

Supporting Information for:

Trapping of carbolithiation-derived tertiary benzylic α -lithio piperidines with carbon electrophiles: Controlling the formation of α -amino quaternary and vicinal stereocenters

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Experimental Section

All experiments involving organolithium reagents were carried out under an inert atmosphere of argon or nitrogen using freshly distilled solvents. Et₂O and THF were distilled either from sodium benzophenone ketyl or pre-dried by degassing with argon for 60 min and passed through activated alumina columns. All electrophile reagents that were not newly purchased from commercial suppliers were distilled immediately before use. Column chromatography was performed on silica gel (60Å, 230-400 mesh). Thin-layer chromatography (TLC) was performed using Silicycle Siliplate™ glass backed plates (250 μm thickness, 60 Å porosity, F-254 indicator) and visualized using UV (254 nm) or CAM, *p*-anisaldehyde, or KMnO₄ stain. Unless otherwise indicated, ¹H, ¹³C, and DEPT-135 NMR, COSY 45, HMQC, and NOESY spectra were acquired using C₆D₆ or CDCl₃ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm). HRMS-EI⁺ data were obtained using either electrospray ionization (ESI) or electron impact (EI) techniques. High-resolution ESI was obtained on an LTQ-FT (ion trap; analyzed using Excalibur). High resolution EI was obtained on an Autospec (magnetic sector; analyzed using MassLynx).

Synthesis of Starting materials

N-Boc-piperidine was prepared according to a literature procedure reported by O'Brien.¹ It is also commercially available.

N-Boc-2-methylpiperidine was synthesized as previously reported.²

All α-aryl enecarbamates were synthesized using our recently developed reductive cross-coupling methodology.³

The substituted lactam precursors used in the synthesis of α-aryl enecarbamates were synthesized by Ru-catalyzed α-oxidation of the saturated piperidine.⁴

The Boc-protected *cis*-2,4-dimethylpiperidine precursor to *cis*-**30** was prepared using the method of Baudoin.⁵

General Procedure A: HMPA-mediated conjugate Addition followed by protonation

To an oven-dried, septum-capped, round-bottomed flask equipped with a stir bar was added a solution of the 2-substituted enecarbamate (1.0 equiv) in THF (5 mL) nitrogen, in the presence of HMPA (1.2 equiv). The mixture was cooled to -78 °C and the organolithium (2 – 3 equiv) was

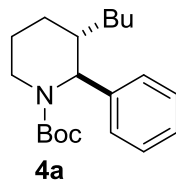
added slowly. After 5 min at this temperature, the solution was transferred to a bath at $-30\text{ }^{\circ}\text{C}$ (internal temperature) and stirred for 2 to 5 h. After complete consumption of the starting material (as judged by LCMS/GCMS and TLC monitoring), the solution was quenched with methanol (0.5 mL). The mixture was warmed to room temperature and *sat.* NH_4Cl was added. After diluting with Et_2O , the layers were separated and the aqueous layer was extracted twice with Et_2O . The combined organic layers were dried over Na_2SO_4 , filtered, and evaporated to obtain the crude product, which was purified as specified.

General Procedure B: HMPA-mediated conjugate Addition followed by direct trapping with a carbon electrophile

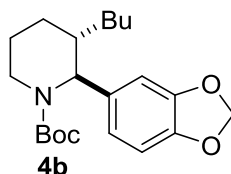
To an oven-dried, septum-capped, round-bottomed flask equipped with a stir bar was added a solution of the 2-substituted enecarbamate (1.0 equiv) in THF (5 mL) nitrogen, in the presence of HMPA (1.2 equiv). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and the organolithium (2 – 3 equiv) was added slowly. After 5 min at this temperature, the solution was transferred to a bath at $-30\text{ }^{\circ}\text{C}$ (internal temperature) and stirred for 2 to 5 h. After complete consumption of the starting material (as judged by LCMS/GCMS and TLC monitoring), the solution was returned to the bath at $-78\text{ }^{\circ}\text{C}$ and trapped with the desired electrophile (3 – 6 equiv). The mixture was slowly warmed to room temperature overnight (in the case of highly reactive electrophiles, it was kept cold) and *sat.* NH_4Cl was added. After diluting with Et_2O , the layers were separated and the aqueous layer was extracted twice with Et_2O . The combined organic layers were dried over Na_2SO_4 , filtered, and evaporated to obtain the crude product, which was purified as specified.

General Procedure C: Removal of Boc group

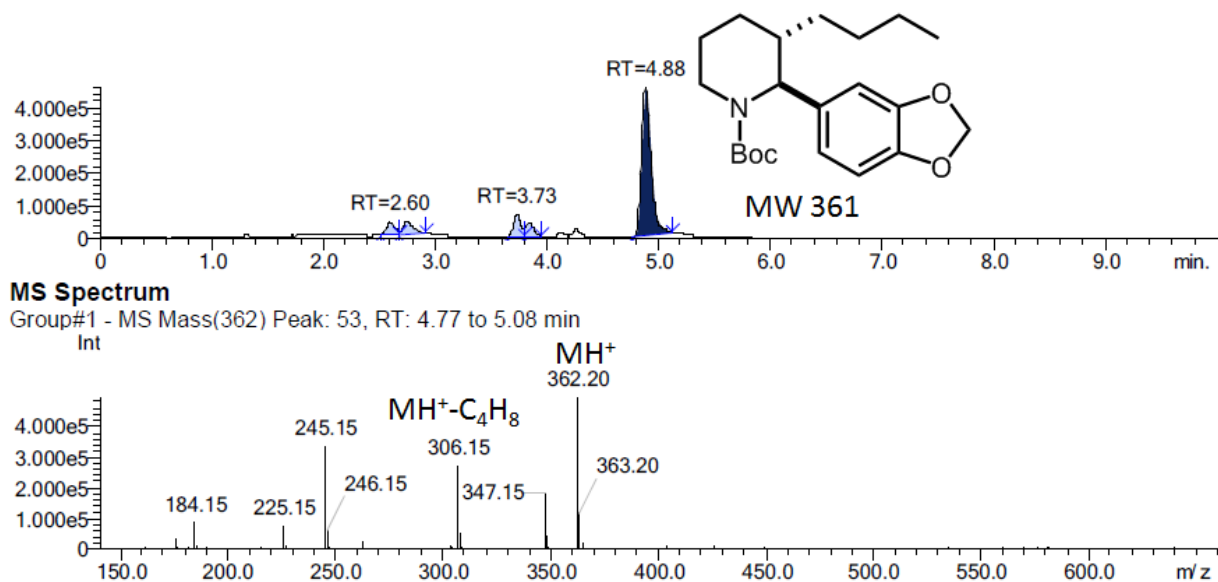
To the *N*-Boc-compound (1.0 equiv) dissolved in freshly distilled CH_2Cl_2 (0.50 M), was added $\text{CF}_3\text{CO}_2\text{H}$ (3 equiv) under argon at $0\text{ }^{\circ}\text{C}$. The resulting solution was stirred for 5 h at this temperature and concentrated in vacuo to obtain the salt. The salt was basified to pH 10–12 with 20% $\text{NaOH}_{(\text{aq})}$. The aqueous layer was extracted with EtOAc (two times) and the combined organic layers were washed with brine, dried over K_2CO_3 and concentrated under reduced pressure to give a residue. The residue was purified by flash chromatography on silica (*pretreated with 1% Et₃N*) eluting with Hexane/ AcOEt (30:1) +1% Et_3N .

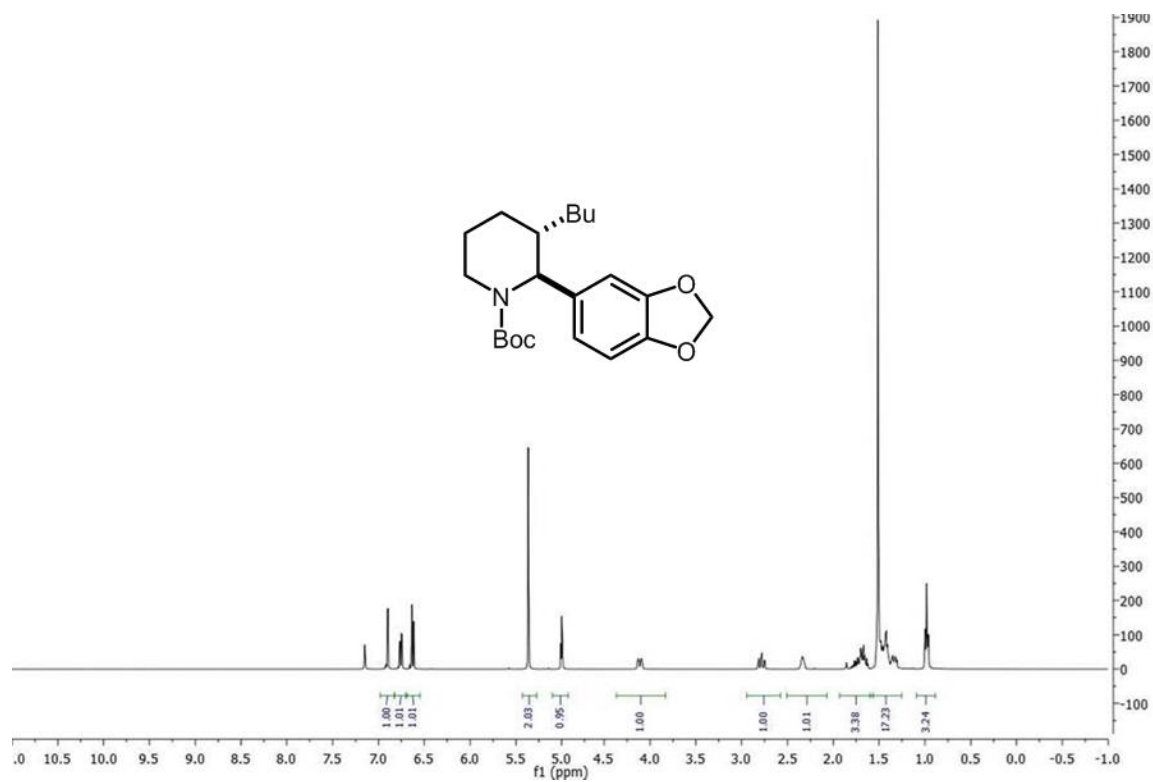


Prepared from **3b** (130 mg, 0.5 mmol) and *n*-BuLi (2.0 equiv), HMPA (1.2 equiv), and MeOH (0.5 mL), using **General Procedure A**. Purification: Flash chromatography on silica eluting with Hexane/EtOAc (95:5). Yield = 111 mg; 70%; spectroscopic data as previously reported by us.⁶

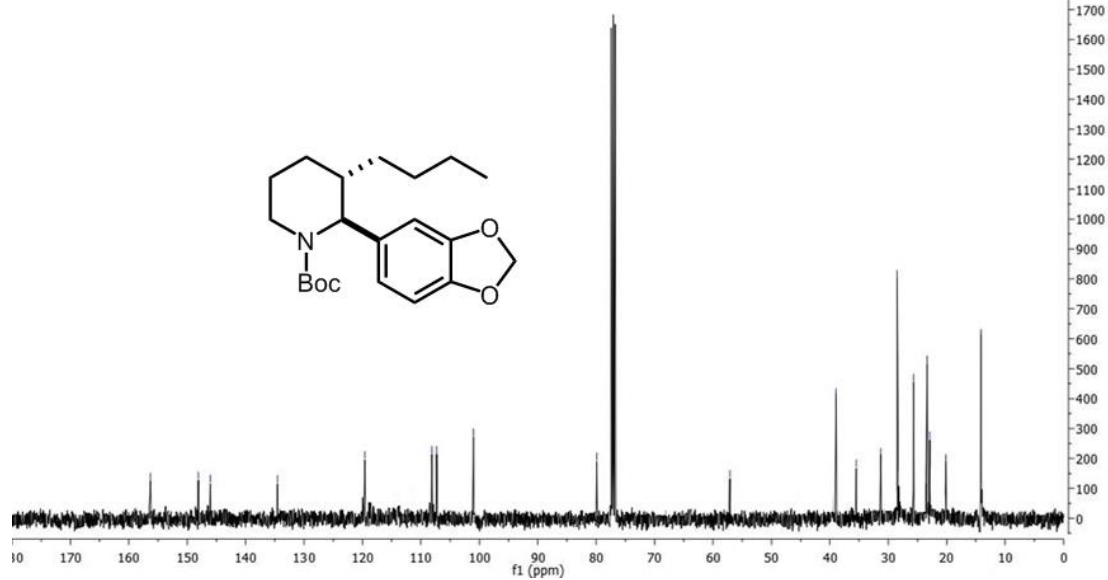


Prepared from **3f** (75.8 mg, 0.25 mmol) and *n*-BuLi (2 equiv), HMPA (1.2 equiv), and MeOH (0.5 mL), using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (50:50). Yield = 60 mg; 67%. ¹H NMR (400 MHz, CDCl₃) δ 6.93 (1H, s), 6.77 (1H, d), 6.73 (1H, d), 5.38 (2H, s), 5.12 (1H, s, br), 4.17 to 4.02 (1H, dd), 3.80 to 3.66 (1H), 2.42 to 2.13 (1H, m), 1.99 to 0.92 (19H, m), 0.79 (3H, t). ¹³C NMR (101 MHz, CDCl₃) δ 156.2, 148.0, 146.0, 134.5, 119.5, 108.1, 107.3, 100.9, 79.9, 57.1, 38.9, 35.4, 31.2, 28.4, 25.6, 23.3, 22.9, 20.1, 14.1. **HRMS-EI⁺** (*m/z*): calc'd for C₂₁H₃₁NO₄ 361.2253; found 361.2249.

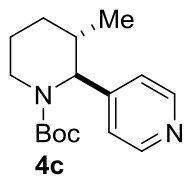
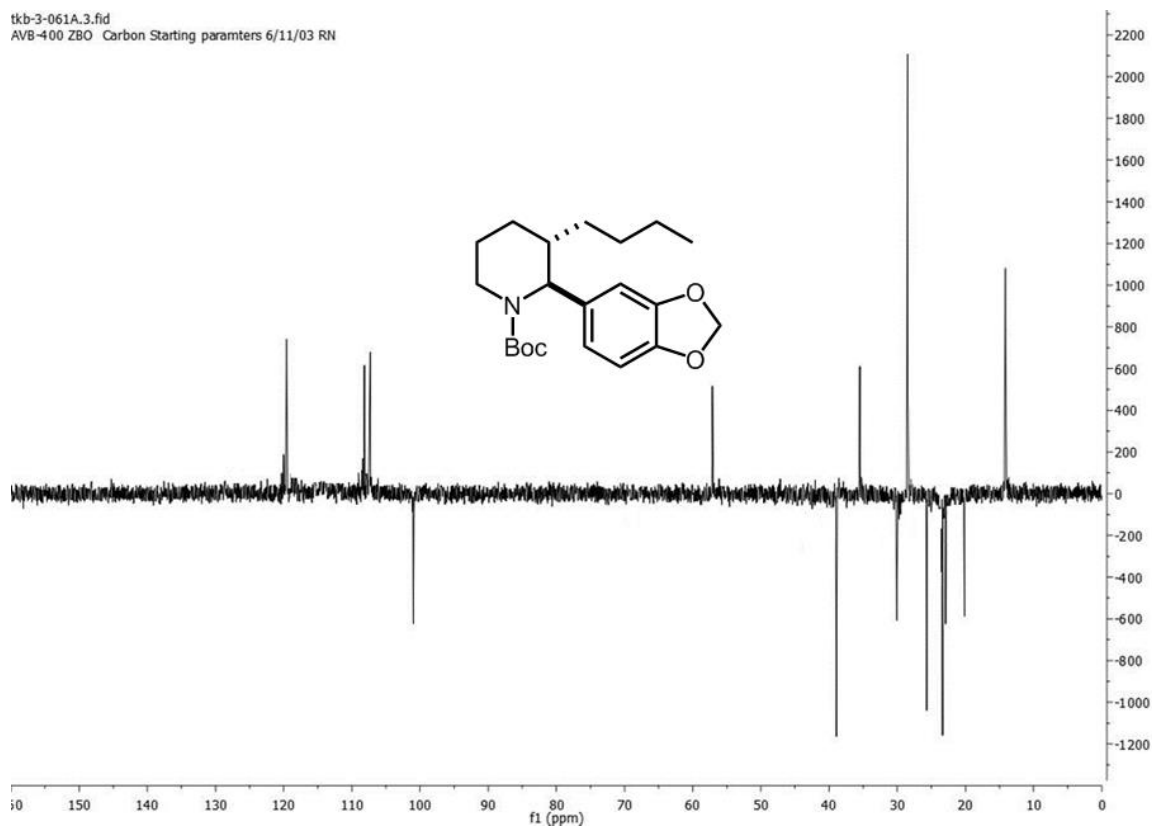




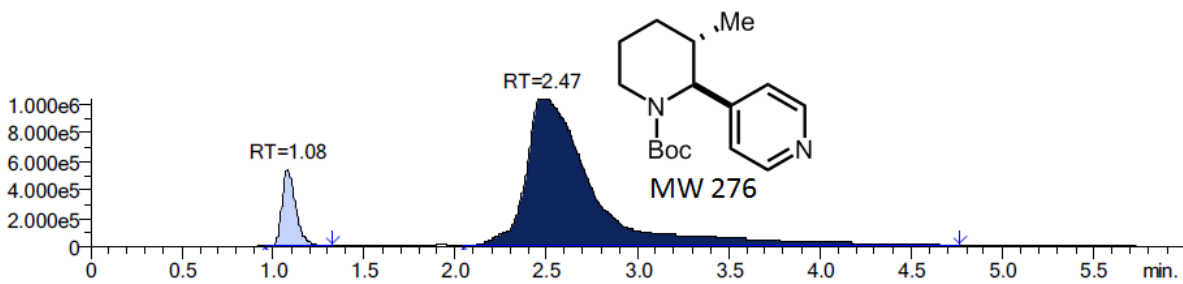
^{13}C NMR (101 MHz, CDCl_3) δ 156.27, 148.09, 146.05, 134.57, 119.58, 108.15, 107.31, 100.99, 79.91, 57.11, 38.93, 35.49, 31.28, 28.49, 25.69, 23.35, 22.90, 20.13, 14.15



tcb-3-061A.3.fid
 AVB-400 ZBO Carbon Starting paramters 6/11/03 RN

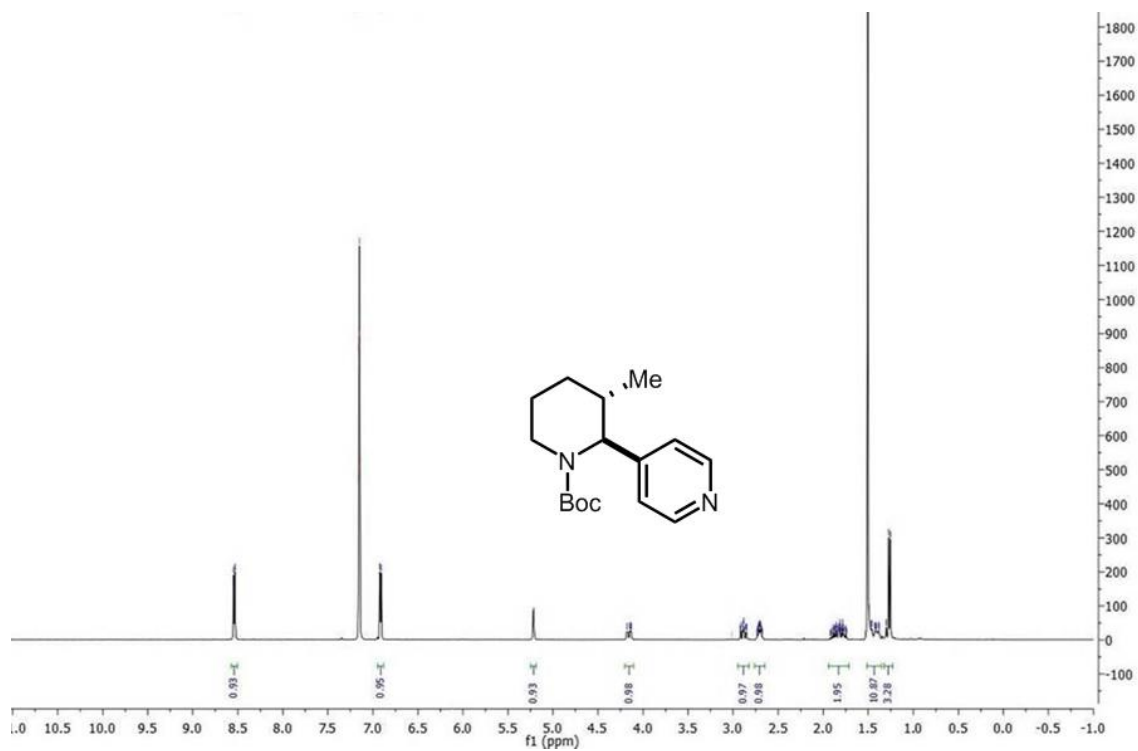
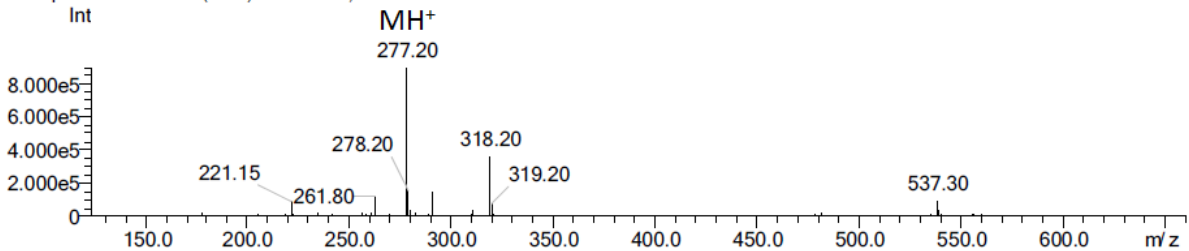


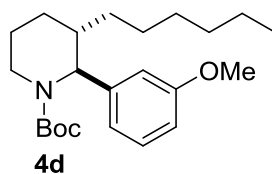
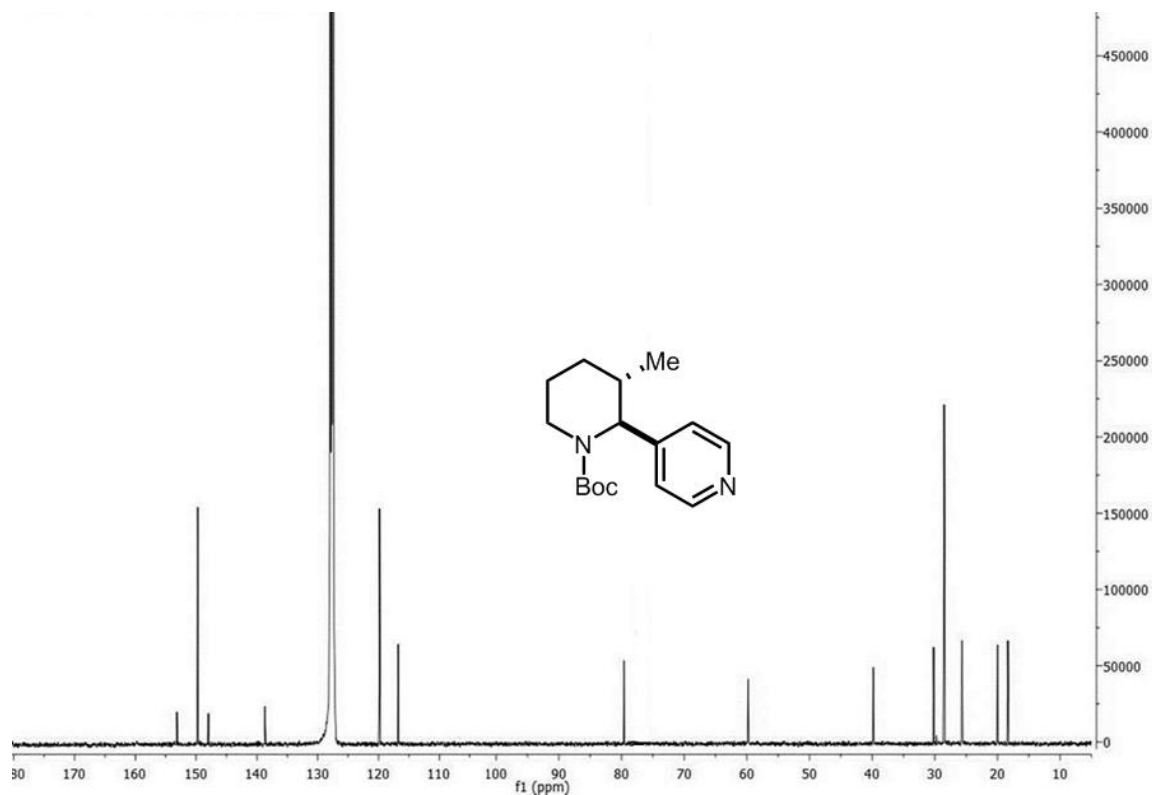
Prepared from **3g** (130 mg, 0.50 mmol), MeLi·LiBr (1.0 mL, 1.5 M in Et₂O, 1.5 mmol, 3.0 equiv), HMPA (1.2 equiv), and MeOH (0.5 mL), using **General Procedure A**. Purification: Flash chromatography on silica eluting with Hexane/EtOAc (80:20 to 30:70). Yield = 108 mg; 78%. ¹H NMR (400 MHz, C₆D₆) δ 8.52 (2H, d), 6.93 (2H, d), 5.22 (1H, s, br), 4.18 to 4.13 (1H, dd), 2.92 to 2.85 (1H, m), 2.74 to 2.66 (1H, m), 1.95 to 1.68 (2H, m), 1.93 to 1.28 (11H, m), 1.23 (3H, d). ¹³C NMR (101 MHz, C₆D₆) δ 153.1, 149.7, 148.0, 138.6, 119.8, 116.8, 79.6, 59.7, 39.8, 30.1, 28.5, 25.6, 20.0, 18.3. **HRMS-EI⁺** (*m/z*): calc'd for C₁₆H₂₄N₂O₂ 276.1838; found 276.1835.



