

Synthesis of Diverse *N*-Acryloyl Azetidines and Evaluation of their Enhanced Thiol Reactivities

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Supporting Information

Protocol for Analysis of Glutathione Reaction with Michael Acceptors

The reactions of Michael acceptors with glutathione were carried out in a 1-ml solution of 70 mM potassium phosphate buffer (pH 7.4), 10 mM fresh GSH, 1 mM EDTA, 10 μ M indoprofen (internal standard), and 0.1–1 mM Michael acceptor in 30% acetonitrile. Compound stability unrelated to thiol addition was assessed in a separate vial containing the above components except GSH. The reaction mixtures were incubated at 37 °C in an autosampler. Ibrutinib was tested in parallel as a control to monitor the reproducibility of the assay. The role of EDTA in the reaction mixture was to minimize oxidation of GSH mediated by trace metals and did not otherwise affect the reactivity of the substrates.¹ Samples of the reaction mixtures (10 μ l) were injected once every 30 minutes, or every 3.5 minutes for fast reacting compounds, onto an LC-triple quadrupole mass spectrometer (4000 QTRAP[®], AB Sciex, Framingham, MA) coupled to a pair of Shimadzu 20AD pumps and a Shimadzu SIL-20A autosampler (Shimadzu, Columbia, MD). Reaction mixture components were separated by HPLC using a Waters Xbridge 2.1 \times 30 mm 3.5 μ M C8 column (Waters, Milford, MA) with a two-solvent system (A: water with 0.1% formic acid; B: 0.1% formic acid in acetonitrile) and a flow rate of 1.2 ml/min. The gradient program was as follows: 0-0.7 min, 0% B; 0.7-1.3 min, 0-95% B; 1.3-1.8 min, 95% B; 1.8-2.3 min, 95-0% B; 2.3-3.0 min, 0% B. The MS acquisition methods used positive electrospray ionization (ESI) in multiple reaction-monitoring (MRM) mode. MRM transitions, collision energy, and declustering potential for each compound were optimized using direct infusion of 10 mM compound solutions. The GSH adducts of the substrates were also monitored based on the theoretical masses of the products using pseudo MRM transitions. Nebulizer gas (GS1), auxiliary gas (GS2), curtain gas (CUR), and collision gas (CAD) were 70, 70, 30, 5 (arbitrary units), respectively. The curtain and collision gases were nitrogen. The ion source temperature was maintained at 600 °C. Ionspray voltage, entrance potential (EP) and cell exit potential (CXP) were 4500 V, 10 V and 15 V, respectively. The calculation of the $t_{1/2}$ was performed with Microsoft Excel using the approach described in the literature.²

(1) Stevens, R.; Stevens, L.; Price, N.C. *Biochemical Education*, **1983**, *11*, 70.

(2) Flanagan et al. *J. Med. Chem.* **2014**, *57*, 10072-10079.

Protocol for Use of $^1\text{H-NMR}$ to Monitor Reaction of **24** and GSH

A 200 mM stock solution of **24** in DMSO- d_6 was diluted to 2 mM, using 20 mM sodium phosphate buffer (pH 7.4, 10% D_2O). A 20 mM GSH stock solution was directly prepared using 20 mM phosphate buffer (pH 7.4, 10% D_2O). An aliquot of the 2 mM solution of **24** (0.55 mL) was transferred to a 5 mm outside diameter (OD) NMR tube and inserted into a Bruker 600 MHz NMR spectrometer (Bruker BioSpin Corporation, Billerica, MA) equipped with a 5 mm QCI quadruple resonance CryoProbe pre-warmed to 37 °C. The sample was locked on D_2O , tuned, and matched prior to shimming. A fresh reaction sample was then prepared in a new NMR tube. An aliquot of the 2.0 mM solution of **24** (0.275 mL) and 20 mM GSH solution (0.275 mL) were combined in a 5 mm OD NMR tube. The NMR tube was immediately transferred to the NMR spectrometer and data acquisition was begun at 37 °C. Spectra were recorded using a standard pulse sequence with presaturation (zgpr) with a sweep width of 9578.5 Hz and a total recycle time of 6.7 s. Each acquisition consisted of 4 dummy scans followed by 32 scans for a total acquisition time of 4.0 min. Data acquisition was repeated at predefined time points based on estimated reaction rates (**Fig S1**). The resulting time-averaged free induction decays were transformed using an exponential line broadening of 2 Hz to enhance signal-to-noise. Integrals of the acrylic protons were plotted against time and subsequently fitted to a pseudo-first-order rate equation using SigmaPlot v12.5 (Systat Software Inc., San Jose, California) to extract the rate constants.

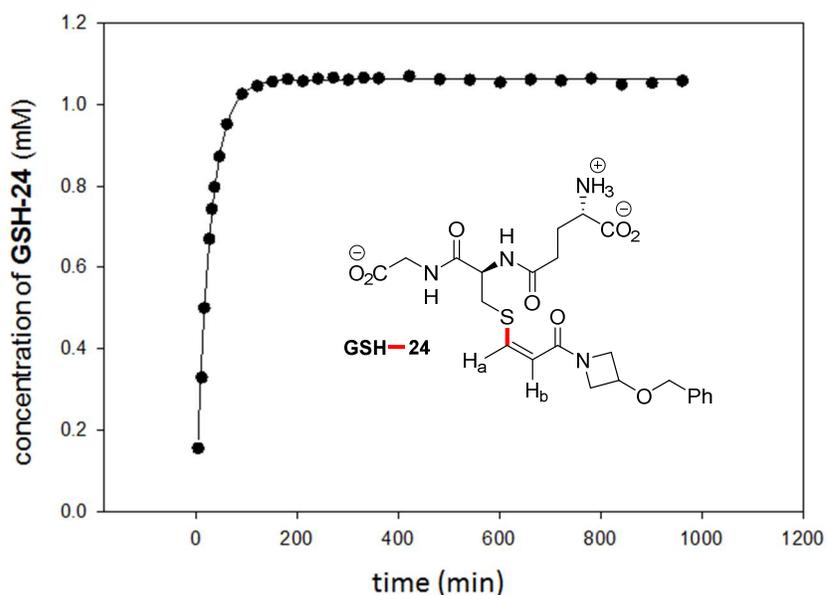


Figure S1. Concentration of GSH-24 over time. The integral of the resonance at 7.46 ppm corresponding to the aromatic protons in **24** was used as a reference and set to 1 mM, and the concentration of the reaction product **GSH-24** was calculated from the average of the integrals for H_a and H_b .

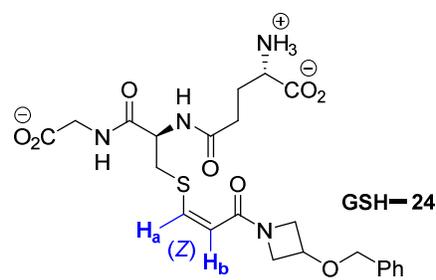
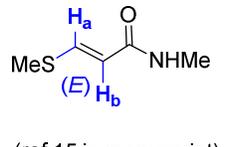
	H_a ppm	H_b ppm	J_{ab} (Hz)	solvent
 <p>GSH-24</p>	7.1	5.9	10.2	20 mM phosphate buffer pH 7.4 (10% D ₂ O)
 <p>(ref 15 in manuscript)</p>	6.7	6.0	9.9	CDCl ₃
 <p>(ref 15 in manuscript)</p>	7.6	5.8	14.5	CDCl ₃

Figure S2. Assignment of (Z) geometry for GSH-24. The J value of 10.2 Hz matches closely with the J value of 9.9 Hz in the (Z)- β -mercaptoacrylamide reported in reference 15 of the manuscript (Krishnan, S.; Miller, R. M.; Tian, B.; Mullins, R. D.; Jacobsen, M. P.; Taunton, J. *J. Am. Chem. Soc.* **2014**, *136*, 12624-12630.).

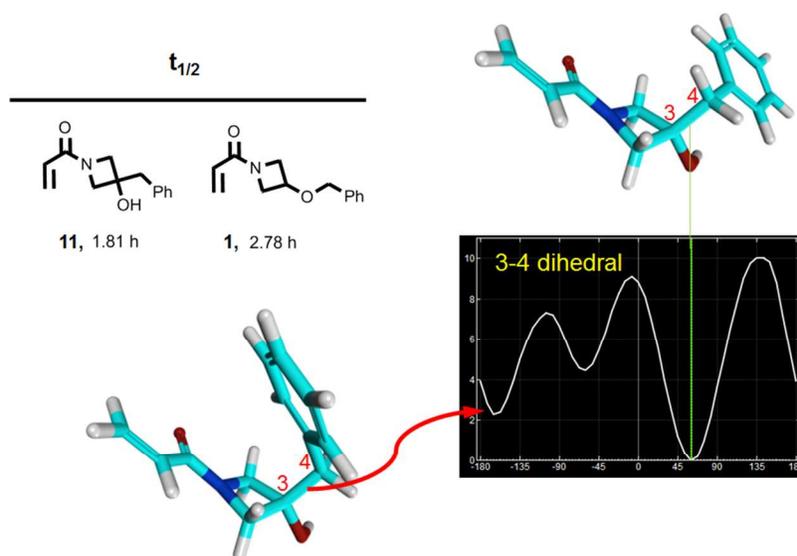


Figure S3. Conformational analysis of **11** suggests a low energy pose where the benzyl group stacks over the acrylamide, potentially exaggerating the degree of amide pyramidalization relative to analog **1**.

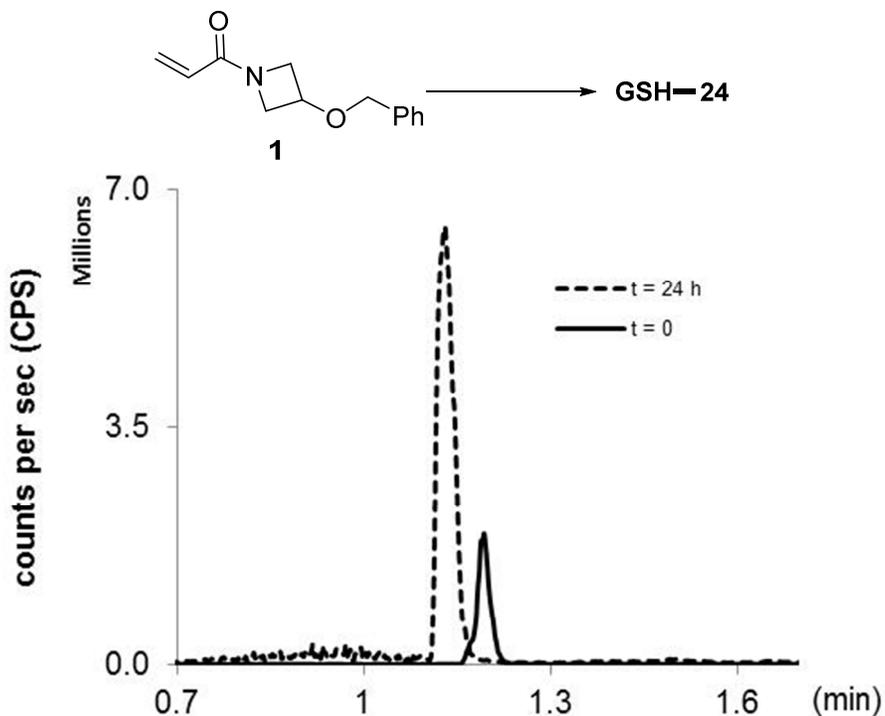
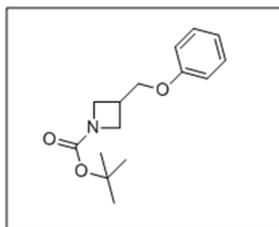


Figure S4. Example of LCMS trace of the reaction of compound **1** with **GSH** shows clean conversion to GSH adduct after 24 h.

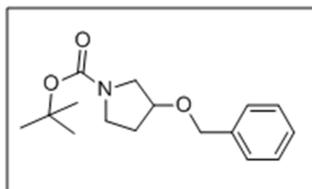
Synthesis of Michael Acceptors and Precursors

General methods. ^1H and ^{13}C NMR spectra were obtained on a Varian Unity INOVA 400 at 400 and 125 MHz, respectively, unless noted otherwise. ^1H NMR spectra are referenced to CDCl_3 (7.26 ppm), CD_3OD (internal TMS 0.00 ppm), and DMSO-d_6 (2.50 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), coupling constants (Hz), and integration. LCMS data were obtained using an Agilent 1100 series HPLC on a Gemini-NX C18 110A, 50 mm \times 2.00 mm column under low pH (0.1% formic acid/water:0.1% formic acid/ MeCN) or high pH (pH 9 NH_4HCO_3 aq:MeCN) conditions with detection at 300 or 214 nm. HRMS data were obtained using an Agilent 1100 series LC and TOF mass spectrometer, with a GeminiNX C18 110A, 50 mm \times 2.00 mm column. Optical rotations were obtained on a PerkinElmer polarimeter 341. Reactions were monitored by thin-layer chromatography using silica gel 60 F254 plates from EMD and visualizing with ceric ammonium molybdate (CAM) or K_2MnO_4 stain. Unless otherwise noted, normal phase purifications were performed using RediSep prepacked columns from Teledyne Isco. On the basis of LCMS, all final compounds were >95% pure unless otherwise noted. All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen. All solvents and reagents were purchased from Aldrich, Alfa Aesar, PharmaBlock, Matrix Scientific, Synthonix, Oakwood, or Acros and used without further purification.



tert-butyl 3-(phenoxy)methylazetidine-1-carboxylate (S1)

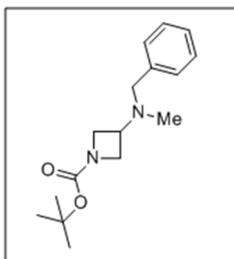
To an oven dried 100 mL round bottom flask containing a solution of phenol (0.830 g, 8.819 mmol, 1.1 equiv) in acetone (40 mL) was added potassium carbonate (3.304 g, 23.91 mmol, 3 equiv) as a solid. *Tert*-butyl 3-(bromomethyl)azetidine-1-carboxylate (2.028 g, 8.109 mmol, 1 equiv) was added to the mixture. The reaction mixture was heated to reflux and stirred overnight. After cooling to room temperature, the mixture was quenched with satd aq NH₄Cl (2 mL) and concentrated under a steady stream of nitrogen. The residue was partitioned between CH₂Cl₂ and satd aq NH₄Cl and the aqueous phase was extracted with additional CH₂Cl₂. The combined organics were washed with brine, dried over MgSO₄, and concentrated to afford a yellow oil. The oil was purified via reverse phase column chromatography to afford a white solid (412.7 mg, 19% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.27 (m, 2H), 6.97 (tt, 1H, *J* = 7.28, 1.1), 6.90 (dd, 2H, *J* = 8.8, 1.0), 4.11-4.05 (m, 4H), 3.79 (dd, 2H, *J* = 8.6, 5.2), 3.01-2.92 (m, 1H), 1.46 (s, 9H). HRMS (ESI) *m/z*: [M⁺] calcd for C₁₅H₂₁NO₃ 263.1521, found 263.1518. LCMS R_t = 1.301 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



tert-butyl 3-(benzyloxy)pyrrolidine-1-carboxylate (S2)

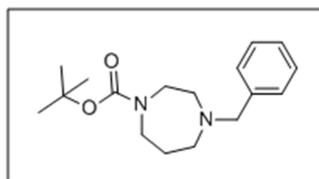
To a dry 100 mL round bottom flask containing *tert*-butyl 3-hydroxypyrrolidine-1-carboxylate (495.4 mg, 2.646 mmol, 1 equiv) was added THF (12 mL). Sodium hydride (143.1 mg, 3.578 mmol, 60% in oil, 1.2 equiv) was added slowly as a solid at 0 °C. The reaction mixture was allowed to stir at 0 °C for 90 min. Benzyl bromide (0.34 mL, 2.90 mmol, 1.1 equiv) was then added dropwise and the reaction mixture was heated to reflux overnight. After cooling to ambient temperature, the mixture was quenched with satd aq NH₄Cl (12 mL). The aqueous layer was extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO₄, and concentrated *in vacuo* to afford a yellow oil (787.4 mg). The crude material was purified via silica gel column chromatography (0-20% EtOAc/Hexanes) to afford the pure product as a colorless oil (320.3 mg, 44% yield). TLC R_f = 0.41 (20% EtOAc/ hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.25 (m, 5H), 4.52 (s, 2H), 4.16-4.09 (m, 1H), 3.54-3.38 (br m, 4H), 2.09-2.00 (m, 1H), 1.99-1.88 (m, 1H), 1.45 (s, 9H). ¹³C NMR δ 156.64, 138.08, 128.47, 127.73, 127.64, 79.23, 77.89, 70.90, 51.14, 43.89, 28.54, 31.05. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₆H₂₃NO₃ 277.1678, found 277.1680. LCMS R_t = 1.289 min (2x50 Xbridge C18 3.5μm

column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



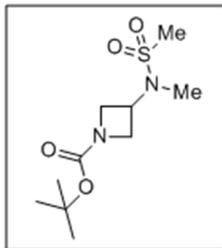
tert-butyl 3-(benzyl(methyl)amino)azetidine-1-carboxylate (S3)

Benzyl bromide (0.35 mL, 2.9 mmol, 1.2 equiv.) was added dropwise to a stirring solution of *tert*-butyl 3-(methylamino)azetidine-1-carboxylate (501.7 mg, 2.613 mmol, 1.0 equiv) and potassium carbonate (725.8 mg, 5.199 mmol, 2.0 equiv) in DMF (4 mL). The solution was allowed to stir at room temperature overnight. The mixture was then concentrated under reduced pressure. The resulting residue was partitioned between EtOAc and brine and the aqueous phase was extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO₄ and concentrated to afford a yellow oil (938.9 mg). The crude oil was purified by silica gel chromatography (0-40% EtOAc/hexanes) to afford a colorless oil (576.9 mg, 80% yield). ¹H-NMR (400 MHz, CDCl₃) δ 7.36-7.26 (m, 5H), 3.93 (t, 2H, *J* = 7.8), 3.89-3.79 (m, 2H), 3.48-3.36 (m, 1H), 3.32-3.21 (m, 1H), 2.09 (br s, 3H), 1.43 (s, 9H). HRMS (ESI) *m/z*: [M⁺] calcd for C₁₆H₂₄N₂O₂ 276.1838, found 276.1834. LCMS R_t = 1.275 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



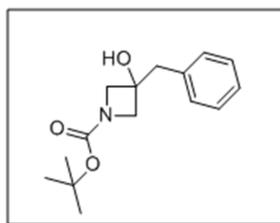
tert-butyl 4-benzyl-1,4-diazepane-1-carboxylate (S4)

To a solution of *tert*-butyl 1,4-diazepane-1-carboxylate (0.250 mL, 1.20 mmol, 1.0 equiv) and potassium carbonate (364.4 mg, 2.610 mmol, 2.0 equiv) in DMF (2 mL), benzyl bromide (0.160 mL, 1.30 mmol, 1.3 equiv.) was added by syringe. The solution was allowed to stir at room temperature overnight. The mixture was then concentrated under reduced pressure. The resulting residue was partitioned between EtOAc and brine and the aqueous phase was extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO₄ and concentrated to afford a yellow oil (300.4 mg). The crude oil was purified by silica gel chromatography (0-20% EtOAc/hexanes) to afford a colorless oil (231.3 mg, 64% yield). TLC R_f = 0.15 (20% EtOAc/ hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.22 (m, 5H), 3.65 (s, 2H), 3.58-3.35 (br m, 4H), 2.64 (br s, 4H), 1.85 (br s, 2H), 1.46 (s, 9H). ¹³C NMR δ 155.66, 128.94, 128.32, 127.14, 79.31, 62.25, 56.20, 55.80, 45.95, 45.17, 28.52. ESI-MS calc. for C₁₇H₂₆N₂O₂ [M-tBu+H]⁺ 291.20, found 291.20. LCMS R_t = 1.285 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



tert-butyl 3-(N-methylmethanesulfonamido)azetidine-1-carboxylate (S5)

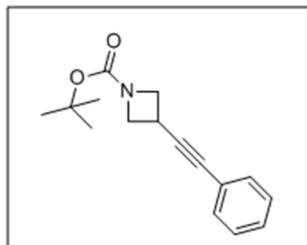
At $-78\text{ }^{\circ}\text{C}$, to a 50 mL round bottom flask containing *tert*-butyl 3-(methylamino)azetidine-1-carboxylate (221.0 mg, 0.992 mmol, 1 equiv) in dichloromethane (10 mL) was added triethylamine (0.140 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while methanesulfonyl chloride (90 μL , 1.16 mmol, 1.1 equiv) was added slowly via syringe at $-78\text{ }^{\circ}\text{C}$. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 2 h. Satd aq NaHCO_3 (20 mL) was added to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a white solid (278.4 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white solid (247.5 mg, 94% yield). ^1H NMR (400 MHz, DMSO) δ 4.53-4.45 (m, 1H), 4.04 (t, 2H, $J = 8.4$), 3.97 (t, 2H, $J = 8.3$), 2.87 (s, 3H), 2.83 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (400 MHz, DMSO) δ 151.27, 79.37, 46.83, 35.84, 30.18, 28.48. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{10}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ 264.1144, found 264.1137. LCMS $R_t = 0.861$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



tert-butyl 3-benzyl-3-hydroxyazetidine-1-carboxylate (S6)

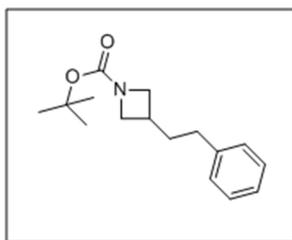
At $0\text{ }^{\circ}\text{C}$, to a 100 mL flask containing *N*-Boc-3-azetidinone (1.503 g, 8.342 mmol, 1 equiv) in THF (17 mL) was added benzylmagnesium chloride (13 mL, 13 mmol, 1 M in Et_2O , 1.5 equiv) slowly via syringe. The mixture was allowed to stir overnight as the cooling bath expired. The reaction was quenched with satd aq NH_4Cl (20 mL) at $0\text{ }^{\circ}\text{C}$. The aqueous phase was extracted with EtOAc (3x). The combined organics were washed with brine, dried over MgSO_4 and concentrated under reduced pressure to afford a viscous yellow oil (2.32 g). The crude material was purified via silica gel column chromatography (0-50% EtOAc/hexanes) to afford a colorless oil (612.9 mg, 28% yield). TLC $R_f = 0.52$ (50% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.21 (m, 5H), 3.99 (d, 2H, $J = 9.2$), 3.79 (d, 2H, $J = 9.2$), 3.05 (s, 2H), 1.44 (s, 9H). ^{13}C -NMR (400 MHz, DMSO) δ 156.23, 137.66, 130.52, 128.32, 126.67, 78.92, 69.55, 55.40,

44.42, 28.51. ESI-MS calc. for $C_{15}H_{21}NO_3$ $[M-tBu+H]^+$ 208.09, found 208.00. LCMS R_t = 1.109 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B). This compound has been previously reported.³



***tert*-butyl 3-(phenylethynyl)azetidine-1-carboxylate (S7)**

To a solution of *tert*-butyl 3-ethynylazetidine-1-carboxylate (1.000 g, 5.518 mmol, 1 equiv), cuprous iodide (20.9 mg, 0.110 mmol, 0.02 equiv), and tetrakis(triphenylphosphane)palladium(0) (509 mg, 0.441 mmol, 0.08 equiv) in THF (28 mL) was added bromobenzene (0.866 mL, 8.277 mmol, 1.5 equiv) and triethylamine (7.68 mL, 55.18 mmol, 10 equiv) at room temperature. The resulting black solution was warmed to 60 °C and stirred overnight. The reaction was filtered over celite and concentrated. The crude product was flashed over SiO_2 using 0 to 40% acetone/hexanes. The desired product eluted at 15% acetone and was isolated as a colorless oil (846 mg, 60% yield). TLC R_f = 0.26 (10% EtOAc/hexanes). 1H -NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 4.15 (dd, 2H, J = 9.0, 8.5), 3.97 (dd, 2H, J = 7.8, 6.5), 3.52-3.40 (m, 1H), 1.42 (s, 9H). ^{13}C -NMR (400 MHz, $CDCl_3$) δ 155.92, 131.51, 128.24, 122.94, 89.26, 83.48, 79.59, 31.54, 28.31, 26.93, 22.61, 19.80. HRMS (ESI) m/z : $[M]^+$ calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1415. LCMS R_t = 1.385 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).

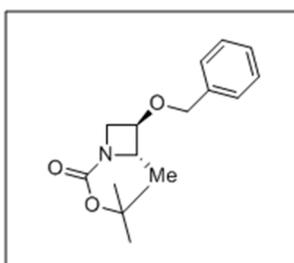


***tert*-butyl 3-phenethylazetidine-1-carboxylate (S8)**

A round bottom flask containing palladium on carbon (177.8 mg, 10% palladium w/w, 0.167 mmol, 0.10 equiv) and *tert*-butyl 3-(phenylethynyl)azetidine-1-carboxylate (430 mg, 1.671 mmol, 1 equiv) in ethyl acetate (8 mL) was equipped with a balloon of H_2 . The H_2 gas was allowed to bubble below the surface of the solution while venting the flask to the atmosphere

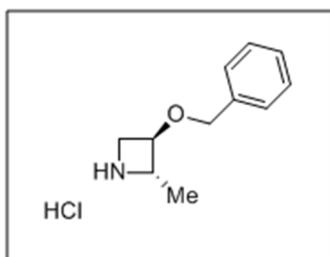
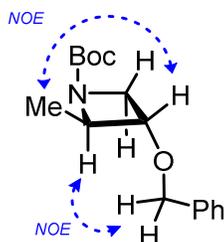
(3) Salituro, F. G.; Saunders, J. O.; Yan, S. US Patent 9221792 B2, 2015.

through a narrow bore needle. After 5 min the H₂ inlet was moved to above the surface of the solution and the mixture was allowed to stir overnight. The reaction suspension was sparged with N₂ gas for 10 minutes and then it was filtered over celite and concentrated. The crude product was purified by flash chromatography (0-40% acetone/hexanes) to afford a colorless oil (415 mg, 95% yield). TLC R_f = 0.23 (10% EtOAc/hexanes) ¹H NMR (400 MHz, CDCl₃) δ 7.29-7.10 (m, 5H), 3.96 (t, 2H, *J* = 8.3), 3.52 (dd, 2H, *J* = 8.3, 5.6), 2.54 (dd, 2H, *J* = 8.8, 7.4), 2.51-2.41 (m, 1H), 1.88 (q, 2H, *J* = 7.7), 1.42 (s, 9H). ¹³C NMR (400 MHz, CDCl₃) 156.35, 141.34, 128.40, 128.92, 125.96, 79.13, 54.33, 36.12, 33.32, 28.39, 28.36. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₆H₂₃NO₂ 261.1729, found 261.1736. LCMS R_t = 1.375 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



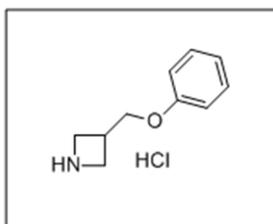
***tert*-butyl 3-(benzyloxy)-2-methylazetidine-1-carboxylate (S9)**

To an oven-dried 250 mL round bottom flask containing racemic *tert*-butyl 3-hydroxy-2-methylazetidine-1-carboxylate (2.04 g, 10.9 mmol, 1 equiv) was added THF (50 mL). Sodium hydride (0.523 g, 13.1 mmol, 60% in oil, 1.2 equiv) was added as a solid at 0 °C. The reaction mixture was allowed to stir at 0 °C for 90 min. Benzyl bromide (1.42 mL, 12.0 mmol, 1.1 equiv) was then added to the mixture dropwise and the reaction was heated to reflux overnight. After cooling to ambient temperature, the mixture was quenched with satd aq NH₄Cl (75 mL). The aqueous layer was extracted with EtOAc (50 mL x 3). The combined organics were washed with brine, dried (MgSO₄), and concentrated to afford a colorless oil. The crude material was purified via silica gel column chromatography (0-20% EtOAc/Hexanes) to afford the pure product as a colorless oil (1.104 g, 37% yield). The racemate was separated into individual enantiomers via chiral chromatography (Chiralpak IC, 4.6 x 150 mm, 10% IPA/CO₂). The resulting (+)- and (-)-enantiomers were carried forward to enantiomerically (+)- and (-)-**S10** and (+)-**15**, and (-)-**15**. Relative stereochemistry was assigned via NOESY measurements. Optical rotations are reported for the final substrates (+)-**15** and (-)-**15**. ¹H NMR (400 MHz, CDCl₃) δ 7.38-7.27 (m, 5H), 4.45 (s, 2H), 4.19-4.09 (m, 1H), 3.95 (ddd, 1H, *J* = 9.3, 6.5, 1.0), 3.84-3.79 (m, 1H), 3.70 (dd, 1H, *J* = 8.9, 4.7), 1.43 (s, 9H), 1.33 (d, 3H, *J* = 7.17). ¹³C NMR (400 MHz, CDCl₃) δ 156.87, 137.30, 128.57, 128.07, 127.95, 79.46, 74.55, 71.97, 65.42, 53.62, 28.43 19.35. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₆H₂₃NO₃ 277.1678, found 277.1671. LCMS R_t = 1.346 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



3-(benzyloxy)-2-methylazetidin-1-ium chloride (S10, ent 1 and ent 2)

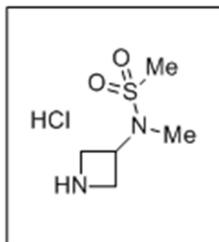
Both enantiomers of **S10** (**ent 1**, **ent 2**) were prepared according to literature procedures³ with small modifications. At ambient temperature, to a 100 mL round bottom flask containing a solution of *tert*-butyl 3-(benzyloxy)-2-methylazetidine-1-carboxylate (380.9 mg, 1.373 mmol, 1 equiv) in methanol (1 mL) was added hydrochloric acid (1 mL, 4 mmol, 4M in 1,4-dioxane, 3 equiv) via syringe. The reaction mixture was allowed to stir at ambient temperature over 3 h. The reaction mixture was concentrated to afford a clear oil (336.9 mg, >99% yield). The crude material was carried on to the next step without any additional purification. ESI-MS [M-Cl]⁺ 178.00. LCMS R_t = 0.725 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



3-(phenoxymethyl)azetidine hydrochloride (S11)

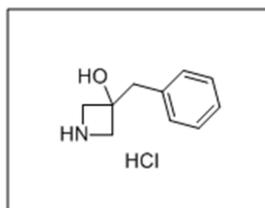
Compound **S11** was prepared according to literature procedures³ with small modifications. At ambient temperature, to a 50 mL round bottom flask containing a solution of *tert*-butyl 3-(phenoxymethyl)azetidine-1-carboxylate (360.8 mg, 1.370 mmol, 1 equiv) in methanol (1 mL) was added HCl (1.1 mL, 4.4 mmol, 4 M in 1,4-dioxane, 3.2 equiv) slowly via syringe. The reaction mixture was allowed to stir at ambient temperature over 3 h. The reaction mixture was

concentrated to afford an orange solid (264.9 mg, 97% yield). The solid was carried over to the next step without any additional purification. ESI-MS $[M-Cl]^+$ 164.00. LCMS $R_t = 0.650$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



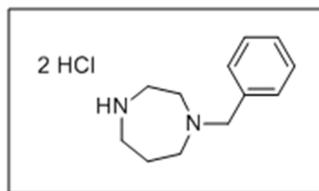
3-(*N*-methylmethanesulfonyl)azetidin-1-ium chloride (S12)

Compound **S12** was prepared according to literature procedures³ with some small modifications. At ambient temperature, to a 50 mL round bottom flask containing a solution of *tert*-butyl 3-(*N*-methylmethanesulfonyl)azetidine-1-carboxylate (202.0 mg, 0.764 mmol, 1 equiv) in methanol (1.5 mL) was added hydrochloric acid (1.5 mL, 6.0 mmol, 4M in 1,4-dioxane, 7.8 equiv) slowly via syringe. The reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was concentrated to afford a yellow solid (146.4 mg, 81% yield). The crude HCl salt was carried on to the next step without additional purification. ESI-MS calc. $[M-Cl]^+$ 165.00. LCMS $R_t = 0.891$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



