Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

Alkyl–(Hetero)Aryl Bond Formation via Decarboxylative Cross-Coupling: A Systematic Analysis

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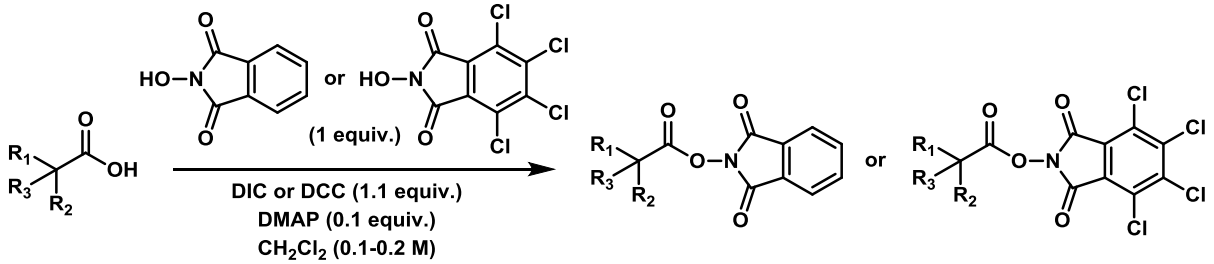
1. General considerations

Tetrahydrofuran (THF), toluene (PhMe), dichloromethane (CH_2Cl_2), and dimethylformamide (DMF) were obtained by passing the previously degassed solvents through an activated alumina column. Reagents were purchased at the highest commercial quality from Aldrich, Combi-Blocks, Acros and Strem, and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous material, unless otherwise stated. Reactions were monitored by GC/FID, 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 or I_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 non-deuterated solvent ($CHCl_3$, ^{1}H NMR at 7.26 ppm, ^{13}C NMR at 77.16 ppm) as an internal reference. 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.

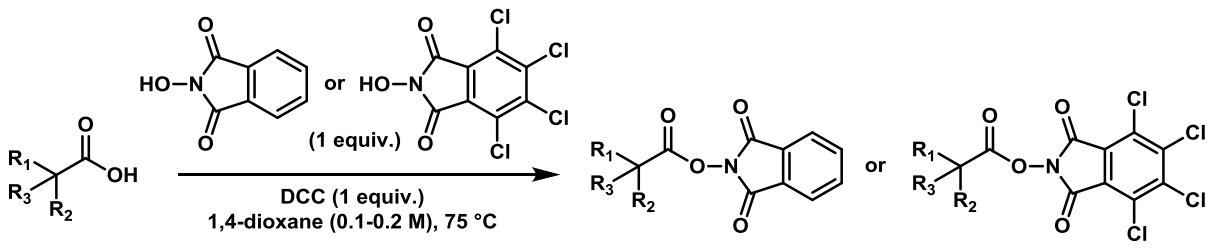
2. General Procedure for the synthesis of NHPI and TCNHPI esters

2.1 General Procedure A: Formation of RAEs at r.t.



A round-bottom flask or culture tube was charged with (if solid) carboxylic acid (1.0 equiv.), nucleophile (NHPI or TCNHPI, 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 or DCC (1.1 equiv.) was then added, and the mixture was allowed to stir until the acid was consumed (determined by TLC). Typical reaction times were between 0.5 to 12 h. The mixture was filtered (over Celite, SiO_2, or through a fritted funnel) and rinsed with additional CH_2Cl_2. The solvent was removed under reduced pressure, and purification by column chromatography afforded corresponding activated esters, which were used without further purification unless otherwise noted. **Note**: *Some esters are prone to hydrolysis on silica gel during column chromatography and should be purified as quickly as possible*.

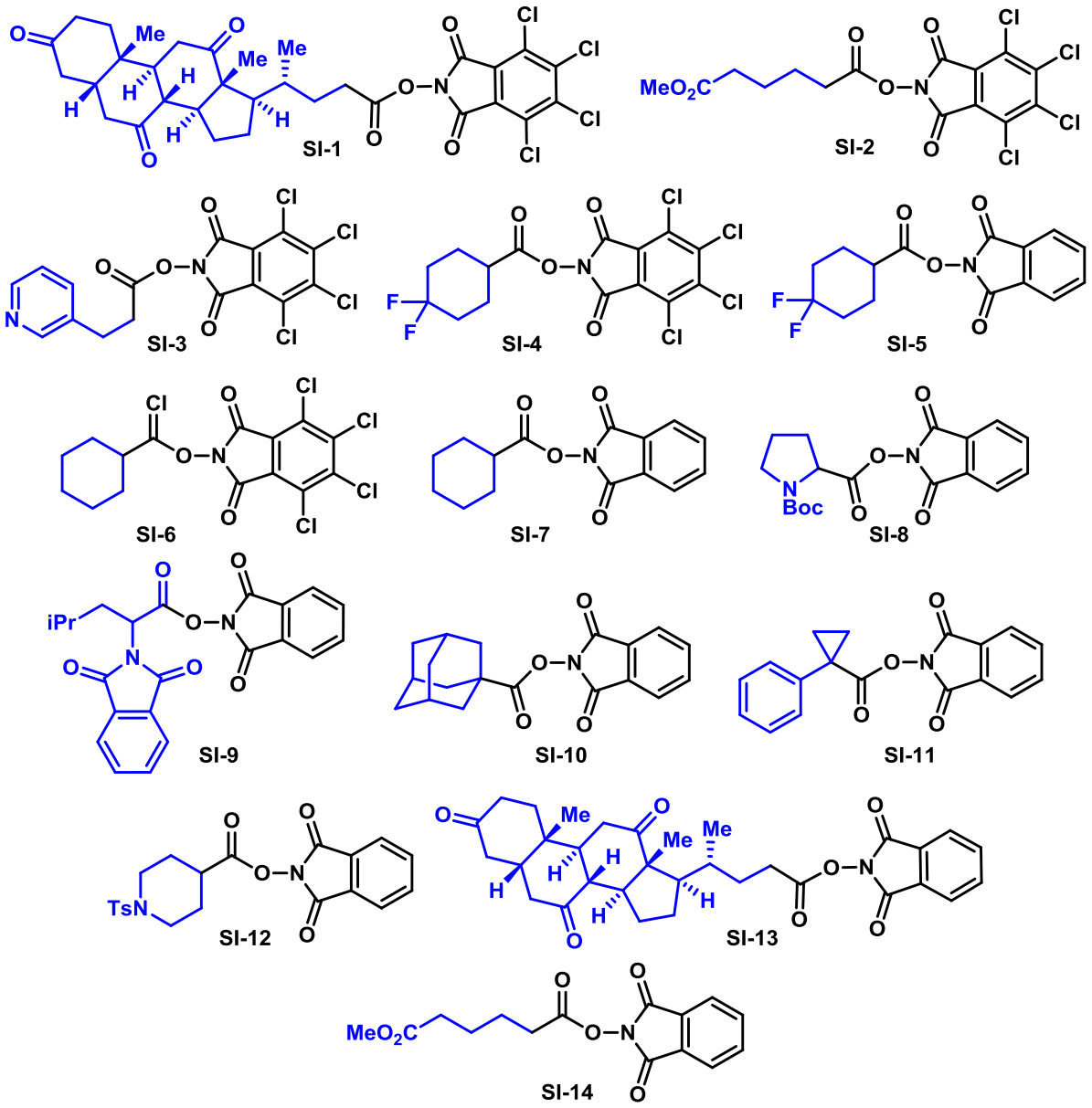
2.2 General Procedure B: Formation of RAEs using DCC at 75 °C



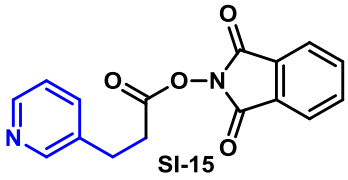
A round-bottom flask or culture tube was charged with (if solid) carboxylic acid (1.0 equiv.), nucleophile (NHPI or TCNHPI, 1.0 equiv.) and DCC (1.0 equiv.). 1,4-Dioxane was added (0.1 – 0.2 M), and the mixture was stirred vigorously. Carboxylic acid (1.0 equiv.) was added via syringe (if liquid), and the resulting mixture was placed in a preheated 75 °C oil bath and stirred until the acid was consumed (determined by TLC). Typical reaction times were between 30 and 45 minutes. The mixture was diluted with diethyl ether and filtered through a fritted funnel. The solvent

was removed under reduced pressure, and purification by recrystallization afforded corresponding activated esters, which were used without further purification unless otherwise noted.

We have previously reported the synthesis of redox-active esters shown below.[1,2,3,4,5]



1,3-Dioxoisoindolin-2-yl 3-(pyridin-3-yl)propanoate (SI-15)



Compound **SI-15** was prepared following General Procedure A, using DCC and 3-pyridinepropionic acid (75.6 mg, 0.5 mmol). Product **SI-15** was isolated by column chromatography (hexanes:ethyl acetate 1:1) to afford 101 mg (68%) as a white solid.

m.p. 78 °C.

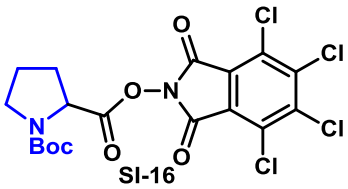
R_f= 0.19 (hexanes:ethyl acetate 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (d, *J* = 2.3 Hz, 1H), 8.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.89 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.80 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.62 (dt, *J* = 7.8, 2.2 Hz, 1H), 7.28 (ddd, *J* = 7.9, 4.9, 0.6 Hz, 1H), 3.12 (t, *J* = 7.6 Hz, 2H), 3.01 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.6, 161.9, 150.0, 148.4, 136.1, 134.9, 134.7, 129.0, 124.2, 123.7, 32.5, 27.9.

HRMS (ESI-TOF): calc'd for $C_{16}H_{13}N_2O_4$ $[M+H]^+$ 297.0870; found 297.0871.

1-(*tert*-Butyl) 2-(4,5,6,7-tetrachloro-1,3-dioxoisoindolin-2-yl) pyrrolidine-1,2-dicarboxylate (SI-16)



Compound **SI-16** was prepared following General Procedure B, using (*tert*-butoxycarbonyl)proline (215 mg, 1.0 mmol). Product **SI-16** was isolated after recrystallization from CH_2Cl_2:MeOH to afford 158 mg (32%) as a slightly yellow solid.

m.p. 178 °C.

R_f= 0.24 (hexanes:ethyl acetate 5:1).

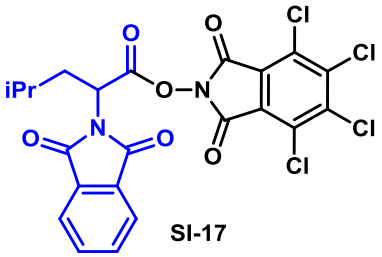
The product gives two sets of NMR signals, owing to the presence of rotamers.

^{1}H NMR (600 MHz, $CDCl_3$): δ 4.70 (dd, *J* = 8.6, 3.7 Hz, 0.2H), 4.61 (dd, *J* = 8.9, 3.6 Hz, 0.8H), 3.66 – 3.53 (m, 1H), 3.53 – 3.40 (m, 1H), 2.48 – 2.30 (m, 2H), 2.14 – 2.04 (m, 1H), 2.03 – 1.95 (m, 1H), 1.51 (s, 7H), 1.48 (s, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 168.8, 156.8, 152.9, 140.6, 130.0, 124.2, 80.8, 80.0, 56.7, 56.6, 46.0, 45.8, 31.0, 29.7, 27.9, 27.7, 24.0, 23.1.

HRMS (ESI-TOF): calc'd for $C_{18}H_{16}Cl_4N_2NaO_6$ $[M+Na]^+$ 518.9655; found 518.9656.

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoate (SI-17)



SI-17

Compound **SI-17** was prepared following General Procedure A, using DCC and 2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoic acid (1.31 g, 5.0 mmol). Product **SI-17** was isolated by column chromatography (hexanes:ethyl acetate 3:1) to afford 1.35 g (50%) as a white solid.

m.p. 193 °C.

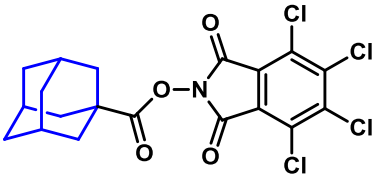
R_f= 0.50 (hexanes:ethyl acetate 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.37 (dd, *J* = 11.2, 4.7 Hz, 1H), 2.52 (ddd, *J* = 14.2, 11.2, 4.3 Hz, 1H), 2.07 (ddd, *J* = 14.5, 10.0, 4.7 Hz, 1H), 1.58 (dtd, *J* = 10.5, 6.7, 4.1 Hz, 1H), 1.01 (d, *J* = 6.5 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.0, 166.3, 157.1, 141.3, 134.6, 131.7, 130.7, 124.7, 124.1, 48.9, 37.5, 25.0, 23.1, 21.3.

HRMS (ESI-TOF): calc'd for $C_{22}H_{14}Cl_4N_2NaO_6$ $[M+Na]^+$ 566.9496; found 566.9470.

1,3-Dioxoisoindolin-2-yl (3*r*,5*r*,7*r*)-adamantane-1-carboxylate (SI-18)



SI-18

Compound **SI-18** was prepared following General Procedure A, using DIC and 1-adamantanecarboxylic acid (721 mg, 4.0 mmol). Product **SI-18** was isolated by column chromatography (CH_2Cl_2:diethyl ether 15:1) to afford 982 mg (55%) as a white solid.

m.p. 201 °C.

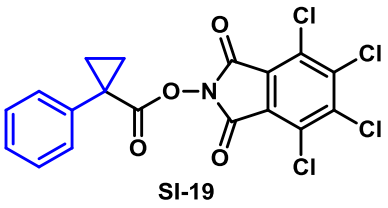
R_f= 0.54 (hexanes:ethyl acetate 10:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 2.14 – 2.08 (m, 9H), 1.82 – 1.75 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.9, 157.9, 141.1, 130.5, 125.0, 40.7, 38.6, 36.3, 27.7.

HRMS (ESI-TOF): calc'd for $C_{19}H_{16}Cl_4NO_4$ $[M+H]^+$ 461.9828; found 461.9833.

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 1-phenylcyclopropane-1-carboxylate (SI-19)



SI-19

Compound **SI-19** was prepared following General Procedure B, using 1-phenylcyclopropane-1-carboxylic acid (215 mg, 1.0 mmol). Product **SI-19** was isolated after recrystallization from CH_2Cl_2:MeOH to afford 294 mg (66%) as a slightly yellow solid.

m.p. 164 °C.

R_f= 0.37 (hexanes:ethyl acetate 10:1).

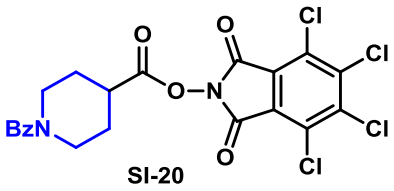
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.52 – 7.48 (m, 2H), 7.39 – 7.35 (m, 2H), 7.34 – 7.30 (m, 1H), 1.90 (q, *J* = 4.3 Hz, 2H), 1.53 – 1.50 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.8, 157.6, 141.1, 136.7, 130.7, 130.5, 128.7,

128.3, 124.9, 27.4, 19.0.

HRMS (ESI-TOF): calc'd for $C_{18}H_{10}Cl_4NO_4$ $[M+H]^+$ 443.9358; found 443.9361.

4,5,6,7-Tetrachloro-1,3-dioxoisoindolin-2-yl 1-benzoylpiperidine-4-carboxylate (SI-20)



SI-20

Compound **SI-20** was prepared following General Procedure A, using DIC and 1-benzoylpiperidine-4-carboxylic acid (700 mg, 3.0 mmol). Product **SI-20** was isolated by column chromatography (hexanes:ethyl acetate 2:1) to afford 1.18 g (76%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 184 °C.

R_f= 0.55 (hexanes:ethyl acetate 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.45 – 7.38 (m, 5H), 4.46 (br, 1H), 3.80 (br, 1H), 3.31 – 3.22 (m, 2H), 3.06 (tt, *J* = 9.9, 4.1 Hz, 1H), 2.28 – 1.81 (m, 4H).

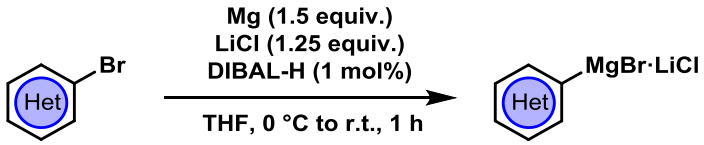
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7, 170.1, 157.7, 141.3, 135.8, 130.7, 130.0, 128.7, 127.0, 124.8, 46.3 (br), 40.9 (br), 38.5, 28.4 (br), 27.7 (br).

HRMS (ESI-TOF): calc'd for $C_{21}H_{15}Cl_4N_2O_5$ $[M+H]^+$ 514.9730; found 514.9727.

3. General Procedure for the preparation of organometallic reagents

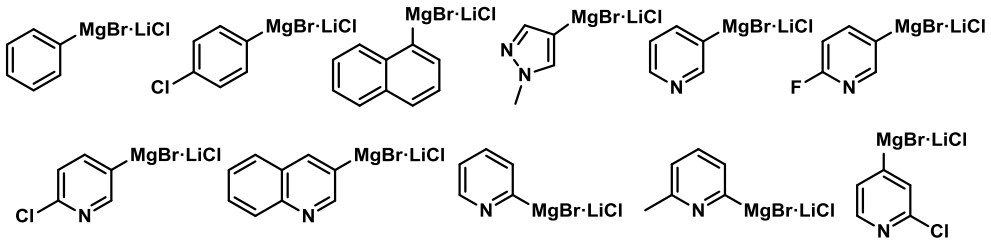
Arylmagnesium and arylzinc reagents were prepared in a manner similar to that report by Knochel and coworkers.[6]

3.1. Preparation of ArylMgBr·LiCl by Mg insertion

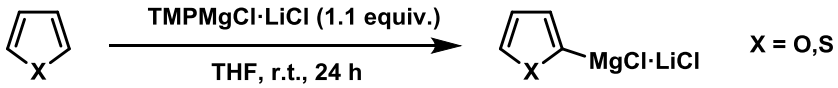


In an oven-dried flask Mg turnings (219 mg, 9.0 mmol, 1.5 equiv.) and LiCl (318 mg, 7.5 mmol, 1.25 equiv.) were weighed and the flask was flame-dried under vacuum. The flask was then sealed, evacuated and back-filled with Ar (3 times). THF (3 mL) was added at r.t. and stirred for 5 minutes. DIBAL-H (0.06 mL, 0.06 mmol, 1 mol%, 1 M in THF) was then added dropwise at r.t. and stirred for 5 minutes. The mixture was then cooled to 0 ºC and ArylBr (6.0 mmol, 1.0 equiv.) was added dropwise (If ArylBr is a solid, it is dissolved in small amounts of THF before the addition). After the initial heat evolution the mixture was removed from the ice bath and allowed to stir for 1 h at r.t. Titration of the mixture with I_2 (50 mg, 0.2 mmol) and LiCl (1.0 mmol, 42 mg) in THF (2 mL) normally affords concentration of about 1–1.3 M (0.6–1.0 M for heteroaryl bromides).

The following Grignard reagents have been prepared according to this procedure.

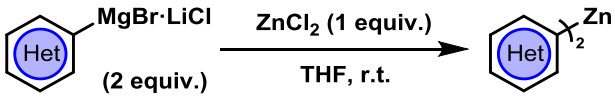


3.2. Preparation of ArylMgCl·LiCl by direct Magnesiation



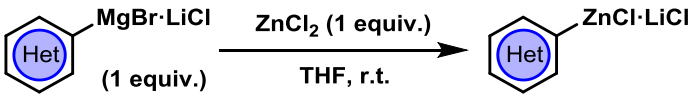
A large culture tube was charged with a stirring bar, sealed, evacuated and back-filled with Ar (3 times). TMPMgCl·LiCl (0.74 M in THF/toluene, 1.5 mL, 1.1 mmol, 1.1 equiv.) was then added, followed by dropwise addtition of the aromatic heterocycle (1.0 mmol, 1.0 equiv.). THF (0.5 mL) was added for rinse. The solution was stirred at r.t. for 24 h and ArylMgCl·LiCl (0.5 M) was used without further titration.

3.3. Preparation of $Aryl_2Zn$



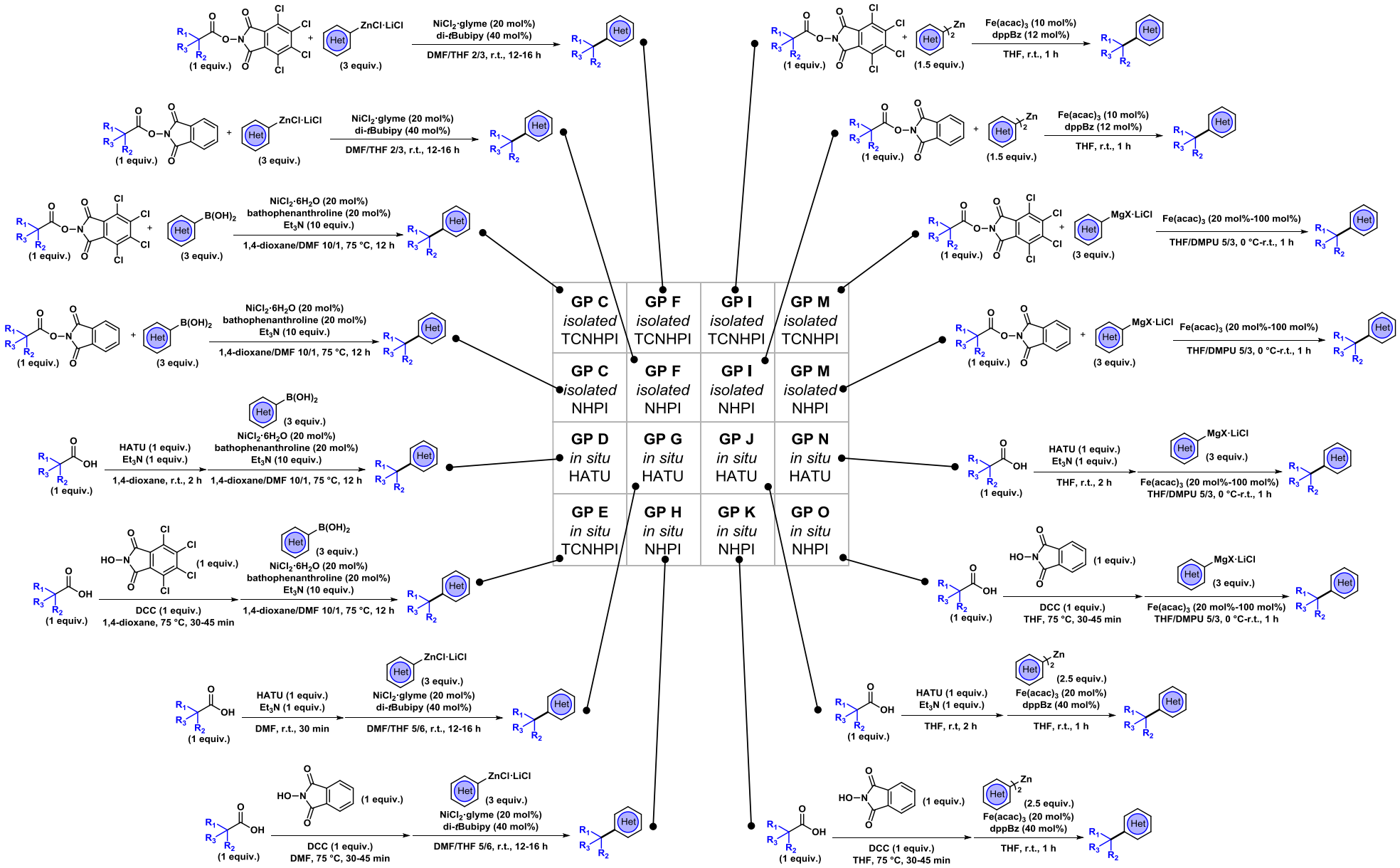
In an oven-dried flask $ZnCl_2$ was weighed (273 mg, 2.0 mmol, 1.0 equiv.) and the flask was heated under vacuum for 5 minutes with the help of a heat gun. After cooling down, THF (2 mL) was added under Ar and the mixture was allowed to stir at r.t. for 5 minutes. Then, ArylMgBr·LiCl (1 M in THF, 4.0 mL, 4.0 mmol, 2.0 equiv.) was added dropwise. A dense solution was formed and used without further titration ($Aryl_2Zn$, c = 0.33 M).

3.4. Preparation of ArylZnCl·LiCl



In an oven-dried flask $ZnCl_2$ was weighed (273 mg, 2.0 mmol, 1.0 equiv.) and the flask was heated under vacuum for 5 minutes with the help of a heat gun. After cooling down, THF (6 mL) was added under Ar and the mixture was allowed to stir at r.t. for 5 minutes. Then, ArylMgBr·LiCl (1 M in THF, 2.0 mL, 2.0 mmol, 1.0 equiv.) was added dropwise. A dense solution was formed and used without further titration (ArylZnCl·LiCl, c = 0.25 M).

4. A guide to the guide: Overview of General Procedures



5. Optimized Procedures for Ni-catalyzed Suzuki reactions of RAEs

5.1. Preparation of $NiCl_2 \cdot 6H_2O$/bathophenanthroline stock solution (0.05 M in DMF)

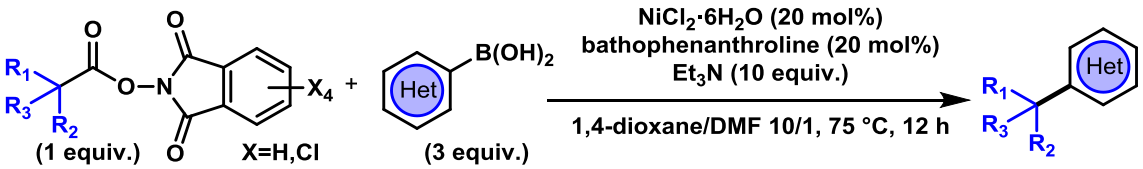
A culture tube was charged with $NiCl_2 \cdot 6H_2O$ (71.3 mg, 0.3 mmol, 1.0 equiv.) and bathophenanthroline (99.7 mg, 0.3 mmol, 1.0 equiv.). The vial was sealed, evacuated and refilled with Ar 3 times. DMF (6.0 mL) was added and the resulting mixture was stirred at r.t. for 3 h to give a homogeneous green solution, which could be used for several days without appreciable deterioration.

5.1.1. Graphical guide for preparation of $NiCl_2 \cdot 6H_2O$/bathophenanthroline stock solution (0.05 M in DMF)

(Left) $NiCl_2 \cdot 6H_2O$ (72 mg). **(Center)** bathophenanthroline (100 mg). **(Right)** $NiCl_2 \cdot 6H_2O$ and bathophenanthroline in vial.

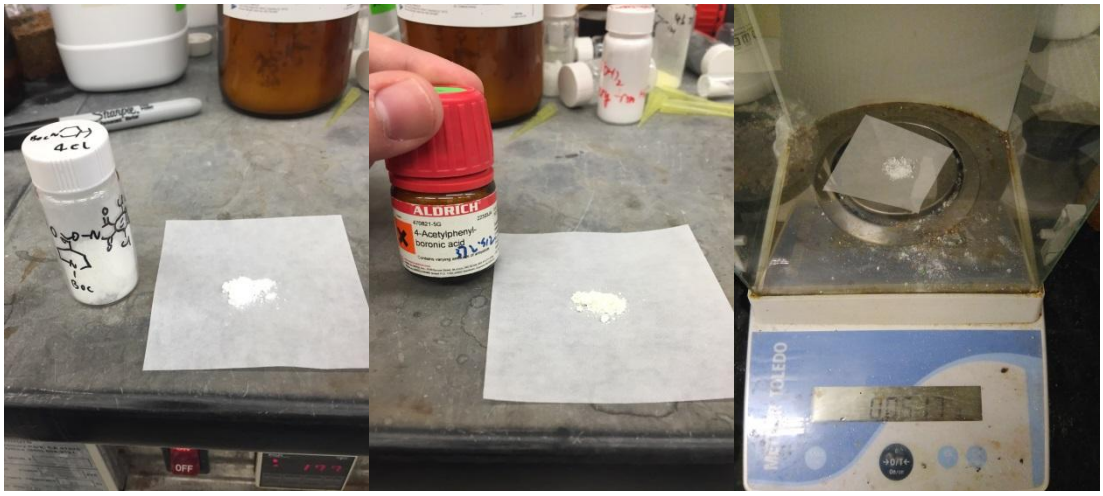
(Left) The flask with a stir bar was sealed with a septum, wrapped with parafilm, evacuated under vacuum and refilled with argon. This was done 3 times in total. **(Center)** Add DMF (6 mL) into the vial. **(Right)** After stirring for 3 h at r.t.

5.2. General Procedure C: Ni-Suzuki with isolated NHPI or TCNHPI esters

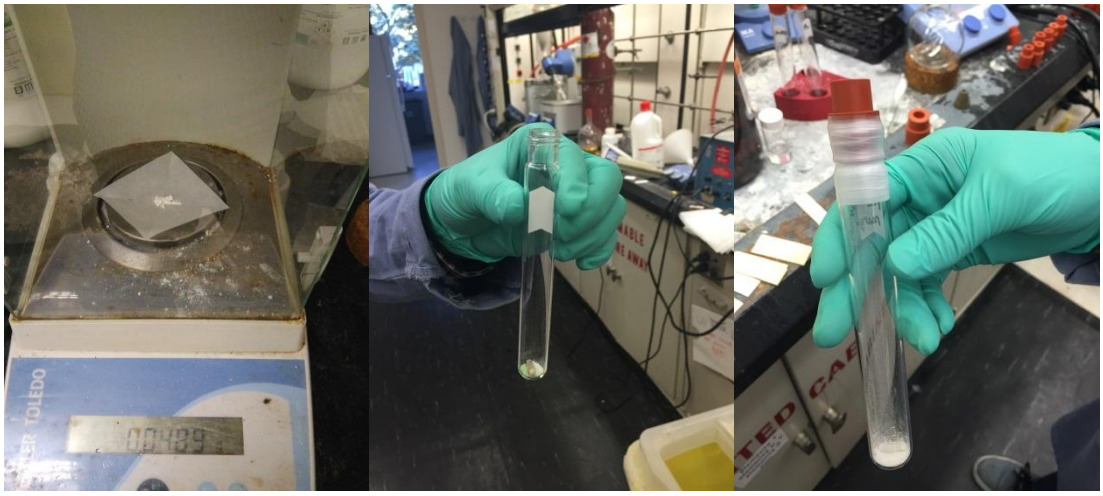


A large culture tube was charged with NHPI or TCNHPI ester (0.1 mmol, 1.0 equiv.), aryl boronic acid (0.3 mmol, 3.0 equiv.) and a stir bar. The vial was sealed, evacuated and refilled with Ar 3 times. 1,4-Dioxane (4.0 mL) was added and the resulting mixture was stirred for 1 minute before Et_3N (139 µL, 1.0 mmol, 10 equiv.) was added. The mixture was stirred for 2-5 minutes until becoming homogeneous. Then, a solution of $NiCl_2 \cdot 6H_2O$/bathophenanthroline (0.05 M in DMF, 0.4 mL, 20 mol%) was added and the tube was immediately placed in a preheated 75 °C oil bath for 12 h under stirring. **NOTE:** *It is very important that the entirety of the reaction mixture is submerged in the heated oil bath to ensure the success and reproducibility of the reaction.* After 12 h, the reaction mixture was allowed to cool to r.t. The mixture was then diluted with diethyl ether or ethyl acetate, washed with 0.1 M aqueous HCl (not for acid sensitive substrates), water and $NaHCO_3$ successively. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated in relation to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

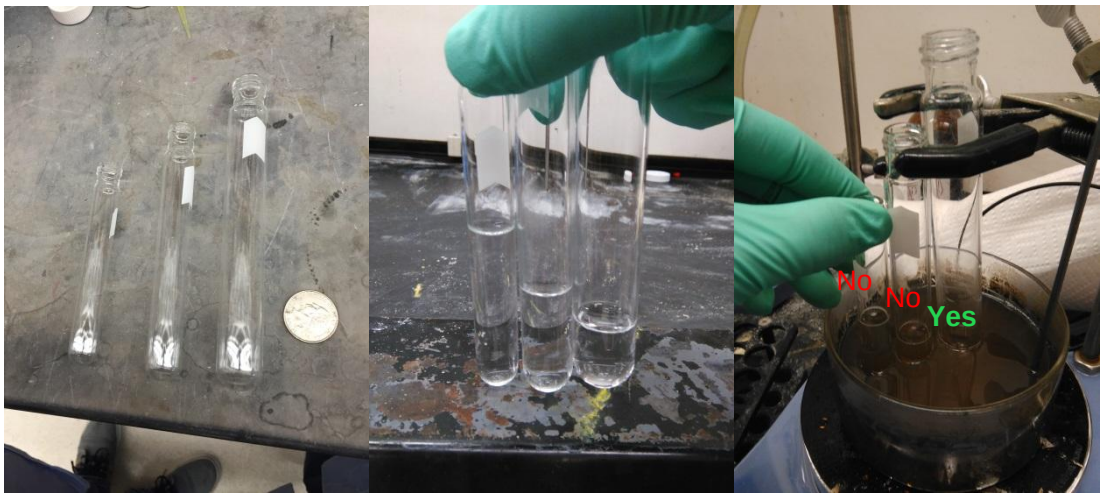
5.2.1. Graphical guide for Ni-Suzuki with isolated RAEs



(Left) Redox-active ester. **(Center)** Boronic acid. **(Right)** Redox active ester weight.

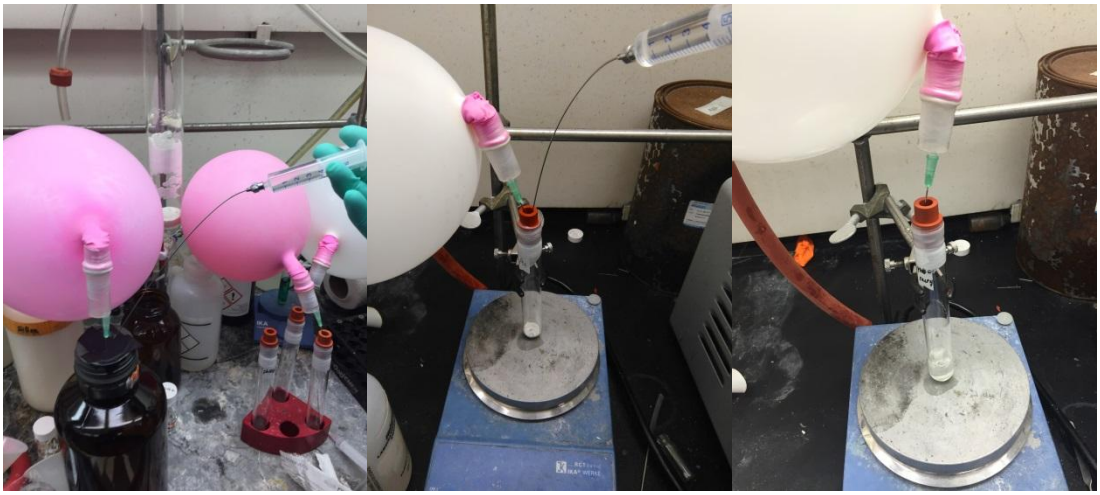


(Left) Boronic acid weight. **(Center)** Redox-active ester and boronic acid were added to a large-sized culture tube. **(Right)** The tube is sealed with an inverted septum and parafilm.

