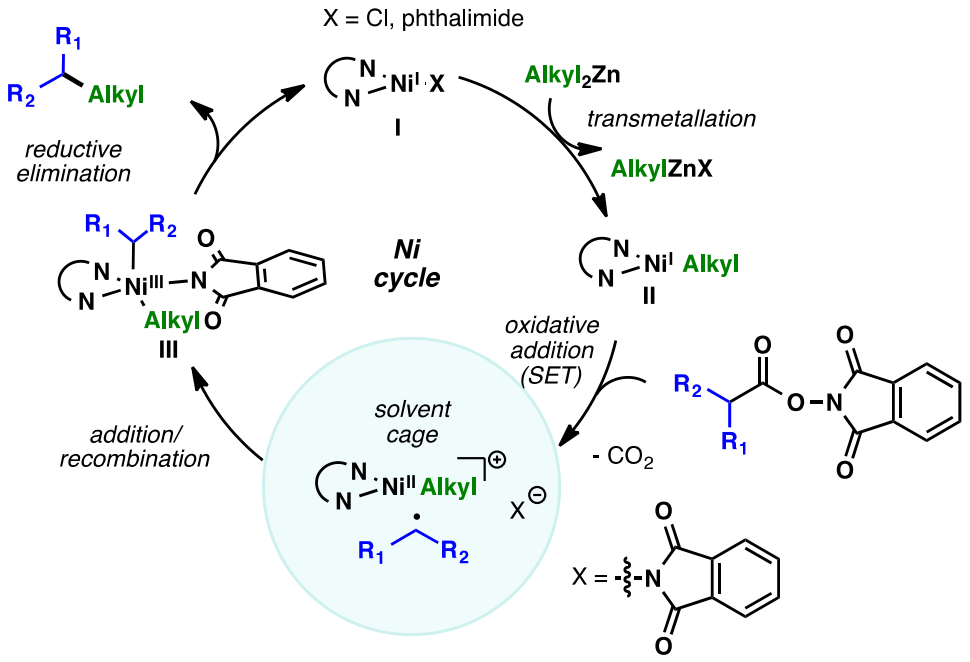


Figure S2. Proposed catalytic cycle for the Ni-catalyzed decarboxylative alkyl-alkyl cross-coupling.

With the results obtained from the above experiments, a possible mechanism for the Ni-catalyzed decarboxylative cross-coupling with alkylzinc is postulated in Figure S2. The cycle would start by the slow generation of Ni(I)-X intermediates (**I**) which would quickly transmetallate with an alkylzinc species delivering the Ni(I) species **II**. This species would then undergo oxidative addition with the redox active ester via SET, thus generating a carbon-centered radical. A short-lived radical species would not leave a possible solvent cage before recombining with the highly electrophilic cationic alkyl-Ni(II) species, forming Ni(III) complex **III**. Reductive elimination would deliver the desired product and regenerate the Ni(I) active species, thus closing the catalytic cycle.

Radical evidence in the conjunctive coupling.

The intermediacy of radical species in the Ni-catalyzed alkyl-alkyl cross coupling of redox-active esters is further evidenced by the possibility of conducting the conjunctive coupling with tertiary redox-active esters, a radical acceptor, and phenylzinc chloride. However, an experiment to support the radical nature of the three-component reaction was designed (Figure S3A). When olefinic redox-active ester **SI-11** was reacted with benzyl acrylate, phenylzinc chloride in the presence of Ni catalyst, cyclopentane **SI-12** was obtained in excellent yields.

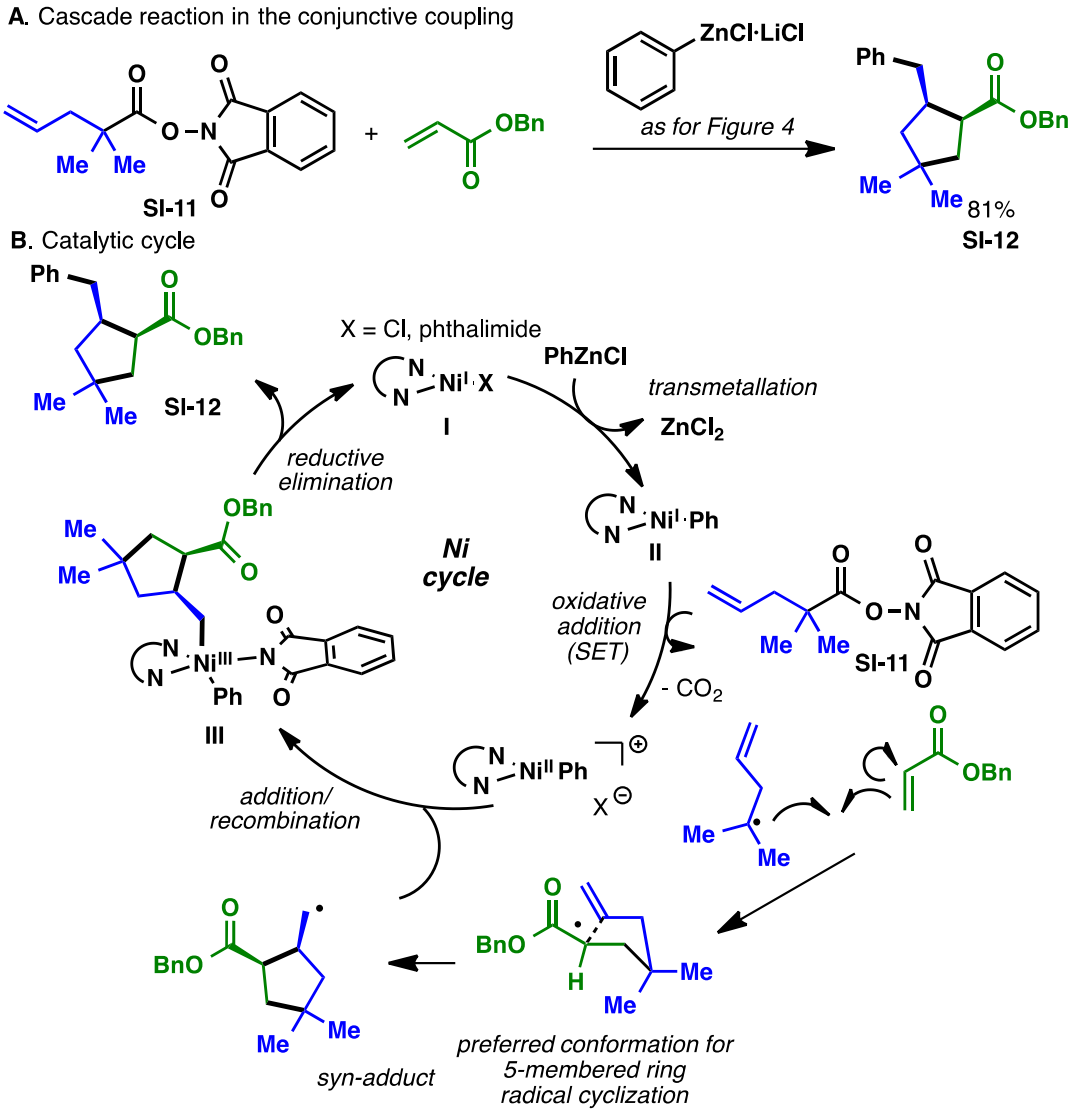
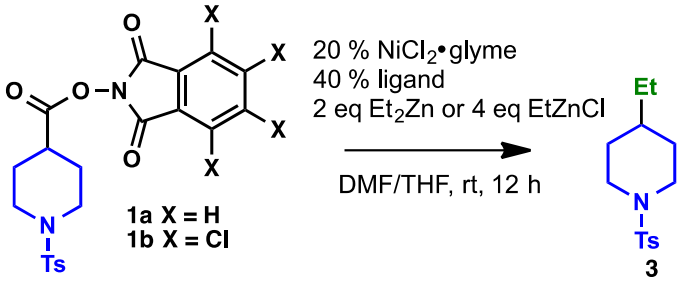


Figure S3. Proposed catalytic cycle for the cascade 3-component Ni-catalyzed conjunctive coupling.

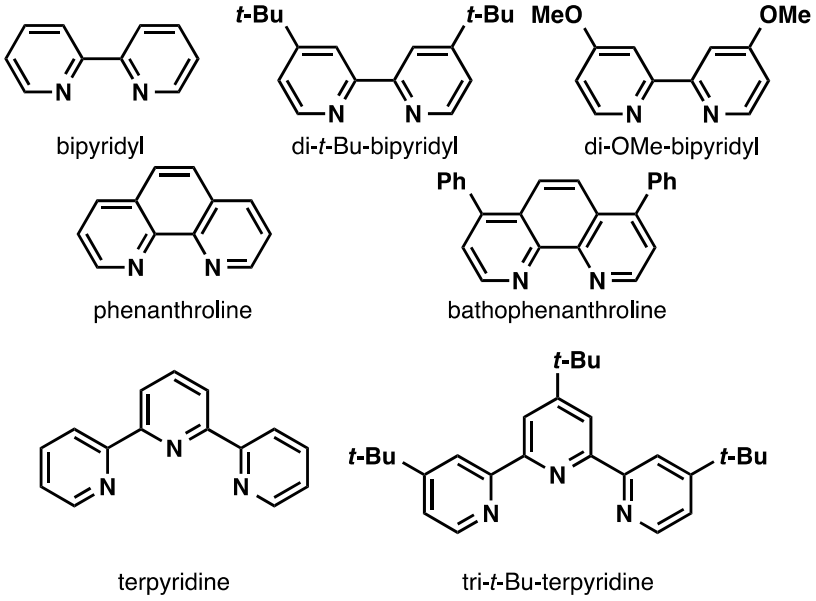
A mechanistic proposal for the cascade conjunctive coupling is depicted in Figure S3B. The tertiary radical (formed after the step-wise oxidative addition via SET as before) undergoes a radical 1,4-addition to benzyl acrylate. Such a radical will then react with the pendant olefin generating a *syn*-substituted 5-member ring with a reactive primary radical.(*34*) Such radical can now be trapped by the cationic Ph–Ni(II) which further delivers the product. This result stresses the fact that cationic Ph–Ni(II) are stable enough of a species to allow the radical to undergo a *5-exo-trig* cyclization before it recombines with the Ph-Ni(II) complex.

Optimization of Reaction Parameters (Table SI-1)

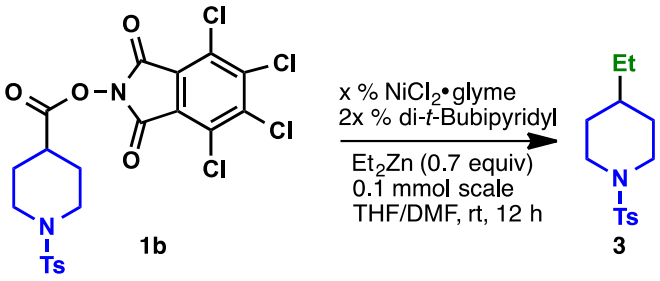


Conditions	X	Ligand	Yield[a,b]
Et_2Zn (1.0 M in hexanes)	Cl	bipyridyl	61%
Et_2Zn (1.0 M in hexanes)	Cl	di-*t*-Bu-bipyridyl	65%
Et_2Zn (from EtMgBr and $ZnCl_2$)	H	bipyridyl	(52%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	H	di-*t*-Bu-bipyridyl	(60%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	bipyridyl	(64%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	di-*t*-Bu-bipyridyl	(91%) 84%
EtZnCl (from EtMgBr and $ZnCl_2$)	Cl	bipyridyl	(33%)
EtZnCl (from EtMgBr and $ZnCl_2$)	Cl	di-*t*-Bu-bipyridyl	(82%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	phenanthroline	(79%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	terpyridine	(26%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	tri-*t*-Bu-terpyridine	(33%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	bathophenanthroline	(47%)
Et_2Zn (from EtMgBr and $ZnCl_2$)	Cl	di-OMe-bipyridyl	(46%)

[a] Isolated yield
[b] Yield in parentheses determined by ^1H NMR using CH_2Br_2 as internal standard



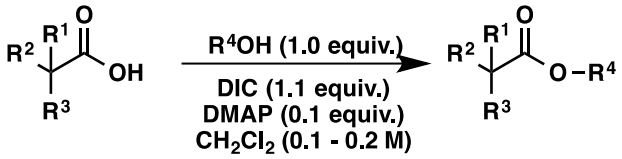
Optimization of Catalyst Loading and Concentration (Table SI-2).



x	DMF (mL)	THF (mL)	NMR yield[a]
20	0.5	0.5	60 %
10	0.25	0.5	22 %
10	0.125	0.5	58 %
5	0.063	0.5	49 %
5	0.125	0.5	66 % (61 %)[b]
5	0.25	0.5	49 %
5	0.5	0.5	43 %
5	0	0.75[c]	24 %
5	0.125	0.25	23 %
5	0.25	0.25	22 %
5	0.5	0.25	17 %
5	0	0.5[d]	25 %

[a] Yield determined by ^{1}H NMR using CH_2Br_2 as internal standard
[b] Isolated yield shown in parentheses
[c] Volume of THF includes 0.5 mL from Et_2Zn solution
[d] Volume of THF includes 0.25 mL from Et_2Zn solution

General Procedure for the synthesis of Redox-active Esters (General Procedure A).

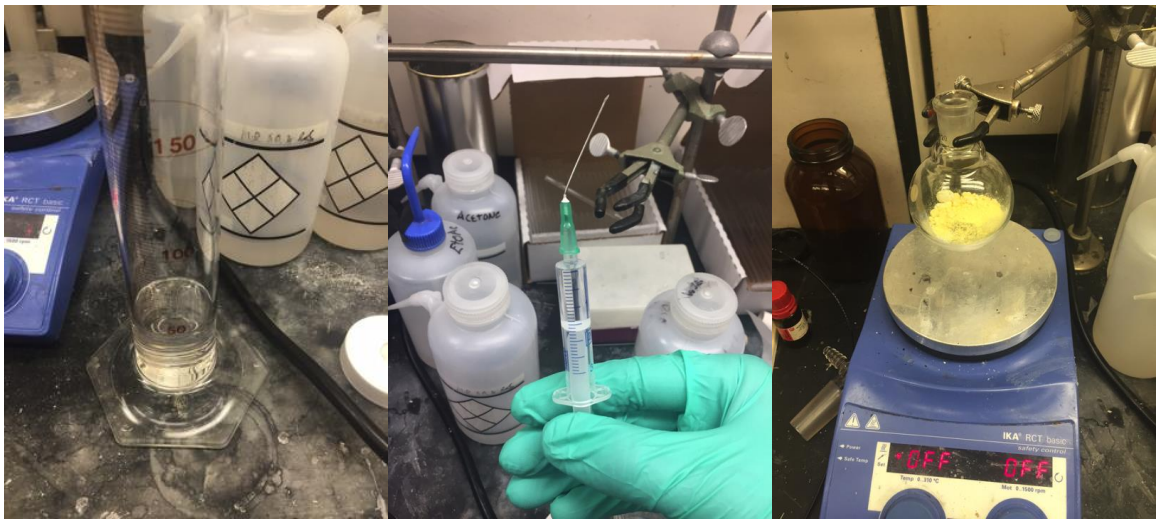


Redox-active esters were prepared according to the previously reported procedure.(*21*) In short, a round-bottom flask or culture tube was charged with (if solid) carboxylic acid (1.0 equiv), nucleophile (*N*-hydroxy-phthalimide or *N*-hydroxy-tetrachlorophthalimide (*37*) (1.0 equiv), and DMAP (0.1 equiv). Dichloromethane was added (0.1 – 0.2 M), and the mixture was stirred vigorously. Carboxylic acid (1.0 equiv) was added via syringe (if liquid). DIC (1.0 equiv) was then added dropwise via syringe, and the mixture was allowed to stir until the acid was consumed (determined by TLC). Typical reaction times were between 0.5 h and 12 h. The mixture was filtered (over Celite, silica gel, or through a fritted funnel) and rinsed with additional CH_2Cl_2/Et_2O. The solvent was removed under reduced pressure, and purification by column chromatography and recrystallization, if necessary, afforded the corresponding redox-active ester.

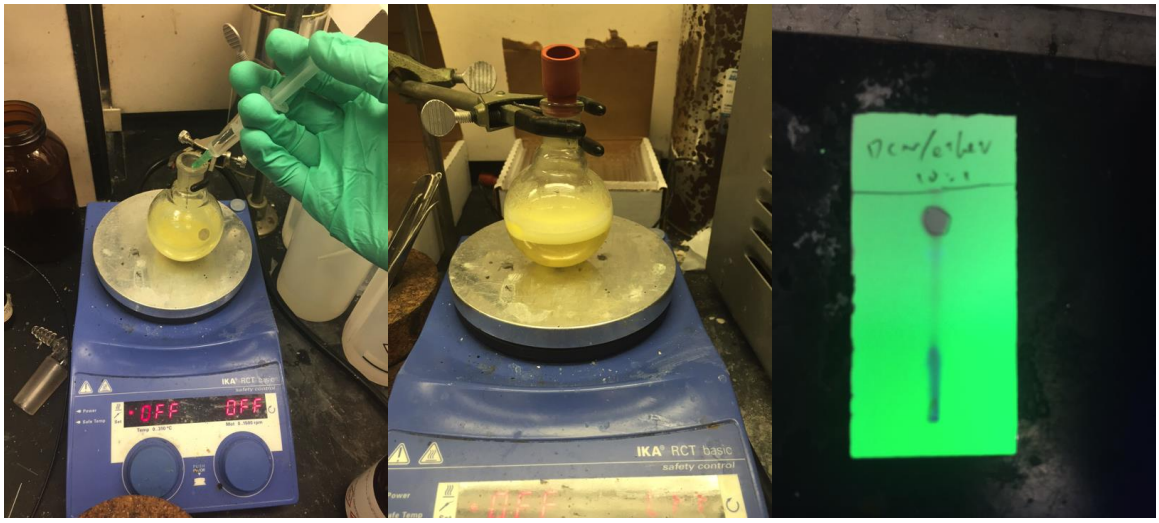
Graphical Supporting Information for the Synthesis of Redox-active Esters (General Procedure A)

(Above) DIC, 1-tosylpiperidine-4-carboxylic acid, and *N*-hydroxy-tetrachlorophthalimide (DMAP not shown).

(Left) 1-tosylpiperidine-4-carboxylic acid **(Center)** *N*-hydroxy-tetrachlorophthalimide (**Right**) DMAP.

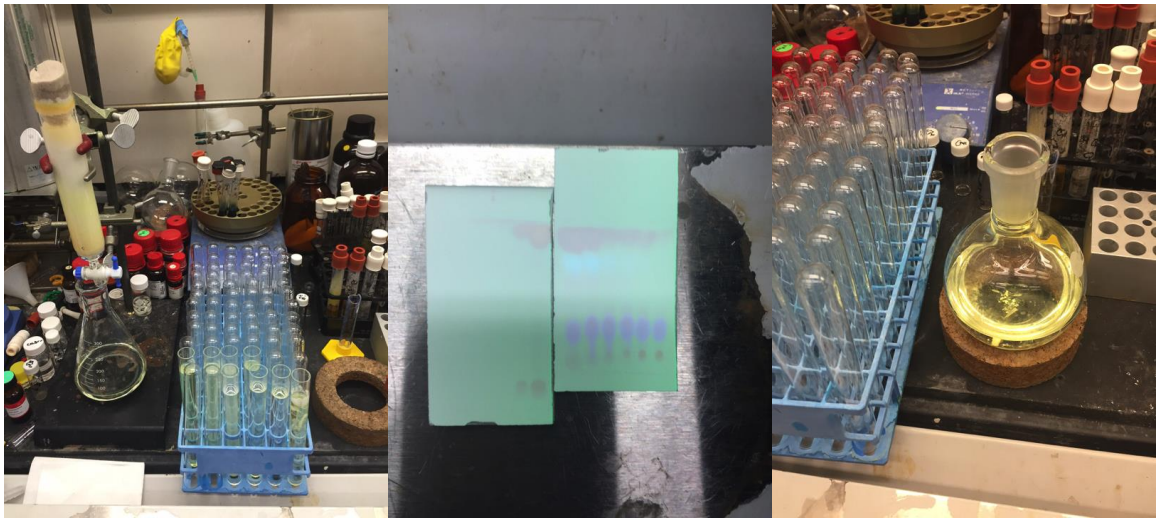


(Left) CH_2Cl_2. **(Center)** DIC in syringe. **(Right)** *N*-hydroxy-tetrachlorophthalimide in the flask.

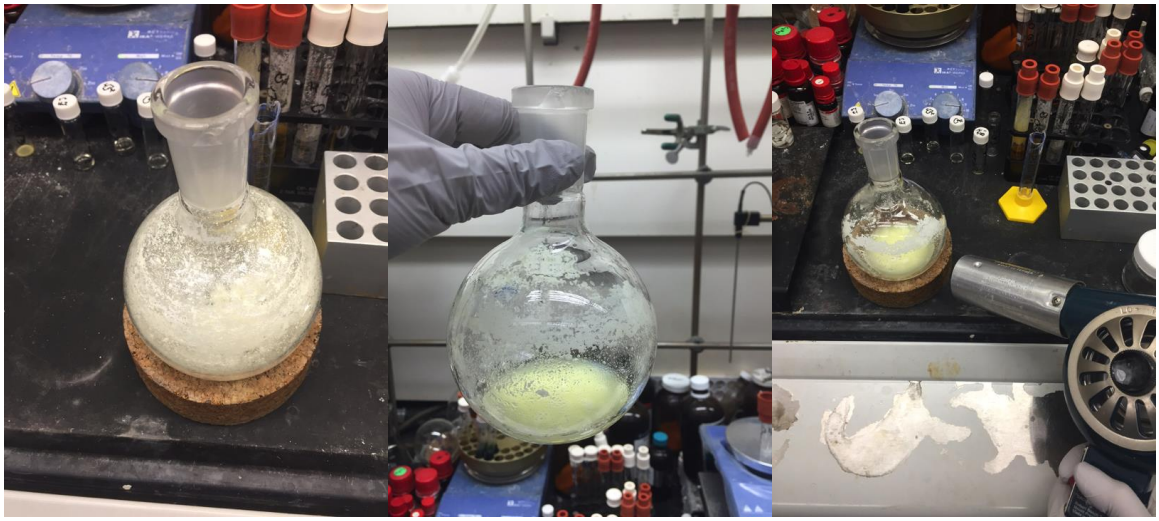


(Left) Addition of DIC to reaction mixture. **(Center)** Reaction mixture after stirring for 2 hours. **(Right)** TLC of reaction mixture (10:1 CH_2Cl_2: Et_2O); top UV active spot is the desired product.

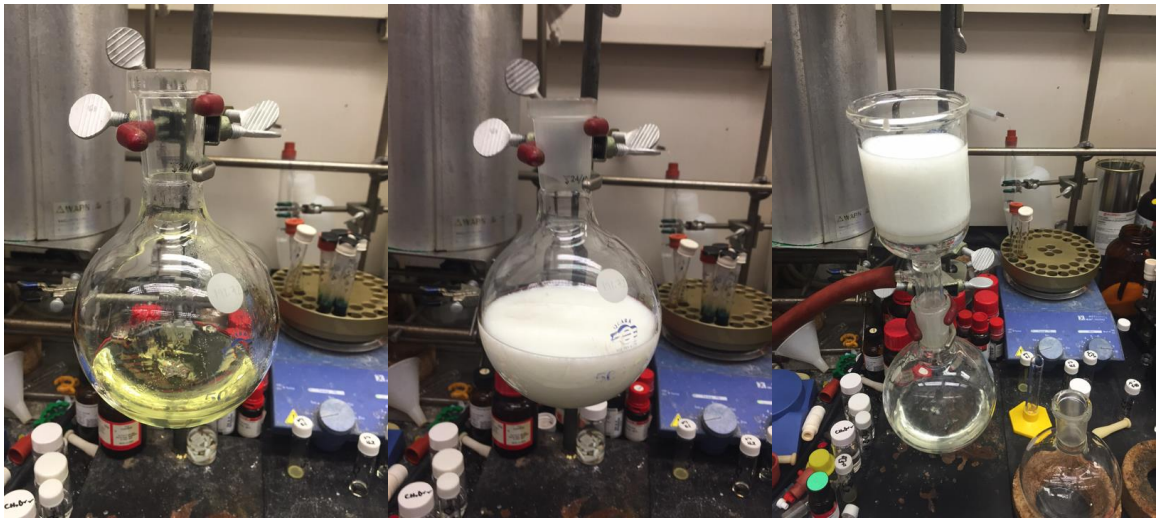
(Left) Crude reaction mixture after reduction of solvent volume. **(Center)** Set up for column chromatography. **(Right)** Reaction mixture is loaded directly onto column.



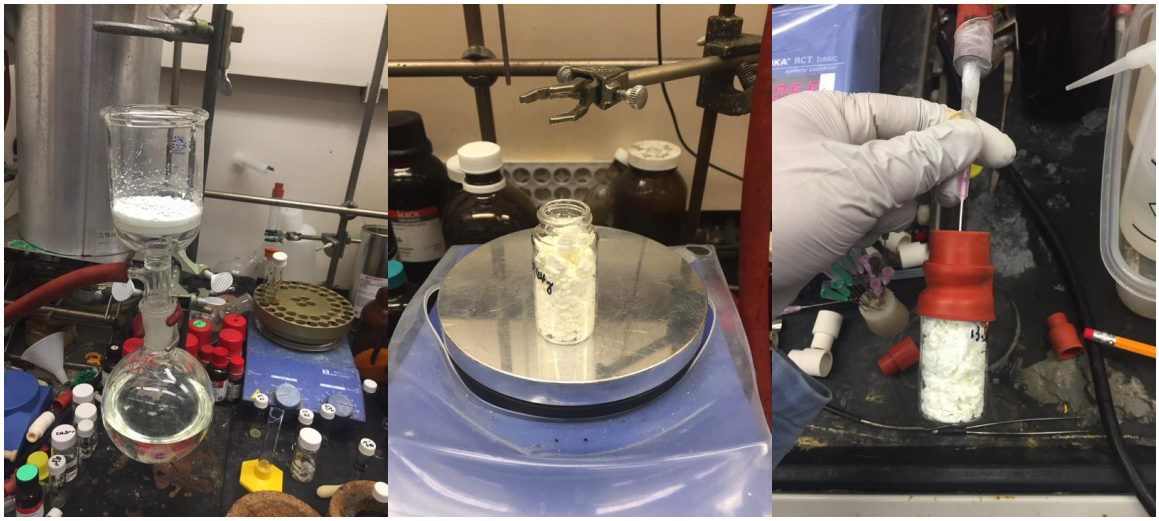
(Left) Fractions from column chromatography. **(Center)** TLC of column fractions. **(Right)** Fractions with product were collected.



(Left) Product after column chromatography. **(Center)** After addition of CH_2Cl_2. **(Right)** The mixture is heated with a heat gun until all material solubilizes.

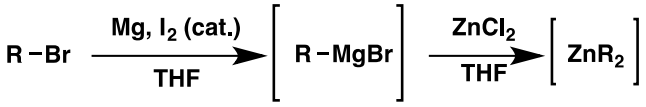


(Left) After heating. **(Center)** After addition of MeOH and cooling in cold room for 2 h. **(Right)** Filtration of the solid product.



(Left) After filtration. The solid was washed with additional cold MeOH. **(Center)** The product was transferred to a vial. **(Right)** Drying under vacuum.

General Procedure for the preparation of alkyl zinc reagents from alkyl bromides.



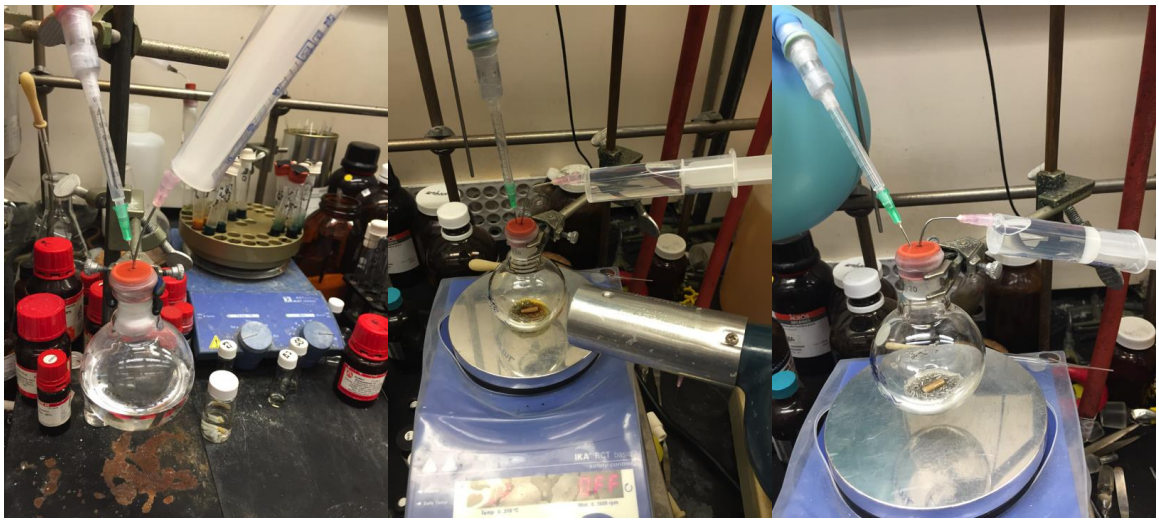
Two round-bottom flasks were flame-dried and allowed to cool under vacuum. Both flasks were then backfilled with argon from a balloon. One flask was charged with Mg turnings (0.730 g, 30 mmol, 1.5 equiv) and I_2 (approx. 0.050 g, 0.2 mmol, 0.02 equiv). In the other flame-dried flask, alkyl bromide (1.0 equiv, 20 mmol) was dissolved in anhydrous THF (20 mL) to make a 0.5 M solution of the alkyl bromide in THF. A small portion of the alkyl bromide solution (approx. 1 mL) was added to the Mg and I_2, and the mixture was stirred. The flask was heated gently with a heat gun until the dark brown color disappeared. The rest of the alkyl bromide solution was added dropwise while the flask was heated with a heat gun. After 1 hour, the resulting solution of Grignard reagent was titrated with I_2 to afford Grignard reagents with titres typically ranging 0.3 – 0.44 M in THF. To a separate flame-dried round-bottom flask, $ZnCl_2$ (0.409 g, 1.0 M in THF, 3 mmol) was added. A portion of the solution of alkyl Grignard reagent (6 mmol) was added dropwise to the $ZnCl_2$ solution, and the mixture was stirred for at least 10 min before use. The yield was assumed to be quantitative for this step.(*38*) On 0.1 mmol scale, the volume of dialkylzinc reagent solution used for the reaction was typically between 1.2 – 1.5 mL (corresponding to 0.2 mmol of dialkylzinc reagent).

Graphical Supporting Information for preparation of alkylzinc reagents from alkyl bromides.

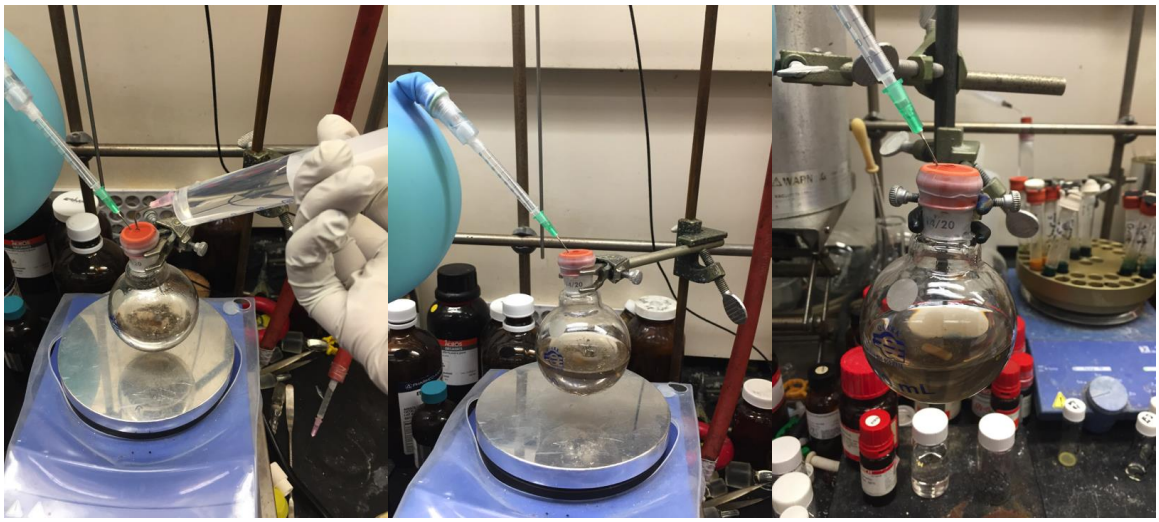
Part I. Alkyl Grignard Preparation

(Left) Two round-bottom flasks under vacuum after flame-drying with a blowtorch. **(Center)** After cooling, one flask was charged with Mg turnings and I_2. **(Right)** Flask containing Mg and I_2 under Ar inert atmosphere.

(Left) Round-bottom flask under Ar inert atmosphere. **(Center)** EtBr is taken up into a syringe. **(Right)** EtBr is added to the flask.

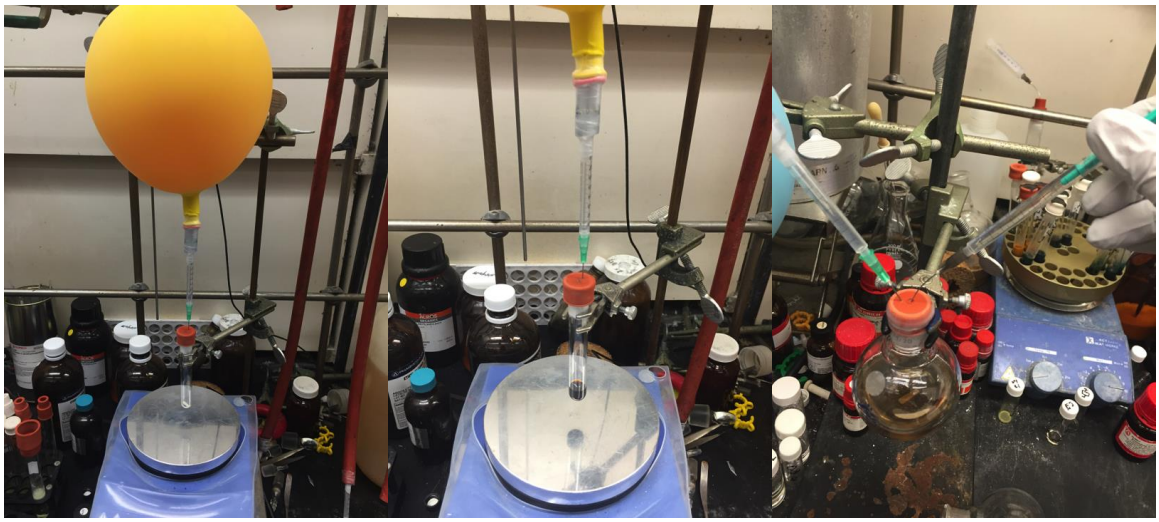


(Left) Addition of THF to EtBr (0.5 M). **(Center)** A portion of the EtBr solution was added to the Mg turnings and I_2. The mixture was gently heated with the heat gun until the I_2 color disappeared. **(Right)** Dropwise addition of the entirety of the EtBr solution. The solution is periodically heated with the heat gun.

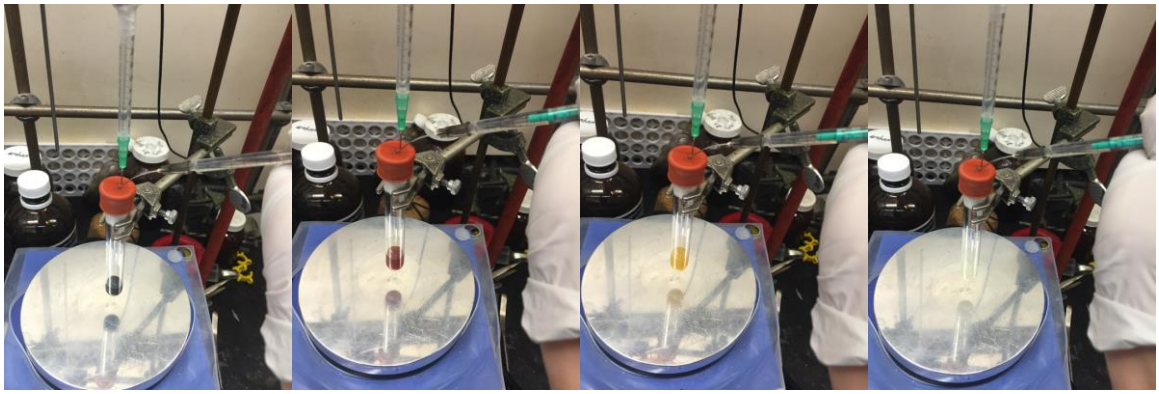


(Left) Progression of addition of EtBr solution. Note the color change to a brown/grey solution. **(Center)** Grignard reagent after addition of EtBr solution. **(Right)** Close up photo of EtMgBr in THF.

Part II. Titration of alkyl Grignard reagent.



(Left) A flame-dried culture tube is placed under inert Ar atmosphere. **(Center)** I_2 (0.051 g, 0.2 mmol) in 1.0 mL of THF. **(Right)** EtMgBr in THF.

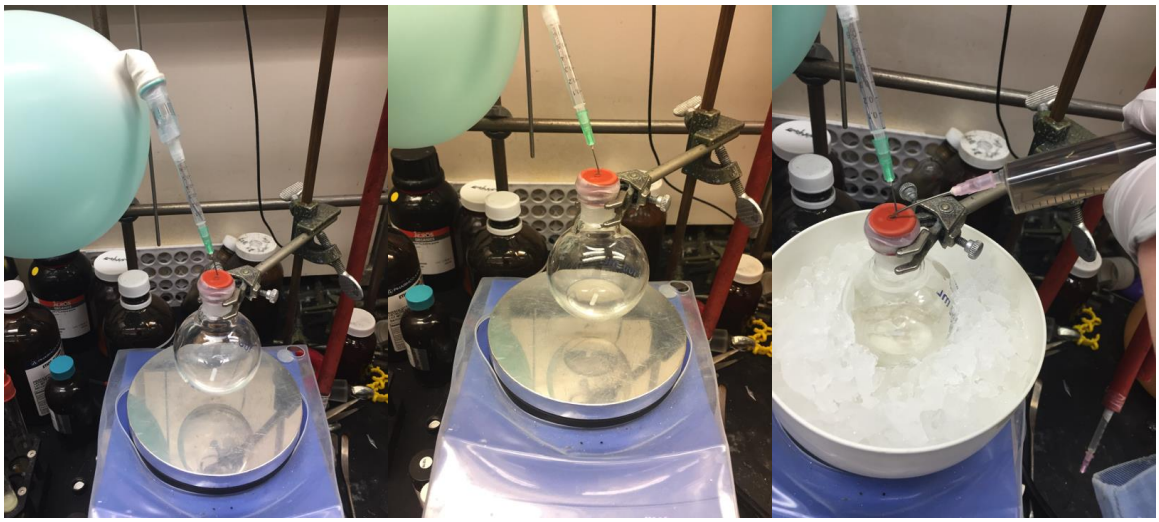


(Left) Start of titration. **(Center, Right and Left)** Progression of titration. **(Right)** End point of titration (disappearance of color).

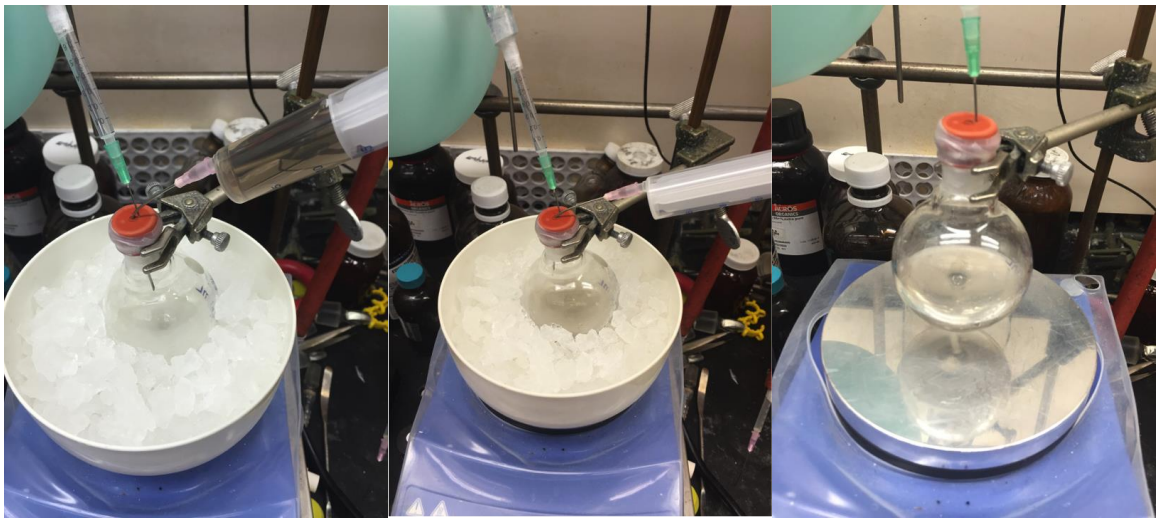
Part III. Preparation of $ZnCl_2$ solution.

(Left) $ZnCl_2$ was weighed and placed in a culture tube under vacuum. **(Left Center)** $ZnCl_2$ was dried under vacuum with a blowtorch until it melts. **(Right Center)** After cooling, THF is added. **(Right)** After stirring all $ZnCl_2$ is dissolved to make a 1.0 M solution in THF.

Part IV. Transmetallation of EtMgBr to $ZnCl_2$.

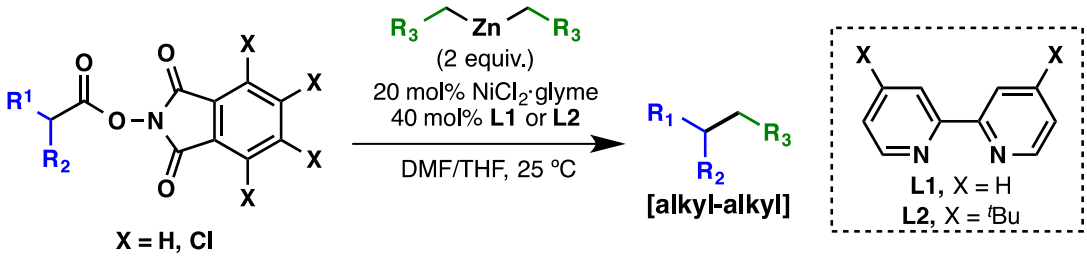


(Left) A flame-dried flask under inert Ar atmosphere. **(Center)** $ZnCl_2$ solution in THF was added to the flask. **(Right)** The $ZnCl_2$ solution was cooled to 0 °C in ice/water bath, and EtMgBr solution was added.



(Left) Progression of addition of EtMgBr solution. **(Center)** After addition of EtMgBr. **(Right)** Et_2Zn solution after stirring for 10 min at rt. The solution was used at this point for the Ni-catalyzed sp^3-sp^3 cross-coupling reaction.

General Procedure for the Ni-catalyzed cross-coupling reaction (General Procedure B).



A culture tube was charged with redox-active ester (0.1 mmol, 1.0 equiv). The tube was then evacuated and backfilled with argon from a balloon. A solution of $NiCl_2$•glyme (4.4 mg, 0.02 mmol, 0.20 equiv) and ligand (bipy (**L1**) or di-*t*BuBipy (**L2**), 6.3 mg or 11 mg, respectively, 0.04 mmol, 0.4 equiv) in DMF (1.0 mL) was added. The mixture was stirred for 5 minutes. A solution of dialkylzinc (0.2 mmol, 2.0 equiv) in THF was added. The argon balloon was removed, and the culture tube was sealed with Teflon tape and electrical tape. The resulting mixture was allowed to stir overnight (8 – 16 h) at rt. The reaction mixture was quenched with 1M HCl (or half-saturated aqueous NH_4Cl solution for acid sensitive substrates) and extracted with Et_2O or EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 40 °C. The crude product was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

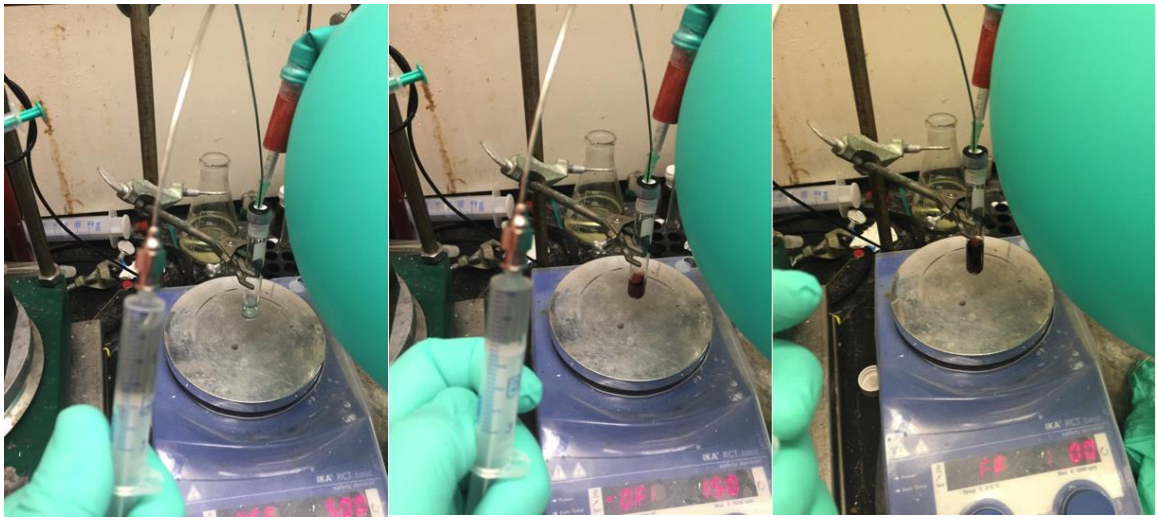
Graphical Supporting Information for the Ni-catalyzed cross-coupling reaction.

Part I. Preparation of $NiCl_2$•glyme/ligand stock solution.

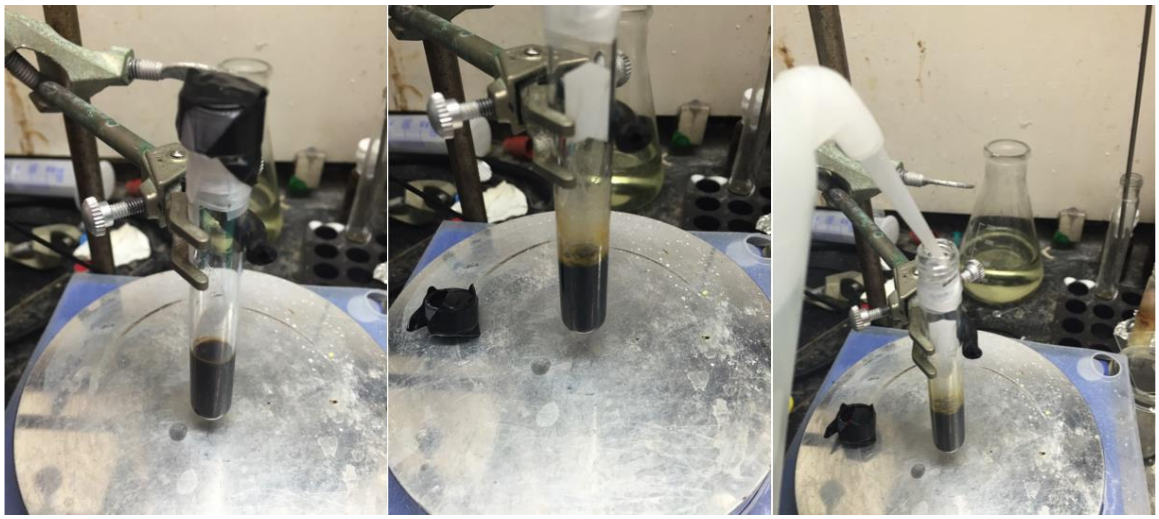
(Left) $NiCl_2$•glyme and di-*t*BuBipy. **(Center)** The culture tube was evacuated and backfilled with argon from a balloon. **(Right)** Addition of DMF (anhydrous).

Part II. Ni-catalyzed cross-coupling reaction.

(Left) Redox-active ester **SI-22** in culture tube. **(Center)** The culture tube was evacuated and backfilled with argon from a balloon. **(Right)** Addition of $NiCl_2$•glyme and di-*t*BuBipy stock solution (1.0 mL).

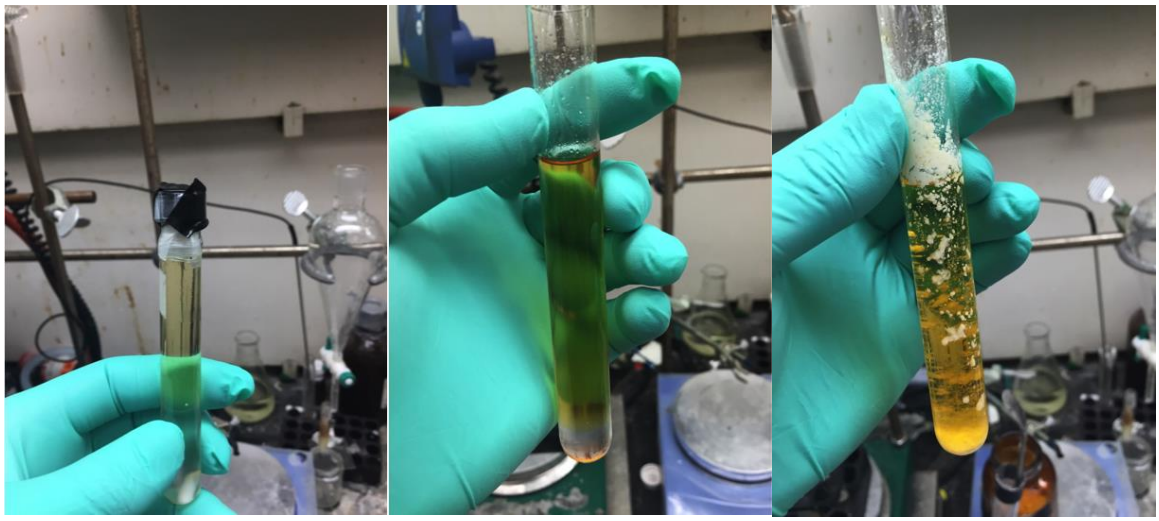


(Left) Before addition of dialkylzinc reagent. **(Center)** Addition of dialkylzinc reagent. **(Right)** After addition of dialkylzinc reagent.

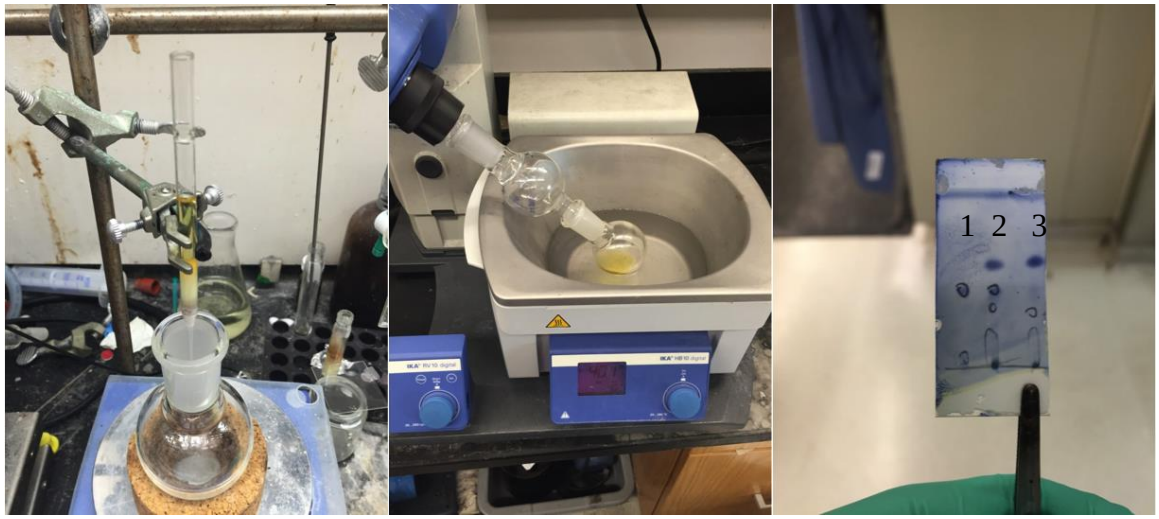


(Left) After removal of balloon. The tube was sealed with Teflon tape and electrical tape. **(Center)** After stirring for 8 hr. **(Right)** Dilution of reaction mixture with Et_2O.

(Left) Sat. NH_4Cl (aq) was added. **(Center)** H_2O was added. **(Right)** Reaction mixture after quench.



(Left) Extraction of aqueous layer with additional Et_2O. **(Center)** Brine wash. **(Right)** Drying over $MgSO_4$.

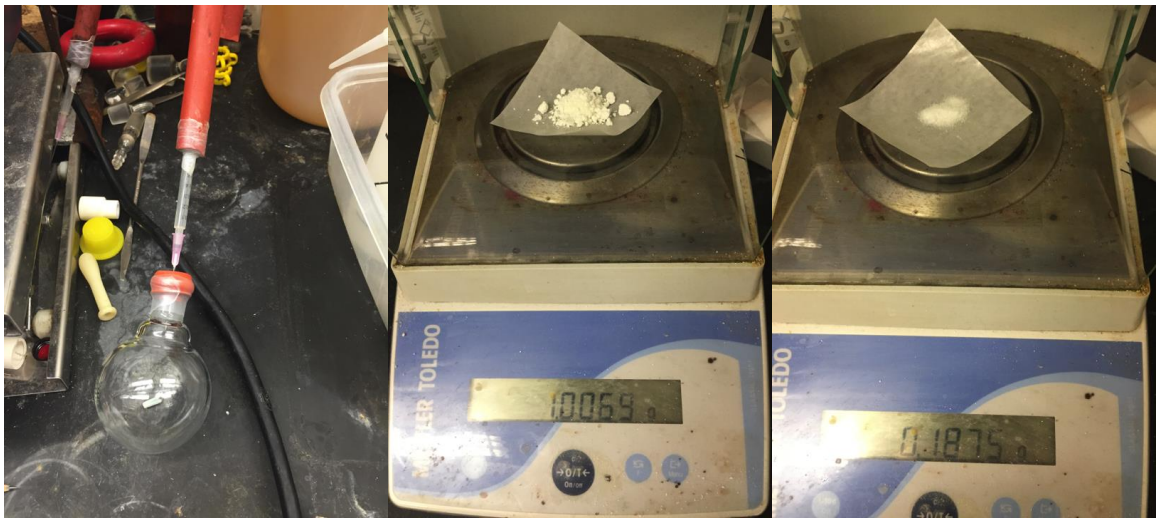


(Left) Filtration of drying agent over optional silica gel pad. **(Center)** Concentrating the organic extracts. **(Right)** TLC (4:1 hexanes:EtOAc). Lane 1: Starting material redox-active ester **SI-22**. Lane 2: Co-spot of starting material redox-active ester **SI-22** and reaction mixture. Lane 3: Reaction mixture. The desired product **31** is the dark-blue stained spot above the starting material spot.

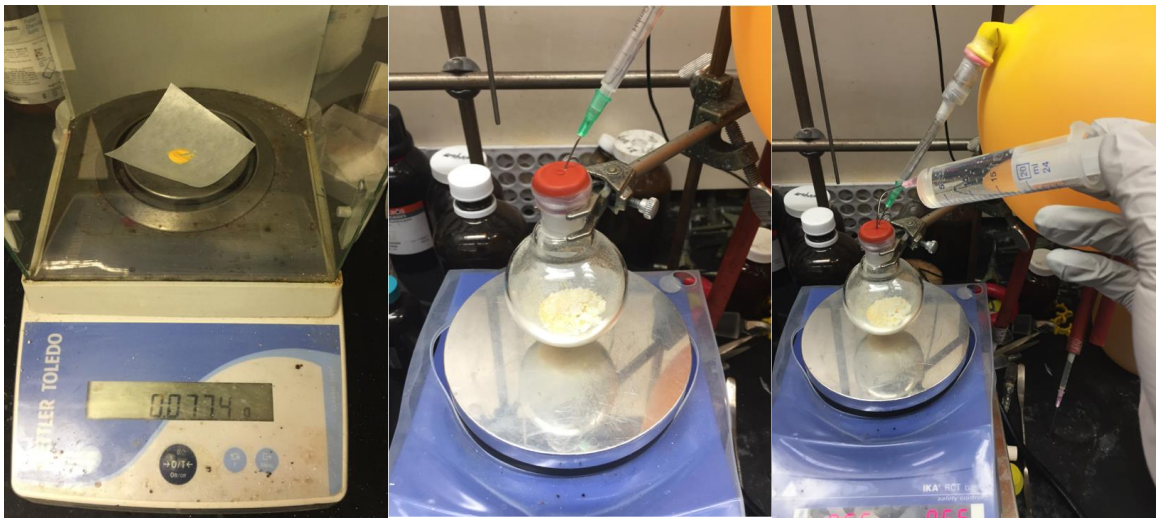
General Procedure for the Gram-Scale Ni-catalyzed cross-coupling reaction (4-ethyl-1-tosylpiperidine, 3).

The gram-scale procedure was minimally modified from **General Procedure B**. A round-bottom flask was flame-dried and allowed to cool under vacuum. The flask was then placed under inert Ar atmosphere via balloon. Redox-active ester **1b** (1.00 g, 1.8 mmol, 1.0 equiv), $NiCl_2$•glyme (0.077 g, 0.36 mmol, 0.2 equiv), and di-*t*BuBipy (0.188 g, 0.72 mmol, 0.4 equiv) were added to the flask. Anhydrous DMF (18 mL) was added, and the mixture was stirred for 5 min. The flask was placed in a room temperature water bath, freshly-prepared Et_2Zn (solution in THF) was added, and the mixture was stirred at rt overnight. The solution was cooled to 0 °C in an ice/water bath, and 1M HCl (aq.) was slowly added. Et_2O was added, and the mixture was transferred to a separatory funnel. The aqueous layer was extracted with Et_2O. The organic extracts were washed with brine and dried over $MgSO_4$. The drying agent was filtered, and the solvent was removed on a rotary evaporator. The crude product was purified by silica gel flash column chromatography with gradient elution (10:1 to 6:1, hexanes:EtOAc).

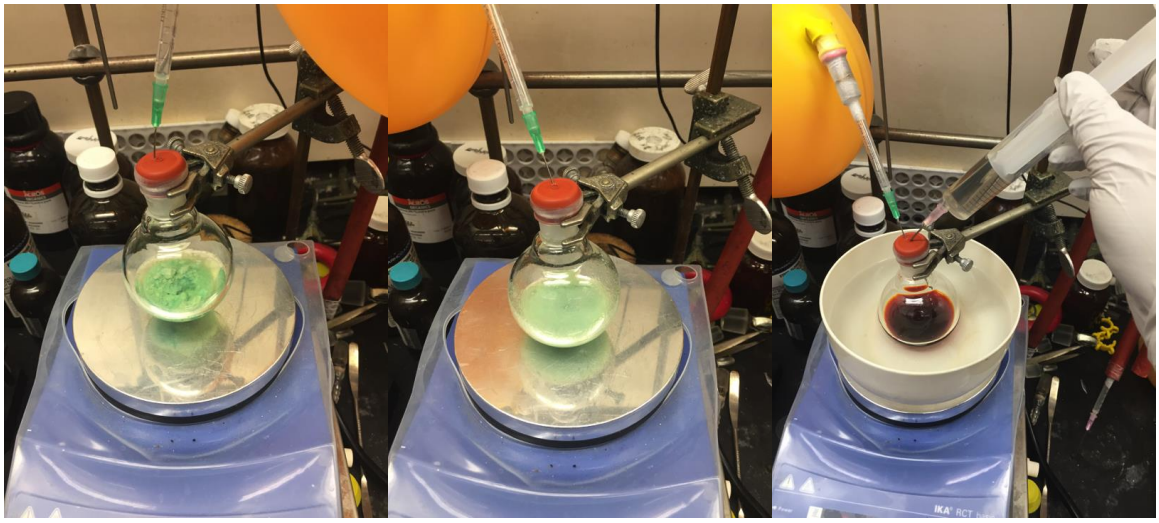
Graphical Supporting Information for the Gram-Scale Ni-catalyzed cross-coupling reaction.



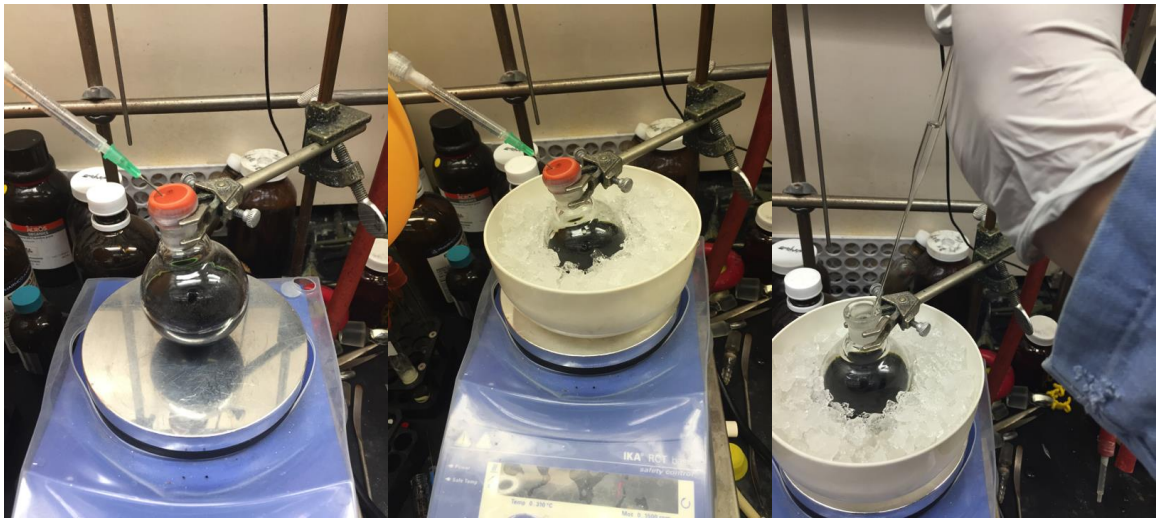
(Left) Flask was flame-dried under vacuum. **(Center)** 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 1-tosylpiperidine-4-carboxylate (**1b**). **(Right)** di-*t*BuBipy.



(Left) $NiCl_2$•glyme. **(Center)** Redox-active ester, $NiCl_2$•glyme, and di-*t*BuBipy in flask. **(Right)** Addition of DMF.

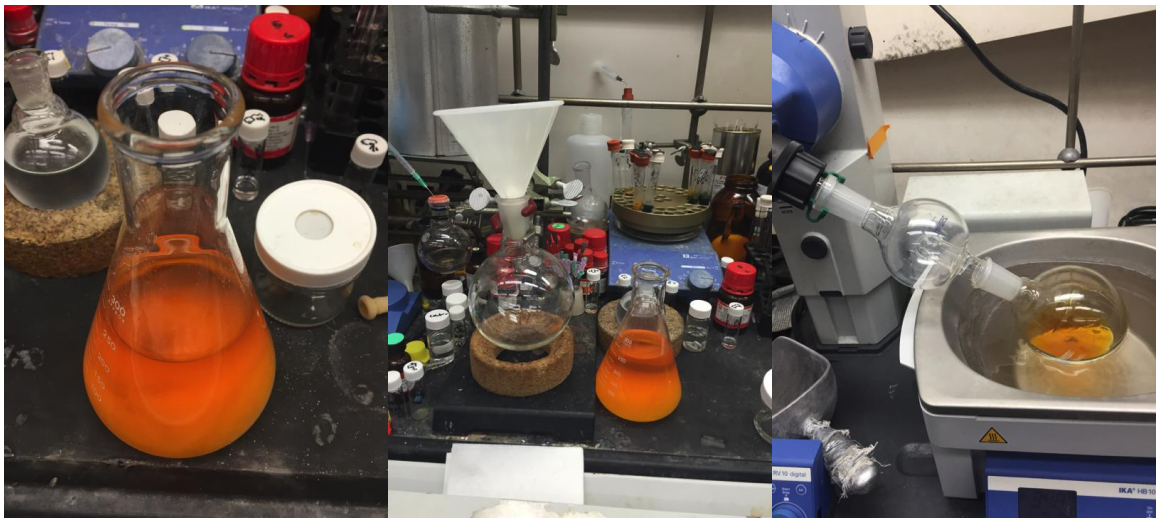


(Left) After addition of DMF. **(Center)** After 5 min of stirring. **(Right)** Addition of Et_2Zn solution after placing the flask in a rt water bath.



(Left) After stirring overnight at room temperature. **(Center)** The reaction mixture was cooled to 0 °C in an ice/water bath. **(Right)** Slow addition of 1M HCl (aq).

(Left) Quenched reaction mixture was transferred to a separatory funnel. **(Center)** Extraction with Et_2O. **(Right)** Brine wash.



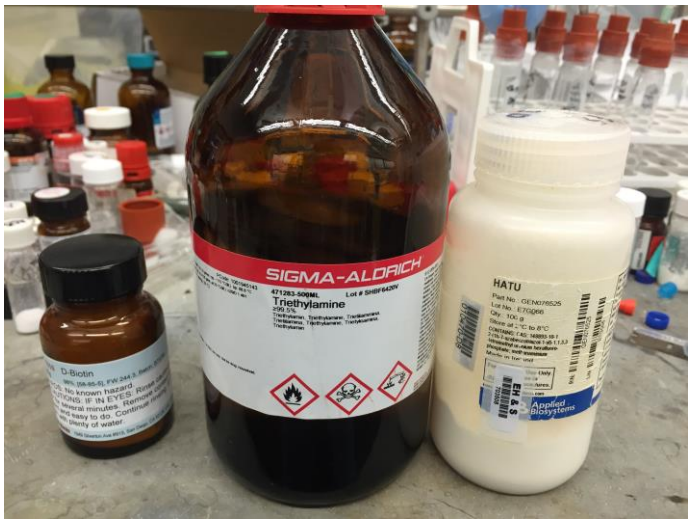
(Left) Drying of organic layers. **(Center)** Filtration of drying agent. **(Right)** Concentration of organic layer.

(Left) TLC of reaction mixture (4:1 hexanes:EtOAc). Lane 1: Reaction mixture. Lane 2: Co-spot. Lane 3: Authentic product **3**. **(Center)** Purification by column chromatography. **(Right)** Concentrating fractions containing pure 4-ethyl-1-tosylpiperidine (**3**).

General Procedure for the *in situ* activation of carboxylic acids with HATU (General Procedure C).

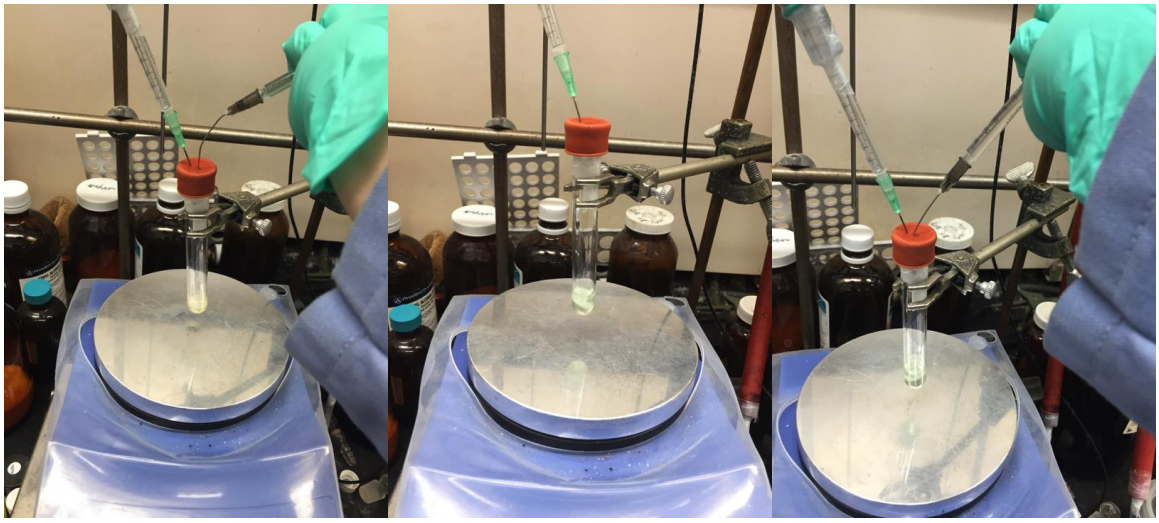
A culture tube was charged with carboxylic acid (0.1 mmol, 1.0 equiv) and HATU (1.0 equiv). The tube was then evacuated and backfilled with argon from a balloon. DMF (0.5 mL) and Et_3N (1.0 equiv) were added. The mixture was stirred for 30 minutes. A solution of $NiCl_2$•glyme (0.2 equiv), and di-*t*BuBipy (0.4 equiv) in DMF (0.5 mL) was added, and the mixture was stirred for 5 min. A solution of dialkylzinc (0.2 mmol, 2.0 equiv) in THF was then added. The argon balloon was removed, and the culture tube was sealed with Teflon tape and electrical tape. The resulting mixture was allowed to stir overnight (8 – 16 h) at rt. The reaction mixture was quenched with 1M HCl (or half-saturated aqueous NH_4Cl solution for acid sensitive substrates) and extracted with Et_2O or EtOAc. The organic layer was washed with water and brine and dried over $MgSO_4$. The organic layer was concentrated under vacuum by rotary evaporator in a water bath at 40 °C. The crude product was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

Graphical Supporting Information for the *in situ* activation of carboxylic acids with HATU (General Procedure C).

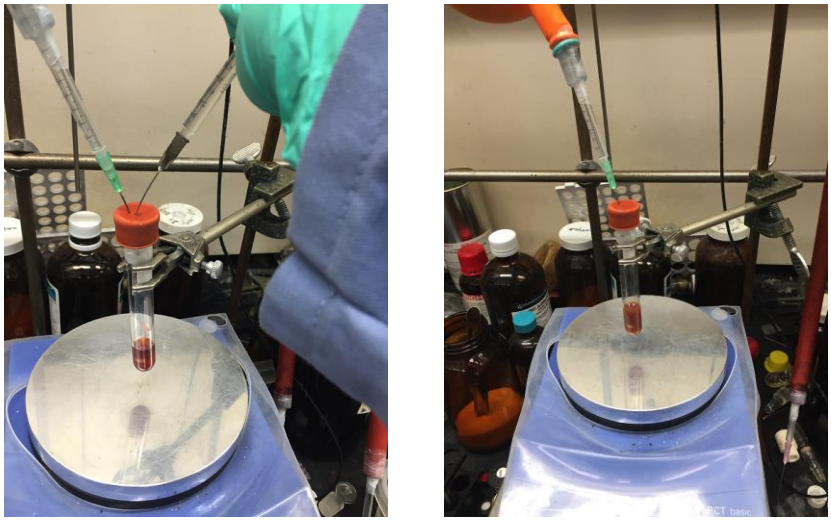


(Left) Biotin, Et_3N, and HATU. **(Right)** Biotin and HATU in culture tube under Ar.

(Left) Addition of DMF. **(Center)** Addition of Et_3N. **(Right)** After addition of Et_3N, mixture becomes homogenous.



(Left) Addition of $NiCl_2$•glyme and di-*t*BuBipy in DMF. **(Center)** After addition of [Ni] and ligand. **(Right)** Before addition dialkylzinc.



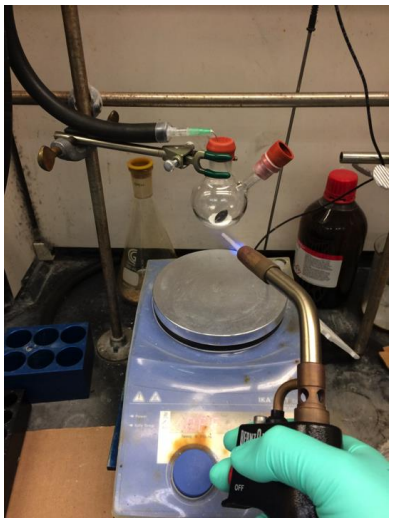
(Left) Addition of dialkylzinc reagent. **(Right)** After addition of dialkylzinc reagent. Work up was performed as before.

General Procedure for the three-component Ni-catalyzed conjunctive cross-coupling reaction (General Procedure D).

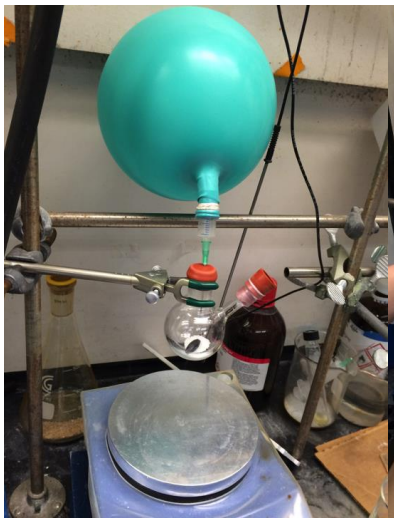
Part I. PhZnCl•LiCl Preparation.

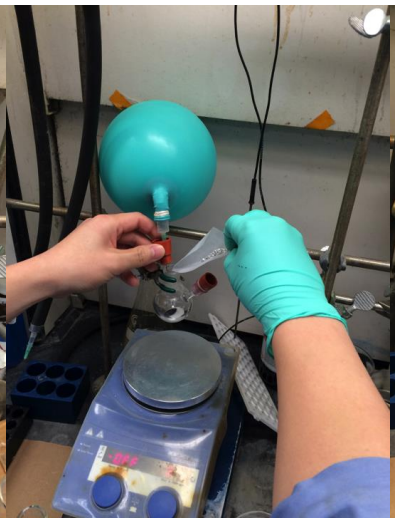
PhZnCl•LiCl was prepared in a manner similar to the report by Knochel and coworkers (*39*, *40*) and our previously reported procedure.(*21*) LiCl (0.663 g, 15.6 mmol, 1.25 equiv.) was added to a round-bottom flask. The flask was placed under vacuum and flame-dried. Upon cooling the flask was backfilled with Ar from a balloon. Magnesium turnings (0.760 g, 31 mmol, 2.5 equiv.) were added by quickly removing the septum, adding the magnesium turnings, and replacing the septum. Tetrahydrofuran (anhydrous, 31.3 mL) was added, and the mixture was stirred vigorously for 5 min. DIBAL–H (1.0 M in THF, 0.2 mL, 0.01 equiv) was added via syringe, and the mixture was stirred vigorously for 5 min. The flask was then cooled to 0 °C in an ice/water bath, and bromobenzene was added (1.33 mL, 12.5 mmol, 1.0 equiv). The mixture was stirred at 0 °C for 1.5 hr. $ZnCl_2$ solution (1.0 M in THF, 12.5 mL, 12.5 mmol) was added to a separate flame-dried flask. To this flask PhMgBr•LiCl was transferred via syringe. Often a white precipitate forms as the solution of PhMgBr•LiCl is added to the solution of $ZnCl_2$, but the precipitate dissolves over the course of the addition. After 10 minutes, the solution of PhZnCl•LiCl was titrated with I_2.

Graphical Procedure PhZnCl•LiCl Preparation.

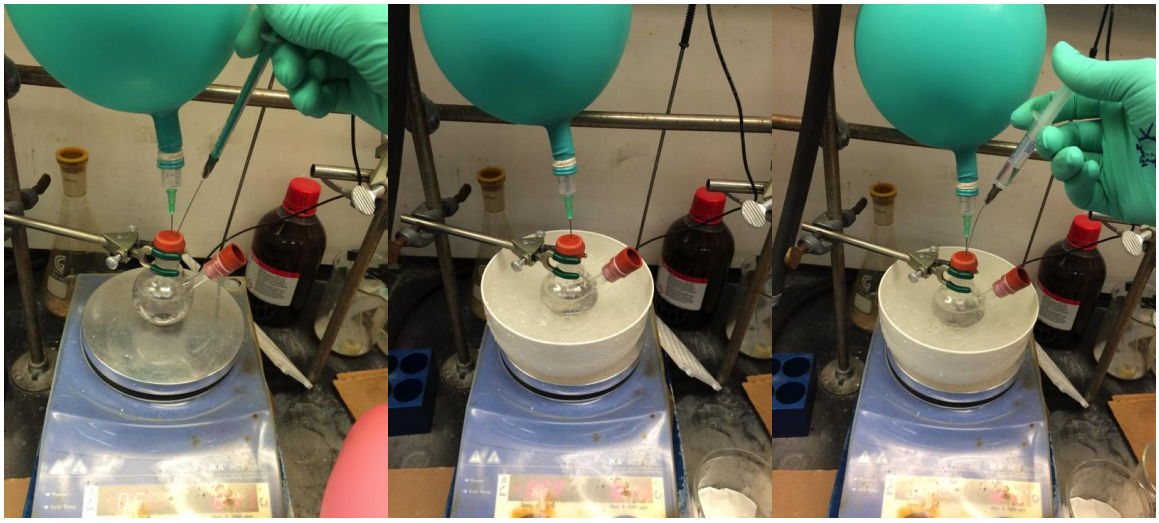


(Left) Round-bottom flask, bromobenzene, LiCl, $ZnCl_2$, and Mg turnings. **(Right)** Flame-drying the flask and LiCl under vacuum.

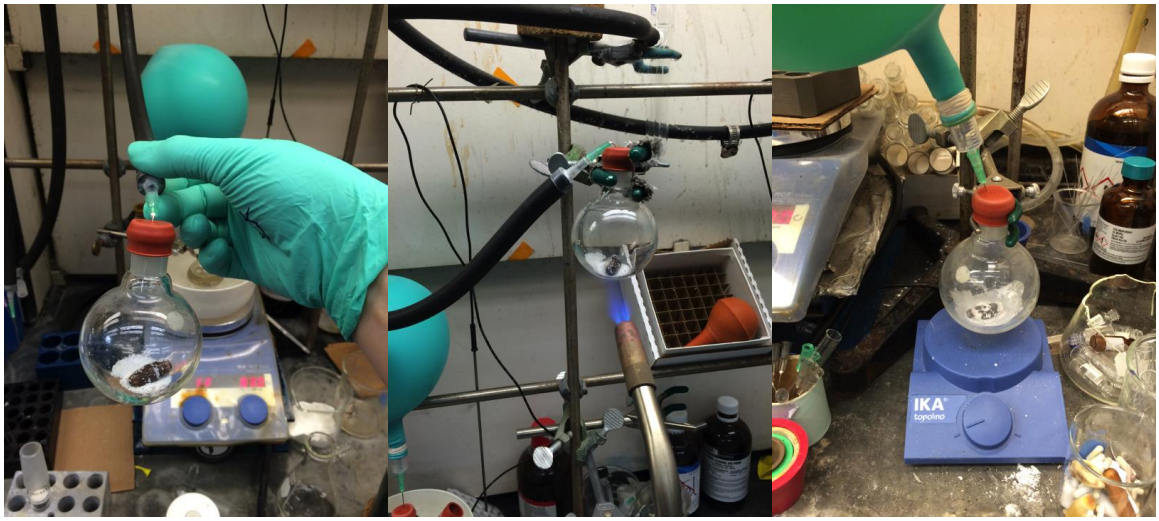




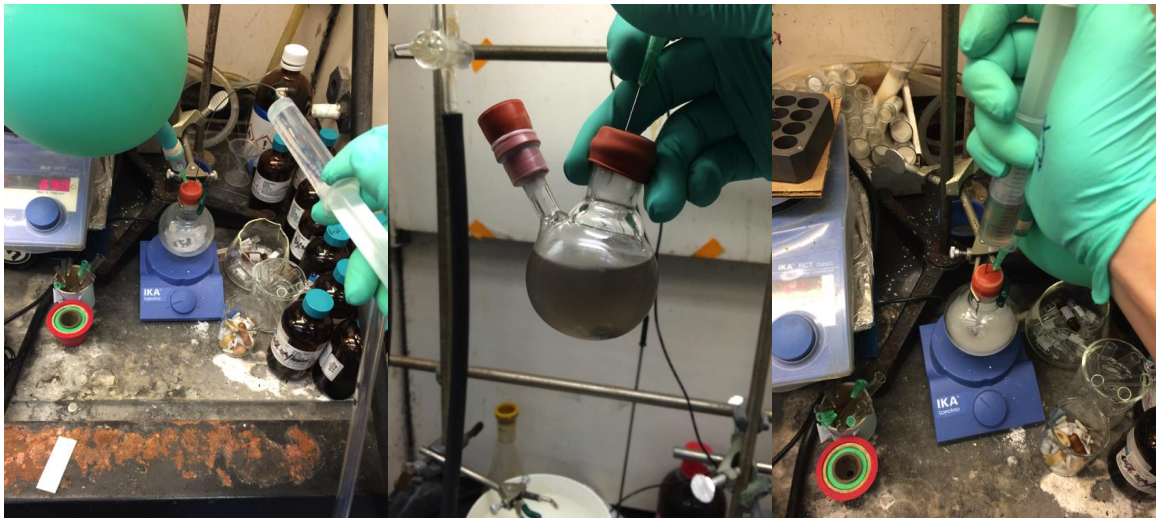
(Left) Flask under inert Ar atmosphere. **(Center)** Addition of Mg turnings. **(Right)** Addition of THF.



(Left) Addition of DIBAL-H. **(Center)** The reaction was cooled to 0 ºC. **(Right)** Addition of bromobenzene.



(Left) $ZnCl_2$. **(Center)** Flame-drying $ZnCl_2$ until the solid melts. **(Right)** After flame-drying, under inert Ar atmosphere.



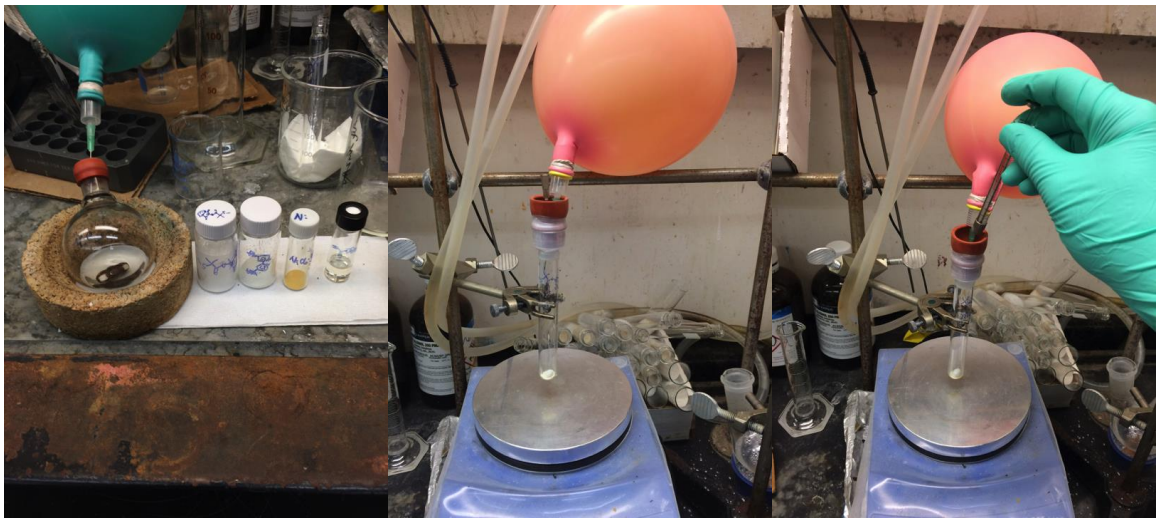
(Left) Addition of THF to $ZnCl_2$. **(Center)** PhMgBr•LiCl. **(Right)** Addition of PhMgBr•LiCl to $ZnCl_2$ solution.

(Above) PhZnCl•LiCl in THF.

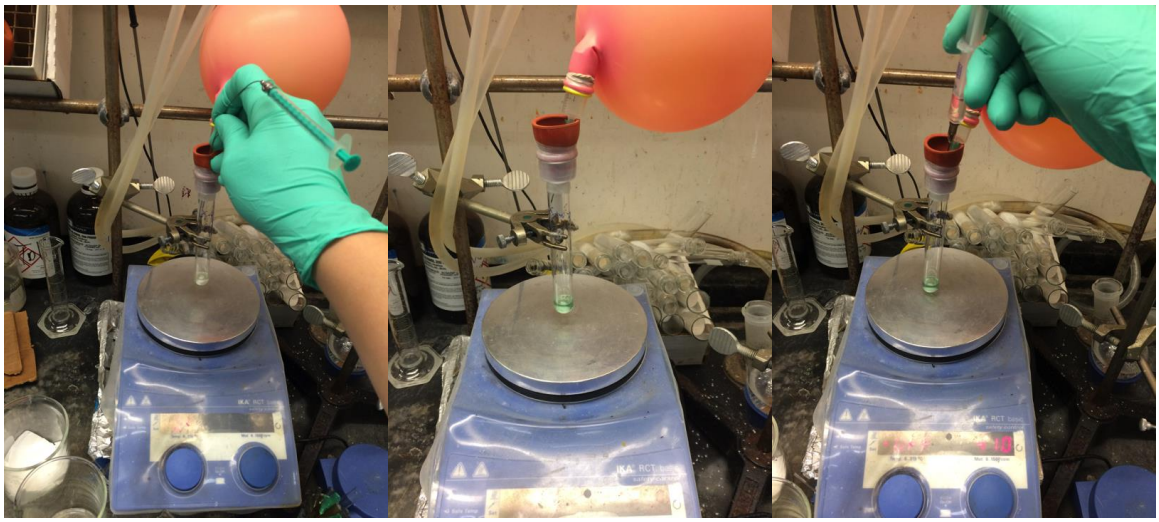
Part II. Three-component Ni-catalyzed conjunctive cross-coupling reaction.

An oven-dried test tube containing a stirring bar was charged with $NiCl_2$·glyme (0.2 eq), di-*t*BuBipy (0.4 equiv) and redox-active *N*-hydroxyphthalimide ester (1.0 equiv). The tube was fitted with a septum and sealed with parafilm. The air in the tube was exchanged with argon using an argon balloon. DMF was then added via syringe and the mixture stirred for 2 minutes at rt. Benzyl acrylate (2.5 equiv) was added via microliter syringe. Then, PhZnCl•LiCl in THF (3.0 equiv) was added under argon at once, and the mixture was stirred for 8 h at rt. The mixture was quenched with half sat. NH_4Cl. The resulting mixture was extracted with EtOAc. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the crude product, which was purified by silica gel flash column chromatography or PTLC.

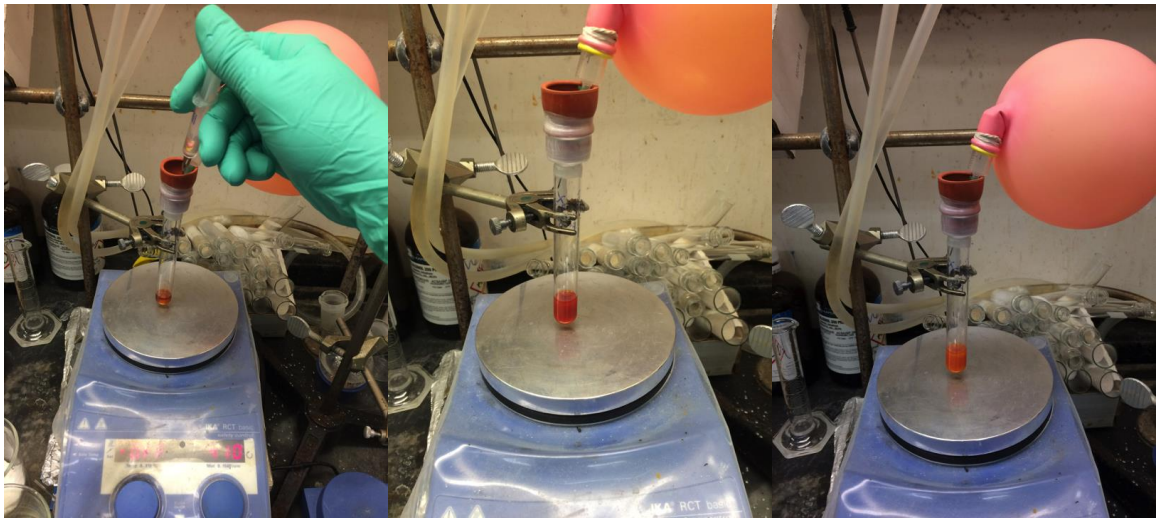
Graphical Supporting Information for the three-component Ni-catalyzed conjunctive cross-coupling reaction (General Procedure D).



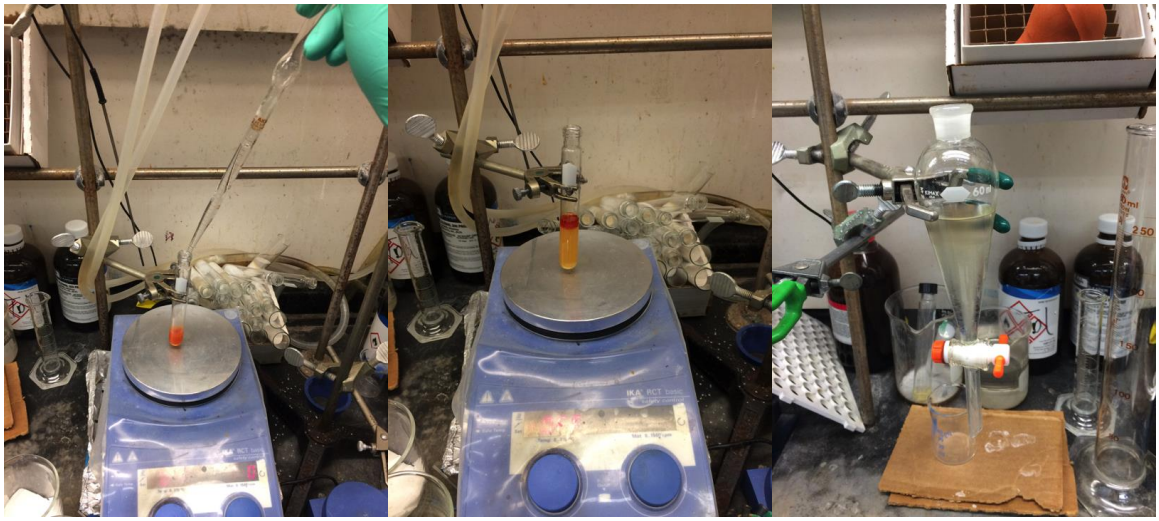
(Left) PhZnCl•LiCl (solution in THF), redox-active NHPI-ester, di-*t*BuBipy, $NiCl_2$·glyme, and benzyl acrylate **(Center)** Tube containing the redox-active ester under for inert Ar. **(Right)** Addition of benzyl acrylate by microliter syringe.



(Left) Addition of DMF. **(Center)** After 2 min of stirring. **(Right)** Before addition of PhZnCl•LiCl (solution in THF).



(Left) Addition of PhZnCl•LiCl. **(Center)** After addition of PhZnCl•LiCl. **(Right)** After stirring for 12 hr.



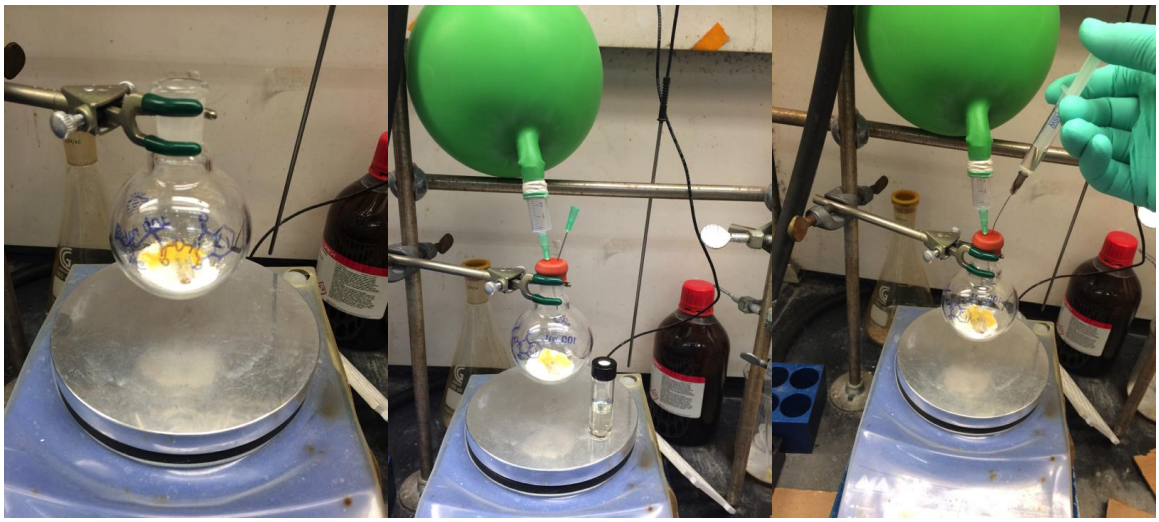
(Left) Quench with half-saturated NH_4Cl (aq). **(Center)** After quench. **(Right)** Quenched reaction mixture was transferred to a separatory funnel and extracted with EtOAc, dried, and concentrated.

(Above) TLC of reaction. Lane 1: Reaction mixture. Lane 2: Co-spot. Lane 3: Starting material redox-active ester. The top spot in the reaction mixture is excess benzyl acrylate, and the spot below it is the desired product.

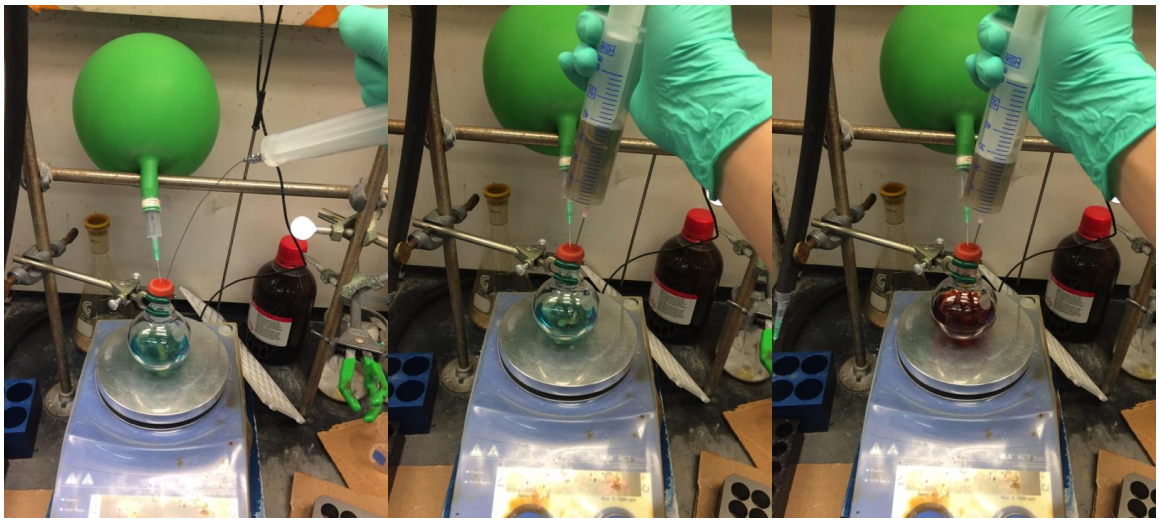
Procedure for Gram Scale three-component Ni-catalyzed conjunctive cross-coupling reaction.

An oven-dried 100 mL round bottom flask containing a stirring bar was charged with $NiCl_2$·glyme (0.2 eq), di-*t*BuBipy (0.4 equiv) and *N*-hydroxy-phthalimide ester (1.0 equiv). The flask was fitted with a septum. The air in the flask was exchanged to argon using an argon balloon and vent needle. DMF (anhydrous) and benzyl acrylate (2.5 equiv) were then added via syringe, and the mixture stirred for 5 minutes at rt. Then, PhZnCl•LiCl in THF (3.0 equiv) was added under argon at once at the same temperature and the mixture was stirred for 8 h at rt. The mixture was poured into half sat. NH_4Cl and the resulting mixture was extracted with EtOAc. The separated organic layer was washed with brine 3 times, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

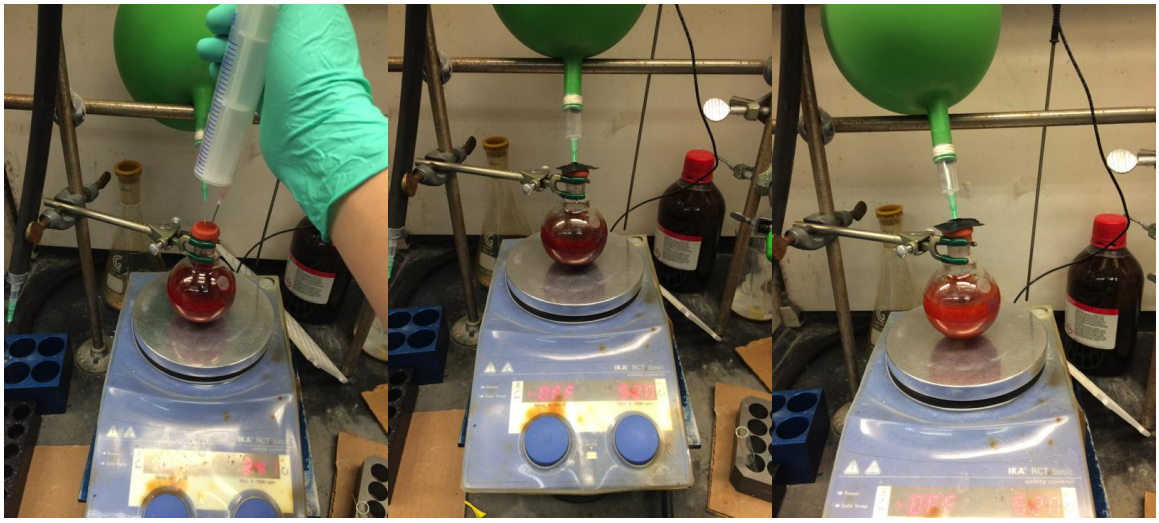
Graphical Supporting Information for the Gram-scale three-component Ni-catalyzed conjunctive cross-coupling reaction.



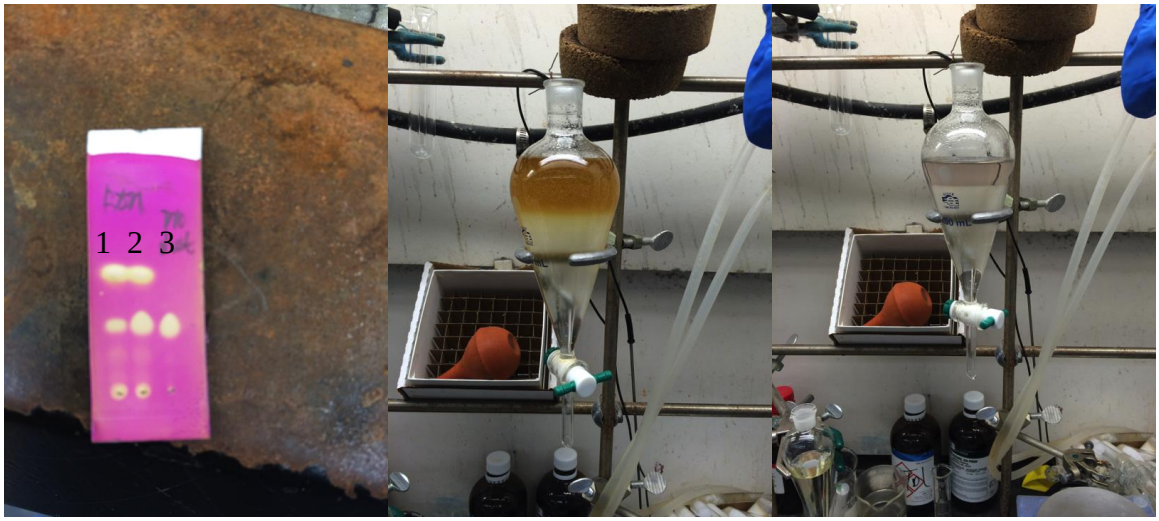
(Left) Flask containing redox-active *N*-hydroxy-phthalimide ester, $NiCl_2$·glyme, and di-*t*BuBipy. **(Center)** Exchange of air for inert Ar atmosphere via Ar balloon and vent needle. **(Right)** Addition of benzyl acrylate via syringe.



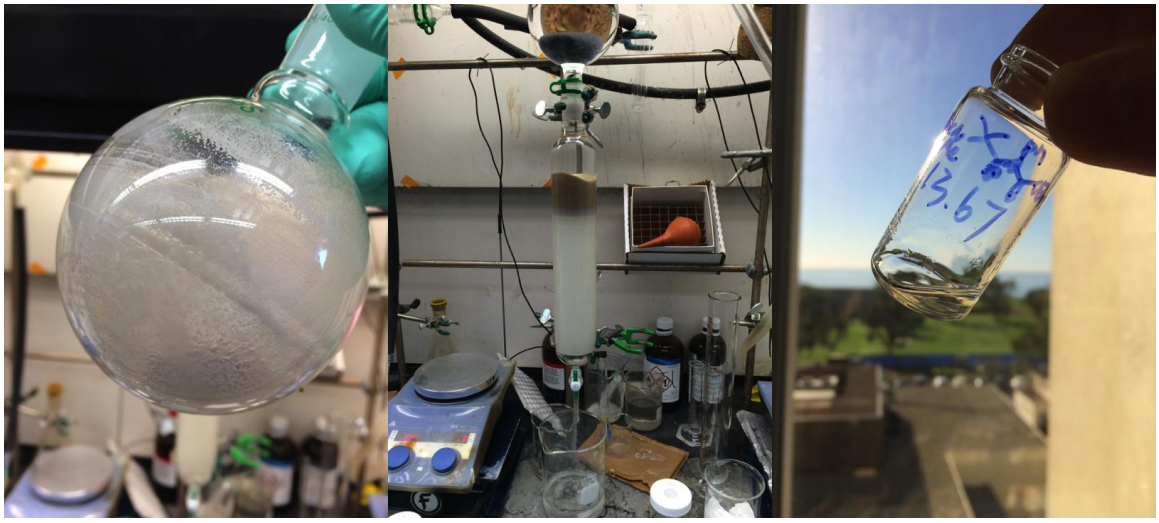
(Left) Addition of DMF. **(Center)** Before addition of PhZnCl•LiCl. **(Right)** Progression of addition of PhZnCl•LiCl (note color change).



(Left) Completed addition of PhZnCl•LiCl. **(Center)** Holes in septum are covered with electrical tape. **(Right)** Reaction mixture after 12 h.



(Left) TLC of the reaction. Lane 1: Reaction mixture. Lane 2: Co-spot. Lane 3: Authentic product. **(Center)** Reaction mixture was poured into half sat. NH_4Cl (aq). **(Right)** Extraction and normal aqueous work up was performed.



(Left) Crude product. **(Center)** Purification by column chromatography. **(Right)** Pure product.

Troubleshooting: Frequently Asked Questions

Part I. Redox-active Ester Synthesis.

Question 1:

How do I monitor the reaction?

Answer:

We use TLC analysis with UV visualization and staining ($KMnO_4$) to monitor the reaction. We do not recommend using LC/MS or GC/MS for reaction monitoring because we have found that on our instruments these redox-active esters are not guaranteed to be stable and show the proper m/z.

Question 2:

How do I purify my redox-active ester?

Answer:

We use a combination of silica gel flash column chromatography and recrystallization. The reaction mixture is typically filtered over silica gel that is eluted with CH_2Cl_2/Et_2O; we do not do an aqueous work up. After the filtrate is concentrated, the mixture is analyzed by ^{1}H and ^{13}C NMR spectroscopy. If the product is pure, it is used in the subsequent coupling reactions as is. If the compound is not pure, the compound can be repurified by silica gel flash column chromatography. Typical eluents for this are hexanes/EtOAc, hexanes/Et_2O, hexanes/CH_2Cl_2, or CH_2Cl_2/Et_2O. For *N*-hydroxy-tetrachlorophthalimide esters, we recommend recrystallization with a small amount of CH_2Cl_2 and MeOH if the compound is still not pure. The residue is dissolved in a small amount of CH_2Cl_2, and MeOH is added. The mixture is heated gently with a heat gun until all solids dissolve, and the solution is cooled to room temperature. After cooling to room temperature, the solution is either placed in a -20 °C freezer or a 4 °C cold room for at least 1 hour. The mixture is then filtered, and the solid is washed with cold MeOH to afford pure ester. Before attempting on large scale, we recommend using a small portion of the material; in some rare cases, we observed transesterification of the ester to the methyl ester for particularly sensitive substrates.

Question 3:

It seems like the coupling is working but that the redox-active ester is unstable to silica gel because it streaks on the TLC plate; how do I purify the product?

Answer:

To purify the product, we recommend a filtration of the reaction mixture over silica gel (eluted with approx. 19:1 CH_2Cl_2:Et_2O). Following this, recrystallization of the esters from a small amount of CH_2Cl_2 with MeOH will result in very pure product. Additionally, we have observed that it is not essential to use pure starting material in the reaction.

Question 4:

Do I have to use CH_2Cl_2 for the coupling reaction?

Answer:

CH_2Cl_2 is not mandatory for the coupling. For some substrates, we also used EtOAc.

Question 5:

How should I store the redox-active ester?

Answer:

We have found that, in general, the redox-active esters are air-, moisture-, and light-stable. As such, we typically store them in a closed vial on the benchtop. However, for long-term storage, we would recommend storing them under an argon or nitrogen atmosphere at – 20 °C to ensure stability.

Question 6:

I am trying to get high-resolution mass spec data for my redox-active ester, but I am having trouble. What do I do?

Answer:

For these types of compounds, obtaining HRMS data by ESI is difficult. We normally rely heavily on ^{1}H and ^{13}C NMR data to determine if we have the correct compound. If necessary, a crystal structure can typically be obtained for *N*-hydroxy-tetrachlorophthalimide redox-active esters.

Part II. Activation with HATU.

Question 1:

Why should I use HATU to activate my carboxylic acid?

Answer:

There are three reasons to use HATU.

1. HATU should be used if the redox-active ester prepared by other methods is unstable and cannot be satisfactorily purified.

2. We have found that for proline-derived substrates, this method gives the highest yields.

3. HATU can be used if you want to run a one-pot reaction and not isolate the redox-active ester.

Part III. Nickel-catalyzed cross coupling.

Question 1:

How do you monitor the reactions?

Answer:

We monitor the reactions by a combination of TLC (and appropriate staining or UV visualization), GC/MS, and LC/MS. For smaller molecules, GC/MS typically shows the formation of the product. For compounds containing basic nitrogen atoms, LC/MS works well.

Question 2:

Do I need a glovebox to run this reaction?

Answer:

We do not set up the reaction in a glovebox. A glovebox is not necessary to run this reaction. The reaction can be setup and run in a glovebox, but this is not necessary as long as you have access to some inert gas (nitrogen or argon) because it is recommended to run the reaction under inert atmosphere.

Question 3:

Is it necessary to use a freshly-prepared Grignard reagent for the reaction?

Answer:

It is not necessary to use a freshly-prepared Grignard reagent for the reaction to work. However, we did find that preparing the Grignard reagent fresh for each batch of reactions resulted in the highest yields.

Question 4:

Can I use monoalkylzinc reagents?

Answer: Monoalkylzinc species prepared from Grignard reagents and $ZnCl_2$ to give an alkyl zinc chloride reagent work for this reaction.

Question 5:

Do commercial dialkylzinc reagents (diethylzinc, dimethylzinc, etc) work in this reaction?

Answer:

Commercial dialkylzinc reagents can be used in this reaction. However, preparing the dialkylzinc from a freshly-prepared Grignard reagent typically resulted in a higher yield than simply using the commercial dialkylzinc reagent.

Question 6:

Can I use THF with an inhibitor such as BHT, or should my solvent be inhibitor-free?

Answer:

We normally use THF that is inhibitor-free. We have found that using THF with BHT as an inhibitor can be very detrimental to the yield of the reaction in some cases. It is recommended that all THF with BHT be purified by distillation from sodium benzophenone ketyl.

Question 7:

Can the reaction be run only in THF, or is the DMF cosolvent necessary?

Answer:

It is detrimental to the yield if the reaction is only run in THF.

Question 8:

Is it necessary to run the reaction for an overnight period (> 8 hours), or can I quench it sooner?

Answer:

The reaction can be stopped sooner if there is complete consumption of the redox-active ester starting material. The best way to determine if the starting material has been completely consumed is by TLC analysis with a co-spot of the reaction mixture and starting material.

Question 9:

Are there any indicative color changes during the reaction?

Answer:

We often observe that the reaction mixture changes from greenish-blue to dark red upon addition of the alkyl zinc reagent. Within a short period of time, the reaction mixture continues to change to a green/black color. However, these color changes are not indicative of the success of the reaction.

Question 10:

How do I work up the reaction?

Answer:

We quench the reaction by diluting the reaction with Et_2O or EtOAc and slowly add 1M HCl (aq) at room temperature. We then extract with additional solvent, wash the organic extracts with brine, and concentrate. The crude product often contains solids that are phthalimide byproducts, but these are easily removed by column chromatography.

Question 11:

My substrate is likely acid-sensitive. What quench do you recommend in place of 1M HCl?

Answer:

For acid-sensitive substrates, half-saturated aqueous NH_4Cl or simply water can be used in place of 1M HCl. However, this quench often results in some formation of byproducts that are insoluble both in water and organic solvent. Additionally, it is sufficient to add a small amount of alcoholic solvent to quench residual alkylzinc species, and the entire reaction mixture can be filtered over silica gel as an additional work up. Aqueous workup is advised as it best removes DMF from the crude product.

Question 12:

How do I purify my product?

Answer:

We use both silica gel flash column chromatography and PTLC. Reverse-phase HPLC can be used for very polar compounds.

Question 13:

How do I determine which redox-active ester to use?

Answer:

Typically all redox-active esters will give the desired product in some amount of yield. For primary redox-active esters, the *N*-hydroxy-tetrachlorophthalimide ester typically gives the highest yield.

Question 14:

What other possible byproduct could be observed in this reaction?

Answer:

We occasionally observed the decarboxylated product, ester, and ketone formation in this reaction at various times.

Question 15:

I obtained the product, but the yield is not satisfactory for my purposes. What do you recommend I try to optimize the reaction?

Answer:

For optimization, we recommend the following:

1. Try the *N*-hydroxy-tetrachlorophthalimide ester. This typically results in about 10% higher yield than the normal NHPI ester.
2. Try heating the reaction, using 60 °C as a starting point.
3. Try excess dialkylzinc reagent.
4. Try using a more concentrated dialkylzinc reagent (the Grignard reagent can be prepared at concentrations of up to 3.0 M).
5. Try bipyridine or dimethoxybipyridine if you used di-*t*Bubipyridine.
6. Try a higher loading of Ni precatalyst.

Part IV. Three-component Coupling.

Question 1:

What types of redox-active esters will work well in this coupling reaction?

Answer:

Redox-active esters that generate tertiary radicals or α-heteroatom-substituted radicals will work well in this reaction.

Question 2:

Do arylzinc reagents other than PhZnCl•LiCl work in this reaction?

Answer:

We anticipate that other aryl zinc reagents from other aryl bromides will also work well in this reaction. In principle, if the aryl zinc reagent can be made, it should work in this reaction.

Question 3:

How do you monitor the reaction?

Answer:

We monitor the reactions by a combination of TLC (and appropriate staining or UV visualization), GC/MS, and LC/MS. For smaller molecules, GC/MS typically shows the formation of the product. For compounds containing basic nitrogen atoms, LC/MS works well.

Question 4:

How do I purify the product?

Answer:

We purify the compounds by silica gel column chromatography or PTLC. Often the desired product is of similar polarity to residual benzyl acrylate, so care is needed when purifying the material by column chromatography. If very pure product is necessary for subsequent steps, we recommend purification by PTLC.

General Procedure for the solid phase Ni-catalyzed coupling.

Methods for peptide synthesis:

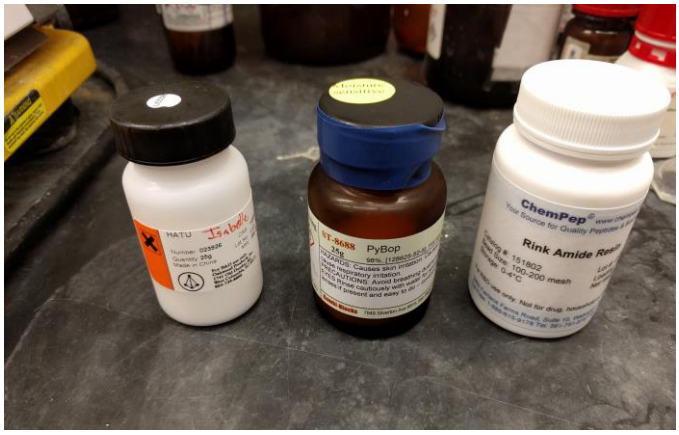
Analytical reverse-phase HPLC was performed on a Hitachi D-7000 separations module equipped with a L-4500A photodiode array detector. Peptides were analyzed using a Vydac 218TP54 Protein & Peptide C18 column (5 μm, 4.6 mm x 250 mm) at a flow rate of 1.5 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B). Results were analyzed using Hitachi Model D-7000 Chromatography Data Station Software.

Preparative reverse-phase HPLC was performed using a Hitachi system comprised of an L-7150 pump and L-4000 programmable UV detector operating at a wavelength of 230 nm coupled to a Hitachi D-2500 Chromato-Integrator. Peptides were purified on a Thermo Scientific Bio-basic C18 10 μm preparative column operating at a flow rate of 12 mL min^{-1} using a mobile phase of 99% water/1% acetonitrile containing 0.1% TFA (Solvent A) and 10% water/90% acetonitrile containing 0.07% TFA (Solvent B) and a linear gradient as specified. Peptides were isolated as white solids (unless otherwise noted) following lyophilization.

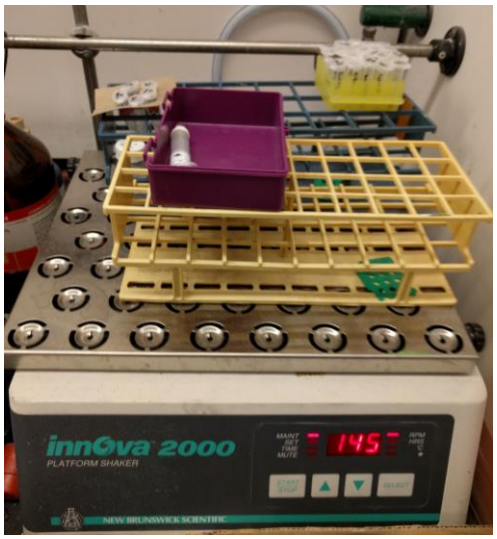
An Innova 2000 portable platform shaker (operating at 145 rpm) was used for the general mixing and agitation of solid-phase reactions (including SPPS and on-resin nickel couplings).

Materials

Commercial materials were used as received unless otherwise noted. Amino acids and coupling reagents were obtained from Novabiochem or Combi-blocks. Rink amide resin (0.8 mmol/g) was purchased from Chempep. Solid-phase reaction vessels and pressure caps were purchased from Torviq. Reagents that were not commercially available were synthesized following literature procedures.



(Left) Solid-phase reaction vessels purchased from Torviq. **(Right)** General coupling reagents (HATU and PyBOP) and Chempep Rink amide resin.



(Above) Orbital shaker for solid-phase peptide synthesis (SPPS).

Solid-phase peptide synthesis

Preloading Rink amide resin

Rink amide resin (1.0 equiv., substitution = 0.8 mmol/g) was swollen in dry DCM for 30 min then washed with DCM (5 x 3 mL) and DMF (5 x 3 mL). A solution of Fmoc-Ala-OH (4.0 equiv.) and *N*,*N*-diisopropylethylamine (DIEA) (8.0 equiv.) in DMF (final concentration of 0.1 M with respect to the resin) was added and the resin agitated on an orbital shaker at rt for 2-3 h. The resin was washed with DMF (5 x 3 mL), DCM (5 x

3 mL), and DMF (5 x 3 mL) and capped with a solution of acetic anhydride/pyridine (1:9 v/v, 3 mL) for 10 min. The resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL) and subsequently submitted to iterative peptide assembly (Fmoc-SPPS).

The loading efficiency was evaluated through treatment of the resin with 20% piperidine/DMF (3 mL, 2 × 3 min) to deprotect the Fmoc group. The combined deprotection solutions were diluted to 10 mL with 20% piperidine/DMF. An aliquot of this mixture (50 μL) was diluted 200-fold with 20% piperidine/DMF and the UV absorbance of the piperidine-fulvene adduct was measured (λ = 301 nm, ε = 7800 M^{-1} cm^{-1}) to quantify the amount of amino acid loaded onto the resin. The theoretical maximum for the reported yields of all isolated peptides are based on the numerical value obtained from the resin loading.

General iterative peptide assembly (Fmoc-SPPS)

Peptides were elongated using iterative Fmoc-solid-phase peptide synthesis (Fmoc-SPPS), according to the following general protocols:

Deprotection: The resin was treated with 20% piperidine/DMF (3 mL, 2 x 3 min) and washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

General amino acid coupling: A preactivated solution of protected amino acid (4 equiv.), PyBOP (4 equiv.) and *N*-methylmorpholine (NMM) (8 equiv.) in DMF (final concentration 0.1 M) was added to the resin. After 1 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

Capping: Acetic anhydride/pyridine (1:9 v/v) was added to the resin (3 mL). After 3 min the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL) and DMF (5 x 3 mL).

Cleavage: A mixture of TFA and water (95:5 v/v) was added to the resin. After 1 h, the resin was washed with TFA (3 x 2 mL) and DCM (3 x 2 mL). Note: The scavenger triisopropylsilane (TIS) was excluded from the cleavage mixture to prevent unwanted reduction of alkene-containing peptides.

Work-up: The combined cleavage solution and TFA and DCM washes were concentrated under a stream of nitrogen. The residue was treated with cold Et_2O to precipitate the crude peptide, which was subsequently dissolved in water/acetonitrile containing 0.1% TFA, filtered and purified by reverse-phase HPLC.

Coupling of Fmoc-Glu(OAllyl)-OH and Fmoc-Asp(OAllyl)-OH

A solution of the Fmoc-protected amino acid (4.0 equiv.), HATU (4.0 equiv.) and DIEA (8.0 equiv.) in DMF (final concentration 0.1 M) was added to the resin (1.0 equiv.) and shaken. After 16 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL). A capping step was performed as described above before proceeding with subsequent solid-phase transformations.

Coupling of H-Pro-OAllyl·TFA

A solution of H-Pro-OAllyl·TFA (10.0 equiv.), PyBOP (10.0 equiv.) and DIEA (20.0 equiv.) in DMF (final concentration 0.1 M) was added to the resin (1.0 equiv.) and shaken. After 3 h, the resin was washed with DMF (5 x 3 mL), DCM (5 x 3 mL), and DMF (5 x 3 mL).

On-resin deallylation

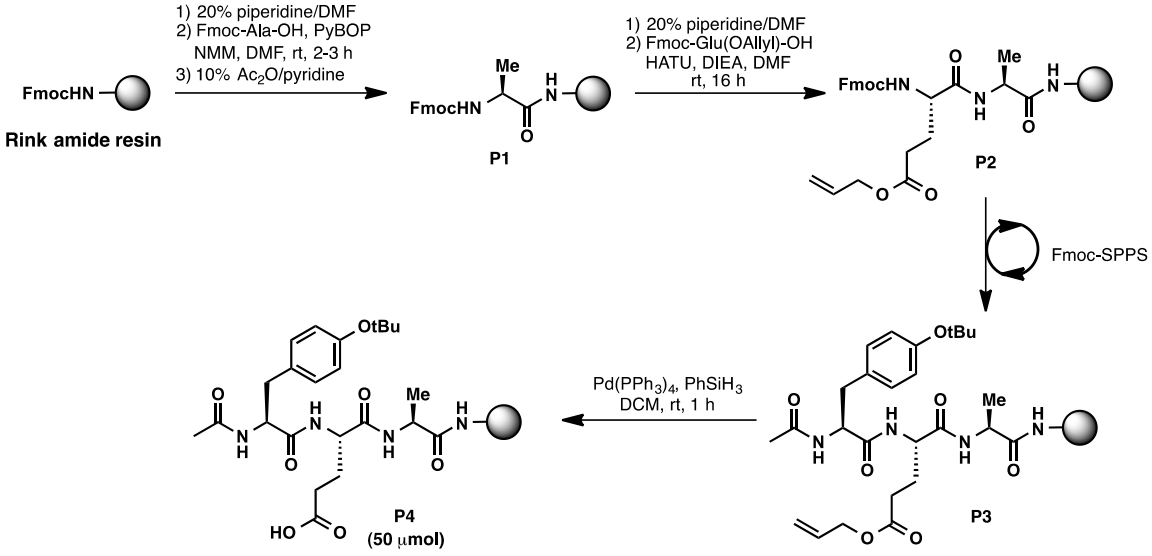
A solution of $Pd(PPh_3)_4$ (25 mg, 22 μmol) and $PhSiH_3$ (123 mL, 1 mmol) in dry DCM (2 mL) was added to the resin (25 μmol). The resin was shaken for 1 h and the progress of the reaction checked by cleavage of a small portion of resin beads and LC-MS analysis. The procedure was repeated if necessary, and upon completion, the resin was washed with DCM (10 x 3 mL) and DMF (10 x 3 mL). To remove residual Pd from the solid support, the resin-bound peptide was washed (2 x 15 min) with a solution of sodium

dimethyldithiocarbamate hydrate (0.02 M in DMF). Following Pd removal, the resin was washed with DMF (5 x 3 mL) and DCM (5 x 3 mL).

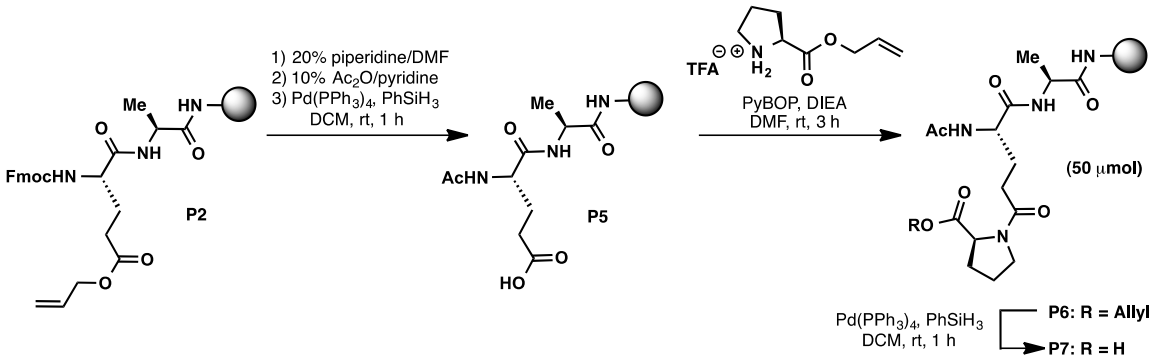
Preparation of substrates for on-resin couplings

Resin-bound peptides for solid-phase nickel couplings were prepared from Rink amide resin using Fmoc-SPPS as described in the general methods. Overall synthetic strategies for the preparation of resin-bound substrates **P4**, **P7**, and **P11** are outlined below:

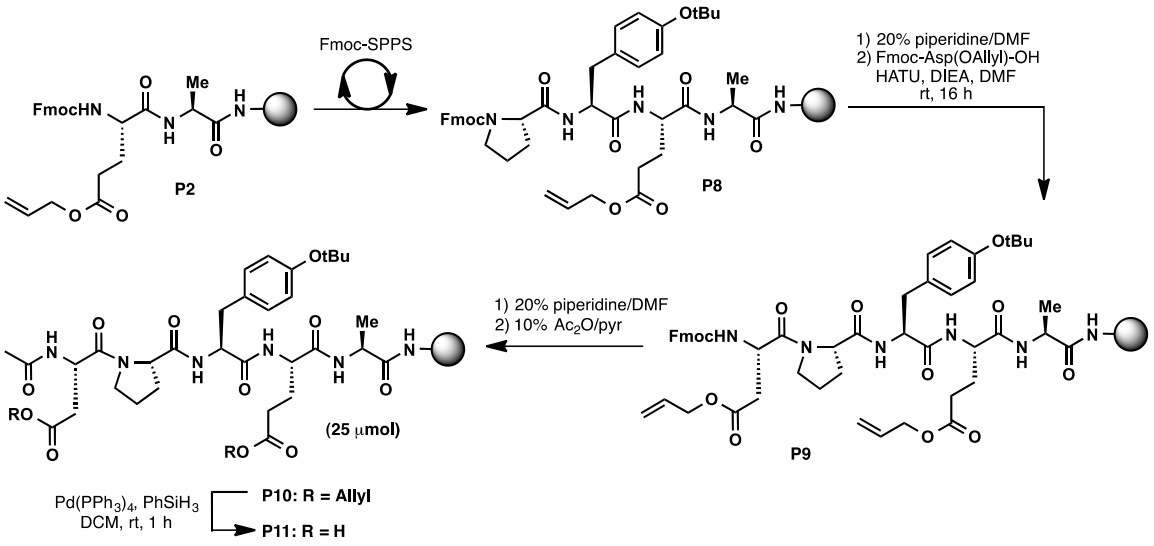
Preparation of **P4**:



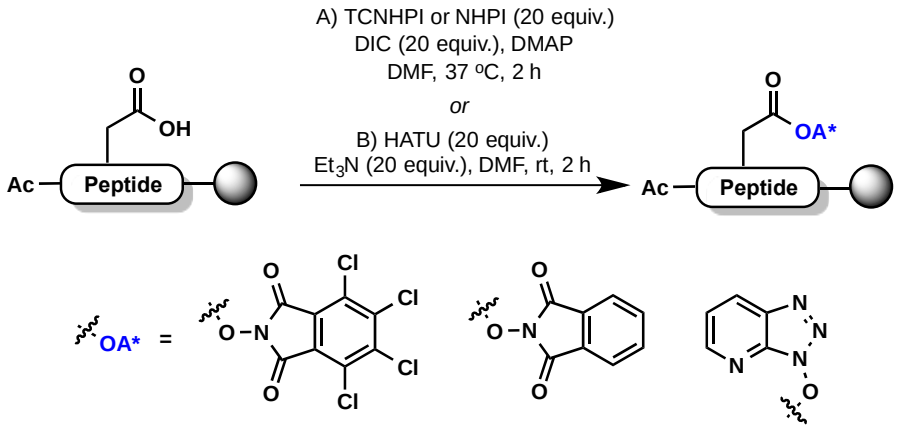
Preparation of **P7**:



Preparation of P11:



General procedures for on-resin activation:



TCNHPI/NHPI:

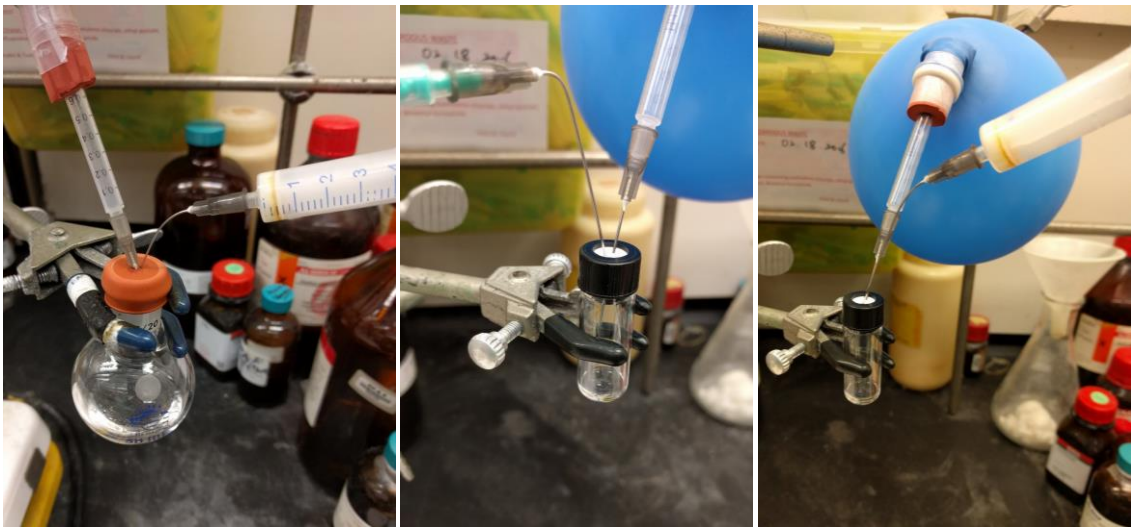
The resin-bound peptide (12.5 – 25 μmol) was washed with dry DMF (5 x 3 mL) under an argon atmosphere. Tetrachloro-*N*-hydroxyphthalimide (TCNHPI) or *N*-hydroxyphthalimide (NHPI) (20.0 equiv.) and DMAP (2.0 equiv.) were added as solids to the reaction vessel by removing the plunger of the fritted syringe. Following addition, the plunger was replaced and a solution of DIC (20.0 equiv.) in dry DMF (40-60 mM concentration with respect to the resin-bound peptide) was added to the resin. The resin was capped, sealed with Teflon tape, and agitated at 37 °C for 2 h on a rotary evaporator

(see graphical representation below for additional details). The activation solution was then expelled and the resin washed under an argon atmosphere with dry DMF (5 x 3 mL), dry MeOH (5 x 3 mL) and dry DMF (5 x 3 mL).

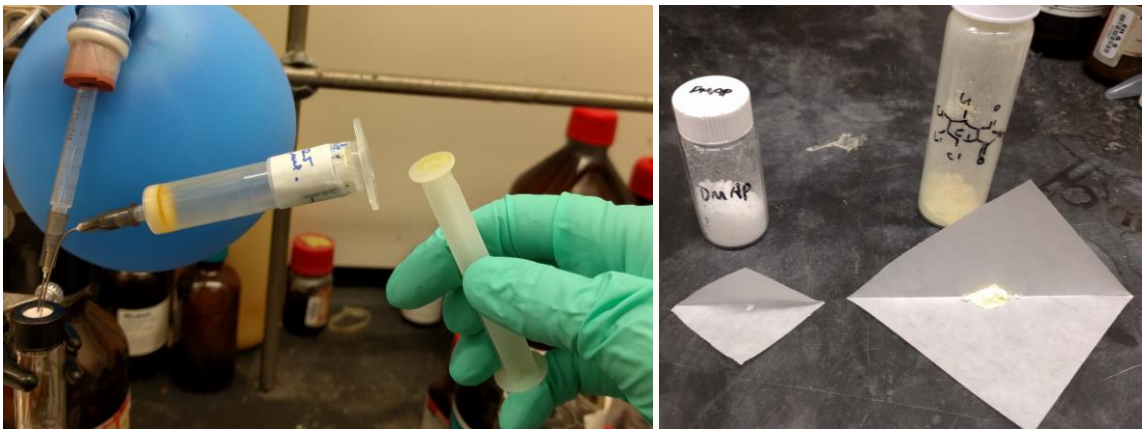
HATU:

The resin-bound peptide was washed with dry DMF (5 x 3 mL) under an argon atmosphere. HATU (20.0 equiv.) was added to the reaction vessel as a solid by removing the plunger of the fritted syringe. Following addition, the plunger was replaced and a solution of Et_3N (20.0 equiv.) in dry DMF (40-60 mM concentration with respect to the resin-bound peptide) was added to the resin. The resin was capped, sealed with Teflon tape, and agitated at rt for 2 h. The activation solution was then expelled and the resin washed with dry DMF (5 x 3 mL), dry MeOH (5 x 3 mL) and dry DMF (5 x 3 mL).

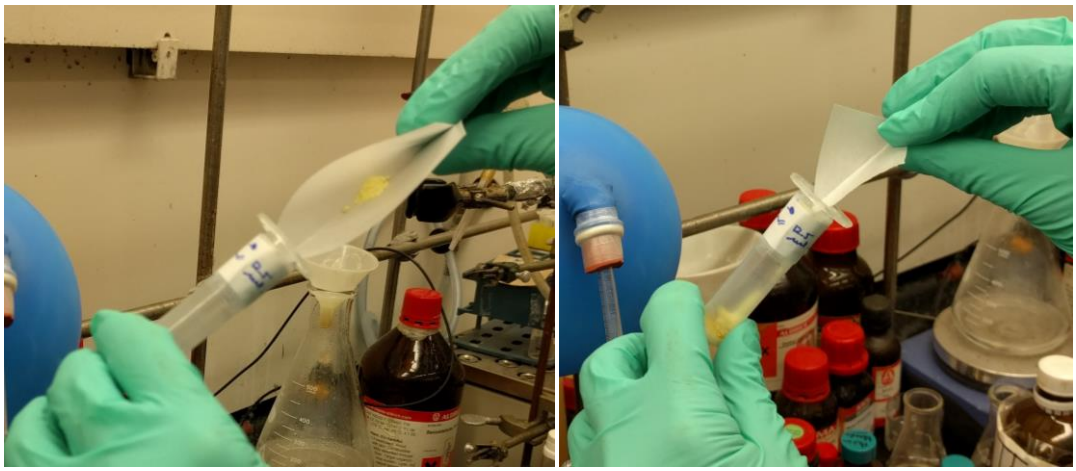
Graphical Supporting Information for activation of resin-bound carboxylic acids with TCNHPI



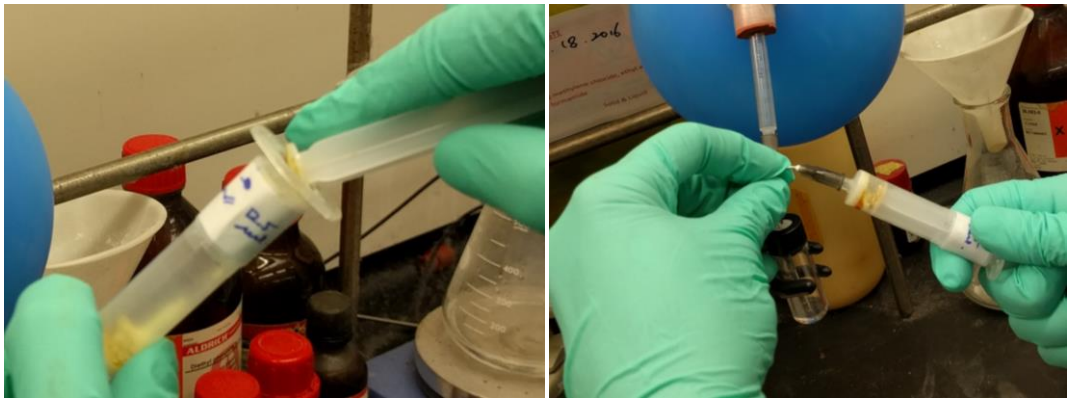
(Left) The resin-bound peptide (contained in the fritted solid-phase reaction vessel) is washed 5 times with dry DMF (round-bottom flask) under an argon atmosphere. **(Center)** A small, flame-dried reaction vial is charged with DMF and DIC. **(Right)** The needle of the solid-phase vessel is pierced into the septum of the small reaction vial.



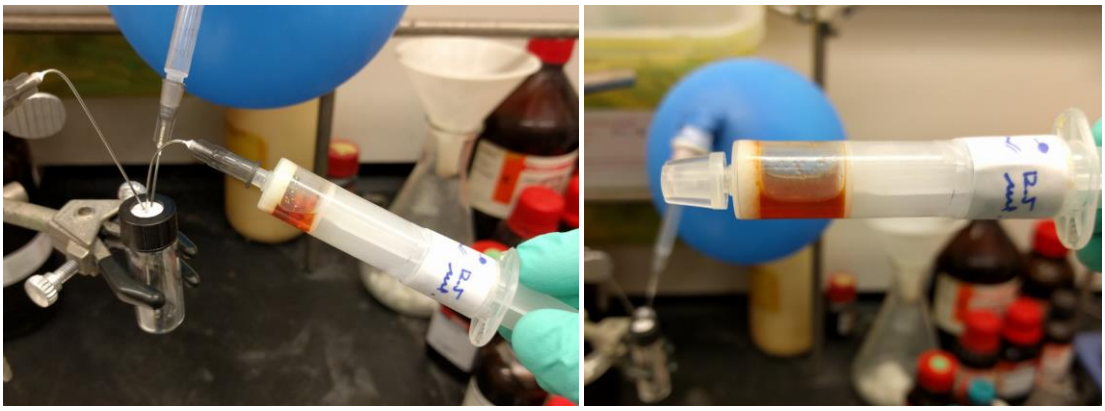
(Left) The plunger of the solid-phase reaction vessel is carefully removed. **(Right)** Appropriate amounts of tetrachloro-*N*-hydroxyphthalimide (20 equiv.) and DMAP (2.0 equiv.) are weighed out.



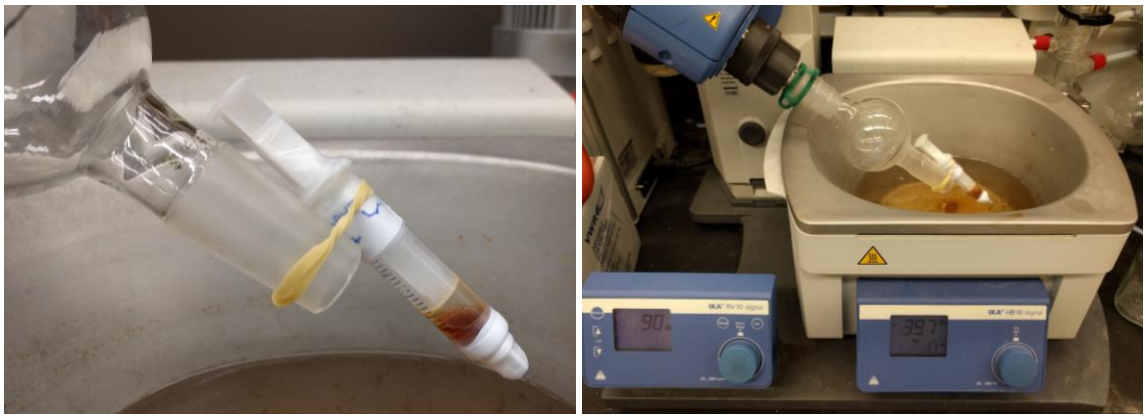
(Left) Tetrachloro-*N*-hydroxyphthalimide is added as a solid to the reaction vessel. **(Right)** DMAP is added as a solid to the reaction vessel.



(Left) The syringe plunger is carefully replaced. **(Right)** The plunger is pushed up toward the frit to reduce the dead volume in the syringe.

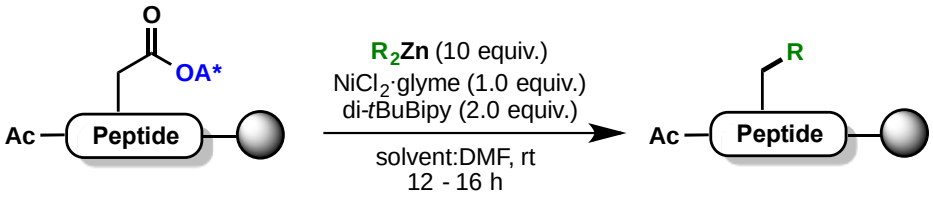


(Left) The solution of DIC and DMF in the small reaction flask is drawn up into the syringe; note the emergence of a dark red-orange color resulting from deprotonation of tetrachloro-*N*-hydroxyphthalimide by DMAP. **(Right)** The reaction vessel is capped with a pressure cap (Torviq) and thoroughly sealed with Teflon tape and parafilm.



(Left) The solid-phase reaction vessel is attached to the bump trap of a rotary evaporator. **(Right)** The resin-bound peptide is lowered into the water bath, heated at 37 ^{o}C and agitated at 90 rpm for 2 h.

General procedure for on-resin nickel coupling:



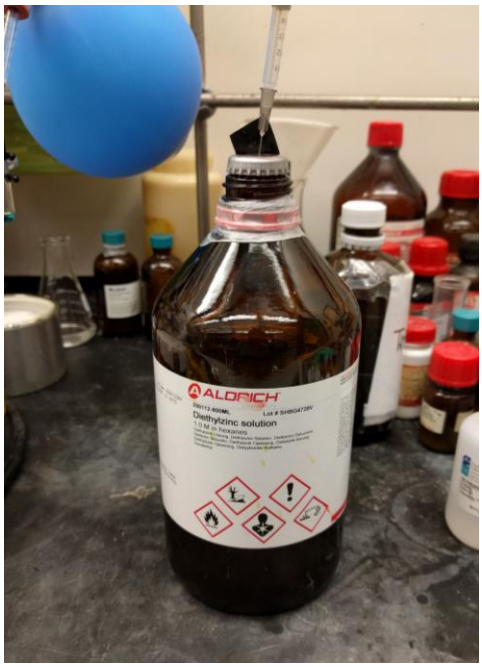
Following on-resin activation, the resin-bound peptide was immediately subjected to on-resin nickel coupling. The activation solution was expelled from the syringe and the resin was washed with dry DMF (5 x 3 mL), dry MeOH (5 x 3 mL) and dry DMF (5 x 3 mL). Under an argon atmosphere, a solution of $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.02 M – 0.04 M with respect to the Ni catalyst) was first added to the resin followed immediately by a solution of dialkylzinc reagent (10.0 equiv.) in THF or hexanes (0.20 M – 1.0 M, prepared as described previously or obtained from commercial sources). The addition of the dialkylzinc reagent to the resin is generally accompanied by a dark red color, which quickly subsides (2-5 seconds) to afford a dark green-black coupling solution. The resin was capped and agitated at rt for 12-16 h. The reaction solution was then expelled and the resin washed thoroughly with DMF (10 x 3 mL), DCM (10 x 3 mL) and DMF (10 x 3 mL). The outcome of the reaction was determined by cleavage of a small number of resin beads by treatment with TFA/H_2O (95:5 v/v) for 1 h at rt and analysis by LC-MS and analytical HPLC. If substantial amounts of unreacted carboxylic acid were observed, the activation-coupling procedure was repeated.

Note: On-resin coupling reactions were found to proceed more efficiently at higher concentrations. As such, the higher end of the concentration ranges provided in the above procedure for both $NiCl_2$·glyme/ligand and dialkylzinc solutions should be preferentially employed.

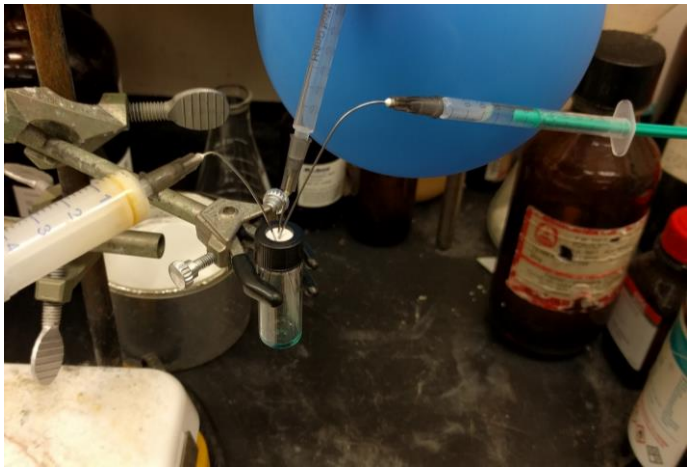
Graphical Supporting Information for on-resin nickel coupling

(Left) Resin-bound peptide following on-resin activation. **(Right)** Dry solutions of DMF (left) and MeOH (right) for washing.

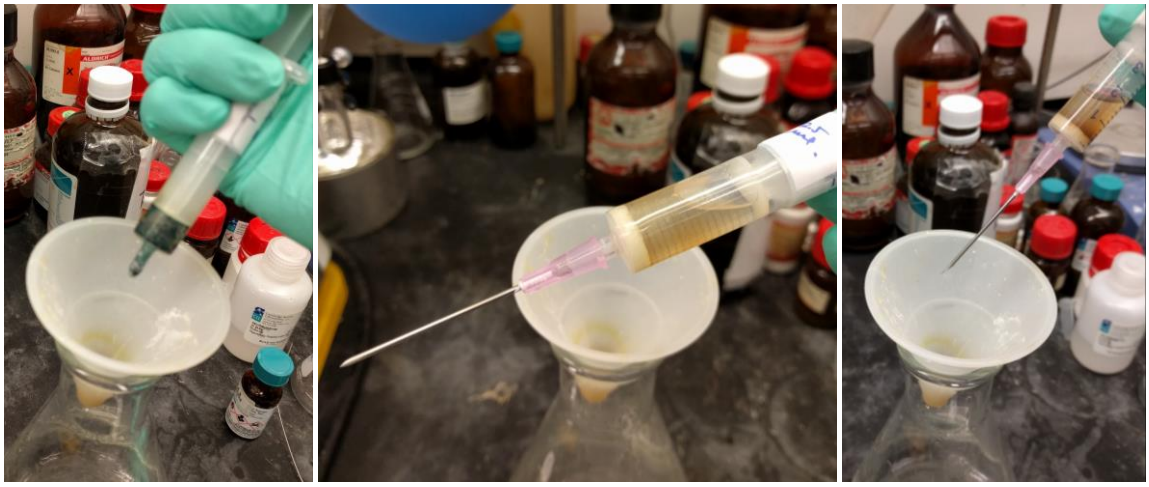
(Left) Following expulsion of the activation solution, the resin-bound peptide is washed with dry DMF (5 x 3 mL), dry MeOH (5 x 3 mL) and dry DMF (5 x 3 mL). **(Right)** Close-up of resin washing with DMF; following brief mixing with the resin, the washing solutions are expelled into the waste.

(Left) A small-flame-dried reaction vial under argon is charged with a solution of $NiCl_2$·glyme, and di-*t*BuBipy in DMF. **(Right)** A commercial bottle of diethylzinc (1.0 M in hexanes) utilized in the on-resin coupling procedure.



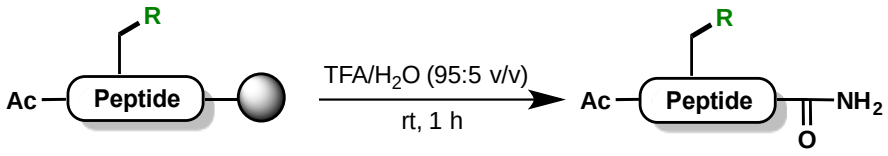

(Left) A syringe containing the diethylzinc solution (right-hand syringe) is pierced into the septum of the small reaction vial containing the DMF solution of ligand and nickel catalyst; the resin-bound peptide (left-hand syringe) is poised for addition of the nickel solution, followed immediately by the addition of the dialkylzinc solution. **(Right)** Capped, resin-bound peptide following addition of nickel and dialkylzinc; note that the dark green color emerges within a few seconds of addition of both reagents to the resin.



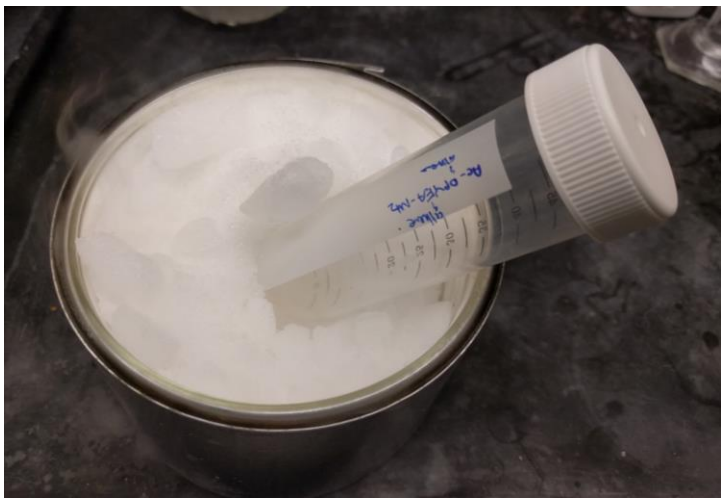
(Left) After 12-16 h on an orbital shaker at rt, the coupling solution is expelled. **(Center)** The resin-bound peptide is washed with DMF (10 x 3 mL). **(Right)** The resin is further washed with DCM (10 x 3 mL) and DMF (10 x 3 mL).

(Left) To evaluate the outcome of the reaction, a few resin beads are removed from the syringe and cleaved upon treatment with a solution TFA/H_2O (95:5 v/v) at rt for 1 h. **(Center)** Close-up of the cleavage solution; note that the Rink amide resin beads employed here typically turn red upon addition of TFA. **(Right)** A filtered LC-MS sample prepared from the crude cleavage solution (following concentration of the TFA and dilution in 1:1 H_2O/MeOH).

Resin cleavage and product purification:



To isolate the peptide product, the resin was first washed with DCM (15 x 3 mL) then cleaved from the resin using TFA/H_2O (95:5 v/v, 3 mL, rt, 1 h). The cleavage mixture was expelled into a 50 mL centrifuge tube and the resin washed with TFA (3 x 2 mL) and DCM (3 x 2 mL). The combined washings were added to the centrifuge tube, and the resulting solution was concentrated under a stream of nitrogen. The crude residue was treated with cold Et_2O and sonicated to precipitate the peptide. The mixture was centrifuged (5 min, 1000 x g), the supernatant was discarded, and the crude peptide product was collected as a solid pellet. The crude product was resuspended in a mixture of H_2O/acetonitrile containing 0.1% TFA and immediately purified by preparative reverse-phase HPLC using a linear gradient as specified. Fractions containing the desired product were concentrated on a rotary evaporator to remove acetonitrile and then lyophilized to afford the target compound as a fluffy white solid.

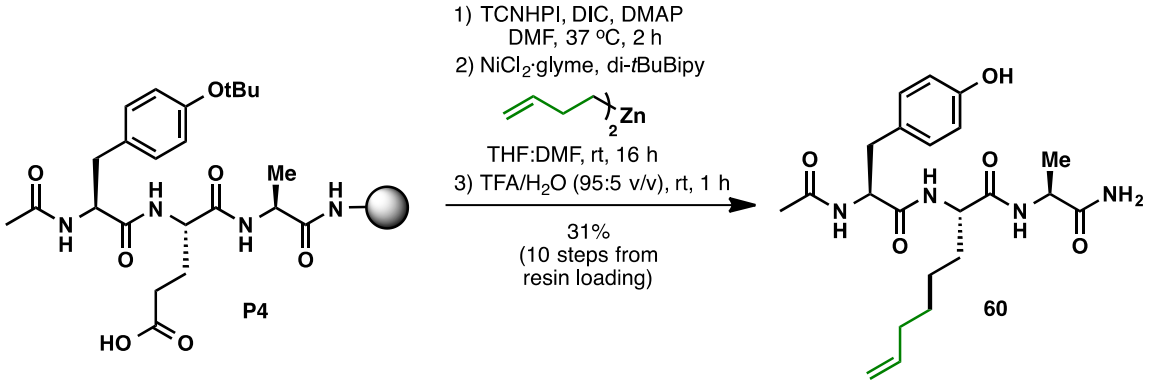


(Above) Ether precipitation of crude cleavage residue in a 50 mL centrifuge tube.

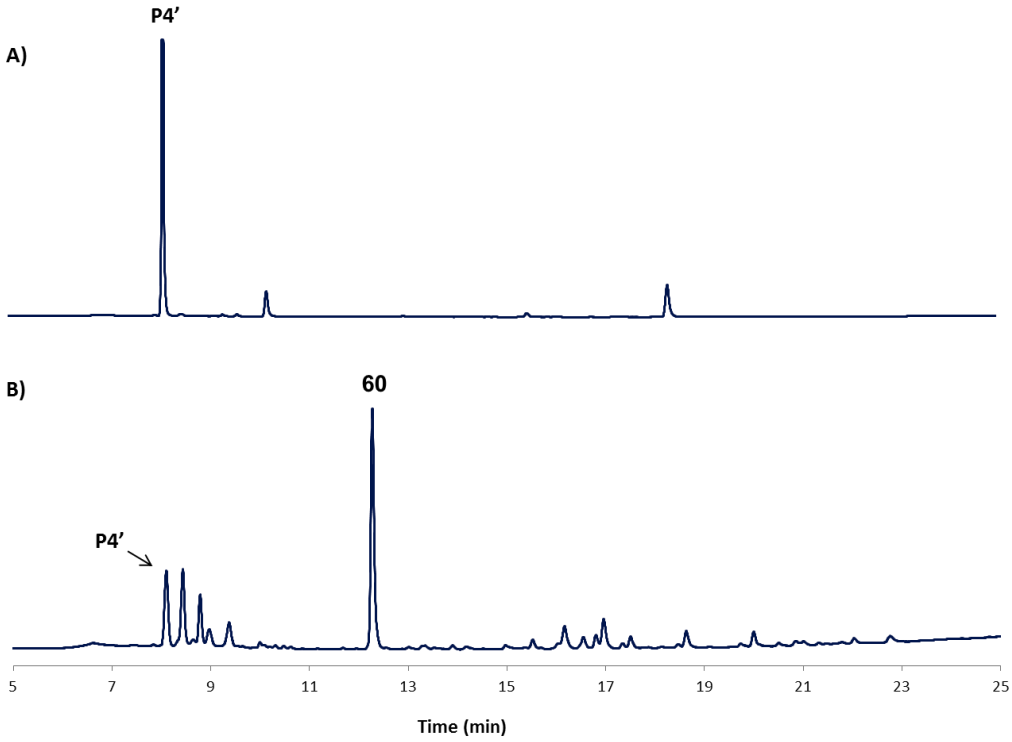
Note on overall yield calculations and step counts: Yields are based on the amount of isolated material relative to the theoretical maximum based on the original loading of the solid-support. Upon attachment of the first amino acid to the resin, an Fmoc deprotection step is performed to quantify the loading of the resin (see general SPPS methods for details). In the step counts given below, this deprotection step is considered to be step #1 in the overall peptide synthesis protocol, as it is the first step following the resin loading. The summation of all subsequent steps allows for the calculation of percent yield over a given number of steps from the original resin loading.

