Supporting Information

Synthesis and Chemoselective Ligations of MIDA Acylboronates with *O*-Me Hydroxylamines

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General methods: Unless otherwise noted, all reactions were carried out in oven-dried glassware sealed with rubber septa under an atmosphere of dry N_2 and were stirred with Teflon-coated magnetic stir bars. Thin layer chromatography (TLC) was performed on Merck TLC plates (0.25 mm) pre-coated with silica gel 60 F254 and visualized by UV quenching and staining with $KMnO_4$ or ninhydrin solution. Flash column chromatography was performed under a forced-flow of air using Silicycle SiliaFlash F60 (40–63 μm particle size). Peptides were purified by high performance liquid chromatography (HPLC) on Jasco analytical and preparative instruments with dual pumps, mixer and degasser, a variable wavelength UV detector and a Rheodyne 7725i injector fitted with a 20 to 1000 µL sample loop. The mobile phase for analytical and preparative HPLC were Millipore-H_2O with 0.1% TFA (Buffer A) and HPLC grade MeCN with 0.1% TFA (Buffer B). The eluent was monitored simultaneously at 220 nm, 254 nm and 301 nm. Flow rates for analytical (4.6 x 250 mm) and preparative (20 x 250mm) HPLC were 1 mL and 10 mL respectively. NMR spectra were recorded on a Bruker AV-300, a Bruker AV-400, a Bruker AV-III-500 or a Bruker DRX-II-500, AV-III-600. Data for ^{1}H NMR are reported as follows: chemical shift (multiplicity, coupling constants where applicable, number of hydrogens). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (doublet of triplet), ddt (doublet of doublet of triplet), m (multiplet), br (broad). In ^{19}F NMR, trifluoroborate multiplets are reported as the average of the observed signals. IR spectra were recorded on a Jasco FT/IR-4100 spectrometer and only major peaks are reported in frequency of absorption (cm^{-1}). Melting points were measured on an Electrothermal Mel-Temp melting point apparatus using open glass capillaries and are uncorrected. Optical rotations were measured on a Jasco P-1010 operating at the sodium D line with a 100 mm path length cell. LCMS analysis was performed on a Dionex UltiMate 3000 RSLC connected to a Surveyor MSQ Plus mass spectrometer; a reversed–phase RESTEK Pinnacle II C18 (4.6 x 50 mm) column was used, running a gradient of 5 to 100% MeCN in H2O over 6.5 min and 100% MeCN for 2.5 min. High-resolution mass spectra were obtained by the mass spectrometry service of the ETH Zürich Laboratorium für Organische Chemie on a Waters AutoSpec Ultima (EI), a Bruker Daltonics maXis ESI-QTOF spectrometer (ESI), or a Bruker Daltonics SOLARIX spectrometer (MALDI).

Solvents and reagents: All organic solvents (*t*BuOH, MeOH, DMF, THF, CH_2Cl_2, MeCN, DMSO) were used as supplied (ACS or HPLC grade) unless otherwise noted. THF was purified by distillation from sodium benzophenone ketyl prior to use. CH_2Cl_2 was purified by distillation from CaH_2. Dry MeOH, MeCN, DMSO and toluene were purchased from commercial suppliers. Et_3N and BF_3•Et_2O were purified by distillation from CaH_2. Pyridine and 2,6-lutidine were purified by distillation from KOH. *N,O*-Bis(trimethylsilyl)trifluoroacetamide was purified by distillation. *N*-

Methyliminodiacetic acid (MIDA),[1] MIDA bissodium salt,[2] potassium acyltrifluoroborates (KATs)[3] and *O*-Bz hydroxylamines[4] were prepared by the reported procedures. All other starting materials were used as supplied by commercial vendors or prepared by the method described in the corresponding reference.

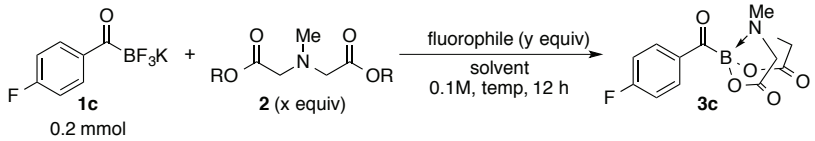
Solid phase peptide synthesis (SPPS): Peptides were synthesized on a CS Bio 136X peptide synthesizer using Fmoc SPPS chemistry. An inline UV detector was used for monitoring Fmoc deprotection. The following Fmoc amino acids with side-chain protection groups were used: Fmoc-Ala-OH, Fmoc-Asp(O*t*Bu)-OH, Fmoc-Cys(Trt)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Glu(O*t*Bu)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Phe-OH. Fmoc deprotections were performed with 20% piperidine in DMF (2 x 8 min) and monitored by UV at 304 nm with a feedback loop to ensure complete Fmoc removal. Couplings were performed with Fmoc-amino acid (4.0 equiv to resin substitution), HCTU (3.9 equiv) and *i*Pr$_2$NEt (6.0 equiv) in DMF. After pre-activating for 3 min, the solution was transferred and allowed to react with the peptide on-resin for either 45 min or 75 min depending on the amino acid. After coupling, the resin was treated with 20% acetic anhydride in DMF for capping any unreacted free amine.

1 Ballmer, S. G.; Gillis, E. P.; Burke, M. D. *Org. Synth.* **2009**, *86*, 344–359.
2 Uno, B. E.; Gillis, E. P.; Burke, M. D. *Tetrahedron* **2009**, *65*, 3130–3138.
3 (a) Dumas, A. M.; Bode, J. W. *Org. Lett.* **2012**, *14*, 2138–2141. (b) Erős, G.; Kushida, Y.; Bode, J. W. *submitted*.
4 (a) Phanstiel, O.; Wang, Q. X.; Powell, D. H.; Ospina, M. P.; Leeson, B. A. *J. Org. Chem.* **1999**, *64*, 803–806. (b) Berman, A. M.; Johnson, J. S. *J. Org. Chem.* **2006**, *71*, 219–224.

1. Preparation of MIDA acylboronates from KATs

1.1 Optimization study:

Table S1. Condition screening for MIDA acylboronate synthesis



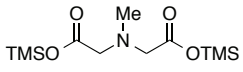
entry	R	equiv	fluorophile (y equiv)	solvent	temp (˚C)	yield[a] (%)	remarks
1	H	1.0	BF_3•Et_2O (1.0)	MeCN	RT	12	2,6-lutidine (2.0 equiv)
2	Na	1.0	BF_3•Et_2O (1.0)	MeCN	RT	33	
3	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	74	
4	TMS	1.0	HBF_4 (1.0)	MeCN	RT	<5	
5	TMS	1.0	TMSCl (1.0)	MeCN	RT	16	
6	TMS	1.0	$SiCl_4$ (1.0)	MeCN	RT	<5	
7	TMS	1.0	silica gel	MeCN	RT	6	150 mg/mmol
8	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	60	51	
9	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	0	49	
10	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	–20	18	
11	TMS	1.0	BF_3•Et_2O (1.0)	THF	RT	70	
12	TMS	1.0	BF_3•Et_2O (1.0)	CH_2Cl_2	RT	48	
13	TMS	1.0	BF_3•Et_2O (1.0)	MeCN/ Toluene	RT	55	
14	TMS	1.5	BF_3•Et_2O (1.0)	MeCN	RT	72	
15	TMS	1.0	BF_3•Et_2O (1.5)	MeCN	RT	<5	
16	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	70	0.025 M
17	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	61	0.5 M
18	TMS	1.0	BF_3•Et_2O (1.0)[b]	MeCN	RT	76	slow addition
19	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	41	pyridine (1.0 equiv)
20	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	48	Et_3N (1.0 equiv)
21	TMS	1.0	BF_3•Et_2O (1.0)	MeCN	RT	20	PPh_3 (1.0 equiv)

[a]Yield was determined by using Bn_2O as an internal standard in ^{1}H-NMR spectrum. [b]BF_3•Et_2O was added over 6 h.

General procedure for Table S1:

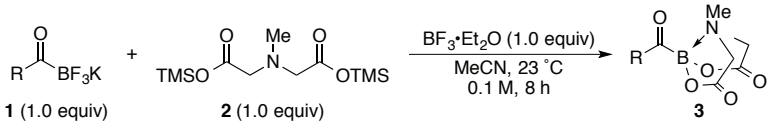
Prior to the reactions, all solvents were degassed by freeze-pump-thaw cycles (3 times). To a flame dried Schlenk flask equipped with a magnetically stirred chip was added potassium 4-fluorobenzoyltrifluoroborate (46.0 mg, 0.2 mmol, 1.0 equiv). Under an N_2 atmosphere, *N*-methyliminodiacetic acid (MIDA) or its derivatives (x equiv) were added as a solution or slurry in the indicated solvent and the flask was kept at the indicated temperature. To this suspension was

added the fluorophile (y equiv) dropwise. After 12 h, Bn_2O (9.7 μL, 0.05 mmol, 0.25 equiv, 4H = 1.0 equiv) was added and an aliquot of the sample was removed, to which d_6-DMSO was added. This sample was connected directly to a vacuum line to remove all volatiles. Crude ^{1}H-NMR was recorded to analyze the reaction. (*NOTE: It is important not to dry crude sample completely and to keep the product in a DMSO solution in order to obtain reproducible results.*)



MIDA bis(trimethylsilyl) ester (2): To a flame dried Schlenk flask equipped with a magnetically stirred chip was added *N*-methyliminodiacetic acid (MIDA) (147.1 mg, 1.0 mmol, 1.0 equiv). Anhydrous MeCN (0.36 mL, 1.0 M) and *N,O*-bis(trimethylsilyl)trifluoroacetamide (640 μL, 2.4 mmol, 2.4 equiv) were added and the reaction was stirred for 3 h at 60 ˚C. After cooling to RT, all volatiles were removed carefully under vacuum and further dried for 4 h at 60 ˚C to give a colorless oil (quantitative yield). Spectroscopic data matched with those reported.[5]

1.2 Substrate scope (Scheme 2):

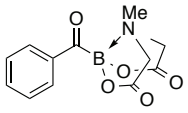


Scheme S1. MIDA acylboronate synthesis

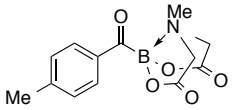
General procedure for MIDA acylboronate formation (Scheme S1)

To a flame dried 25 mL Schlenk flask equipped with a magnetically stirred chip was added potassium acyltrifluoroborate **1** (1.0 mmol, 1.0 equiv). A solution of MIDA bis(trimethylsilyl) ester **2** (292 mg, 1.0 mmol, 1.0 equiv) in anhydrous MeCN (7.0 mL; washed with 3.0 mL) was added. To this suspension was added BF_3•Et_2O (123 μL, 1.0 mmol, 1.0 equiv) dropwise. The mixture became homogeneous and was stirred for 8 h at RT. After the addition of DMSO (*ca.* 0.5 mL), the reaction mixture was carefully evaporated, maintaing the temperature of the water bath at less than 30 ˚C until total volume was *ca.* 1 mL. This solution was directly placed on silica gel column chromatography and the product eluted with hexanes/EtOAc 3:2 to 0:1 to afford a pale yellow solid, which was washed with anhydrous Et_2O to give MIDA acylboronate **3** as a white solid. (*NOTE: It is important to maintain the bath temperature during the evaporation and not to dry crude sample completely in order to obtain reproducible results.*)

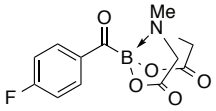
5. Bagutski, V.; Grosso, A. D.; Carrillo, J. A.; Cade, I. A.; Helm, M. D.; Lawson, J. R.; Singleton, P. J.; Solomon, S. A.; Marcelli, T.; Ingleson, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 474–487.



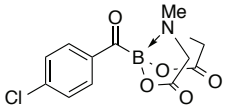
MIDA benzoylboronate (3a): Prepared by the general procedure from potassium benzoyltrifluoroborate **1a** (212 mg, 1.0 mmol), and isolated as a white solid (159 mg, 61% yield). Spectroscopic data matched those reported.[6]



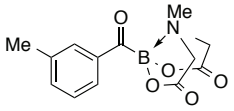
MIDA 4-methylbenzoylboronate (3b): Prepared by the general procedure from potassium 4-methylbenzoyltrifluoroborate **1b** (226 mg, 1.0 mmol), and isolated as a white solid (157 mg, 57% yield). Spectroscopic data matched those reported.[6]



MIDA 4-fluorobenzoylboronate (3c): Prepared by the general procedure from potassium 4-fluorobenzoyltrifluoroborate **1c** (230 mg, 1.0 mmol), and isolated as a white solid (181 mg, 65% yield). Spectroscopic data matched those reported.[6]

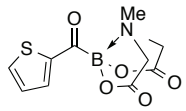


MIDA 4-chlorobenzoylboronate (3d): Prepared by the general procedure from potassium 4-chlorobenzoyltrifluoroborate **1d** (246 mg, 1.0 mmol), and isolated as a white solid (204 mg, 69% yield). **IR** (thin film) 3235, 3019, 2963, 2916, 1770, 1565, 1282, 1081 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3CN) δ 8.07-8.03 (m, 2H), 7.55-7.52 (m, 2H), 4.10 (d, *J* = 16.8 Hz, 2H), 3.99 (d, *J* = 16.8 Hz, 2H), 2.93 (s, 3H); **^{13}C NMR** (150 MHz, CD_3CN) δ 225.0, 168.8, 140.1, 139.8, 130.9, 129.7, 62.9, 47.4; **^{11}B NMR** (160 MHz, CD_3CN) δ 5.37; **HRMS** (ESI) calc'd for $C_{12}H_{12}BClNO_5$ $[M + H]^+$: 296.0494, found: 296.0500.

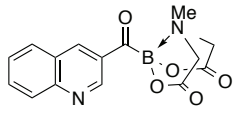


MIDA 3-methylbenzoylboronate (3e): Prepared by the general procedure from potassium 3-methylbenzoyltrifluoroborate **1e** (226 mg, 1.0 mmol), and isolated as a white solid (176 mg, 64% yield). **IR** (thin film) 3013, 2955, 1775, 1266, 1042 cm^{-1}; **^{1}H NMR** (300 MHz, CD_3CN) δ 7.89-7.82 (m, 1H), 7.84-7.82 (m, 1H), 7.45-7.38 (m, 2H), 4.09 (d, *J* = 16.8 Hz, 2H), 3.98 (d, *J* = 16.8 Hz, 2H), 2.93 (s, 3H), 2.41 (s, 3H); **^{13}C NMR** (150 MHz, CD_3CN) δ 226.4, 169.0, 141.9, 139.4, 134.8, 129.5, 129.2, 126.7, 63.0, 47.4, 21.4; **^{11}B NMR** (160 MHz, CD_3CN) δ 5.43; **HRMS** (ESI) calc'd for $C_{13}H_{14}BKNO_5$ $[M + K]^+$: 314.0599, found: 314.0604.

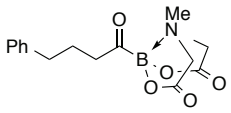
6. He, Z.; Trinchera, P.; Adachi, S.; St Denis, J. D.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2012**, *51*, 11092–11096.



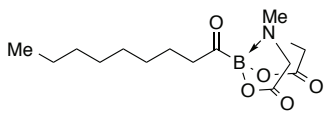
MIDA 2-thienoylboronate (3g): Prepared by the general procedure from potassium 2-thienoylborate **1g** (218 mg, 1.0 mmol), purified by column chromatography (hexanes/EtOAc from 3:2 to 1:4) and isolated as a pale yellow solid (168 mg, 63% yield). **IR** (thin film) 2956, 2917, 2849, 1767, 1589, 1408, 1268, 1027, 767 cm^{-1}; **^{1}H NMR** (300 MHz, CD_3CN) δ 8.17 (dd, *J* = 1.2, 3.9 Hz, 1H), 7.83 (dd, *J* = 1.2, 4.8 Hz, 1H), 7.24 (dd, *J* = 3.9, 4.8 Hz, 1H), 4.10 (d, *J* = 17.0 Hz, 2H), 3.98 (d, *J* = 17.0 Hz, 2H), 2.89 (s, 3H); **^{13}C NMR** (150 MHz, CD_3CN) δ 216.0, 168.9, 150.4, 136.1, 135.6, 130.0, 62.9, 47.5; **^{11}B NMR** (160 MHz, CD_3CN) δ 5.33; **HRMS** (ESI) calc'd for $C_{10}H_{11}BNO_5S$ $[M + Na]^+$: 268.0447, found: 268.0452.



MIDA 3-quinolinoylboronate (3h): Prepared by the general procedure from potassium 3-quinolinoylborate **1h** (263 mg, 1.0 mmol), purified by column chromatography (*t*BuOMe/MeCN from 3:1 to 3:2) and isolated as a pale brown solid (163 mg, 52% yield). **IR** (thin film) 2953, 2923, 2854, 1774, 1462, 1274, 1096, 1043 cm^{-1}; **^{1}H NMR** (600 MHz, CD_3CN) δ 9.35 (d, *J* = 1.8 Hz, 1H), 9.03 (dd, *J* = 0.8, 1.8 Hz, 1H), 8.13-8.00 (m, 2H), 7.88 (ddd, *J* = 1.2, 6.6, 8.4 Hz, 1H), 7.68 (ddd, *J* = 1.2, 6.6, 7.8 Hz, 1H), 4.15 (d, *J* = 16.8 Hz, 2H), 4.04 (d, *J* = 16.8 Hz, 2H), 2.97 (s, 3H); **^{13}C NMR** (150 MHz, CD_3CN) δ 226.0, 168.8, 150.5, 149.5, 139.3, 133.6, 132.9, 130.9, 130.1, 128.4, 127.9, 63.0, 47.6; **^{11}B NMR** (160 MHz, CD_3CN) δ 5.40; **HRMS** (ESI) calc'd for $C_{15}H_{14}BN_2O_5$ $[M + H]^+$: 313.0993, found: 313.0997.



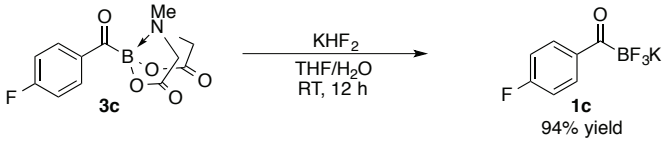
MIDA 4-phenylbutanoylboronate (3i): Prepared by the general procedure from potassium 4-phenylbutanoyltrifluoroborate (254 mg, 1.0 mmol), and isolated as a white solid (224 mg, 74% yield). **IR** (thin film) 3024, 2927, 2859, 1771, 1454, 1283, 1061, 989 cm^{-1}; **^{1}H NMR** (400 MHz, CD_3CN) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 4.02 (d, *J* = 17.0 Hz, 2H), 3.88 (d, *J* = 17.0 Hz, 2H), 2.80 (s, 3H), 2.65 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 1.81 (tt, *J* = 7.2, 7.8 Hz, 2H); **^{13}C NMR** (150 MHz, CD_3CN) δ 239.3, 169.0, 143.4, 129.4, 129.3, 126.7, 63.0, 47.4, 46.8, 35.8, 24.6; **^{11}B NMR** (160 MHz, CD_3CN) δ 4.26; **HRMS** (MALDI) calc'd for $C_{15}H_{18}BNNaO_5$ $[M + Na]^+$: 326.1173, found: 326.1171.



MIDA nonanoylboronate (3j): Prepared by the general procedure from potassium nonanoylborate (248 mg, 1.0 mmol), and isolated as a white solid (229 mg, 77% yield). **IR** (thin film) 3524, 2924, 2854, 1764, 1656, 1466, 1292, 1057, 994, 872 cm^{-1}; **^{1}H NMR** (300 MHz, CD_3CN) δ 4.02 (d, *J* = 16.8 Hz, 2H), 3.88 (d, *J* = 16.8 Hz, 2H), 2.80 (s, 3H), 2.62 (t, *J* = 7.2 Hz), 1.54-1.44 (m, 2H), 1.34-1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR** (150 MHz, CD_3CN) δ 239.8, 169.1, 63.0, 47.5, 47.4, 32.6, 30.2, 30.0, 29.9,

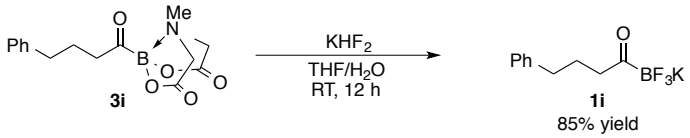
23.4, 22.8, 14.4; **^{11}B NMR** (160 MHz, CD_3CN) δ 4.26; **HRMS** (MALDI) calc'd for $C_{14}H_{24}BNNaO_5$ [M + Na]$^+$: 320.1642, found: 320.1640.

1.3 Conversion of MIDA Acylboronates to KATs (eq 1):



Scheme S2. Conversion to KAT **1c**

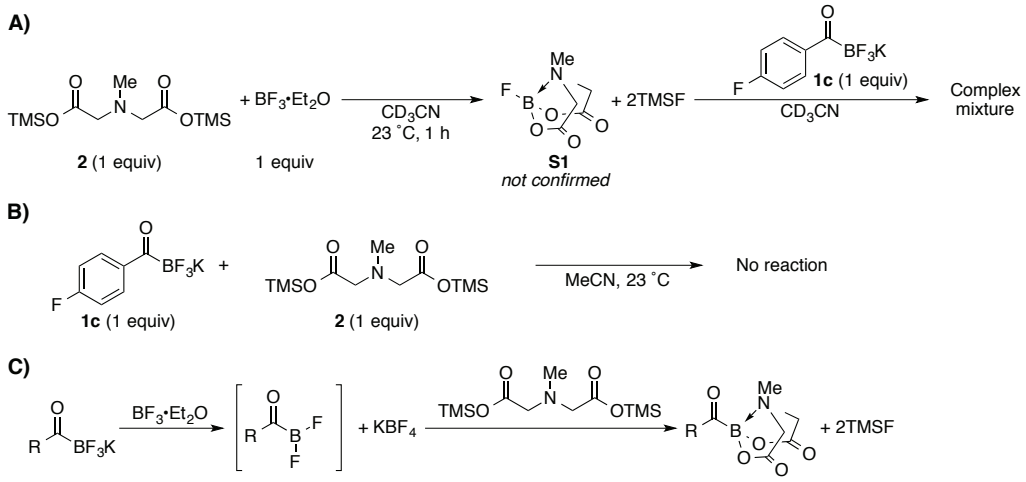
MIDA acylboronate **3c** (27.9 mg, 0.10 mmol, 1.0 equiv) was dissolved in THF (500 μL) and sat aq KHF_2 (250 μL) was added. The mixture was stirred for 12 h at RT and evaporated under reduced pressure. The obtained solid was further dried under vacuum at 60 ˚C for 4 h and acetone was added. The suspension was filtered and the filtrate was evaporated to give a white solid, which was washed with Et_2O to afford **1c** (21.6 mg, 94% yield).



Scheme S3. Conversion to KAT **1i**

MIDA acylboronate **3i** (30.3 mg, 0.10 mmol, 1.0 equiv) was dissolved in THF (500 μL) and sat aq KHF_2 (250 μL) was added. The mixture was stirred for 12 h at RT and evaporated under reduced pressure. The obtained solid was further dried under vacuum at 60 ˚C for 5 h, and acetone was added. The suspension was filtered and the filtrate was evaporated to give white solid, which was washed with Et_2O to afford **1i** (21.5 mg, 85% yield).

1.4 Mechanism of conversion of KATs to MIDA acylboronates:



Scheme S4. Mechanism of MIDA acylboronate formation. A) A control experiment to mix TMS_2-MIDA **2** and BF_3•Et_2O first, and then KAT **1c**. B) A control experiment to mix KAT **1c** and TMS_2-MIDA **2** in the absence of BF_3•Et_2O. C) A proposed mechanism for MIDA acylboronate formation.

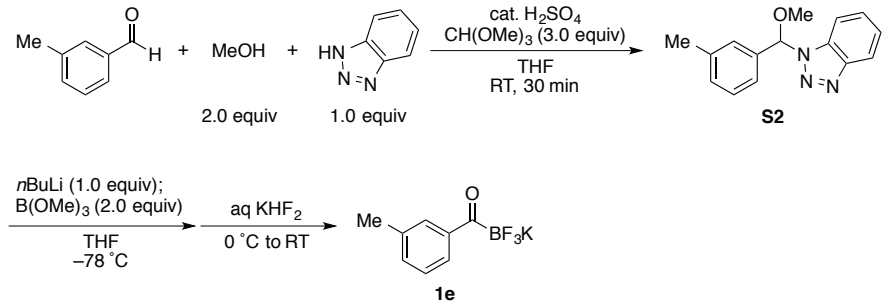
Discussion: In the control experiment Scheme S4A, TMS_2-MIDA **2** and BF_3•Et_2O were mixed in the absence of KAT**.** New peaks, including TMSF appeared in the NMR spectrum, but adding KAT **1c** to this solution did not form the MIDA acylboronate and a complex mixture was obtained. In the control experiment Scheme S4B, a mixture of KAT **1c** and TMS_2-MIDA **2** was prepared but no reaction was occurred without the addition of BF_3•Et_2O. Based on these results and the literature precedents, a proposed mechanism for formation of MIDA acylboroante is shown in Scheme S4C: BF_3•Et_2O first abstracts one fluorine atom from the KAT, generating acyldifluoroborane and KBF_4. This unstable intermediate reacts with TMS_2-MIDA **2** to form the product and TMSF (2 equiv)

Procedure for Scheme S4

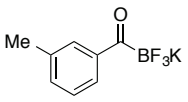
Experiment A: Prior to the reaction, a NMR tube was dried under vacuum for 3 h. To a solution of TMS_2-MIDA **2** (11.6mg, 0.04 mmol, 1 equiv) in dry CD_3CN (0.5 mL) in the dried NMR tube was added BF_3•Et_2O (0.4 M in CD_3CN, 100 μL, 0.04 mmol, 1 equiv) dropwise. ^1H NMR was recorded after 1 h. To this was directly added KAT **1c** (9.2 mg, 0.04 mmol, 1 equiv) carefully. The solution became homogenous soon, and the ^1H NMR spectra was recorded.

Experiment B: To a flame dried 10 mL Schlenk flask equipped with a magnetically stirred chip was added KAT **1c** (23.0 mg, 0.1 mmol, 1.0 equiv). A solution of MIDA bis(trimethylsilyl) ester **2** (0.1 mmol, 1.0 equiv) in anhydrous MeCN (1.0 mL) was added. The reaction was monitored by TLC and LC-MS.

1.5 Preparation of new KATs:



Scheme S5. Synthesis of KAT **1e**



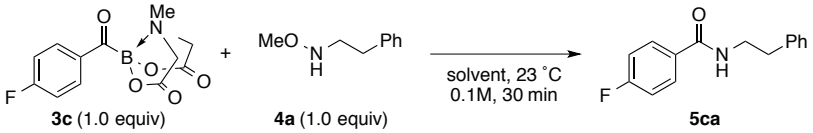
Potassium 3-methylbenzoyltrifluoroborate: 1e was prepared by following the reported procedure[3a] from 3-Methylbenzaldehyde and obtained as a white solid (1.78 g, 39% yield for 2 steps). **m.p.** 254 ˚C (decomp.); **IR** (thin film) 3397, 3022, 1637, 1594 cm^{-1}; **^{1}H NMR** (600 MHz, d_6-acetone) 7.90-7.88 (m, 2H), 7.28-7.24 (m, 2H), 2.34 (s, 3H); **^{13}C NMR** (150 MHz, d_6-acetone), 235.9, 142.3, 137.8, 132.5, 129.6, 128.4, 126.6, 21.4; **^{19}F NMR** (470 MHz, d_6-acetone) –144.5; **^{11}B NMR** (160 MHz, d_6-acetone) –0.79; **HRMS** (ESI) calc'd for $C_8H_7BF_3O$ $[M - K]^-$: 187.0549, found: 187.0540.

2. Amide-bond forming ligation of MIDA acylboronate with *O*-Me hydroxylamine

2.1 Condition screening for ligation:

2.1.1 Solvent screening:

Table S2. Solvent study for the amide-formation



3c (1.0 equiv) **4a** (1.0 equiv) **5ca**

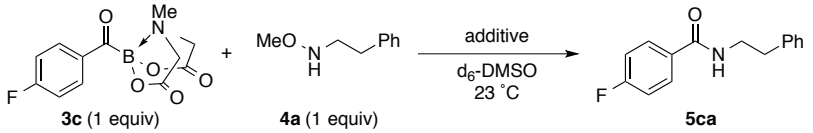
entry	solvent	conversion[a] (%)	remarks
1	DMSO	<5	
2	THF	<5	
3	MeCN	ND	
4	CH_2Cl_2	ND	
5	MeOH	70	
6	1:1 *t*BuOH/H_2O	60	
7	1:1 DMSO/H_2O	>90	
8	1:1 THF/H_2O	>90	The reaction was biphasic.
9	1:1 MeCN/H_2O	>90	
10	1:1 NMP/H_2O	>90	
11	9:1 DMSO/H_2O	>90	
12	2:8 DMSO/H_2O	>90	
13	1:1 DMSO/H_2O	50	**4a·(COOH)$_2$** was used.
14	1:1 DMSO/H_2O	50	**4a·HCl** was used.

[a] Conversion was determined by LC-MS analysis.

