钴催化环状烯胺的区域选择性和非对映选择性硼氢化反应

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目录

一般信息

除非另有说明, 所有的反应都是在氮气氛围下用磁子在烘箱干燥的烧瓶中进行的. 使用溶剂纯化系统在氮气下对溶剂进行纯化. 通过紫外荧光和/或磷酸钼酸和/或高锰酸钾实现可视化. 实验中所用芳基溴化镁 (1.0 mol/L in THF)、芳基溴化物、N-甲基吡咯烷酮、N-乙基吡咯烷酮、1-甲基-2-哌啶酮、钴催化剂均购自安徽泽升科技股份有限公司(安耐吉, 纯度大于 99%. 频哪醇硼烷购自上海毕得医药科技有限公司. 实验中所用到的三联吡啶类配体, 均根据文献制备. 实验所用溶剂正己烷、四氢呋喃、甲苯等购自安徽泽升科技股份有限公司(安耐吉). GF254 薄层层析和柱层析用硅胶(200~300 目)购自山东青岛海浪硅胶干燥剂有限公司. 石油醚、乙酸乙酯、二氯甲烷购自安徽泽升科技股份有限公司(安耐吉).

^{1}H 核磁共振(^{1}H NMR), ^{13}C 核磁共振(^{13}C NMR), ^{19}F 核磁共振(^{19}F NMR), and ^{11}B 核磁共振(^{11}B NMR)谱通过 20 ºC 下, 400 MHz Bruker 核磁共振仪采集, 溶剂使用氘代氯仿、氘代苯或氘代丙酮. 化学位移(ppm)为溶剂相对参考值：氘代氯仿的参考值分别为 7.26 ppm (^{1}H NMR)和 77.16 ppm (^{13}C NMR)；氘代苯的参考值分别为 7.16 ppm (^{1}H NMR)和 128.06 ppm (^{13}C NMR)；氘代丙酮的参考值为 2.05 ppm (^{1}H NMR)和 206.26 ppm/29.84 ppm (^{13}C NMR). 数据表示如下：化学位移（ppm）, 多重峰（s =单重峰, d =双重峰, dd =双重峰的双重峰, t =三重峰, m =多重峰, mc =中心多重峰, br =宽峰）, 耦合常数 J （Hz）和积分. 采用电喷雾电离（ESI）技术在 Bruker Maxis 系统上记录了高分辨率质谱. 单晶体通过 X 射线单晶体衍射仪 Bruker D8 Venture 采集.

手性化合物的旋光度在 Jasco P-1010 仪器上测定, 并根据下式转化为给定温度下的比旋光度：

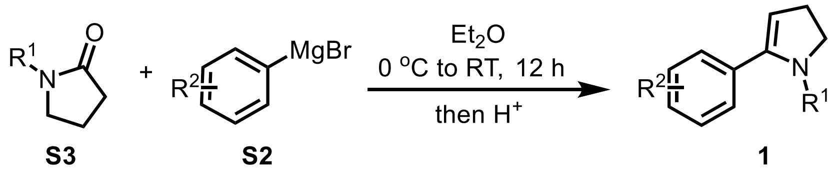
$$[\alpha]_D^T = \frac{\alpha * 100}{c * d}$$

其中, T 表示温度（摄氏度）, α 表示旋光度测量值（º）, d 表示比色皿长度（分米）, c 表示浓度（g: 100mL）.

手性高效液相色谱在 Agilent 高效液相色谱仪上进行, 色谱柱为 Chiralpak IC；Chiralcel OD-H, OJ-H, AD-H, AS-H, 250 mm × 4.6 mm).

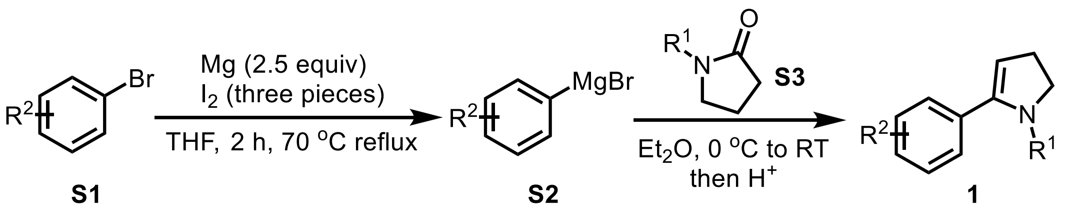
原料的合成和表征数据

通用方法 A



按照文献的方法[1,2], 在 0 ºC , N_2气氛下, 将 N -吡咯烷酮 **S3** (100.0 mmol)的 Et_2O (50 mL)溶液缓慢加入到市售 ArMgBr **S2** (150 mmol, 1 M in THF, 150 mL)的溶液中. 将所得混合物在室温下搅拌 12 小时. 反应结束后, 将反应液冷却至 0 ºC, 用 6 N 盐酸溶液调节 pH 至 3~4. 加入乙醚和水进行萃取, 分离水相. 向水相中缓慢加入 NaOH 水溶液(3.0 M), 调节 pH 至 13. 水相用 DCM 萃取 3 次(每次 100 mL), 合并有机相, 用无水 Na_2SO_4 干燥. 浓缩干燥后的有机相, 在无水无氧环境下, 通过减压蒸馏得到目标产物烯胺 **1**.

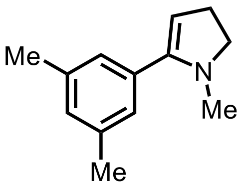
通用方法 B



按照文献方法[3], 在 N_2 气氛下, 将 THF (50.0 mL)加入含有镁 (125.0 mmol, 3.0 g)和 I_2 (3 粒)的双颈烧瓶中. 用 THF (20.0 mL)稀释 **S1** (75.0 mmol), 缓慢加入烧瓶. 反应体系在 70 ºC 下回流 2 h, 制得 **S2**. 使用冰浴冷却至 0 ºC, 将 N-吡咯烷酮 **S3** (50.0 mmol) 的 Et_2O (50 mL)溶液加入如上所述制备的 ArMgBr (**S2**)四氢呋喃溶液中, 室温反应 12 小时. 反应结束后, 将反应液冷却至 0 ºC, 用 6 N 盐酸溶液调节 pH 至 3~4. 加入乙醚和水进行萃取, 分离水相. 向水相中缓慢加入 NaOH 水溶液(3.0 M), 调节 pH 至 13. 水相用 DCM 萃取 3 次(每次 100 mL), 合并有机相, 用无水 Na_2SO_4 干燥. 浓缩干燥后的有机相, 在无水无氧环境下, 通过减压蒸馏得到目标产物烯胺 **1**.

按照通用方法 A 制备 **1a**, **1b**, **1c**, **1g**, **1h**, **1k**, **1l**, **1o**, **1p**, **1s**, **1t**, 表征数据与文献报道数据一致[4].

5-(3,5-Dimethylphenyl)-1-methyl-2,3-dihydro-1H-pyrrole (1d)



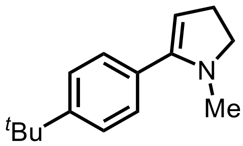
参考通用方法 B, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和 1-溴-3, 5-二甲苯 (70 mmol, 13.0 g) 为原料可以以 43%产率合成浅黄色的油状液体 **1d** (4.02 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 6.93 (s, 1H), 4.93 (t, J = 2.6 Hz, 1H), 3.23 (t, J = 9.1 Hz, 3H), 2.58 – 2.51 (m, 2H), 2.50 (s, 3H), 2.32 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 137.8, 134.1, 129.4, 124.9, 103.7, 56.9, 40.6, 29.2, 21.4.

HRMS (ESI$^+$): calculated for $C_{13}H_{18}N^+$ $[M+H]^+$: 188.1434, found: 188.1431.

5-(4-(*tert*-Butyl)phenyl)-1-methyl-2,3-dihydro-1H-pyrrole (1e)



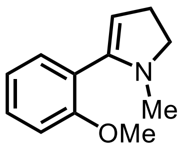
参考通用方法 B, 以 N-甲基吡咯烷酮 (45 mmol, 4.5 g) 和 4-叔丁基溴苯 (70 mmol, 14.9 g) 为原料可以以 17%产率合成浅黄色的油状液体 **1e** (1.83 g).

^{1}H NMR (400 MHz, C_6D_6) δ 7.17 (d, J = 8.2 Hz, 2H), 6.95 (d, J = 8.2 Hz, 2H), 4.66 (t, J = 2.6 Hz, 1H), 2.79 (t, J = 9.1 Hz, 2H), 2.18 - 2.12 (m, 2H), 2.11 (s, 3H), 0.91 (s, 9H).

^{13}C NMR (101 MHz, C_6D_6) δ 155.2, 150.6, 132.3, 127.4, 125.5, 102.8, 57.0, 40.4, 34.6, 31.5, 29.6.

HRMS (ESI$^+$): calculated for $C_{15}H_{21}NNa^+$ $[M+Na]^+$: 238.1662, found: 238.1662.

5-(2-Methoxyphenyl)-1-methyl-2,3-dihydro-1H-pyrrole (1f)



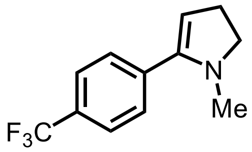
参考通用方法 B, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和 1-溴-2-甲氧基苯 (70 mmol, 13.1 g) 为原料可以以 12%产率合成浅黄色的油状液体 **1f** (1.17 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.5 Hz, 2H), 6.89 (s, 2H), 4.89 (t, J = 2.7 Hz, 1H), 3.82 (s, 3H), 3.16 (t, J = 8.9 Hz, 2H), 2.52 (s, 2H), 2.35 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.0, 151.5, 130.6, 129.1, 123.2, 120.4, 110.9, 104.1, 56.9, 55.7, 39.6, 29.4.

HRMS (ESI$^+$): calculated for $C_{15}H_{21}NNa^+$ $[M+Na]^+$: 212.1046, found: 212.1046.

1-Methyl-5-(4-(trifluoromethyl)phenyl)-2,3-dihydro-1H-pyrrole (1i)



参考通用方法 B, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和对溴三氟甲苯 (60 mmol, 13.6 g) 为原料可以以 6%产率合成浅黄色的油状液体 **1i** (0.62 g).

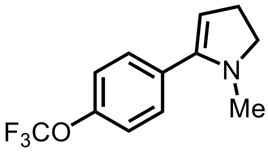
^{1}H NMR (400 MHz, C_6D_6) δ 7.31 (d, *J* = 8.2 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 4.84 (t, *J* = 2.7 Hz, 1H), 2.99 (t, *J* = 9.2 Hz, 2H), 2.39 – 2.29 (m, 2H), 2.22 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ 153.8, 138.4, 129.6 (q, J = 32.3 Hz), 127.5, 125.5 (q, J = 3.8 Hz), 125.0 (q, J = 272.7 Hz), 105.6, 56.7, 40.1, 29.5.

^{19}F NMR (377 MHz, C_6D_6) δ -62.26.

HRMS (ESI$^+$): calculated for $C_{12}H_{13}F_3N^+$ $[M+H]^+$: 228.0995, found: 228.0993.

1-Methyl-5-(4-(trifluoromethoxy)phenyl)-2,3-dihydro-1H-pyrrole (1j)



参考通用方法 B, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和对溴三氟甲氧基苯 (70 mmol, 16.9 g) 为原料可以以 7%产率合成浅黄色的油状液体 **1j** (0.88 g).

^{1}H NMR (400 MHz, C_6D_6) δ 7.20 (d, *J* = 6.7 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.80 (s, 1H), 3.00 (t, *J* = 9.1 Hz, 2H), 2.34 (t, *J* = 9.1 Hz, 2H), 2.23 (s, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ 153.7, 148.8 (q, *J* = 2.0 Hz), 133.7, 128.7, 121.2 (q, *J* = 258.6 MHz), 121.1, 104.3, 56.7, 40.1, 29.5.

^{19}F NMR (377 MHz, C_6D_6) δ -57.81.

HRMS (ESI$^+$): calculated for $C_{12}H_{13}F_3NO^+$ $[M+H]^+$: 244.0944, found: 244.0943.

5-(3-Chlorophenyl)-1-methyl-2,3-dihydro-1H-pyrrole (1m)

参考通用方法 A, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和 3-氯苯基溴化镁 (60 mmol 0.5 mol/L, 120 mL) 为原料可以以 5%产率合成浅黄色的油状液体 **1d** (0.50 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.26 (s, 3H), 5.02 – 4.89 (m, 1H), 3.30 – 3.15 (m, 2H), 2.60 – 2.49 (m, 2H), 2.48 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 136.2, 134.2, 129.6, 127.7, 127.2, 125.2, 105.2, 56.8, 40.5, 29.2.

HRMS (ESI^{+}): calculated for $C_{11}H_{13}ClN^{+}$ $[M+H]^{+}$: 194.0731, found: 194.0732.

1-Methyl-5-(4-(trimethylsilyl)phenyl)-2,3-dihydro-1H-pyrrole (1n)

参考通用方法 B, 以 N-甲基吡咯烷酮 (45 mmol, 4.5 g) 和 1-溴 4-三甲基硅基苯 (68 mmol, 15.6 g) 为原料可以以 25%产率合成浅黄色的油状液体 **1n** (2.61 g).

^{1}H NMR (400 MHz, C_6D_6) δ 7.52 (d, J = 7.5 Hz, 2H), 7.44 (d, J = 7.4 Hz, 2H), 4.98 (m, 1H), 3.08 (t, J = 9.1 Hz, 2H), 2.48 – 2.41 (m, 2H), 2.40 (s, 3H), 0.21 (s,9H).

^{13}C NMR (101 MHz, C_6D_6) δ 155.3, 139.7, 135.6, 133.7, 126.9, 103.6, 56.9, 40.4, 29.6, -1.0.

HRMS (ESI^{+}): calculated for $C_{14}H_{21}KNSi^{+}$ $[M+K]^{+}$: 270.1075, found: 270.1075.

1-Ethyl-5-(*p*-tolyl)-2,3-dihydro-1H-pyrrole (1q)

参考通用方法 A, 以 N-甲基吡咯烷酮 (50 mmol, 5.0 g) 和对甲苯基溴化镁 (60 mmol, 1.0 mol/L, 60 mL) 为原料可以以 21%产率合成浅黄色的油状液体 **1q** (1.96 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 7.1 Hz, 2H), 7.15 (d, J = 7.9 Hz, 2H), 4.93 – 4.87 (m, 1H), 3.31 – 3.23 (m, 2H), 2.78 (q, J = 7.1 Hz, 2H), 2.61 – 2.52 (m, 2H), 2.35 (s, 3H), 1.06 (t, J = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 137.3, 131.7, 129.0, 127.0, 103.1, 53.3, 47.0, 29.1, 29.1, 21.3, 13.5.

HRMS (ESI$^+$): calculated for $C_{13}H_{17}NNa^+$ $[M+Na]^+$: 210.1253, found: 210.1250.

1-Ethyl-5-(*m*-tolyl)-2,3-dihydro-1H-pyrrole (1r)

参考通用方法 A, 以 N-乙基吡咯烷酮 (40 mmol, 4.53 g) 和间甲苯基溴化镁 (50 mmol, 1.0 mol/L, 50 mL) 为原料可以以 48%产率合成浅黄色的油状液体 **1r** (0.50 g).

^{1}H NMR (400 MHz, C_6D_6) δ 7.33 (d, *J* = 6.0 Hz, 2H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.94 (d, *J* = 2.5 Hz, 1H), 3.13 (t, *J* = 9.2 Hz, 2H), 2.77 (q, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 9.3 Hz, 2H), 2.12 (s, 3H), 0.95 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, C_6D_6) δ 154.5, 137.9, 135.4, 128.6, 128.5, 128.2, 124.7, 103.0, 53.3, 47.1, 29.5, 21.4, 13.7.

HRMS (ESI$^+$): calculated for $C_{13}H_{17}NNa^+$ $[M+Na]^+$: 210.1253, found: 210.1250.

产物的合成和表征数据

通用方法 C：

在手套箱中, 将 $Co(acac)_2$ (5 mol%, 0.025 mmol, 6.5 mg)和 **L6** (6 mol%, 0.03 mmol, 11.7 mg)加入 15 mL 的干燥耐压管中. 加入正己烷(2.5 mL), 室温搅拌 20 分钟. 然后加入 HBpin (2.0 equiv, 1.0 mmol, 0.15 mL), 在相同温度下再搅拌 5 分钟. 随后, 加入烯胺 **1** (0.5 mmol), 在 70 ºC 下搅拌 24 h, 在氮气下减压除去溶剂. 加入 THF (5.0 mL), 然后在 0 ºC 下加入 $NaOH/H_2O_2$ (3.0 M, 1.0 mL), 反应 30 分钟. 反应用 $Na_2S_2O_3$ 水溶液淬灭, 用 EtOAc (5.0 mL)萃取三次, 有机相用 Na_2SO_4 干燥, 减压浓缩, 所得粗产物用硅胶(DCM/MeOH)柱层析纯化, 得到所需产物 **3**.

***trans*-1-Methyl-2-phenylpyrrolidin-3-ol (3a)**

参考通用方法 C, 以 **1a** (0.5 mmol, 79.5 mg) 为原料可以以 72%产率合成浅黄色的固体 **3a** (63.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) 7.34 (d, J = 4.4 Hz, 4H), 7.30 – 7.24 (m, 1H), 4.16 – 4.06 (m, 1H), 3.21 – 3.12 (m, 1H), 2.94 (d, J = 6.2 Hz, 1H), 2.55 (q, J = 9.1 Hz, 1H), 2.37 – 2.24 (m, 1H), 2.15 (s, 3H), 2.07 (br, 1H), 1.76 – 1.67 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8, 128.7, 127.8, 127.7, 80.0, 79.8, 54.8, 40.7, 32.6.

HRMS (ESI$^+$): calculated for $C_{11}H_{16}NO^+$ $[M+H]^+$: 178.1226, found: 178.1224.

***trans*-1-Methyl-2-(*p*-tolyl)pyrrolidin-3-ol (3b)**

参考通用方法 C, 以 **1b** (0.5 mmol, 86.5 mg)为原料可以以 83%产率合成浅黄色的固体 **3b** (79.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) 7.18 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 4.09 – 3.94 (m, 1H), 3.23 (br, 1H), 3.11 – 3.01 (m, 1H), 2.85 (d, J = 6.4 Hz, 1H), 2.46 (q, J = 9.1 Hz, 1H), 2.32 (s, 3H), 2.26 – 2.14 (m, 1H), 2.07 (s, 3H), 1.70 – 1.57 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 137.1, 129.2, 127.8, 79.3, 54.7, 40.5, 32.4, 21.1.

HRMS (ESI$^+$): calculated for $C_{12}H_{17}NNaO^+$ $[M+Na]^+$: 214.1202, found: 214.1200.

***trans*-1-Methyl-2-(*m*-tolyl)pyrrolidin-3-ol (3c)**

参考通用方法 C, 以 **1c** (0.5 mmol, 95.6 mg)为原料可以以 71%产率合成浅黄色的固体 **3c** (67.9 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (t, J = 7.1 Hz, 1H), 7.18 – 7.11 (m, 2H), 7.09 (d, J = 7.6 Hz, 1H), 4.14 – 4.06 (m, 1H), 3.19 – 3.11 (m, 1H), 2.89 (d, J = 5.8 Hz, 1H), 2.53 (q, J = 8.9 Hz, 1H), 2.35 (s, 3H), 2.33 – 2.25 (m, 1H), 2.15 (s, 3H), 2.06 (br, 1H), 1.76 – 1.66 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 138.4, 128.6, 128.5, 128.3, 125.0, 79.9, 79.8, 54.9, 40.8, 32.5, 21.5.

HRMS (ESI$^+$): calculated for $C_{12}H_{17}NNaO^+$ $[M+Na]^+$: 214.1202, found: 214.1202.

***trans*-2-(3,5-dimethylphenyl)-1-methylpyrrolidin-3-ol (3d)**

参考通用方法 C, 以 **1d** (0.5 mmol, 102.7 mg)为原料可以以 69%产率合成浅黄色的固体 **3d** (70.7 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (s, 2H), 6.90 (s, 1H), 4.11 – 4.03 (m, 1H), 3.12 (t, J = 8.9 Hz, 1H), 3.00 (br, 1H), 2.84 (d, J = 6.2 Hz, 1H), 2.50 (q, J = 9.3 Hz, 1H), 2.29 (s, 6H), 2.24 (d, J = 9.5 Hz, 1H), 2.12 (s, 3H), 1.74 – 1.63 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 138.1, 129.3, 125.6, 79.7, 79.5, 54.8, 40.7, 32.5, 21.3.

HRMS (ESI$^+$): calculated for $C_{13}H_{19}KNO^+$ $[M+K]^+$: 244.1098, found: 244.1099.

***trans*-2-(4-(*tert*-Butyl)phenyl)-1-methylpyrrolidin-3-ol (3e)**

参考通用方法 C, 以 **1e** (0.5 mmol, 107.5 mg)为原料可以以 85%产率合成浅黄色的固体 **3e** (99.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 4.16 – 4.07 (m, 1H), 3.21 – 3.12 (m, 1H), 2.92 (d, J = 6.4 Hz, 1H), 2.54 (q, J = 9.1 Hz, 1H), 2.37 – 2.25 (m, 1H), 2.16 (s, 3H), 1.91 (br, 1H), 1.78 – 1.68 (m, 1H), 1.32 (d, J = 1.6 Hz, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 137.5, 127.4, 125.6, 79.9, 79.4, 54.9, 40.8, 34.6, 32.4, 31.5.

HRMS (ESI$^+$): calculated for $C_{15}H_{23}NNaO^+$ $[M+Na]^+$: 256.1672, found: 256.1670.

***trans*-2-(2-methoxyphenyl)-1-methylpyrrolidin-3-ol (3f)**

参考通用方法 C, 以 **1f** (0.5 mmol, 103.6 mg)为原料可以以 55%产率合成浅黄色的固体 **3f** (57.0 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 8.2 Hz, 1H), 4.12 – 4.07 (m, 1H), 3.88 (s, 3H), 3.49 (d, J = 4.5 Hz, 1H), 3.16 (t, J = 8.3 Hz, 1H), 2.75 – 2.62 (m, 2H), 2.30 (s, 3H), 2.13 (m, 1H), 1.80 – 1.70 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.6, 129.6, 127.8, 126.9, 121.3, 110.4, 80.3, 74.5, 55.7, 55.4, 41.4, 32.8.

HRMS (ESI$^+$): calculated for $C_{12}H_{17}NNaO_2^+$ $[M+Na]^+$: 230.1152, found: 230.1152.

***trans*-2-(3-Methoxyphenyl)-1-methylpyrrolidin-3-ol (3g)**

参考通用方法 C, 以 **1g** (0.5 mmol, 94.5 mg)为原料可以以 78%产率合成浅黄色的固体 **3g** (80.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 8.0 Hz, 1H), 6.93 (d, J = 6.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 1H), 4.13 – 4.06 (m, 1H), 3.80 (s, 3H), 3.14 (t, J = 8.3 Hz, 1H), 2.92 (d, J = 6.2 Hz, 1H), 2.53 (q, J = 9.1 Hz, 1H), 2.48 – 2.41 (br, 1H), 2.35 – 2.22 (m, 1H), 2.16 (s, 3H), 1.76 – 1.65 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 142.4, 129.7, 120.2, 113.3, 112.8, 79.8, 79.7, 55.3, 54.8, 40.7, 32.5.

HRMS (ESI$^+$): calculated for $C_{12}H_{17}NNaO_2^+$ $[M+Na]^+$: 230.1152, found: 230.1153.

***trans*-2-(4-Methoxyphenyl)-1-methylpyrrolidin-3-ol (3h)**

参考通用方法 C, 以 **1h** (0.5 mmol, 94.5 mg)为原料可以以 62%产率合成浅黄色的固体 **3h** (64.1 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 4.14 – 4.06 (m, 1H), 3.78 (s, 3H), 3.20 – 3.11 (m, 1H), 2.89 (d, J = 6.3 Hz, 1H), 2.53 (q, J = 9.1 Hz, 1H), 2.36 – 2.25 (m, 1H), 2.13 (s, 3H), 1.77 – 1.66 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 132.4, 129.0, 114.2, 79.8, 79.1, 55.4, 54.7, 40.6, 32.4.

HRMS (ESI$^+$): calculated for $C_{12}H_{18}NO_2^+$ $[M+H]^+$: 208.1332, found: 208.1331.

***trans*-1-Methyl-2-(4-(trifluoromethyl)phenyl)pyrrolidin-3-ol (3i)**

参考通用方法 C, 以 **1i** (0.5 mmol, 113.5 mg)为原料可以以 58%产率合成无色的固体 **3i** (71.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 4.12 – 4.03 (m, 1H), 3.22 – 3.13 (m, 1H), 3.04 (d, J = 6.1 Hz, 1H), 2.58 (q, J = 9.1 Hz, 1H), 2.37 – 2.23 (m, 1H), 2.16 (s, 3H), 2.00 (br, 1H), 1.79 – 1.69 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 129.9 (q, J = 32.3 Hz), 128.0, 125.6 (q, J = 3.6 Hz), 124.3 (q, J = 272.7 Hz), 80.2, 79.1, 54.8, 40.7, 33.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.41.

HRMS (ESI$^+$): calculated for $C_{12}H_{15}F_3NO^+$ $[M+H]^+$: 246.1097, found: 246.1100.

***trans*-1-Methyl-2-(4-(trifluoromethoxy)phenyl)pyrrolidin-3-ol (3j)**

参考通用方法 C, 以 **1j** (0.5 mmol, 121.5 mg)为原料 可以以 58%产率合成无色的固体 **3j** (73.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.2 Hz, 2H), 4.12 – 4.01 (m, 1H), 3.20 – 3.12 (m, 1H), 2.98 (d, J = 6.1 Hz, 1H), 2.56 (q, J = 9.1 Hz, 1H), 2.36 – 2.24 (m, 1H), 2.15 (s, 3H), 1.92 (br, 1H), 1.79 – 1.67 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 139.8, 129.0, 121.2, 120.6 (q, J = 257.6 Hz), 80.2, 78.9, 54.7, 40.7, 32.7.

^{19}F NMR (377 MHz, $CDCl_3$) δ -57.85.

HRMS (ESI^+): calculated for $C_{12}H_{14}F_3NONa^+$ $[M+Na]^+$: 284.0869, found: 284.0870.

***trans*-2-(3-Fluorophenyl)-1-methylpyrrolidin-3-ol (3k)**

参考通用方法 C, 以 **1k** (0.5 mmol, 97.6 mg)为原料可以以 76%产率合成浅黄色的固体 **3k** (74.5 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 1H), 7.14 – 7.03 (m, 2H), 6.98 – 6.90 (m, 1H), 4.09 – 4.01 (m, 1H), 3.17 – 3.10 (m, 1H), 2.95 (d, J = 6.0 Hz, 1H), 2.54 (q, J = 9.1 Hz, 1H), 2.33 – 2.20 (m, 1H), 2.14 (d, J = 1.4 Hz, 3H), 1.98 (br, 1H), 1.76 – 1.65 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3 (d, J = 245.8 Hz), 143.9 (d, J = 6.9 Hz), 130.1 (d, J = 8.2 Hz), 123.4 (d, J = 2.8 Hz), 114.44 (d, J = 1.6 Hz), 114.43 (d, J = 41.3 Hz), 80.1, 79.2 (d, J = 1.9 Hz), 54.7, 40.7, 32.7.

^{19}F NMR (377 MHz, $CDCl_3$) δ -113.18.

HRMS (ESI^+): calculated for $C_{11}H_{18}FN2O^+$ $[M+NH_4]^+$: 213.1398, found: 213.1398.

***trans*-2-(4-Fluorophenyl)-1-methylpyrrolidin-3-ol (3l)**

参考通用方法 C, 以 **1l** (0.5 mmol, 88.5 mg)为原料可以以 72%产率合成浅黄色的固体 **3l** (70.3 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 2H), 7.01 (t, J = 8.7 Hz, 2H), 4.09 – 4.00 (m, 1H), 3.19 – 3.09 (m, 1H), 2.91 (d, J = 6.2 Hz, 1H), 2.53 (q, J = 9.1 Hz, 1H), 2.34 – 2.17 (m, 2H), 2.12 (s, 3H), 1.76 – 1.65 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4 (d, J = 245.2 Hz), 136.5 (d, J = 3.0 Hz), 129.3 (d, J = 7.9 Hz), 115.5 (d, J = 21.2 Hz), 80.0, 78.9, 54.7, 40.6, 32.6.
^{19}F NMR (377 MHz, $CDCl_3$) δ -115.25.
HRMS (ESI$^+$): calculated for $C_{11}H_{14}FKNO^+$ $[M+K]^+$: 234.0691, found: 234.0692.

***trans*-2-(3-chlorophenyl)-1-methylpyrrolidin-3-ol (3m)**

参考通用方法 C, 以 **1m** (0.5 mmol, 96.8 mg)为原料可以以 55%产率合成浅黄色的固体 **3m** (58.3 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 2.3 Hz, 1H), 7.24 (d, J = 5.2 Hz, 3H), 4.12 – 4.02 (m, 1H), 3.20 – 3.11 (m, 1H), 2.94 (d, J = 6.0 Hz, 1H), 2.55 (q, J = 9.1 Hz, 1H), 2.35 – 2.22 (m, 1H), 2.16 (s, 3H), 1.90 (br, 1H), 1.77 – 1.65 (m, 1H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 134.7, 130.0, 127.8, 127.7, 126.0, 80.1, 79.2, 54.7, 40.8, 32.8.
HRMS (ESI$^+$): calculated for $C_{11}H_{15}ClNO^+$ $[M+H]^+$: 212.0837, found: 212.0836.

***trans*-1-Methyl-2-(4-(trimethylsilyl)phenyl)pyrrolidin-3-ol (3n)**

参考通用方法 C, 以 **1n** (0.5 mmol, 115.5 mg)为原料可以以 77%产率合成黄色的固体 **3n** (96.0 mg).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 2H), 4.11 – 4.04 (m, 1H), 3.12 (t, J = 8.6 Hz, 1H), 2.93 (d, J = 6.3 Hz, 1H), 2.83 (br, 1H), 2.52 (q, J = 9.1 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.12 (s, 3H), 1.75 – 1.64 (m, 1H), 0.26 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 139.7, 133.7, 127.2, 79.7, 79.6, 54.8, 40.7, 32.5, -1.0.

HRMS (ESI$^+$): calculated for $C_{14}H_{24}NOSi^+$ $[M+H]^+$: 250.1622, found: 250.1620.