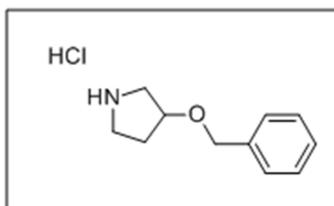
3-benzylazetidin-1-ium-3-ol chloride (S13)

The compound **S13** was prepared according to literature procedures³ with some small modifications. At ambient temperature, to a 50 mL round bottom flask containing a solution of *tert*-butyl 3-benzyl-3-hydroxyazetidine-1-carboxylate (421.8 mg, 1.602 mmol, 1 equiv) in methanol (1.2 mL) was added hydrochloric acid (1.2 mL, 4.8 mmol, 4M in 1,4-dioxane, 3 equiv) via syringe. The reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was concentrated *in vacuo* to afford a white solid (236.2 mg, 74% yield). The solid was carried over to the next step without additional purification. ESI-MS $[M-Cl]^+$ 164.11, found 164.00. LCMS $R_t = 0.512$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



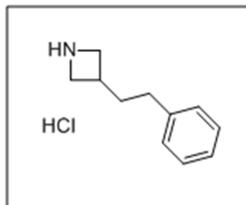
1-benzyl-1,4-diazepane-1,4-dium dichloride (S14)

Compound **S14** was prepared according to literature procedures³ with some small modifications. At ambient temperature, to a 20 mL round vial containing a solution of *tert*-butyl 4-benzyl-1,4-diazepane-1-carboxylate (214.9 mg, 0.740 mmol, 1 equiv) in methanol (0.5 mL) was added hydrochloric acid (0.5 mL, 2 mmol, 4M in 1,4-dioxane, 3 equiv) via syringe. The reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was concentrated to afford a green solid (223.6 mg, >99% yield). The solid was carried over to the next step without any additional purification. ESI-MS $[M-2Cl-H]^+$ 191.00. LCMS $R_t = 0.742$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



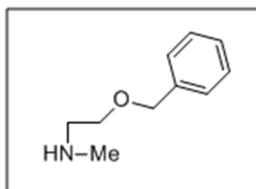
3-(benzyloxy)pyrrolidin-1-ium chloride (S15)

Compound **S15** was prepared according to literature procedures³ with some small modifications. At ambient temperature, to a 20 mL round vial containing a solution of *tert*-butyl 3-benzyloxypyrrolidine-1-carboxylate (297.9 mg, 1.074 mmol, 1 equiv) in methanol (0.9 mL) was added hydrochloric acid (0.9 mL, 4 mmol, 4M in 1,4-dioxane, 4 equiv) via syringe. The reaction mixture was allowed to stir at ambient temperature for 3 hours. The reaction mixture was concentrated to afford a yellow oil (247.1 mg, >99% yield). The solid was carried on to the next step without any additional purification. ESI-MS $[M-Cl]^+$ 178.00. LCMS $R_t = 0.704$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



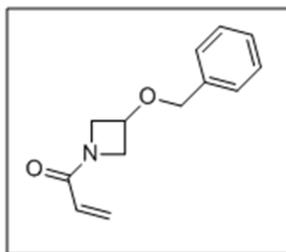
3-phenethylazetidinium chloride (S16)

The compound **S16** was prepared according to literature procedures³ with some small modifications. At ambient temperature, to a 50 mL round vial containing a solution of *tert*-butyl 3-phenethylazetidinium-1-carboxylate (300 mg, 1.148 mmol, 1 equiv) in methanol (2 mL) was added hydrochloric acid (0.9 mL, 3.4 mmol, 4M in 1,4-dioxane, 3 equiv) via syringe. The reaction mixture was allowed to stir at ambient temperature for 12 h. The reaction mixture was concentrated to afford a brown oil (253 mg, >99% yield). The solid was carried on to the next step without any additional purification. TLC $R_f = 0.1$ (5% DCM/MeOH + 1% NEt_3), ESI-MS $[\text{M}-\text{Cl}]^+ 162.0$. LCMS $R_t = 0.657$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



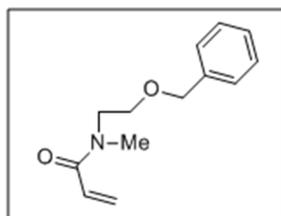
2-(benzyloxy)-N-methylethan-1-amine (S17)

To a stirring solution of methylamine (17 mL, 2M in THF), 1-benzyloxy-2-iodoethane (836.6 mg, 3.03 mmol, 1.0 equiv) was added dropwise and the resulting mixture was allowed to stir at ambient temperature for 16 h. Upon completion, the reaction mixture was concentrated to afford a yellow oil. The crude product was desalted by passage through a strong cation exchange (SCX) column to afford a yellow oil (436.6 mg, 77% yield). The oil was a mixture of the desired product and minor impurity resulting from bis-alkylation of methylamine according to LCMS. The material was carried forward without any additional purification. TLC $R_f = 0.07$ (50% EtOAc/ hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.23 (m, 5H), 3.65-3.55 (m, 2H), 2.85-2.77 (m, 2H), 2.46 (s, 3H), 2.11 (br s, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 138.18, 128.45, 127.81, 127.72, 73.28, 57.21, 51.19, 37.85. ESI-MS $[\text{M}+\text{H}]^+ 166.0$. LCMS $R_t = 0.702$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)azetid-1-yl)prop-2-en-1-one (1)

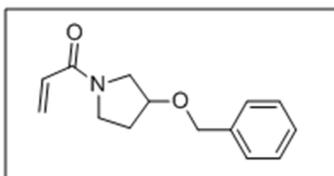
At $-78\text{ }^{\circ}\text{C}$, to a 15 mL round bottom flask containing 3-(benzyloxy)azetidine hydrochloride (105.1 mg, 0.526 mmol, 1 equiv) in dichloromethane (5.2 mL) was added triethylamine (0.148 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (49 μL , 0.579 mmol, 1.1 equiv) was added dropwise via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (8 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH_2Cl_2 (20 mL) 3x. The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a colorless oil (75.0 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford the desired product as a white oil (59.6 mg, 52% yield). TLC: $R_f = 0.52$ (60% EtOAc /Hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (br m, 5H), 6.32 (dd, 1H $J = 16.9, 1.9$), 6.16 (dd, 1H, $J = 16.9, 10.3$), 5.66 (dd, 1H, $J = 10.4, 1.9$), 4.49 (d, 2H, $J = 5.5$), 4.41 (m, 1H), 4.34-4.28 (m, 1H), 4.23-4.17 (m, 1H), 4.10-4.05 (m, 1H), 3.99-3.94 (m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 138.61, 136.86, 128.60, 128.22, 127.98, 127.42, 125.86, 71.48, 67.17, 48.60. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{15}\text{NO}_2$ 217.1103, found 217.1108. LCMS $R_t = 0.892$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



N-(2-(benzyloxy)ethyl)-N-methylacrylamide (2)

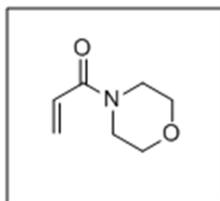
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 2-benzyloxy-N-methylethan-1-amine (159.8 mg, 0.851 mmol, 1 equiv) in dichloromethane (8 mL) was added triethylamine (0.230 mL, 1.600 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (75 μL , 0.890 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a colorless oil (191.9 mg). The crude material was purified via silica gel column chromatography (0-75% EtOAc/ hexanes) to afford a colorless oil (124.6 mg, 67% yield). TLC $R_f = 0.43$ (60% EtOAc/ hexanes). ^1H NMR (400 MHz, DMSO) (two amide rotamers observed) δ 7.39-7.23 (m, 5H), 6.77 (td, 1H, $J = 15.6, 10.7$), 6.09 (ddd, 1H, $J = 17.1, 6.2, 2.2$), 5.64 (ddd,

^1H , $J = 21.9, 10.7, 2.7$), 4.47 (s, 2H), 3.58 (dd, 2H, $J = 19.1, 5.0$), 3.55 (s, 2H), 3.09 (s, 1.5H), 2.91 (s, 1.5H). ^{13}C NMR (400 MHz, CDCl_3) (two amide rotamers observed) δ 167.01, 166.42, 138.24, 137.76, 128.48, 128.42, 128.04, 127.82, 127.64, 127.56, 73.39, 73.11, 68.82, 67.94, 49.85, 49.29, 37.26, 34.52. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ 219.1259, found 219.1252. LCMS $R_t = 0.889$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)pyrrolidin-1-yl)prop-2-en-1-one (3)

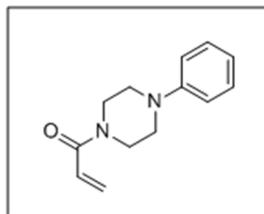
At -78 $^\circ\text{C}$, to a 25 mL round bottom flask containing 3-(benzyloxy)pyrrolidin-1-ium chloride (183.2 mg, 0.857 mmol, 1 equiv) in dichloromethane (8.5 mL) was added triethylamine (0.240 mL, 1.700 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (80 μL , 0.930 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at -78 $^\circ\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were washed with brine, dried (MgSO_4) and concentrated under reduced pressure to afford a yellow oil (157.1 mg). The crude material was purified via silica gel column chromatography (0-75% EtOAc/hexanes) to afford a colorless oil (109.6 mg, 55% yield). TLC $R_f = 0.19$ (60% EtOAc/ hexanes) ^1H NMR (400 MHz, DMSO) δ 7.35-7.21 (m, 5H), 6.56 (dd, 0.5H, $J = 16.5, 10.3$, rotamer A), 6.52 (dd, 0.5H, $J = 17.0, 10.1$, rotamer B), 6.10 (dt, 1H, $J = 16.8, 2.4$), 5.64 (dd, 0.5H, $J = 4.0, 2.3$, rotamer A), 5.61 (dd, 0.5H, $J = 4.1, 2.4$, rotamer B), 4.47 (d, 2H, $J = 5.1$), 4.21-4.16 (m, 0.5 H, rotamer A), 4.14-4.09 (m, 0.5H, rotamer B), 3.67-3.27 (br m, 4H), 2.12-1.82 (br m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 164.72, 164.59, 137.81, 128.52, 127.83, 127.64, 71.07, 70.88, 52.00, 50.95, 44.67, 43.87, 31.91, 29.75. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found 231.1265. LCMS $R_t = 0.889$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-morpholinoprop-2-en-1-one (4)

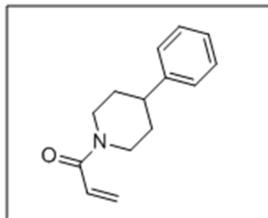
At 0 $^\circ\text{C}$, to a 50 mL round bottom flask containing morpholine (0.100 mL, 1.13 mmol, 1 equiv) in dichloromethane (11.4 mL) was added triethylamine (0.325 mL, 2.31 mmol, 2 equiv) via

syringe. The mixture was vigorously stirred while acryloyl chloride (100 μ L, 1.18 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to warm to room temperature and stir overnight. Satd aq NaHCO_3 (22 mL) was added slowly to the stirring mixture. The aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a yellow solid (149.6 mg). The crude material was purified via silica gel chromatography (0-80% EtOAc/Hexanes) to afford a colorless oil (94.1 mg, 59% yield). TLC $R_f = 0.43$ (60% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 6.56-6.47 (dd, 1H, $J = 16.5, 10.5$), 6.35-6.27 (dd, 1H, $J = 16.8, 2.0$), 5.74-5.69 (dd, 1H, $J = 10.8, 1.9$), 3.70-3.63 (br s, 4H), 3.58-3.51 (br s, 4H). ^{13}C NMR (400 MHz, CDCl_3) δ 165.48, 128.37, 127.02, 77.0, 66.80. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_7\text{H}_{11}\text{NO}_2$ 141.0790, found 141.0793. LCMS $R_t = 0.358$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



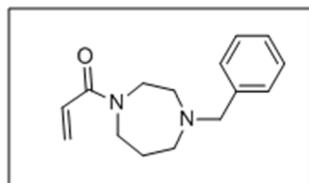
1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (5)

At 0 $^\circ\text{C}$, to a 25 mL round bottom flask containing 1-phenylpiperazine (0.150 mL, 0.970 mmol, 1 equiv) in dichloromethane (9.8 mL) was added triethylamine (0.270 mL, 1.90 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (90 μ L, 1.06 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at 0 $^\circ\text{C}$ for 2 h. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH_2Cl_2 (20 mL x 3). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a yellow residue (266.4 mg). The crude material was purified via silica gel chromatography (0-50% EtOAc/Hexanes) to afford a white oil (174.5 mg, 83% yield). TLC $R_f = 0.34$ (60% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.30 (dd, 2H, $J = 8.7, 7.4$), 7.05-6.85 (br m, 3H), 6.60 (dd, 1H, $J = 16.4, 10.3$), 6.33 (dd, 1H, $J = 16.9, 1.9$), 5.74 (dd, 1H, $J = 10.6, 1.9$), 3.92-3.81 (br s, 2H), 3.75 (br s, 2H), 3.21 (t, 4H, $J = 5.3$). ^{13}C NMR (400 MHz, CDCl_3) δ 165.41, 129.31, 128.25, 127.92, 120.90, 120.84, 116.77, 53.45, 49.98, 49.50, 45.68, 41.82. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$ 216.1263, found 216.1263. LCMS $R_t = 0.895$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(4-phenylpiperidin-1-yl)prop-2-en-1-one (6)

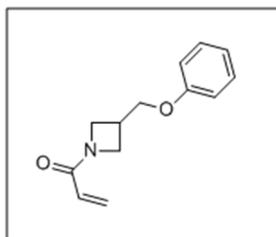
At 0 °C, to a 25 mL round bottom flask containing 4-phenylpiperidine (154.5 mg, 0.939 mmol, 1 equiv) in dichloromethane (9.5 mL) was added triethylamine (0.270 mL, 1.90 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (90 μ L, 1.06 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at 0 °C for 4 hr. Satd aq NaHCO₃ (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH₂Cl₂ (20 mL x 3). The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a brown oil (205.8 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a colorless oil (156.5 mg, 77% yield). TLC R_f = 0.45 (50% EtOAc/hexanes) ¹H NMR (400 MHz, CDCl₃) δ 7.32 (t, 2H, *J* = 7.7), 7.25-7.16 (m, 3H), 6.63 (dd, 1H, *J* = 16.8, 10.5), 6.30 (dd, 1H, *J* = 17.0, 1.9), 5.72 (dd, 1H, *J* = 10.5, 1.9), 4.93-4.80 (br s, 1H), 4.23-4.09 (br s, 1H), 3.29-3.01 (m, 2H), 2.76 (tt, 1H, *J* = 12.2, 3.9), 1.95 (d, 2H, *J* = 13.0), 1.77-1.61 (m, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 165.45, 145.13, 128.62, 127.93, 127.54, 126.75, 126.56, 46.6, 42.85, 21.2. ESI-MS calc. for C₁₄H₁₇NO [M+H]⁺ 216.13, found 216.00. LCMS R_t = 0.984 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(4-benzyl-1,4-diazepan-1-yl)prop-2-en-1-one (8)

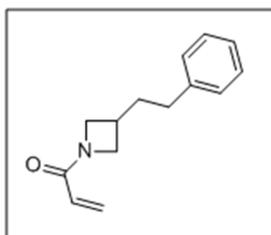
At -78 °C, to a 25 mL round bottom flask containing 1-benzyl-1,4-diazepane-dium dichloride (144 mg, 0.547 mmol, 1 equiv) in dichloromethane (5.75 mL) was added triethylamine (0.160 mL, 1.10 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (50 μ L, 0.600 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO₃ (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH₂Cl₂ (3 x 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated to afford a colorless oil (131.6 mg). The crude material was purified via silica gel column chromatography to afford a pure colorless oil (131.6 mg, 50% yield). TLC R_f = 0.05 (50% EtOAc/ hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.23 (m, 5H), 6.63-6.49 (m, 1H), 6.33 (ddd, 1H, *J* = 17.0, 9.5, 2.0), 5.68 (td, 1H, *J* = 10.4, 2.0), 3.86-3.65 (br m, 4H), 3.74 (br s, 2H), 2.88-2.56 (br m, 4H), 1.93 (br s, 2H). ¹³C NMR (400 MHz, CDCl₃) δ 166.46, 128.85, 128.43, 128.38, 127.99, 127.83, 127.71, 62.41, 56.21, 55.51, 46.86, 44.85, 21.07. HRMS (ESI) *m/z*:

[M⁺] calcd for C₁₅H₂₀N₂O 244.1576, found 244.1574. LCMS R_t = 0.890 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(phenoxy)methyl)azetidin-1-yl)prop-2-en-1-one (9)

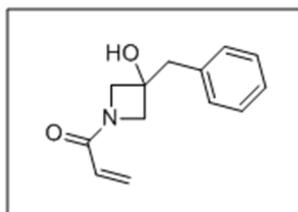
At -78 °C, to a 25 mL round bottom flask containing 3-(phenoxy)methylazetidine hydrochloride (100.1 mg, 0.501 mmol, 1 equiv) in dichloromethane (5 mL) was added triethylamine (0.140 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was stirred vigorously while acryloyl chloride (48 μL, 0.550 mmol, 1.1 equiv) was added dropwise. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO₃ (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The aqueous phase was extracted with CH₂Cl₂ (20 mL) 3x. The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil (111.4 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (45.2 mg, 42% yield). TLC: R_f = 0.35 (60% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.27 (m, 2H), 6.98 (t, 1H, *J* = 7.41), 6.90 (d, 1H, *J* = 8.20), 6.36 (dd, 1H, *J* = 16.78, 1.95), 6.21 (dd, 1H, *J* = 16.68, 10.54), 5.71 (dd, 1H, *J* = 10.4, 1.9), 4.30 (br t, 2H, *J* = 9.46), 4.12 (d, 2H, *J* = 6.54), 4.04 (br t, 2H, *J* = 7.71), 3.17-3.02 (m, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 158.53, 139.46, 129.60, 127.56, 125.63, 121.28, 114.50, 77.23, 68.80, 24.43. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₃H₁₅NO₂ 217.1103, found 217.1096. LCMS R_t = 0.929 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-phenethylazetidin-1-yl)prop-2-en-1-one (10)

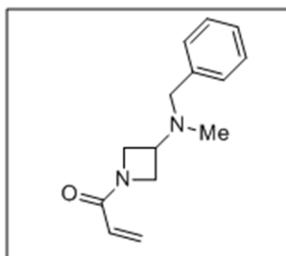
At -78 °C, to a solution of 3-phenethylazetidin-1-ium chloride (240 mg, 1.214 mmol, 1 equiv) in dichloromethane (6 mL) was added triethylamine (0.524 mL, 3.642 mmol, 3 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (0.122 mL, 1.457 mmol, 1.2 equiv) was added via syringe. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO₃ (2 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture

was diluted with brine and extracted with CH₂Cl₂ (10 mL x 2). The combined organics were washed with brine, dried (Na₂SO₄) and concentrated to afford a yellow oil. The crude material was purified via silica gel column chromatography (1-5% MeOH/ CH₂Cl₂) to afford a yellow oil (211 mg, 81% yield). TLC R_f = 0.33 (5% MeOH/ CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) 7.34-7.12 (m, 5H), 6.33 (dd, 1H, *J* = 17.1, 2.0), 6.17 (dd, 1H, *J* = 17.3, 10.2), 5.65 (dd, 1H, *J* = 10.3, 2.0), 4.20 (m, 2H), 3.74 (m, 2H), 2.69-2.55 (m, 1H), 2.61 (t, 2H, *J* = 7.1), 1.96 (q, 2H, *J* = 7.4). ¹³C NMR (400 MHz, CDCl₃) δ 165.60, 141.06, 128.53, 128.34, 127.01, 126.15, 125.88, 55.24, 53.00, 36.04, 33.34, 28.48. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₄H₁₇NO 215.1310, found 215.1311. LCMS R_t = 1.029 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



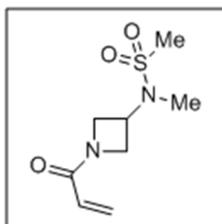
1-(3-benzyl-3-hydroxyazetidin-1-yl)prop-2-en-1-one (11)

At -78 °C, to a 25 mL round bottom flask containing 3-benzylazetidin-1-ium-3-ol chloride (149.6 mg, 0.749 mmol, 1 equiv) in dichloromethane (7.5 mL) was added triethylamine (0.210 mL, 1.490 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (70 μL, 0.827 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO₃ (12 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH₂Cl₂ (3 x 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated to afford a white oil (169.5 mg). The crude material was purified via silica gel chromatography (0-100% EtOAc/Hexanes) to afford a white solid (95.8 mg, 59% yield). TLC R_f = 0.08 (50% EtOAc/hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.39-7.22 (m, 5H), 6.34 (dd, 1H, *J* = 17.1, 1.7), 6.19 (dd, 1H, *J* = 16.6, 10.3), 5.68 (dd, 1H, *J* = 10.2, 1.8), 4.21 (br s, 2H), 4.09 (br s, 1H), 3.96 (br s, 1H), 3.08 (s, 2H), 1.83 (br s, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 165.91, 135.39, 129.68, 128.95, 127.75, 127.47, 125.89, 77.49, 70.31, 44.71. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₃H₁₅NO₂ 217.1103, found 217.1109. LCMS R_t = 0.733 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



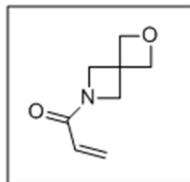
1-(3-(benzyl(methyl)amino)azetid-1-yl)prop-2-en-1-one (12)

At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(benzyl(methyl)ammonio)azetid-1-ium (108.6 mg, 0.436 mmol, 1 equiv) in dichloromethane (4 mL) was added triethylamine (0.130 mL, 0.920 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (40 μL , 0.473 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (8 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a yellow oil (111.4 mg). The crude material was purified via silica gel chromatography (0-80% EtOAc/Hexanes) to afford a white oil (67.8 mg, 68% yield). TLC $R_f = 0.55$ (60% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.26 (m, 5H), 6.32 (dd, 1H, $J = 17.0, 2.0$), 6.17 (dd, 1H, $J = 17.1, 10.4$), 5.65 (dd, 1H, $J = 10.4, 2.1$), 4.20 (t, 1H, $J = 8.5$), 4.16-4.07 (m, 2H), 4.05-3.95 (br m, 1H), 3.60-3.36 (br m, 3H), 2.15 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ 165.66, 137.96, 129.46, 128.62, 127.55, 127.52, 125.79, 77.22, 58.94, 53.78, 37.79. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}$ 230.1419, found 230.1416. LCMS $R_t = 0.885$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



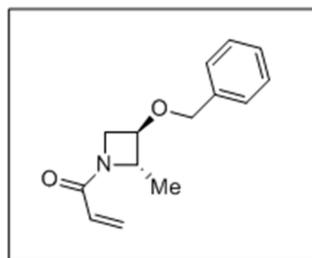
N-(1-acryloylazetid-3-yl)-N-methylmethanesulfonamide (13)

At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(*N*-methylmethanesulfonamido)azetid-1-ium chloride (103.4 mg, 0.436 mmol, 1 equiv) in dichloromethane (4.5 mL) was added triethylamine (0.130 mL, 0.920 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (50 μL , 0.591 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a white solid (86.7 mg). The crude material was purified via silica gel chromatography (0-100% EtOAc/Hexanes) to afford a white solid (56.6 mg, 60% yield). TLC $R_f = 0.16$ (100% EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 6.35 (dd, 1H, $J = 16.9, 1.7$), 6.17 (dd, 1H, $J = 17.3, 10.3$), 5.71 (dd, 1H, $J = 10.8, 1.7$), 4.77-4.66 (m, 1H), 4.50-4.15 (m, 4H), 2.95 (s, 3H), 2.81 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ 165.64, 128.36, 125.46, 54.34, 51.54, 46.76, 36.98, 29.96. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_8\text{H}_{14}\text{N}_2\text{O}_3\text{S}$ 218.0725, found 218.0723. LCMS $R_t = 0.459$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)prop-2-en-1-one (14)

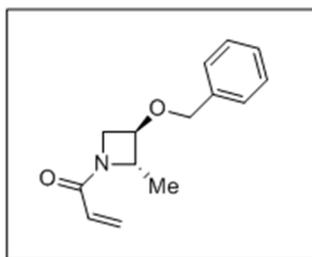
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 2-oxa-6-azaspiro[3.3]heptane (106.6 mg, 1.043 mmol, 1 equiv) in dichloromethane (10 mL) was added triethylamine (0.300 mL, 2.00 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (0.11 mL, 1.3 mmol, 1.3 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated with a steady stream of N_2 to afford a pale yellow solid (114.1 mg). The crude material was purified via high pH reverse phase chromatography (5-95% ACN/10mM NH_4HCO_3 in water, pH = 9) to afford a white solid (14.1 mg, 9% yield). TLC $R_f = 0.02$ (100% EtOAc). ^1H NMR (400 MHz, CDCl_3) δ 6.33 (dd, 1H, $J = 17.0, 1.7$), 6.15 (dd, 1H, $J = 16.6, 10.2$), 5.69 (dd, 1H, $J = 10.2, 1.8$), 4.80 (s, 4H), 4.30 (br s, 4H). ^{13}C NMR (400 MHz, CDCl_3) δ 165.58, 127.93, 125.55, 80.79, 59.45, 27.72. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_8\text{H}_{11}\text{NO}_2$ 153.0790, found 153.0795. LCMS $R_t = 0.322$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



(+)-1-(3-(benzyloxy)-2-methylazetidin-1-yl)prop-2-en-1-one (15 ent 1)

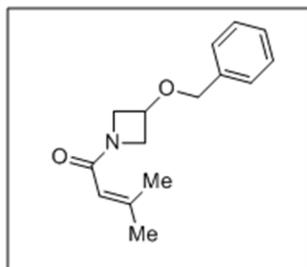
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(benzyloxy)-2-methylazetidin-1-ium chloride (190.2 mg, 0.890 mmol, 1 equiv) in dichloromethane (9 mL) was added triethylamine (0.250 mL, 1.780 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (85 μL , 0.980 mmol, 1.1 equiv) was added dropwise via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a colorless oil (121.6 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford the desired product as a colorless oil (98.2 mg, 48% yield). TLC: $R_f = 0.33$ (60% EtOAc /Hexanes). Optical Rotation (measured): $+0.056^{\circ}$, Specific Rotation (calculated): $+1.87^{\circ}$ (20.00 $^{\circ}\text{C}$, 3 mg/mL in Methanol). ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.28 (m, 5H), 6.34 (dd, 1H, $J = 17.1, 1.8$), 6.13 (dd, 1H, $J = 17.5, 10.4$), 5.65 (dd, 1H, $J = 10.2, 1.8$), 4.49 (s, 2H), 4.42-4.32 (m, 1H), 4.28-4.17 (br m, 1H), 3.95-3.85

(m, 2H), 1.43 (d, 3H, $J = 6.3$). ^{13}C NMR (400 MHz, CDCl_3) δ 166.22, 137.05, 128.63, 128.20, 127.99, 127.42, 126.54, 76.11, 74.71, 71.36, 65.18. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found 231.1259. LCMS $R_t = 0.932$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B). *The absolute stereochemistry was not assigned (relative stereochemistry shown).*



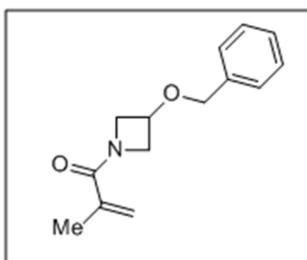
(-)-1-(3-(benzyloxy)-2-methylazetidin-1-yl)prop-2-en-1-one (15 ent 2)

At -78 °C, to a 25 mL round bottom flask containing 3-(benzyloxy)-2-methylazetidin-1-ium chloride (148.6 mg, 0.695 mmol, 1 equiv) in dichloromethane (7 mL) was added triethylamine (0.200 mL, 1.434 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while acryloyl chloride (65 μL , 0.770 mmol, 1.1 equiv) was added dropwise via syringe. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a colorless oil (168.4 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford the desired product as a colorless oil (97.7 mg, 61% yield). TLC: $R_f = 0.33$ (60% EtOAc/Hexanes). Optical Rotation (measured): -0.026° , Specific Rotation (calculated): -0.87° (20.00 °C, 3 mg/mL in MeOH). ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.28 (m, 5H), 6.34 (dd, 1H, $J = 16.9, 1.9$), 6.13 (dd, 1H, $J = 17.1, 10.6$), 5.65 (dd, 1H, $J = 10.2, 1.9$), 4.49 (s, 2H), 4.42-4.33 (m, 1H), 4.29-4.16 (br m, 1H), 3.95-3.85 (m, 2H), 1.43 (d, 3H, $J = 6.3$). ^{13}C NMR (400 MHz, CDCl_3) δ 166.22, 137.04, 128.63, 128.20, 127.99, 127.45, 126.53, 76.06, 74.71, 71.37, 65.19. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found 231.1257. LCMS $R_t = 0.932$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B). *The absolute stereochemistry was not assigned (relative stereochemistry shown).*



1-(3-(benzyloxy)azetidin-1-yl)-3-methylbut-2-en-1-one (16)

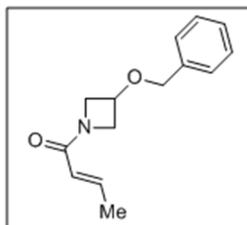
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(benzyloxy)azetidine hydrochloride (105.8 mg, 0.530 mmol, 1 equiv) in dichloromethane (5 mL) was added triethylamine (0.140 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while 3,3-dimethacryloyl chloride (63 μL , 0.579 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a yellow oil (110 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (89.2 mg, 69% yield). TLC: $R_f = 0.60$ (60% EtOAc / hexanes). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 5.54 (s, 1H), 4.48 (s, 2H), 4.40-4.32 (m, 1H), 4.20 (dd, 2H, $J = 10.1, 6.4$), 3.98 (dd, 2H, $J = 10.2, 3.7$), 2.13 (s, 3H), 1.85 (s, 3H). HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ 245.1416, found 245.1422. LCMS $R_t = 1.058$ min (2x50 Xbridge C18 $3.5\mu\text{m}$ column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)azetidin-1-yl)-2-methylprop-2-en-1-one (17)

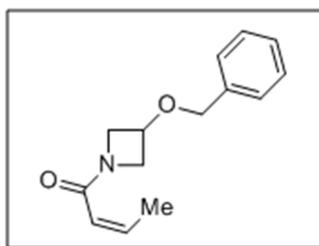
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(benzyloxy)azetidine hydrochloride (101.1mg, 0.506 mmol, 1 equiv) in dichloromethane (5 mL) was added triethylamine (0.140 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while methacryloyl chloride (55 μL , 0.579 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a yellow oil (105.2 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (32.1 mg, 27% yield). TLC: $R_f = 0.46$ (60% EtOAc/hexanes). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 5.37 (t, 1H $J = 1.4, 1.2$), 5.28 (t, 1H, $J = 1.0, 0.9$), 4.47 (s, 2H), 4.42-4.34 (m, 1H), 4.30-4.23 (br t, 2H, $J = 8.2, 5.1$), 4.05 (br d, 2H, $J = 9.5$), 1.91 (s, 3H). HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found

231.1261. LCMS $R_t = 0.969$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



(E)-1-(3-(benzyloxy)azetidin-1-yl)but-2-en-1-one (18)