General procedure for Table S2: *O*-Methylhydroxylamine **4a** or its acid salt (0.05 mmol, 1.0 equiv) was dissolved in the indicated solvent and the MIDA acylboronate **3c** (11.5 mg, 0.05 mmol, 1.0 equiv) was added. An aliquot of the solution was removed and analyzed by LC-MS.

2.1.2 Additive screening:

Table S3. Additive study for the amide-formation



3c (1 equiv) **4a** (1 equiv) **5ca**

entry	additive	time	conversion (%)	remarks
1	none	20 h	20	
2	Tf_2NH (5 equiv)	20 h	20	**4a** was protonated.[a]
3	10% TFA	20 h	30	**4a** was protonated.[a]
4	10% HFIP	16 h	>90	
5	10% pyridine	12 h	35	
6	DABCO (5 equiv)	20 h	20	
7	PPh_3 (5 equiv)	20 h	20	
8	10% D_2O	15 min	>90	

[a] See Figure S1 for details.

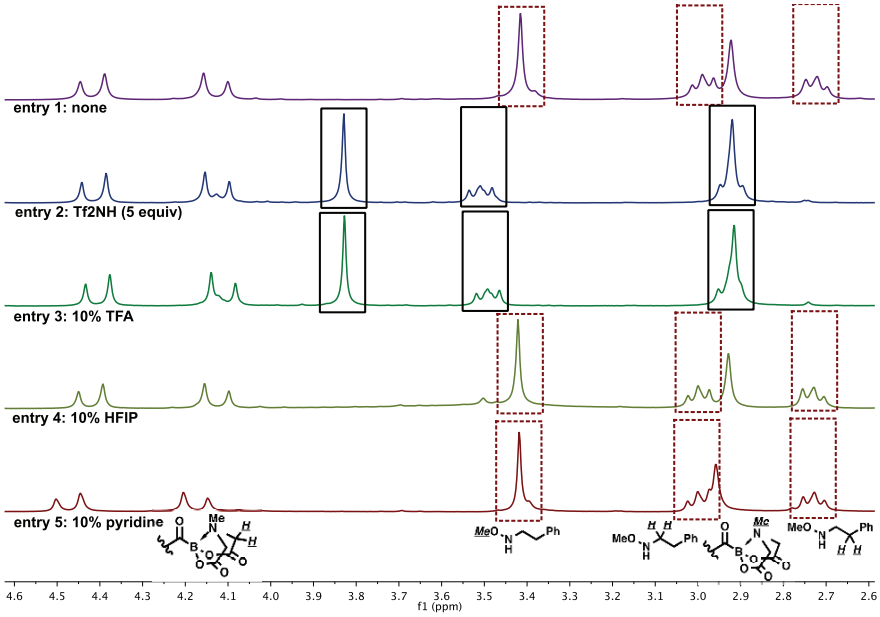


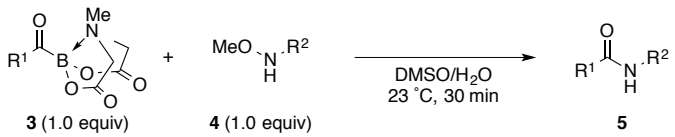
Figure S1. NMR spectra with additives at 5 min (Table S3)

Discussion: Strong Brønsted acids protonated hydroxylamine **4a**, but not the nitrogen in the MIDA moiety (Figure S1). Under these conditions, the reactions were neither retarded nor accelerated (Table S3, entries 1–3). Less acidic protic additives enhanced the reaction rate, and water was essential for rapid kinetics (entries 4 and 8). Pyridine also promoted the reaction, but other nucleophilic or Lewis basic additives were not beneficial (entires 5–7).

General procedure for additive screening (Table S3)

To MIDA acylboronate **3c** (8.3 mg, 0.03 mmol, 1 equiv) was added hydroxylamine **4a** (4.5 mg, 0.03 mmol, 1 equiv) in d_6-DMSO (0.6 mL). To this was added the indicated additive and the resulting homogenous solution was transferred to an NMR tube. The reaction was monitored by ^{1}H NMR (300 MHz).

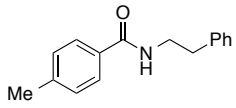
2.2 Substrate scope (Scheme 4):



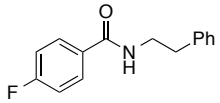
Scheme S6. Amide-formation of MIDA acylboronates and *O*-Me hydroxylamines

General procedure for Scheme S6: To a solution of hydroxylamine **4** (0.3 mmol) in 9:1 DMSO/H_2O (3.0 mL) was added the MIDA acylboronate **3** (0.3 mmol, 1.0 equiv) in one portion.

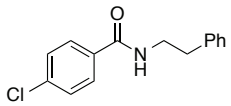
After the dilution with Et_2O, sat aq NH_4Cl was added. The aqueous phase was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography eluting hexane/EtOAc to afford the desired amide **5**.



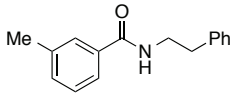
4-Methyl-*N*-phenethylbenzamide (5ba): Prepared by the general procedure from MIDA acylboronate **3b** (82.5 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a**[7] (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (65.3 mg, 91% yield). Spectroscopic data matched those reported.[8]



4-Fluoro-*N*-phenethylbenzamide (5ca): Prepared by the general procedure from MIDA acylboronate **3c** (83.7 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (67.9 mg, 93% yield). **IR** (thin film) 3348, 3070, 2929, 2860, 1640, 1546, 846 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.75-7.68 (m, 2H), 7.38-7.24 (m, 5H), 7.13-7.05 (m, 2H), 6.20 (brs, 1H), 3.72 (dt, *J* = 6.3, 6.9 Hz, 2H), 2.95 (t, *J* = 6.9 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.5, 164.8 (d, *J* = 249.8 Hz), 138.9, 130.9 (d, *J* = 3.2 Hz), 129.2 (d, *J* = 8.8 Hz), 128.9, 128.9, 126.8, 115.7 (d, *J* = 21.8 Hz), 41.3, 35.8; **^{19}F NMR** (282 MHz, $CDCl_3$) δ –108.4; **HRMS** (ESI) calc'd for $C_{15}H_{15}FNO$ $[M + H]^+$: 244.1132, found: 244.1138.

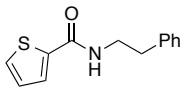


4-Chloro-*N*-phenethylbenzamide (5da): Prepared by the general procedure from MIDA acylboronate **3d** (88.6 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (70.1 mg, 90% yield). Spectroscopic data matched those reported.[9]

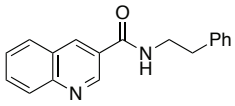


2-Methyl-*N*-phenethylbenzamide (5ea): Prepared by the general procedure from MIDA acylboronate **3e** (82.5 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (61.7 mg, 86% yield). Spectroscopic data matched those reported.[10]

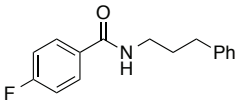
7. Major, R. T.; Ohly, K. W. *J. Med. Chem.* **1961**, *4*, 51–65.
8. Xing, D.; Xu, X.; Yang, L. *Synthesis* **2009**, 3399–3404.
9. Hioki, K.; Kameyama, S.; Tani, S.; Kunishima, M. *Chem. Pharm. Bull.* **2007**, *55*, 825–828.
10. Vanjari, R.; Guntreddi, T.; Singh, K. N. *Org. Lett.* **2013**, *15*, 4908–4911.



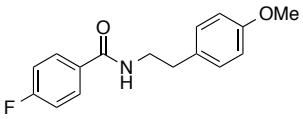
***N*-Phenethylthiophene-2-carboxamide (5ga):** Prepared by the general procedure from MIDA acylboronate **3g** (80.1 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (55.5 mg, 80% yield). **IR** (thin film) 3309, 3084, 3025, 2929, 1625, 1548, 1305 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 0.9, 4.8 Hz, 1H), 7.42 (dd, *J* = 0.9, 4.0 Hz, 1H), 7.35-7.30 (m, 2H), 7.27-7.21 (m, 3H), 7.04 (dd, *J* = 4.0, 4.8 Hz, 1H), 6.14 (brs, 1H), 3.68 (dt, *J* = 6.0, 6.8 Hz, 2H), 2.92 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.0, 139.2, 138.9, 129.9, 128.9, 128.8, 128.0, 127.7, 126.7, 41.2, 35.9; **HRMS** (ESI) calc'd for $C_{13}H_{14}NOS$ $[M + H]^+$: 232.0791, found: 232.0796.



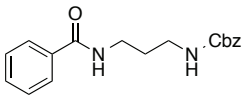
***N*-Phenethylquinoline-3-carboxamide (5ha):** Prepared by the general procedure from MIDA acylboronate **3h** (93.6 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (69.6 mg, 84% yield). **IR** (thin film) 3274, 3060, 3025, 2922, 1641, 1544, 1304, 787 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.16 (d, *J* = 2.4 Hz, 1H), 8.51 (d, *J* = 2.4 Hz, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.58 (dd, *J* = 7.6, 8.4 Hz, 1H), 7.35-7.23 (m, 5H), 6.63 (t, *J* = 6.4 Hz, 1H), 3.79 (dt, *J* = 6.4, 6.8 Hz, 2H), 2.99 (t, *J* = 6.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.8, 149.3, 148.1, 138.8, 135.7, 131.3, 129.4, 128.9, 128.9, 128.8, 127.6, 127.3, 127.0, 126.8, 41.4, 35.7; **HRMS** (ESI) calc'd for $C_{18}H_{17}N_2O$ $[M + H]^+$: 277.1355, found: 277.1336.



4-Fluoro-*N*-(3-phenylpropyl)benzamide (5cb): Prepared by the general procedure from MIDA acylboronate **3c** (83.7 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-(3-phenylpropyl)hydroxylamine **4b** (49.5 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (67.1 mg, 87% yield). Spectroscopic data matched those reported.[11]



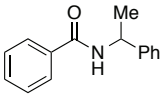
4-Fluoro-*N*-(4-methoxyphenethyl)benzamide (5cc): Prepared by the general procedure from MIDA acylboronate **3c** (83.7 mg, 0.3 mmol, 1.0 equiv) and *N*-(4-methoxyphenethyl)-*O*-methylhydroxylamine **4c** (54.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (72.2 mg, 88% yield). Spectroscopic data matched those reported.[12]



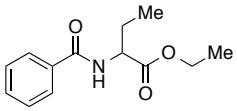
Benzyl (3-benzamidopropyl)carbamate (5ad): Prepared by the general procedure from MIDA acylboronate **3a** (78.3 mg, 0.3 mmol, 1.0 equiv) and

11. Kang, B.; Fu, Z.; Hong, S. H. *J. Am. Chem. Soc.* **2013**, *135*, 11704–11707.
12. Mu, L.; Fischer, C. R.; Holland, J. P.; Becaud, J.; Schubiger, P. A.; Schibli, R.; Ametamey, S. M.; Graham, K.; Stellfeld, T.; Dinkelborg, L. M.; Lehmann, L. *Eur. J. Org. Chem.* **2012**, 889–892.

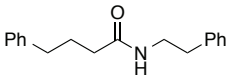
benzyl (3-(methoxyamino)propyl)carbamate **4d**[13] (71.5 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (86.2 mg, 92% yield). **IR** (thin film) 3321, 2941, 1700, 1643, 1537, 1260 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.52-7.41 (m, 3H), 7.36-7.26 (m, 5H), 7.05 (brs, 1H), 5.29 (d, *J* = 6.4 Hz, 1H), 5.12 (s, 3H), 3.51 (dt, *J* = 6.0, 6.4 Hz, 2H), 3.31 (dt, *J* = 6.0, 6.4 Hz, 2H), 1.74 (tt, *J* = 6.0, 6.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.8, 157.5, 136.6, 134.6, 131.6, 128.7, 128.7, 128.3, 128.2, 127.1, 67.0, 37.7, 36.2, 30.3; **HRMS** (ESI) calc'd for $C_{18}H_{21}N_2O_3$ [M + H]$^+$: 313.1547, found: 313.1553.



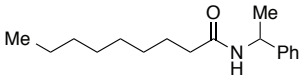
***N*-(1-phenylethyl)benzamide (5ae):** Prepared by the general procedure from MIDA acylboronate **3a** (78.3 mg, 0.3 mmol, 1.0 equiv) and (*rac*)-*O*-methyl-*N*-(1-phenylethyl)hydroxylamine **4e**[14] (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (54.1 mg, 80% yield). Spectroscopic data matched those reported.[15]



Ethyl 2-benzamidobutanoate (5af): Prepared by the general procedure from MIDA acylboronate **3a** (78.3 mg, 0.3 mmol, 1.0 equiv) and *O*-methylhydroxylamine **4f** (48.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (55.1 mg, 78% yield). Spectroscopic data matched those reported.[16]



***N*-Phenethyl-4-phenylbutanamide (5ia):** Prepared by the general procedure from MIDA acylboronate **3i** (90.9 mg, 0.3 mmol, 1.0 equiv) and *O*-methyl-*N*-phenethylhydroxylamine **4a** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (67.4 mg, 84% yield). Spectroscopic data matched those reported.[17]



***N*-(1-phenylethyl)nonanamide (5ge):** Prepared by the general procedure from MIDA acylboronate **3g** (89.1 mg, 0.3 mmol, 1.0 equiv) and (*rac*)-*O*-methyl-*N*-(1-phenylethyl)hydroxylamine **4e** (45.4 mg, 0.3 mmol, 1.0 equiv) and isolated as a white solid (57.2 mg, 73% yield). **IR** (thin film) 3281, 2926, 2855, 1641, 1545, 1453, 759 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.24 (m, 5H), 5.76 (d, *J* = 7.6 Hz, 1H), 5.14 (dq, *J* = 7.2, 7.6 Hz, 1H), 2.16 (t, *J* = 7.2 Hz, 2H), 1.62 (tt, *J* = 7.2, 7.6 Hz, 2H), 1.48 (d, *J* = 7.2 Hz, 3H), 1.33-1.23 (m, 10H), 0.87 (t, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 172.3, 143.5, 128.8, 127.4, 126.3, 48.7, 37.0, 31.9, 29.4, 29.4, 29.3, 25.9, 22.8, 21.8, 14.2; **HRMS** (ESI) calc'd for $C_{17}H_{28}NO$ [M + H]$^+$: 262.2165, found: 262.2171.

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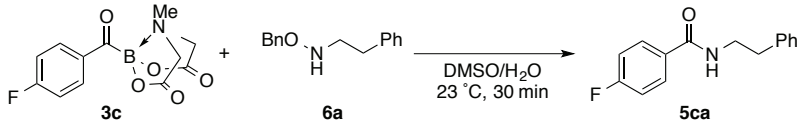
14. Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016–6023.
15. Kondo, K.; Sekimoto, E.; Nakao, J.; Murakami, Y. *Tetrahedron* **2000**, *56*, 5843–5856.
16. Basra, S.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 2659–2662.
17. Dumas, A. M.; Molander, G. A.; Bode, J. W. *Angew. Chem. Int. Ed.* **2012**, *51*, 5683–5686.

2.3 Other investigations:

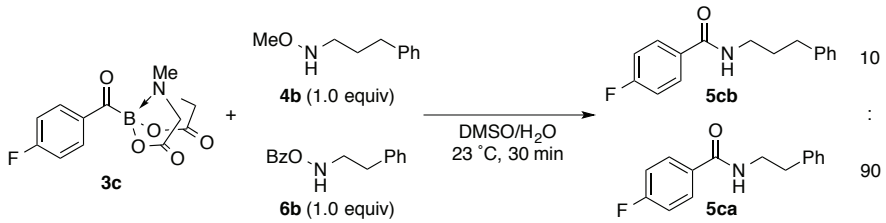
2.3.1 Amide-formation with *O*-Bn hydroxylamine (Figure 1):



Scheme S7. Amide-formation between MIDA acylboroante **3c** and *O*-Bn hydroxylamine **6a**

To a solution of *O*-benzyl-*N*-phenetylhydroxylamine **6a** (48.3 mg, 0.2 mmol, 1.0 equiv) in 9:1 DMSO/H_2O (2.0 mL) was added MIDA acylboronate **3c** (55.8 mg, 0.2 mmol, 1.0 equiv) in one portion, and the mixture was stirred for 30 min at RT. After the dilution with Et_2O, sat aq NH_4Cl was added. The aqueous phase was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc) to afford **5ca** (43.7 mg, 90% yield).

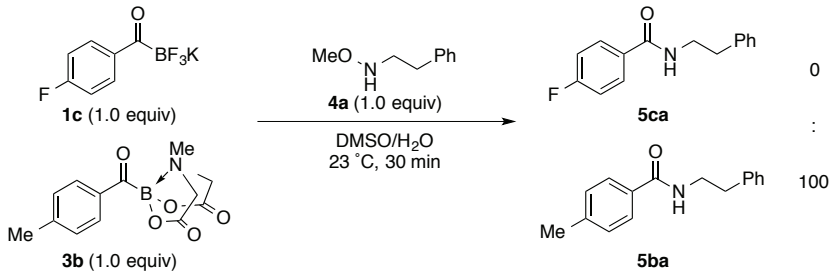
2.3.2 Competition experiments between *O*-Me and *O*-Bz hydroxylamines:



Scheme S8. A competition experiment between *O*-Me and *O*-Bz hydroxylamines with MIDA acylboronate

A solution of *O*-methylhydroxylamine **4b** (0.2 M in 9:1 DMSO:H_2O, 500 μL, 0.1 mmol, 1.0 equiv) and a solution of *O*-benzoylhydroxylamine **6b** (0.2 M in 9:1 DMSO:H_2O, 500 μL, 0.1 mmol, 1.0 equiv) were mixed. This solution was added to MIDA acylboronate **3c** (27.9 mg, 0.1 mmol, 1.0 equiv), and the solution was stirred for 30 min at RT. An aliquot of the solution was removed and analyzed.

2.3.3 Competition experiments of KAT and MIDA acylboroante with *O*-Me hydroxylamine:

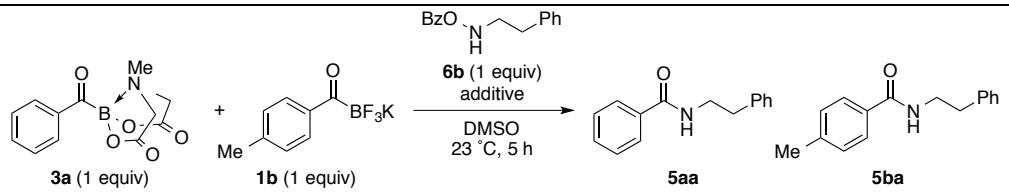


Scheme S9. A competition experiment between KAT and MIDA acylboronate with *O*-Me hydroxylamine

A solution of KAT **1c** (0.3 M in DMSO, 100 μL, 0.03 mmol, 1.0 equiv) and a solution of MIDA acylboronate **3b** (0.3 M in DMSO, 100 μL, 0.03 mmol, 1.0 equiv) were mixed. This solution was added to a solution of *O*-Me hydroxylamine **4a** (0.1 M in 5:1 DMSO/H_2O, 300 μL, 0.03 mmol, 1.0 equiv), and the mixture was stirred for 30 min at RT. An aliquot of the solution was removed and analyzed.

2.3.4 Competition experiments of KAT and MIDA acylboronate with *O*-Bz hydroxylamine:

Table S4. Competition experiments of KAT and MIDA acylboronate



3a (1 equiv) **1b** (1 equiv) **5aa** **5ba**

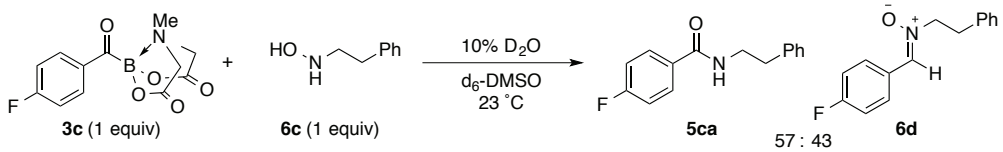
entry	additive	conversion[a] (%)	**5aa**:**5ba**[b]
1	none	>95	83:17
2	10% H_2O	>95	71:29
3	50% H_2O	>95	65:35
4	10% AcOH	>95	72:28
5	10% HFIP	>95	83:17
6	10% *t*BuOH	>95	90:10
7	10% pyridine	>95	77:23
8	10% Et_3N	60	95:5

[a] The consumption of **6b** was monitored by LC-MS. [b] Determined by LC-MS.

General procedure for Table S4:

A solution of MIDA acylboronate **3a** in DMSO (0.4 M, 300 μL) and a solution of KAT **1b** in DMSO (0.4M, 300 μL) were mixed. To this solution (20 μL, 4.0 μmol each, 1.0 equiv) was added a solution of hydroxylamine **6b** in DMSO (0.2M, 20 mL, 4.0 μmol, 1.0 equiv), followed by the indicated additive. An aliquot of the solution was removed and analyzed by LC-MS.

2.3.5 Amide-formation with *O*-unsubstituted hydroxylamine (Figure 1):



3c (1 equiv) **6c** (1 equiv) **5ca** 57 : 43 **6d**

Scheme S10. Amide-formation between MIDA acylboronate **3c** and *O*-unsubstituted hydroxylamine **6c**

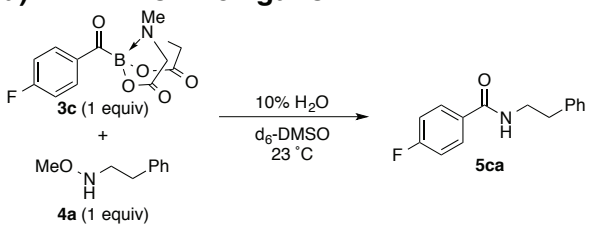
Procedure: MIDA acylboronate **3c** (11.2 mg, 0.04 mmol, 1 equiv) and hydroxylamine **6c** (5.5 mg, 0.04 mmol, 1 equiv) were dissolved in d_6-DMSO (0.6 mL). This solution was transferred into a

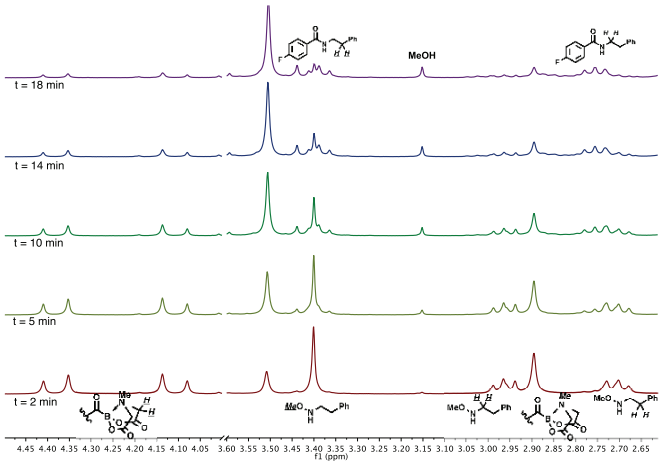
NMR tube. To this was added D_2O (60 μL), and the measurement started quickly (^{19}F NMR, 282 MHz).

2.4 Control experiments for mechanistic investigations:

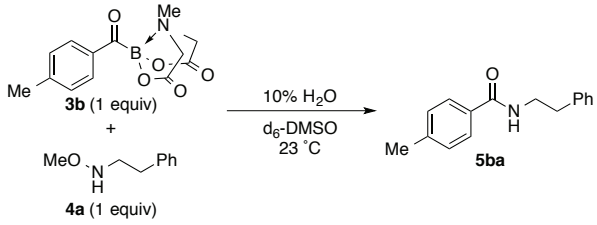
2.4.1 NMR experiments:

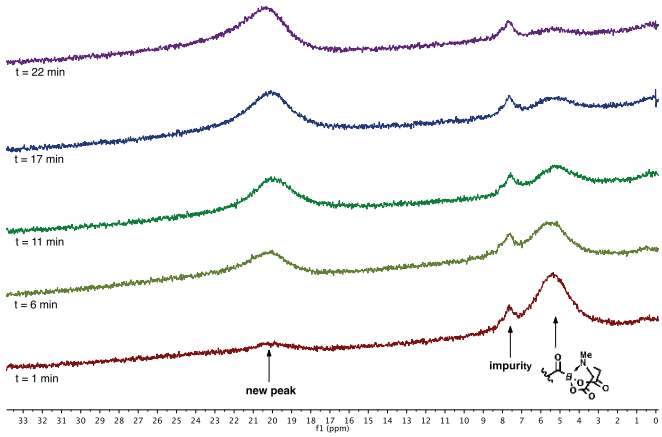
a) ^{1}H NMR of the ligation



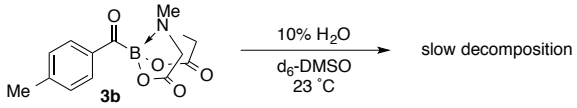


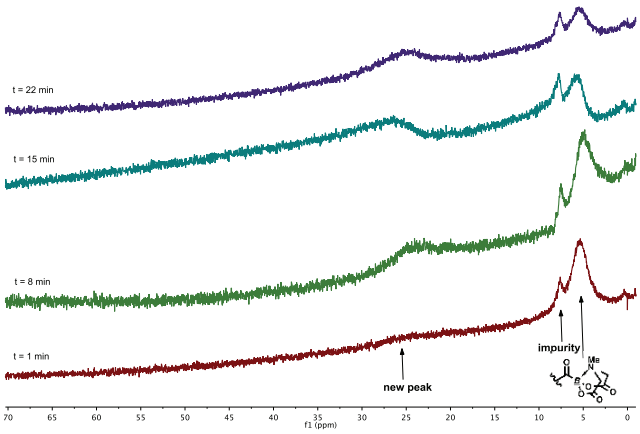
b) ^{11}B NMR of the ligation





c) ^{11}B-NMR of the decomposition





d) Comparison of b and c

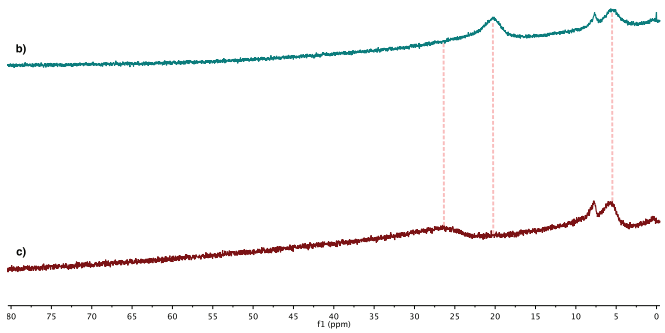


Figure S2. A panel of NMR spectra

Discussion: The results in Figure S2 showed the following: 1) The amide-formation is faster than the decomposition of MIDA acylboronate, which is probably a reason for the success of this ligation. 2) Condition b and c gave different boron-containing compounds, both of which are considered as trivalent boron species.[18] Since we did not observe any accumulation of intermediates in ^{1}H and ^{11}B NMR spectra, the reactivity of decomposed compounds were examined (Scheme S11).

Procedures for Figure S2

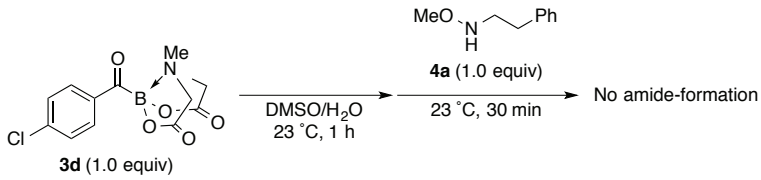
Experiment a: To a solution of MIDA acylboronate **3c** (14.0 mg, 0.05 mmol, 1.0 equiv) and *O*-methylhydroxylamine **4a** (7.6 mg, 0.05 mmol, 1.0 equiv) in d_6-DMSO (0.6 mL) was added D_2O (60 μL). This solution was quickly transferred into a NMR tube, and the measurements started (^{1}H NMR, 300 MHz).

Experiment b: MIDA acylboronate **3b** (13.8 mg, 0.05 mmol, 1.0 equiv) and *O*-methylhydroxylamine **4a** (7.6 mg, 0.05 mmol, 1.0 equiv) were dissolved in d_6-DMSO (0.6 mL). This solution was transferred into a NMR tube. ^{1}H (500 MHz) and ^{11}B NMR (160 MHz) were recorded for adjusting a shim level. To this was added D_2O (60 μL), and the measurements started quickly (^{11}B NMR, 160 MHz).

Experiment c: MIDA acylboronate **3b** (13.8 mg, 0.05 mmol) was dissolved in d_6-DMSO (0.6 mL). This solution was transferred into a NMR tube. ^{1}H (500 MHz) and ^{11}B NMR (160 MHz) were recorded for adjusting a shim level. To this was added D_2O (60 μL), and the measurement started quickly (^{11}B NMR, 160 MHz).

