Supporting Information

Conformational Preference of *N*-Difluoromethylated Amides: Contributions of Hydrogen-Bonding, Steric, and Stereoelectronic Effects

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1, General

Melting points were determined by using a Yanaco melting point apparatus MP-S3 and are uncorrected. FT-IR spectra were recorded on a Horiba FT-710 or JASCO FT/IR-4X. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECZ400S, Bruker AV-300M, or AV-600 and chemical shifts are expressed in parts per million relative to tetramethylsilane (TMS) or a residual solvent peak (7.24 ppm for $CDCl_3$ (^{1}H), 77.0 ppm for $CHCl_3$ (^{13}C), 5.32 ppm for CD_2Cl_2 (^{1}H), 5.95 ppm for 1,1,2,2-tetrachloroethane (^{1}H), 73.78 ppm for 1,1,2,2-tetrachloroethane (^{13}C), 2.49 ppm for DMSO-d_6 (^{1}H), 39.5 ppm for DMSO-d_6 (^{13}C), 53.8 ppm for CD_2Cl_2 (^{13}C). ^{19}F NMR spectra were recorded on a Bruker AV-300M using $C_6H_5CF_3$ (–63.7 ppm) as an internal standard. Mass spectra were measured on a JEOL MS700V or HX110. Silica gel (CHROMATOREX PSQ100 (Fuji Silysia Chemical Co., Inc.)) was used for all chromatographic procedures.

2, Synthesis

***N*-Difluoromethylbenzanilide (3F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in two-necked flask (50 mL), then a solution of benzanilide (197 mg, 1.00 mmol), in THF (10 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise over 10 min at 0 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (20 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:8) to afford **3F** as a pale yellow solid (161 mg, 65%). Recrystallization afforded colorless needles (CH_2Cl_2-hexane). mp 95.8–97.0 ºC. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ : 7.58 (t, 1H, J = 60.9 Hz, CF_2H), 7.41 (dd, 2H, J = 6.2, 1.6 Hz, CO-Ph_{ortho}), 7.33–7.40 (m, 4H) , 7.26 (t, 2H, J = 7.7 Hz, CO-Ph_{meta}), 7.21–7.24 (m, 2H, N-Ph_{ortho}). $^{13}C\{^{1}H\}$-NMR (100 MHz, CD_2Cl_2) δ : 170.9 (C=O), 135.3 (N-Ph_{ipso}), 134.0 (CO-Ph_{ipso}), 131.4 (Ph_{para}), 130.5 (N-Ph_{ortho}), 129.5 (N-Ph_{meta}), 128.12 (Ph_{para}), 129.10 (CO-Ph_{ortho}), 128.4 (CO-Ph_{meta}), 110.1 (t, J = 244 Hz, CF_2H). ^{19}F-NMR (283 MHz, $CDCl_3$) δ : –101.3 (d, J = 61.3 Hz). IR (KBr): 1671, 1587, 1492, 1448, 1403, 1328, 1278, 1151, 1105, 1018, 923, 879, 800, 700, 669 cm^{-1}. EI -LRMS *m*/*z*: 247 (M^+, 14), 105 (100), 77 (26). EI-HRMS: calcd for $C_{14}H_{11}F_2NO$ [M^+] 247.0803, found 247.0809.

The deuteration ratio of difluoromethane in the reaction of entry 9 (Table 1) was estimated by EI^+ MS.

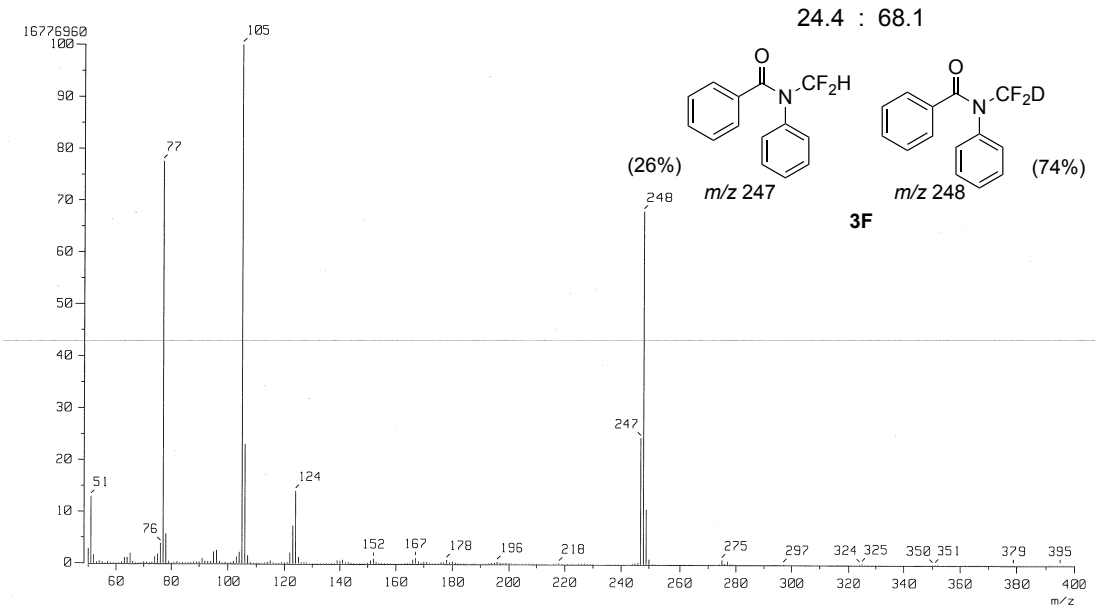


Figure S1. Determination of H/D ratio of partially deuterated product by EI^+ MS.

***N*-Difluoromethyl-acetanilide (2F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in two-necked flask (50 mL), then a solution of acetanilide (135 mg, 1.00 mmol), in THF (10 mL) was added at –78 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise over 10 min at –78 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (20 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:10 to 1:5) to afford **2F** as a colorless oil (69 mg, 37%). Recrystallization afforded colorless granules (CH_2Cl_2-hexane). mp 76.8–78.5 ºC. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ : 7.53 (t, 1H, J = 61.3 Hz, CF_2H), 7.47–7.51 (m, 3H, Ph_{meta} and Ph_{para}), 7.28–7.31 (m, 2H, Ph_{ortho}), 1.85 (s, 3H, CH_3). $^{13}C\{^1H\}$-NMR (150 MHz, $CDCl_3$) δ : 171.5 (*C*=O), 134.5 (Ph_{ipso}), 130.4 ($Ph_{meta\ or\ para}$), 129.81 ($Ph_{meta\ or\ para}$), 129.78 (Ph_{ortho}), 108.2 (t, J = 245 Hz, *C*F_2H), 23.9 (*C*H_3). ^{19}F-NMR (282 MHz, $CDCl_3$) δ : –102.8 (d, J = 61.3 Hz). IR (KBr): 3423, 3359, 3058, 2921, 1905, 1697, 1592, 1500, 1375,

1315, 1278, 1120, 1039, 952, 752, 703, 647 cm^{-1}. EI -HRMS: calcd for $C_9H_9F_2NO$ [M^+] 185.0647, found 185.0651.

***p*-Nitrobenzoyl-benzanilide.** Aniline (0.60 mL, 6.6 mmol) and triethylamine (0.90 mL, 6.5 mmol) were added to a solution of 4-nitrobenzoyl chloride (766 mg, 4.13 mmol) in dry CH_2Cl_2 (12 mL) in a 30 mL two-necked flask. The mixture was stirred for 26 hr at room temperature, and after confirming completion of the reaction by TLC, it was extracted with CH_2Cl_2 (150 mL). The organic solution was washed with 10% HCl (100 mL), sat. $NaHCO_3$ aq. (50 mL), and brine, then dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a solid (735 mg, 74%). Recrystallization from AcOEt-hexane afforded colorless needles. mp 219.5–221.0 ºC. ^{1}H-NMR (400 MHz, 30 ºC, DMSO-*d*$_6$) δ : 10.53 (brs, 1H, NH), 8.36 (d, 2H, *J* = 9.0 Hz, $Ph_{ortho(NO2)}$), 8.18 (d, 2H, *J* = 9.0 Hz, $Ph_{meta(NO2)}$), 7.77 (d, 2H, *J* = 8.2 Hz, Ph_{ortho}), 7.37 (dd, 2H, *J* = 8.2, 8.3 Hz, Ph_{meta}), 7.13 (t, 1H, *J* = 8.3 Hz, Ph_{para}), 6.98 (d, 2H, *J* = 8.9 Hz, $Ph_{meta\ (OCH3)}$). ^{13}C{^{1}H}-NMR (100 MHz, 30 ºC, DMSO-*d*$_6$) δ : 163.8 (*C*=O), 149.1, 140.6, 138.6, 129.1, 128.6, 124.1, 123.5, 120.4. IR (KBr): 3321, 2925, 1653, 1598, 1530, 1441, 1348, 1321, 1106, 760 cm^{-1}. EI -LRMS *m*/*z*: 243 (13), 242 (M^+, 91), 150 (100), 120 (14). EI-HRMS: calcd for $C_{13}H_{10}N_2O_3$ [M^+] 242.0686, found 242.0699.

***p*-Nitrobenzoyl-*N*-difluoromethyl- benzanilide (6F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in two-necked flask (50 mL), then a solution of *p*-nitrobenzoylbenzanilide (242 mg, 1.0 mmol) in THF (20 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (50 mL) and the mixture was extracted with Et_2O and AcOEt (50 mL each). The combined organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:6) and purified by silica gel column chromatography (eluent, CH_2Cl_2:hexane = 3:2) to afford **6F** as a colorless solid (24 mg, 8%). Recrystallization from AcOEt-hexane afforded colorless granular crystals. mp 105.0–106.2 ºC. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ : 8.06 (d, 2H, *J* = 8.7 Hz, $ArNO_{2meta}$), 7.63 (t, 1H, *J* = 60.4 Hz, CF_2H), 7.54 (d, 2H, *J* = 8.7 Hz, $ArNO_{2ortho}$), 7.34–7.35 (m, 3H, N-$Ph_{meta,\ para}$), 7.21 (m, 2H, N-Ph_{ortho}). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ : 168.7 (*C*=O), 148.8 ($Ar_{para\ (NO2)}$), 139.4 ($Ar_{ipso\ (NO2)}$), 134.1(Ph_{opso}), 130.1 (Ph_{ortho}), 129.7 ($Ar_{ortho(NO2)}$), 129.6 (Ph_{meta}), 129.5 (Ph_{para}), 123.3 ($Ar_{meta(NO2)}$), 108.4 (t, *J* = 245 Hz, *C*F_2H). ^{19}F-NMR (376 MHz, CD_2Cl_2, –70 ºC) δ : –103.4 (d, *J* = 55.2 Hz), –94.5 (minor peak, d, *J* = 69.0 Hz). IR (KBr): 2924, 2854, 1682, 1604, 1527, 1403,

1329, 1283, 1162, 1119, 1079, 1009, 849, 742, 703, 651 cm^{-1}. EI -LRMS *m*/*z*: 292 (M^+, 38), 151 (10), 150 (100), 123 (28), 104 (28), 76 (13). EI -HRMS: calcd for $C_{14}H_{10}F_2N_2O_3$ [M^+] 292.0654, found 292.0659.

***p*-Methoxybenzoyl-benzanilide.** [1]

Aniline (0.60 mL, 6.6 mmol) and triethylamine (0.90 mL, 6.5 mmol) were added to a solution of 4-methoxybenzoyl chloride (0.60 mL, 4.4 mmol) in dry CH_2Cl_2 (5 mL) in a 20 mL two-necked flask. The mixture was stirred for 23 h at room temperature, and after confirming completion of the reaction by TLC, it was extracted with CH_2Cl_2 (100 mL). The organic solution was washed with 10% HCl (50 mL x 2), sat. $NaHCO_3$ aq. (100 mL x 3), and brine, then dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a solid (972 mg, 97%). Recrystallization from AcOEt-hexane afforded colorless plates. mp 175.5–176.0 ºC. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ : 7.85 (d, 2H, *J* = 8.9 Hz, $Ar_{ortho(OCH3)}$), 7.74 (brs, 1H), 7.63 (d, 2H, *J* = 7.5 Hz, Ph_{ortho}), 7.37 (dd, 2H, *J* = 7.5, 7.5 Hz, Ph_{meta}), 7.14 (t, 1H, *J* = 7.5 Hz, Ph_{para}), 6.98 (d, 2H, *J* = 8.9 Hz, $Ar_{meta\ (OCH3)}$), 3.88 (s, 3H, OC*H*$_3$). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ : 165.2 (*C*=O), 162.5 ($Ar_{para\ (OCH3)}$), 138.1(Ph_{ipso}), 129.1(Ph_{meta}), 128.9 ($Ar_{ortho(OCH3)}$), 127.1($Ar_{ipso\ (OCH3)}$), 124.3 (Ph_{para}), 120.1(Ph_{ortho}), 114.0 ($Ar_{meta\ (OCH3)}$), 55.5 (O*C*H$_3$). IR (KBr): 3338, 2958, 1657, 1599, 1528, 1507, 1437, 1249, 1182, 1030, 846, 822, 753, 692, 659 cm^{-1}. EI -HRMS: calcd for $C_{14}H_{13}NO_2$ [M^+] 227.0941, found 227.0953.

***p*-Methoxybenzoyl-*N*-difluoromethyl- benzanilide (7F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *p*-methoxybenzoylbenzanilide (227 mg, 1.0 mmol), in THF (20 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise for 10 min at 0 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (50 mL) and the mixture was extracted with Et_2O (100 mL). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, CH_2Cl_2:hexane = 1:2 to 1:1) to afford **7F** as a colorless solid (121 mg, 53%). Recrystallization from hexane afforded a colorless granular solid. mp 40.5–42.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.61 (t, 1H, *J* = 60.9 Hz, CF_2H), 7.39 (d, 2H, *J* = 9.0 Hz, $Ar_{ortho(OCH3)}$), 7.30–7.35 (m, 3H, $Ph_{meta,\ para}$), 7.21 (d, 2H, *J* = 7.8 Hz, Ph_{ortho}), 6.71 (dd, 2H, *J* = 9.0 Hz, $Ar_{meta(OCH3)}$), 3.76 (s, 3H, OC*H*$_3$). ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ : 170.1 (*C*=O), 161.8 ($Ar_{para\ (OCH3)}$), 135.5 (Ph_{ipso}), 131.4 ($Ar_{ortho(OCH3)}$), 129.9 (Ph_{ortho}), 129.1(Ph_{meta}), 128.5 (Ph_{para}), 125.4 ($Ar_{ipso\ (OCH3)}$), 113.3 ($Ar_{meta\ (OCH3)}$), 109.7 (t, *J* = 243 Hz, *C*F_2H), 55.3 (O*C*H$_3$). ^{19}F-NMR (376 MHz, $CDCl_3$) δ : –101.1 (d, *J* = 62.4 Hz). IR (KBr): 2957, 2845, 1675, 1605, 1512,

1325, 1304, 1278, 1030, 843, 735 cm^{-1}. EI -HRMS: calcd for $C_{15}H_{13}F_2NO_2$ [M^+] 277.0909, found 277.0914.

***N*-Difluoromethyl-*p*-nitro-benzanilide (8F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in two-necked flask (50 mL), then a solution of *N*-*p*-nitrobenzanilide (242 mg, 1.0 mmol) in THF (20 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 15 min. The reaction was quenched by adding sat. NH_4Cl aq. (2 mL) and the mixture was extracted with CH_2Cl_2 (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:7) to afford **8F** as a colorless solid (154 mg, 53%). Recrystallization from AcOEt-hexane afforded colorless granular crystals. mp 91.0–92.0 ºC. ^{1}H-NMR (400 MHz, CD_2Cl_2) δ : 8.20 (d, 2H, *J* = 9.0 Hz, $Ar_{meta(NO2)}$), 7.73 (t, 1H, *J* = 60.0 Hz, CF_2H), 7.38–7.44 (m, 5H, Ph_{ortho}, $Ph_{para,}$ $Ar_{ortho(NO2)}$), 7.28 (dd, 2H, *J* = 7.8, 7.6 Hz, Ph_{meta}). ^{13}C{^{1}H}-NMR (150 MHz, CD_2Cl_2) δ : 170.2 (*C*=O), 147.8 ($Ar_{para(NO2)}$), 141.2 ($Ar_{ipso\ (NO2)}$), 133.1 (Ph_{ipso}), 132.2, 131.1, 129.2 (Ph_{meta}), 128.8, 124.8 ($Ar_{ortho(NO2)}$), 110.2 (t, *J* = 244 Hz, *C*F_2H). ^{19}F-NMR (376 MHz, CD_2Cl_2) δ : –100.3 (d, *J* = 60.9 Hz). IR (KBr): 2953, 2923, 2854, 1687, 1673, 1608, 1595, 1525, 1493, 1461, 1449, 1386, 1349, 1322, 1307, 1286, 1145, 1101, 1079, 1041, 851, 798, 777, 742, 704, 665 cm^{-1}. EI -HRMS: calcd for $C_{14}H_{10}F_2N_2O_3$ [M^+] 292.0654, found 292.0655.

***N*-Difluoromethyl- *N*- *p*-methoxy-benzanilide (9F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *p*-methoxybenzoylbenzanilide (227 mg, 1.0 mmol) in THF (10 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.47 mL, 3.00 mmol) was added dropwise over 10 min at 0 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (30 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:8) to afford **9F** as a colorless solid (158 mg, 57%). Recrystallization from AcOEt-hexane afforded colorless prisms. mp 74.5–76.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.56 (t, 1H, *J* = 61.3Hz, CF_2H), 7.39 (d, 2H, *J* = 7.7 Hz, Ph_{ortho}), 7.32 (t, 1H, *J* = 7.3 Hz, Ph_{para}), 7.23 (dd, 2H, *J* = 7.3, 7.7 Hz, Ph_{meta}), 7.10 (d, 2H, *J* = 9.1 Hz, $Ar_{ortho(OCH3)}$), 6.81 (d, 2H, *J* = 9.1 Hz, $Ar_{meta\ (OCH3)}$), 3.76 (s, 3H, O*C*H_3). ^{13}C{^{1}H}-NMR (100 MHz, 40 ºC, $CDCl_3$) δ : 170.8 (*C*=O), 159.7 ($Ar_{para\ (OCH3)}$), 133.9 (Ph_{ipso}), 131.3 ($Ar_{ortho(OCH3)}$),

130.9 (Ph_{para}), 128.8 (Ph_{ortho}), 128.0 (Ph_{meta}), 127.4 ($Ar_{ipso(OCH3)}$), 114.4 ($Ar_{meta\ (OCH3)}$), 110.2 (t, *J* = 243 Hz, *C*F_2H), 55.4 (O*C*H_3). ^{19}F-NMR (376 MHz, 40 ºC, $CDCl_3$) δ : –101.7 (m). IR (KBr): 3434, 3069, 2954, 2931, 2838, 1669, 1606, 1583, 1511, 1462, 1446, 1422, 1384, 1331, 1296, 1252, 1171, 1153, 1091, 1036, 935, 879, 835, 807, 794, 748, 713 cm^{-1}. EI -LRMS *m*/*z*: 278 (11), 277 (M^+, 62), 153 (45), 138 (10), 105 (100), 77 (26). EI -HRMS: calcd for $C_{15}H_{13}F_2N_2O_3$ [M^+] 277.0909, found 277.0903.

***N*-Difluoromethyl-*N*-pentafluorophenyl-benzanilide (10F).** NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *N*-pentafluorophenylbenzanilide, prepared by the reported method [2] (287 mg, 1.0 mmol), in THF (20 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.31 mL, 2.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 15 min. The reaction was quenched by adding sat. NH_4Cl aq. (2 mL) and the mixture was extracted with CH_2Cl_2 (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, Et_2O:hexane = 1:11 to 1:13) to afford **10F** as a colorless oil (117 mg, 35%). Recrystallization from hexane afforded colorless granular crystals. mp 57.0–57.5 ºC. ^{1}H-NMR (400 MHz, 80 ºC, $(CDCl_2)_2$) δ : 7.46–7.53 (m, 3H, $Ph_{ortho,}$ Ph_{para}), 7.41 (t, 1H, *J* = 60.4 Hz, CF_2H), 7.39-41 (m, 2H, Ph_{meta}). ^{13}C{^{1}H}-NMR (100 MHz, 90 ºC, $(CDCl_2)_2$) δ : 169.3 (*C*=O), 145.2 (d, *J* = 254.3 Hz), 139.7 (d, *J* = 265.9 Hz), 137.6 (d, *J* = 262.0 Hz), 132.2(Ph_{ipso}), 132.1 (Ph_{para}), 128.6 (Ph_{meta}), 127.0 (Ph_{ortho}), 109.6 (t, *J* = 249.5 Hz, *C*F_2H). 1 peak missing (*ipso* carbon of C_6F_5 moiety) due to intense coupling. ^{19}F-NMR (376 MHz, 120 ºC, $(CDCl_2)_2$) δ : –101.6 (d, *J* = 63 Hz, 2F, C*F*$_2$H), -142.8 (d, *J* = 15 Hz, 2F, $Ar_{ortho\ (F5)}$), -151.3 (t, *J* = 21 Hz, 1F, $Ar_{para\ (F5)}$), -162.1 (dd, *J* = 20, 20 Hz, 2F, $Ar_{meta\ (F5)}$). IR (KBr): 2925, 1813, 1603, 1521, 1479, 1447, 1391, 1324, 1300, 1288, 1233, 1152 cm^{-1}. EI -LRMS *m*/*z*: 337 (M^+, 4), 213 (2), 105 (100), 77 (46). EI -HRMS: calcd for $C_{14}H_6F_7NO$ [M^+] 337.0332, found 337.0328.

Methyl-*p*-(acetamidomethyl)benzoate. [3]

Methyl 4-(aminomethyl) benzoate Hydrochloride (1.00 g, 4.96 mmol) was placed into a 50 mL round flask and dissolved with CH_2Cl_2 (10 mL). To this solution acetyl chloride (530 µl, 7.43 mmol) triethylamine (2.0 mL, 14 mmol) were added under iced bath and the mixture was stirred for 24 hr at room temperature, and the reaction was confirmed to be completed by monitoring TLC. The mixture was extracted with CH_2Cl_2 (250 mL) and washed with 2N HCl (50 mL), sat. $NaHCO_3$ aq. (50 mL x 2), and brine, then dried over Na_2SO_4. The organic layer was filtered then evaporated under reduced

pressure to afford yellow solid. The crude was purified by silica gel column chromatography (AcOEt : hexane = 1:2 to 2:1) to afford product as colorless solid (897 mg, 87%). Recrystallization from AcOEt-hexane afforded colorless prisms. mp 113.0–114.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.00 (d, 2H, *J* = 8.3 Hz, $Ar_{metaCO2CH3}$), 7.35 (d, 2H, *J* = 8.3 Hz, $Ar_{orthoCO2CH3}$), 5.80 (brs, 1H, N*H*), 4.50 (d, 2H, *J* = 6.0 Hz, CH_2Ar), 3.92 (s, 3H, CO_2CH_3), 2.06 (s, 3H, CH_3CO). EI -HRMS: calcd for $C_{11}H_{13}NO_3$ [M^+] 207.0890, found 207.0899.

Methyl-*p*-((*N*-difluromethyl)acetamido)methyl)benzoate (11F). NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of methyl-*p*-(acetamidomethyl)benzoate (199 mg, 1.0 mmol) in THF (10 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.467 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (30 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:6) to afford **11F** as a colorless oil (98 mg, 38%). ^{1}H-NMR (400 MHz, 90 ºC, DMSO-*d*$_6$) δ : 7.91 (d, 2H, *J* = 8.2 Hz, $Ar_{metaCO2CH3}$), 7.48 (t, 1H, *J* = 60.4 Hz, CF_2H), 7.39 (d, 2H, *J* = 8.2 Hz, $Ar_{orthoCO2CH3}$), 4.69 (s, 2H, CH_2Ar), 3.85 (s, 3H, COOCH_3), 2.19 (s, 3H, CH_3CO). ^{13}C{^{1}H}-NMR (100 MHz, 100 ºC, DMSO-*d*$_6$) δ : 169.4 (CH_3CO), 165.5 ($COOCH_3$), 142.5 ($Ar_{ipsoCO2CH3}$), 128.7 ($Ar_{metaCO2CH3}$), 128.3 ($Ar_{paraCO2CH3}$), 126.5 ($Ar_{orthoCO2CH3}$), 111.5 (t, *J* = 234.3 Hz, CF_2H), 51.3 ($COOCH_3$), 42.8 (CH_2Ar), 21.2 (CH_3CO). ^{19}F-NMR (376 MHz, 130 ºC, DMSO-*d*$_6$) δ : –99.1 (brs, 2F). IR (KBr): 3432, 2923, 2853, 1722, 1702, 1658, 1614, 1402, 1398, 1323, 1282, 1192, 1114, 1020, 981, 753 cm^{-1}. EI -LRMS *m*/*z*: 257 (M^+, 100), 226 (40), 215 (25), 214 (17), 206 (14), 200 (20), 164 (62), 156 (43), 136 (11). EI -HRMS: calcd for $C_{11}H_{13}F_2NO_3$ [M^+] 257.0858, found 257.0870.

N-CHO product was also isolated. (18 mg, 0.8%)
Methyl-*p*-((*N*-formyl)acetamido)methyl)benzoate; colorless needles (recryst. from CH_2Cl_2-hexane). mp 76.5–77.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 9.24 (s, 1H, C*H*O), 7.95 (d, 2H, *J* = 8.7 Hz, $Ar_{metaCO2CH3}$), 7.35 (d, 2H, *J* = 8.7 Hz, $Ar_{orthoCO2CH3}$), 4.90 (s, 2H, CH_2Ar), 3.88 (s, 3H, COOCH_3), 2.38 (s, 3H, CH_3CO). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ : 170.9 (CH_3CO), 166.7 ($COOCH_3$), 162.5 (*C*HO), 141.4 ($Ar_{ipsoCO2CH3}$) , 129.9 ($Ar_{metaCO2CH3}$), 129.5 ($Ar_{paraCO2CH3}$), 128.3 ($Ar_{orthoCO2CH3}$), 52.1 ($COOCH_3$), 42.8 (CH_2Ar), 22.9 (CH_3CO). IR (KBr): 2953, 1721, 1664, 1613, 1434, 1375, 1333, 1309, 1277, 1186, 1109, 1043, 976, 937, 634 cm^{-1}. EI -LRMS *m*/*z*: 235

(M^+, 39), 204 (25), 194 (16), 193 (100), 192 (63), 178 (13), 165 (10), 164 (76), 134 (14). EI -HRMS: calcd for $C_{12}H_{13}NO_4$ [M^+] 235.0839, found 235.0849.

Methyl-*p*-((*N*-methyl)acetamido)methyl)benzoate (11). NaH (29 mg, 60% oil suspension, 0.725 mmol) was washed with hexane twice and dried, then placed in a 10 mL two-necked flask. To the flask, a solution of methyl-*p*-(acetamidomethyl)benzoate (75 mg, 0.362 mmol) in THF (1 mL) was added at 0 ºC and the mixture was stirred or 10 min at this temperature. Next, CH_3I (45 µL, 0.723 mmol) was added at 0 ºC, and stirring was continued at room temperature for 2 h. The reaction was quenched by adding sat. NH_4Cl aq. (20 mL) and the mixture was extracted with Et_2O (15 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:2) to afford **11** as a colorless oil (12 mg, 15%). ^{1}H-NMR (400 MHz, 140 ºC, DMSO-d_6) δ : 7.92 (d, 2H, J = 8.2 Hz, $Ar_{metaCO2CH3}$), 7.35 (d, 2H, J = 8.2 Hz, $Ar_{orthoCO2CH3}$), 4.59 (s, 2H, CH_2Ar), 3.87 (s, 3H, COOCH_3), 2.05 (s, 3H, CH_3CO). ^{13}C{^{1}H}-NMR (100 MHz, 140 ºC, DMSO-d_6) δ : 169.2 (CH_3CO), 165.4 ($COOCH_3$), 142.7 ($Ar_{ipsoCO2CH3}$), 128.6 ($Ar_{metaCO2CH3}$), 128.3 ($Ar_{paraCO2CH3}$), 126.6 ($Ar_{orthoCO2CH3}$), 50.9 (COOCH_3), 20.2 (CH_3CO). HSQC spectra showed the missing *N*-CH_3 peak at 35.8 ppm and CH_2Ar peak at 50.6 ppm. IR (KBr): 3435, 2953, 2927, 1721, 1643, 1580, 1546, 1479, 1435, 1407, 1281, 1111, 1018, 750 cm^{-1}. EI -LRMS *m*/*z*: 222 (15), 221 (M^+, 100), 220 (10), 190 (20), 178 (27), 164 (20), 149 (14), 120 (13). EI -HRMS: calcd for $C_{12}H_{15}NO_3$ [M^+] 221.1046, found 221.1045.

Methyl-*p*-(benzamidomethyl)benzoate. [4]

Methyl 4-(aminomethyl)benzoate hydrochloride (1.00 g, 4.96 mmol) was placed in a 50 mL round flask and dissolved in THF (20 mL). To this solution, benzoyl chloride (863 µL, 7.43 mmol) and triethylamine (2.0 mL, 14 mmol) were added on an ice bath. The mixture was stirred for 24 hr at room temperature, and after confirming completion of the reaction by TLC, it was extracted with AcOEt (150 mL). The organic solution was washed with H_2O (50 mL), 2 N HCl (50 mL), sat. $NaHCO_3$ aq. (50 mL x 2), and brine, then dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a colorless solid. The crude product was purified by silica gel column chromatography (AcOEt : hexane = 1:2) to afford a colorless solid (1.13 g, 85%). Recrystallization from AcOEt afforded colorless needles. mp 157.0–159.0 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.01 (d, 2H, J = 7.2 Hz, $Ar_{metaCO2CH3}$), 7.80 (d, 2H, J = 7.2 Hz, Ph_{ortho}), 7.52 (t, 1H, J = 7.3 Hz, Ph_{para}), 7.40-7.63 (m, 4H, $Ar_{orthoCO2CH3}$, Ph_{meta}), 6.56 (brs, 1H, N*H*), 4.71 (d, 2H, J = 6.0 Hz, CH_2Ar), 3.91 (s, 3H, COOCH_3). ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ : 167.5 (CH_3CO), 166.8

(*C*OOCH$_3$), 143.4 (Ar$_{ipsoCO2CH3}$), 134.1 (Ar$_{paraCO2CH3}$), 131.7 (Ph$_{para}$), 130.1 (Ar$_{metaCO2CH3}$), 129.4 (Ph$_{ipso}$), 128.7 (Ar$_{orthoCO2CH3}$), 127.6 (Ph$_{meta}$), 127.0 (Ph$_{ortho}$), 52.1 (COO*C*H$_3$), 43.7 (*C*H$_2$Ar). IR (KBr): 3293, 1712, 1640, 1610, 1549, 1489, ,1436, 1412, 1359, 1317, 1285, 1265, 1187, 1173, 1158, 1113, 1078, 1058, 1013, 989, 967, 934, 860, 807, 789, 752 cm^{-1}. EI -HRMS: calcd for $C_{16}H_{15}NO_3$ [M$^+$] 269.1046, found 269.1051.

Methyl-*p*-((*N*-difluromethyl)benzamido)methyl)benzoate (12F). NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of methyl-*p*-(benzamidomethyl)benzoate (269 mg, 1.0 mmol), in THF (10 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then TMSCF$_2$Br (0.467 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH$_4$Cl aq. (30 mL) and the mixture was extracted with Et$_2$O (40 mL x 2). The organic solution was washed with brine, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:6) to afford **12F** as a colorless oil (118 mg, 37%). mp 69.5–71.5 ºC.^{1}H-NMR (400 MHz, 80 ºC, DMSO-*d$_6$*) δ : 7.92 (d, 2H, *J* = 8.2 Hz, Ar$_{metaCO2CH3}$), 7.49–7.57 (m, 5H, Ph), 7.45 (d, 2H, *J* = 8.2 Hz, Ar$_{orthoCO2CH3}$), 7.19 (t, 1H, *J* = 59.5 Hz, CF$_2$*H*), 4.81 (s, 2H, C*H*$_2$Ar), 3.85 (s, 3H, COO*C*H$_3$). ^{13}C{^{1}H}-NMR (150 MHz, DMSO-*d$_6$*) δ : 169.7 (CH$_3$*C*O), 166.0 (*C*OOCH$_3$), 142.9 (Ar$_{ipsoCO2CH3}$), 133.4, 131.5 (Ph$_{para}$), 129.3, 128.9, 128.4 (Ar$_{metaCO2CH3}$), 127.4, 127.2 (Ar$_{orthoCO2CH3}$), 112.8 (t, *J* = 239.9 Hz, *C*F$_2$H), 52.1 (COO*C*H$_3$), 43.1 (*C*H$_2$Ar). ^{19}F-NMR (376 MHz, 80 ºC, DMSO-*d$_6$*) δ : –98.3 (d, *J* = 59.0 Hz, 2F). IR (KBr): 3450, 1722, 1682, 1640, 1438, 1411, 1376, 1330, 1281, 1194, 1152, 1108, 1021, 976, 794, 752 cm^{-1}. EI -LRMS *m*/*z*: 319 (M$^+$, 50), 288 (12), 105 (74), 88 (11), 86 (67), 84 (100), 77 (13). EI -HRMS: calcd for $C_{17}H_{15}F_2NO_3$ [M$^+$] 319.1015, found 319.1022.

Methyl-*p*-((*N*-methyl)benzamido)methyl)benzoate (12). NaH (30 mg, 60% oil suspension, 0.75 mmol) was washed with hexane twice and dried, then placed into 10 mL two-necked flask. To the flask, a solution of methyl-*p*-(benzamidomethyl)benzoate (100 mg, 0.371 mmol) in THF (2 mL) was added at 0 ºC and the mixture was stirred for 10 min at this temperature. Next, CH$_3$I (47 μL, 0.755 mmol) was added at 0 ºC, and stirring was continued at room temperature for 24 hr. The reaction was quenched by adding H$_2$O (20 mL) and the mixture was extracted with Et$_2$O (20 mL x 2). The organic solution was dried over Na$_2$SO$_4$, then evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:1) to afford **12** as a colorless oil (8 mg, 8%). ^{1}H-NMR (400 MHz, 80 ºC, DMSO-*d$_6$*) δ : 7.95 (d, 2H, *J* = 8.2 Hz, Ar$_{metaCO2CH3}$), 7.43 (m(s), 7H), 4.67 (s, 2H, -C*H*$_2$Ar), 3.86

(s, 3H, COOCH_3), 2.89 (s, 3H, N-CH_3). $^{13}C\{^1H\}$-NMR (100 MHz, 130 ºC, DMSO-d_6) δ : 170.3 (CH_3CO), 165.5 ($COOCH_3$), 142.3 ($Ar_{ipsoCO2CH3}$), 136.0, 128.8 ($Ar_{metaCO2CH3}$), 128.7, 128.6, 127.7, 126.9, 126.0, 51.1 (-CH_2Ar), 34.8 (N-CH_3). IR (KBr): 3450, 1719, 1627, 1526, 1279, 1111, 1072, 1020, 699 cm^{-1}. EI -LRMS *m*/*z*: 284 (18), 283 (M^+, 100), 252 (16), 178 (13), 176 (14), 105 (99), 77 (25). EI -HRMS: calcd for $C_{17}H_{17}NO_3$ [M^+] 283.1203, found 283.1206.

***N*-(1-Naphthalenylmethyl)acetamide**. [5] 1-Naphthalenylmethylamine (1.00 g, 6.36 mmol) was placed in a 30 mL round flask and dissolved in CH_2Cl_2 (10 mL). To this solution, acetyl chloride (0.54 mL, 9.56 mmol) and triethylamine (1.32 mL, 9.52 mmol) were added on an ice bath. The mixture was stirred for 18 hr at room temperature, and after confirming complete consumption of the amine by TLC, it was extracted with CH_2Cl_2 (20 mL). The organic solution was washed with H_2O (20 mL), 2 N HCl (20 mL), 2 N NaOH aq. (20 mL) and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a colorless solid. The crude product was purified by silica gel column chromatography (AcOEt : hexane = 1:1 to 2:1) to afford a colorless solid (1.08 g, 85%). Recrystallization from CH_2Cl_2-hexane afforded colorless needles. mp 129.0–130.5 ºC. ^{1}H-NMR (400 MHz, $CDCl_3$) δ :8.02 (d, 1H, *J* = 6.3 Hz), 7.89 (d, 1H, *J* = 6.3 Hz), 7.83 (dd, 1H, *J* = 6.3, 6.3 Hz), 7.52–7.58 (m, 2H), 7.43–7.44 (m, 2H), 5.65 (brs, 1H, N*H*), 4.90 (d, 2H, *J* = 5.3 Hz, -CH_2Ar), 2.01 (s, 3H, CH_3CO). $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ : 169.6 (CH_3CO), 133.9, 133.5, 131.4, 128.8, 128.7, 126.9, 126.7, 126.1, 125.4, 123.5, 42.0 (-CH_2Ar), 23.3 (CH_3CO). IR (KBr): 3299, 1638, 1549, 1287, 1071, 778 cm^{-1}. LRMS *m*/*z*: 200 (15), 199 (M^+, 100), 157 (36), 156 (95), 141 (25), 129 (22), 128 (14), 127 (10). EI -HRMS: calcd for $C_{13}H_{13}NO$ [M^+] 199.0992, found 199.0998.

***N*-Difluoromethyl-(1-naphthalenylmethyl)acetamide (13F)**. NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *N*-(1-naphthalenylmethyl)acetamide (199 mg, 1.0 mmol) in THF (10 mL) was added at 0 ºC and the mixture was stirred for 10 min at this temperature. Next, $TMSCF_2Br$ (0.467 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (30 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduce pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:5) to afford **13F** as a colorless oil (55 mg, 22%). Recrystallization from CH_2Cl_2-hexane afforded colorless prisms. mp 97.5–99.0 ºC. ^{1}H-NMR (400 MHz, 80 ºC, DMSO-d_6) δ : 8.10 (d, 1H, *J* = 8.2 Hz, Ar-8), 7.95 (d, 1H, *J* = 7.3 Hz, Ar-5), 7.83 (d, 1H, *J* = 8.2 Hz, Ar-4), 7.55–7.60 (m, 2H), 7.57 (t, 1H, *J* = 60.6 Hz, CF_2H), 7.47

(dd, 1H, *J* = 7.8, 7.8 Hz, Ar-3), 7.29 (d, 1H, *J* = 6.9 Hz, Ar-2), 5.12 (s, 2H, -C*H*$_2$Ar), 2.23 (s, 3H, C*H*$_3$CO). ^{13}C{^{1}H}-NMR (100 MHz, 95 ºC, DMSO-*d*$_6$) δ : 169.8 (CH$_3$*C*O), 132.8 (Ar-10), 132.1 (Ar-1, *ipso*), 129.8 (Ar-9), 128.1 (Ar-5), 126.9 (Ar-4), 125.8 (Ar-6), 125.3 (Ar-7), 124.8 (Ar-3), 122.7 (Ar-2), 122.2 (Ar-8), 111.5 (t, *J* = 242.0 Hz, *C*F$_2$H), 41.0 (-*C*H$_2$Ar), 21.3 (*C*H$_3$CO). ^{19}F-NMR (376 MHz, 130 ºC, DMSO-*d*$_6$) δ : –99.7 (brs). IR (KBr): 1684, 1599, 1426, 1377, 1346, 1327, 1203, 1125, 1058, 1005, 975, 944, 794, 771 cm^{-1}. EI -LRMS *m*/*z*: 250 (16), 249 (M$^+$, 100), 207 (39), 206 (60), 186 (13), 156 (35), 141 (41), 129 (14). EI -HRMS: calcd for $C_{14}H_{13}F_2NO$ [M$^+$] 249.0960, found 249.0961.

***N*-(1-Naphthalenylmethyl)benzamide**. [6] 1-Naphthalenylmethylamine (1.00 g, 6.36 mmol) was placed in a 30 mL round flask and dissolved in CH_2Cl_2 (10 mL). To this solution benzoyl chloride (1.11 mL, 9.55 mmol) and triethylamine (1.32 mL, 9.52 mmol) were added on an ice bath and the mixture was stirred for 24 hr at room temperature. After confirming complete consumption of the amine by TLC, the mixture was extracted with AcOEt (100 mL). The organic solution was washed with H_2O (30 mL), 2 N HCl (50 mL), sat. $NaHCO_3$ aq. (30 mL), and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to afford a colorless solid. The crude product was purified by silica gel column chromatography (AcOEt : hexane = 1:2 to 1:1) to afford a colorless solid (1.27 g, 76%). Recrystallization from AcOEt -hexane afforded a colorless fluffy solid. mp 145.0–146.5 ºC. ^{1}H-NMR (600 MHz, $CDCl_3$) δ : 8.09 (d, 1H, *J* = 8.3 Hz), 7.90 (d, 1H, *J* = 7.5 Hz), 7.86 (d, 1H, *J* = 7.5 Hz), 7.76 (d, 2H, *J* = 7.5 Hz, Ph$_{ortho}$), 7.44–7.57 (m, 5H), 7.40 (d, 2H, *J* = 8.3, 7.5 Hz, Ph$_{meta}$), 6.33 (brs, 1H, N*H*), 5.11 (d, 2H, *J* = 5.3 Hz, -C*H*$_2$Ar). ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ : 167.1 (*C*=O), 134.3, 133.9, 133.3, 131.6 (2 carbon peaks are observed as a single peak as confirmed by HSQC analysis), 131.5, 128.8, 128.6 (Ph$_{meta}$), 127.0, 126.9 (Ph$_{ortho}$), 126.8, 126.1, 125.4, 123.5, 42.4 (-*C*H$_2$Ar). IR (KBr): 3277, 2922, 1635, 1547, 1487, 1314, 1026, 1008, 786, 768, 695 cm^{-1}. EI -LRMS *m*/*z*: 262 (20), 261 (M$^+$, 100), 260 (10), 156 (37), 129 (11), 105 (57), 77 (12). EI -HRMS: calcd for $C_{18}H_{15}NO$ [M$^+$] 261.1148, found 261.1149.