Compound preparation and characterization data:

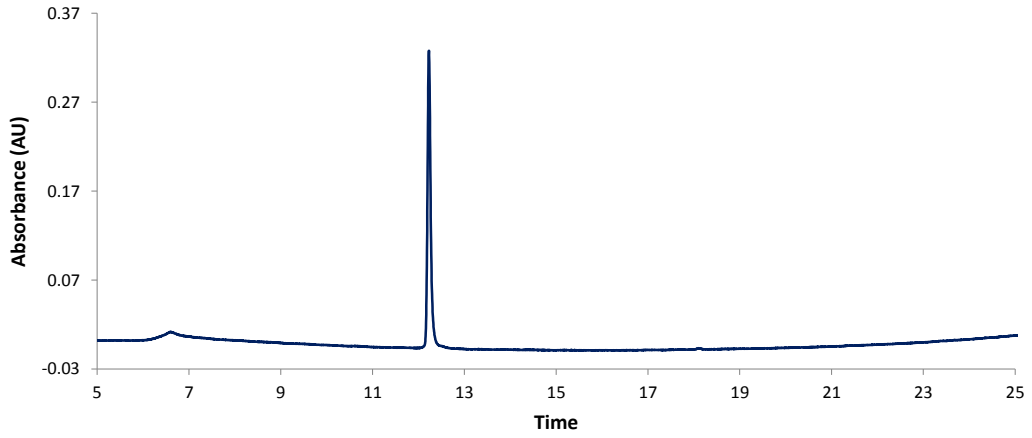
Peptide 60



Peptide **60** was prepared on a 22.5 μmol scale from resin-bound substrate **P4** through activation as the corresponding TCNHPI ester and subsequent treatment with $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.04 M with respect to the Ni catalyst) followed by the dialkylzinc reagent (10.0 equiv., ~0.5 M in THF). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (10% B for 5 min, 10% to 50% B over 35 min) and lyophilized to afford peptide **60** as a fluffy white solid (3.0 mg, 31% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P4** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P4'** designates the TFA-cleaved peptide, accompanied by loss of side-chain protecting groups]; **B)** Crude reaction mixture depicting the formation of target peptide **60** following on-resin activation, on-resin nickel coupling, and TFA cleavage.



Purified peptide product **60** (0 to 100% B over 25 min, λ = 230 nm, R_t = 12.2 min).

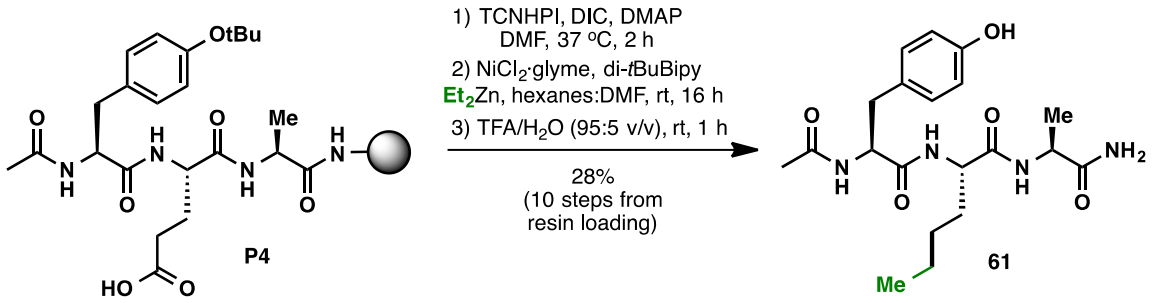
^{1}H NMR (600 MHz, DMSO-d_6): δ 9.14 (s, 1H), 8.01 (dd, *J* = 8.1, 3.0 Hz, 2H), 7.80 (d, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 1H), 6.62 (d, *J* = 8.5 Hz,

2H), 5.79 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.03 – 4.96 (m, 1H), 4.96 – 4.90 (m, 1H), 4.55 – 4.34 (m, 1H), 4.25 – 4.09 (m, 2H), 2.88 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.60 (dd, *J* = 14.0, 10.0 Hz, 1H), 2.09 – 1.89 (m, 2H), 1.75 (s, 3H), 1.71 – 1.62 (m, 1H), 1.59 – 1.45 (m, 1H), 1.39 – 1.23 (m, 4H), 1.20 (d, *J* = 7.1 Hz, 3H) ppm;

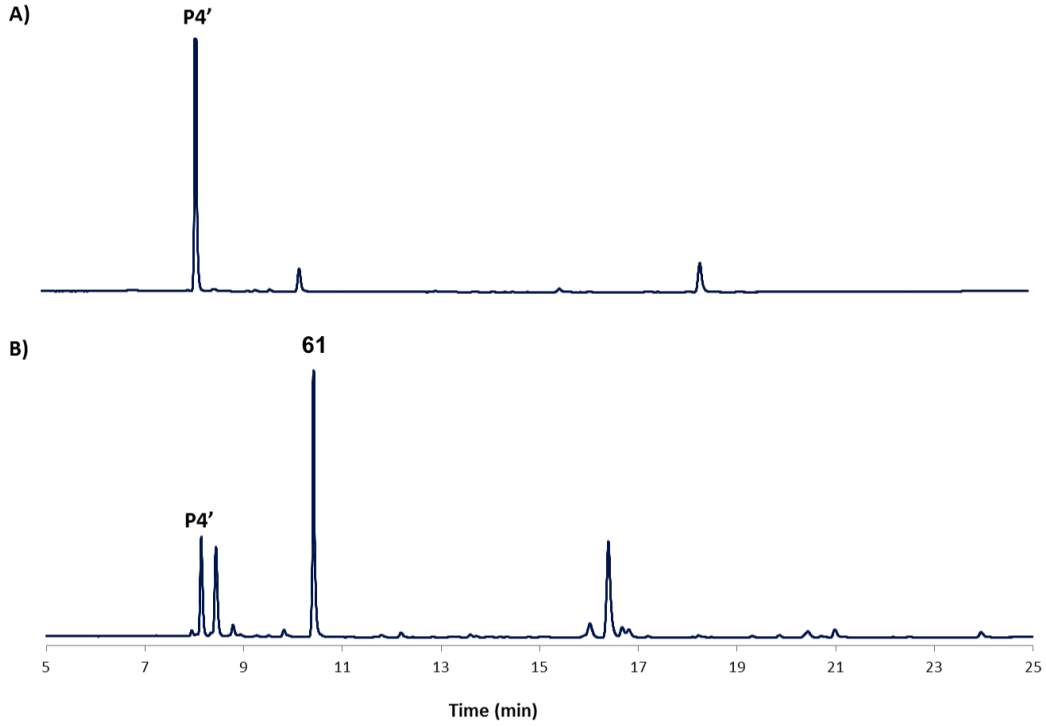
^{13}C NMR (151 MHz, DMSO-d_6): δ 174.0, 171.6, 171.0, 169.2, 155.7, 138.7, 130.0, 128.1, 114.8, 114.7, 54.4, 52.5, 47.9, 36.6, 33.1, 31.7, 28.1, 24.7, 22.5, 18.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{22}H_{32}N_4O_5Na$ $[M+Na]^+$ 455.2265; found 455.2245.

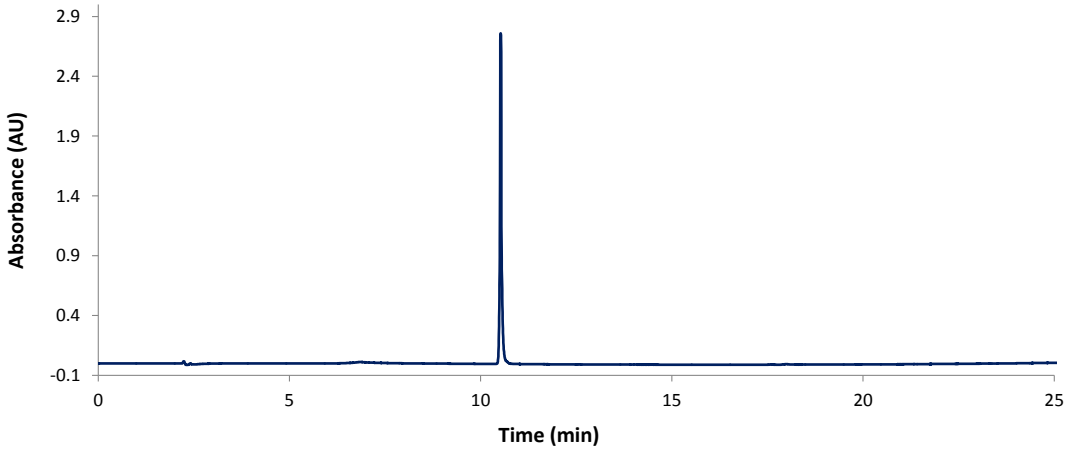
Peptide 61



Peptide **61** was prepared on a 20 μmol scale from resin-bound substrate **P4** through activation as the corresponding TCNHPI ester and subsequent treatment with $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.02 M with respect to the Ni catalyst) followed by diethylzinc (10.0 equiv., 1.0 M in hexanes). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (10% B for 5 min, 10% to 40% B over 25 min) and lyophilized to afford peptide **61** as a fluffy white solid (2.3 mg, 28% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P4** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P4'** designates the TFA-cleaved peptide, accompanied by loss of side-chain protecting groups]; **B)** Crude reaction mixture depicting the formation of target peptide **61** following on-resin activation, on-resin nickel coupling, and TFA cleavage.



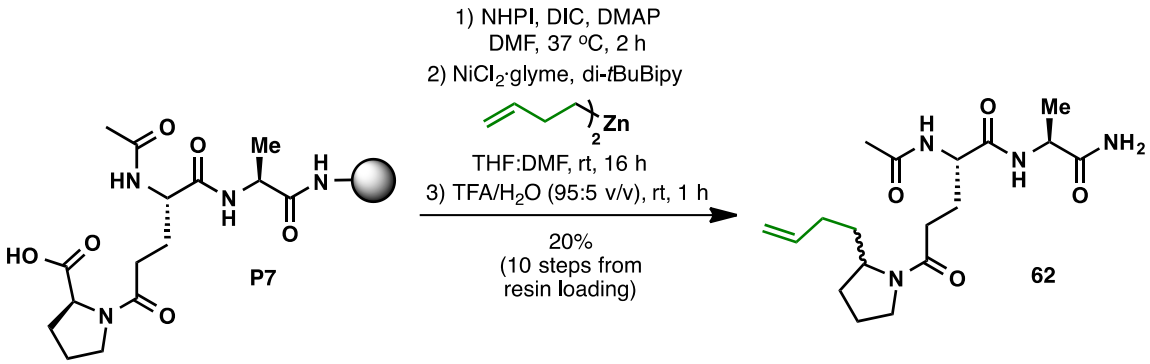
Purified peptide product **61** (0 to 100% B over 25 min, λ = 230 nm, R_t = 10.5 min).

^{1}H NMR (600 MHz, DMSO-d_6): δ 9.14 (br s, 1 H), 8.07 – 7.96 (m, 2H), 7.80 (d, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.99 (s, 1H), 6.62 (d, *J* = 8.5 Hz, 2H), 4.47 – 4.36 (m, 1H), 4.24 – 4.12 (m, 2H), 2.88 (dd, *J* = 14.0, 4.2 Hz, 1H), 2.60 (dd, *J* = 14.0, 10.0 Hz, 1H), 1.75 (s, 3H), 1.70 – 1.62 (m, 1H), 1.56 – 1.44 (m, 1H), 1.31 – 1.22 (m, 4H), 1.20 (d, J = 7.1 Hz, 3H), 0.91 – 0.72 (m, 3H) ppm;

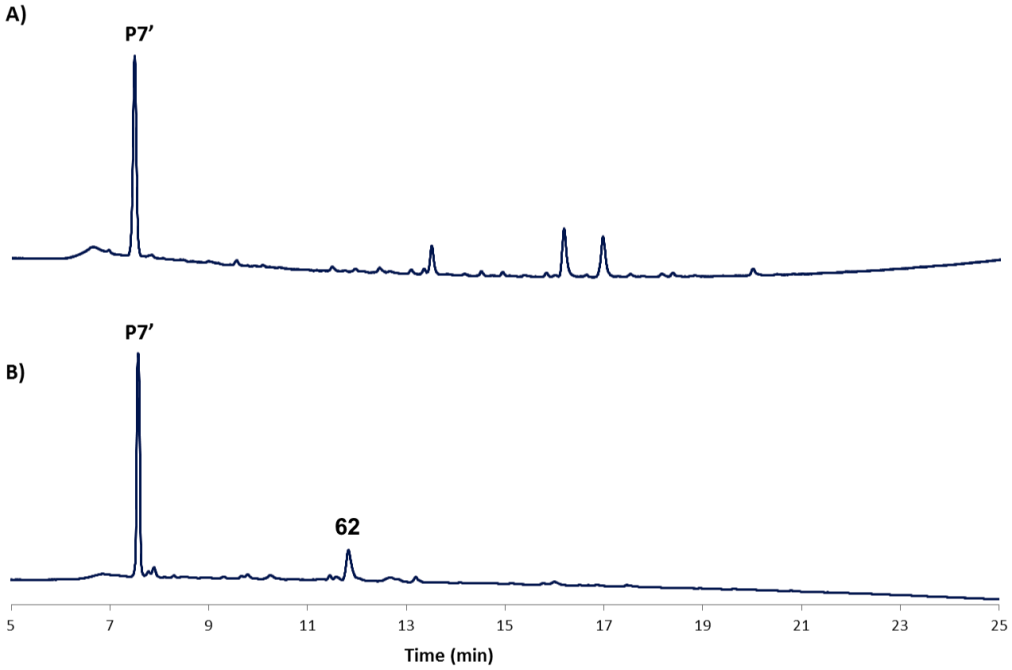
^{13}C NMR (151 MHz, DMSO-d_6): δ 174.0, 171.6, 171.0, 169.2, 155.7, 130.0, 128.1, 114.8, 54.3, 52.6, 47.9, 36.6, 31.5, 27.4, 22.5, 21.9, 18.4, 13.9 ppm; [note: residual TFA remaining after lyophilization can be observed in the ^{13}C NMR spectrum].

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{30}N_4O_5Na$ $[M+Na]^+$ 429.2108; found 429.2154.

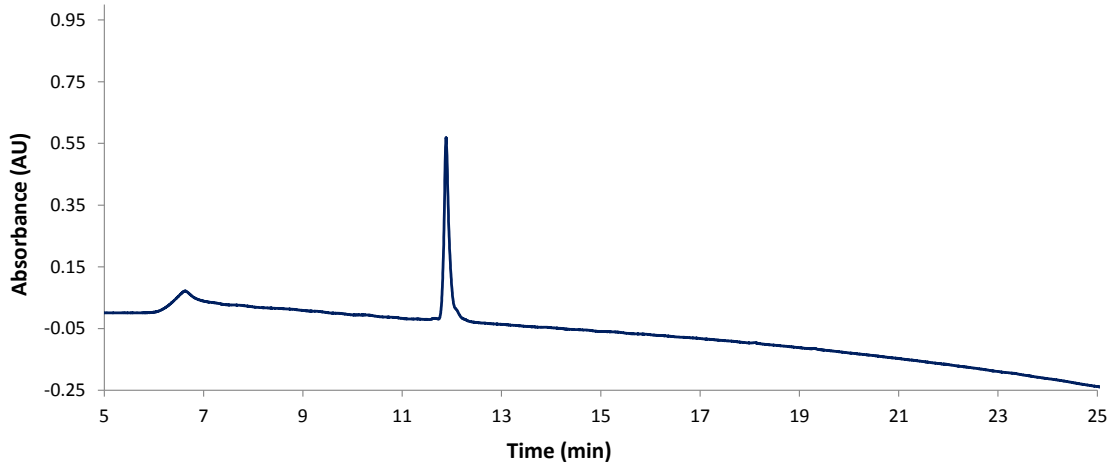
Peptide 62



Peptide **62** was prepared on a 17.3 μmol scale from resin-bound substrate **P7** through activation as the corresponding NHPI ester and subsequent treatment with $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.04 M with respect to the Ni catalyst) followed by the dialkylzinc reagent (10.0 equiv., ~0.5 M in THF). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (5% B for 5 min, 5% to 50% B over 35 min) and lyophilized to afford peptide **62** as an opaque oil (1.3 mg, 20% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P7** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P7'** designates the TFA-cleaved peptide]; **B)** Crude reaction mixture (λ = 210 nm) depicting the formation of target peptide **62** following on-resin activation, on-resin nickel coupling, and TFA cleavage.



Purified peptide product **62** (0 to 100% B over 25 min, λ = 210 nm, R_t = 11.9 min).

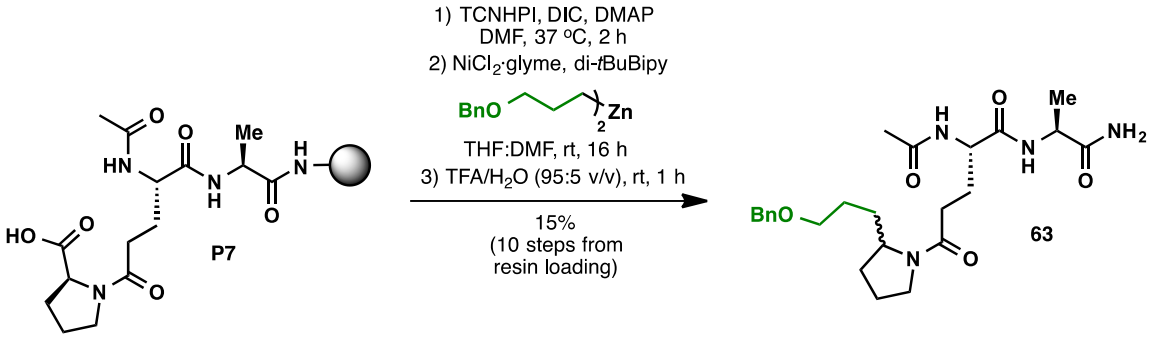
The product was isolated as a mixture of diastereomers (***dr* ~ 7:3**).

^{1}H NMR (600 MHz, 9:1 v/v DMSO-d_6/D_2O, diastereomers): δ δ 5.98 – 5.55 (m, 1H), 5.10 – 5.00 (m, 1H), 4.98 – 4.94 (m, 0.3H), 4.94 – 4.91 (m, 0.7H), 4.31 – 4.07 (m, 2H), 3.93 – 3.85 (m, 0.7H), 3.85 – 3.76 (m, 0.3H), 3.39 – 3.13 (m, 2H), 2.30 – 2.15 (m, 2H), 2.09 – 1.24 (m, 10H), 1.83 (s, 3H), 1.20 (d, *J* = 7.2 Hz, 3H) ppm;

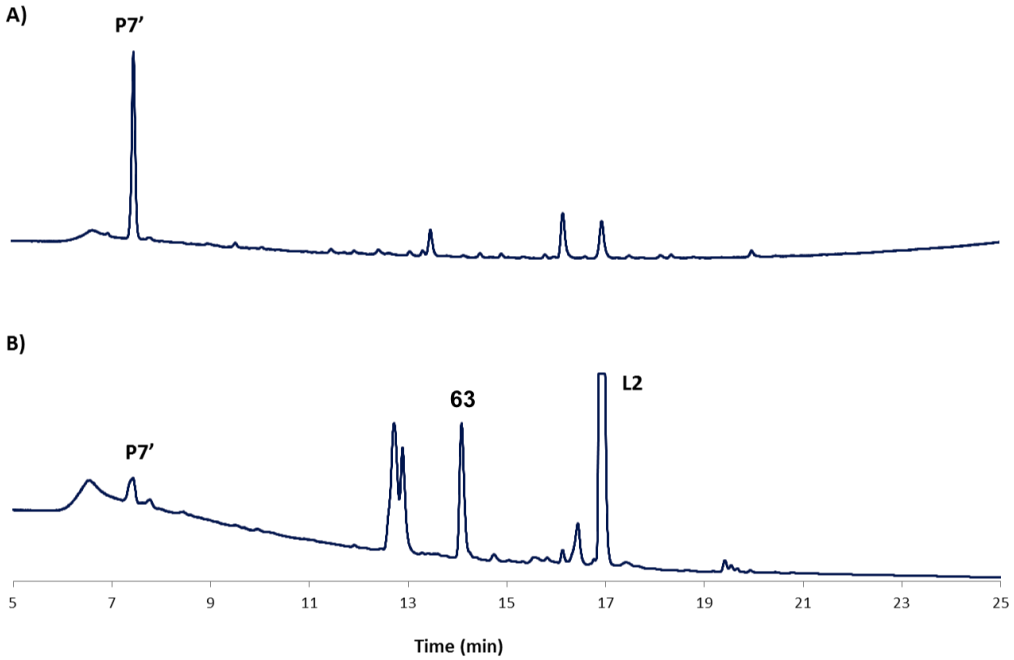
^{13}C NMR (151 MHz, DMSO-d_6, diastereomers): δ 174.1, 171.0, 169.9, 169.4, 138.4, 138.0, 115.2, 114.6, 56.4, 56.1, 52.4, 52.2, 47.9, 46.1, 33.3, 31.7, 30.5, 30.5, 30.1, 29.6, 28.6, 27.7, 27.4, 27.3, 23.5, 22.5, 21.5, 18.2. ppm; [note: additional signals are observed in the ^{13}C NMR spectrum owing to the presence of diastereomers; a small amount of residual TFA remaining after lyophilization can also be observed (δ 157.8, quartet)].

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{31}N_4O_4$ $[M+H]^+$ 367.2340; found 367.2335.

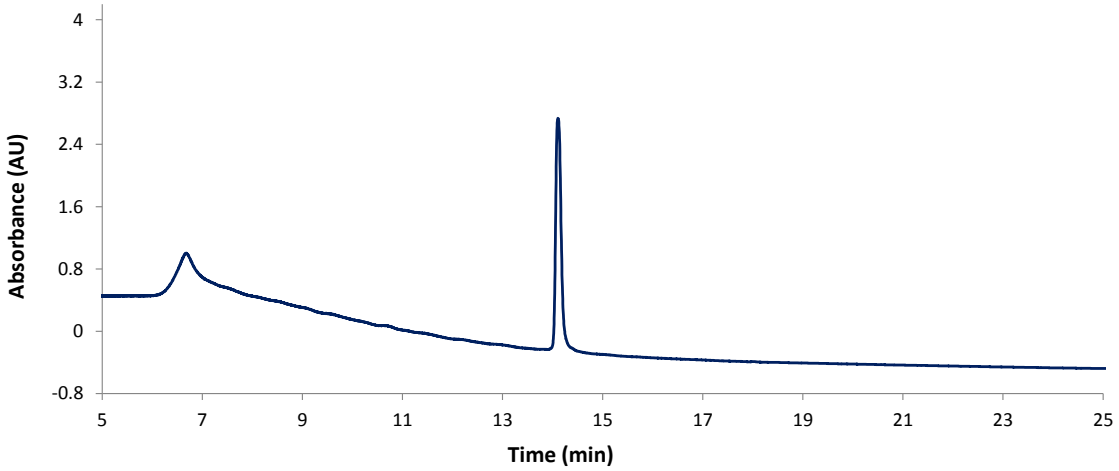
Peptide 63



Peptide **63** was prepared on a 20 μmol scale from resin-bound substrate **P7** through activation as the corresponding TCNHPI ester and subsequent treatment with $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.02 M with respect to the Ni catalyst) followed by the dialkylzinc reagent (10.0 equiv., 0.2 M in THF). After cleavage from the resin and ether precipitation, the crude peptide was purified by reverse-phase HPLC (25% B for 5 min, 25% to 60% B over 30 min) and lyophilized to afford peptide **63** as a yellow-orange oil (1.4 mg, 15% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P7** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P7'** designates the TFA-cleaved peptide]; **B)** Crude reaction mixture (λ = 210 nm) depicting the formation of target peptide **63**, following on-resin activation, on-resin nickel coupling, and TFA cleavage. [**L2** = di-*t*BuBipy]



Purified peptide product **63** (0 to 100% B over 25 min, λ = 210 nm, R_t = 14.1 min).

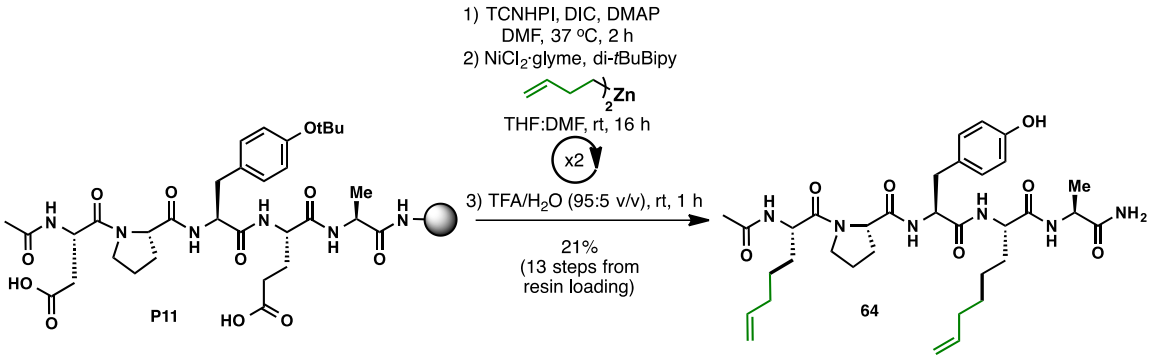
The product was isolated as a mixture of diastereomers (***dr* ~ 3:1**).

^{1}H NMR (600 MHz, 9:1 v/v DMSO-d_6/D_2O, diastereomers): δ 7.45 – 7.18 (m, 5H), 4.48 – 4.38 (m, 2H), 4.24 – 4.10 (m, 2H), 3.91 – 3.85 (m, 0.75H), 3.85 – 3.79 (m, 0.25H), 3.41 – 3.27 (m, 4H, partially obscured by the water signal), 2.34 – 2.19 (m, 2H), 1.83 (s, 3H), 1.85 – 1.20 (m, 10H), 1.20 (d, *J* = 7.2 Hz, 3H) ppm;

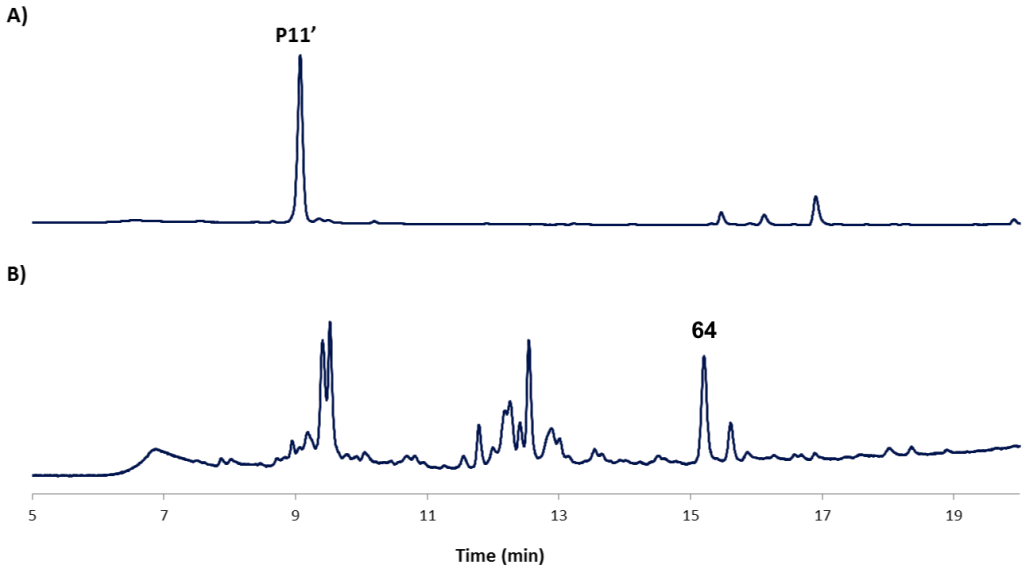
^{13}C NMR (151 MHz, DMSO-d_6, diastereomers): δ 174.1, 171.0, 169.9, 169.4, 138.7, 128.2, 127.4, 127.3, 71.8, 69.7, 56.3, 52.4, 52.2, 47.9, 46.1, 31.1, 30.5, 29.6, 28.7, 27.4, 27.3, 26.2, 23.5, 22.5, 21.5, 18.2 ppm; [note: a complex mixture is observed in the ^{13}C NMR spectrum owing to the presence of diastereomers; a small amount of residual TFA remaining after lyophilization can also be observed (δ 157.9, quartet)].

HRMS (ESI-TOF, *m/z*): calcd for $C_{24}H_{37}N_4O_5$ $[M+H]^+$ 461.2758; found 461.2754.

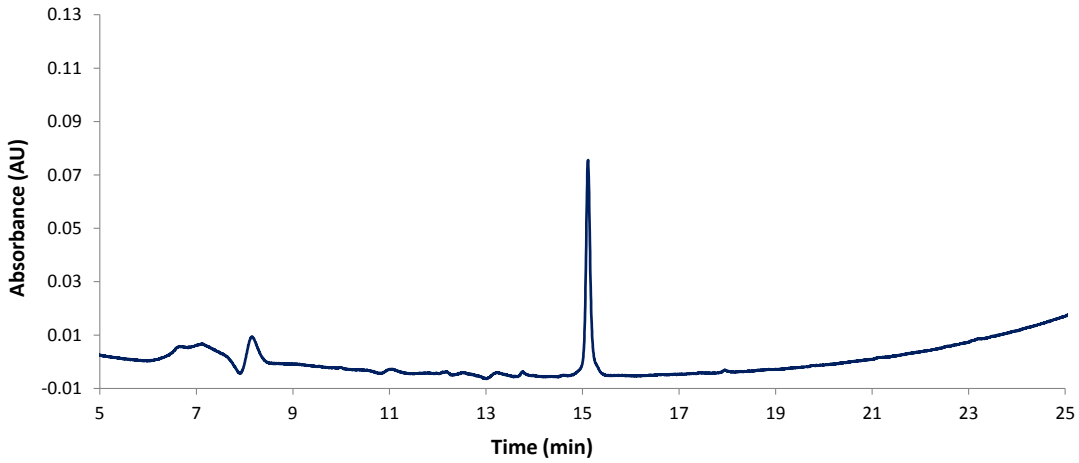
Peptide 64



Peptide **64** was prepared on a 12.5 μmol scale from resin-bound substrate **P11**. Double activation of the resin-bound Asp and Glu carboxylic acids was achieved via treatment with TCNHPI (40.0 equiv. with respect to the resin-bound peptide), DIC (40.0 equiv.) and DMAP (3.0 eq.). The doubly-activated peptide was then treated with $NiCl_2$·glyme (2.0 equiv.) and di-*t*BuBipy (4.0 equiv.) in DMF (0.04 M with respect to the Ni catalyst) followed by the dialkylzinc reagent (20.0 equiv., ~0.5 M in THF). The activation-coupling procedure was repeated one time prior to resin cleavage and ether precipitation of the crude product. The peptide was purified by reverse-phase HPLC (15% B for 5 min, 15% to 60% B over 35 min) and lyophilized to afford peptide **64** as an oily white solid (1.7 mg, 21% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P11** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P11'** designates the TFA-cleaved peptide]; **B)** Crude reaction mixture (λ = 230 nm) depicting the formation of target peptide **64**, following two cycles of on-resin activation, and on-resin nickel coupling, then TFA cleavage and ether precipitation.



Purified peptide product **64** (0 to 100% B over 25 min, λ = 230 nm, R_t = 15.1 min).

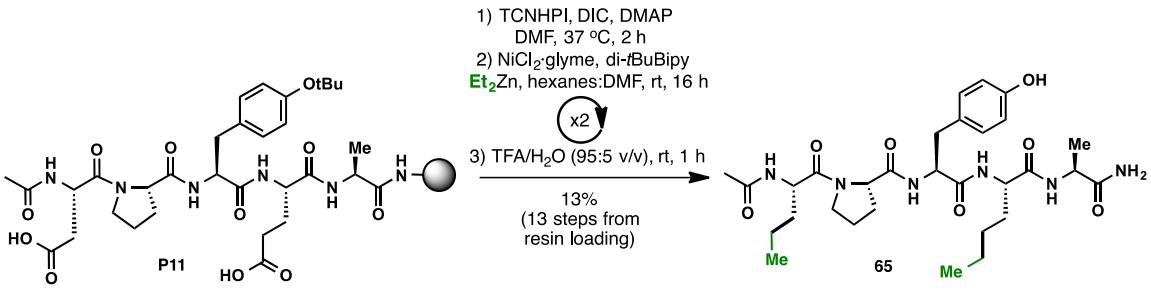
^{1}H NMR (600 MHz, 9:1 v/v DMSO-d_6/D_2O): δ 7.96 – 7.60 (m, 2H, N-H protons exhibit slow exchange with D_2O), 7.00 (d, *J* = 8.2 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 6.57 (br s, 2H, partial exchange with D_2O), 5.99 – 5.55 (m, 2H), 5.02 – 4.96 (m, 2H), 4.95 – 4.91 (m, 2H), 4.47 – 4.40 (m, 1H), 4.39 – 4.29 (m, 1H), 4.29 – 4.25 (m, 1H), 4.24 – 4.11 (m,

2H), 3.72 – 3.58 (m, 1H), 2.90 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.72 (dd, *J* = 14.2, 8.8 Hz, 1H), 2.05 – 1.22 (m, 18H), 1.82 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H) ppm; [note: one hydrogen is obscured by the water signal].

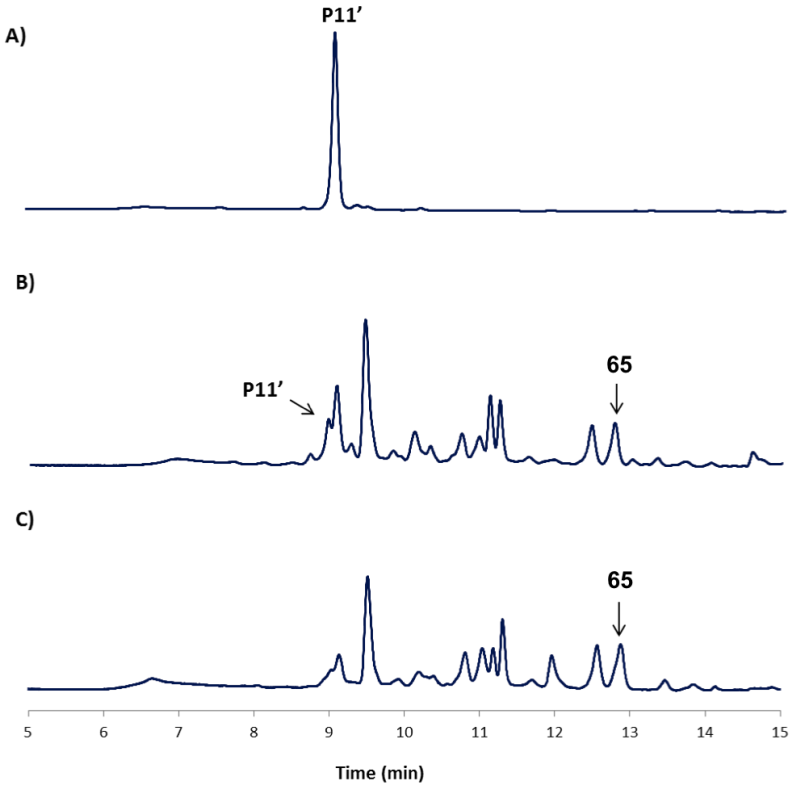
^{13}C NMR (151 MHz, DMSO-d$_6$): δ 174.0, 171.4, 170.9, 170.6, 169.1, 155.7, 138.7, 138.4, 130.1, 127.6, 114.9, 114.8, 114.7, 109.5, 59.5, 54.3, 52.5, 50.3, 48.0, 46.8, 36.2, 33.1, 32.9, 31.7, 30.6, 28.8, 28.1, 24.7, 24.3, 24.3, 22.2, 18.3 ppm; [note: residual TFA remaining after lyophilization can be observed in the ^{13}C NMR spectrum – δ 157.7 (quartet), 117.3 (quartet)].

HRMS (ESI-TOF, *m/z*): calcd for $C_{34}H_{50}N_6O_7Na$ $[M+Na]^+$ 677.3633; found 677.3693.

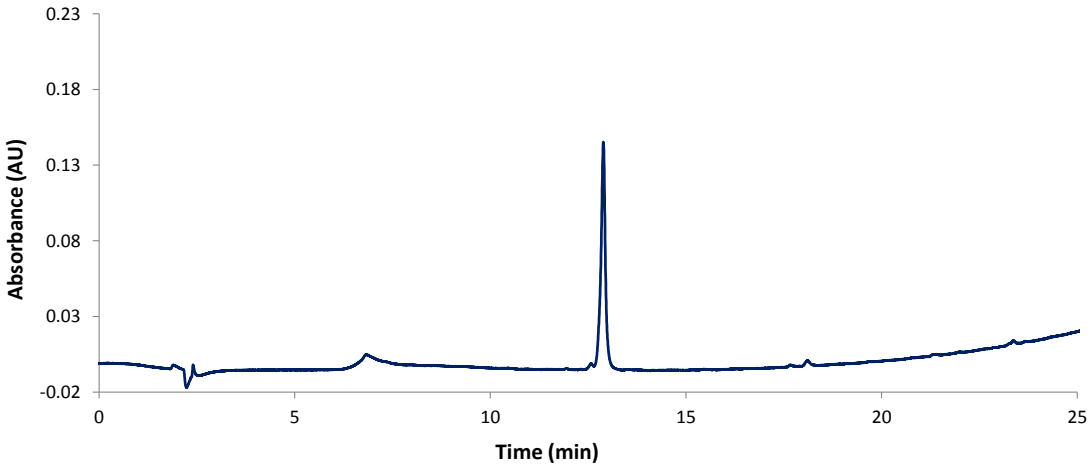
Peptide 65



Peptide **65** was prepared on a 12.5 μmol scale from resin-bound substrate **P11**. Double activation of the resin-bound Asp and Glu carboxylic acids was achieved via treatment with TCNHPI (40.0 equiv. with respect to the resin-bound peptide), DIC (40.0 equiv.) and DMAP (3.0 eq.). The doubly-activated peptide was then treated with $NiCl_2$·glyme (2.0 equiv.) and di-*t*BuBipy (4.0 equiv.) in DMF (0.02 M with respect to the Ni catalyst) followed by diethylzinc (20.0 equiv., 1.0 M in hexanes). The activation-coupling procedure was repeated one time prior to resin cleavage and ether precipitation of the crude product. The peptide was purified by reverse-phase HPLC (10% B for 5 min, 10% to 60% B over 35 min) and lyophilized to afford peptide **65** as an oily white solid (1.0 mg, 13% yield based on the original resin loading).



A) Crude analytical HPLC trace of peptide **P11** following SPPS (0 to 100% B over 25 min, λ = 230 nm) [note that **P11'** designates the TFA-cleaved peptide]; **B)** Crude reaction mixture (λ = 230 nm) depicting the formation of target peptide **65**, after one cycle of on-resin activation and on-resin nickel coupling; **C)** Crude reaction mixture (λ = 230 nm) following the second cycle of on-resin activation and on-resin nickel coupling.



Purified peptide product **65** (0 to 100% B over 25 min, λ = 230 nm, R_t = 12.9 min).

^{1}H NMR (600 MHz, 9:1 v/v DMSO-d_6/D_2O): δ 7.83 – 7.71 (m, 2H, N-H protons exhibit slow exchange with D_2O), 6.99 (d, *J* = 8.4 Hz, 2H), 6.62 (d, *J* = 8.4 Hz, 2H), 4.46 – 4.38 (m, 1H), 4.37 – 4.29 (m, 1H), 4.29 – 4.24 (m, 1H), 4.24 – 4.09 (m, 2H), 3.69 – 3.55 (m, 1H), 2.90 (dd, *J* = 14.2, 4.8 Hz, 1H), 2.73 (dd, *J* = 14.1, 8.7 Hz, 1H), 2.01 – 1.91 (m, 1H), 1.82 (s, 3H), 1.80 – 1.21 (m, 13H), 1.20 (d, *J* = 7.1 Hz, 3H), 0.90 – 0.79 (m, 6H) ppm; [note: one hydrogen is obscured by the water signal]

^{13}C NMR (151 MHz, DMSO-d_6): δ 174.0, 171.4, 170.9, 170.9, 170.8, 169.1, 155.8, 130.1, 127.6, 114.8, 59.5, 54.3, 52.6, 50.1, 48.0, 46.8, 36.1, 33.3, 31.6, 28.8, 27.4, 24.3, 22.2, 21.9, 18.4, 18.2, 13.9, 13.7 ppm; [note: residual TFA remaining after lyophilization can be observed in the ^{13}C NMR spectrum – δ 157.7 (quartet), 117.3 (quartet)].

HRMS (ESI-TOF, *m/z*): calcd for $C_{30}H_{46}N_6O_7Na$ $[M+Na]^+$ 625.3320; found 625.3271.

Troubleshooting: Frequently Asked Questions

Question 1:

How do you monitor the reactions?

Answer:

Monitoring the progress of reactions directly on-resin can be difficult and generally requires cleavage of the peptide from the solid-support prior to analysis using conventional methods (for Rink amide resin, cleavage requires treatment with TFA). As such, the on-resin activation of the carboxylic acid cannot be monitored without hydrolyzing the active ester. Excess equivalents of activating agents are therefore utilized to ensure complete activation of the acid. Following the nickel coupling, however, the outcome of the activation-coupling sequence can be evaluated by performing a "test cleavage," whereby a small number of resin beads are treated with TFA to cleave the peptide and the resultant peptide-containing residue is analyzed by LC-MS and analytical HPLC (210 nm, 230 nm and 280 nm are generally the most useful for reaction monitoring).

Question 2:

What if the reaction does not proceed to completion?

Answer:

If there is still starting material bearing a free carboxylic acid after a single activation-coupling procedure, the activation-coupling protocol may be repeated additional times without issue. In the event of repeated couplings, we suggest replacing the fritted syringe, which can gradually lose its integrity through repeated heating in the activation step.

Question 3:

What major byproducts should I look out for?

Answer:

Decarboxylation accompanied by reduction (net loss of 44 mass units from the starting peptide) is the major byproduct observed in the on-resin coupling protocol. In addition, during activation of the side-chain carboxylic acids of Asp and Glu, one might observe cyclization of the amide backbone onto the activated acid resulting in a byproduct

consistent with the mass of the starting peptide-H_2O (this can be particularly problematic with Asp when the C-terminally adjacent residue is not Pro or a bulky residue such as Val or Ile). Backbone protection of the amide (e.g. with a Dmb group) can help resolve this issue.

Question 4:

What is the best method for activation of the resin-bound carboxylic acid?

Answer:

We have found that TCNHPI is generally the most favorable method for on-resin activation prior to the on-resin nickel coupling. However, in some cases (e.g. the preparation of peptide **62**), cleaner reactions were obtained using NHPI. Although LC-MS analysis after the activation-coupling protocol generally shows a larger amount of unreacted acid starting material when the NHPI ester is employed in place of the TCNHPI ester, the possibility of iterative on-resin couplings might make a very clean reaction with lower overall conversion preferable for some substrates.

Question 5:

How anhydrous does the reaction need to be? Is moisture tolerated at all?

Answer:

While reactions were not performed strictly anhydrously (activations and couplings were carried out in solid-phase reaction vessels which were capped and placed on an orbital shaker rather than in round bottom flasks under an inert atmosphere), we did make an effort to exclude water and oxygen from both the solvents used in the reaction steps as well as the solvents used to wash the peptide immediately before the reaction and in-between the activation and coupling steps. To wash the resin "anhydrously," we simply charged a round bottom flask with dry DMF under an inert atmosphere and syringed out portions of this solution to perform the wash steps (see photos for more details). Care was taken specifically to wash the activated ester (e.g. the on-resin TCNHPI ester) with dry solvent to minimize hydrolysis. We found a slight increase in overall yield using the "anhydrous" technique as opposed to general solid-phase protocol where washings and couplings are performed open flask (see additional optimization section for details).

Question 6:

The reaction appears to be clean but my isolated yields are low. What might be the issue?

Answer:

Some model peptides bearing large hydrophobic side-chains were found to exhibit minimal solubility in water and acetonitrile mixtures. Loss of material before and during HPLC purification may therefore be a concern. Try dissolving the peptide residue in a small amount of DMSO prior to HPLC purification (note that DMSO was also the preferential solvent for NMR analysis). You should also carefully check LC-MS and analytical HPLC results from the crude reaction mixture to ensure that the starting material (generally more polar than the coupled product) is not eluting in the injection peak of the chromatogram, leading to an overestimation of reaction conversion.

Question 7:

How do I wash the resin after the coupling?

Answer:

We have found that standard washings (10 x DMF, 10 x DCM, 10 x DMF) are sufficient to remove the majority of excess reagents in the coupling step. However, in some cases, the bipyridine-based ligands were difficult to remove entirely and could be seen in the crude LC-MS traces following on-resin coupling. If it is essential to remove excess bipyridine, an additional washing step with $CuSO_4$ in DMF (2 x 10 min) may also be performed. In some instances, however, this step resulted in the adherence of excess copper to the resin, as evidenced by a green tinge of the resin following treatment with $CuSO_4$. To remove the copper, wash the resin repeatedly with sodium dimethyldithiocarbamate hydrate (0.02 M in DMF), until the dark yellow-brown color dissipates from the washing solution.

Question 8:

How many equivalents of dialkylzinc reagent should I use?

Answer:

In general, 10 equivalents of the dialkylzinc reagent (per activated ester) were used in the coupling reaction. In the preparation of model tripeptide **60**, increasing to 20 equivalents did not have a substantial impact on the reaction yield or conversion. However, the

appropriate number of equivalents in any given experiment should be carefully judged by considering the nature of the peptide substrate. The basic dialkylzinc reagent may deprotonate backbone amides, resulting in consumption of multiple equivalents of the dialkylzinc reagent, depending on the length of the peptide. Consumption of the reagent can be accounted for by adding additional equivalents.

Question 9:

How important is the concentration of reagents to the success of the nickel coupling?

Answer:

In general, the higher the concentration, the better. More concentrated nickel/ligand solutions and more concentrated dialkylzinc reagents were consistently higher yielding than more dilute preparations, specifically minimizing the amount of observed decarboxylation byproducts and recovered starting material. In comparison to solution-phase couplings, resin-bound substrates generally exhibit a "pseudo-dilution" effect, requiring higher concentrations of reactive species to facilitate efficient couplings.

Question 10:

Do I need to use excess catalyst and ligand relative to the solution-phase coupling protocol?

Answer:

In optimization reactions, we found that 20 mol% nickel catalyst and 40 mol% ligand loading resulted in lower conversion rates relative to stoichiometric nickel and 2.0 equivalents of the ligand. We suspect that some of the catalyst and ligand might adhere to the resin or bind to the peptide substrate, reducing turnover of the catalyst. This phenomenon may be substrate or resin-specific, so we recommend screening catalyst loadings if problems arise during the coupling.

Question 11:

What resins are acceptable?

Answer:

We utilized Rink amide resin as a robust support for our resin-bound peptides. However, we hypothesize that additional resins may be employed so long as they are stable to

treatment with organozinc reagents and have suitable swelling properties in the ideal reaction solvents (DMF/THF or DMF/hexanes).

Question 12:

What steps can be taken to optimize the reaction?

Answer:

There are a number of approaches to optimizing the reaction. Problems can arise either during the on-resin activation step or during the nickel coupling step, so efforts can be made to optimize both steps.

Optimization of on-resin activation:

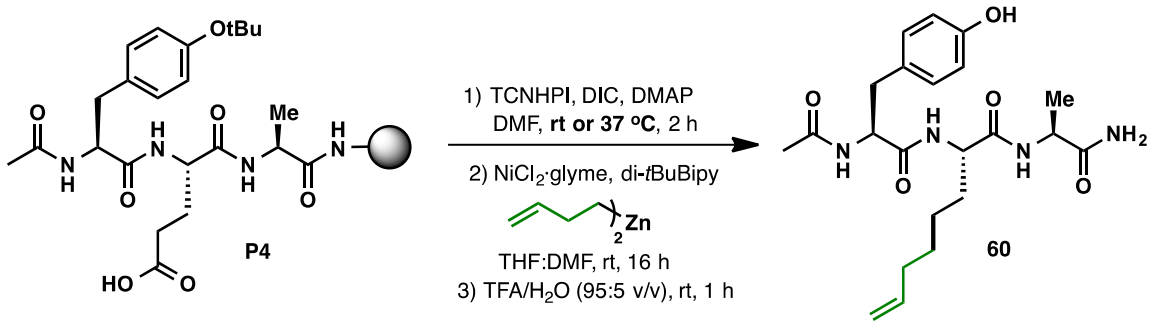
1. To optimize on-resin activation, try increasing the number of equivalents of activating agent (TCNHPI/DIC or HATU) and increasing the concentration of the activation solution (ideally aim for a 0.1 M final reaction concentration with respect to the resin-bound peptide).
2. Extend the length of the activation protocol.
3. Run the reaction at elevated temperatures (37 ^{o}C or slightly higher).

Optimization of on-resin nickel coupling:

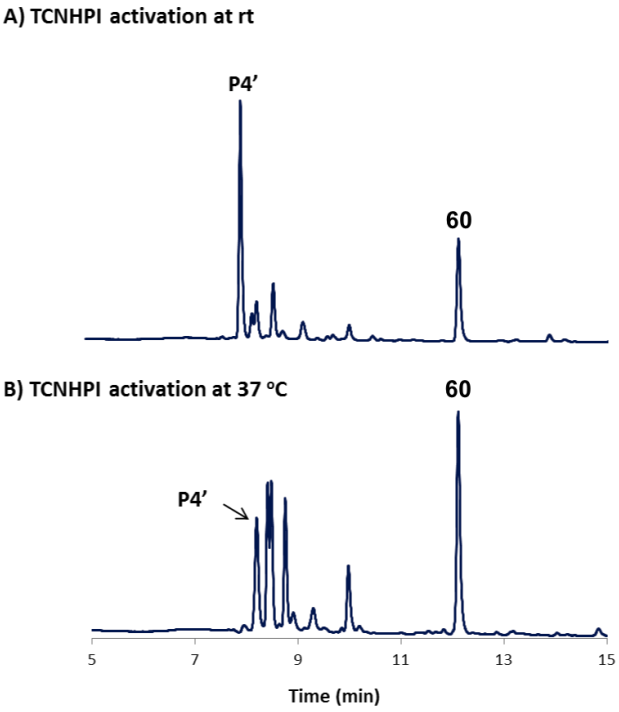
1. Add more equivalents of the nickel catalyst, ligand, and dialkylzinc reagent.
2. Increase the concentration of the reaction by preparing a more concentrated dialkylzinc reagent or a more concentrated solution of catalyst and ligand.
3. Try a different mode of activation – TCNHPI was generally the most reactive for on-resin couplings but occasionally resulted in additional byproduct formation. NHPI or HATU may be employed instead.
4. Increase the length of the coupling or try heating the reaction (37 ^{o}C or slightly higher).
5. Make sure that the reaction is sufficiently anhydrous in order to avoid hydrolysis of the activated ester.

Additional Optimization Studies:

1) Activation temperature:

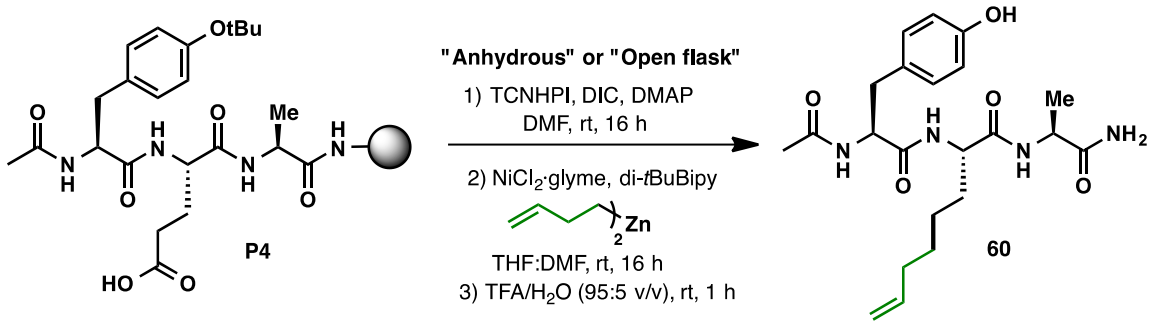


To probe the effect of temperature on the on-resin activation step, peptide **P4** was activated with TCNHPI according to the general methods at either rt or at 37 °C for 2 h. The resin-bound peptide was then subjected to the on-resin nickel coupling by treatment with $NiCl_2$·glyme (1.0 equiv.) and di-*t*BuBipy (2.0 equiv.) in DMF (0.02 M with respect to the Ni catalyst) followed by the addition of dialkylzinc reagent (10.0 equiv., 0.2 M in THF). Following TFA cleavage, the crude reaction mixtures were evaluated by analytical HPLC.

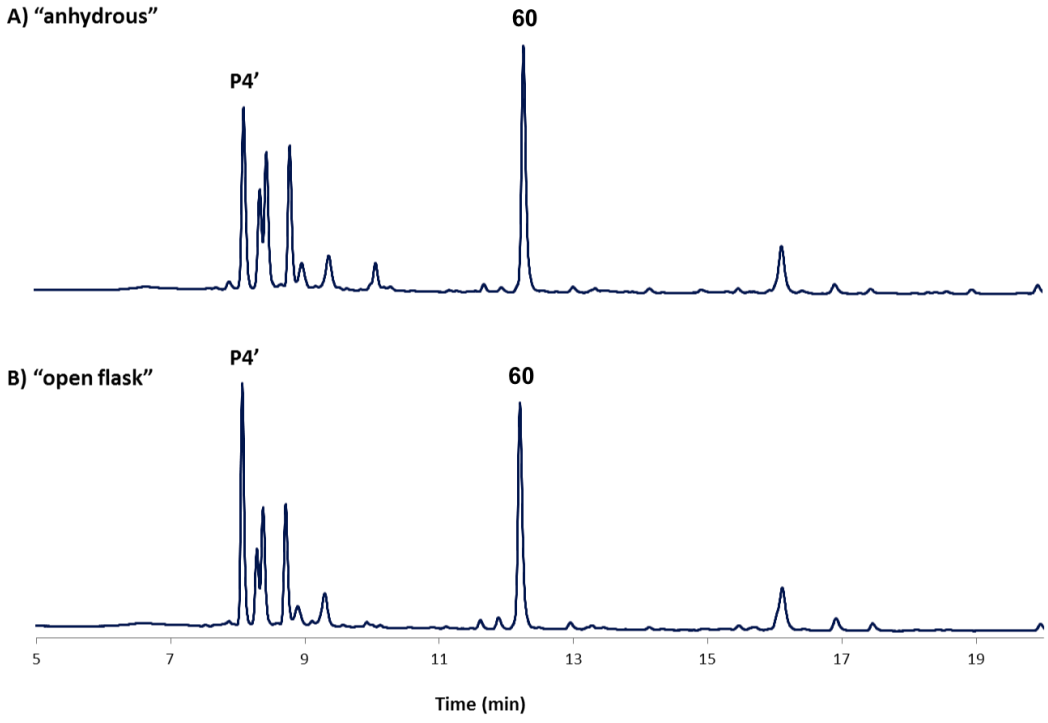


A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the preparation of peptide **60** using room temperature activation of **P4** with TCNHPI. **B)** Crude preparation of peptide **60** using 37 °C activation of **P4** with TCNHPI.

2) Sensitivity to moisture:

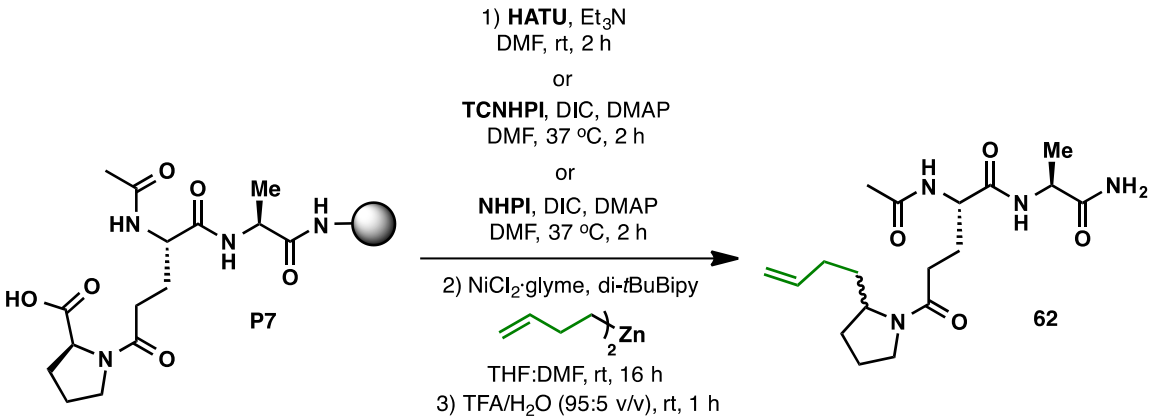


The requirement for "anhydrous" conditions in the activation and coupling steps was probed by subjecting peptide **P4** to the activation-coupling under "anhydrous" or "open flask" conditions. "Anhydrous" activation with TCNHPI for 16 h at rt was performed using dry DMF and washing steps were carried out under an argon atmosphere with dry solvents. Transfer of the nickel/ligand solution and dialkylzinc reagent to the solid-phase reaction vessel was also performed under argon. For the "open flask" protocol, addition of the activation and nickel coupling solutions were not carried out under an argon atmosphere and no special precautions were taken when washing the resin.

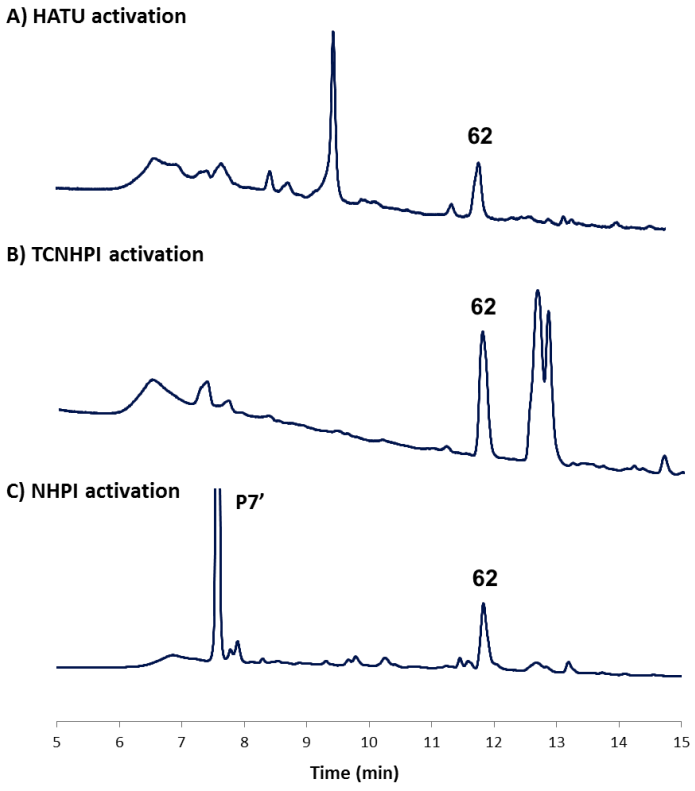


A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 230 nm) of the "anhydrous" preparation of peptide **60**. **B)** Crude analytical HPLC trace of the "open flask" preparation of peptide **60**.

3) Modes of activation:



Peptide **P7** was activated with HATU, TCNHPI, or NHPI according to the general procedures and then subjected to on-resin nickel coupling. Following cleavage from the resin the crude peptides were evaluated using analytical HPLC.

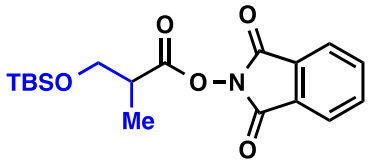


A) Crude analytical HPLC trace (0 to 100% B over 25 min, λ = 210 nm) of HATU activation of peptide **P7** and subsequent on-resin nickel coupling. **B)** Crude analytical HPLC trace (λ = 210 nm) of TCNHPI activation of peptide **P7** and subsequent on-resin

nickel coupling; **C)** Crude analytical HPLC trace (λ = 210 nm) of NHPI activation of peptide **P7** and subsequent on-resin nickel coupling.

While HATU and TCNHPI activation resulted in complete consumption of the starting peptide, substantial byproducts were also observed. Overall conversion was lower with NHPI activation, but the crude reaction mixture indicated cleaner formation of peptide **62**, accompanied only by uncoupled starting material (**P7'**).

Experimental Procedures and Characterization Data for Redox-active Esters



(+)-SI-1

(+)-1,3-dioxoisoindolin-2-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate ((+)-SI-1)

On 1.0 mmol scale, general procedure A was followed with (+)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoic acid (*41*) and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) afforded *N*-hydroxypthalimide ester **(+)-SI-1** as a colorless oil (0.295 g, 81%).

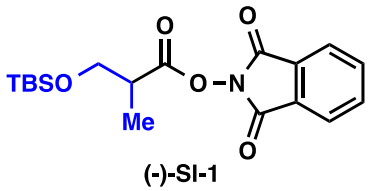
R_f = 0.46 (4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.94 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.80 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.12 – 2.97 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.10 (d, *J* = 1.0 Hz, 6H, overlapping peaks) ppm;

^{13}C NMR (151 MHz, $CDCl_3$:) δ 171.2, 134.8, 129.2, 124.0, 64.6, 40.6, 26.0, 18.4, 13.7, -5.4 (2C) ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{26}NO_5Si$ $[M+H]^+$ 364.1575; found 364.1575;

$[\alpha]_D^{20}$ = 27.9 ° (c = 1.0, CH_2Cl_2).



(-)-SI-1

(-)-1,3-dioxoisoindolin-2-yl 3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoate ((-)-SI-1)

On 1.0 mmol scale, general procedure A was followed with (-)-3-((*tert*-butyldimethylsilyl)oxy)-2-methylpropanoic acid (*41*) and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) afforded *N*-hydroxypthalimide ester **(-)-SI-1** as a colorless oil (0.296 g, 81%).

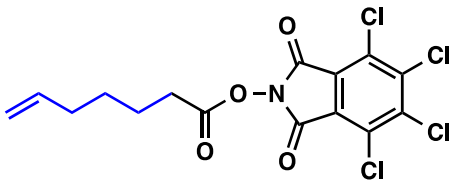
R_f = 0.46 (4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.78 (dd, *J* = 5.5, 3.1 Hz, 2H), 3.94 (dd, *J* = 9.9, 6.6 Hz, 1H), 3.80 (dd, *J* = 9.8, 6.1 Hz, 1H), 3.12 – 2.97 (m, 1H), 1.36 (d, *J* = 7.1 Hz, 3H), 0.92 (s, 9H), 0.10 (d, *J* = 1.0 Hz, 6H, overlapping peaks) ppm;

^{13}C NMR (151 MHz, $CDCl_3$:) δ 171.2, 134.8, 129.2, 124.0, 64.6, 40.6, 26.0, 18.4, 13.7, -5.4 (2C) ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{26}NO_5Si$ $[M+H]^+$ 364.1575; found 364.1574;

$[\alpha]_D^{20}$ = - 27.6 º (c = 1.0, CH_2Cl_2).



SI-3

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl hept-6-enoate (SI-3).

On 2.5 mmol scale, general procedure A was followed with 6-heptenoic acid, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-3** (839 mg, 81% yield) as a yellow solid.

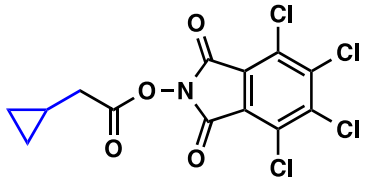
m.p. = 79 °C;

***R*$_f$** = 0.79 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 16.9, 10.0, 6.7 Hz, 1H), 5.16 – 4.79 (m, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.14 (q, *J* = 7.2 Hz, 2H), 1.82 (p, *J* = 7.5 Hz, 2H), 1.57 (p, *J* = 7.3 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 157.7, 141.1, 138.0, 130.6, 124.9, 115.3, 33.3, 30.9, 28.0, 24.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{12}Cl_4NO_4^+$ $[M+H]^+$ 409.9515; found 409.9523.



SI-8

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-cyclopropylacetate (SI-8).

On 5.0 mmol scale, general procedure A was followed with cyclopropane acetic acid. Purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-8** as a yellow solid. This compound was then recrystallized from CH_2Cl_2/MeOH to yield a pale yellow solid (1.55 g, 81 %).

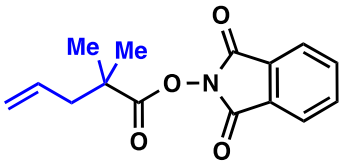
m.p.= 141-142°C

***R*$_f$** = 0.56 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.58 (d, *J* = 7.1 Hz, 2H), 1.22 – 1.13 (m, 1H), 0.71 – 0.66 (m, 2H), 0.36 – 0.30 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.6, 157.7, 141.2, 130.6, 124.9, 36.1, 6.7, 4.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_8Cl_4NO_4$ $[M+H]^+$ 381.9202; found 381.9204.



SI-11

1,3-dioxoisoindolin-2-yl 2,2-dimethylpent-4-enoate (SI-11).

Following the General Procedure A with 2,2-dimethylpent-4-enoic acid (5 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded **SI-11** (1.19 g, 87% yield) as a white solid.

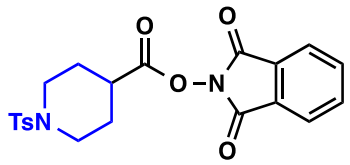
m.p.= 35-36 ºC;

***R*$_f$** = 0.50 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87-7.89 (m, 2H), 7.76-7.80 (m, 2H), 5.86-5.95 (m, 1H), 5.17-5.21 (m, 2H), 2.49 (d, J = 7.5 Hz, 2H), 1.39 (s, 6H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 173.6, 162.2, 134.8, 133.1, 129.2, 124.0, 119.4, 44.7, 42.1, 24.8 ppm;

HRMS (ESI-TOF): calc'd for $C_{15}H_{16}NO_4$ $[M+H]^+$ 274.1074; found 274.1080.



1a

1,3-dioxoisoindolin-2-yl 1-tosylpiperidine-4-carboxylate (1a).

On 10.0 mmol scale, general procedure A was followed with 1-tosylpiperidine-4-carboxylic acid (*42*) and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-phthalimide ester **1a** as a white solid. This compound was further washed with small amount of hexanes and MeOH to yield a white solid (4.79 g, 85 %).

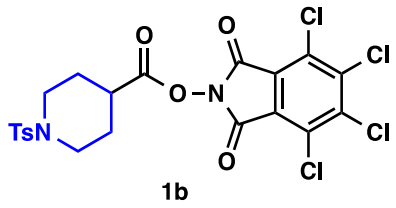
m.p.= 209 °C;

$\boldsymbol{R_f}$ = 0.79 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.90 – 7.84 (m, 2H), 7.81 – 7.76 (m, 2H), 7.67 – 7.64 (m, 2H), 7.36 – 7.31 (m, 2H), 3.64 (d, *J* = 12.3 Hz, 2H), 2.72 (td, *J* = 9.8, 4.9 Hz, 1H), 2.65 (ddd, *J* = 12.7, 10.3, 3.1 Hz, 2H), 2.44 (s, 3H), 2.15 (dq, *J* = 12.8, 4.1 Hz, 2H), 2.03 (dtd, *J* = 13.8, 10.1, 3.9 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 161.9, 143.9, 135.0, 133.3, 129.9, 129.0, 127.8, 124.1, 45.0, 37.7, 27.4, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{21}N_2SO_6$ $[M+H]^+$ 429.1115; found 429.1114.



1b

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 1-tosylpiperidine-4-carboxylate (1b).

On 10.0 mmol scale, general procedure A was followed with 1-tosylpiperidine-4-carboxylic acid (*42*) and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **1b** as a pale yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (3.81 g, 67 %).

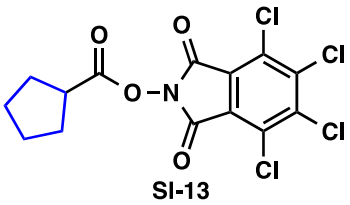
m.p.= 209 °C;

***R*$_f$** = 0.21 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.66 – 7.63 (m, 2H), 7.35 – 7.32 (m, 2H), 3.62 (dt, *J* = 11.8, 4.4 Hz, 2H), 2.73 (tt, *J* = 9.9, 4.1 Hz, 1H), 2.65 (ddd, *J* = 12.7, 10.2, 3.1 Hz, 2H), 2.44 (s, 3H), 2.17 – 2.10 (m, 2H), 2.01 (dtd, *J* = 13.8, 10.0, 3.8 Hz, 2H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 169.8, 157.5, 143.9, 141.3, 133.2, 130.7, 129.9, 127.8, 124.7, 44.9, 37.6, 27.4, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{17}Cl_4N_2O_6S$ $[M+H]^+$ 564.9556; found 564.9556.



SI-13

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl cyclopentanecarboxylate (SI-13).

On 2.3 mmol scale, general procedure A was followed with cyclopentane carboxylic acid, and purification by flash column chromatography (silica gel, 10:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-13** as a white solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (645 mg, 61 %).

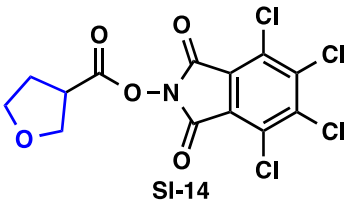
m.p.= 110 °C;

***R*$_f$** = 0.79 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 3.16 – 3.07 (m, 1H), 2.13 – 1.98 (m, 4H), 1.85 – 1.74 (m, 2H), 1.73 – 1.63 (m, 2H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 172.6, 157.9, 141.1, 130.6, 124.9, 40.7, 30.4, 26.1 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{10}Cl_4NO_4$ $[M+H]^+$ 395.9358; found 395.9349.



SI-14

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl tetrahydrofuran-3-carboxylate (SI-14).

On 5.0 mmol scale, general procedure A was followed with tetrahydrofuran-3-carboxylic acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O)

furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-14** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.06 g, 53 %).

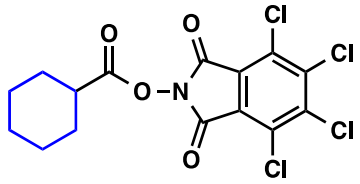
m.p.= 122 °C;

R_f = 0.24 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.17 – 4.10 (m, 2H), 3.95 (ddd, *J* = 8.7, 7.3, 6.6 Hz, 1H), 3.90 (ddd, *J* = 8.7, 7.3, 6.2 Hz, 1H), 3.50 – 3.42 (m, 1H), 2.41 – 2.31 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.2, 157.6, 141.3, 130.7, 124.8, 70.1, 68.4, 41.0, 30.1 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_8Cl_4NO_5$ $[M+H]^+$ 397.9151; found 397.9153.



SI-15

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (SI-15).

On 5.0 mmol scale, general procedure A was followed with cyclohexane carboxylic acid, and purification by flash column chromatography (silica gel, 10:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-15** as a white solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.34 g, 65 %).

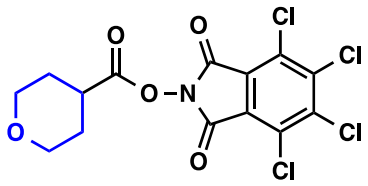
m.p.= 150 °C;

R_f = 0.79 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.74 (tt, *J* = 10.9, 3.7 Hz, 1H), 2.12 – 2.04 (m, 2H), 1.83 (dt, *J* = 12.9, 3.8 Hz, 2H), 1.72 – 1.61 (m, 3H), 1.44 – 1.26 (m, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.9, 157.2, 140.5, 130.0, 124.3, 39.9, 28.3, 25.0, 24.5 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{12}Cl_4NO_4$ $[M+H]^+$ 409.9515; found 409.9525.



SI-16

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl tetrahydro-2H-pyran-4-carboxylate (SI-16).

On 5.0 mmol scale, general procedure A was followed with tetrahydro-2H-pyran-4-carboxylic acid, and purification by flash column chromatography (silica gel, 10:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-16** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a pale yellow solid (1.86 g, 90 %).

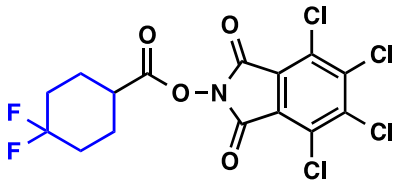
m.p.= 156 °C;

$\boldsymbol{R_f}$ = 0.35 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.02 (dt, *J* = 11.8, 3.9 Hz, 2H), 3.54 (ddd, *J* = 11.8, 10.3, 2.9 Hz, 2H), 3.01 (ddd, *J* = 14.7, 10.2, 4.4 Hz, 1H), 2.07 – 1.92 (m, 4H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.2, 157.7, 141.3, 130.7, 124.8, 66.6, 37.7, 28.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{11}Cl_4NO_5$ $[M+H]^+$ 411.9308; found 411.9303.



SI-17

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 4,4-difluorocyclohexane-1-carboxylate (SI-17).

On 5 mmol scale, general procedure A was followed with 4,4-difluorocyclohexanecarboxylic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) followed by recrystallization from CH_2Cl_2 and MeOH furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-17** as a white solid (1.63 g, 73%).

m.p.= 186 - 189 °C;

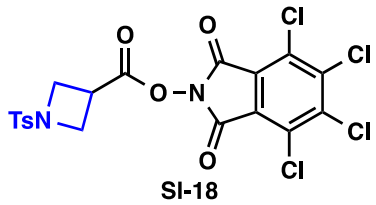
$\boldsymbol{R_f}$ = 0.14 (silica gel, 9:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.96 – 2.82 (m, 1H), 2.24 – 2.13 (m, 4H), 2.09 (m, 2H), 1.98 – 1.84 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.1, 157.7, 141.3, 130.7, 124.8, 122.2 (t, *J* = 241.6 Hz), 37.9, 32.1 (t, *J* = 24.8 Hz), 25.1 (t, *J* = 5.0 Hz) ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ -96.18 (d, *J* = 241.9 Hz), -98.80 (d, *J* = 244.4 Hz) ppm;

HRMS (ESI-TOF, *m/z*): High-resolution mass spec data could not be obtained for this compound.



SI-18

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 1-tosylazetidine-3-carboxylate (SI-18). On 5.0 mmol scale, general procedure A was followed with 1-tosylazetidine-3-carboxylic acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-18** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.70 g, 63 %).

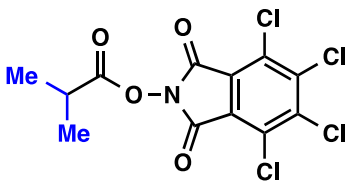
m.p.= 183 °C;

***R*$_f$** = 0.10 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (d, *J* = 8.3 Hz, 2H), 7.41 – 7.38 (m, 2H), 4.18 (dd, *J* = 8.9 Hz, 2H), 4.07 (dd, *J* = 8.9, 6.6 Hz, 2H), 3.63 (tt, *J* = 9.1, 6.5 Hz, 1H), 2.44 (d, *J* = 0.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.6, 157.2, 144.8, 141.4, 131.1, 130.8, 130.2, 128.5, 124.6, 52.5, 29.2, 21.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{19}H_{13}Cl_4N_2O_6S$ $[M+H]^+$ 536.9243; found 536.9252.



SI-19

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl isobutyrate (SI-19).

On 1 mmol scale, general procedure A was followed with isobutryic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-19** as a white solid (0.272 g, 73%).

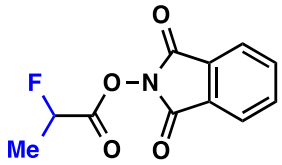
m.p.= 107 - 110 °C;

$\boldsymbol{R_f}$ = 0.50 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.96 (hept, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 7.0 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7, 157.8, 141.1, 130.6, 124.9, 31.9, 19.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{12}H_8Cl_4NO_4$ $[M+H]^+$ 369.9202; found 369.9203.



SI-20

1,3-Dioxoisoindolin-2-yl 2-fluoropropanoate (SI-20).

On 2.9 mmol scale, general procedure A (30 min reaction time) was followed with 2-fluoropropionic acid, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-20** (385 mg, 56% yield) as a white solid (*NOTE*: **SI-20** is unstable to silica gel. Therefore, the purification was quickly performed with a short path of silica gel).

m.p.= 79 - 81 °C;

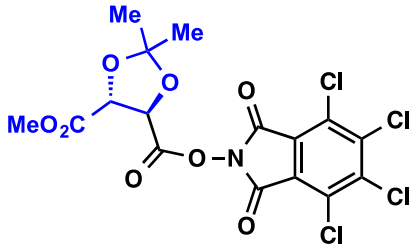
$\boldsymbol{R_f}$ = 0.13 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.87 – 7.80 (m, 2H), 5.44 (dq, *J* = 47.6, 6.9 Hz, 1H), 1.85 (dd, *J* = 23.5, 7.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.4, 160.9, 134.5, 128.3, 123.7, 83.8 (d, *J* = 185.9 Hz), 18.2 (d, *J* = 22.1 Hz) ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ -187.00 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{11}H_9FNO_4$ $[M+H]^+$ 238.0510; found 238.0516.



SI-21

4-methyl 5-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (SI-21)

On 0.5 mmol scale, general procedure A was followed with (-)-(4R,5R)-5-(methoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid (*43*) and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) afforded *N*-hydroxy-tetrachlorophthalimide ester **SI-21** as a waxy white-yellow amorphous solid (0.105 g, 45%).

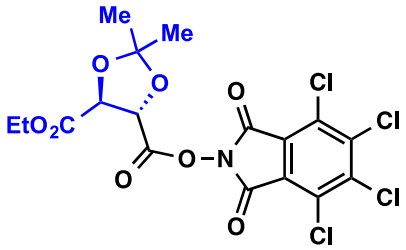
R_f = 0.18 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, C_6D_6): δ 5.14 (d, *J* = 4.5 Hz, 1H), 5.07 (d, *J* = 4.5 Hz, 1H), 3.23 (s, 3H), 1.52 (s, 3H), 1.40 (s, 3H) ppm;

^{13}C NMR (151 MHz, C_6D_6): δ 169.2, 167.6, 157.0, 140.4, 130.1, 124.7, 115.5, 77.9, 75.9, 52.3, 26.6, 26.4 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

$[\alpha]_D^{20}$ = -32.8 º (c = 1.0, CH_2Cl_2).



SI-22

4-ethyl 5-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (SI-22).

On 2.5 mmol scale, general procedure A was followed with (+)-(4S,5S)-5-(ethoxycarbonyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid,(*43*) and purification by flash column chromatography (silica gel, CH_2Cl_2) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-22** as an amorphous yellow solid (0.240 g, 19%).

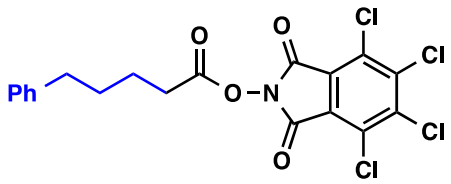
R_f = 0.43 (silica gel, CH_2Cl_2);

^{1}H NMR (600 MHz, C_6D_6): δ 5.17 (d, *J* = 4.7 Hz, 1H), 5.15 (d, *J* = 4.6 Hz, 1H), 3.92 – 3.79 (m, 2H), 1.52 (d, *J* = 0.8 Hz, 3H), 1.41 (d, *J* = 0.8 Hz, 3H), 0.86 (t, *J* = 7.1 Hz, 3H) ppm;

^{13}C NMR (151 MHz, C_6D_6): δ 168.7, 167.7, 157.0, 140.3, 130.1, 124.8, 115.5, 78.2, 76.0, 62.0, 26.7, 26.5, 13.9 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

$[\alpha]_D^{20}$ = +30.6 º (c = 1.0, CH_2Cl_2).



SI-23

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 5-phenylpentanoate (SI-23).

On 5.0 mmol scale, general procedure A was followed with 5-phenylvaleric acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-23** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a pale yellow solid (1.29 g, 56 %).

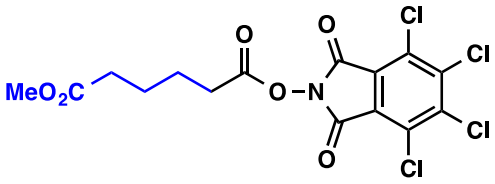
m.p.= 80 °C;

R_f = 0.64 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.21 – 7.17 (m, 3H), 2.72 – 2.65 (m, 4H), 1.86 – 1.75 (m, 4H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.1, 157.7, 141.7, 141.1, 130.6, 128.5 (2C), 126.1, 124.8, 35.5, 30.9, 30.5, 24.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{19}H_{14}Cl_4NO_4$ $[M+H]^+$ 459.9761; found 459.9674.



SI-24

methyl (4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) adipate (SI-24).

On 5.0 mmol scale, general procedure A was followed with adipic acid monomethyl ester, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-24** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.59 g, 72 %).

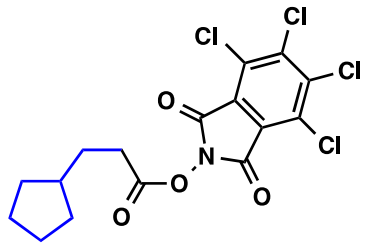
m.p.= 97 °C;

R_f = 0.59 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, Acetone-d_6): δ 3.63 (s, 3H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.74 (m, 4H) ppm;

^{13}C NMR (151 MHz, Acetone-d_6): δ 173.8, 170.2, 158.6, 141.1, 130.8, 126.5, 51.7, 33.8, 31.0, 25.0, 24.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{12}Cl_4NO_4$ $[M+H]^+$ 441.9413; found 441.9416.



SI-25

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 3-cyclopentylpropanoate (SI-25).

On 2.0 mmol scale, general procedure A was followed with 3-cyclopentylpropanoic acid, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-25** (0.14 g, 17% yield) as a white solid.

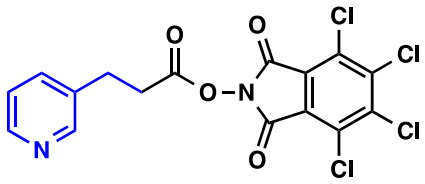
m.p.= 94 °C;

***R*$_f$** = 0.64 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.70 (t, *J* = 7.6 Hz, 2H), 1.98 – 1.73 (m, 5H), 1.73 – 1.47 (m, 4H), 1.25 – 1.07 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 169.3, 157.6, 141.0, 130.4, 124.7, 39.4, 32.3, 30.8, 30.3, 25.1 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.



SI-26

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 3-(pyridin-3-yl)propanoate (SI-26).

On 2.0 mmol scale, general procedure A was followed with 3-(pyridin-3-yl)propanoic acid, and purification by flash column chromatography (silica gel, 4:1 CH_2Cl_2:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-26** as a yellow solid (611 mg, 70 %).

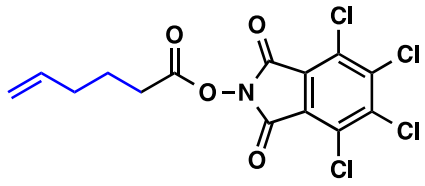
m.p.= 133-134 °C;

***R*$_f$** = 0.48 (silica gel, 4:1 CH_2Cl_2:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.53 (d, *J* = 2.2 Hz, 1H), 8.50 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.59 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.28 – 7.27 (m, 1H), 3.10 (t, *J* = 7.6 Hz, 2H), 3.03 – 2.97 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.2, 157.5, 149.8, 148.4, 141.2, 136.0, 134.5, 130.6, 124.7, 123.7, 32.3, 27.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_9Cl_4N_2O_4$ $[M+H]^+$ 432.9311; found 432.9310.



SI-27

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl hex-5-enoate (SI-27).

On 1 mmol scale, general procedure A was followed with 5-hexenoic acid, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-27** as a white solid (0.344 g, 87%).

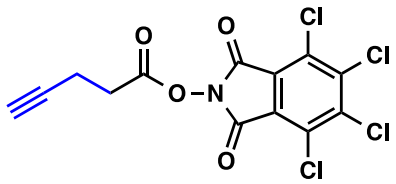
m.p.= 75 °C;

R_f = 0.29 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.79 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.11 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.06 (ddt, *J* = 10.2, 1.9, 1.2 Hz, 1H), 2.68 (t, *J* = 7.4 Hz, 2H), 2.29 – 2.17 (m, 2H), 1.89 (p, *J* = 7.3 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.2, 157.7, 141.2, 137.0, 130.6, 124.9, 116.5, 32.7, 30.2, 23.9 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{10}Cl_4NO_4$ $[M+H]^+$ 395.9358; found 395.9360.



SI-28

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl pent-4-ynoate (SI-28).

On 5.0 mmol scale, general procedure A was followed with pent-4-ynoic acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-28** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a yellow needle (1.09 g, 57 %).

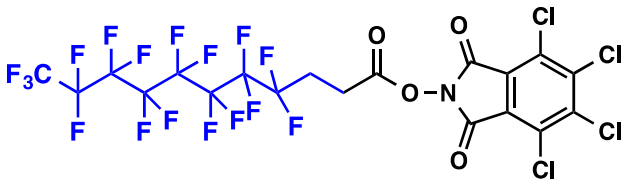
m.p.= 178 °C;

R_f = 0.59 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.94 (dd, *J* = 8.0, 6.8 Hz, 2H), 2.66 (ddd, *J* = 8.3, 6.8, 2.7 Hz, 2H), 2.08 (t, *J* = 2.7 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.7, 157.5, 141.3, 130.7, 124.8, 80.8, 70.4, 30.5, 14.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_6Cl_4NO_4$ $[M+H]^+$ 379.9045; found 379.9049.



SI-29

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoate (SI-29).

On 0.41 mmol scale, general procedure A was followed with 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoic acid, and purification by flash column chromatography (silica gel, 95:5 CH_2Cl_2:Et_2O) and trituration with MeOH furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-29** as a fluffy white solid (0.140 g, 44%). **Note**: This reaction was run in EtOAc due to the insolubility of the starting material in CH_2Cl_2.

m.p.= 107 - 110 °C;

***R*$_f$** = 0.63 (silica gel, 1:1 hexanes:CH_2Cl_2);

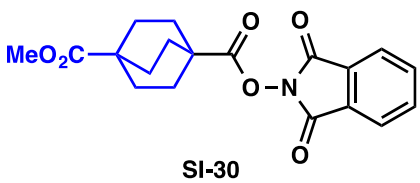
^{1}H NMR (600 MHz, C_6D_6): δ 2.27 – 2.20 (m, 2H), 1.96 – 1.85 (m, 2H) ppm;

^{13}C NMR (151 MHz, C_6D_6): δ 167.8, 157.2, 140.4, 130.2, 110.4, 26.0 (t, *J* = 21.9 Hz), 22.5 (t, *J* = 4.1 Hz) ppm;

^{19}F NMR (376 MHz, C_6D_6): δ -81.74 (t, *J* = 9.8 Hz), -115.29 (t, *J* = 14.1 Hz), -122.51 (d, *J* = 86.5 Hz), -123.48, -124.07, -126.76 – -127.10 (m) ppm;

Note: ^{19}F shifts are relative to C_6F_6 in C_6D_6 (-163.6 ppm).

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.



SI-30

1-(1,3-Dioxoisoindolin-2-yl) 4-methyl bicyclo[2.2.2]octane-1,4-dicarboxylate (SI-30).

On 2.5 mmol scale, general procedure A was followed with 4-(methoxycarbonyl)bicyclo[2.2.2]octane-1-carboxylic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-30** (802 mg, 89% yield) as a white solid.

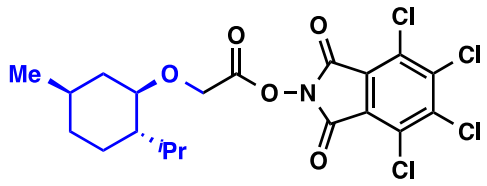
m.p.= 156 – 158 °C;

$\boldsymbol{R_f}$ = 0.32 (silica gel, 9:1 hexanes:EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (ddd, *J* = 5.5, 3.1, 1.0 Hz, 2H), 7.85 (ddd, *J* = 5.6, 3.1, 1.0 Hz, 2H), 3.74 (s, 3H), 2.17 – 2.06 (m, 6H), 2.04 – 1.94 (m, 6H) ppm;

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 173.7, 162.4, 135.1, 129.4, 124.3, 52.3, 38.9, 38.7, 28.0, 27.9 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{19}H_{20}NO_6$ $[M+H]^+$ 358.1285; found 358.1284.



SI-31

(-) - 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-(((1R,2S,4S)-2-isopropyl-4-methylcyclohexyl)oxy)acetate (SI-31).

On 5.0 mmol scale, general procedure A was followed with (-)-menthoxyacetic acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-31** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.72 g, 63 %).

m.p.= 125-126°C;

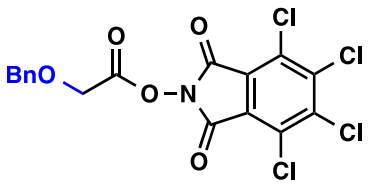
$\boldsymbol{R_f}$ = 0.80 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.52 (s, 2H), 3.28 (td, *J* = 10.6, 4.2 Hz, 1H), 2.28 (pd, *J* = 6.9, 2.5 Hz, 1H), 2.12 (dd, *J* = 10.6, 6.0 Hz, 1H), 1.65 (m, 2H), 1.38 (m, 1H), 1.30 (ddt, *J* = 13.0, 10.3, 3.1 Hz, 1H), 1.04 – 0.82 (m, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 7.1 Hz, 3H), 0.79 (d, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.1, 157.4, 141.3, 130.7, 124.8, 81.1, 63.6, 48.3, 39.8, 34.5, 31.6, 25.6, 23.4, 22.4, 21.1, 16.4 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

$[\alpha]_D^{20}$= -55.6° (c= 1.0, CH_2Cl_2).



SI-32

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-(benzyloxy)acetate (SI-32).

On 5.0 mmol scale, general procedure A was followed with benzyloxyacetic acid, and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-32** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a pale yellow solid (1.46 g, 63 %).

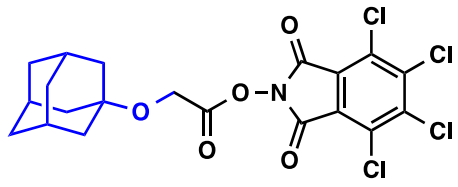
m.p.= 91-92 °C;

***R*$_f$** = 0.45 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 4H), 7.36 – 7.32 (m, 1H), 4.72 (s, 2H), 4.50 (s, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.5, 157.4, 141.3, 136.3, 130.7, 128.8, 128.6, 128.4, 124.7, 73.8, 64.9 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.



SI-33

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-(((3s,5s,7s)-adamantan-1-yl)oxy)acetate (SI-33).

On 5.0 mmol scale, general procedure A was followed with 2-(((3s,5s,7s)-adamantan-1-yl)oxy)acetic acid,(*44*) and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-33** as a pale yellow

solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.65 g, 67 %).

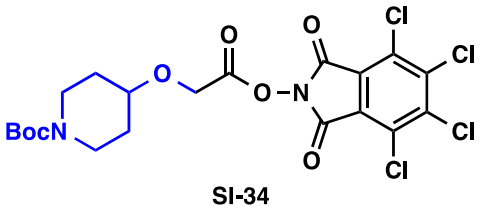
m.p.= 139-140°C;

R_f = 0.61 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.49 (s, 2H), 2.22 – 2.17 (m, 3H), 1.81 (d, *J* = 2.9 Hz, 6H), 1.64 (q, *J* = 12.2 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.9, 157.4, 141.2, 130.6, 124.8, 75.4, 57.2, 41.2, 36.3, 30.7 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.



SI-34

tert-butyl 4-(2-oxo-2-((4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)oxy)ethoxy)piperidine-1-carboxylate (SI-34).

On 5.0 mmol scale, general procedure A was followed with 2-((1-(*tert*-butoxycarbonyl)piperidin-4-yl)oxy)acetic acid,(*45*) and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-34** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (1.72 g, 63 %).

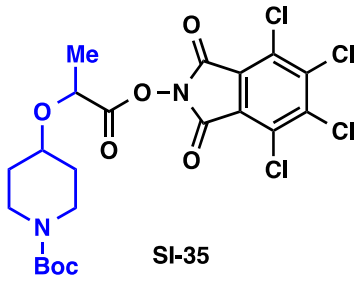
m.p.= 107-109 °C;

R_f = 0.25 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.53 (s, 2H), 3.80 – 3.72 (m, 2H), 3.67 (dt, *J* = 8.1, 4.2 Hz, 1H), 3.14 (ddd, *J* = 13.5, 8.9, 3.6 Hz, 2H), 1.93 – 1.84 (m, 2H), 1.61 (tq, *J* = 8.8, 4.3 Hz, 2H), 1.45 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 166.9, 157.4, 154.9, 141.4, 130.7, 124.7, 79.8, 76.8, 63.8, 41.0, 30.8, 28.6 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{21}Cl_4N_2O_7$ $[M+H]^+$ 541.0097; found 541.0099.



SI-35

tert-butyl 4-((1-oxo-1-((4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)oxy)propan-2-yl)oxy)piperidine-1-carboxylate (SI-35).

On 2.5 mmol scale, general procedure A was followed with 2-((1-(tert-butoxycarbonyl)piperidin-4-yl)oxy)propanoic acid,(*46*) and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-35** as a white solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a white solid (712 mg, 52 %).

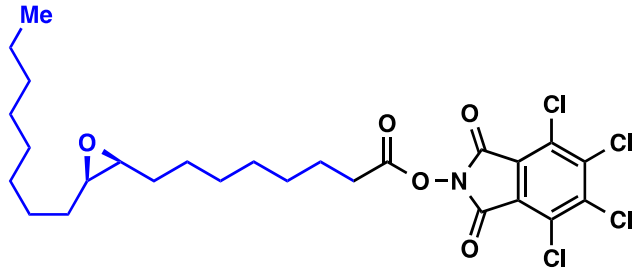
m.p.= 127-128°C;

R_f = 0.25 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.47 (q, *J* = 6.8 Hz, 1H), 3.81 – 3.73 (m, 2H), 3.66 (tt, *J* = 8.0, 3.7 Hz, 1H), 3.13 (dddd, *J* = 13.4, 8.9, 3.6, 1.9 Hz, 2H), 1.86 (m, 2H), 1.66 – 1.59 (m, 1H), 1.62 (d, *J* = 6.9 Hz, 3H), 1.58 – 1.52 (m, 1H), 1.44 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.7, 157.5, 154.9, 141.3, 130.7, 124.8, 79.7, 75.7, 71.0, 41.1 (br, weak), 31.7, 30.4, 28.6, 19.5 ppm; Note: ^{13}C resonances 31.7 and 30.4 belong to the same carbon atom, as verified by HSQC.

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{23}Cl_4N_2O_7$ $[M+H]^+$ 554.0254; found 554.0255.



SI-36

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 10-(3-hexyloxiran-2-yl)decanoate (SI-36).

On 5.0 mmol scale, general procedure A was followed with trans-9,10-epoxystearic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) and recrystallization from CH_2Cl_2 and MeOH furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-36** as a yellow solid (1.46 g, 50%). Due to the low solubility of the starting material in CH_2Cl_2, the reaction was run for an extended period of time (5 days).

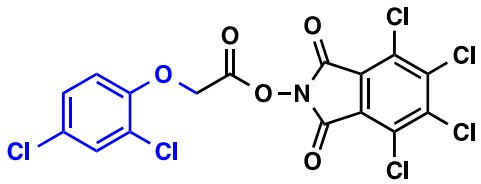
m.p.= 44 – 45 °C;

$\boldsymbol{R_f}$ = 0.22 (silica gel, 1:1 hexanes:CH_2Cl_2);

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.68 – 2.64 (m, 4H), 1.83 – 1.75 (m, 2H), 1.54 – 1.18 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.3, 157.7, 141.1, 130.6, 124.9, 59.1, 59.0, 32.3, 32.2, 32.0, 31.0, 29.7, 29.6, 29.39, 29.27, 29.1, 28.8, 26.2, 26.1, 24.8, 22.8, 14.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{26}H_{34}Cl_4NO_5$ $[M+H]^+$ 580.1186; found 580.1188.



SI-37

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 2-(2,4-dichlorophenoxy)acetate (SI-37).

On 5.0 mmol scale, general procedure A was followed with 2,4-dichlorophenoxyacetic acid (2,4-D), and purification by flash column chromatography (silica gel, 10:1 CH_2Cl_2:Et_2O) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-37** as a yellow solid. This compound was further recrystallized from CH_2Cl_2/MeOH to yield a yellow solid (1.73 g, 69 %).

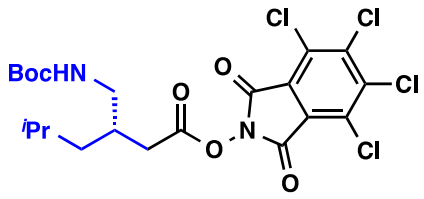
m.p.= 206-207°C;

$\boldsymbol{R_f}$ = 0.46 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.5 Hz, 1H), 7.25 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 5.10 (s, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 164.7, 157.2, 151.9, 141.5, 130.9, 130.7, 128.5, 128.1, 124.8, 124.6, 115.7, 64.7 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.



SI-38

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl (*S*)-3-(((*tert*-butoxycarbonyl)amino) methyl)-5-methylhexanoate (SI-38).

On 0.20 mmol scale, general procedure A was followed with pregabalin, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-38** (92 mg, 85% yield) as a white solid.

m.p.= 129 – 131 °C;

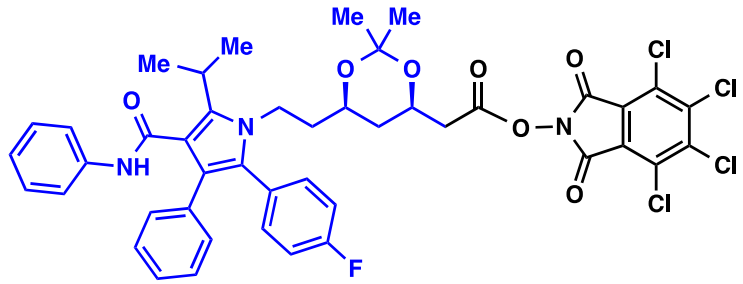
R_f = 0.64 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.88 – 4.79 (m, 1H), 3.42 – 3.23 (m, 1H), 3.20 – 3.00 (m, 1H), 2.66 (d, *J* = 6.3 Hz, 2H), 2.38 – 2.17 (m, 1H), 1.74 (hept, *J* = 6.7 Hz, 1H), 1.46 (s, 9H), 1.29 (t, *J* = 7.3 Hz, 2H), 0.95 (dd, *J* = 9.5, 6.6 Hz, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 157.5, 156.1, 141.1, 130.5, 124.7, 43.8, 41.0, 34.3, 33.8, 28.4, 25.2, 22.7, 22.6 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{25}Cl_4N_2O_6$ $[M+H]^+$ 541.0461; found 541.0459;

$[\alpha]_D^{20}$ = + 2.0° (c = 0.82, $CHCl_3$).



SI-39

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (SI-39).

Acetal protection: Atorvastatin calcium salt (20 mg, 0.017 mmol) was weighed in a round-bottomed flask. Under Ar atmosphere, 2,2-dimethoxypropane (0.6 mL, 4.896

mmol) was added via syringe followed by a solution of conc. H_2SO_4 (5 μL) in 5 mL of acetone. The mixture turned yellow, and after 30 minutes, the solution was evaporated to dryness and the crude product was taken to the next step without further purification.

***N*-hydroxy-tetrachlorophthalimide ester formation**: The above crude mixture, was dissolved in CH_2Cl_2 (5 mL) and *N*-hydroxy-tetrachlorophthalimide (11 mg, 0.035 mmol), DMAP (1 mg, 0.008 mmol) and DIC (7 μL, 0.040 mmol) were added. After stirring for 30 minutes, the mixture was evaporated to dryness and purified by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) to afford **SI-39** (11 mg, 35% yield over 2 steps) as a yellow solid.

m.p. = 120 – 122 ºC;

R_f = 0.3 (silica gel, 4:1 hexanes:EtOAc);

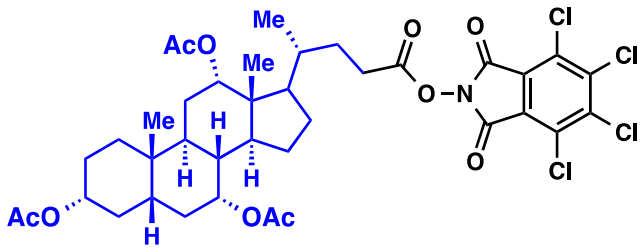
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 – 7.12 (m, 9H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.99 (dt, *J* = 11.2, 7.8 Hz, 3H), 6.86 (bs, 1H), 4.28 (ddt, *J* = 9.1, 6.7, 3.2 Hz, 1H), 4.11 – 4.05 (m, 1H), 3.92 – 3.82 (m, 1H), 3.77 – 3.68 (m, 1H), 3.59 (p, *J* = 7.2 Hz, 1H), 2.85 (dd, *J* = 15.2, 6.8 Hz, 1H), 2.69 (dd, *J* = 15.3, 6.5 Hz, 2H), 1.80 – 1.59 (m, 2H), 1.54 (d, *J* = 7.1 Hz, 5H), 1.50 (dt, *J* = 12.8, 2.5 Hz, 1H), 1.39 (s, 3H), 1.35 (s, 3H), 1.32 – 1.10 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.8, 164.3, 161.8 (d, *J* = 247.8 Hz), 156.9, 141.1, 140.6, 137.9, 134.2, 132.7 (d, *J* = 7.8 Hz), 130.6, 130.0, 128.3, 128.2, 127.9, 127.8 (d, *J* = 3.2 Hz), 126.1, 124.2, 123.0, 121.4, 118.7, 115.0 (d, *J* = 21.7 Hz), 98.7, 65.8, 64.9, 40.3, 37.8, 37.5, 35.2, 29.3, 29.3, 25.6, 21.3, 21.1, 19.1 ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.94 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{44}H_{39}Cl_4FN_3O_7$ $[M+H]^+$ 880.1521; found 880.1527;

$[\alpha]_D^{20}$ = +8.0º (c = 0.4, $CHCl_3$).



SI-40

(3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*)-10,13-dimethyl-17-((*R*)-5-oxo-5-((4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl)oxy)pentan-2-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,7,12-triyl triacetate (SI-40).

On 2.5 mmol scale, general procedure A was followed with acylated cholic acid,(*47*) and purification by flash column chromatography (silica gel, 1:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-40** as a yellow-white fluffy solid (0.700 g, 34%).

m.p.= 128 - 129 °C;

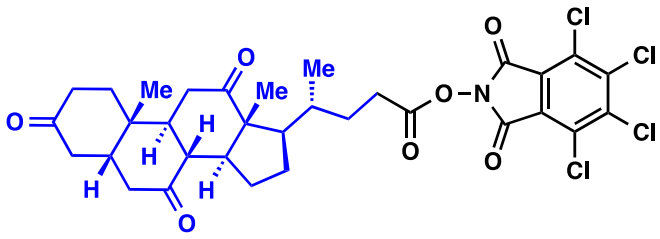
R_f = 0.52 (silica gel, 1:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.10 (d, *J* = 2.9 Hz, 1H), 4.91 (m, *J* = 3.2 Hz, 1H), 4.57 (m, 1H), 2.70 (m, *J* = 14.6, 9.5, 4.4 Hz, 1H), 2.56 (ddd, *J* = 15.9, 9.1, 7.0 Hz, 1H), 2.15 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.04 – 1.99, (m, 1H), 1.98 – 1.83 (m, 4H), 1.77 (tt, *J* = 14.5, 3.6 Hz, 2H), 1.72 – 1.58 (m, 6H), 1.54 – 1.39 (m, 5H), 1.38 – 1.30 (m, 2H), 1.17 – 1.03 (m, 2H), 0.92 (s, 3H), 0.88 (d, *J* = 6.2 Hz, 3H), 0.76 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7, 170.6, 170.5, 169.6, 157.7, 141.2, 130.6, 124.8, 75.5, 74.2, 70.8, 47.5, 45.3, 43.6, 41.1, 37.9, 34.9, 34.8, 34.7, 34.5, 31.4, 30.8, 29.0, 28.1, 27.4, 27.1, 25.7, 23.0, 22.7, 21.8, 21.7, 21.6, 17.6, 12.4 ppm;

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

$[\alpha]_D^{20}$ = + 38.7 º (c = 1.0, CH_2Cl_2).



SI-41

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl (*R*)-4-((5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-3,7,12-trioxohexadecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)pentanoate (SI-41).

On 2.0 mmol scale, general procedure A was followed with dehydrocholic acid, and purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-41** (1.12 g, 82% yield) as a yellow solid.

mp: >200 ºC;

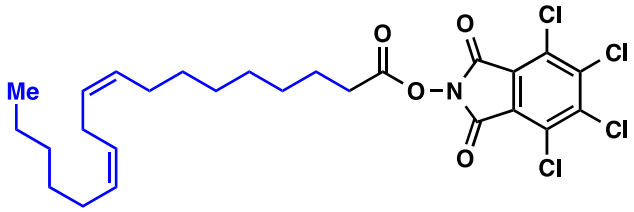
R_f = 0.41 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$) δ 2.99 – 2.85 (m, 3H), 2.78 (ddd, *J* = 16.0, 8.7, 5.2 Hz, 1H), 2.67 (dt, *J* = 16.1, 8.2 Hz, 1H), 2.43 – 2.22 (m, 6H), 2.20 – 2.14 (m, 2H), 2.13 – 1.97 (m, 5H), 1.89 (td, *J* = 11.5, 7.2 Hz, 1H), 1.73 – 1.51 (m, 5H), 1.48 – 1.30 (m, 3H), 1.14 (s, 3H), 0.95 (d, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 211.4, 208.5, 208.2, 169.0, 157.1, 140.5, 130.0, 124.3, 56.5, 51.3, 48.5, 46.4, 45.1, 44.5, 42.3, 38.2, 36.0, 35.6, 34.9, 34.8, 29.9, 27.9, 27.2, 24.7, 21.5, 18.0, 13.7, 11.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{32}H_{34}Cl_4NO_7$ $[M+H]^+$ 684.1084; found 684.1081.

$[\alpha]_D^{20}$ = +13.2º (c = 1.05, $CHCl_3$).



SI-42

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl (9*Z*,12*Z*)-octadeca-9,12-dienoate (SI-42). On 2.5 mmol scale, general procedure A was followed with linoleic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-42** as a yellow oil (1.08 g, 77%).

R_f = 0.28 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.41 – 5.30 (m, 4H), 2.80 – 2.75 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.05 (qd, *J* = 7.2, 1.3 Hz, 4H), 1.81 – 1.75 (m, 2H), 1.48 – 1.40 (m, 2H), 1.40 – 1.23 (m, 12H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.3, 157.7, 141.1, 130.6, 130.4, 130.1, 128.2, 128.0, 124.9, 31.7, 31.0, 29.7, 29.5, 29.1 (2C), 28.9, 27.4, 27.3, 25.8, 24.8, 22.8, 14.3.

HRMS (ESI-TOF, *m/z*): High resolution mass spec data could not be obtained for this compound.

SI-43

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl (*E*)-octadec-9-enoate (SI-43).

On 2.5 mmol scale, general procedure A was followed with elaidic acid, and purification by flash column chromatography (silica gel, 9:1 hexanes:EtOAc) furnished *N*-hydroxy-tetrachlorophthalimide ester **SI-43** as a yellow-white solid (1.24 g, 88%).

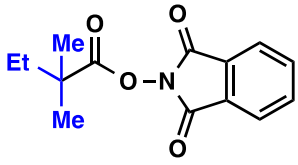
m.p.= 42 - 43 °C;

***R*$_f$** = 0.25 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.40 – 5.36 (m, 2H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.01 – 1.92 (m, 5H), 1.78 (p, *J* = 7.6 Hz, 2H), 1.48 – 1.40 (m, 2H), 1.37 – 1.16 (m, 17H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.3, 157.7, 141.1, 130.7, 130.6, 130.3, 124.9, 32.8, 32.7, 32.1, 31.0, 29.8, 29.7, 29.6, 29.5, 29.3, 29.1, 29.0, 28.9, 24.8, 22.8, 14.23.

HRMS (ESI-TOF, *m/z*): calcd for $C_{26}H_{34}Cl_4NO_4$ $[M+H]^+$ 564.1236; found 564.1240.



SI-44

1,3-dioxoisoindolin-2-yl 2,2-dimethylbutanoate (SI-44).

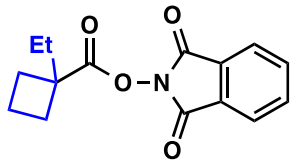
Following the General Procedure A with 2,2-dimethylbutanoic acid (5.0 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-44** (1.31 g, 90% yield) as a colorless oil.

***R*$_f$** = 0.46 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.85-7.88 (m, 2H), 7.76-7.79 (m, 2H), 1.78 (q, *J* = 7.8 Hz, 2H), 1.38 (s, 6H), 1.04 (t, *J* = 7.8 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.0, 162.3, 134.8, 129.2, 124.0, 42.6, 33.7, 24.8, 9.23 ppm;

HRMS (ESI-TOF): calc'd for $C_{14}H_{16}NO_4$ $[M+H]^+$ 262.1074; found 262.1075.



SI-45

1,3-dioxoisoindolin-2-yl 1-ethylcyclobutane-1-carboxylate (SI-45).

Following the General Procedure A with 1-ethylcyclobutane-1-carboxylic acid (*48*) (3.2 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-45** (705 mg, 81% yield) as a white solid.

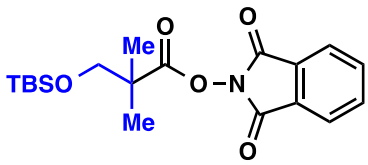
m.p.= 50-51 ºC;

***R*$_f$** = 0.46 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.90 (m, 2H), 7.77-7.80 (m, 2H), 2.66-2.70 (m, 2H), 1.99-2.10 (m, 6H), 1.03 (t, J = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 173.1, 162.4, 134.8, 129.3, 124.0, 47.4, 30.9, 30.1, 16.0, 9.1 ppm;

HRMS (ESI-TOF): calc'd for $C_{15}H_{16}NO_4$ $[M+H]^+$ 274.1074; found 274.1075.



SI-46

1,3-dioxoisoindolin-2-yl 3-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethylpropanoate (SI-46).

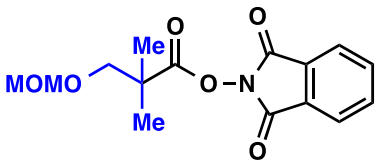
Following the General Procedure A with 3-((tert-butyldimethylsilyl)oxy)-2,2-dimethylpropanoic acid (*49*) (5.0 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-46** (1.73 g, 92% yield) as colorless oil.

***R**f* = 0.55 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86-7.88 (m, 2H), 7.76-7.79 (m, 2H), 3.75 (s, 2H), 1.39 (s, 6H), 0.92 (s, 9H), 0.09 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9, 162.0, 134.7, 129.2, 124.0, 69.3, 45.0, 26.0, 22.0, 18.4, -5.50 ppm;

HRMS (ESI-TOF): calc'd for $C_{19}H_{28}NO_5Si$ $[M+H]^+$ 378.1731; found 378.1735.



SI-47

1,3-dioxoisoindolin-2-yl 3-(methoxymethoxy)-2,2-dimethylpropanoate (SI-47).

Following the General Procedure A with 3-(methoxymethoxy)-2,2-dimethylpropanoic acid (*50*) (2.0 mmol), purification by flash column (silica gel, 15:1 to 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-47** (522 mg, 85% yield) as a white solid.

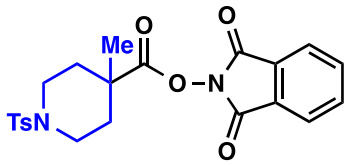
m.p.= 30-31 ºC;

***R**f* = 0.31 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86-7.88 (m, 2H), 7.77-7.78 (m, 2H), 4.71 (s, 2H), 3.70 (s, 2H), 3.41 (s, 3H), 1.44 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ172.6, 162.1, 134.8, 129.2, 124.0, 97.0, 74.0, 55.5, 43.4, 22.5 ppm;

HRMS (ESI-TOF): calc'd for $C_{15}H_{18}NO_6$ $[M+H]^+$ 308.1129; found 308.1131.



SI-48

1,3-dioxoisoindolin-2-yl 4-methyl-1-tosylpiperidine-4-carboxylate (SI-48).

Following the General Procedure A with 4-methyl-1-tosylpiperidine-4-carboxylic acid (1 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-48** (316 mg, 71 % yield) as a white solid.

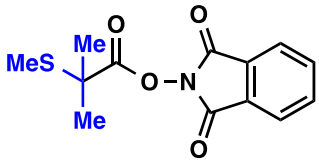
m.p.= 159-160 ºC;

R_f = 0.75 (silica gel, 10:1 CH_2Cl_2:Et_2O);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.81-7.84 (m, 2H), 7.76-7.79 (m, 2H), 7.65 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 3.63 (d, *J* = 13.2 Hz, 2H), 2.70 (t, *J* = 11.4 Hz, 2H), 2.44 (s, 3H), 2.33 (d, d, *J* = 13.8 Hz, 2H), 1.69-1.74 (m, 2H), 1.44 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.4, 161.8, 143.7, 134.9, 133.4, 129.9, 129.0, 127.7, 124.0, 43.6, 41.2, 34.5, 26.2, 21.7 ppm.

HRMS (ESI-TOF): calc'd for $C_{22}H_{23}N_2O_6S$ $[M+H]^+$ 443.1271; found 443.1274.



SI-49

1,3-dioxoisoindolin-2-yl 2-methyl-2-(methylthio)propanoate (SI-49).

Following the General Procedure A with 2-methyl-2-(methylthio)propanoic acid (*51*) (7.45 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-49** (1.75 g, 84% yield) as a white solid.

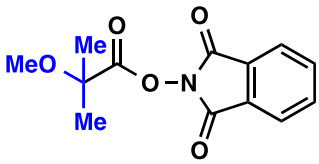
m.p.= 118-120 ºC;

R_f = 0.56 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86-7.90 (m, 2H), 7.77-7.80 (m, 2H), 2.28 (s, 3H), 1.69 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3, 162.0, 134.9, 129.1, 124.1, 45.6, 25.1, 13.2 ppm;

HRMS (ESI-TOF): calc'd for $C_{13}H_{14}NO_4S$ $[M+H]^+$ 280.0638; found 280.0643.



SI-50

1,3-dioxoisoindolin-2-yl 2-methoxy-2-methylpropanoate (SI-50).

Following the General Procedure A with 2-methoxy-2-methylpropanoic acid (*52*) (1.0 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-50** (270 mg, 99% yield) as a white solid.

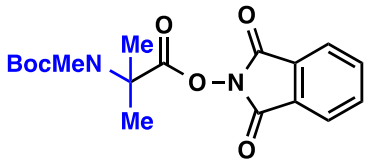
m.p.= 63 ºC;

R_f = 0.41 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.87-7.92 (m, 2H), 7.77-7.81 (m, 2H), 3.45 (s, 3H), 1.63 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.1, 162.0, 135.0, 129.1, 124.1, 77.9, 53.1, 24.6 ppm;

HRMS (ESI-TOF): calc'd for $C_{13}H_{14}NO_5$ $[M+H]^+$ 264.0866; found 264.0866.



SI-51

1,3-dioxoisoindolin-2-yl 2-((*tert*-butoxycarbonyl)(methyl)amino)-2-methylpropanoate (SI-51).

Following the General Procedure A with 2-((tert-butoxycarbonyl)(methyl)amino)-2-methylpropanoic acid (*53*) (5.0 mmol), purification by flash column (silica gel, 4:1 to 3:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-51** (1.18 g, 65% yield) as a white solid.

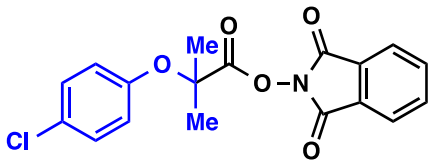
m.p.= 124 ºC;

R_f = 0.33 silica gel, (4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.84-7.87 (m, 2H), 7.74-7.77 (m, 2H), 2.98 (s, 3H), 1.65 (s, 6H), 1.54 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.6, 162.0, 155.2, 134.7, 129.2, 123.9, 81.3 (*br*), 60.3, 29.6, 28.2, 24.7 (*br*) ppm;

HRMS (ESI-TOF): calc'd for $C_{18}H_{23}N_2O_6$ $[M+H]^+$ 363.1551; found 363.1551.



SI-52

1,3-dioxoisoindolin-2-yl 2-(4-chlorophenoxy)-2-methylpropanoate (SI-52).

Following the General Procedure A with clofibric acid (5.0 mmol), purification by flash column (silica gel, 10:1 hexanes:EtOAc) afforded *N*-hydroxy-phthalimide ester **SI-52** (1.65 g, 92% yield) as a white solid.

m.p. = 103 ºC;

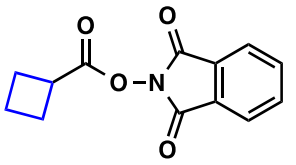
R_f = 0.48 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89-7.93 (m, 2H), 7.79-7.82 (m, 2H), 7.28-7.30 (m, 2H), 7.03-7.06 (m, 2H), 1.78 (s, 6H) ppm.

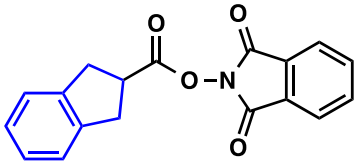
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7, 161.9, 153.3, 135.0, 129.5, 129.1, 128.6, 124.2, 121.8, 79.1, 25.7 ppm;

HRMS (ESI-TOF): calc'd for $C_{18}H_{15}ClNO_5$ $[M+H]^+$ 360.0633; found 360.0639.

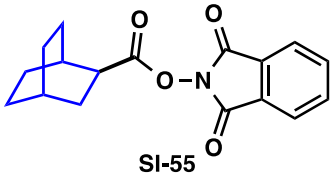
The following redox-active esters were prepared following the literature procedure, and all spectra data matches that which is previously reported. See ref. 21 for SI-53 – SI-56 and ref. 54 for SI-57 – SI-59.



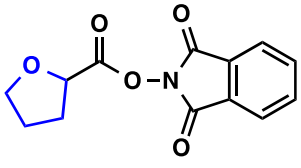
SI-53



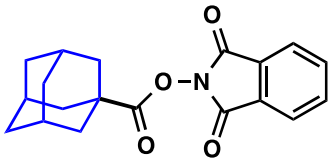
SI-54



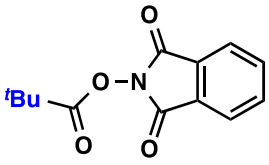
SI-55



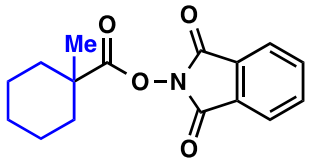
SI-56



SI-57

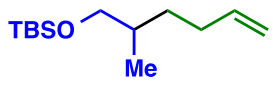


SI-58



SI-59

Experimental Procedures and Characterization Data for Products



SI-2

***tert*-butyldimethyl((2-methylhex-5-en-1-yl)oxy)silane (SI-2)**

On 1.0 mmol scale, general procedure B was followed with both (+)-**SI-1** and (-)-**SI-1** seperately. Purification by PTLC (silica gel, 97.5:2.5 hexanes:EtOAc) afforded **SI-2** as a colorless oil (0.011 g, 48%). The reported value for the R-enantiomer of **SI-2** is $[\alpha]_D^{30}$ = + 2.2 (c = 2.68, CH_2Cl_2).(*55*)

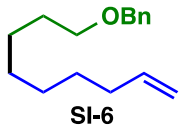
R_f = 0.34 (hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.1, 6.6 Hz, 1H), 5.00 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 3.45 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.38 (dd, *J* = 9.8, 6.4 Hz, 1H), 2.14 – 2.08 (m, 1H), 2.06 – 1.99 (m, 1H), 1.65 – 1.57 (m, 1H), 1.53 – 1.46 (m, 1H), 1.16 (dddd, *J* = 13.6, 9.6, 8.1, 5.6 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.4, 114.2, 68.4, 35.4, 32.6, 31.4, 26.1, 18.5, 16.7, -5.2 (2C).

GC/MS (EI): 213 (1%, -Me), 171 (20%, -*t*Bu), 75 (100%).

$[\alpha]_D^{20}$ = 0 ° (c = 1.0, CH_2Cl_2)



SI-6

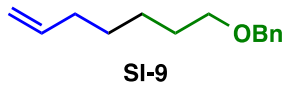
((Non-8-en-1-yloxy)methyl)benzene (SI-6). On 0.1 mmol scale, general procedure B was followed. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **SI-6** (12 mg, 53% yield) as a colorless oil.

R_f = 0.62 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, 5H), 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 4.50 (s, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.06 – 2.01 (m, 2H), 1.68 – 1.58 (m, 2H), 1.45 – 1.21 (m, 8H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.7, 138.3, 127.9, 127.2, 127.0, 113.7, 72.4, 70.04, 33.3, 29.3, 28.9, 28.6, 28.4, 25.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{25}O$ $[M+H]^+$; 233.1900, found 233.1912.



SI-9

((hept-6-en-1-yloxy)methyl)benzene (SI-9).

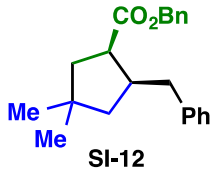
On 0.1 mmol scale, *N*-hydroxy-tetrachlorophthalimide **SI-8** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes: Et_2O) furnished coupling product **SI-9** as a colorless oil (10.4 mg, 51 %).

***R*$_f$** = 0.64 (silica gel, 10:1 hexanes:Et_2O);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.33 (m, 4H), 7.32 – 7.26 (m, 1H), 5.81 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 5.00 (ddt, *J* = 17.1, 2.2, 1.6 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 4.51 (s, 2H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.06 (tdd, *J* = 6.8, 5.2, 1.5 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.44 – 1.36 (m, 4H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.1, 138.8, 128.5, 127.8, 127.6, 114.4, 73.0, 70.6, 34.0, 29.7, 28.9, 25.9 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587; found 205.1591.



SI-12

benzyl (1*R*,2*R*)-2-benzyl-4,4-dimethylcyclopentane-1-carboxylate (SI-12).

Following the General Procedure D with **SI-11** (0.1 mmol), purification by flash column (silica gel, 20:1 hexanes:EtOAc) and PTLC (silica gel, 20:1 hexanes:EtOAc) afforded **SI-12** (26.1 mg, 81% yield) as a colorless oil.

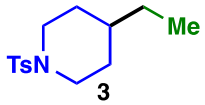
***R*$_f$** = 0.64 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09-7.37 (m, 10H), 5.08 (dd, *J* = 42.5, 12.0 Hz, 2H), 3.11 (dd, *J* = 16.5, 8.0 Hz, 1H), 2.80 (dd, *J* = 13.0, 5.0 Hz, 1H), 2.63-2.71 (m, 1H), 2.39

(dd, *J* = 13.0, 10.5 Hz, 1H), 1.93 (dd, *J* = 13.5, 8.5 Hz, 1H), 1.68 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.41 (d, *J* = 8.5 Hz, 2H), 1.11 (s, 3H), 0.92 (s, 3H) ppm;

^{13}C NMR (125 MHz, $CDCl_3$): δ 175.4, 141.3, 136.2, 128.9, 128.7, 128.6, 128.4 (2C), 126.0, 66.3, 47.1, 46.6, 43.8, 43.5, 38.4, 38.0, 30.1, 29.4 ppm;

HRMS (ESI-TOF): calc'd for $C_{22}H_{27}O_2$ $[M+H]^+$ 323.2006; found 323.2018.



3

4-ethyl-1-tosylpiperidine (3).

I. 0.1 mmol scale.

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 6:1 hexanes:EtOAc) furnished coupling product **3** as a white solid (22.4 mg, 84 %).

II. Gram-scale.

One gram of **1b** was used, following the gram-scale procedure B. After purification by column chromatography (silica gel, 10:1 to 6:1 hexanes:EtOAc) afforded **3** as a white solid (0.379 g, 79%).

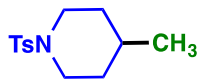
m.p.= 58 °C;

***R*$_f$** = 0.58 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 – 7.62 (m, 2H), 7.33 – 7.29 (m, 2H), 3.77 – 3.72 (m, 2H), 2.43 (s, 3H), 2.20 (td, *J* = 12.0, 2.6 Hz, 2H), 1.74 – 1.68 (m, 2H), 1.30 – 1.20 (m, 4H), 1.05 (dddd, *J* = 14.5, 11.4, 7.0, 3.2 Hz, 1H), 0.84 (t, *J* = 7.5 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.4, 129.7, 127.9, 46.7, 37.0, 31.3, 28.9, 21.7, 11.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{22}NSO_2$ $[M+H]^+$ 268.1366; found 268.1365.



4

4-methyl-1-tosylpiperidine (4).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **4** as a white solid (18.3 mg, 72 %).

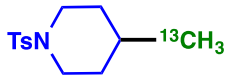
m.p.= 66 °C;

R_f = 0.62 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 11.8 Hz, 2H), 2.45 (s, 3H), 2.28 – 2.19 (m, 2H), 1.72 – 1.63 (m, 2H), 1.36 – 1.24 (m, 3H), 0.92 (d, *J* = 5.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.8, 132.9, 129.1, 127.3, 46.0, 32.9, 29.7, 21.1, 21.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_{20}NSO_2$ $[M+H]^+$ 254.1209; found 254.1208.



4-^{13}C

4-(methyl-^{13}*C*)-1-tosylpiperidine (4-^{13}C)

Part I. Procedure for preparation of Zn(^{13}Me)$_2$:

To a dry two-necked 25 ml flask with stir bar under nitrogen was weighed $ZnCl_2$ (13.6 mg, 0.100 mmol). This was placed under vacuum at 150 °C for 3 h, cooled to room temperature and then to 0 °C in an ice-water bath under nitrogen. To a separate dry flask with stir bar under nitrogen was weighed Mg powder (5.4 mg, 0.22 mmol) and 0.20 ml of anhydrous Et_2O was added. To this was syringed in $^{13}CH_3I$ (12.4 µL, 0.20 mmol, Isotec 99 atom %) in 0.20 mL diethyl ether. After stirring at room temperature for 30 min, only a small amount of Mg remained. To the $ZnCl_2$ was syringed in the freshly prepared Grignard reagent in ether dropwise over 5 min. The reaction was then stirred at room temperature for 1h.

Part II. Procedure for Ni-catalyzed coupling reaction.

To a second dry 25 ml flask with stir bar under nitrogen was weighed 4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl 1-tosylpiperidine-4-carboxylate (114.0 mg, 0.201 mmol). To this was syringed in a solution of $NiCl_2$•glyme (8.8 mg, 0.040 mmol) and di-*t*BuBipy (21.4 mg, 0.080 mmol) in DMF (2.0 mL + 0.3 mL DMF rinse). The [Ni]/L and

piperidine solution was syringed into the $Zn(^{13}CH_3)_2$ solution at room temperature. The resulting dark rust colored solution was stirred at room temperature overnight. To the reaction was added 1N HCl (1.7 mL, 1.7 mmol). After stirring for 10 min, diethyl ether (15 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2 x 15 mL). The combined ether extracts were washed with brine (1 x 10 mL), dried over Na_2SO4, filtered and the solvent was removed under reduced pressure to give a dark yellow orange solid. The crude product was coated onto silica gel (0.56 g) and then was purified by flash chromatography 2x (12.0 g RediSep Rf Gold, eluent = 6:1 hexane:EtOAc). Pure fractions of the product were pooled, and the solvent was removed under reduced pressure and then dried under vacuum to give 29.1 mg of white solid (56 % yield).

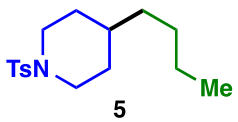
LC/MS Conditions:

Finnigan LXQ LC/MS System. Detection = ESI (+) ion LC Column = Phenomenex Luna 3 μm, C18, 50 X 3.0 mm, Flowrate = 0.50 ml/min, UV detection by PDA from 200 - 400 nm. Gradient (Mobile Phase A = 1000 H_2O : 1 Formic acid, Mobile Phase B = 1000 MeCN : 1 Formic acid) 0 min 10% B, 10 min 100% B).

LC/MS of product. Retention time = 7.17 min, m/z (+ ion) = 255.25(100%) /256.17(12%) /257.17(7%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.68 - 7.65 (m, 2H), 7.36 - 7.32 (m, 2H), 3.79 - 3.73 (m, 2H), 2.45 (s, 3H), 2.29 - 2.21 (m, 2H), 1.68 (dd, *J* = 9.4, 2.4 Hz, 2H), 1.29 - 1.27 (m, 3H), 1.08 (d, *J* = 5.7 Hz, 1.5H), 0.77 (d, *J* = 5.6 Hz, 1.5H). The two peaks at 1.08 and 0.77 ppm are actually a single system with a large J ^{13}C-^1H coupling constant of 124 Hz. Taking this into account gives 0.93 (dd, *J* = 5.6 Hz and *J* ^{13}C-^1H = 124 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$): δ 143.3, 133.4, 129.5, 127.7, 46.5, 33.4, 30.0, 24.7, 21.5. Peak at 21.5 ppm is the ^{13}C methyl.



5

4-(cyclohexylmethyl)-1-tosylpiperidine (5).

On 0.1 mmol scale, **1b** was used following general procedure B with bipyridine as the ligand. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **5** as a white solid (22.7 mg, 77 %).

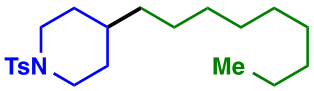
m.p.= 48-50 °C;

R_f = 0.62 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 3.75 (d, *J* = 11.6 Hz, 2H), 2.43 (s, 3H), 2.20 (td, *J* = 11.9, 2.6 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.34 – 1.17 (m, 8H), 1.13 (tdd, *J* = 10.0, 6.2, 2.9 Hz, 1H), 0.86 (t, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.4, 129.7, 127.9, 46.7, 35.9, 35.3, 31.7, 28.9, 22.9, 21.7, 14.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{26}NSO_2$ $[M+H]^+$ 296.1679; found 296.1680.



6

4-nonyl-1-tosylpiperidine (6).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **6** as a white solid (22.7 mg, 62 %).

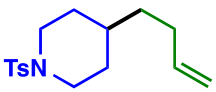
m.p.= 45°C;

R_f = 0.55 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.74 (d, *J* = 11.7 Hz, 2H), 2.42 (s, 3H), 2.20 (td, *J* = 11.9, 2.5 Hz, 2H), 1.70 (d, *J* = 12.9 Hz, 2H), 1.31 – 1.16 (m, 18H), 1.15 – 1.09 (m, 1H), 0.86 (t, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.4, 129.6, 127.9, 46.7, 36.2, 35.2, 32.0, 31.7, 29.8, 29.7, 29.7, 29.4, 26.7, 22.8, 21.7, 14.2 ppm;

HRMS (ESI-TOF, *m/z*): calcfd for $C_{21}H_{36}NSO_2$ $[M+H]^+$ 366.2461; found 366.2454.



7

4-(but-3-en-1-yl)-1-tosylpiperidine (7).

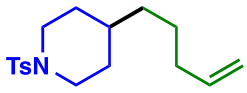
On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **7** as a colorless oil (22.4 mg, 76 %).

R_f = 0.43 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 – 7.62 (m, 2H), 7.33 – 7.29 (m, 2H), 5.73 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 4.96 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.91 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 3.75 (dt, *J* = 11.3, 2.6 Hz, 2H), 2.42 (s, 3H), 2.20 (td, *J* = 11.9, 2.6 Hz, 2H), 2.04 – 1.99 (m, 2H), 1.74 – 1.68 (m, 2H), 1.34 – 1.23 (m, 4H), 1.18 (dtt, *J* = 18.5, 8.0, 3.6 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 138.6, 133.3, 129.7, 127.9, 114.7, 46.6, 35.2, 34.6, 31.5, 30.8, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{24}NSO_2$ $[M+H]^+$ 294.1522; found 294.1526.



8

4-(pent-4-en-1-yl)-1-tosylpiperidine (8).

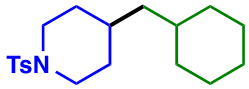
On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **8** as a colorless oil (22.0 mg, 72 %).

R_f = 0.57 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 – 7.62 (m, 2H), 7.31 (d, *J* = 7.7 Hz, 2H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.96 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.92 (ddt, *J* = 10.2, 2.2, 1.2 Hz, 1H), 3.78 – 3.72 (m, 2H), 2.43 (s, 3H), 2.20 (td, *J* = 11.9, 2.6 Hz, 2H), 2.03 – 1.96 (m, 2H), 1.74 – 1.67 (m, 2H), 1.36 – 1.29 (m, 2H), 1.29 – 1.25 (m, 2H), 1.25 – 1.19 (m, 2H), 1.18 – 1.09 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.8, 133.3, 129.7, 127.9, 127.9, 114.6, 46.7, 35.6, 35.2, 33.9, 31.6, 26.0, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{17}H_{26}NSO_2$ $[M+H]^+$ 308.1679; found 308.1664.



9

4-(cyclohexylmethyl)-1-tosylpiperidine (9).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **9** as a white solid (18.8 mg, 56 %).

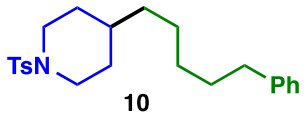
m.p.= 99-101 °C;

R_f = 0.54 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.34 – 7.29 (m, 2H), 3.74 (d, *J* = 11.7 Hz, 2H), 2.43 (s, 3H), 2.25 – 2.14 (m, 2H), 1.70 – 1.54 (m, 7H), 1.29 – 1.21 (m, 4H), 1.20 – 1.08 (m, 3H), 1.06 (t, *J* = 6.3 Hz, 2H), 0.84 – 0.75 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.3, 129.7, 127.9, 46.7, 44.1, 34.3, 33.6, 32.1, 31.9, 26.8, 26.4, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{19}H_{30}NSO_2$ $[M+H]^+$ 336.1992; found 336.1996.



10

4-(5-phenylpentyl)-1-tosylpiperidine (10).

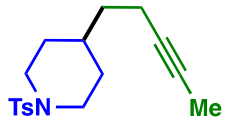
On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **10** as a colorless oil (32.4 mg, 84 %).

R_f = 0.57 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.2 Hz, 2H), 7.34 – 7.29 (m, 2H), 7.28 – 7.24 (m, 1H), 7.18 – 7.12 (m, 4H), 3.74 (d, *J* = 11.7 Hz, 2H), 2.62 – 2.53 (t, *J* = 7.2, 2H), 2.43 (s, 3H), 2.19 (td, *J* = 12.0, 2.6 Hz, 2H), 1.73 – 1.65 (m, 2H), 1.57 (dd, *J* = 15.2, 7.3 Hz, 2H), 1.31 – 1.22 (m, 6H), 1.19 (dd, *J* = 8.6, 5.0 Hz, 2H), 1.11 (dddt, *J* = 14.1, 10.9, 6.6, 3.3 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 142.8, 133.4, 129.7, 128.5, 128.4, 127.9, 125.8, 46.7, 36.1, 36.1, 35.2, 31.7, 31.5, 29.5, 26.6, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{23}H_{32}NSO_2$ $[M+H]^+$ 386.2148; found 386.2138.



11

4-(pent-3-yn-1-yl)-1-tosylpiperidine (11).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **11** as a white solid (25.6 mg, 84 %).

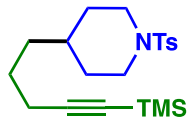
m.p.= 107-108 °C;

R_f = 0.39 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 – 7.61 (m, 2H), 7.34 – 7.29 (m, 2H), 3.75 (d, *J* = 11.7 Hz, 2H), 2.43 (s, 3H), 2.23 (td, *J* = 11.6, 2.5 Hz, 2H), 2.11 (tq, *J* = 7.2, 2.6 Hz, 2H), 1.75 – 1.69 (m, 5H), 1.38 (q, *J* = 6.8 Hz, 2H), 1.35 – 1.23 (m, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 142.9, 132.8, 129.1, 127.3, 78.1, 75.3, 45.9, 34.6, 33.4, 30.6, 21.1, 15.4, 3.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{17}H_{24}NSO_2$ $[M+H]^+$ 306.1522; found 306.1516.



12

1-tosyl-4-(5-(trimethylsilyl)pent-4-yn-1-yl)piperidine (12).

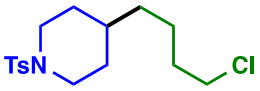
On 0.1 mmol scale, **1a** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **12** as a colorless oil (29.8 mg, 77 %).

R_f = 0.57 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.31 (dd, *J* = 8.5, 0.8 Hz, 2H), 3.81 – 3.68 (m, 2H), 2.42 (s, 3H), 2.21 (td, *J* = 11.8, 2.6 Hz, 2H), 2.16 (t, *J* = 7.1 Hz, 2H), 1.71 (d, *J* = 12.4 Hz, 2H), 1.51 – 1.42 (m, 2H), 1.33 – 1.24 (m, 4H), 1.22 – 1.13 (m, 1H), 0.11 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.3, 129.7, 127.9, 107.2, 84.8, 46.6, 35.3, 34.8, 31.6, 25.8, 21.7, 20.0, 0.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{32}NSiSO_2$ $[M+H]^+$ 378.1918; found 378.1919.



13

4-(4-chlorobutyl)-1-tosylpiperidine (13).

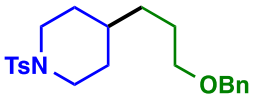
On 0.1 mmol scale, **1a** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **13** as a white solid (26.6 mg, 81 %).

***R*$_f$** = 0.36 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 3.75 (dt, *J* = 12.2, 3.2 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 2.42 (s, 3H), 2.20 (td, *J* = 12.0, 2.5 Hz, 2H), 1.75 – 1.66 (m, 4H), 1.44 – 1.35 (m, 2H), 1.32 – 1.24 (m, 2H), 1.24 – 1.19 (m, 2H), 1.19 – 1.10 (m, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.5, 133.3, 129.7, 127.8, 46.6, 45.1, 35.4, 35.1, 32.7, 31.6, 24.0, 21.6 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{25}NClSO_2$ $[M+H]^+$ 330.1289; found 330.1277.



14

4-(3-(benzyloxy)propyl)-1-tosylpiperidine (14).

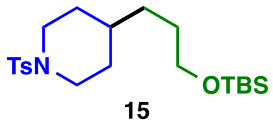
On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **14** as a colorless oil (29.9 mg, 77 %).

***R*$_f$** = 0.55 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 – 7.61 (m, 2H), 7.34 – 7.29 (m, 6H), 7.28 – 7.25 (m, 1H), 4.47 (s, 2H), 3.75 (dt, *J* = 11.3, 3.3 Hz, 2H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 2.19 (td, *J* = 11.9, 2.6 Hz, 2H), 1.74 – 1.68 (m, 2H), 1.60 – 1.53 (m, 2H), 1.32 – 1.23 (m, 4H), 1.14 (dtd, *J* = 15.0, 7.9, 7.4, 3.5 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 138.6, 133.3, 129.7, 128.5, 127.9, 127.7, 127.7, 73.1, 70.5, 46.6, 35.1, 32.7, 31.6, 27.0, 21.6 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{22}H_{30}NSO_3$ $[M+H]^+$ 388.1941; found 388.1942.



15

4-(3-((tert-butyldimethylsilyl)oxy)propyl)-1-tosylpiperidine (15).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **15** as a white solid (30.8 mg, 75 %).

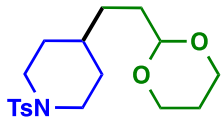
m.p.= 39-41 °C;

R_f = 0.54 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.65 – 7.61 (m, 2H), 7.33 – 7.29 (m, 2H), 3.74 (dt, *J* = 11.3, 2.5 Hz, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 2.42 (s, 3H), 2.21 (td, *J* = 11.9, 2.6 Hz, 2H), 1.75 – 1.68 (m, 2H), 1.50 – 1.42 (m, 2H), 1.32 – 1.21 (m, 4H), 1.15 (dddd, *J* = 14.8, 8.0, 6.9, 3.6 Hz, 1H), 0.86 (s, 9H), 0.01 (s, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.4, 129.7, 127.9, 63.3, 46.6, 35.1, 32.4, 31.7, 30.0, 26.0, 21.7, 18.5, -5.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{38}NSO_3$ $[M+H]^+$ 412.2336; found 412.2327.



16

4-(2-(1,3-dioxan-2-yl)ethyl)-1-tosylpiperidine (16).

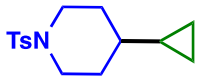
On 0.1 mmol scale, **1b** was used following general procedure B with bipyridine. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **16** as a colorless oil (25.8 mg, 73 %).

R_f = 0.16 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.6 Hz, 2H), 4.45 (t, *J* = 5.1 Hz, 1H), 4.07 (ddt, *J* = 10.5, 5.0, 1.4 Hz, 2H), 3.77 – 3.69 (m, 4H), 2.42 (s, 3H), 2.20 (td, *J* = 11.9, 2.6 Hz, 2H), 2.04 (dtt, *J* = 13.5, 12.5, 5.0 Hz, 1H), 1.74 – 1.67 (m, 2H), 1.57 – 1.50 (m, 2H), 1.35 – 1.21 (m, 5H), 1.13 (dtd, *J* = 15.0, 7.8, 7.4, 3.5 Hz, 1H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.3, 129.7, 127.9, 102.4, 67.0, 46.6, 35.2, 32.6, 31.6, 30.3, 25.9, 21.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{28}NSO_4$ $[M+H]^+$ 354.1734; found 354.1722.



17

4-cyclopropyl-1-tosylpiperidine (17).

On 0.1 mmol scale, **1b** was used following general procedure B. The reaction was quenched with 1M HCl and purified by PTLC (silica gel, 6:1 hexanes:EtOAc) to furnish coupling product **17** as a white solid (20.5 mg, 73 %)

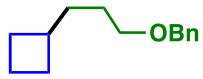
m.p.= 94-95°C;

R_f = 0.67 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 3.73 (d, *J* = 12.0, 2H), 2.42 (s, 3H), 2.19 (td, *J* = 11.8, 2.7 Hz, 2H), 1.83 – 1.73 (m, 2H), 1.45 (qd, *J* = 12.0, 4.1 Hz, 2H), 0.49 (ddt, *J* = 13.3, 8.8, 4.4 Hz, 1H), 0.38 (m, 3H), -0.02 (q, *J* = 4.9 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.4, 133.3, 129.6, 127.8, 46.6, 40.7, 31.4, 21.6, 16.4, 3.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{22}SNO_2$ $[M+H]^+$ 280.1366; found 280.1367.



18

((3-cyclobutylpropoxy)methyl)benzene (18).

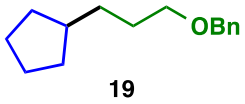
On 0.1 mmol scale, **SI-53** was used following general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **18** (15 mg, 75% yield) as a colorless oil.

R_f = 0.78 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.15 (m, 5H), 4.52 (s, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 2.28 (p, *J* = 7.8 Hz, 1H), 2.13 – 1.95 (m, 2H), 1.93 – 1.75 (m, 2H), 1.69 – 1.41 (m, 6H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.5, 72.8, 70.6, 36.0, 33.4, 28.3, 27.5, 18.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{21}O$ $[M+H]^+$ 205.1587; found 205.1588.



19

((3-cyclopentylpropoxy)methyl)benzene (19).

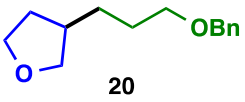
On 0.1 mmol scale, **SI-13** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **19** as a colorless oil (14.3 mg, 66 %).

***R*$_f$** = 0.70 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 4H), 7.30 – 7.27 (m, 1H), 4.51 (s, 2H), 3.47 (t, *J* = 6.8 Hz, 2H), 1.81 – 1.71 (m, 3H), 1.68 – 1.62 (m, 2H), 1.62 – 1.56 (m, 2H), 1.54 – 1.67 (m, 2H), 1.40 – 1.34 (m, 2H), 1.12 – 1.04 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.3, 127.9, 127.2, 127.0, 72.4, 70.4, 39.6, 32.2, 32.1, 28.6, 24.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{23}O$ $[M+H]^+$ 219.1743; found 219.1743.



20

3-(3-(benzyloxy)propyl)tetrahydrofuran (20).

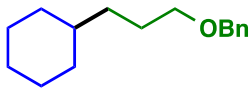
On 0.1 mmol scale, **SI-14** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **20** as a colorless oil (14.5 mg, 66 %).

***R*$_f$** = 0.48 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 4H), 7.30-7.26 (m, 1H), 4.50 (s, 2H), 3.90 (t, *J* = 7.7 Hz, 1H), 3.84 (td, *J* = 8.2, 4.6 Hz, 1H), 3.74 (q, *J* = 7.8 Hz, 1H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.33 (t, *J* = 7.8 Hz, 1H), 2.18 (hept, *J* = 7.5 Hz, 1H), 2.03 (dtd, *J* = 12.2, 7.5, 4.6 Hz, 1H), 1.70 – 1.57 (m, 2H), 1.54 – 1.42 (m, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.1, 127.9, 127.2, 127.1, 73.0, 72.5, 69.8, 67.5, 38.8, 32.0, 29.4, 28.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{21}O$ $[M+H]^+$ 221.1536; found 221.1536.



21

((3-cyclohexylpropoxy)methyl)benzene (21).

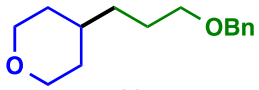
On 0.1 mmol scale, **SI-15** was used following general procedure B. Bipyridyl was used as the ligand. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished coupling product **21** as a colorless oil (17.5 mg, 75 %).

R_f = 0.70 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.31 (m, 4H), 7.31 – 7.26 (m, 1H), 4.51 (s, 2H), 3.45 (t, *J* = 6.7 Hz, 2H), 1.74 – 1.66 (m, 4H), 1.66 – 1.60 (m, 3H), 1.29 – 1.08 (m, 6H), 0.92 – 0.88 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.3, 127.9, 127.2, 127.0, 72.4, 70.5, 37.1, 33.4, 32.9, 26.7, 26.3, 26.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{25}O$ $[M+H]^+$ 233.1900; found 233.1902.



22

4-(3-(benzyloxy)propyl)tetrahydro-2H-pyran (22).

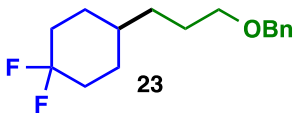
On 0.1 mmol scale, **SI-16** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **22** as a colorless oil (14.3 mg, 61 %)

R_f = 0.57 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 – 7.31 (m, 4H), 7.30 – 7.27 (m, 1H), 4.51 (s, 2H), 3.94 (ddd, *J* = 11.7, 4.8, 1.7 Hz, 2H), 3.46 (t, *J* = 6.6 Hz, 2H), 3.36 (td, *J* = 11.7, 2.1 Hz, 2H), 1.68 – 1.56 (m, 4H), 1.51 – 1.42 (m, 1H), 1.35 – 1.29 (m, 2H), 1.29 – 1.23 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.7, 128.5, 127.8, 127.7, 73.1, 70.7, 68.3, 35.0, 33.5, 33.3, 26.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{23}O_2$ $[M+H]^+$ 235.1693; found 235.1693.



23

((3-(4,4-difluorocyclohexyl)propoxy)methyl)benzene (23)

On 0.1 mmol scale, general procedure B was followed with **SI-17** and bipyridine. Purification by PTLC (97.5:2.5 hexanes:EtOAc) afforded **23** as a colorless oil (0.019 g, 71%).

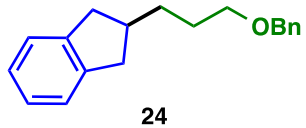
***R*$_f$** = 0.50 (silica gel, 9:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 4.50 (s, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.11 – 2.01 (m, 2H), 1.81 – 1.74 (m, 2H), 1.74 – 1.58 (m, 4H), 1.36 – 1.31 (m, 3H), 1.29 – 1.20 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.7, 128.5, 127.8, 127.7, 124.0 (dd, J_1 = 241.4, 240.0 Hz), 73.1, 70.6, 35.8, 33.6 (dd, *J* = 25.3, 22.1 Hz), 32.4, 29.1 (d, *J* = 9.7 Hz), 27.6 ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ -91.74 (d, *J* = 234.7 Hz), -102.23 (d, *J* = 234.1 Hz) ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{21}F_2O$ $[M-H]^-$ 267.1566; found 267.1563.



24

2-(3-(Benzyloxy)propyl)-2,3-dihydro-1*H*-indene (24).

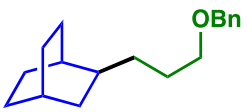
On 0.1 mmol scale, **SI-54** was used following general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **24** (24 mg, 89% yield) as a colorless oil.

***R*$_f$** = 0.57 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.38 (m, 4H), 7.36 – 7.28 (m, 1H), 7.25 – 7.19 (m, 2H), 7.19 – 7.11 (m, 2H), 4.55 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.08 (dd, *J* = 15.4, 7.8 Hz, 2H), 2.63 (dd, *J* = 15.5, 8.2 Hz, 2H), 2.49 (h, *J* = 7.7 Hz, 1H), 1.81 – 1.69 (m, 2H), 1.68 – 1.55 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 138.6, 128.4, 127.6, 127.5, 126.0, 124.4, 73.0, 71.0, 40.1, 39.3, 32.3, 28.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{19}H_{23}O$ $[M+H]^+$ 267.1743; found 267.1741.



25

2-(3-(benzyloxy)propyl)bicyclo[2.2.2]octane (25).

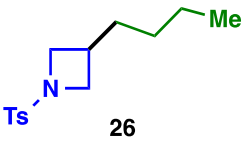
On 0.1 mmol scale, **SI-55** was used and followed general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **25** (17 mg, 65% yield) as a colorless oil.

***R*$_f$** = 0.67 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 6.95 (m, 5H), 4.51 (s, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 1.85 – 0.94 (m, 18H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.7, 128.3, 127.6, 127.5, 72.8, 70.8, 35.7, 34.2, 32.4, 28.3, 27.8, 27.4, 26.1, 25.3, 24.8, 20.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{27}O$ $[M+H]^+$ 259.2056; found 259.2052.



26

3-butyl-1-tosylazetidine (26).

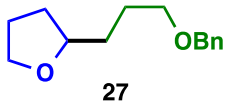
On 0.1 mmol scale, **SI-18** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 6:1 hexanes:EtOAc) furnished coupling product **26** as a colorless oil (12.3 mg, 46%).

***R*$_f$** = 0.46 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 3.83 (t, *J* = 8.0 Hz, 2H), 3.37 (dd, *J* = 7.8, 6.2 Hz, 2H), 2.46 (s, 3H), 2.37 (pt, *J* = 7.8, 6.2 Hz, 1H), 1.35 – 1.29 (m, 2H), 1.23 – 1.16 (m, 2H), 1.11 – 1.02 (m, 2H), 0.82 (t, *J* = 7.3 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 144.0, 131.9, 129.8, 128.5, 56.2, 33.4, 28.9, 28.8, 22.5, 21.7, 14.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{22}NSO_2$ $[M+H]^+$ 268.1366; found 268.1358.



27

2-(3-(Benzyloxy)propyl)tetrahydrofuran (27).

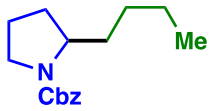
On 0.1 mmol scale, **SI-56** was used following general procedure B. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished the desired product **27** (11 mg, 51% yield) as a yellow oil.

R_f = 0.42 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.22 (m, 5H), 4.50 (s, 2H), 3.91 – 3.77 (m, 2H), 3.71 (q, *J* = 7.4 Hz, 1H), 3.50 (q, *J* = 5.9 Hz, 2H), 2.03 – 1.55 (m, 7H), 1.45 (dq, *J* = 11.9, 8.0 Hz, 1H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.6, 128.3, 127.6, 127.5, 79.1, 72.8, 70.3, 67.7, 32.3, 31.4, 26.6, 25.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{21}O_2$ $[M+H]^+$ 221.1536; found 221.1536.



28

benzyl 2-butylpyrrolidine-1-carboxylate (28)

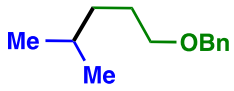
On 0.1 mmol scale, general procedure C was followed with N-Benzyloxycarbonyl-L-proline with the following modification: the reaction mixture was heated to 60 ºC for a period of 12h. Purification by flash column chromatography (silica gel, 4:1 hexanes:EtOAc) afforded **28** (0.012 g, 46%) as a colorless oil.