18 Hermanek, S. *Chem. Rev.* **1992**, *92*, 325–362.

2.4.2 Reactivity of the decomposed compounds:



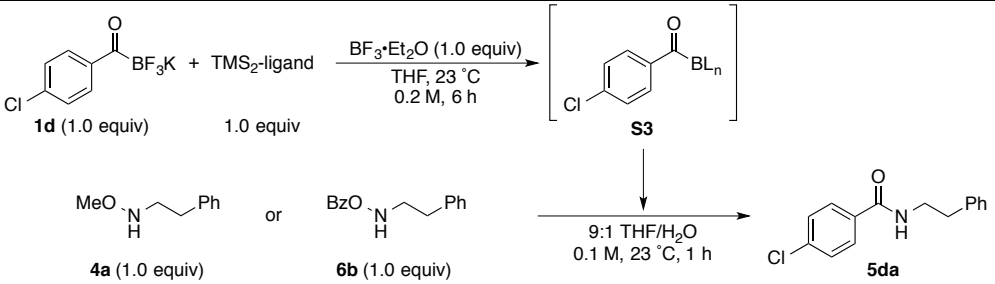
Scheme S11. A reactivity check of the decomposed compounds

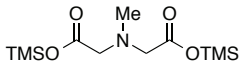
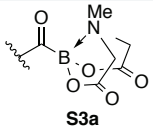
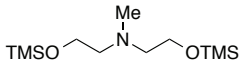
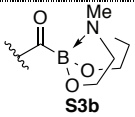
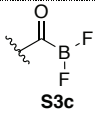
Discussion: The decomposed compounds showed no reactivity towards hydroxylamine

Procedure: MIDA acylboronate **3d** (13.8 mg, 0.05 mmol, 1.0 equiv) was dissolved in 1:1 DMSO /H_2O (250 μL), and stirred for 1 h. To this solution was added a solution of *O*-methylhydroxylamine **4a** (7.6 mg, 0.05 mmol, 1.0 equiv) in 1:1 DMSO/H_2O (250 μL). An aliquot of the solution was removed and analyzed by LC-MS after 30 min.

2.4.3 Reactivities of possible reactive intermediate:

Table S5. Use of possible reactive intermediates in amide-formation



entry	TMS_2-ligand	**S3**	hydroxylamine	amide formation	remark
1		 **S3a**	**4a**	Yes	control
2			**6b**	Yes	control
3		 **S3b**	**4a**	No	
4			**6b**	No	
5	none	 **S3c**	**4a**	No	
6	none		**6b**	No	

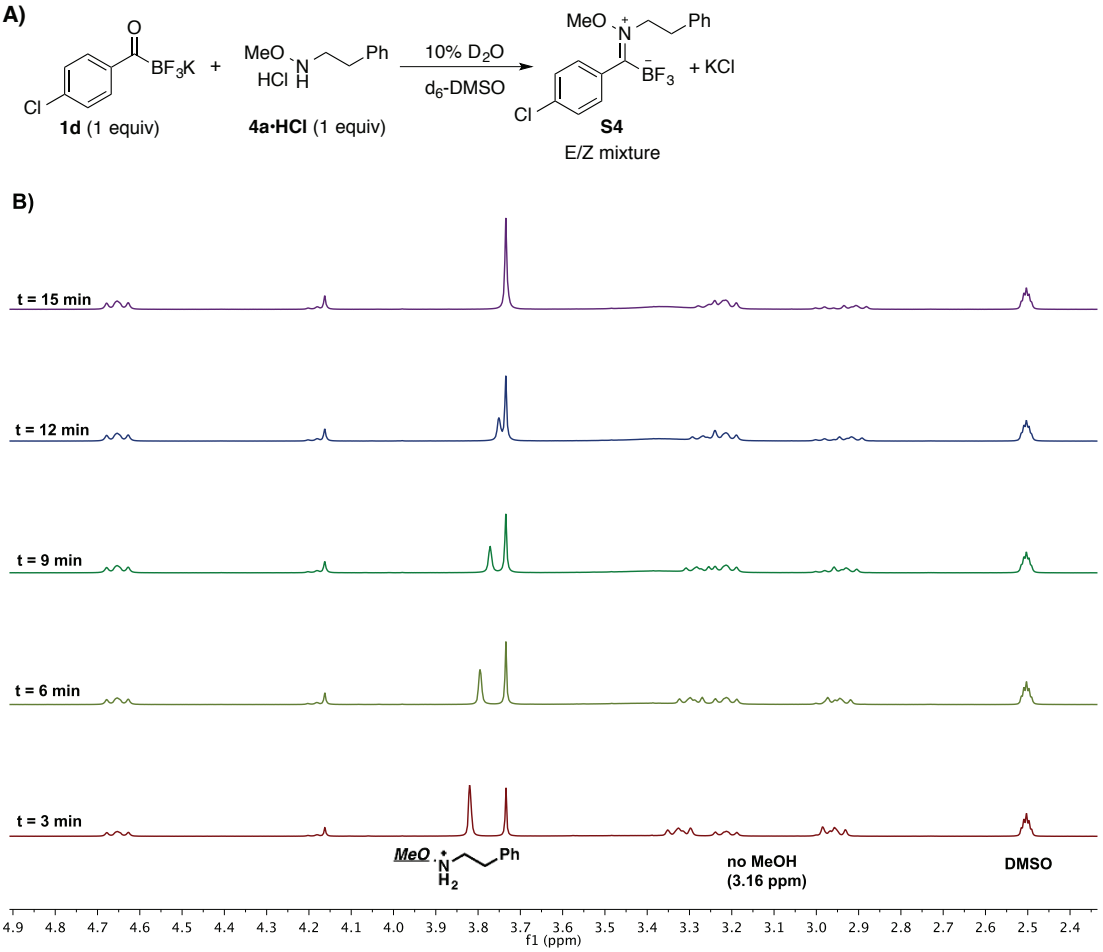
Discussions: KBF_4 and other side-products did not affect this ligation (entries 1 and 2). Boronates **S3b** formed with *N*-Methyldiehanolamine are known to be conformationally more flexible than

MIDA boronates.[19] Even though we were not able to isolate it, this boronate presumably exists in the reaction mixture and is likely to decompose into the same compounds as MIDA acylboronate does. The addition of the boronate solution to hydroxylamines did not form any amides even with the more reactive *O*-Bz hydroxylamaine **6b** (entries 3 and 4). A solution of the acyldifluoroborane **S3c** was subjected to the ligation condition in the same manner, but no amide-formation was observed.

General procedure for Table S5: To a flame dried Schlenk flask equipped with a magnetically stirred chip was added potassium 4-chlorobenzoyltrifluoroborate **3d** (246 mg, 1.0 mmol). After refill of N_2 gas into the flask, TMS_2-ligand (1.0 mmol) was added as a solution in dry THF (5.0 mL, 0.2 M). To this suspension was added BF_3•Et_2O (123 μL, 1.0 mmol) dropwise at RT. After 6 h, the part of this solution (1.25 mL, 0.25 mmol, 1.0 equiv) was removed and added to the solution of hydroxylamine **4a** or **6b** (0.25 mmol, 1.0 equiv) in THF (1.0 mL)/H_2O (250 μL). An aliquot of the solution was removed and analyzed by LC-MS after 1 h.

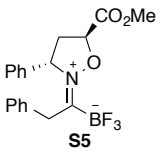
19 (a) Contreras, R.; García, C.; Mancilla, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1983**, *246*, 213–217. (b) Mancilla, T.; Contreras, R.; Wrackmeyer, B. *J. Organomet. Chem.* **1986**, *307*, 1–6.

2.4.4 Iminium-formation from KAT and *O*-methylhydroxylamine HCl salt:



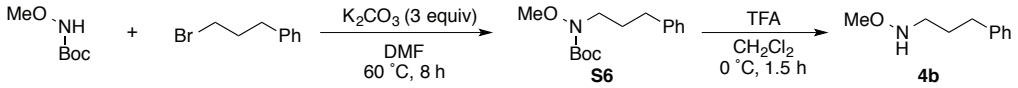
Scheme S12. Observation of iminium species **S4** in ^{1}H-NMR

Procedure: KAT **1d** (9.9 mg, 0.04 mmol, 1 equiv) and *O*-methylhydroxylamine HCl salt **4a·HCl** (7.5 mg, 0.04 mmol, 1 equiv) were dissolved in d_6-DMSO (0.6 mL). This solution was quickly transferred into a NMR tube, and the measurements started (^{1}H NMR, 300 MHz). (*Note*: A similar compound **S5** was isolated and characterized previously.[17])

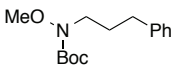


S5

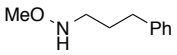
2.5 Preparation of hydroxylamines



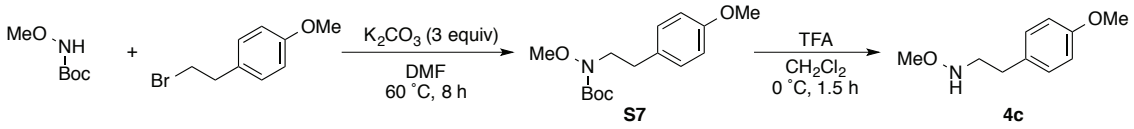
Scheme S13. Synthesis of hydroxylamine **4b**



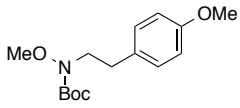
***O*-Methyl-*N*-*tert*-butoxycarbonyl-*N*-phenethylhydroxylamine (S6):** To a solution of *O*-methyl-*N*-*tert*-butoxylcarbonylhydroxylamine (1.50 g, 10.2 mmol, 1.0 equiv) in DMF (10.0 mL) were added K_2CO_3 (4.20 g, 30.4 mmol, 3.0 equiv) and 1-bromo-3-phenylpropane (1.85 mL, 12.2 mmol, 1.2 equiv). The mixture was stirred for 8 h at 60 ˚C, cooled to RT, and diluted with Et_2O. After addition of H_2O, the aqueous phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc from 20:1 to 9:1) to give **S6** (2.46 g, 91% yield). Colorless oil; **IR** (thin film) 2976, 2934, 1725, 1701, 1391, 1163, 1099 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 3H), 3.69 (s, 3H), 3.47 (t, *J* = 7.2 Hz, 2H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.95 (tt, *J* = 7.2, 7.6 Hz, 2H), 1.49 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 156.4, 141.7, 128.5, 128.5, 126.0, 81.3, 62.4, 48.8, 33.2, 28.9, 28.4; **HRMS** (ESI) calc'd for $C_{15}H_{23}NNaO_3$ $[M + Na]^+$: 288.1570, found: 288.1578.



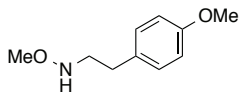
***O*-Methyl-3-phenylpropylhydroxylamine (4b):** To a solution of **S6** (1.80 g, 6.80 mmol) in CH_2Cl_2 (3.4 mL) was added TFA (3.4 mL) at 0 ˚C, and the solution was stirred for 1.5 h at 0 ˚C. After dilution with CH_2Cl_2, sat aq $NaHCO_3$ was added carefully to basify the solution. The aqueous phase was extracted with CH_2Cl_2 (x 3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc from 13:1 to 7:1) to 4:1, affording **4b** (1.01 g, 90% yield). Colorless oil; **IR** (thin film) 3261, 3025, 2938, 1603, 1496, 1454, 1030, 957 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.17 (m, 3H), 5.56 (brs, 1H), 3.55 (s, 3H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.69 (t, *J* = 8.0 Hz, 2H), 1.86 (tt, *J* = 6.8, 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 142.1, 128.5, 128.5, 126.0, 62.1, 51.5, 33.6, 29.1; **HRMS** (EI) calc'd for $C_{10}H_{15}NO$ $[M]^+$: 165.1149, found: 165.1146.



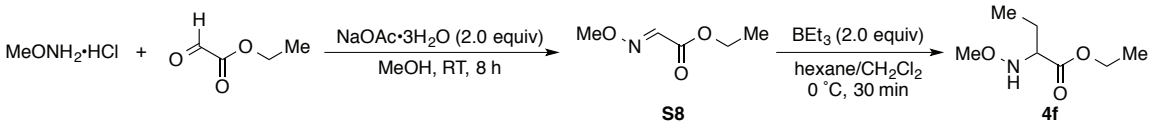
Scheme S14. Synthesis of hydroxylamine **4c**



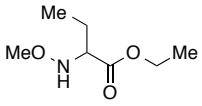
***N-tert*-butoxycarbonyl-*N*-(4-methoxylphenethyl)-*O*-methylhydroxylamine (S7):** To a solution of *O*-methyl-*N*-*tert*-butoxycarbonylhydroxylamine (1.1 g, 7.4 mmol, 1.0 equiv) in DMF (7.0 mL) were added K_2CO_3 (3.1 g, 22 mmol, 3.0 equiv) and 1-(2-chloroethyl)-4-methoxybenzene (1.2 mL, 8.2 mmol, 1.1 equiv). The mixture was stirred for 8 h at 60 ˚C, cooled to RT, and diluted with Et_2O. After addition of H_2O, the aqueous phase was extracted with Et_2O (3x). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc from 20:1 to 8:1) to give **S7** (1.77 g, 85% yield). Colorless oil; **IR** (thin film) 2976, 2935, 1723, 1703, 1513, 1367, 1247, 1161, 1035, 977, 830 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz), 3.76 (s, 3H), 3.66 (s, 3H), 3.62 (t, *J* = 7.6 Hz, 2H), 2.84 (t, *J* = 7.6 Hz, 2H), 1.43 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 156.1, 131.0, 129.9, 114.0, 81.1, 62.2, 55.3, 50.8, 32.6, 28.3; **HRMS** (ESI) calc'd for $C_{15}H_{23}NNaO_4$ $[M + Na]^+$: 304.1519, found: 304.1522.



***N*-(4-methoxylphenethyl)-*O*-methylhydroxylamine (4c):** To a solution of **S7** (740 mg, 2.62 mmol) in CH_2Cl_2 (2.5 mL) was added TFA (2.5 mL) at 0 ˚C, and the solution was stirred for 1.5 h at the same temperature. After dilution with CH_2Cl_2, sat aq $NaHCO_3$ was added carefully to basify the solution. The aqueous phase was extracted with CH_2Cl_2 (x 3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude material was purified by flash column chromatography (hexanes/EtOAc from 13:1 to 7:1 to 2:1) affording **4c** (423 mg, 89% yield). Colorless oil; **IR** (thin film) 3261, 2937, 2061, 1881, 1612, 1512, 1246, 1178, 1035, 944, 828 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 5.54 (brs, 1H), 3.79 (s, 3H), 3.55 (s, 3H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.2, 131.5, 129.9, 114.1, 61.8, 55.4, 53.2, 32.8; **HRMS** (EI) calc'd for $C_{10}H_{15}NO_2$ $[M]^+$: 181.1098, found: 181.1095.



Scheme S15. Synthesis of hydroxylamine **4f**

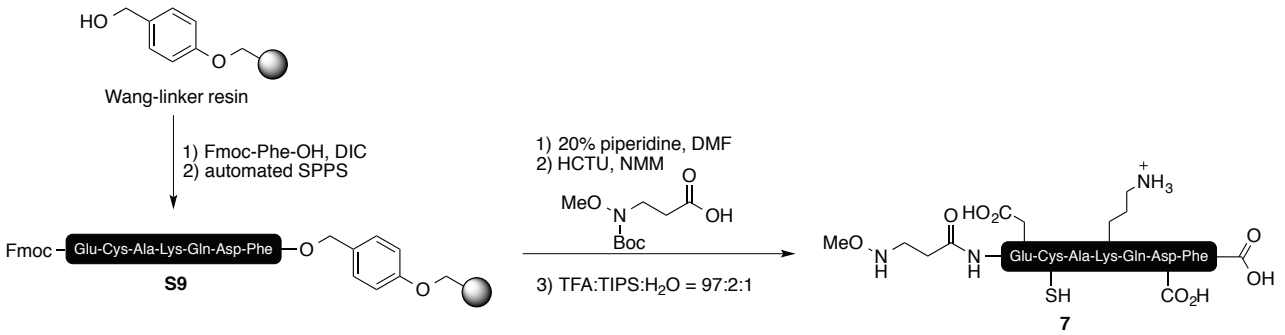


Ethyl 2-(methoxyamino)butanoate (4f): To a mixture of *O*-methylhydroxylamine hydrochloride (1.50 g, 17.9 mmol) and NaOAc•$3H_2O$ (4.89 g, 35.8 mmol, 2.0 equiv) in MeOH (90.0 mL) was added ethyl glyoxalate (50% in toluene, 3.56 mL, 17.9 mmol, 1.0 equiv), and the solution was stirred for 8 h at RT. After evaporation of MeOH, H_2O and Et_2O were added. The aqueous phase was extracted with Et_2O (x 3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure to give **S8**. The crude material was used in the next step without further purification. For analytical purposes, small amounts were purified by flash column chromatography (hexanes/EtOAc 13:1 to 7:1). Spectroscopic data matched those reported.[20]

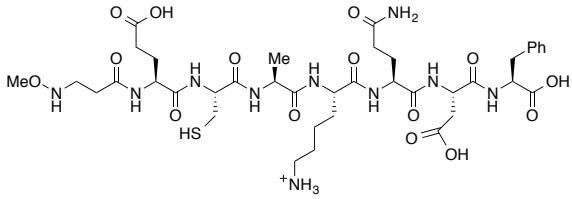
Based on a literature procedure,[21] the imine **S8** (*ca.* 2.5 mmol) was dissolved in CH_2Cl_2 (5.0 mL) under air. To this was added slowly BEt_3 (1.0M in hexane, 5.0 mL, 5.0 mmol, 2.0 equiv) at 0 ˚C. After dilution with CH_2Cl_2, sat aq $NaHCO_3$ was added. The aqueous phase was extracted with CH_2Cl_2 (x 3). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and removed under reduced pressure. The crude materials were purified by flash column chromatography (hexanes/EtOAc 13:1 to 7:1) to give **4f** (132 mg, 32% yield for 2 steps). Colorless oil; **IR** (thin film) 3262, 2975, 2939, 1738, 1464, 1201, 1024, 970 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.94 (brs, 1H), 4.21 (ddq, *J* = 1.5, 1.8, 7.2 Hz, 2H), 3.57-3.50 (m, 4H), 1.66-1.50 (m, 1H), 1.28 (t, *J* = 7.2 Hz, 3H), 0.96 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 174.2, 64.8, 61.8, 61.0, 23.0, 14.4, 10.5; **HRMS** (EI) calc'd for $C_7H_{15}NO_3$ $[M]^+$: 161.1052, found: 161.1052.

20. Donohoe, T. J.; Jones, C. R.; Barbosa, L. C. A. *J. Am. Chem. Soc.* **2011**, *133*, 16418–16421.
21. Miyabe, H.; Shibata, R.; Sangawa, M.; Ushiro, C.; Naito, T. *Tetrahedron* **1998**, *54*, 11431–11444.

3. Ligation with peptide hydroxylamine (Scheme 5)



Scheme S16. Synthesis of peptide hydroxylamine **7**



Peptide 7: Peptide hydroxylamine **7** was synthesized on Wang-linker polystyrene resin with a loading capacity of 1.08 mmol/g. The synthesis was performed on 1.09 mmol scale (1.01 g of resin) by the treatment of a solution of Fmoc-Phe-OH (4.27 g, 10.9 mmol, 10.0 equiv to resin) and *N,N'*-diisopropylcarbodiimide (843 μL, 5.45 mmol, 5.0 equiv to resin) in CH_2Cl_2/DMF for 36 h. The synthesis continued by using automated Fmoc SPPS up to Glu using the procedure described in the general methods section. At this step, 0.50 mmol of resin **S9** was separated and the Fmoc group was removed using 20% piperidine in DMF. 3-Amino-*N*-(*tert*-butyloxylcarbonyl)-*N*-methoxypropionic acid[22] (447 mg, 2.0 mmol, 4.0 equiv to resin) was coupled to the amine using HCTU (827 mg, 2.0 mmol, 4.0 equiv to resin) and NMM (445 μL, 4.0 mmol, 8.0 equiv to resin) in DMF for 3 h. The resin supported peptide was treated with TFA:TIPS:H_2O (97:2:1) for 2 h and filtered to remove the solid support. Volatiles from the filtrate were evaporated under vacuum. The residue was triturated with Et_2O and centrifuged (three cycle repeated) to obtain the crude peptide. Purification was performed by preparative HPLC using a Vydac C18 column (20 x 250 mm) with a gradient of 10 to 70 % MeCN with 0.1% TFA in 30 min. The product peak eluting at t_R = 16.4 min was collected and lyophilized to obtain 31 mg of pure **7** (6.6% yield for synthesis from starting resin, cleavage and purification steps). Analytical HPLC (Shiseido C18 column with a gradient of 10 to 90% MeCN with 0.1% TFA in 20 min) and HRMS were used to confirm the purity and exact mass of the product. m/z calc'd for $C_{39}H_{61}N_{10}O_{15}S$ $[M + H]^+$: 941.4033, found: 941.4029.

22. Fehrentz, J. A.; Paris, M.; Velek, J.; Winternitz, F.; Martinez, J. *J. Org. Chem.* **1997**, *62*, 6792–6796.

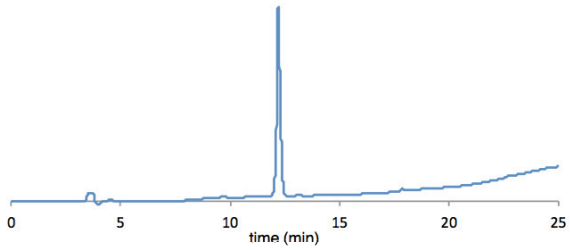


Figure S3. Analytical HPLC of purified **7**

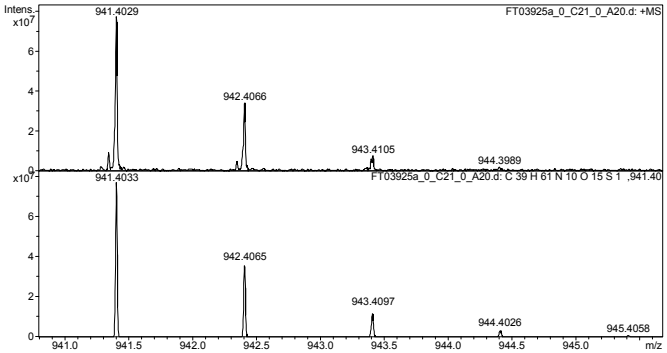
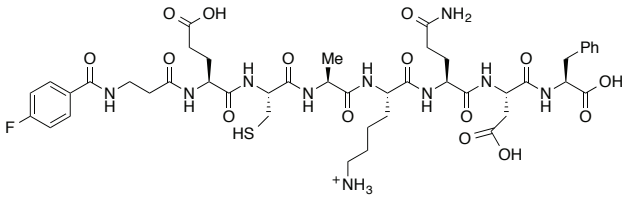


Figure S4. HMRS (MALDI) of purified **7**



Ligation with peptide 7: To a solution of peptide hydroxylamine **7** (4.60 mg, 4.9 μmol, 1.0 equiv) in 1:1 DMSO/H_2O (84 μL) was added a solution of MIDA acylboronate **3c** in DMSO (100 mM, 146 μL, 14.6 μmol, 3.0 equiv). The solution was stirred for 30 min, and another portion of the boronate solution (100 mM, 98 μL, 9.8 μmol, 2.0 equiv, total 5.0 equiv) was added. The full conversion to product **8** was confirmed by crude HPLC analysis (>90% HPLC yield, Figure S5). Analytical HPLC (Shiseido C18 column with a gradient of 10 to 90% MeCN with 0.1% TFA in 20 min) and HRMS were used to confirm the purity and exact mass of the product **8**. m/z calc'd for $C_{45}H_{61}FN_{10}O_{15}S$ $[M + H]^+$: 1033.4095, found: 1033.4096. (*Note: MIDA acylboronate **3c** is not stable under HPLC condition. See Figure S6.*). The NMR spectra (^1H, ^{13}C, H,H-COSY, HSQC, HMBC, ROESY) were recorded in d_6-DMSO to further confirm the structure and the purity of the product **8**.

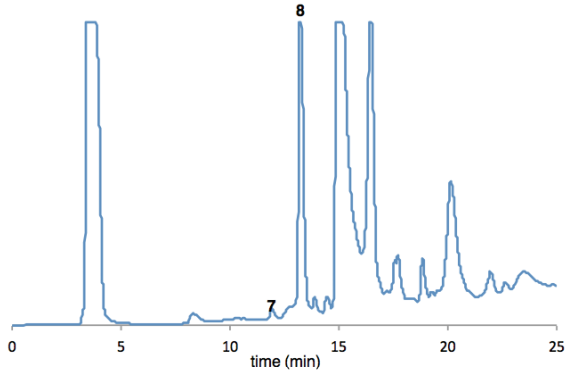


Figure S5. A crude HPLC trace at 1 h

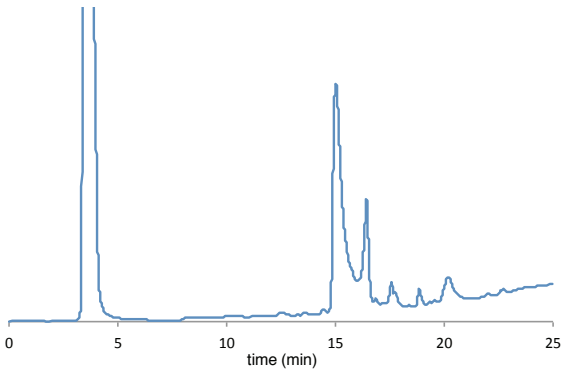


Figure S6. Analytical HPLC of the MIDA boronate **3c** in the absence of peptide **7**

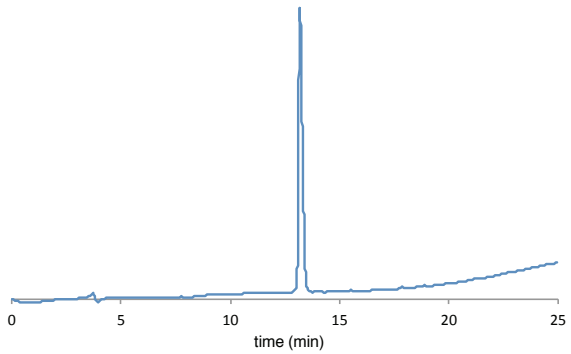


Figure S7. Analytical HPLC of purified **8**

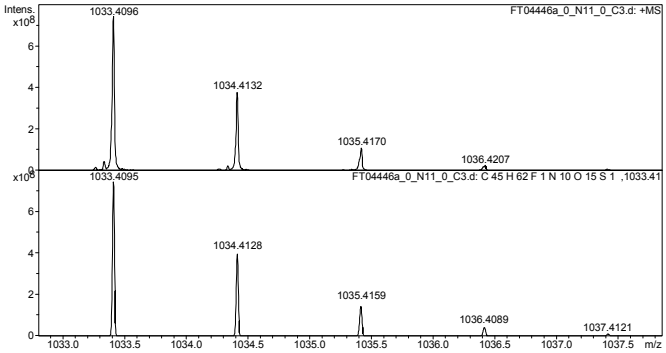


Figure S8. HRMS (MALDI) of purified **8**

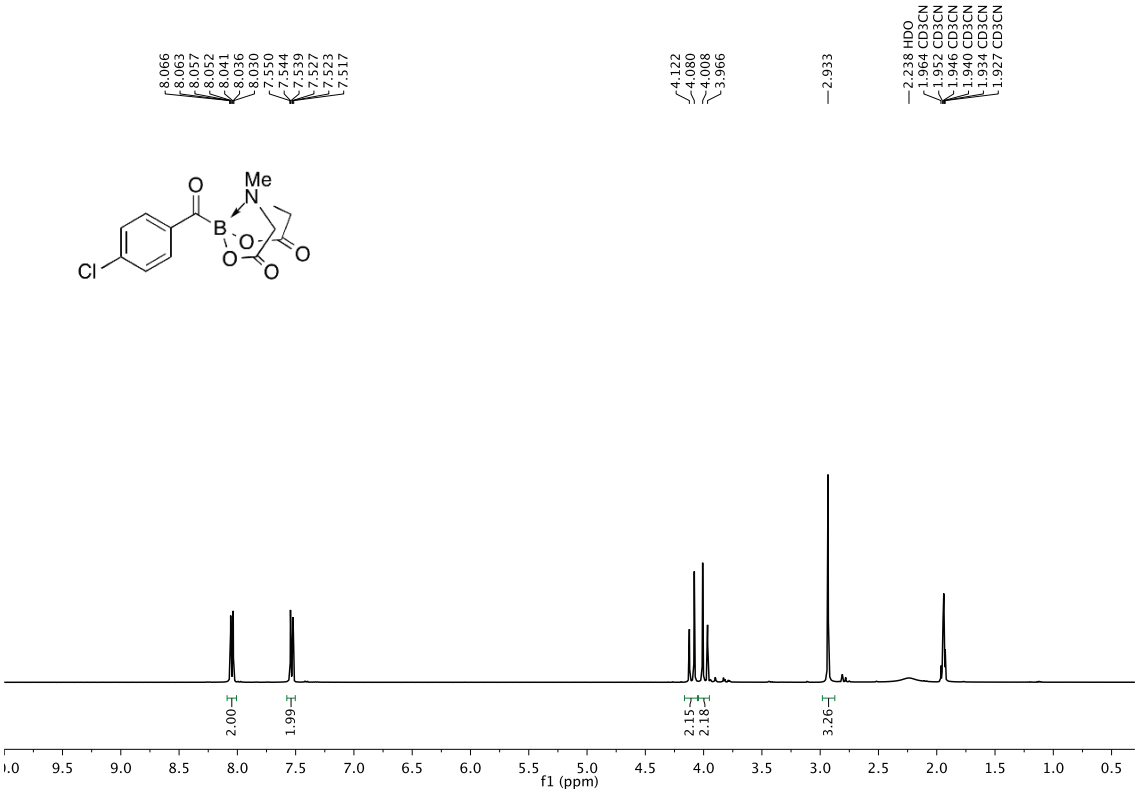
Table S6. ^{1}H and ^{13}C NMR chemical shifts of peptide **8**

amino acid	NH	α	β	γ	δ	ε
β-Alanine	8.50	2.43 (2H)	3.45 (2H)			
		35.1	35.9			
Glu	8.18	4.25	1.87 (2H)	2.26 (2H)		
		52.0	27.0	30.1		
Cys	7.70	4.37	2.73 (2H)			
		54.6	26.5			
Ala	8.16	4.27	1.24 (3H)			
		52.1	18.7			
Lys	8.00	4.22	1.50 (2H)	1.31 (2H)	1.74 (2H)	2.07 (2H)
		50.4	26.5	22.0	27.8	31.2
Gln	7.60	4.20	1.50/1.66	2.73 (2H)		
		50.4	31.5	38.5		
Asp	7.85	4.52	2.46/2.62			
		53.1	35.4			
Phe	7.90	4.33	2.91/3.02			
		53.7	36.5			