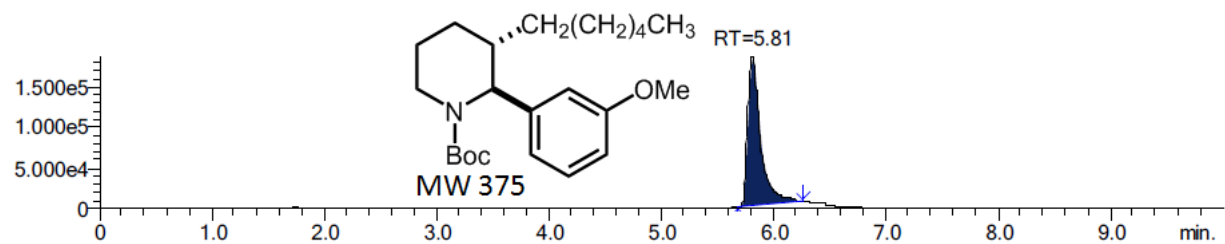
MS Spectrum

Group#1 - MS Mass(277) Peak: 30, RT: 2.31 to 2.90 min
Int

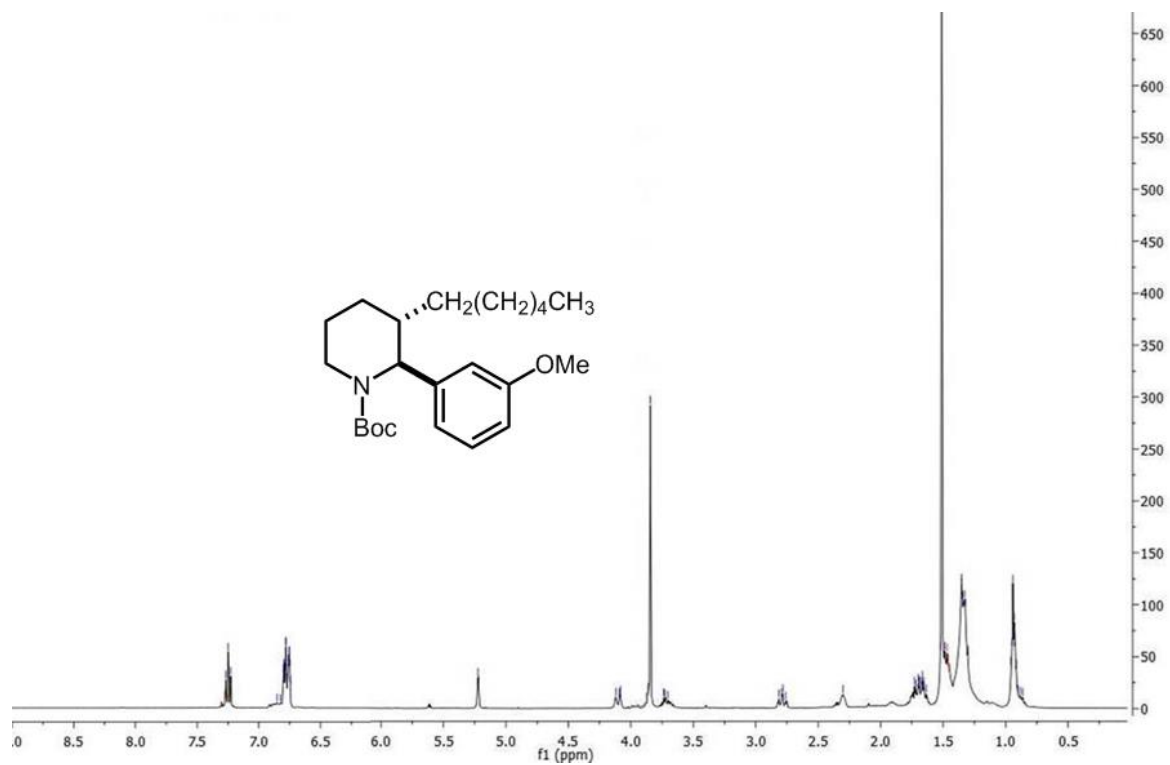
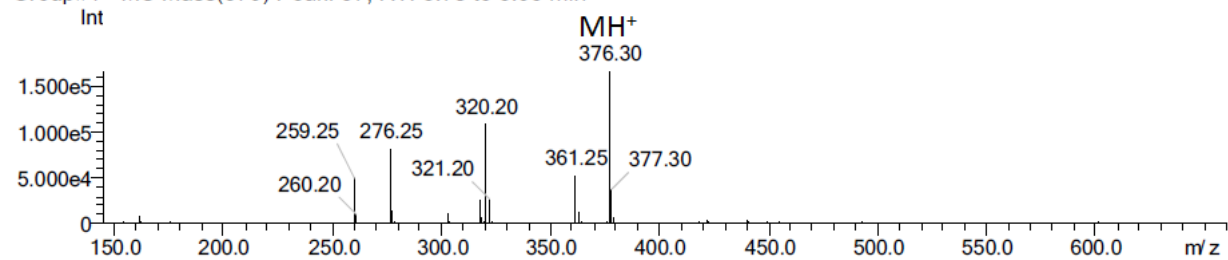


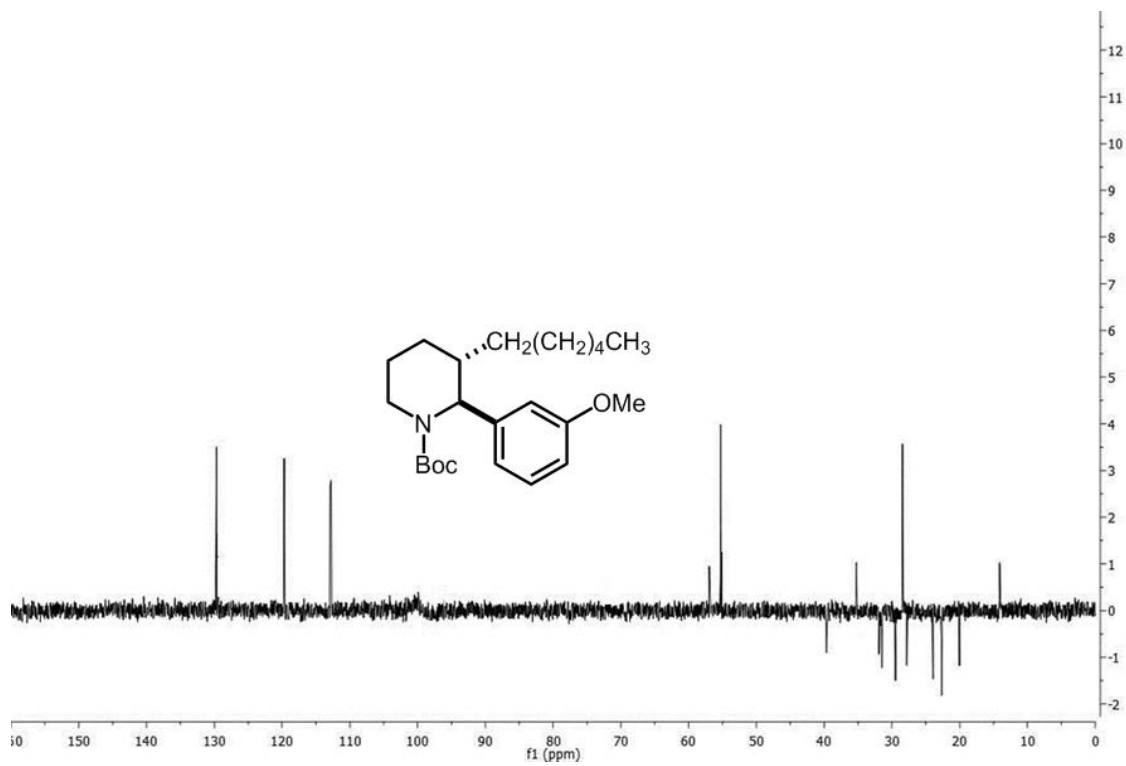
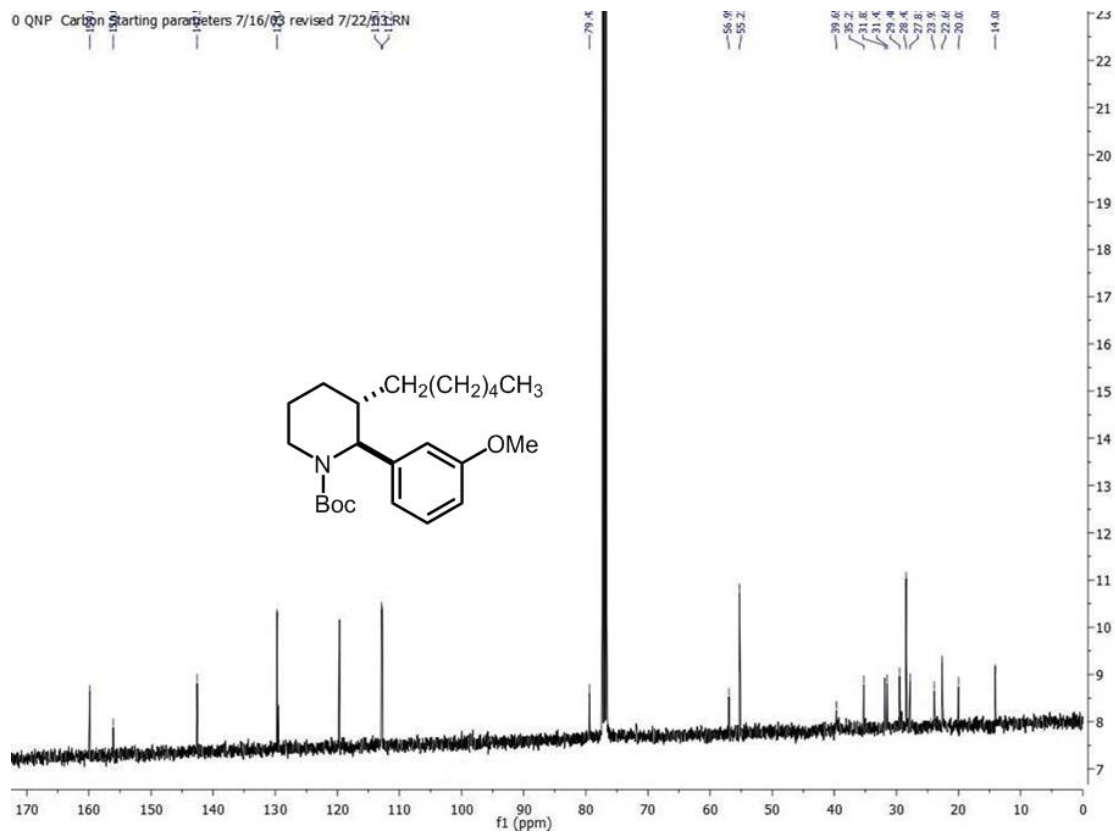


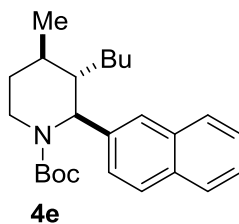
Prepared from **3c** (145 mg, 0.50 mmol), *n*-BuLi (2 equiv), HMPA (1.2 equiv), and MeOH (0.2 mL) using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (50:50). Yield = 131 mg; 70%. ¹H NMR (400 MHz, CDCl₃) δ 7.42 to 7.21 (2H, m), 6.96 to 6.81 (3H, m), 5.22 (1H, s, br), 4.12 to 4.08 (1H, dd), 3.86 (3H, s), 3.74 to 3.70 (1H, m), 2.82 to 2.76 (1H, t), 2.30 (1H, m), 1.73 to 1.30 (21H, m), 0.96 to 0.86 (3H, t). ¹³C NMR (101 MHz, CDCl₃) δ 159.8, 156.1, 142.6, 129.7, 112.9, 112.8, 79.4, 56.9, 55.3, 39.6, 35.3, 31.8, 31.4, 29.4, 28.4, 27.8, 23.9, 22.6, 20.0, 14.0. **HRMS-EI⁺** (*m/z*): calc'd for C₂₃H₃₇NO₃ 375.2773; found 375.2770.

**MS Spectrum**

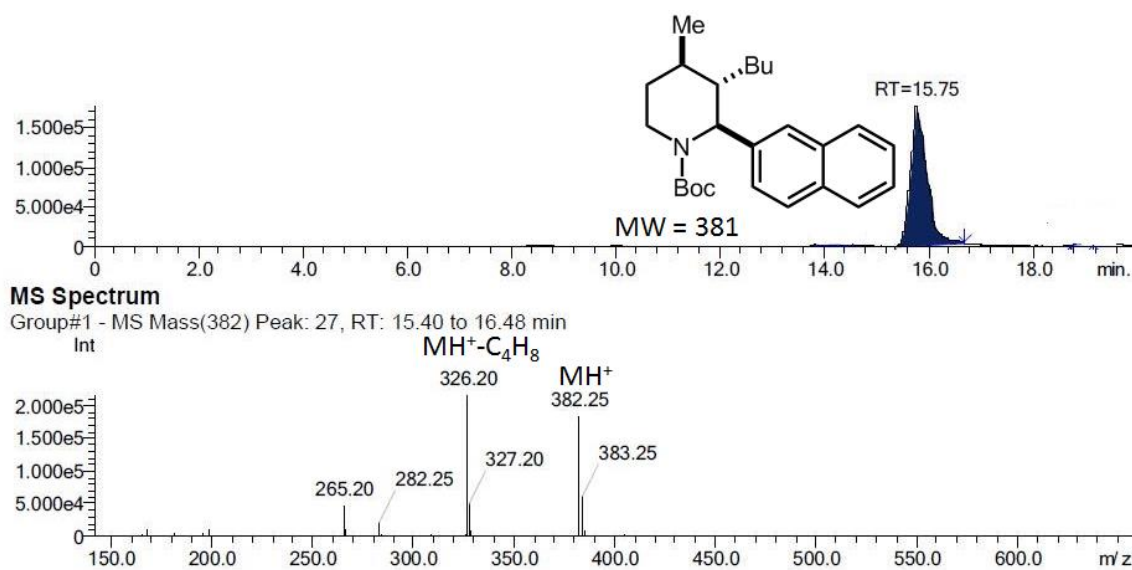
Group#1 - MS Mass(376) Peak: 37, RT: 5.70 to 5.98 min



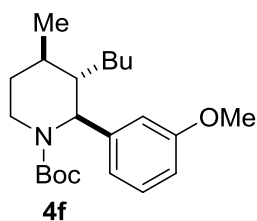
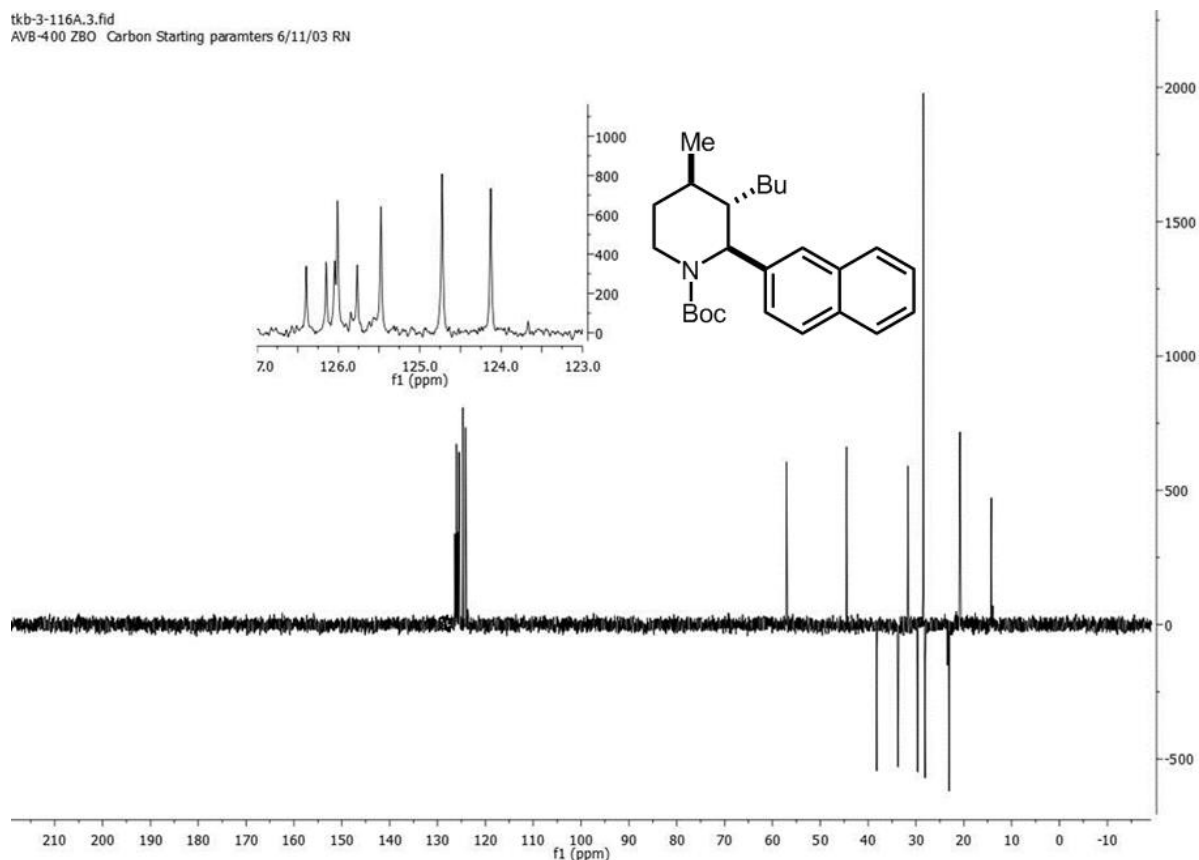




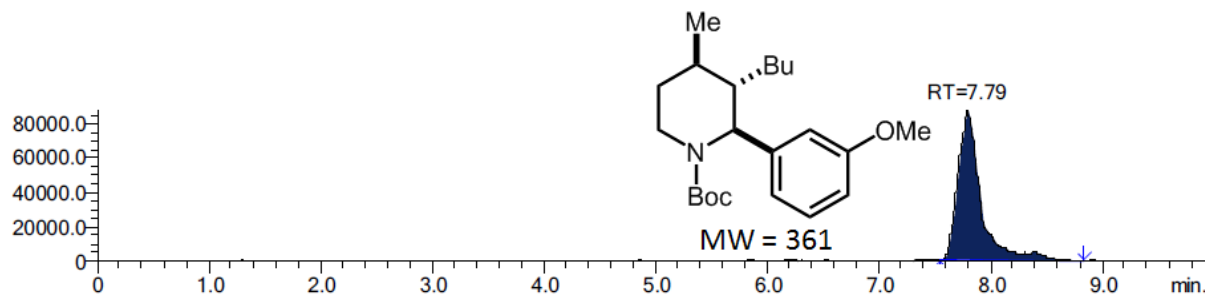
Prepared from **3j** (81 mg, 0.25 mmol) and *n*-BuLi (2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (90:10). Yield = 76 mg; 80%. ^1H NMR (400 MHz, CDCl_3) δ 8.02 to 7.41 (7H, m), 5.25 (1H, s, br), 4.01 to 3.95 (1H, dd), 3.47, to 3.40 (1H, t), 2.18 to 2.13 (1H, t), 1.93 to 1.85 (1H, m), 1.70 to 1.26 (18H, m), 1.00 to 0.93 (3H, t), 0.81 (3H, d). ^{13}C NMR (101 MHz, CDCl_3) δ 156.3, 140.9, 133.4, 132.1, 127.9, 127.9, 127.5, 126.0, 125.4, 124.7, 124.1, 79.5, 57.0, 44.5, 38.2, 33.7, 31.6, 29.6, 28.4, 28.0, 23.0, 20.7, 14.2. **HRMS-EI⁺** (m/z): Calcd. for $\text{C}_{25}\text{H}_{35}\text{NO}_2$ [M]⁺ 381.2668; found, 381.2665.



tkb-3-116A.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN

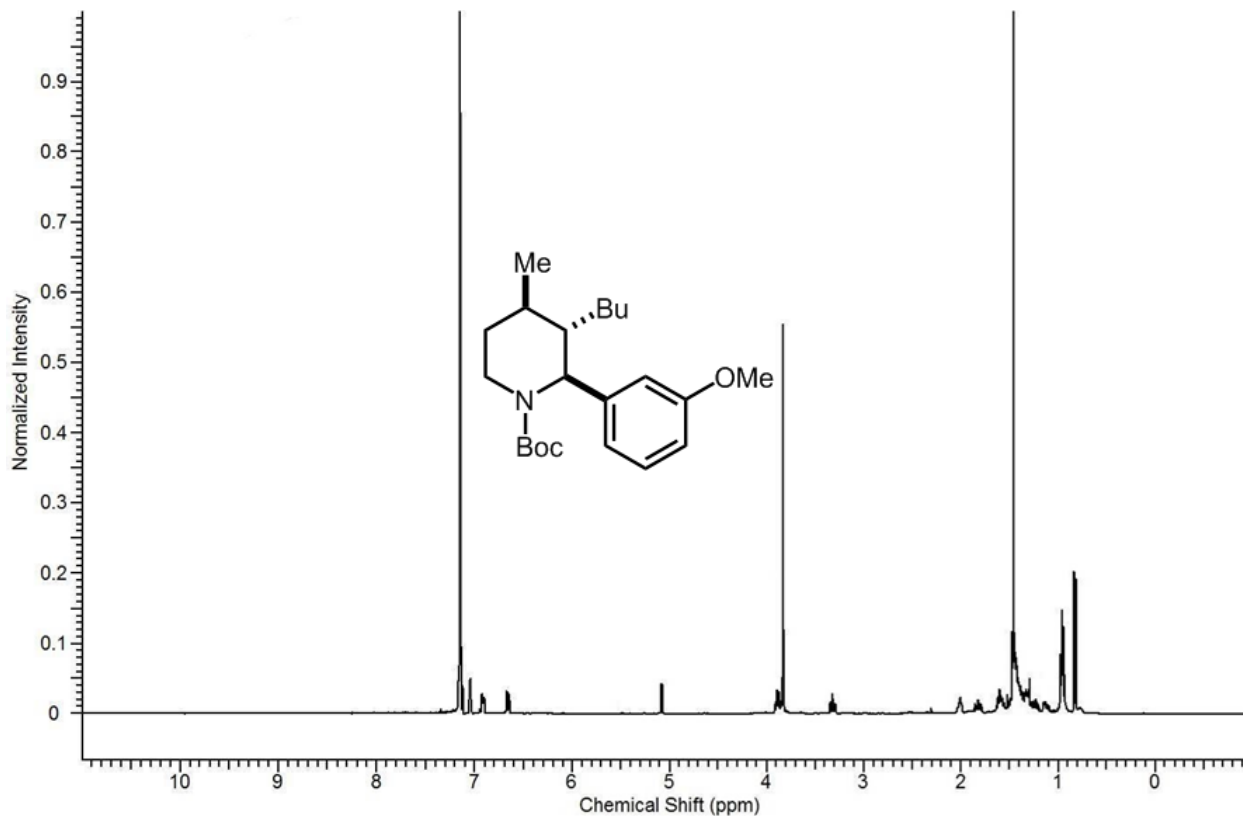
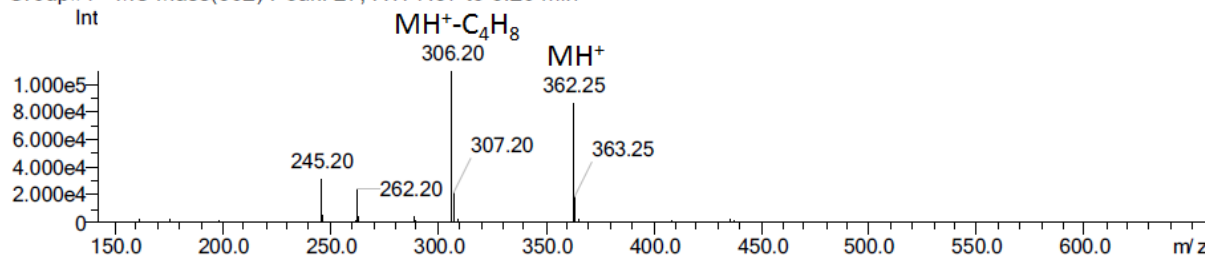


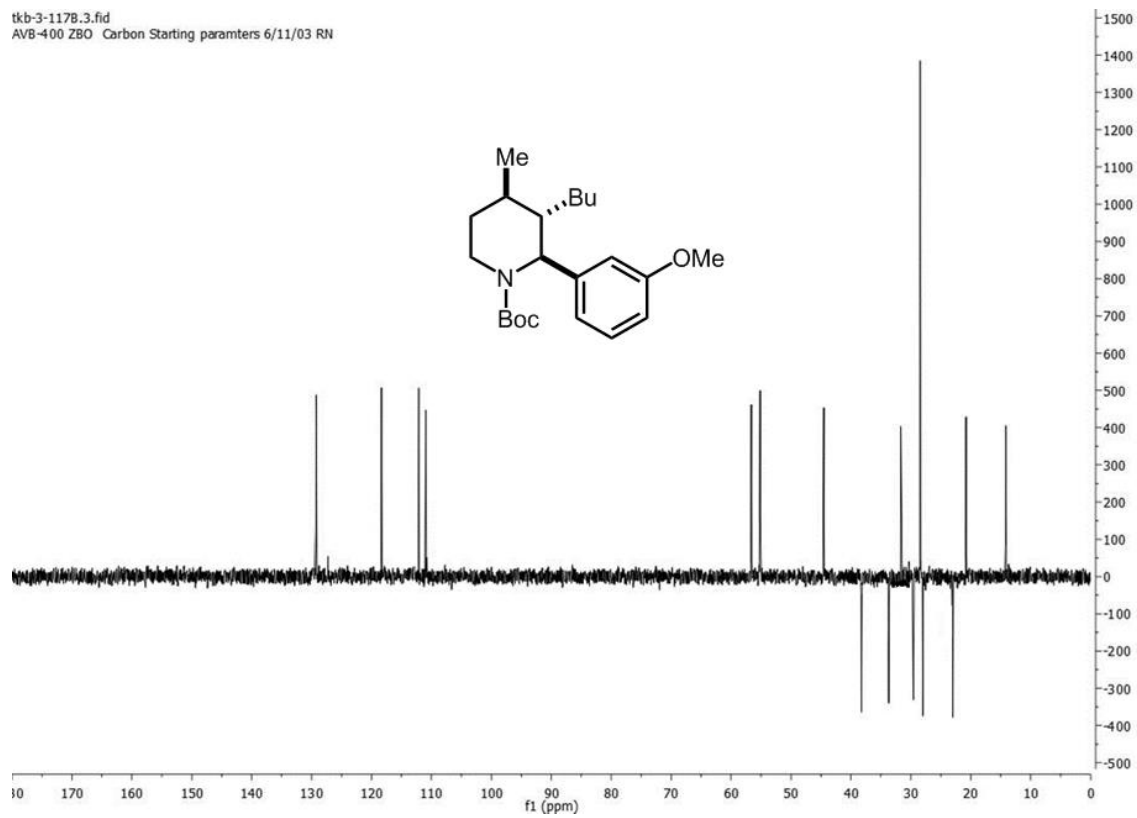
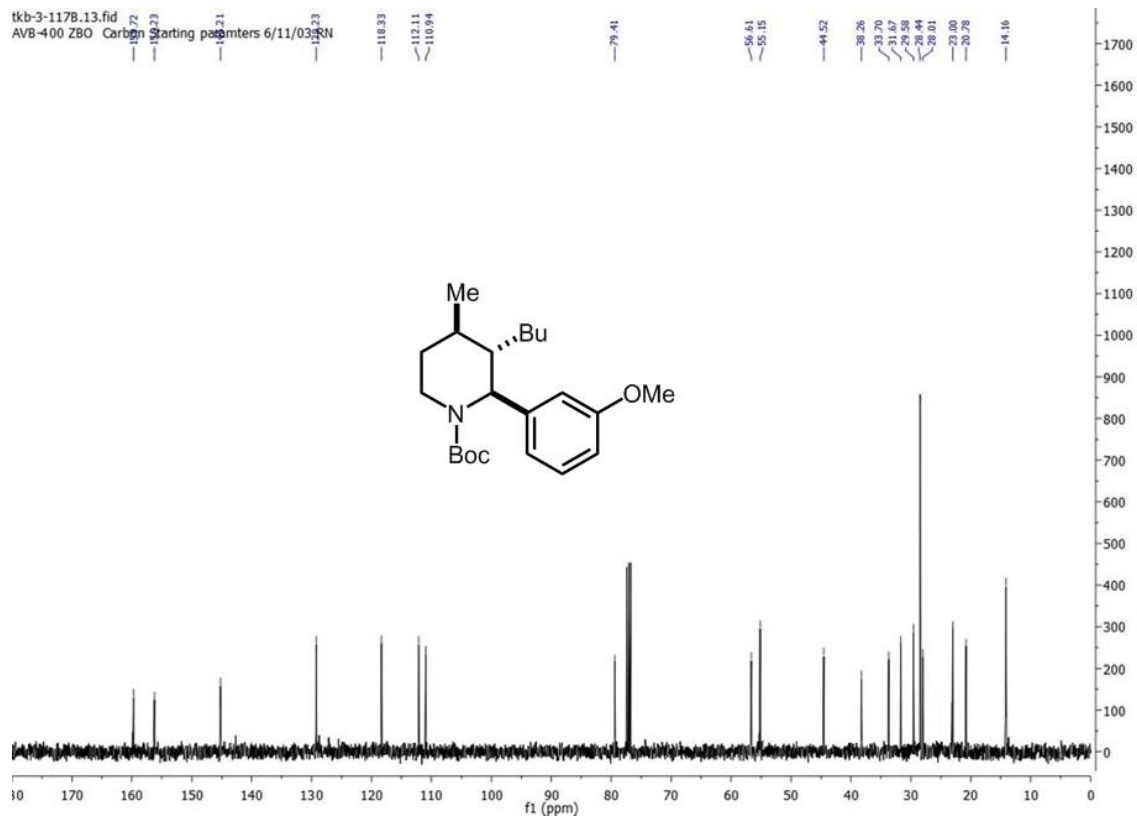
Prepared from **3k** (76 mg, 0.25 mmol) and *n*-BuLi (2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (60:40). Yield = 68 mg; 75%. ^1H NMR (400 MHz, CDCl_3) δ 7.12 to 6.93 (3H, m), 6.85 (1H, d), 5.08 (1H, s, br), 3.91 to 3.79 (4H, m), 3.35 to 3.08 (1H, dd), 2.05 to 1.98 (1H, t), 1.86 to 1.78 (1H), 1.63 to 1.20 (18H, m), 0.98 to 0.93 (3H, t), 0.83 (3H, d). ^{13}C NMR (101 MHz, CDCl_3) δ 159.7, 156.2, 145.2, 129.2, 118.3, 112.1, 110.9, 79.4, 56.6, 55.1, 44.5, 38.2, 33.7, 31.6, 29.5, 28.4, 28.0, 23.0, 20.7, 14.1. **HRMS-EI⁺** (*m/z*): Calcd. for $\text{C}_{25}\text{H}_{35}\text{NO}_3$ [M]⁺ 361.2617; found, 361.2614.

