

Supporting Information

Development of Scalable Routes to 1-Bicyclo[1.1.1]pentylpyrazoles

Cayetana Zarate,^{*††} Michael Ardolino,^{††} Gregori J. Morriello,[§] Kaitlyn M. Logan,[†] William P. Kaplan,[†] Luis Torres,[§] Derun Li,[†] Meng Chen,[‡] Hongming Li,[†] Jing Su,[§] Peter Fuller,[†] Matthew L. Maddess,[†] Zhiguo Jake Song^{||}

Affiliations:

[†]Department of Process Research and Development, Merck & Co., Inc., Boston, Massachusetts 02115, United States

[§]Department of Discovery Chemistry, Merck & Co., Inc., Kenilworth, NJ 07033, United States

[†]Department of Discovery Chemistry, Merck & Co., Inc., Boston, Massachusetts 02115, United States

[‡]WuXi AppTec (Tianjin), Chemistry Service Unit, Tianjin 300457, China

^{||}Department of Process Research and Development, Merck & Co., Inc., Rahway, NJ 07065, United States

cayetana.zarate.saez@merck.com

Table of Contents

I.	General Considerations	S3
	I.A. Materials	S3
	I.B. Methods	S3
	I.C. Instrumentation and Software	S4
II.	Preparation of C3-methyl ester BCPP	S5
	II.A. Synthesis via decarboxylative C1–N coupling	S5
	II.B. Synthesis of 3 via Chan-Lam C1–N coupling	S6
III.	Preparation of 4	S11
IV.	Preparation of 6	S12
V.	Preparation of 11	S16
	V.A. Decarboxylative hydrazination	S16
	V.B. N-amination of BCP amine	S17

VI.	Preparation of 14	S22
VII.	Preparation of 16	S24
	VII.A. Preparation of 16 from 15	S24
	VII.B. Preparation of 16 from [1.1.1]propellane	S27
VIII.	Unsuccessful synthetic approaches	S28
	VIII.A. Decarboxylative C1–N coupling attempts	S28
	VIII.B. Chan-Lam C1–N coupling attempts	S30
	VIII.C. C3-Functionalization attempts	S31
	VIII.D. Attempted synthesis of BCP pyrazole intermediates	S36
IX.	NMR Spectra	S39
X.	References	S62

I. General Considerations

I.A. Materials

1¹ and **9**² were prepared according to literature procedures. Anhydrous solvents were purchased from Sigma-Aldrich in Sure-Seal™ bottles and used as received. Deuterated solvents were purchased from Cambridge Isotope Laboratories, Inc. and used as received. All other substrates were purchased from commercial sources and used as received.

I.B. Methods

Reactions were performed in round-bottomed flasks or scintillation vials with Teflon septa. Reactions were monitored by liquid chromatography/mass spectrometry (LC/MS), ¹H NMR or gas chromatography/mass spectrometry (GC/MS) analysis. Thin-layer chromatography (TLC) was carried out on silica gel60 F254 plates (EMD) and visualized with UV light (254 nm) and/or a ninhydrin in EtOH stain solution. Air- and moisture-sensitive manipulations were carried out using a high vacuum Schlenk line. Flash column chromatographic purification was performed using prepacked RediSep gold Rf silica gel columns on a Teledyne Isco CombiFlash Rf automated chromatography system. Volatiles were concentrated under reduced pressure on a Buchi rotary evaporator.

HTE Experiments (Scheme 4) were conducted in an MBraun glove-box (oxygen typically <5 ppm), and the reactions carried out in microvials in a 96-well plate aluminum reactor block. Liquid chemicals were dosed using an Eppendorf pipetter. The stirring was accomplished with parylene stir bars and a tumble stirring mechanism with a heating block to insure uniform stirring throughout the 96-well plate. The bases (30 μmol) were dosed into the 1 mL shell vials as slurry, and the solvent removed by evacuation on a Genovac. The reactions were sealed in the 96-well plate during reaction. Below each reactor vial in the aluminum 96-well plate was a 0.062 mm thick

silicon-rubber gasket. Directly above the glass vial reactor tops was a (0.002 mm) Teflon PFA (perfluoroalkoxy copolymer resin) sealing gasket and above that, two more 0.062 mm thick silicon-rubber gaskets. The entire assembly was compressed between an aluminum top and the reactor base with 9 evenly-placed screws.

I.C. Instrumentation and Software

^1H , proton-decoupled $^{13}\text{C}\{^1\text{H}\}$ and ^{19}F NMR spectra were recorded at 23 °C on 400 or 600 MHz NMR spectrometers. All ^1H and ^{13}C NMR chemical shifts (δ) are reported in part per million (ppm) using the ^1H (CDCl_3 : 7.26 ppm; dimethyl sulfoxide- d_6 : 2.50 ppm) and $^{13}\text{C}\{^1\text{H}\}$ (CDCl_3 : 77.16 ppm; dimethyl sulfoxide- d_6 : 39.51 ppm) chemical shifts of the solvent as a standard. NMR data is reported as follows: chemical shift (multiplicity, coupling constants J in Hz, integration) where s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet). NMR spectra were processed using the MestReNova software suite.³

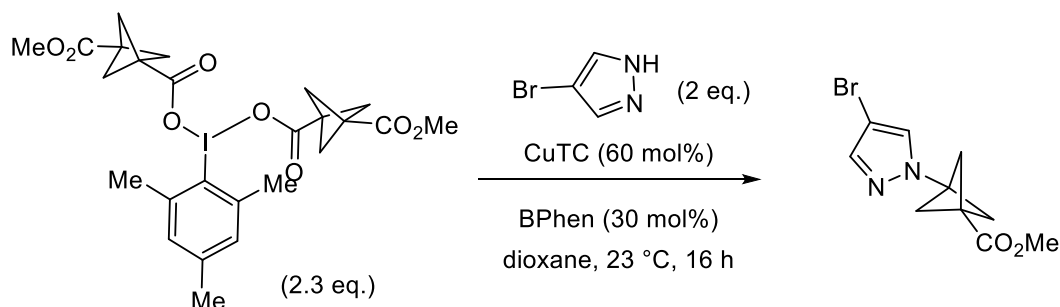
Reaction monitoring was carried out by: (a) LC/MS analysis using an Agilent 1100 or 1200 instrument with an Inductively Coupled Plasma (IPC), (b) GC/MS analysis using a GCMS-004 GCMS-005 (Shimadzu GC2030) instrument with an AB-5 (30 m-0.32 mm-0.25 μm) or HP-5MS column and an FID detector, or (c) Agilent 1290 UPLC instrument. High-resolution mass spectrometry (HRMS) data was recorded on a Waters Acquity UPLC with Synapt G1 Q-ToF MS instrument in ESI+ (electrospray) ionization mode with an Acquity UPLC BEH C18 1.7 μm column.

J-Kem® temperature controller was employed to monitor the temperature during selected reactions.

Photochemical transformations were carried out in an integrated Merck photoreactor.⁴

II. Preparation of C3-methyl ester BCPP

II.A. Synthesis via decarboxylative C1–N coupling⁵

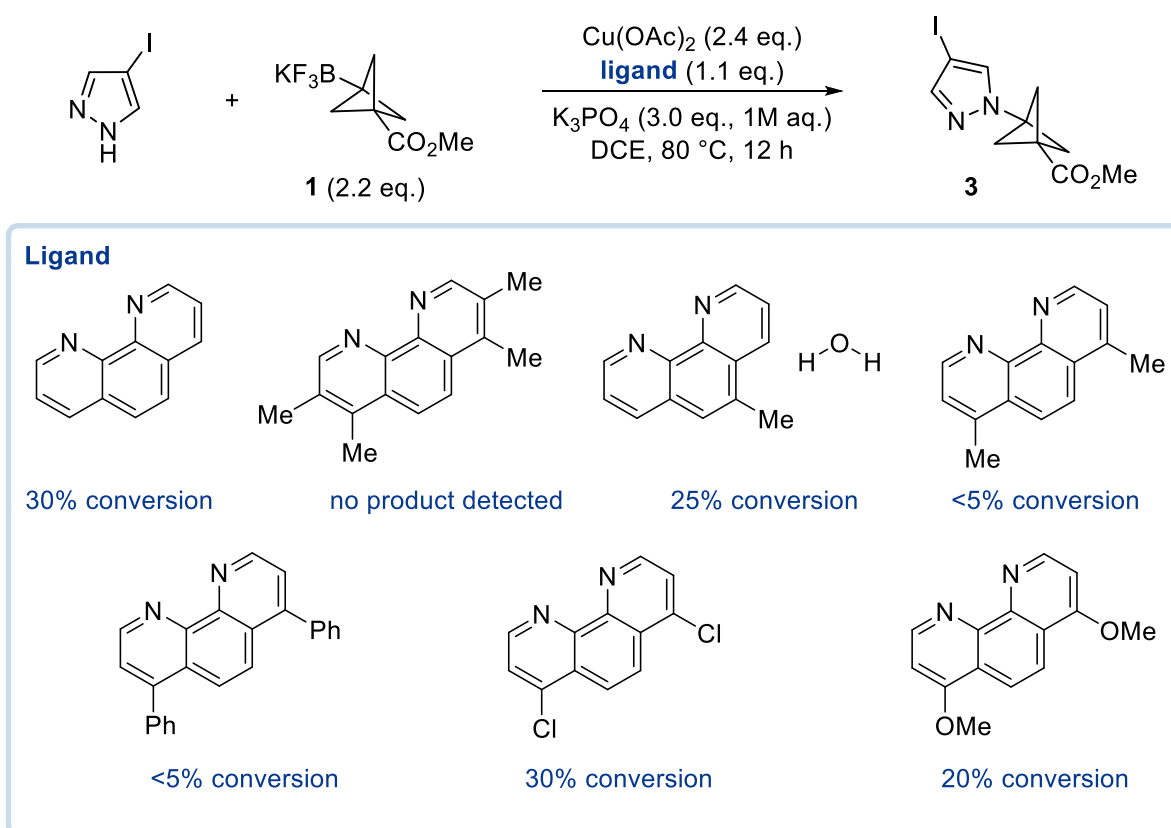


A flask was charged with 4-bromo-1H-pyrazole (72.4 g, 493 mmol, 2.0 eq.), O'1,O1-(mesityl-1,3-iodanediyl) 3,3'-dimethyl bis(bicyclo[1.1.1]pentane-1,3-dicarboxylate)⁵ (331 g, 567 mmol, 2.3 eq.), bathophenanthroline (BPhen, 24.6 g, 73.9 mmol, 30 mol%), thiophene-2-carboxylatecopper (CuTc, 28.2 g, 148 mmol, 60 mol%) and dioxane (2.0 L). The solution was degassed by sparging with N₂ for 5 min and then sonicated for 1 min. The resulting reaction mixture was stirred at 25 °C for 16 h. TLC analysis showed that starting material was consumed. The reaction was then filtered and concentrated under vacuum to give the crude product. Purification of the crude reaction mixture by silica gel chromatography with 0-50% EtOAc in petroleum ether as eluent afforded methyl 3-(4-bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (25.6 g, 93.7 mmol, 38% yield) as a white solid. ¹H NMR (600 MHz, CDCl₃): δ 7.49 (s, 1H), 7.45 (s, 1H), 3.74 (s, 3H), 2.55 (s, 6H). ¹³C{¹H} NMR (151 MHz, CDCl₃): 169.4, 141.0, 127.9, 93.9, 54.5, 52.3, 51.2, 34.0. HRMS [M+H]⁺: calculated 271.0082, found 271.0085.

II.B. Synthesis of **3** via Chan-Lam C1–N coupling

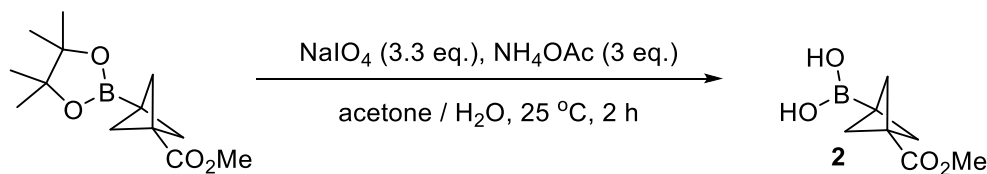
Ligand screening for Chan-Lam C1–N coupling

Table S1. Ligand screening for Chan-Lam C1–N_{pyrazole} bond coupling.



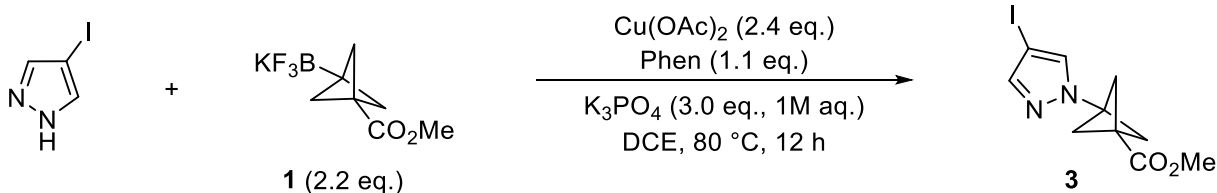
General procedure. To a scintillation vial with a stir bar was added 4-iodo-1H-pyrazole (5 mg, 0.03 mmol, 1.0 eq.), **1** (16 mg, 0.07 mmol, 2.2 eq.),¹ Cu(OAc)₂ (13mg, 0.07 mmol, 2.4 eq.) and ligand (0.03 mmol, 1.1 eq.). The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. DCE (25 μ L) and K₃PO₄ (1 M aq., 90 μ L, 0.09 mmol, 3.0 eq.) were then added under a positive pressure of N₂. The resulting suspension was stirred at 80 °C for 12 h and the mixture was then analyzed by LC/MS. Tabulated LC/MS conversions (uncorrected) correspond to the ratio of absorbances of **3**/biphenyl (IS).

Synthesis of 2



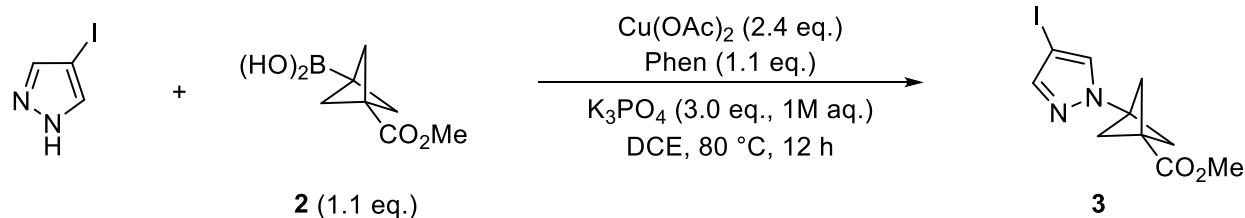
Three reactions were carried out in parallel. To a suspension of methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[1.1.1]pentane-1-carboxylate (50.0 g, 198 mmol, 1.0 eq.)¹ in acetone (500 mL) and H₂O (250 mL) was added NH₄OAc (45.9 g, 595 mmol, 3.0 eq.) and NaIO₄ (140 g, 654 mmol, 36.3 mL, 3.3 eq.) in one portion. The resulting mixture was stirred at 25 °C and after 1 h, TLC analysis showed that starting material was consumed. The three reaction mixtures were combined and the resulting suspension was filtered through a fritted glass. The filter cake was washed with acetone (200 mL x 4) and the filtrate was concentrated under vacuum. The resulting residue was extracted with EtOAc (300 mL x 3) and the combined organic phases were concentrated under vacuum to give the crude product as a brown solid. The crude product was triturated with petroleum ether (500 mL) for 10 min and the resulting suspension was filtered. The filter cake was collected and dried under vacuum to give (3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)boronic acid (**2**, 85.0 g, 500 mmol, 84% yield) as a white solid. ¹H NMR (600 MHz, DMSO-*d*₆): δ 7.66 (s, 2H), 3.55 (s, 3H), 1.95 (s, 6H). ¹³C{¹H} NMR (151 MHz, DMSO-*d*₆): 169.5, 51.6, 51.1, 41.5. HRMS [M+H]⁺: not found, poor/weak ionization.

Chan-Lam C1–N coupling with BCP trifluoroborate salt **1**



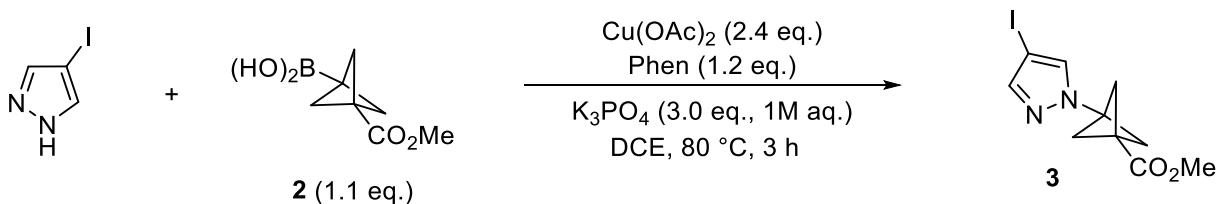
To a 25 mL round-bottomed flask with a stir bar was added 4-iodo-1H-pyrazole (200 mg, 1.03 mmol, 1.0 eq.), **1** (526 mg, 2.27 mmol, 2.2 eq.), Cu(OAc)₂ (449 mg, 2.47 mmol, 2.4 eq.) and 1,10-phenanthroline (204 mg, 1.13 mmol, 1.1 eq.). The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. DCE (25 V) and K₃PO₄ (1 M aq., 3.1 mL, 3.09 mmol, 3.0 eq.) were then added under a positive pressure of N₂. The resulting suspension was stirred at 80 °C for 12 h. The reaction mixture was then diluted with H₂O (10 mL) and the organic phase was extracted with EtOAc (20 mL x 3), washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum. Purification of the resulting crude by silica gel chromatography with 0-45% EtOAc in hexanes as eluent afforded methyl 3-(4-iodo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (**3**, 105 mg, 0.330 mmol, 32% yield) as a white solid. **¹H NMR (600 MHz, CDCl₃):** δ 7.53 (s, 1 H), 7.47 (s, 1 H), 3.73 (s, 3 H), 2.55 (s, 6 H). **¹³C{¹H} NMR (151 MHz, CDCl₃):** 169.3, 145.4, 132.2, 56.8, 54.6, 52.2, 51.0, 34.0. **HRMS [M+H]⁺:** calculated 318.9943, found 318.9951. **Note:** low conversion (~5%) was obtained during the scale-up reaction (119 mmol 4-iodopyrazole) with **1** under the same reaction conditions. Scale-up was successful with boronic acid **2** (vide infra).

Chan-Lam C1–N coupling with BCP boronic acid **2**



To a 500 mL two-necked round-bottomed flask with a stir bar was added 4-iodo-1H-pyrazole (3.0 g, 15.5 mmol, 1.0 eq.), **2** (2.9 g, 17.1 mmol, 1.1 eq.), $\text{Cu}(\text{OAc})_2$ (6.8 g, 37.2 mmol, 2.4 eq.) and 1,10-phenanthroline (3.1 g, 17.1 mmol, 1.1 eq.). A reflux condenser was attached to one of the necks of the flask and the other neck was capped with a Teflon septum. The flask was submitted to three vacuum/ N_2 refill cycles. DCE (30 V) and K_3PO_4 (1 M aq., 46.5 mL, 46.5 mmol, 3.0 eq.) were then added via syringe under a positive pressure of N_2 . The resulting suspension was stirred at 80 °C for 12 h. The reaction mixture was then diluted with H_2O (100 mL) and the organic phase was extracted with EtOAc (100 mL x 3), washed with brine (100 mL), dried over Na_2SO_4 , filtered and concentrated under vacuum. Purification of the resulting crude by silica gel chromatography with 0-45% EtOAc in hexanes as eluent afforded **3** (2.1 g, 6.7 mmol, 43% yield) as a white solid. Spectroscopic data match those reported above.

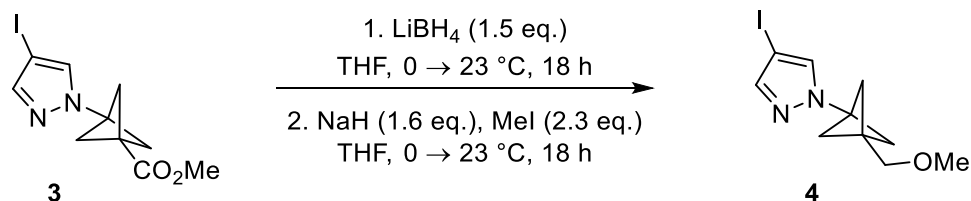
Scale-up synthesis of **3**



Three reactions were carried out in parallel. 4-Iodopyrazole (20.8 g, 107 mmol, 1.0 eq.), **2** (20 g, 118 mmol, 1.1 eq.), $\text{Cu}(\text{OAc})_2$ (23.3 g, 128 mmol, 1.2 eq.) and 1,10-phenanthroline (21.2 g, 118 mmol, 1.1 eq.) were added to a 2 L two-necked round-bottomed flask containing a stir bar. A reflux condenser was attached to one of the necks of the flask and the other neck was capped

with a Teflon septum. DCE (600 mL) and K_3PO_4 (1 M aq., 321 mL, 321 mmol, 3 eq.) were then added via syringe under a positive pressure of N_2 . The resulting suspension was stirred at 80 °C for 3 h. After this time, TLC analysis showed full consumption of 4-iodopyrazole. The three reaction mixtures were combined and the resulting suspension was filtered through a plug of Celite. The filter cake was washed with DCM (500 mL x 3) and the organic phase of the filtrate was extracted. The aqueous phase was washed with DCM (300 mL x 2) and the combined organic phases were concentrated under vacuum. The resulting residue was extracted with EtOAc (300 mL x 3) and the combined organic phases were concentrated under vacuum to give a black oil residue. The residue was dissolved with DCM/petroleum ether (2:1, 600 mL) and the resulting solution was passed through a pad of silica gel, washing the pad with additional DCM/petroleum ether (2:1, 200 mL). The solution was concentrated under vacuum to give the crude product as an off-white solid, which was triturated with petroleum ether (300 mL) for 30 min. The resulting suspension was filtered through a fritted glass filter and the filter cake was dried under vacuum providing **3** (46 g, 145 mmol, 45% yield) as a white solid. **Note:** isolated yield was calculated as the media of the three reactions run in parallel. Spectroscopic data match those reported above.

III. Preparation of 4

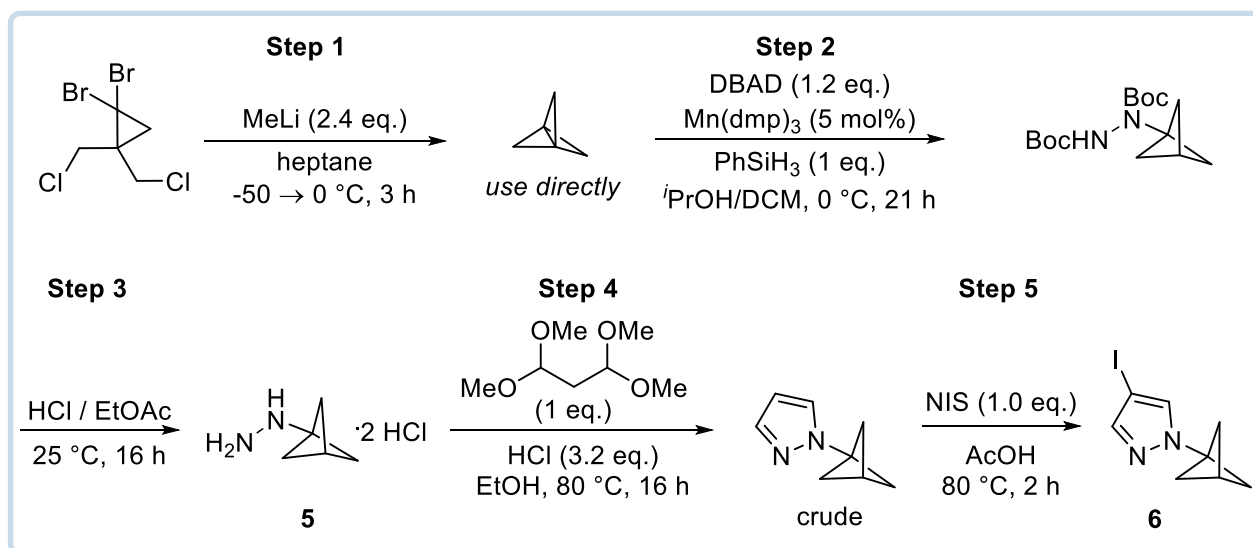


A 1 L round-bottomed flask with a stir bar was charged with **3** (15.0 g, 47.2 mmol, 1.0 eq.) and the flask was submitted to three vacuum/ N_2 refill cycles. Then, anhydrous THF (240 ml) was added under a positive pressure of N_2 and the mixture was cooled to 0 $^\circ\text{C}$ in an ice/water bath. Lithium tetrahydroborate (2 M in THF, 35 mL, 70.8 mmol, 1.5 eq.) was added dropwise under a N_2 atmosphere and the reaction was stirred at 23 $^\circ\text{C}$ for 24 h (reaction temperature monitored with J-Kem $^\circ$ temperature controller, no significant exothermicity observed). The reaction mixture was quenched with MeOH (130 mL) at 0 $^\circ\text{C}$, warmed to 23 $^\circ\text{C}$ and stirred at this temperature for 90 min. The resulting solution was concentrated under vacuum to give a sticky white foam. Upon addition of EtOAc (130 mL) a white precipitate was formed. The suspension was filtered through a fritted glass filter washing with EtOAc (100 mL x 2). The resulting clear filtrate was dried under vacuum and the crude product was transferred to a 500 mL round-bottomed flask with a stir bar. The flask was evacuated and refilled with N_2 (x3). Then, anhydrous THF (100 mL) was added and the resulting solutions was stirred at 23 $^\circ\text{C}$ for 15 min. A 1 L three-necked round-bottomed flask with a stir bar was charged with NaH (60% dispersion in mineral oil, 3.00 g, 75 mmol, 1.6 eq.). A J-Kem $^\circ$ temperature controller was connected to one of the flask necks. The second neck was connected to the N_2 Schlenk line and the third neck was sealed with a Teflon septum. The flask was submitted to three vacuum/ N_2 refill cycles and anhydrous THF (100 mL) was then added under a positive pressure of N_2 . The resulting suspension was cooled to 0 $^\circ\text{C}$ using an ice/water bath. To the cooled suspension was added dropwise the previously prepared reaction crude solution. The solid residue that remained in the flask was transferred with additional anhydrous

THF (40 mL). The resulting mixture was stirred at 0 °C for 45 min under a positive pressure of N₂. Then, methyl iodide (6.74 ml, 108 mmol, 2.3 eq.) was added dropwise at 0 °C and the resulting reaction mixture was stirred for 18 h at 23 °C. The reaction mixture was then cooled to 0 °C and quenched by slow addition of a saturated, aqueous solution of NH₄Cl (150 mL). The organic phase was extracted with EtOAc (150 mL x 3) and the organic layers were combined, washed with brine, dried over Na₂SO₄, filtered and concentrated under vacuum to give a yellow oil. Purification of the crude oil by silica gel chromatography with 0-70% EtOAc in hexanes as eluent afforded 4-iodo-1-(3-(methoxymethyl)bicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (**4**, 8.2 g, 27.1 mmol, 59% yield over two steps) as a white solid. ¹H NMR (600 MHz, CDCl₃): δ 7.49 (s, 1H), 7.44 (s, 1H), 3.54 (s, 2H), 3.35 (s, 3H), 2.19 (s, 6H). ¹³C{¹H} NMR (151 MHz, CDCl₃): 144.9, 132.0, 71.1, 59.2, 56.3, 52.4, 51.6, 34.4. HRMS [M+H]⁺: calculated 305.0151, found 305.0162.

IV. Preparation of **6**

BCP Hydrazine **5** is commercially available in bulk quantities and can be synthesized through in situ generation of [1.1.1]propellane, followed by Bunker hydrohydrazination⁶ as follows.



Step 1: [1.1.1]propellane.⁷ To a 5 L round-bottomed flask with a stir bar was added 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (100 g, 337 mmol, 1.0 eq.) and pentane (200 mL) under a N₂

atmosphere. Then, MeLi (1.6 M in Et₂O, 505 mL, 809 mmol, 2.4 eq.) was added dropwise at -50 °C for 2.5 h. Upon MeLi addition, the resulting mixture was warmed to 0 °C and stirred at this temperature for 3 h. GC/MS analysis showed full conversion of the starting material. The mixture was warmed to 23 °C and distilled using a water pump at 23 °C followed by distillation with an oil pump at 60 °C. The title compound (22 g, 333 mmol) was obtained as solution in Et₂O/pentane. The solution was used directly in the following step. **Note:** [1.1.1]propellane is highly volatile and the yield is lower and less reproducible at smaller reaction scales (i.e. 10 g).