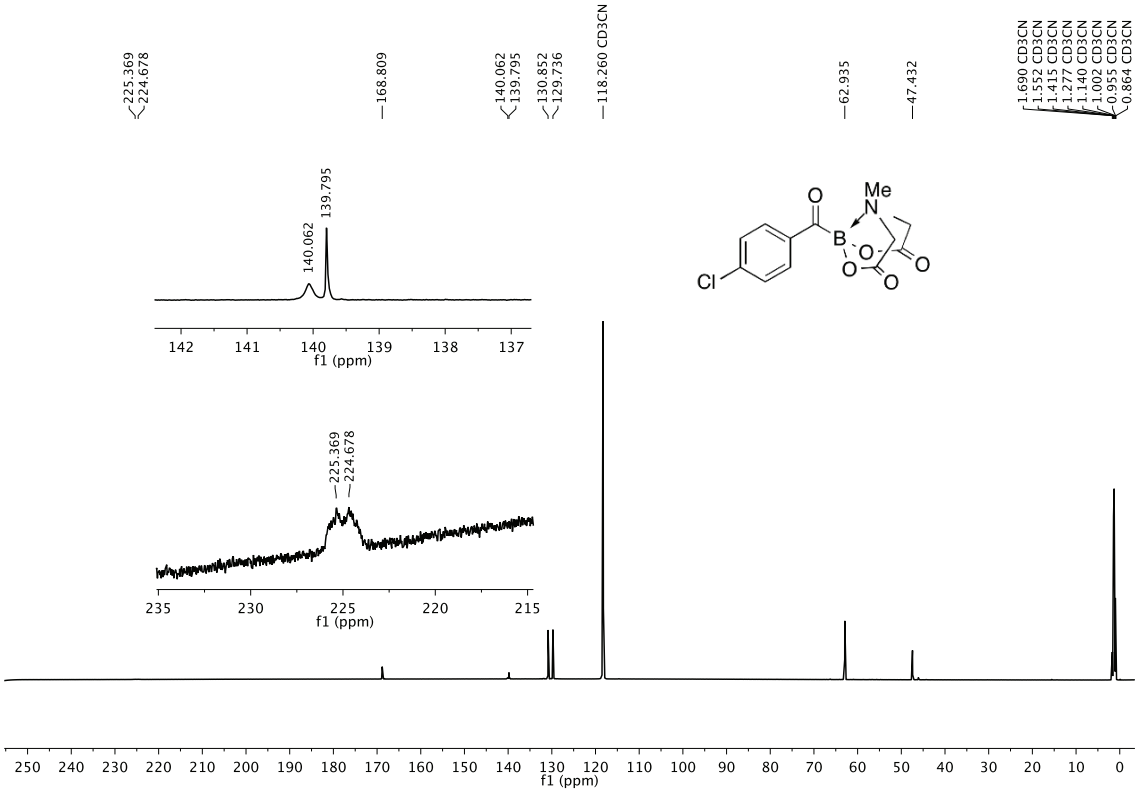
4. Spectroscopic Data:

MIDA 4-chlorobenzoylboronate (3d):

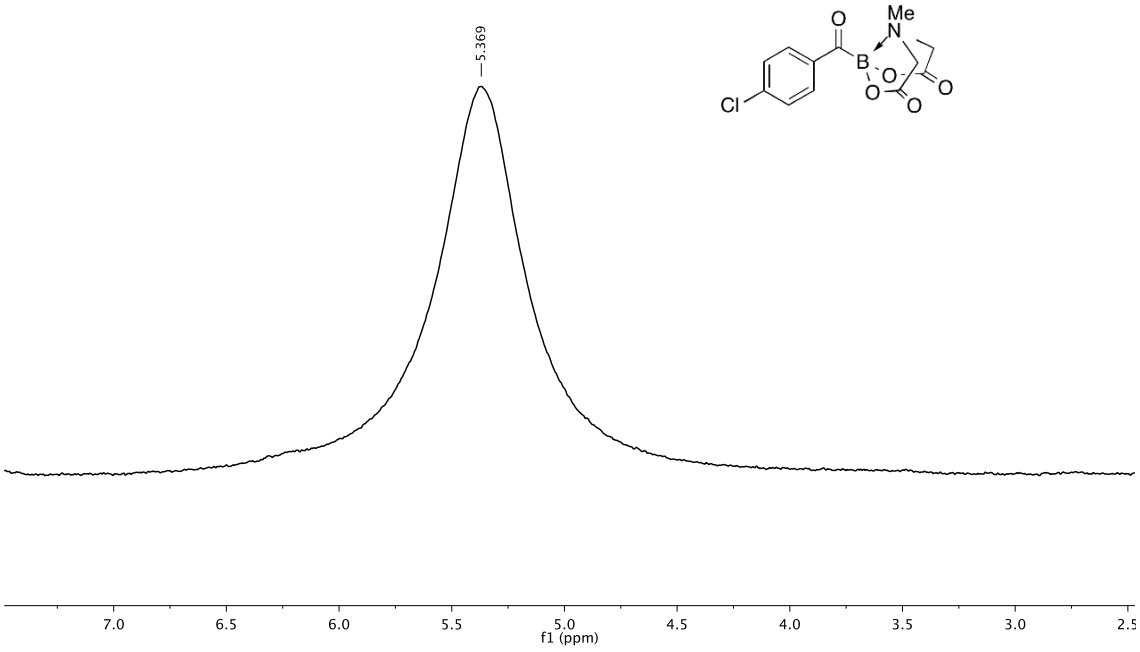
^{1}H NMR (400 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

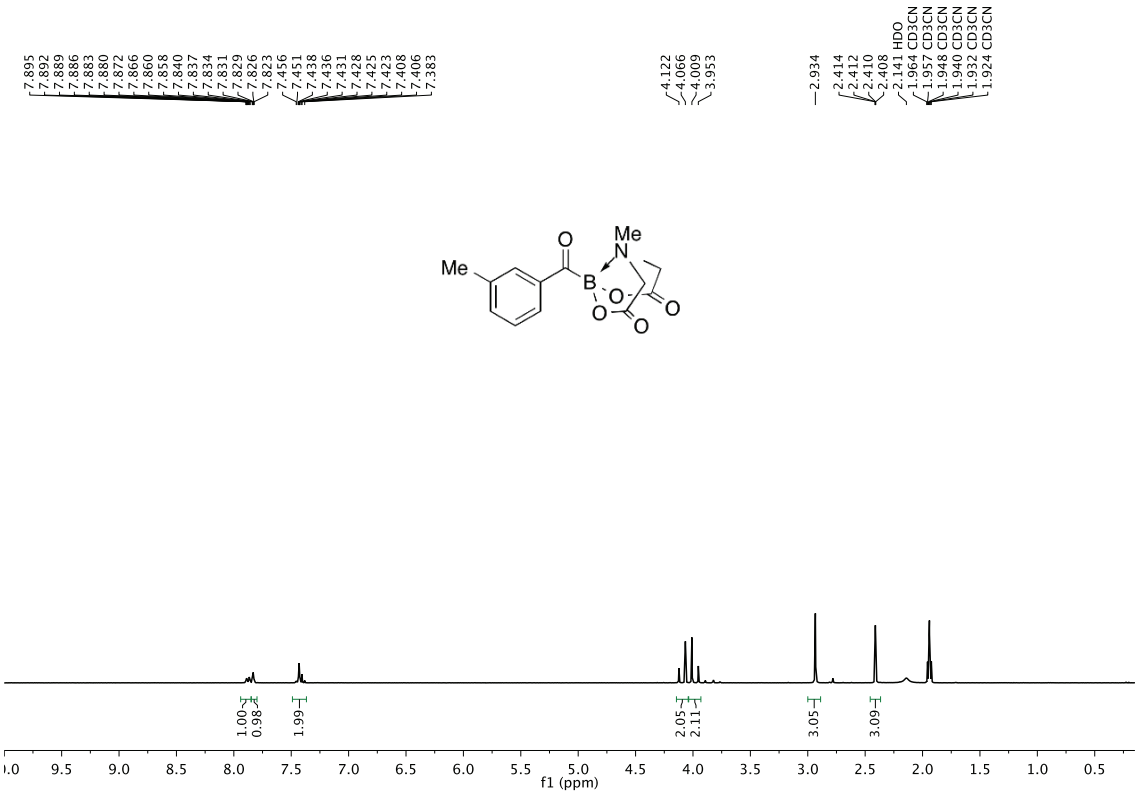


^{11}B NMR (160 MHz, CD_3CN)

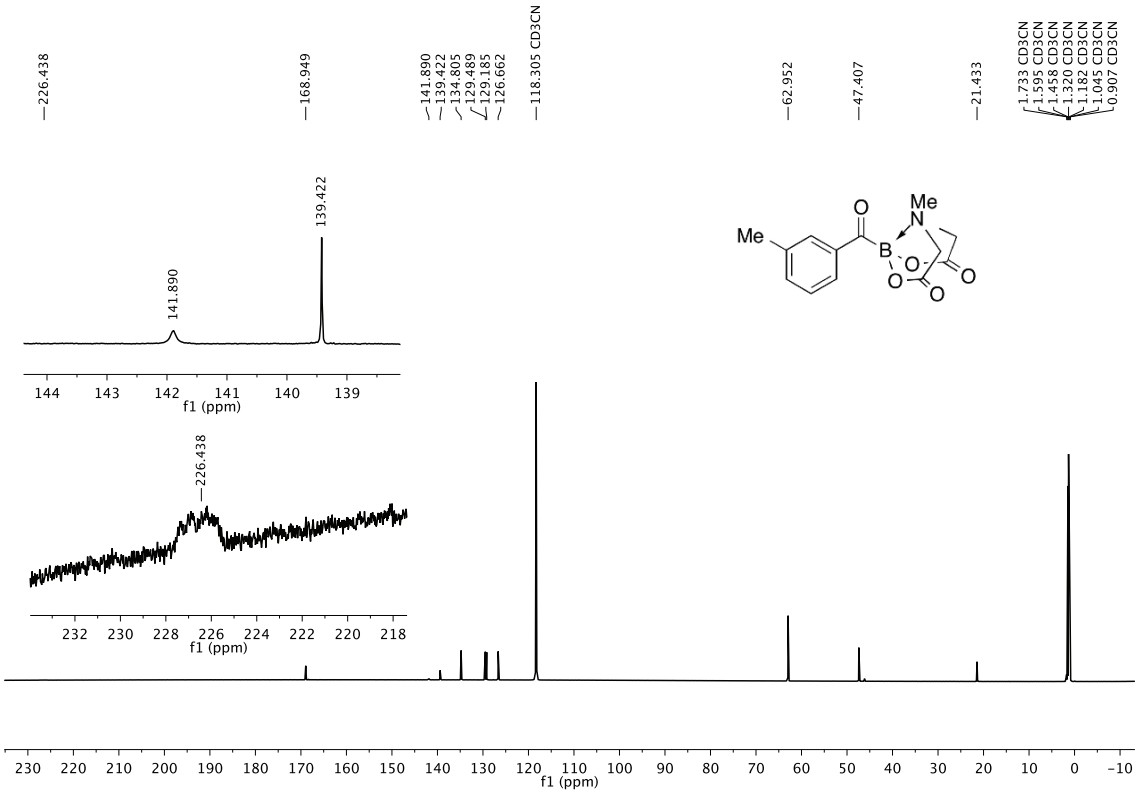


MIDA 3-methylbenzoylboronate (3e):

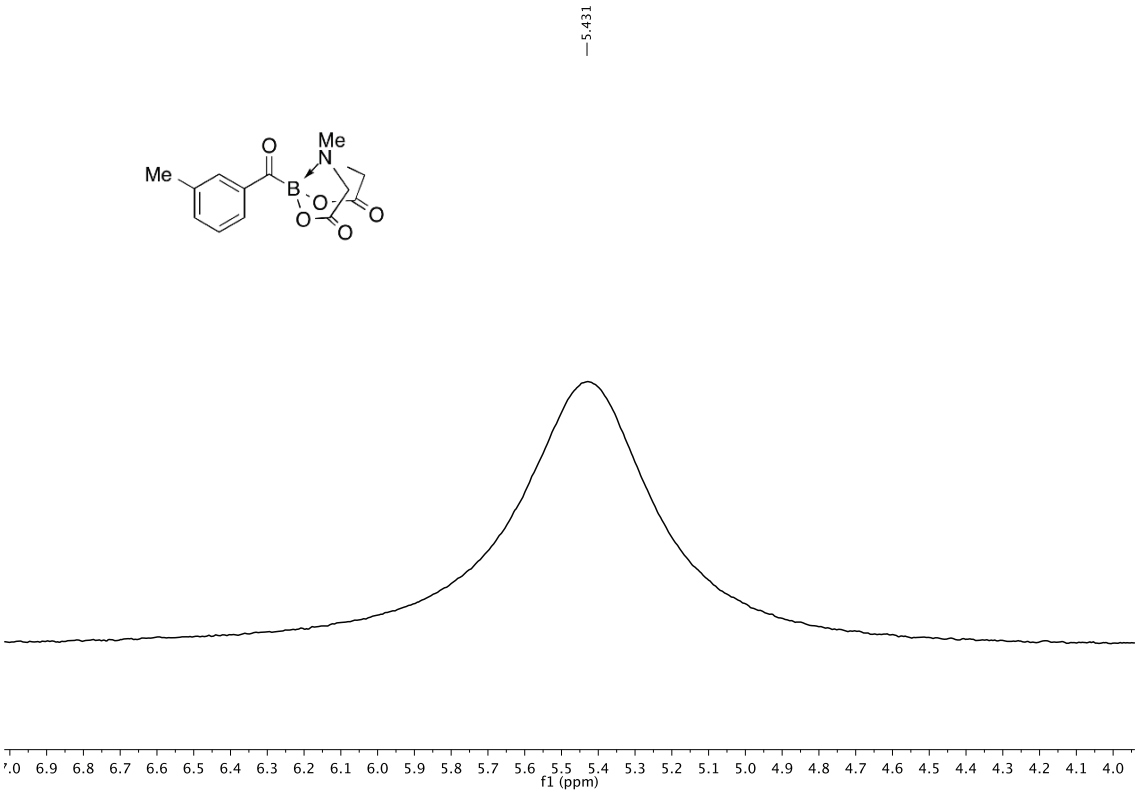
^{1}H NMR (300 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

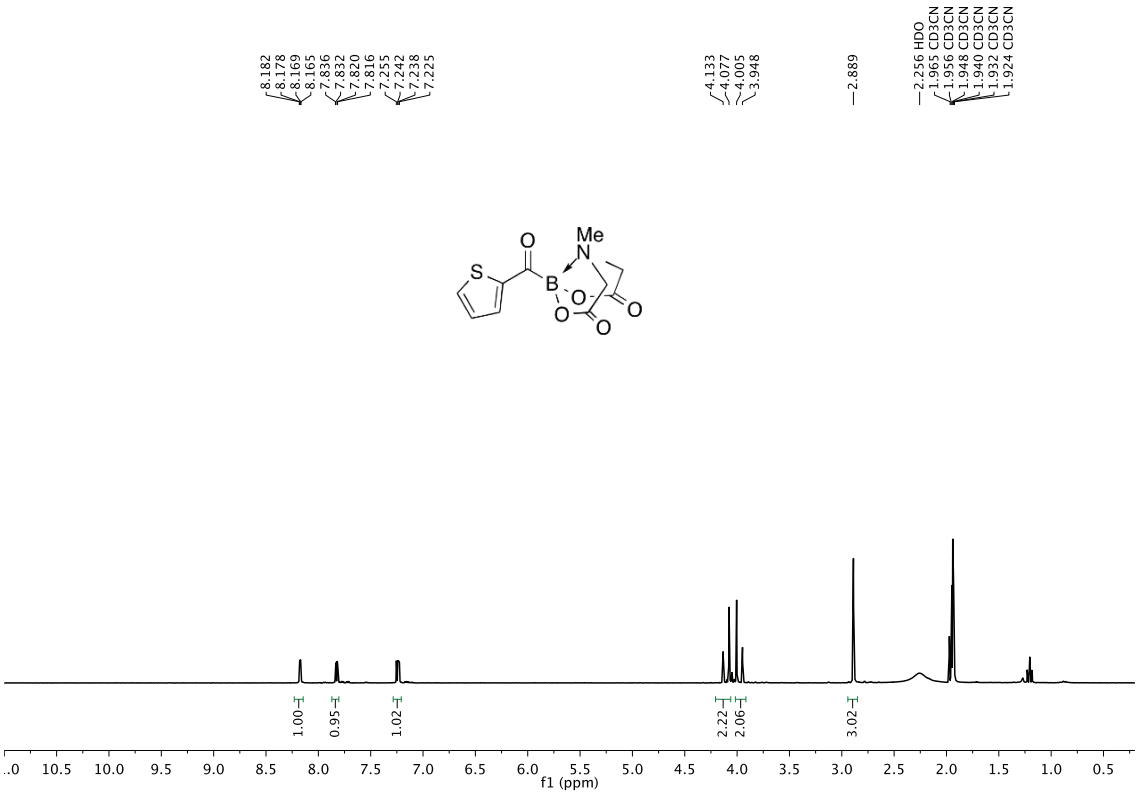


^{11}B NMR (160 MHz, CD_3CN)

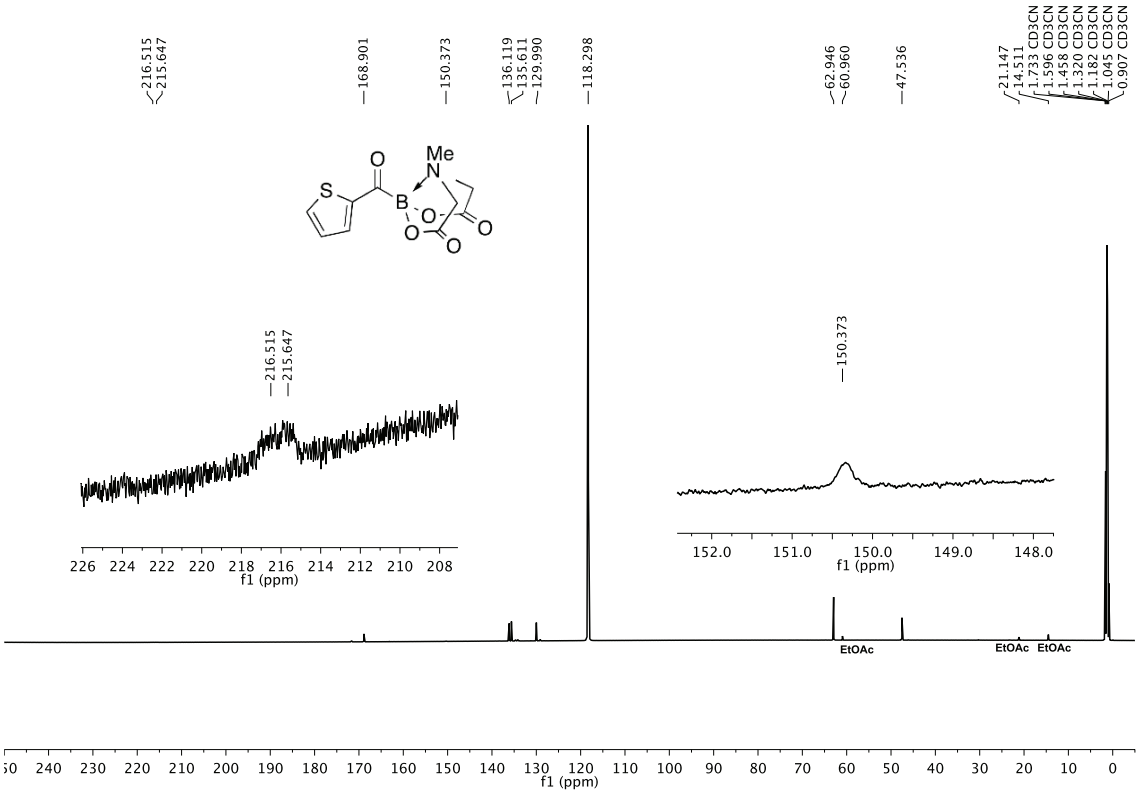


MIDA 2-thienoylboronate (3g):

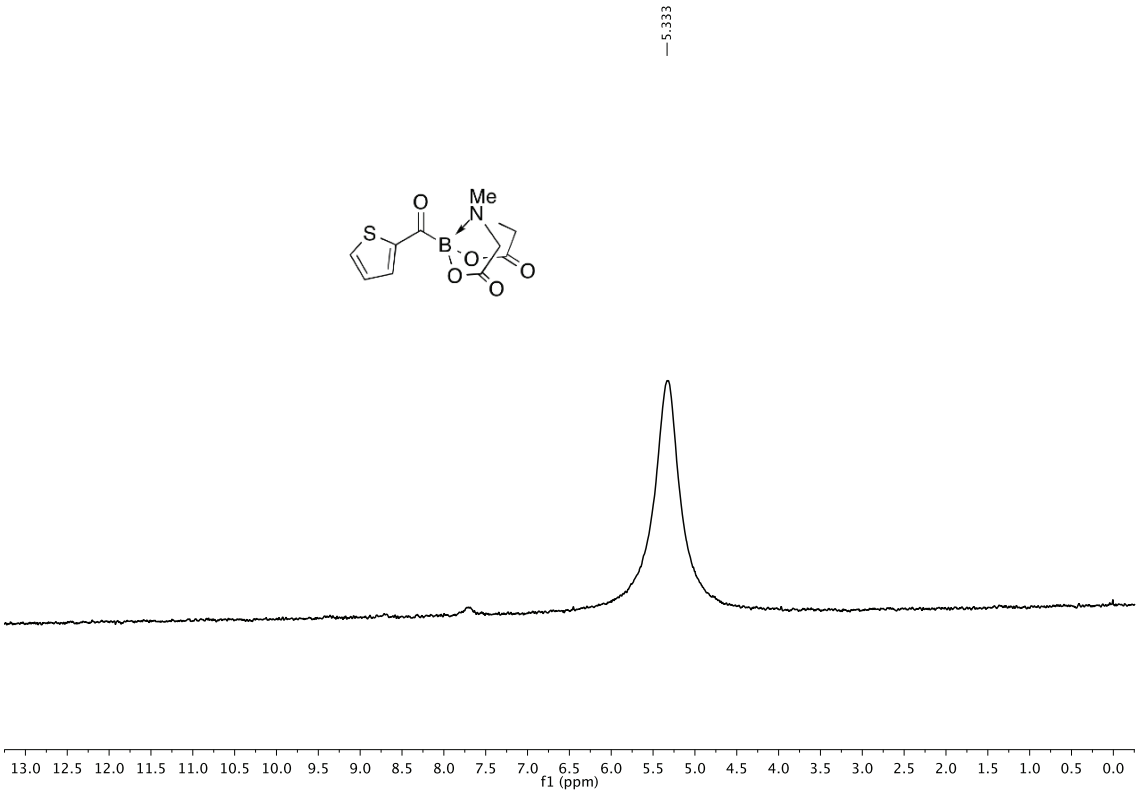
^{1}H NMR (300 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

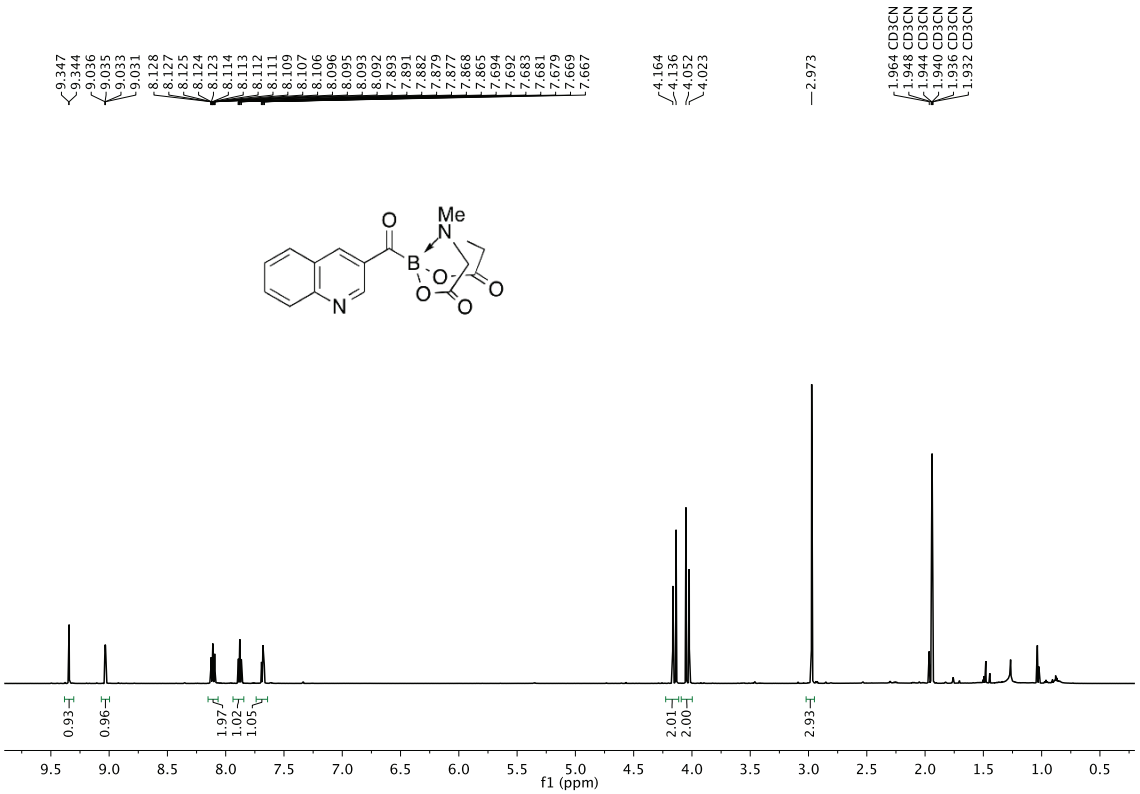


^{11}B NMR (160 MHz, CD_3CN)

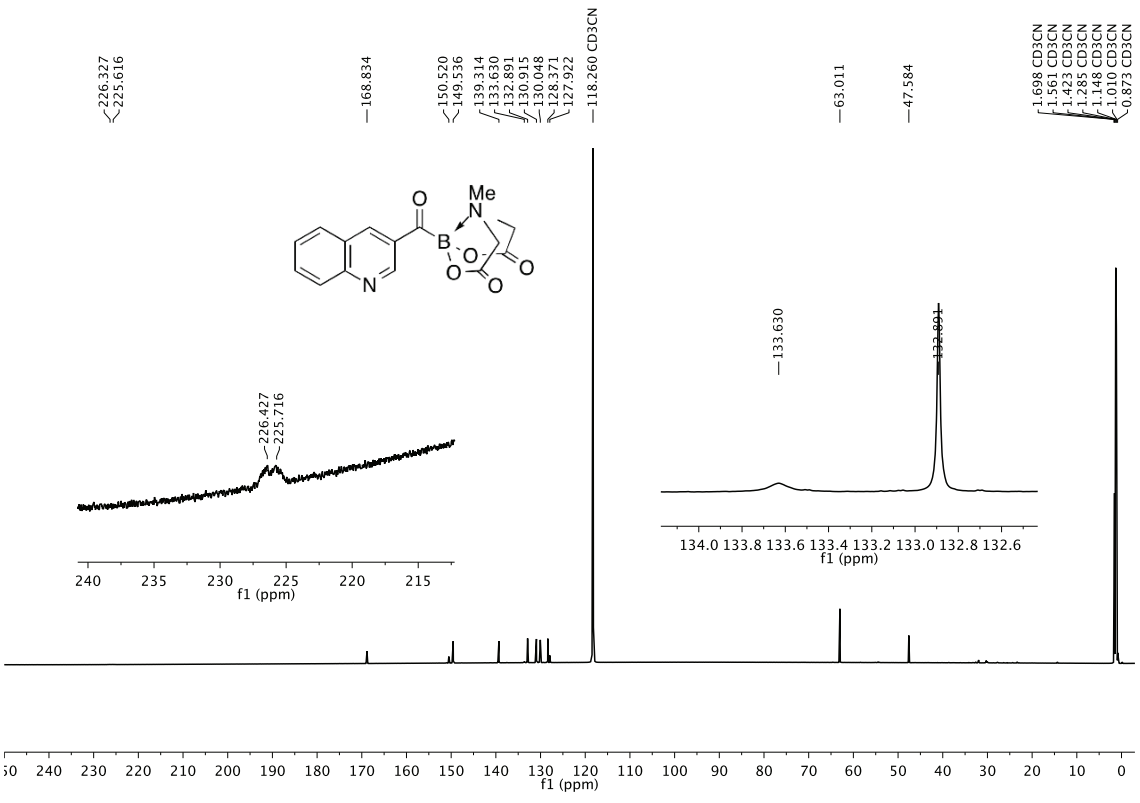


MIDA 3-quinolinoylboronate (3h):