***N*-Difluoromethyl-(1-naphthalenylmethyl)benzamide (14F)**. NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *N*-(1-naphthalenylmethyl)benzamide (261 mg, 1.0 mmol) in THF (10 mL) was added at 0 ºC and the mixture was stirred for 10 min at this temperature. Next, $TMSCF_2Br$ (0.467 mL, 3.00 mmol) was added dropwise over 10 min at –50 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (30 mL) and the mixture was extracted with Et_2O (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel

column chromatography (eluent, AcOEt:hexane = 1:8 to 1:5) to afford **14F** as a colorless oil (75 mg, 24%). mp 88.5–89.5 ºC. ^{1}H-NMR (400 MHz, 40 ºC, $CDCl_3$) δ : 8.06 (d, 1H, *J* = 8.7 Hz), 7.96 (d, 1H, *J* = 7.3 Hz), 7.79 (d, 1H, *J* = 8.2 Hz), 7.41–7.56 (m, 9H), 7.00 (t, 1H, *J* = 59.5 Hz, CF_2H), 5.33 (s, 2H, -CH_2Ar). ^{13}C{^{1}H}-NMR (150 MHz, 40 ºC, $CDCl_3$) δ : 170.4 (*C*=O), 133.9, 133.8, 132.2, 131.5, 131.1, 129.0, 128.9, 128.1, 127.7, 126.3, 125.7, 125.3, 125.0, 122.8, 113.1 (t, *J* = 241.0 Hz, CF_2H), 41.3 (-*C*H_2Ar). ^{19}F-NMR (376 MHz, 40 ºC, $CDCl_3$) δ : –97.9 (brs, 2F). IR (KBr): 3423, 3057, 2925, 1676, 1417, 1342, 1290, 1153, 1090, 1023, 977, 789 cm^{-1}. EI -LRMS *m*/*z*: 312 (12), 311 (M^+, 57), 206 (37), 141 (21), 105 (71), 86 (65), 84 (100), 77 (14). EI -HRMS: calcd for $C_{19}H_{15}F_2NO$ [M^+] 311.1116, found 311.1119.

***N*-Acetyl-*N*-difluoromethyl-L-phenylalanine methyl ester** (**15F**). NaOtBu (288 mg, 3.00 mmol) was measured in a glove box and placed in a two-necked flask (50 mL), then a solution of *N*-acetyl-L-phenylalanine methyl ester (221 mg, 1.0 mmol) in THF (10 mL) was added at 0 ºC. The mixture was stirred for 10 min at this temperature, then $TMSCF_2Br$ (0.467 mL, 3.00 mmol) was added dropwise over 10 min at –78 ºC, and stirring was continued at this temperature for 30 min. The reaction was quenched by adding sat. NH_4Cl aq. (30 mL) and the mixture was extracted with AcOEt (30 mL x 2). The organic solution was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt:hexane = 1:8 to 1:5) to afford **15F** as a colorless oil (37 mg, 14%). Recrystallization from CH_2Cl_2-hexane afforded colorless prisms. mp 57.5–58.5 ºC. ^{1}H-NMR (400 MHz, 20 ºC, CD_2Cl_2) δ : 7.29 (dd, 2H, *J* = 7.3, 6.9 Hz, Ph_{meta}), 7.22 (t, 1H, *J* = 6.9 Hz, Ph_{para}), 7.19 (d, 2H, *J* = 7.3 Hz, Ph_{ortho}), 6.65 (t, 1H, *J* = 59.5 Hz, CF_2H), 4.53 (dd, 1H, *J* = 9.1, 5.5 Hz, Cα*H*), 3.70 (s, 3H, COOCH_3), 3.49 (dd, 1H, *J* = 14.2, 5.5 Hz, -CH_2Ar), 3.13 (dd, 1H, *J* = 14.2, 9.1 Hz, -CH_2Ar), 2.18 (s, 3H, CH_3CO). ^{13}C{^{1}H}-NMR (150 MHz, CD_2Cl_2) δ : 170.3 (*C*=O), 169.0 (*C*OOCH$_3$), 138.1 (Ph_{ipso}), 129.7 (Ph_{ortho}), 128.7 (Ph_{meta}), 127.0 (Ph_{para}), 112.2 (t, *J* = 264.1 Hz, *C*F_2H), 56.8 (*C*α), 52.8 (COO*C*H$_3$), 36.1 (-*C*H_2Ar), 22.6 (*C*H_3CO). ^{19}F-NMR (376 MHz, CD_2Cl_2) δ : –94.6 (d, *J* = 60.3 Hz, 2F). IR (KBr): 2924, 2854, 1747, 1689, 1640, 1441, 1375, 1254, 1071, 1036 cm^{-1}. EI -LRMS *m*/*z*: 271 (M^+, 2), 170 (29), 163 (15), 162 (100), 161 (13), 138 (21), 131 (33), 91 (21). EI -HRMS: calcd for $C_{13}H_{15}F_2NO_3$ [M^+] 271.1015, found 271.1018.

***N*-Methyl-L-phenylalanine methyl ester hydrochloride.** Synthesized as reported.[7] LiOH-H_2O (418 mg, 9.96 mmol) and 4 Å molecular sieves (1.8 g) were placed in a 50 mL flask. DMF (15 mL) was added and the mixture was stirred for 20 min at rt. Next, L-phenylalanine methyl ester hydrochloride (1.00 g, 4.64 mmol) was added and stirring was continued for an additional 45

min at rt under an Ar atmosphere. To this mixture, CH_3I (320 µl, 5.14 mmol) was added. Stirring was continued for 21 h at room temperature, then the brown suspension was filtered and washed with AcOEt. The organic layer was washed with H_2O (50 mL x 2), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The resulting yellow oil was purified by silica gel column chromatography (eluent, AcOEt only) to afford a pale yellow oil (138 mg, 13%). ^{1}H-NMR (400 MHz, $CDCl_3$) δ : 7.29 (dd, 2H, *J* = 6.5, 7.0 Hz, Ph_{meta}), 7.21 (t, 1H, *J* = 7.0 Hz, Ph_{para}), 7.17 (d, 2H, *J* = 7.5 Hz, Ph_{ortho}), 3.67 (s, 3H, COOC*H*$_3$), 3.45 (t, *J* = 7.0 Hz, 4H, N*H*$_4^+$), 2.94-2.96 (m, 2H, -C*H*$_2$Ar), 2.36 (s, 3H, C*H*$_3$CO). EI -HRMS: calcd for $C_{11}H_{16}NO_2$ [[M+H–Cl]$^+$] 194.1181, found 194.1180.

***N*-Acetyl-*N*-methyl-L-phenylalanine methyl ester** (**15**).[8] To a solution of *N*-methyl-L-phenylalanine methyl ester hydrochloride (128 mg, 557 µmol) in CH_2Cl_2 (2 mL) in a 30 mL round flask were added acetyl chloride (80 µl, 1.13 mmol) and triethylamine (240 µl, 1.73 mmol) on an ice bath. The mixture was stirred for 21 h at rt, then diluted with CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ aq. (50 mL), 2 N HCl (50 mL) and brine (50 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt-hexane = 1:1) to give the title compound as a yellow oil (109 mg, 83%). H-NMR (400 MHz, 130 ºC, DMSO-*d*$_6$) δ : 7.22-7.27 (m(s), 5H), 5.04 (brs, 2H,), 3.67 (s, 3H, COOC*H*$_3$), 3.21-3.26 (dd, 1H, *J* = 14.4, 5.6 Hz, -C*H*$_2$Ar), 3.00-3.07 (dd, 1H, *J* = 14.4, 9.7 Hz, -C*H*$_2$Ar), 2.80 (brs, 3H, N-C*H*$_3$), 1.86 (s, 3H, C*H*$_3$CO).^{13}C{^{1}H}-NMR (100 MHz, 130 ºC, DMSO-*d*$_6$) δ : 170.1 (*C*=O), 169.4 (*C*OOCH$_3$), 137.0 (Ph_{ipso}), 128.1 (Ph_{ortho}), 127.5 (Ph_{meta}), 125.6 (Ph_{para}), 51.0 (COO*C*H$_3$), 33.8 (-*C*H$_2$Ar), 20.3 (*C*H$_3$CO). (Two carbon peaks, *N*-CH$_3$ (28.6 and 34.0 ppm) and α-H (58.3 and 61.5 ppm) observed at room temperature with two conformers, are missing in the spectra measured at 130 ºC.) IR (KBr): 3028, 2952, 1740, 1651, 1435, 1402, 1220, 1019, 752, 702 cm^{-1}. EI -LRMS *m*/*z*: 235 (M$^+$, 2), 176 (20), 163 (11), 144 (23), 134 (63), 102 (100), 91 (10). EI -HRMS: calcd for $C_{13}H_{17}NO_3$ [M$^+$] 235.1203, found 235.1208.

***N*-Isopropyl benzanilide (17).** To the solution of *N*-isopropylaniline (500 mg, 3.70 mmol) in CH_2Cl_2 (10 mL) in a 50 mL round flask were added benzoyl chloride (350 µl, 3.01mmol) and triethylamine (650 µl, 4.69 mmol) on an ice bath. The mixture was stirred for 3 h at rt, then diluted with CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ aq. (30 mL), 2 N HCl (30 mL) and brine (30 mL), dried over Na_2SO_4 and filtered. The filtrate was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent, AcOEt-hexane = 1:4) to give the title product as a colorless solid (791 mg, q. y.). Recrystallization from

AcOEt-hexane afforded colorless prisms. mp 64.0–65.0 ºC. H-NMR (400 MHz, 50 ºC, $CDCl_3$) δ : 7.08-7.25 (m, 8H), 7.01 (d, 2H, J = 6.9 Hz, $PhCO_{ortho}$), 5.06 (septet, 1H, J = 6.9 Hz, N-C*H*$(CH_3)_2$), 1.21 (d, 6H, J = 6.9 Hz, N-CH(C*H*$_3)_2$).$^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ : 170.7 (*C*=O), 139.6 ($PhCO_{ipso}$), 137.3 (PhN_{ipso}), 130.6 ($PhCO_{ortho}$), 128.9, 128.6, 128.1 ($PhCO_{para}$), 127.6, 127.3, 47.7 (N-*C*H$(CH_3)_2$), 21.1 (N-CH(*C*H$_3)_2$). IR (KBr): 2979, 2927, 1635, 1492, 1383, 1339, 1248, 1114, 701 cm^{-1}. EI -LRMS *m*/*z*: 240 (10), 239 (M^+, 53), 238 (20), 178 197 (13), 105 (100). EI -HRMS: calcd for $C_{16}H_{17}NO$ [M^+] 239.1305, found 239.1304.

Variable-temperature NMR and line shape analysis.

Temperature (*T*) was calibrated using 80% ethylene glycol in DMSO-d_6 (from +25 to +100 ºC) [9] or CD_3OD (from –90 to +20 ºC).[10] Line shape analysis to determine the kinetic parameter (*k*) was performed by using the DNMR program (in Bruker TopSpin 4.3.0).

The activation parameters ($\Delta H^‡$, $\Delta S^‡$, $\Delta G^‡$) were determined from an Arrhenius plot of ln(*k*/*T*) against 1/*T*. The activation enthalpy ($\Delta H^‡$) was determined from the slope of the plot according to eq 1.

$$\Delta H^‡ = -R \times \text{Slope} \qquad (1)$$

where *R* is the gas constant, 1.987 cal/(K·mol).

The activation entropy ($\Delta S^‡$) was determined from the intercept according to eq 2.

$$\Delta S^‡ = R \times (\text{intercept} - \ln(h/k_B)) \qquad (2)$$

where *h* is Planck's constant, k_B is the Boltzmann constant, and ln (h/k_B) =23.7600.

3. X-Ray crystallography

Crystals for analysis were obtained by slow evaporation of designated solvents, except for **7** which was obtained by recrystallization from hexane in a dry-ice-cooled acetone bath. Variable-temperature single-crystal X-ray diffraction experiments were carried out on a Rigaku RAXIS Rapid II (graphite-monochromated Cu Kα radiation, λ = 1.541Å) or XtaLAB Synergy Custom. Crystals were mounted on MiTeGen dual-thickness MicroMounts using parabar oil : mineral oil = 1:8. Data collection was carried out at 93 K using liquid nitrogen as a coolant. The crystal structures were solved by direct methods using SHELXT[11] and refined by SHELXL.[12] All non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were geometrically constrained. The CIF files of all structures are available at www.ccdc.cam.ac.uk. Structure analysis was performed with Mercury ver. 2022.3.0 (CCDC) programs.

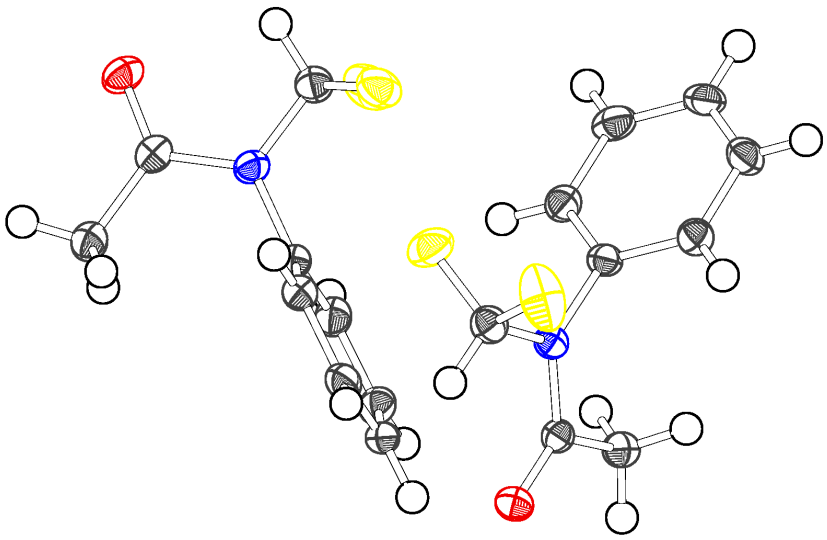


Figure S2. Solid-state structure of **2F**. Two molecules exist in an asymmetric unit. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427406.

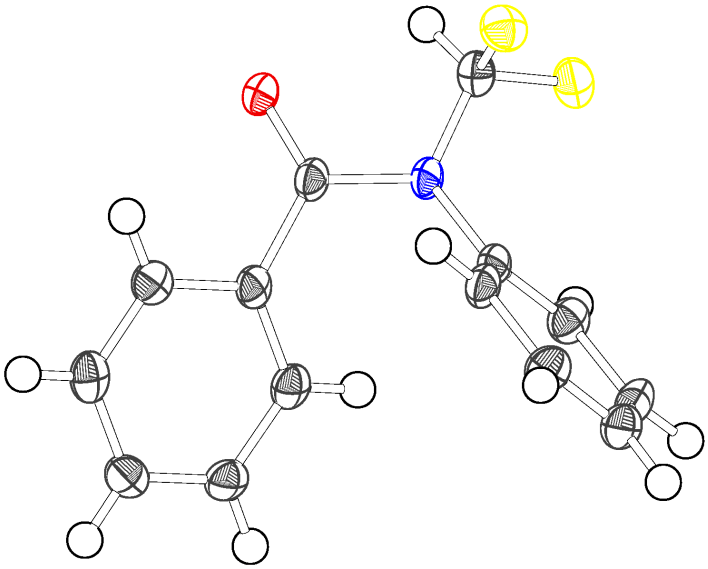


Figure S3. Solid-state structure of **3F**. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427407.

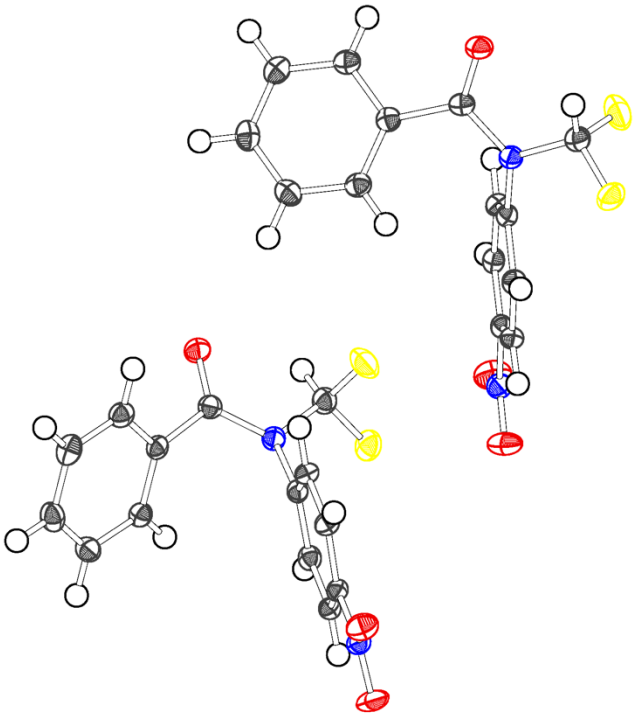


Figure S4. Solid-state structure of **8F**. Two molecules exist in an asymmetric unit. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427408.

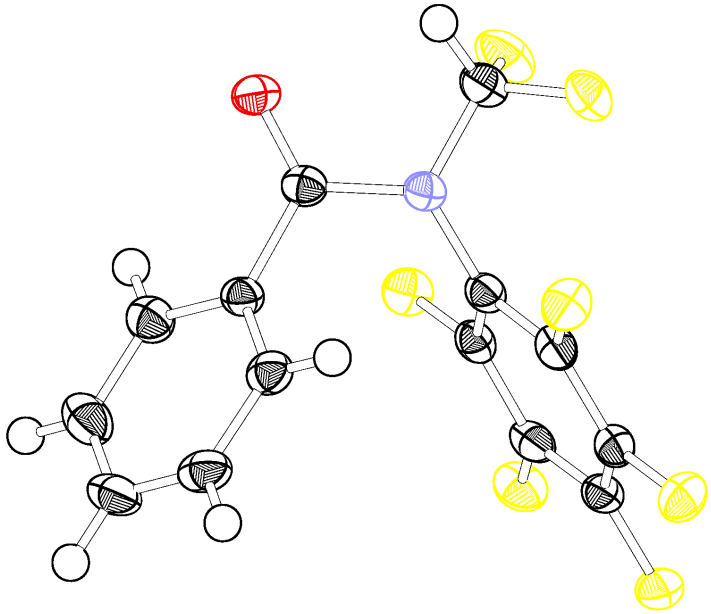


Figure S5. Solid-state structure of **10F**. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427409.

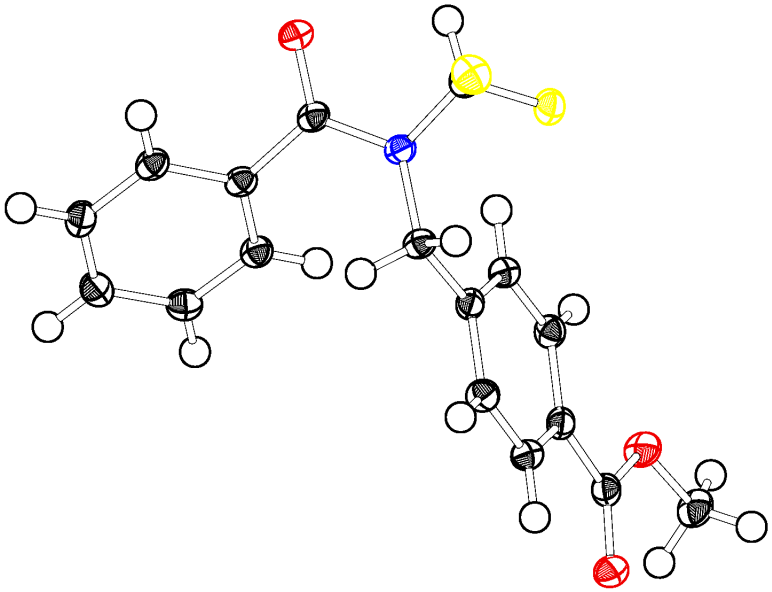


Figure S6. Solid-state structure of **12F**. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427410.

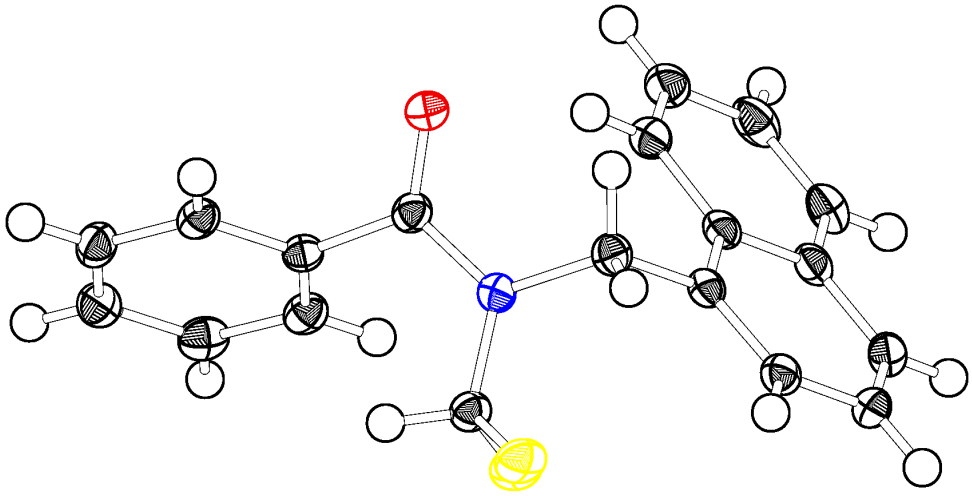


Figure S7. Solid-state structure of **14F**. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427411.

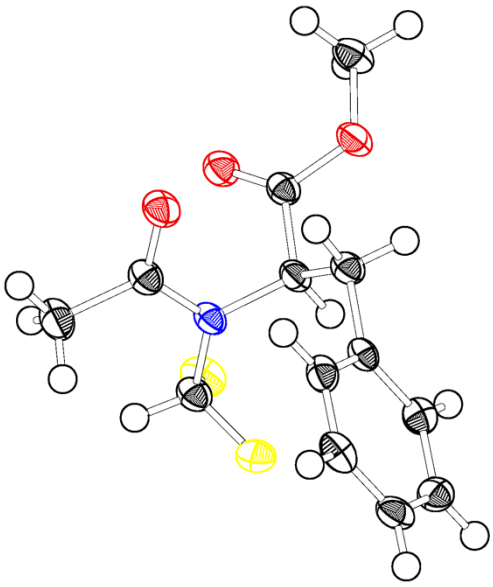


Figure S8. Solid-state structure of **15F**. Thermal ellipsoids are shown at the 50% probability level. Color code: C / gray, O / red, N / blue and F / yellow. CCDC Deposit No. 2427412.

Table S1. Crystallographic parameters.

	2F	**3F**	**8F**	**10F**
recrystallization solvent	CH_2Cl_2-*n*hex	CH_2Cl_2-*n*hex	AcOEt-*n*hex	AcOEt-*n*hex
chemical formula	$C_9H_9F_2NO$	$C_{14}H_{11}F_2NO$	$C_{14}H_{10}F_2N_2O_3$	$C_{14}H_6F_7NO$
formula weight	185.17	247.24	292.24	337.20
crystal system	triclinic	monoclinic	monoclinic	monoclinic
space group	$P\bar{1}$	$P2_1$	$P2_1/n$	$P2_1/c$
a/Å	7.2772(2)	8.0428(3)	10.36230(10)	11.5847(4)
b/Å	7.3942(3)	6.0775(3)	24.6801(3)	7.5874(2)
c/Å	16.1268(5)	12.1408(4)	10.66670(10)	15.3165(5)
α/º	81.500(3)	90	90	90
β/º	83.412(2)	90.734(4)	110.6000(10)	108.138(4)
γ/º	89.984(3)	90	90	90
Z	4	2	8	4
V/Å^3	852.45(5)	593.40(4)	2553.50(5)	1279.39(7)
T/K	93	93	93	93
D_{calc}/g cm^{-3}	1.184	1.384	1.520	1.751
μ/mm^{-1}	1.074(CuKα)	0.923(CuKα)	1.103(CuKα)	1.634(CuKα)
reflns collected	9618	3235	19618	2464
unique reflns	3008	1688	4580	2055
R_1[I > 2σ(I)]	0.0353	0.0507	0.0300	0.0368
wR_2 [all]	0.0922	0.1381	0.0775	0.1036
GOF	1.055	1.092	1.048	1.043
CCDC	2427406	2427407	2427408	2427409

Table S2. Crystallographic parameters.

	12F	**14F**	**15F**
recrystallization solvent	AcOEt-*n*hex	CH_2Cl_2-*n*hex	CH_2Cl_2-*n*hex
chemical formula	$C_{17}H_{15}F_2NO_3$	$C_{19}H_{15}F_2NO$	$C_{13}H_{15}F_2NO_3$
formula weight	319.30	311.32	271.26
crystal system	triclinic	orthorhombic	monoclinic
space group	$P\overline{1}$	*Pbca*	$P2_1/n$
a/Å	5.6213 (3)	9.22942(11)	10.0791(3)
b/Å	8.9645(3)	10.17453(12)	12.0372 (3)
c/Å	14.5753(7)	31.5753(3)	10.7937(3)
α/º	84.447(4)	90	90
β/º	87.484(5)	90	90.258(3)
γ/º	81.834(5)	90	90
Z	2	8	4
V/Å^3	723.28(7)	2965.08(6)	1309.53(6)
T/K	93	93	93
D_{calc}/g cm^{-3}	1.466	1.384	1.376
μ/mm^{-1}	1.001(CuKα)	0.861(CuKα)	0.996(CuKα)
reflns collected	7733	7784	2672
unique reflns	2435	2692	2359
R_1[I > 2σ(I)]	0.0340	0.0328	0.0331
wR_2 [all]	0.0931	0.0914	0.0878
GOF	1.040	1.050	1.054
CCDC	2427410	2427411	2427412

Table S3. Structural parameters in crystal structures.

		2F[a]	**3F**	**8F**[a]	**10F**	**12F**	**14F**	**15F**
Bond lengths (Å)	(O=)C–N	1.382 1.382	1.401	1.390 1.398	1.408	1.389	1.383	1.379
	C=O	1.221 1.221	1.219	1.217 1.218	1.210	1.223	1.220	1.219
Dihedral angles (deg)	(N)Ph–Am[b]	85.7 87.7	34.7	74.0 68.3	74.3	N/A	N/A	N/A
	(O=)C–N–C–H	18.8 -8.09	-26.3	32.9 -30.5	33.7	-26.4	-12.7	-9.63
Pyramidal parameters (deg)	τ	5.18 2.94	11.0	13.4 16.1	13.7	13.5	12.2	0.29
	χ_N	3.59 0.50	22.5	24.7 19.3	22.0	24.0	9.38	0.31

[a] Two independent molecules exist in an asymmetrical unit. [b] Ph; phenyl plane, Am; amide plane (O–C–N).

4. Figures related to NMR experiments

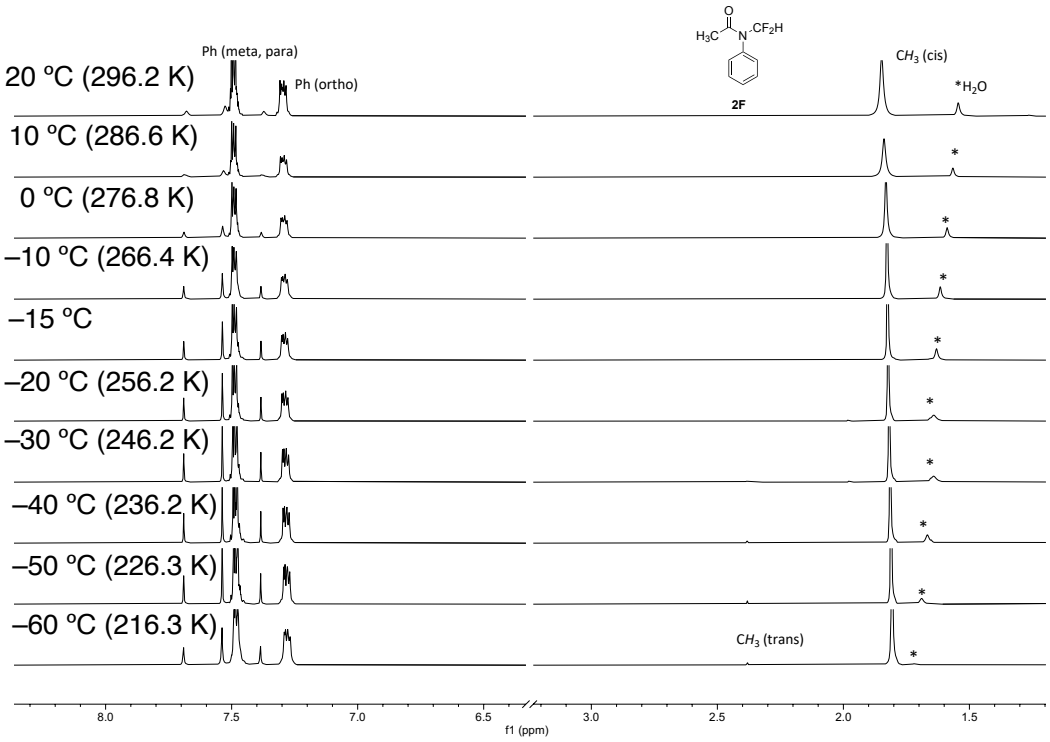
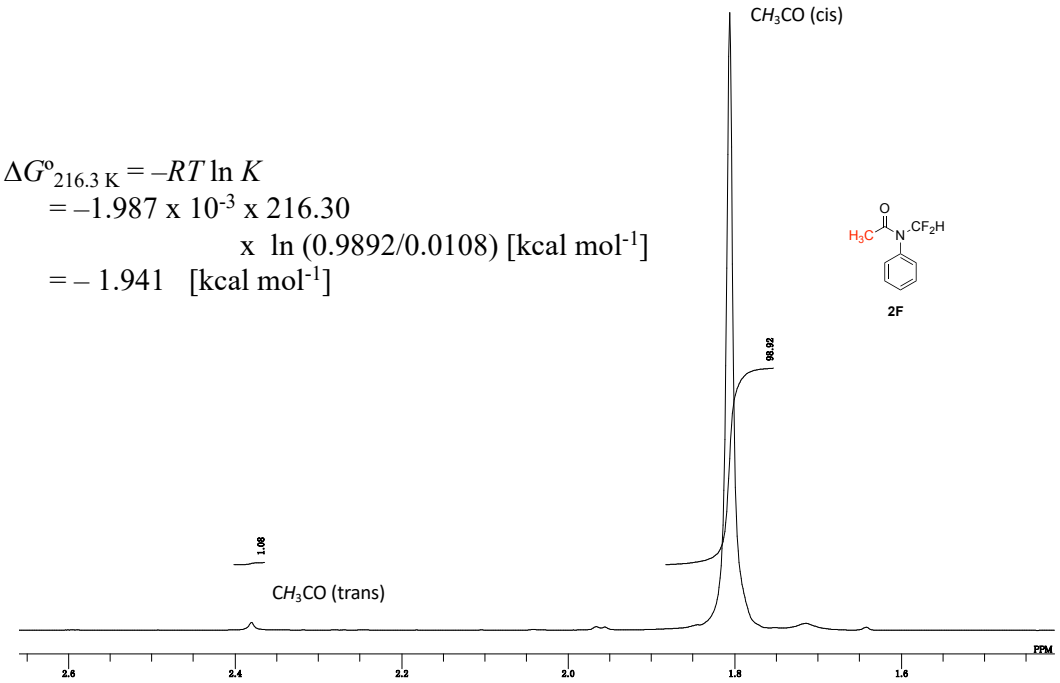


Figure S9. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **2F**.



$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.9892/0.0108)\ [\text{kcal mol}^{-1}]$$
$$= -1.941\ [\text{kcal mol}^{-1}]$$

Figure S10. ^{1}H NMR integration of **2F** (CD_2Cl_2, 400 MHz, 216 K).

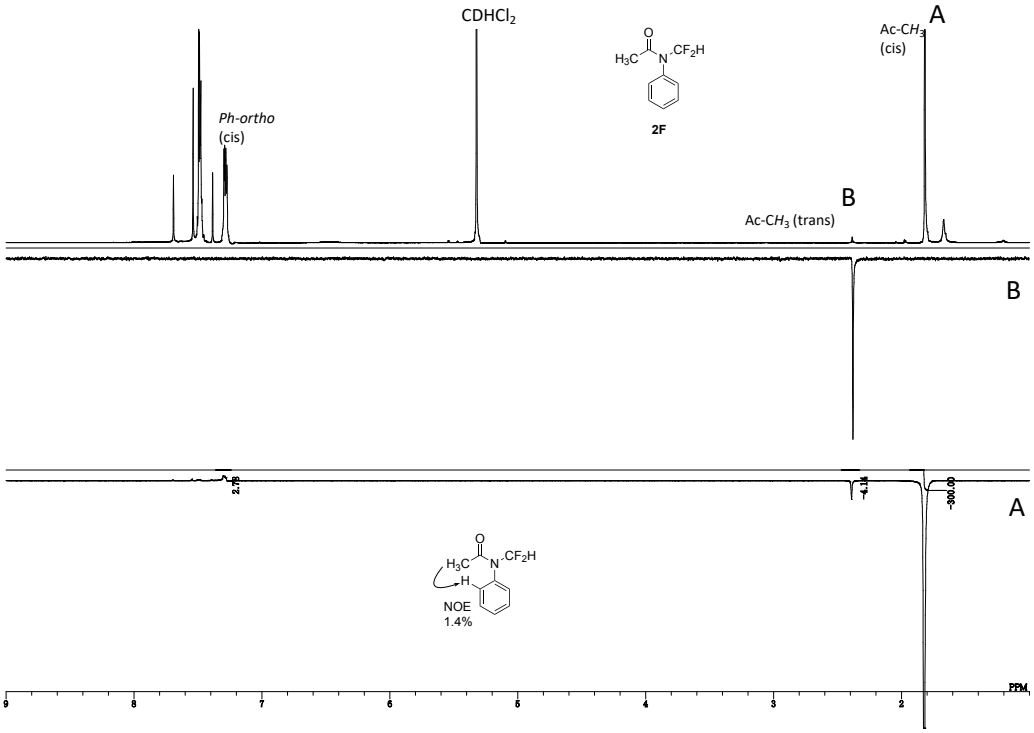


Figure S11. 1D-NOE spectrum of **2F** (CD_2Cl_2, 400 MHz, 236 K).

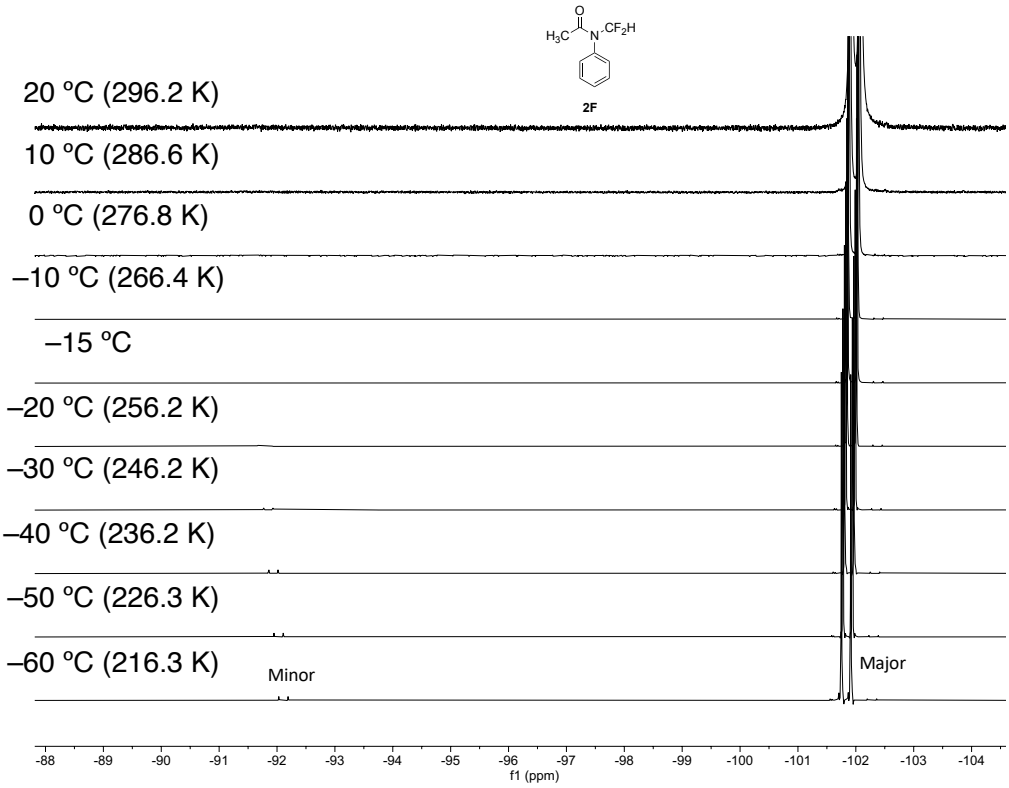


Figure S12. VT-^{19}F NMR (CD_2Cl_2, 400 MHz) of **2F**.

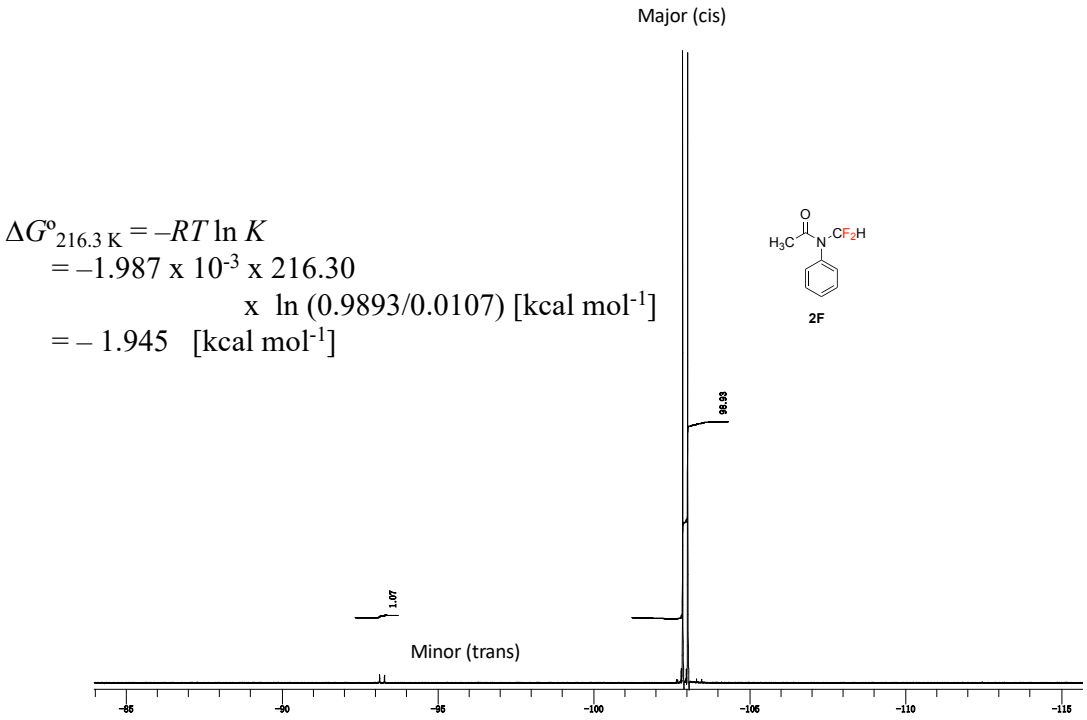


Figure S13. ^{19}F NMR integration of **2F** (CD_2Cl_2, 376 MHz, 216 K).

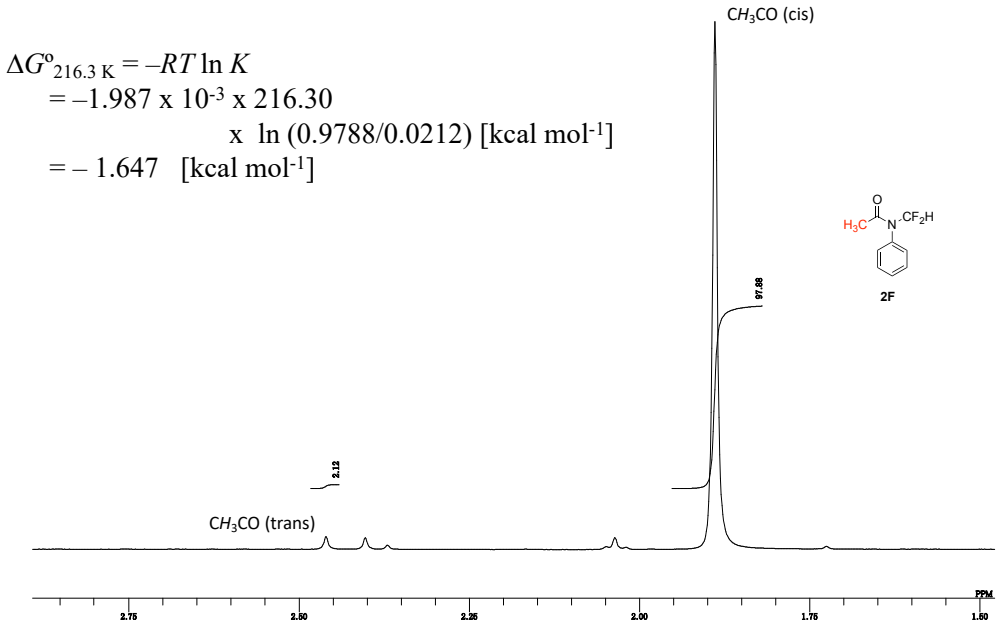


Figure S14. ^{1}H NMR integration of **2F** (CD_3OD, 400 MHz, 216 K).