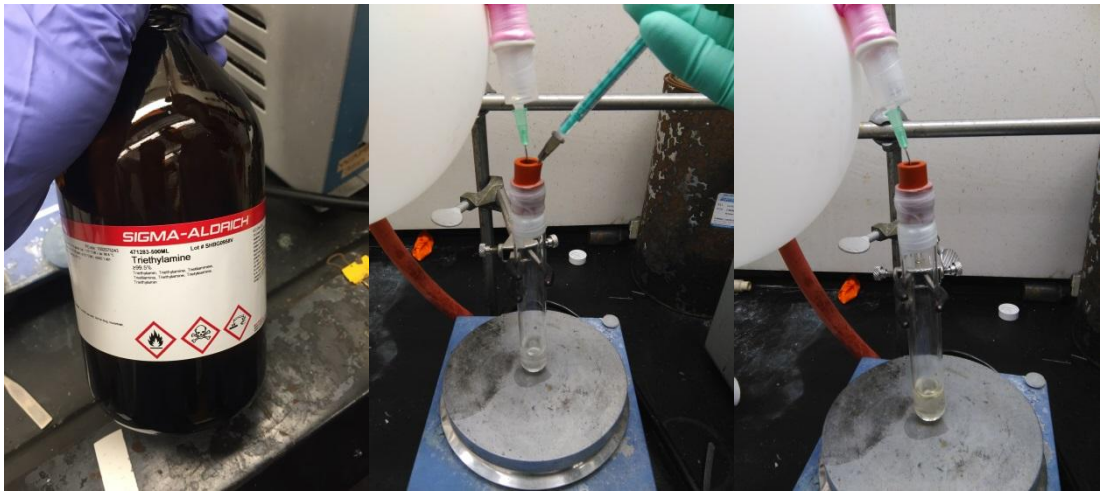


(Left) Three sizes of reaction tube: small, medium and large. **(Center)** The three different sized tubes containing 4.4 mL solvent each. **(Right)** Put them in the oil bath. **Note:** *we use the LARGE size for this reaction (the right one) to make sure the entirety of the reaction mixture is submerged in the heated oil bath. When we perform this reaction in the small or medium size tube, yield dropped 30% and 10% respectively because the mixture was not completely submerged.*

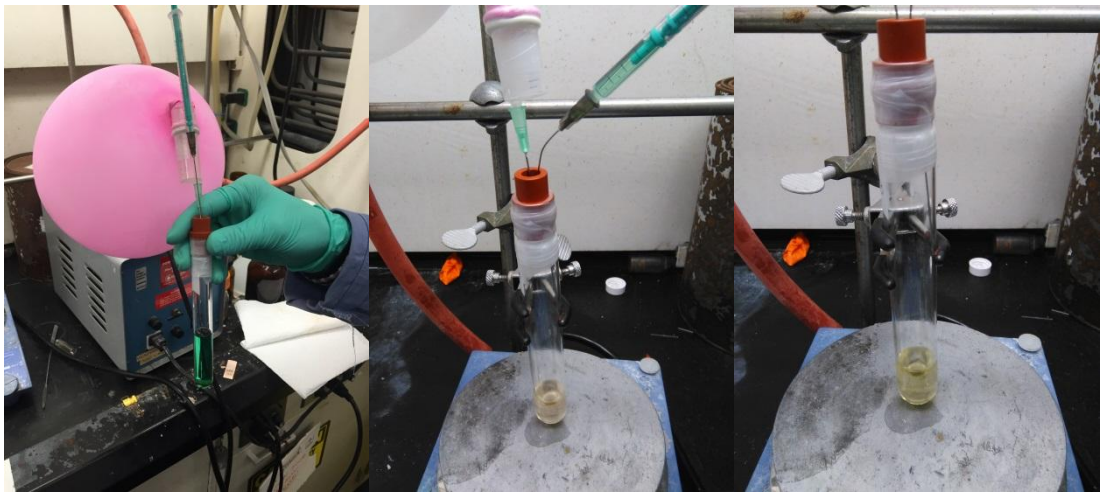
(Left) Evacuating the air from the tube. **(Center)** The tube is refilled with argon from a balloon. These steps are repeated for three times in total. **(Right)** 1,4-dioxane (1 L sealed bottle, Acros).



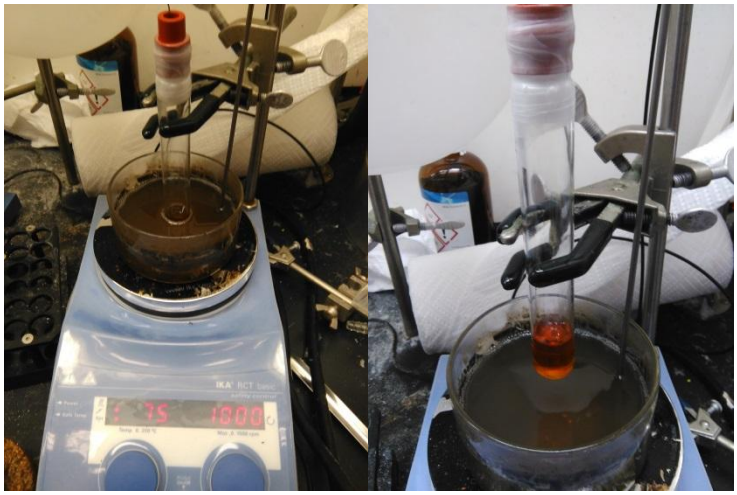
(Left) 1,4-Dioxane is removed from the AcroSeal bottle. **(Center)** Addition of 1,4-dioxane. **(Right)** After addition, the mixture is stirred for 1 min.



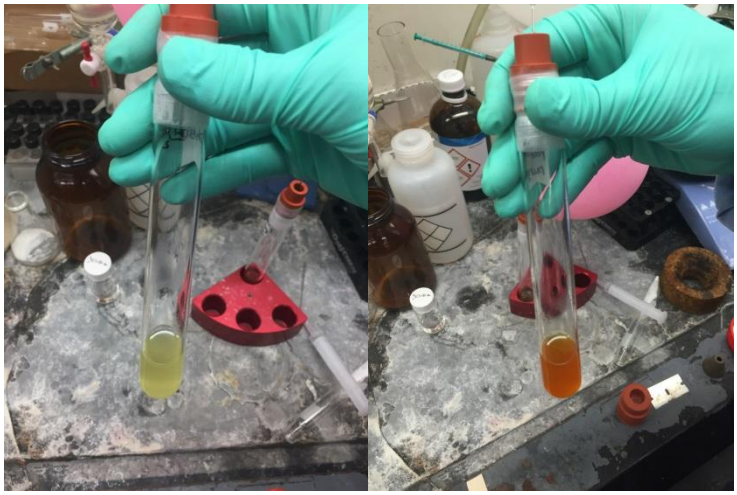
(Left) Triethylamine (500 mL sealed bottle, Sigma-Aldrich). **(Center)** Adding Et_3N (139 µL, 10.0 equiv.) to the reaction mixture. **(Right)** The reaction mixture was stirried for 2-5 min until it became homogenous. For this example, the mixture became homogeneous immediately. For some boronic acids, it could take a while, typically 2-5 min.



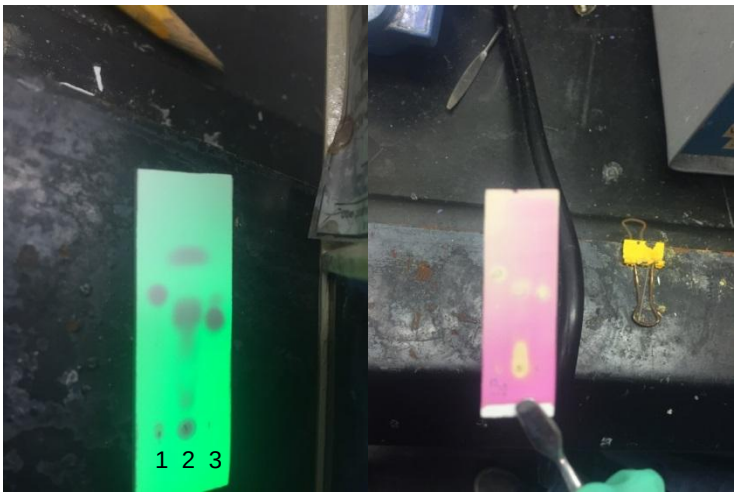
(Left) Prepared Ni/ligand complex stock solution in DMF. **(Center)** 0.4 mL Nickel complex DMF solution was added into the tube while stirring. **(Right)** After addition.



(Left) After addition of Ni/ligand complex, directly placed in preheated 75 ºC oil bath. **(Right)** 5 min after heating, the reaction mixture turns red. **Note:** *the red color changing is crucial for the success of the reaction*.

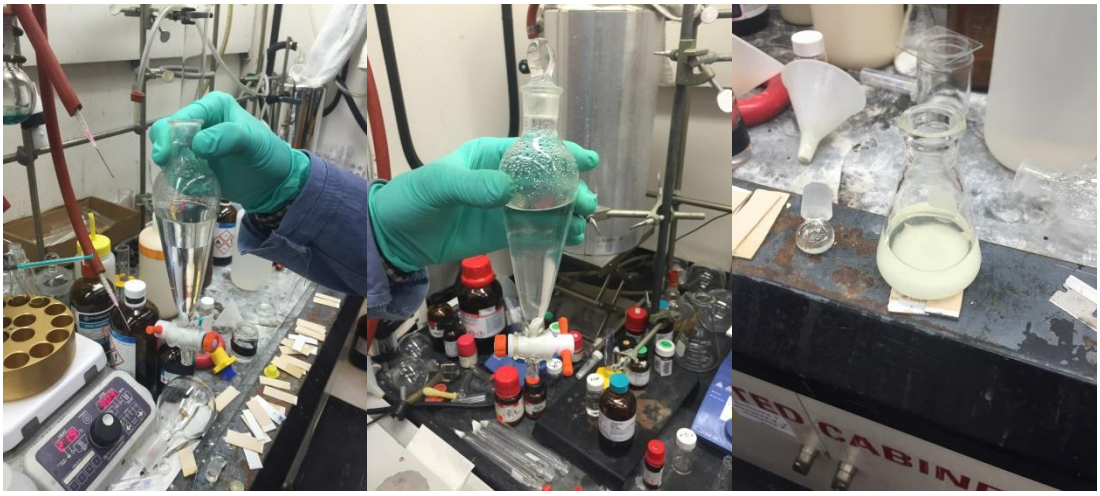


(Left) After 12 h, the color turned light green, which is also observed for most substrates. **(Right)** For some other cases we have observed a reddish color.



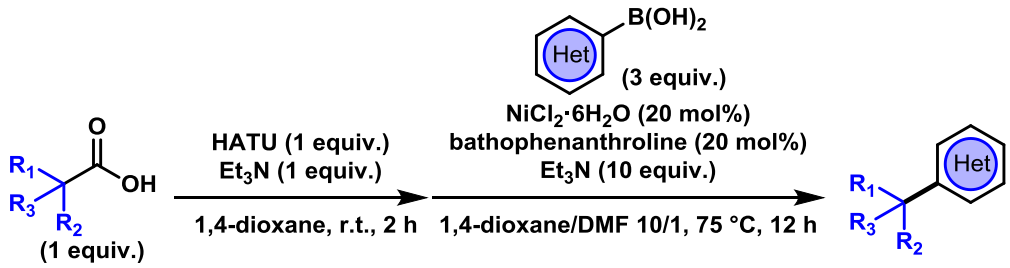
(Left) TLC under UV (hexanes/ethyl acetate 3:1), Lane 1: starting material, redox-active ester; Lane 2: reaction mixture; Lane 3: pure product. **(Right)** After $KMnO_4$ stain.

(Left) Dilution with Et_2O. **(Center)** Transfer to a separatory funnel. **(Right)** 0.1 M HCl wash.



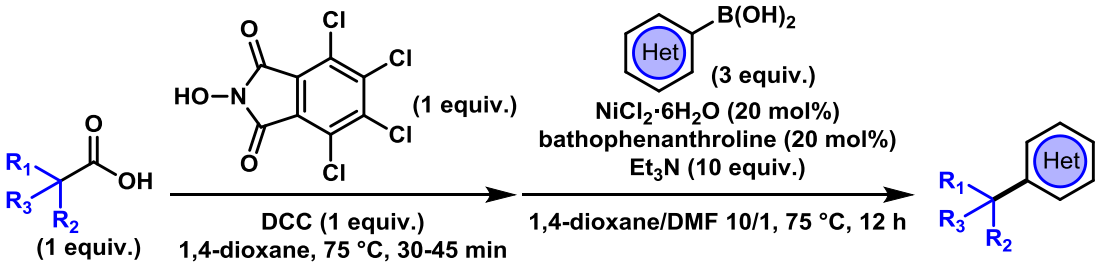
(Left) H_2O wash. (**Center**) $NaHCO_3$ wash. **(Right)** Drying over $MgSO_4$.

5.3. General Procedure D: Ni-Suzuki with HATU *in situ*



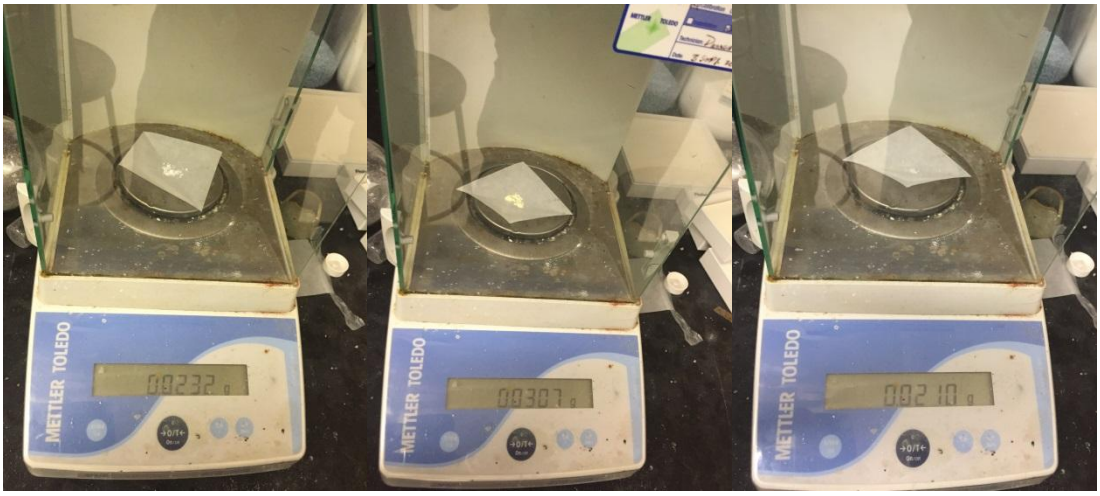
A large culture tube was charged with alkyl carboxylic acid (0.1 mmol, 1.0 equiv.), HATU (38 mg, 0.1 mmol, 1.0 equiv.) and a stir bar. The vial was sealed, evacuated and refilled with Ar 3 times. Then, Et_3N (14 µL, 0.1 mmol, 1.0 equiv.) and 1,4-dioxane (3.0 mL) were added and the resulting mixture was stirred for 2 h at r.t., at which point the solution usually became clear and homogenous. Aryl boronic acid (0.3 mmol, 3.0 equiv.) was added quickly and more 1,4-dioxane (1 mL) was added for rinse. Et_3N (139 µL, 1.0 mmol, 10 equiv.) and a solution of $NiCl_2 \cdot 6H_2O$/bathophenanthroline (0.05 M in DMF, 0.4 mL, 20 mol%) were added successively and the tube was immediately placed in a preheated 75 °C oil bath for 12 h under stirring. **NOTE:** *It is very important that the entirety of the reaction mixture is submerged in the heated oil bath to ensure the success and reproducibility of the reaction.* After 12 h, the reaction mixture was allowed to cool to r.t. The mixture was then diluted with diethyl ether or ethyl acetate, washed with 0.1 M aqueous HCl (not for acid sensitive substrates), water and $NaHCO_3$ successively. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

5.4. General Procedure E: Ni-Suzuki with TCNHPI *in situ*

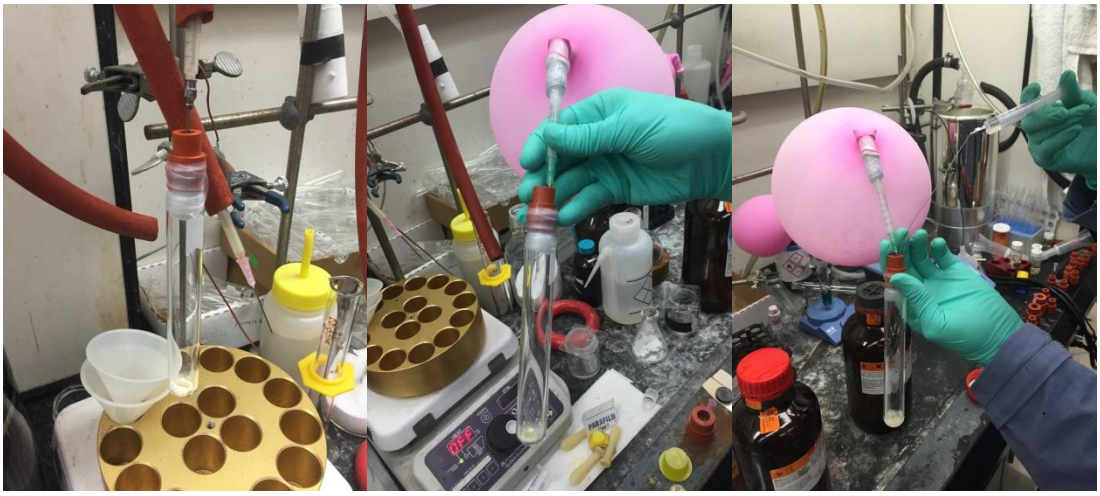


A large culture tube was charged with alkyl carboxylic acid (0.1 mmol, 1.0 equiv.), TCNHPI (30.1 mg, 0.1 mmol, 1.0 equiv.), DCC (20.6 mg, 0.1 mmol, 1.0 equiv.) and a stir bar. The vial was sealed, evacuated and refilled with Ar 3 times. 1,4-Dioxane (3.0 mL) was added and the resulting mixture was placed in a preheated 75 ^{o}C oil bath and stirred until completion as indicated by TLC (typically 30-45 minutes). Aryl boronic acid (0.3 mmol, 3.0 equiv.) was added quickly and more 1,4-dioxane (1 mL) was added for rinse. Et_3N (139 µL, 1.0 mmol, 10 equiv.) and a solution of $NiCl_2.6H_2O$/bathophenanthroline (0.05 M in DMF, 0.4 mL, 20 mol%) was added successively and the tube was immediately placed in a preheated 75 °C oil bath for 12 h under stirring. **NOTE:** *It is very important that the entirety of the reaction mixture is submerged in the heated oil bath to ensure the success and reproducibility of the reaction.* After 12 h, the reaction mixture was allowed to cool to r.t. The mixture was then diluted with diethyl ether or ethyl acetate, washed with 0.1 M aqueous HCl (not for acid sensitive substrates), water and $NaHCO_3$ successively. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

5.4.1. Graphical guide for Ni-Suzuki with TCNHPI *in situ*

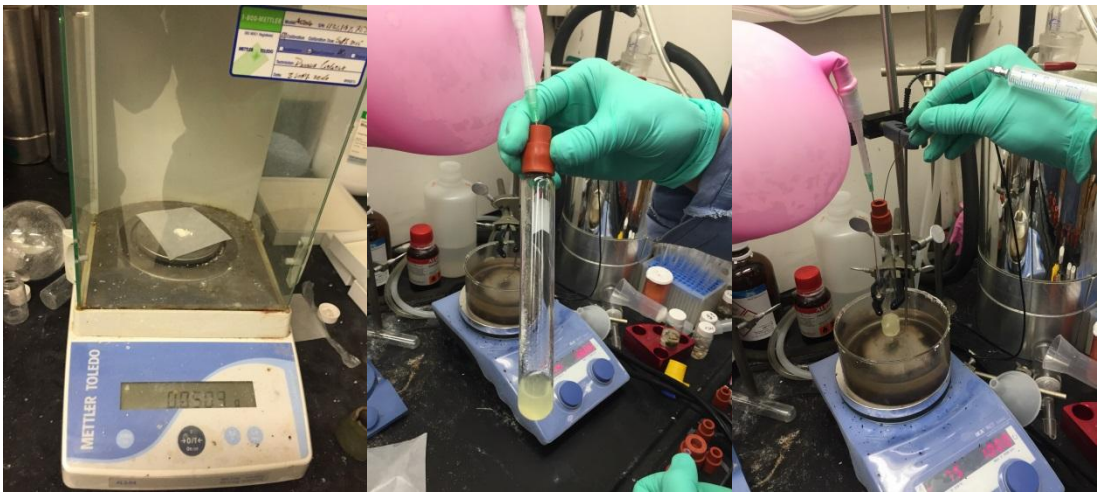


(Left) Carboxylic acid weight. **(Center)** TCNHPI weight. **(Right)** DCC weight.



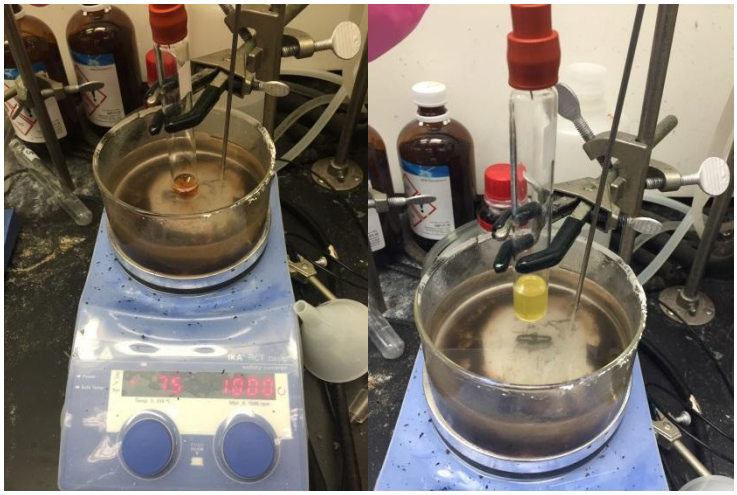
(Left) Put them into a vial with a stir bar. The vial was sealed with a septum, wrapped with parafilm and evacuated under vacuum. **(Center)** Refill the vial with argon. This was done 3 times in total. **(Right)** Add 1,4-dioxane (3 mL) into the vial.

(Left) The vial was put in a preheated 75 ^{o}C oil bath. **(Center)** After heating for 30 min. **(Right)** TLC (hexanes/ethyl acetate 2:1) under UV indicates completion of the redox-active ester formation. Lane 1: starting material of TCNHPI; Lane 2: co-spot of starting material and reaction mixture; Lane 3: reaction mixture.

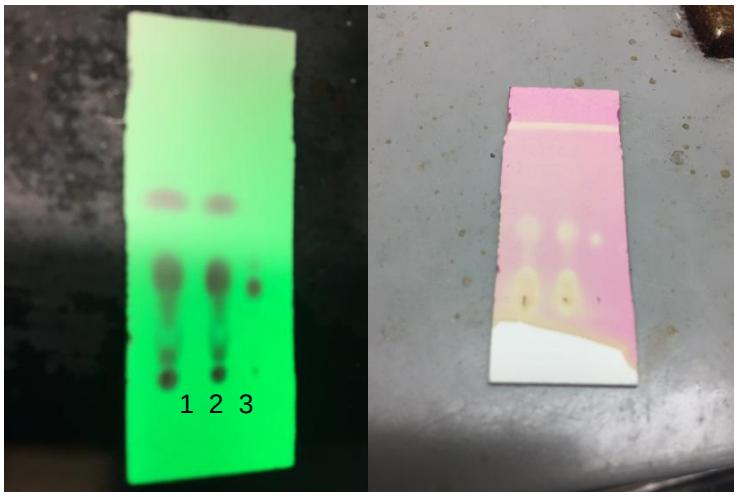


(Left) Boronic acid weight. **(Center)** Add boronic acid to reaction mixture quickly. **(Right)** Add 1,4-dioxane (1 mL) for rinse.

(Left) Add Et_3N (0.14 mL). **(Center)** Add $NiCl_2 \cdot 6H_2O$/bathophenanthroline stock solution (0.4 mL). **(Right)** Place the vial in a preheated 75 ^oC oil bath immediately.



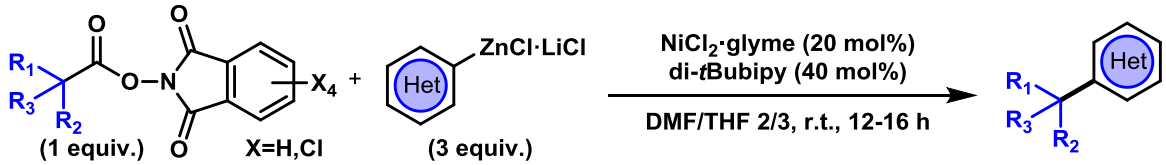
(Left) After heating for 5 min, the reaction mixture turned red. **(Right)** Reaction mixture after stirring for 12 h.



(Left) TLC under UV (hexanes/ethyl acetate 5:1), Lane 1: reaction mixture; Lane 2: co-spot; Lane 3: desired product. **(Right)** The same TLC after $KMnO_4$ stain.

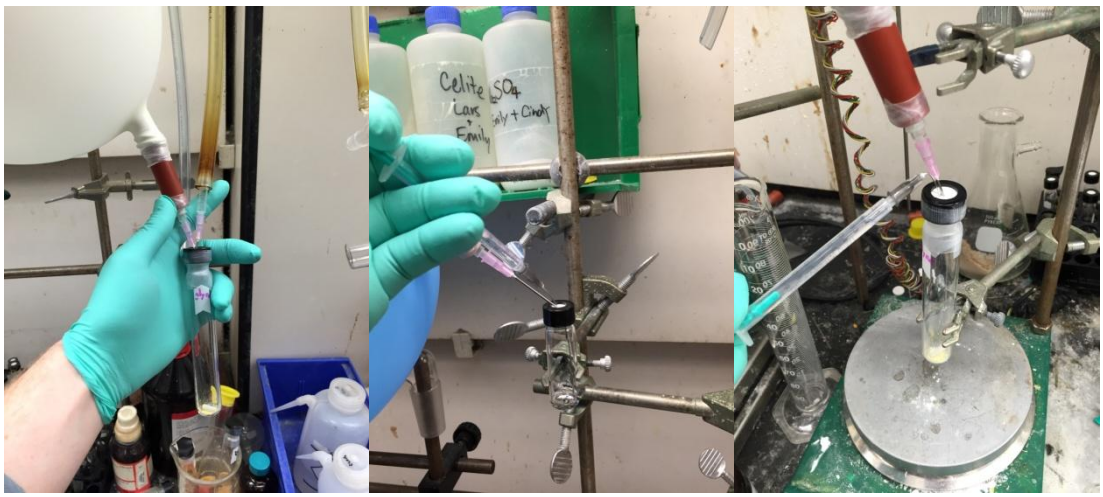
6. Optimized Procedures for Ni-catalyzed Negishi reactions of RAEs

6.1. General Procedure F: Ni-Negishi with isolated NHPI or TCNHPI esters



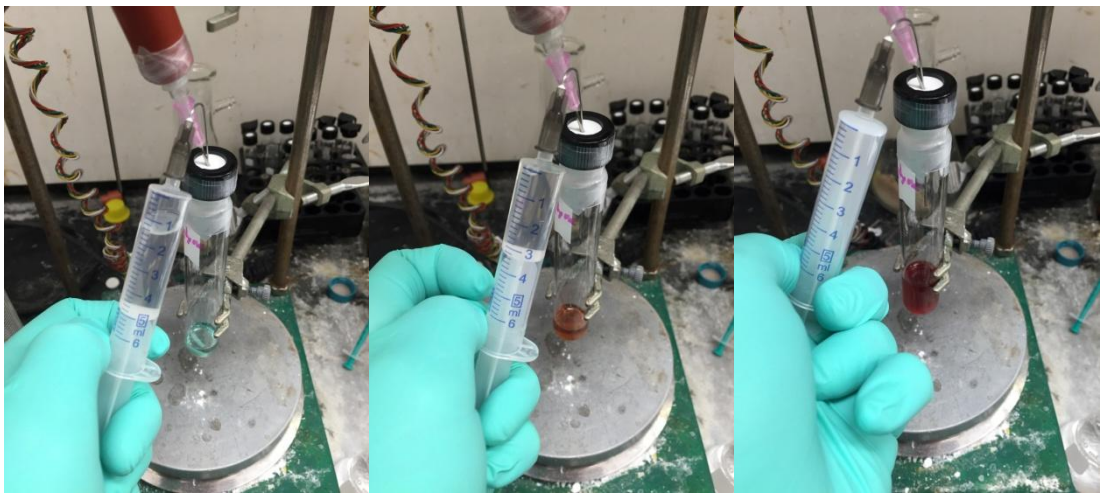
A 10 mL screwed-capped vial with a stir bar was charged with $NiCl_2$·glyme (4.4 mg, 20 mol%), di-*t*Bubipy (10.7 mg, 40 mol%) and NHPI or TCNHPI ester (0.1 mmol, 1.0 equiv.). The vial was sealed, evacuated and refilled with Ar 3 times. DMF (anhydrous, 0.8 mL) was added via syringe, and the mixture stirred for 2 minutes at r.t. Then, ArylZnCl·LiCl (0.25 M in THF, 1.2 mL, 0.3 mmol, 3.0 equiv.) was added in one portion, and the mixture was stirred for 12–16 h at r.t. The mixture was diluted with ethyl acetate or diethyl ether and quenched with 1M HCl (aq). The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

6.1.1. Graphical guide for Ni-Negishi with isolated RAEs

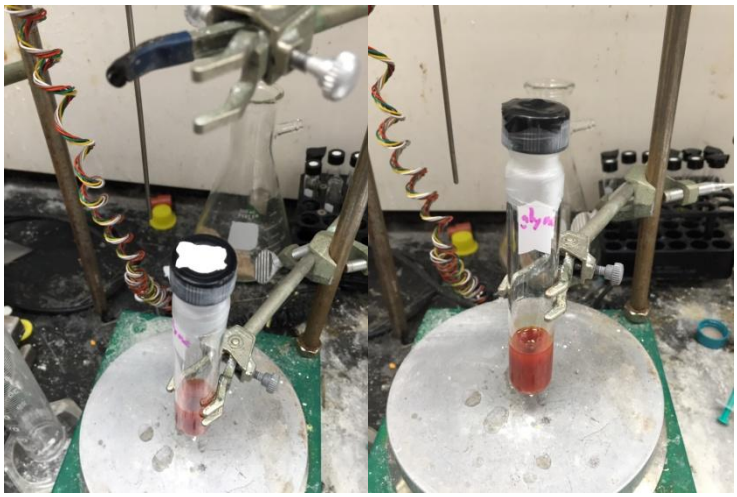


(Left) Backfilling with Ar a culture tube containing $NiCl_2$·glyme, di-*t*Bubipy, and a stir bar. **(Center)** A solution of redox-active ester in DMF. **(Right)** Adding the solution of DMF and redox-active ester to the culture tube.

(Left) Blue color develops as the DMF solution is added. **(Right)** After all of the redox-active ester solution has been added and stirred for 5 min.



(Left) Prior to addition of ArylZnCl·LiCl. **(Center)** A red/brown color is immediately evident. **(Right)** Completed addition of ArylZnCl·LiCl solution.



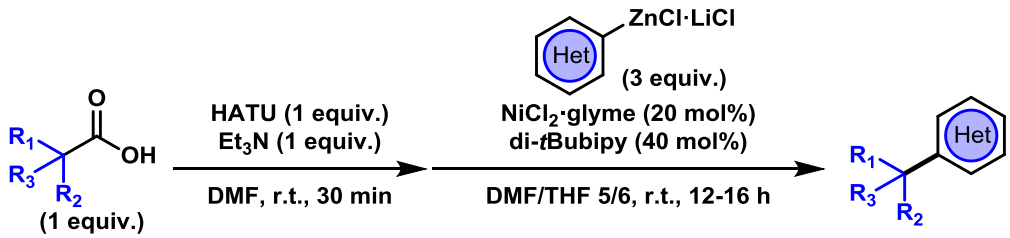
(Left) Removal of Ar balloon and covering septum with Teflon™ tape. **(Right)** Covering the Teflon™ tape with electrical tape.

(Left) Reaction with $NiCl_2$·glyme after 12 h. A black color is often observed but is not imperative to the success of the reaction. **(Center)** Dilution with Et_2O. **(Right)** Slow addition of 1M HCl (aq).

(Left) After 1M HCl (aq) wash. **(Center)** After $NaHCO_3$ wash. **(Right)** Filtering the drying agent.

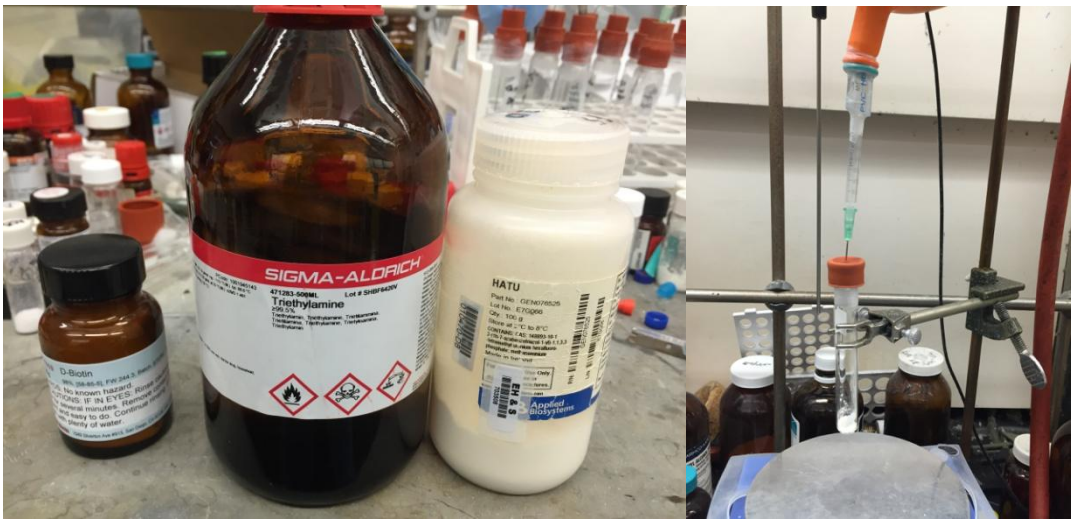
(Left) TLC (4:1 hexanes:ethyl acetate). Lane 1: redox-active ester; Lane 2: Co-spot; Lane 3: Reaction mixture **(Center and Right)** TLC (9:1 hexanes:DCM) Lane 1: Reaction mixture; Lane 2: Co-spot; Lane 3: Authentic sample of product.

6.2. General Procedure G: Ni-Negishi with HATU *in situ*



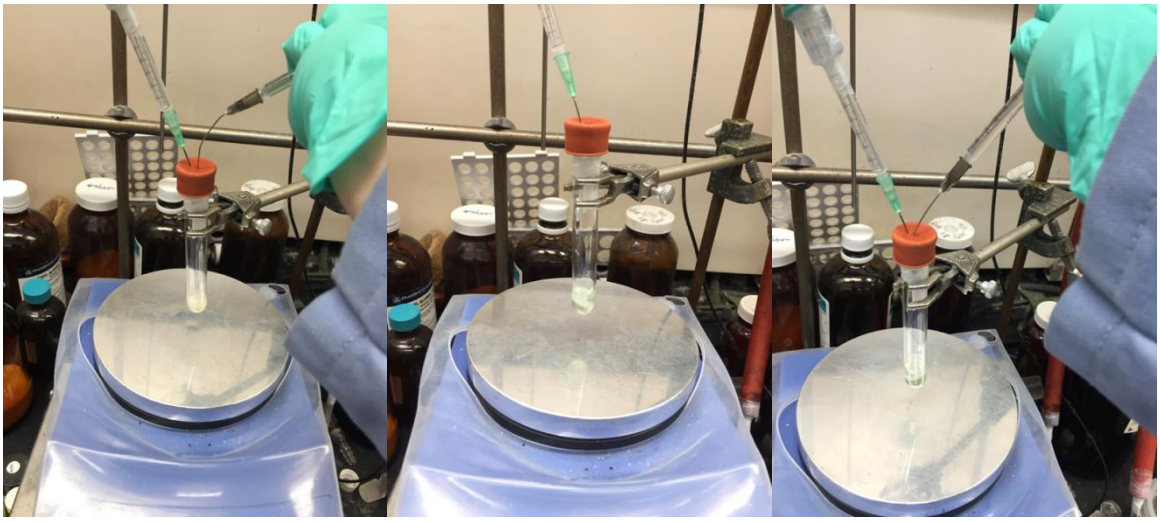
A 10 mL screwed-capped vial with a stir bar was charged with carboxylic acid (0.1 mmol, 1.0 equiv.) and HATU (38 mg, 0.1 mmol, 1.0 equiv.) in DMF (anhydrous, 0.5 mL) followed by the addition of Et_3N (14 µL, 0.1 mmol, 1.0 equiv.). The mixture was stirred at r.t. for 30 minutes. A solution of $NiCl_2$·glyme (4.4 mg, 20 mol%) and di-*t*Bubipy (10.7 mg, 40 mol%) in DMF (anhydrous, 0.5 mL) was added to the reaction mixture and stirred at r.t. for 5 minutes. ArylZnCl·LiCl (0.25 M in THF, 1.2 mL, 0.3 mmol, 3.0 equiv.) was added in one portion to the reaction mixture, which was stirred for 12–16 h. The mixture was diluted with ethyl acetate or diethyl ether and quenched with 1M HCl (aq). The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

6.2.1. Graphical guide for Ni-Negishi with HATU *in situ*

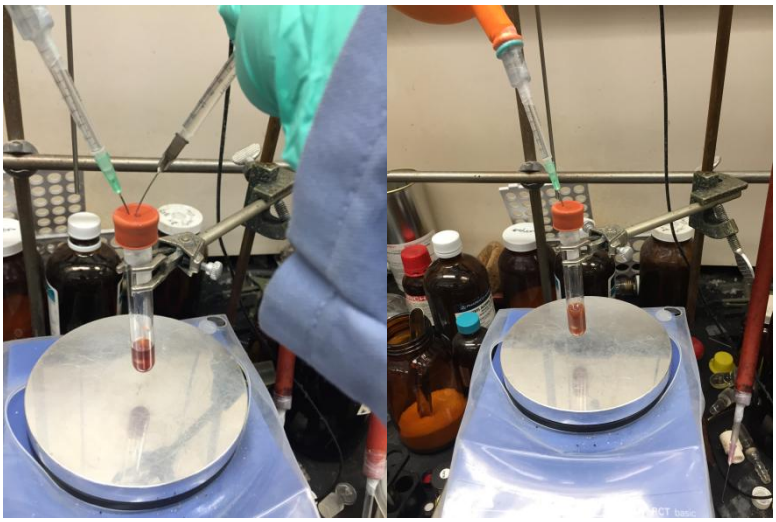


(Left) Carboxylic acid, Et_3N, and HATU. **(Right)** Carboxylic acid and HATU in culture tube under Ar.