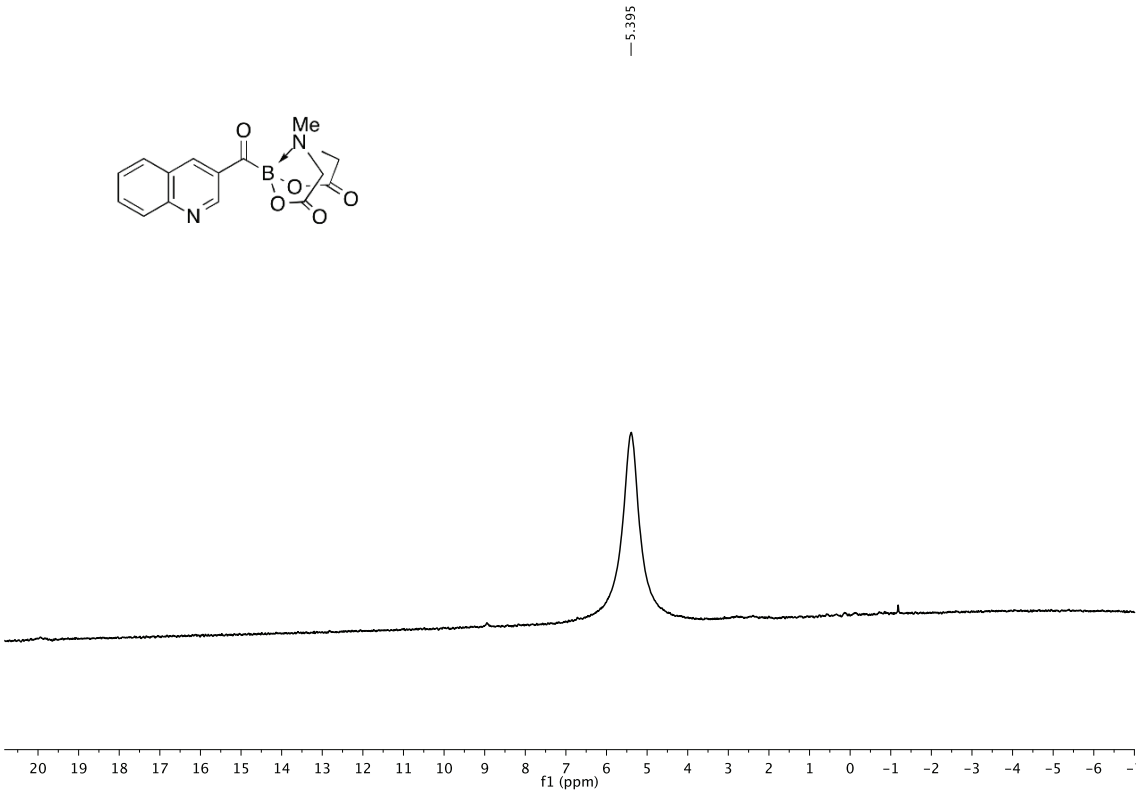
^{1}H NMR (600 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

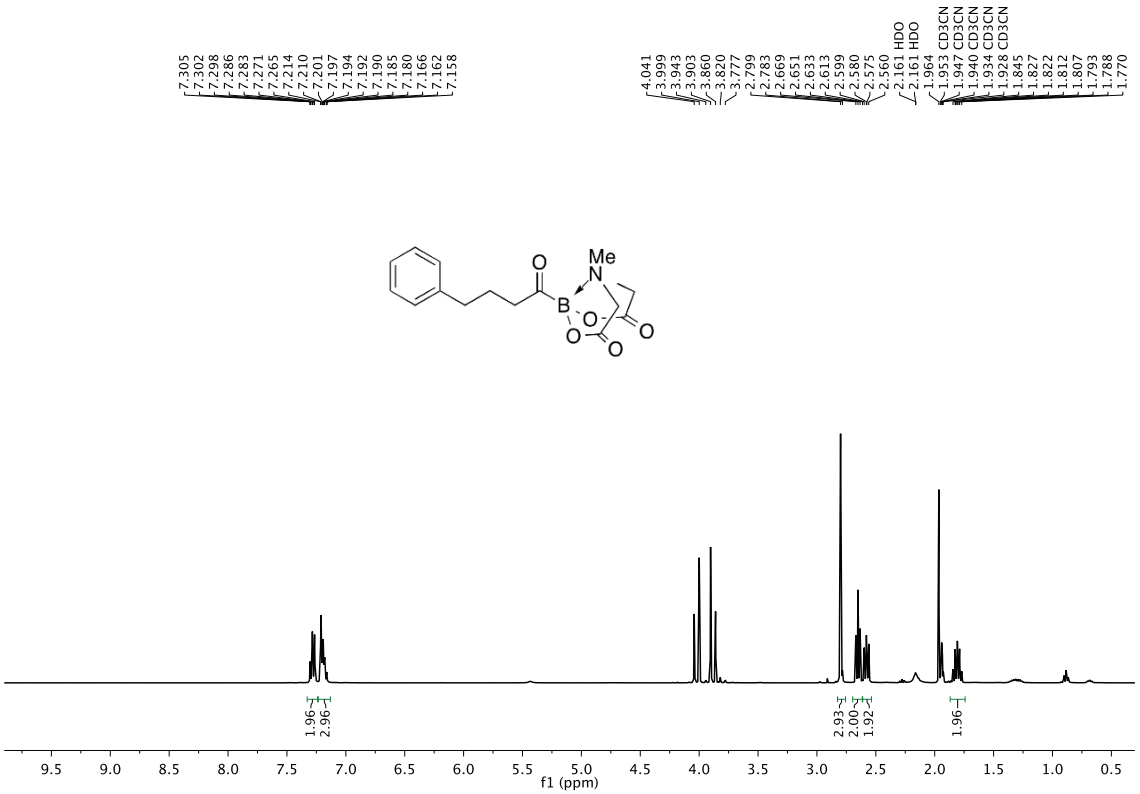


^{11}B NMR (160 MHz, CD_3CN)

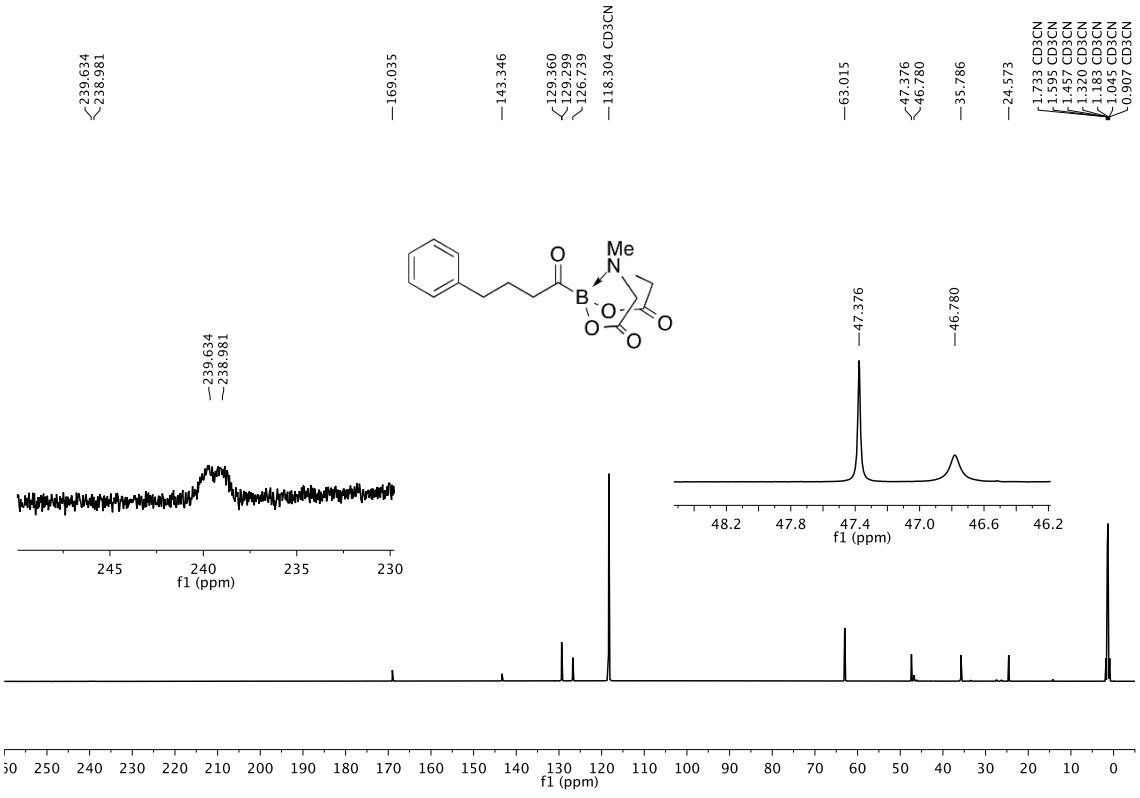


MIDA 4-phenylbutanoylboronate(3i):

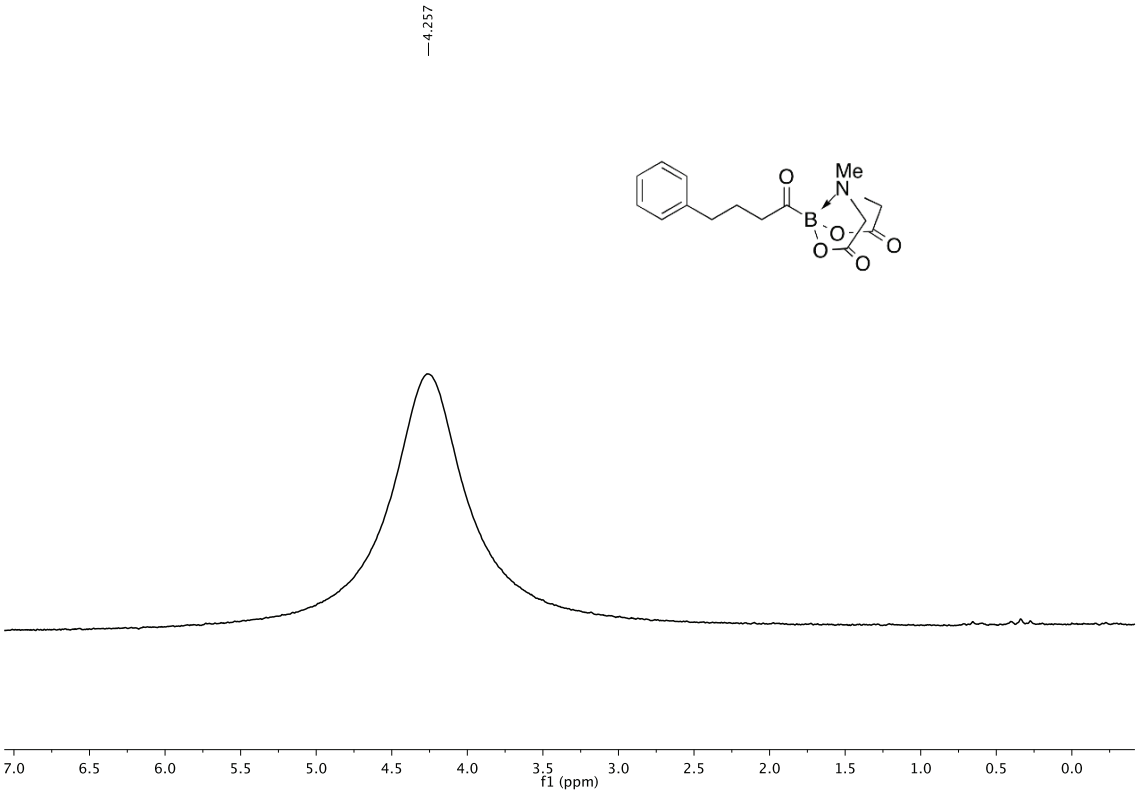
^{1}H NMR (400 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

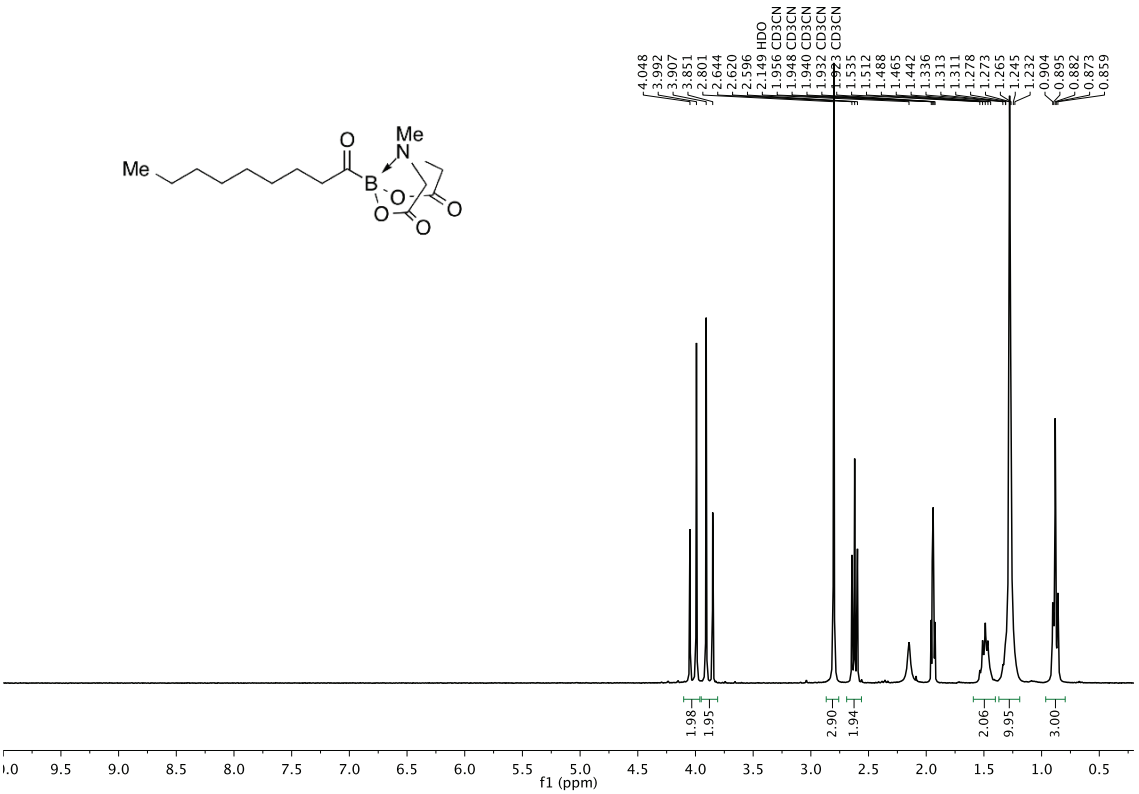


^{11}B NMR (160 MHz, CD_3CN)

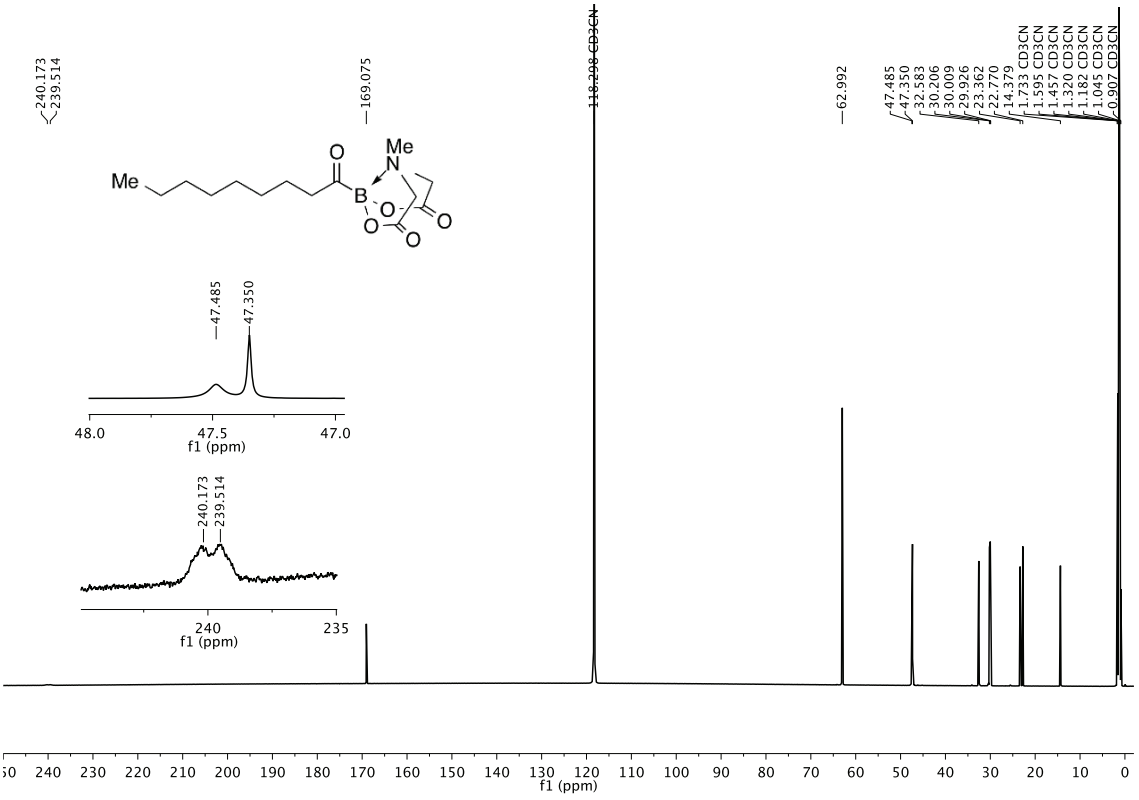


MIDA nonanoylboronate (3j):

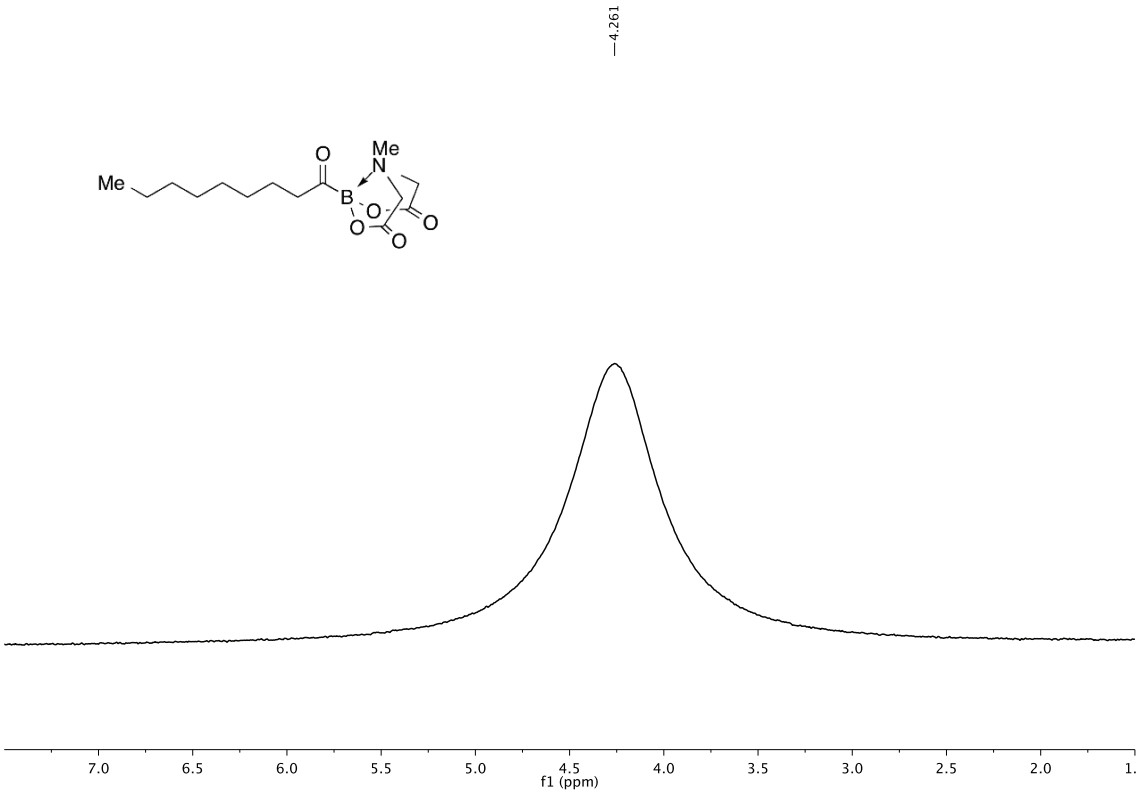
^{1}H NMR (300 MHz, CD_3CN)



^{13}C NMR (150 MHz, CD_3CN)

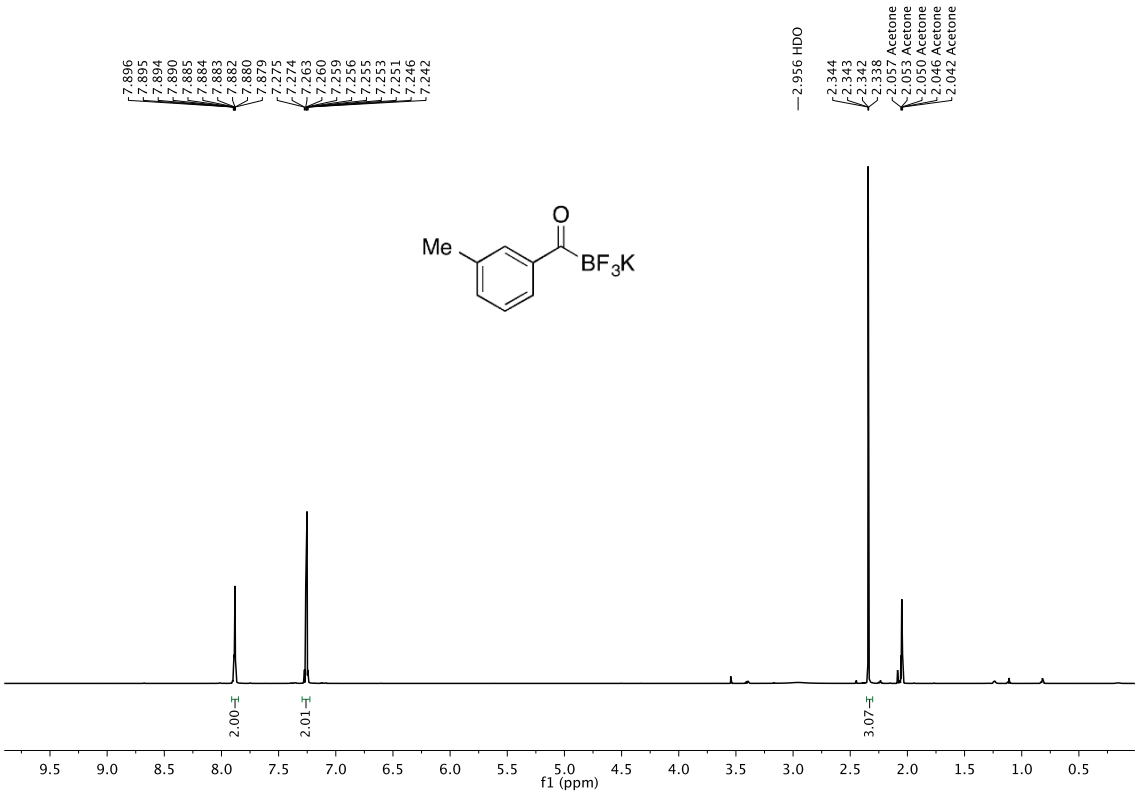


^{11}B NMR (160 MHz, CD_3CN)

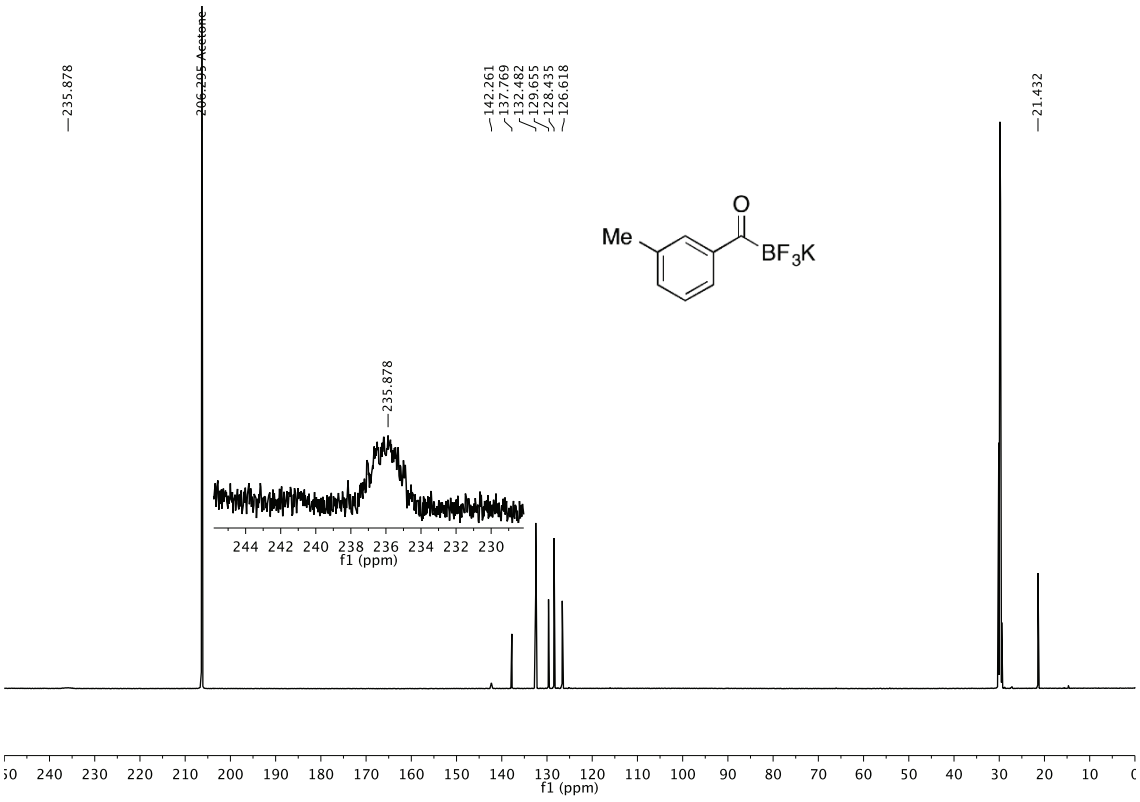


Potassium 3-methylbenzoyltrifluoroborate (1e):

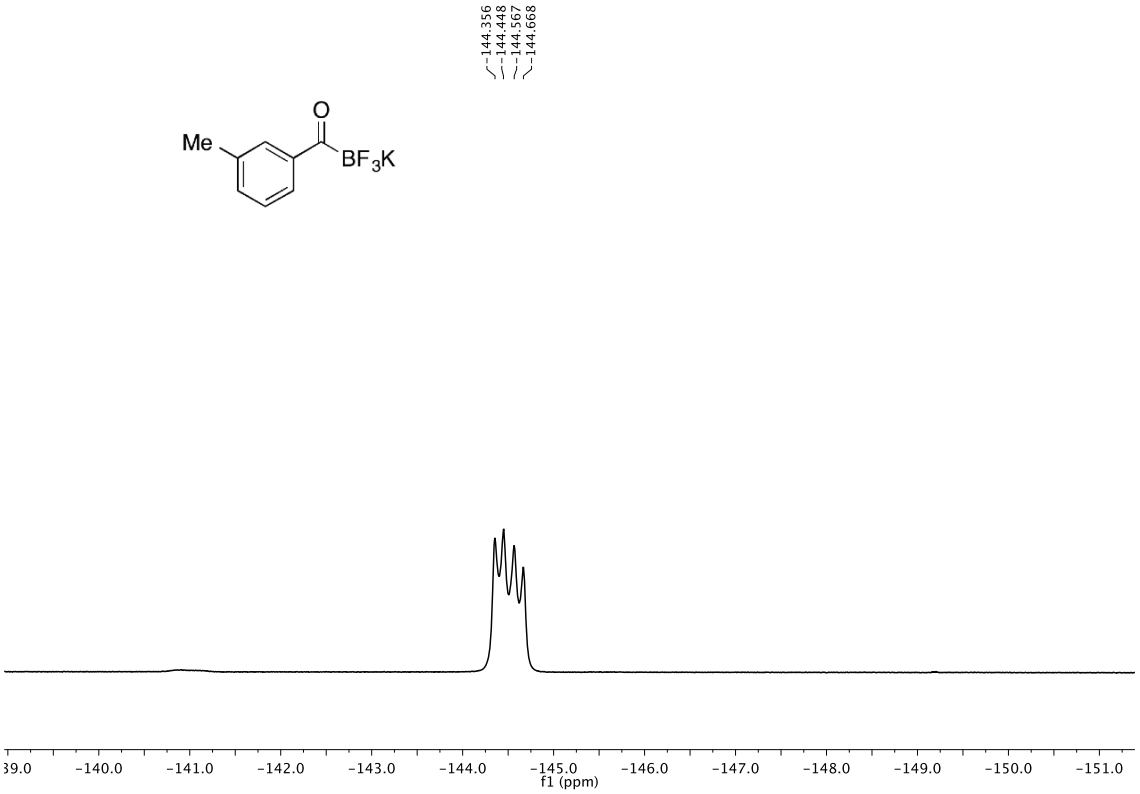
^{1}H NMR (600 MHz, d_6-acetone)