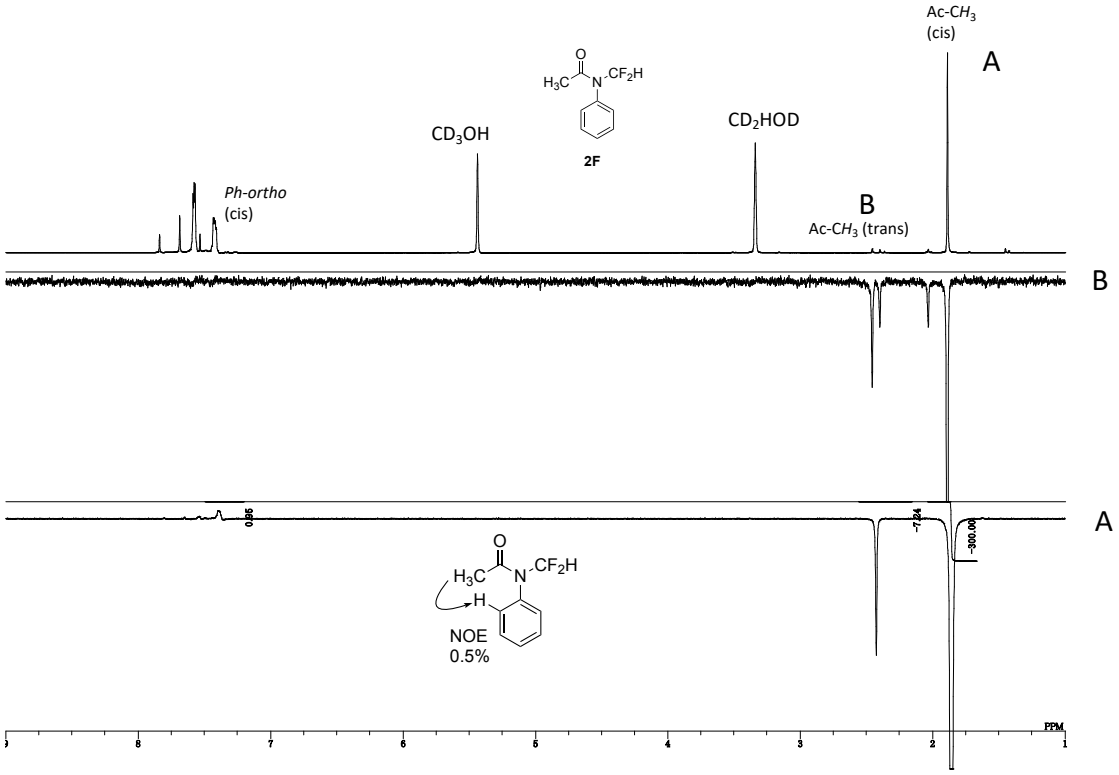


Figure S15. 1D-NOE spectrum of **2F** (CD_3OD, 400 MHz, 236 K).

$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.9767/0.0233)\ [\text{kcal mol}^{-1}]$$
$$= -1.605\ [\text{kcal mol}^{-1}]$$

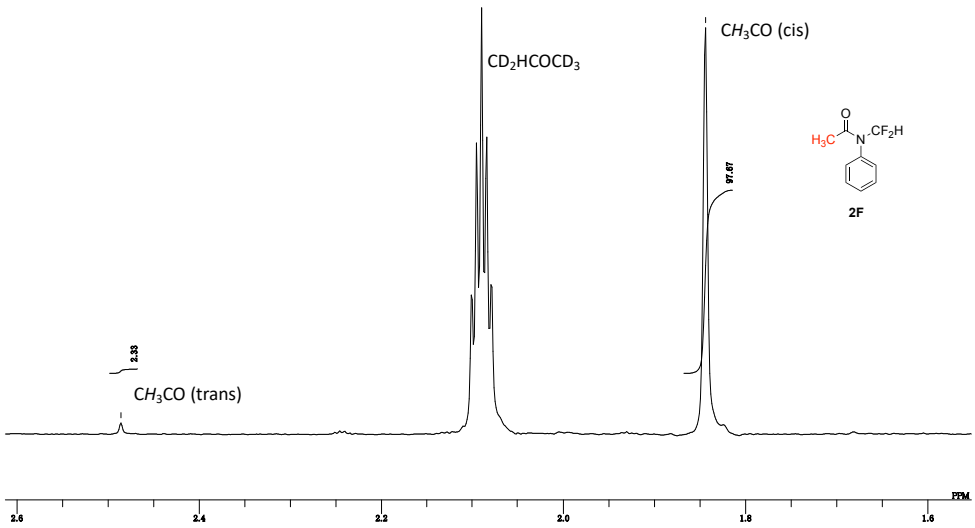


Figure S16. ^1H NMR integration of **2F** ($(CD_3)_2CO$, 400 MHz, 216 K).

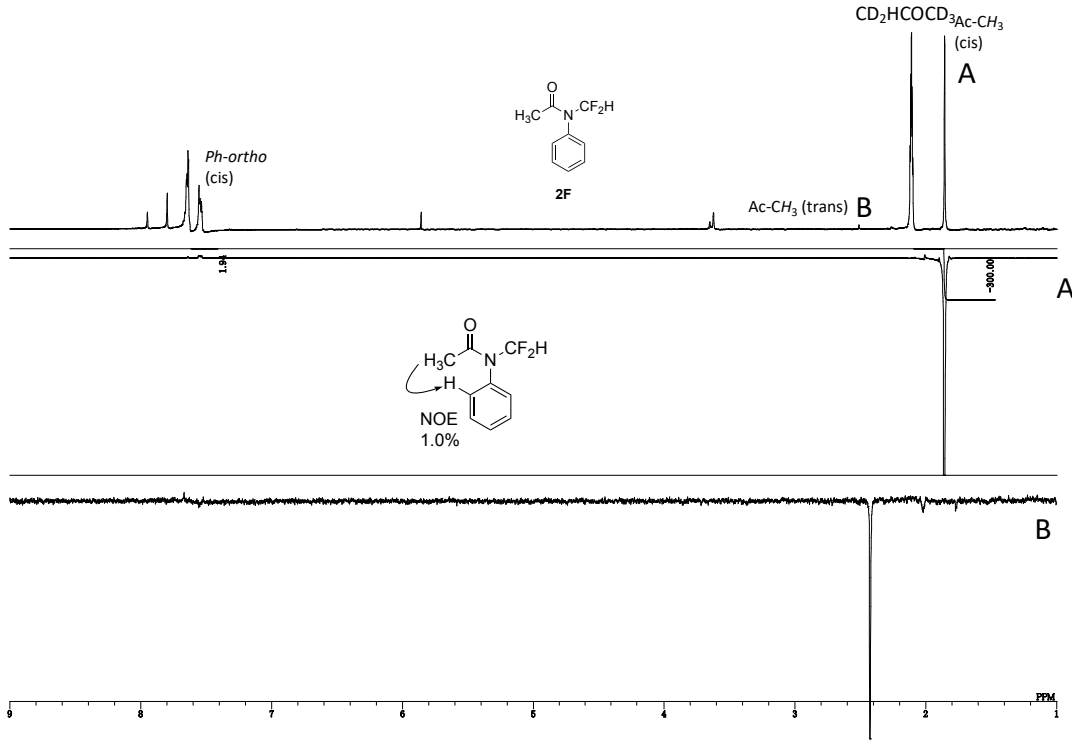


Figure S17. 1D-NOE spectrum of **2F** ($(CD_3)_2CO$, 400 MHz, 236 K).

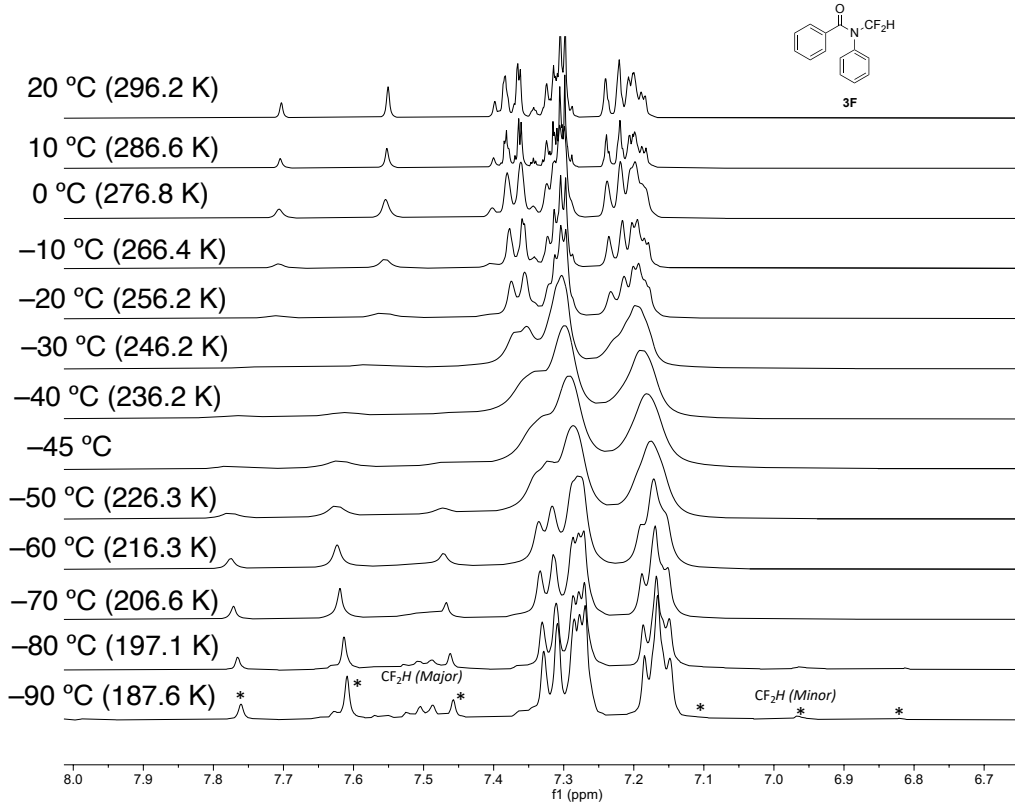


Figure S18. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **3F**.

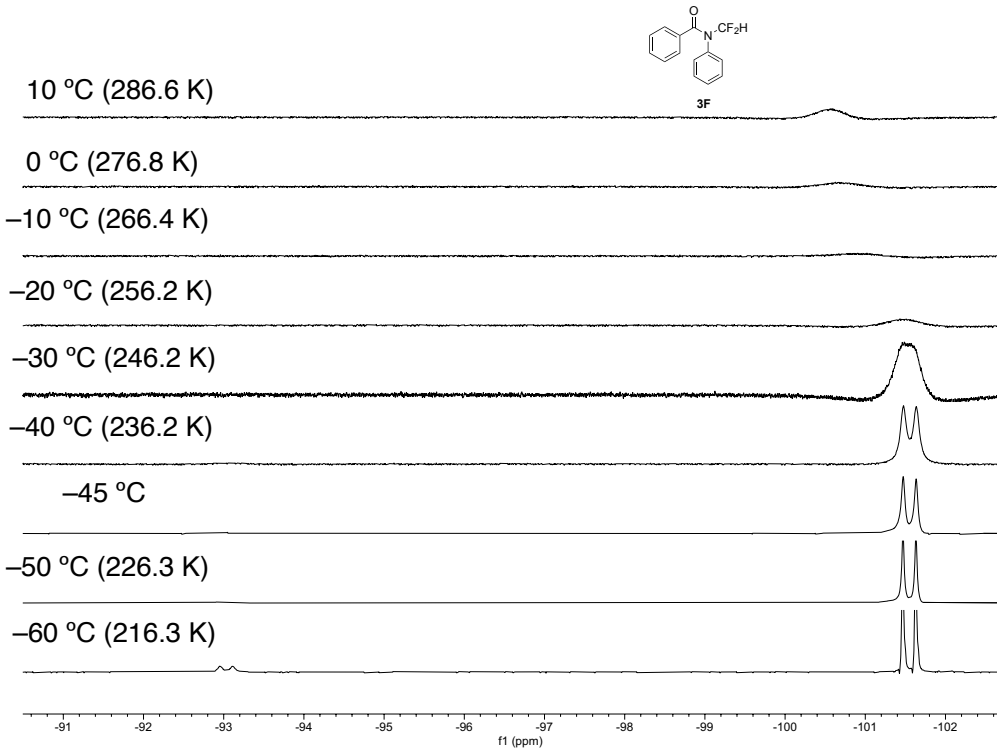
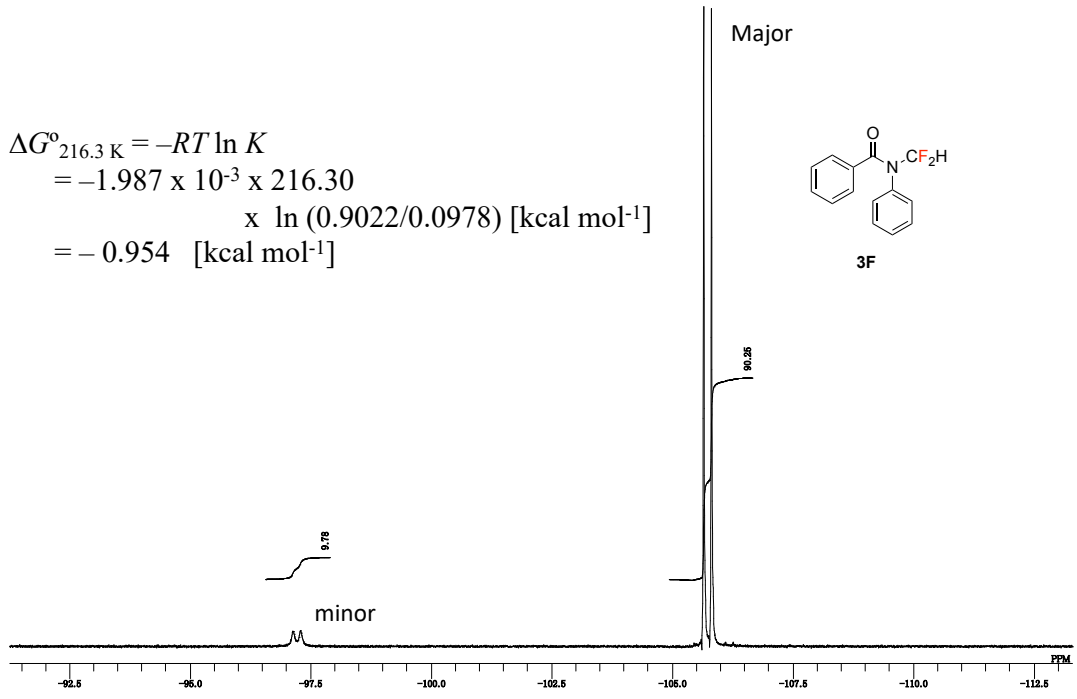


Figure S19. VT-^{19}F NMR (CD_2Cl_2, 400 MHz) of **3F**.



$\Delta G^{o}_{216.3\ K} = -RT \ln K$

$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.9022/0.0978)$ [kcal mol^{-1}]

$= -0.954$ [kcal mol^{-1}]

Figure S20. ^{19}F NMR integration of **3F** (CD_2Cl_2, 376 MHz, 216 K).

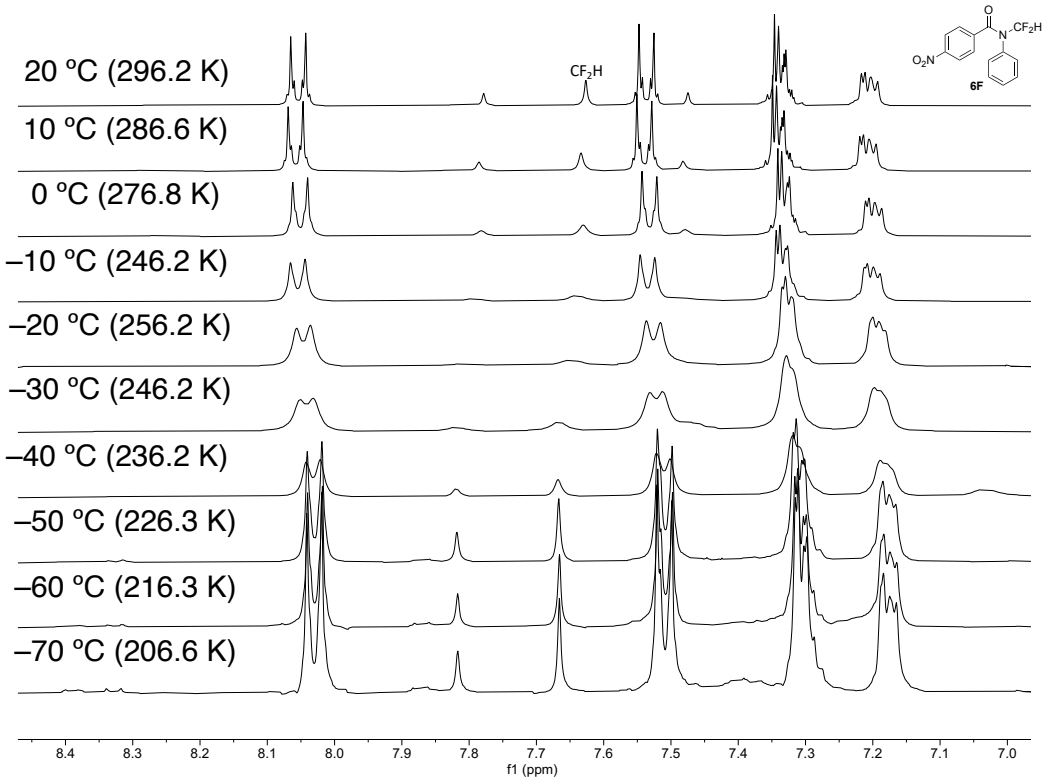


Figure S21. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **6F**.

$$\Delta G^{o}_{197.1\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 197.14 \times \ln (0.9613/0.0387)\ [\text{kcal mol}^{-1}]$$
$$= -1.258\ [\text{kcal mol}^{-1}]$$

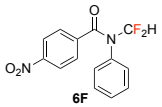


Figure S22. ^{19}F NMR integration of **6F** (CD_2Cl_2, 376 MHz, 216 K).

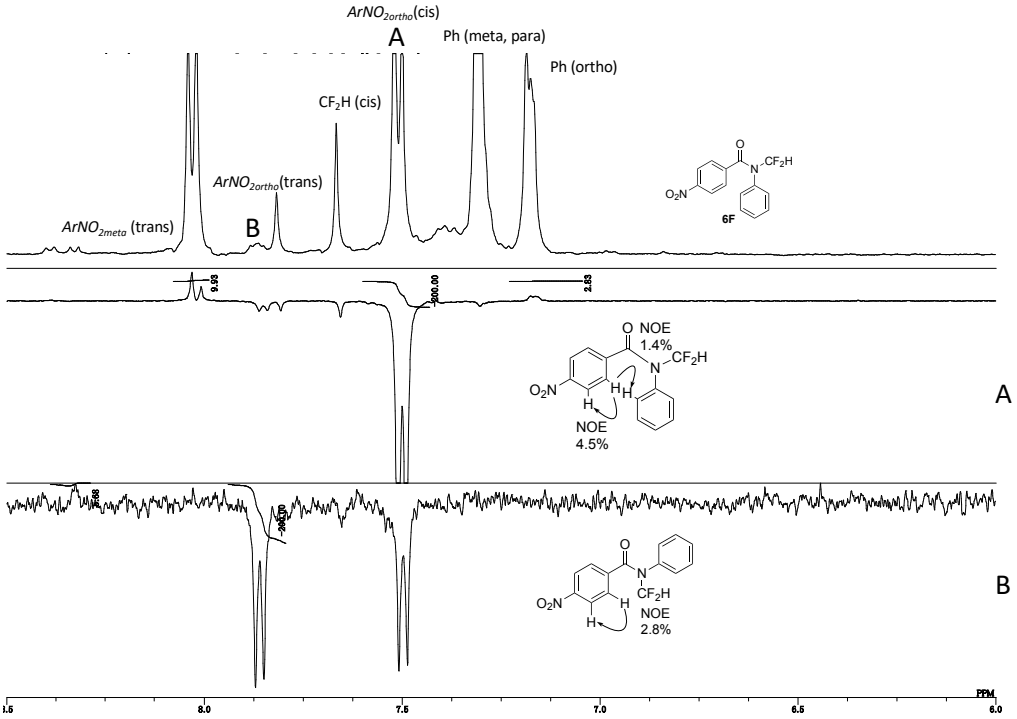


Figure S23. 1D-NOE spectrum of **6F** (CD_2Cl_2, 400 MHz, 206 K).

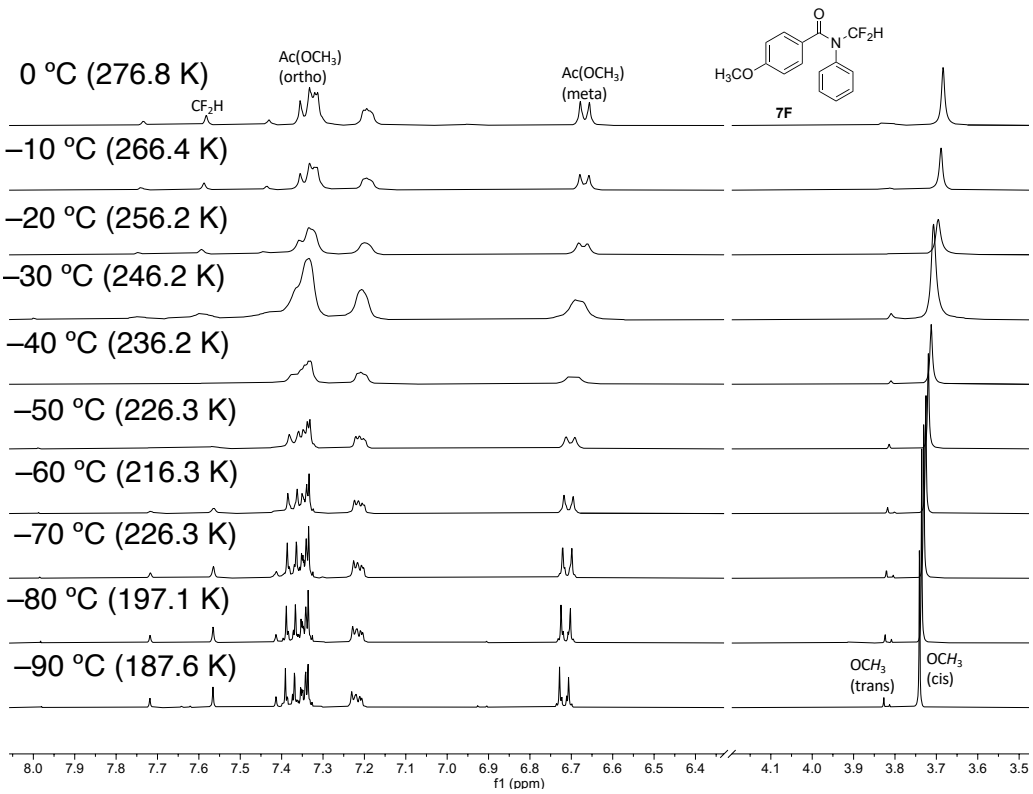


Figure S24. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **7F**.

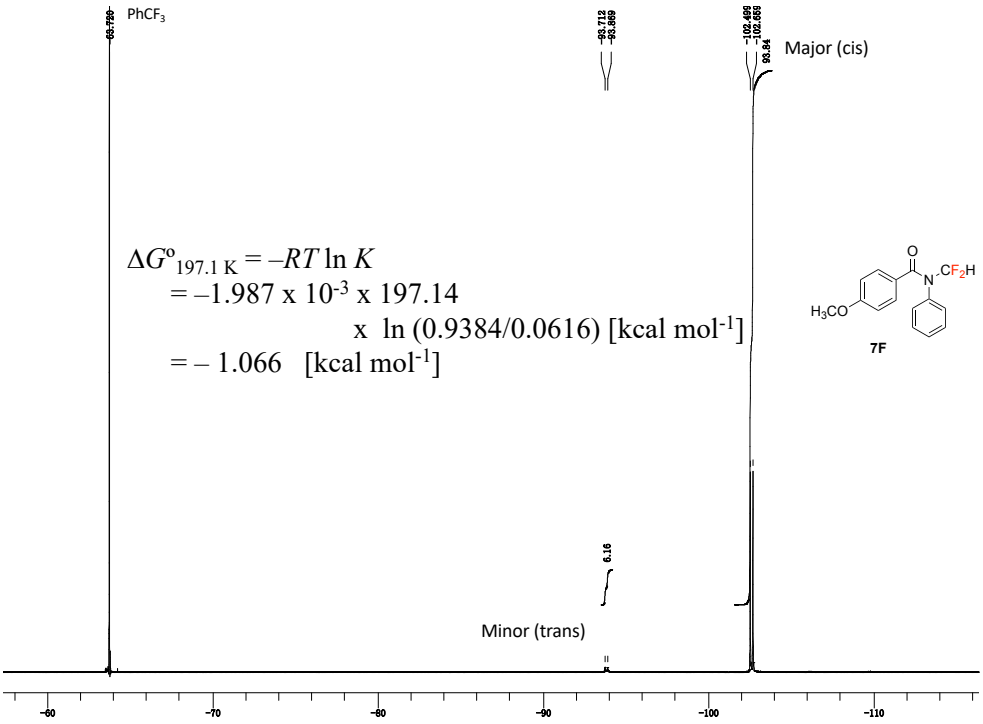


Figure S25. ^{19}F NMR integration of **7F** (CD_2Cl_2, 376 MHz, 197 K)

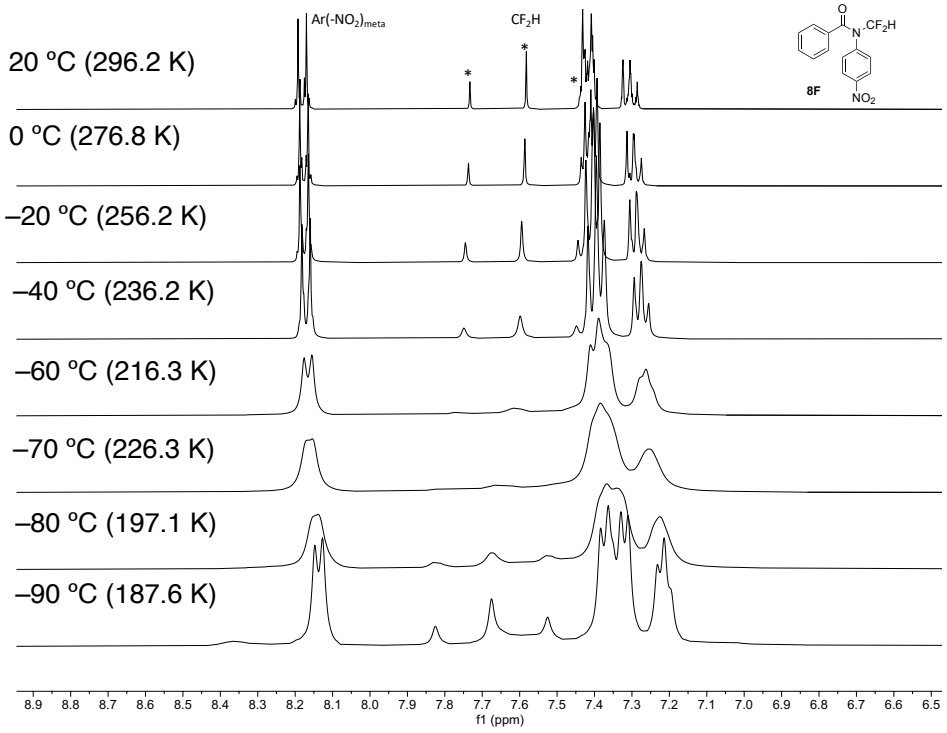


Figure S26. VT-^1H NMR (CD_2Cl_2, 400 MHz) of **8F**.

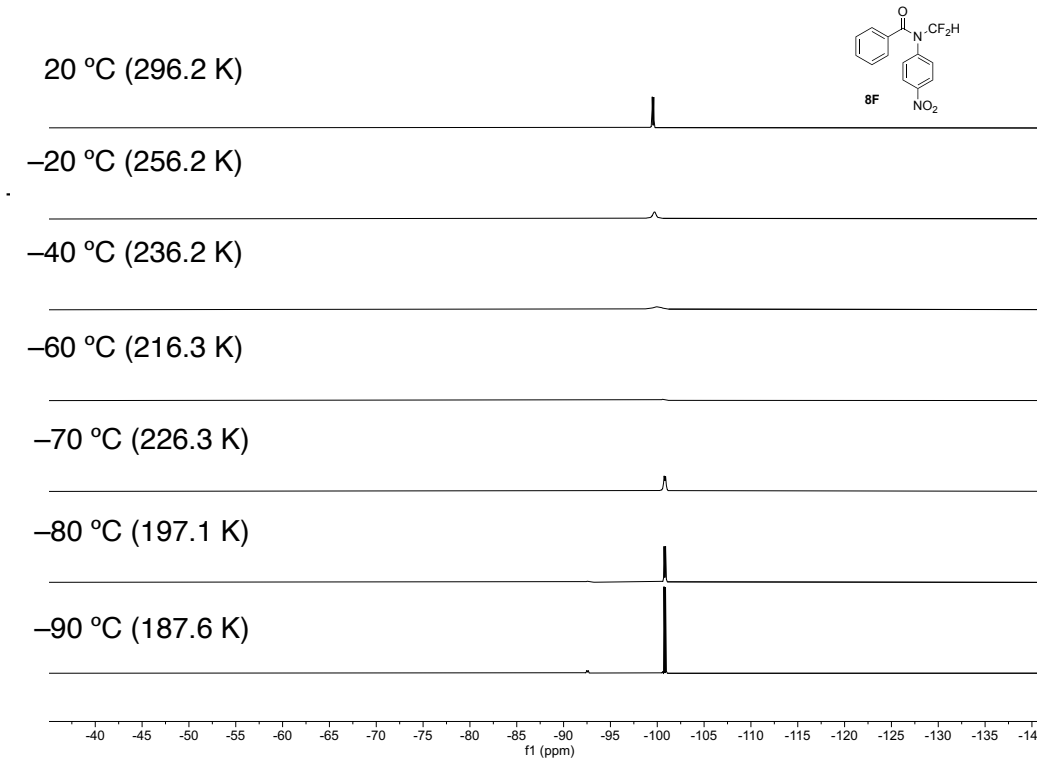


Figure S27. VT-^{19}F NMR (CD_2Cl_2, 376 MHz) of **8F**.

$$\Delta G^{o}_{197.1\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 197.14 \times \ln (0.8946/0.1054)\ [\text{kcal mol}^{-1}]$$
$$= -0.837\ [\text{kcal mol}^{-1}]$$

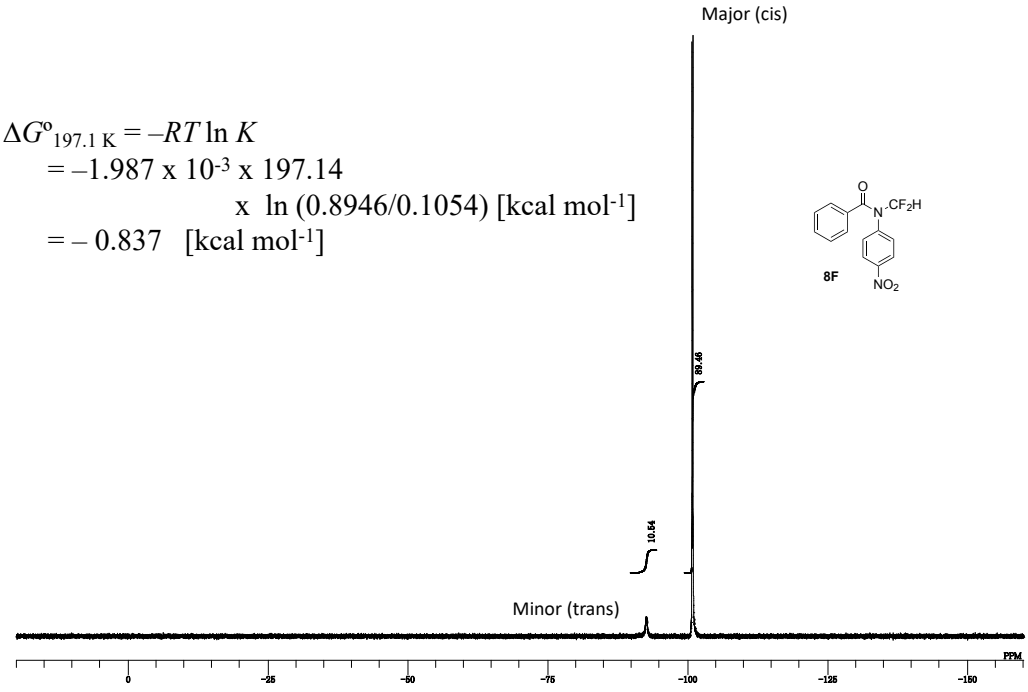


Figure S28. ^{19}F NMR integration of **8F** (CD_2Cl_2, 376 MHz, 197 K)

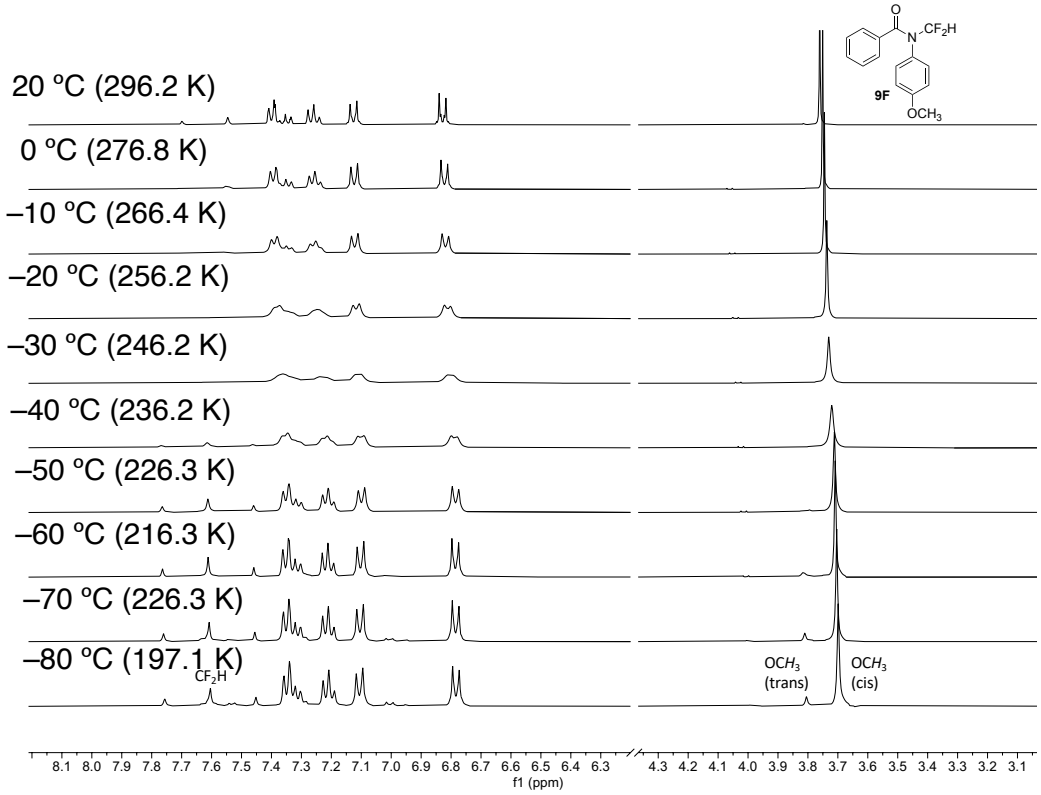


Figure S29. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **9F**.

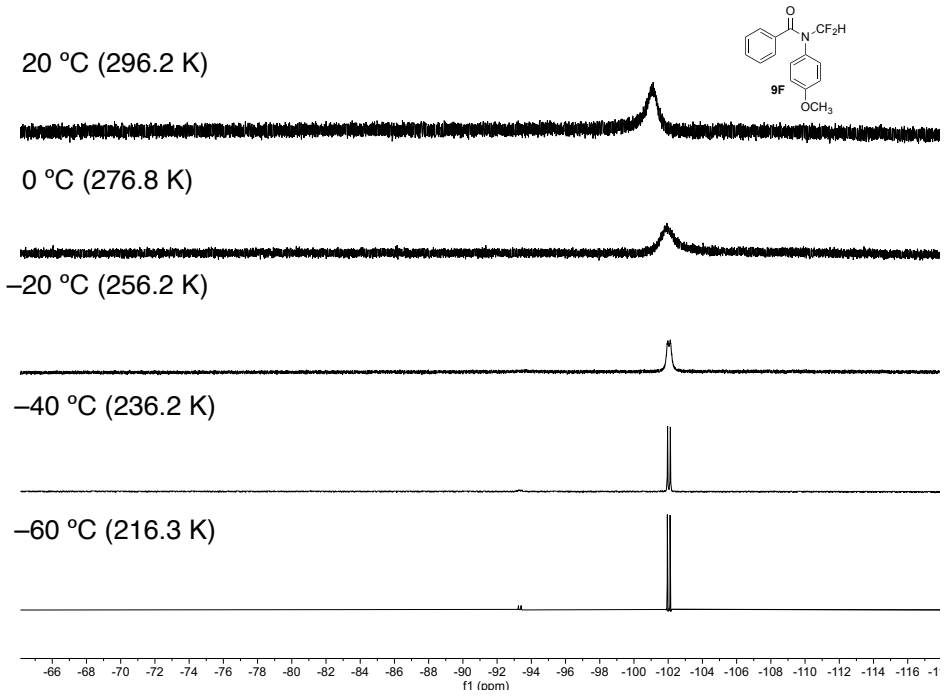


Figure S30. VT-^{19}F NMR (CD_2Cl_2, 400 MHz) of **9F**.

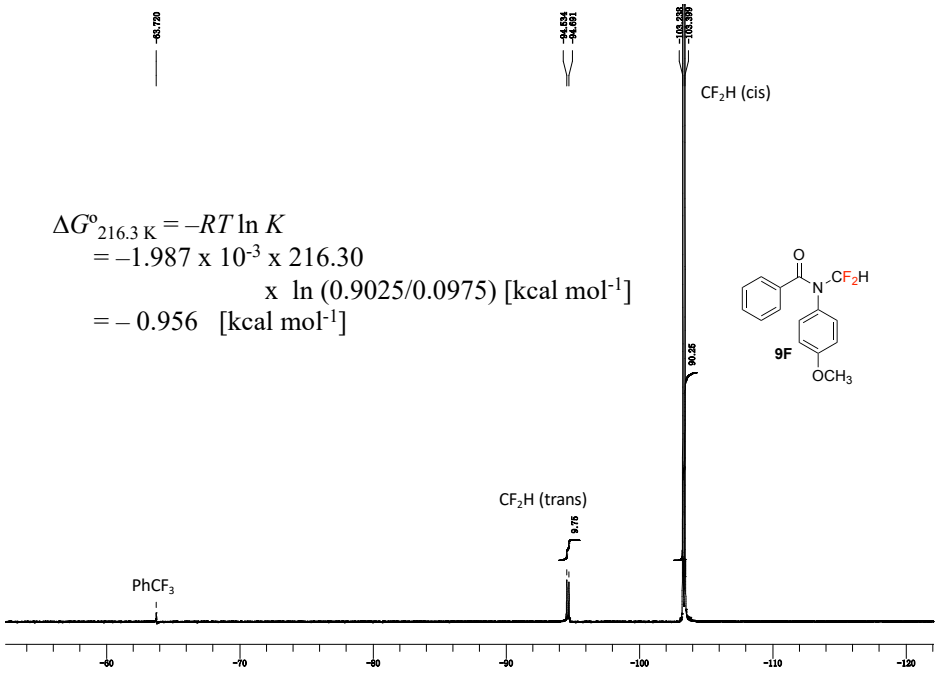


Figure S31. ^{19}F NMR integration of **9F** (CD_2Cl_2, 376 MHz, 216 K)

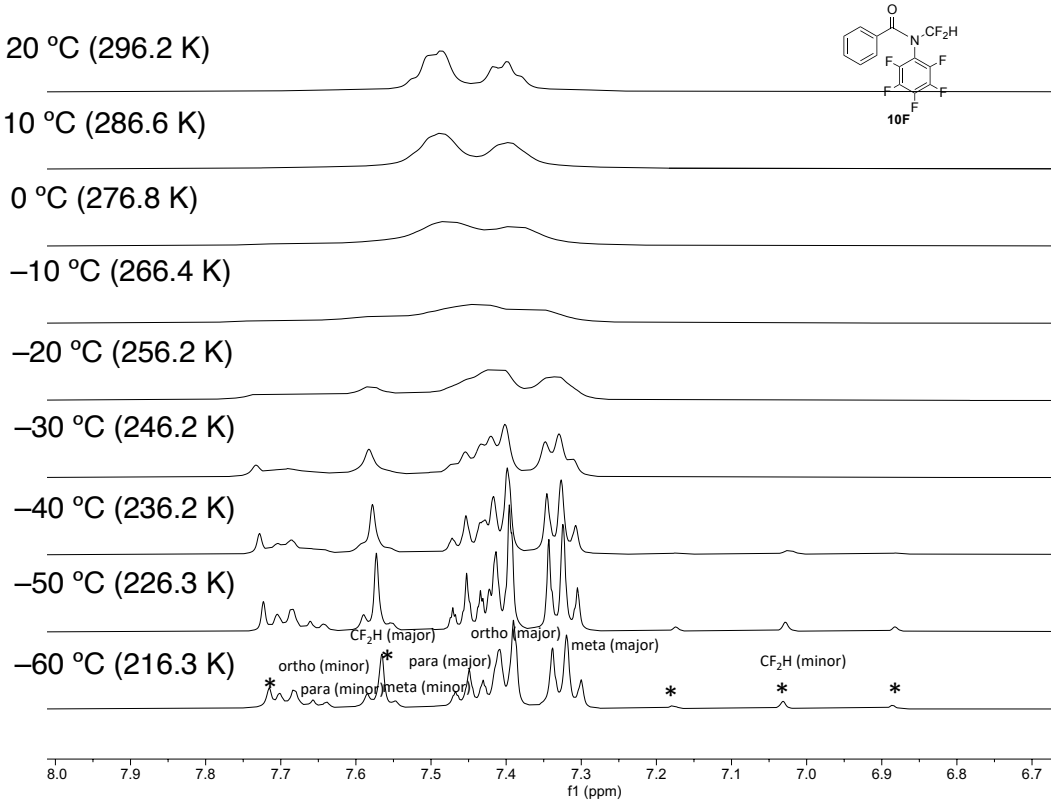


Figure S32. VT-^1H NMR (CD_2Cl_2, 400 MHz) of **10F**.