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

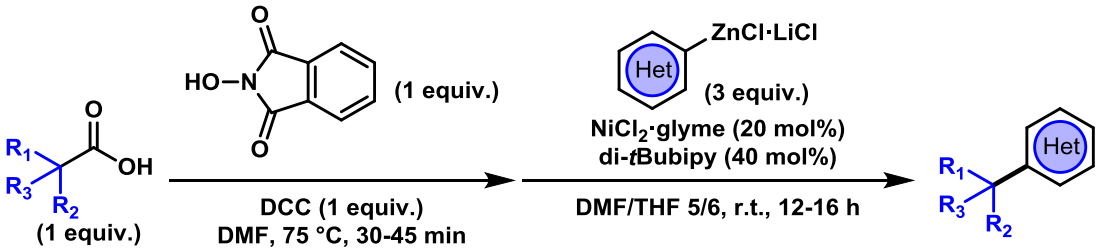


(Left) Addition of $NiCl_2$·glyme and di-*t*Bubipy in DMF. **(Center)** After addition of [Ni] and ligand. **(Right)** Before addition diarylzinc.



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

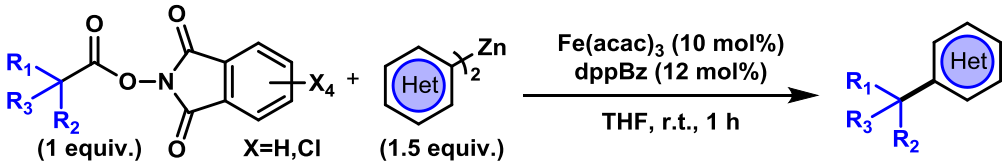
6.3. General Procedure H: Ni-Negishi with NHPI *in situ*



A 10 mL screwed-capped vial with a stir bar was charged with carboxylic acid (0.1 mmol, 1.0 equiv.), DCC (20.6 mg, 0.1 mmol, 1.0 equiv.) and NHPI (16.3 mg, 0.1 mmol, 1.0 equiv.). The vial was sealed, evacuated and refilled with Ar 3 times. Then, DMF (anhydrous, 0.5 mL) was added. The mixture was heated to 75 ºC and stirred until completion as indicated by TLC (typically 30-45 minutes). The reaction mixture was allowed to cool to r.t. and a solution of $NiCl_2$·glyme (4.4 mg, 20 mol%) and di-*t*Bubipy (10.7 mg, 40 mol%) in DMF (anhydrous, 0.5 mL) was added to the reaction mixture and stirred at r.t. for 5 min. ArylZnCl·LiCl (0.25 M in THF, 1.2 mL, 0.3 mmol, 3.0 equiv.) was added in one portion to the reaction mixture, which was then stirred for 12–16 h. The mixture was diluted with ethyl acetate or diethyl ether and quenched with 1M HCl (aq). The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

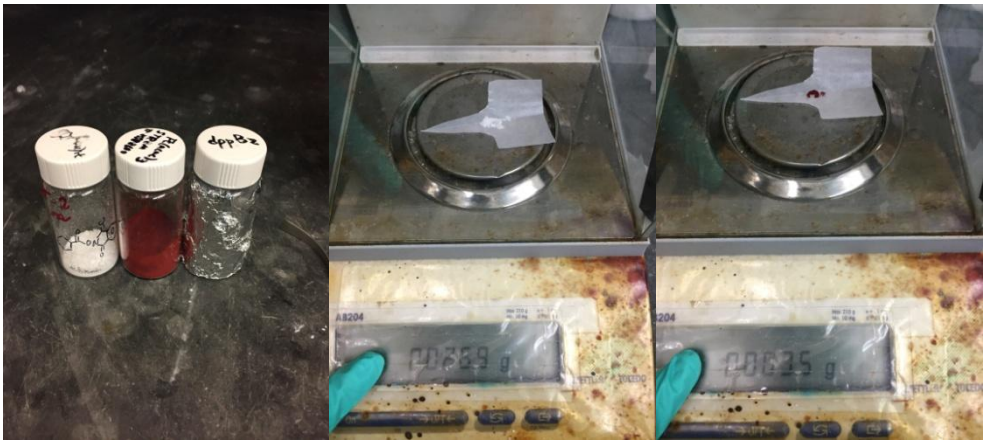
7. Optimized Procedures for Fe-catalyzed Negishi reactions of RAEs

7.1. General Procedure I: Fe-Negishi with isolated NHPI or TCNHPI esters

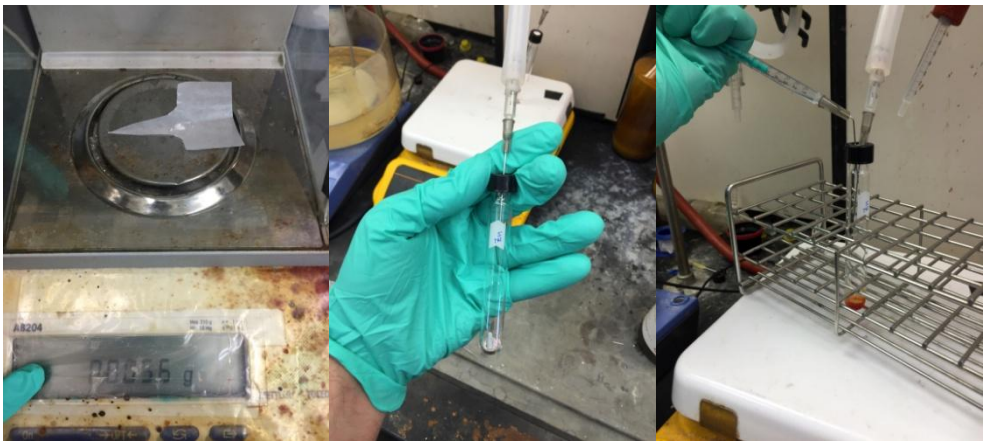


In a 10 mL screwed-capped vial NHPI or TCNHPI ester (0.1 mmol, 1.0 equiv.), $Fe(acac)_3$ (3.5 mg, 10 mol%) and dppBz (5.4 mg, 12 mol%) were weighed. The vial was then sealed, evacuated and back-filled with Ar 3 times. Then, THF (0.5 mL) was added. The mixture was stirred for 5 minutes and $Aryl_2Zn$ reagent (0.33 M in THF, 0.46 mL, 0.15 mmol, 1.5 equiv.) was added in one portion at r.t. to the mixture and stirred at the same temperature for 1 h. The mixture was quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

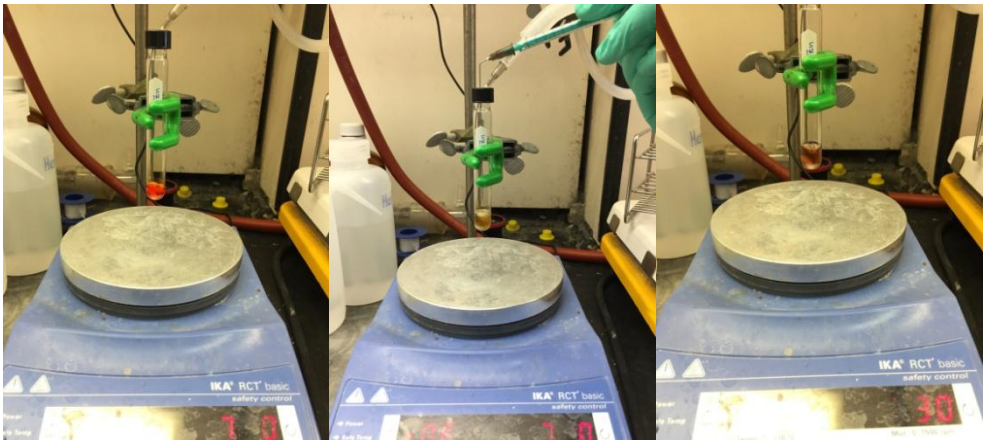
7.1.1. Graphical guide for Fe-Negishi with isolated RAEs



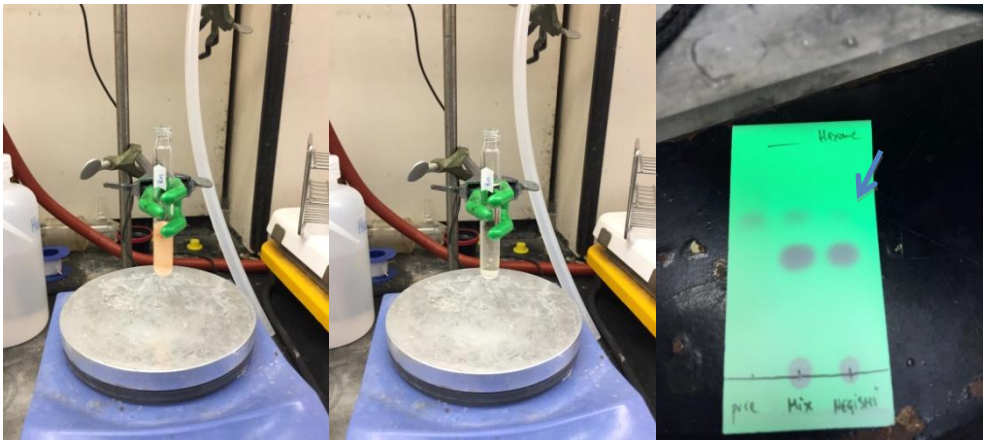
Left: Redox-active ester, $Fe(acac)_3$, dppBz. **Center:** Redox-active ester weight. **Right:** $Fe(acac)_3$ weight.



Left: DppBz weight. **Center:** Reagents in a culture tube under vacuum. **Right:** Addition of THF to the reaction vessel.

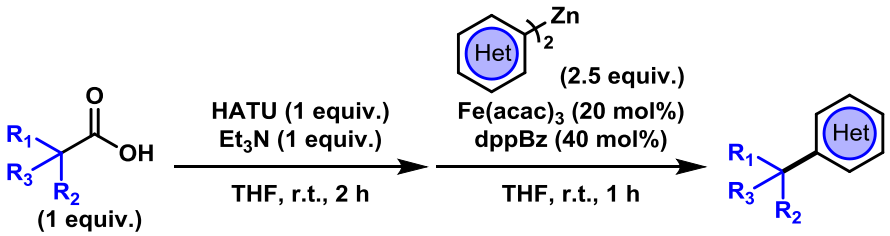


Left: Reaction vessel after addition of THF. **Center:** Addition of $Aryl_2Zn$. **Right:** After addition of $Aryl_2Zn$.



Left. Quench of the reaction after 1 h with HCl 1M. **Center:** Dilution of the mixture with diethyl ether. **Right:** TLC plate of the reaction (left: Pure product; center: cross-spot; right: reaction crude).

7.2. General Procedure J: Fe-Negishi with HATU *in situ*

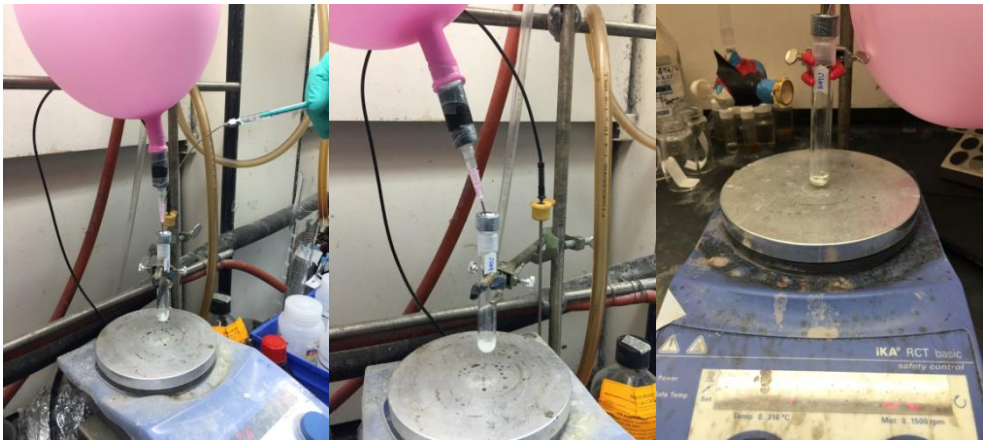


In a 10 mL screwed-capped vial carboxylic acid (0.1 mmol, 1.0 equiv.) and HATU (38 mg, 0.1 mmol, 1.0 equiv.) were weighed. The vial was sealed, evacuated and refilled with Ar 3 times. Then, Et_3N (14 µL, 0.1 mmol, 1.0 equiv.) followed by THF (0.2 mL) were added via syringe. The mixture was stirred for 2 h at r.t. (usually, the solution becomes clear after this time). A solution of $Fe(acac)_3$ (7.1 mg, 20 mol%) and dppBz (17.9 mg, 40 mol%) in THF (0.3 mL) under Ar was added at r.t. and the mixture was stirred for 5 minutes. Ar_2Zn (0.33 M in THF, 0.76 mL, 0.25 mmol, 2.5 equiv.) was added in one portion via syringe. The mixture was stirred at r.t. for 1 h and was then quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

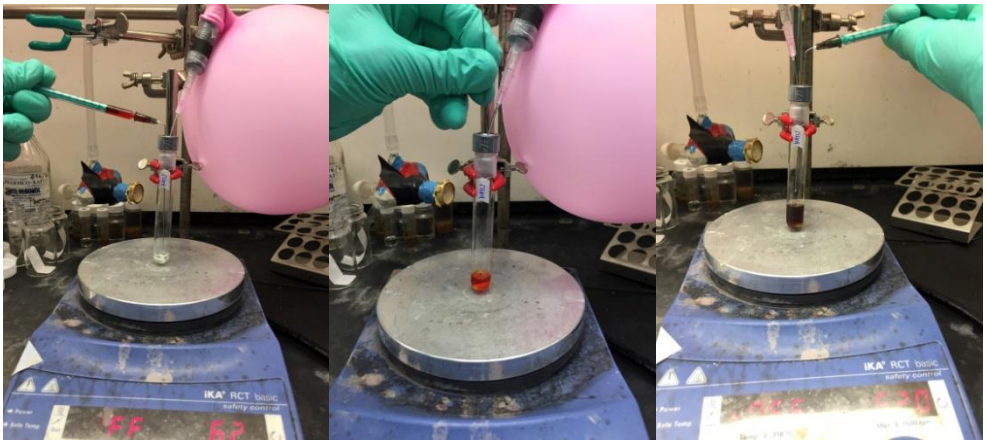
7.2.1. Graphical guide for Fe-Negishi with HATU *in situ*

Left: Carboxylic acid and HATU**. Center:** Weight of carboxylic acid. **Right:** Weight of HATU.

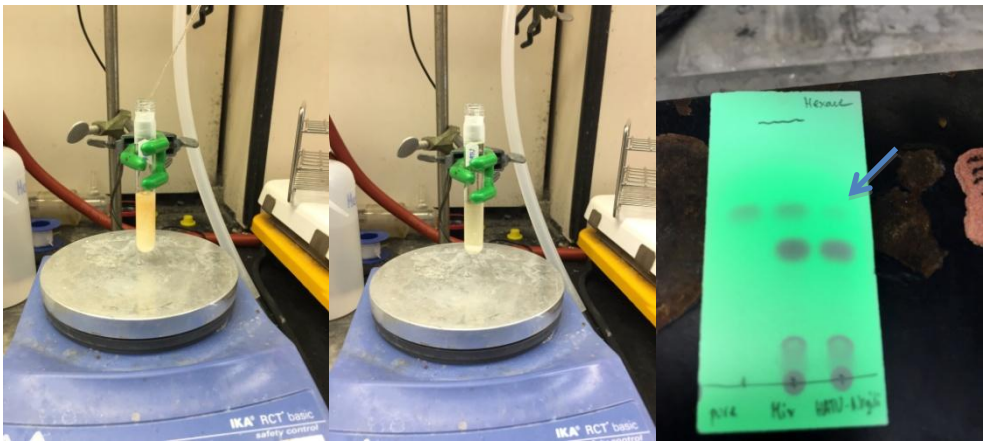
Left: Weighted solids in a culture test tube under Ar. **Center:** Anhydrous triethylamine utilized. **Right:** Addition of triethylamine.



Left: Addition of THF. **Center:** After addition of THF (white suspension). **Right:** Solution after 2 h stirring at r.t. (it becomes a clear solution).

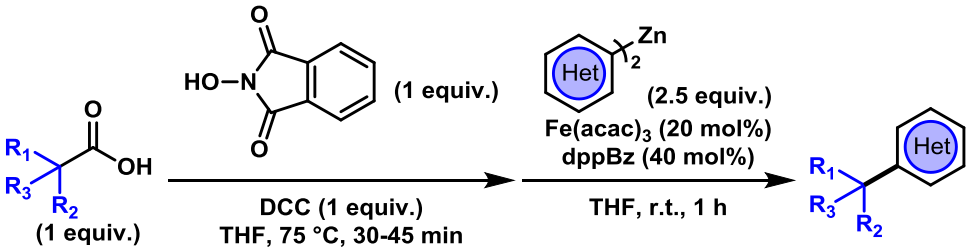


Left: Reaction prior to addition of Fe/ligand solution. **Center:** Solution after addition of Fe/ligand solution. **Right:** Addition of Ph_2Zn in one portion.



Left. Quench of the reaction after 1 h with 1 M HCl. **Center:** Dilution of the mixture with diethyl ether. **Right:** TLC plate of the reaction (left: Pure product; center: cross-spot; right: reaction crude).

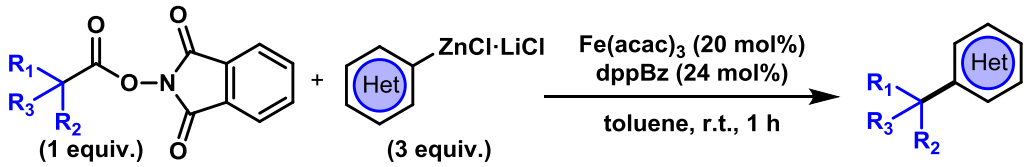
7.3. General Procedure K: Fe-Negishi with NHPI *in situ*



In a 10 mL screwed-capped vial carboxylic acid (0.1 mmol, 1.0 equiv.), DCC (20.6 mg, 0.1 mmol, 1.0 equiv.) and NHPI (16.3 mg, 0.1 mmol, 1.0 equiv.) were weighed. The vial was sealed, evacuated and refilled with Ar 3 times. THF (0.2 mL) was added via syringe. Then, the mixture was heated to 75 ºC and stirred until completion as indicated by TLC (typically 30-45 minutes). The mixture was allowed to cool to r.t. and a solution of $Fe(acac)_3$ (7.1 mg, 20 mol%) and dppBz (17.9 mg, 40 mol%) in THF (0.3 mL) under Ar was added. The mixture was stirred for 5 minutes at which point Ar_2Zn (0.33 M in THF, 0.76 mL, 0.25 mmol, 2.5 equiv.) was added in one portion via syringe. The mixture was stirred at r.t. for 1 h and was then quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR

and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

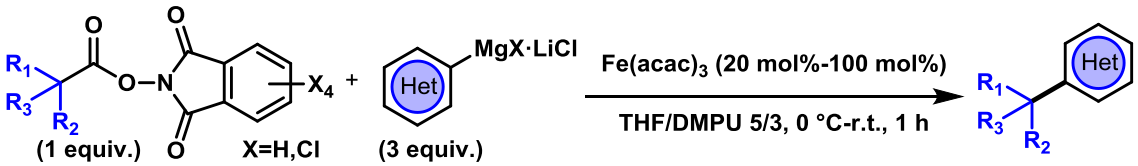
7.4. General Procedure L: Fe-Negishi for heterocyclic cross coupling



In a 10 mL screwed-capped vial NHPI ester (0.1 mmol, 1.0 equiv.), $Fe(acac)_3$ (7.1 mg, 20 mol%) and dppBz (10.7 mg, 24 mol%) were weighed. The vial was then sealed, evacuated and back-filled with Ar 3 times. Then, toluene (0.5 mL) was added. The mixture was stirred for 5 minutes and ArylZnCl·LiCl (0.3 M in THF, 1.0 mL, 0.3 mmol, 3.0 equiv.) was added in one portion at r.t. The mixture was stirred at the same temperature for 1 h and was then quenched with H_2O or half-saturated NH_4Cl (aq) solution and diluted with ethyl acetate. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

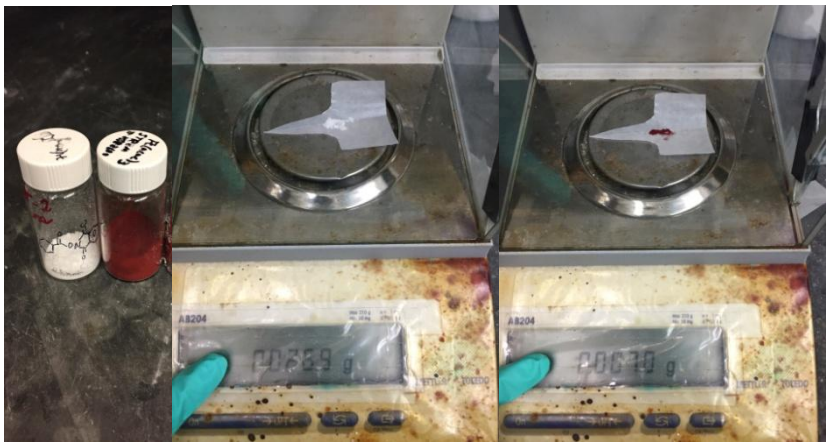
8. Optimized Procedures for Fe-catalyzed Kumada reactions of RAEs

8.1. General Procedure M: Fe-Kumada with isolated NHPI or TCNHPI esters

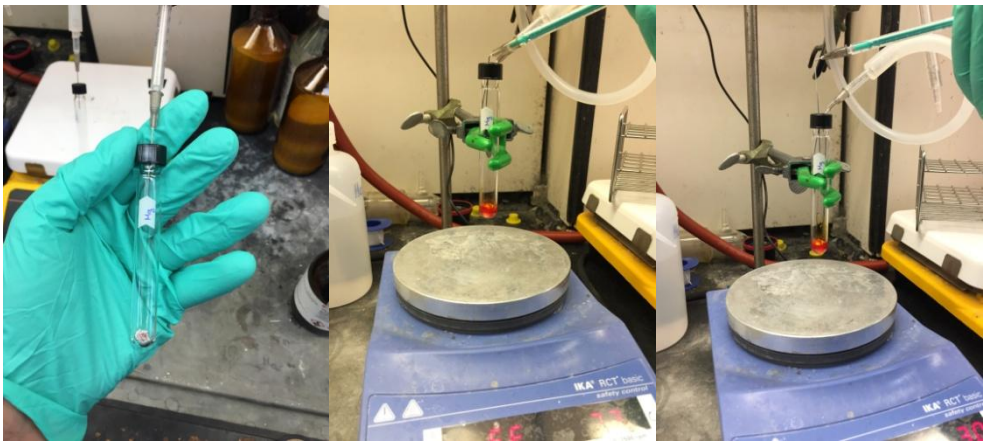


In a 10 mL screwed-capped vial NHPI or TCNHPI ester (0.1 mmol, 1.0 equiv.) and $Fe(acac)_3$ (7.1 mg, 20 mol% for primary or secondary esters, or 35.3 mg, 100 mol% for tertiary esters) were weighed. The vial was then sealed, evacuated and back-filled with Ar (this process was repeated 3 times). Then, THF (0.35 mL) and DMPU (anhydrous, 0.21 mL) were added. The mixture was stirred for 5 minutes at r.t. At this point, ArMgX·LiCl in THF (0.3 mmol, 3.0 equiv.) was added in one portion at 0 °C (for primary or secondary esters) or 25 ºC (for tertiary esters), and stirred at this temperature for 1 h. The mixture was quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

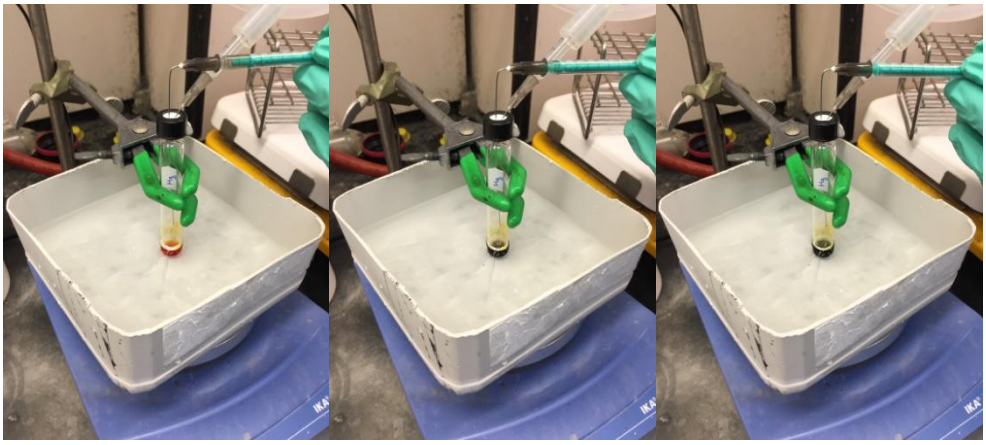
8.1.1. Graphical guide for Fe-Kumada with isolated RAEs



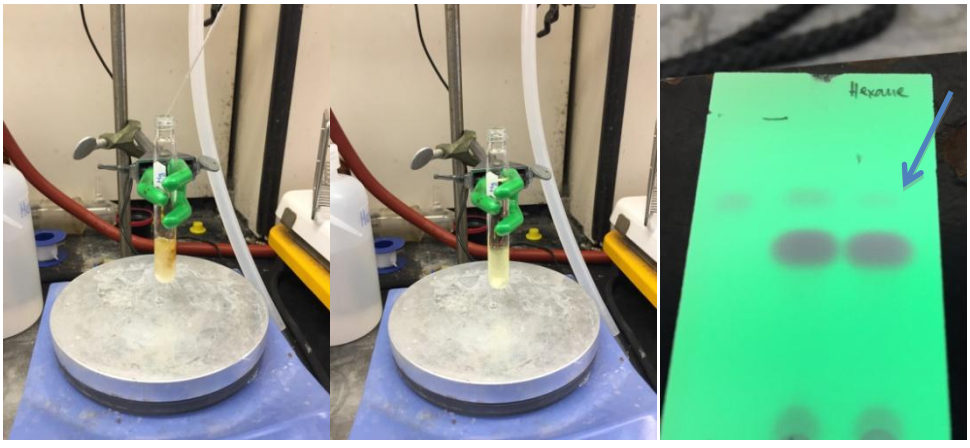
Left: Redox-active ester and catalyst. **Center:** Redox-active ester weight. **Right:** $Fe(acac)_3$ weight.



Left: Reagents in a culture tube under vacuum. **Center:** Addition of THF. **Right:** Addition of DMPU.

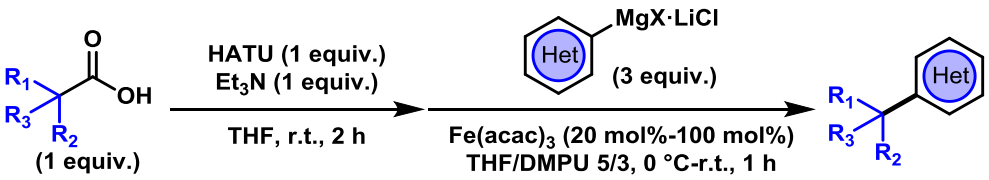


Addition of Grignard. Left: Before the addition. **Center:** During addition. **Right:** After addition.



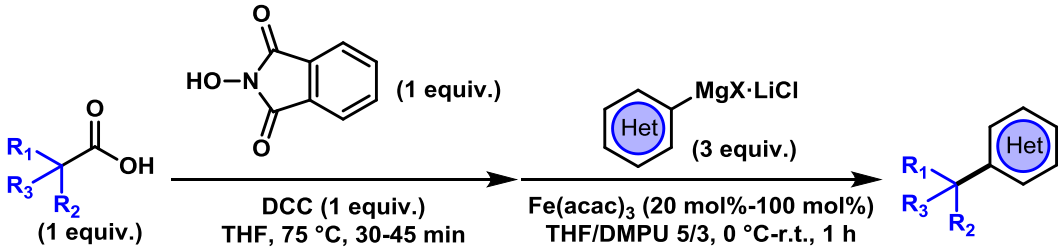
Left: Quench with HCl 1M. **Center:** Dilution with diethyl ether. **Right:** TLC plate of the reaction (left: Pure product; center: cross-spot; right: reaction crude).

8.2. General Procedure N: Fe-Kumada with HATU *in situ*



In a 10 mL screwed-capped vial carboxylic acid (0.1 mmol, 1.0 equiv.) and HATU (38 mg, 0.1 mmol, 1.0 equiv.) were weighed. The vial was sealed, evacuated and refilled with Ar 3 times. Then, Et_3N (14 µL, 0.1 mmol, 1.0 equiv.) followed by THF (0.2 mL) were added via syringe. The mixture was stirred for 2 h at r.t. (usually, the solution becomes clear after this time). A solution of $Fe(acac)_3$ (7.1 mg, 20 mol% for primary and secondary acids, 35.3 mg, 100 mol% for tertiary acids) in THF (0.15 mL) and DMPU (anhydrous, 0.21 mL) under Ar was added at r.t. and the mixture was stirred for 5 minutes. At this point, ArMgX·LiCl in THF (0.3 mmol, 3.0 equiv.) was added in one portion at 0 °C (for primary or secondary acids) or 25 ºC (for tertiary acids), and stirred at this temperature for 1 h. The mixture was quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

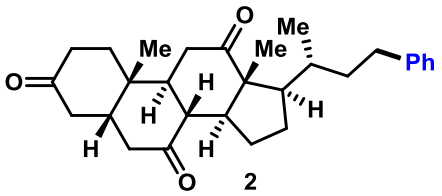
8.3. General Procedure O: Fe-Kumada with NHPI *in situ*



In a 10 mL screwed-capped vial carboxylic acid (0.1 mmol, 1.0 equiv.), DCC (20.6 mg, 0.1 mmol, 1.0 equiv.) and NHPI (16.3 mg, 0.1 mmol, 1.0 equiv.) were weighed. The vial was sealed, evacuated and refilled with Ar 3 times. THF (0.2 mL) was added via syringe. Then, the mixture was heated to 75 ºC and stirred until completion as indicated by TLC (typically 30-45 minutes). The mixture was allowed to cool to r.t. and a solution of $Fe(acac)_3$ (7.1 mg, 20 mol% for primary and secondary acids, 35.3 mg, 100 mol% for tertiary acids) in THF (0.15 mL) and DMPU (anhydrous, 0.21 mL) under Ar was added at r.t. and the mixture was stirred for 5 minutes. At this point, ArMgX·LiCl in THF (0.3 mmol, 3.0 equiv.) was added in one portion at 0 °C (for primary or secondary acids) or 25 ºC (for tertiary acids), and stirred at this temperature for 1 h. The mixture was quenched with 1M HCl (aq) and diluted with ethyl acetate or diethyl ether. The reaction can also be quenched with H_2O or half-saturated NH_4Cl (aq) solution for acid-sensitive substrates. The organic layer was washed with H_2O and $NaHCO_3$, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was dissolved in $CDCl_3$ and an exact amount of standard (1,4-difluorobenzene or mesitylene, *ca*. 1 equiv.) was added. The crude sample was analyzed by ^{1}H-NMR and the yield was calculated relative to the standard. For isolated yields, the crude sample was purified by silica gel flash column chromatography or preparative TLC (PTLC) to yield the pure compound.

9. Description of compounds

(5*S*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-((*R*)-4-phenylbutan-2-yl)dodecahydro-3*H*-cyclopenta[*a*]phenanthrene-3,7,12(2*H*,4*H*)-trione (2)



2

Compound **2** was prepared using TCNHPI ester **SI-1** (69.9 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-13** (56.2 mg, 0.1 mmol, 1.0 equiv.) or dehydrocholic acid (40.3 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-1** afforded **2** in 89% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes:ethyl acetate 3:2) afforded 33.7 mg (75%) as a white solid.

General Procedure C using *NHPI* ester **SI-13** afforded **2** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **2** in <2% NMR-yield (mesitylene).

General Procedure E afforded **2** in 32% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-1** afforded **2** in 62% NMR-yield (1,4-difluorobenzene).

General Procedure F using *NHPI* ester **SI-13** afforded **2** in 32% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **2** in 51% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **2** in 21% NMR-yield (mesitylene).

General Procedure I using *TCNHPI* ester **SI-1** afforded **2** in 57% NMR-yield (mesitylene).

General Procedure I using *NHPI* ester **SI-13** afforded **2** in 47% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **2** in 62% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **2** in 35% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-1** afforded **2** in 20% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-13** afforded **2** in 41% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **2** in 8% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **2** in 29% NMR-yield (mesitylene).

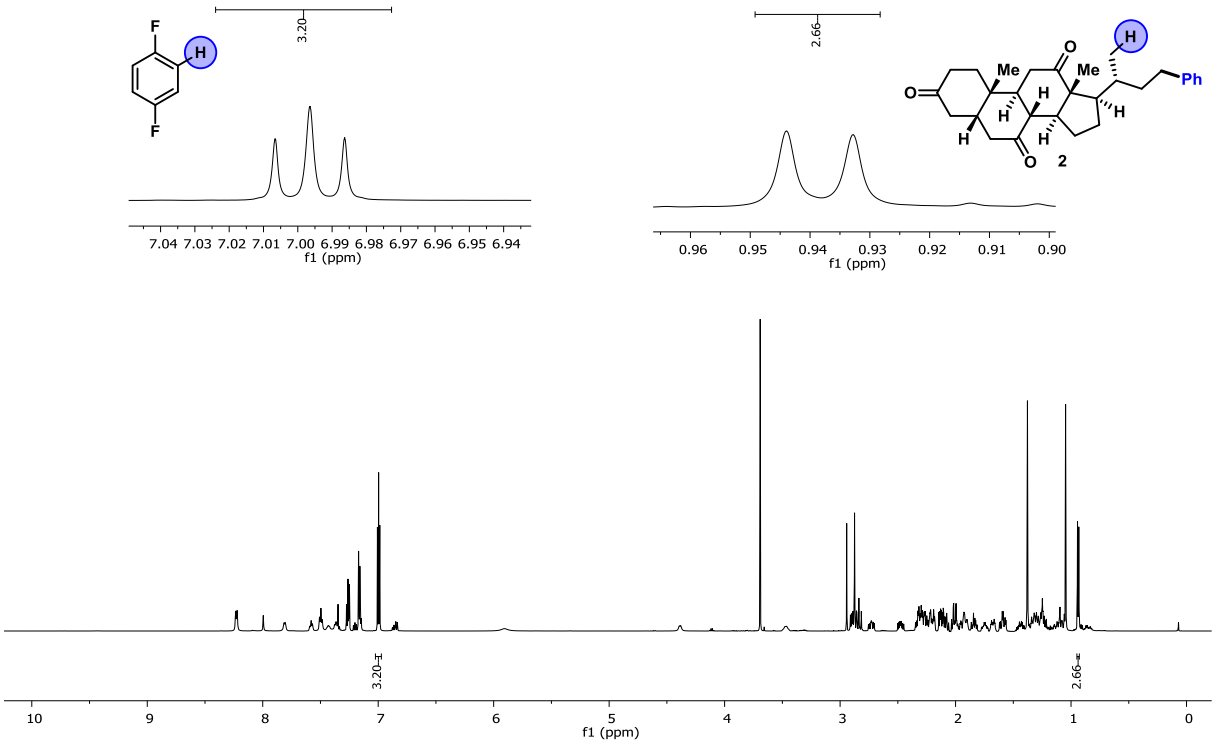
R_f = 0.33 (hexanes:ethyl acetate 1.25:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32 – 7.29 (m, 2H), 7.22 – 7.16 (m, 3H), 3.00– 2.83 (m, 3H), 2.77 (ddd, *J* = 13.5, 11.0, 4.9 Hz, 1H), 2.51 (ddd, *J* = 13.6, 10.7, 6.2 Hz, 1H), 2.40 – 2.21 (m, 6H), 2.19 – 2.14 (m, 2H), 2.13 – 2.11 (m, 1H), 2.08 – 1.95 (m, 3H), 1.88 (td, *J* = 11.3, 7.0 Hz, 1H), 1.78 (dddd, *J* = 13.6, 11.0, 6.2, 2.7 Hz, 1H), 1.64 (td, *J* = 14.4, 4.6 Hz, 1H), 1.52 – 1.44 (m, 1H), 1.43 (s, 3H), 1.39 – 1.24 (m, 3H), 1.09 (s, 3H), 0.97 (d, *J* = 6.7 Hz, 3H).