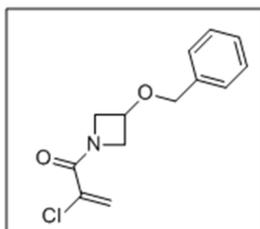
At -78 °C, to a 15 mL round bottom flask containing 3-(benzyloxy)azetidine hydrochloride (105.4 mg, 0.528 mmol, 1 equiv) in dichloromethane (5.2 mL) was added triethylamine (0.141 mL, 1.053 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while (*E*)-but-2-enoyl chloride (58 μ L, 0.579 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at -78 °C for 30 min. Satd aq NaHCO_3 (8 mL) was added slowly to the stirring mixture and the cooling bath was removed. The mixture was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a yellow oil (75.0 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (33.7 mg, 28% yield). TLC: $R_f = 0.50$ (60% EtOAc / hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 6.88 (dt, 1H, $J = 22.1, 7.0$), 5.84 (dd, 1H, $J = 15.3, 1.7$), 4.48 (s, 2H), 4.43-4.35 (m, 1H), 4.24 (t, 2H, $J = 8.8, 7.9$), 4.06-3.95 (br s, 2H), 1.85 (dd, 3H, $J = 7.1, 1.7$). HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found 231.1255. LCMS $R_t = 0.944$ min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



(Z)-1-(3-(benzyloxy)azetidin-1-yl)but-2-en-1-one (19)

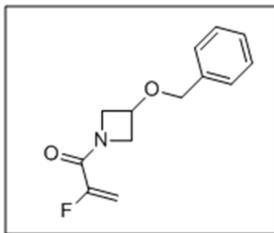
To a stirring suspension of 1-(3-benzyloxyazetidin-1-yl)but-2-yn-1-one (19.5 mg, 0.085 mmol, 1 equiv), Lindlar's catalyst (18.5 mg, 0.009 mmol, 5% mass, 10 mol%), and quinoline (12 μ L, 0.10 mmol, 1.1 equiv) in methanol (3 mL) was equipped a balloon of hydrogen gas. The reaction was allowed to stir at ambient temperature under positive H_2 pressure. Upon stirring overnight, the H_2 balloon was removed and the reaction vessel was purged with nitrogen. The quenched reaction mixture was filtered over celite and concentrated to afford a colorless oil (36.2 mg). The crude material was purified via silica gel chromatography (0-50% EtOAc/hexanes) to afford a colorless oil (7.6 mg, 39% yield). TLC $R_f = 0.28$ (50% EtOAc/hexanes). ^1H NMR (400 MHz,

DMSO) δ 7.40-7.29 (m, 5H), 6.15-6.05 (m, 1H), 5.80 (dd, 1H, $J = 11.4, 2.0$), 4.45 (s, 2H), 4.42-4.35 (m, 1H), 4.28 (dd, 1H, $J = 9.7, 6.4$), 4.05 (dd, 1H, $J = 10.7, 6.2$), 3.94 (dd, 1H, $J = 9.4, 3.4$), 3.69 (dd, 1H, $J = 10.6, 4.2$), 2.01 (dd, 3H, $J = 7.1, 1.8$). ^{13}C NMR (400 MHz, DMSO) δ 166.64, 140.18, 138.06, 128.80, 128.48, 128.21, 119.73, 70.44, 67.18, 57.51, 55.08, 15.26. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_2$ 231.1259, found 231.1257. LCMS $R_t = 0.935$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



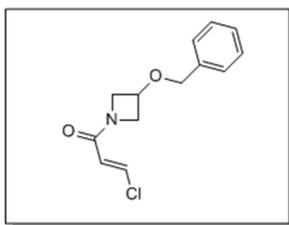
1-(3-(benzyloxy)azetidin-1-yl)-2-chloroprop-2-en-1-one (20)

At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added 2-chloroacrylic acid (59.7 mg, 0.549 mmol, 1.2 equiv) and triethylamine (0.140 mL, 0.990 mmol, 2.0 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetidin-1-ium chloride (102.3 mg, 0.512 mmol, 1.0 equiv) was added quickly as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added dropwise via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and CH_2Cl_2 . After separating the aqueous layer, it was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a yellow oil (335.9 mg). The crude material was purified via silica gel chromatography (0-50% EtOAc/Hexanes) to afford a colorless oil (66.7 mg, 52% yield). TLC: R_f 0.50 (50% EtOAc / hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 6.12 (d, 1H, $J = 1.5$), 5.75 (d, 1H, $J = 1.6$), 4.59-4.45 (br m, 1H), 4.49 (s, 2H), 4.42-4.35 (m, 1H), 4.33-4.19 (br m, 2H), 4.07-3.95 (br m, 1H). ^{13}C NMR (400 MHz, CDCl_3) δ 163.44, 136.82, 131.77, 128.66, 128.27, 128.03, 122.30, 76.11, 71.40, 67.36. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}_2$ 251.0713, found 251.0714. LCMS $R_t = 1.007$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)azetid-1-yl)-2-fluoroprop-2-en-1-one (21)

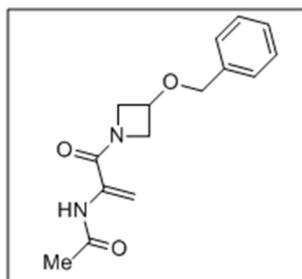
At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added 2-fluoroacrylic acid (56 mg, 0.603 mmol, 1.2 equiv) and triethylamine (0.140 mL, 0.990 mmol, 2.0 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetid-1-ium chloride (98.9 mg, 0.495 mmol, 1.0 equiv) was added quickly as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added dropwise via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and CH₂Cl₂. After separating the aqueous layer, it was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated to afford a yellow oil (335.9 mg). The crude material was purified via silica gel chromatography (0-50% EtOAc/Hexanes) to afford a clear oil (49.8 mg, 43% yield). TLC: R_f 0.49 (1:1 hexanes:EtOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.29 (m, 5H), 5.59 (dd, 1H, *J* = 46.5, 3.4), 5.06 (dd, 1H, *J* = 15.6, 3.3), 4.44-4.37 (m, 1H), 4.48 (s, 2H), 4.32-4.19 (br m, 2H), 4.03-3.96 (dd, 1H, *J* = 11.5, 3.6). ¹³C NMR (400 MHz, CDCl₃) δ 160.11, 159.79, 158.72, 156.02, 136.86, 128.65, 128.25, 128.02, 99.95, 71.37, 67.96, 59.65, 56.12. ESI-MS [M+H]⁺ 236.00. LCMS R_t = 0.962 min (2x50 Xbridge C18 3.5μm column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B). *This product decomposes on standing at room temperature.*



(E)-1-(3-(benzyloxy)azetid-1-yl)-3-chloroprop-2-en-1-one (22)

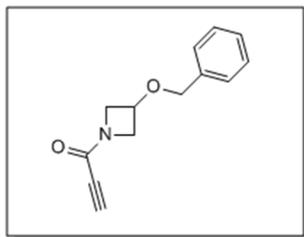
At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added trans-3-chloroacrylic acid (60.6 mg, 0.563 mmol, 1.1 equiv) and triethylamine (0.140 mL, 0.990 mmol, 1.9 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetid-1-ium chloride (105.4 mg, 0.528 mmol, 1.0 equiv) was in one portion as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added dropwise via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and CH₂Cl₂. After separating the aqueous layer, it was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil (403.9 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (79.5 mg,

58% yield). TLC: $R_f = 0.61$ (60% EtOAc / hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.38-7.28 (m, 5H), 7.24 (d, $J = 1.8$, 1H), 6.24 (d, 1H, $J = 12.8$), 4.47 (s, 1H), 4.42-4.35 (m, 1H), 4.33-4.13 (m, 2H), 4.10-3.88 (m, 2H). ^{13}C NMR (400 MHz, CDCl_3) δ 163.64, 136.95, 135.03, 128.69, 128.36, 128.05, 122.24, 71.52, 67.04, 57.40, 55.45. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{14}\text{ClNO}_2$ 251.0713, found 251.0711. LCMS $R_t = 1.025$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



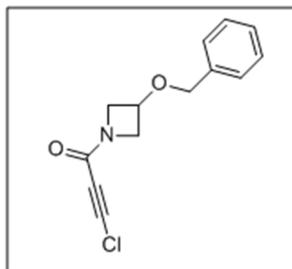
***N*-(3-(3-(benzyloxy)azetidin-1-yl)-3-oxoprop-1-en-2-yl)acetamide (23)**

At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added acetamidoacrylic acid (74.3 mg, 0.570 mmol, 1.2 equiv) and triethylamine (0.140 mL, 0.990 mmol, 2.0 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetidin-1-ium chloride (110.8 mg, 0.555 mmol, 1.0 equiv) was added quickly as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and CH_2Cl_2 . After separating the aqueous layer, it was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated *in vacuo* to afford a yellow oil (354.2 mg). The crude material was purified via silica gel chromatography (0-70% EtOAc/Hexanes) to afford a colorless oil (35.0 mg, 23% yield). TLC $R_f = 0.15$ (60% EtOAc/hexanes). ^1H NMR (400 MHz, DMSO) δ 9.35 (s, 1H), 7.40-7.28 (m, 5H), 5.67 (s, 1H), 4.94 (s, 1H), 4.46 (s, 2H), 4.43-4.36 (m, 1H), 4.43-4.31 (br m, 1H), 4.15-4.01 (br m, 2H), 3.75 (br d, 1H, $J = 8.5$), 1.95 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ 169.38, 166.80, 138.04, 135.67, 128.79, 128.51, 128.23, 104.72, 70.49, 67.75, 60.22, 55.39, 23.66. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}_3$ 274.1317, found 274.1313. LCMS $R_t = 0.801$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)azetidin-1-yl)prop-2-yn-1-one (24)

At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added propionic acid (34 μ L, 0.540 mmol, 1.1 equiv) and triethylamine (0.140 mL, 0.990 mmol, 1.9 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetidin-1-ium chloride (105.5 mg, 0.528 mmol, 1.0 equiv) was added quickly as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added dropwise via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and CH₂Cl₂. After separating the aqueous layer, it was extracted with EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO₄) and concentrated *in vacuo* to afford a yellow oil (280.0 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (48.3 mg, 39% yield). TLC: R_f 0.38 (1:1 hexanes:EtOAc) ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.30 (m, 5H), 4.50 (s, 2H), 4.47-4.38 (m, 1H), 4.38-4.31 (m, 1H), 4.24-4.16 (m, 1H), 4.16-4.09 (m, 1H), 3.98-3.90 (m, 1H), 2.98 (s, 1H). ¹³C NMR (400 MHz, CDCl₃) δ 152.87, 136.72, 128.67, 128.31, 128.04, 77.86, 74.63, 71.53, 67.20, 57.92, 55.73. HRMS (ESI) *m/z*: [M⁺] calcd for C₁₃H₁₃NO₂ 215.0946, found 215.0940. LCMS R_t = 0.926 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).

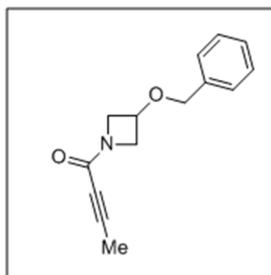


1-(3-(benzyloxy)azetidin-1-yl)-3-chloroprop-2-yn-1-one (25)

Compound **25** was prepared according to literature procedures⁴ with small modifications. To a 2 dram vial charged with 1-(3-(benzyloxy)azetidin-1-yl)prop-2-yn-1-one (**24**) (26 mg, 0.121 mmol, 1 equiv.) and potassium carbonate (20 mg, 0.143 mmol, 1.2 equiv), carbon tetrachloride (0.5 mL) was added via syringe. After 1 min tetrabutylammonium fluoride (20 μ L, 0.020 mmol, 1M in THF, 0.15 equiv) and THF (0.5 mL) were added by syringe. The mixture was allowed to stir for 1 h at room temperature. The mixture was concentrated under reduced pressure to afford an orange paste (66.2 mg). The crude paste was purified via silica gel chromatography (0-50% EtOAc/Hexanes) to afford a colorless oil (14.1 mg, 47% yield). TLC R_f

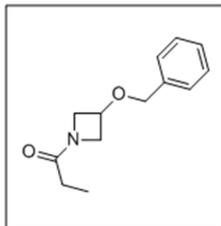
(4) Oakdale, J. S.; Sit, R. K.; Fokin, V. V. *Chemistry – A European Journal*. 2014, 20, 11101–11110

= 0.43 (50% EtOAc/Hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.28 (m, 5H), 4.47 (s, 2H), 4.42-4.35 (m, 1H), 4.31 (ddd, 1H, $J = 9.3, 6.4, 1.3$), 4.16 (ddd, 1H, $J = 10.8, 6.4, 1.4$), 4.09 (ddd, 1H, $J = 9.8, 4.2, 1.2$), 3.90 (ddd, 1H, $J = 11.1, 4.4, 1.1$). ^{13}C NMR (400 MHz, CDCl_3) δ 152.45, 136.69, 128.69, 128.33, 128.04, 71.53, 67.21, 61.67, 57.75, 55.88. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{12}\text{ClNO}_2$ 249.0557, found 249.0559. LCMS $R_t = 1.005$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



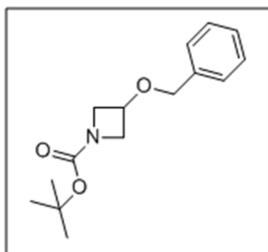
1-(3-(benzyloxy)azetidin-1-yl)but-2-yn-1-one (26)

At 0 °C, to a 25 mL round bottom flask containing DMF (2 mL), were added 2-butynoic acid (47.5 mg, 0.554 mmol, 1.1 equiv) and triethylamine (0.140 mL, 0.990 mmol, 2.0 equiv). The reaction mixture was vigorously stirred while 3-benzyloxyazetidin-1-ium chloride (107 mg, 0.536 mmol, 1.0 equiv) was added in one portion as a solid. Next, 1-propanephosphonic anhydride (0.450 mL, 0.76 mmol, 50% in EtOAc, 1.5 equiv) was added via syringe over 3 min. The contents were allowed to stir at 0 °C for 2 h. Water (11 mL) was added slowly to the stirring mixture and the cooling bath was removed. The reaction mixture was partitioned between water and EtOAc. The aqueous layer was extracted with additional EtOAc (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a yellow oil (303.6 mg). The crude material was purified via silica gel chromatography (0-75% EtOAc/Hexanes) to afford a white oil (70.6 mg, 58% yield). TLC: $R_f = 0.58$ (60% EtOAc/hexanes). ^1H NMR (400 MHz, CDCl_3) δ 7.41-7.30 (m, 5H), 4.49 (s, 2H), 4.43-4.36 (m, 1H), 4.33 (dd, 1H, $J = 9.7, 1.4$), 4.16 (dd, 1H, $J = 11.1, 1.5$), 4.09 (dd, 1H, $J = 9.7, 4.2$), 3.92 (dd, 1H, $J = 11.0, 4.2$), 1.98 (s, 3H). ^{13}C NMR (400 MHz, CDCl_3) δ 154.48, 136.95, 128.66, 128.25, 128.02, 88.58, 72.18, 71.47, 67.25, 57.70, 55.59, 3.90. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{14}\text{H}_{15}\text{NO}_2$ 229.1103, found 229.1103. LCMS $R_t = 0.987$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



1-(3-(benzyloxy)azetidin-1-yl)propan-1-one (S18, also *dihydro-1*)

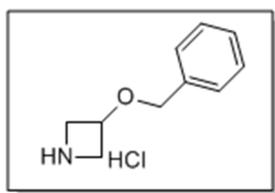
At $-78\text{ }^{\circ}\text{C}$, to a 25 mL round bottom flask containing 3-(benzyloxy)azetidine hydrochloride (103.2 mg, 0.517 mmol, 1 equiv) in dichloromethane (5 mL) was added triethylamine (0.140 mL, 0.990 mmol, 2 equiv) via syringe. The mixture was vigorously stirred while propionyl chloride (50 μL , 0.561 mmol, 1.1 equiv) was added slowly via syringe. The contents were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 30 min. Satd aq NaHCO_3 (10 mL) was added slowly to the stirring mixture and the cooling bath was removed. After separation, the aqueous phase was extracted with additional CH_2Cl_2 (3 x 20 mL). The combined organics were washed with brine, dried (MgSO_4) and concentrated to afford a white oil (102.3 mg). The crude material was purified via silica gel chromatography (0-80% EtOAc/Hexanes) to afford a white oil (56.0 mg, 49% yield). TLC $R_f = 0.52$ (60% EtOAc/hexanes) ^1H NMR (400 MHz, CDCl_3) δ 7.40-7.29 (m, 5H), 4.47 (s, 2H), 4.41-4.33 (m, 1H), 4.18 (dd, 2H, $J = 9.8, 7.1$), 3.95 (dd, 1H, $J = 9.8, 5.0$), 2.10 (q, 2H, $J = 7.6$), 1.12 (t, 3H, $J = 7.8$). ^{13}C NMR (400 MHz, CDCl_3) δ 174.08, 136.95, 128.64, 128.21, 128.02, 76.91, 71.34, 67.04, 24.83, 8.94. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ 219.1264, found 219.1259. LCMS $R_t = 0.904$ min (2x50 Xbridge C18 3.5 μm column, A: 10mM NH_4HCO_3 in H_2O [pH = 9], B: CH_3CN ; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



***tert*-butyl 3-(benzyloxy)azetidine-1-carboxylate (S19)**

To an oven-dried 250 mL round bottom flask containing *tert*-butyl 3-hydroxyazetidine-1-carboxylate (3.197 g, 18.46 mmol, 1 equiv) was added THF (70 mL). Sodium hydride (0.887 g, 22.2 mmol, 60% in oil, 1.2 equiv) was added slowly as a solid at $0\text{ }^{\circ}\text{C}$. The reaction mixture was allowed to stir at $0\text{ }^{\circ}\text{C}$ for 90 min. Benzyl bromide (2.41 mL, 14.83 mmol, 1.1 equiv) was then added to the mixture dropwise and the reaction mixture was heated to reflux overnight. After cooling to ambient temperature, the mixture was quenched with satd aq NH_4Cl (75 mL). The aqueous layer was extracted with EtOAc (50 mL, 3x). The combined organics were washed with brine, dried (MgSO_4), and concentrated to afford a colorless oil. The crude material was purified via silica gel column chromatography (0-20% EtOAc/Hexanes) to afford the pure product as a colorless oil (3.907 g, 80% yield). ^1H NMR (400 MHz, CDCl_3) δ 7.43-7.30 (m, 5H), 4.47 (s, 2H), 4.37-4.30 (m, 1H) 4.08 (dd, 2H, $J = 6.4, 2.9$), 3.89 (dd, 2H, $J = 5.3, 4.4$), 1.46 (s, 9H). ^{13}C -NMR δ 156.37, 137.16, 128.57, 128.08, 127.97, 79.56, 71.09, 67.30, 56.57, 28.37. HRMS (ESI) m/z : $[\text{M}^+]$ calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_3$ 263.1521, found 263.1516. LCMS $R_t = 1.264$ min (2x50

Xbridge C18 3.5 μ m column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).



3-(benzyloxy)azetidinium chloride (S20)

At ambient temperature, to a 100 mL round bottom flask containing a solution of *tert*-butyl 3-(benzyloxy)azetidine-1-carboxylate (1.006 g, 3.78 mmol, 1 equiv) in methanol (3 mL) was added hydrochloric acid (2.9 mL, 12 mmol, 4M in 1,4-dioxane, 3 equiv) slowly via syringe. The reaction mixture was allowed to stir at ambient temperature for 3 h. The reaction mixture was concentrated to afford a white solid (694.8 mg, 92% yield). The solid was carried over to the next step without any additional purification. ESI-MS [M-Cl]⁺ 164.00. LCMS R_t = 0.650 min (2x50 Xbridge C18 3.5 μ m column, A: 10mM NH₄HCO₃ in H₂O [pH = 9], B: CH₃CN; 5-95% B gradient over 1.5 minutes with a 0.25 minute hold at 95% B).

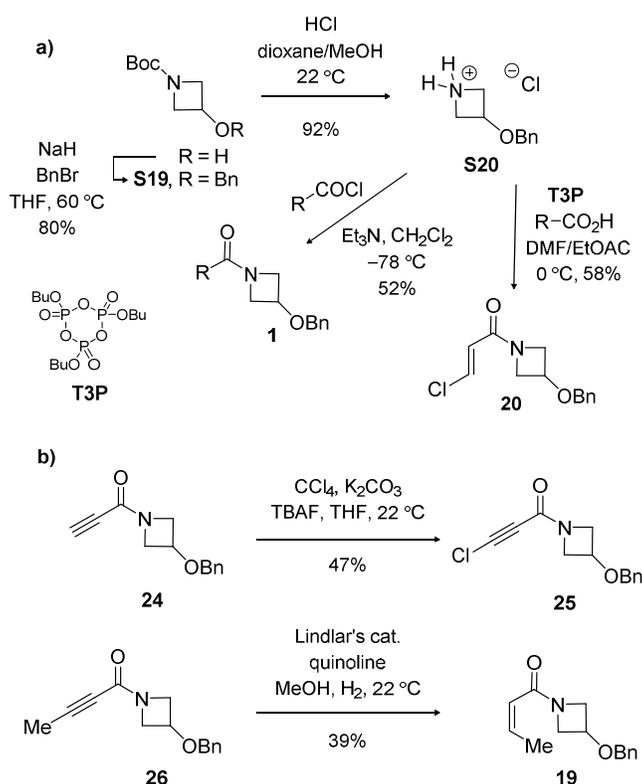
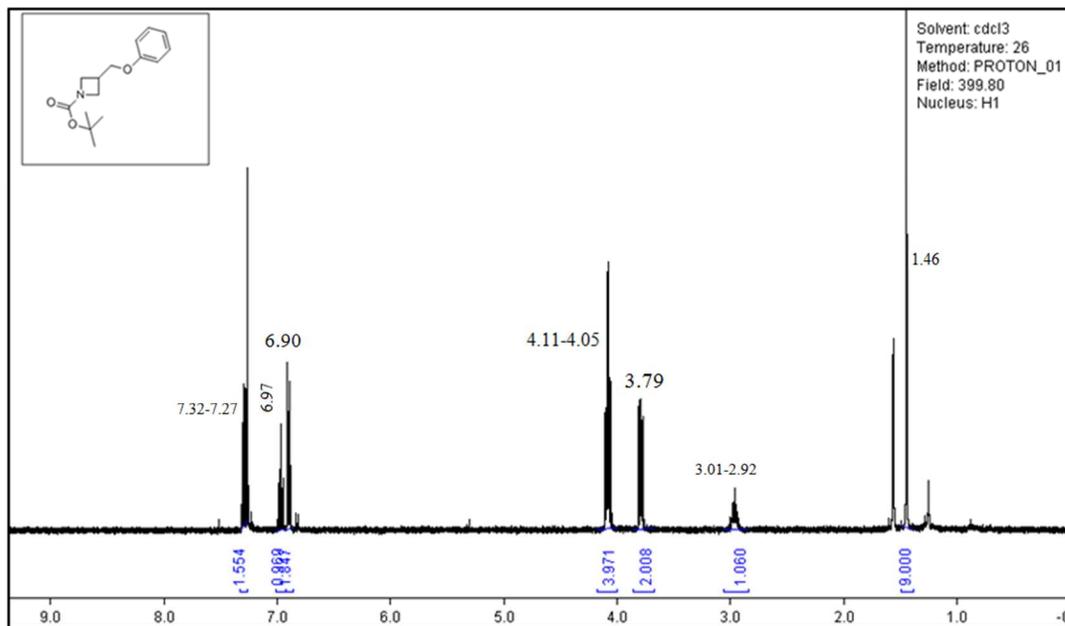


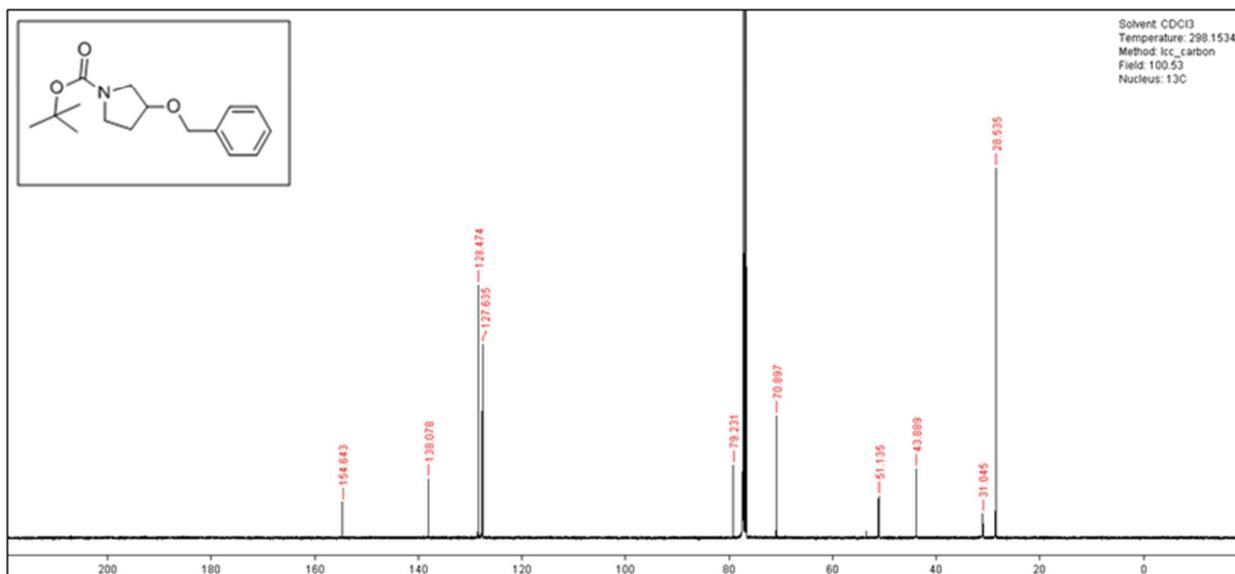
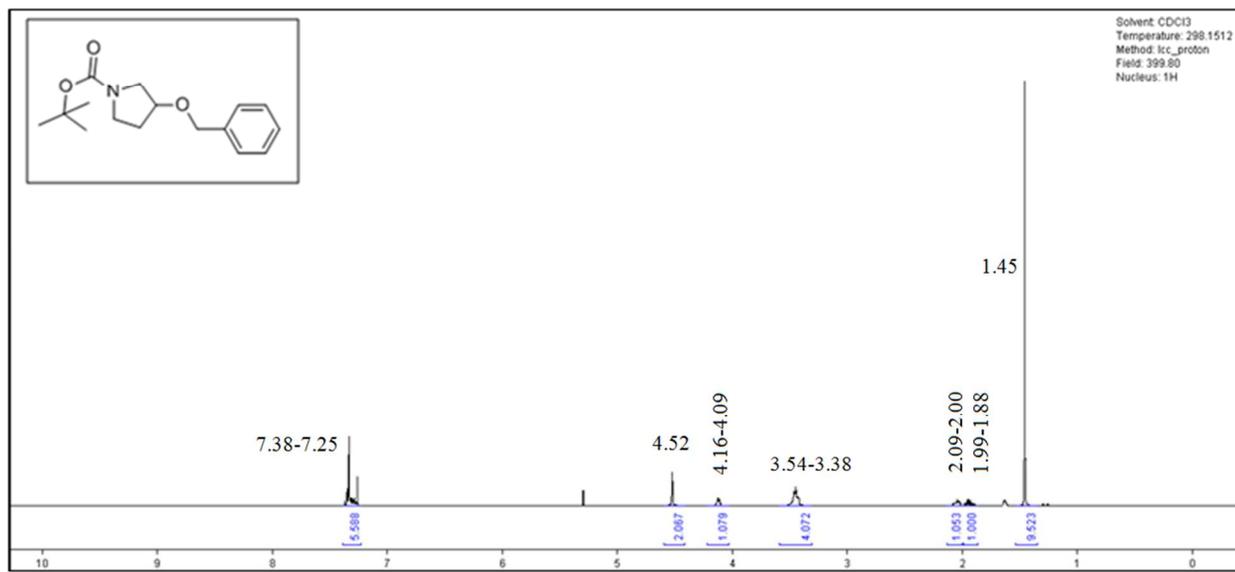
Figure S5. (a) Synthesis of *N*-acryloyl and *N*-propynoyl azetidines using acid chlorides or T3P coupling of acids. (b) Electrophile tailoring reactions offer access to diverse substrates.