$\Delta G^{o}_{216.3\ K} = -RT \ln K$

$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.8178/0.1822)$ [kcal mol^{-1}]

$= -0.645$ [kcal mol^{-1}]

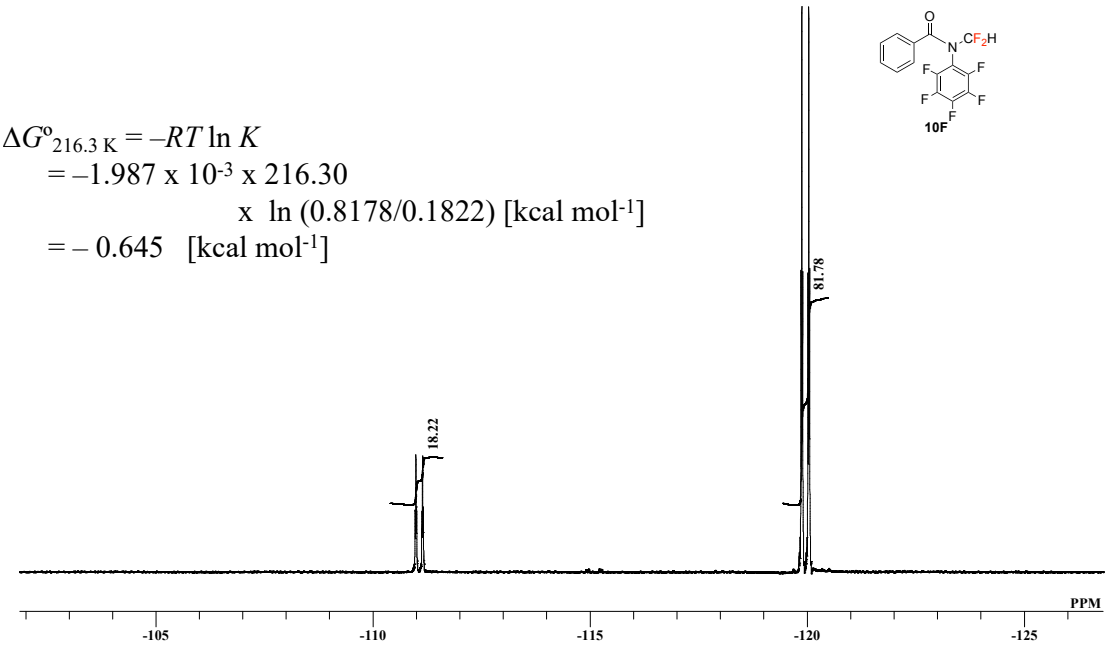


Figure S33. ^{19}F NMR integration of **10F** (CD_2Cl_2, 376 MHz, 216 K).

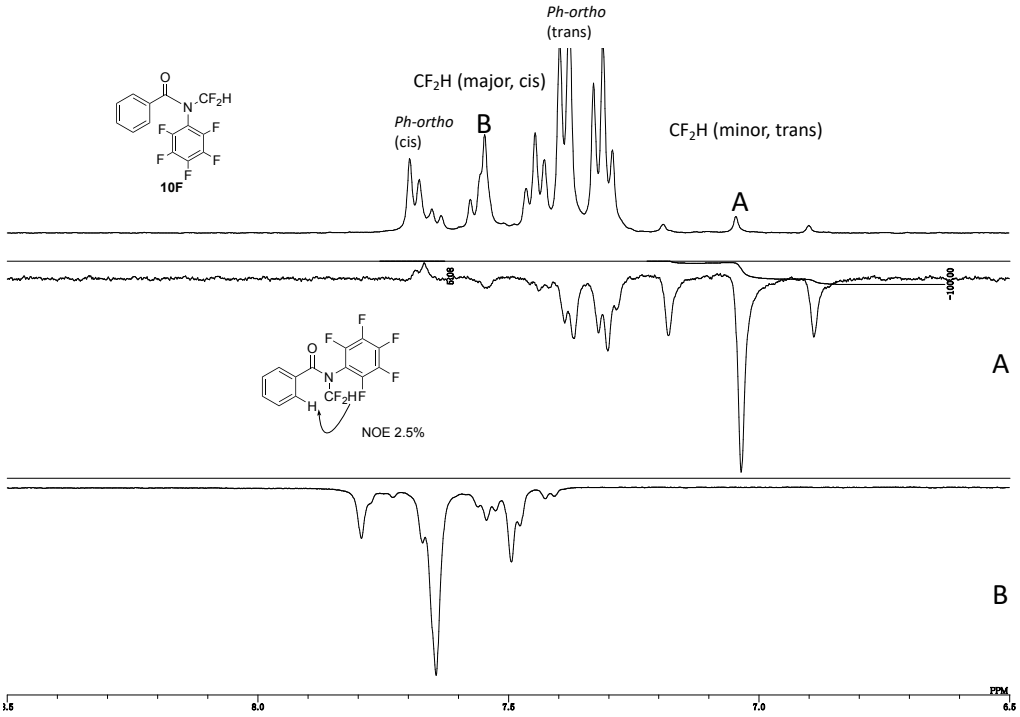


Figure S34. 1D-NOE spectrum of **10F** (CD_2Cl_2, 400 MHz, 236 K).

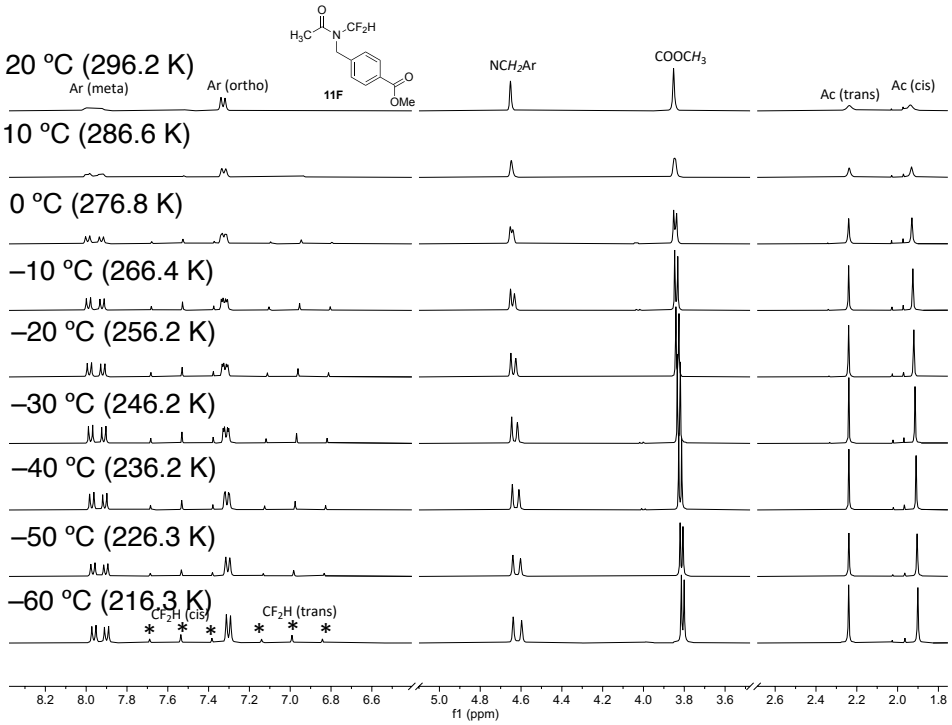
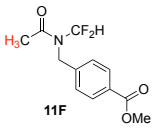


Figure S35. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **11F**.



$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.4968/0.5032)\ [\text{kcal mol}^{-1}]$$
$$= -0.0055\ [\text{kcal mol}^{-1}]$$

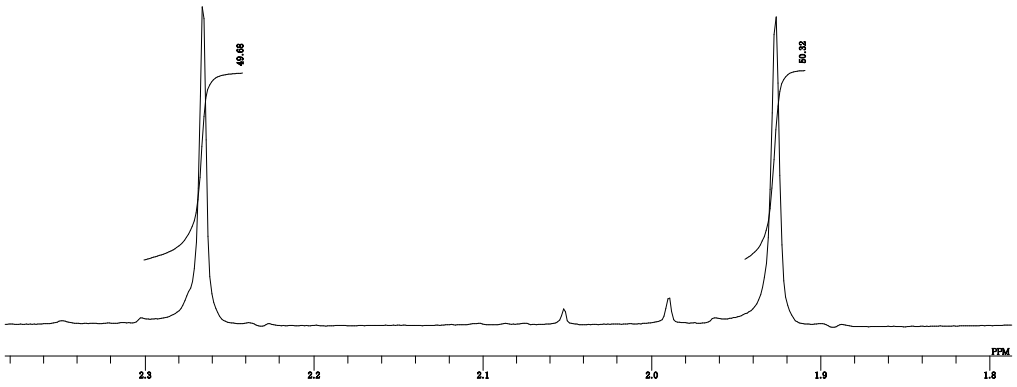


Figure S36. ^{1}H NMR integration of **11F** (CD_2Cl_2, 400 MHz, 216 K).

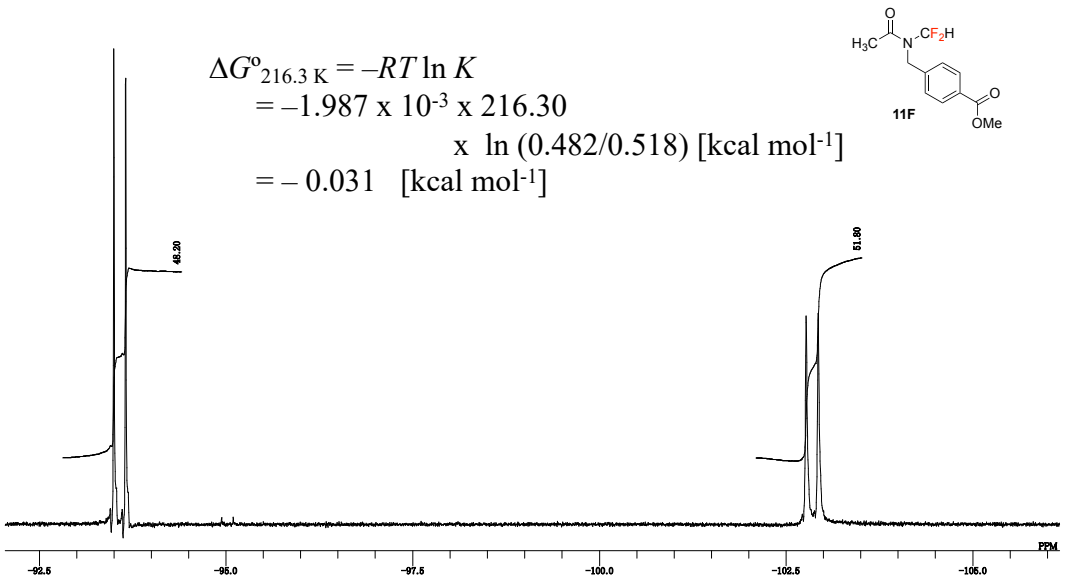


Figure S37. ^{19}F NMR integration of **11F** (CD_2Cl_2, 400 MHz, 216 K).

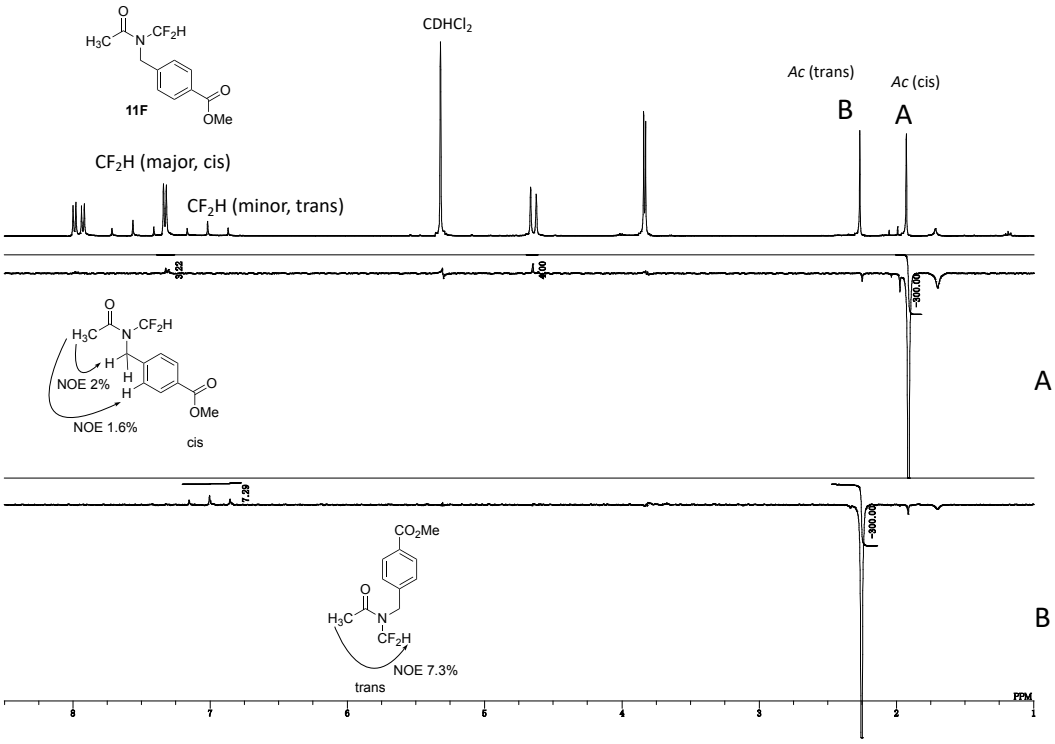


Figure S38. 1D-NOE spectrum of **11F** (CD_2Cl_2, 400 MHz, 216 K).

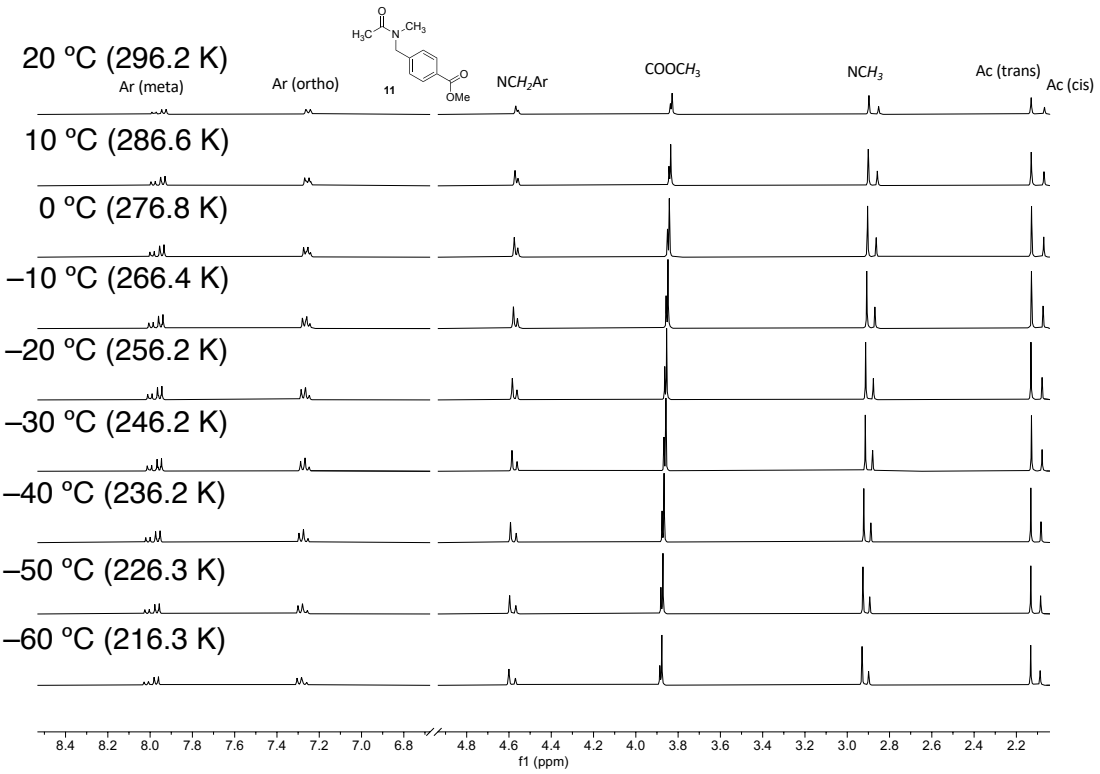


Figure S39. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **11**.

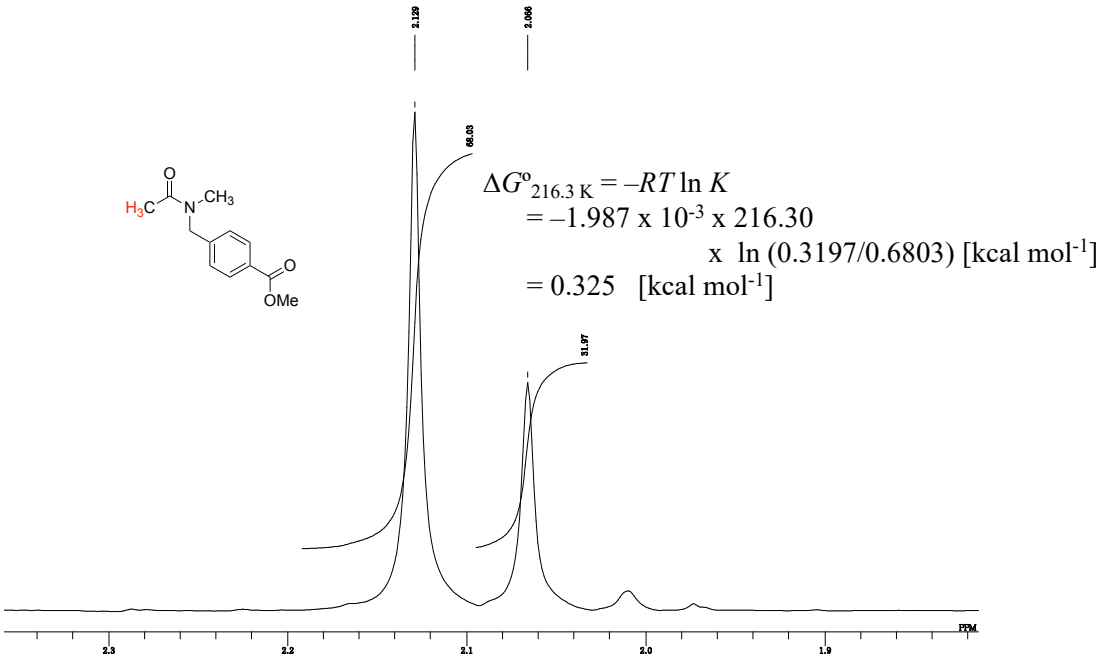


Figure S40. ^{1}H NMR integration of **11** (CD_2Cl_2, 400 MHz, 216 K).

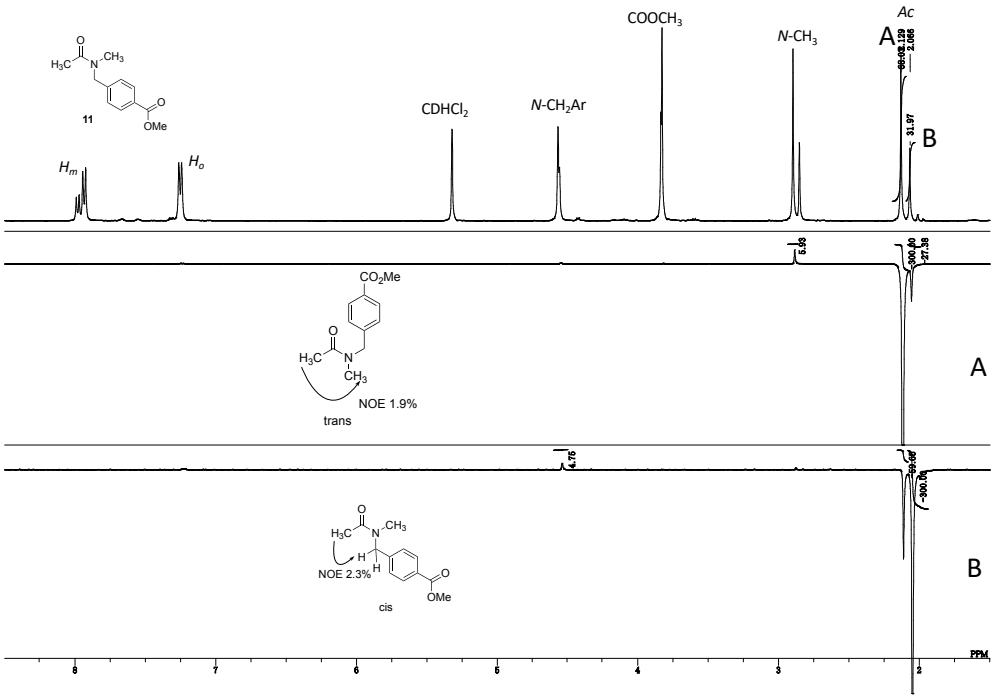


Figure S41. 1D-NOE spectrum of **11** (CD_2Cl_2, 400 MHz, 216 K).

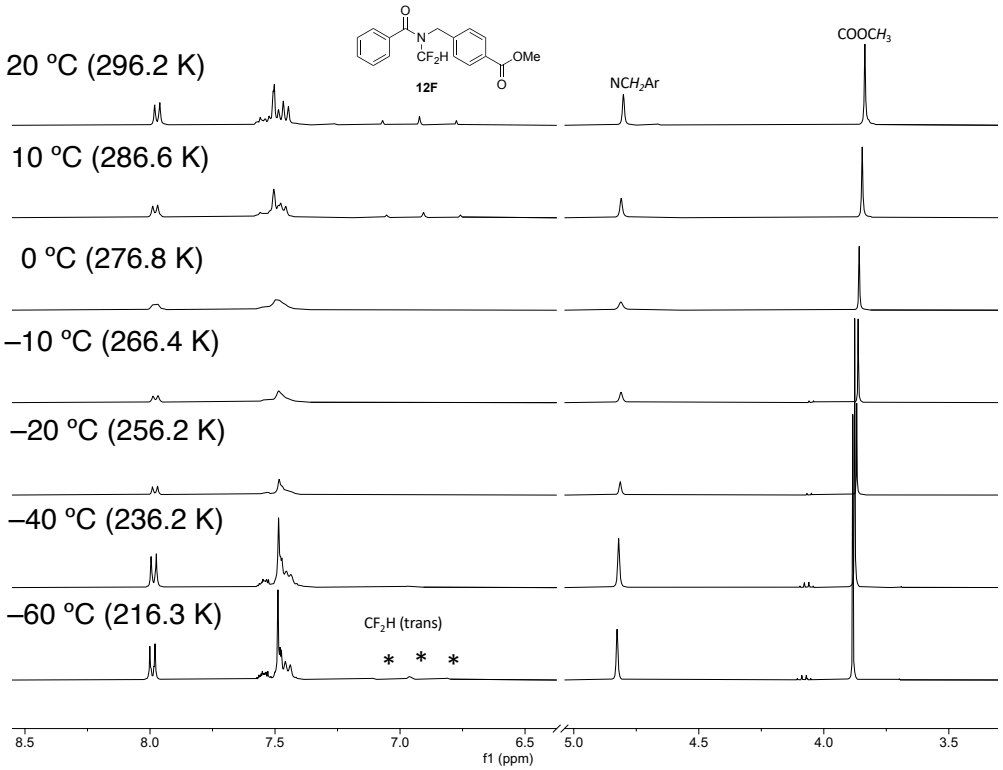
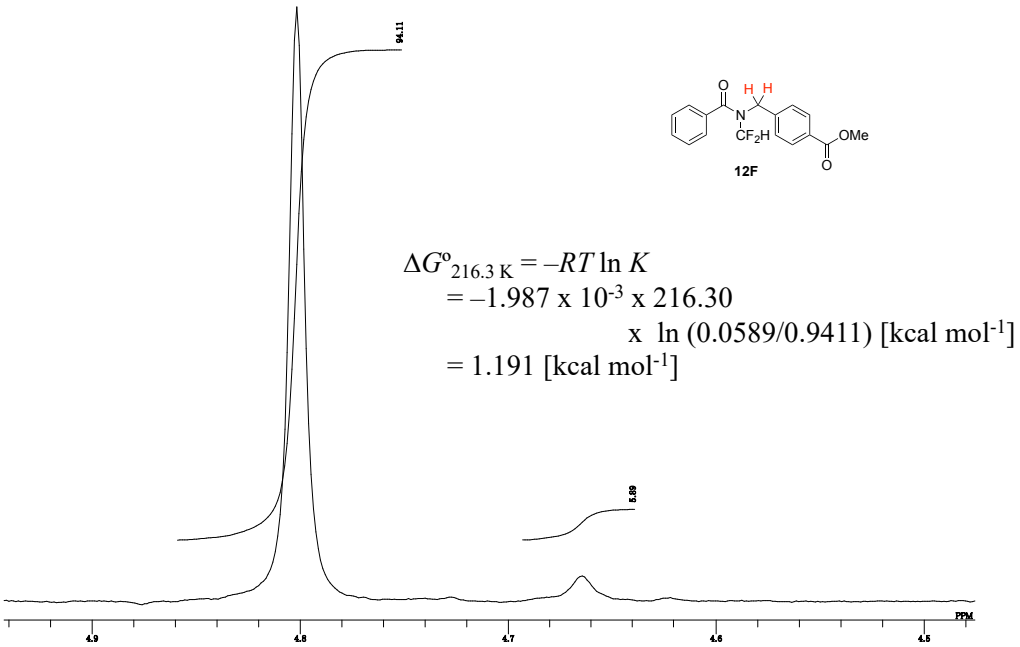


Figure S42. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **12F**.



$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.0589/0.9411)\ [\text{kcal mol}^{-1}]$$
$$= 1.191\ [\text{kcal mol}^{-1}]$$

Figure S43. ^{1}H NMR integration of **12F** (CD_2Cl_2, 400 MHz, 216 K).

$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.0740/0.9260)\ [\text{kcal mol}^{-1}]$$
$$= 1.085\ [\text{kcal mol}^{-1}]$$

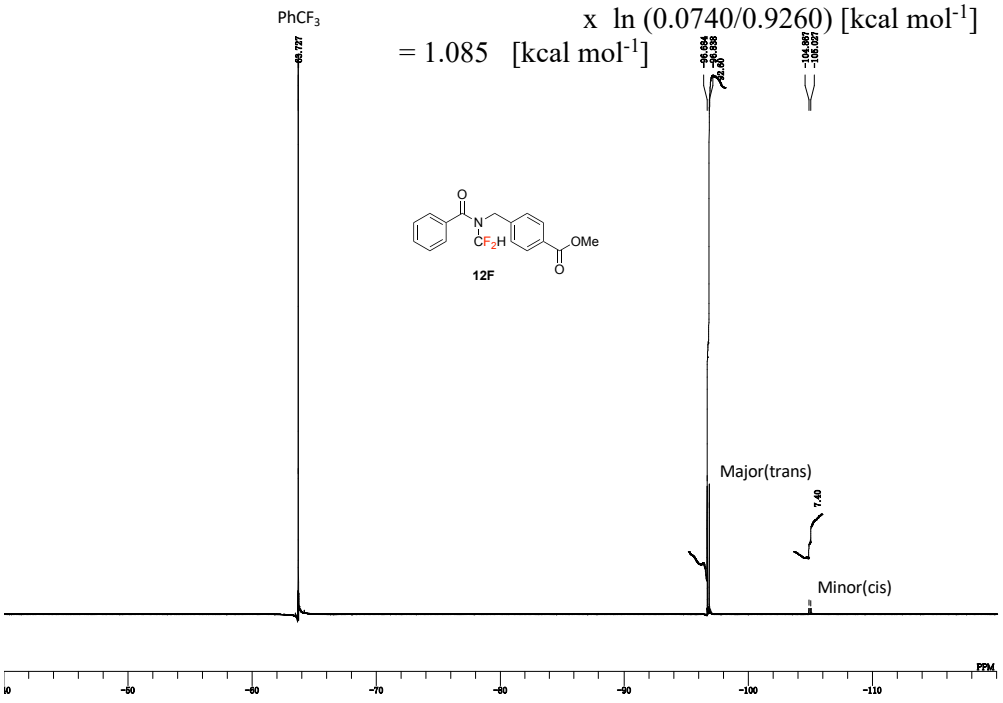


Figure S44. ^{19}F NMR integration of **12F** (CD_2Cl_2, 376 MHz, 216 K).

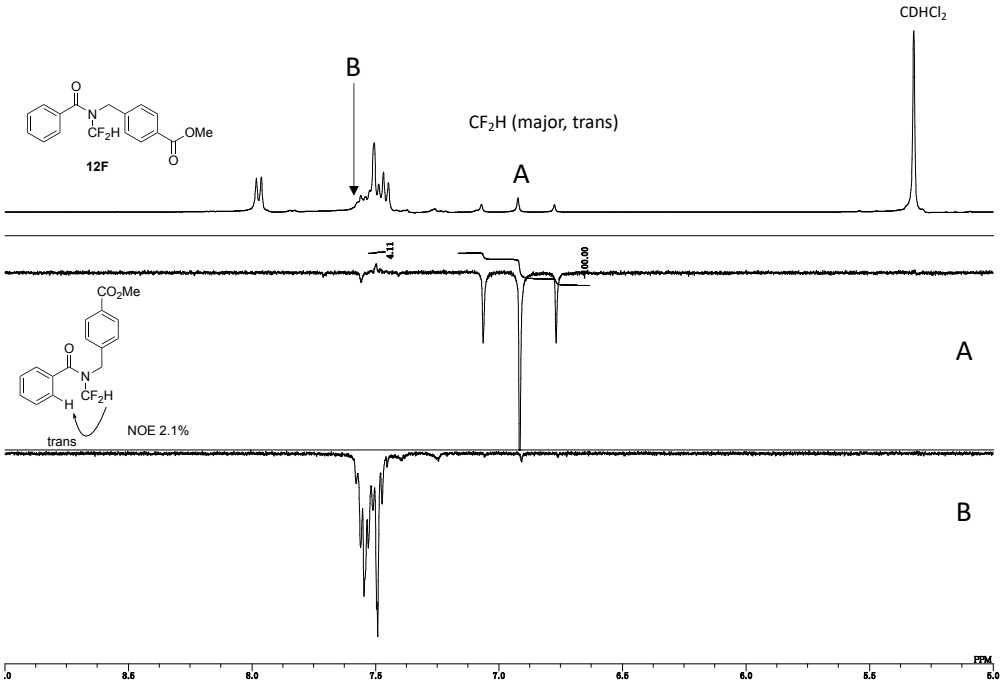


Figure S45. 1D-NOE spectrum of **12F** (CD_2Cl_2, 400 MHz, 216 K).

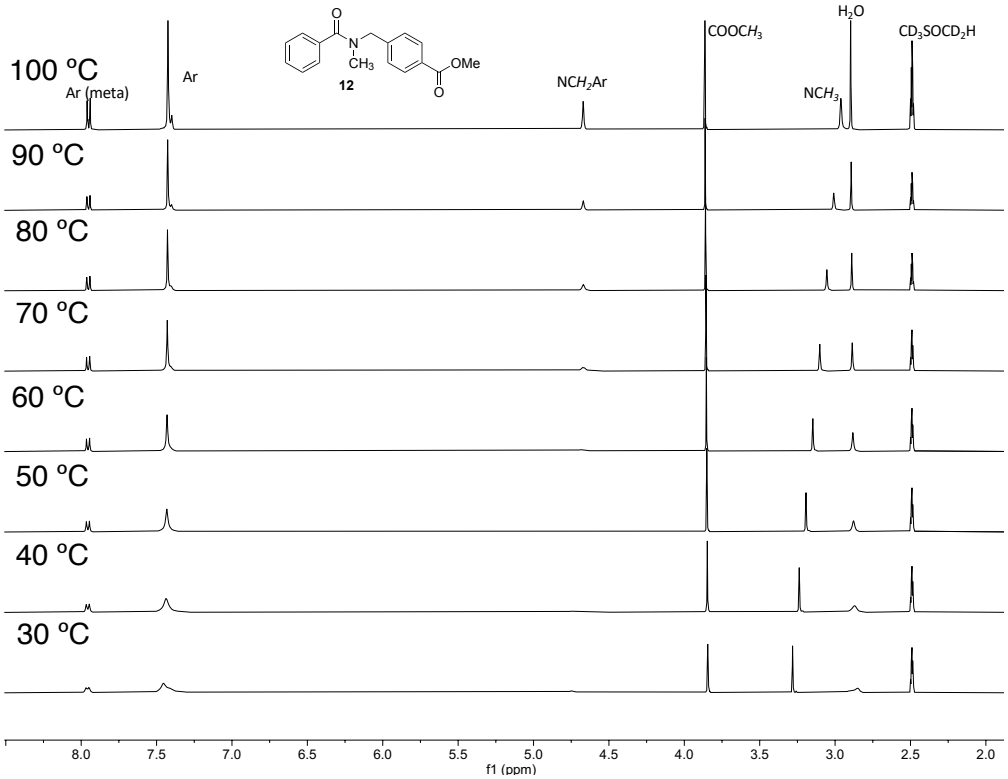


Figure S46. VT-^{1}H NMR (DMSO-d_6, 400 MHz) of **12**.

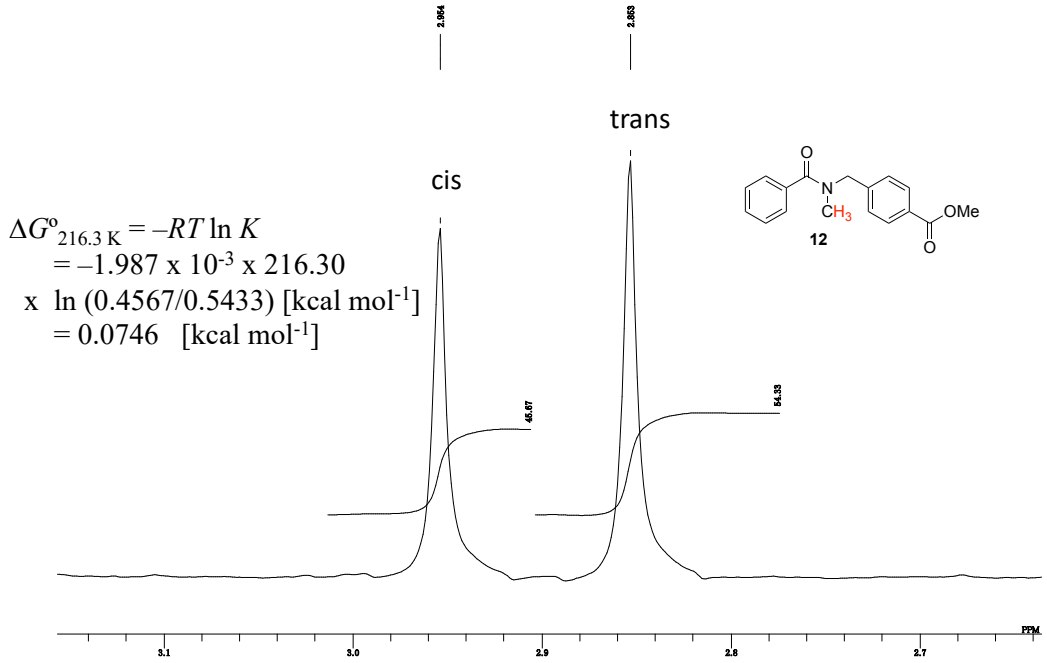


Figure S47. ^{1}H NMR integration of **12** (CD_2Cl_2, 400 MHz, 216 K).

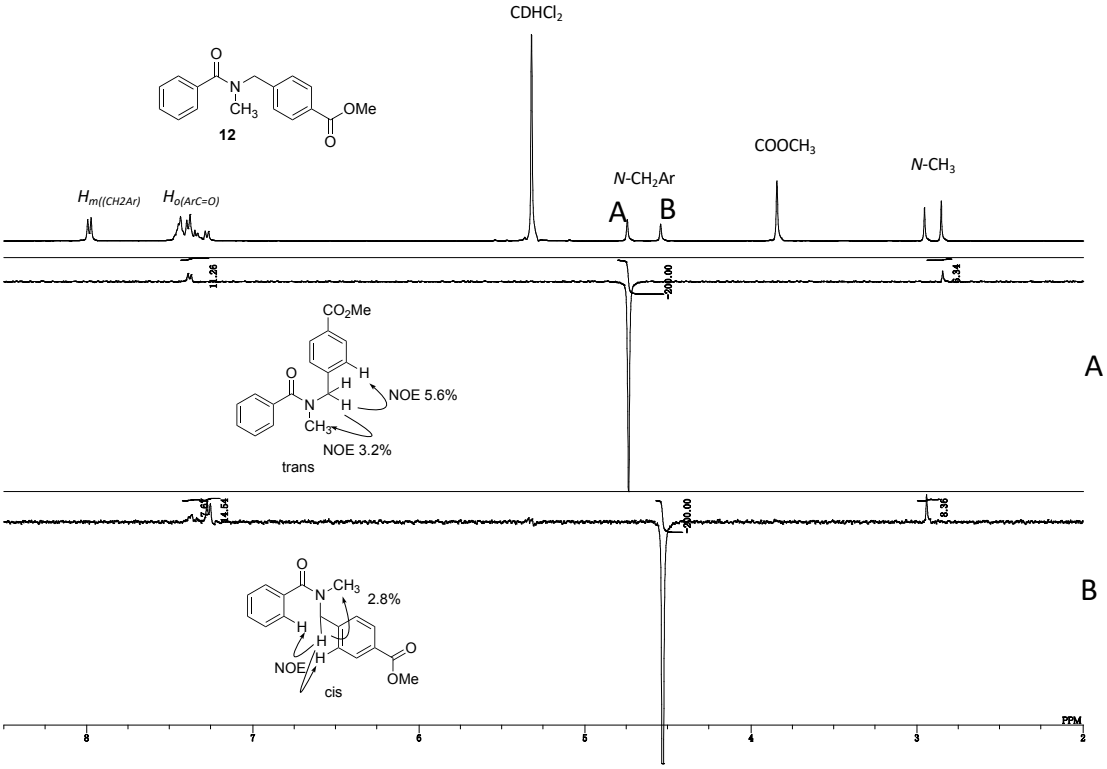


Figure S48. 1D-NOE spectrum of **12** (CD_2Cl_2, 400 MHz, 216 K).

