Supporting Information for:

Regiocontrolled synthesis of hetero(aryl) and alkenyl dehyropyrrolidines, dehydropiperidines and azepenes by Ru-catalyzed heteroatom-directed α-C-H activation/cross-coupling of cyclic enamides with boronic acids

Timothy K. Beng, Spencer Langevin, Hannah Braunstein and Monique Khim*

Department of Chemistry, Central Washington University,
Ellensburg, WA 98926, USA
TimothyB@cwu.edu

Contents:

2. Experimental Section

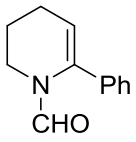
All experiments involving air and moisture-sensitive reagents were carried out under an inert atmosphere of argon or nitrogen and using freshly distilled solvents. Et_2O and THF were distilled either from sodium benzophenone ketyl or using the Grubbs system. All electrophiles that were not newly purchased were distilled immediately before use. TMEDA was distilled on a short path, over CaH_2. Column chromatography was performed on silica gel (230-400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by $KMnO_4$, CAM, and *p*-anisaldehyde staining. All reported cold temperatures were internal to a reaction vessel. Unless otherwise indicated, ^1H, ^{13}C, and DEPT-135, COSY 45 and HMQC (or HSQC) spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

(General) Representative Procedure A: Ru-catalyzed arylation

A mixture of *enamide* **1a** (111 mg, 1.00 mmol), phenylboronic acid (183 mg, 1.50 mmol, 1.5 equiv), $[RuCl_2(p\text{-cymene})]_2$ (6 mg, 2.0 mol %) and $Cu(OTf)_2$ (362 mg, 1.0 mmol, 1.0 equiv), Ag_2O (347 mg, 1.5 mmol, 1.5 equiv) in dioxane (5.0 mL) was stirred at 80 °C under nitrogen atmosphere for 18 h. After cooling to room temperature, the reaction mixture was diluted with saturated aq. NH_4Cl solution (25 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phase was washed with brine (15 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents *in vacuo*, the crude product was purified by flash chromatography on silica.

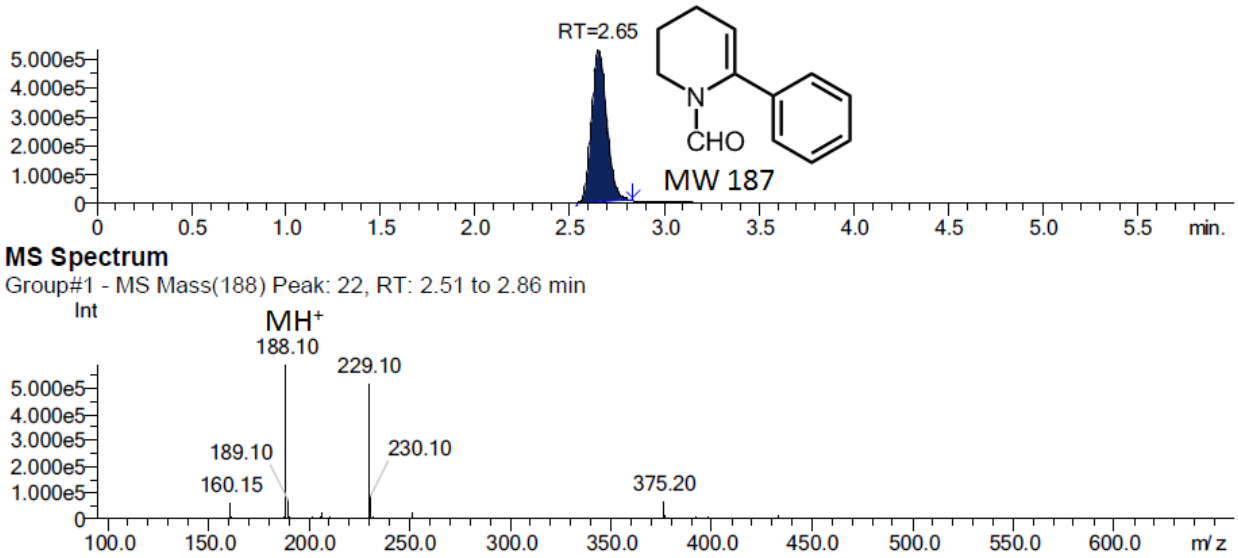
General Procedure B: Catalytic hydrogenation

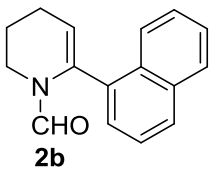
EtOAc was added to a flask containing 10% Pd/C at room temperature. The flask was degassed and placed under an inert atmosphere of nitrogen. A solution of the enamide in EtOAc was added. After complete addition, the nitrogen line was cut off and then replaced with a balloon of hydrogen. After complete consumption of the enamide (based on LC-MS and TLC monitoring), the mixture was filtered through a plug of Celite and concentrated under reduced pressure.



2a

Prepared from **1a** (111 mg, 1.0 mmol) and phenyl boronic acid (183 mg, 1.5 equiv), using General Procedure A. T = 80 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 133 mg, 70%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.39 (1H), 7.07 to 6.98 (5H), 4.76 (1H), 3.66 to 3.63 (2H), 1.72 to 1.68 (2H), 1.37 to 1.28 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.4, 138.5, 137.0, 128.5, 128.0, 127.8, 111.4, 39.0, 23.0, 21.9. HRMS calc for $C_{12}H_{13}NO$ 187.0997, found 187.0995. Data as previously reported by us.[1]

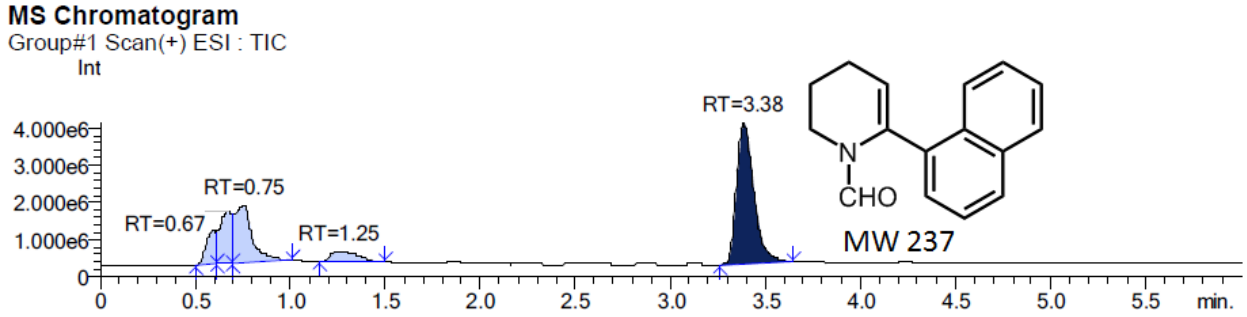


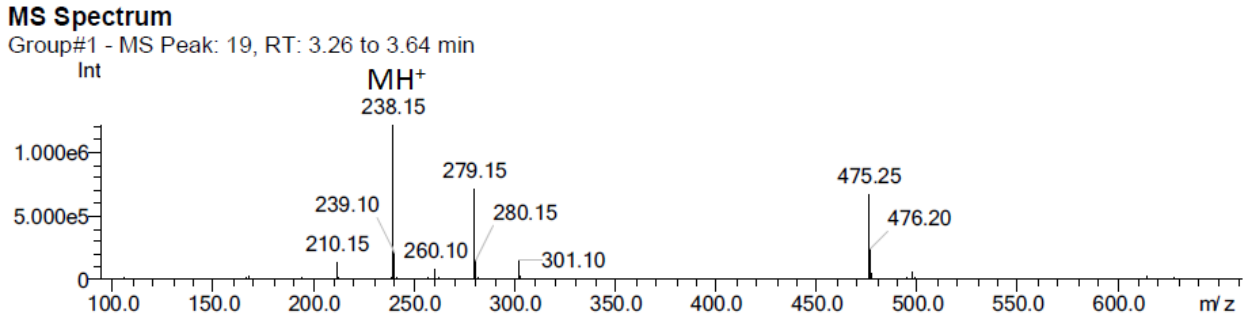


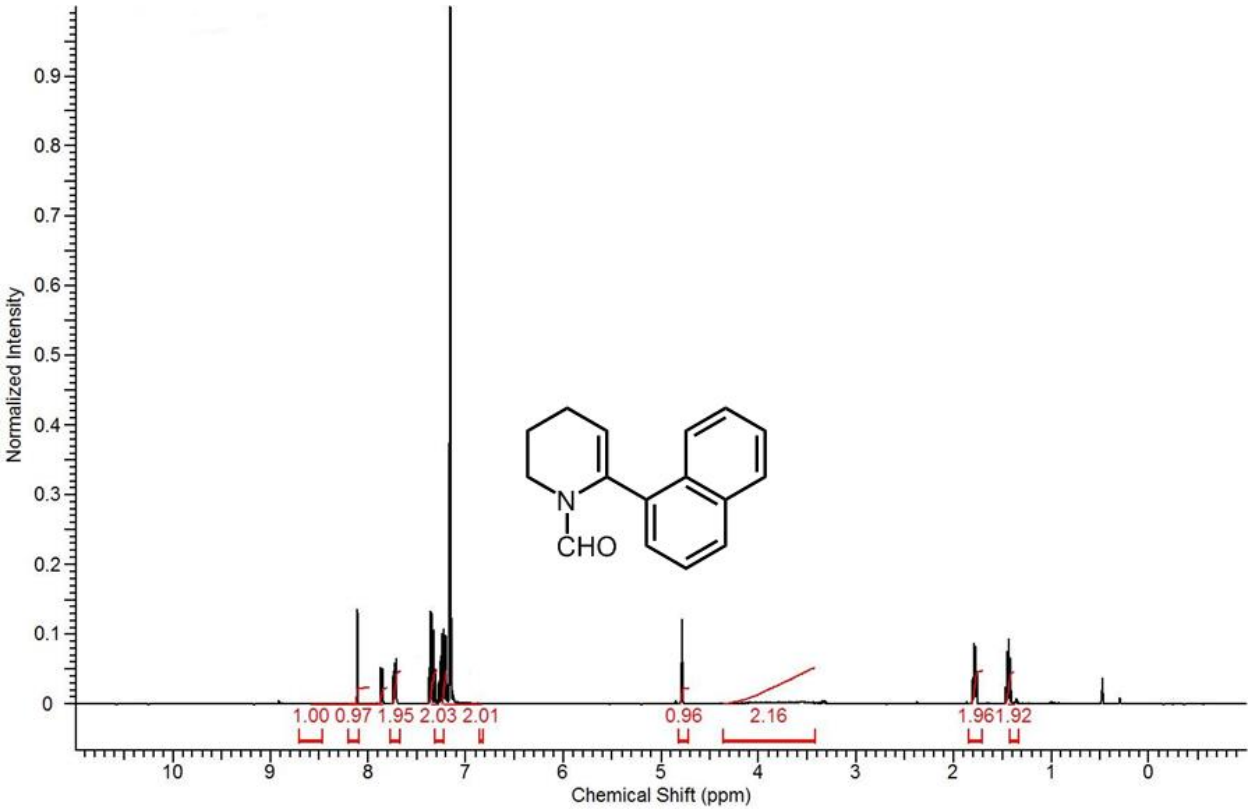
2b

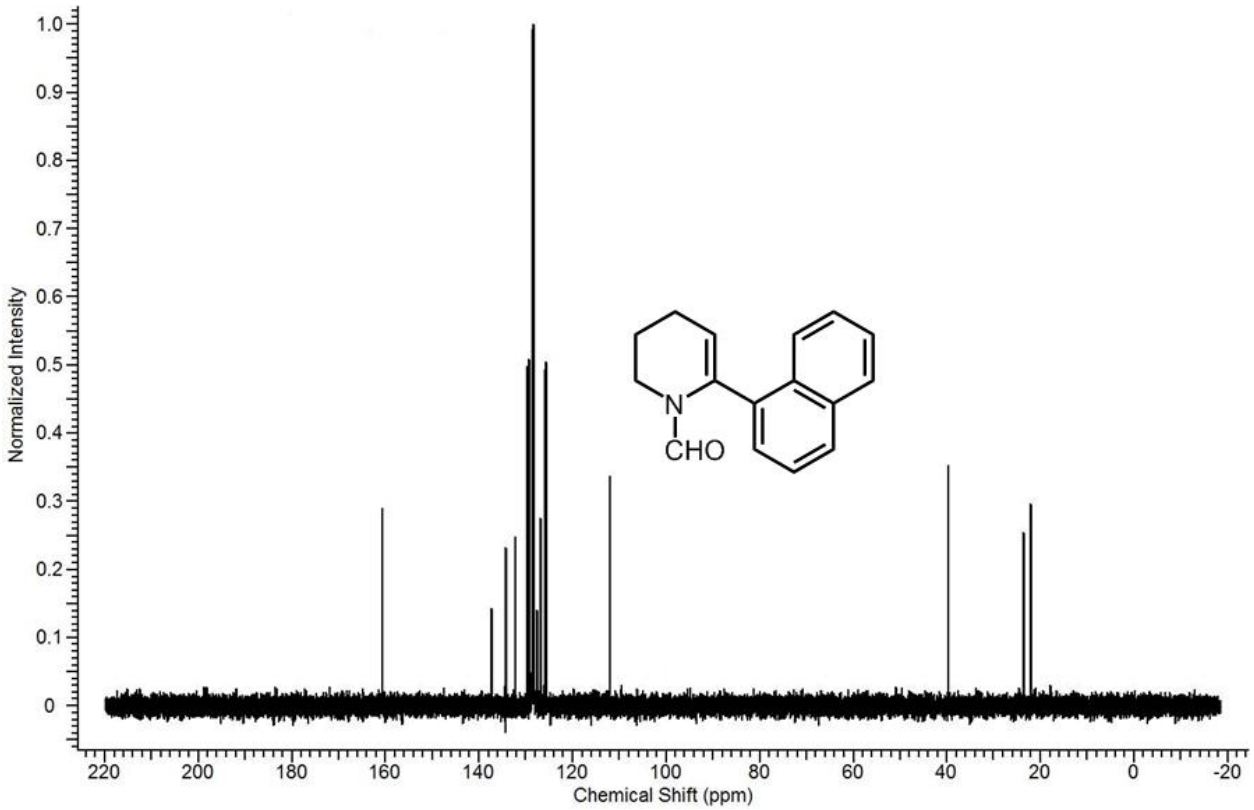
Prepared from **1a** (111 mg, 1.0 mmol) and 1-naphthyl boronic acid (258 mg, 1.5 equiv), using General Procedure A. T = 80 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 149 mg, 63%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.12 (1H), 7.85 (1H), 7.72 (2H), 7.59 to 7.00 (4H), 4.79 (1H), 3.82 (2H, br), 1.81 to 1.77 (2H), 1.47 to 1.41 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.6, 139.3, 137.3, 134.4,

134.3, 133.8, 132.3, 129.7, 129.1, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.5, 127.3, 126.8, 126.7, 126.4, 126.0, 125.9, 125.6, 112.0, 39.6, 23.5, 22.0. HRMS calc for $C_{16}H_{15}NO$ 237.1154, found 237.1158.



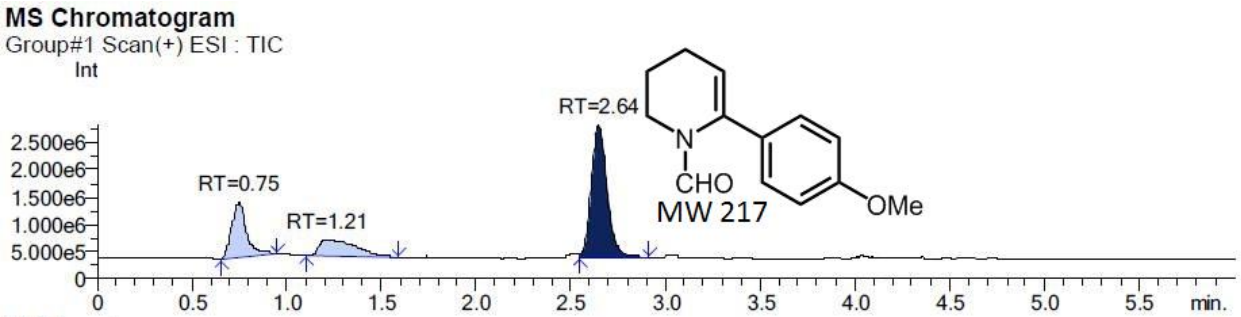






2c

Prepared from **1a** (111 mg, 1.0 mmol) and 4-methoxyphenylboronic acid (229 mg, 1.5 equiv) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 173.6 mg, 80%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.43 (1H), 7.04 to 7.01 (2H), 6.68 to 6.65 (2H), 4.81 to 4.79 (1H), 3.69 to 3.66 (2H), 3.33 (3H), 1.82 to 1.78 (2H), 1.43, 1.36 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.6, 159.7, 138.2, 133.5, 129.1, 129.1, 114.0, 110.4, 54.6, 39.1, 23.0, 22.1. HRMS calc for $C_{13}H_{15}NO_2$ 217.1103, found 217.1106. Data as previously reported by us.[1]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5.000e5
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RT=1.21
RT=2.64
N
CHO
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OMe
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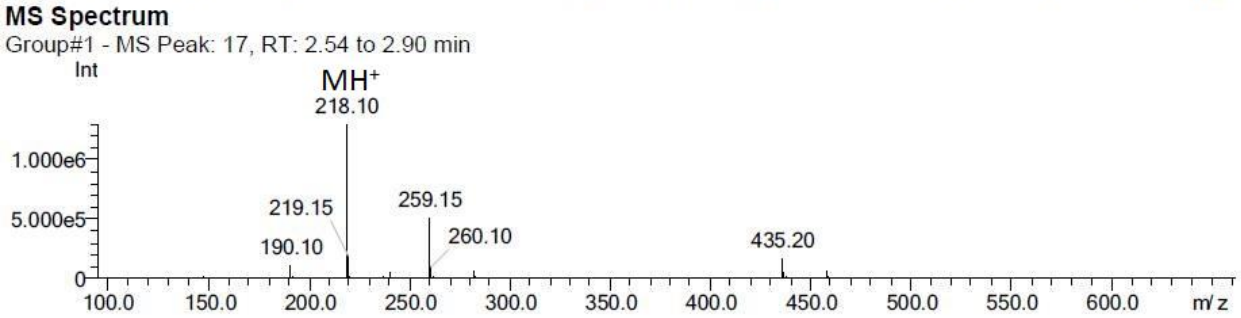
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
min.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190.10
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260.10
435.20
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400.0
450.0
500.0
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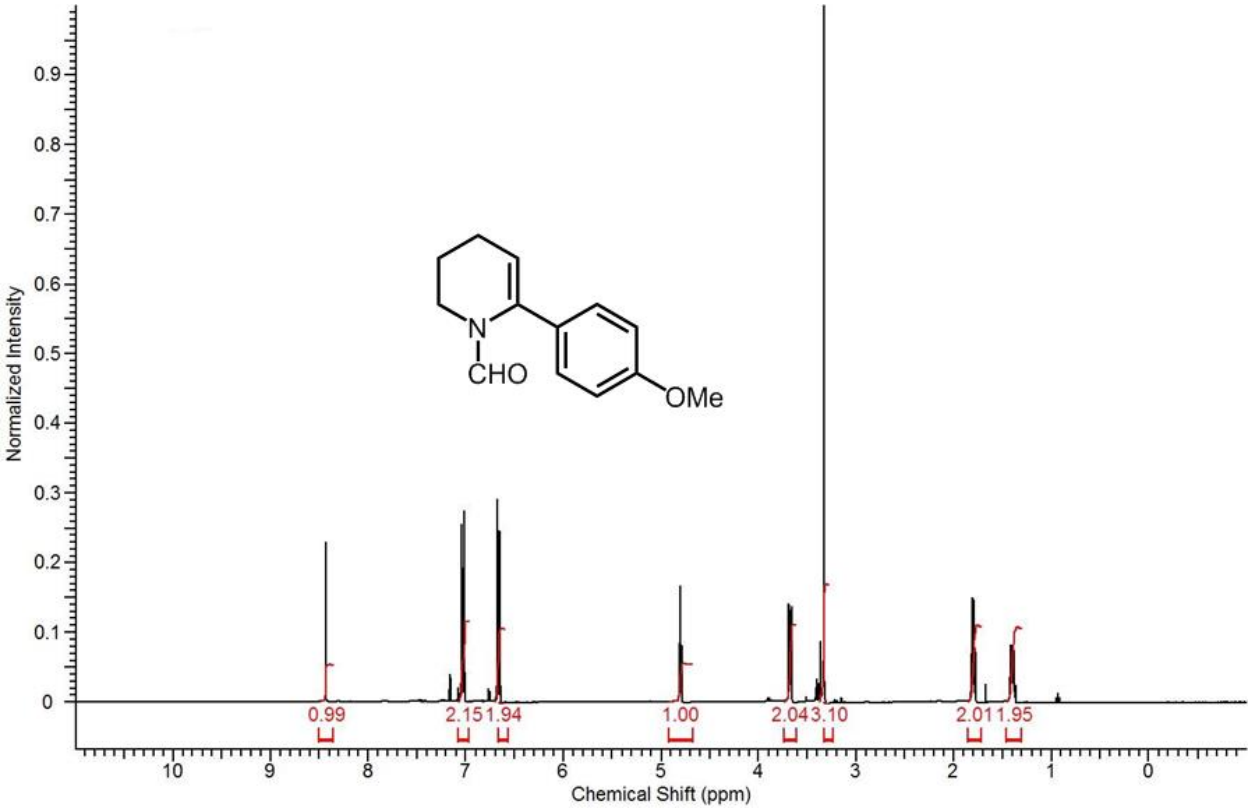
600.0
m/z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0.1
0
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CHO
OMe
0.99
2.15
1.94
1.00
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3.10
2.01
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9
8
7
6
5
4
3
2
1
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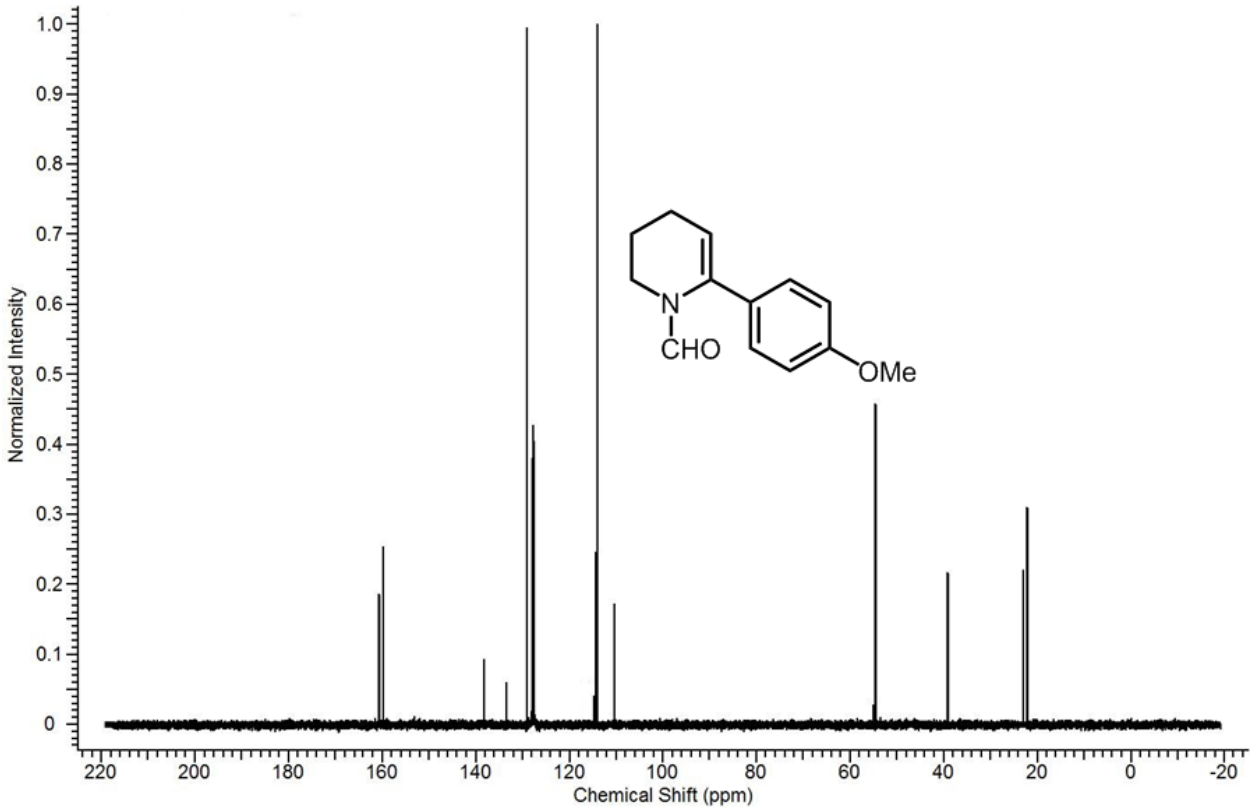
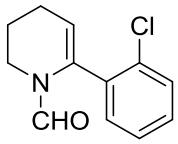
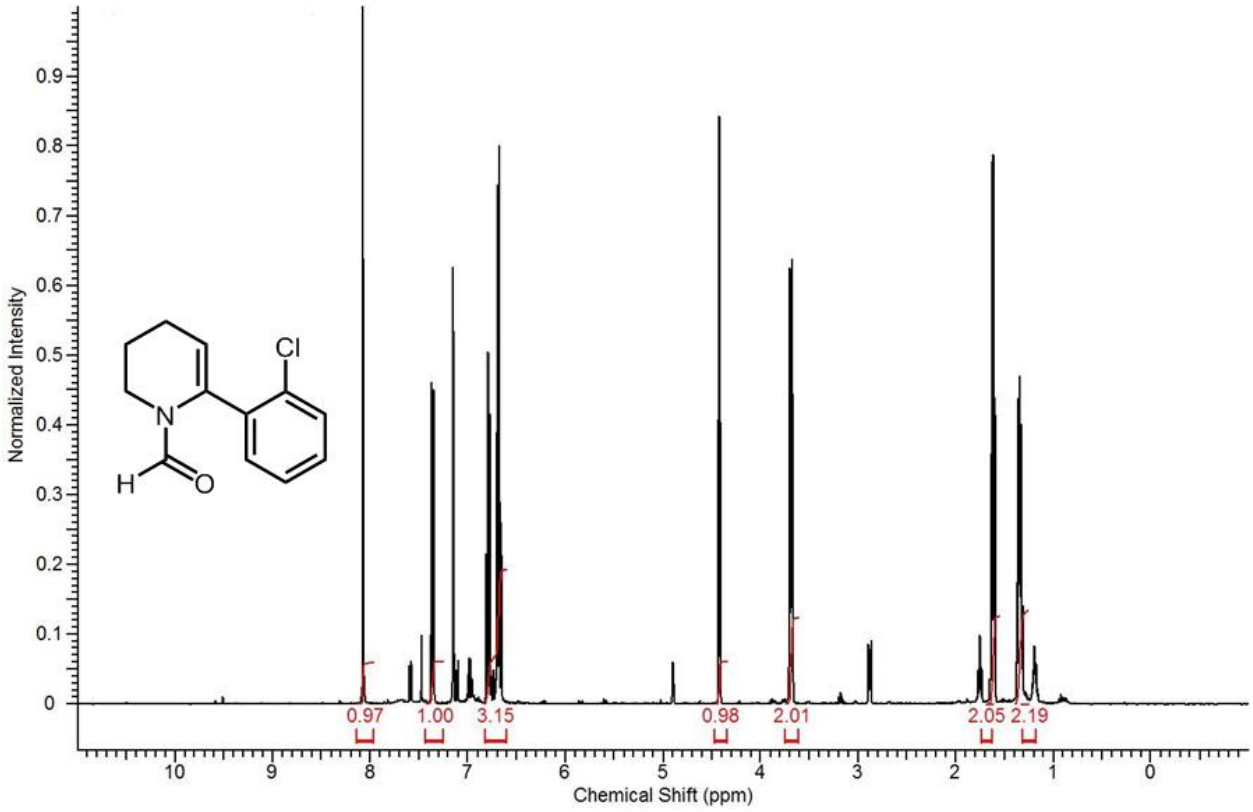
Chemical Shift (ppm)





2d

Prepared from **1a** (111 mg, 1 mmol) and *o*-chlorophenyl boronic acid (235 mg, 1.5 equiv) using **General Procedure A** at 80 ^{o}C for 30 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (20:80). Yield = 115 mg, 52%. ^{1}H NMR (400 MHz, C_6D6, mixture of rotamers) δ 8.09 (1H), 7.30 to 7.28 (1H), 6.70 to 6.54 (3H), 4.40 to 4.38 (1H), 3.71 to 3.68 (2H), 1.60 to 1.56 (2H), 1.34 to 1.25 (2H). ^{13}C NMR (101 MHz, C_6D6) δ 160.0, 134.6, 132.9, 132.0, 131.4, 129.7, 124.7, 111.7, 39.9, 23.3, 21.6. HRMS calc for $C_{12}H_{12}ClNO$ 221.0607, found 221.0610.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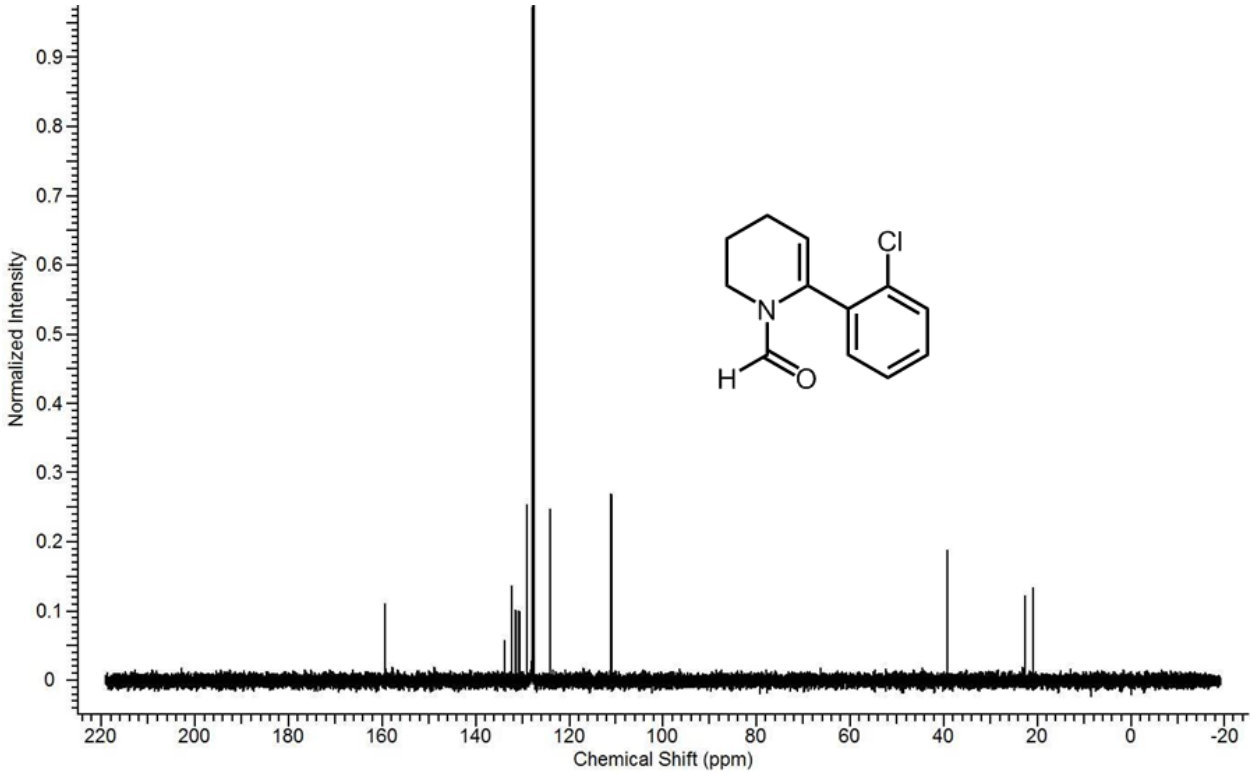
Normalized Intensity
Chemical Shift (ppm)
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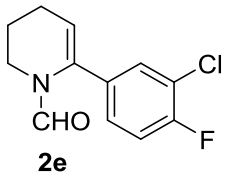
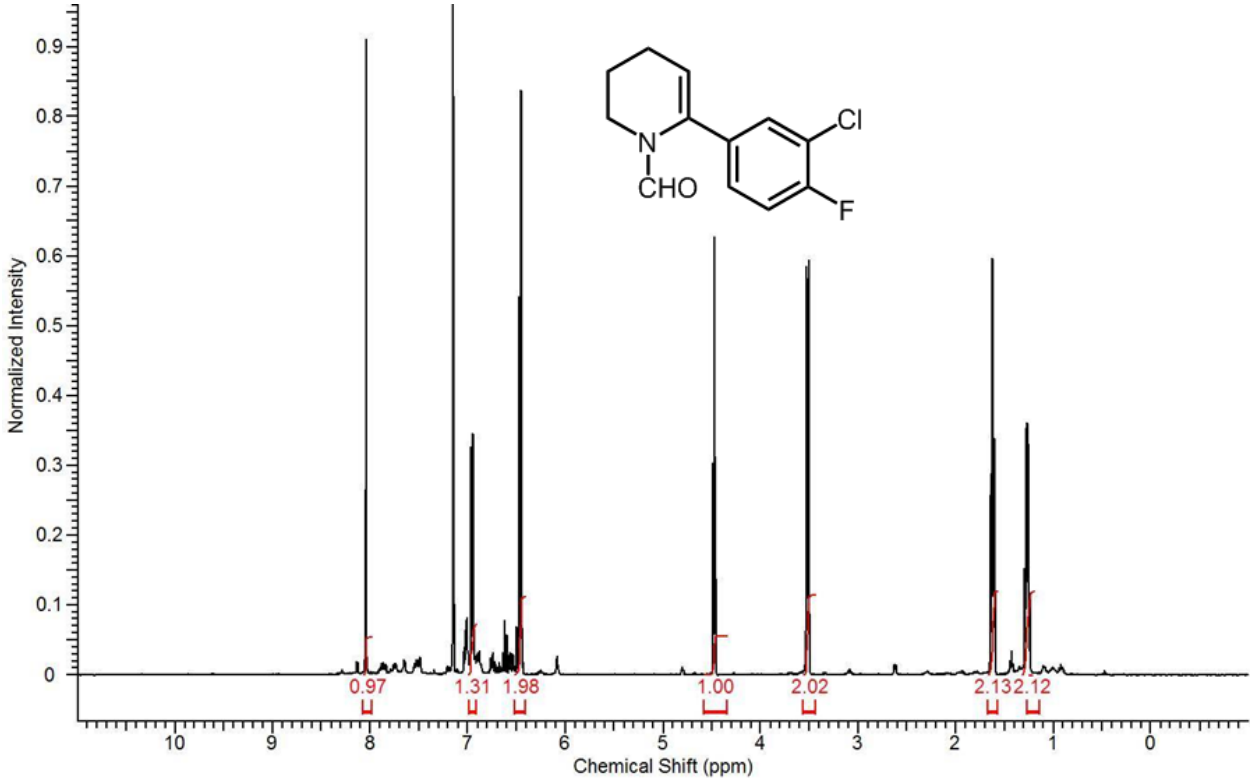
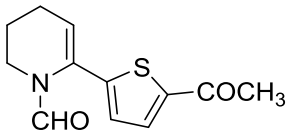
H
O



2e

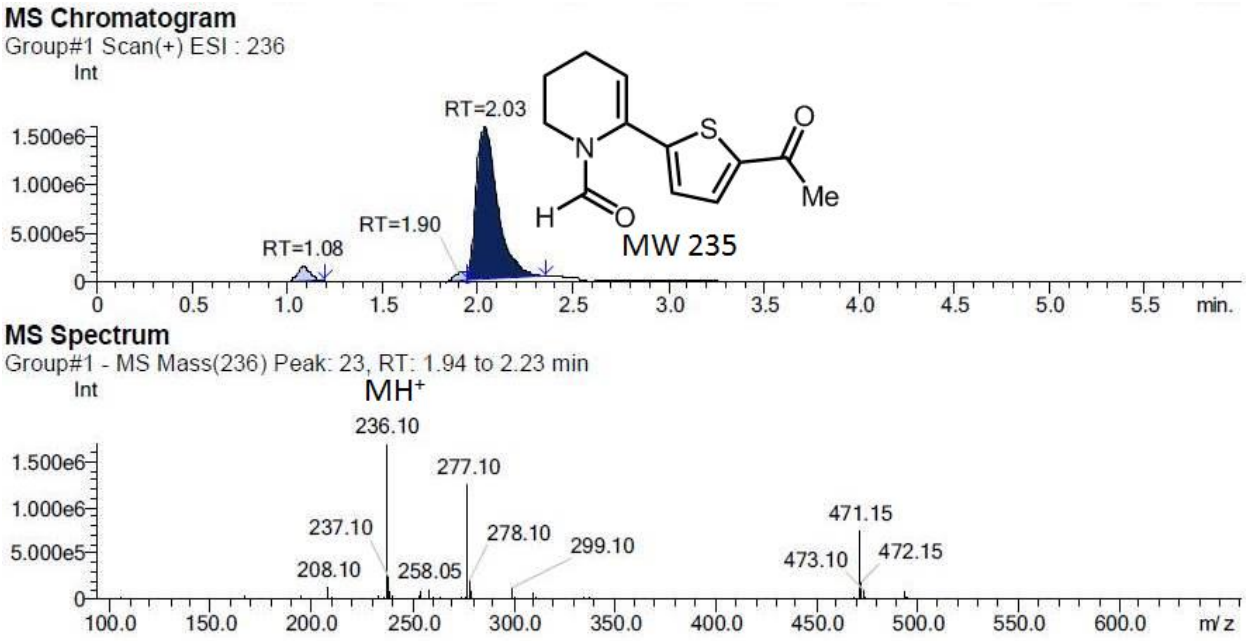
Prepared from **1a** (111 mg, 1.0 mmol) and 3-chloro-4-fluorophenylboronic acid (1.5 equiv) using **General Procedure A** at 80 °C for 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 136 mg, 57%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.04 (1H), 6.97 to 6.95 (1H), 6.47 to 6.45 (2H), 4.48 to 4.46 (1H), 3.53 to 3.50 (2H), 1.64 to 1.60 (2H), 1.28 to 1.25 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.3, 136.1, 134.3, 129.9, 127.4, 127.3, 116.6, 116.4, 112.6, 39.0, 22.8, 21.7. HRMS calc for $C_{12}H_{11}ClFNO$ 239.0513, found 239.0511. Data as previously reported by us.[1]

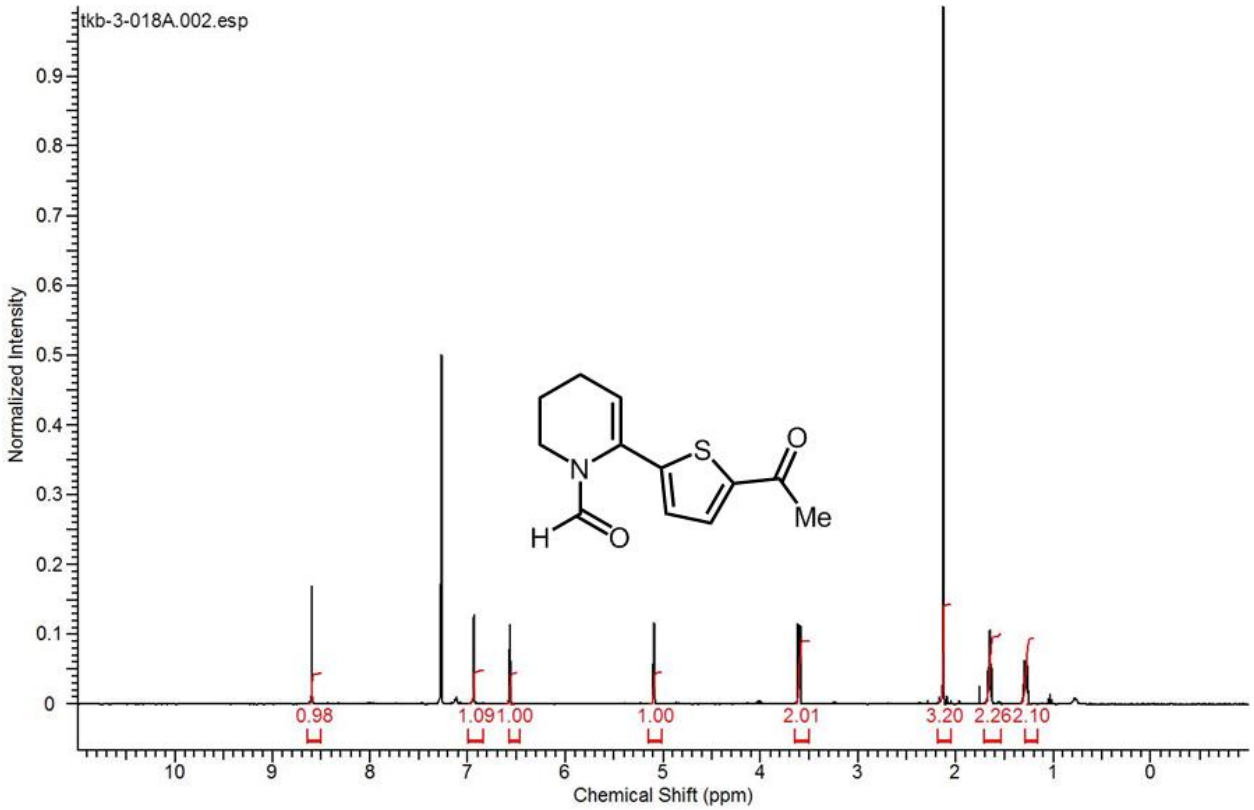




2f

Prepared from **1a** (111 mg, 1.0 mmol) and 5-acetyl-2-thiopheneboronic acid (1.5 equiv), using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 181 mg, 77%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.49 (1H), 6.83 (1H), 6.46 (1H), 4.99 to 4.97 (1H), 3.51 to 3.48 (2H), 2.02 (3H), 1.56 to 1.52 (2H), 1.20 to 1.14 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 189.80, 160.91, 147.28, 144.41, 132.88, 132.38, 126.80, 115.79, 39.62, 26.54, 23.74, 22.39. HRMS calc for $C_{12}H_{13}NO_2S$ 235.0667, found 235.0662.