***trans*-1-Ethyl-2-phenylpyrrolidin-3-ol (3p)**

参考通用方法 C, 以 **1p** (0.5 mmol, 86.5 mg)为原料可以以 88%产率合成浅黄色油状液体 **3p** (84.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.28 (m, 4H), 7.27 – 7.21 (m, 1H), 4.09 – 4.01 (m, 1H), 3.29 – 3.20 (m, 1H), 3.09 (d, J = 6.1 Hz, 1H), 2.62 – 2.50 (m, 1H), 2.44 (q, J = 9.0 Hz, 1H), 2.32 – 2.16 (m, 2H), 2.16 – 2.04 (m, 1H), 1.76 – 1.66 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.4, 128.6, 127.8, 127.5, 79.6, 78.1, 50.9, 48.1, 32.1, 13.1.

HRMS (ESI$^+$): calculated for $C_{12}H_{17}NNaO^+$ $[M+Na]^+$: 214.1202, found: 214.1199.

***trans*-1-Ethyl-2-(p-tolyl)pyrrolidin-3-ol (3q)**

参考通用方法 C, 以 **1q** (0.5 mmol, 102.7 mg)为原料可以以 64%产率合成浅黄色油状液体 **3q** (66.0 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.2 Hz, 2H), 7.15 (d, J = 7.7 Hz, 2H), 4.11 – 4.02 (m, 1H), 3.26 (t, J = 8.3 Hz, 1H), 3.07 (d, J = 6.1 Hz, 1H), 2.64 – 2.53 (m, 1H), 2.46 (q, J = 9.0 Hz, 1H), 2.34 (s, 3H), 2.32 – 2.24 (m, 1H), 2.16 – 2.03 (m, 2H), 1.78 – 1.68 (m, 1H), 1.03 – 0.95 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.2, 129.4, 127.8, 79.6, 77.9, 50.9, 48.1, 32.0, 21.2, 13.1.

HRMS (ESI$^+$): calculated for $C_{13}H_{20}NO^+$ $[M+H]^+$: 206.1539, found: 206.1537.

***trans*-1-Ethyl-2-(*m*-tolyl)pyrrolidin-3-ol (3r)**

参考通用方法 C, 以 **1r** (0.5 mmol, 93.0 mg)为原料可以以 72%产率合成棕色油状液体 **3r** (73.8 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.11 (m, 3H), 7.06 (d, J = 7.3 Hz, 1H), 4.07 – 3.99 (m, 1H), 3.27 – 3.17 (m, 1H), 3.04 (d, J = 6.1 Hz, 1H), 2.78 (br, 1H), 2.64 – 2.53 (m, 1H), 2.43 (q, J = 9.0 Hz, 1H), 2.34 (s, 3H), 2.30 – 2.16 (m, 1H), 2.15 – 2.03 (m, 1H), 1.74 – 1.64 (m, 1H), 0.98 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.2, 138.1, 128.41, 128.39, 128.2, 124.9, 79.3, 78.0, 50.9, 48.1, 32.0, 21.5, 13.0.

HRMS (ESI$^+$): calculated for $C_{13}H_{19}KNO^+$ $[M+K]^+$: 244.1098, found: 244.1097.

***trans*-1-Ethyl-2-(4-methoxyphenyl)pyrrolidin-3-ol (3s)**

参考通用方法 C, 以 **1s** (0.5 mmol, 101.5 mg)为原料可以以 68%产率合成黄色油状液体 **3s** (75.2 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.3 Hz, 2H), 4.11 – 4.00 (m, 1H), 3.79 (s, 3H), 3.29 – 3.20 (m, 1H), 3.04 (d, J = 6.3 Hz, 1H), 2.63 – 2.51 (m, 1H), 2.44 (q, J = 9.0 Hz, 1H), 2.34 – 2.20 (m, 2H), 2.14 – 2.02 (m, 1H), 1.77 – 1.66 (m, 1H), 0.98 (t, J = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 133.0, 128.9, 114.0, 79.4, 55.4, 50.9, 48.0, 31.9, 13.1.

HRMS (ESI$^+$): calculated for $C_{13}H_{19}NNaO_2^+$ $[M+Na]^+$: 244.1308, found: 244.1309.

***trans*-1-Ethyl-2-(4-fluorophenyl)pyrrolidin-3-ol (3t)**

参考通用方法 C, 以 **1t** (0.5 mmol, 95.5 mg)为原料可以以 74%产率合成棕色油状液体 **3t** (77.4 mg).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, J = 6.2 Hz, 2H), 6.97 (t, J = 8.1 Hz, 2H), 4.00 – 3.89 (m, 1H), 3.18 (t, J = 8.7 Hz, 1H), 3.04 (d, J = 5.6 Hz, 1H), 2.94 (br, 1H), 2.57 – 2.44 (m, 1H), 2.44 – 2.34 (m, 1H), 2.24 – 2.12 (m, 1H), 2.11 – 2.00 (m, 1H), 1.71 – 1.59 (m, 1H), 0.93 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.2 (d, J = 245.0 Hz), 137.0 (d, J = 3.1 Hz), 129.2 (d, J = 7.9 Hz), 115.3 (d, J = 21.2 Hz), 79.3, 77.2, 50.8, 48.0, 32.1, 13.0.

^{19}F NMR (377 MHz, $CDCl_3$) δ -115.43.

HRMS (ESI^+): calculated for $C_{12}H_{16}FKNO^+$ $[M+K]^+$: 248.0848, found: 248.0850.

环状烯胺的不对称硼氢化

通用方法 D：

在手套箱中, 将钴催化剂 (5 mol%, 0.01 mmol, 2.6 mg)和 **L*** (6 mol%, 0.012 mmol, 4.6 mg)加入 10 mL 的干燥耐压管中. 加入溶剂(1.0 mL), 室温搅拌 20 分钟. 然后加入 HBpin (2.0 equiv, 0.4 mmol, 60 μL), 在相同温度下再搅拌 5 分钟. 随后, 加入烯胺 **1a** (31.8 mg, 0.2 mmol), 在 60 ºC 下搅拌 12 h, 在氮气下减压除去溶剂. 加入 THF (1.0 mL), 然后在 0 ºC 下加入 $NaOH/H_2O_2$ (3.0 M, 0.2 mL), 反应 30 分钟. 反应用 $Na_2S_2O_3$ 水溶液淬灭, 用 EtOAc (3.0 mL)萃取三次, 有机相用 Na_2SO_4 干燥, 减压浓缩, 所得粗产物用硅胶(DCM/MeOH = 20/1)柱层析纯化, 得到所需产物 **3a**.

按照通用方法 D, 我们尝试了多种不同的配体和溶剂(Table S1 and S2). 当催化剂使用 $Co(acac)_2$ (0.01 mmol, 2.6 mg), 手性催化剂使用(*S*,*S*)-Ph-BPE (0.012 mmol, 4.6 mg), 加入 **1a** (0.2 mmol, 31.8 mg), 甲苯(1.0 mL), 60 ºC 反应时, 以 39% 产率, 74% ee 生成 **3a**.

$[\alpha]_D^{20.0}$ = 18.61 (c = 1.01, $CHCl_3$, 74% ee); 通过手性高效液相色谱法测定对映体比例 (Daicel Chiralcel IC 正己烷：异丙醇 = 90/10, 流速 = 1.0 mL/min, λ = 220 nm), t^1 = 8.0 min (minor), t^2 = 9.0 min (major).

表 S1. 烯胺不对称硼氢化反应的配体筛选 [a)].

Table S1. Ligand Screening for asymmetric hydroboration of enamines[a)].

a) 反应条件：**1a** (0.2 mmol), HBpin (2.0 equiv), $Co(acac)_2$ (5 mol%), ligand (6 mol%), THF (1.0 mL), T = 60 ^oC, 12 h; ^1H NMR 产率.

表 S2. 烯胺不对称硼氢化反应的条件优化 a).

Table S2. Asymmetric hydroboration condition optimization[a)].

a) 反应条件：**1a** (0.2 mmol), HBpin (2.0 equiv), [Co] (5 mol%), (*S*,*S*)-Ph-BPE (6 mol%), THF (1.0 mL), T = 60 °C, 12 h.

克级反应和应用转化

克级反应

在手套箱中, 将 Co(acac)$_2$ (5 mol%, 0.4 mmol, 102.8 mg)和 **L6** (6 mol%, 0.48 mmol, 181.0 mg)加入 150.0 mL 的干燥耐压管中. 加入正己烷(20.0 mL), 室温搅拌 20 分钟. 然后加入 HBpin (2.0 equiv, 2.05 g, 2.32 mL), 在相同温度下继续搅拌 5 分钟. 随后加入正己烷(20.0 mL)稀释的烯胺 **1a** (8.0 mmol, 1.27 g), 在 70 ºC 搅拌 24 h, 在氮气气氛下减压除去溶剂. 将得到的滤液冷却至室温, 用正己烷过滤, 真空浓缩得到 **2a** 的粗产物. 加入 20 mL 四氢呋喃, 冷却至 0 ºC, 加入 NaOH/H_2O_2 (3.0 M, 6.0 mL), 在 0 ºC 下反应 1 h. 使用 $Na_2S_2O_3$ 水溶液淬灭, EtOAc 萃取 (20.0 mL)水层三次, 合并有机相, Na_2SO_4 干燥, 减压浓缩, 粗产物用硅胶柱层析法纯化(DCM/MeOH= 20/1)得到所需的产物 **3a**, 分离收率为 78% (1.10 g, dr > 20:1).

2a: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.40 – 7.31 (m, 2H), 7.33 – 7.24 (m, 2H), 7.25 – 7.14 (m, 1H), 3.33 – 3.23 (m, 1H), 3.12 (d, J = 10.5 Hz, 1H), 2.33 (q, J = 9.1 Hz, 1H), 2.23 – 2.04 (m, 4H), 1.79 (q, J = 10.8, 9.4 Hz, 1H), 1.66 – 1.54 (m, 1H), 1.19 (d, J = 6.2 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.7, 128.3, 127.7, 127.1, 83.3, 74.3, 57.0, 40.3, 25.4, 24.9, 24.7.

HRMS (ESI$^+$): calculated for $C_{17}H_{27}BNO2^+$ $[M+H]^+$: 288.2129, found: 288.2130.

合成转化

化合物 4 的合成

根据通用方法 C 对 **1a** (0.5 mmol, 79.5 mg)进行处理. 得到的混合液冷却至室温, 使用硅藻土过滤（正己烷冲洗）减压浓缩得到 **2a** 在手套箱中, 向 10 mL 的 Schlenk 管中依次加入 ^{t}BuOK (0. 5 mmol, 56.1 mg), THF (1.0 mL), **2a** (0.2 mmol). 将 Schlenk 管拿出手套箱加入 H_2O (0.2 mL). 反应体系在 80 ºC 下反应 2 小时. 反应混合物用水淬灭, 用 EA 萃取三次. 合并有机相, 用无水硫酸钠干燥. 浓缩溶剂, 粗产物用硅胶柱层析提纯, (洗脱剂为 DCM/MeOH/NH_4OH=10:1:0.1)以 75% yield 得到白色固体 **4** (24.5 mg).

4: **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.35 (d, J = 7.6 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 6.45 (d, J = 15.9 Hz, 1H), 6.19 (dt, J = 15.1, 7.1 Hz, 1H), 2.72 (t, J = 6.8 Hz, 2H), 2.45 (s, 3H), 2.43 - 2.37 (m, 2H), 1.66 (s, 1H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 137.5, 131.7, 128.6, 128.2, 127.2, 126.1, 51.4, 36.4, 33.5.

Synthesis of 5[5]

根据通用方法 C 对 **1a** (0.5 mmol, 79.5 mg)进行处理. 得到的混合液冷却至室温, 使用硅藻土过滤(正己烷冲洗)减压浓缩得到 **2a**. 室温下加入 MeOH (5.0 mL)、逐滴加入 KHF_2 (1.25 mL 饱和水溶液 (4.0–4.5 M), 5.0 mmol). 溶液在室温下搅拌 2 小时, 减压除去溶剂. 得到的白色固体溶解在热丙酮中, 加入 5.0 mL 乙酸乙酯. 使用乙醚洗涤沉淀 (5.0 mL×3), 得到的沉淀溶解在丙酮中, 减压除去溶剂得到黄色固体三氟硼酸钾盐 **5** (90.1 mg, 67% yield).

5: **^{1}H NMR** (400 MHz, Acetone- d_6) δ 7.50 (d, J = 7.3 Hz, 2H), 7.37 – 7.24 (m, 3H), 3.82 (d, J = 10.8 Hz, 1H), 3.57 – 3.46 (m, 1H), 2.89 (q, J = 9.2 Hz, 1H), 2.47 (s, 3H), 2.05 – 1.94 (m, 2H), 1.49 – 1.36 (m, 1H).

^{13}C NMR (101 MHz, Acetone- d_6) δ 139.3, 129.4, 129.0, 128.6, 77.6, 57.2, 38.8, 26.5.

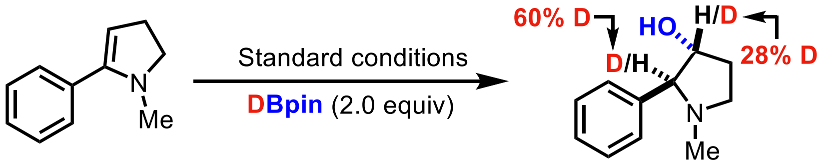
^{19}F NMR (376 MHz, Acetone-d_6) δ -145.27.

^{11}B NMR (128 MHz, Acetone-d_6) δ 4.54.

HRMS (ESI$^+$): calculated for $C_{11}H_{14}BF_3KNa^+$ $[M+Na]^+$: 290.0701, found: 290.0701.

机理研究

氘标记实验



1a

3a-d_2, 65%

化合物 **3a**-d_2为黄色固体, 以 65% 产率被合成(34.3 mg, eluent: DCM/MeOH = 30/1), 合成步骤参考通用方法 C, 使用烯胺 **1a** (47.7 mg, 0.3 mmol, 1.0 equiv), Co(acac)$_2$ (3.9 mg, 0.015 mmol, 5 mol%), **L6** (6.8 mg, 0.018 mmol, 6 mol%), DBpin (77.4 mg, 0.6 mmol, 2.0 equiv), n-hexane (1.0 mL), NaOH (0.5 mL, 3.0 M) and H_2O_2 (0.5 mL, 30%). ^{1}H NMR 谱图显示氘沿着碳链各个原子上的氘含量(依次为 60%, 28%).

3a-d_2**: ^{1}H NMR (400 MHz, CDCl$_3$)** δ 7.37 – 7.30 (m, 4H), 7.30 – 7.23 (m, 1H), 4.21 – 3.97 (m, 0.72H), 3.21 – 3.07 (m, 1H), 2.97 – 2.85 (m, 0.40 H), 2.54 (q, J = 9.1 Hz, 1H), 2.43 (br, 1H), 2.36 – 2.21 (m, 1H), 2.14 (s, 3H), 1.77 – 1.65 (m, 1H).

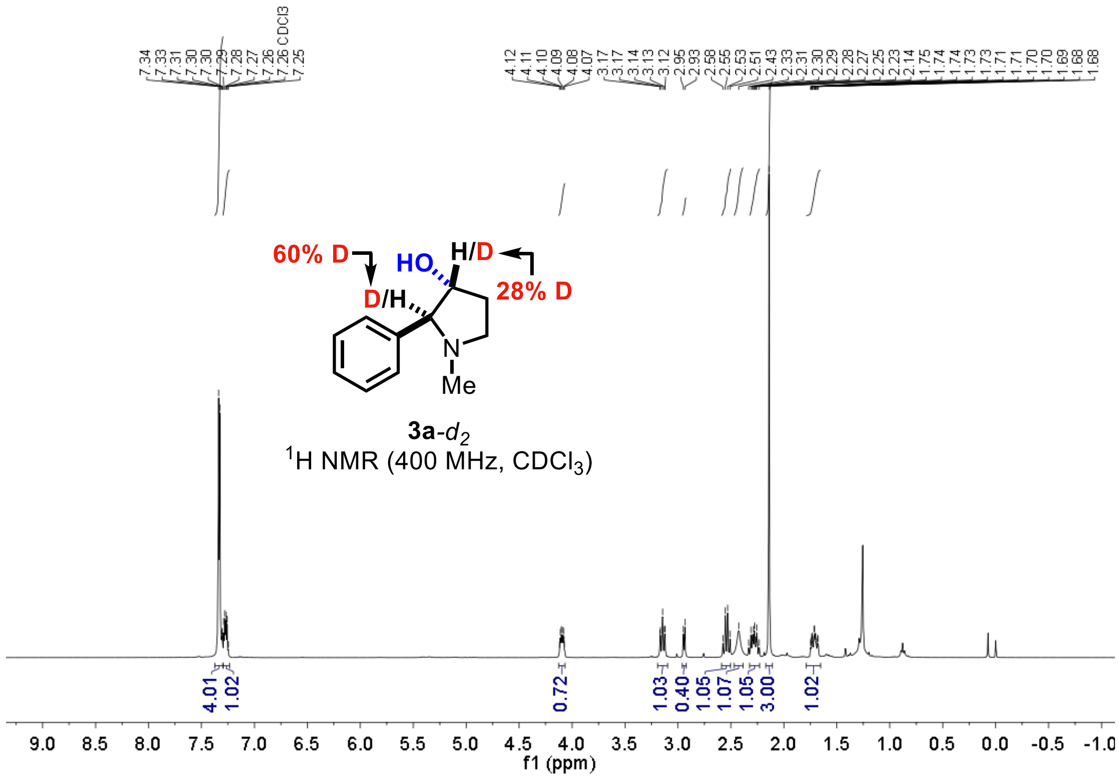


图 **S1. 3a**-d_2 的 ^{1}H NMR 谱图.

Figure S1. ^{1}H NMR spectrum for compound **3a**-d_2

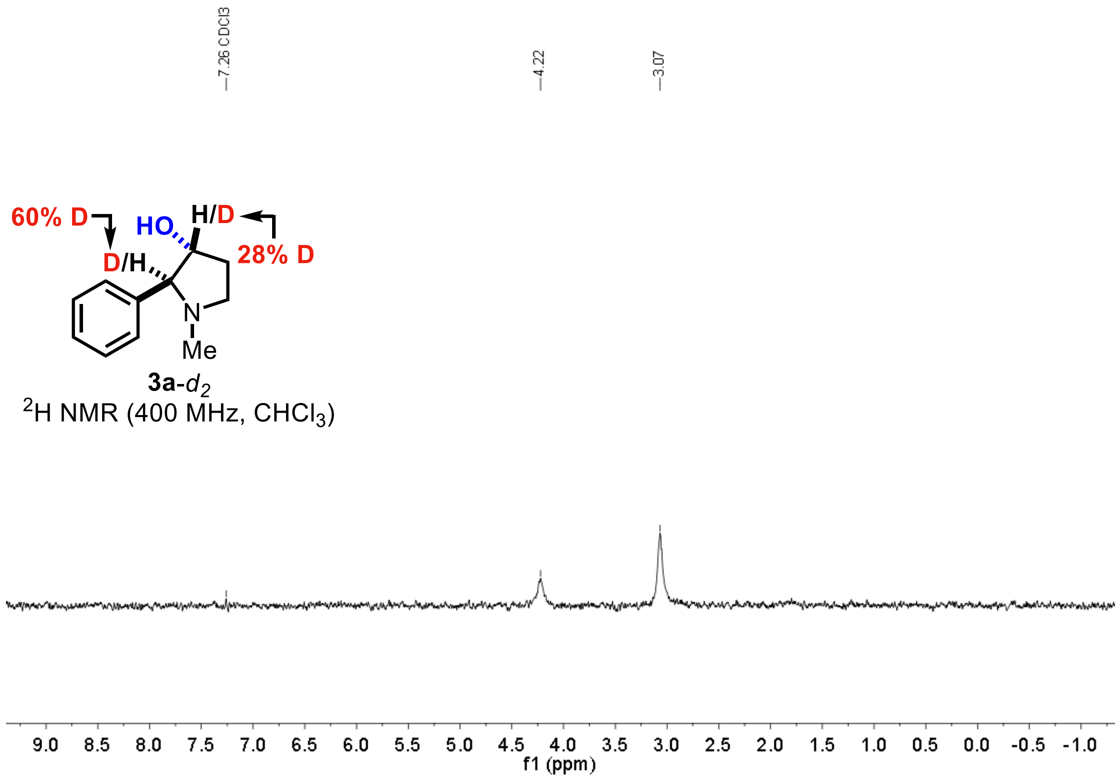


图 **S1. 3a**-d_2 的 ^{2}H NMR 谱图.

Figure S2. ^{2}H NMR spectrum for compound **3a**-d_2**.**

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3. Dhayalan, V., Gadekar, S. C., Alassad, Z., & Milo, A. Unravelling mechanistic features of organocatalysis with in situ modifications at the secondary sphere. *Nat. Chem.*, **2019**, *11*, 543-551.
4. Hou, H., Xie, J., Yan, P, Zhou Q. Iridium-catalyzed asymmetric hydrogenation of cyclic enamines *J Am Chem Soc*. **2009**, 131: 1366-1367.
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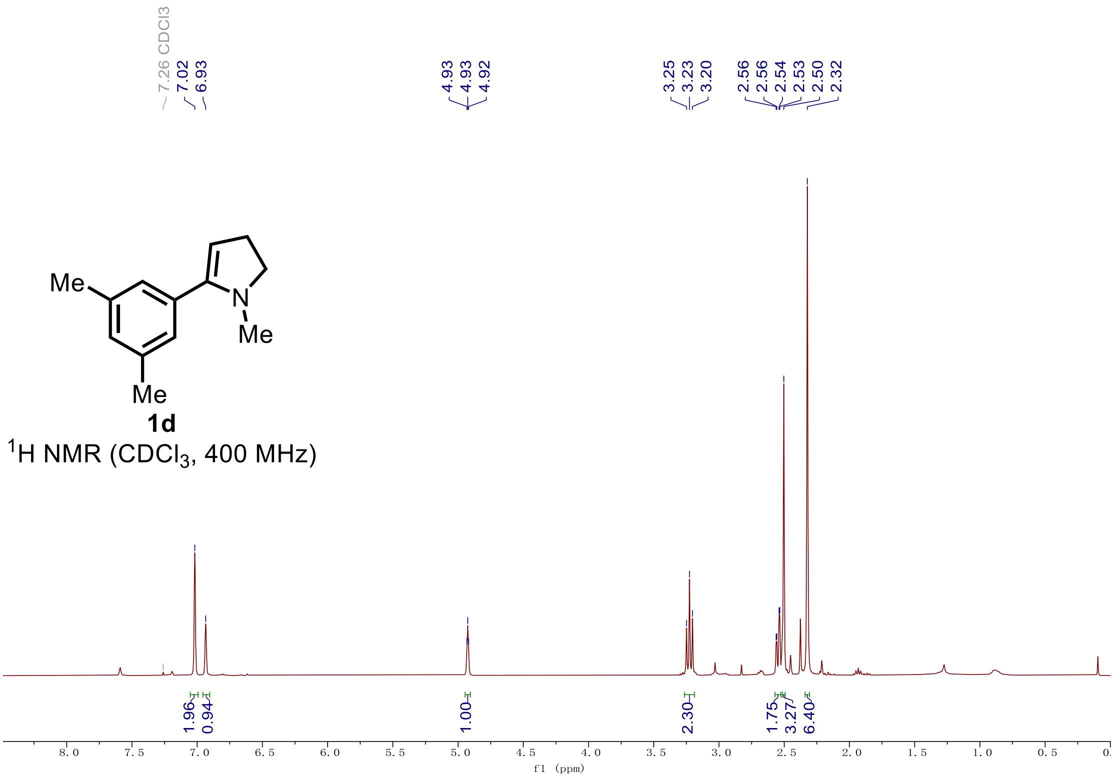
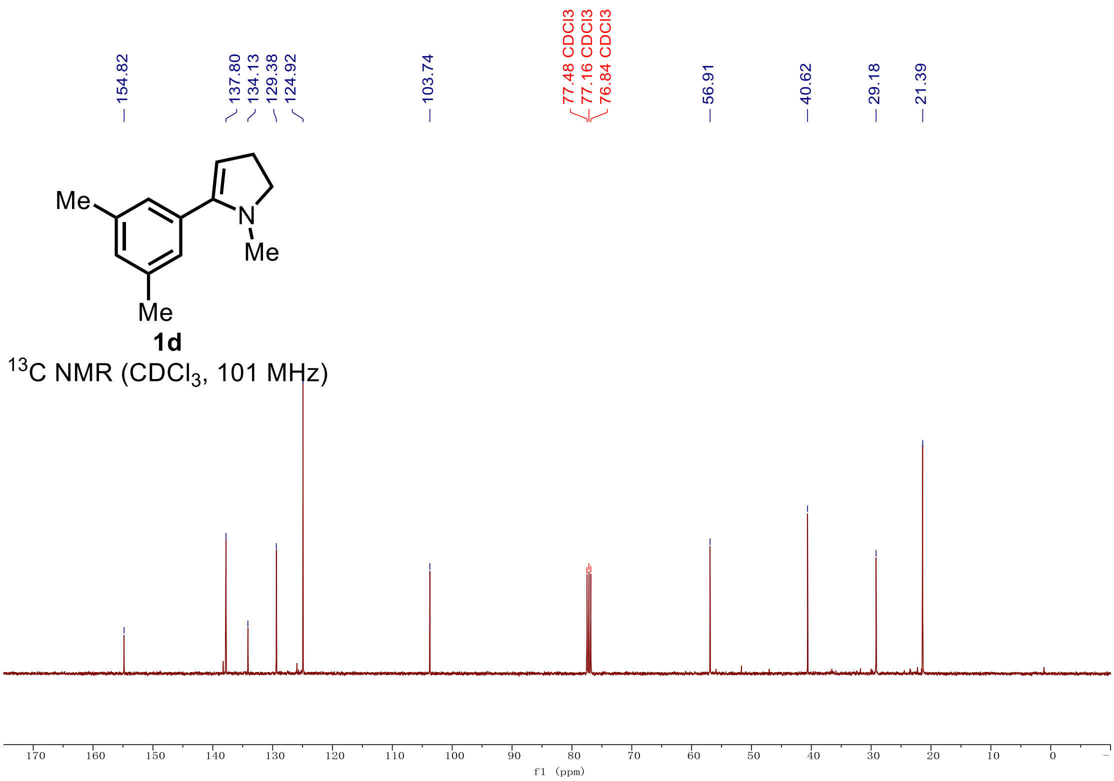
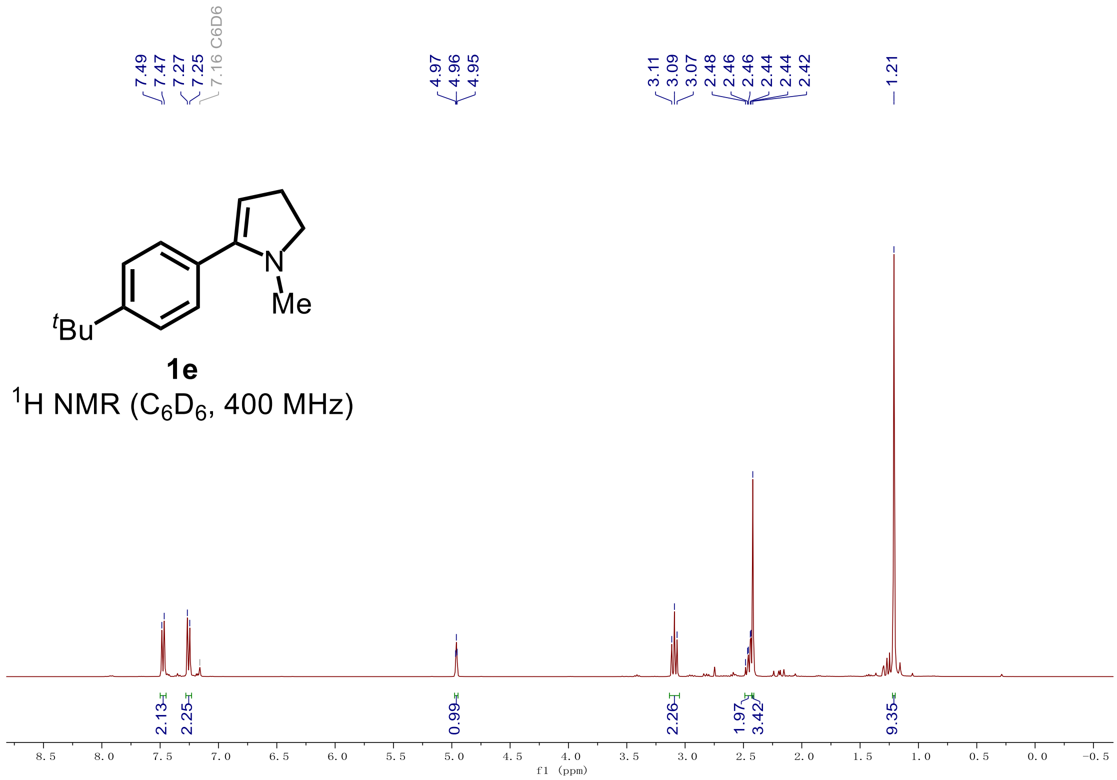
核磁共振谱图



7.26 CDCl3
7.02
6.93
4.93
4.93
4.92
3.25
3.23
3.20
2.56
2.56
2.54
2.53
2.50
2.32
Me
Me
N
Me
1d
^{1}H NMR (CDCl$_3$, 400 MHz)
1.96
0.94
1.00
2.30
1.75
3.27
6.40
f1 (ppm)