^1H and ^{13}C Spectra

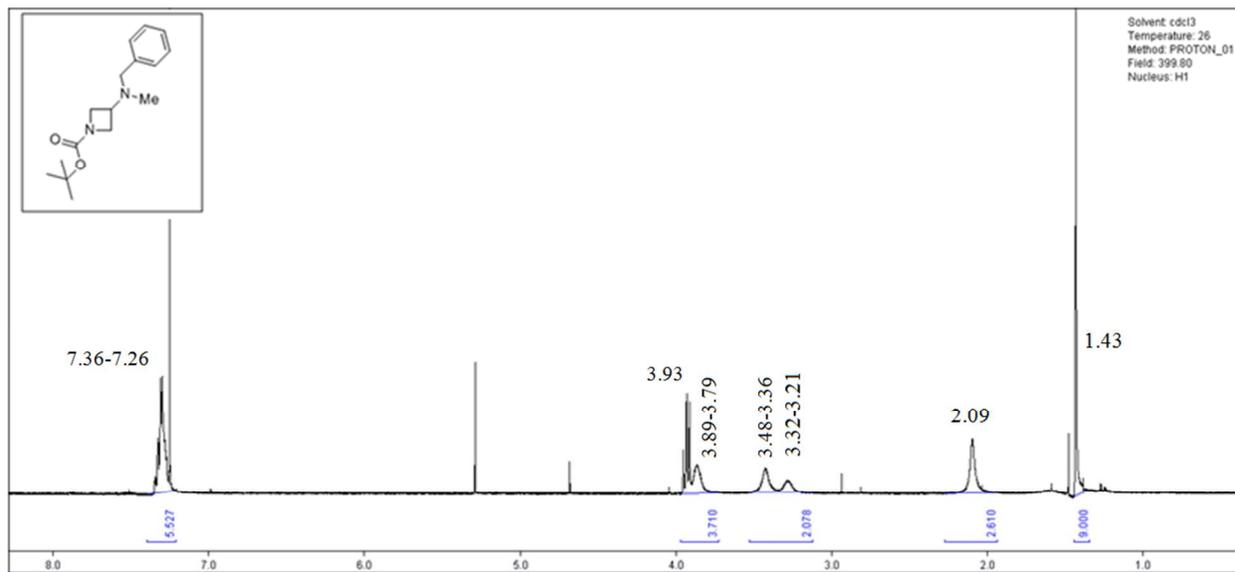
tert-butyl 3-(phenoxyethyl)azetidine-1-carboxylate (S1)



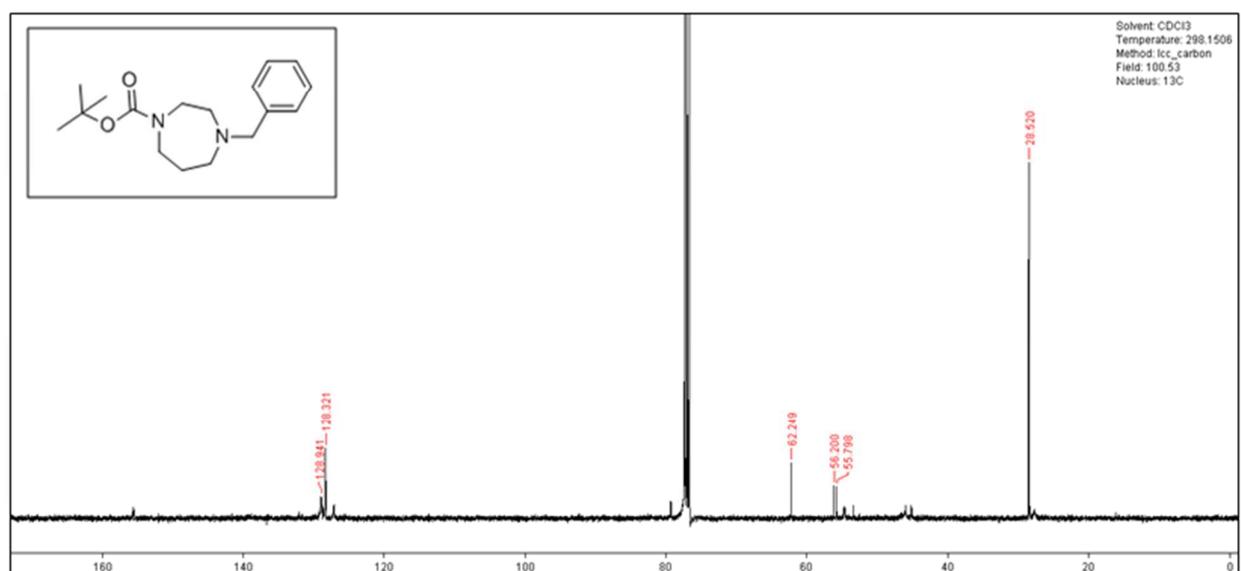
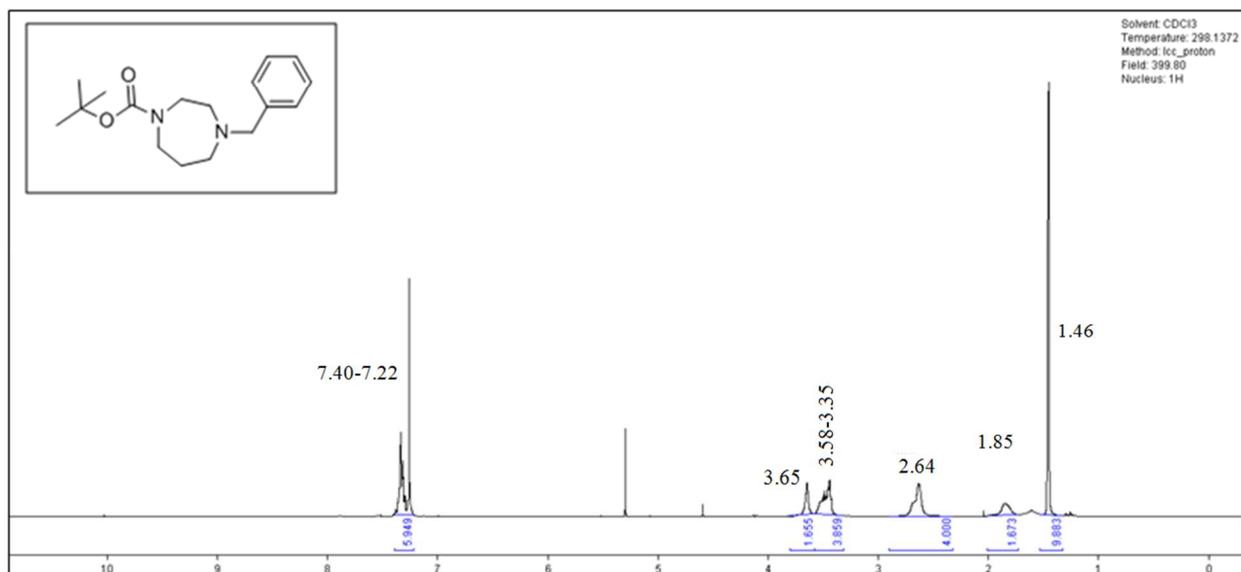
tert-butyl 3-(benzyloxy)pyrrolidine-1-carboxylate (S2)



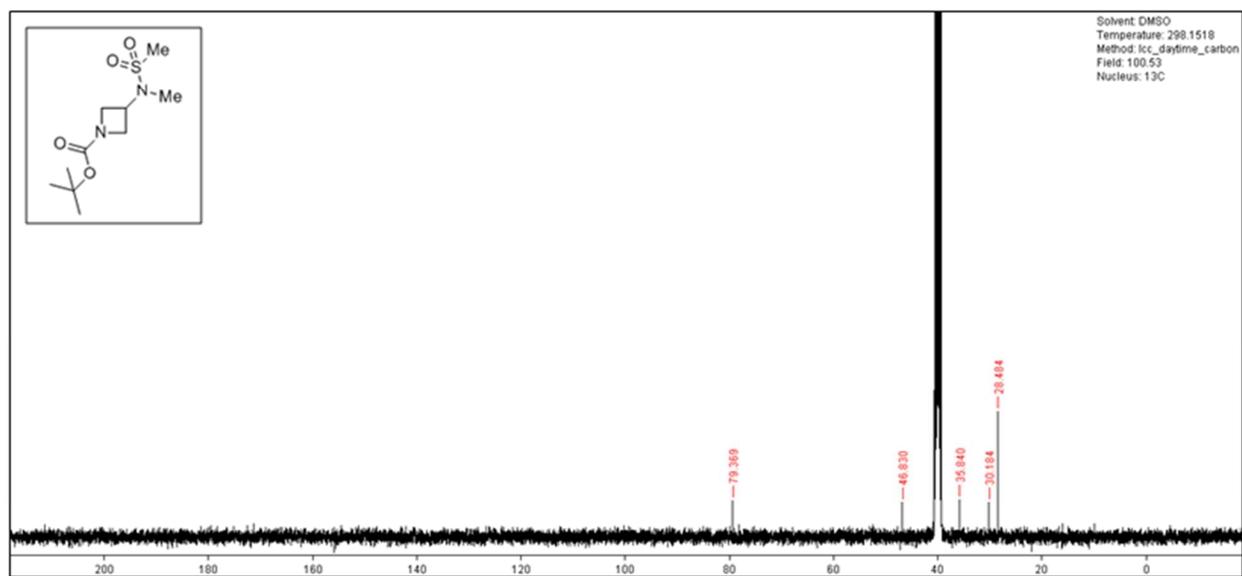
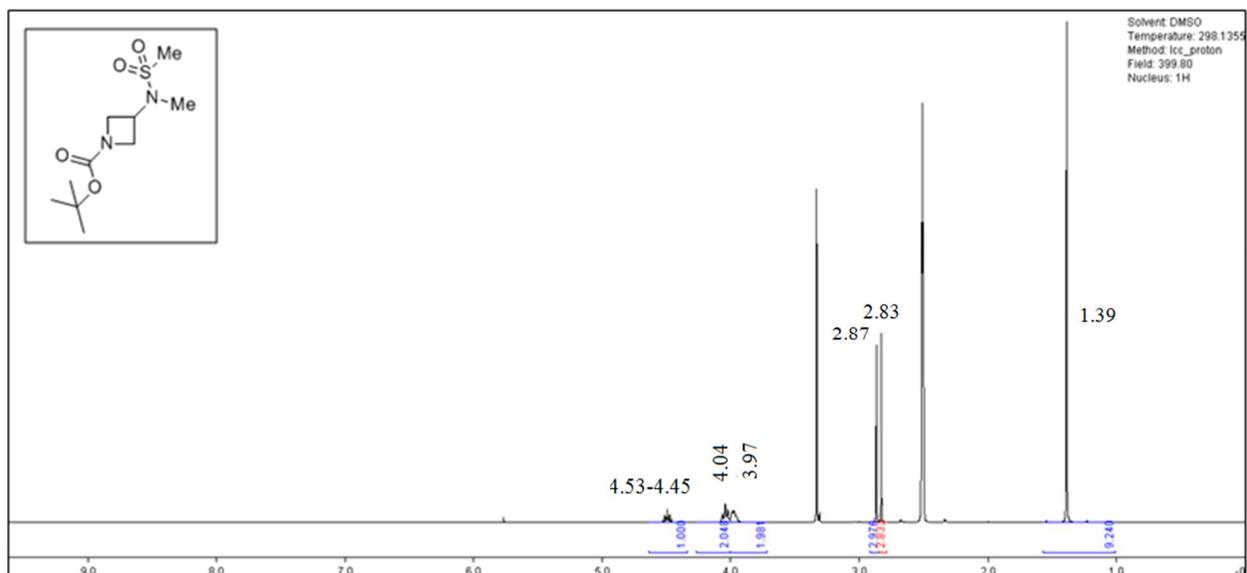
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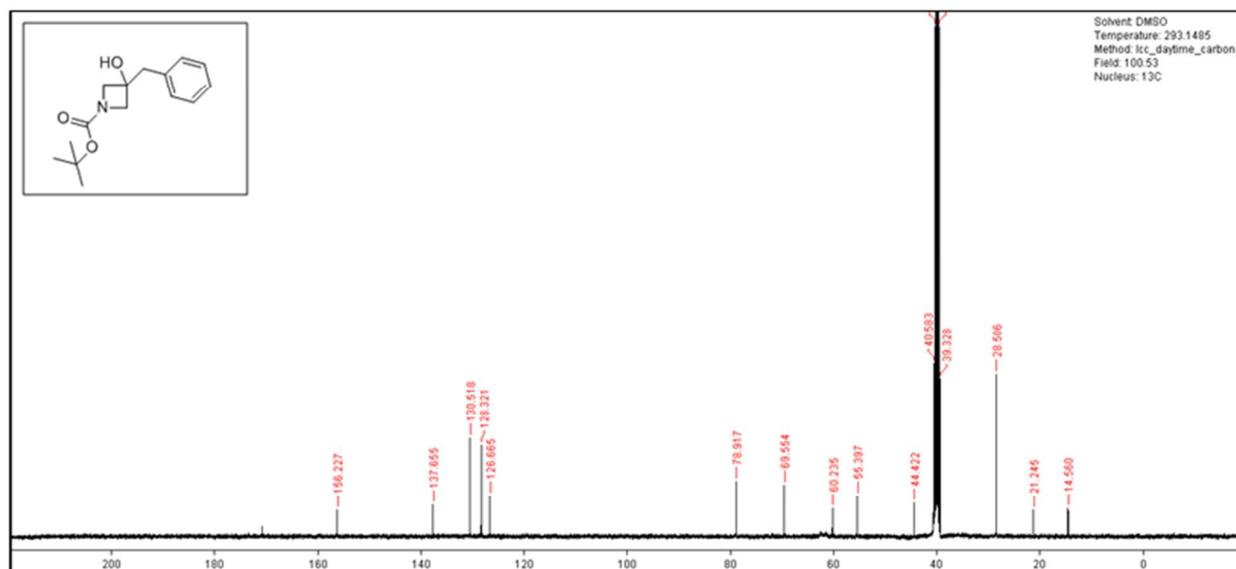
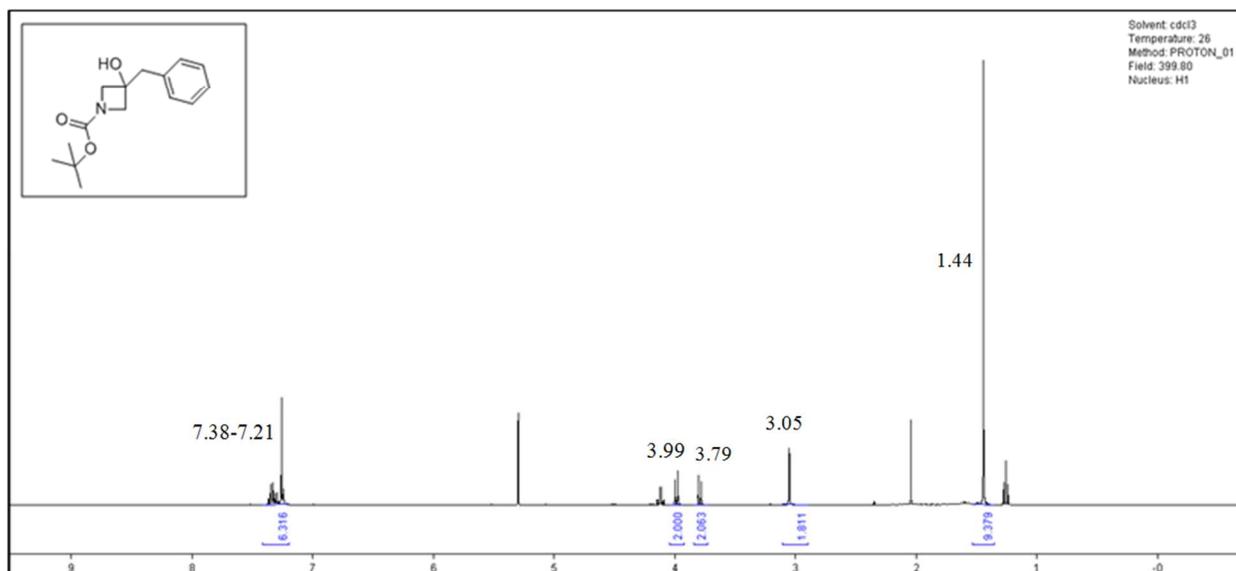
tert-butyl 4-benzyl-1,4-diazepane-1-carboxylate (S4)



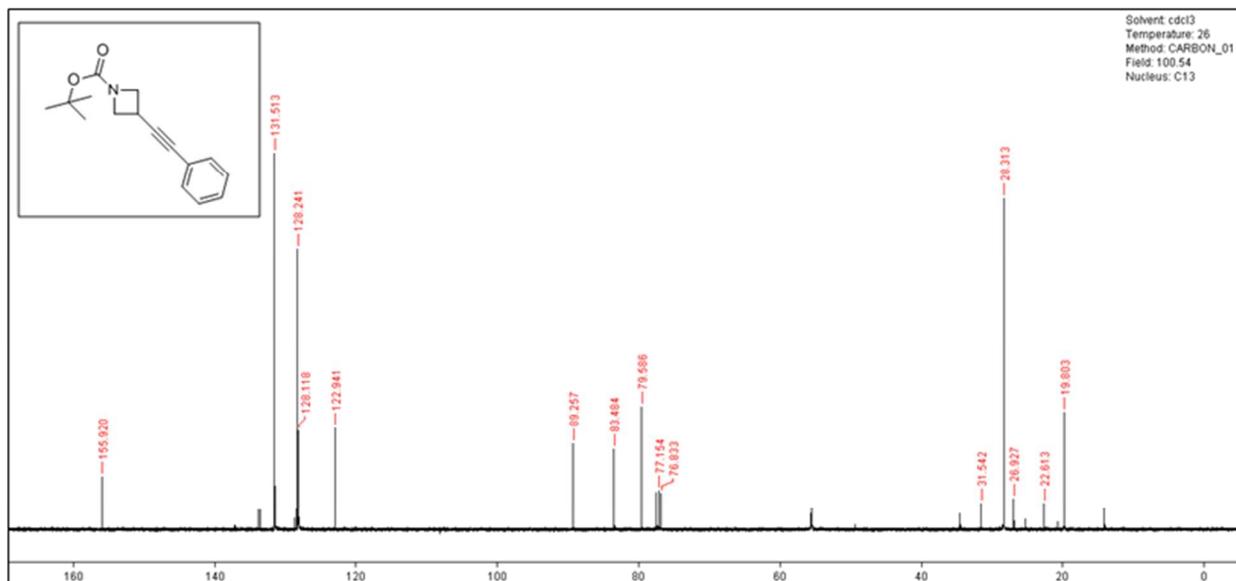
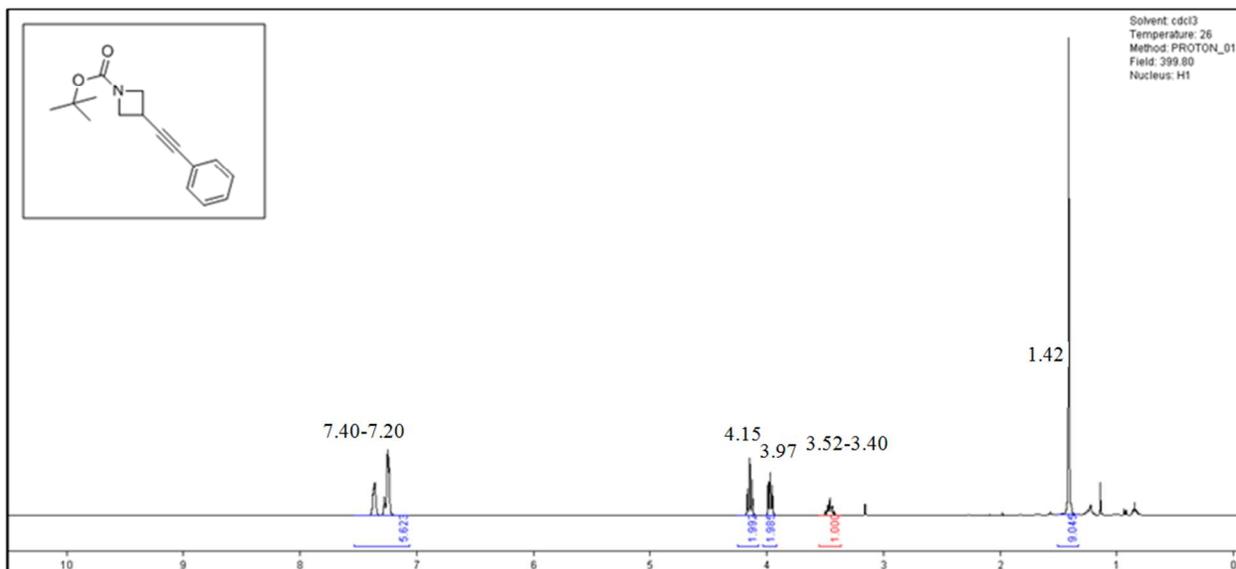
***tert*-butyl 3-(*N*-methylmethylsulfonamido)azetidine-1-carboxylate (S5)**



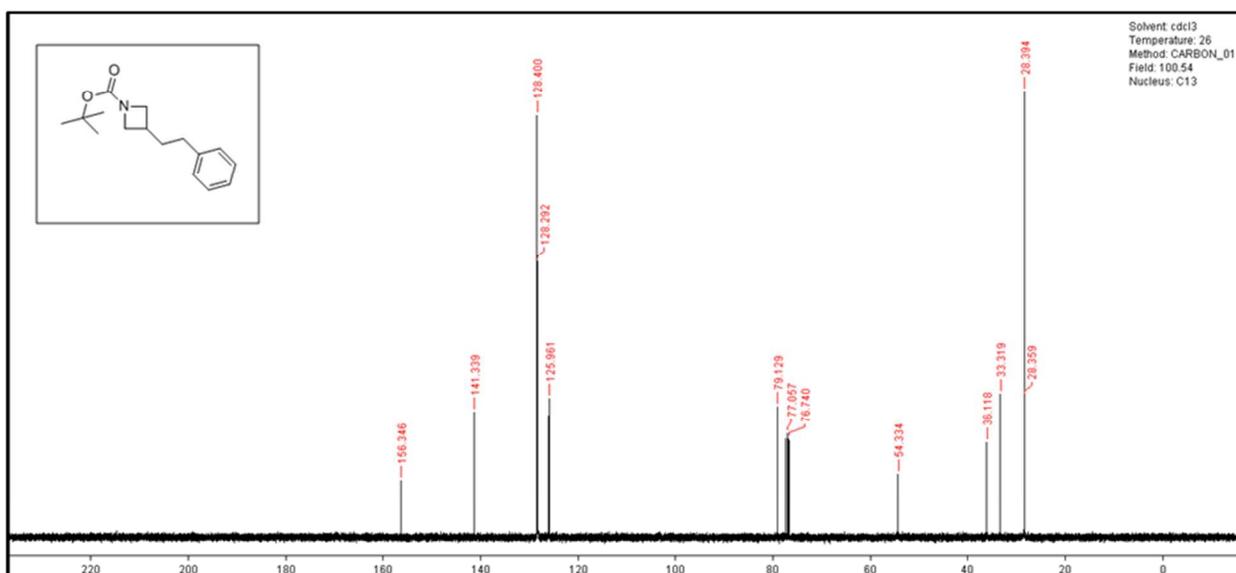
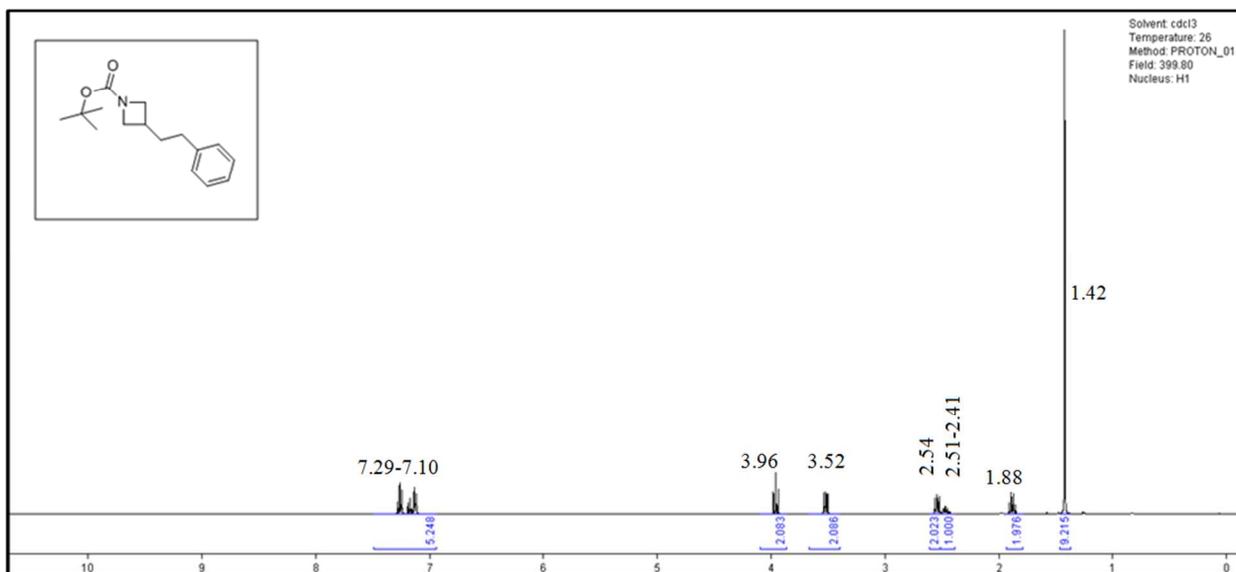
***tert*-butyl 3-benzyl-3-hydroxyazetidine-1-carboxylate (S6)**



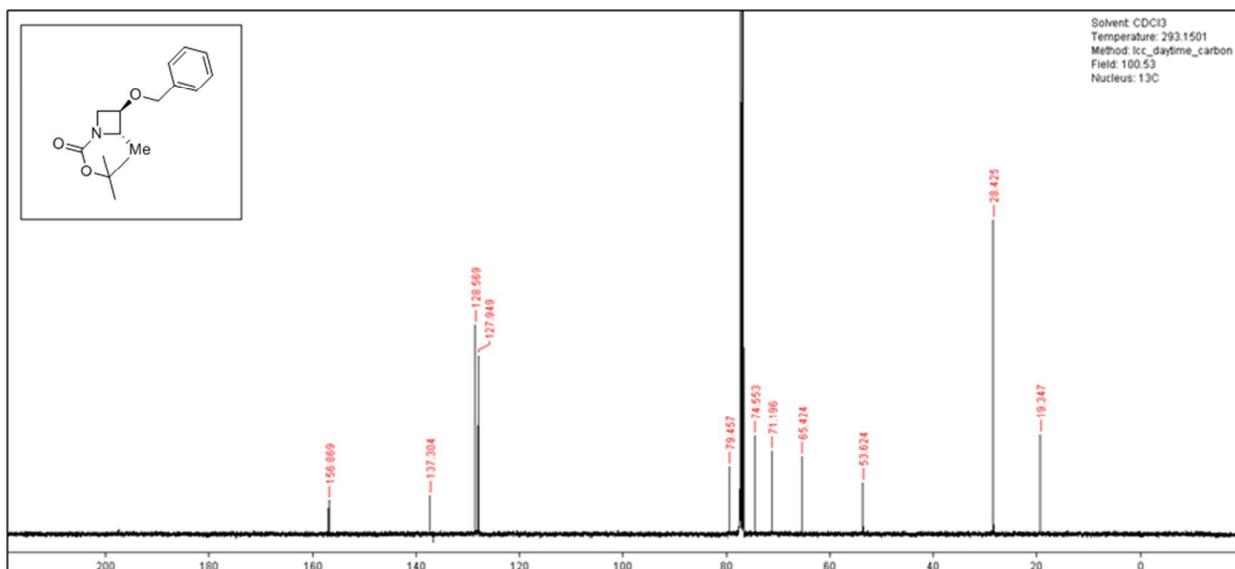
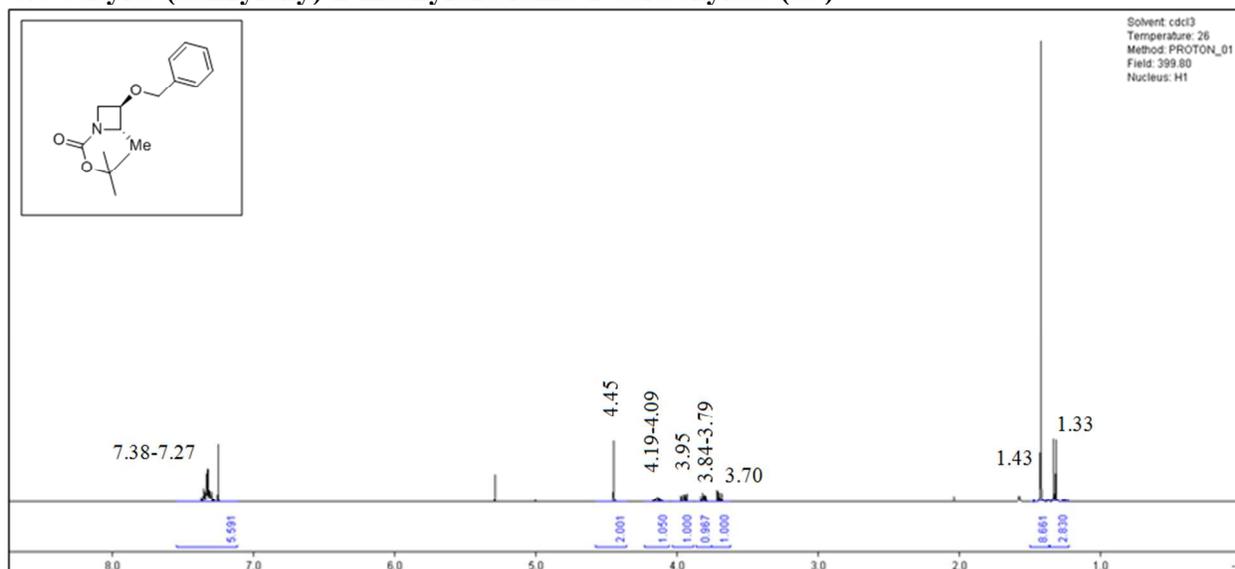
***tert*-butyl 3-(phenylethynyl)azetidine-1-carboxylate (S7)**



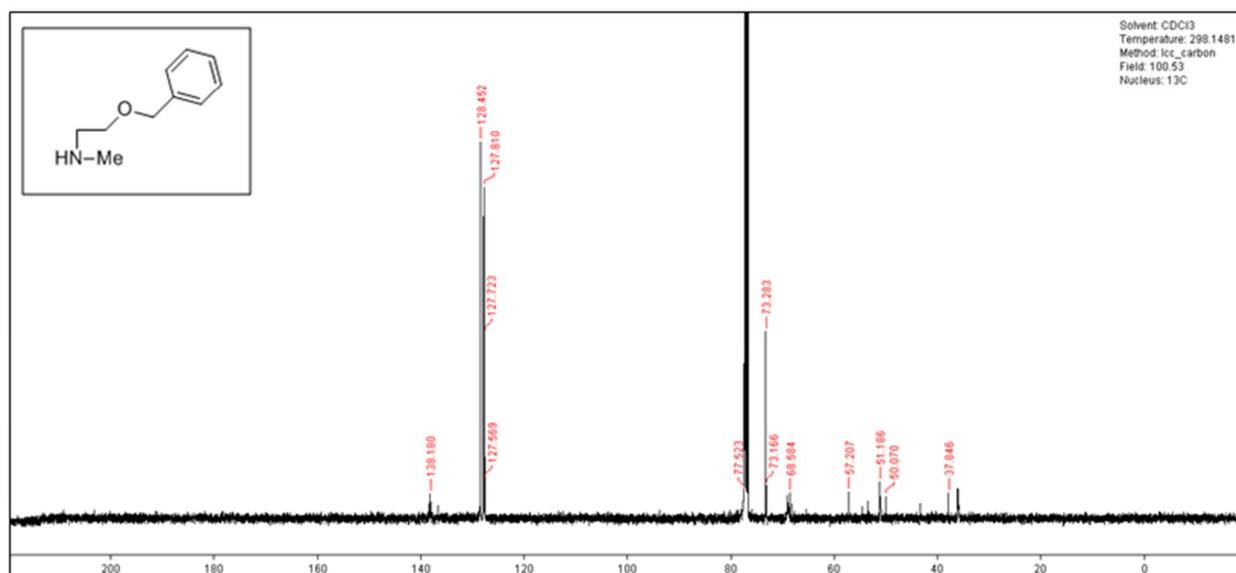
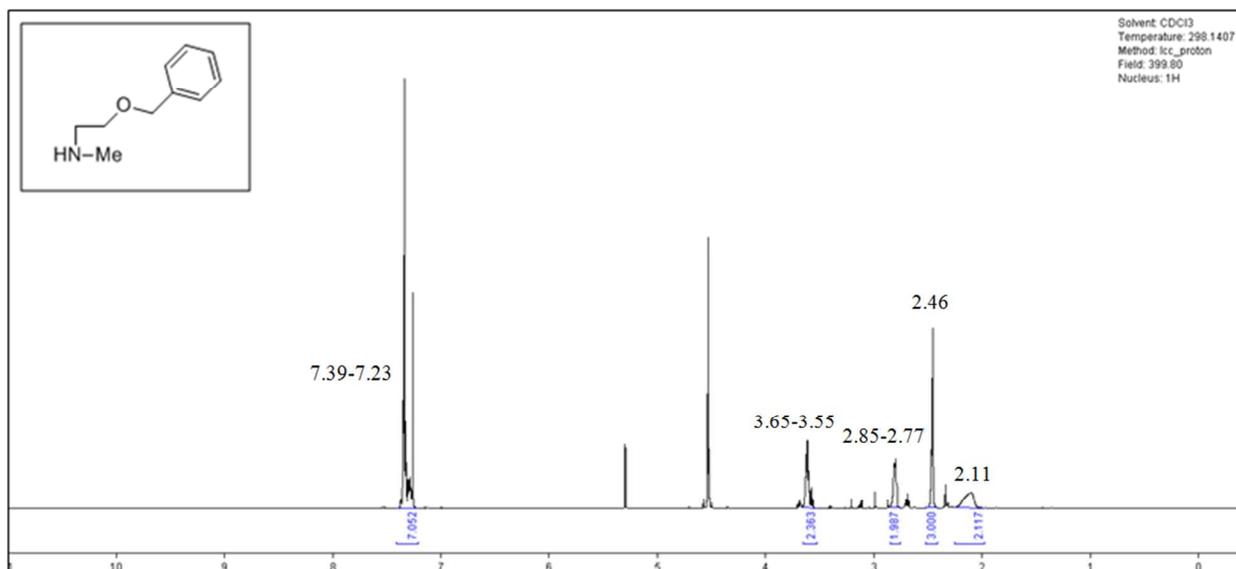
tert-butyl 3-phenethylazetidine-1-carboxylate (S8)