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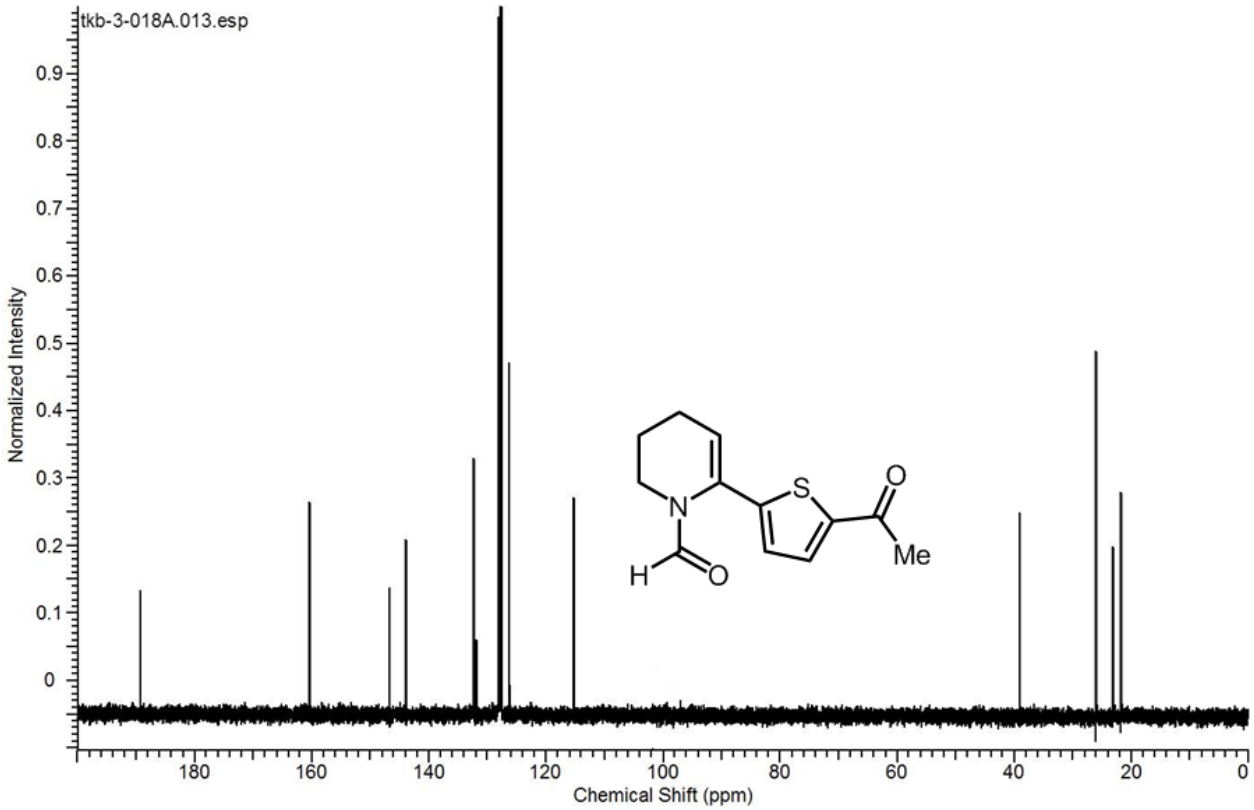
O
Me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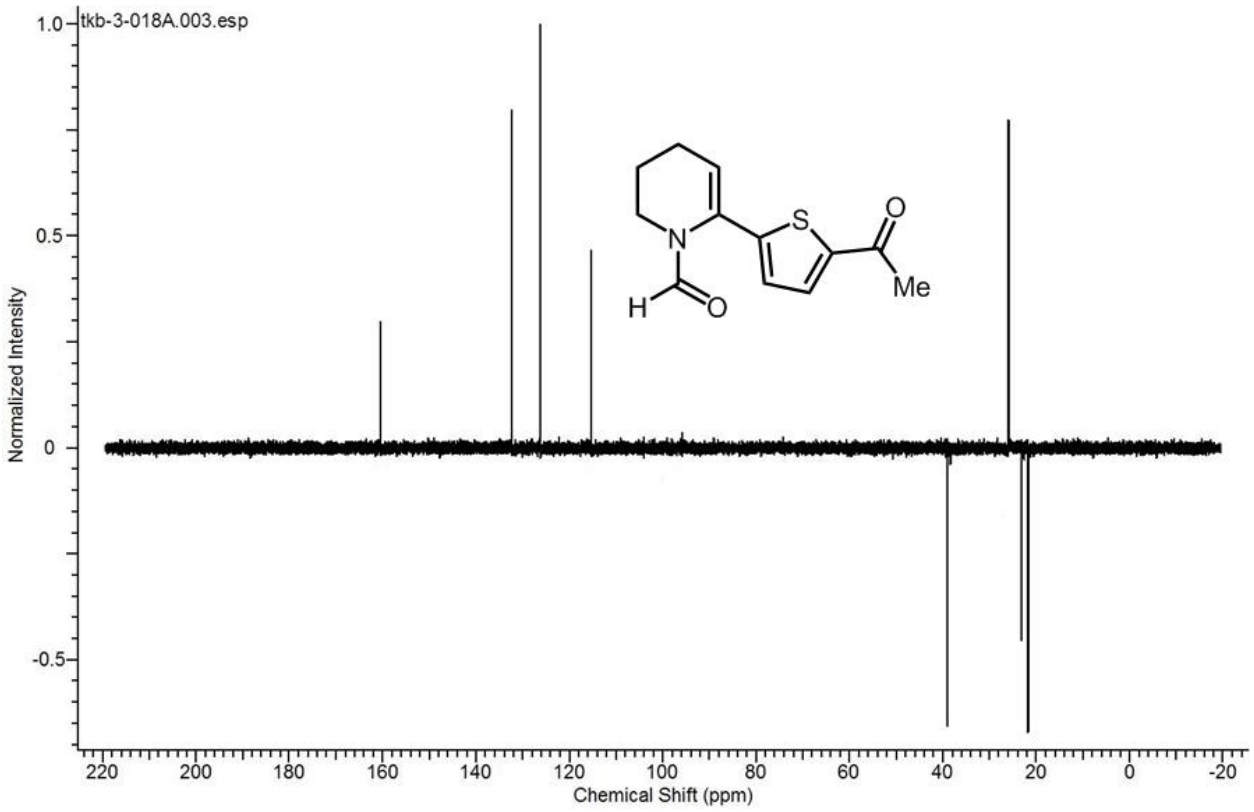
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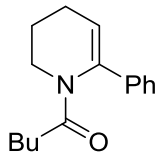
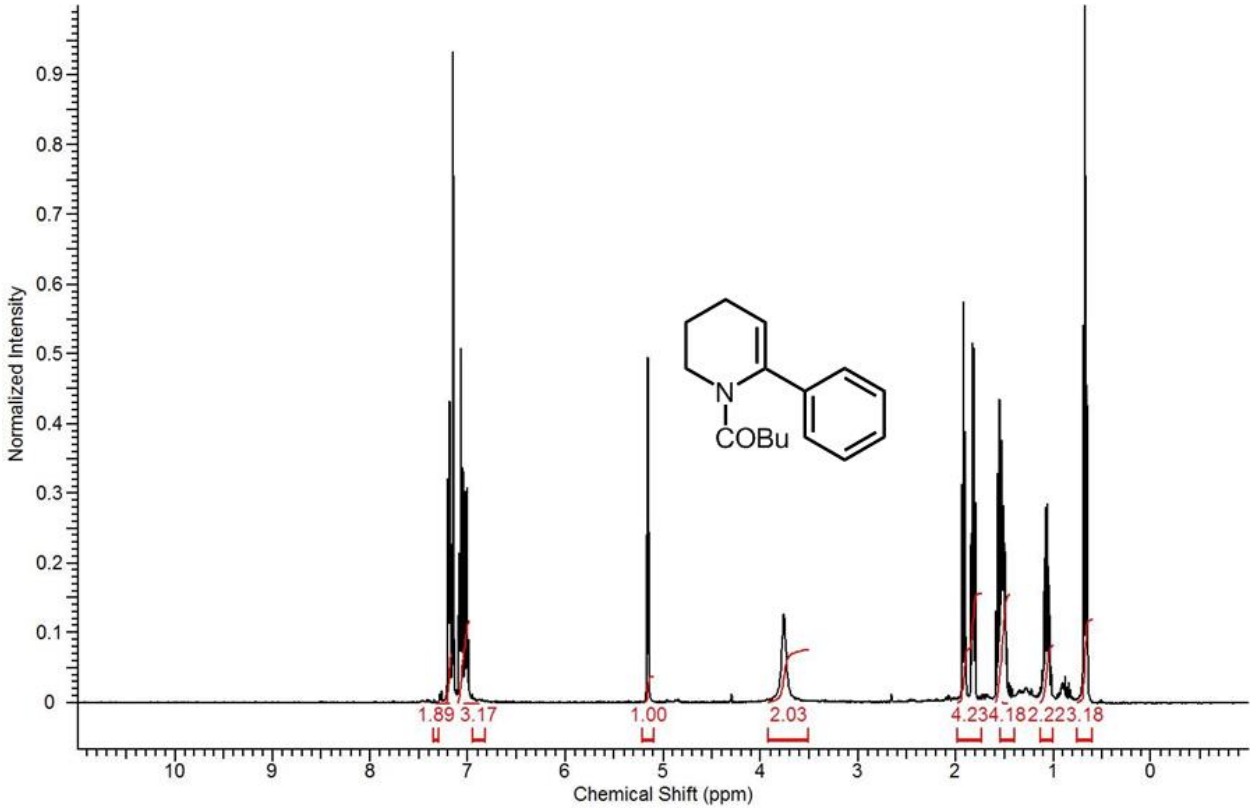
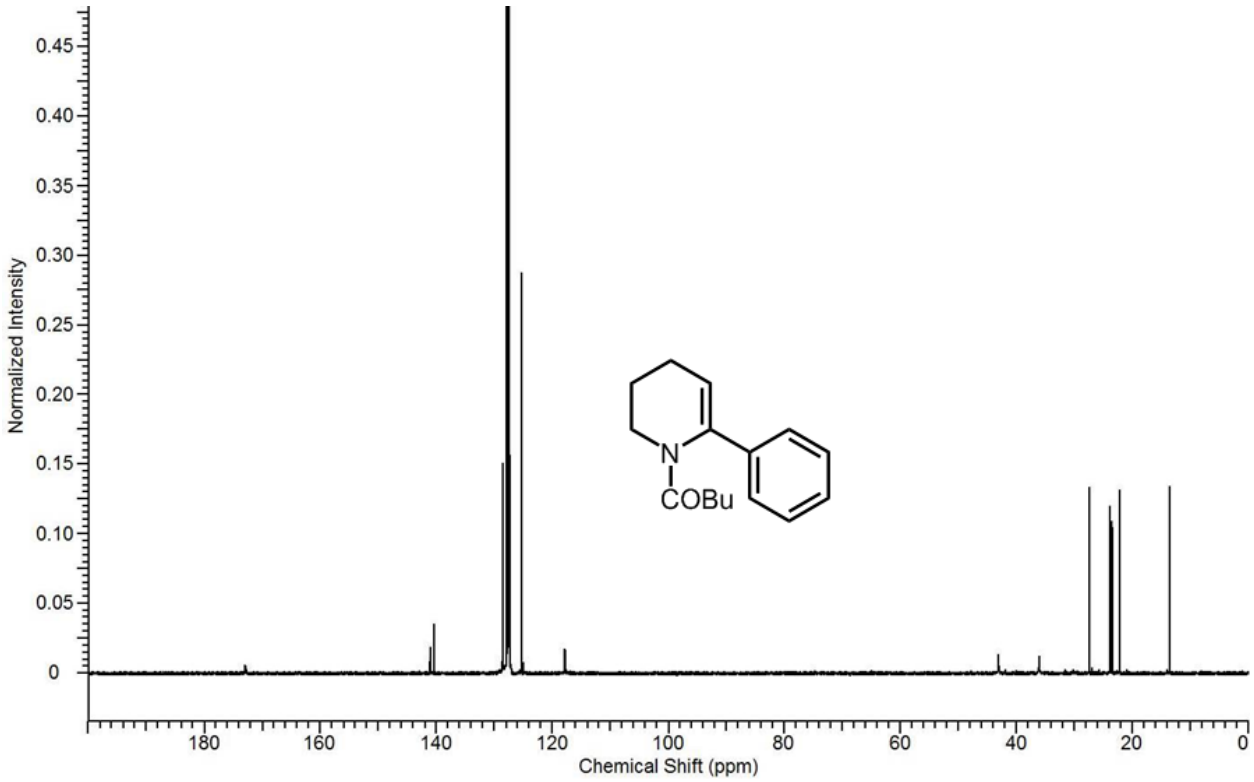
S
O
Me

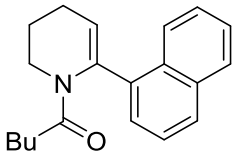


2i

Prepared from **1b** (167 mg, 1.0 mmol) and phenyl boronic acid (1.5 equiv), using General Procedure A. T = 80 °C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 136 mg, 56%. **^{1}H NMR** (400 MHz, C_6D_6) δ 7.46–6.99 (m, 5H), 5.16 (t, *J* = 4.0 Hz, 1H), 3.76 (br s, 2H), 1.92 (t, *J* = 4.0 Hz, 2H), 1.84–1.80 (m, 2H), 1.59–1.47 (m, 4H), 1.07 (m, *J* = 8.0 Hz, 2H), 0.67 (t, *J* = 8.0 Hz, 3H). **^{13}C NMR** (101 MHz, C_6D_6) δ 173.2, 141.5, 140.7, 128.9, 127.8, 125.7, 118.2, 43.4, 36.4, 27.8, 24.3, 23.9, 22.6, 13.9. **HRMS-EI$^+$** (*m/z*): Calcd. for $C_{16}H_{21}NO$ $[M]^+$ 243.1623; found, 243.1627.

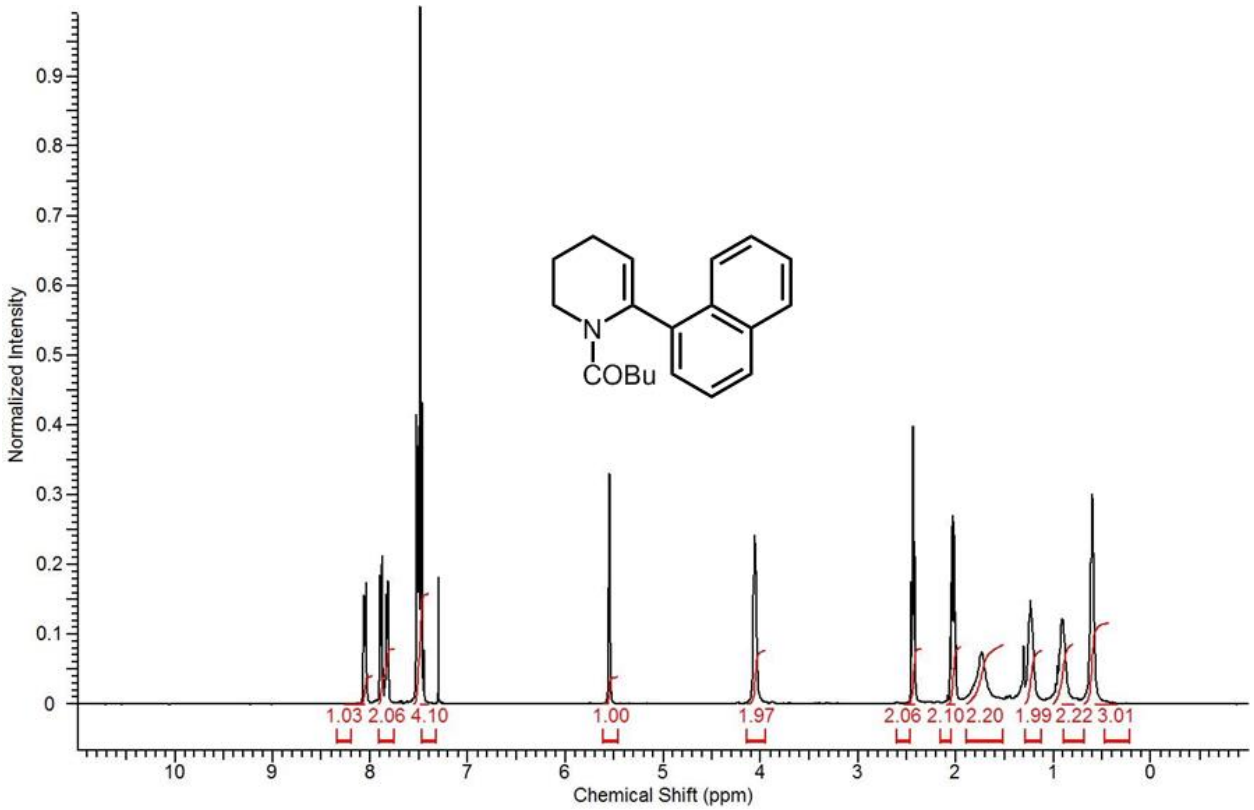






2j

Prepared from **1b** (167 mg, 1.0 mmol) and 1-naphthyl boronic acid (1.5 equiv), using **General Procedure A.** T = 80 ^{o}C, time = 18 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 144 mg, 49%. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.02–8.00 (m, 1H), 7.86–7.83 (m, 1H), 7.79–7.77 (m, 1H), 7.48–7.43 (m, 4H), 5.51 (m, 1H), 4.01 (s, 2H), 2.41–2.37 (m, 2H), 2.01–1.95 (m, 2H), 1.69 (br s, 2H), 1.19 (br s, 2H), 0.87 (br s, 2H), 0.56 (br s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.7, 138.9, 137.7, 133.9, 130.8, 128.7, 128.3, 126.5, 126.0, 125.8, 125.5, 124.9, 120.6, 43.2, 35.9, 27.3, 24.1, 24.1, 22.2, 13.6. **HRMS-EI^{+}** (*m/z*): Calcd. for $C_{20}H_{23}NO$ $[M]^{+}$ 293.1780; found, 293.1785.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2.06 2.10 2.20 1.99 2.22 3.01
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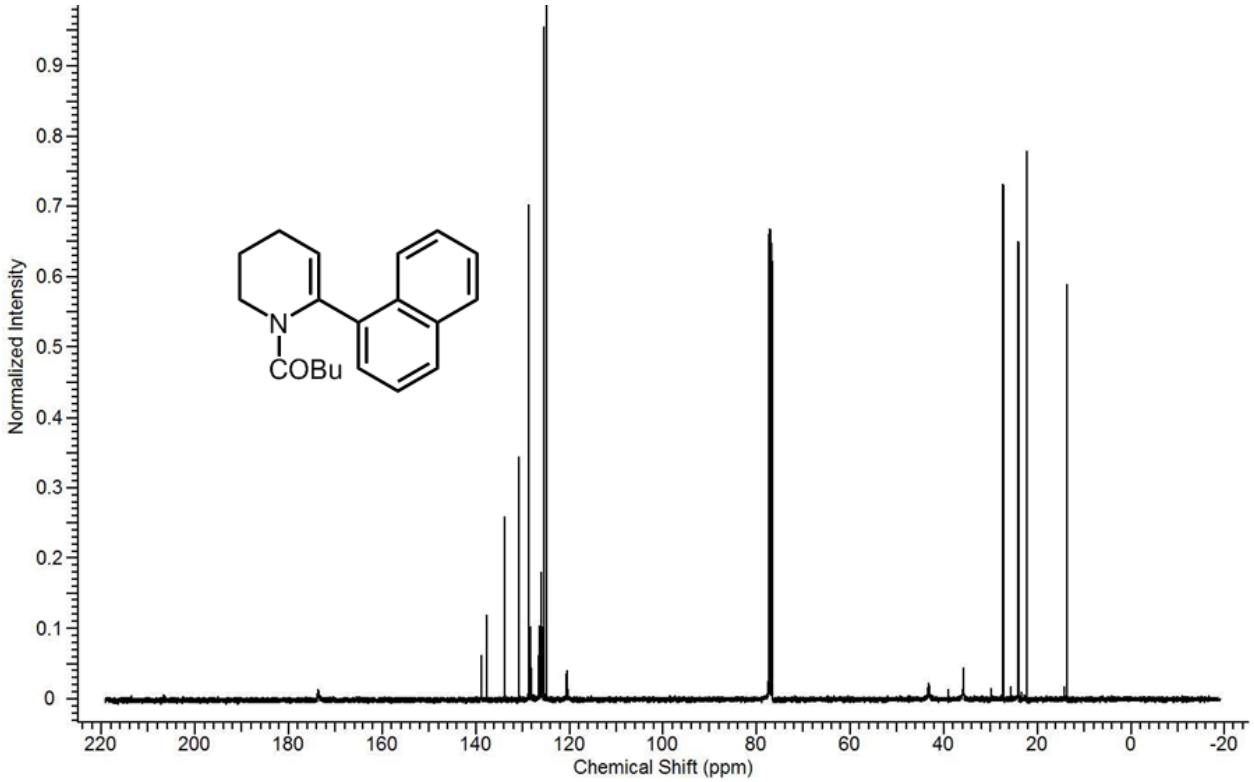
Normalized Intensity
Chemical Shift (ppm)
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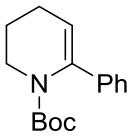
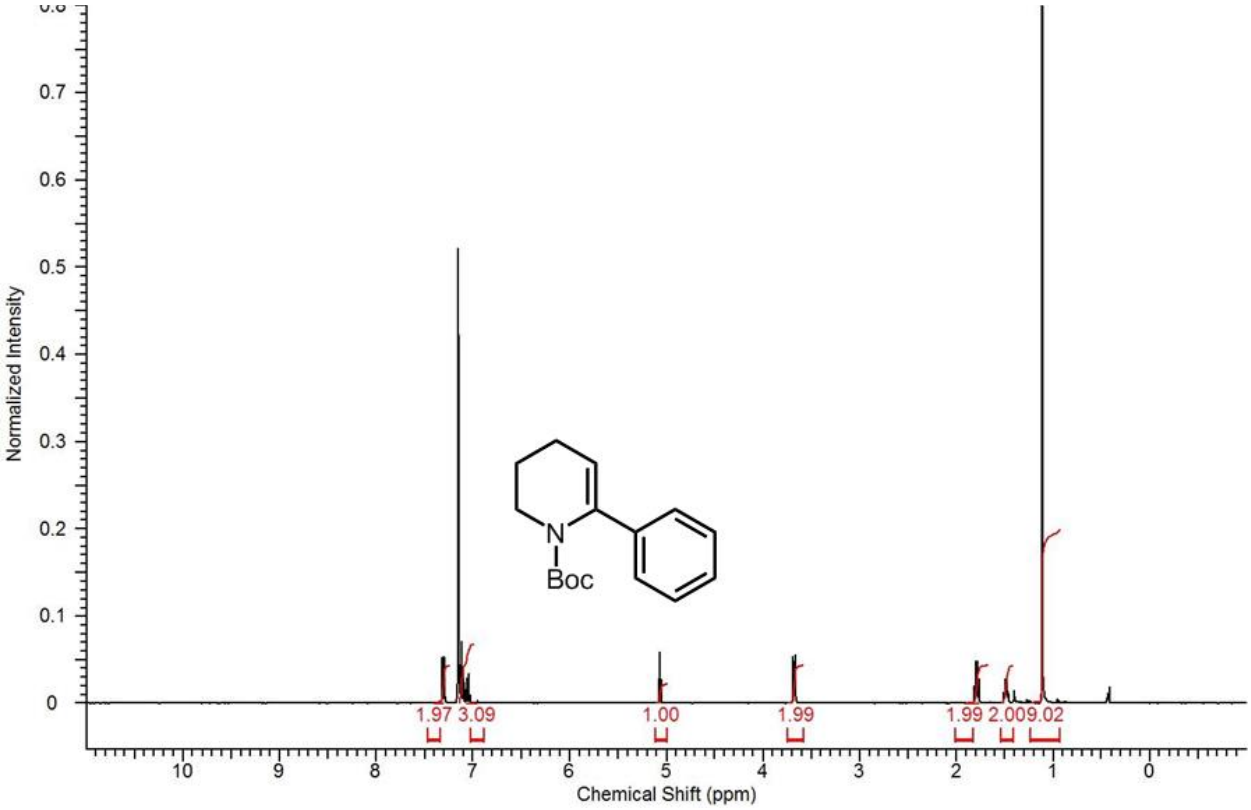
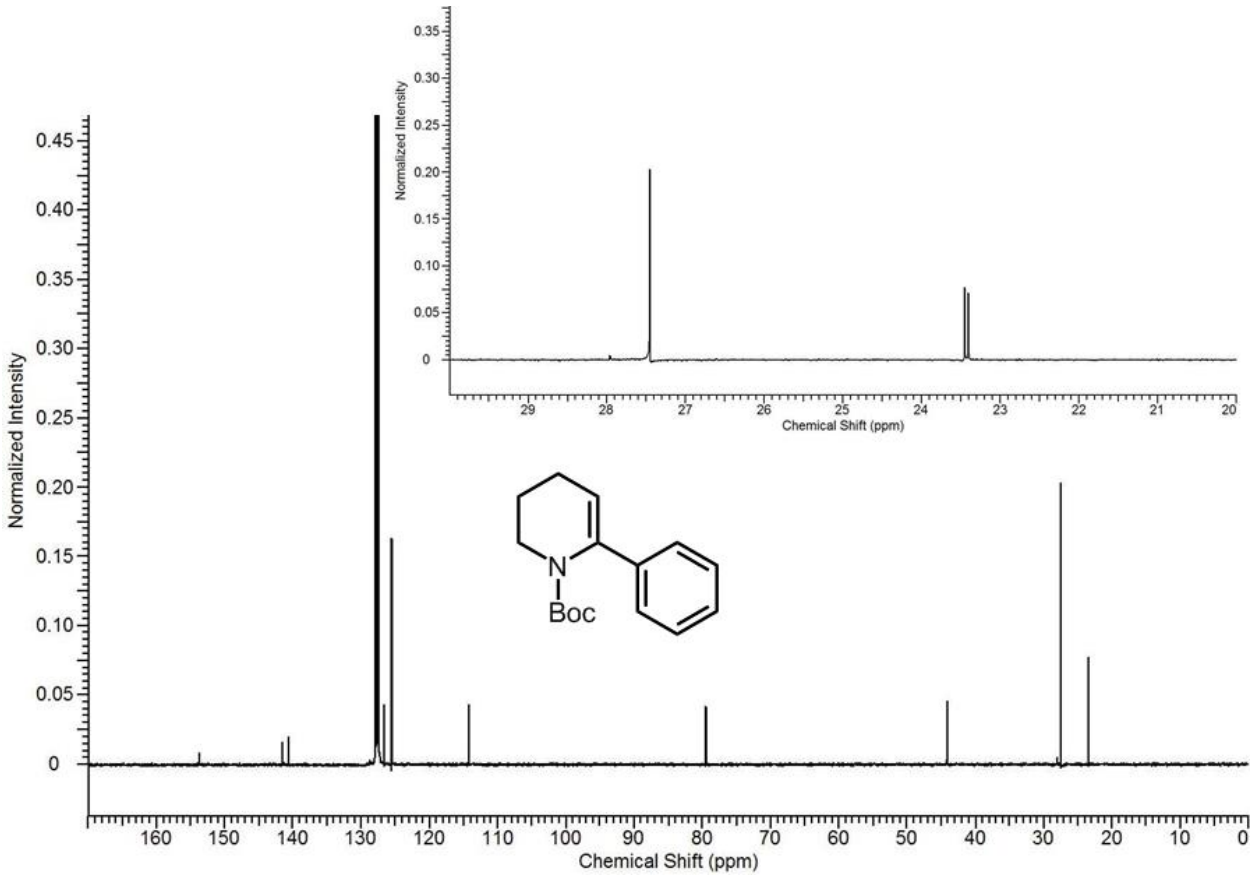
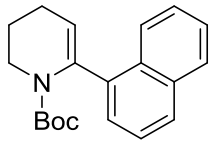


2k

Prepared from **1c** (183 mg, 1.0 mmol) and phenyl boronic acid (1.5 equiv) using **General Procedure A1**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Yield = 192 mg; 80%. NMR data in $CDCl_3$ has been reported.[2]

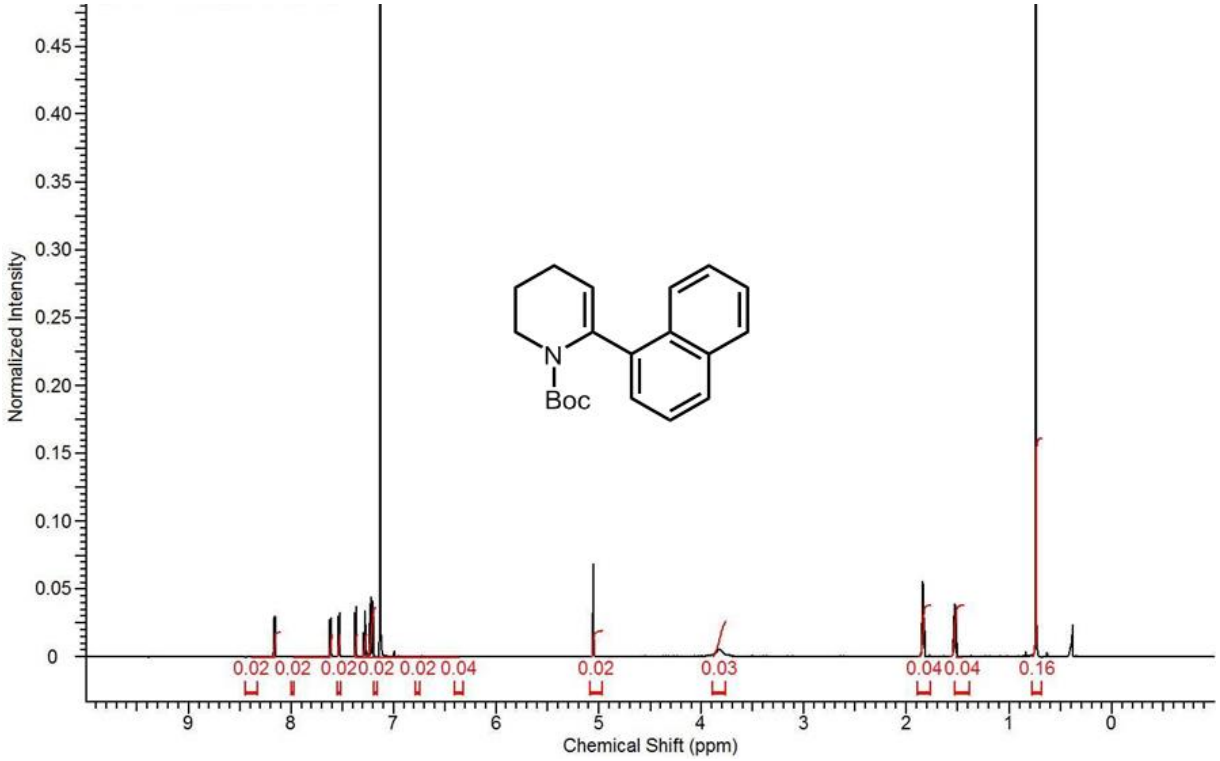


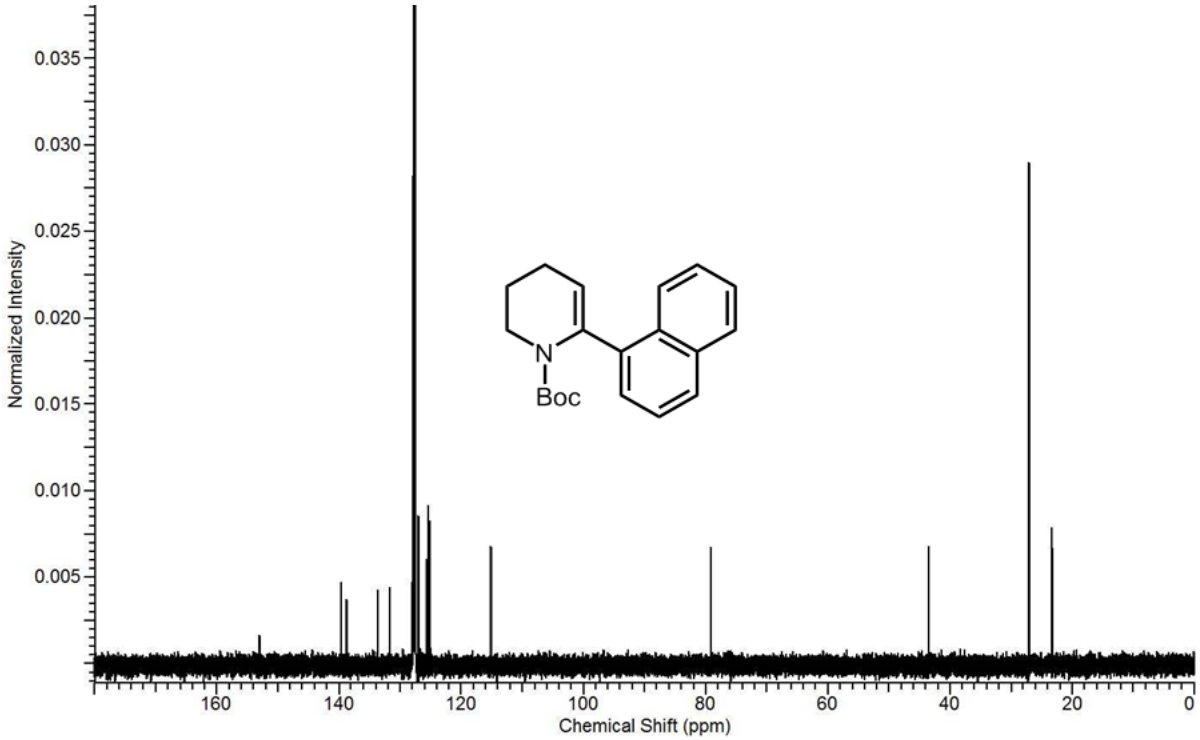


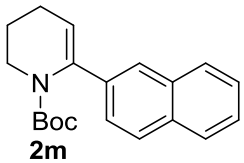


2l

Prepared from **1c** (183 mg, 1 mmol) and 1-naphthylboronic acid (258, 1.5 equiv) using **General Procedure D.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Yield = 229 mg; 74%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.16 (1H, d), 7.81 to 7.85 (6H, m), 5.18 to 5.17 (1H, t), 3.79 to 3.71 (2H, dd), 1.88 to 1.83 (2H, m), 1.55 to 1.52 (2H, m), 0.98 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 153.7, 140.5, 138.9, 133.6, 132.7, 128.5, 128.2, 127.8, 127.5, 127.2, 126.0, 125.3, 124.5, 123.7, 114.9, 79.5, 44.2, 27.3, 23.6, 23.4. HRMS calc for $C_{20}H_{23}NO_2$ 309.1729, found 309.1733. Data as previously reported by us.[3]