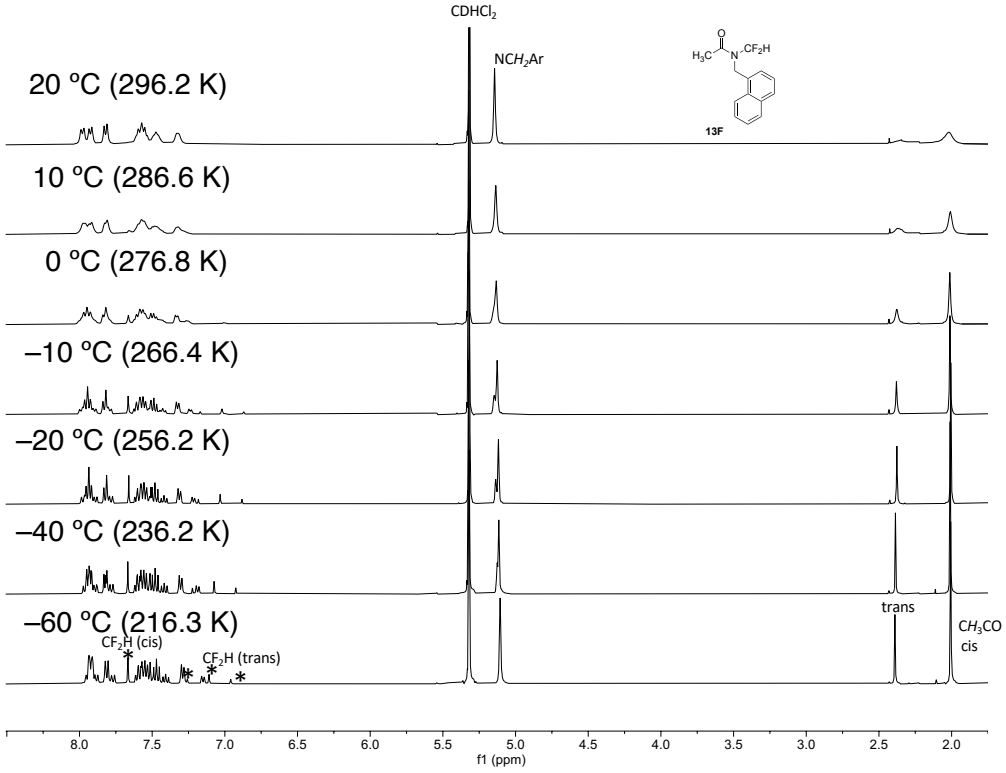


Figure S49. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **13F**.

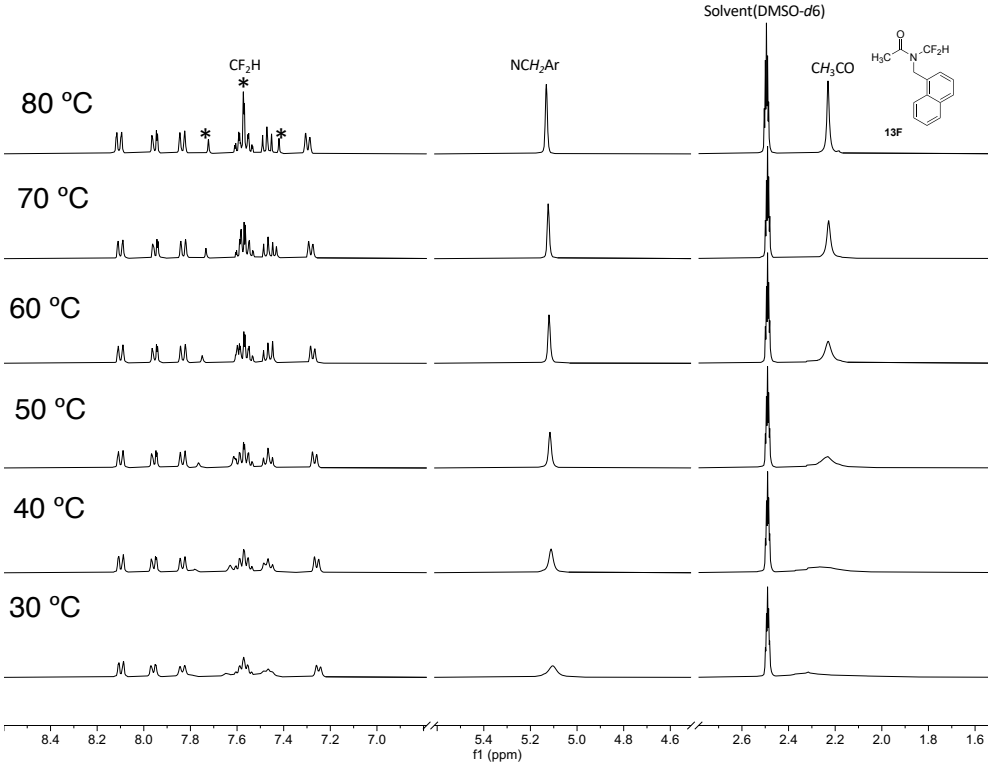


Figure S50. VT-^{1}H NMR (DMSO-d_6, 400 MHz) of **13F**.

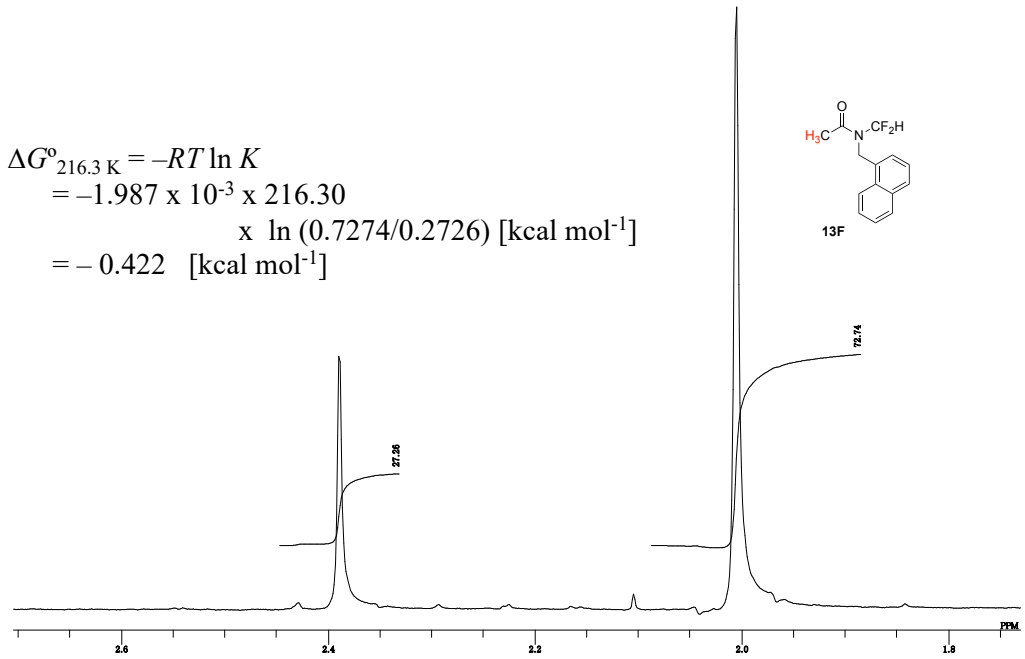


Figure S51. ^{1}H NMR integration of **13F** (CD_2Cl_2, 400 MHz, 216 K).

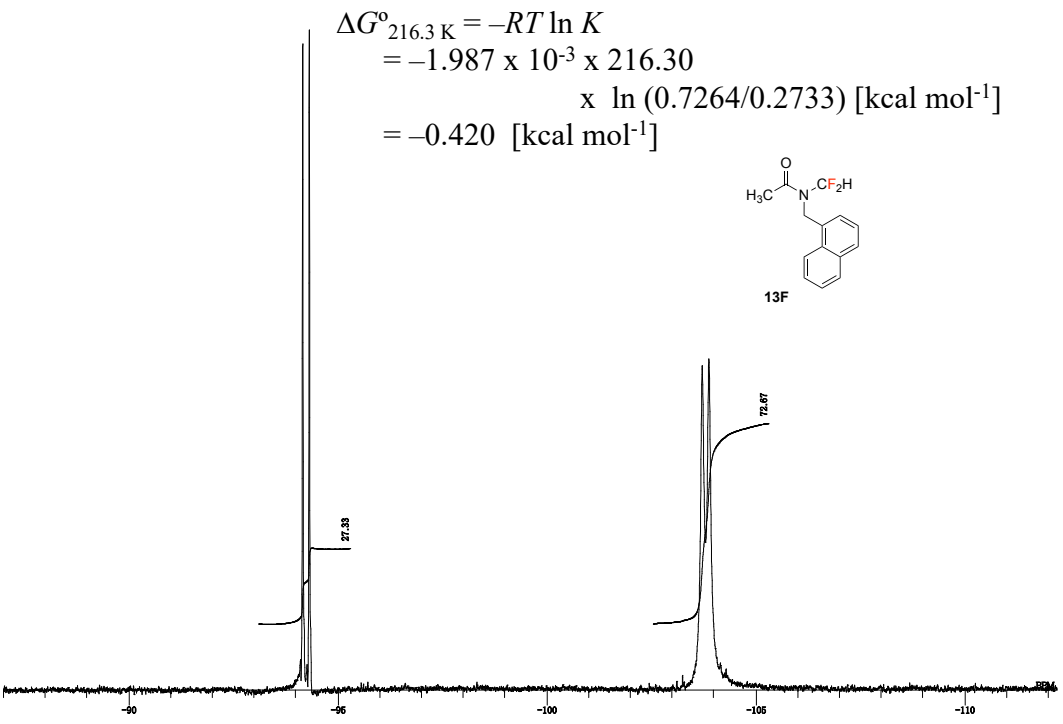


Figure S52. ^{19}F NMR integration of **13F** (CD_2Cl_2, 376 MHz, 216 K).

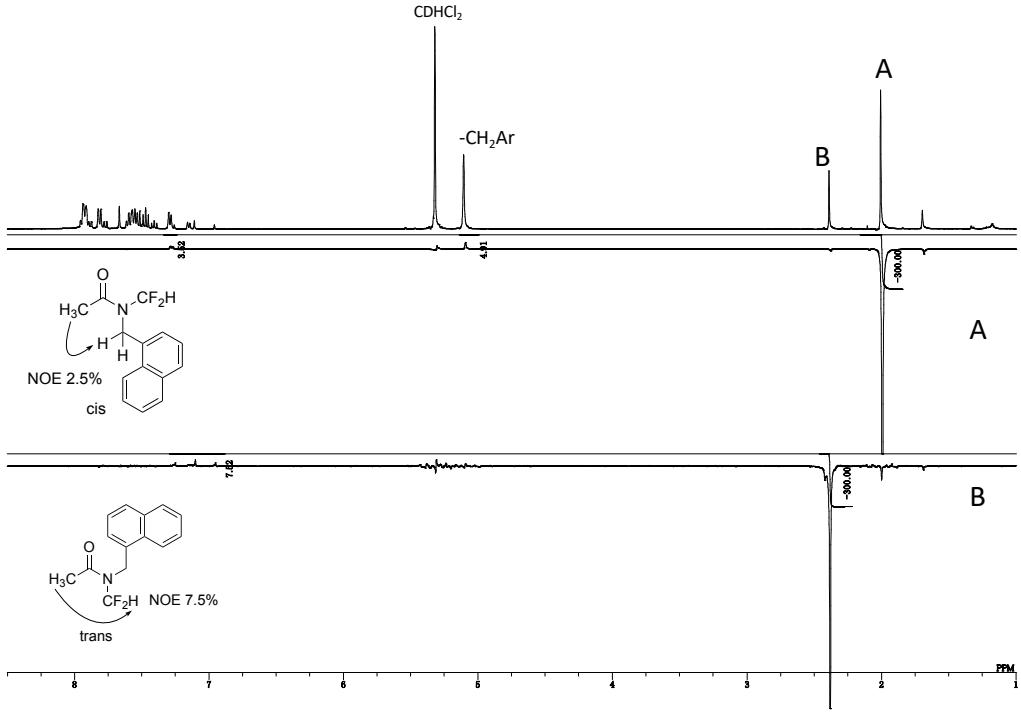


Figure S53. 1D-NOE spectrum of **13F** (CD_2Cl_2, 400 MHz, 216 K).

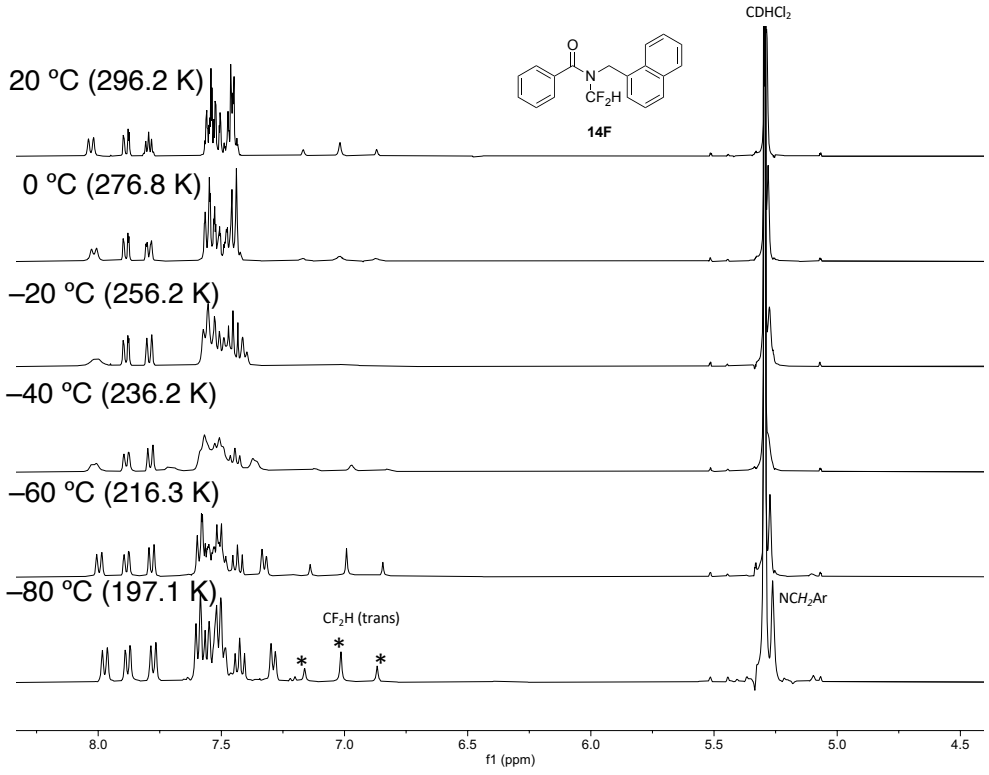


Figure S54. VT-^{1}H NMR (CD_2Cl_2, 400 MHz) of **14F**.

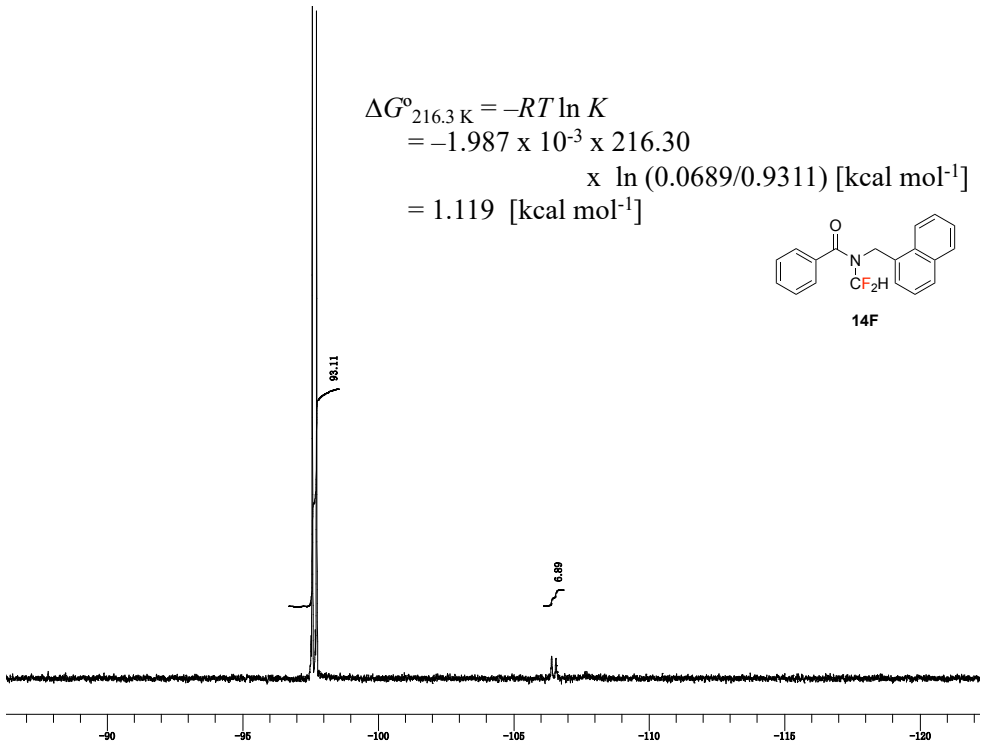


Figure S55. ^{19}F NMR integration of **14F** (CD_2Cl_2, 376 MHz, 216 K).

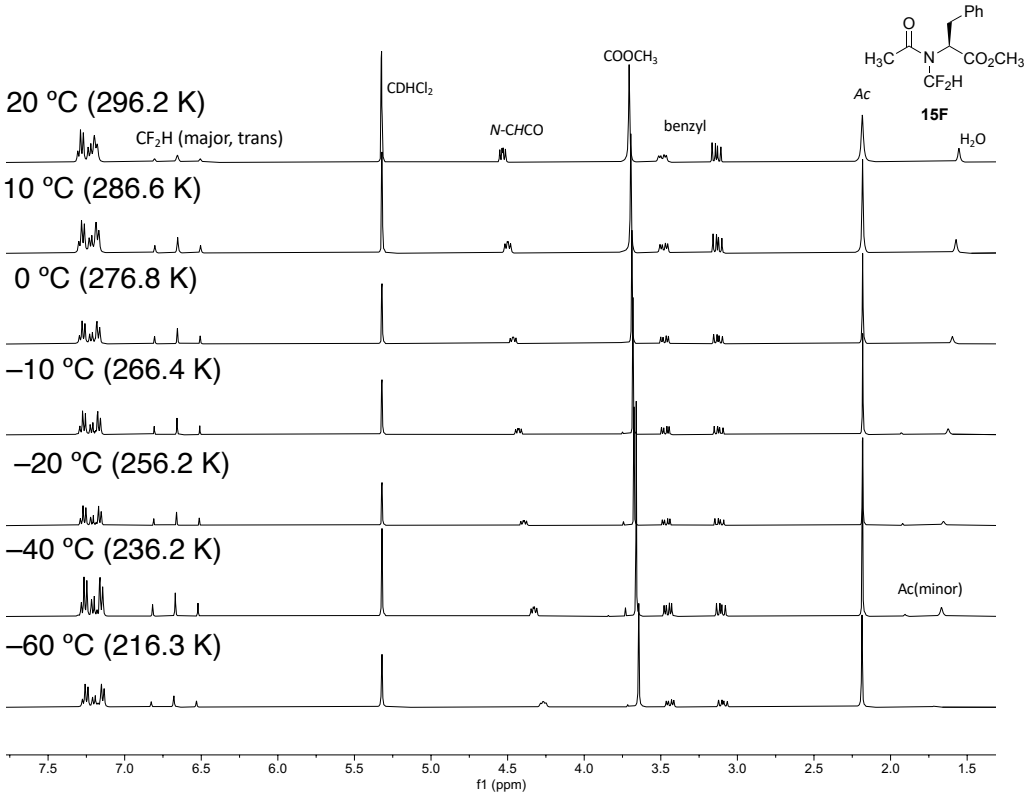


Figure S56. VT-^1H NMR (CD_2Cl_2, 400 MHz) of **15F**.

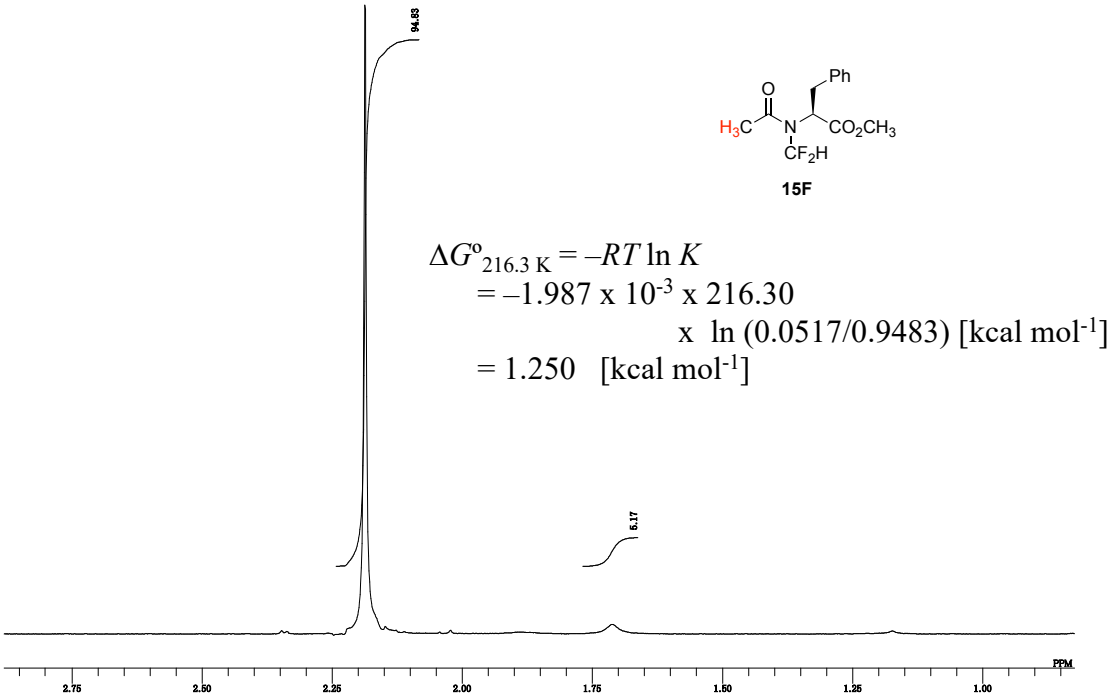


Figure S57. ^{1}H NMR integration of **15F** (CD_2Cl_2, 400 MHz, 216 K).

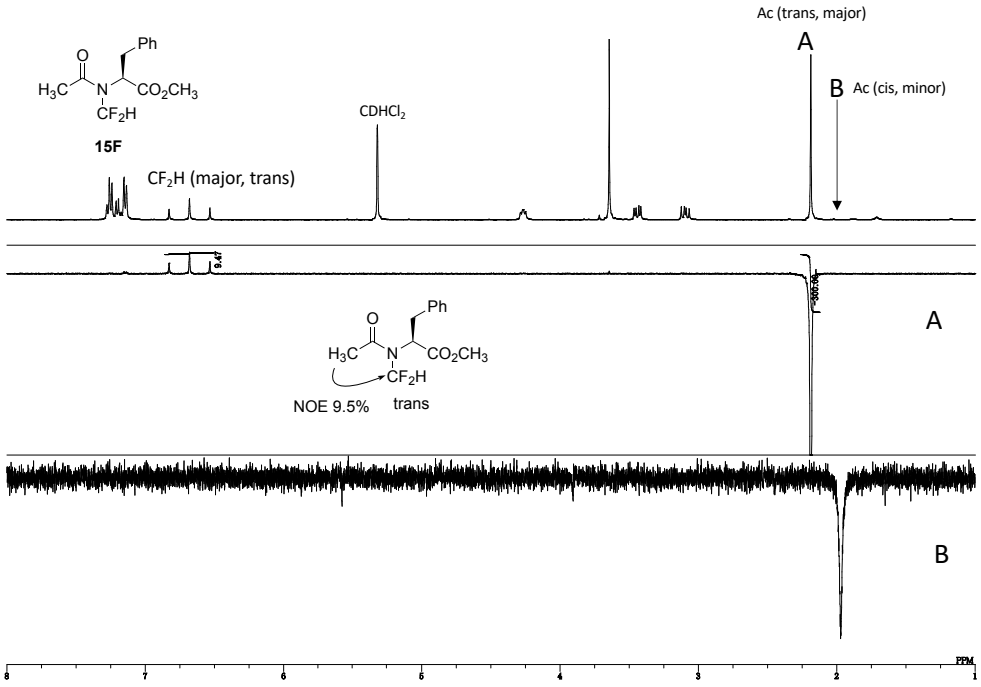


Figure S58. 1D-NOE spectrum of **15F** (CD_2Cl_2, 400 MHz, 216 K).

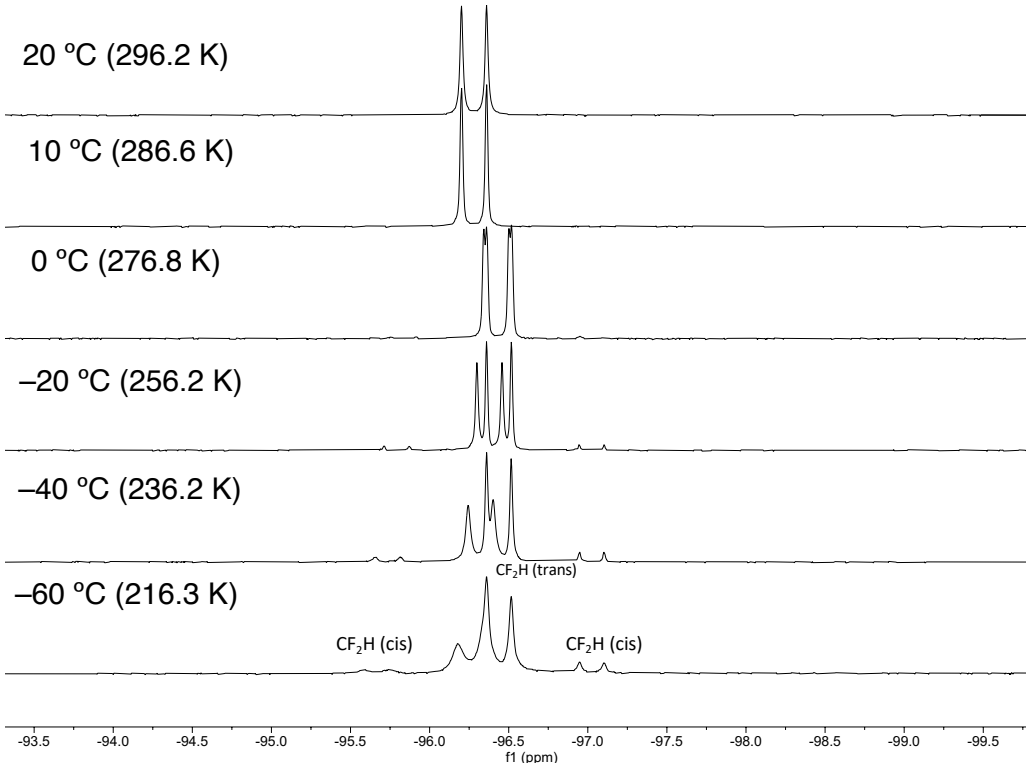


Figure S59. VT-^{19}F NMR (CD_2Cl_2, 376 MHz) of **15F**.

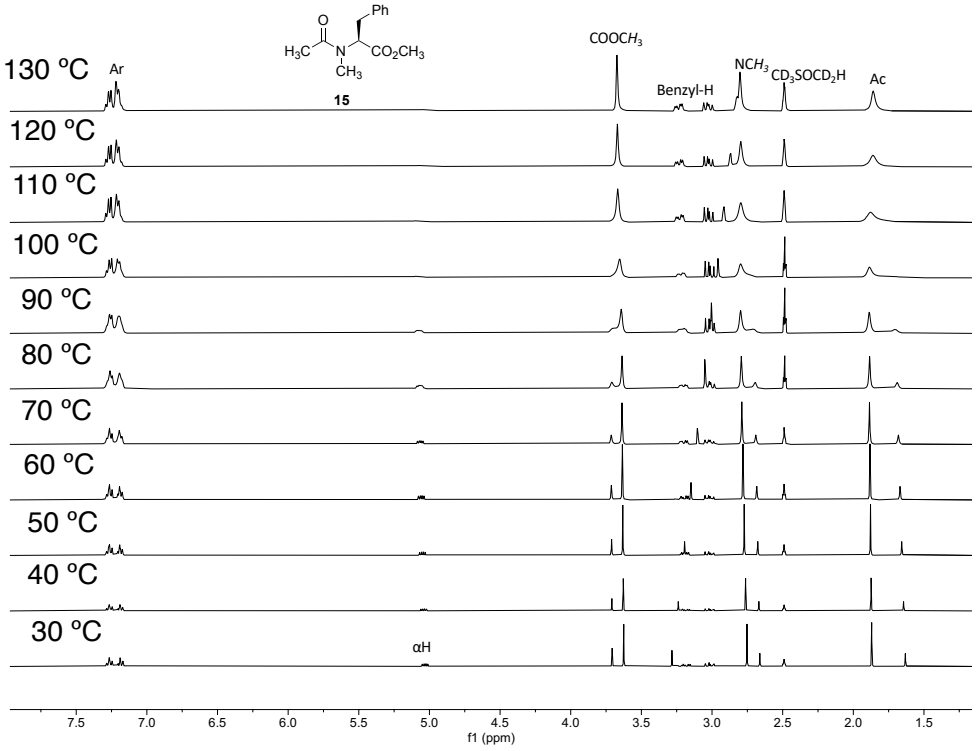


Figure S60. VT-^{1}H NMR (DMSO-d_6, 400 MHz) of **15**.

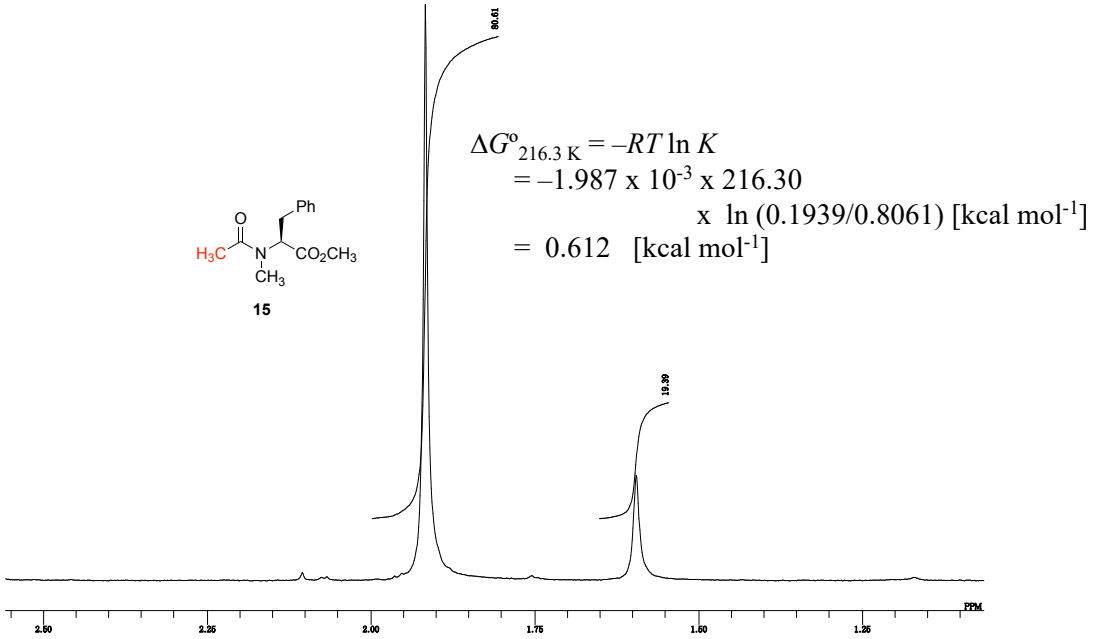


Figure S61. ^{1}H NMR integration of **15H** (CD_2Cl_2, 400 MHz, 216 K).

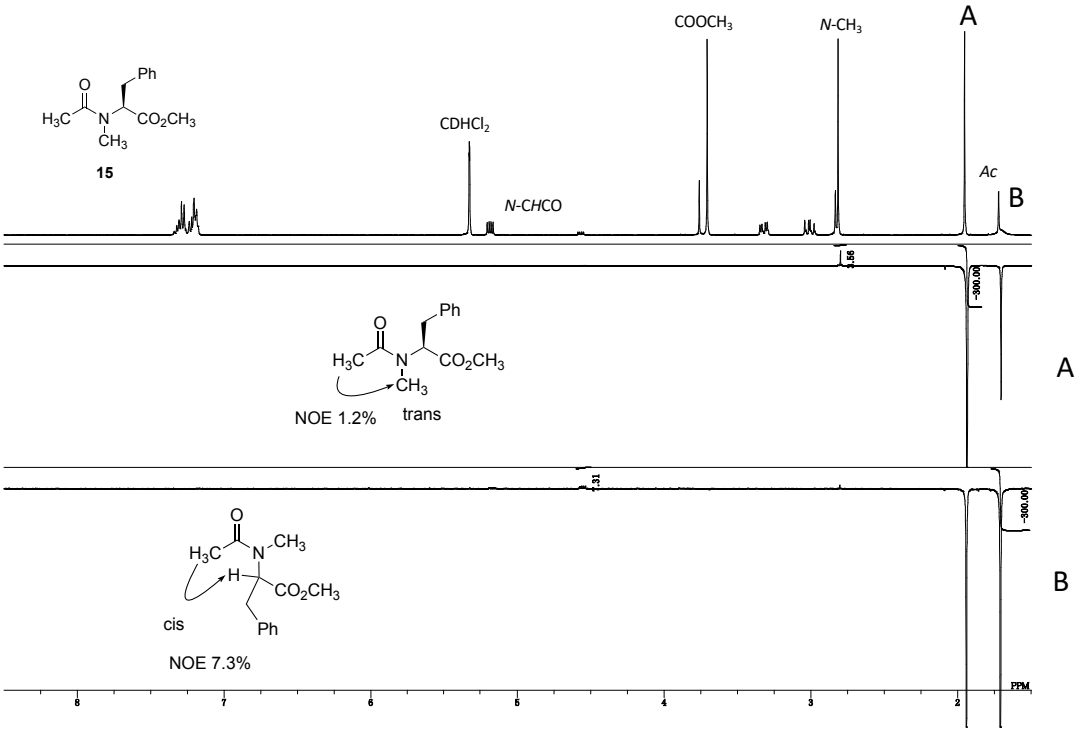


Figure S62. 1D-NOE spectrum of **15H** (CD_2Cl_2, 400 MHz, 216 K).

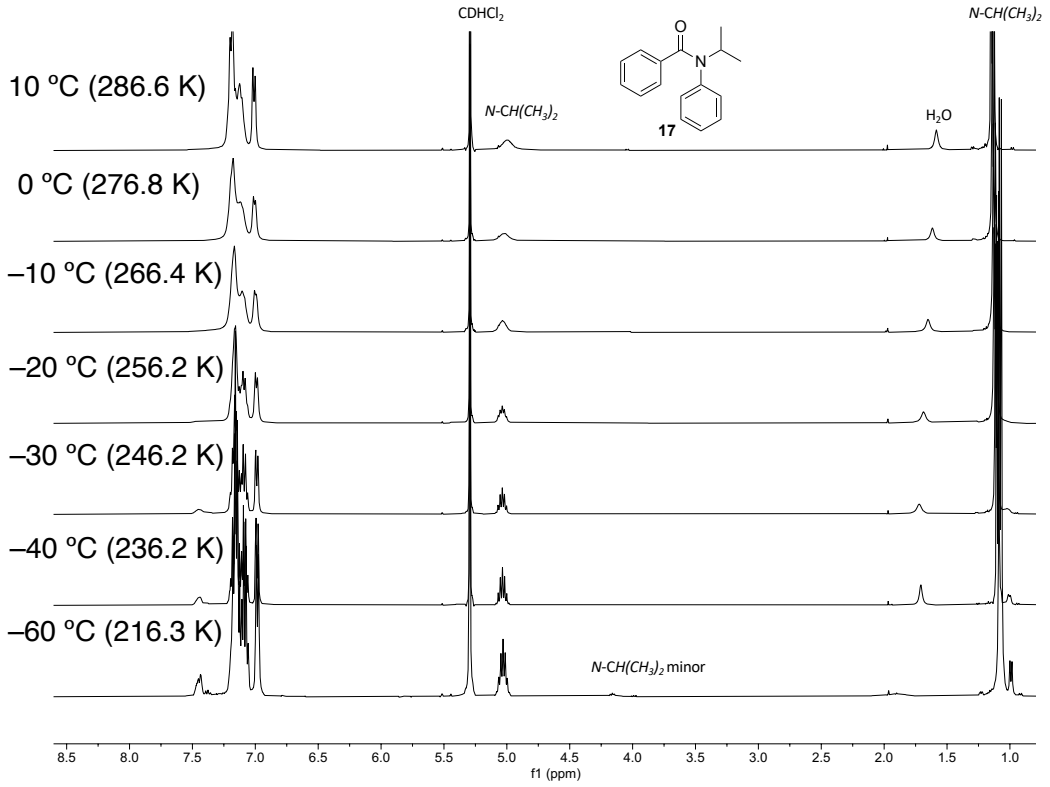
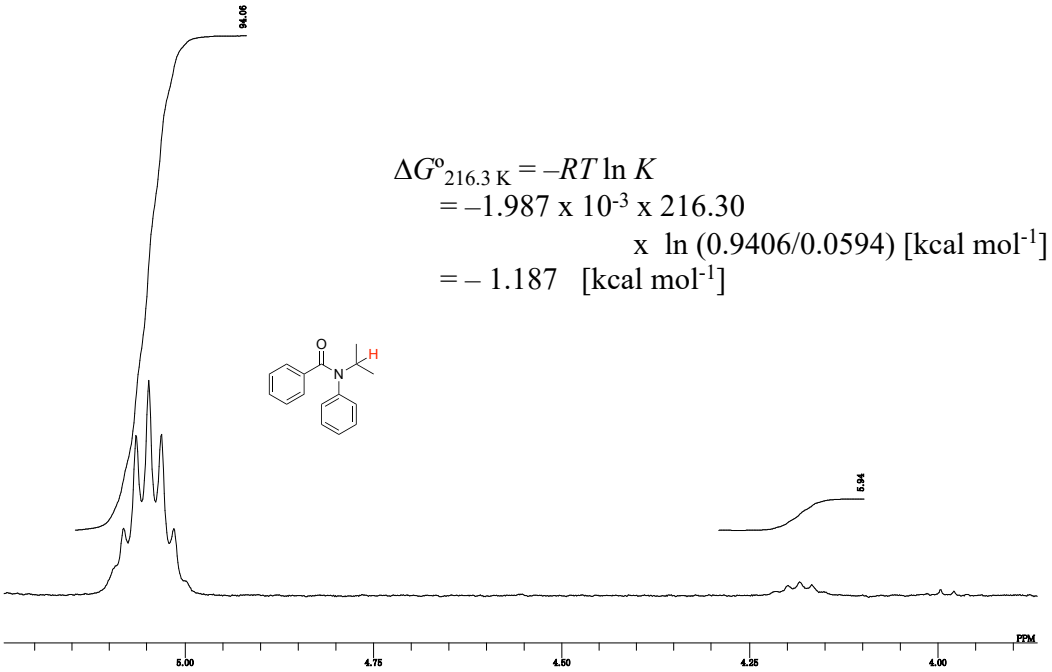


Figure S63. VT-^{1}HNMR (CD_2Cl_2, 400 MHz) of **17**.



$$\Delta G^{o}_{216.3\ K} = -RT \ln K$$
$$= -1.987 \times 10^{-3} \times 216.30 \times \ln (0.9406/0.0594)\ [\text{kcal mol}^{-1}]$$
$$= -1.187\ [\text{kcal mol}^{-1}]$$

Figure S64. ^{1}H NMR integration of **17** (CD_2Cl_2, 400 MHz, 216 K).