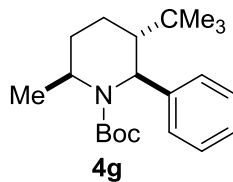


MS Spectrum

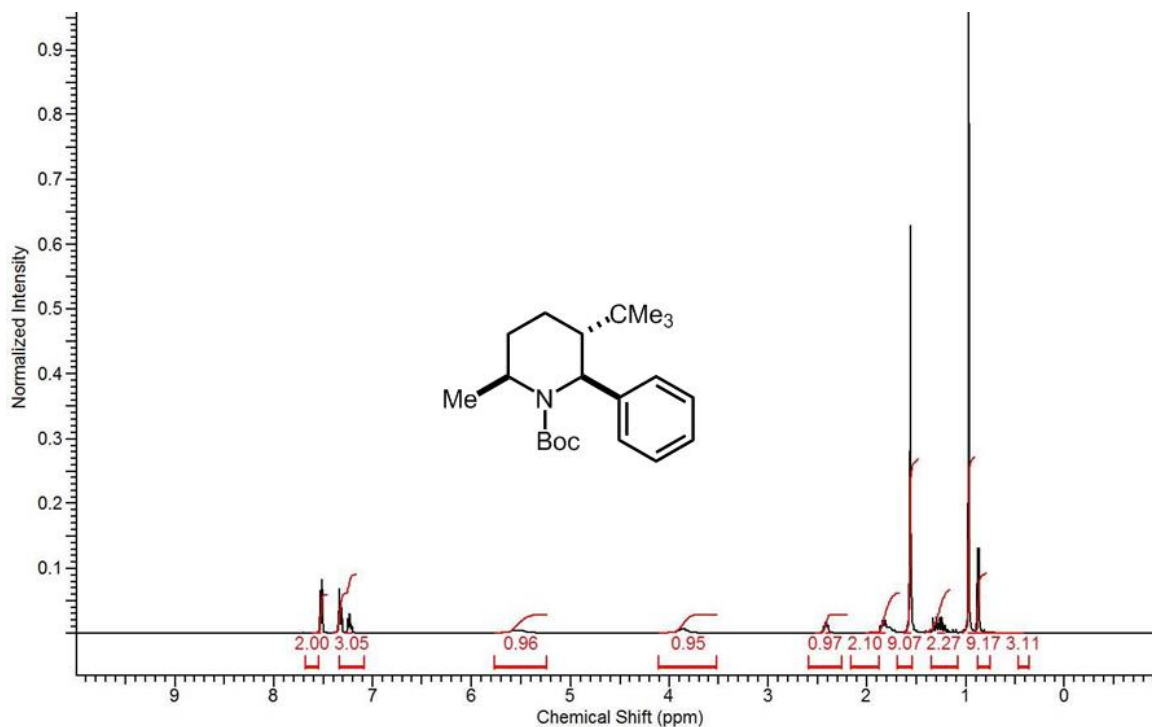
Group#1 - MS Mass(362) Peak: 27, RT: 7.57 to 8.26 min

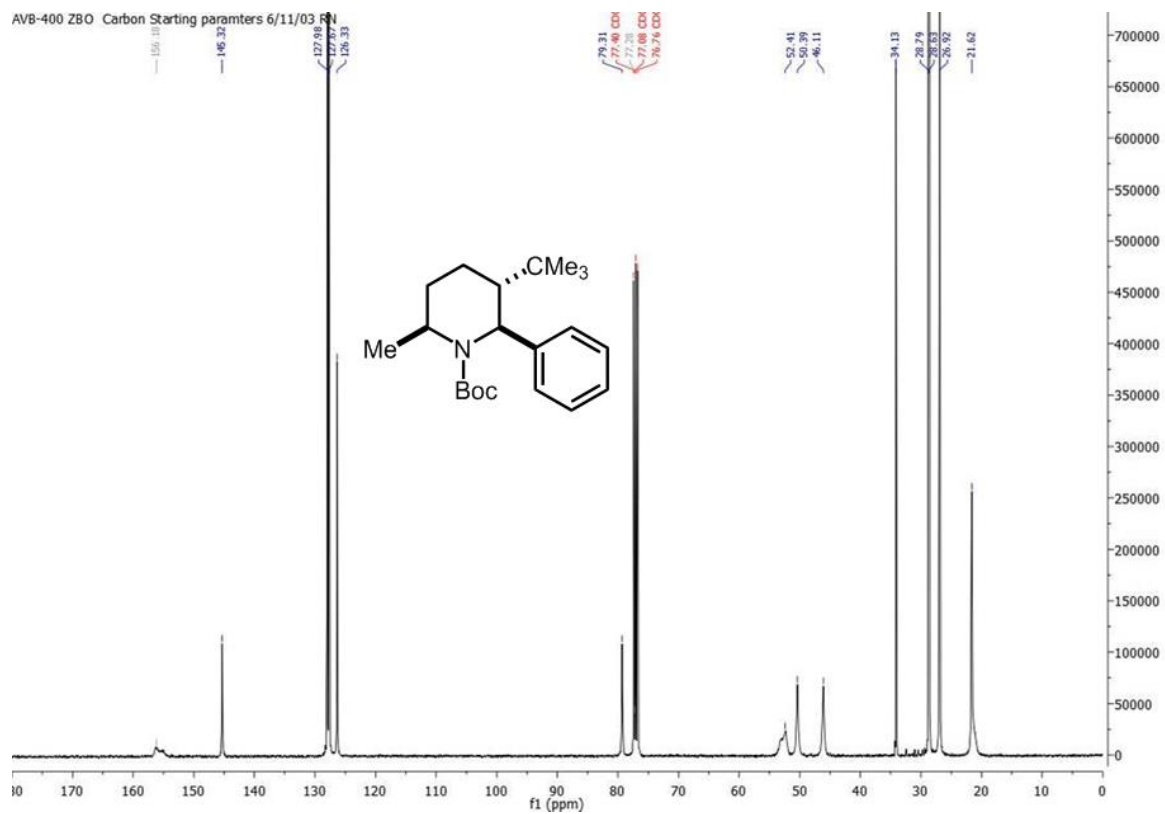


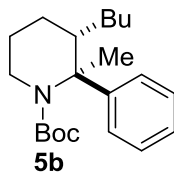




Prepared from **31** (68 mg, 0.25), and *tert*-BuLi in pentane (2.0 equiv), and MeOH (0.5 mL) using **General Procedure A**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (90:10). Yield = 73 mg, 88%. ^1H NMR (400 MHz, CDCl_3) δ 7.54 to 7.51 (2H, m), 7.35 to 7.30 (2H, m), 7.25 to 7.21 (1H, t), 5.55 (1H, s, br), 3.86 (1Hs, br), 2.44 to 2.39 (1H, t), 1.87 to 0.87 (25H, m). ^{13}C NMR (101 MHz, CDCl_3) δ 156.1, 145.3, 127.9, 127.6, 126.3, 79.3, 77.4, 77.3, 77.1, 76.7, 52.4, 50.4, 46.1, 34.1, 28.8, 28.6, 26.9, 21.6. **HRMS- EI^+** (m/z): Calcd. for $\text{C}_{21}\text{H}_{33}\text{NO}_2$ $[\text{M}]^+$ 331.2511; found, 331.2505.



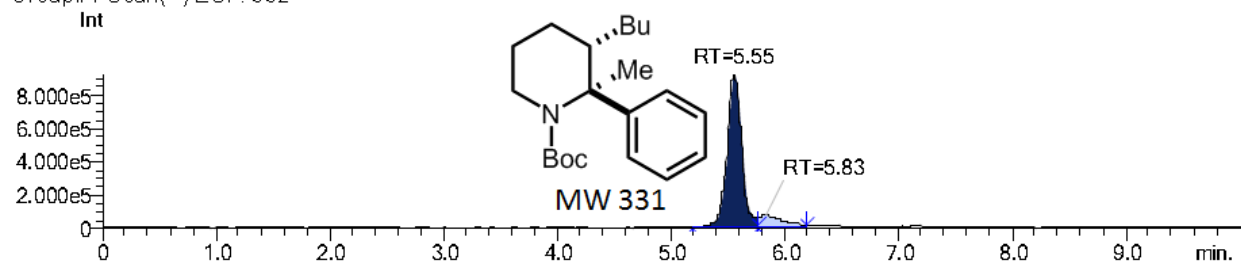




Prepared from **3b** (129.5 mg, 0.5 mmol), *n*-BuLi (2.0 equiv), HMPA (1.2 equiv) and Me₂SO₄ (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 54 mg; 69%. ¹H NMR (400 MHz, CDCl₃) δ 7.47 to 7.22 (5H, m), 3.82 to 3.75 (1H, dd), 3.69 to 3.58 (1H, dd), 1.82 to 0.75 (23H, m), 0.70 (3H, t). **HRMS-EI⁺** (*m/z*): calc for C₂₁H₃₃NO₂ 331.2511, found 331.2505.

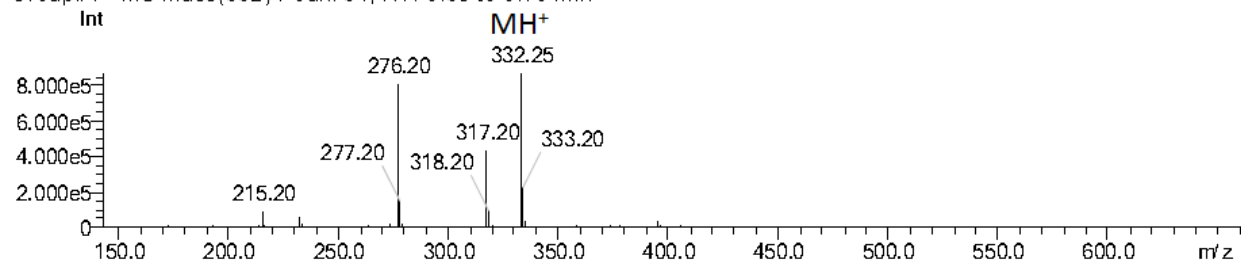
MS Chromatogram

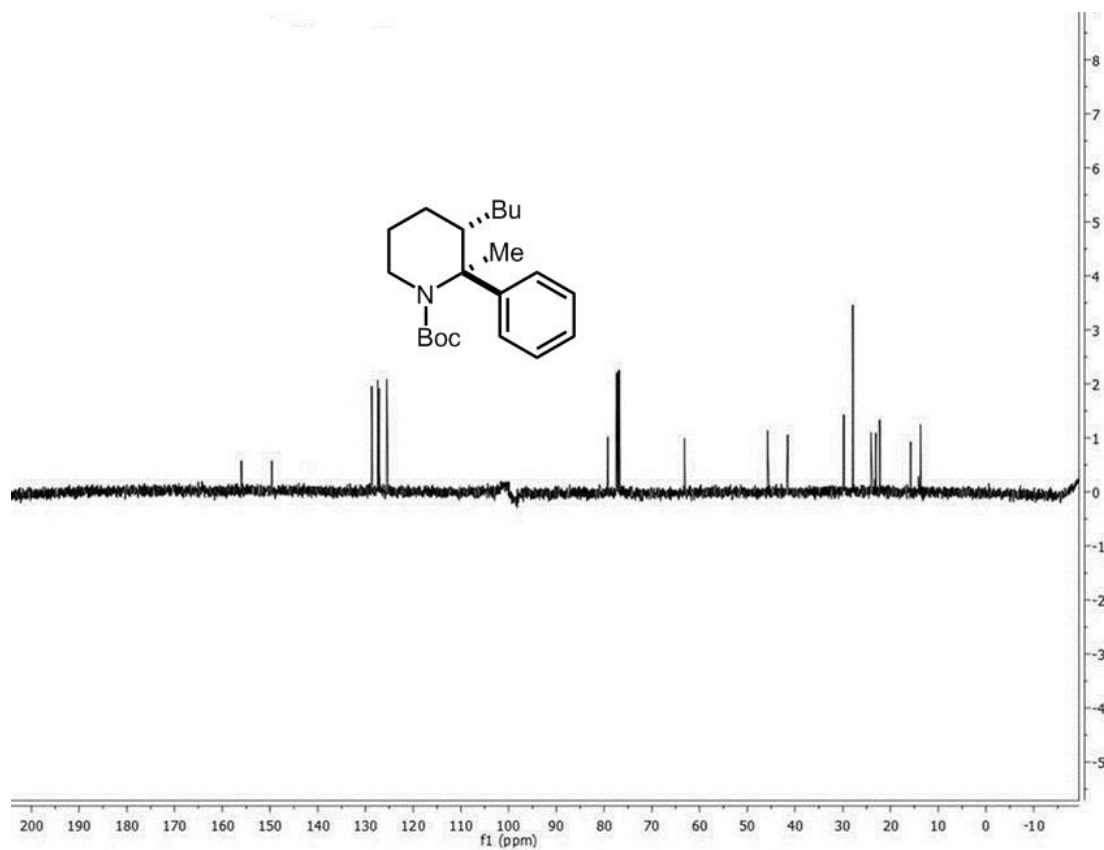
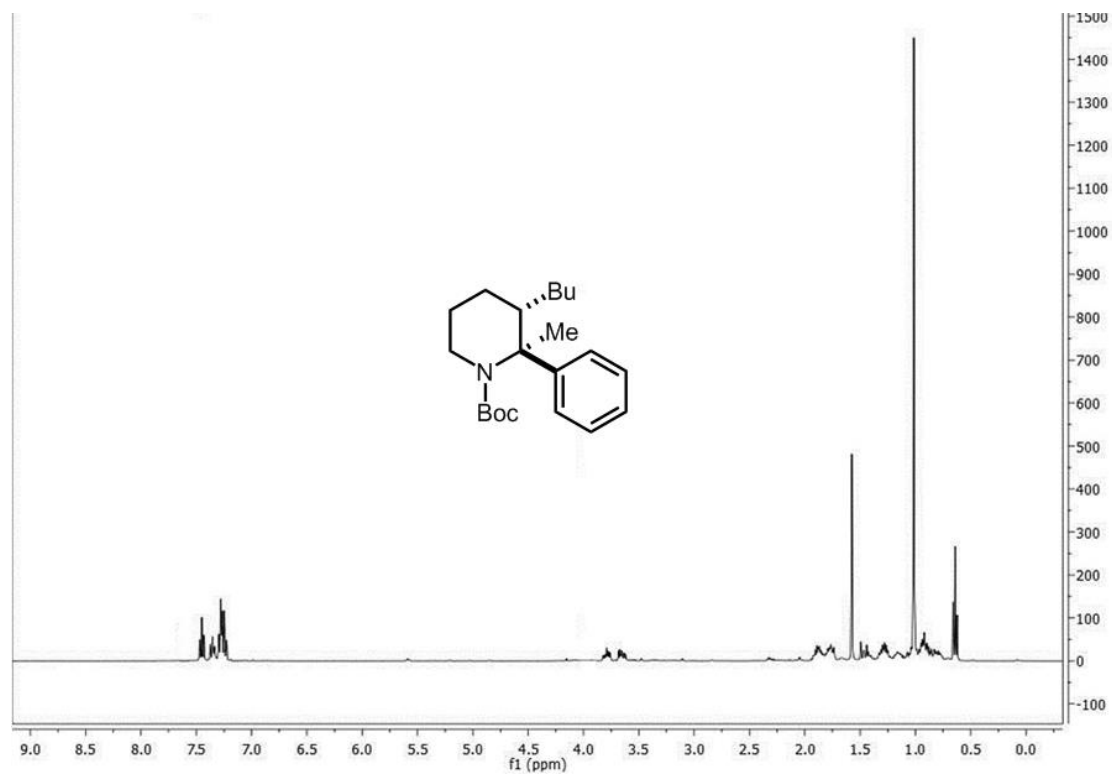
Group#1 Scan(+) ESI : 332

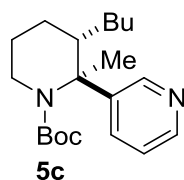
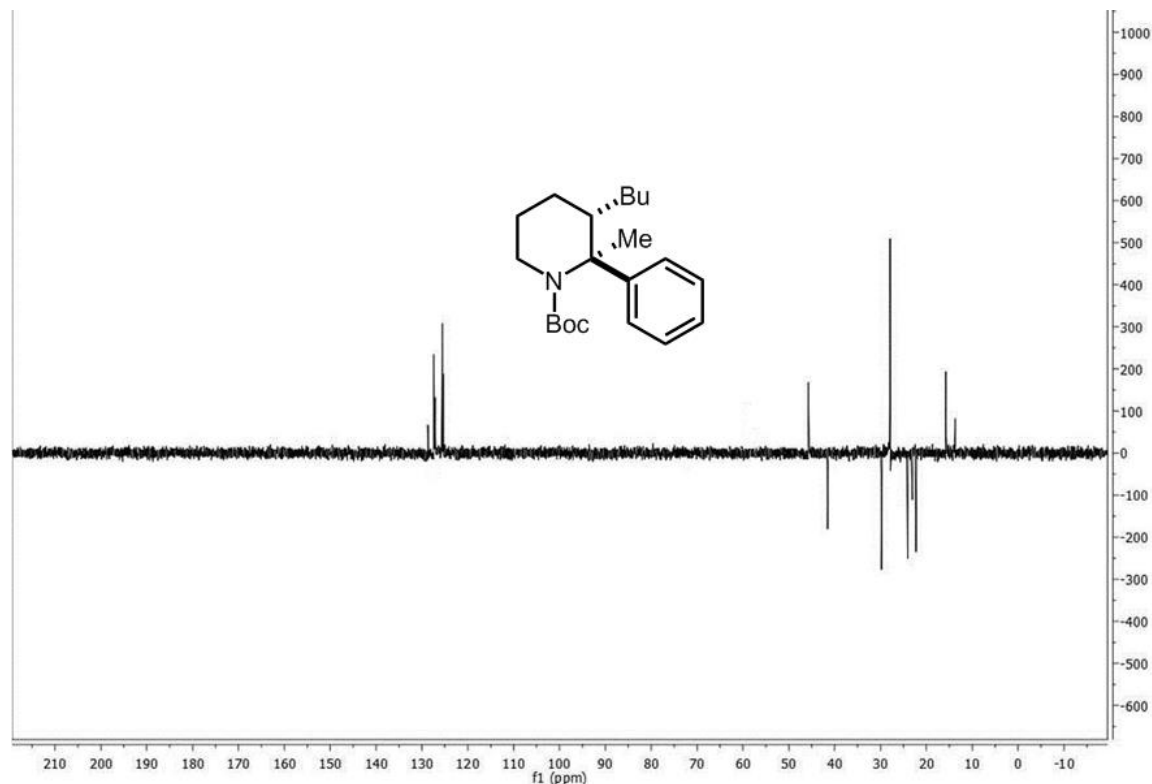


MS Spectrum

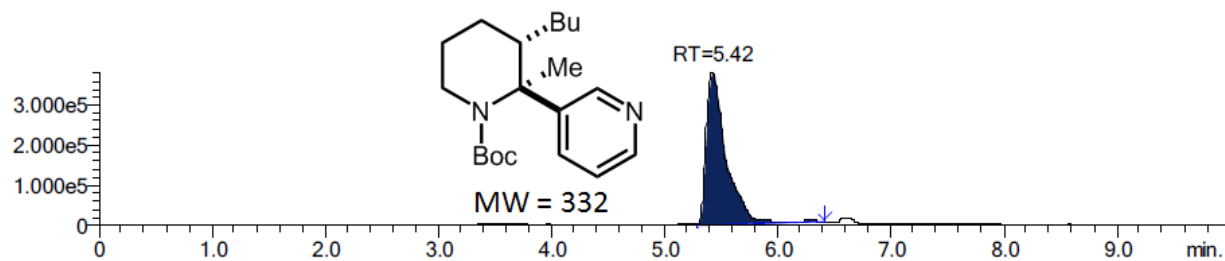
Group#1 - MS Mass(332) Peak: 34, RT: 5.39 to 5.75 min





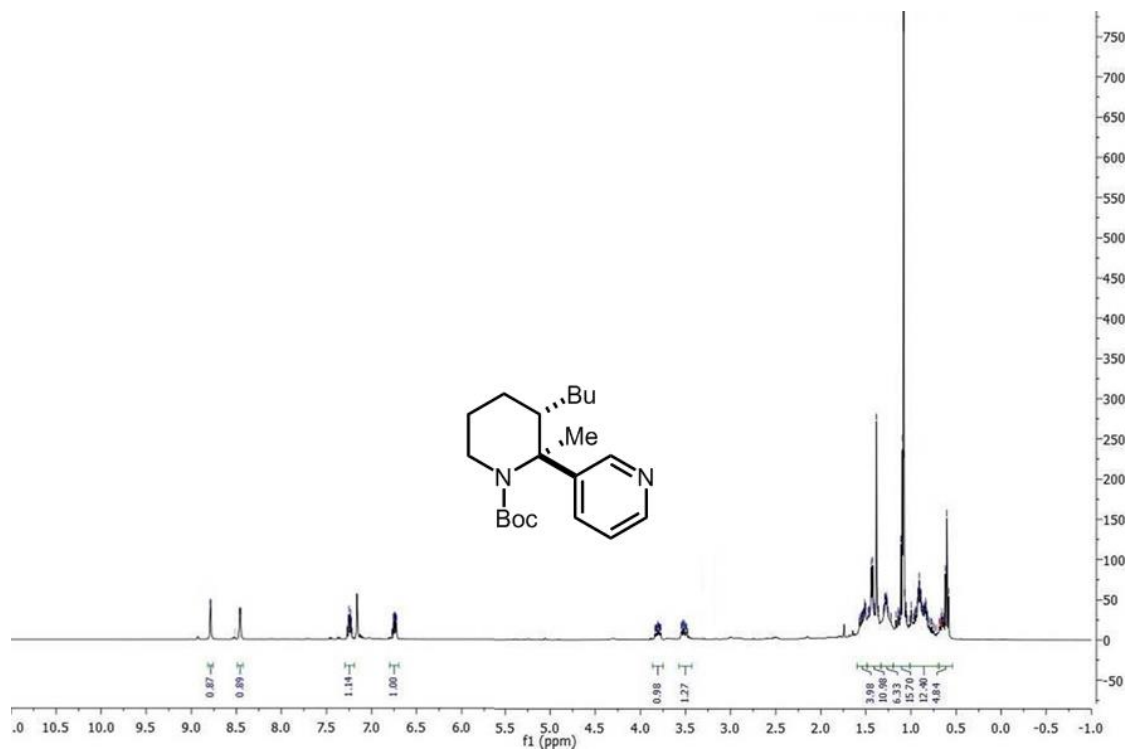
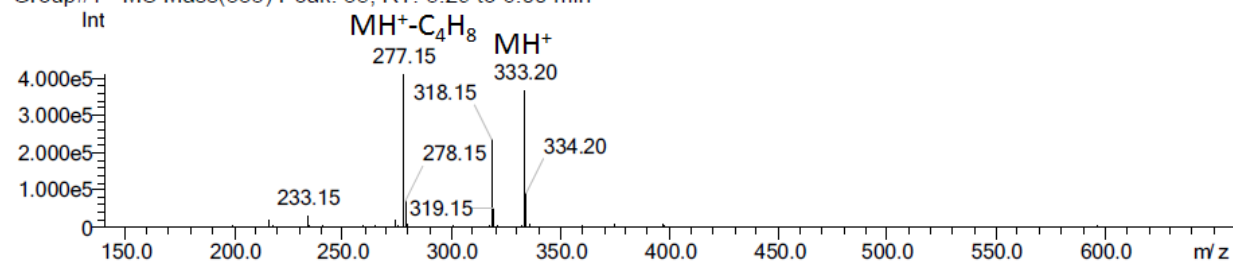


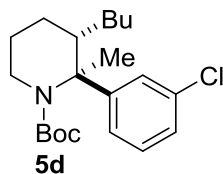
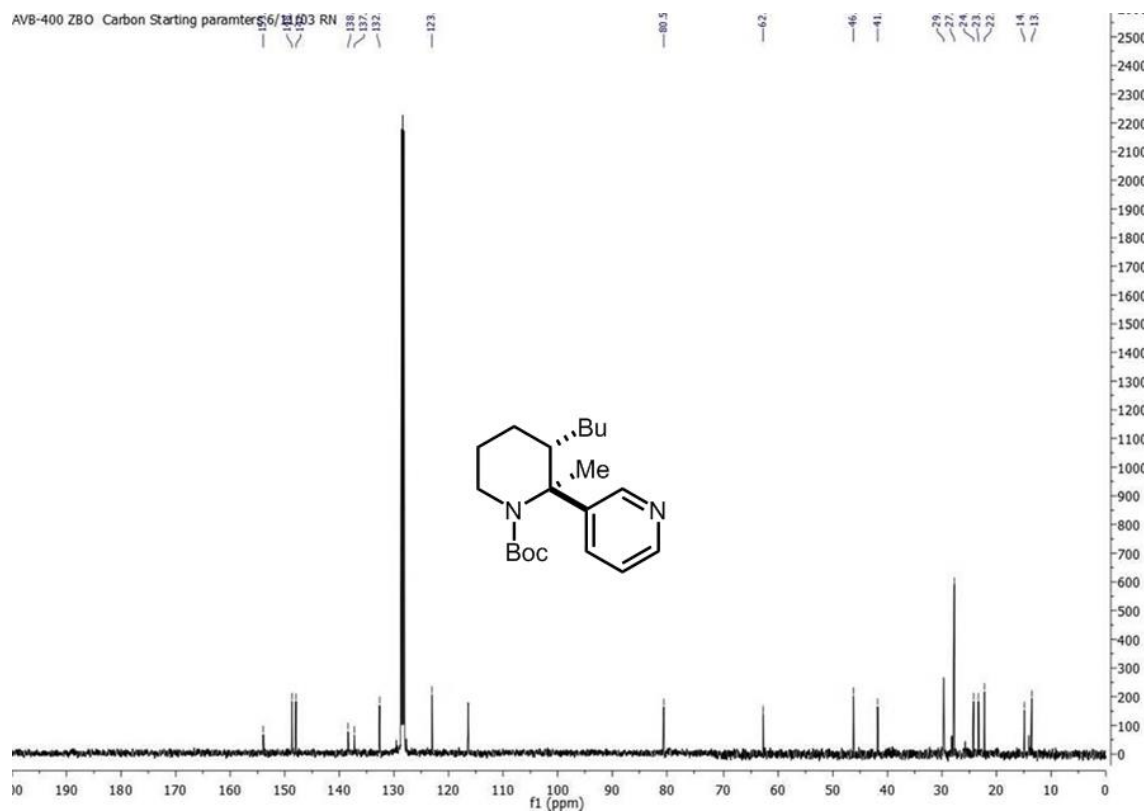
Prepared from enecarbamate **3h** (130 mg, 0.5 mmol) and Me_2SO_4 (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with Hexane/EtOAc (80:20 to 30:70). Yield = 136 mg; 82%. ^1H NMR (400 MHz, C_6D_6) δ 8.79 (1H, s), 8.46 (1H, d), 7.27 to 7.22 (1H, t), 6.77 to 6.72 (1H, t), 3.85 to 3.78 (1H, dd), 3.55 to 3.47 (1H, dd), 1.57 to 0.58 (26H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 153.9, 148.7, 147.9, 138.3, 137.2, 132.6, 123.0, 80.5, 62.7, 46.2, 41.8, 29.7, 27.7, 24.2, 23.3, 22.2, 14.8, 13.5. **HRMS-EI⁺** (m/z): calc for $\text{C}_{20}\text{H}_{32}\text{N}_2\text{O}_2$ 332.2464, found 332.2469.