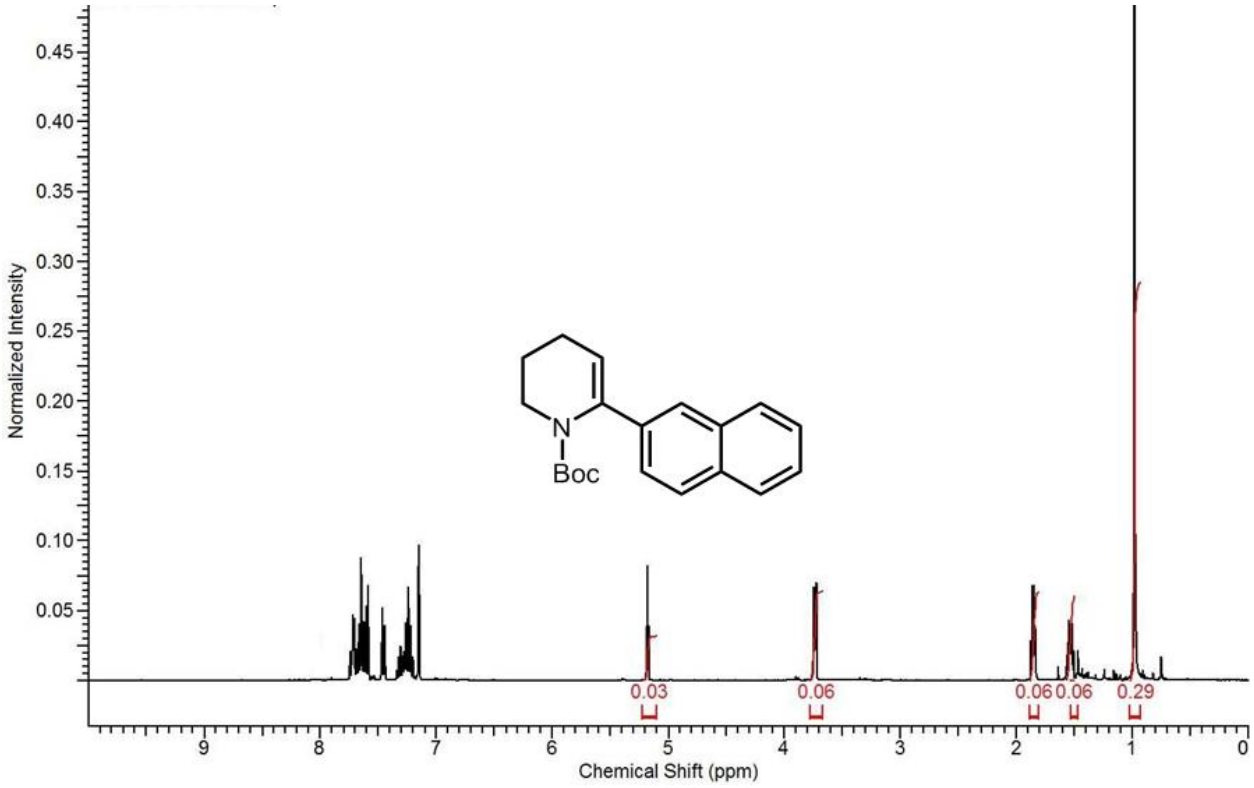

Normalized Intensity
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
N
Boc
0.02 0.02 0.02 0.02 0.02 0.04
0.02
0.03
0.04 0.04
0.16
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

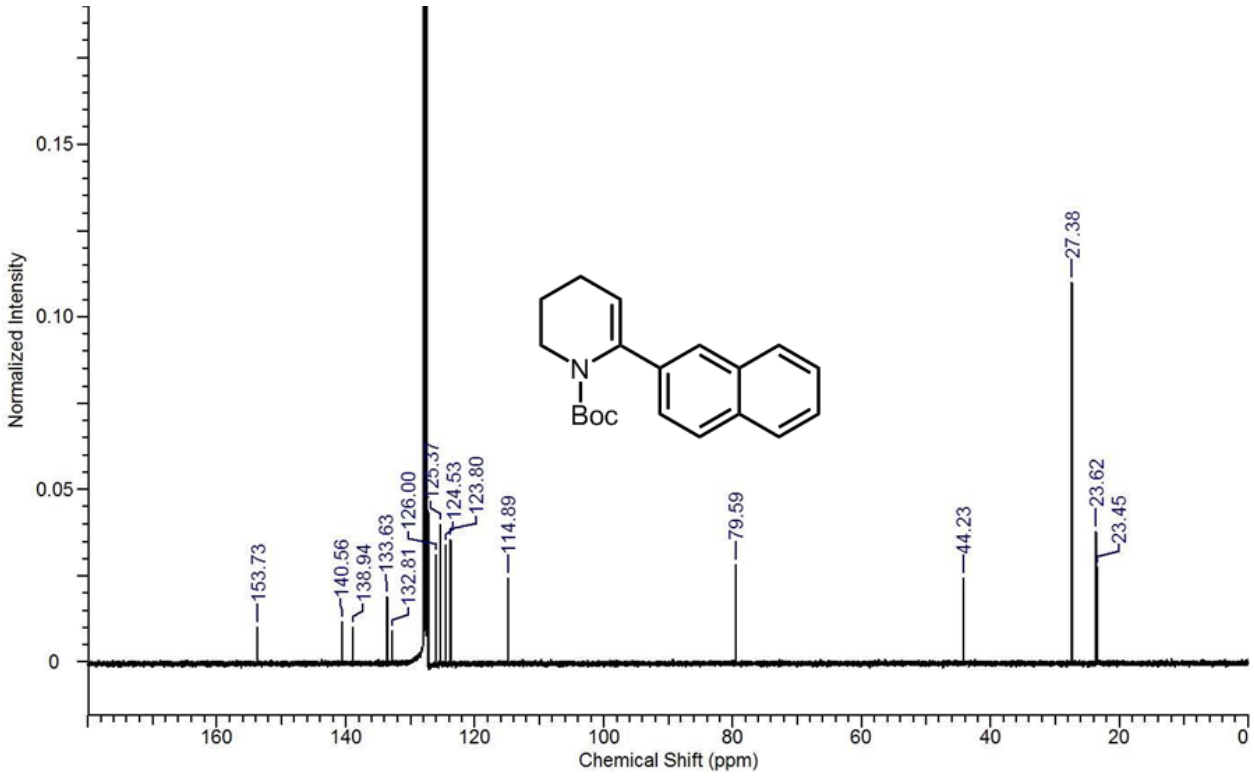

Normalized Intensity
0.035
0.030
0.025
0.020
0.015
0.010
0.005
N
Boc
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

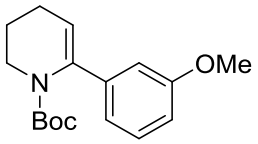


2m

Prepared from **1c** (183 mg, 1.0 mmol) and 2-naphthyl boronic acid (258 mg, 1.5 equiv) using **General Procedure A** but at 80 ^{o}C for 18 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Yield = 241 mg; 78%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.03 (1H), 7.81 to 7.20 (6H), 5.18 to 5.17 (1H), 3.75 to 3.73 (2H), 1.88 to 1.83 (2H), 1.55 to 1.52 (2H), 0.98 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.71, 140.51, 138.91, 133.61, 132.79, 128.52, 128.27, 127.81, 127.56, 127.22, 126.00, 125.37, 124.51, 123.77, 114.90, 79.58, 44.22, 27.37, 23.62, 23.45. HRMS calc for $C_{20}H_{23}NO_2$ 309.1729, found 309.1733. Data as previously reported by us.[1]

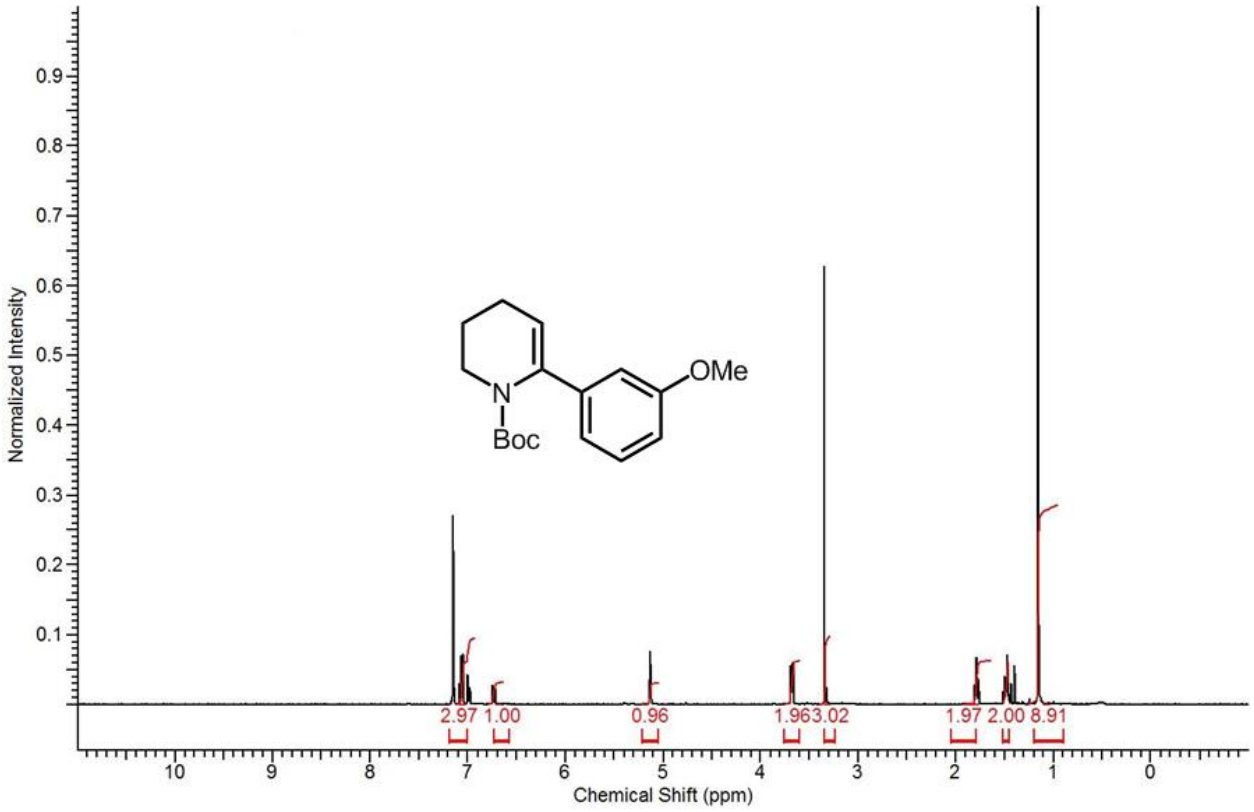


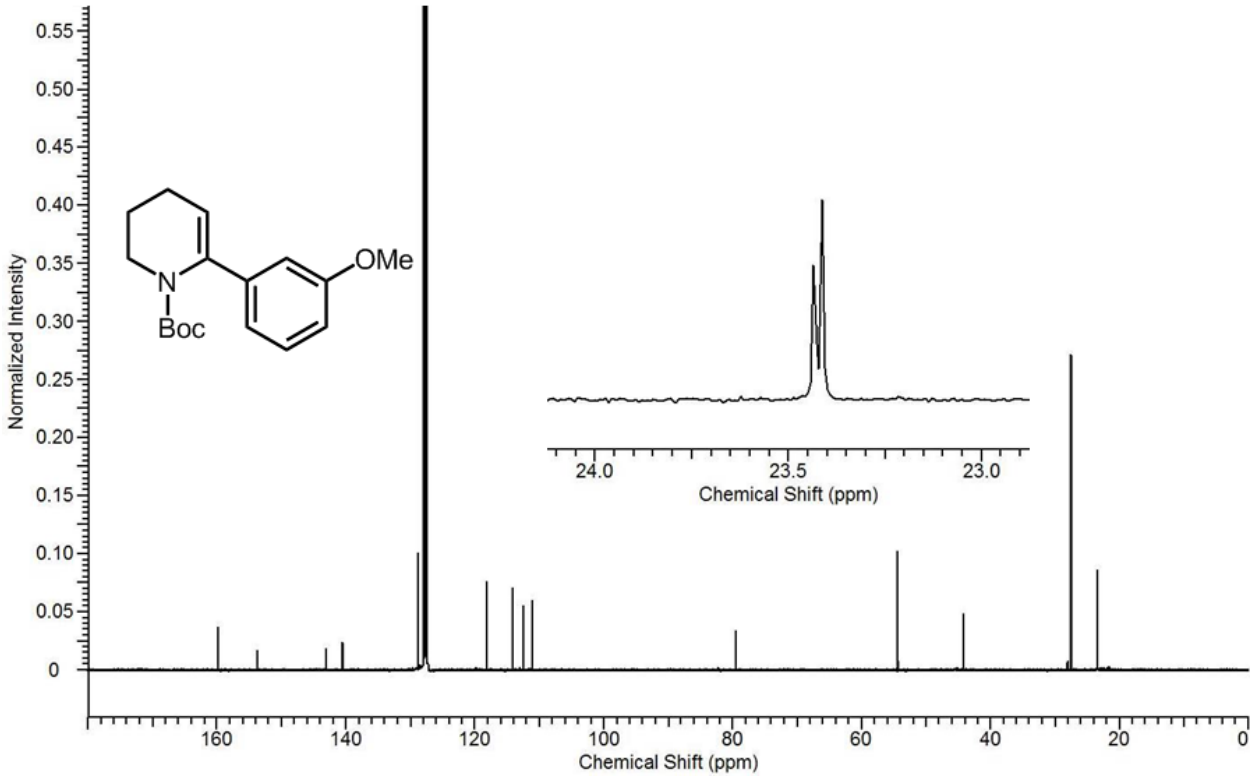


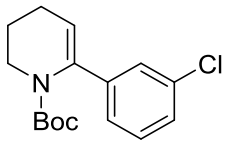


2n

Prepared from **1c** (183 mg, 1.0 mmol) and 3-methoxyphenylmagnesium bromide (3 equiv), using **General Procedure D**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:1). Yield = 249 mg; 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.22 (1H, s), 7.18 to 6.96 (2H, m), 6.80 to 6.71 (2H, t), 5.14 to 5.12 (1H, t), 3.68 to 3.66 (2H, dd), 3.34 (3H, s), 1.82 to 1.78 (2H, m), 1.52 to 1.46 (2H, m), 1.14 (9H, s). ^{13}C NMR (101 MHz, C_6D6) δ 160.3, 153.7, 142.9, 140.5, 129.7, 119.6, 112.9, 112.9, 112.4, 79.5, 54.4, 44.2, 27.5, 23.4, 23.4. HRMS calc for $C_{17}H_{23}NO_3$ 289.1678, found 289.1600. Data as previously reported by us.[3]

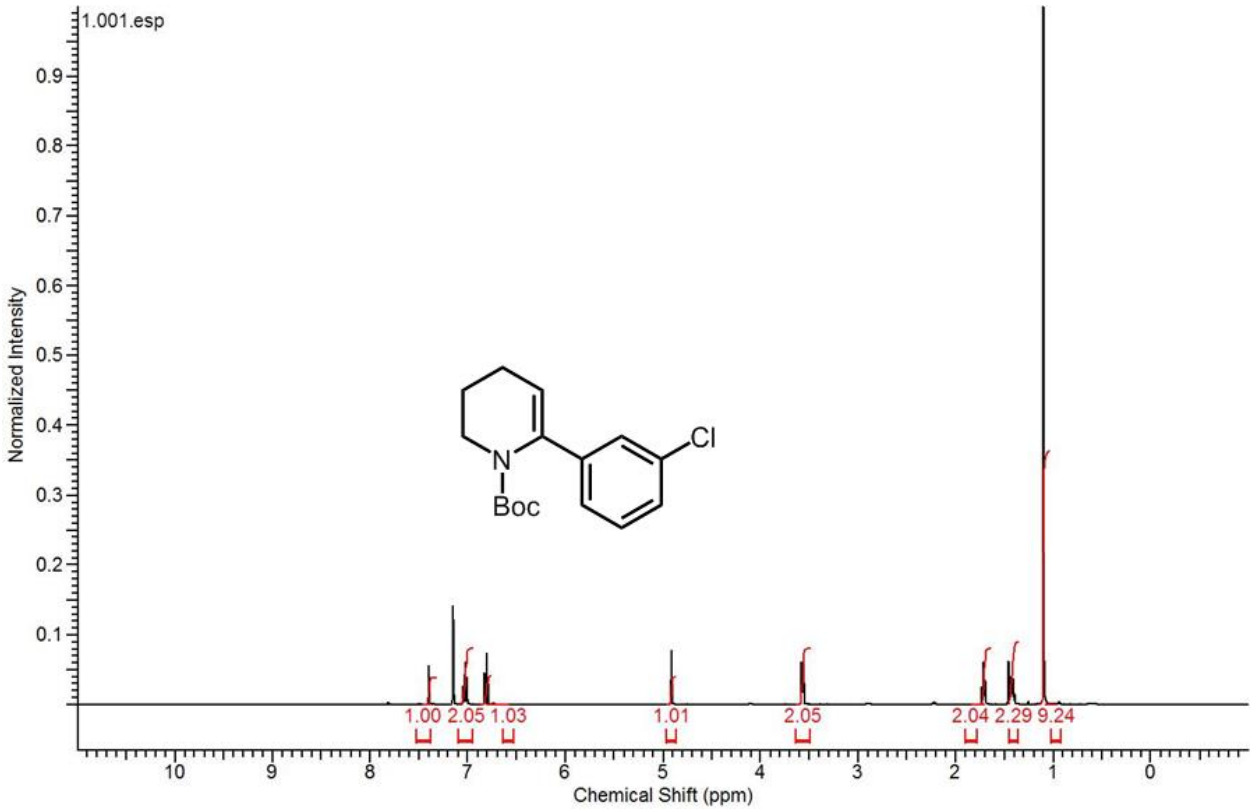

Normalized Intensity
Chemical Shift (ppm)
OMe
N
Boc
2.97 1.00
0.96
1.96 3.02
1.97 2.00 8.91

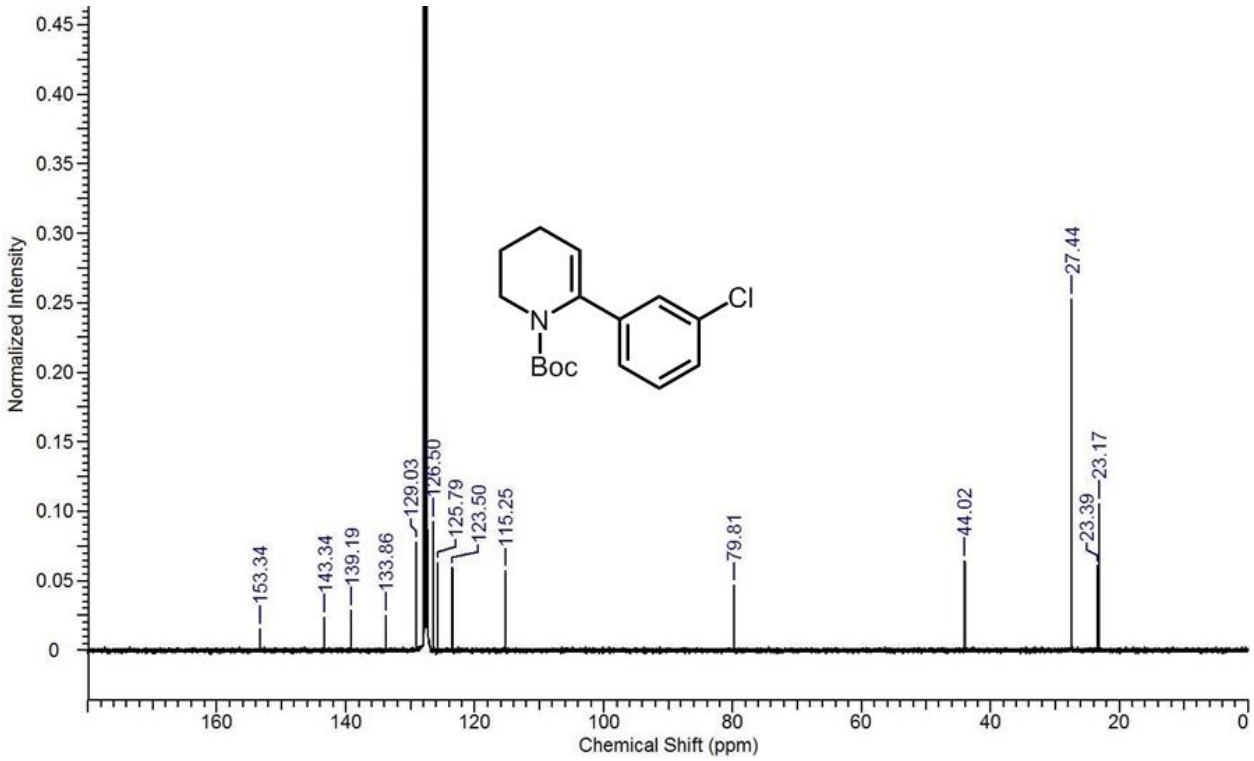

Normalized Intensity
Chemical Shift (ppm)
OMe
N
Boc
24.0
23.5
23.0
Chemical Shift (ppm)

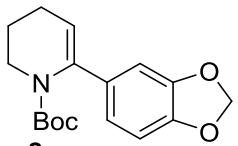


2o

Prepared from **1c** (183 mg, 1.0 mmol) and 3-chlorophenylboronic acid (1.5 equiv) using **General Procedure A.** Temp = 80 ^{o}C, time = 22 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:1). Yield = 205 mg; 70%. ^{1}H NMR (400 MHz, C_6D6) δ 7.22 (1H, s), 7.18 to 6.96 (2H, m), 6.80 to 6.71 (1H, t), 5.14 to 5.12 (1H, t), 3.68 to 3.66 (2H, dd), 1.82 to 1.78 (2H, m), 1.52 to 1.46 (2H, m), 1.14 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 153.3, 143.3, 139.2, 133.8, 129.0, 126.5, 125.8, 123.5, 115.2, 79.8, 44.0, 27.4, 23.4, 23.1. HRMS calc for $C_{16}H_{20}ClNO_2$ 293.1183, found 293.1178. Data as previously reported by us.[3]

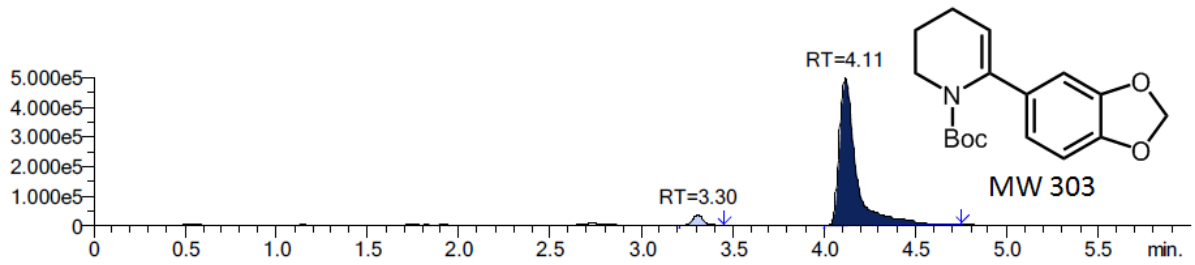






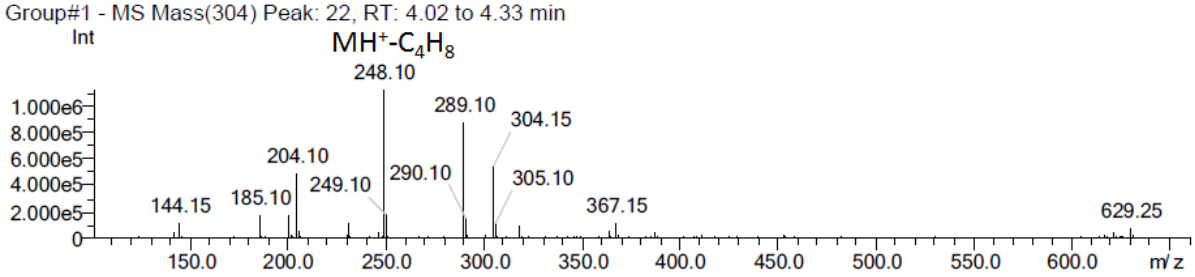
2p

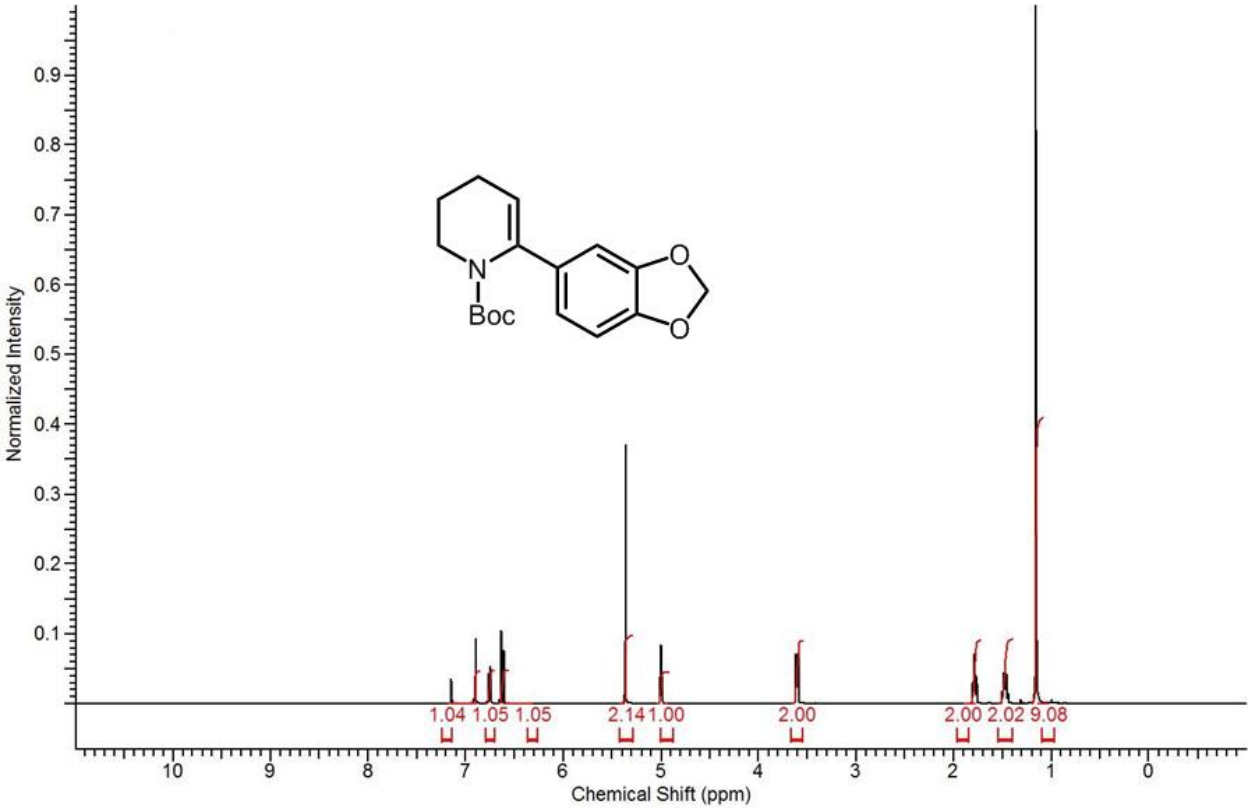
Prepared from **1c** (183 mg, 1 mmol) and 5-benzo[*d*][1,3]dioxolylboronic acid (1.5 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:3). Yield = 267 mg; 88%. ^{1}H NMR (400 MHz, C_6D_6) δ 6.94 (1H), 6.79 to 6.63 (1H), 5.33 (1H), 5.02 to 5.00 (2H), 3.65 to 3.62 (2H), 1.80 to 1.76 (2H), 1.52 to 1.19 (11H). ^{13}C NMR (101 MHz, C_6D_6) δ 154.4, 148.3, 147.3, 140.9, 136.1, 119.5, 114.0, 109.1, 107.1, 101.3, 80.1, 44.9, 28.3, 24.1, 24.1. HRMS calc for $C_{17}H_{21}NO_4$ 303.1471, found 303.1466. Data as previously reported by us.[1]

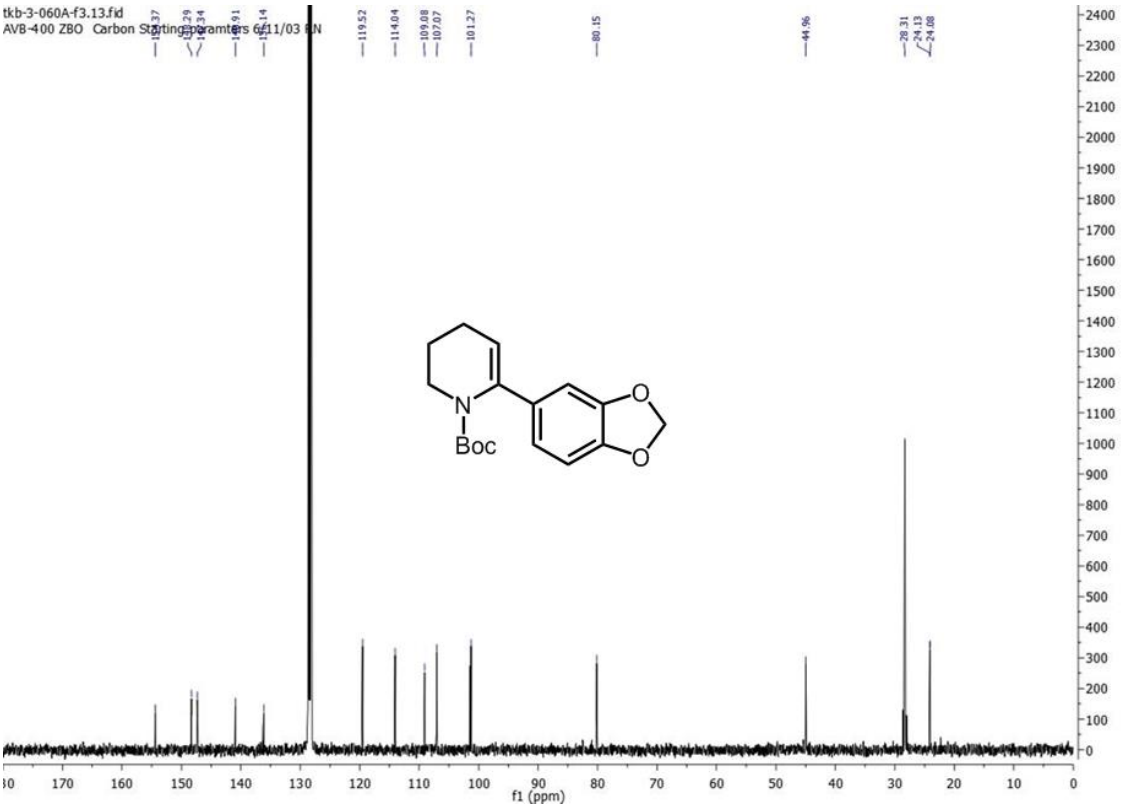


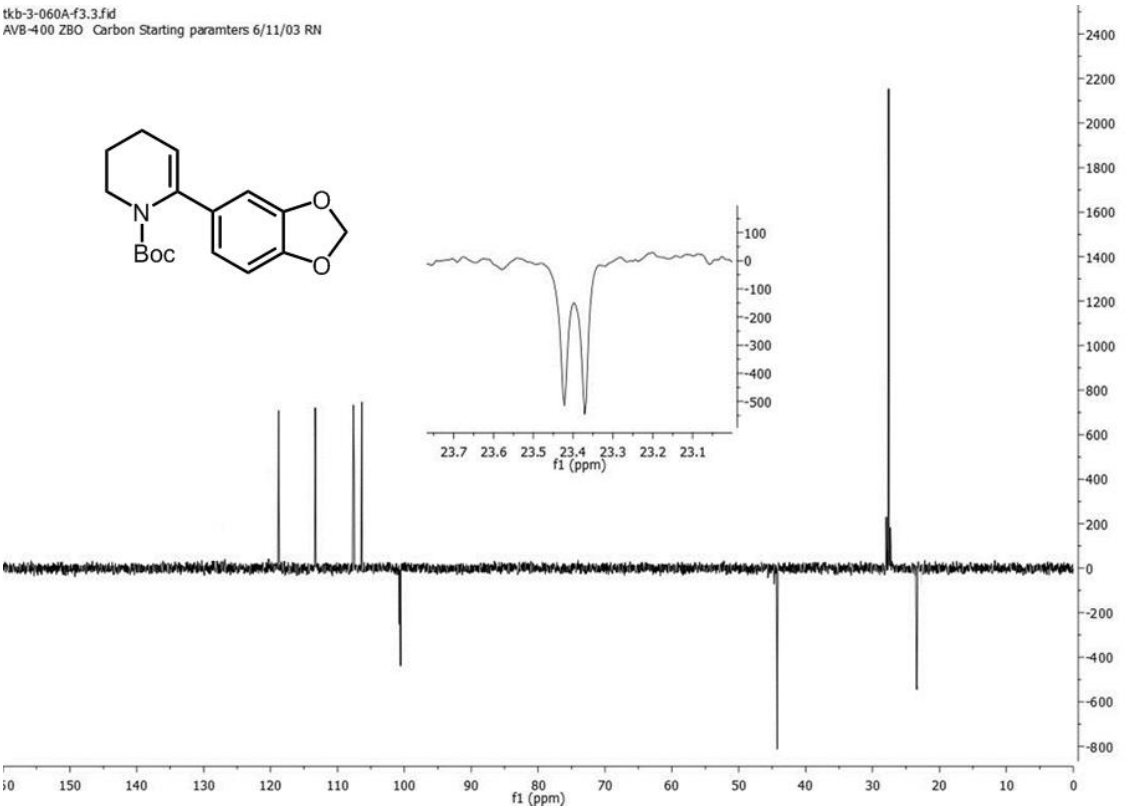
MS Spectrum

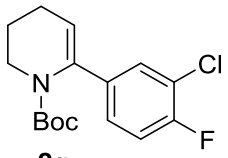
Group#1 - MS Mass(304) Peak: 22, RT: 4.02 to 4.33 min





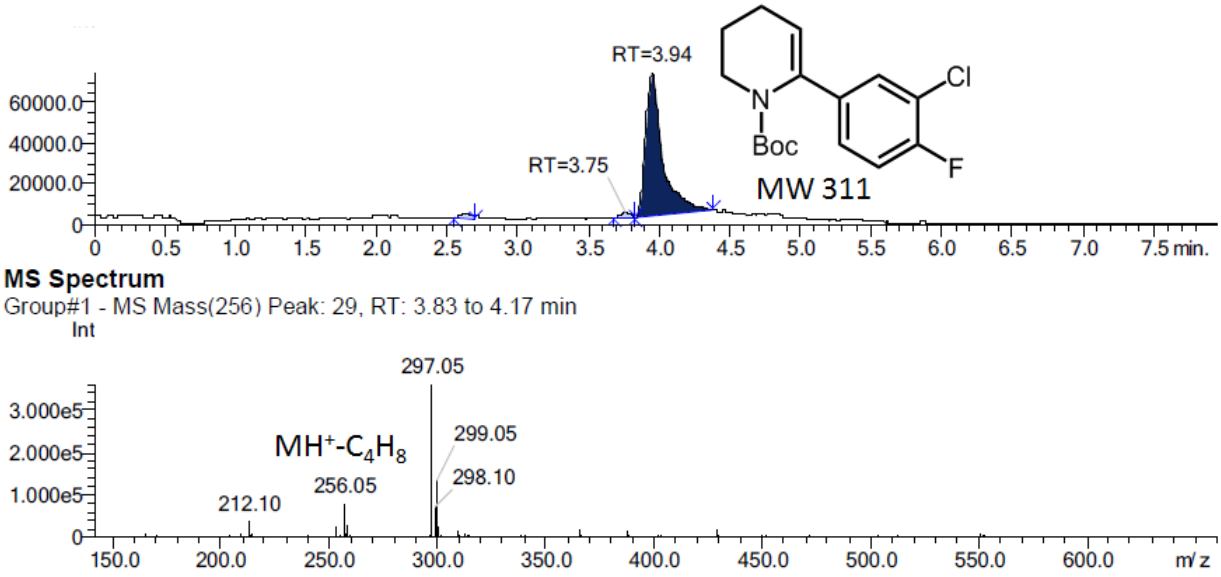

tkb-3-060A-f3.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
119.52
114.04
109.08
107.07
101.27
80.15
44.96
28.31
24.13
24.08
N
Boc
O
O
f1 (ppm)