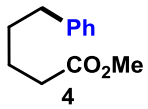
^{13}C NMR (151 MHz, $CDCl_3$): δ 211.6, 208.6, 208.3, 142.7, 127.9, 127.8, 125.1, 56.5, 51.3, 48.6, 46.4, 45.3, 45.1, 44.5, 42.4, 38.2, 37.1, 36.0, 35.6, 35.4, 34.9, 32.5, 27.3, 24.7, 21.5, 18.5, 11.4.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signal 3H), affording an NMR-yield of 89% (*General Procedure C* using *TCNHPI* ester **SI-1**).



Methyl 5-phenylpentanoate (4)



4

Compound **4** was prepared using TCNHPI ester **SI-2** (44.3 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-14** (30.5 mg, 0.1 mmol, 1.0 equiv.) or mono-methyl adipate (16.0 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-2** afforded **4** in 65% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-14** afforded **4** in 8% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **4** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **4** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-2** afforded **4** in 71% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes:ethyl acetate 12:1) afforded 12.1 mg (63%) as a white solid.

General Procedure F using *NHPI* ester **SI-14** afforded **4** in 52% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **4** in 54% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **4** in 26% NMR-yield (mesitylene).

General Procedure I using *TCNHPI* ester **SI-2** afforded **4** in 26% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-14** afforded **4** in 64% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **4** in 62% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **4** in 37% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-2** afforded **4** in 10% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-14** afforded **4** in 28% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **4** in 72% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **4** in 24% NMR-yield (mesitylene).

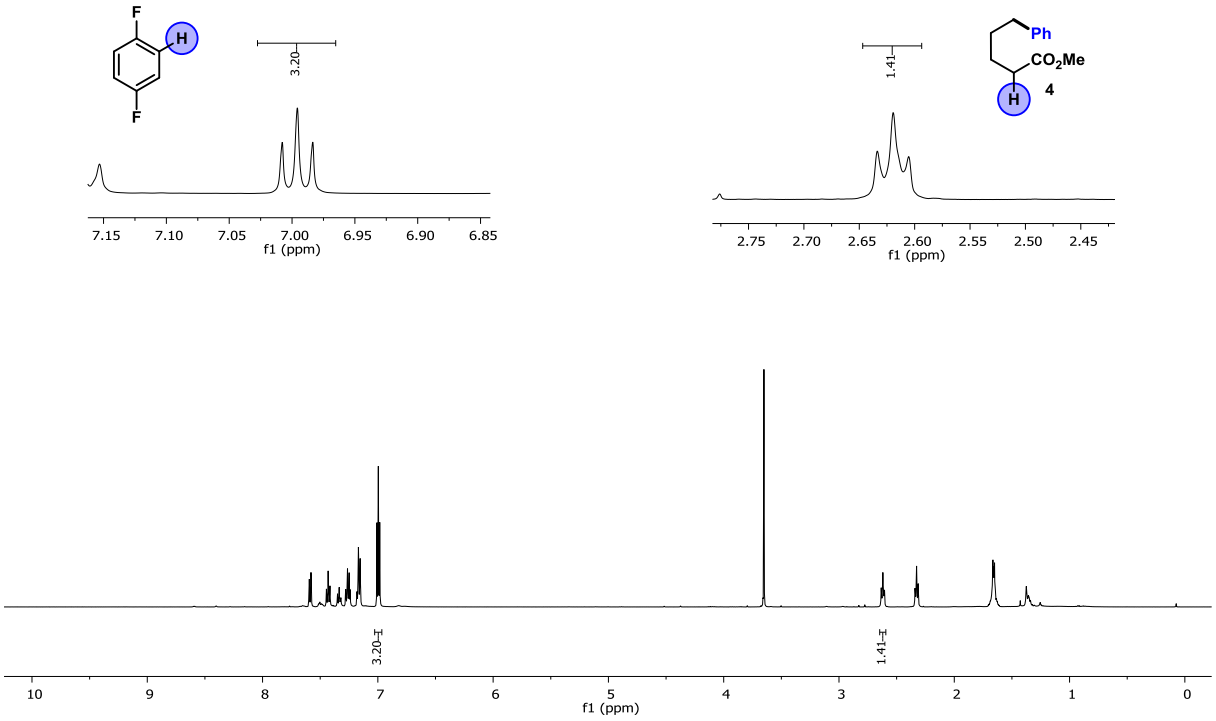
R_f = 0.50 (hexanes:ethyl acetate 12:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.29 – 7.27 (m, 2H), 7.19 – 7.17 (m, 3H), 3.67 (s, 3H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H), 1.71 – 1.63 (m, 4H).

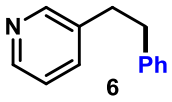
^{13}C NMR (151 MHz, $CDCl_3$): δ 174.2, 142.3, 128.5, 128.5, 125.9, 51.6, 35.7, 34.1, 31.0, 24.7.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signal 2H), affording an NMR-yield of 71% (*General Procedure F* using *TCNHPI* ester **SI-2**).



3-Phenethylpyridine (6)



Compound **6** was prepared using TCNHPI ester **SI-3** (43.4 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-15** (29.6 mg, 0.1 mmol, 1.0 equiv.) or 3-pyridinepropionic acid (15.1 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-3** afforded **6** in <2% NMR-yield (mesitylene).

General Procedure C using *NHPI* ester **SI-15** afforded **6** in <2% NMR-yield (mesitylene).

General Procedure D afforded **6** in <2% NMR-yield (mesitylene).

General Procedure E afforded **6** in <2% NMR-yield (mesitylene).

General Procedure F using *TCNHPI* ester **SI-3** afforded **6** in <2% NMR-yield (mesitylene).

General Procedure F using *NHPI* ester **SI-15** afforded **6** in 37% NMR-yield (mesitylene). Isolation by PTLC (hexanes:ethyl acetate 1:1) afforded 7.4 mg (40%) as a white solid.

General Procedure G afforded **6** in 33% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **6** in 30% NMR-yield (mesitylene).

General Procedure I using *TCNHPI* ester **SI-3** afforded **6** in <2% NMR-yield (mesitylene).

General Procedure I using *NHPI* ester **SI-15** afforded **6** in 30% NMR-yield (mesitylene).

General Procedure J afforded **6** in 72% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **6** in 24% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-3** afforded **6** in 34% NMR-yield (mesitylene).

General Procedure M using *NHPI* ester **SI-15** afforded **6** in 43% NMR-yield (mesitylene).

General Procedure N afforded **6** in 45% NMR-yield (mesitylene, cf. representative evaluation).

General Procedure O afforded **6** in 27% NMR-yield (mesitylene).

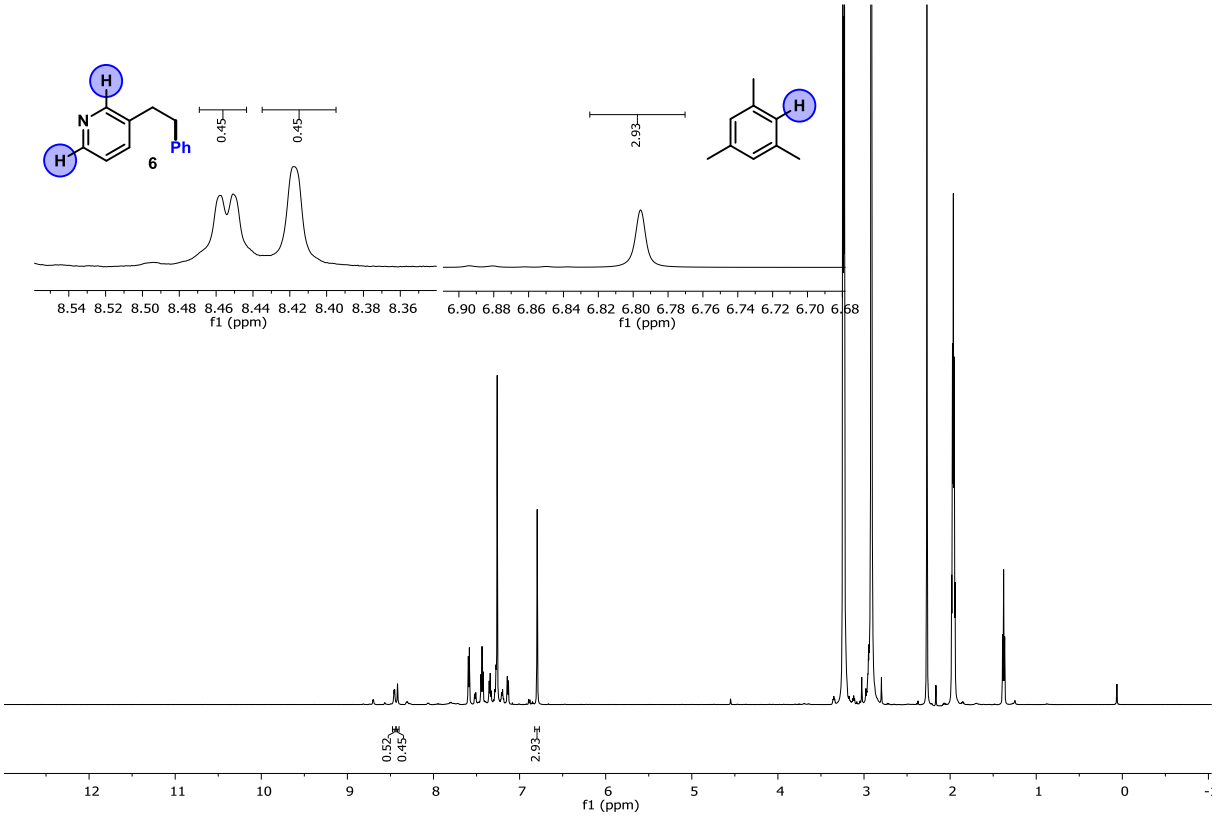
R_f = 0.43 (hexanes:ethylacetate 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.44 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.43 (d, *J* = 2.3 Hz, 1H), 7.43 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.22 – 7.17 (m, 2H), 7.17 – 7.13 (m, 2H), 2.93 (s, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.5, 147.0, 140.3, 136.4, 135.5, 128.0, 127.9, 125.7, 122.8, 37.00, 34.5.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using mesitylene (14 µL, 0.098 mmol). Standard signal refers to 2.93 equivalents (product signal 1H), affording an NMR-yield of 45% (*General Procedure N*).



1-Chloro-4-(4,4-difluorocyclohexyl)benzene (8)

8

Compound **8** was prepared using TCNHPI ester **SI-4** (44.7 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-5** (30.9 mg, 0.1 mmol, 1.0 equiv.) or 4,4-difluorocyclohexanecarboxylic acid (16.4 mg, 0.1 mmol, 1.0 equiv.) and 4-chlorophenylboronic acid (46.9 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-4** afforded **8** in 60% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-5** afforded **8** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **8** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **8** in 12% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-4** afforded **8** in 79% NMR-yield (mesitylene, cf. representative evaluation).

General Procedure F using *NHPI* ester **SI-5** afforded **8** in 62% NMR-yield (mesitylene).

General Procedure G afforded **8** in 24% NMR-yield (mesitylene).

General Procedure H afforded **8** in 27% NMR-yield (mesitylene).

General Procedure I using *TCNHPI* ester **SI-4** afforded **8** in 52% NMR-yield (mesitylene).

General Procedure I using *NHPI* ester **SI-5** afforded **8** in 40% NMR-yield (mesitylene). Isolation by PTLC (hexanes) afforded 8.0 mg (35%) as a white solid.

General Procedure J afforded **8** in 63% NMR-yield (mesitylene).

General Procedure K afforded **8** in 42% NMR-yield (mesitylene).

General Procedure M using *TCNHPI* ester **SI-4** afforded **8** in 25% NMR-yield (mesitylene).

General Procedure M using *NHPI* ester **SI-5** afforded **8** in 11% NMR-yield (mesitylene).

General Procedure N afforded **8** in 11% NMR-yield (mesitylene).

General Procedure O afforded **8** in 4% NMR-yield (mesitylene).

m.p. 55 °C.

R_f= 0.23 (hexanes).

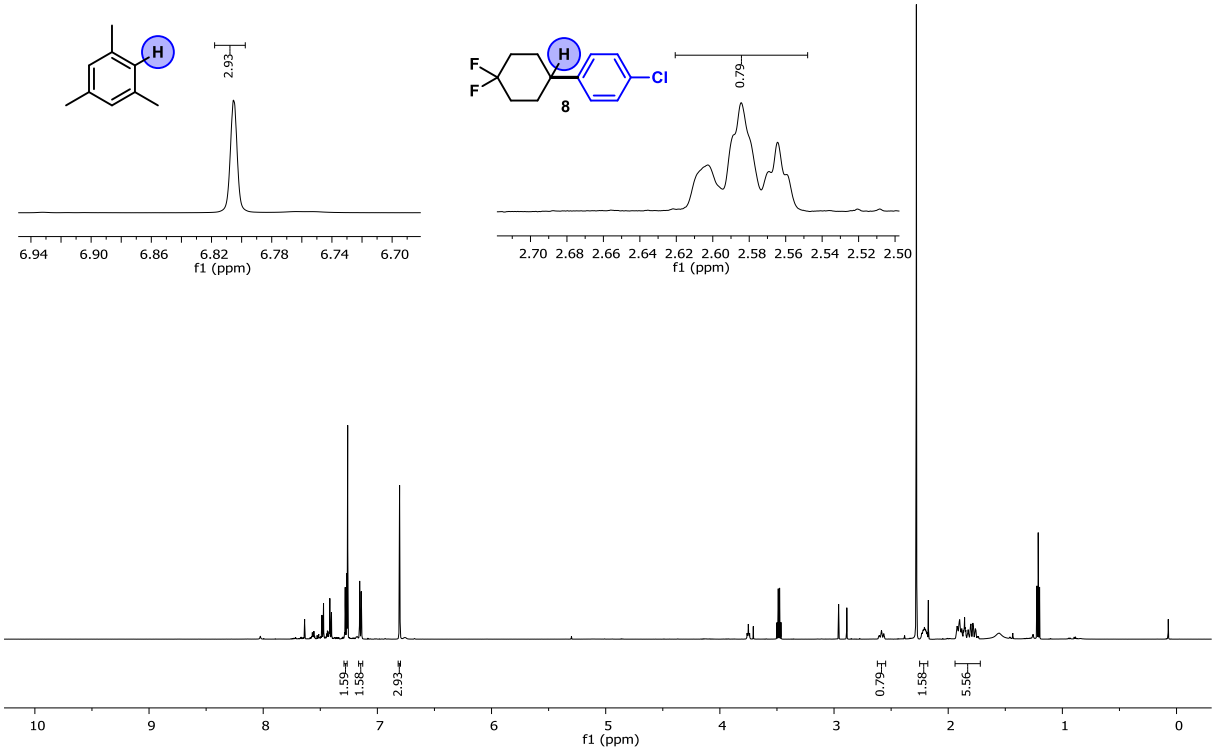
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 2.58 (td, *J* = 10.4, 9.0, 5.9 Hz, 1H), 2.20 (qd, *J* = 7.6, 6.8, 3.6 Hz, 2H), 1.94 – 1.72 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.8 (d, *J* = 2.3 Hz), 132.2, 128.8, 128.2, 123.1 (dd, *J* = 242.7, 239.3 Hz), 42.1, 34.1 (dd, *J* = 25.8, 22.7 Hz), 30.4 (d, *J* = 10.1 Hz).

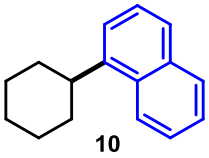
^{19}F NMR (376 MHz, $CDCl_3$) δ -92.08 (d, *J* = 236.3 Hz), -102.69 (d, *J* = 236.3 Hz).

m/z (GC-MS, EI): calc'd for $C_{12}H_{13}ClF_2$ $[M]^+$ 230.0674; found 230.

Representative evaluation of crude NMR spectrum after work-up using mesitylene (14 µL, 0.098 mmol). Standard signal refers to 2.93 equivalents (product signal 1H), affording an NMR-yield of 79% (*General Procedure F* using *TCNHPI* ester **SI-4**).



1-Cyclohexylnaphthalene (10)



Compound **10** was prepared using TCNHPI ester **SI-6** (41.1 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-7** (27.3 mg, 0.1 mmol, 1.0 equiv.) or cyclohexanecarboxylic acid (12.8 mg, 0.1 mmol, 1.0 equiv.) and naphthalene-1-boronic acid (51.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-6** afforded **10** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-7** afforded **10** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **10** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **10** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-6** afforded **10** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure F using *NHPI* ester **SI-7** afforded **10** in 17% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **10** in 30% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **10** in <2% NMR-yield (mesitylene).

General Procedure I using *TCNHPI* ester **SI-6** afforded **10** in 22% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-7** afforded **10** in 64% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **10** in 83% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes) afforded 15.9 mg (76%) as a white solid.

General Procedure K afforded **10** in 78% NMR-yield (mesitylene).

General Procedure M using *TCNHPI* ester **SI-6** afforded **10** in 10% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-7** afforded **10** in 67% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **10** in 24% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **10** in 57% NMR-yield (mesitylene).

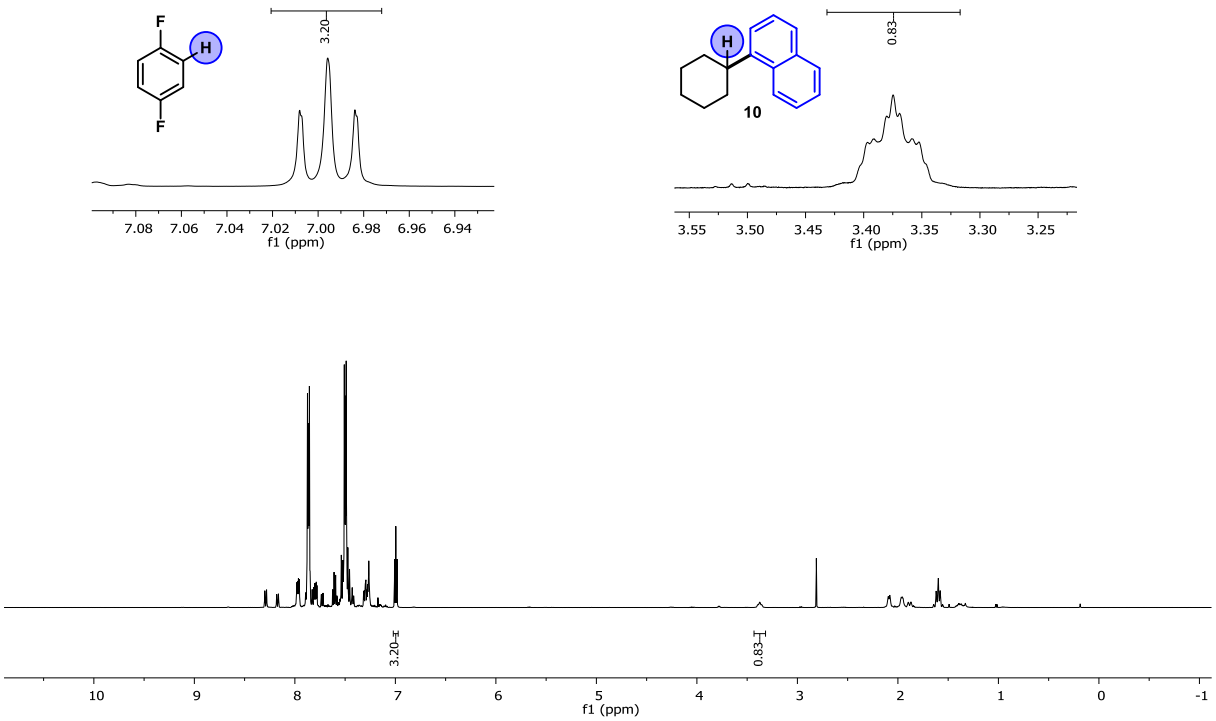
R_f = 0.55 (hexanes).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.51 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.47 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H), 7.45 (d, 1H), 7.40 (dd, *J* = 7.3, 1.3 Hz, 1H), 3.34 (tt, *J* = 11.3, 3.1 Hz, 1H), 2.09 – 2.01 (m, 2H), 1.98 – 1.90 (m, 2H), 1.88 – 1.83 (m, 1H), 1.62 – 1.52 (m, 4H), 1.40 – 1.32 (m, 1H).

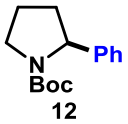
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0, 134.1, 131.5, 129.1, 126.3, 125.8, 125.7, 125.3, 123.3, 122.4, 39.4, 34.4, 27.5, 26.7.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signal 1H), affording an NMR-yield of 83% (*General Procedure J*).



***tert*-Butyl 2-phenylpyrrolidine-1-carboxylate (12)**



12

Compound **12** was prepared using TCNHPI ester **SI-16** (49.8 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-8** (36.0 mg, 0.1 mmol, 1.0 equiv.) or (*tert*-butoxycarbonyl)proline (21.5 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-16** afforded **12** in 23% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-8** afforded **12** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **12** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **12** in 16% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-16** afforded **12** in 17% NMR-yield (1,4-difluorobenzene).

General Procedure F using *NHPI* ester **SI-8** afforded **12** in 52% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes:ethyl acetate 20:3) afforded 10.6 mg (43%) as a white solid.

General Procedure G afforded **12** in 34% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **12** in 26% NMR-yield (1,4-difluorobenzene).

General Procedure I using *TCNHPI* ester **SI-16** afforded **12** in 63% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-8** afforded **12** in 63% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **12** in 57% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **12** in 57% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-16** afforded **12** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-8** afforded **12** in 59% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **12** in 40% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **12** in 23% NMR-yield (1,4-difluorobenzene).

R_f = 0.53 (20:3 hexanes:ethyl acetate).

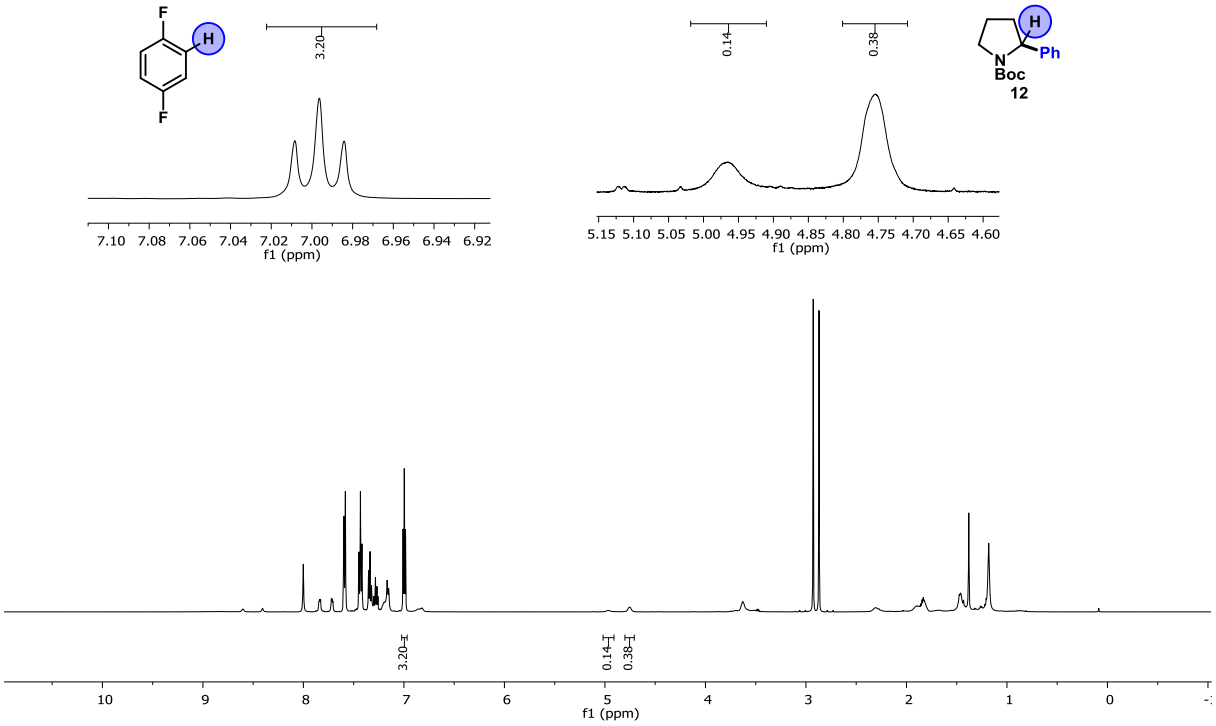
The product gives two sets of NMR signals, owing to the presence of rotamers.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 – 7.23 (m, 2H), 7.19 – 7.13 (m, 3H), 4.93 (brs, 0.3H), 4.73 (brs, 0.7H), 3.60 – 3.49 (m, 2H), 2.30 (br, 1H), 1.89 (br, 1H), 1.85 – 1.75 (m, 2H), 1.43 (s, 3H), 1.15 (s, 6H).

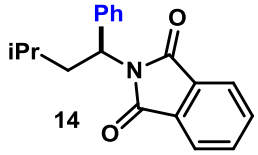
^{13}C NMR (151 MHz, $CDCl_3$): δ 154.7, 145.3, 144.2, 128.4, 128.2, 126.6, 125.6, 125.5, 79.3, 61.5, 60.8, 47.5, 47.2, 36.2, 35.0, 28.7, 28.3, 23.6, 23.3.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signals totaled up 1H), affording an NMR-yield of 52% (*General Procedure F* using *NHPI* ester **SI-8**).



2-(3-Methyl-1-phenylbutyl)isoindoline-1,3-dione (14)



Compound **14** was prepared using TCNHPI ester **SI-17** (54.4 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-9** (40.6 mg, 0.1 mmol, 1.0 equiv.) or 2-(1,3-dioxoisoindolin-2-yl)-4-methylpentanoic acid (26.1 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-17** afforded **14** in 64% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-9** afforded **14** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **14** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **14** in 40% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-17** afforded **14** in 87% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes:ethyl acetate 10:1) afforded 23.8 mg (81%) as a white solid.

General Procedure F using *NHPI* ester **SI-9** afforded **14** in 24% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **14** in 40% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **14** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure I using *TCNHPI* ester **SI-17** afforded **14** in 24% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-9** afforded **14** in 35% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **14** in 48% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **14** in 30% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-17** afforded **14** in 6% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-9** afforded **14** in 16% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **14** in 3% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **14** in <2% NMR-yield (1,4-difluorobenzene).

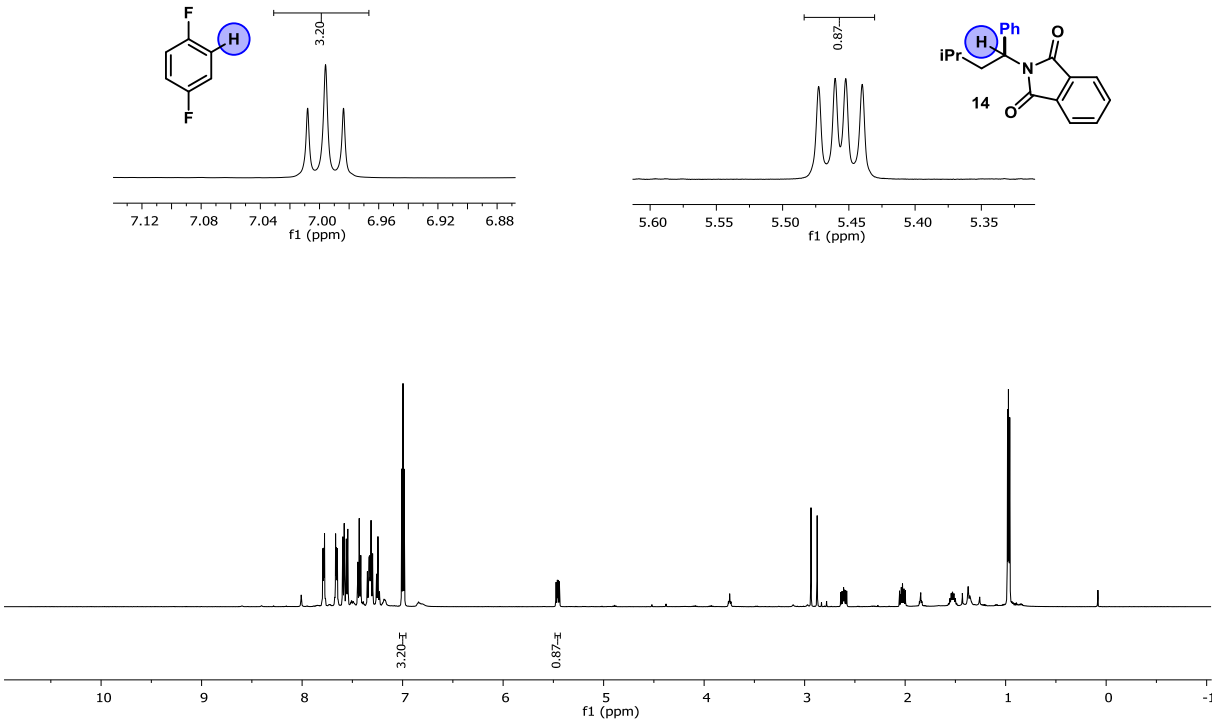
R_f= 0.30 (hexanes:ethyl acetate 10:1).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 – 7.78 (m, 2H), 7.70 – 7.67 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.5 Hz, 1H), 5.45 (dd, *J* = 10.0, 6.5 Hz, 1H), 2.64 – 2.58 (m, 1H), 2.64 – 2.58 (m, 1H), 2.06 – 2.00 (m, 1H), 1.57 – 1.49 (m, 1H), 0.98 (d, *J* = 4.0 Hz, 3H), 0.97 (d, *J* = 4.0 Hz, 3H).

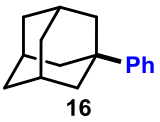
^{13}C NMR (151 MHz, $CDCl_3$): δ 168.6, 140.1, 134.0, 132.0, 128.6, 128.3, 127.8, 123.3, 53.2, 39.9, 25.6, 23.1, 22.1.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signal 1H), affording an NMR-yield of 87% (*General Procedure F* using *TCNHPI* ester **SI-17**).



1-Phenyladamantane (16)



16

Compound **16** was prepared using TCNHPI ester **SI-18** (46.3 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-10** (32.5 mg, 0.1 mmol, 1.0 equiv.) or 1-adamantanecarboxylic acid (18.0 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-18** afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-10** afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure E afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-18** afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure F using *NHPI* ester **SI-10** afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure I using *TCNHPI* ester **SI-18** afforded **16** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-10** afforded **16** in 55% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **16** in 20% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **16** in 35% NMR-yield (1,4-difluorobenzene). Isolation by PTLC (hexanes) afforded 5.9 mg (28%) as a white solid.

General Procedure M using *TCNHPI* ester **SI-18** afforded **16** in 16% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-10** afforded **16** in 68% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **16** in 24% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **16** in 37% NMR-yield (mesitylene, cf. representative evaluation).

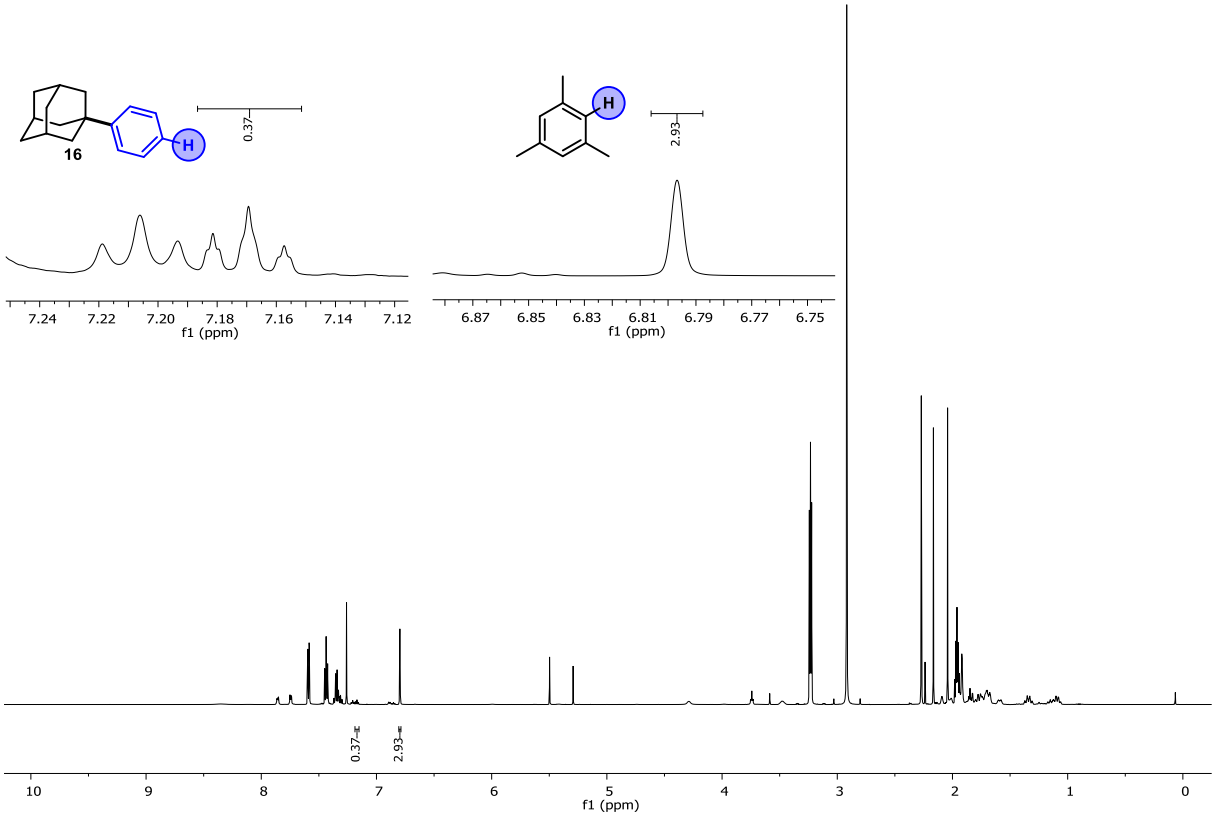
R_f = 0.47 (hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 2.11 (m, 3H), 1.93 (d, *J* = 3.0 Hz, 6H), 1.84 – 1.74 (m, 6H).

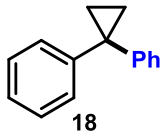
^{13}C NMR (151 MHz, $CDCl_3$): δ 151.5, 128.2, 125.6, 125.0, 43.3, 37.0, 36.3, 29.1.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using mesitylene (14 µL, 0.098 mmol). Standard signal refers to 2.93 equivalents (product signal 1H), affording an NMR-yield of 37% (*General Procedure O*).



1,1-Diphenylcyclopropane (18)



18

Compound **18** was prepared using TCNHPI ester **SI-19** (44.5 mg, 0.1 mmol, 1.0 equiv.), NHPI ester **SI-11** (30.7 mg, 0.1 mmol, 1.0 equiv.) or 1-phenylcyclopropane-1-carboxylic acid (16.2 mg, 0.1 mmol, 1.0 equiv.) and phenylboronic acid (36.6 mg, 0.3 mmol, 3.0 equiv.).

General Procedure C using *TCNHPI* ester **SI-19** afforded **18** in 50% NMR-yield (1,4-difluorobenzene).

General Procedure C using *NHPI* ester **SI-11** afforded **18** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure D afforded **18** in <2% NMR-yield (mesitylene).

General Procedure E afforded **18** in 22% NMR-yield (1,4-difluorobenzene).

General Procedure F using *TCNHPI* ester **SI-19** afforded **18** in 69% NMR-yield (1,4-difluorobenzene, cf. representative evaluation). Isolation by PTLC (hexanes) afforded 12.3 mg (63%) as a white solid.