MS Spectrum

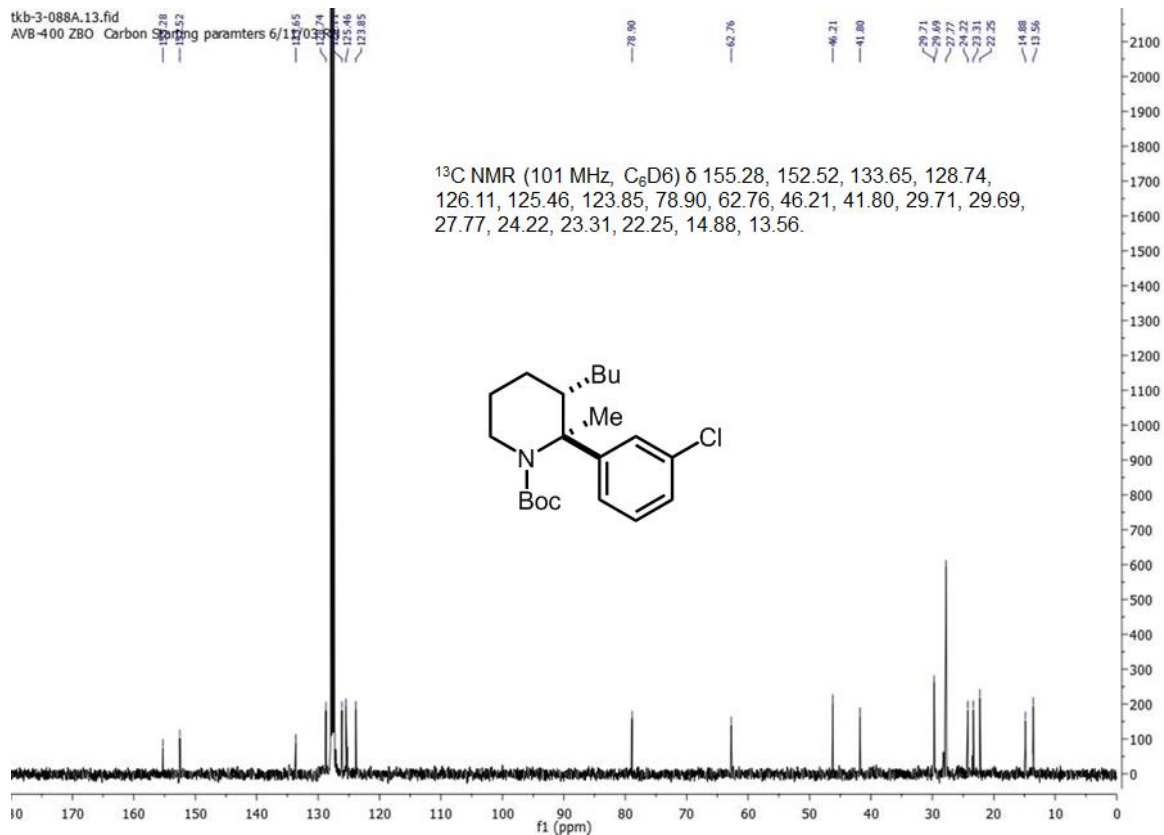
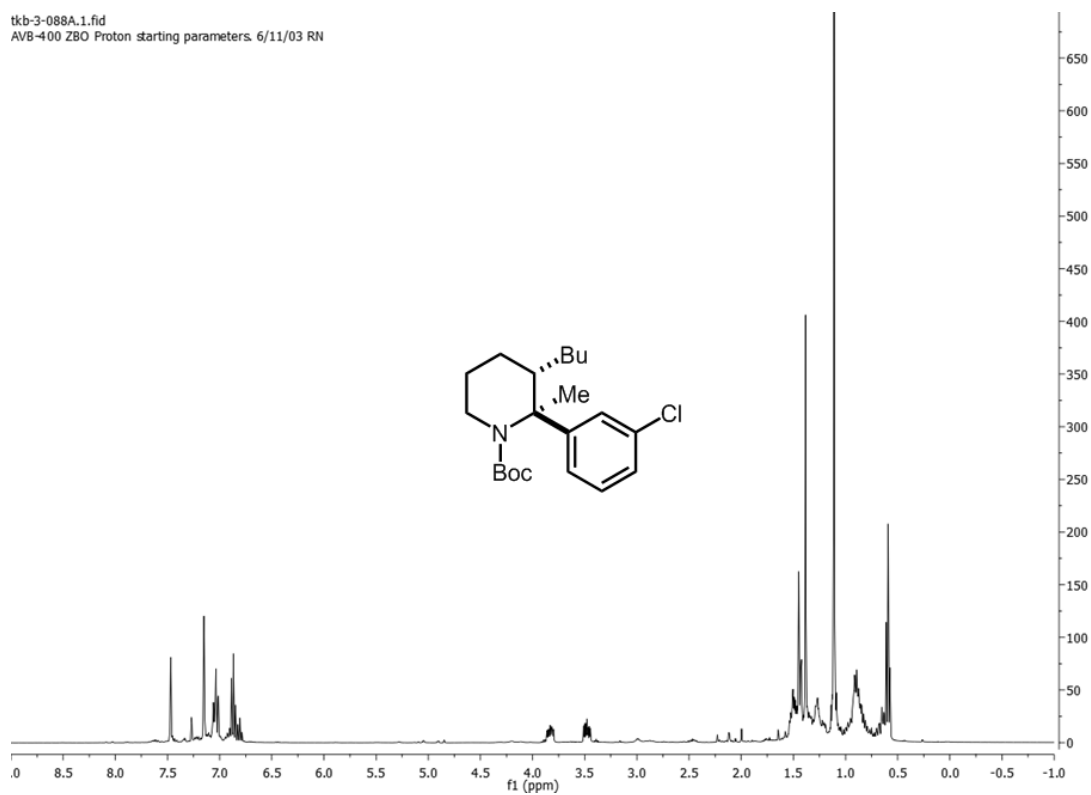
Group#1 - MS Mass(333) Peak: 35, RT: 5.29 to 6.00 min



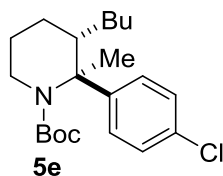
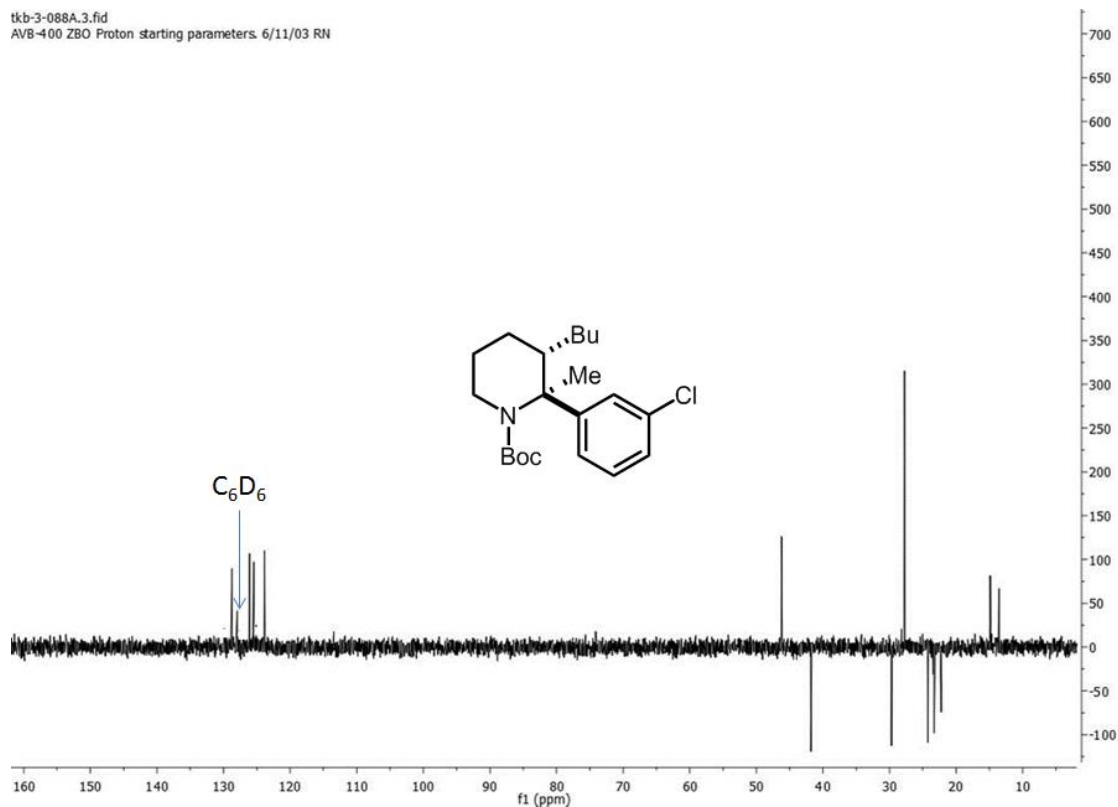


Prepared from **3d** (293 mg, 1.0 mmol) and Me₂SO₄ (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 256 mg; 70%. ¹H NMR (400 MHz, C₆D₆) δ 7.47 (1H, s), 7.07 to 6.81 (3H, m), 3.88 to 3.80 (1H, dd), 3.51 to 3.40 (1H, dd), 1.62 to 0.55 (26H, m). ¹³C NMR (101 MHz, C₆D₆) δ 155.3, 152.5, 133.6, 128.7, 126.1, 125.5, 123.8, 78.9, 62.8, 46.2, 41.8, 29.7, 29.9, 27.8, 24.2, 23.3, 22.2, 14.9, 13.5. **HRMS-EI⁺** (*m/z*): calc for C₂₁H₃₂ClNO₂ 365.2122, found 365.2125.

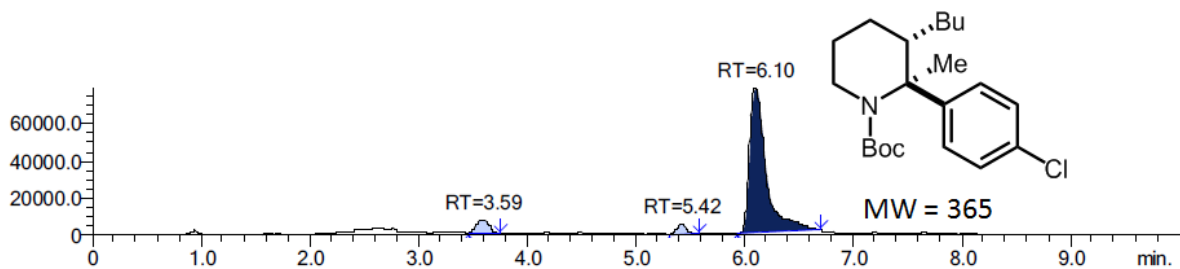
tcb-3-088A.1.fid
AVB-400 ZBO Proton starting parameters. 6/11/03 RN



tkb-3-088A.3.fid
AVB-400 ZBO Proton starting parameters. 6/11/03 RN

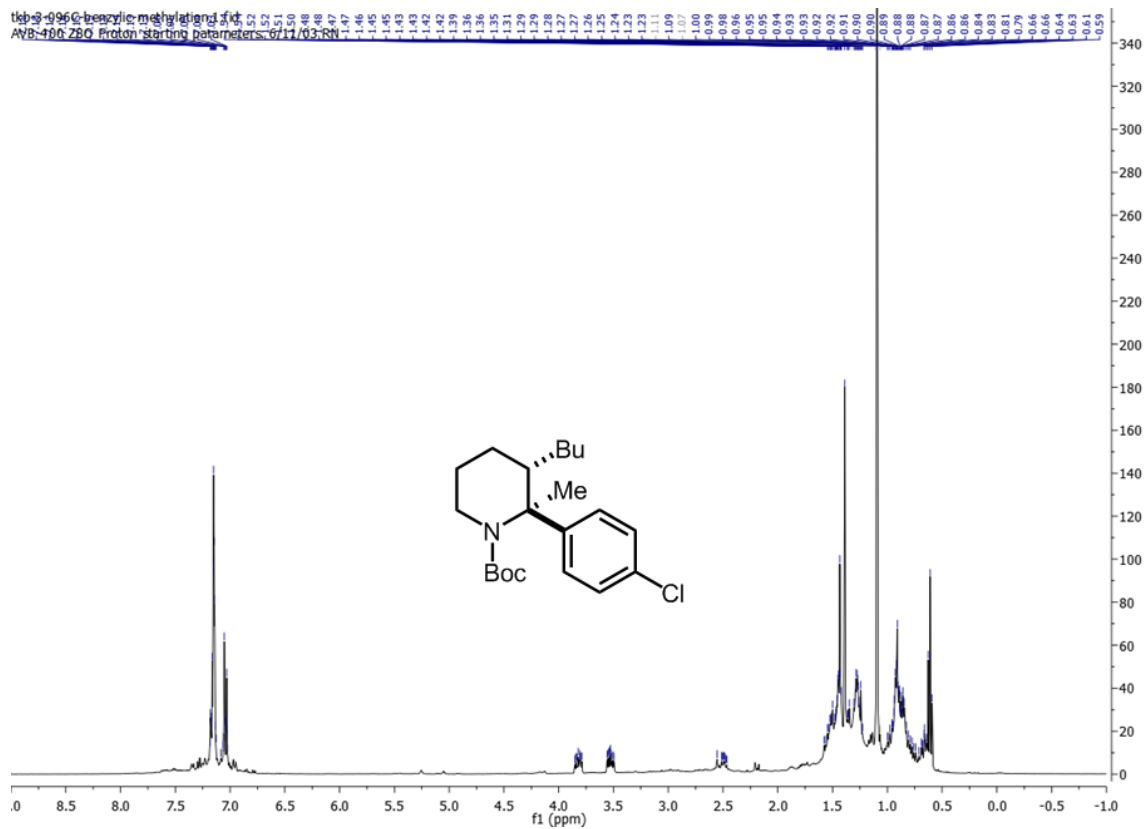
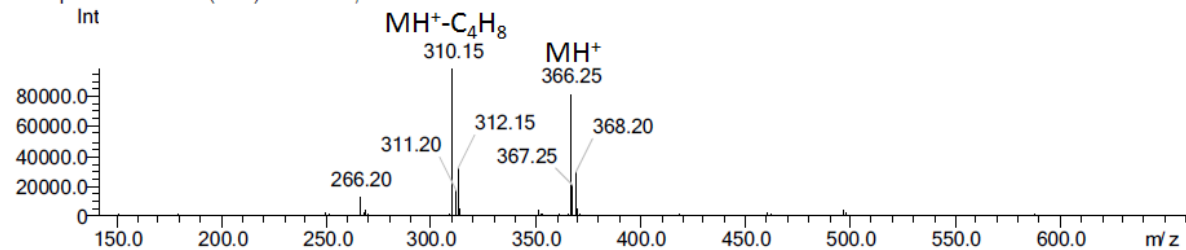


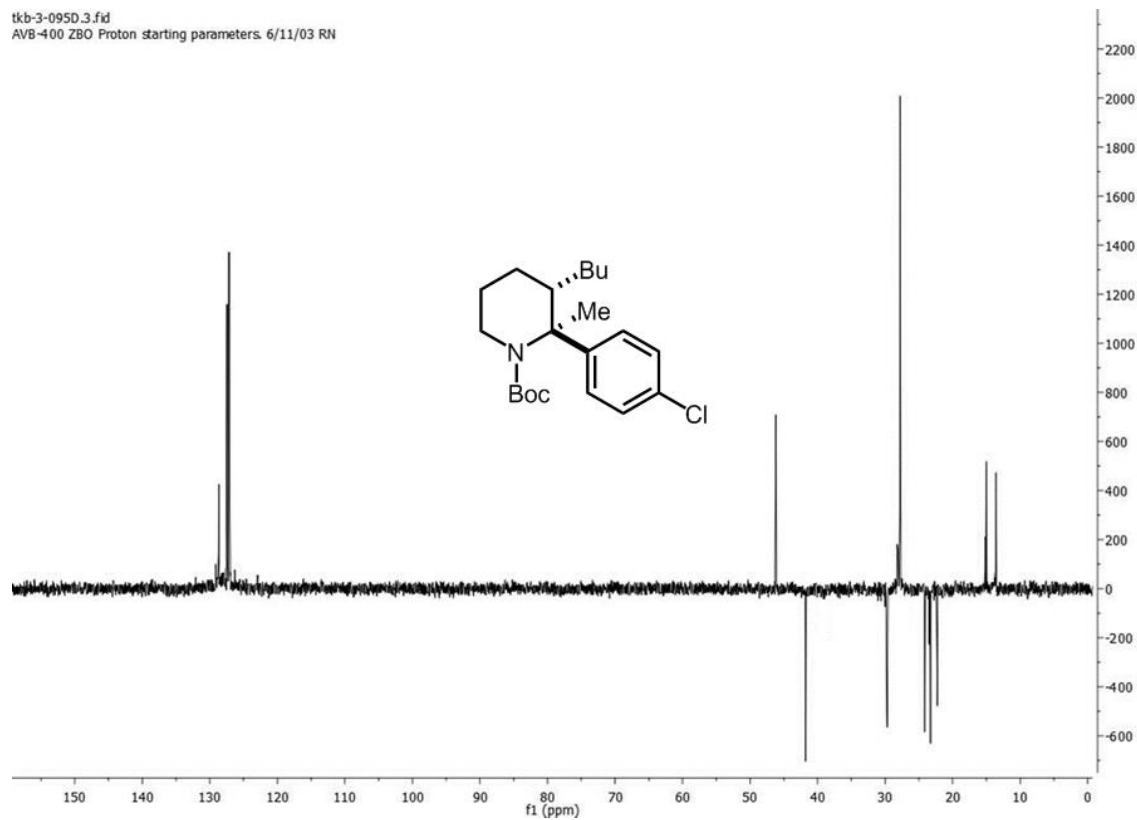
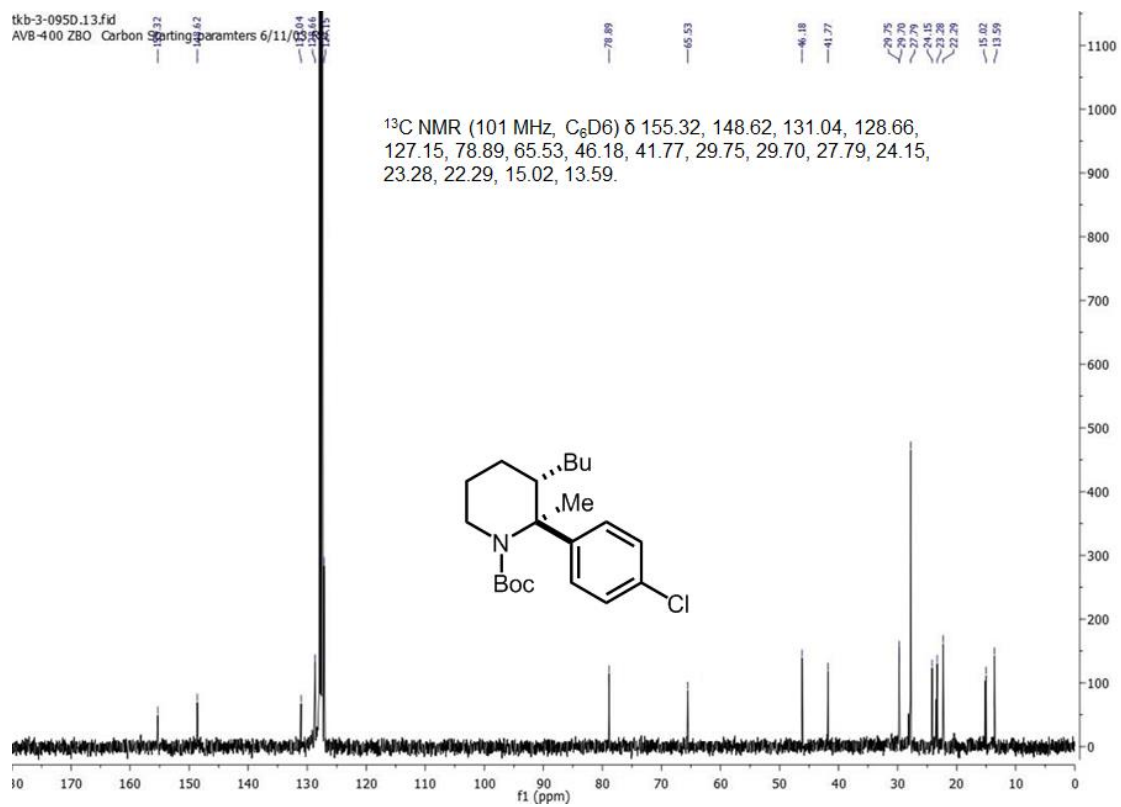
Prepared from **3e** (146.5 mg, 0.50 mmol), *n*-BuLi (1.1 equiv), and Me₂SO₄ (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 137 mg; 75%. ¹H NMR (400 MHz, C₆D₆) δ 7.17 to 7.00 (4H, m), 3.84 to 3.77 (1H, dd), 3.60 to 3.45 (1H, dd), 1.89 to 0.54 (26H, m). ¹³C NMR (101 MHz, C₆D₆) δ 155.3, 148.6, 131.0, 128.6, 127.1, 78.9, 65.5, 46.1, 41.7, 29.7, 29.7, 27.7, 24.1, 23.2, 22.2, 15.0, 13.6. **HRMS-EI⁺** (*m/z*): calc for C₂₁H₃₂ClNO₂ 365.2122, found 365.2125.

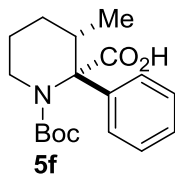


MS Spectrum

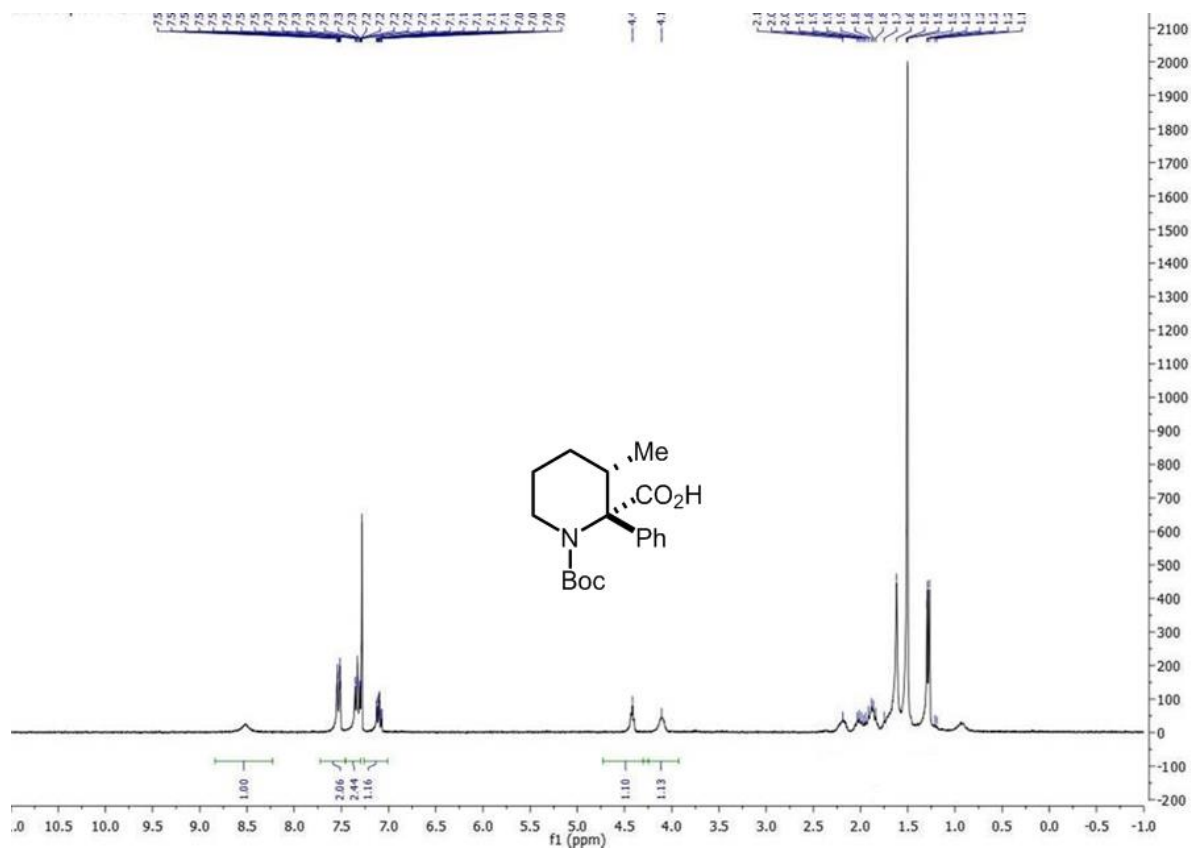
Group#1 - MS Mass(366) Peak: 43, RT: 5.97 to 6.72 min

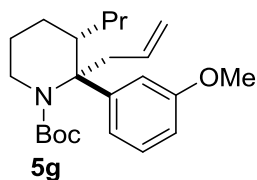
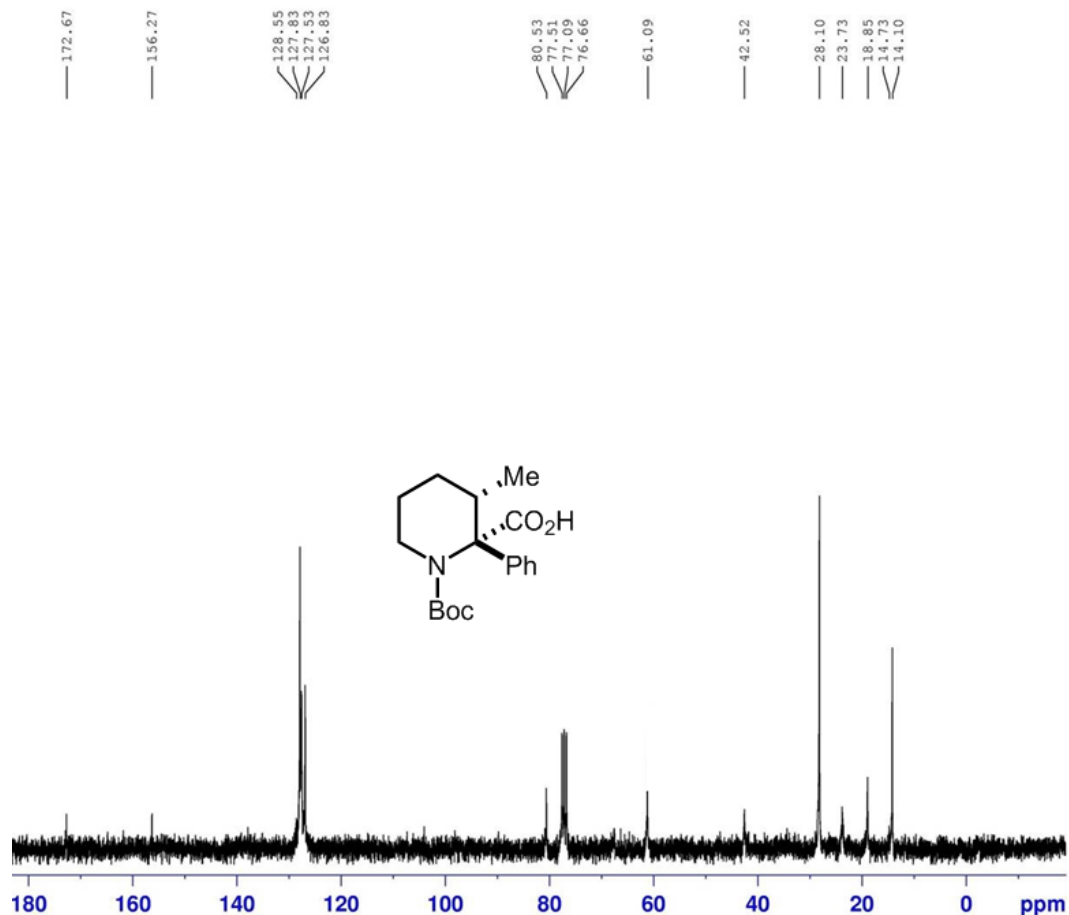






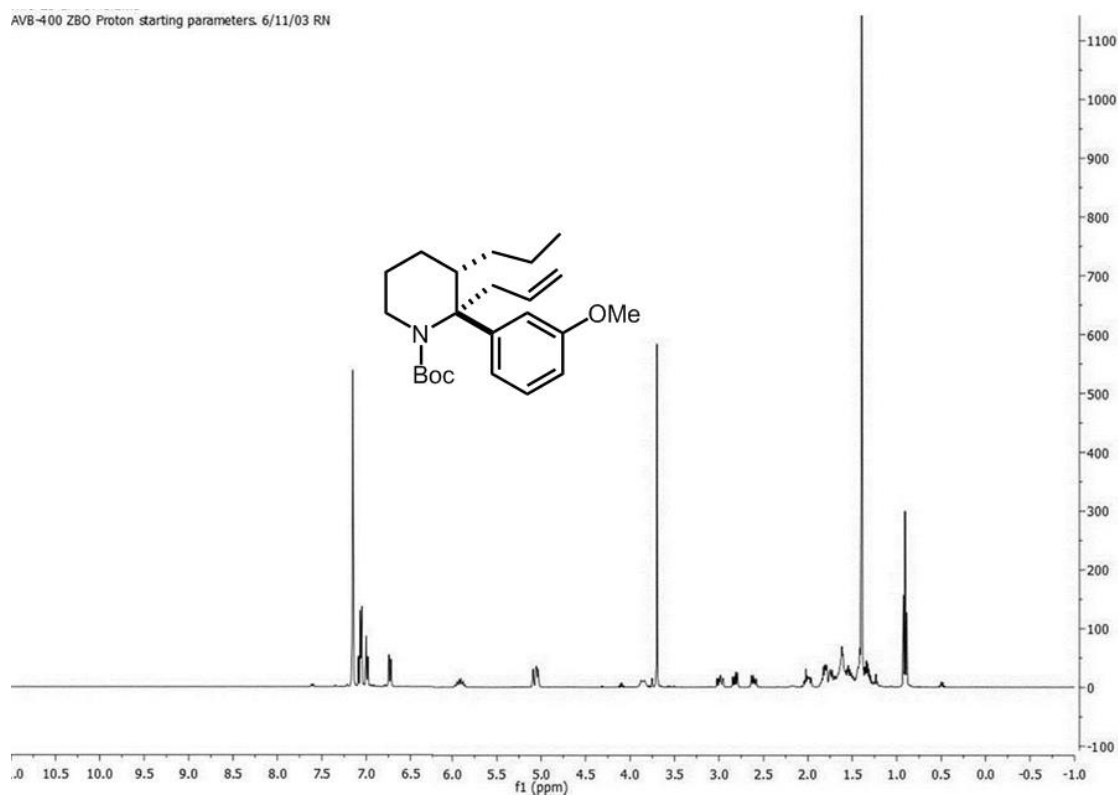
Prepared from **3b** (129.5 mg, 0.5 mmol), MeLi (3.0 equiv), HMPA (1.2 equiv) and dry ice (6 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 113 mg; 71%. ^1H NMR (400 MHz, CDCl_3) δ = 8.56 (1H, br), 7.60 to 7.57 (2H, m), 7.28 to 7.23 (2H, m), 7.18 (1H, t), 4.42 (1H, br), 4.13 (1H, br), 2.23 to 0.93 (17H, m) ^{13}C NMR (101 MHz, CDCl_3) δ = 172.7, 156.3, 138.3, 127.8, 127.5, 126.8, 80.5, 61.0, 42.5, 28.1, 23.7, 18.9, 14.7, 14.1. **HRMS-EI⁺** (m/z): calc'd for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ 319.1714, found 319.1717.