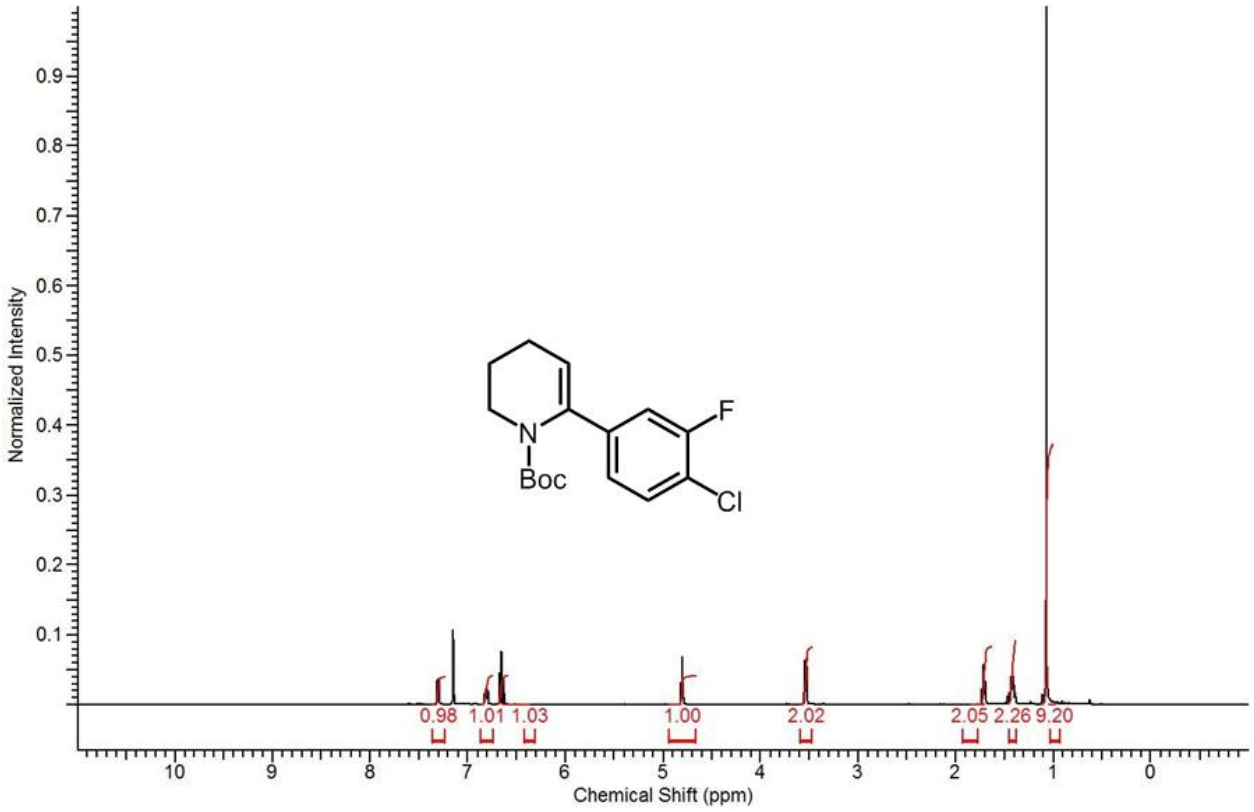

tkb-3-060A-f3.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
N
Boc
O
O
23.7 23.6 23.5 23.4 23.3 23.2 23.1
f1 (ppm)
f1 (ppm)

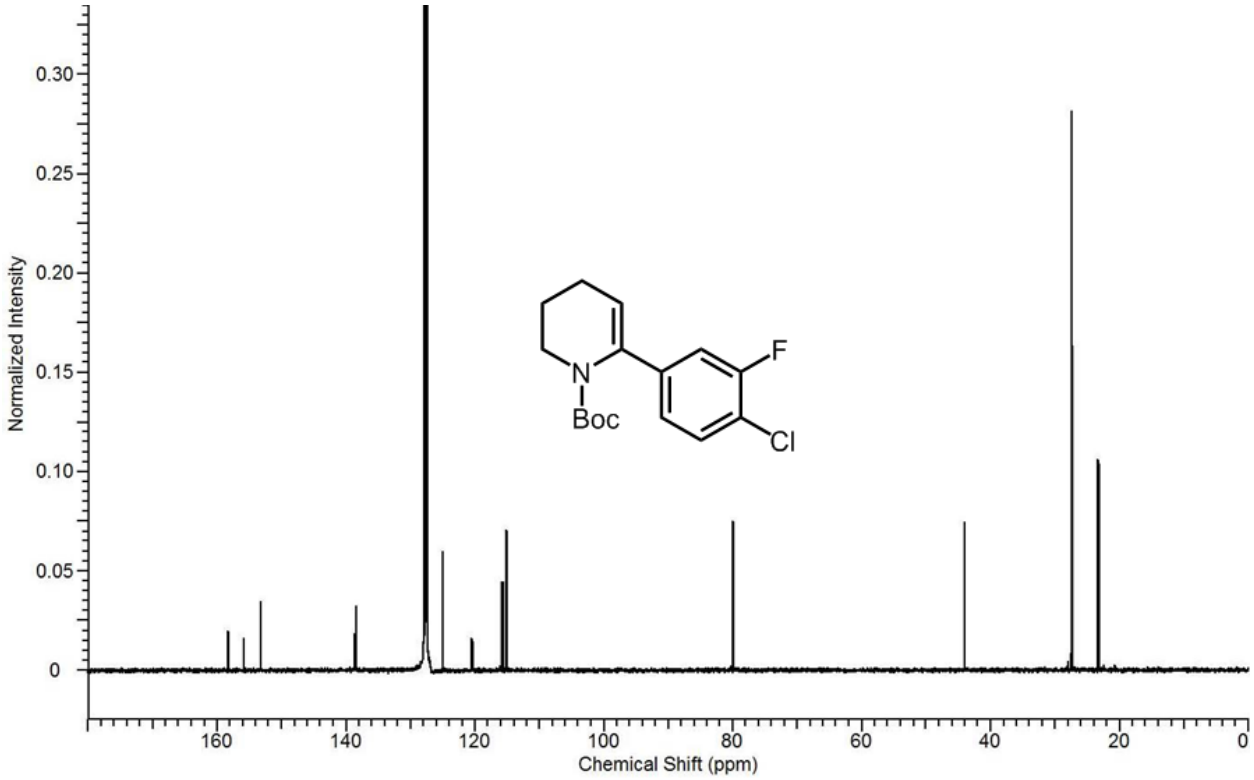


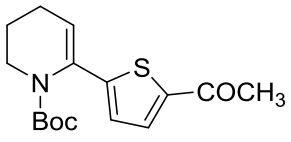
2q

Prepared from **1a** (183 mg, 1.0 mmol) and 3-chloro-4-fluorophenylboronic acid (1.5 equiv) using **General Procedure A** at 80 °C for 36 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 215 mg, 69%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.32 to 7.29 (1H), 6.68 to 6.66 (1H), 6.63 (1H), 4.81 to 4.79 (1H, t), 3.55 to 3.53 (2H, dd), 1.73 to 1.69 (2H, dd), 1.46 to 1.39 (2H, m), 1.07 (9H, s). ^{13}C NMR (101 MHz, C_6D_6) δ 158.2, 155.8, 153.2, 138.5, 138.5, 138.3, 124.9, 124.9, 120.4, 120.2, 115.8, 115.5, 115.1, 79.8, 44.0, 27.4, 23.3, 23.1. HRMS calc for $C_{16}H_{19}ClFNO_2$ 311.1088, found 311.1084.



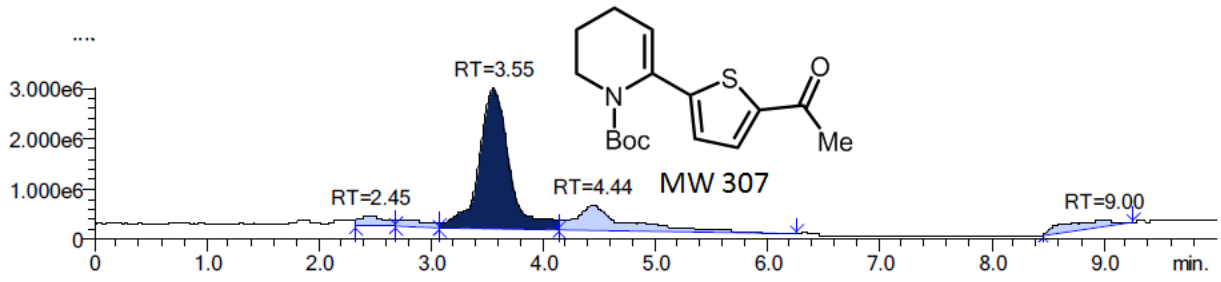

Normalized Intensity
0.98
1.01
1.03
1.00
2.02
2.05
2.26
9.20
Chemical Shift (ppm)
N
Boc
F
Cl

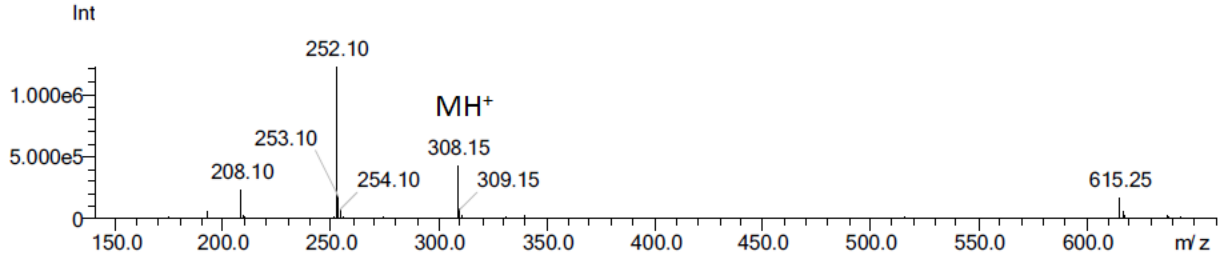

Normalized Intensity
Chemical Shift (ppm)
N
Boc
F
Cl

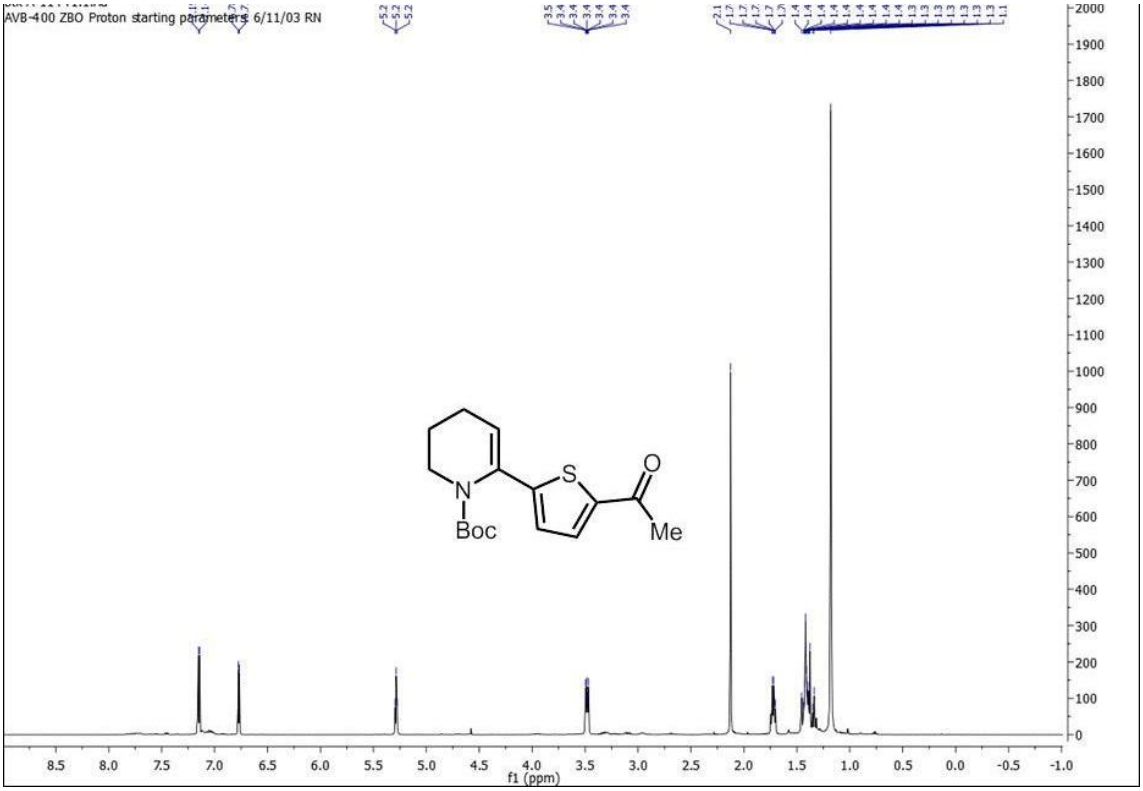


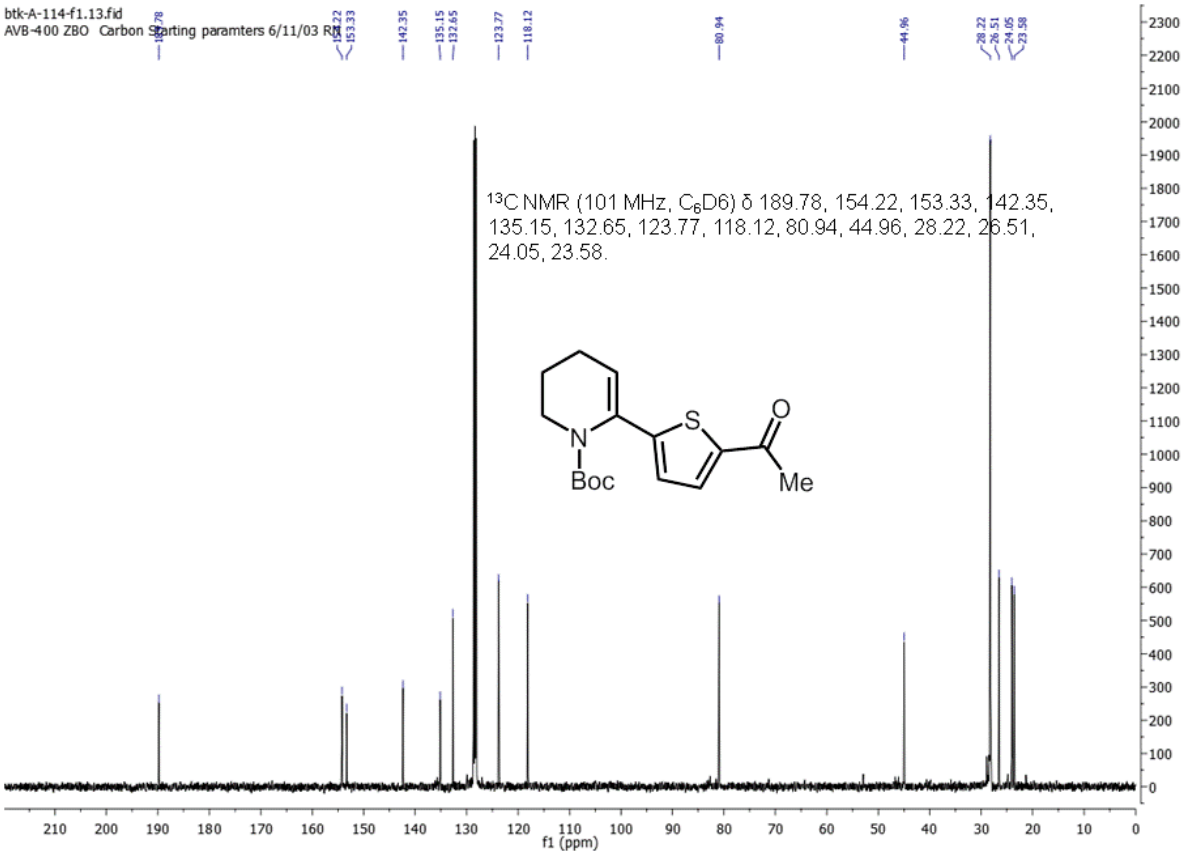
2r

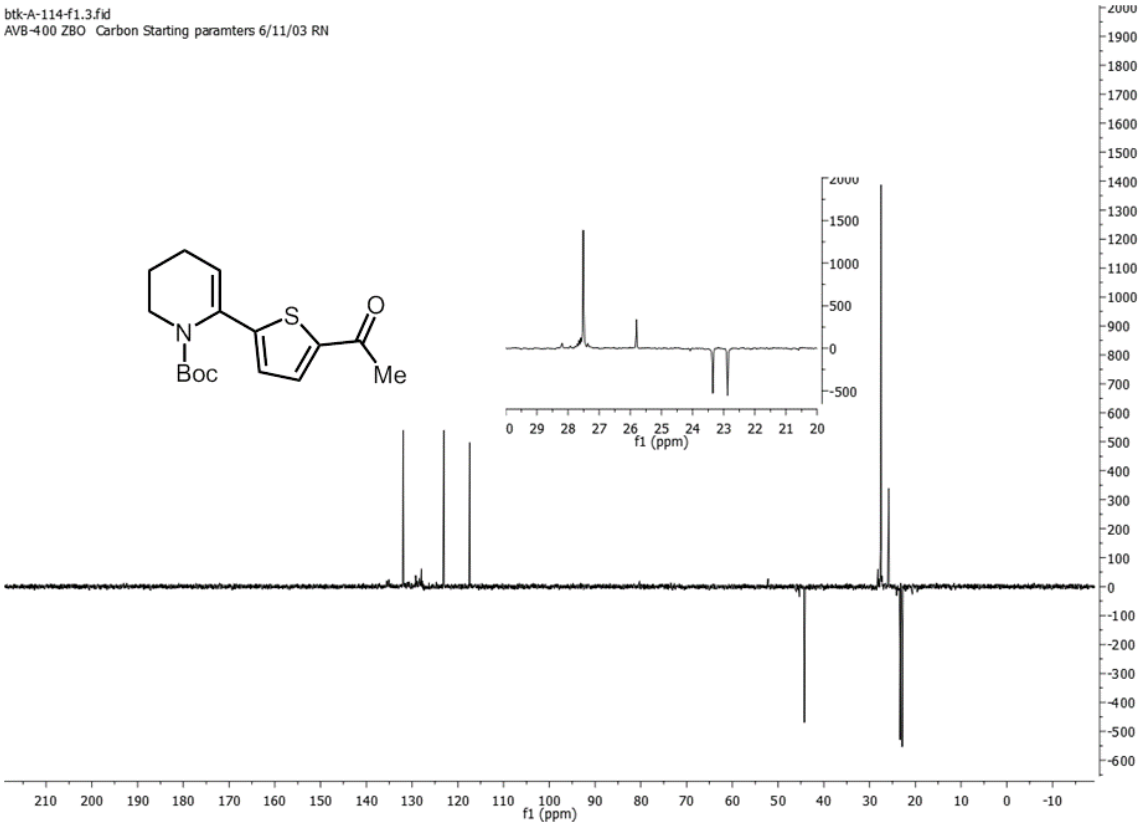
Prepared from **1c** (183 mg, 1.0 mmol) and 5-acetyl-2-thiopheneboronic acid using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:1). Yield = 273 mg; 89%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.15 (1H), 6.78 (1H), 5.29 (1H), 3.49 (1H), 2.13 (3H), 1.74 to 1.70 (2H), 1.45 to 1.35 (11H). ^{13}C NMR (101 MHz, C_6D_6) δ 189.78, 154.22, 153.33, 142.35, 135.15, 132.65, 123.77, 118.12, 80.94, 44.96, 28.22, 26.51, 24.05, 23.58. HRMS calc for $C_{16}H_{21}NO_3S$ 307.1242, found 307.1248.

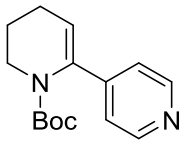





AVB-400 ZBO Proton starting parameters 6/11/03 RN
N
Boc
S
O
Me
f1 (ppm)

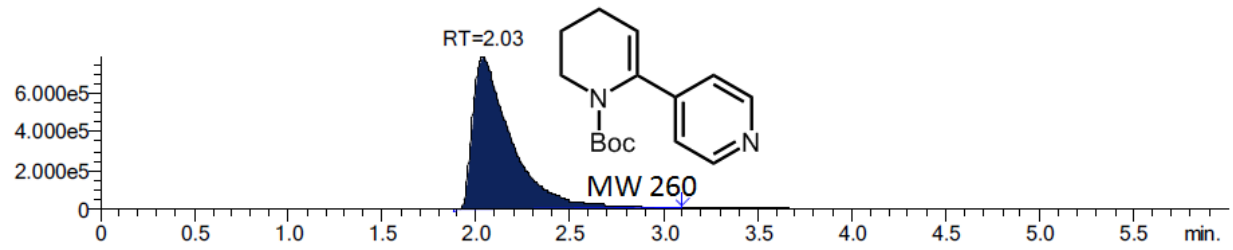

btk-A-114-f1.13.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
189.78
154.22
153.33
142.35
135.15
132.65
123.77
118.12
80.94
44.96
28.22
26.51
24.05
23.58
^{13}C NMR (101 MHz, C_6D6) δ 189.78, 154.22, 153.33, 142.35, 135.15, 132.65, 123.77, 118.12, 80.94, 44.96, 28.22, 26.51, 24.05, 23.58.
N
Boc
S
O
Me
f1 (ppm)





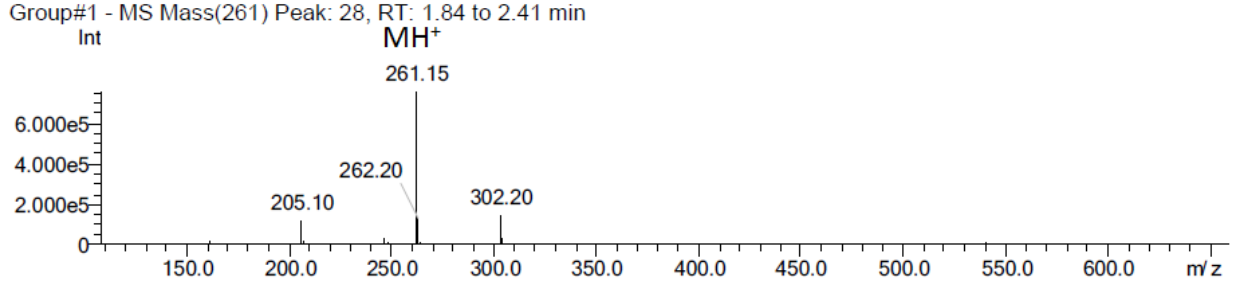
2s

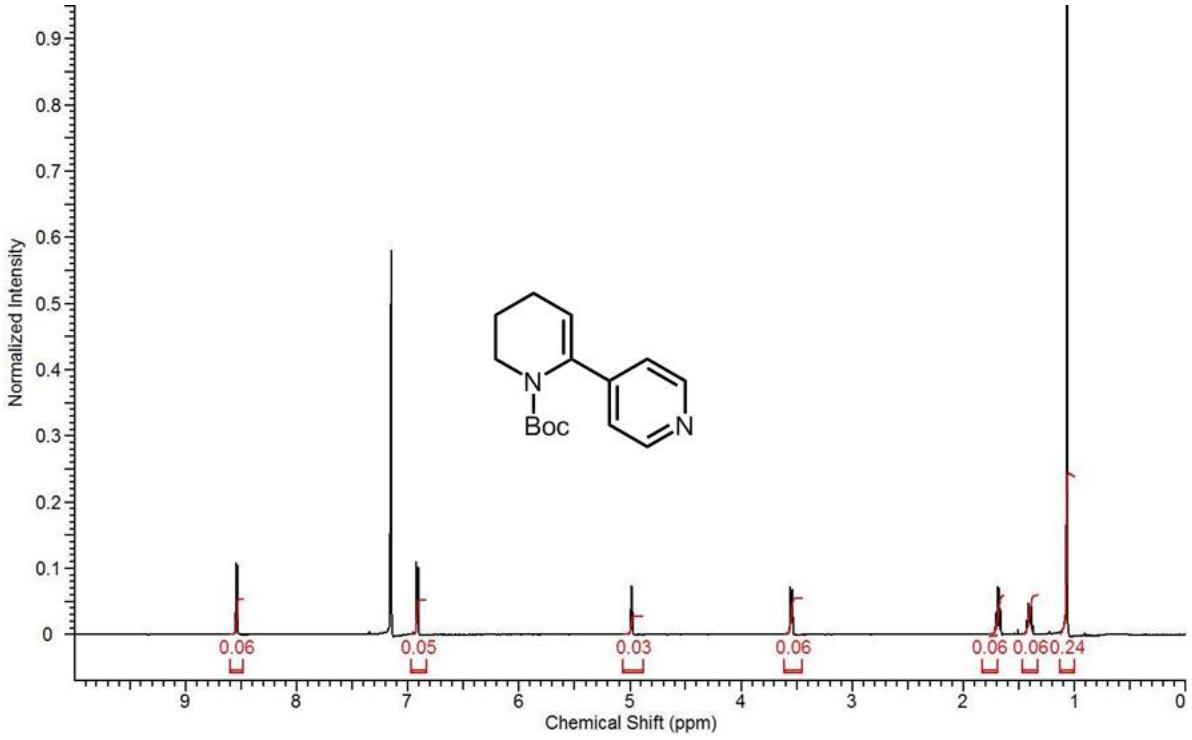
Prepared from **1c** (183 mg, 1.0 mmol) and 4-pyridylboronic acid (1.5 equiv), using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with DCM/MeOH (95:5). Yield = 180 mg; 69%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.56 to 8.55 (2H), 6.92 to 6.90 (2H), 4.99 to 4.97 (1H), 3.56 to 3.53 (2H), 1.71 to 1.66 (2H), 1.45 to 1.37 (2H), 1.07 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.1, 149.8, 148.1, 138.6, 119.9, 116.9, 80.2, 43.9, 27.4, 23.4, 23.0. HRMS calc for $C_{15}H_{20}N_2O_2$ 260.1525, found 260.1521. Data as previously reported by us.[3]

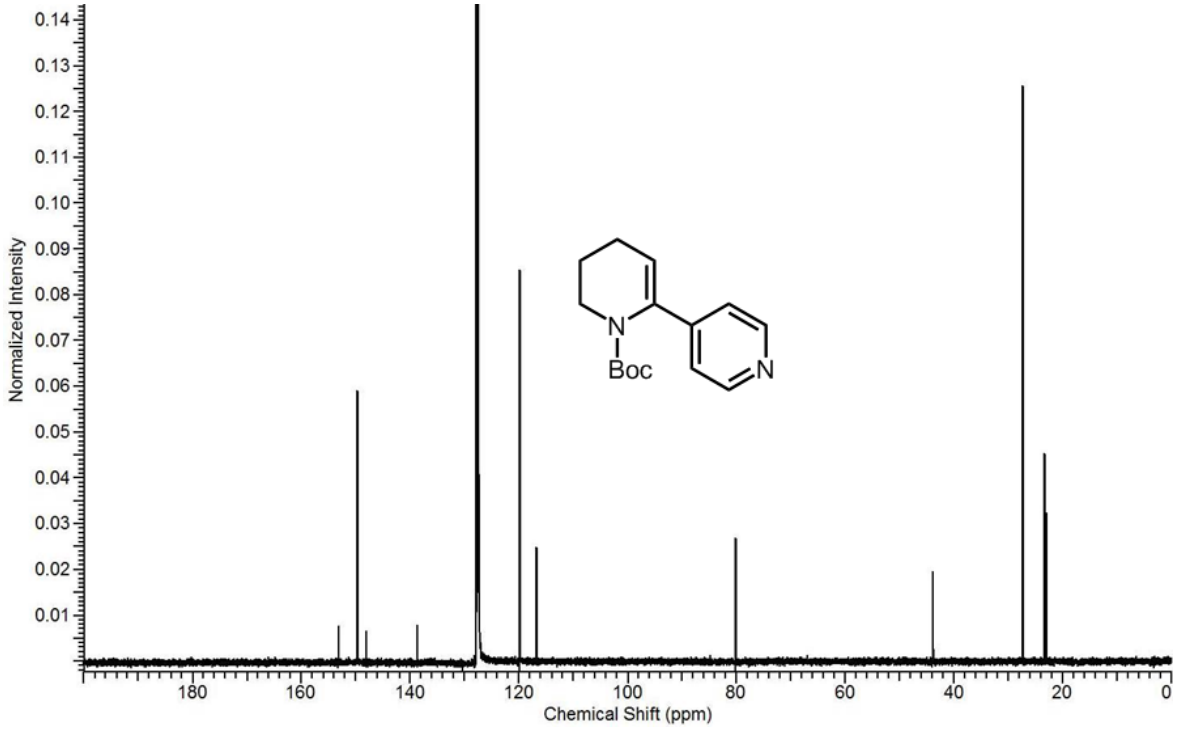


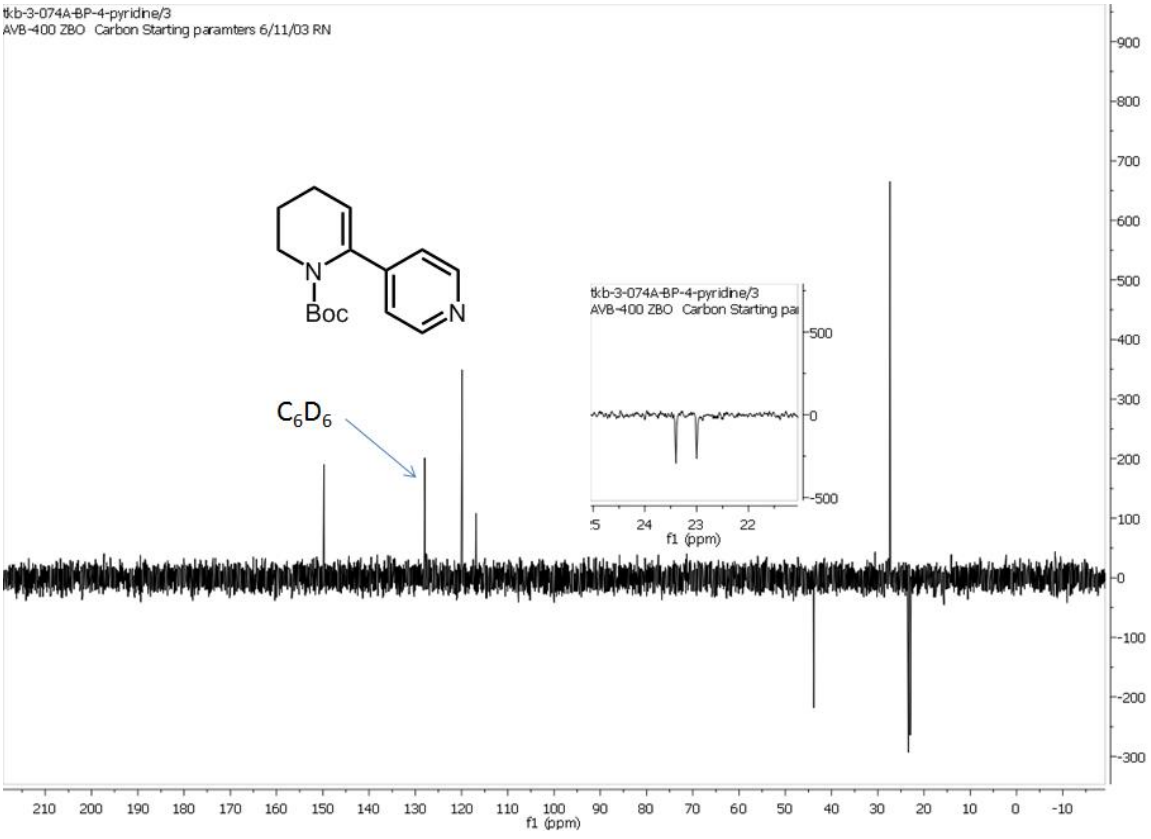
MS Spectrum

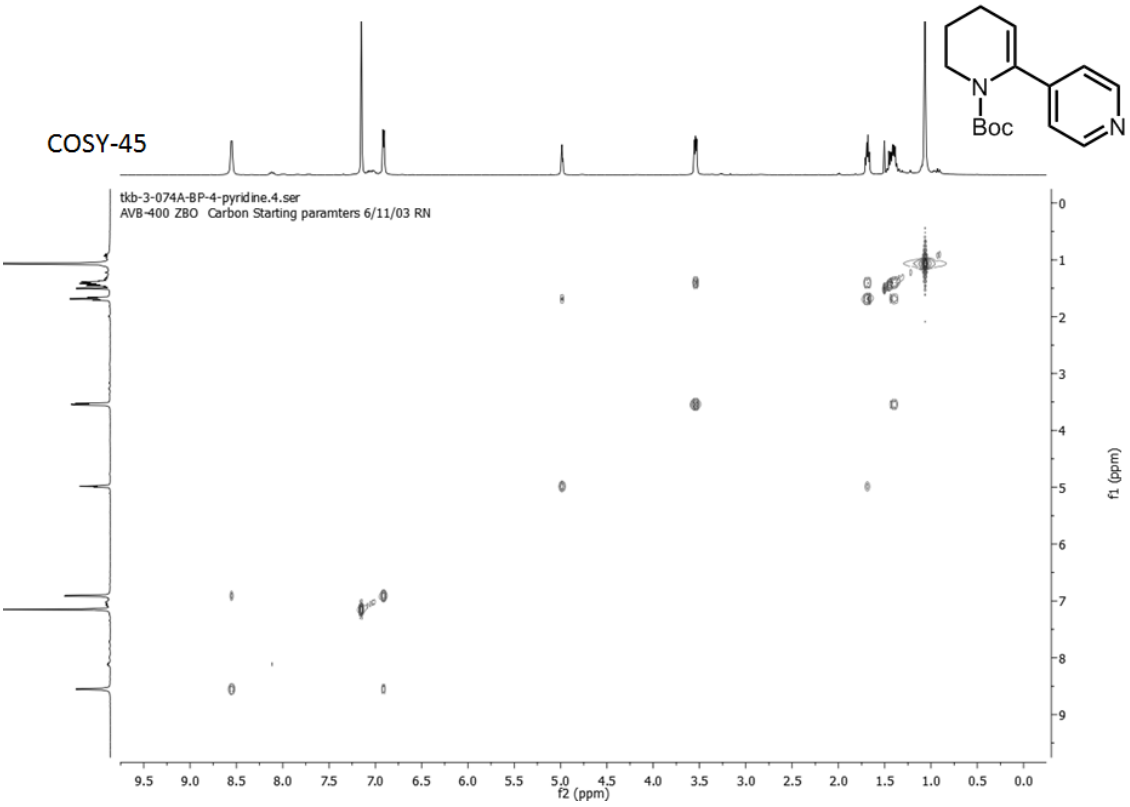
Group#1 - MS Mass(261) Peak: 28, RT: 1.84 to 2.41 min

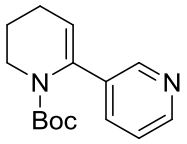





Normalized Intensity
Chemical Shift (ppm)
N
Boc
N

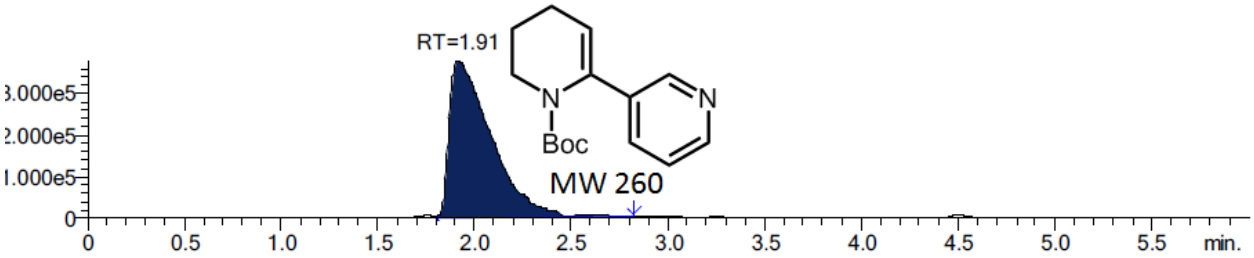

tkb-3-074A-BP-4-pyridine/3
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
N
Boc
N
C6D6
f1 (ppm)





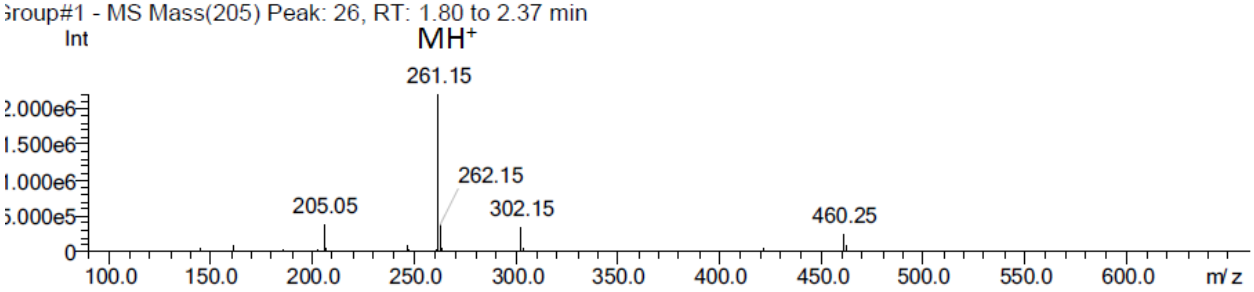
2t

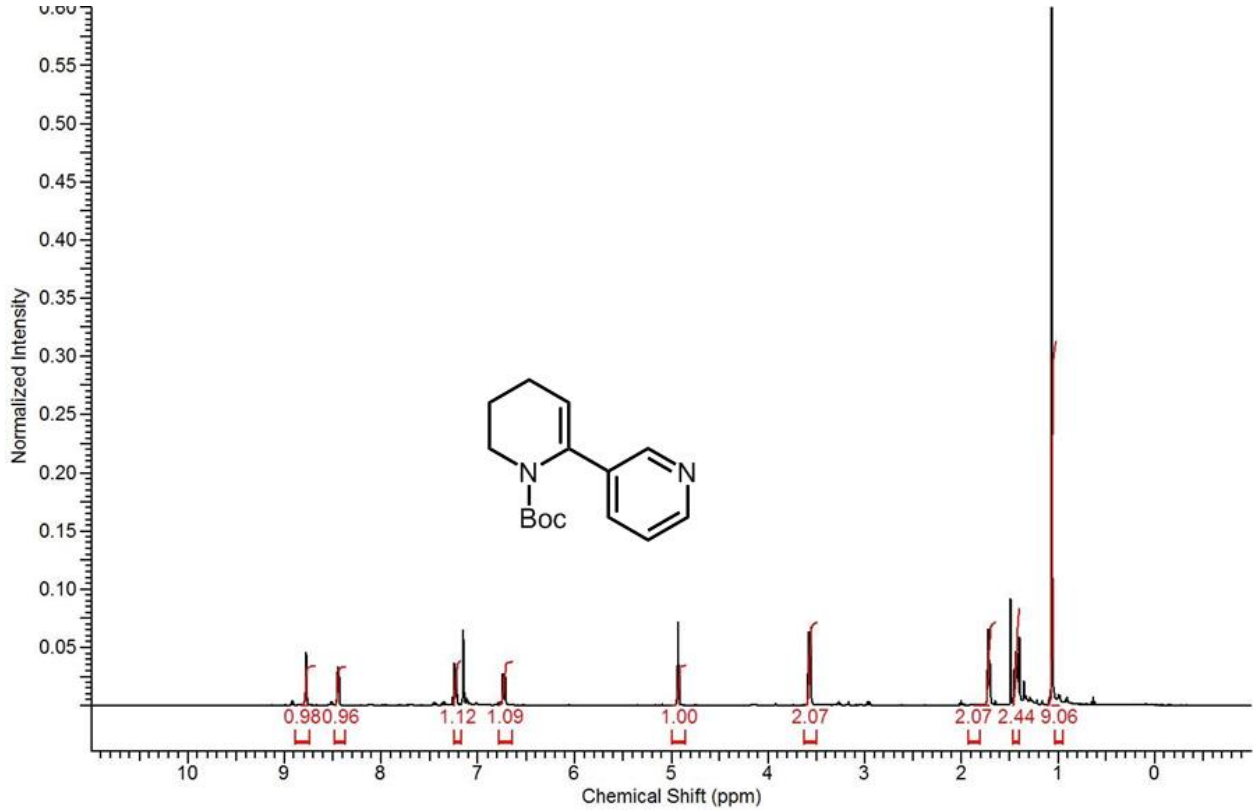
Prepared from **1c** (183 mg, 1.0 mmol) and 3-pyridylboronic acid (1.5 equiv), using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with DCM/MeOH (98:2). Yield = 148 mg; 57%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.79 & 8.78 (1H), 8.47 to 8.45 (1H), 7.26 to 7.23 (1H), 6.76 to 6.72 (1H), 4.95 to 4.93 (1H), 3.59 to 3.57 (2H), 1.75 to 1.70 (2H), 1.51 to 1.03 (11H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.9, 148.7, 147.9, 138.3, 137.2, 132.6, 123.0, 116.4, 80.5, 44.7, 28.1, 24.1, 23.8. HRMS calc for $C_{15}H_{20}N_2O_2$ 260.1525, found 260.1522.