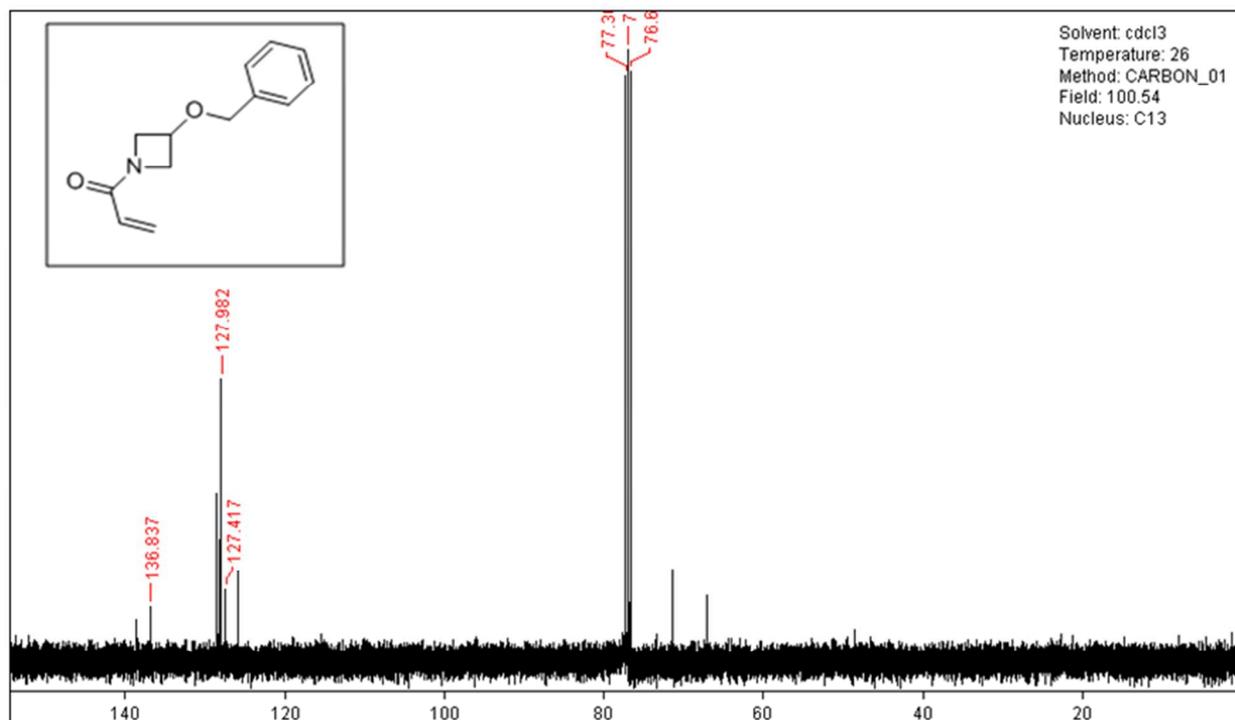
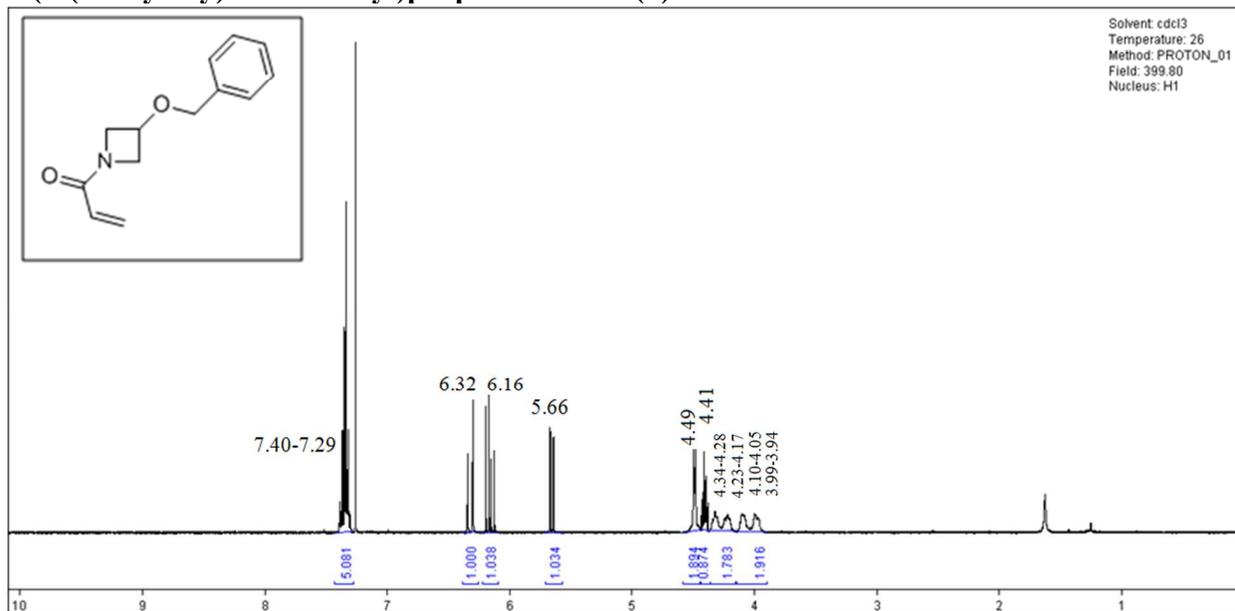
tert-butyl 3-(benzyloxy)-2-methylazetidine-1-carboxylate (S9)



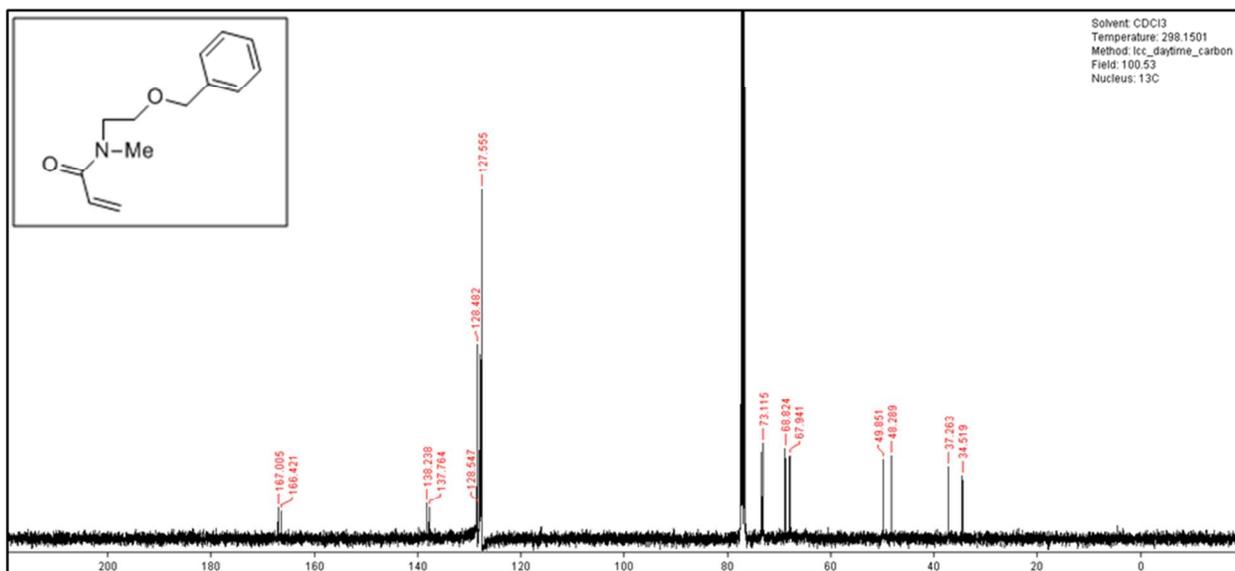
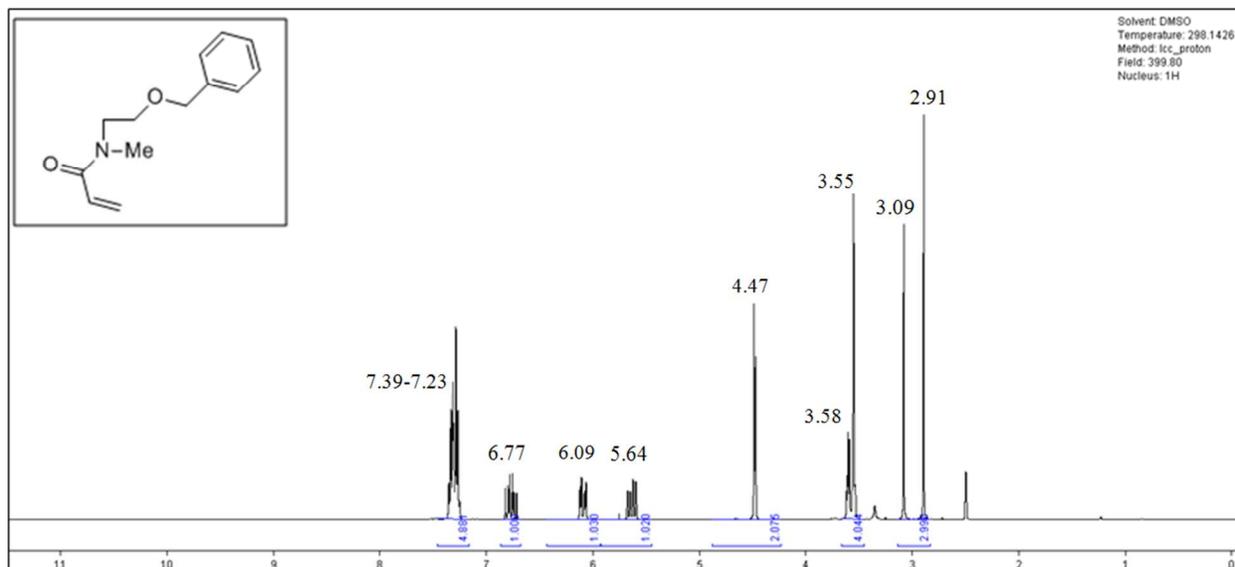
2-(benzyloxy)-*N*-methylethan-1-amine (S17)



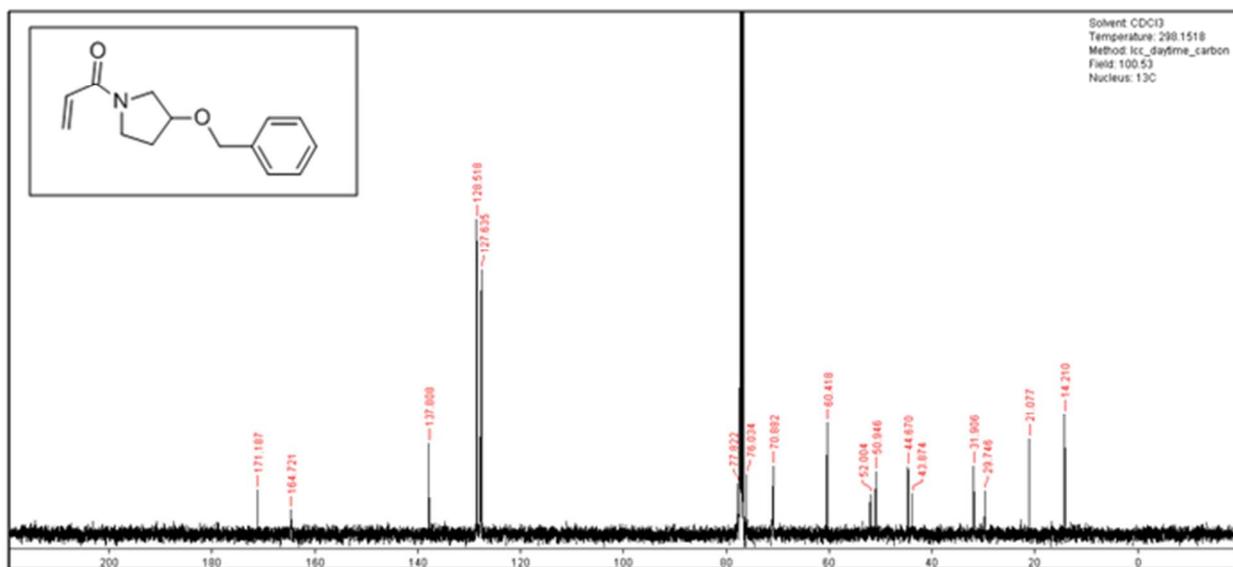
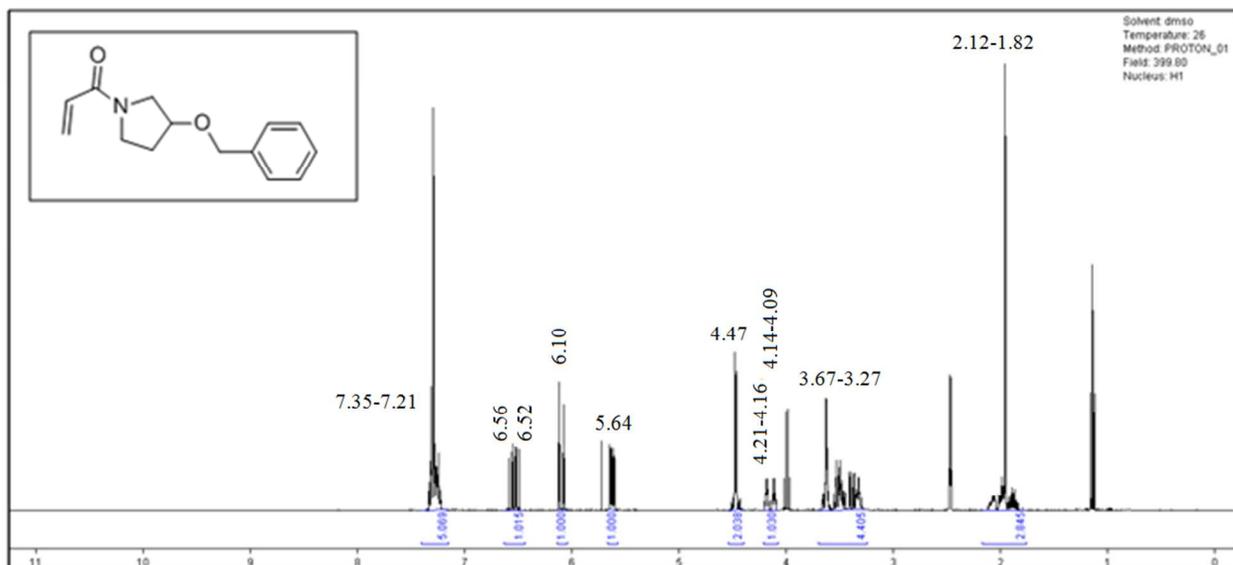
1-(3-(benzyloxy)azetidin-1-yl)prop-2-en-1-one (1)



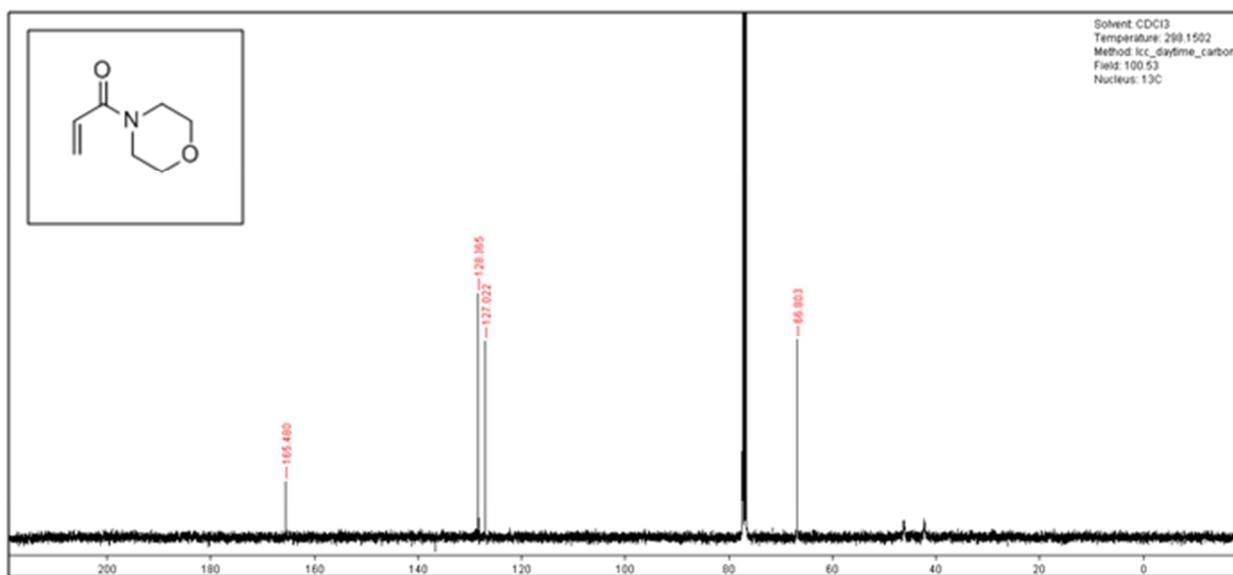
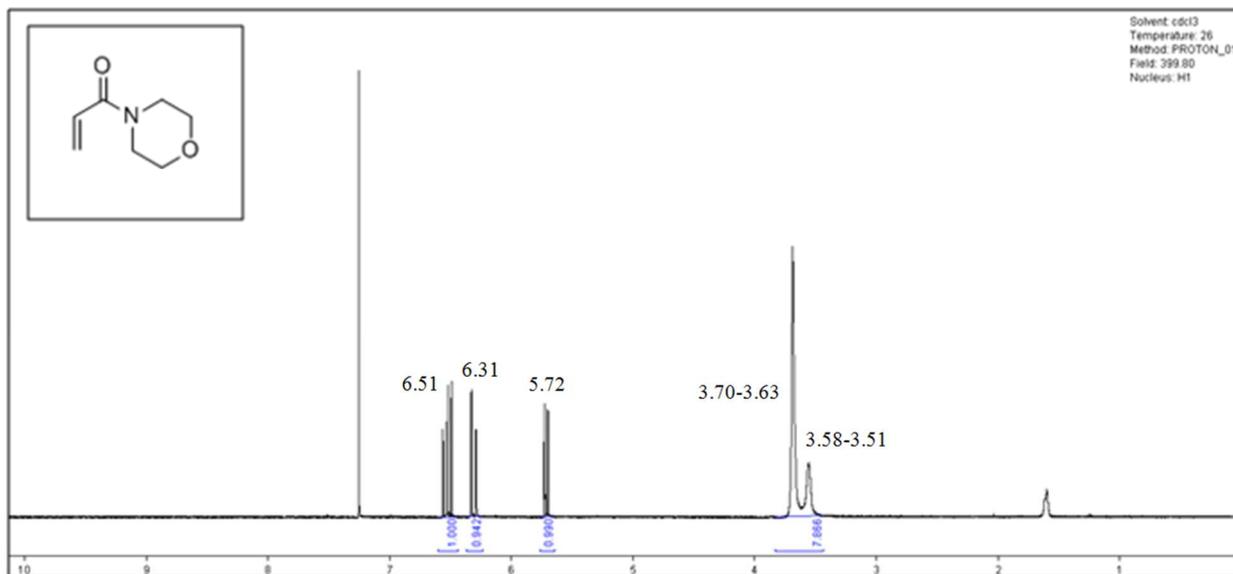
***N*-(2-(benzyloxy)ethyl)-*N*-methylacrylamide (2)**



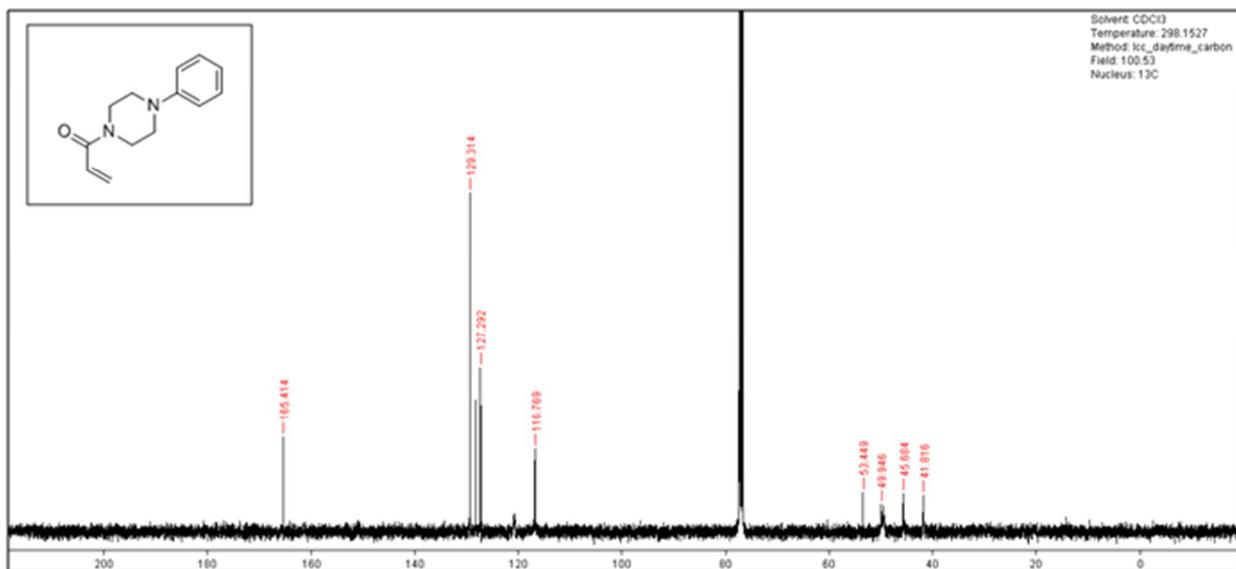
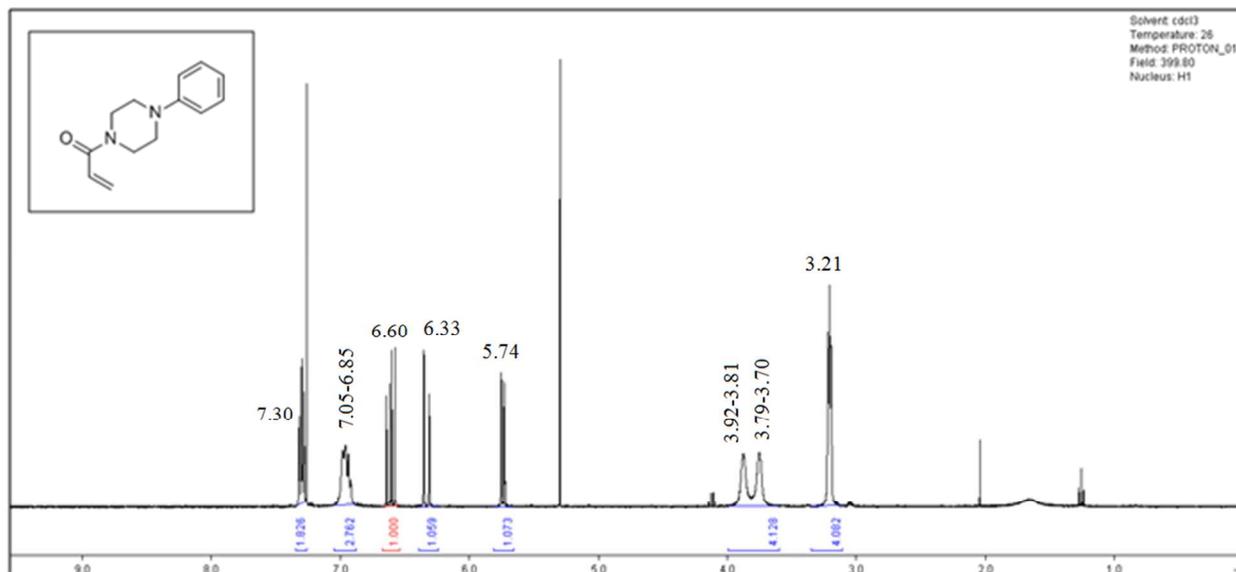
1-(3-(benzyloxy)pyrrolidin-1-yl)prop-2-en-1-one (3)



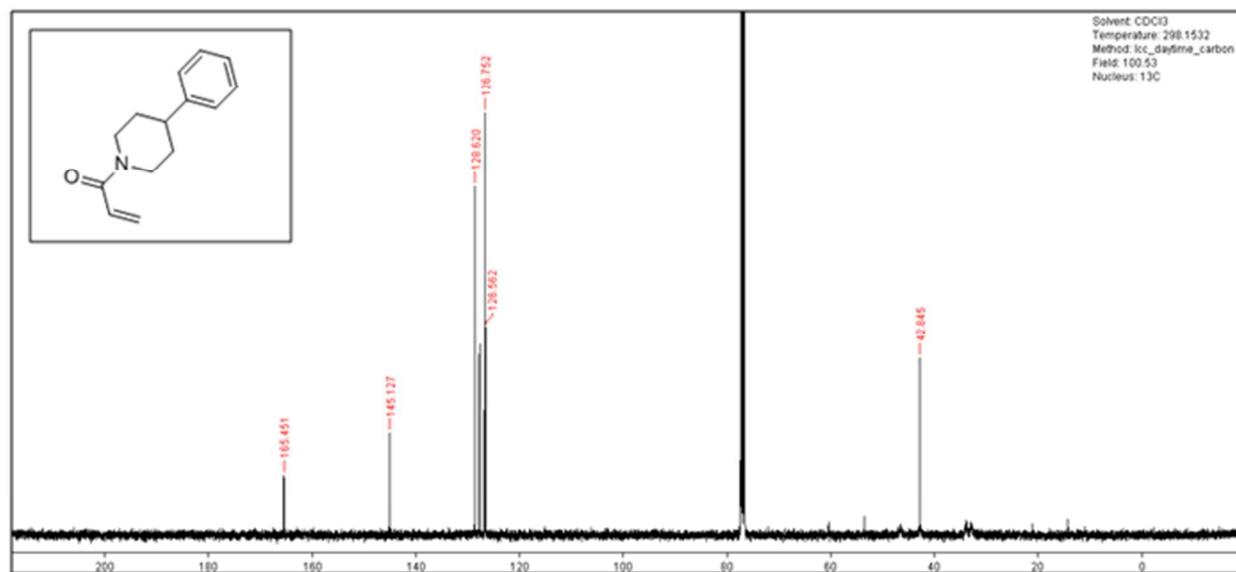
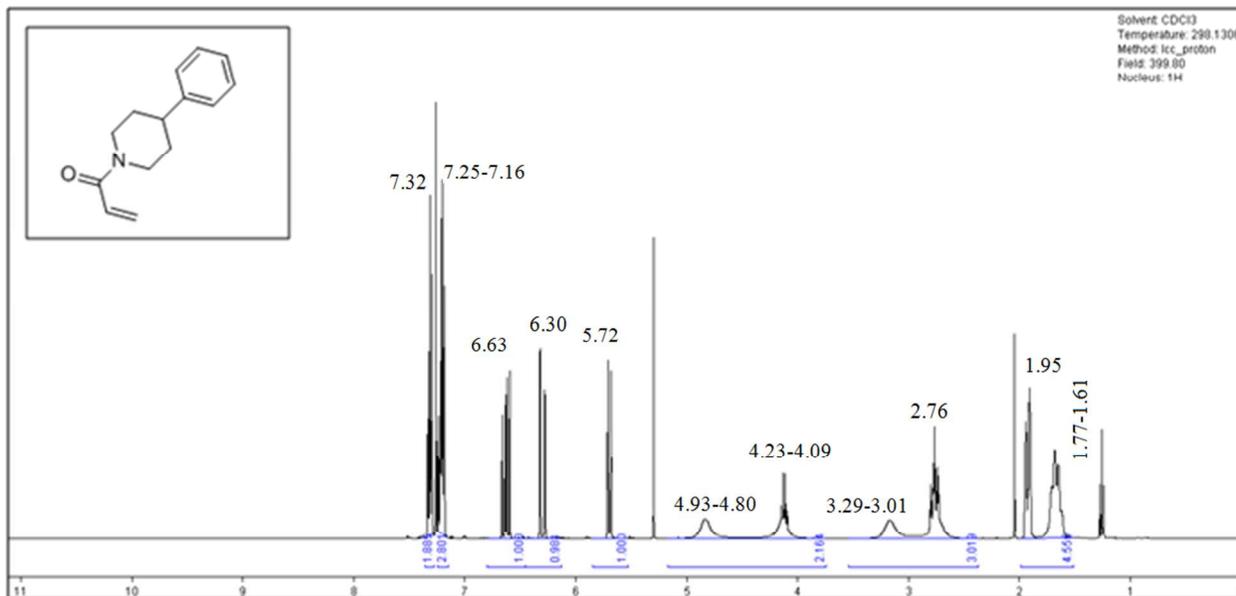
1-morpholinoprop-2-en-1-one (4)



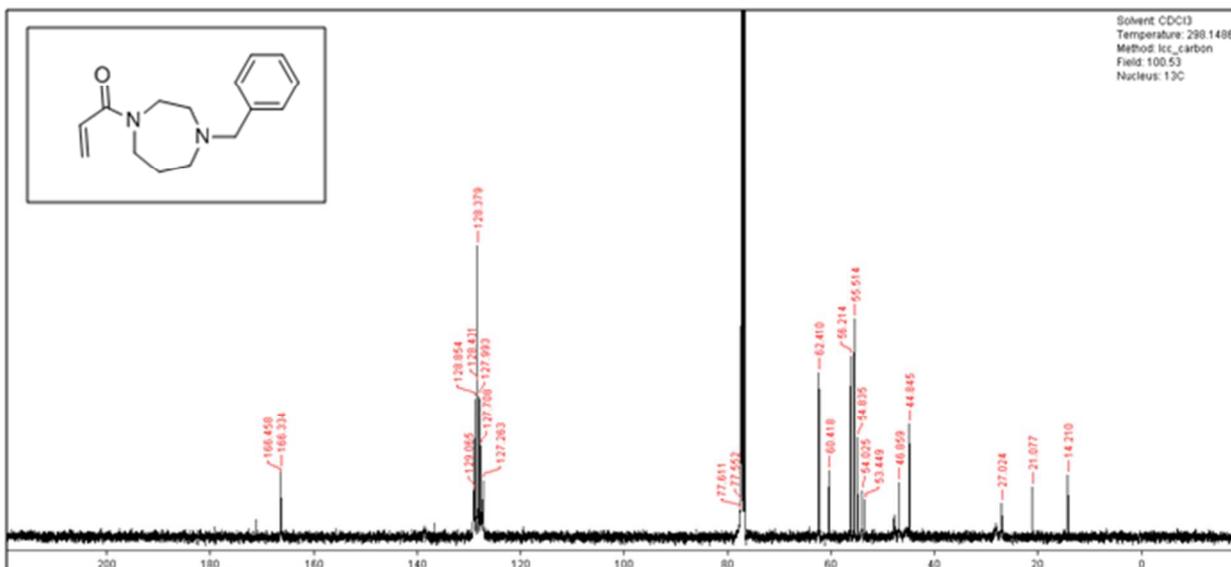
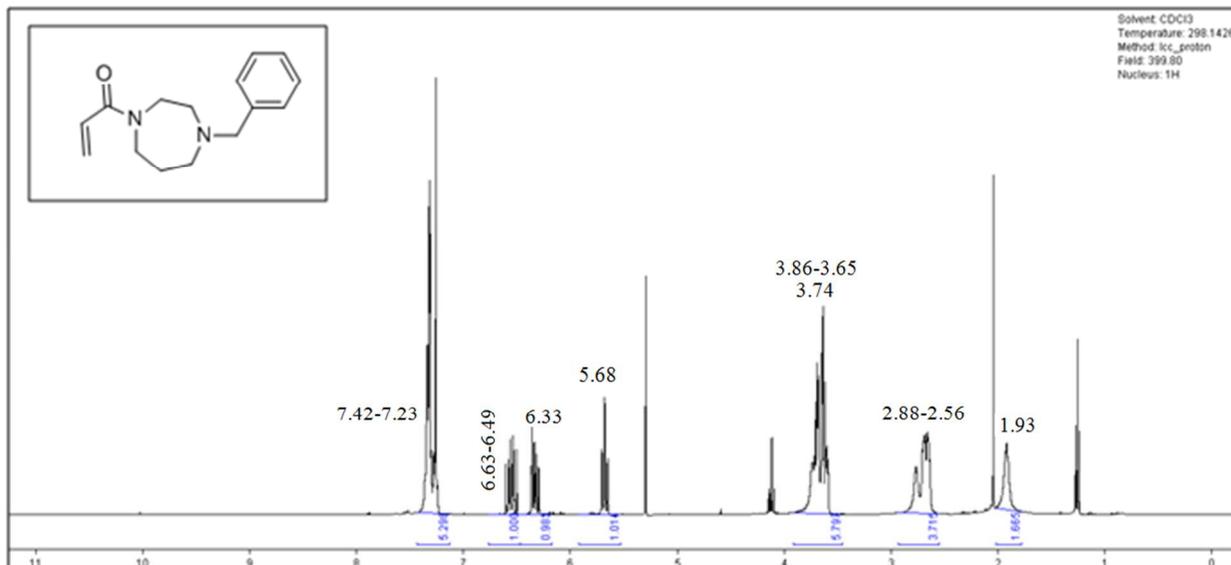
1-(4-phenylpiperazin-1-yl)prop-2-en-1-one (5)