R_f = 0.59 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, Acetone-d_6): δ 7.42 – 7.33 (m, 4H), 7.33 – 7.27 (m, 1H), 5.19 – 5.00 (m, 2H), 3.79 (s, 1H), 3.47 – 3.25 (m, 2H), 2.00 – 1.62 (m, 3H), 1.29 (d, *J* = 37.0 Hz, 7H), 0.98 – 0.68 (m, 3H) ppm;

Note: Due to an issue with rotamers, the ^{13}C NMR spectrum is complex. For details, please see the attached corresponding spectra.

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{24}NO_2$ $[M+H]^+$ 262.1802; found 262.1804.



29

(((4-methylpentyl)oxy)methyl)benzene (29).

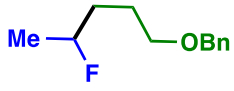
On 0.1 mmol scale, general procedure B was followed with **SI-19** and bipyridine. Purification by PTLC (97.5:2.5 hexanes:EtOAc) afforded **29** as a colorless oil (0.012 g, 62%).

R_f = 0.71 (silica gel, 9:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.35 (m, 4H), 7.30 – 7.26 (m, 1H), 4.51 (s, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 1.66 – 1.59 (m, 2H), 1.55 (h, *J* = 6.7 Hz, 1H), 1.27 – 1.22 (m, 2H), 0.89 (d, *J* = 6.7 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.9, 128.5, 127.8, 127.6, 73.1, 71.0, 35.5, 28.1, 27.8, 22.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_{21}O$ $[M+H]^+$ 193.1587; found 193.1585.



30

(((4-Fluoropentyl)oxy)methyl)benzene (30).

On 0.1 mmol scale, **SI-20** was used following general procedure B. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished the desired product **30** (11 mg, 56% yield) as a colorless oil.

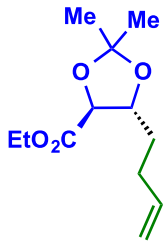
R_f = 0.47 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.28 (m, 5H), 4.85 – 4.59 (m, 1H), 4.53 (s, 2H), 3.65 – 3.41 (m, 2H), 1.88 – 1.62 (m, 4H), 1.35 (dd, *J* = 23.9, 6.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.1, 127.9, 127.2, 127.1, 90.4 (d, *J* = 164.1 Hz), 72.4, 69.5, 33.2 (d, *J* = 21.0 Hz), 25.0 (d, *J* = 4.5 Hz), 20.6 (d, *J* = 22.7 Hz) ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ -173.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{12}H_{18}FO$ $[M+H]^+$ 197.1336; found 197.1337.



31

ethyl (4*S*,5*R*)-5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (31)

On 0.1 mmol scale, general procedure B was followed with **SI-22**. Purification by PTLC (9:1 hexanes:EtOAc) afforded **31** (10:1 dr) as a colorless oil (0.009 g, 40%).

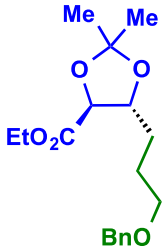
R_f = 0.59 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.83 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.00 (ddt, *J* = 10.2, 1.9, 1.3 Hz, 1H), 4.29 – 4.20 (m, 2H), 4.16 – 4.11 (m, 2H), 2.31 – 2.22 (m, 1H), 2.22 – 2.12 (m, 1H), 1.92 – 1.83 (m, 1H), 1.82 – 1.73 (m, 1H), 1.47 (d, *J* = 0.7 Hz, 3H), 1.44 (d, *J* = 0.7 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.0, 137.7, 115.3, 111.0, 79.2, 78.7, 61.5, 32.9, 29.8, 27.3, 25.8, 14.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{12}H_{21}O_4$ $[M+H]^+$ 229.1434; found 229.1437.

$[\alpha]_D^{20}$ = +16.7 º (c = 0.33, CH_2Cl_2).



32

ethyl (4*S*,5*R*)-5-(but-3-en-1-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (32)

On 0.1 mmol scale, general procedure B was followed with **SI-22**. Purification by PTLC (9:1 hexanes:EtOAc) afforded **32** (dr > 20:1) as a colorless oil (0.019 g, 59%).

R_f = 0.50 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 5.7 Hz, 4H), 7.28 (ddd, *J* = 8.3, 3.6, 2.5 Hz, 1H), 4.51 (s, 2H), 4.28 – 4.18 (m, 2H), 4.17 – 4.09 (m, 2H), 3.57 – 3.48 (m, 2H), 1.95 –

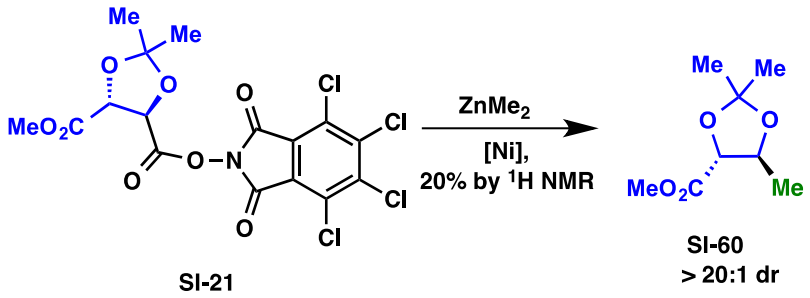
1.86 (m, 1H), 1.86 – 1.79 (m, 1H), 1.79 – 1.71 (m, 2H), 1.46 (s, 3H), 1.43 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.0, 138.7, 128.5, 127.73, 127.68, 111.0, 79.2, 79.1, 73.0, 70.0, 61.5, 30.4, 27.3, 26.0, 25.8, 14.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{18}H_{27}O_5$ $[M+H]^+$ 323.1853; found 323.1855.

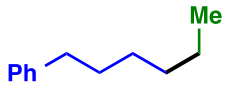
$[\alpha]_D^{20}$ = +13.4 ° (c = 1.0, CH_2Cl_2).

Assignment of stereochemistry for **31** and **32**:



SI-21 **SI-60**
> 20:1 dr

The stereochemistry of **31** and **32** was assigned to be predominantly trans based on the reaction shown above. Diagnostic peaks from the crude ^{1}H NMR spectrum of **SI-60** matches that which is published for the trans diastereomer shown above.(*56*, *57*)



33

hexylbenzene (33).

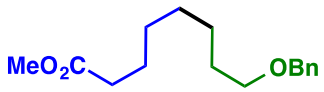
On 0.1 mmol scale, **SI-23** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, hexanes) furnished coupling product **33** as a colorless oil (9.7 mg, 60%).

***R*$_f$** = 0.88 (silica gel, hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.27 (m, 2H), 7.20 – 7.16 (m, 3H), 2.61 (t, J = 7.9 Hz, 2H), 1.66 – 1.58 (m, 2H), 1.37 – 1.27 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.1, 128.5, 128.4, 125.7, 36.2, 31.9, 31.7, 29.2, 22.8, 14.3 ppm;

The NMR data matches the reported data.(*58*)



34

methyl 8-(benzyloxy)octanoate (34).

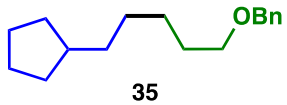
On 0.1 mmol scale, **SI-24** was used following general procedure B. Bipyridyl was used as the ligand. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **34** as a colorless oil (16.0 mg, 61 %).

R_f = 0.34 (silica gel, 10:1 hexanes:Et_2O);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 – 7.32 (m, 4H), 7.30 – 7.27 (m, 1H), 4.50 (s, 2H), 3.66 (s, 3H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.30 (t, *J* = 7.5 Hz, 2H), 1.65 – 1.57 (m, 4H), 1.40 – 1.29 (m, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 138.8, 128.5, 127.8, 127.6, 73.0, 70.5, 51.6, 34.2, 29.8, 29.2 (2C), 26.2, 25.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{25}O_3$ $[M+H]^+$ 265.1798; found 265.1798.



35

(((5-Cyclopentylpentyl)oxy)methyl)benzene (35).

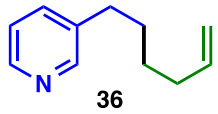
On 0.1 mmol scale, **SI-25** was used and followed general procedure B with bipyridine as the ligand. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **35** (14 mg, 59% yield) as a colorless oil.

R_f = 0.76 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39 – 7.35 (m, 4H), 7.33 – 7.28 (m, 1H), 4.53 (s, 2H), 3.49 (t, *J* = 6.7 Hz, 2H), 1.79 – 1.71 (m, 3H), 1.68 – 1.57 (m, 4H), 1.55 – 1.49 (m, 2H), 1.42 – 1.30 (m, 6H), 1.15 – 1.03 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.3, 127.9, 127.2, 127.0, 72.4, 70.1, 39.6, 35.7, 32.3, 29.4, 28.2, 26.0, 24.7 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{17}H_{27}O$ $[M+H]^+$ 247.2056; found 247.2057.



36

3-(hex-5-en-1-yl)pyridine (36).

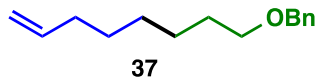
On 0.1 mmol scale, **SI-26** was used following general procedure B. The reaction was quenched with saturated NH_4Cl, and purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished coupling product **36** as a colorless oil (11.7 mg, 73%)

R_f = 0.29 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.48 – 8.41 (m, 2H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 7.8, 4.8 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.00 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.3, 1.3 Hz, 1H), 2.61 (t, *J* = 7.7 Hz, 2H), 2.13 – 2.04 (m, 2H), 1.64 (tt, *J* = 9.3, 6.9 Hz, 2H), 1.44 (tt, *J* = 7.5, 7.5 Hz, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 150.0, 147.3, 138.7, 138.0, 136.0, 123.4, 114.8, 33.6, 33.0, 30.7, 28.5 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{11}H_{16}N$ $[M+H]^+$ 162.1277; found 162.1279.



37

((oct-7-en-1-yloxy)methyl)benzene (37)

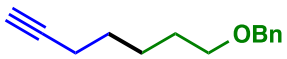
On 0.1 mmol scale, general procedure B was followed with **SI-27** and bipyridine as ligand. Purification by PTLC (PhMe) afforded **37** as a colorless oil (0.015 g, 69%).

R_f = 0.14 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.34 (m, 4H), 7.31 – 7.27 (m, 1H), 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 4.99 (dd, *J* = 17.1, 1.9 Hz, 1H), 4.93 (d, *J* = 10.2, 1.6 Hz, 1H), 4.50 (s, 2H), 3.47 (t, *J* = 6.6 Hz, 2H), 2.04 (q, *J* = 7.1 Hz, 2H), 1.62 (p, *J* = 6.7 Hz, 2H), 1.45 – 1.23 (m, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.3, 138.9, 128.5, 127.8, 127.6, 114.3, 73.0, 70.6, 33.9, 29.9, 29.1, 29.0, 26.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{23}O$ $[M+H]^+$ 219.1743; found 219.1752.



38

((hept-6-yn-1-yloxy)methyl)benzene (38).

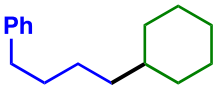
On 0.1 mmol scale, **SI-28** was used following general procedure B. The reaction was quenched with 1M HCl, and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **38** as a colorless oil (11.2 mg, 55 %).

R_f = 0.67 (silica gel, 10:1 hexanes:Et_2O);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.34 (d, *J* = 5.2 Hz, 4H), 7.30 – 7.27 (m, 1H), 4.50 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.20 (td, *J* = 7.0, 2.6 Hz, 2H), 1.94 (t, *J* = 2.7 Hz, 1H), 1.64 (dq, *J* = 7.9, 6.5 Hz, 2H), 1.59 – 1.52 (m, 2H), 1.52 – 1.46 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.8, 128.5, 127.8, 127.6, 84.7, 73.1, 70.4, 68.4, 29.4, 28.5, 25.6, 18.5 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{14}H_{19}O$ $[M+H]^+$ 203.1430; found 203.1429.



39

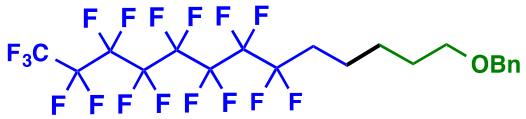
(4-cyclohexylbutyl)benzene (39). On 0.1 mmol scale, **SI-23** was used and followed general procedure B. The temperature of this reaction was 60 °C. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, hexanes) furnished coupling product **39** as a colorless oil (8.6 mg, 40%).

R_f = 0.89 (silica gel, hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.30 – 7.26 (m, 2H), 7.19 – 7.16 (m, 3H), 2.60 (t, J = =7.7 Hz, 2H), 1.72 – 1.67 (m, 4H), 1.66 – 1.52 (m, 3H), 1.40 – 1.33 (m, 2H), 1.24 – 1.11 (m, 6H), 0.91 – 0.82 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.1, 128.5, 128.4, 125.7, 37.8, 37.5, 36.2, 33.6, 32.0, 26.9, 26.7, 26.6 ppm.

The NMR data matches the previous reported synthetic sample. (*59*)



40

(((6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,13-heptadecafluorotridecyl)oxy)methyl)benzene (40)

On 0.1 mmol scale, general procedure A was followed with **SI-29**. Purification by PTLC (PhMe) afforded **40** as a colorless oil (0.032 g, 54%).

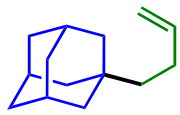
R_f = 0.77(silica gel, PhMe);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 – 7.34 (m, 4H), 7.33 – 7.29 (m, 1H), 4.53 (s, 2H), 3.51 (t, *J* = 6.4 Hz, 2H), 2.18 – 1.97 (m, 2H), 1.76 – 1.60 (m, 4H), 1.56 – 1.46 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.6, 128.5, 127.8, 127.7, 73.1, 70.0, 31.0 (t, *J* = 22.3 Hz), 29.6, 26.0, 20.1 (t, *J* = 3.5 Hz) ppm;

^{19}F NMR (376 MHz, $CDCl_3$): δ -81.07 (t, *J* = 10.1 Hz), -114.69 (t, *J* = 14.2 Hz), -121.90 – -122.40 (m), -122.84 – -123.20 (m), -123.85 (t, *J* = 14.3 Hz), -126.42 (t, *J* = 13.0 Hz) ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{17}F_{17}NaO$ $[M+Na]^+$ 619.0900; found 619.0882.



41

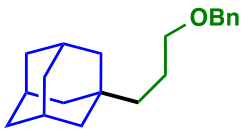
1-(But-3-en-1-yl)adamantine (41). Following general procedure B with **SI-57** (33 mg, 0.1 mmol), $Ni(acac)_2$ (5.1 mg, 0.02 mmol), 6,6'-dimethylbipyridine (3.4 mg, 0.02 mmol) in MeCN (1 mL) at 80 ºC. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **41** (11 mg, 58% yield) as a colorless oil.

R_f = 0.79 (silica gel, hexanes);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.85 (ddt, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.2, 1.6 Hz, 1H), 4.93 (ddt, *J* = 10.2, 2.4, 1.3 Hz, 1H), 2.06 – 1.99 (m, 2H), 1.97 (t, *J* = 3.1 Hz, 3H), 1.76 – 1.62 (m, 6H), 1.50 (d, *J* = 2.8 Hz, 6H), 1.21 – 1.14 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 139.7, 113.1, 43.4, 42.0, 36.8, 31.8, 28.3, 26.6 ppm;

MS (GCMS, EI): *m/z* = 190 (12%), 148 (34%), 135 (100%), 93 (30%), 79 (35%).



42

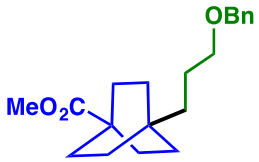
1-(3-(Benzyloxy)propyl)adamantine (42). Following general procedure B with **SI-57** (33 mg, 0.1 mmol), $Ni(acac)_2$ (10.2 mg, 0.04 mmol), 6,6'-dimethylbipyridine (7.4 mg, 0.04 mmol) in MeCN (1 mL) at 80 ºC. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **42** (19 mg, 66% yield) as a colorless oil.

R_f = 0.86 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.13 (m, 5H), 4.53 (s, 2H), 3.46 (t, *J* = 6.9 Hz, 2H), 1.97 (s, 3H), 1.78 – 1.56 (m, 8H), 1.50 (s, 6H), 1.17 – 1.07 (m, 2H) ppm;

^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7, 128.3, 127.6, 127.5, 72.9, 71.6, 42.4, 40.7, 37.3, 32.0, 28.8, 22.9 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{29}O$ $[M+H]^+$ 285.2213; found 285.2209.



43

Methyl 4-(3-(benzyloxy)propyl)bicyclo[2.2.2]octane-1-carboxylate (43).

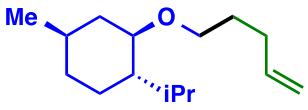
Following general procedure B with **SI-30** (35 mg, 0.1 mmol), $Ni(acac)_2$ (10.2 mg, 0.04 mmol), 6,6'-dimethylbipyridine (7.4 mg, 0.04 mmol) in MeCN (1 mL) at 80 ºC. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished the desired product **43** (16 mg, 51% yield) as a colorless oil.

R_f = 0.31 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 – 7.09 (m, 5H), 4.51 (s, 2H), 3.66 (s, 3H), 3.45 (t, *J* = 6.7 Hz, 2H), 1.82 – 1.69 (m, 6H), 1.59 – 1.50 (m, 2H), 1.47 – 1.35 (m, 6H), 1.21 – 1.15 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.7, 138.6, 128.4, 127.6, 127.5, 72.9, 71.3, 51.6, 38.9, 37.5, 30.4, 30.3, 28.6, 24.2 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{20}H_{29}O_3$ $[M+H]^+$317.2111; found 317.2114.



45

(1S,2R,4R)-1-isopropyl-4-methyl-2-(pent-4-en-1-yloxy)cyclohexane (45).

On 0.1 mmol scale, **SI-31** was used following general procedure B. The reaction was quenched with 1M HCl, and purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished coupling product **45** as a colorless oil (14.0 mg, 62%).

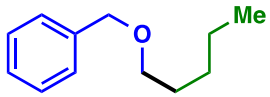
R_f = 0.68 (silica gel, 6:1 hexanes:Et_2O);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.02 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.1, 1.3 Hz, 1H), 3.62 (dt, *J* = 9.1, 6.2 Hz, 1H), 3.27 (ddd, *J* = 9.1, 7.1, 6.4 Hz, 1H), 2.99 (td, *J* = 10.6, 4.1 Hz, 1H), 2.22 (pd, *J* = 7.0, 2.8 Hz, 1H), 2.16 – 2.05 (m, 3H), 1.72 – 1.58 (m, 4H), 1.39 – 1.29 (m, 1H), 1.24 – 1.18 (m, 1H), 0.98 – 0.94 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.88 – 0.82 (m, 2H), 0.77 (d, *J* = 6.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.7, 114.7, 79.3, 67.9, 48.5, 40.7, 34.8, 31.7, 30.6, 29.7, 25.7, 23.5, 22.5, 21.1 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{29}O$ $[M+H]^+$ 225.2213; found 225.2214;

$[\alpha]_D^{20}$ = -65.7 ° (c= 1.0, CH_2Cl_2).



46

((pentyloxy)methyl)benzene (46).

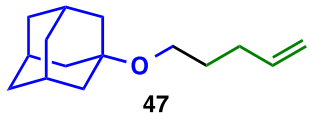
On 0.1 mmol scale, **SI-32** was used following general procedure B. The reaction was quenched with 1M HCl, and purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished coupling product **46** as a colorless oil (11.3 mg, 63 %).

R_f = 0.64 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.33 (m, 4H), 7.30 – 7.27 (m, 1H), 4.51 (s, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.39 – 1.30 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.9, 128.5, 127.8, 127.6, 73.0, 70.7, 29.6, 28.5, 22.7, 14.2 ppm.

The NMR data matches the previous reported synthetic sample. (*60*)



47

1-(pent-4-en-1-yloxy)adamantane (47).

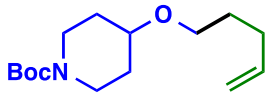
On 0.1 mmol scale, **SI-33** was used following general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:Et_2O) furnished the desired product **47** (16.9 mg, 77% yield) as a colorless oil.

***R*$_f$** = 0.68 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.95 (dq, *J* = 10.2, 1.5 Hz, 1H), 3.40 (t, *J* = 6.6 Hz, 2H), 2.17 – 2.08 (m, 5H), 1.74 (d, *J* = 2.9 Hz, 6H), 1.68 – 1.55 (m, 8H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.8, 114.6, 71.9, 59.2, 41.8, 36.7, 30.7, 30.6, 30.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{25}O$ $[M+H]^+$ 221.1900; found 221.1901.



48

tert-butyl 4-(pent-4-en-1-yloxy)piperidine-1-carboxylate (48).

On 0.1 mmol scale, **SI-34** was used following general procedure B. The reaction was quenched with 1M HCl and purification by PTLC (silica gel, 6:1 hexanes:EtOAc) furnished coupling product **48** as a colorless oil (14.2 mg, 54%)

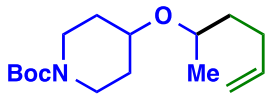
***R*$_f$** = 0.61 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.8 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.2 Hz, 1H), 3.75 (s, 2H), 3.44 (t, *J* = 6.5 Hz, 2H), 3.41 (tt, *J* = 8.0, 3.7 Hz, 1H), 3.07 (ddd, *J* = 13.1, 9.1, 3.5 Hz, 2H), 2.17 – 2.09 (m, 2H), 1.79

(d, *J* = 8.1 Hz, 2H), 1.66 (dt, *J* = 14.7, 6.7 Hz, 2H), 1.54 – 1.48 (m, 2H), 1.45 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 154.4, 137.8, 114.3, 78.9, 74.0, 66.8, 40.7 (br), 30.7, 29.9, 28.7, 28.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{15}H_{28}NO_3$ $[M+H]^+$ 270.2064; found 270.2056.



49

tert-butyl 4-(hex-5-en-2-yloxy)piperidine-1-carboxylate (49).

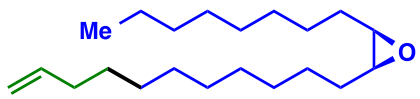
On 0.1 mmol scale, **SI-35** was used following general procedure B at 60 °C. Purification by PTLC (silica gel, 6:1 hexanes:EtOAc) furnished the desired product **49** (11.9 mg, 42 % yield) as a colorless oil.

***R*$_f$** = 0.54 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 5.81 (ddt, *J* = 16.9, 10.2, 6.5 Hz, 1H), 5.01 (dq, *J* = 17.5, 2.0 Hz, 1H), 4.95 (ddq, *J* = 10.3, 2.3, 1.2 Hz, 1H), 3.77 (s, 2H), 3.49 (ddt, *J* = 20.4, 8.1, 4.7 Hz, 2H), 3.06 (dddd, *J* = 13.1, 9.9, 7.2, 3.4 Hz, 2H), 2.21 – 2.12 (m, 1H), 2.12 – 2.01 (m, 1H), 1.76 (d, *J* = 8.1 Hz, 2H), 1.67 – 1.54 (m, 2H), 1.50 – 1.46 (m, 2H), 1.45 (d, *J* = 0.9 Hz, 9H), 1.13 (dd, *J* = 6.2, 0.9 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.0, 138.8, 114.6, 79.5, 72.3, 72.1, 41.3 (br, weak), 36.6, 32.6, 31.5, 30.2, 28.6, 20.8 ppm; Note: ^{13}C resonances 32.6 and 31.5 belong to the same carbon atom, as verified by HSQC.

HRMS (ESI-TOF, *m/z*): calcd for $C_{16}H_{30}NO_3$ $[M+H]^+$ 284.2220; found 284.2220.



50

(2*S*,3*R*)-2-octyl-3-(undec-10-en-1-yl)oxirane (50)

On 0.1 mmol scale, general procedure B was followed with **SI-36**. Purification by PTLC (97.5:2.5 hexanes:EtOAc) afforded **50** as a colorless oil (0.013 g, 42%).

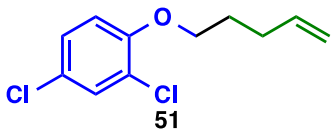
***R*$_f$** = 0.76 (silica gel, PhMe);

^{1}H NMR (600 MHz, CDCl$_3$): δ 5.81 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.01 – 4.96 (m, 1H), 4.93 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 2.66 – 2.62 (m, 2H), 2.06 – 2.01 (m, 2H), 1.61 – 1.20 (m, 30H), 0.90 – 0.86 (t, J = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 139.4, 114.2, 59.1 (2C), 34.0, 32.3, 32.0, 29.7, 29.69, 29.64, 29.61, 29. 59, 29.4, 29.3, 29.1, 26.2, 22.8, 14.3 ppm;

Note: Some ^{13}C resonances cannot be clearly observed due to overlapping peaks.

HRMS (ESI-TOF, *m/z*): calcd for $C_{21}H_{41}O$ $[M+H]^+$ 309.3152; found 309.3151.



51

2,4-dichloro-1-(pent-4-en-1-yloxy)benzene (51).

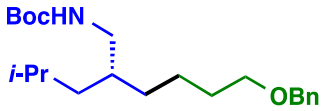
On 0.1 mmol scale, **SI-37** was used following general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:Et$_2$O) furnished the desired product **51** (13.6 mg, 59 % yield) as a colorless oil.

***R*$_f$** = 0.68 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.38 (d, *J* = 2.6 Hz, 1H), 7.18 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 1H), 5.88 (ddt, *J* = 17.0, 10.1, 6.7 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.03 (ddt, *J* = 10.2, 2.2, 1.3 Hz, 1H), 4.03 (t, *J* = 6.4 Hz, 2H), 2.35 – 2.25 (m, 2H), 2.00 – 1.90 (m, 2H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 153.5, 137.7, 130.1, 127.6, 125.7, 123.9, 115.6, 114.2, 68.7, 30.1, 28.3 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{11}H_{13}Cl_2O$ $[M+H]^+$ 231.0338; found 231.0338.



52

***tert-butyl (R)-(6-(benzyloxy)-2-isobutylhexyl)carbamate* (52).** On 0.1 mmol scale, **SI-38** was used following general procedure B. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished the desired product **52** (22 mg, 61% yield) as a yellow oil.

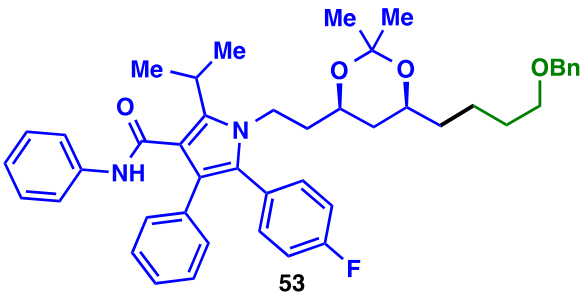
***R*$_f$** = 0.49 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44 – 7.22 (m, 5H), 4.53 (s, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 3.07 (q, *J* = 6.3 Hz, 1H), 1.71 – 1.55 (m, 6H), 1.47 (s, 9H), 1.48 – 1.43 (m, 2H), 1.32 – 1.22 (m, 2H), 1.11 (t, *J* = 7.0 Hz, 2H), 0.89 (dd, *J* = 7.5, 6.6 Hz, 6H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 155.7, 138.2, 127.9, 127.2, 127.0, 72.5, 69.8, 43.4, 41.0, 35.4, 31.4, 29.6, 28.0, 24.8, 22.7, 22.5, 22.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{22}H_{38}NO_3$ $[M+H]^+$ 364.2846; found 364.2854;

$[\alpha]_D^{20}$ = –1.1° (c = 2.2, $CHCl_3$).



53

1-(2-((4*R*,6*S*)-6-(4-(Benzyloxy)butyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethyl)-5-(4-fluorophenyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (53).

On 0.1 mmol scale, **SI-39** was used following general procedure B. Purification by PTLC (silica gel, 4:1 hexanes:EtOAc) furnished the desired product **53** (4.1 mg, 53% yield) as a thin white film.

***R*$_f$** = 0.24 (silica gel, 4:1 hexanes:EtOAc);

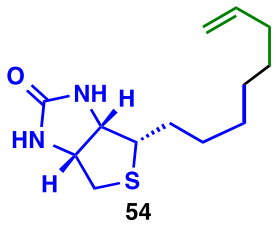
^{1}H NMR (600 MHz, Acetone-d_6): δ 8.31 (bs, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.39 – 7.26 (m, 8H), 7.25 – 7.19 (m, 2H), 7.17 – 7.11 (m, 6H), 7.10 – 7.06 (m, 1H), 6.99 (tt, *J* = 7.4, 1.2 Hz, 1H), 4.50 (s, 2H), 4.11 (ddd, *J* = 15.4, 10.8, 5.0 Hz, 1H), 3.92 (ddd, *J* = 14.6, 10.7, 5.7 Hz, 1H), 3.85 – 3.73 (m, 2H), 3.48 (t, *J* = 6.4 Hz, 2H), 3.44 (p, *J* = 7.1 Hz, 1H), 1.82 – 1.53 (m, 4H), 1.49 (d, *J* = 2.3 Hz, 3H), 1.48 (d, *J* = 2.3 Hz, 3H), 1.47 – 1.28 (m, 5H), 1.36 (s, 3H), 1.25 (s, 3H) ppm;

^{13}C NMR (151 MHz, Acetone-d_6): δ 165.0, 161.8 (d, *J* = 245.4 Hz), 139.2, 138.8, 138.0, 134.8, 133.1 (d, *J* = 8.6 Hz), 129.5, 128.6 (d, *J* = 3.3 Hz), 127.9, 127.6, 127.3, 126.9, 126.7, 125.3, 122.4, 121.1, 118.8, 116.6, 114.6 (d, *J* = 21.4 Hz), 97.5, 71.8, 69.4, 67.8, 66.0, 39.9, 37.9, 36.0, 35.6, 29.2, 29.1, 29.0, 25.6, 21.09, 21.08, 20.9, 18.8 ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ -113.76 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{45}H_{52}FN_2O_4$ $[M+H]^+$ 703.3906; found 703.3909;

$[\alpha]^{20}_D$ = + 7.3° (c = 0.12, Acetone-d_6).



54

(3aS,4S,6aR)-4-(oct-7-en-1-yl)tetrahydro-1H-thieno[3,4-d]imidazol-2(3H)-one (54).

On 0.1 mmol scale, D-biotin was used following general procedure C. Purification by reverse-phase HPLC (H_2O:MeCN, 15% B to 20 % B over 5 min, then 20 % B to 85 % B over 35 min; 208 nm) and lyophilization afforded the desired product **54** (6.8 mg, 27% yield) as a fluffy amorphous white solid.

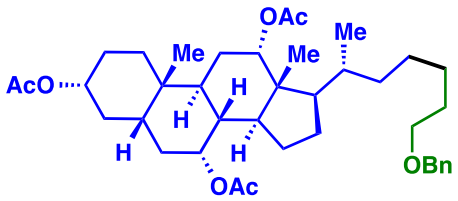
***R*$_f$** = 0.43 (silica gel, 10:1 CH_2Cl_2:MeOH);

^{1}H NMR (600 MHz, Methanol-*d*$_4$): δ 5.83 (ddt, *J* = 16.9, 9.8, 6.8 Hz, 1H), 5.01 (dt, *J* = 17.1, 2.0 Hz, 1H), 4.96 – 4.90 (m, 1H), 4.51 (dd, *J* = 7.8, 5.1 Hz, 1H), 4.32 (dd, *J* = 7.9, 4.6 Hz, 1H), 3.22 (dt, *J* = 9.7, 5.1 Hz, 1H), 2.95 (dd, *J* = 12.7, 5.0 Hz, 1H), 2.72 (d, *J* = 12.7 Hz, 1H), 2.11 – 2.02 (m, 2H), 1.79 – 1.69 (m, 1H), 1.64 – 1.53 (m, 1H), 1.48 – 1.33 (m, 8H) ppm;

^{13}C NMR (151 MHz, Methanol-*d*$_4$): δ 166.2, 140.1, 114.7, 63.5, 61.6, 57.3, 41.0, 34.9, 30.5, 30.3, 30.1 (2C), 29.8 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{13}H_{23}N_2SO$ $[M+H]^+$ 255.1526; found 255.1527;

$[\alpha]_D^{20}$ = +47.0° (c = 0.3, MeOH).



55

(3*R*,5*S*,7*R*,8*R*,9*S*,10*S*,12*S*,13*R*,14*S*,17*R*)-17-((*R*)-7-(benzyloxy)heptan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,7,12-triyl triacetate (55).

On 0.1 mmol scale, general procedure B was followed with **SI-40**. Purification by PTLC (19:1 CH_2Cl_2:EtOAc) afforded **55** as a colorless oil (0.045 g, 70%).

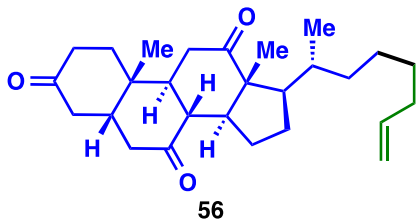
***R*$_f$** = 0.25 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 5.09 (t, *J* = 3.1 Hz, 1H), 4.90 (q, *J* = 3.2 Hz, 1H), 4.57 (tt, *J* = 11.4, 4.3 Hz, 1H), 4.49 (s, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.12 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 2.04 – 1.98 (m, 2H), 1.94 (ddd, *J* = 15.4, 5.5, 3.5 Hz, 1H), 1.89 – 1.70 (m, 4H), 1.70 – 1.55 (m, 8H), 1.56 – 1.45 (m, 2H), 1.45 – 1.20 (m, 8H), 1.20 – 0.93 (m, 4H), 0.91 (s, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.72 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.69, 170.65, 170.5, 138.8, 128.5, 127.7, 127.6, 75.7, 74.3, 73.0, 70.9, 70.6, 47.9, 45.2, 43.5, 41.1, 37.9, 35.8, 35.2, 34.9, 34.8, 34.5, 31.4, 30.0, 29.1, 27.5, 27.1, 26.7, 26.0, 25.7, 23.0, 22.7, 21.8, 21.64, 21.58, 18.0, 12.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{39}H_{59}O_7$ $[M+H]^+$ 639.4255; found 639.4248.

$[\alpha]_D^{20}$ = 54.4 ° (c = 1.0, CH_2Cl_2).



56

(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-oct-7-en-2-yl)dodecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,7,12(2*H*,4*H*)-trione (56).

On 0.1 mmol scale, **SI-41** was used following general procedure B. Purification by PTLC (silica gel, 10:1 hexanes:EtOAc) furnished the desired product **56** (30 mg, 73% yield) as a yellow solid.

mp: >200 °C;

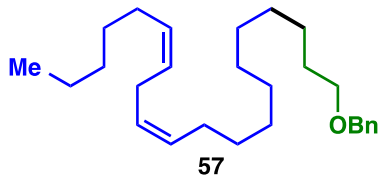
***R*$_f$** = 0.32 (silica gel, 6:4 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$) δ 5.83 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 5.02 (dq, *J* = 17.1, 1.7 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.3, 1.2 Hz, 1H), 2.99 – 2.77 (m, 3H), 2.42 – 2.20 (m, 6H), 2.20 – 2.12 (m, 1H), 2.12 – 1.95 (m, 6H), 1.87 (td, *J* = 11.2, 7.0 Hz, 1H), 1.64 (td, *J* = 14.5, 4.6 Hz, 1H), 1.47 – 1.20 (m, 9H), 1.42 (s, 3H), 1.14 (m, 1H), 1.09 (s, 3H), 0.86 (d, *J* = 6.6 Hz, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$) δ 211.6, 208.6, 208.3, 138.7, 113.7, 56.5, 51.4, 48.6, 46.4, 45.4, 45.1, 44.5, 42.4, 38.2, 36.0 (2C), 35.6, 34.9, 34.8, 33.4, 28.9, 27.4, 25.6, 24.8, 21.5, 18.6, 11.4 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{27}H_{41}O_3$ $[M+H]^+$; 413.3050, found 413.3051;

$[\alpha]_D^{20}$ = + 15.7 º(c =0.9, $CHCl_3$).



57

4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl (10Z,12Z)-octadeca-10,12-dienoate (57).

On 0.1 mmol scale, general procedure B was followed with **SI-42**. Purification by PTLC (PhMe) afforded **57** as a colorless oil (0.025 g, 65%).

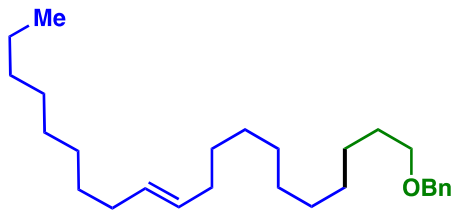
***R*$_f$** = 0.28 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.34 (d, *J* = 4.4 Hz, 4H), 7.30 – 7.26 (m, 1H), 5.41 – 5.31 (m, 4H), 4.50 (s, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 2.80 – 2.74 (m, 2H), 2.08 – 2.02 (m, 4H), 1.65 – 1.57 (m, 2H), 1.40 – 1.23 (m, 20H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 138.9, 130.3, 128.5, 128.1, 127.8, 127.6, 73.0, 70.7, 31.7, 29.9, 29.84, 29.75, 29.73, 29.69, 29.65, 29.51, 29.48, 27.40, 27.36, 26.4, 25.8, 22.7, 14.2 ppm;

Note: Some ^{13}C resonances cannot be clearly observed due to overlapping peaks.

HRMS (ESI-TOF, *m/z*): calcd for $C_{27}H_{45}O$ $[M+H]^+$ 385.3465; found 385.3474.



58

(*E*)-((icos-11-en-1-yloxy)methyl)benzene (58).

On 0.1 mmol scale, general procedure B was followed with **SI-43**. Purification by PTLC (PhMe) afforded **58** as a colorless oil (0.025 g, 65%).

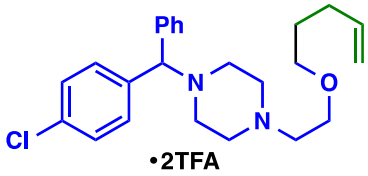
R_f = 0.14 (silica gel, 19:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36 – 7.26 (m, 5H), 5.40 – 5.38 (m, 2H), 4.50 (s, 2H), 3.46 (t, *J* = 6.7 Hz, 2H), 1.99 – 1.93 (m, 4H), 1.64 – 1.59 (m, 2H), 1.40 – 1.19 (m, 26H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 138.9, 130.52, 130.50, 128.5, 127.8, 127.6, 73.0, 70.7, 32.8, 32.1, 30.0, 29.82, 29.76, 29.74, 29.67, 29.65, 29.48, 29.34, 29.32, 26.4, 22.9, 14.3.

Note: Some ^{13}C resonances cannot be clearly observed due to overlapping peaks.

HRMS (ESI-TOF, *m/z*): calcd for $C_{27}H_{47}O$ $[M+H]^+$ 387.3621; found 387.3619.



59

1-((4-chlorophenyl)(phenyl)methyl)-4-(2-(pent-4-en-1-yloxy)ethyl)piperazine (diTFA salt) (59)

On 0.05 mmol scale, cetirizine was used following general procedure C. Purification by reverse-phase HPLC (H_2O:MeCN, 50% B for 5 min, then 50 to 100 % B over 30 min; 230 nm) and lyophilization afforded the desired product **59** (18.4 mg, 59% yield) as a colorless oil.

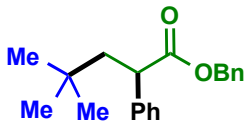
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.46 (m, 4H), 7.38 – 7.28 (m, 5H), 5.76 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1H), 4.99 (dq, *J* = 17.2, 1.7 Hz, 1H), 4.96 (dq, *J* = 10.2, 1.4 Hz, 1H),

4.61 (s, 1H), 3.81 – 3.74 (m, 2H), 3.54 (m, 4H), 3.42 (t, *J* = 6.6 Hz, 2H), 3.33 – 3.26 (m, 2H), 3.10 (s, 4H), 2.06 (dtd, *J* = 8.0, 6.7, 1.4 Hz, 2H), 1.66 – 1.59 (m, 2H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 137.8, 137.6, 136.6, 134.7, 129.7, 129.6, 129.4, 129.0, 127.9, 115.2, 75.6, 71.1, 65.2, 56.8, 51.7, 48.8, 30.2, 28.6 ppm;

^{19}F NMR (376 MHz, $CDCl_3$) δ -76.0 ppm;

HRMS (ESI-TOF, *m/z*): calcd for $C_{24}H_{32}ClON_2$ $[M+H]^+$ 399.2198; found 399.2195.



66

benzyl 4,4-dimethyl-2-phenylpentanoate (66).

Following the General Procedure D with **SI-58** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **66** (26.0 mg, 88% yield) as a white solid.

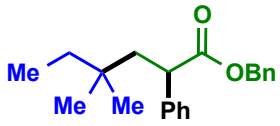
m.p. = 38 ºC;

***R*$_f$** = 0.59 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.34 (m, 10H), 5.07 (dd, *J* = 57.6, 12.6 Hz, 2H), 3.71 (dd, *J* = 9.2, 3.8 Hz, 1H), 2.34 (dd, *J* = 14.0, 9.2 Hz, 1H), 1.60 (dd, *J* = 14.0, 3.8 Hz, 1H), 0.88 (s, 9H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ174.7, 141.0, 136.0, 128.8, 128.6, 128.2, 128.2, 128.0, 127.2, 66.7, 48.4, 47.4, 31.2, 29.6 ppm;

HRMS (ESI-TOF): calc'd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1849; found 297.1851.



67

benzyl 4,4-dimethyl-2-phenylhexanoate (67).

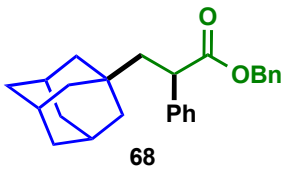
Following the General Procedure D with **SI-44** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **67** (26.9 mg, 87% yield) as a colorless oil.

***R*$_f$** = 0.58 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.22-7.34 (m, 10H), 5.07 (dd, *J* = 64.8, 12.0 Hz, 2H), 3.69 (dd, *J* = 9.0, 3.6 Hz, 1H), 2.31 (dd, *J* = 14.4, 9.0 Hz, 1H), 1.59 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.24 (q, *J* = 7.2 Hz, 2H), 0.82 (s, 3H), 0.81 (s, 3H), 0.78 (t, *J* = 7.8 Hz, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.8, 141.1, 136.0, 128.7, 128.6, 128.2 (2C), 128.0, 127.1, 66.7, 47.9, 45.2, 34.5, 33.7, 26.7, 26.5, 8.5 ppm;

HRMS (ESI-TOF): calc'd for $C_{21}H_{27}O_2$ $[M+H]^+$ 311.2006; found 311.2006.



68

benzyl 3-adamantan-1-yl-2-phenylpropanoate (68).

Following the General Procedure D with **SI-57** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **68** (34.6 mg, 92% yield) as a white solid.

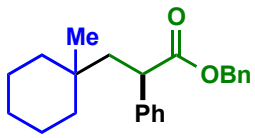
m.p.= 64-66 ºC;

***R*$_f$** = 0.66 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.21-7.32 (m, 10H), 5.08 (dd, *J* = 86.4 Hz, 12 Hz, 2H), 3.75 (dd, *J* = 9.6, 3.5 Hz, 1H), 2.20 (dd, *J* = 14.1, 9.6 Hz, 1H), 1.88 (s, br, 3H), 1.61 (dd, *J* = 12.0, 53 Hz, 6H), 1.43 (dd, *J* = 12.0, 65 Hz, 6H), 1.43 (dd, *J* = 3.6, 14.4 Hz, 1H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.7, 141.1, 136.0, 128.7, 128.5, 128.3, 128.2, 128.0, 127.1, 66.6, 48.2, 46.4, 42.4, 37.1, 33.0, 28.7 ppm;

HRMS (ESI-TOF): calc'd for $C_{26}H_{31}O_2$ $[M+H]^+$ 375.2319; found 375.2318.



69

benzyl 3-(1-methylcyclohexyl)-2-phenylpropanoate (69).

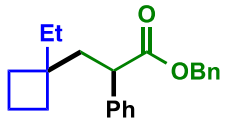
Following the General Procedure D with **SI-59** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **69** (31.5 mg, 94% yield) as a colorless oil.

***R*$_f$** = 0.46 (silica gel, 10:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.36 (m, 10H), 5.08 (dd, *J* = 74.4, 12.6 Hz, 2H), 3.74 (dd, *J* = 9.0, 3.6 Hz, 1H), 2.35 (dd, *J* = 13.8, 9.0 Hz, 1H), 1.64 (dd, *J* = 13.8, 3.6 Hz, 1H), 1.35-1.46 (m, 5H), 1.19-1.30 (m, 5H), 0.86 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.8, 141.2, 136.0, 128.7, 128.5, 128.2, 128.2, 128.0, 127.1, 66.7, 46.3, 38.0 (2C), 37.8, 33.6, 26.5, 22.0 ppm;

HRMS (ESI-TOF): calc'd for $C_{23}H_{29}O_2$ $[M+H]^+$ 337.2162; found 337.2163.



70

benzyl 3-(1-ethylcyclobutyl)-2-phenylpropanoate (70).

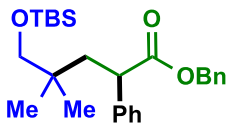
Following the General Procedure D with **SI-45** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **70** (22 mg, 68% yield) as a colorless oil.

***R*$_f$** = 0.58 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.24-7.38 (m, 10H), 5.08 (dd, *J* = 56.4, 12.6 Hz, 2H), 3.61 (dd, *J* = 8.4, 5.4 Hz, 1H), 2.41 (dd, *J* = 13.8, 8.4 Hz, 1H), 1.87 (dd, *J* = 13.8, 4.2 Hz, 1H), 1.74-1.82 (m, 3H), 1.63-1.69 (m, 1H), 1.47-1.59 (m, 4H), 0.76 (t, *J* = 7.2 Hz, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 140.5, 136.0, 128.7, 128.6, 128.2 (2C), 127.2, 66.7, 48.0, 42.0, 41.9, 31.7, 31.4, 30.1, 15.4, 8.2 ppm;

HRMS (ESI-TOF): calc'd for $C_{22}H_{27}O_2$ $[M+H]^+$ 323.2006; found 323.2006.



71

benzyl 5-((*tert*-butyldimethylsilyl)oxy)-4,4-dimethyl-2-phenylpentanoate (71).

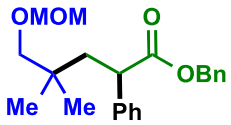
Following the General Procedure D with **SI-46** (0.1 mmol), purification by flash column chromatography (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **71** (35.7 mg, 84% yield) as a colorless oil.

***R*$_f$** = 0.59 (Hexanes:Ethyl acetate 8:1);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.23-7.35 (m, 10H), 5.08 (dd, *J* = 64.8, 12.0 Hz, 2H), 3.79 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.25 (dd, *J* = 23.4, 9.6 Hz, 2H), 2.29 (dd, *J* = 13.8, 8.4 Hz, 1H), 1.75 (dd, *J* = 13.8, 4.2 Hz, 1H), 0.88 (s, 9H), 0.82 (s, 3H), 0.81 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.7, 140.9, 136.0, 128.7, 128.6, 128.2, 128.1 (2C), 127.1, 71.8, 66.6, 47.8, 42.3, 36.0, 26.0, 24.7, 23.8, 18.4, -5.4 (2C).

HRMS (ESI-TOF): calc'd for $C_{26}H_{39}O_3Si$ $[M+H]^+$ 427.2663; found 427.2662.



72

benzyl 5-(methoxymethoxy)-4,4-dimethyl-2-phenylpentanoate (72).

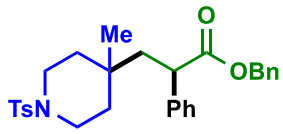
Following the General Procedure D with **SI-47** (0.1 mmol), purification by flash column (5%-7% EtOAc/Hexane) and PTLC (12% EtOAc/Hexane) afforded **72** (33.1 mg, 93% yield) as a colorless oil.

***R*$_f$** = 0.33 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, CDCl$_3$): δ 7.22-7.34 (m, 10H), 5.07 (dd, *J* = 49.2, 12.0 Hz, 2H), 4.52 (dd, *J* = 16.8, 6.6 Hz, 2H), 3.77 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.31 (s, 3H), 3.19 (s, 2H), 2.37 (dd, *J* = 13.8, 9.0 Hz, 1H), 1.76 (dd, *J* = 13.8, 3.6 Hz, 1H), 0.90 (s, 3H), 0.88 (s, 3H) ppm;

^{13}C NMR (151 MHz, CDCl$_3$): δ 174.6, 140.8, 136.0, 128.7, 128.6, 128.2, 128.1, 128.0, 127.2, 96.7, 76.7, 66.7, 55.2, 47.8, 42.7, 34.9, 24.8, 24.6 ppm;

HRMS (ESI-TOF): calc'd for $C_{22}H_{29}O_4$ $[M+H]^+$ 357.2060; found 357.2065.



73

benzyl 3-(4-methyl-1-tosylpiperidin-4-yl)-2-phenylpropanoate (73).

Following the General Procedure D with **SI-48** (0.1 mmol), purification by flash column (5%-10% EtOAc/Hexane) and PTLC (15% EtOAc/Hexane) afforded **73** (35.2 mg, 72% yield) as a white solid.

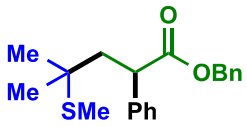
m.p.= 134-136 ºC;

R_f = 0.52 (silica gel, 4:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, *J* = 13.8, 9.0 Hz, 2H), 7.19-7.32 (m, 12H), 5.04 (dd, *J* = 73.2, 12.6 Hz, 2H), 3.65 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.12-3.22 (m, 2H), 2.69-2.64 (m, 2H), 2.44 (s, 3H), 2.26 (dd, *J* = 14.4, 9.0 Hz, 1H), 1.58 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.48-1.52 (m, 1H), 1.39-1.44 (m, 1H), 1.29-1.34 (m, 2H), 0.77 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.2, 143.5, 140.3, 135.7, 133.6, 129.7, 128.9, 128.6, 128.3 (2C), 127.9, 127.8, 127.4, 66.9, 47.1, 45.4, 42.1, 36.4, 36.2, 31.6, 22.9, 21.7 ppm;

HRMS (ESI-TOF): calc'd for $C_{29}H_{34}NO_4S$ $[M+H]^+$ 492.2203; found 492.2203.



74

benzyl 4-methyl-4-(methylthio)-2-phenylpentanoate (74).

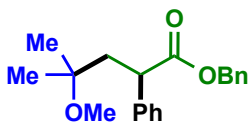
Following the General Procedure D with **SI-49** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **74** (25.9 mg, 79% yield) as a colorless oil.

R_f = 0.61 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.34 (m, 10H), 5.08 (dd, *J* = 66.0, 12.6 Hz, 2H), 3.95 (dd, *J* = 9.0, 3.0 Hz, 1H), 2.65 (dd, *J* = 14.4, 9.0 Hz, 1H), 1.91 (s, 3H), 1.80 (dd, *J* = 15.0, 3.6 Hz, 1H), 1.23 (s, 3H), 1.21 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3, 140.6, 136.0, 128.8, 128.5, 128.2, 128.2, 128.0, 127.3, 66.8, 48.3, 44.4, 44.3, 28.7, 28.2, 11.2.

HRMS (ESI-TOF): calc'd for $C_{20}H_{25}O_2S$ $[M+H]^+$ 329.1570; found 329.1573.



75

benzyl 4-methoxy-4-methyl-2-phenylpentanoate (75).

Following the General Procedure D with **SI-50** (0.1 mmol), purification by flash column (5%-7% EtOAc/Hexane) and PTLC (10% EtOAc/Hexane) afforded **75** (23.7 mg, 76% yield) as a white solid.

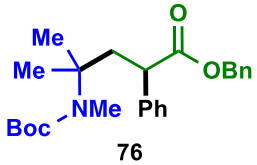
m.p.= 38-40 ºC;

R_f = 0.59 (silica gel, 6:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.36 (m, 10H), 5.08 (dd, *J* = 70.2, 12.6 Hz, 2H), 3.84 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.10 (s, 3H), 2.60 (dd, *J* = 14.4, 9.0 Hz, 1H), 1.81 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.15 (s, 3H), 1.12 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.5, 140.6, 136.2, 128.8, 128.5, 128.1 (2C), 128.0, 127.2, 74.3, 66.7, 49.5, 47.1, 43.6, 25.5, 25.0 ppm;

HRMS (ESI-TOF): calc'd for $C_{20}H_{25}O_3$ $[M+H]^+$ 313.1798; found 313.1802.



76

benzyl 4-((*tert*-butoxycarbonyl)(methyl)amino)-4-methyl-2-phenylpentanoate (76).

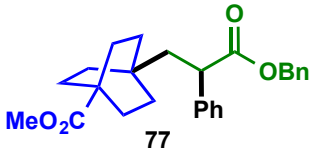
Following the General Procedure D with **SI-51** (2.8 mmol), purification by flash column (5%-7% EtOAc/Hexane) afforded **76** (844 mg, 74% yield) as a colorless oil.

R_f = 0.41 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.21-7.33 (m, 10H), 5.07 (dd, *J* = 55.8, 12.6 Hz, 2H), 3.67 (dd, *J* = 7.8, 4.2 Hz, 1H), 2.79 (s, 3H), 2.72 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.40 (dd, *J* = 14.4, 4.8 Hz, 1H), 1.39 (s, 9H), 1.28 (s, 3H), 1.22 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.4, 156.0, 140.3, 136.0, 128.7, 128.5, 128.2 (2C), 128.2, 127.2, 79.7, 66.7, 57.6, 48.2, 44.1, 32.1, 28.6, 28.2 (2C) ppm;

HRMS (ESI-TOF): calc'd for $C_{25}H_{34}NO_4$ $[M+H]^+$ 412.2482; found 412.2487.



77

methyl 4-(3-(benzyloxy)-3-oxo-2-phenylpropyl)bicyclo[2.2.2]octane-1-carboxylate (77).

Following the General Procedure D with **SI-30** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (10% EtOAc/Hexane) afforded **77** (29.7 mg, 73% yield) as a white solid.

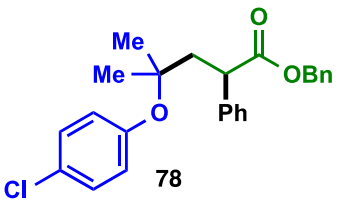
m.p.= 108-110 ºC;

R_f = 0.27 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.23-7.33 (m, 10H), 5.07 (dd, *J* = 81.0, 12.0 Hz, 2H), 3.68 (dd, *J* = 9.0, 3.6 Hz, 1H), 3.62 (s, 3H), 2.23 (dd, *J* = 13.8, 9.0 Hz, 1H), 1.71 (t, *J* = 7.8 Hz, 6H), 1.51 (dd, *J* = 14.4, 4.2 Hz, 1H), 1.37-1.43 (m, 3H), 1.28-1.34 (m, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 178.5, 174.5, 140.7, 135.9, 128.8, 128.6, 128.3 (2C), 127.9, 127.3, 66.8, 51.8, 47.4, 44.9, 38.9, 31.2, 30.4, 28.5 ppm;

HRMS (ESI-TOF): calc'd for $C_{26}H_{31}O_4$ $[M+H]^+$ 407.2217; found 407.2218.



78

benzyl 4-(4-chlorophenoxy)-4-methyl-2-phenylpentanoate (78).

Following the General Procedure D with **SI-52** (0.1 mmol), purification by flash column (5% EtOAc/Hexane) and PTLC (5% EtOAc/Hexane) afforded **78** (20 mg, 49% yield) as a colorless oil.

R_f = 0.62 (silica gel, 8:1 hexanes:EtOAc);

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.16-7.39 (m, 12H), 6.85 (d, *J* = 9.0 Hz, 2H), 5.06 (dd, *J* = 55, 12.6 Hz, 2H), 4.05 (dd, *J* = 10.2, 3.0 Hz, 1H), 2.81 (dd, *J* = 14.4, 9.6 Hz, 1H), 1.99 (dd, *J* = 14.4, 3.6 Hz, 1H), 1.23 (s, 3H), 1.22 (s, 3H) ppm;

^{13}C NMR (151 MHz, $CDCl_3$): δ 174.3, 153.7, 140.1, 136.0, 129.1, 128.9, 128.8, 128.5, 128.2 (2C), 128.1, 127.4, 125.4, 80.2, 66.8, 47.5, 46.0, 27.0, 26.4.

HRMS (ESI-TOF): calc'd for $C_{25}H_{26}ClO_3$ $[M+H]^+$ 409.1565; found 409.1565.

X-ray crystallographic data for compound **11**.

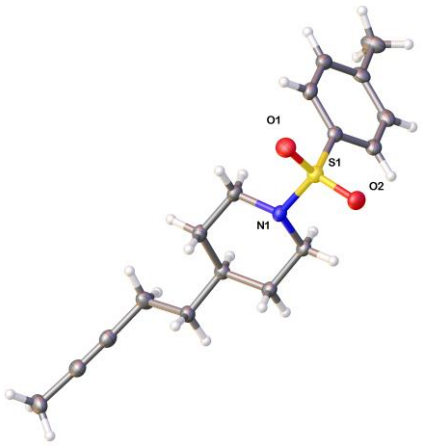


Table SI-3. Crystal data and structure refinement for **11**.

Identification code	CCDC 1457710	
Empirical formula	C17 H23 N O2 S	
Molecular formula	C17 H23 N O2 S	
Formula weight	305.42	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 8.3294(5) Å	α= 90°.
	b = 8.3397(4) Å	β= 90°.
	c = 23.1298(13) Å	γ = 90°.
Volume	1606.70(15) $Å^3$	
Z	4	
Density (calculated)	1.263 Mg/m^3	
Absorption coefficient	0.206 mm^{-1}	
F(000)	656	
Crystal size	0.24 x 0.125 x 0.1 mm^3	
Crystal color, habit	colourless block	
Theta range for data collection	1.761 to 26.408°.	
Index ranges	-10<=h<=10, -10<=k<=10, -28<=l<=28	
Reflections collected	15368	

Independent reflections	3305 [R(int) = 0.0439]
Completeness to theta = 25.242°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.4908 and 0.4567
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3305 / 0 / 192
Goodness-of-fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0319, wR2 = 0.0768
R indices (all data)	R1 = 0.0348, wR2 = 0.0790
Absolute structure parameter	0.01(3)
Extinction coefficient	n/a
Largest diff. peak and hole	0.232 and -0.210 e.$Å^{-3}$

Table SI-4. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Baran565. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	11919(1)	354(1)	8872(1)	22(1)
O(1)	11484(2)	-1005(2)	9217(1)	30(1)
O(2)	13422(2)	363(2)	8570(1)	28(1)
N(1)	10507(2)	569(2)	8385(1)	21(1)
C(1)	1687(3)	469(3)	6027(1)	33(1)
C(2)	2917(3)	888(3)	6458(1)	26(1)
C(3)	3864(3)	1265(3)	6814(1)	25(1)
C(4)	5006(3)	1727(3)	7271(1)	28(1)
C(5)	6754(3)	1338(3)	7131(1)	22(1)
C(6)	7885(3)	1640(3)	7642(1)	20(1)
C(7)	9631(3)	1600(3)	7444(1)	21(1)
C(8)	10788(3)	1827(3)	7943(1)	21(1)
C(9)	8847(3)	606(3)	8612(1)	23(1)
C(10)	7651(3)	406(3)	8124(1)	23(1)
C(11)	11842(3)	2077(3)	9313(1)	21(1)
C(12)	12589(3)	3481(3)	9132(1)	24(1)
C(13)	12400(3)	4871(3)	9451(1)	27(1)
C(14)	11490(3)	4875(3)	9958(1)	26(1)
C(15)	10808(3)	3443(3)	10140(1)	26(1)
C(16)	10948(3)	2050(3)	9821(1)	24(1)
C(17)	11219(4)	6405(3)	10290(1)	37(1)

X-ray crystallographic data for compound **73**.

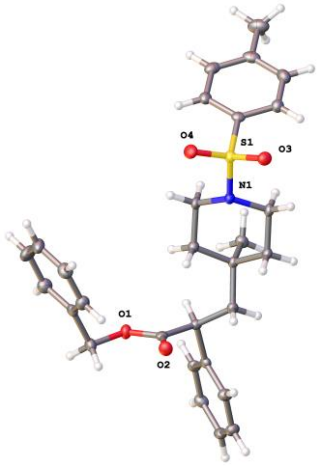


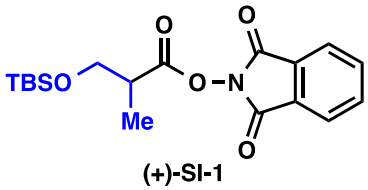
Table SI-5. Crystal data and structure refinement for **73**.

Identification code	CCDC 1457711	
Empirical formula	C29 H33 N O4 S	
Molecular formula	C29 H33 N O4 S	
Formula weight	491.62	
Temperature	100.0 K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	C 1 c 1	
Unit cell dimensions	a = 6.0487(2) Å	α= 90°.
	b = 28.2917(10) Å	β= 99.794(2)°.
	c = 14.8950(5) Å	γ = 90°.
Volume	2511.80(15) $Å^3$	
Z	4	
Density (calculated)	1.300 Mg/m^3	
Absorption coefficient	1.431 mm^{-1}	
F(000)	1048	
Crystal size	0.2 x 0.04 x 0.04 mm^3	
Crystal color, habit	colorless needle	
Theta range for data collection	3.124 to 68.554°.	
Index ranges	-7<=h<=7, -34<=k<=34, -17<=l<=17	
Reflections collected	19040	
Independent reflections	4157 [R(int) = 0.0414]	
Completeness to theta = 67.500°	99.7 %	
Absorption correction	Semi-empirical from equivalents	

Max. and min. transmission	0.5210 and 0.4363
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4157 / 2 / 318
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0630
R indices (all data)	R1 = 0.0305, wR2 = 0.0645
Absolute structure parameter	0.031(9)
Extinction coefficient	n/a
Largest diff. peak and hole	0.195 and -0.190 e.$Å^{-3}$

Table SI-6. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for Baran575. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	9861(1)	10570(1)	2521(1)	17(1)
O(1)	2054(3)	8445(1)	1305(1)	20(1)
O(2)	5746(3)	8282(1)	1597(1)	22(1)
O(3)	12220(3)	10593(1)	2497(1)	22(1)
O(4)	9090(3)	10521(1)	3374(1)	23(1)
N(1)	8870(3)	10118(1)	1889(2)	16(1)
C(1)	3964(5)	8586(1)	3523(2)	25(1)
C(2)	4074(5)	8896(1)	4249(2)	27(1)
C(3)	2197(5)	9142(1)	4386(2)	30(1)
C(4)	181(5)	9080(1)	3802(2)	36(1)
C(5)	54(5)	8766(1)	3080(2)	27(1)
C(6)	1942(4)	8521(1)	2929(2)	19(1)
C(7)	1741(5)	8191(1)	2127(2)	22(1)
C(8)	4157(4)	8456(1)	1118(2)	17(1)
C(9)	4201(4)	8693(1)	207(2)	16(1)
C(10)	3664(4)	8304(1)	-510(2)	16(1)
C(11)	1590(4)	8284(1)	-1063(2)	19(1)
C(12)	1067(5)	7921(1)	-1689(2)	22(1)
C(13)	2635(5)	7570(1)	-1766(2)	22(1)
C(14)	4729(5)	7592(1)	-1216(2)	24(1)
C(15)	5249(5)	7955(1)	-594(2)	22(1)
C(16)	6476(4)	8938(1)	188(2)	17(1)
C(17)	6639(4)	9458(1)	495(2)	16(1)
C(18)	5214(4)	9761(1)	-239(2)	21(1)
C(19)	5914(4)	9527(1)	1429(2)	18(1)
C(20)	6447(4)	10020(1)	1826(2)	18(1)
C(21)	9129(4)	9596(1)	603(2)	16(1)
C(22)	9622(4)	10088(1)	996(2)	17(1)
C(23)	8592(4)	11082(1)	1975(2)	18(1)
C(24)	9579(4)	11306(1)	1312(2)	20(1)
C(25)	8530(5)	11692(1)	861(2)	26(1)
C(26)	6501(5)	11863(1)	1057(2)	25(1)
C(27)	5561(5)	11636(1)	1734(2)	24(1)
C(28)	6576(4)	11246(1)	2194(2)	20(1)
C(29)	5303(6)	12269(1)	527(2)	36(1)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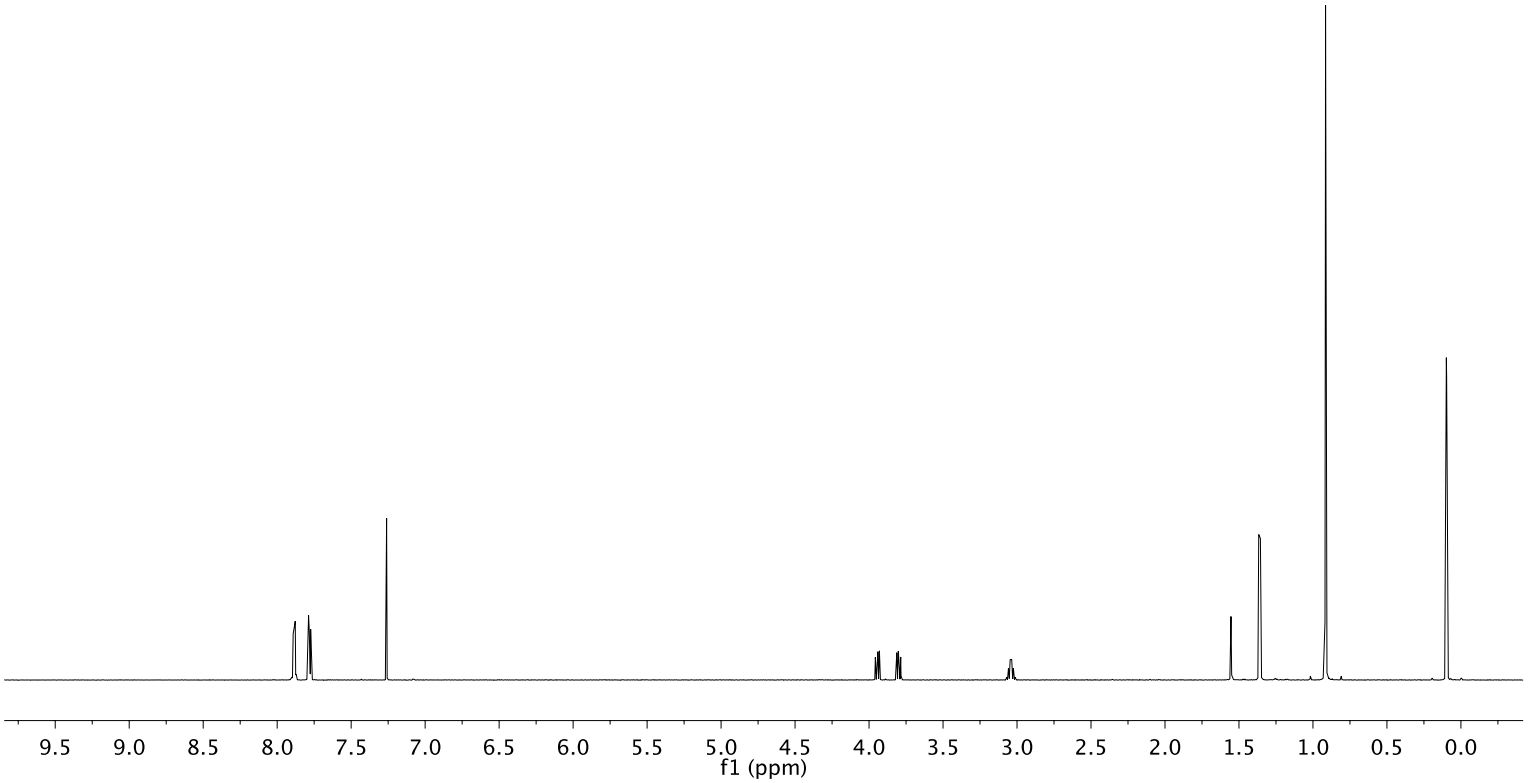
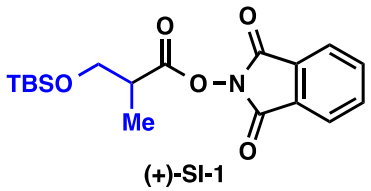
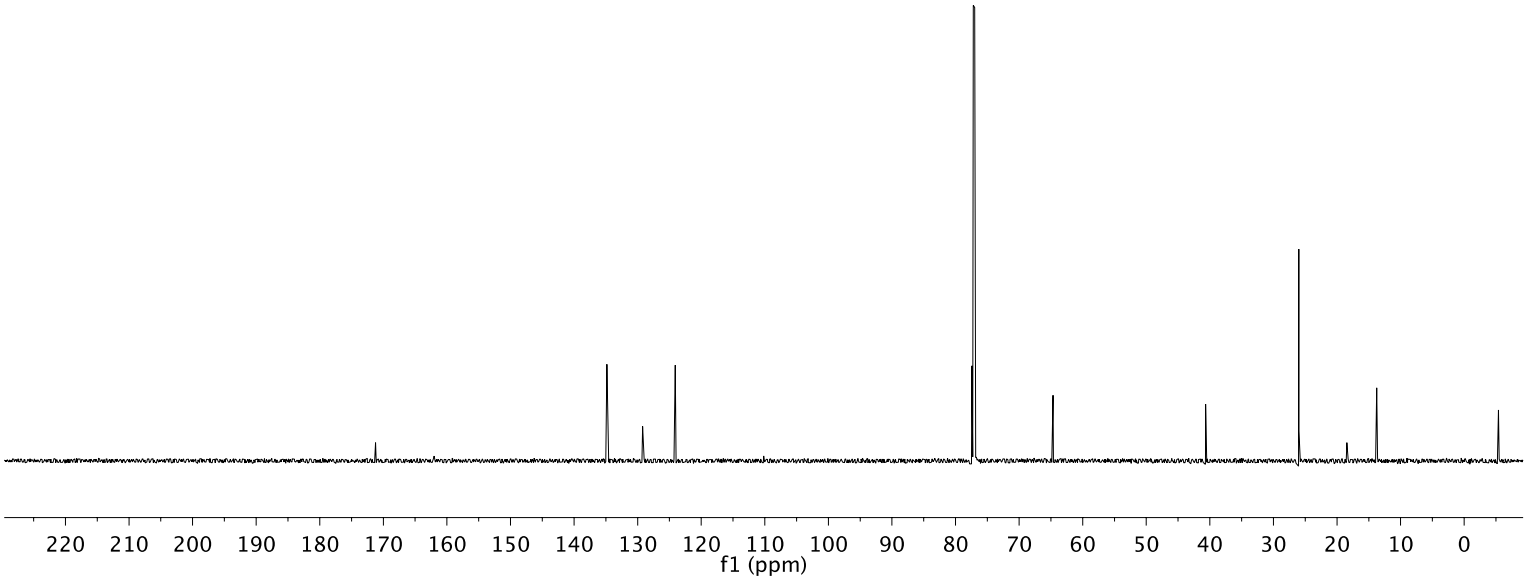
O

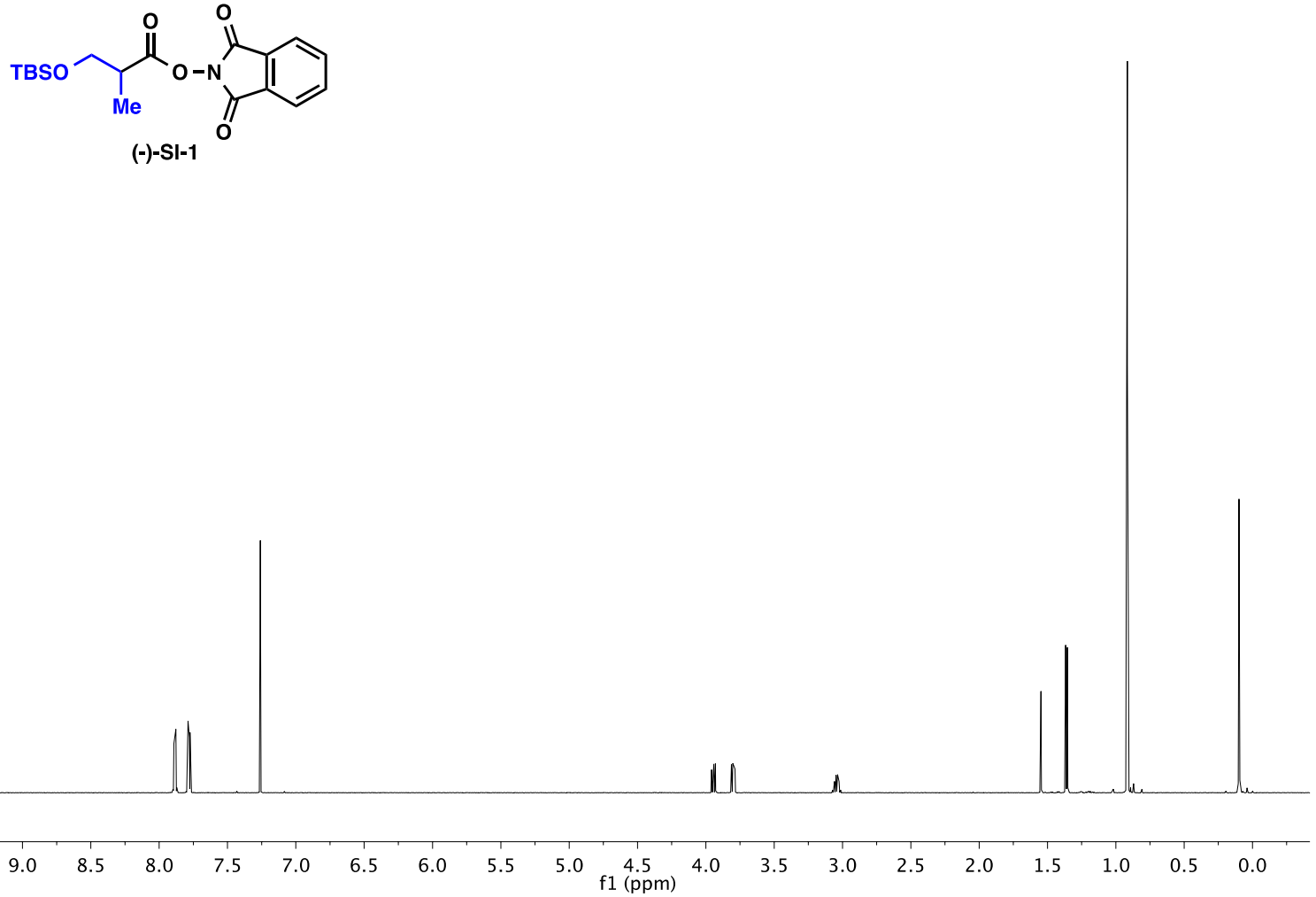
(+)-SI-1

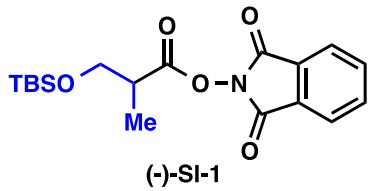

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


TBSO
Me
O
O
O
N
O
O

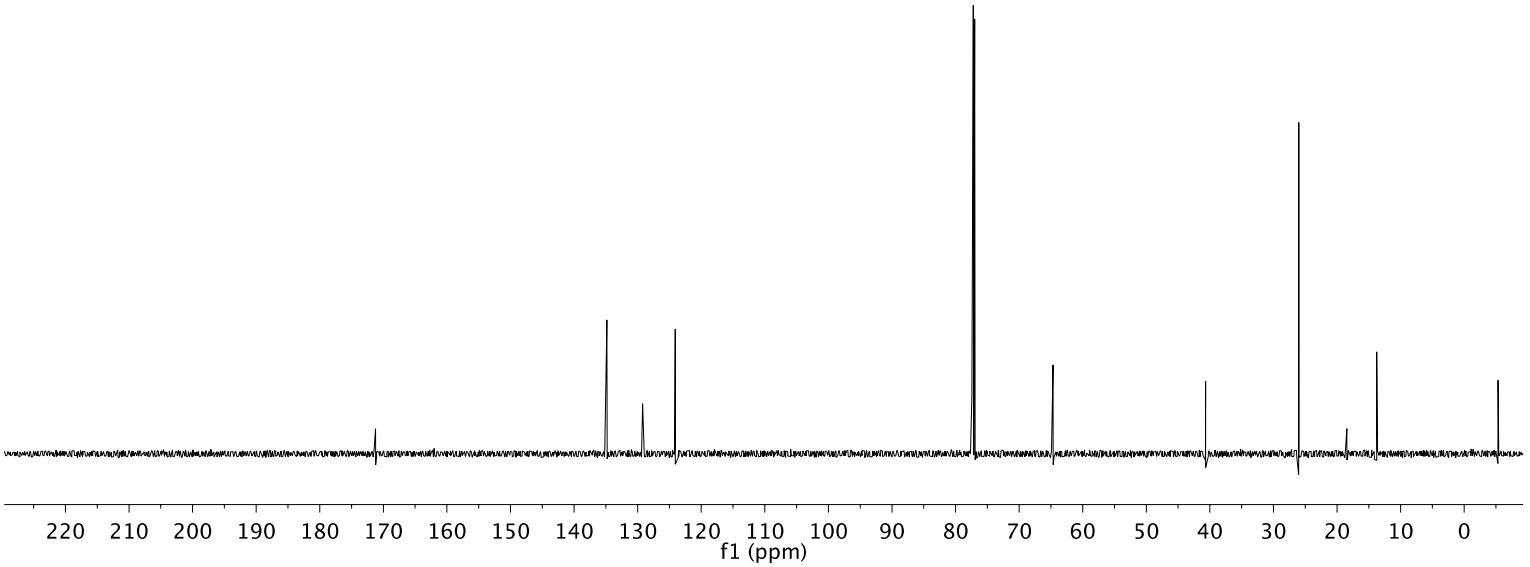
(+)-SI-1

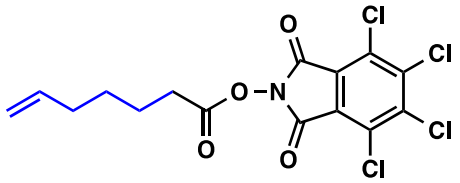

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TBSO
Me
O
O
O
N
O
(-)-SI-1
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

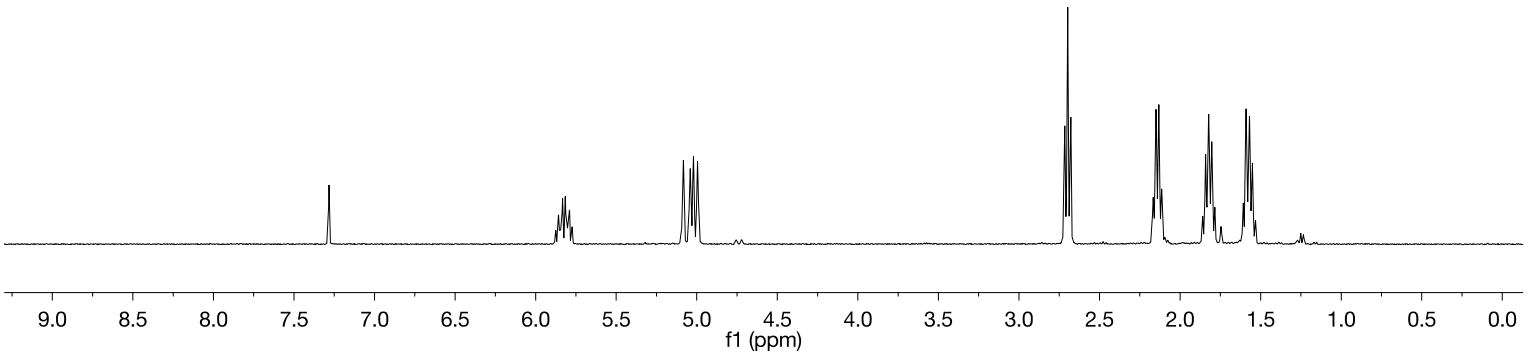

TBSO
Me
O
O
O
N
O

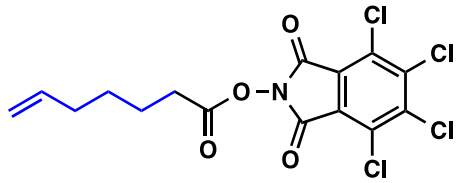
(-)-SI-1


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

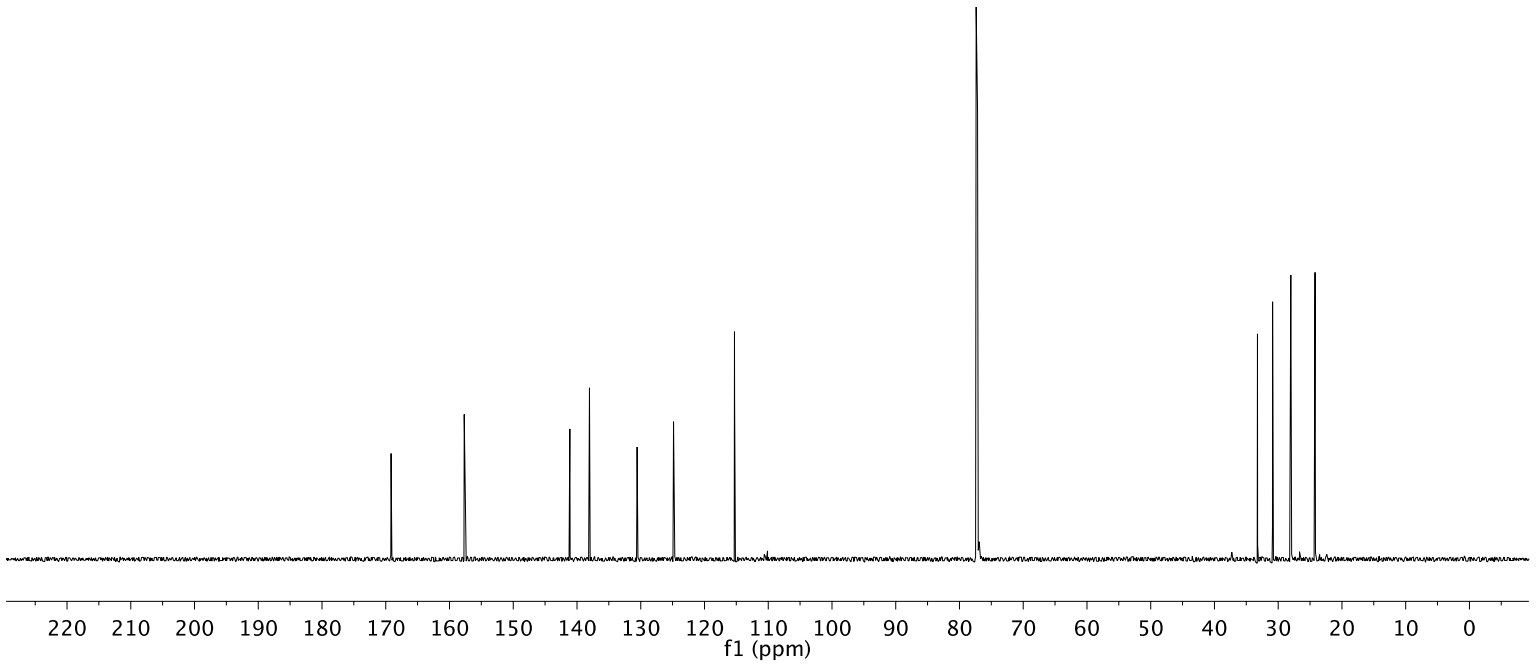

O
Cl
Cl
O
N
Cl
O
O
Cl

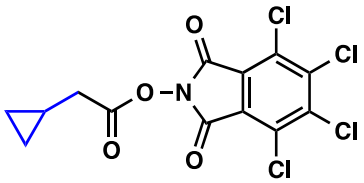
SI-3


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
Cl
Cl
O
N
O
Cl
O
Cl

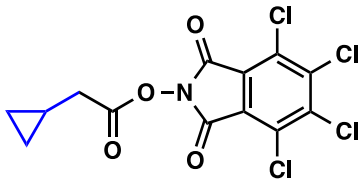
SI-3


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
Cl
Cl
O
N
Cl
O
O
Cl

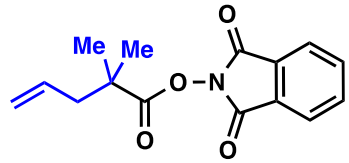
SI-8

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
Cl
Cl
O
N
Cl
O
O
Cl

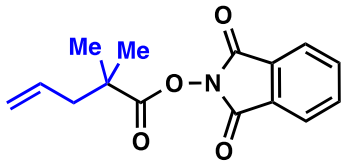
SI-8

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

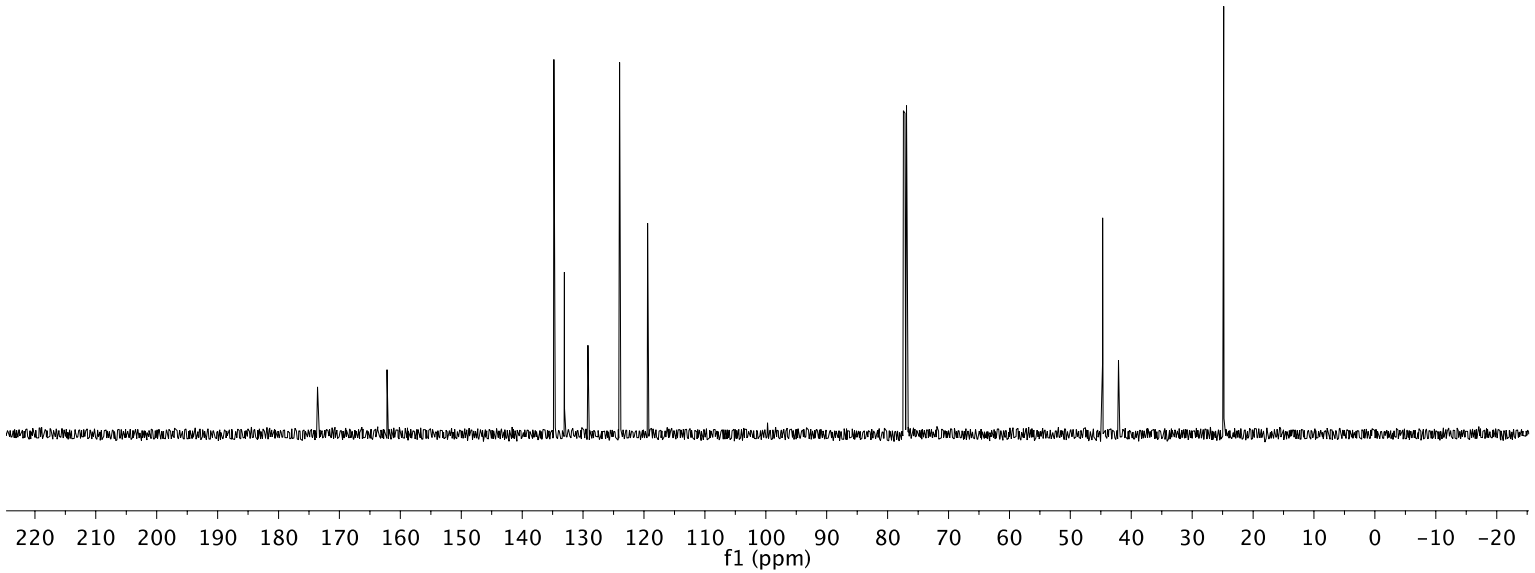

Me
Me
O
O
N
O
O

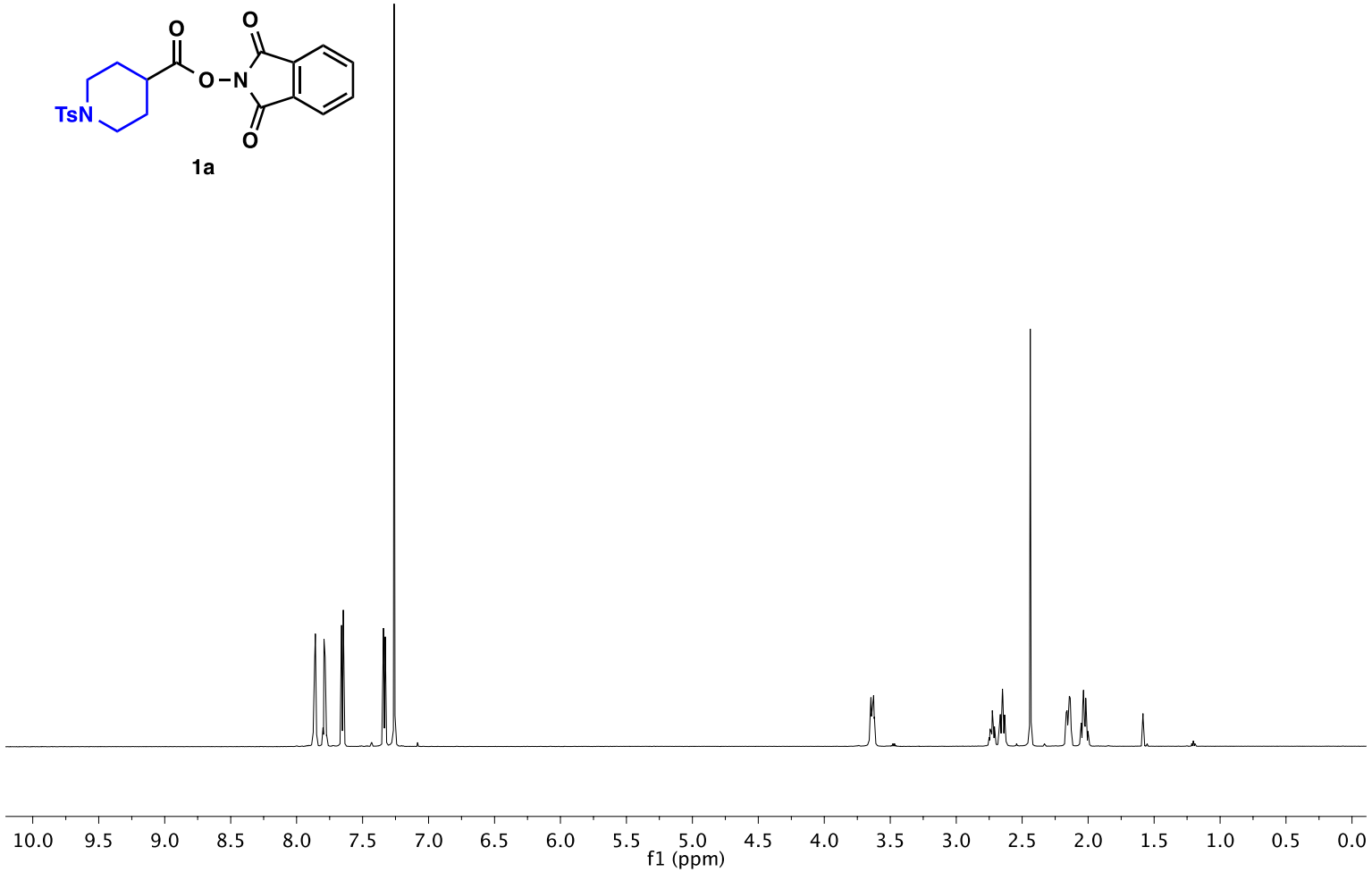
SI-11

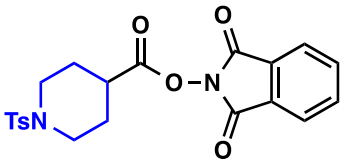
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
O
O
N
O
O

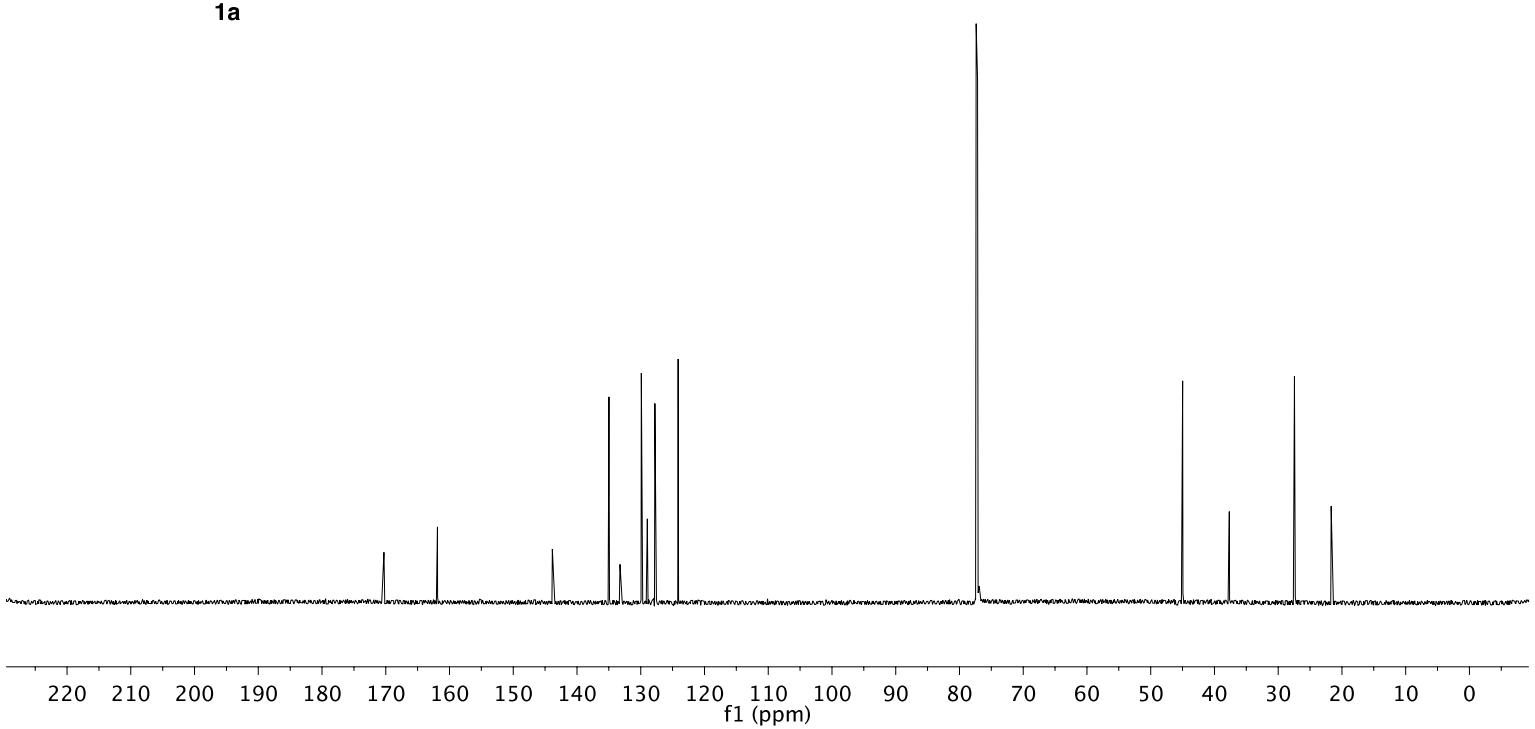
SI-11

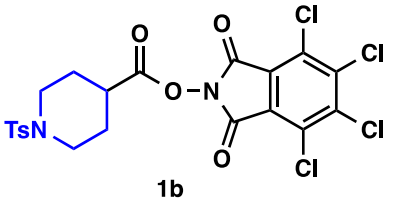

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


O
O
O
O–N
TsN
O
1a
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

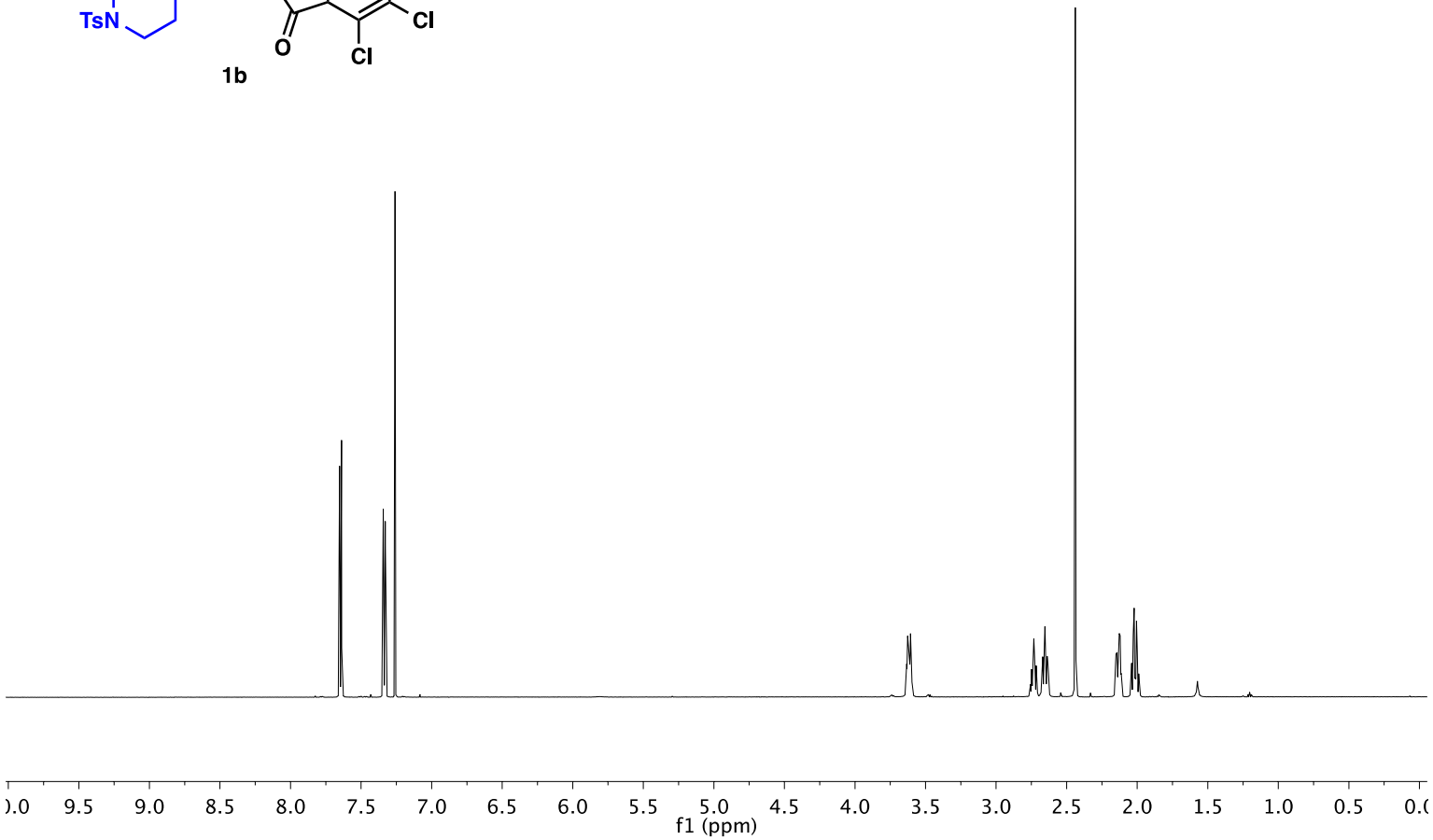

O
O
O–N
O
TsN

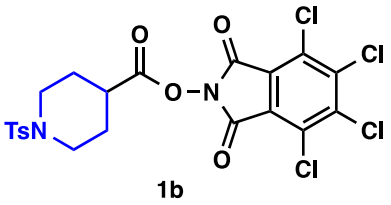
1a


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

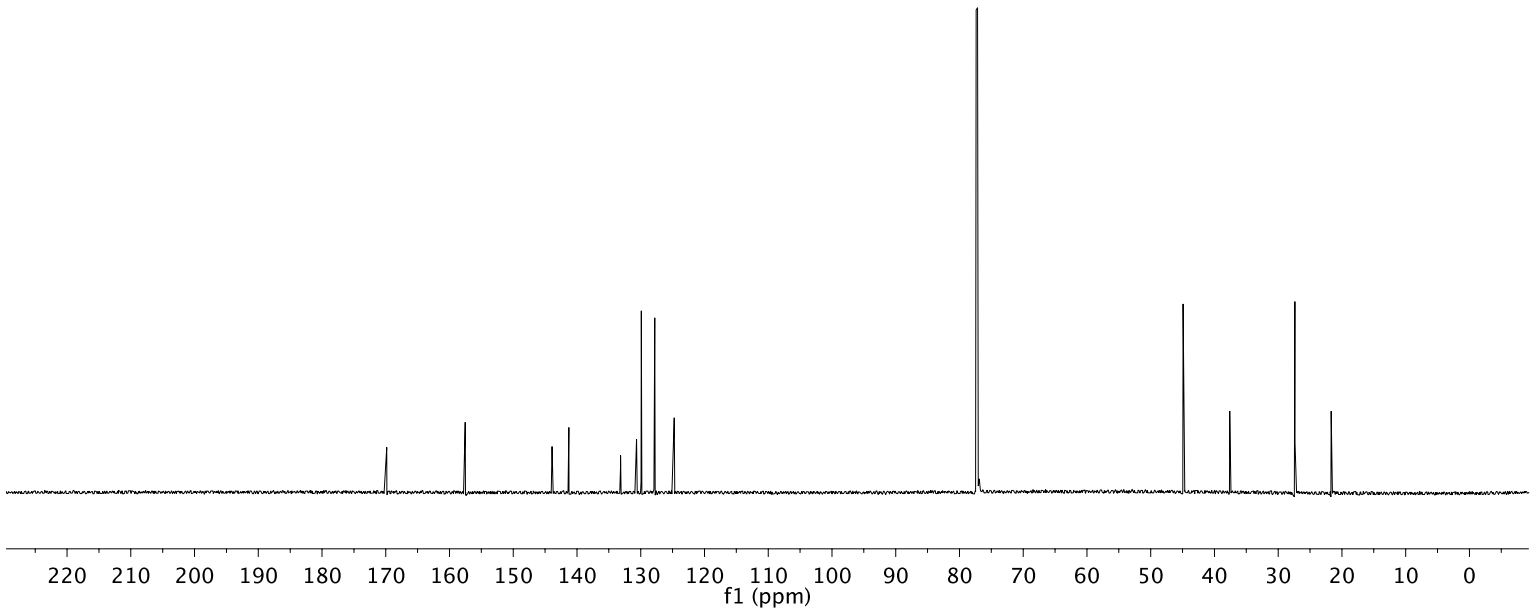

O
O
Cl
Cl
TsN
O–N
Cl
O
Cl

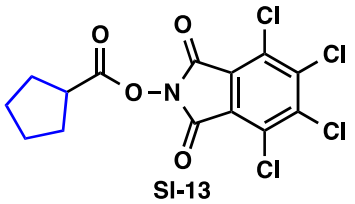
1b


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

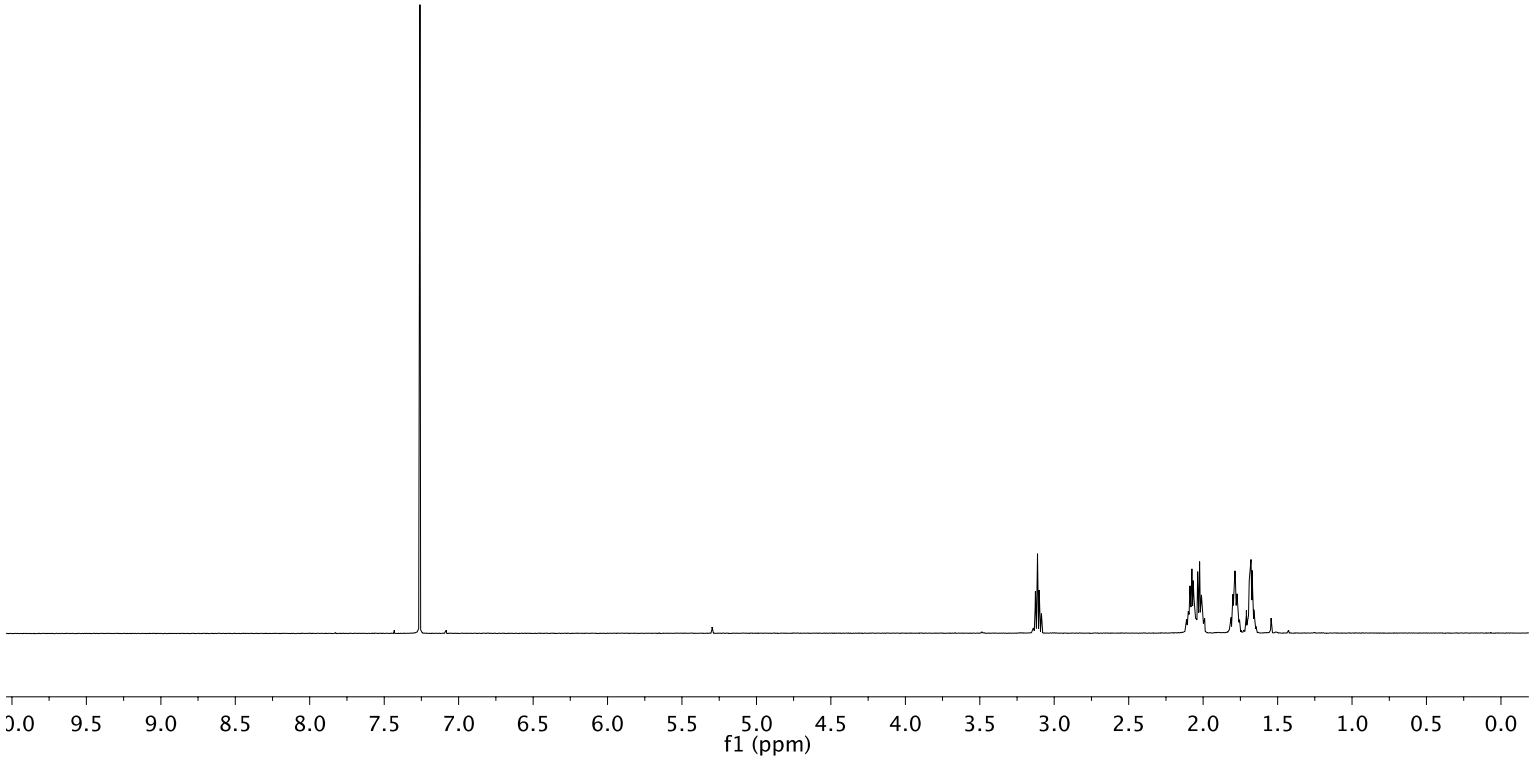

O
O
Cl
Cl
O–N
TsN
Cl
O
Cl

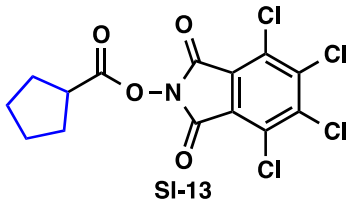
1b


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

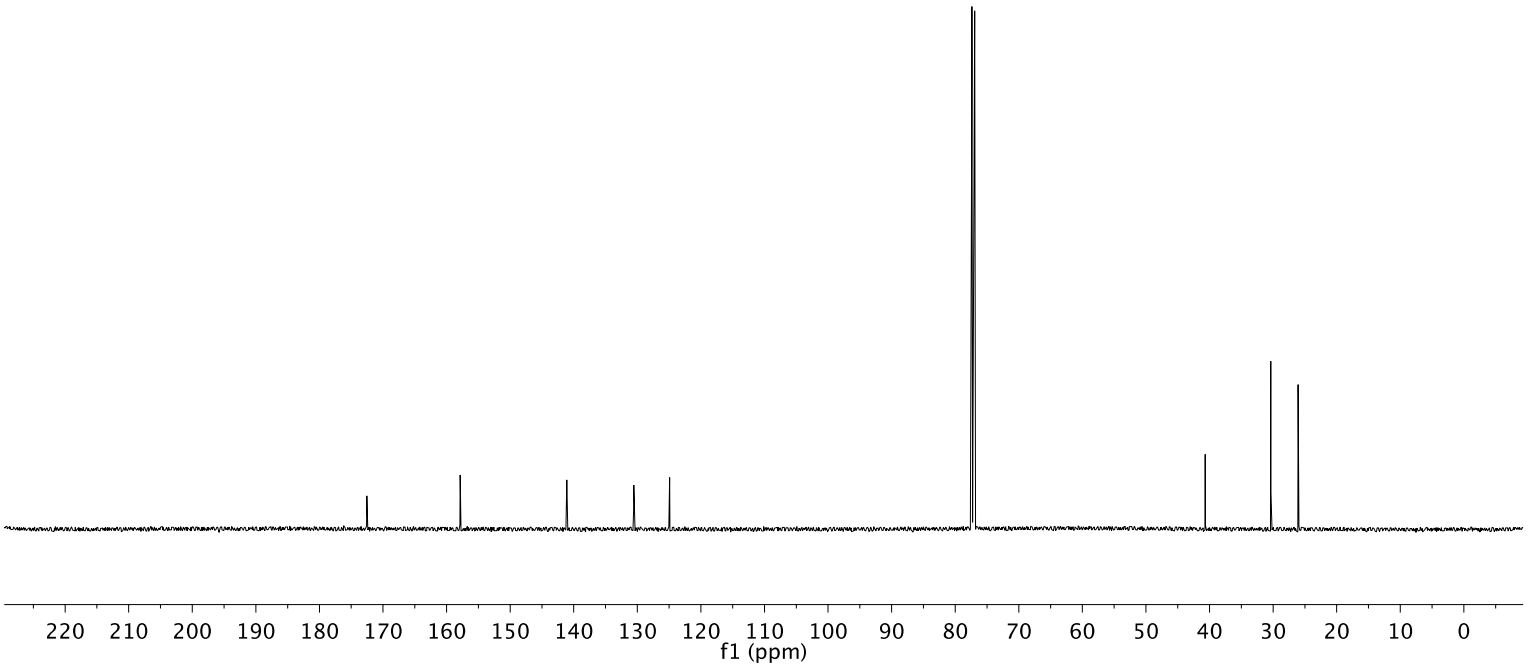

O
O
O
O
N
Cl
Cl
Cl
Cl

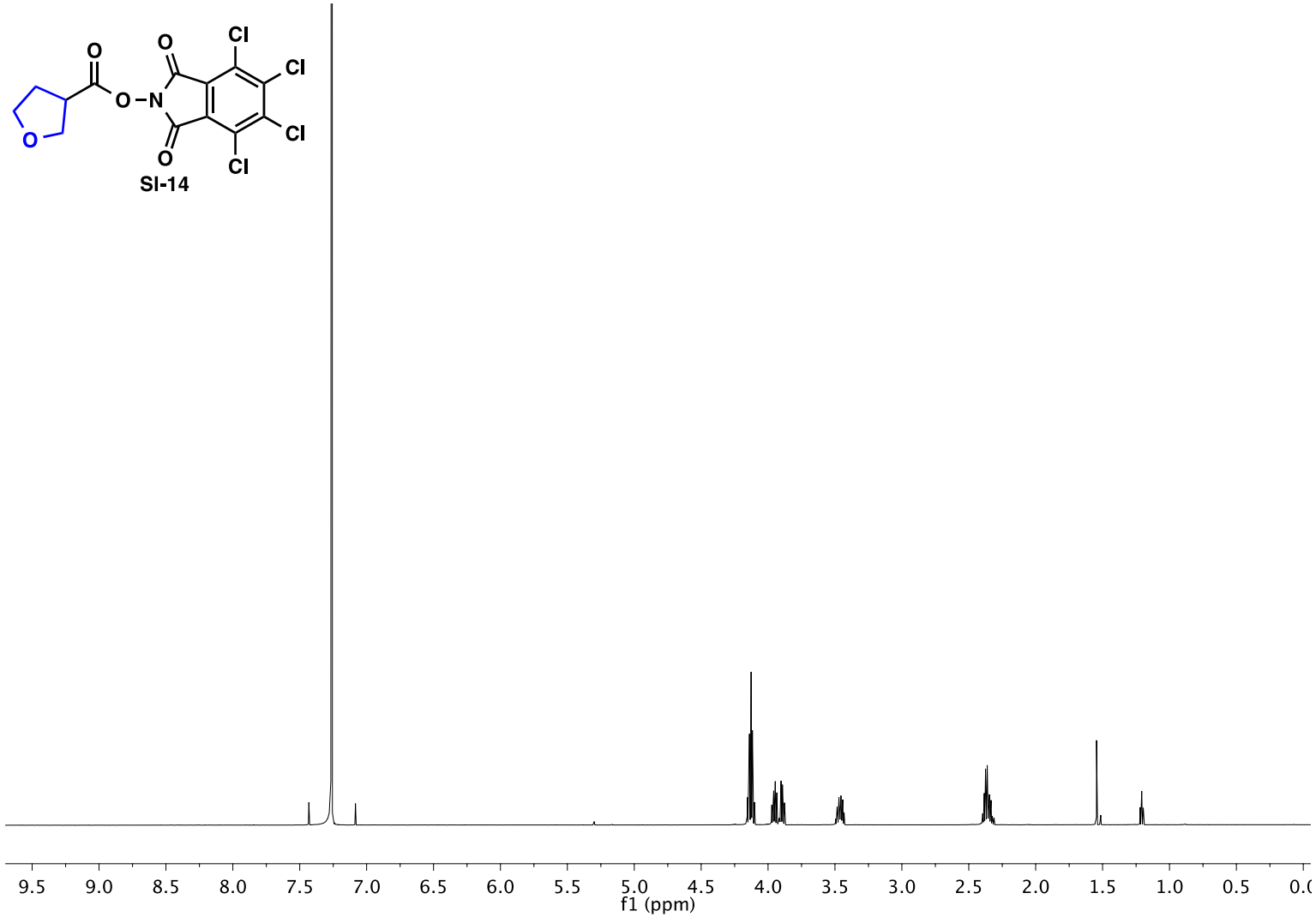
SI-13

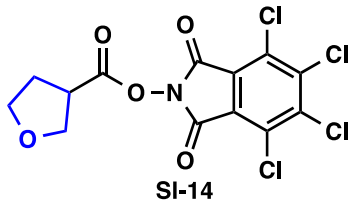

0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
O–N
O
Cl
Cl
Cl
Cl

SI-13

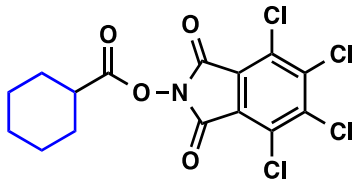

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O
O
N
O
Cl
Cl
Cl
Cl
SI-14
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

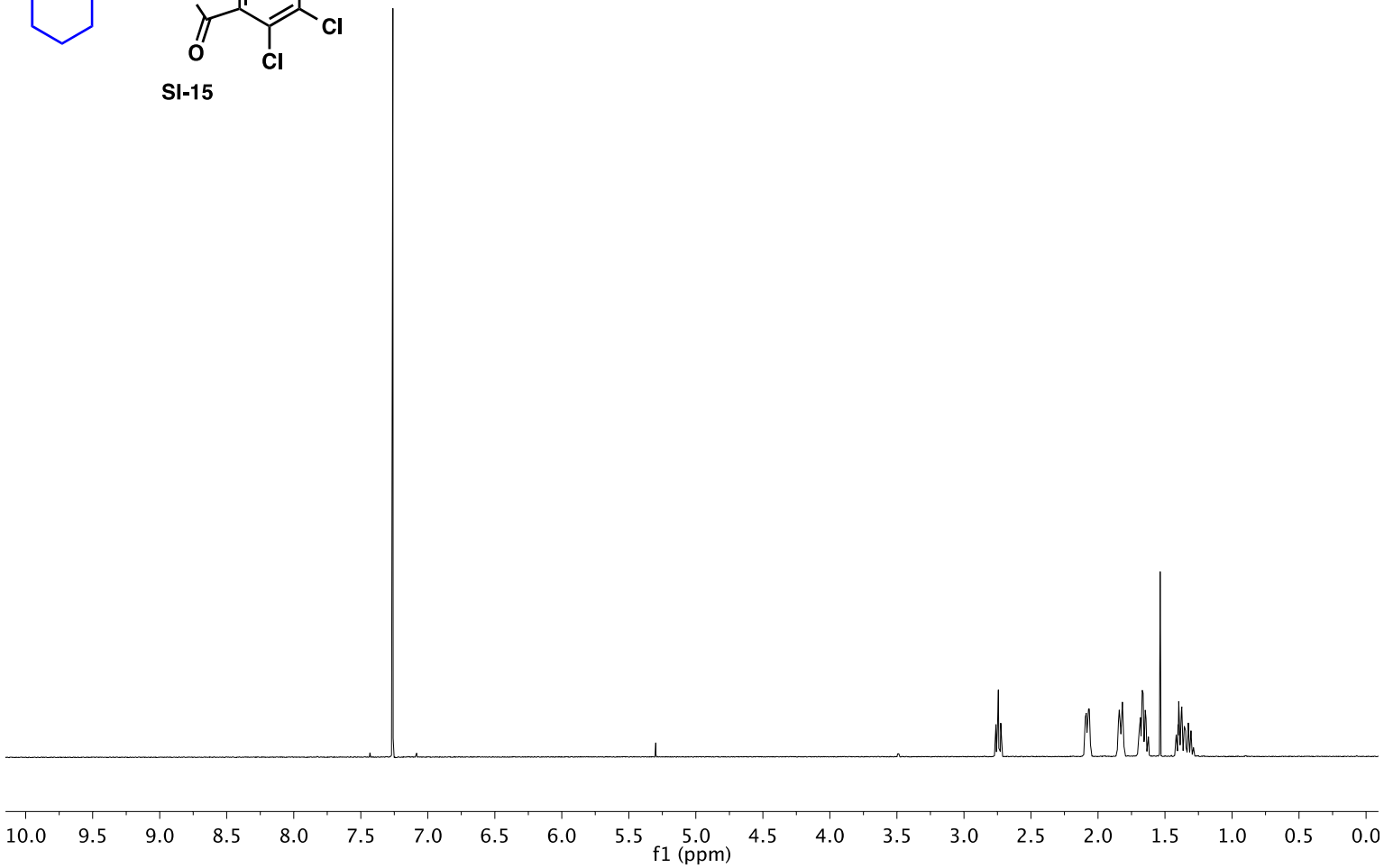

O
O
O
O
N
Cl
Cl
Cl
Cl

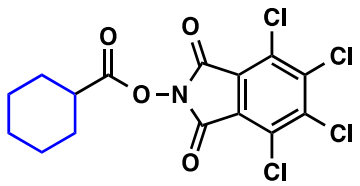
SI-14

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
Cl
Cl
O–N
Cl
O
Cl

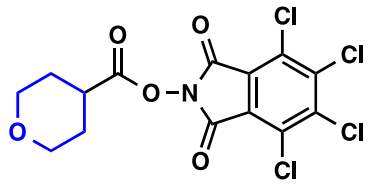
SI-15


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

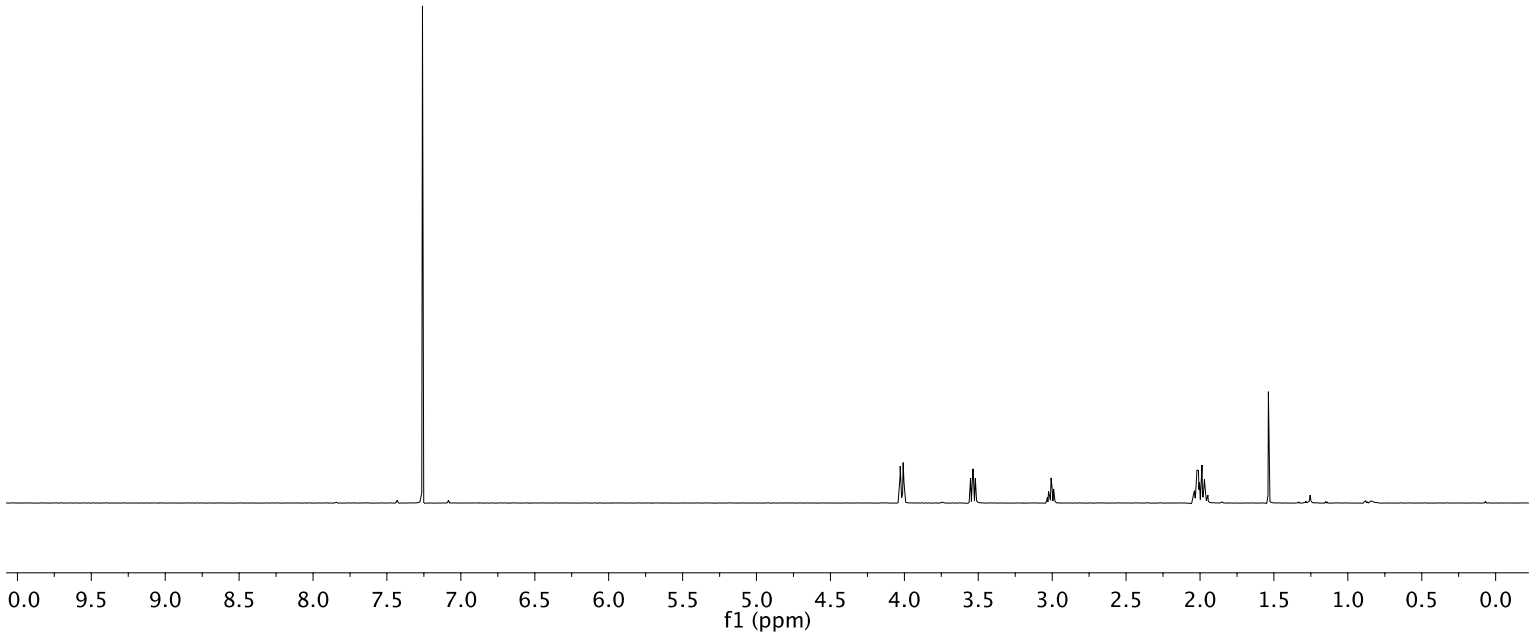

O
O
O
O–N
O
Cl
Cl
Cl
Cl

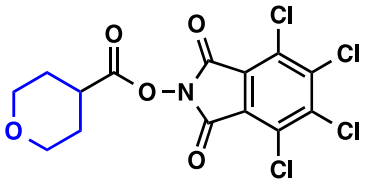
SI-15

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
O
N
O
O
Cl
Cl
Cl
Cl

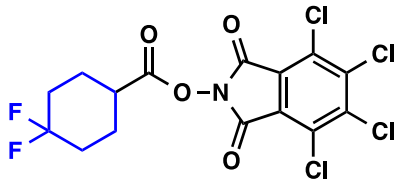
SI-16


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
O
N
O
Cl
Cl
Cl
Cl
O

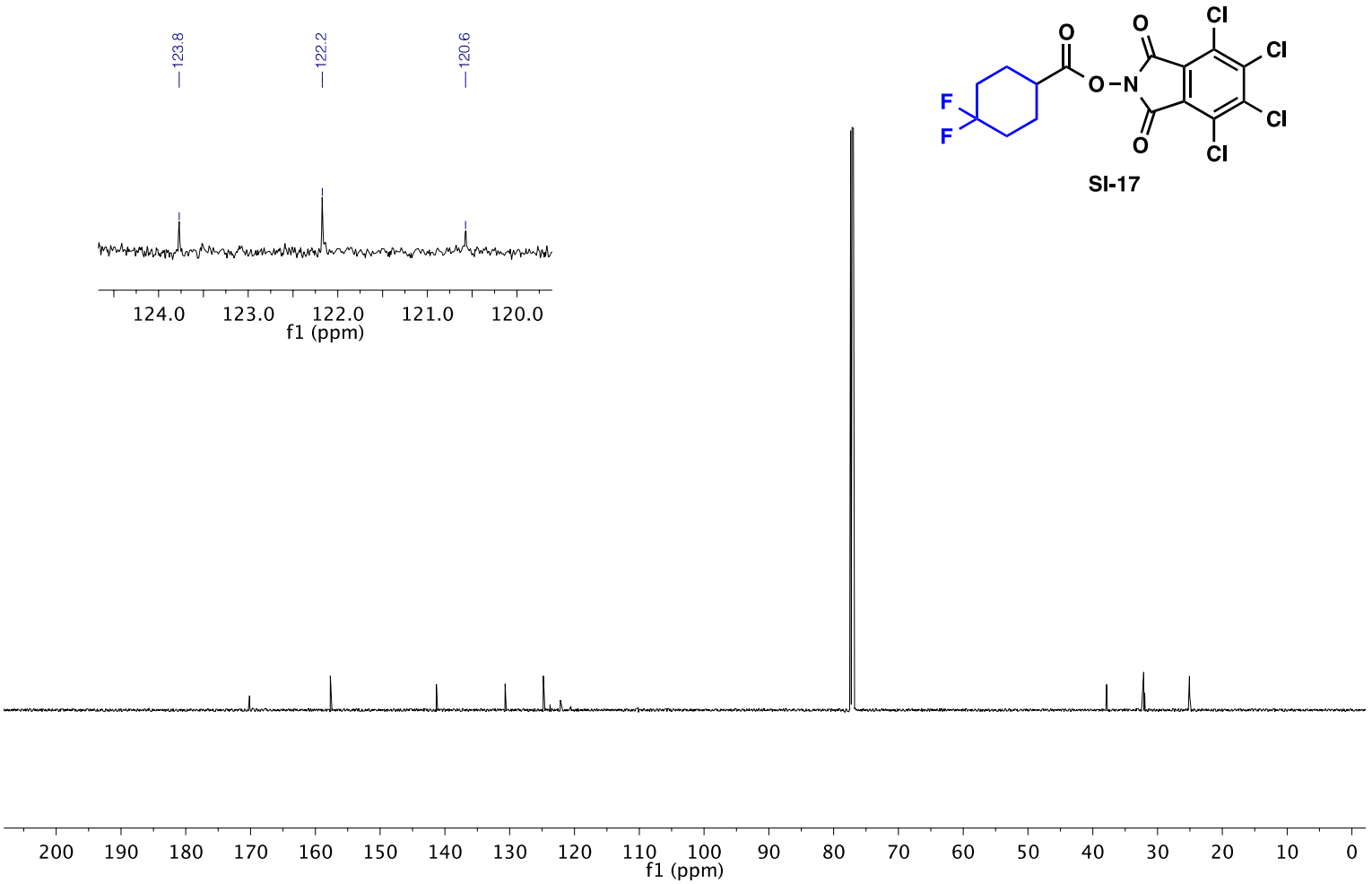
SI-16

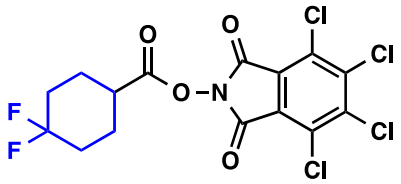
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O
N
O
F
F
Cl
Cl
Cl
Cl

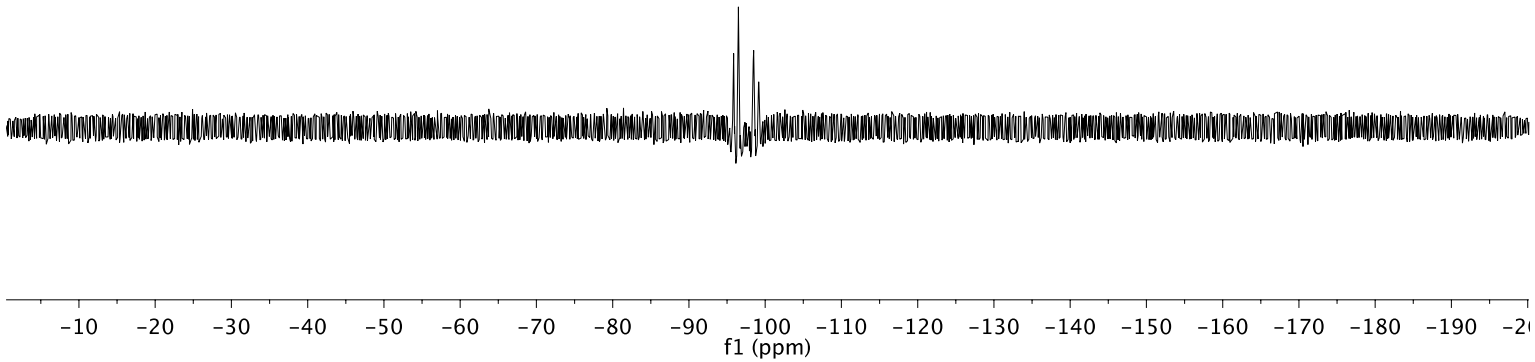
SI-17

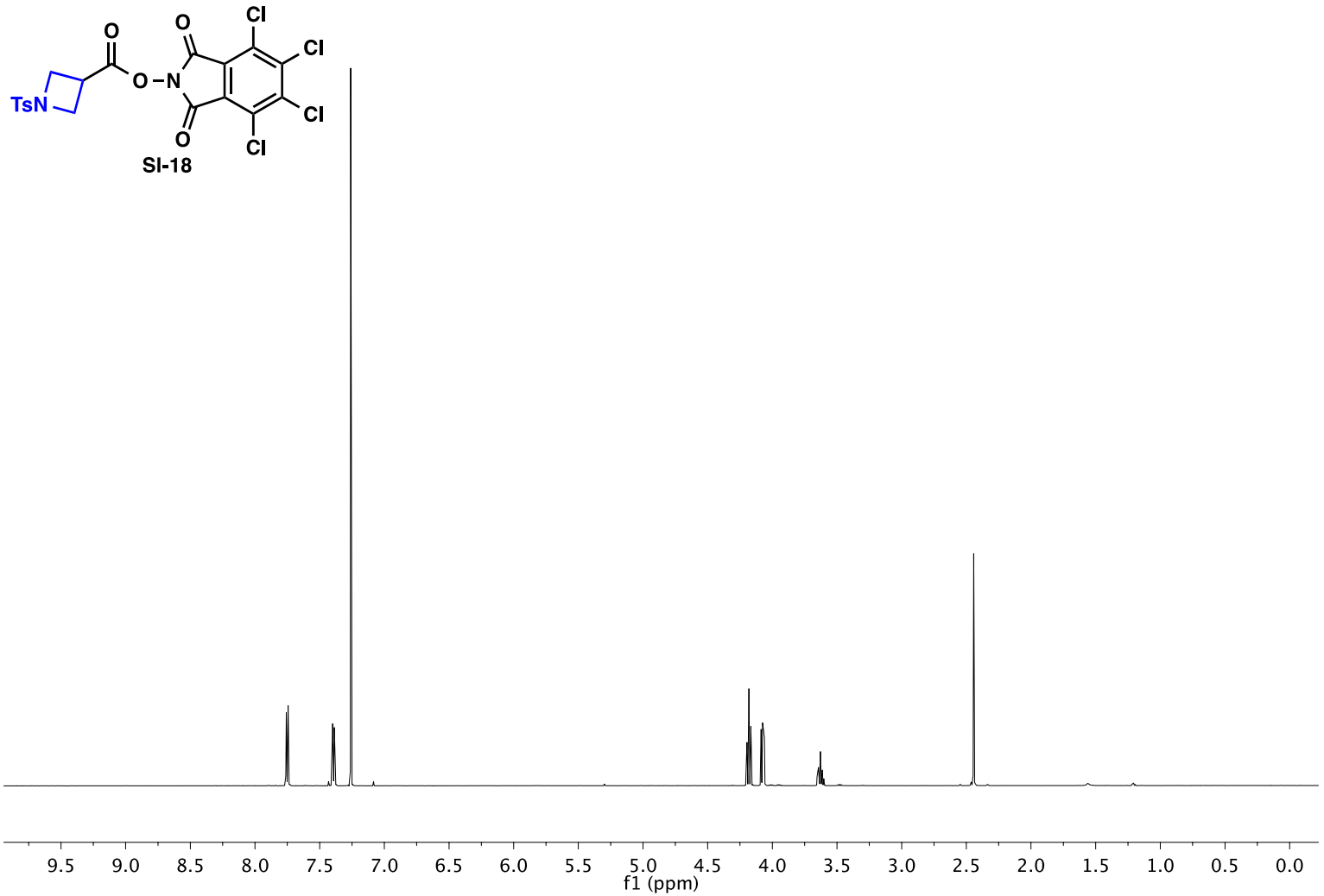
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

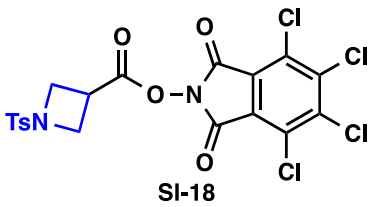

123.8
122.2
120.6
124.0
123.0
122.0
121.0
120.0
f1 (ppm)
O
O
O
N
O
F
F
Cl
Cl
Cl
Cl
SI-17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
Cl
Cl
O–N
Cl
F
F
O
Cl

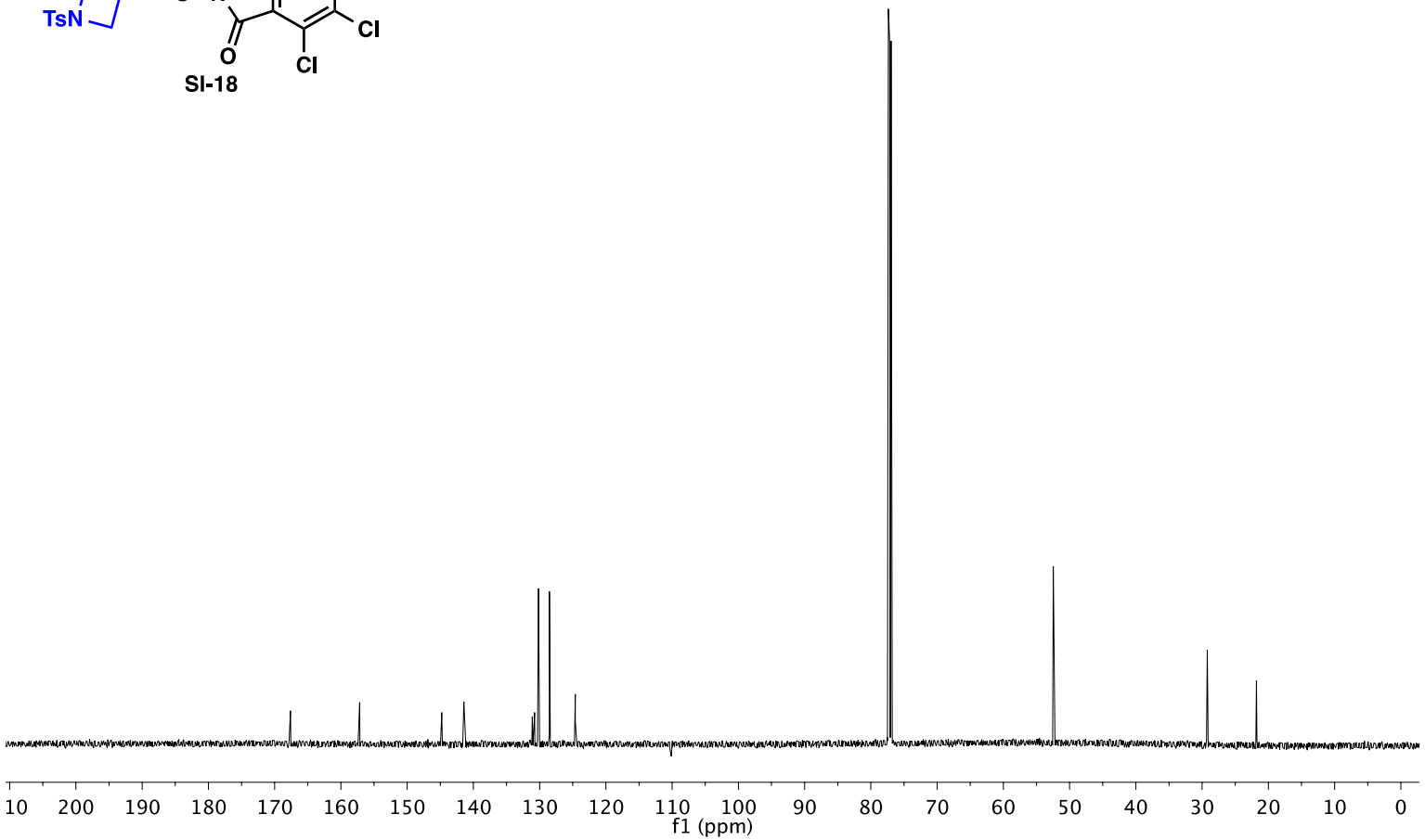
SI-17

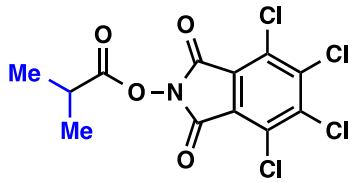

−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
f1 (ppm)


TsN
O
O
O
O
N
Cl
Cl
Cl
Cl
SI-18
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

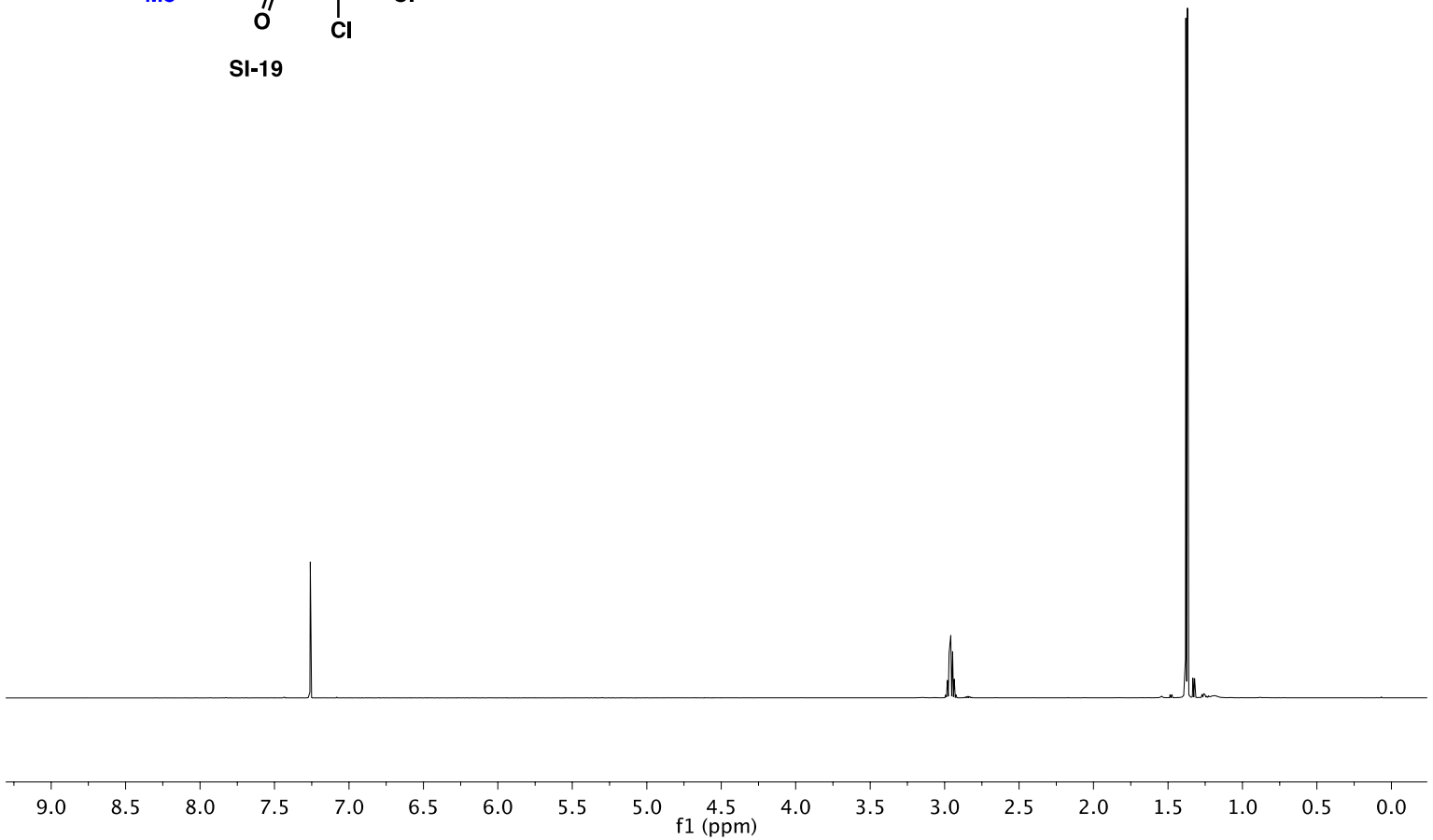

O
O
Cl
Cl
O–N
TsN
Cl
O
Cl

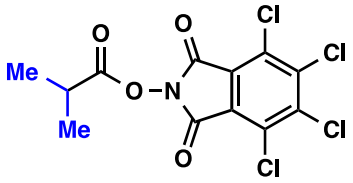
SI-18


10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

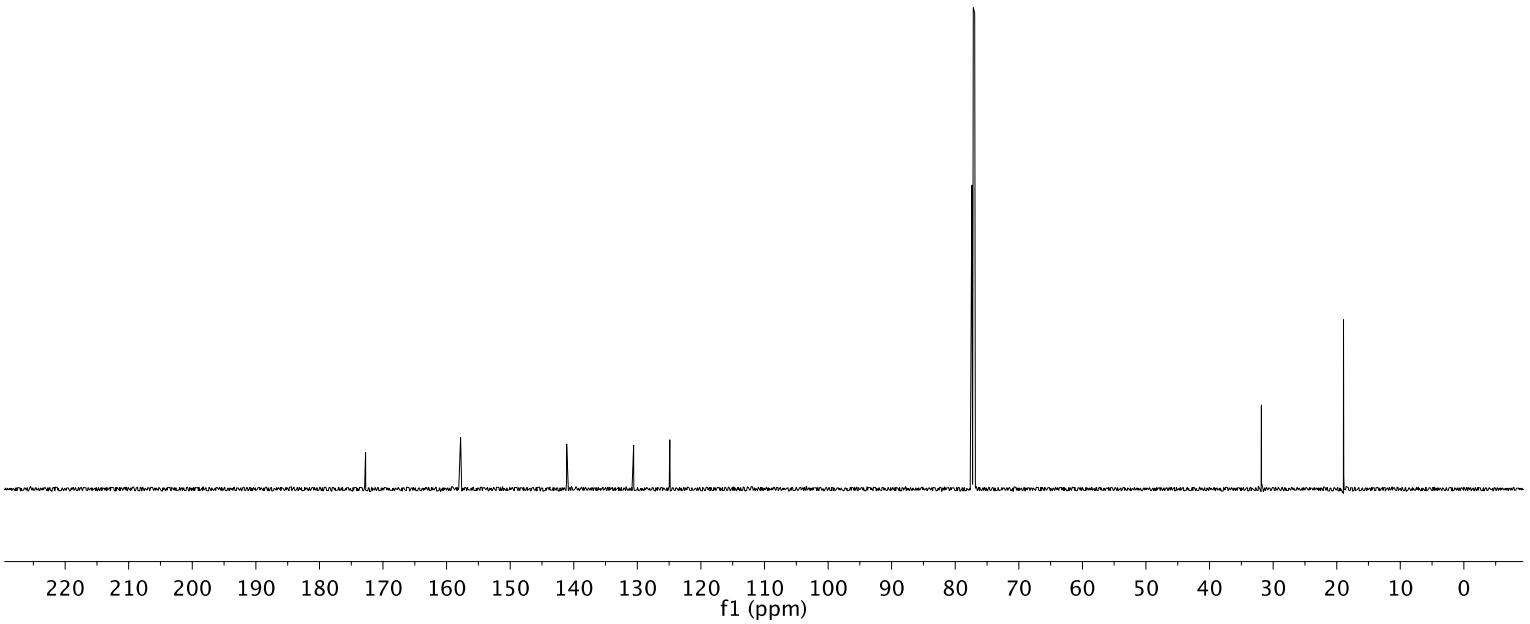

Me
Me
O
O
O
N
O
Cl
Cl
Cl
Cl

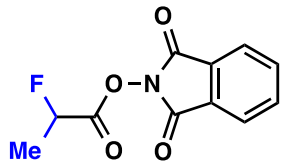
SI-19


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

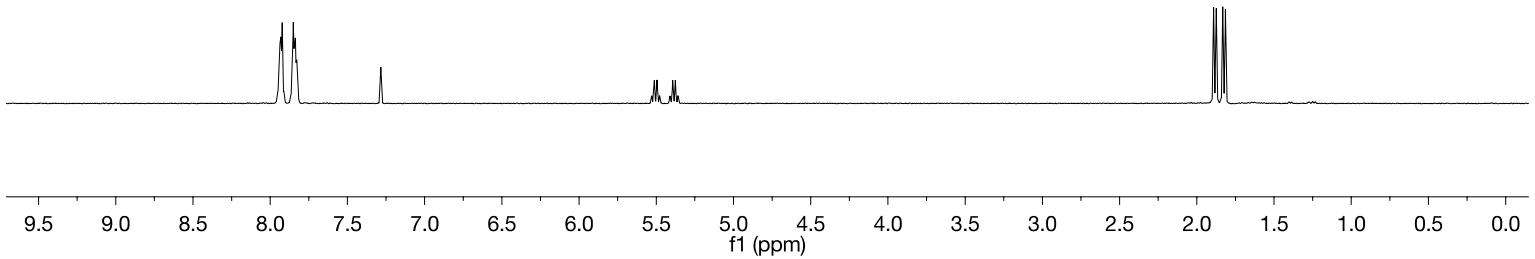

Me
Me
O
O
O
N
O
O
Cl
Cl
Cl
Cl

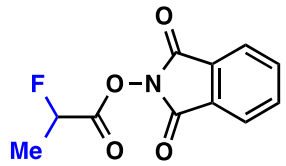
SI-19


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

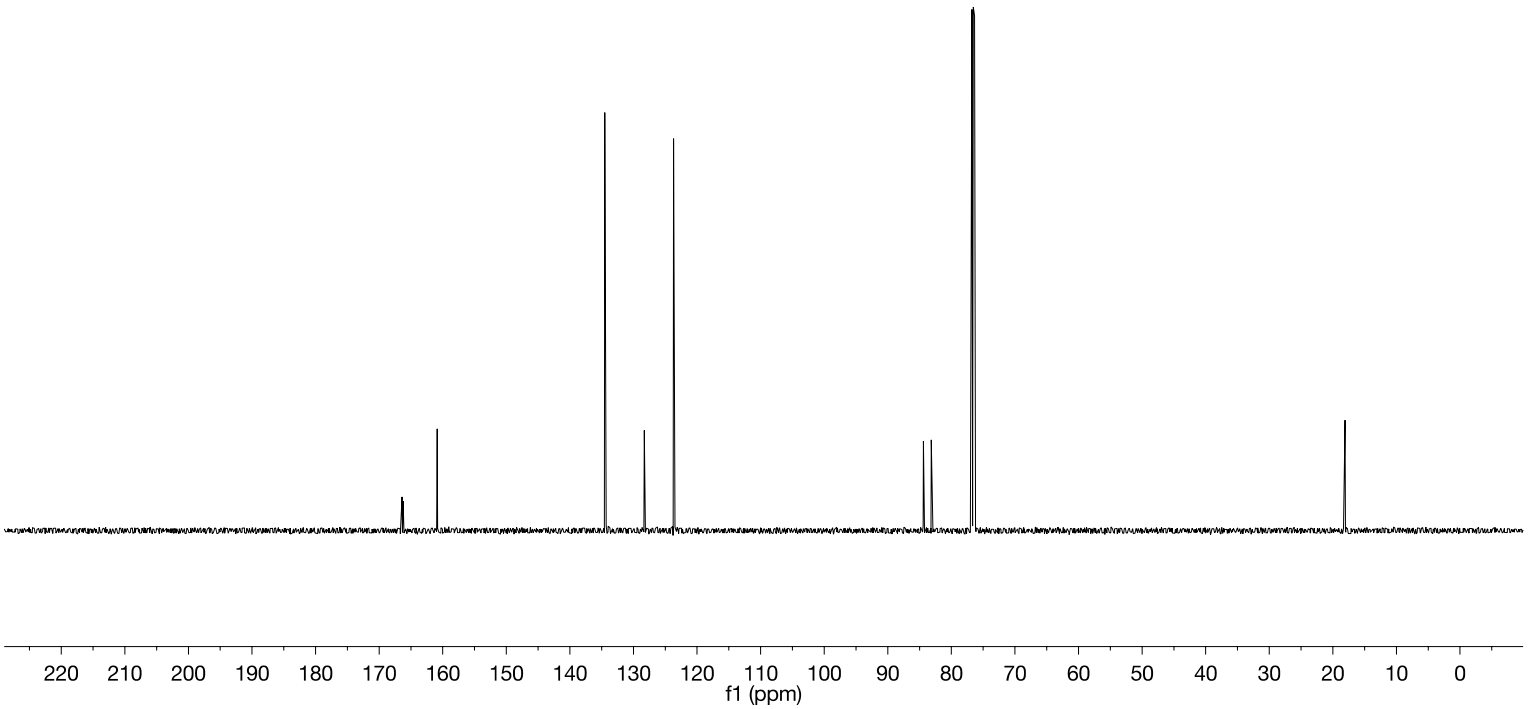

O
F
O
N
Me
O
O

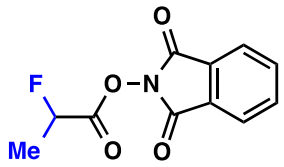
SI-20


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


F
O
O
N
Me
O
O
O

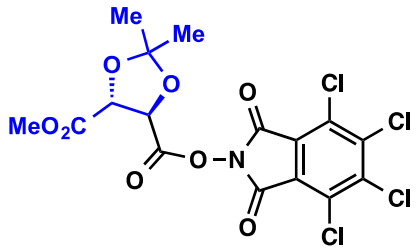
SI-20


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

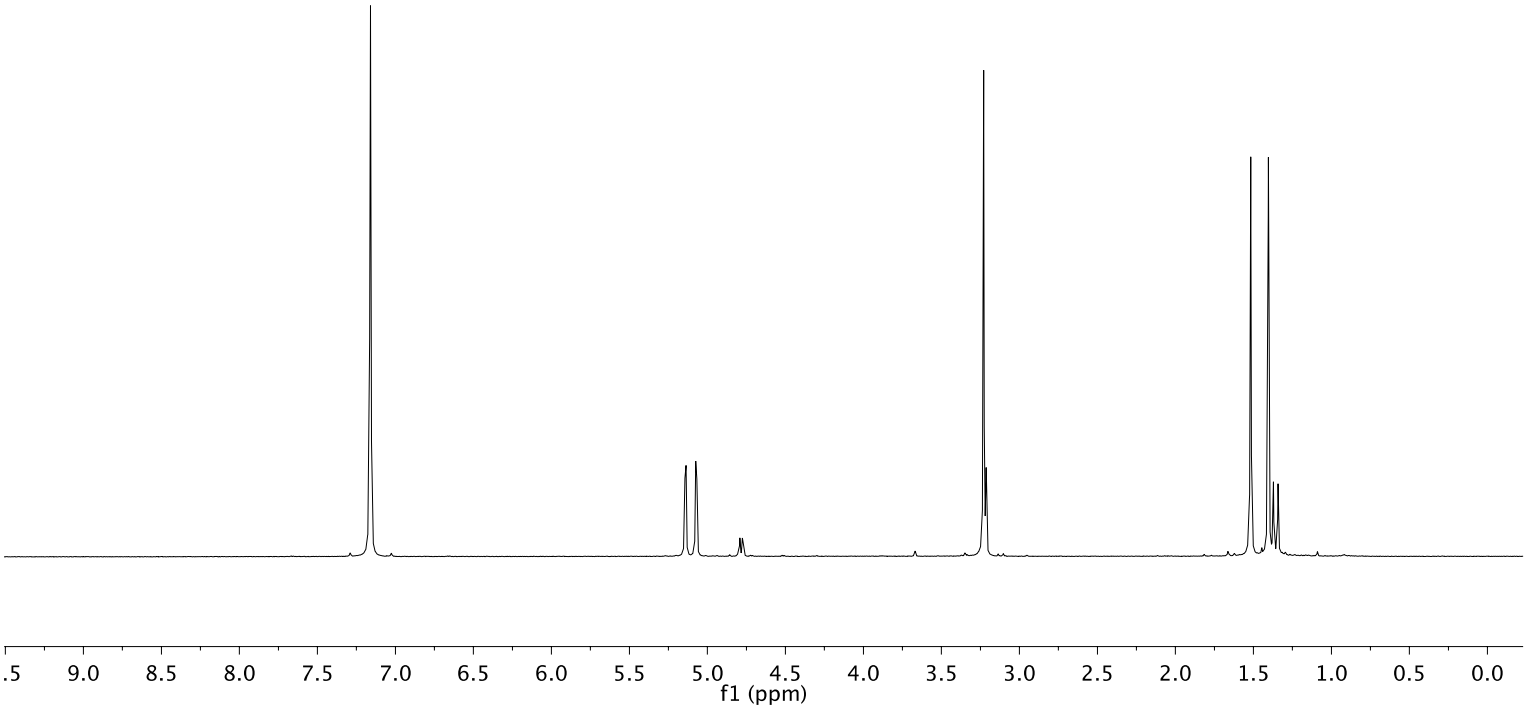

F
O
N
Me
O
O
O

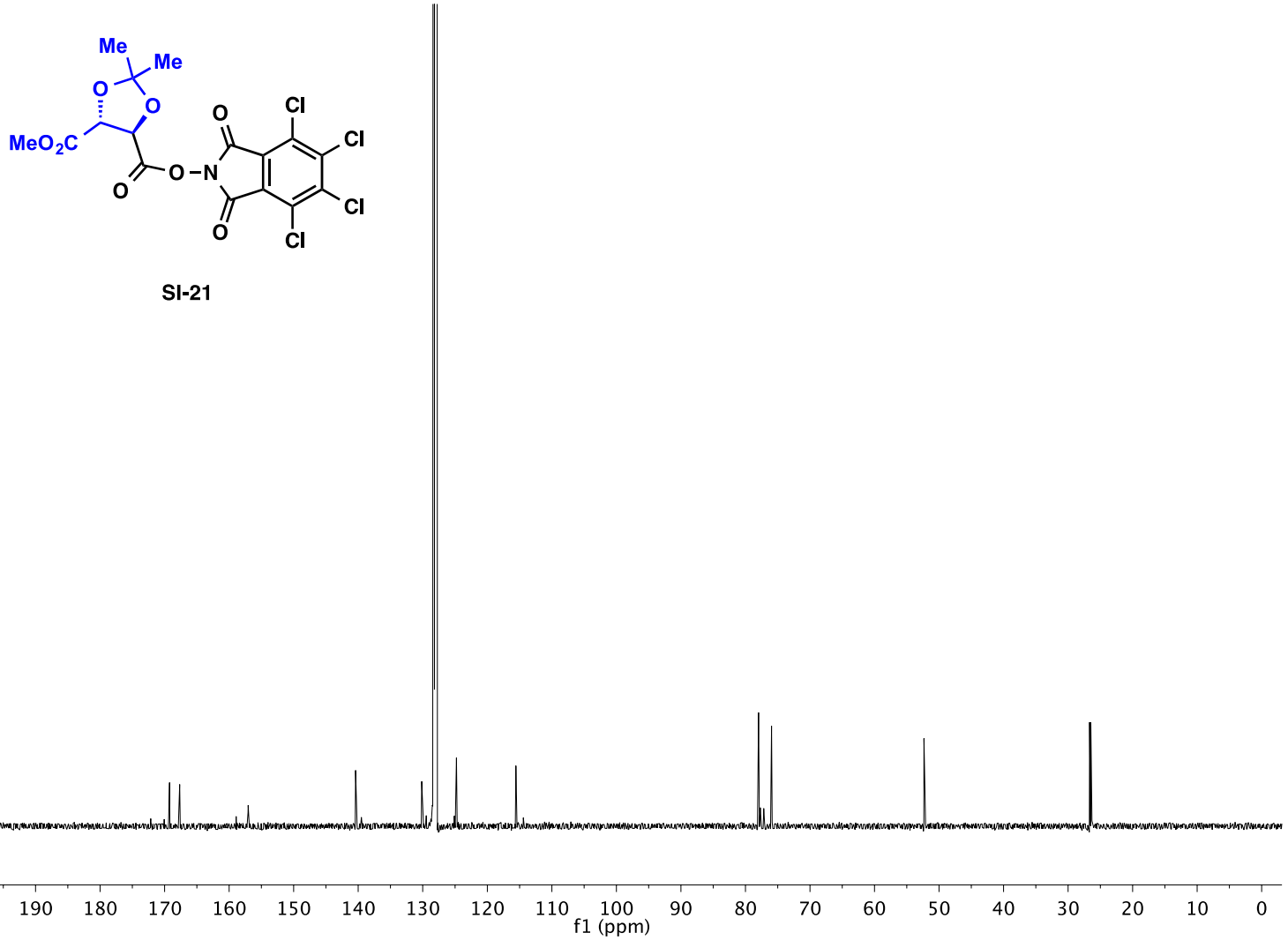
SI-20

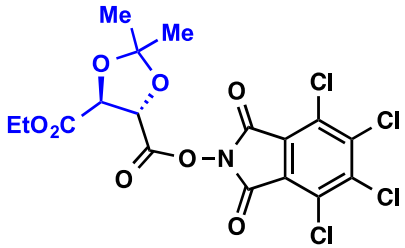
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