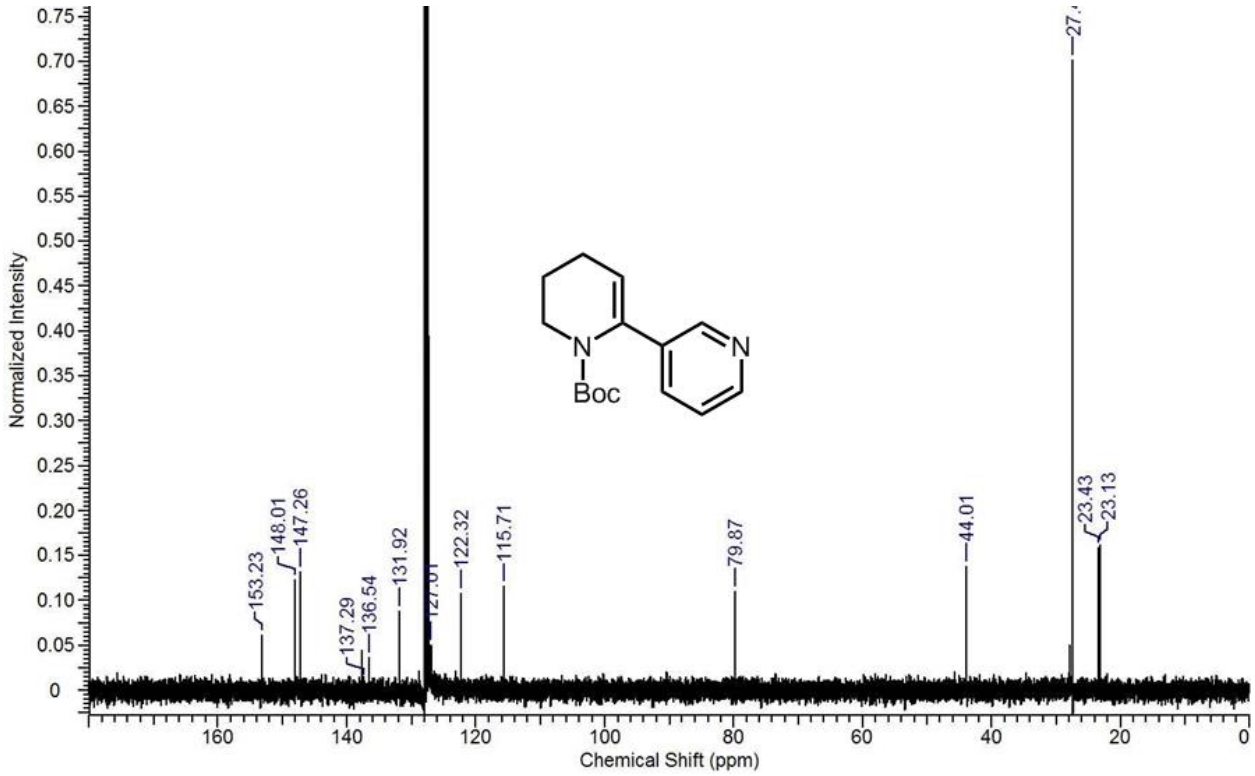


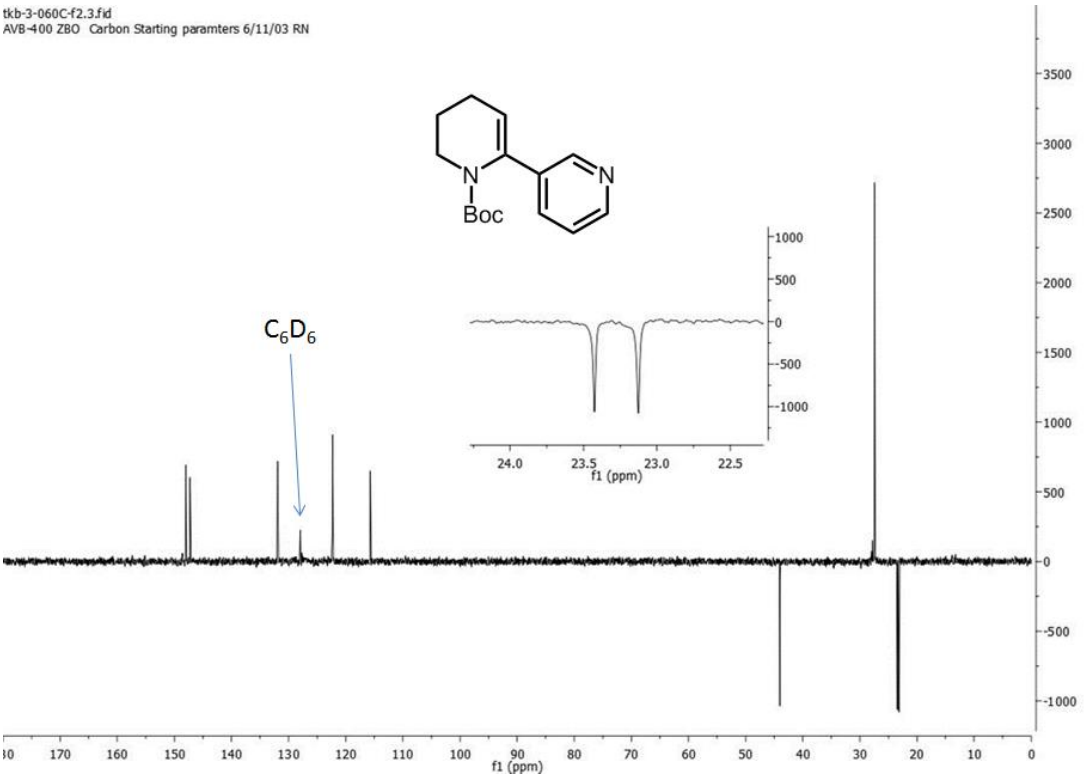
MS Spectrum

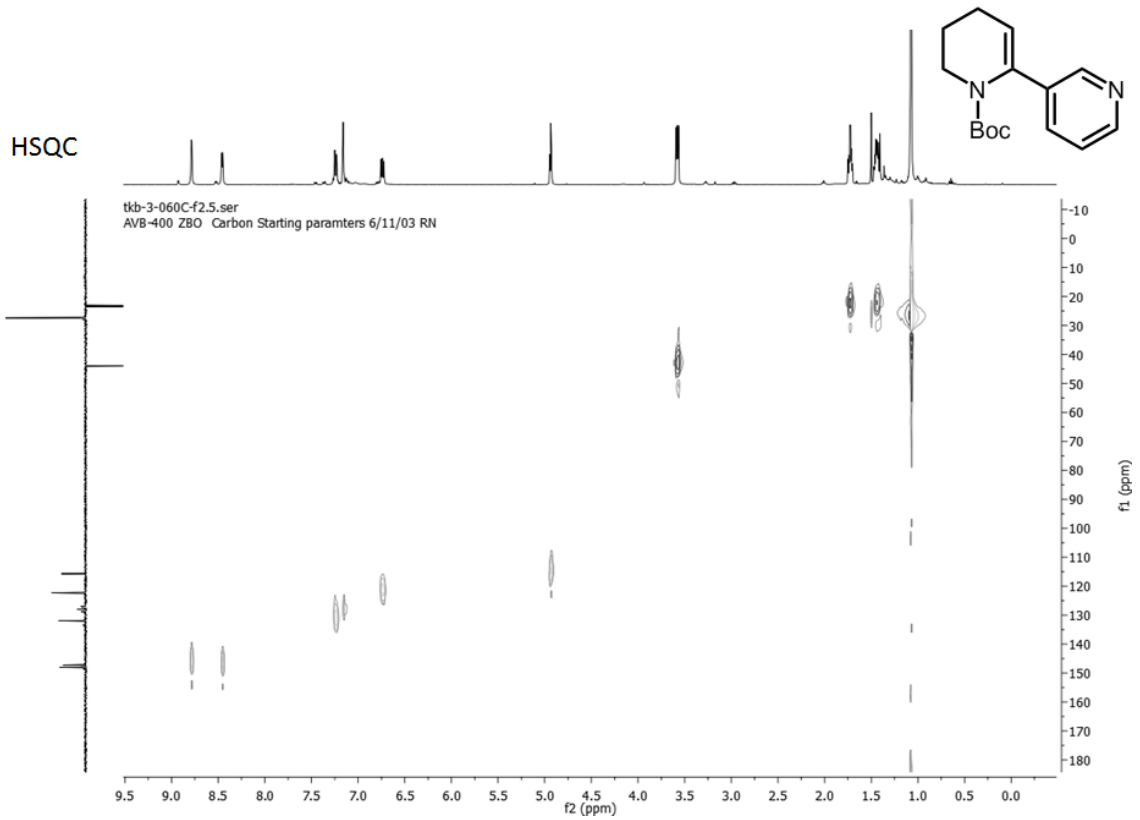
Group#1 - MS Mass(205) Peak: 26, RT: 1.80 to 2.37 min

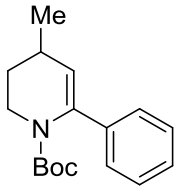





Normalized Intensity
Chemical Shift (ppm)
153.23
148.01
147.26
137.29
136.54
131.92
122.32
115.71
79.87
44.01
23.43
23.13
N
Boc

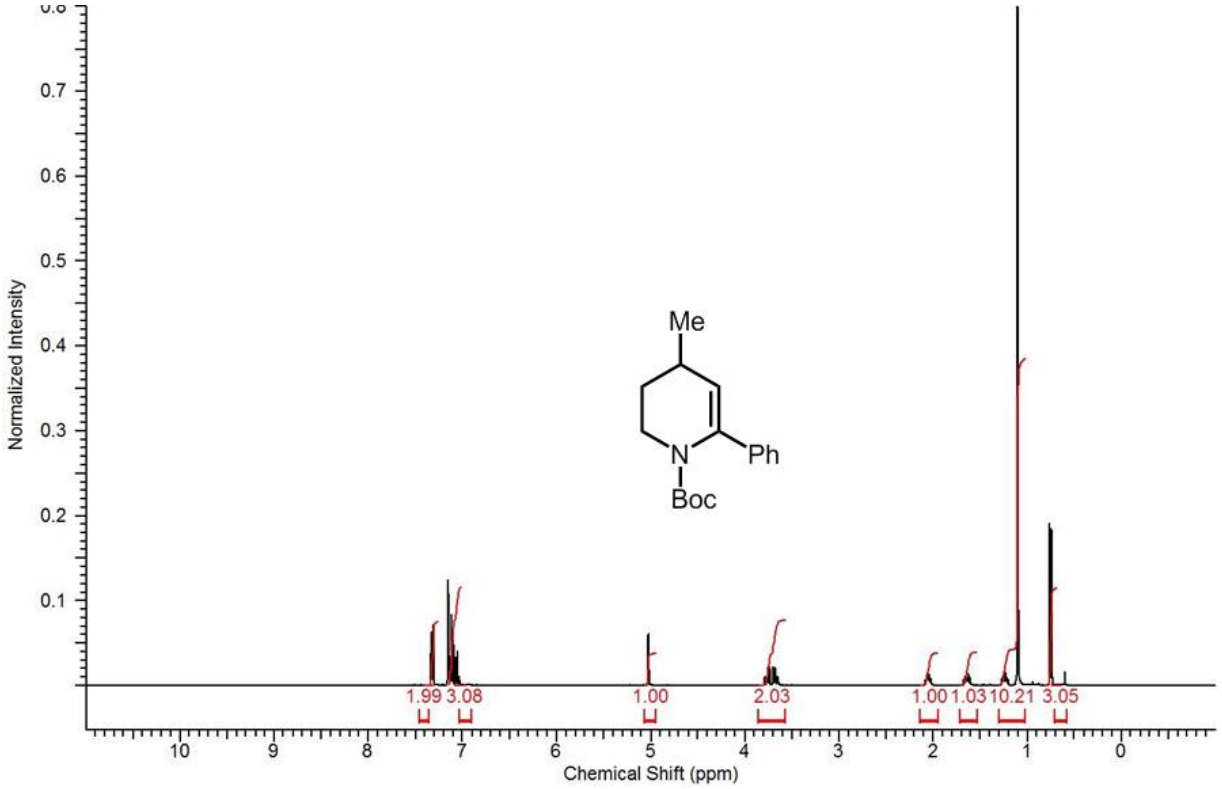

tkb-3-060C-f2.3.fid
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
C6D6
f1 (ppm)
N
Boc

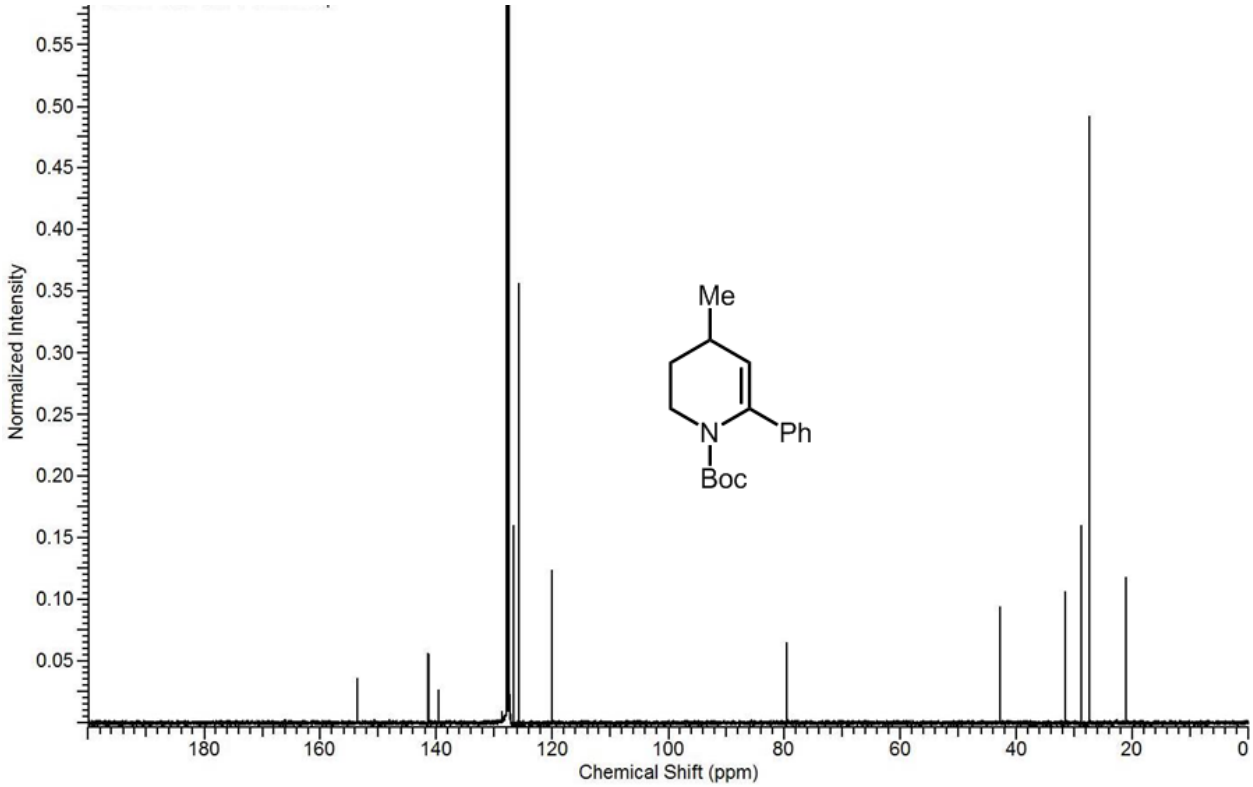


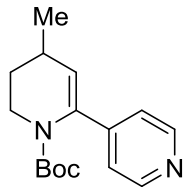


2u

Prepared from **1d** (197 mg, 1.0 mmol) and phenylboronic acid (1.5 equiv), using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N). PE/DCM (2:1). Yield = 53.2 mg; 78%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 7.45 to 6.99 (5H), 5.01 (1H), 3.91 to 3.55 (2H), 2.09 to 2.03 (1H), 1.68 to 1.50 (1H), 1.46 to 1.02 (11H), 0.86 to 0.60 (3H). ^{13}C NMR (101 MHz, C_6D_6, mixture of rotamers) δ 153.5, 141.3, 141.3, 139.5, 128.6, 127.0, 126.6, 125.6, 120.0, 79.5, 78.3, 42.7, 31.5, 28.8, 28.2, 27.9, 27.4, 21.5, 21.1. HRMS calc for $C_{17}H_{23}NO_2$ 273.1729, found 273.1734.

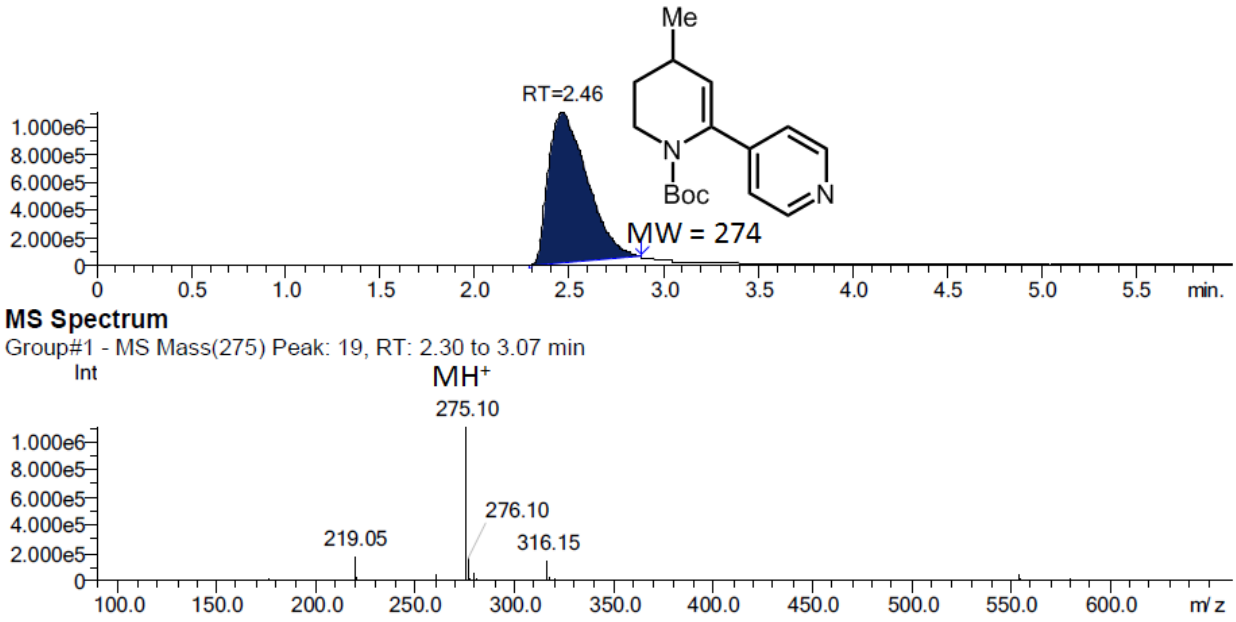

Normalized Intensity
Chemical Shift (ppm)
Me
N
Ph
Boc
1.99
3.08
1.00
2.03
1.00
1.03
10.21
3.05

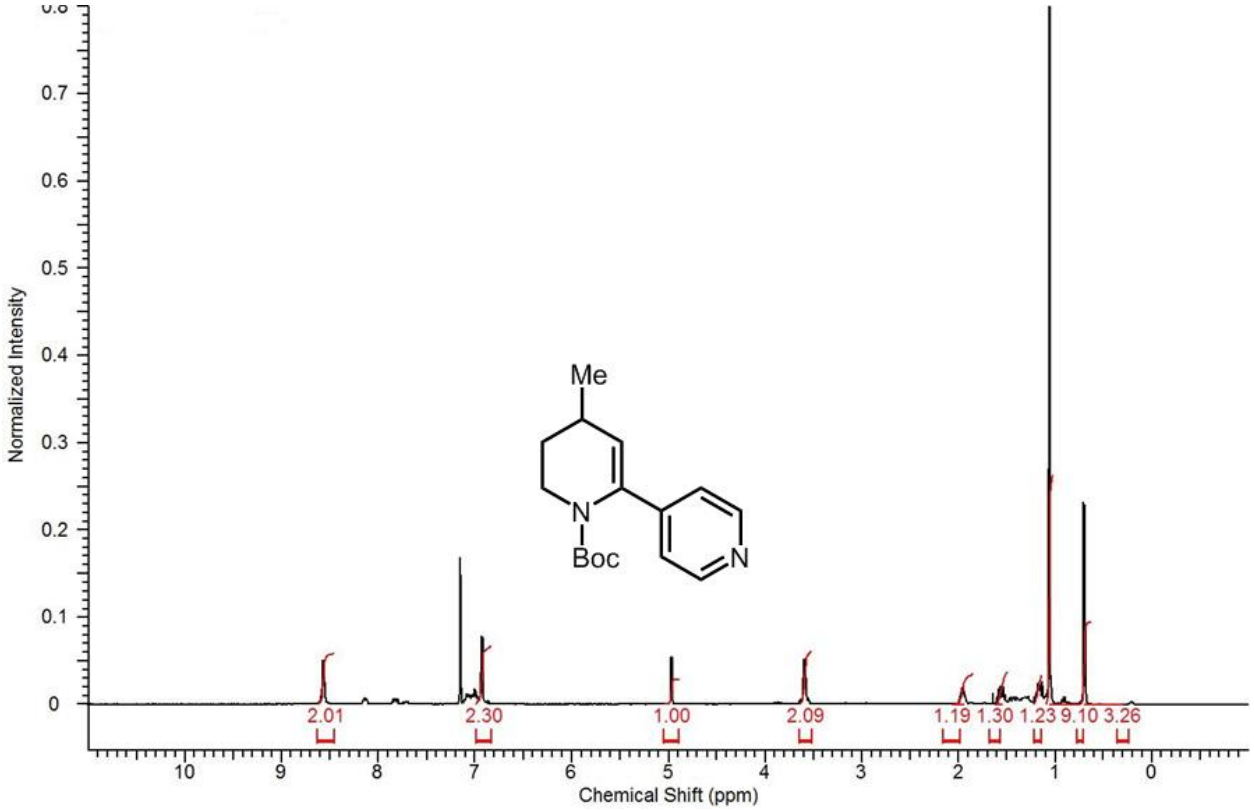

Normalized Intensity
Chemical Shift (ppm)
Me
N
Ph
Boc

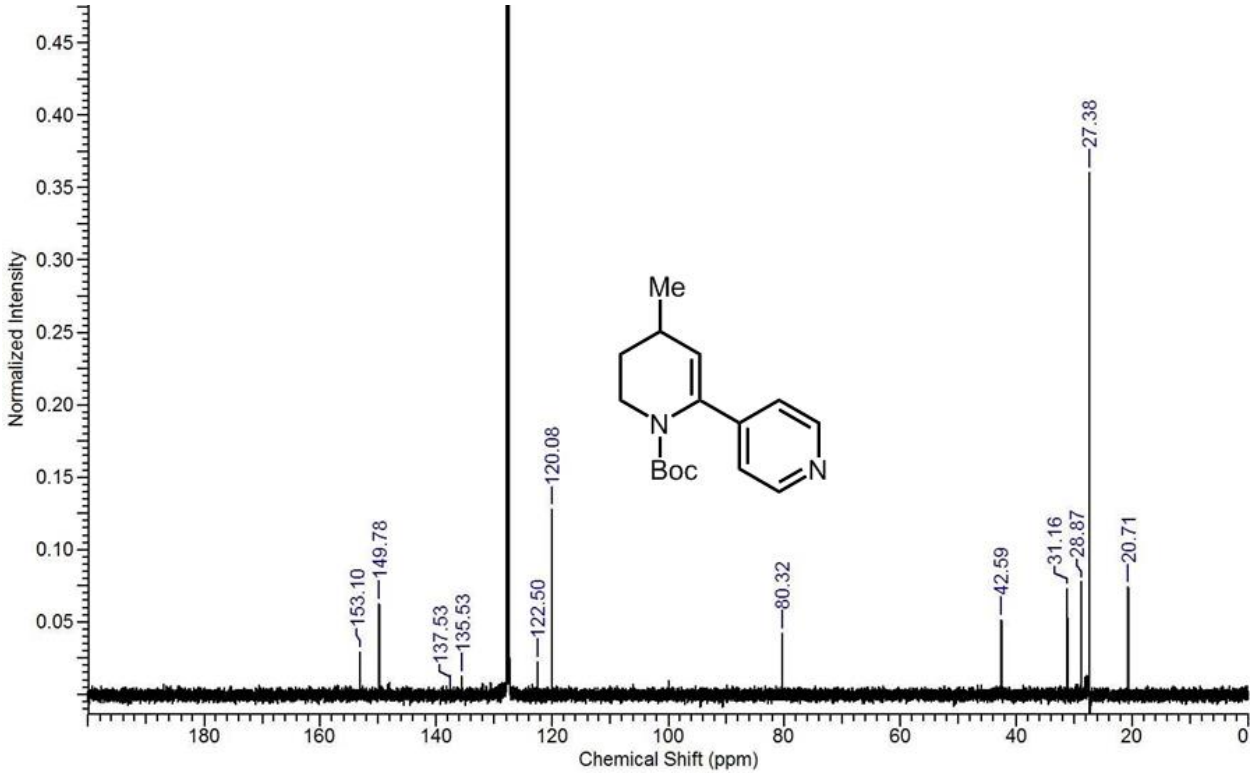


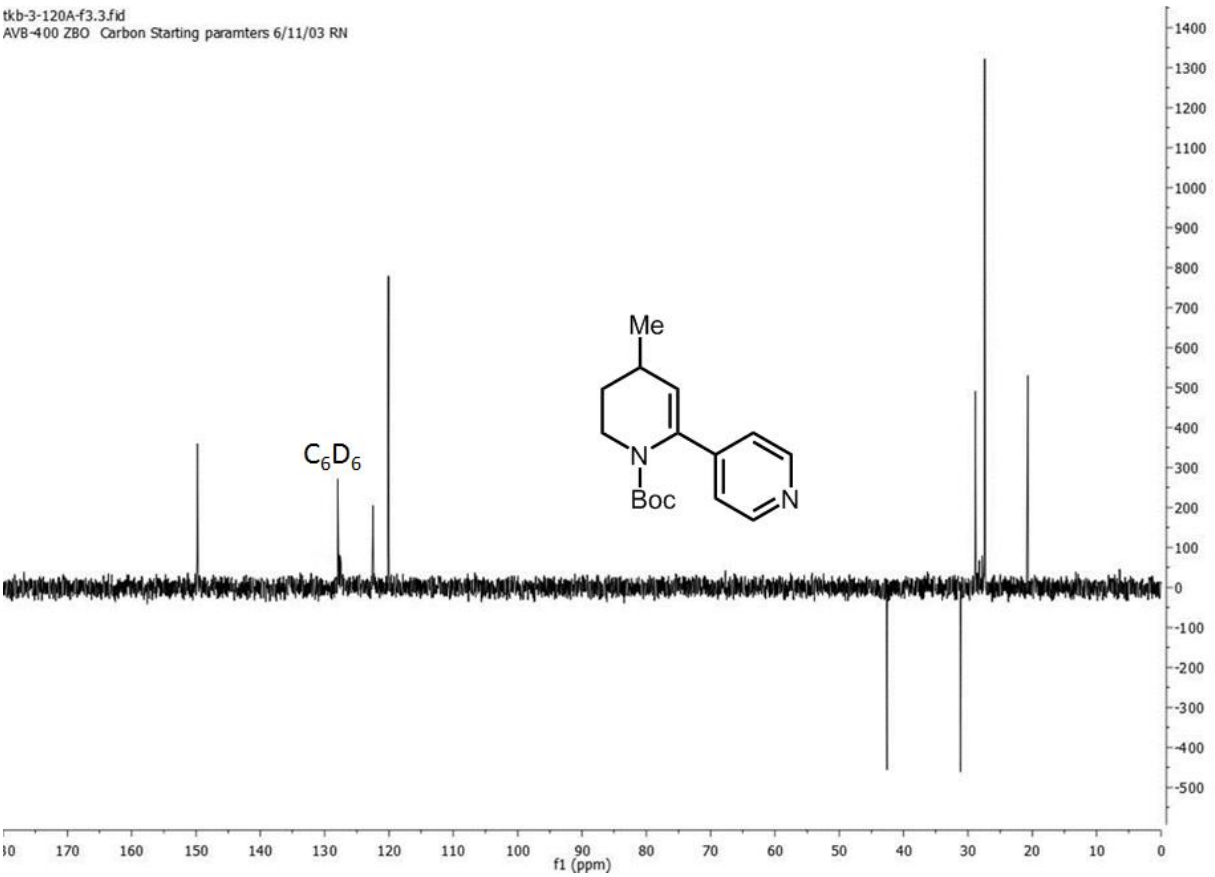
2v

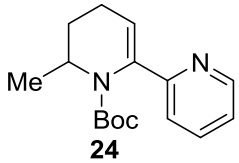
Prepared from **1d** (197 mg, 1.00 mmol) and 4-pyridylboronic acid (1.5 equiv), using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with DCM/MeOH (95:5). Yield = 16.4 mg; 60%. ^{1}H NMR (400 MHz, C_6D6) δ 8.56 & 8.55 (2H), 6.94 to 6.92 (2H), 4.97 & 4.96 (1H), 3.62 to 3.56 (2H), 1.98 to 1.92 (1H), 1.59 to 1.03 (11H), 0.72 to 0.69 (3H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.1, 149.7, 137.6, 135.5, 122.5, 120.0, 80.3, 42.5, 31.1, 28.8, 27.3, 20.7. HRMS calc for $C_{16}H_{22}N_2O_2$ 274.1681, found 274.1679.