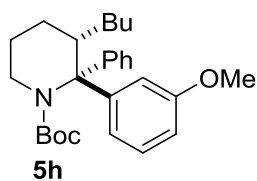
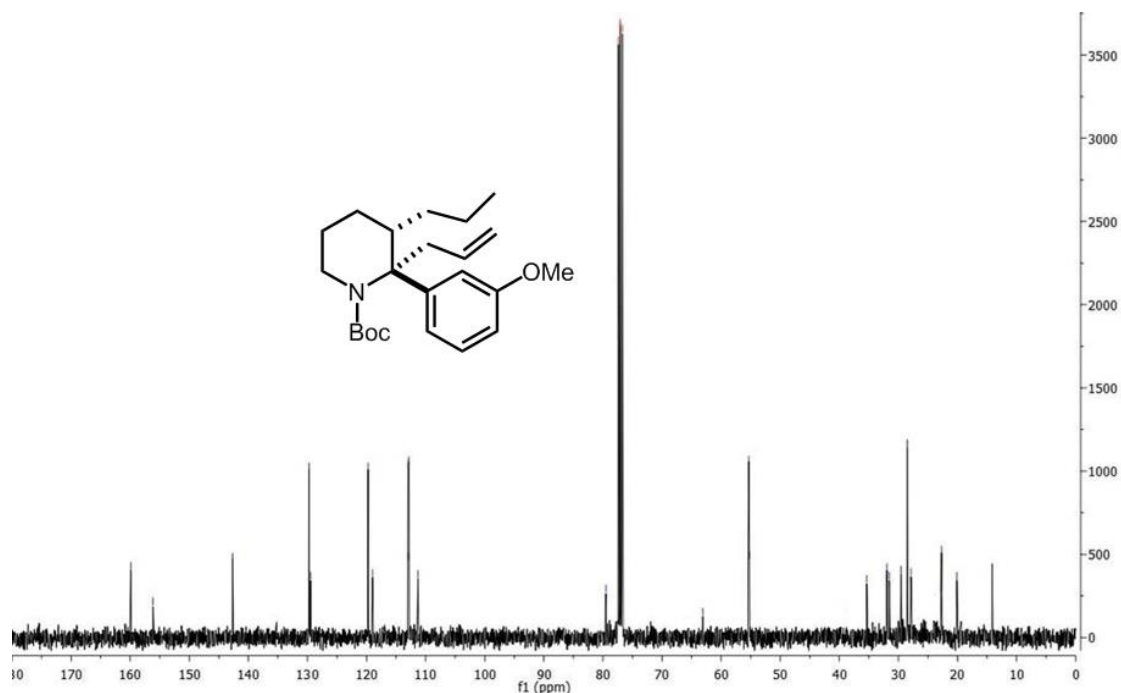




To an oven-dried, septum-capped, round-bottomed flask equipped with a stir bar was added a solution of **3c** (289 mg, 1.0 equiv) in THF (10 mL) nitrogen, in the presence of TMEDA (1.2 equiv). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-propyllithium (3 equiv) was added slowly. After 5 min at this temperature, the solution was transferred to a bath at $0\text{ }^{\circ}\text{C}$ and stirred for 10 min. After complete consumption of the starting material (as judged by LCMS and TLC), the solution was returned to the bath at $-78\text{ }^{\circ}\text{C}$ and a solution of ZnCl_2 (1.3 mL, 1.0 M in THF, 1.3 equiv) was added slowly. After 30 min, a solution of $\text{CuCN}\cdot 2\text{LiCl}$ [prepared from CuCN (1.2 equiv) and LiCl (2.5 equiv)] in THF (1.0 mL) was added. After 30 min, allyl bromide (3 equiv) was added. The mixture was allowed to stir for 10 h at this temperature prior to the addition of MeOH (0.2 mL) and warming to room temperature. A solution of NH_4Cl (5 mL) was added and

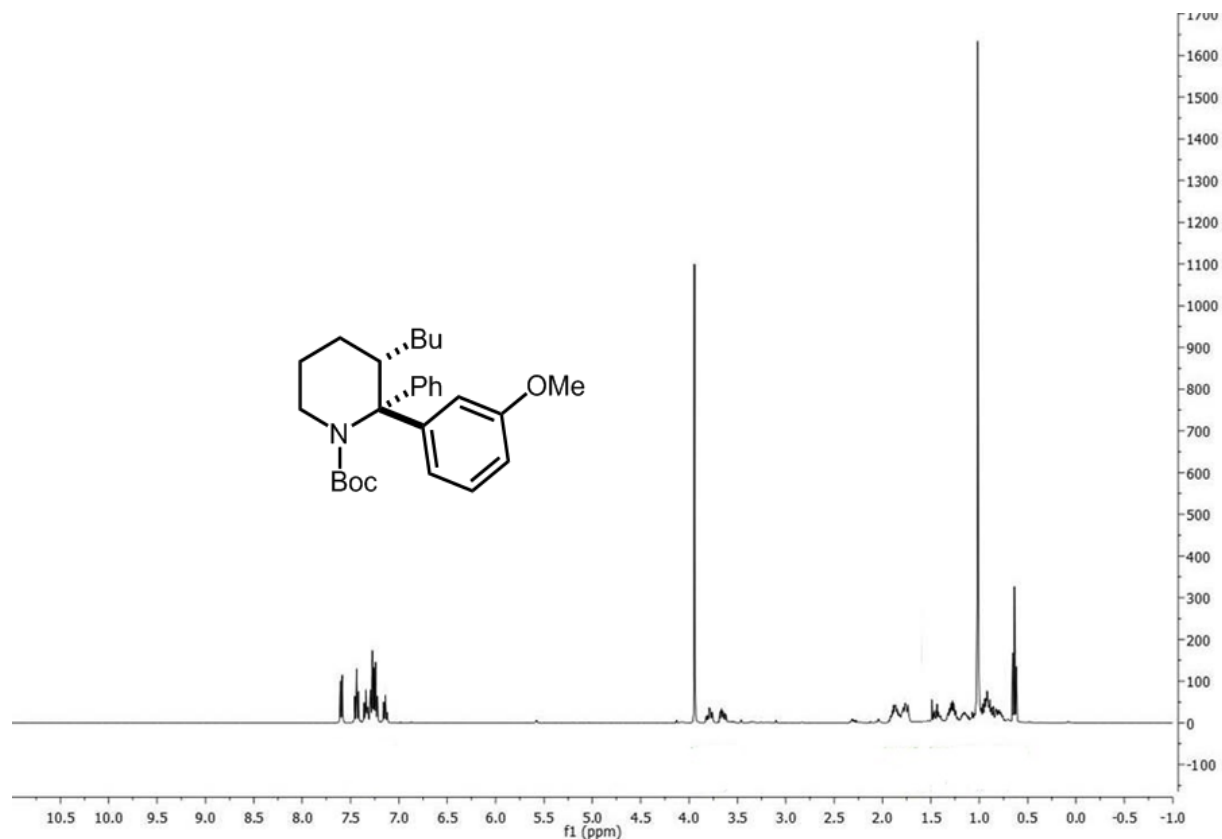
the aqueous layer was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and evaporated to give the crude product. **Purification:** Flash chromatography on silica eluting with hexane-EtOAc (90:10). Yield = 243 mg, 65%. ¹H NMR (400 MHz, CDCl₃) δ 7.21 to 7.12 (3H, m), 6.75 (1H, d), 5.96 to 5.82 (1H, m), 5.08 to 5.01 (2H, m), 3.84 to 3.70 (1H, m), 3.68 (3H, s), 3.14 to 2.67 (3H, m), 1.98 to 1.20 (18H, m), 0.86 to 0.82 (3H, t). ¹³C NMR (101 MHz, CDCl₃) δ 159.8, 156.0, 142.6, 129.7, 129.4, 119.9, 119.1, 112.9, 111.8, 79.4, 63.2, 55.2, 35.2, 31.8, 31.4, 29.5, 28.4, 27.8, 23.9, 20.0, 14.1. **HRMS-EI⁺** (*m/z*): calc'd for C₂₃H₃₅NO₃ 373.2617, found 373.2620.

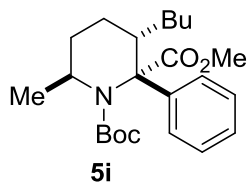
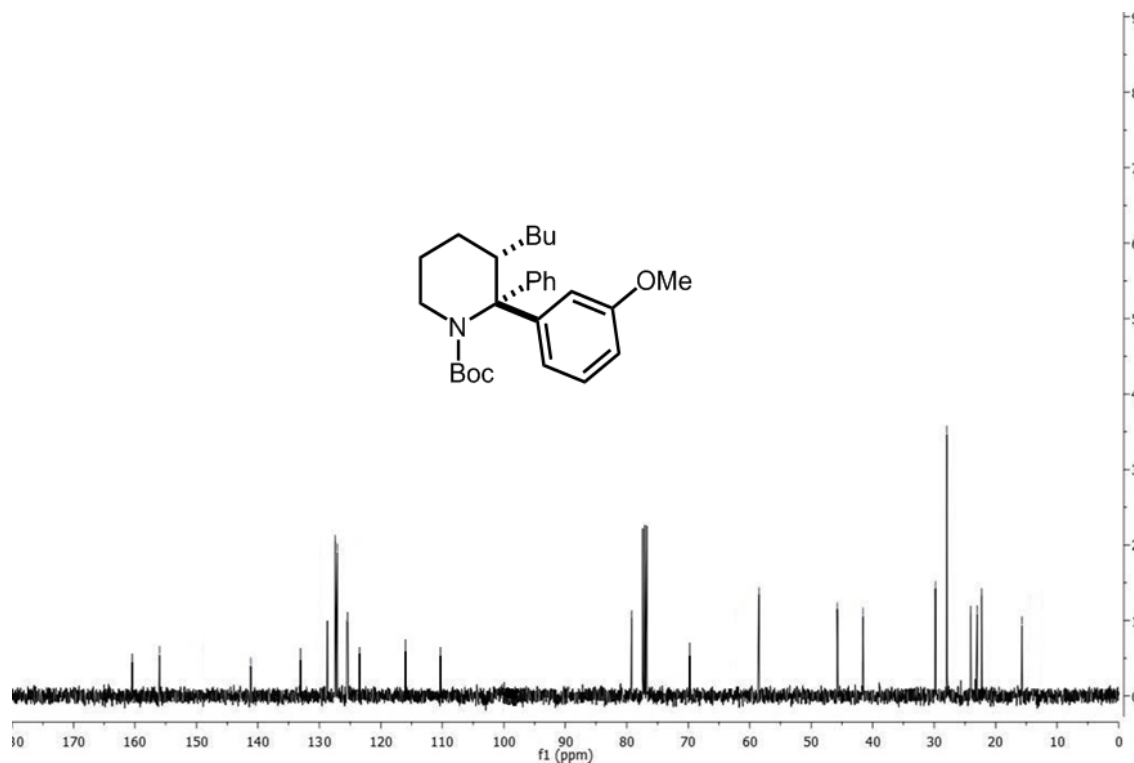




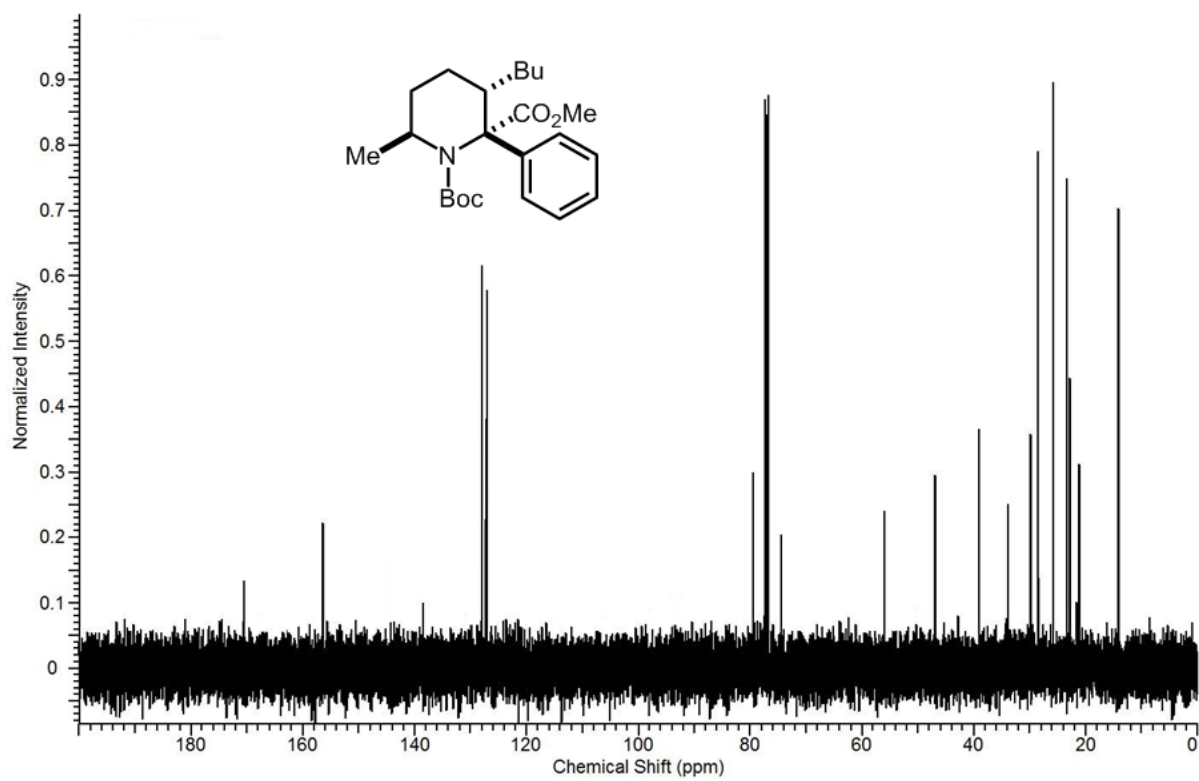
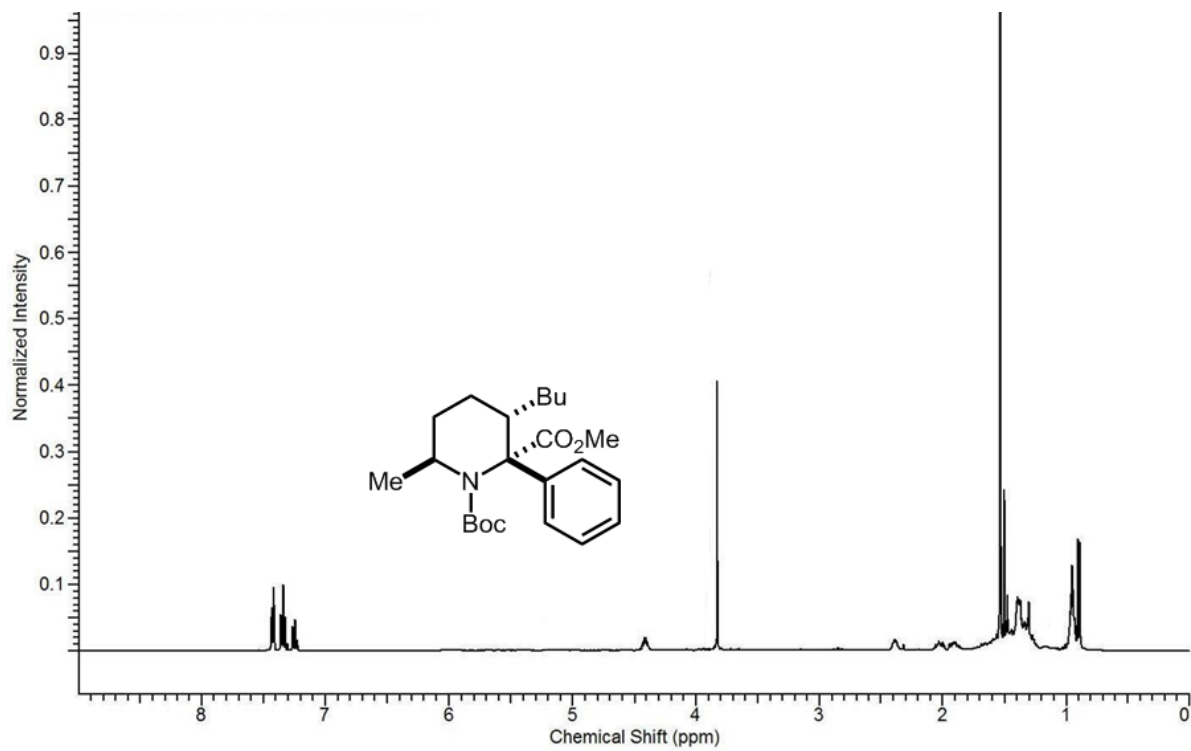
To an oven-dried, septum-capped, round-bottomed flask equipped with a stir bar was added a solution of **3c** (289 mg, 1.0 equiv) in THF (10 mL) nitrogen, in the presence of TMEDA (1.2 equiv). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and *n*-BuLi (2 equiv) was added slowly. After 5 min at this temperature, the solution was transferred to a bath at $0\text{ }^{\circ}\text{C}$ and stirred for 10 min. After complete consumption of the starting material (as judged by LCMS and TLC), the solution was returned to the bath at $-78\text{ }^{\circ}\text{C}$ and a solution of ZnCl_2 (1.3 mL, 1.0 M in THF, 1.3 equiv) was added slowly. After 30 min, the mixture was warmed to room temperature slowly. After 30 min at room temperature, $\text{Pd}_2(\text{dba})_3$ (37 mg, 0.04 mmol, 4 mol%), *t*- $\text{Bu}_3\text{P}\cdot\text{HBF}_4$ (23 mg, 0.08 mmol, 8 mol%) and bromobenzene (1.1 equiv), were added sequentially prior to warming to $50\text{ }^{\circ}\text{C}$. After stirring for 48 h at $50\text{ }^{\circ}\text{C}$, the mixture was diluted with Et_2O and *sat.* NH_4Cl was added. The phases were separated and the aqueous layer was extracted *four* times with Et_2O . The combined organic layers were washed with brine and dried over Na_2SO_4 for 30 min, filtered and concentrated to obtain the crude product.

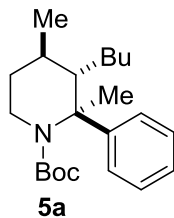
Purification: Flash chromatography on silica eluting with hexane-EtOAc (90:10). Yield = 93 mg, 22%. ^1H NMR (400 MHz, CDCl_3) δ 7.61 to 7.12 (10H, m), 3.94 (3H, s), 3.82 to 3.62 (2H, m), 1.93 to 1.57 (2H, m), 1.49 to 0.70 (17H, m), 0.65 to 0.62 (3H, t). ^{13}C NMR (101 MHz, CDCl_3) δ 161.1, 156.3, 140.8, 132.6, 128.8, 127.7, 127.1, 125.3, 115.4, 110.6, 79.2, 69.4, 57.3, 45.8, 42.1, 29.4, 28.3, 24.5, 22.1, 15.6. **HRMS- EI^+** (m/z): calc'd for $\text{C}_{27}\text{H}_{37}\text{NO}_3$ 423.2773, found 423.2776.



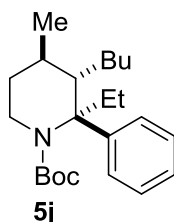


Prepared from **3i** (68.3 mg, 0.25 mmol), *n*-BuLi (2.5 equiv), and methyl chloroformate (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 81 mg; 83%. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.48 to 7.24 (m, 5H), 4.41 to 4.36 (m, 1H), 3.83 (s, 3H), 2.43 to 2.35 (m, 1H), 2.17 to 1.83 (m, 2H), 1.68 to 1.21 (m, 17H), 1.00 to 0.80 (m, 6H overlapping doublet and triplet). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.4, 156.4, 139.8, 128.0, 127.0, 126.3, 79.6, 75.2, 56.4, 46.9, 38.7, 34.1, 30.8, 29.8, 28.5, 23.4, 22.3, 21.6, 21.2, 14.4. **HRMS-EI** $^+$ (m/z): Calcd. for $\text{C}_{23}\text{H}_{35}\text{NO}_4$ $[\text{M}]^+$ 389.2566; found, 389.2561.

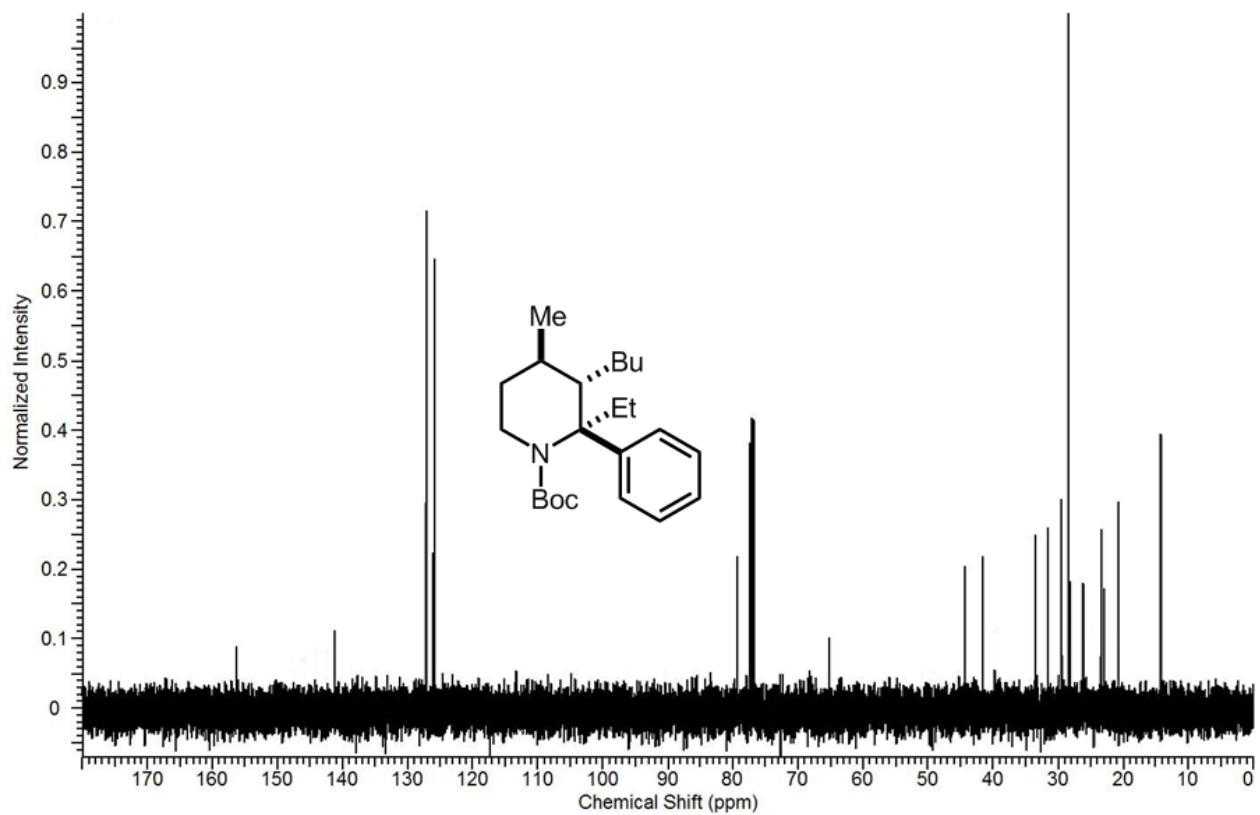
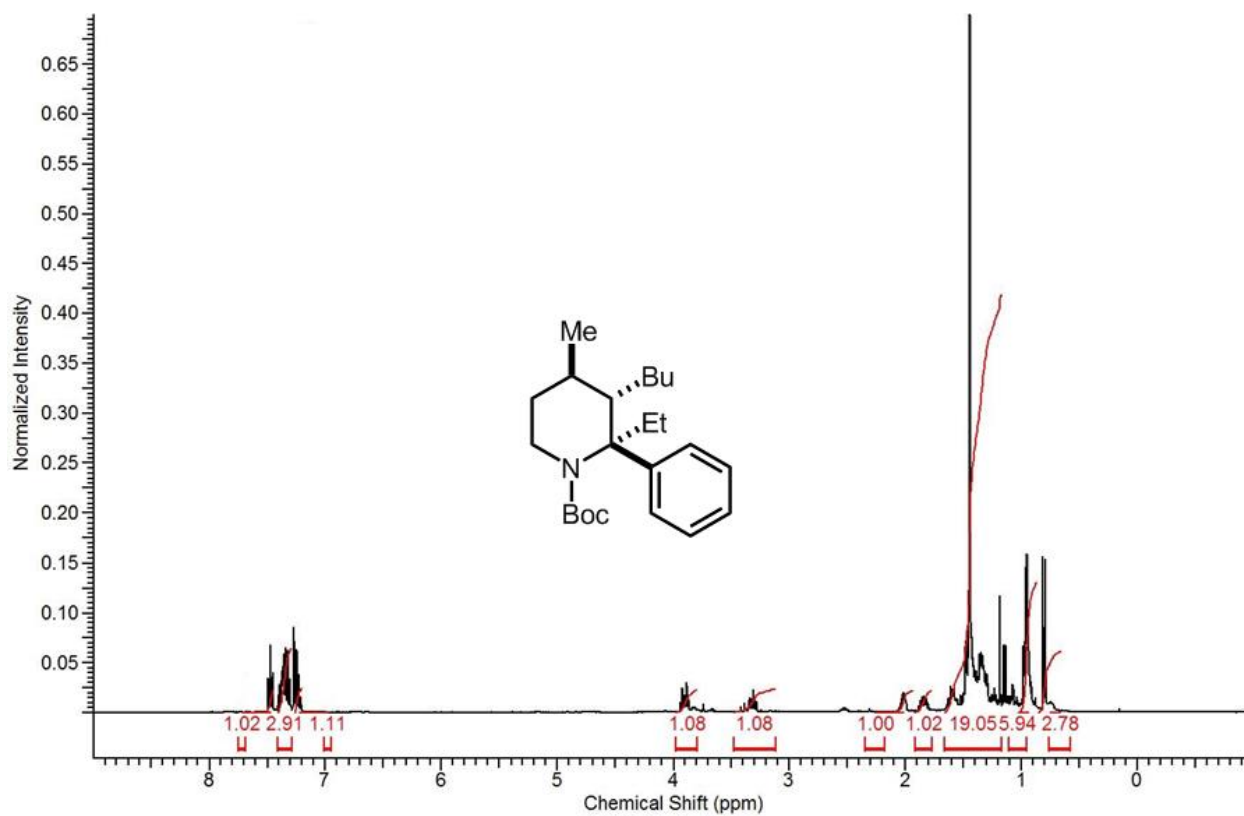