Step 2: di-*tert*-butyl 1-(bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate.⁶ To a 5 L three-necked round-bottomed flask was added Mn(dpm)₃ (10.1 g, 16.6 mmol, 5 mol%) and ⁱPrOH (1650 mL) at 23 °C and the resulting mixture was cooled to 0 °C. Then, PhSiH₃ (41 mL, 333 mmol, 1.0 eq.) and di-*tert*-butyl azodicarboxylate (DBAD, 115 g, 499 mmol) in anhydrous DCM (1650 mL) were added at 0 °C during 15 min. Next, the [1.1.1]propellane (22 g, 333 mmol) solution in Et₂O/pentane prepared in step 1 was added at 0 °C. The mixture was stirred at 0 °C for 21 h. GC/MS analysis showed full conversion of the starting material and formation of the desired product. The reaction mixture was quenched by adding a saturated, aqueous solution of brine (500 mL) and the organic layer was extracted with EtOAc (500 mL x 3). The organic layers were combined and concentrated under reduced pressure to give the crude product, which was purified by column chromatography on silica gel with 0-5% EtOAc in petroleum ether as eluent to give the title compound (35.6 g, 0.12 mmol, 35% yield over two steps) as a white solid. Signal broadening and additional splitting was observed due to the presence of amide rotamers. **¹H NMR (600 MHz, CDCl₃):** δ: 6.29 (s, 0.65 H), 6.02 (s, 0.35 H), 2.38 (s, 1H), 2.03 (s, 6H), 1.46 (s, 18H). **¹³C{¹H} NMR (151 MHz, CDCl₃):** 81.1, 54.6, 52.6, 28.4, 28.3, 23.0 (carbonyl signal not detected). Spectroscopic data match those previously reported in the literature.^{Error! Bookmark not defined.}

Step 3: bicyclo[1.1.1]pentan-1-ylhydrazine, HCl salt (5). To a 500 mL round-bottomed flask with a stir bar was added di-*tert*-butyl 1-(bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate (35.6 g, 119 mmol, 1.0 eq.) and the flask was evacuated/refilled with N₂. Then, HCl (4M in EtOAc, 356 mL) was added to the mixture at 25 °C under N₂. The resulting mixture was stirred at 25 °C for 16 h and during this time a solid precipitate was formed. TLC analysis showed full conversion of the starting material. The suspension was filtered through a fritted glass filter and the filtered solid was washed with EtOAc (50 mL x 2) under N₂ protection and dried under high vacuum at 40 °C. The title product (14 g, 82 mmol, 69% yield) was obtained as a white solid. **¹H NMR (600 MHz, DMSO-*d*₆):** δ 2.44 (s, 1H), 1.82 (s, 6H). **¹³C{¹H} NMR (101 MHz, DMSO-*d*₆):** 54.8, 50.2, 22.3. Spectroscopic data match those previously reported in the literature.^{Error! Bookmark not defined.} **Note:** filtration was carried out under N₂ as the product is hygroscopic.

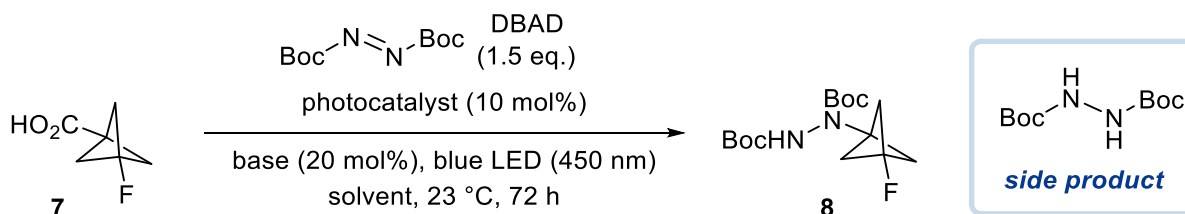
Step 4: 1-(bicyclo[1.1.1]pentan-1-yl)-1H-pyrazole. Four reactions were carried out in parallel. Bicyclo[1.1.1]pentan-1-ylhydrazine, HCl salt (20 g, 117 mmol, 1.0 eq.), 1,1,3,3-tetramethoxypropane (19 mL, 117 mmol, 1.0 eq.) and EtOH (140 mL) were added to a 250 mL round-bottomed flask containing a stir bar. Then, concentrated HCl (37% wt., 36.9 g, 374 mmol, 3.2 eq.) was added to the suspension and a color change from white to yellow was immediately observed. A reflux condenser was attached to the flask and the reaction mixture was stirred at 80 °C for 16 h. During this time the reaction mixture turned brown. GC/MS analysis showed full conversion of the starting material. The four reaction mixtures were combined and H₂O (500 mL) was added to the resulting mixture. The organic phase was extracted with DCM (200 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum (30 mmHg, 30 °C) providing a light yellow solid (crude, 60 g) that was directly used in the next step. **Note:** 1-(bicyclo[1.1.1]pentan-1-yl)-1H-pyrazole is volatile and concentration should be carried out under specified pressure and temperature.

Step 5: 1-(bicyclo[1.1.1]pentan-1-yl)-4-iodo-1H-pyrazole (6). Four reactions were carried out in parallel. In a 500 mL round-bottomed flask with a stir bar, 1-(bicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (crude, 15.3 g, 114 mmol, 1.0 eq.) and NIS (25.6 g, 114 mmol, 1.0 eq.) were dissolved in acetic acid (381 mL). The reaction mixture was then stirred at 80 °C for 2 h. During this time, the reaction mixture turned from a light yellow to a brown solution. LC/MS analysis showed that the reaction was completed. The four reaction mixtures were combined and concentrated under vacuum. The residue was diluted with H₂O (300 mL) and extracted with DCM 300 mL x 3). The combined organic layers were washed with aqueous Na₂S₂O₃ (300 mL x 3), dried over Na₂SO₄, filtered and concentrated under vacuum. The resulting residue was purified by silica gel chromatography with 0-15% EtOAc in petroleum ether as eluent providing **6** (105 g, 396 mol, 85% yield over two steps) as a light yellow solid. **¹H NMR (600 MHz, CDCl₃):** δ 7.51 (s, 1H), 7.45 (s, 1H), 2.60 (s, 1H), 2.27 (s, 6H). **¹³C{¹H} NMR (101 MHz, DMSO-*d*6):** 144.8, 131.9, 56.2, 53.7, 52.8, 22.8. **HRMS [M+H]⁺:** calculated 260.9888, found 260.9893. **Note 1:** isolated yield was calculated as the media of the four reactions run in parallel. **Note 2:** scale-up of steps 4 and 5 with commercial bicyclo[1.1.1]pentan-1-ylhydrazine (345 g, 2.02 mol) afforded **6** (300 g, 1.12 mol, 55% yield over two steps).

V. Preparation of 11

V.A. Decarboxylative hydrazination

Table S2. Optimization of photodecarboxylative hydrazination (selected reactions).⁸



Entry	mmol SM	Solvent	Photocatalyst	Base	GC 7/8 ratio ^a
1	0.38	MeCN (23 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	AY: 5-30B ^{b,c}
2	0.38	MeCN (23 V)	CeCl ₃	Cs ₂ CO ₃	15:2
3	0.38	MeCN (23 V)	CeCl ₃ ·7H ₂ O	DBU	1:1
4	0.38	MeCN/DMA (11.5 V/11.5 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	4:1
5	0.38	MeCN/DMSO (11.5 V/11.5 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	1:1
6	0.38	MeCN/Dioxane (11.5 V/11.5 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	12:1
7	0.3	MeCN (31.5 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	11:5
8	0.3	MeCN (31.5 V)	CeCl ₃ ·7H ₂ O	BTMG	20:11; AY: 11% ^b
9	2 or 4	MeCN (30 V)	CeCl ₃ ·7H ₂ O	Cs ₂ CO ₃	AY: 10-40% ^{b,c}
10	2	MeCN (30 V)	CeCl ₃ ·7H ₂ O	BTMG	15:1, AY: 0.8% ^b

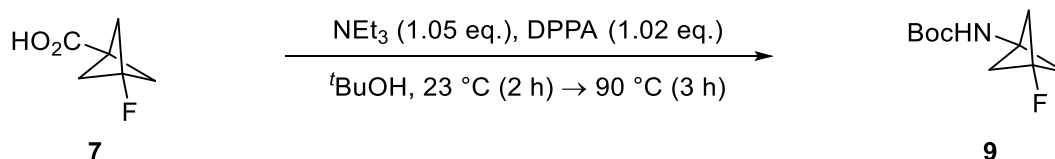
^aNormalized ratio of absorbances of **7** and **8**. ^bAssay yield calculated by GC analysis. ^cAverage of 5 independent reactions.

General procedure for decarboxylative hydrazination of 7 (entry 9 as reference). To a scintillation vial with a stir bar was added **7** (260 mg, 2 mmol, 1.0 eq.), di-*tert*-butyl azodicarboxylate (DBAD, 691 mg, 3 mmol, 1.5 eq.), CeCl₃·7H₂O (grinded to a fine powder in a mortar, 75 mg, 0.2 mmol, 10 mol%), Cs₂CO₃ (130 mg, 0.4 mmol, 20 mol%) and MeCN (30 V). The vial was capped with a Teflon septum and N₂ was bubbled through the resulting solution with a needle for 15 min. Then, the mixture was stirred in an integrated Merck photoreactor (450 nm,

100% LED, stir: 2000 rpm, fan: 6800 rpm)⁴ for 72 h. Ratios of absorbances of **7** and **8** and assay yields were determined by GC analysis of the reaction crude. The reaction crude was then quenched with a saturated solution of NaHCO₃ (10 mL) and the organic phase was extracted with EtOAc (20 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum. Purification of the crude residue by silica gel chromatography with 0–50% EtOAc in hexanes as eluent provided **8** (165 mg, 0.52 mmol, 26% yield) as a white solid. Signal broadening and additional splitting was observed due to the presence of amide rotamers. **¹H NMR (600 MHz, CDCl₃):** δ 6.70 – 6.06 (m, 1 H), 2.36 (s, 6 H), 1.46 (s, 18 H). **Note 1:** running the reaction at the specified stir rate and fan speed was crucial for product formation. **Note 2:** batch-to-batch inconsistencies were observed (entry 1 & 9). **Note 3:** conditions shown in Table S2 were inspired by a literature report.⁸ Other conditions inspired by related photocatalyzed processes were also employed but only trace amounts of product **8** were detected.⁹

V.B. N-amination of BCP amine

Synthesis of **9**¹⁰

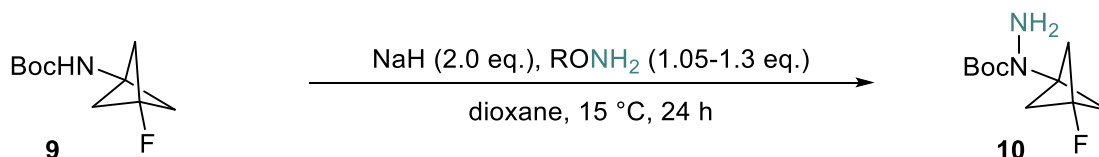


To a 100 mL round-bottomed flask with a stir bar was added **7** (2.50 g, 19.2 mmol, 1.0 eq.). The flask was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Anhydrous ^tBuOH (25 mL) and anhydrous triethylamine (2.04 g, 20.0 mmol, 1.05 eq.) were then added at 23 °C under a positive pressure of N₂. Diphenyl phosphoryl azide (DPPA, 4.47 mL, 19.6 mmol, 1.02 eq.) was added dropwise to the mixture via syringe during 20 min. The resulting reaction mixture was stirred at 23 °C for 2 h and then at 90 °C for 3 h. GC/MS analysis showed full consumption of **7**. The reaction mixture was concentrated under vacuum and the crude residue was diluted with

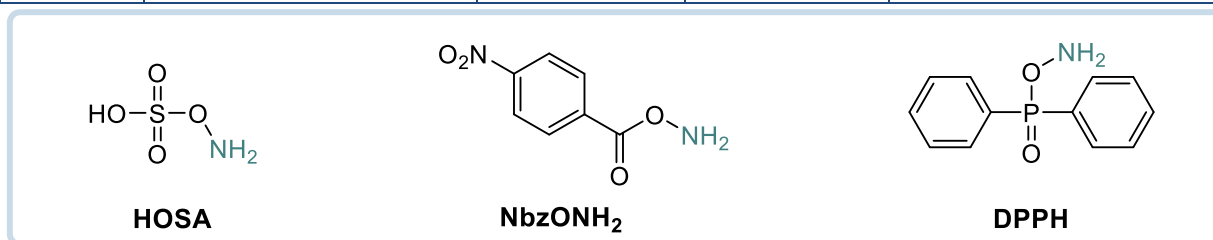
MTBE (25 mL) and washed with a saturated aqueous solution of NaHCO₃ (15 mL x 3). The organic layer was dried over Na₂SO₄, filtered and concentrated under vacuum. Purification of the crude residue by silica gel chromatography with 0-5% EtOAc in petroleum ether as eluent provided **9** (3.2 g, 15.9 mmol, 83% yield) as a white solid. Signal broadening and additional splitting was observed due to the presence of amide rotamers. ¹H NMR (600 MHz, CDCl₃): δ 5.01 (s, 1H), 2.30 (s, 6H), 1.43 (s, 9H). ¹³C NMR (151 MHz, CDCl₃): δ 154.9, 77.8, 75.8, 55.3 (d, *J* = 20.3 Hz), 39.9 (d, *J* = 71.5 Hz), 28.5. ¹⁹F NMR (564 MHz, CDCl₃): δ -169.1. Spectroscopic data match those previously reported in the literature.¹⁰ **Note:** reaction run with **7** (26 g, 196 mmol) under the same conditions afforded **9** (35 g, 174 mmol, 89% yield).

Optimization of N-amination of **9**

Table S3. Optimization of N-amination of **9** (selected reactions).

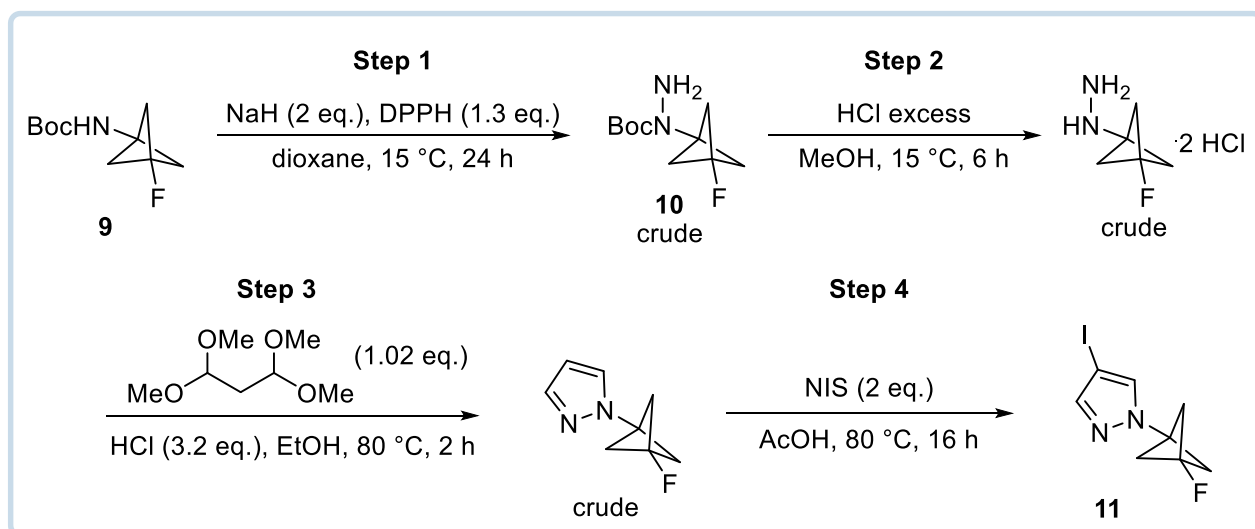


Entry	RONH ₂	NaH	Temp. (°C)	¹ H NMR 9 / 10 ratio
1	HOSA (1.05 eq.)	1.1 eq.	15	1 : 0
2	NbzONH ₂ (1.05 eq.)	1.1 eq.	15	1 : 0
3	DPPH (1.05 eq.)	1.1 eq.	15	3 : 2
4	DPPH (1.05 eq.)	2.0 eq.	40	full conversion, messy mixture
5	DPPH (1.05 eq.)	2.0 eq.	15	1 : 11
6	DPPH (1.3 eq.)	2.0 eq.	15	1 : 95



General procedure for N-amination of 9 (entry 6 as reference). To a scintillation vial with a stir bar was added **9** (50 mg, 0.25 mmol, 1.0 eq.). The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Anhydrous 1,4-dioxane (20 V) and NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol, 2.0 eq.) were then added at 15 °C under a positive pressure of N₂. The mixture was stirred at 15 °C for 1 h. Then, O-(Diphenylphosphinyl)hydroxylamine (DPPH, 76 mg, 0.325 mmol, 1.3 eq.) was added under a positive pressure of N₂ and the resulting mixture was stirred at 15 °C for 24 h. Formation of **10** was confirmed by GC/MS analysis. **9/10** Ratio was determined by ¹H NMR analysis in DMSO-*d*₆ (see NMR characterization below).

Scale-up synthesis of 11



Step 1: tert-butyl 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)hydrazine-1-carboxylate (10). A 100 mL round-bottomed flask with a stir bar and **9** (1.00 g, 4.97 mmol, 1.0 eq.) was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Then, anhydrous 1,4-dioxane (20 mL) and NaH (60% dispersion in mineral oil, 398 mg, 9.94 mmol, 2.0 eq.) were added to the flask under a positive pressure of N₂ at 15 °C and the resulting mixture was stirred for 3 h. After addition of DPPH (1.51 g, 6.46 mmol, 1.3 eq.) under a positive pressure of N₂, the mixture was stirred at

15 °C for 21 h. GC/MS analysis showed full consumption of **9**. The reaction mixture was then quenched with H₂O (10 mL) and the organic phase was extracted with EtOAc (20 mL x 3). The combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under vacuum (30 mmHg, 40 °C, 5 h). The crude was purified by silica gel chromatography with 0-15% EtOAc in petroleum ether as eluent providing **10** (912 mg, 4.22 mmol, 85% yield) as a yellow solid. **¹H NMR (400 MHz, DMSO-*d*₆):** δ 4.50 (s, 2H), 2.28 (d, *J* = 2.1 Hz, 6H), 1.41 (s, 9H). **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ -170.2. **Note:** reaction run with **9** (35 g, 174 mmol) under the same conditions afforded **10** (crude directly carried out to step 2 without chromatographic purification, 21 g, 92.5 mmol, 53% yield).

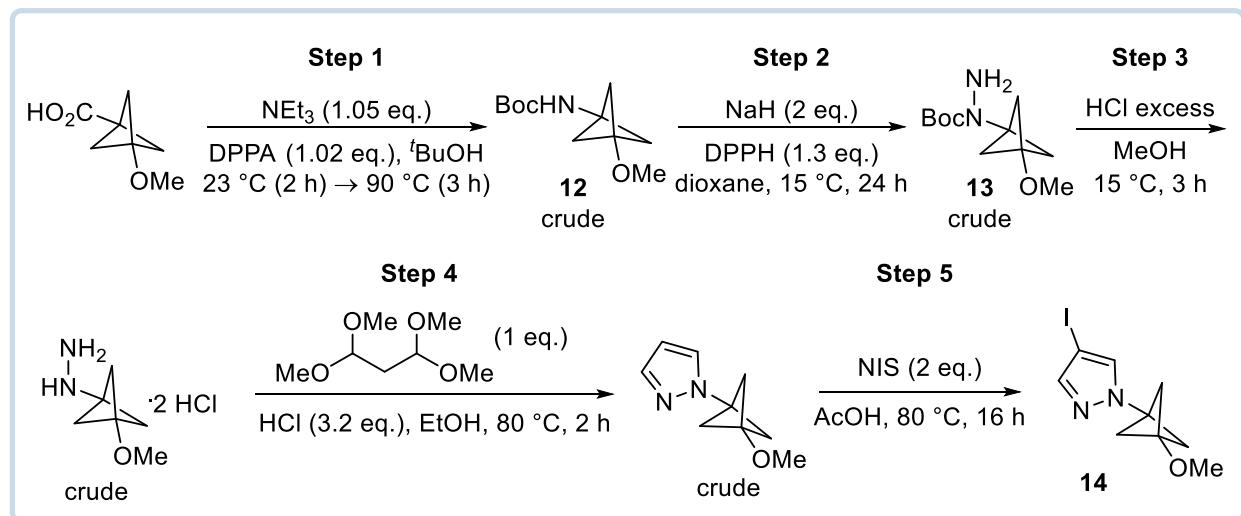
Step 2: (3-fluorobicyclo[1.1.1]pentan-1-yl)hydrazine, HCl salt. To a 50 mL round-bottomed flask was added **10** (720 mg, 3.33 mmol, 1.0 eq.) and HCl in MeOH (4 M, 14 mL, 56 eq.). The reaction mixture was stirred at 15 °C for 6 h. ¹H NMR in DMSO-*d*₆ showed full consumption of **10**. The reaction mixture was concentrated under vacuum to give the title product (crude, 500 mg, 2.64 mmol, 79% yield) as a yellow solid that was directly employed in the following step without further purification. **¹H NMR (400 MHz, DMSO-*d*₆):** δ 2.18 (d, *J* = 2.1 Hz, 6H). **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ -166.6. **Note:** reaction run with **10** (14 g, 64.8 mmol) under the same conditions afforded the title product (crude, 12 g, 63.5 mmol, 98% yield).

Step 3: 1-(3-Fluorobicyclo[1.1.1]pentan-1-yl)-1H-pyrazole. (3-Fluorobicyclo[1.1.1]pentan-1-yl)hydrazine, HCl salt (500 mg, 2.64 mmol, 1.0 eq.) and 1,1,3,3-tetramethoxypropane (448 μL, 2.70 mmol, 1.02 eq.) were added to a two-necked 50 mL round-bottomed flask. Then, EtOH (5 mL) and concentrated HCl (37% wt., 257 μL, 8.45 mmol, 3.2 eq.) were added to the suspension and one neck of the flask was attached to a reflux condenser while the other neck was capped with a Teflon septum. The reaction mixture was then stirred at 80 °C for 2 h. LC/MS analysis showed product formation. To the reaction mixture was added H₂O (5 mL) and the organic phase

was extracted with DCM (10 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum (30 mmHg, 30 °C). The title product (crude, 400 mg, 2.63 mmol, 99% yield) containing residual DCM and EtOH was obtained and used in the following step without further purification. **¹H NMR (400 MHz, DMSO-*d*₆):** 7.79 (d, *J* = 2.3 Hz, 1H), 7.52 (m, 1H), 6.31 (t, *J* = 2.0 Hz, 1H), 2.61 (d, *J* = 2.1 Hz, 6H). **¹⁹F NMR (376 MHz, DMSO-*d*₆):** δ -171.0. **Note 1:** (3-fluorobicyclo[1.1.1]pentan-1-yl)-1H-pyrazole is volatile and concentration should be carried out under specified pressure and temperature. **Note 2:** reaction run with (3-fluorobicyclo[1.1.1]pentan-1-yl)hydrazine, HCl salt (11 g, 90.4 mmol) under the same conditions afforded the title product (crude, 12 g, 78.9 mmol, 87% yield).

Step 4: 1-(3-fluorobicyclo[1.1.1]pentan-1-yl)-4-iodo-1H-pyrazole (11). In a 50 mL round-bottomed flask with a stir bar, (3-fluorobicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (400 mg, 8.87 mmol, 1.0 eq.) and NIS (2.00 g, 5.26 mmol, 2.0 eq.) were dissolved in acetic acid (10 mL). The reaction mixture was stirred at 80 °C for 16 h. During this time, the reaction mixture turned from a light yellow to a brown solution. LC/MS analysis showed that the reaction was completed. The solution was concentrated under vacuum and the resulting residue was purified by silica gel chromatography with 0-10% EtOAc in petroleum ether as eluent providing a crude yellow solid (580 mg). Then, the crude product was further purified by prep-TLC with 10:1 petroleum ether/EtOAc as eluent affording **11** (492 mg, 1.77 mmol, 67% yield) as a yellow solid. **¹H NMR (600 MHz, CDCl₃):** δ 7.54 (s, 1H), 7.43 (s, 1H), 2.61 (d, *J* = 2.0 Hz, 6H). **¹³C{¹H} NMR (151 MHz, CDCl₃):** 145.1, 133.3, 77.3, 75.1, 57.0, 56.2 (d, *J* = 21.1 Hz). **¹⁹F NMR (564 MHz, CDCl₃):** -173.5 ppm. **HRMS [M+H]⁺:** calculated 278.9794, found 278.9800. **Note:** reaction run with (3-fluorobicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (10 g, 65.7 mmol) under the same conditions afforded **11** (12 g, 43.2 mmol, 66% yield).

VI. Preparation of 14



Step 1: *tert*-butyl (3-methoxybicyclo[1.1.1]pentan-1-yl)carbamate (12). Same procedure as the one used for the synthesis of **9** (vide supra) was followed using 3-methoxybicyclo[1.1.1]pentane-1-carboxylic acid (1.00 g, 7.03 mmol, 1.0 eq.). Compound **12** (1.47 g, 6.89 mmol, 98% yield) was obtained as a pale yellow crude solid that was used in the next step after work-up/concentration without further purification. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 3.30 (s, 3H), 2.13 (s, 6H), 1.44 (s, 9H). $^{13}\text{C}\{^1\text{H}\}$ NMR (151 MHz, CDCl_3): δ 130.2, 67.3, 54.9, 53.0, 52.8, 41.8, 28.5.

Step 2: *tert*-butyl 1-(3-methoxybicyclo[1.1.1]pentan-1-yl)hydrazine-1-carboxylate (13). Same procedure as the one used for the synthesis of **10** (step 1 of scale-up synthesis of **11**, vide supra) was followed using **12** (1.05 g, 4.93 mmol, 1.0 eq.). Compound **13** (835 mg, 3.66 mmol, 74% yield) was obtained as a pale yellow crude solid that was used in the next step after work-up/concentration without further purification. Signal broadening and additional splitting was observed due to the presence of amide rotamers. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 3.30 (s, 1.57H), 3.29 (s, 1.40H), 2.15 (s, 3.58H), 2.12 (s, 2.32H), 1.47 (s, 5.45H), 1.44 (s, 3.87H).

Step 3: (3-methoxybicyclo[1.1.1]pentan-1-yl)hydrazine, HCl salt. Same procedure as the one used in step 2 of scale-up synthesis of **11** (vide supra) was followed using **13** (804 mg, 3.52 mmol, 1.0 eq.). After concentrating the reaction mixture under vacuum, the title compound was obtained as a yellow crude solid (517 mg crude) and was used in the next step without further purification.

Step 4: 1-(3-methoxybicyclo[1.1.1]pentan-1-yl)-1H-pyrazole. Same procedure as the one used in step 3 of scale-up synthesis of **11** (vide supra) was followed using (3-methoxybicyclo[1.1.1]pentan-1-yl)hydrazine, HCl salt (310 mg, crude). The title product (crude, 298 mg, 1.814 mmol, 75% yield) was obtained as a pale yellow and used in the following step without further purification. **¹H NMR (600 MHz, CDCl₃):** δ 7.57 – 7.54 (m, 1H), 7.43 – 7.34 (m, 1H), 6.34 – 6.19 (m, 1H), 3.39 (s, 3H), 2.45 (s, 6H).

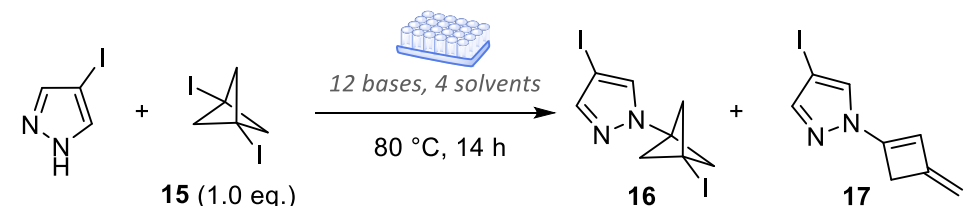
Step 5: 4-iodo-1-(3-methoxybicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (14). Same procedure as the one used in step 4 of scale-up synthesis of **11** (vide supra) was followed using 1-(3-methoxybicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (241 mg, 1.468 mmol, 1.0 eq.). Compound **14** compound (332 mg, 1.145 mmol, 78% yield) was obtained as yellow oil after purification by silica gel chromatography with 0-20% EtOAc in hexanes as eluent. **¹H NMR (600 MHz, CDCl₃):** δ 7.54 (s, 1H), 7.45 (s, 1H), 3.37 (s, 3H), 2.42 (s, 6H). **¹³C{¹H} NMR (151 MHz, CDCl₃):** δ 145.4, 133.0, 66.7, 56.5, 55.2, 53.6, 48.2. **HRMS [M+H]⁺:** calculated 290.9994, found 290.9995.

VII. Preparation of 16

VII.A. Preparation of 16 from 15

Ligand-Screening Procedure

Table S4. HTS of ligands in the synthesis of 16 from 15



Reaction scheme showing the synthesis of 16 and 17 from 4-iodo-1H-pyrazole and 1,3-diiodobicyclo[1.1.1]pentane (**15**, 1.0 eq.) using 12 bases and 4 solvents at 80 °C for 14 h.