General Procedure F using *NHPI* ester **SI-11** afforded **18** in 16% NMR-yield (1,4-difluorobenzene).

General Procedure G afforded **18** in <2% NMR-yield (1,4-difluorobenzene).

General Procedure H afforded **18** in 28% NMR-yield (1,4-difluorobenzene).

General Procedure I using *TCNHPI* ester **SI-19** afforded **18** in 39% NMR-yield (1,4-difluorobenzene).

General Procedure I using *NHPI* ester **SI-11** afforded **18** in 37% NMR-yield (1,4-difluorobenzene).

General Procedure J afforded **18** in 64% NMR-yield (1,4-difluorobenzene).

General Procedure K afforded **18** in 26% NMR-yield (1,4-difluorobenzene).

General Procedure M using *TCNHPI* ester **SI-19** afforded **18** in 33% NMR-yield (1,4-difluorobenzene).

General Procedure M using *NHPI* ester **SI-11** afforded **18** in 60% NMR-yield (1,4-difluorobenzene).

General Procedure N afforded **18** in 22% NMR-yield (1,4-difluorobenzene).

General Procedure O afforded **18** in 20% NMR-yield (1,4-difluorobenzene).

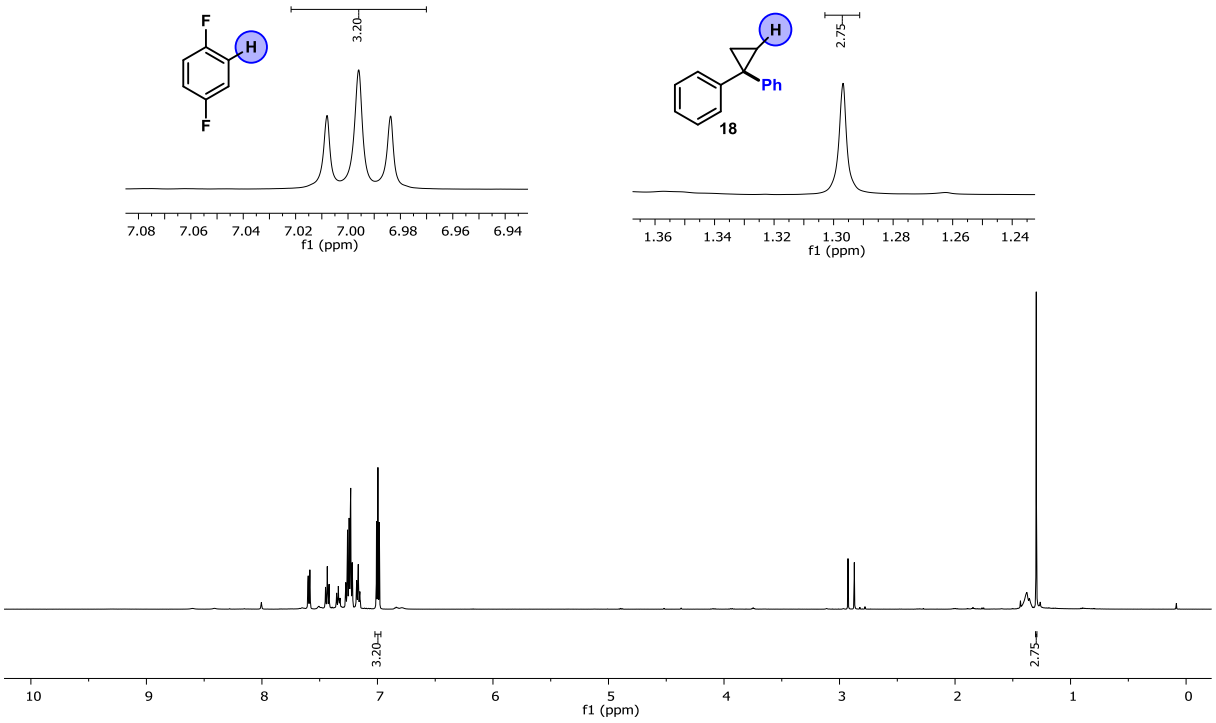
R_f = 0.37 (hexanes).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.4 Hz, 4H), 7.24 – 7.21 (m, 4H), 7.20 – 7.15 (m, 2H), 1.30 (s, 4H).

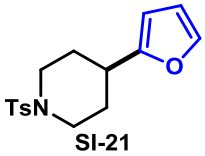
^{13}C NMR (151 MHz, $CDCl_3$): δ 145.9, 128.6, 128.4, 126.1, 30.0, 16.6.

Spectral data are in accordance with those reported in the literature.[4]

Representative evaluation of crude NMR spectrum after work-up using 1,4-difluorobenzene (8.2 µL, 0.08 mmol). Standard signal refers to 3.2 equivalents (product signal 4H), affording an NMR-yield of 69% (*General Procedure F* using *TCNHPI* ester **SI-19**).



4-(Furan-2-yl)-1-tosylpiperidine (SI-21)



Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-21** was isolated by column chromatography (hexanes:ethyl acetate 6:1) to afford 14.1 mg (46%) as a white solid.

m.p. 160 °C.

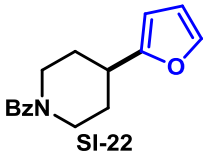
R_f= 0.39 (hexanes:ethyl acetate 4:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 7.9 Hz, 2H), 7.28 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.27 (dd, *J* = 3.2, 1.8 Hz, 1H), 5.95 (d, *J* = 3.2 Hz, 1H), 3.80 (d, *J* = 11.9 Hz, 2H), 2.60 – 2.52 (m, 1H), 2.44 (s, 3H), 2.40 (td, *J* = 11.9, 2.6 Hz, 2H), 2.07 – 2.01 (m, 2H), 1.82 – 1.74 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 158.0, 143.6, 141.2, 133.3, 129.8, 127.9, 110.1, 103.8, 46.1, 34.7, 30.0, 21.7.

HRMS (ESI-TOF): calc'd for $C_{16}H_{20}NO_3S$ $[M+H]^+$ 306.1158; found 306.1153.

(4-(Furan-2-yl)piperidin-1-yl)(phenyl)methanone (SI-22)



Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 2-furanylboronic acid (33.6 mg, 0.3 mmol, 3.0 equiv.). **SI-22** was isolated by PTLC (hexanes:ethyl acetate 3:2) to afford 7.0 mg (27%) as a waxy solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

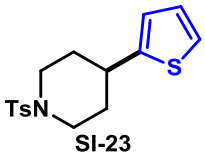
R_f= 0.30 (hexanes:ethyl acetate 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (s, 5H), 7.32 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.30 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.03 – 6.00 (m, 1H), 4.70 (br, 1H), 3.80 (br, 1H), 3.20 – 2.89 (m, 3H), 2.19 – 1.90 (m, 2H), 1.83 – 1.61 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 158.3, 141.2, 136.4, 129.7, 128.6, 127.0, 110.2, 103.8, 47.6 (br), 42.1 (br), 35.6, 31.3 (br), 30.3 (br).

HRMS (ESI-TOF): calc'd for $C_{16}H_{18}NO_2$ $[M+H]^+$ 256.1332; found 256.1332.

4-(Thiophen-2-yl)-1-tosylpiperidine (SI-23)



SI-23

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-23** was isolated by PTLC (hexanes:ethyl acetate 3:1) to afford 24.5 mg (76%) as a white solid.

m.p. 158 °C.

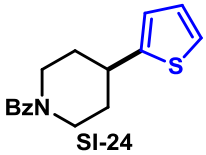
R_f= 0.53 (hexanes:ethyl acetate 3:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.13 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.77 (d, *J* = 3.5 Hz, 1H), 3.88 (d, *J* = 11.8 Hz, 2H), 2.80 – 2.70 (m, 1H), 2.45 (s, 3H), 2.38 (td, *J* = 12.0, 2.6 Hz, 2H), 2.09 – 2.03 (m, 2H), 1.84 (dtd, *J* = 13.3, 11.9, 4.1 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 148.8, 143.7, 133.3, 129.8, 127.9, 126.8, 123.1, 122.6, 46.6, 36.9, 33.7, 21.7.

HRMS (ESI-TOF): calc'd for $C_{16}H_{20}NO_2S_2$ $[M+H]^+$ 322.0930; found 322.0931.

Phenyl(4-(thiophen-2-yl)piperidin-1-yl)methanone (SI-24)



SI-24

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 2-thienylboronic acid (38.4 mg, 0.3 mmol, 3.0 equiv.). **SI-24** was isolated by PTLC (hexanes:ethyl acetate 3:2) to afford 5.7 mg (21%) as a waxy solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

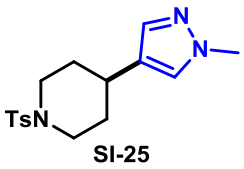
R_f= 0.30 (hexanes:ethyl acetate 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 – 7.38 (m, 5H), 7.16 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.95 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.86 – 6.83 (m, 1H), 4.81 (br, 1H), 3.86 (br, 1H), 3.22 – 3.05 (m, 2H), 2.94 (br, 1H), 2.16 (br, 1H), 2.02 (br, 1H), 1.88 – 1.61 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 149.2, 136.3, 129.7, 128.6, 127.0, 126.9, 123.1, 122.7, 48.1 (br), 42.6 (br), 37.8, 35.1 (br), 34.1 (br).

HRMS (ESI-TOF): calc'd for $C_{16}H_{18}NOS$ $[M+H]^+$ 272.1104; found 272.1104.

4-(1-Methyl-1H-pyrazol-4-yl)-1-tosylpiperidine (SI-25)



SI-25

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-25** was isolated by column chromatography (hexanes:ethyl acetate 1:1) to afford 18.7 mg (59%) as a white solid.

m.p. 88 °C.

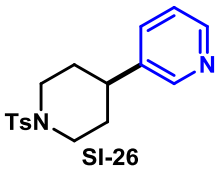
R_f= 0.29 (hexanes:ethyl acetate 1:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.35 – 7.32 (m, 2H), 7.27 (s, 1H), 7.11 (s, 1H), 3.84 (s, 3H), 3.82 (d, *J* = 11.8 Hz, 2H), 2.44 (s, 3H), 2.40 (tt, *J* = 11.9, 3.8 Hz, 1H), 2.35 (td, *J* = 12.0, 2.6 Hz, 2H), 1.95 – 1.90 (m, 2H), 1.69 (dtd, *J* = 13.3, 11.9, 4.0 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 143.6, 137.2, 133.3, 129.8, 127.9, 127.0, 125.7, 46.6, 39.0, 32.9, 31.7, 21.7.

HRMS (ESI-TOF): calc'd for $C_{16}H_{22}N_3O_2S$ $[M+H]^+$ 320.1427; found 320.1426.

3-(1-Tosylpiperidin-4-yl)pyridine (SI-26)



SI-26

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-26** was isolated by column chromatography (hexanes:ethyl acetate 1:1) to afford 16.6 mg (53%) as a white solid.

m.p. 95 °C.

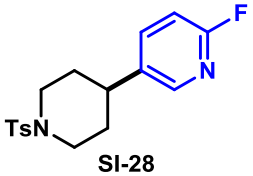
R_f= 0.32 (hexanes:ethyl acetate 1:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.41 (d, *J* = 2.4 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.46 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.23 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 3.95 (dt, *J* = 11.6, 2.3 Hz, 2H), 2.49 – 2.43 (m, 4H), 2.36 (td, *J* = 11.8, 3.1 Hz, 2H), 1.92 – 1.80 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.0, 148.4, 143.8, 140.1, 134.0, 133.2, 129.8, 127.9, 123.7, 46.8, 39.5, 32.4, 21.7.

HRMS (ESI-TOF): calc'd for $C_{17}H_{21}N_2O_2S$ $[M+H]^+$ 317.1318; found 317.1319.

2-Fluoro-5-(1-tosylpiperidin-4-yl)pyridine (SI-28)



SI-28

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-28** was isolated by column chromatography (hexanes:ethyl acetate 4:1) to afford 19.5 mg (58%) as a white solid.

Fe-Negishi: Following General Procedure L with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-28** was isolated by PTLC (hexanes:ethyl acetate 1:1) to afford 14.5 mg (43%) as a white solid.

m.p. 132 °C.

R_f= 0.25 (hexanes:ethyl acetate 2:1).

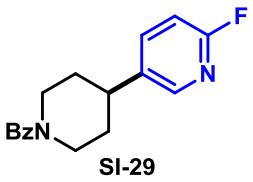
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.99 (d, *J* = 2.5 Hz, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.57 (td, *J* = 8.0, 2.6 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 6.88 (dd, *J* = 8.5, 2.9 Hz, 1H), 3.95 (dt, *J* = 11.7, 2.3 Hz, 2H), 2.51 – 2.43 (m, 4H), 2.36 (td, *J* = 12.0, 2.8 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.85 – 1.77 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 162.7 (d, *J* = 238.2 Hz), 146.1 (d, *J* = 14.3 Hz), 143.8, 139.3 (d, *J* = 7.9 Hz), 137.9 (d, *J* = 4.6 Hz), 133.2, 129.8, 127.9, 109.6 (d, *J* = 37.4 Hz), 46.7, 38.7, 32.6, 21.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.15.

HRMS (ESI-TOF): calc'd for $C_{17}H_{20}FN_2O_2S$ $[M+H]^+$ 335.1224; found 335.1222.

(4-(6-Fluoropyridin-3-yl)piperidin-1-yl)(phenyl)methanone (SI-29)



SI-29

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 2-fluoropyridine-5-boronic acid (42.3 mg, 0.3 mmol, 3.0 equiv.). **SI-29** was isolated by PTLC (hexanes:ethyl acetate 1:2) to afford 8.9 mg (31%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 116 °C.

R_f= 0.31 (hexanes:ethyl acetate 1:2).

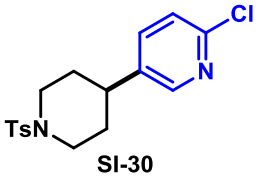
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.09 (d, *J* = 2.5 Hz, 1H), 7.64 (td, *J* = 8.1, 2.6 Hz, 1H), 7.48 – 7.39 (m, 5H), 6.90 (dd, *J* = 8.4, 3.0 Hz, 1H), 4.92 (br, 1H), 3.93 (br, 1H), 3.14 (br, 1H), 3.00 – 2.80 (m, 2H), 2.09 – 1.69 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 162.7 (d, *J* = 238.2 Hz), 146.1 (d, *J* = 14.4 Hz), 139.4 (d, *J* = 7.7 Hz), 138.1 (d, *J* = 4.7 Hz), 136.1, 129.9, 128.7, 127.1, 109.6 (d, *J* = 37.4 Hz), 48.3 (br), 42.7 (br), 39.7, 34.0 (br), 32.9 (br).

^{19}F NMR (376 MHz, $CDCl_3$): δ -71.24.

HRMS (ESI-TOF): calc'd for $C_{17}H_{18}FN_2O$ $[M+H]^+$ 285.1398; found 285.1399.

2-Chloro-5-(1-tosylpiperidin-4-yl)pyridine (SI-30)



SI-30

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-30** was isolated by column chromatography (hexanes:ethyl acetate 4:1) to afford 13.0 mg (37%) as a white solid.

m.p. 170 °C.

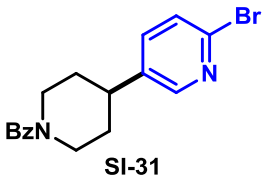
R_f= 0.33 (hexanes:ethyl acetate 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.18 (d, *J* = 2.5 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 2H), 7.44 (dd, *J* = 8.3, 2.6 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 1H), 3.95 (dt, *J* = 11.7, 2.3 Hz, 2H), 2.49 – 2.43 (m, 4H), 2.35 (td, *J* = 12.0, 2.8 Hz, 2H), 1.90 – 1.85 (m, 2H), 1.85 – 1.77 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 149.9, 148.6, 143.8, 139.1, 137.0, 133.2, 129.8, 127.9, 124.4, 46.7, 38.9, 32.4, 21.7.

HRMS (ESI-TOF): calc'd for $C_{17}H_{20}ClN_2O_2S$ $[M+H]^+$ 351.0929; found 351.0930.

(4-(6-Bromopyridin-3-yl)piperidin-1-yl)(phenyl)methanone (SI-31)



SI-31

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 6-bromo-3-pyridinylboronic acid (60.5 mg, 0.3 mmol, 3.0 equiv.). **SI-31** was isolated by PTLC (hexanes:ethyl acetate 1:1) to afford 7.8 mg (23%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 103 °C.

R_f= 0.24 (hexanes:ethyl acetate 1:1).

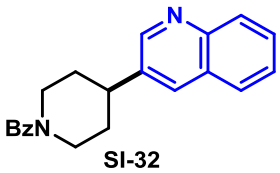
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.26 (d, *J* = 2.5 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.44 – 7.42 (m, 5H), 7.41 (dd, *J* = 8.2, 2.5 Hz, 1H), 4.91 (br, 1H), 3.97 (br, 1H), 3.13 (br, 1H), 2.88 (br, 1H), 2.81 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.04 – 1.59 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 149.2, 140.4, 139.7, 136.9, 136.1, 129.9, 128.7, 128.2, 127.1, 39.9.

The piperidine ring shows broad signals for some carbon atoms, which could not be identified for **SI-31** despite >100 scans on a Bruker DRX-600 with CryoProbe.

HRMS (ESI-TOF): calc'd for $C_{17}H_{18}BrN_2O$ $[M+H]^+$ 345.0597; found 345.0590.

Phenyl(4-(quinolin-3-yl)piperidin-1-yl)methanone (SI-32)



SI-32

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 3-quinolineboronic acid (51.9 mg, 0.3 mmol, 3.0 equiv.). **SI-32** was isolated by PTLC (ethyl acetate:MeOH 95:5) to afford 7.1 mg (23%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. >300 °C.

R_f= 0.51 (ethyl acetate:MeOH 95:5).

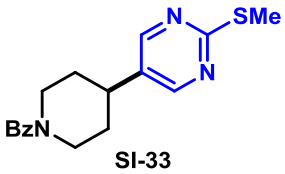
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.83 (d, *J* = 2.3 Hz, 1H), 8.11 – 8.08 (m, 1H), 7.95 (d, *J* = 2.3 Hz, 1H), 7.80 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.69 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.48 – 7.45 (m, 2H), 7.45 – 7.42 (m, 3H), 4.97 (br, 1H), 3.97 (br, 1H), 3.21 (br, 1H), 3.03 (tt, *J* = 12.3, 3.6 Hz, 1H), 2.96 (br, 1H), 2.19 – 1.67 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.7, 151.0, 147.4, 137.7, 136.2, 132.6, 129.9, 129.4, 129.2, 128.7, 128.2, 127.7, 127.1, 127.0, 40.5.

The piperidine ring shows broad signals for some carbon atoms, which could not be identified for **SI-32** despite >100 scans on a Bruker DRX-600 with CryoProbe.

HRMS (ESI-TOF): calc'd for $C_{21}H_{21}N_2O$ $[M+H]^+$ 317.1648; found 317.1646.

(4-(2-(Methylthio)pyrimidin-5-yl)piperidin-1-yl)(phenyl)methanone (SI-33)



SI-33

Ni-Suzuki: Following General Procedure C in 0.05 mmol scale with TCNHPI ester **SI-20** (25.8 mg, 0.05 mmol, 1.0 equiv.) and 2-(methylthio)pyrimidine-5-boronic acid (25.5 mg, 0.15 mmol, 3.0 equiv.). **SI-33** was isolated by PTLC (ethyl acetate) to afford 8.7 mg (56%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 97 °C.

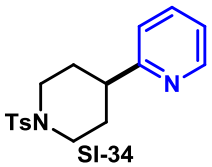
R_f= 0.51 (ethyl acetate).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.41 (s, 2H), 7.43 (s, 5H), 4.92 (br, 1H), 3.93 (br, 1H), 3.14 (br, 1H), 2.90 (br, 1H), 2.76 (tt, *J* = 12.3, 3.7 Hz, 1H), 2.56 (s, 3H), 2.07 – 1.60 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.2, 170.7, 156.0, 136.0, 132.5, 129.9, 128.7, 127.1, 48.1 (br), 42.6 (br), 38.0, 33.5 (br), 32.4 (br), 14.3.

HRMS (ESI-TOF): calc'd for $C_{17}H_{20}N_3OS$ $[M+H]^+$ 314.1322; found 314.1322.

2-(1-Tosylpiperidin-4-yl)pyridine (SI-34)



SI-34

Fe-Negishi: Following General Procedure L with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-34** was isolated by PTLC (hexanes:ethyl acetate 1:1) to afford 13.2 mg (42%) as a white solid.

R_f= 0.28 (hexanes:ethyl acetate 1:1).

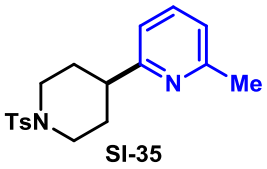
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.51 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 2H), 7.14 – 7.10 (m, 2H), 3.93

(dt, *J* = 11.5, 2.5 Hz, 2H), 2.62 (tt, *J* = 12.0, 3.8 Hz, 1H), 2.45 (s, 3H), 2.39 (td, *J* = 12.0, 2.7 Hz, 2H), 2.03 – 1.97 (m, 2H), 1.95 – 1.87 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.7, 149.4, 143.6, 136.8, 133.4, 129.8, 127.9, 121.8, 120.8, 46.7, 43.7, 31.3, 21.7.

Spectral data are in accordance with those reported in the literature.[7]

2-Methyl-6-(1-tosylpiperidin-4-yl)pyridine (SI-35)



SI-35

Fe-Negishi: Following General Procedure L with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-35** was isolated by PTLC (hexanes:ethyl acetate 1:1) to afford 16.4 mg (50%) as a white solid.

m.p. 109 °C.

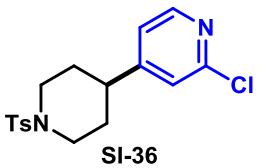
R_f= 0.41 (hexanes:ethyl acetate 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1H), 3.96 – 3.89 (m, 2H), 2.58 (tt, *J* = 12.1, 3.7 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 2.38 (td, *J* = 12.0, 2.6 Hz, 2H), 2.01 – 1.96 (m, 2H), 1.92 – 1.83 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 163.2, 158.0, 143.6, 137.0, 133.4, 129.7, 127.9, 121.3, 117.4, 46.7, 43.9, 31.4, 24.6, 21.7.

HRMS (ESI-TOF): calc'd for $C_{18}H_{23}N_2O_2S$ $[M+H]^+$ 331.1475; found 331.1480.

2-Chloro-4-(1-tosylpiperidin-4-yl)pyridine (SI-36)



SI-36

Fe-Kumada: Following General Procedure M with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-36** was isolated by column chromatography (hexanes:ethyl acetate 5:1) to afford 7.5 mg (21%) as a white solid.

Fe-Negishi: Following General Procedure L with NHPI ester **SI-12** (42.9 mg, 0.1 mmol, 1.0 equiv.). **SI-36** was isolated by PTLC (hexanes:diethyl ether 1:2) to afford 6.4 mg (18%) as a white solid.

m.p. 108 °C.

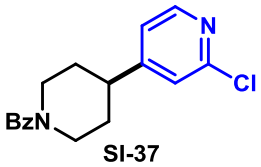
R_f= 0.26 (hexanes:diethyl ether 2:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 5.2, 0.7 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.38 – 7.33 (m, 2H), 7.10 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.00 (dd, *J* = 5.1, 1.5 Hz, 1H), 3.95 (dt, *J* = 11.4, 2.4 Hz, 2H), 2.48 – 2.40 (m, 4H), 2.36 (td, *J* = 12.1, 2.7 Hz, 2H), 1.91 – 1.86 (m, 2H), 1.81 (dtd, *J* = 13.3, 12.0, 4.1 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 157.0, 152.1, 150.0, 143.9, 133.2, 129.9, 127.9, 122.8, 121.0, 46.5, 41.2, 31.7, 21.7.

HRMS (ESI-TOF): calc'd for $C_{17}H_{20}ClN_2O_2S$ $[M+H]^+$ 351.0929; found 351.0928.

(4-(2-Chloropyridin-4-yl)piperidin-1-yl)(phenyl)methanone (SI-37)



SI-37

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 2-chloropyridine-4-boronic acid (47.2 mg, 0.3 mmol, 3.0 equiv.). **SI-37** was isolated by PTLC (ethyl acetate:MeOH 98:2) to afford 15.2 mg (51%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 117 °C.

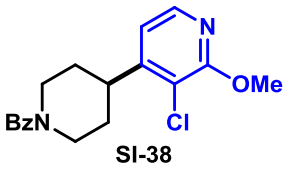
R_f= 0.38 (ethyl acetate:MeOH 98:2).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.31 (d, *J* = 5.1 Hz, 1H), 7.42 (s, 5H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.07 (dd, *J* = 5.2, 1.5 Hz, 1H), 4.90 (br, 1H), 3.92 (br, 1H), 3.12 (br, 1H), 2.87 (br, 1H), 2.80 (tt, *J* = 12.2, 3.7 Hz, 1H), 2.10 – 1.48 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 157.2, 152.1, 150.0, 136.0, 129.9, 128.7, 127.0, 122.8, 121.1, 48.0 (br), 42.5 (br), 42.0, 33.0 (br), 32.1 (br).

HRMS (ESI-TOF): calc'd for $C_{17}H_{18}ClN_2O$ $[M+H]^+$ 301.1102; found 301.1107.

(4-(3-Chloro-2-methoxypyridin-4-yl)piperidin-1-yl)(phenyl)methanone (SI-38)



SI-38

Ni-Suzuki: Following General Procedure C with TCNHPI ester **SI-20** (51.6 mg, 0.1 mmol, 1.0 equiv.) and 3-chloro-2-methoxypyridine-4-boronic acid (56.2 mg, 0.3 mmol, 3.0 equiv.). **SI-38** was isolated by PTLC (hexanes:ethyl acetate 1:1) to afford 14.0 mg (42%) as a white solid.

Note: The benzoyl protected piperidine shows two sets of signals for the CH_2-groups in the ^{13}C-NMR as a result of two conformational isomers.

m.p. 149 °C.

R_f= 0.51 (hexanes:ethyl acetate 1:1).

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 5.3 Hz, 1H), 7.46 – 7.37 (m, 5H), 6.79 (d, *J* = 5.3 Hz, 1H), 4.93 (br, 1H), 4.02 (s, 3H), 3.92 (br, 1H), 3.34 (ddd, *J* = 12.1, 8.6, 3.5 Hz, 1H), 3.18 (br, 1H), 2.90 (br, 1H), 2.03 – 1.78 (m, 2H), 1.78 – 1.48 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 159.8, 152.7, 144.5, 136.1, 129.8, 128.7, 127.1, 117.2, 115.2, 54.6, 48.2 (br), 42.7 (br), 38.9, 31.9 (br), 30.8 (br).

HRMS (ESI-TOF): calc'd for $C_{18}H_{20}ClN_2O_2$ $[M+H]^+$ 331.1208; found 331.1209.

10. Troubleshooting and FAQ

Should I choose DCC or DIC for the preparation of my RAE?

In general both activating agents work fine. For certain polar RAE such as NHPI ester of 3-pyridinepropionic acid (**SI-15**) removal of the urea byproduct can be difficult using DIC. In such cases we recommend DCC as the coupling reagent, as the urea byproduct can be precipitated entirely by dilution of the reaction mixture with diethyl ether.

I observe a noticeable instability of my isolated RAE, which affects my yield.

Some RAEs are prone to hydrolysis which can affect the reaction outcome (see substrate **6**). In these cases we highly recommend the use of *in situ* activation (e.g. HATU in combination with Fe-Negishi).

I am running a Fe-Kumada reaction with a heteroaromatic nucleophile and have problems to find my product.

The products of RAE couplings with heteroaromatic nucleophiles can be difficult to identify just by means of TLC. We observed that the most reliable way to ensure product formation of nitrogenated compounds in these reactions is LC/MS analysis of the crude reaction mixture.

How general are the results for the nine different substrates presented in Table 1?

The substrates in this user guide have been chosen carefully in order to cover a broad chemical space and to make further implementation and application of the methodology to other substrates straightforward. Among the primary carboxylic acids, **1** represents a typical aliphatic example. Substrates sensitive to hydrolysis are

covered by substrate **3** containing a methyl ester while 3-pyridinepropionic acid (**5**) is a representative for acids bearing heteroaromatic groups with basic nitrogens. The two carboxylic acids **7** and **9** represent the broad group of secondary acids with low functionalization. Amino acid derivatives **11** and **13** cover secondary carboxylic acids containing a nitrogen atom in the α-position. From our experience, α-oxygenated and other α-heterogenated compounds should behave similarly. At last, the class of tertiary carboxylic acids forming non-planar radicals has been investigated, as coupling of planar tertiary radicals is not viable with our methodology so far. While **15** is a typical aliphatic example for this class of compounds, **17** forms a more stabilized radical showing unique reactivity.

Can heteroaromatic nucleophiles be used in couplings with primary or tertiary carboxylic acids?

From our experience, the presented methodology using heteroaromatic nucleophiles should easily be adoptable to primary carboxylic acids. Tertiary carboxylic acids will most probably not undergo Ni-Suzuki coupling, we suggest using Fe-Kumada or Fe-Negishi reactions instead.

What is the best work-up procedure for heteroaromatic substrates containing basic nitrogens?

For heteroaromatic substrates, we usually quench the reaction with H_2O or half-saturated NH_4Cl-solution followed by extraction with ethyl acetate (at least 5 times). In this procedure, separation of organic and aqueous layer can be difficult. This issue can usually be solved by addition of a few drops of methanol.

Which is the best method to prepare heteroaryl-Grignard solutions?

We observed that Mg insertion into heteroaryl bromides using a Knochel-type protocol is suitable for a broad range of heterocycles.[6] Still, it should be noted that

certain Grignard reagents, such as pyrimidine or imidazole Grignards, could not be obtained. In such cases we recommend the use of the corresponding boronic acid in a Ni-Suzuki coupling.

My heteroaryl-Grignard solution turned black and is highly viscous. What should I do?

Some heteroaryl-Grignards, especially pyridine-based reagents, turn out to be a black and highly viscous solution. Viscosity can easily be lowered by diluting the reagent with more THF. Generally, the dark color has no influence on the quality of the Grignard reagent or the reaction outcome, but it can make titration using iodine be rather challenging. However, a noticeable color change from light brown to nearly black can be observed, when adding a slight excess of the Grignard reagent after all iodine was consumed.

What is the best choice of method for a RAE cross coupling with heteroaryl nucleophiles?

The Ni-Suzuki protocol proved to be most versatile in the choice of the heteroaryl nucleophile. Besides, electron rich carbons in (nitrogenated) heteroarenes (e.g. 3-pyridyl systems) can easily be subjected to simple Fe-Kumada couplings. However, very electron deficient heterocyclic nucleophiles, such as pyrimidines or quinoxalines, did not result in product formation under these conditions. For 2-pyridyl nucleophiles the Fe-Negishi coupling is the only reliable option, owing to the instability of the corresponding boronic acid.

Why does the *in situ* reaction of carboxylic acid 9 with NHPI give a higher yield than the corresponding reaction of the isolated NHPI ester SI-7?

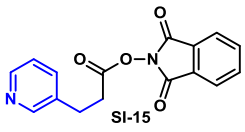
In order to compensate the generally lower yields over two steps in *in situ* reactions, we chose to carry out the *in situ* reactions in Fe-Negishi couplings with higher

catalyst loading and greater excess of the organozinc reagent. For this specific example the slightly higher yield of the *in situ* reaction is most probably caused by overcompensation.

Where can I find additional information about each RAE coupling reaction?

For Ni-Negishi coupling see ref. [1] and [2], for Ni-Suzuki coupling see ref. [3], for Fe-Negishi and Fe-Kumada see ref. [4].