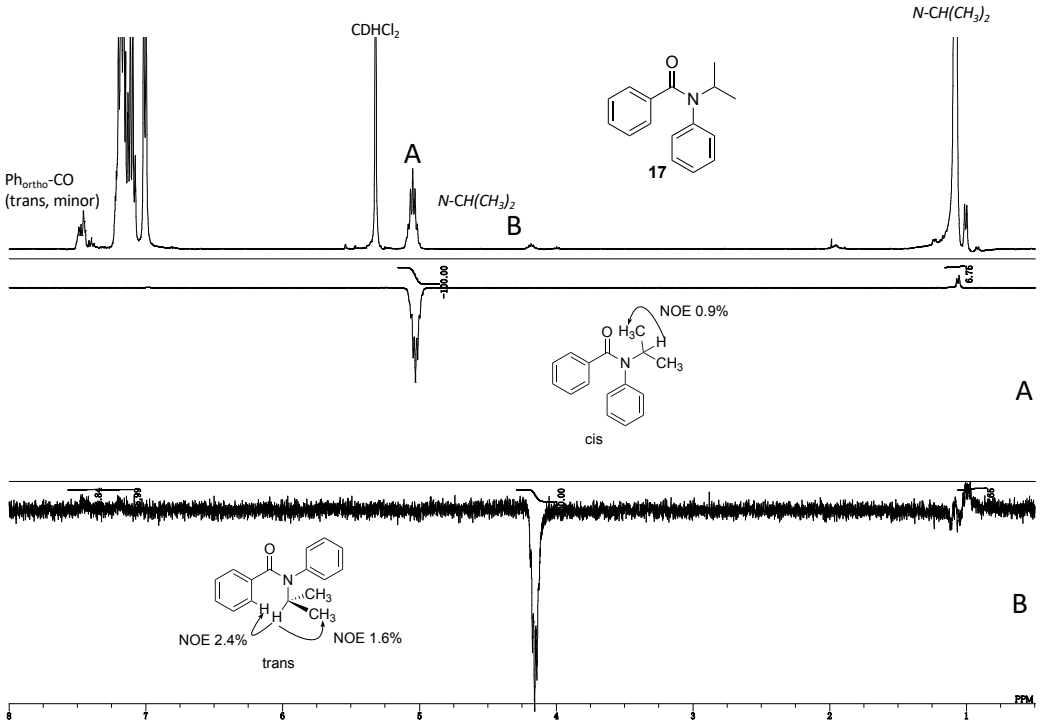
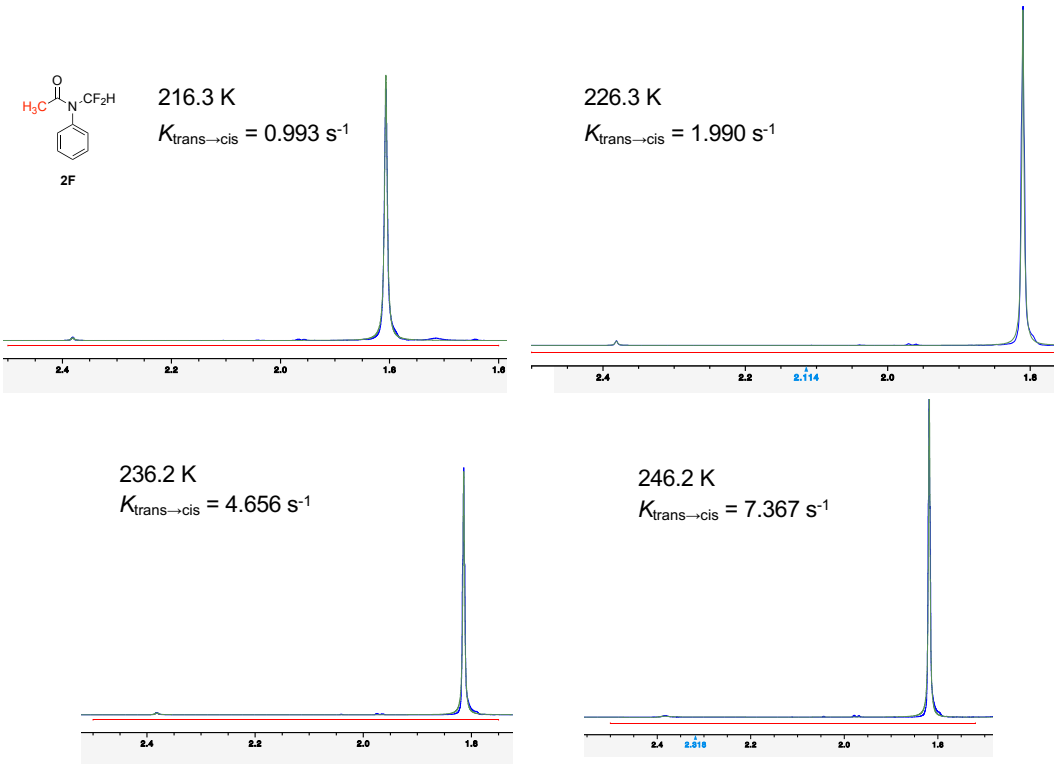


Figure S65. 1D-NOE spectrum of **17** (CD_2Cl_2, 400 MHz, 216 K)



Blue; Experimental Spectra Green; Simulated Curve (Topspin dnmr)

Figure S66. ^{1}HNMR line-shape analysis (CD_2Cl_2, 400 MHz) of **2F**.

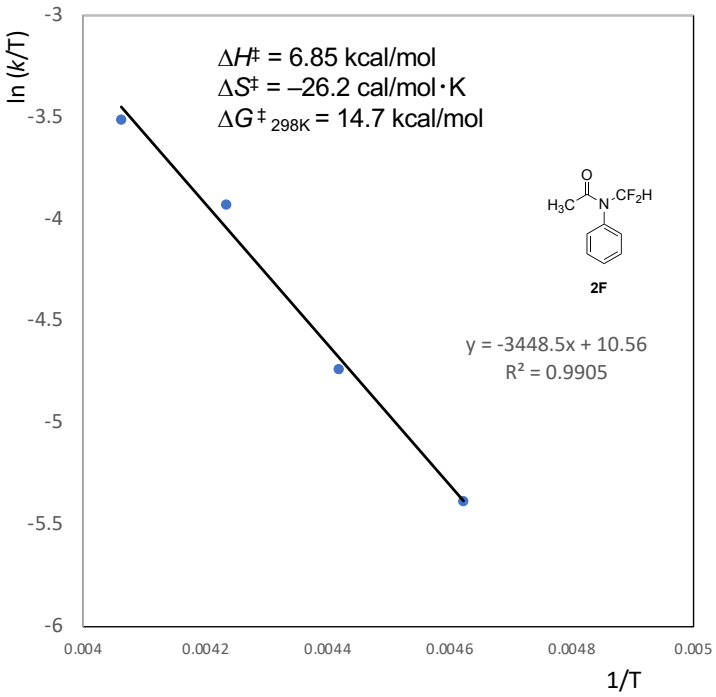


Figure S67. Arrenius plot of line-shape analysis of **2F**.

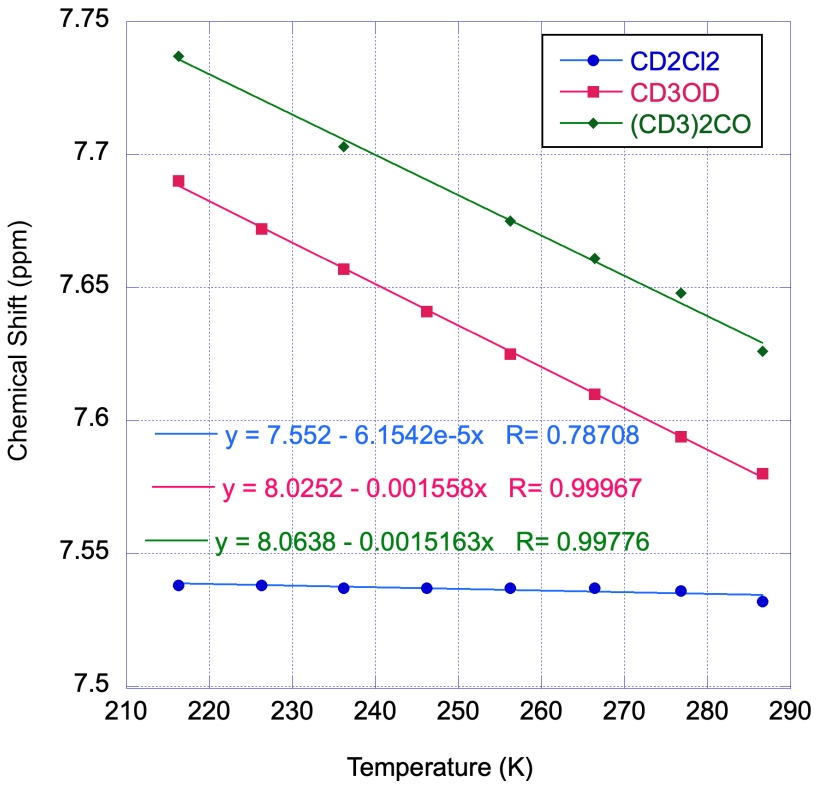
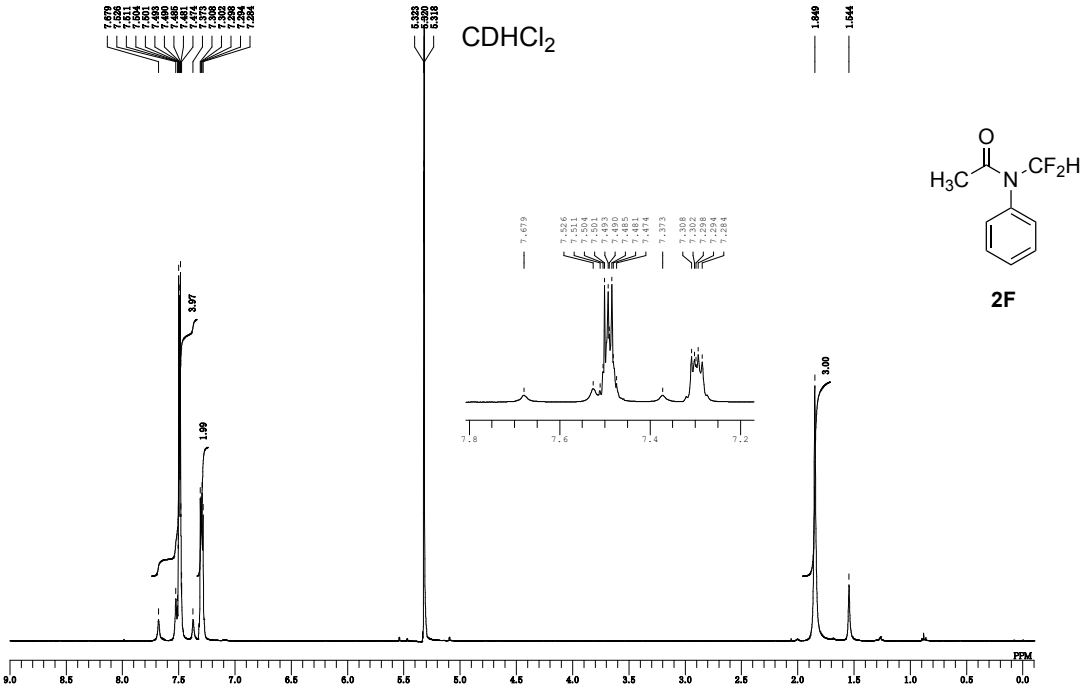


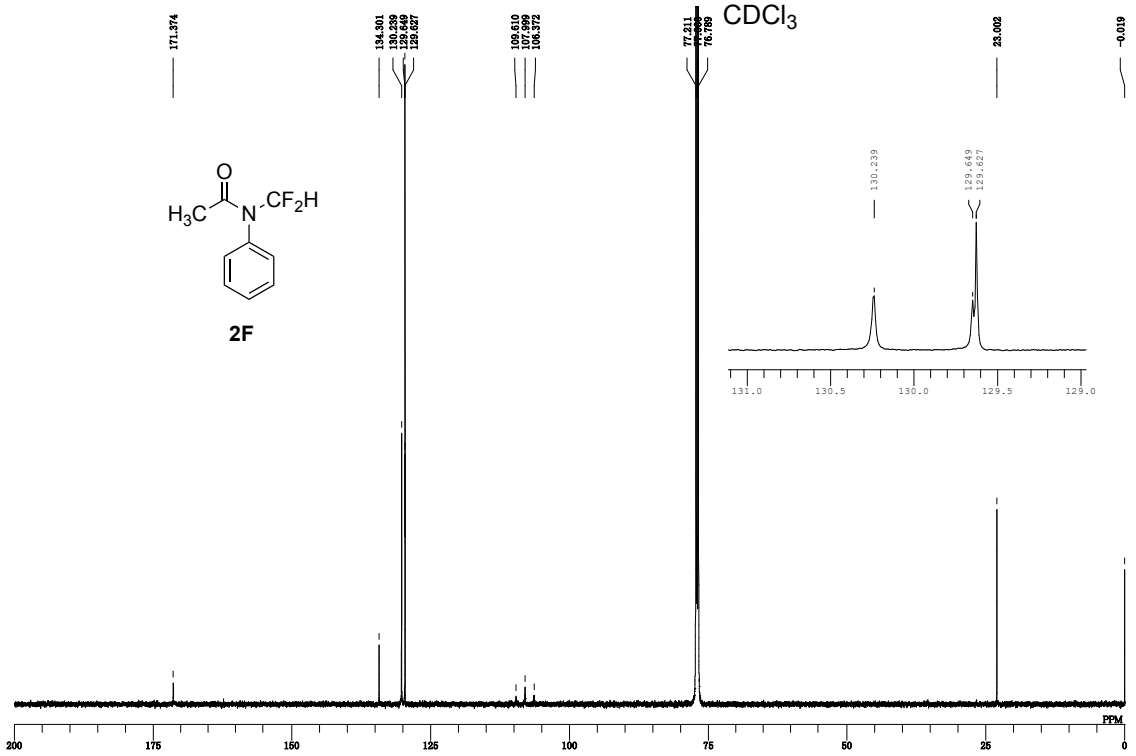
Figure S68. Solvent and temperature dependence of CF_2H (cis conformer) chemical shift in ^1H NMR of **2F**.

5. NMR spectra

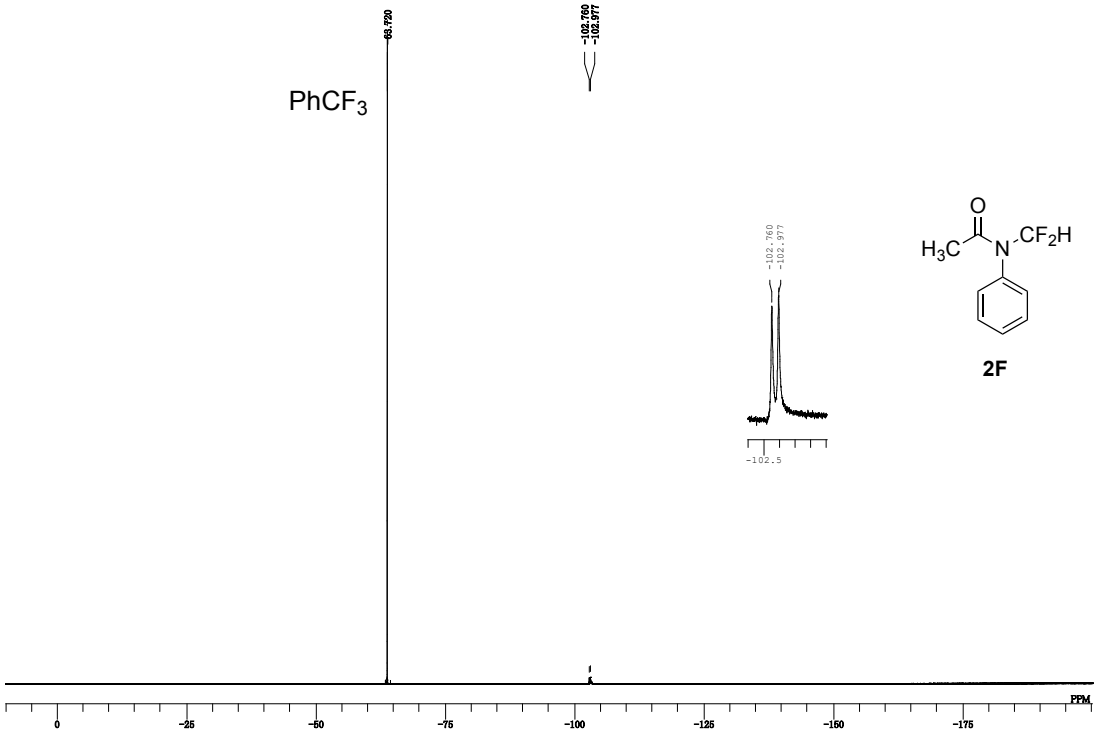
^{1}H NMR (400 MHz, CD_2Cl_2) spectrum of **2F**



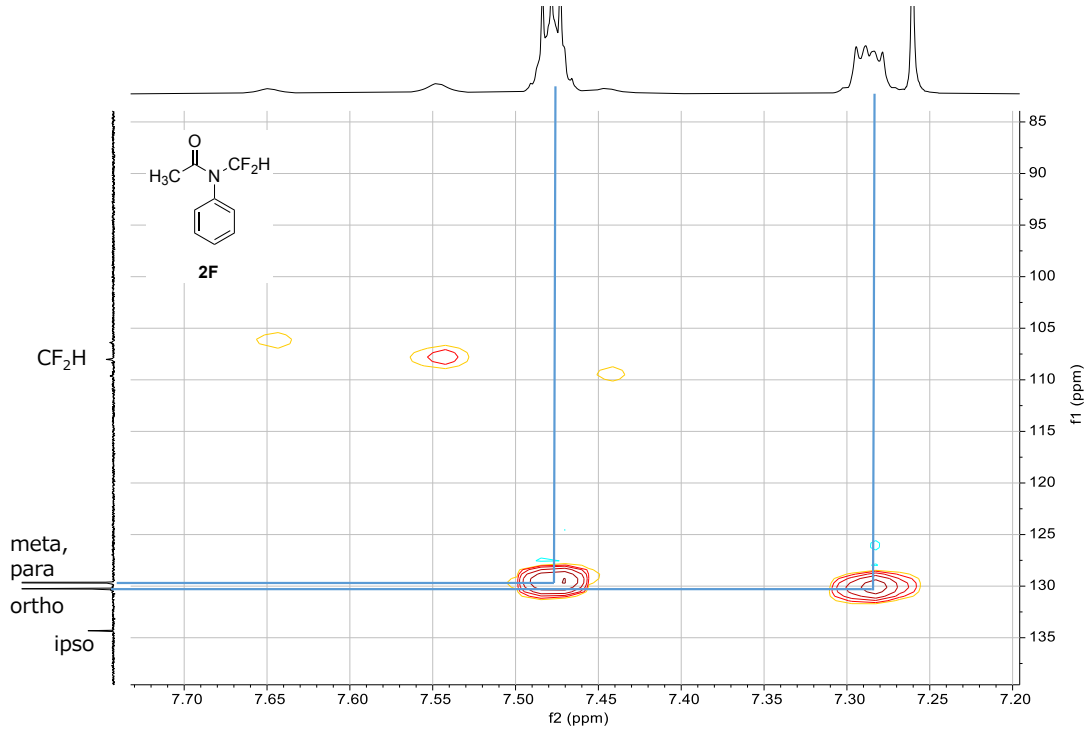
^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) spectrum of **2F**



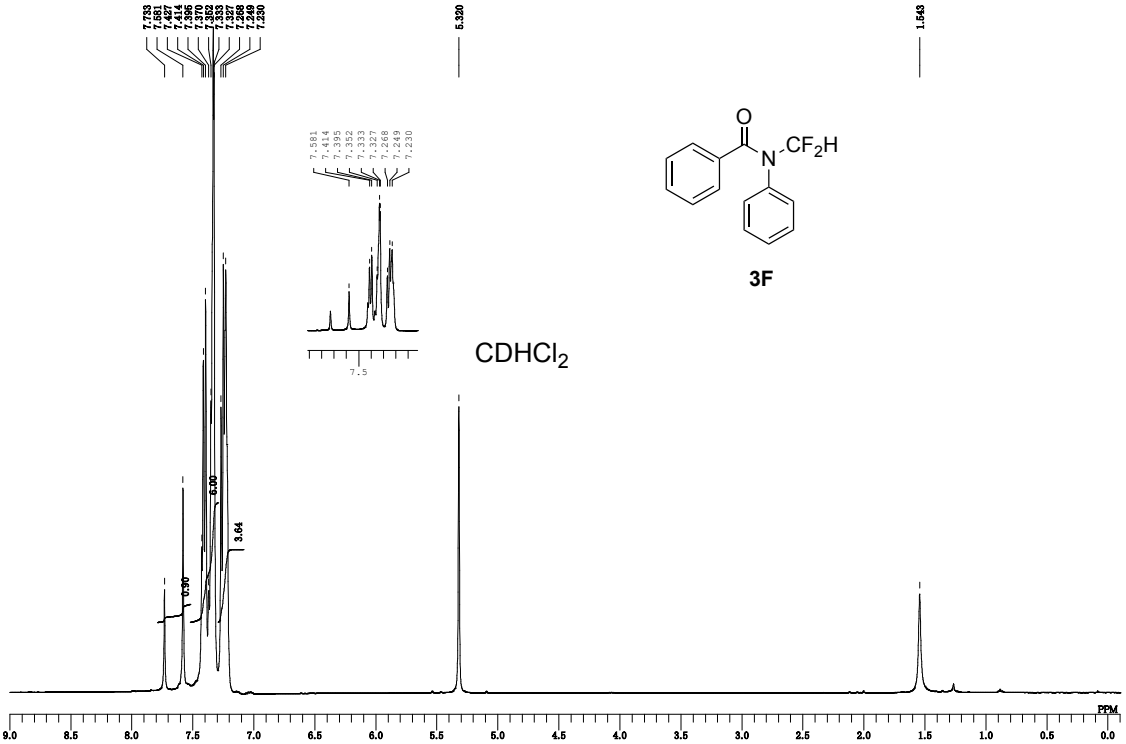
^{19}F NMR (283 MHz, $CDCl_3$) spectrum of **2F**



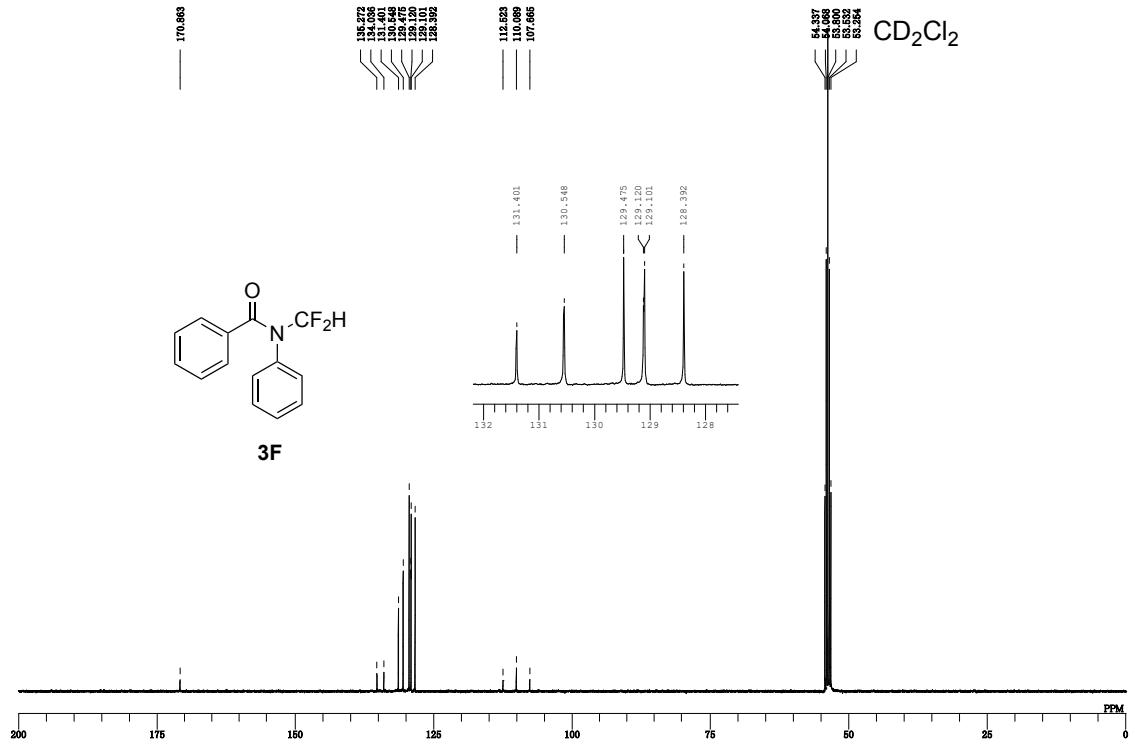
HSQC ($CDCl_3$) spectrum of **2F**



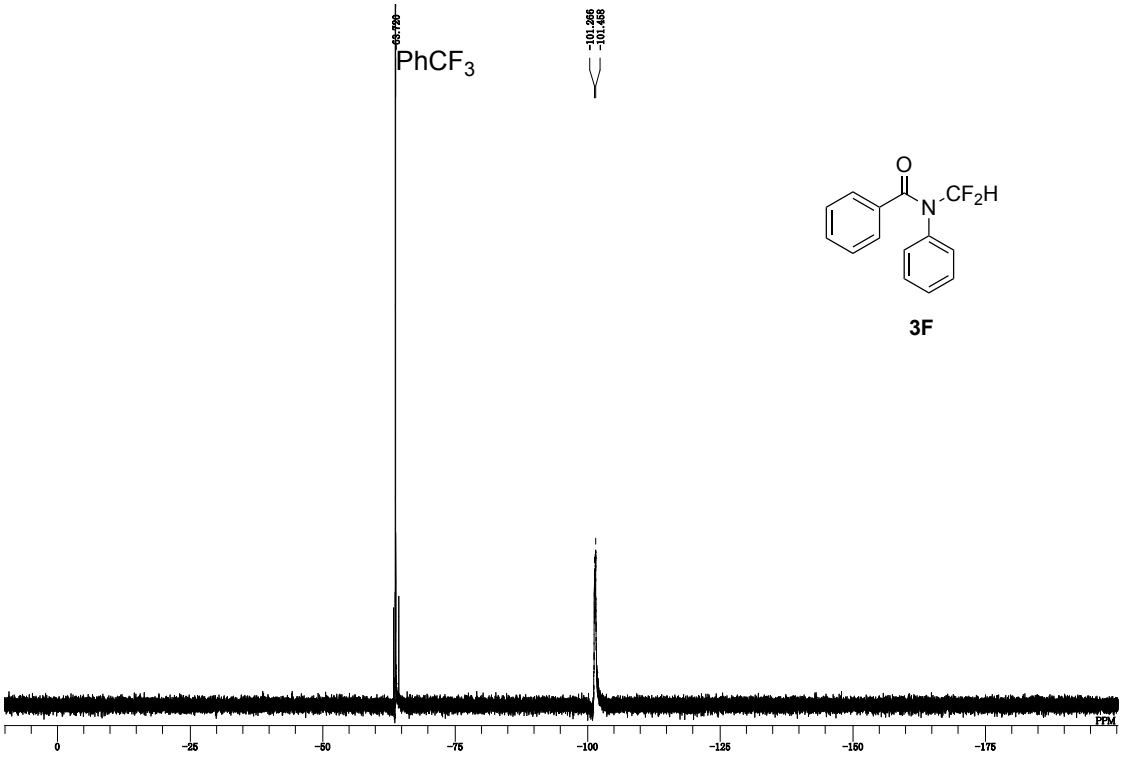
^{1}H NMR (400 MHz, CD_2Cl_2) spectrum of **3F**



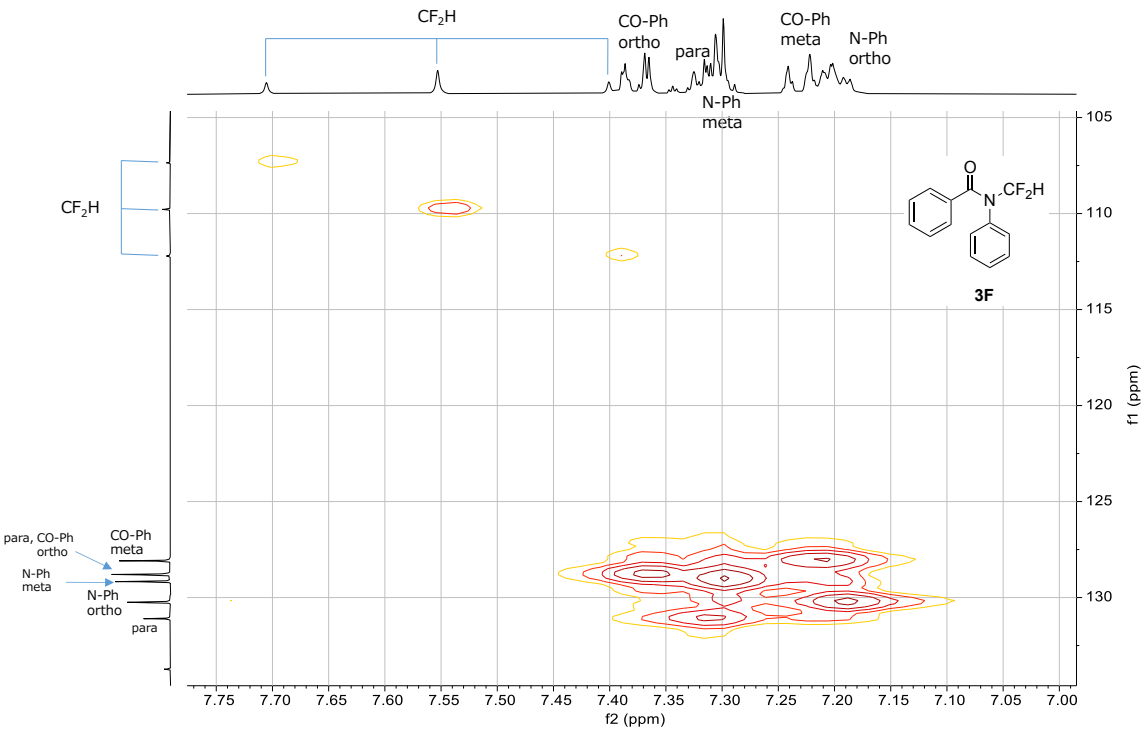
^{13}C{^{1}H} NMR (100 MHz, CD_2Cl_2) spectrum of **3F**



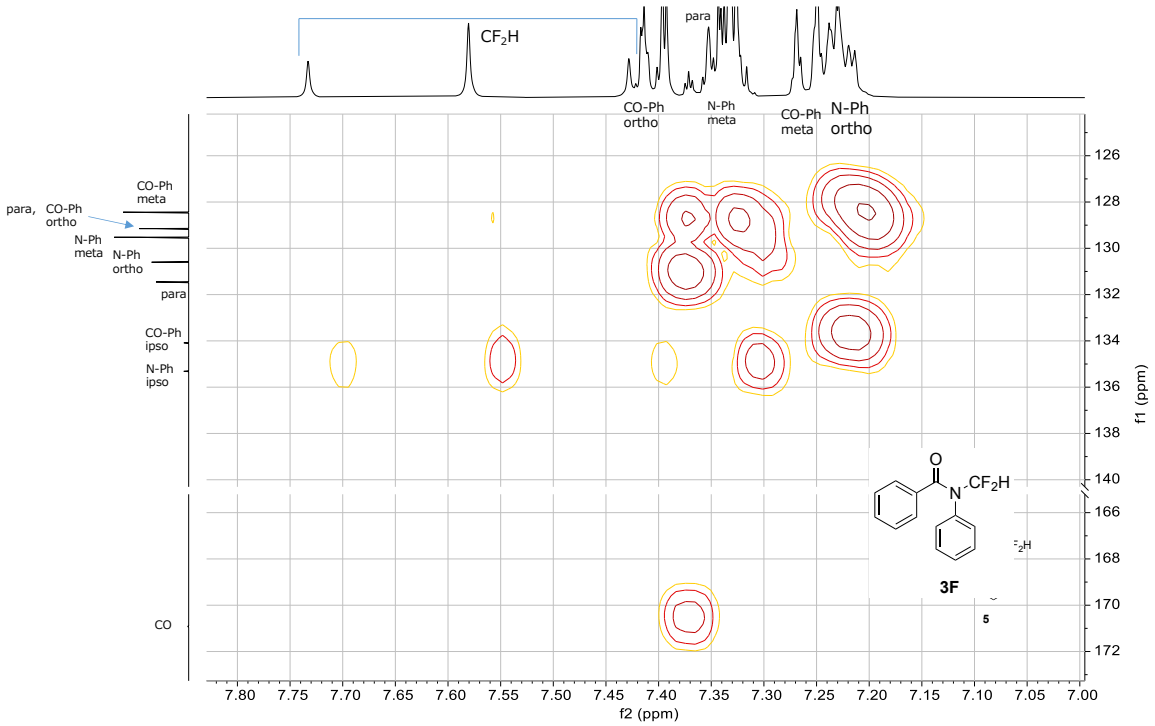
^{19}F NMR (282 MHz, $CDCl_3$) spectrum of **3F**



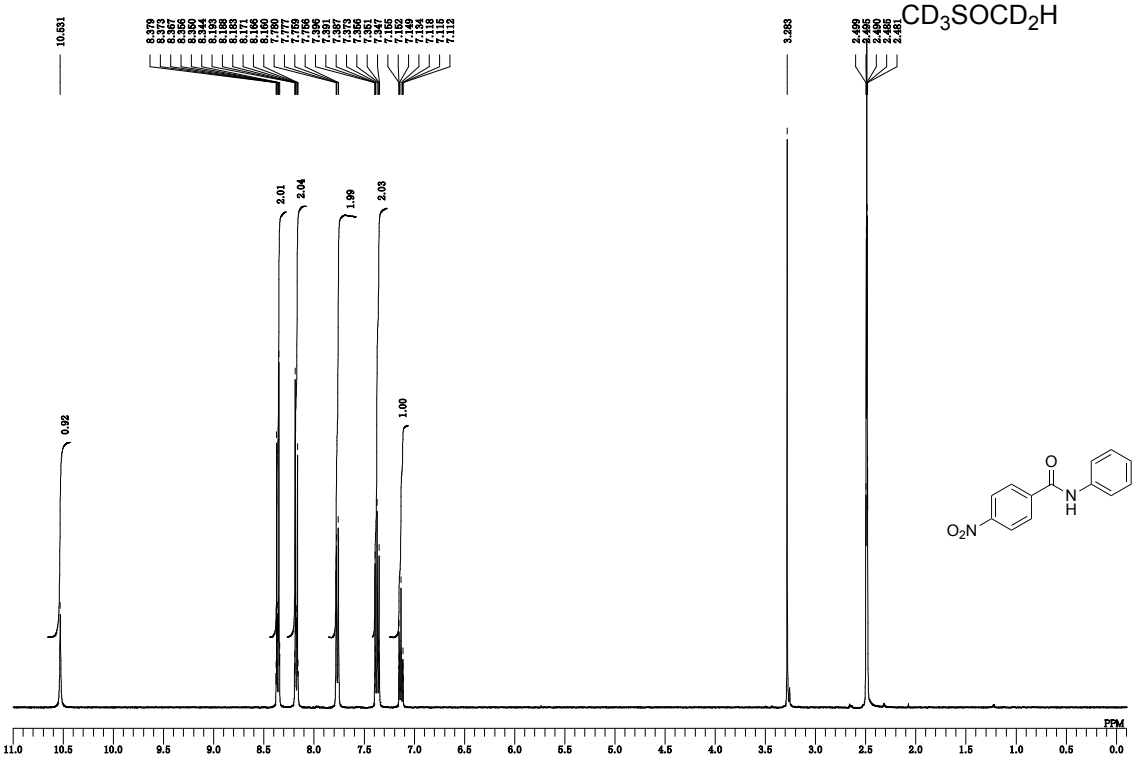
HSQC ($CDCl_3$) spectrum of **3F**



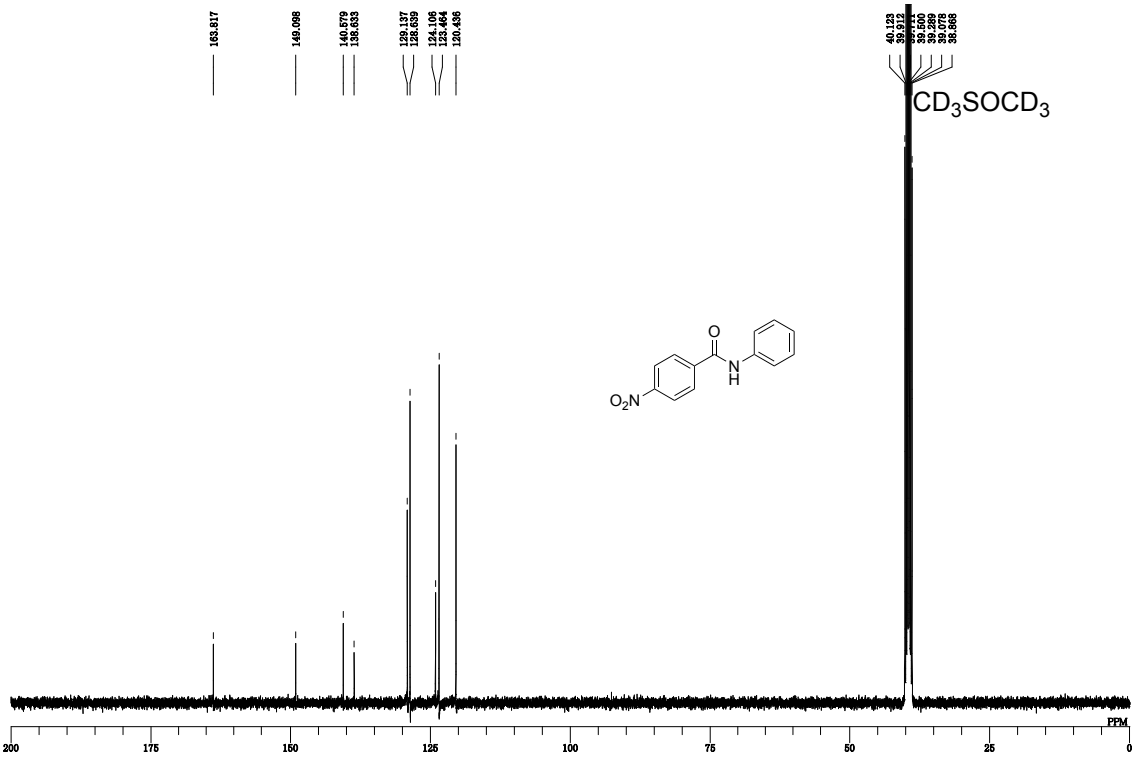
HMBC ($CDCl_3$) spectrum of **3F**



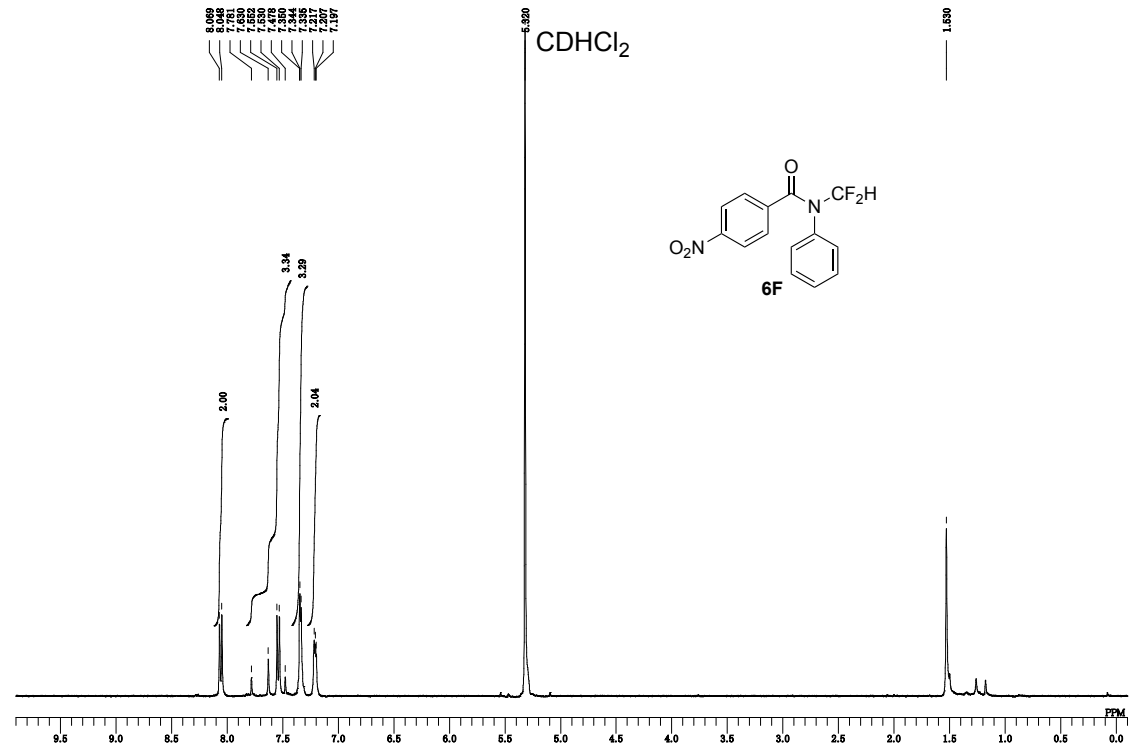
^{1}H NMR (400 MHz, 30 ºC, DMSO-d_6) spectrum of *p*-nitro benzoyl benzanilide



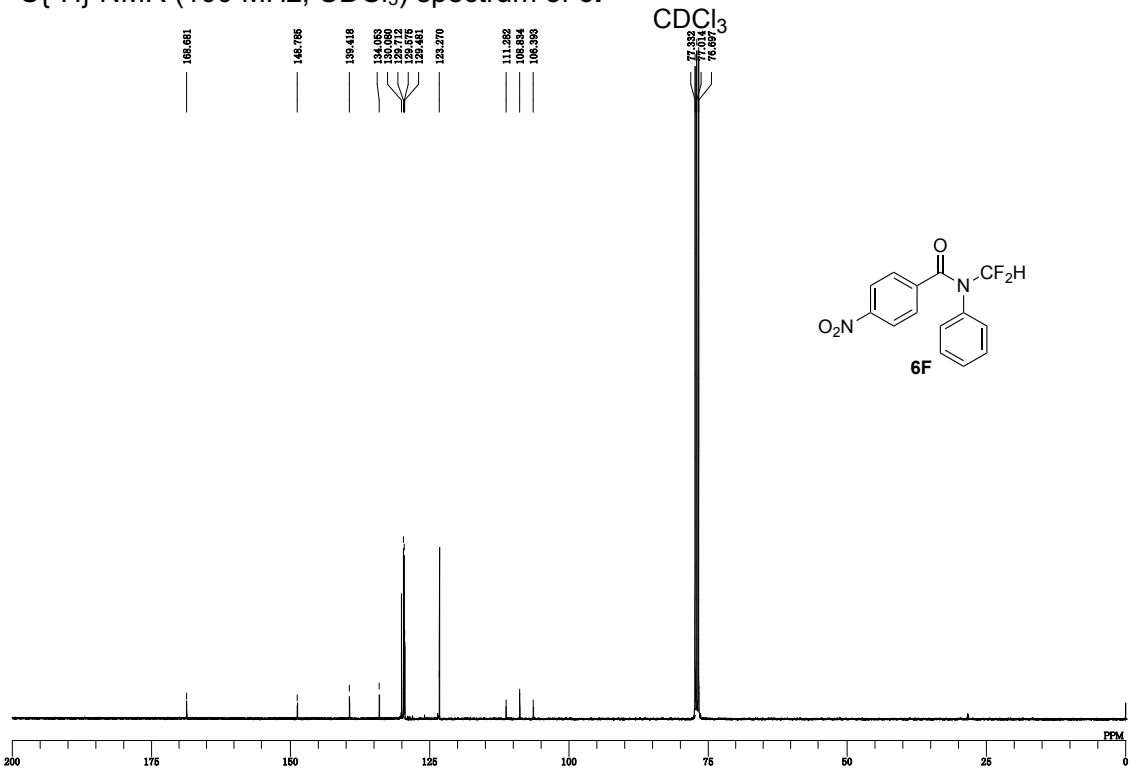
$^{13}C\{^{1}H\}$ NMR (100 MHz, 30 ºC, DMSO-d_6) spectrum of *p*-nitro benzoyl benzanilide