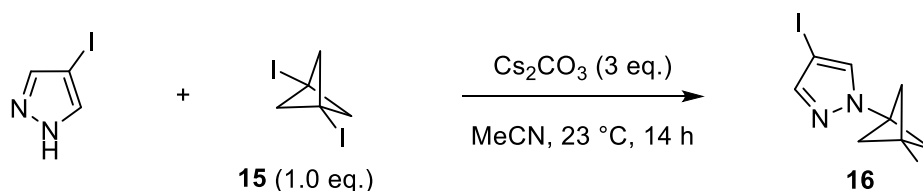
	LiCO ₃	K ₂ CO ₃	NaCO ₃	CsCO ₃	NaHCO ₃	KOAc	K ₃ PO ₄	KOH	NaOH	LiOH	LiHMDS	NaOtBu
Dioxane	0.18	0.19	0.26	0.39	0.26	0.13	0.14	0.20	0.30	0.39	0.94	0.33
EtOH	1.93	1.12	1.71	1.00	1.77	1.24	0.31	0.93	1.23	1.51	0.37	0.33
MeCN	2.01	6.05	4.40	2.49	4.34	5.73	3.68	2.35	2.70	1.75	0.31	0.23
DCE	0.03	0.17	0.94	0.33	1.07	0.69	0.49	0.59	1.16	0.00	0.93	1.35

In the glovebox, four 2-dram vials with stir bars were charged with 4-iodo-1H-pyrazole (29.1g, 150 μ mol), 1,3-diiodobicyclo[1.1.1]pentane (**15**, 48g, 150 μ mol, 1.0 eq.) and 750 μ l of one of the four solvents listed. These solutions were stirred to dissolve the reagents, then 50 μ l of the four stock solutions was added to the corresponding vials containing 30 μ mol of the corresponding base using an Eppendorf pipetter as arrayed above. The reactions were then sealed and heated at 80 °C for 14 h. After cooling to ambient temperature, the reactions were diluted with 500 μ l of a 0.002 M biphenyl in 3:1 MeCN/DMSO quench solution (this provided 0.25 μ mol biphenyl in each well). A silicon-rubber storage mat was added, and the contents were shaken to homogenize. 15 μ l of each of the diluted reaction mixtures were then added to 250 μ l of MeCN in separate wells of a 96-well analytical plate, which was sealed and analyzed on an Agilent UPLC system. Reported values correspond to the ratio of absorbances of **16+17**/biphenyl (IS).

Further screening of bases was carried out in the same manner using one stock solution in MeCN to investigate additional inorganic bases. Pertinent data is shown below.

Base	Equiv.	Conversion	16 : 17
K ₂ CO ₃	3	>95%	<1:20
KOAc	3	>95%	<1:20
TBAOAc	3	>95%	<1:20
Cs ₂ CO ₃	3	95%	1:1
Cs ₂ CO ₃	1.5	95%	1:2
none	-	88%	trace

Scale-up synthesis of 16 from 15

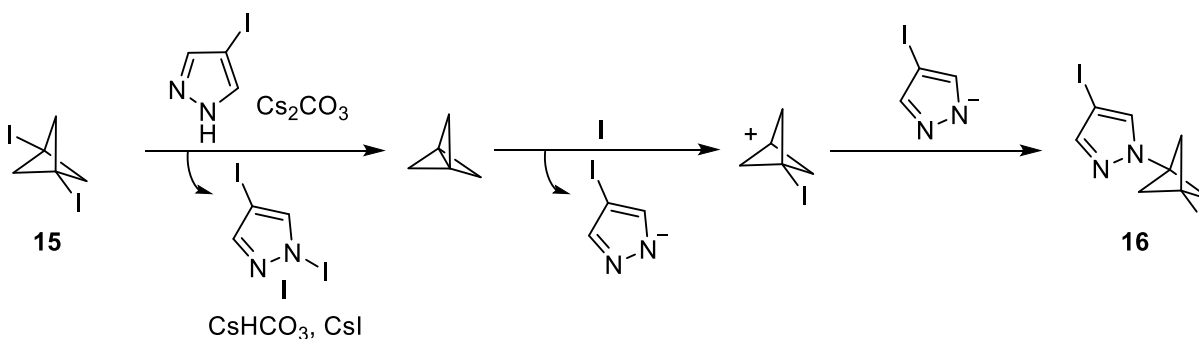


A 30 mL round-bottomed vial with a stir-bar was charged with 4-iodo-1H-pyrazole (0.61 g, 3.13 mmol), **15** (1.0 g, 3.13 mmol, 1.0 eq.) and cesium carbonate (3.06 g, 9.38 mmol, 3.0 eq.). MeCN (16 ml) was then added and the reaction was capped with a Teflon septum cap and stirred at room temperature for 14 h. The reaction mixture was then diluted with MeCN (10 mL) and filtered through a pad of Celite. The resulting solution was concentrated under vacuum. Purification of the resulting crude by silica gel chromatography with 0-40% EtOAc in hexanes as eluent afforded 4-iodo-1-(3-iodobicyclo[1.1.1]pentan-1-yl)-1H-pyrazole (**16**, 340 mg, 0.881 mmol, 28% yield) as a white solid. ¹H NMR (600 MHz, CDCl₃): δ 7.52 (s, 1 H), 7.40 (s, 1 H), 2.72 (s, 6 H). ¹³C{¹H} NMR (151 MHz, CDCl₃): 145.3, 132.1, 61.7, 56.8, 56.4, -2.1. HRMS [M+H]⁺: calculated 386.8855, found 386.8860.

Note: We were unable to cleanly isolate diene byproduct **17** from the reaction mixture. Its identity was assumed based on LC/MS analysis (observed LCMS [M+H]⁺: 259) and analogy to know reaction patterns of BCP's (see page S36).

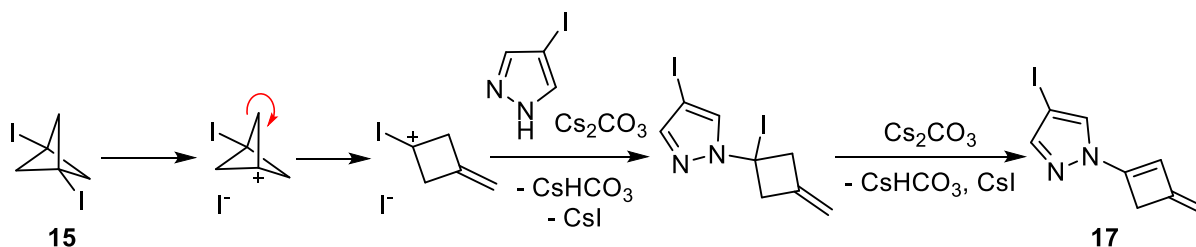
Mechanistic proposal for the formation of **16** and **17**

Based on proposed mechanisms for related monosubstitution reactions of **15**,¹¹ we hypothesized that the formation of **16** proceeds through in situ formation of [1.1.1]propellane followed by addition of the resulting N-iodopyrazole **I** across the central bond of [1.1.1]propellane (Scheme S1).



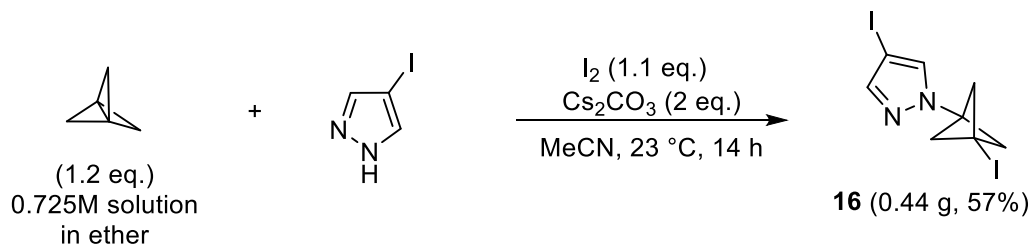
Scheme S1. Proposed mechanism for the formation of **16**.

Reaction monitoring experiments suggested that **17** is not generated via thermal or base-promoted decomposition of **16**. Instead, we hypothesized that **17** is generated from **15** via iodide abstraction followed by C3-carbocation rearrangement and subsequent β -proton abstraction (Scheme S2).^{11c,12}



Scheme S2. Proposed mechanism for the formation of **17**.

VII.B. Preparation of **16** from [1.1.1]propellane



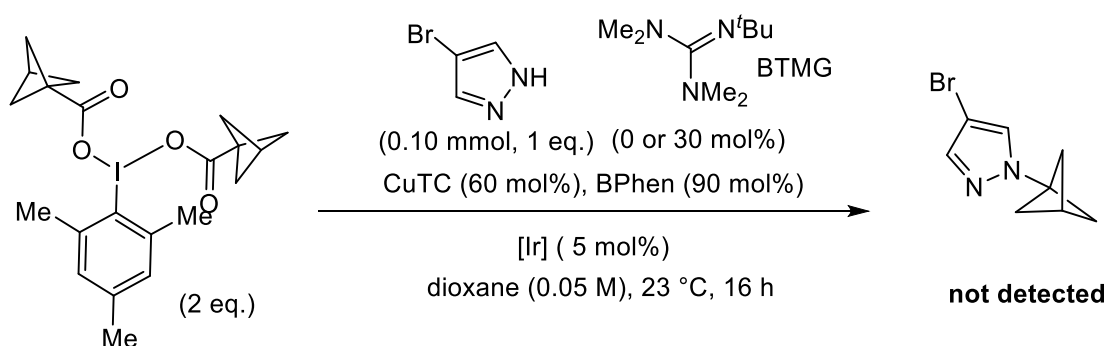
A 30 mL round-bottomed vial with a stir-bar was charged with iodine (533 mg, 2.10 mmol, 1.1 eq.), 4-iodo-1H-pyrazole (388 mg, 2.00 mmol), cesium carbonate (1.30 g, 4.00 mmol, 2.0 eq.) and MeCN (10 ml), then sealed with a Teflon septum cap and stirred at room temperature for 30 min. The vial was then charged with 3.31 ml of a solution of [1.1.1]propellane in ether (0.725 M, 2.4 mmol, 1.2 eq., prepared and titrated as reported above)^{7b}, and the reaction was stirred at room temperature for 14 h. The reaction mixture was then diluted with MeCN (10 mL) and filtered through a pad of Celite. The resulting solution was concentrated under vacuum. Purification of the resulting crude by silica gel chromatography with 0-40% EtOAc in hexanes as eluent afforded **16** (440 mg, 1.14 mmol, 57% yield) as a white solid. Spectroscopic data is in accordance with the material prepared from **15** (vide supra).

VIII. Unsuccessful synthetic approaches

VIII.A. Decarboxylative C–N coupling attempts

Synthesis of BCP idonium carboxylate reagents was carried out following a literature report.⁵ General method for decarboxylative C–N coupling described in section II.A. was followed with the deviations depicted in Tables S5-S7. Different conditions employed in the absence or presence of light, photocatalyst, base and/or ligand were inspired by conditions reported by the MacMillan group.¹³

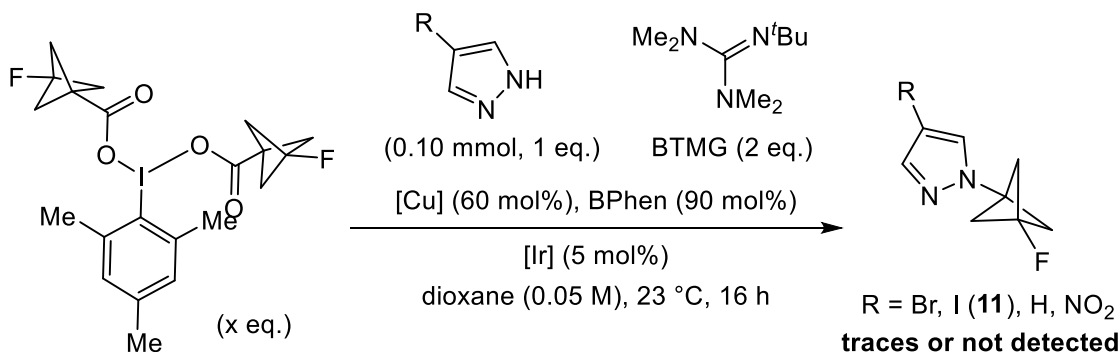
Table S5. Attempted synthesis of methyl 3-(4-bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate via decarboxylative C1–N coupling.



Entry	Pyrazole (mmol)	[Ir]	BTMG (mol%)	LED	product LC/MS
1	0.20	X	X	X	no
2	0.34	Ir-1	30	√ ^a	no
3	0.10	Ir-2	X	√ ^a	no
4 ^b	0.10	X	X	X	no

Ir-1: Ir(F-Meppy)₂(dtbbpy)PF₆; **Ir-2:** Ir(ppy)₃. ^aAn integrated Merck photoreactor (450 nm, 100% LED, stir: 2000 rpm, fan: 6800 rpm) was used. ^bIodonium carboxylate (2.3 eq.).

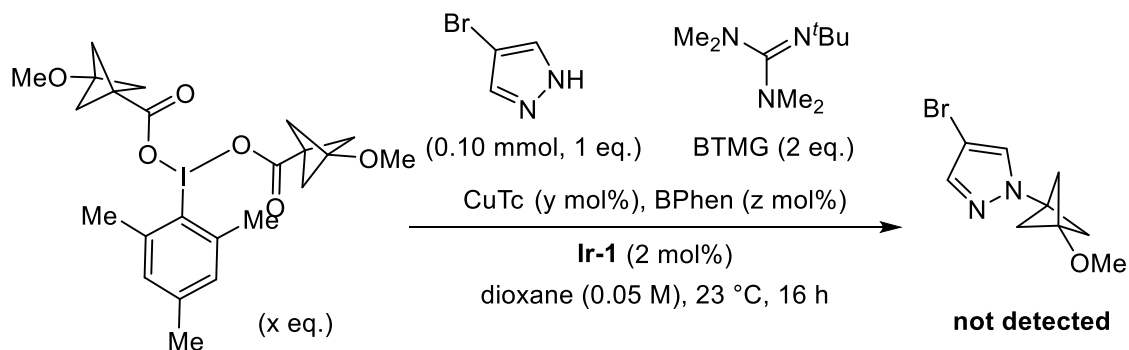
Table S6. Attempted synthesis of C3-fluoro BCPP via decarboxylative C1–N coupling.



Entry	R	x (eq.)	[Ir]	BTMG	[Cu]	BPhen	LED	Product LC/MS
1	Br	1.0	Ir-2	X	Cu(acac) ₂	X	√ ^a	no
2	Br	1.0	Ir-2	✓	Cu(acac) ₂		√ ^a	traces
3	Br	1.0	Ir-2	X	Cu(acac) ₂		√ ^a	no
4	Br	1.0	Ir-2	✓	Cu(acac) ₂		√ ^a	no
5	Br	2.3	X	X	CuTc	✓	X	traces
6	NO ₂	2.0	Ir-1	X	Cu(acac) ₂	X	✓	no
7	H	2.0	Ir-1	X	Cu(acac) ₂	X	✓	3% ^{b,c,d,e}
8	I	2.0	Ir-1	X	Cu(acac) ₂	X	✓	traces
9	I	2.3	X	X	CuTc	✓	X	traces

Ir-1: Ir(F-Meppy)₂(dtbbpy)PF₆; **Ir-2:** Ir(ppy)₃. ^a34 W Kessil blue LED lamps (3 cm away, with cooling fan to keep the reaction at room temperature). ^bAn integrated Merck photoreactor (450 nm, 100% LED, stir: 2000 rpm, fan: 6800 rpm) was used. ^c9% conversion of 1H-pyrazole. ^dUncorrected LC/MS yield and conversion calculated using biphenyl as internal standard. ^eNo significant increase in product formation was observed after stirring the reaction mixture at 23 °C for 16 h and, then, at 40 °C for 24 h.

Table S7. Attempted synthesis of 4-bromo-1-(3-methoxybicyclo[1.1.1]pentan-1-yl)-1H-pyrazole via decarboxylative C1–N coupling.

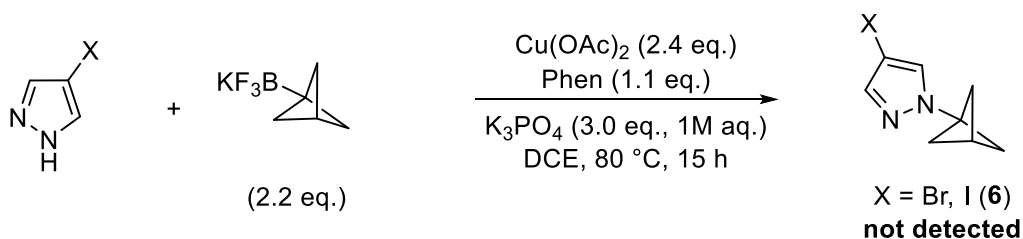


Entry	x (eq.)	[Ir]	BTMG	y (mol%)	z (mol%)	LED	18 LC/MS
1	1.0	Ir-1	✓	20	30	✓ ^a	no
2	2.3	X	X	60	90	X	no

Ir-1: Ir(F-Meppy)₂(dtbbpy)PF₆. ^aAn integrated Merck photoreactor (450 nm, 100% LED, stir: 2000 rpm, fan: 6800 rpm) was used.

VIII.B. Chan-Lam C1–N coupling attempts

Potassium bicyclo[1.1.1]pentan-1-yltrifluoroborate was synthesized according to a literature report.¹ Photodecarboxylative borylation to access C3-fluoro boryl reagents failed under reported conditions.¹

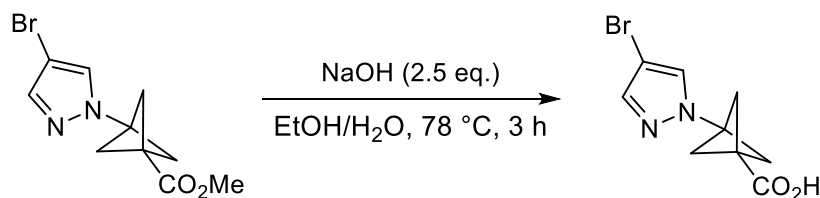


General method for Chan-Lam coupling described in section II.B. was followed using 4-iodo-1H-pyrazole (30 mg, 0.15 mmol, 1.0 eq.) or 4-bromo-1H-pyrazole (23 mg, 0.15 mmol, 1.0 eq.) and potassium bicyclo[1.1.1]pentan-1-yltrifluoroborate (54 mg, 0.31 mmol, 2.0 eq.). No product formation was observed by LC/MS analysis of both reactions.

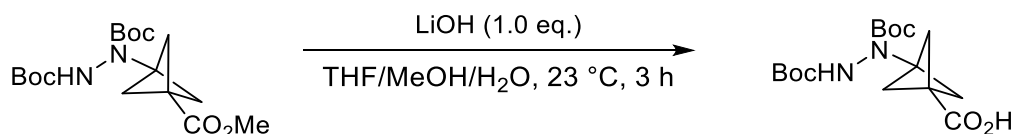
VIII.C. C3-Functionalization attempts

Attempted fluorodecarboxylation on pyrazole or hydrazine BCP-CO₂H

Synthesis of BCP carboxylic acids



A 100 mL round-bottomed flask with a stir bar was charged with methyl 3-(4-bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylate (825 mg, 3.04 mmol, 1.0 eq.) and EtOH (30 mL). After the addition of an aqueous solution of NaOH (2.5 M, 3.04 mL, 7.61 mmol, 2.5 eq.), the flask was connected to a reflux condenser. The reaction mixture was stirred at 78 °C for 3 h and then allowed to cool to ambient temperature. The volatiles were then removed under vacuum and the resulting yellow pale solid was dissolved in water (50 mL). The mixture was acidified with HCl (1 N) to pH = 7 and formation of a white solid was observed. Water (100 mL) was added and the organic layer was extracted with DCM (100 mL x 3), dried over Na₂SO₄, filtered, and concentrated under vacuum. 3-(4-Bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (594 mg, 2.311 mmol, 76 % yield) was obtained as a white solid. ¹H NMR (600 MHz, DMSO-*d*₆): δ 8.12 (s, 1H), 7.60 (s, 1H), 2.43 (s, 6H). ¹³C{¹H} NMR (151 MHz, CDCl₃): 170.2, 139.9, 129.0, 92.5, 53.7, 50.6, 33.6.

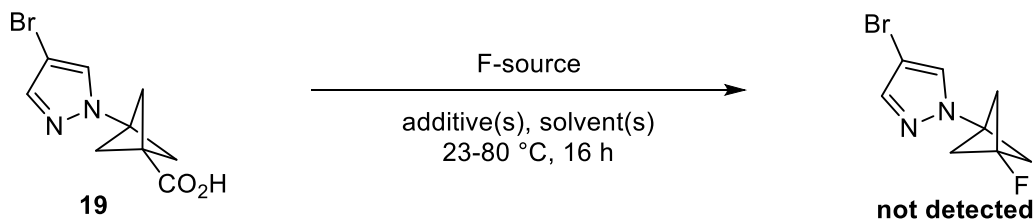


Di-*tert*-butyl 1-(3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-dicarboxylate was synthesized following a literature procedure.¹⁴ A 50 mL round-bottomed flask with a stir bar was charged with di-*tert*-butyl 1-(3-(methoxycarbonyl)bicyclo[1.1.1]pentan-1-yl)hydrazine-1,2-

dicarboxylate (400 mg, 1.12 mmol, 1.0 eq.), LiOH (47 mg, 1.12 mmol, 1.0 eq.), MeOH (3 mL), THF (3 mL) and H₂O (3 mL). The reaction mixture was stirred at 23°C for 16 h and then the resulting mixture was acidified with HCl (1 N) to pH = 7. The organic layer was extracted with ethyl acetate (20 mL x 2) and the combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 3-(1,2-bis(*tert*-butoxycarbonyl)hydrazineyl)bicyclo[1.1.1]pentane-1-carboxylic acid (354 mg, 1.03 mmol, 92 % yield) as a white solid. Signal broadening and additional splitting was observed due to the presence of amide rotamers. **¹H NMR (600 MHz, DMSO-*d*₆):** δ 12.44 (s, 1H), 9.05 – 8.58 (m, 1H), 2.14 (s, 2H), 2.11 (s, 4H), 1.43 – 1.38 (m, 18H). **¹³C{¹H} NMR (151 MHz, DMSO-*d*₆):** 170.8, 155.2, 153.9, 79.4, 79.3, 66.4, 28.0, 27.9, 27.8.

Fluorodecarboxylation attempts

Table S8. Selected fluorodecarboxylation attempts of 3-(4-Bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylic acid.



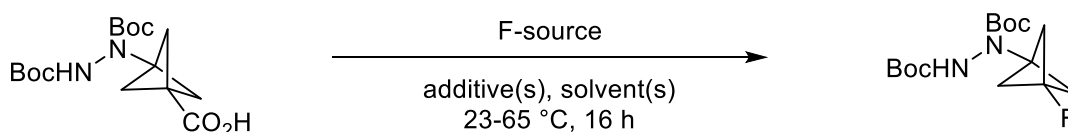
Entry	F-source	Additive(s)	Solvent(s) ^a	M (mol/L)	T (°C)
1	Selectfluor (2.5 eq.)	AgNO ₃ (7.5 mol%)	H ₂ O	0.2	65
2	Selectfluor (1.8 eq.)	AgNO ₃ (20 mol%)	H ₂ O	0.2	80
3	Selectfluor (2.0 eq.)	AgNO ₃ (30 mol%)	Acetone/ H ₂ O 1:1	0.1	80
4	Selectfluor (2.0 eq.)	AgNO ₃ (30 mol%) +Na ₂ S ₂ O ₈ (0.5 eq.)	Acetone/ H ₂ O 1:1	0.1	80
5	Selectfluor (4.0 eq.)	AgNO ₃ (30 mol%)	Acetone/ H ₂ O 1:1	0.1	70
6	Selectfluor (4.0 eq.)	AgNO ₃ (30 mol%)	3-Pentanone/ H ₂ O 1:1	0.1	100
7	XeF ₂ (4.0 eq.)	X	DCE	0.1	23
8 ^b	Selectfluor (3.0 eq.)	Ir-3 (1 mol%) ^c +Na ₂ HPO ₄ (2.0 eq.)	MeCN/ H ₂ O 1:1	0.1	23

^aSolvents were degassed by sparging with N₂. ^bAn integrated Merck photoreactor (450 nm, 100% LED, stir: 2000 rpm, fan: 6800 rpm) was used. ^cIr-3: (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆.

General procedure. To a scintillation vial with a stir bar was added 3-(4-Bromo-1H-pyrazol-1-yl)bicyclo[1.1.1]pentane-1-carboxylic acid (20 mg, 0.078 mmol, 1.0 eq.), F-source and additive(s). The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Degassed solvent(s) was then added via syringe under a positive pressure of N₂. The resulting mixture was stirred at the corresponding temperature for 16 h. An aliquot of the reaction crude was analyzed by LC/MS. For all entries in Table S8, unreacted starting material was detected and

either none or traces of desired fluorinated product were detected. **Note 1:** conditions shown in Table S8 were inspired by a literature report.¹⁵ **Note 2:** conditions employed in entry 1 proved to be effective for the decarboxylative fluorination of bicyclo[1.1.1]pentane-1,3dicarboxylic acid.^{15a}

Table S9. Selected fluorodecarboxylation attempts of 3-(1,2-bis(*tert*-butoxycarbonyl)hydrazineyl)bicyclo[1.1.1]pentane-1-carboxylic acid.



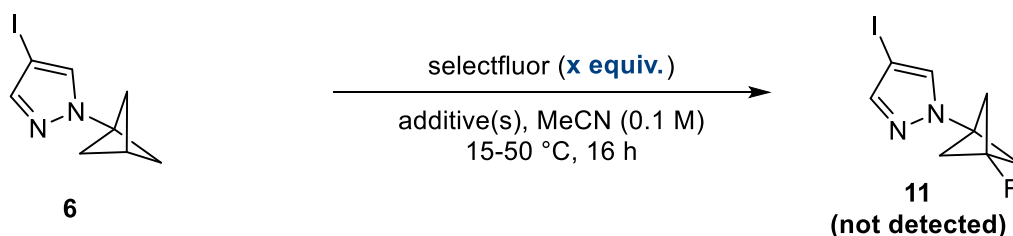
Entry	F-source	Additive(s)	Solvent(s) ^a	M (mol/L)	T (°C)
1	Selectfluor (2.5 eq.)	AgNO ₃ (1.0 eq.)	H ₂ O	0.2	65
2 ^b	Selectfluor (3.0 eq.)	Ir-3 (1 mol%) ^c +Na ₂ HPO ₄ (2.0 eq.)	MeCN/ H ₂ O 1:1	0.1	23
3 ^b	Selectfluor (6.0 eq.)	Ir-3 (1 mol%) ^c +Na ₂ HPO ₄ (4.0 eq.)	MeCN/ H ₂ O 1:1	0.1	23

^aSolvents were degassed by sparging with N₂. ^bAn integrated Merck photoreactor (450 nm, 100% LED, stir: 2000 rpm, fan: 6800 rpm) was used. ^cIr-3: (Ir[dF(CF₃)ppy]₂(dtbpy))PF₆.

General procedure. To a scintillation vial with a stir bar was added 3-(1,2-bis(*tert*-butoxycarbonyl)hydrazineyl)bicyclo[1.1.1]pentane-1-carboxylic acid (50 mg, 0.15 mmol, 1.0 eq.), F-source and additive(s). The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Degassed solvent(s) was then added via syringe under a positive pressure of N₂. The resulting mixture was stirred at the corresponding temperature for 16 h. An aliquot of the reaction crude was analyzed by LC/MS. For all entries in Table S9, unreacted starting material was detected and either none or traces of desired fluorinated product were detected.

Attempted fluorodehydrogenation on 6

Table S10. Selected fluorodehydrogenation attempts of **6**.



Entry	x equiv.	Additive	Solvent(s) ^a	T (°C)
1	3	BEt ₃ (40 mol%)	MeCN	50
2	3	V ₂ O ₃ (20 mol%)	MeCN	15
3	2.5	NDHPI (2.5 mol%)	MeCN	50

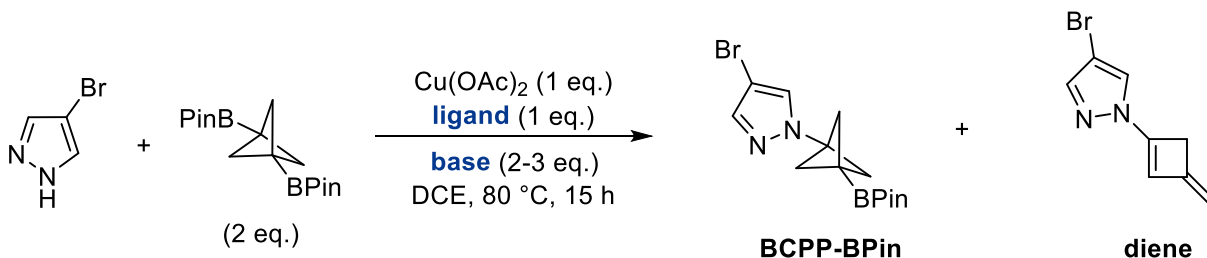
NDHPI = N-hydroxyphthalimide.

General procedure. To a scintillation vial with a stir bar was added **6** (40 mg, 0.15 mmol, 1.0 eq.), F-source and additive. The vial was capped with a Teflon septum and submitted to three vacuum/N₂ refill cycles. Degassed MeCN (1.5 mL) was then added via syringe under a positive pressure of N₂. The resulting mixture was stirred at the corresponding temperature for 16 h. An aliquot of the reaction crude was analyzed by LC/MS. For all entries in Table S10, remained starting material was detected and either none or traces of **11** were detected. **Note 1:** conditions shown in Table S10 were inspired by a literature report.¹⁶

VIII.D. Attempted synthesis of BCP pyrazole intermediates

Attempted synthesis of BCP–boryl intermediate

Table S11. Attempted synthesis of BCP–boryl intermediate via Chan-Lam coupling.