11. NMR spectra



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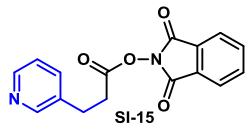
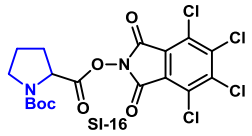


SI-15



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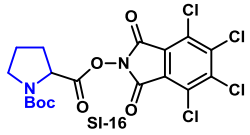
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Cl
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Cl
O
O
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N
Boc

SI-16

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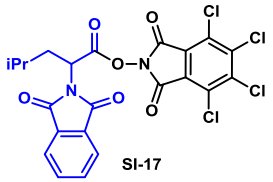

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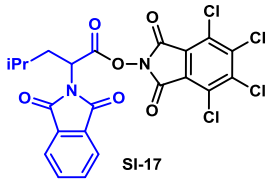
iPr
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N
O
O
Cl
Cl
Cl
Cl

SI-17

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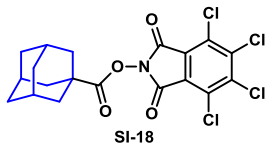
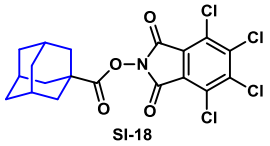
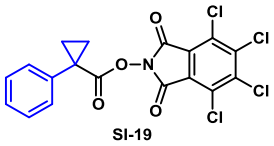


SI-18



SI-18



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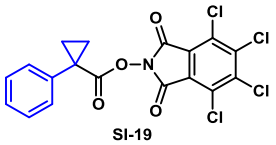
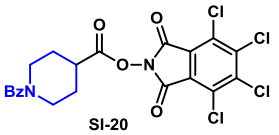


SI-19



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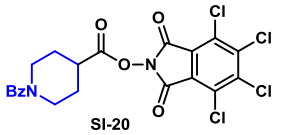
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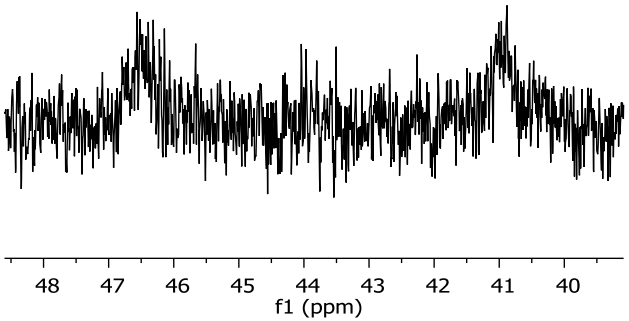
Cl
O–N
Cl
BzN
O
Cl

SI-20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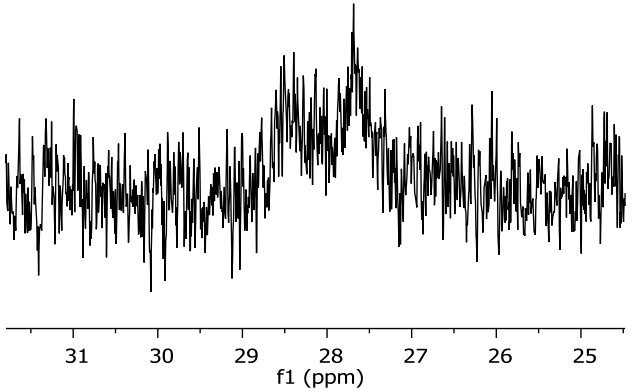
45
44
43
42
41
40
f1 (ppm)


31
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28
27
26
25
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20
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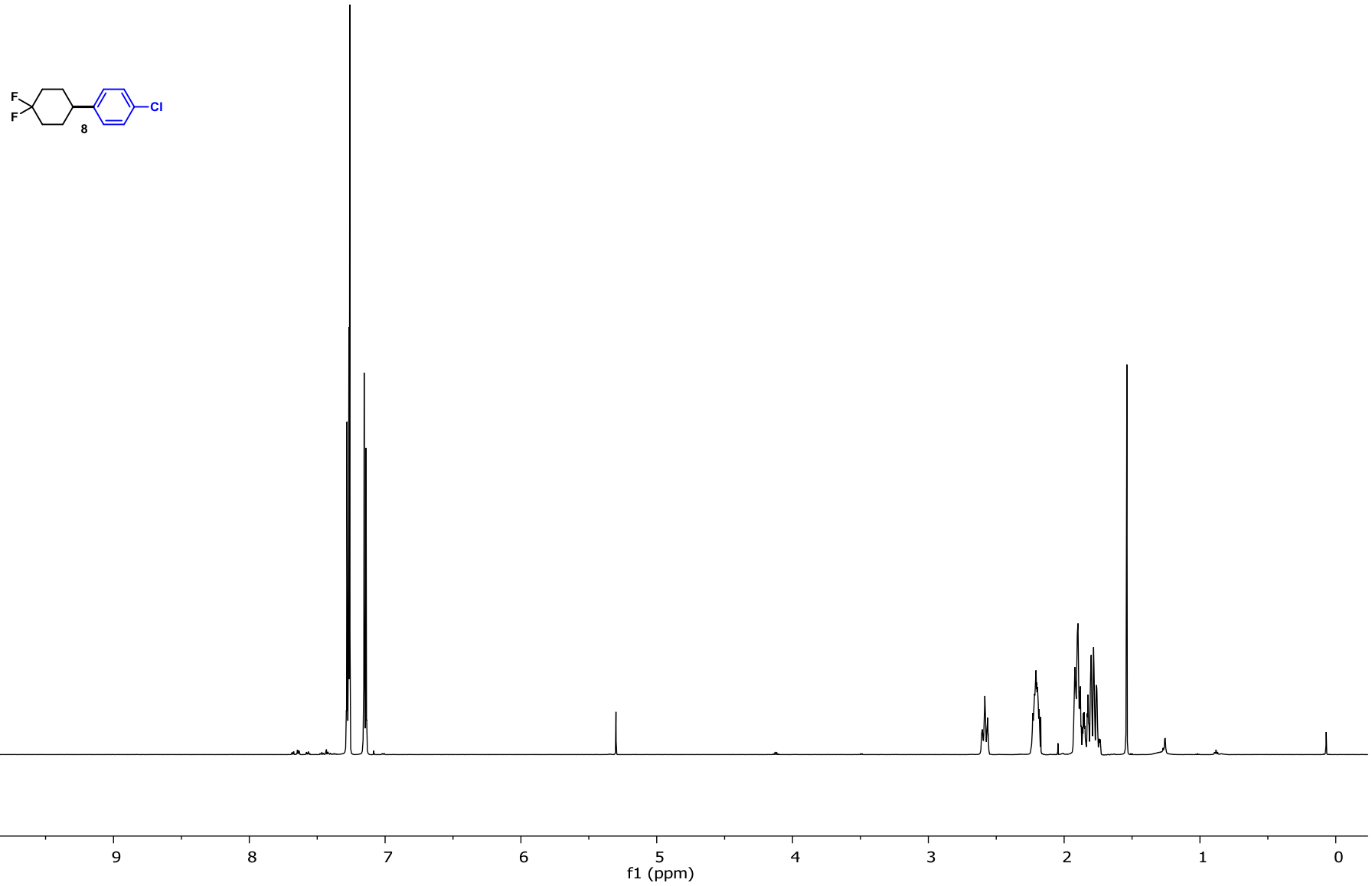
f1 (ppm)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Cl
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6
5
4
3
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1
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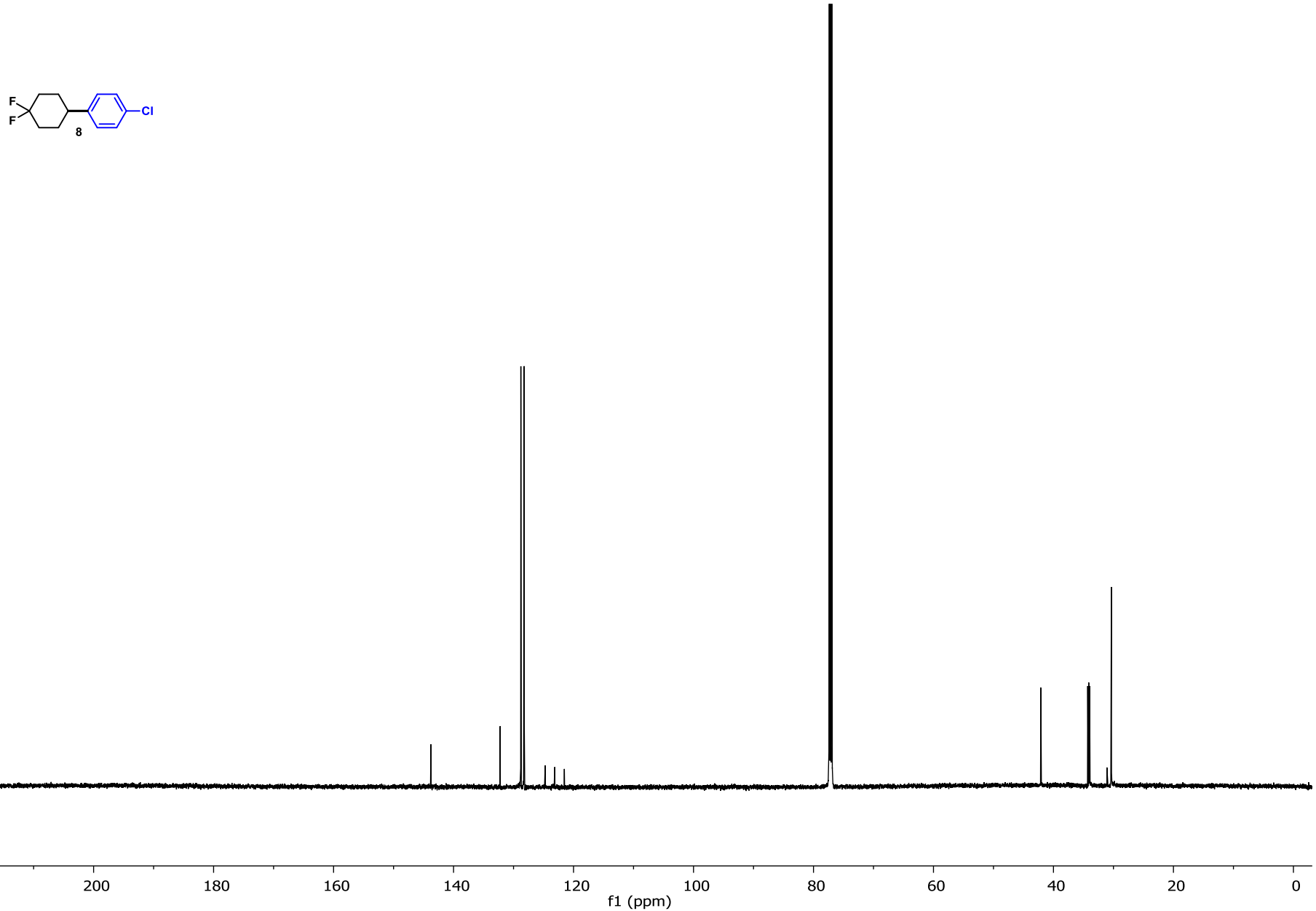
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Cl
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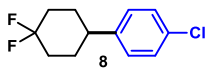
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F
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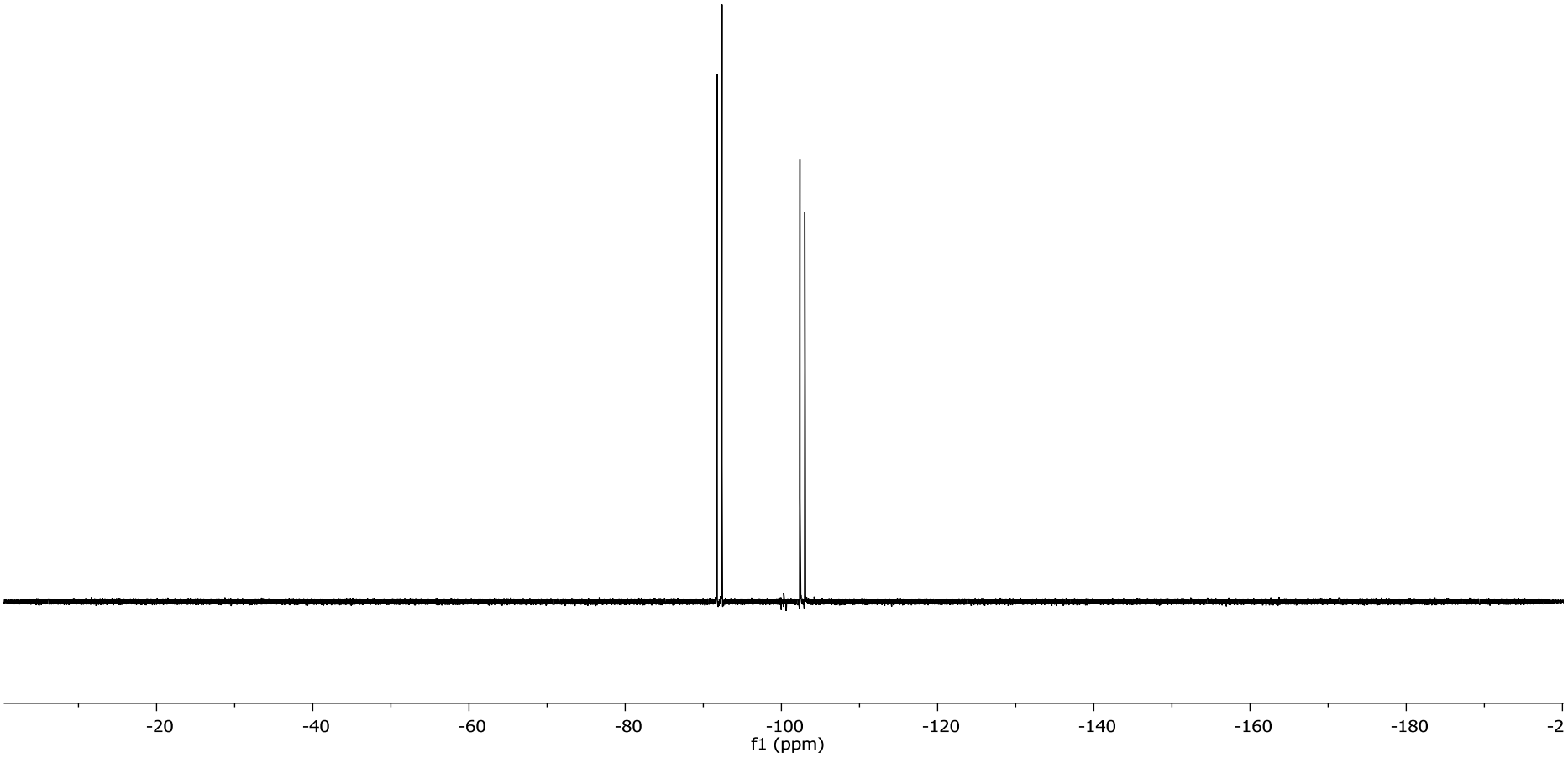
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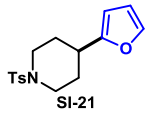
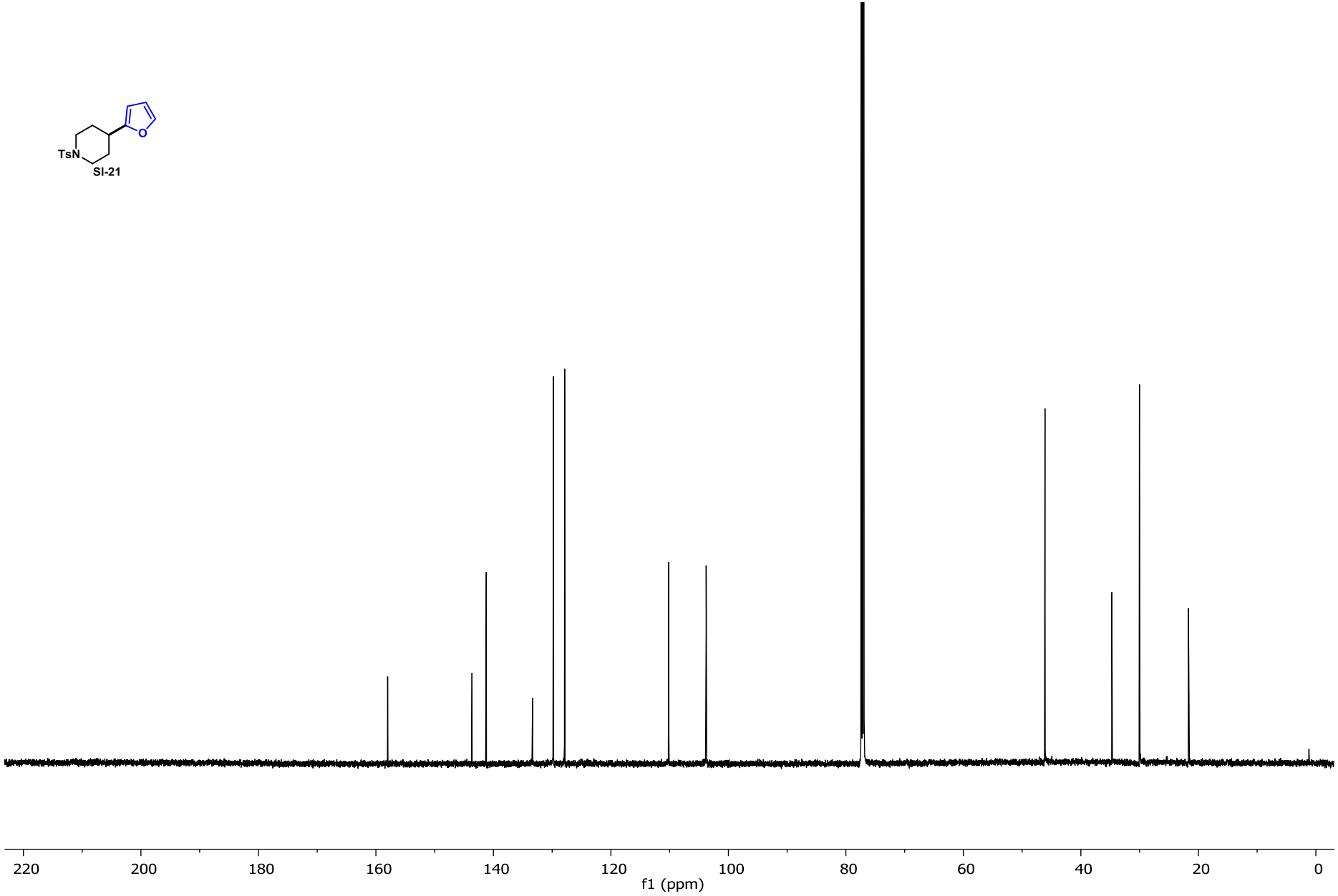


SI-21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SI-21
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100
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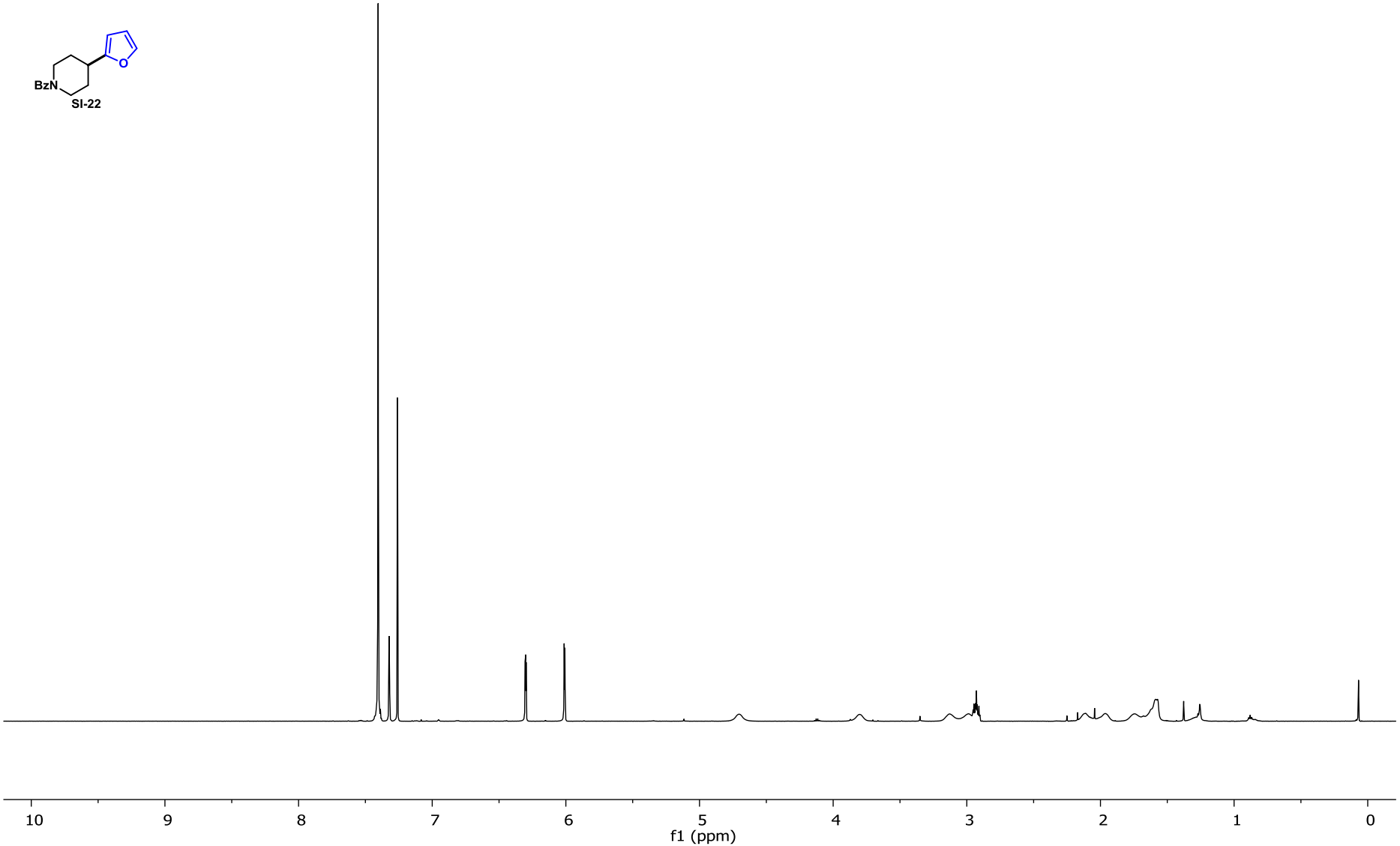
60
40
20
0
f1 (ppm)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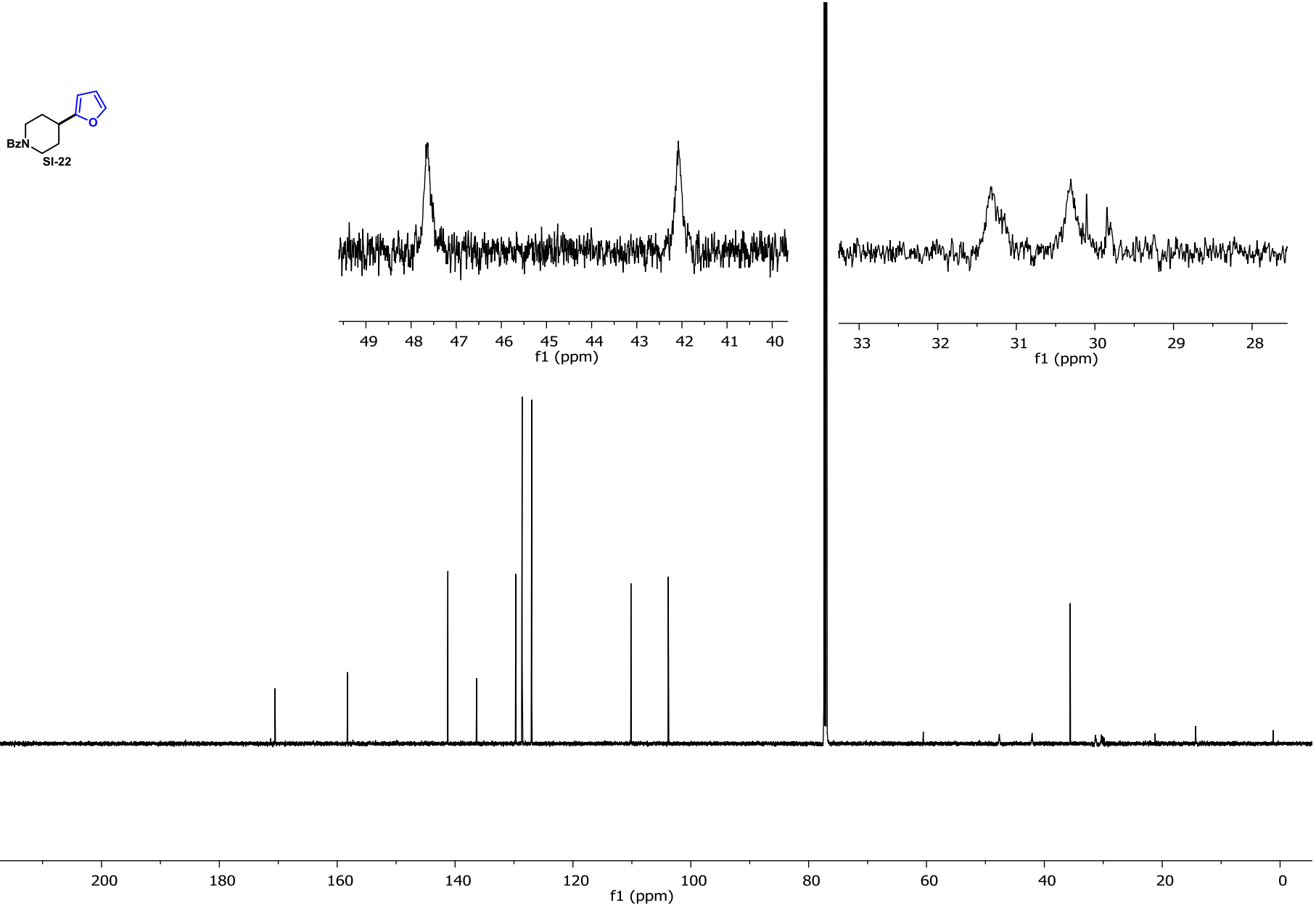
BzN
O
SI-22
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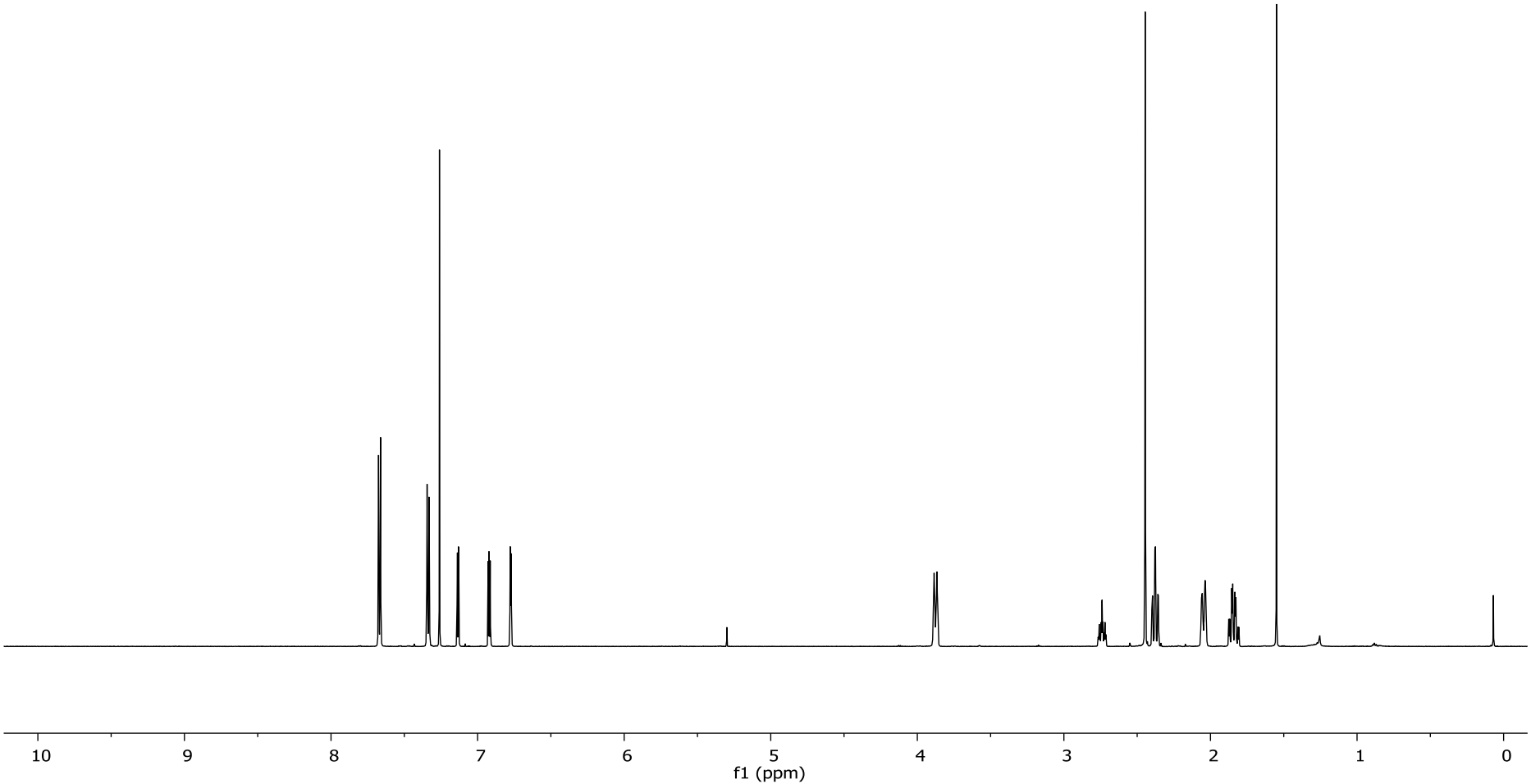
f1 (ppm)