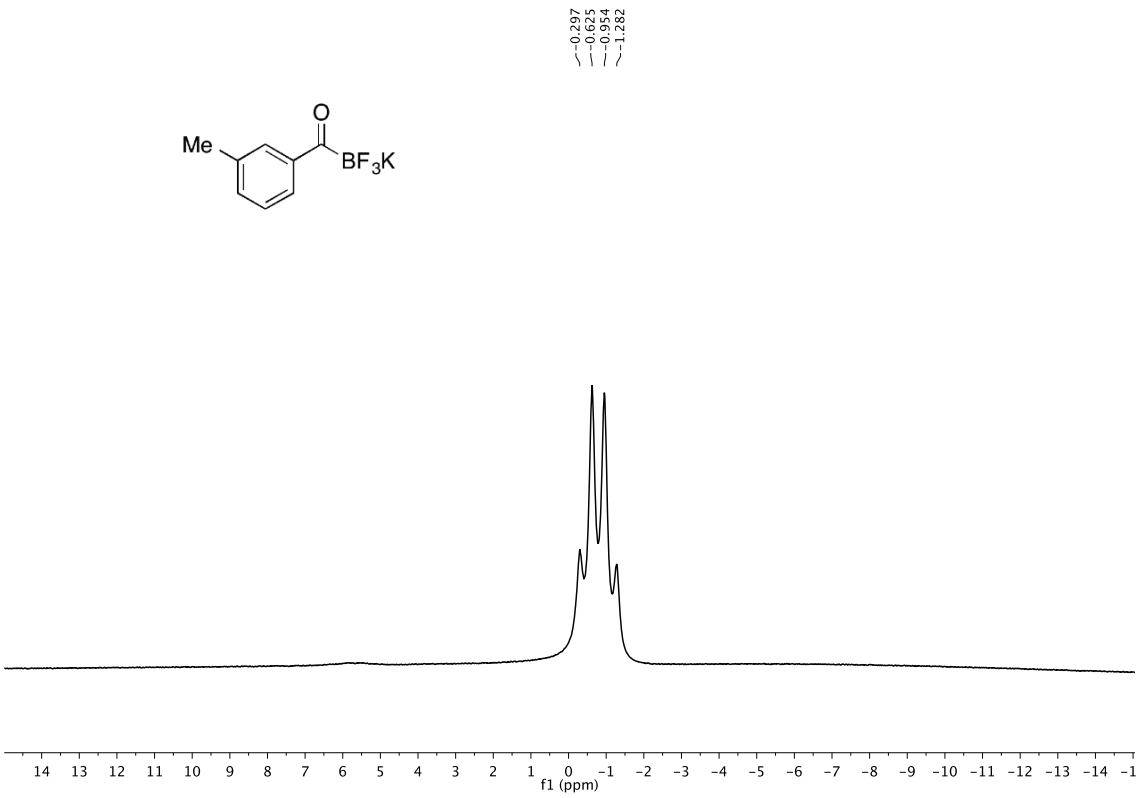
^{13}C NMR (150 MHz, d_6-acetone)



^{19}F NMR (470 MHz, d_6-acetone)

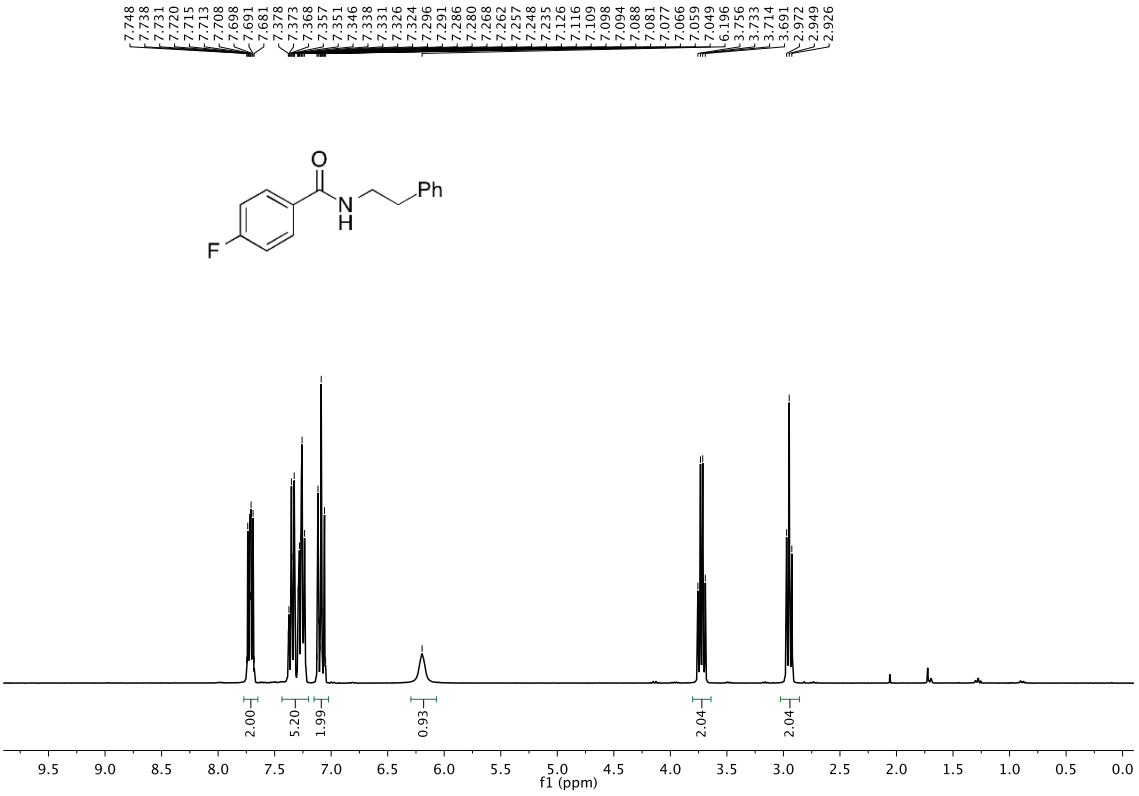


^{11}B NMR (160 MHz, d_6-acetone)

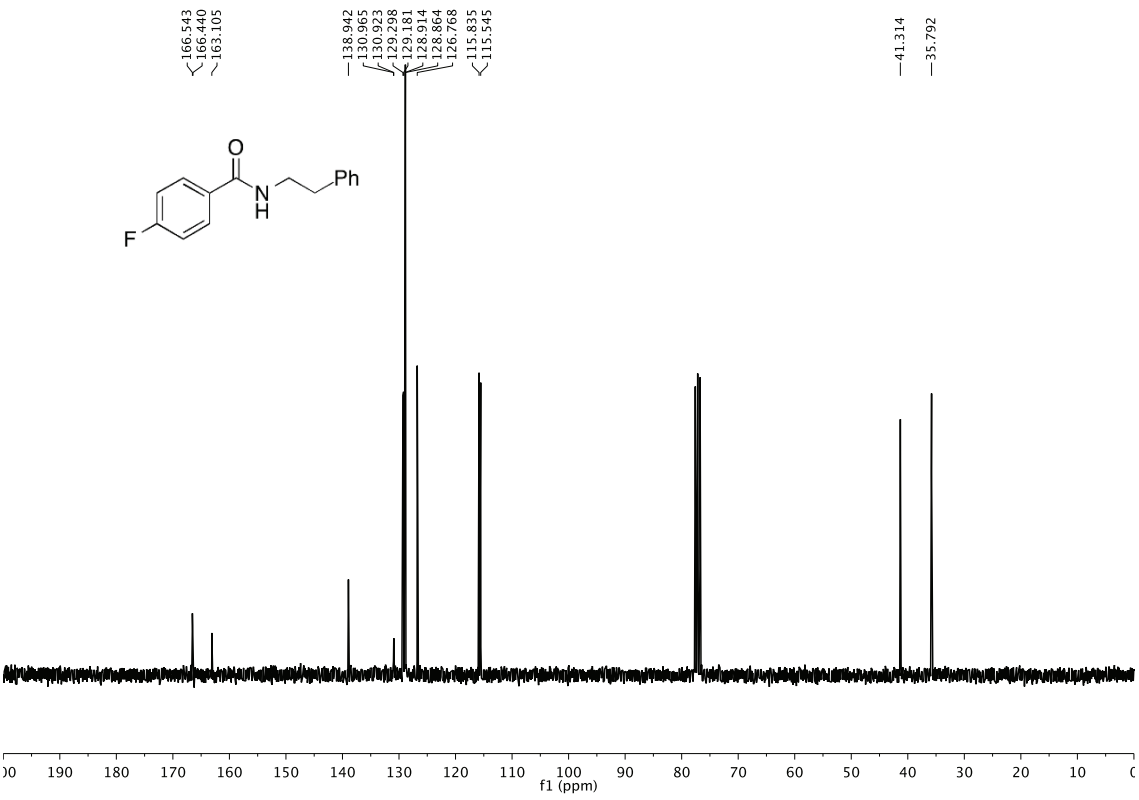


4-Fluoro-*N*-phenethylbenzamide (5ca):

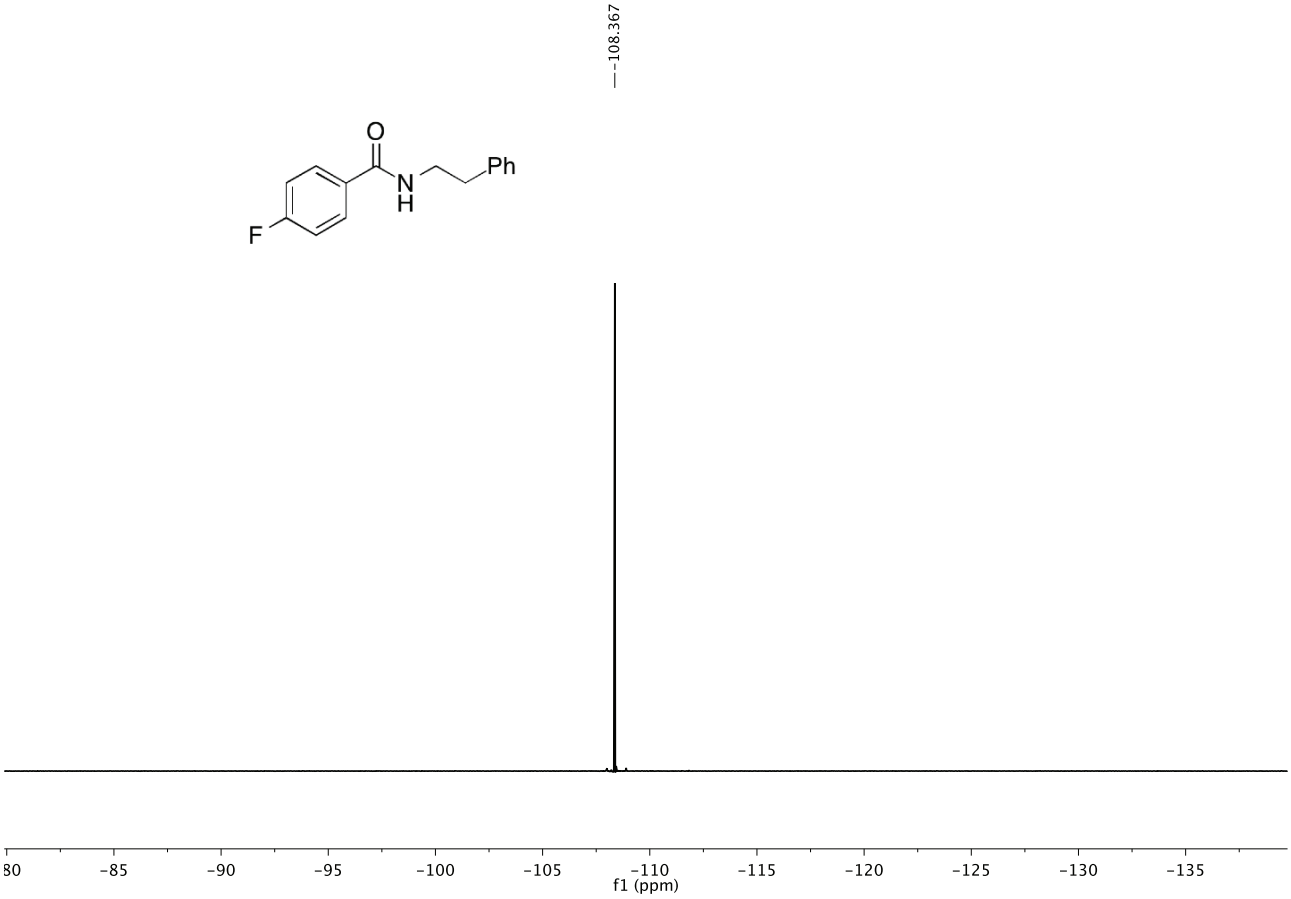
^{1}H NMR (300 MHz, $CDCl_3$)



^{13}C NMR (75 MHz, $CDCl_3$)

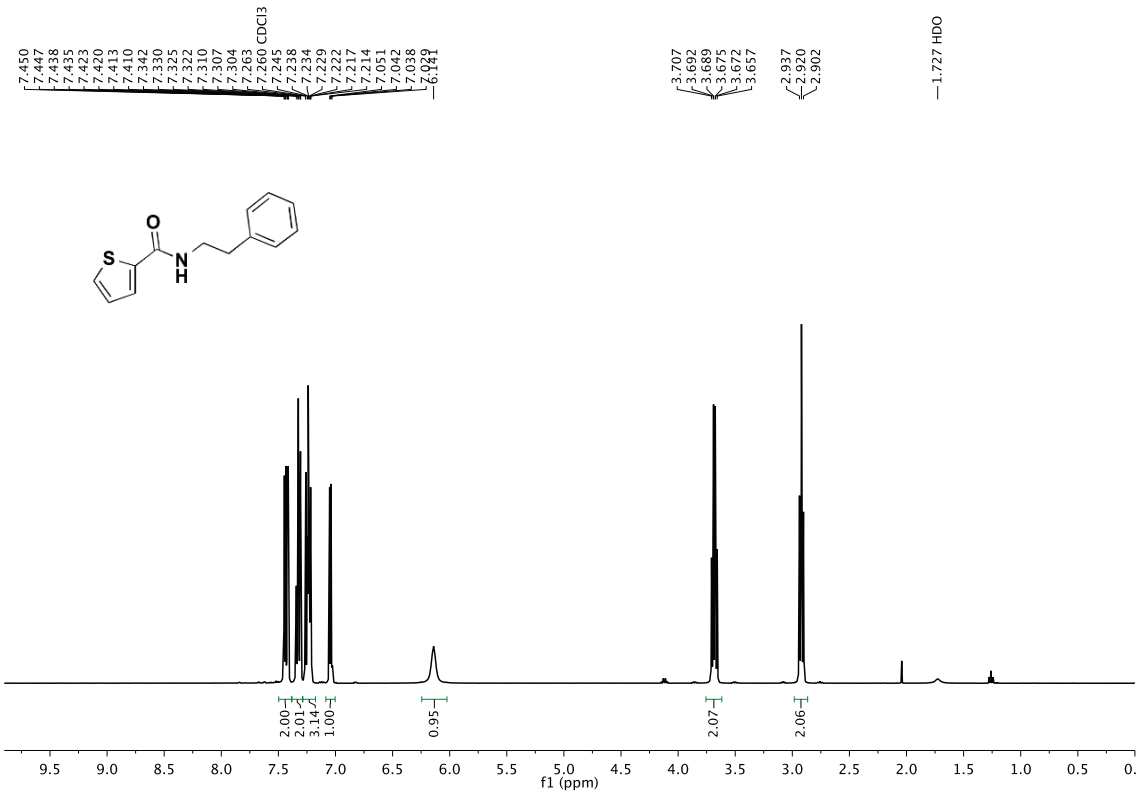


^{19}F NMR (282 MHz, $CDCl_3$)

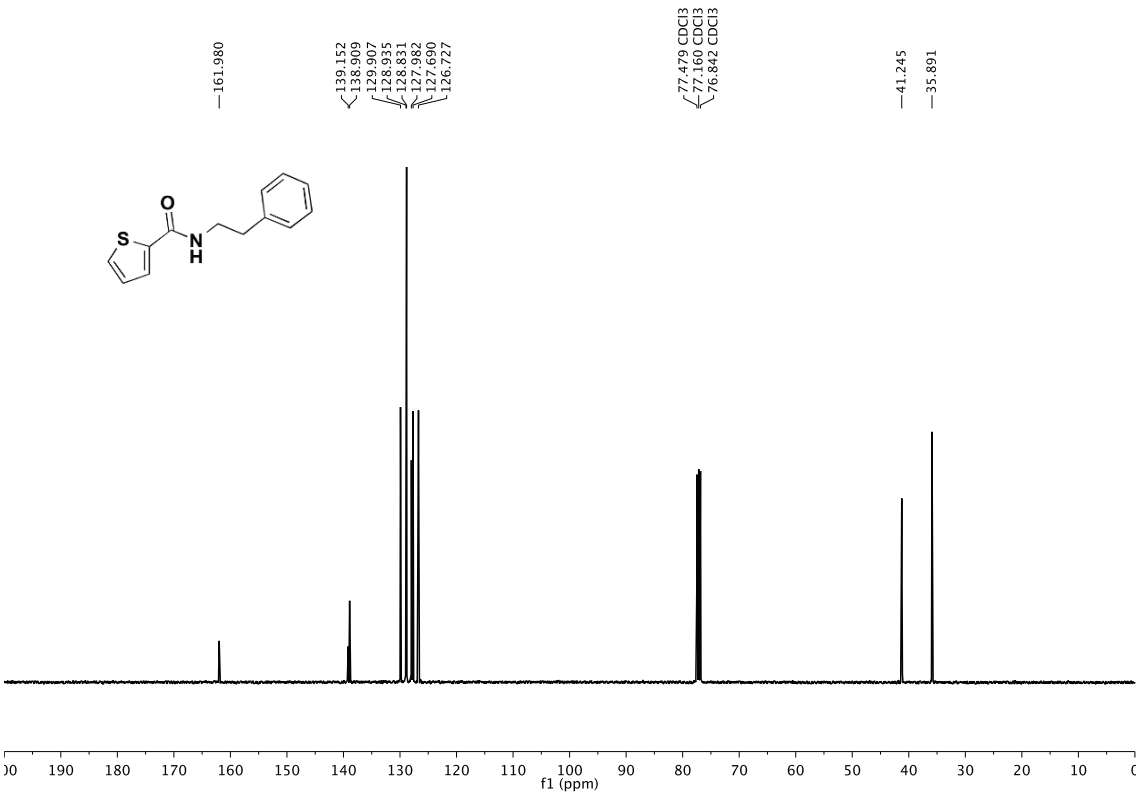


N-phenethylthiophene-2-carboxamide (5ga):

^{1}H NMR (400 MHz, $CDCl_3$)

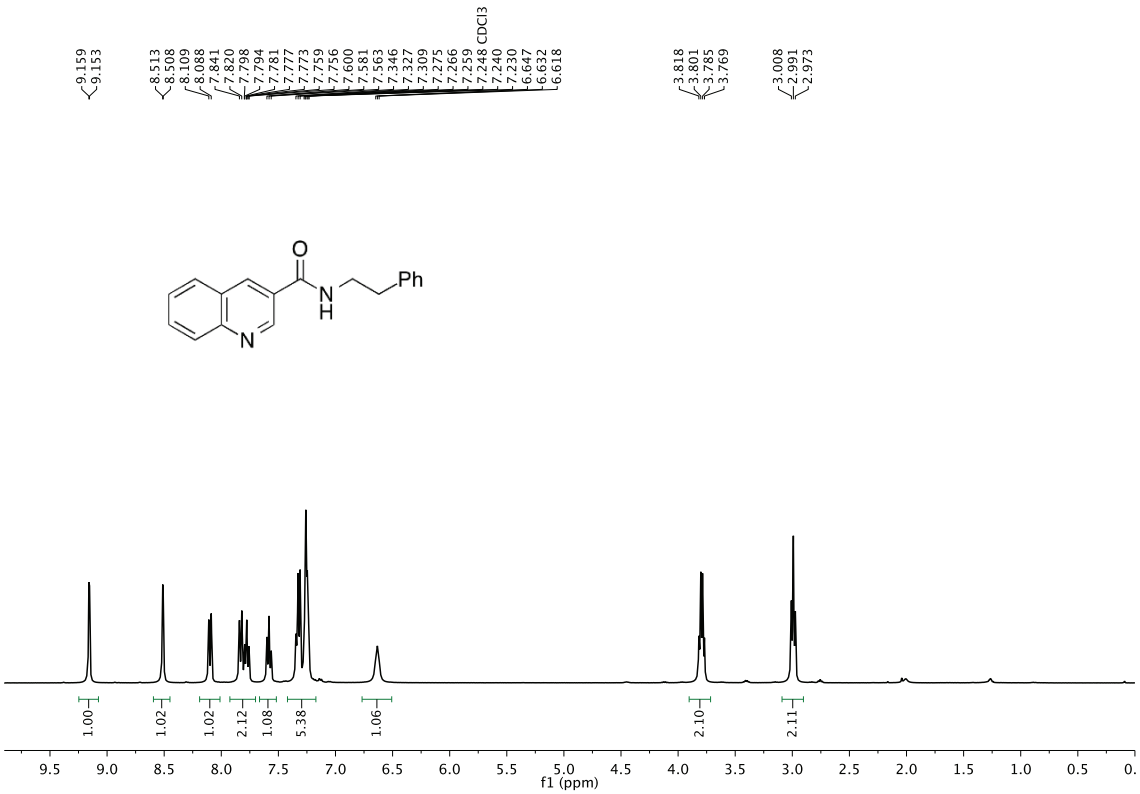


^{13}C NMR (100 MHz, $CDCl_3$)

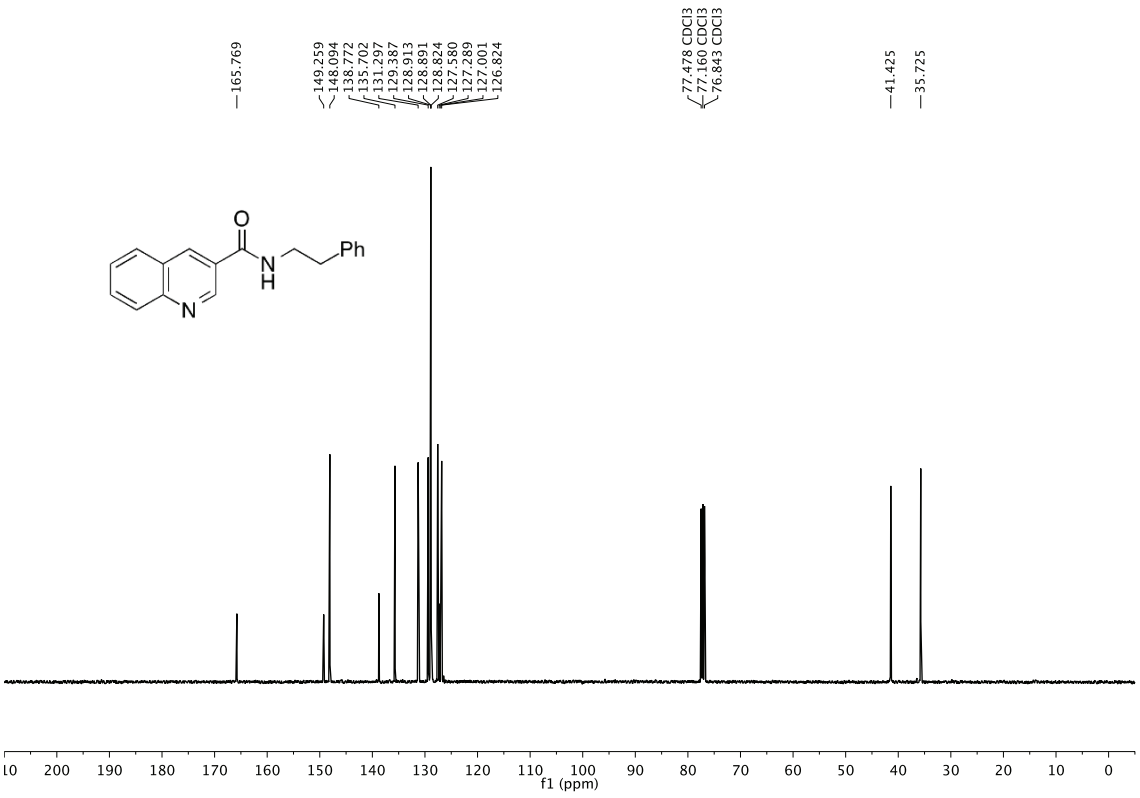


N-Phenethylquinoline-3-carboxamide (5ha):

^{1}H NMR (400 MHz, $CDCl_3$)

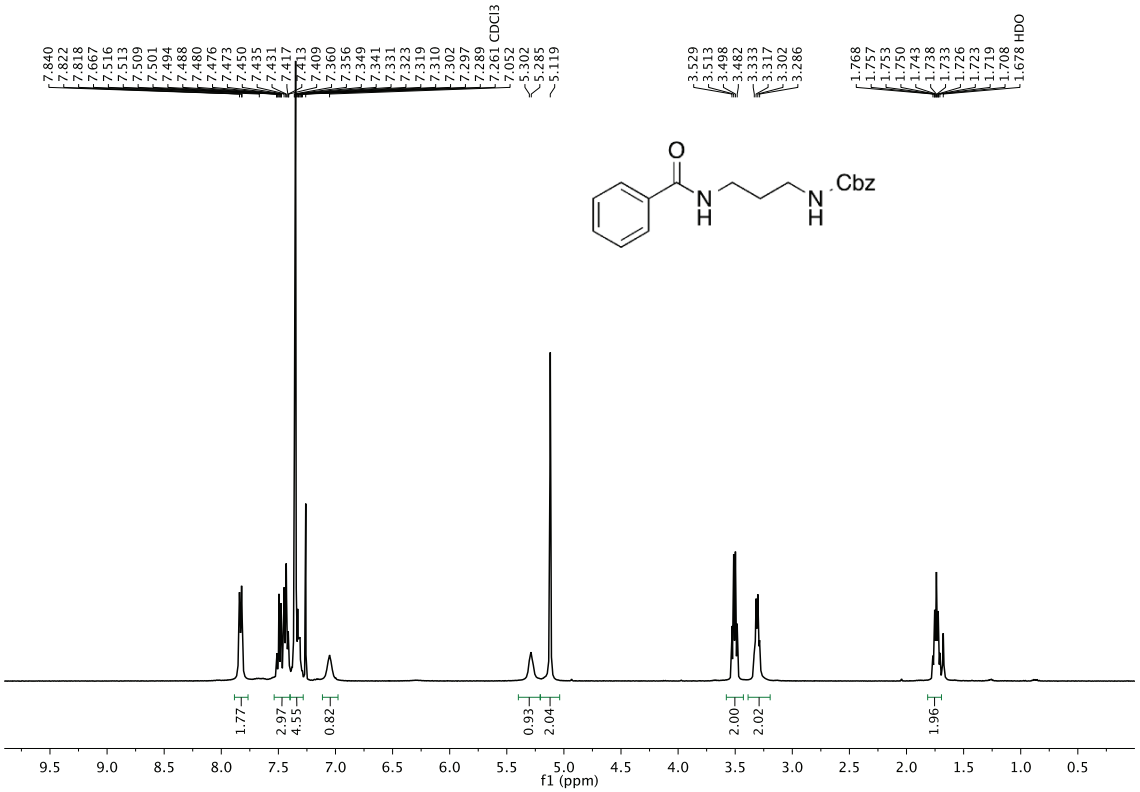


^{13}C NMR (100 MHz, $CDCl_3$)