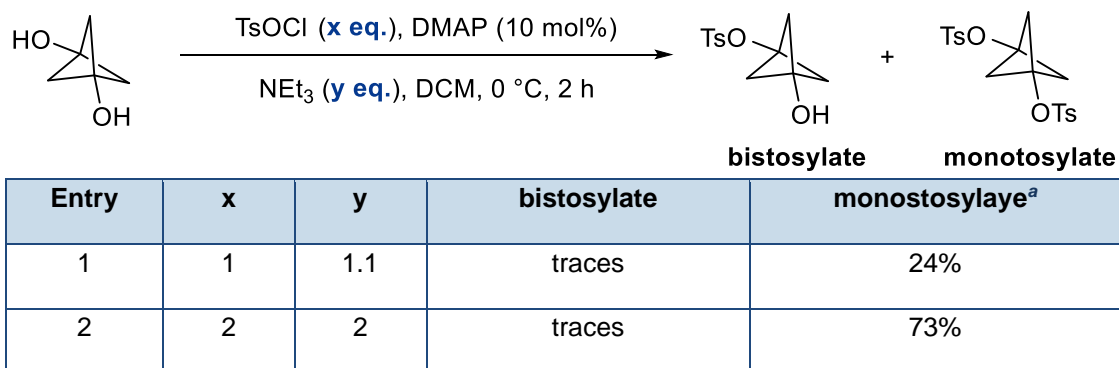
Entry	ligand	base	BCPP-BPin	diene
1		K_3PO_4 aq. (1 M, 3 eq.)	X	major product
2		Na_2CO_3 (2 eq.)	X	major product

General method for Chan-Lam coupling described in section II.B. was followed for entry 1. Entry 2 was carried out as follows.¹⁷ To a 5 mL scintillation vial containing a stir bar, $\text{Cu}(\text{OAc})_2$ (45 mg, 0.25 mmol, 1.0 eq.), 2,2'-bipyridine (39 mg, 0.25 mmol, 1.0 eq.), Na_2CO_3 (53 mg, 0.50 mmol, 2.0 eq.), 1,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)bicyclo[1.1.1]pentane (160 mg, 0.50 mmol, 2.0 eq.) and 4-bromo-1H-pyrazole (37 mg, 0.25 mmol, 1.0 eq.) were added. The vial was capped with a Teflon septum and submitted to three vacuum/ N_2 refill cycles. Anhydrous 1,2-dichloroethane (2.5 mL) was added via syringe under a positive pressure of N_2 . The resulting mixture was stirred at 80 °C for 15 h. The reaction mixture was analyzed by LC/MS. No desired BCPP–BPin product was detected and diene product was detected instead as the major product. The crude mixture was directly purified by silica gel chromatography with 0-70% EtOAc in hexanes as eluent affording 4-bromo-1-(3-methylenecyclobut-1-en-1-yl)-1H-pyrazole (**diene**) as

a white solid. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 7.67 (s, 1H), 7.64 (s, 1H), 6.00 (s, 1H), 4.85 (s, 1H), 4.67 (s, 1H), 3.36 (s, 2H).

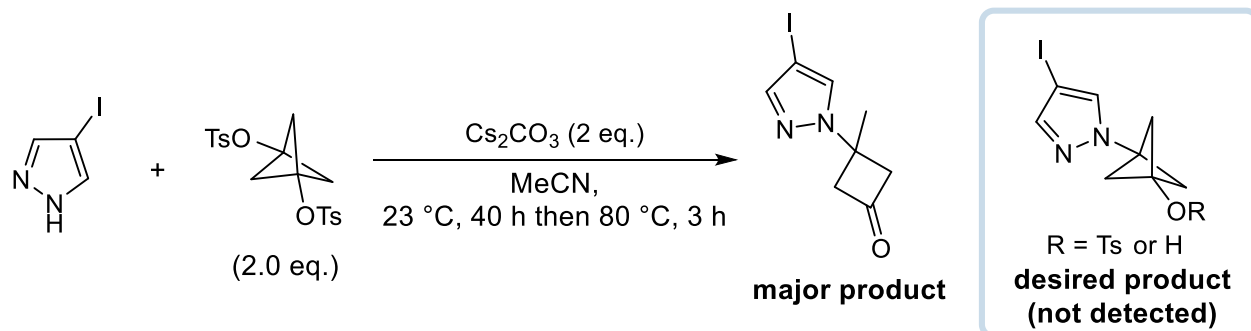
Attempted synthesis of BCP–tosylate intermediate

Table S12. Attempted synthesis of BCP–OTs intermediate



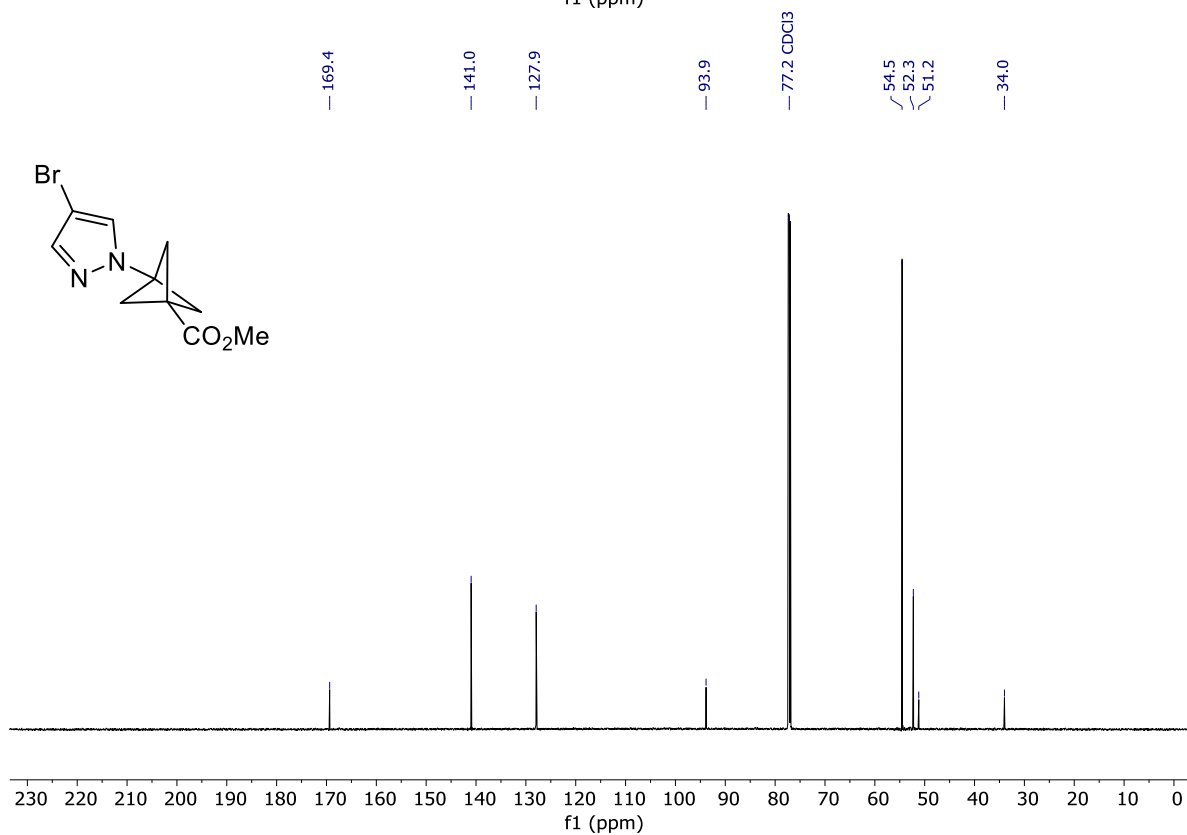
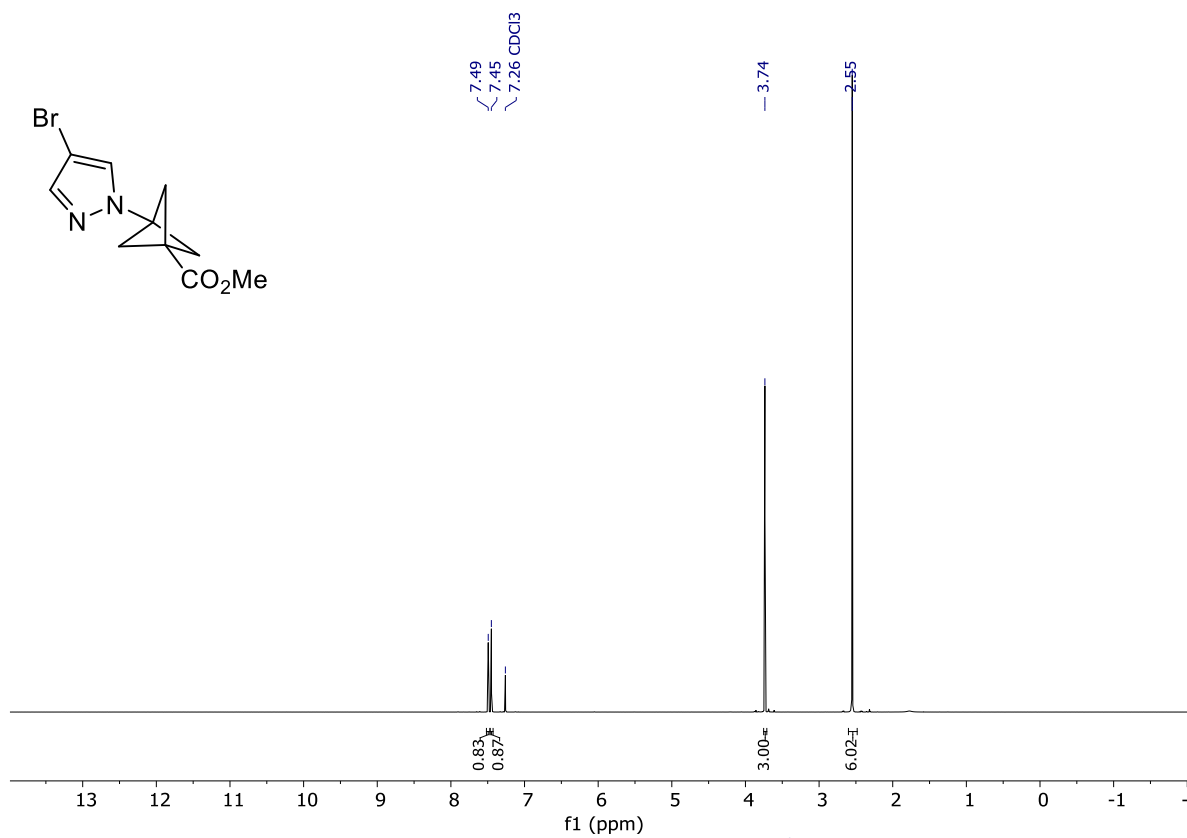
^aIsolated yield.

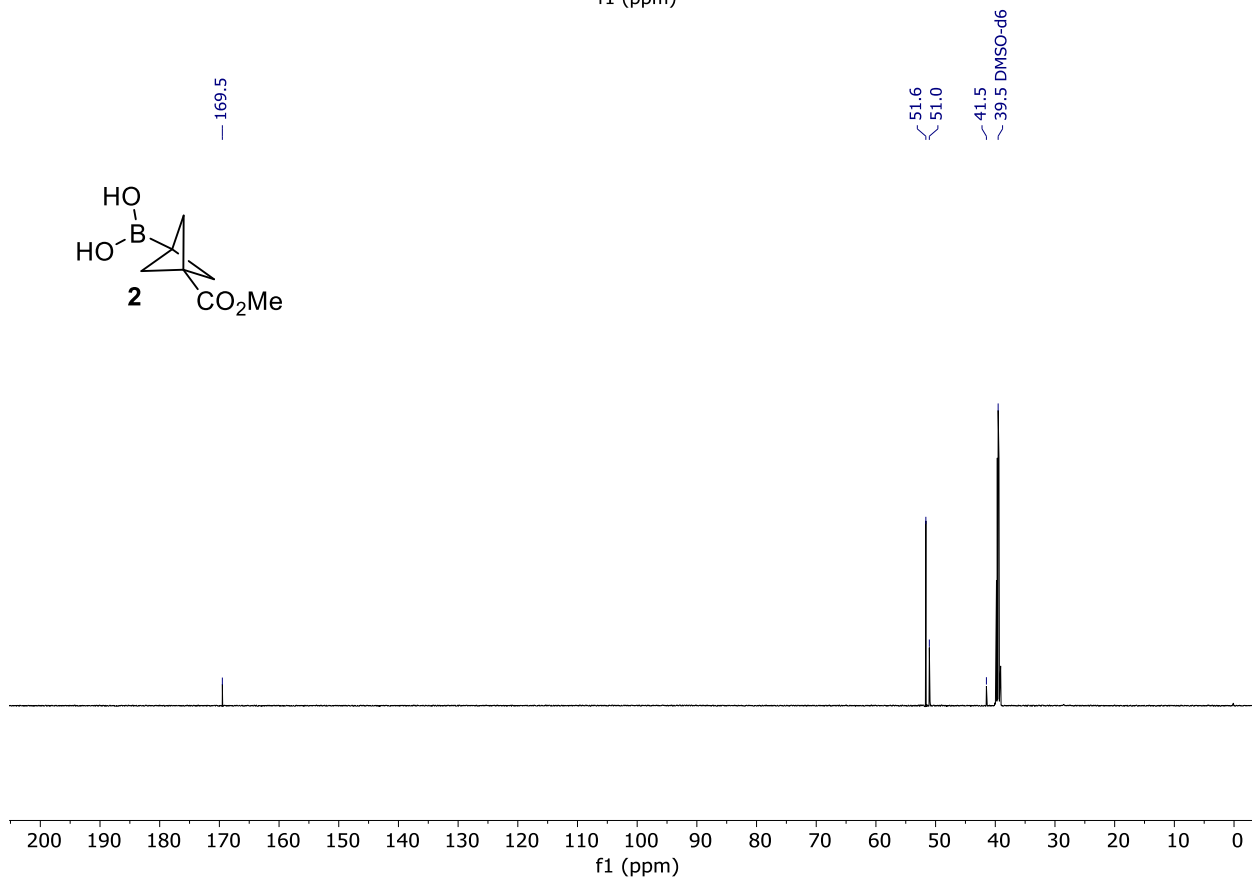
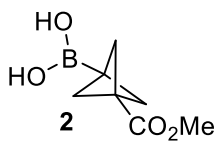
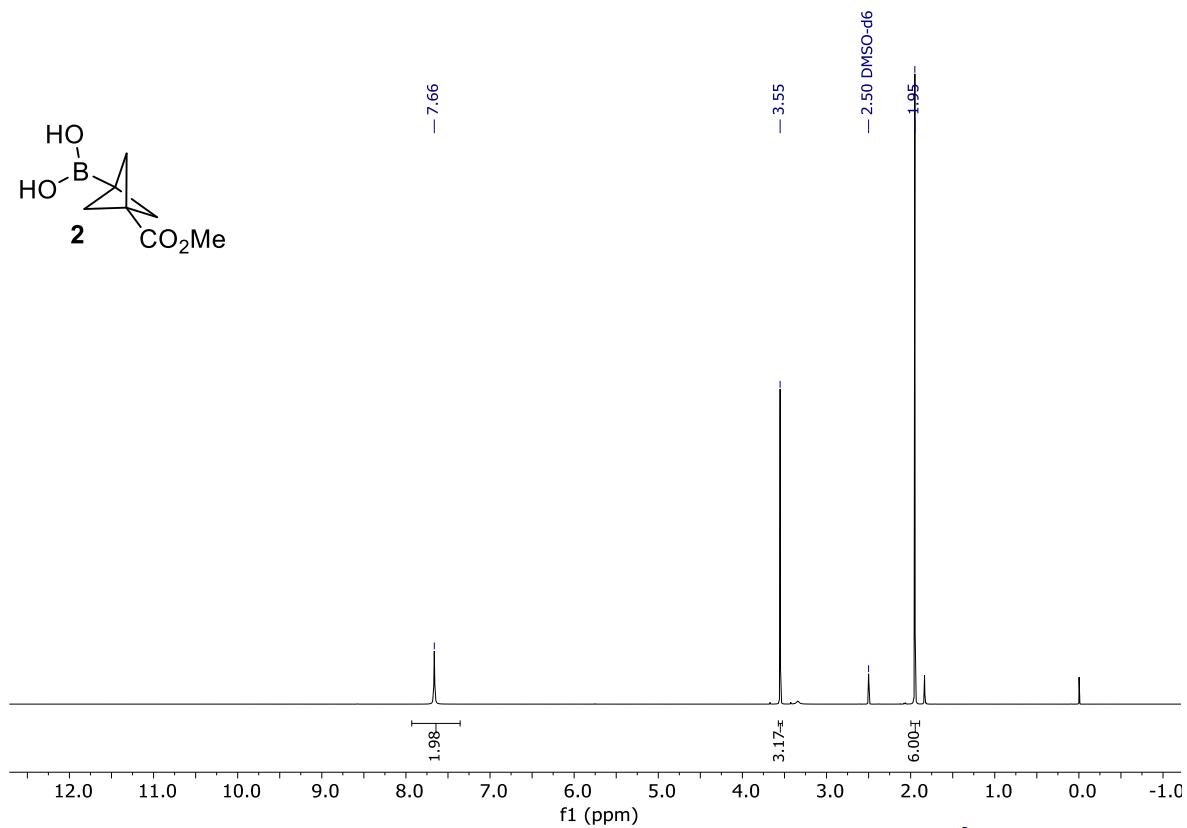
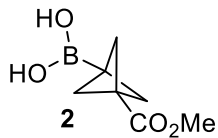
Synthesis of bicyclo[1.1.1]pentane-1,3-diyl bis(4-(trifluoromethyl)benzenesulfonate (entry 2 as reference). To a 5 mL scintillation vial with a stir bar was added bicyclo[1.1.1]pentane-1,3-diol (15 mg, 0.15 mmol, 1.0 eq.), 4-dimethylaminopyridine (DMAP, 1.83 mg, 0.02 mmol, 10 mol%) and 4-(trifluoromethyl)benzenesulfonyl chloride (73 mg, 0.30 mmol, 2.0 eq.). The vial was capped with a Teflon septum and submitted to three vacuum/ N_2 refill cycles. Then, anhydrous DCM (750 μL) and anhydrous triethylamine (42 μL , 0.300 mmol, 2.0 eq.) were added at 0 °C and the reaction mixture was stirred at this temperature for 2 h. **Note:** For both entry 1 and 2, LC/MS analysis after 40 min showed formation of bistosylate product and only traces of monotosylate product. Purification of the crude reaction mixture by silica gel chromatography with 0-50% EtOAc in hexanes as eluent afforded bicyclo[1.1.1]pentane-1,3-diyl bis(4-methylbenzenesulfonate) (**bistosylate**, 57 mg, 0.110 mmol, 73% yield) as a white crystalline solid. $^1\text{H NMR}$ (600 MHz, CDCl_3): δ 8.02 (d, $J = 8.3$ Hz, 4H), 7.84 (d, $J = 8.3$ Hz, 4H), 2.45 (s, 6H), 1.53 (s, 6H).

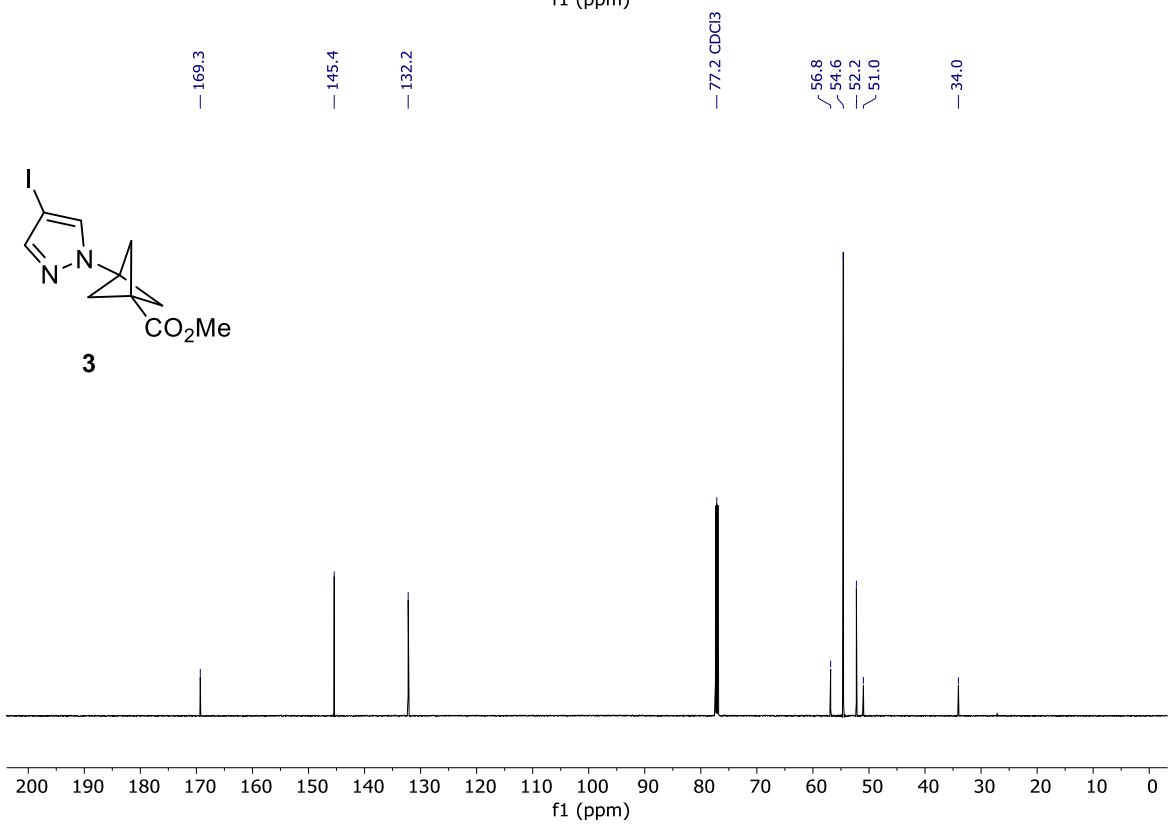
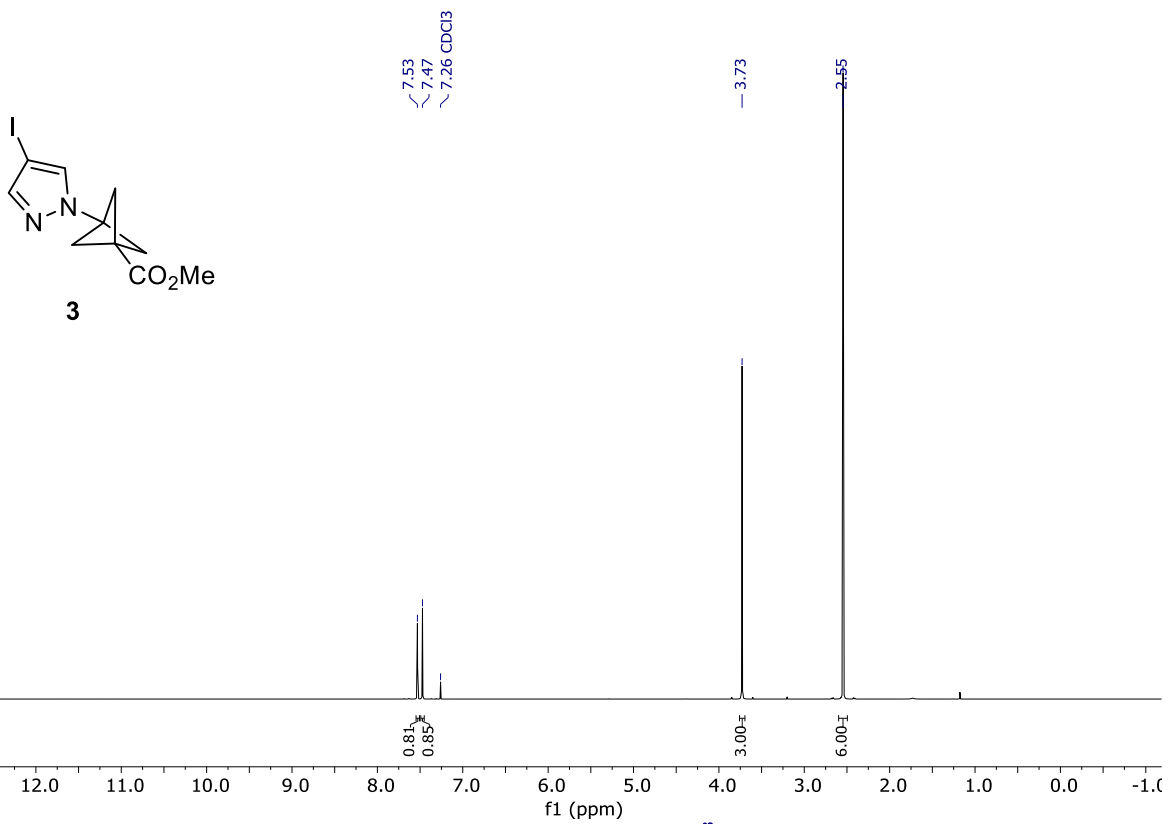


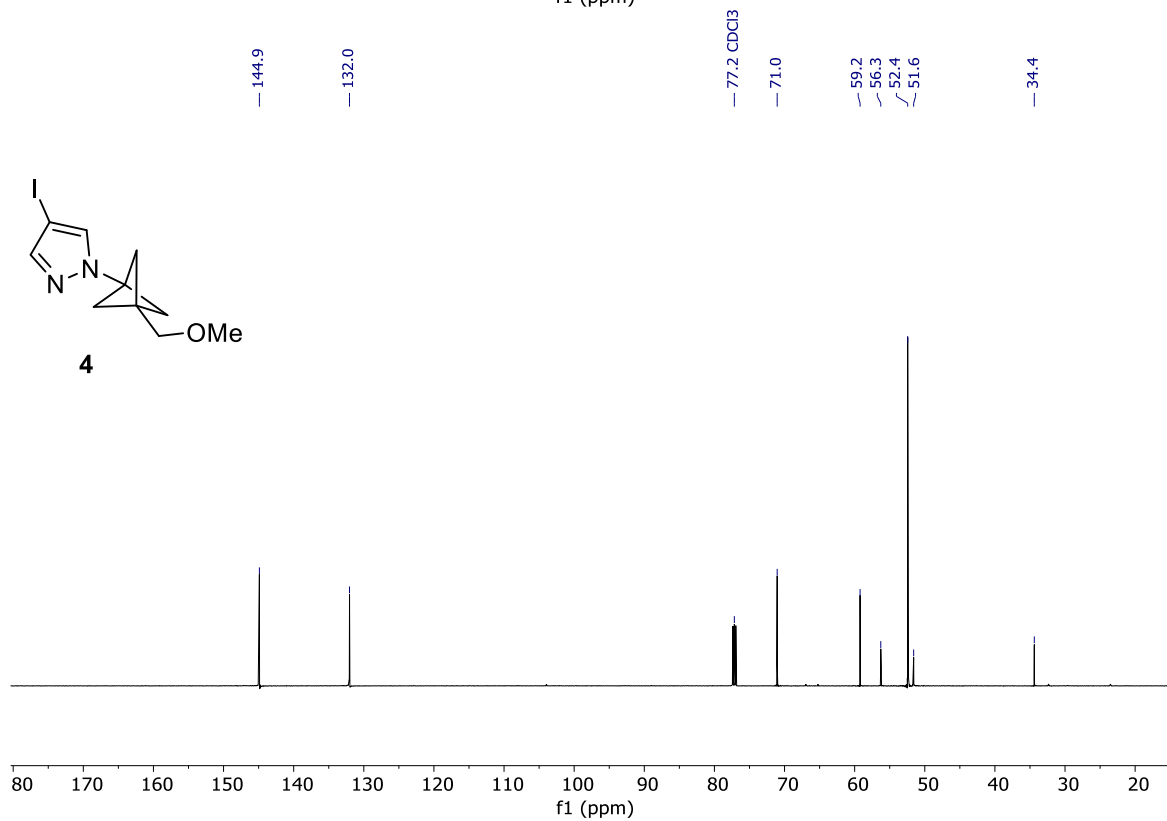
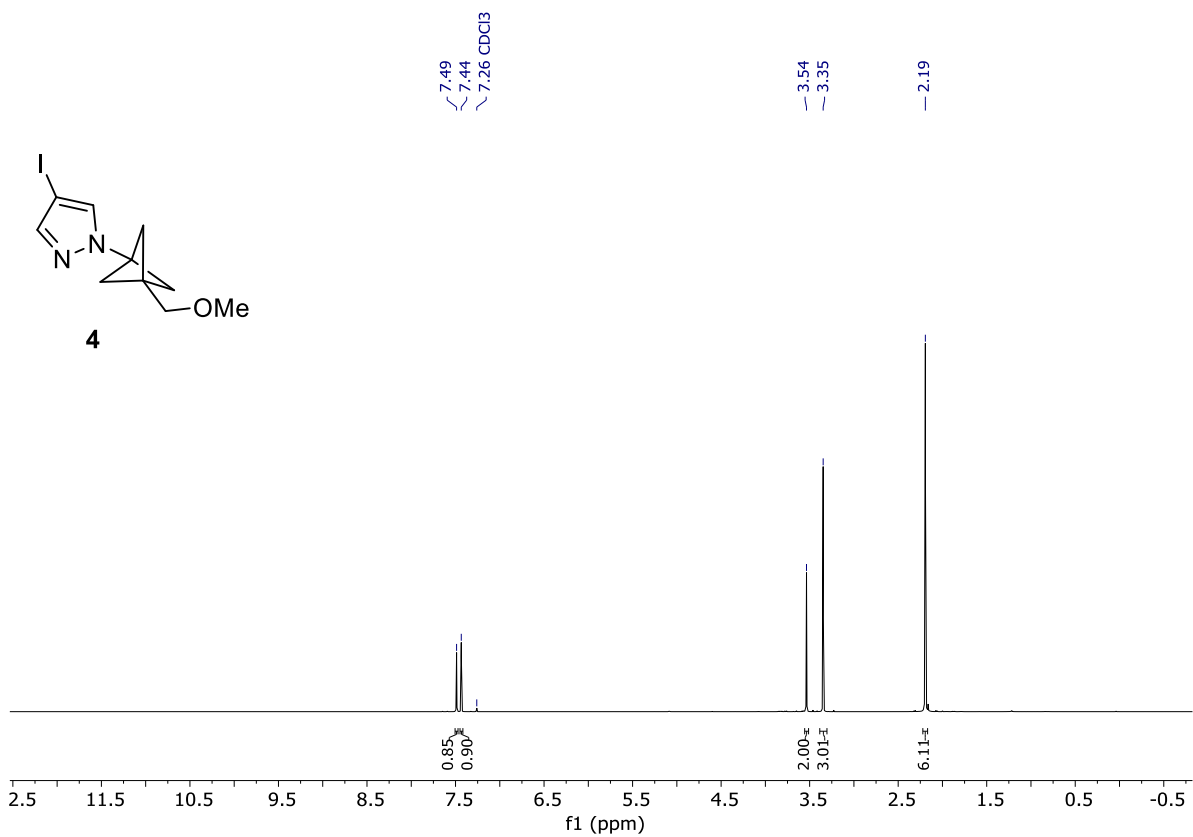
Monosubstitution attempt of bicyclo[1.1.1]pentane-1,3-diyl bis(4-(trifluoromethyl)benzenesulfonate). To a 5 mL scintillation vial with a stir bar was added 4-iodo-1H-pyrazole (20 mg, 0.11 mmol, 1.0 eq.), 2 bicyclo[1.1.1]pentane-1,3-diyl bis(4-(trifluoromethyl)benzenesulfonate) (54 mg, 0.11 mmol, 1.0 eq.) and Cs_2CO_3 (68 mg, 0.21 mmol, 2.0 eq.). The vial was capped with a Teflon septum and submitted to three vacuum/ N_2 refill cycles. Then, anhydrous MeCN (1.1 mL) was added under a N_2 atmosphere and the reaction mixture was stirred at 23 °C for 40 h. LC/MS analysis showed low conversion to 3-(4-iodo-1H-pyrazol-1-yl)-3-methylcyclobutan-1-one (10:1 4-iodopyrazole/3-(4-iodo-1H-pyrazol-1-yl)-3-methylcyclobutan-1-one) and no formation of desired product. The reaction was then stirred at 80 °C for 3 h and LCMS analysis showed increased amount of 3-(4-iodo-1H-pyrazol-1-yl)-3-methylcyclobutan-1-one (1:1 4-iodopyrazole/3-(4-iodo-1H-pyrazol-1-yl)-3-methylcyclobutan-1-one) but no formation of desired product. Purification of the crude reaction mixture by silica gel chromatography with 0-50% EtOAc in hexanes as eluent afforded 3-(4-iodo-1H-pyrazol-1-yl)-3-methylcyclobutan-1-one (10 mg, 0.04 mmol, 35% yield) as a white crystalline solid. **$^1\text{H NMR}$ (600 MHz, CDCl_3):** δ 7.63 (s, 1H), 7.58 (s, 1H), 3.99 – 3.77 (m, 2H), 3.44 – 3.10 (m, 2H), 1.89 (s, 3H).