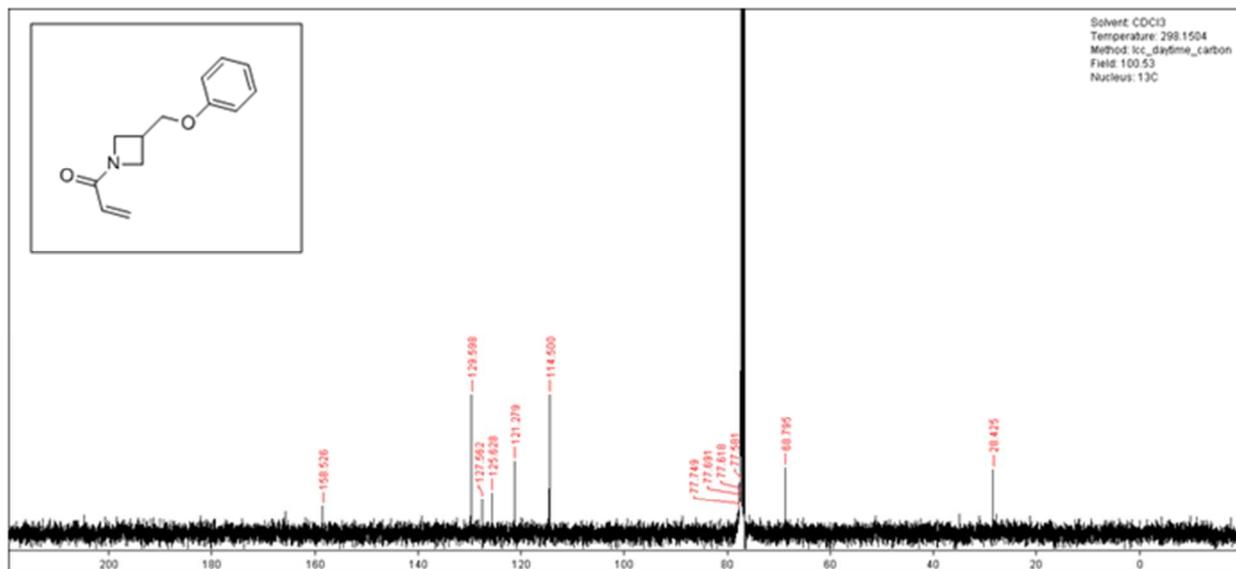
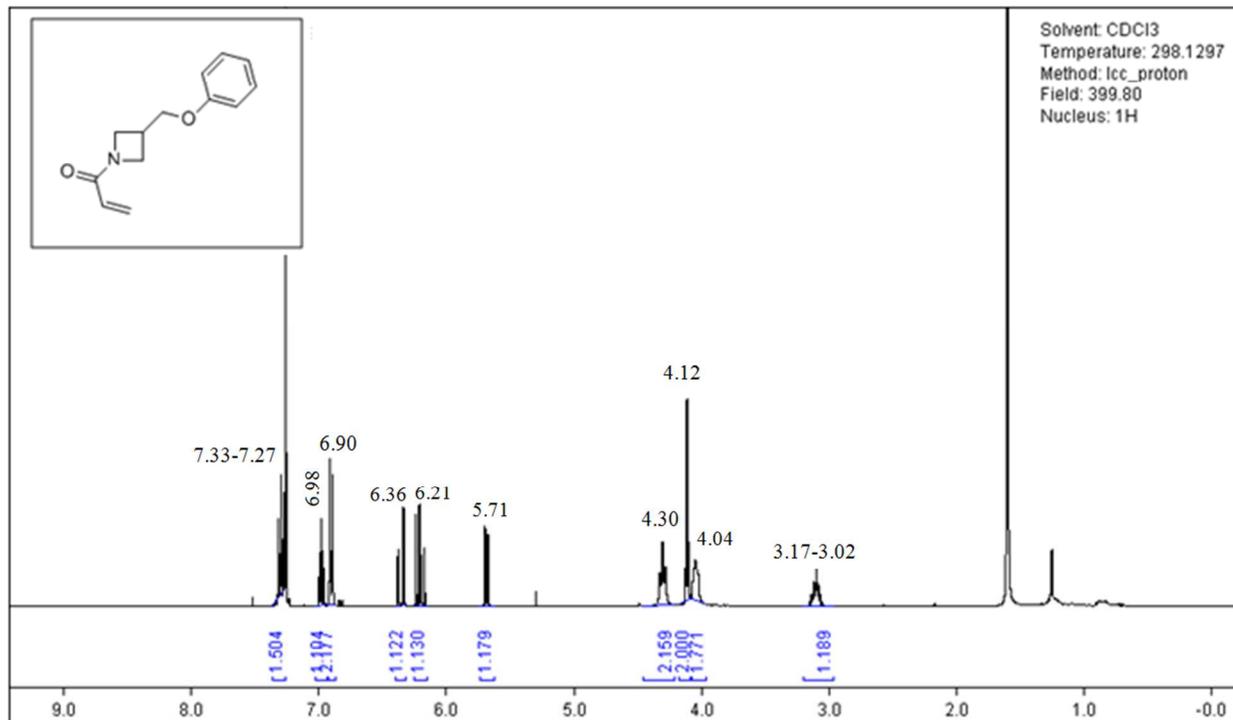
1-(4-phenylpiperidin-1-yl)prop-2-en-1-one (6)



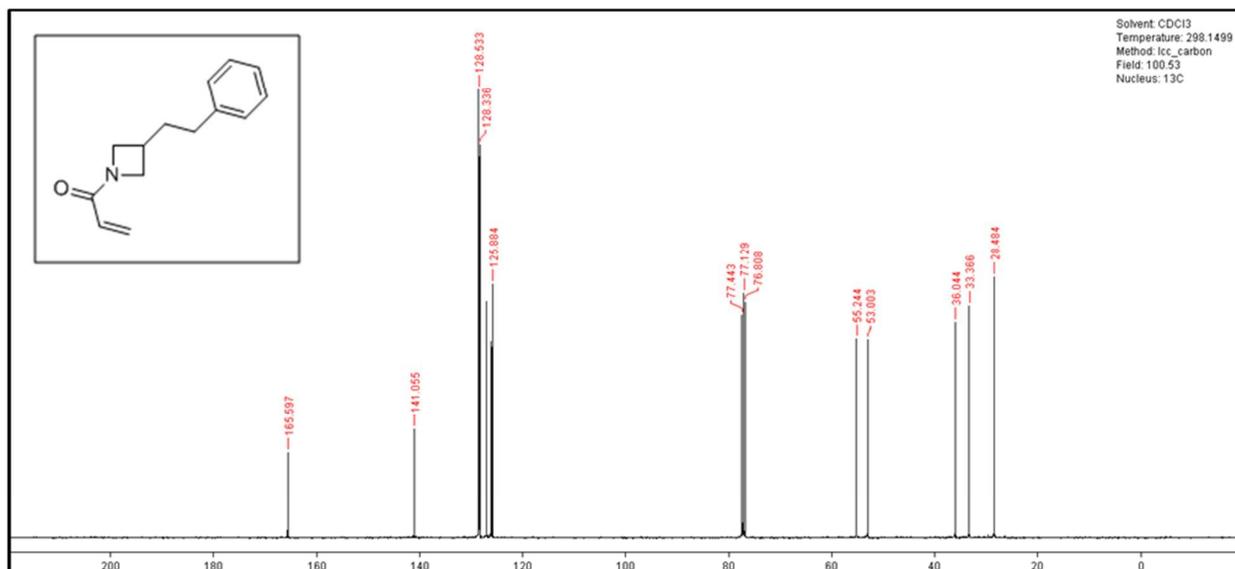
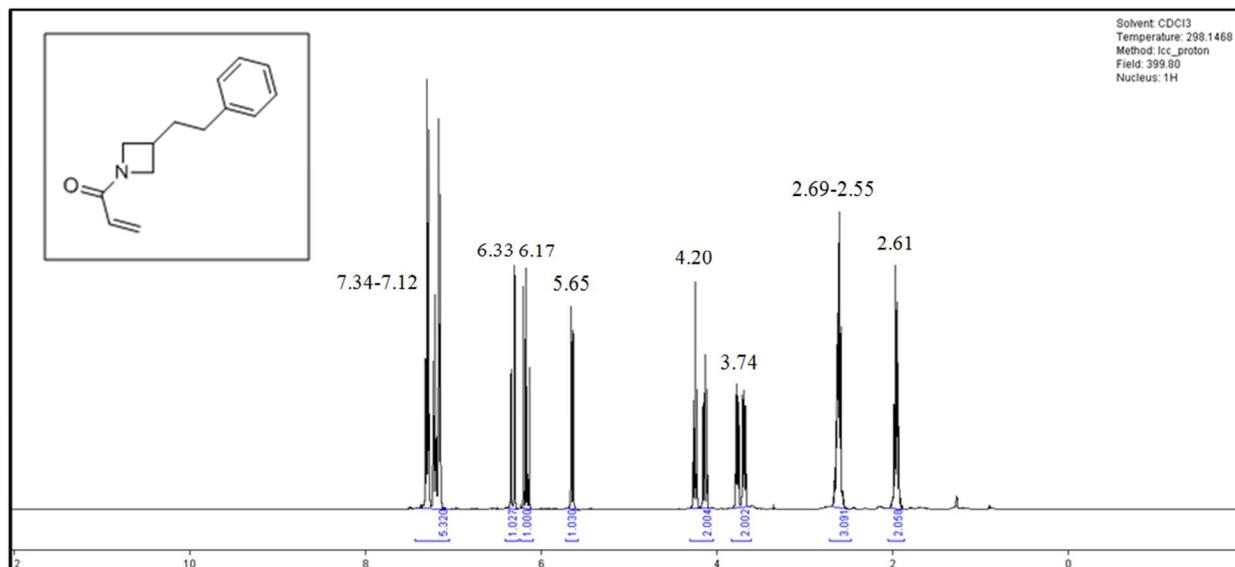
1-(4-benzyl-1,4-diazepan-1-yl)prop-2-en-1-one (8)



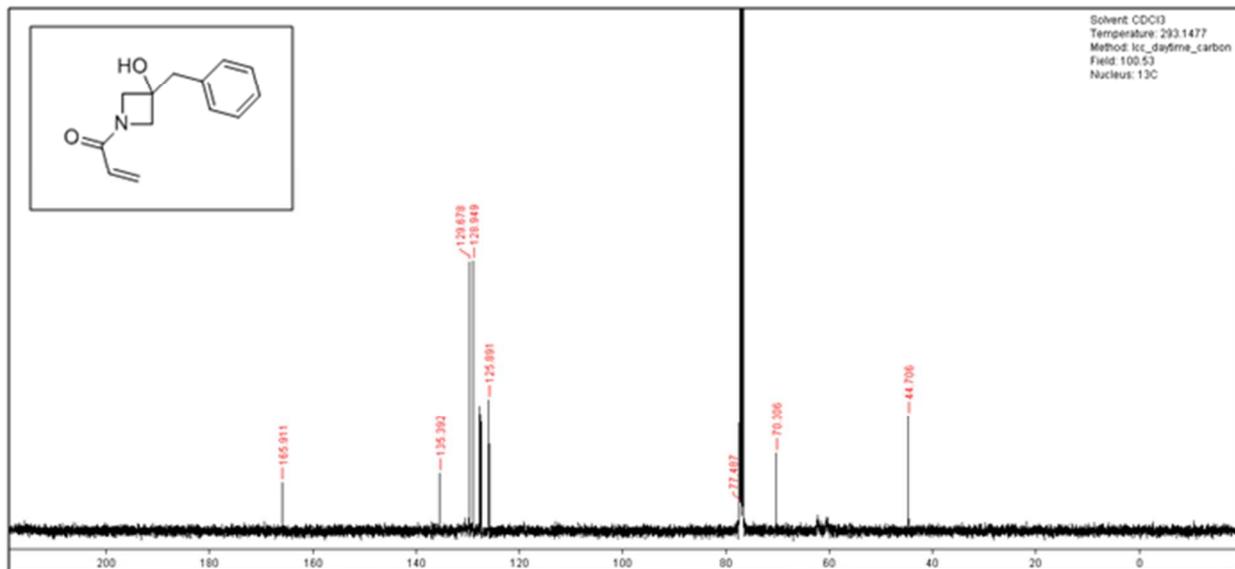
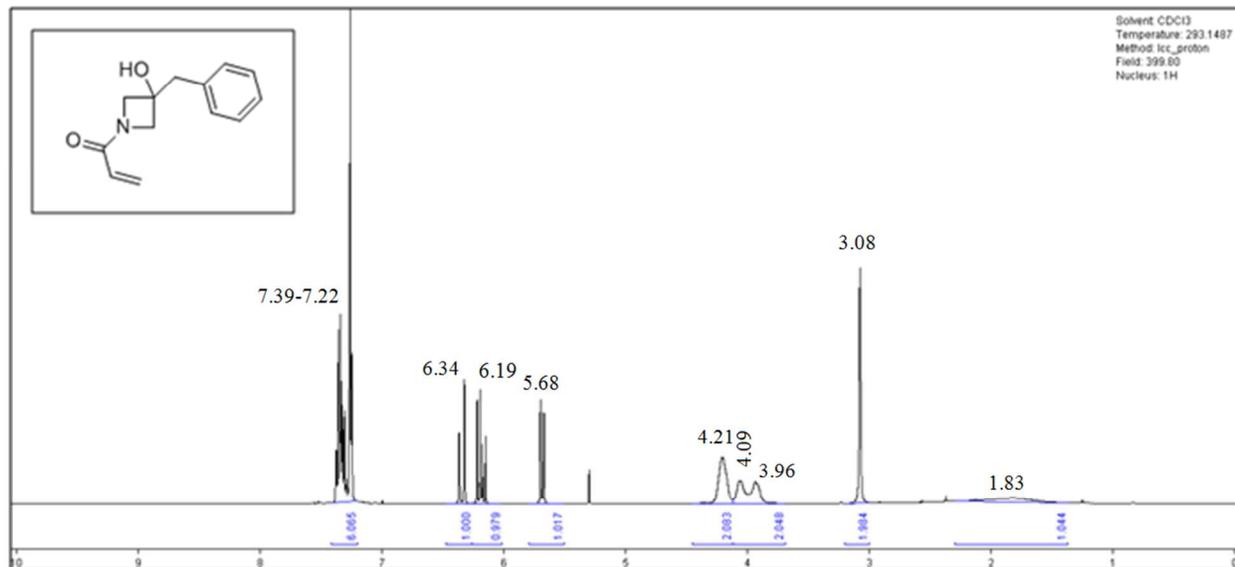
1-(3-(phenoxyethyl)azetidin-1-yl)prop-2-en-1-one (9)



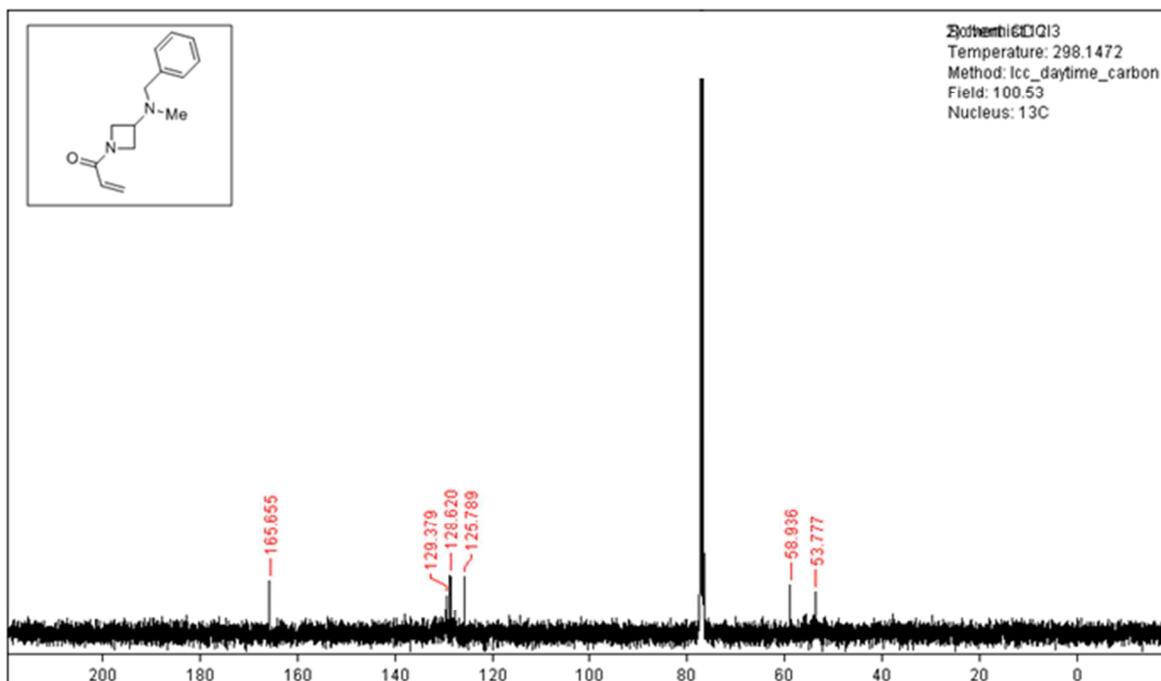
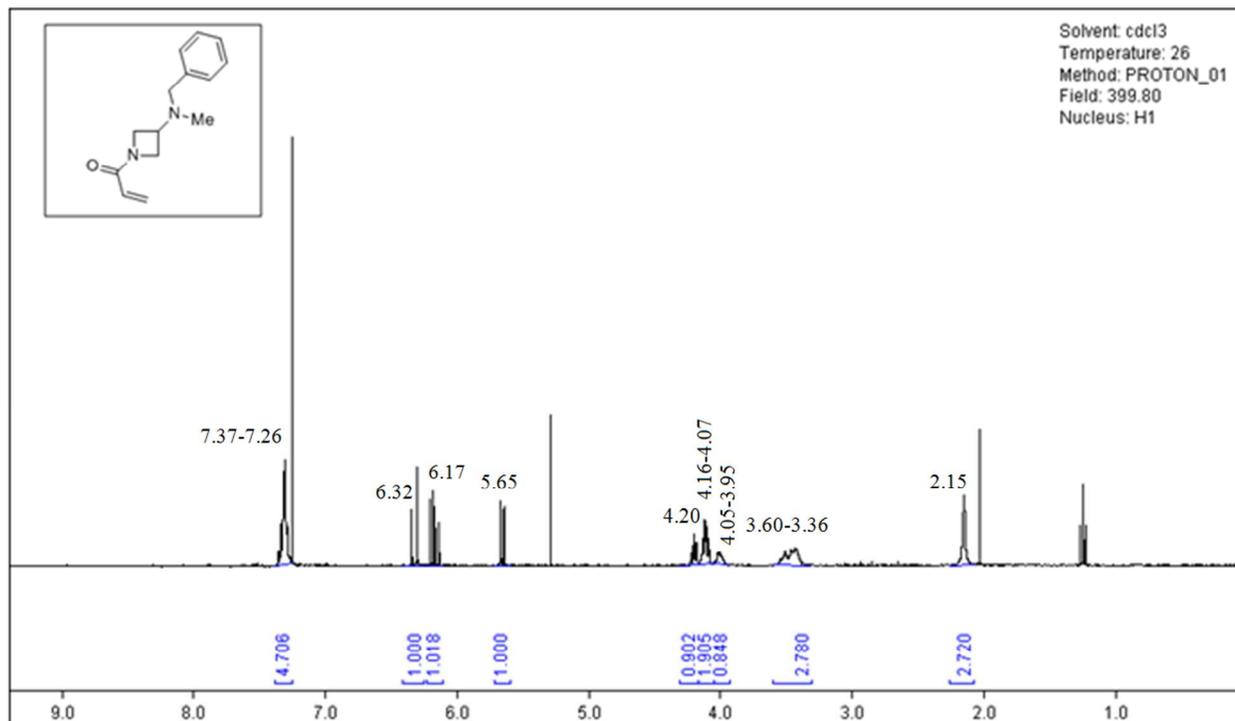
1-(3-phenethylazetididin-1-yl)prop-2-en-1-one (10)



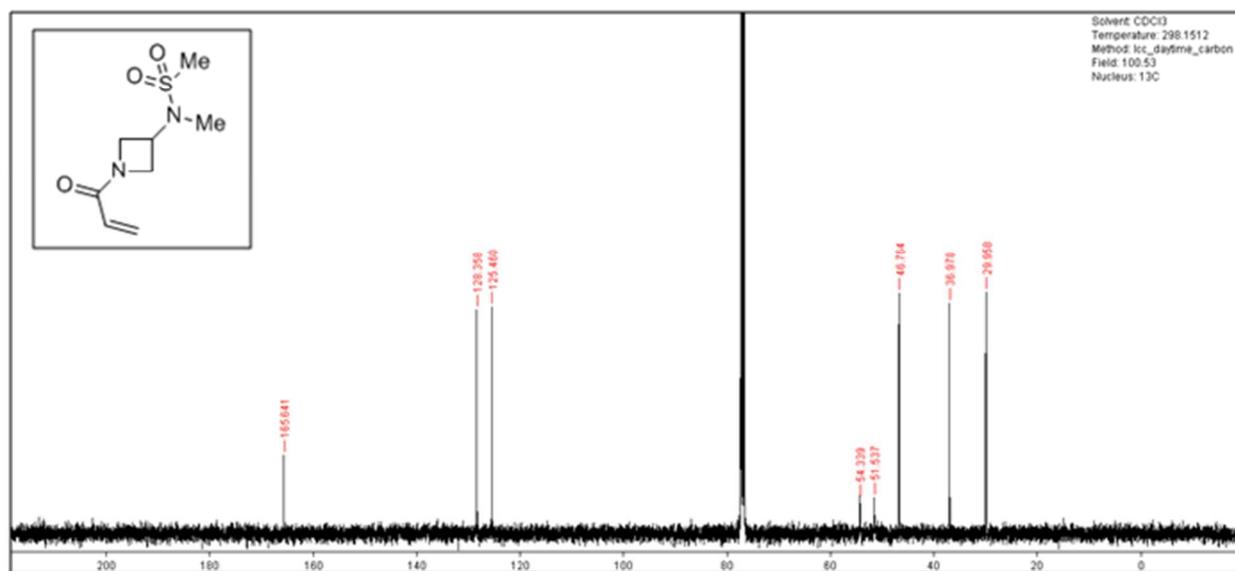
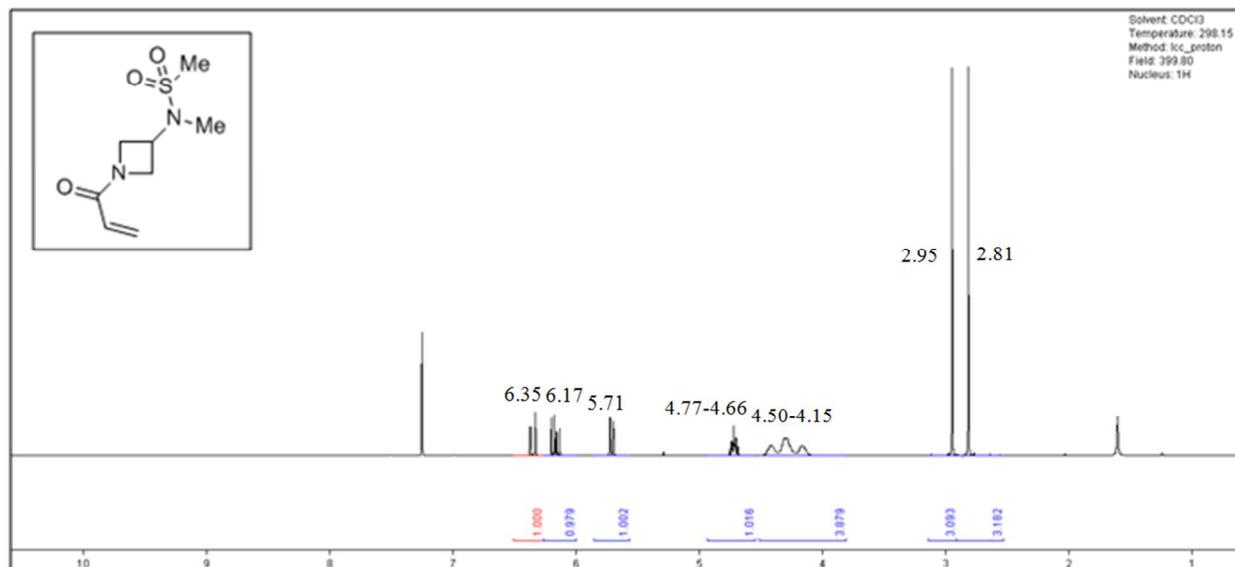
1-(3-benzyl-3-hydroxyazetidin-1-yl)prop-2-en-1-one (11)



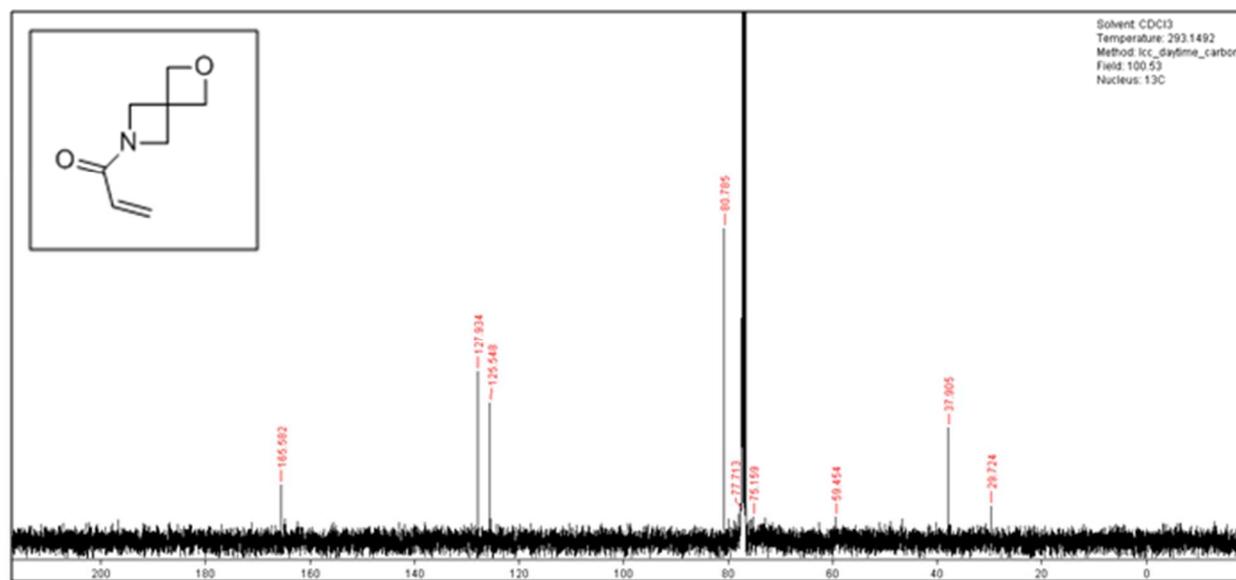
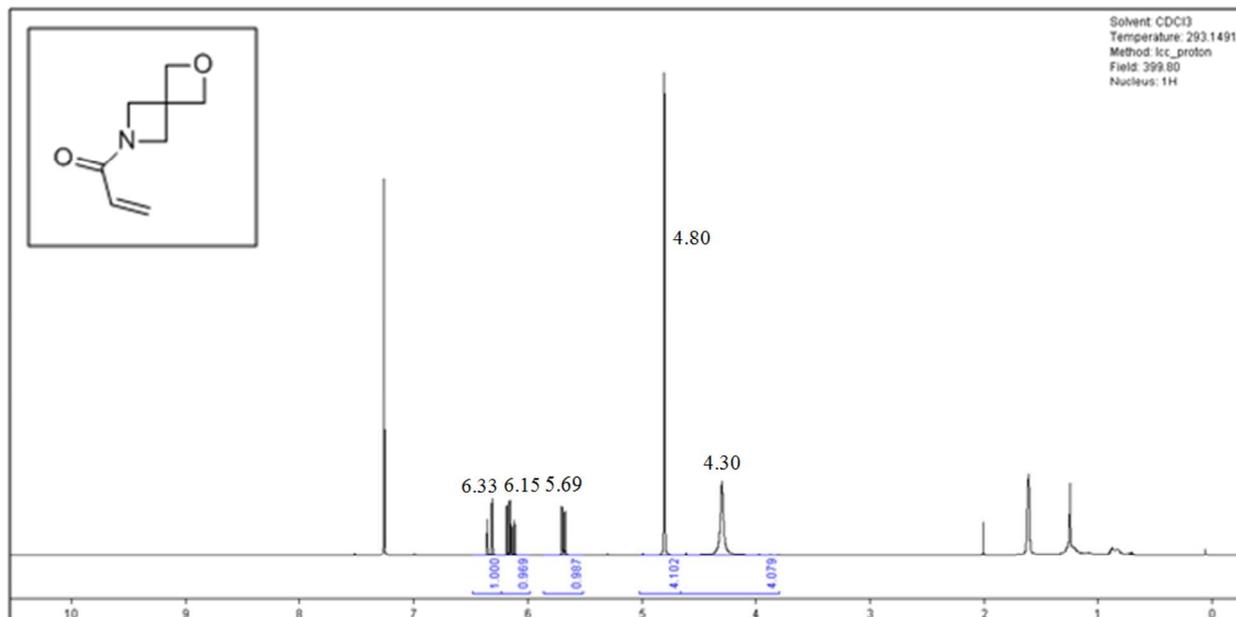
1-(3-(benzyl(methyl)amino)azetidin-1-yl)prop-2-en-1-one (12)