TsN
S
SI-23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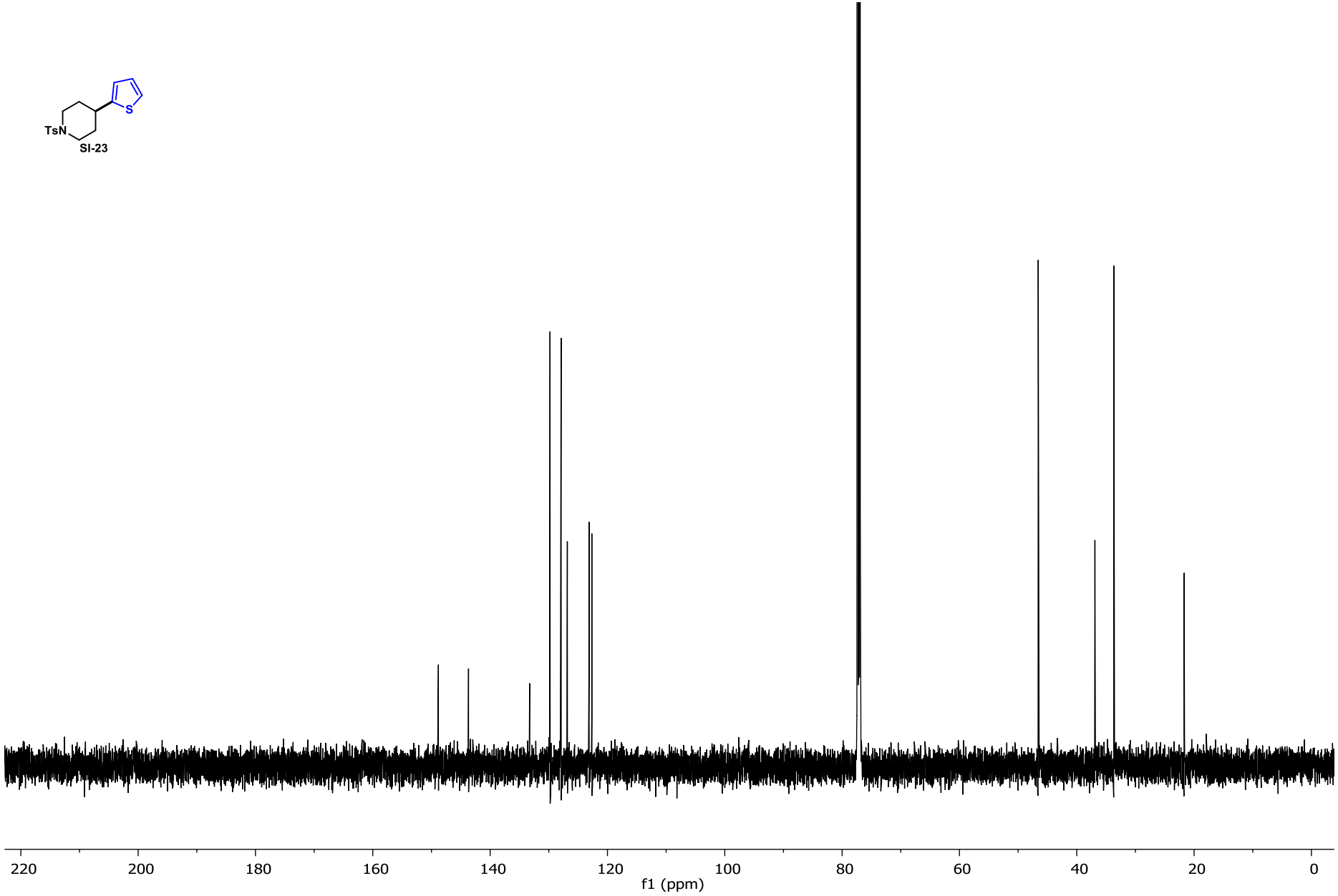
TsN
S
SI-23
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100
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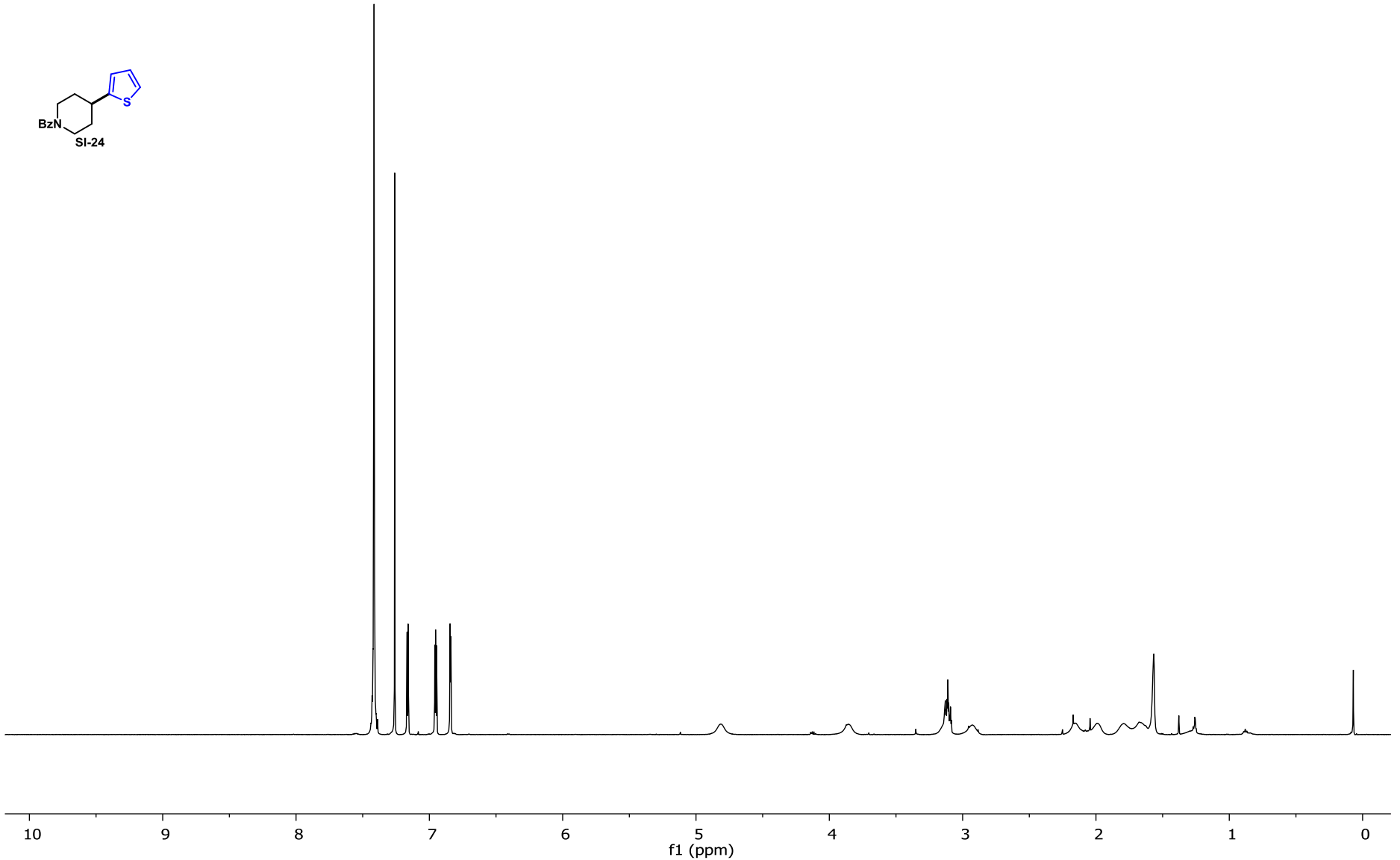
f1 (ppm)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SI-24
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5
4
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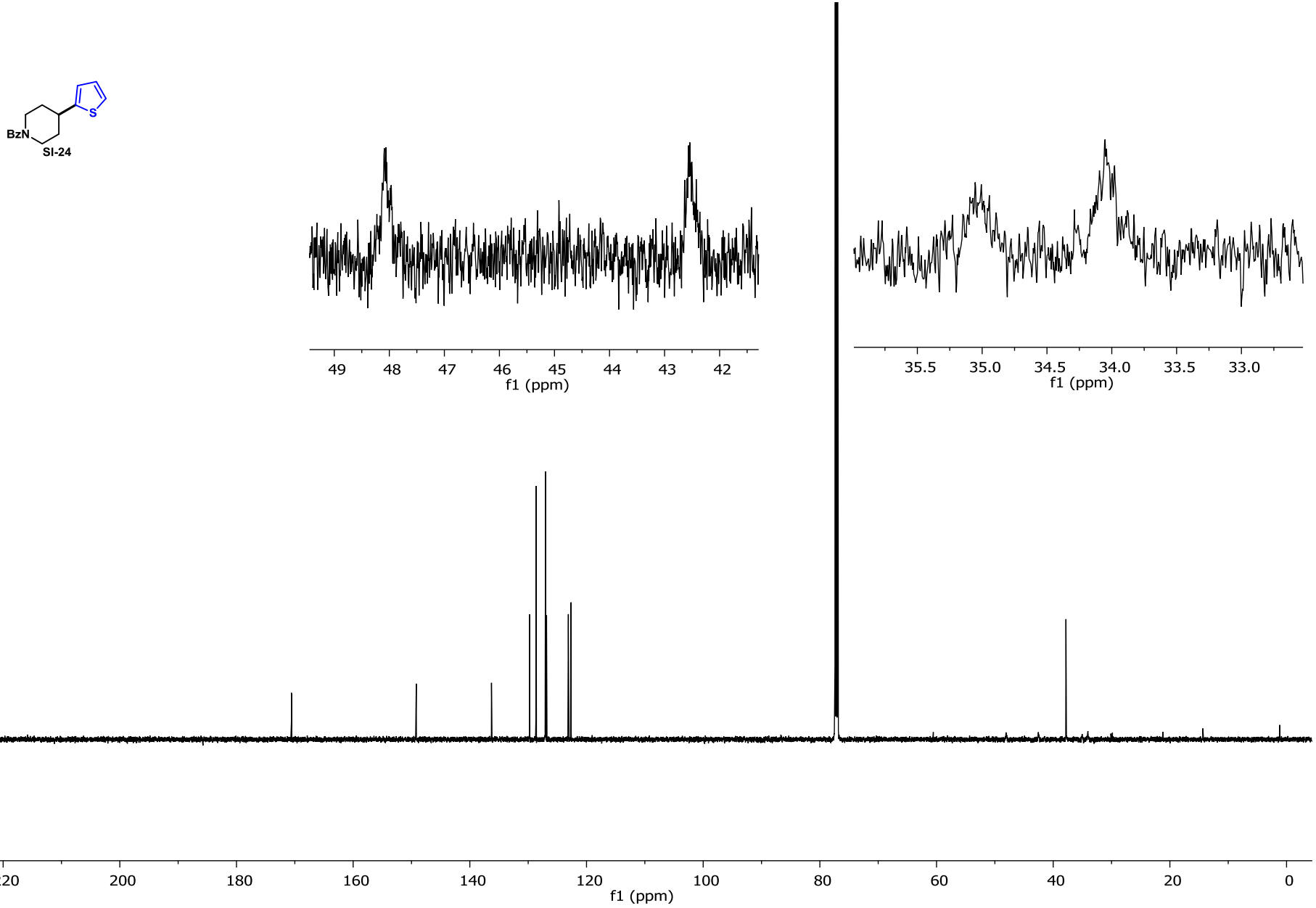
2
1
0
f1 (ppm)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SI-24
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34.0
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f1 (ppm)
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100
80
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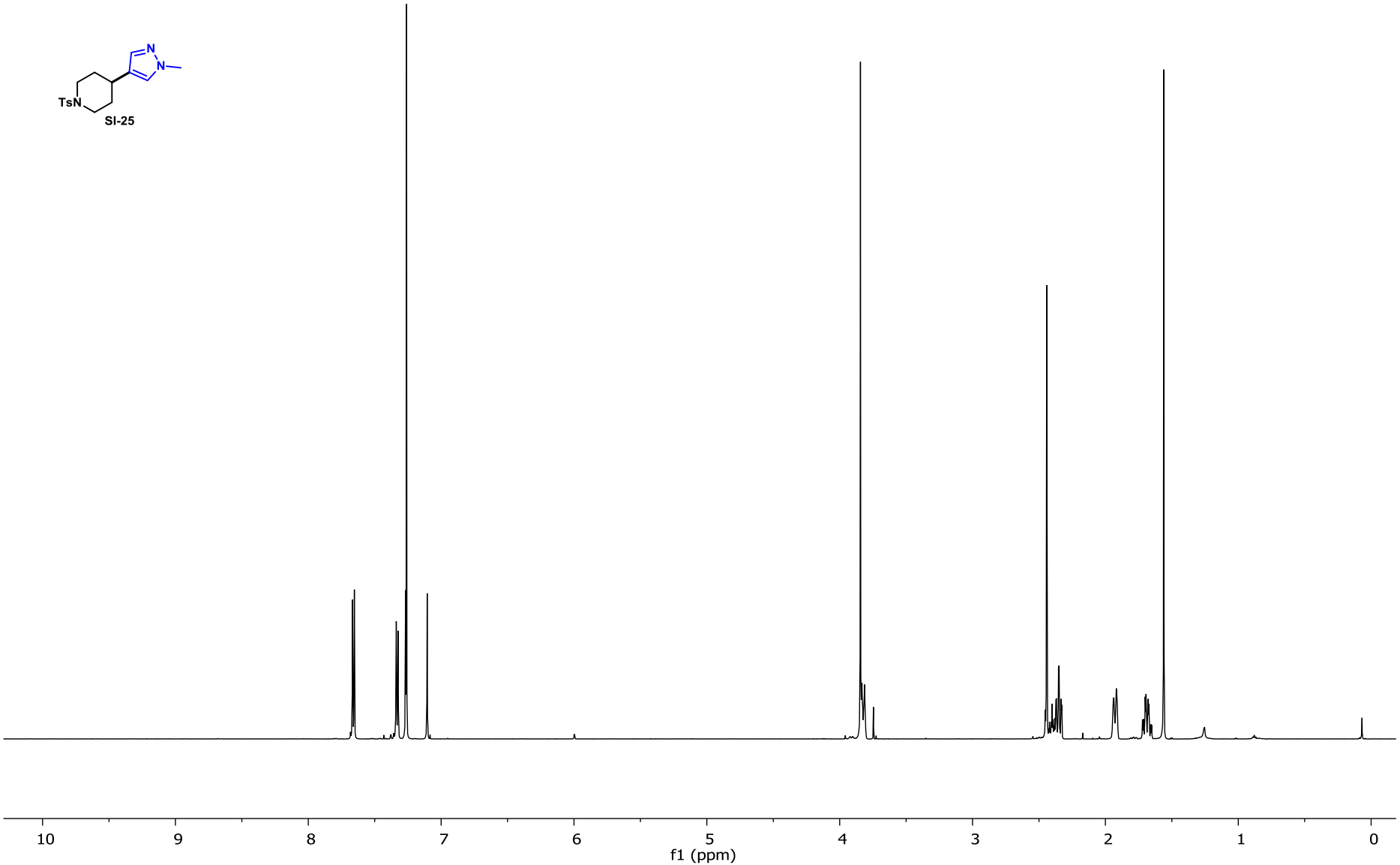
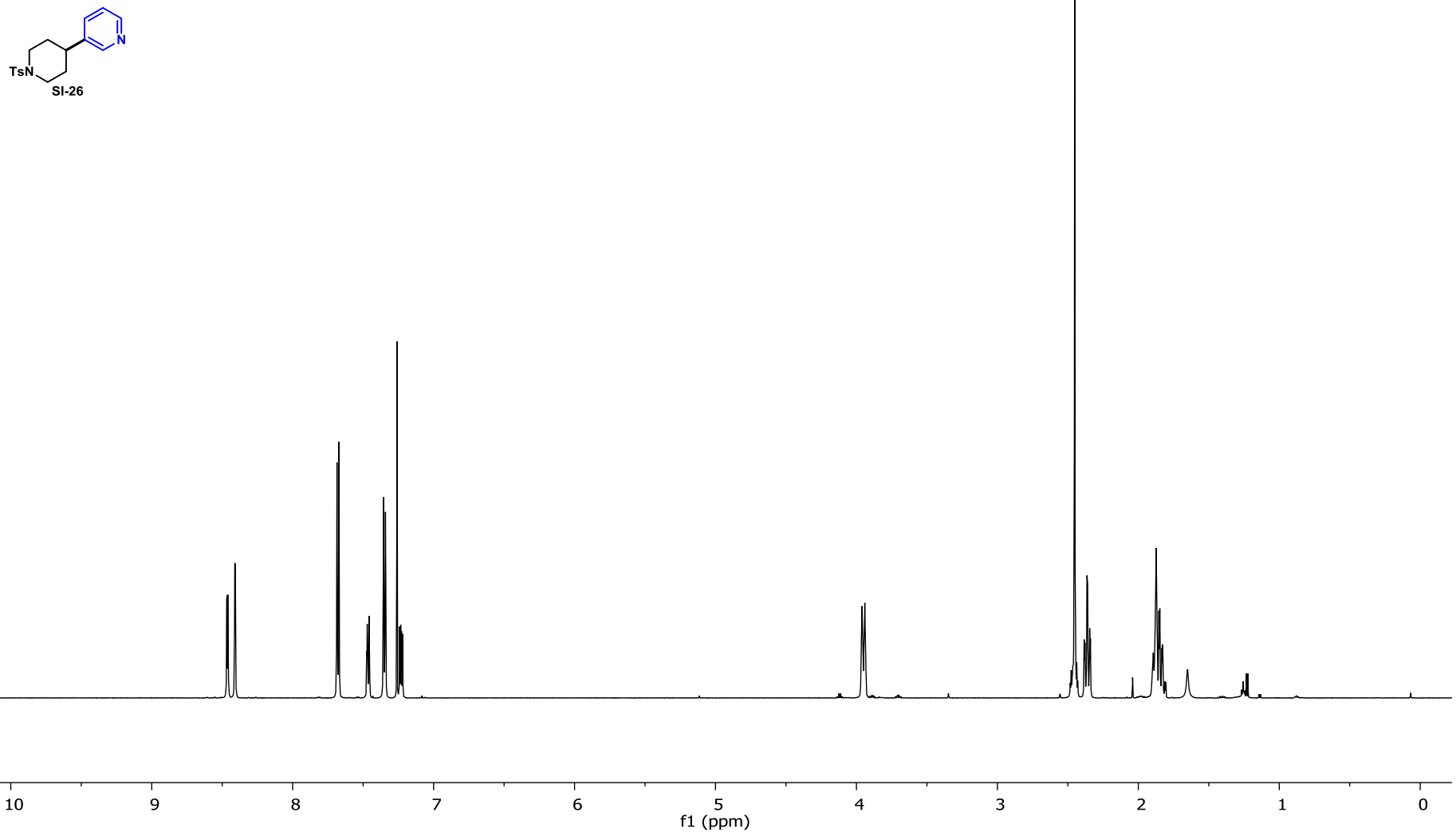
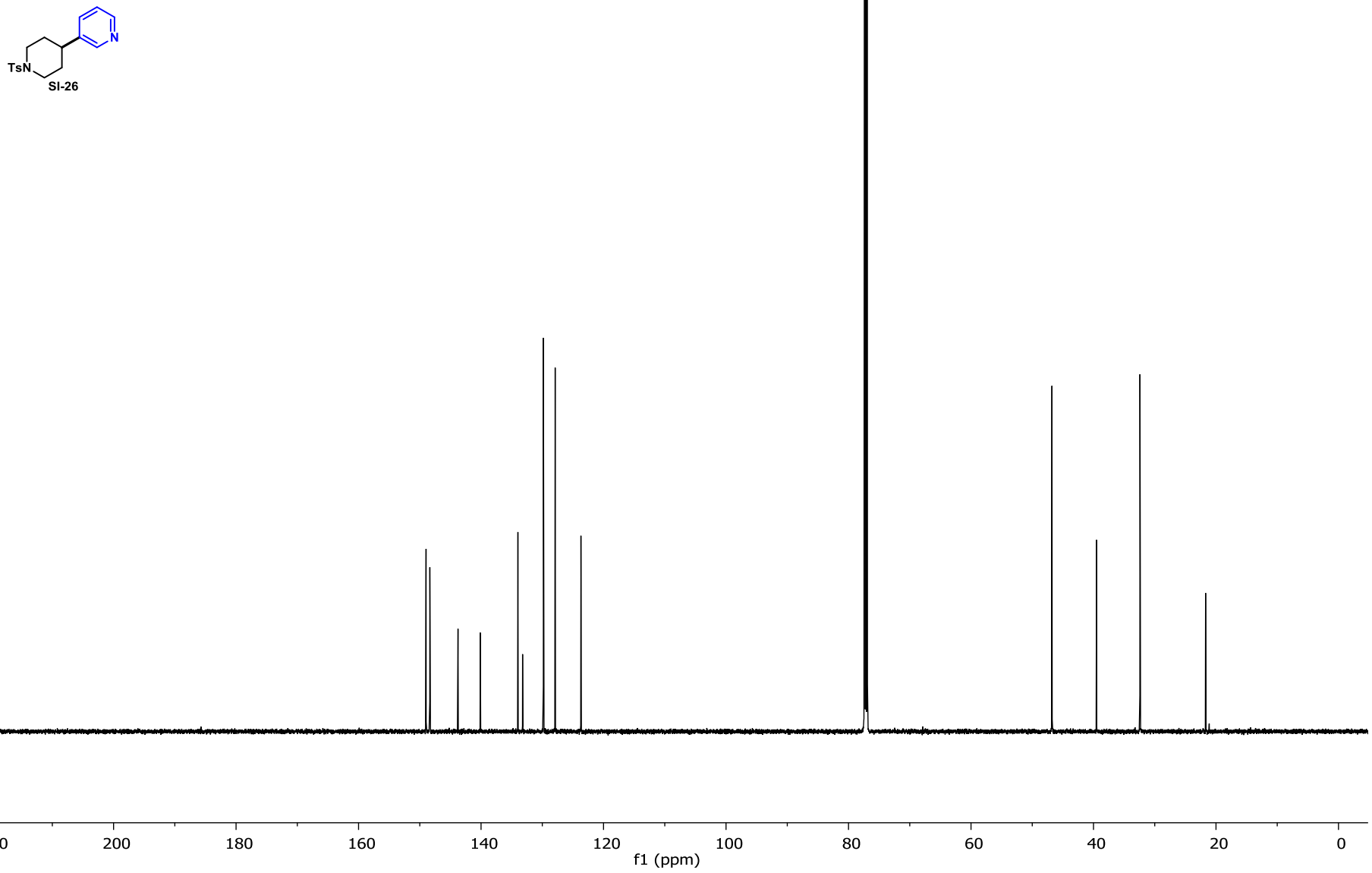
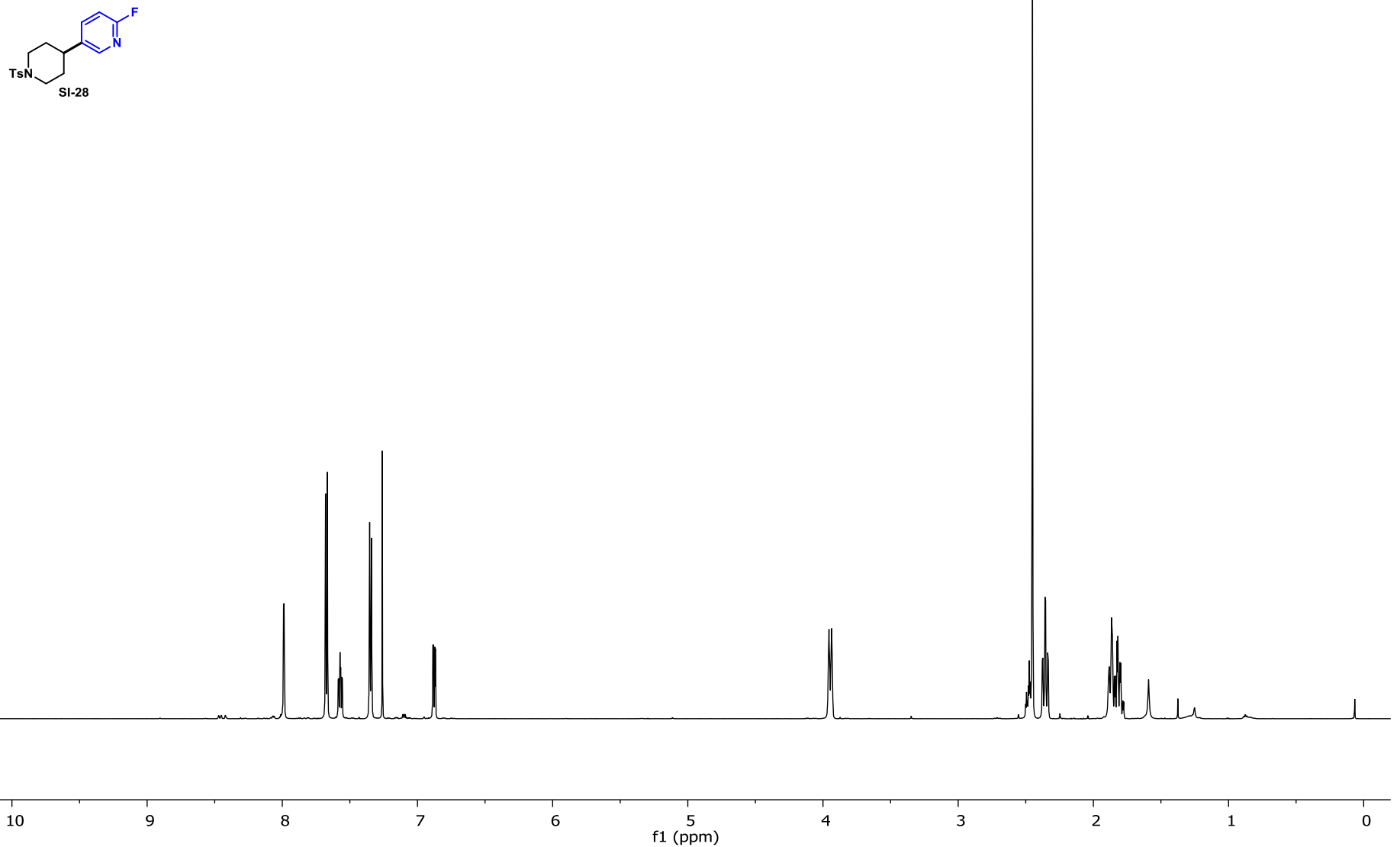
20
0
f1 (ppm)

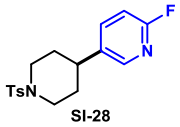

TsN
SI-25
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

SI-25

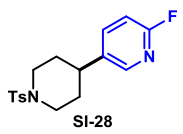

TsN
N
SI-26
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


TsN
N
SI-26
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

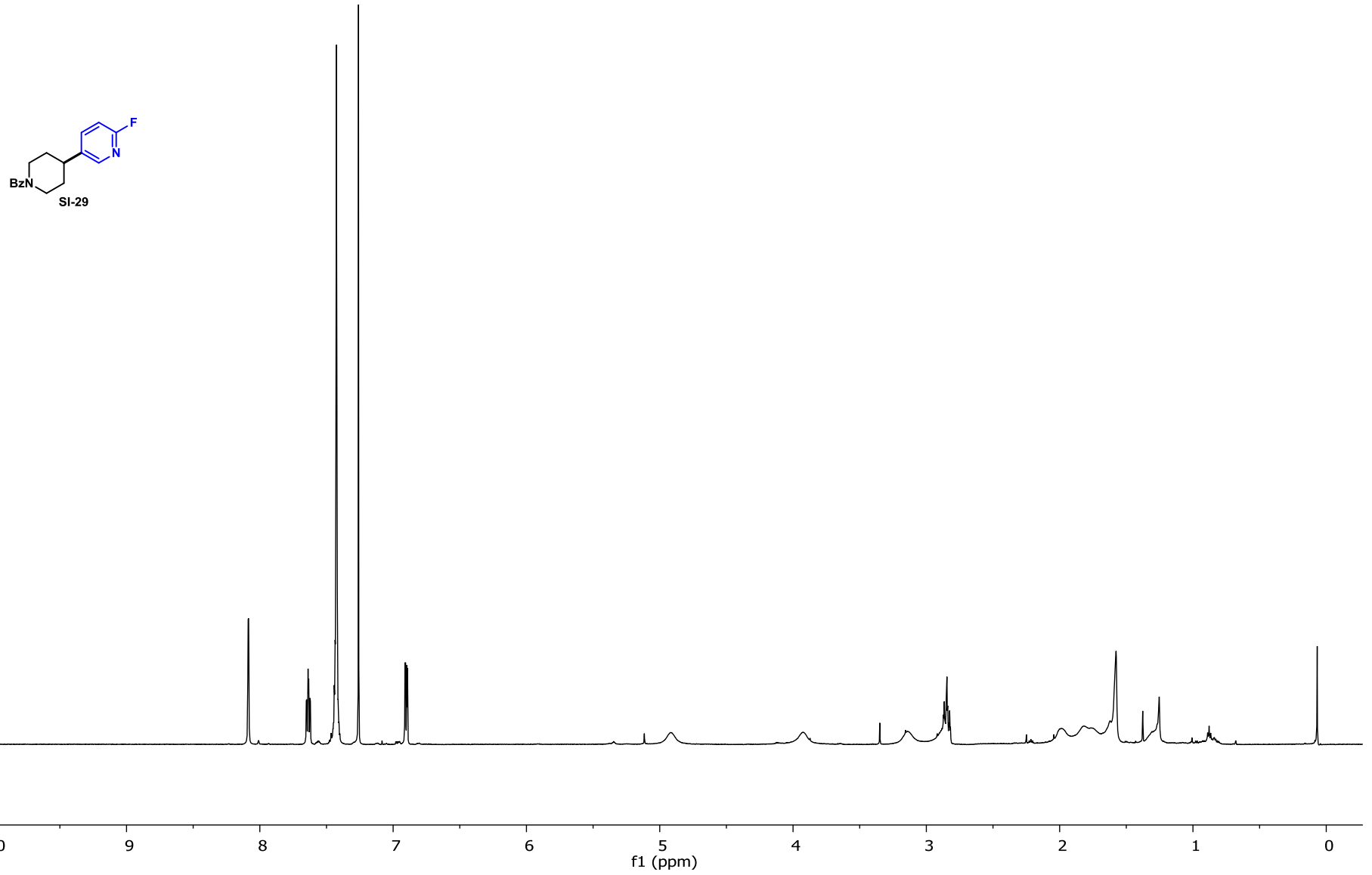

F
N
TsN
SI-28
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

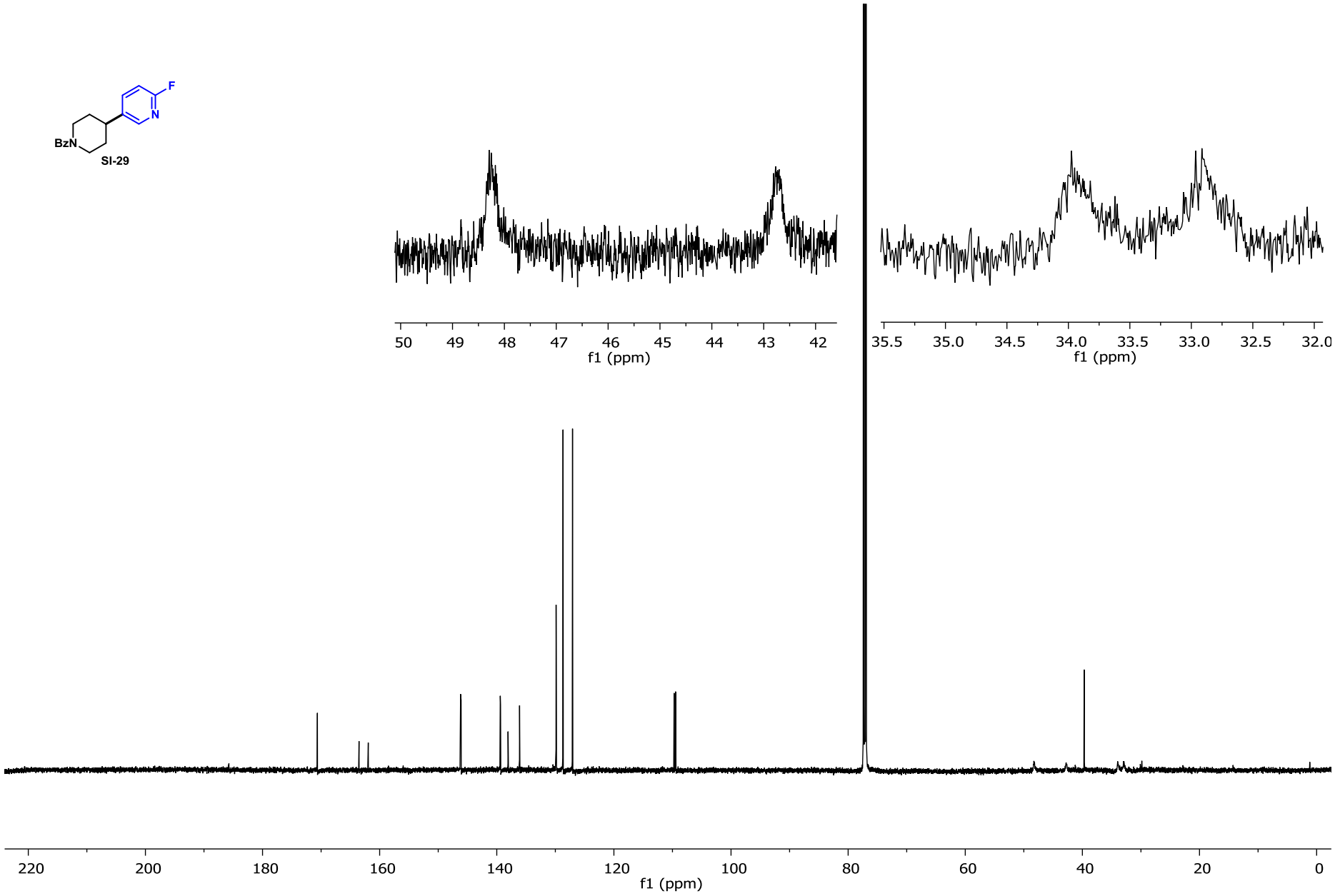


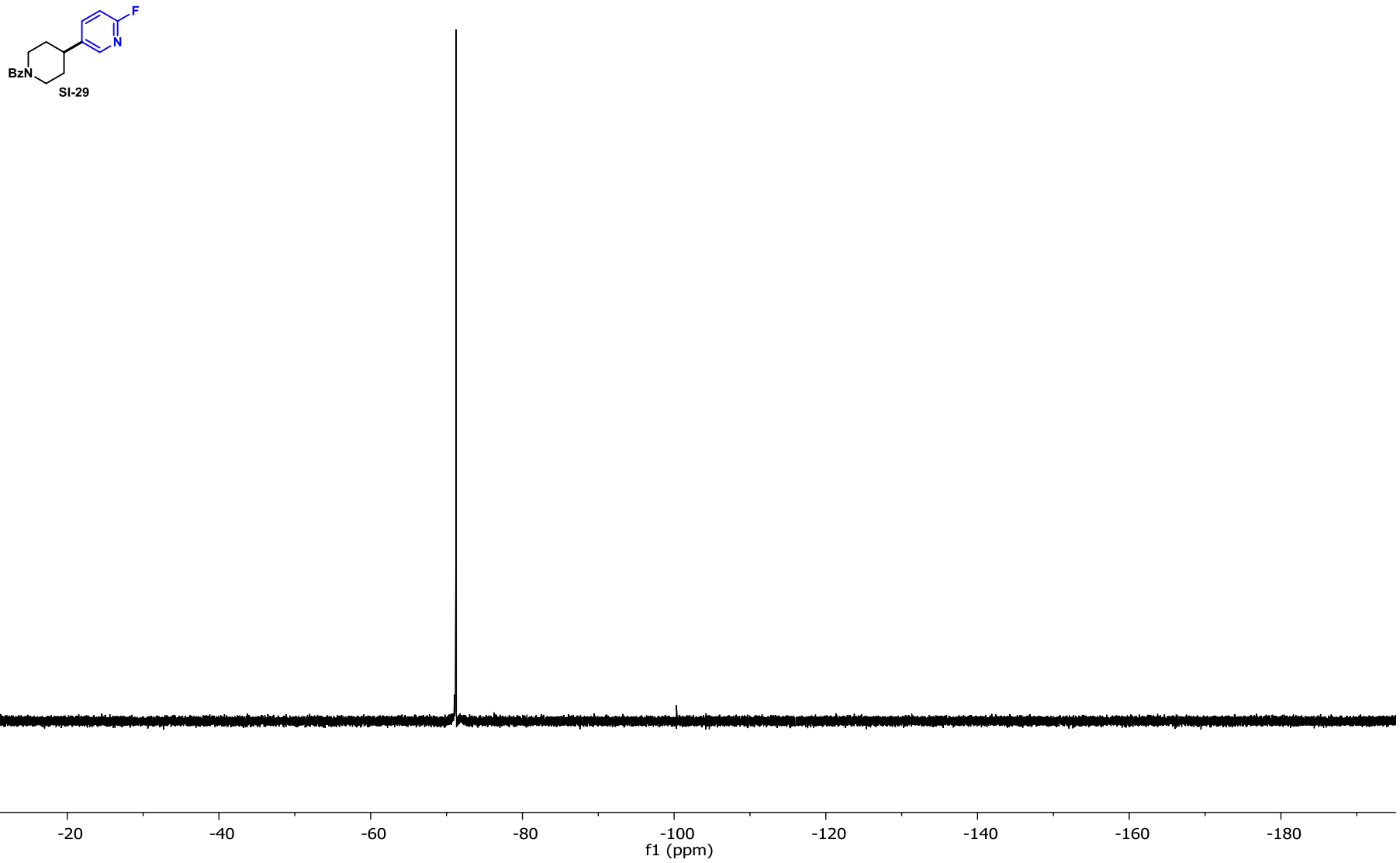
SI-28

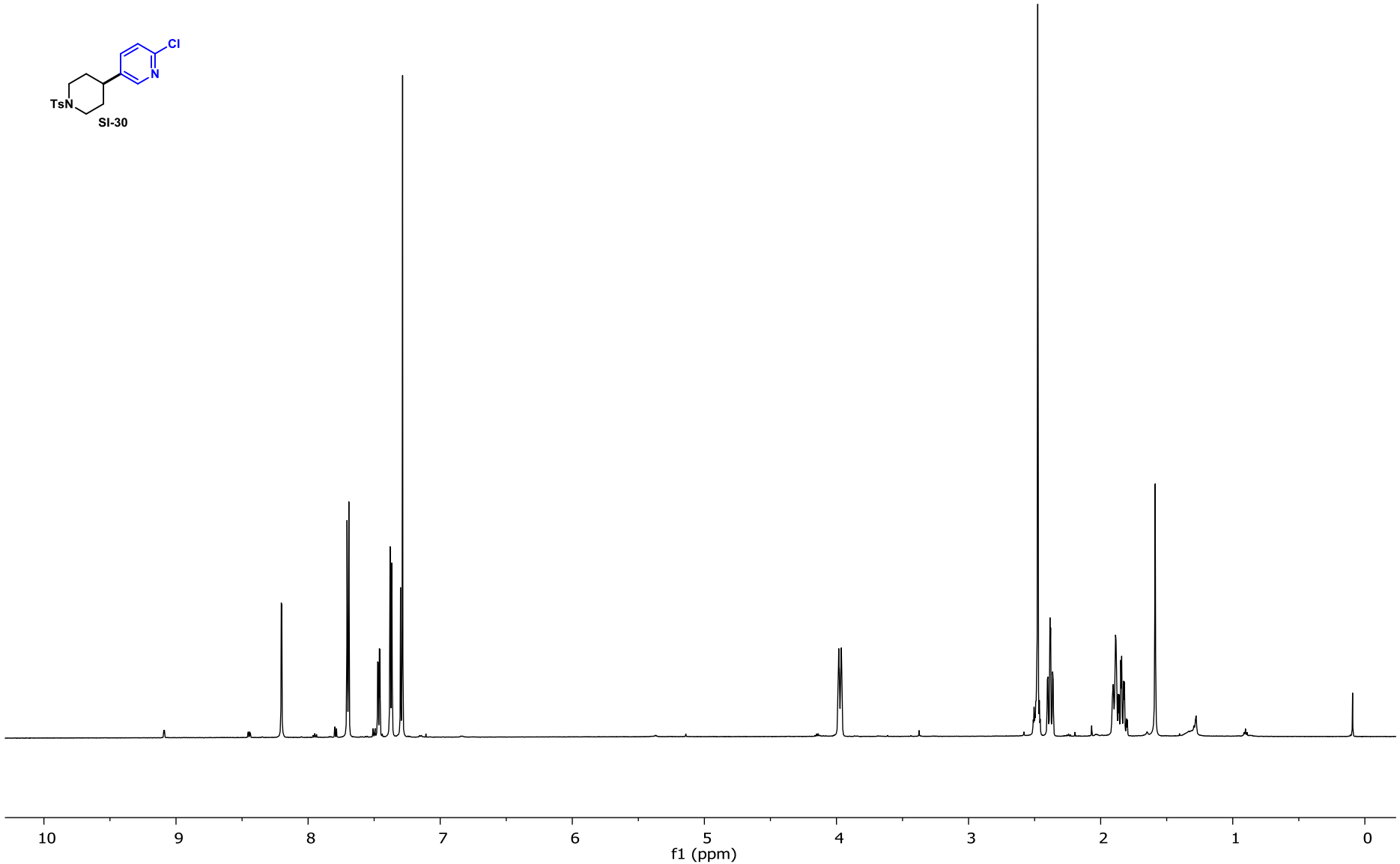


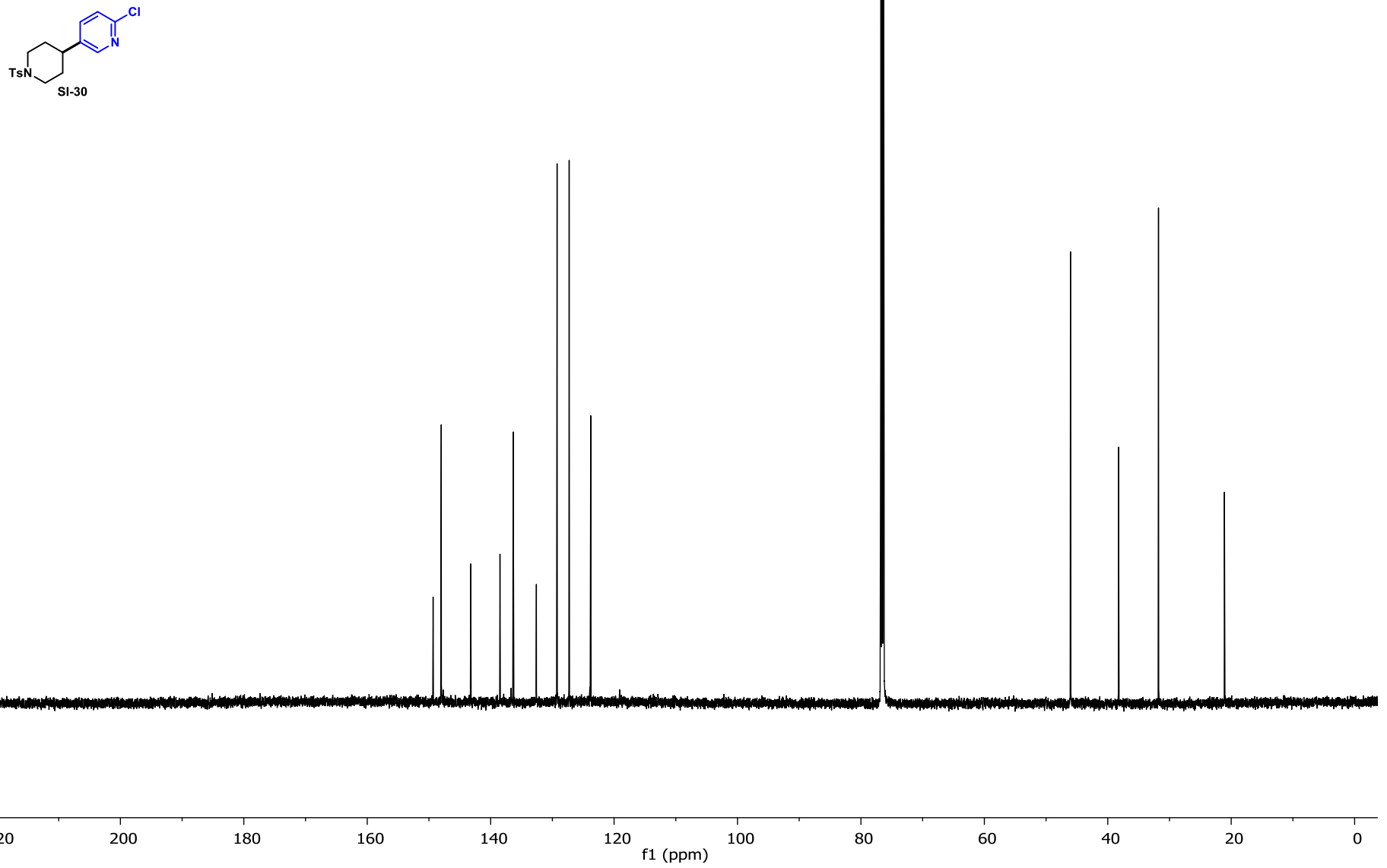
SI-28

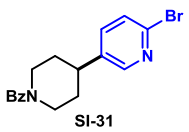

F
N
BzN
SI-29
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


F
N
BzN
SI-29
50 49 48 47 46 45 44 43 42
f1 (ppm)
35.5 35.0 34.5 34.0 33.5 33.0 32.5 32.0
f1 (ppm)
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

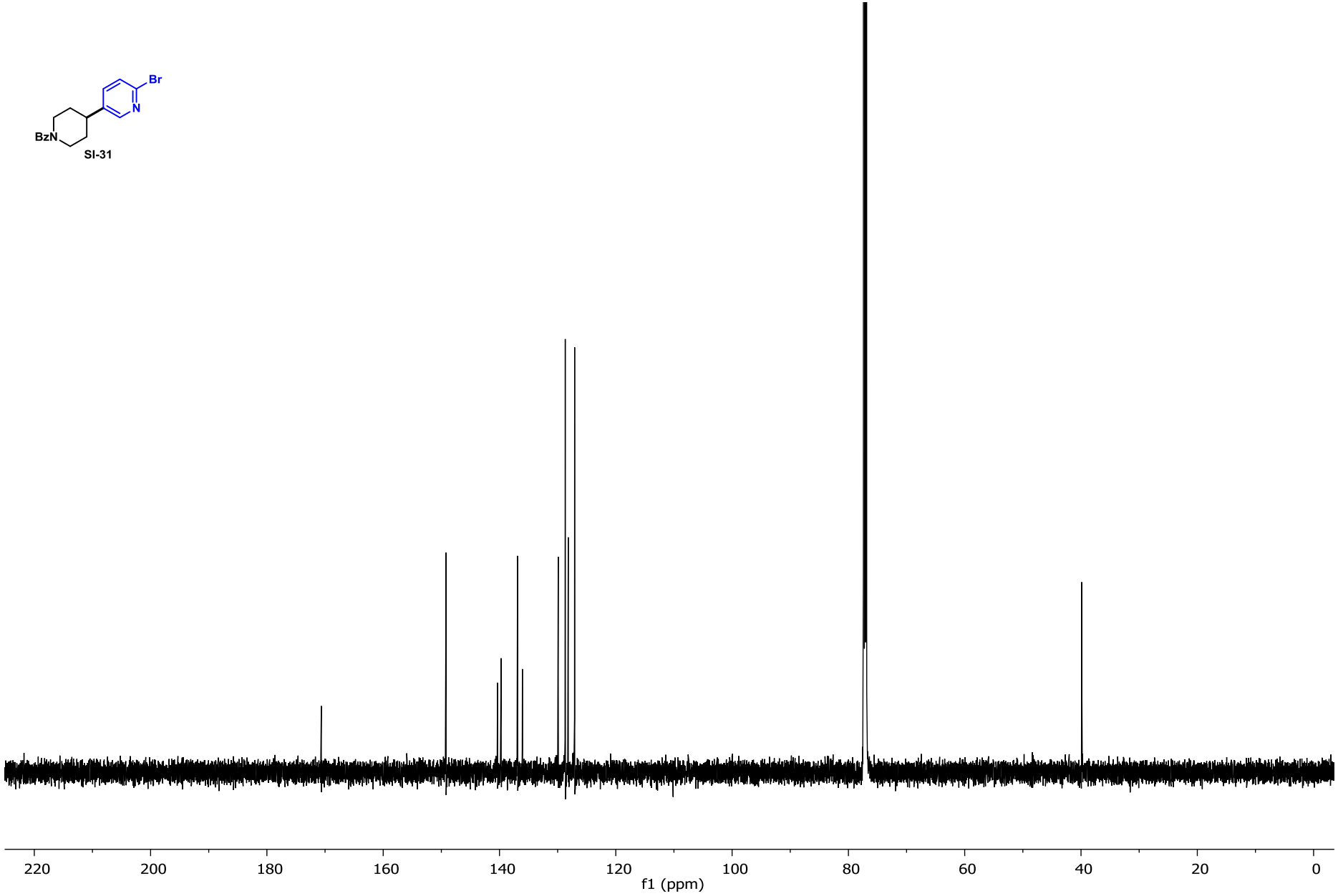

F
N
BzN
SI-29
-20
-40
-60
-80
-100
-120
-140
-160
-180
f1 (ppm)