Normalized Intensity
Chemical Shift (ppm)
Me
N
Boc
N
2.01
2.30
1.00
2.09
1.19
1.30
1.23
9.10
3.26

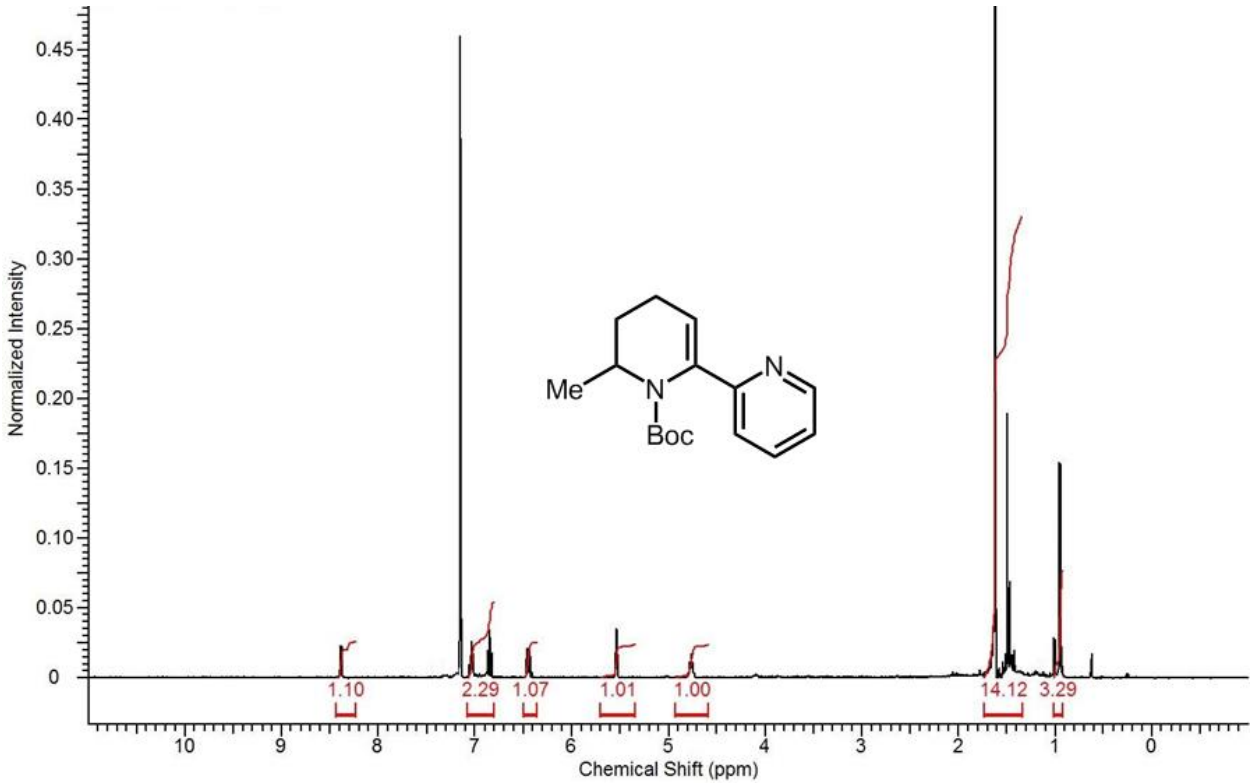

Normalized Intensity
Chemical Shift (ppm)
Me
N
Boc
N
153.10
149.78
137.53
135.53
122.50
120.08
80.32
42.59
31.16
28.87
27.38
20.71

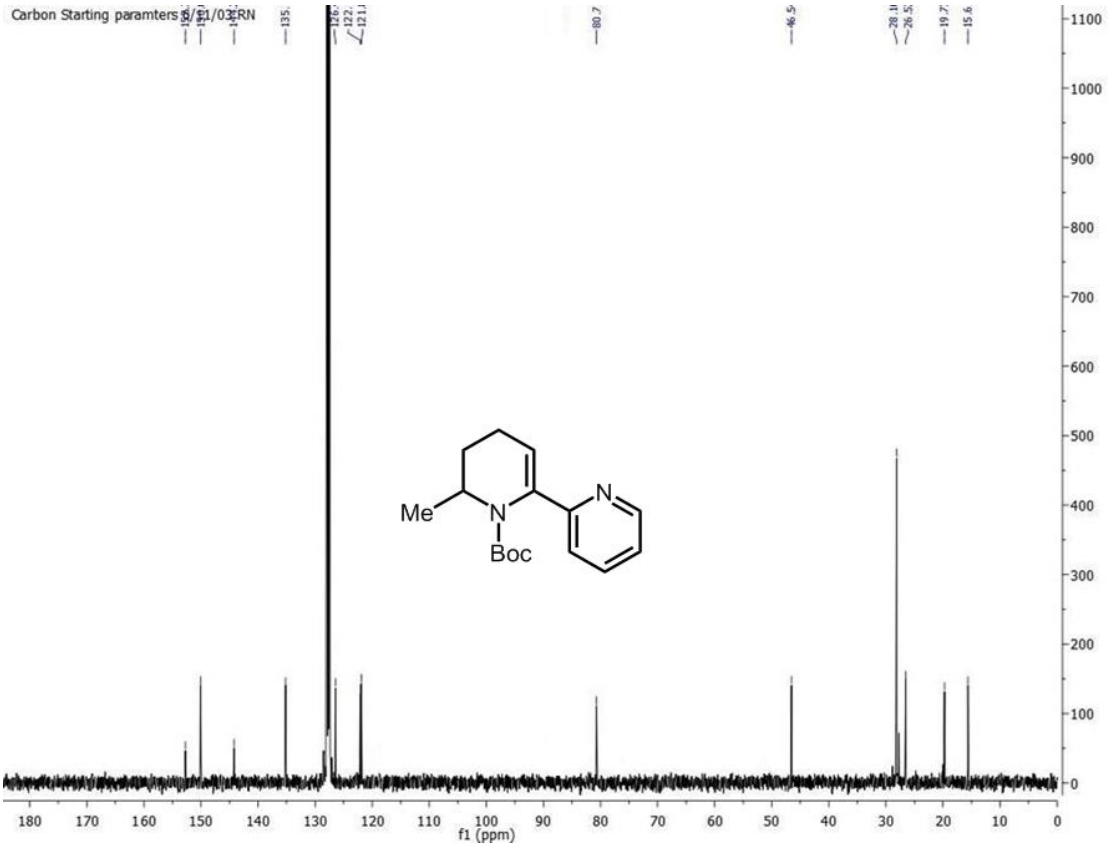


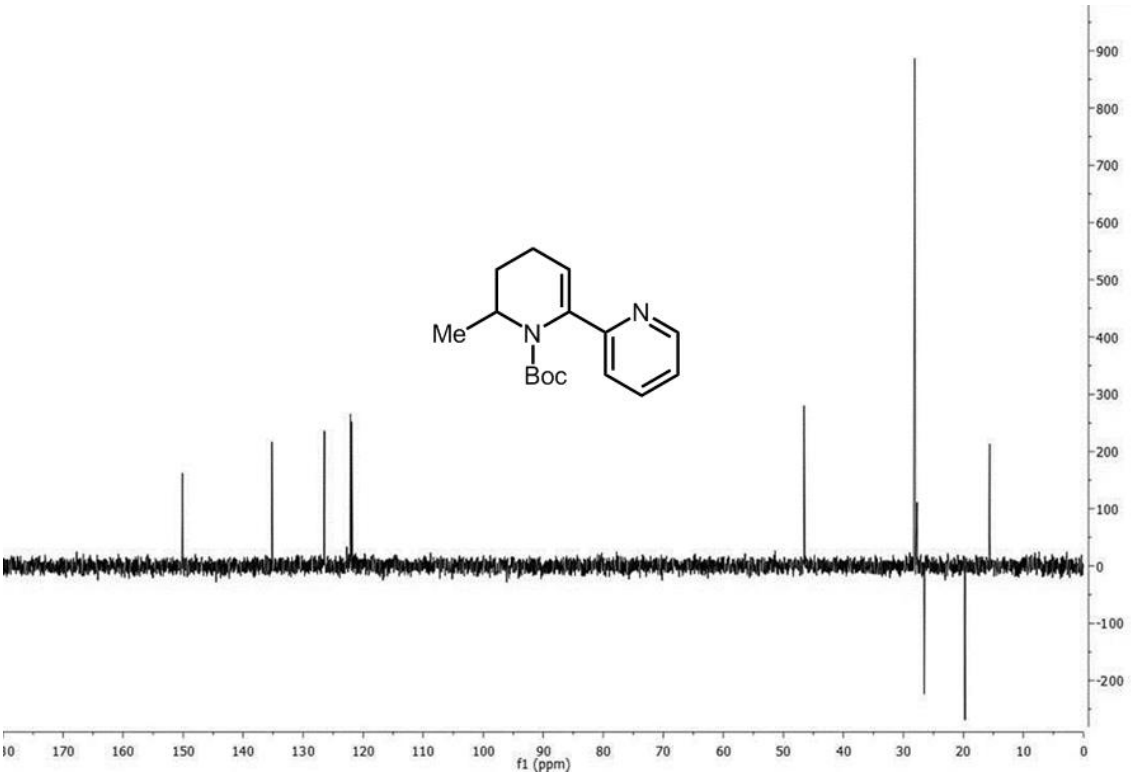


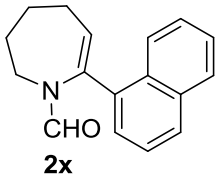
24

Prepared from enecarbamate **1e** (197 mg, 1.0 mmol) and 2-pyridylboronic acid (1.5 equiv), using **General Procedure A**. Yield = 186 mg, 68%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.39 (1H), 7.04 (1H), 6.90 to 6.73 (1H), 6.47 to 6.43 (1H), 5.55 to 5.52 (1H), 4.78 to 4.74 (1H), 1.68 to 0.92 (16H). ^{13}C NMR (101 MHz, C_6D_6) δ 152.7, 150.0, 144.2, 135.1, 126.4, 122.1, 121.8, 80.7, 46.5, 28.1, 26.5, 19.7, 15.6. **HRMS** calcd. for $C_{16}H_{22}N_2O_2$ 274.1681; found, 274.1685.


Normalized Intensity
Chemical Shift (ppm)
Me
N
Boc
N
1.10
2.29
1.07
1.01
1.00
14.12
3.29

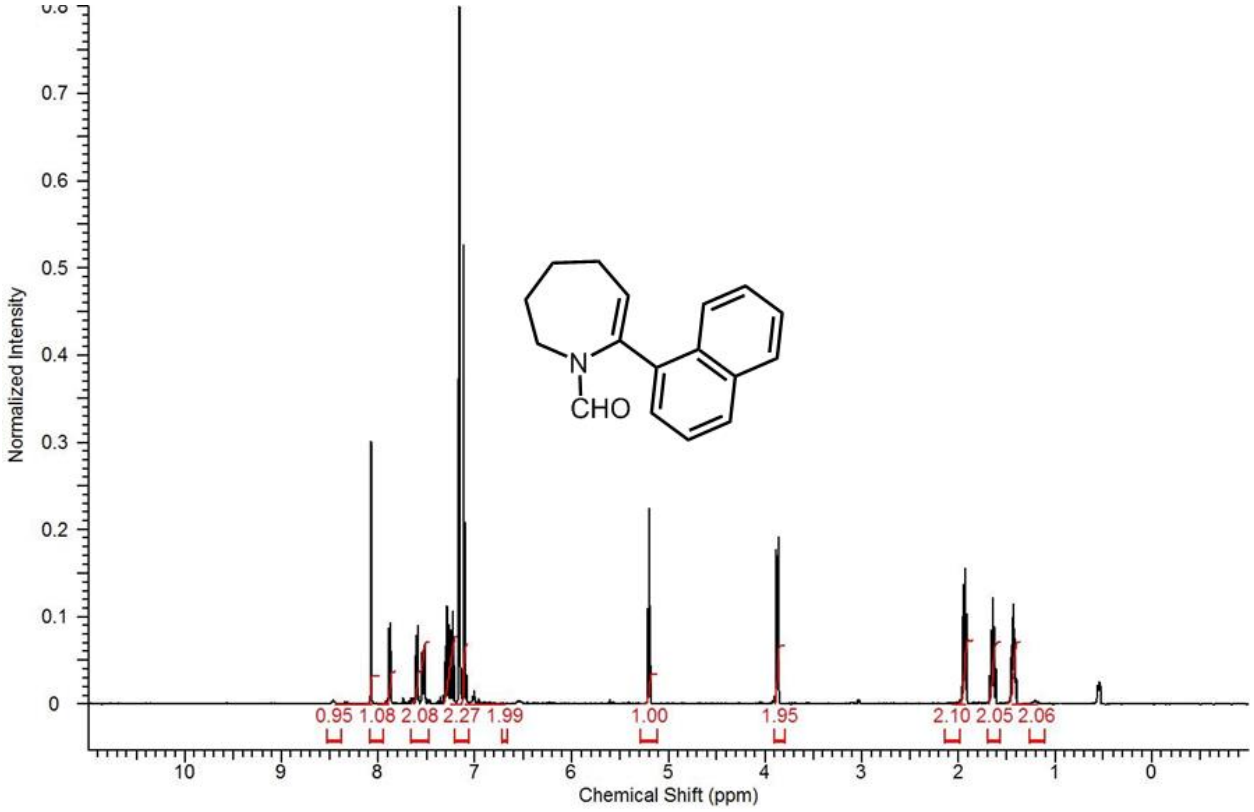

Carbon Starting paramters
f1 (ppm)
Me
N
Boc
N

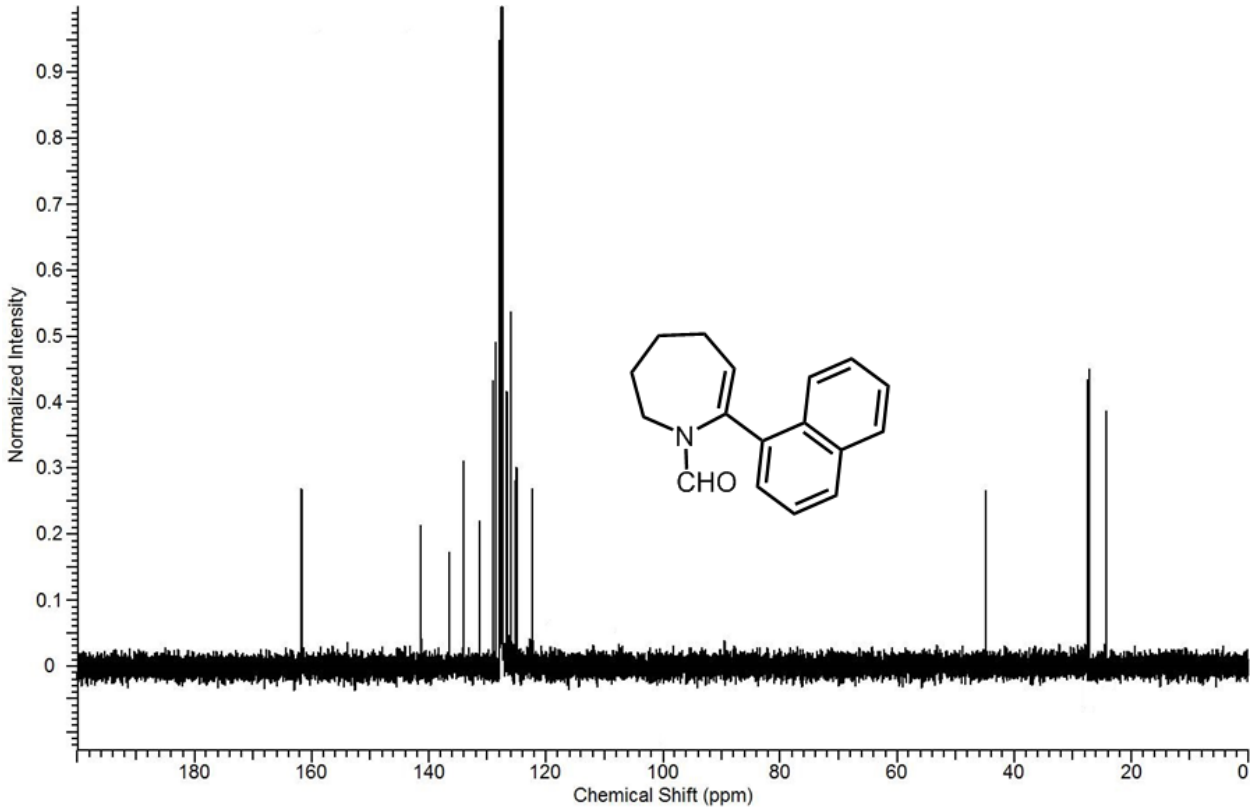


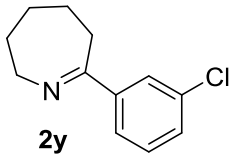


2x

Prepared from **1f** (125 mg, 1 mmol) and 1-naphthyl boronic acid (258 mg, 1.5 equiv), using **General Procedure A**. Time = 12 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 183 mg, 73%.[1]H NMR (400 MHz, C_6D_6) δ 8.07 (1H), 7.91 to 7.86 (1H), 7.61 to 7.51 (2H), 7.31 to 7.09 (4H), 5.21 to 5.19 (1H), 3.92 to 3.86 (2H), 1.97 to 1.91 (2H), 1.67 to 1.61 (2H), 1.46 to 1.40 (2H).[13]C NMR (101 MHz, C_6D_6) δ 161.6, 141.3, 136.5, 134.0, 131.2, 129.0, 128.6, 126.6, 125.9, 125.1, 124.9, 122.2, 119.1, 44.8, 27.4, 27.1, 24.2. HRMS calc for $C_{17}H_{17}NO$ 251.1310, found 251.1315. Data as previously reported.[4]


Normalized Intensity
0.95 1.08 2.08 2.27 1.99
1.00
1.95
2.10 2.05 2.06
N
CHO
Chemical Shift (ppm)

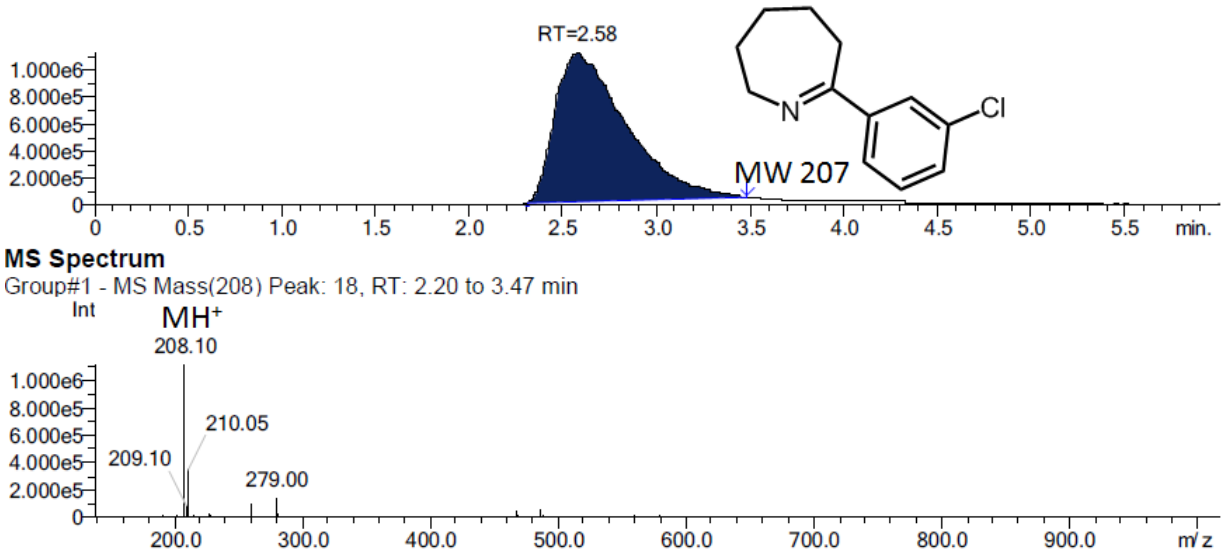

Normalized Intensity
N
CHO
Chemical Shift (ppm)

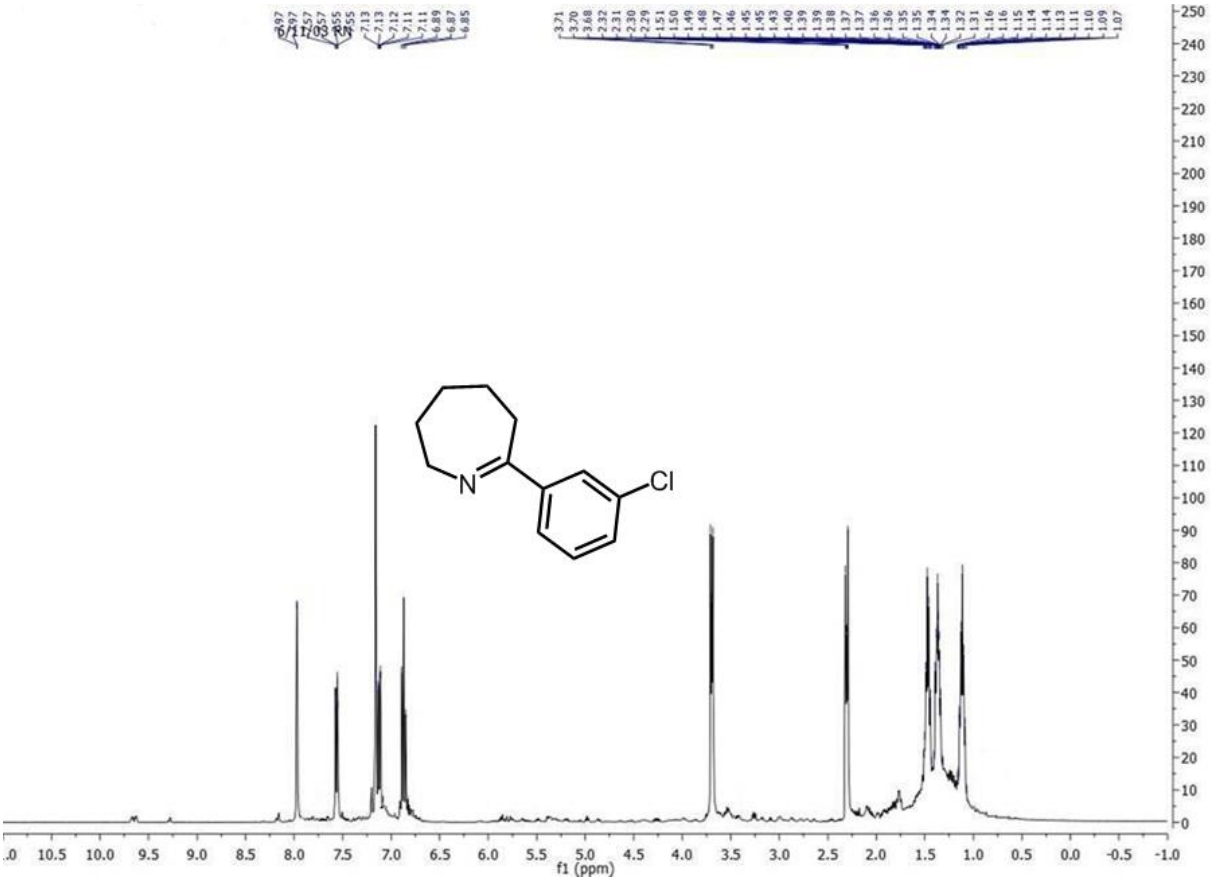


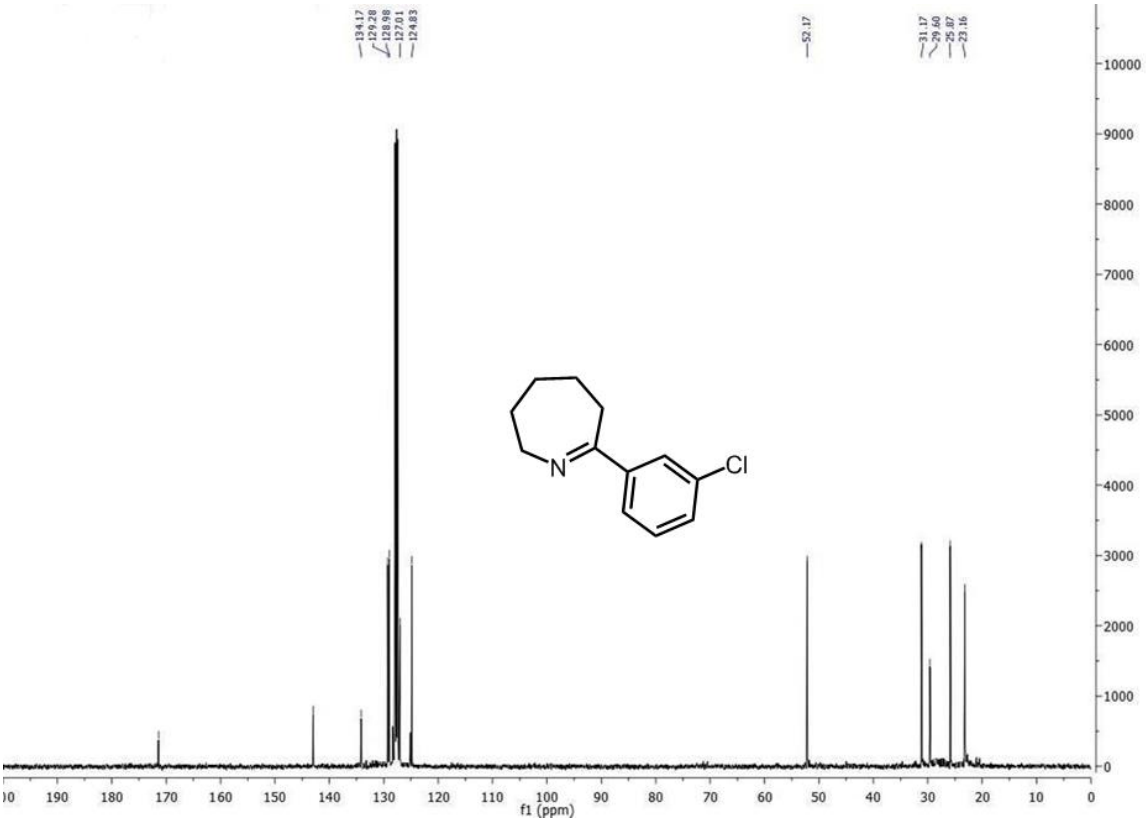
2y

Prepared from **1f** (125 mg, 1 mmol) and 3-chlorophenylboronic acid (188 mg, 1.2 equiv), using **General Procedure A**. Time = 12 h. The crude product was deformylated as follows:

To the crude eneformamide dissolved in freshly distilled THF (5 mL) was added *n*-BuLi (0.6 mL, 1.2 mmol, 2.0 M in hexanes, 1.2 equiv) at –78 °C. After complete deprotection of the eneformamide (~30 min, as indicated by TLC and LCMS-monitoring), the mixture was quenched with H_2O and diluted with EtOAc. It was washed with *sat*. $NaHCO_3$ and with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil. Yield = 162 mg, 78%. ^{13}C NMR (101 MHz, C_6D_6) δ 171.4, 142.9, 134.1, 129.2, 128.9, 127.0, 124.8, 52.1, 31.1, 29.6, 25.8, 23.1. HRMS calc for $C_{12}H_{14}ClN$ 207.0815, found 207.0811.




N
Cl
f1 (ppm)


134.17
129.28
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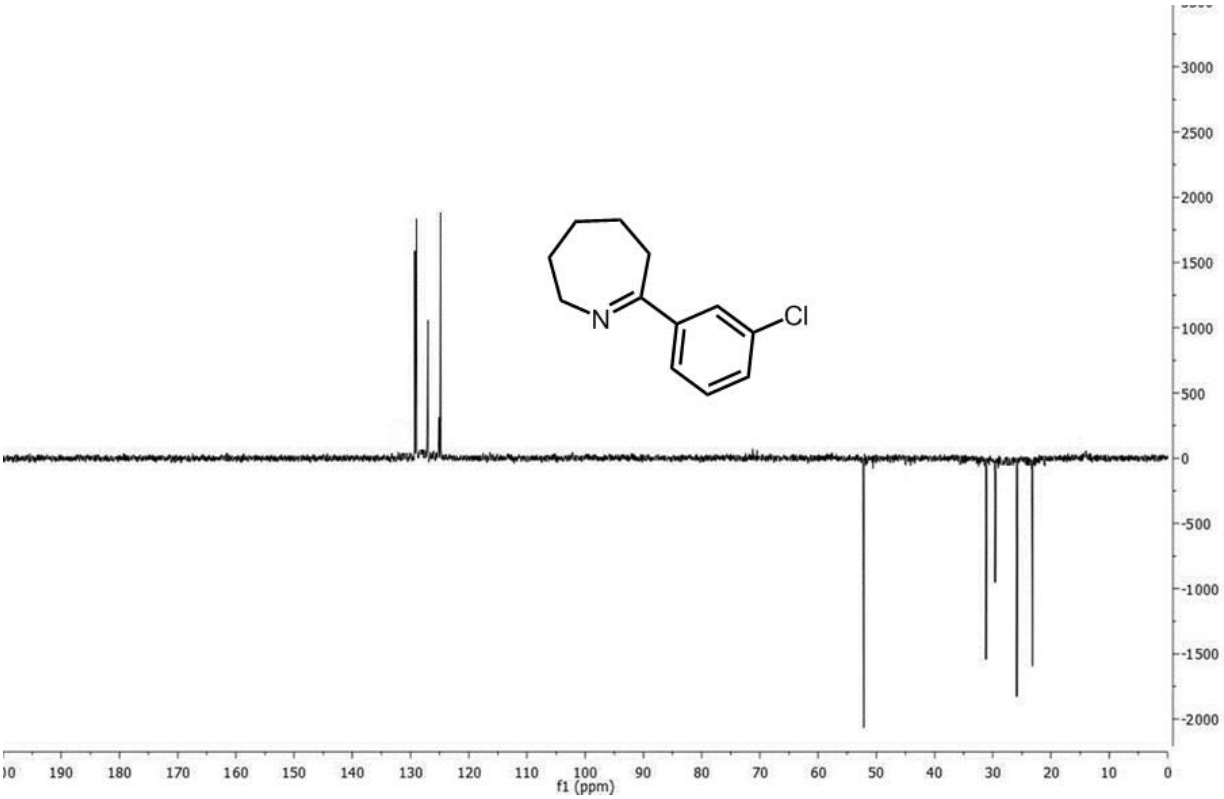
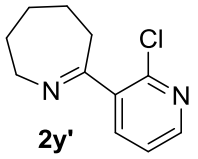
127.01
124.83
52.17
31.17
29.60
25.87
23.16
N
Cl
f1 (ppm)

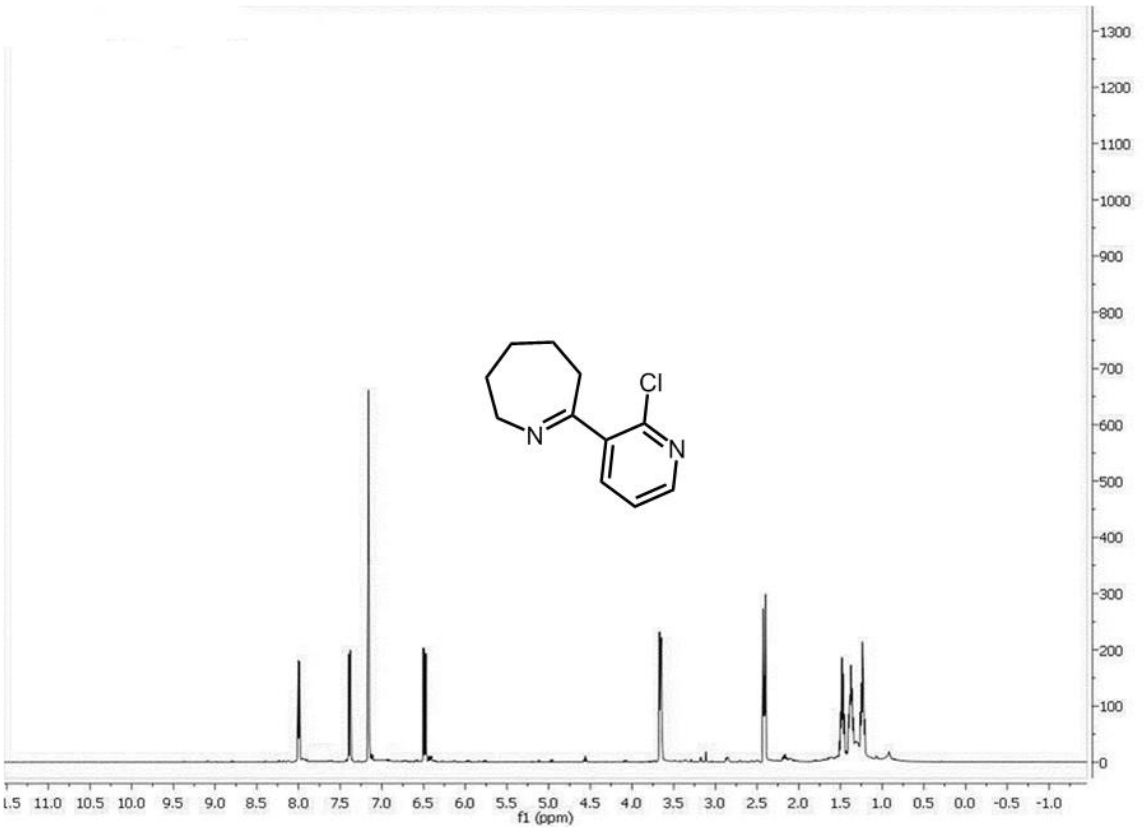


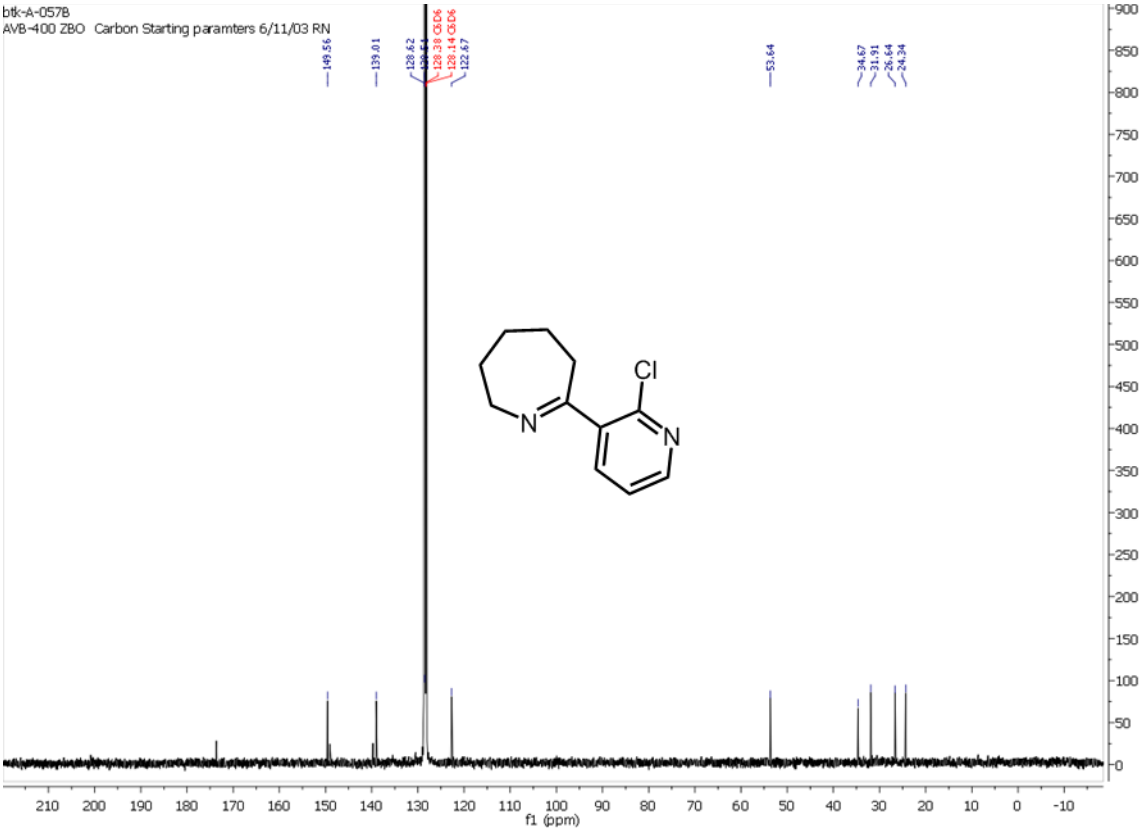


2y'

Prepared from **1f** (125 mg, 1.0 mmol), 2-chloro-3-pyridylboronic acid (236 mg, 1.5 mmol, 1 equiv), Temp = 90 ^{o}C, time = 36 h. The crude product was deformylated as follows:

To the crude eneformamide dissolved in freshly distilled THF (5 mL) was added *n*-BuLi (0.60 mL, 1.2 mmol, 2.0 M in hexanes, 1.2 equiv) at –78 °C. After complete deprotection of the eneformamide (~30 min, as indicated by TLC and LCMS-monitoring), the mixture was quenched with H_2O and diluted with EtOAc. It was washed with *sat*. $NaHCO_3$ and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the product as an oil. Yield = 127 mg, 61%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.01 (1H, d), 7.39 (1H, d), 6.51 to 6.46 (1H, dd), 3.67 to 3.65 (2H, dd), 2.43 to 2.39 (2H, dd), 1.53 to 1.18 (6H, m). ^{13}C NMR (101 MHz, C_6D_6) δ 149.5, 139.0, 128.6, 128.5, 128.3, 128.1, 122.6, 53.6, 34.6, 31.9, 26.6, 24.3. . HRMS calc for $C_{11}H_{13}ClN_2$ 208.0767, found 208.0770.