Me
Me
O
O
MeO2C
O
O
O
N
O
Cl
Cl
Cl
Cl

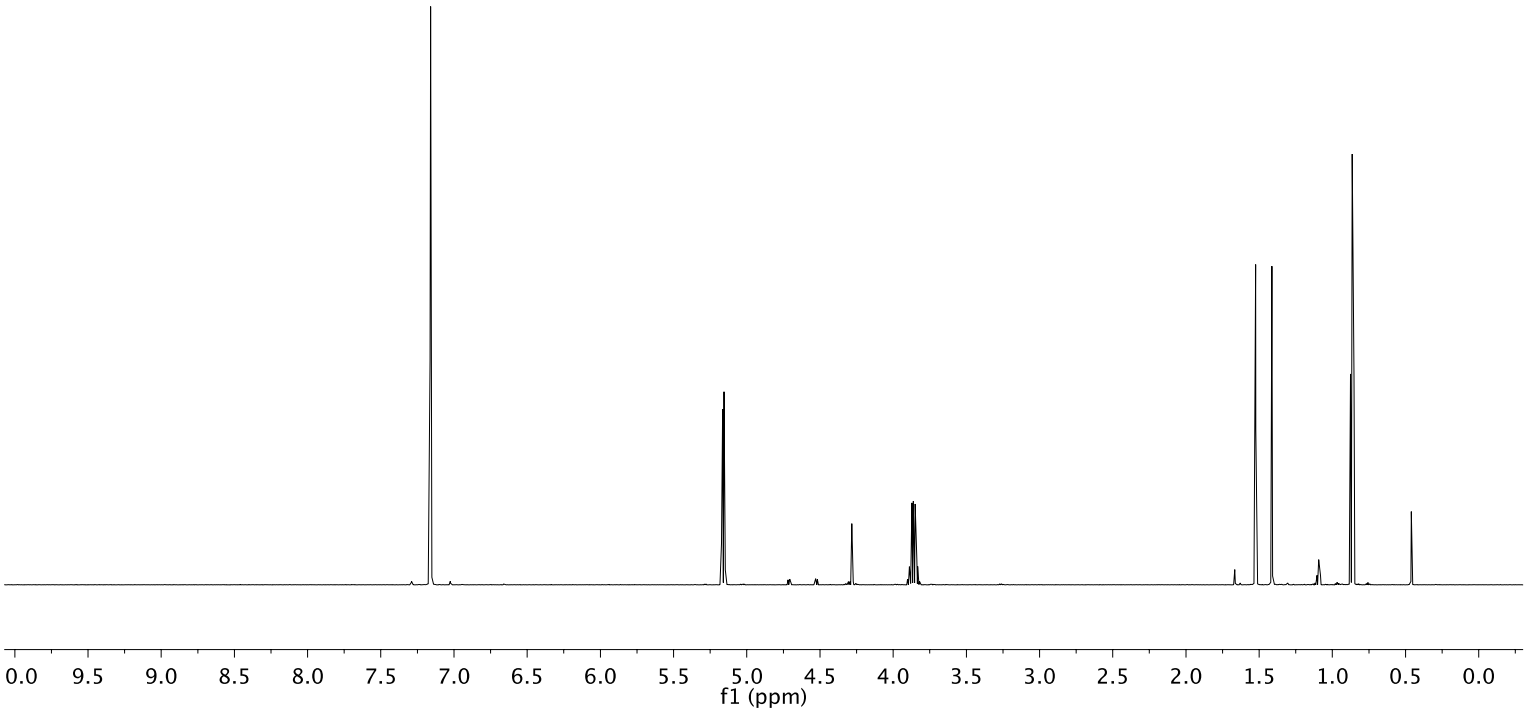
SI-21

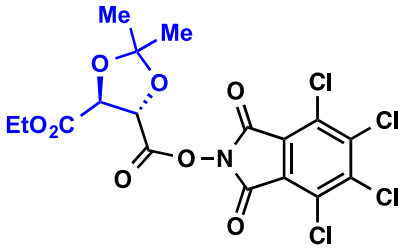

.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
O
O
MeO2C
O
O
O
N
O
Cl
Cl
Cl
Cl
SI-21
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
O
O
EtO2C
O
O
O
N
O
Cl
Cl
Cl
Cl

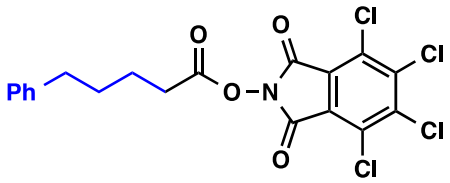
SI-22


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

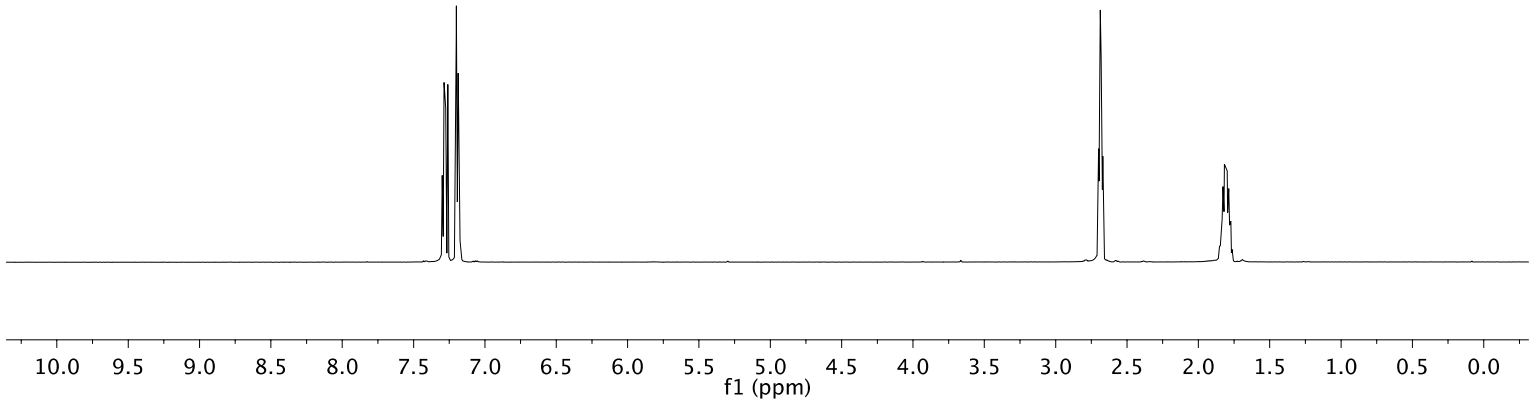

Me
Me
O
O
EtO2C
O
O
O
O–N
O
Cl
Cl
Cl
Cl

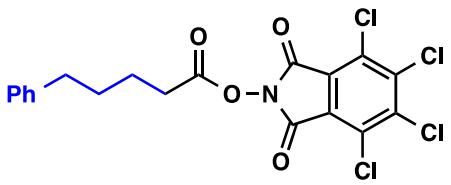
SI-22

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

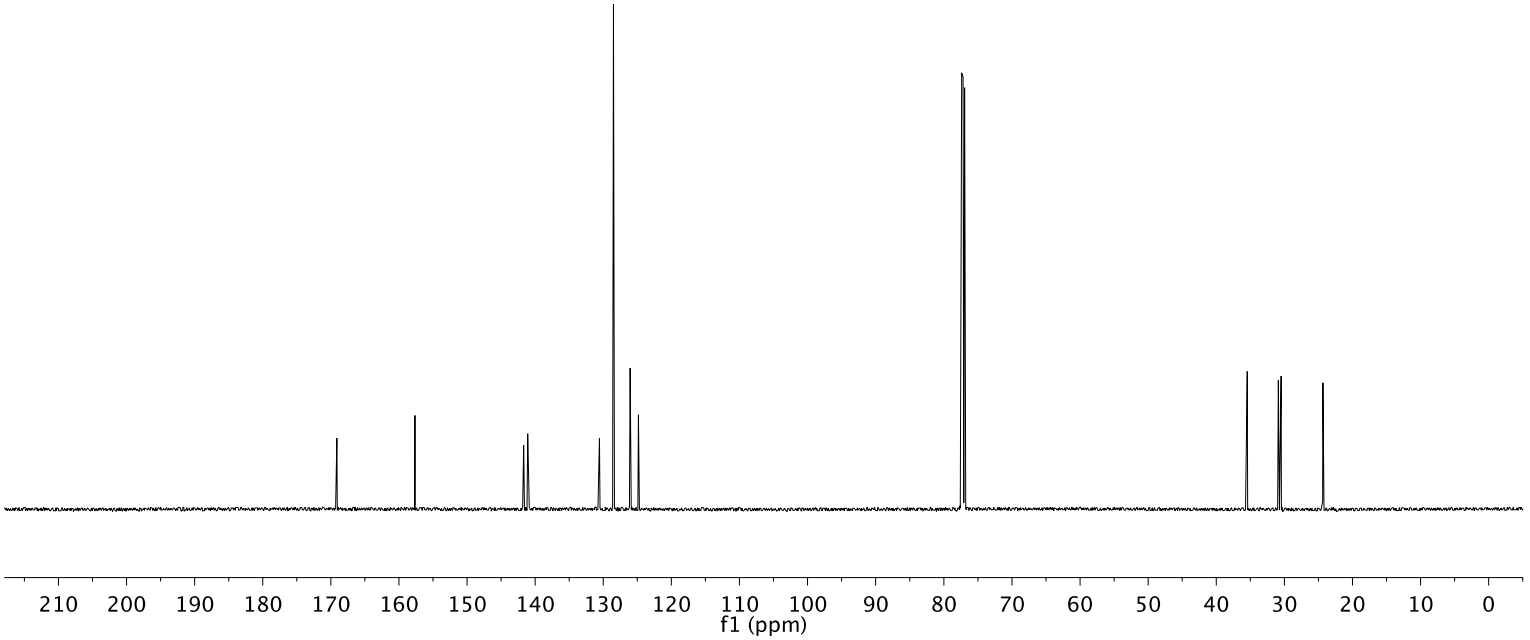

Ph
O
O
O
N
O
Cl
Cl
Cl
Cl

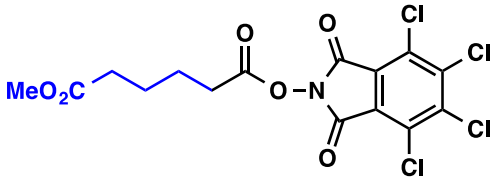
SI-23


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

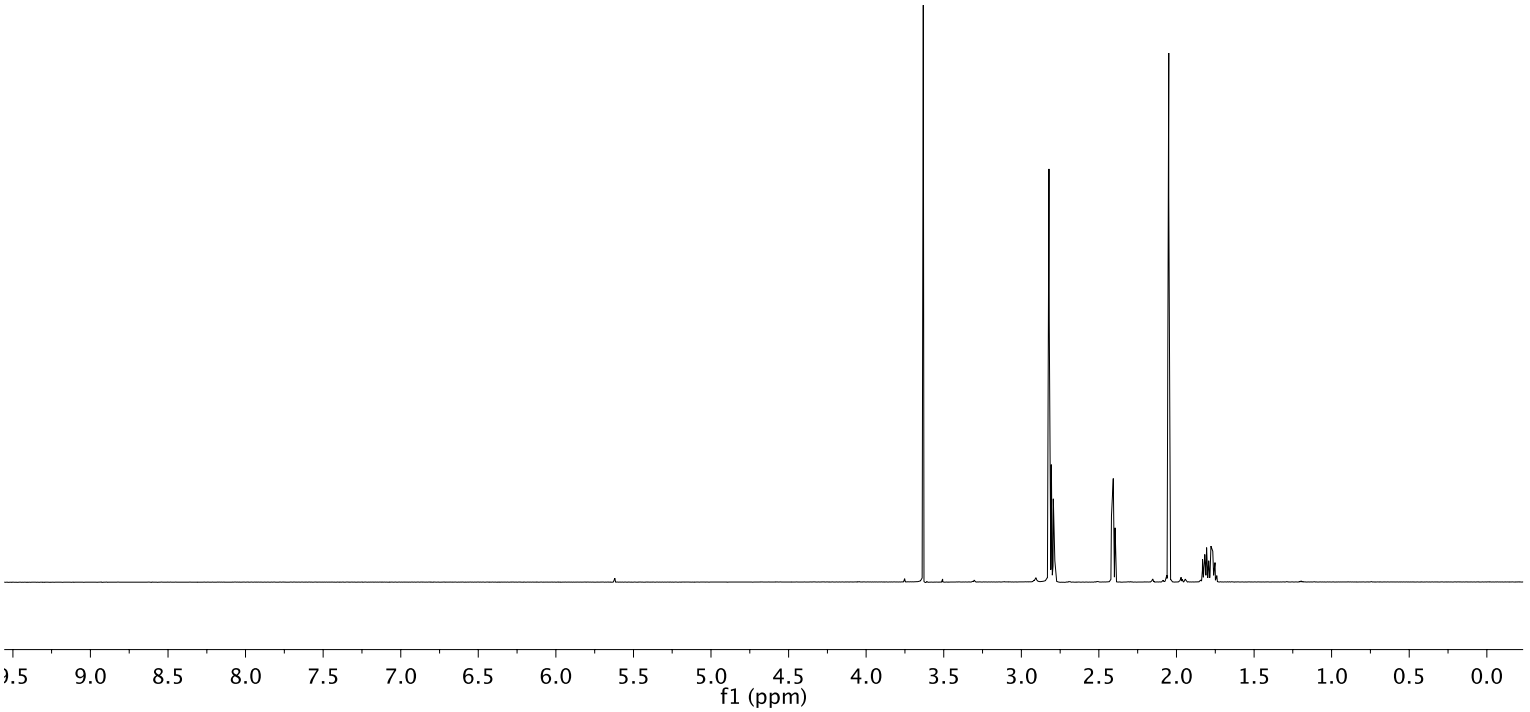

Ph
O
O
O
N
O
Cl
Cl
Cl
Cl

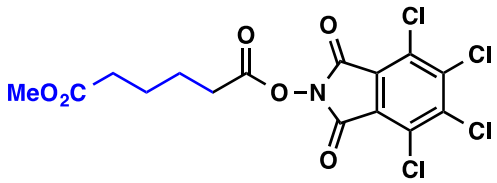
SI-23


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO2C
O
O
O
N
O
Cl
Cl
Cl
Cl

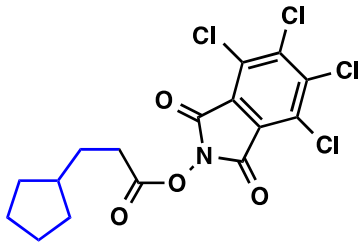
SI-24


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

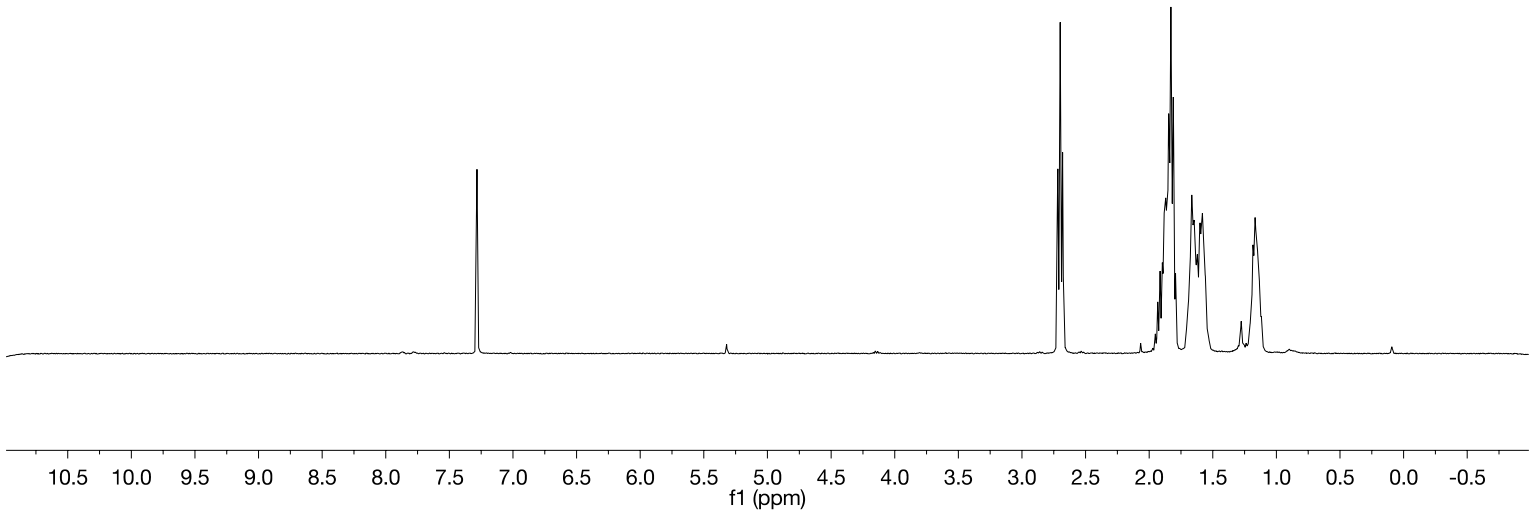

MeO2C
O
O
O
N
O
Cl
Cl
Cl
Cl

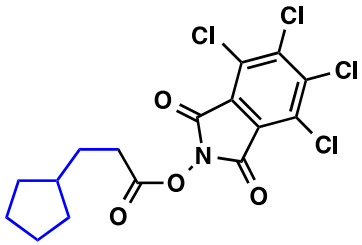
SI-24

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

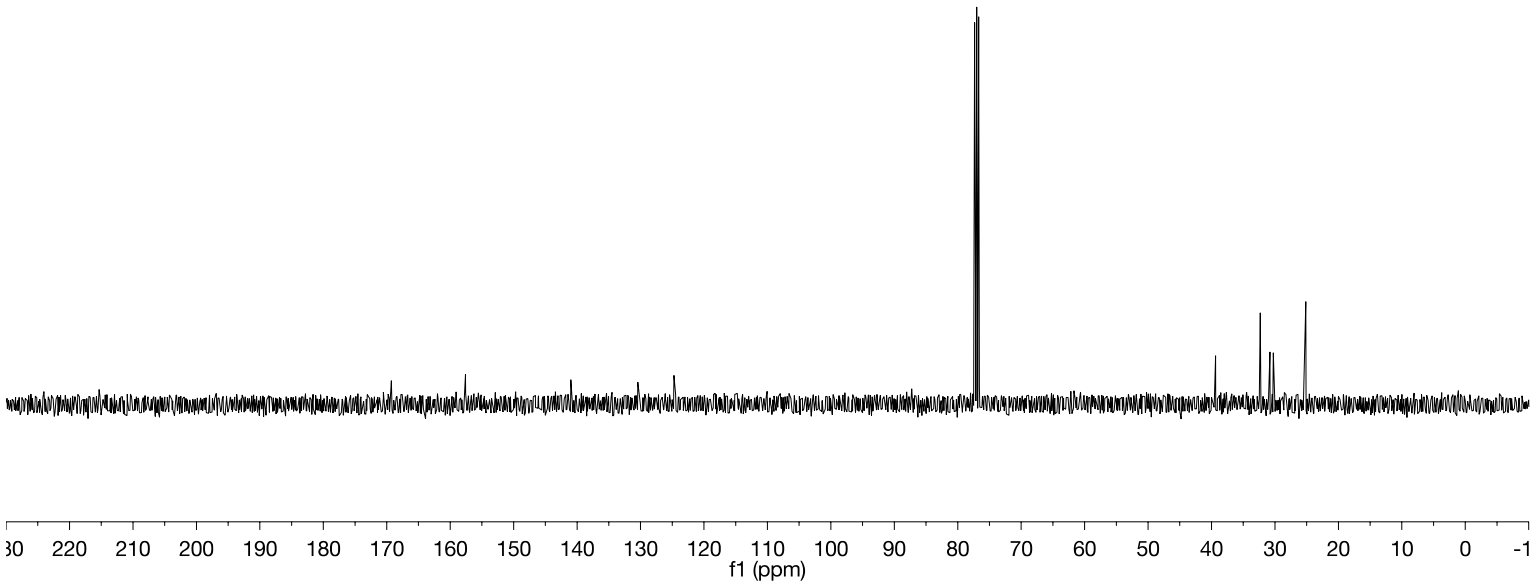

Cl
Cl
Cl
Cl
O
N
O
O
O
O

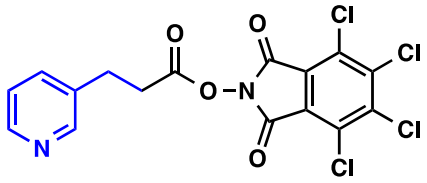
SI-25


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

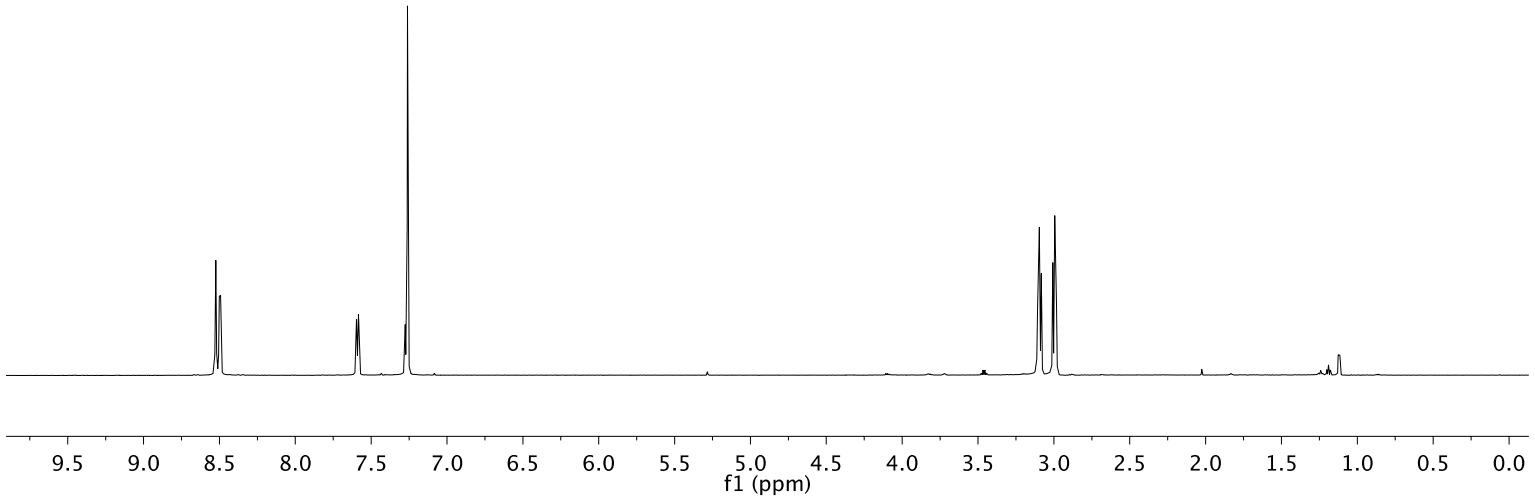

Cl
Cl
Cl
Cl
O
N
O
O
O
O

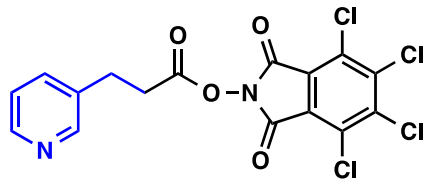
SI-25


30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

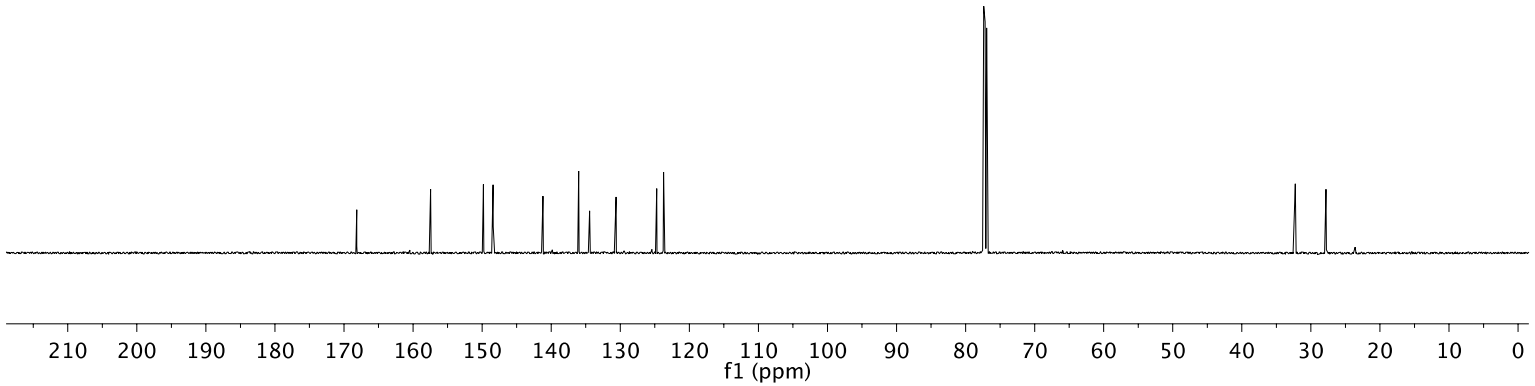

O
O
O
N
O
Cl
Cl
Cl
Cl
N

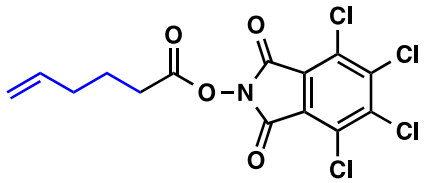
SI-26


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

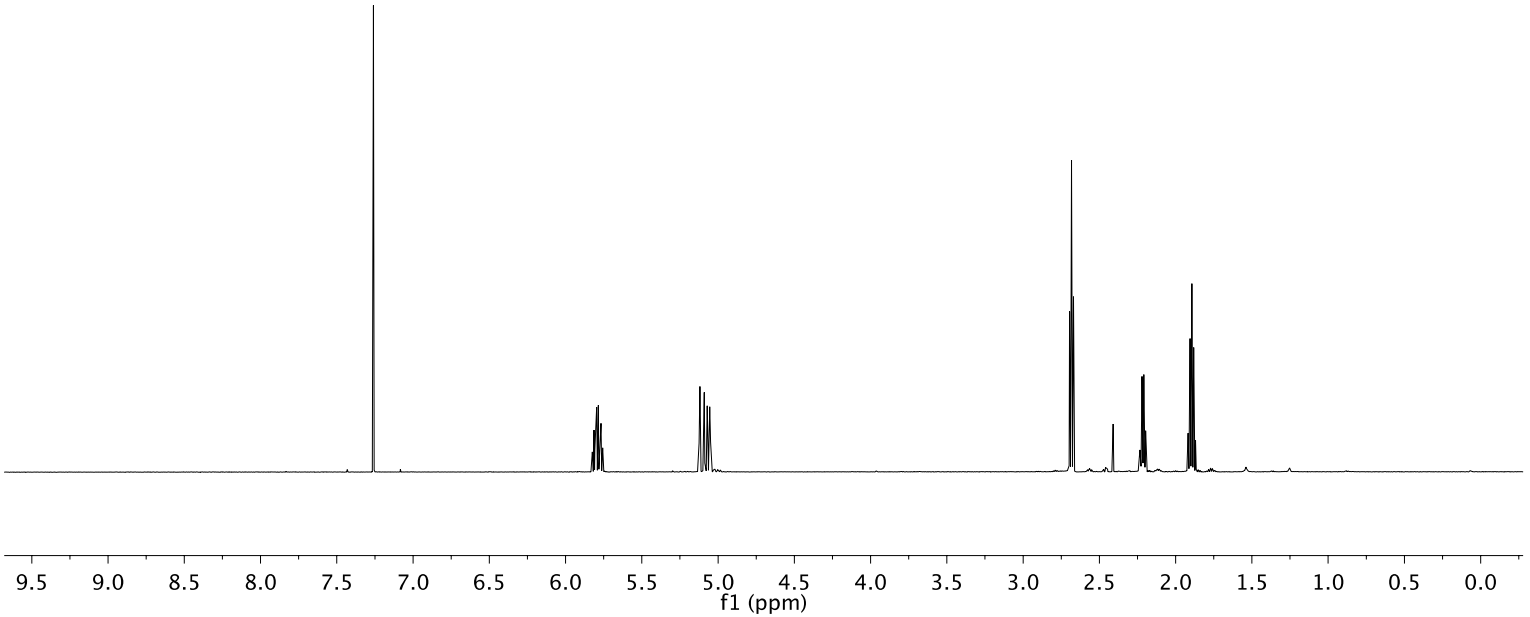

O
O
Cl
Cl
O
N
Cl
N
O
Cl

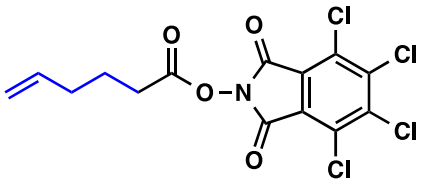
SI-26


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

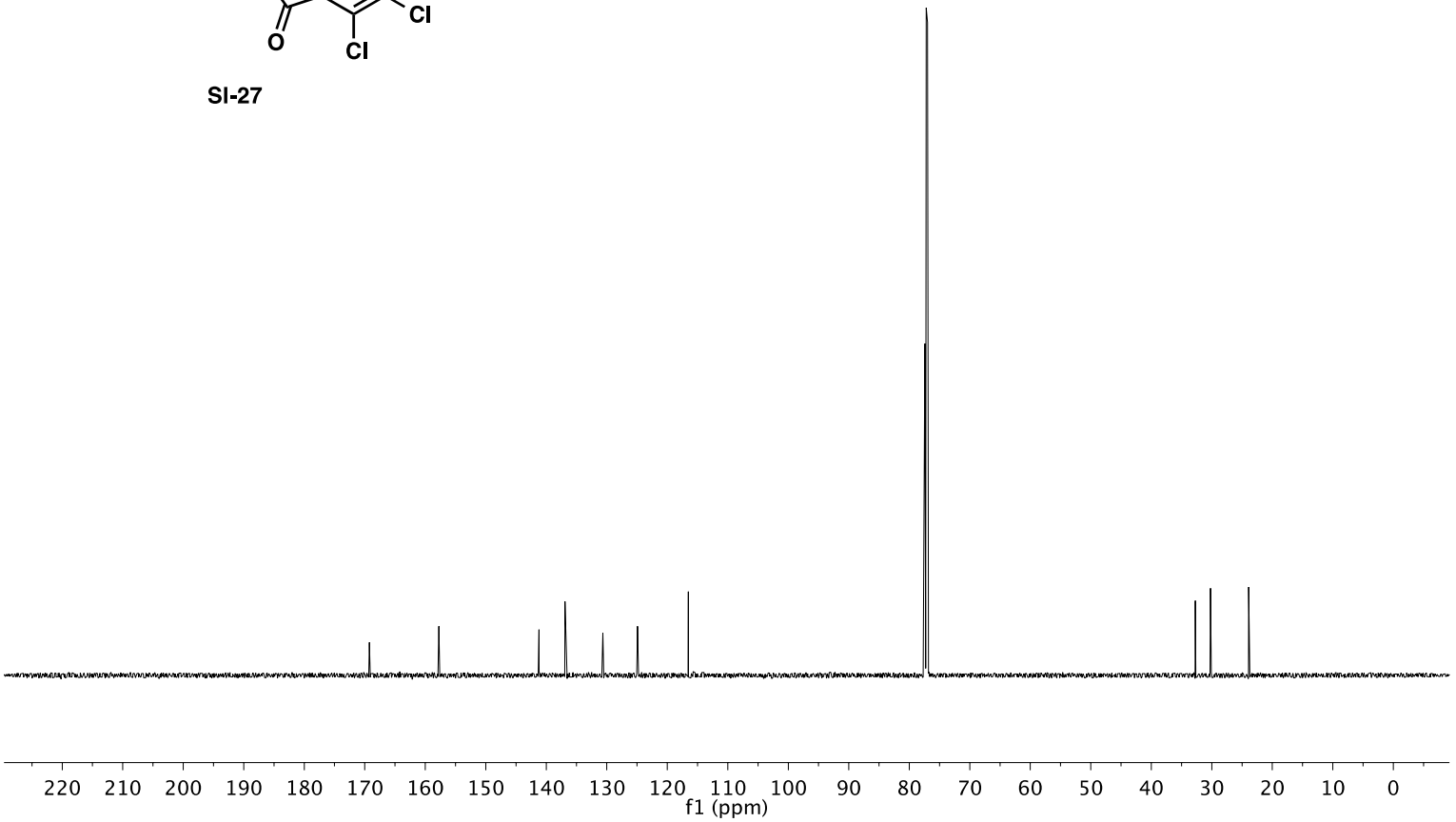

O
O
Cl
Cl
O–N
Cl
O
Cl

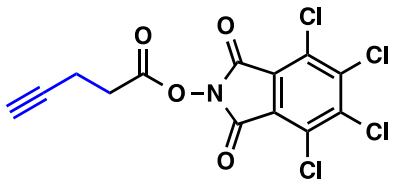
SI-27


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

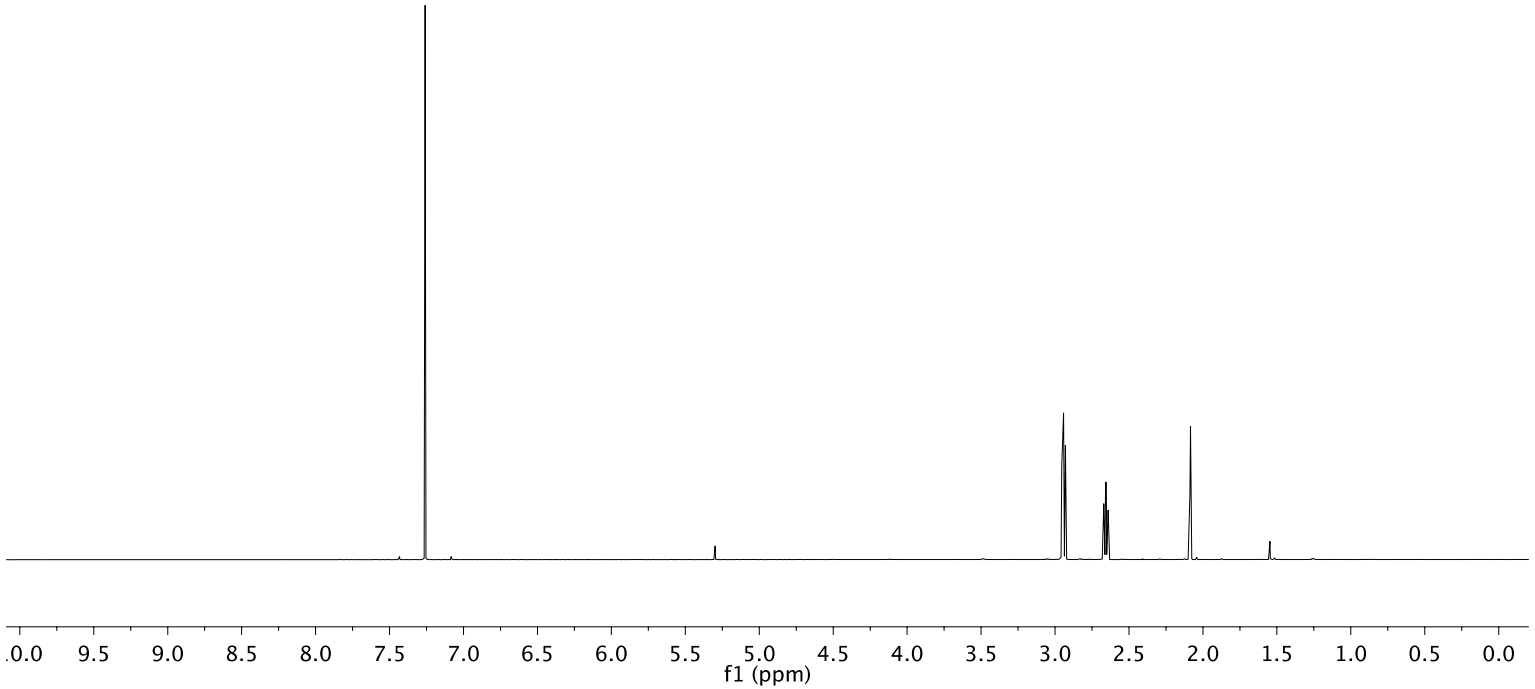

O
O
O
N
O
Cl
Cl
Cl
Cl

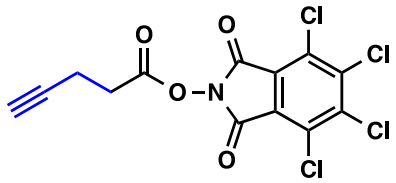
SI-27


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O–N
O
O
Cl
Cl
Cl
Cl

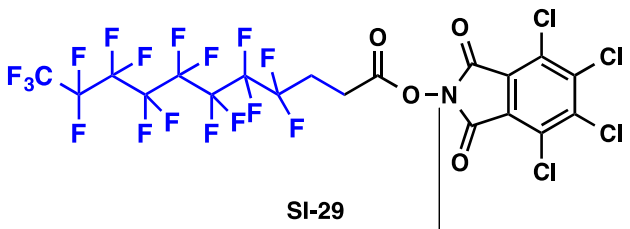
SI-28


.0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

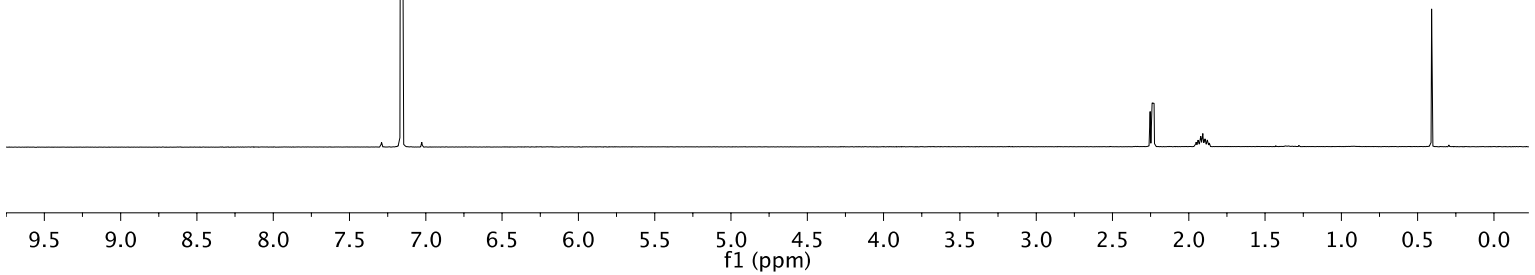

O
O
O
N
O
Cl
Cl
Cl
Cl

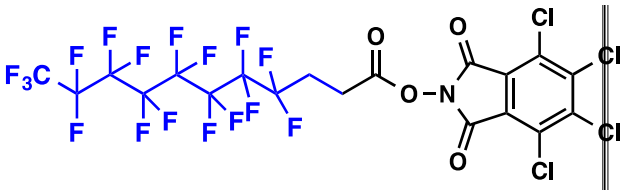
SI-28

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

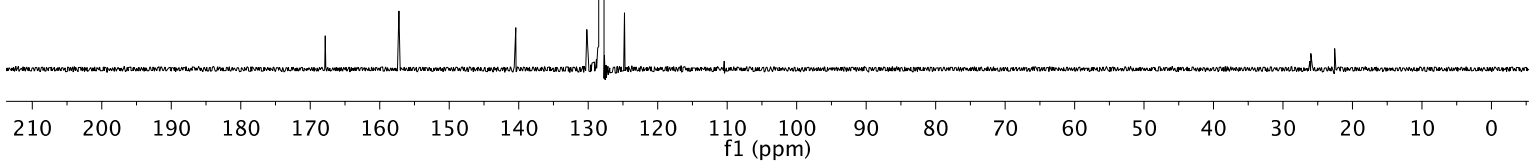

F3C
F
F
F
F
F
F
F
F
F
F
F
F
F
F
O
O
O
N
O
Cl
Cl
Cl
Cl

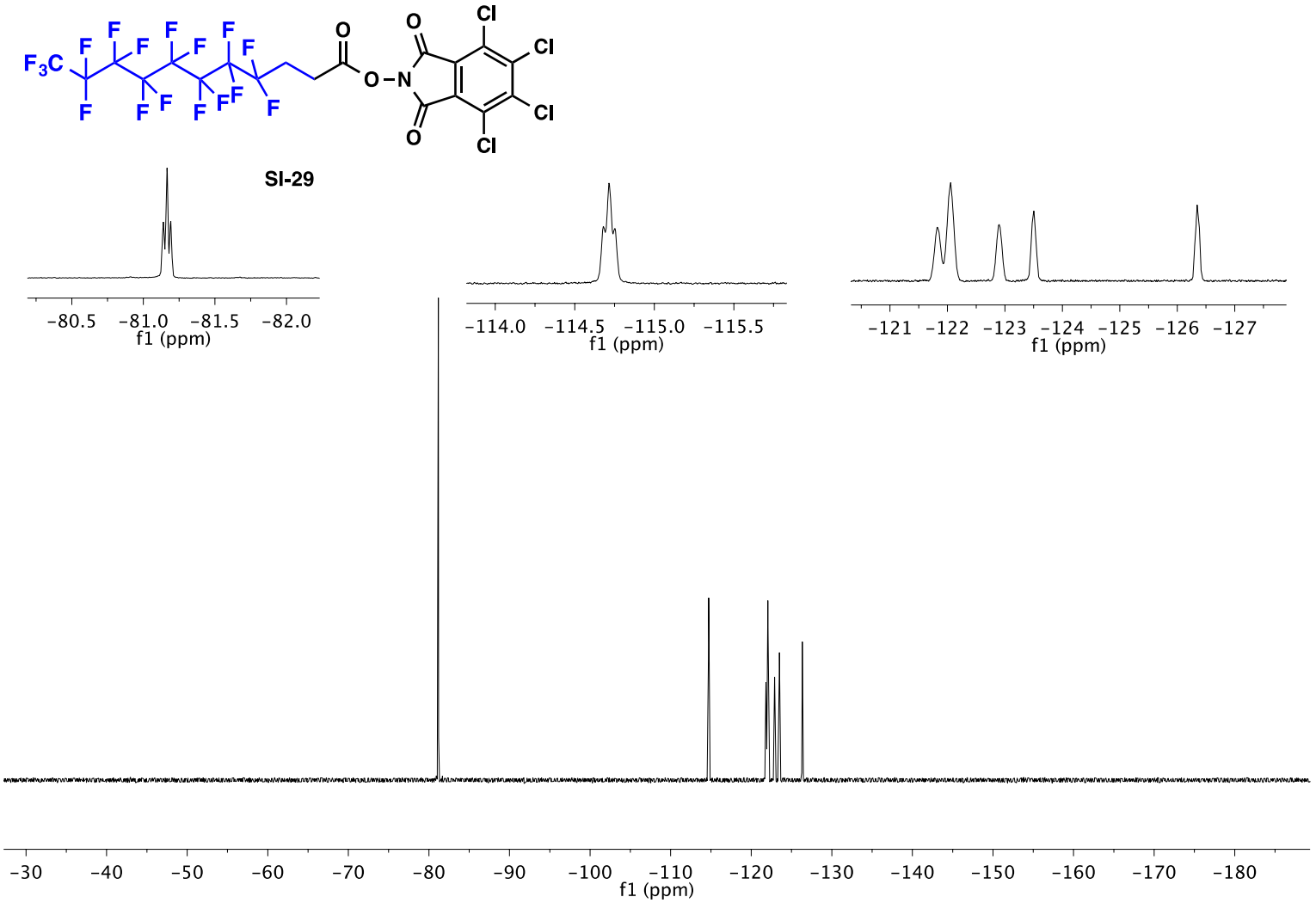
SI-29

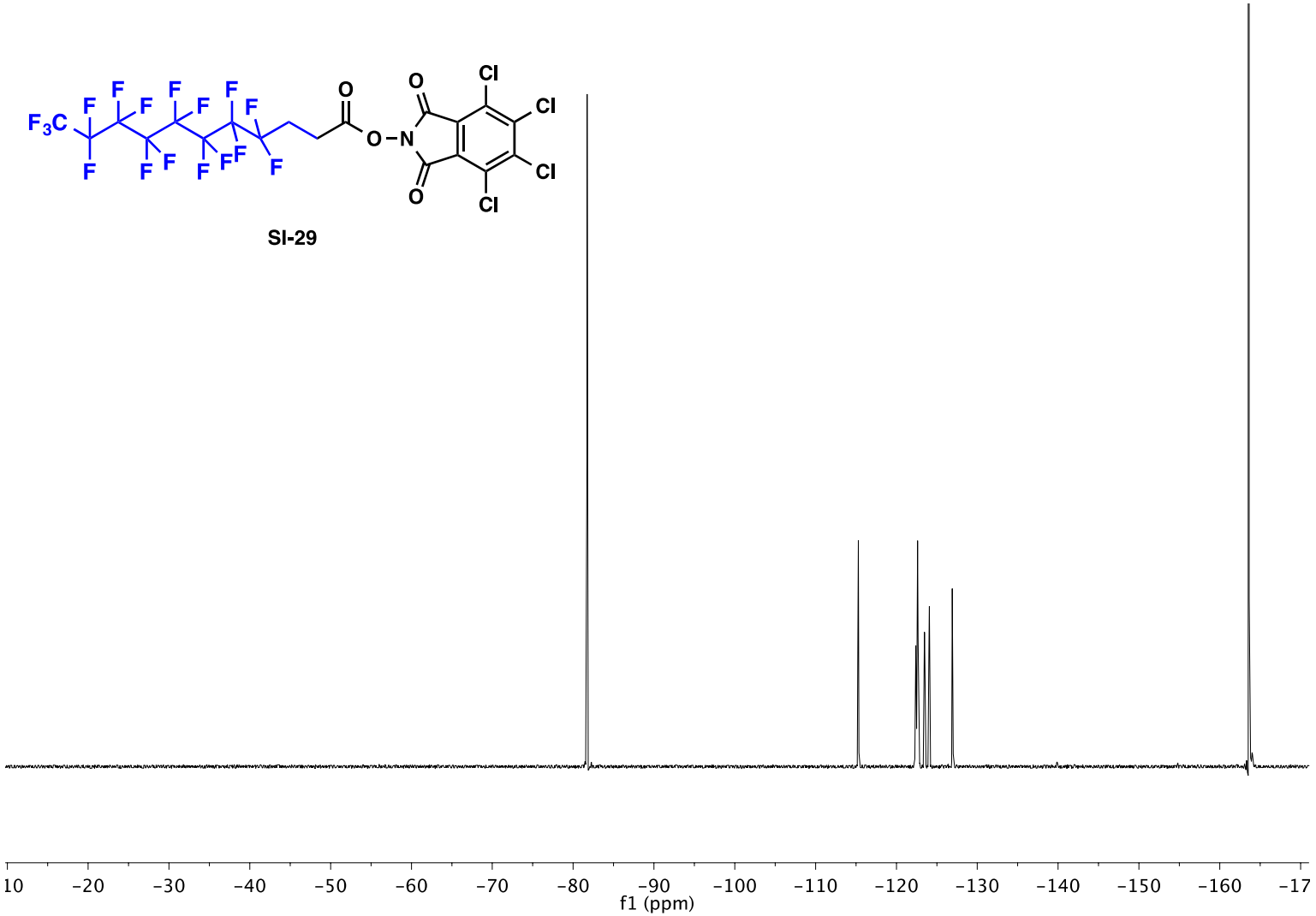

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

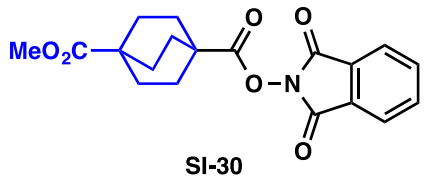


SI-29

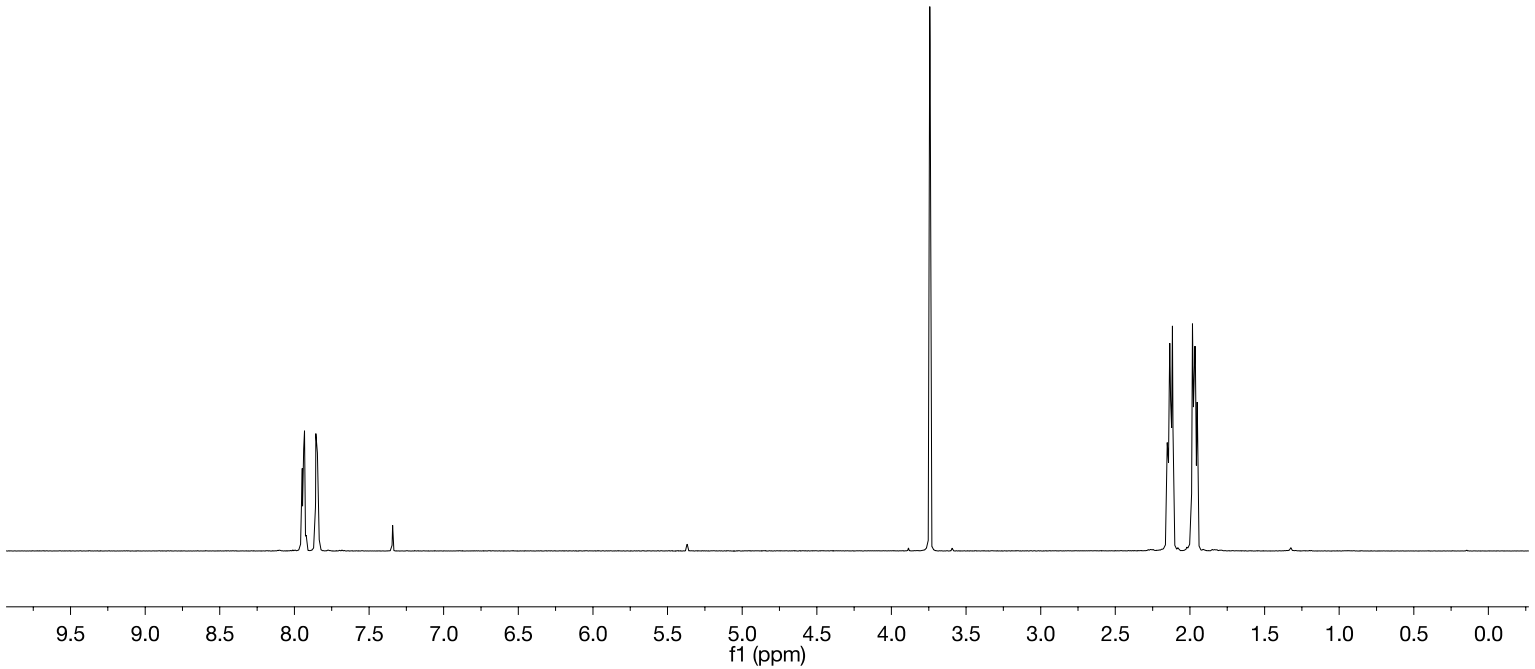

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

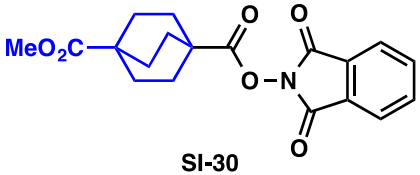

SI-29
F3C
F
O
O–N
O
Cl
Cl
Cl
Cl
−80.5 −81.0 −81.5 −82.0
f1 (ppm)
−114.0 −114.5 −115.0 −115.5
f1 (ppm)
−121 −122 −123 −124 −125 −126 −127
f1 (ppm)
−30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180
f1 (ppm)


F3C
F
O
O–N
O
Cl
Cl
Cl
Cl
SI-29
10
−20
−30
−40
−50
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−17
f1 (ppm)

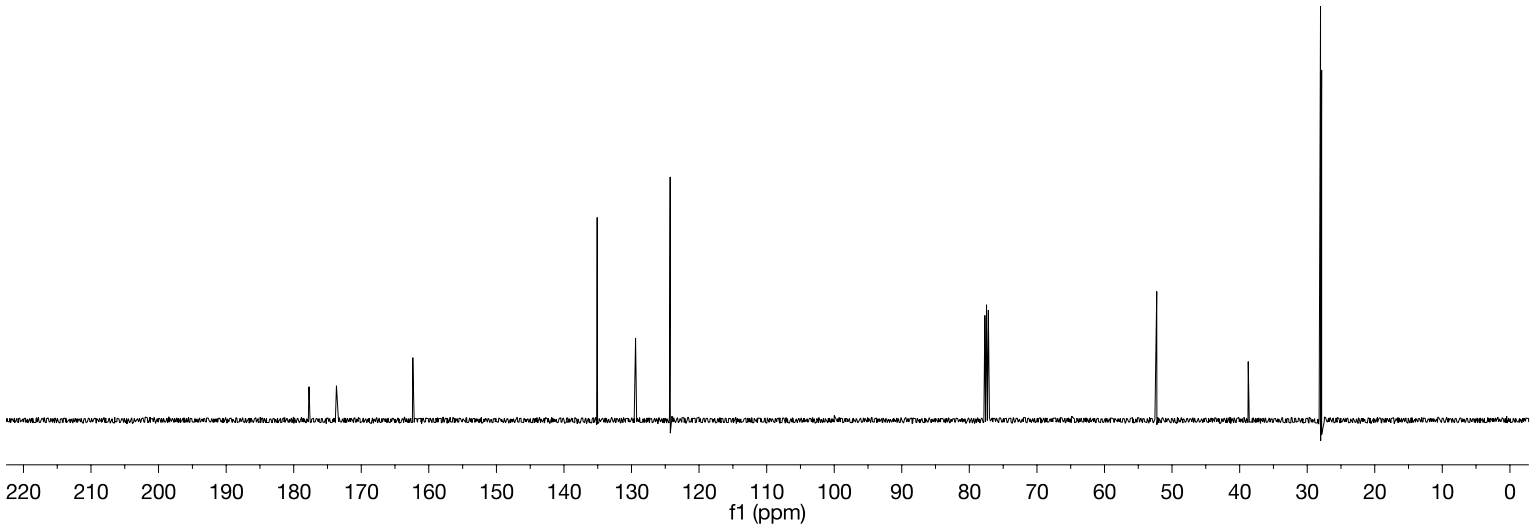

MeO2C
O
O
O
O
N
O

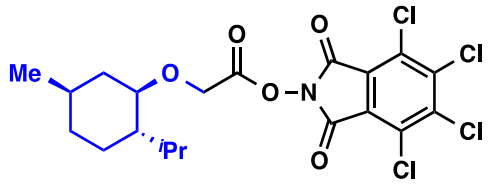
SI-30


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

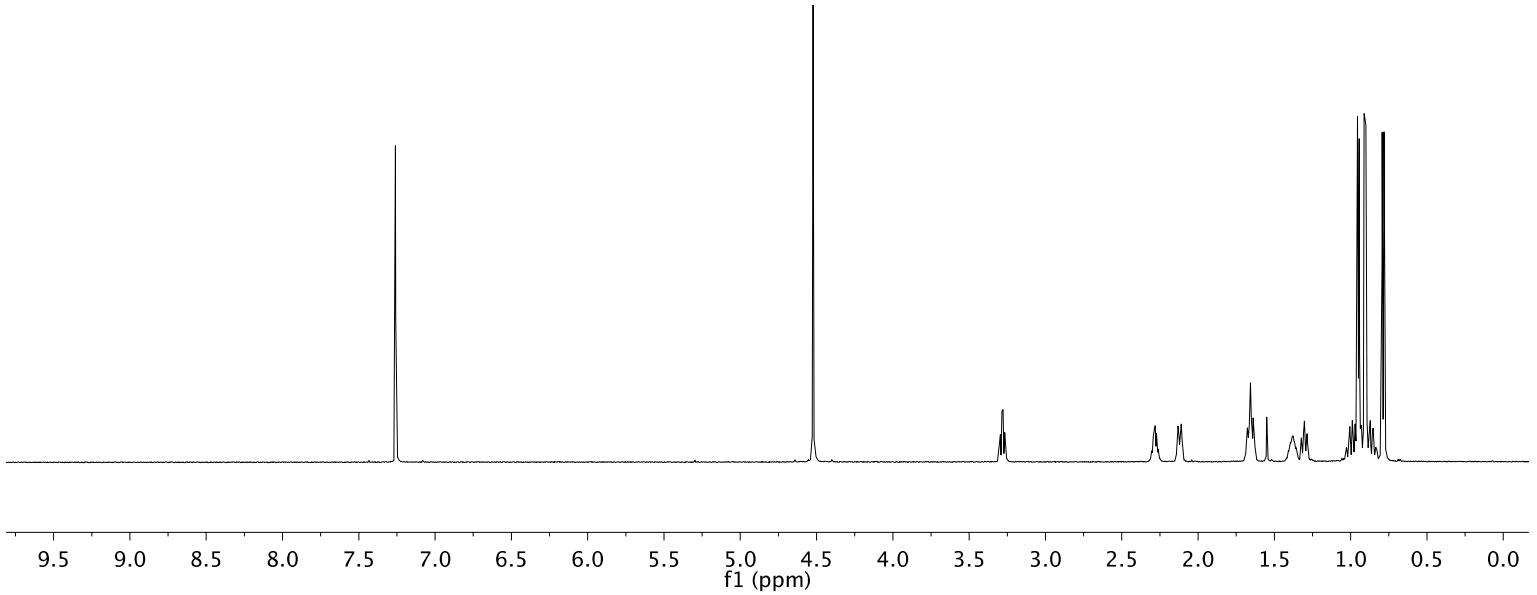

MeO2C
O
O
O
O
N
O

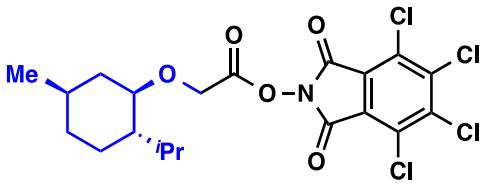
SI-30


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

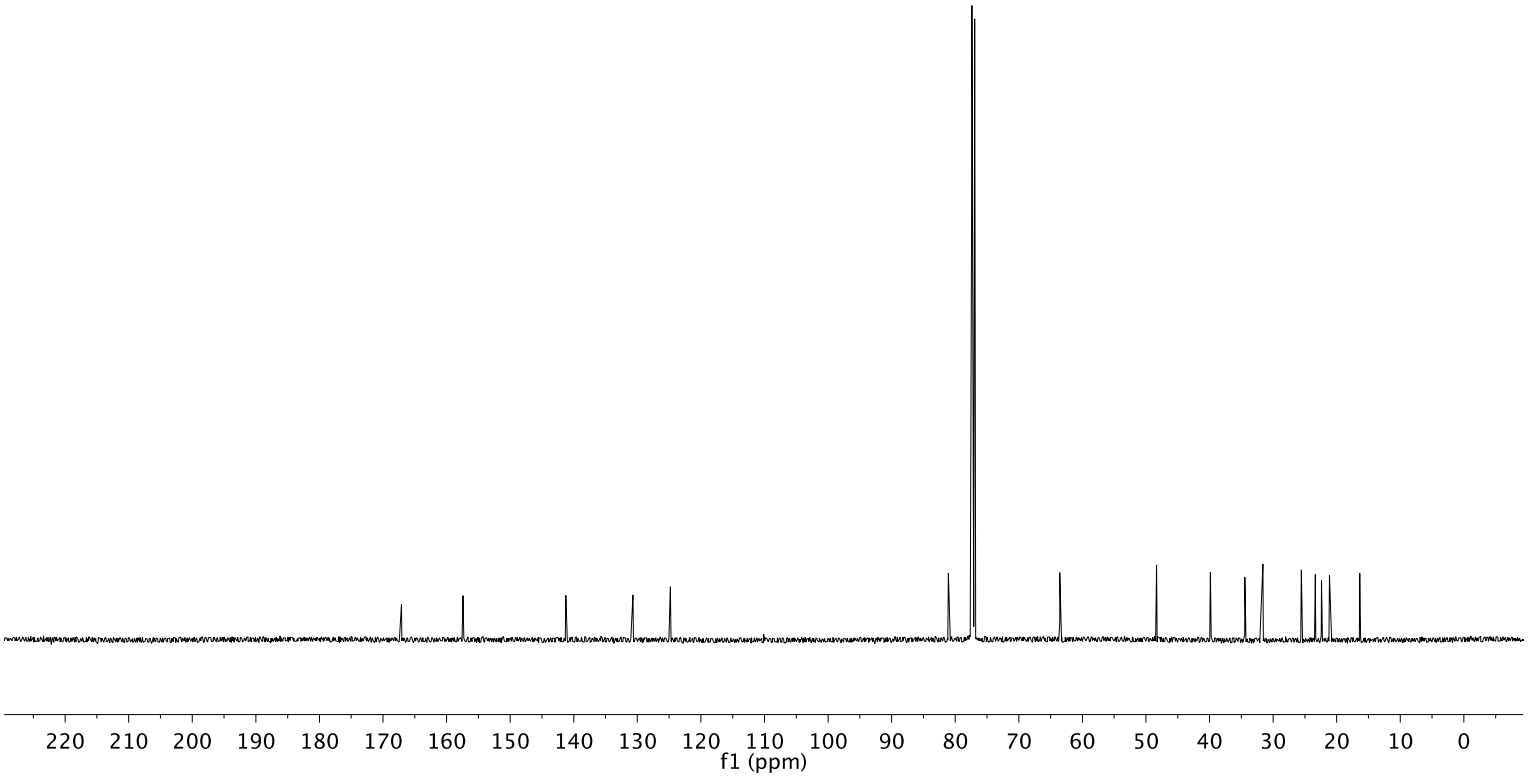

Me
O
O
O
O
N
O
Cl
Cl
Cl
Cl
iPr

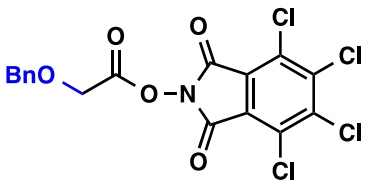
SI-31


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

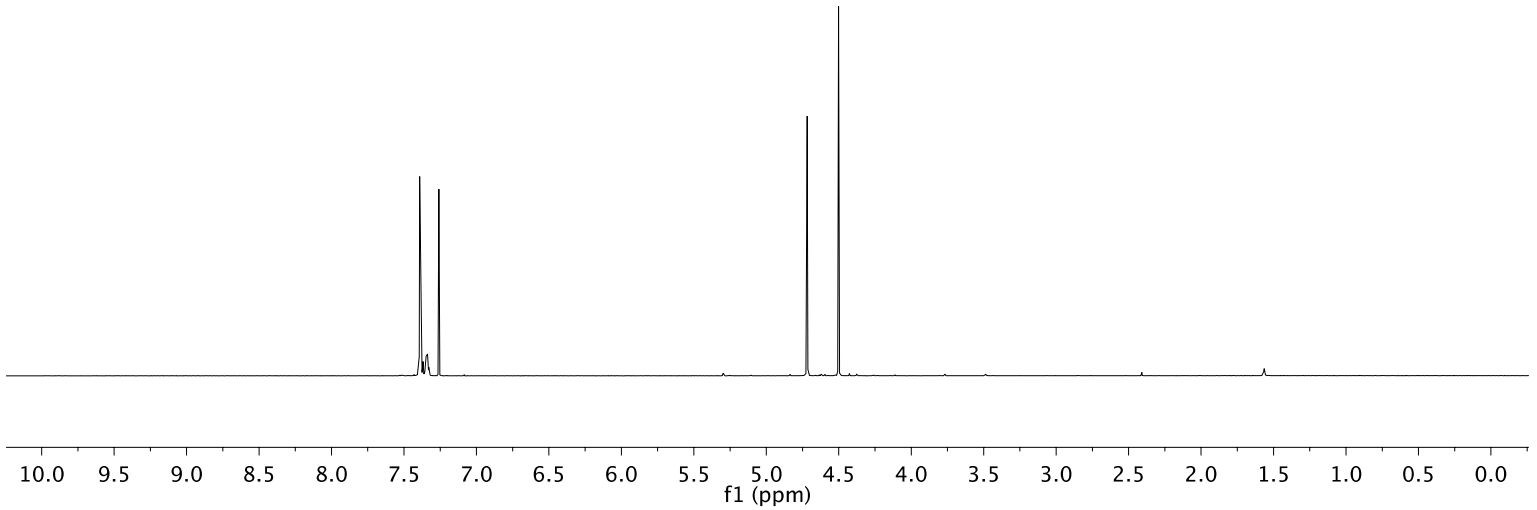

Me
O
O
O
O
N
O
O
Cl
Cl
Cl
Cl
iPr

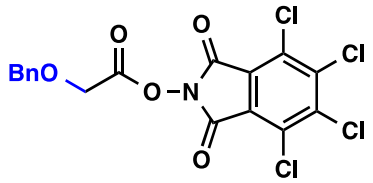
SI-31


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

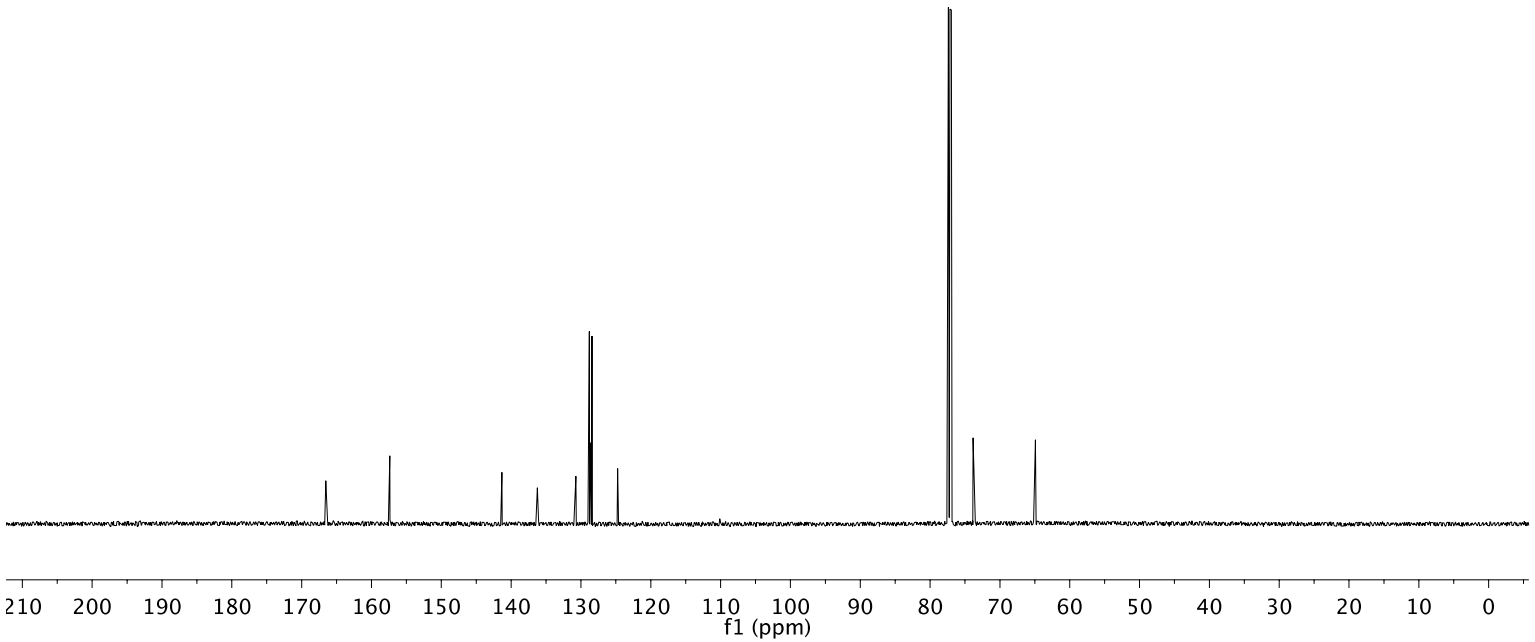

BnO
O
O
O
N
O
Cl
Cl
Cl
Cl

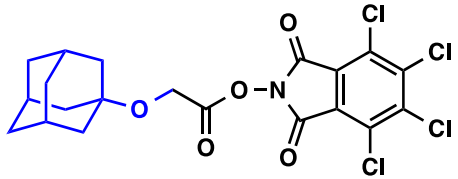
SI-32


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

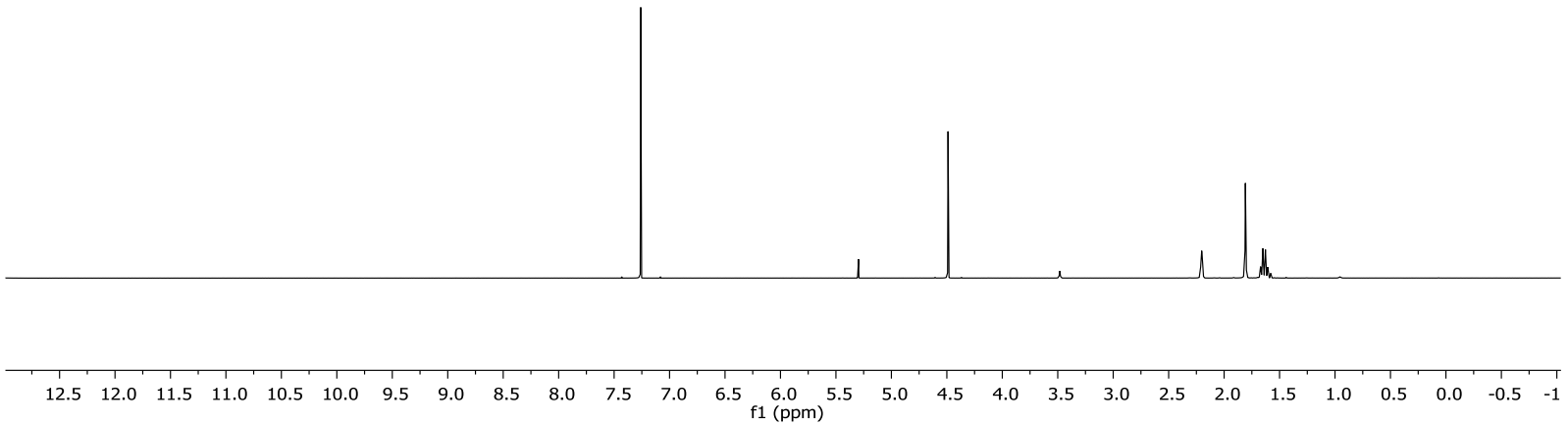

BnO
O
O
O
N
O
Cl
Cl
Cl
Cl

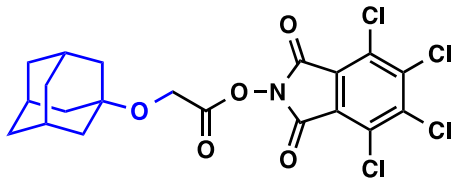
SI-32


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

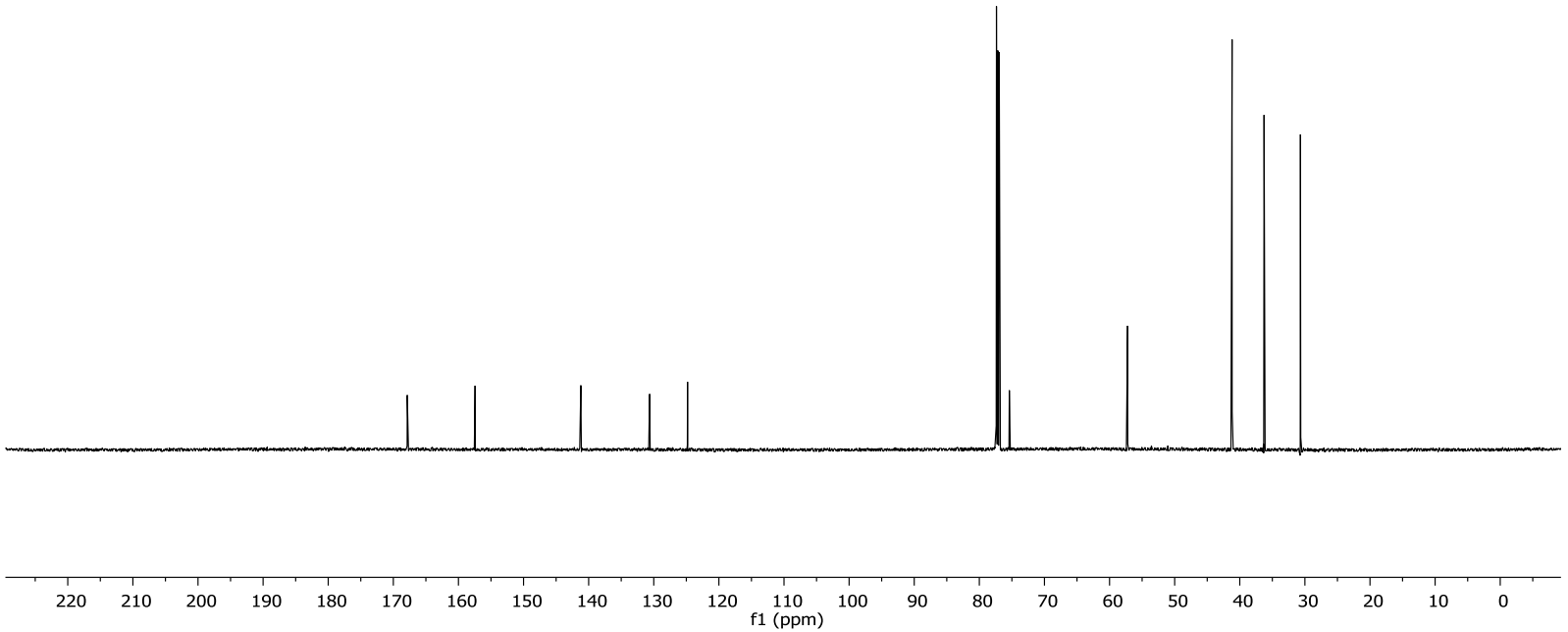

O
Cl
Cl
O
N
Cl
O
O
Cl

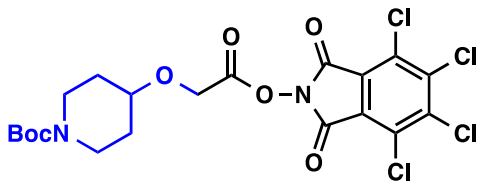
SI-33


12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


O
Cl
Cl
O
O
N
Cl
O
O

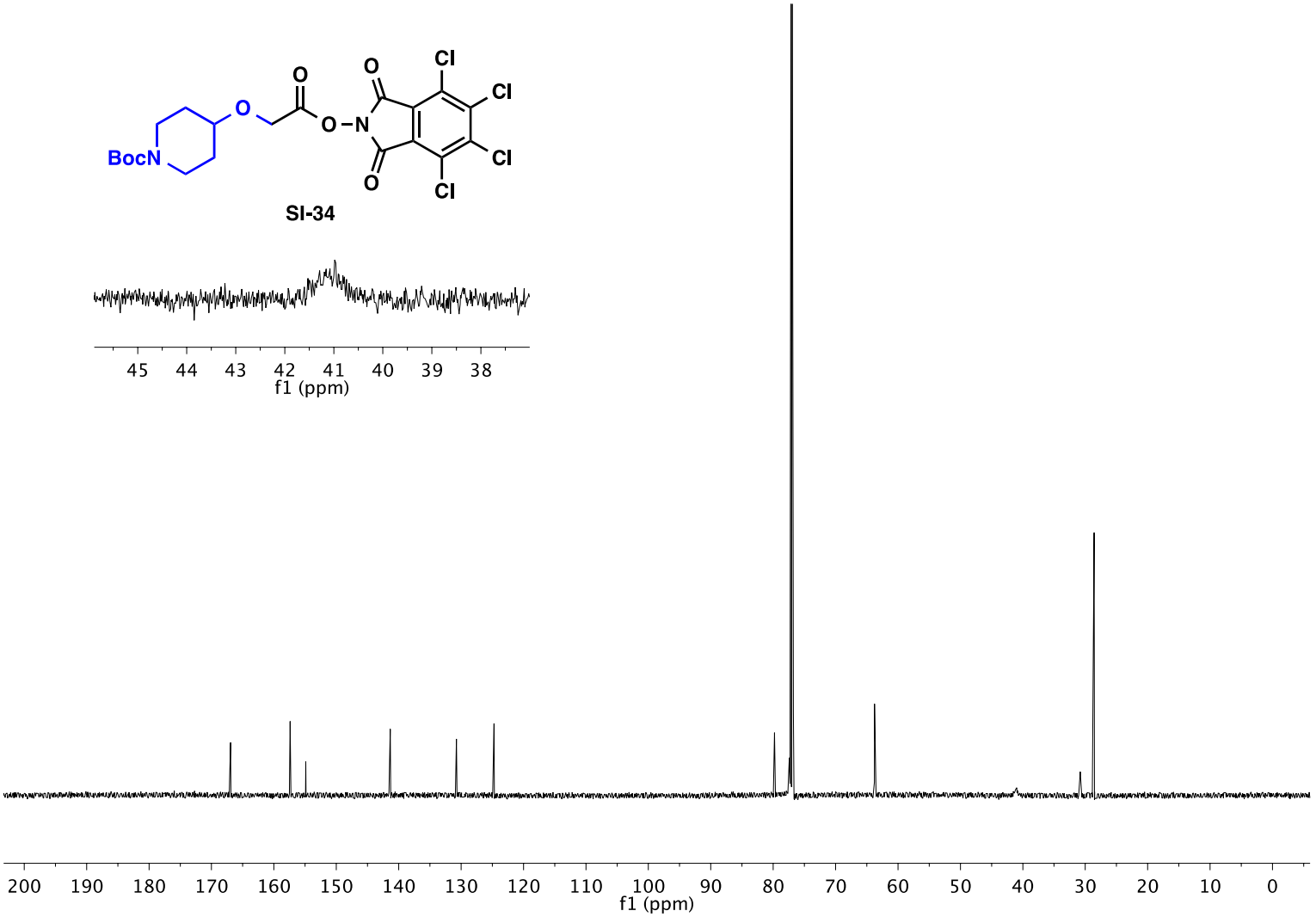
SI-33

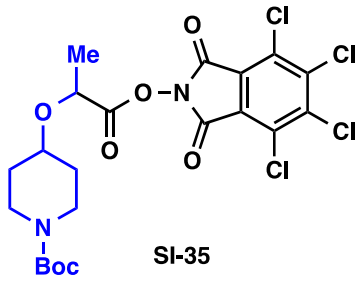

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


BocN
O
O
O
O–N
O
Cl
Cl
Cl
Cl

SI-34

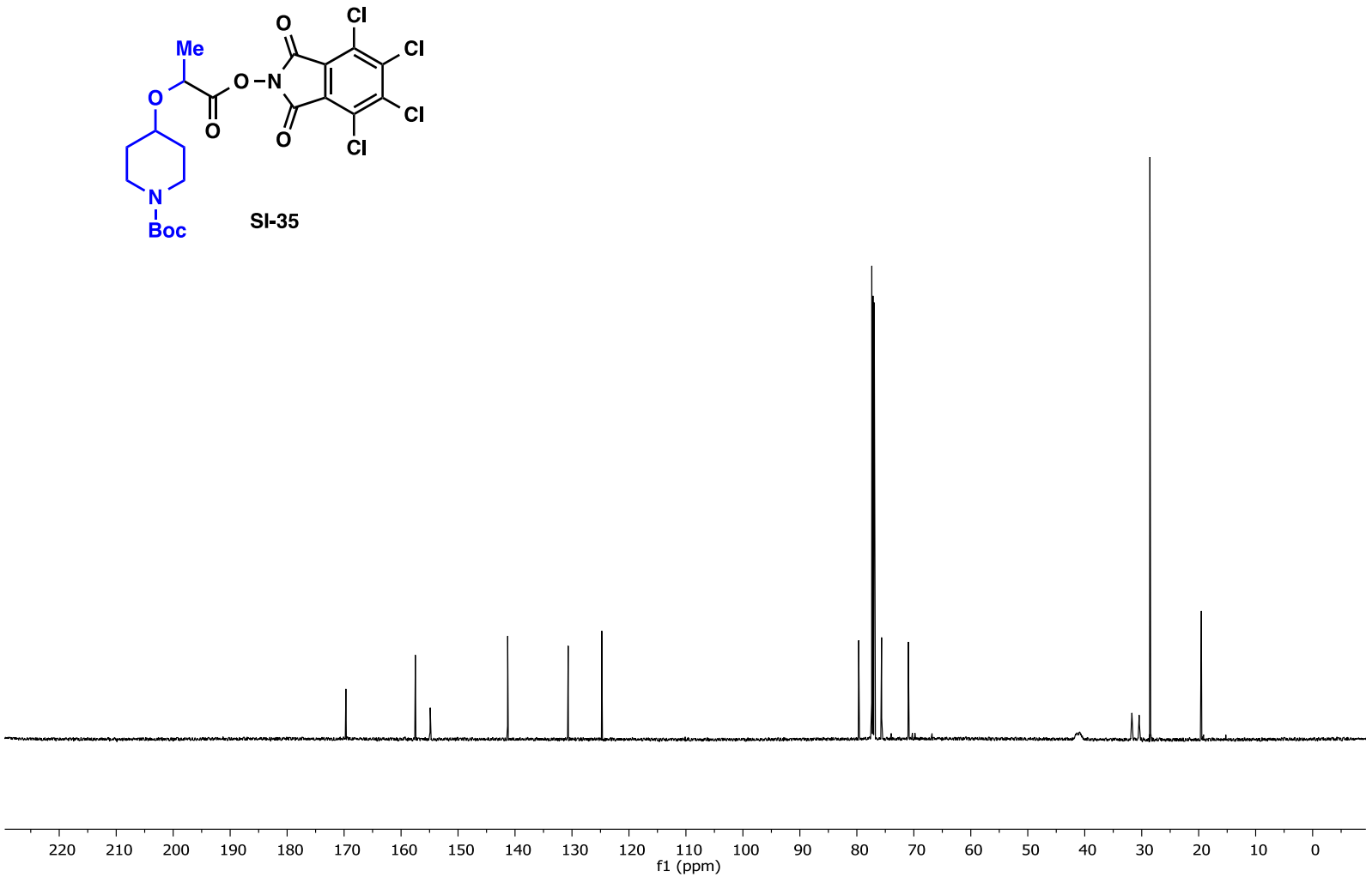
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


BocN
O
O
O
O–N
O
Cl
Cl
Cl
Cl
SI-34
45 44 43 42 41 40 39 38
f1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

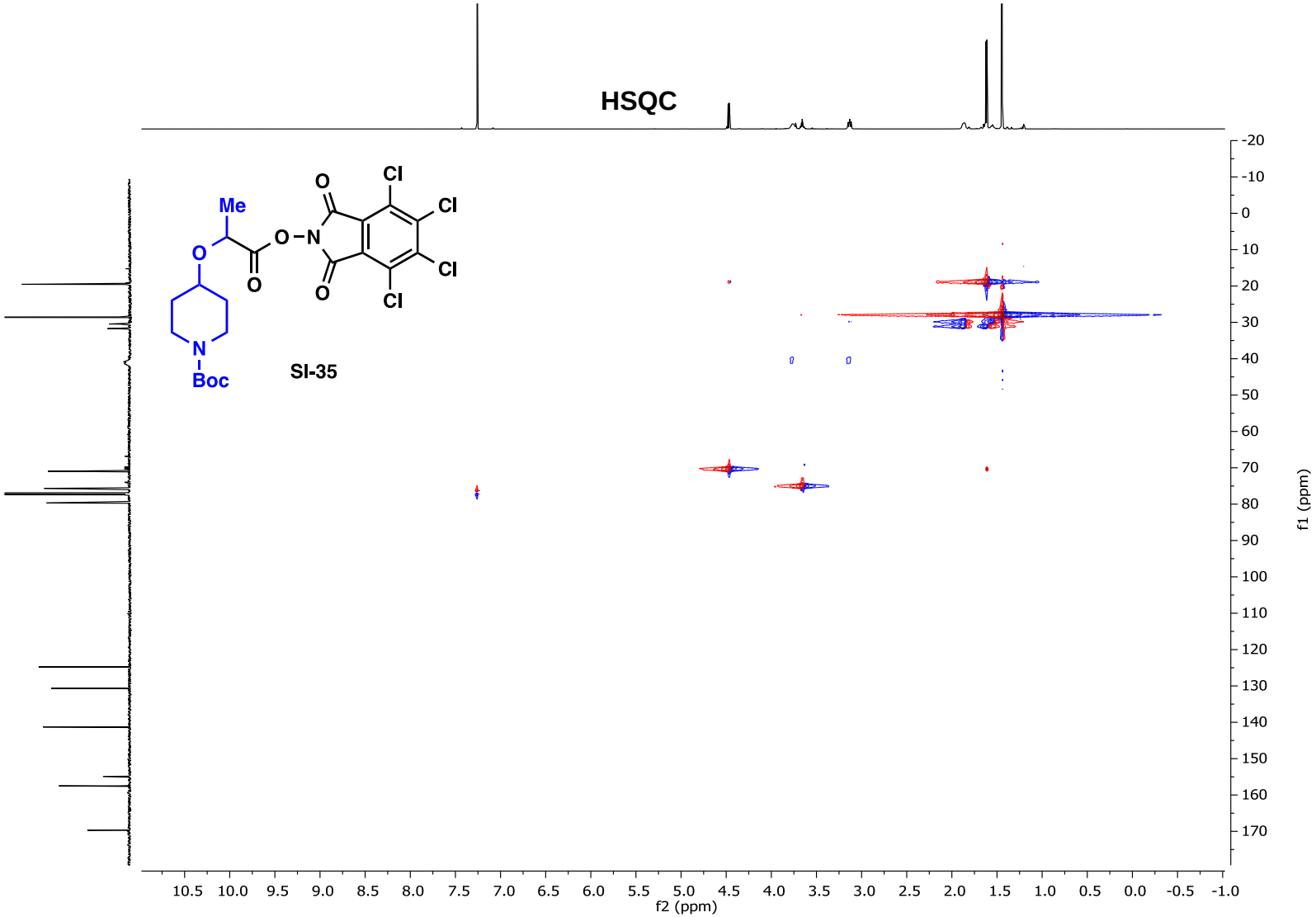

Me
O
O
O
N
O
O
Cl
Cl
Cl
Cl
N
Boc

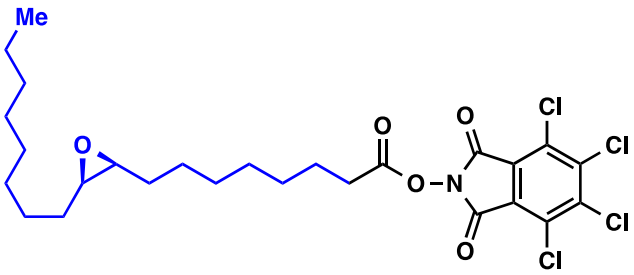
SI-35

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

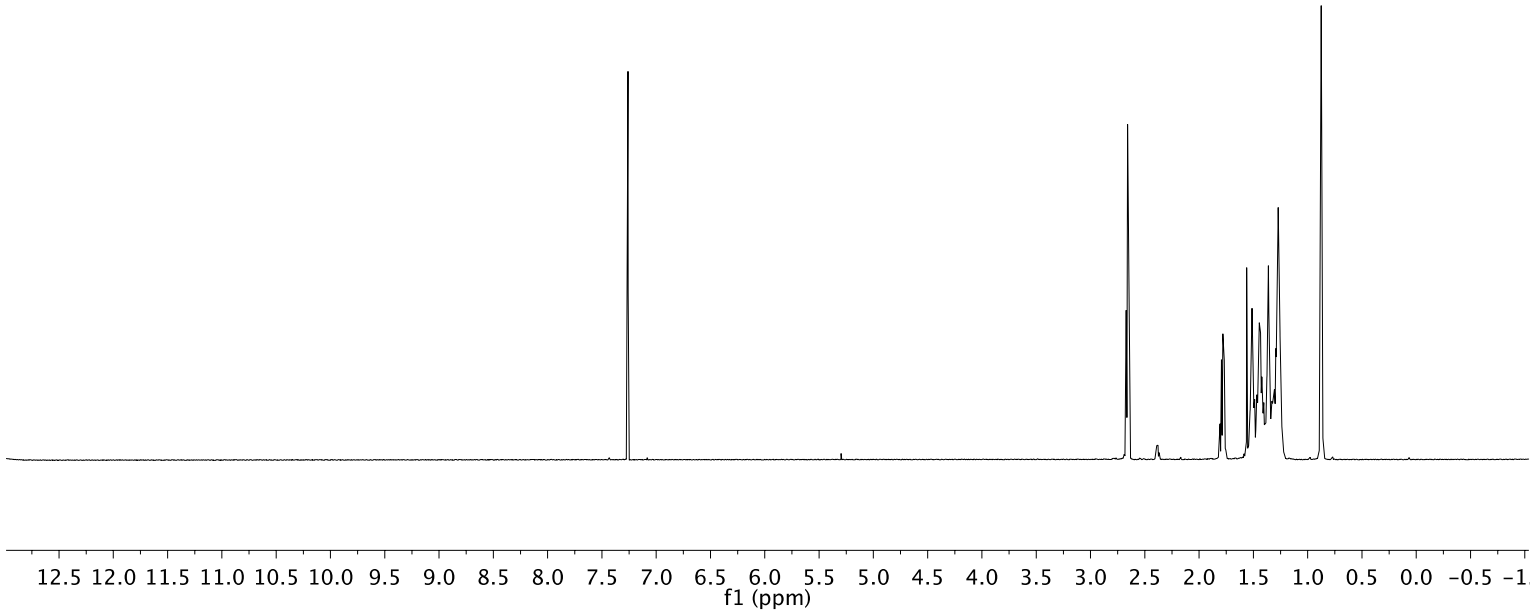

Me
O
O
O
N
O
O
Cl
Cl
Cl
Cl
N
Boc
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

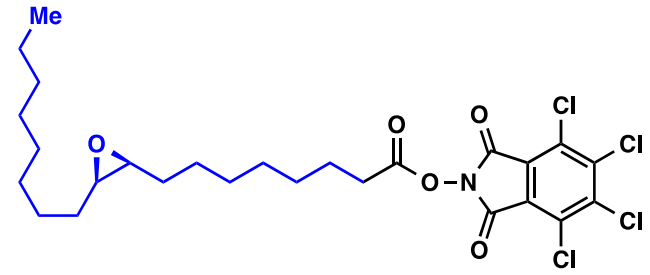
SI-35


HSQC
Me
O
O
O
N
O
O
Cl
Cl
Cl
N
Boc
SI-35
f2 (ppm)
f1 (ppm)


Me
O
O
O
O
N
O
Cl
Cl
Cl
Cl

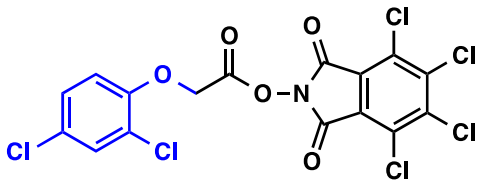
SI-36


12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

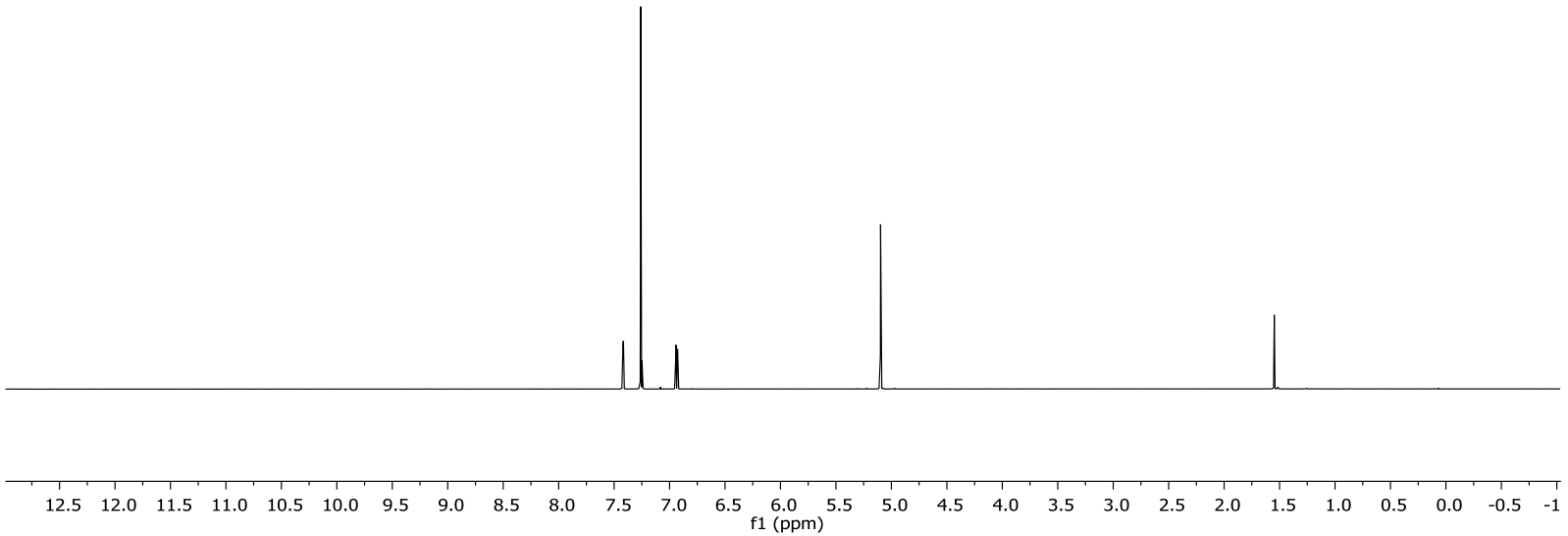

Me
O
O
O
O–N
O
Cl
Cl
Cl
Cl

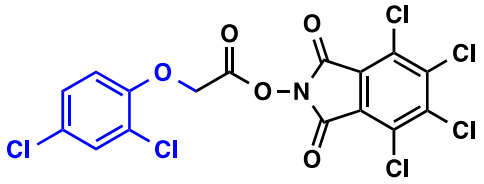
SI-36

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
O
O–N
O
Cl
Cl
Cl
Cl
Cl
Cl

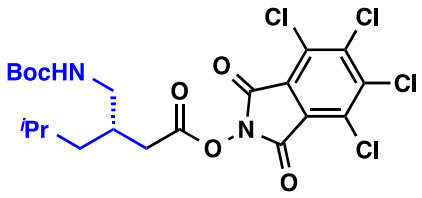
SI-37


12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

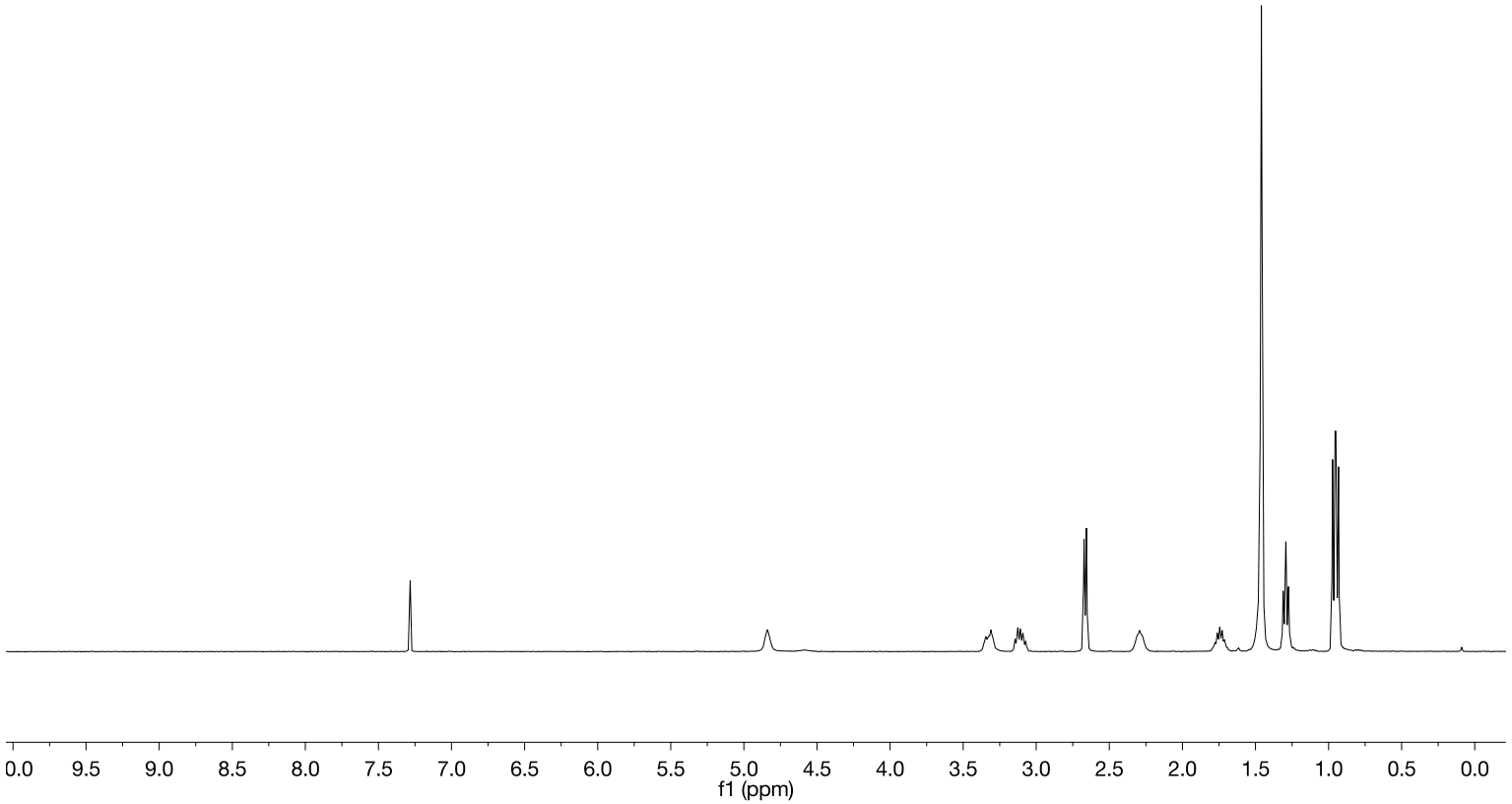

O
O
O
O–N
O
Cl
Cl
Cl
Cl
Cl
Cl

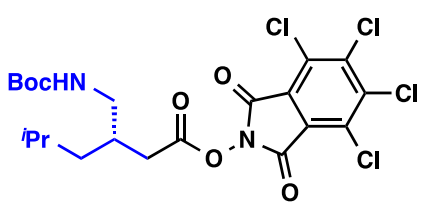
SI-37

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


BocHN
iPr
Cl
Cl
Cl
Cl
O
O
O
O
N

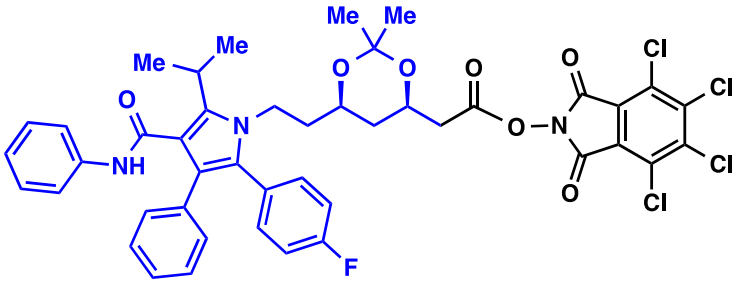
SI-38


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

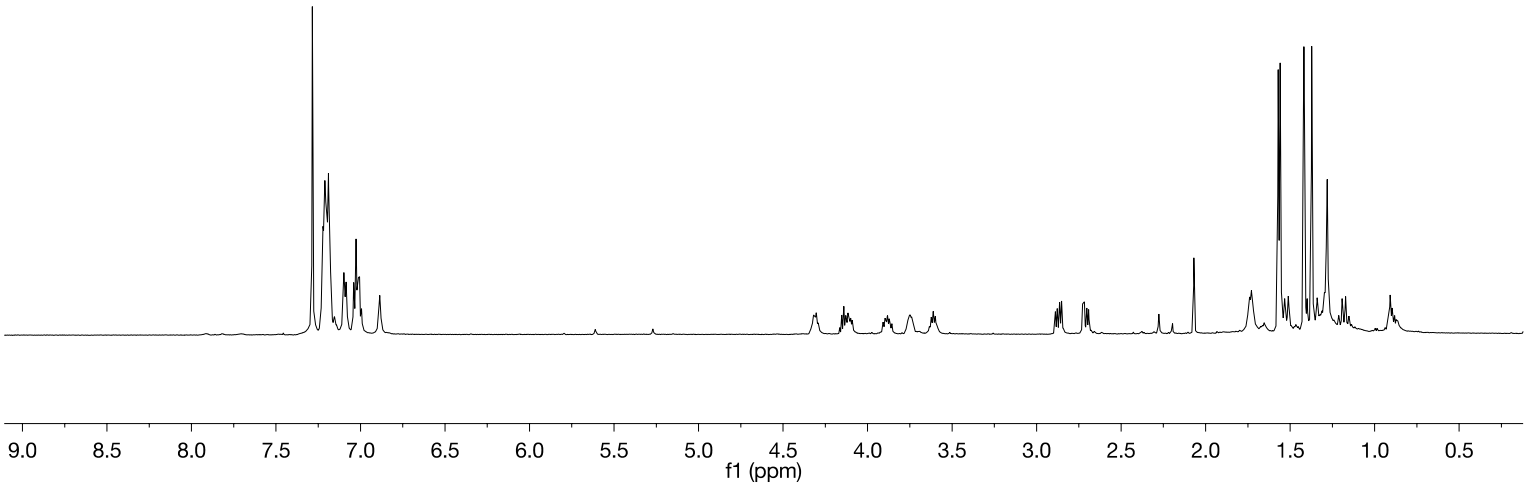

BocHN
iPr
O
O
O
N
O
Cl
Cl
Cl
Cl

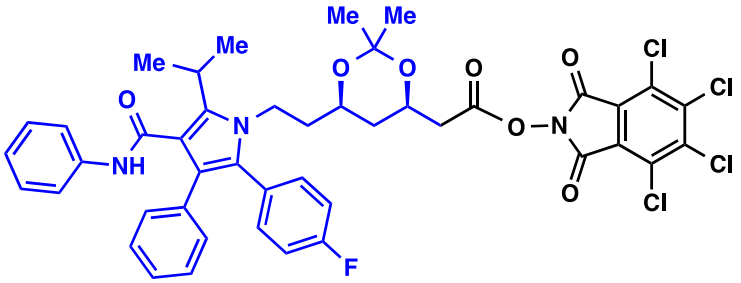
SI-38

30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

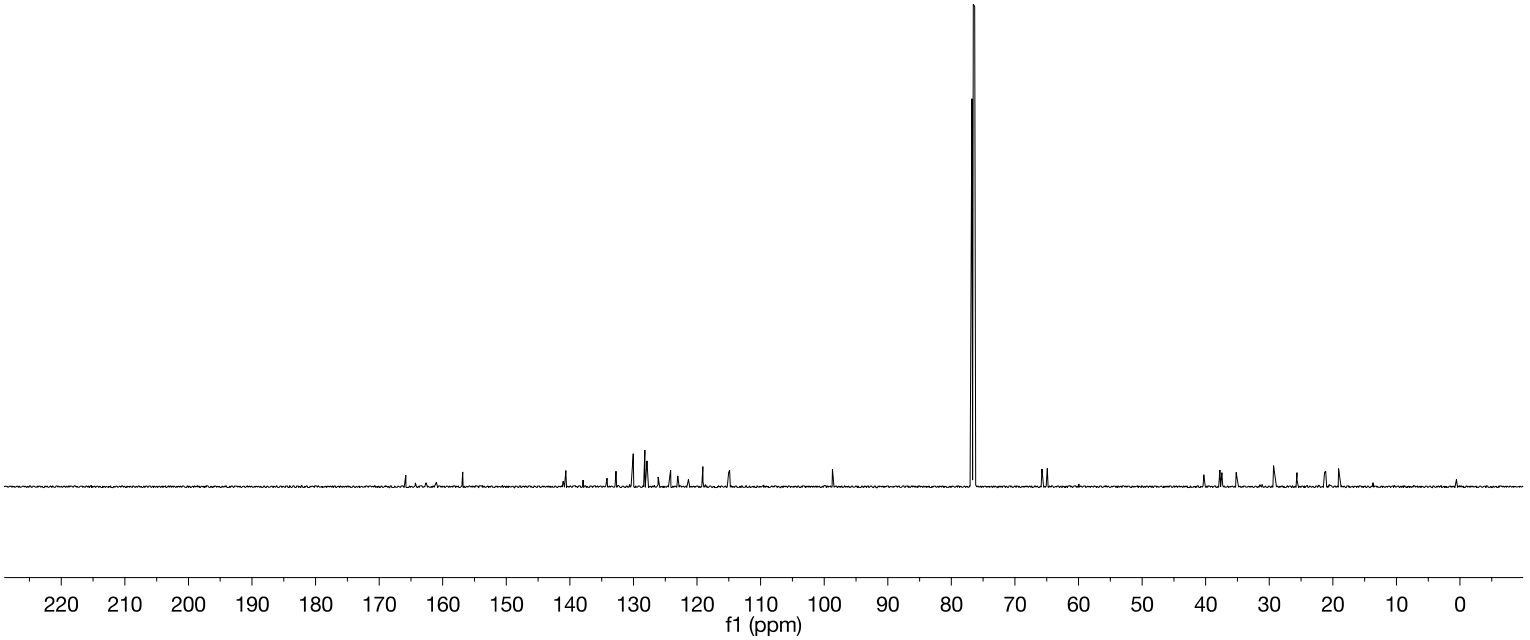

Me
Me
Me
Me
O
O
O
O
O
N
NH
O
O
N
O
Cl
Cl
Cl
Cl
F

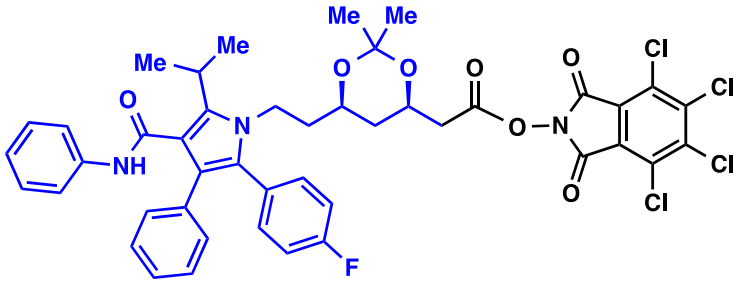
SI-39


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

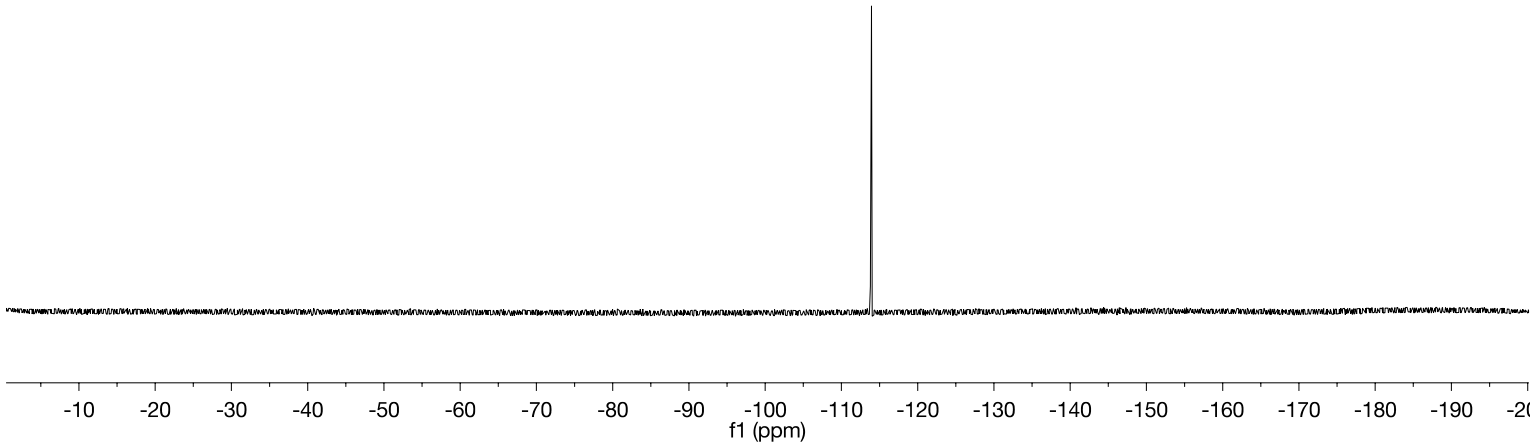

Me
Me
Me
Me
O
O
O
O
O
N
O
NH
N
O
Cl
Cl
Cl
Cl
F

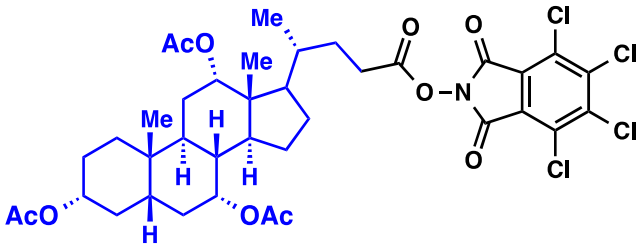
SI-39


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

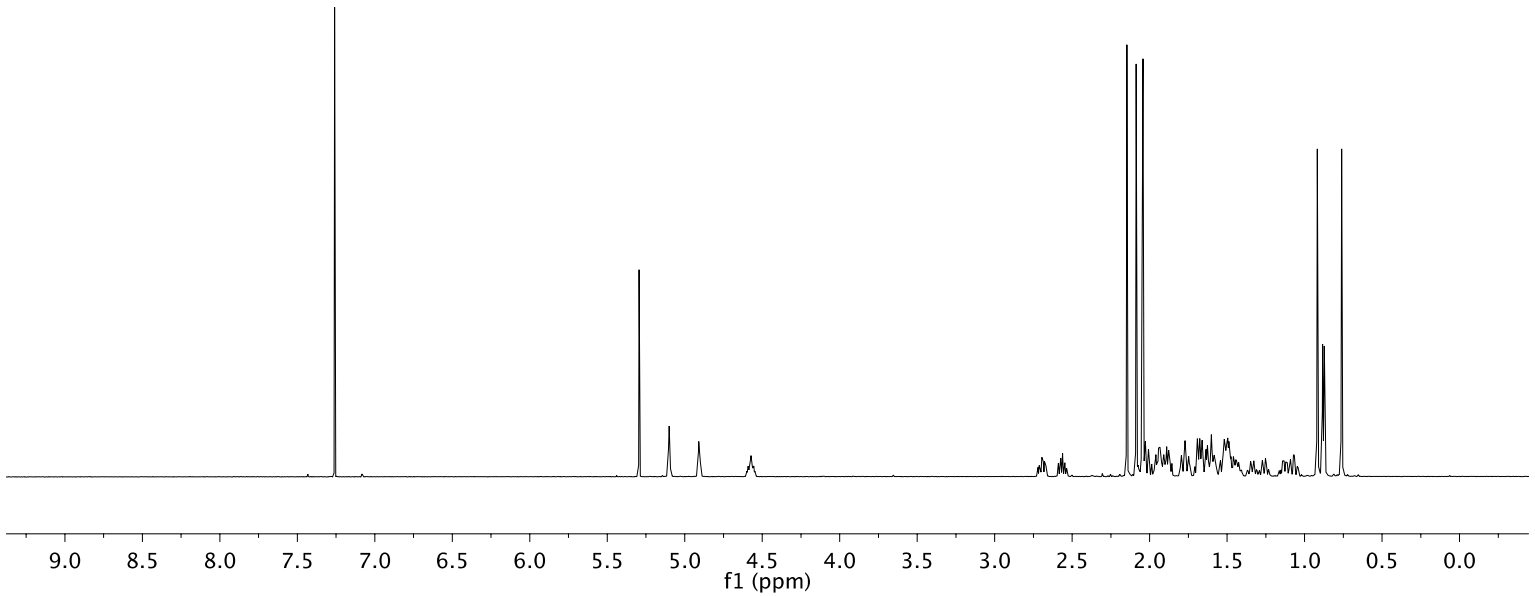

Me
Me
Me
Me
O
O
O
O
N
NH
O
O
N
O
Cl
Cl
Cl
Cl
F

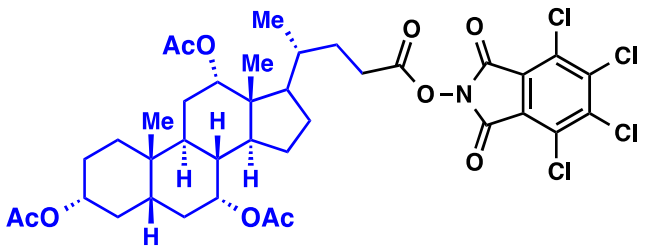
SI-39


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

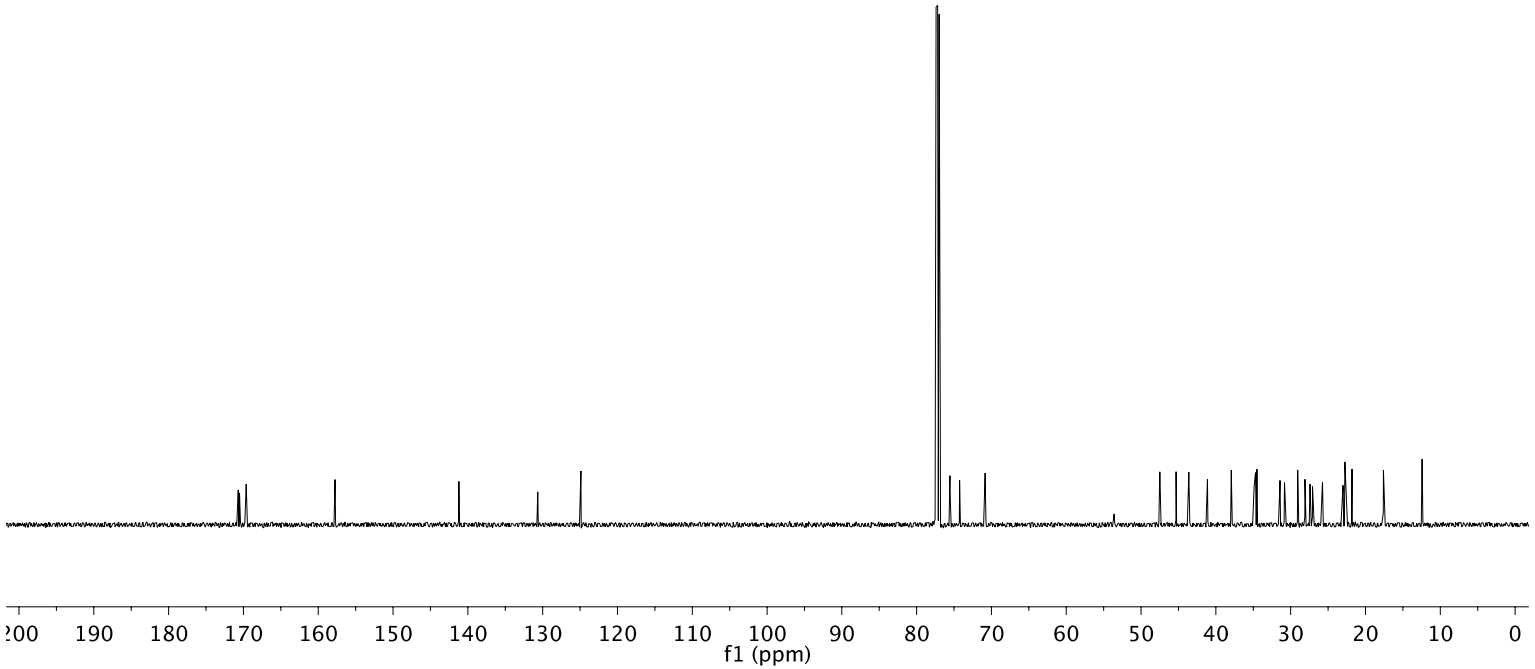

Me
AcO
Me
Me
H
H
H
AcO
OAc
H
O
O
O–N
O
Cl
Cl
Cl
Cl

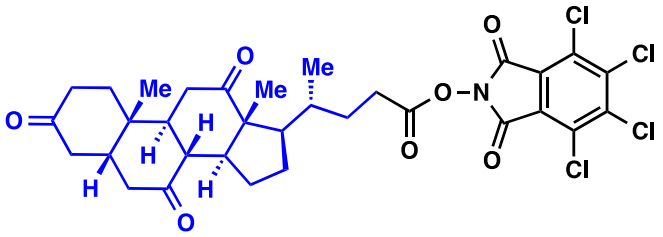
SI-40


9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

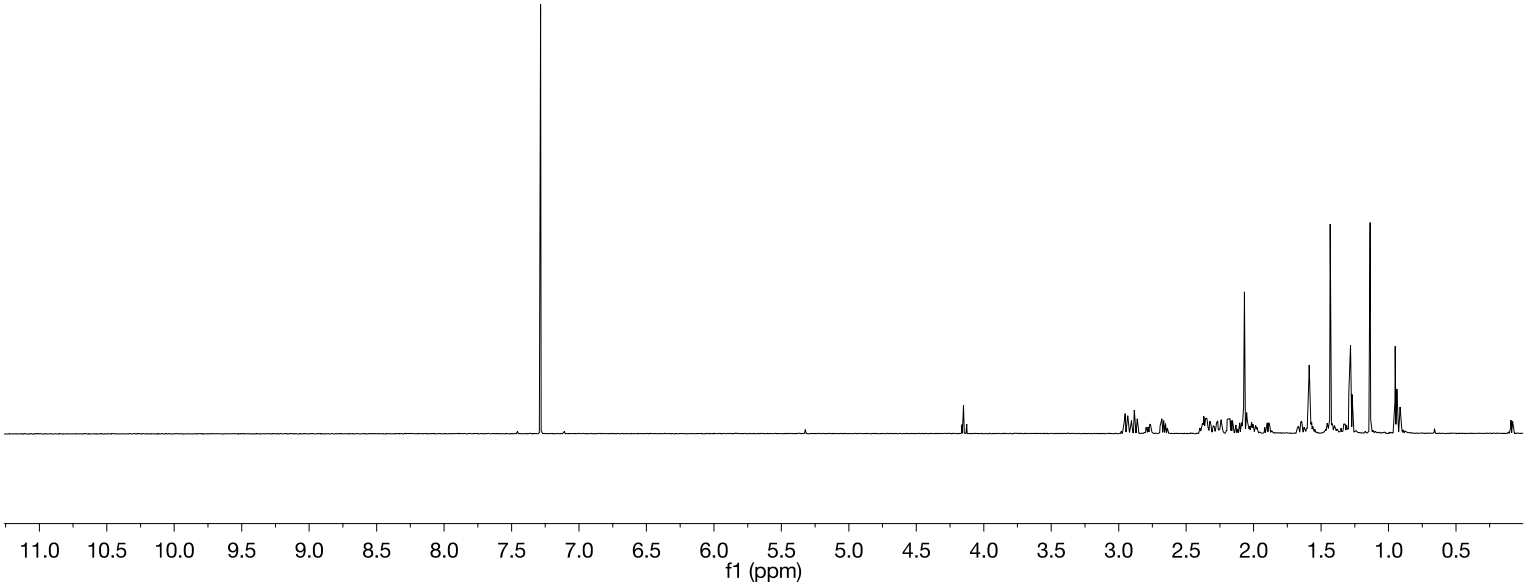

Me
AcO
Me
O
O
Cl
Cl
Me
H
O–N
Cl
H
H
H
AcO
OAc
H
O

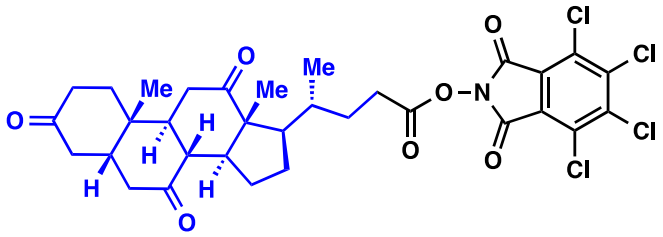
SI-40


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Me
Me
Me
O
H
H
H
O
O
O
O
N
O
Cl
Cl
Cl
Cl

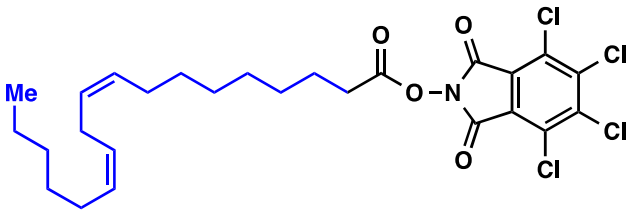
SI-41


11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

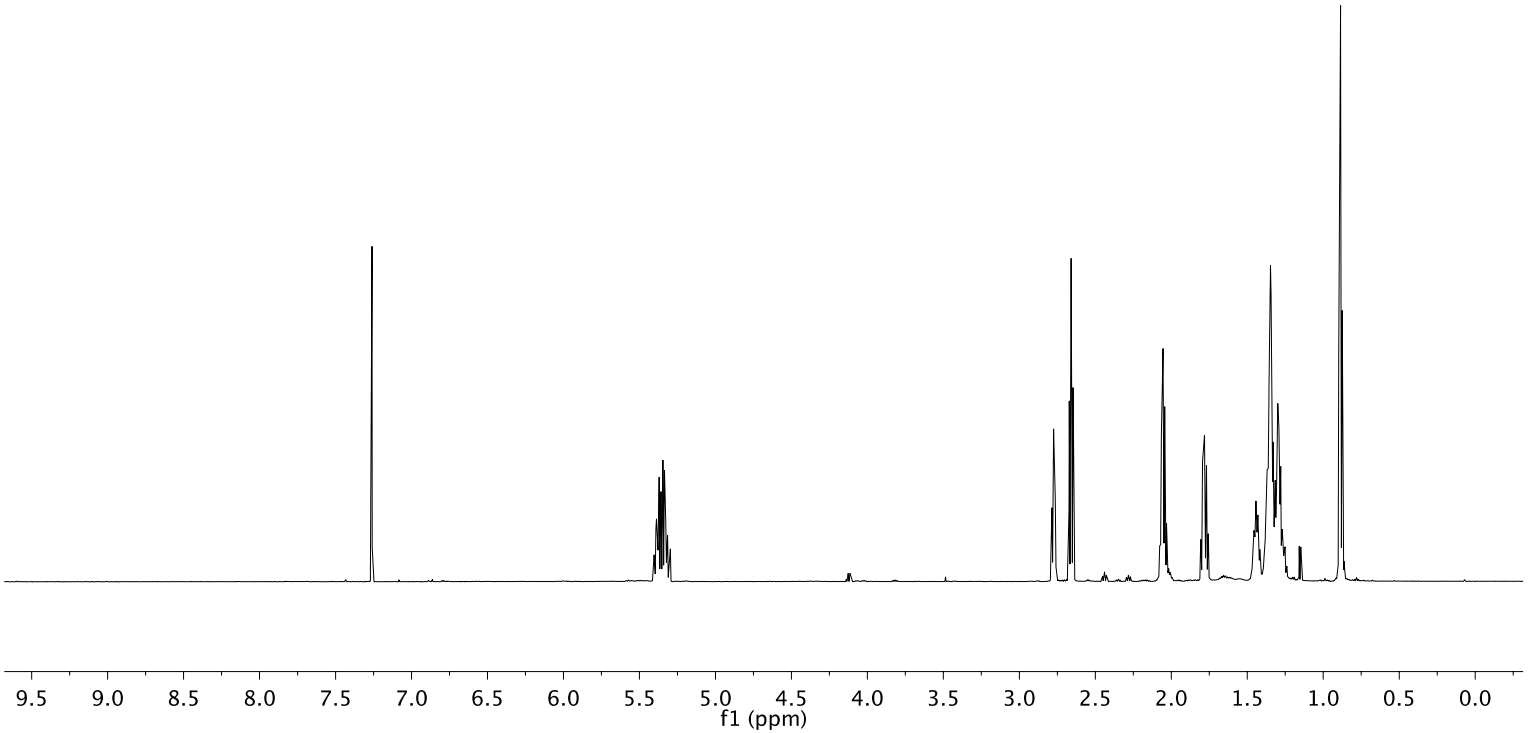

O
Me
Me
O
H
H
H
H
O
O
O–N
O
O
Cl
Cl
Cl
Cl

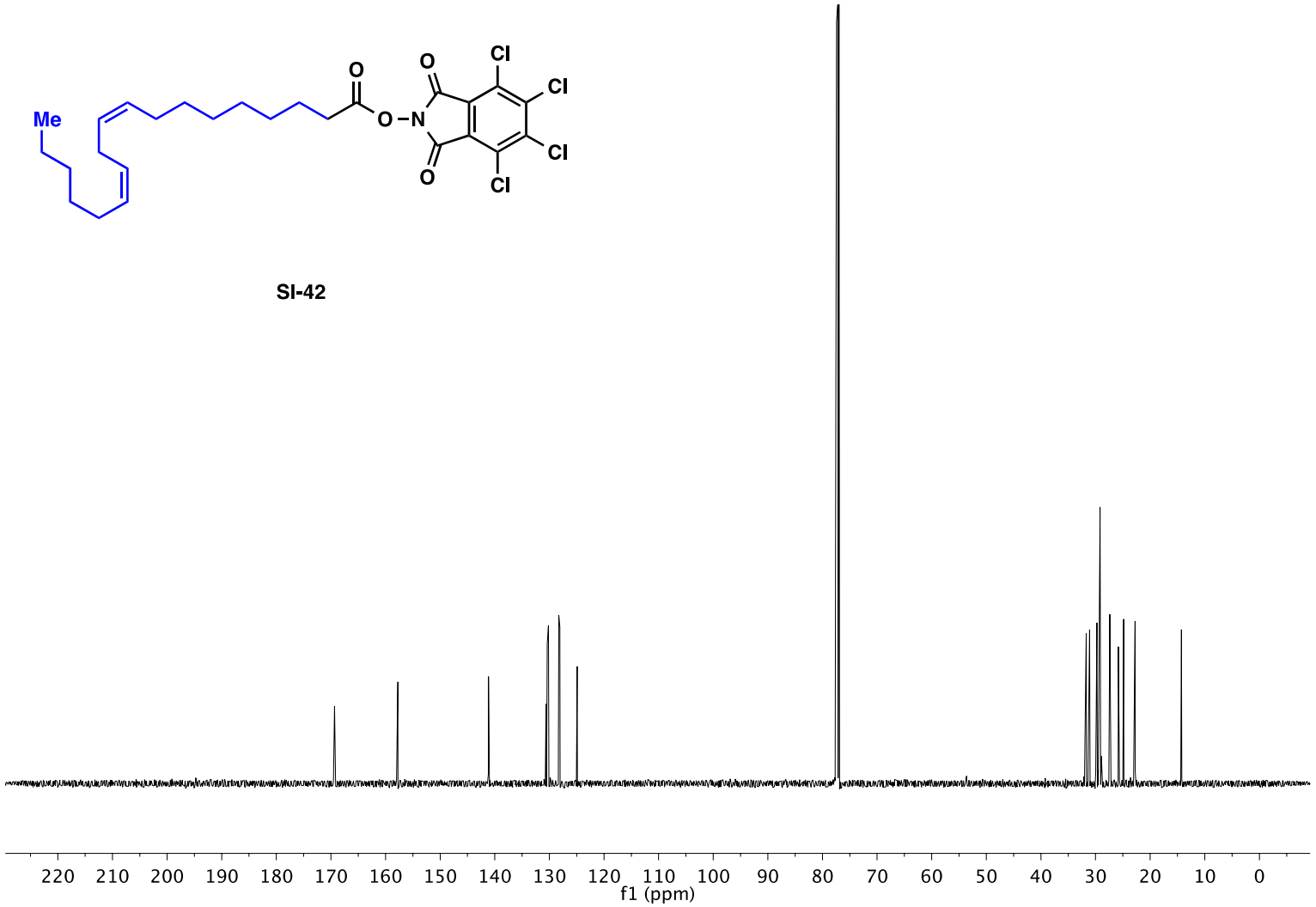
SI-41

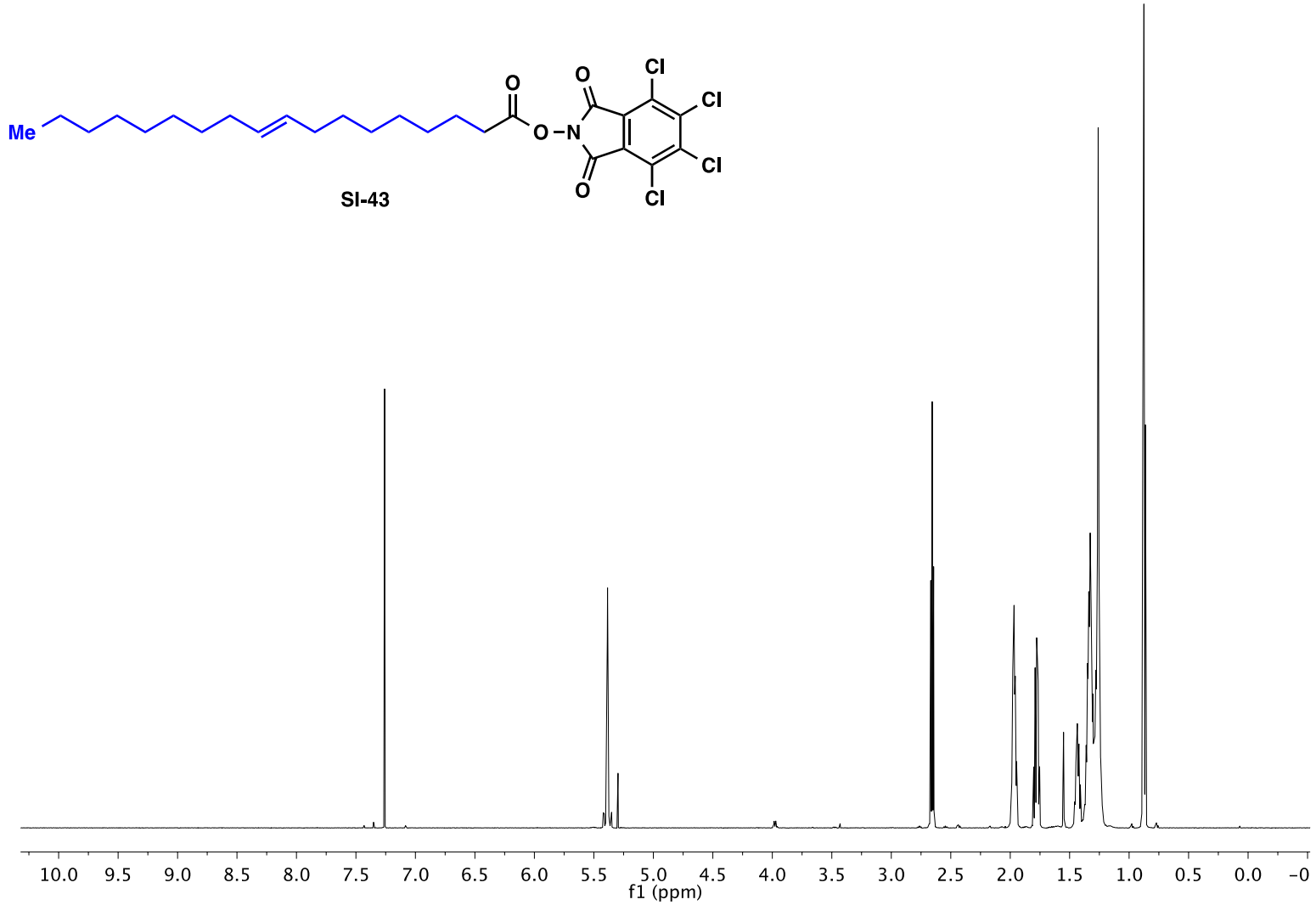
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
O
O
N
O
Cl
Cl
Cl
Cl

SI-42

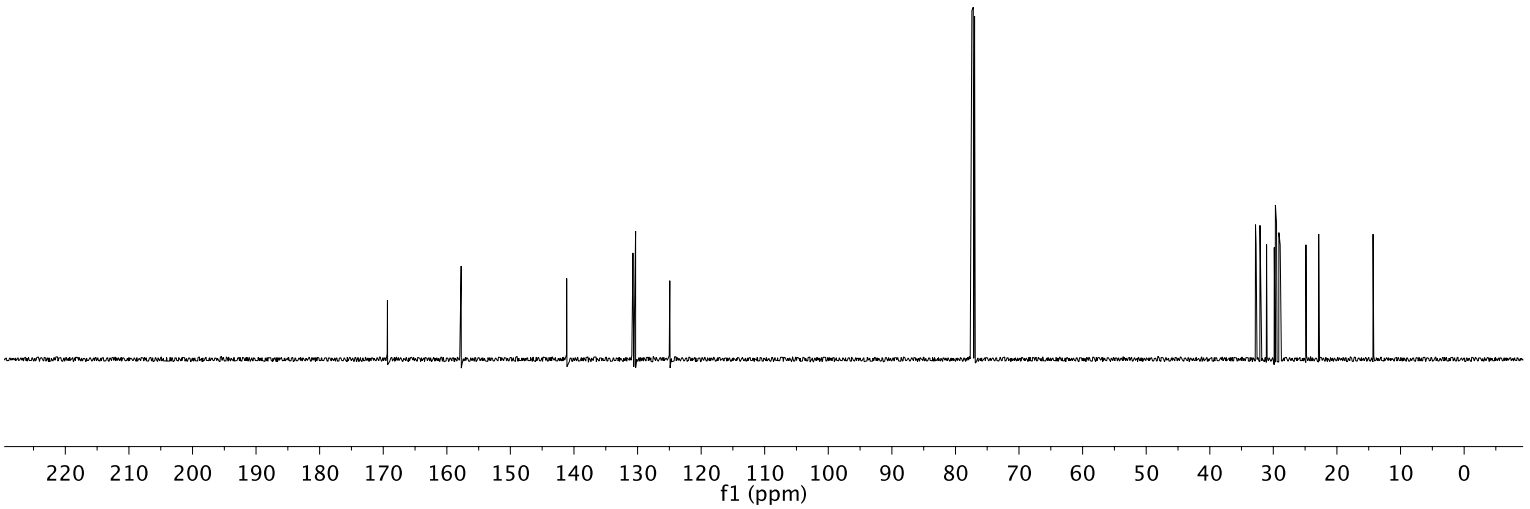

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

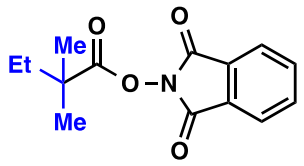

Me
O
O
O
N
O
Cl
Cl
Cl
Cl
SI-42
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Me
O
O
O
N
O
Cl
Cl
Cl
Cl
SI-43
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0
f1 (ppm)


Me
O
O
O
N
O
Cl
Cl
Cl
Cl

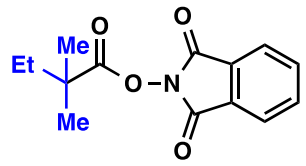
SI-43


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

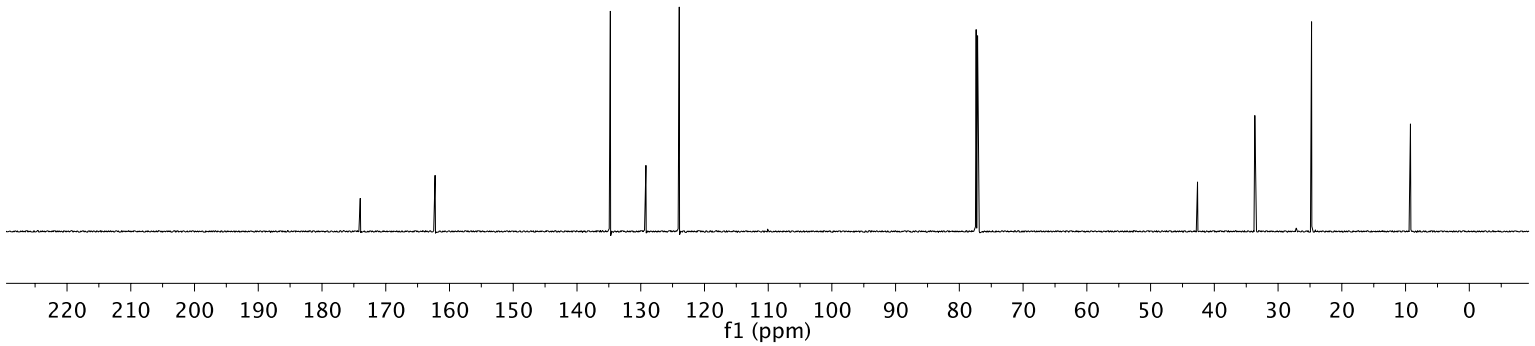

Et
Me
Me
O
O
O
N
O

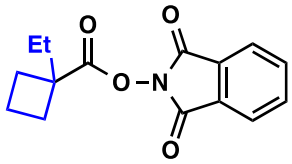
SI-44

0.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

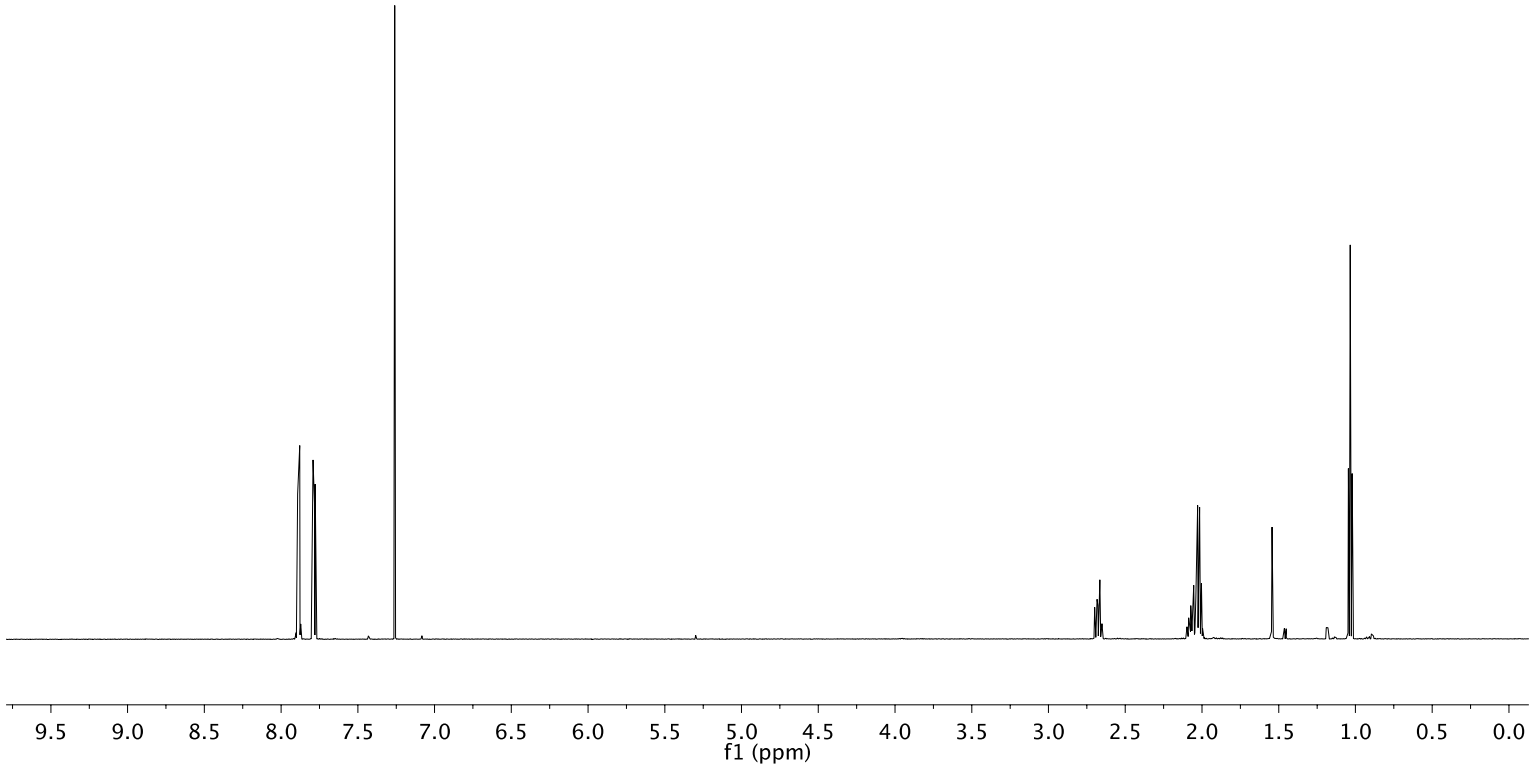

Et
Me
Me
O
O
O
O
N

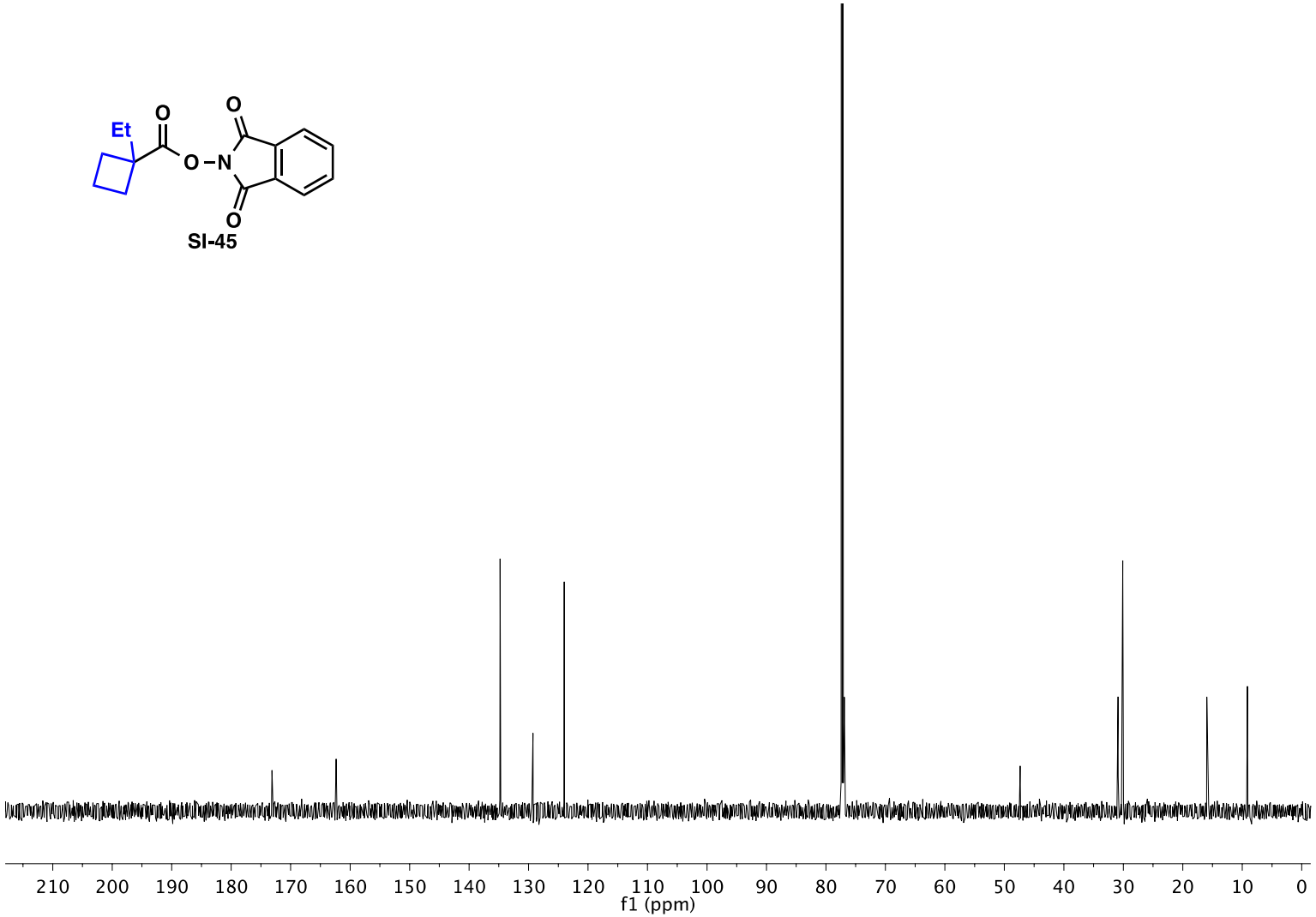
SI-44

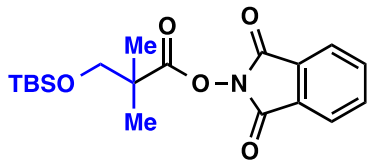

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Et
O
O
O
N
O
O

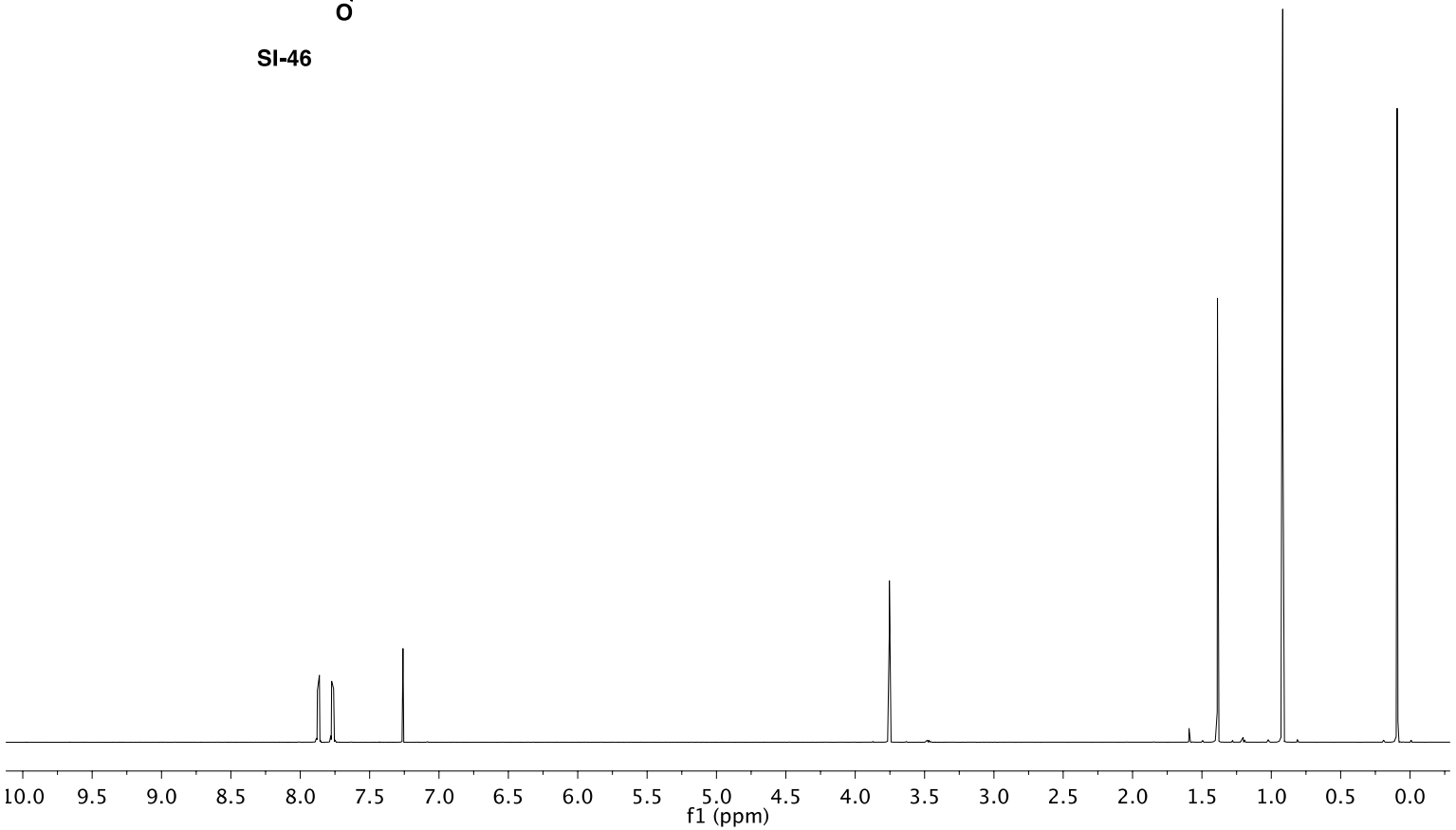
SI-45

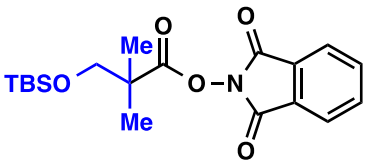

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Et
O
O
O
O
N
SI-45
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