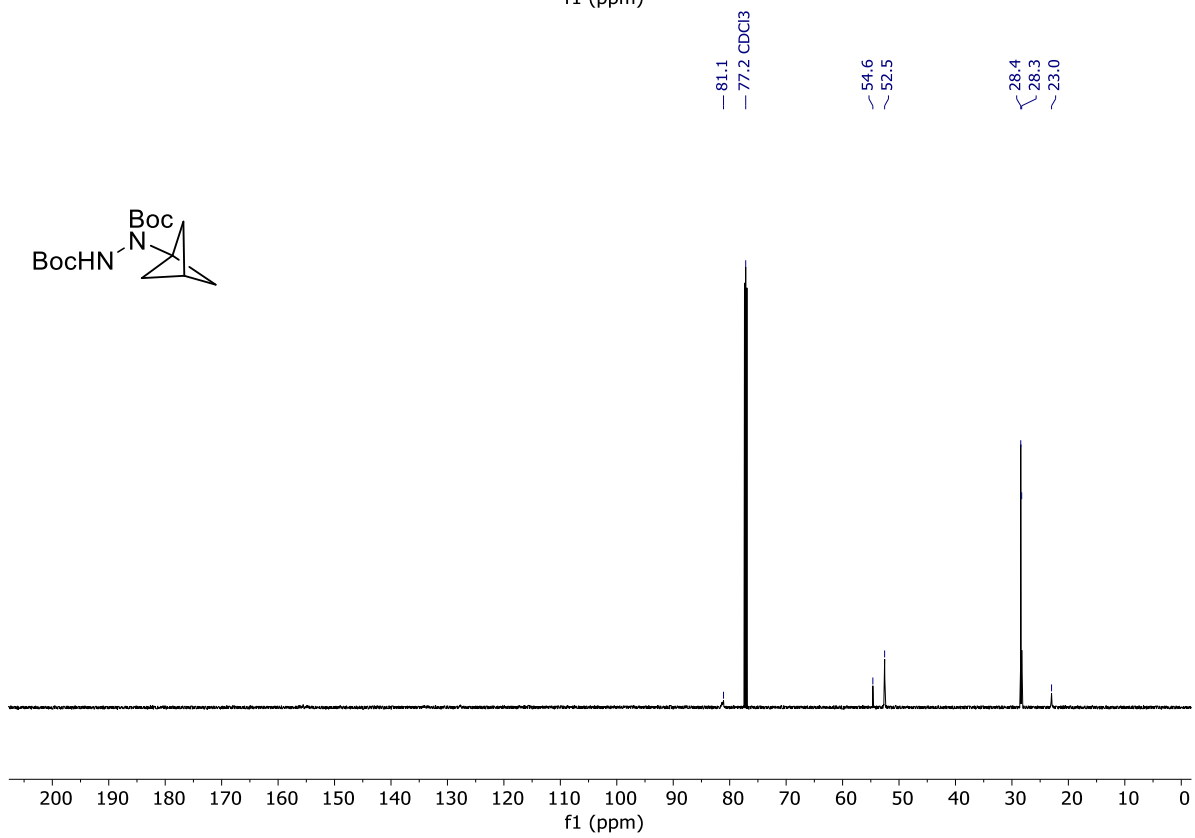
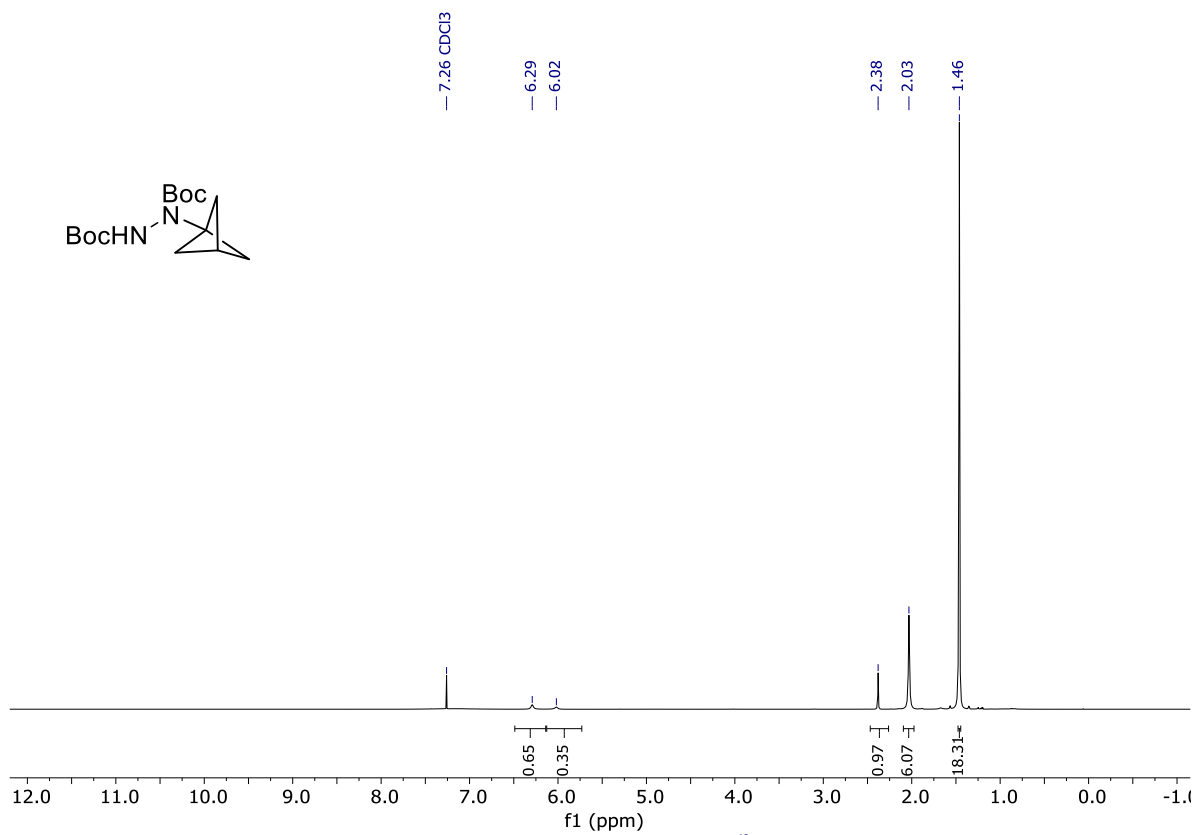
IX. NMR spectra

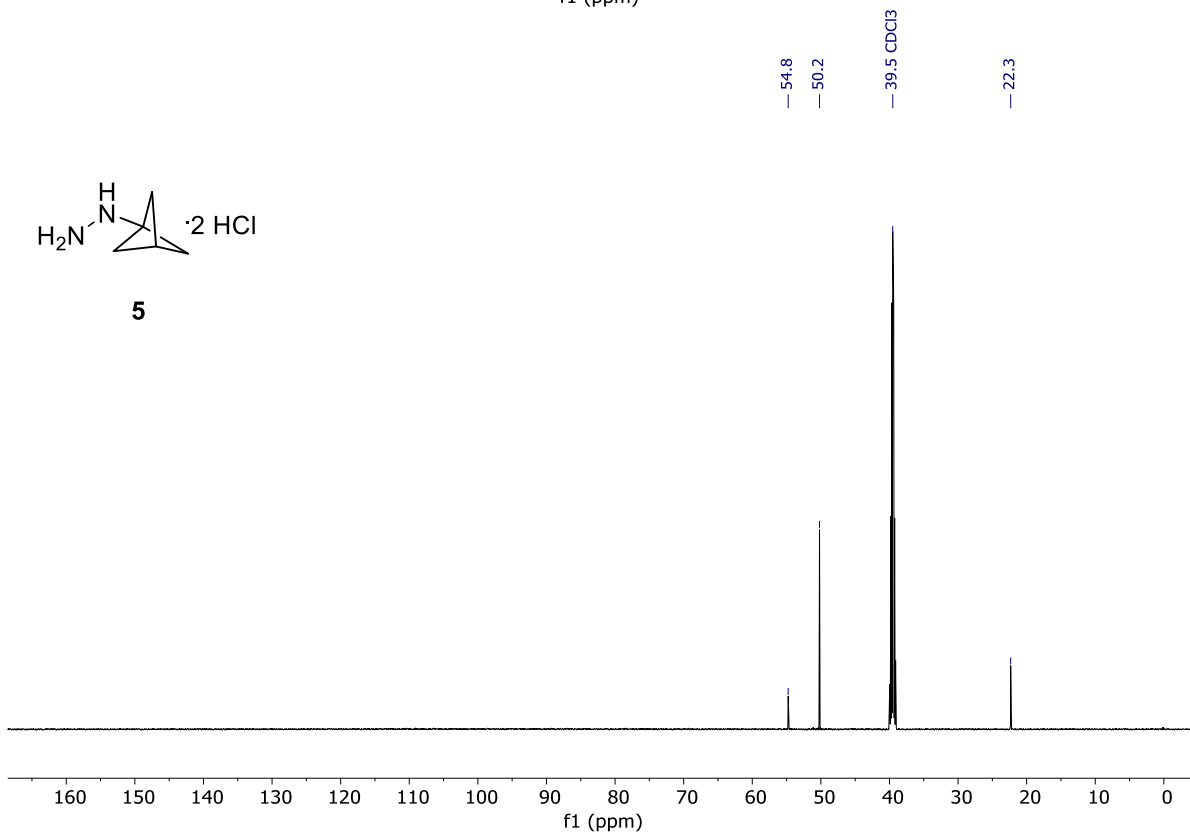
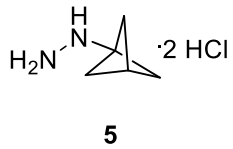
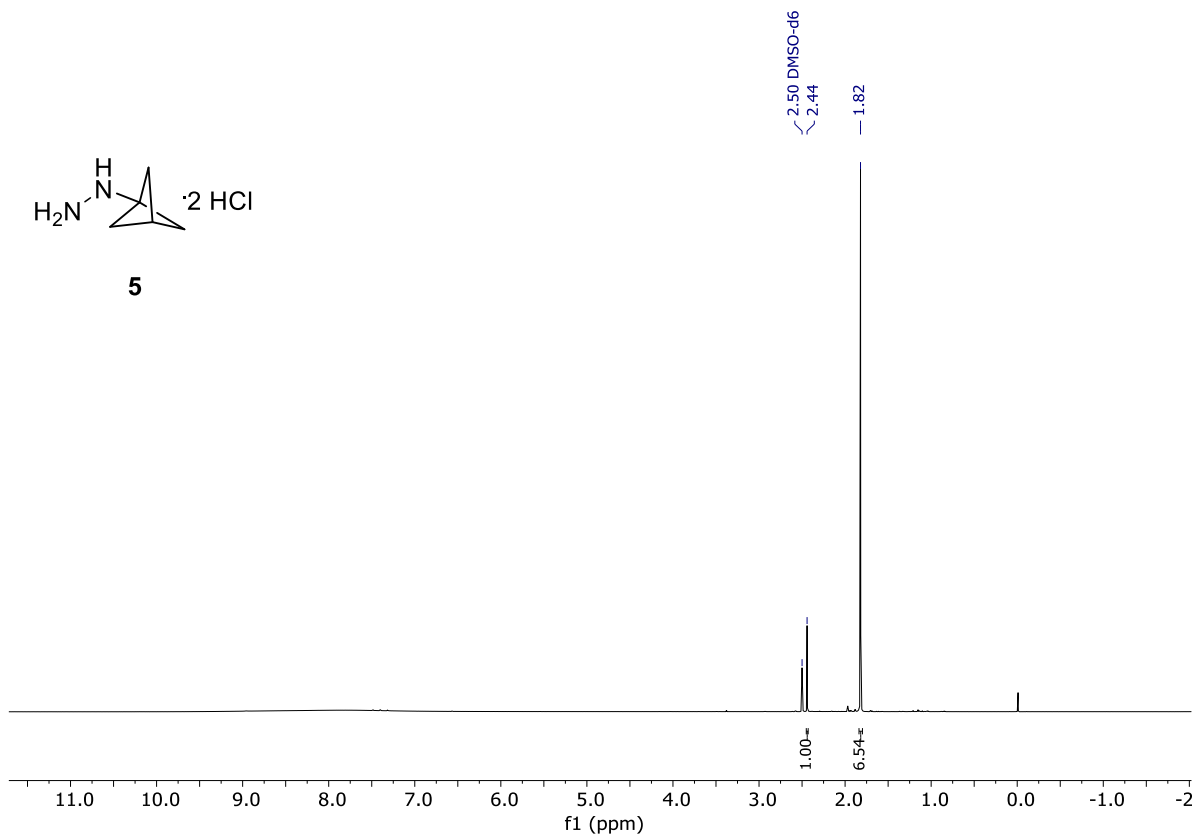
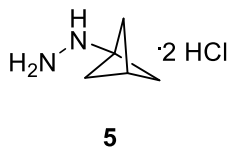


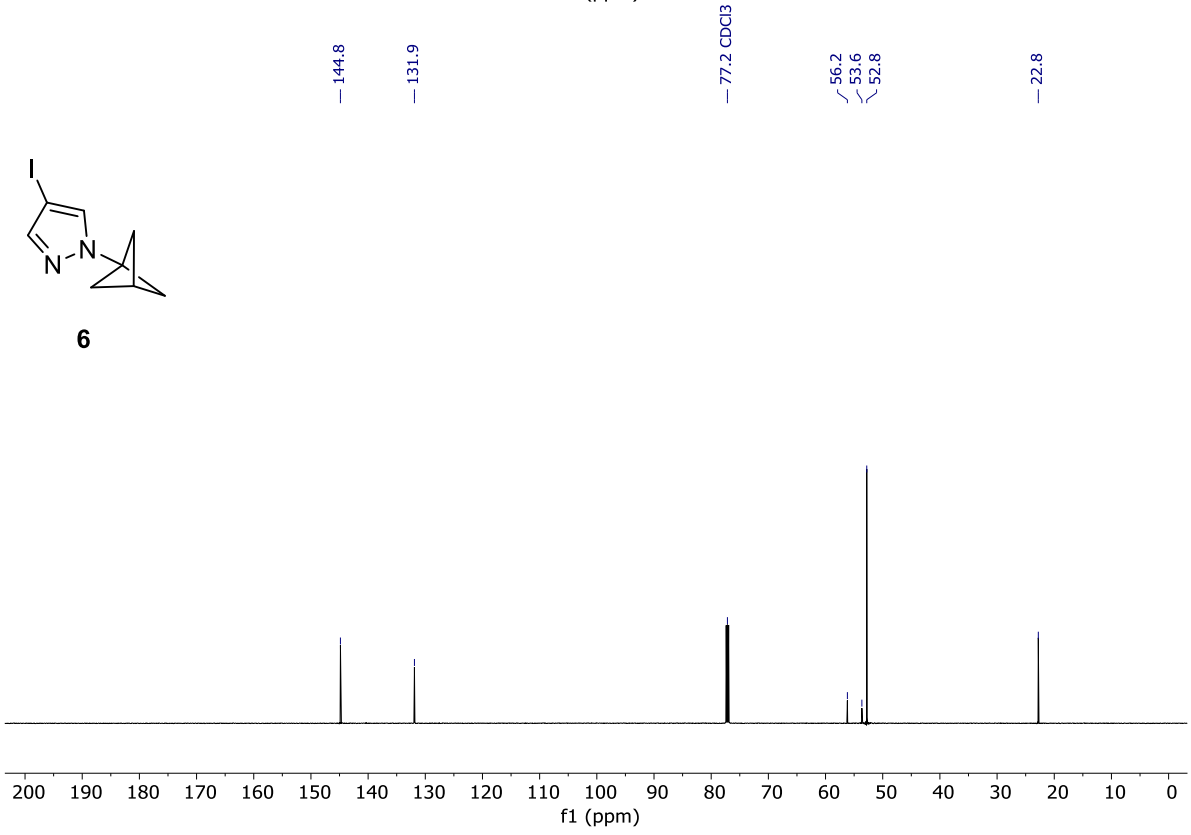
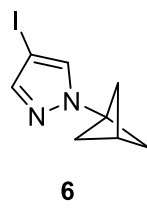
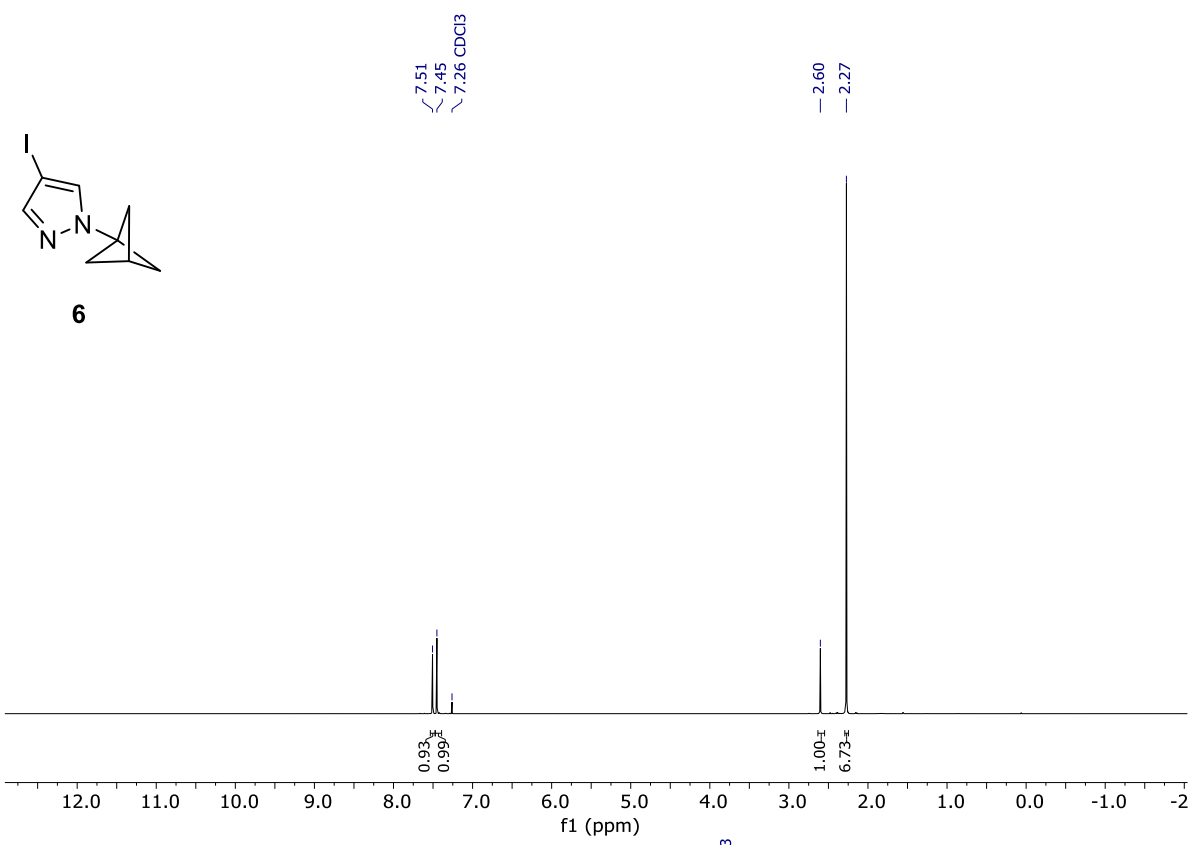
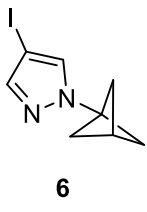


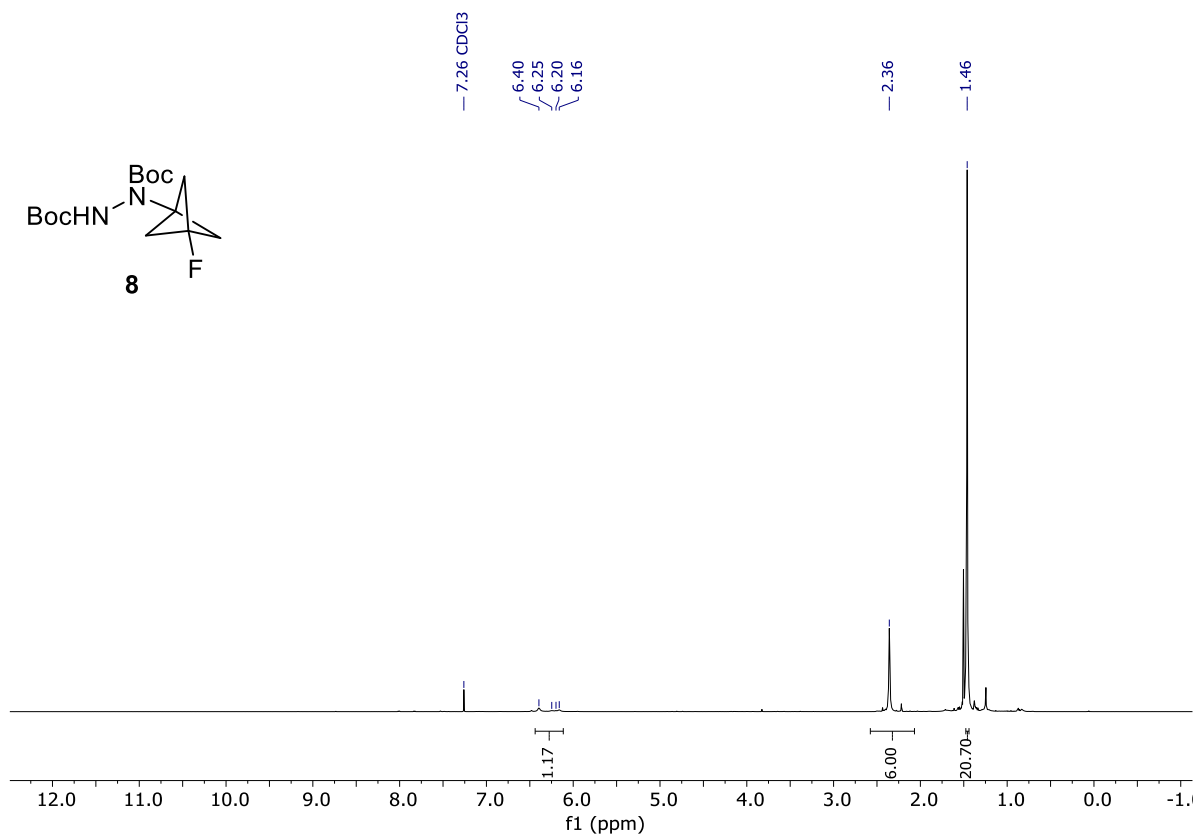


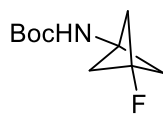




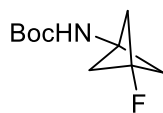
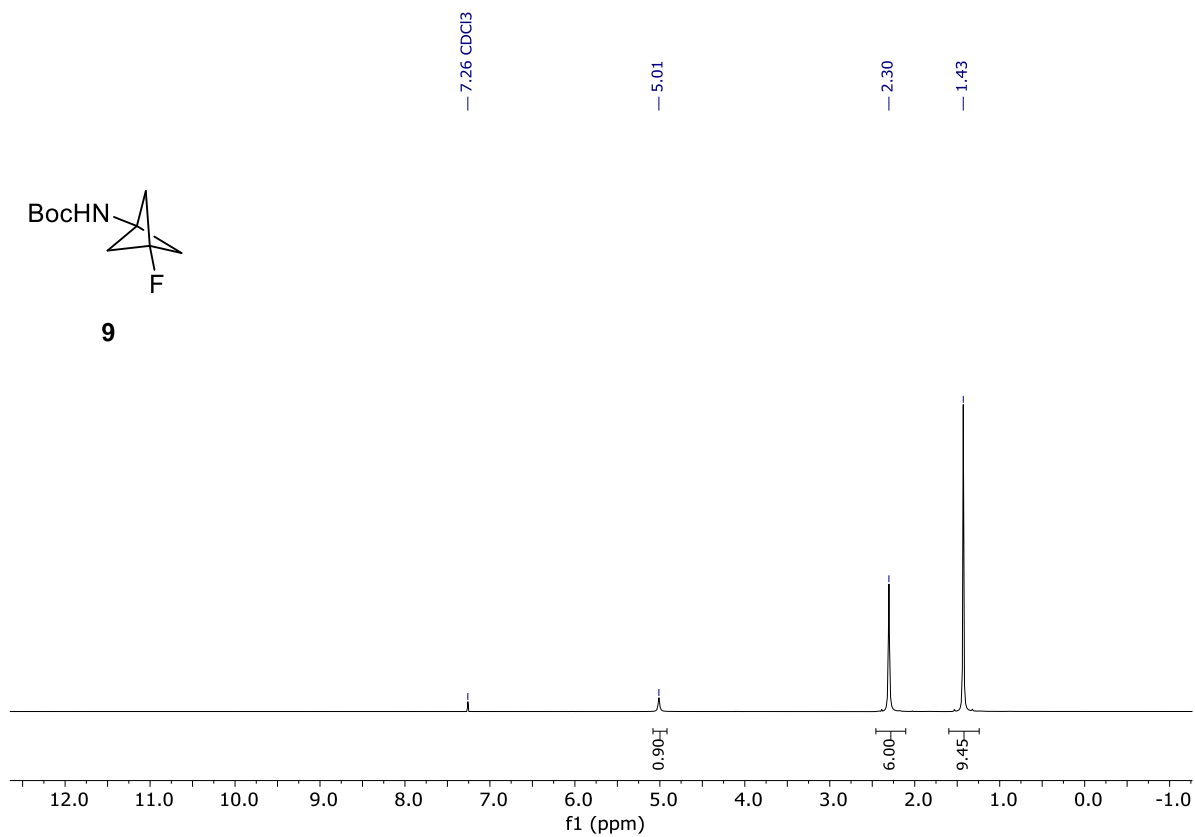