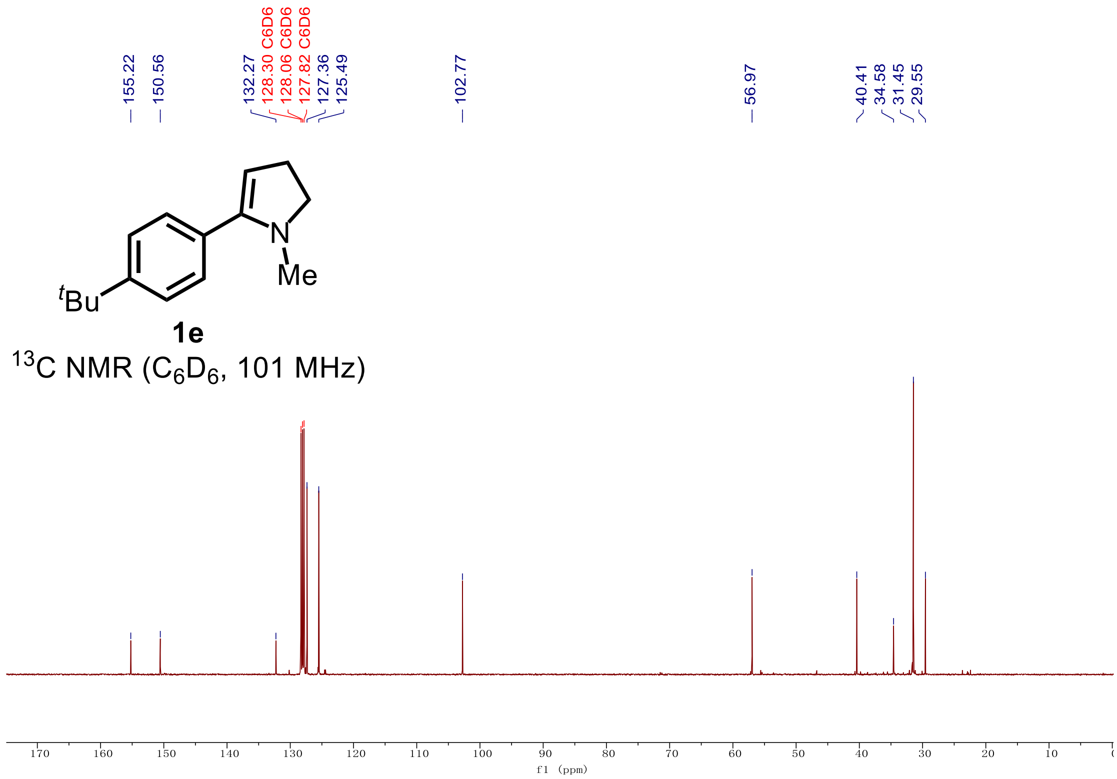


154.82
137.80
134.13
129.38
124.92
103.74
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
56.91
40.62
29.18
21.39
Me
Me
N
Me
1d
^{13}C NMR (CDCl$_3$, 101 MHz)
f1 (ppm)



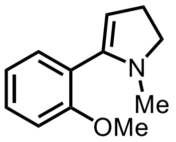
1e

^{1}H NMR (C_6D_6, 400 MHz)



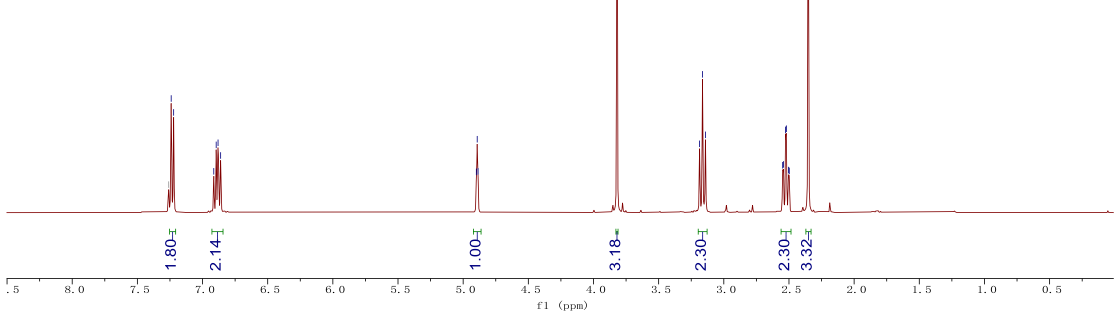
1e

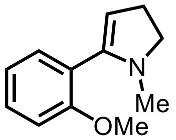
^{13}C NMR (C_6D_6, 101 MHz)



1f

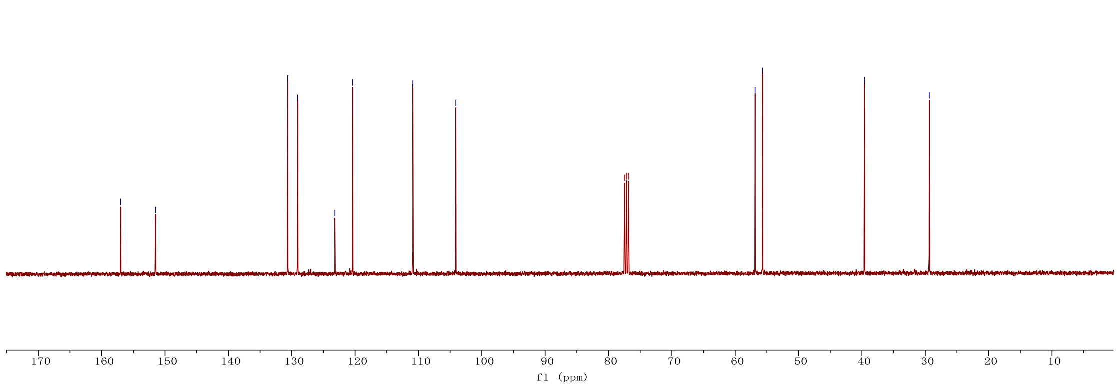
^{1}H NMR ($CDCl_3$, 400 MHz)

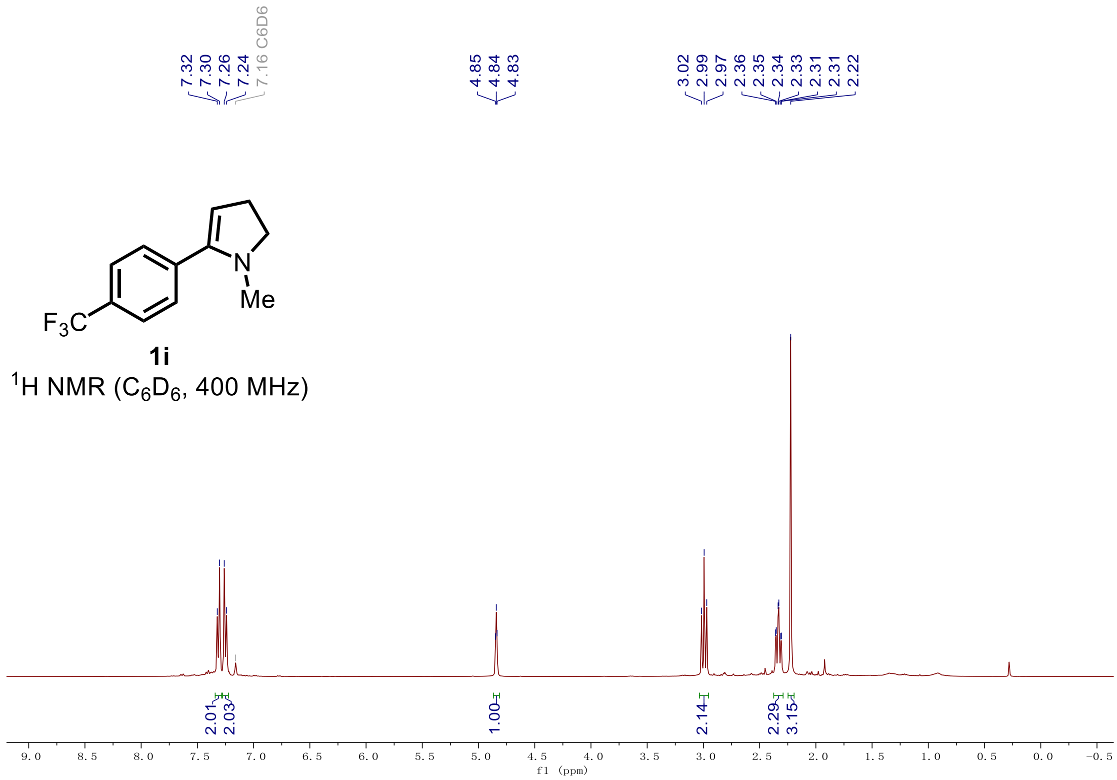




1f

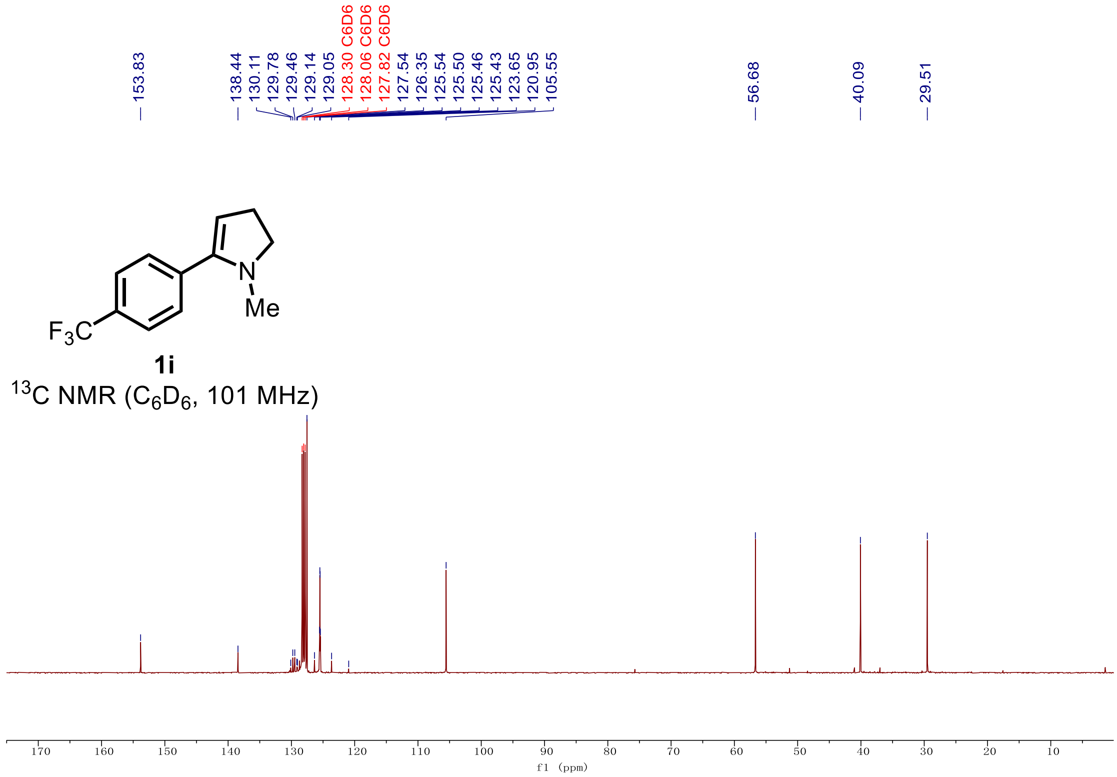
^{13}C NMR ($CDCl_3$, 101 MHz)





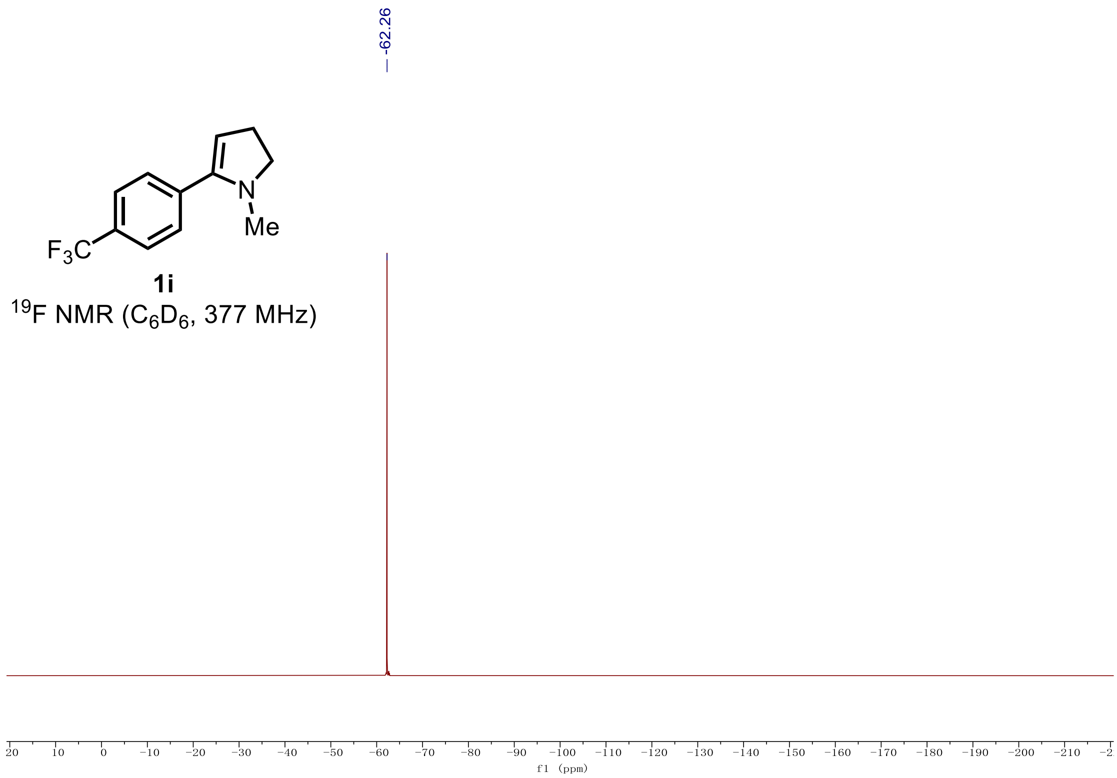
1i

^{1}H NMR (C_6D_6, 400 MHz)



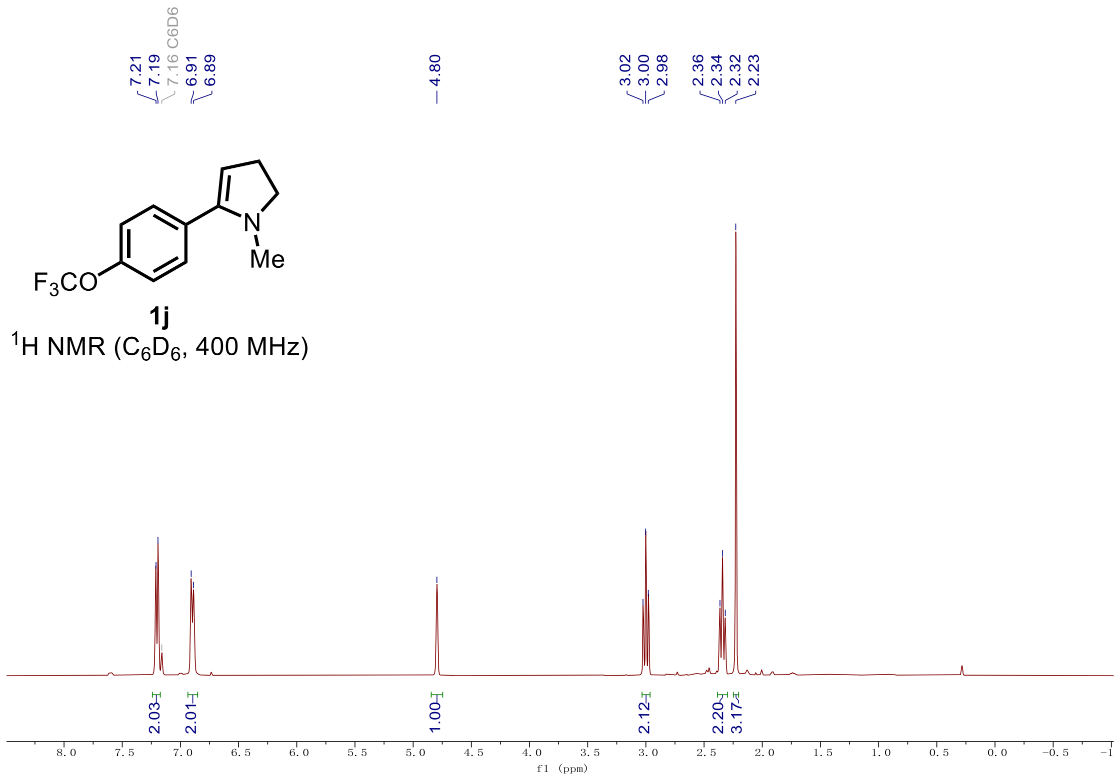
1i

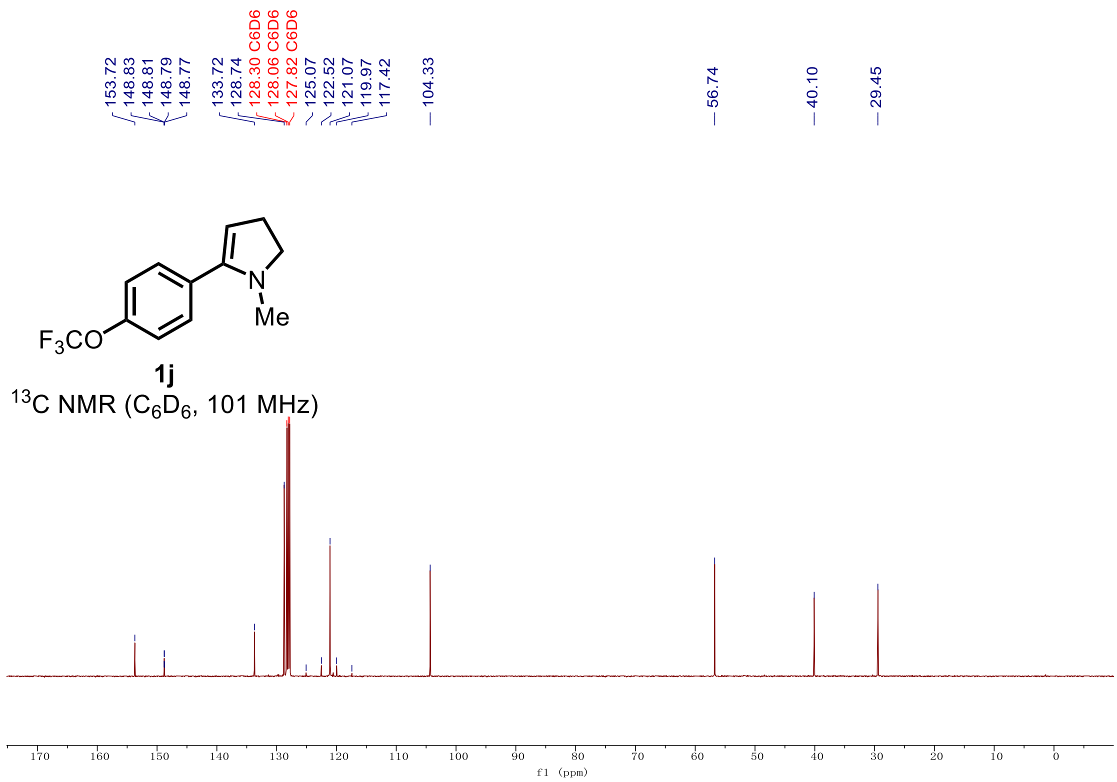
^{13}C NMR (C_6D_6, 101 MHz)

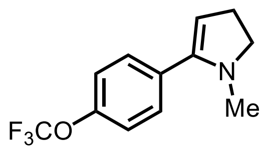


1i

^{19}F NMR (C_6D_6, 377 MHz)

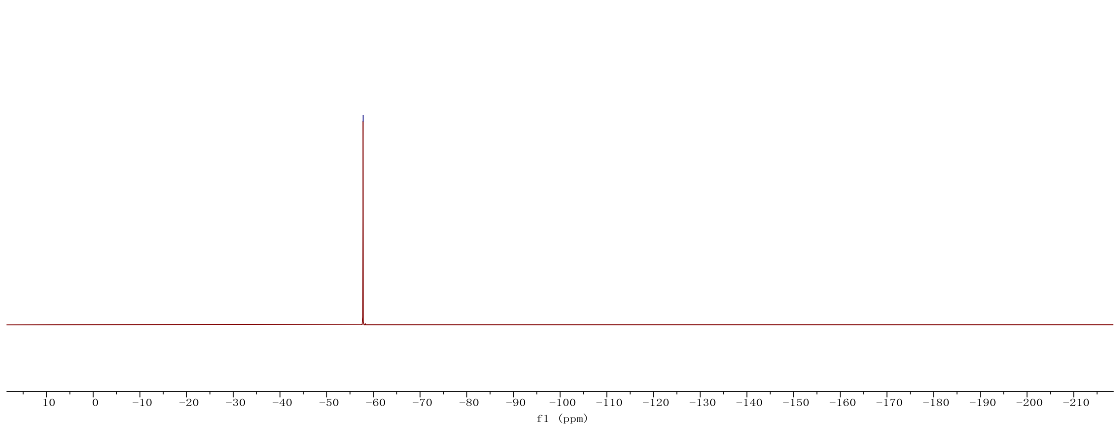

7.21
7.19
7.16 C6D6
6.91
6.89
4.80
3.02
3.00
2.98
2.36
2.34
2.32
2.23
F3CO
N
Me
1j
1H NMR (C6D6, 400 MHz)
2.03
2.01
1.00
2.12
2.20
3.17
f1 (ppm)

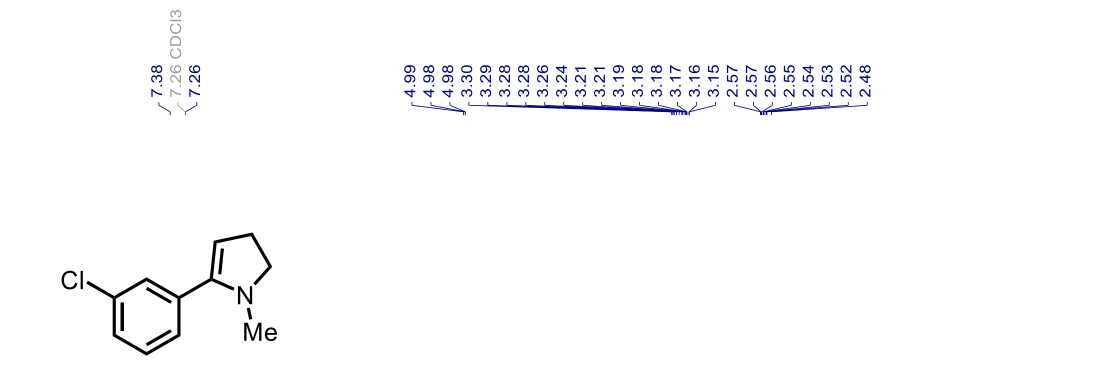

153.72
148.83
148.81
148.79
148.77
133.72
128.74
128.30 C6D6
128.06 C6D6
127.82 C6D6
125.07
122.52
121.07
119.97
117.42
104.33
56.74
40.10
29.45
F3CO
N
Me
1j
13C NMR (C6D6, 101 MHz)
f1 (ppm)



1j

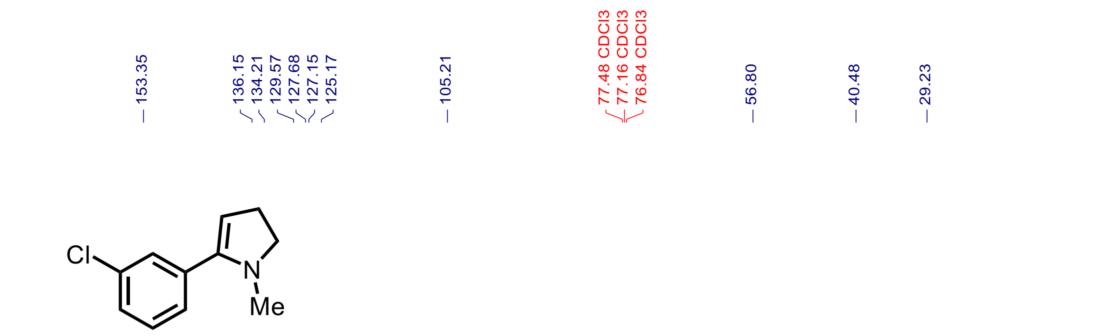
^{19}F NMR (C_6D_6, 377 MHz)





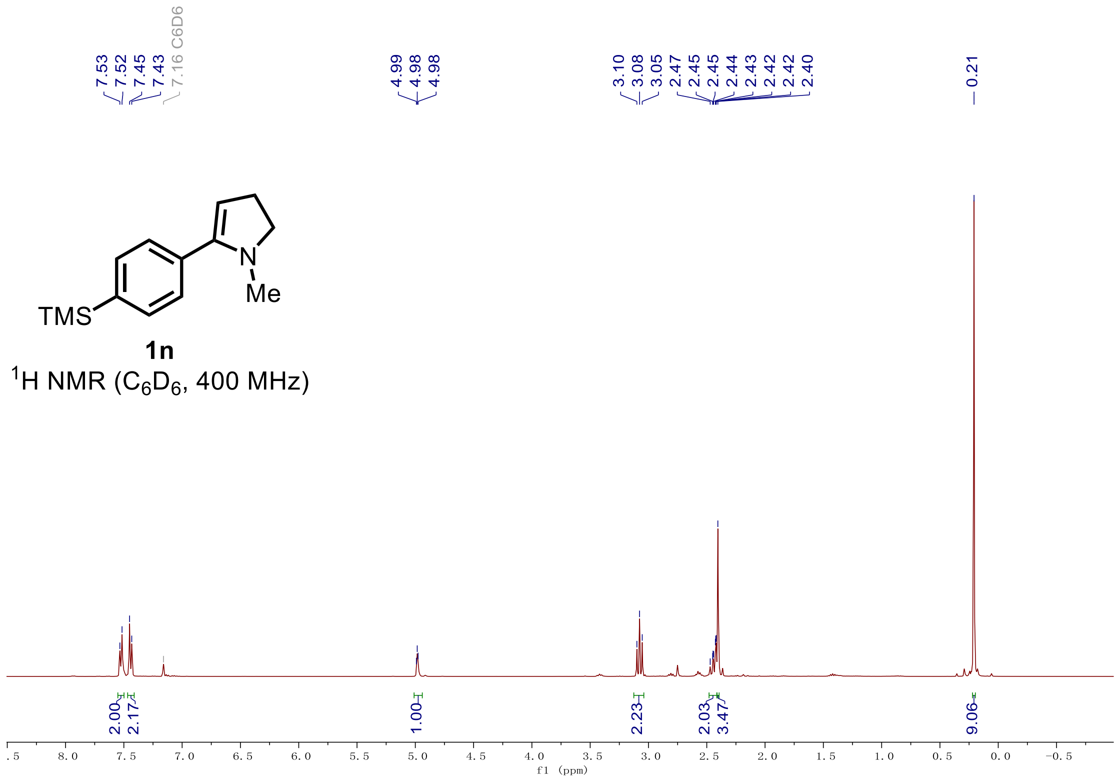
1m

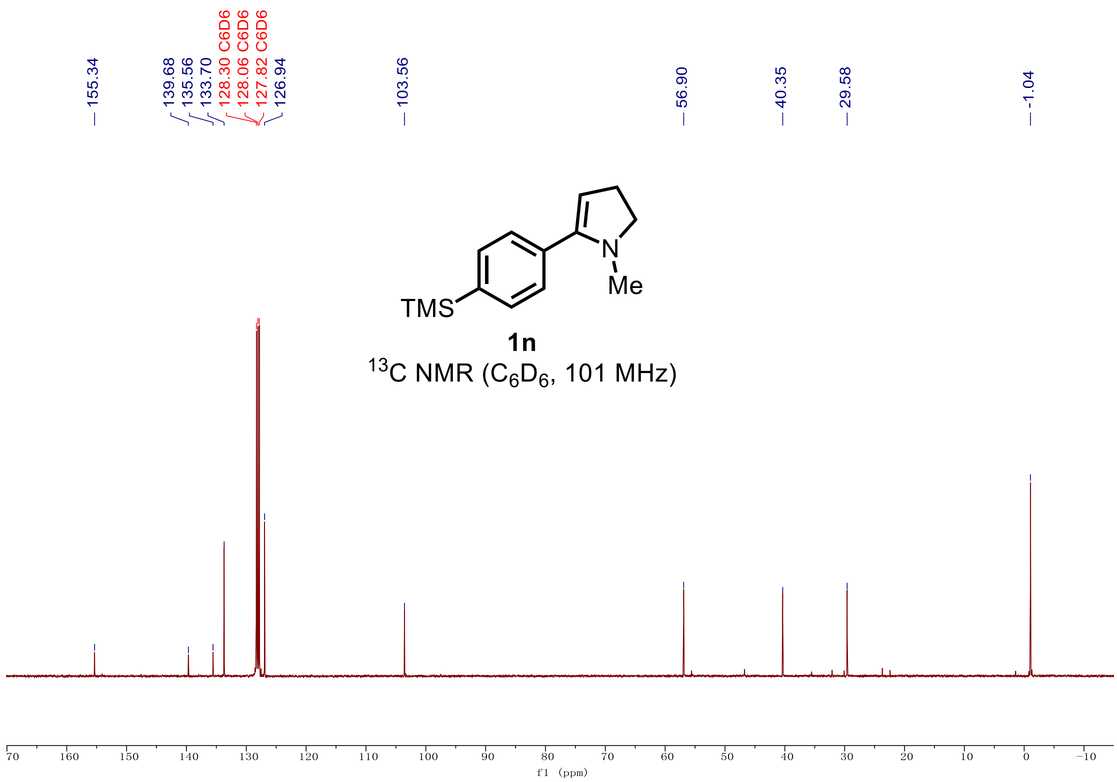
^{1}H NMR ($CDCl_3$, 400 MHz)

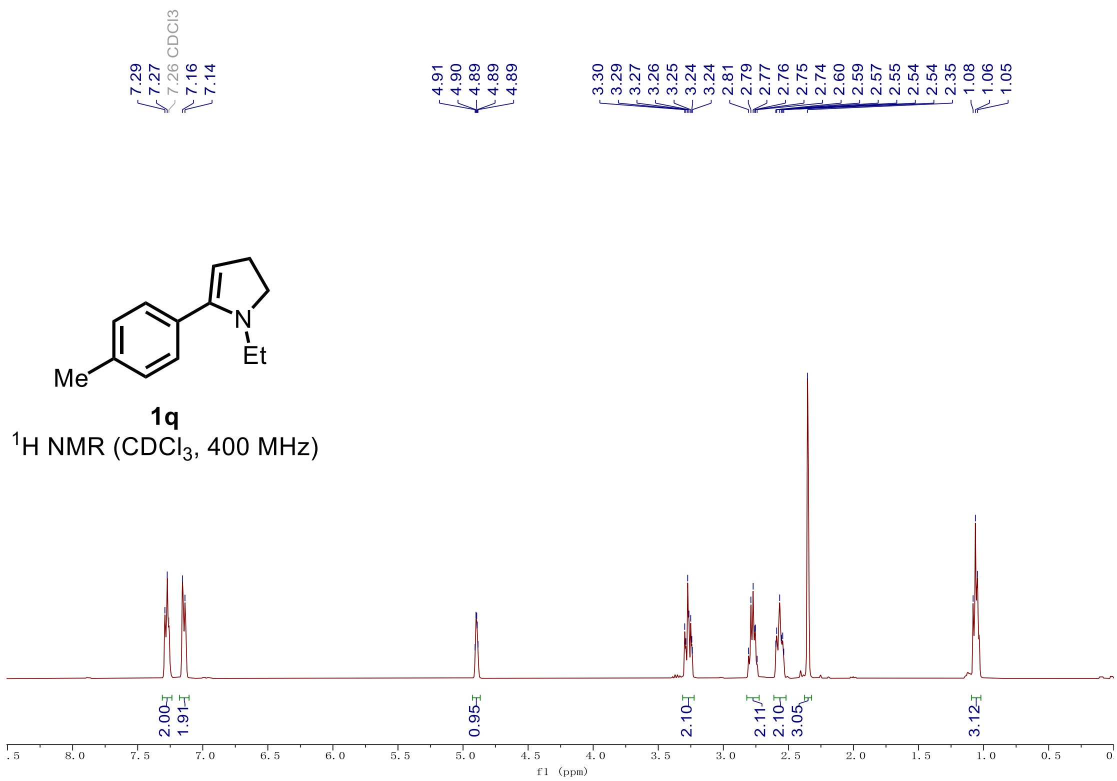


1m

^{13}C NMR ($CDCl_3$, 101 MHz)