Cl
N
N
f1 (ppm)


btk-A-057B
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
149.56
139.01
128.62
128.38 CDCl3
128.14 CDCl3
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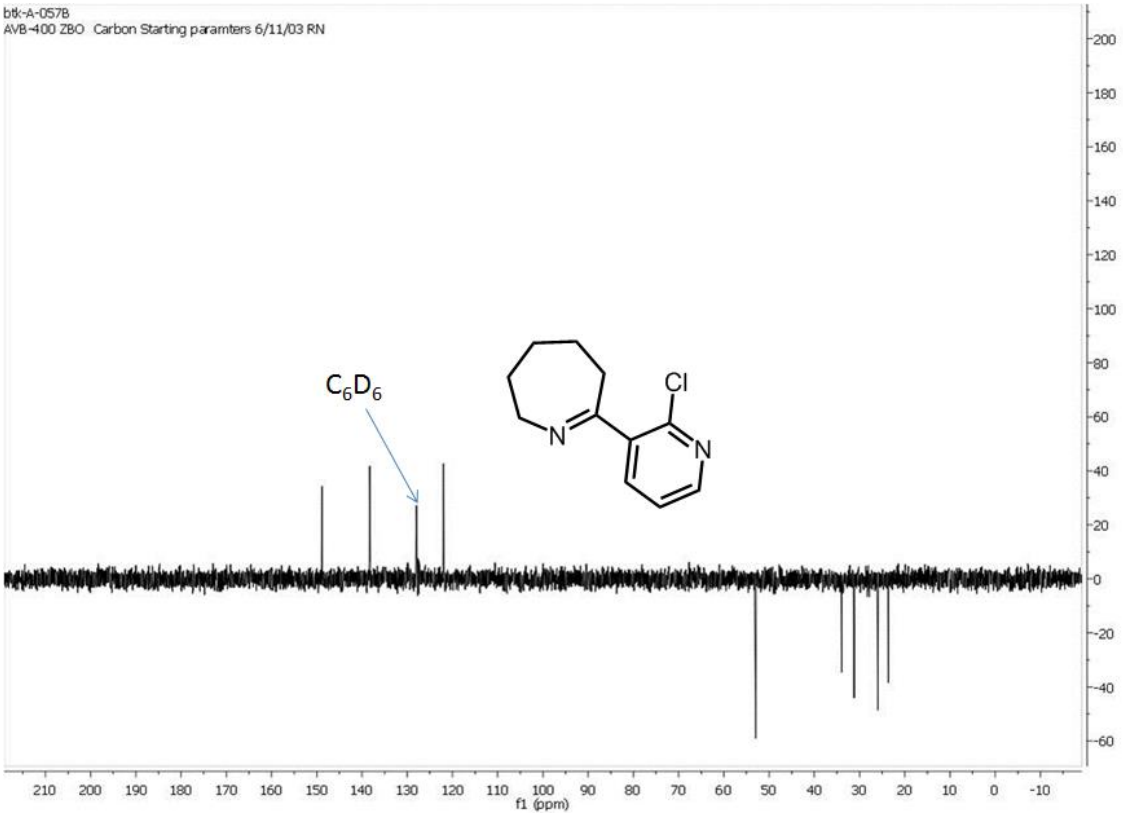
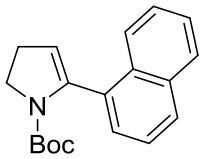
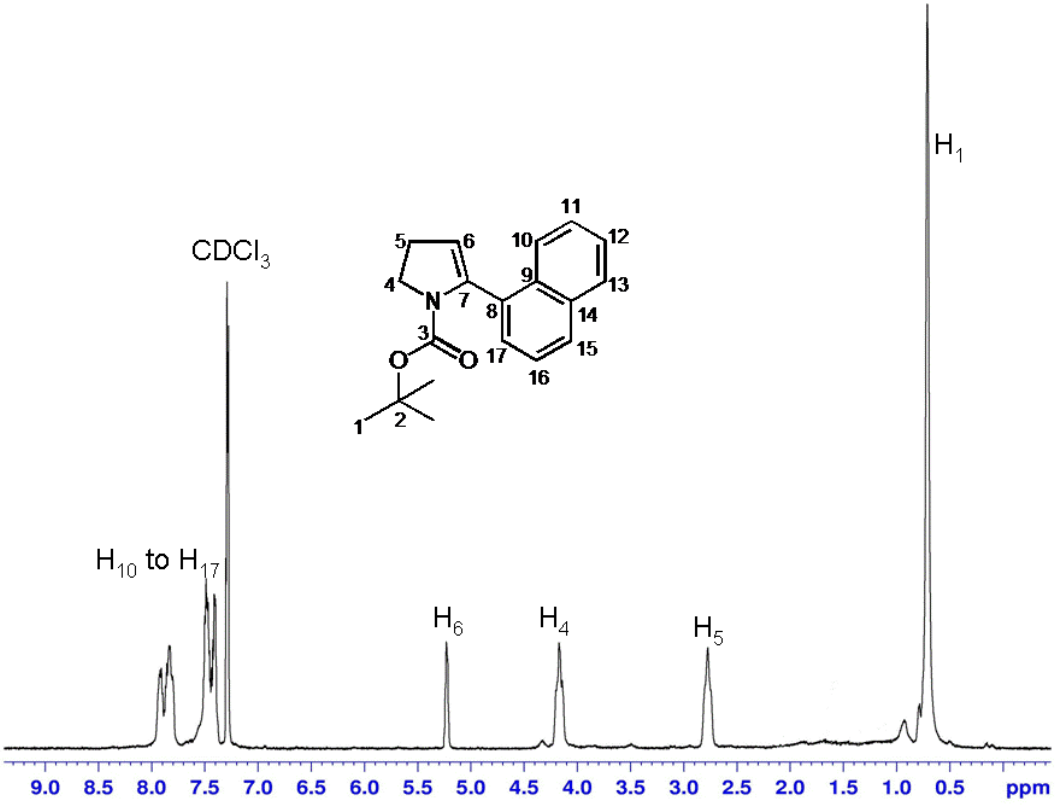
26.64
24.34
Cl
N
N
f1 (ppm)

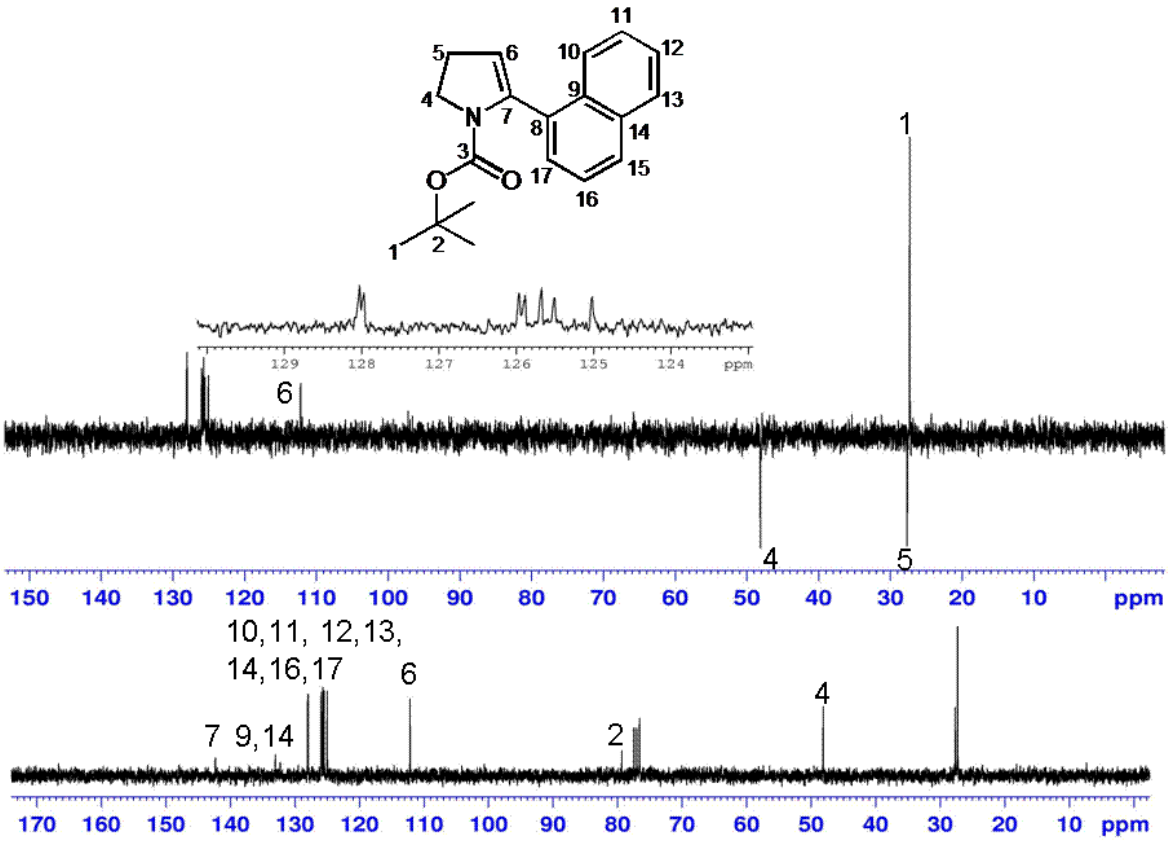

btk-A-057B
AVB-400 ZBO Carbon Starting paramters 6/11/03 RN
C_6D_6
Cl
N
N
f1 (ppm)



2z

Prepared from **1g** (169 mg, 1.0 mmol) and 1-naphthyl boronic acid (258 mg, 1.5 equiv), using **General Procedure A.** Time = 12 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:1). Yield = 79%. ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers)) δ 8.23–7.37 (7H), 5.23 (1H), 4.26 (2H), 2.81 (2H), 1.01 – 0.61 (9H) ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 155.4, 142.1, 141.8, 134.0, 131.5, 128.9, 127.3, 125.8, 125.4, 124.9, 123.5, 123.2, 112.2, 79.8, 48.2, 28.8, 28.3. HRMS calc for $C_{19}H_{21}NO_2$ 295.1572, found 295.1569.




11
5
6
10
12
4
9
13
N
7
8
14
3
17
15
O
O
16
1
2
1
129
128
127
126
125
124
ppm
6
4
5
150
140
130
120
110
100
90
80
70
60
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30
20
10
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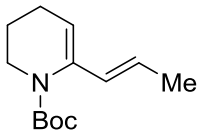
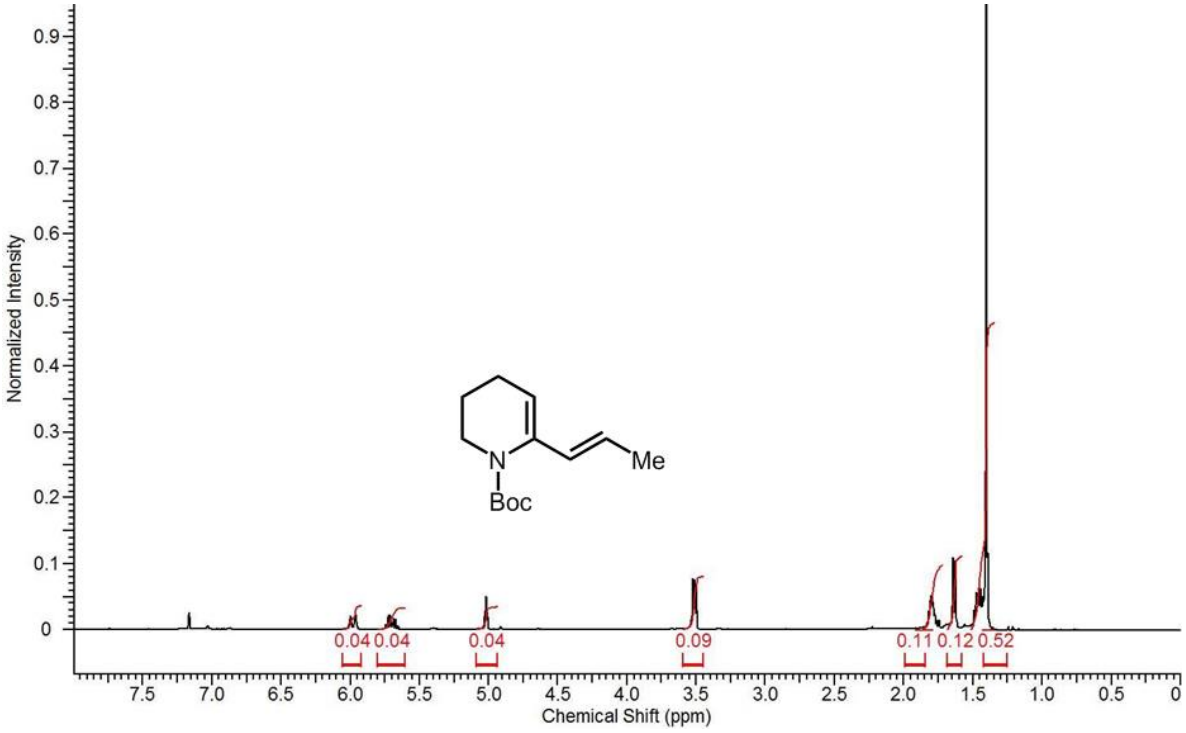
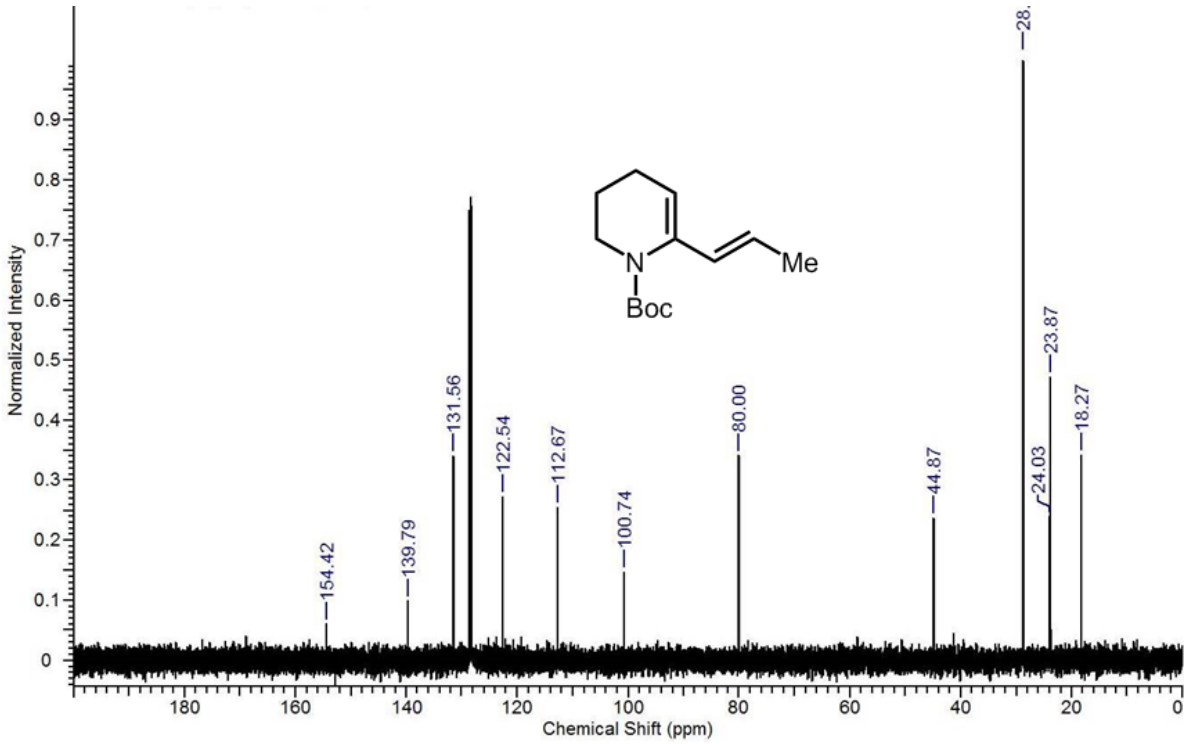
14,16,17
6
4
7 9,14
2
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

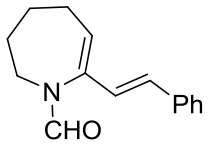


3a

Prepared from **1c** (183 mg, 1.0 mmol) and 1-propenylboronic acid (2 equiv), using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Yield = 154 mg; 69%. Data as previously reported by us.[1]

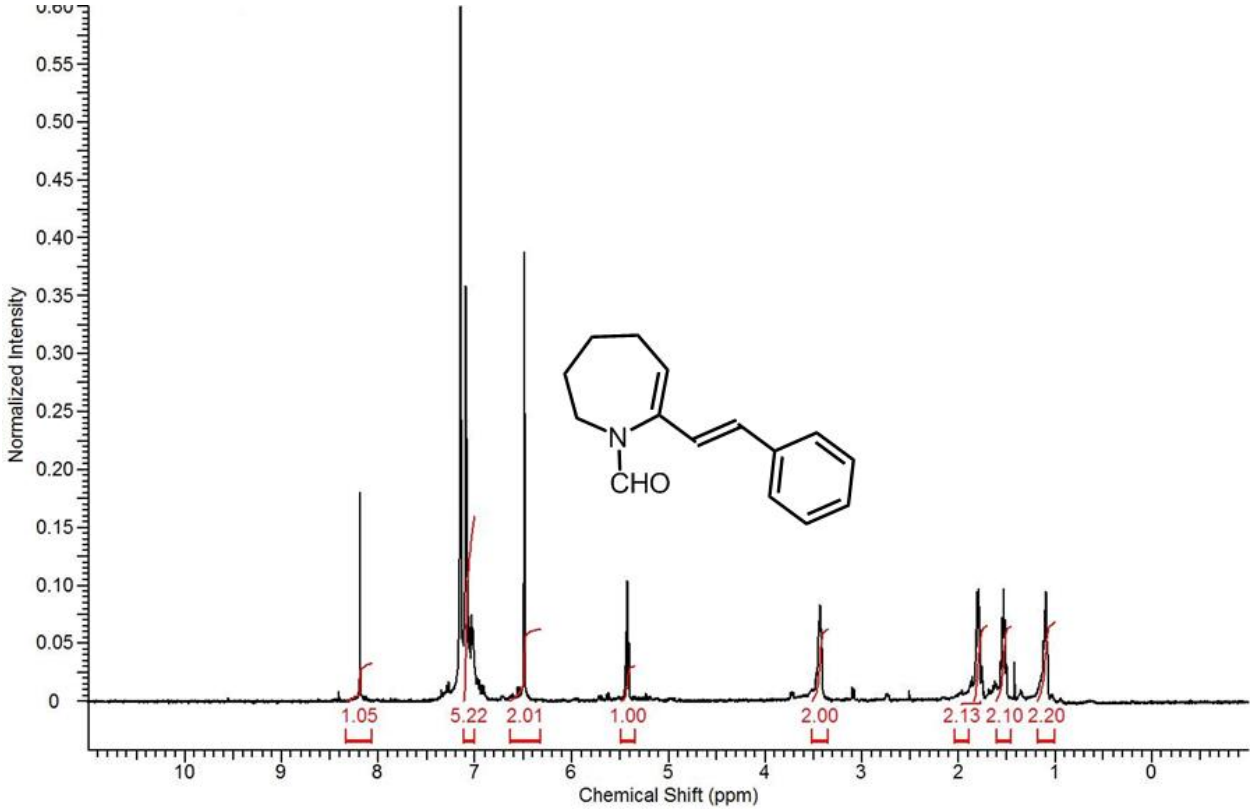






3b

Prepared from **1f** (125 mg, 1 mmol) and β-styrenylboronic acid (2 equiv) using **Procedure A**. Time = 32 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 136 mg, 60%. Data as previously reported by us.[4]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1.00
2.00
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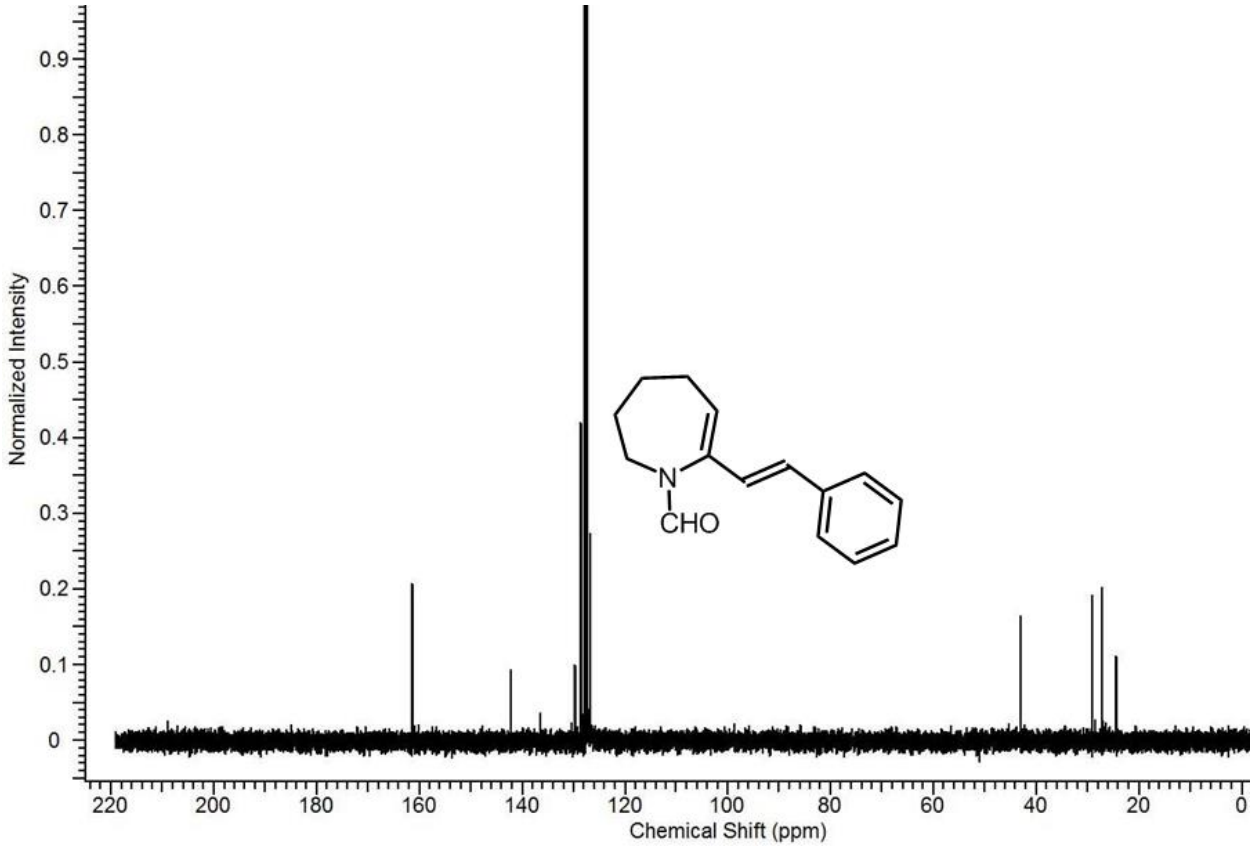
2.10
2.20
N
CHO


Normalized Intensity
Chemical Shift (ppm)
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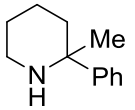


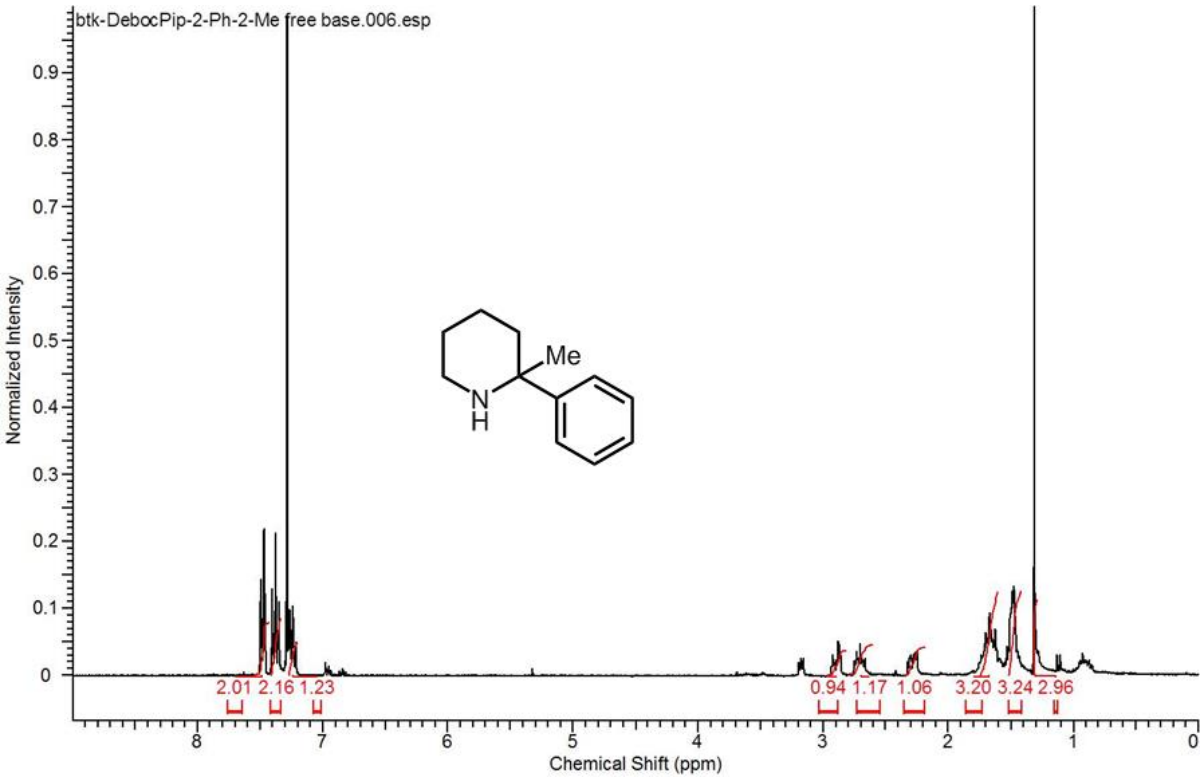
4

Imine formation

To eneformamide **2a** (47 mg, 0.25 mmol, 1.0 equiv) dissolved in freshly distilled THF (5 mL) was added *n*-BuLi (0.15 mL, 0.30 mmol, 2.0 M in hexanes, 1.2 equiv) at –78 °C. After complete deprotection of the eneformamide (~30 min, as indicated by TLC and LCMS-monitoring), the mixture was quenched with H_2O and diluted with EtOAc. It was washed with *sat*. $NaHCO_3$ and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as an oil.

Grignard addition

To the crude imine dissolved in freshly distilled THF (2 mL), was slowly added methyl magnesium bromide (0.1 mL, 3.0 M solution in Et_2O, 1.2 equiv) under nitrogen at 0 °C. The mixture was stirred for 10 min at 0 °C, then warmed slowly to room temperature. After complete consumption of the imine (as indicated by TLC and LC-MS, ~12 h), the mixture was cooled to 0 °C, diluted with Et_2O. Water was then added slowly and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2). Yield = 39 mg; 88%. Data as reported.[5]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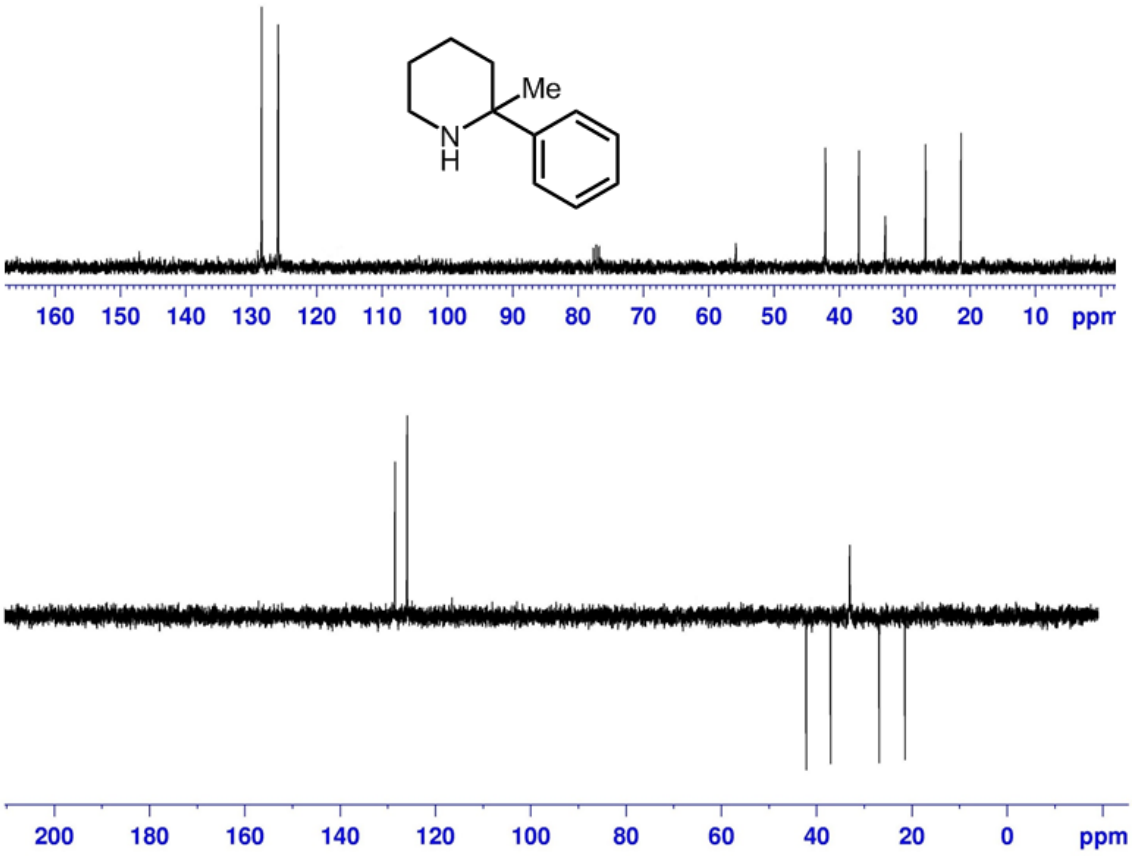
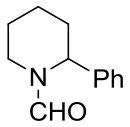
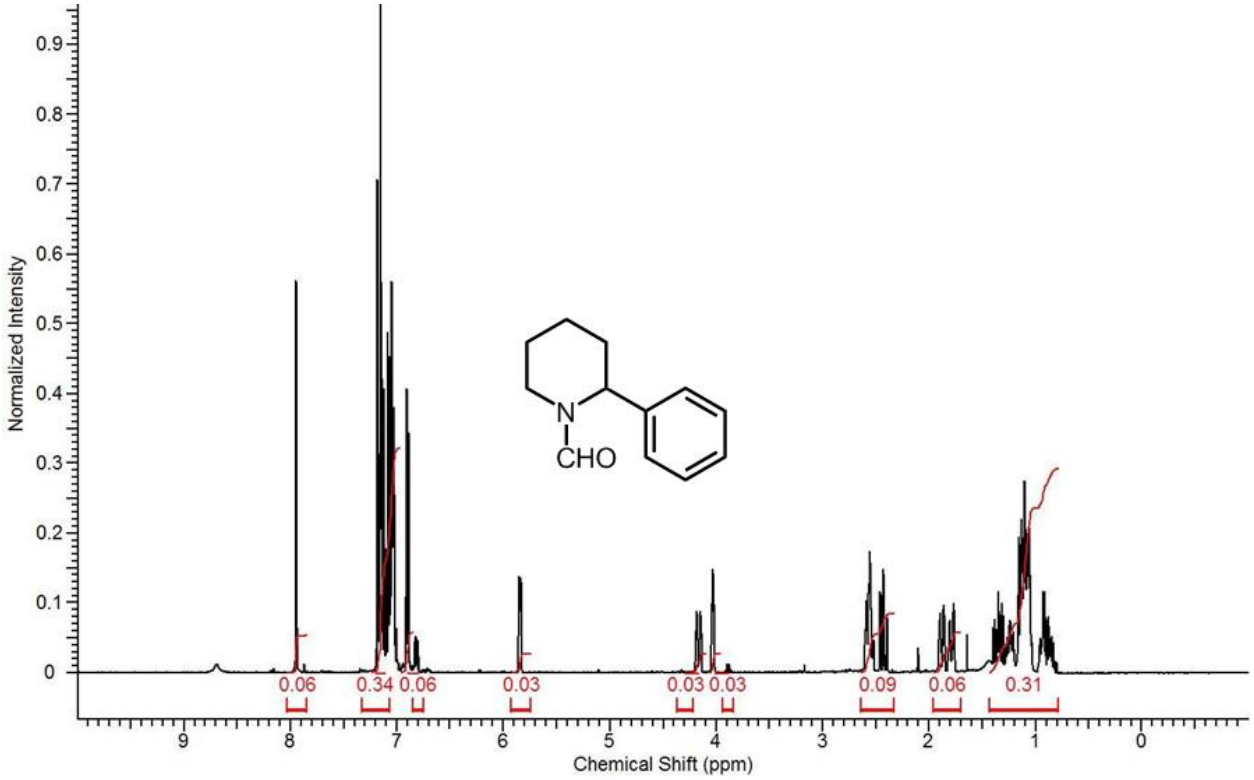
0.6
0.7
0.8
0.9
Me
N
H
2.01 2.16 1.23
0.94 1.17 1.06 3.20 3.24 2.96
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)





5

Prepared from **2a** (47 mg, 0.25 mmol), 10% Pd/C (100 mg) and EtOAc (5 mL), using **General Procedure B**. Time = 18 h. Yield = 46 mg, 99%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 7.96 (1H, s) 7.19 to 6.90 (5H), 5.80 (0.5H, dd), 4.20 to 4.15 (0.5H, dd), 4.04 (0.5 H, dd), 2.60 to 2.40 (1.5, m), 1.91 to 1.78 (1H, m) 1.39 to 0.89 (5H, m). ^{13}C NMR (101 MHz, C_6D6) δ 161.4, 161.1, 129.4, 128.6, 128.5, 127.9, 127.6, 127.4, 126.8, 126.7, 126.4, 115.7, 56.0, 49.1, 42.0, 37.0, 28.9, 26.6, 26.2, 24.8, 20.3, 19.8. HRMS calc for $C_{12}H_{15}NO$ 189.1154, found 189.1157.


Normalized Intensity
Chemical Shift (ppm)
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0.09
0.06
0.31
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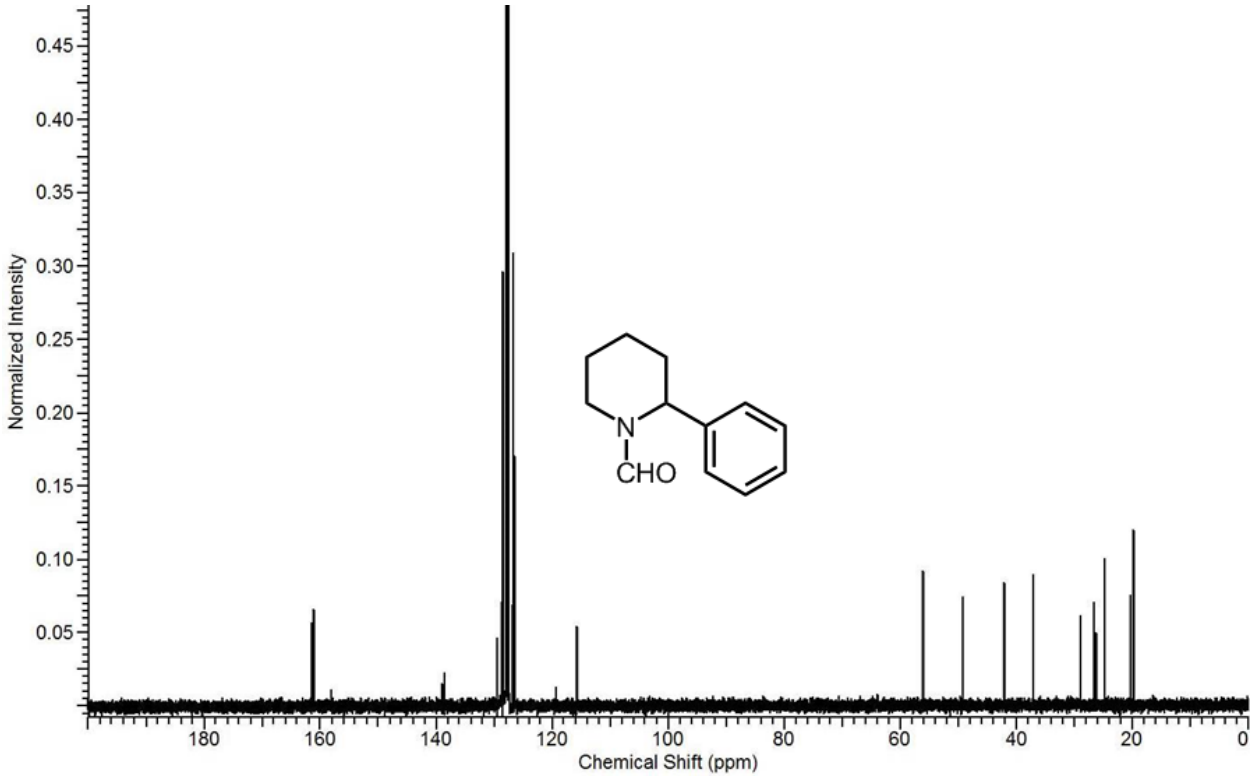
Normalized Intensity
Chemical Shift (ppm)
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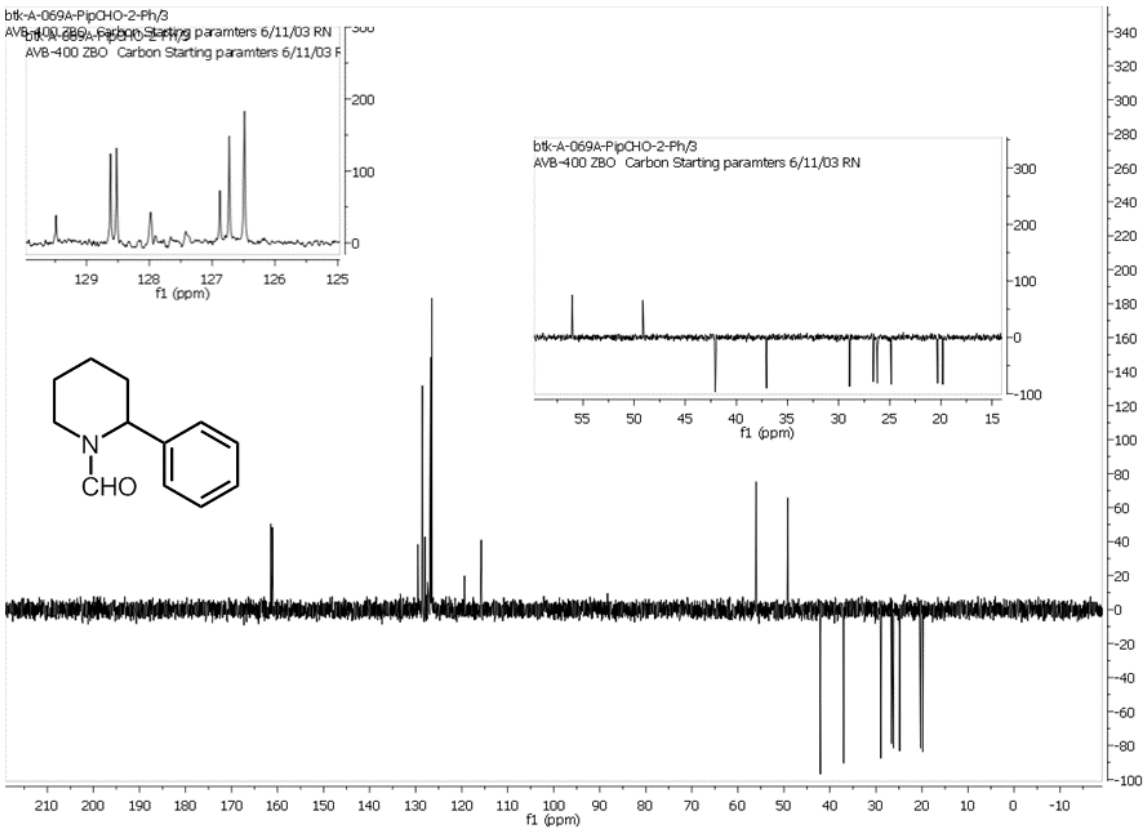
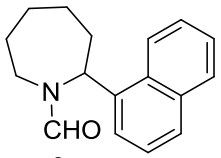
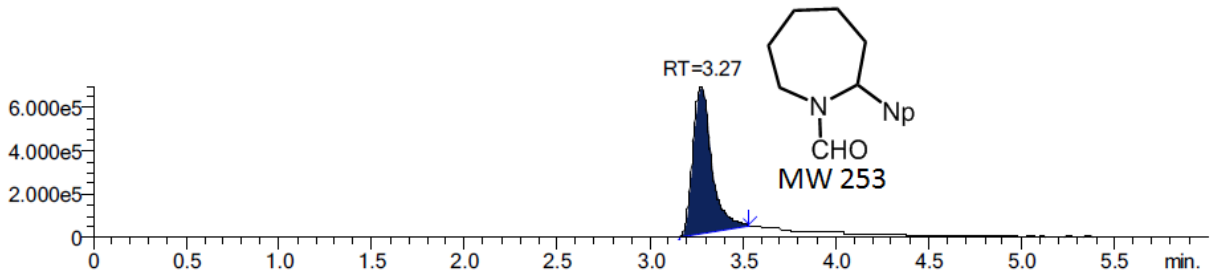
CHO