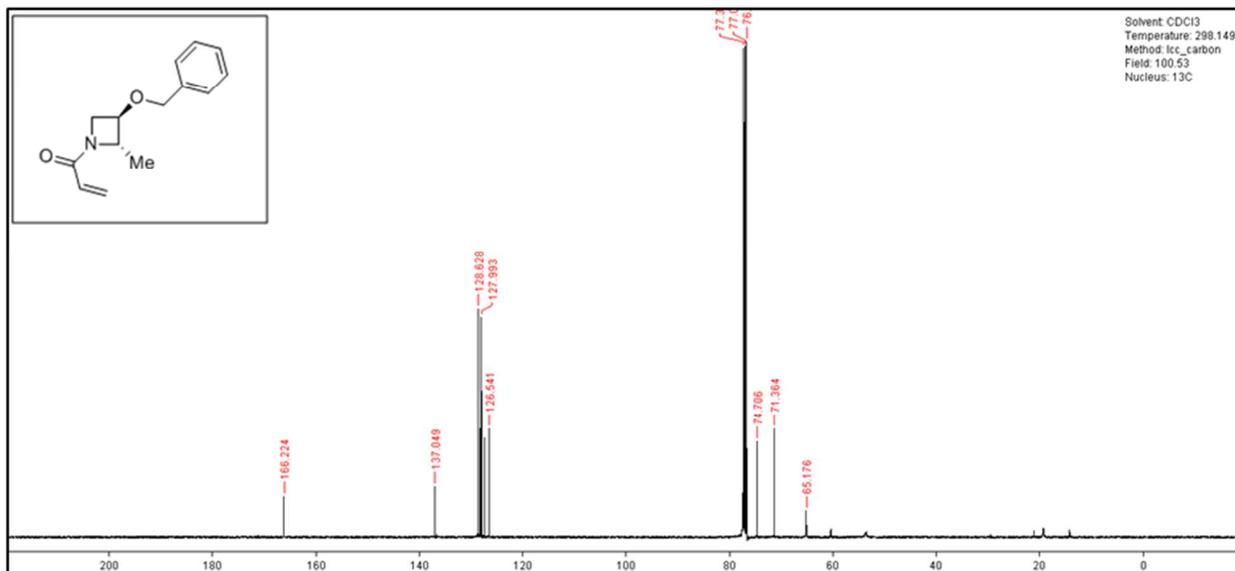
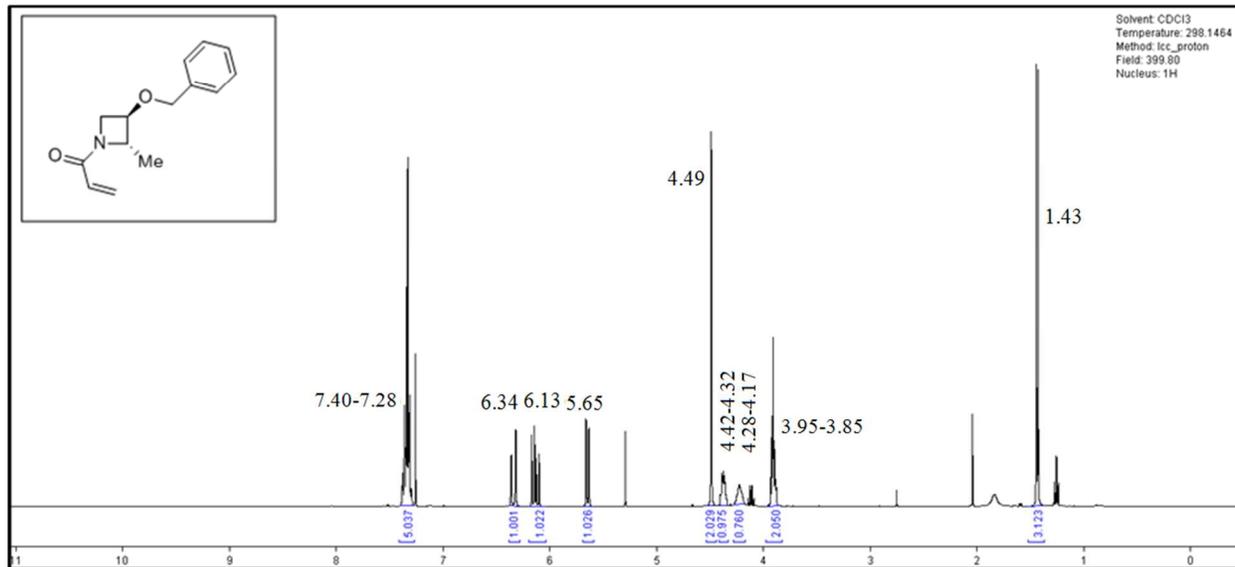
***N*-(1-acryloylazetid-3-yl)-*N*-methylmethanesulfonamide (13)**



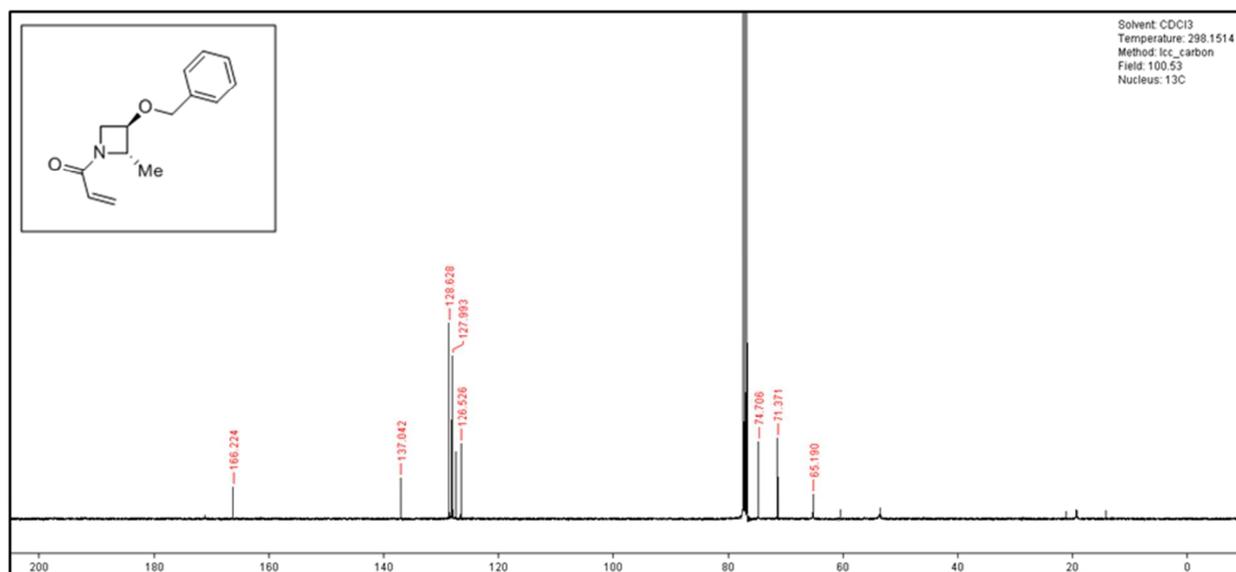
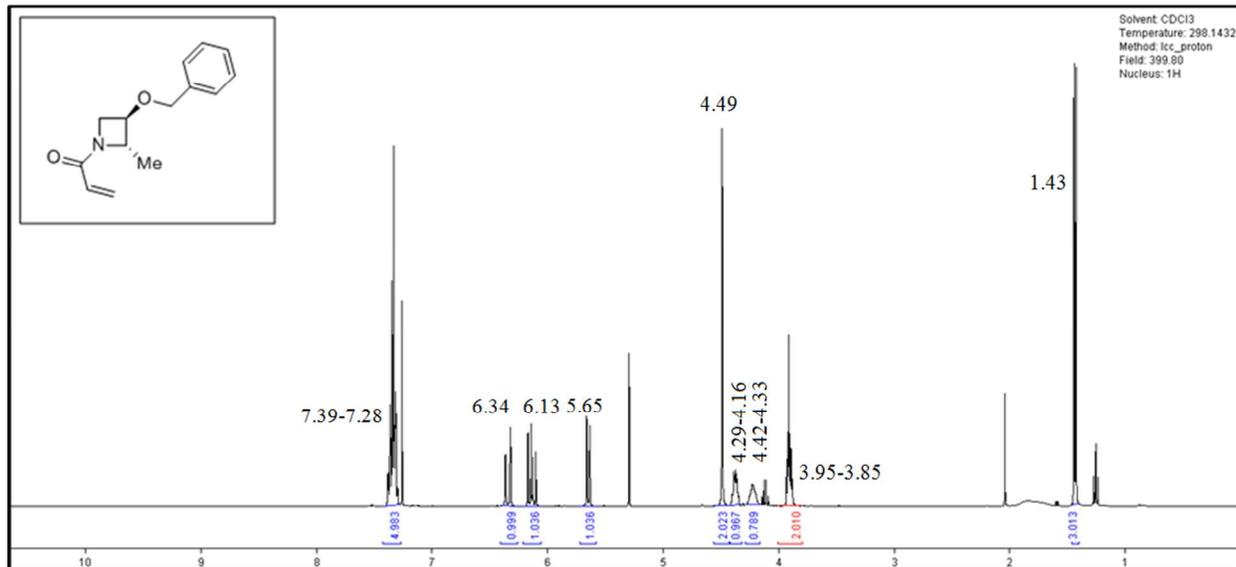
1-(2-oxa-6-azaspiro[3.3]heptan-6-yl)prop-2-en-1-one (14)



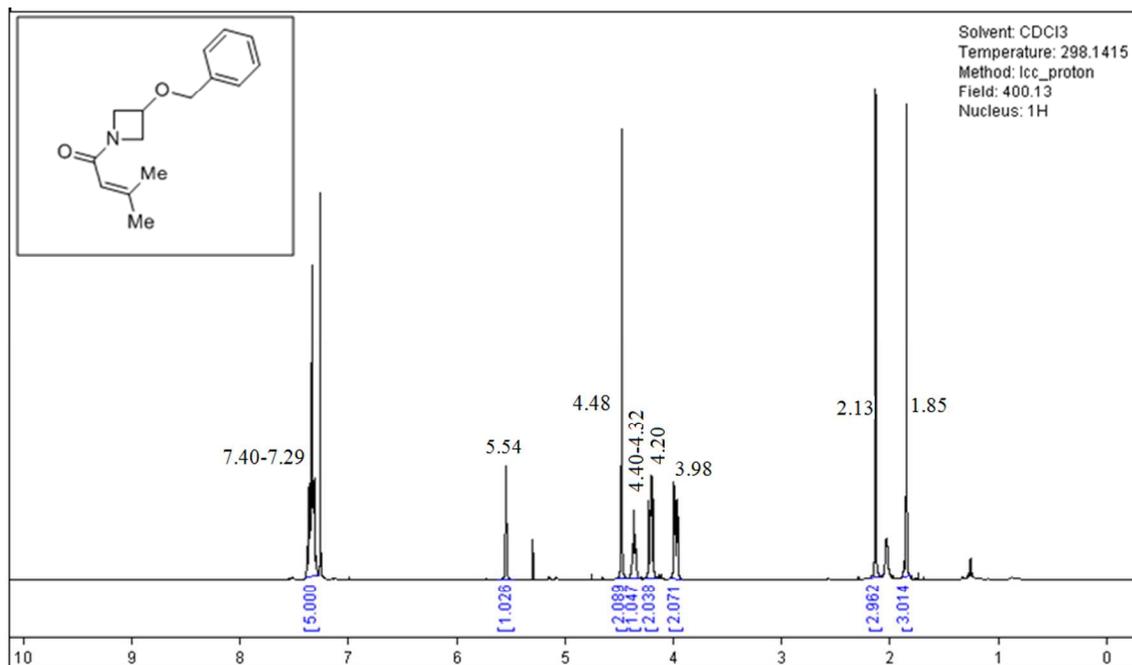
(+)-1-(3-(benzyloxy)-2-methylazetidin-1-yl)prop-2-en-1-one (15 ent 1)



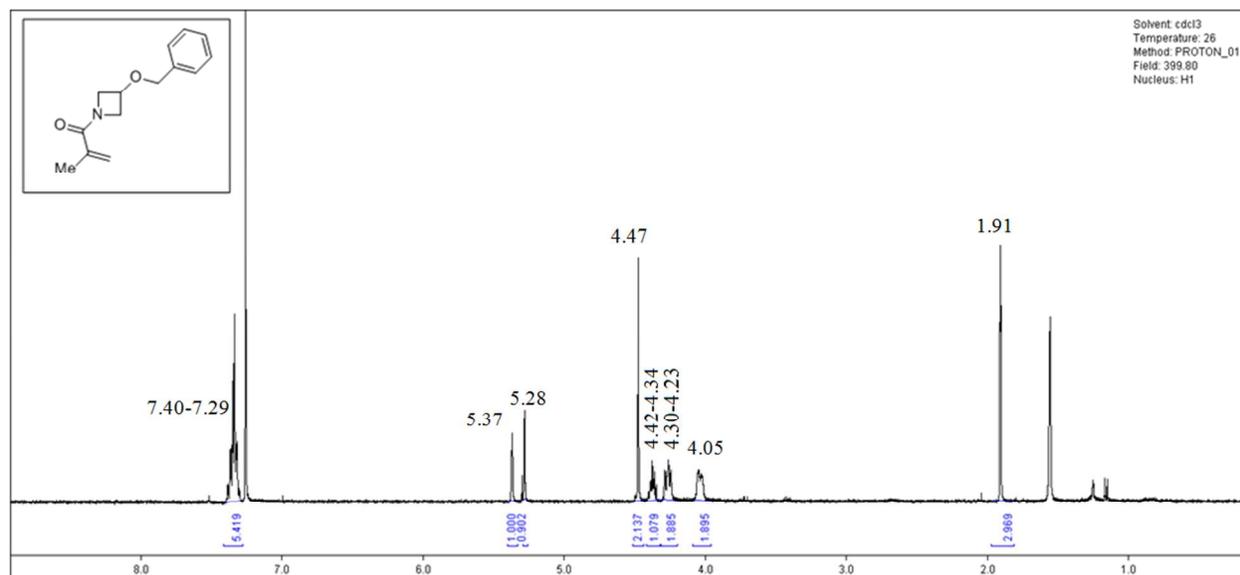
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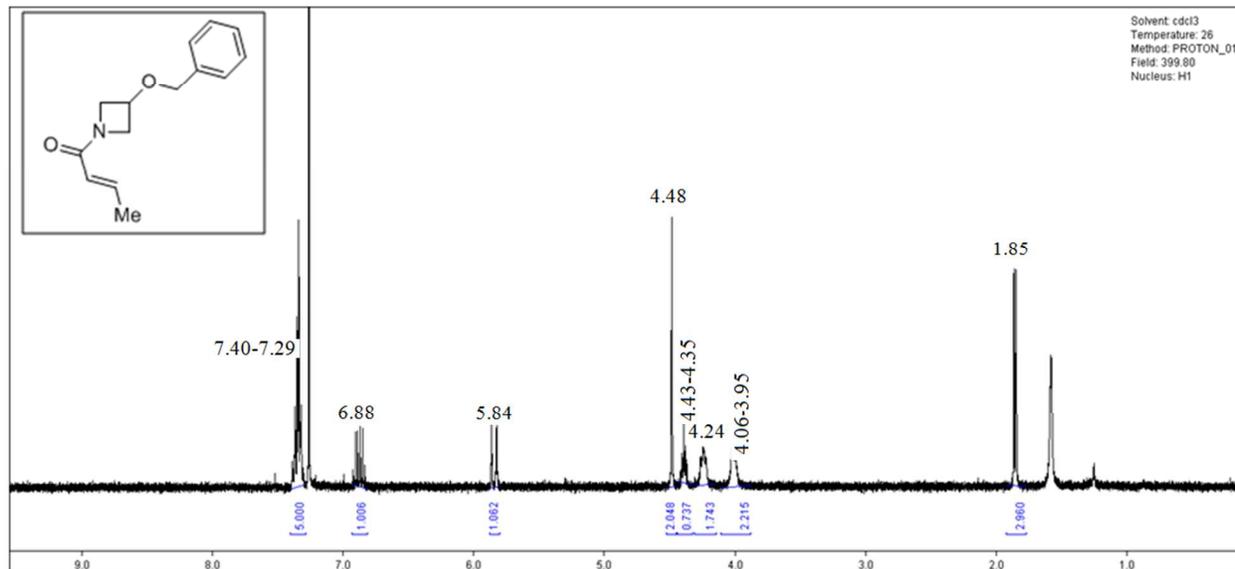
1-(3-(benzyloxy)azetidin-1-yl)-3-methylbut-2-en-1-one (16)



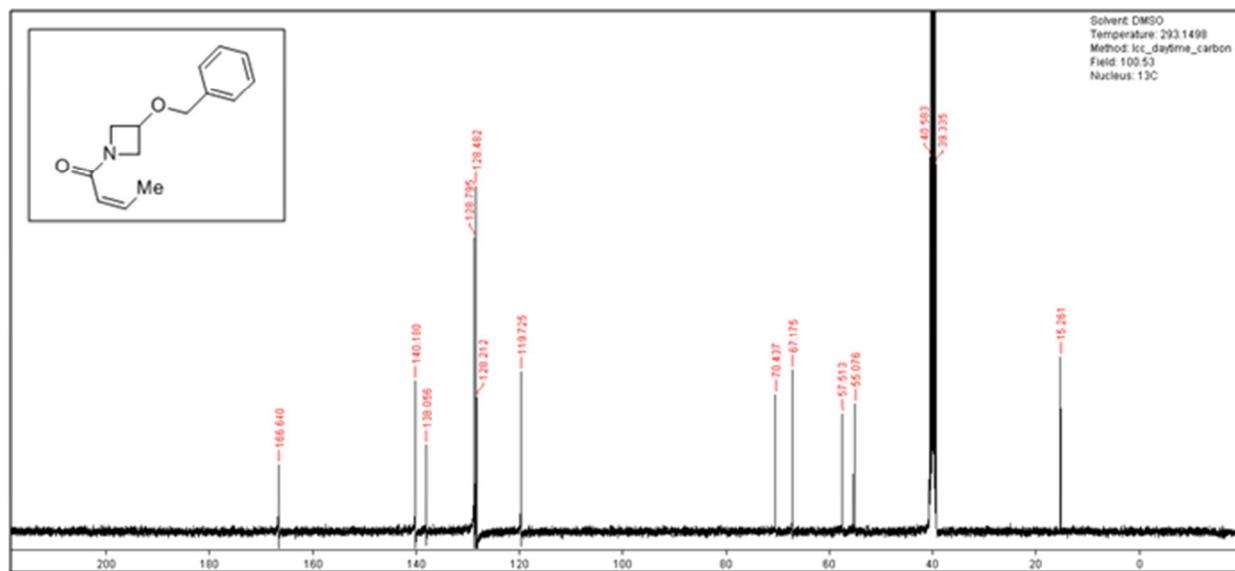
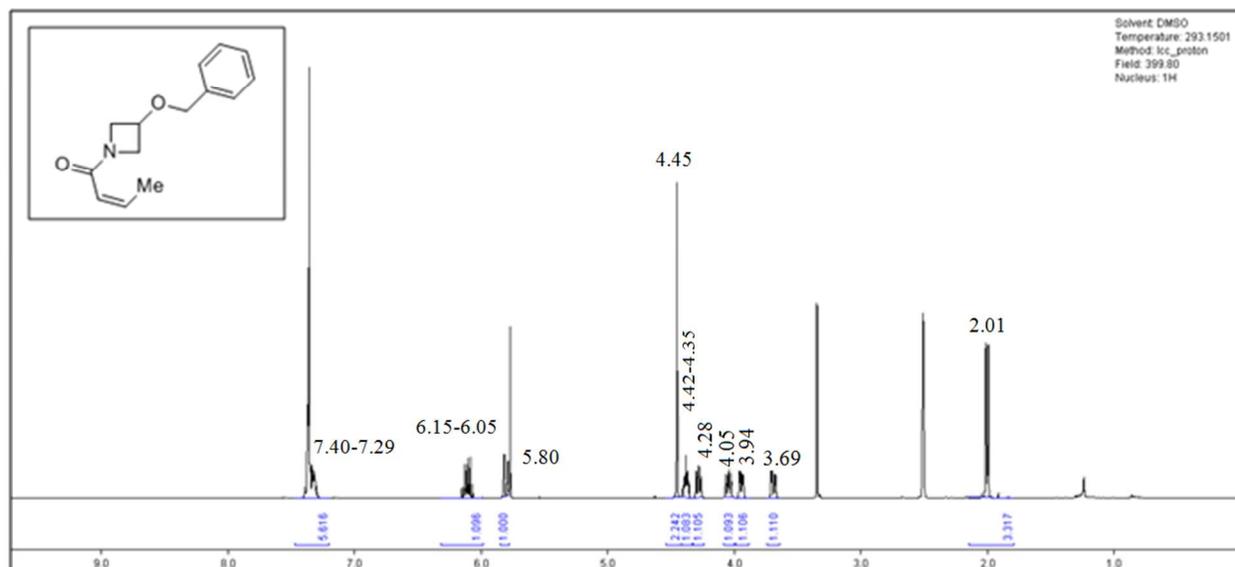
1-(3-(benzyloxy)azetidin-1-yl)-2-methylprop-2-en-1-one (17)



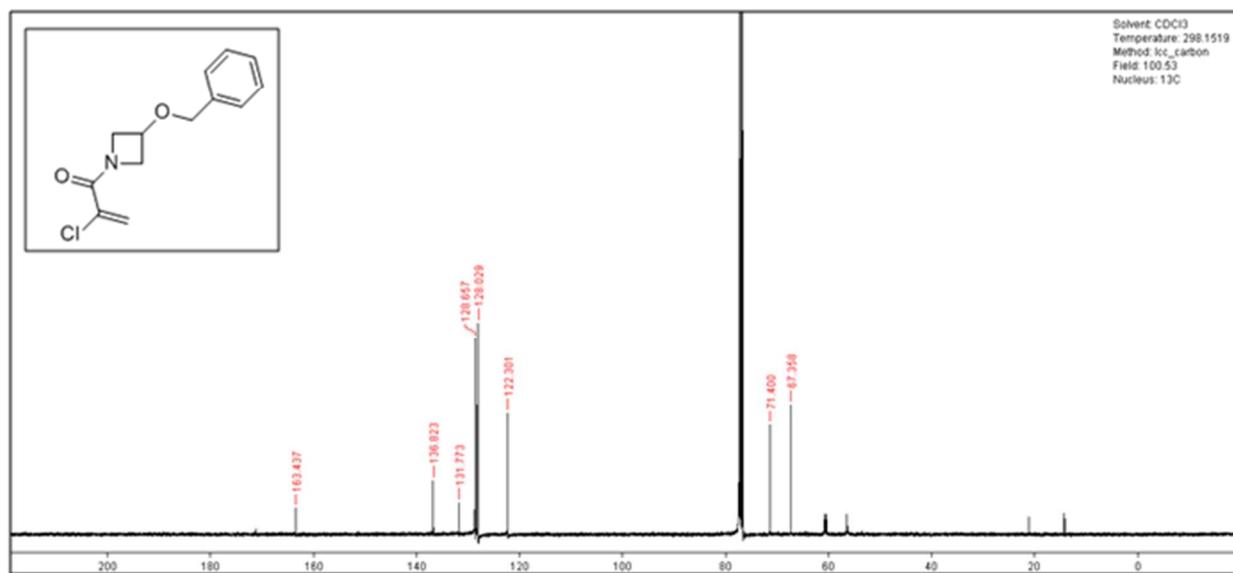
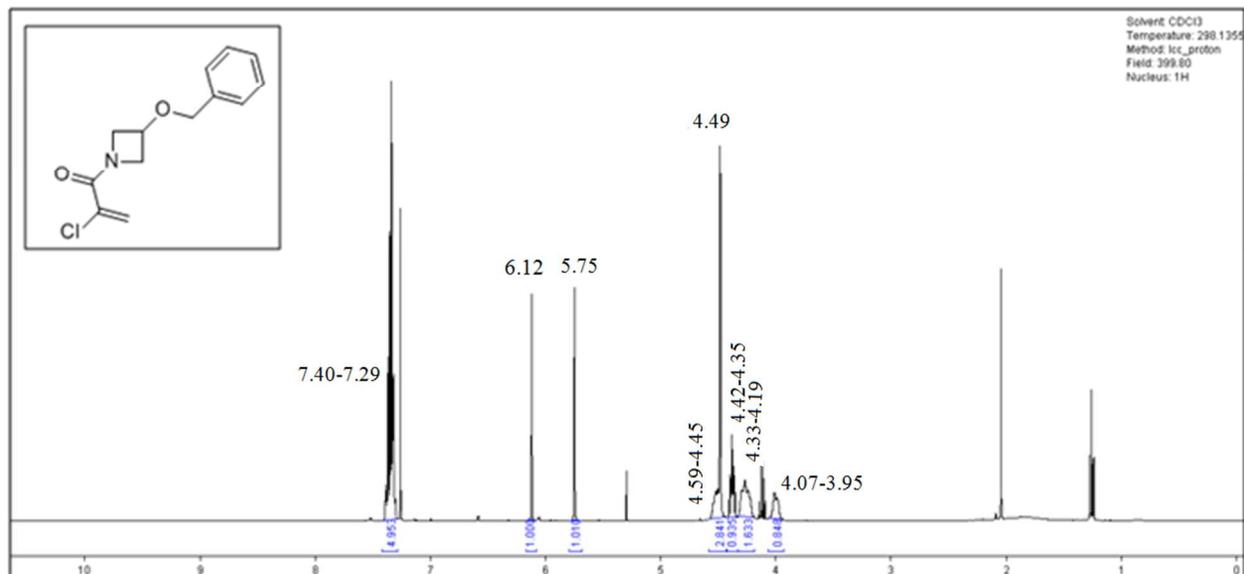
(E)-1-(3-(benzyloxy)azetidin-1-yl)but-2-en-1-one (18)



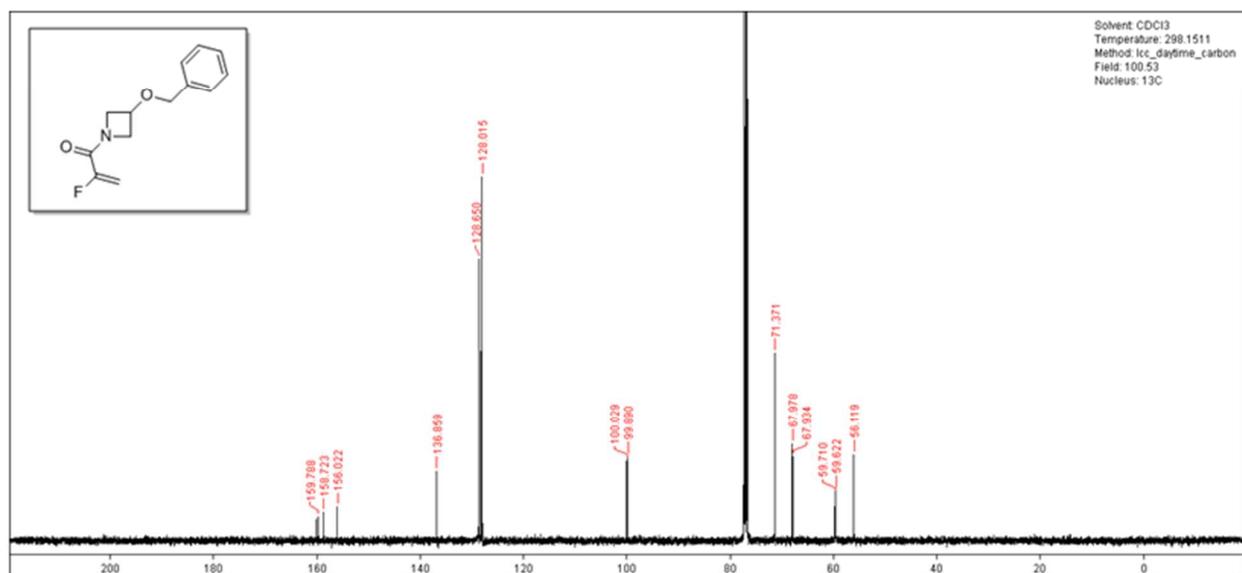
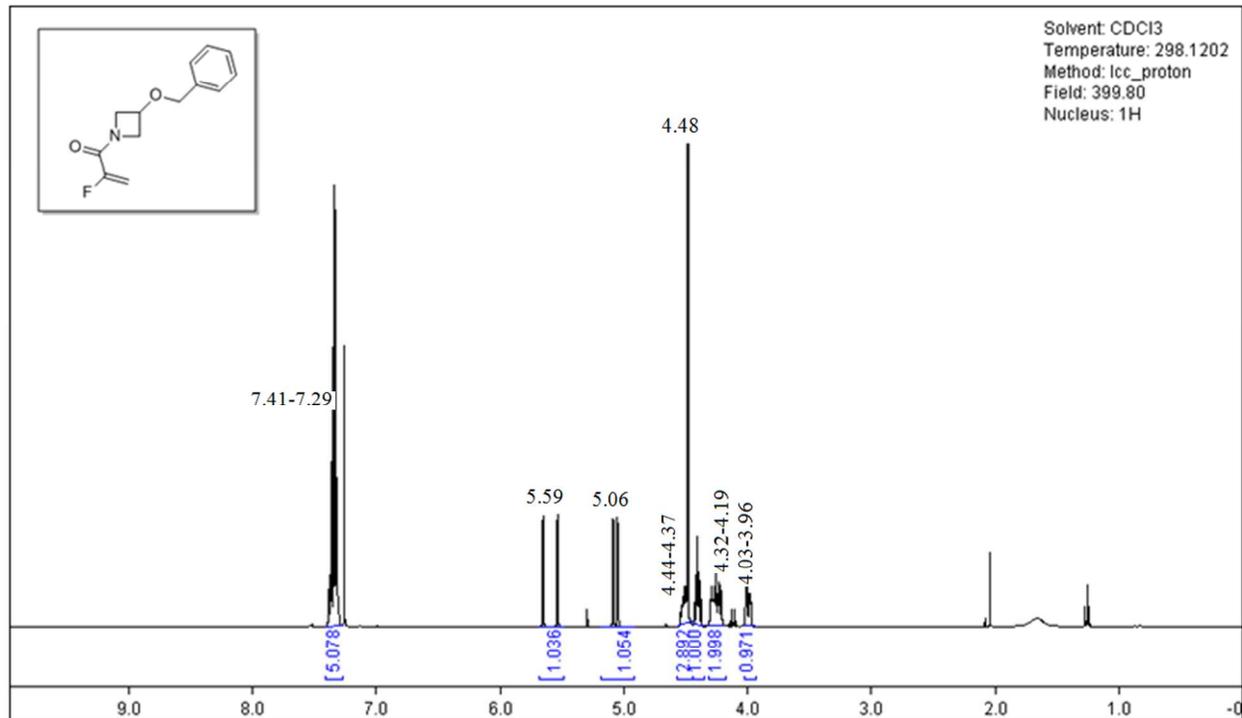
(Z)-1-(3-(benzyloxy)azetidin-1-yl)but-2-en-1-one (19)