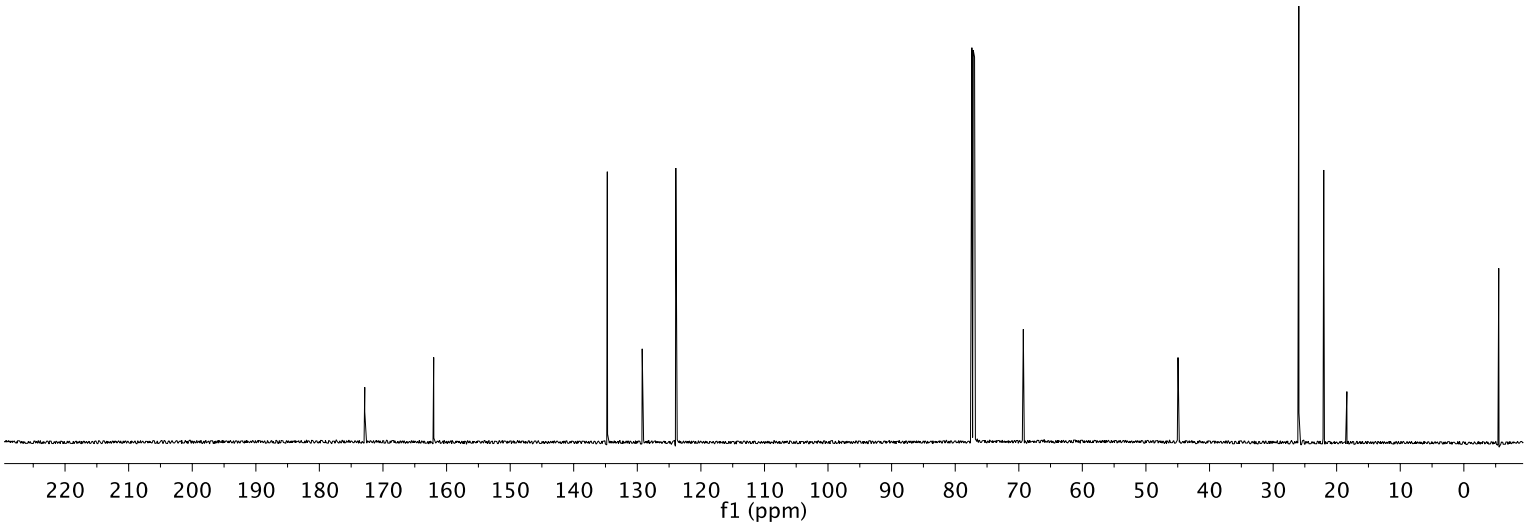

TBSO
Me
Me
O
O
O
N
O

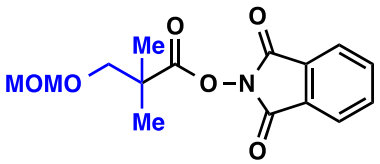
SI-46


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

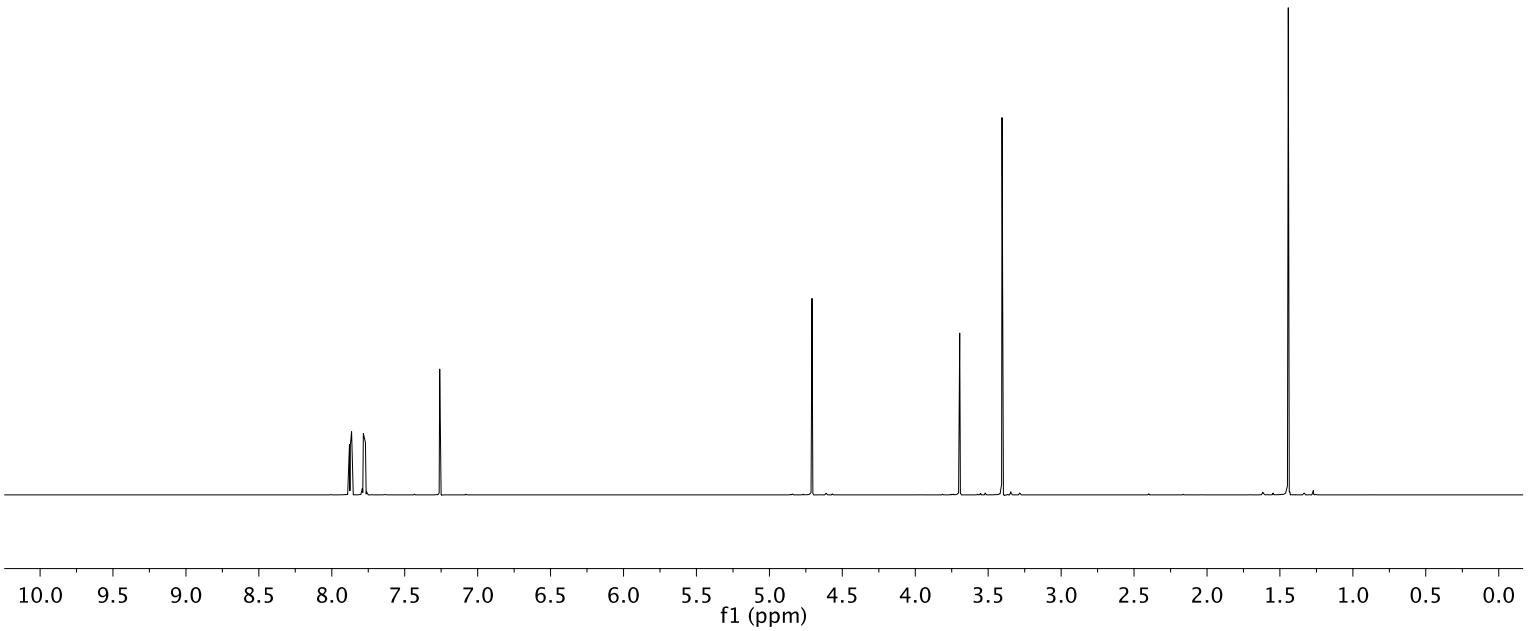

TBSO
Me
Me
O
O
O
N
O

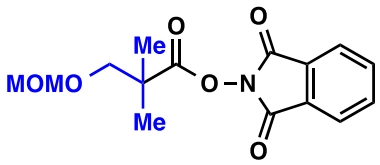
SI-46


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

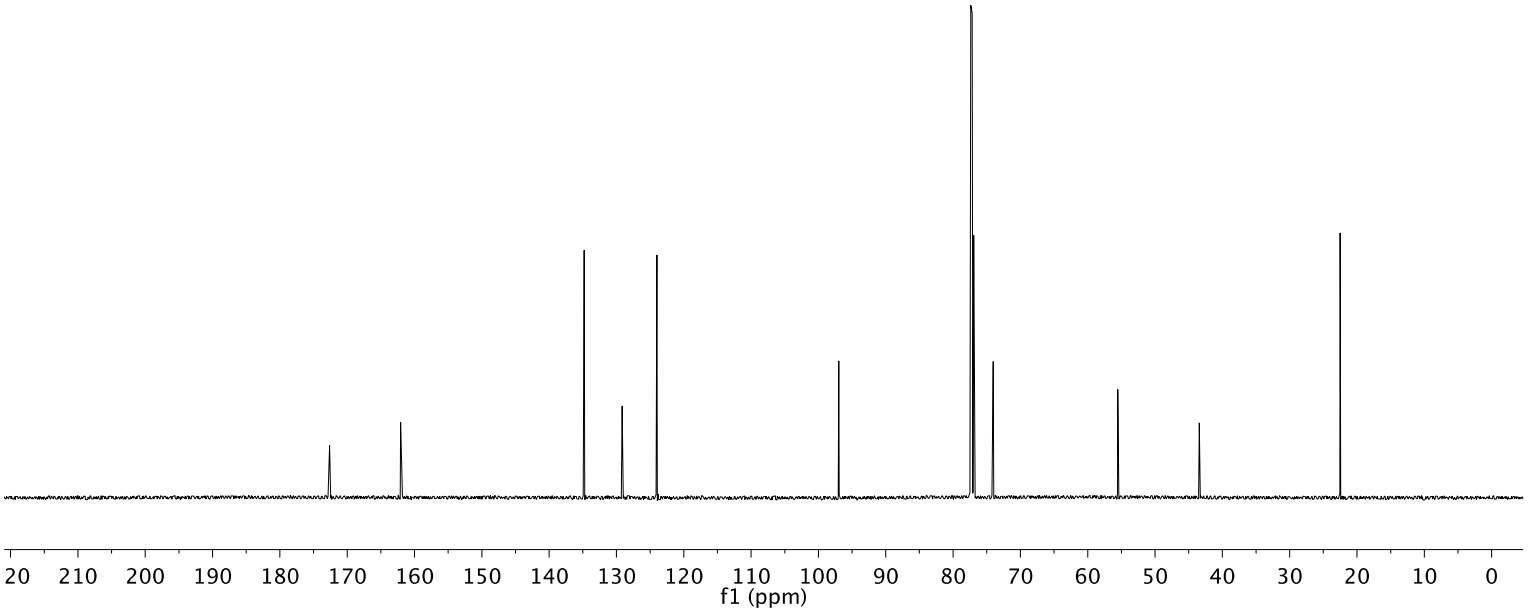

MOMO
Me
Me
O
O
O
N
O
O

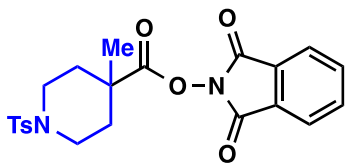
SI-47


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

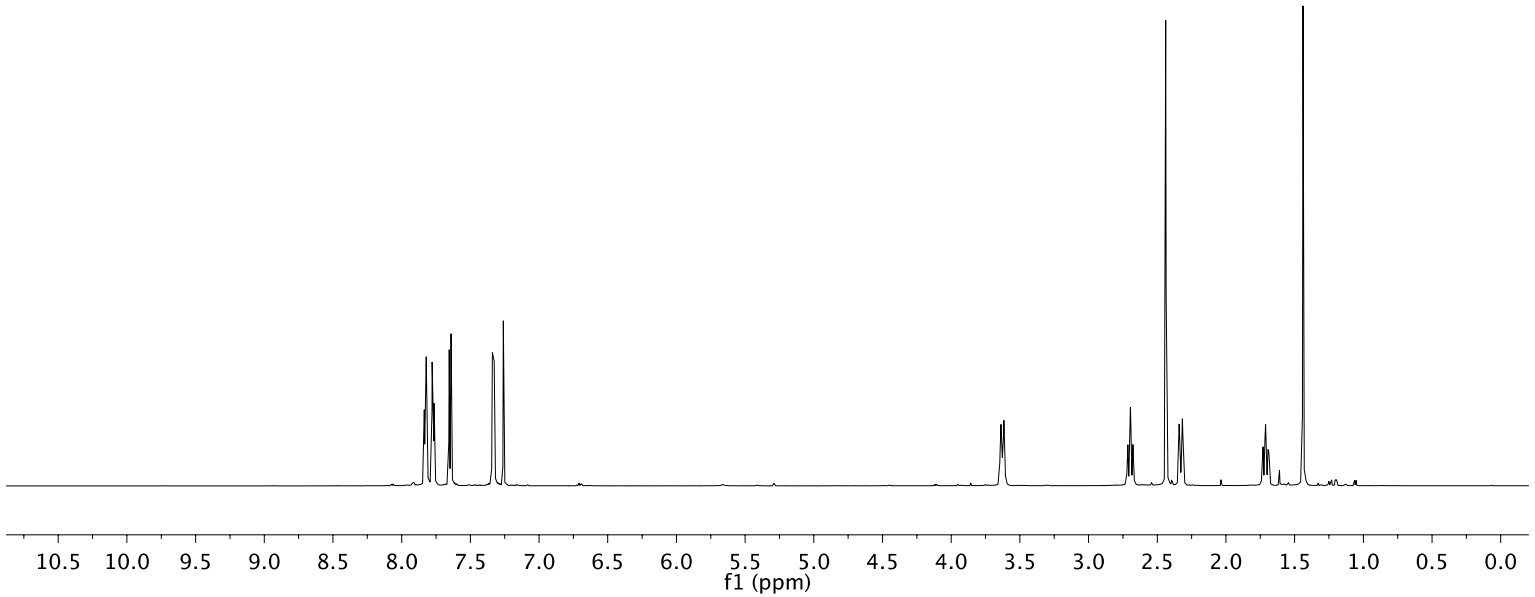

MOMO
Me
Me
O
O
O
N
O

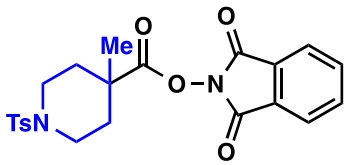
SI-47


20
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

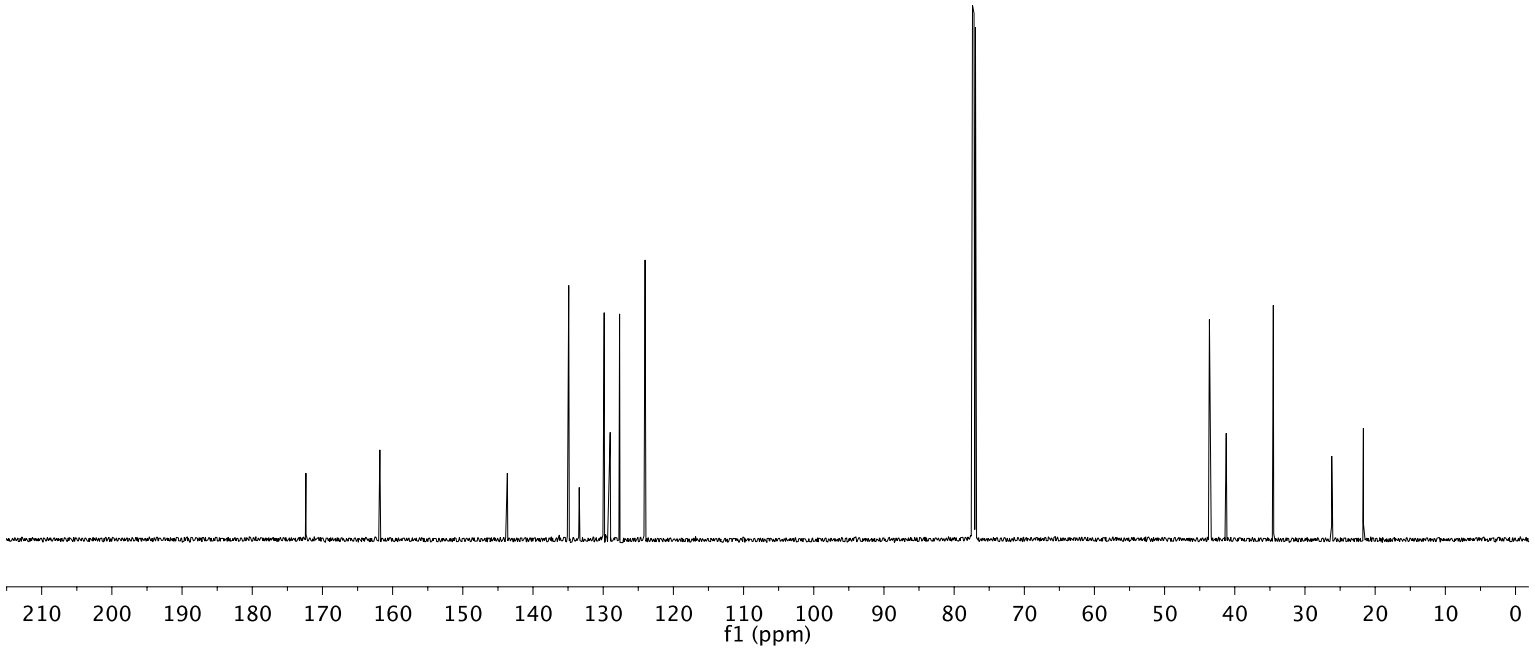

Me
O
O
O
O
N
TsN
O

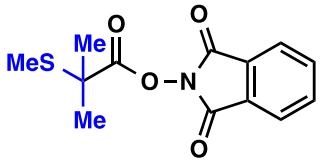
SI-48


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

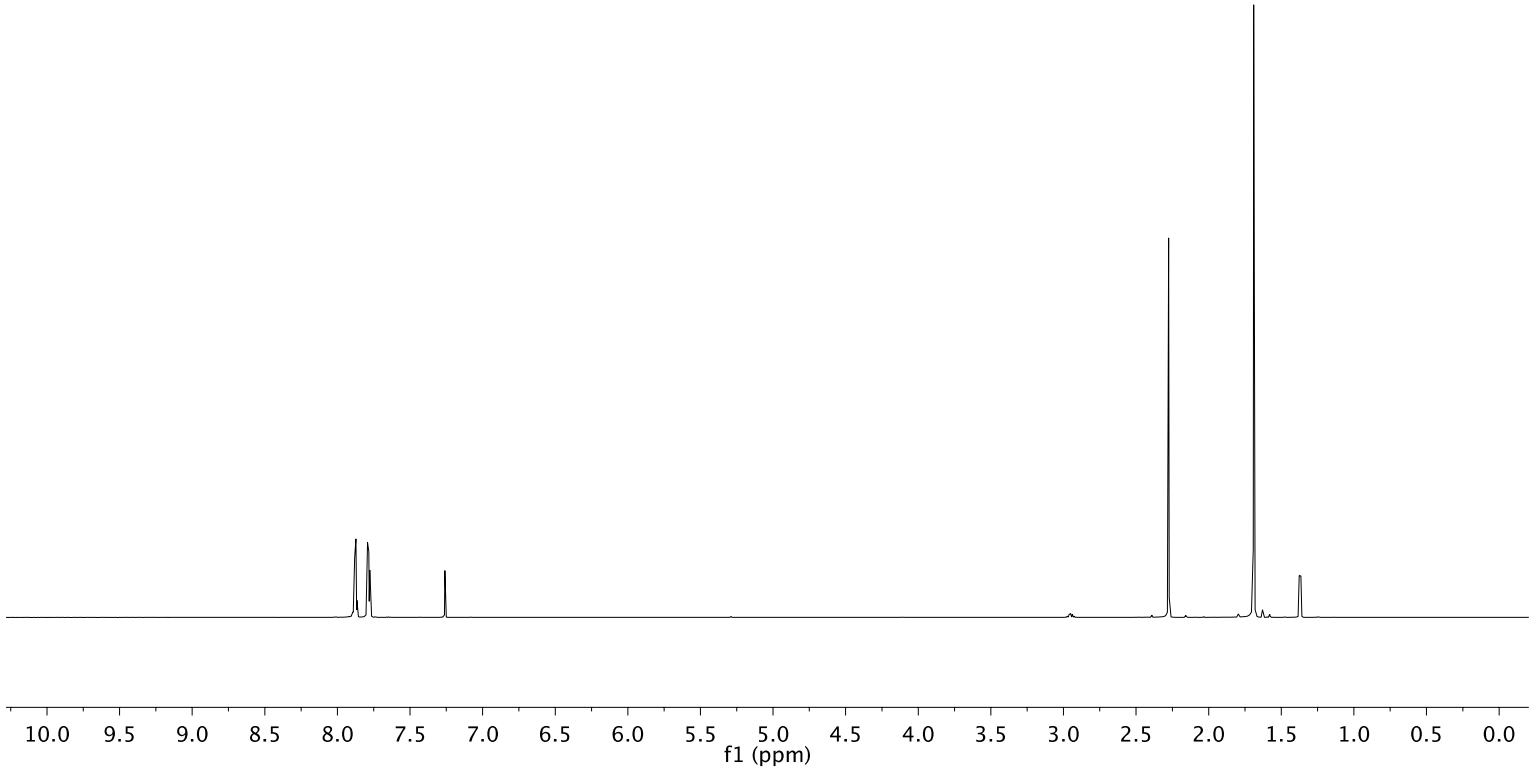

Me
O
O
O
O
N
TsN

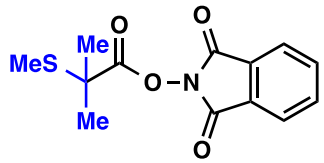
SI-48


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

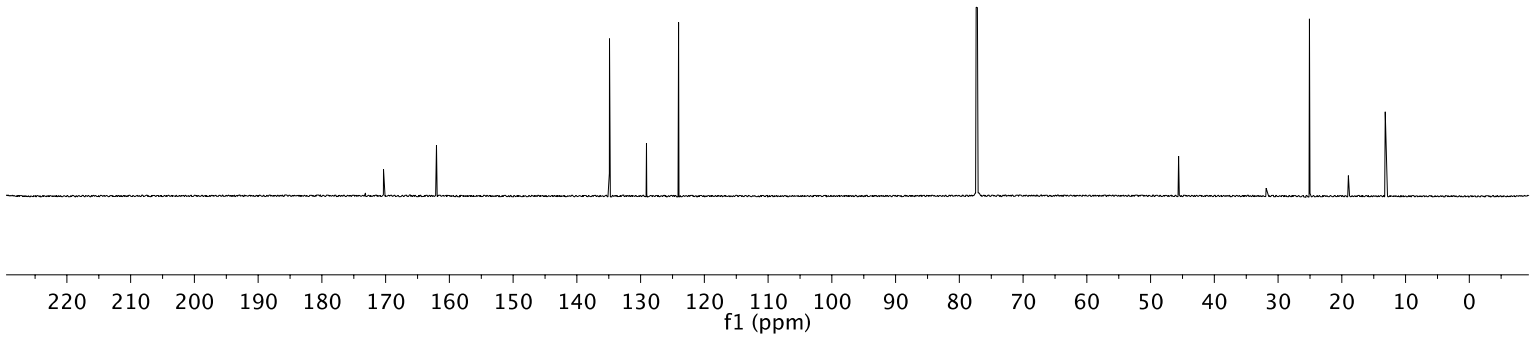

MeS
Me
Me
O
O
O–N
O
O

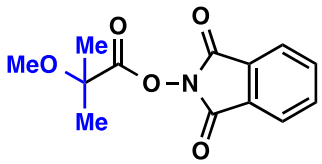
SI-49


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

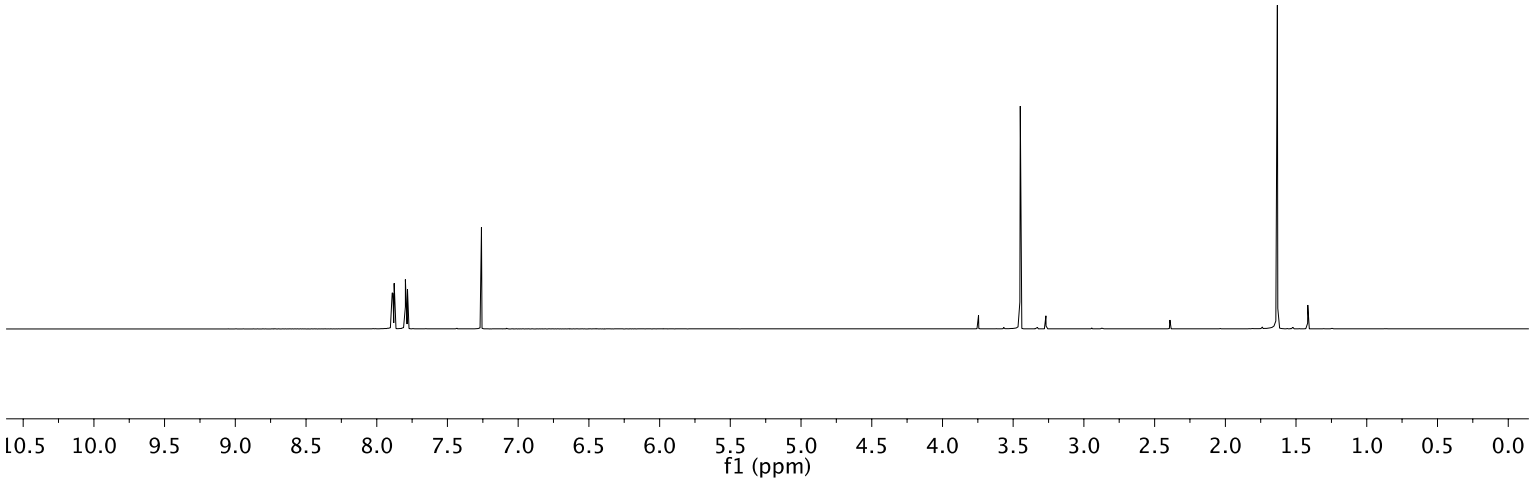

MeS
Me
Me
O
O
O
O
N

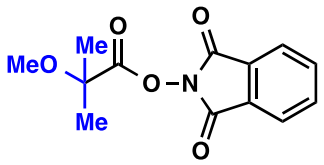
SI-49


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

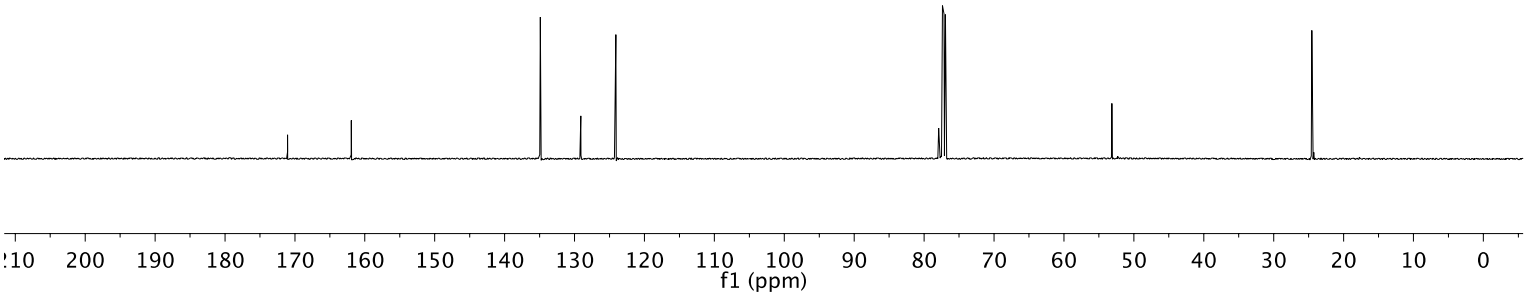

Me
O
MeO
O–N
O
Me
O

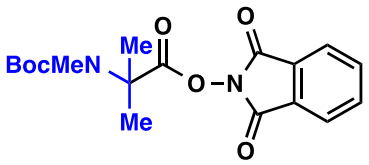
SI-50


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

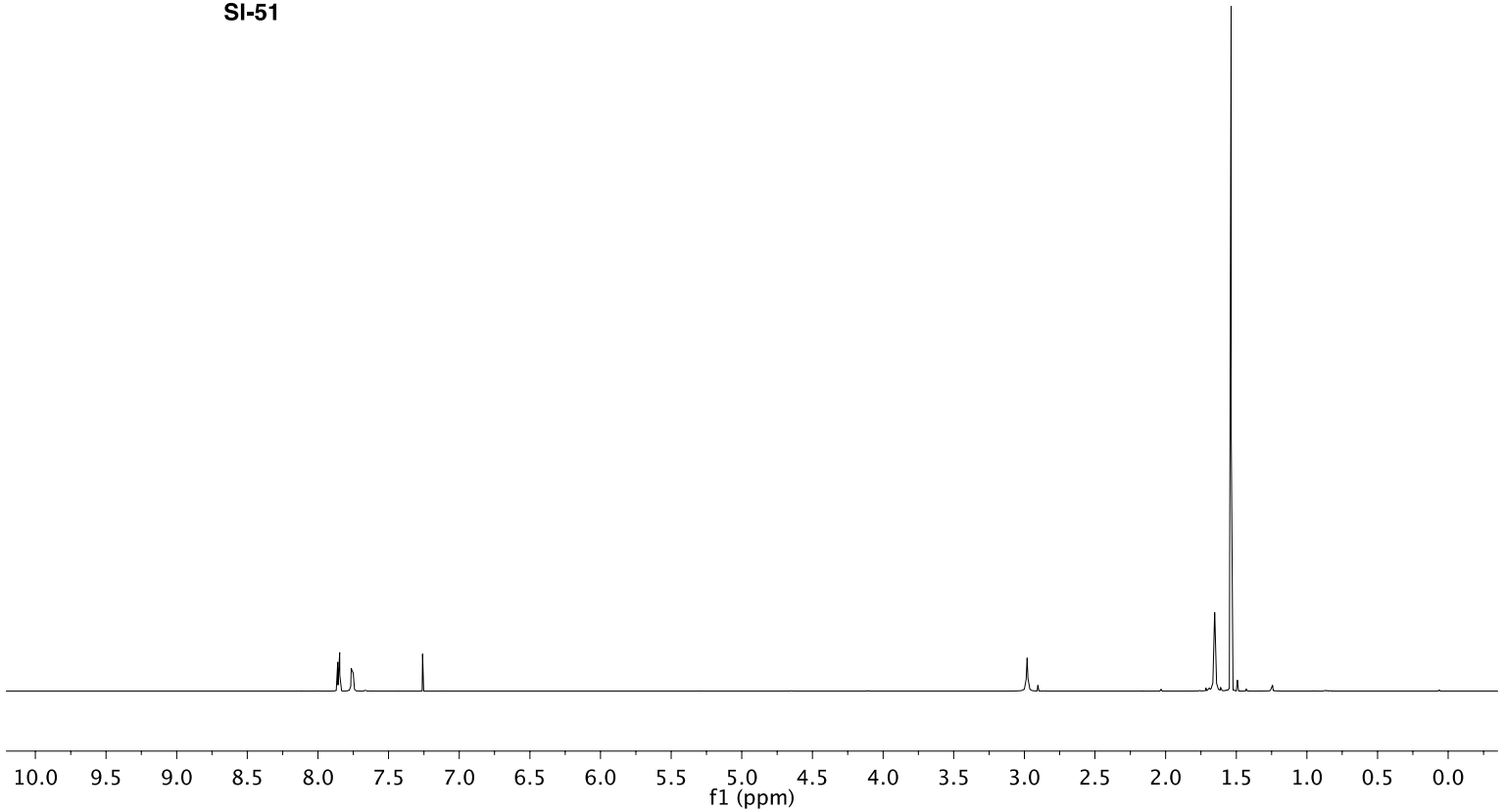

MeO
Me
Me
O
O
O
O
N

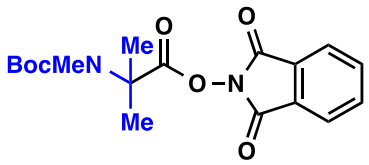
SI-50


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

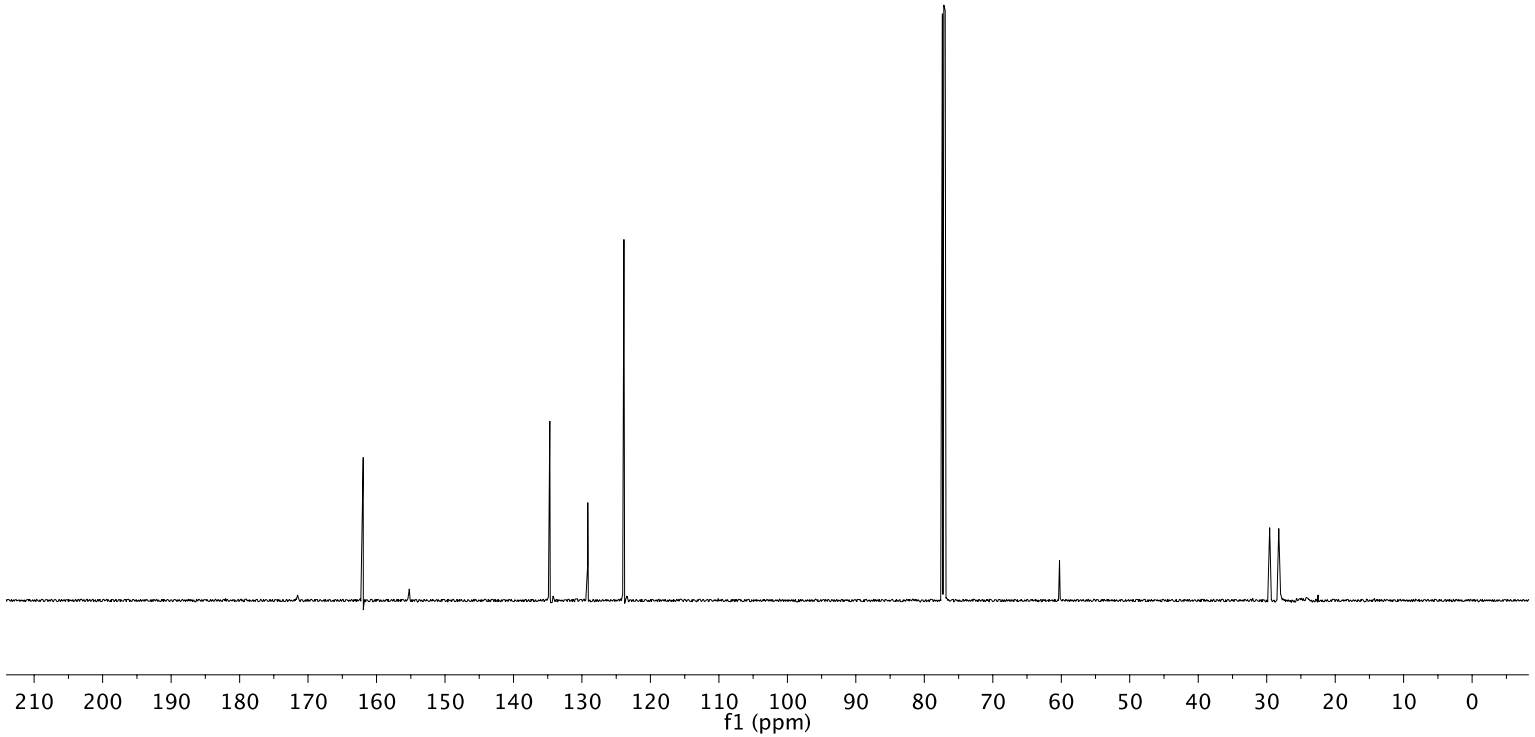

BocMeN
Me
Me
O
O
O
O
N

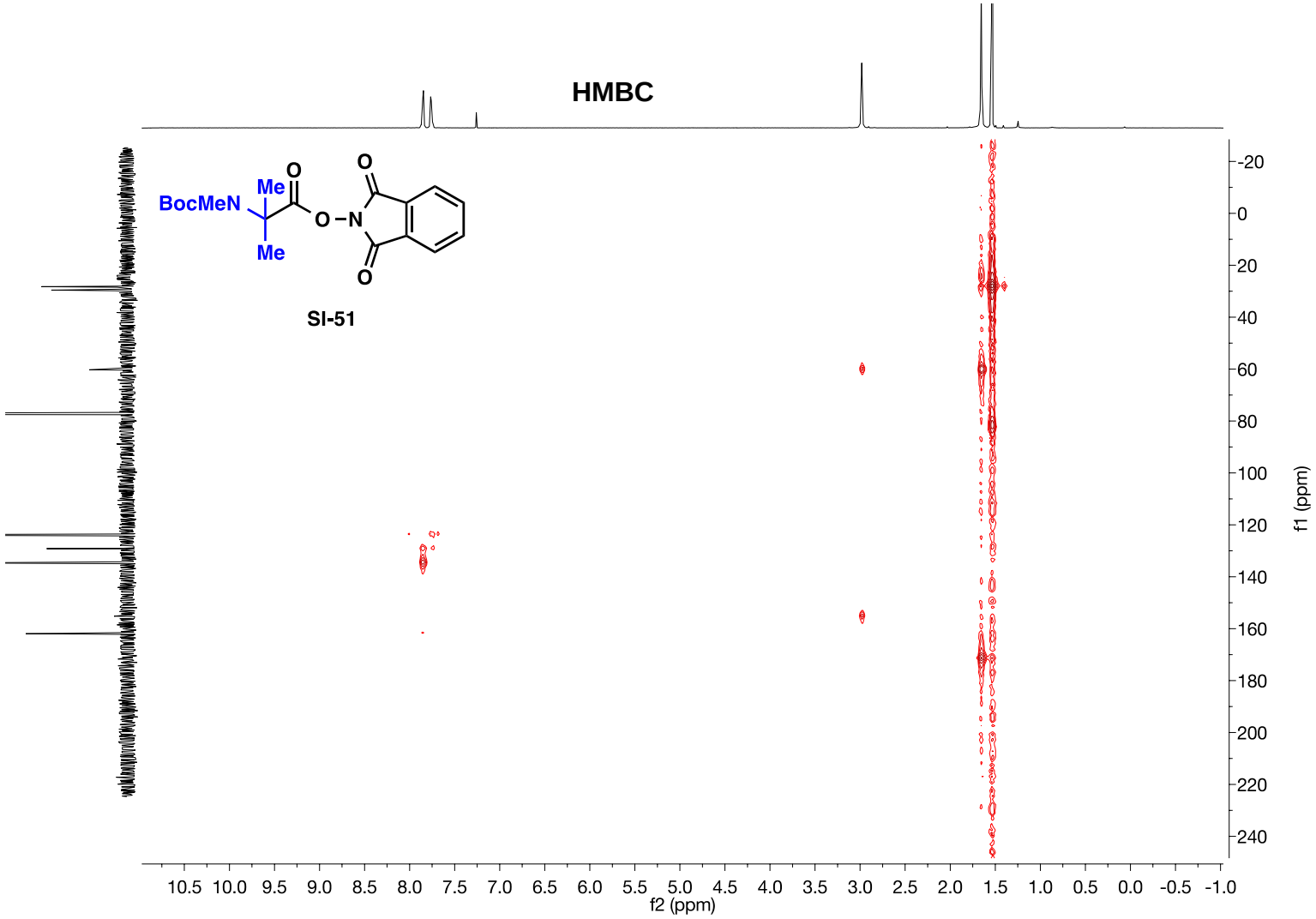
SI-51

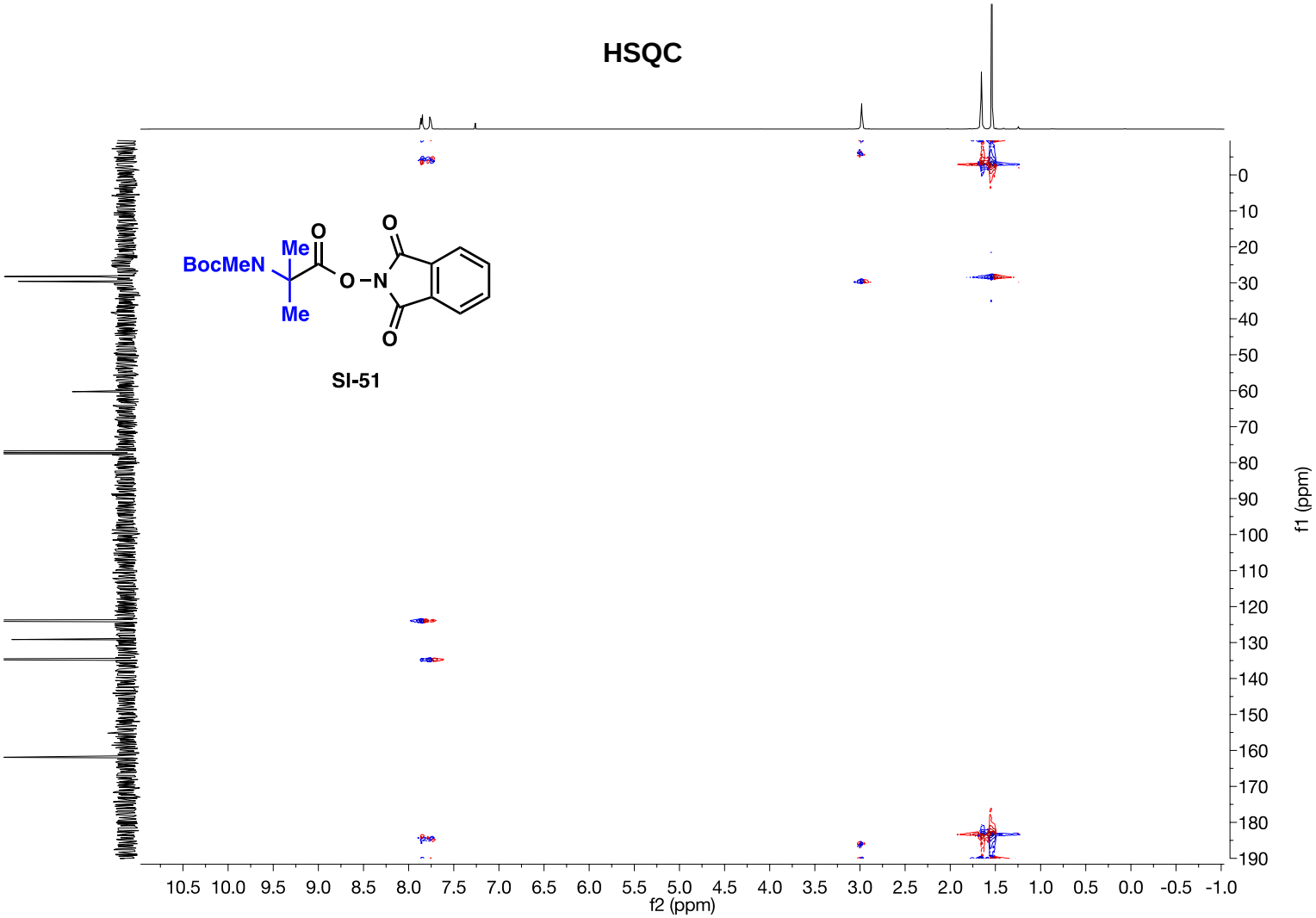

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

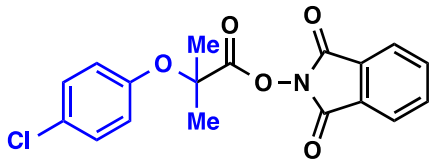

BocMeN
Me
Me
O
O
O
N
O
O

SI-51

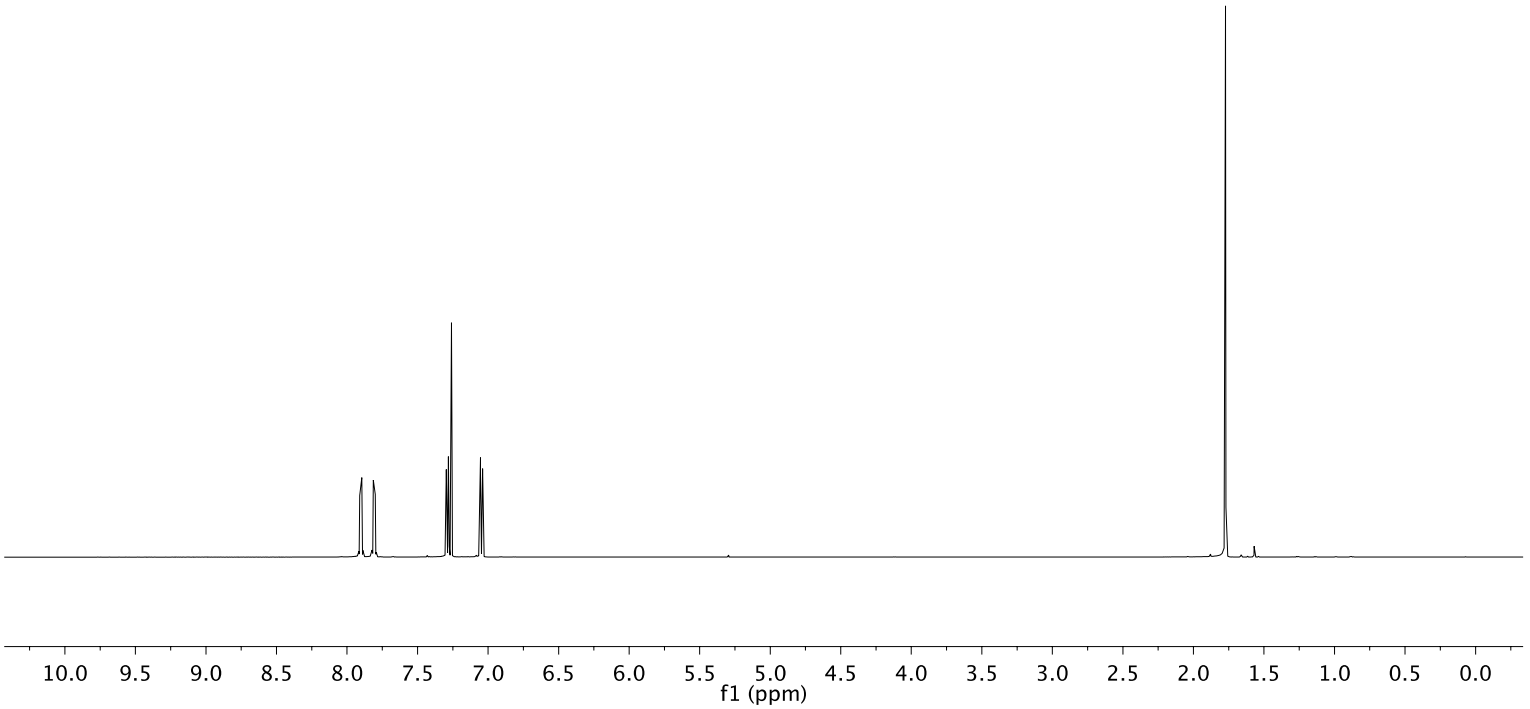

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

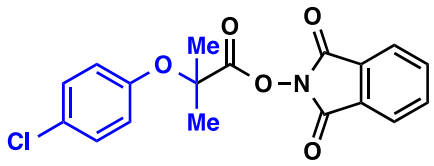

HMBC
BocMeN
Me
Me
O
O
O
N
O
O
SI-51
f1 (ppm)
f2 (ppm)


HSQC
BocMeN
Me
Me
O
O
O
O
N
SI-51
f2 (ppm)
f1 (ppm)

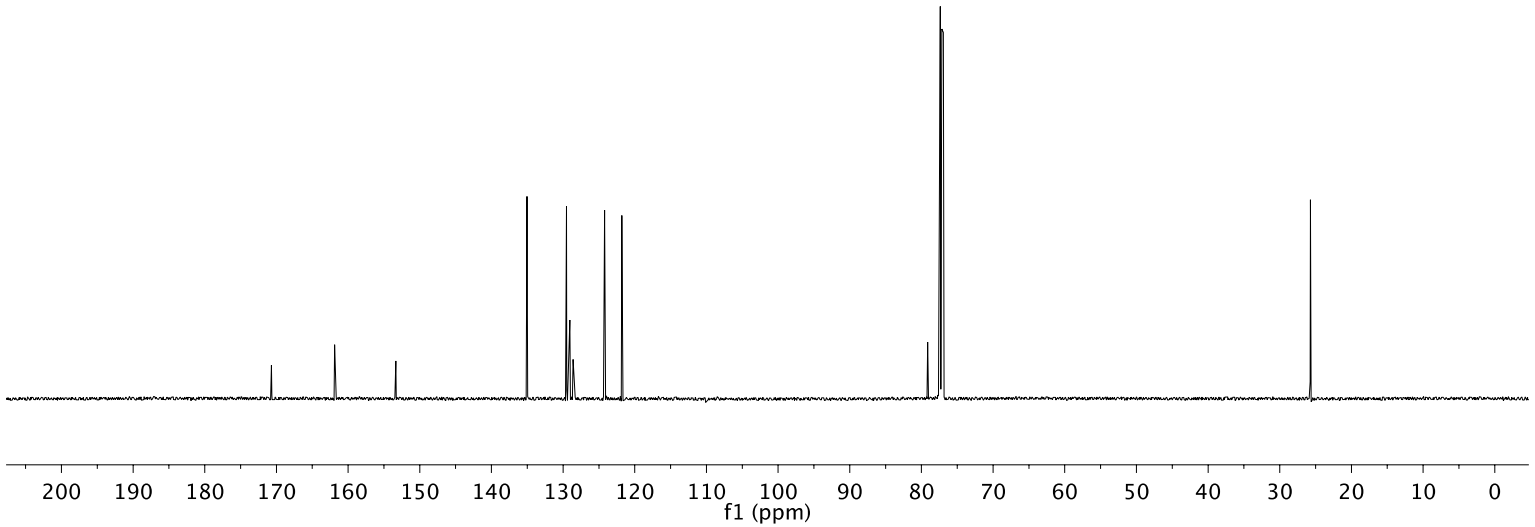

Me
O
O
O
N
O
O
Me
Cl

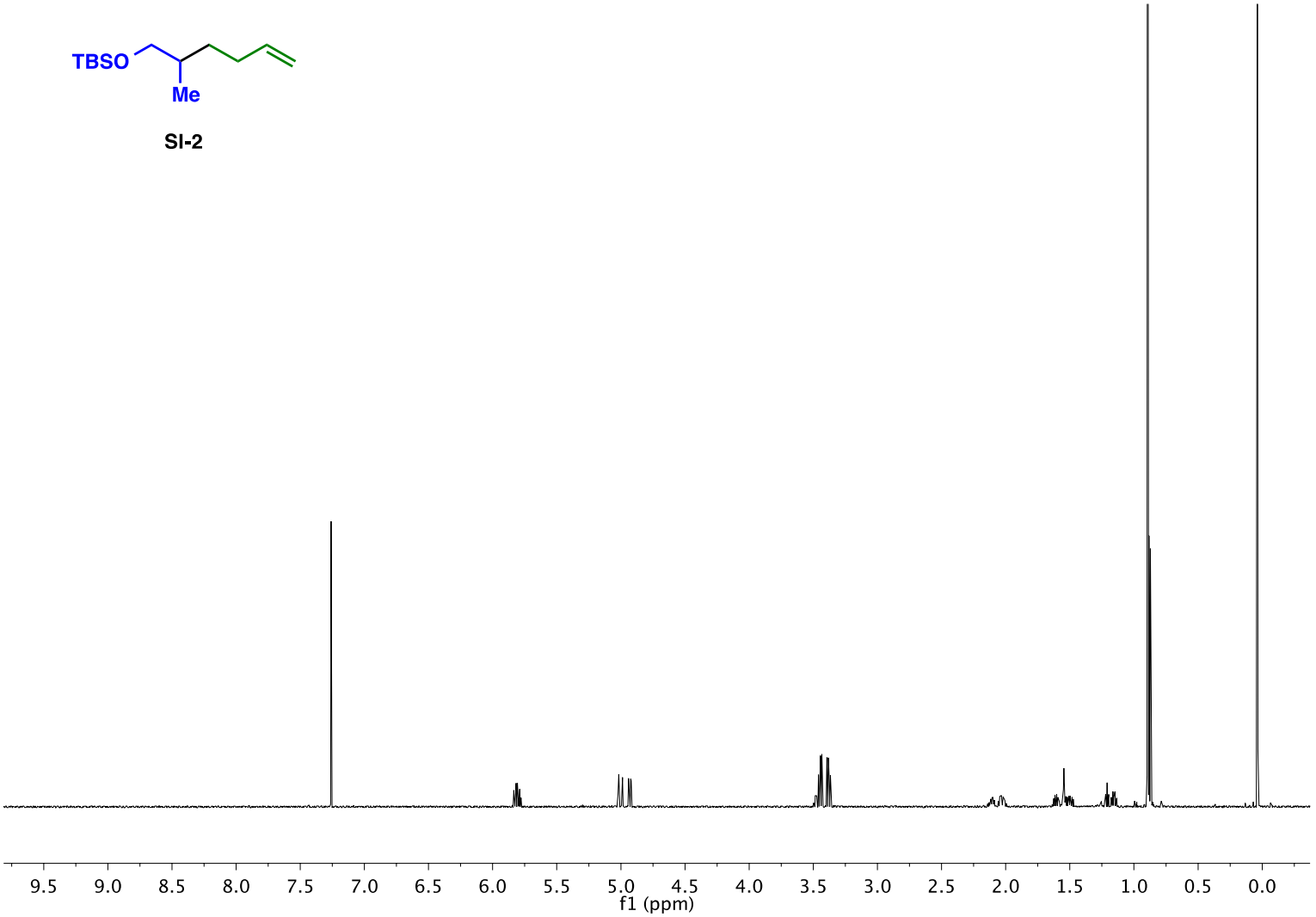
SI-52

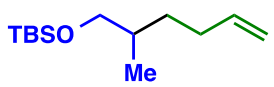

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
O
O
O
N
O
O
Me
Cl

SI-52

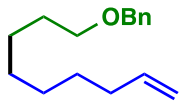

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


TBSO
Me
SI-2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

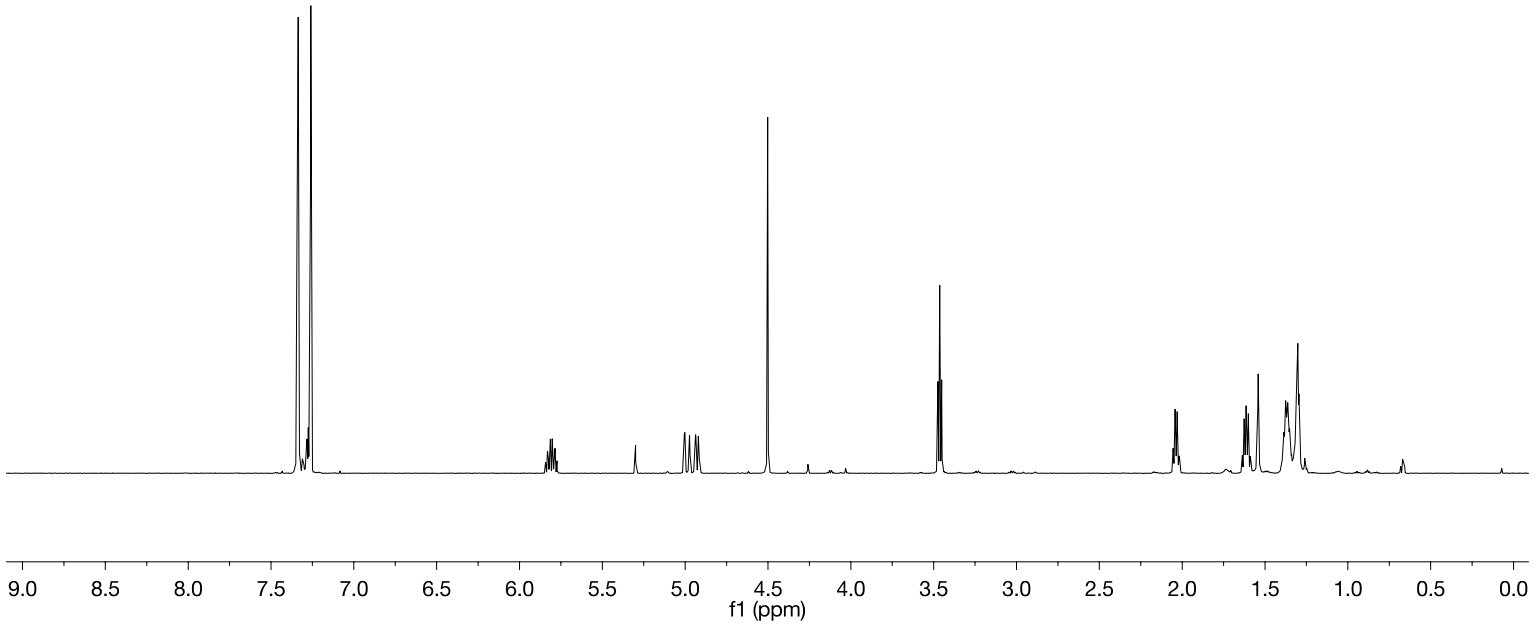

TBSO
Me

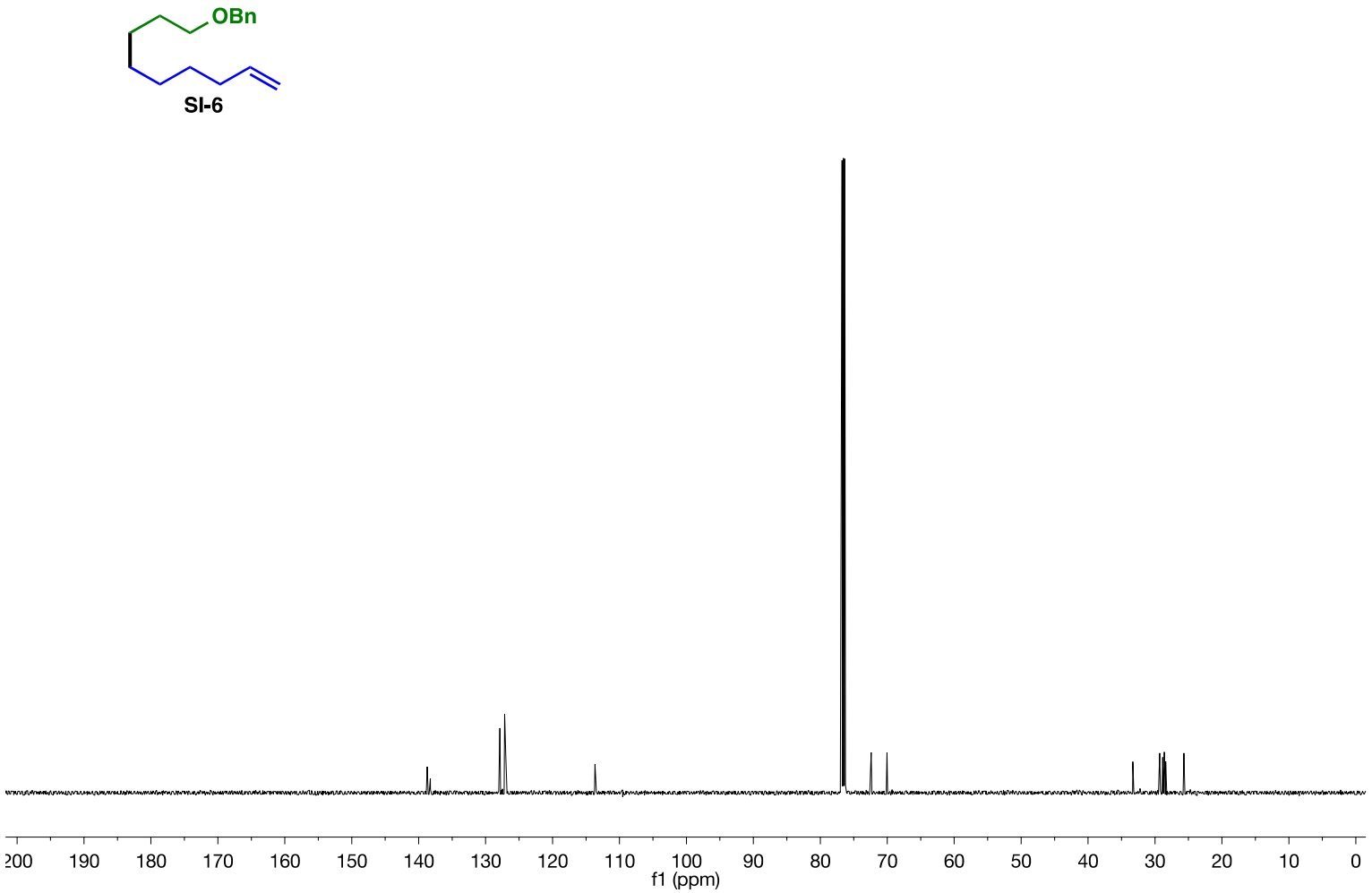
SI-2

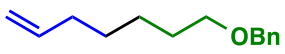
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



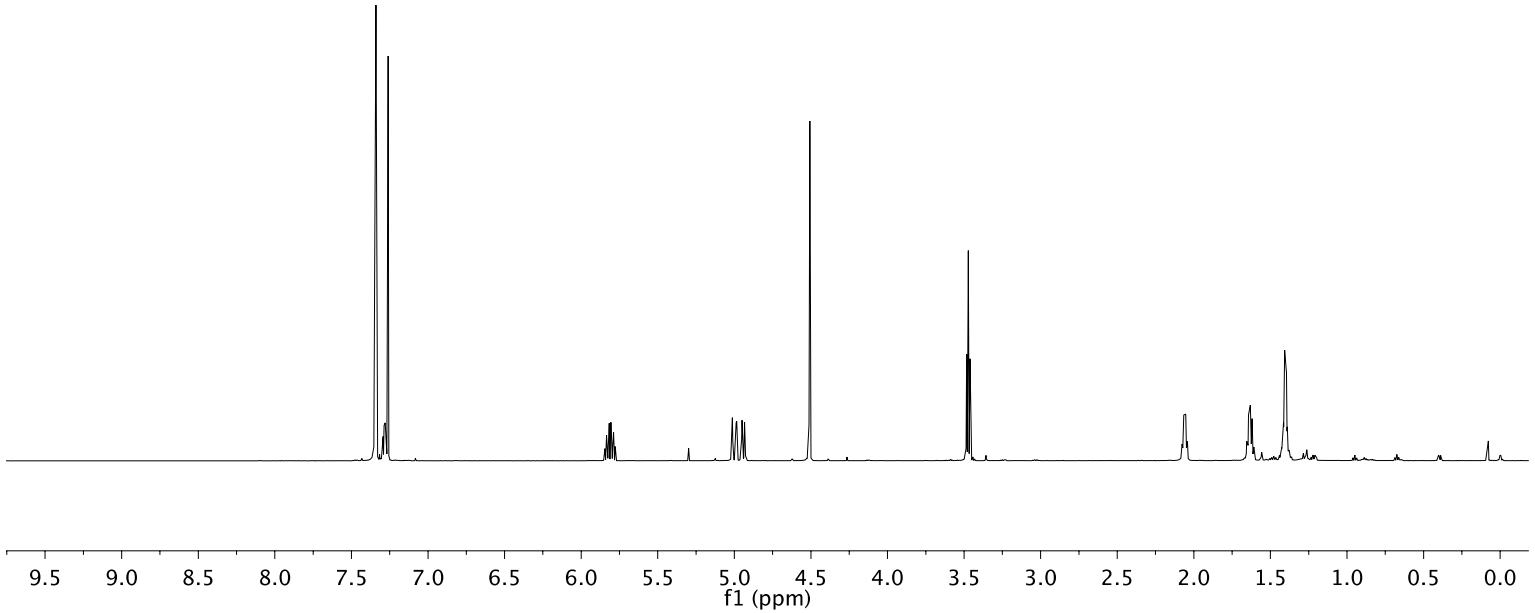
SI-6

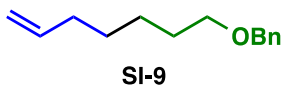



OBn
SI-6
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

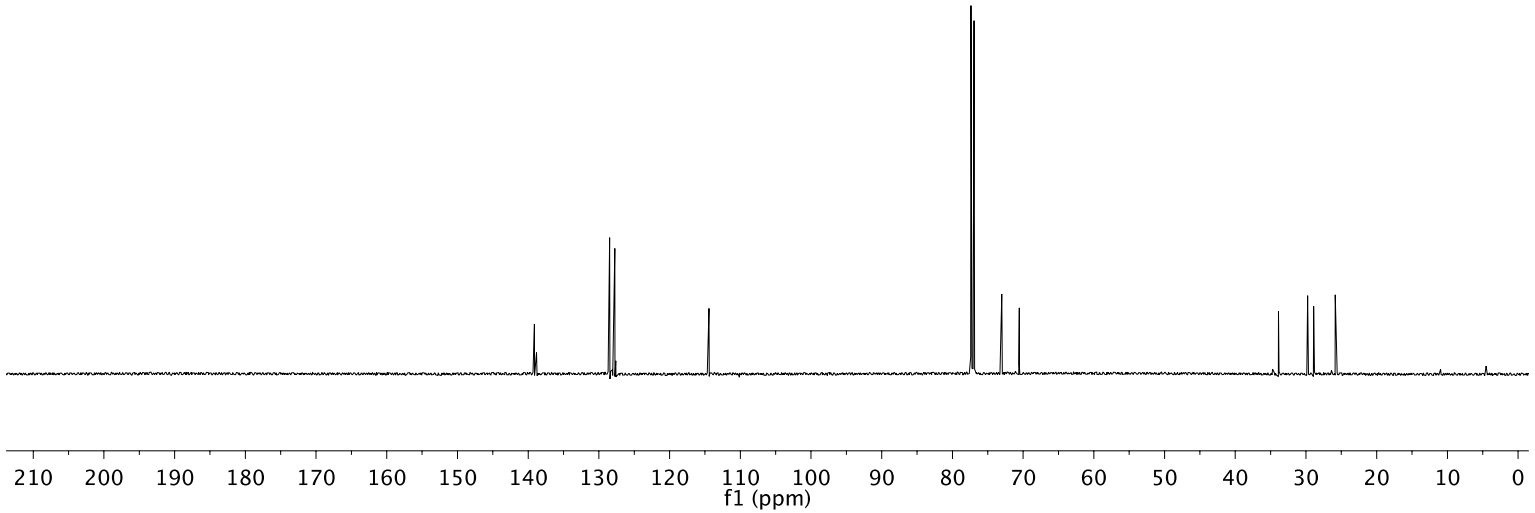


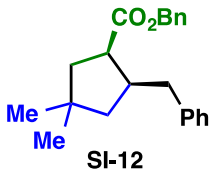
SI-9



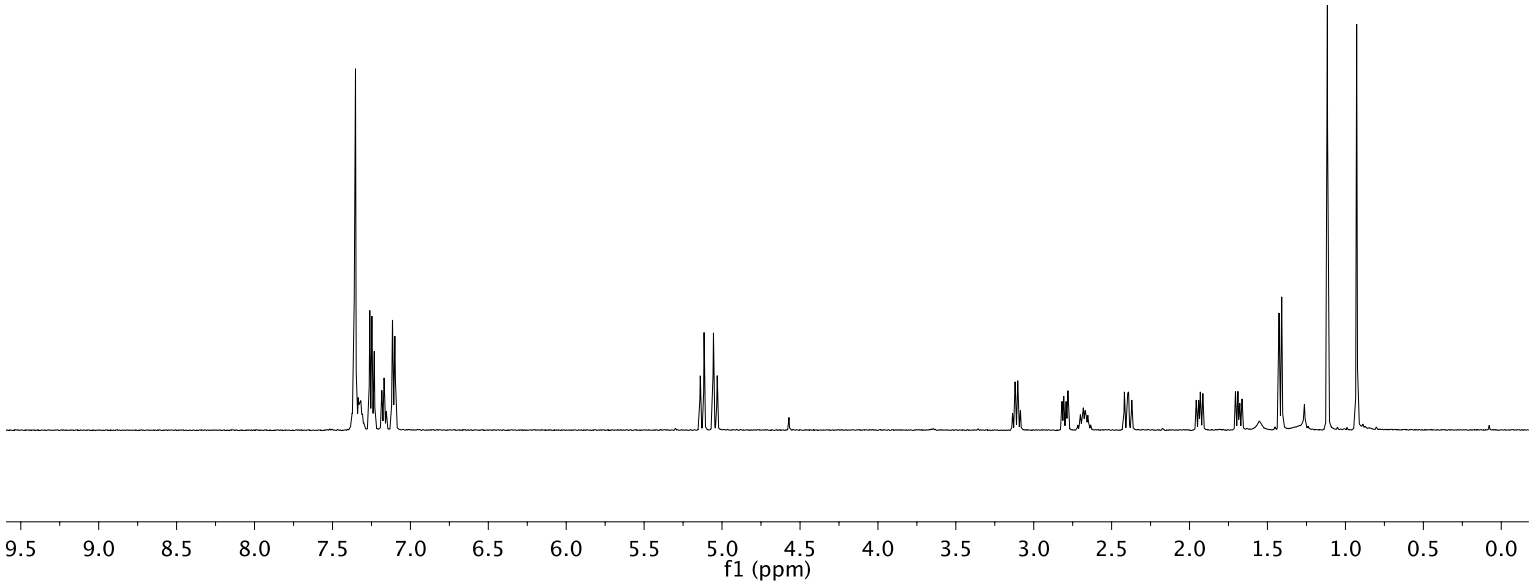

OBn

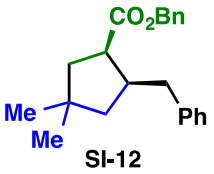
SI-9


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

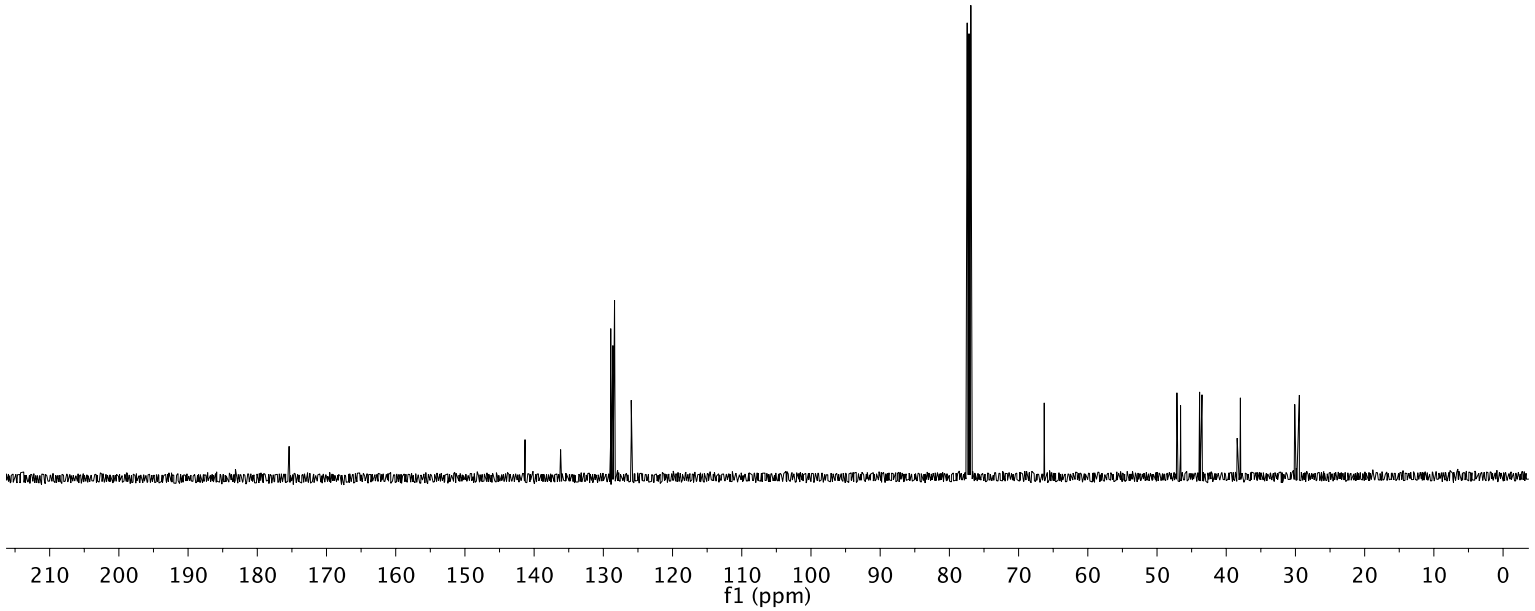

CO2Bn
Me
Me
Ph

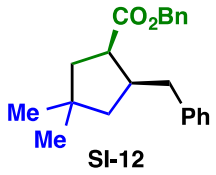
SI-12


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

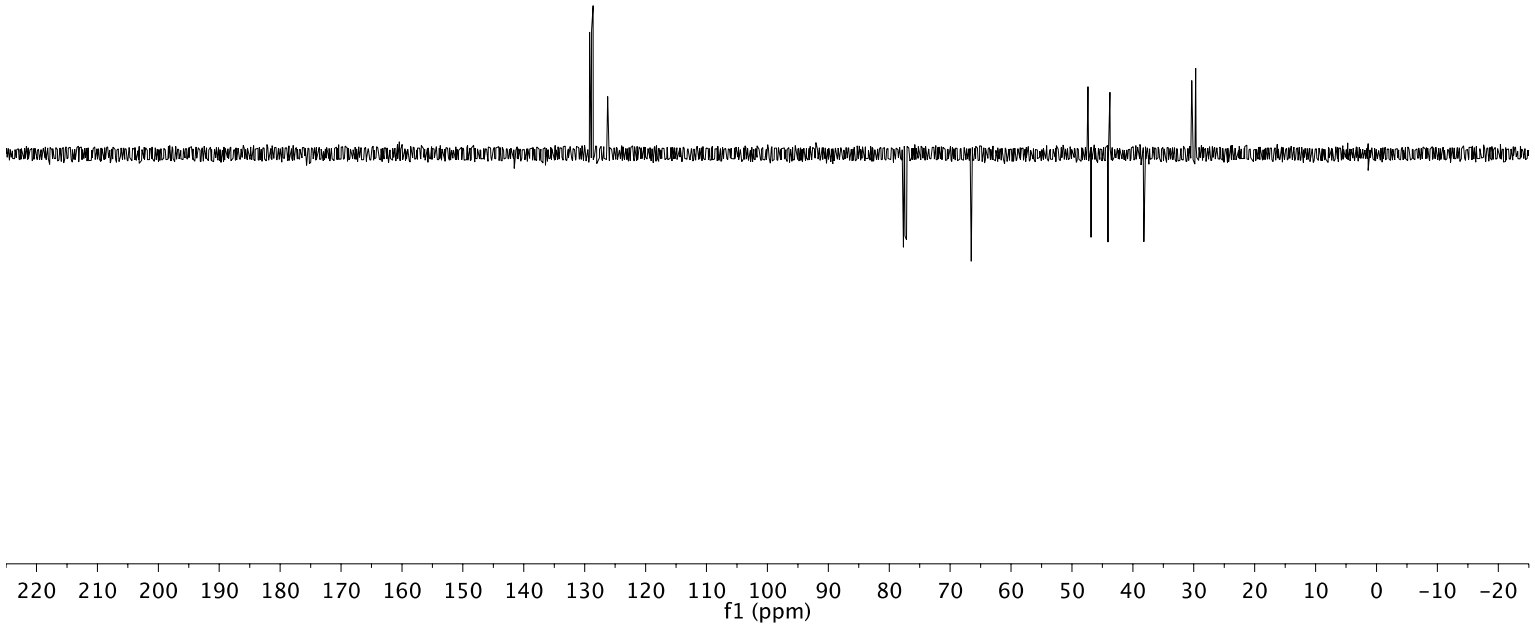

CO2Bn
Me
Me
Ph

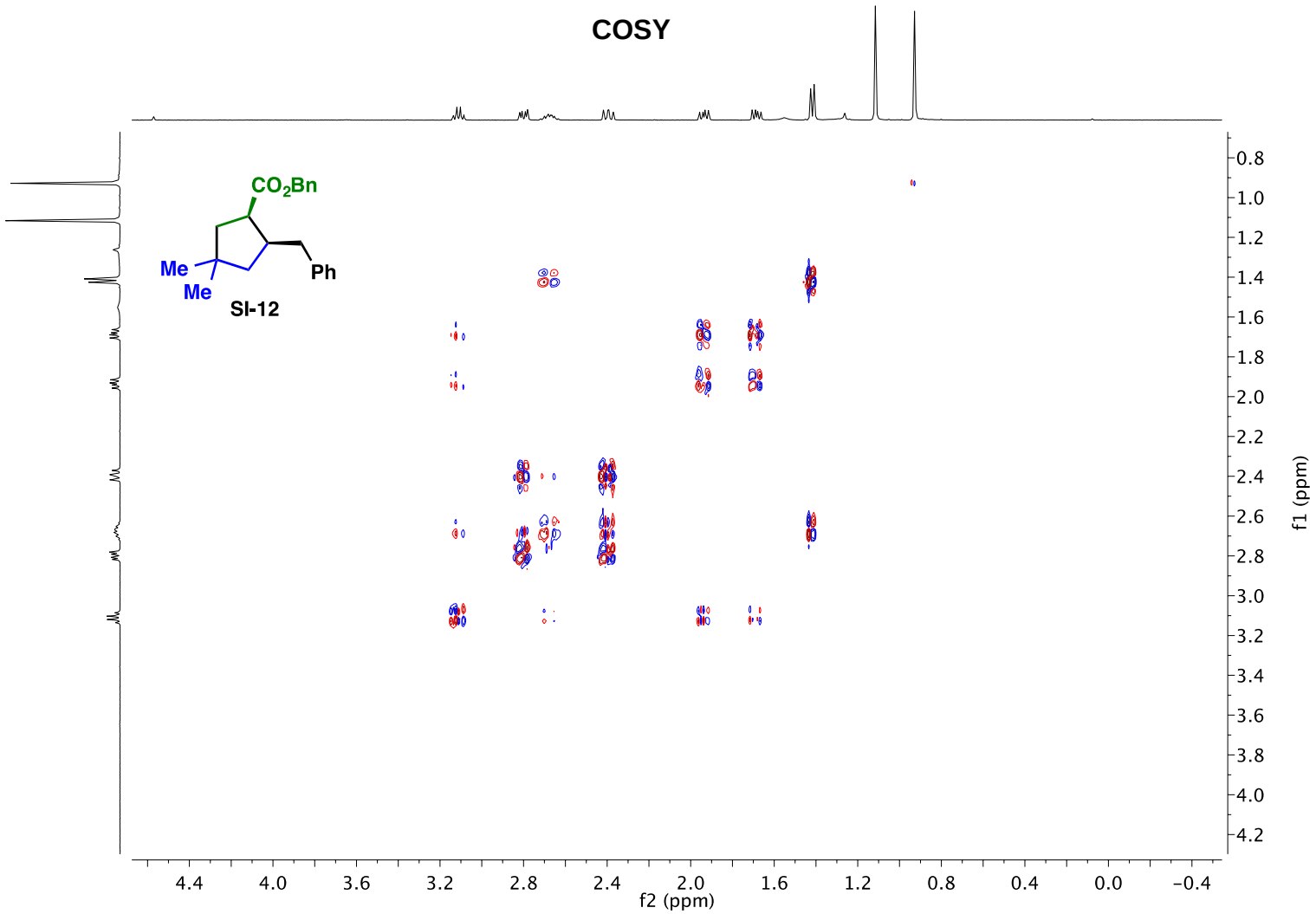
SI-12

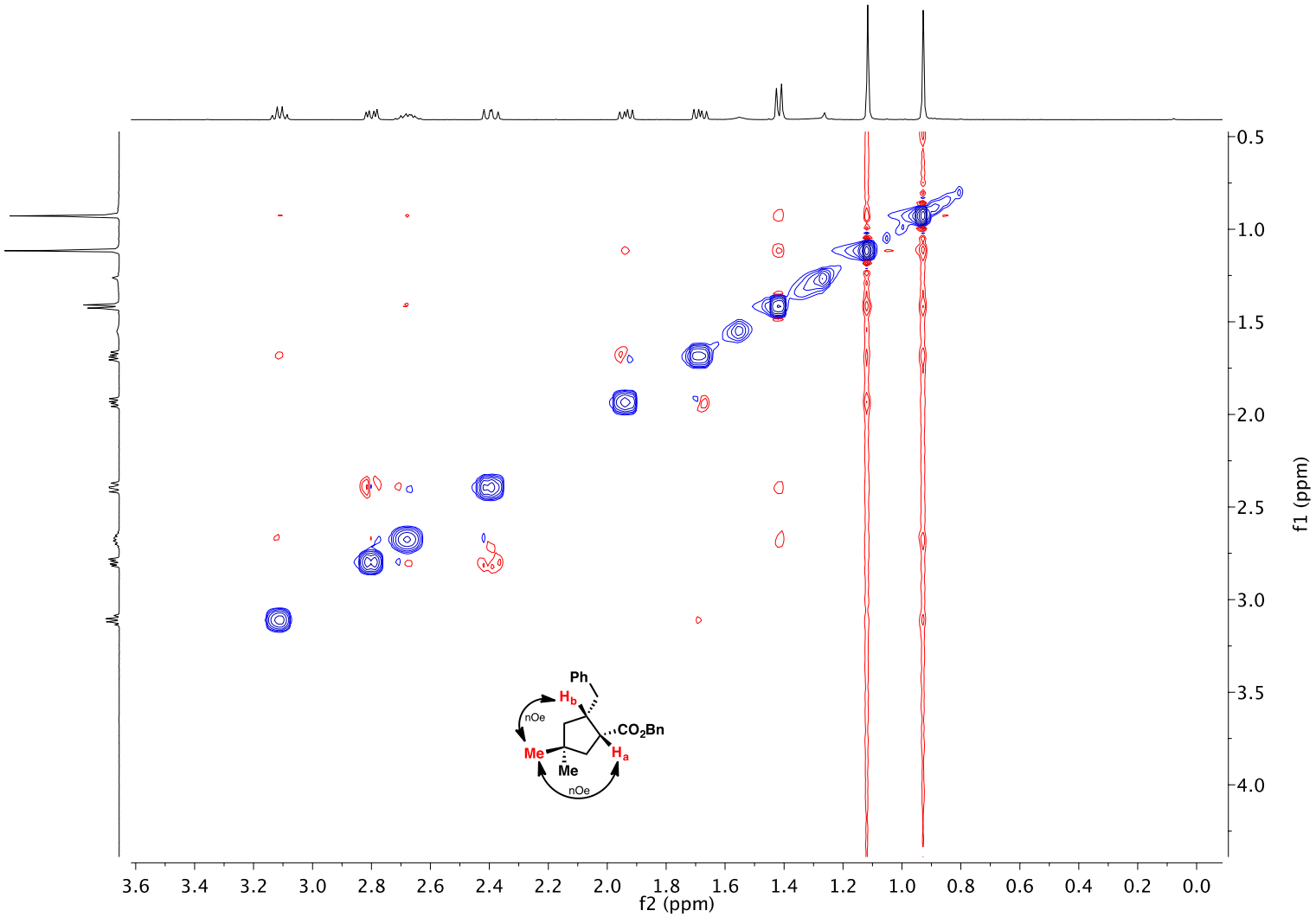

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

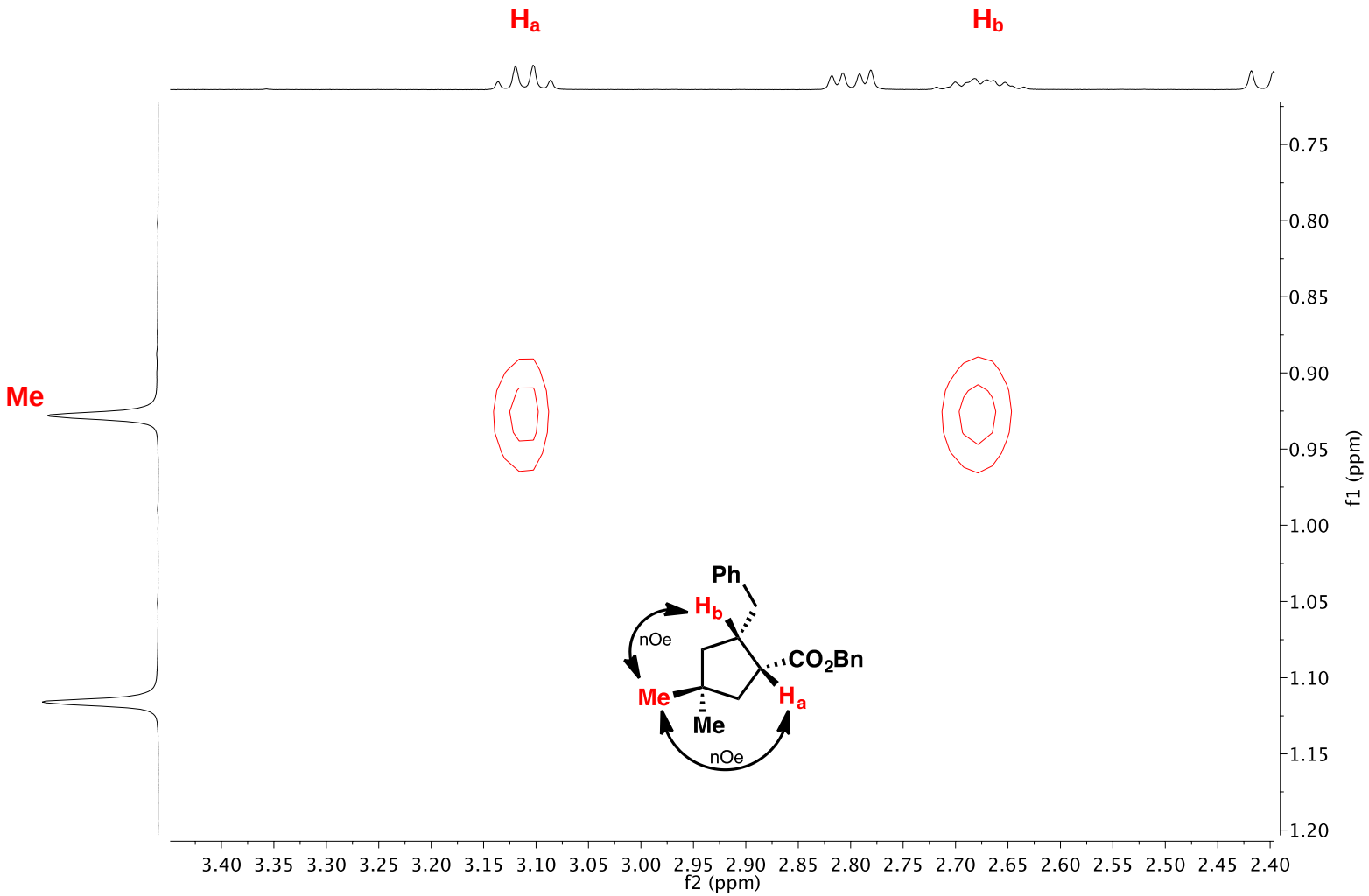

CO2Bn
Me
Me
Ph

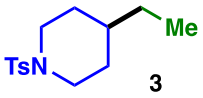
SI-12


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

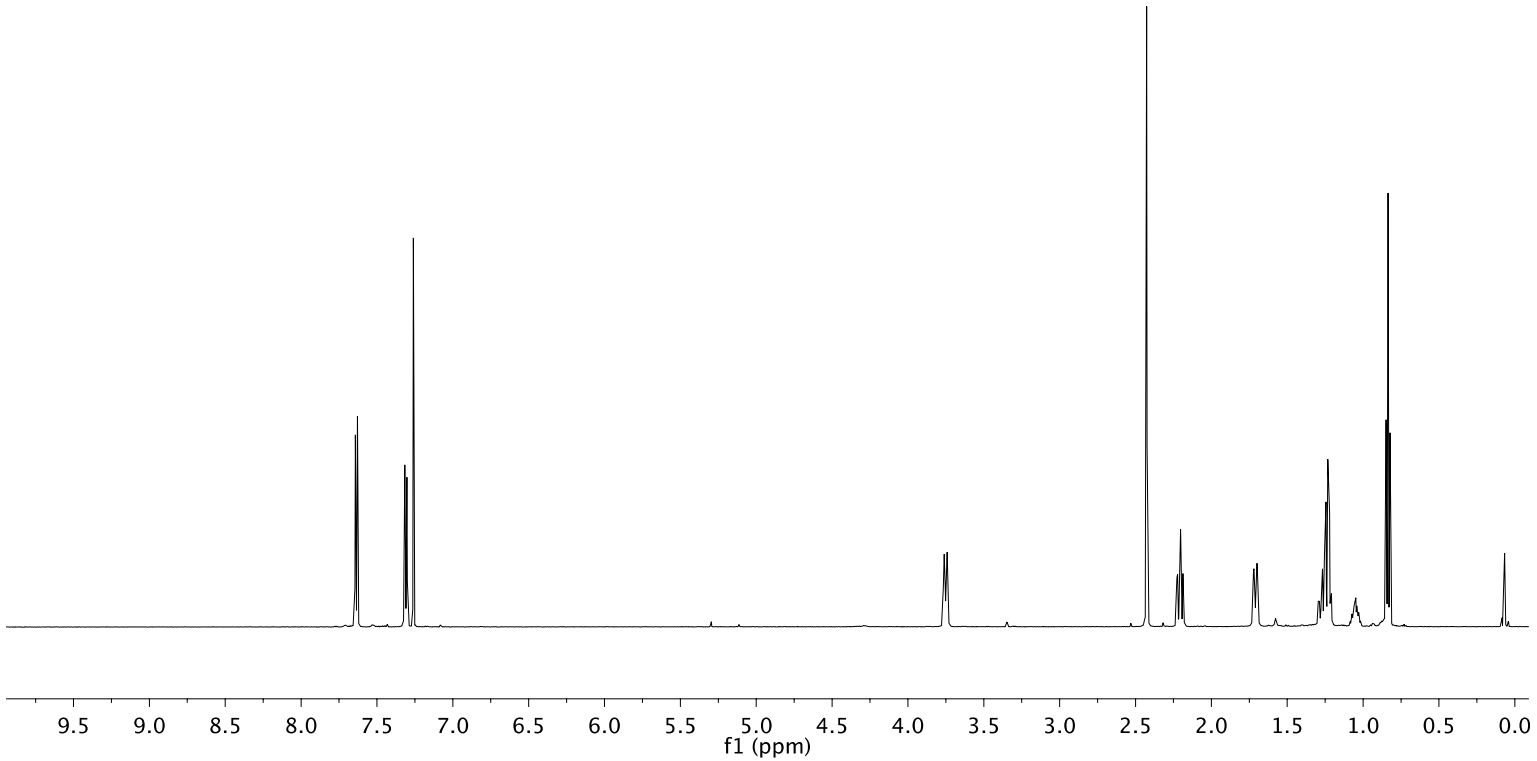

COSY
CO2Bn
Me
Me
Ph
SI-12
f2 (ppm)
f1 (ppm)

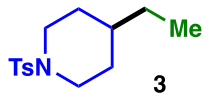

Ph
H_b
nOe
CO_2Bn
Me
H_a
Me
nOe
f2 (ppm)
f1 (ppm)


Ha
Hb
Me
Ph
Hb
nOe
CO2Bn
Me
Ha
Me
nOe
0.75
0.80
0.85
0.90
0.95
1.00
1.05
1.10
1.15
1.20
f1 (ppm)
3.40 3.35 3.30 3.25 3.20 3.15 3.10 3.05 3.00 2.95 2.90 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.45 2.40
f2 (ppm)

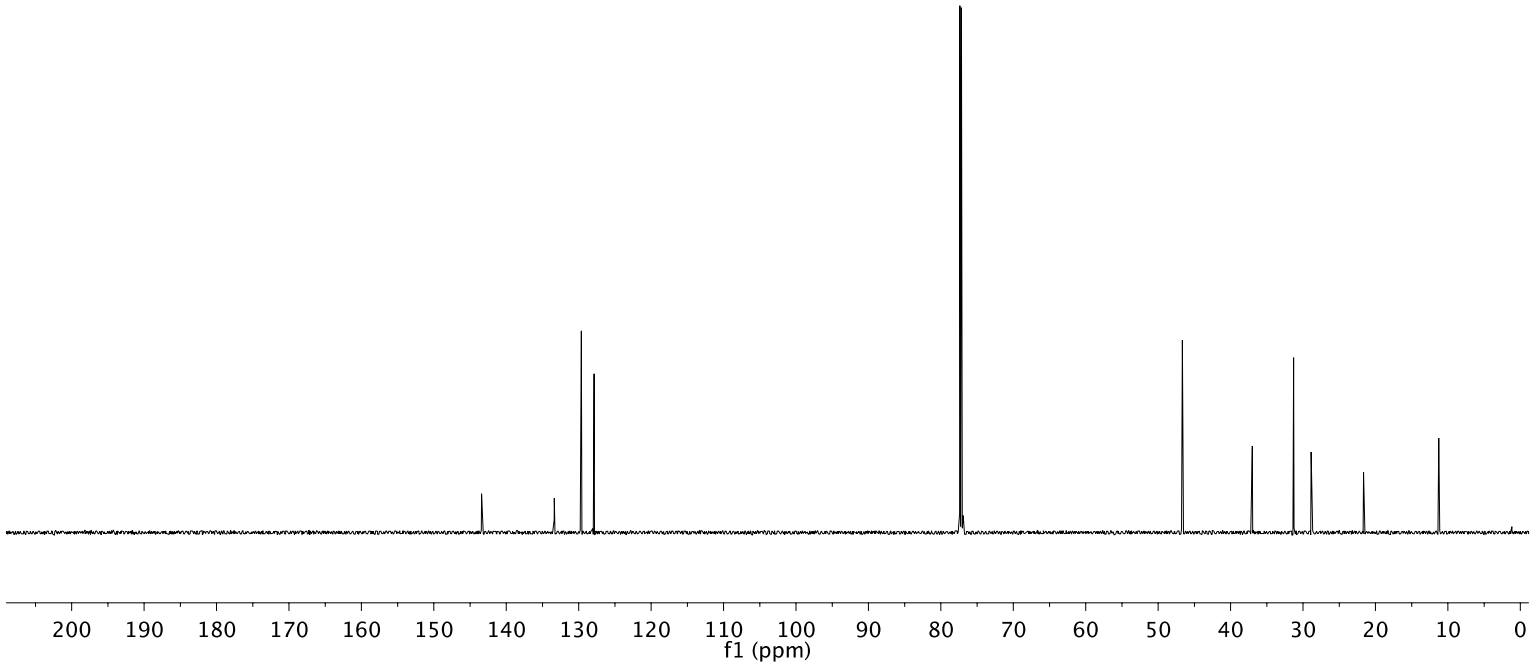

Me
TsN

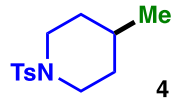
3


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

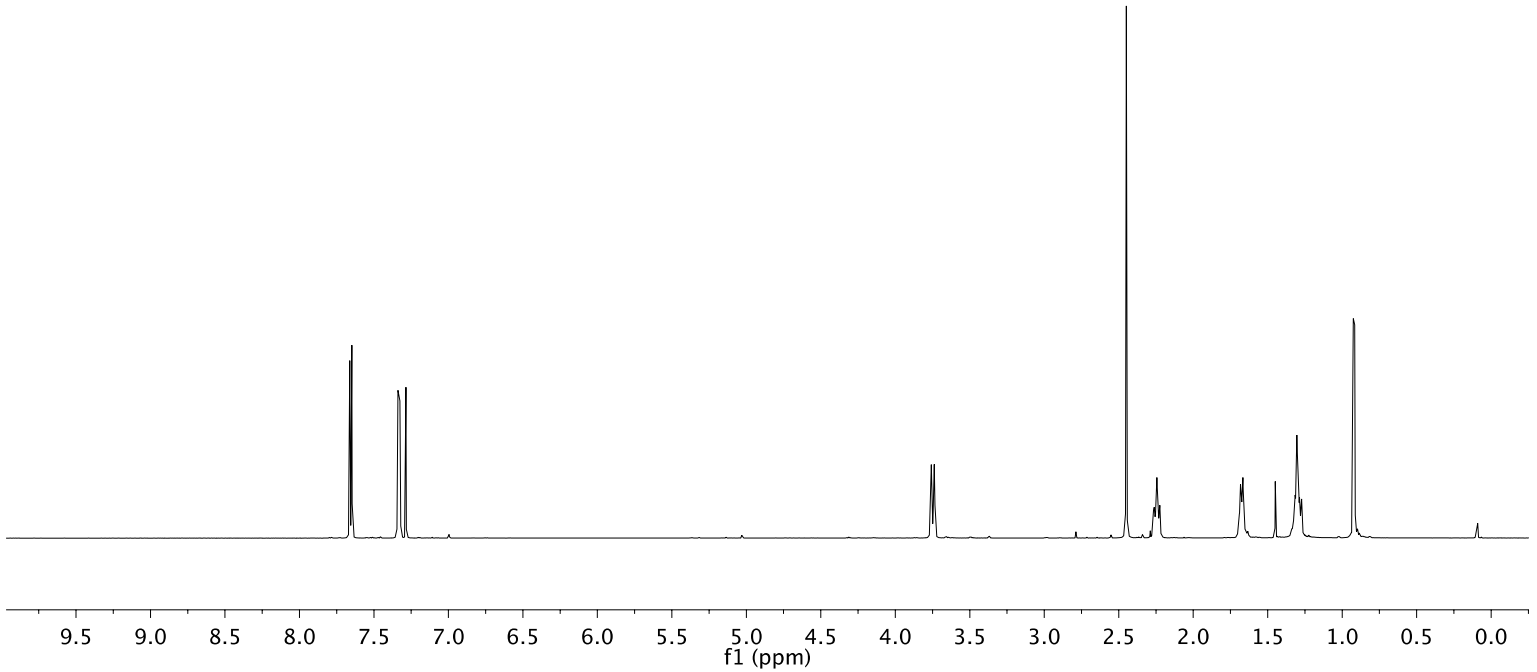

Me
TsN

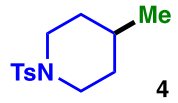
3


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

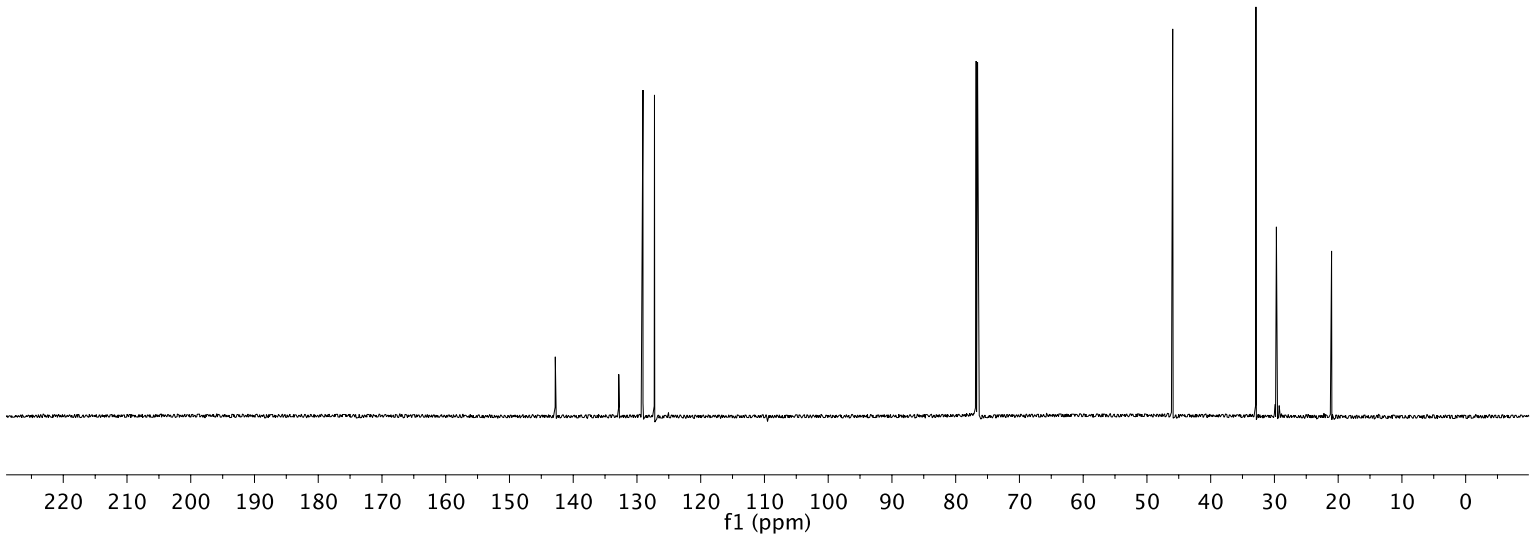

Me
TsN

4


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
TsN

4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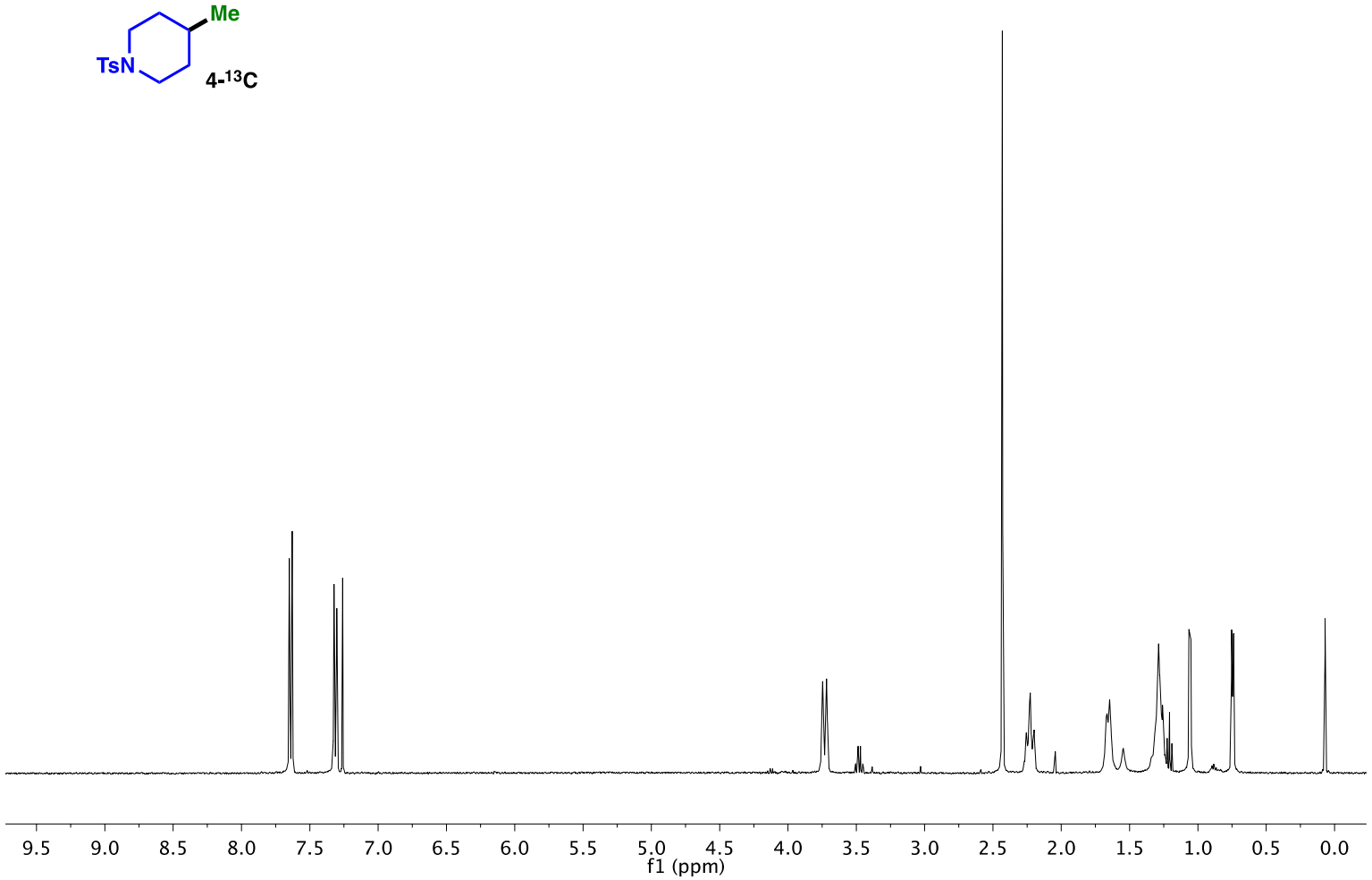
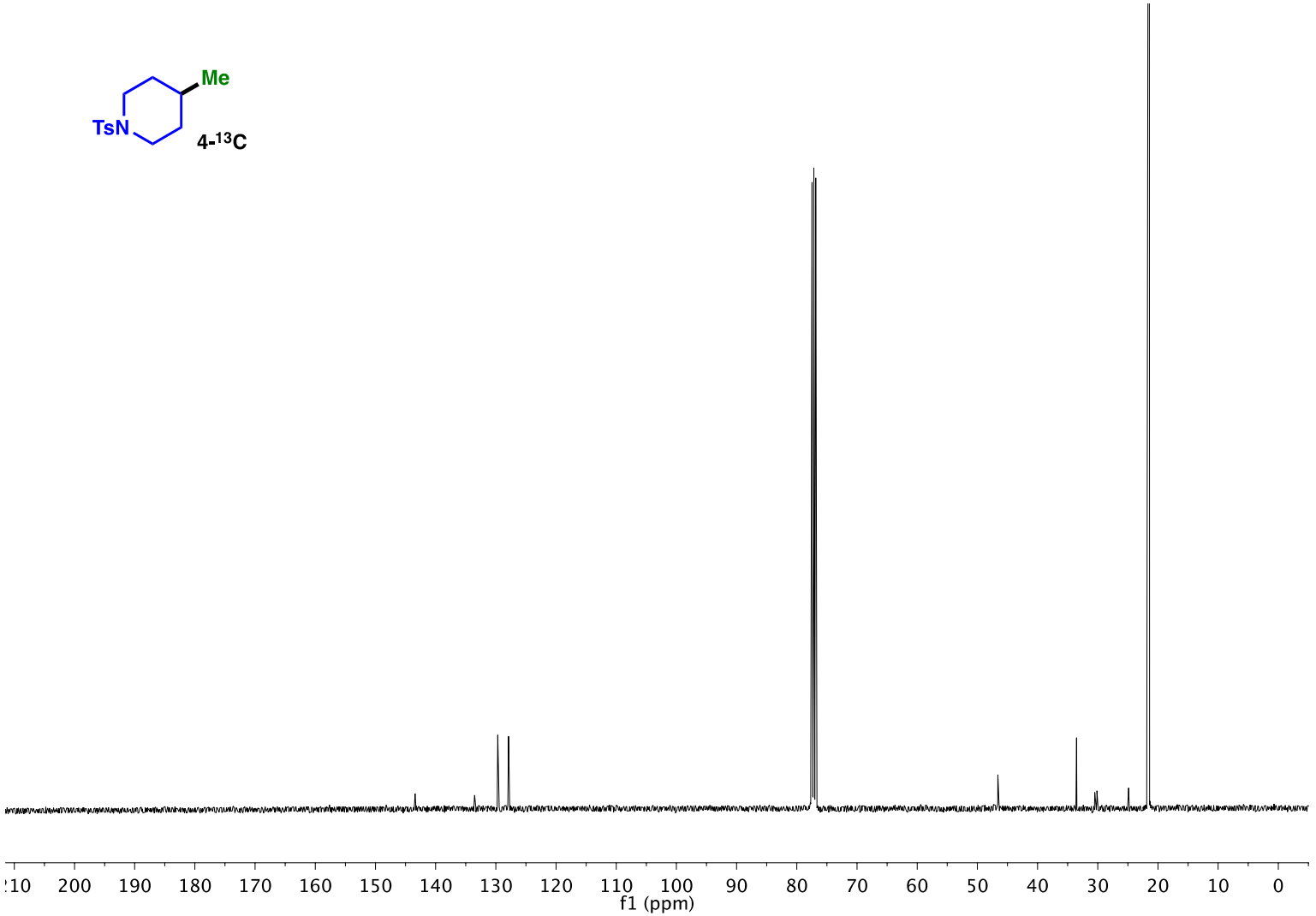
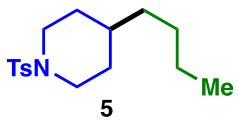
f1 (ppm)


Me
TsN
4-13C
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
TsN
4-13C
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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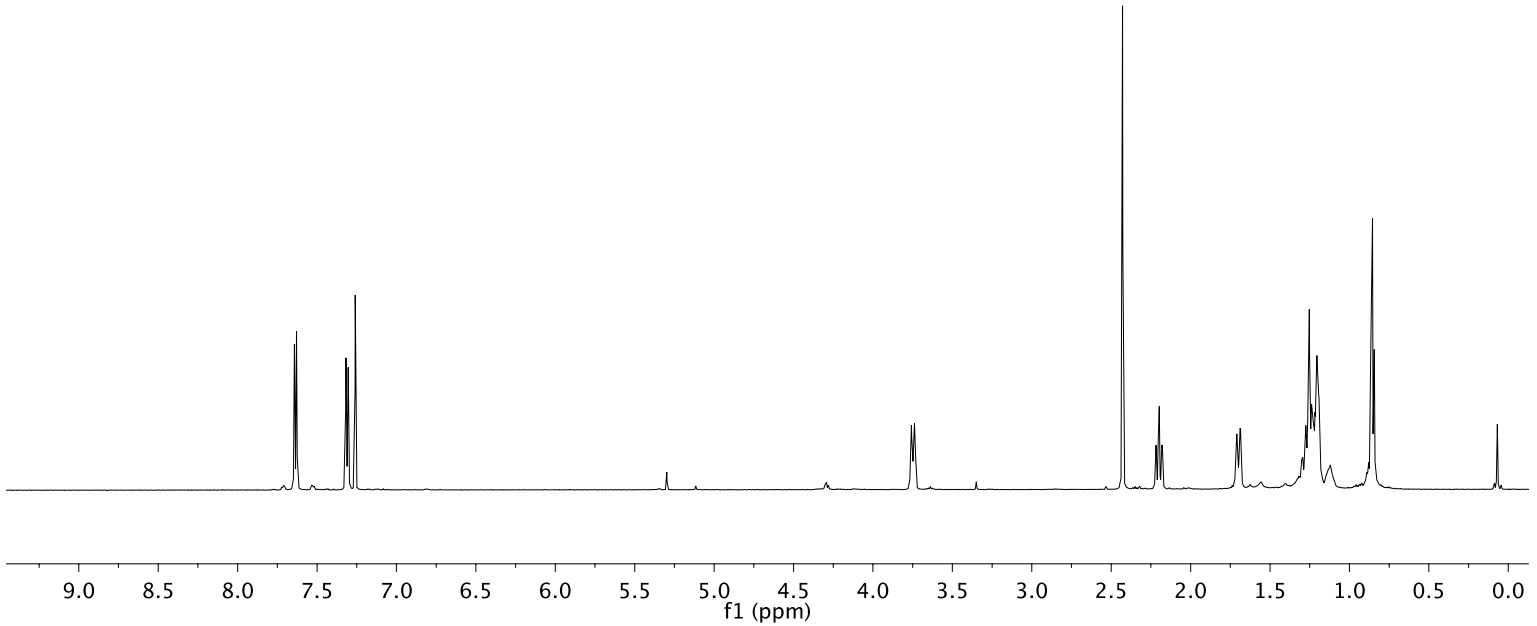
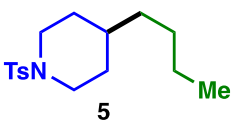
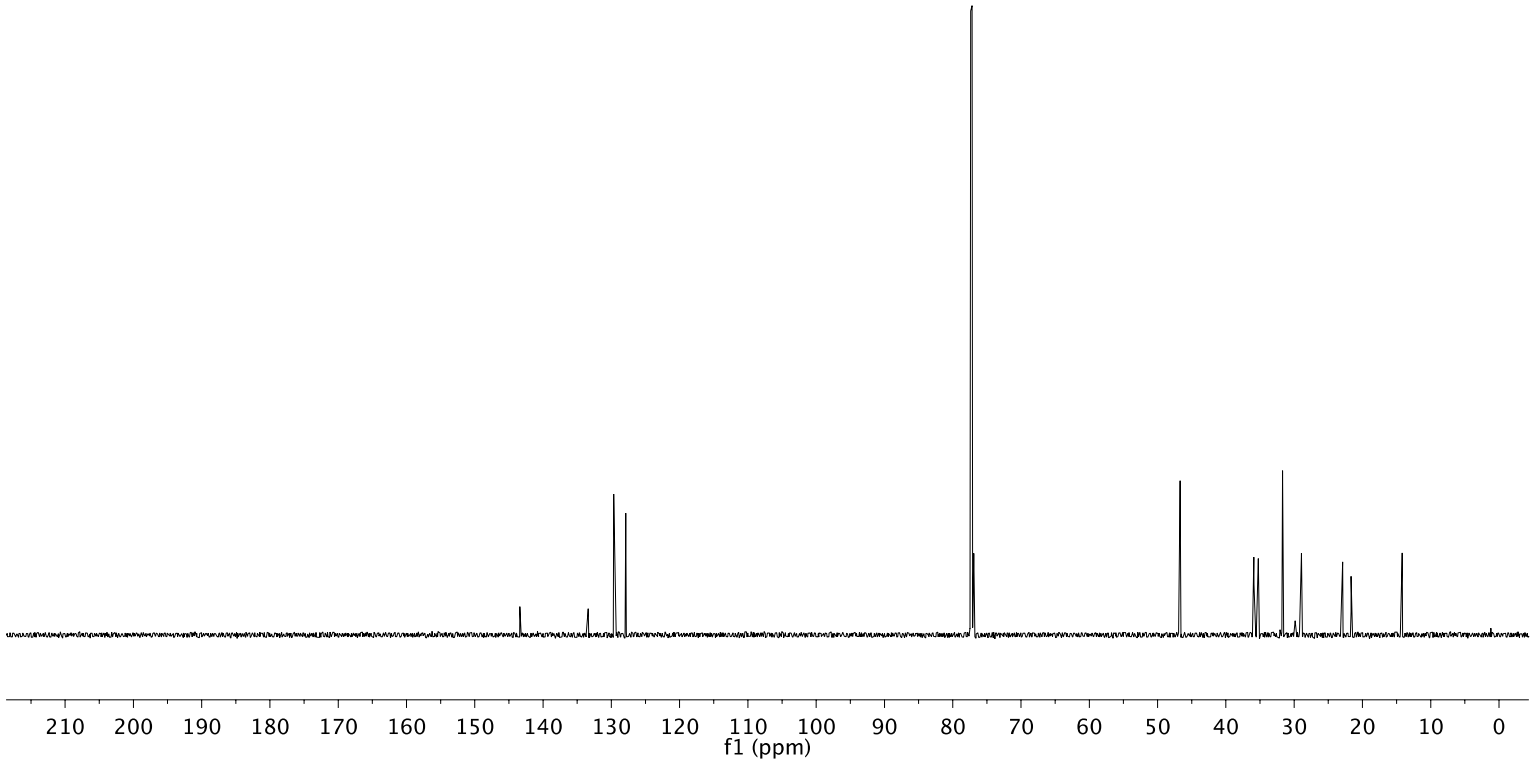



TsN
Me

5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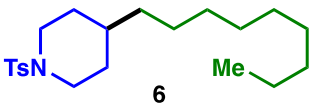
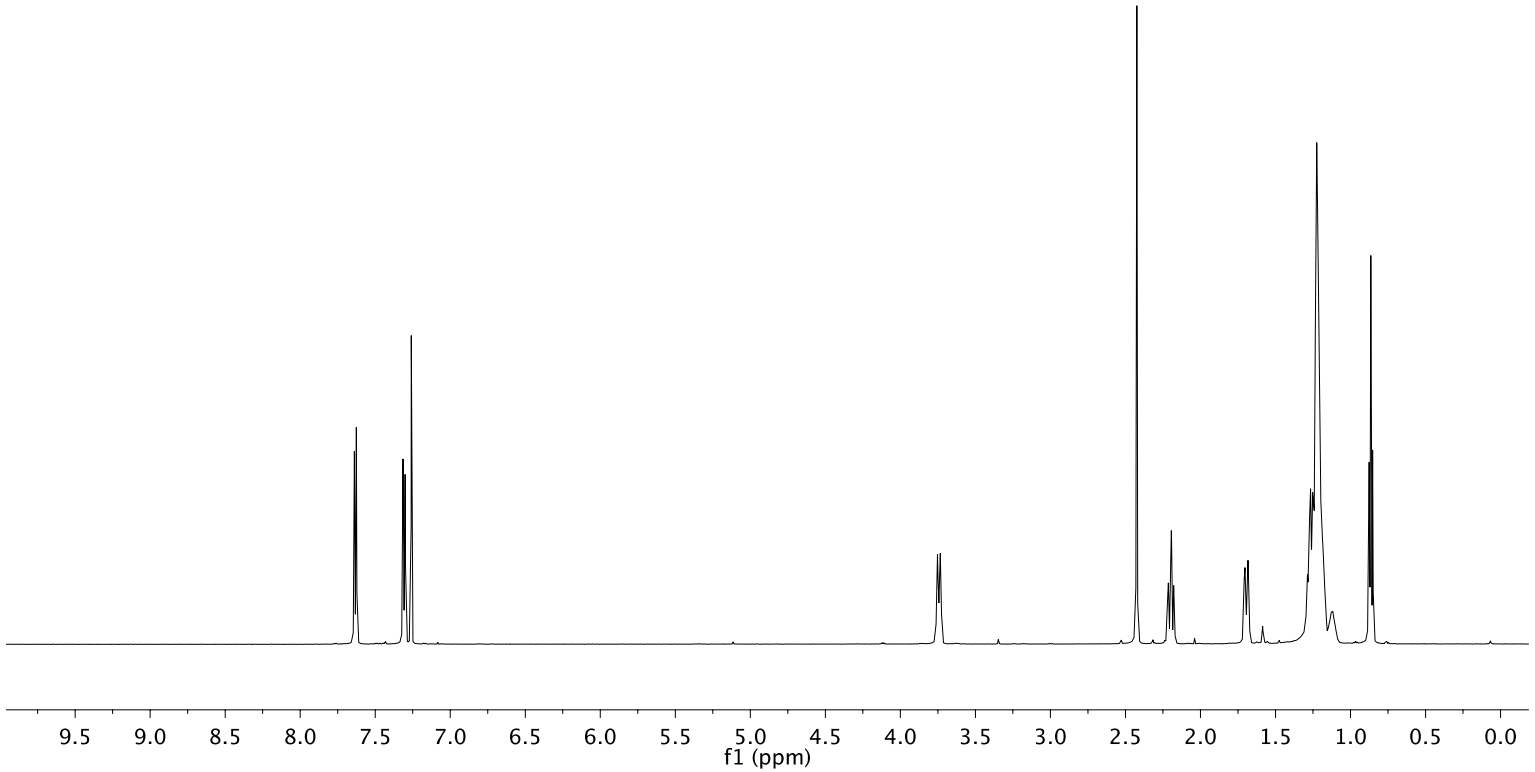
f1 (ppm)


TsN
Me

6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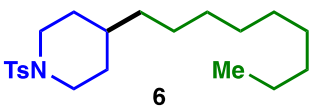
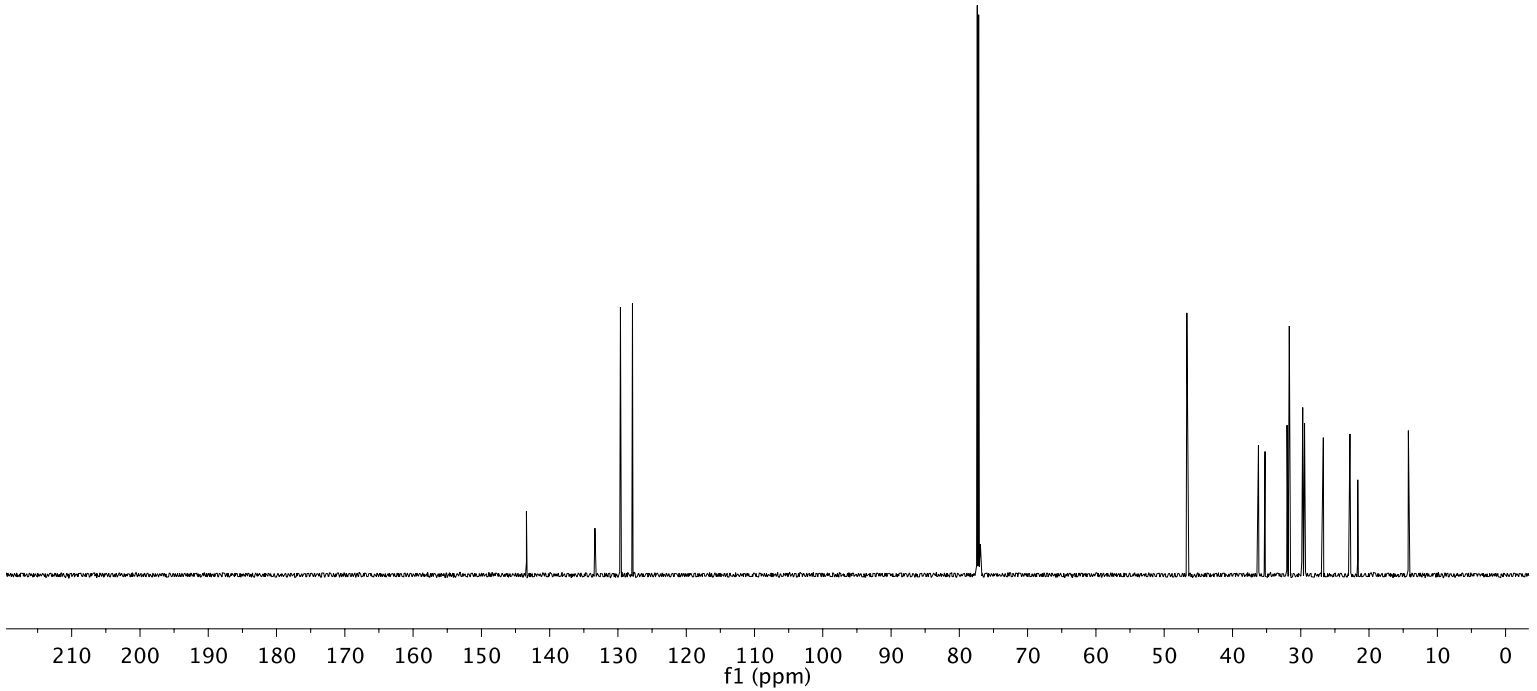
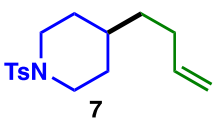
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


TsN
Me

6


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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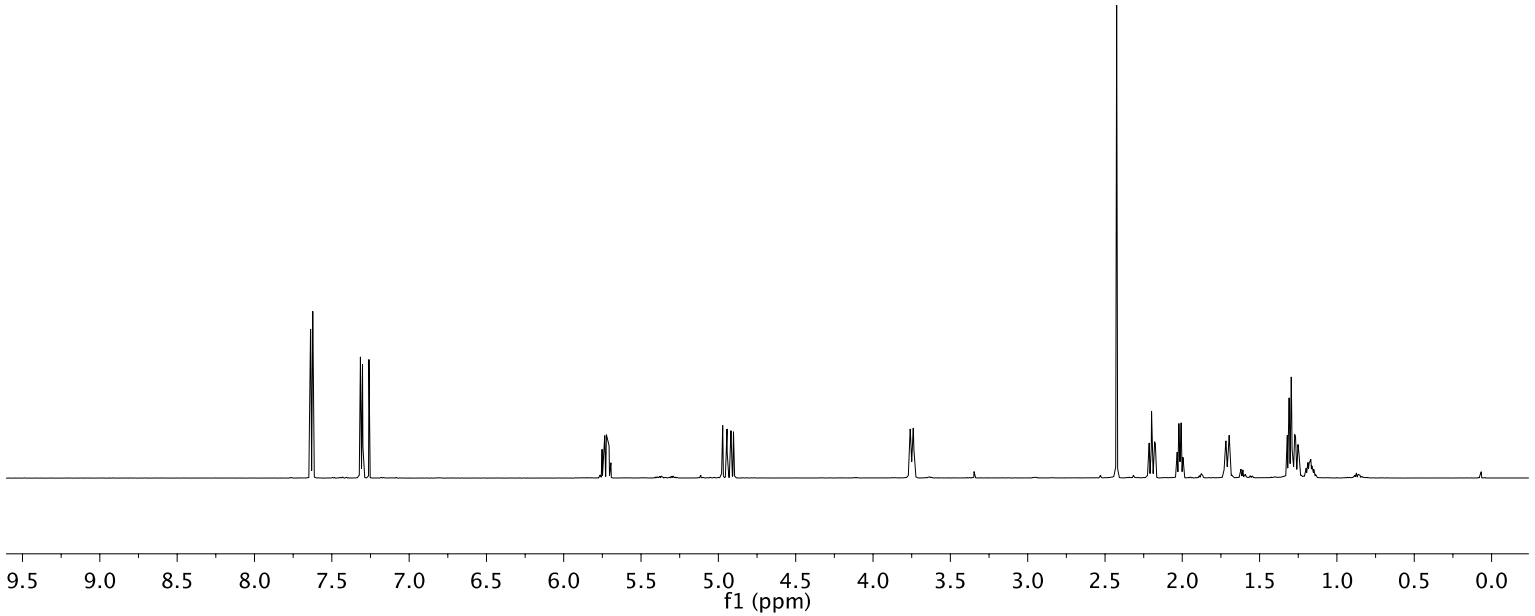
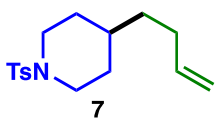
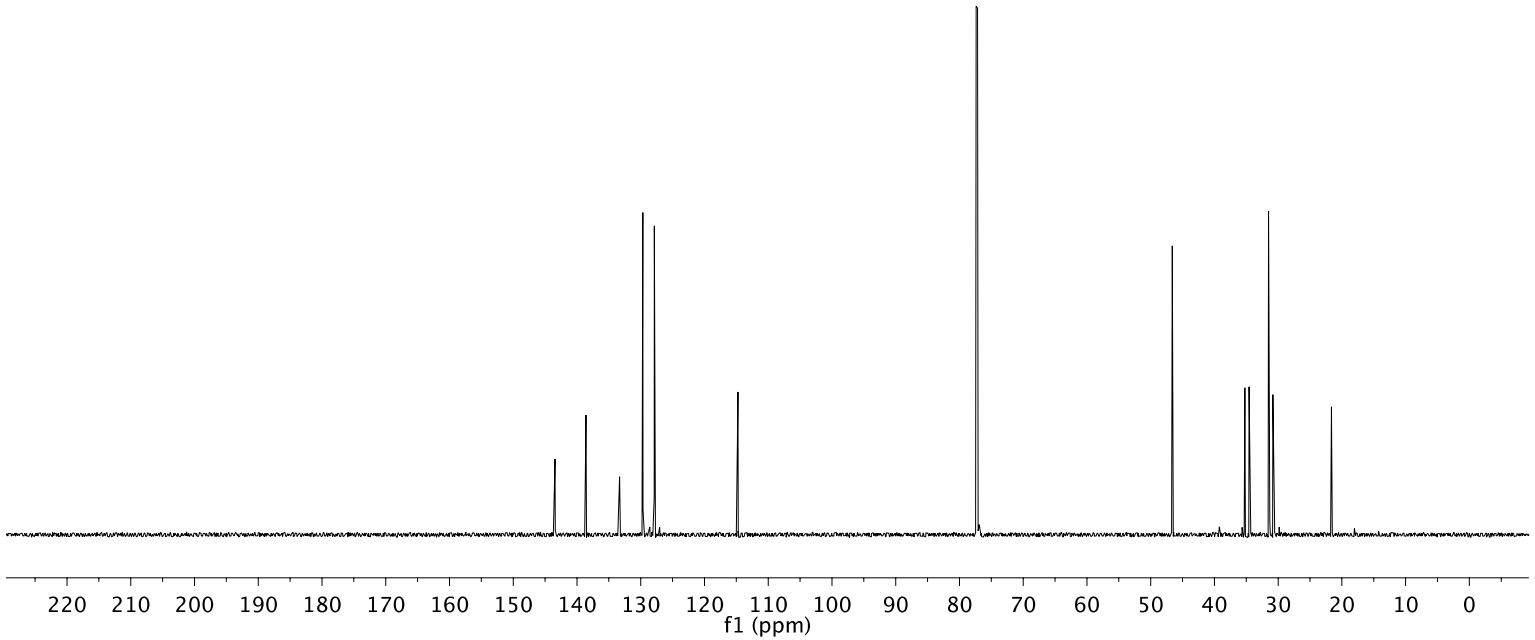



TsN

7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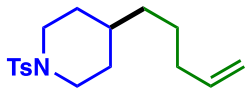
f1 (ppm)



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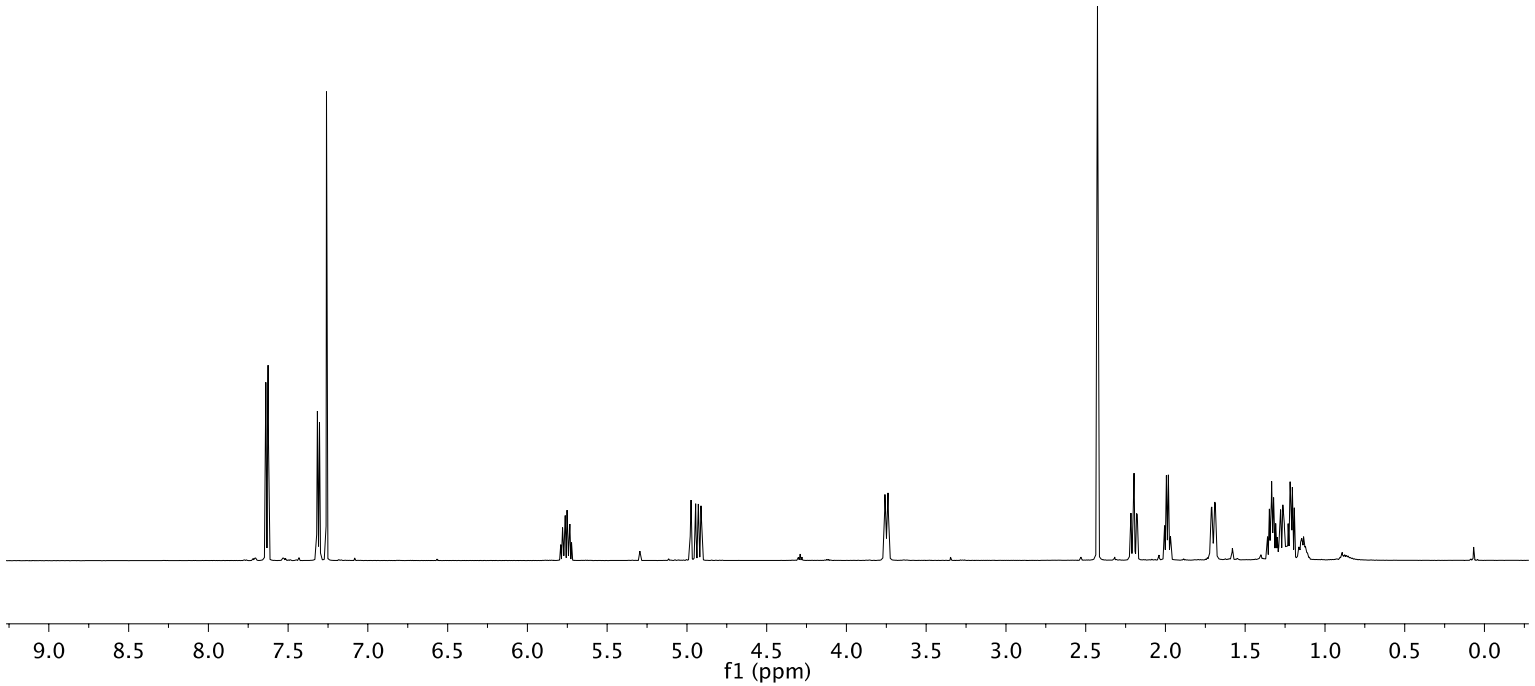
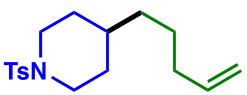
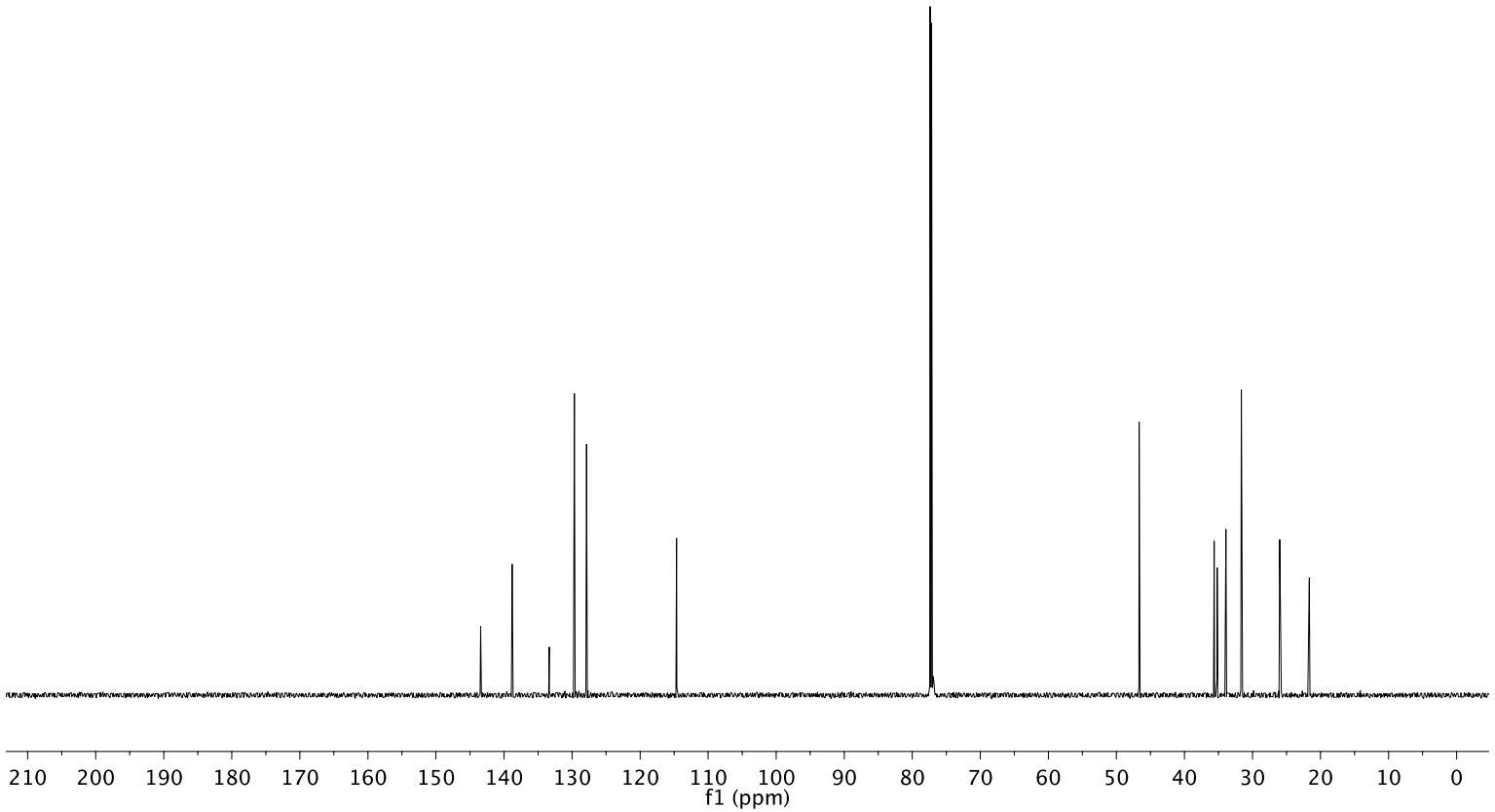
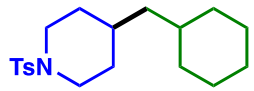



TsN

8


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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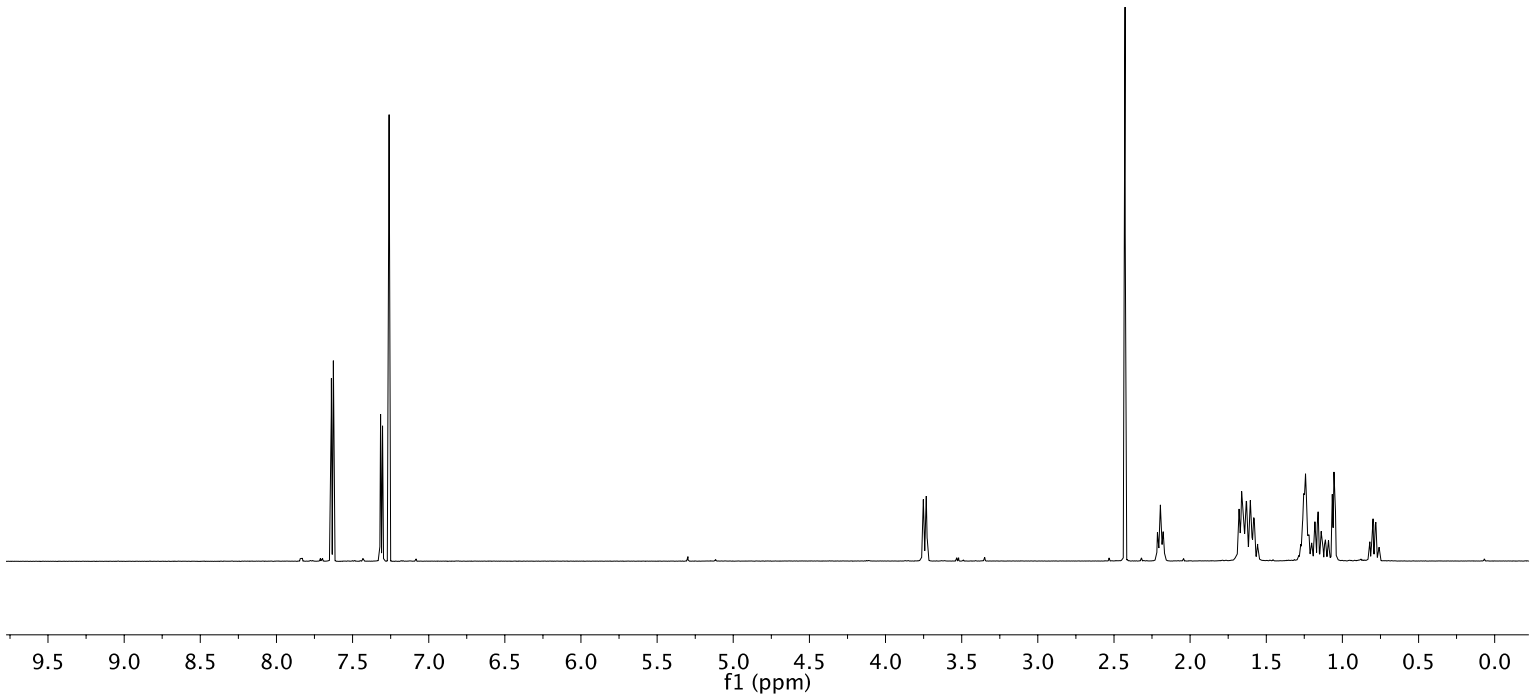
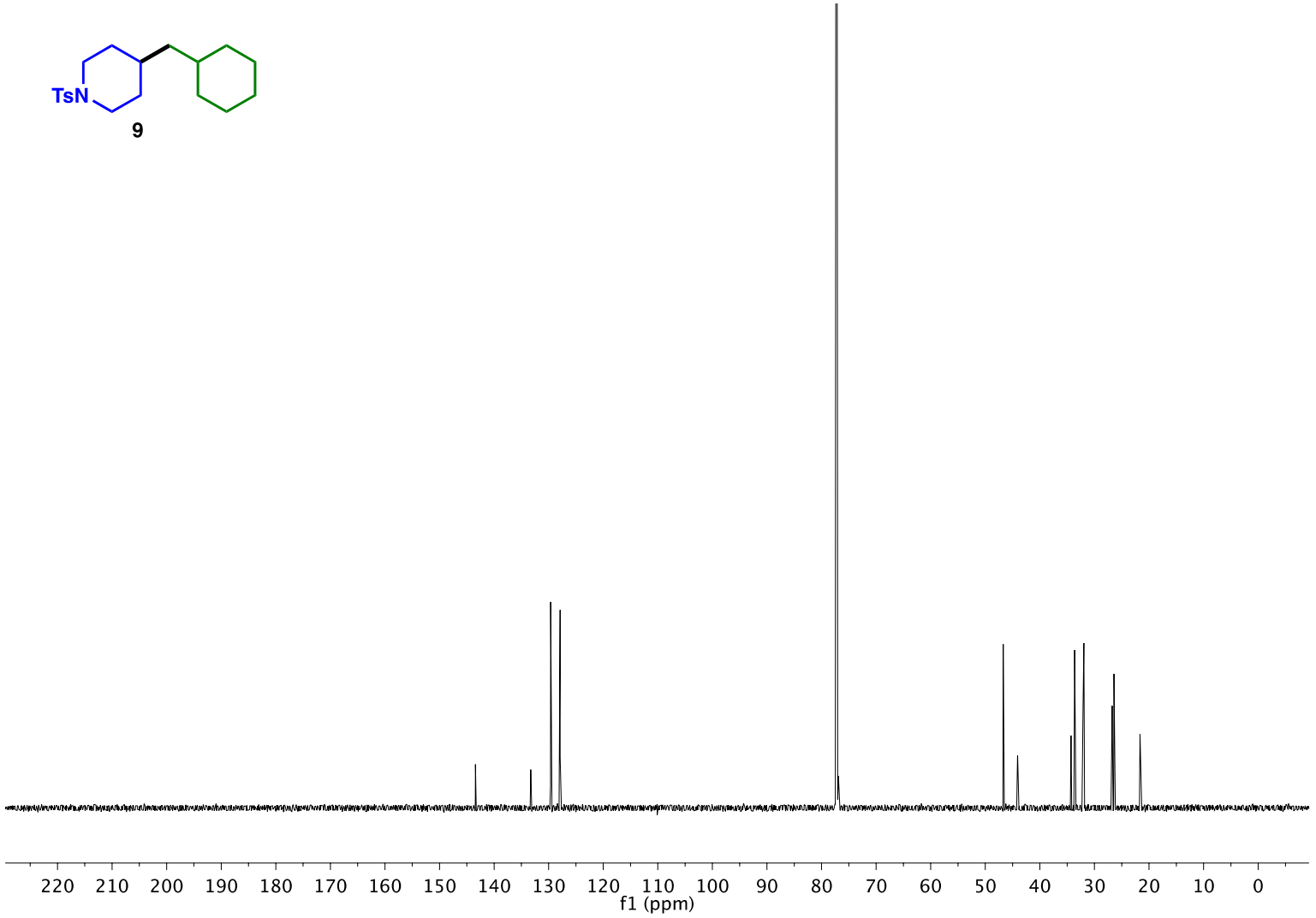
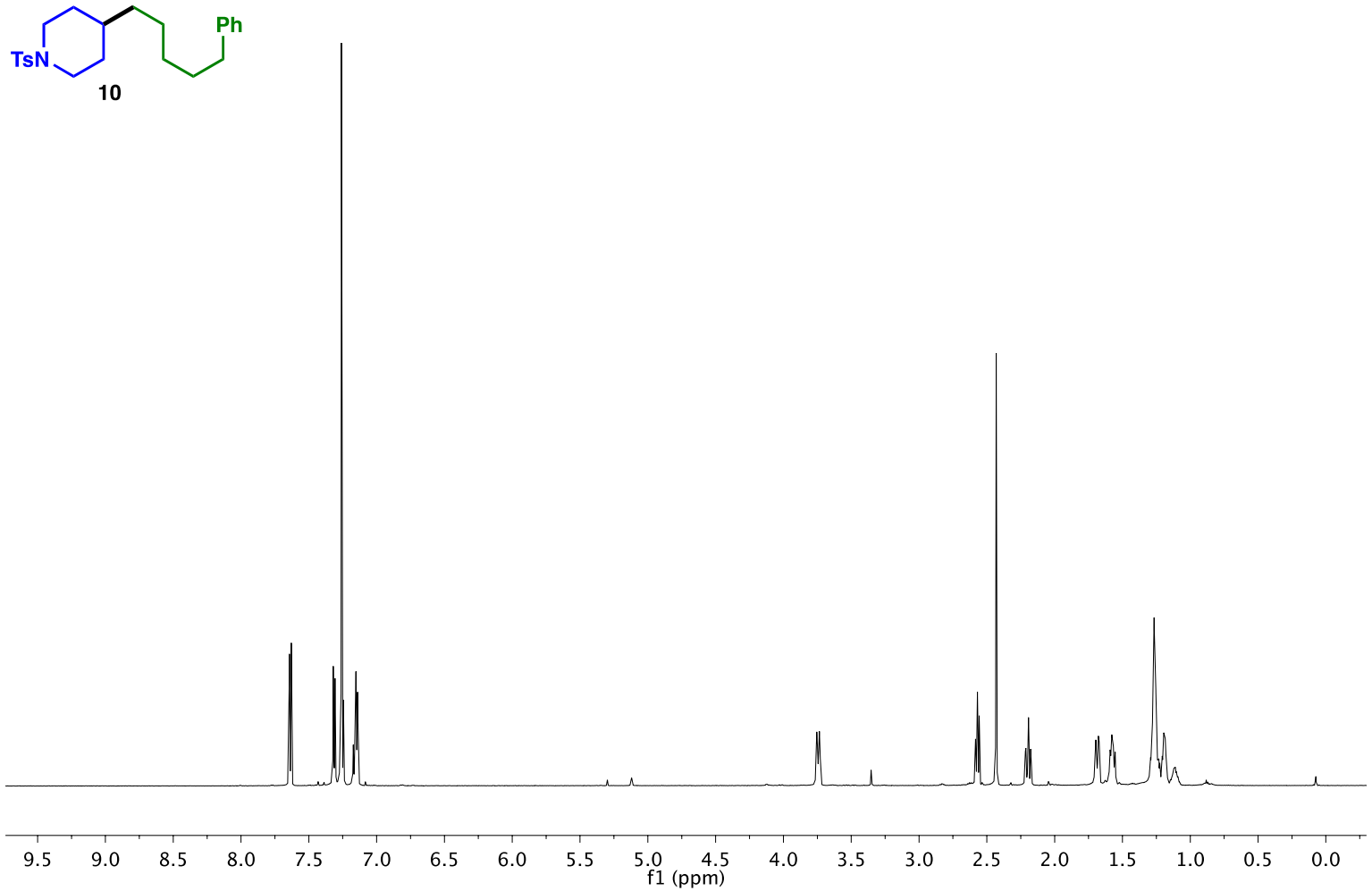
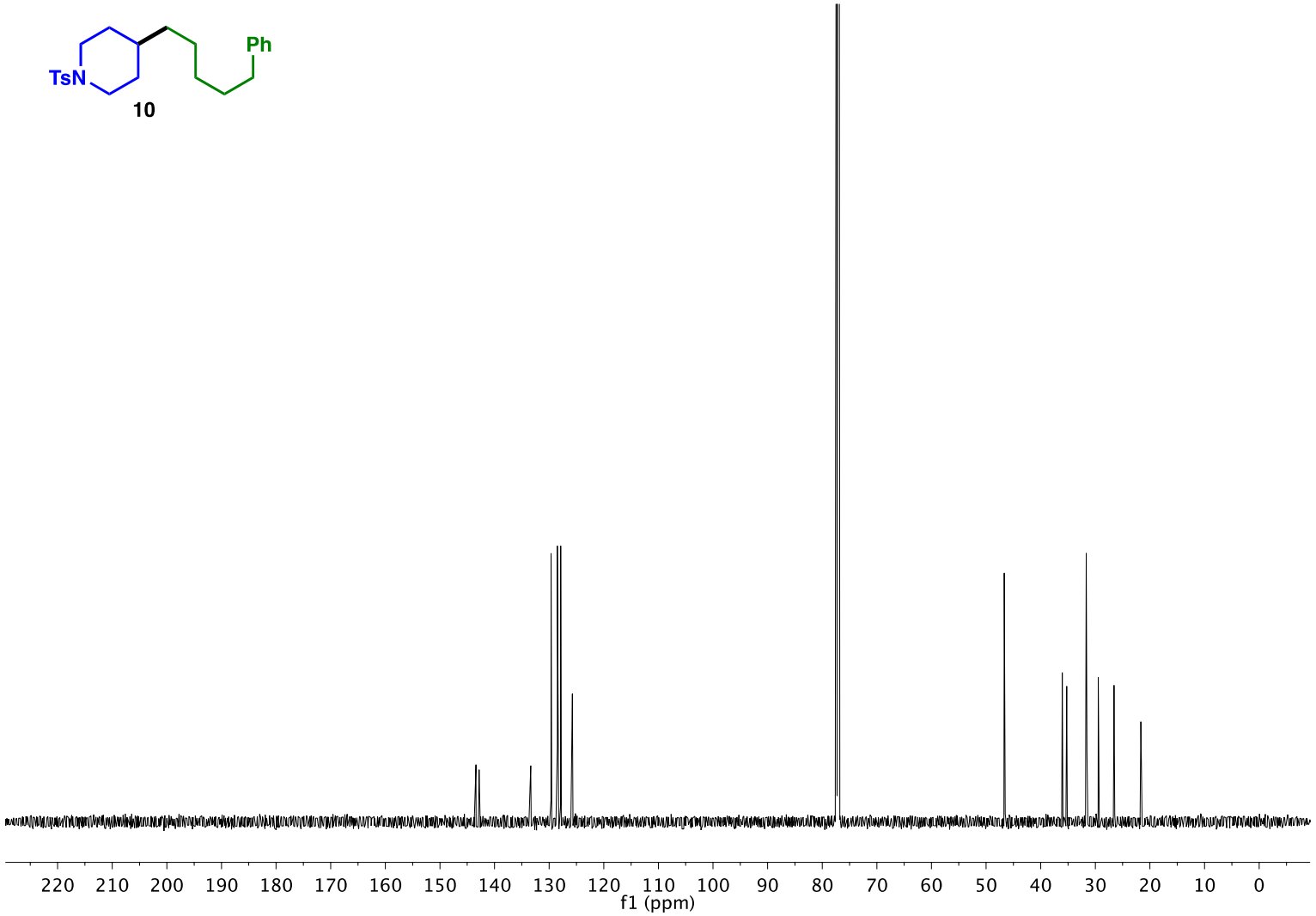



TsN
9
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


TsN
Ph
10
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Ph
TsN
10
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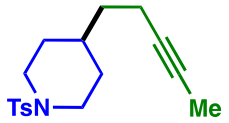
f1 (ppm)