7.53
7.52
7.45
7.43
7.16 C6D6
4.99
4.98
4.98
3.10
3.08
3.05
2.47
2.45
2.45
2.44
2.43
2.42
2.42
2.40
0.21
TMS
N
Me
1n
^{1}H NMR (C_6D_6, 400 MHz)
2.00
2.17
1.00
2.23
2.03
3.47
9.06
f1 (ppm)


155.34
139.68
135.56
133.70
128.30 C6D6
128.06 C6D6
127.82 C6D6
126.94
103.56
56.90
40.35
29.58
-1.04
TMS
N
Me
1n
^{13}C NMR (C_6D_6, 101 MHz)
f1 (ppm)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7.27
7.26 CDCl3
7.16
7.14
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4.90
4.89
4.89
4.89
3.30
3.29
3.27
3.26
3.25
3.24
3.24
2.81
2.79
2.77
2.76
2.75
2.74
2.60
2.59
2.57
2.55
2.54
2.54
2.35
1.08
1.06
1.05
Me
N
Et
1q
1H NMR (CDCl3, 400 MHz)
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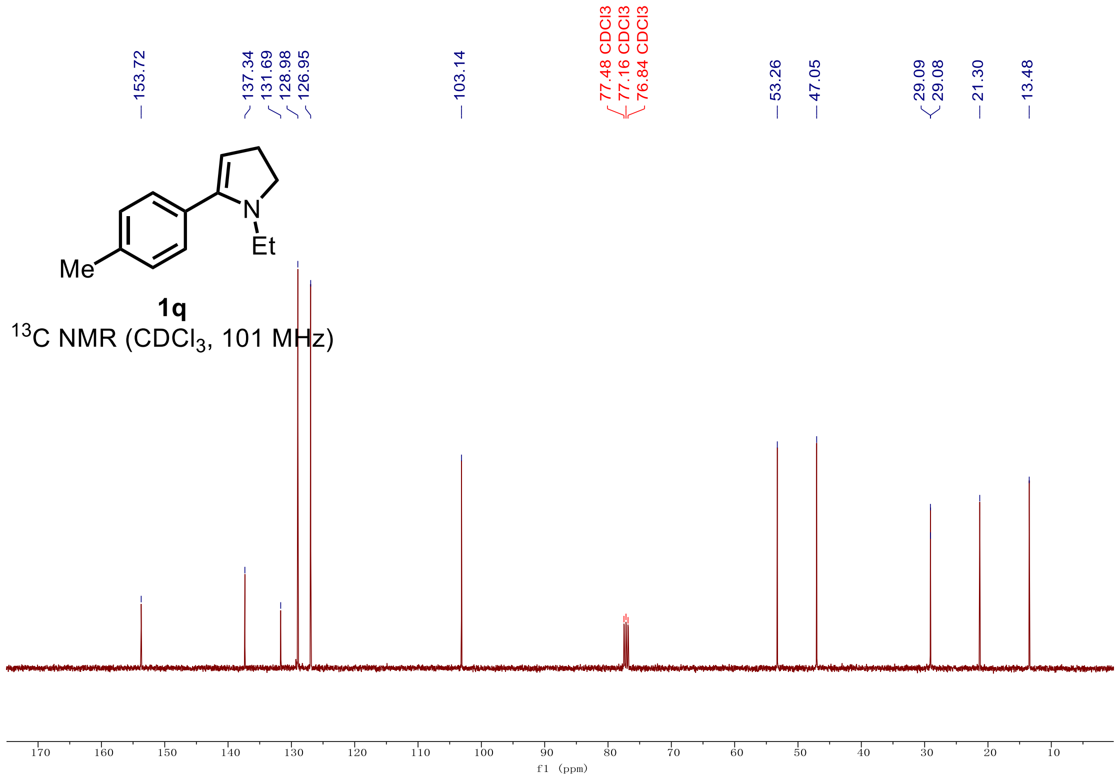
1.91
0.95
2.10
2.11
2.10
3.05
3.12
f1 (ppm)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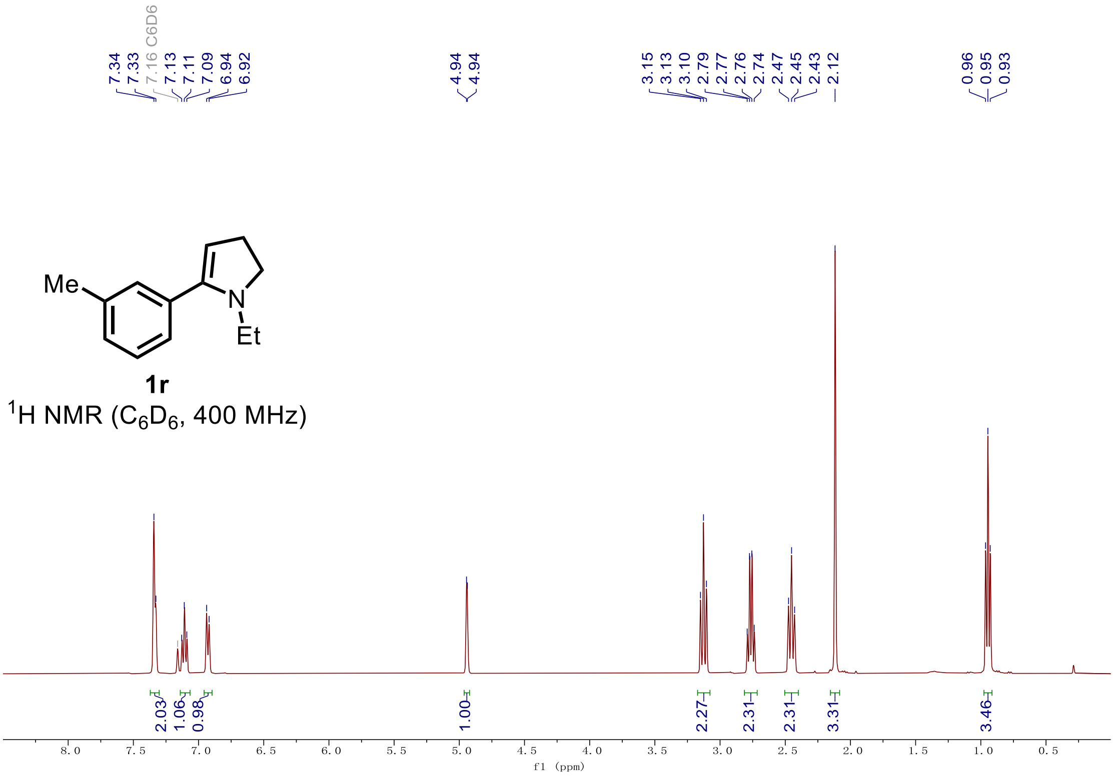
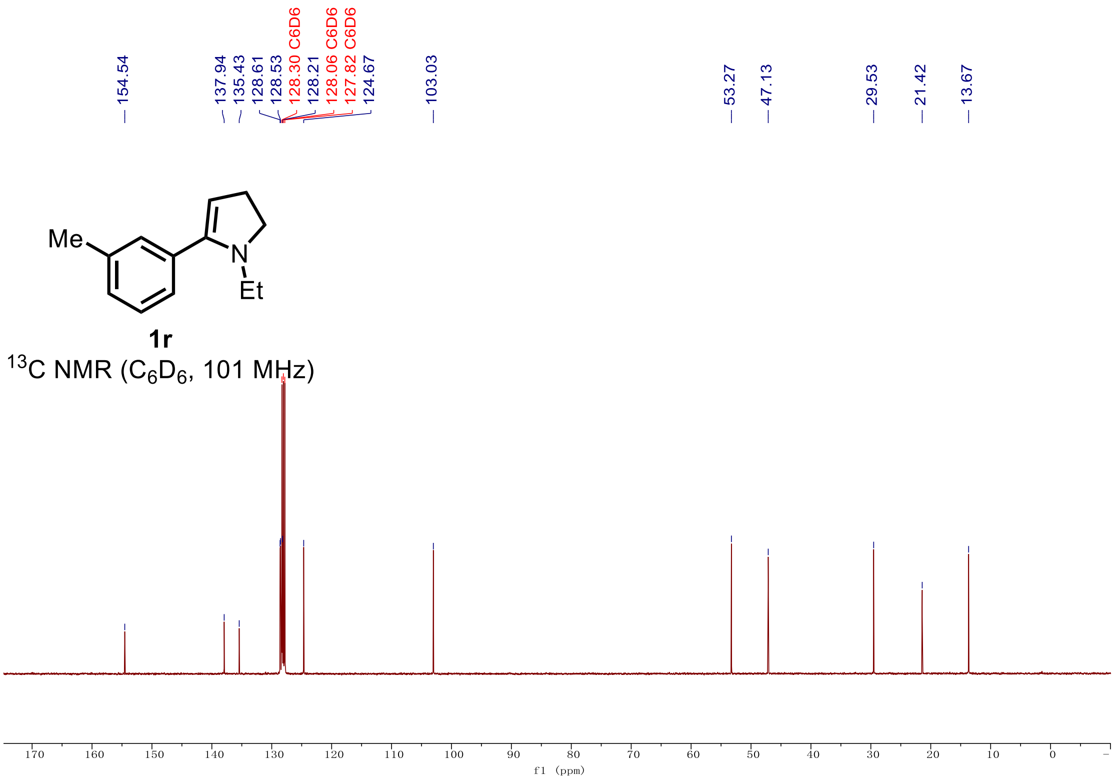
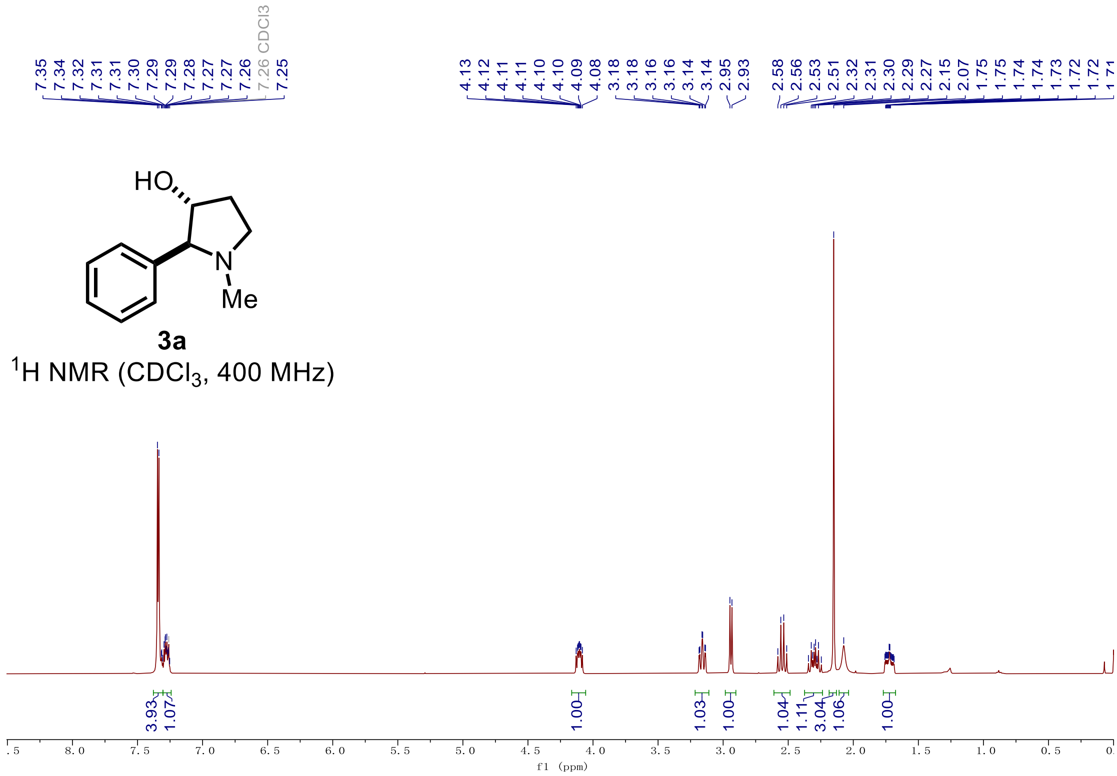
137.34
131.69
128.98
126.95
103.14
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
53.26
47.05
29.09
29.08
21.30
13.48
Me
N
Et
1q
13C NMR (CDCl3, 101 MHz)
f1 (ppm)

^{13}C NMR spectrum of **1p** (101 MHz, $CDCl_3$)

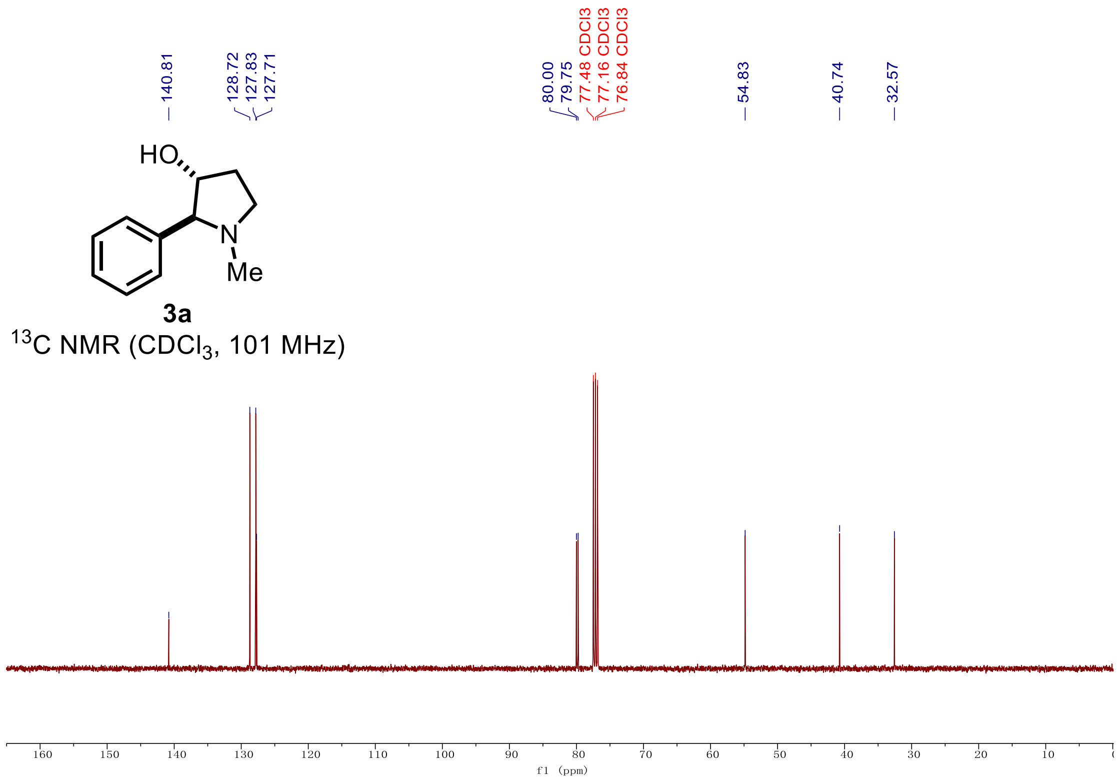






3a

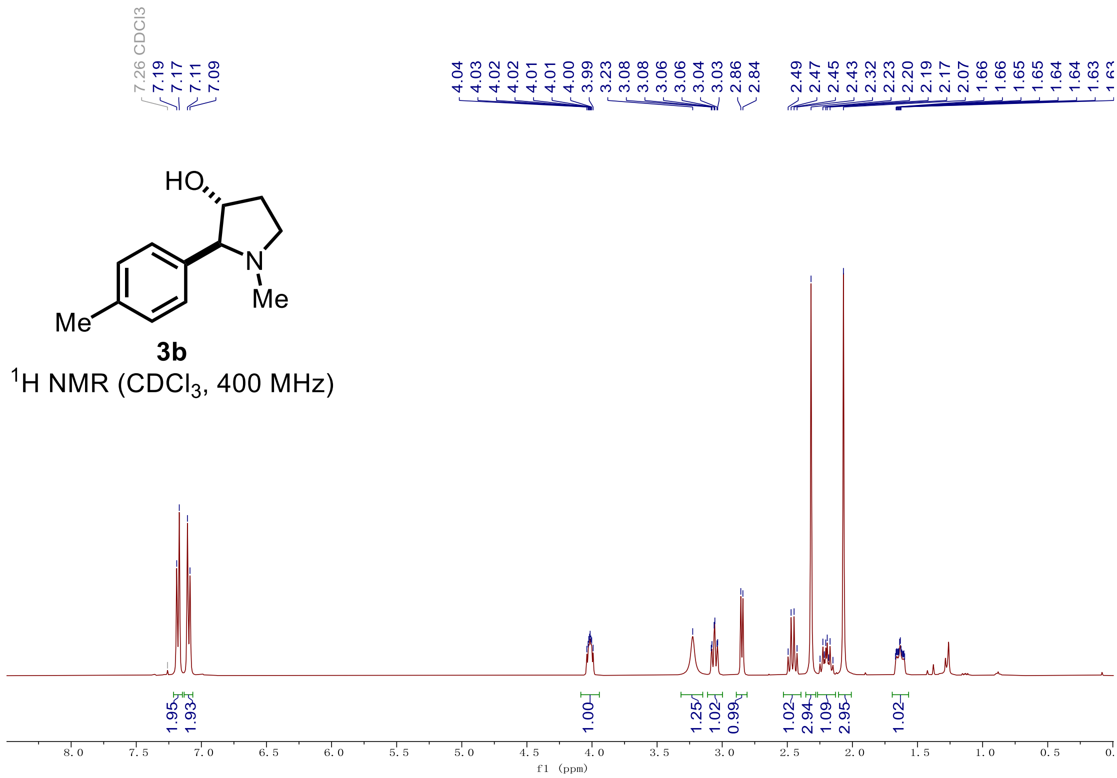
^{1}H NMR ($CDCl_3$, 400 MHz)

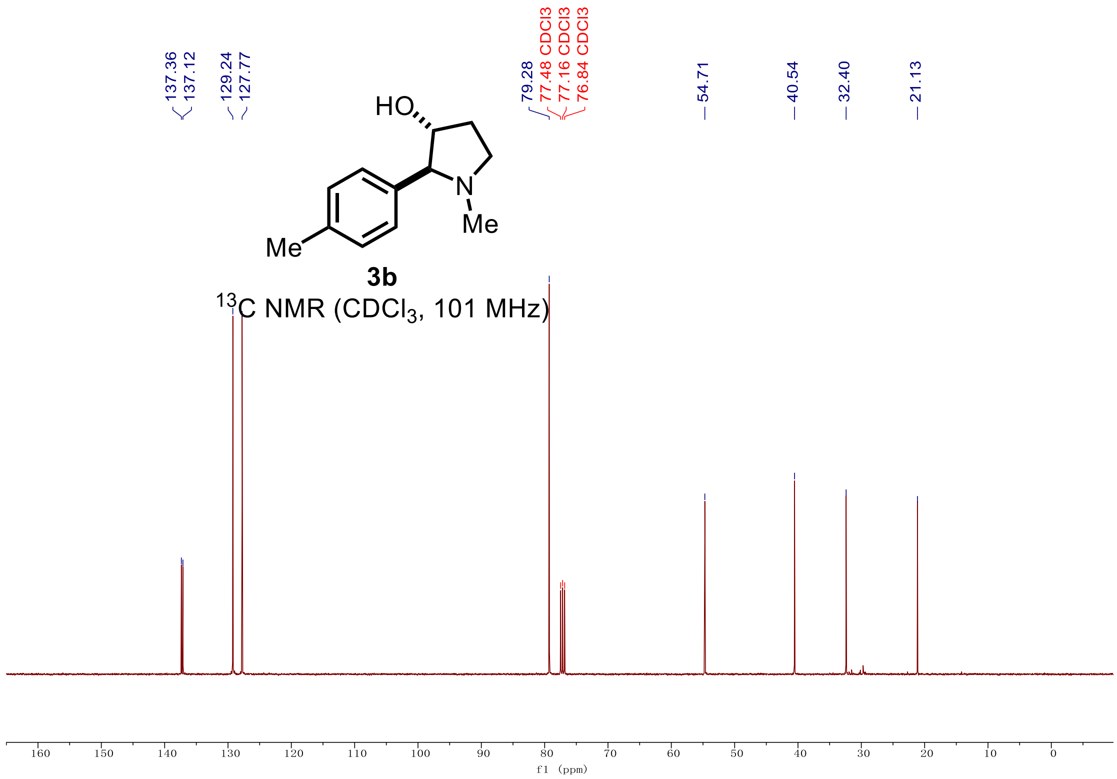


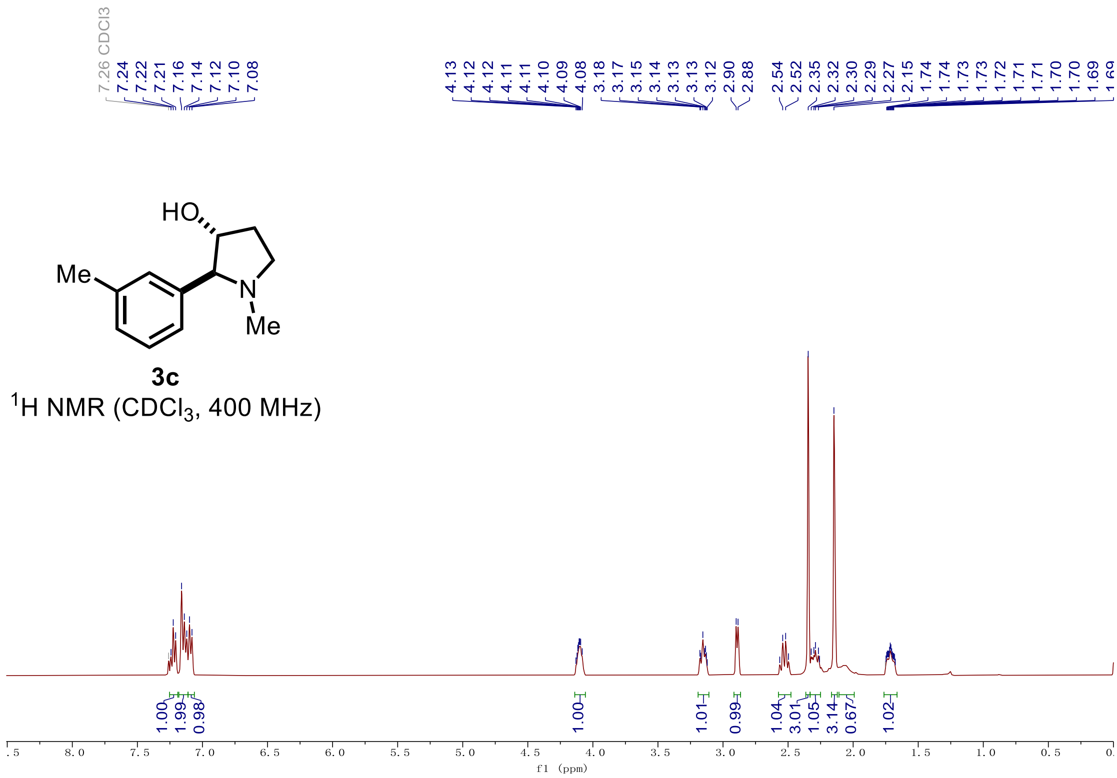
3a

^{13}C NMR ($CDCl_3$, 101 MHz)

1

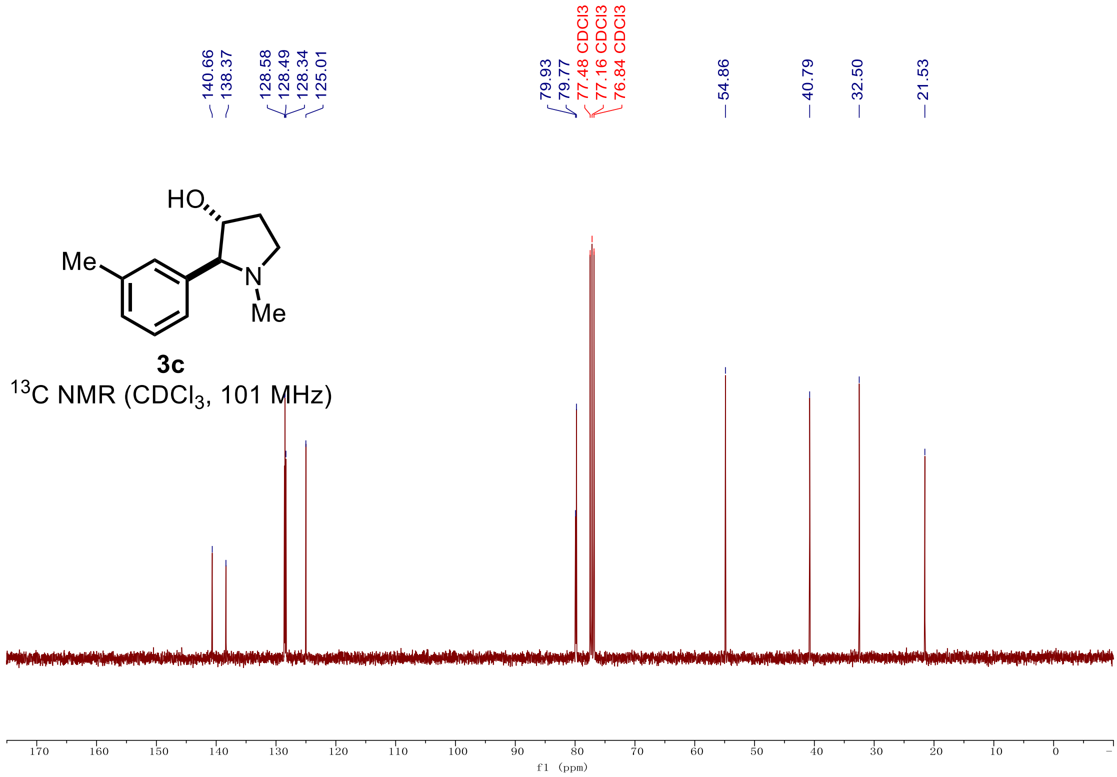

7.26 CDCl3
7.19
7.17
7.11
7.09
4.04
4.03
4.02
4.02
4.01
4.01
4.00
3.99
3.23
3.08
3.08
3.06
3.06
3.04
3.03
2.86
2.84
2.49
2.47
2.45
2.43
2.32
2.23
2.20
2.19
2.17
2.07
1.66
1.66
1.65
1.64
1.64
1.63
HO
N
Me
Me
3b
¹H NMR (CDCl3, 400 MHz)
1.95
1.93
1.00
1.25
1.02
0.99
1.02
2.94
1.09
2.95
1.02
f1 (ppm)


137.36
137.12
129.24
127.77
79.28
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
54.71
40.54
32.40
21.13
HO
N
Me
Me
3b
¹³C NMR (CDCl3, 101 MHz)
f1 (ppm)