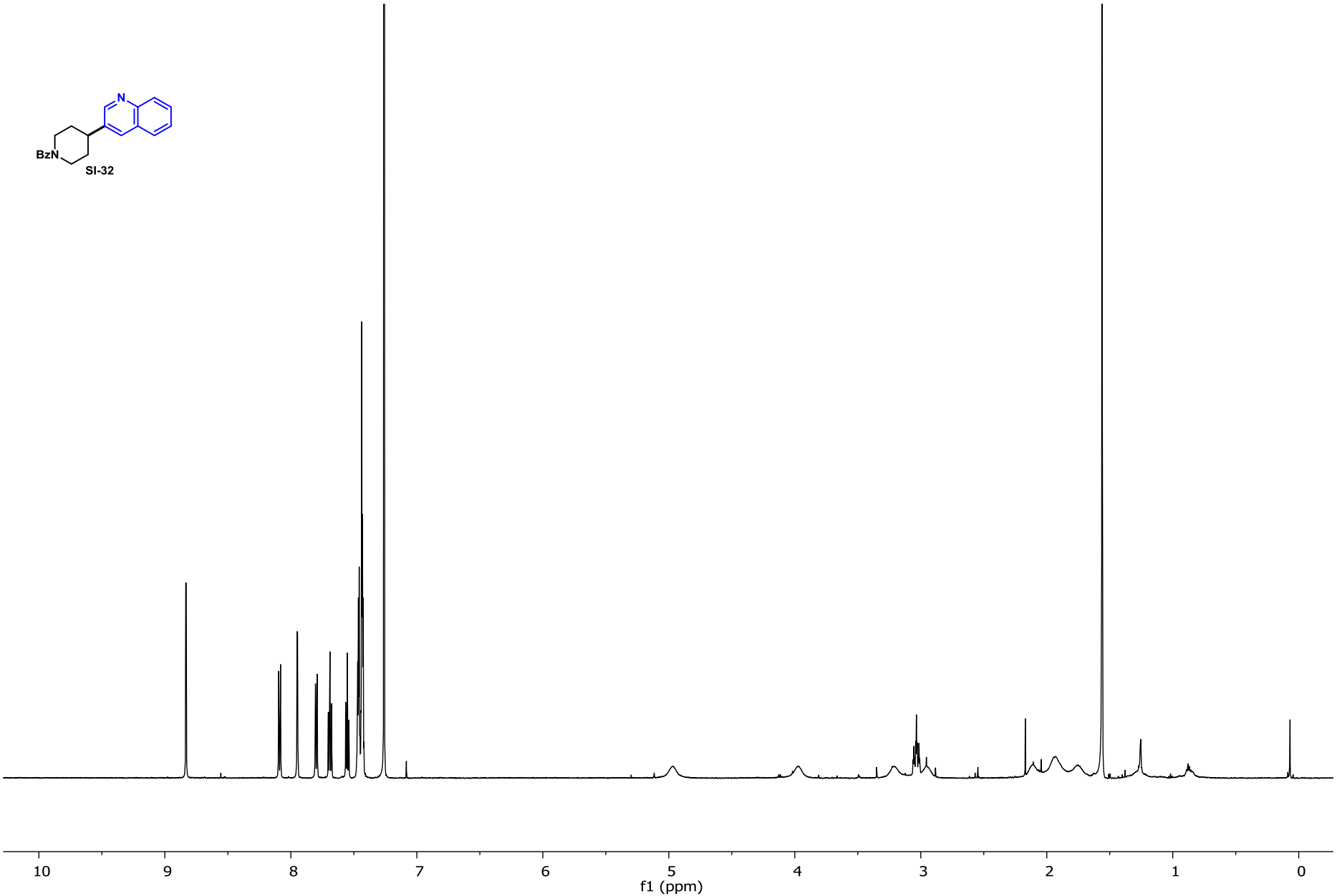

Cl
N
TsN
SI-30
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

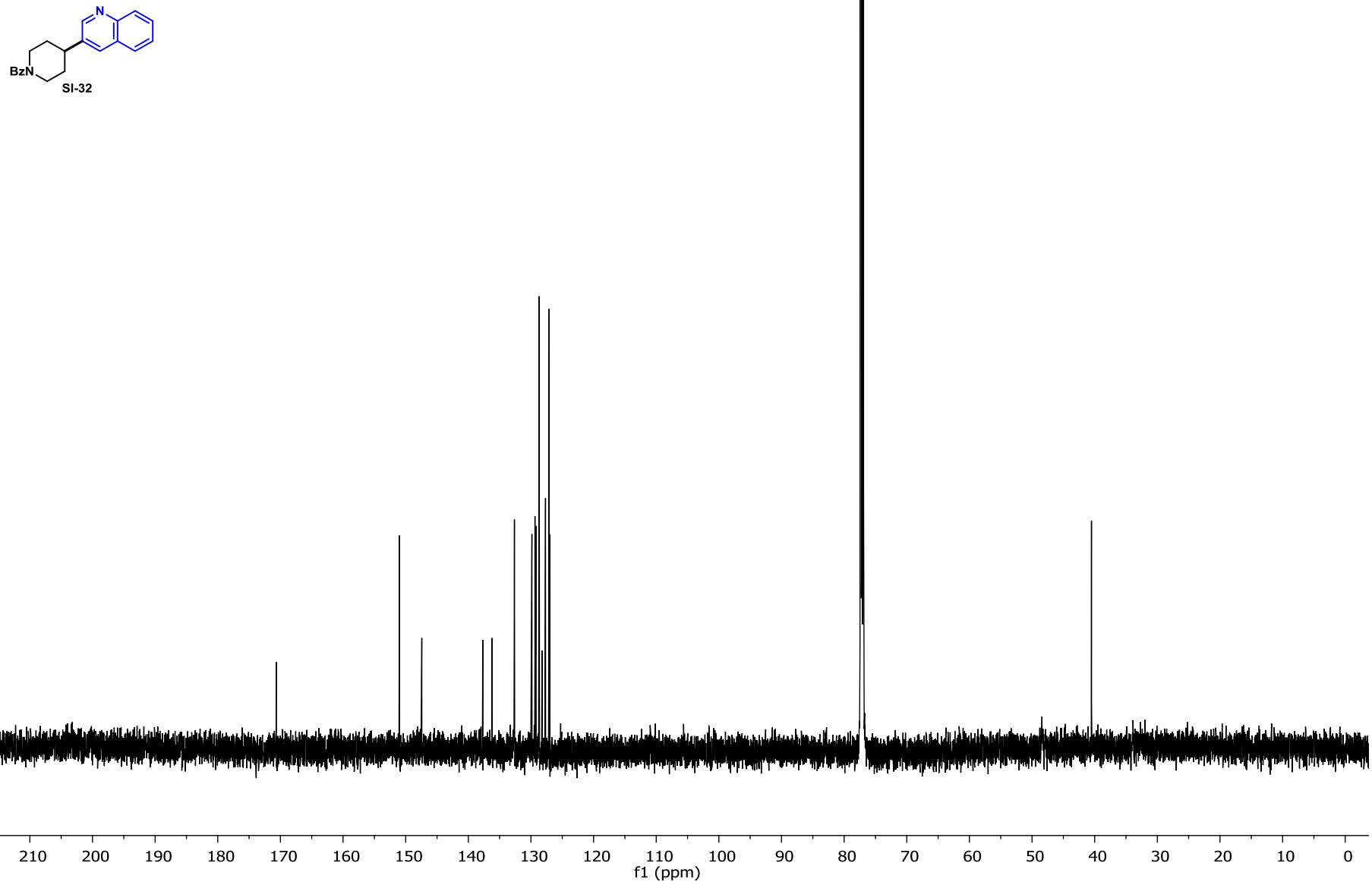

Cl
N
TsN
SI-30
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

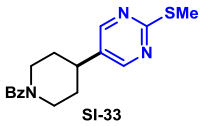


SI-31

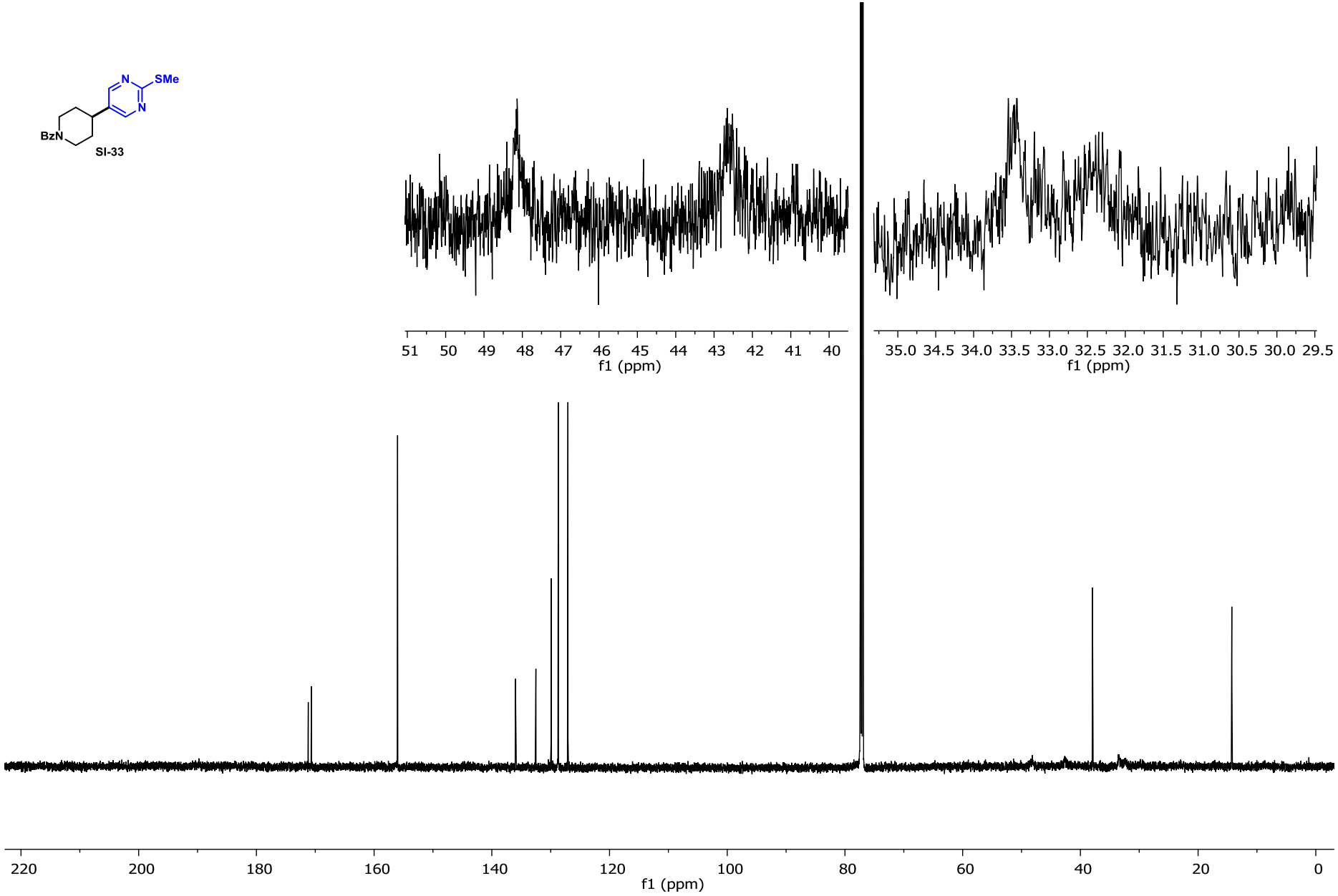

Br
N
BzN
SI-31
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

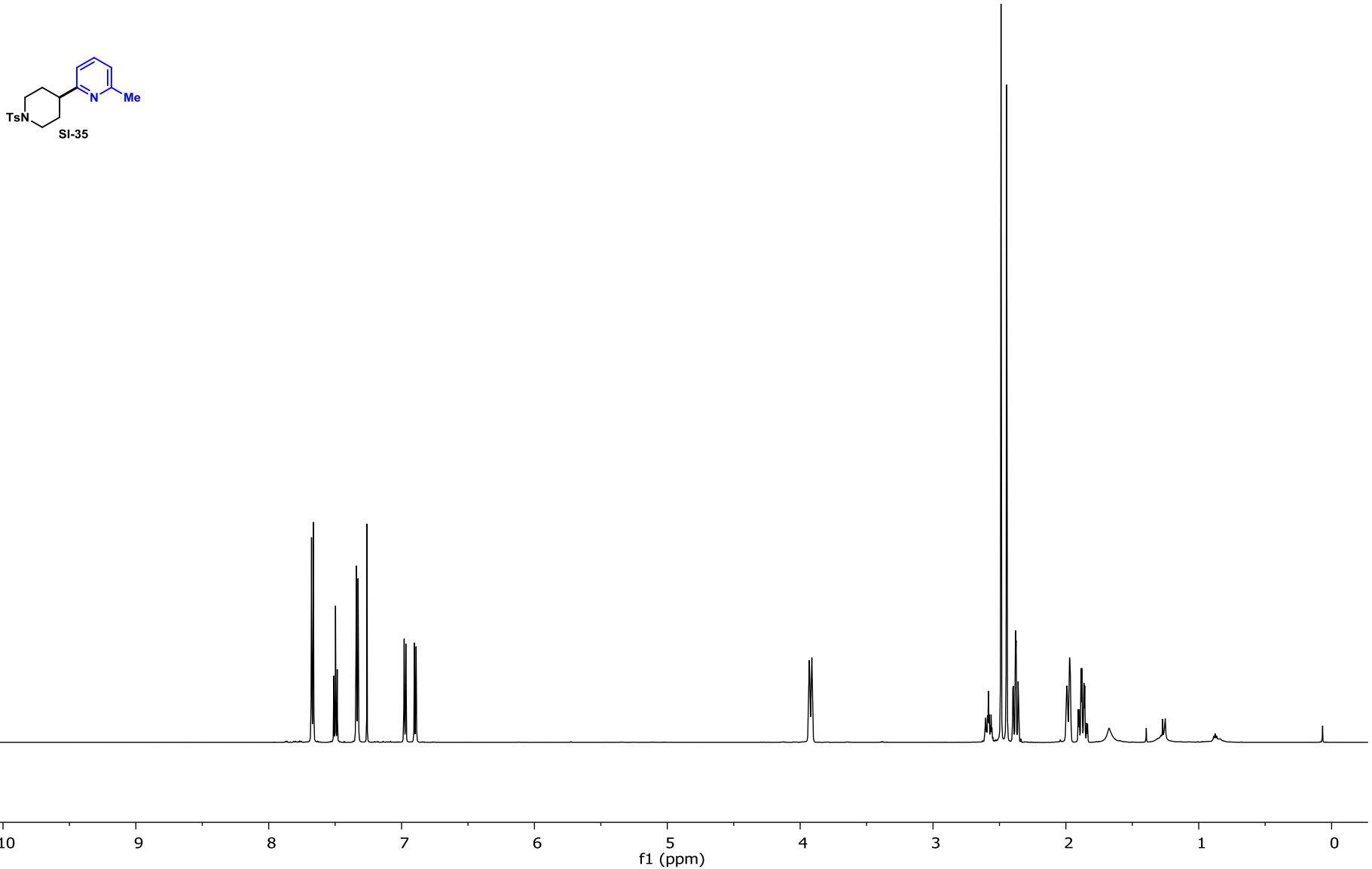

N
BzN
SI-32
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

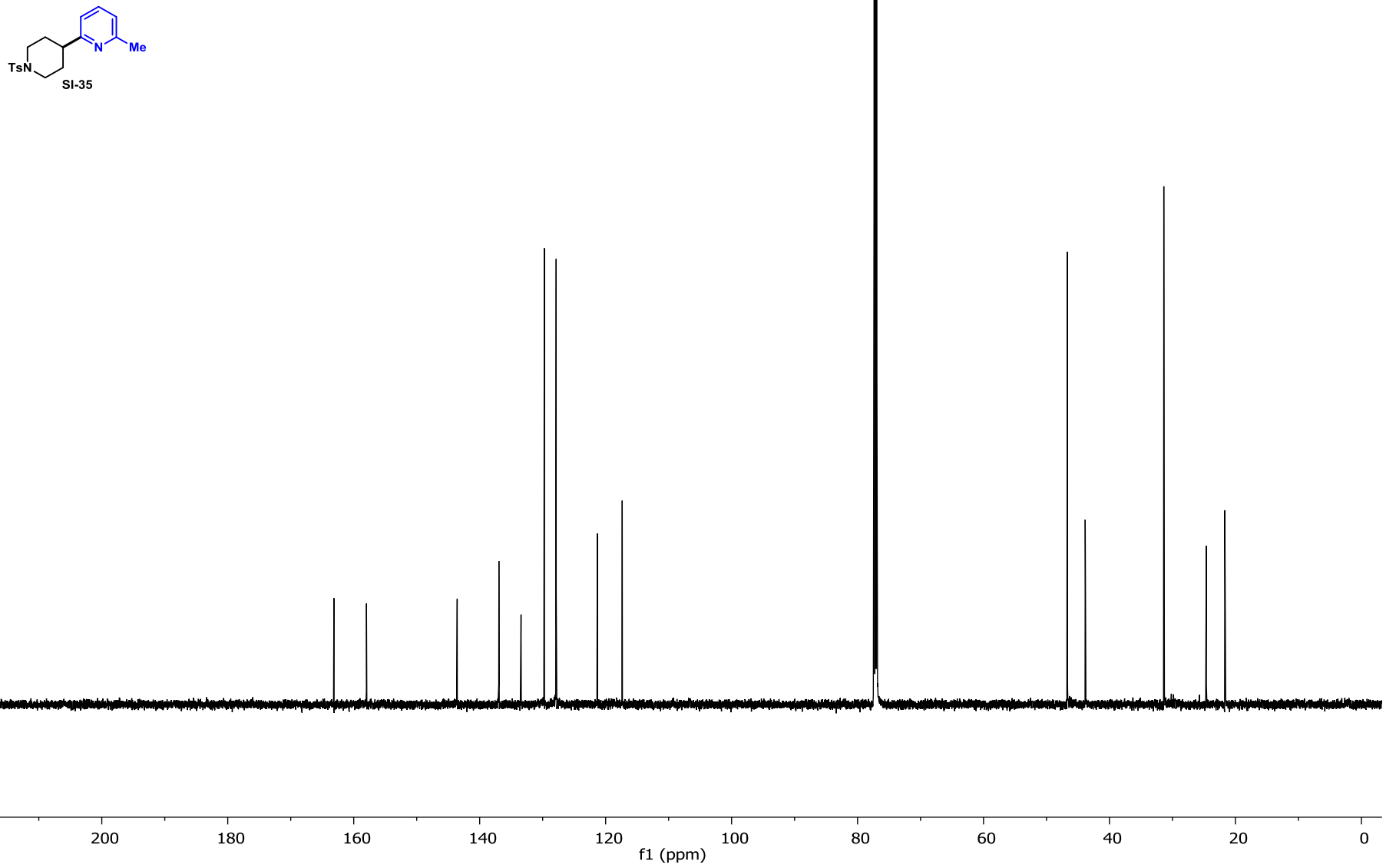

N
BzN
SI-32
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

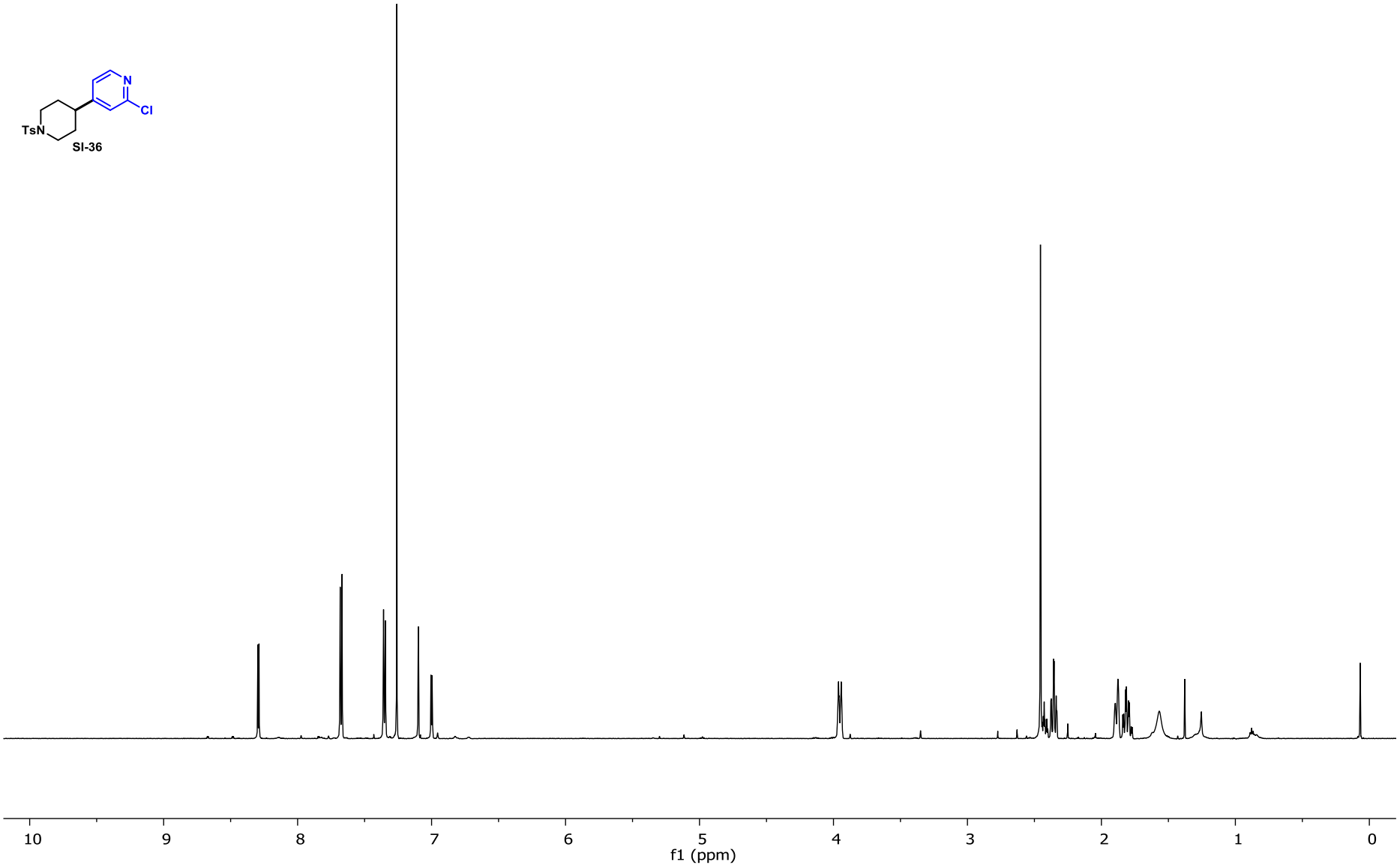


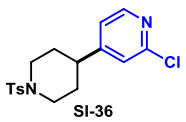
SI-33


N
SMe
N
BzN
SI-33
51 50 49 48 47 46 45 44 43 42 41 40
f1 (ppm)
35.0 34.5 34.0 33.5 33.0 32.5 32.0 31.5 31.0 30.5 30.0 29.5
f1 (ppm)
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

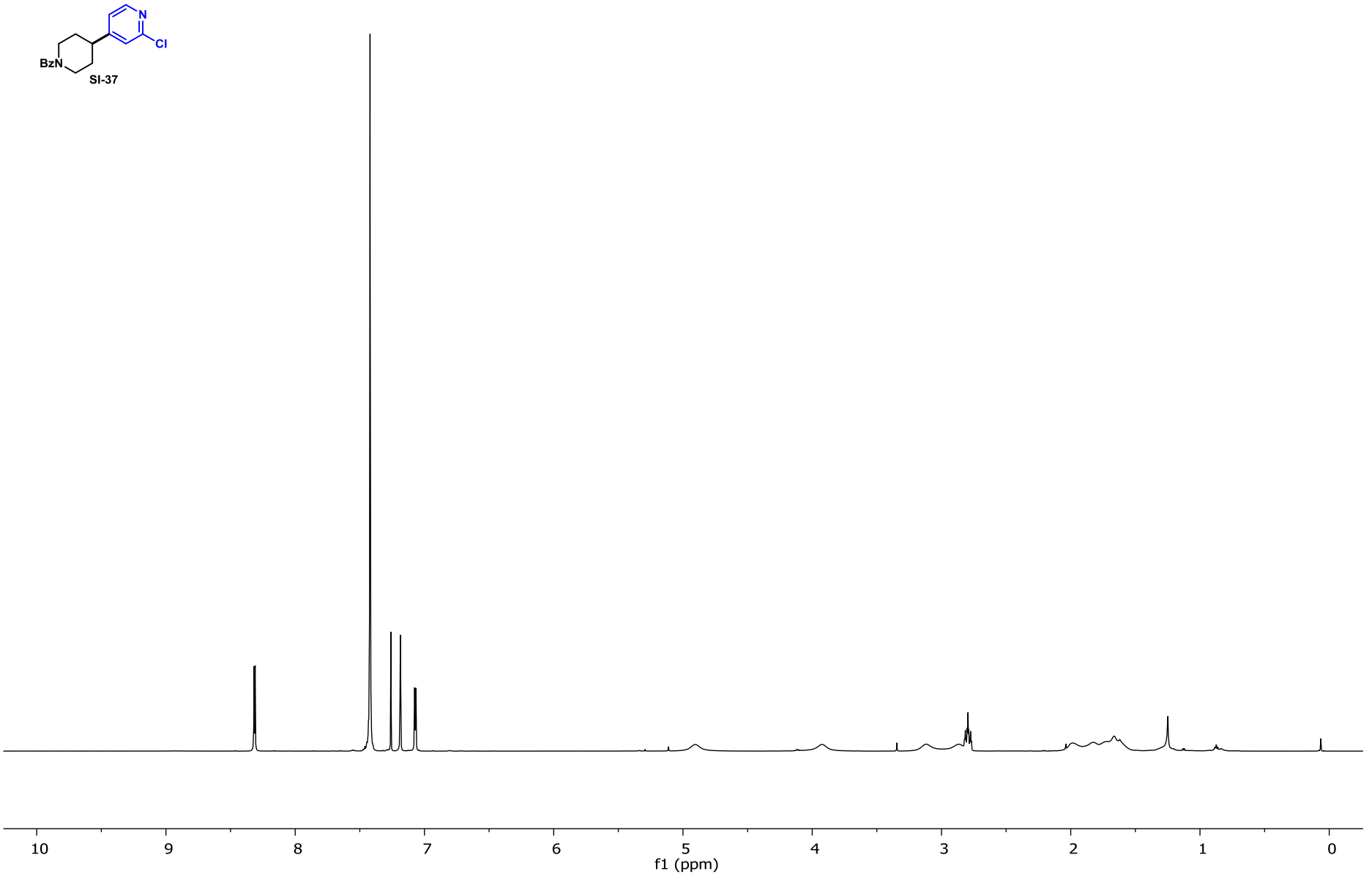

TsN
N
Me
SI-35
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

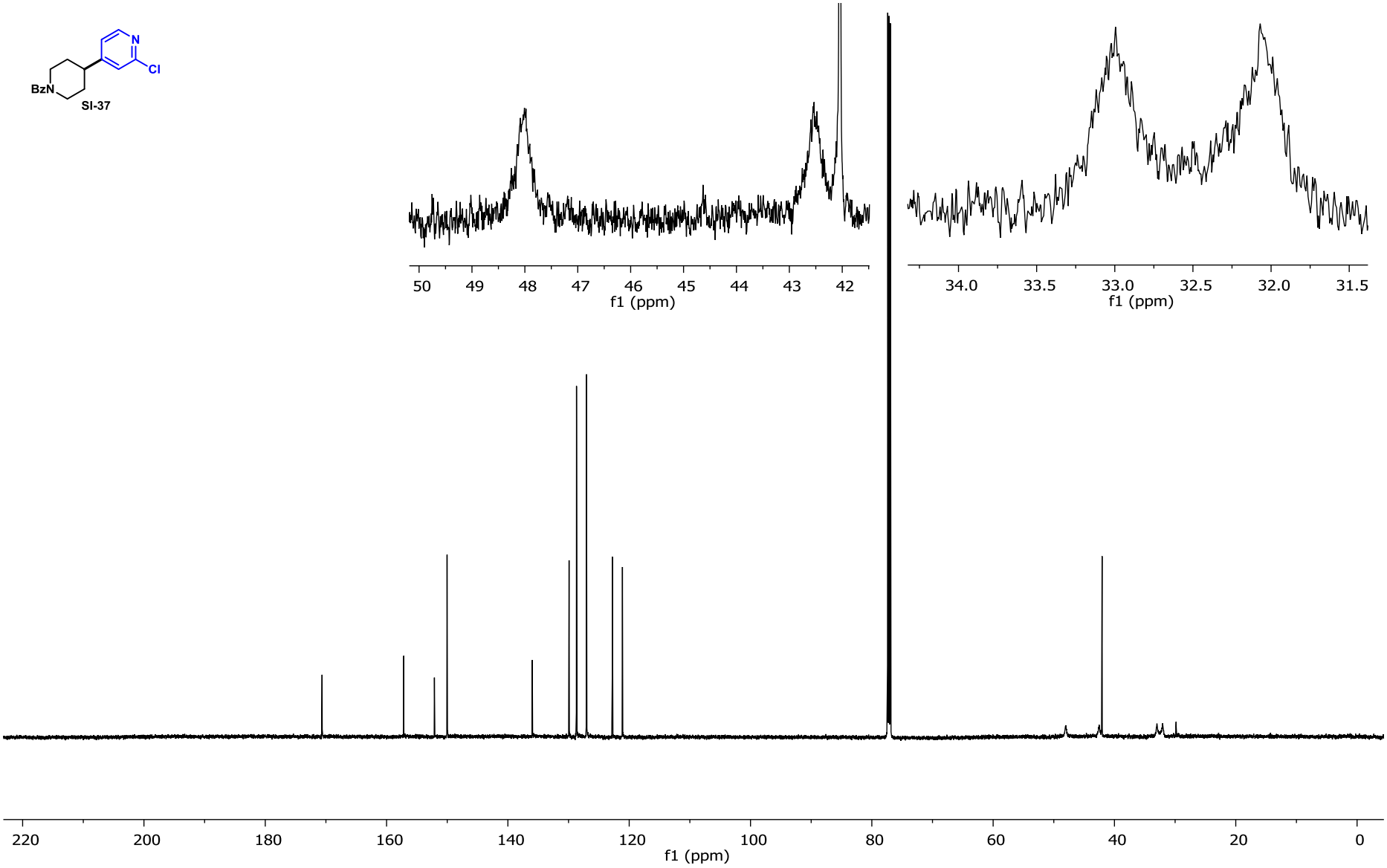

TsN
N
Me
SI-35
220
200
180
160
140
120
100
80
60
40
20
0
f1 (ppm)

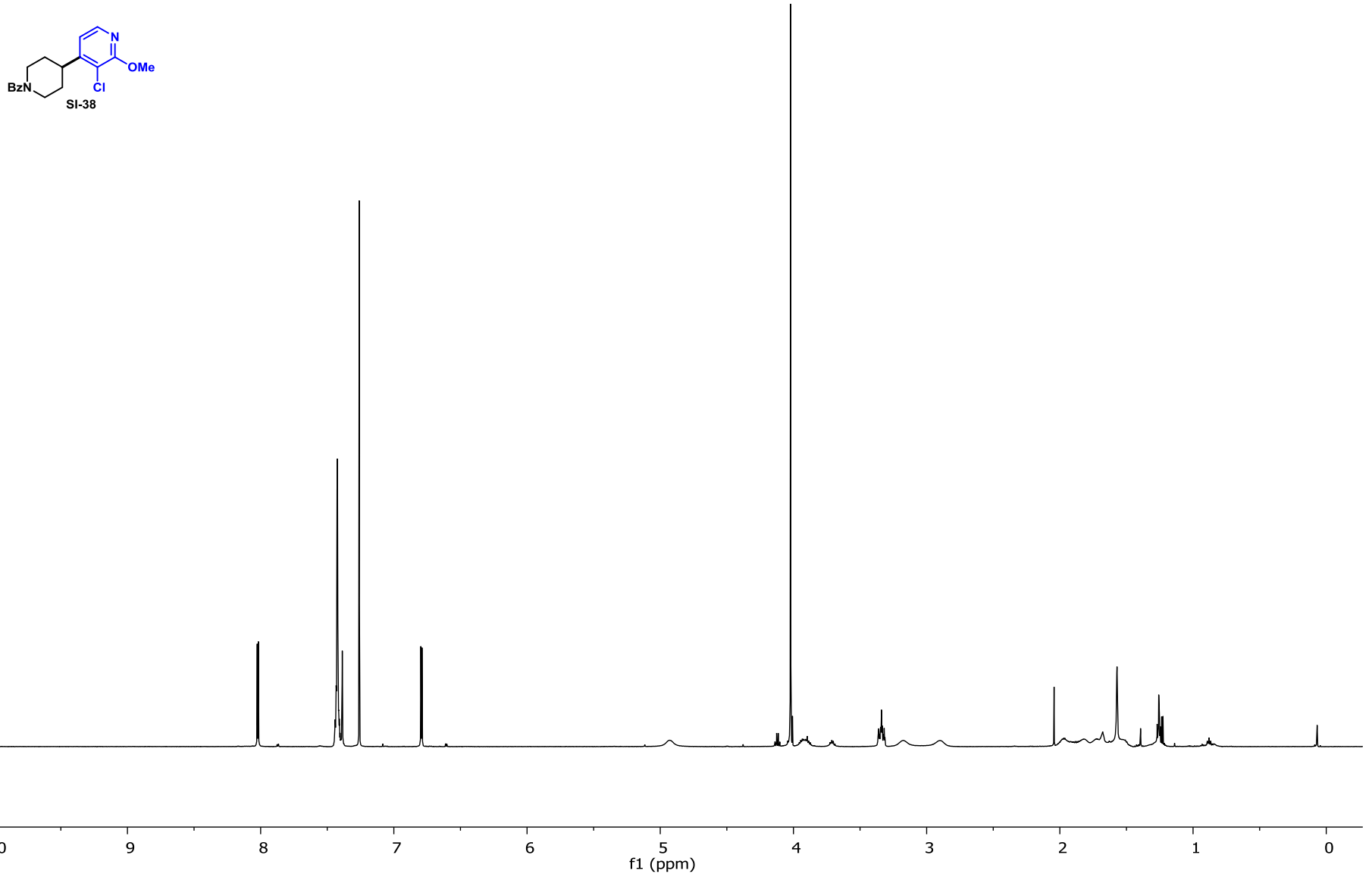

N
Cl
TsN
SI-36
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

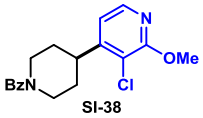


SI-36


N
Cl
BzN
SI-37
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


N
Cl
BzN
SI-37
50 49 48 47 46 45 44 43 42
f1 (ppm)
34.0 33.5 33.0 32.5 32.0 31.5
f1 (ppm)
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)


N
OMe
Cl
BzN
SI-38
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


N
OMe
Cl
BzN

SI-38

50 49 48 47 46 45 44 43 42 41
f1 (ppm)
33 32 31 30 29 28
f1 (ppm)
220 200 180 160 140 120 100 80 60 40 20 0
f1 (ppm)

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