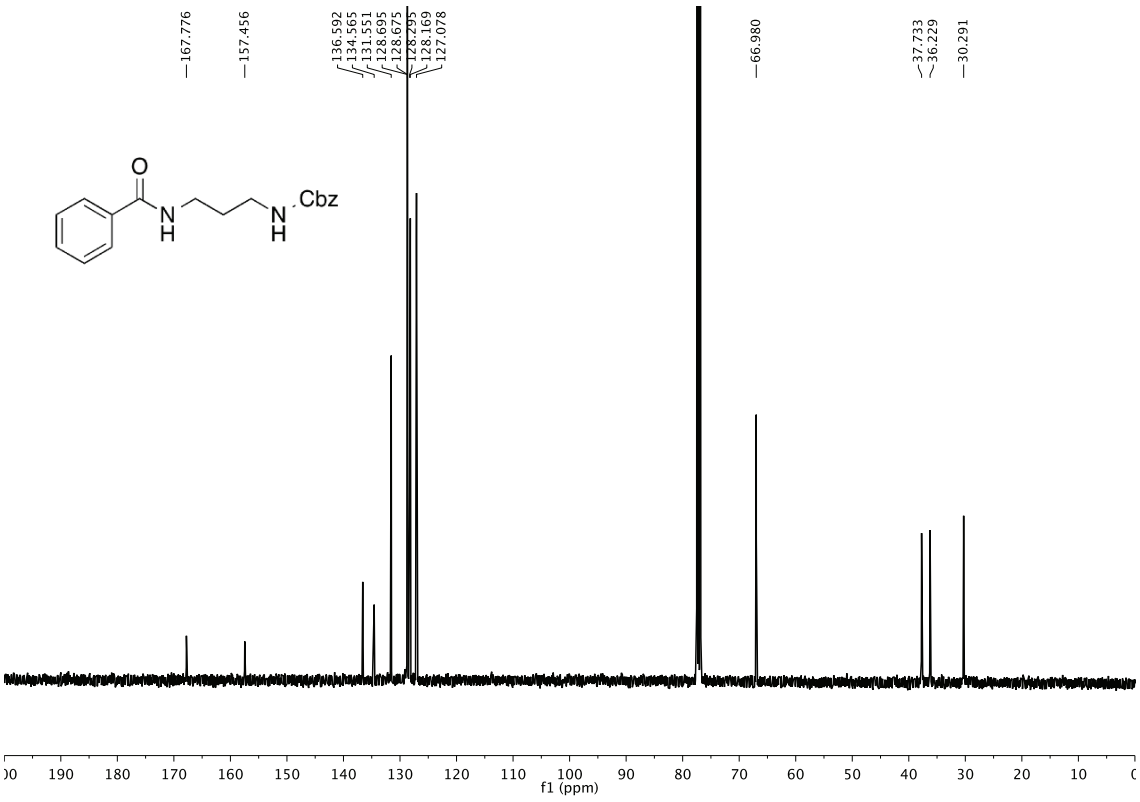


Benzyl (3-benzamidopropyl)carbamate (5ad):

^{1}H NMR (400 MHz, $CDCl_3$)

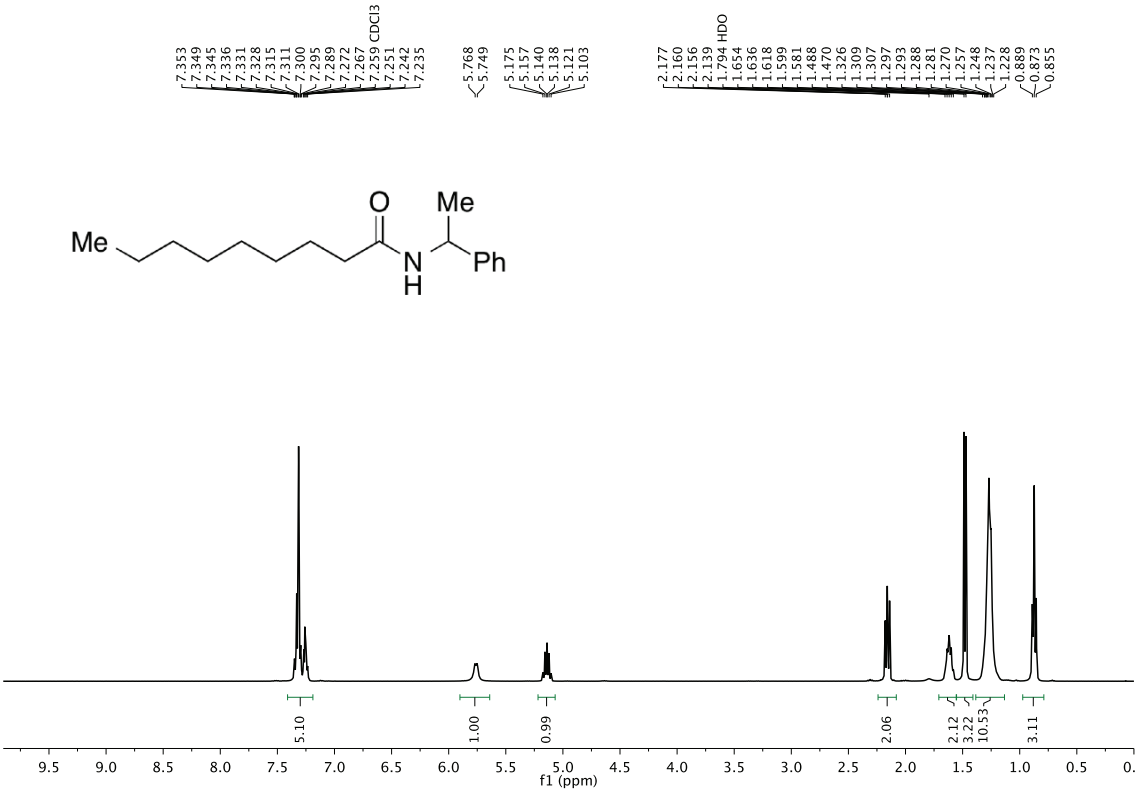


^{13}C NMR (100 MHz, $CDCl_3$)

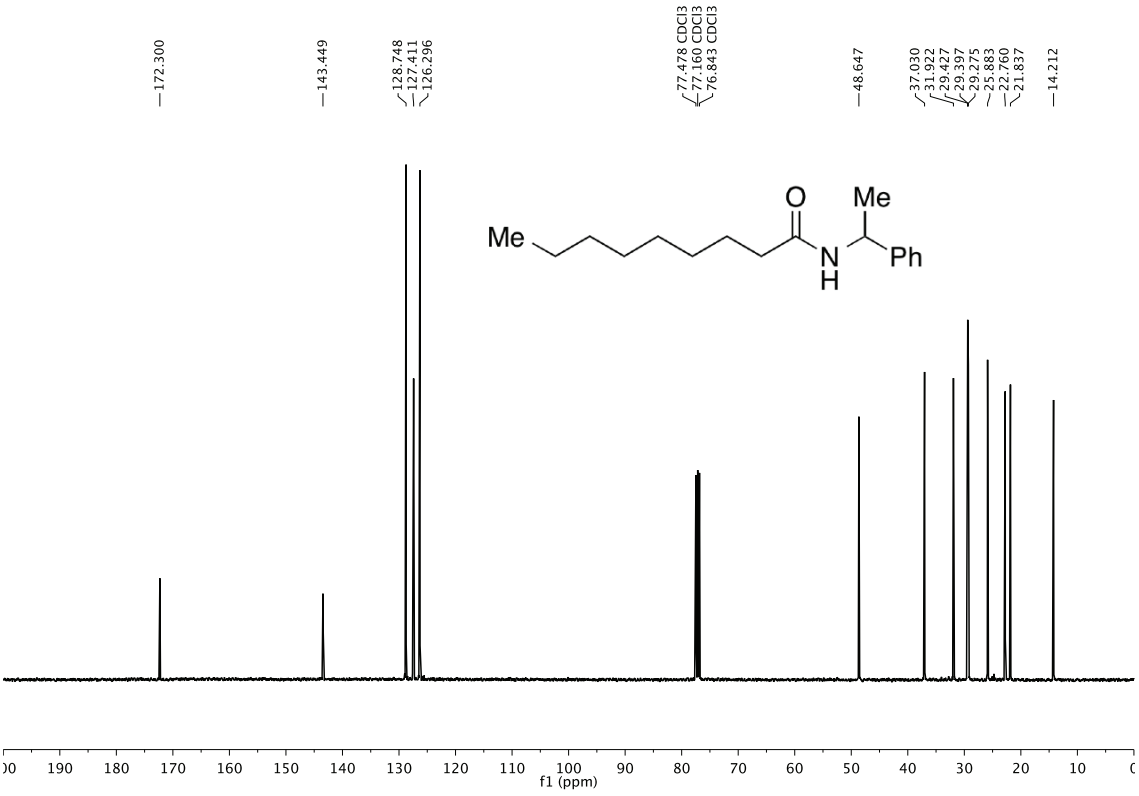


N-(1-phenylethyl)nonanamide (5ge):

^{1}H NMR (400 MHz, $CDCl_3$)

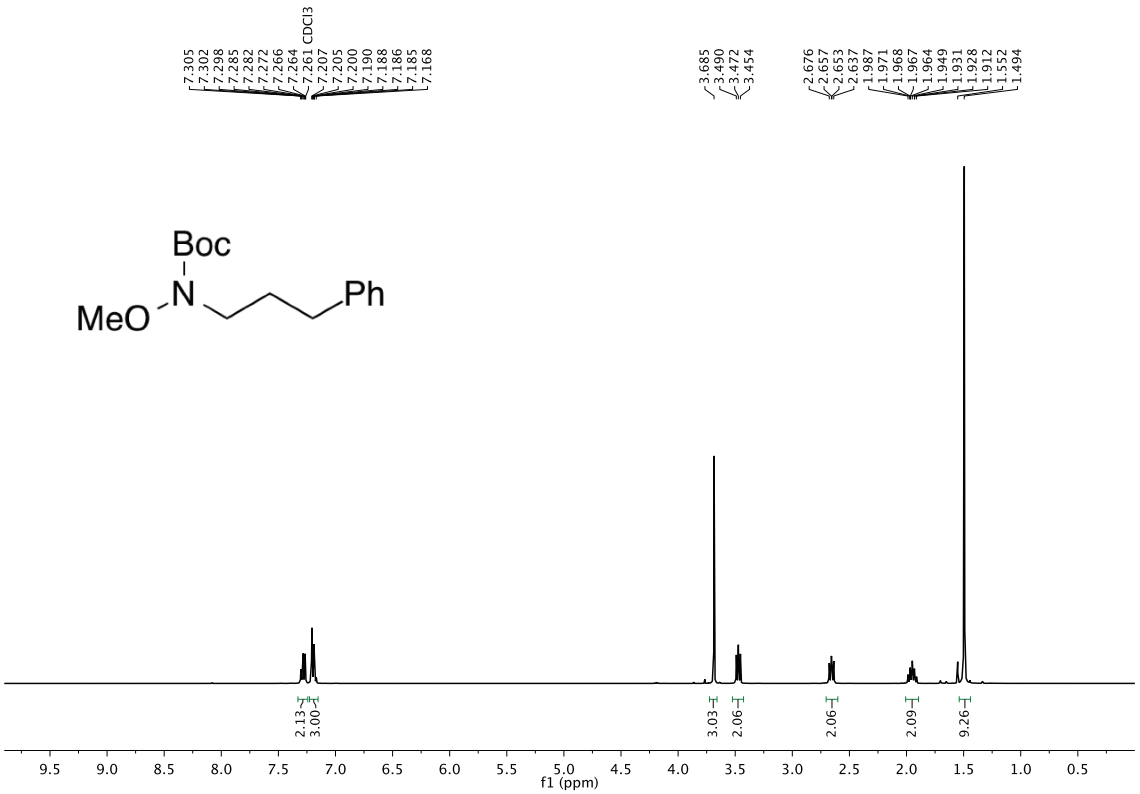


^{13}C NMR (100 MHz, $CDCl_3$)

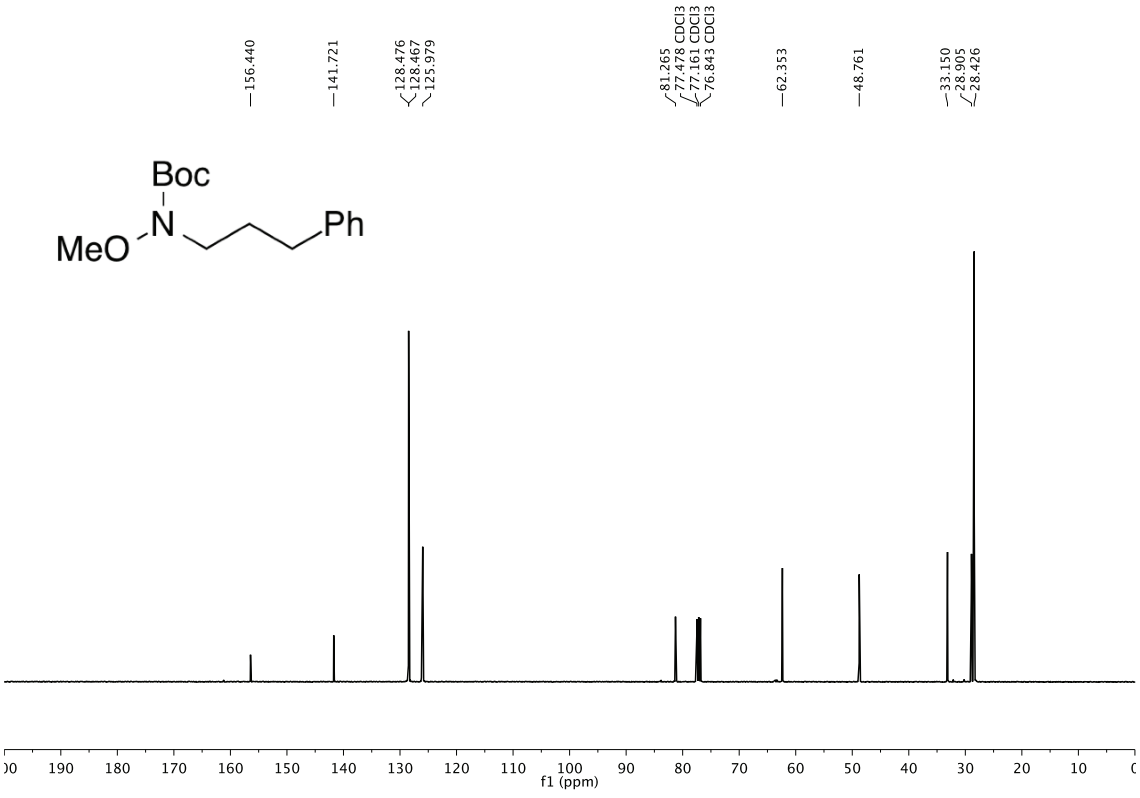


_O_-Methyl-_N_-_tert_-butoxycarbonyl-_N_-phenethylhydroxylamine (S6):

^{1}H NMR (400 MHz, $CDCl_3$)

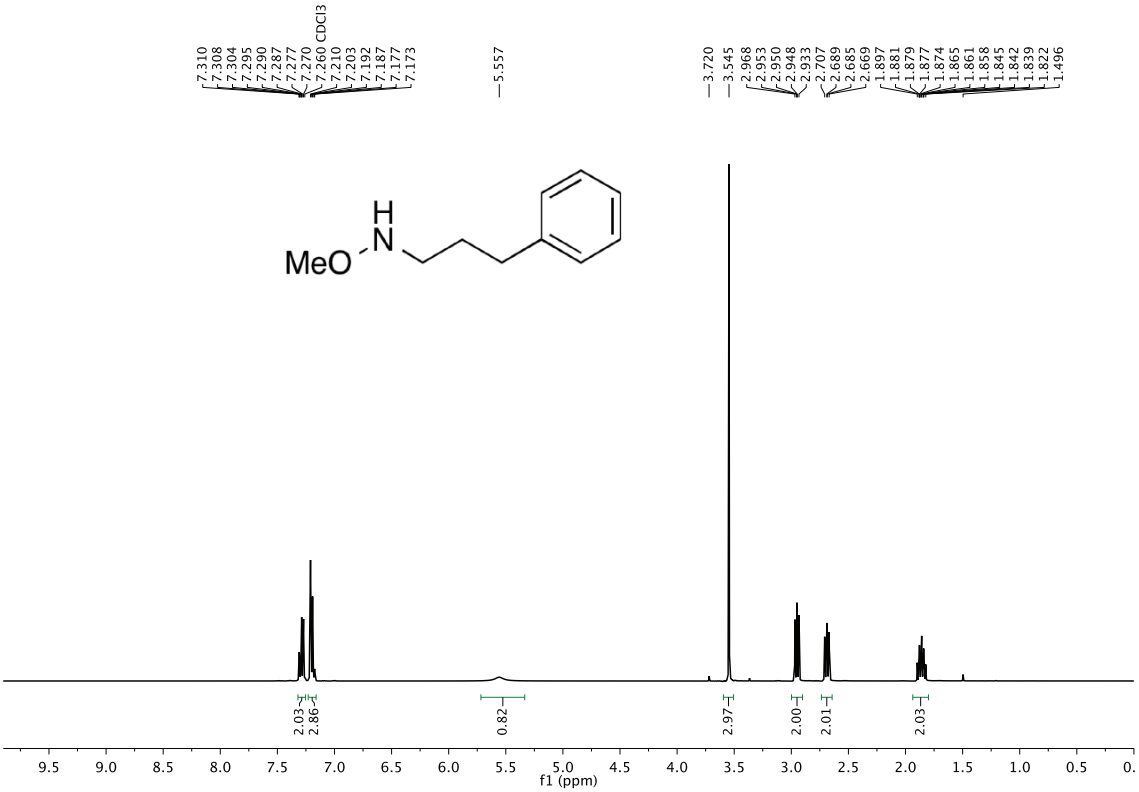


^{13}C NMR (100 MHz, $CDCl_3$)

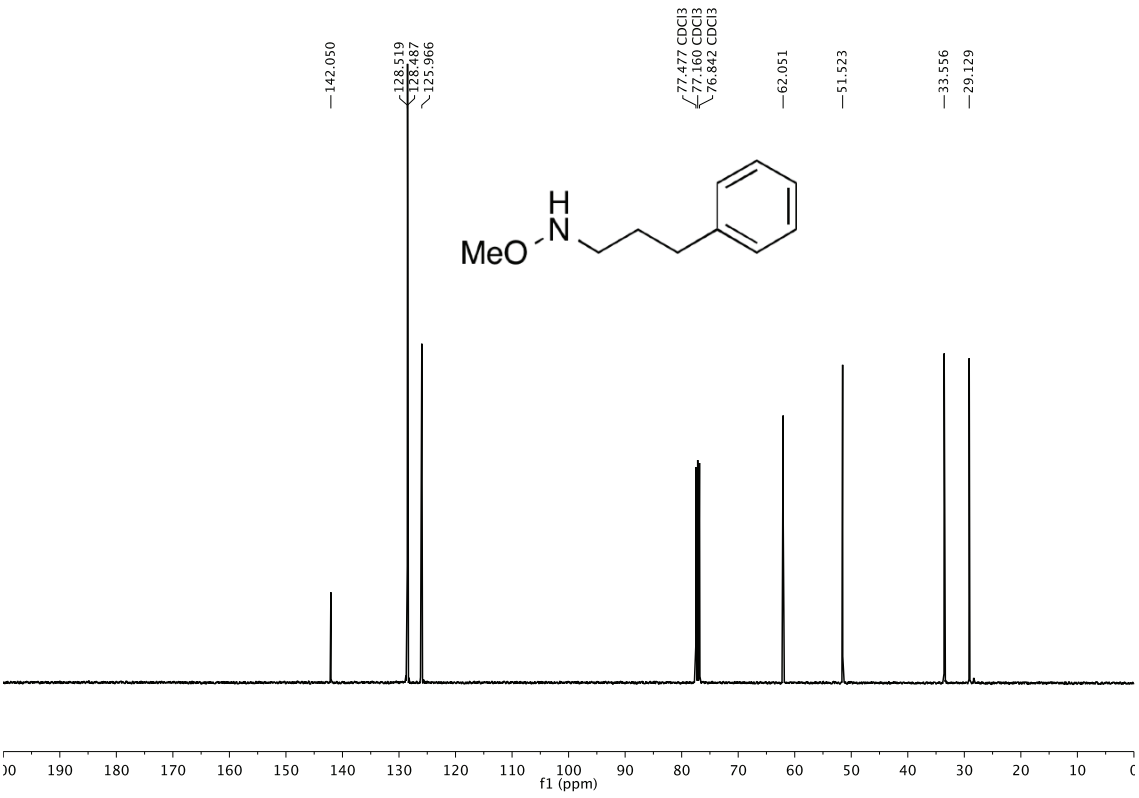


O-Methyl-3-phenylpropylhydroxylamine (4b):

^{1}H NMR (400 MHz, $CDCl_3$)

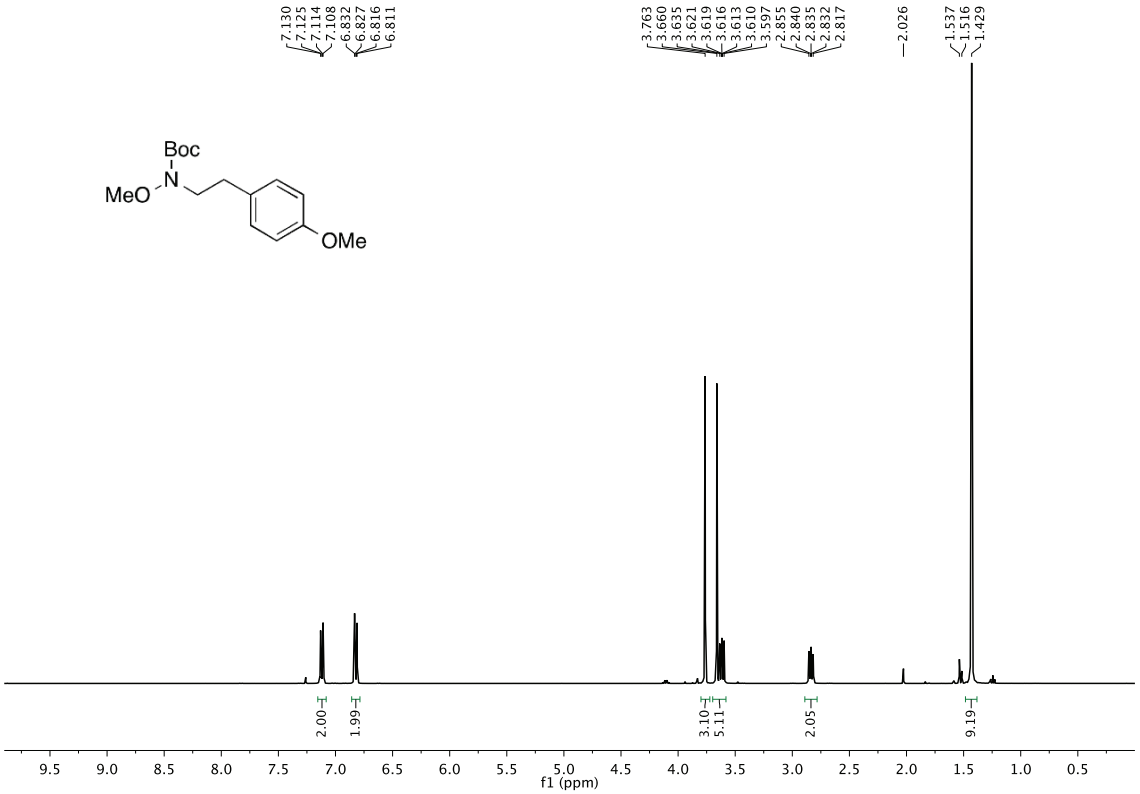


^{13}C NMR (100 MHz, $CDCl_3$)

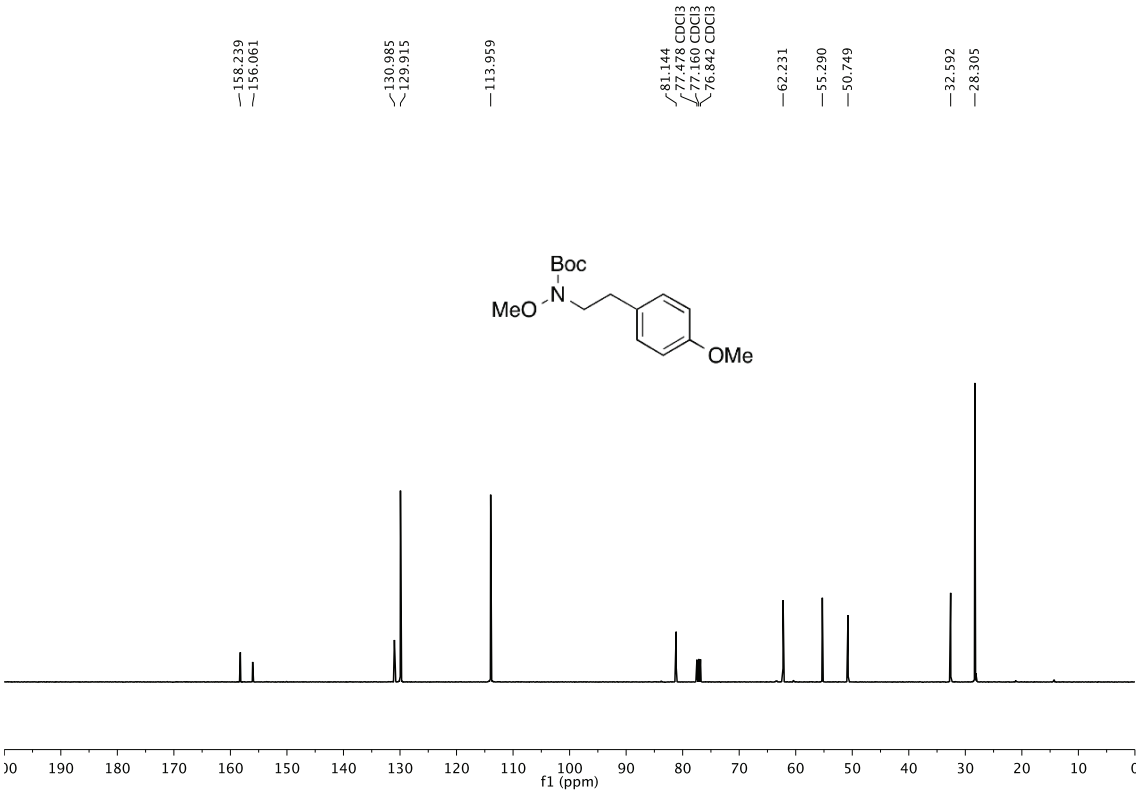


N-tert-butoxycarbonyl-_N_-(4-methoxylphenethyl)-_O_-methylhydroxylamine (S7):

^{1}H NMR (400 MHz, $CDCl_3$)

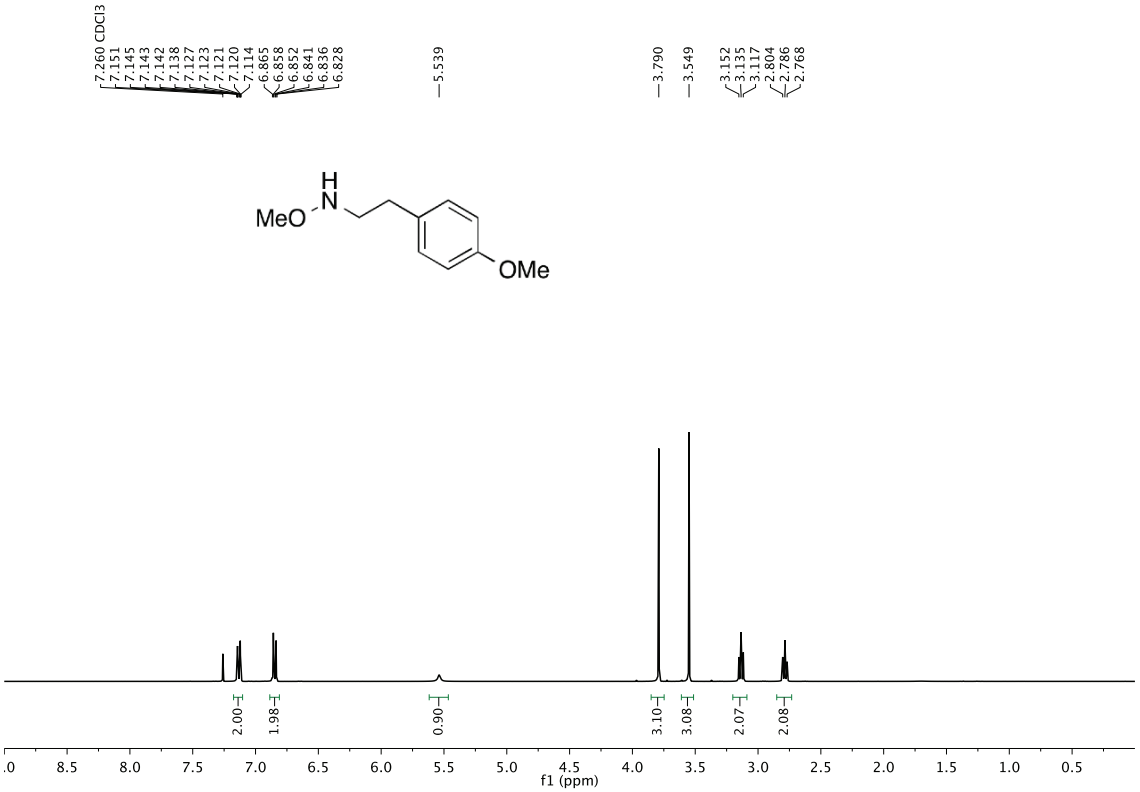


^{13}C NMR (100 MHz, $CDCl_3$)