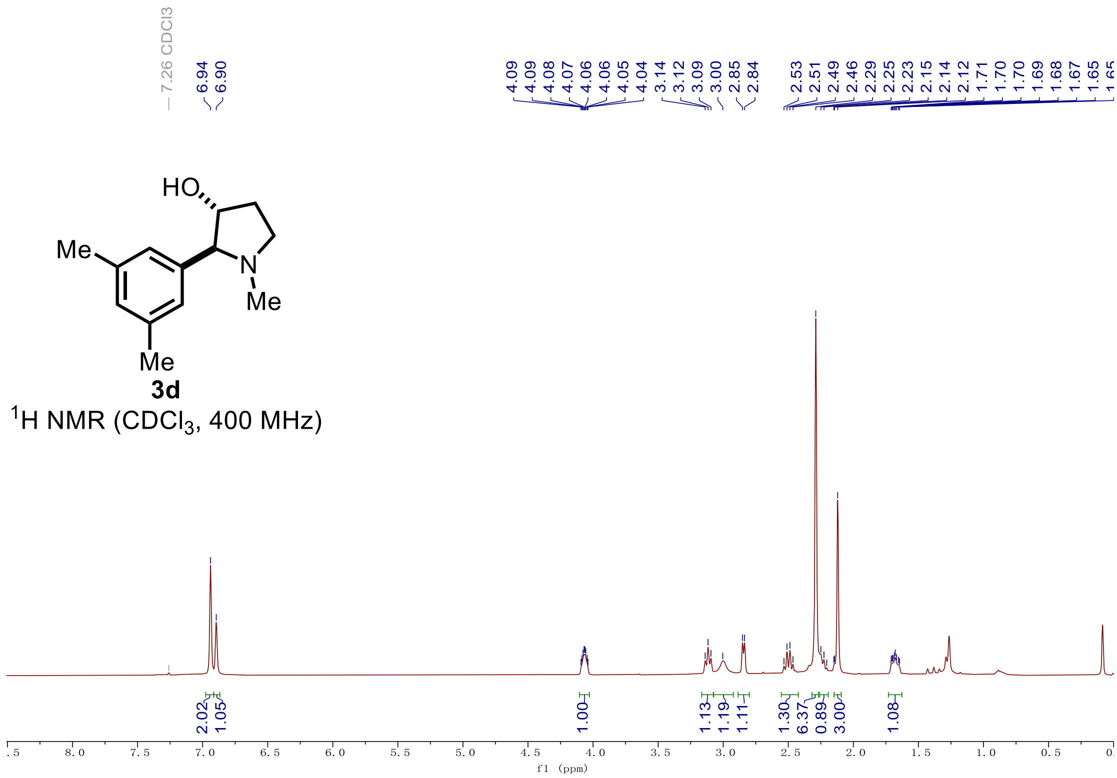
3c

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



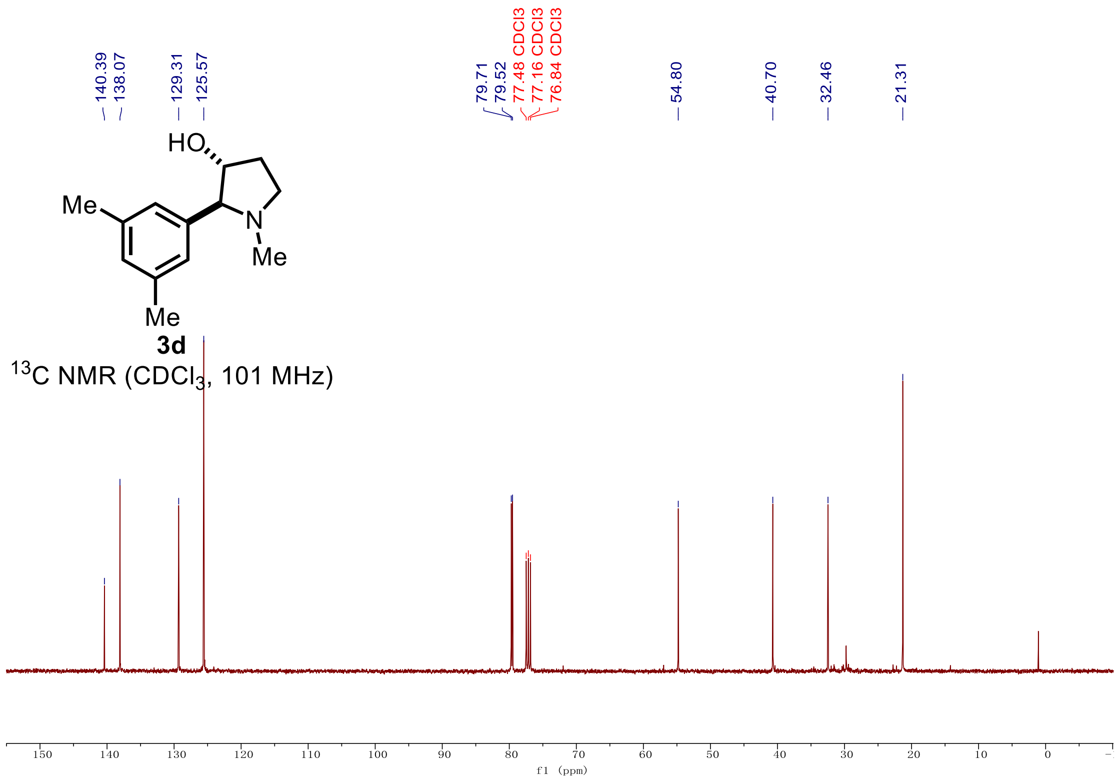
3c

^{13}C NMR ($CDCl_3$, 101 MHz)



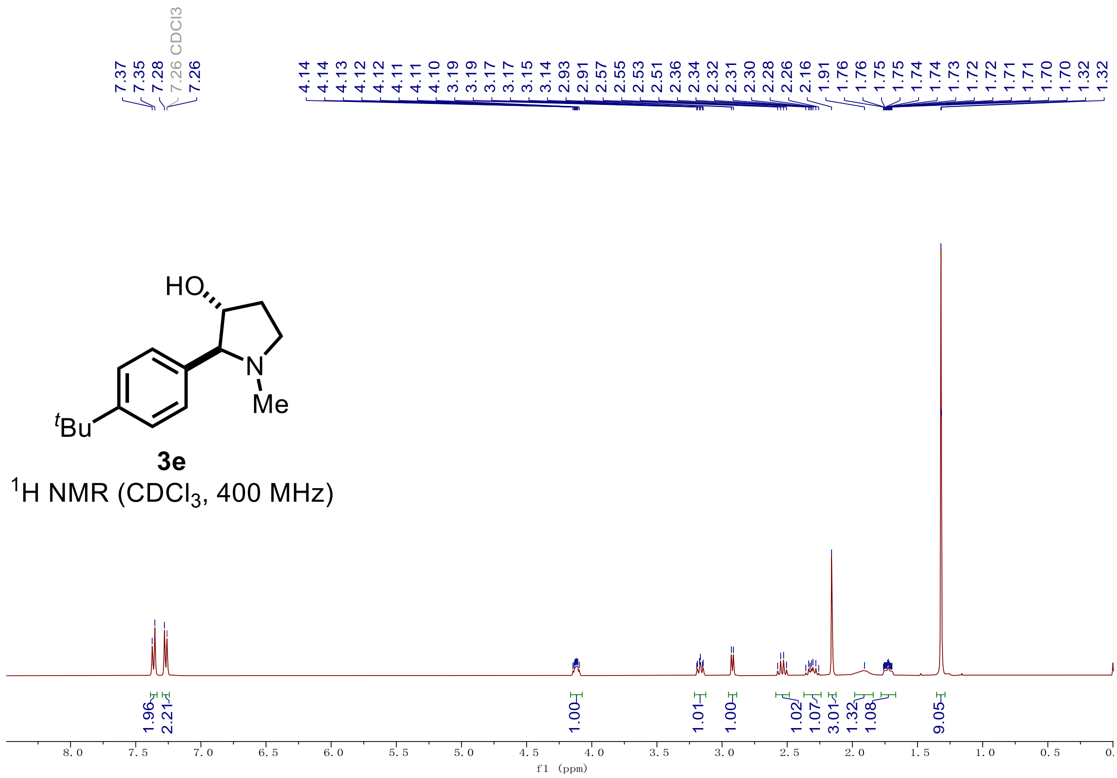
3d

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

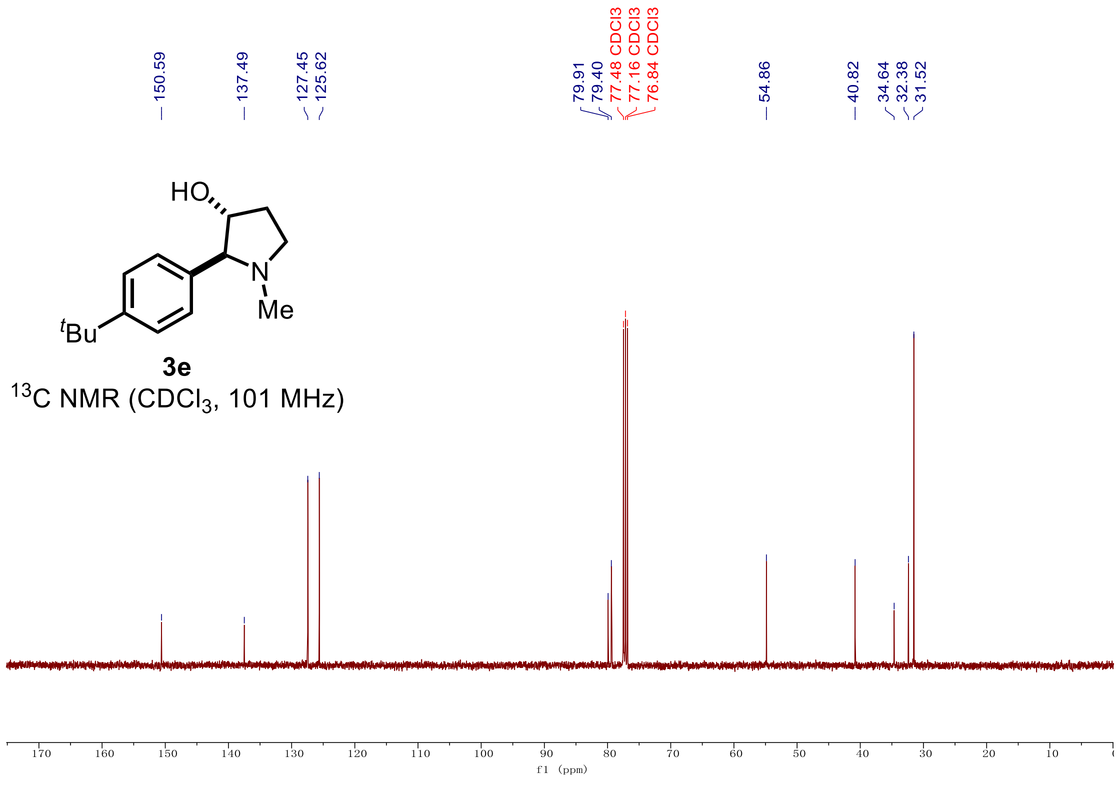


3d

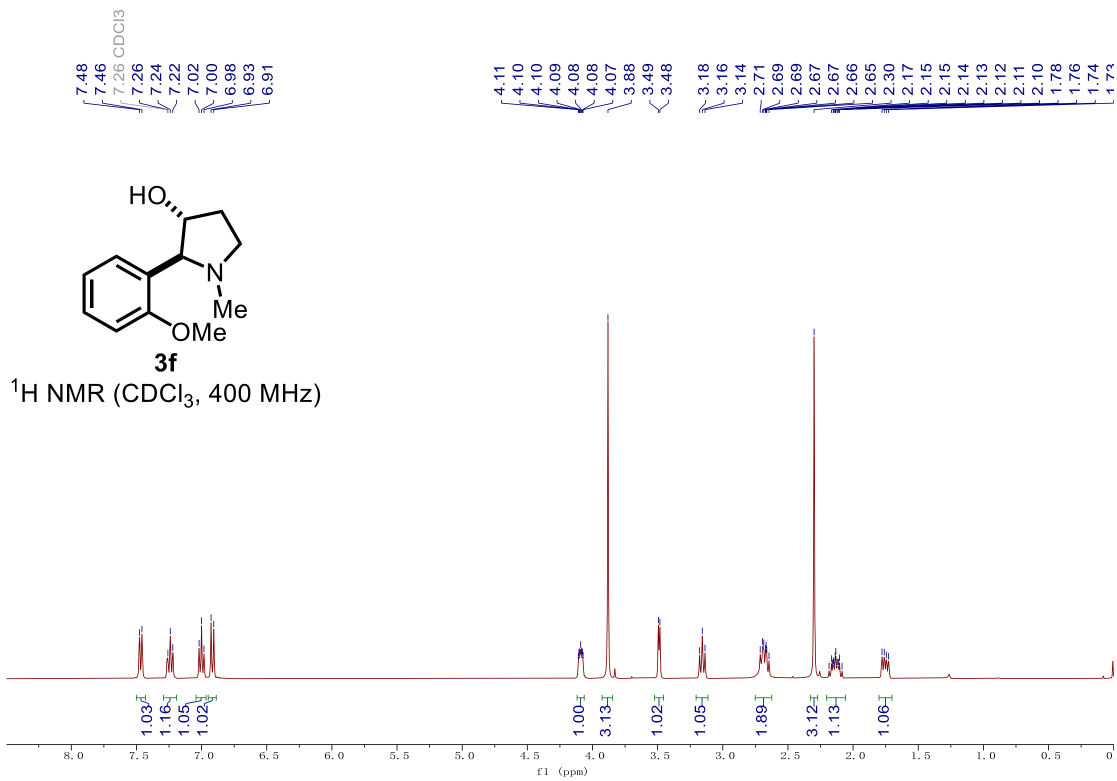
^{13}C NMR ($CDCl_3$, 101 MHz)



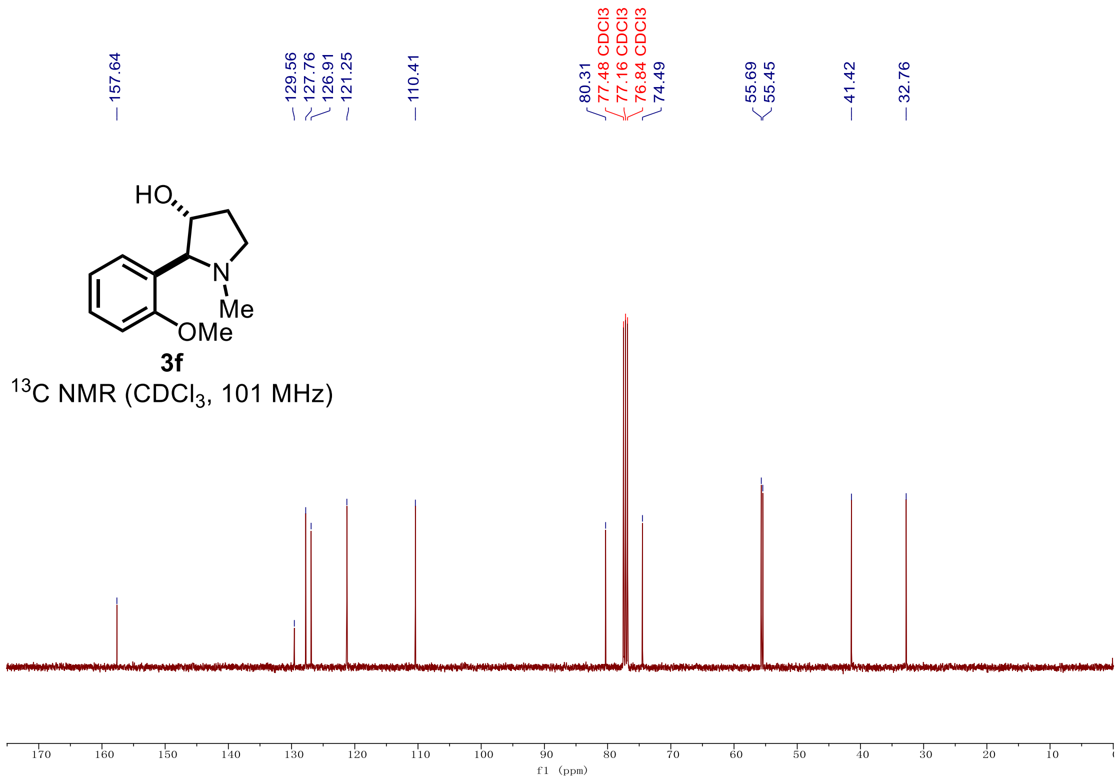
7.37
7.35
7.28
7.26 CDCl3
7.26
4.14 4.14 4.13 4.12 4.12 4.11 4.11 4.10 3.19 3.19 3.17 3.17 3.15 3.14 2.93 2.91 2.57 2.55 2.53 2.51 2.36 2.34 2.32 2.31 2.30 2.28 2.26 2.16 1.91 1.76 1.76 1.75 1.75 1.74 1.74 1.73 1.72 1.72 1.71 1.71 1.70 1.32 1.32
HO
N
Me
tBu
3e
1H NMR (CDCl3, 400 MHz)
1.96
2.21
1.00
1.01
1.00
1.02
1.07
3.01
1.32
1.08
9.05
f1 (ppm)



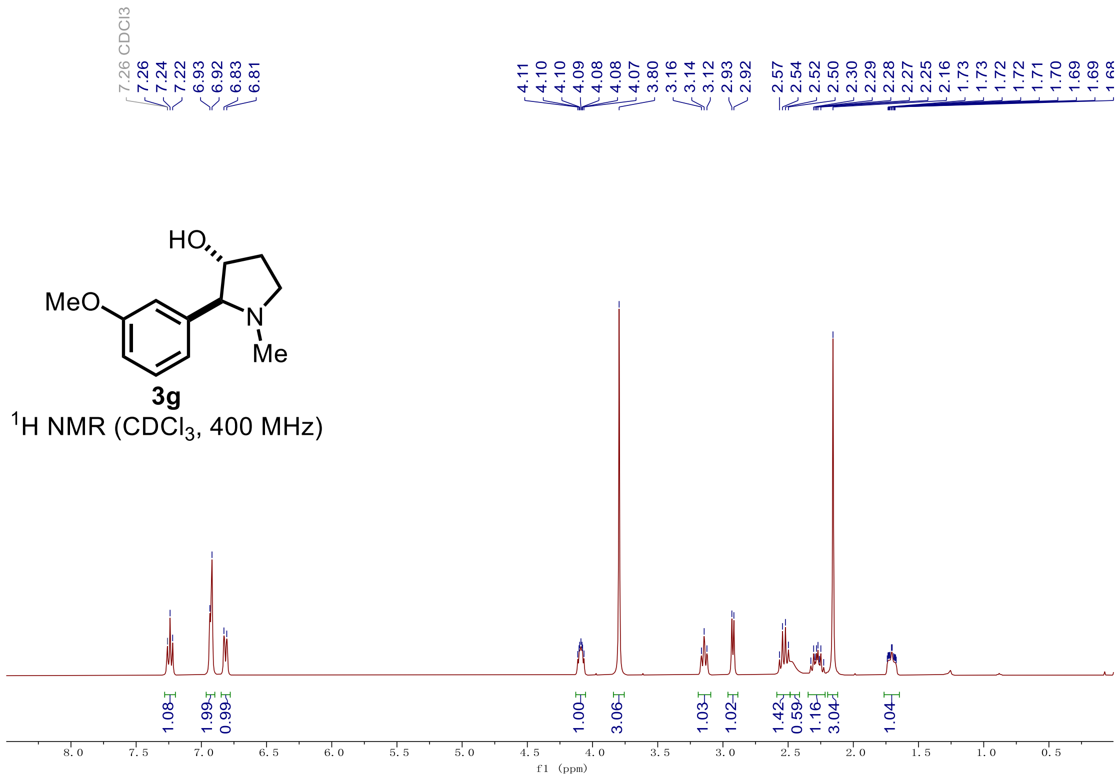
150.59
137.49
127.45
125.62
79.91
79.40
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
54.86
40.82
34.64
32.38
31.52
HO
N
Me
tBu
3e
13C NMR (CDCl3, 101 MHz)
f1 (ppm)

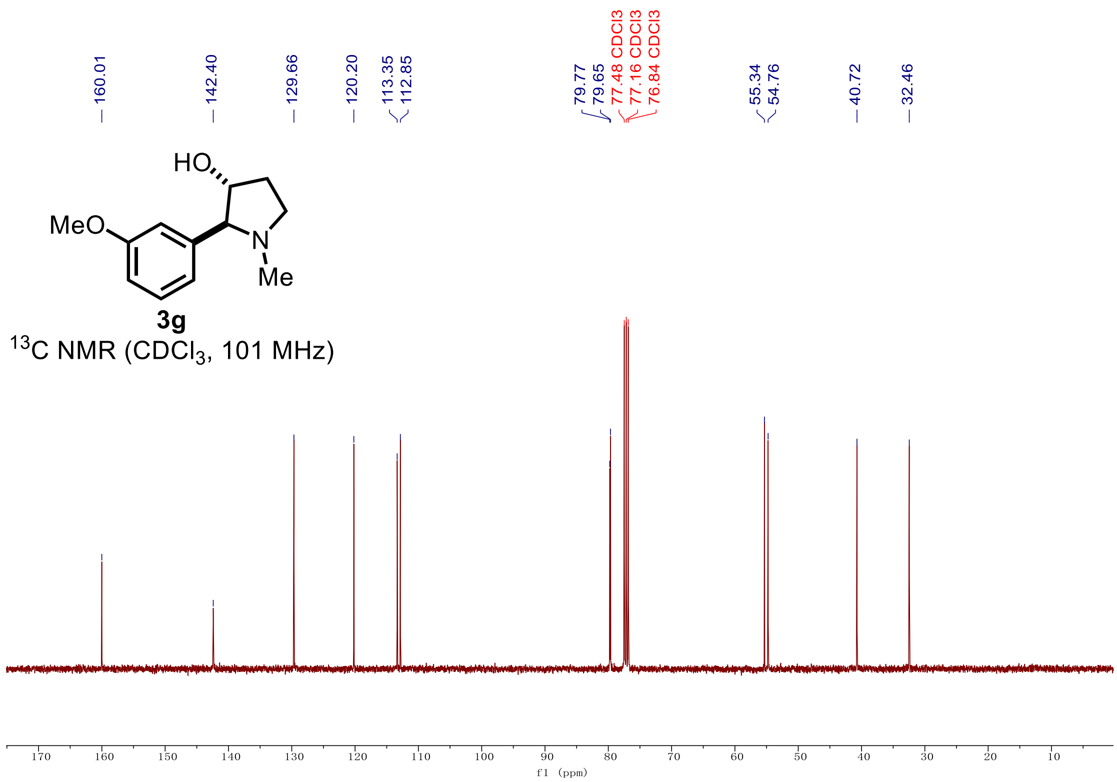


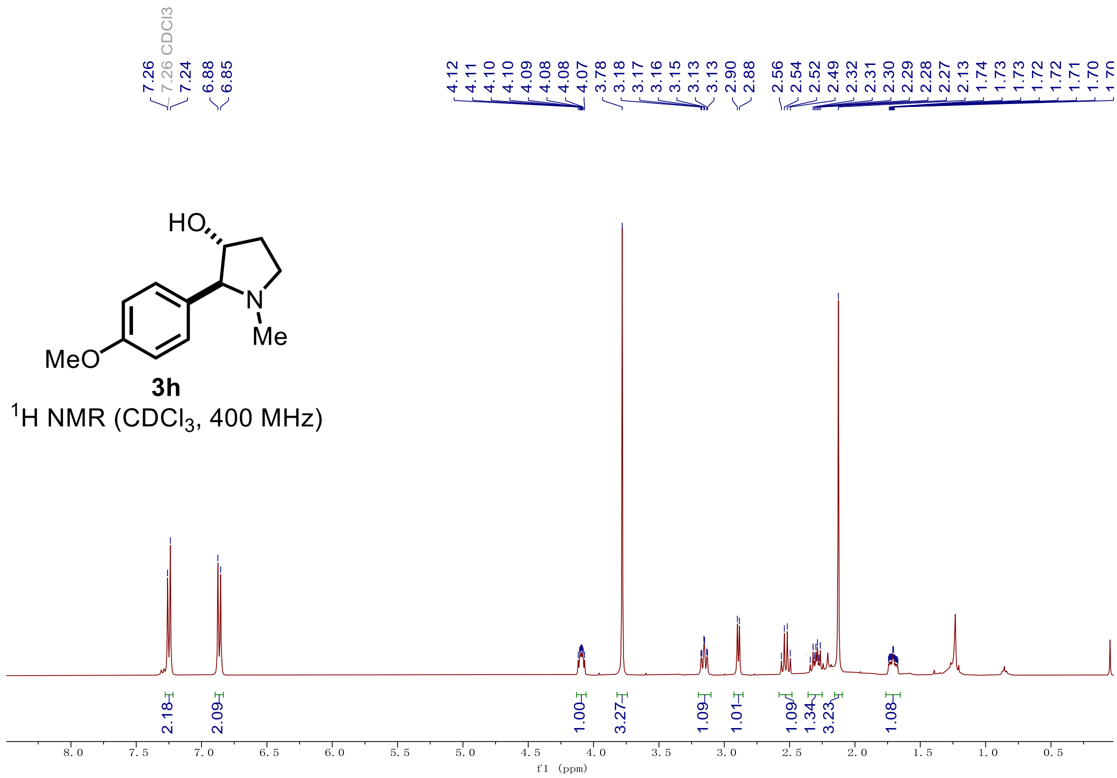
^{1}H NMR ($CDCl_3$, 400 MHz)

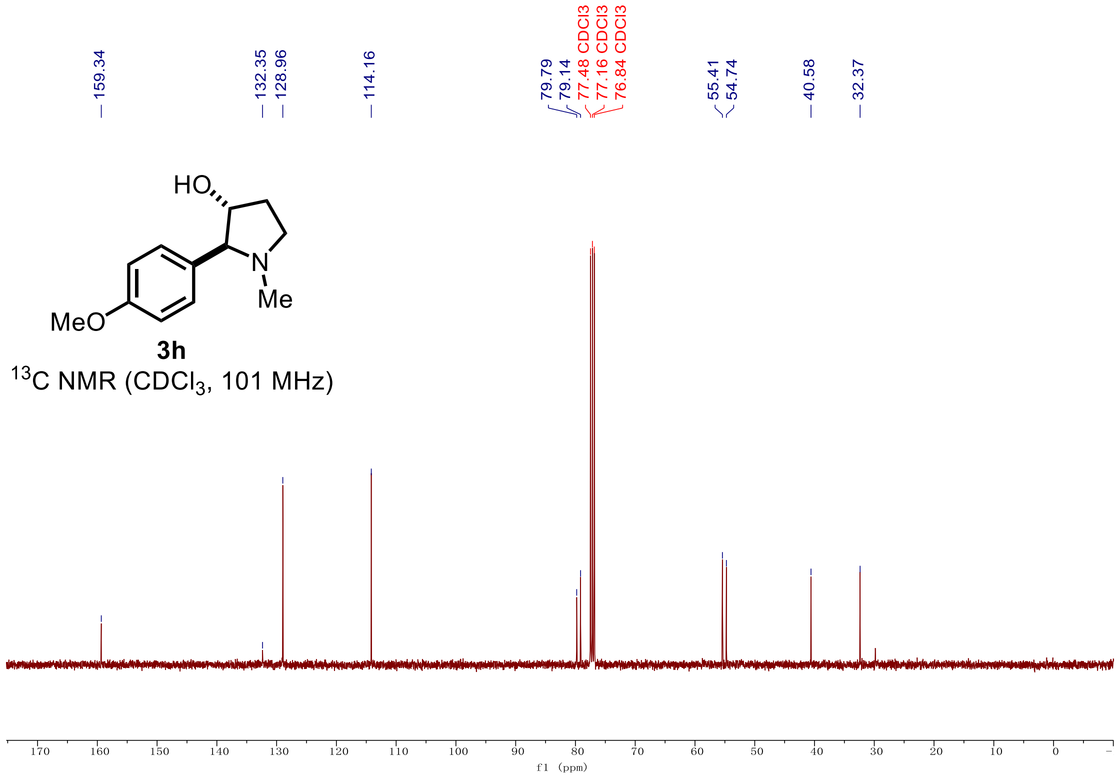


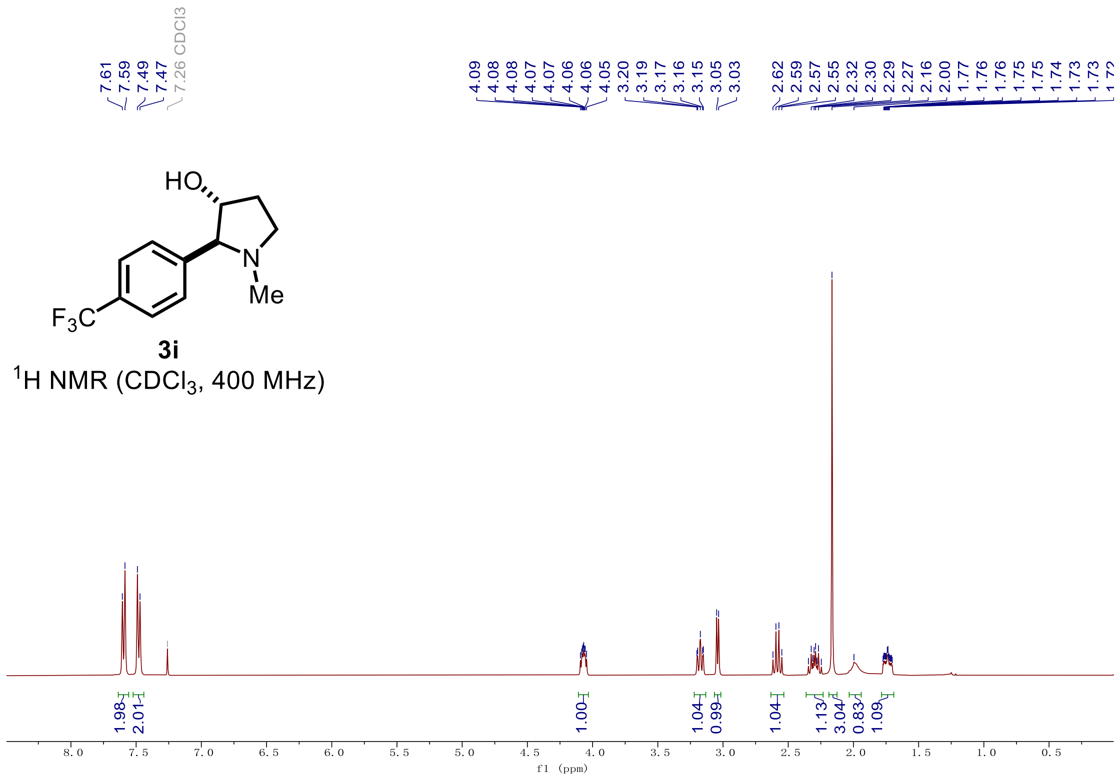
^{13}C NMR ($CDCl_3$, 101 MHz)

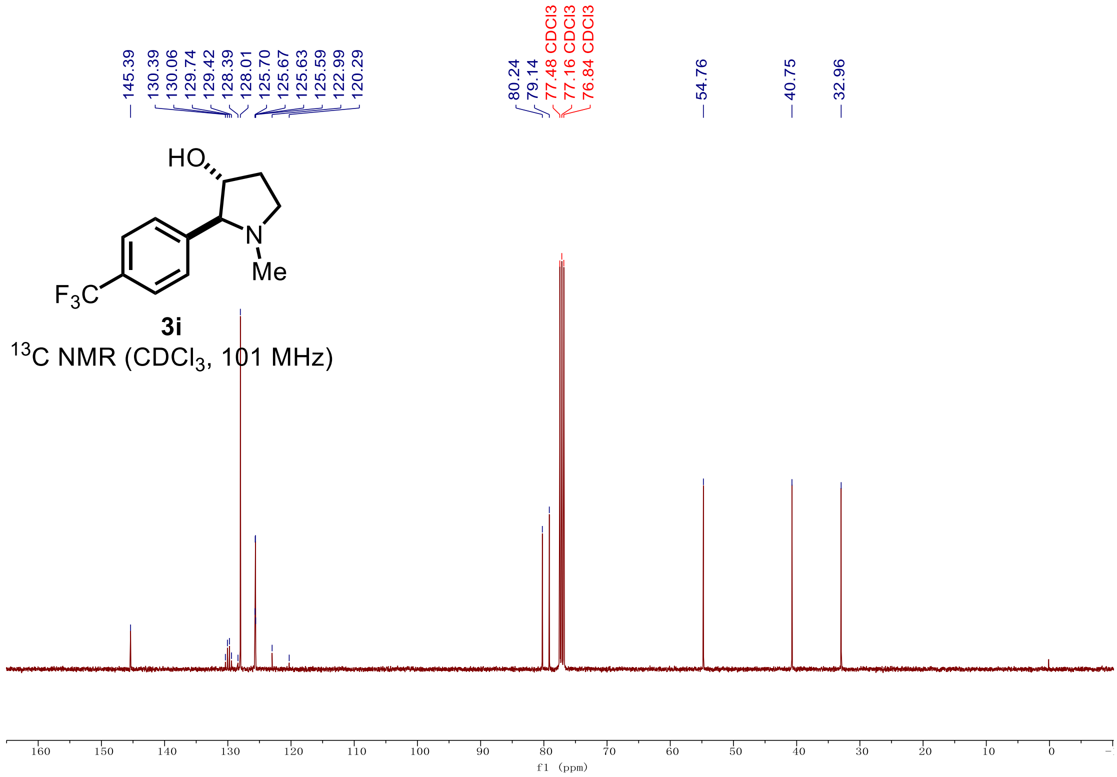

7.26 CDCl3
7.26
7.24
7.22
6.93
6.92
6.83
6.81
4.11
4.10
4.10
4.09
4.08
4.08
4.07
3.80
3.16
3.14
3.12
2.93
2.92
2.57
2.54
2.52
2.50
2.30
2.29
2.28
2.27
2.25
2.16
1.73
1.73
1.72
1.72
1.71
1.70
1.69
HO
MeO
N
Me
3g
^{1}H NMR (CDCl$_3$, 400 MHz)
1.08
1.99
0.99
1.00
3.06
1.03
1.02
1.42
0.59
1.16
3.04
1.04
f1 (ppm)