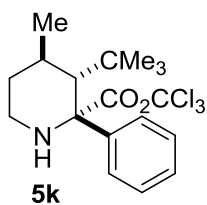
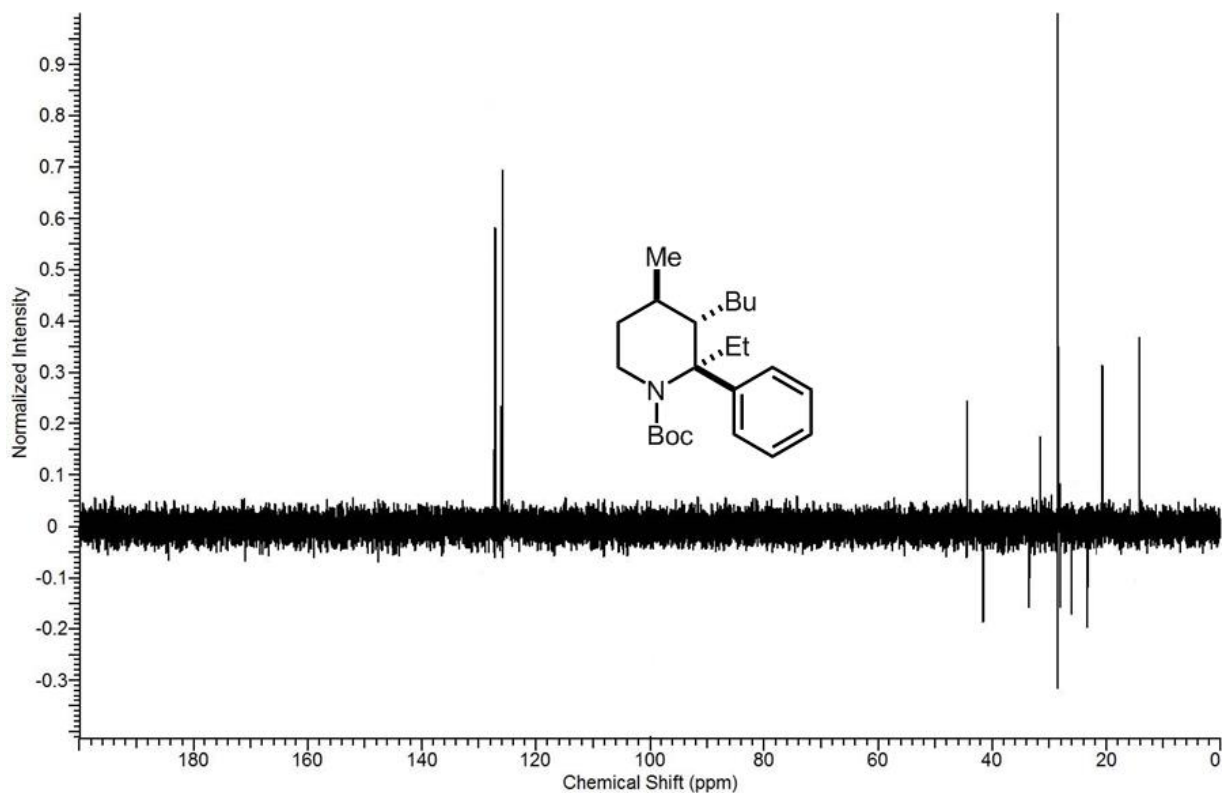


Prepared from **3a** (136.5 mg, 0.50 mmol), *n*-BuLi (2 equiv), and Me₂SO₄ (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 147 mg; 85%. Data as reported.⁶

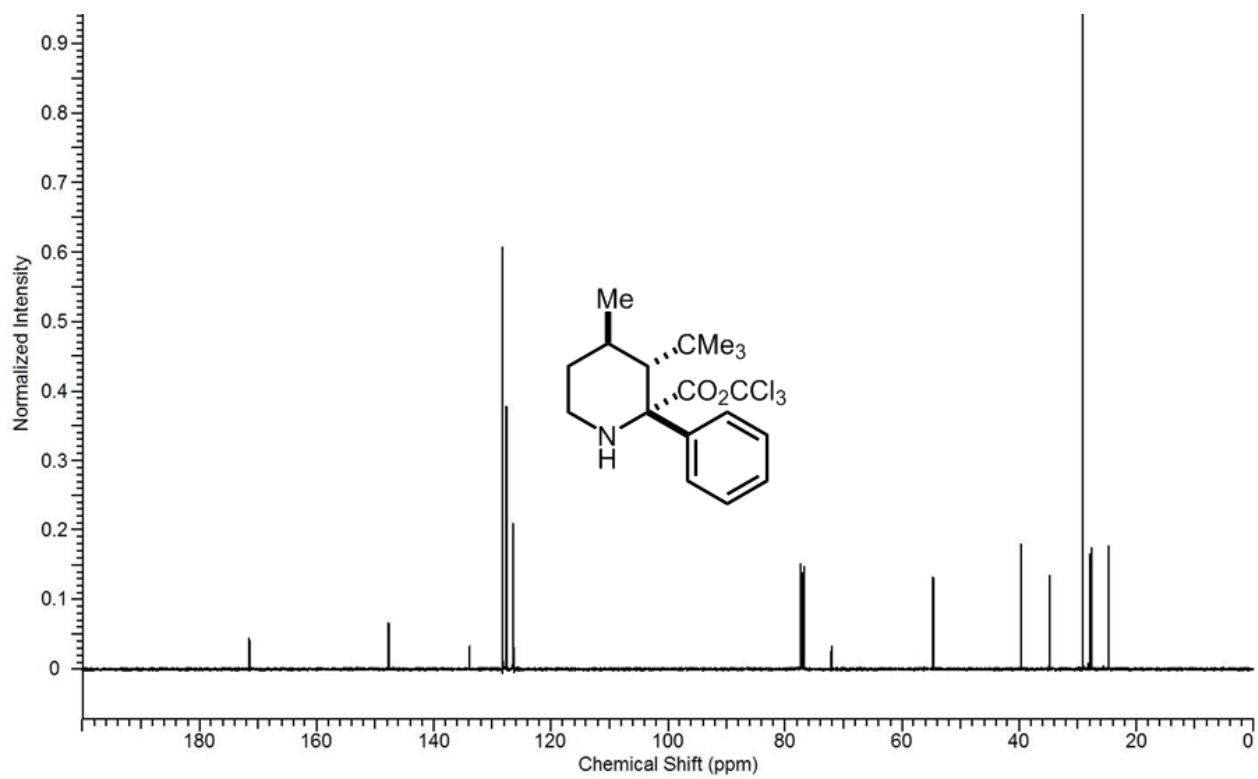
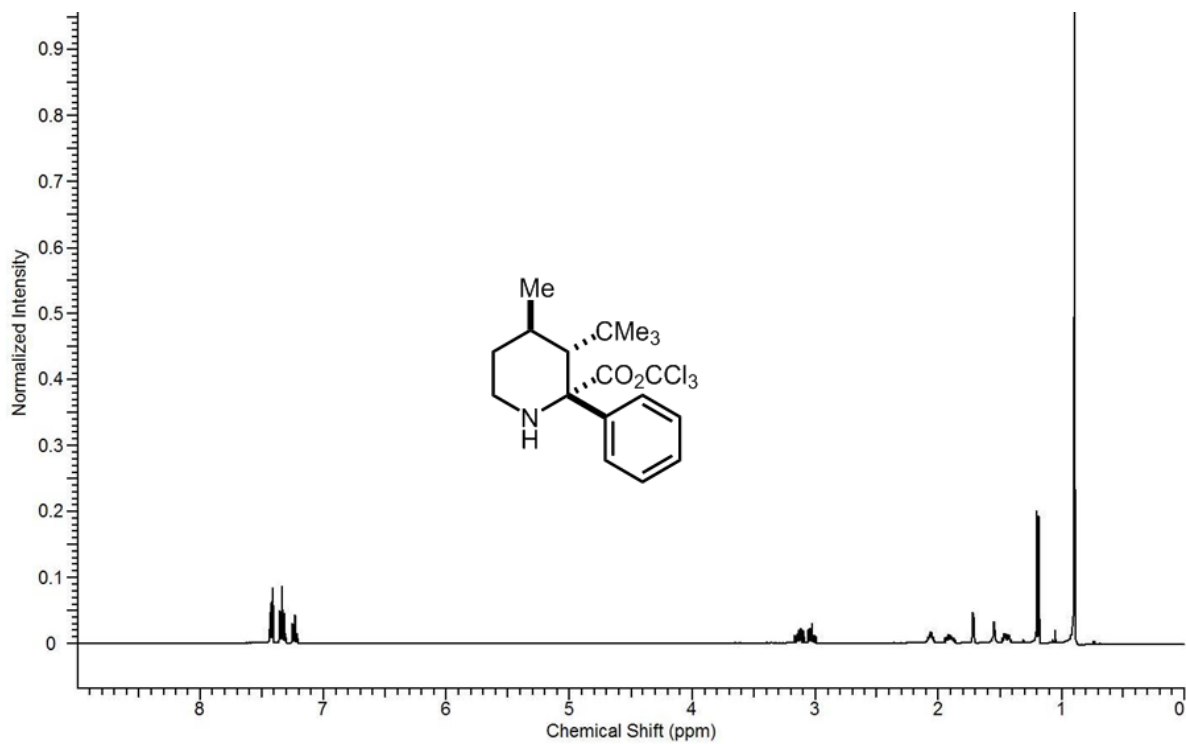


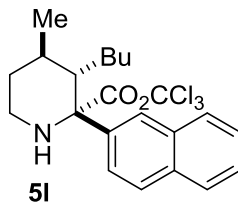
Prepared from **3a** (136.5 mg, 0.50 mmol), *n*-BuLi (2 equiv), and ethyl iodide (3 equiv) using **General Procedure B**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (95:5). Yield = 119 mg; 66%. ¹H NMR (400 MHz, CDCl₃) δ 7.40 to 7.21 (5H, m), 3.93 to 3.87 (1H, m), 3.35 to 3.28 (1H, m), 2.05 to 2.00 (1H, m), 1.88 to 1.80 (1H, m), 1.65 to 1.06 (17H, m), 1.01 to 0.80 (6H, m), 0.75 (3H, d). ¹³C NMR (101 MHz, CDCl₃) δ 156.2, 143.2, 141.2, 128.7, 128.2, 127.2, 127.1, 126.1, 125.8, 79.4, 65.3, 44.4, 41.6, 33.5, 31.5, 29.5, 28.4, 26.1, 23.3, 23.0, 22.5, 20.8, 14.2. **HRMS-EI**⁺ (*m/z*): Calcd. for C₂₃H₃₇NO₂ [M]⁺ 359.2824; found, 359.2819.



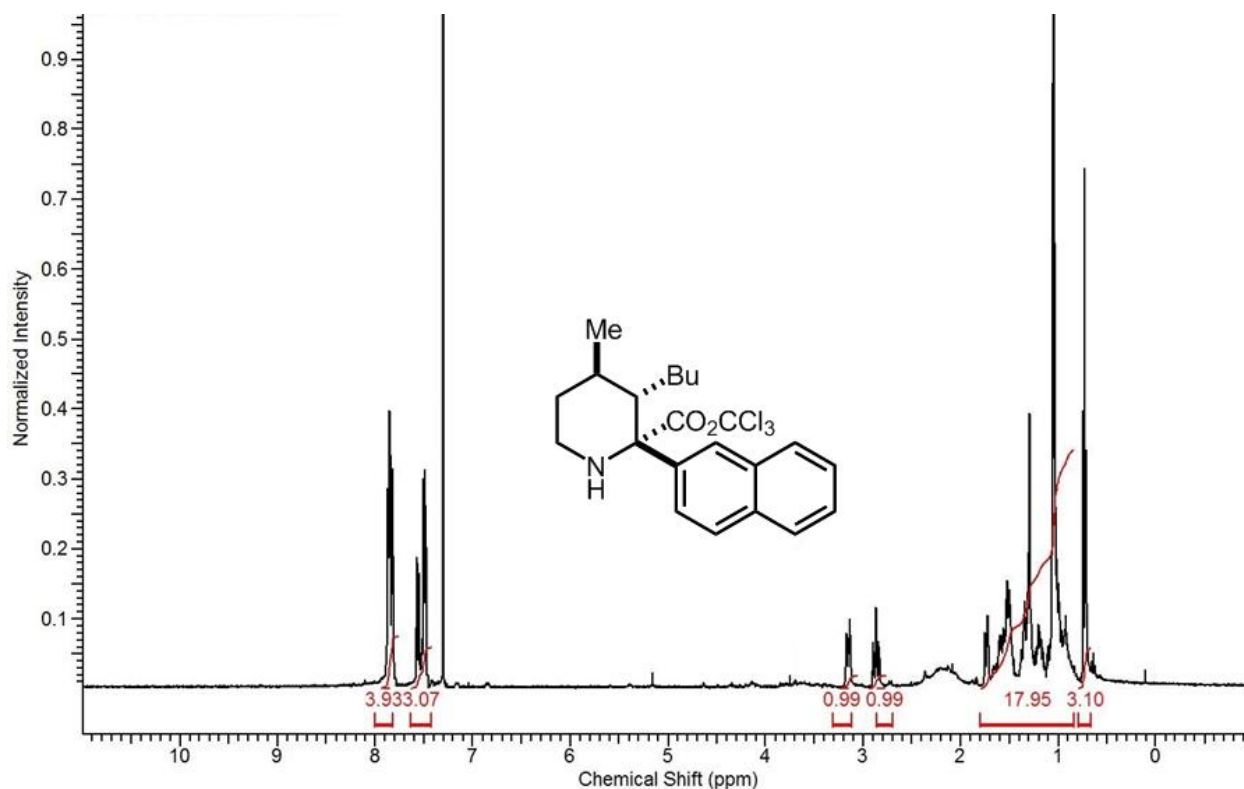


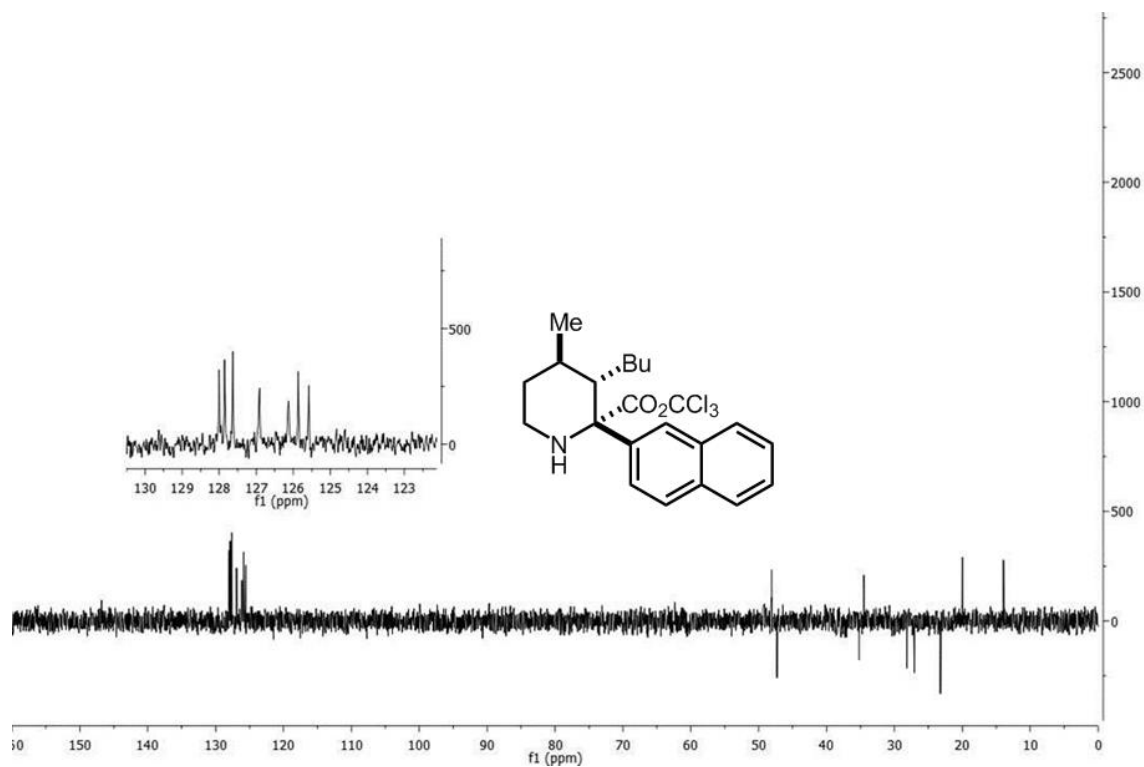
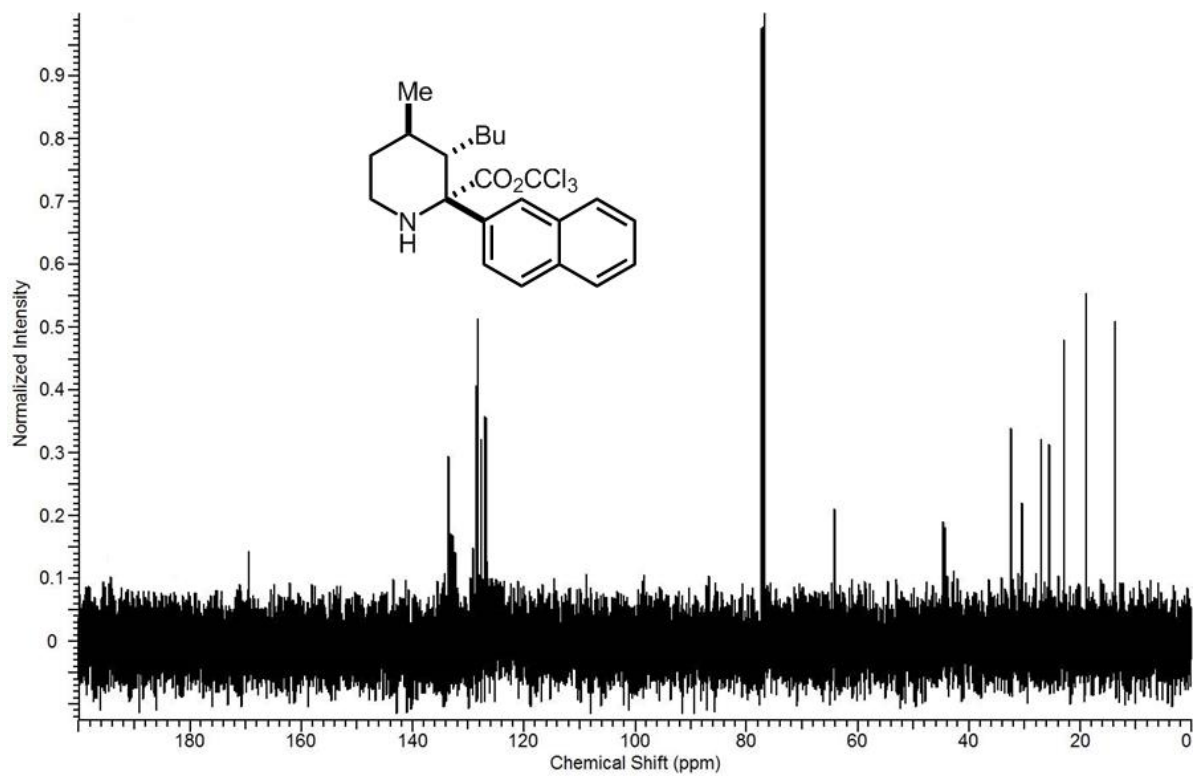
Prepared from **3a** (138 mg, 0.505 mmol), 1.7 M *t*-BuLi in pentane (2.5 equiv), and trichloromethyl chloroformate (3 equiv) using **General Procedures B & C**. Yield = 68 mg, 35% yield (over 2 steps). $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.43 to 7.21 (m, 5H), 3.17 to 3.00 (m, 2H), 2.10 to 2.02 (m, 1H), 1.95 to 1.86 (m, 1H), 1.72 to 1.71 (m, 1H), 1.48 to 1.41 (m, 1H), 1.32 (d, 3H), 0.89 (s, 9H). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.6, 147.7, 134.0, 128.2, 127.5, 126.3, 72.1, 54.6, 39.7, 34.8, 29.2, 27.9, 27.6, 24.7. **HRMS- EI^+** (m/z): Calcd. for $\text{C}_{18}\text{H}_{24}\text{Cl}_3\text{NO}_2$ $[\text{M}]^+$ 391.0873; found, 391.0870.

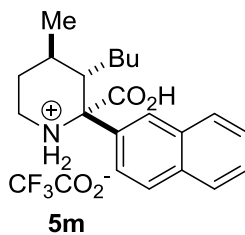




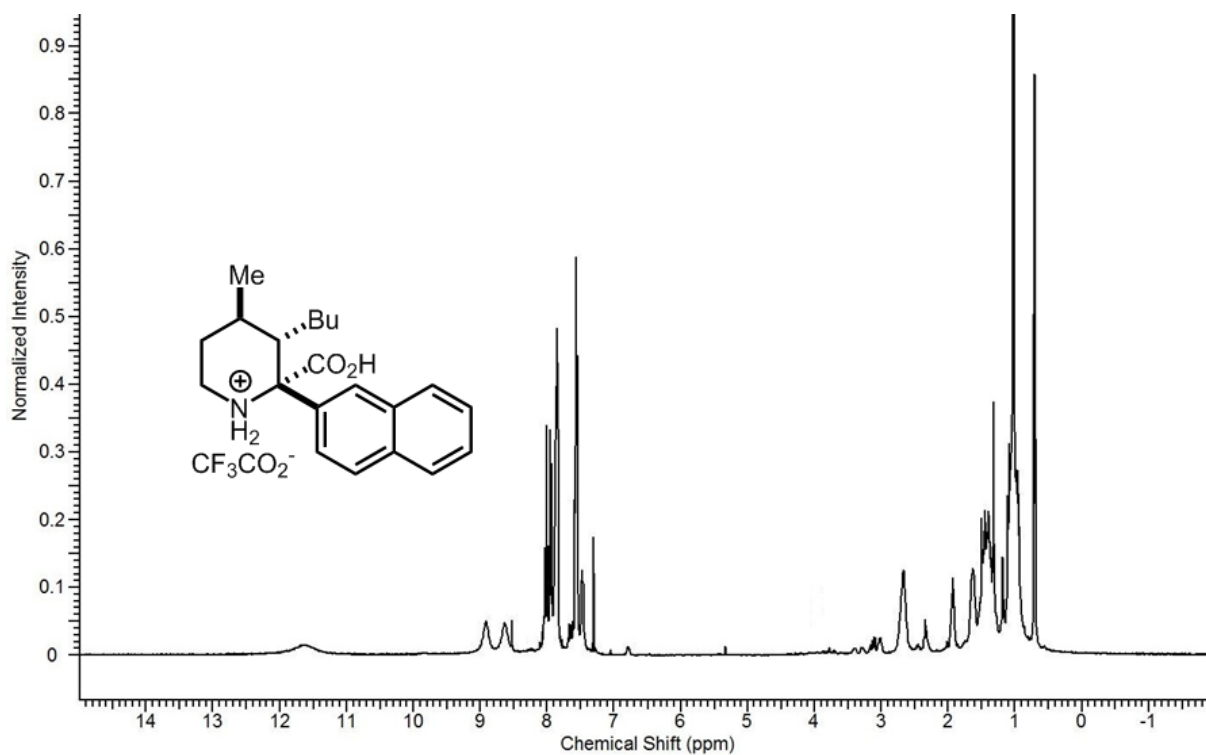
Prepared from **3j** (81 mg, 0.25 mmol) and *n*-BuLi (2 equiv), and trichloromethyl chloroformate (3 equiv) using **General Procedures B** and **C**. Purification: Flash chromatography on silica eluting with hexane:EtOAc (80:20). Yield = 94 mg; 85%. ^1H NMR (400 MHz, CDCl_3) δ 7.88 to 7.79 (4H, m), 7.57 to 7.30 (3H, m), 3.18 to 3.13 (1H, dd), 2.90 to 2.83 (1H, t), 1.76 to 0.62 (17H, m). ^{13}C NMR (101 MHz, CDCl_3) δ 170.3, 138.4, 133.7, 132.6, 132.4, 128.9, 128.3, 127.7, 127.6, 126.8, 126.3, 125.7, 64.1, 44.6, 44.1, 32.5, 30.4, 29.7, 27.0, 22.9, 19.0, 13.7. **HRMS-EI⁺** (*m/z*): Calcd. for $\text{C}_{22}\text{H}_{26}\text{Cl}_3\text{NO}_2$ [M]⁺ 441.1029; found, 441.1032.