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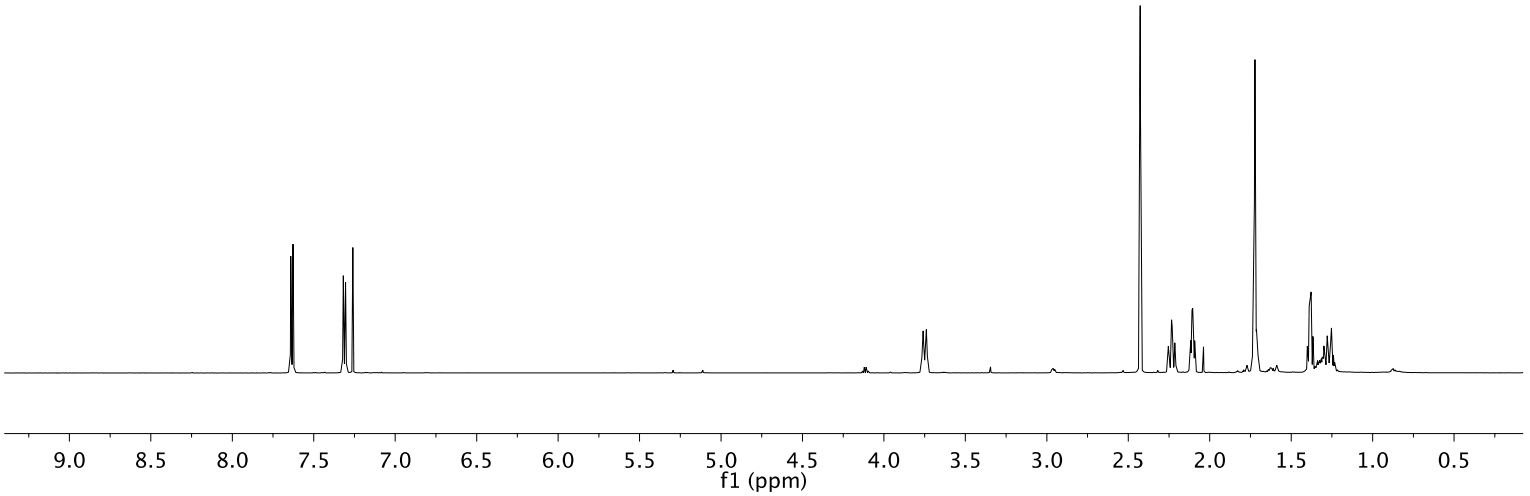
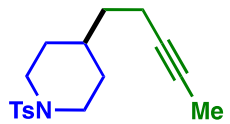
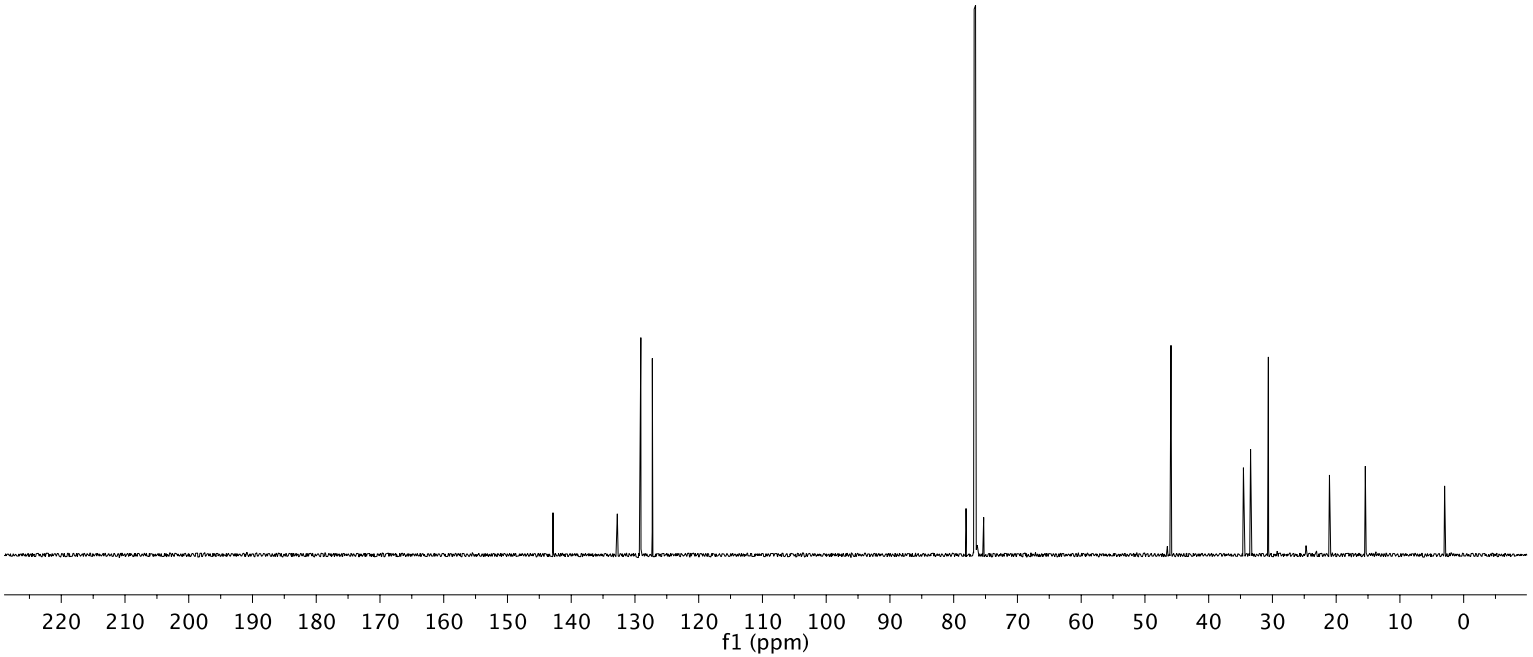
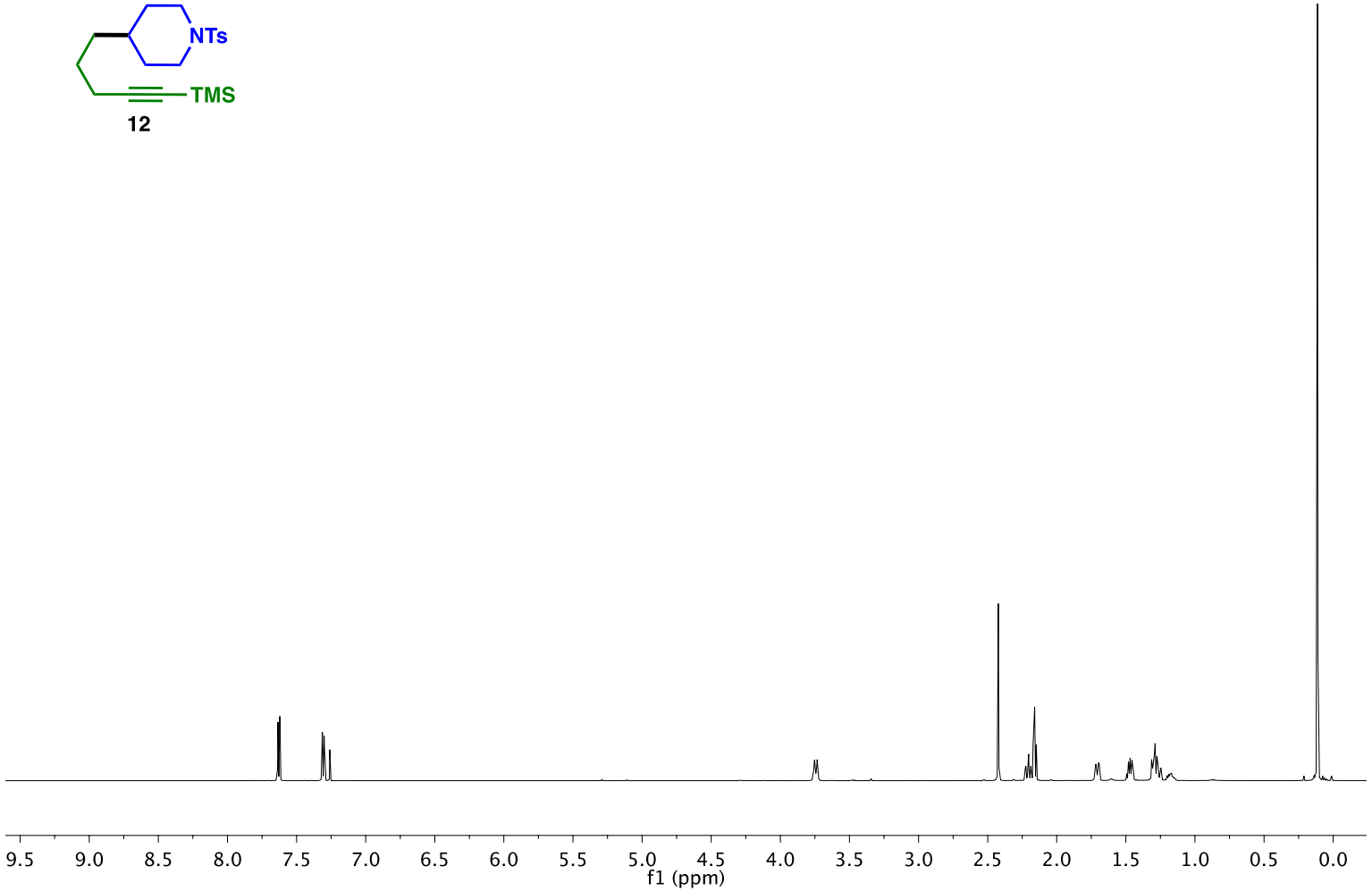
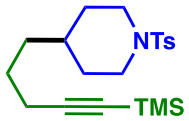



TsN
Me

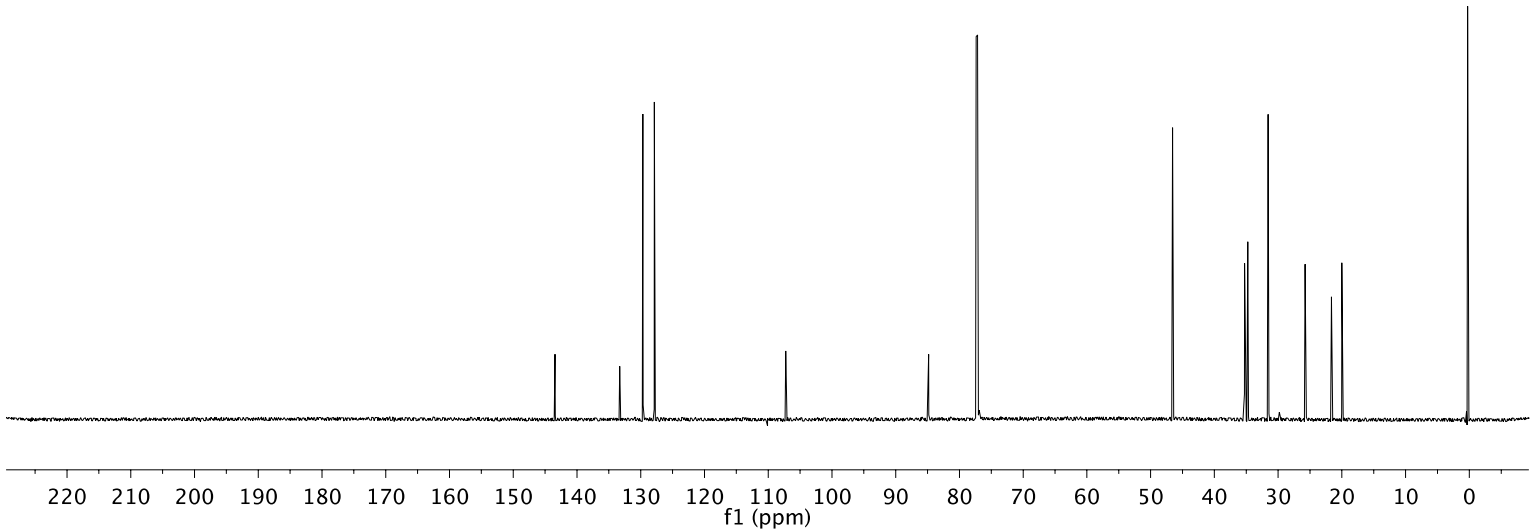
11

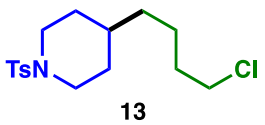

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


NTs
TMS
12
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

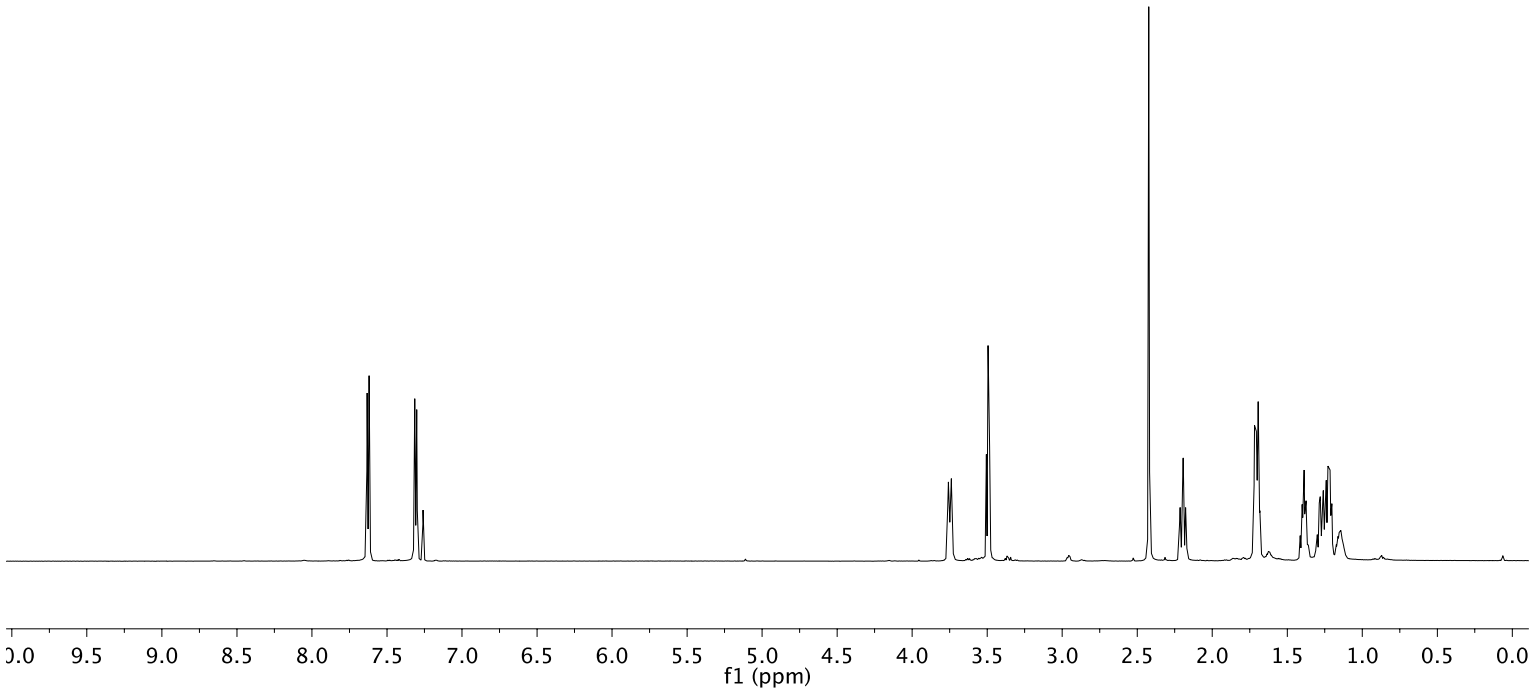

NTs
TMS

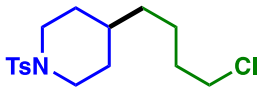
12


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

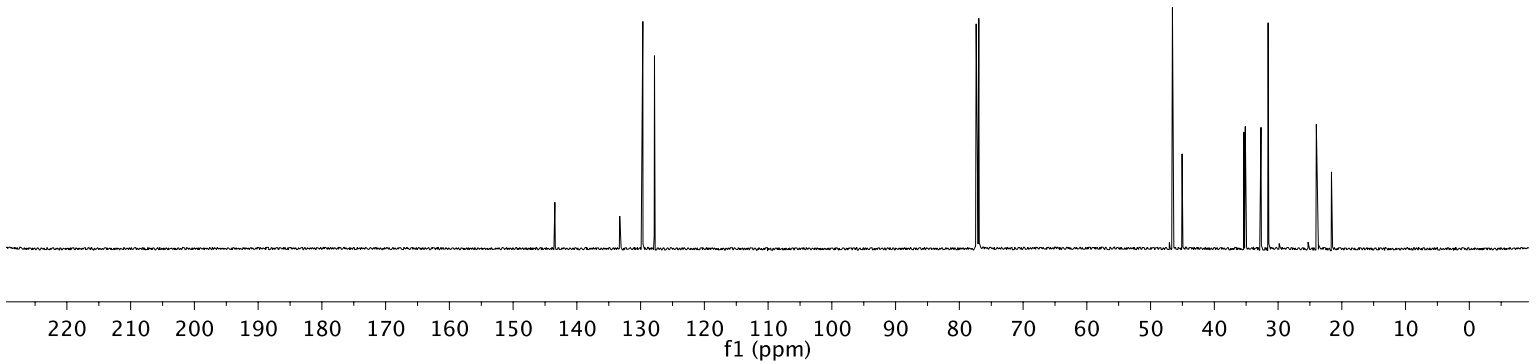

TsN
Cl

13


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


TsN
Cl

13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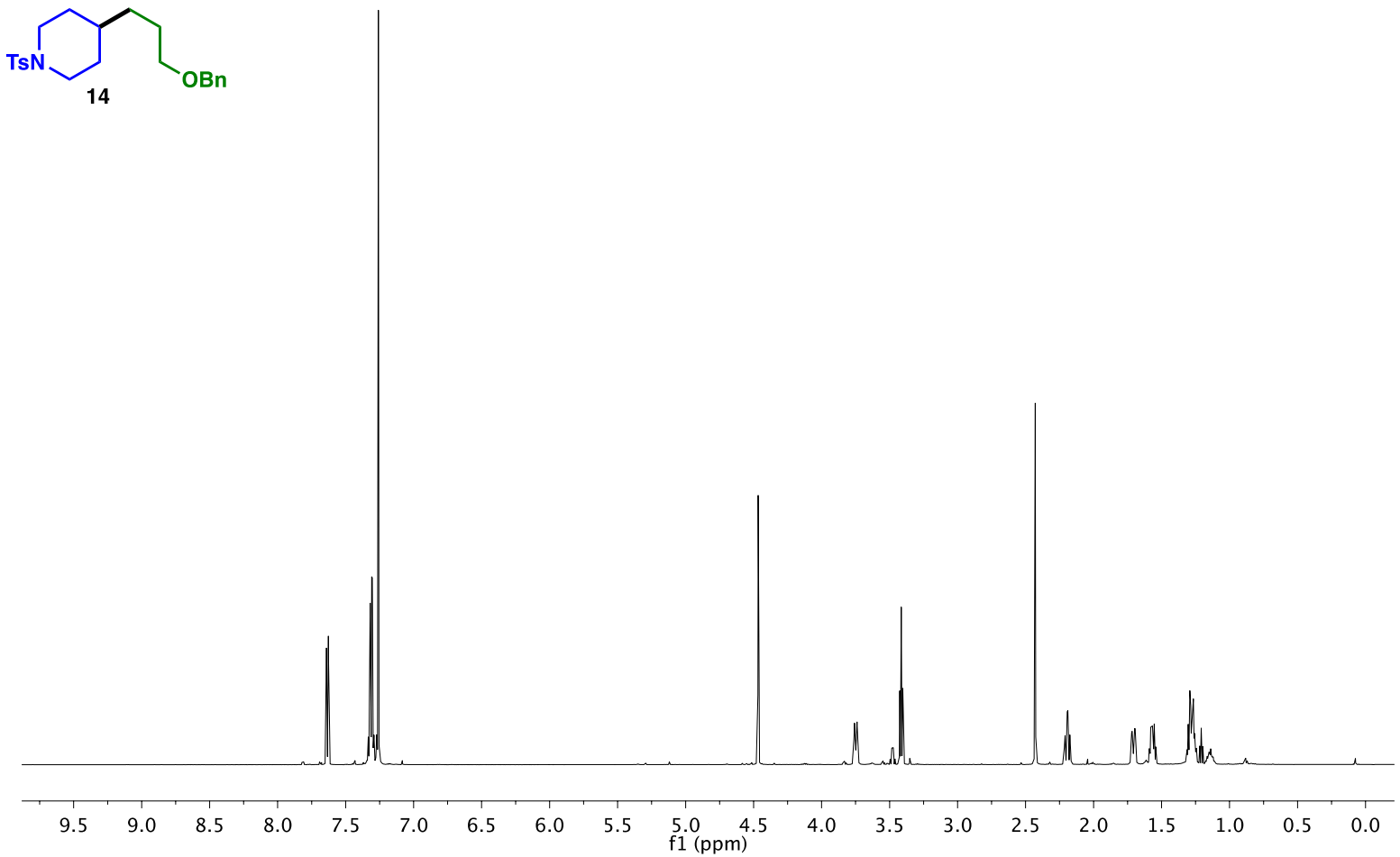
f1 (ppm)


TsN
OBn
14
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8.0
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6.5
6.0
5.5
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3.5
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2.5
2.0
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1.0
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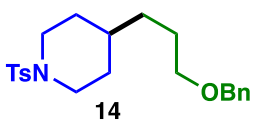
0.0
f1 (ppm)


TsN
OBn

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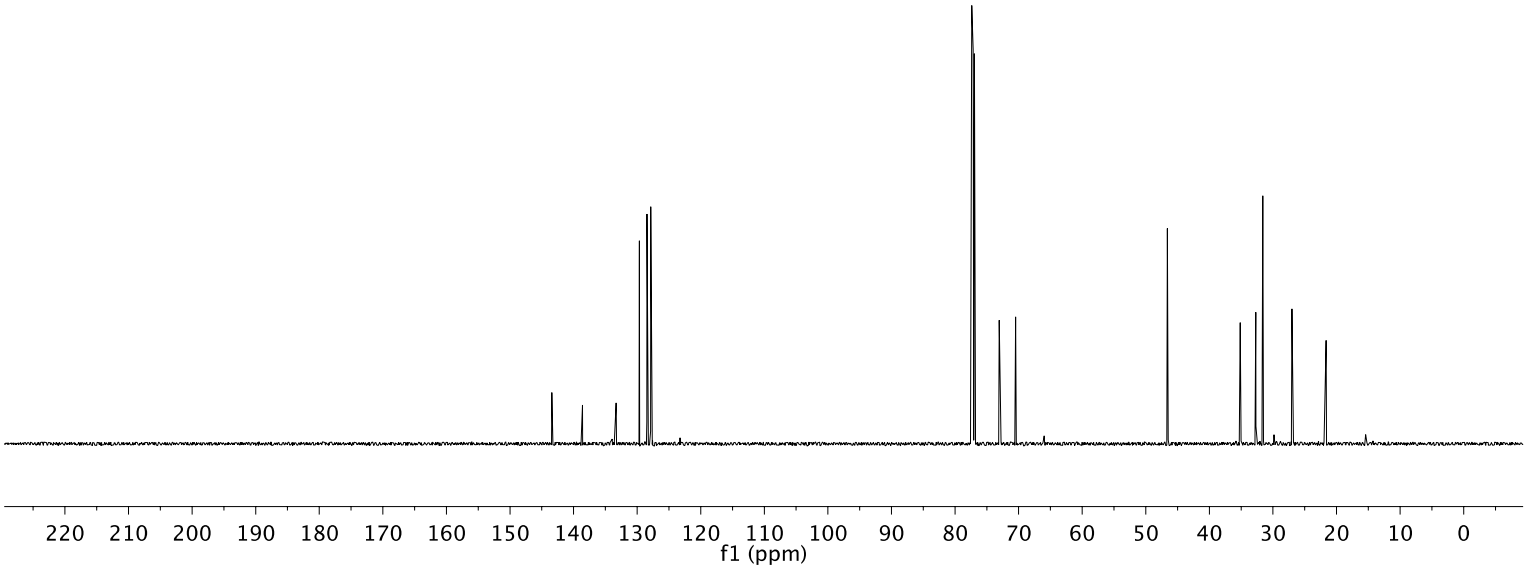
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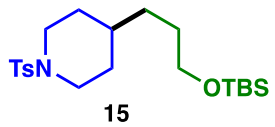
TsN
OTBS

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2.0
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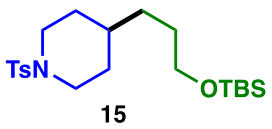
0.0
f1 (ppm)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OTBS

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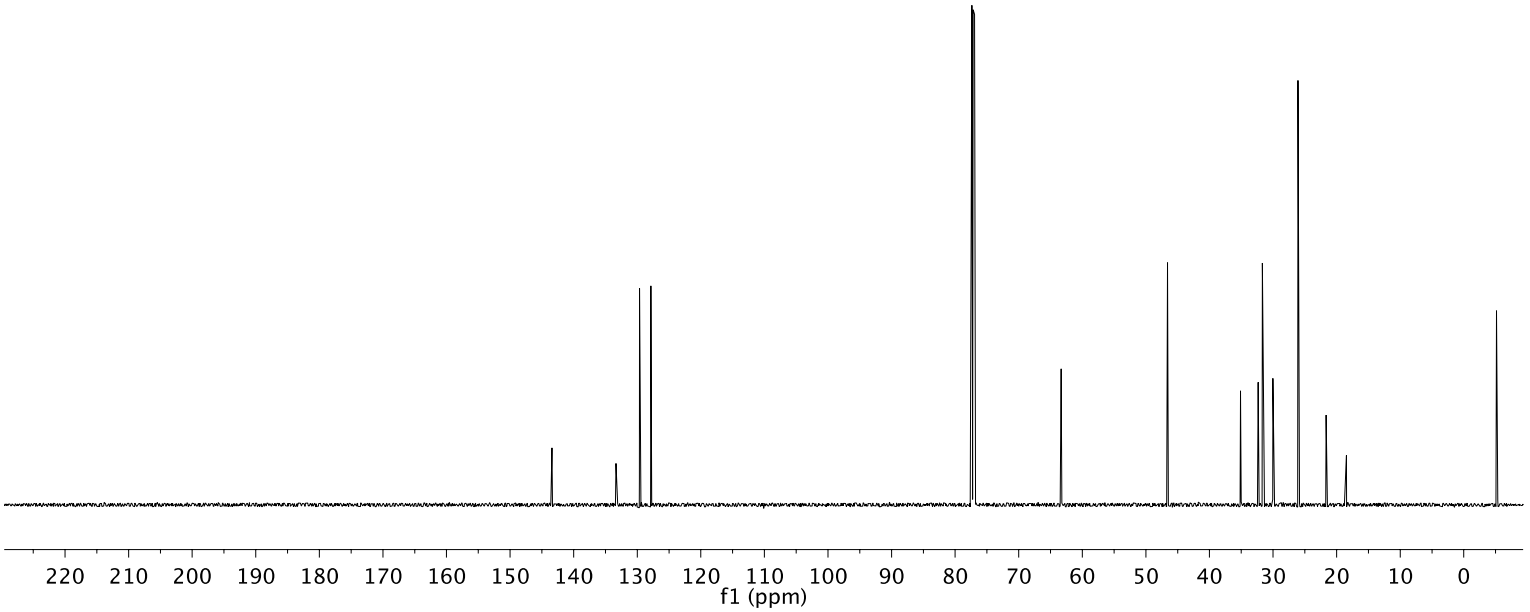
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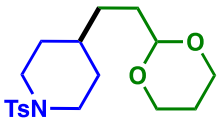
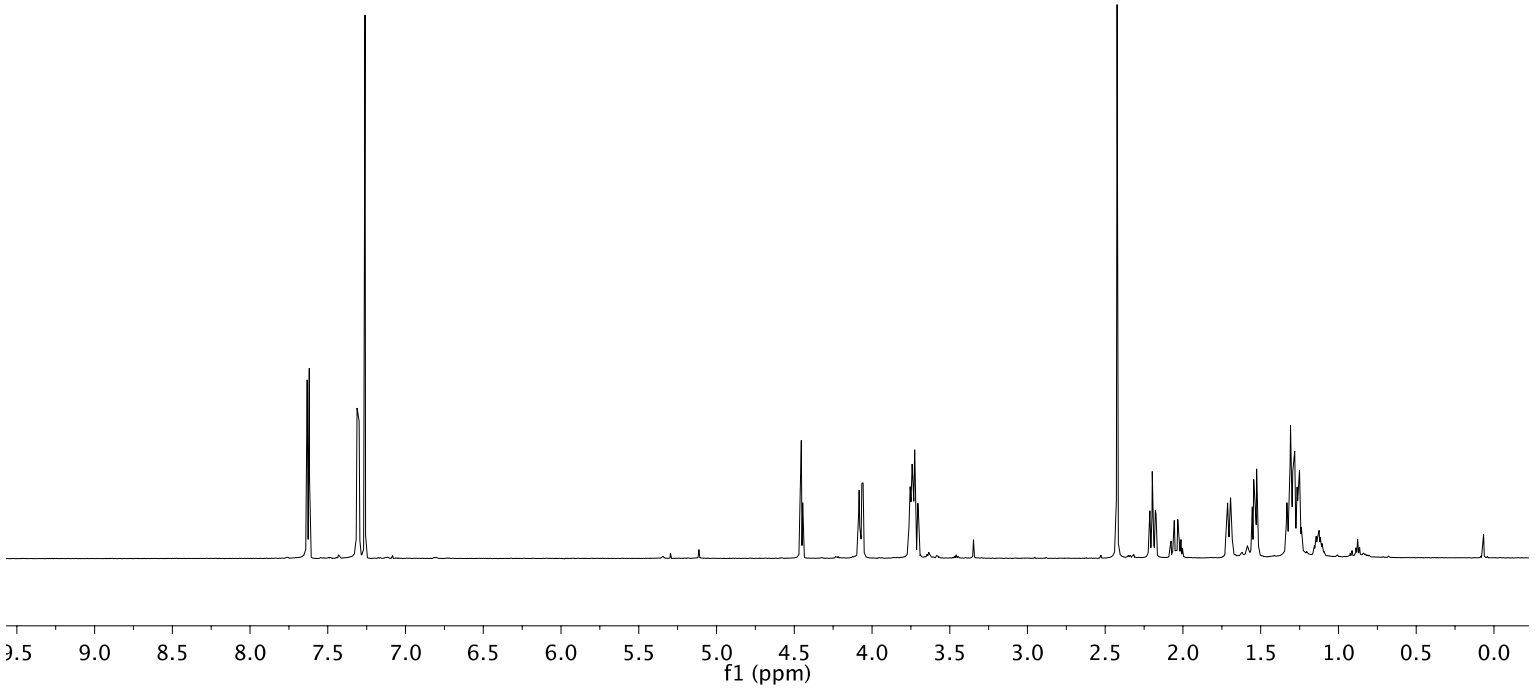

TsN
O
O

16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1.5
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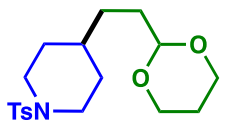
0.0
f1 (ppm)


TsN
O
O

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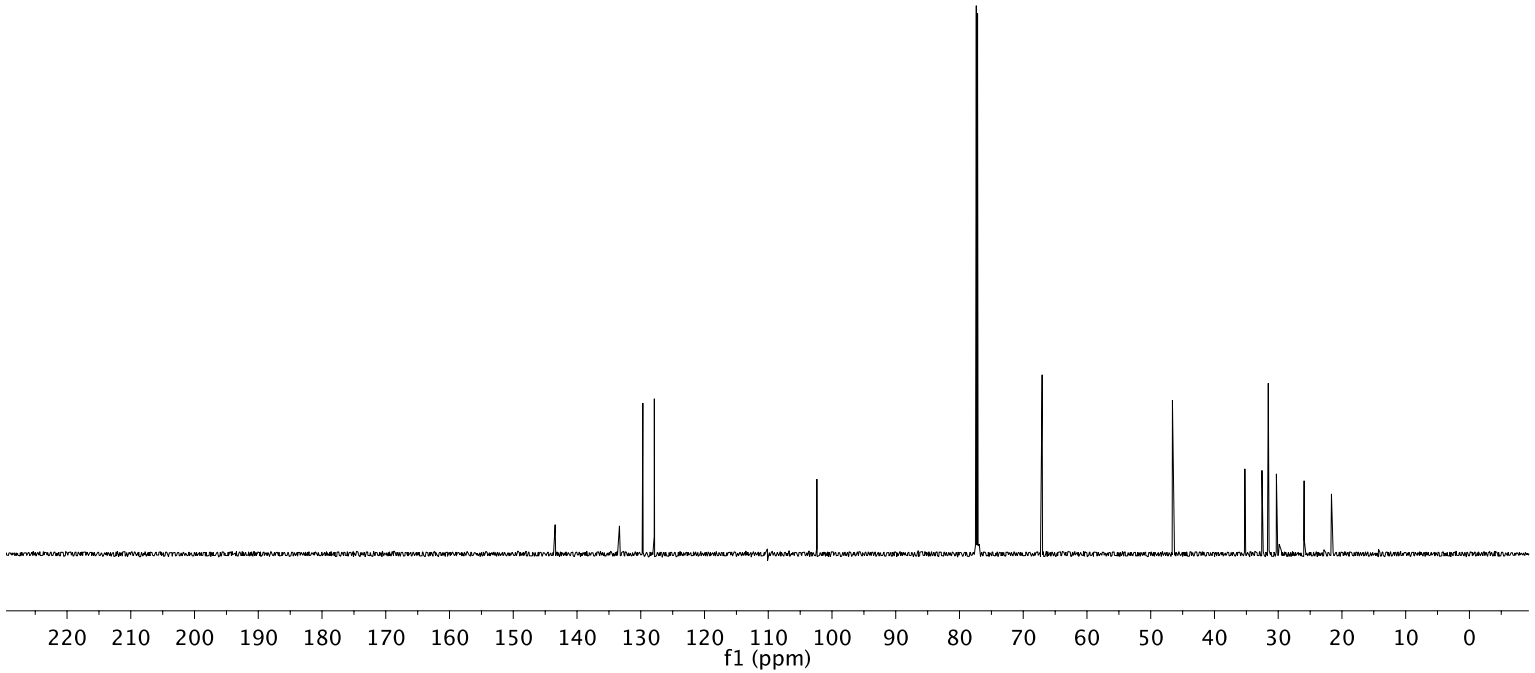
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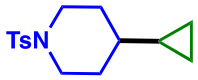

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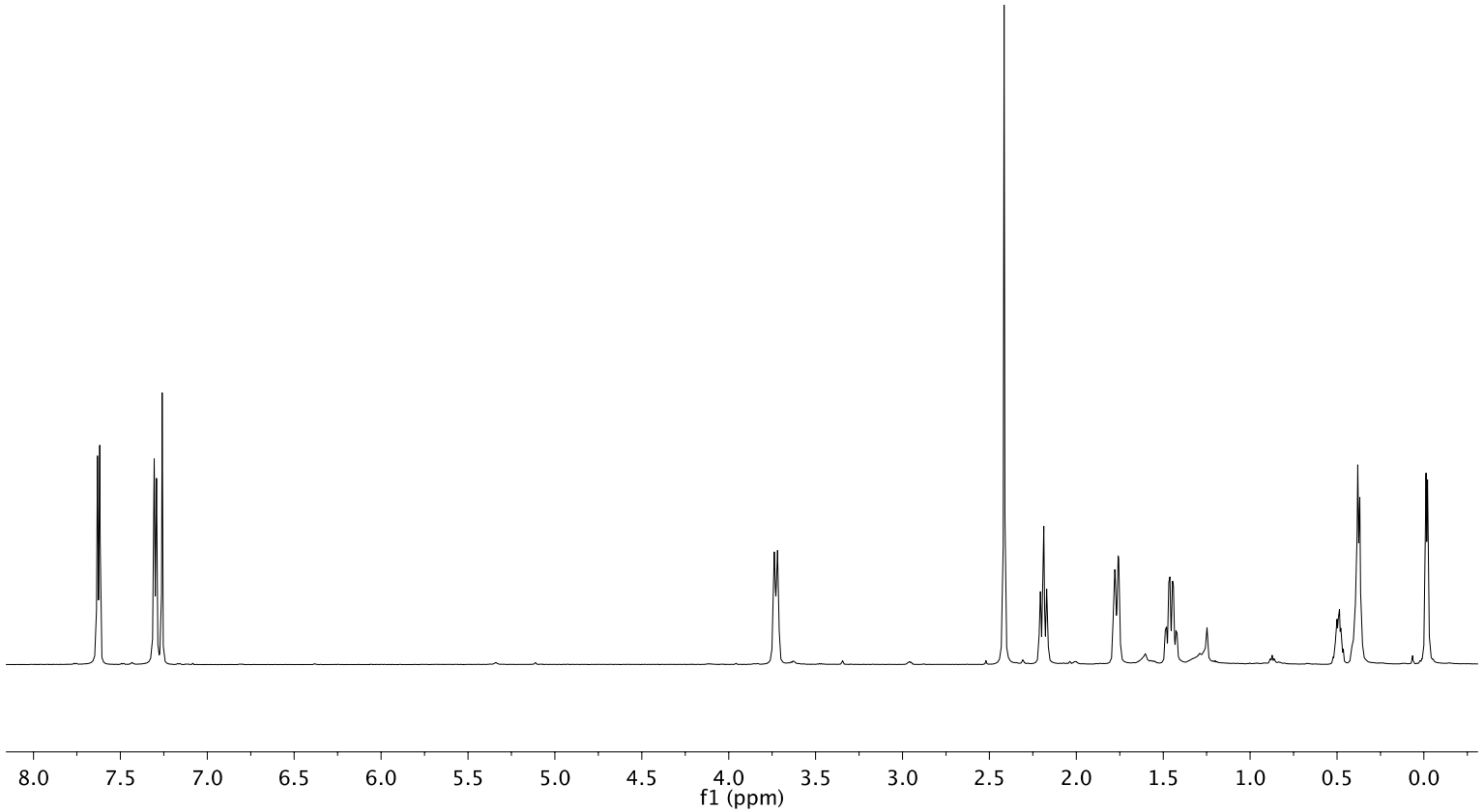

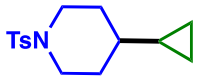
TsN

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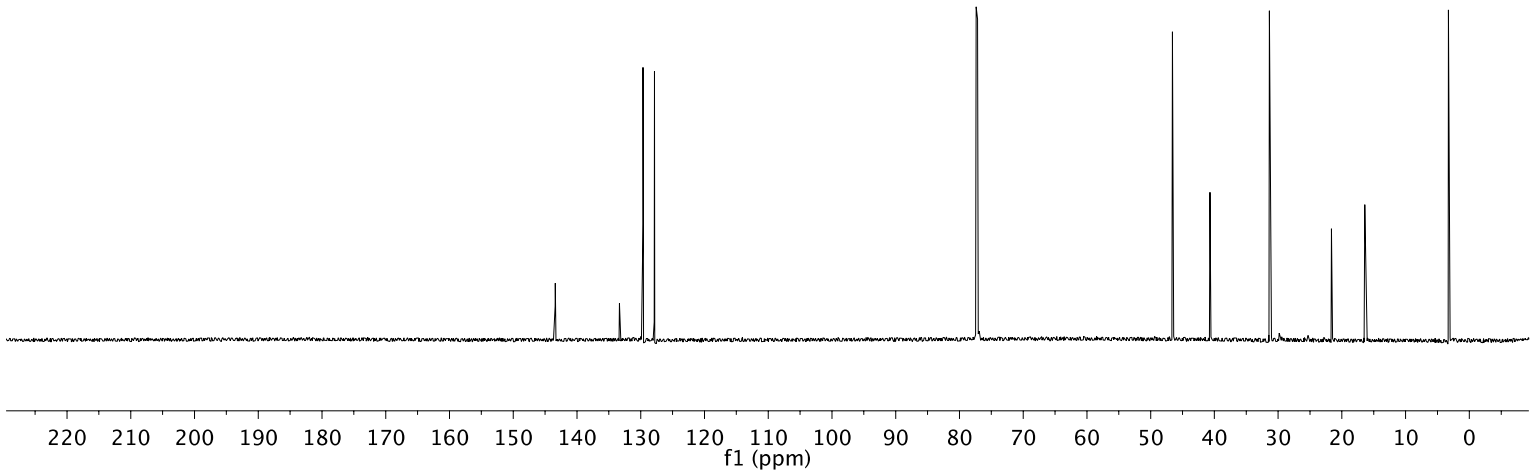
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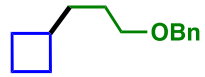
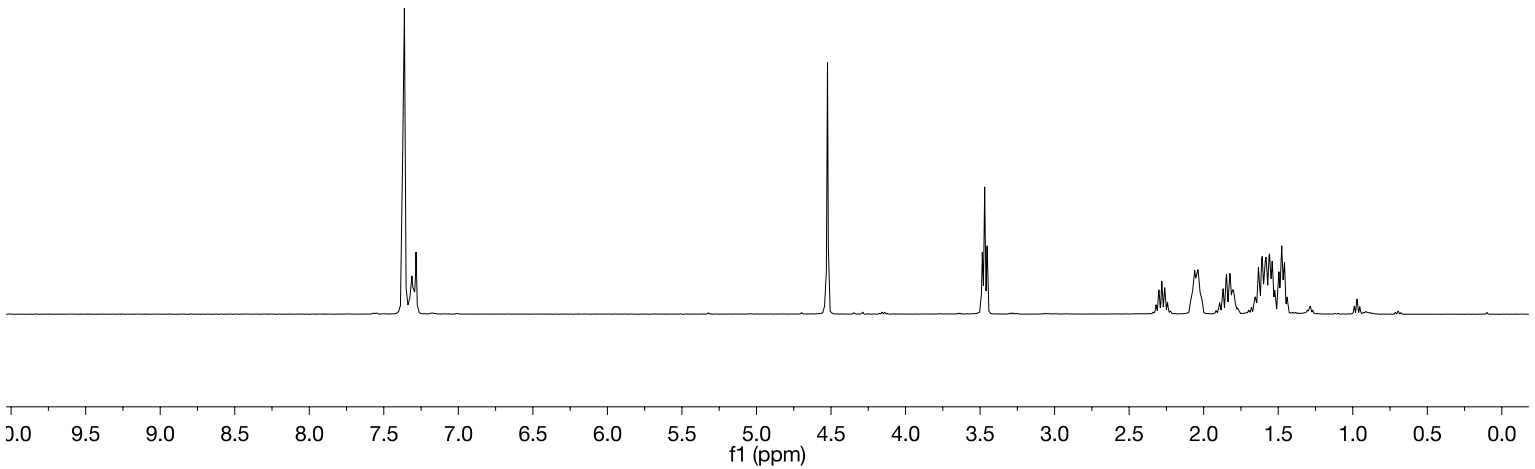

OBn

18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1.5
1.0
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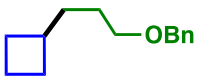
0.0
f1 (ppm)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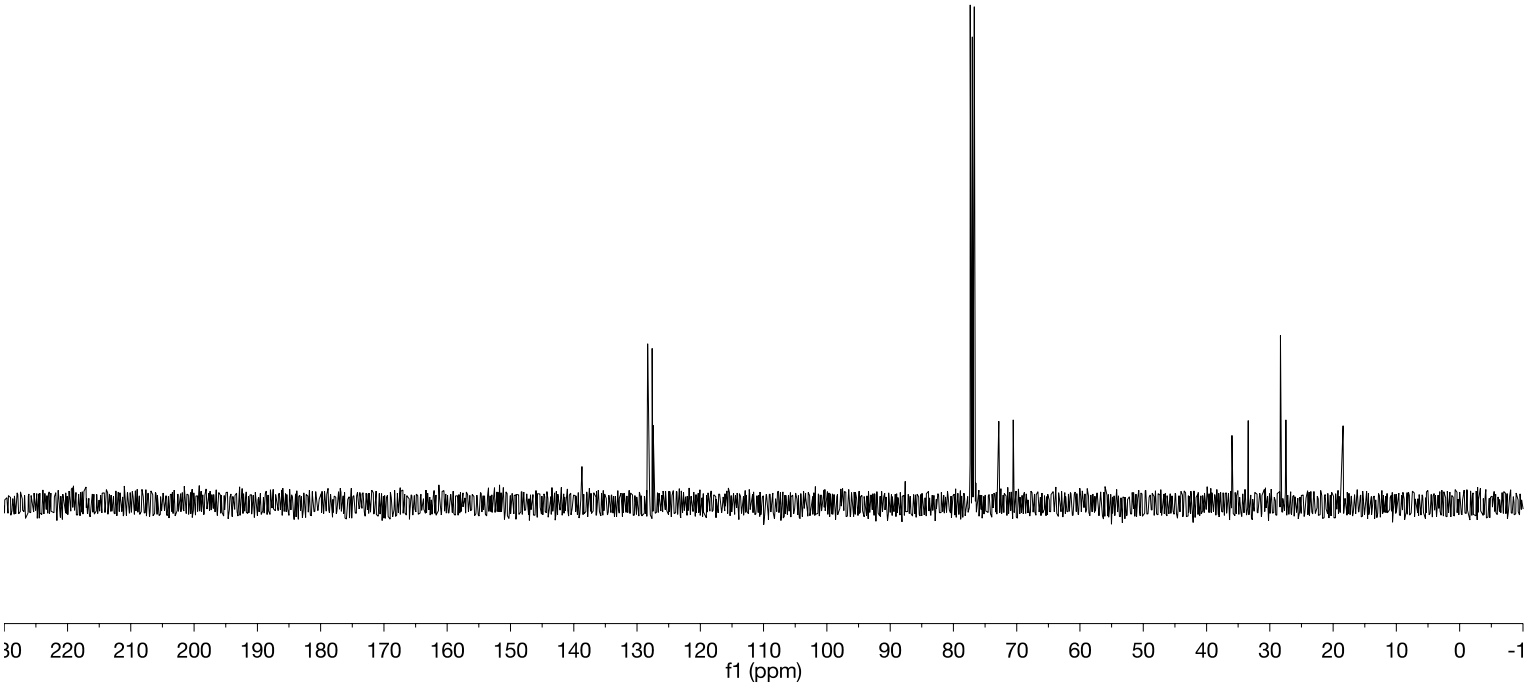
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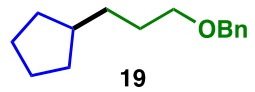
f1 (ppm)



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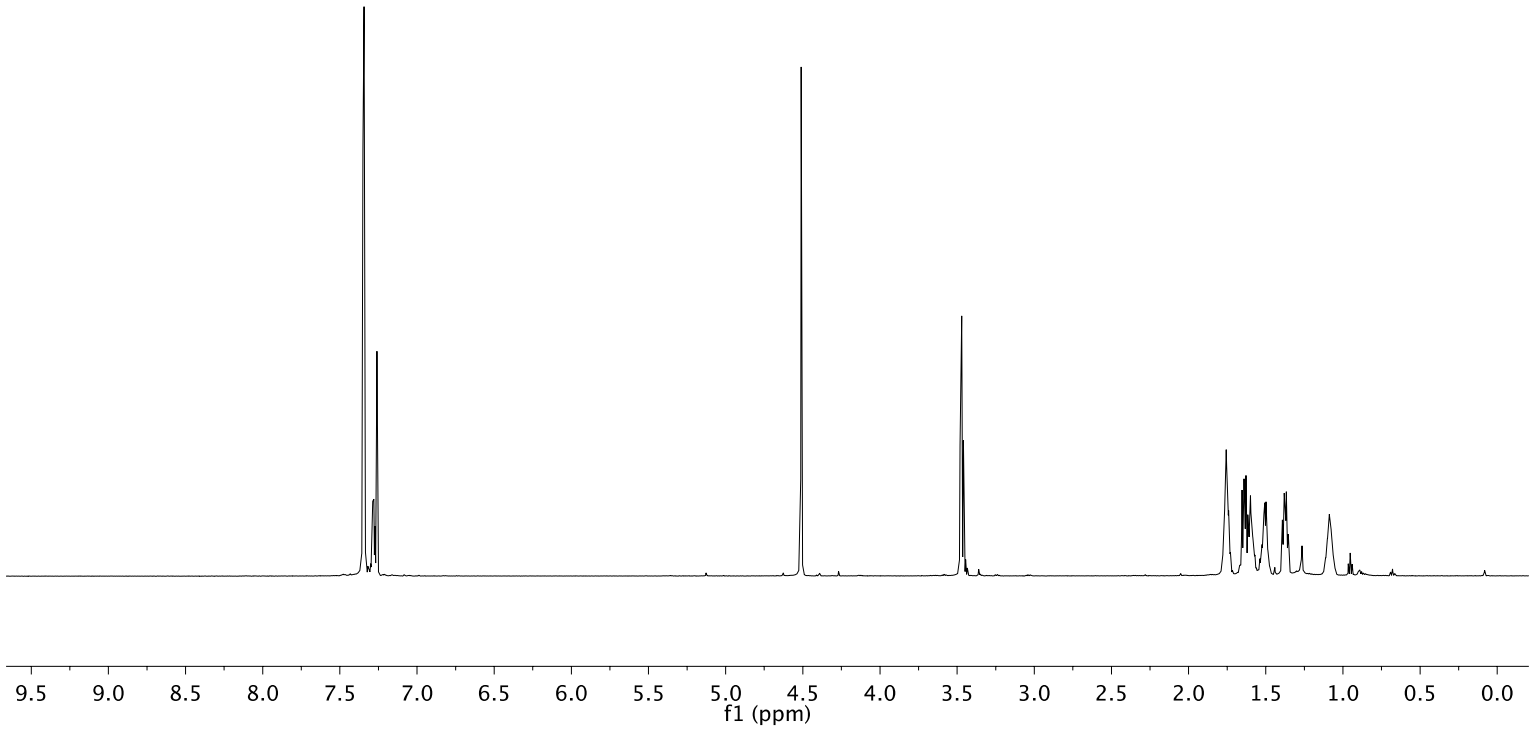

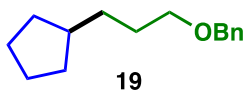
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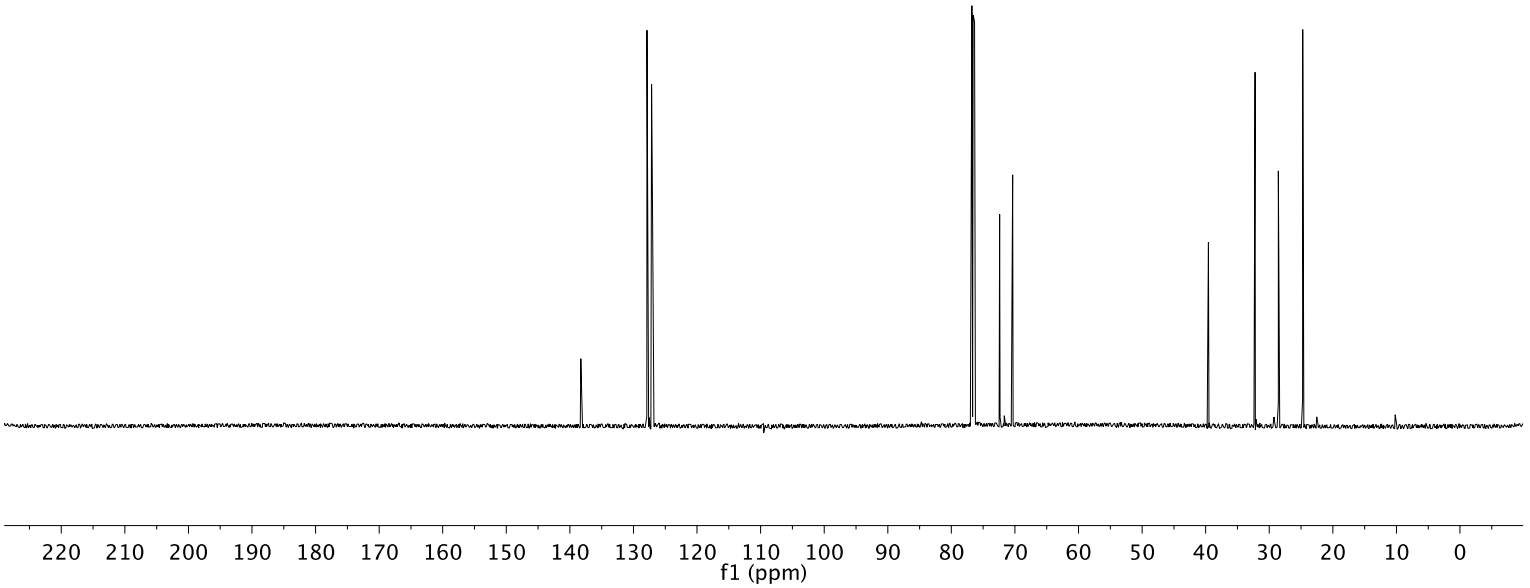
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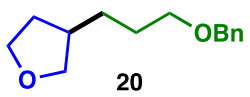

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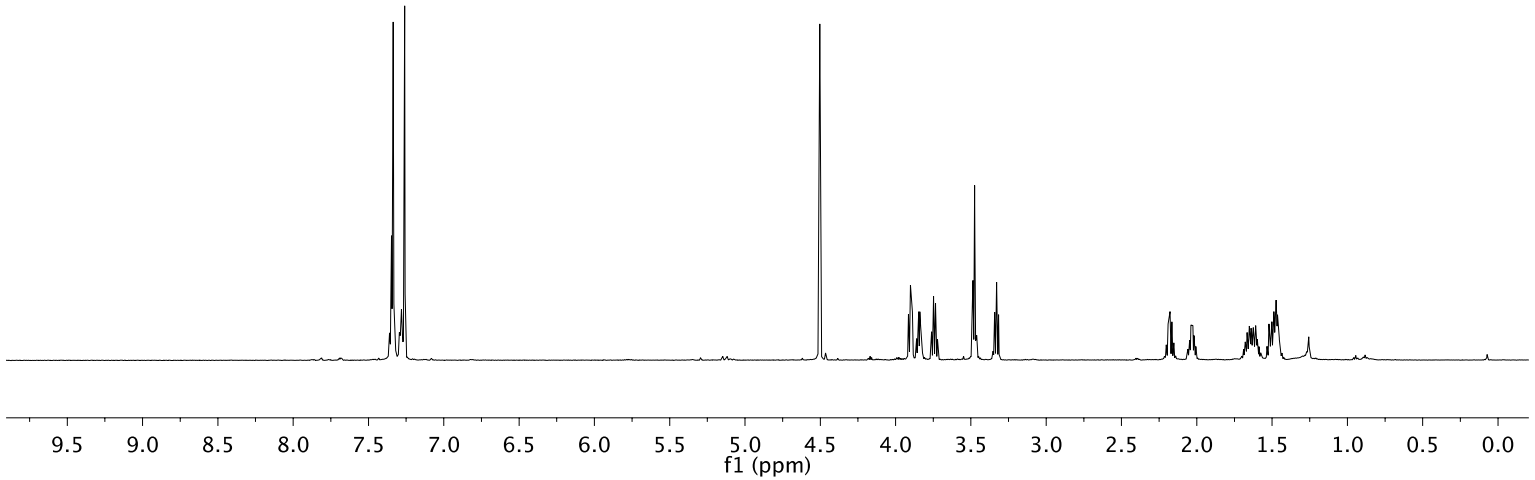

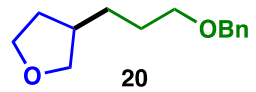
OBn
O

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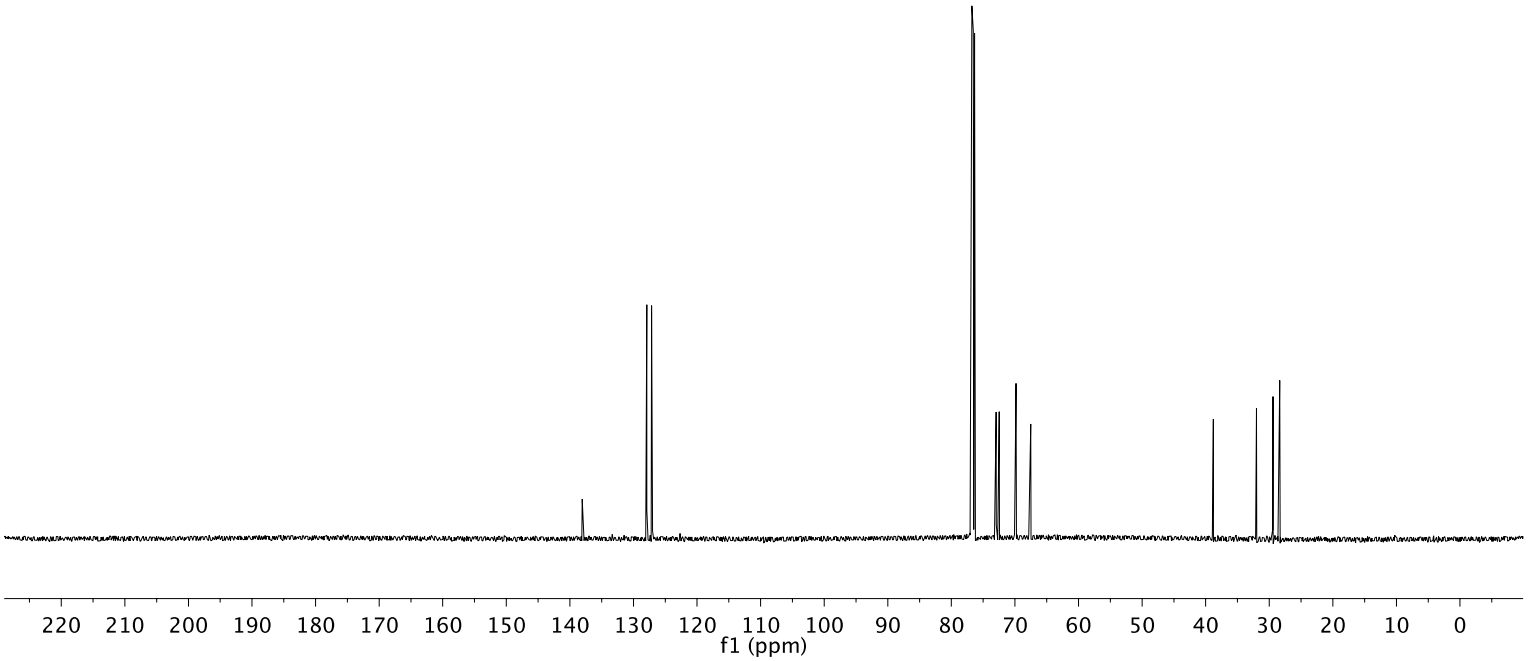
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f1 (ppm)

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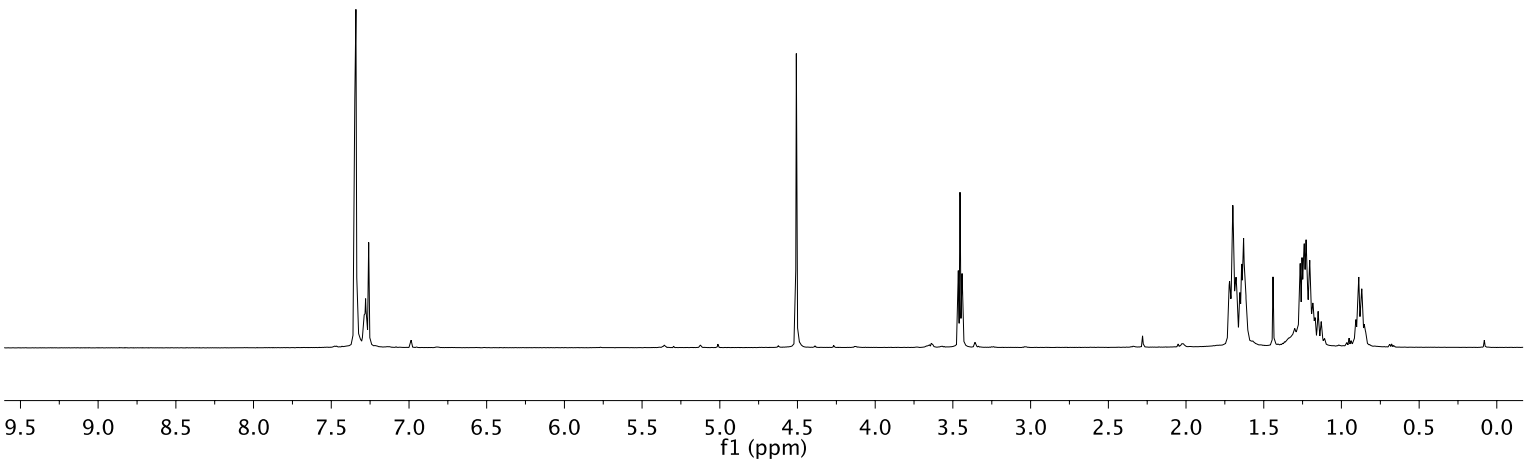

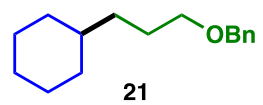
OBn

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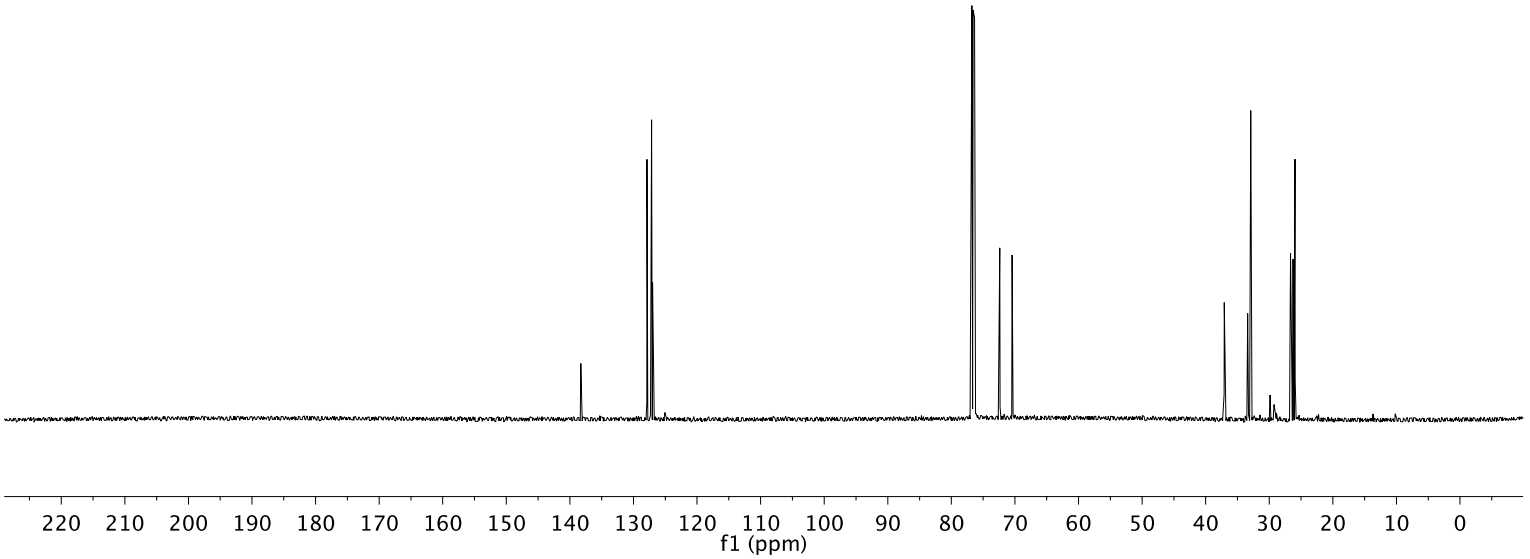
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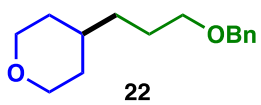

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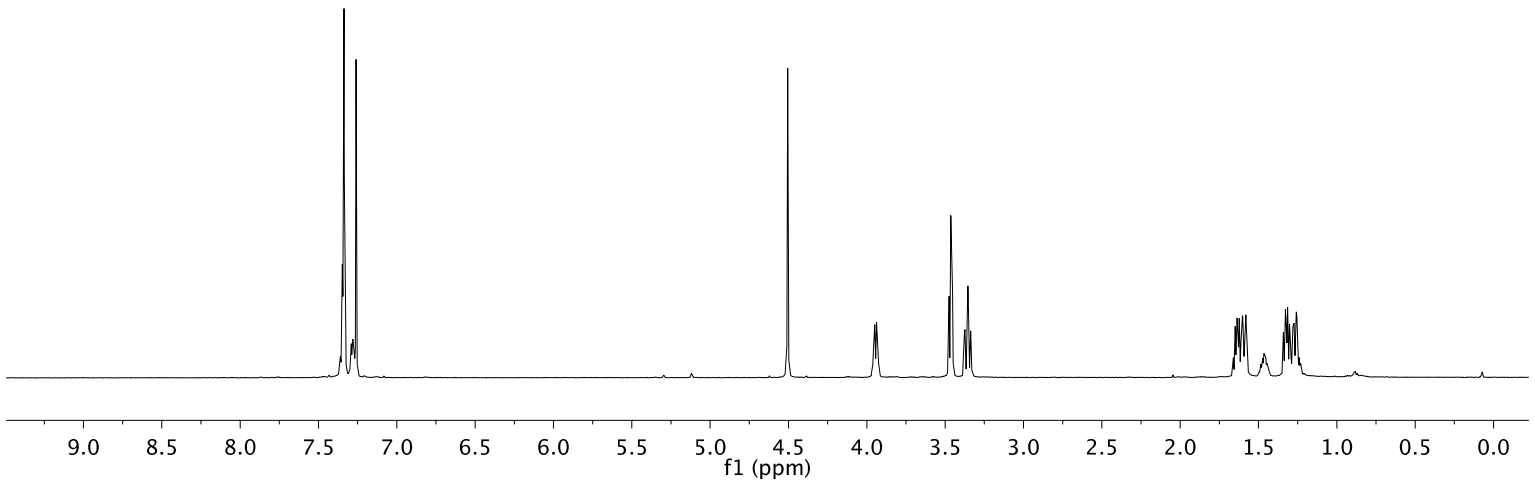

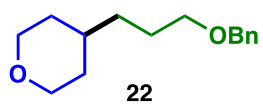
OBn
O

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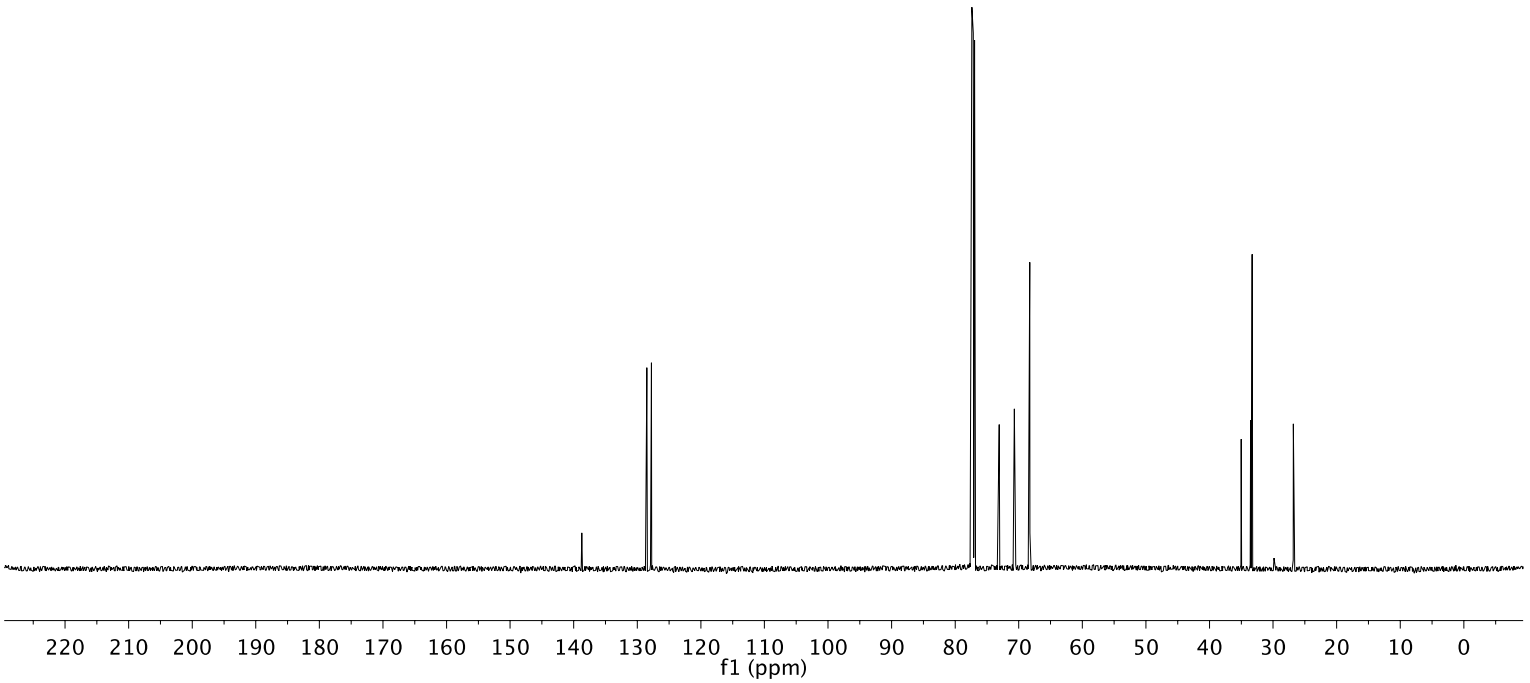
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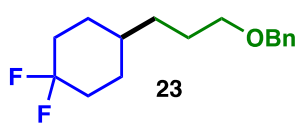

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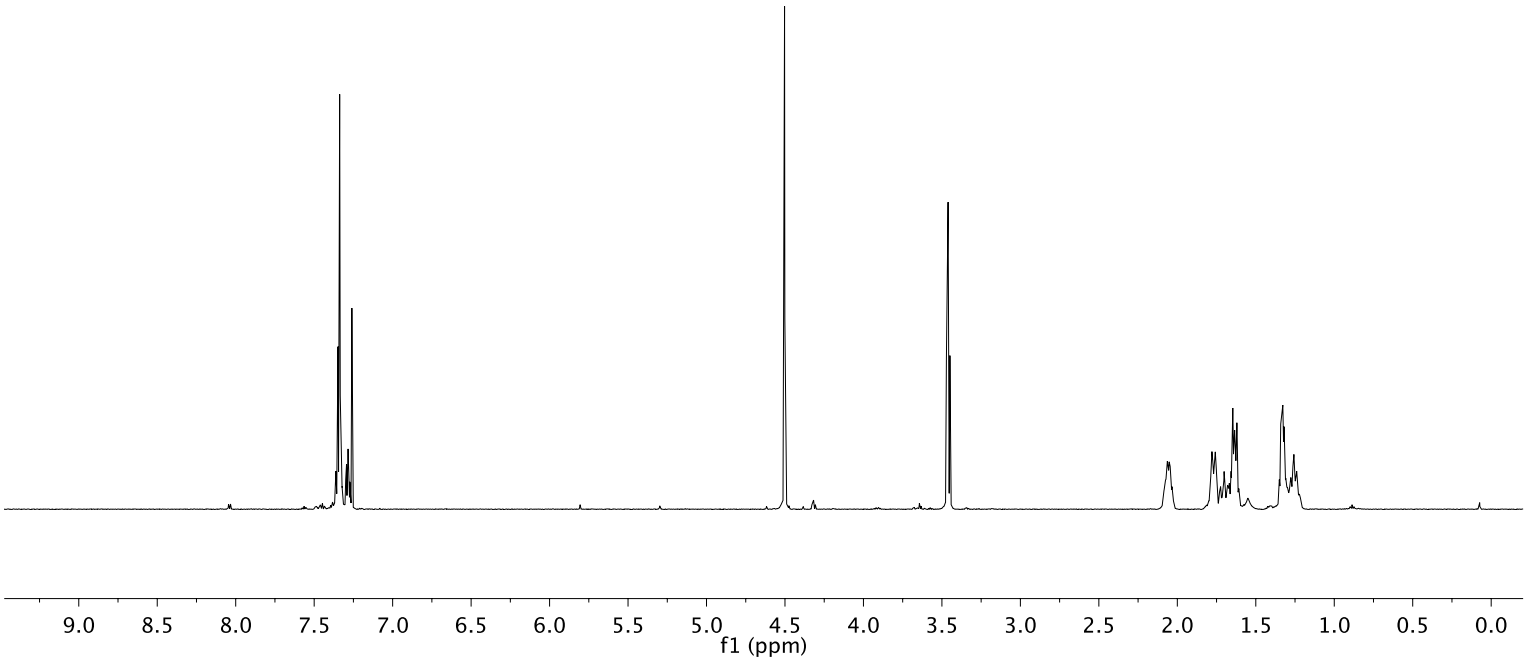

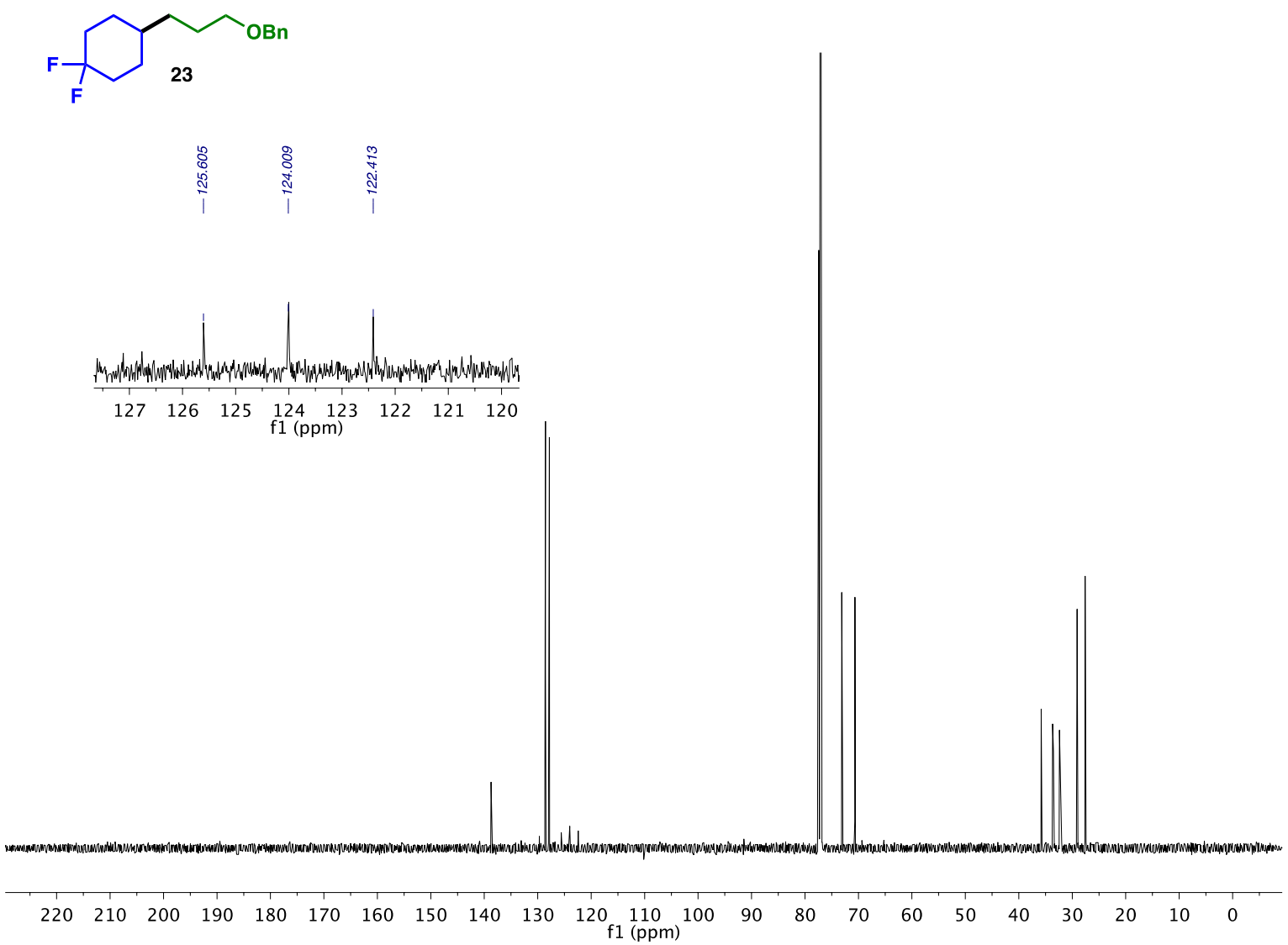
OBn
F
F
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122.413
127 126 125 124 123 122 121 120
f1 (ppm)
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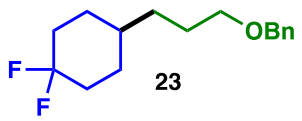
f1 (ppm)


OBn
F
F

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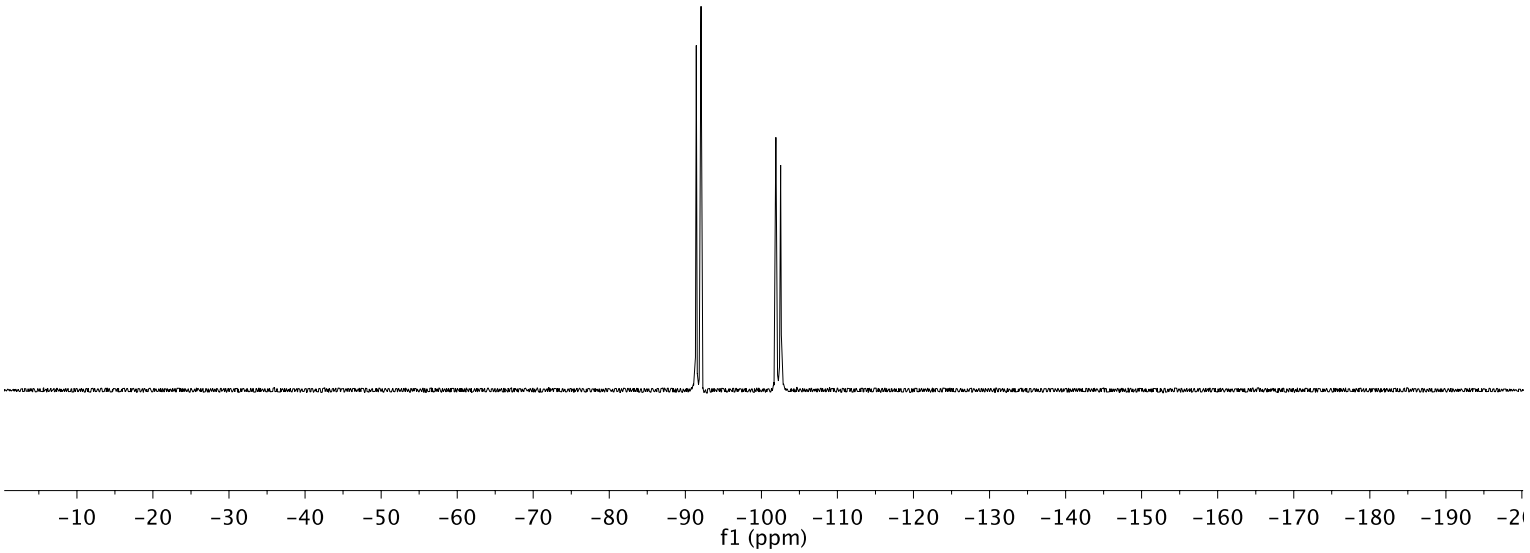
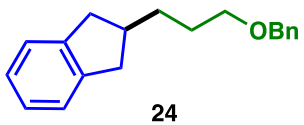

−10 −20 −30 −40 −50 −60 −70 −80 −90 −100 −110 −120 −130 −140 −150 −160 −170 −180 −190
f1 (ppm)


OBn

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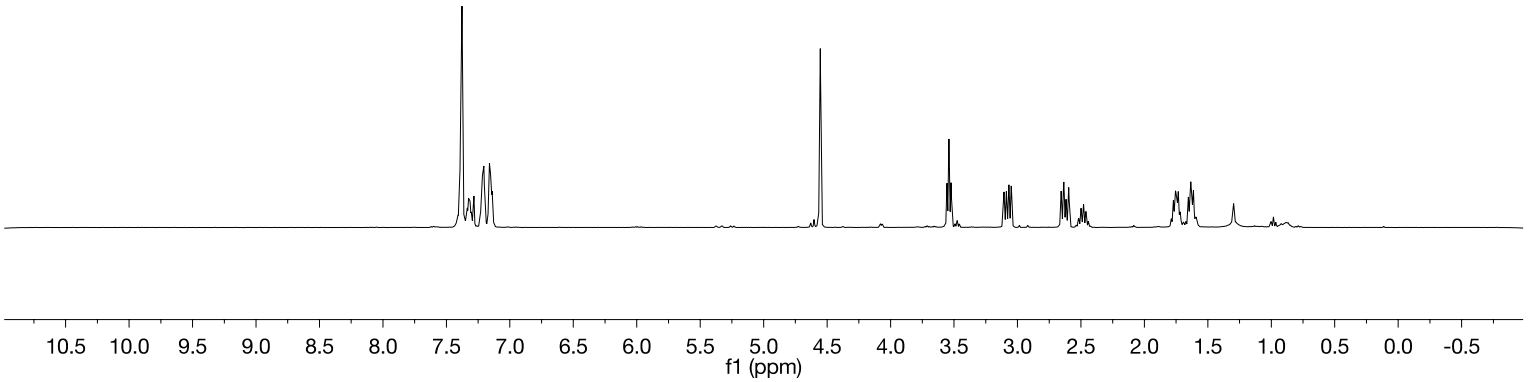
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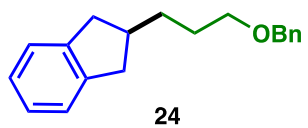
f1 (ppm)


OBn

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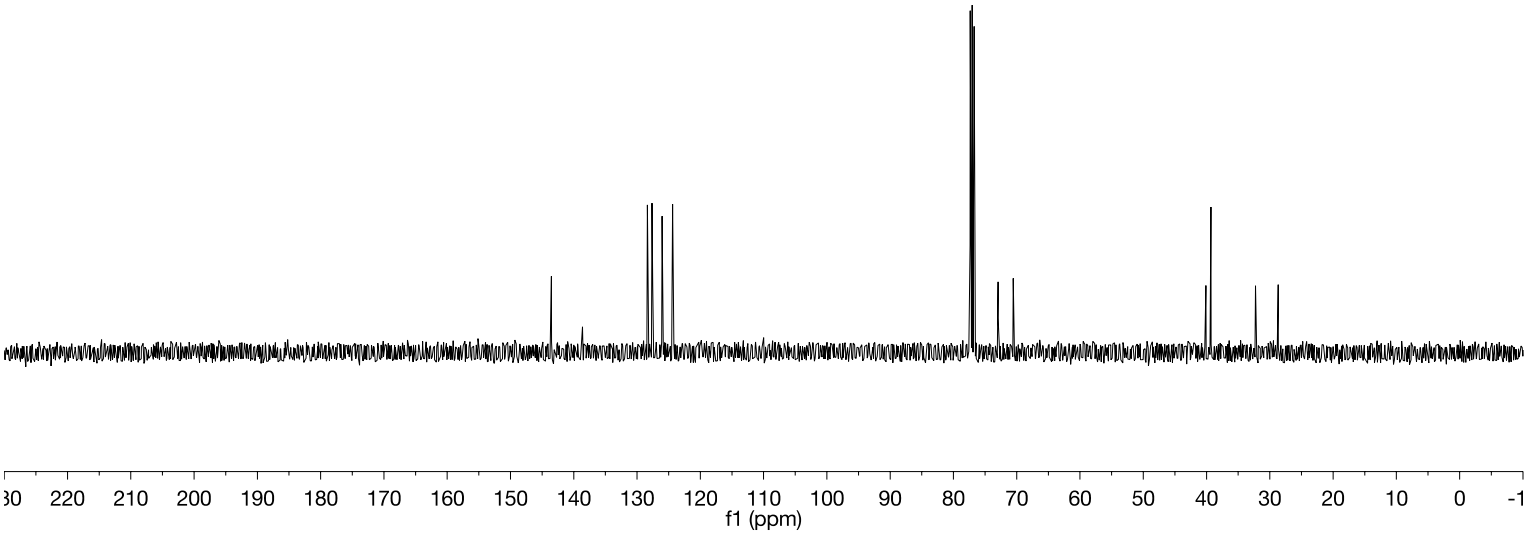
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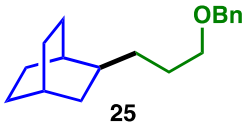
OBn

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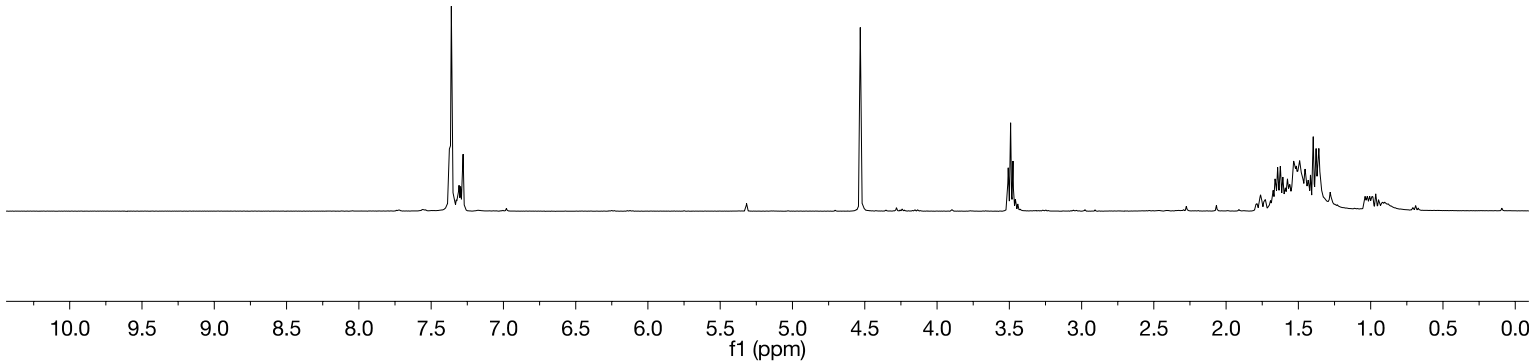
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6.5
6.0
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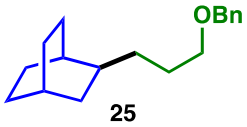
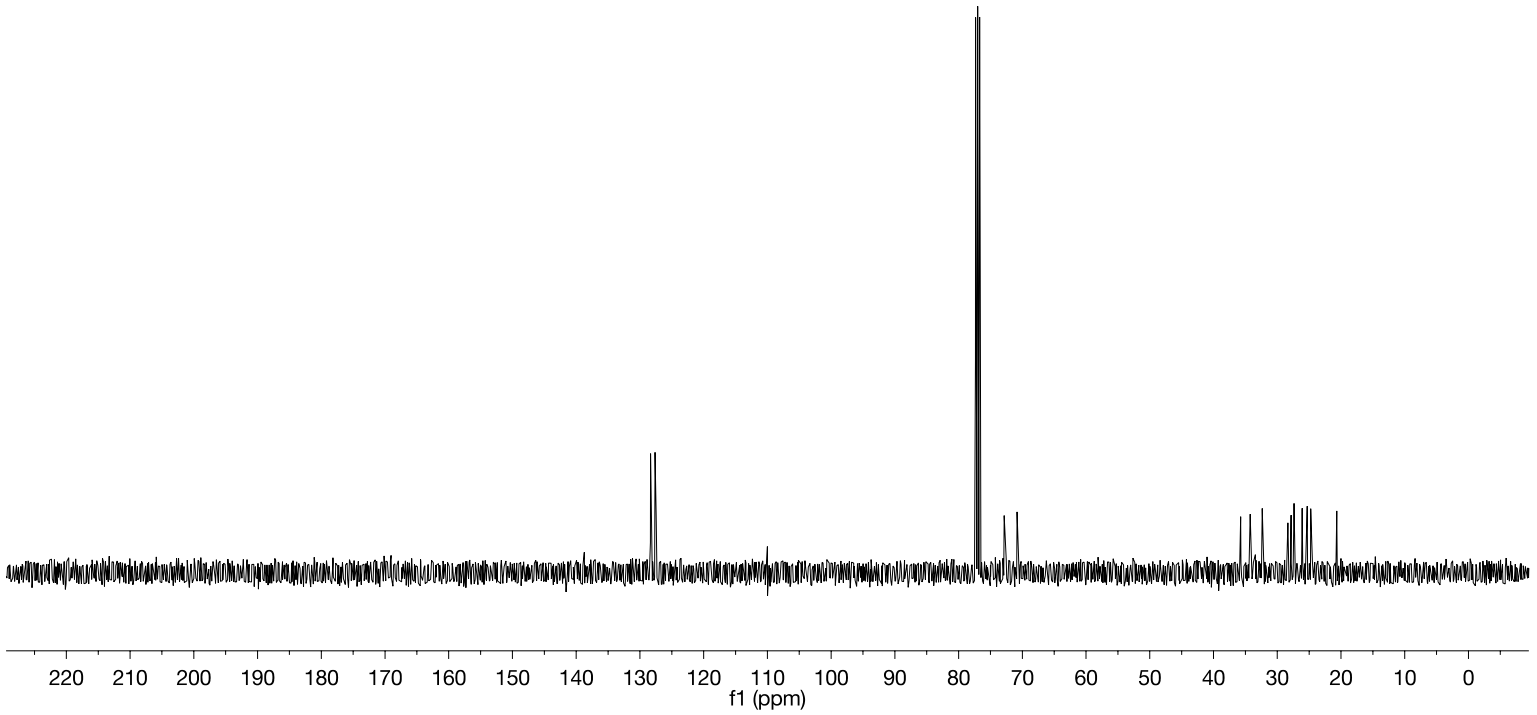
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OBn

25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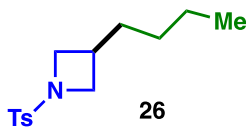
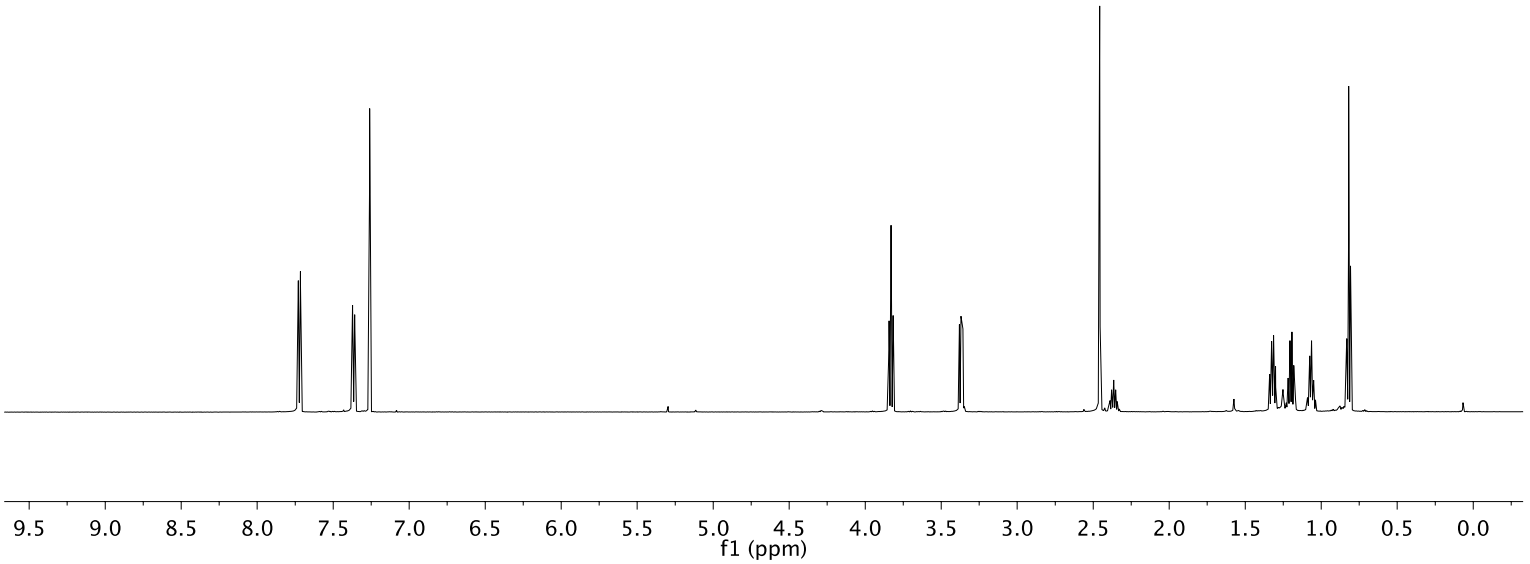
f1 (ppm)


Me
N
Ts

26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6.5
6.0
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4.5
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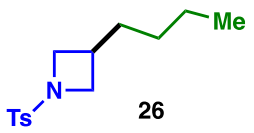
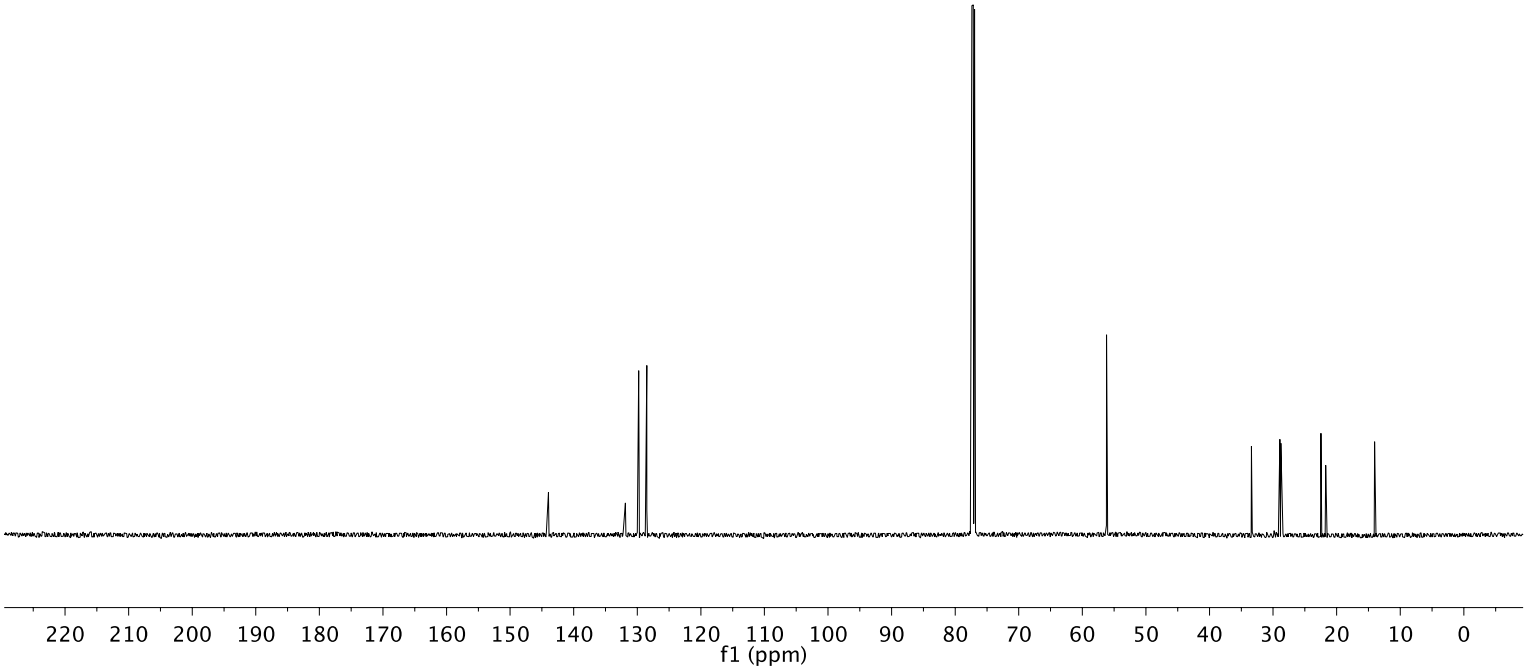
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
N
Ts

26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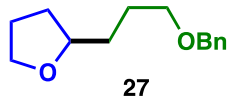
f1 (ppm)



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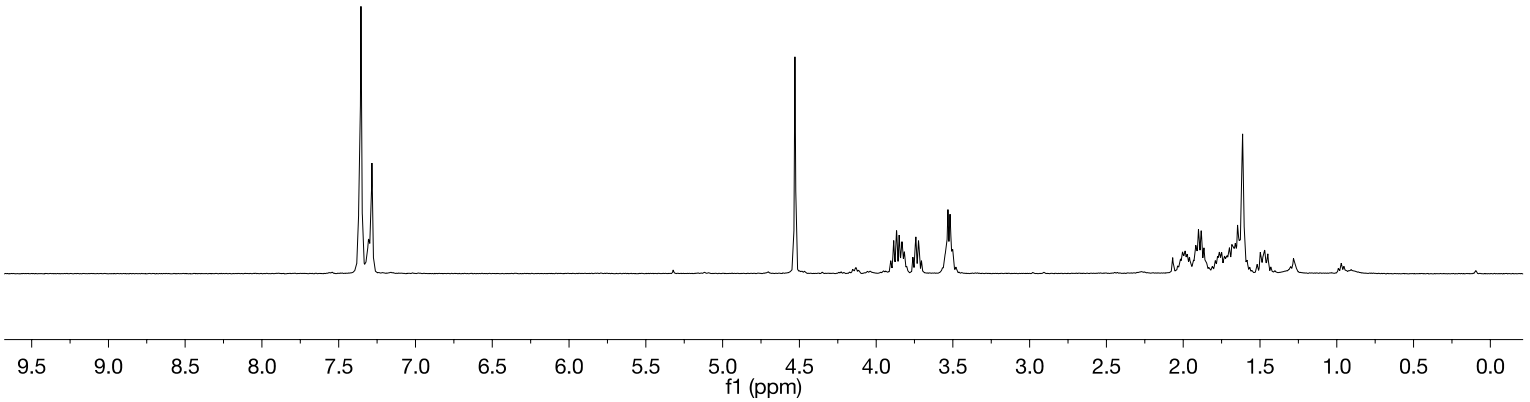
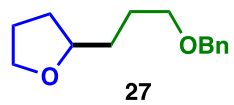
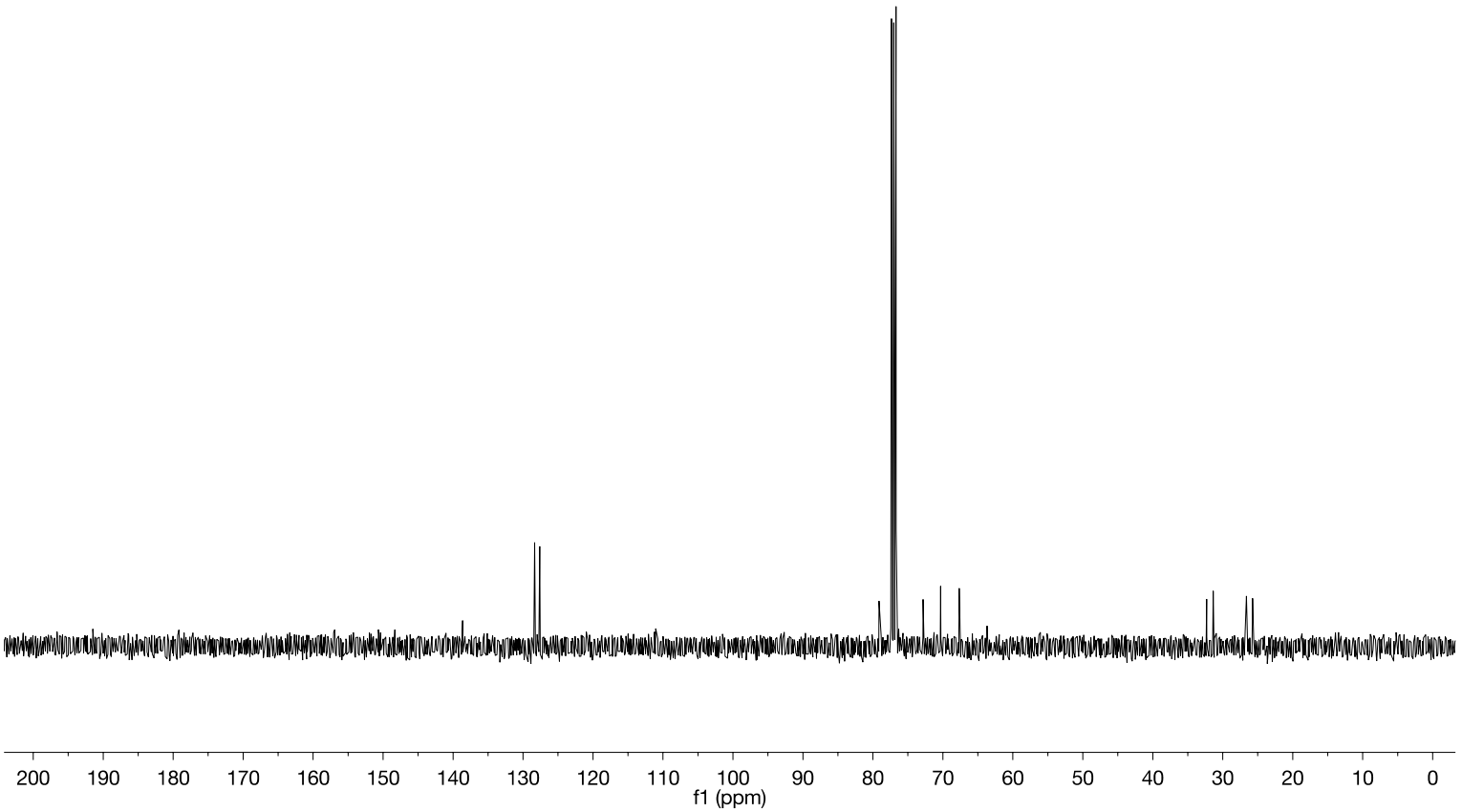
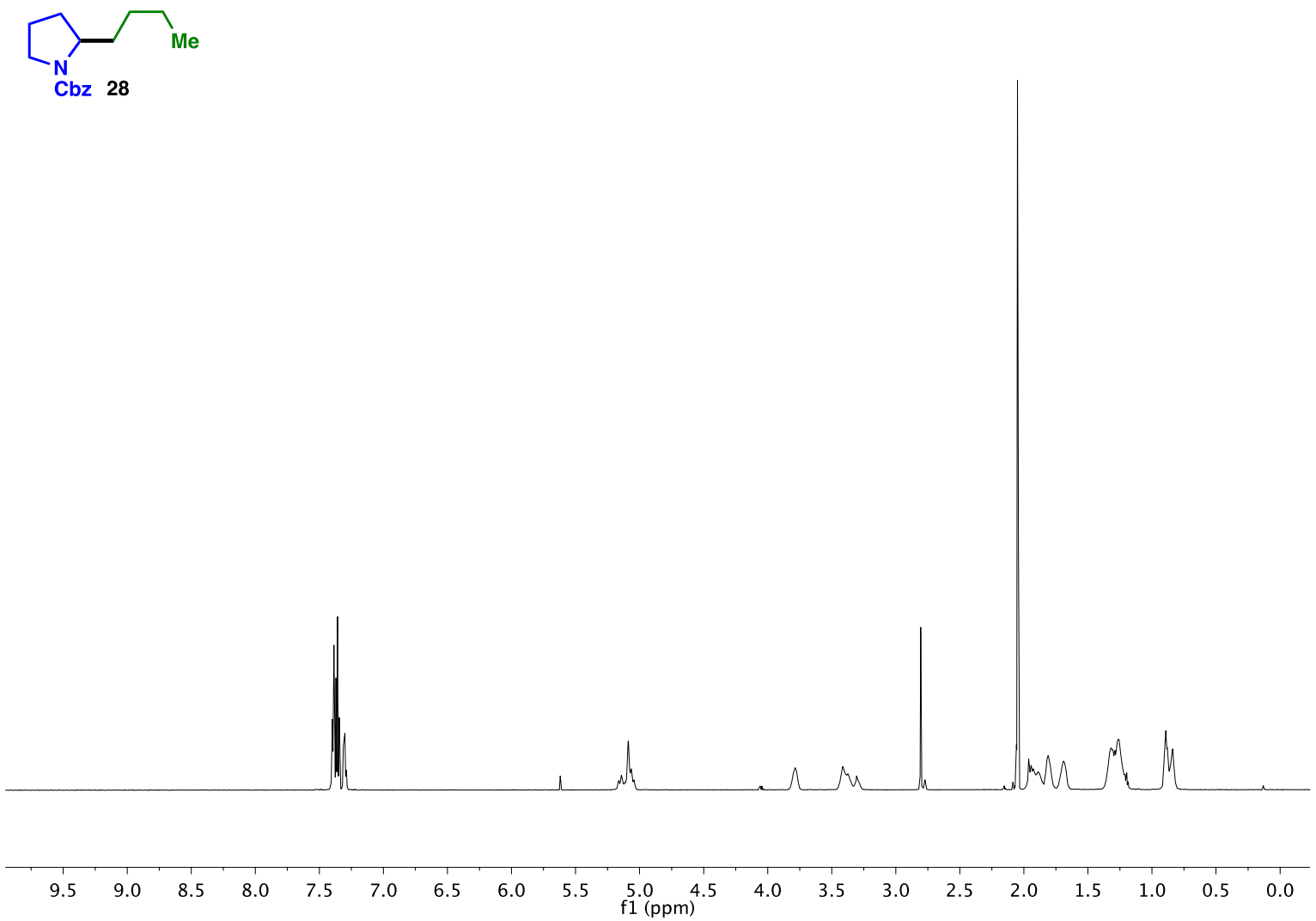



OBn
O

27


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
N
Cbz
28
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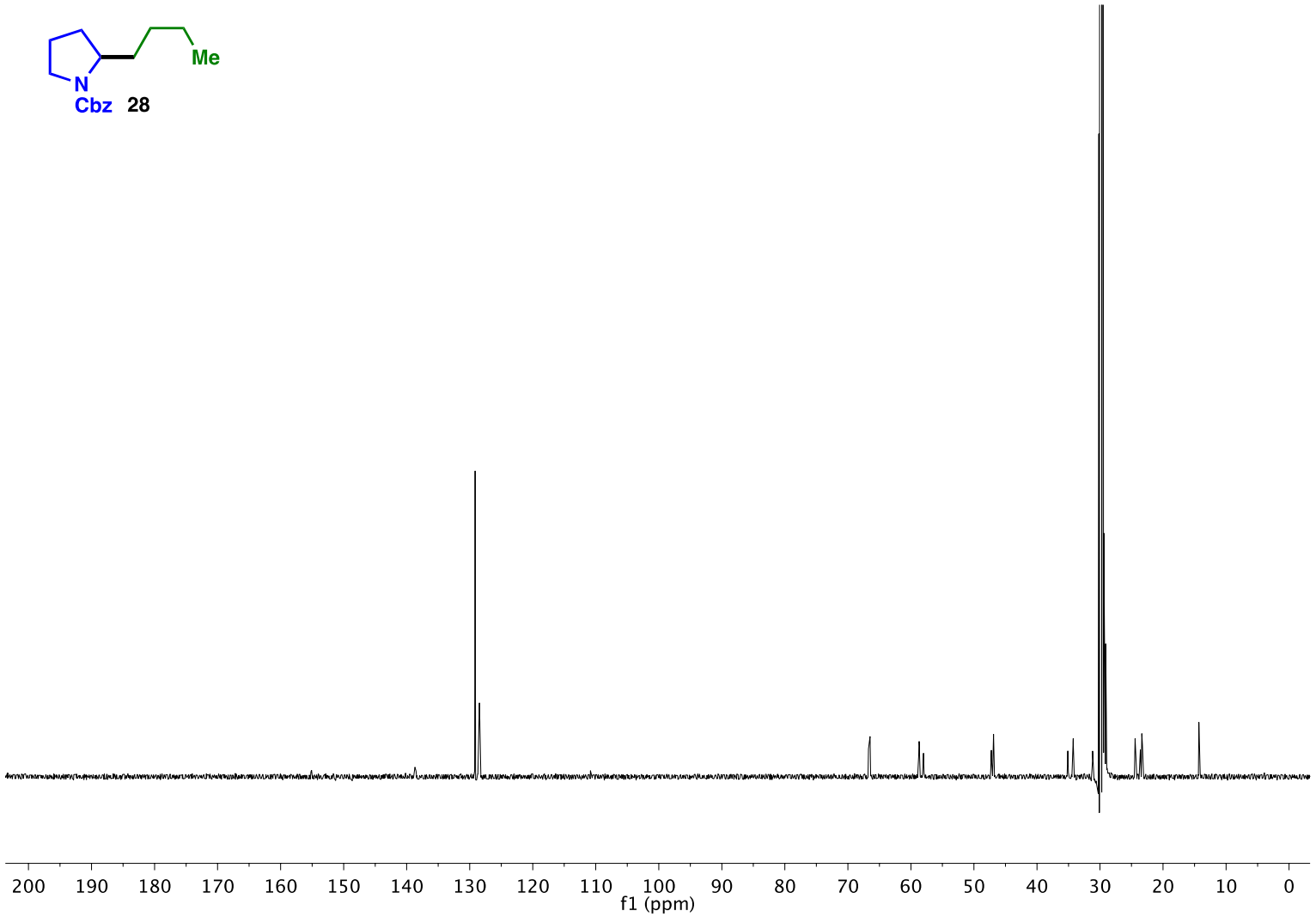
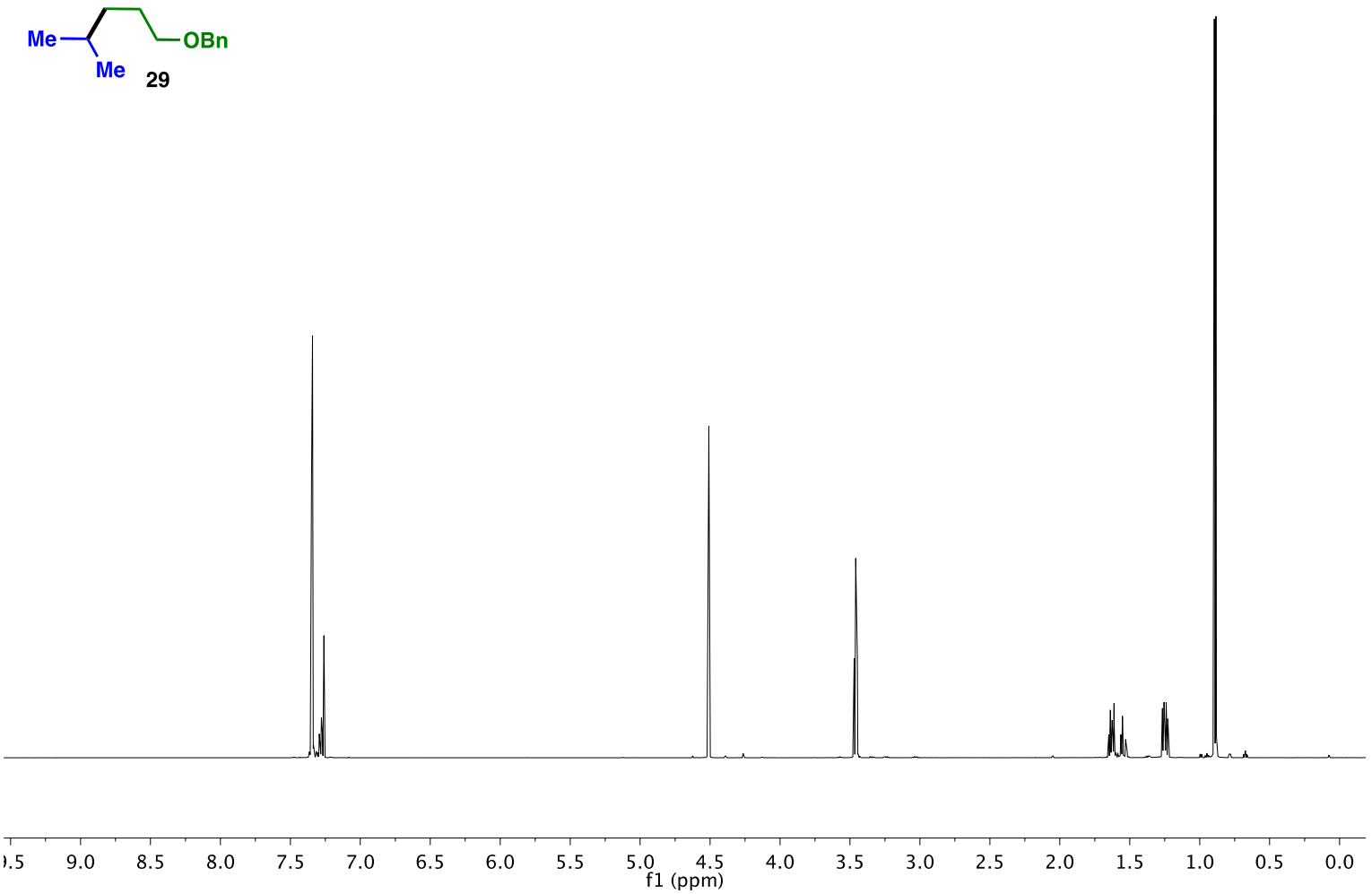
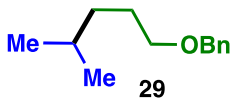
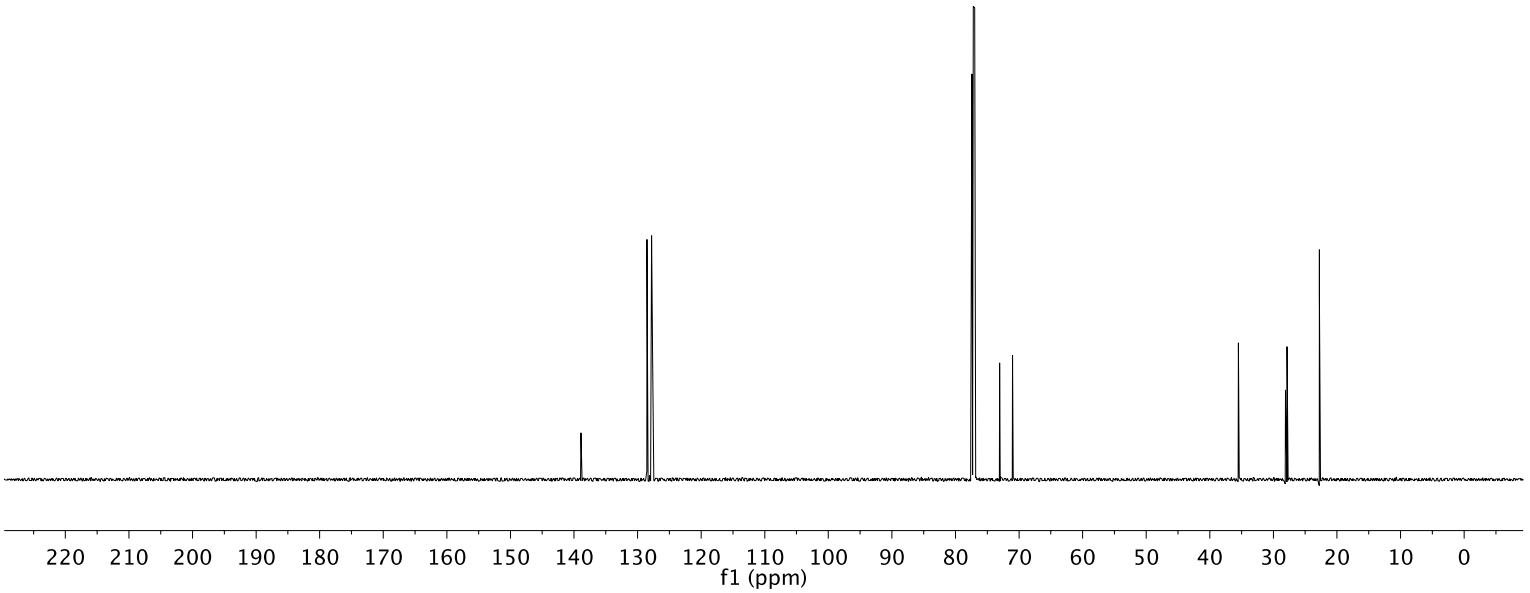
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
N
Cbz
28
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
Me
OBn
29
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
OBn

29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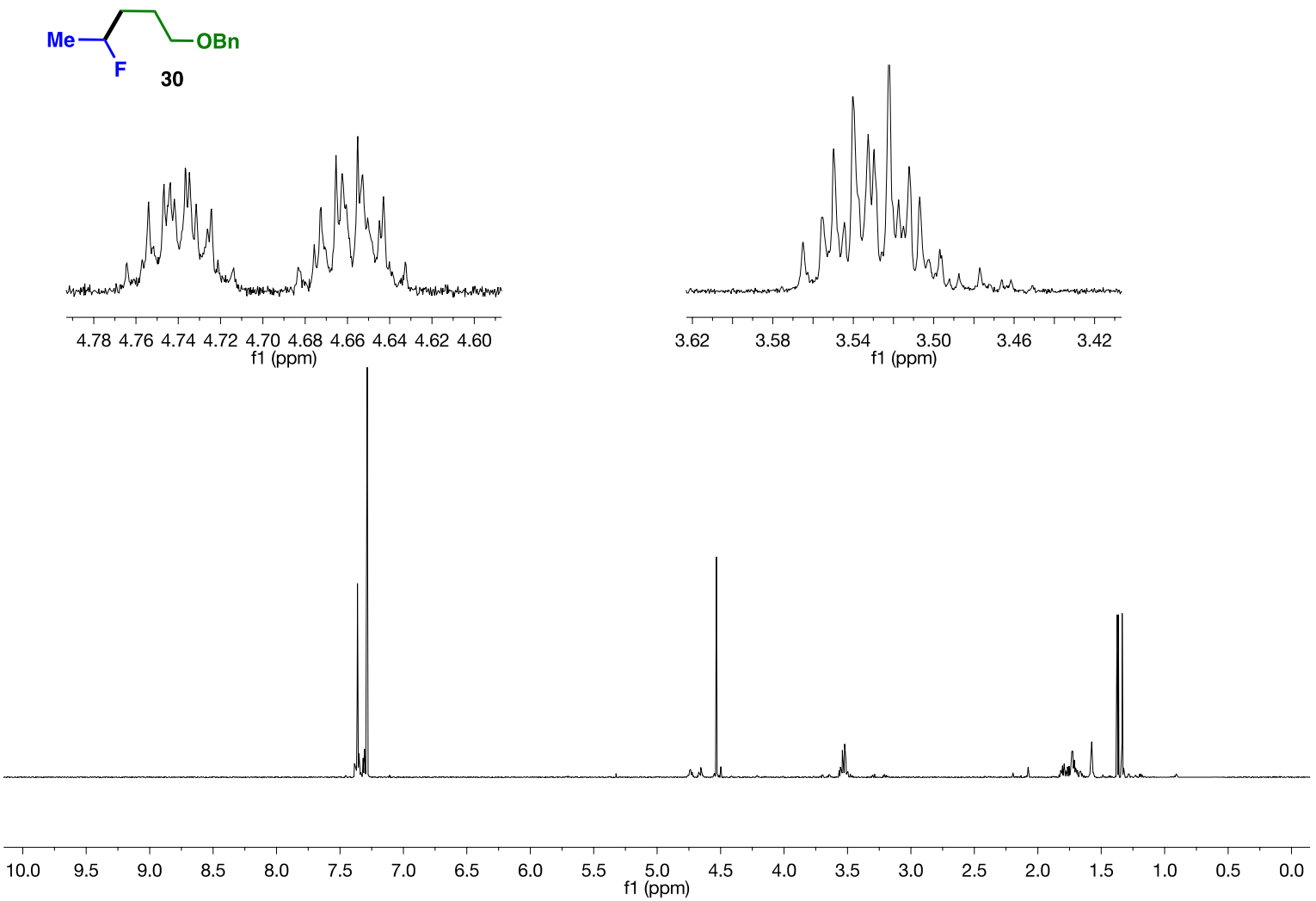
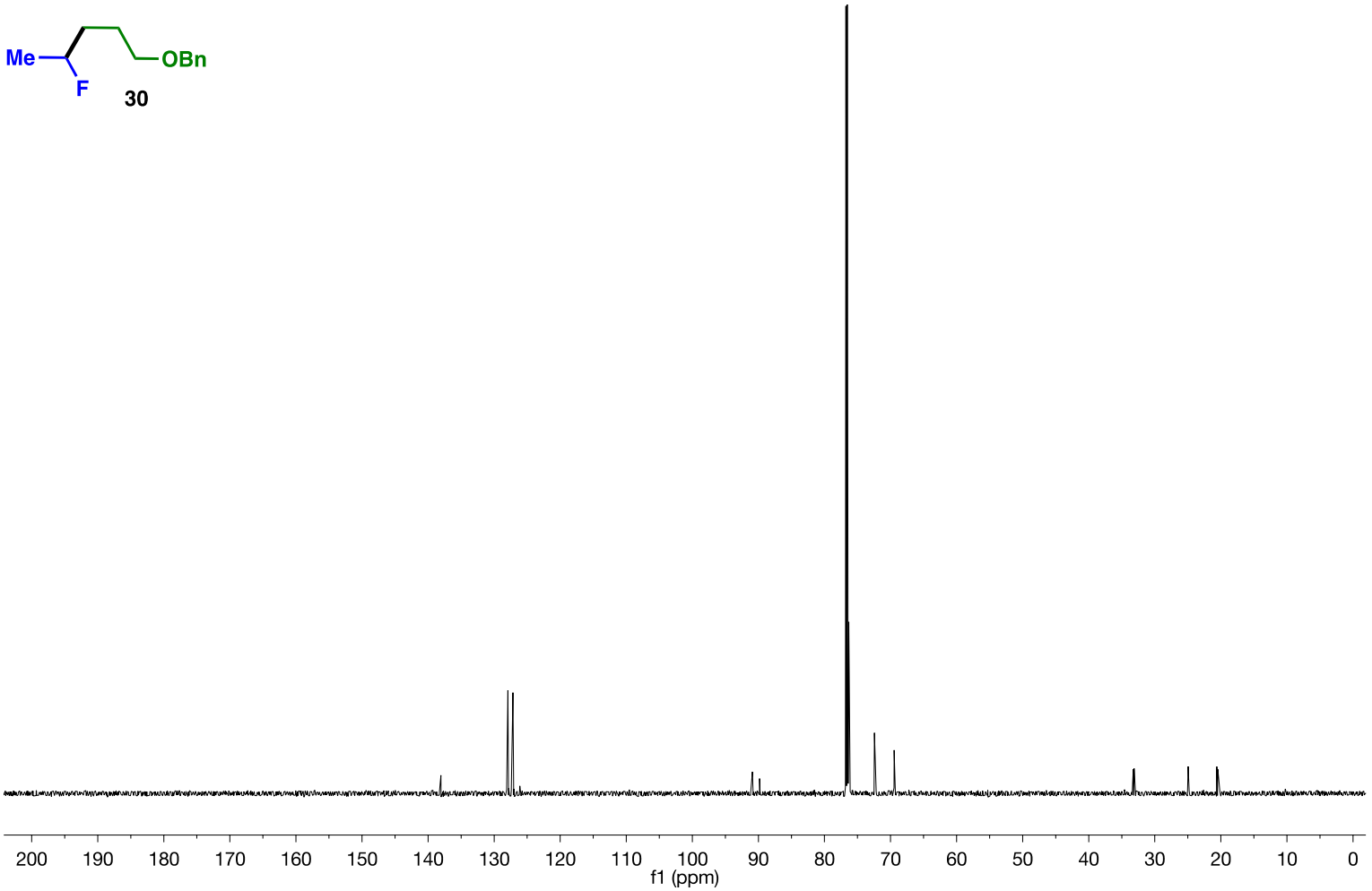
f1 (ppm)


Me
F
OBn
30
4.78 4.76 4.74 4.72 4.70 4.68 4.66 4.64 4.62 4.60
f1 (ppm)
3.62 3.58 3.54 3.50 3.46 3.42
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


Me
F
OBn
30
200
190
180
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160
150
140
130
120
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100
90
80
70
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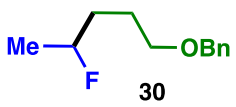
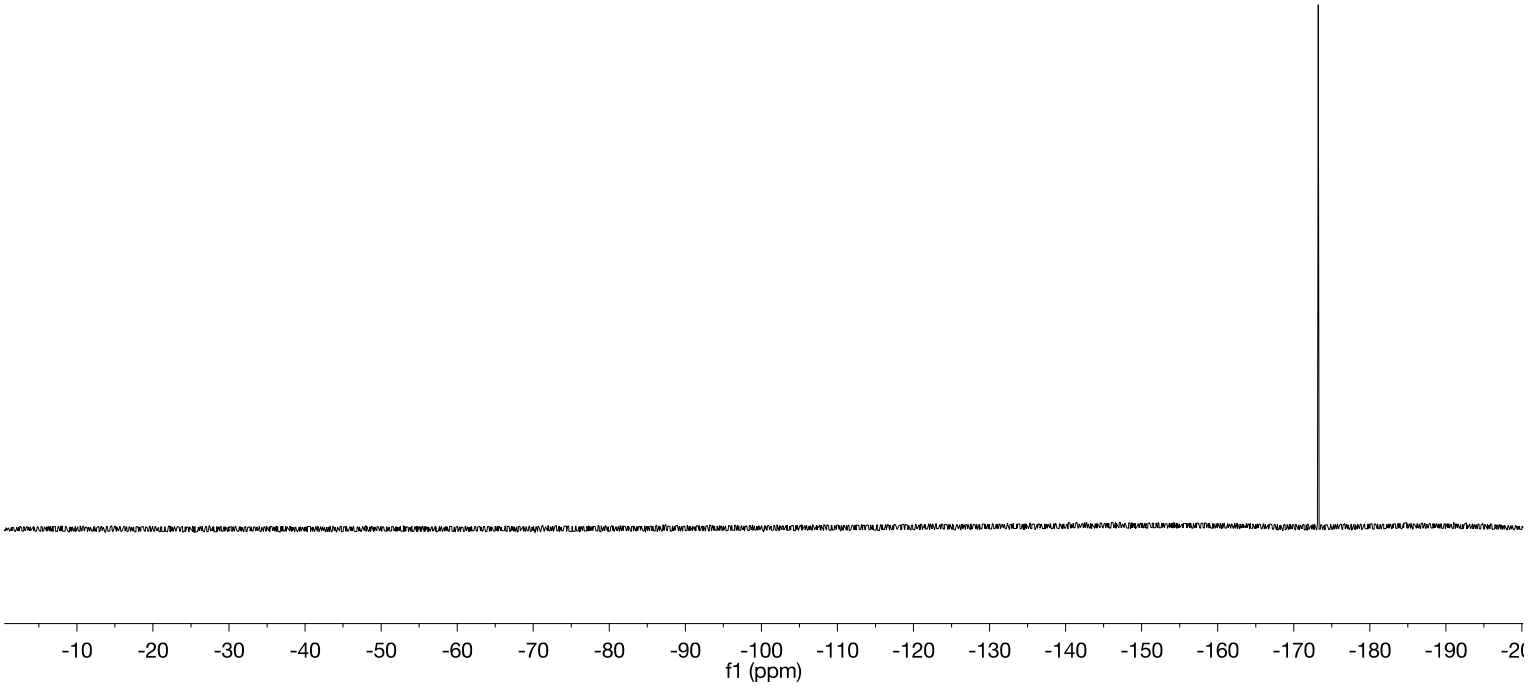
50
40
30
20
10
0
f1 (ppm)


Me
F
OBn

30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-50
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-70
-80
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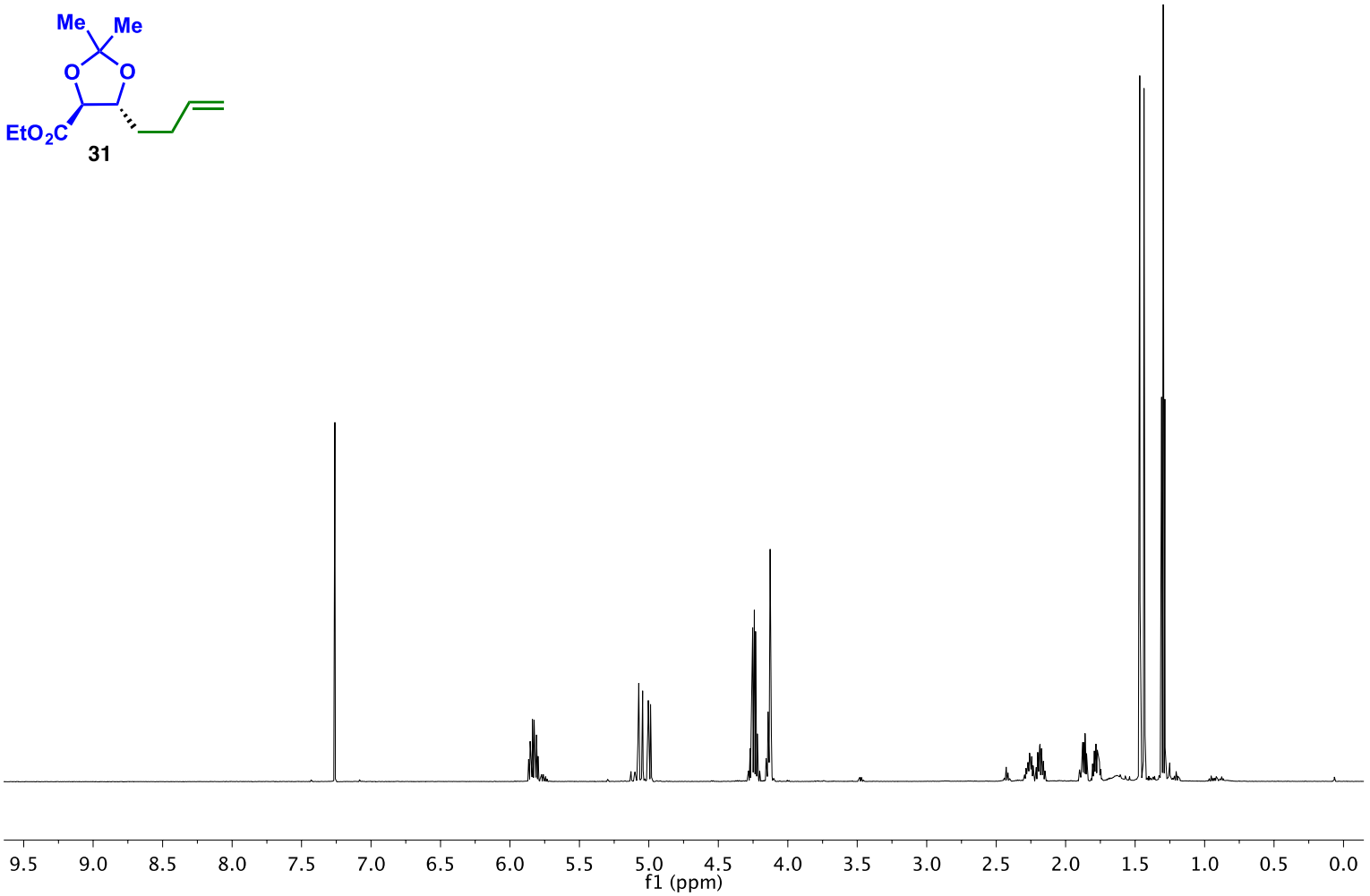
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)


Me
Me
O
O
EtO2C
31
9.5
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8.5
8.0
7.5
7.0
6.5
6.0
5.5
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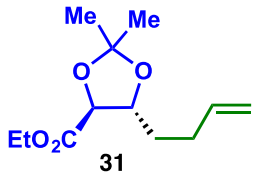
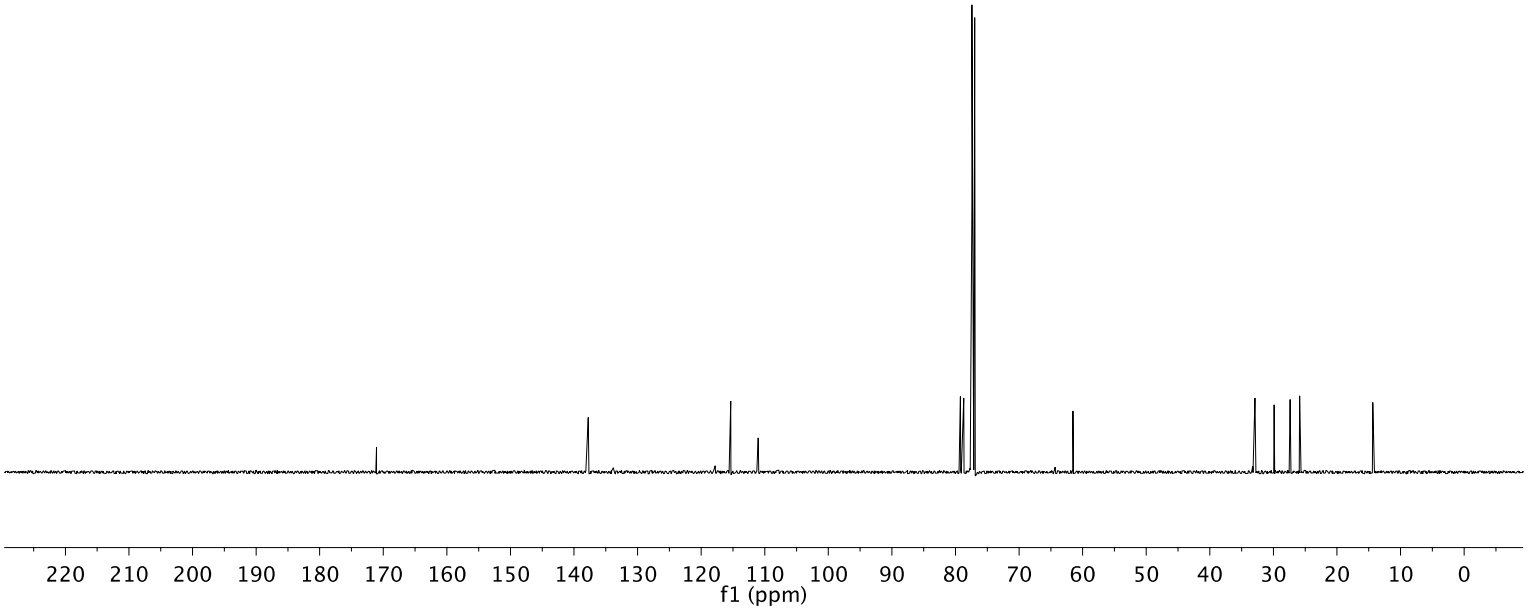
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
O
O
EtO2C

31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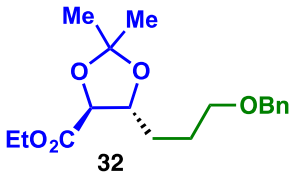
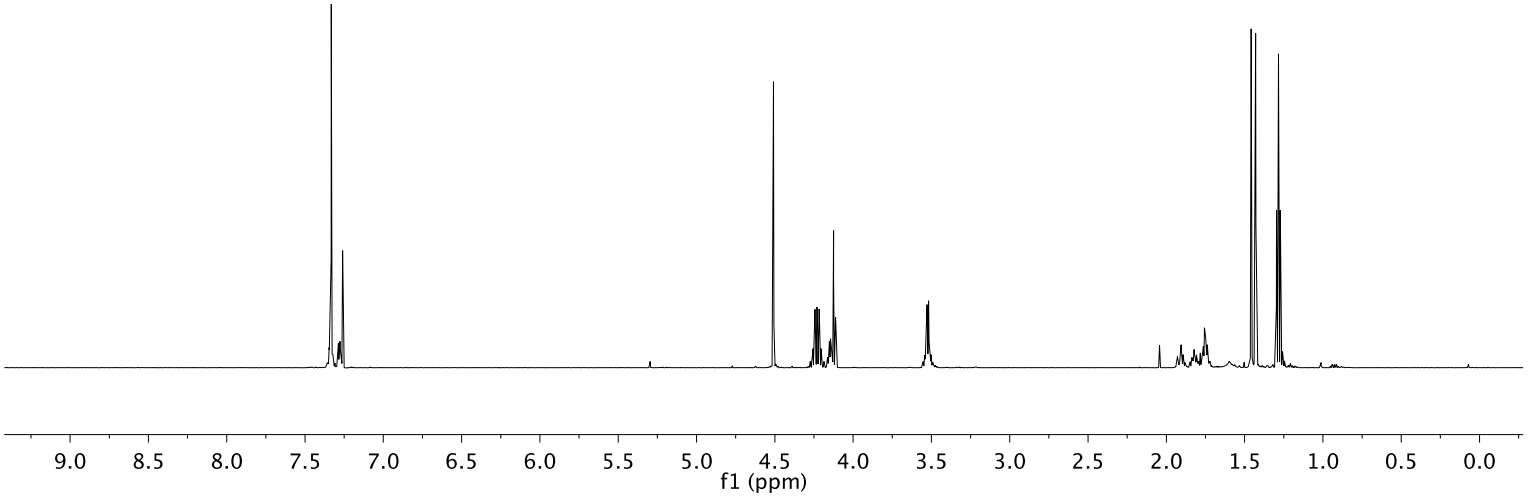
f1 (ppm)


Me
Me
O
O
OBn
EtO2C

32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8.0
7.5
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6.5
6.0
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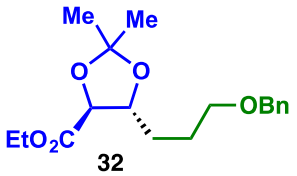
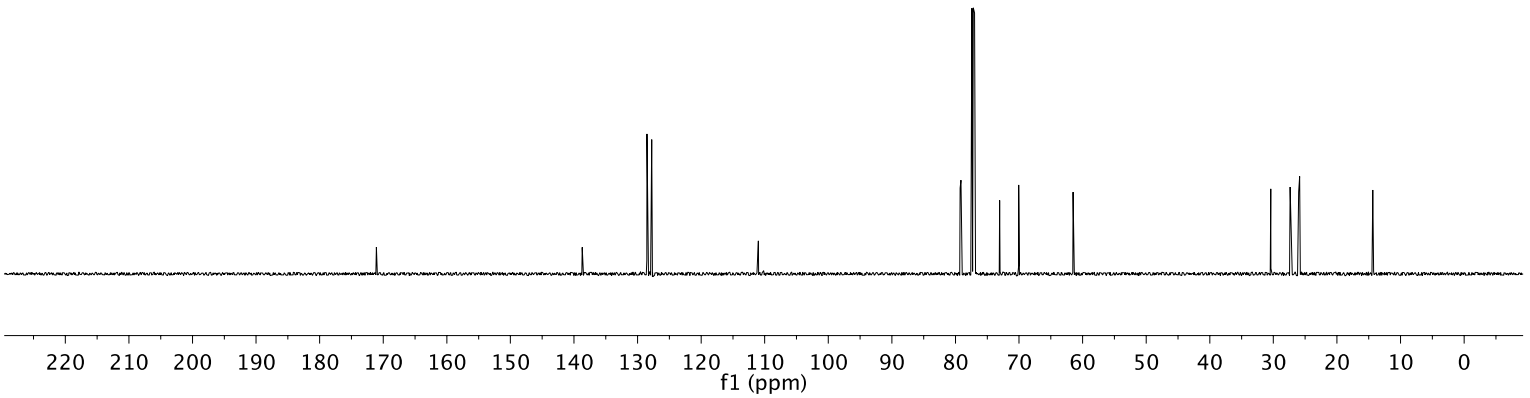
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
Me
O
O
OBn
EtO2C

32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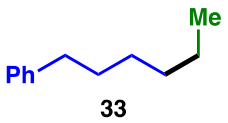
f1 (ppm)



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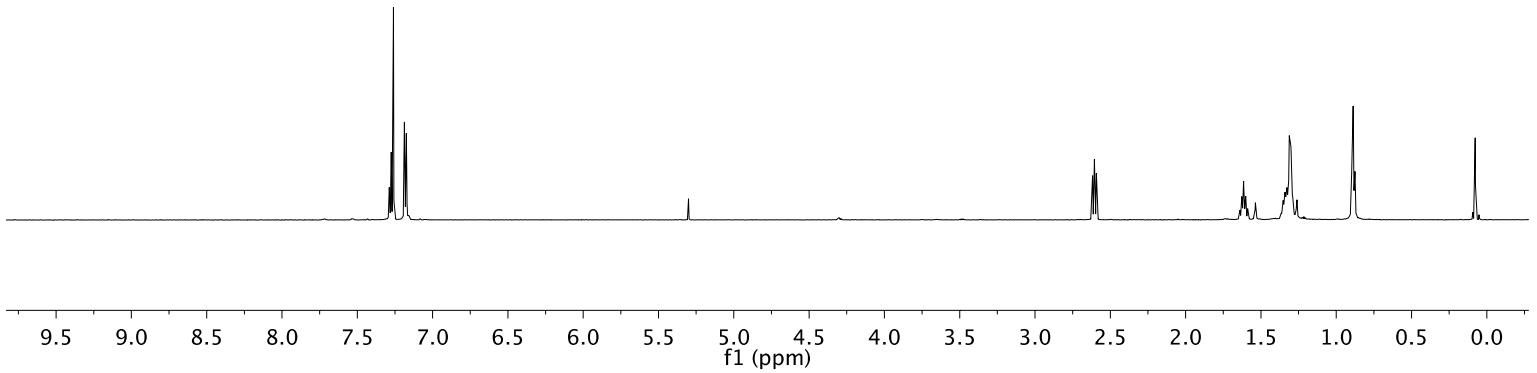
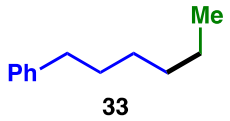
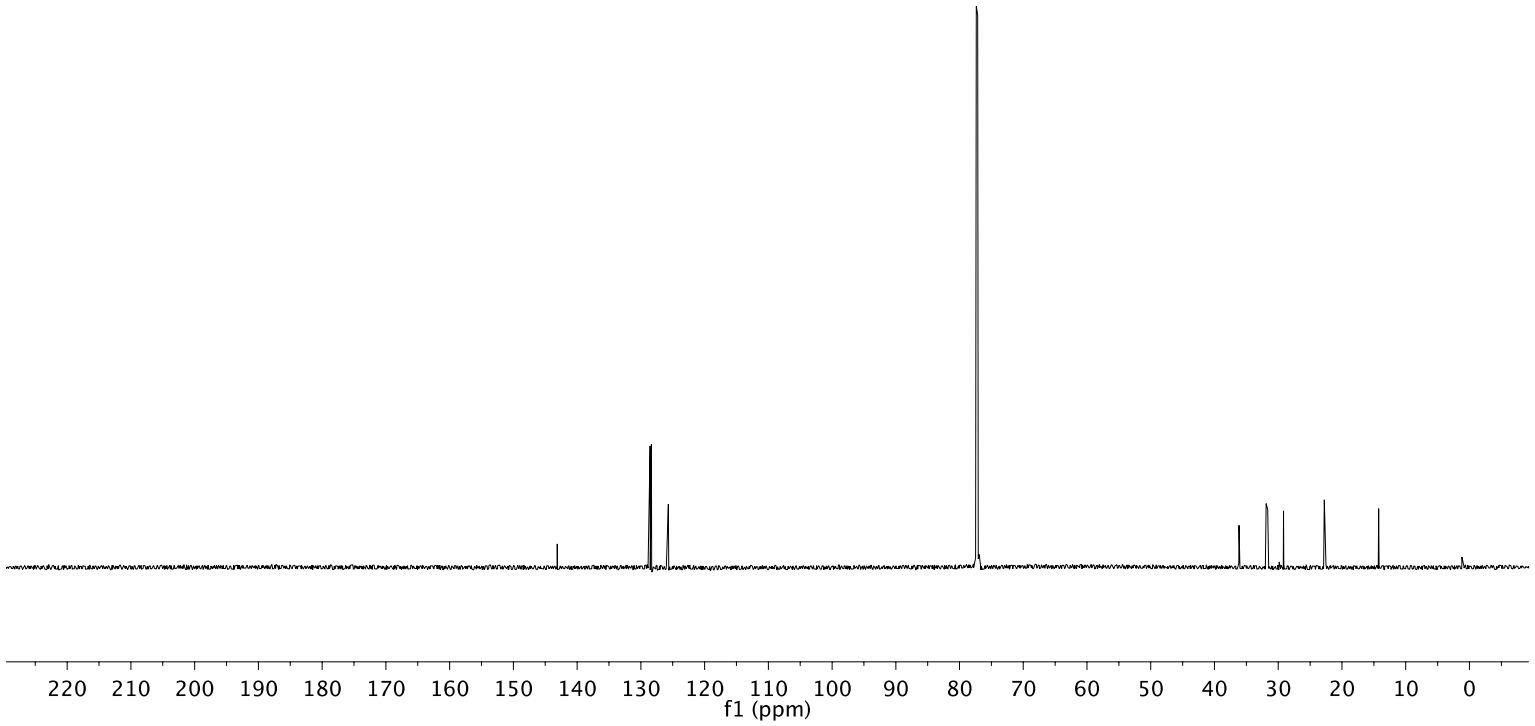



Me
Ph

33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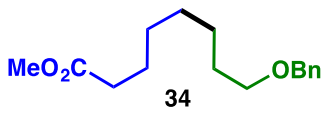
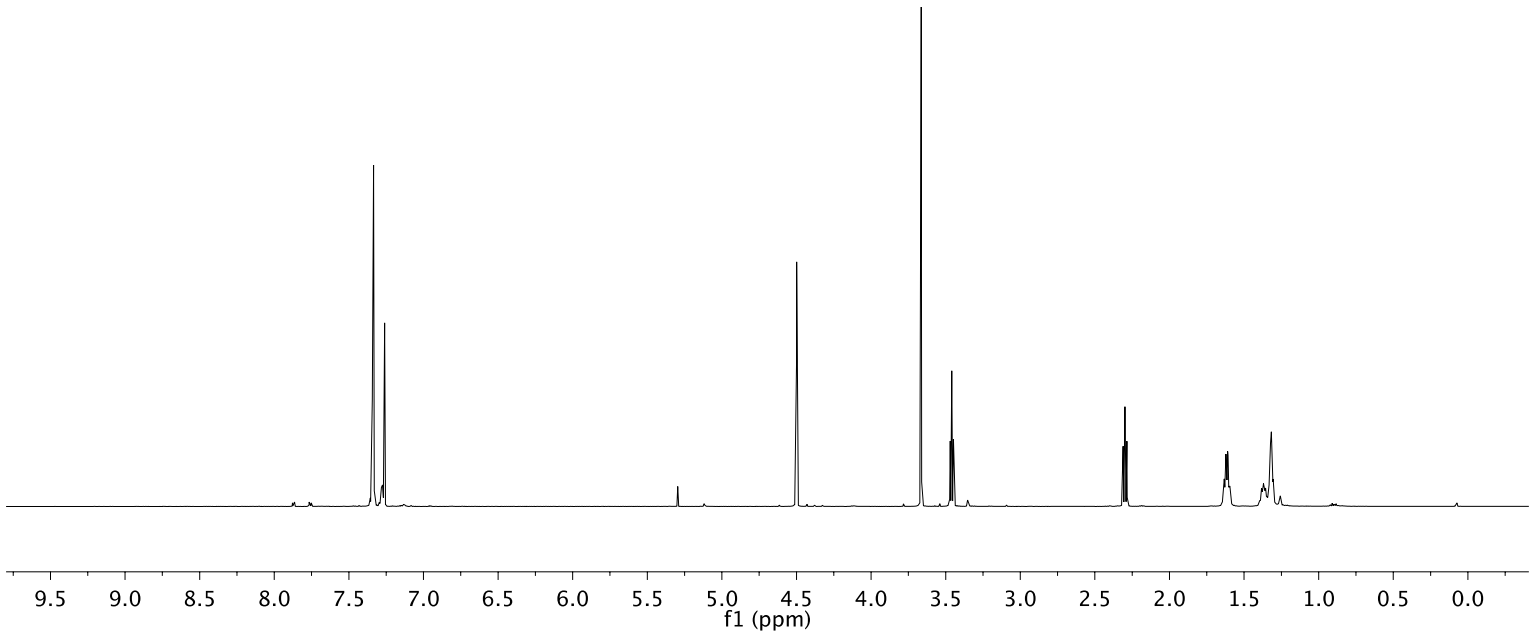
f1 (ppm)


MeO2C
OBn

34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7.5
7.0
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6.0
5.5
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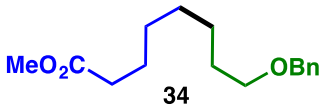
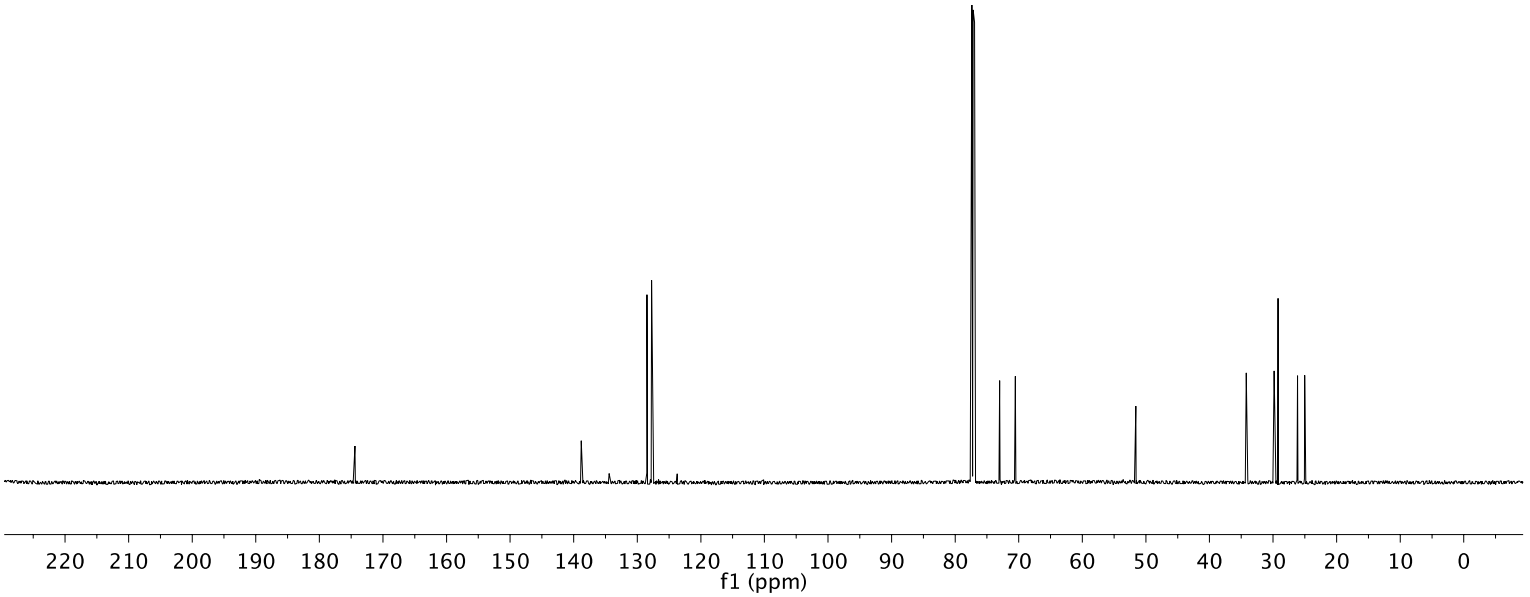
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


MeO2C
OBn

34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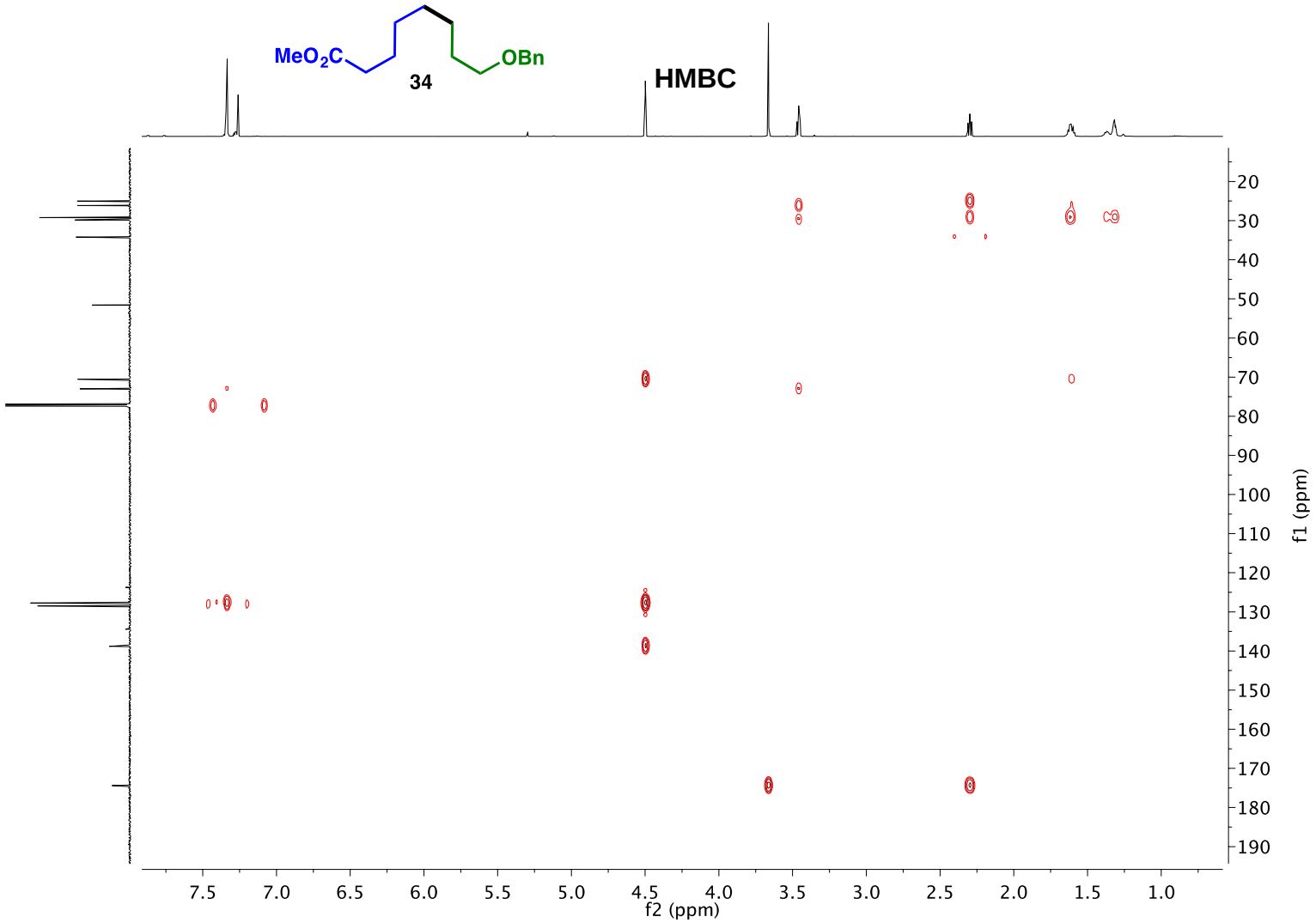
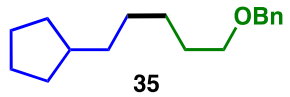
f1 (ppm)


MeO2C
OBn
34
HMBC
f2 (ppm)
f1 (ppm)