160.01
142.40
129.66
120.20
113.35
112.85
79.77
79.65
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.34
54.76
40.72
32.46
HO
MeO
N
Me
3g
^{13}C NMR (CDCl$_3$, 101 MHz)
f1 (ppm)

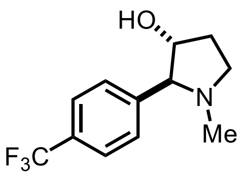

7.26
7.26 CDCl3
7.24
6.88
6.85
4.12
4.11
4.10
4.10
4.09
4.08
4.08
4.07
3.78
3.18
3.17
3.16
3.15
3.13
3.13
3.13
2.90
2.88
2.56
2.54
2.52
2.49
2.32
2.31
2.30
2.29
2.28
2.27
2.13
1.74
1.73
1.72
1.72
1.71
1.70
HO
N
Me
MeO
3h
^{1}H NMR (CDCl$_3$, 400 MHz)
2.18
2.09
1.00
3.27
1.09
1.01
1.09
1.34
3.23
1.08
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


159.34
132.35
128.96
114.16
79.79
79.14
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
55.41
54.74
40.58
32.37
HO
N
Me
MeO
3h
^{13}C NMR (CDCl$_3$, 101 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)



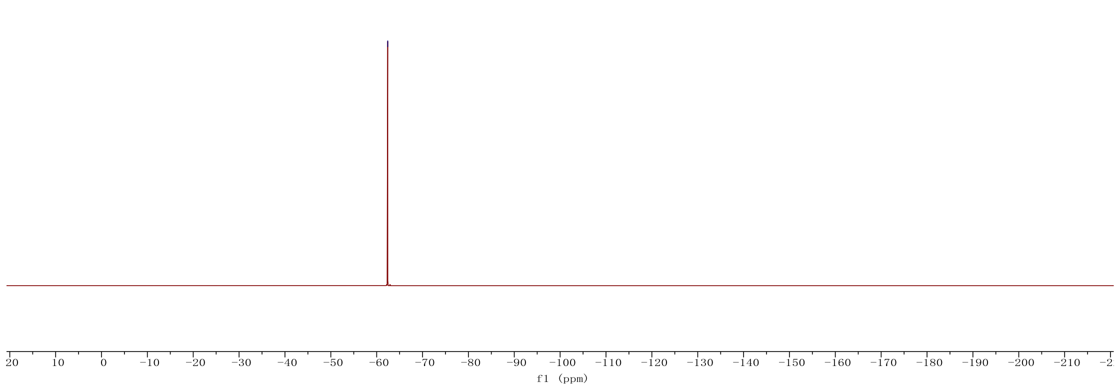


^{13}C NMR spectrum of **3g** (101 MHz, $CDCl_3$)

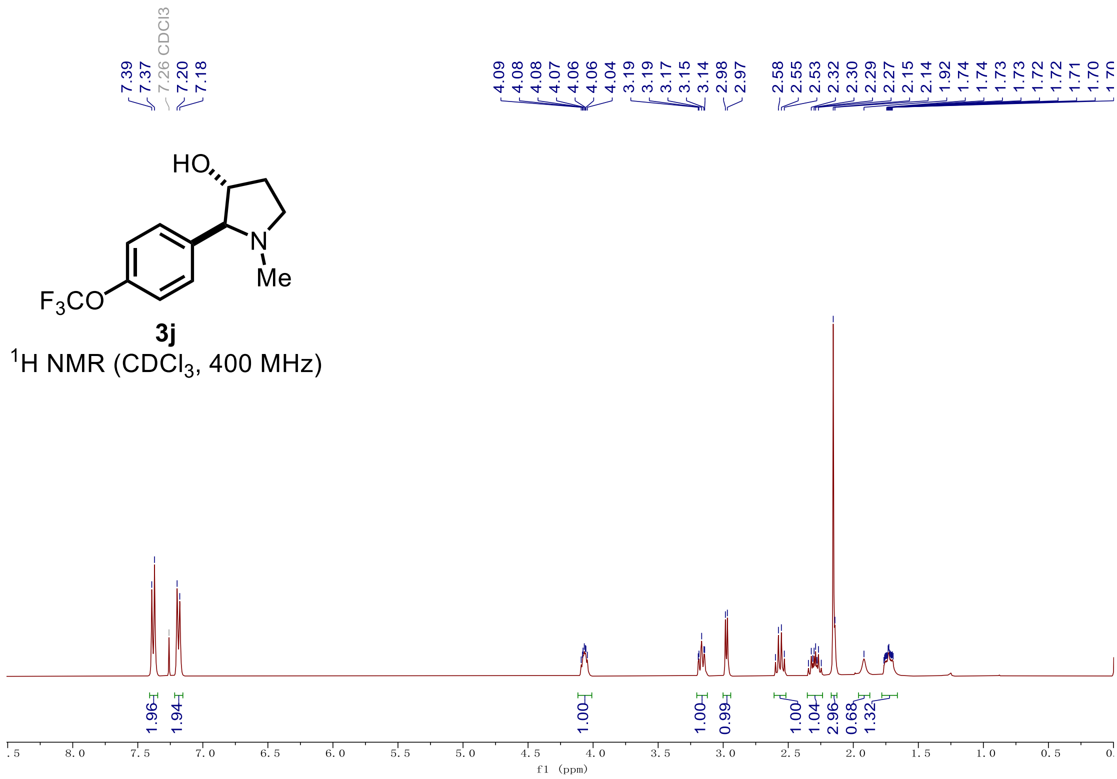


3i

^{19}F NMR ($CDCl_3$, 377 MHz)

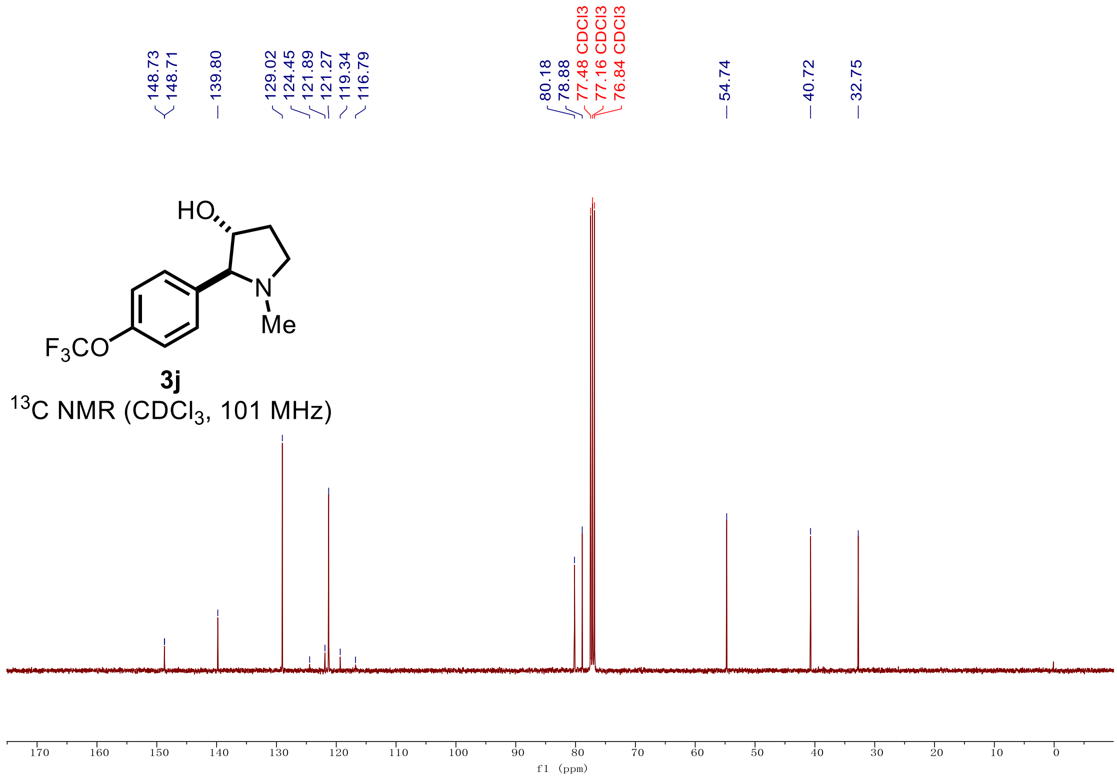


W



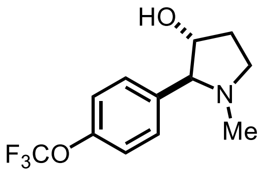
3j

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



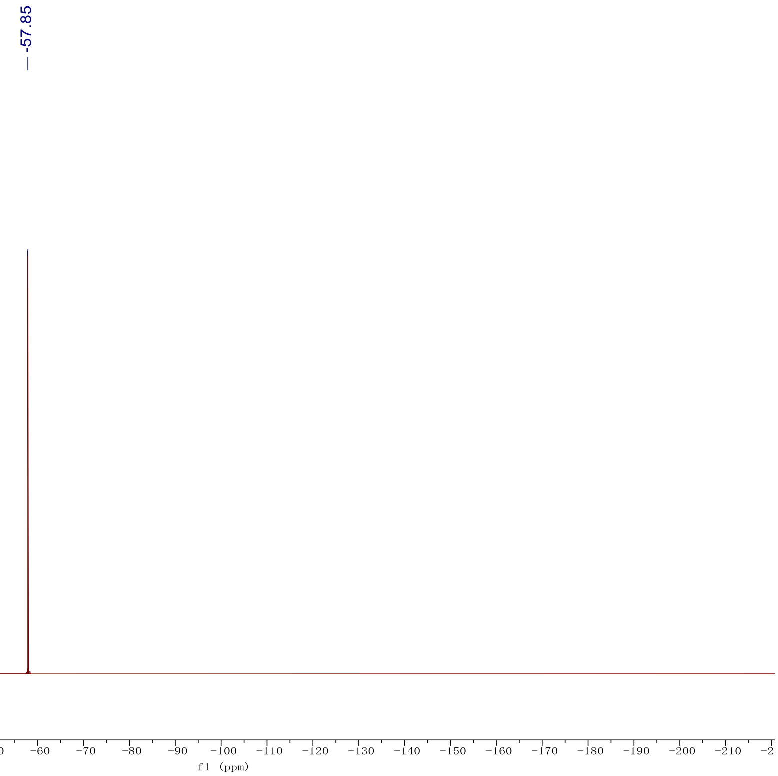
3j

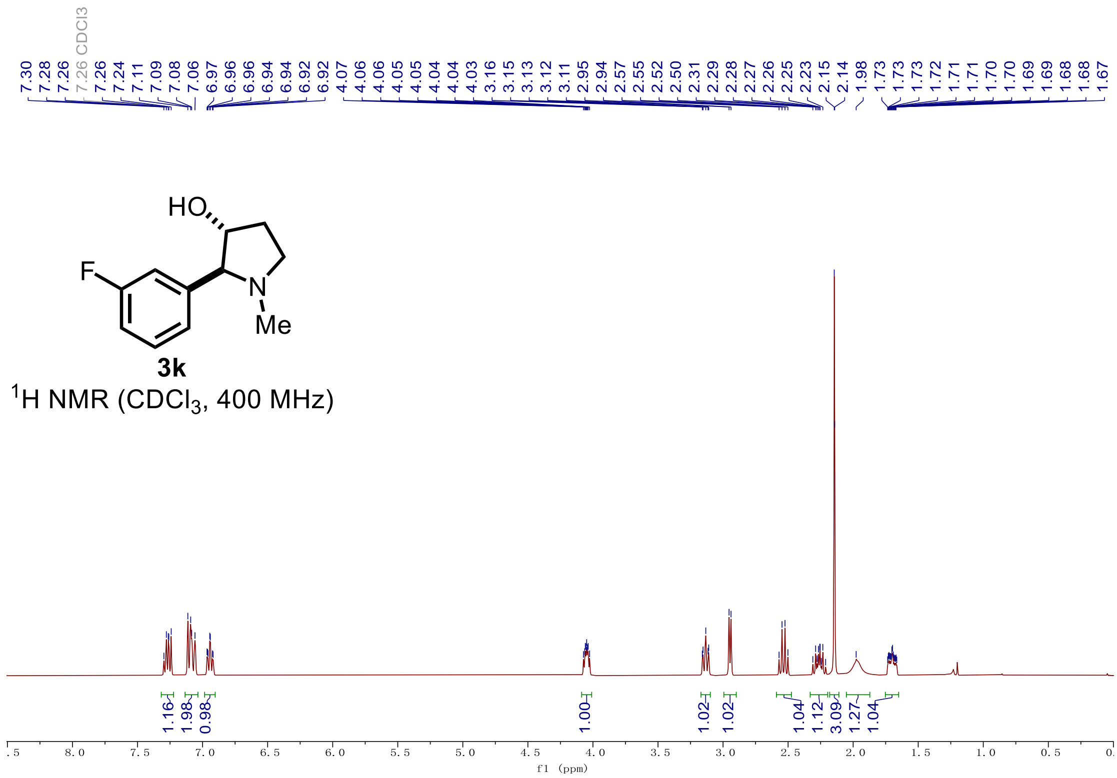
^{13}C NMR ($CDCl_3$, 101 MHz)

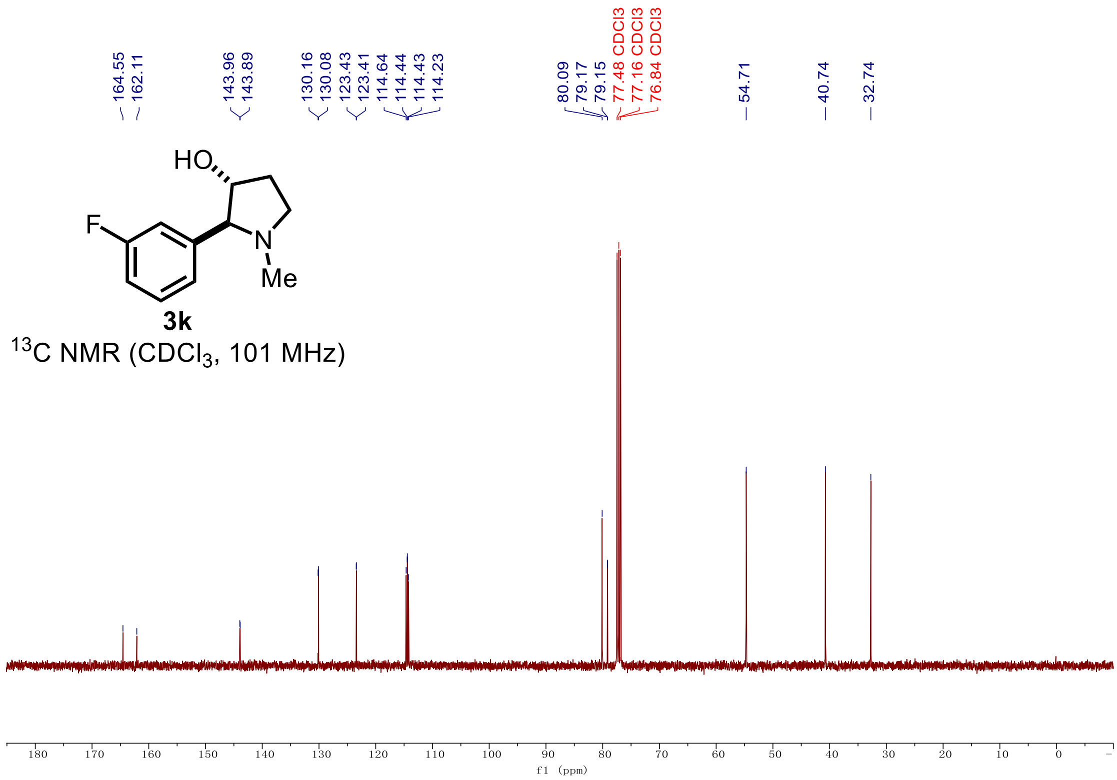


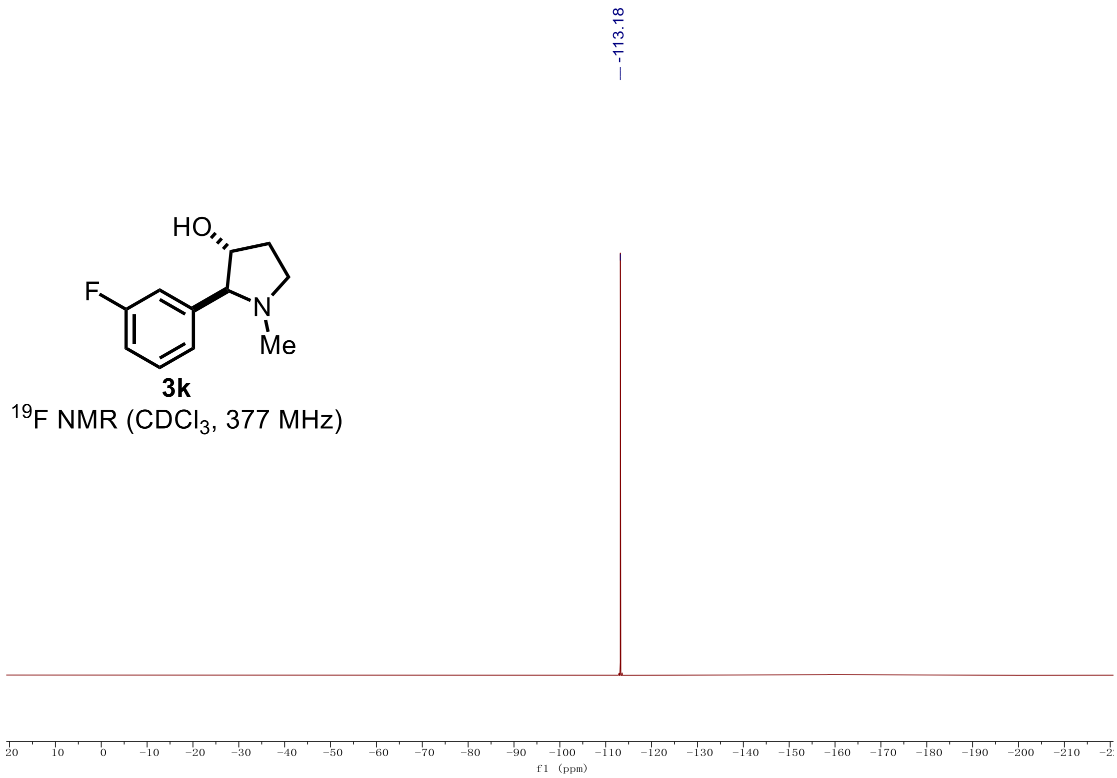
3j

^{19}F NMR (CDCl$_3$, 377 MHz)



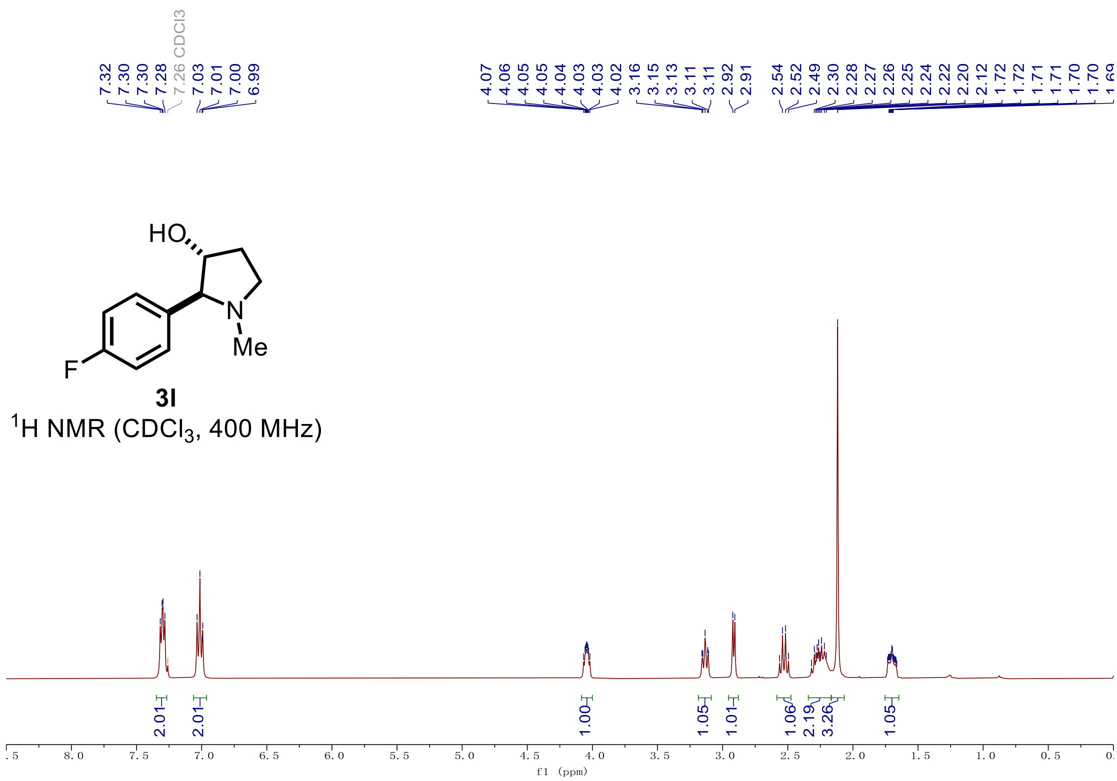

7.30
7.28
7.26
7.26 CDCl3
7.26
7.24
7.11
7.09
7.08
7.06
6.97
6.96
6.96
6.94
6.94
6.92
6.92
4.07
4.06
4.06
4.05
4.05
4.04
4.04
4.03
3.16
3.15
3.13
3.12
3.11
2.95
2.94
2.57
2.55
2.52
2.50
2.31
2.29
2.28
2.27
2.26
2.25
2.23
2.15
2.14
1.98
1.73
1.73
1.73
1.72
1.71
1.71
1.70
1.70
1.69
1.68
1.68
1.67
HO
F
N
Me
3k
1H NMR (CDCl3, 400 MHz)
1.16
1.98
0.98
1.00
1.02
1.02
1.04
1.12
3.09
1.27
1.04
f1 (ppm)


164.55
162.11
143.96
143.89
130.16
130.08
123.43
123.41
114.64
114.44
114.43
114.23
80.09
79.17
79.15
77.48 CDCl3
77.16 CDCl3
76.84 CDCl3
54.71
40.74
32.74
HO
F
N
Me
3k
13C NMR (CDCl3, 101 MHz)
f1 (ppm)



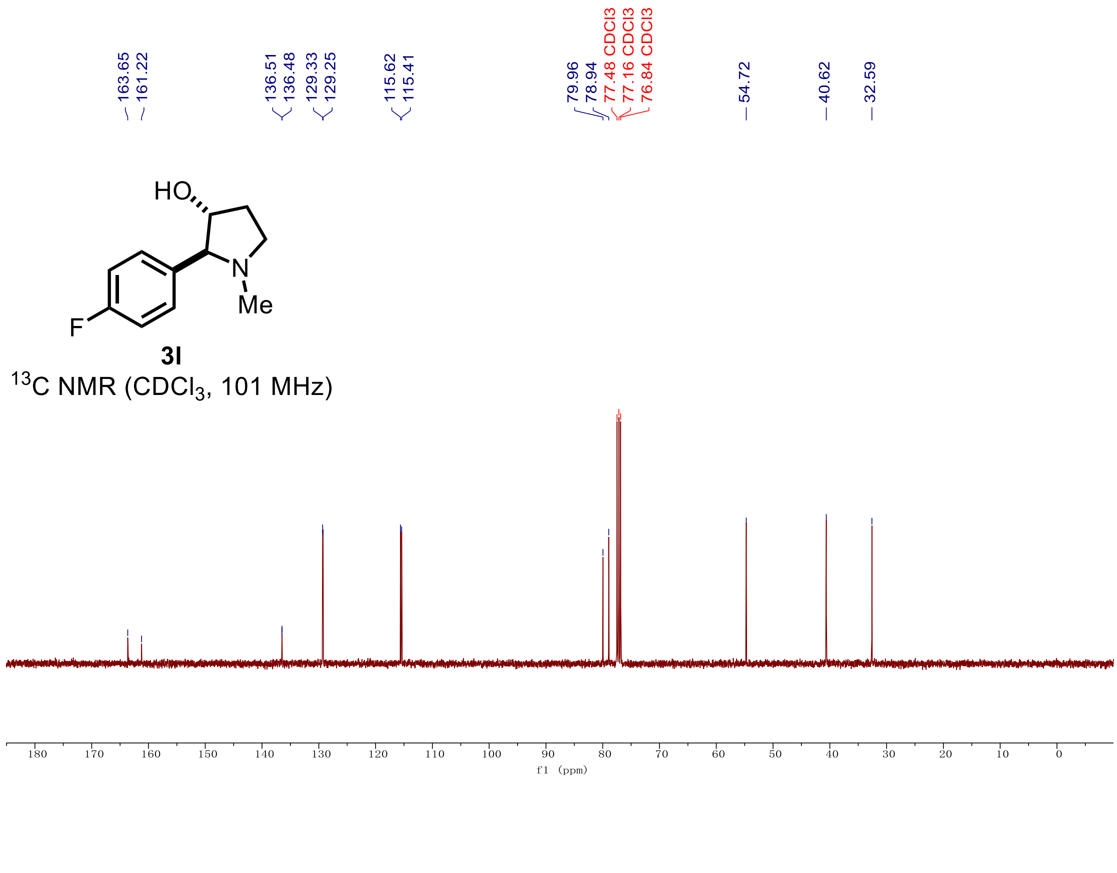
3k

^{19}F NMR (CDCl$_3$, 377 MHz)



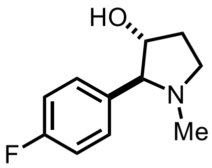
3l

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



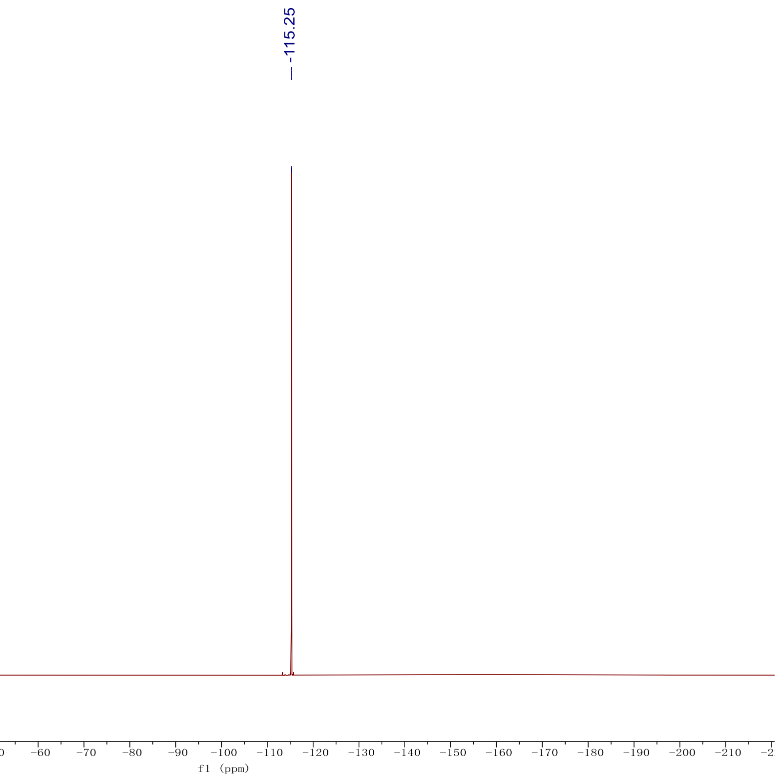
3l

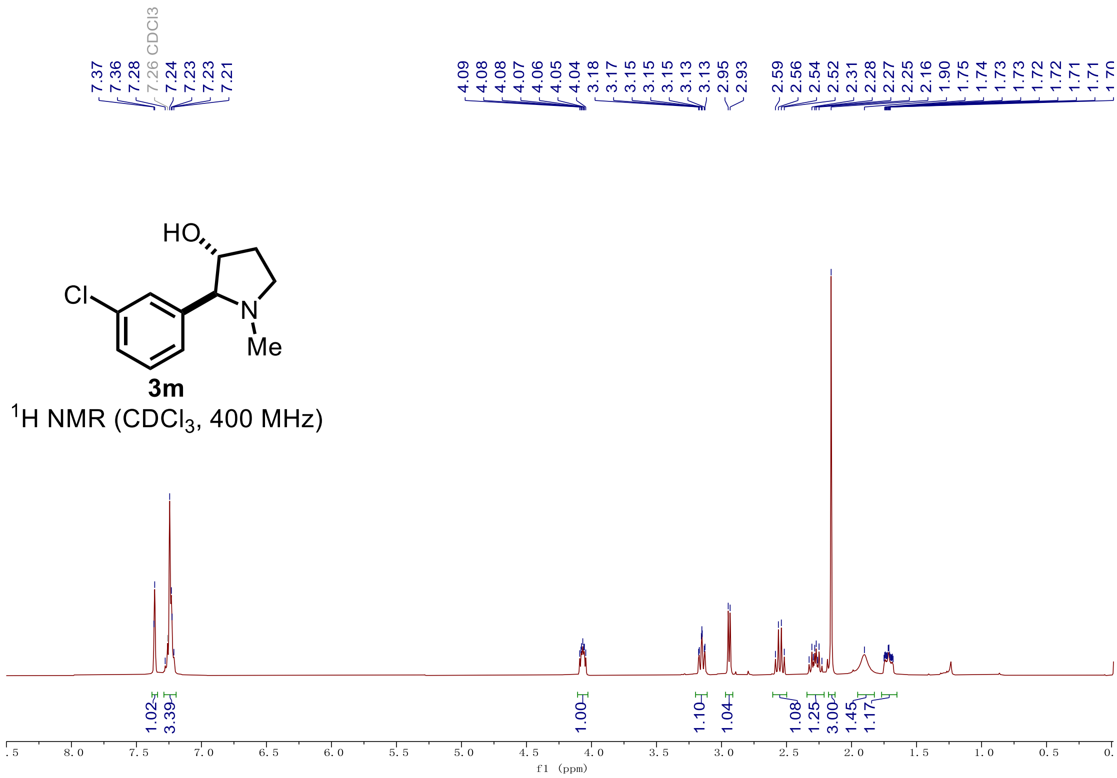
^{13}C NMR ($CDCl_3$, 101 MHz)