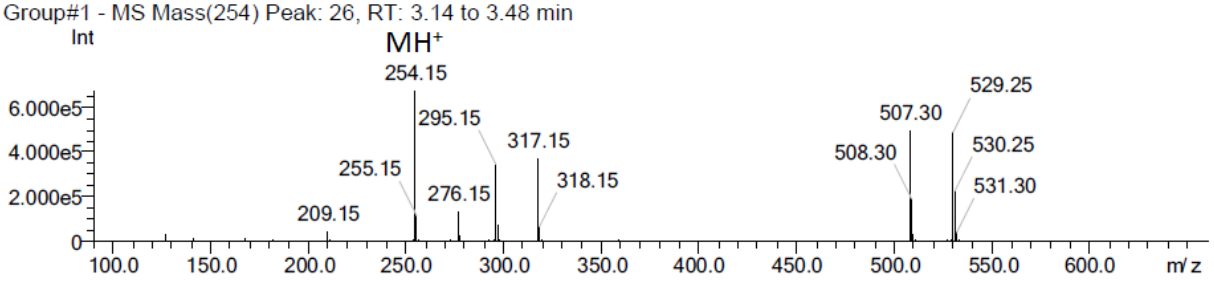
6

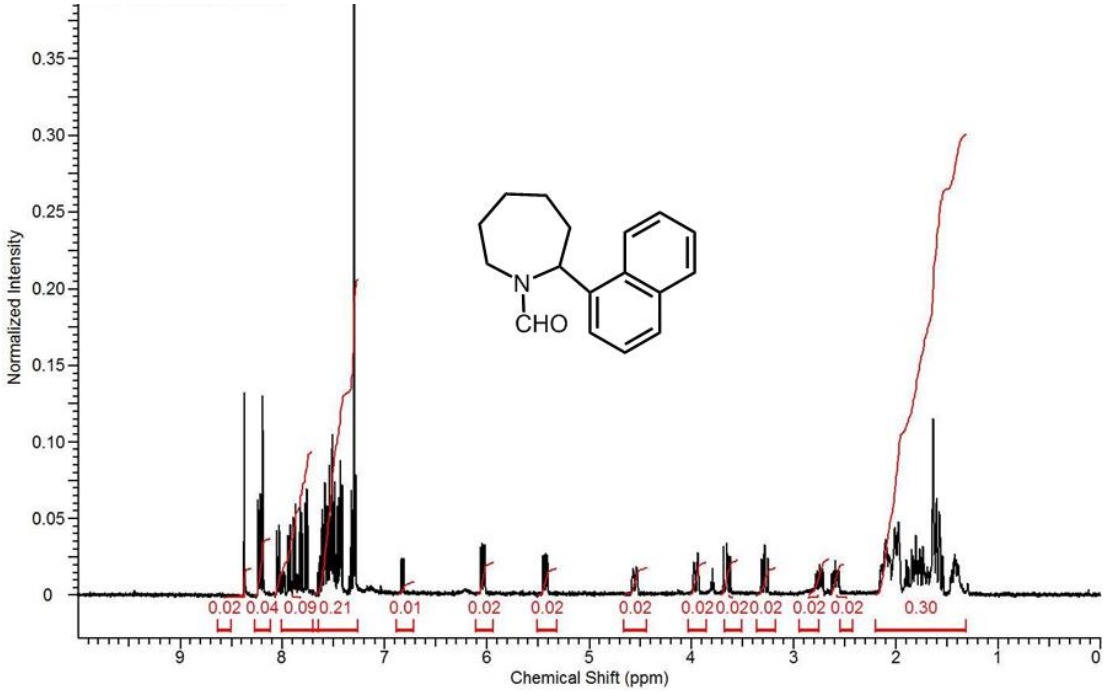
Prepared from **2x** (63 mg, 0.25 mmol), 10% Pd/C (100 mg) and EtOAc (5 mL), using **General Procedure B**. Time = 18 h. Yield = 60 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.37 to 7.28 (16H), 6.06 to 6.02 (1H), 5.45 to 5.41 (1H), 4.58 to 4.53 (1H), 3.98 to 3.93 (1H), 3.69 to 3.62 (1H), 3.32 to 3.25 (1H), 2.78 to 2.67 (1H), 2.63 to 2.56 (1H), 2.16 to 1.30 (14H). ^{13}C NMR (101 MHz, C_6D6) δ 163.8, 163.0, 154.0, 139.7, 139.7, 134.1, 134.0, 131.0, 130.0, 129.0, 128.7, 126.0, 126.0, 125.5, 125.5, 125.5, 125.1, 123.4, 122.7, 122.2, 121.2, 108.4, 58.6, 53.8, 45.1, 41.1, 34.9, 34.3, 32.4, 29.4, 29.1, 28.7, 26.2, 26.1. HRMS calc for $C_{17}H_{19}NO$ 253.1467, found 253.1470.

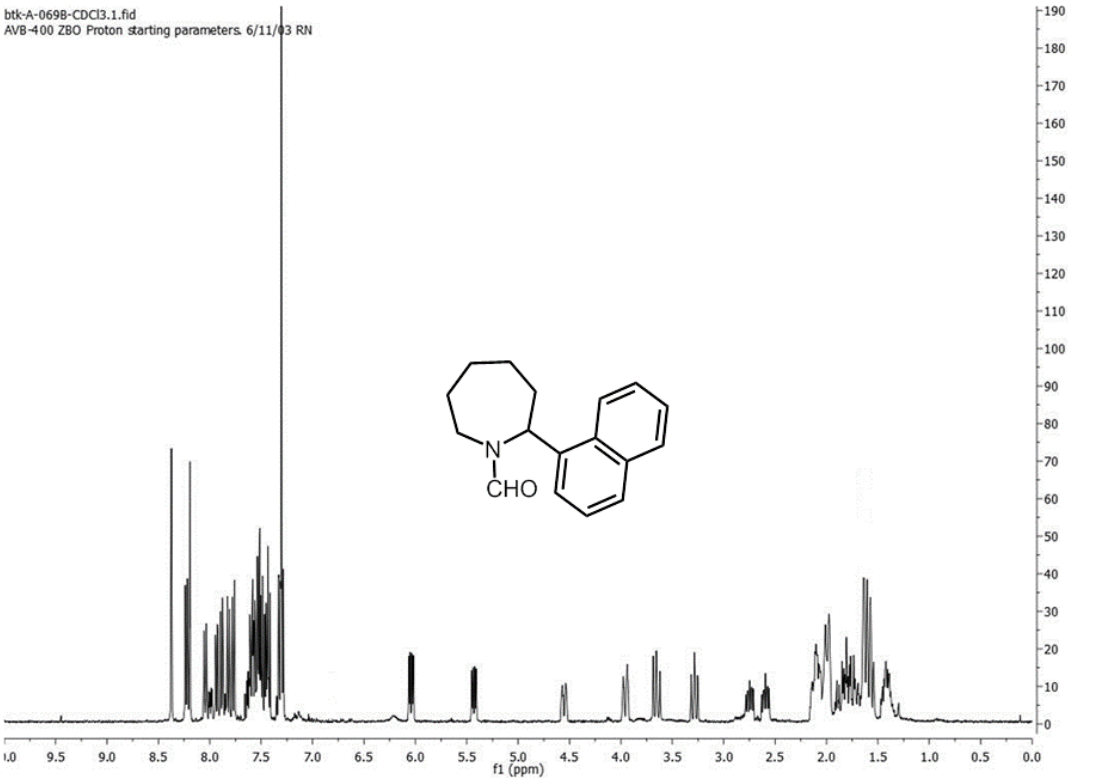


MS Spectrum

Group#1 - MS Mass(254) Peak: 26, RT: 3.14 to 3.48 min



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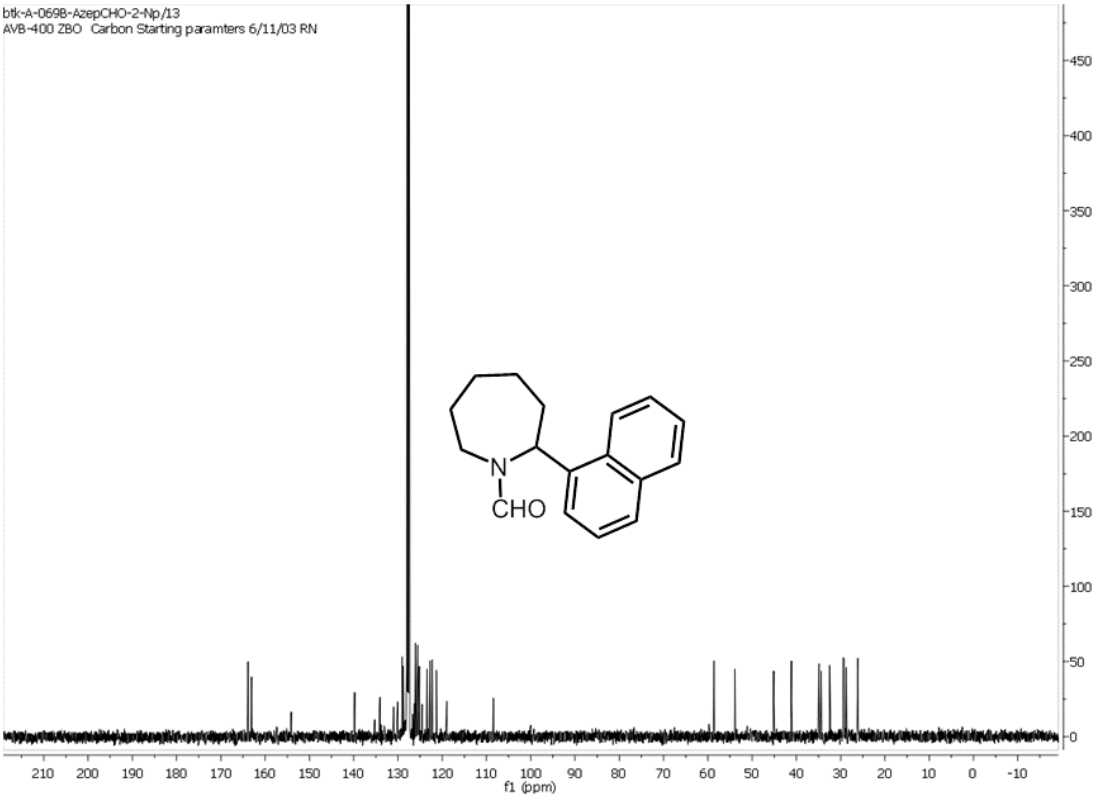
AVB-400 ZBO Proton starting parameters. 6/11/03 RN
N
CHO
f1 (ppm)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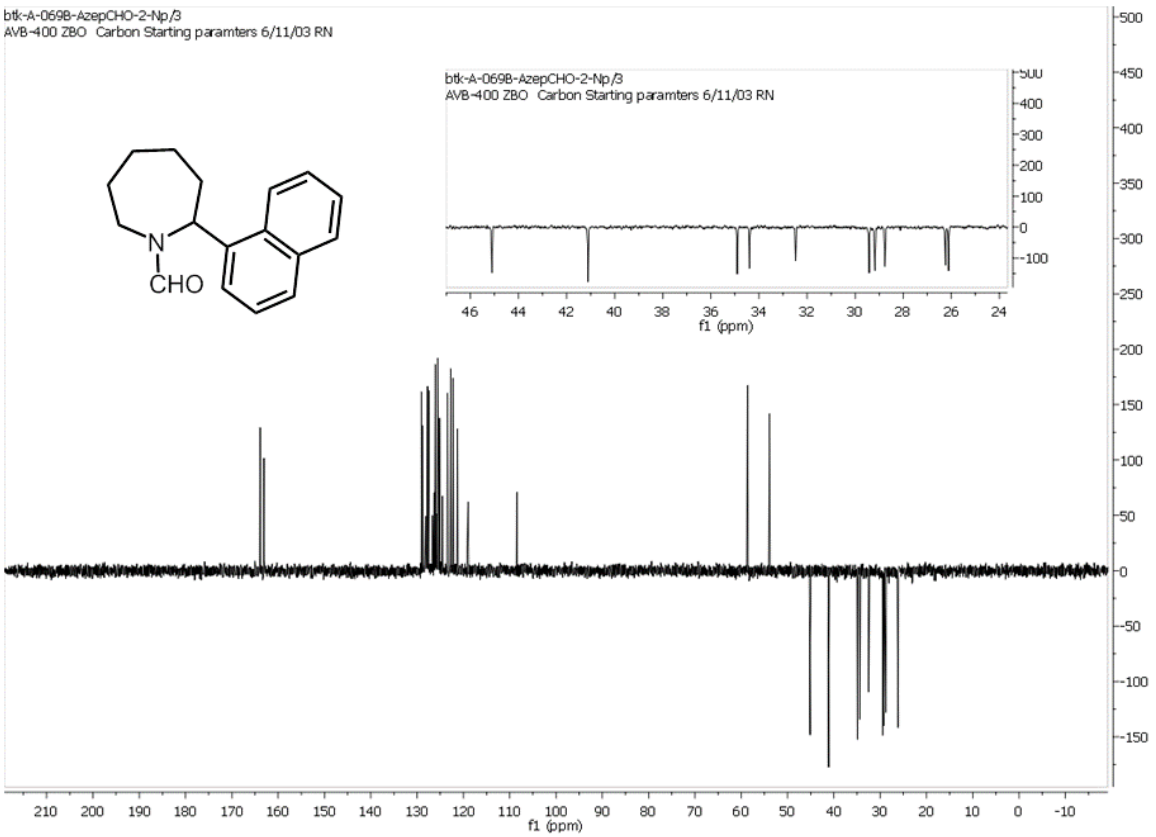
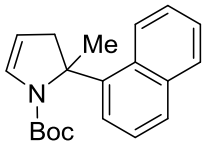
N
CHO
f1 (ppm)





rac-**7**

Catalytic Hydrogenation:

Enecarbamate **2z** (1 mmol) was hydrogenated **General Procedure B**, time = 22 h.

Benzylic lithiation/methylation

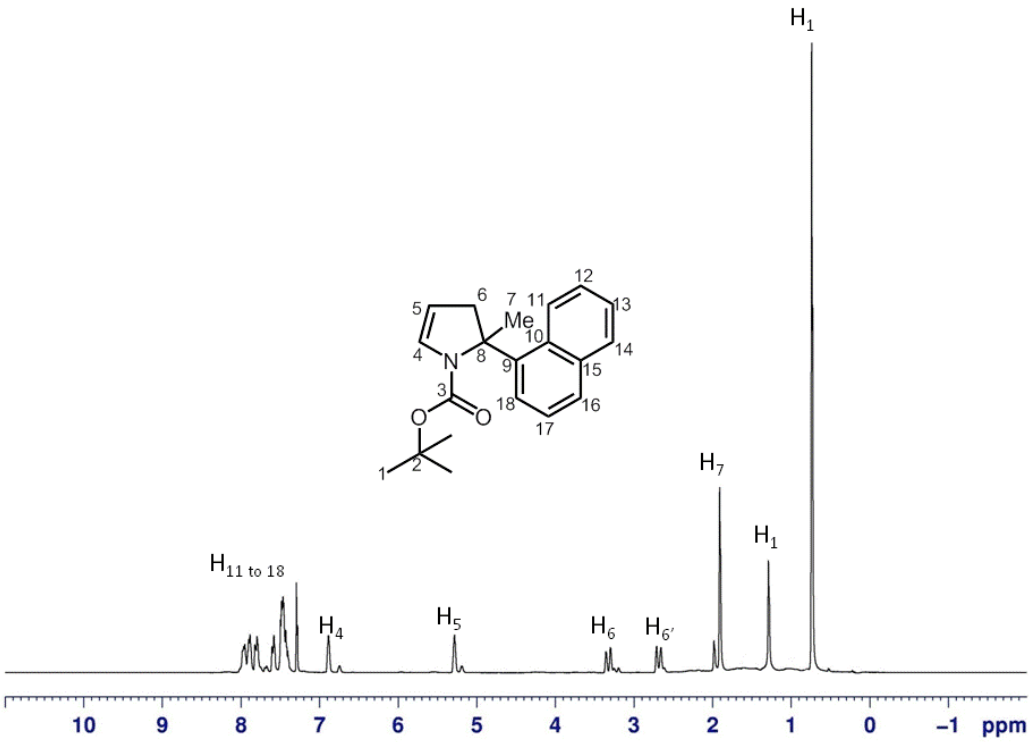
To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (0.2 mL, 1.2 mmol, 1.2 equiv) and a solution of the reduced enecarbamate (1 mmol, 1.0 equiv) in THF (6 mL) under nitrogen. The mixture was cooled to –60 °C and a solution of *n*-BuLi (1.0 mL, 2.0 M in hexanes, 2.0 mmol, 2.0 equiv) was added slowly. After 2 h at this temperature, dimethylsulfate (3 equiv) was added and the 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 (2 mL) was added and the aqueous layer was extracted with

Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude quaternary pyrrolidine.

Lithiation-transmetalation-oxidation:

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added a solution of the disubstituted pyrrolidine (156 mg, 0.5 mmol, 1.0 equiv) in THF (5 mL) and TMEDA (0.09 mL, 0.6 mmol, 1.2 equiv). The solution was cooled to –60 °C and *s*-BuLi (0.60 mL, 1.0 M solution in cyclohexane, 0.60 mmol, 1.2 equiv) was added slowly. After 1 h, a solution of $ZnCl_2$ (0.7 mL, 1.0 M solution in THF, 0.7 mmol, 1.4 equiv) was added. After 30 min, a solution of I_2 in THF (1.5 mL, 1.0 M, 3.0 equiv) was added slowly. The mixture was allowed to stir for 1 h at this temperature before warming to room temperature slowly. After 18 h, a solution of 10% NH_4OH(aq) was added slowly and the mixture was stirred for 20 min. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with saturated $Na_2S_2O_{3(aq)}$ and dried with for ~30 min with Na_2SO_4, filtered and evaporated to give crude **7**. **Purification**: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM. Yield: 110 mg (71%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 8.20 to 7.46 (7H), 6.93 (1H), 5.26 (1H), 3.42 to 3.21 (1H), 2.71 to 2.53 (1H), 1.91 (3H), 1.32 and 0.71 (9H), ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 153.5, 141.4, 135.2, 130.2, 129.5, 128.4, 127.8, 125.6, 124.9, 124.6, 124.3, 124.0, 105.1, 78.9, 66.9, 48.1, 28.9, 27.7. HRMS calc for $C_{20}H_{23}NO_2$ 309.1729, found 309.1731.

Caution: Enecarbamate **7** *is acid labile and should be stored in the refrigerator.*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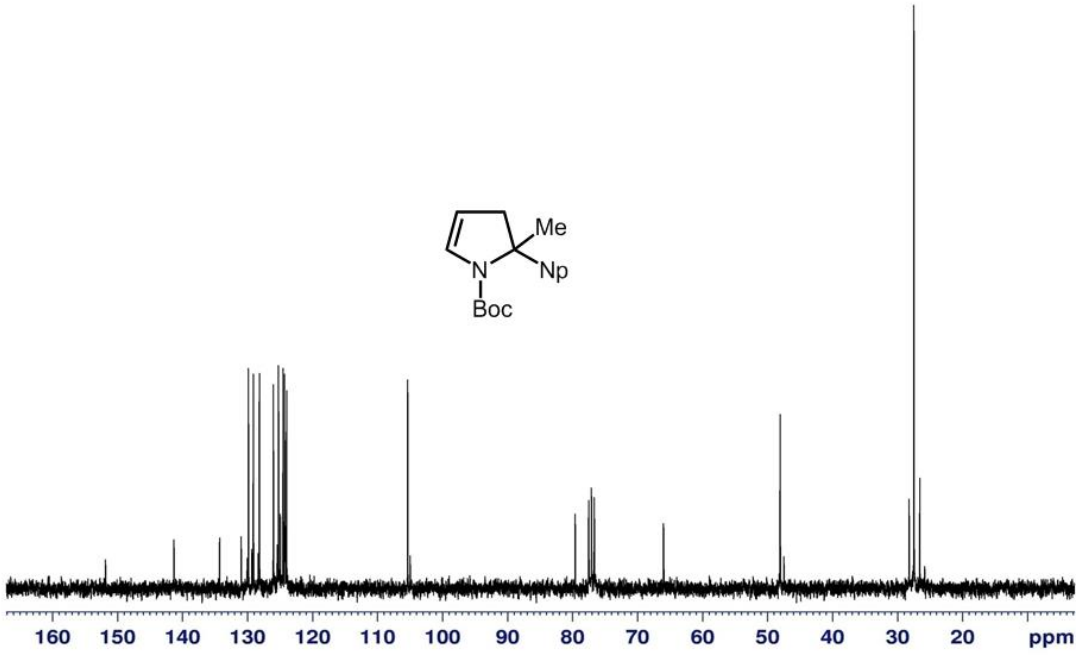
H7
H1
H11 to 18
H4
H5
H6
H6'
10 9 8 7 6 5 4 3 2 1 0 –1 ppm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Np
Boc
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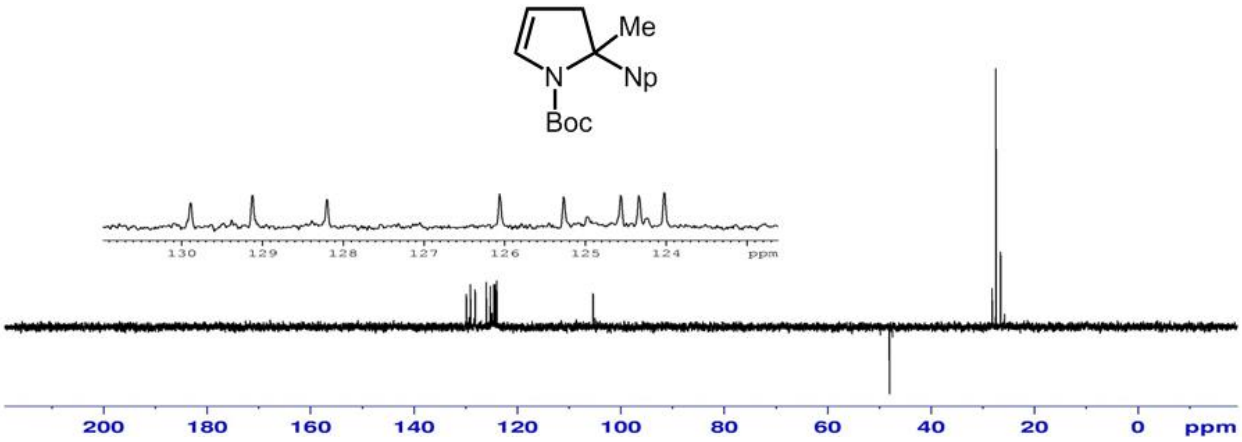
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Boc
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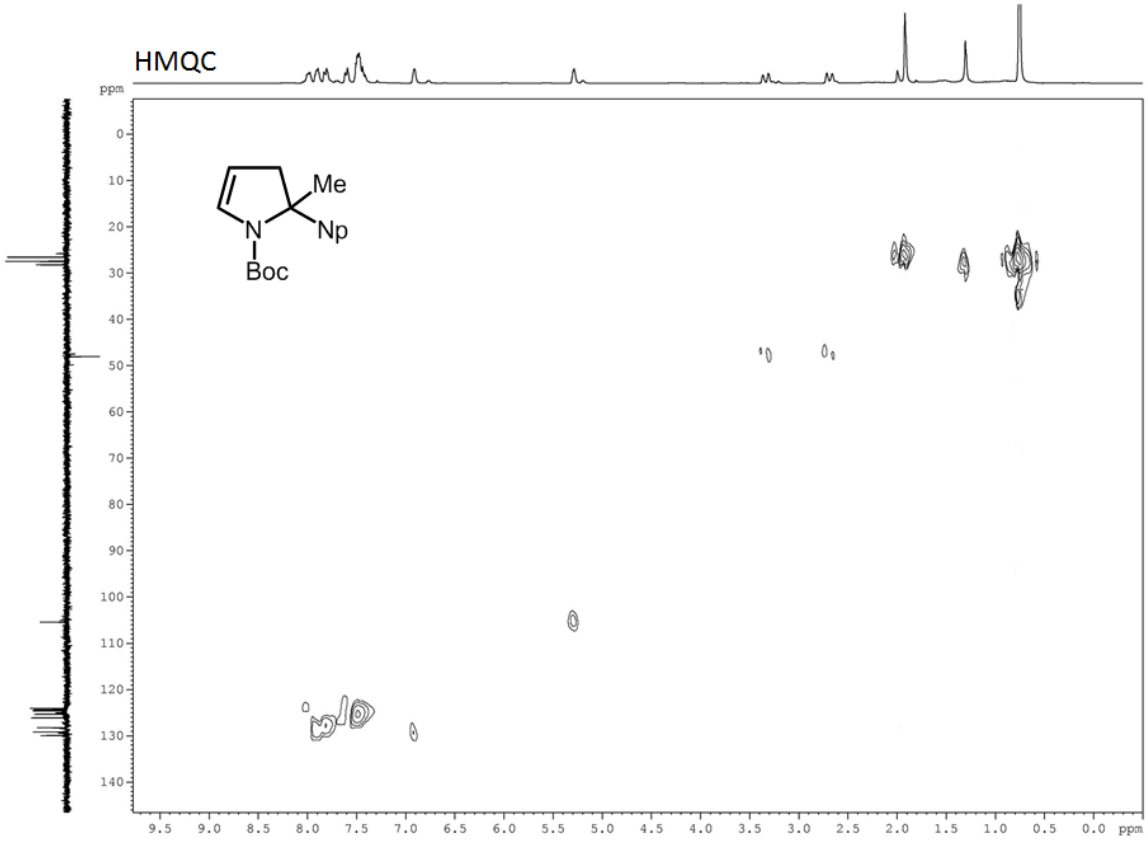
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1.5
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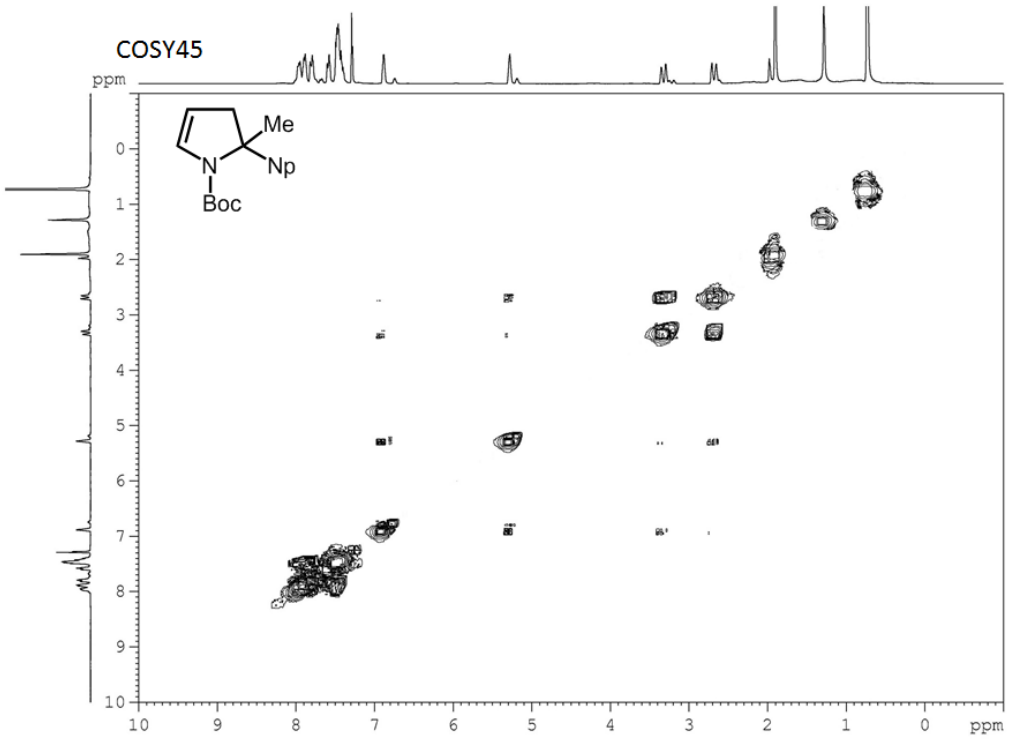
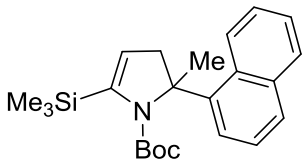
ppm

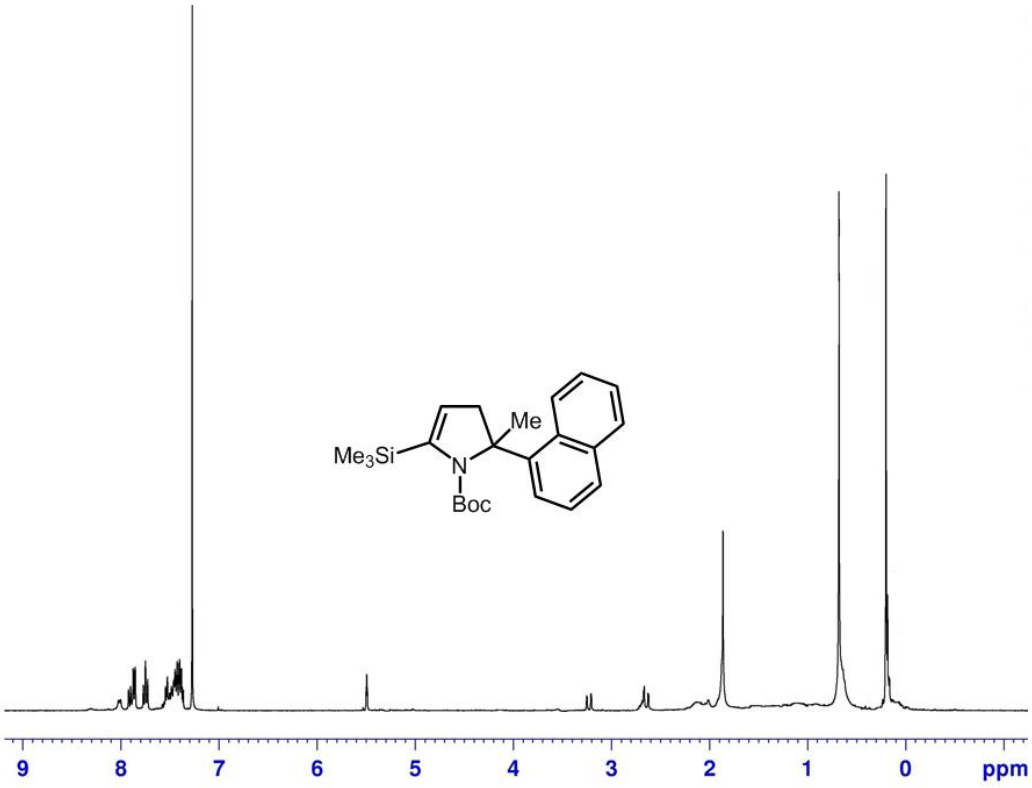


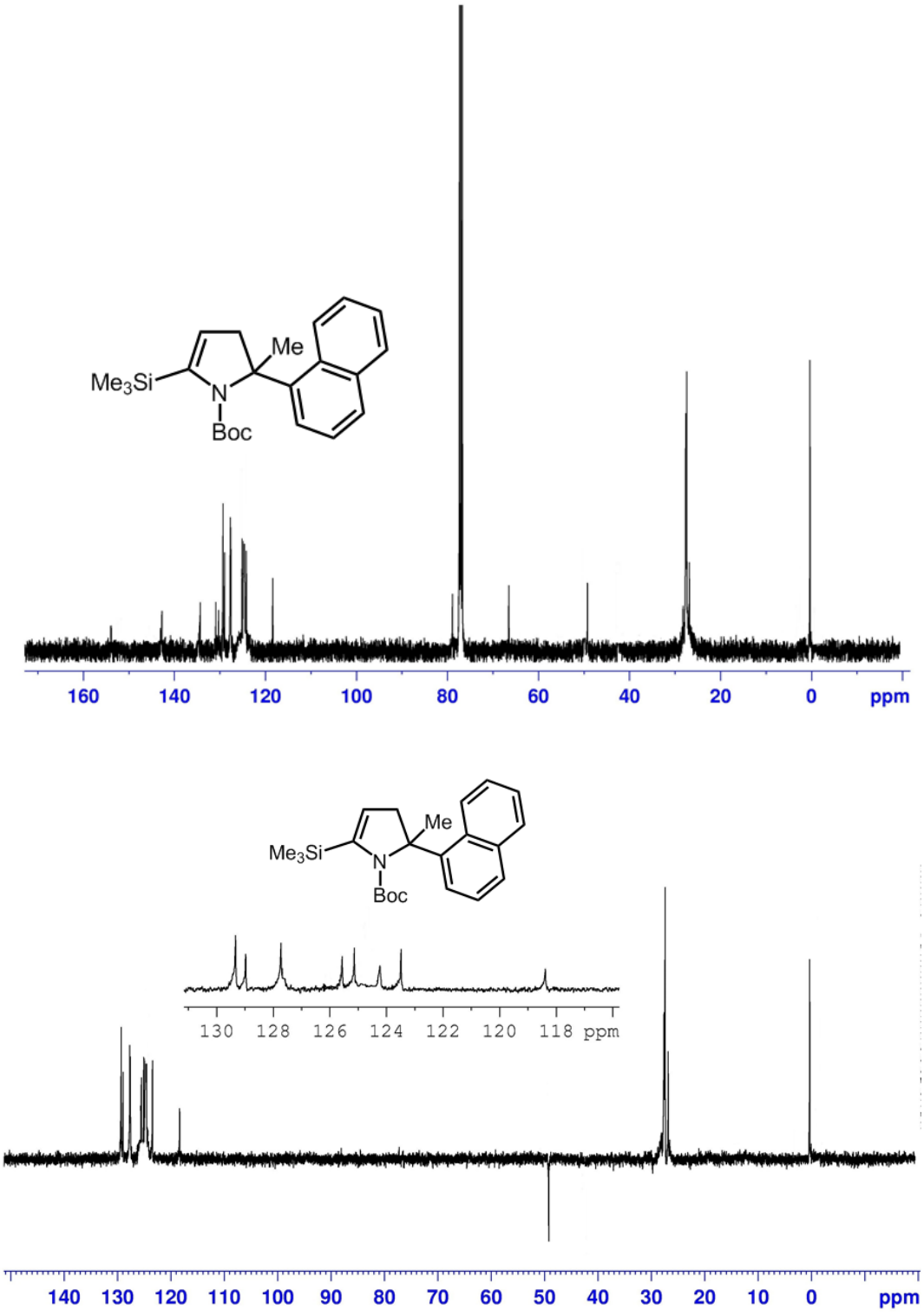


rac-**8**

To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (0.05 mL, 0.5 mmol, 1.2 equiv) and a solution of enecarbamate **7** (78 mg, 0.25 mmol, 1.0 equiv) in THF (2 mL) under argon. The mixture was cooled to –60 °C and a solution of *n*-BuLi (0.12 mL, 2.5 M in hexanes, 0.3 mmol, 1.2 equiv) was added slowly. After 1 to 3 h at this temperature, the mixture was quenched with TMSCl (0.1 mL, 3 equiv). The mixture was slowly warmed to room temperature and *sat*. NH_4Cl was added. The layers were separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered and evaporated to obtain the crude product. **Purification**: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with petroleum ether-DCM (1:1). Yield = 84 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.97 to 7.29 (7H), 5.50 (1H), 3.23 to 3.15 (1H), 2.72 to 2.61 (1H), 1.85 (3H), 0.77 (9H), 0.15 (9H), ^{13}C NMR (101 MHz, $CDCl_3$, mixture of rotamers) δ 154.3, 141.6, 134.8, 130.6, 129.5, 127.7, 125.9, 124.7, 124.2,

123.8, 124.1, 118.5, 79.3, 67.2, 49.6, 27.8, 26.4, 0.2. HRMS calc for $C_{23}H_{31}NO_2Si$ 381.2124 found 381.2122.




Me
Me3Si
N
Boc
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140
120
100
80
60
40
20
0
ppm
Me
Me3Si
N
Boc
130
128
126
124
122
120
118 ppm
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

References

(1) Bassler, D. P.; Alwali, A.; Spence, L.; Beale, O.; Beng, T. K. *J. Organomet. Chem.* **2015**, *780*, 6.

(2) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459.

(3) Beng, T. K.; Silaire, A. W. V.; Alwali, A.; Bassler, D. P. *Org. Biomol. Chem.* **2015**, *13*, 7915.

(4) Beng, T. K.; Wilkerson-Hill, S. M.; Sarpong, R. *Org. Lett.* **2014**, *16*, 916.

(5) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1080.