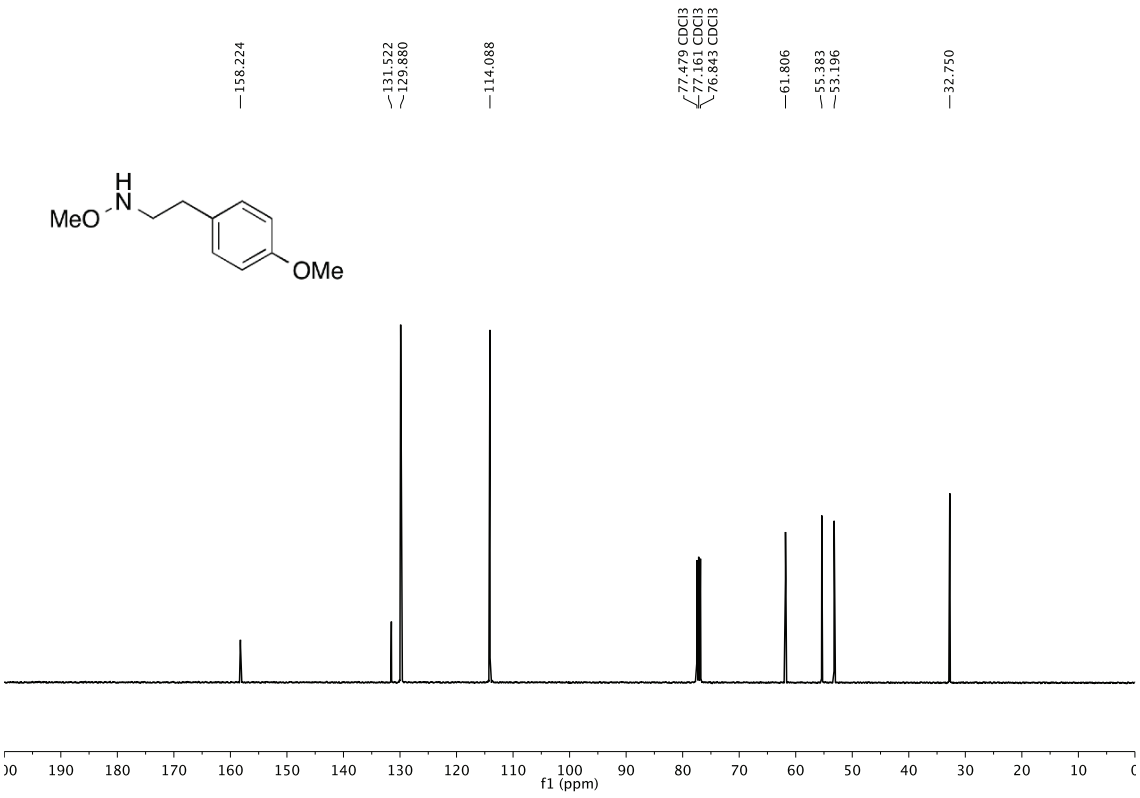


N-(4-methoxylphenethyl)-*O*-methylhydroxylamine (4c):

^{1}H NMR (400 MHz, $CDCl_3$)

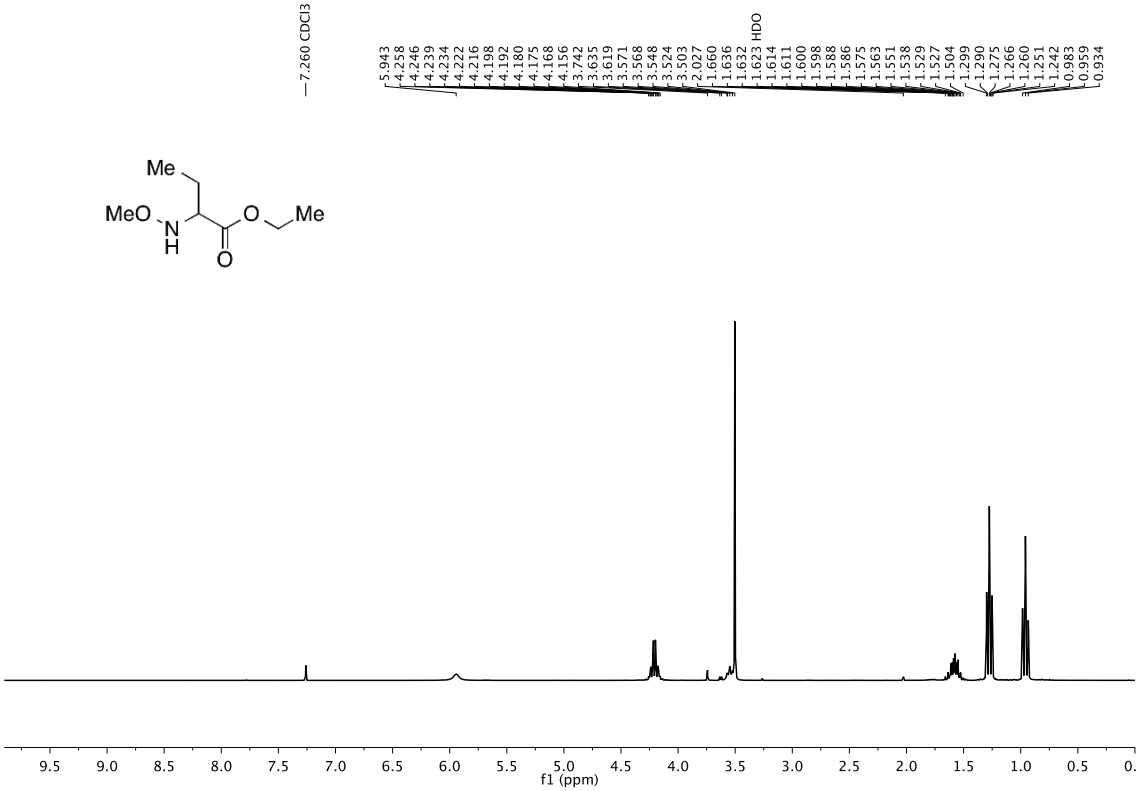


^{13}C NMR (100 MHz, $CDCl_3$)

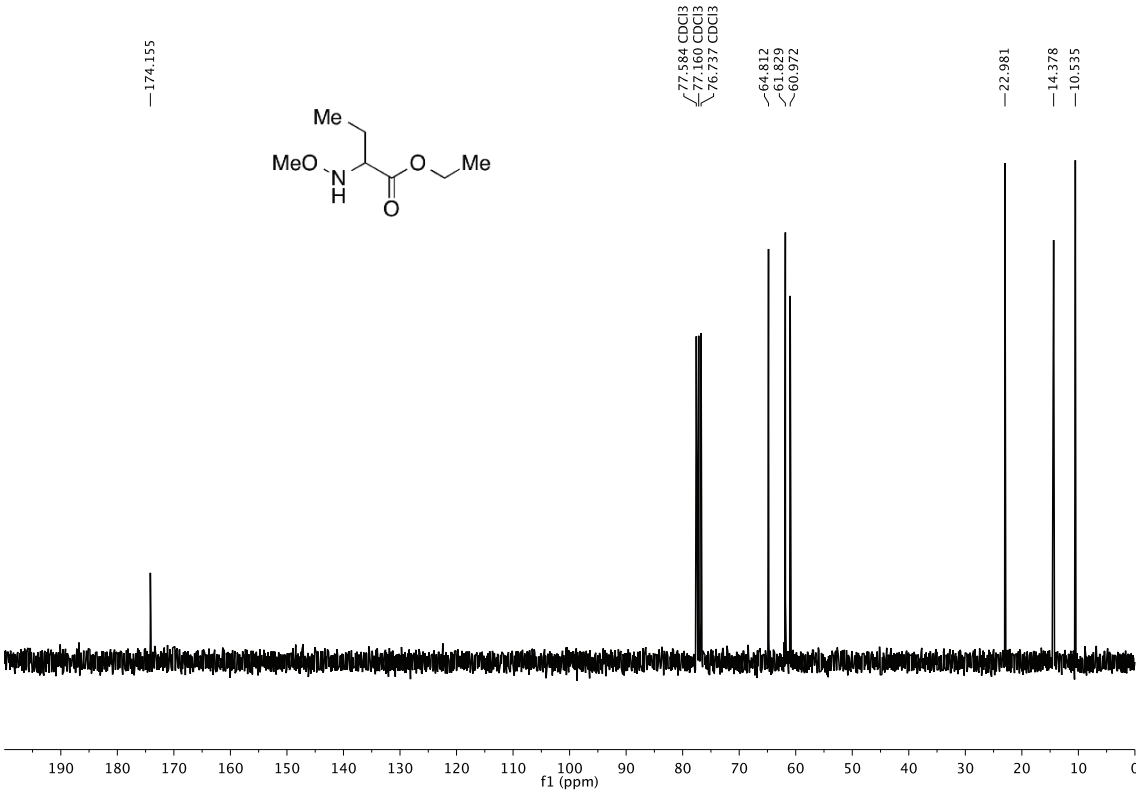


Ethyl 2-(methoxyamino)butanoate (4f):

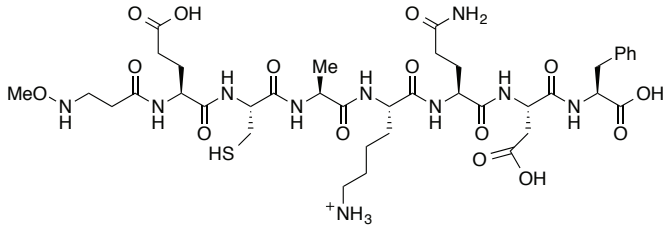
^{1}H NMR (300 MHz, $CDCl_3$)



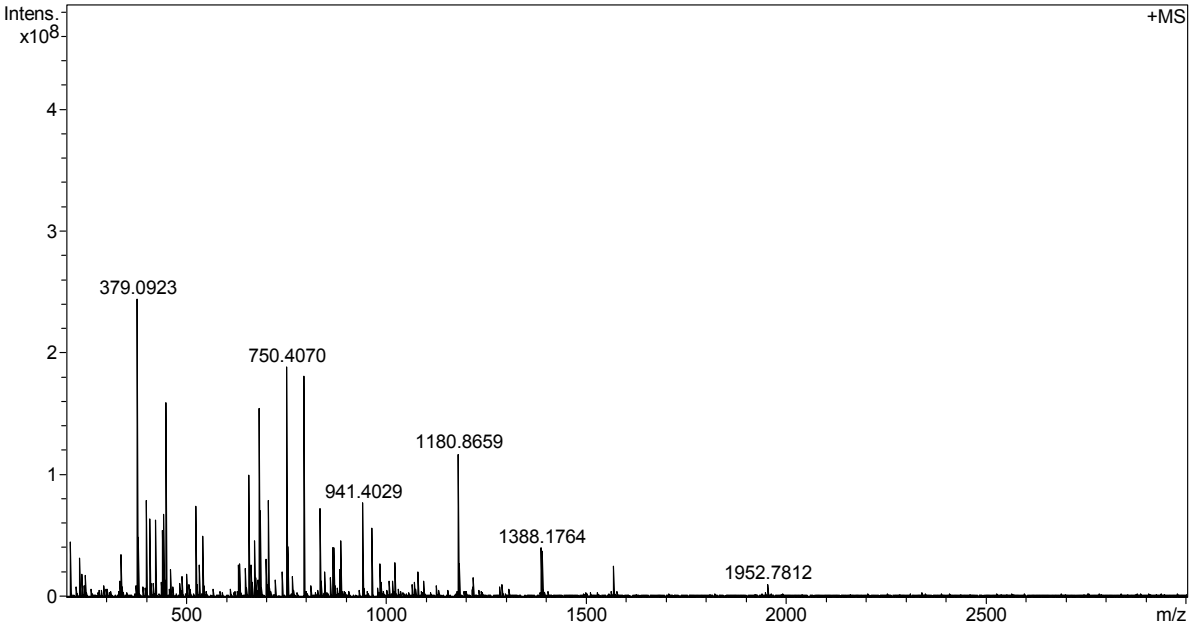
^{13}C NMR (75 MHz, $CDCl_3$)

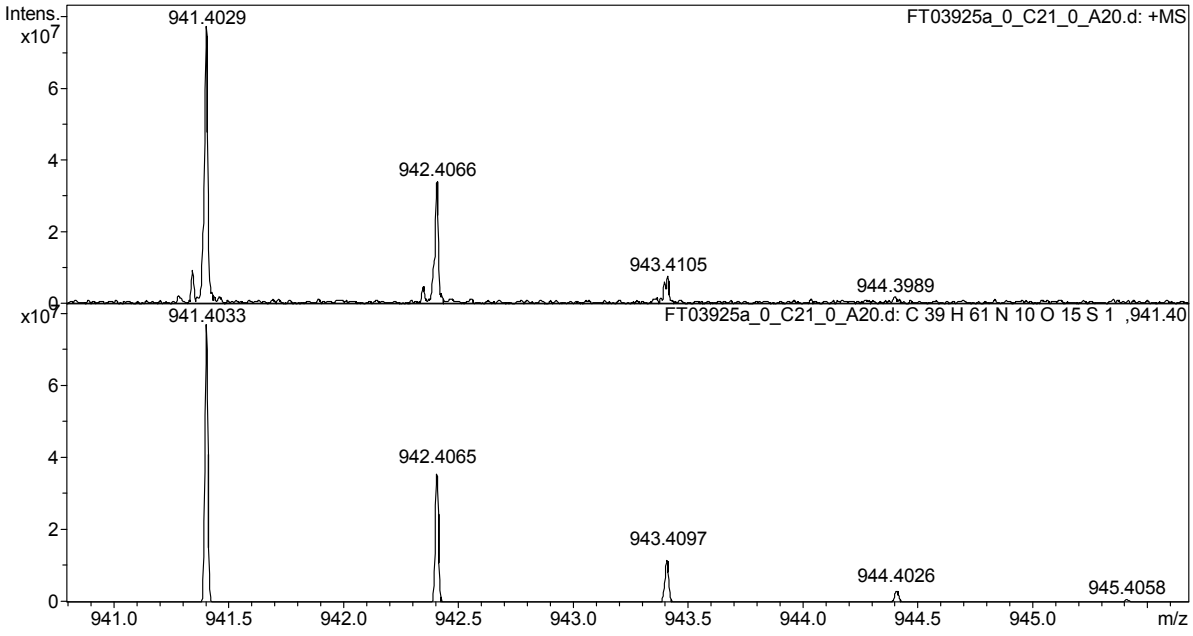


Peptide 7:

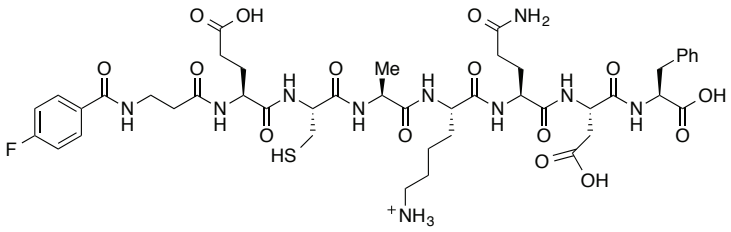


Box 1: Full scale spectra with internal reference peaks (ESI: Na-PFHA 408.9481, 794.9069, 1180.8659, 1566.8244); **Box 2:** Measured isotopic pattern of the product peak; **Box 3:** Calculated isotopic pattern of the product peak.

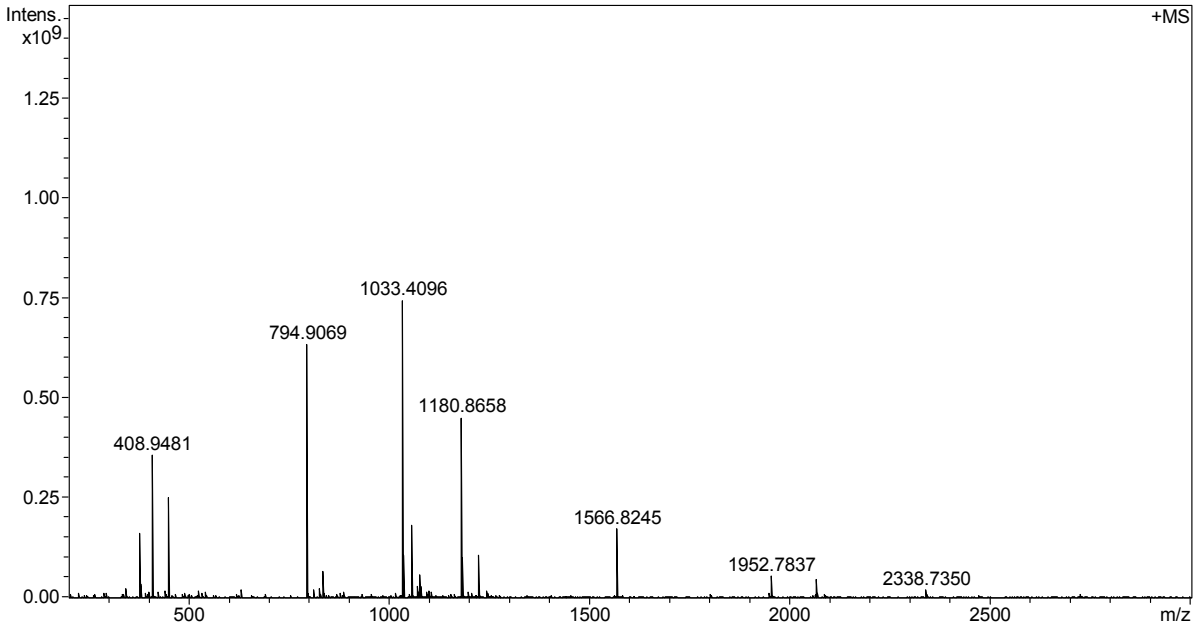


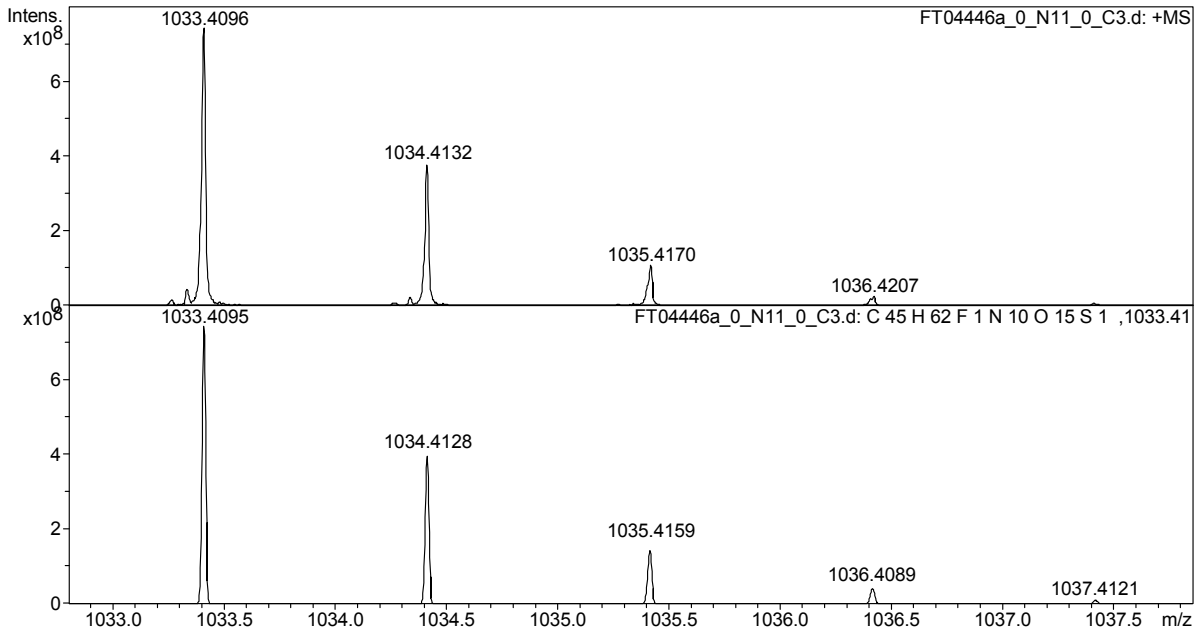


Peptide 8:

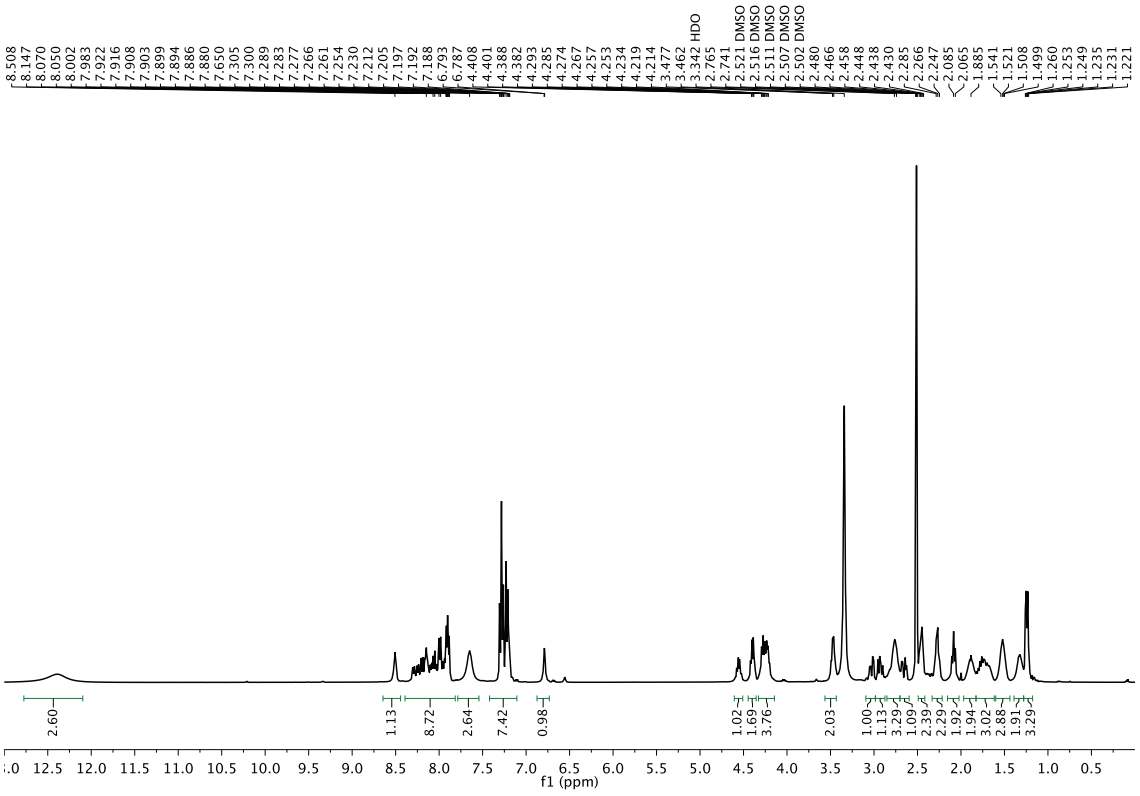


Box 1: Full scale spectra with internal reference peaks (ESI: Na-PFHA 408.9481, 794.9069, 1180.8658, 1566.8245); **Box 2:** Measured isotopic pattern of the product peak; **Box 3:** Calculated isotopic pattern of the product peak.

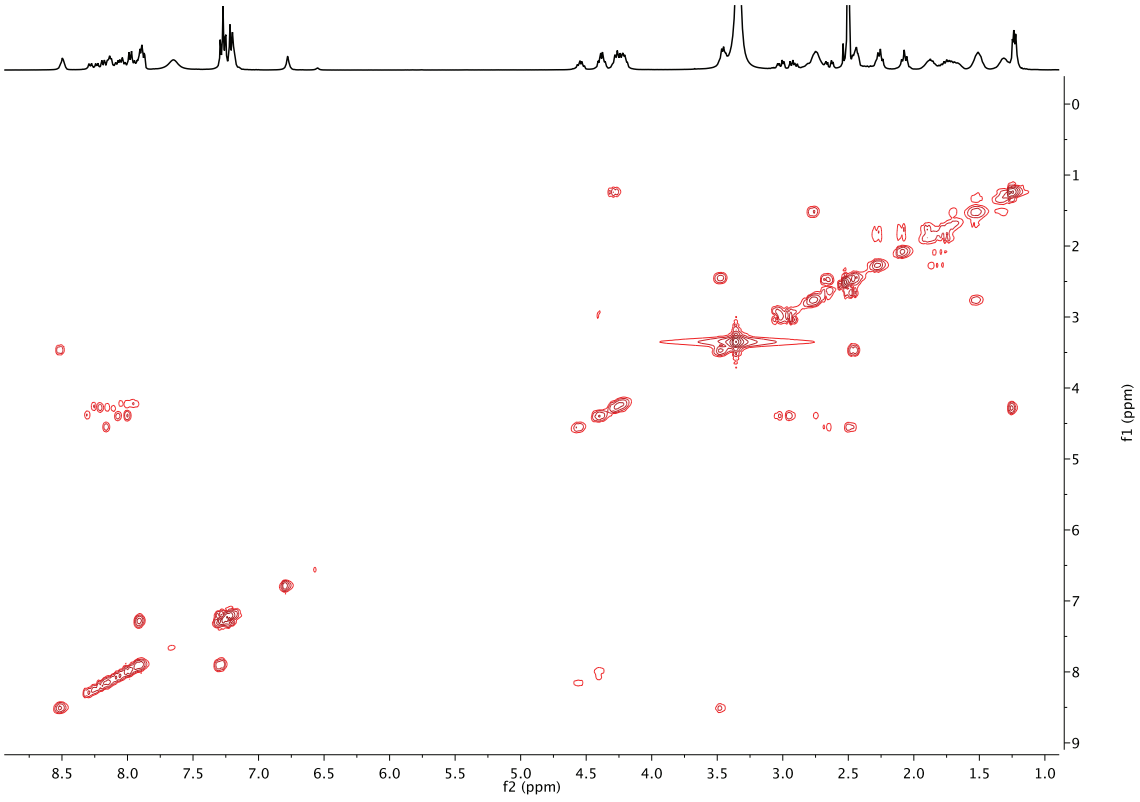




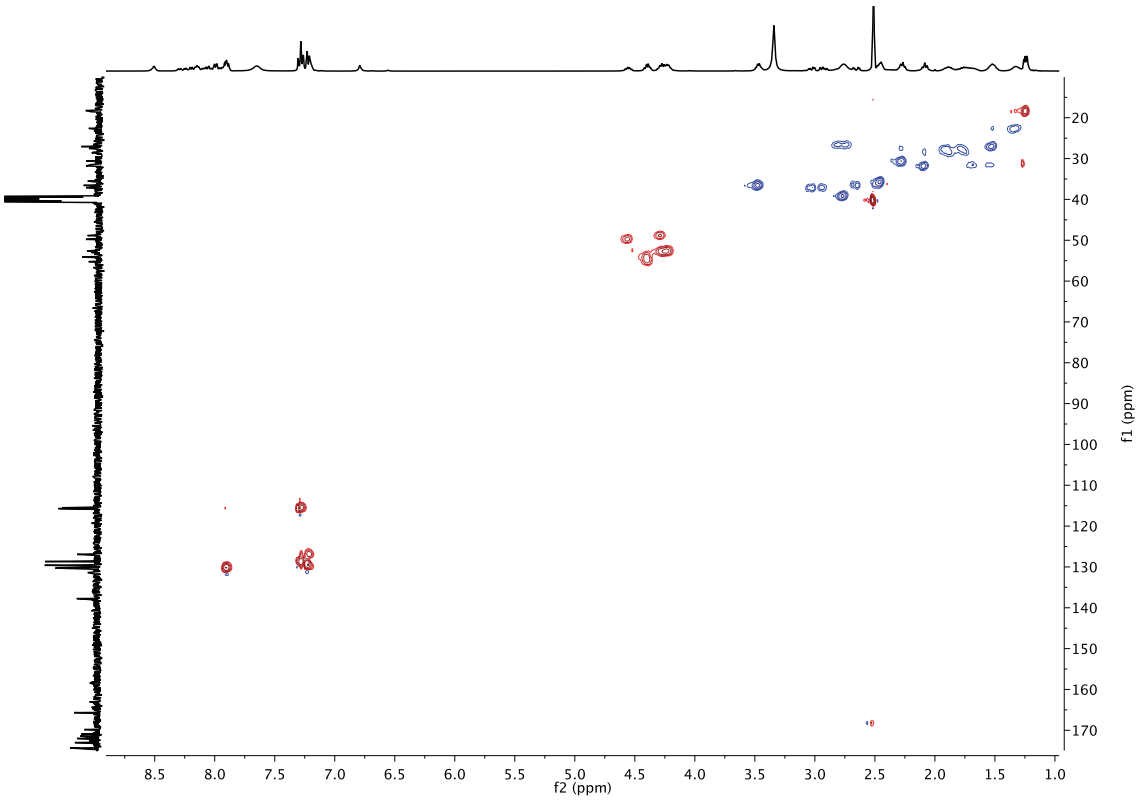
^{1}H NMR (400 MHz, d_6-DMSO)



COSY



HSQC



HMBC