3l

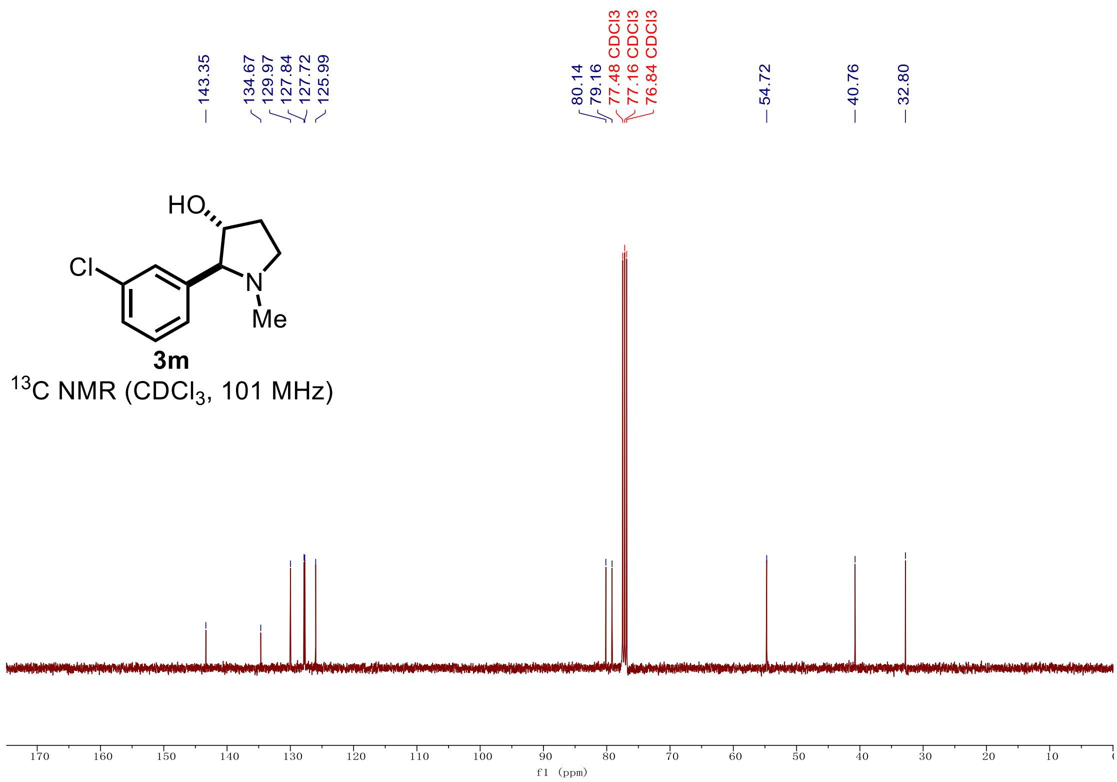
^{19}F NMR ($CDCl_3$, 377 MHz)





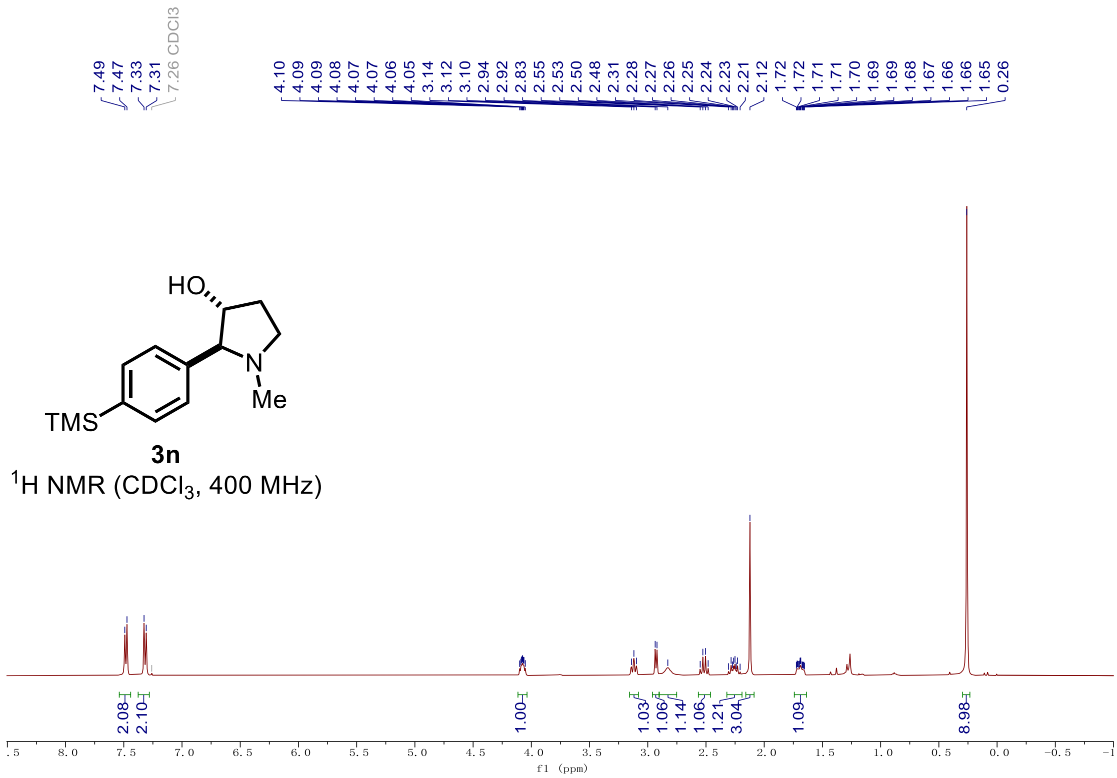
3m

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



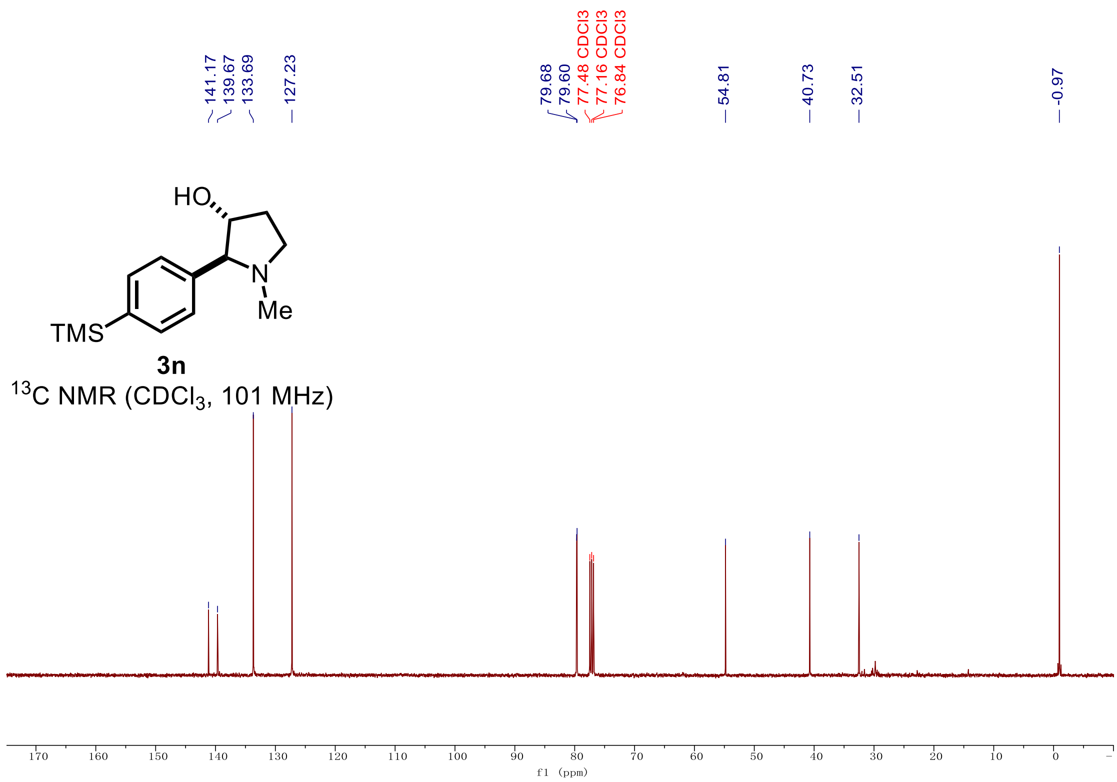
3m

^{13}C NMR ($CDCl_3$, 101 MHz)



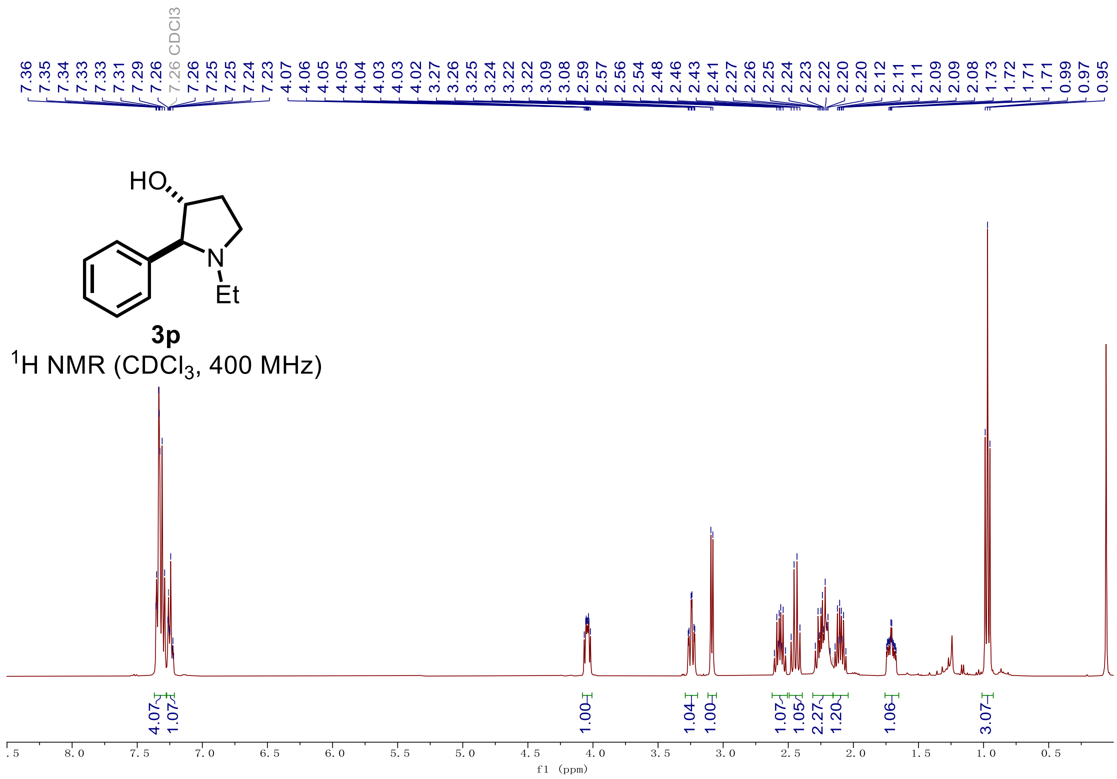
3n

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



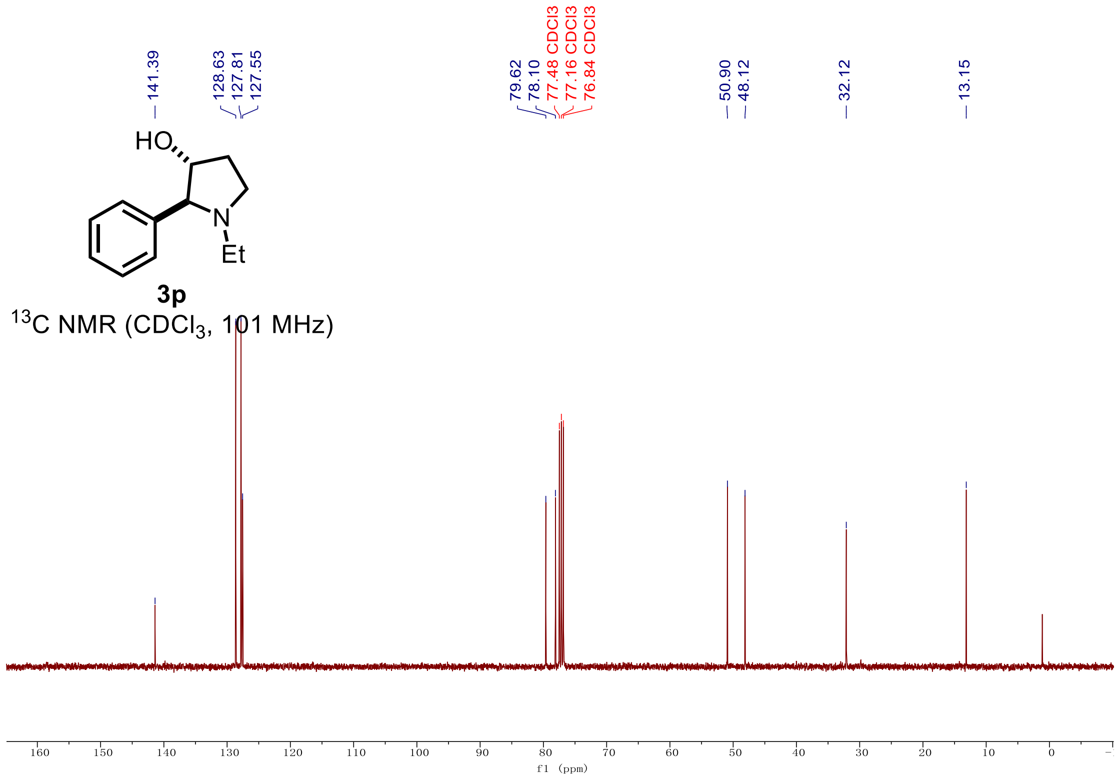
3n

^{13}C NMR ($CDCl_3$, 101 MHz)



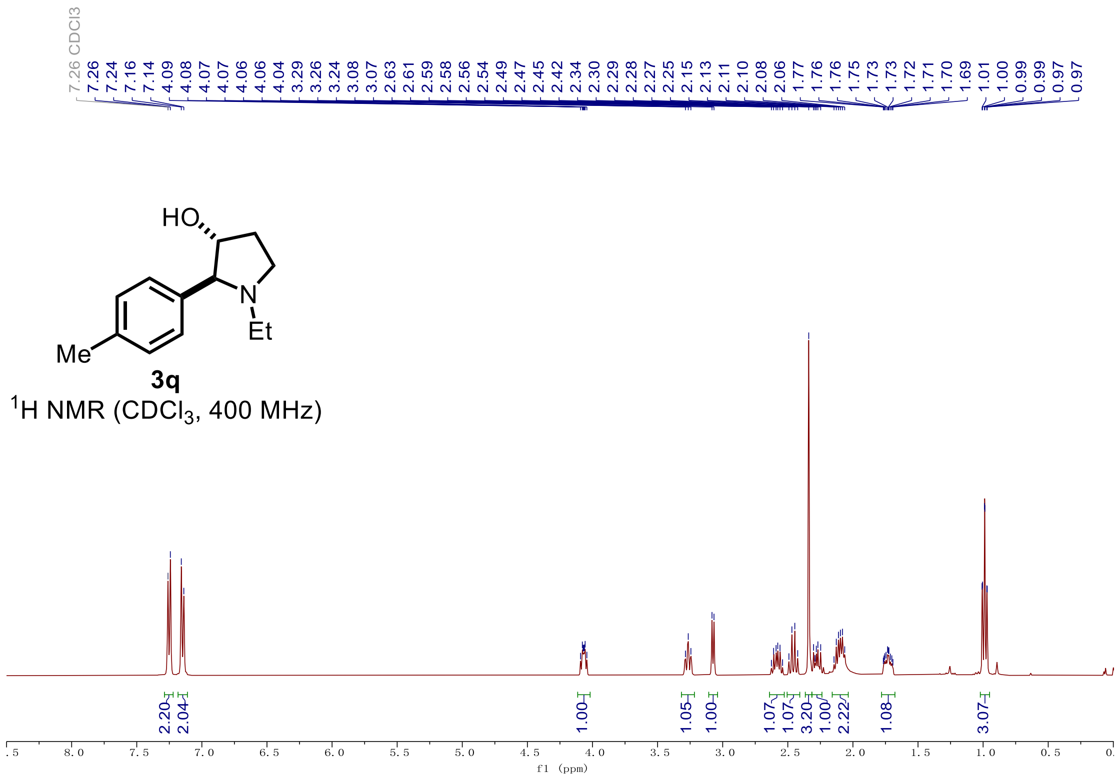
3p

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



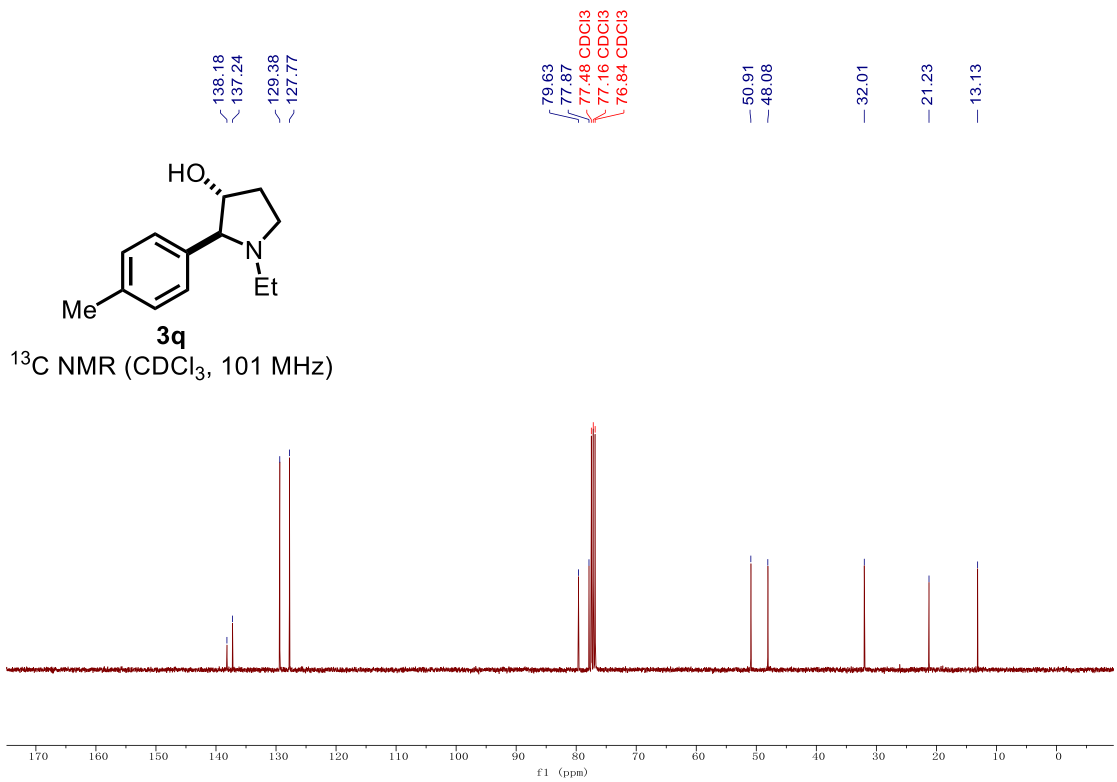
3p

^{13}C NMR ($CDCl_3$, 101 MHz)



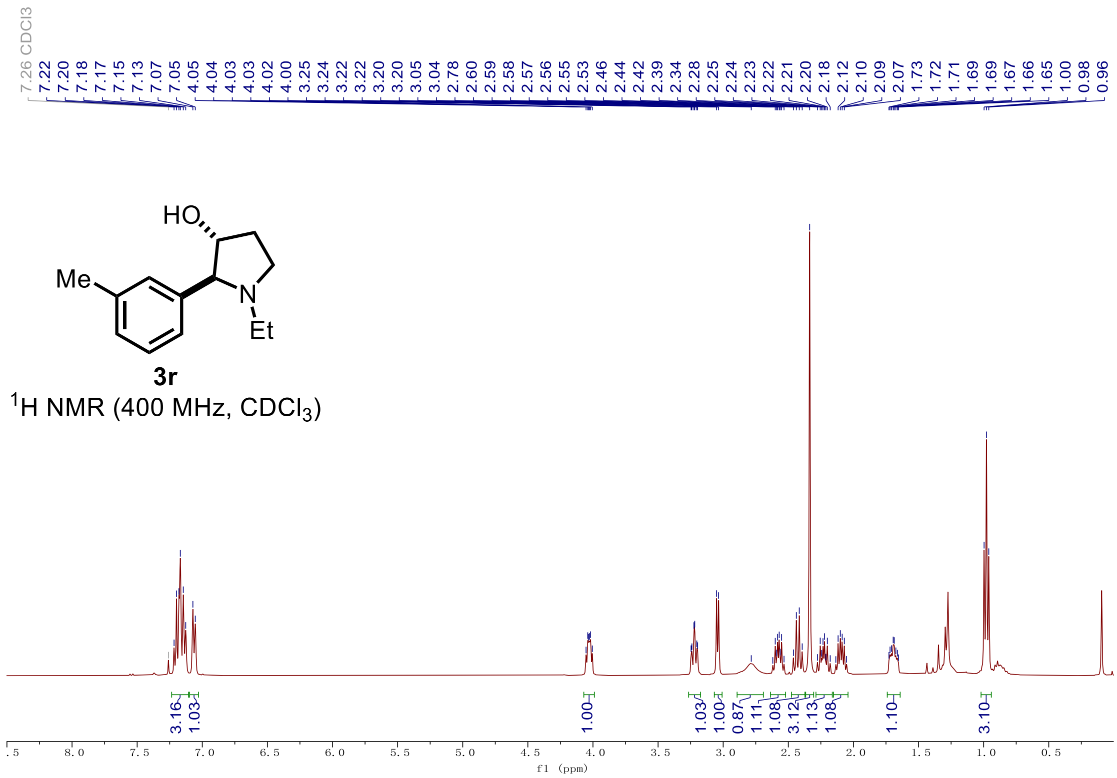
3q

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



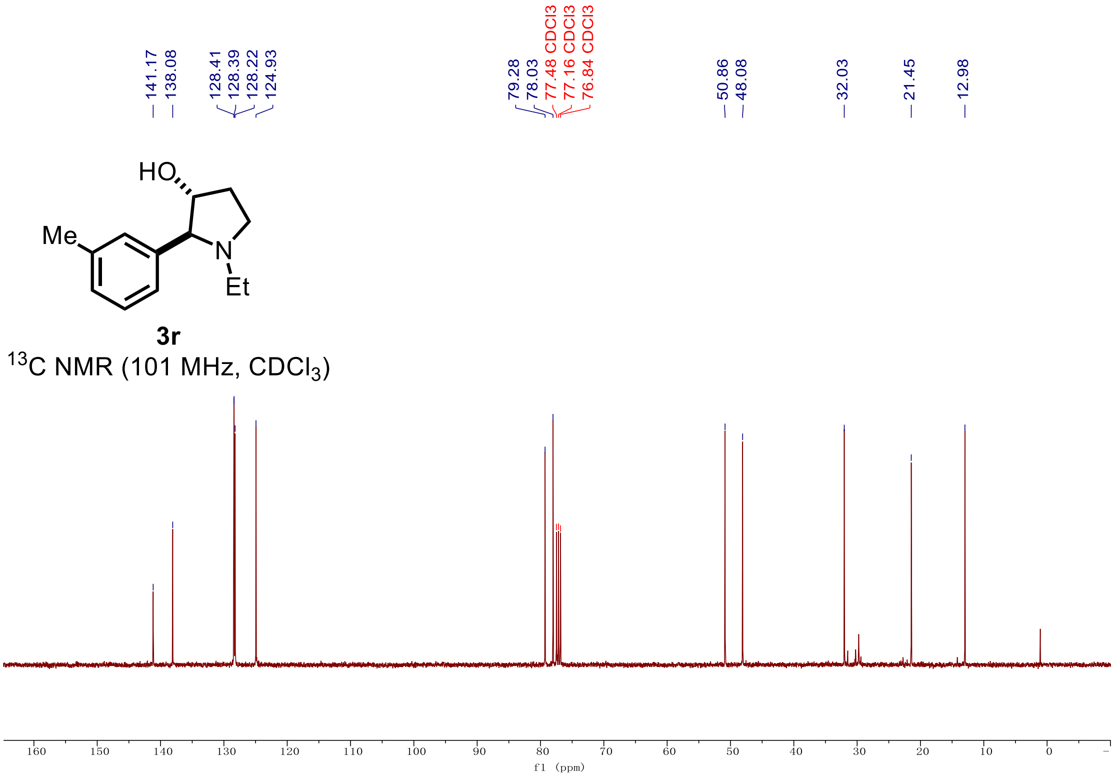
3q

^{13}C NMR ($CDCl_3$, 101 MHz)



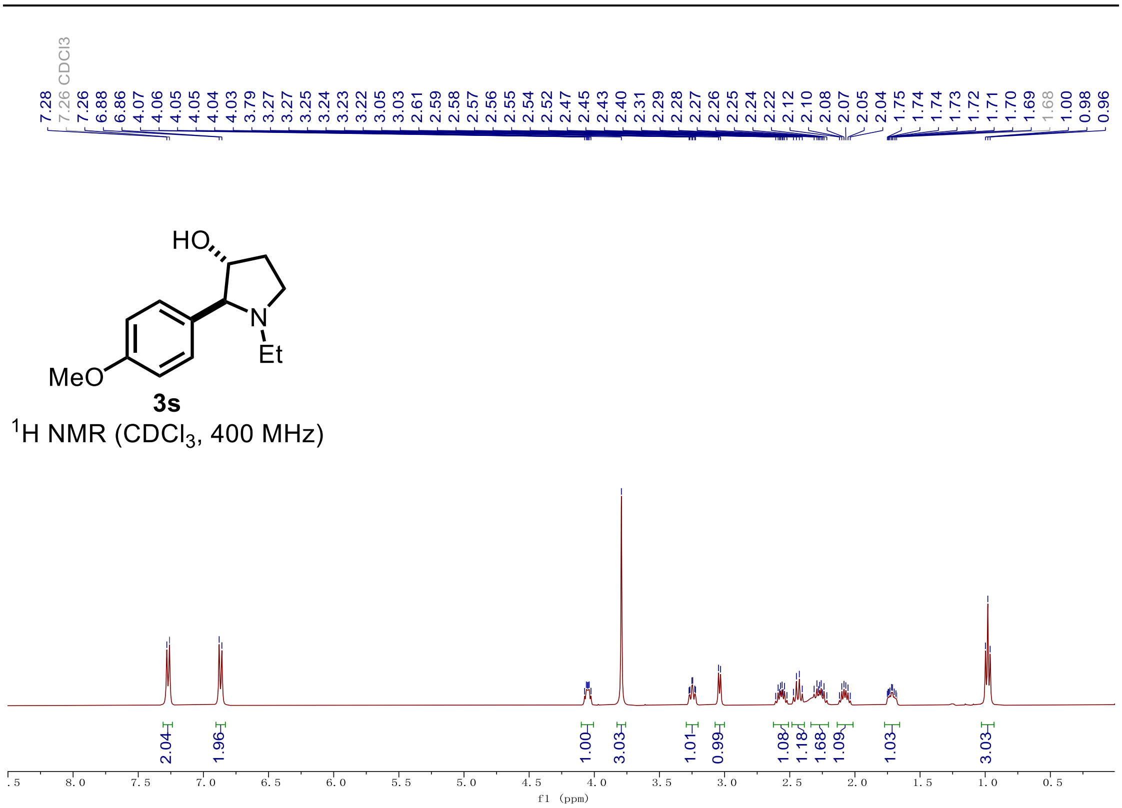
3r

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



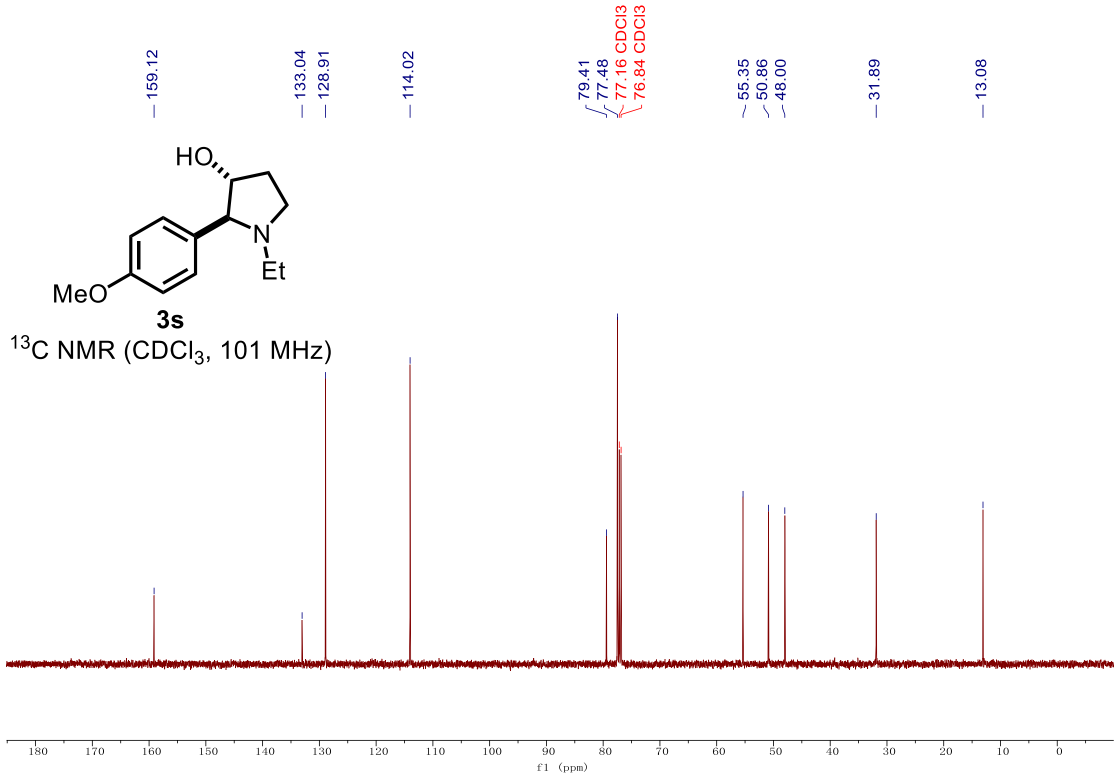
3r

^{13}C NMR (101 MHz, $CDCl_3$)