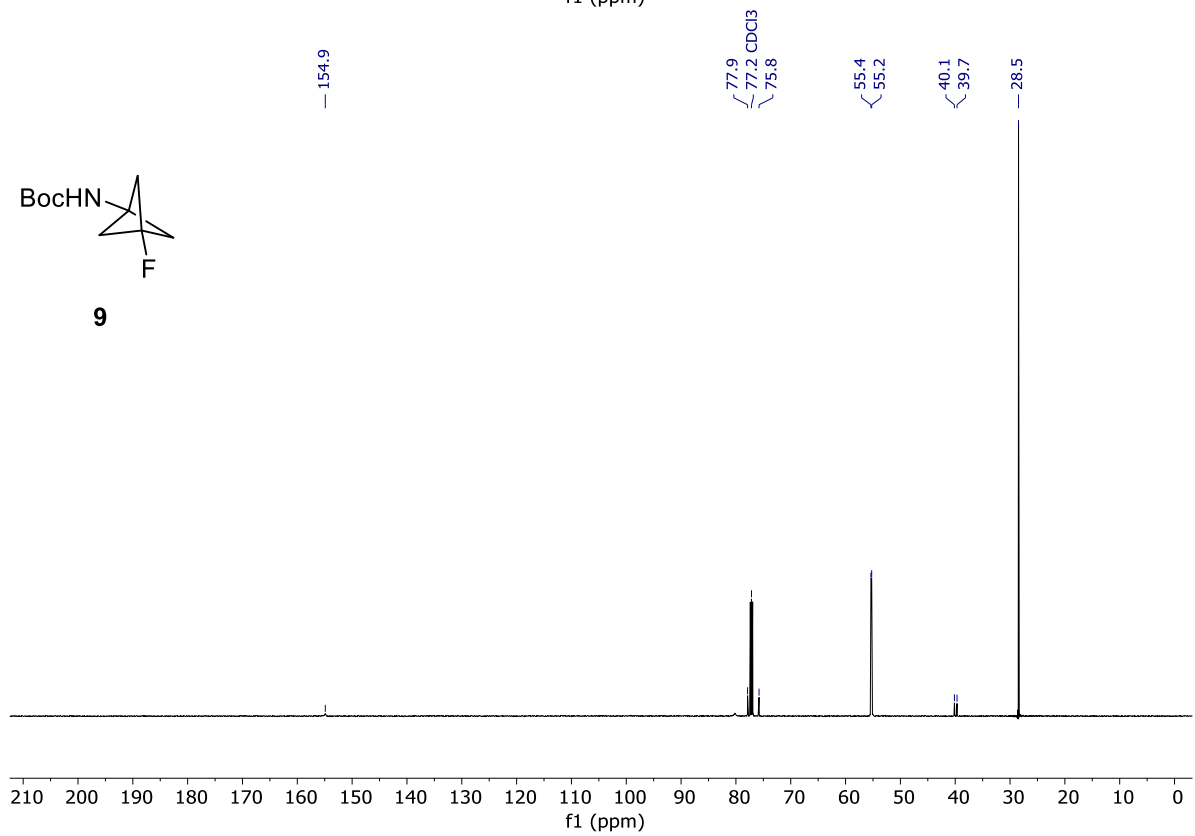


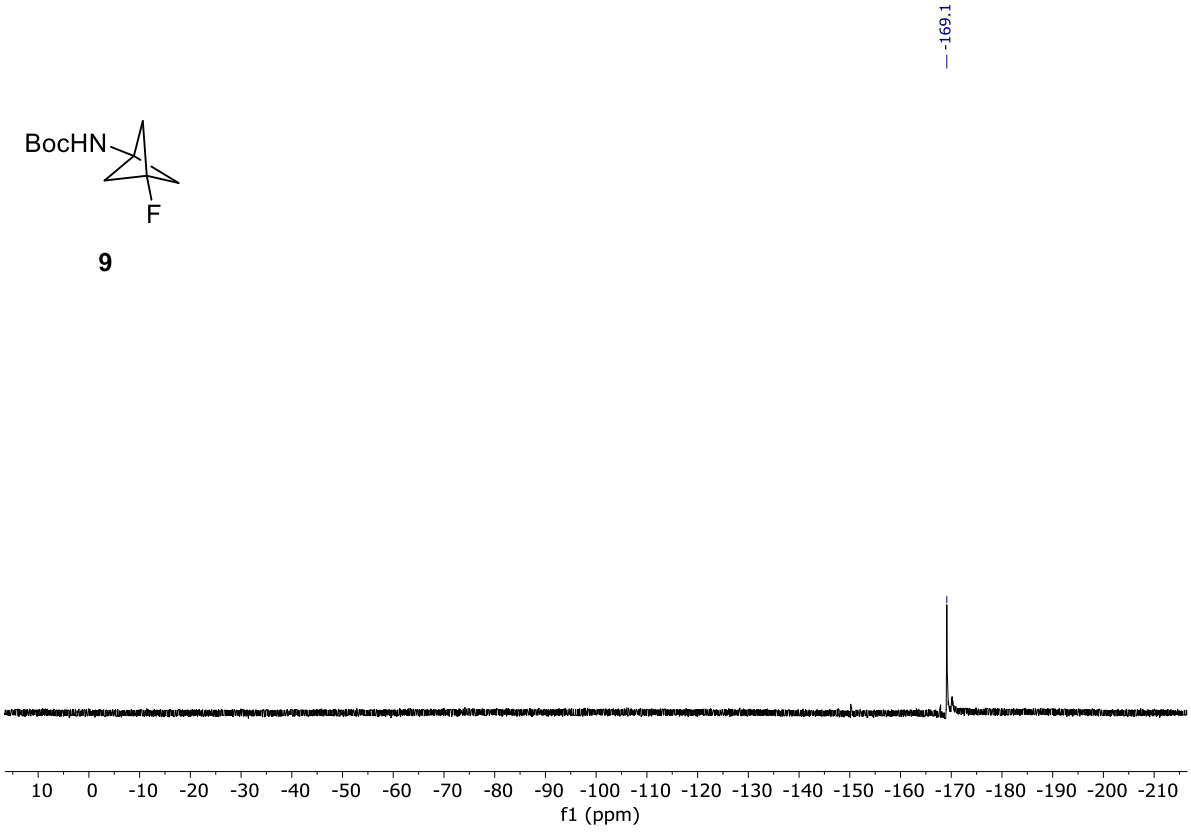
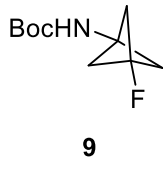


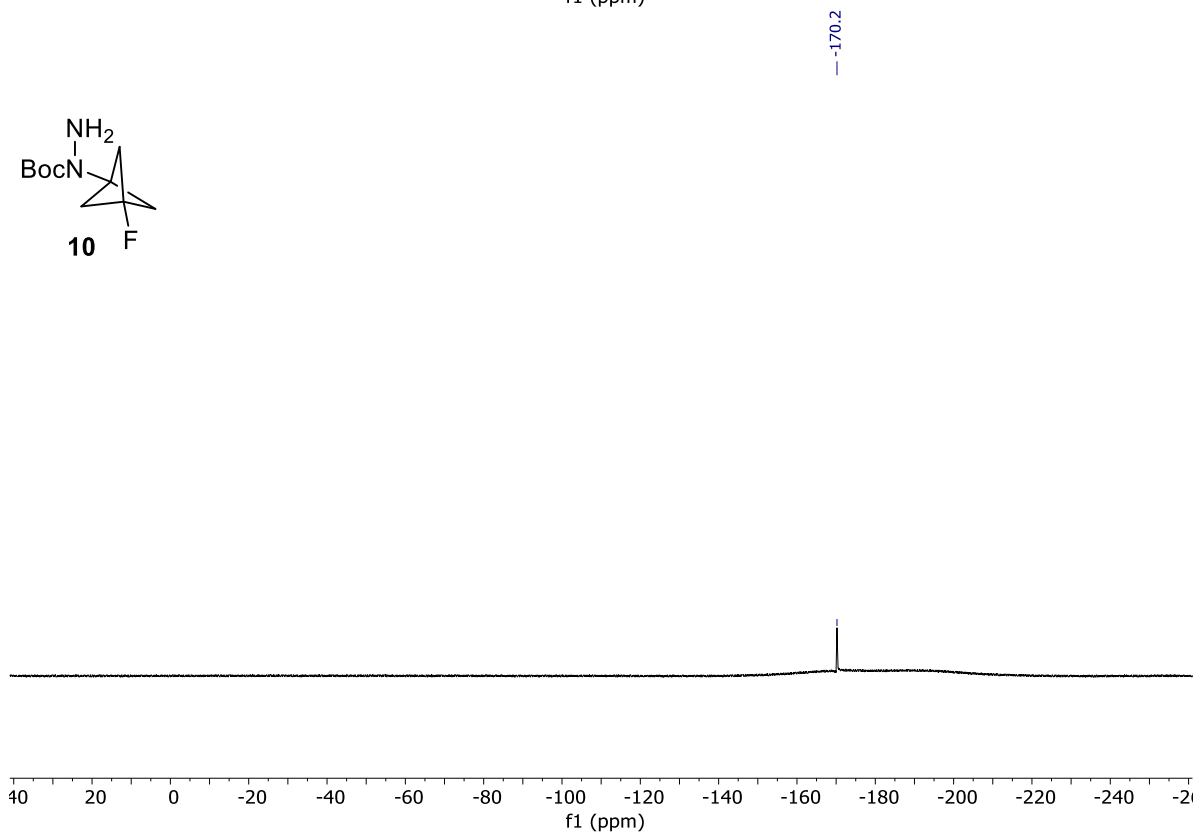
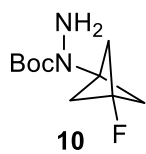
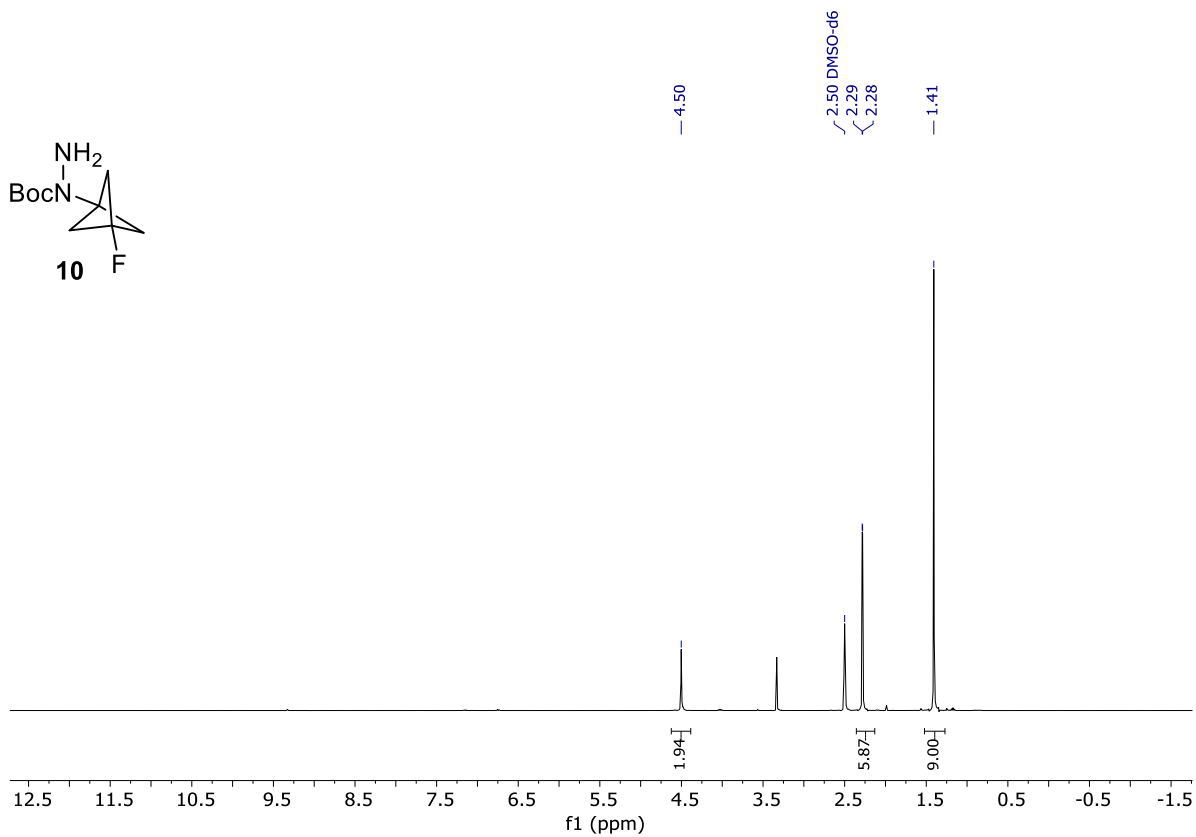
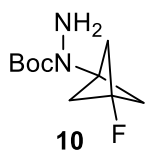
9

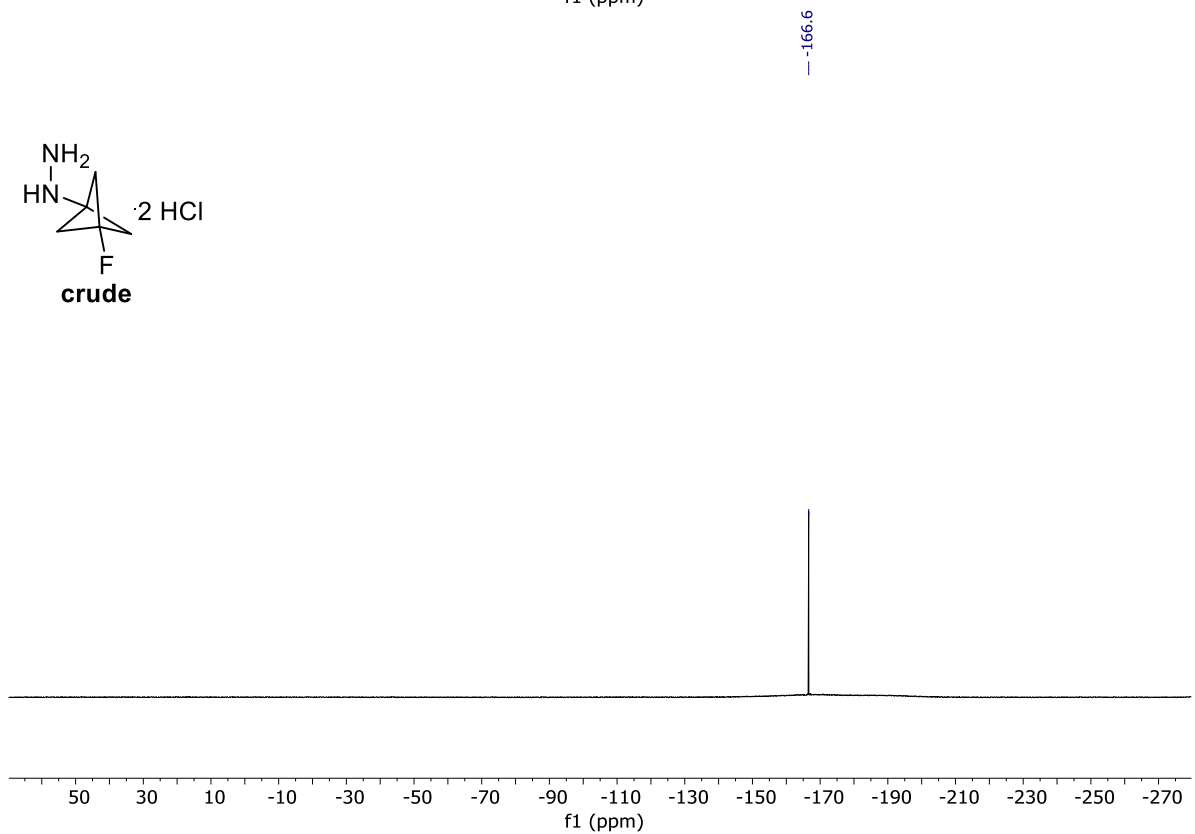
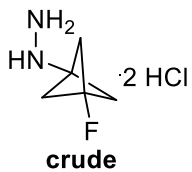
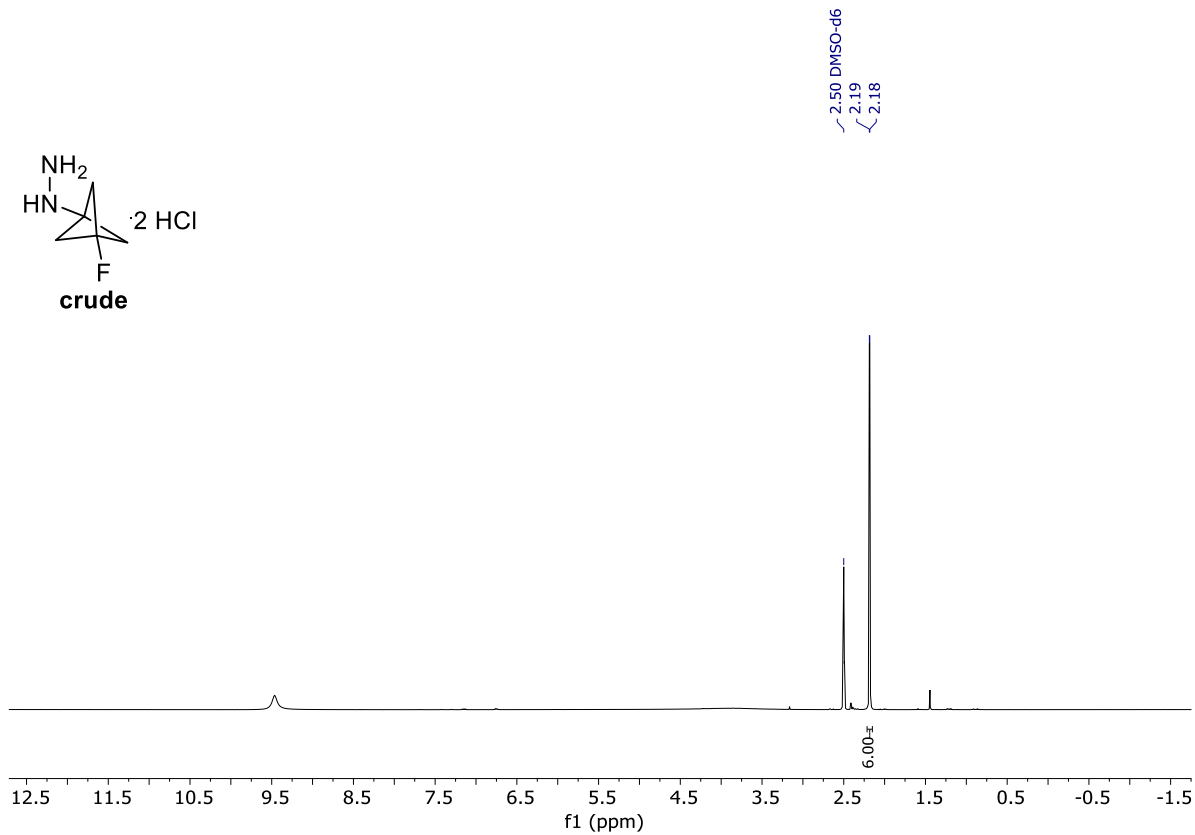
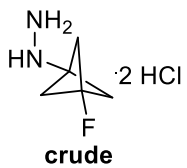


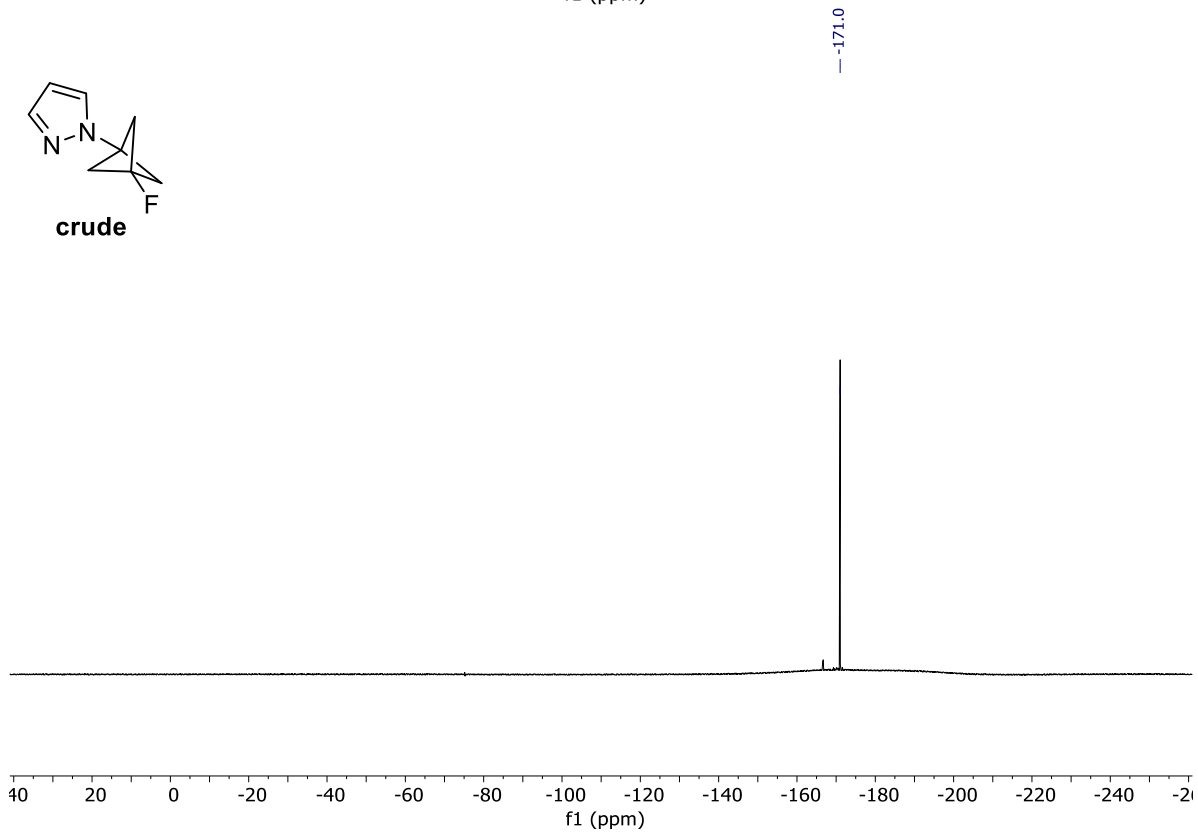
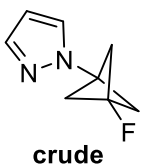
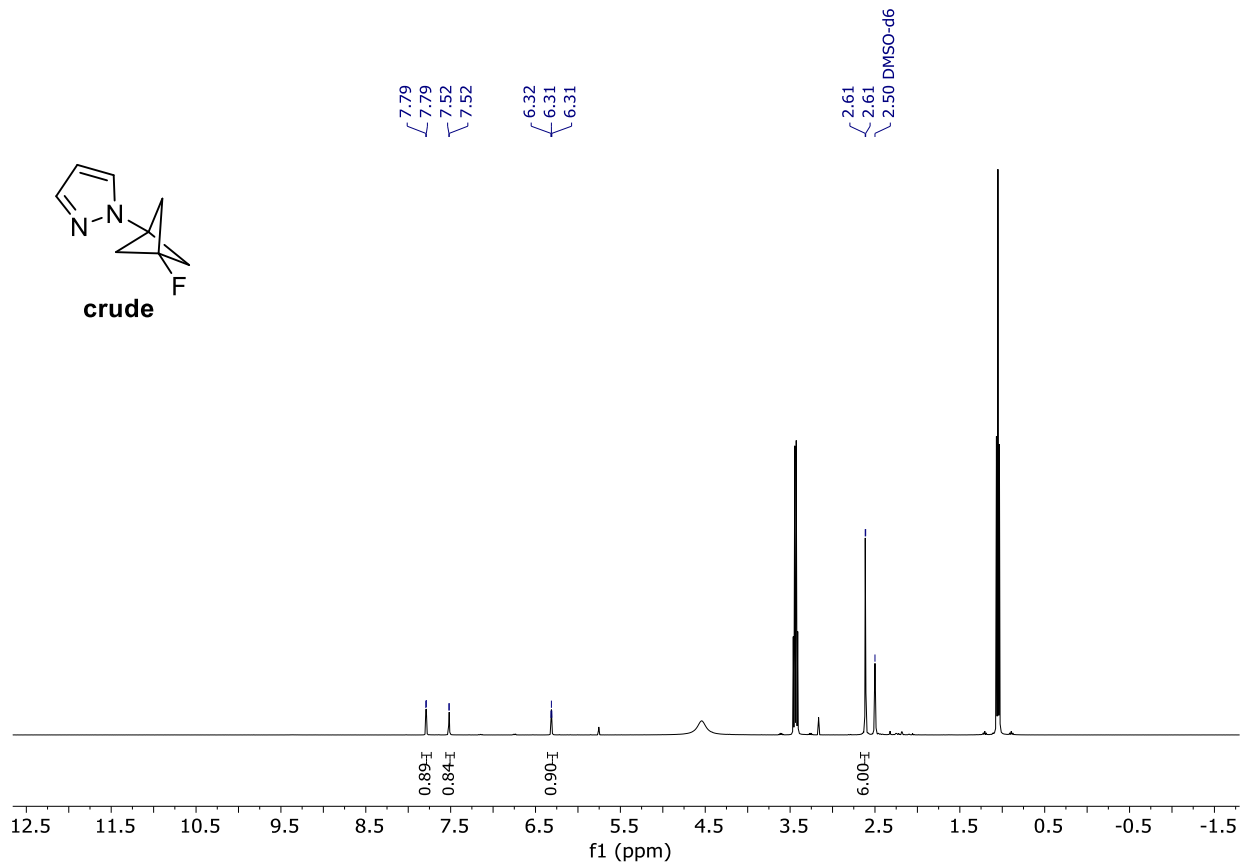
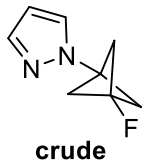
9

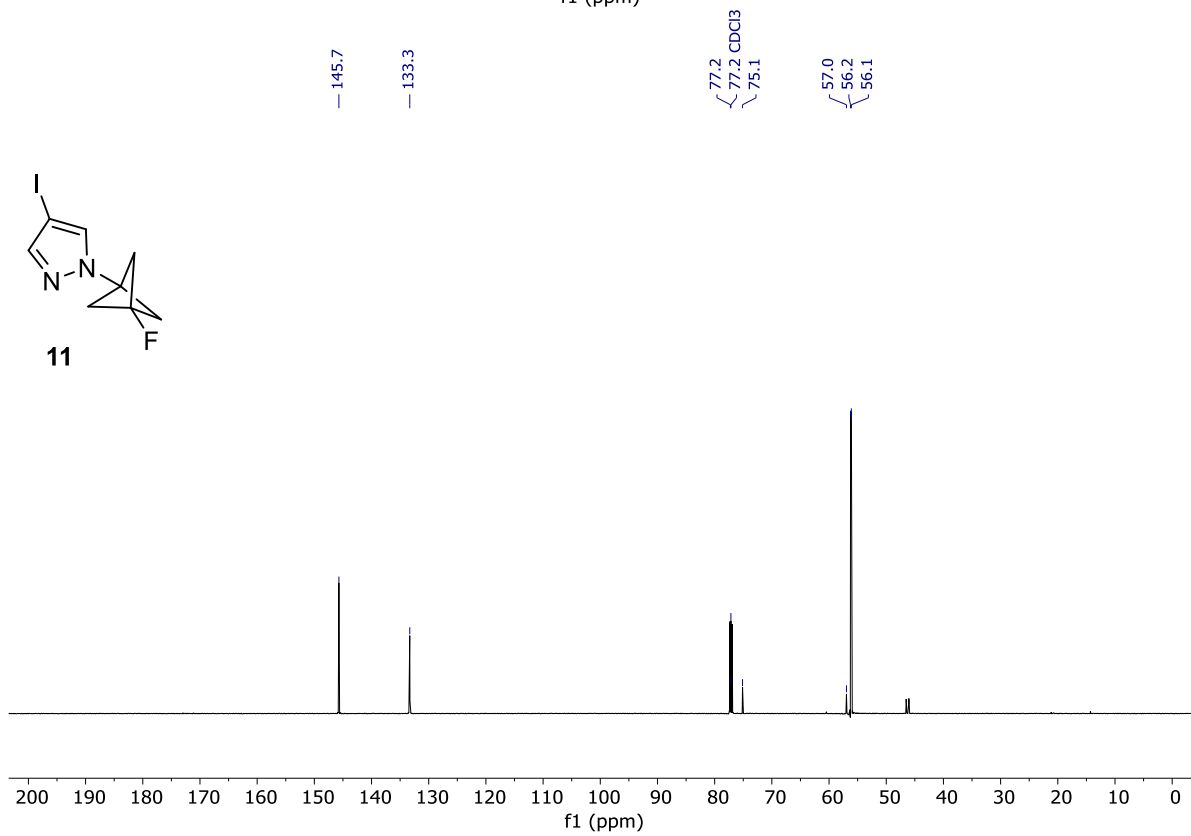
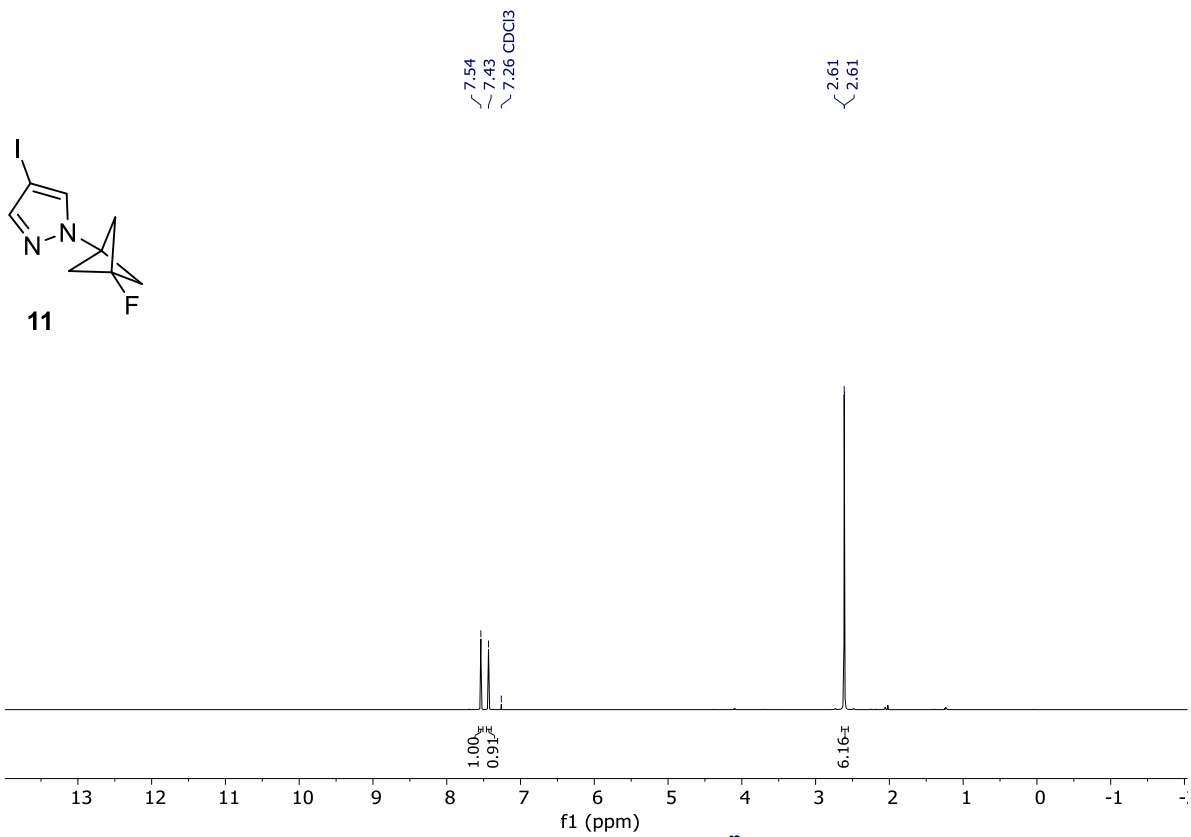