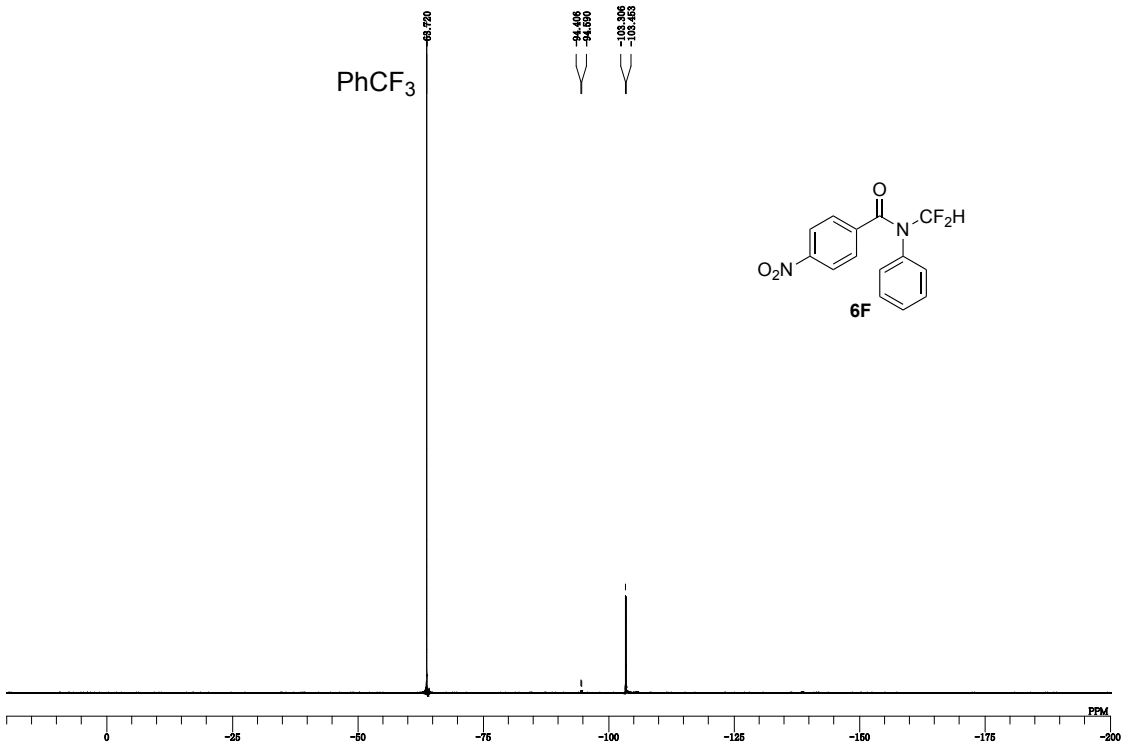
^{1}H NMR (400 MHz, CD_2Cl_2) spectrum of **6F**



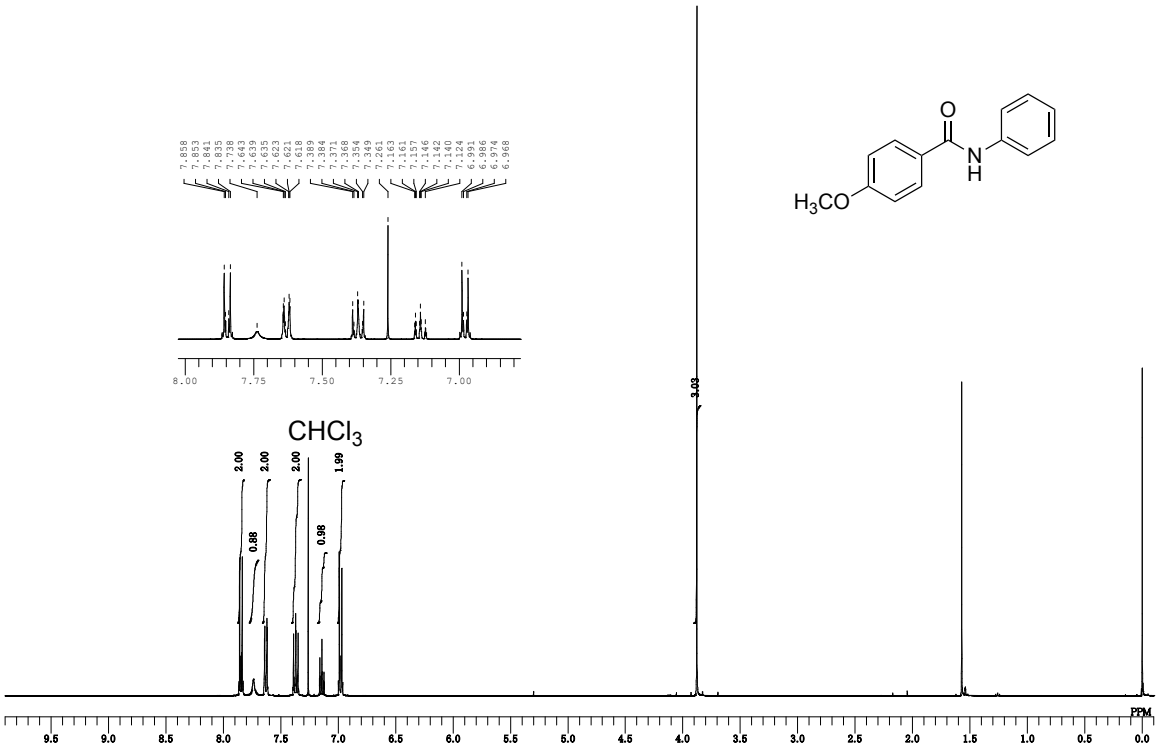
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **6F**



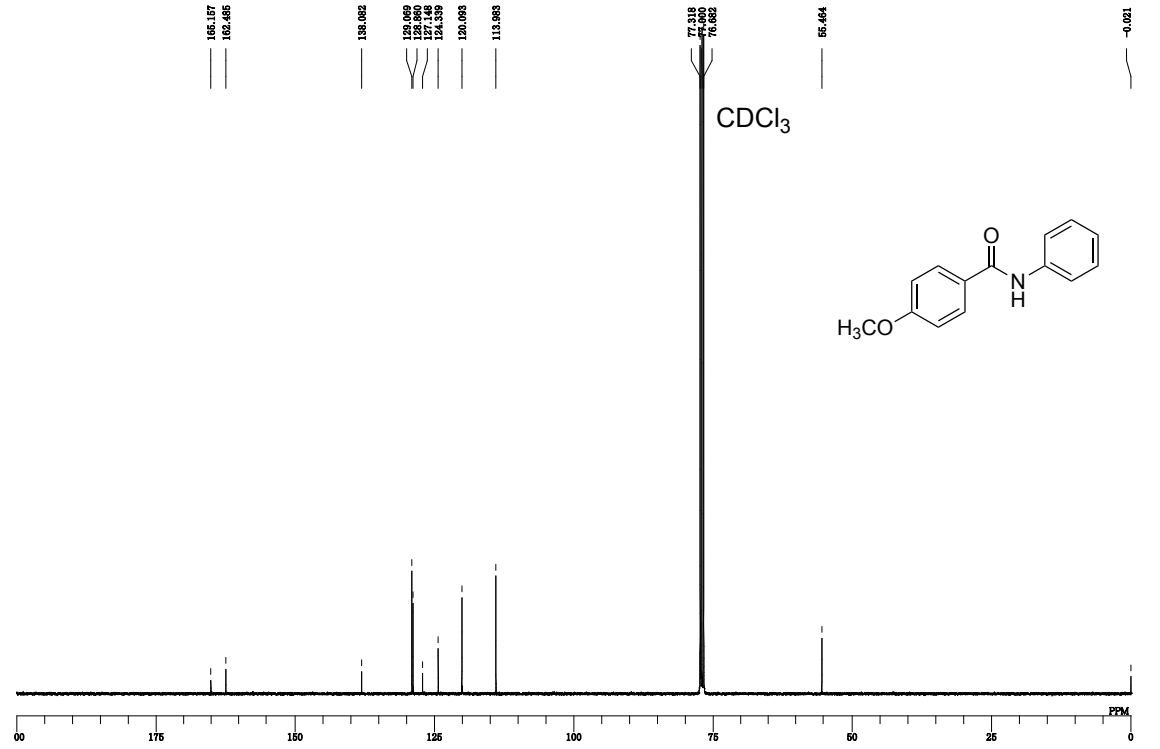
^{19}F NMR (376 MHz, CD_2Cl_2, 226 K) spectrum of **6F**



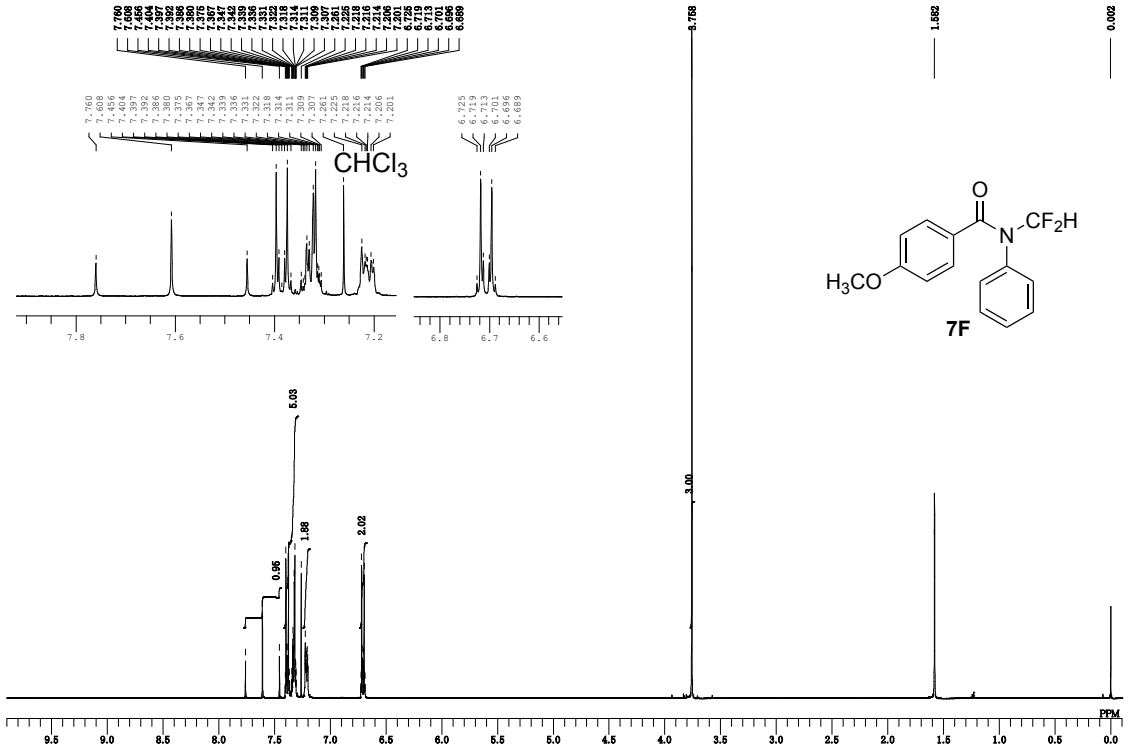
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *p*-methoxy benzoyl benzanilide



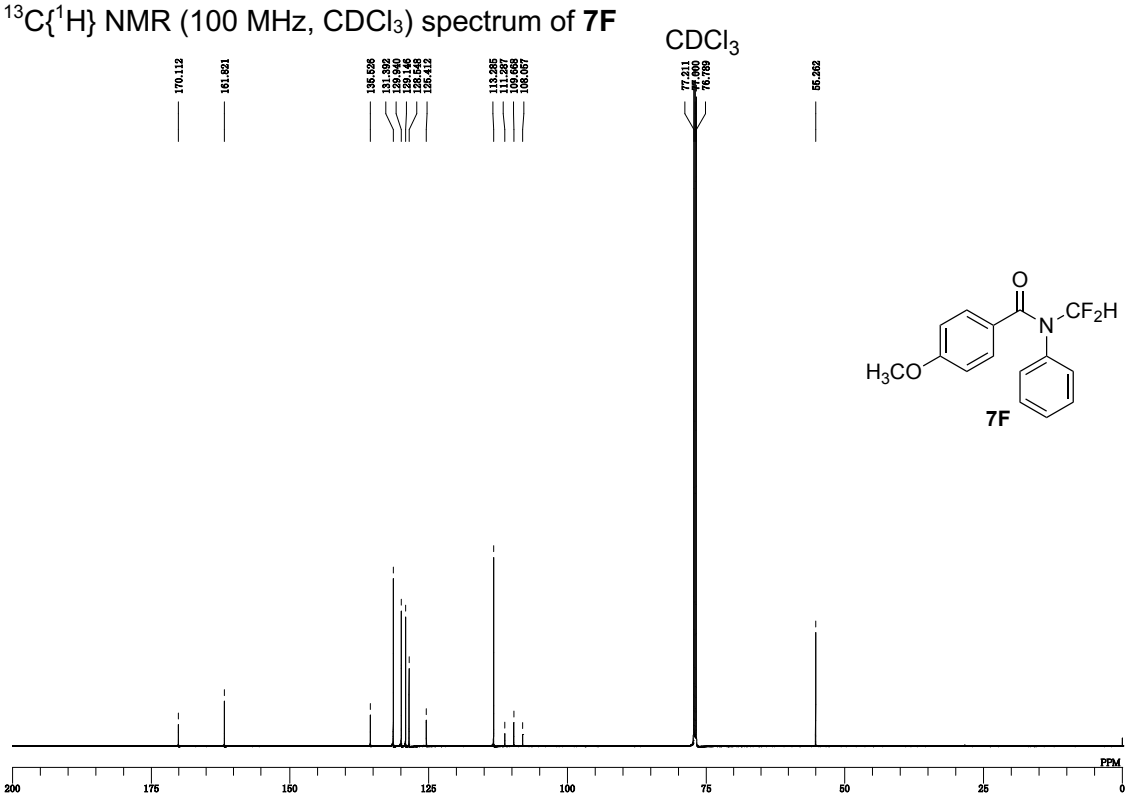
^{13}C{^{1}H} NMR (100 MHz) spectrum of *p*-methoxy benzoyl benzanilide



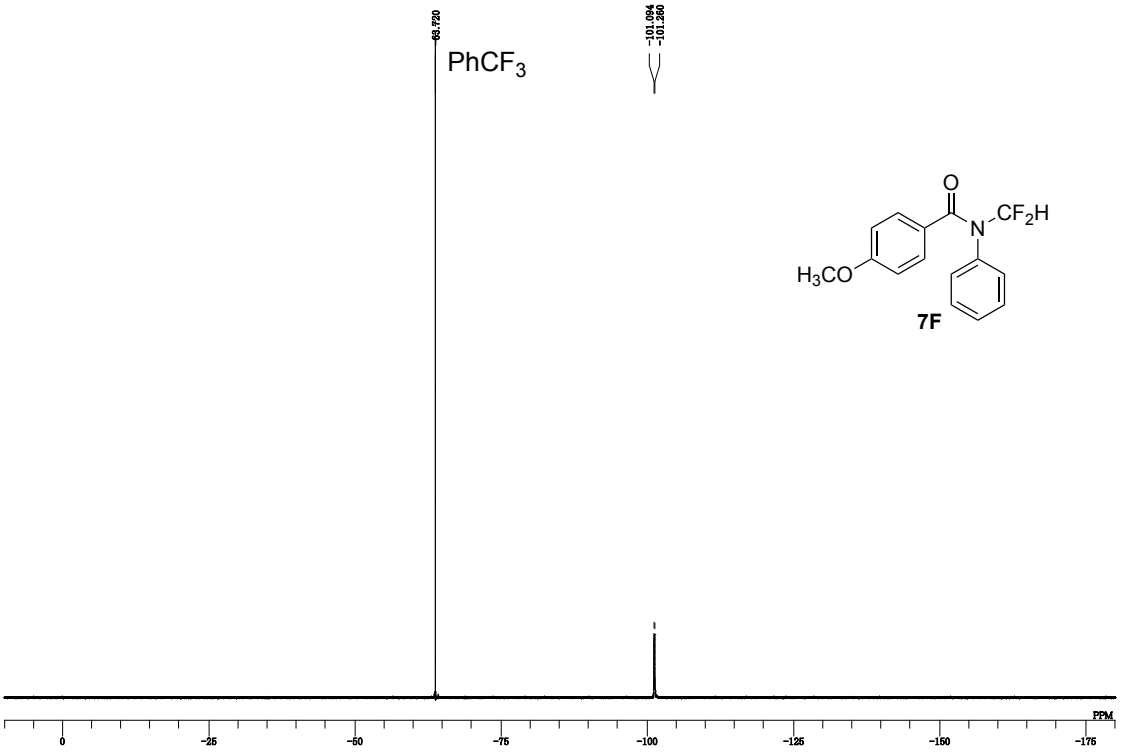
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **7F**



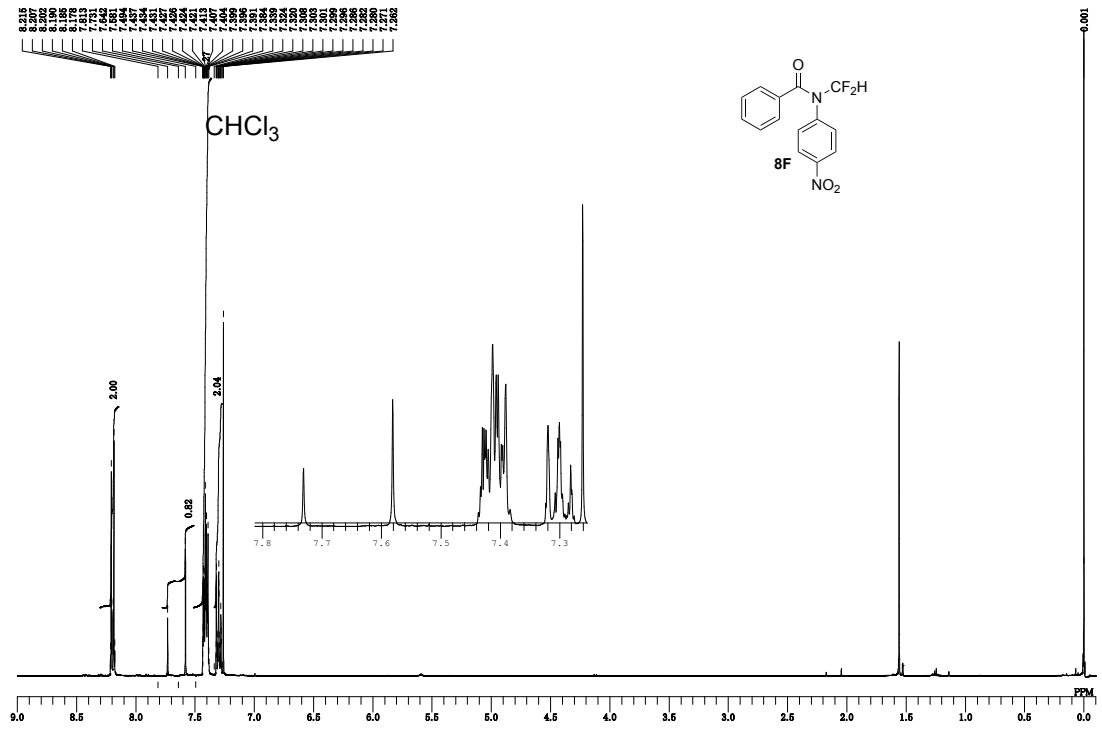
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of **7F**



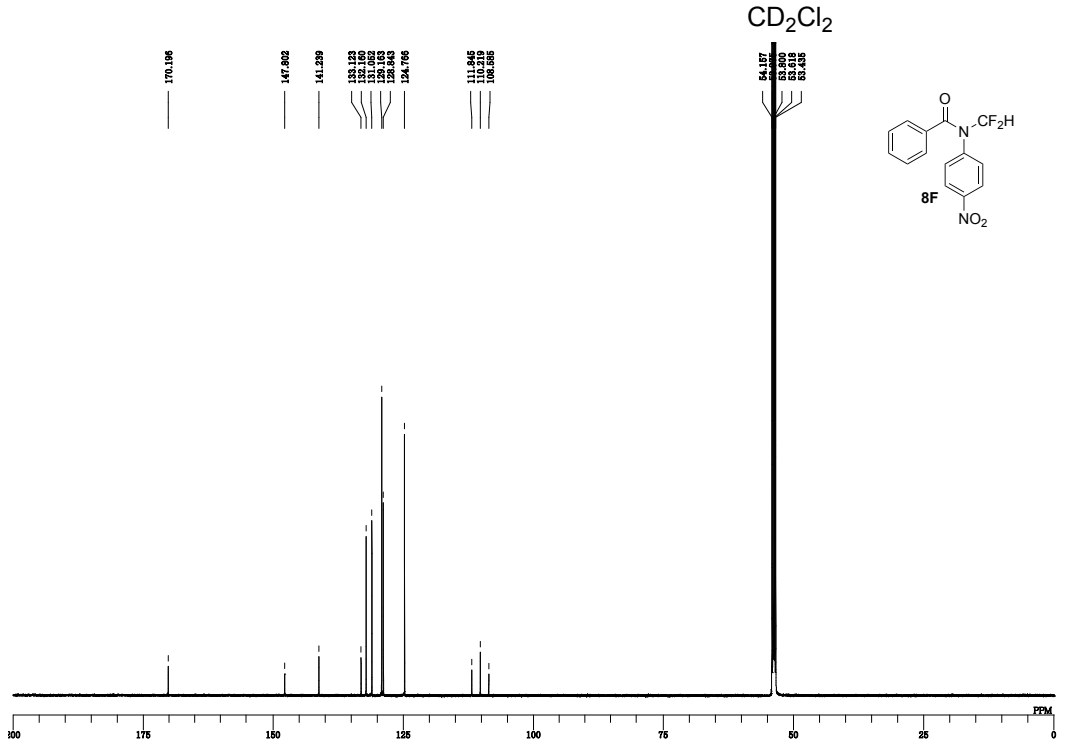
^{19}F NMR (376 MHz, $CDCl_3$) spectrum of **7F**



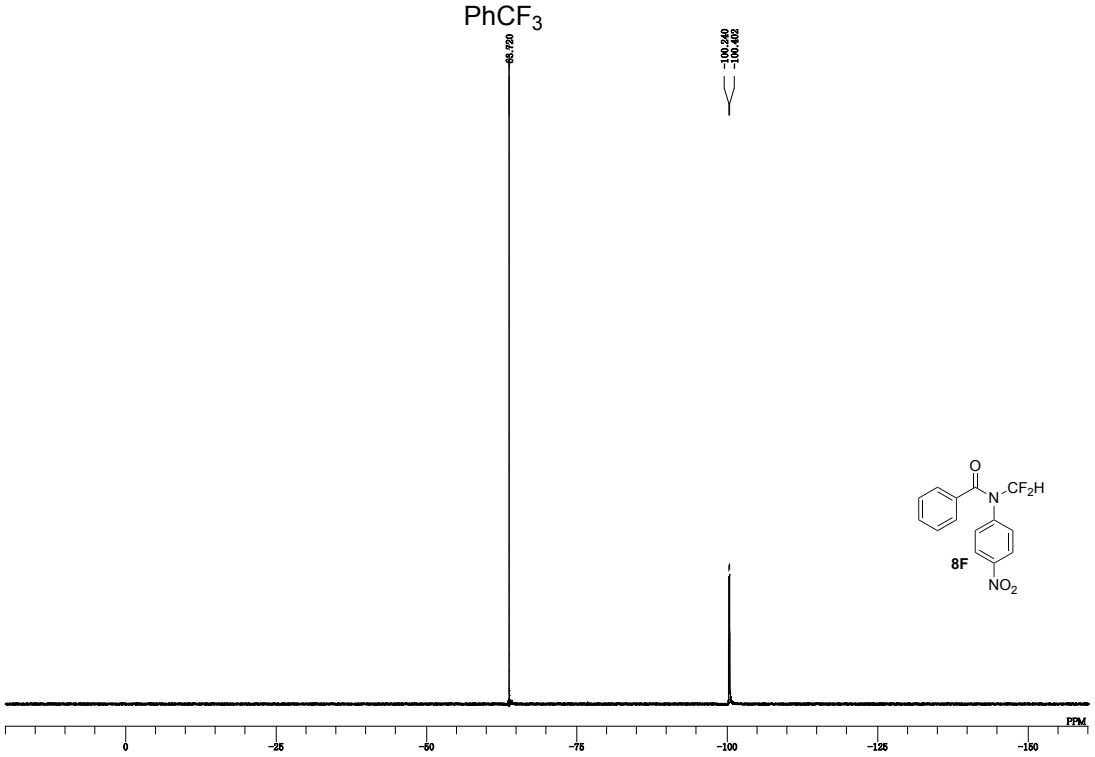
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8F**



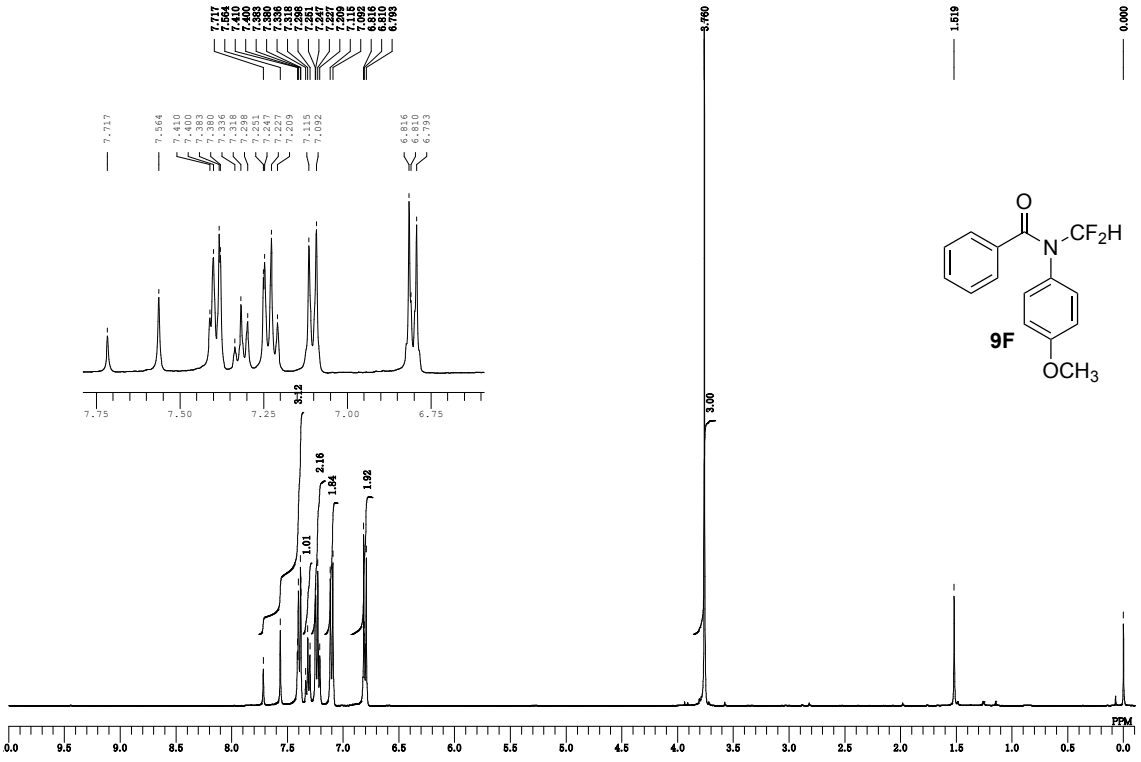
$^{13}C\{^{1}H\}$ NMR (100 MHz, CD_2Cl_2) spectrum of **8F**



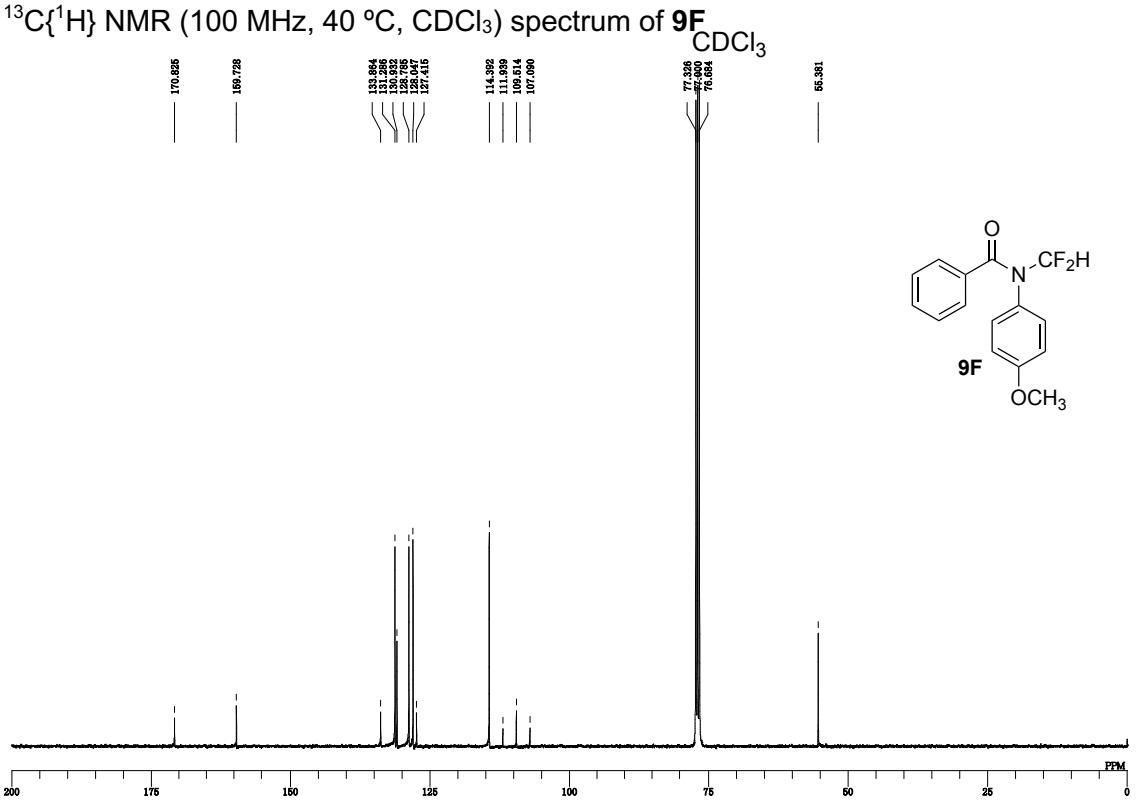
^{19}F NMR (376 MHz, CD_2Cl_2) spectrum of **8F**



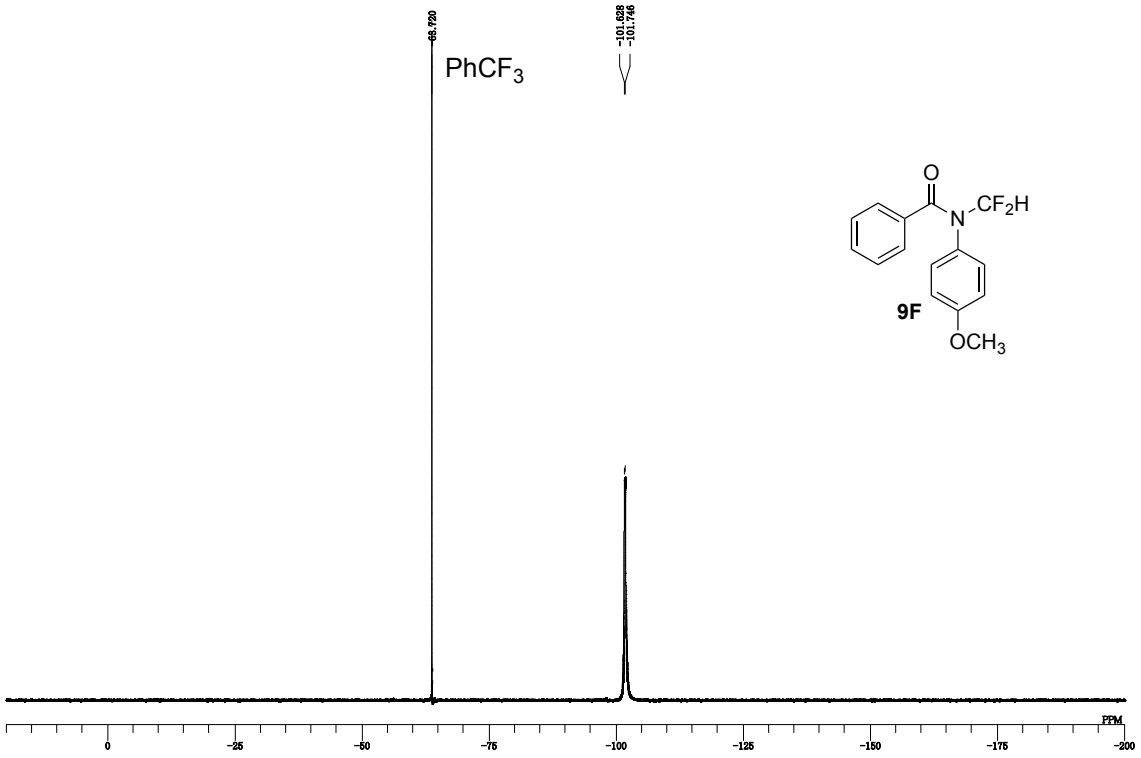
^{1}H NMR (400 MHz, 40 ºC, $CDCl_3$) spectrum of **9F**



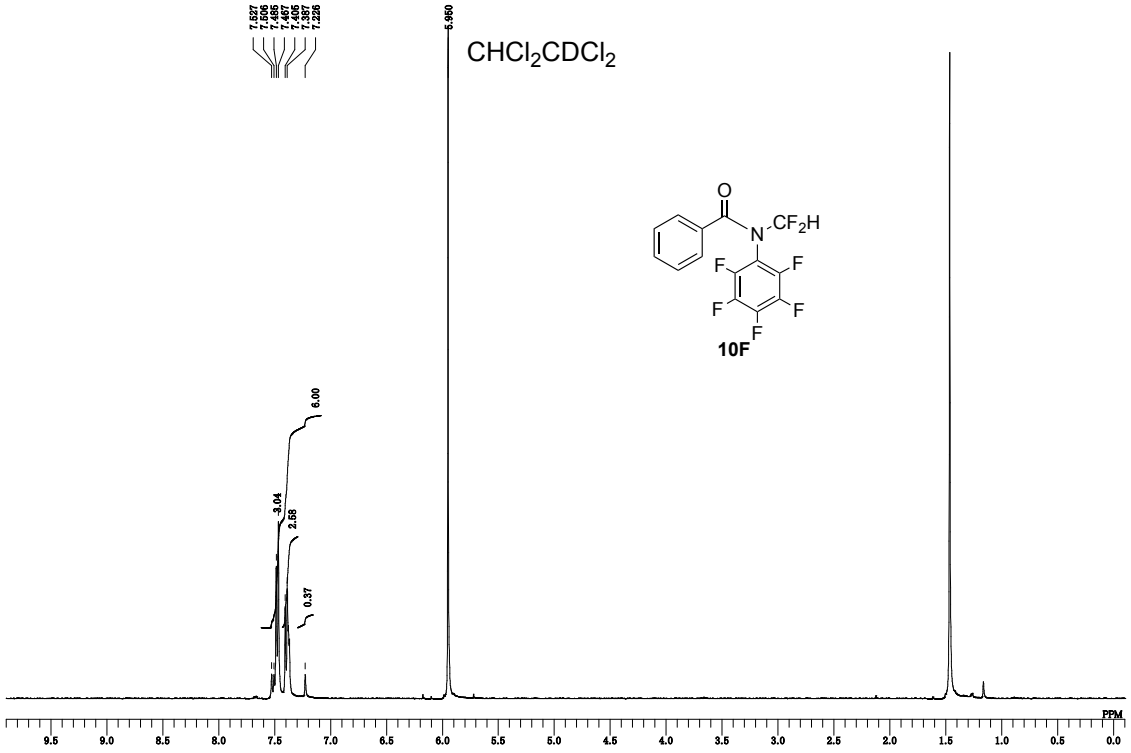
^{13}C{^{1}H} NMR (100 MHz, 40 ºC, $CDCl_3$) spectrum of **9F**



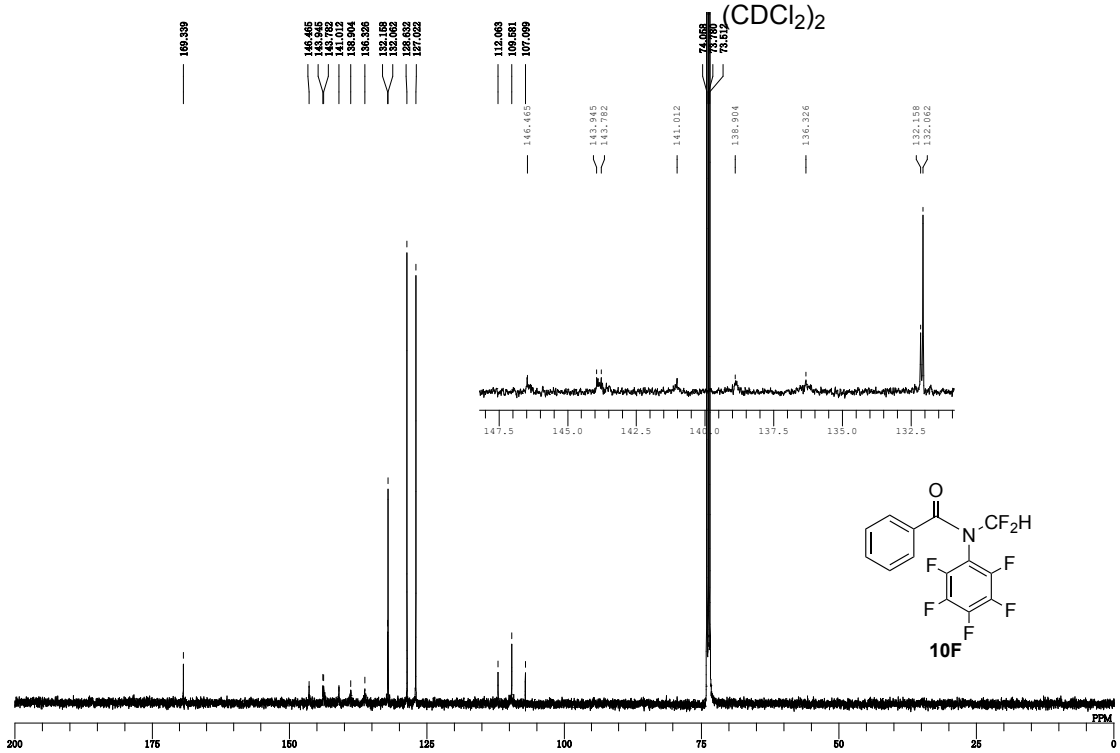
^{19}F NMR (376 MHz, 40 ºC, $CDCl_3$) spectrum of **9F**