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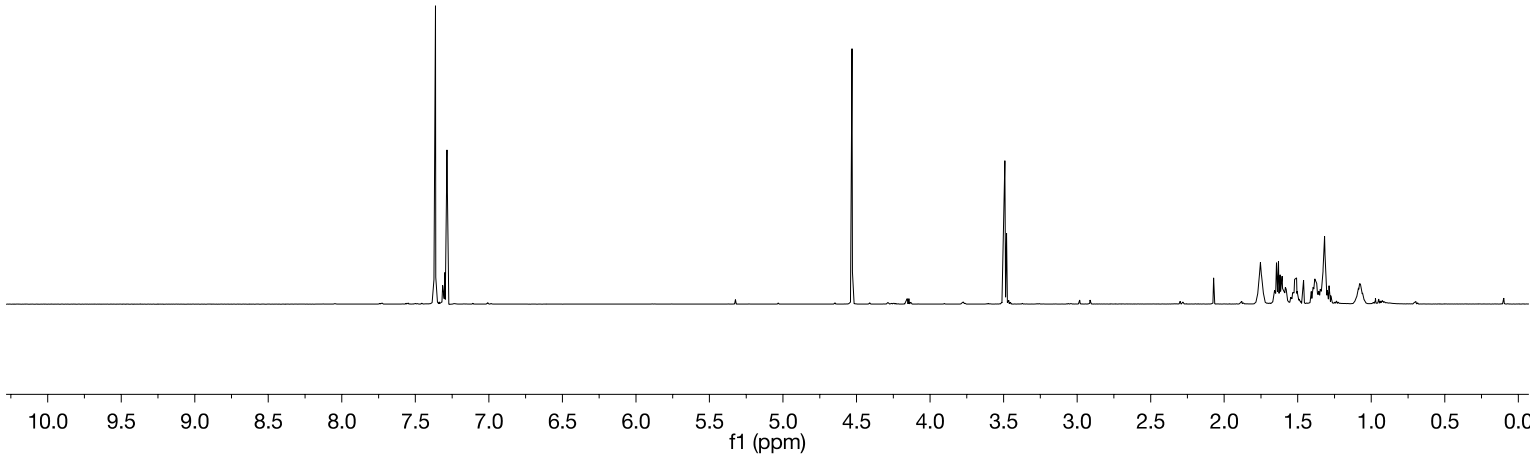
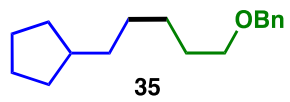
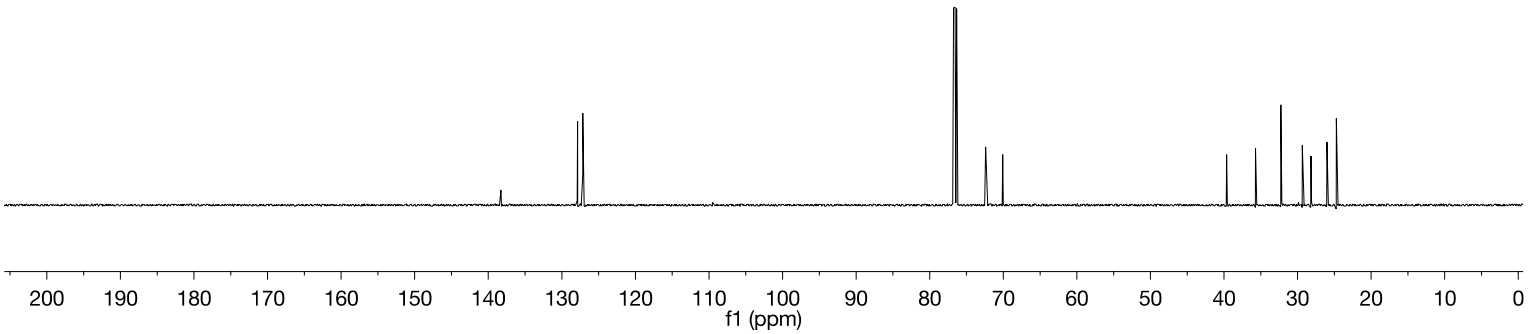



OBn

35


200
190
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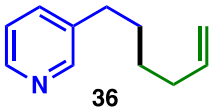
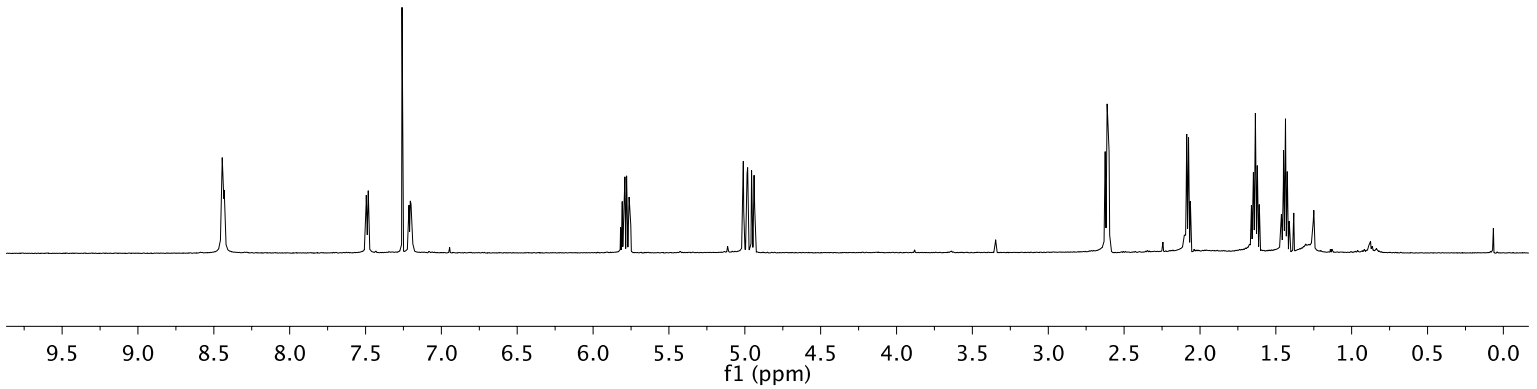
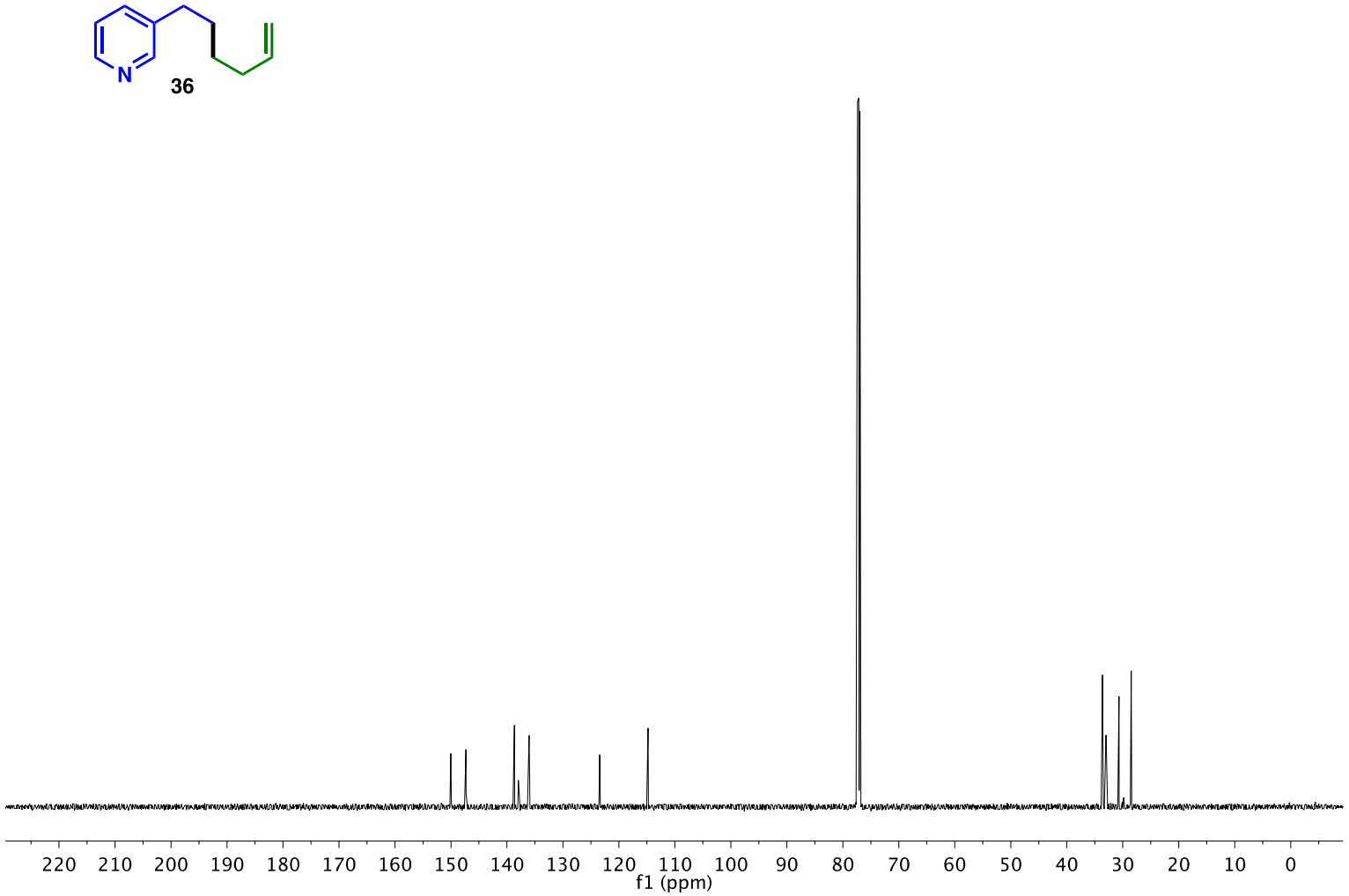
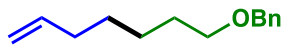
50
40
30
20
10
0
f1 (ppm)



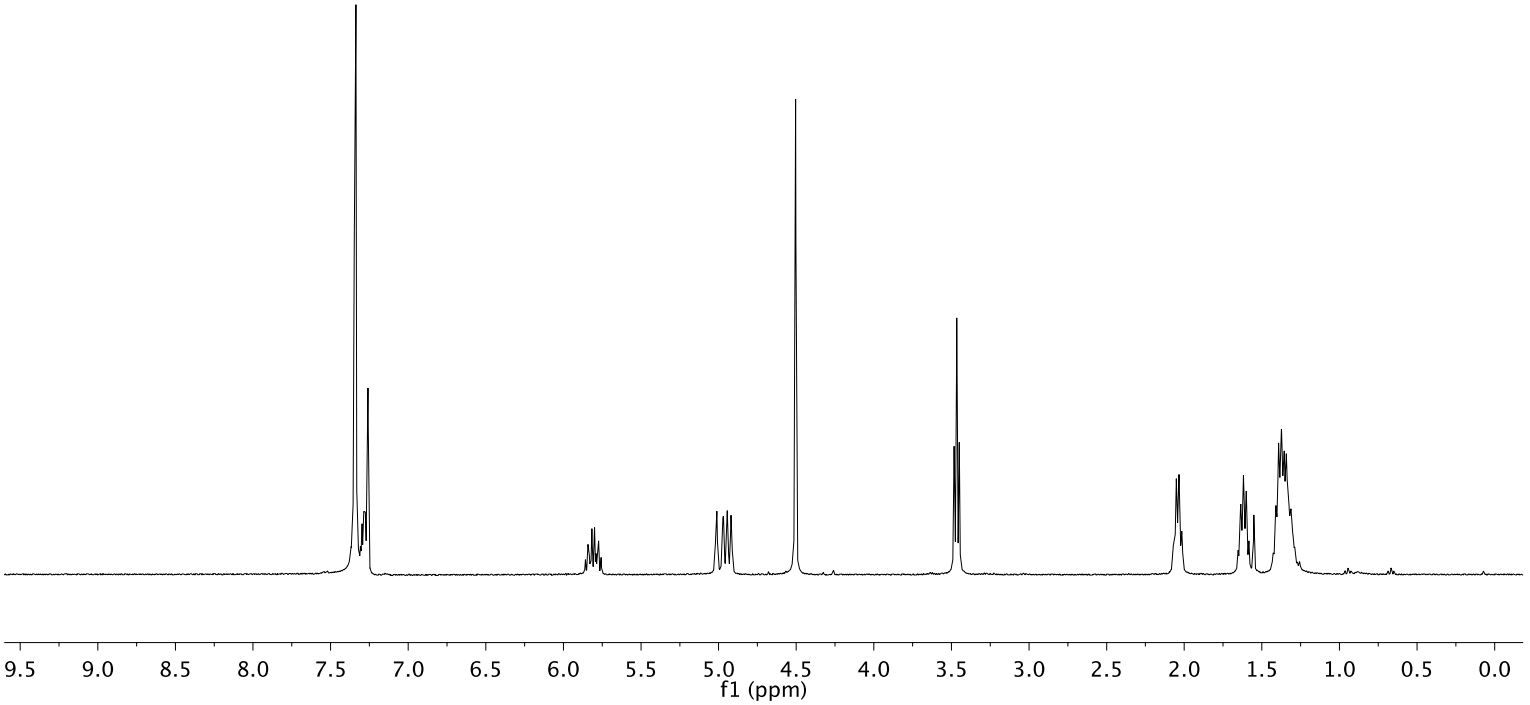
36




N
36
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

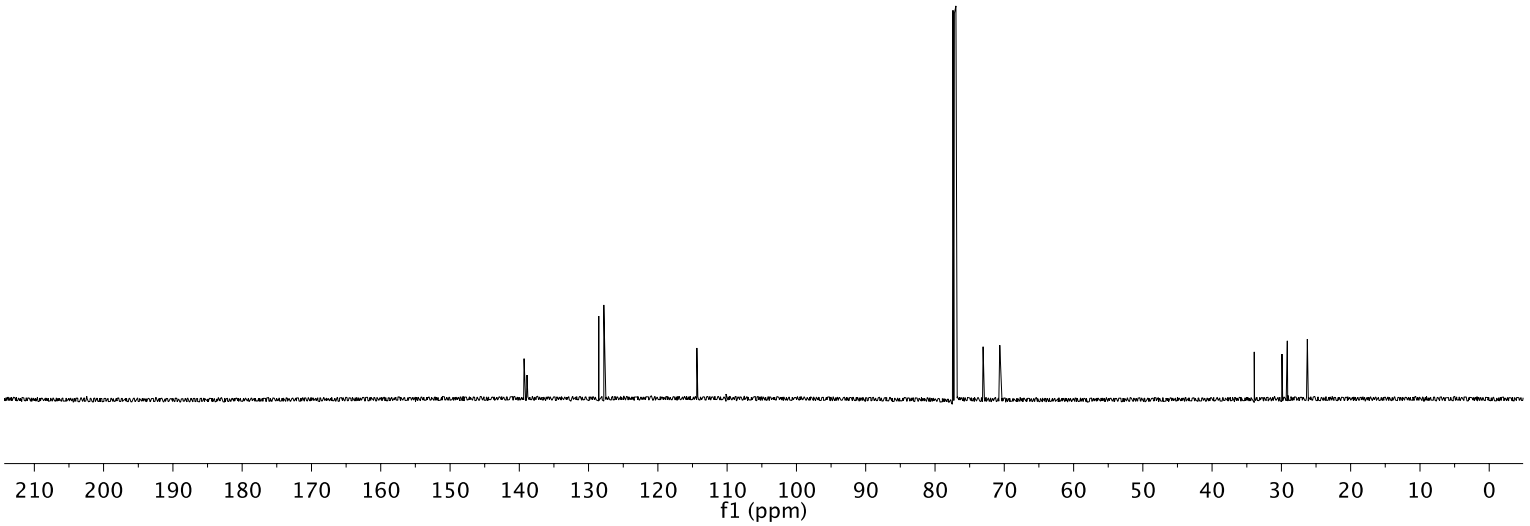


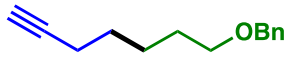
37




OBn

37


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



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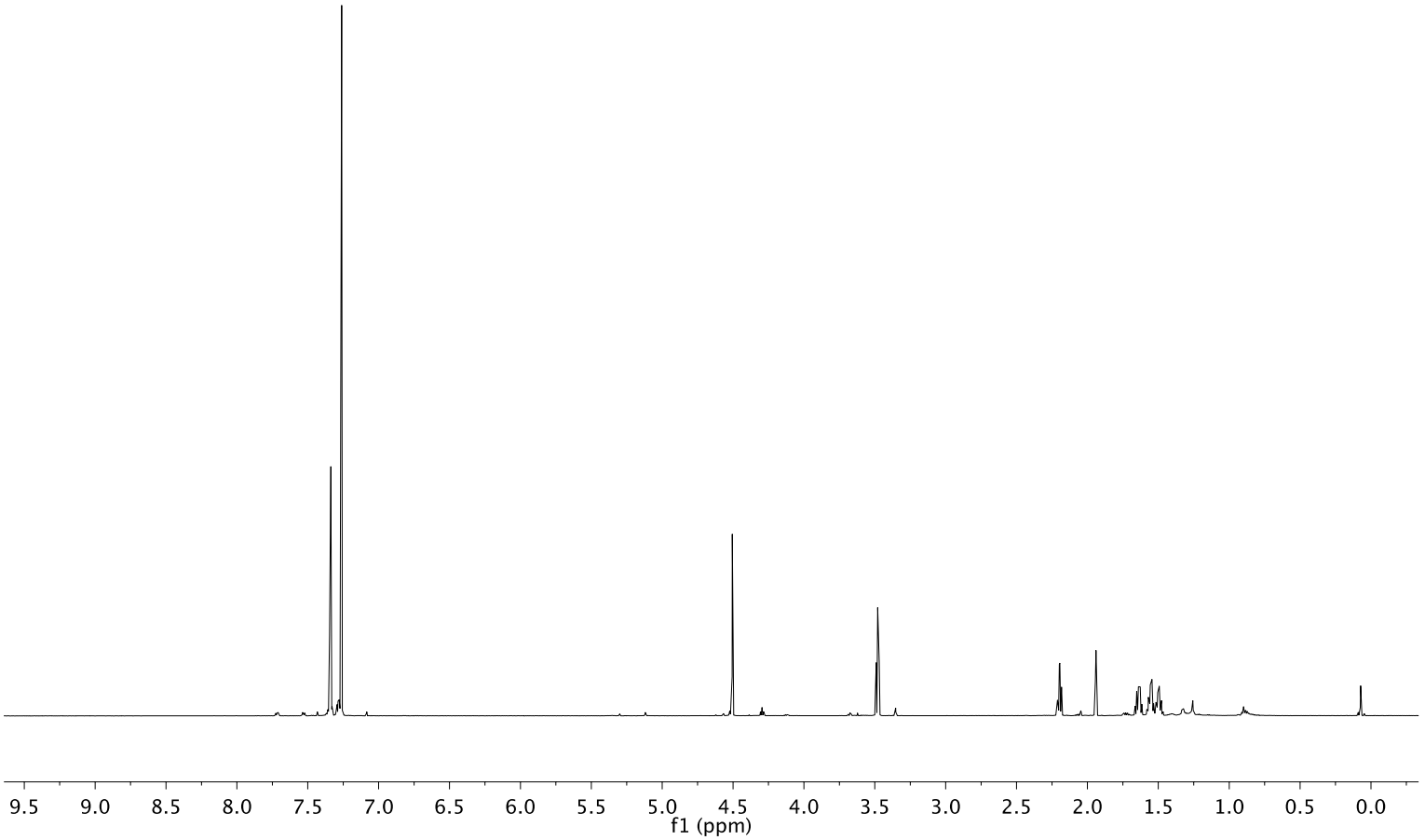
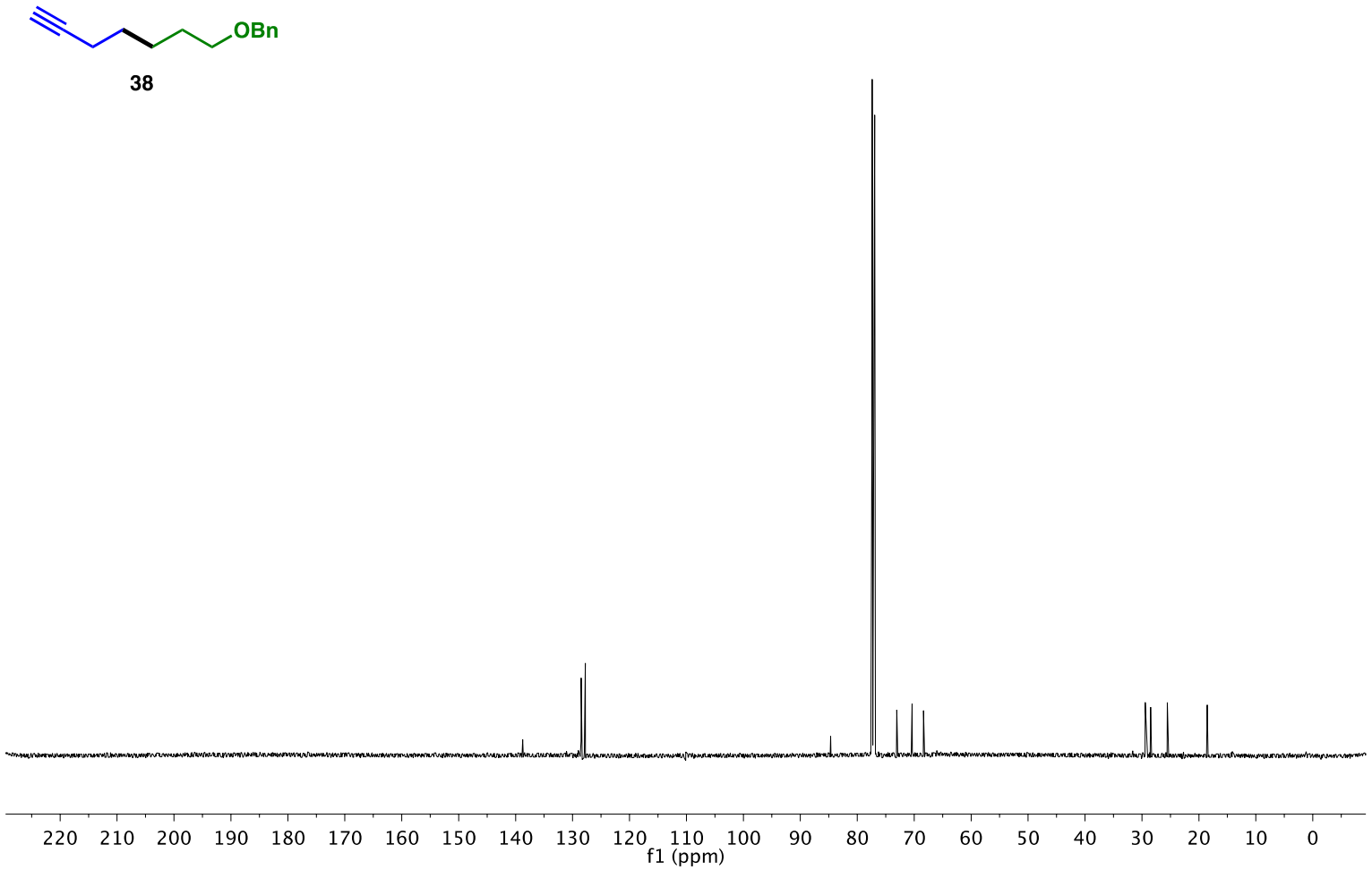
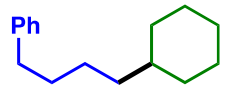
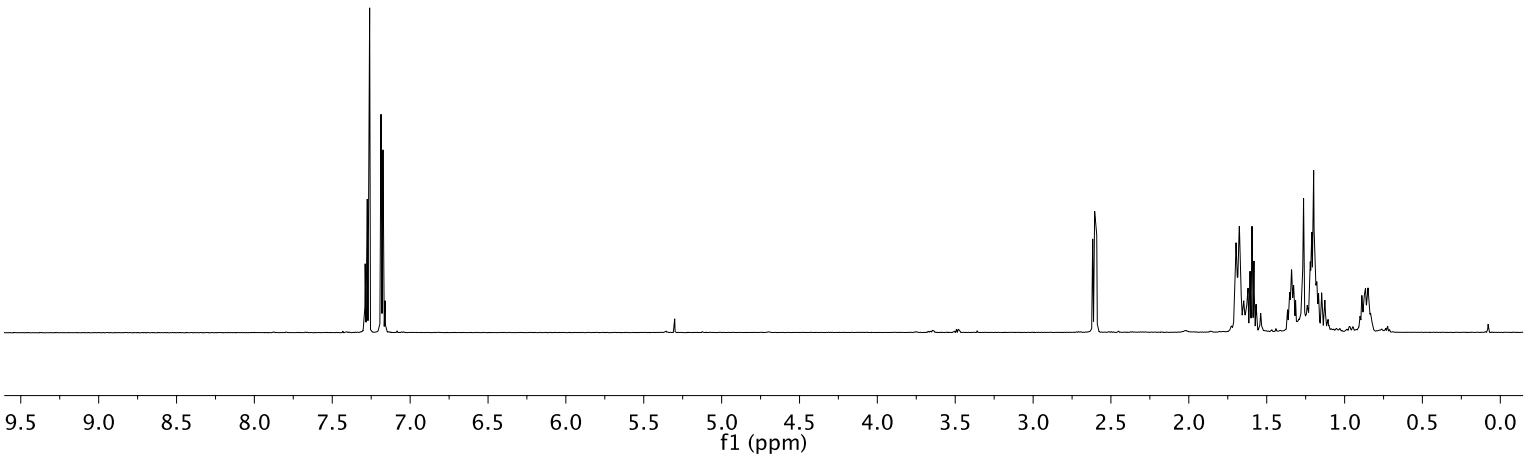
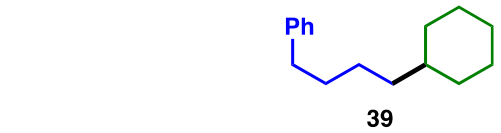



OBn
38
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

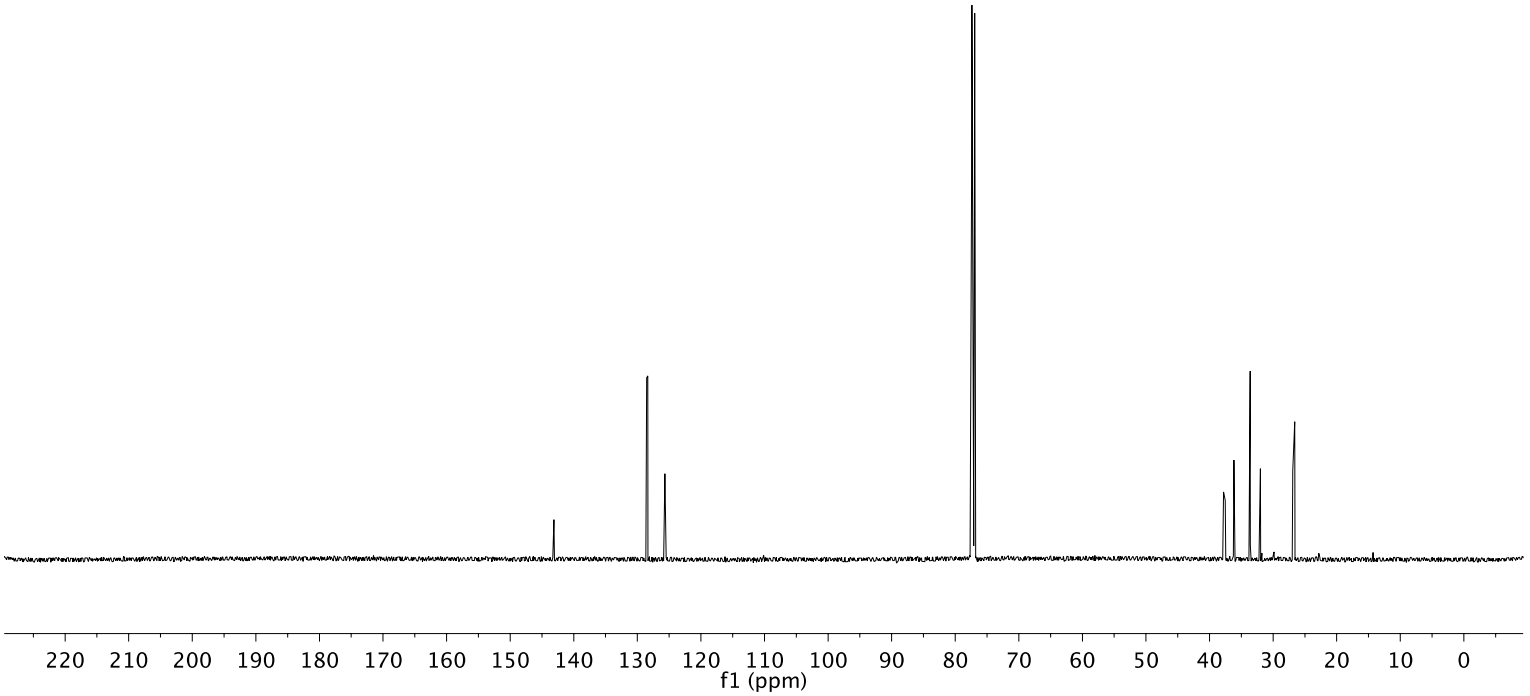


39




Ph

39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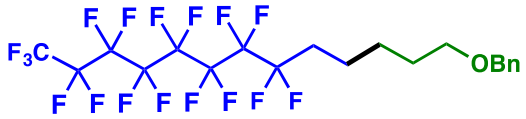
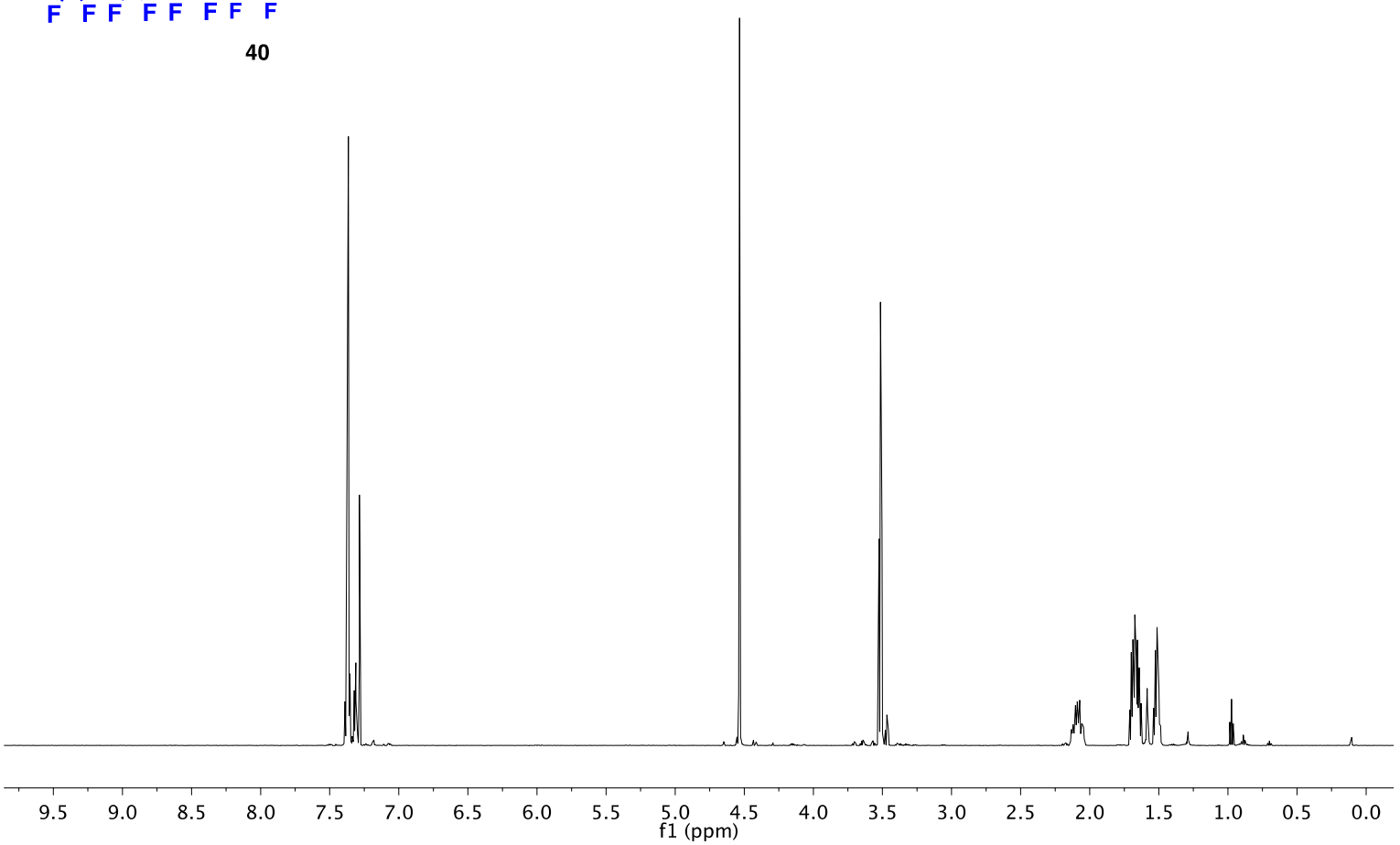
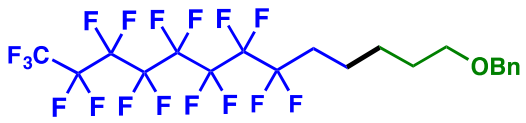
f1 (ppm)

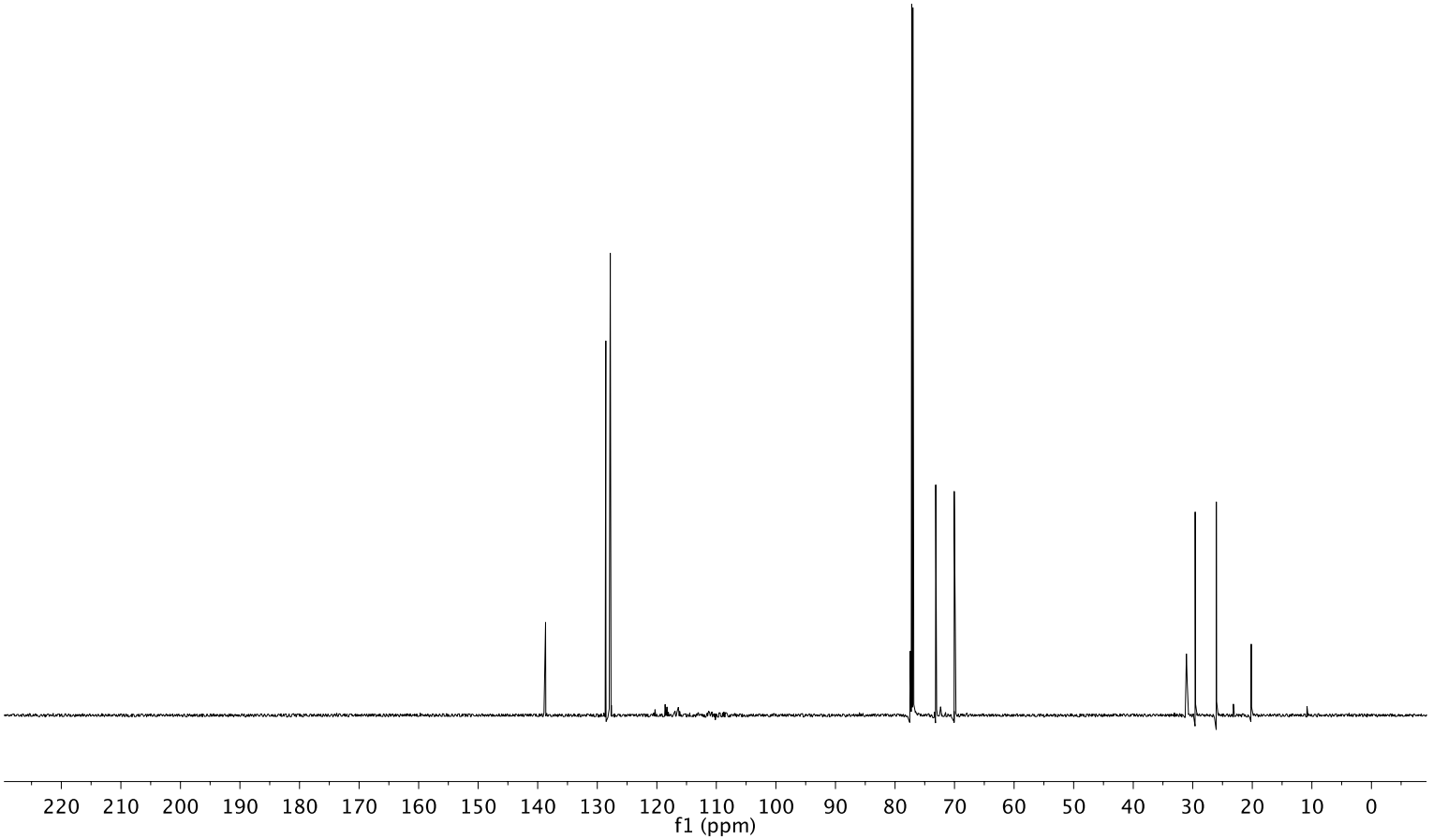

F F F F F F
F3C
F F F F F F F F
OBn

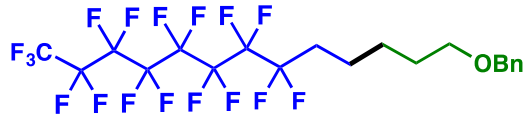
40


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

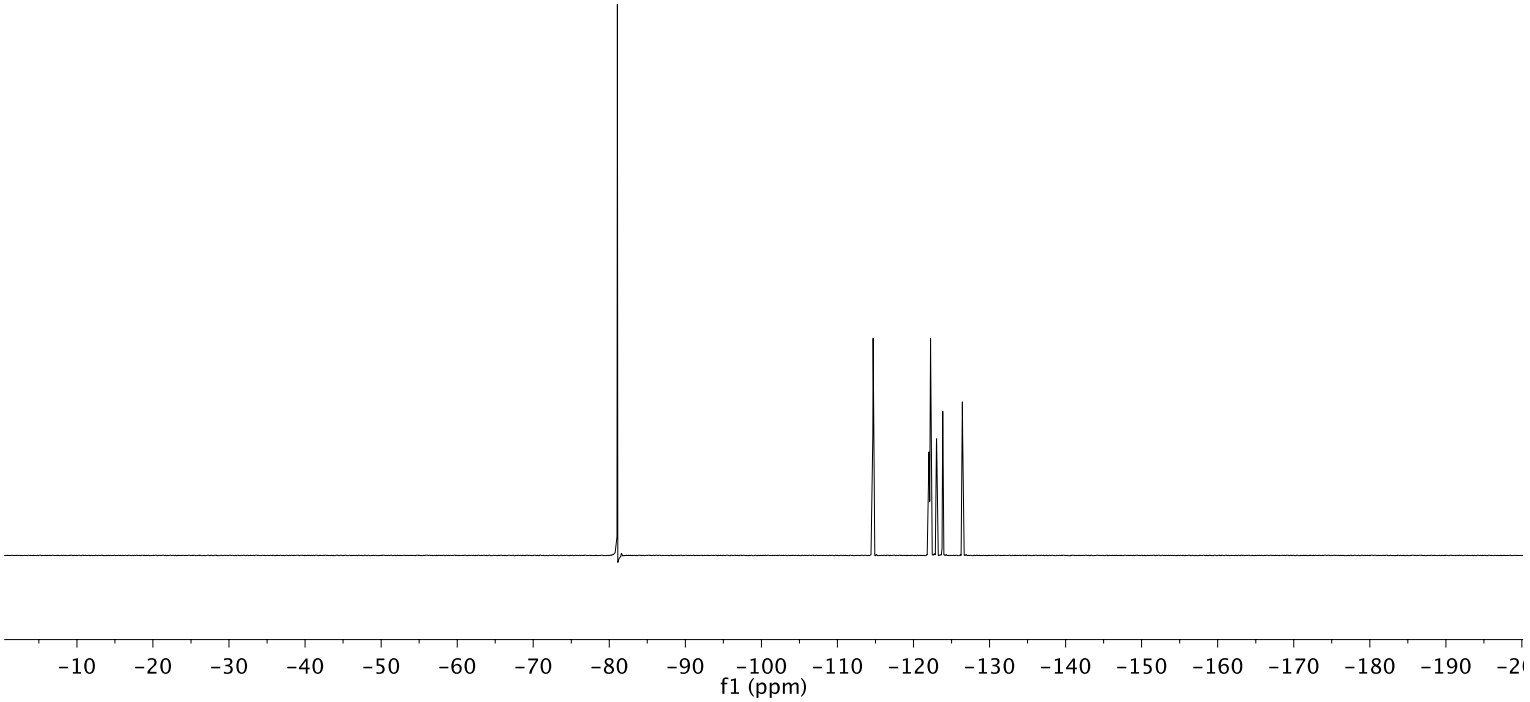

F F F F F F
F3C
OBn
F F F F F F F F

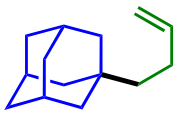
40


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


F F F F F F
F3C
OBn
F F F F F F F F

40


-10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)



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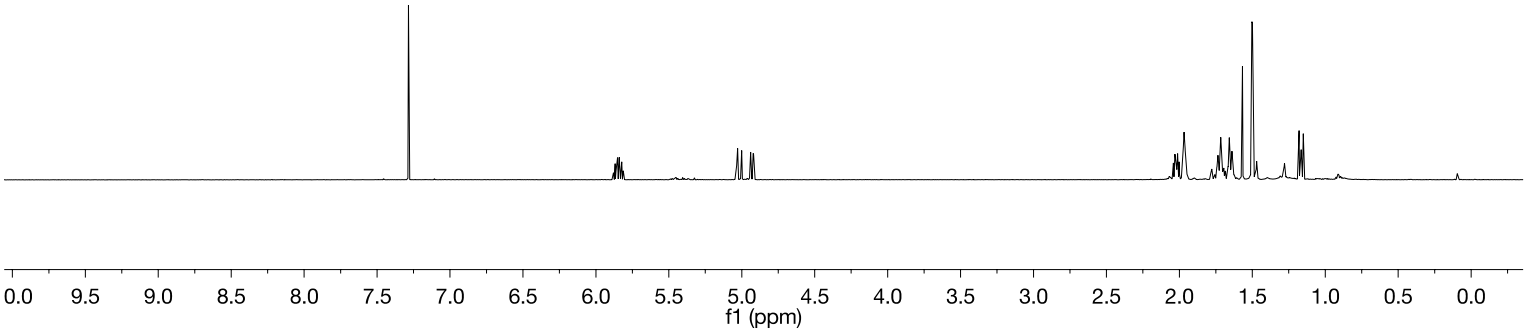

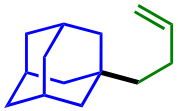

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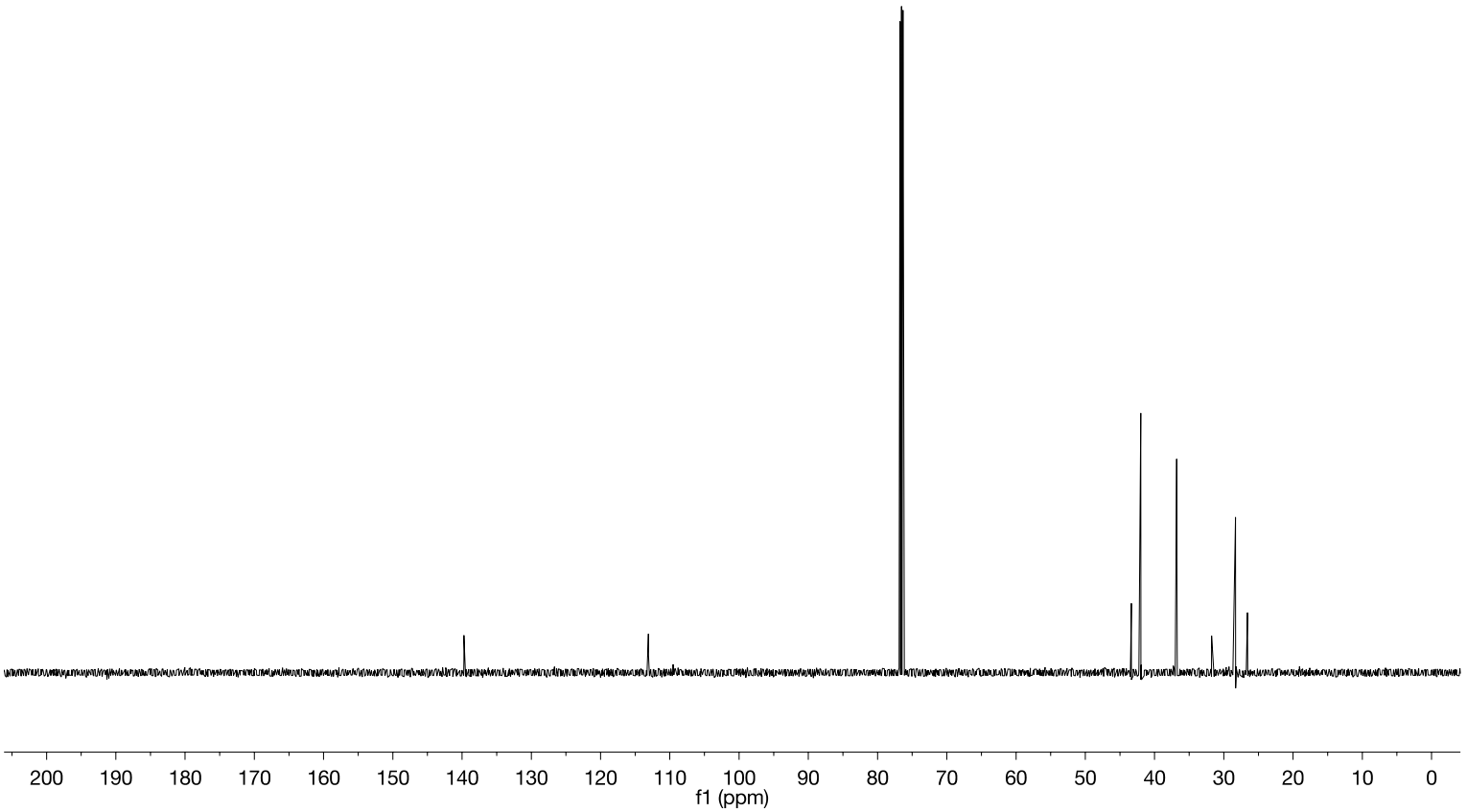
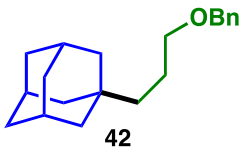
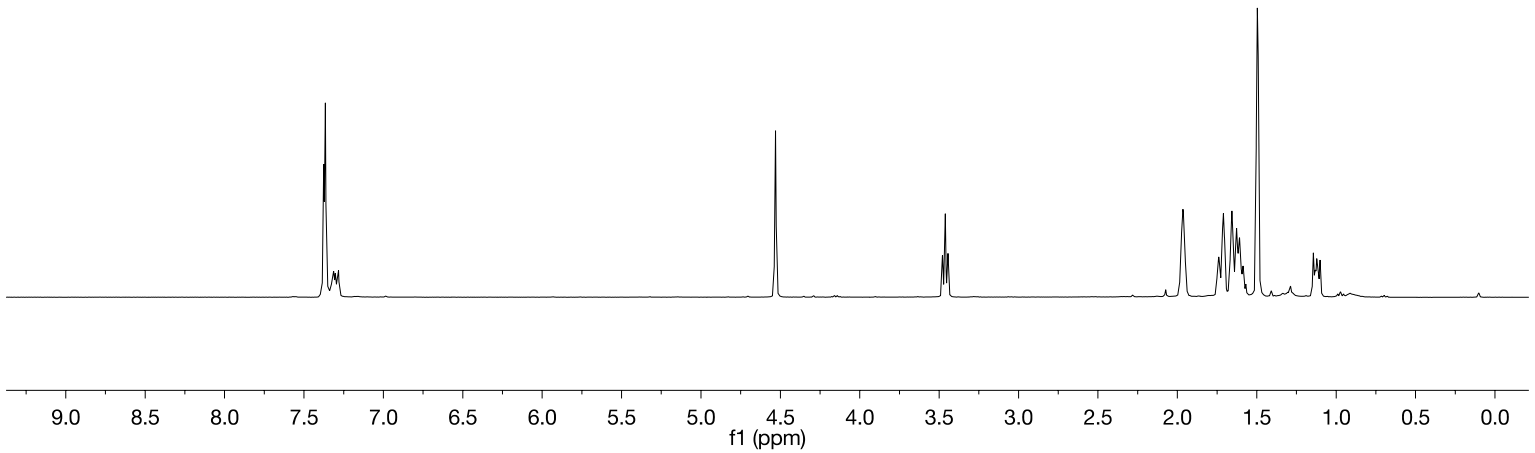
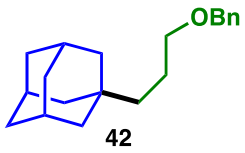

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

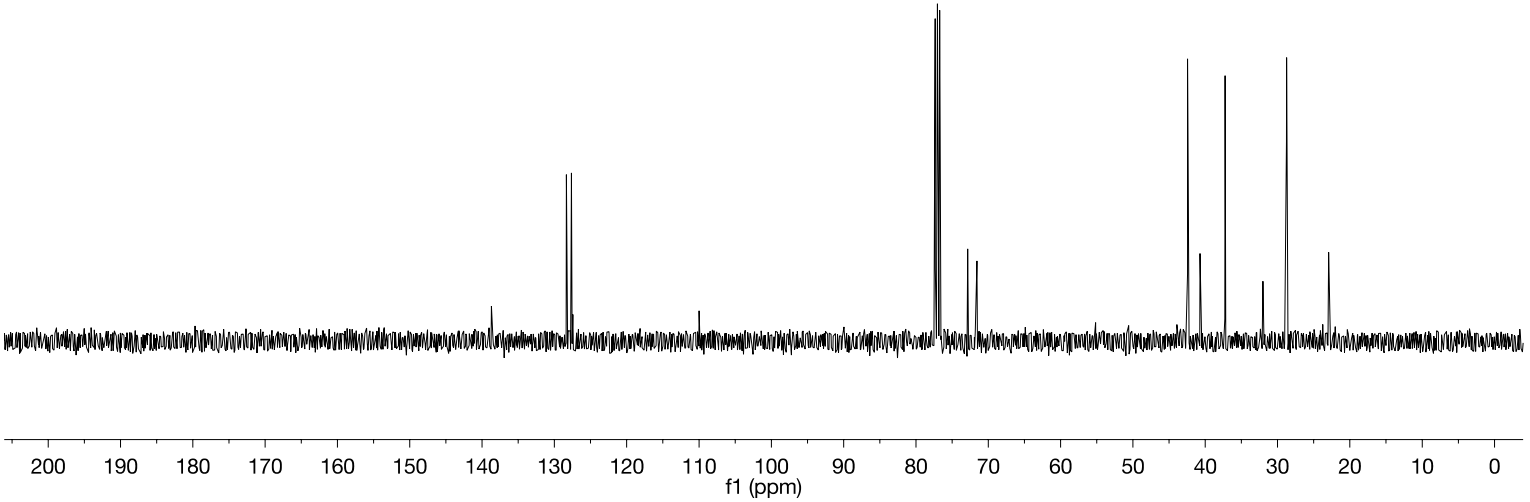


42




OBn

42


200
190
180
170
160
150
140
130
120
110
100
90
80
70
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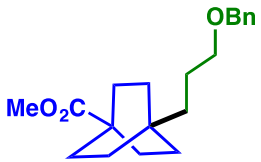
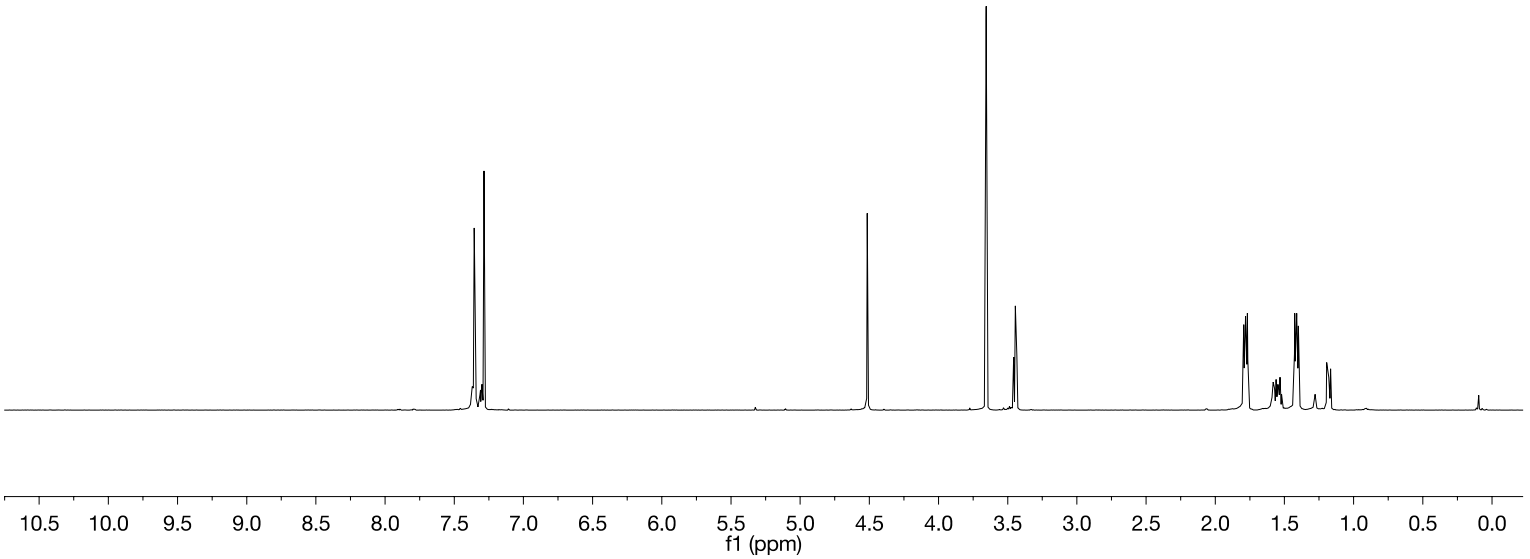
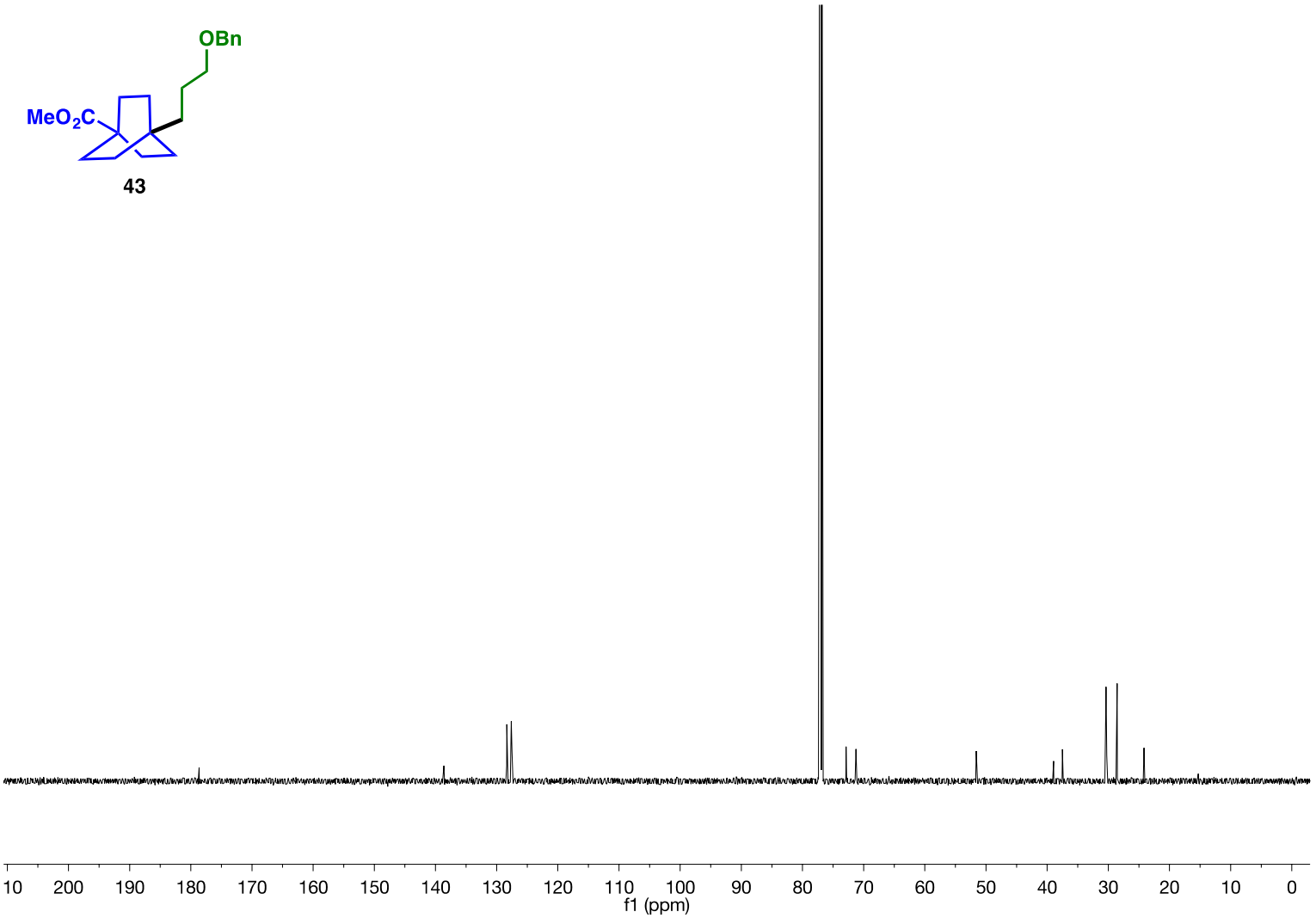
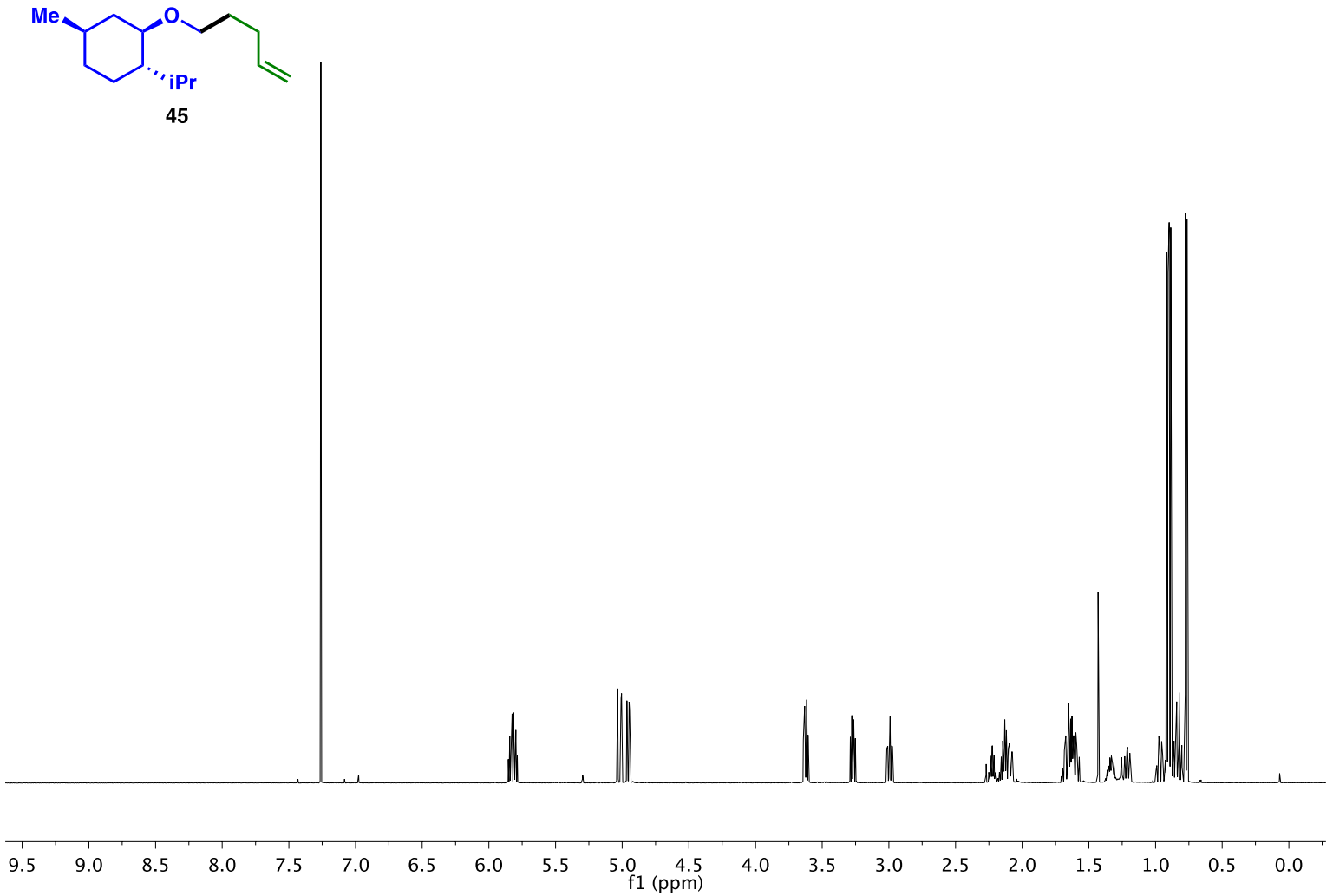
50
40
30
20
10
0
f1 (ppm)

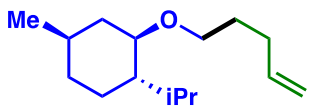

OBn
MeO2C

43

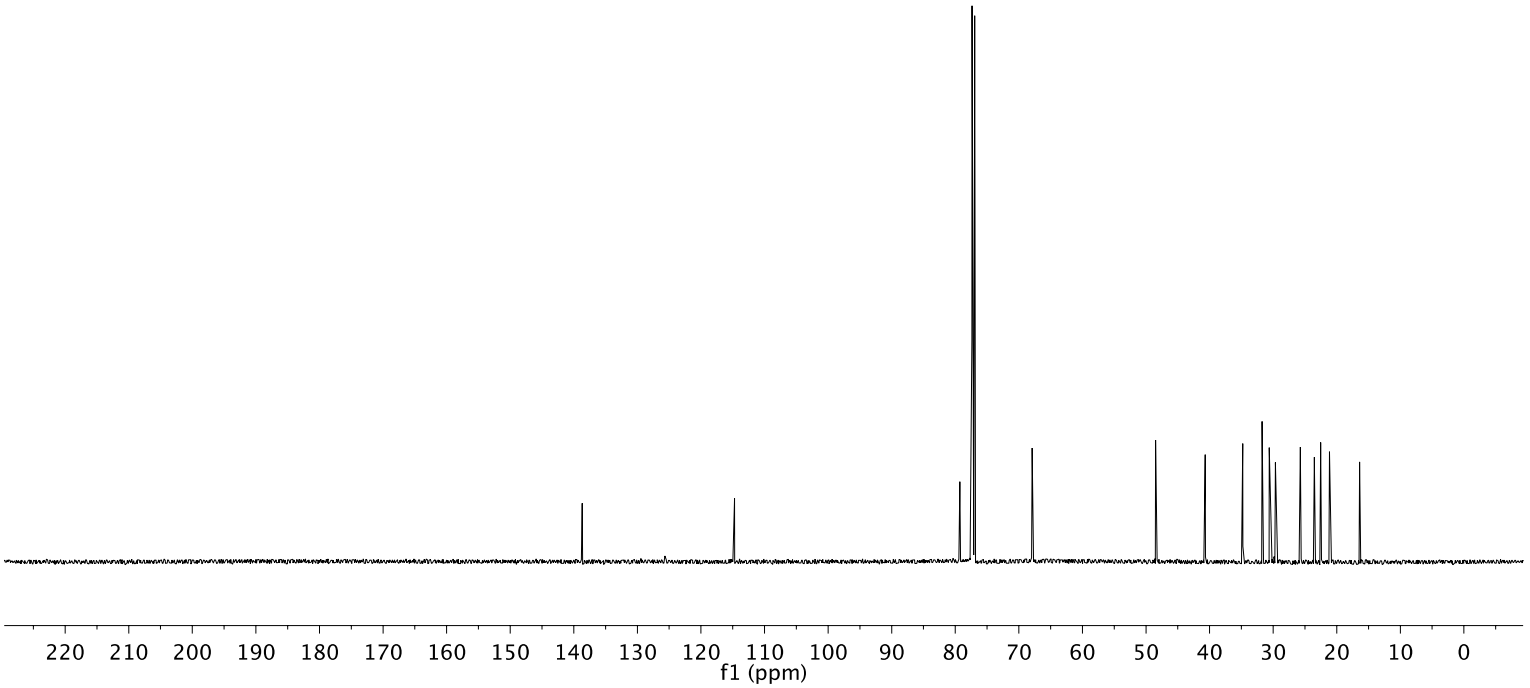

10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


OBn
MeO2C
43
10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
iPr
45
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Me
O
iPr

45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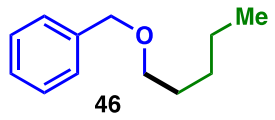
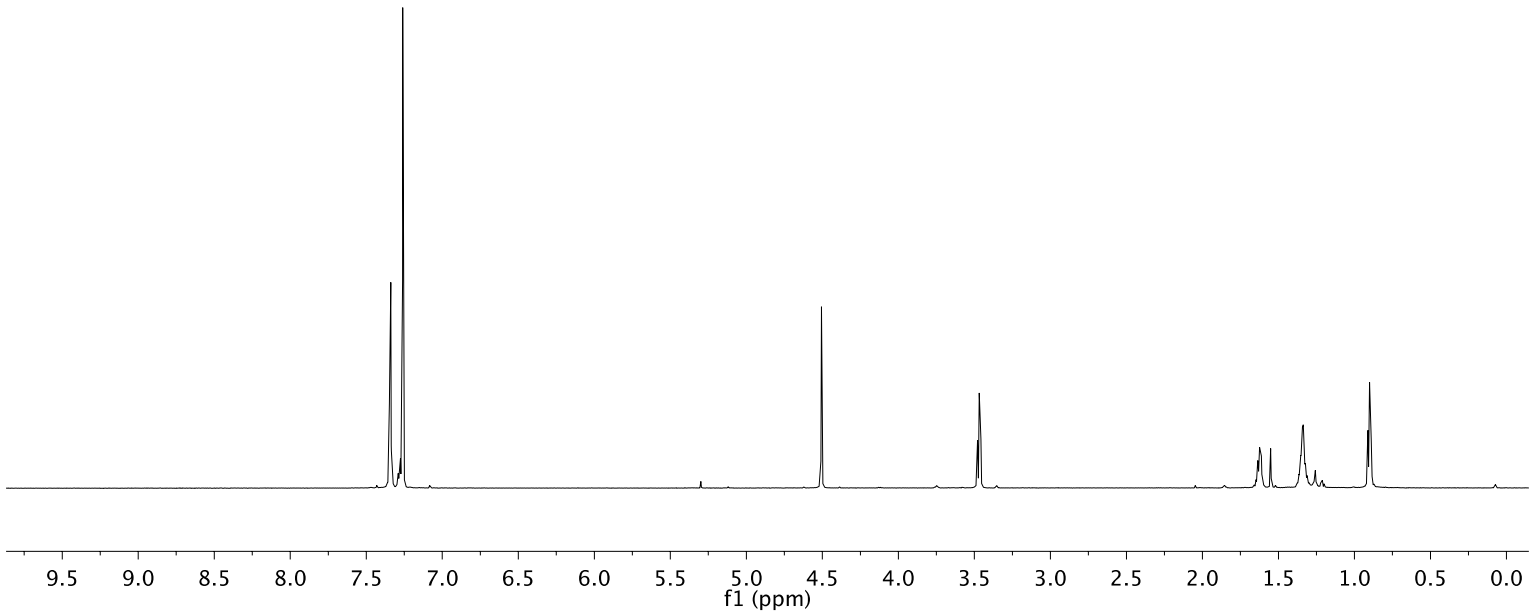
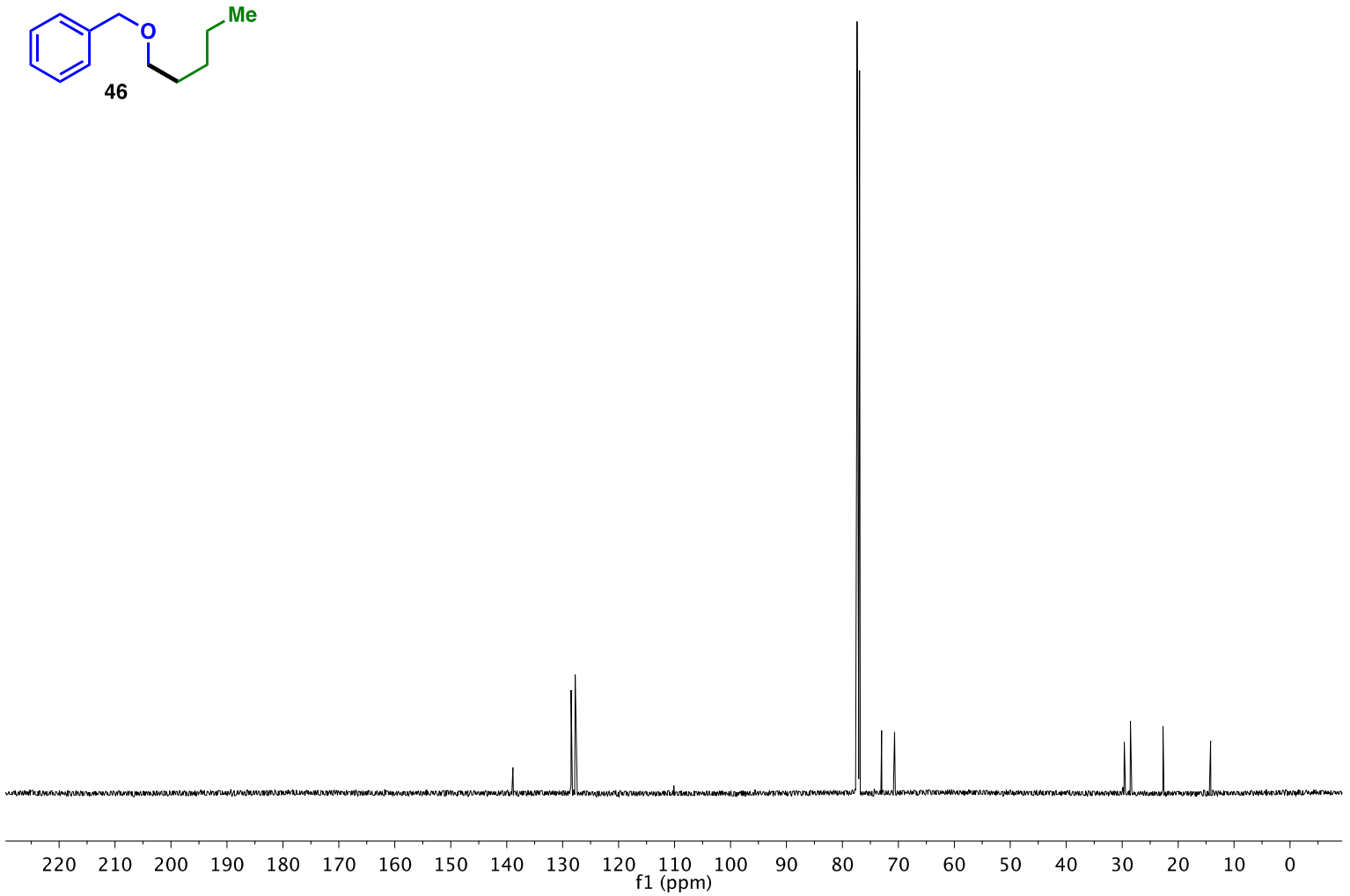
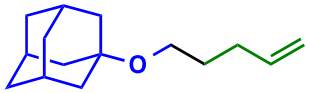
f1 (ppm)



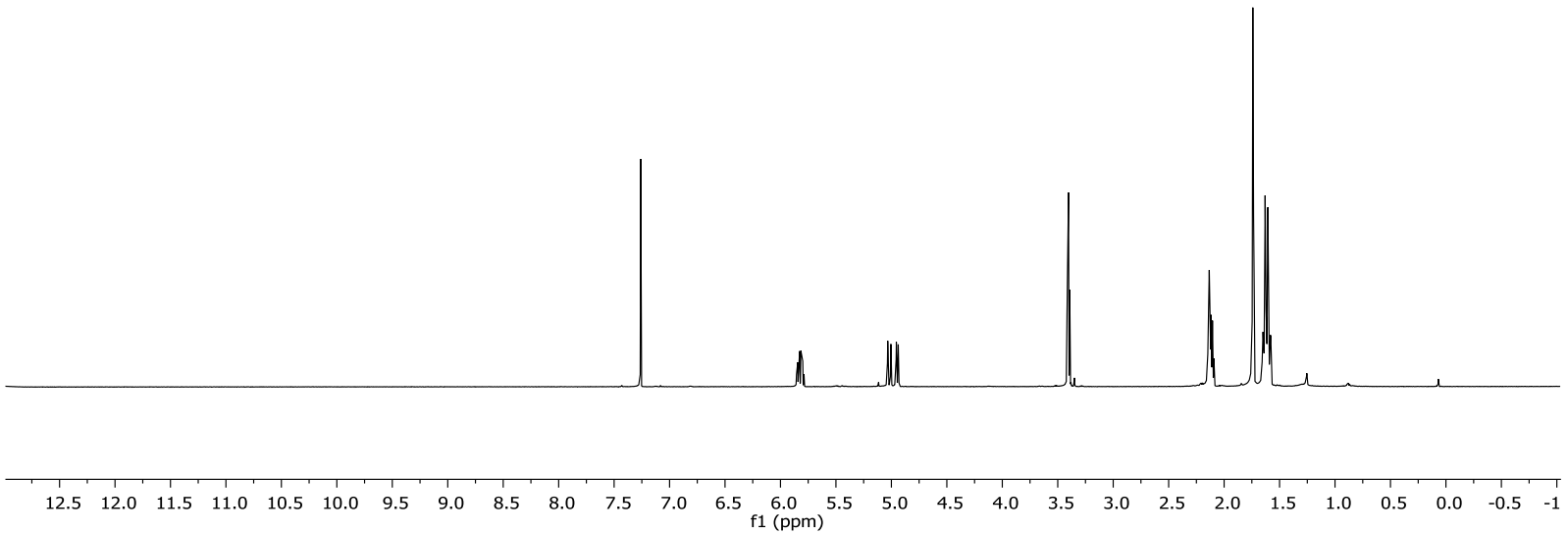
46

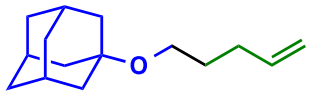



Me
O
46
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

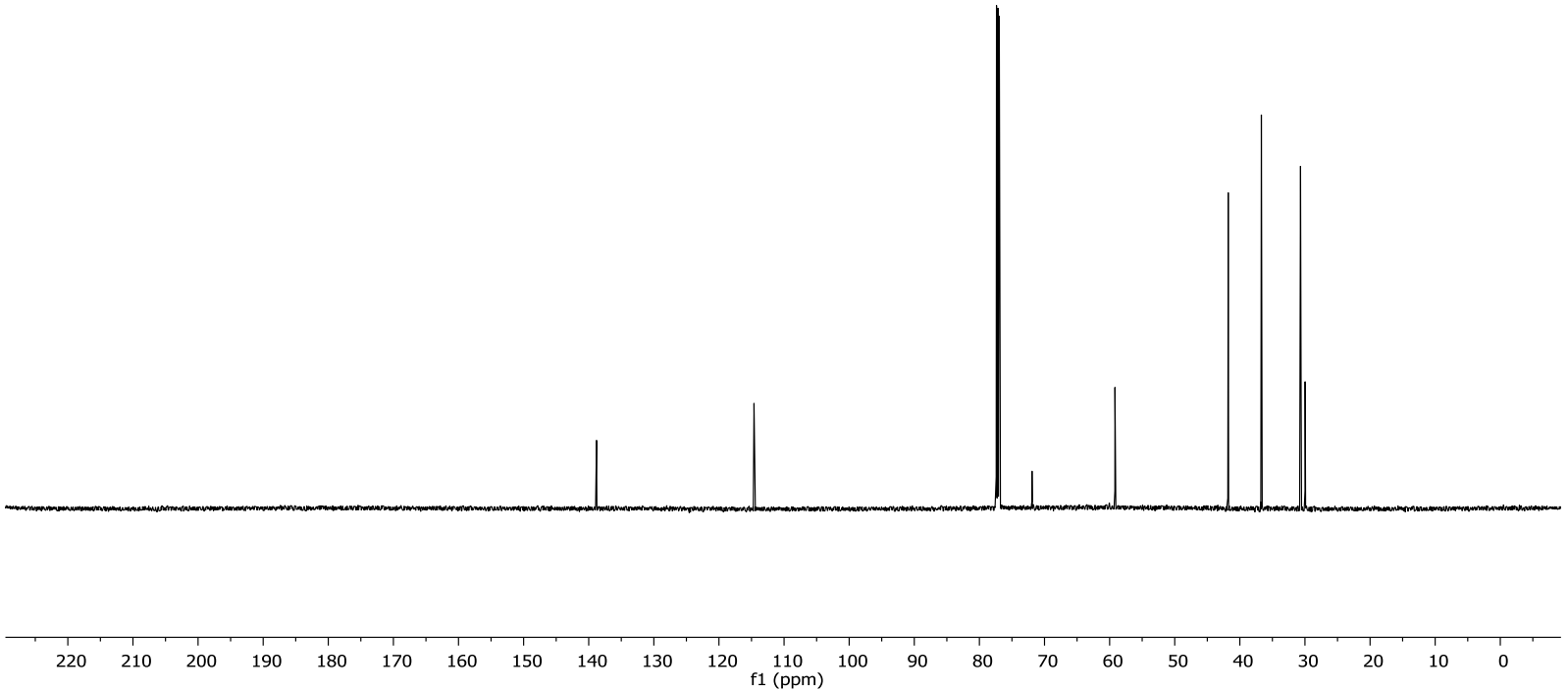

O

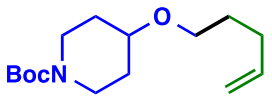
47


12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

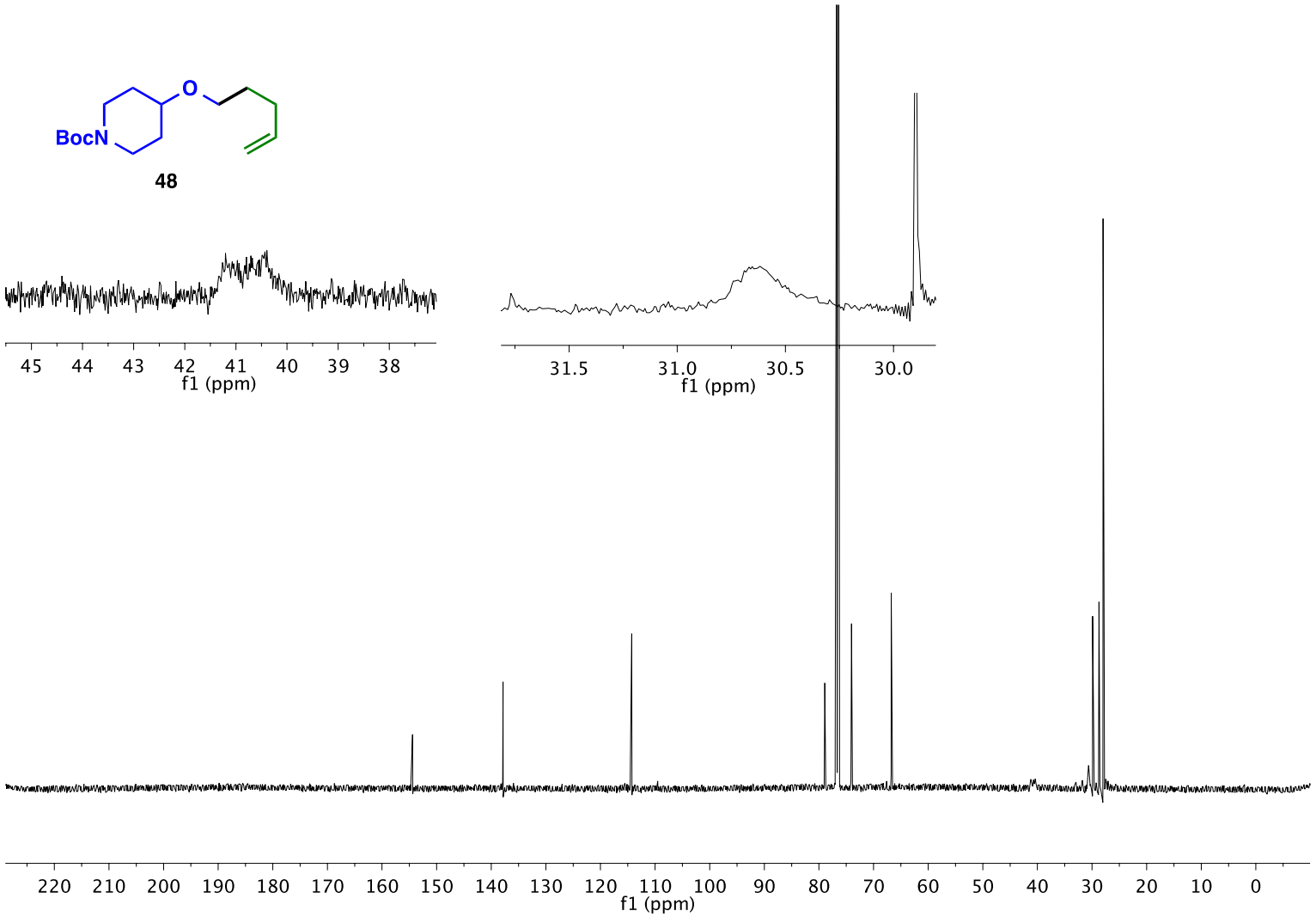

O

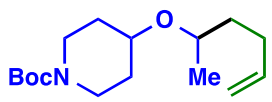
47


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



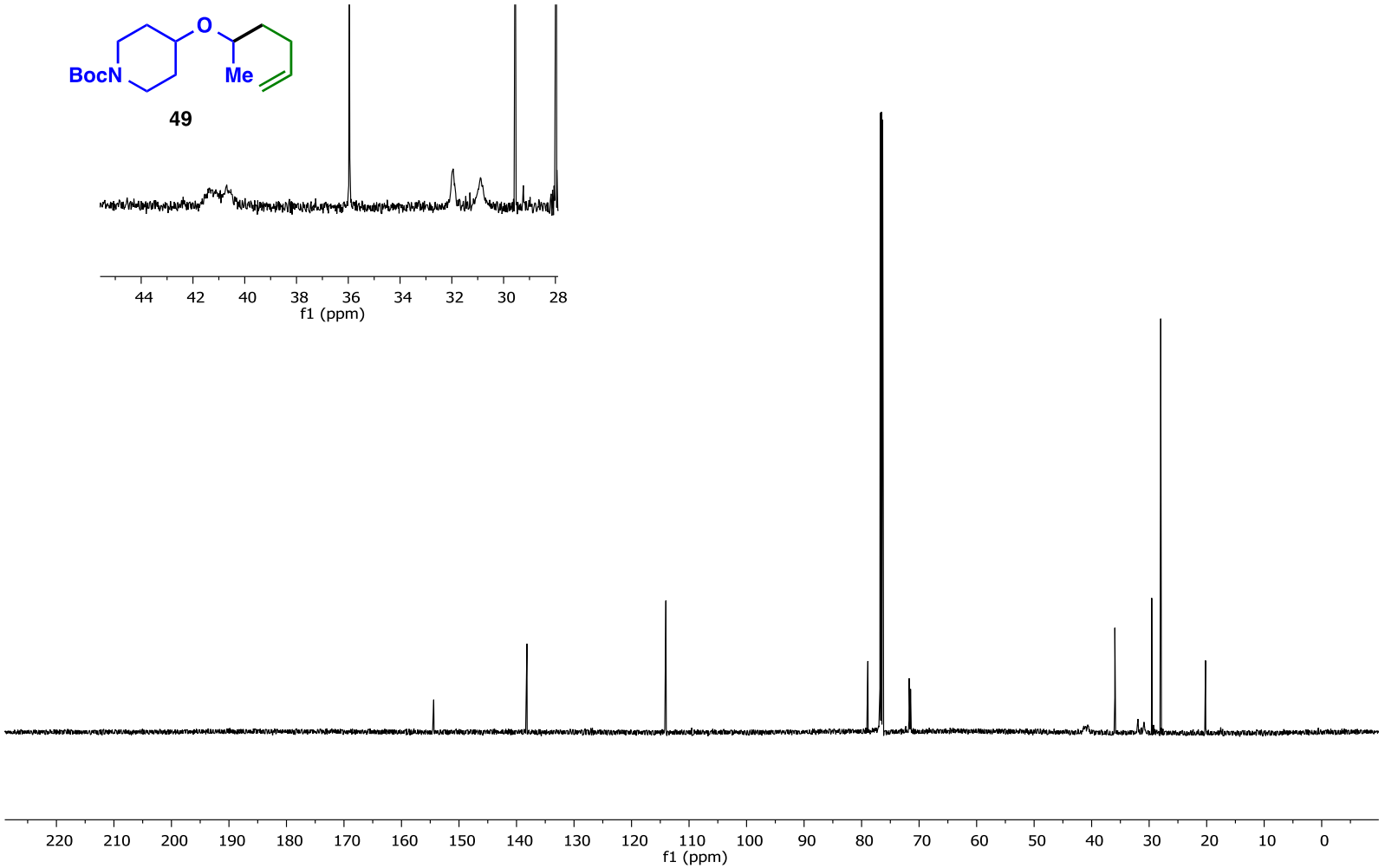
48

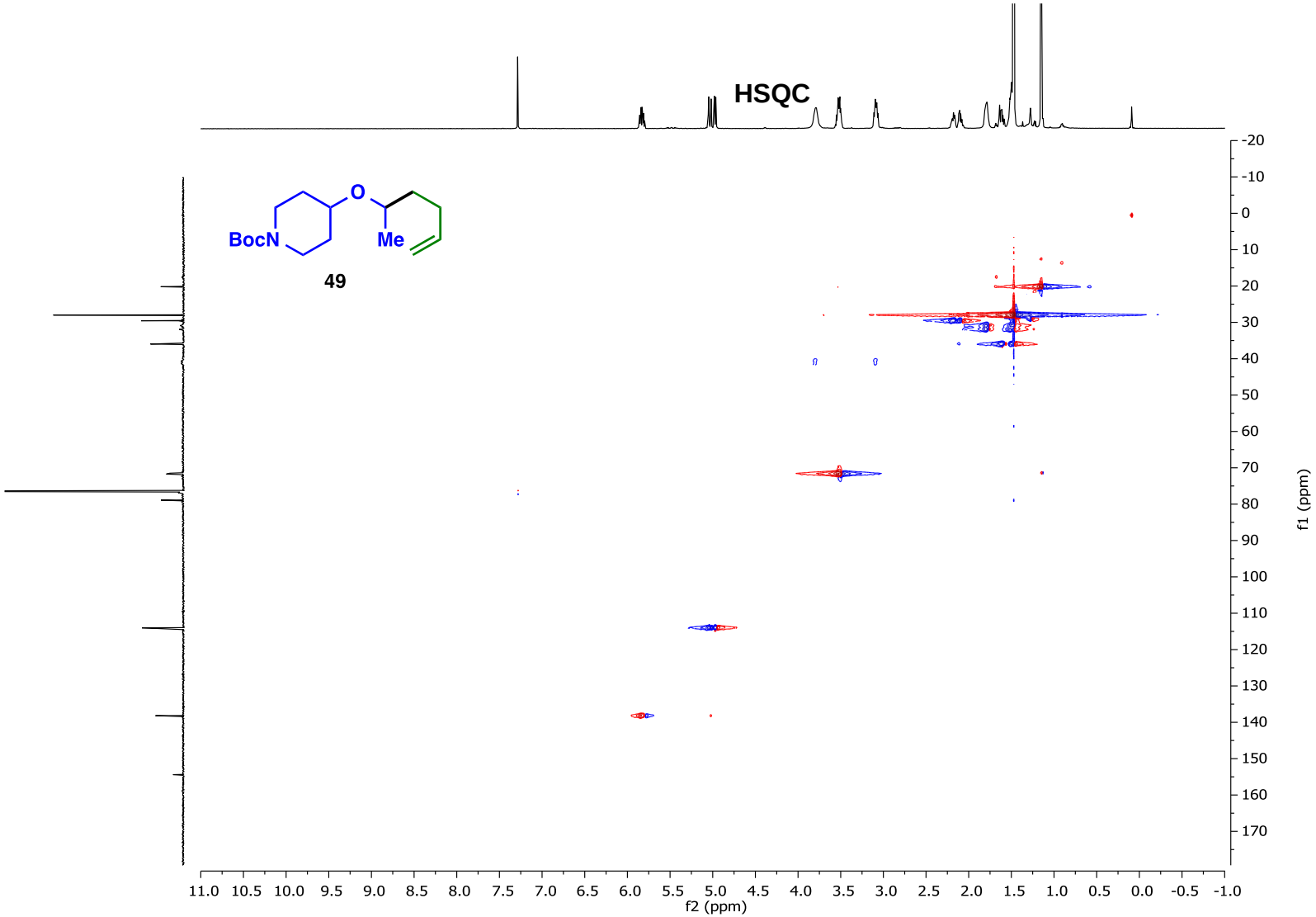

BocN
O
48
45 44 43 42 41 40 39 38
f1 (ppm)
31.5 31.0 30.5 30.0
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

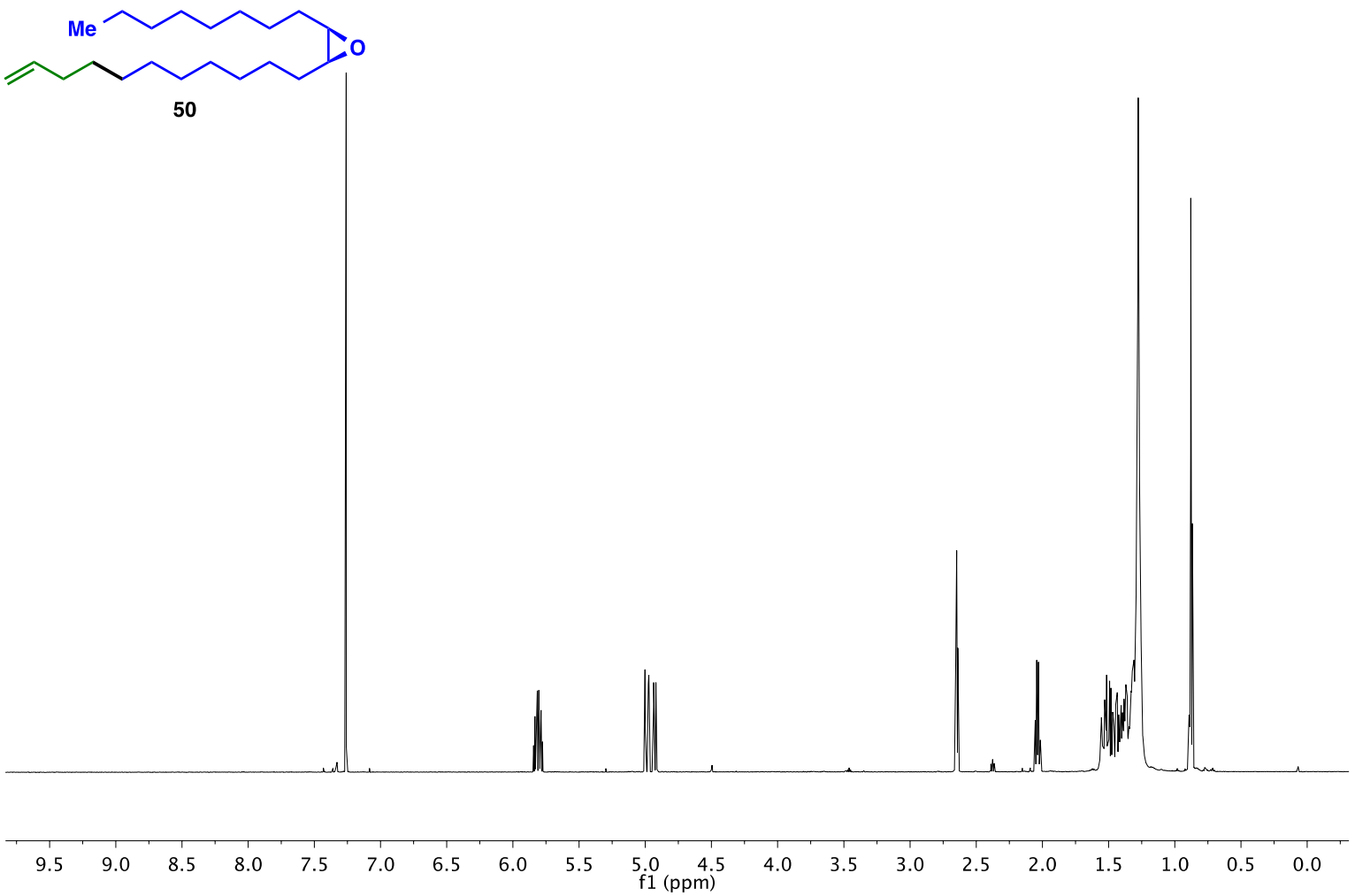

O
BocN
Me

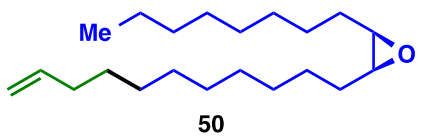
49

3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


BocN
O
Me
49
44
42
40
38
36
34
32
30
28
f1 (ppm)
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

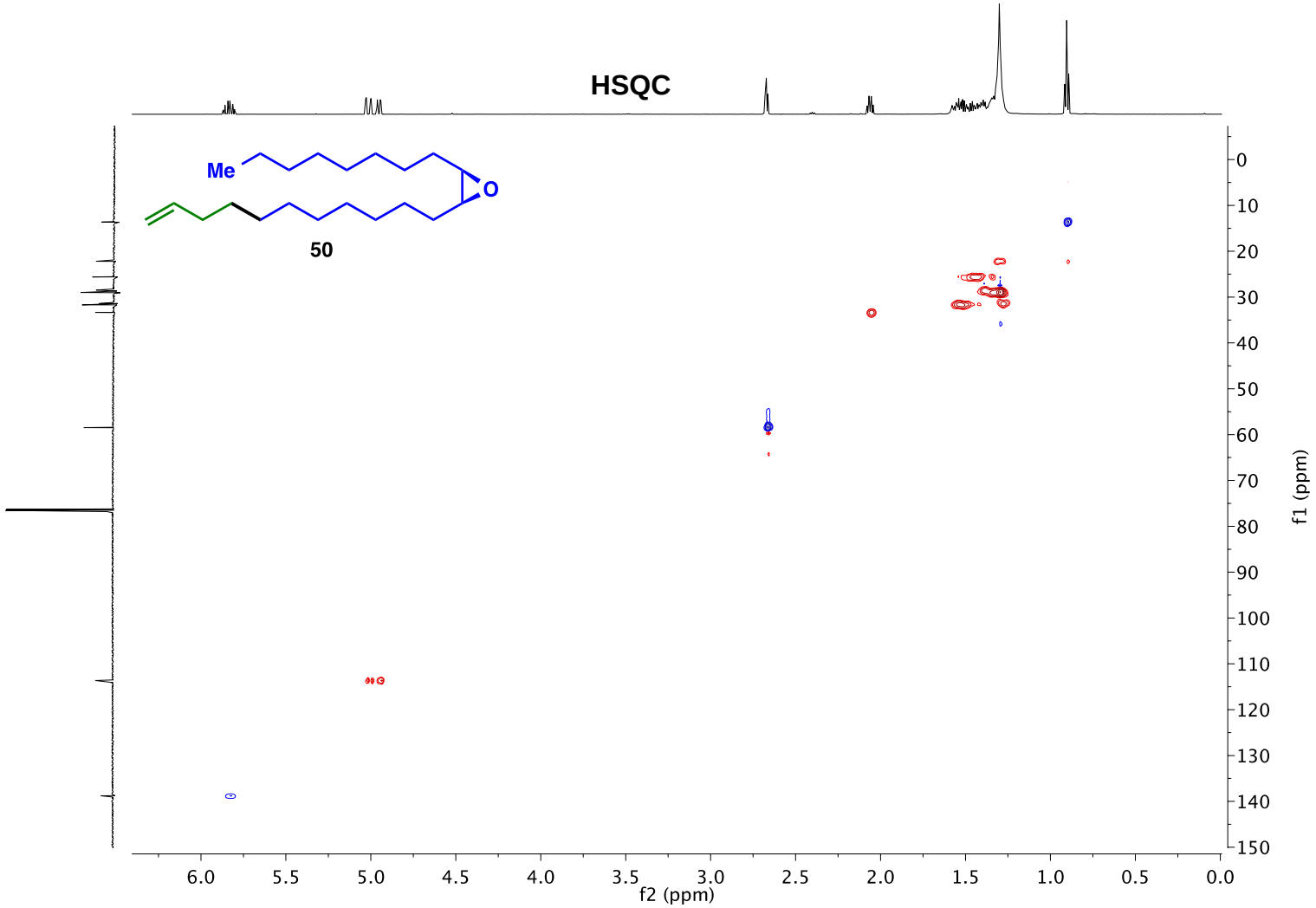

HSQC
BocN
O
Me
49
f2 (ppm)
f1 (ppm)

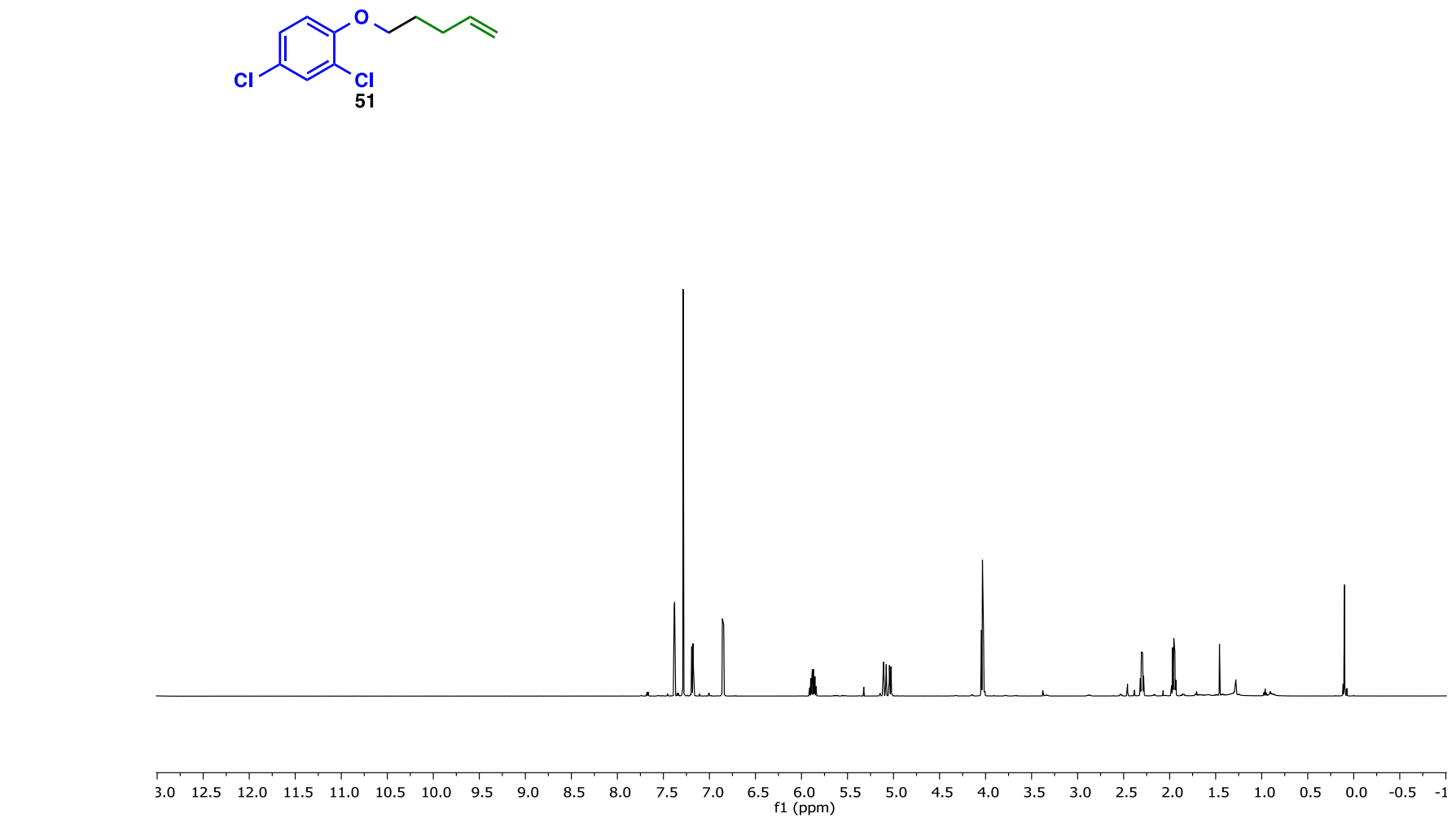

Me
O
50
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

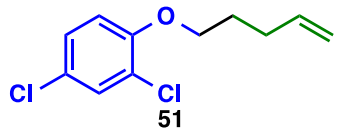

Me
O

50

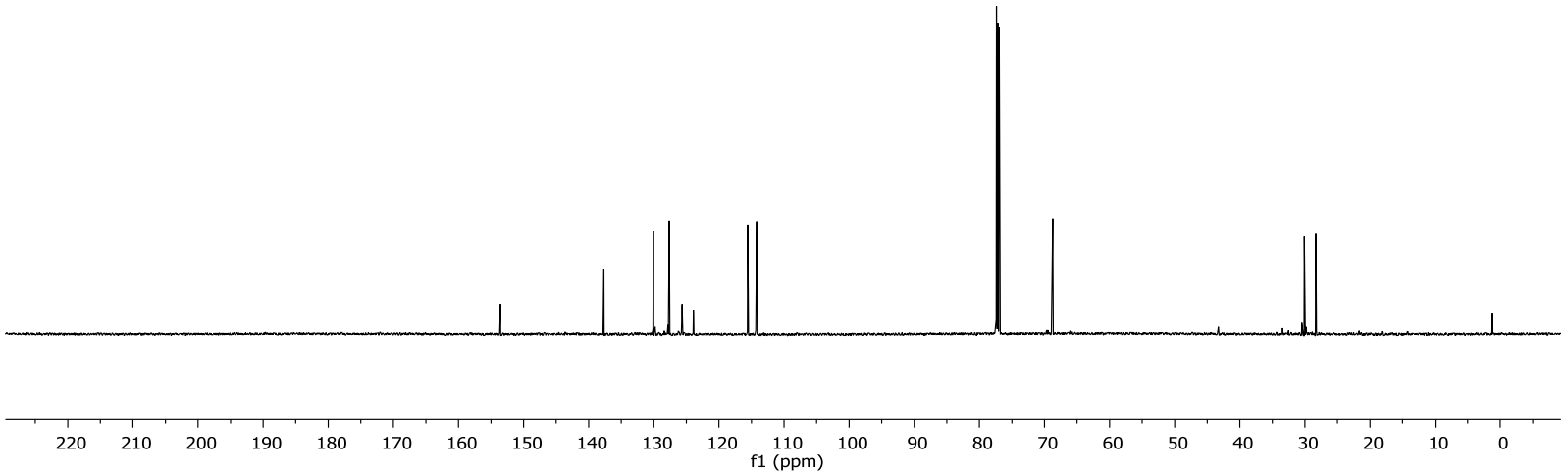
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

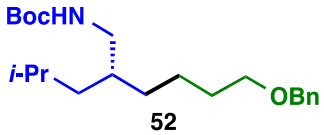

HSQC
Me
O
50
f2 (ppm)
f1 (ppm)


O
Cl
Cl
51
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

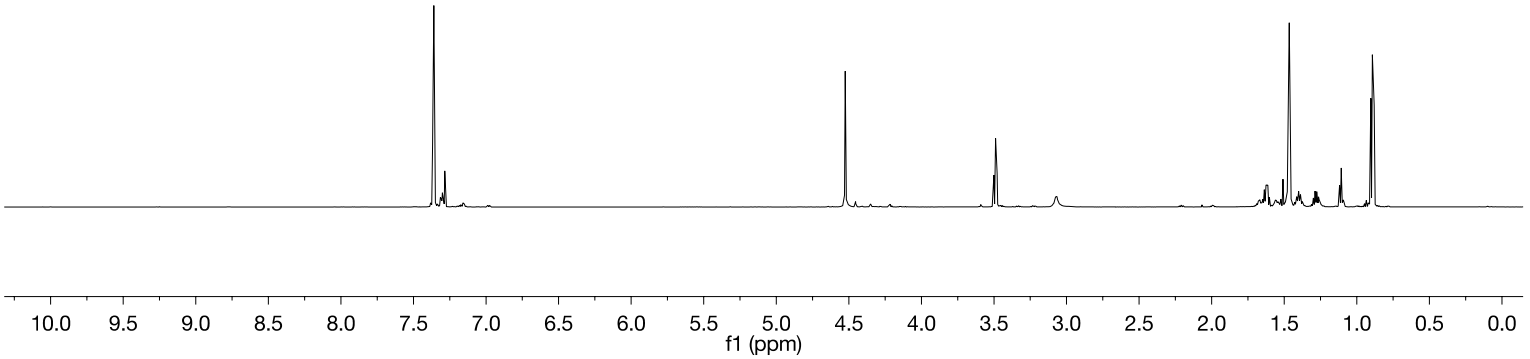

O
Cl
Cl

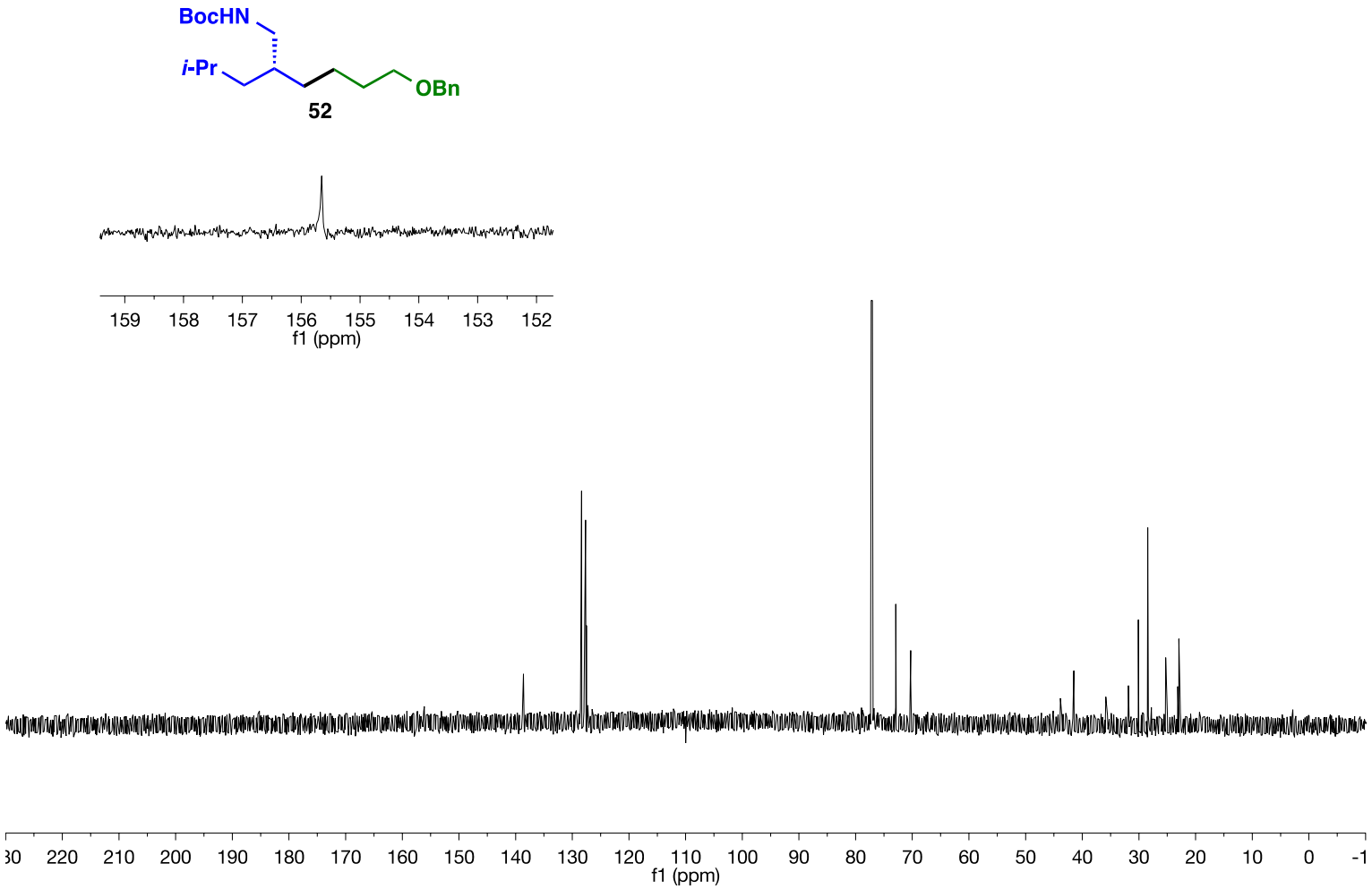
51

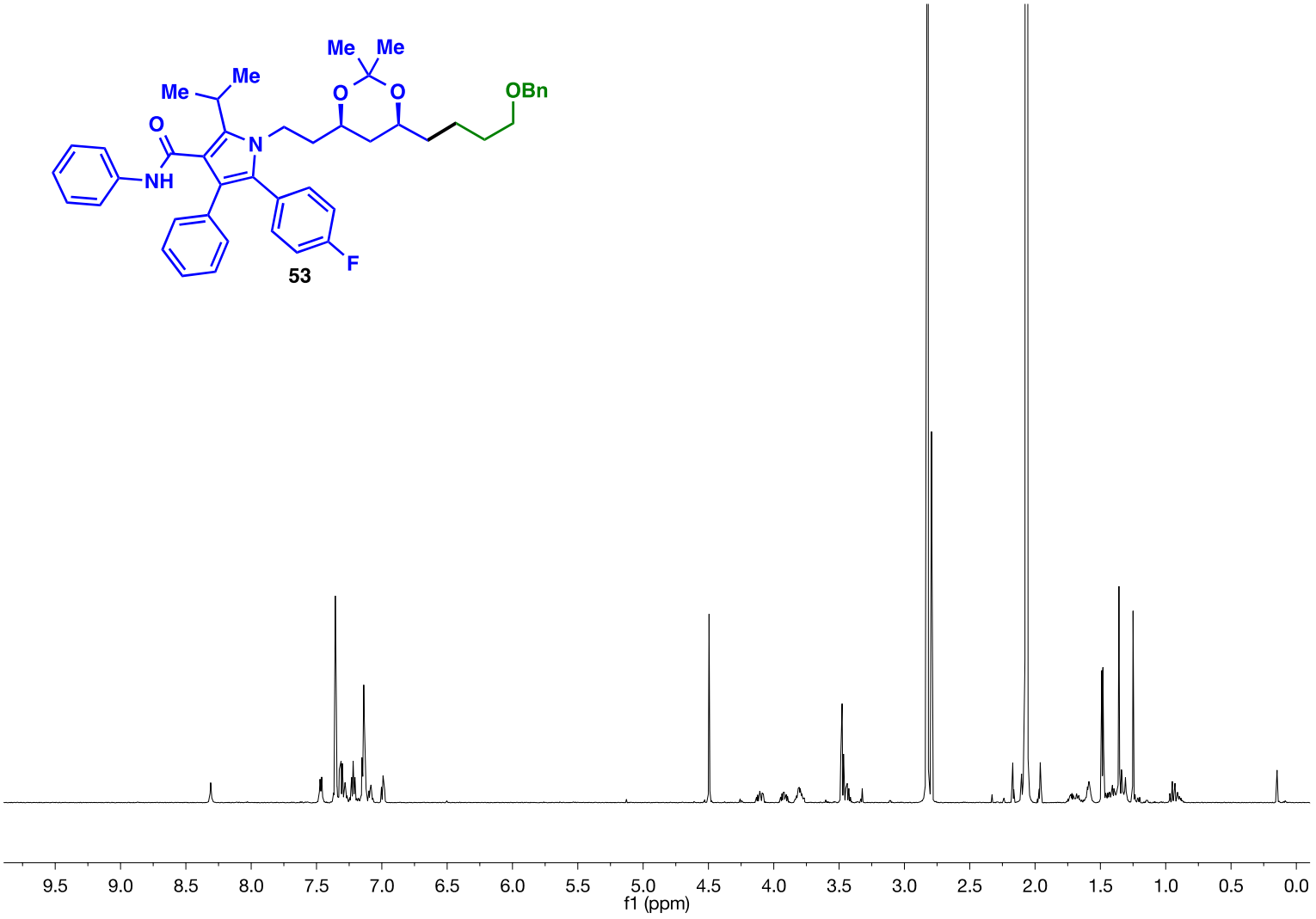

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

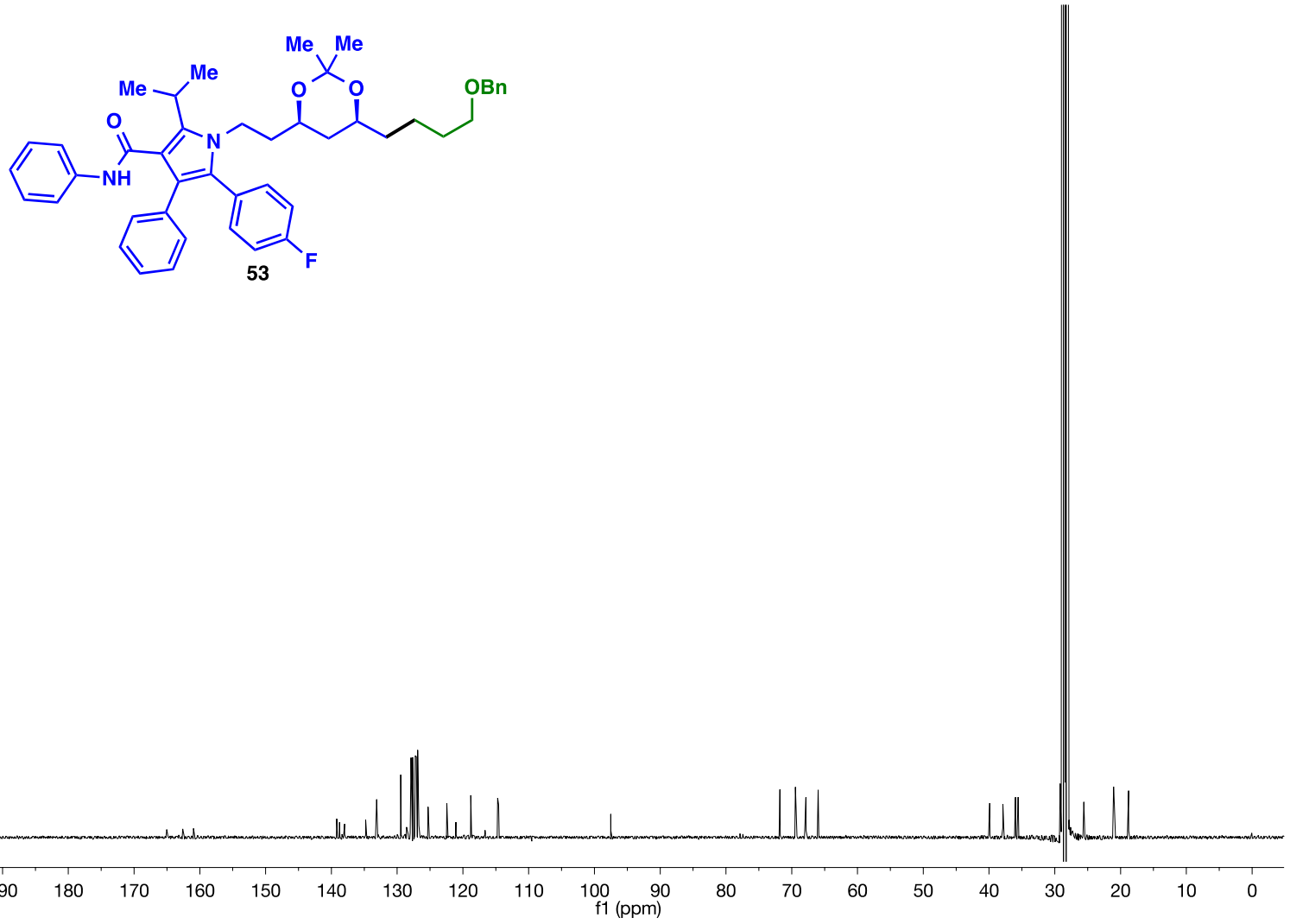

BocHN
i-Pr
OBn

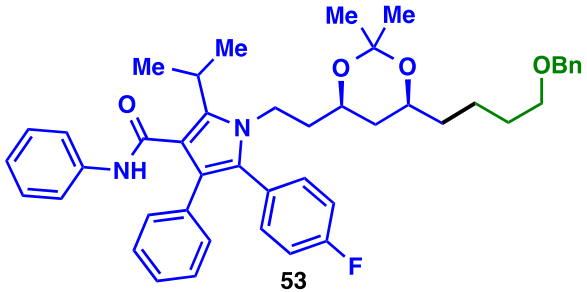
52


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

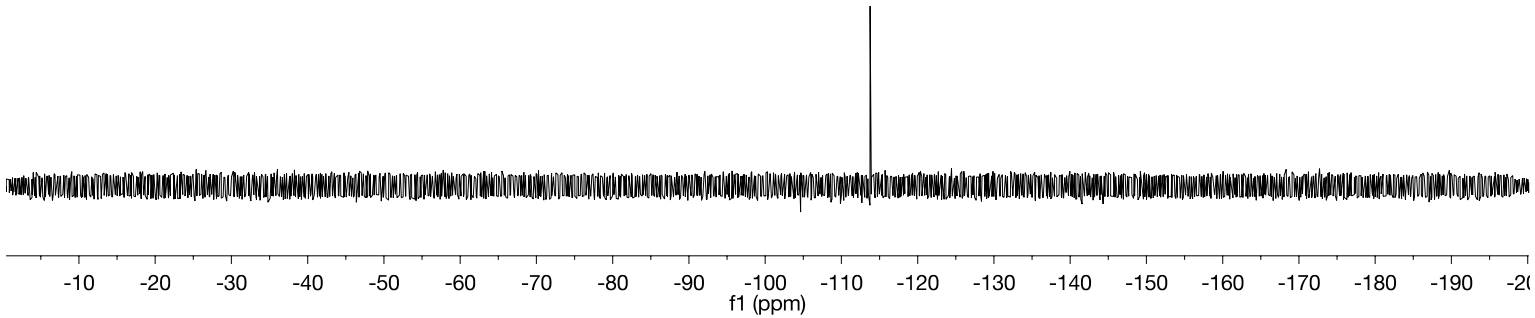

BocHN
i-Pr
OBn
52
159 158 157 156 155 154 153 152
f1 (ppm)
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

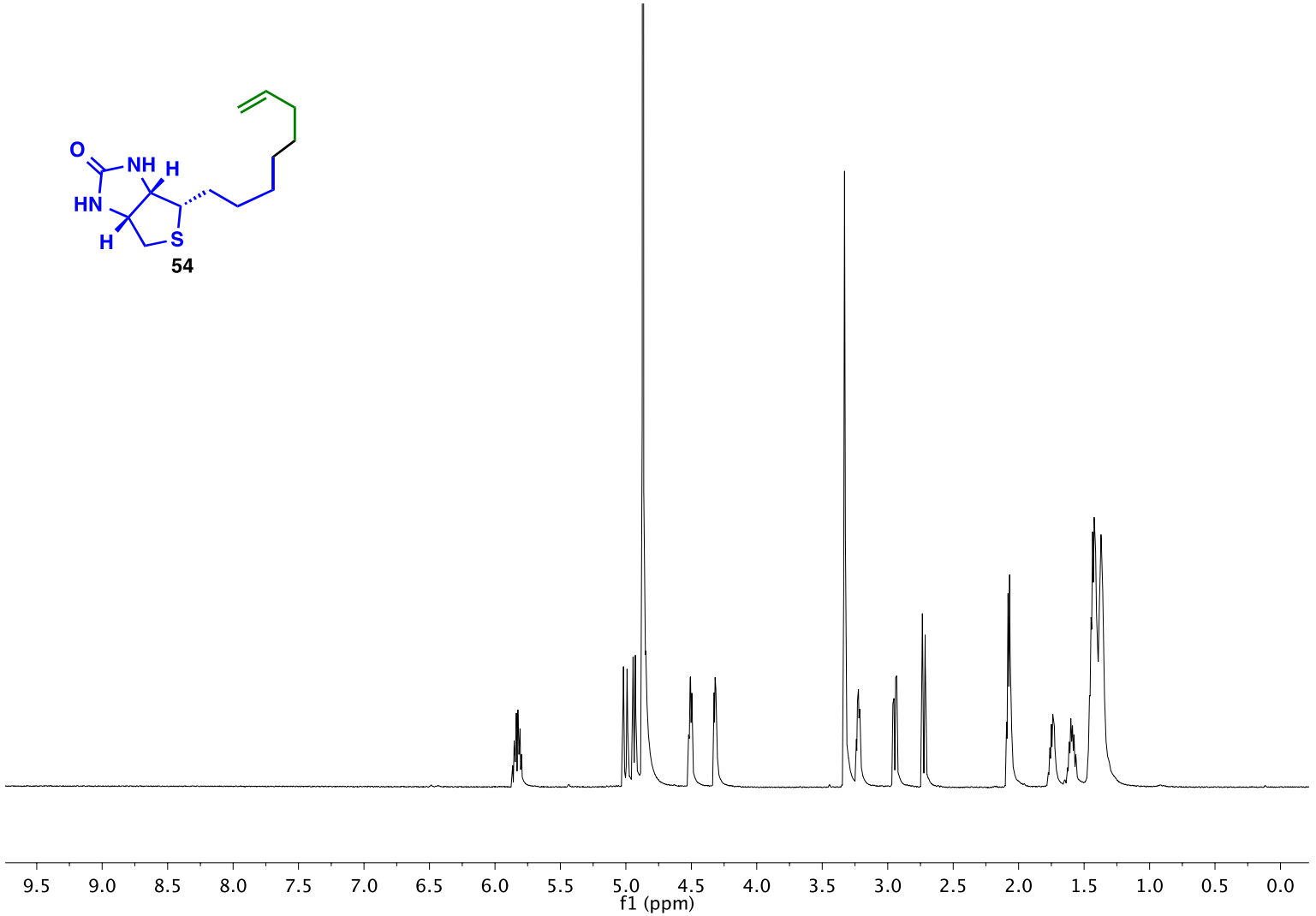

Me
Me
Me
Me
O
O
O
OBn
N
NH
F
53
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

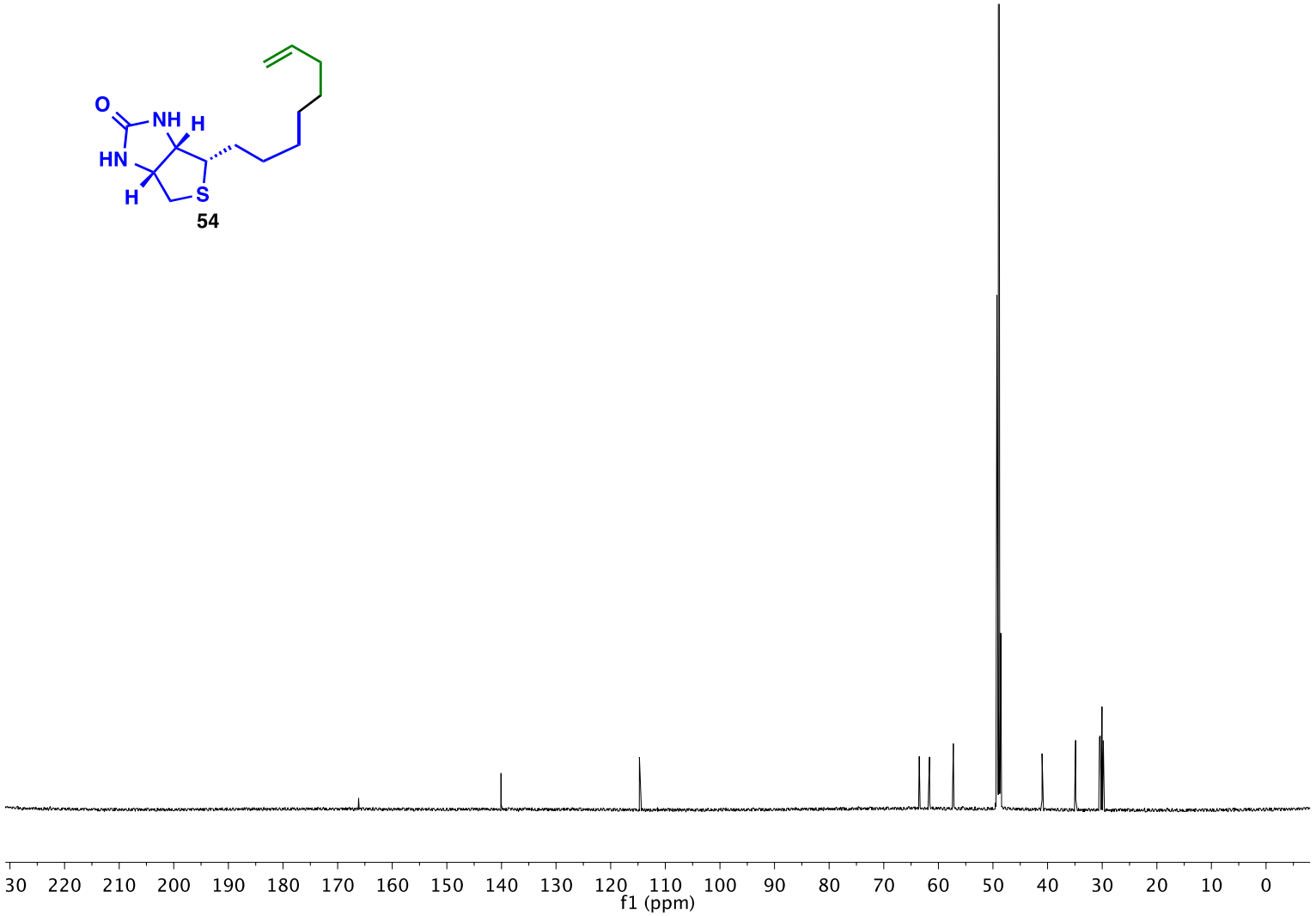

Me
Me
Me
Me
O
O
O
OBn
N
NH
F
53
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

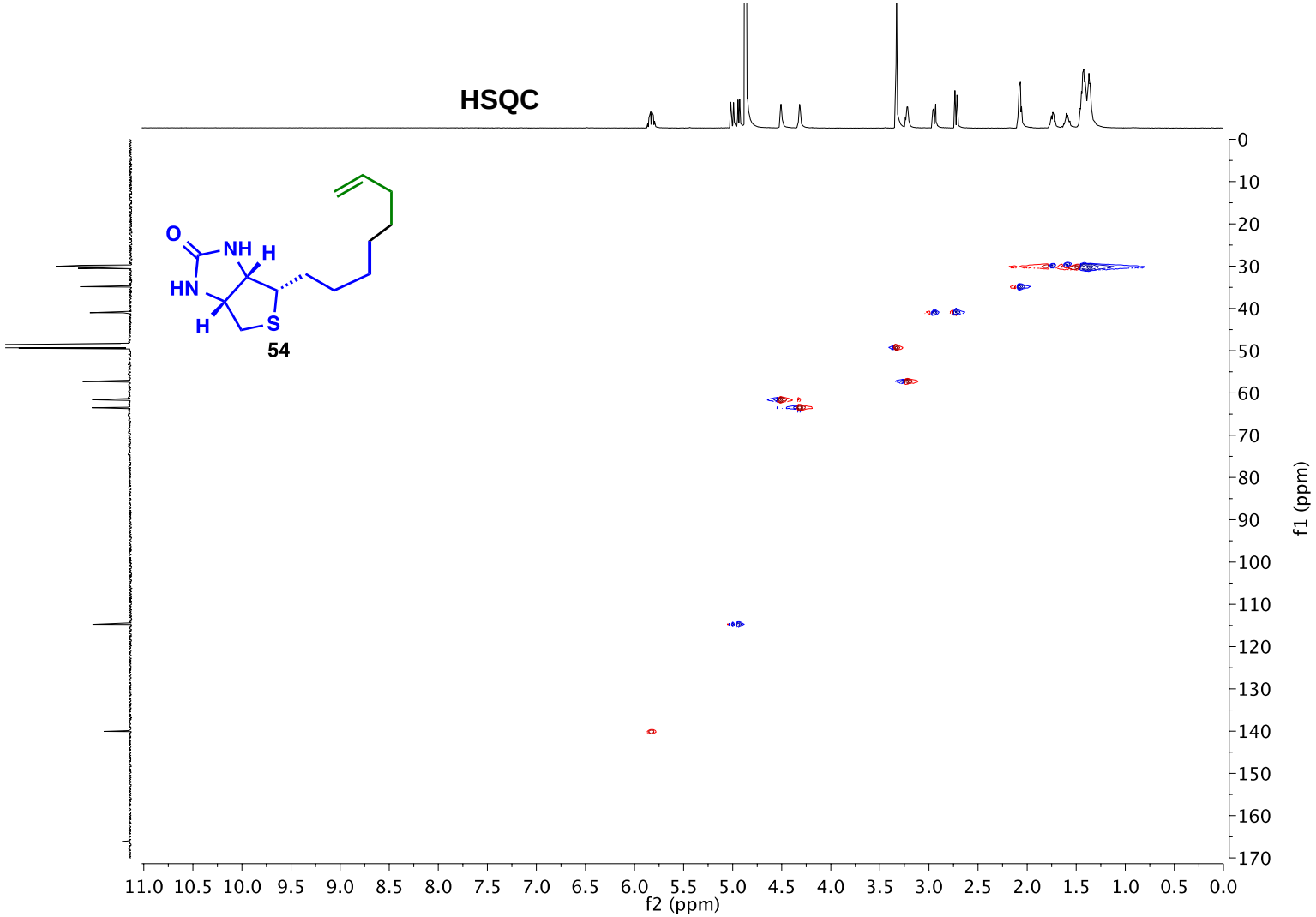

Me
Me
Me
O
NH
N
O
O
OBn
F

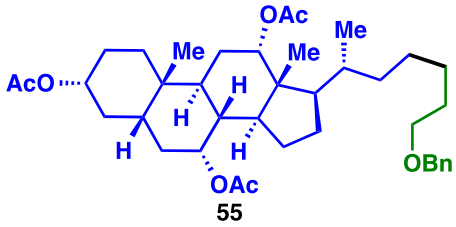
53


-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

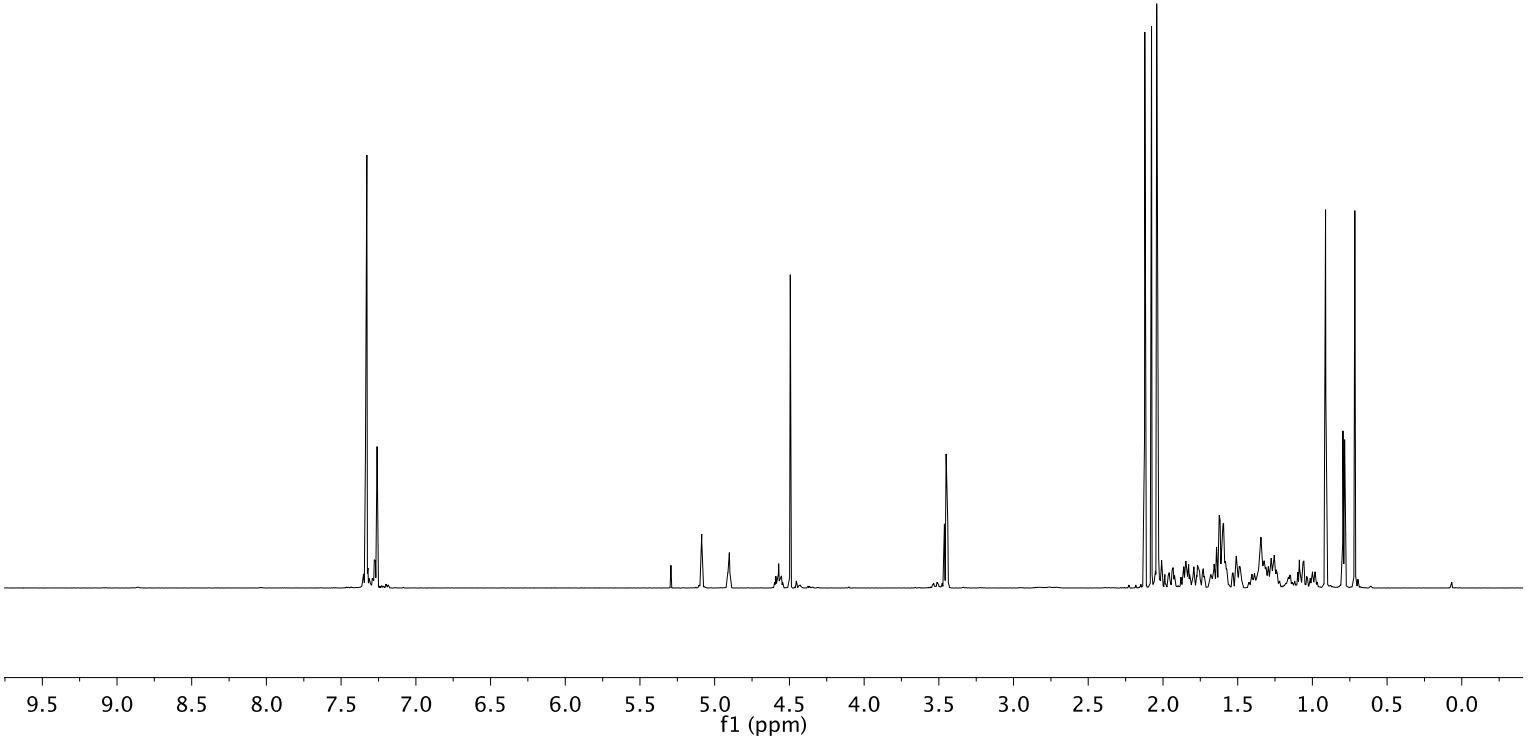

O
NH
H
HN
H
S
54
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

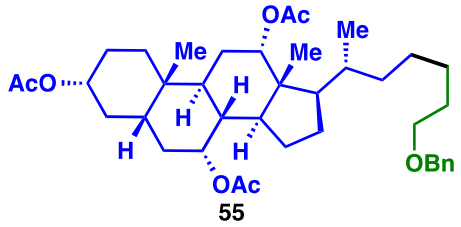

O
NH
H
HN
H
S
54
30 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HSQC
O
NH
H
HN
H
S
54
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
0 10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170
f1 (ppm)


OAc
Me
Me
Me
AcO
H
H
H
H
OAc
OBn

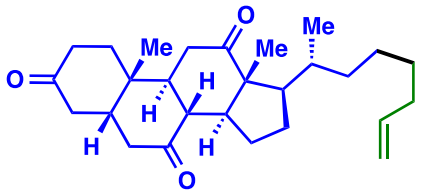
55


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

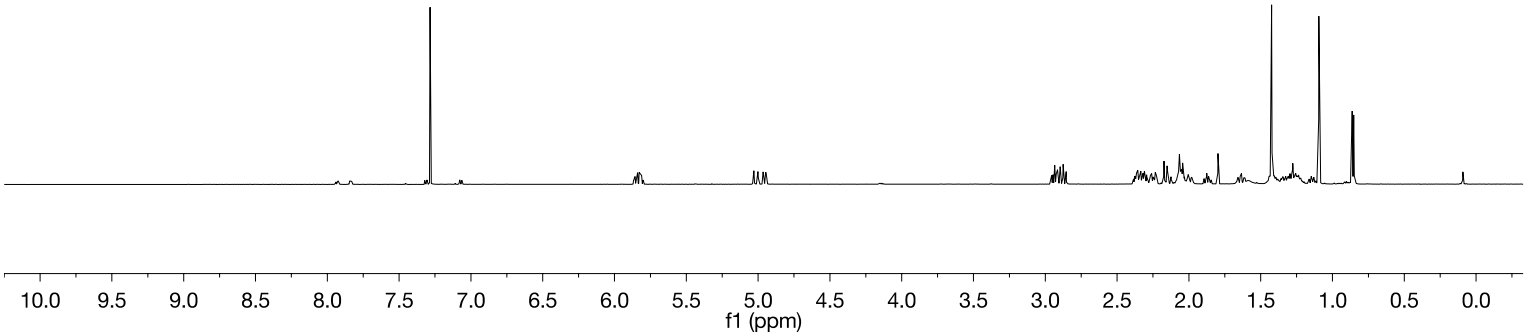

OAc
Me
Me
Me
AcO
H
H
H
H
OAc
OBn

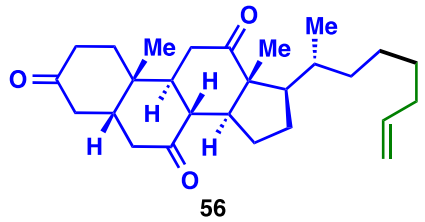
55

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

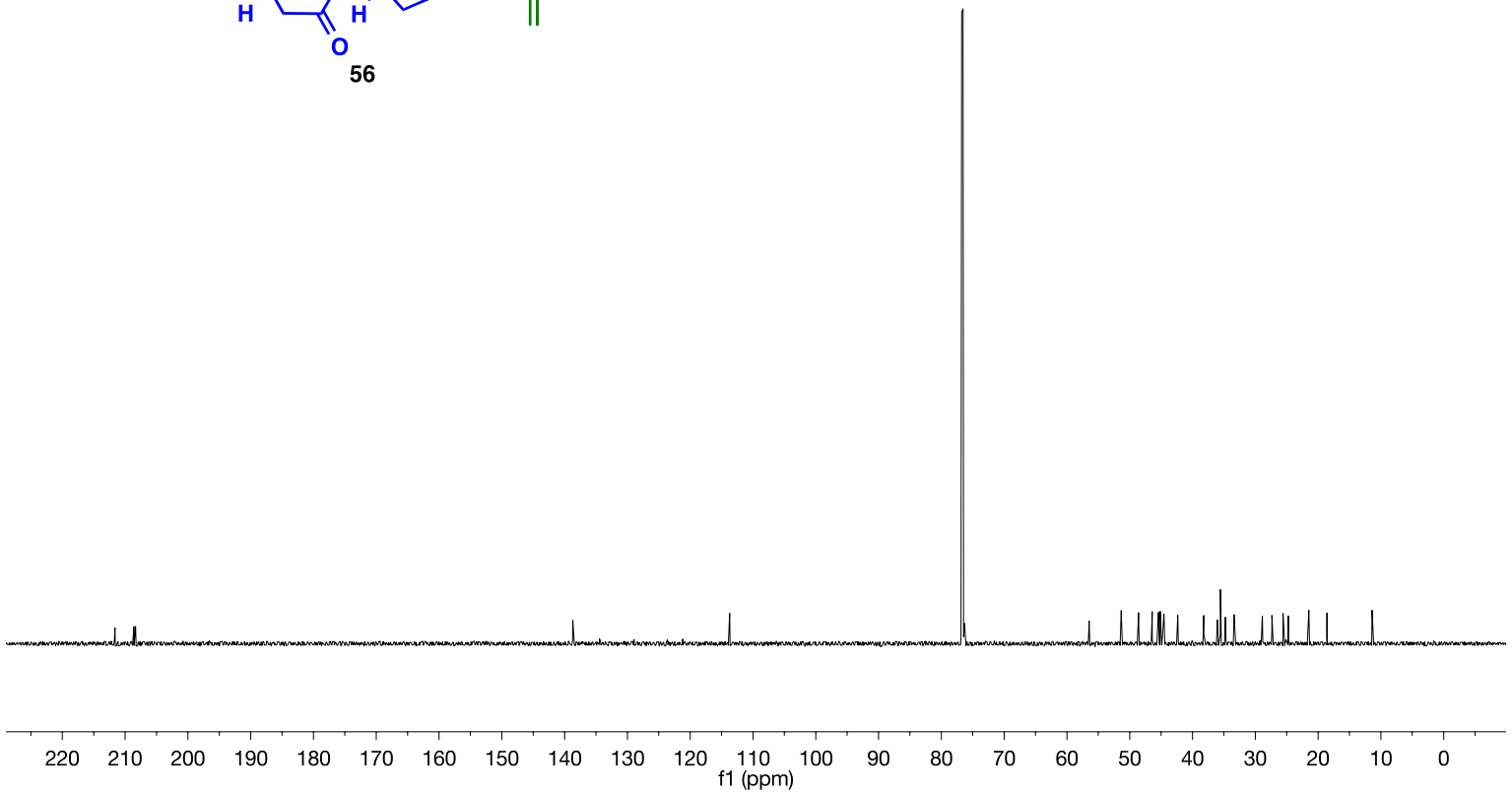

O
Me
Me
Me
H
H
H
H
O
O

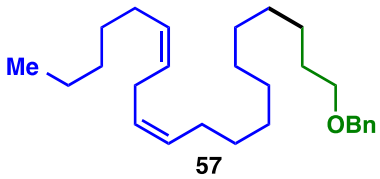
56


10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

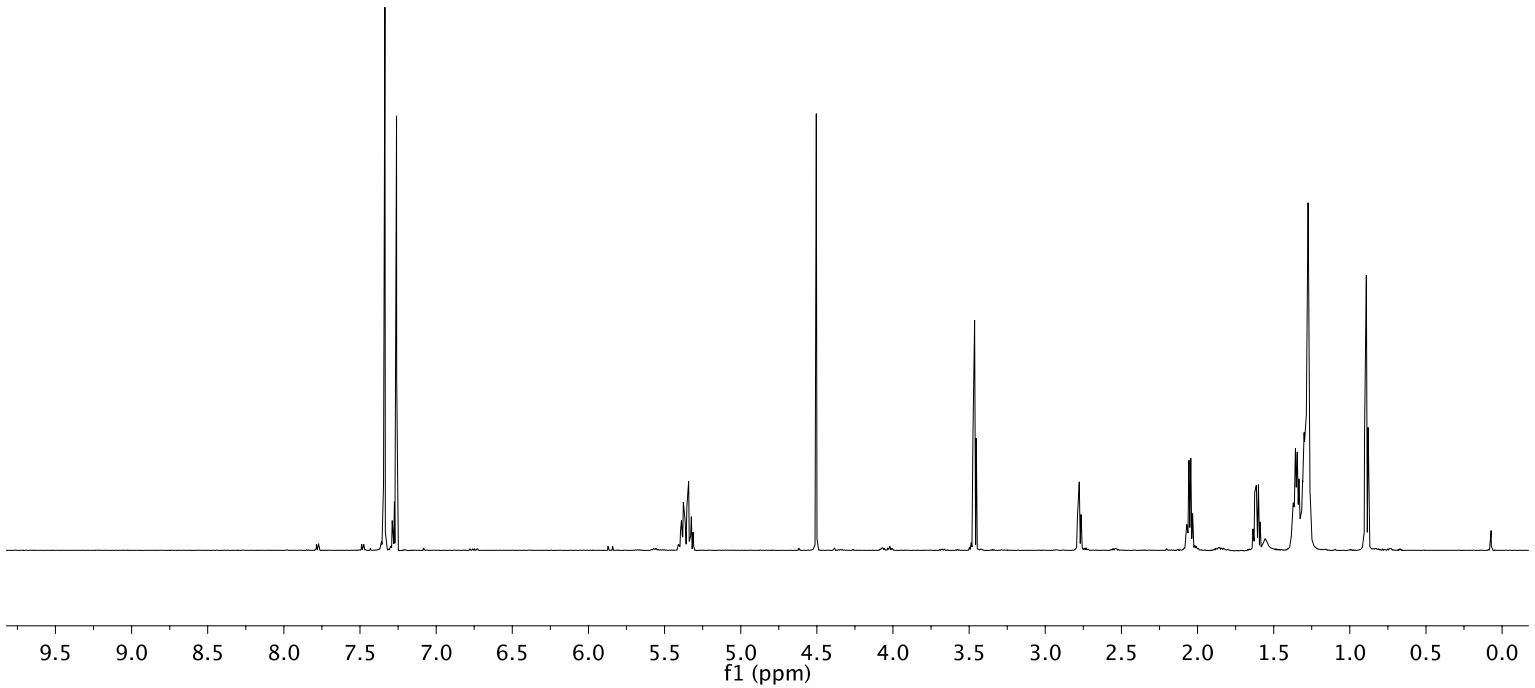

O
Me
Me
O
Me
H
H
H
H
O

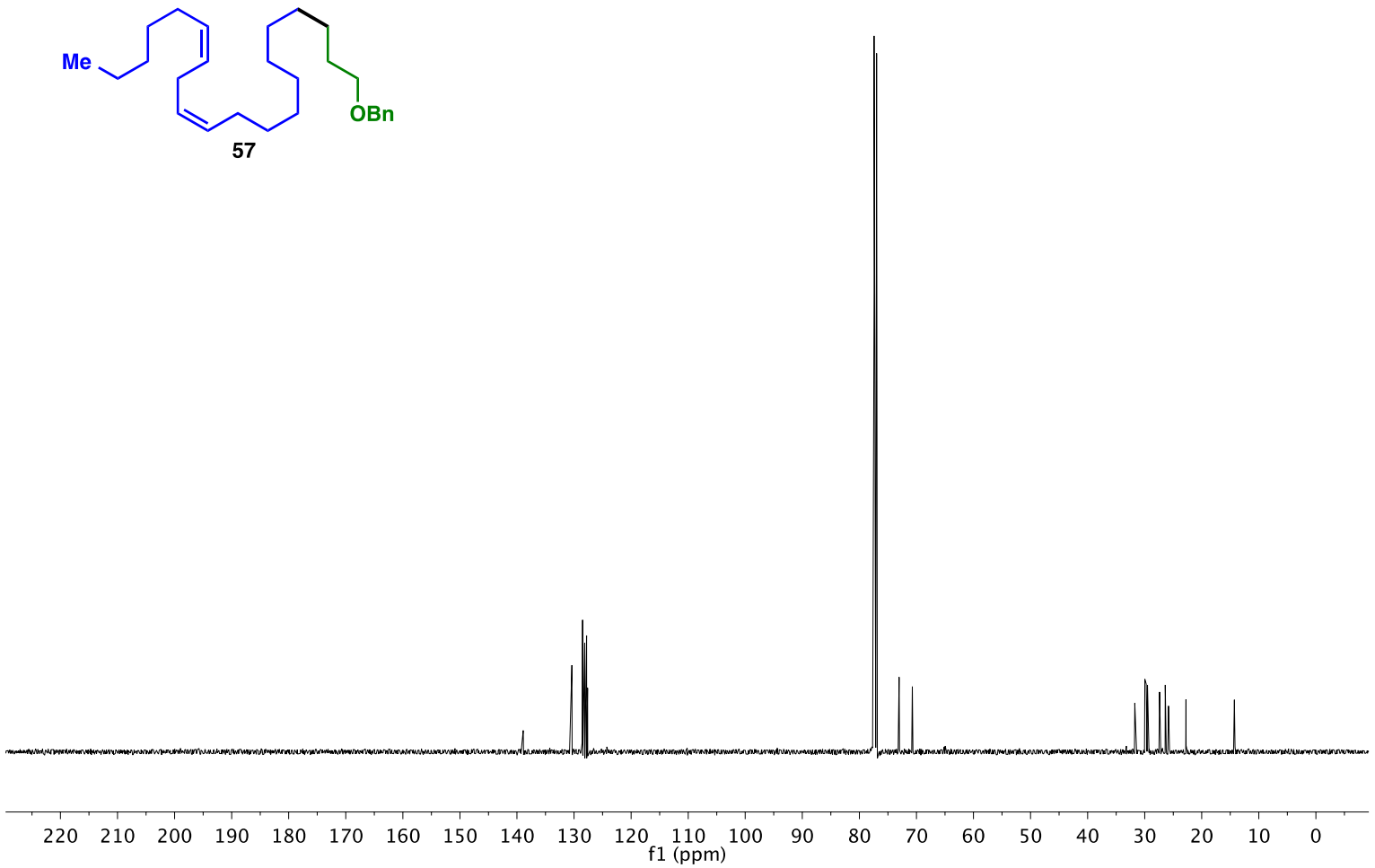
56

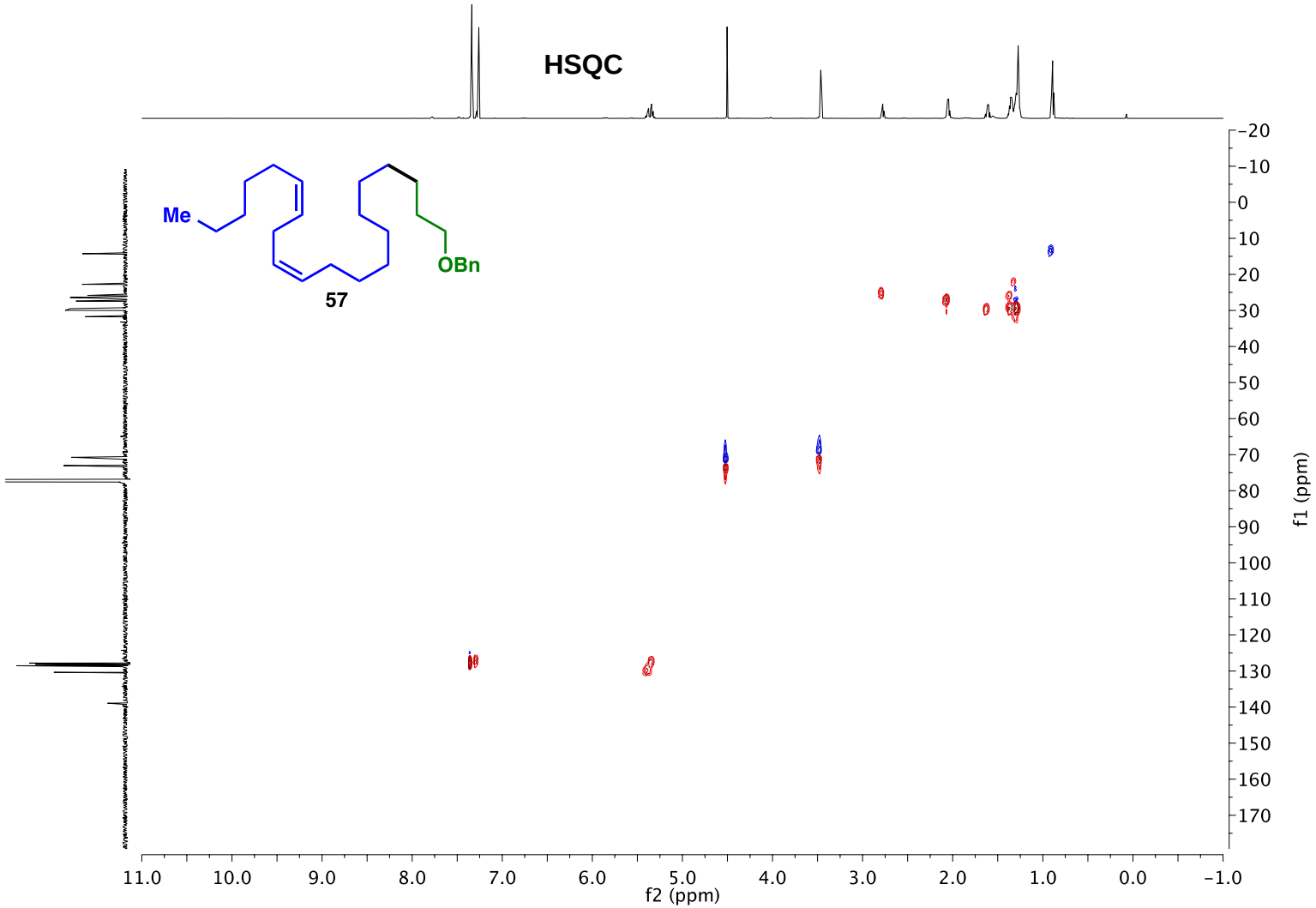

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

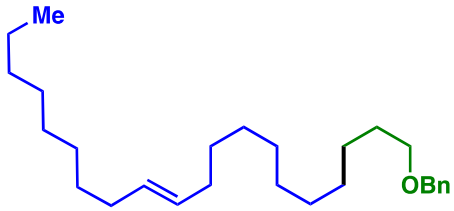

Me
OBn

57

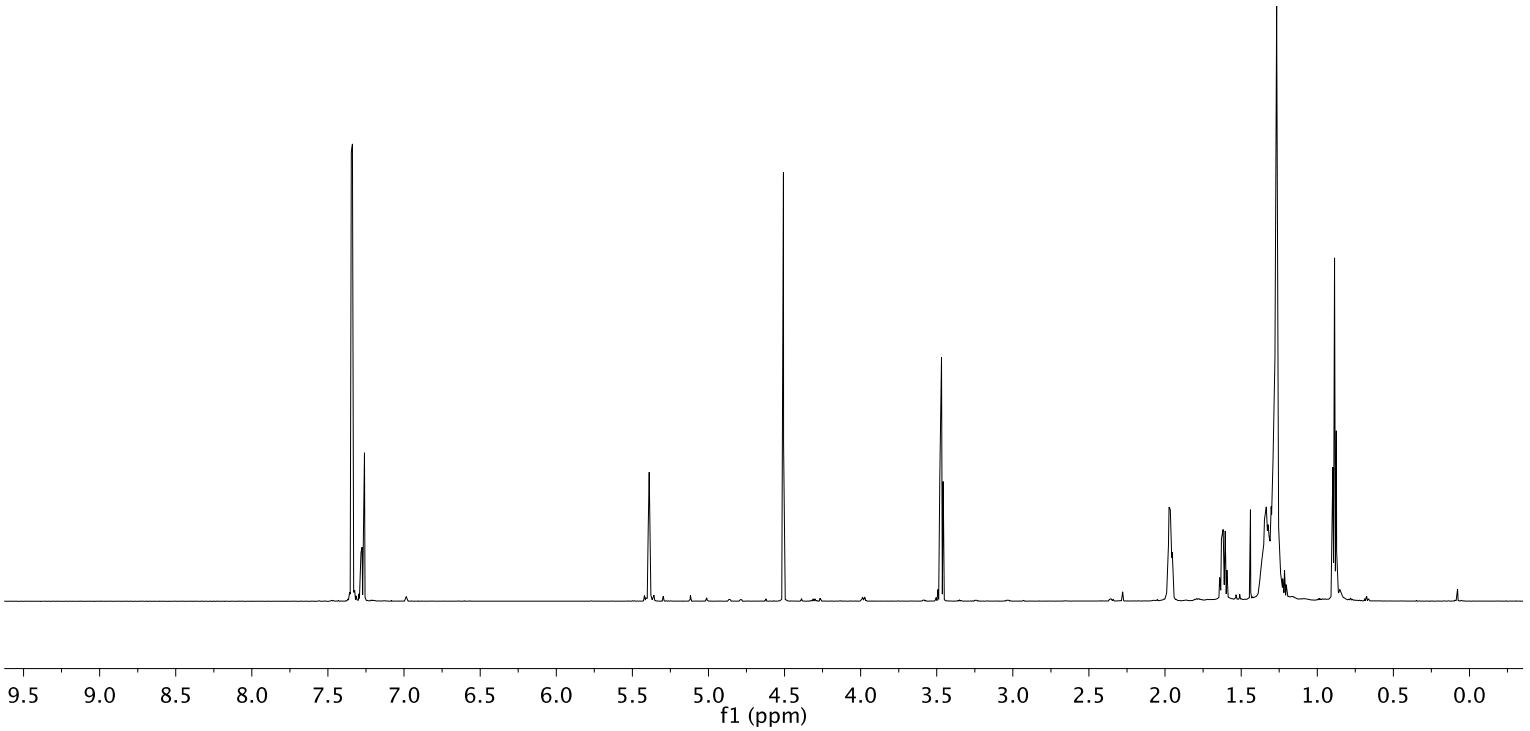

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

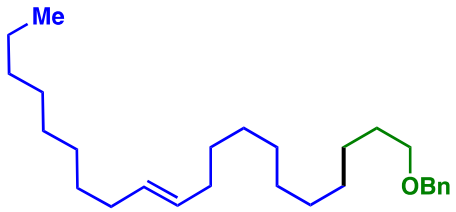

Me
OBn
57
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


HSQC
Me
OBn
57
f2 (ppm)
f1 (ppm)