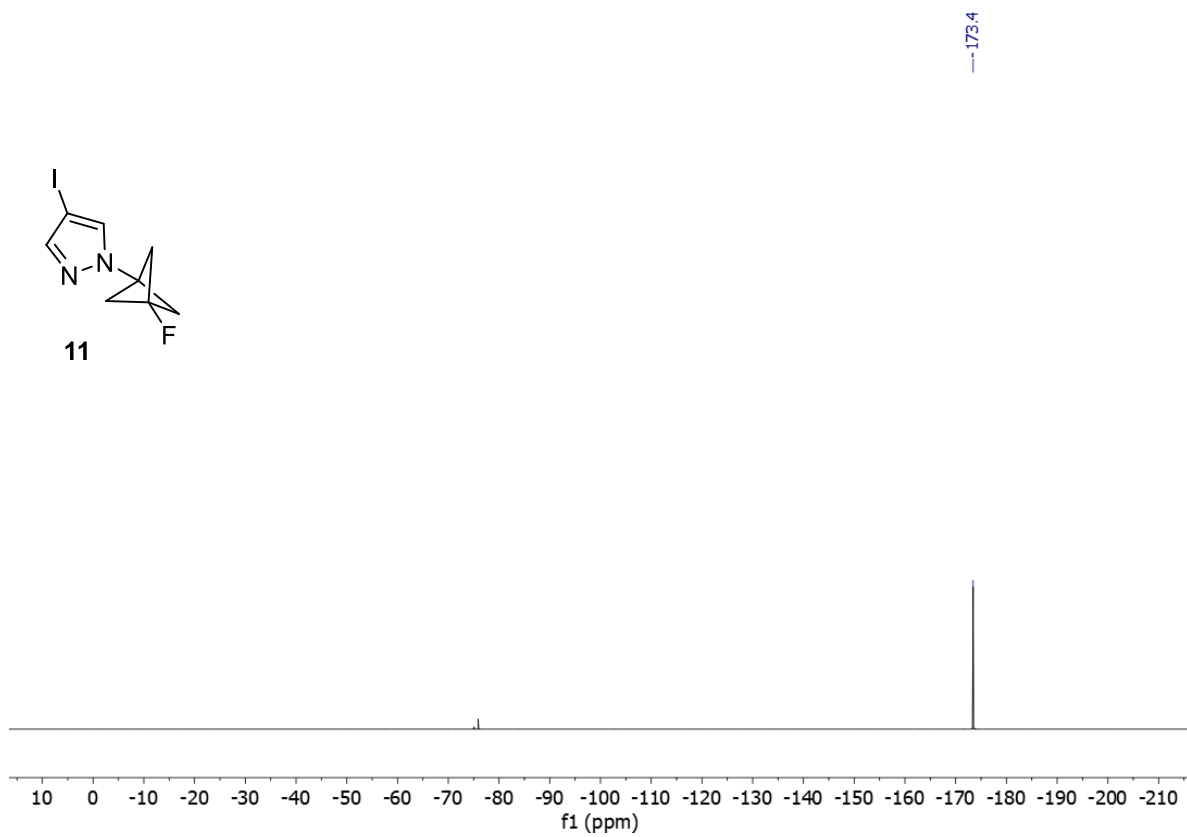
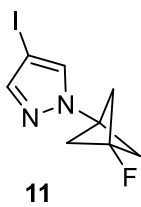


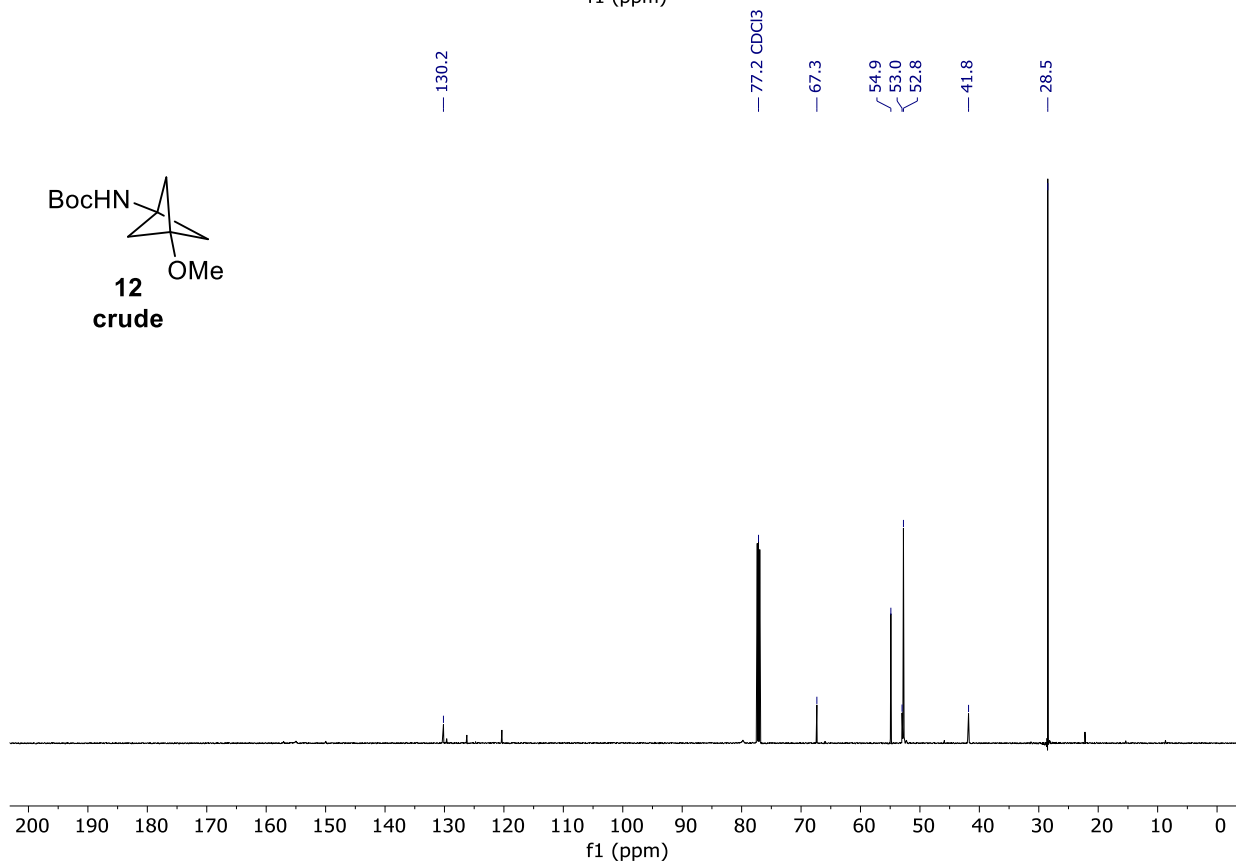
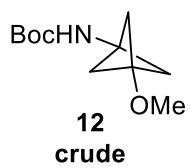
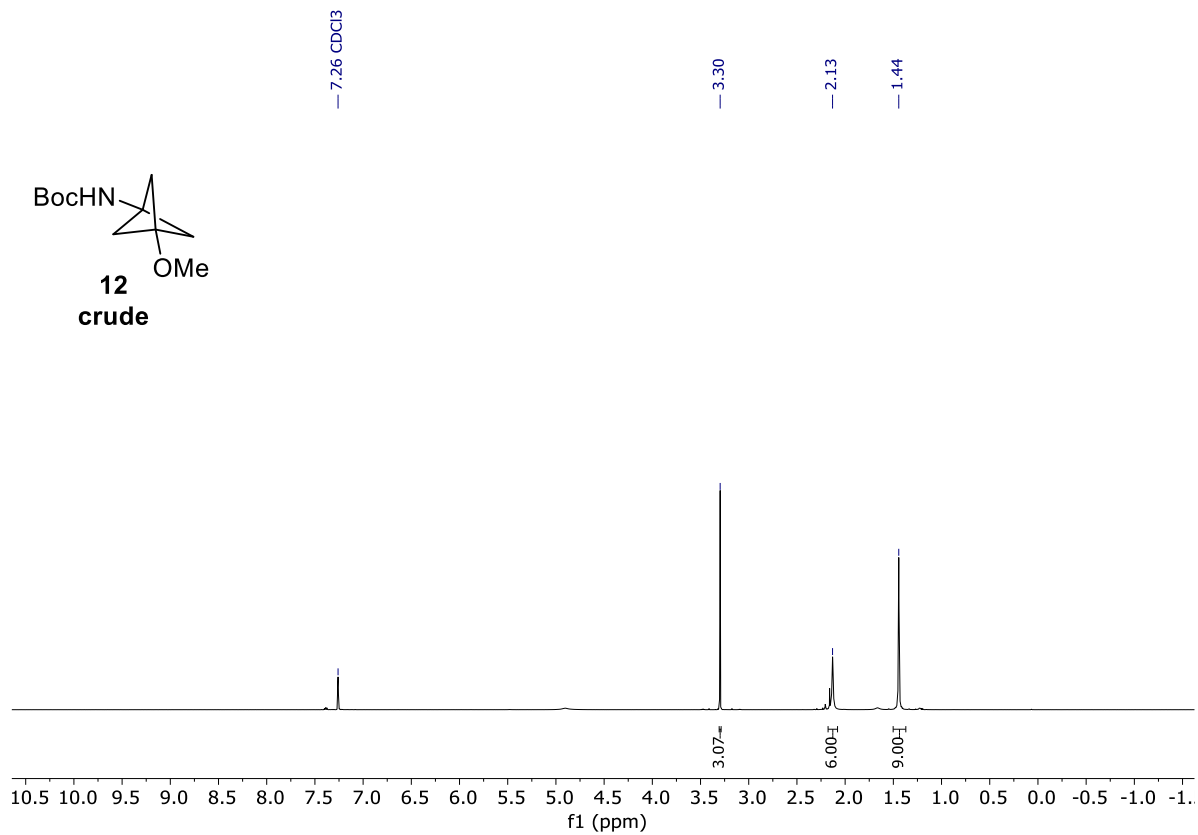
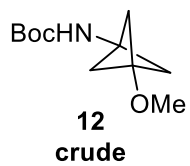


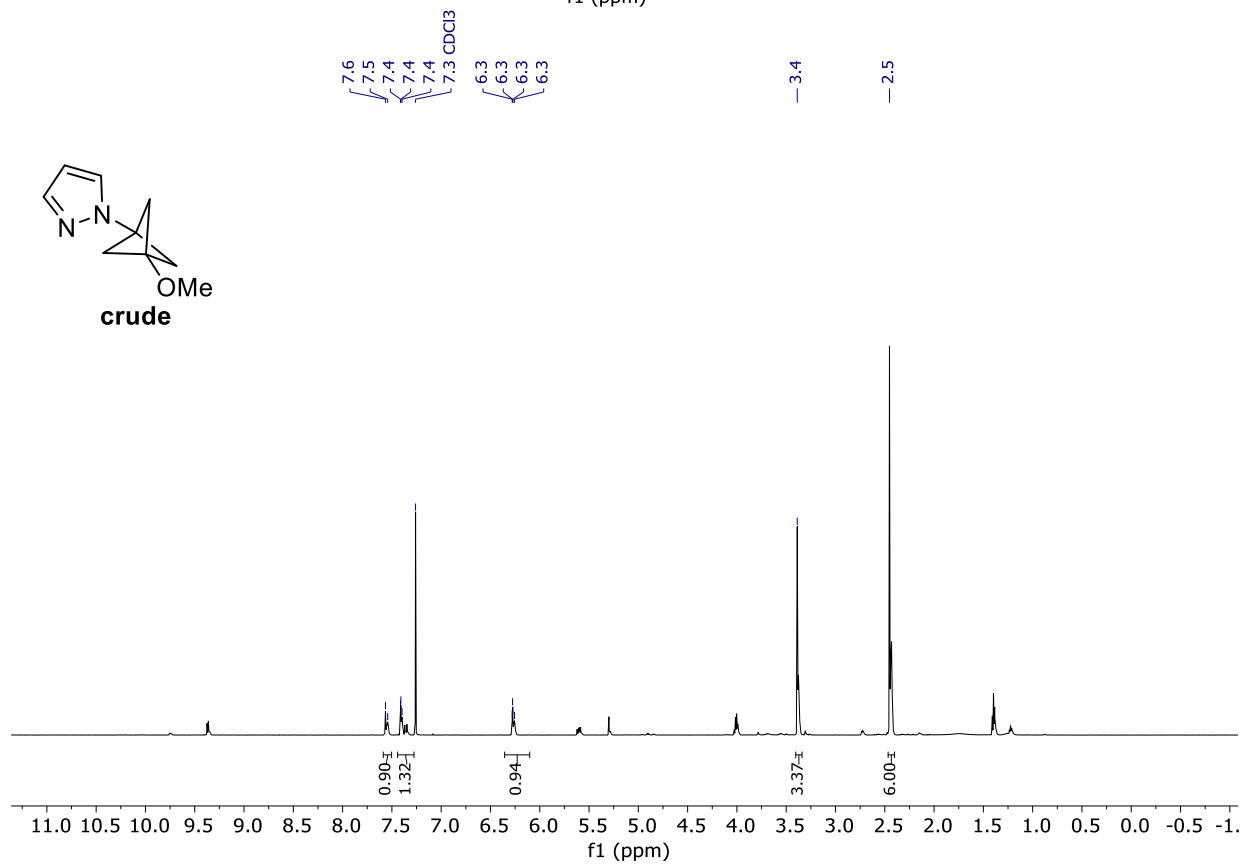
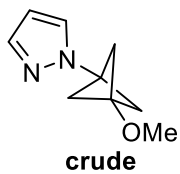
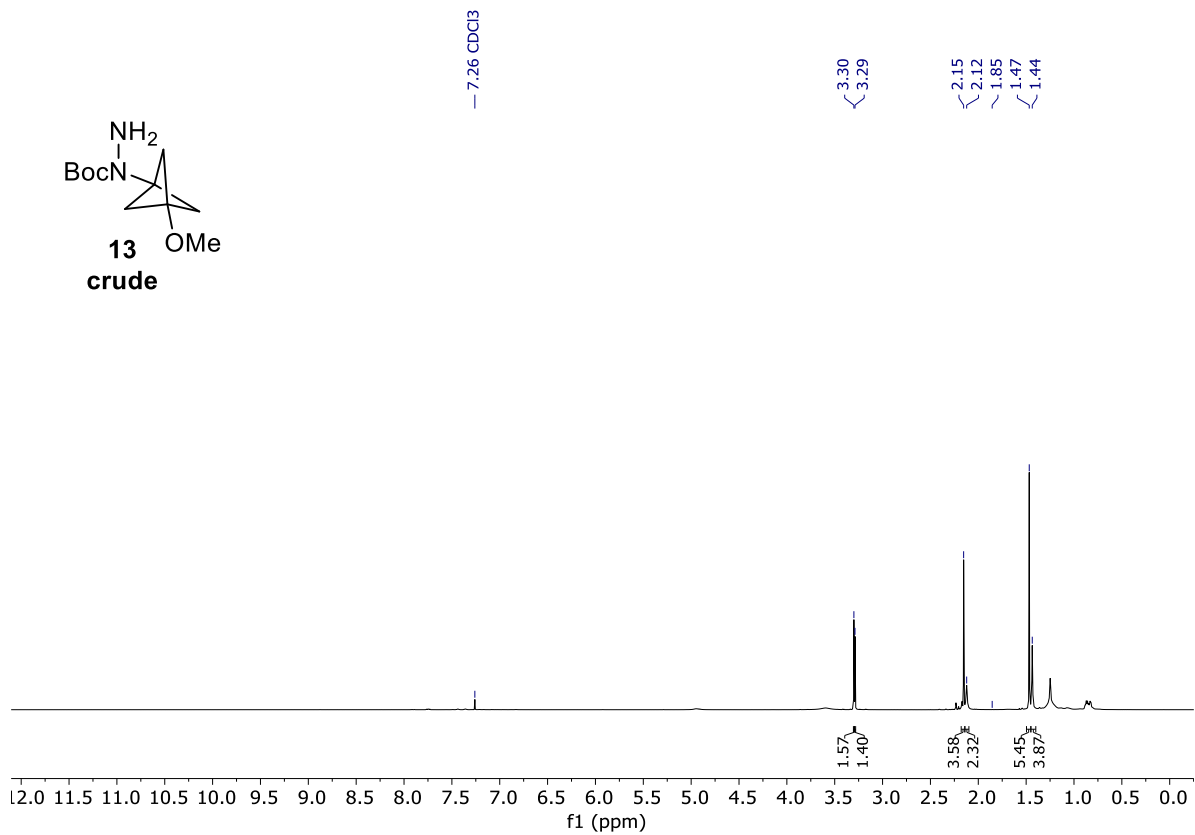
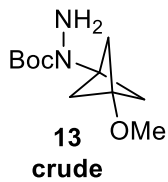


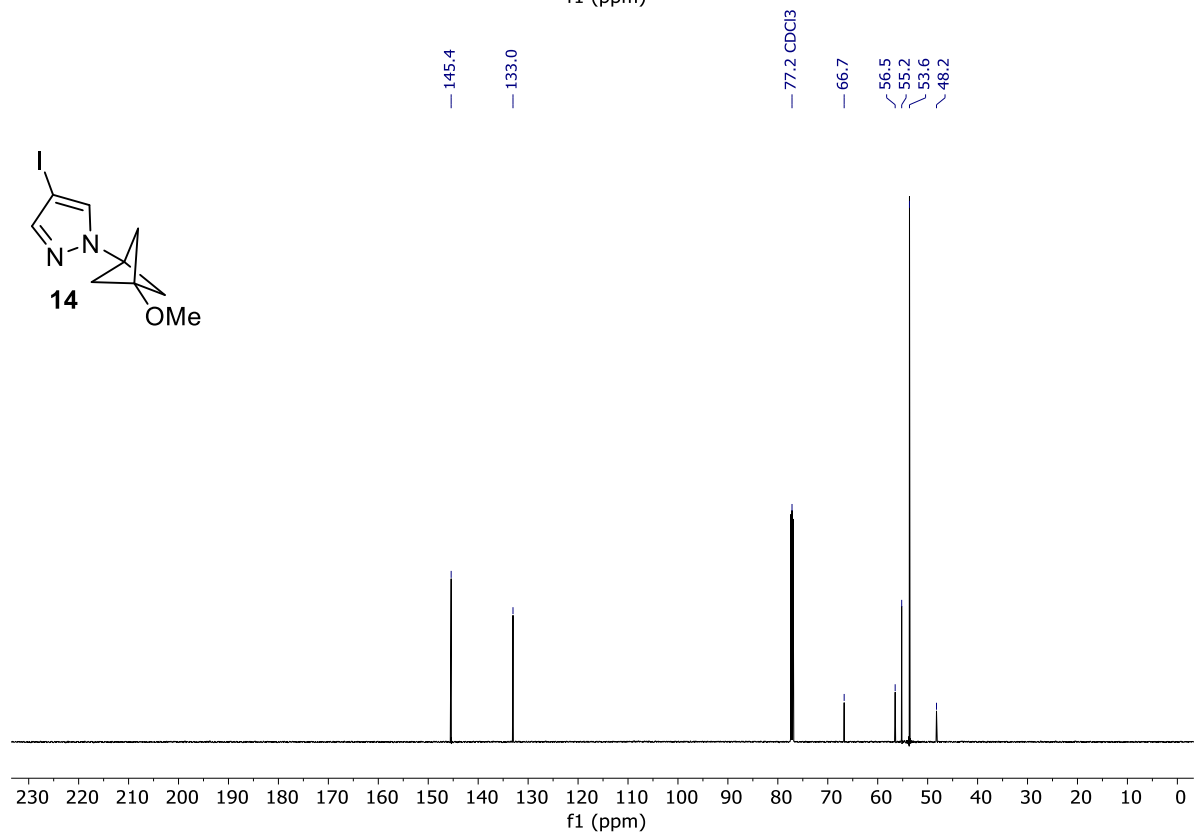
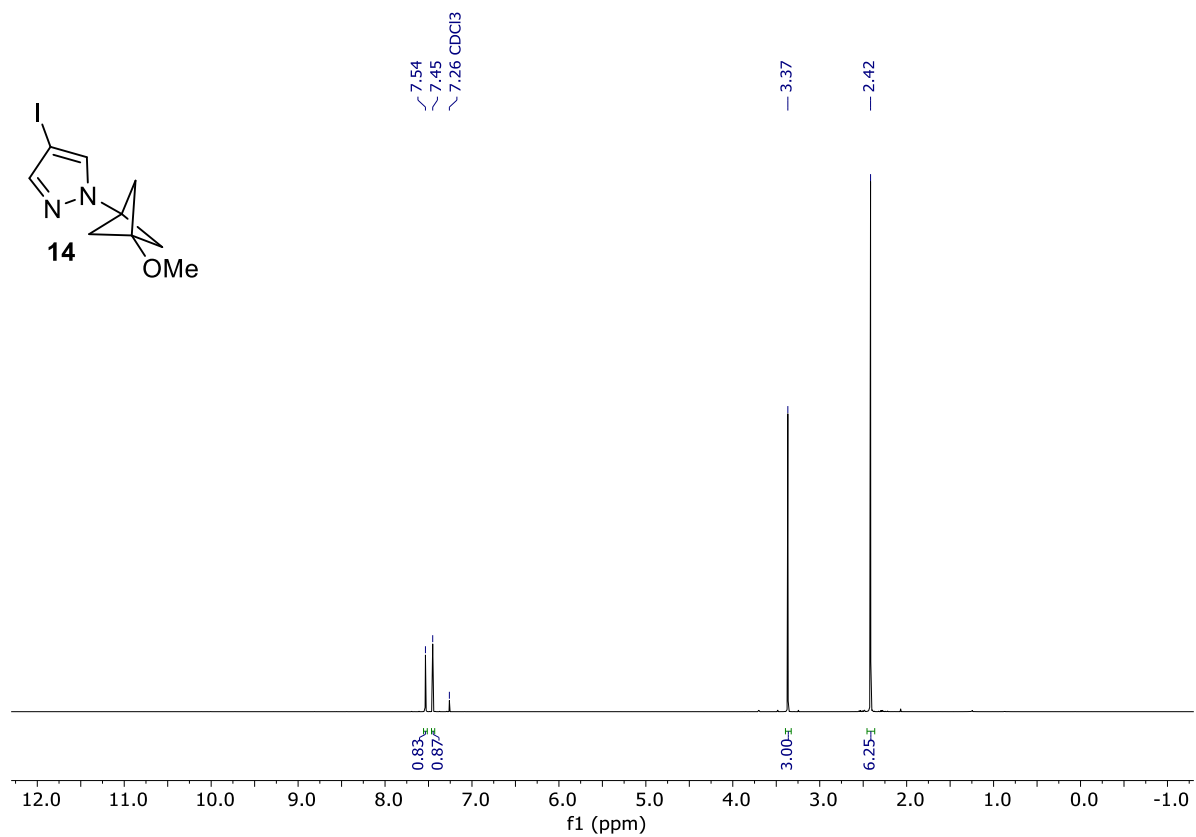


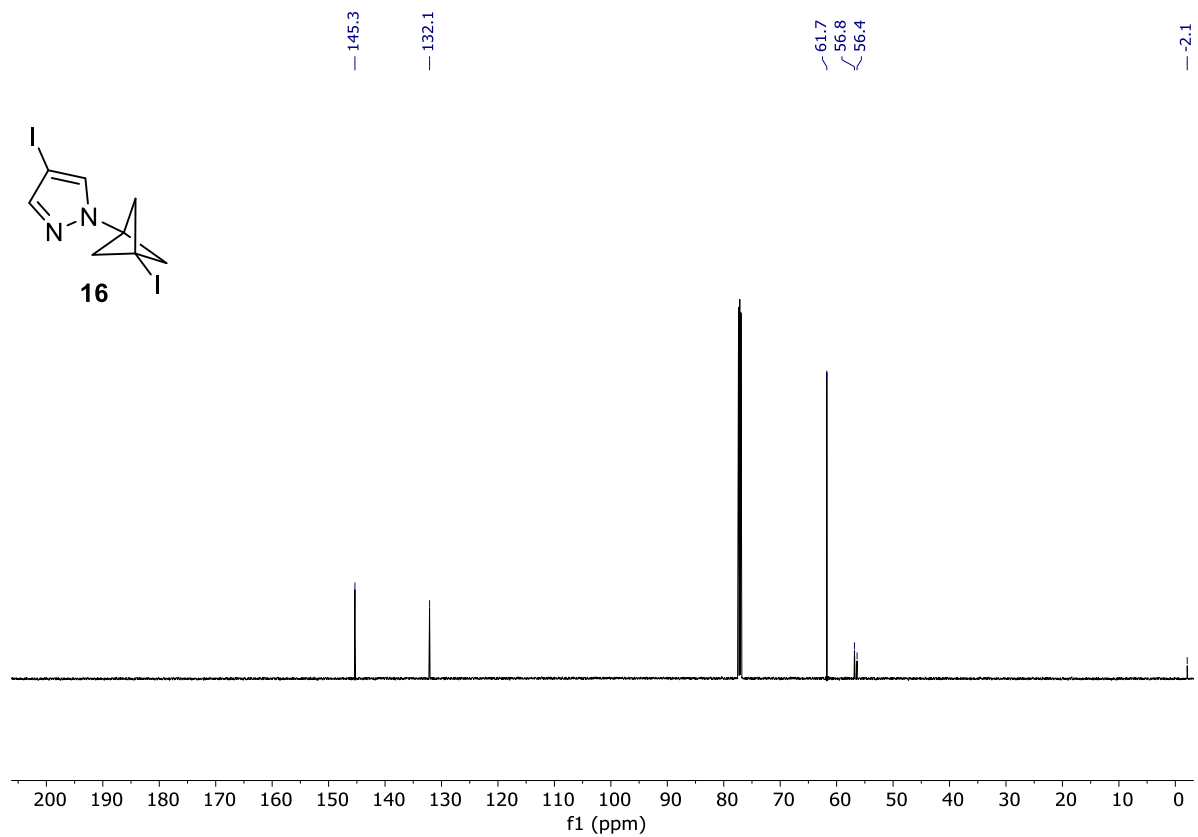
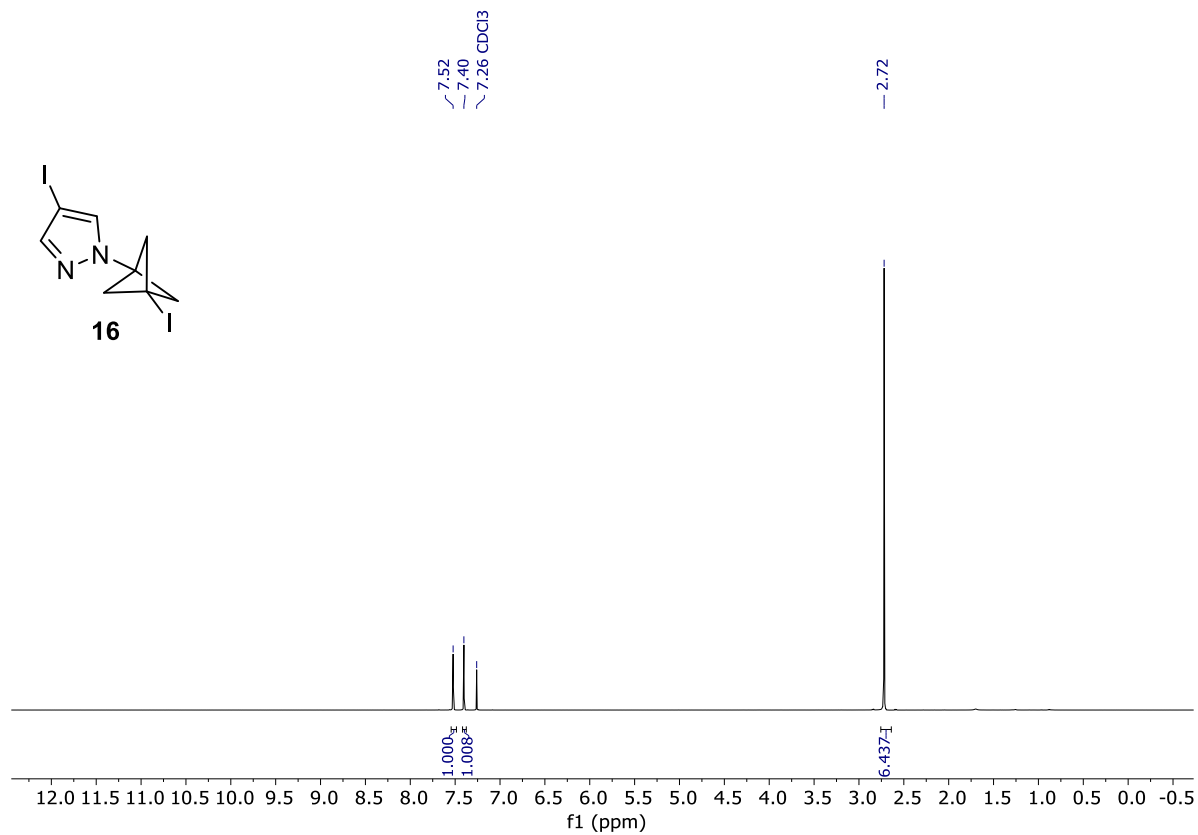