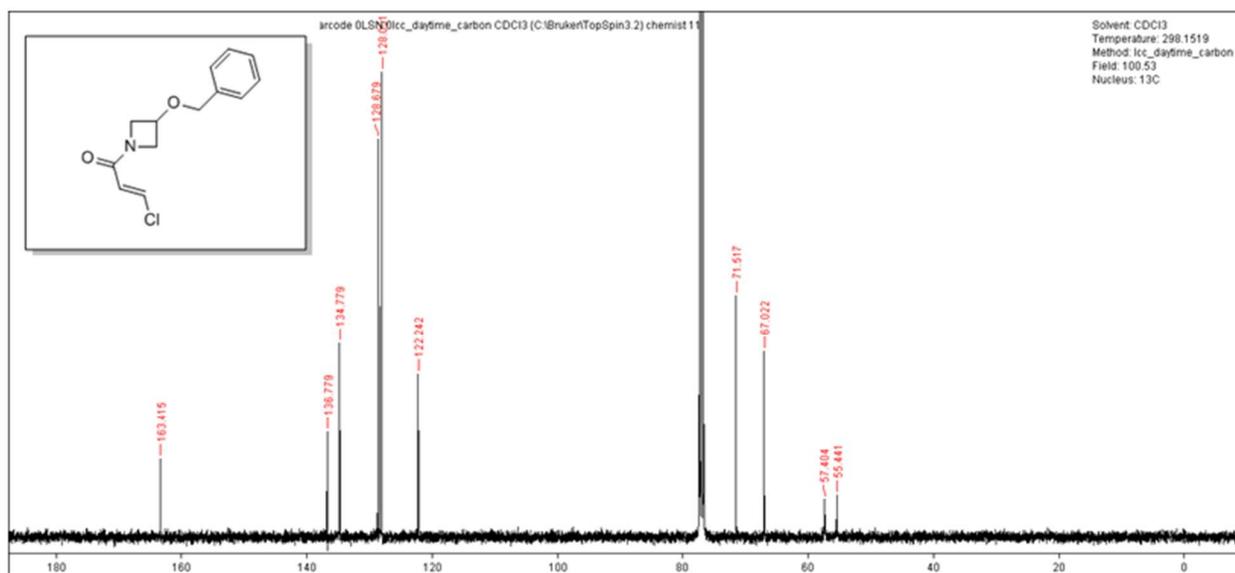
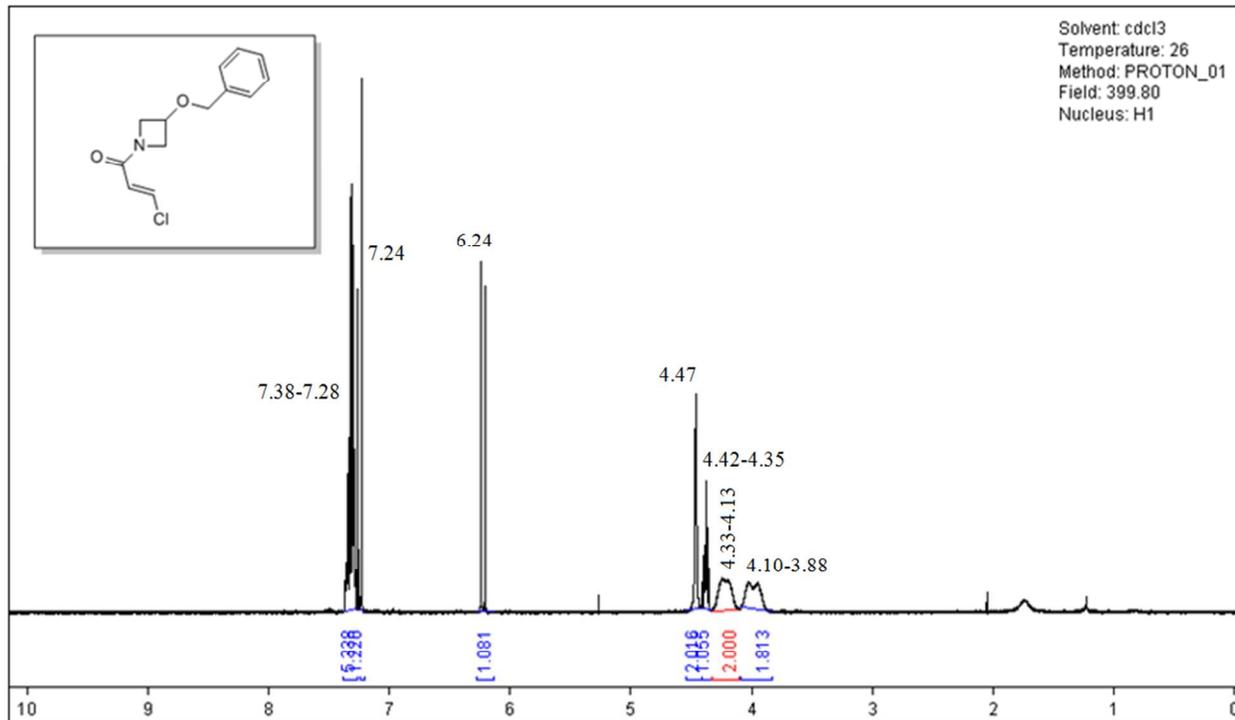
1-(3-(benzyloxy)azetidin-1-yl)-2-chloroprop-2-en-1-one (20)



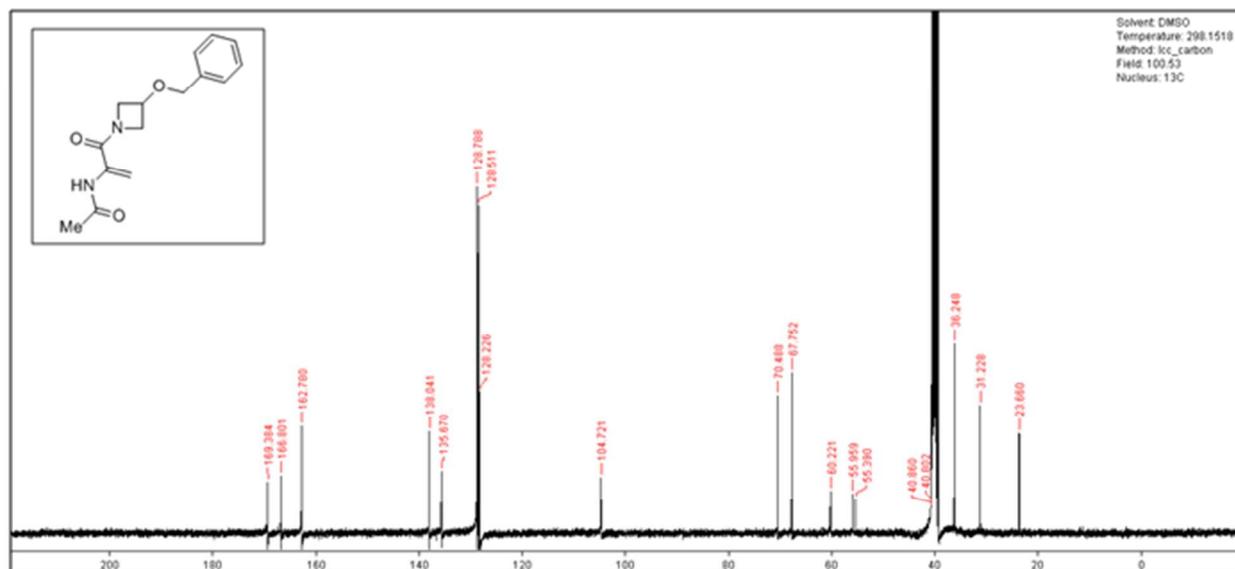
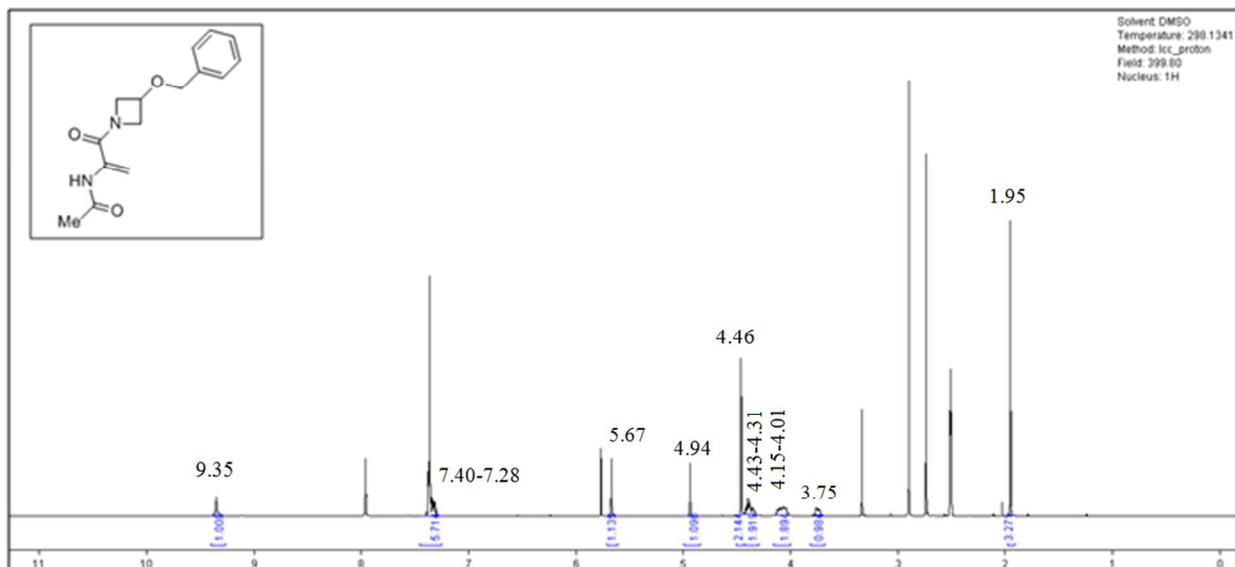
1-(3-(benzyloxy)azetidin-1-yl)-2-fluoroprop-2-en-1-one (21)



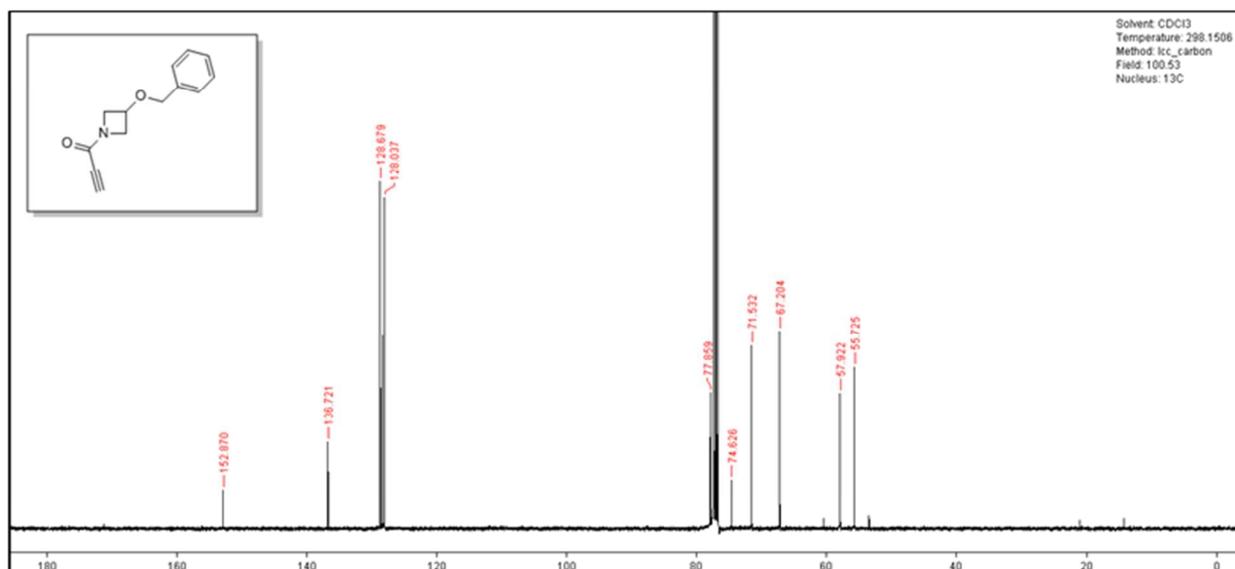
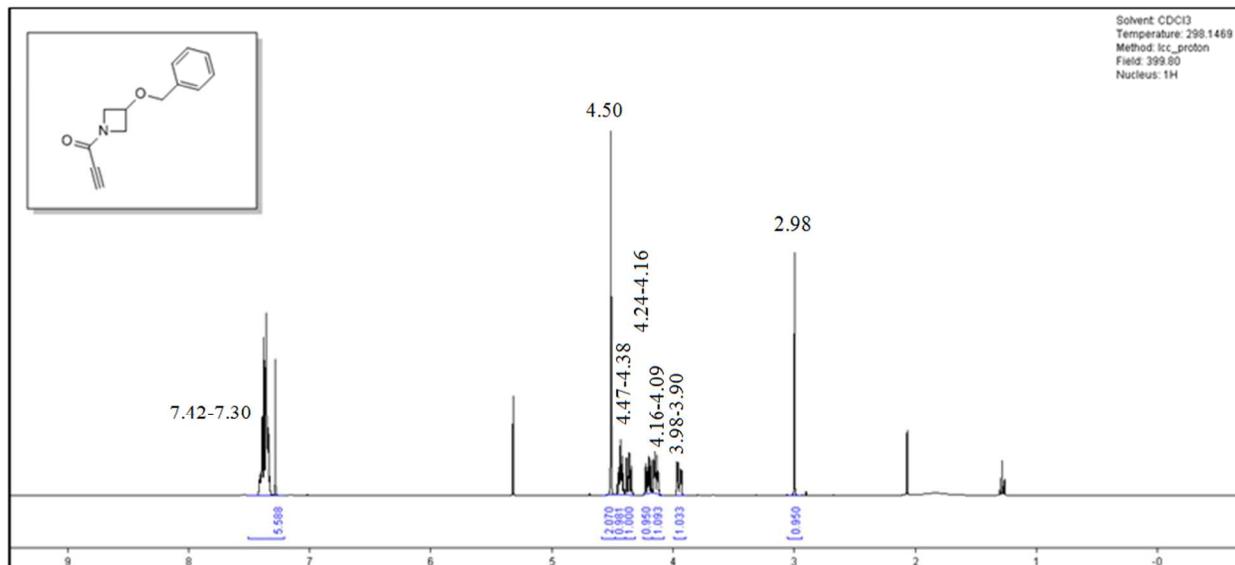
(E)-1-(3-(benzyloxy)azetidin-1-yl)-3-chloroprop-2-en-1-one (22)



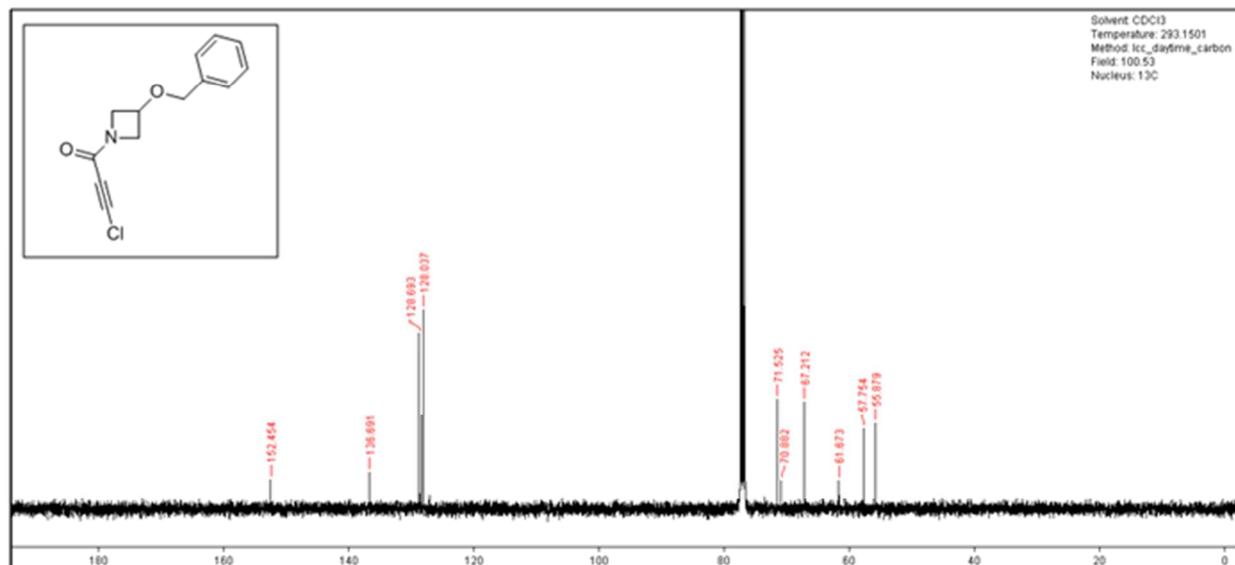
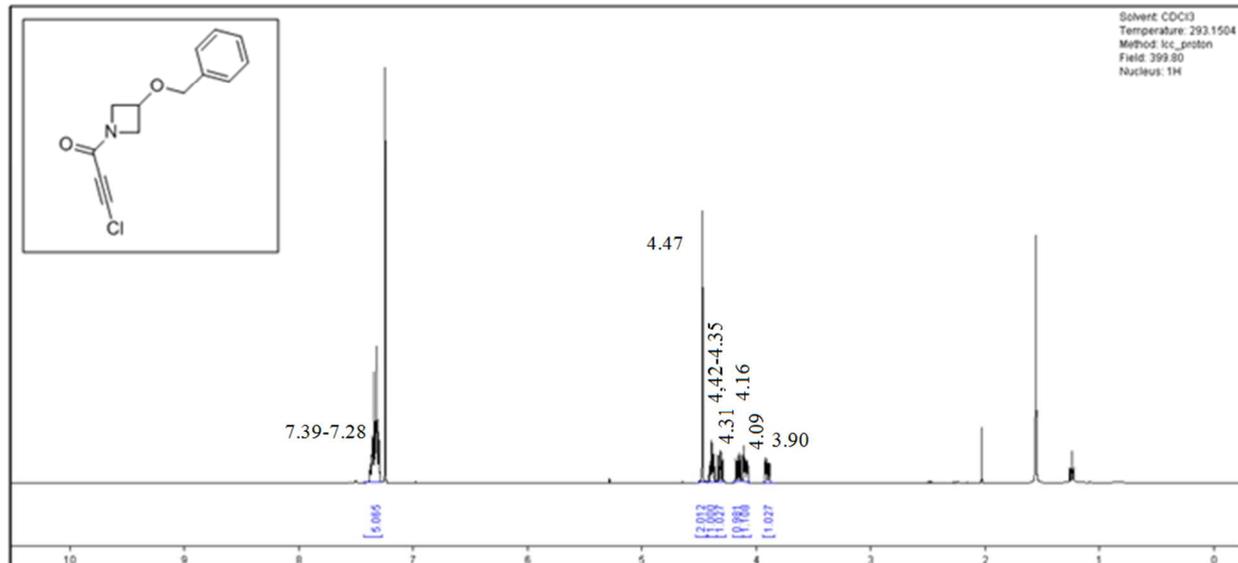
N-(3-(3-(benzyloxy)azetidin-1-yl)-3-oxoprop-1-en-2-yl)acetamide (23)



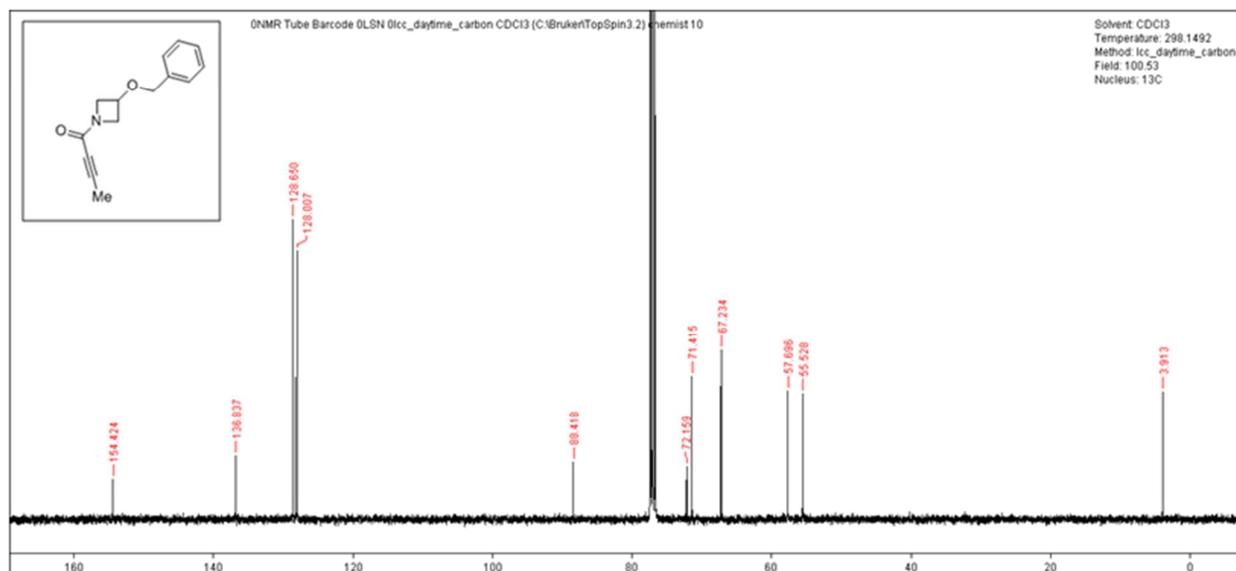
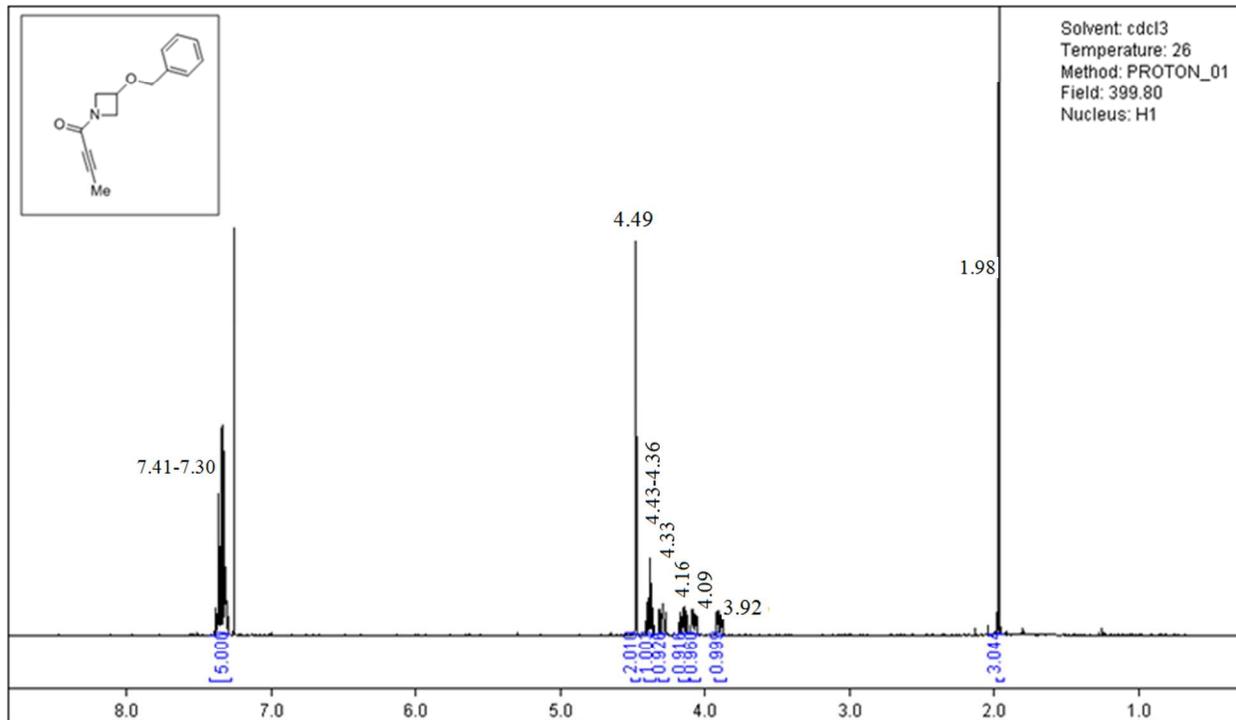
1-(3-(benzyloxy)azetidin-1-yl)prop-2-yn-1-one (24)



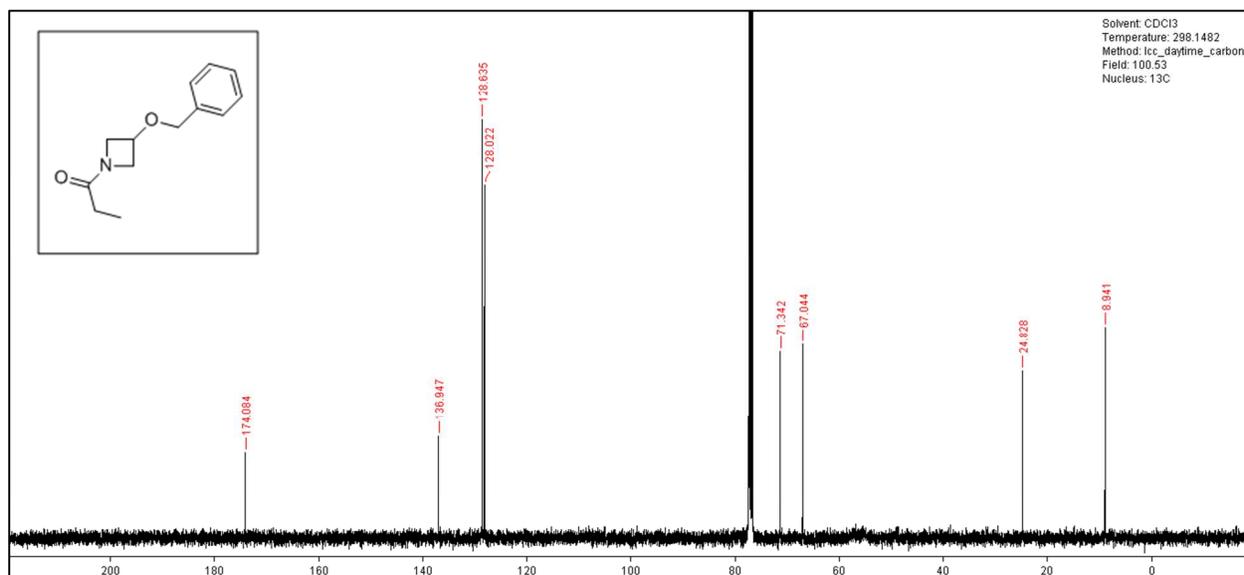
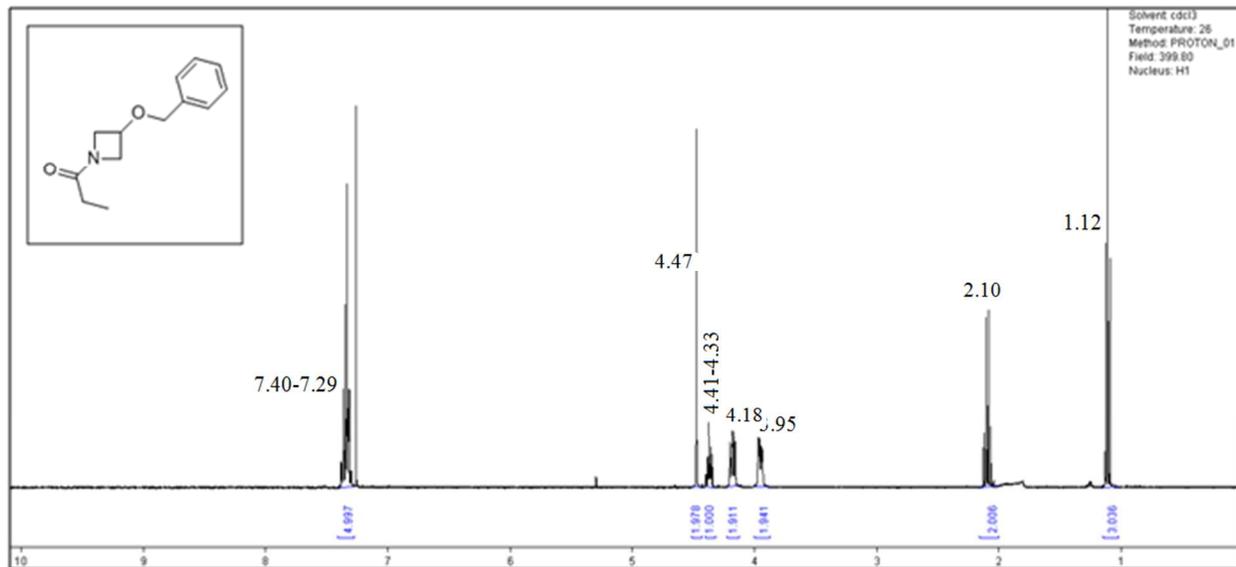
1-(3-(benzyloxy)azetid-1-yl)-3-chloroprop-2-yn-1-one (25)



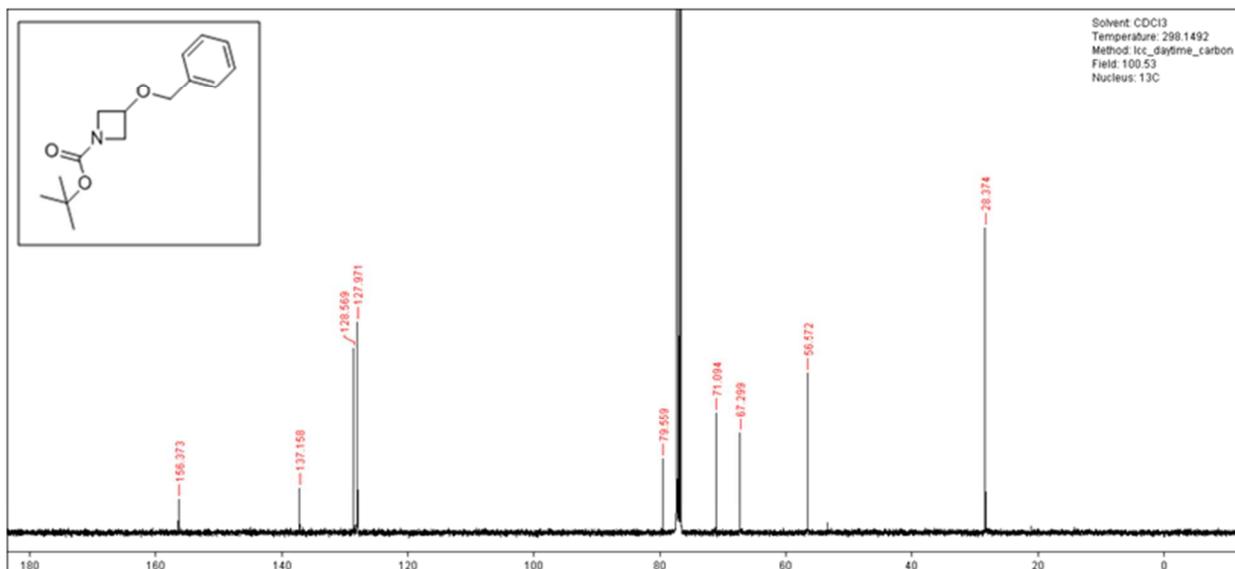
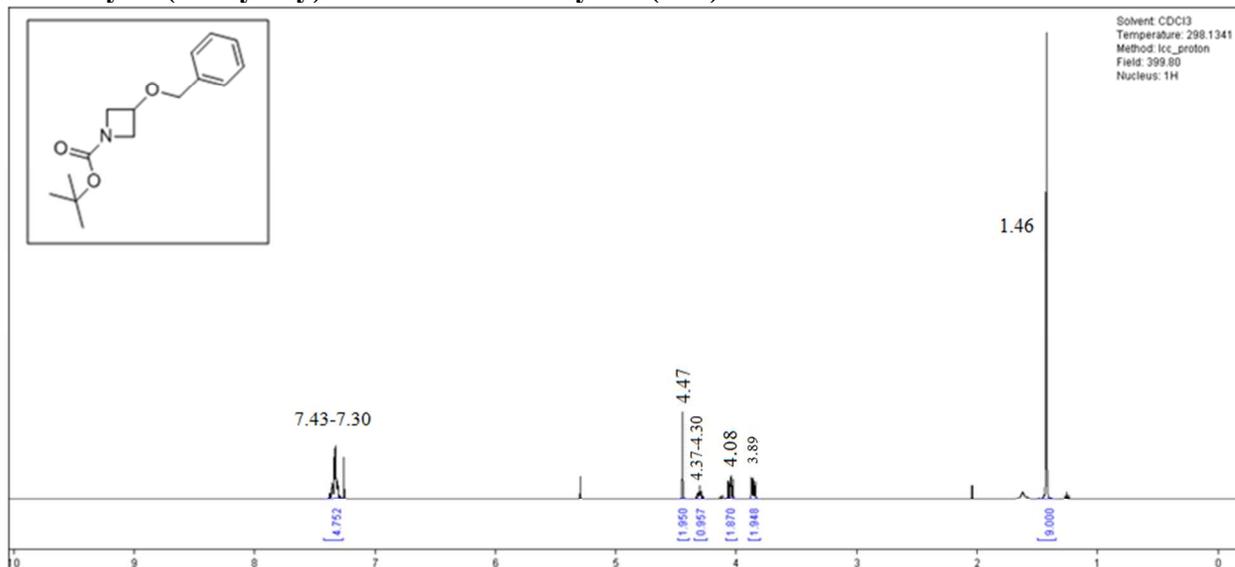
1-(3-(benzyloxy)azetidin-1-yl)but-2-yn-1-one (26)



1-(3-(benzyloxy)azetidin-1-yl)propan-1-one (S18, also dihydro-1)



tert-butyl 3-(benzyloxy)azetidine-1-carboxylate (S19)



^1H -NMR spectra of 24 and glutathione (GSH) in 20 mM phosphate buffer (pH 7.4)