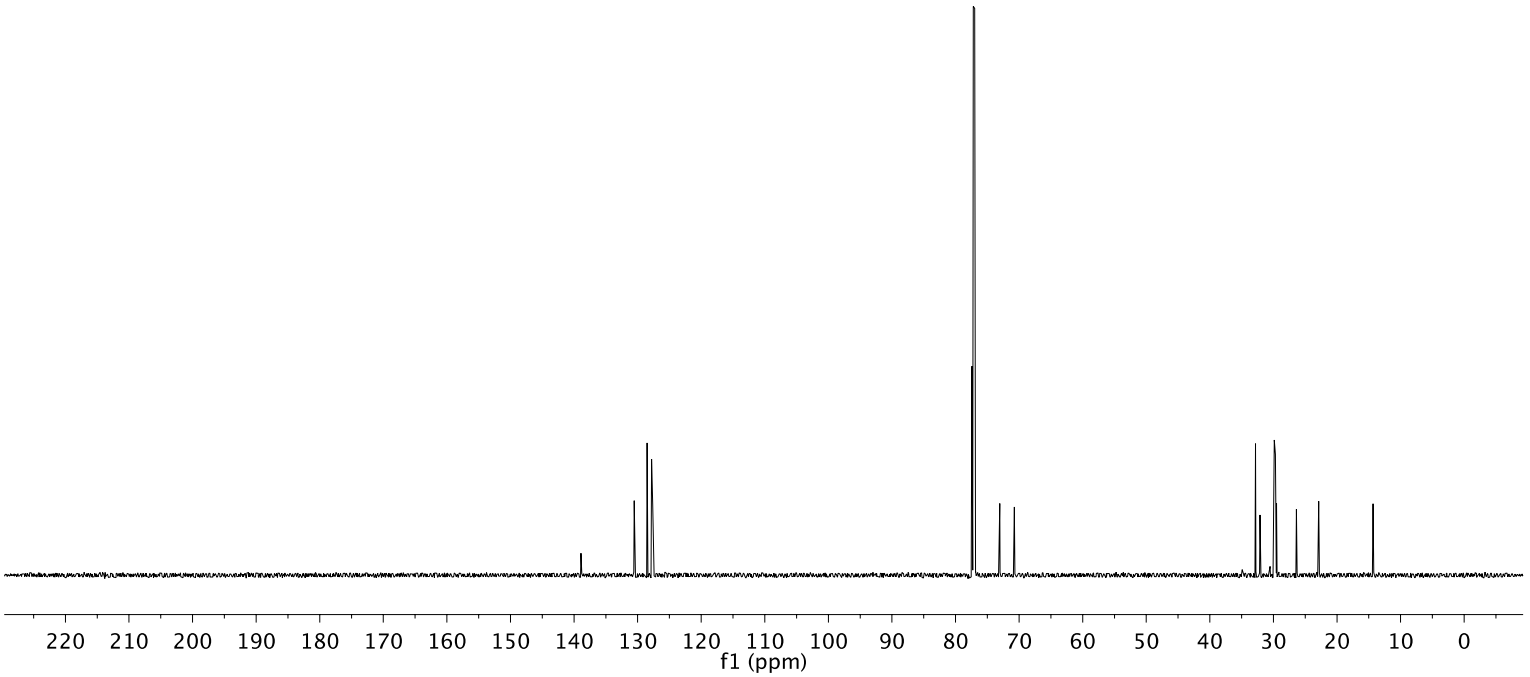

Me
OBn

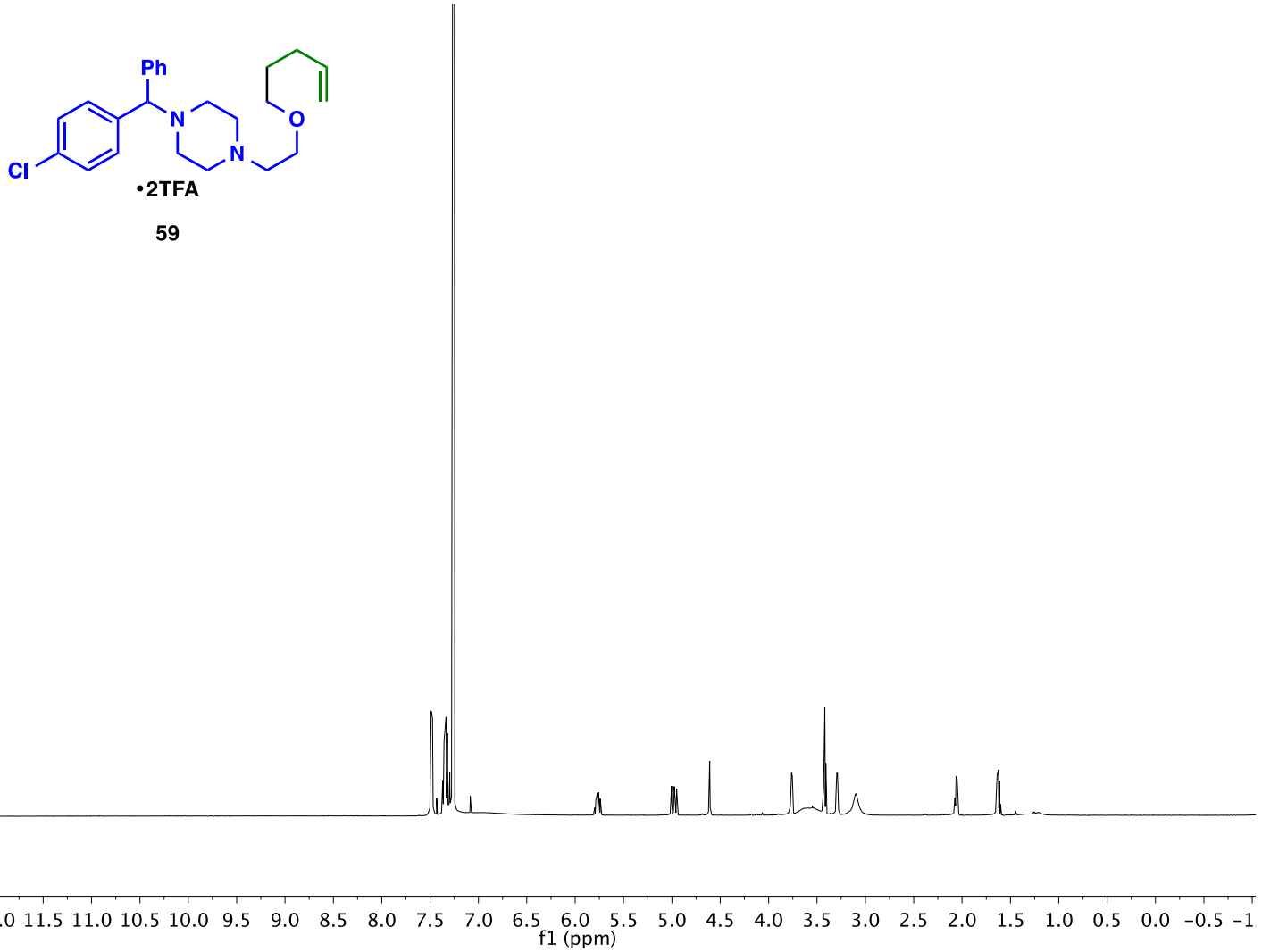
58

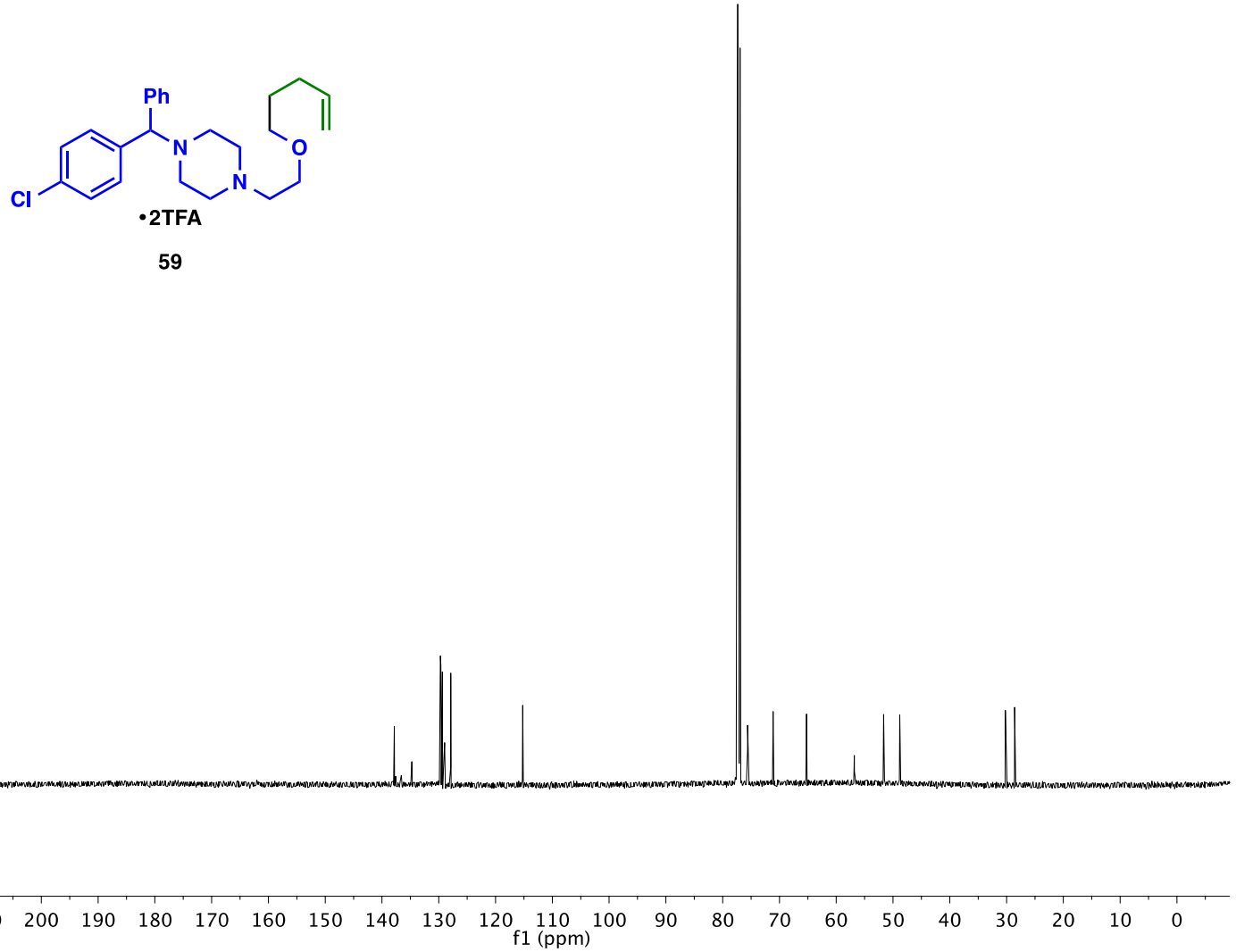

9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

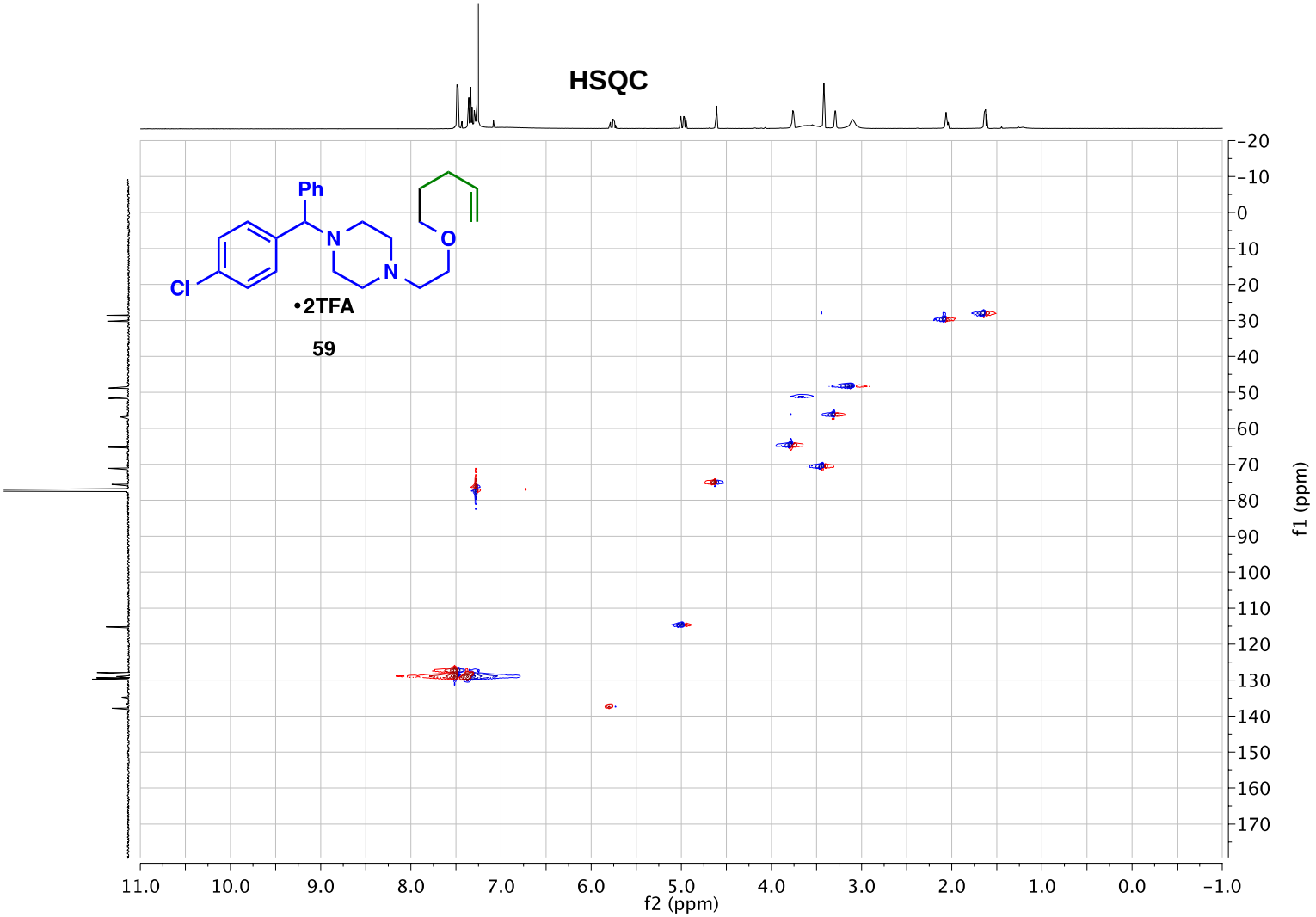

Me
OBn

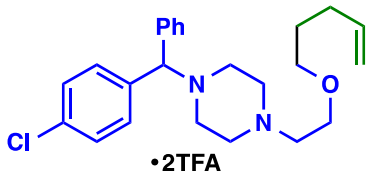
58


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


Ph
N
N
O
Cl
•2TFA
59
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

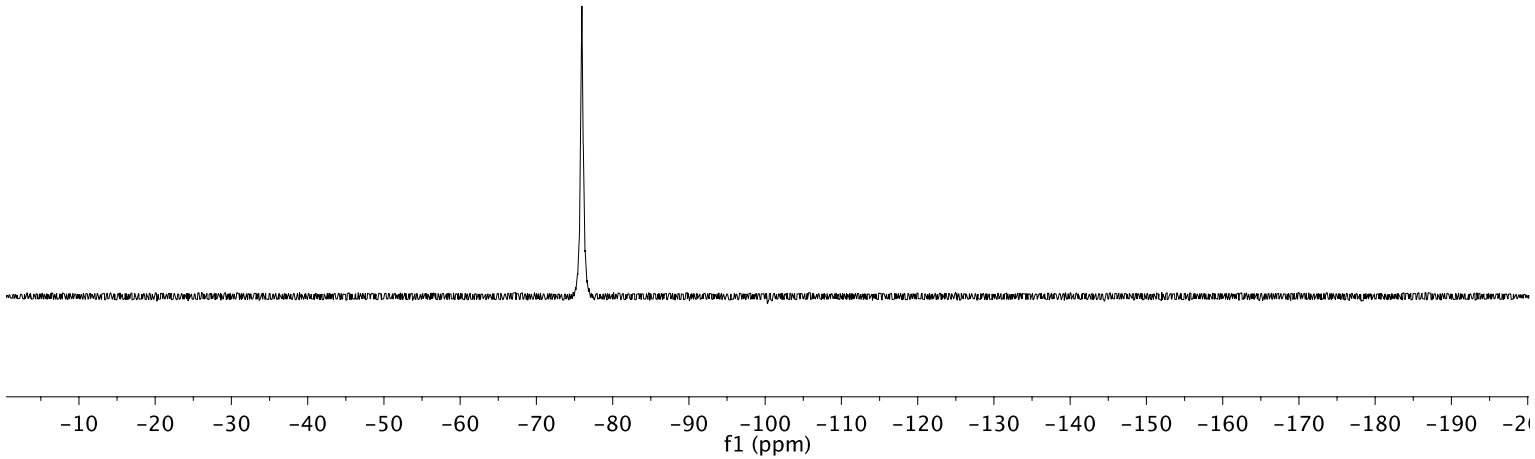

Ph
N
N
O
Cl
•2TFA
59
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

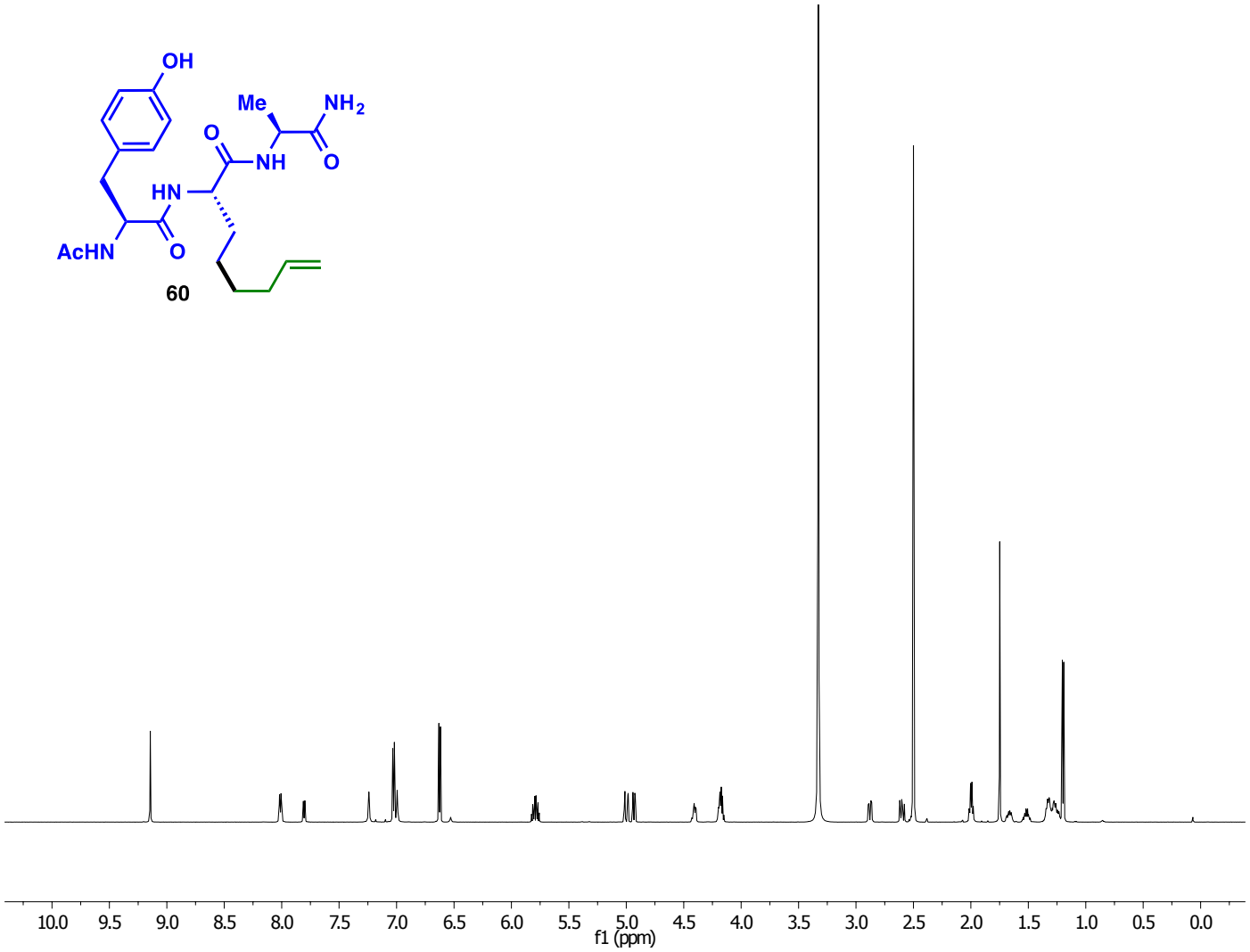

HSQC
Ph
N
N
O
Cl
•2TFA
59
f2 (ppm)
f1 (ppm)

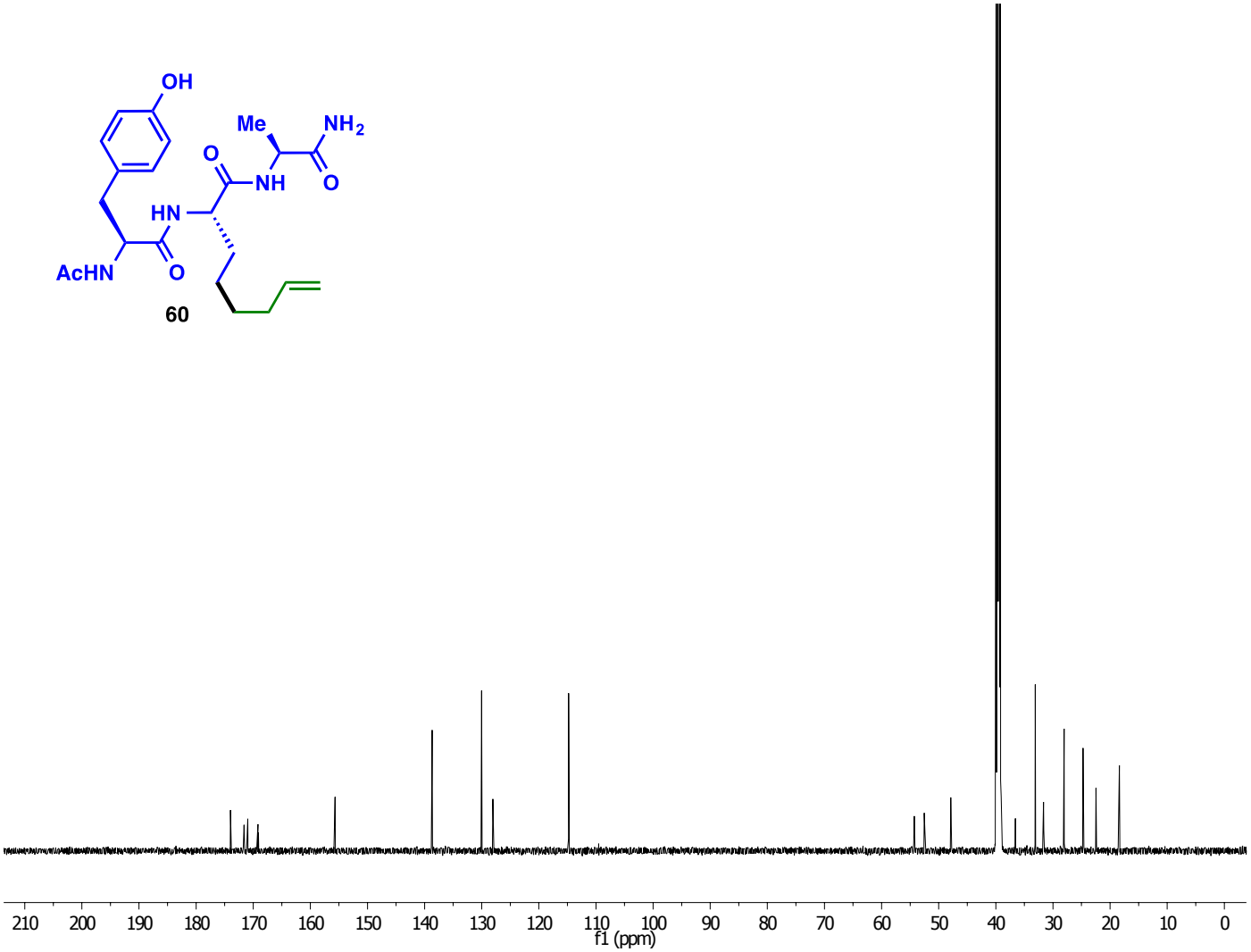

Ph
N
O
N
Cl

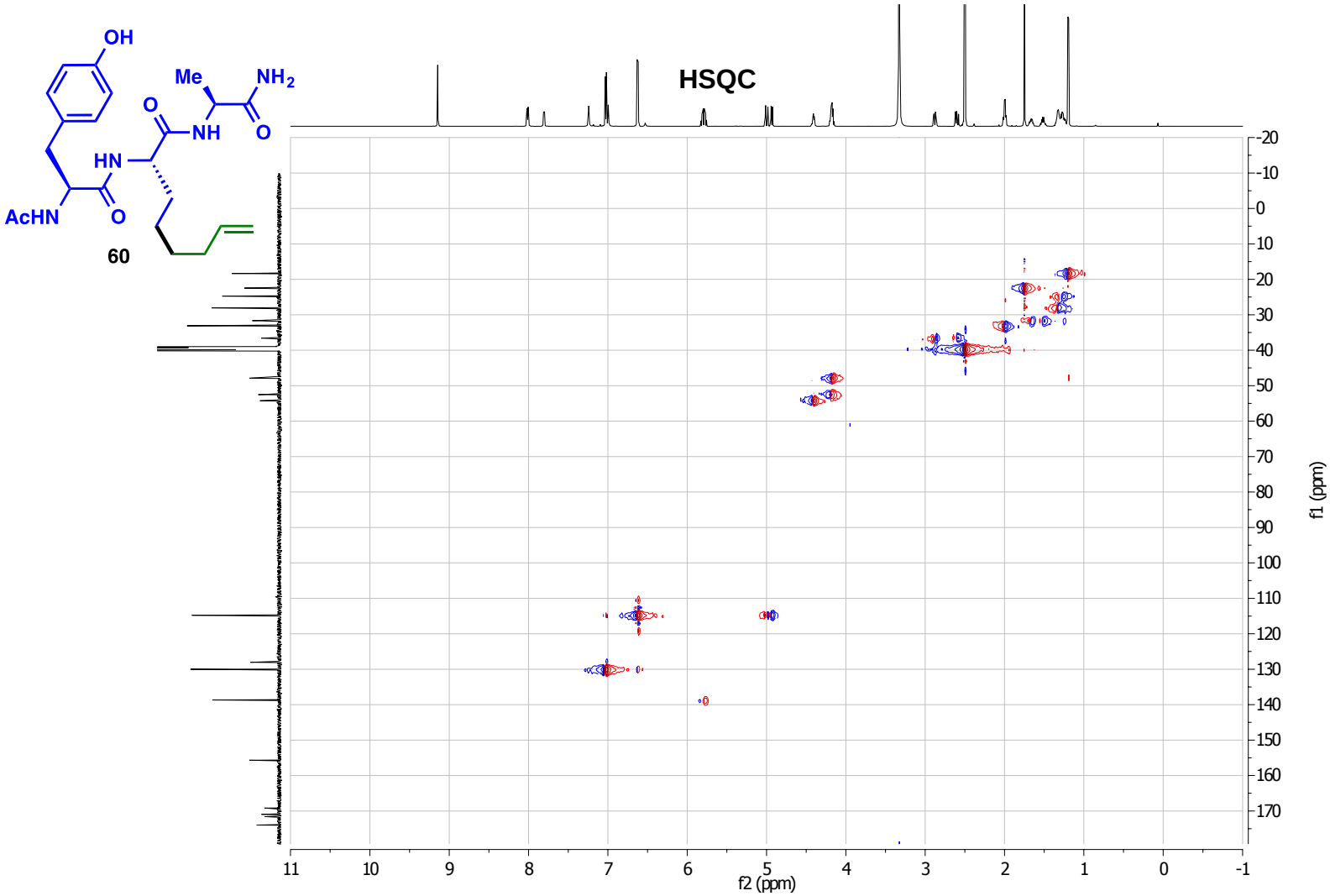
•2TFA

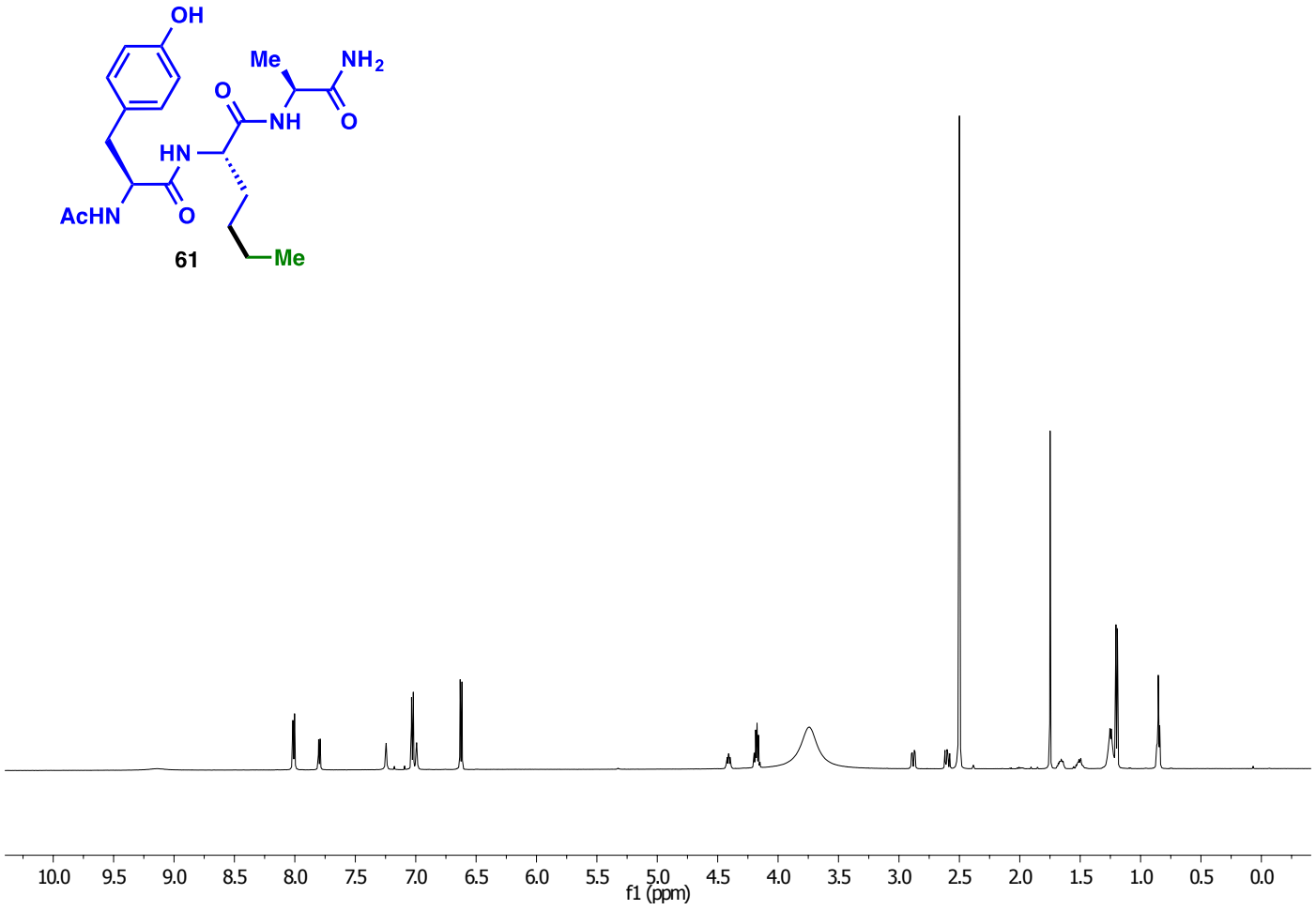
59

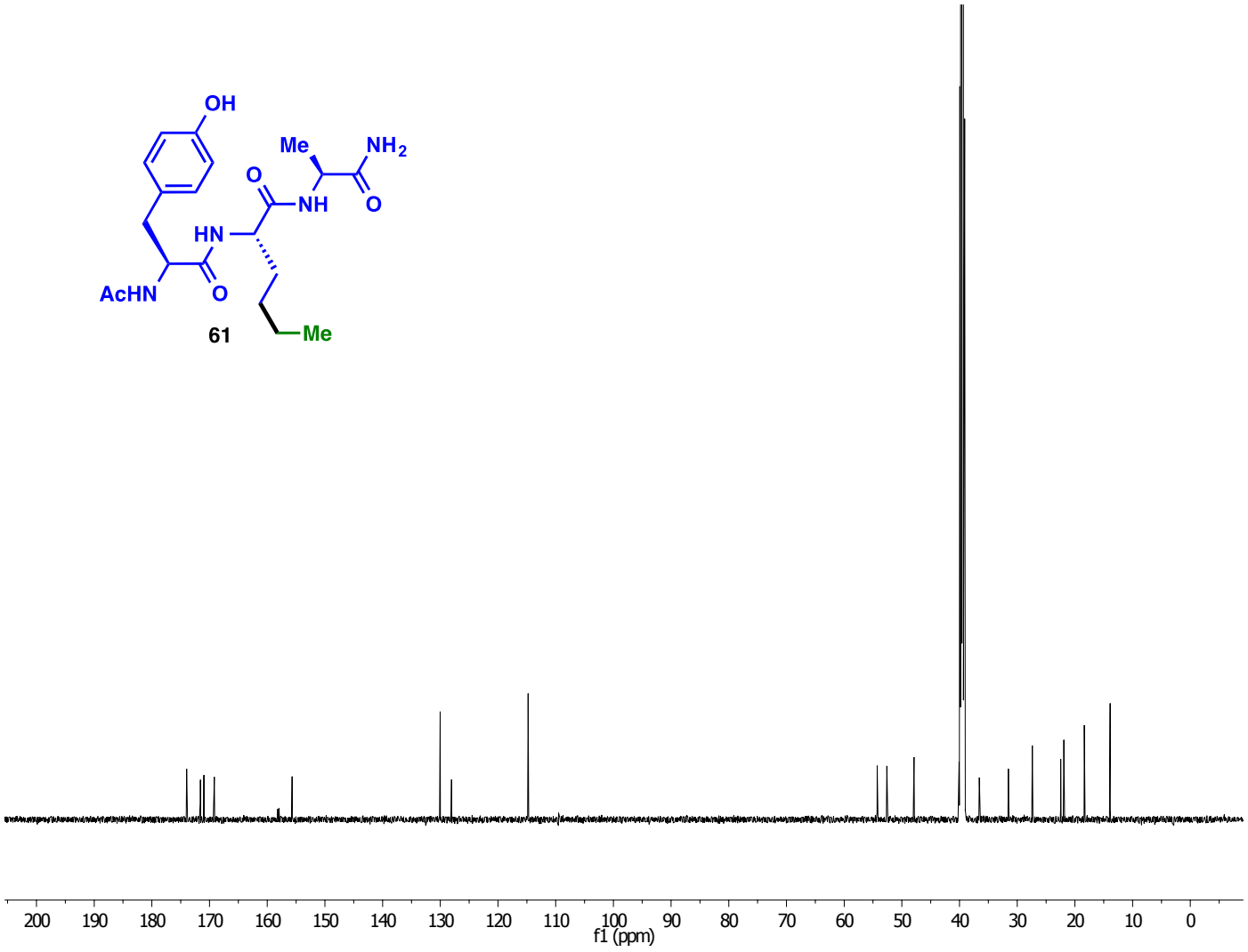

-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)

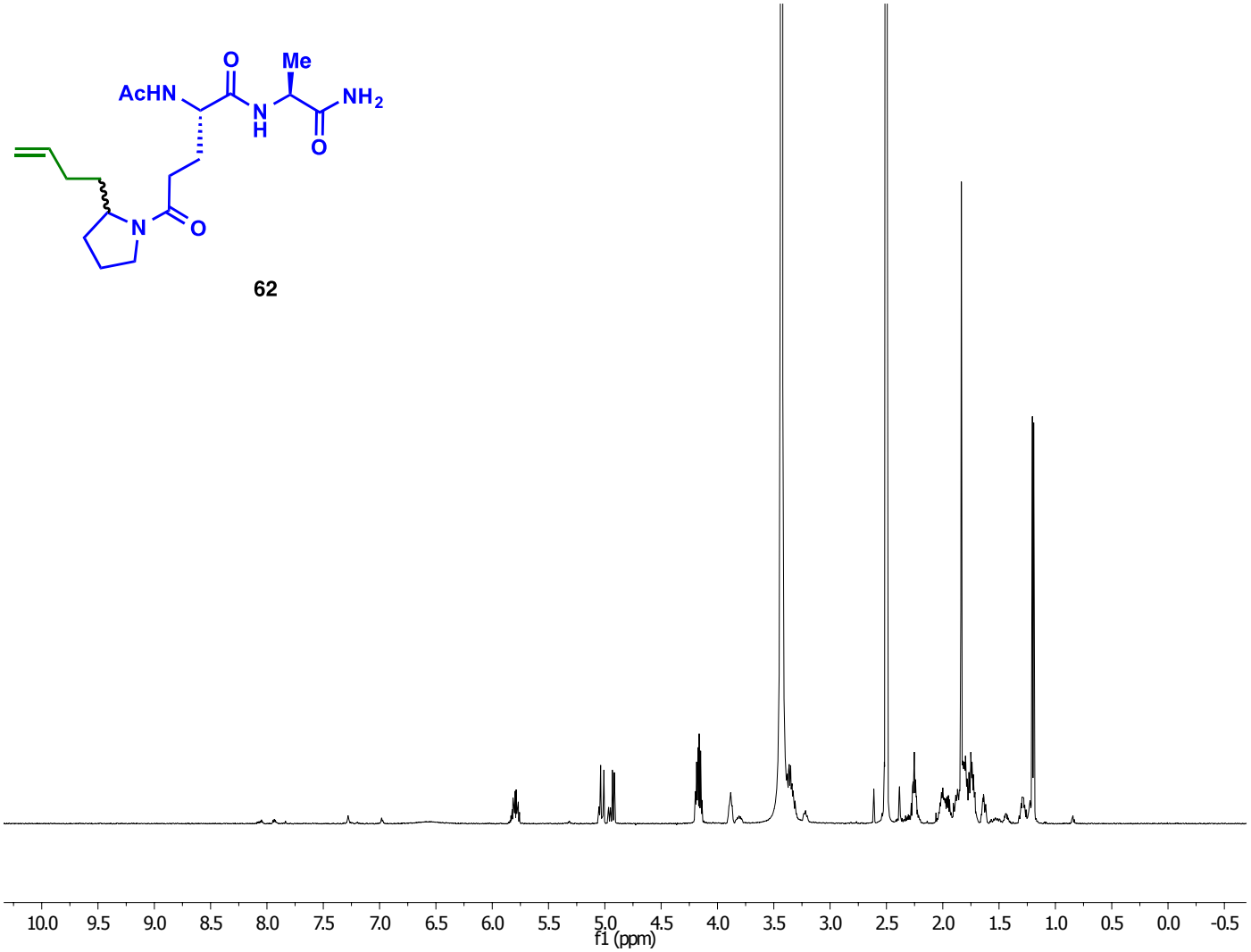

OH
Me
NH2
O
NH
O
HN
AcHN
O
60
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

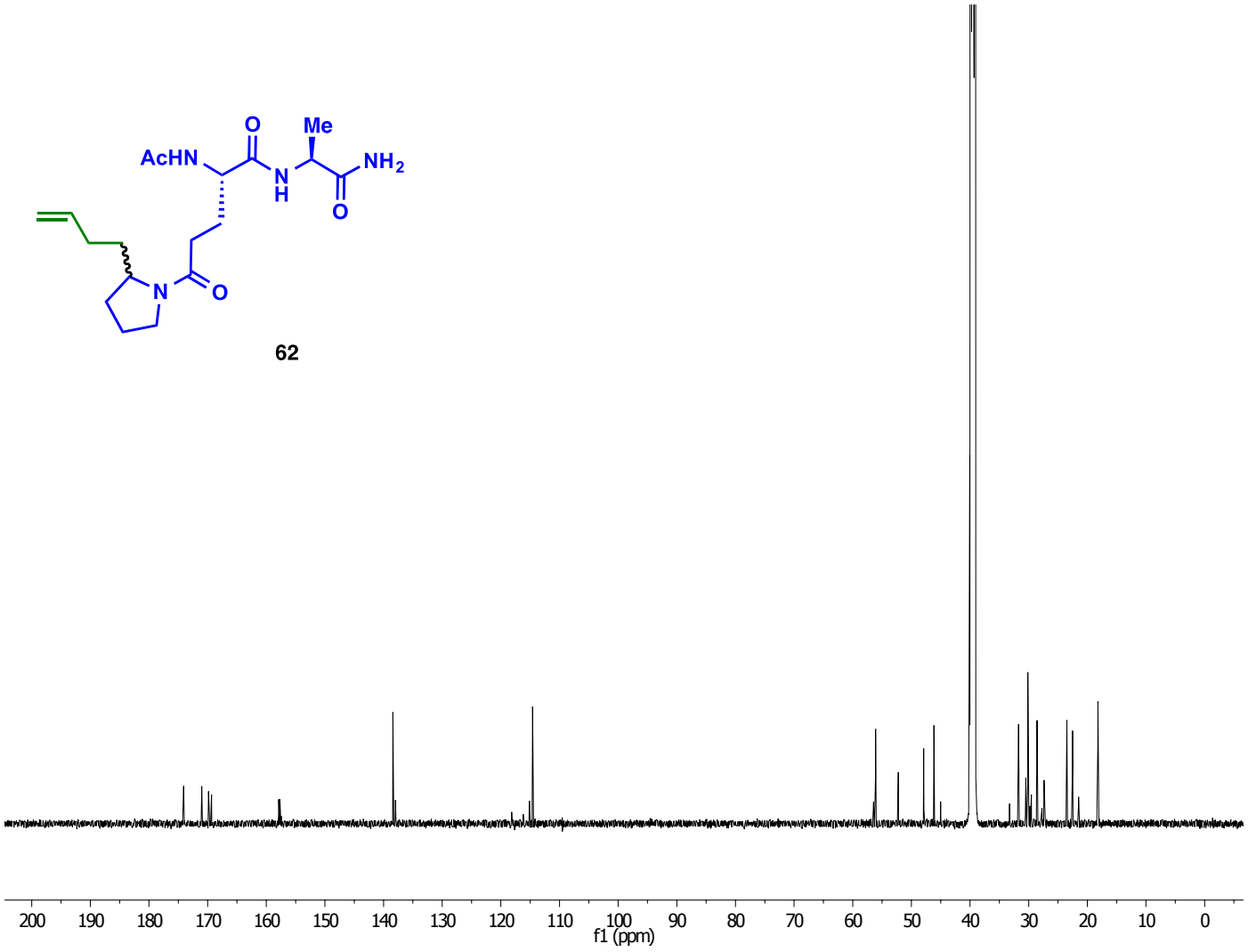

OH
Me
NH2
O
NH
O
HN
AcHN
O
60
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

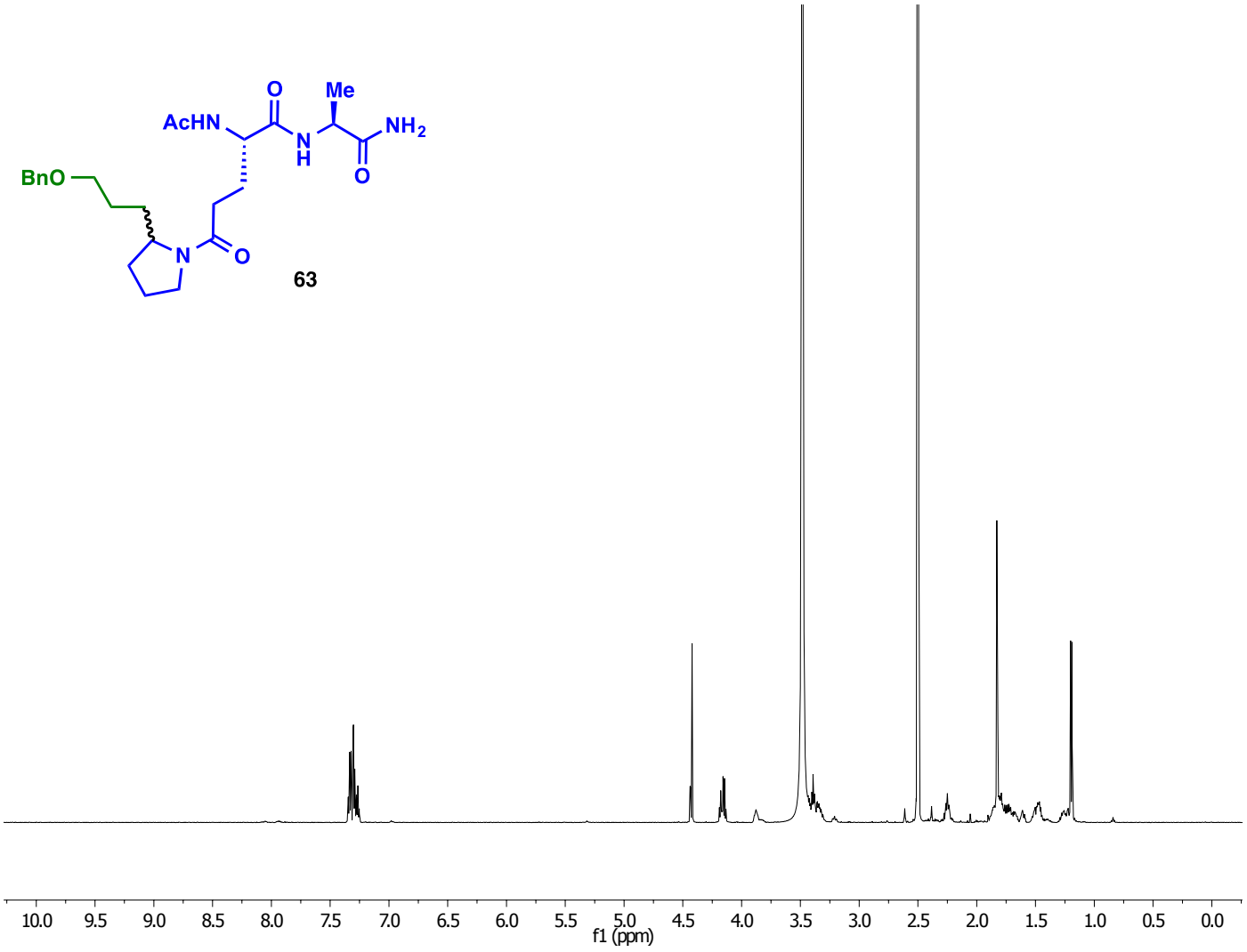

HSQC
OH
Me
NH2
O
NH
O
HN
AcHN
O
60
f2 (ppm)
f1 (ppm)

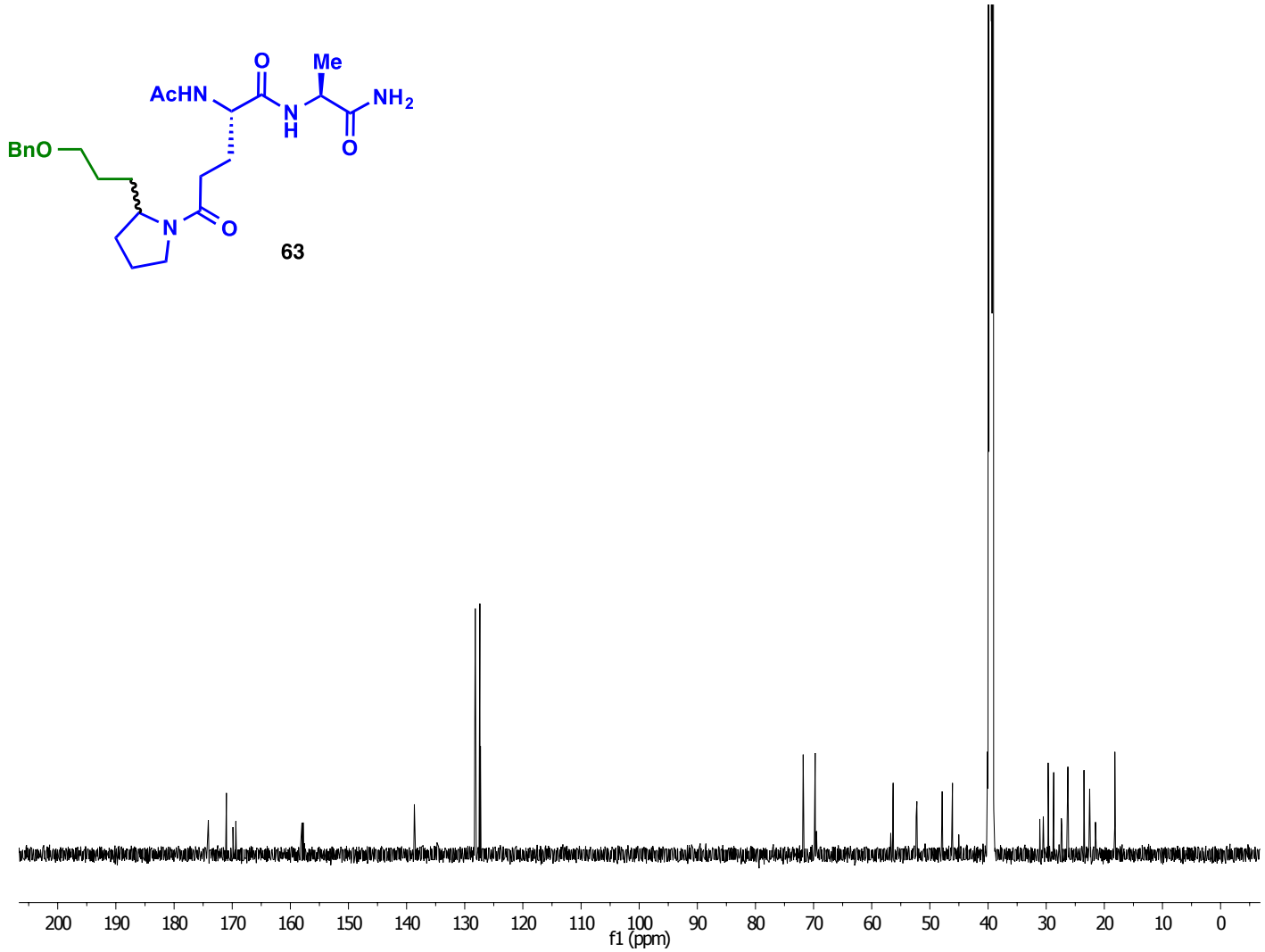

OH
Me
NH2
O
NH
O
HN
AcHN
O
Me
61
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

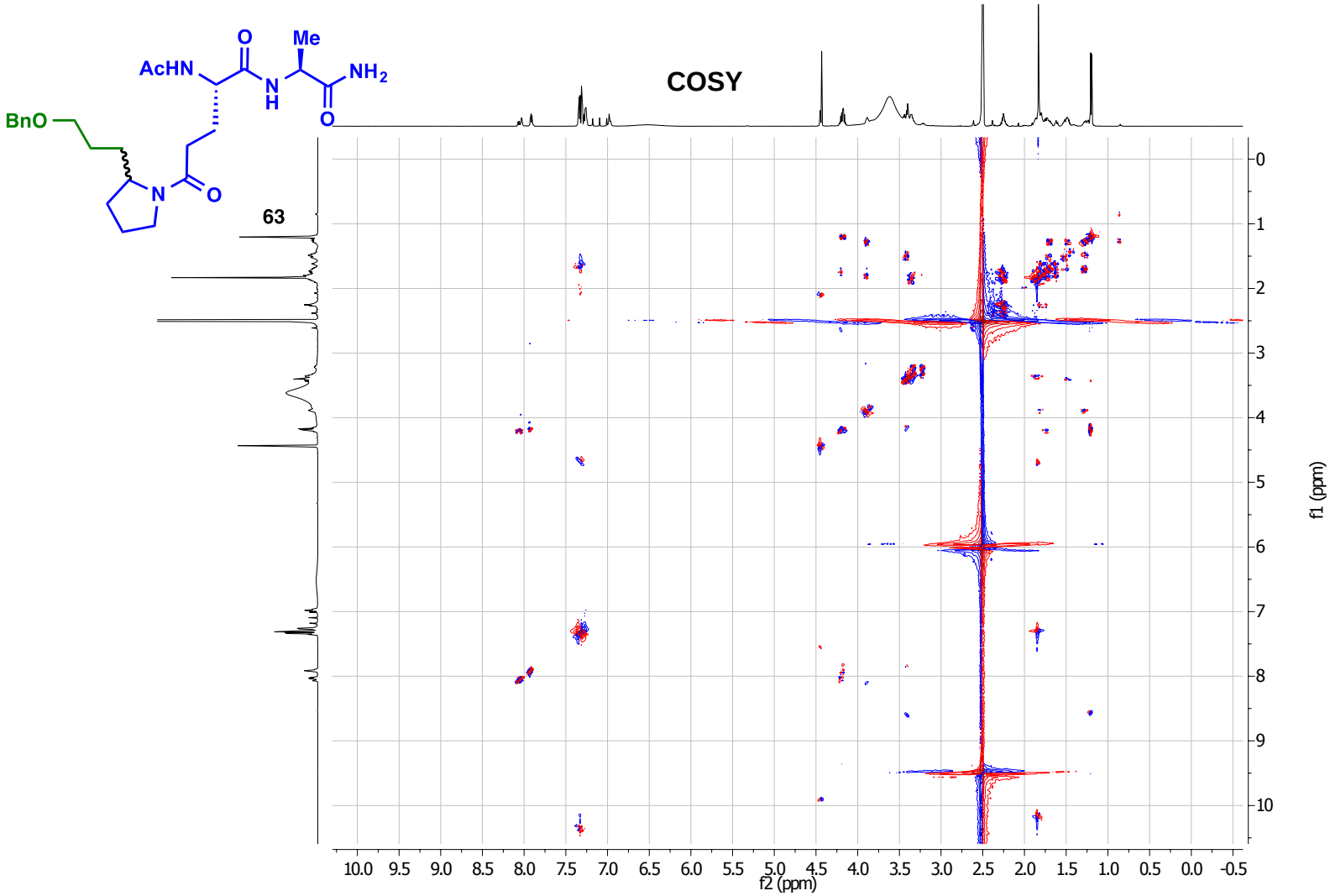

OH
Me
NH2
O
NH
O
HN
AcHN
O
Me
61
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

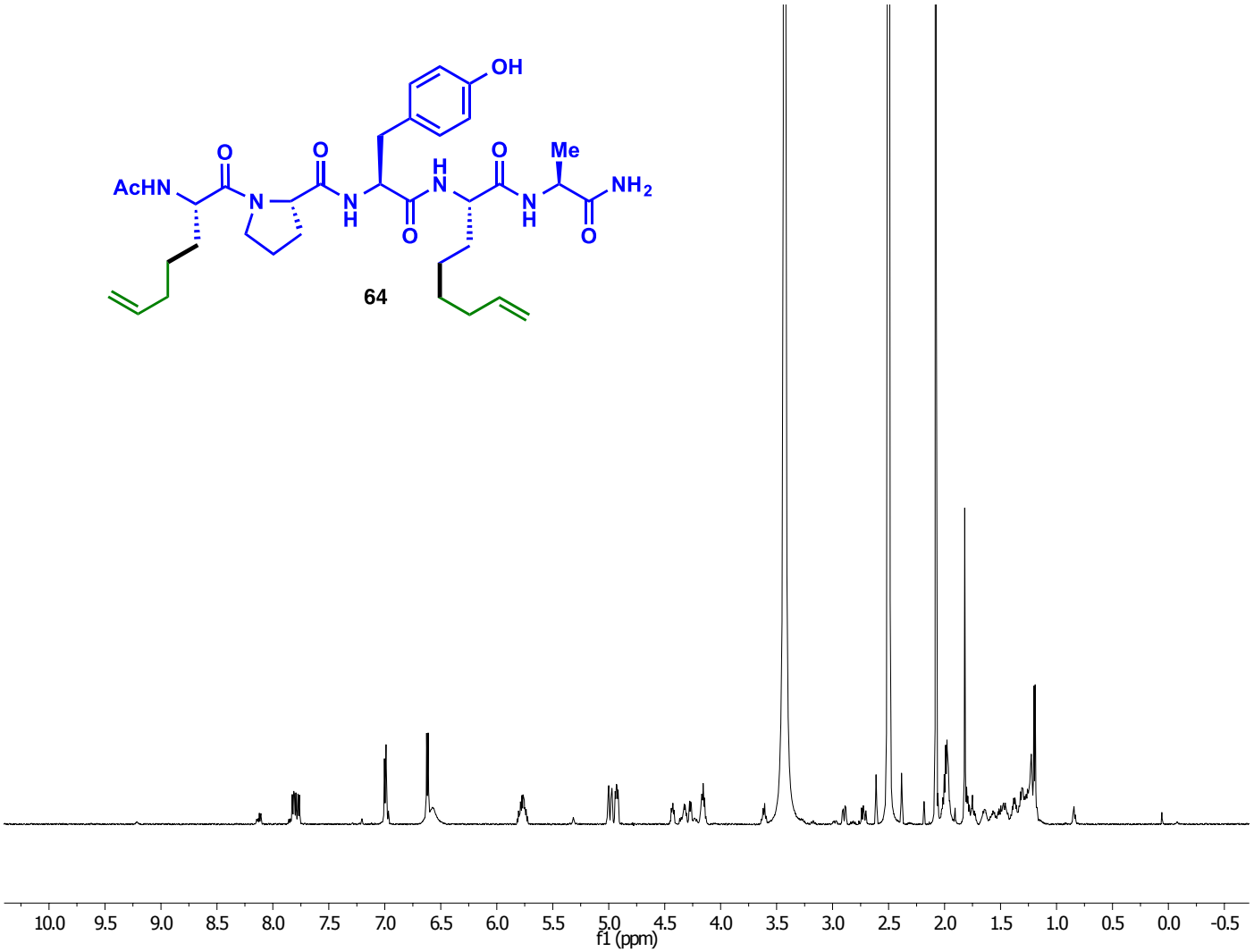

AcHN
O
Me
N
H
NH2
O
N
O
62
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

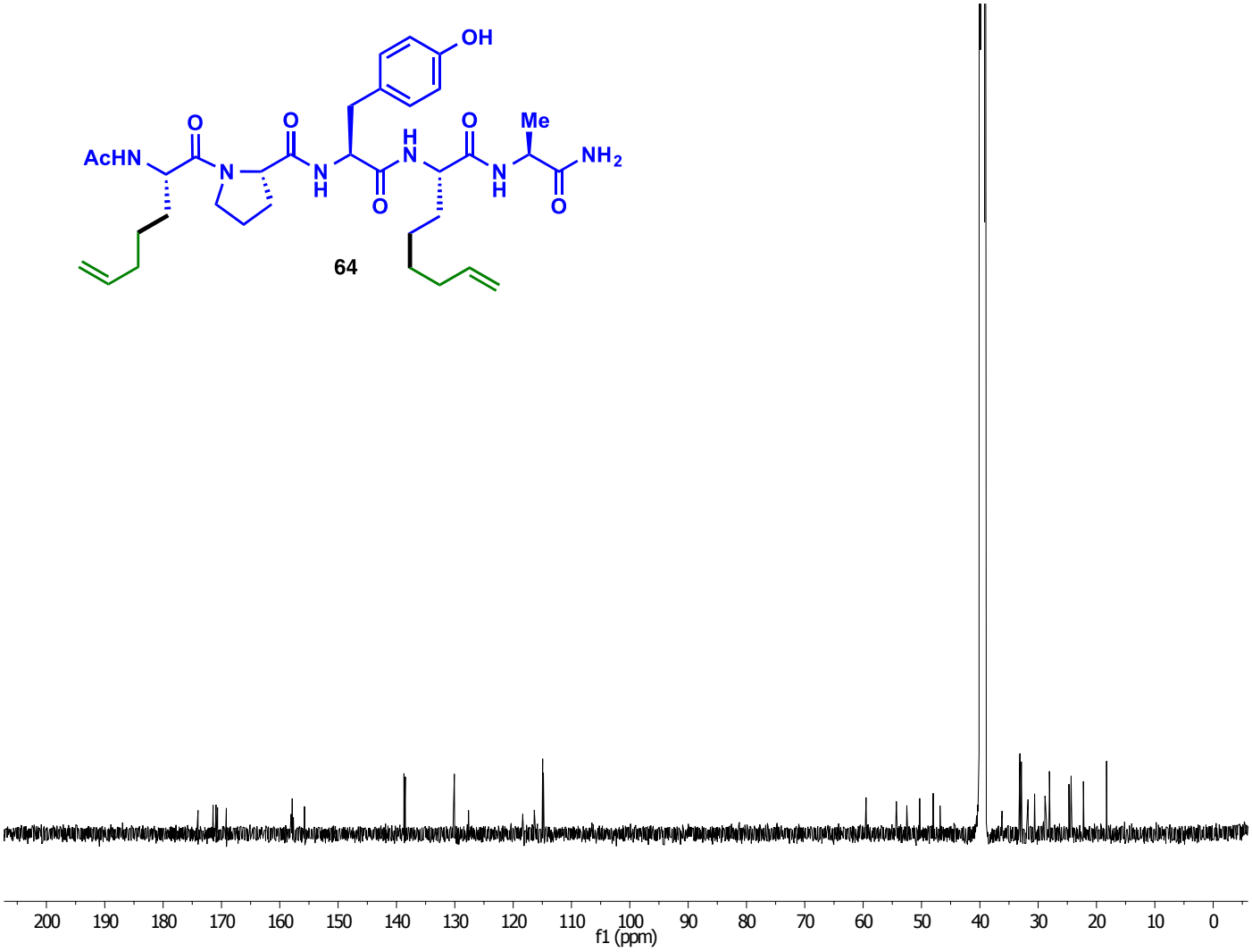

AcHN
O
Me
NH2
N
H
O
N
O
62
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

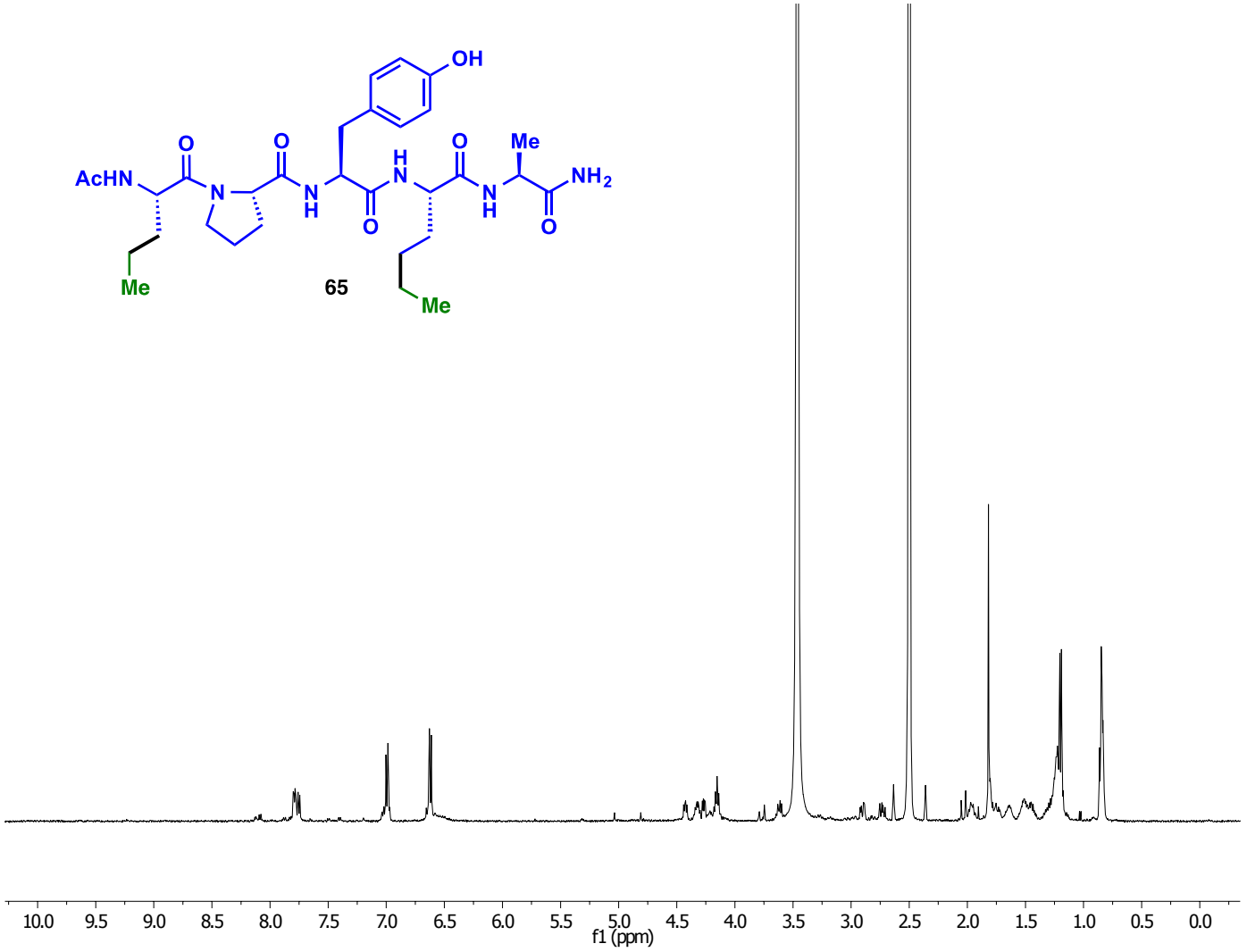

AcHN
O
Me
NH2
N
H
O
BnO
N
O
63
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

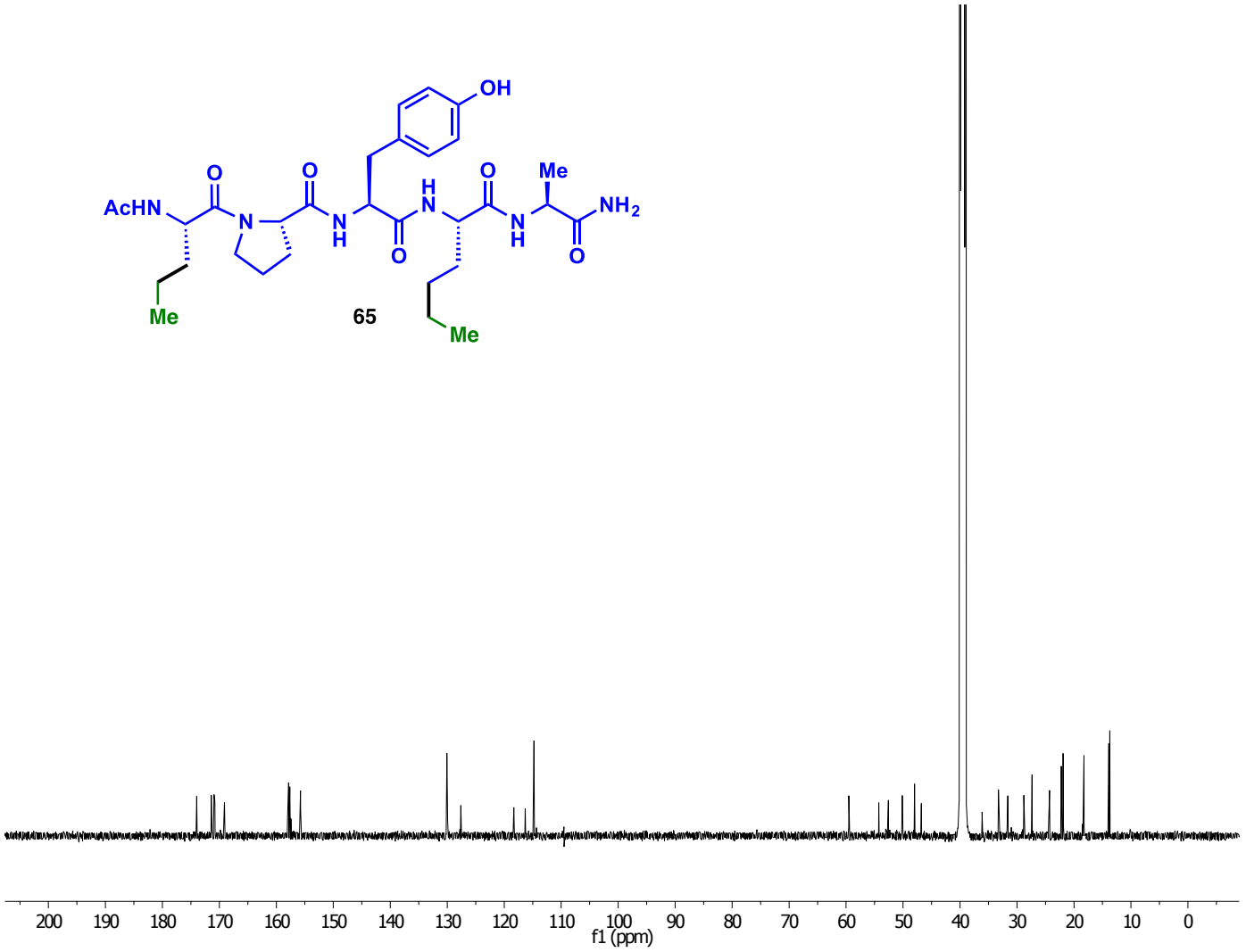

AcHN
O
Me
N
H
NH2
O
BnO
N
O
63
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

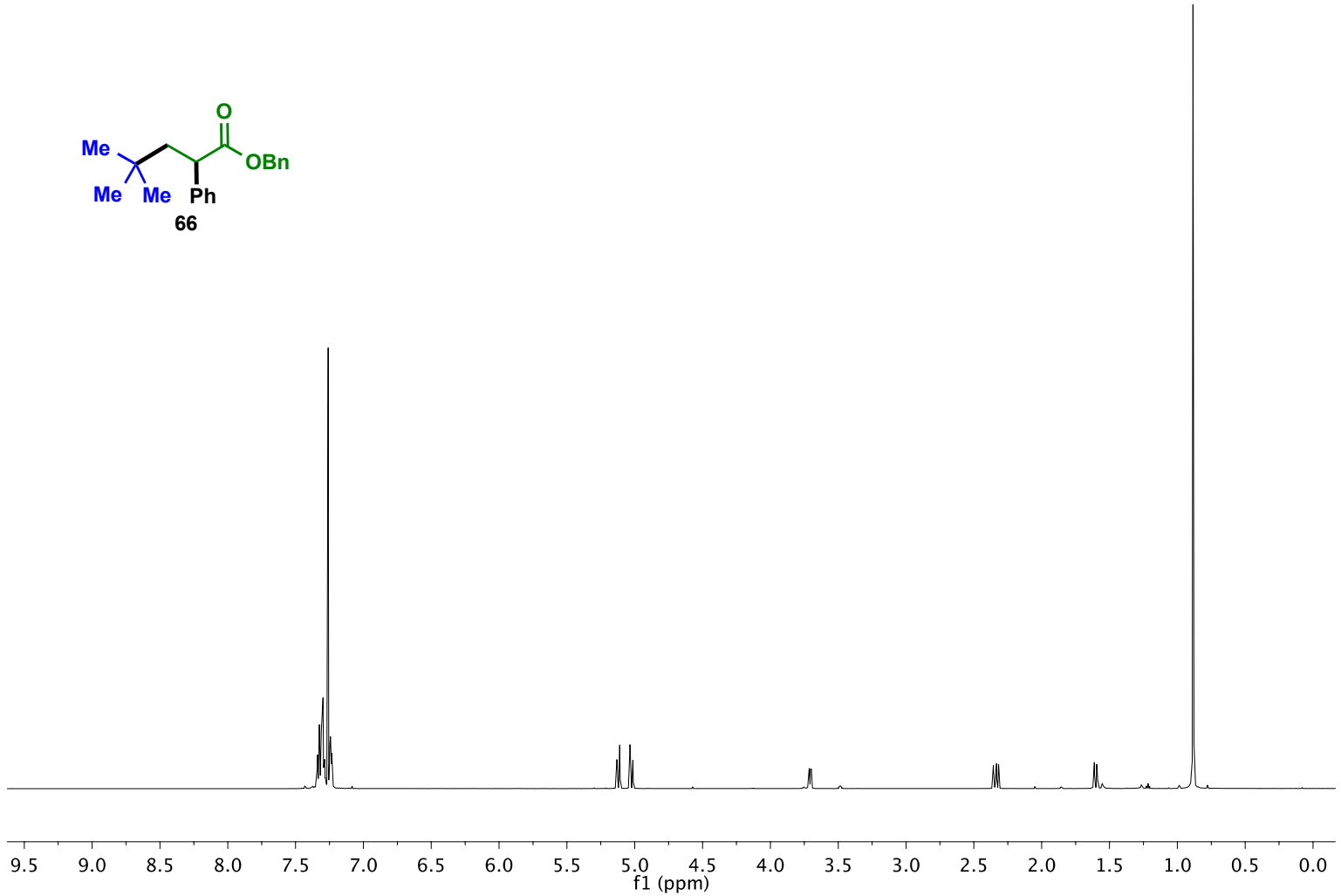

COSY
63
AcHN
O
Me
N
H
NH2
O
BnO
N
O
f2 (ppm)
f1 (ppm)

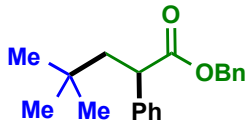

OH
AcHN
O
O
N
N
H
H
N
O
O
N
H
Me
NH2
O
64
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


OH
AcHN
O
O
N
N
H
H
N
O
O
N
H
Me
NH2
O
64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

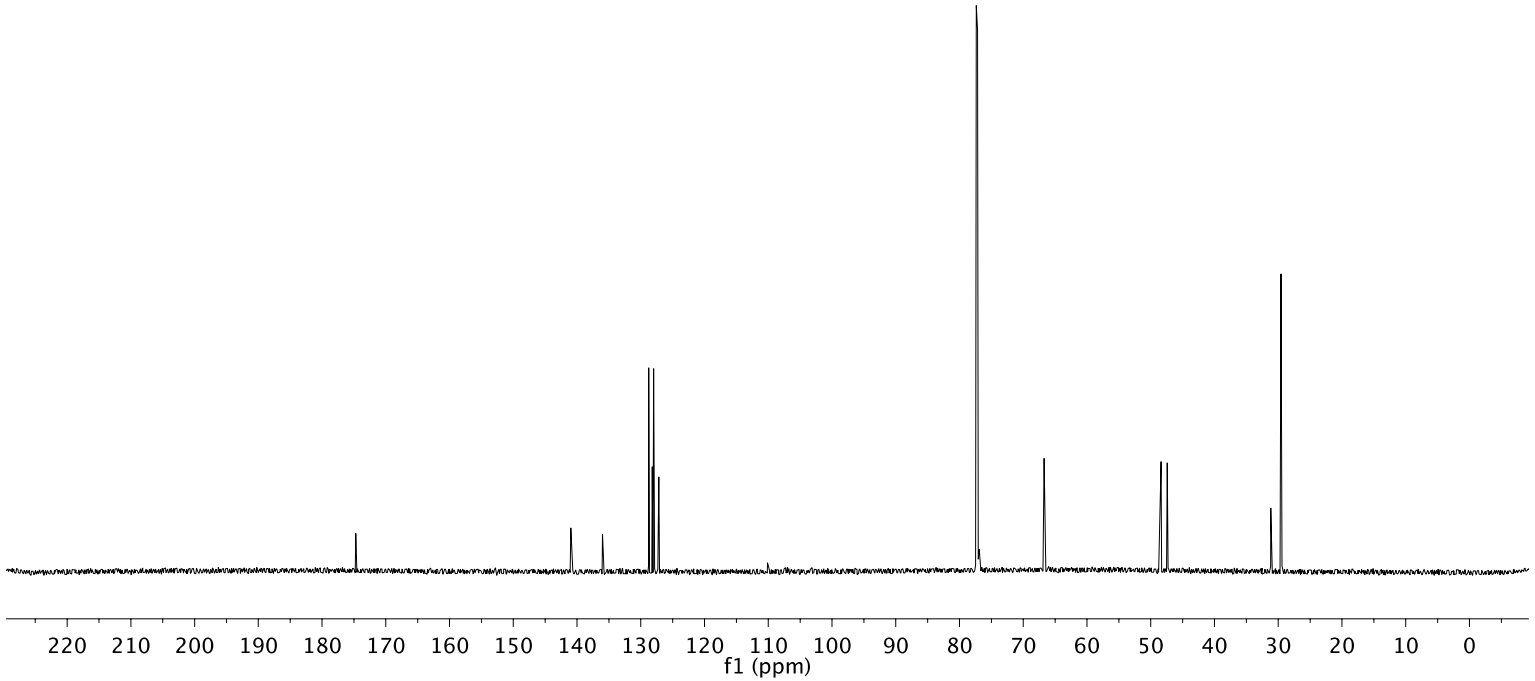

OH
AcHN
O
O
O
Me
NH2
N
H
N
H
N
H
O
O
O
Me
Me
65
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

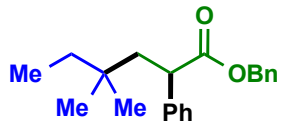

OH
AcHN
O
O
N
N
H
H
N
O
O
O
N
H
Me
NH2
O
Me
Me
65
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
Me
OBn
Me
Me
Ph
66
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

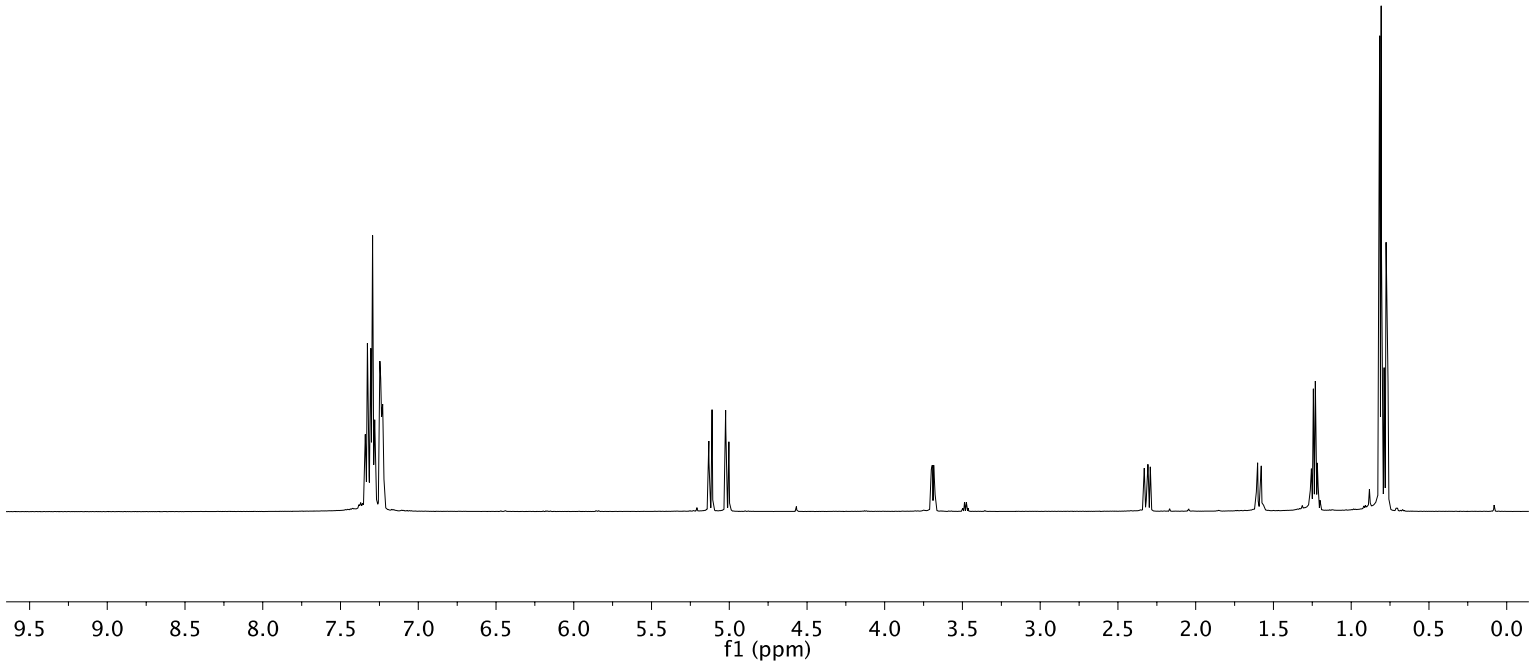

O
Me
OBn
Me
Me
Ph

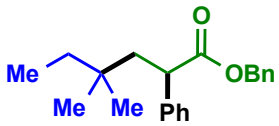
66


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

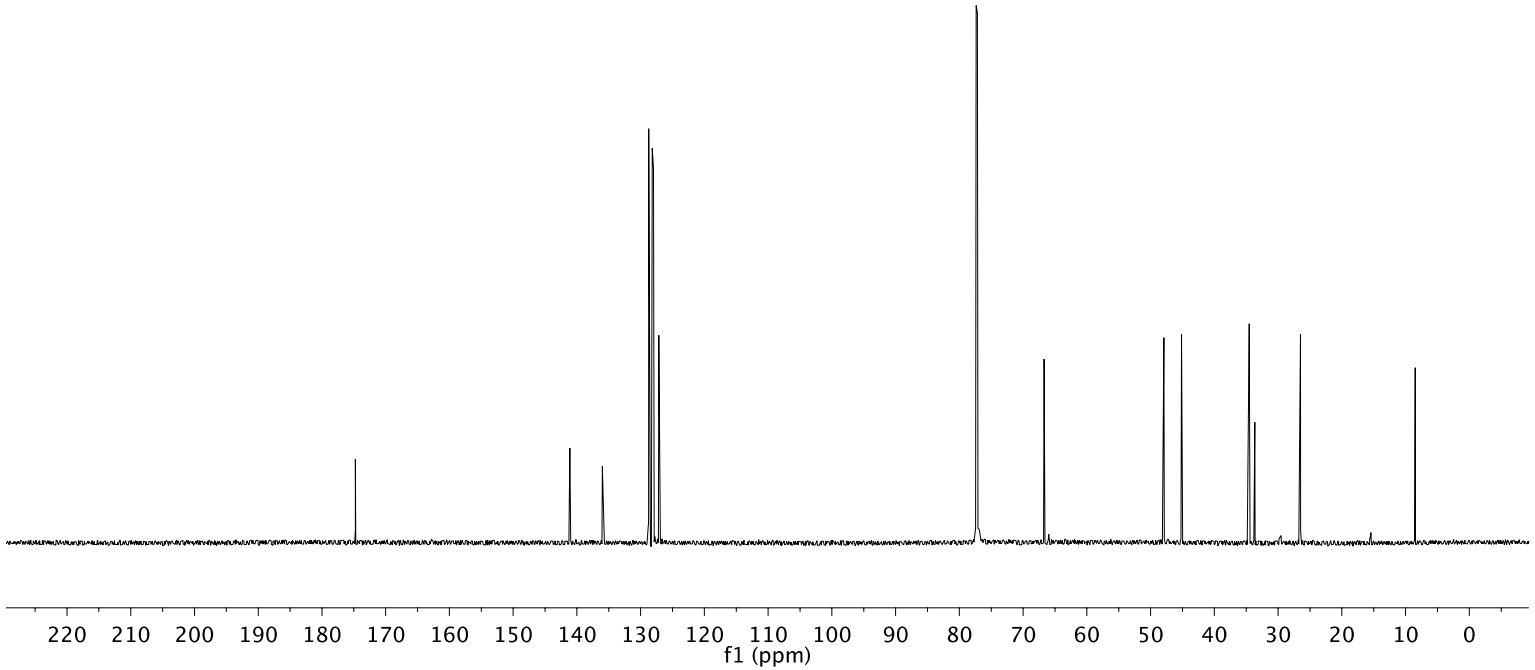

O
Me
OBn
Me
Me
Ph

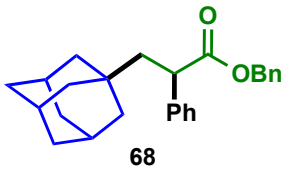
67


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

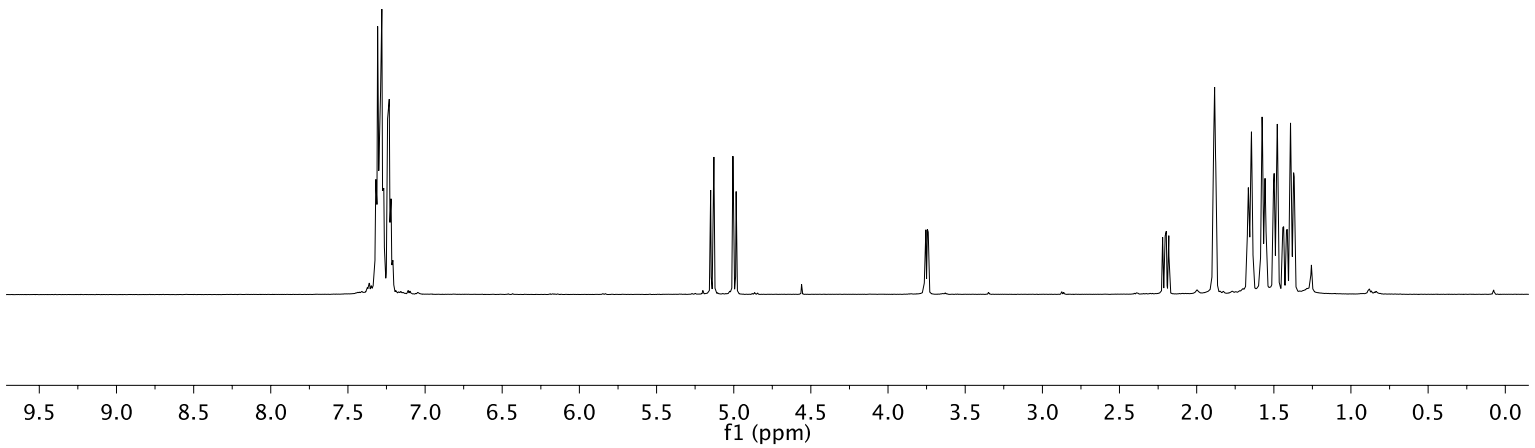

O
Me
OBn
Me
Me
Ph

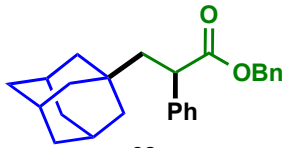
67


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

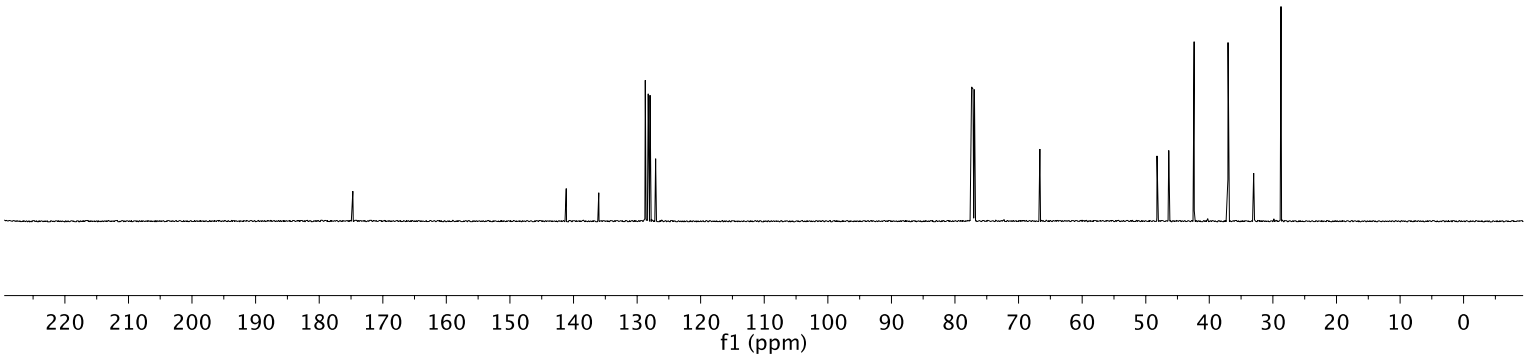

O
OBn
Ph

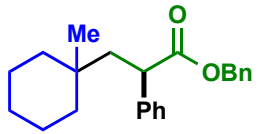
68


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

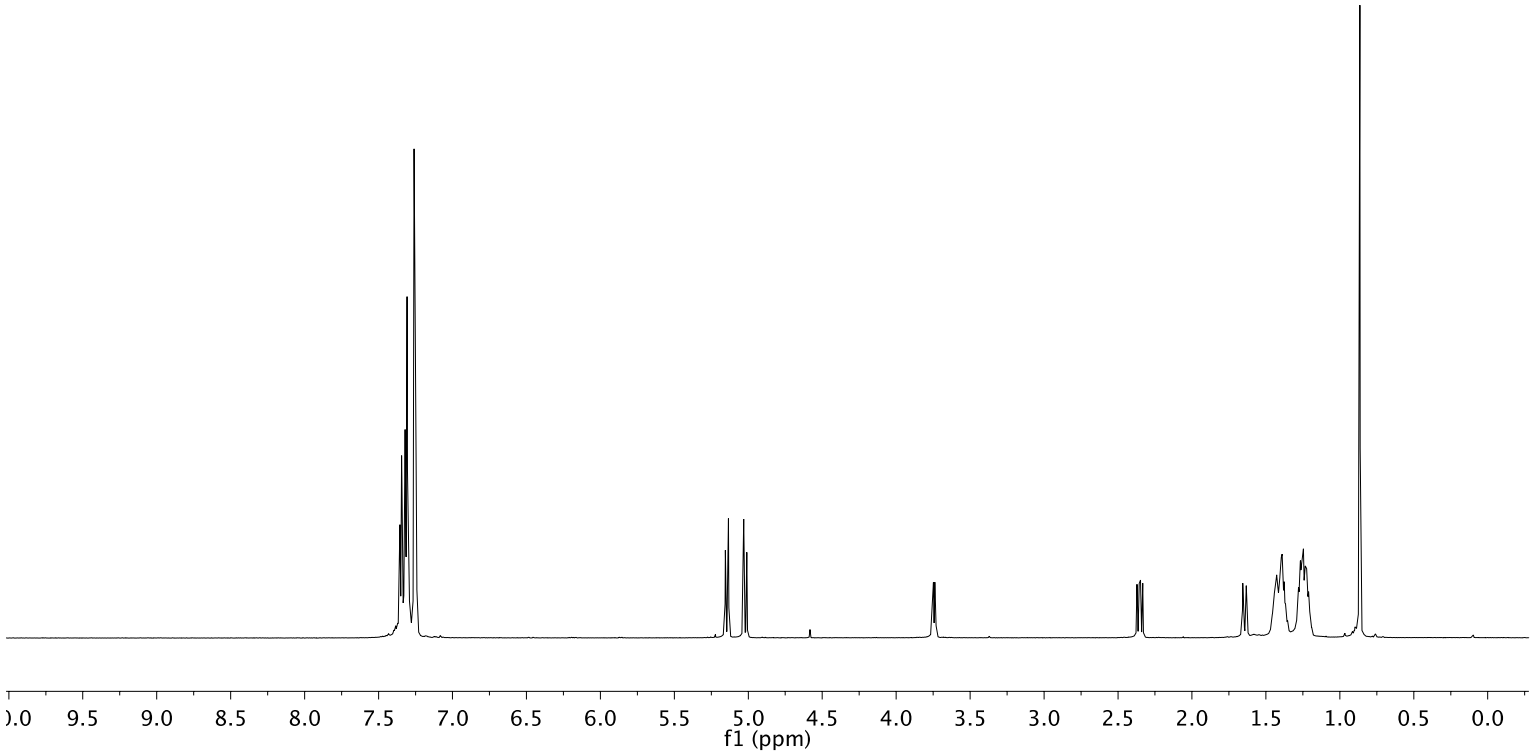

O
OBn
Ph

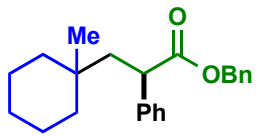
68


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

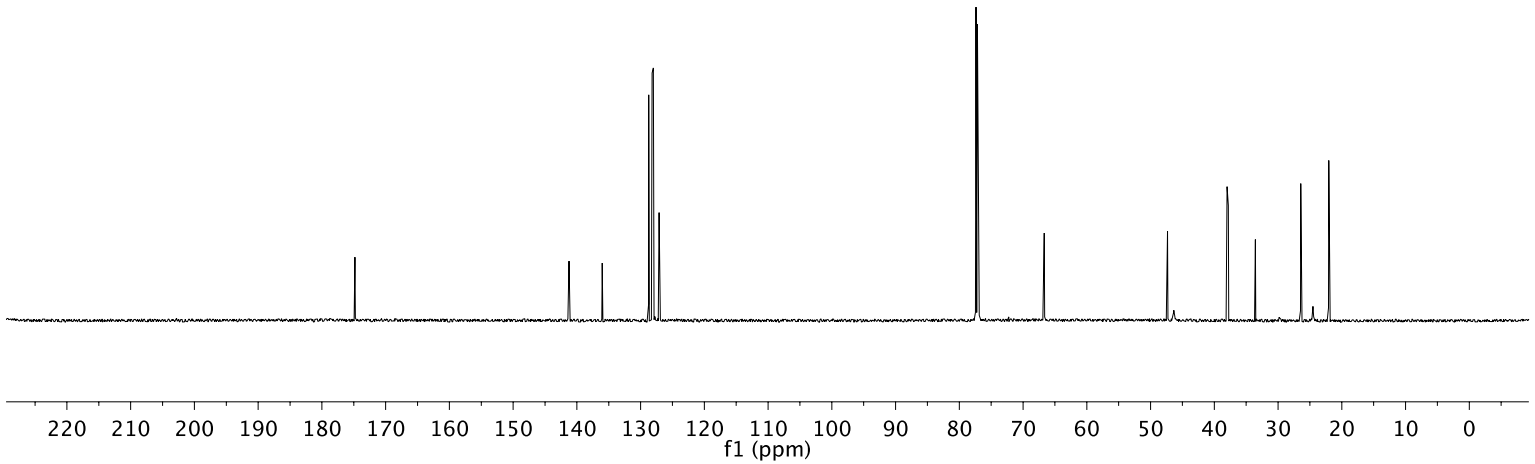

Me
O
OBn
Ph

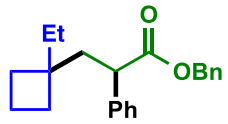
69


0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

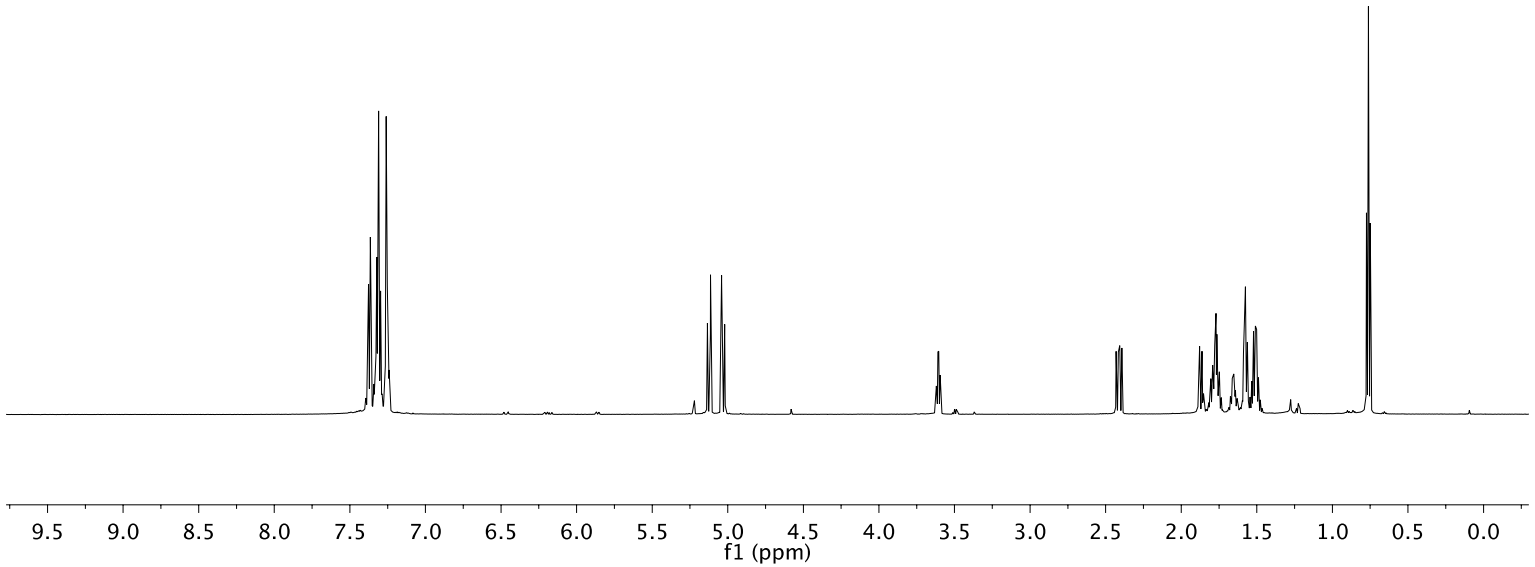

Me
O
OBn
Ph

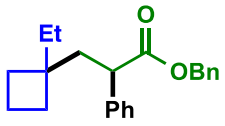
69


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

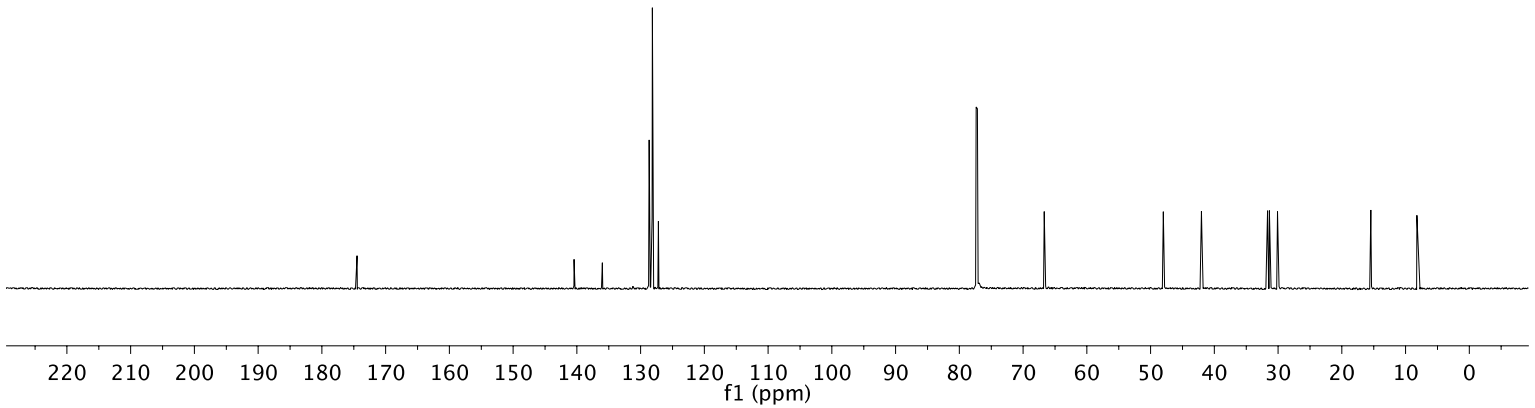

Et
O
OBn
Ph

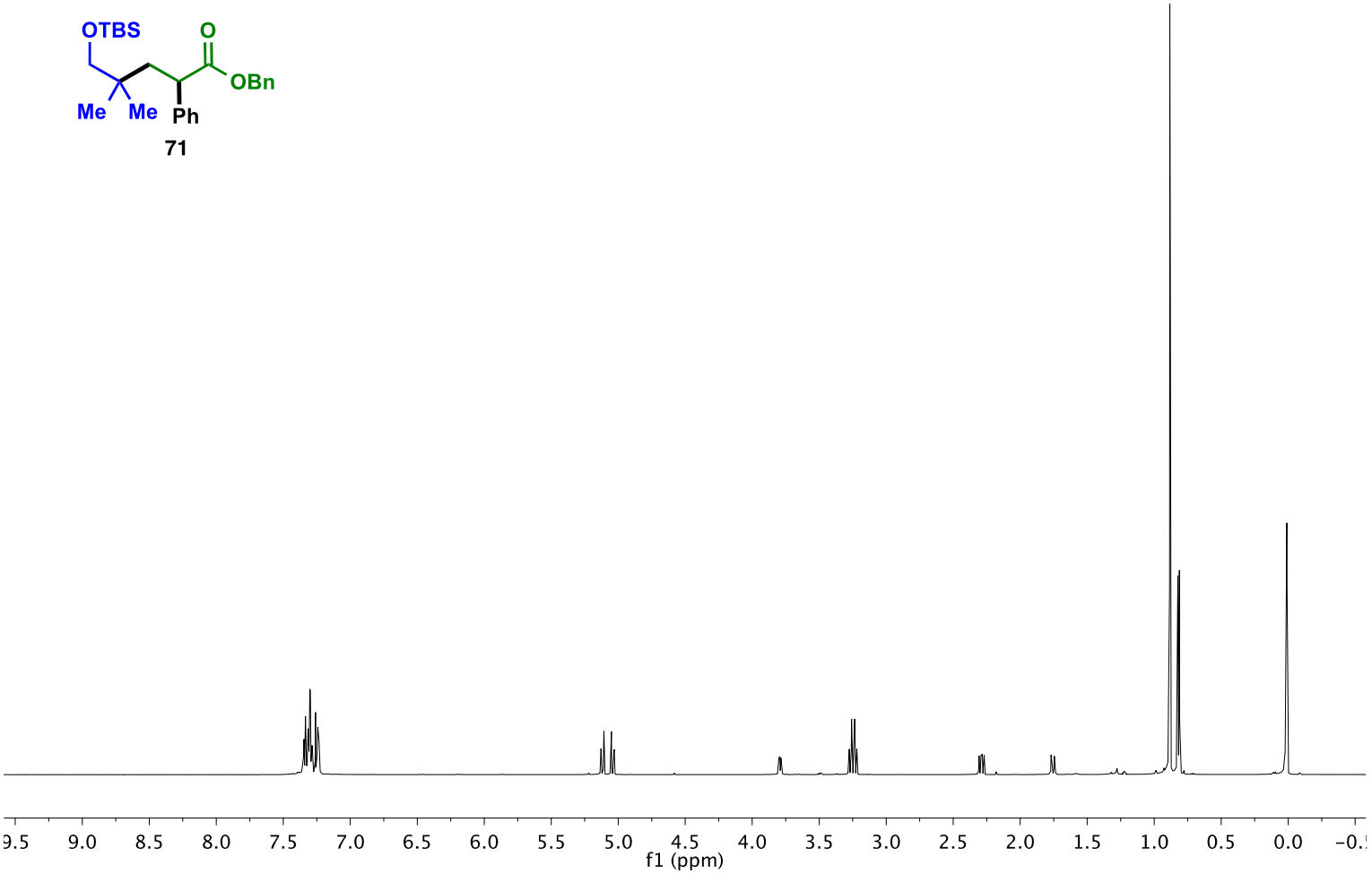
70


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


Et
O
OBn
Ph

70


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OTBS
O
OBn
Me
Me
Ph
71
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
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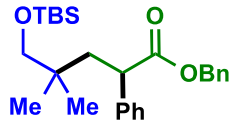
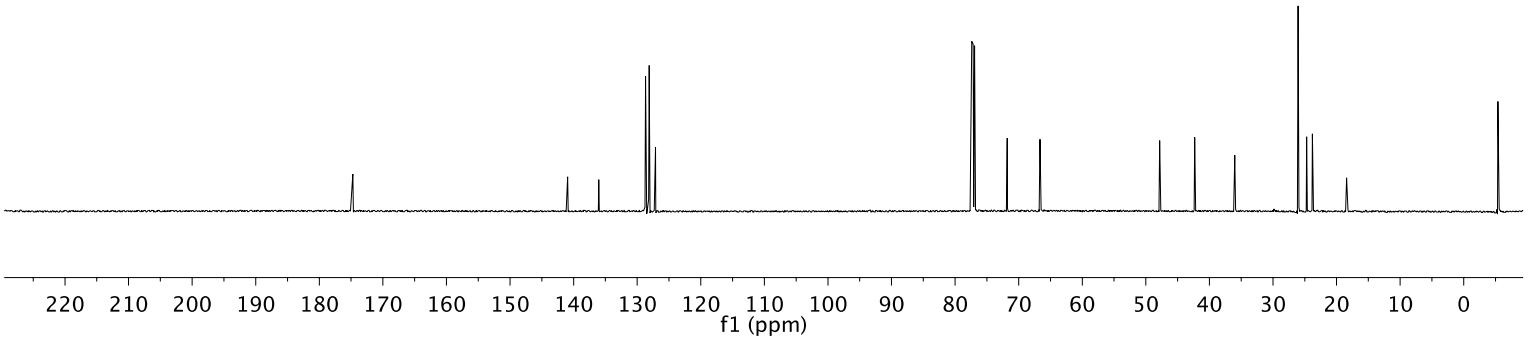
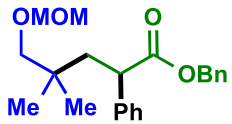
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

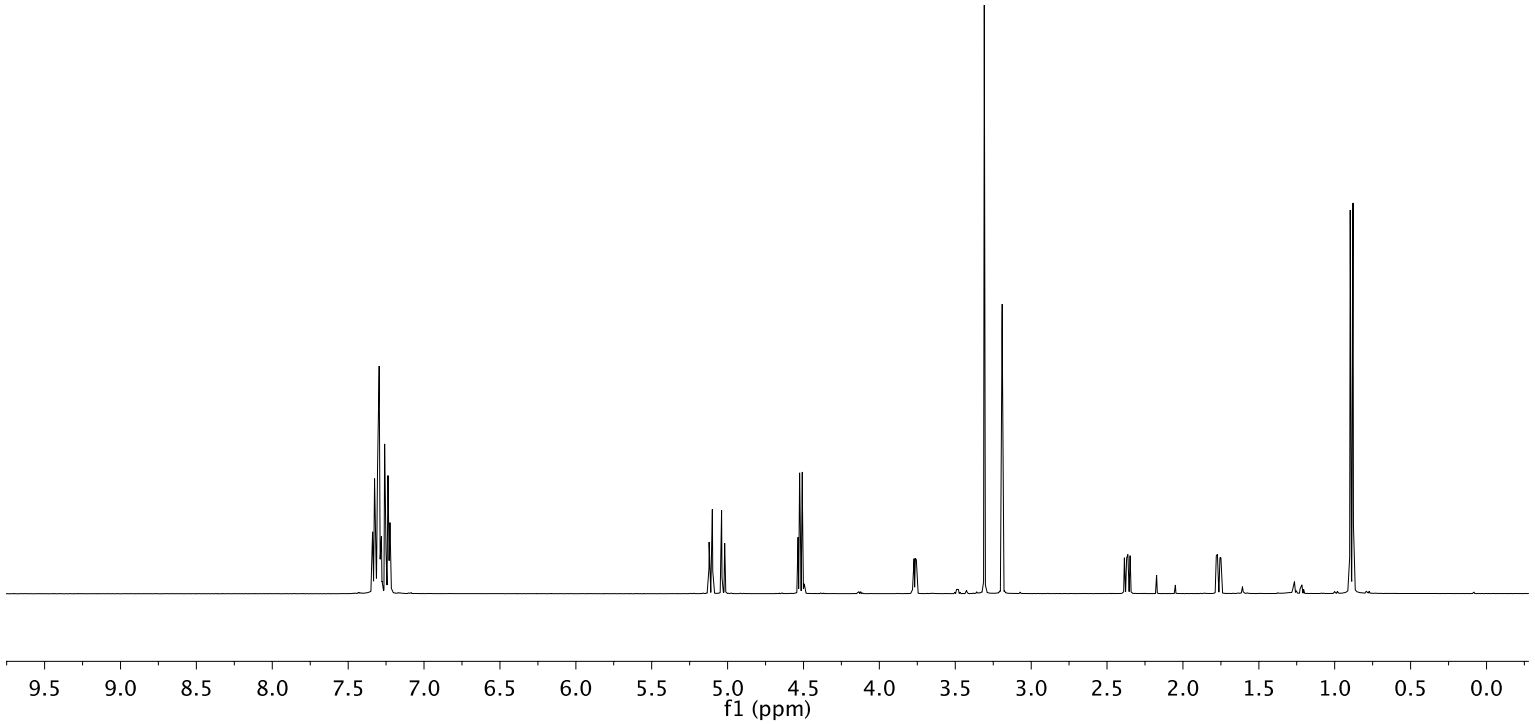

OTBS
O
OBn
Me
Me
Ph

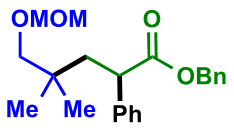
71


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMOM
O
OBn
Me
Me
Ph

72


9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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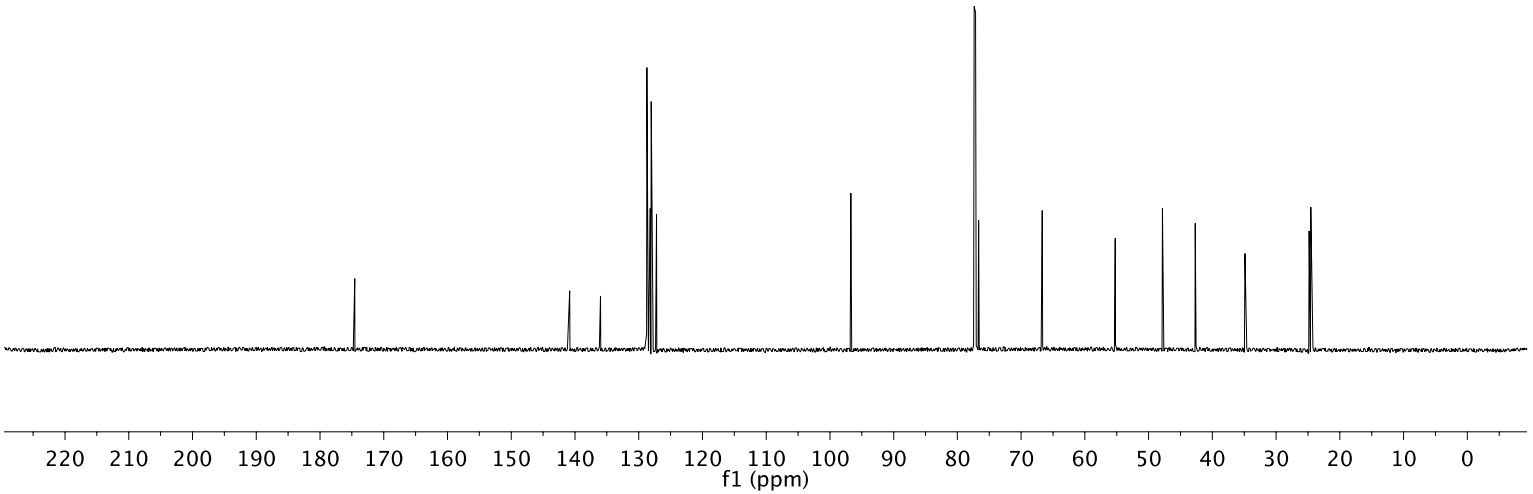
OBn
Me
Me
Ph

72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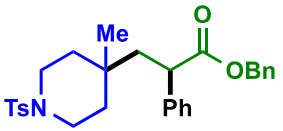
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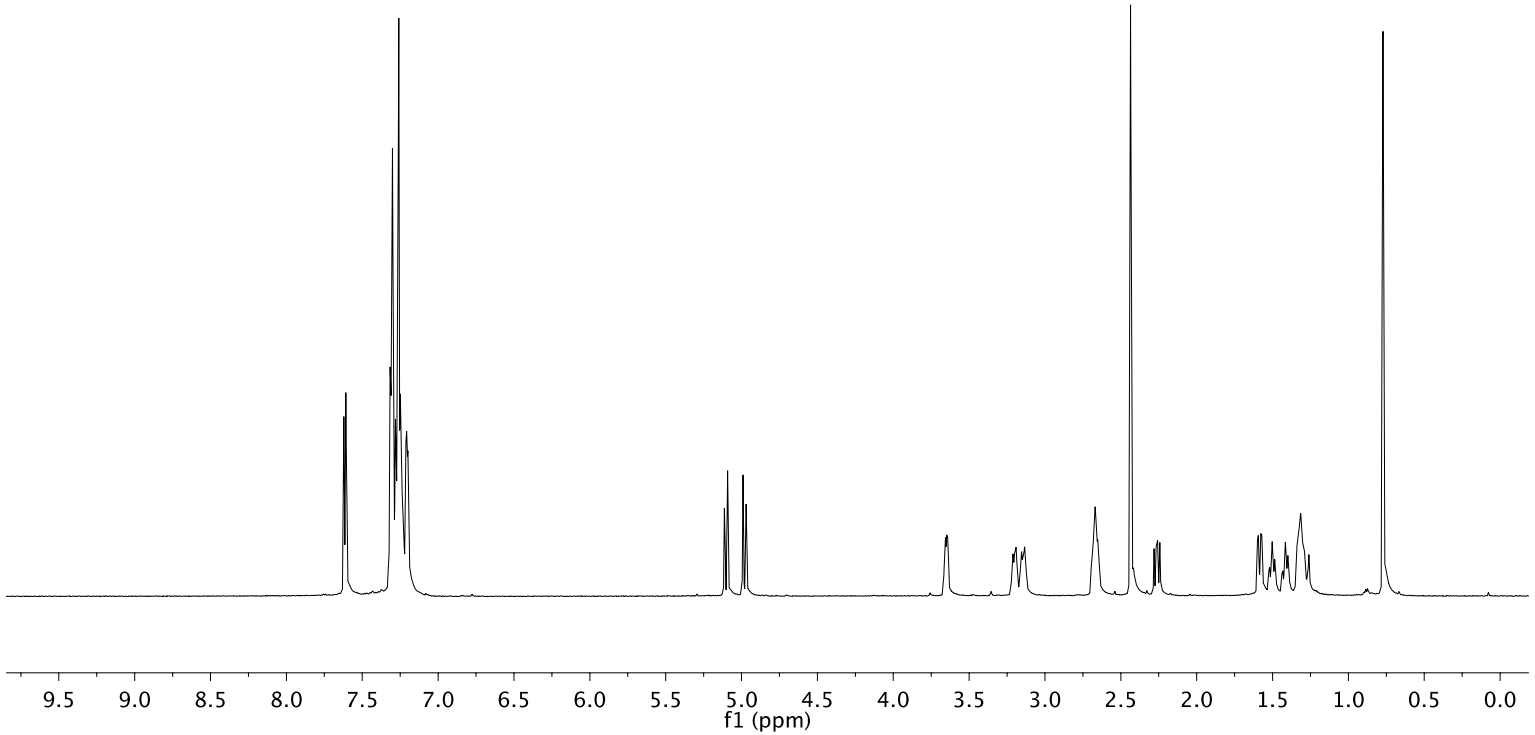
OBn
TsN
Ph

73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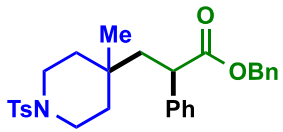
0.0
f1 (ppm)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Ph

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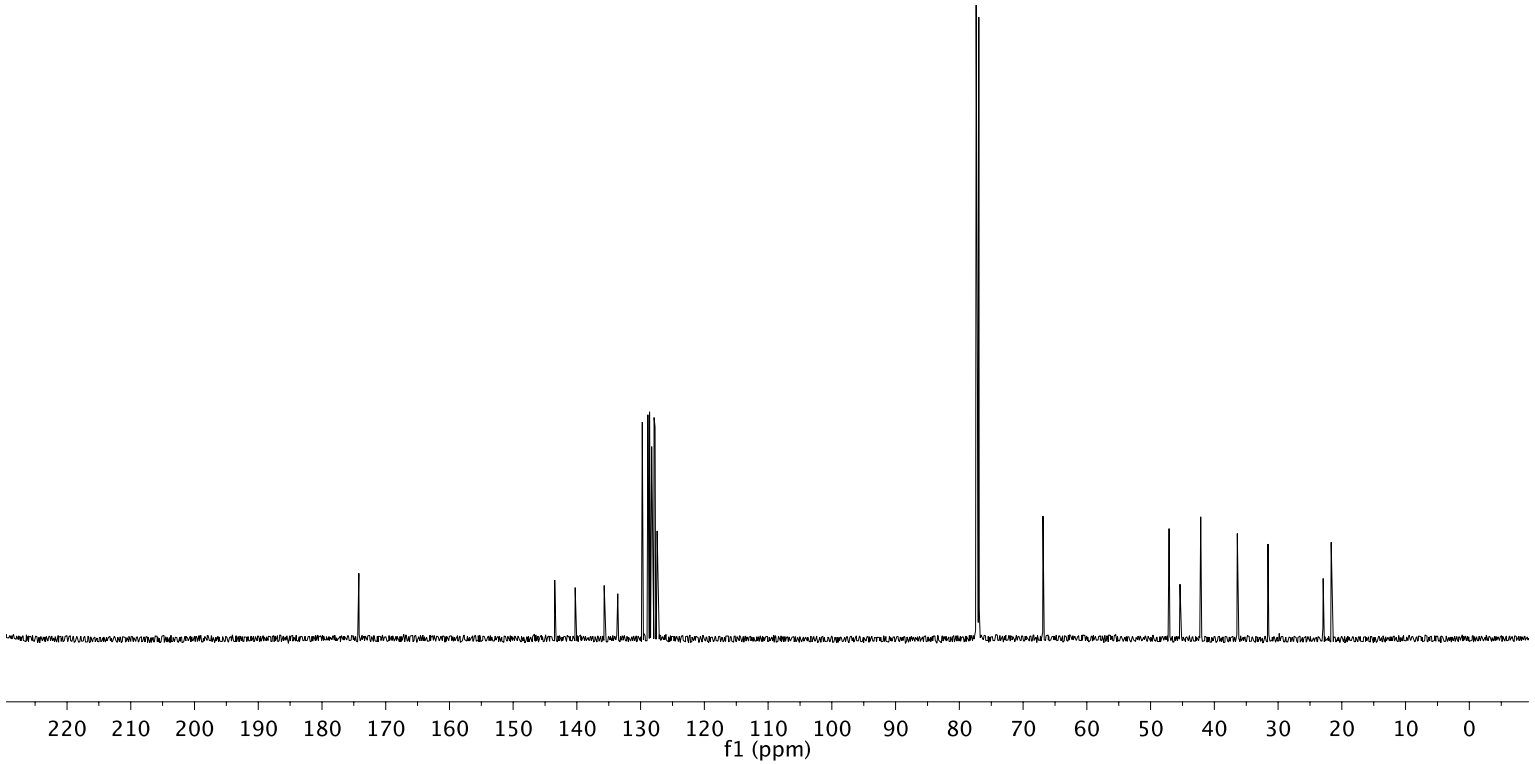
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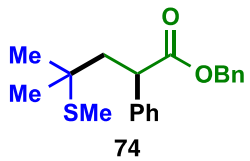
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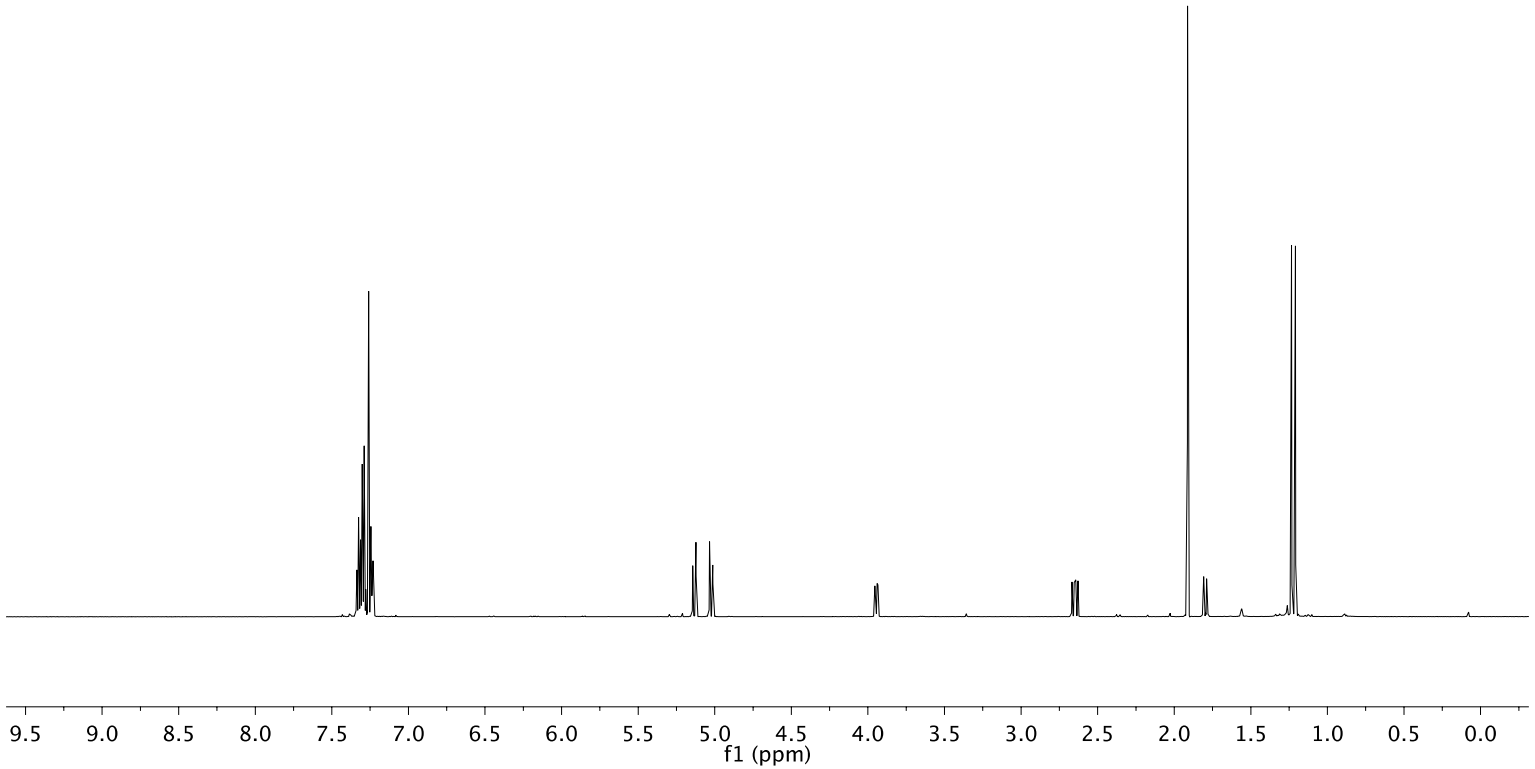
Ph
O
OBn

74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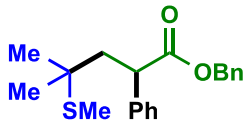
f1 (ppm)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OBn
SMe
Ph

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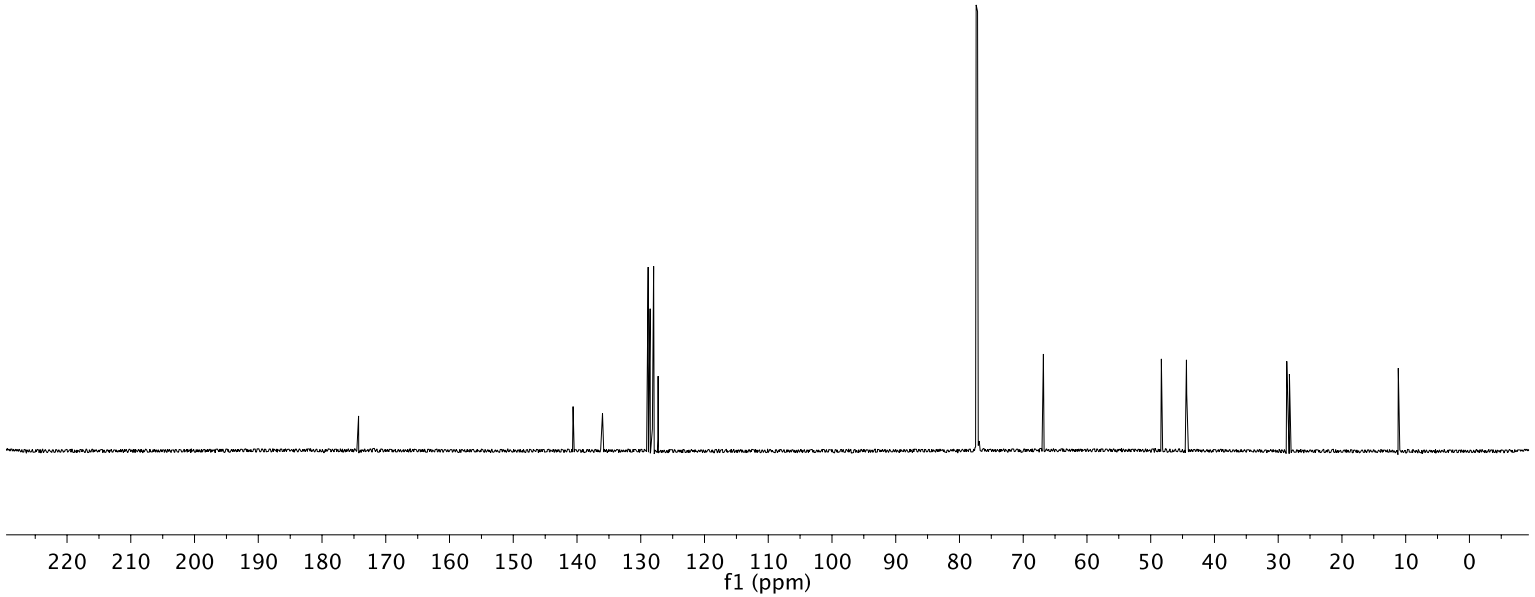
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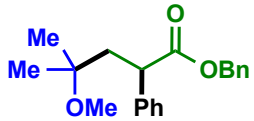
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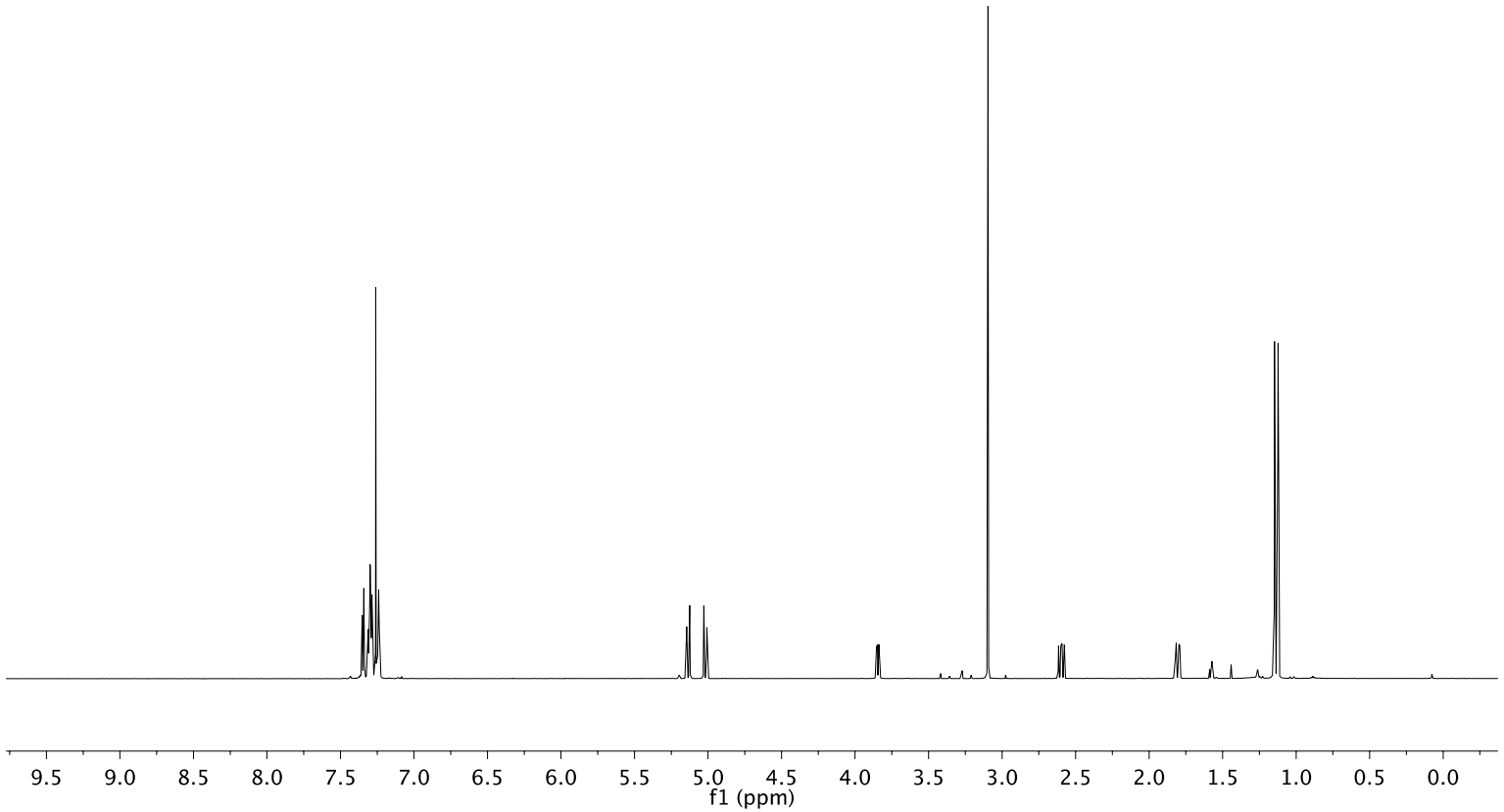
Ph
O
OBn

75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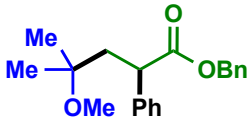
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OMe
Ph
O
OBn

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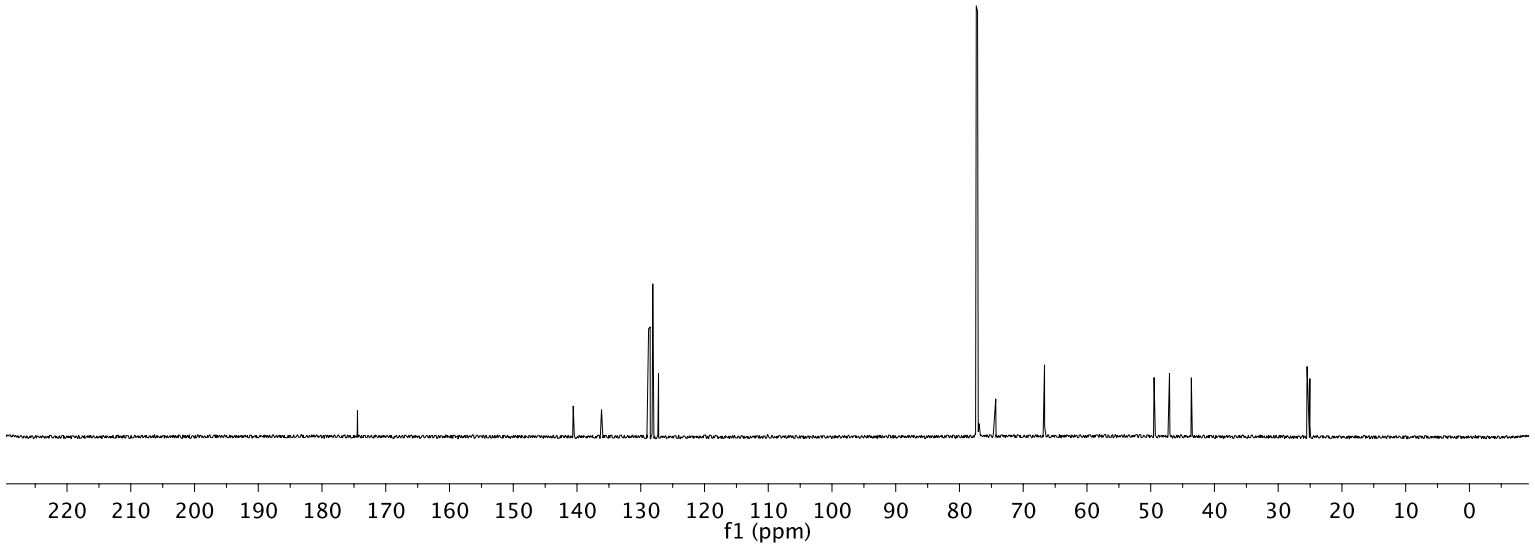
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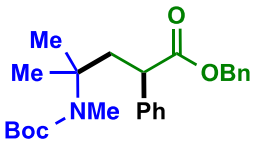
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76

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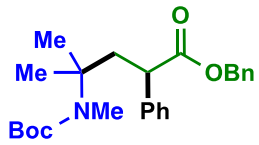
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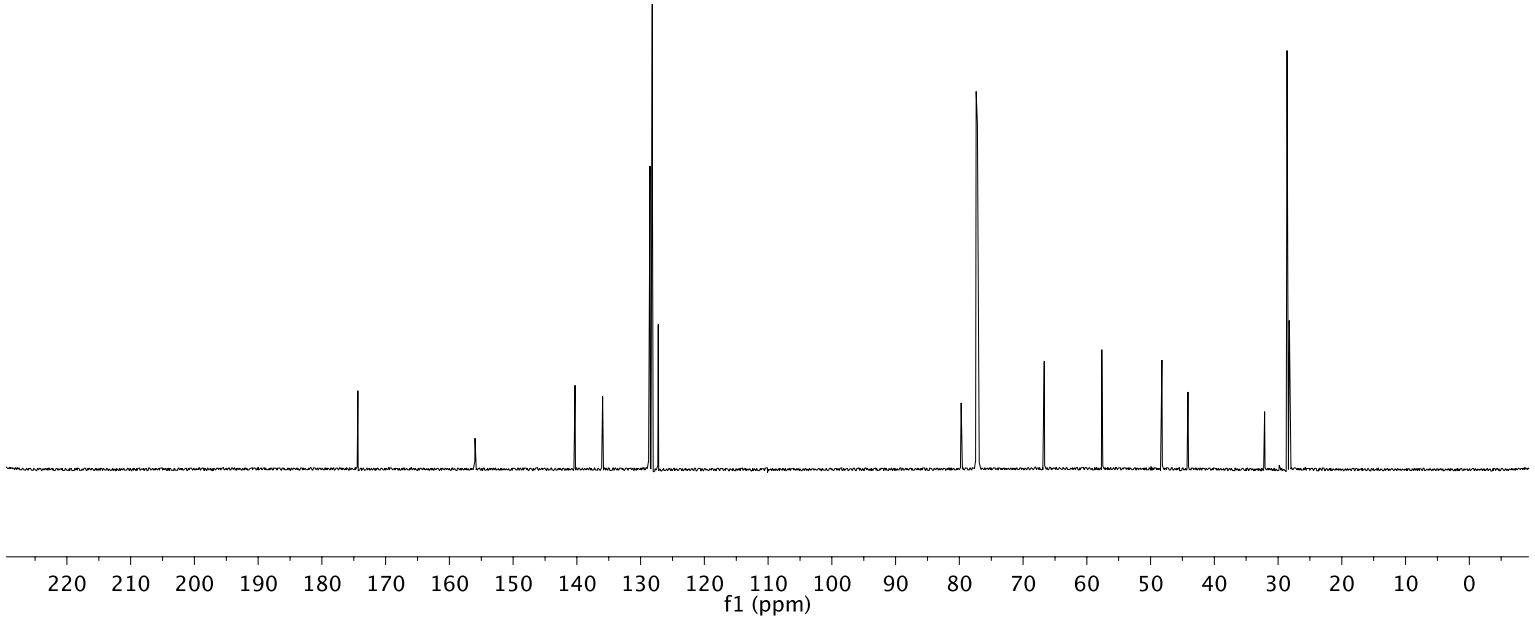
76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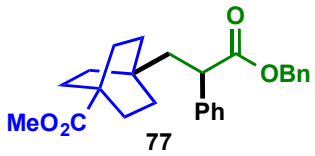
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Ph
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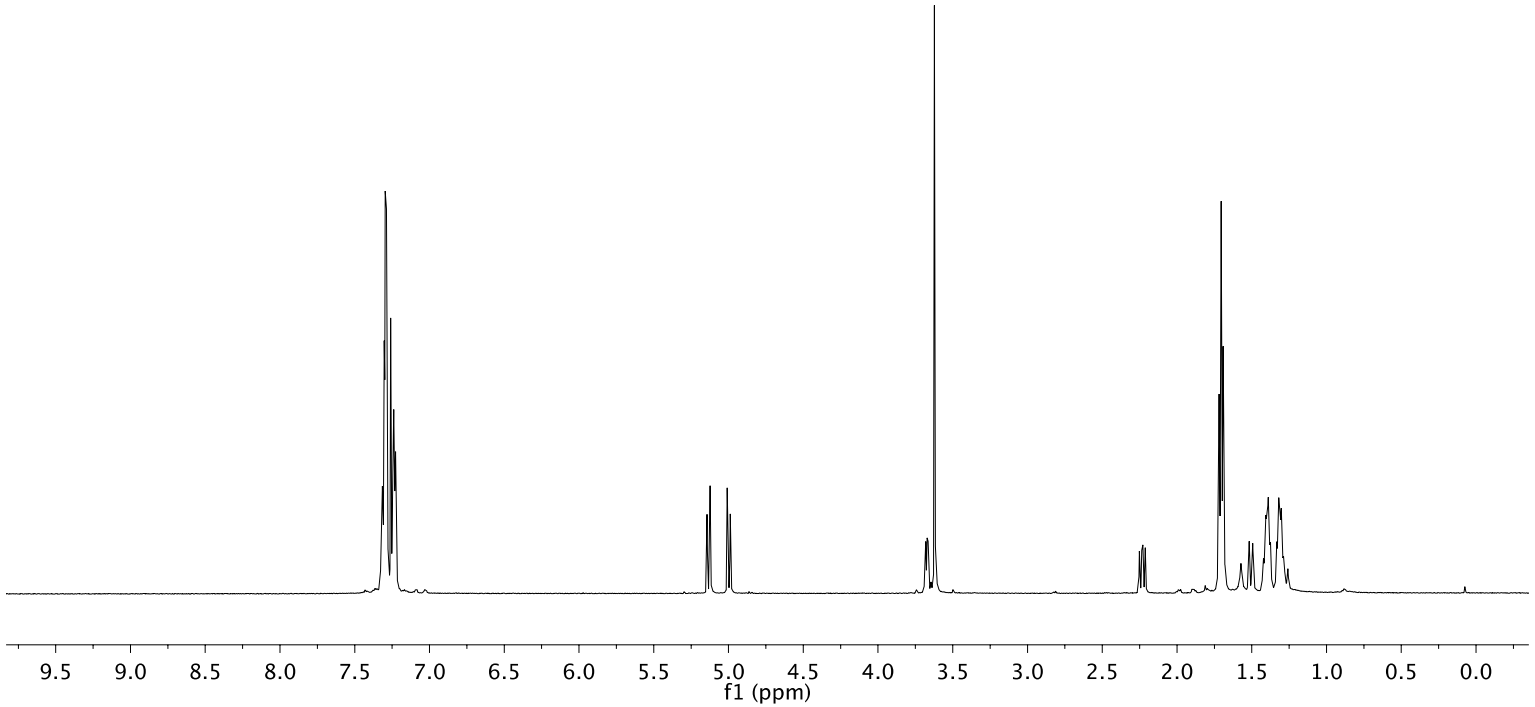
77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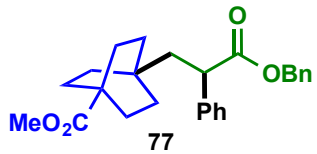
f1 (ppm)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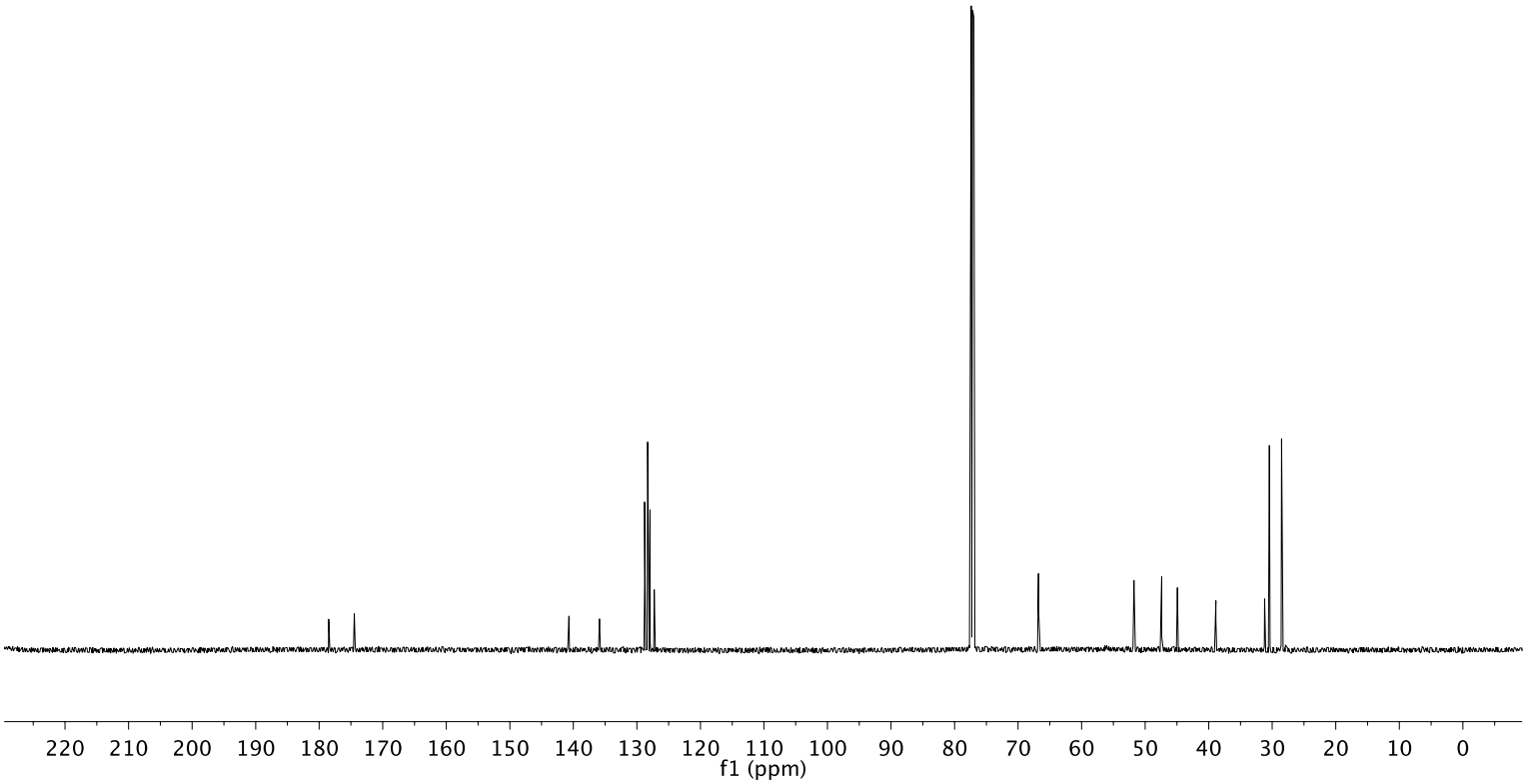
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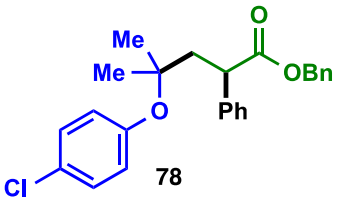
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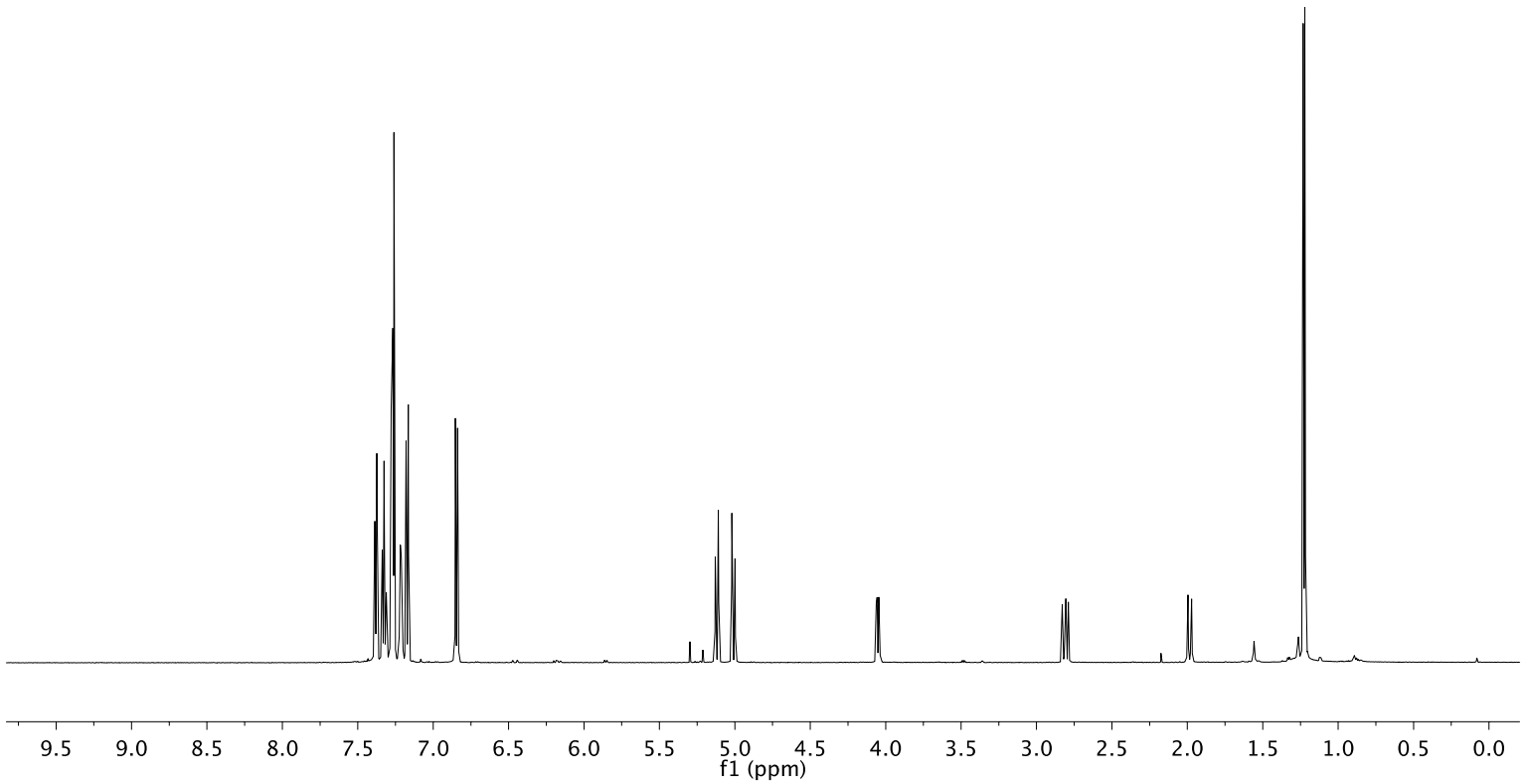
Me
O
O
OBn
Ph
Cl

78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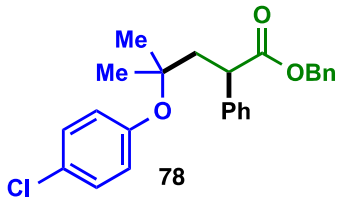
f1 (ppm)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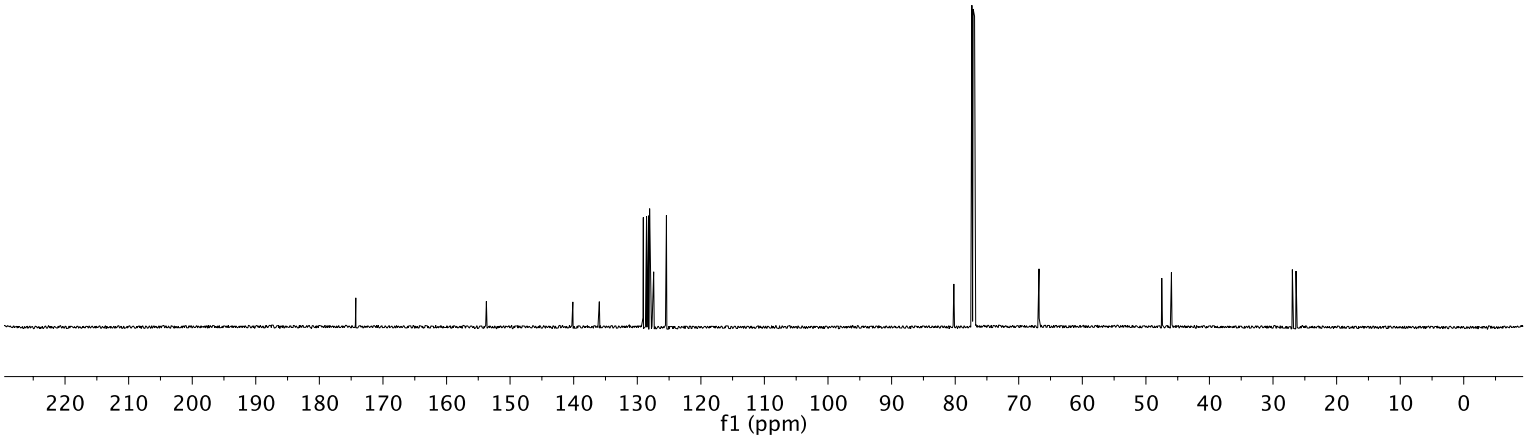
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f1 (ppm)

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