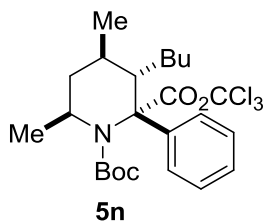
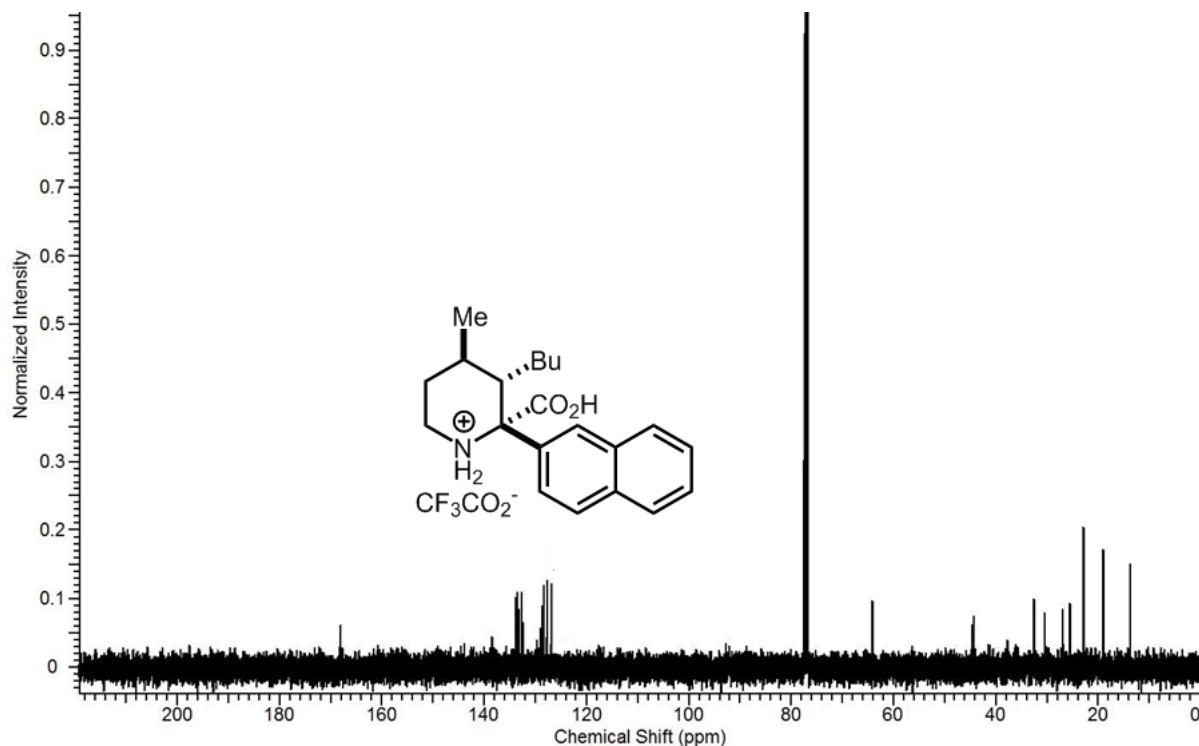




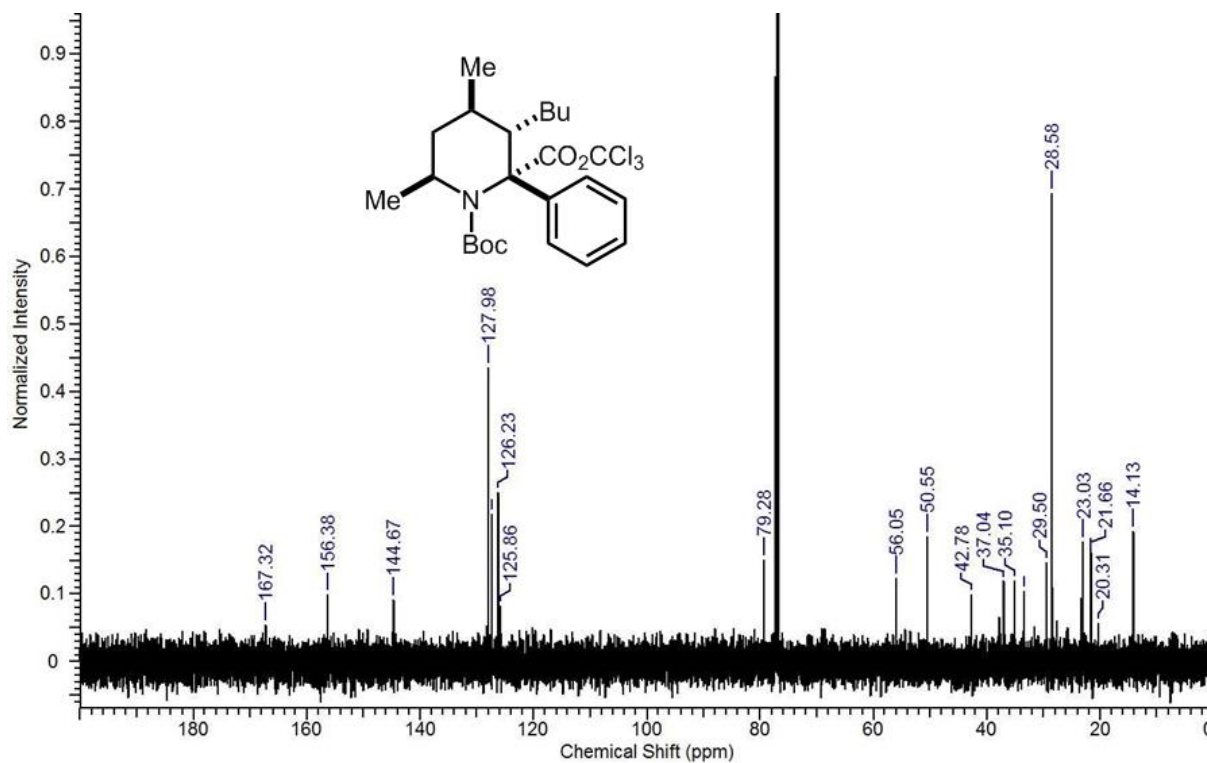
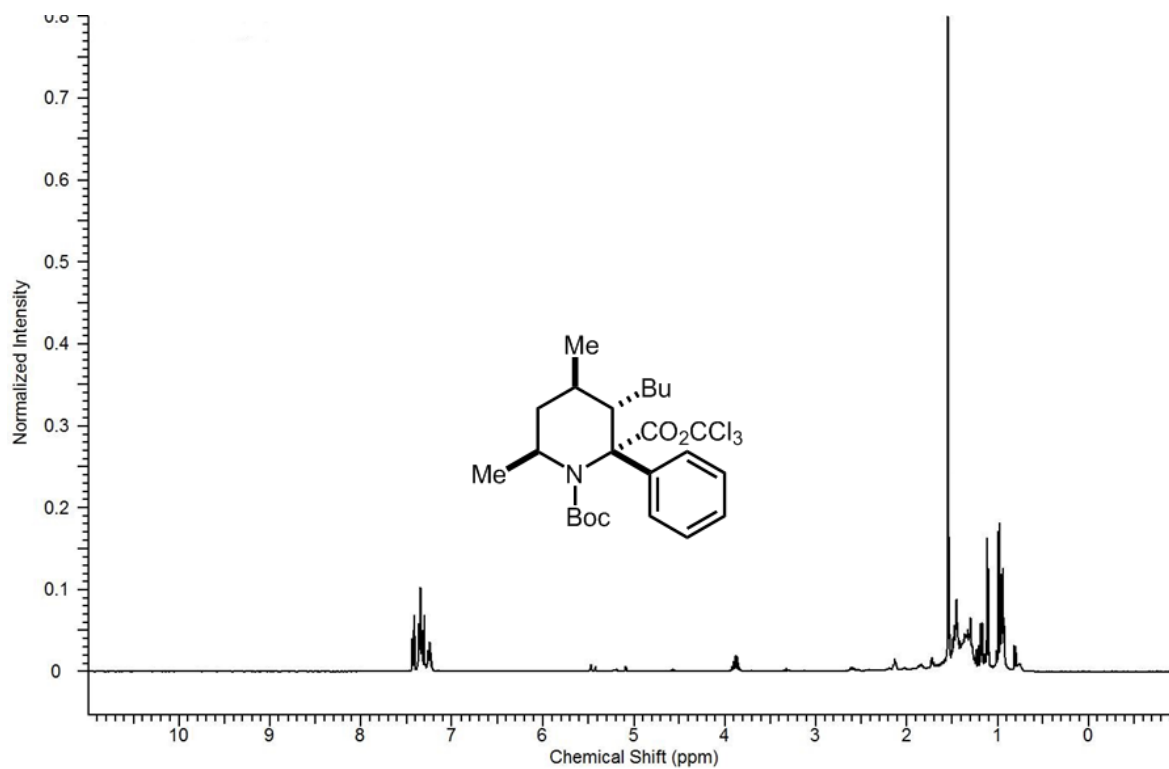


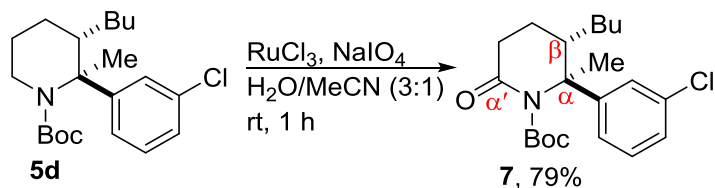
Prepared from **3j** (81 mg, 0.25 mmol) and *n*-BuLi (2 equiv), and dry ice (~5 equiv) using **General Procedures B** and **C**. Yield = 83 mg, 75% yield (over 2 steps). ^1H NMR (400 MHz, CDCl_3) δ 11.74, (1H), 8.91 (1H), 8.63 (1H), 8.05 to 7.40 (7H), 3.97 (1H), 2.67 (1H), 2.02 (1H), 1.68 to 0.69 (16H). ^{13}C NMR (101 MHz, CDCl_3) δ 169.1, 138.4, 133.5, 133.2, 128.6, 128.3, 127.7, 127.0, 126.7, 126.4, 125.7, 64.2, 44.6, 44.2, 32.4, 30.5, 27.1, 25.6, 22.9, 19.0, 13.6.



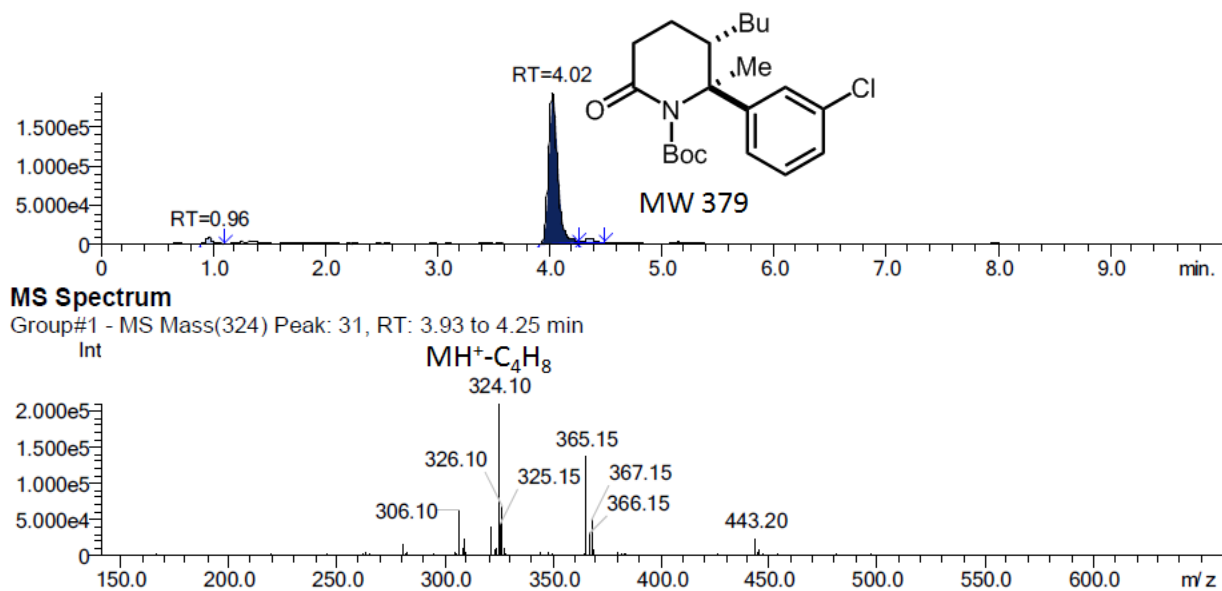


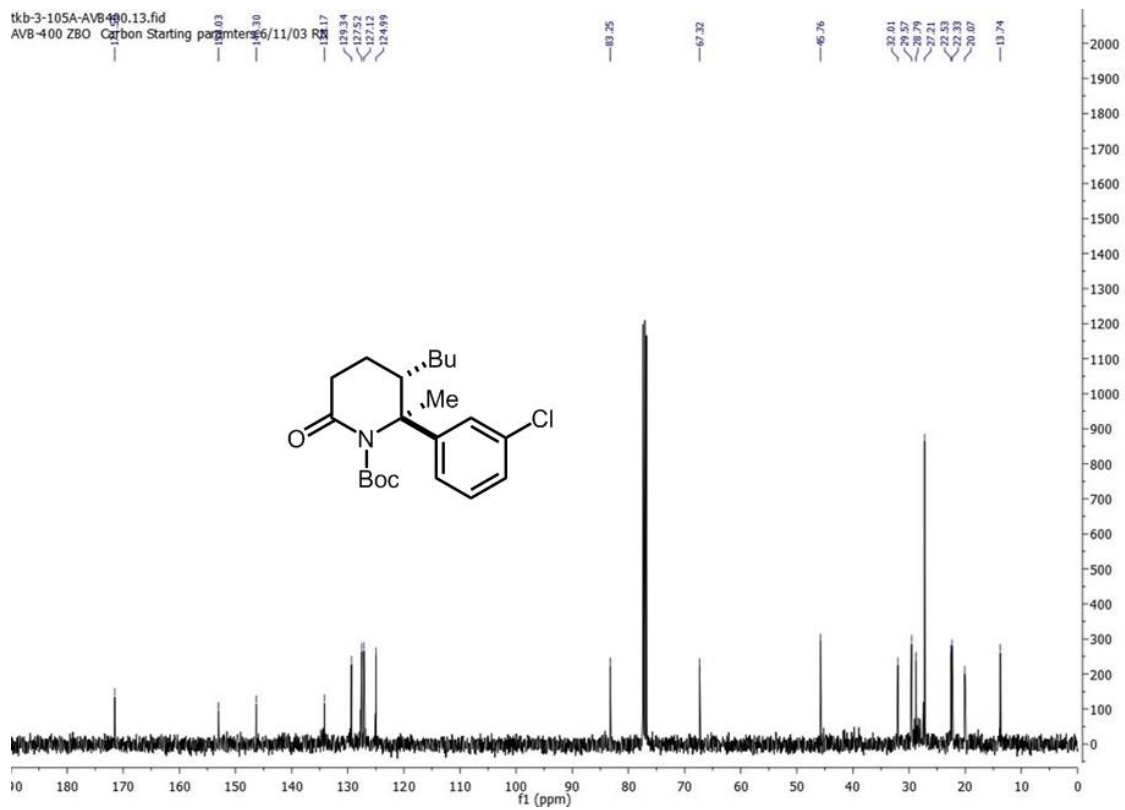
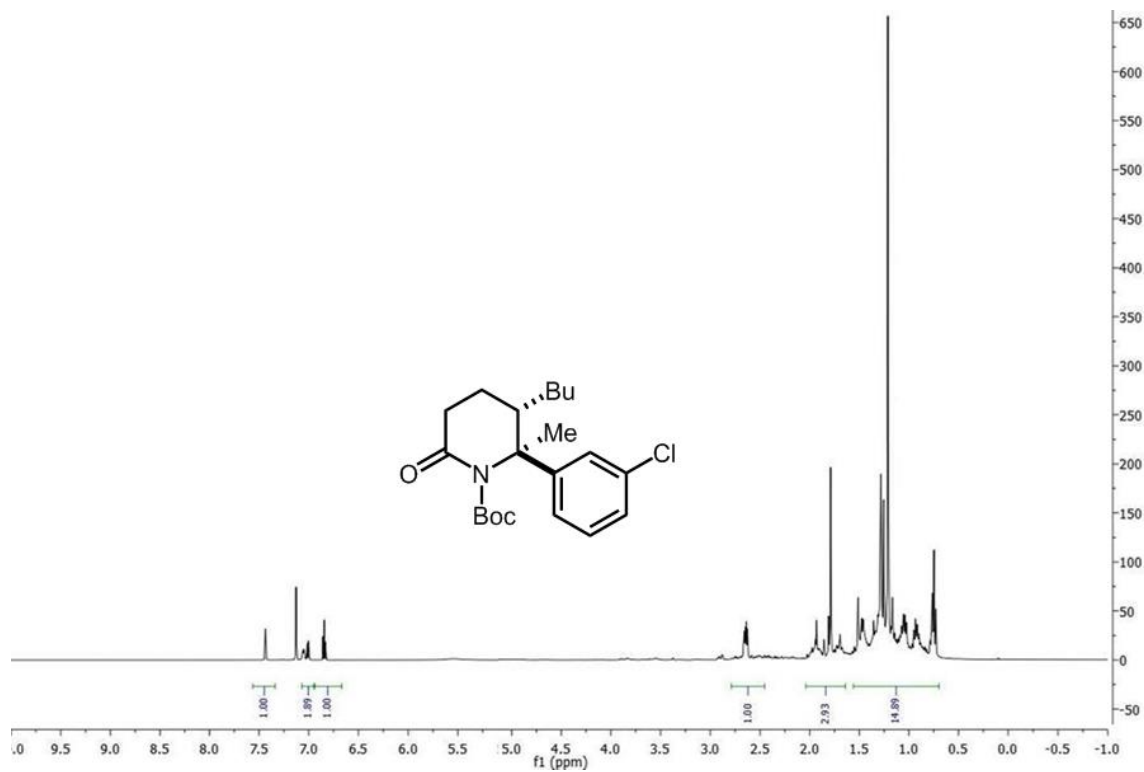
Prepared from **3l** (68.3 mg, 0.25 mmol), *n*-BuLi (2.5 equiv), and methyl chloroformate (3 equiv) using **General Procedure B**. Yield = 100 mg, 79%. ^1H NMR (400 MHz, CDCl₃) δ 7.44 to 7.22 (5H, m), 3.90 to 3.84 (1H, m), 2.19 to 2.11 (1H, m), 1.89 to 0.89 (27H, m). ^{13}C NMR (101 MHz, CDCl₃) δ 167.3, 156.3, 144.6, 127.9, 127.3, 126.2, 79.3, 56.0, 50.5, 42.8, 37.0, 35.0, 33.4, 29.5, 28.5, 23.0, 21.6, 20.3, 14.1.



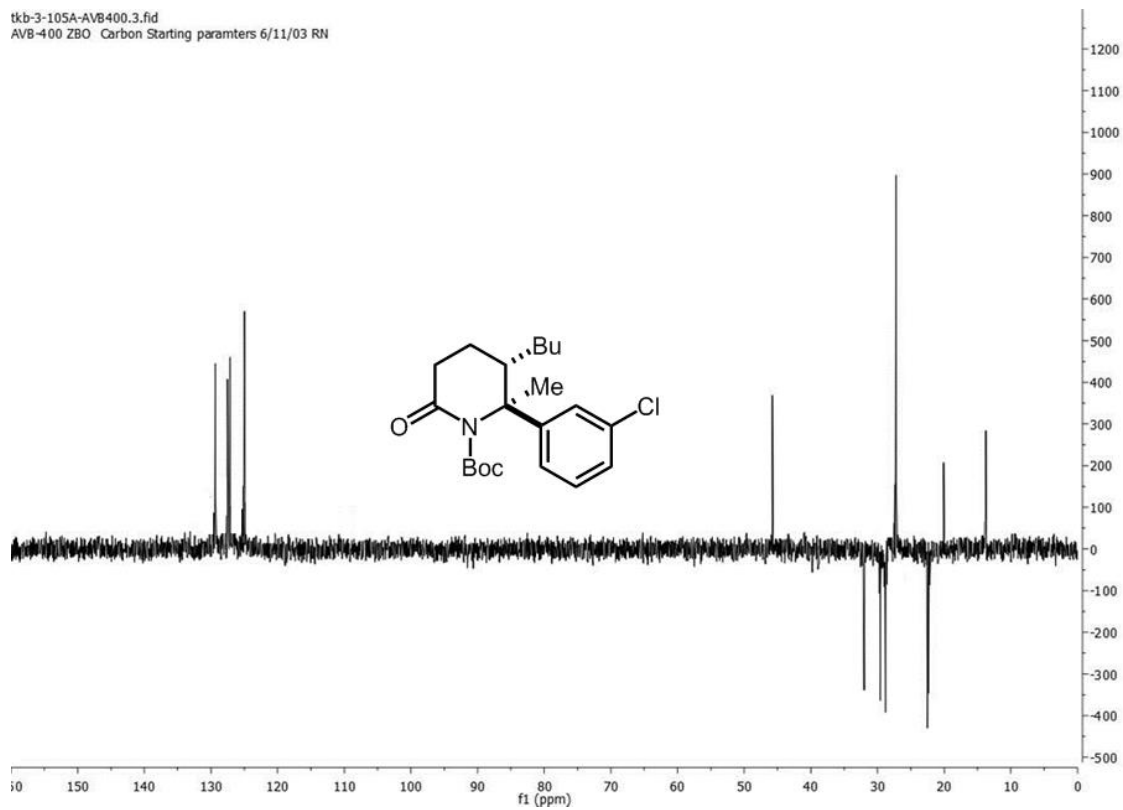


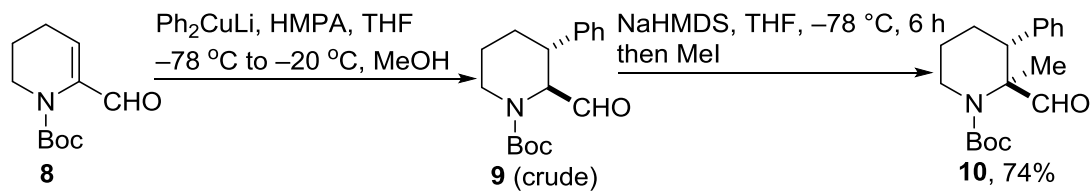
To a solution of NaIO_4 (638 mg, 3 mmol) in H_2O (15 mL) was added $\text{RuCl}_3 \cdot \text{H}_2\text{O}$ (2 mol%) and a yellow solution was formed. The mixture was added to a solution of **5d** (365 mg, 1 mmol, 1 equiv) in acetonitrile (5 mL) and then vigorously stirred at room temperature for 1 h. The mixture was diluted with EtOAc and the organic layer was separated. The aqueous layer was extracted twice with EtOAc. The combined organic layers were dried over Na_2SO_4 , filtered through silica gel to remove a black precipitate and then concentrated under reduced pressure to obtain the desired lactam as an oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.39 (1H, s) 7.20 to 7.16 (2H, m), 6.87 (1H, d), 2.66 to 2.63 (1H, t), 1.93 to 0.73 (24H, m). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 171.5, 153.0, 146.3, 134.1, 129.3, 127.5, 127.1, 124.9, 83.2, 67.3, 45.7, 32.0, 29.6, 28.8, 27.2, 22.5, 22.3, 20.0, 13.7. HRMS calc for $\text{C}_{21}\text{H}_{30}\text{ClNO}_3$ 379.1914, found 379.1917.





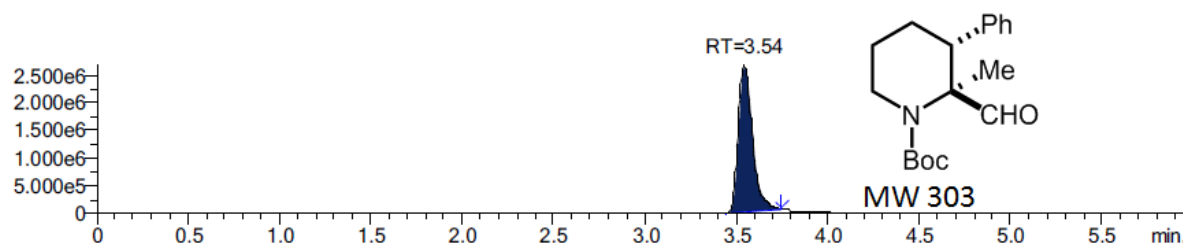
tcb-3-105A-AVB400.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN





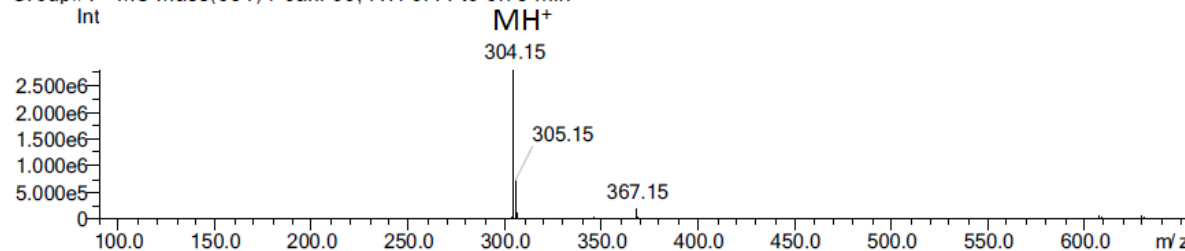
Crude pipercolinal **9** was prepared from enal **8** (211 mg, 1 mmol, 1 equiv), lithium diphenyl cuprate (2 equiv), and HMPA (1.2 equiv), using **General Procedure A**.

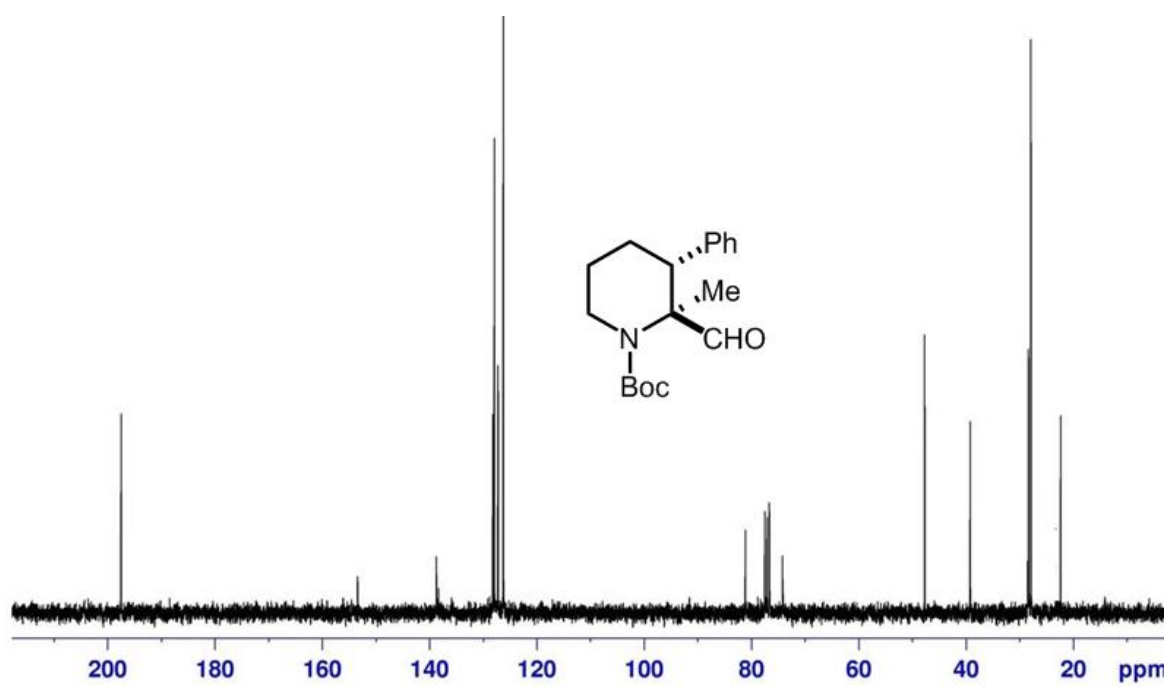
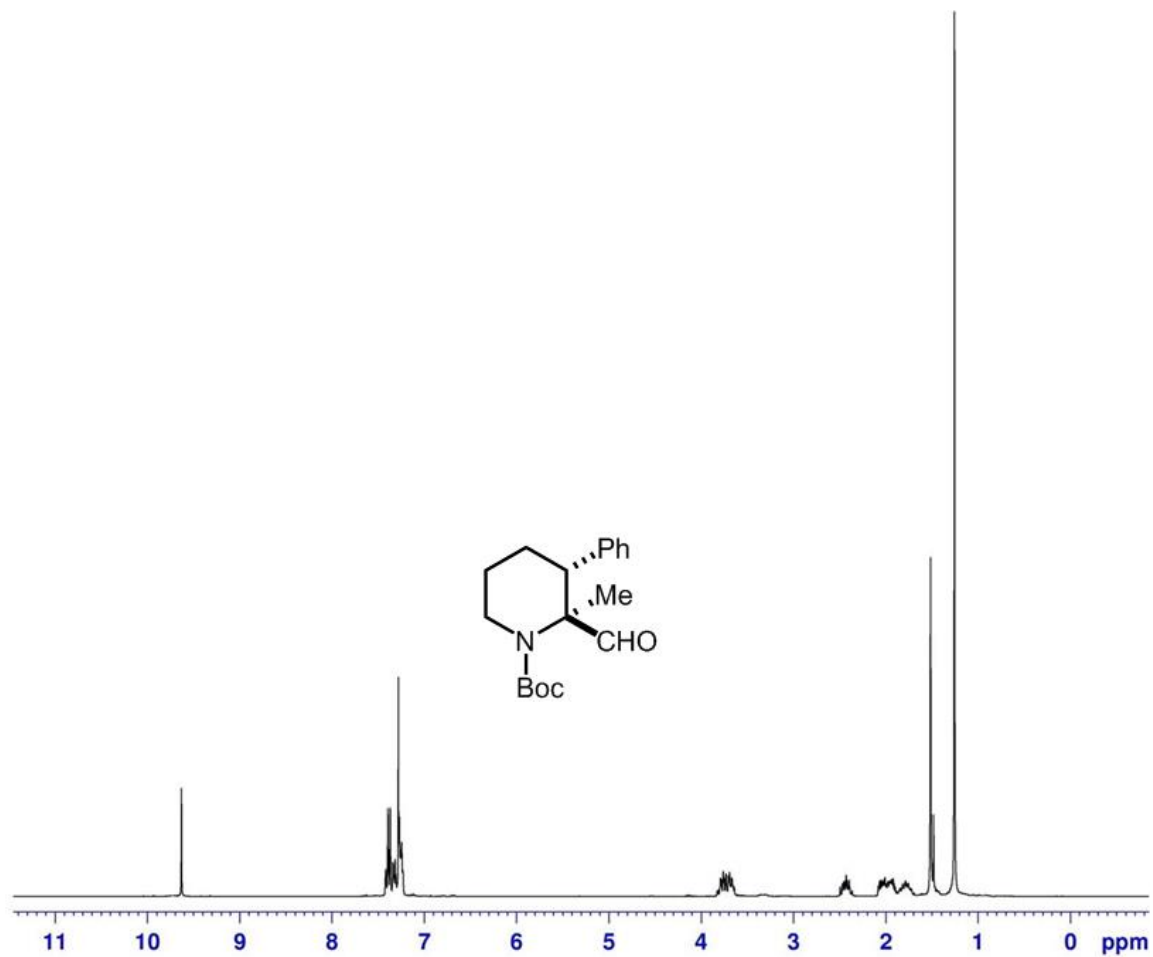
Methylation: A solution of NaHMDS (1.5 mL, 1.5 mmol, 1.0 M in THF, 1.5 equiv) was added dropwise to a solution of **9** in THF (5 mL) and the mixture was stirred for 10 min at -78 °C then for 1 h at -40 °C (LCMS-monitoring). After cooling to -78 °C, methyl iodide (3 equiv) was added slowly. The mixture was allowed to warm slowly to room temperature overnight. After quenching with saturated NH_4Cl (aq), extractive workup with EtOAc followed by brine washes afforded the desired quaternary pipercolinal. Purification by flash chromatography on silica eluting with Hexane/EtOAc (50:50) afforded the pure product in 74% yield from **8**. ^1H NMR (400 MHz, CDCl_3), δ 9.72 (1H, s), 7.55–7.10 (5H, m), 3.72 (2H, m), 2.44 (1H, m), 2.02–1.15 (19H, m). ^{13}C NMR (101 MHz, CDCl_3) δ = 198.2, 153.7, 138.8, 128.3, 128.0, 127.3, 126.3, 81.2, 80.6, 74.3, 47.9, 39.3, 38.3, 28.4, 28.0, 23.4, 22.4. **HRMS-EI⁺** (m/z): calc for $\text{C}_{18}\text{H}_{25}\text{NO}_3$ 303.1834, found 303.1830.