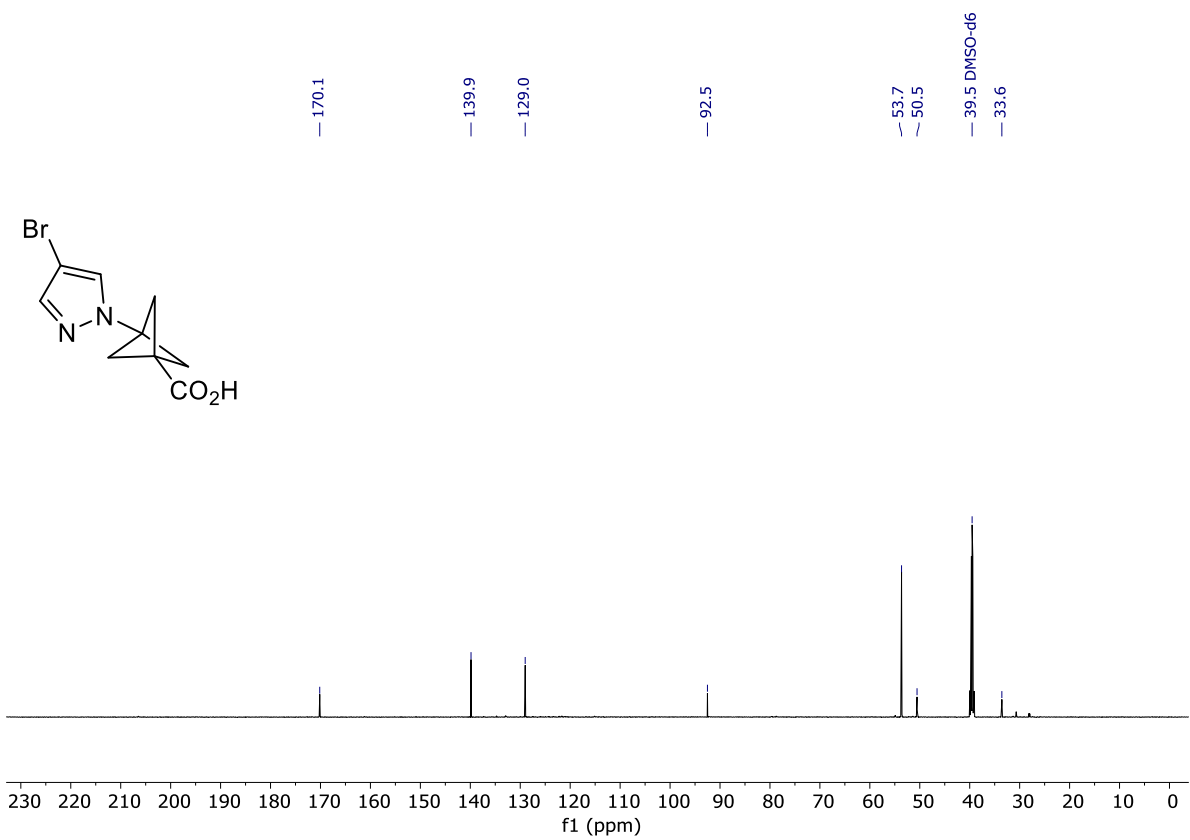
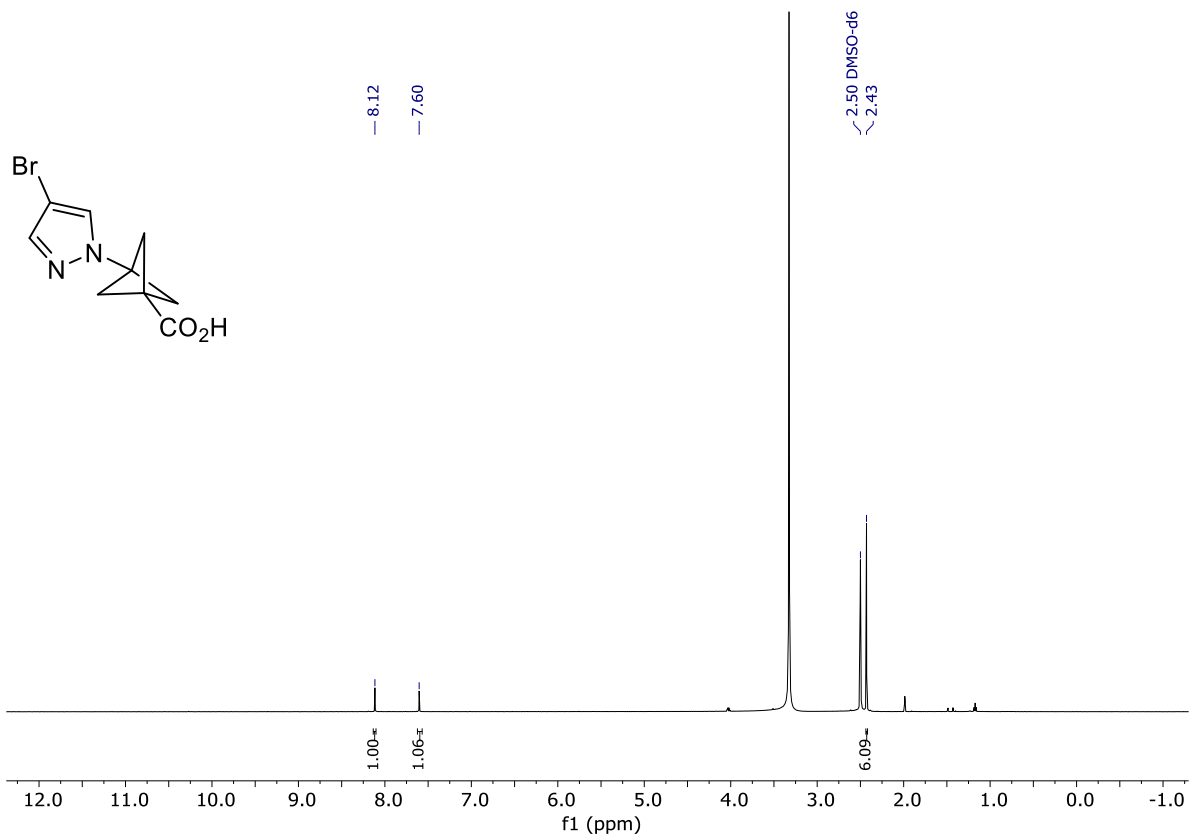


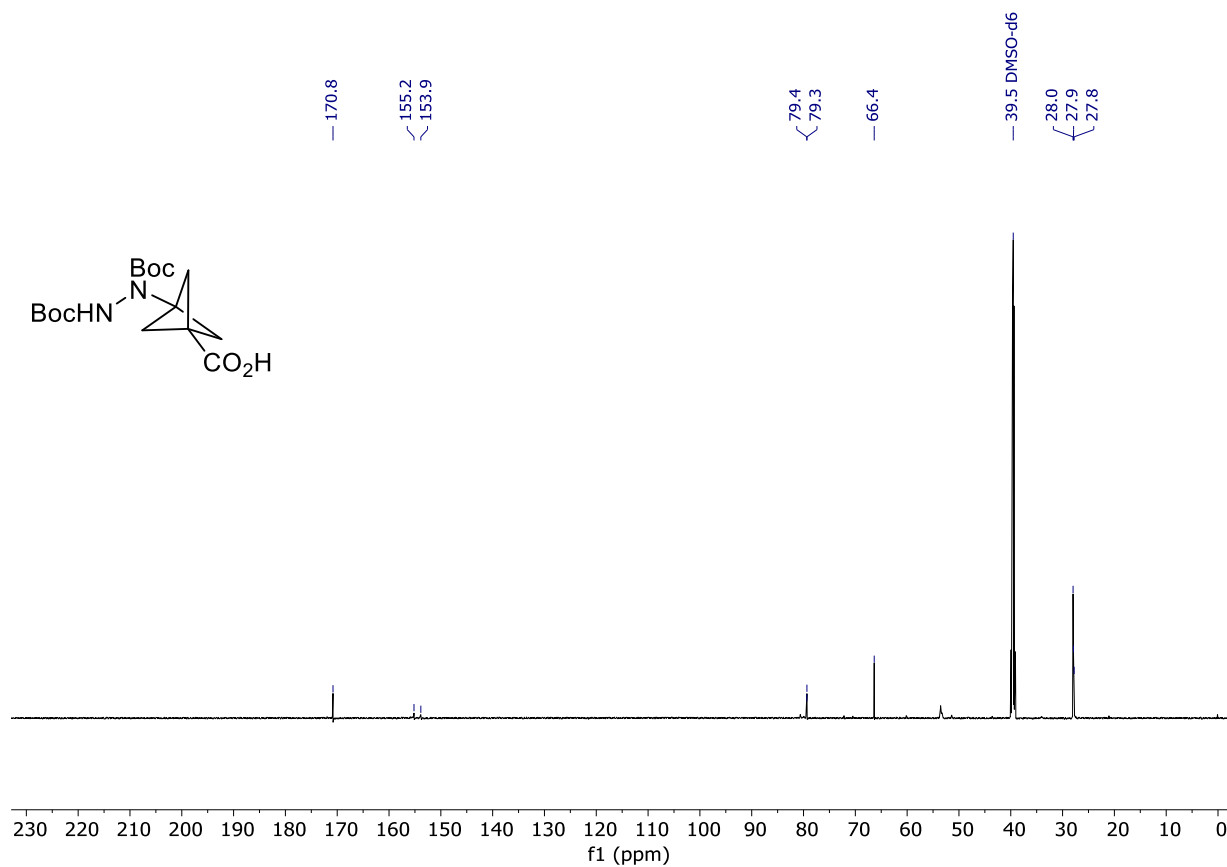
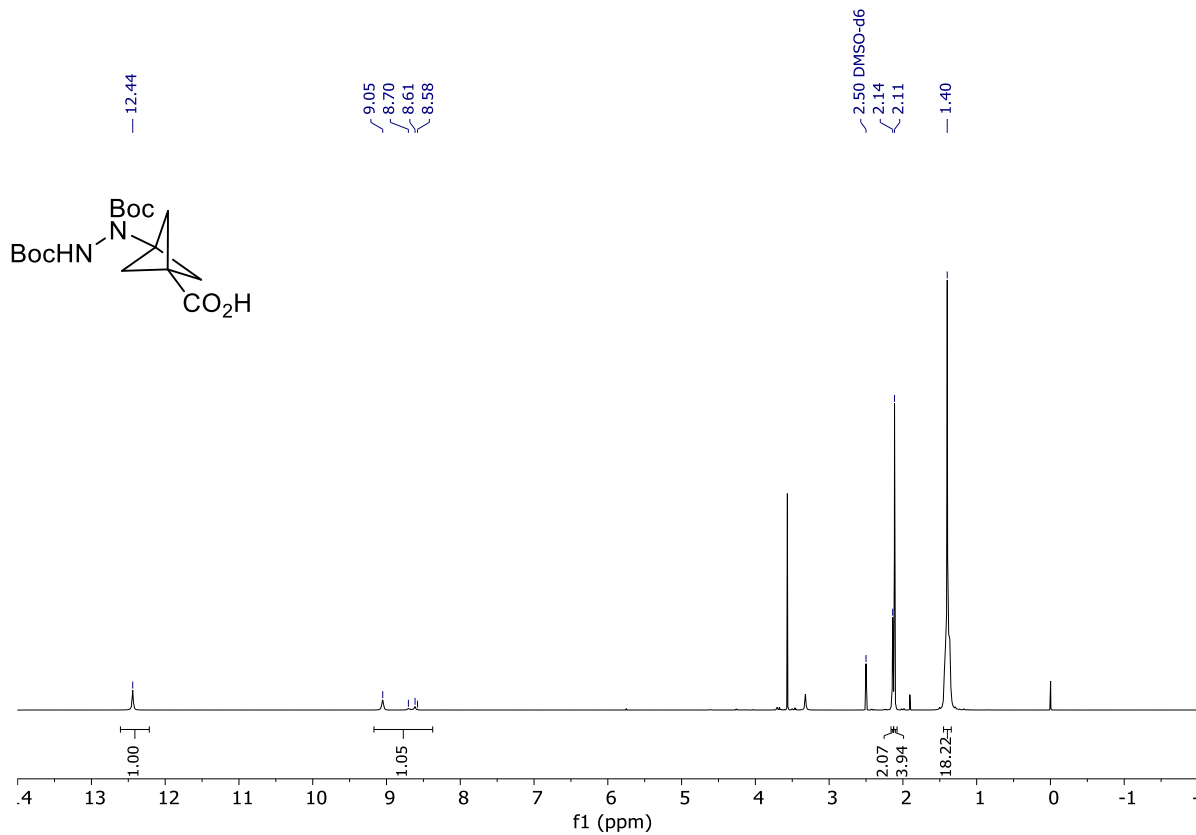


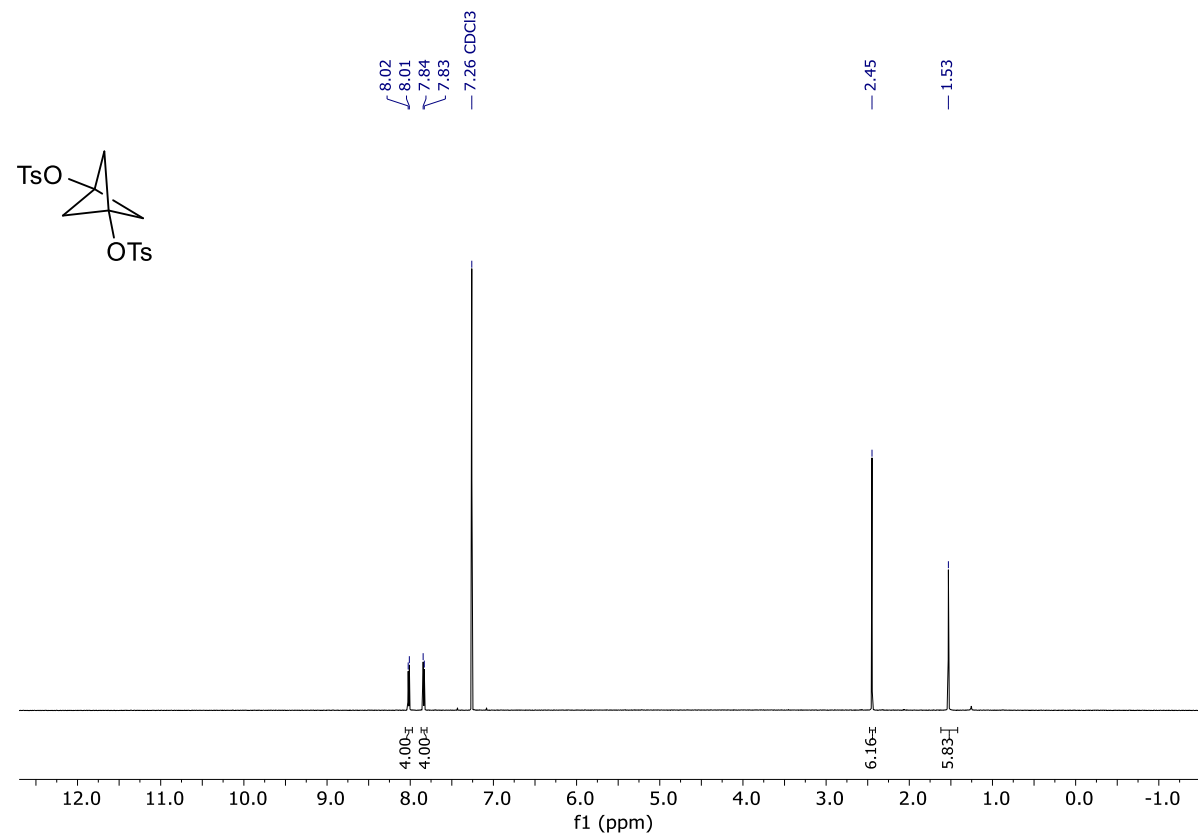
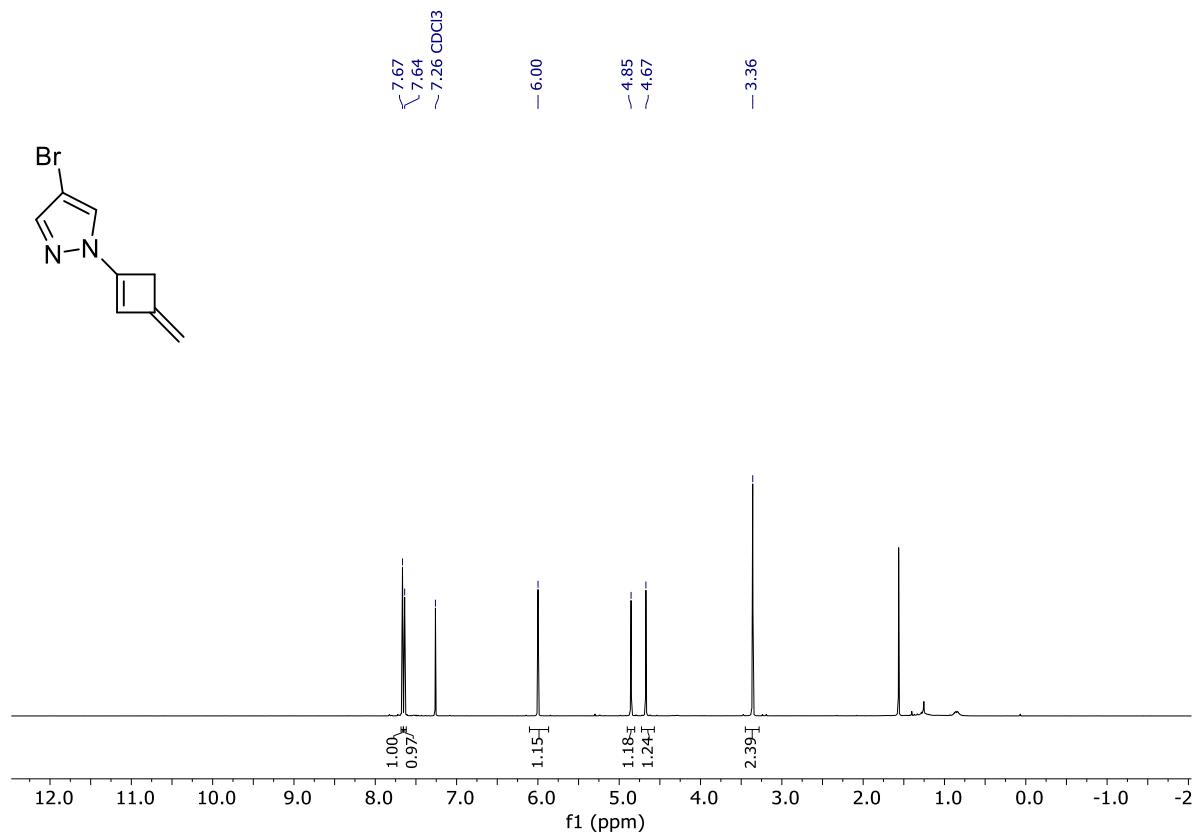


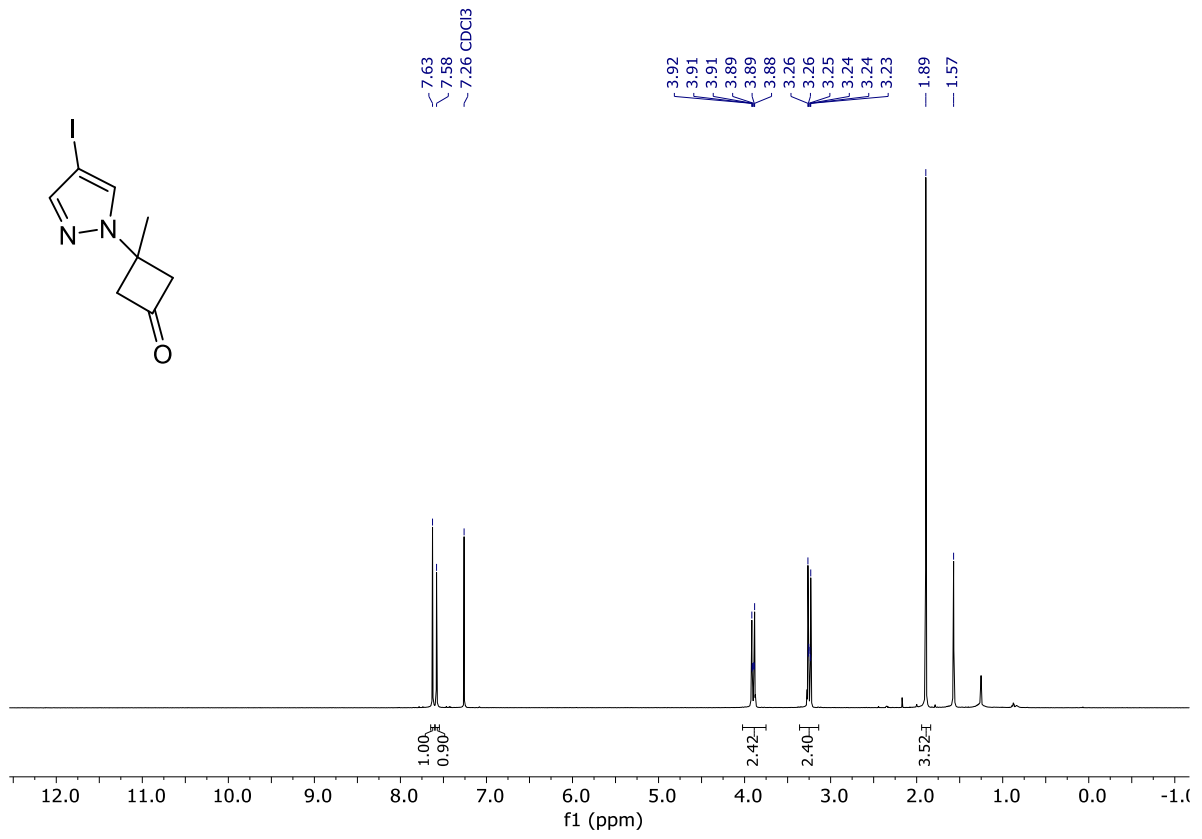












X. References

1. VanHeyst, M. D.; Qi, J.; Roecker, A. J.; Hughes, J. M. E.; Cheng, L.; Zhao, Z.; Yin, J. Continuous Flow-Enabled Synthesis of Bench-Stable Bicyclo[1.1.1]pentane Trifluoroborate Salts and Their Utilization in Metallaphotoredox Cross-Couplings. *Org. Lett.* **2020**, *22*, 1648–1654.
2. Goh, Y. L.; Adsool, V. A. Radical Fluorination Powered Expedient Synthesis of 3-Fluorobicyclo[1.1.1]pentan-1-amine. *Org. Biomol. Chem.* **2015**, *13*, 11597–11601.
3. MestReNova Version 12.0.1-20560 © 2018 Mestrelab Research S.L.
4. Le, C.; Wismer, M. K.; Shi, Z.-C.; Zhang, R.; Conway, D. V.; Li, G.; Vachal, P.; Davies, I. W.; MacMillan, D. W. C. A General Small-Scale Reactor To Enable Standardization and Acceleration of Photocatalytic Reactions. *ACS Cent. Sci.* **2017**, *3*, 647–653.
5. Yufan, L.; Zhang, X.; MacMillan, D. W. C. Decarboxylative sp³ C-N Coupling via Dual Copper and Photoredox Catalysis. *Nature* **2018**, *559*, 83–88.
6. Bunker, K. D.; Sach, N. W.; Huang, Q.; Richardson, P. F. Scalable Synthesis of 1-Bicyclo[1.1.1]pentylamine via a Hydrohydrazination Reaction. *Org. Lett.* **2011**, *13*, 4746–4748.
7. (a) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S. Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209–3226. (b) Hughes, J. M. E.; Scarlata, D. A.; Chen, A. C.-Y.; Burch, J. D.; Gleason, J. L. Aminoalkylation of [1.1.1]Propellane Enables Direct Access to High Value 3-Alkylbicyclo[1.1.1]pentan-1-amines. *Org. Lett.* **2019**, *21*, 6800–6804.
8. Yatham, V. R.; Bellotti, P.; König, B. Decarboxylative hydrazination of unactivated carboxylic acids by cerium photocatalysis. *Chem. Commun.* **2019**, *55*, 3489–3492.
9. (a) Lang, S. B.; Cartwright, K. C.; Welter, R. S.; Locascio, T. M.; Tunge, J. A. Photocatalytic Aminodecarboxylation of Carboxylic Acids. *Eur. J. Org. Chem.* **2016**, 3331–3334. (b) Hu, A.; Guo, J.-J.; Pan, H.; Zuo, Z. Selective Functionalization of Methane, Ethane, and Higher Alkanes by Cerium Photocatalysis. *Science* **2018**, *361*, 668–672.
10. Goh, Y. L.; Adsool, V. A. Radical Fluorination Powered Expedient Synthesis of 3-Fluorobicyclo[1.1.1]pentan-1-amine. *Org. Biomol. Chem.* **2015**, *13*, 11597–11601.
11. (a) Adcock, J. L.; Gakh, A. A. Synthesis of Novel Cage Quaternary Salts via Nucleophilic Substitution of 1,3-Diiodobicyclo[1.1.1]pentane. Further Evidence for a Stable 3-Iodo-1-bicyclo[1.1.1]pentyl Cation. *Tett. Lett.* **1992**, *33*, 4875–4878. (b) Adcock, J. L.; Gakh, A. A. Nucleophilic Substitution in 1-Substituted 3-Iodobicyclo[1.1.1]pentanes. A New Synthetic Route to Functionalized Bicyclo[1.1.1]pentane Derivatives. *J. Org. Chem.* **1992**, *57*, 6206–6210. (c) Wiberg, K. B.; McMurdie, N. Formation and Reactions of Bicyclo[1.1.1]pentyl-I Cations. *J. Am. Chem. Soc.* **1994**, *116*, 11990–11998.

12. Wiberg, K. B.; McMurdie, N. Formation of [1.1.1]propellane by nucleophilic attack on 1,3-diiodobicyclo[1.1.1]pentane. Unrearranged carbocation intermediates in the reaction of [1.1.1]propellane with electrophiles. *J. Am. Chem. Soc.* **1991**, *113*, 8995-8996.
13. <http://chemlabs.princeton.edu/macmillan/wp-content/uploads/sites/6/Decarboxylative-C-N-coupling-recent-progress-09-20182.pdf>
14. Kanazawa, J.; Maeda, K.; Uchiyama, M. Radical multicomponent carboamination of [1.1.1]propellane. *J. Am. Chem. Soc.* **2017**, *139*, 17791–17794.
15. (a) Goh, Y. L.; Adsool, V. A. Radical Fluorination Powered Expedient Synthesis of 3-Fluorobicyclo[1.1.1]pentan-1-amine. *Org. Biomol. Chem.* **2015**, *13*, 11597–11601. (b) Ventre, S.; Petronijevic, F. R.; MacMillan, D. W. C. Decarboxylative Fluorination of Aliphatic Carboxylic Acids via Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 5654-5657. (c) Patrick, T. B.; Johri, K. K.; White, D. H. Fluorodecarboxylation with Xenon Difluoride. *J. Org. Chem.* **1983**, *48*, 4158–4159.
16. (a) Xia, J.-B.; Ma, Y.; Chen, C. Vanadium-Catalyzed C(sp³)–H Fluorination Reactions. *Org. Chem. Front.* **2014**, *1*, 468–472; (b) Amaoka, Y.; Nagatomo, M.; Inoue, M. Metal-Free Fluorination of C(sp³)-H Bonds Using a Catalytic N-Oxyl Radical. *Org. Lett.* **2013**, *15*, 2160–2163; (c) Pitts, C. R.; Ling, B.; Woltornist, R.; Liu, R.; Lectka, T. Triethylborane-Initiated Radical Chain Fluorination: A Synthetic Method Derived from Mechanistic Insight. *J. Org. Chem.* **2014**, *79*, 8895–8899.
17. Conditions inspired by: (a) Harris, M. R.; Li, Q.; Lian, Y.; Xiao, J.; Londregan, A. T. Construction of 1-Heteroaryl-3-azabicyclo[3.1.0]hexanes by sp³–sp² Suzuki–Miyaura and Chan–Lam Coupling Reactions of Tertiary Trifluoroborates. *Org. Lett.* **2017**, *19*, 2450–2453. (b) Bénard, S.; Neuville, L.; Zhu, J. Copper-Mediated *N*-Cyclopropylation of Azoles, Amides, and Sulfonamides by Cyclopropylboronic Acid. *J. Org. Chem.* **2008**, *73*, 6441–6444.