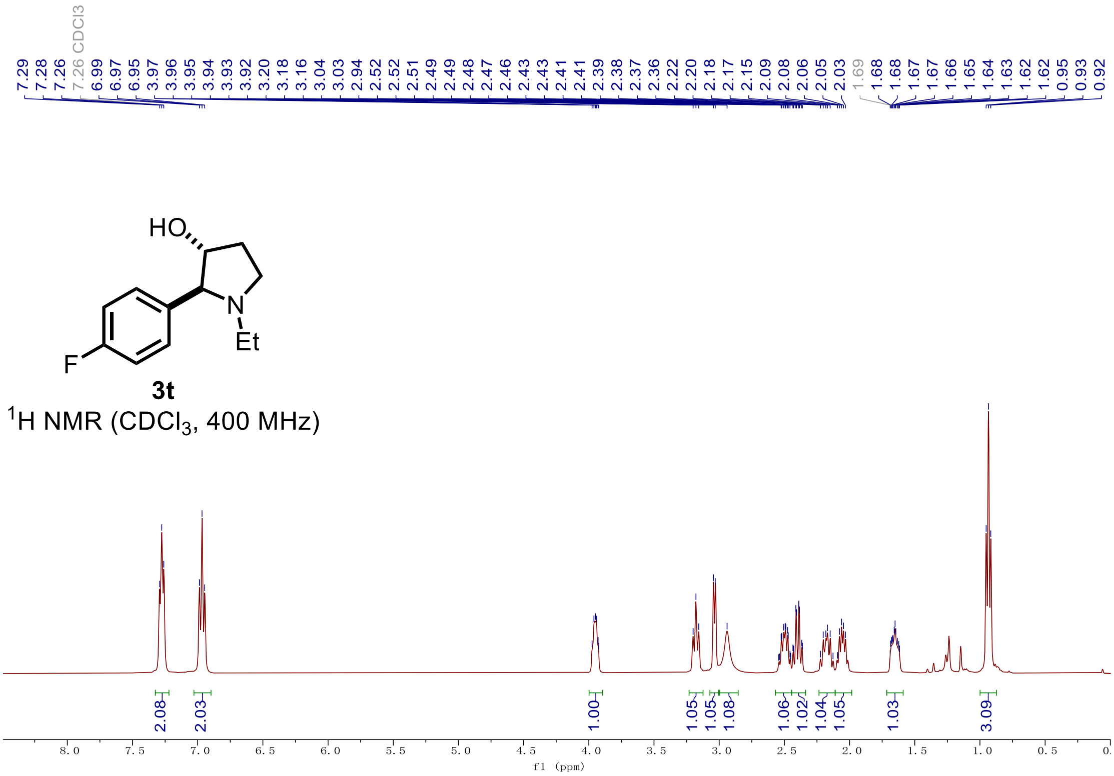
3s

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



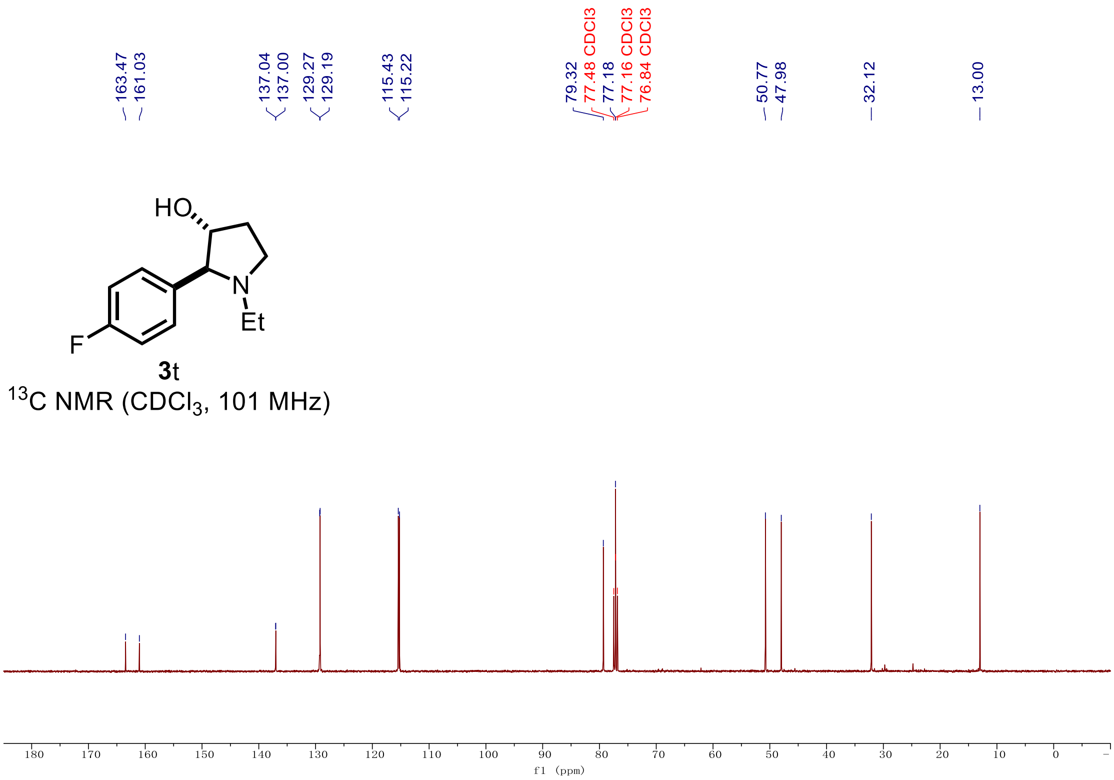
3s

^{13}C NMR ($CDCl_3$, 101 MHz)



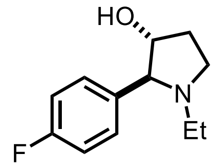
3t

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



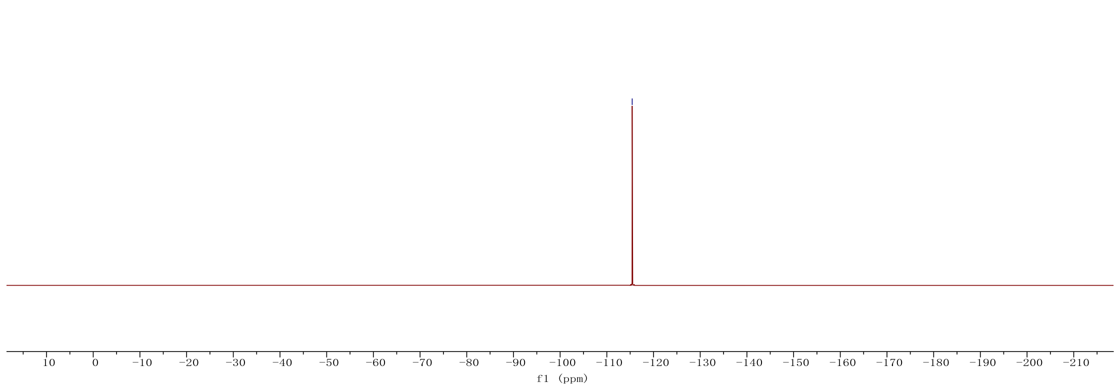
3t

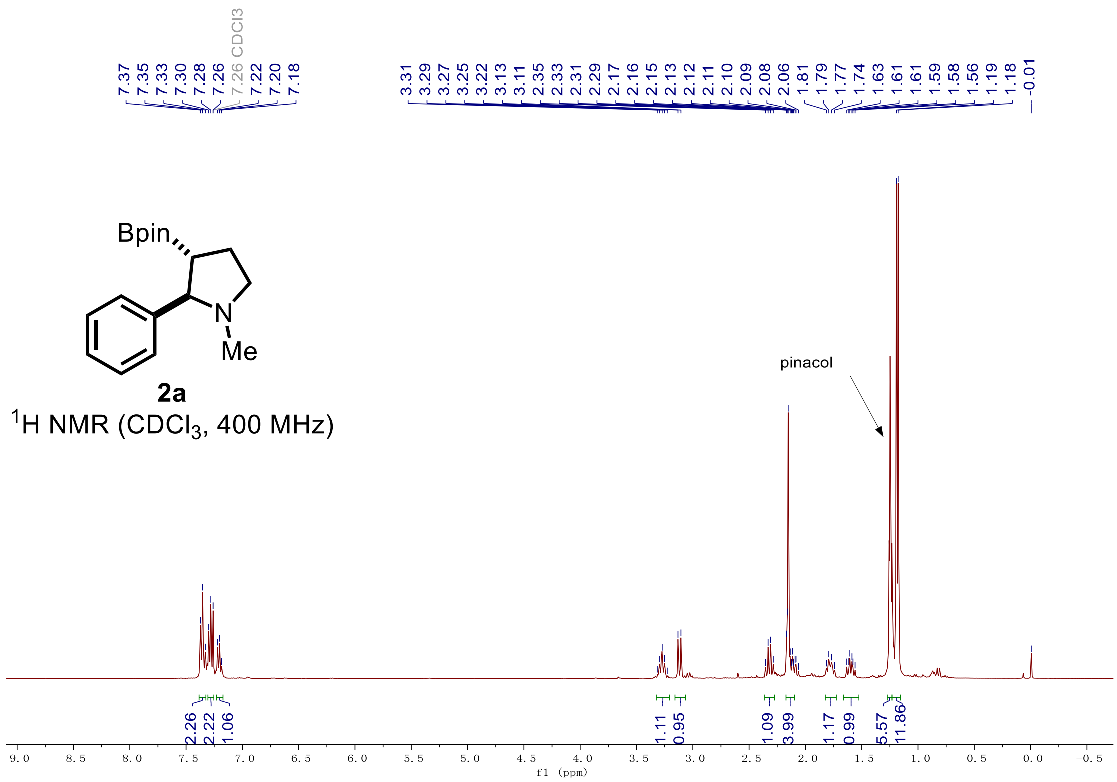
^{13}C NMR ($CDCl_3$, 101 MHz)



3t

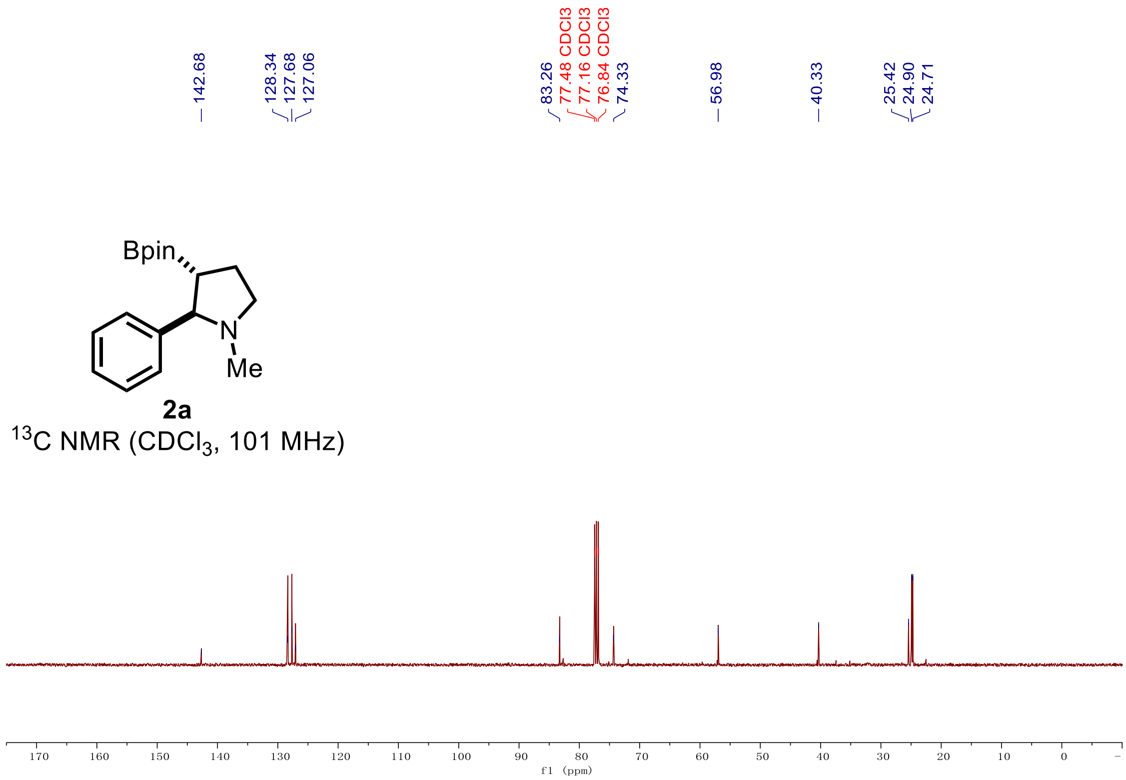
^{19}F NMR ($CDCl_3$, 377 MHz)





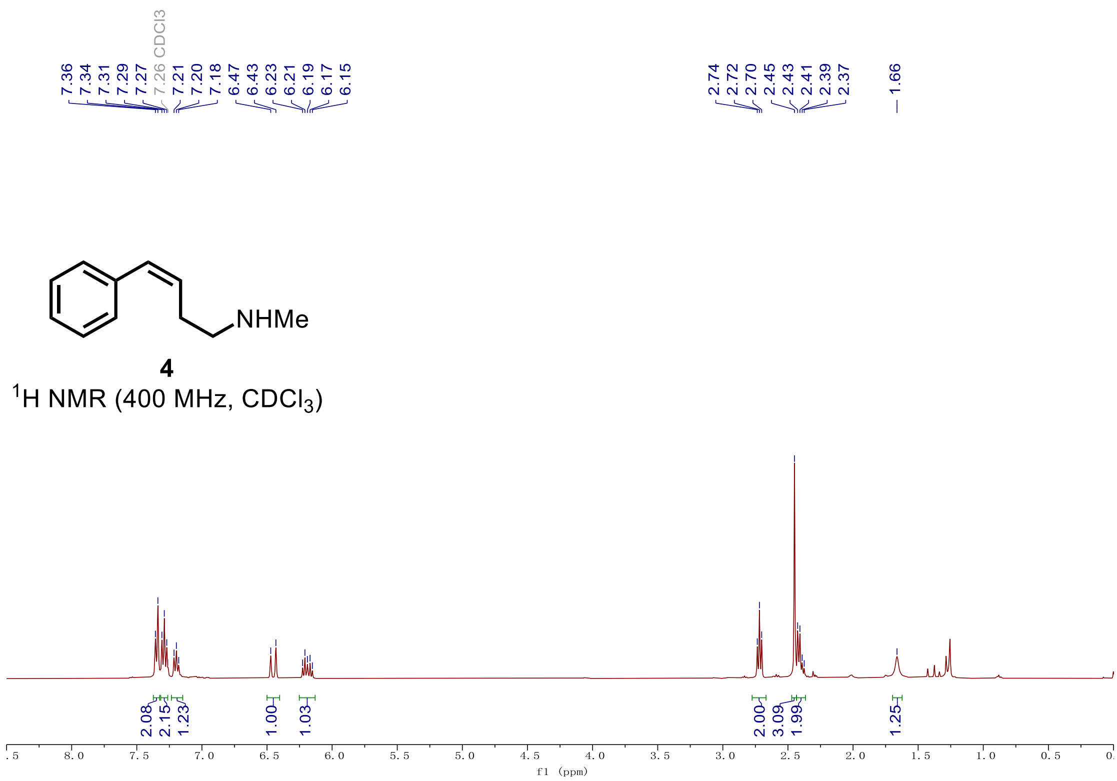
2a

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



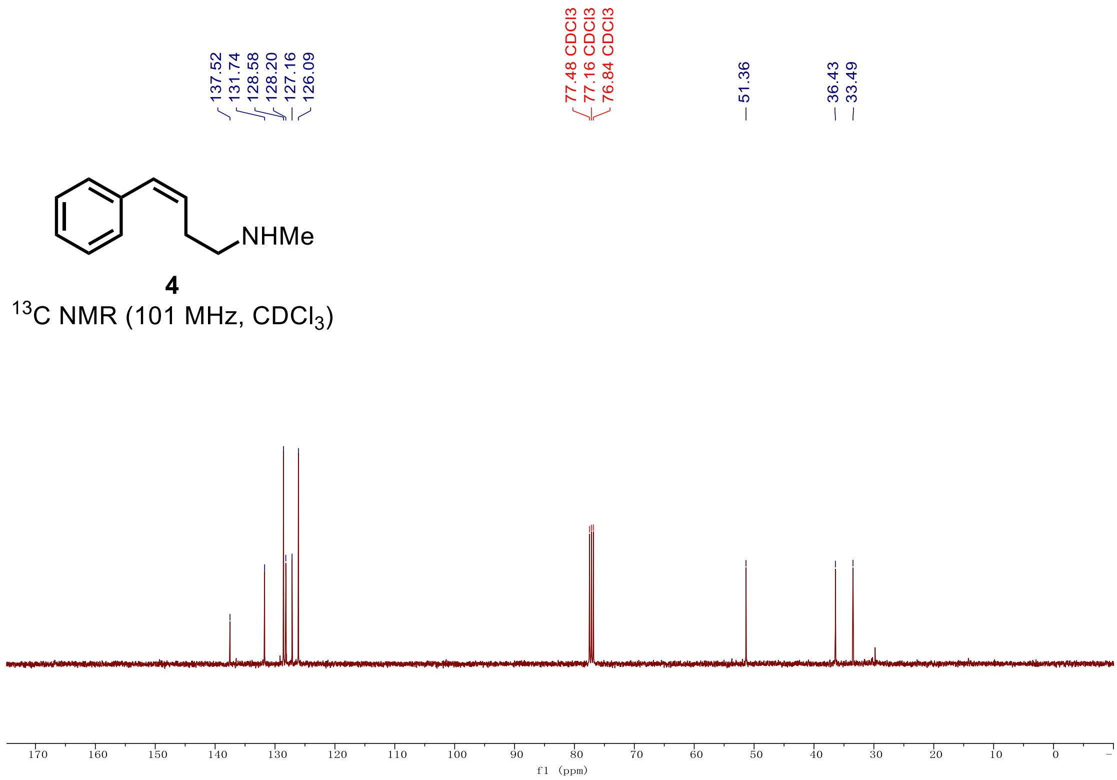
2a

^{13}C NMR ($CDCl_3$, 101 MHz)



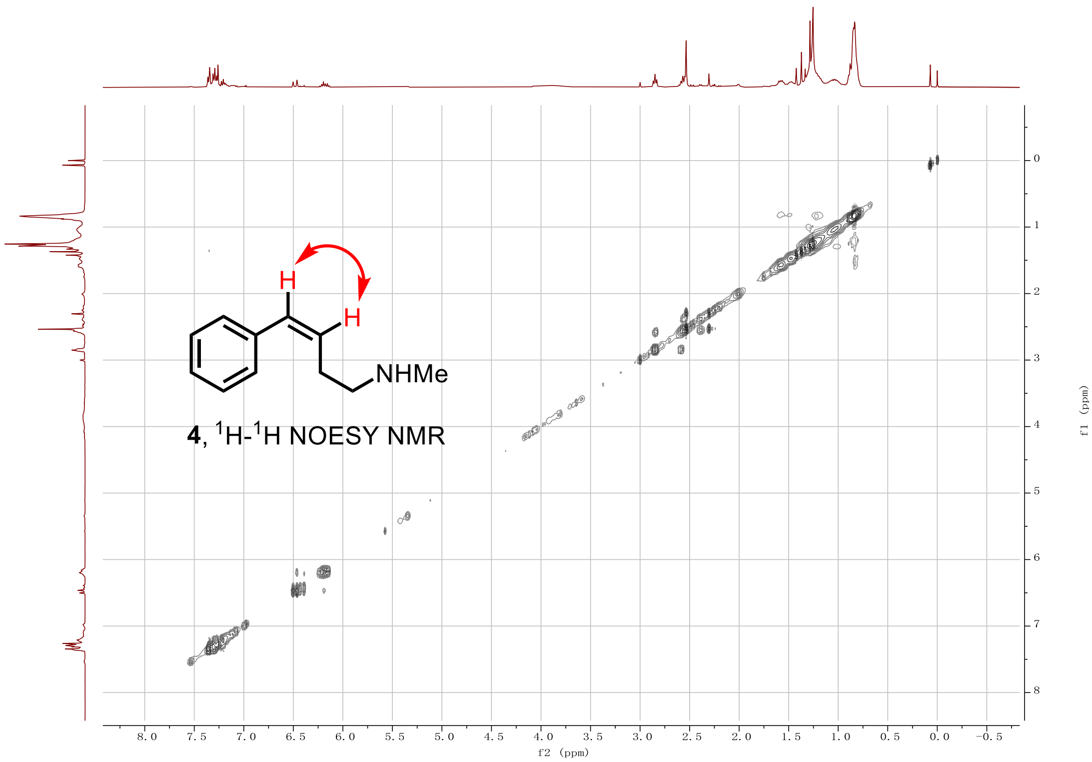
4

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

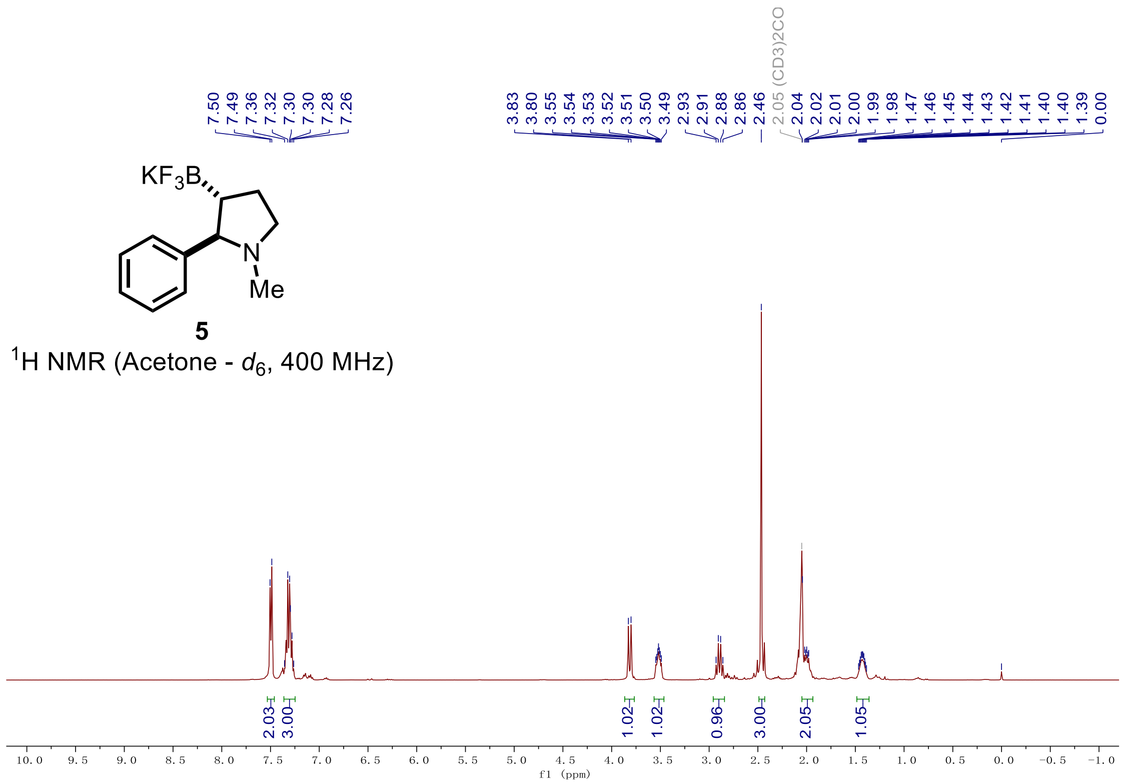


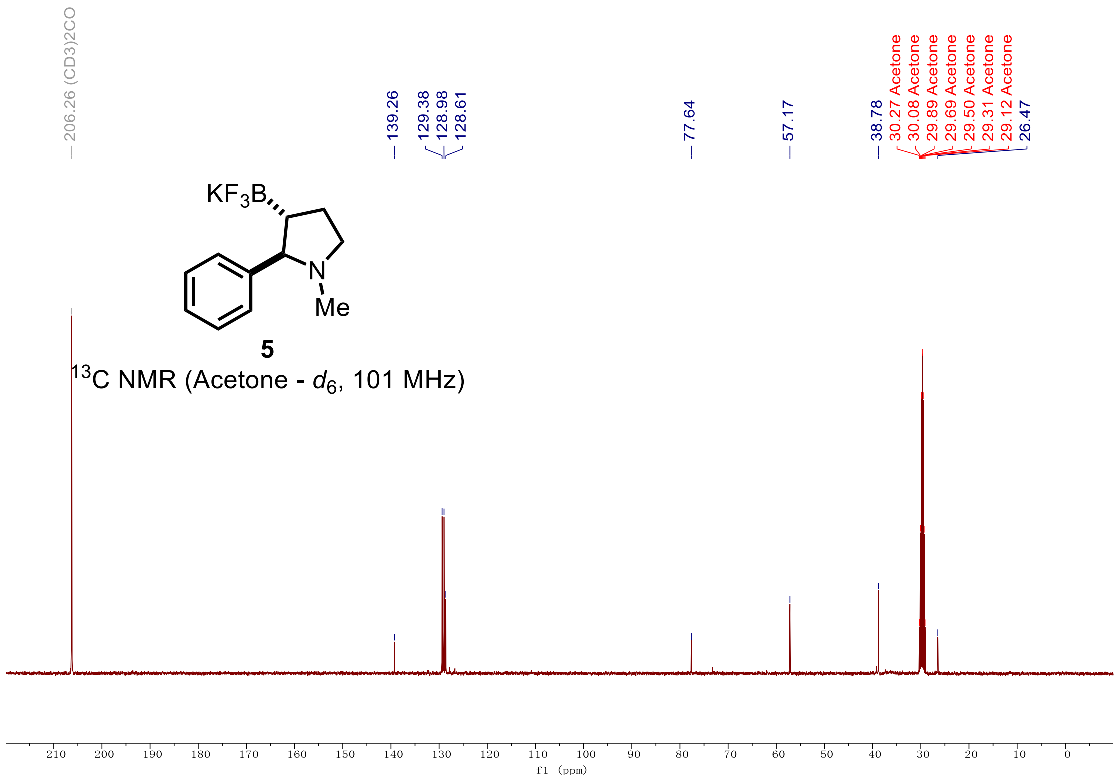
4

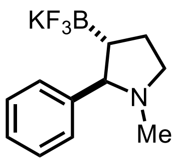
^{13}C NMR (101 MHz, $CDCl_3$)



H
H
NHMe
4, 1H-1H NOESY NMR
f2 (ppm)
f1 (ppm)

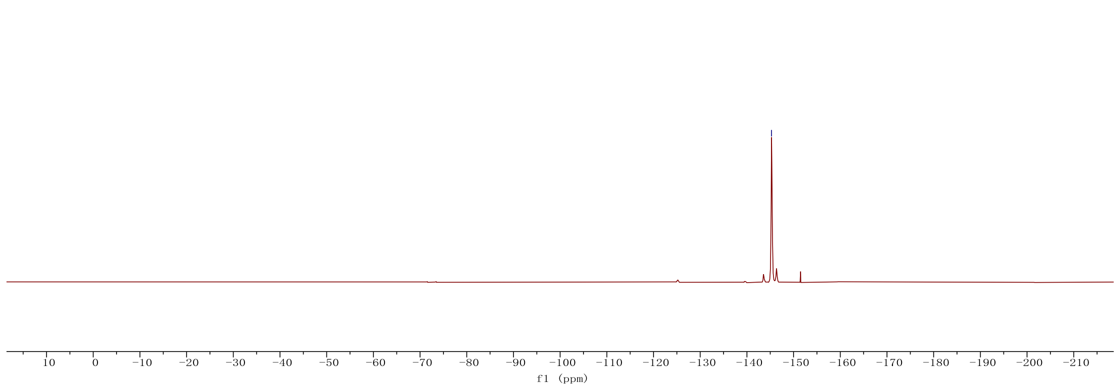

7.50
7.49
7.36
7.32
7.30
7.30
7.28
7.26
3.83
3.80
3.55
3.54
3.53
3.52
3.51
3.50
3.49
2.93
2.91
2.88
2.86
2.46
2.05 (CD3)2CO
2.04
2.02
2.01
2.00
1.99
1.98
1.47
1.46
1.45
1.44
1.43
1.42
1.41
1.40
1.40
1.39
0.00
KF3B
N
Me
5
1H NMR (Acetone - d6, 400 MHz)
2.03
3.00
1.02
1.02
0.96
3.00
2.05
1.05
f1 (ppm)

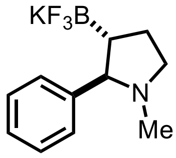

206.26 (CD3)2CO
139.26
129.38
128.98
128.61
77.64
57.17
38.78
30.27 Acetone
30.08 Acetone
29.89 Acetone
29.69 Acetone
29.50 Acetone
29.31 Acetone
29.12 Acetone
26.47
KF3B
N
Me
5
13C NMR (Acetone - d6, 101 MHz)
f1 (ppm)



5

^{19}F NMR (Acetone - d_6, 376 MHz)





5

^{11}B NMR (Acetone - d_6, 128 MHz)