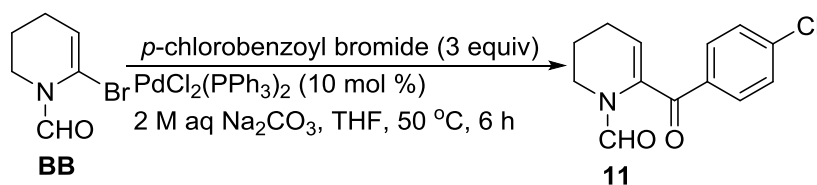


MS Spectrum

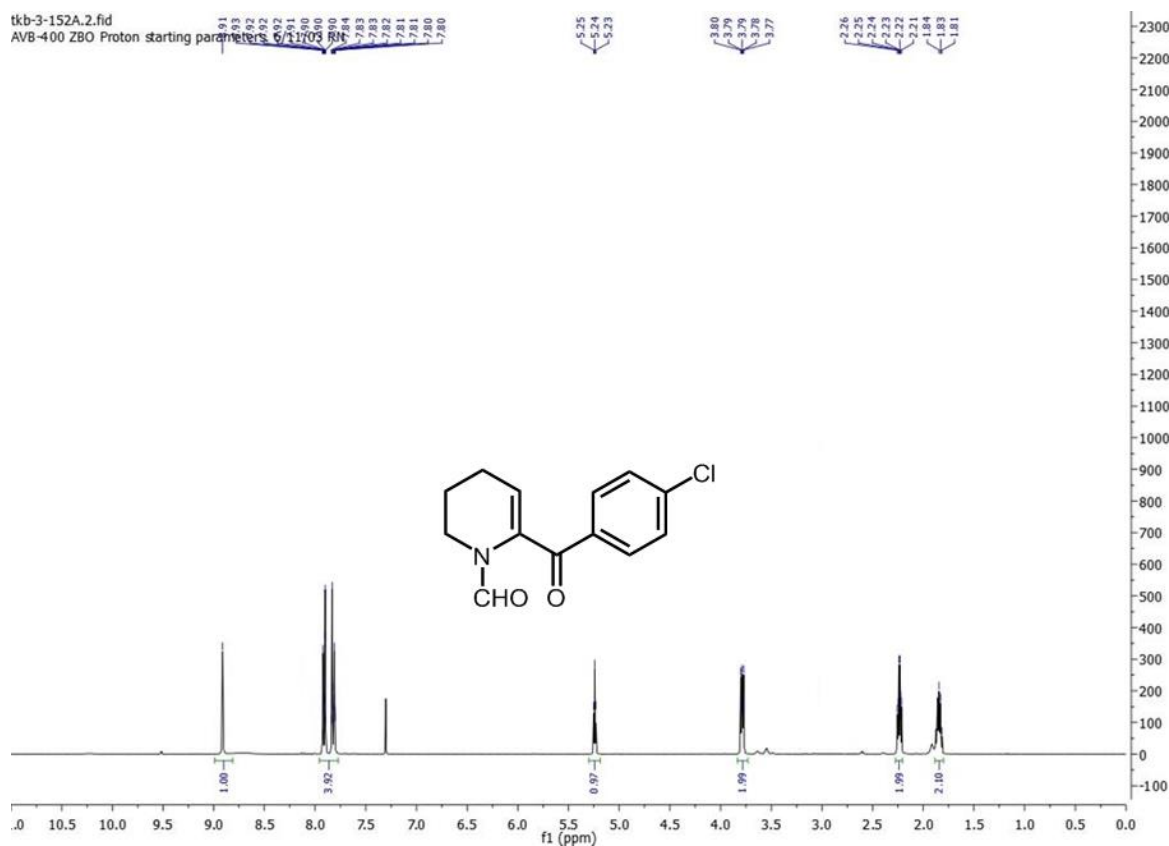
Group#1 - MS Mass(304) Peak: 35, RT: 3.44 to 3.70 min

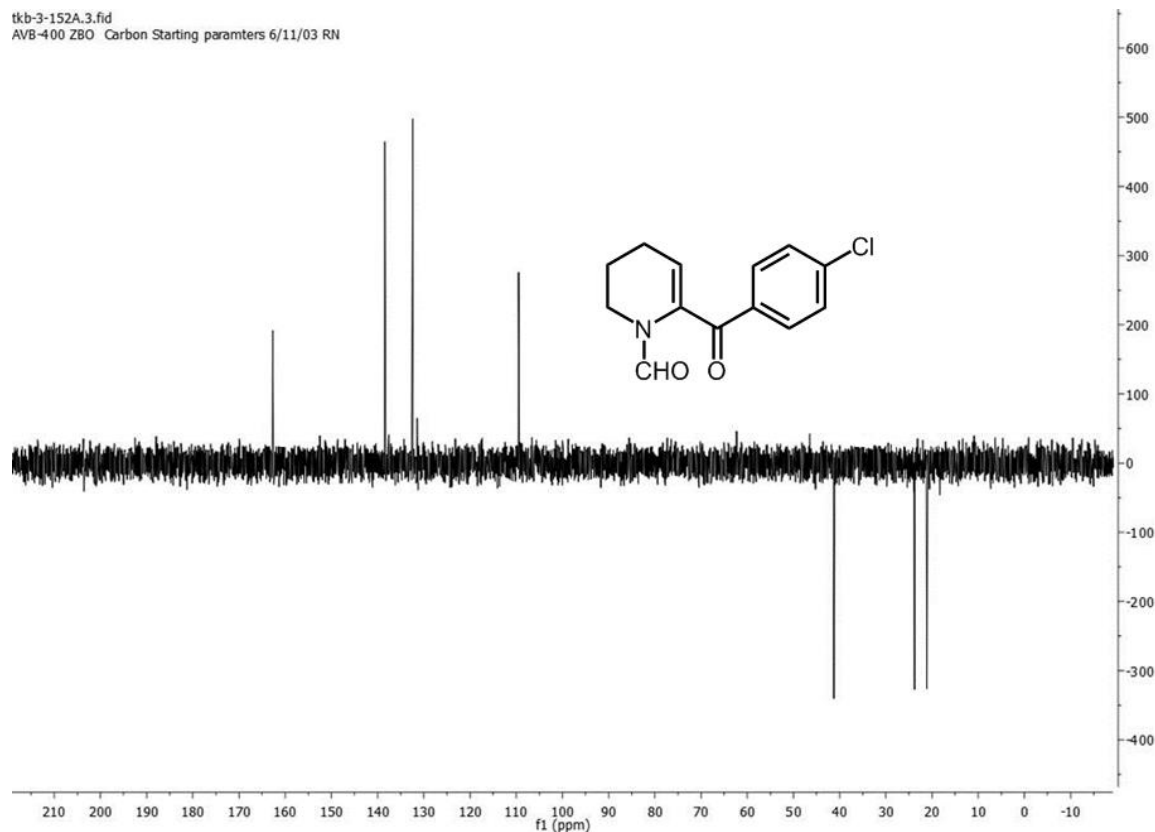
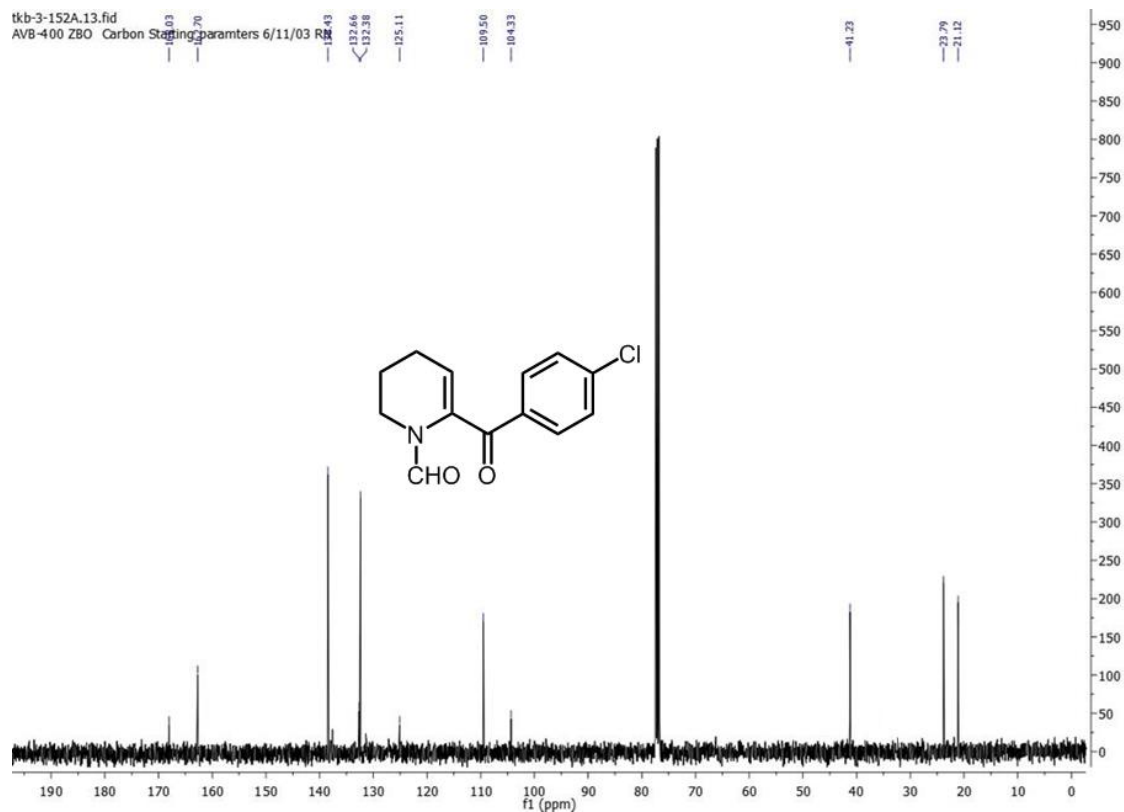


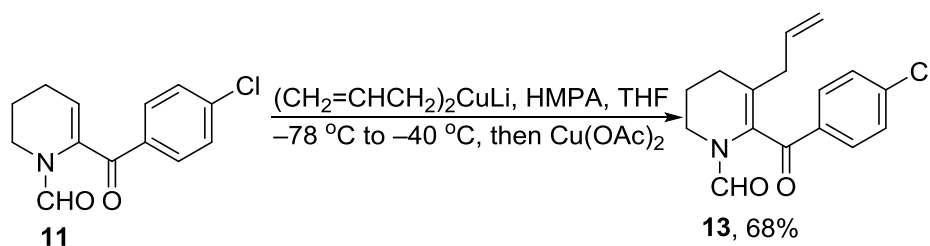




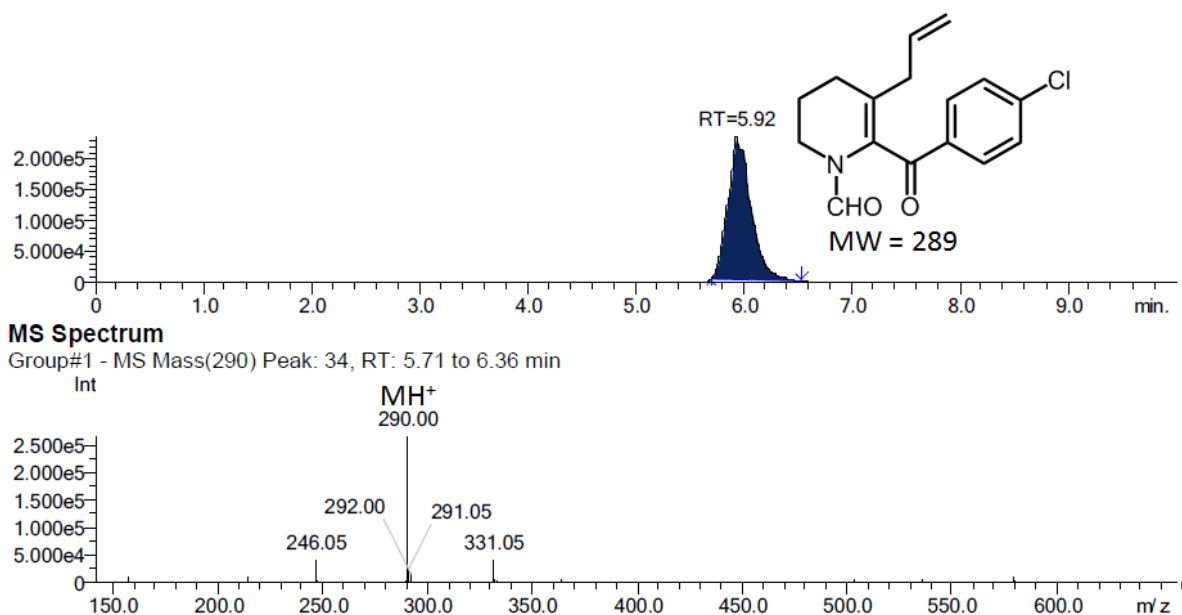
To a stirred solution of **BB** (230 mg, 1.0 mmol) in THF (10 mL) were added, under a nitrogen atmosphere, 2 M Na_2CO_3 (aq) (5 mL), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (70 mg, 10 mol%), and 4-chloro-benzoyl chloride (0.4 mL, 3 equiv). The mixture was heated to 50 °C, and allowed to stir for 6 h. After cooling to room temperature, it was diluted with water (10 mL) and extracted with Et_2O . The organic phase was dried for 30 min over K_2CO_3 and concentrated in vacuo to afford the crude product as an oil. $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.91 (1H, d), 7.93 (2H, d), 7.82 (2H, d), 5.23 (1H, t), 3.80 to 3.77 (2H, dd), 2.26 to 2.21 (2H, m), 1.84 to 1.81 (2H, m). $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 168.0, 162.7, 138.4, 132.7, 132.4, 125.1, 109.5, 104.3, 41.3, 23.8, 21.1. **HRMS- EI^+** (m/z): calc'd for $\text{C}_{13}\text{H}_{12}\text{ClNO}_2$ 249.0557, found 249.0560.

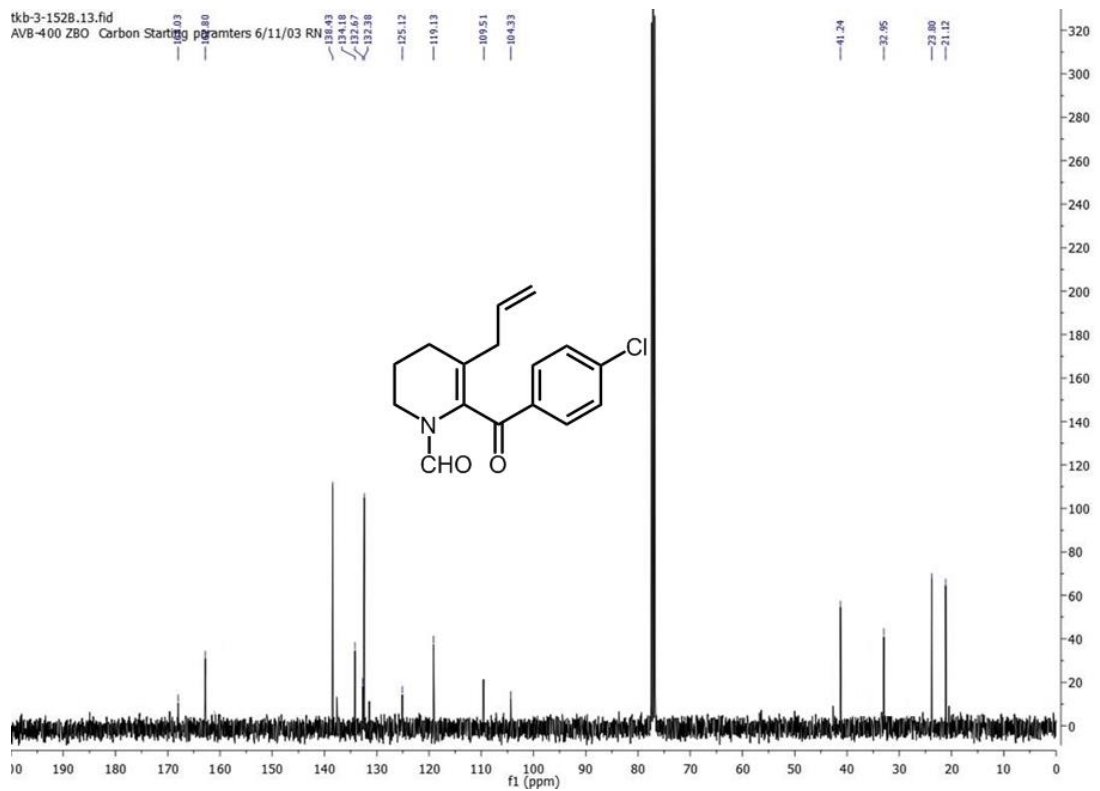
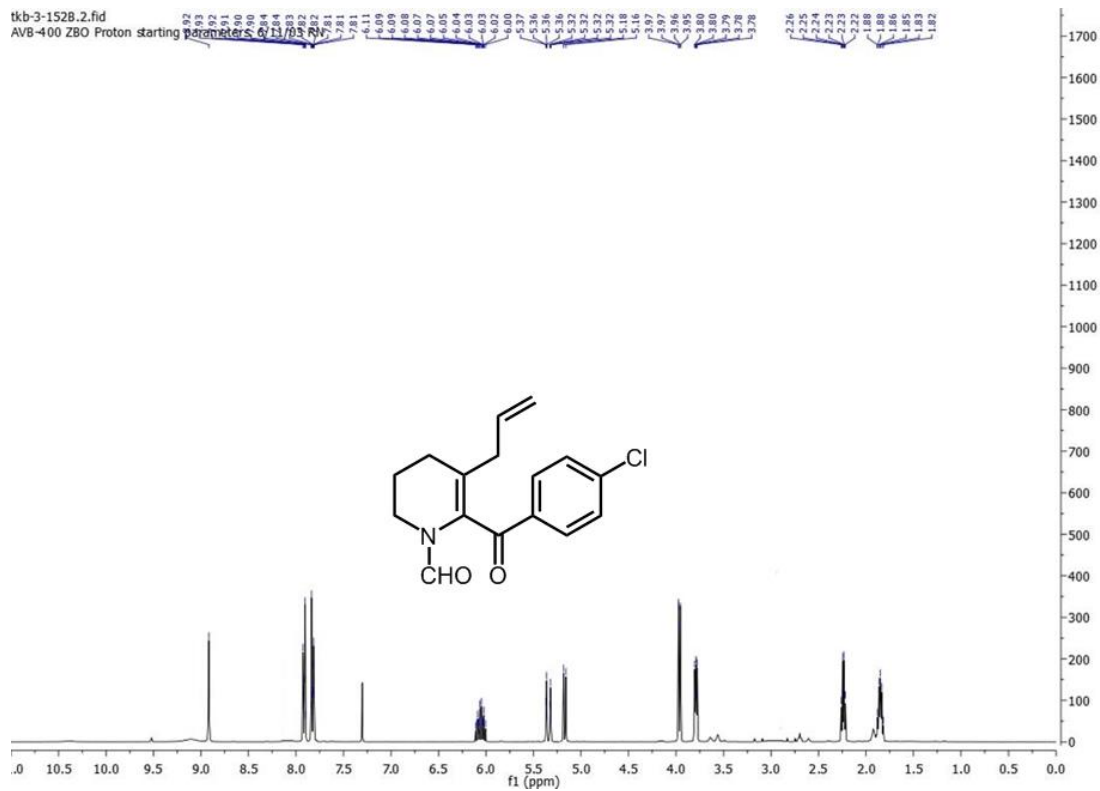




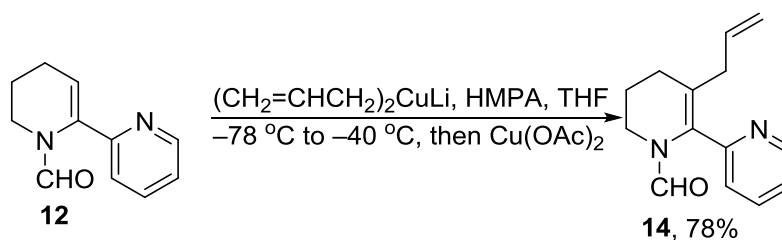
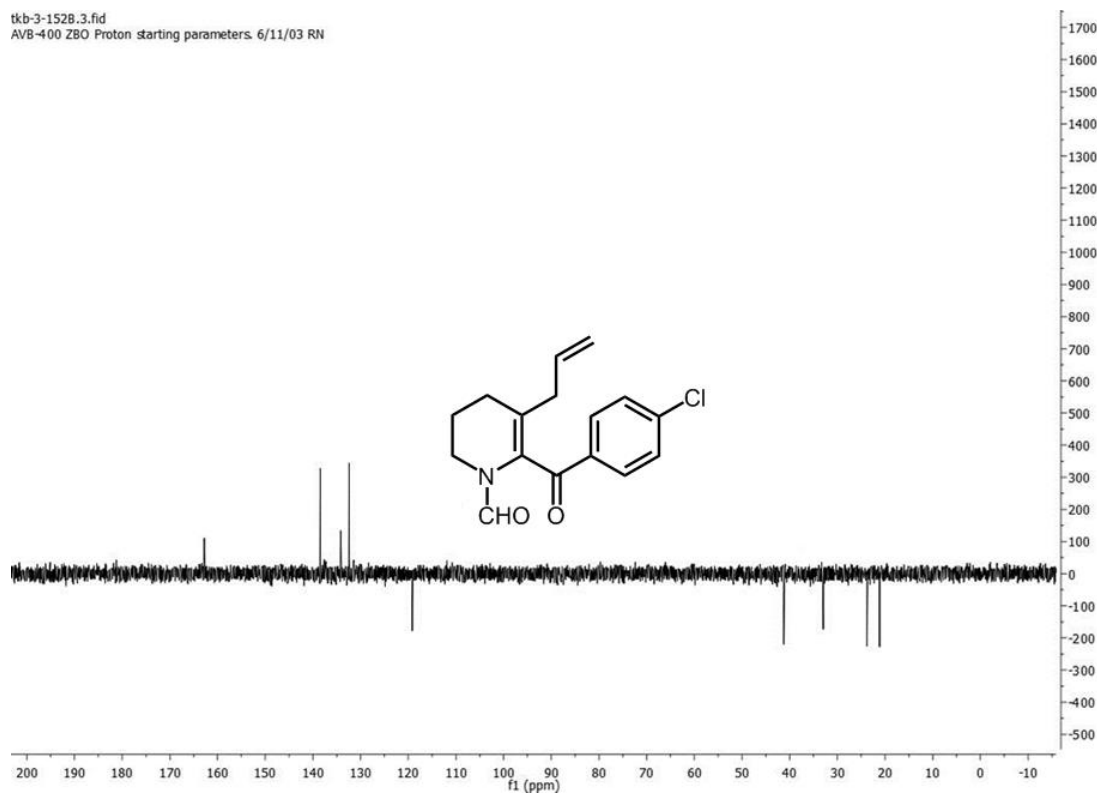


Prepared from **11**, lithium diallyl cuprate (2 equiv) and copper (II) acetate (3 equiv) using **General Procedure B. Purification**: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (90:10). Yield = 20.5 mg, 70%. ¹H NMR (400 MHz, CDCl₃) δ 8.92 (1H, s), 7.91 (2H, d), 7.82 (2H, d), 6.11 to 6.00 (1H, m), 5.36 (1H, d), 5.32 (1H, d), 3.96 (2H, d), 3.80 to 3.78 (2H, dd), 2.26 to 2.22 (2H, m), 1.88 to 1.82 (2H, m). ¹³C NMR (101 MHz, CDCl₃) δ 162.8, 138.4, 134.1, 132.6, 132.3, 125.1, 119.1, 109.5, 104.3, 41.2, 32.9, 23.8, 21.1. HRMS calc for C₁₆H₁₆ClNO₂ 289.0870, found 289.0873.



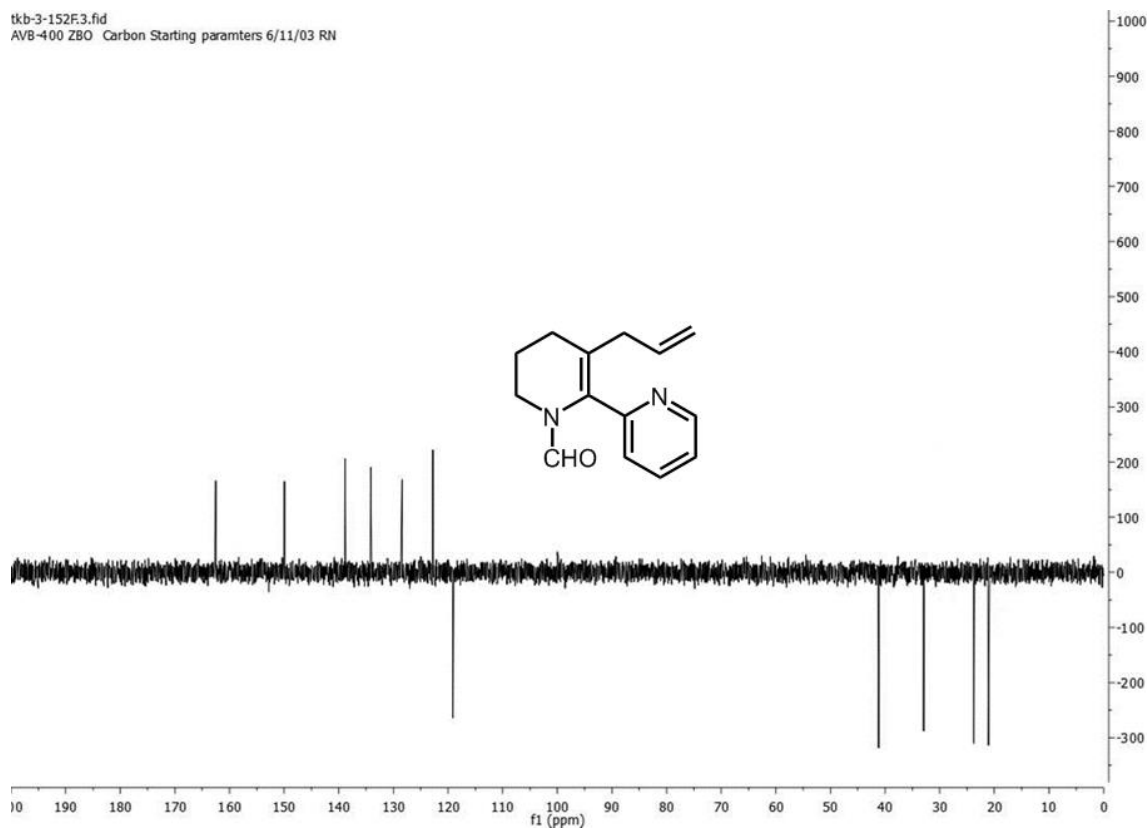


tkb-3-152B.3.fid
AVB-400 ZBO Proton starting parameters. 6/11/03 RN



Prepared from **12**,³ lithium diallyl cuprate (2 equiv) and copper (II) acetate (3 equiv) using **General Procedure B**: Flash chromatography on silica (pretreated with 1% Et₃N) eluting with hexane/EtOAc (20:80 to 0:100). Yield = 13 mg, 55%. ¹H NMR (400 MHz, CDCl₃) δ 8.87 (1H, s), 8.37 (1H, d), 7.60 to 7.48 (2H, m), 7.30 to 7.26 (1H, dd), 6.05 to 5.96 (1H, m), 5.32 to 5.28 (1H, d), 5.14 to 5.11 (1H, d), 3.92 (2H, d), 3.76 to 3.73 (2H, dd), 2.22 to 2.17 (2H, m), 1.86 to 1.77 (2H, m). ¹³C NMR (101 MHz, CDCl₃) δ 162.5, 149.9, 141.8, 138.8, 134.1, 128.4, 125.1, 122.7, 119.1, 109.5, 41.2, 36.5, 23.7, 21.1. **HRMS-EI⁺** (*m/z*): calc for C₁₄H₁₆N₂O 228.1263, found 228.1265.

tkb-3-152E3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN



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