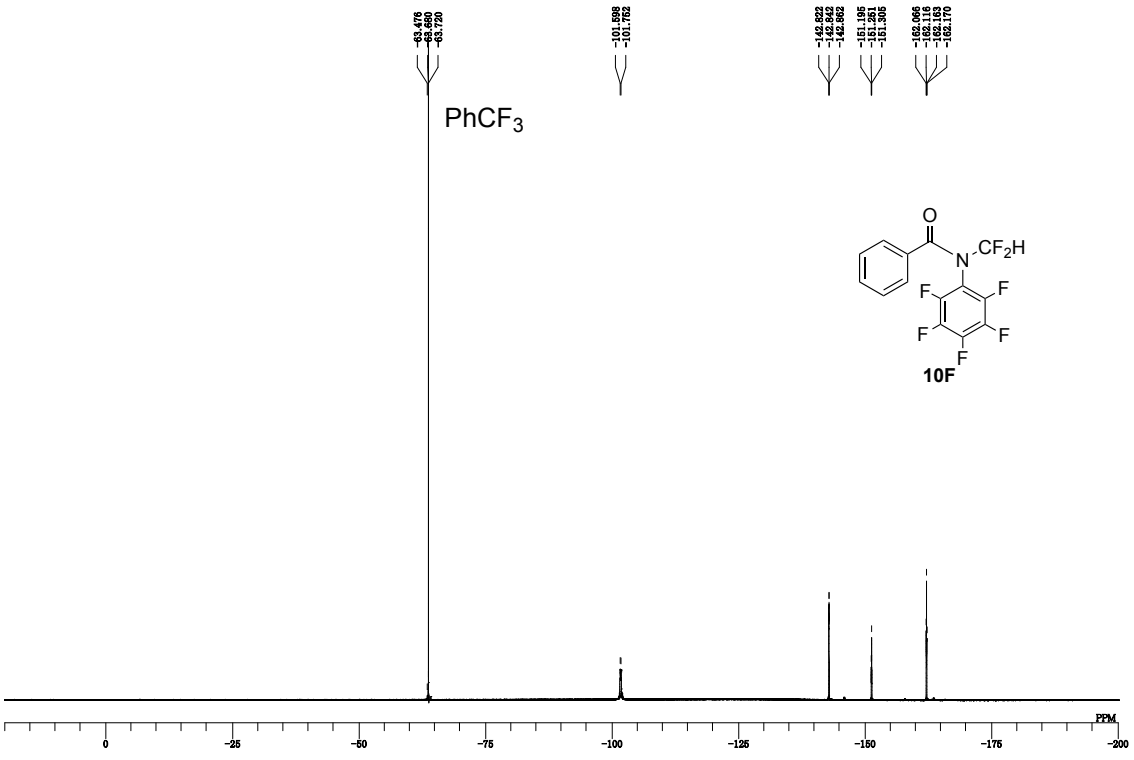
^{1}H NMR (400 MHz, 80 ºC, $(CD_2Cl_2)_2$) spectrum of **10F**



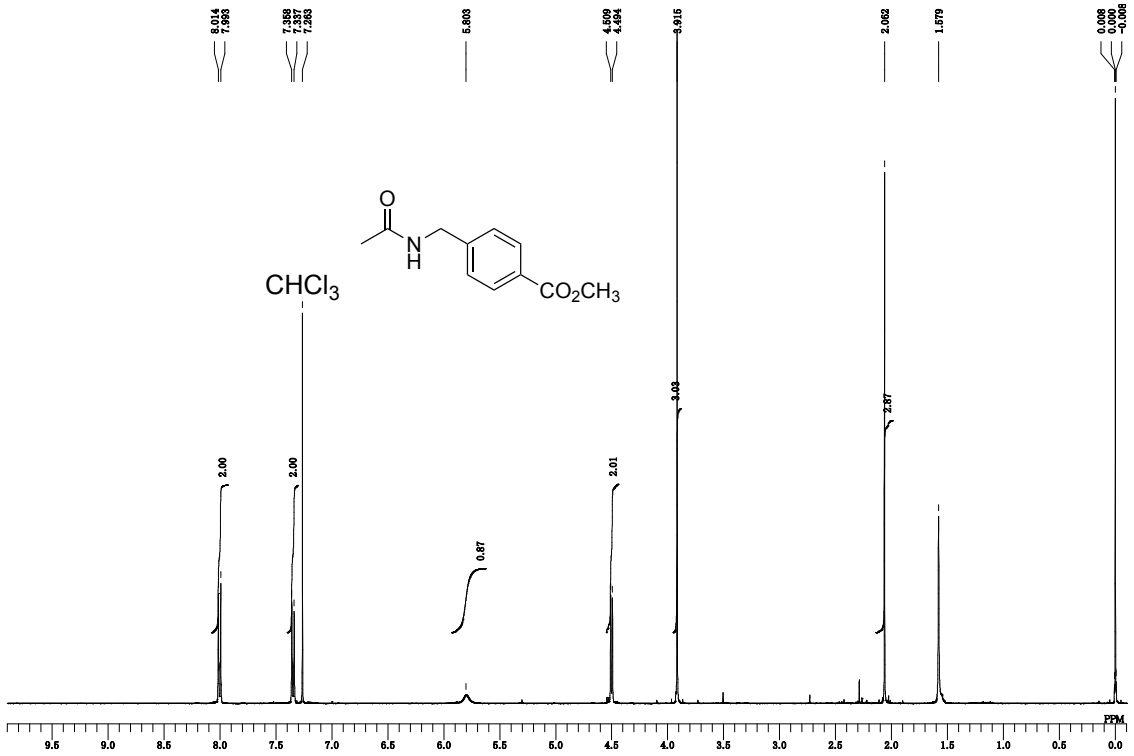
$^{13}C\{^{1}H\}$ NMR (100 MHz, 90 ºC, $(CD_2Cl_2)_2$) spectrum of **10F**



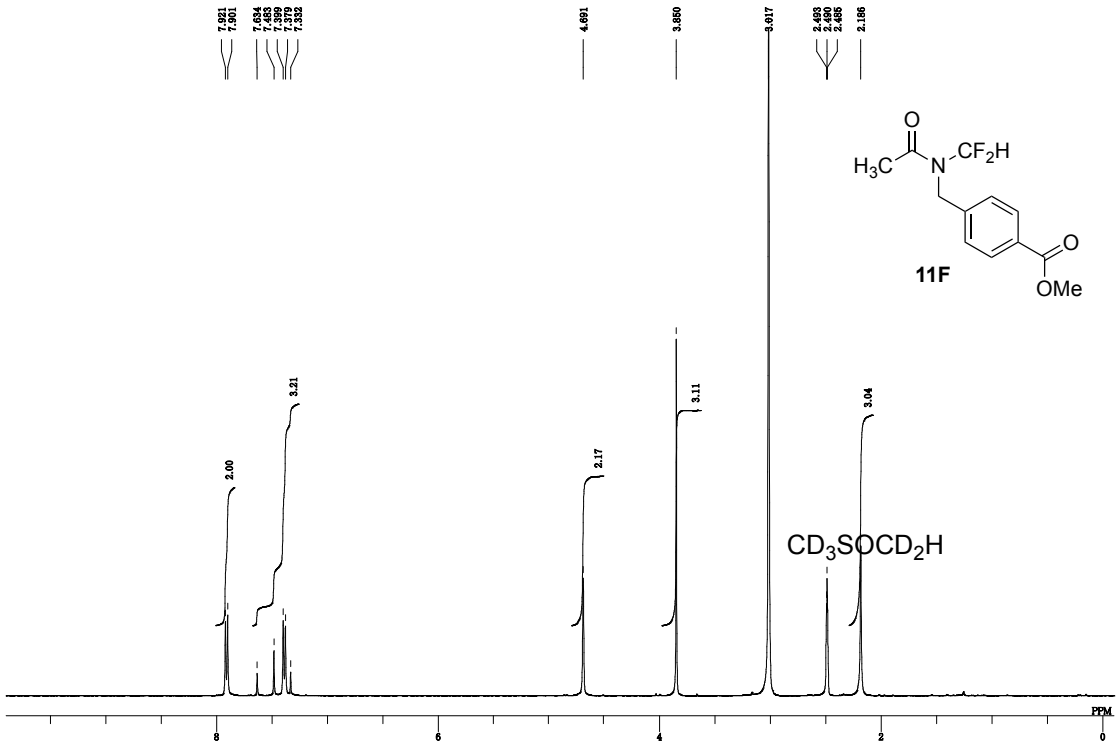
^{19}F NMR (376 MHz, 120 ºC, $(CD_2Cl_2)_2$) spectrum of **10F**



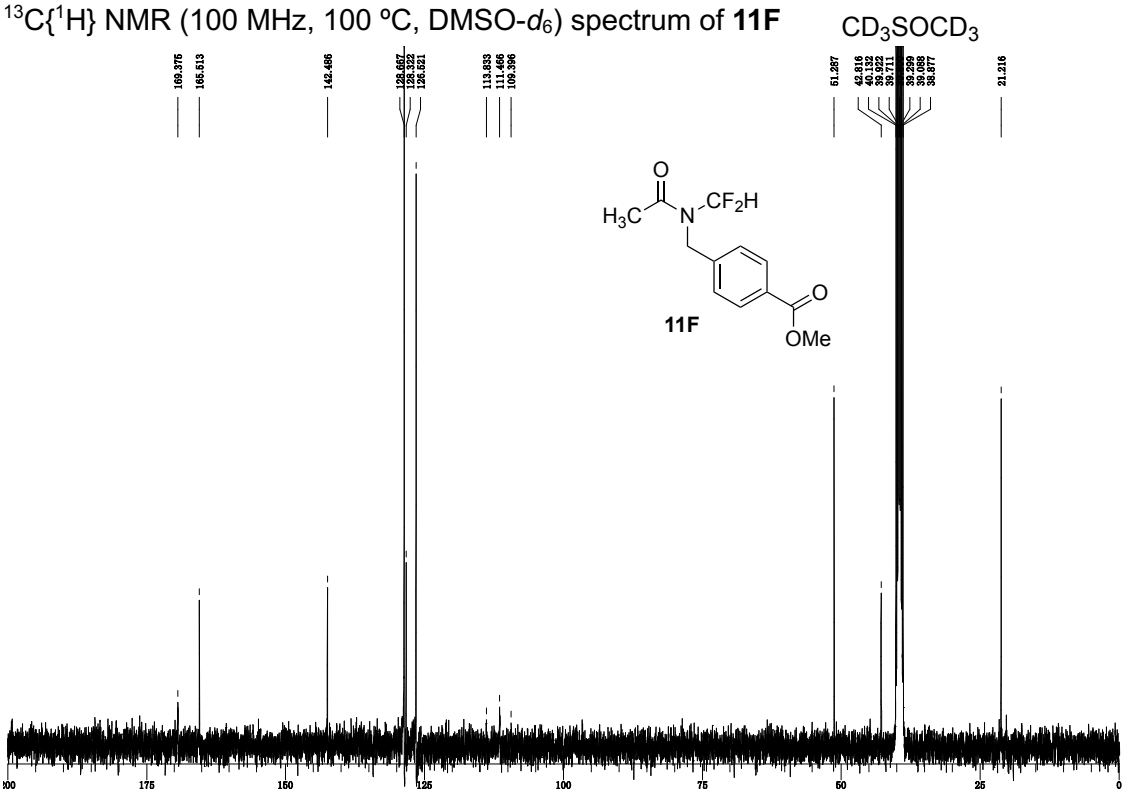
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of Methyl-*p*-(acetamidomethyl)benzoate



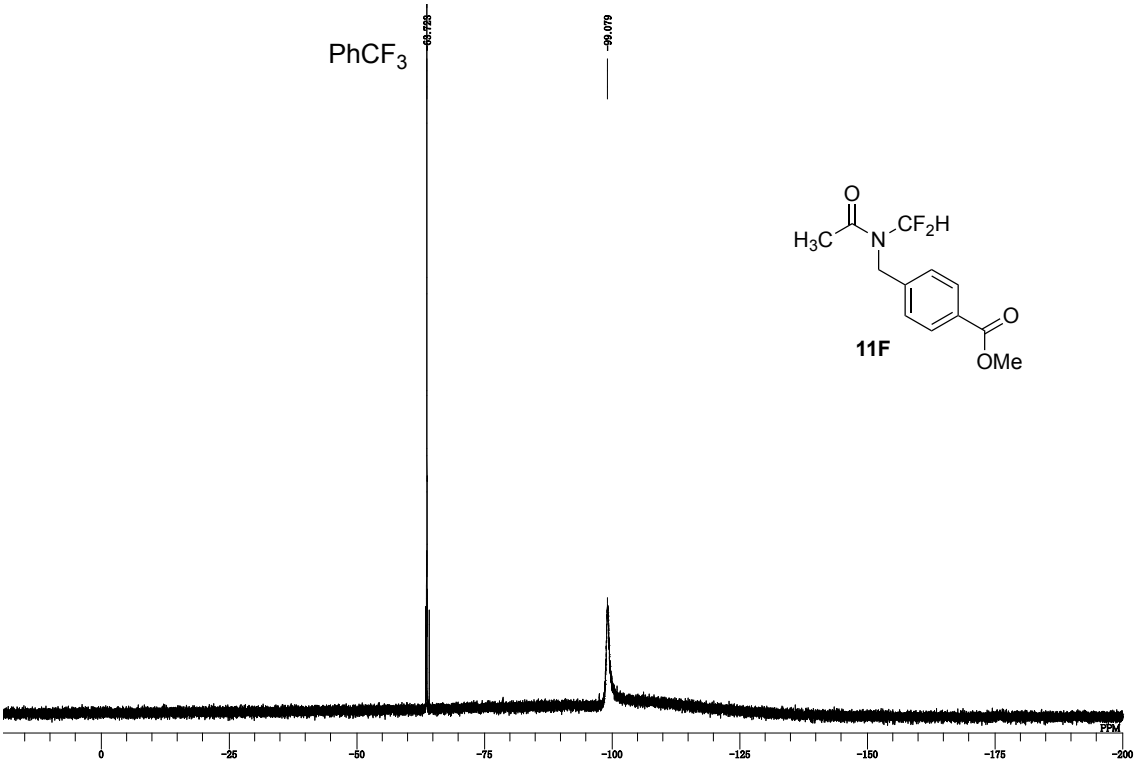
^{1}H NMR (400 MHz, 90 ºC, DMSO-d_6) spectrum of **11F**



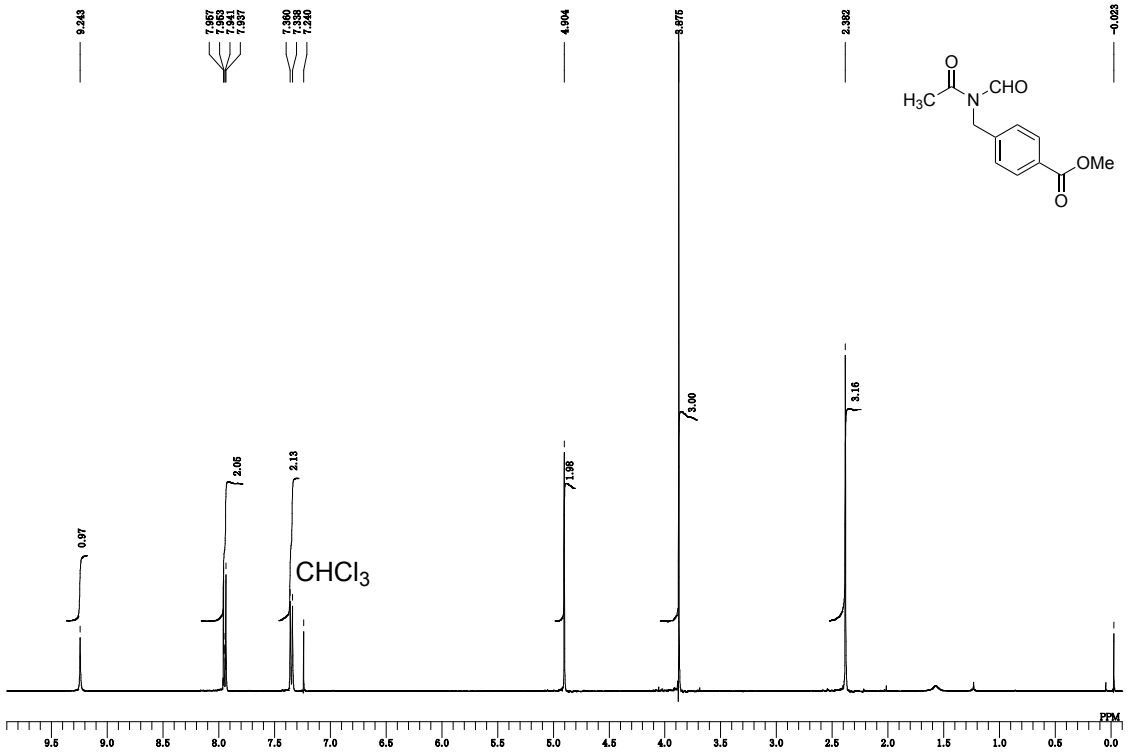
$^{13}C\{^{1}H\}$ NMR (100 MHz, 100 ºC, DMSO-d_6) spectrum of **11F**



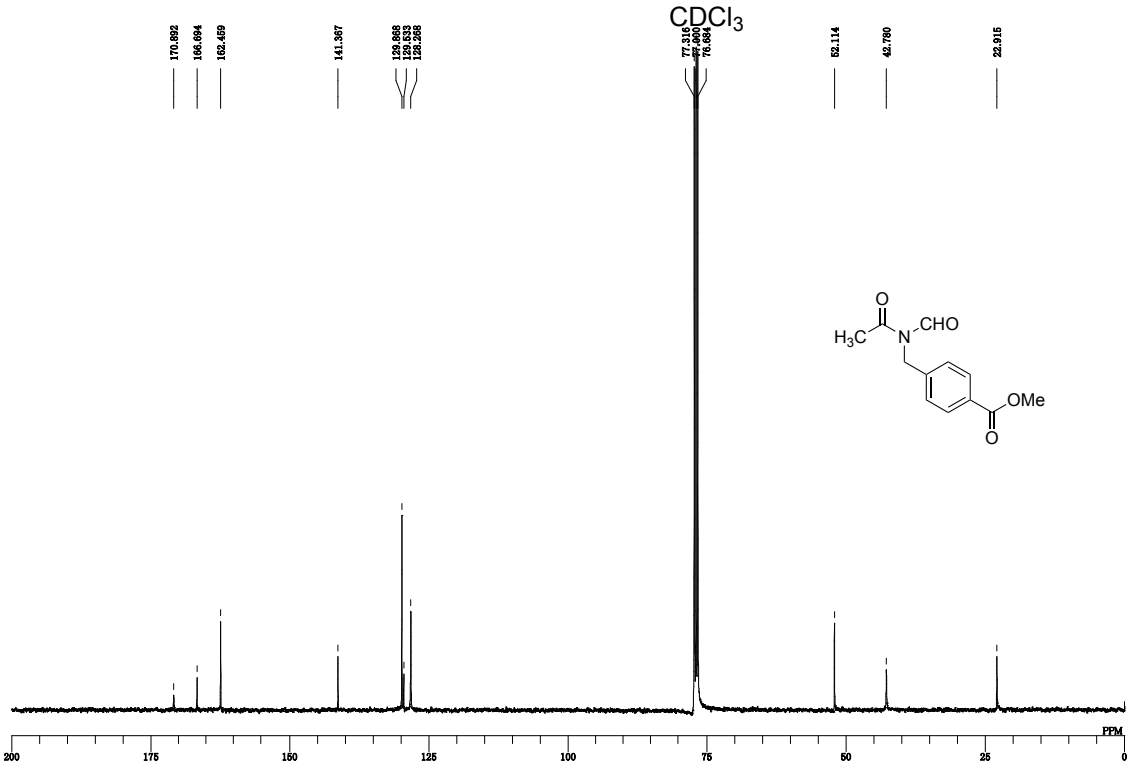
^{19}F NMR (376 MHz, 130 ºC, DMSO-d_6) spectrum of **11F**



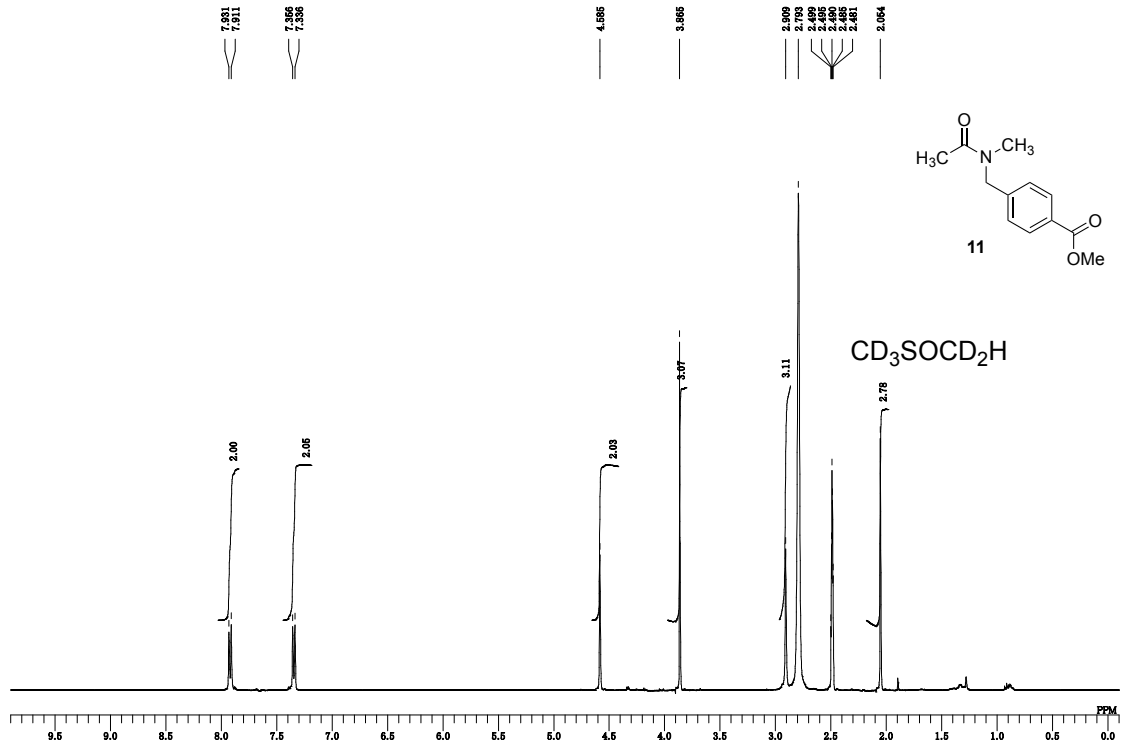
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of Methyl-*N*-formyl-*p*-(acetamidomethyl)benzoate



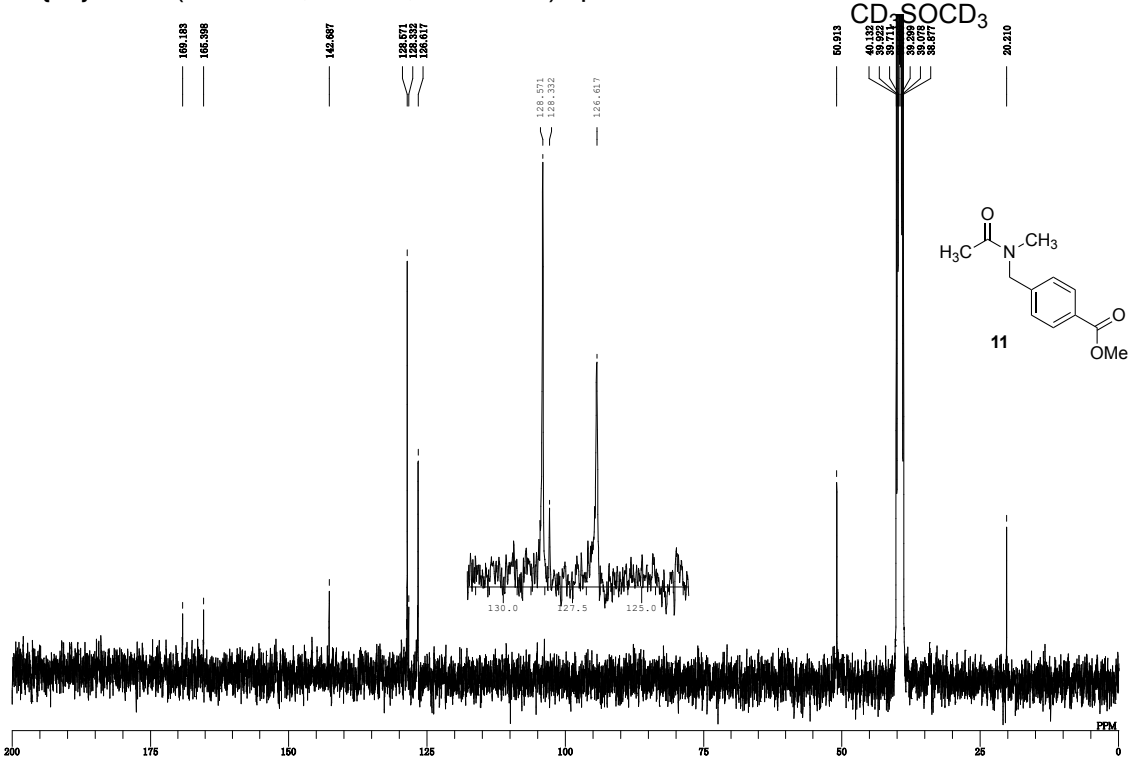
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of Methyl-*N*-formyl-*p*-(acetamidomethyl)benzoate



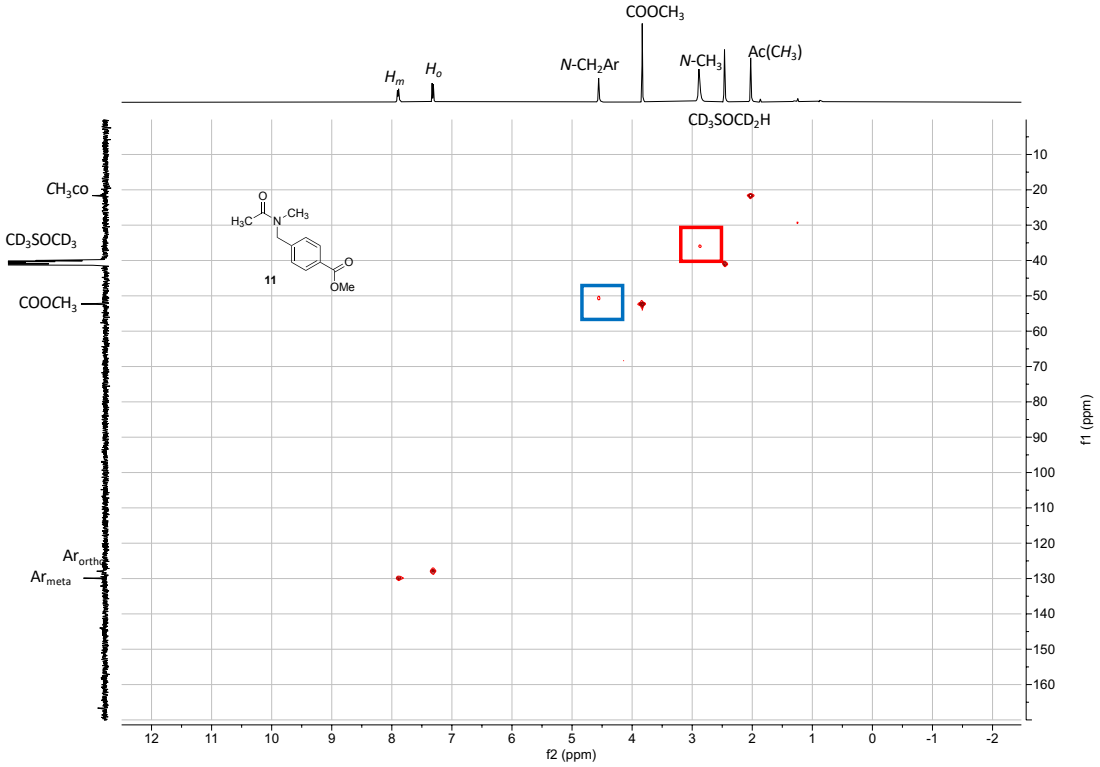
^{1}H NMR (400 MHz, 140 ºC, DMSO-d_6) spectrum of **11**



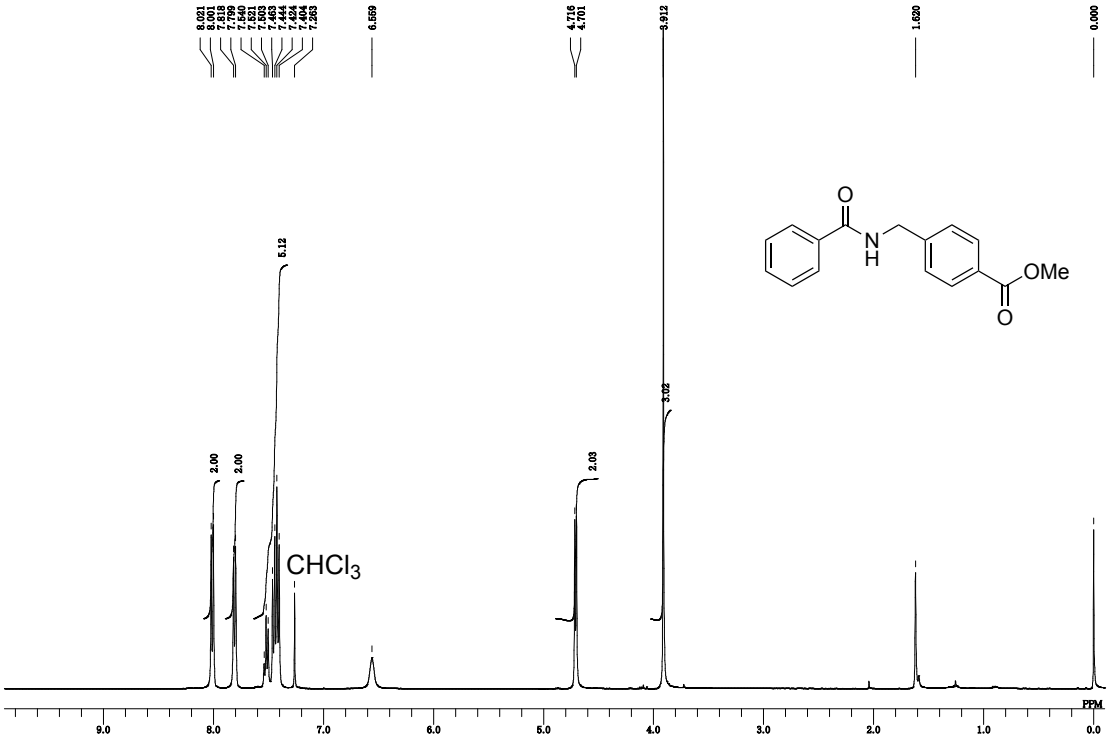
^{13}C{^{1}H} NMR (100 MHz, 140 ºC, DMSO-d_6) spectrum of **11**



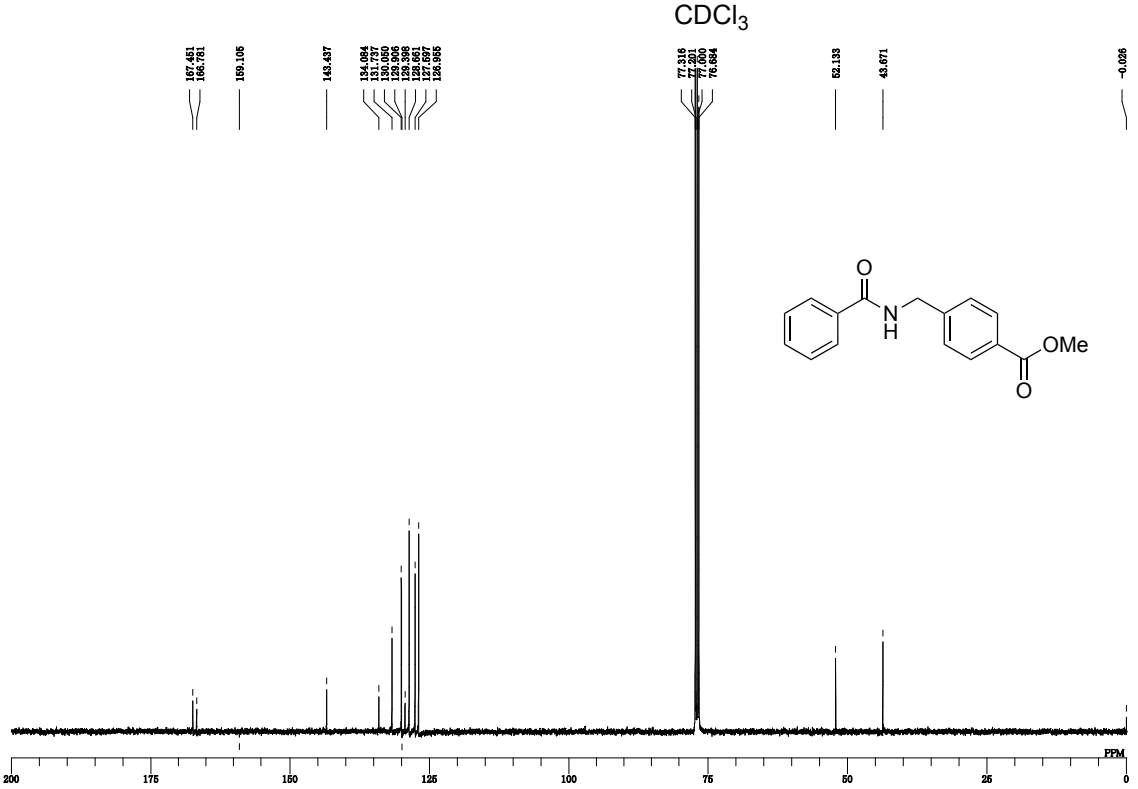
HSQC (400 MHz, 110 ºC, DMSO-d_6) spectrum of **11**



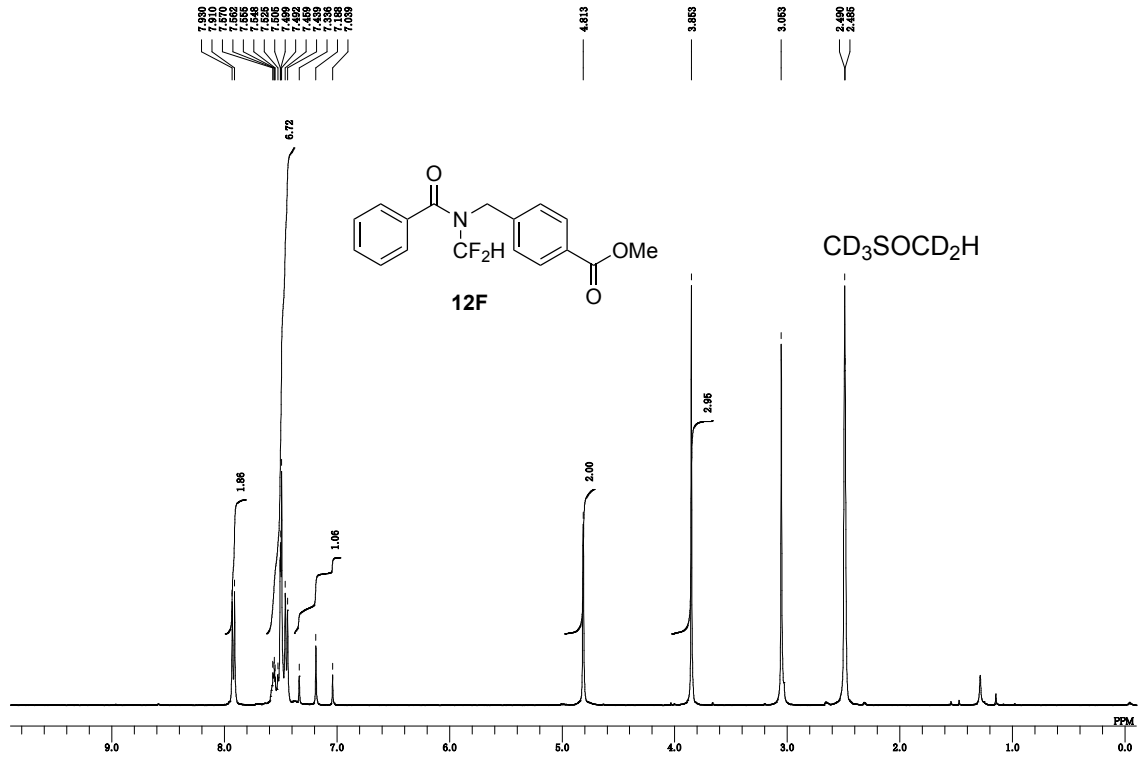
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of Methyl-*p*-(benzamidomethyl)benzoate



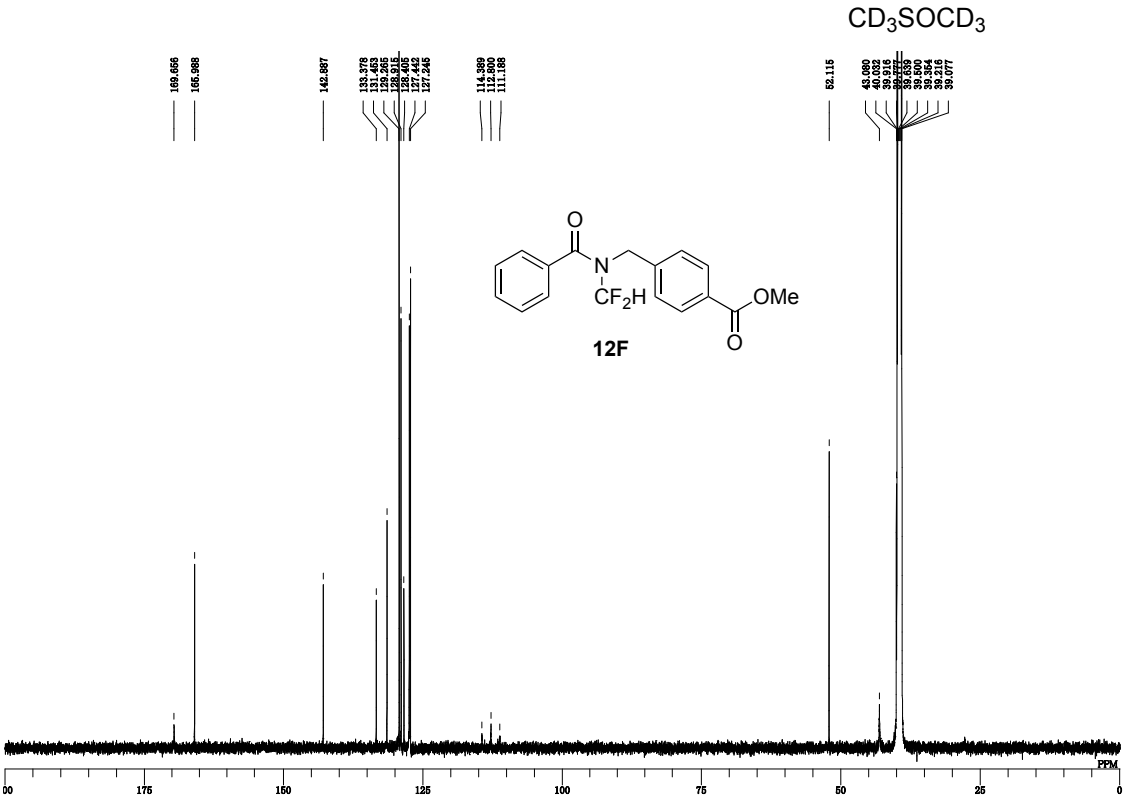
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of Methyl-*p*-(benzamidomethyl)benzoate



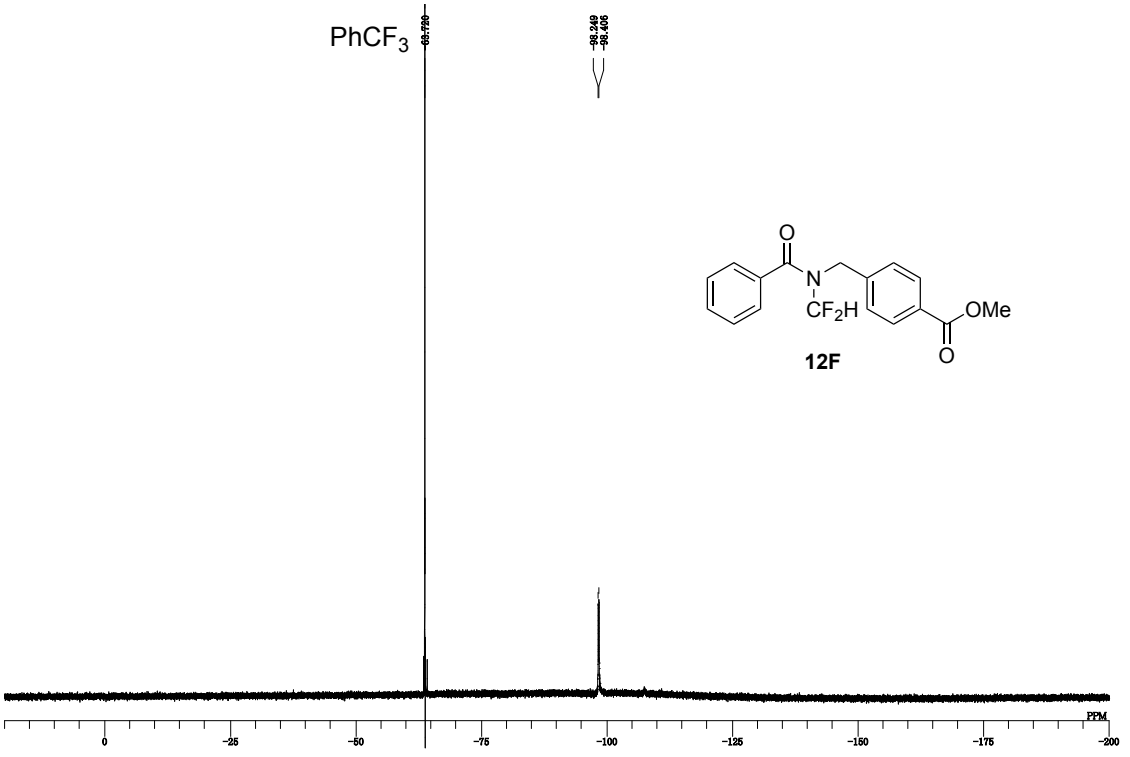
^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) spectrum of **12F**



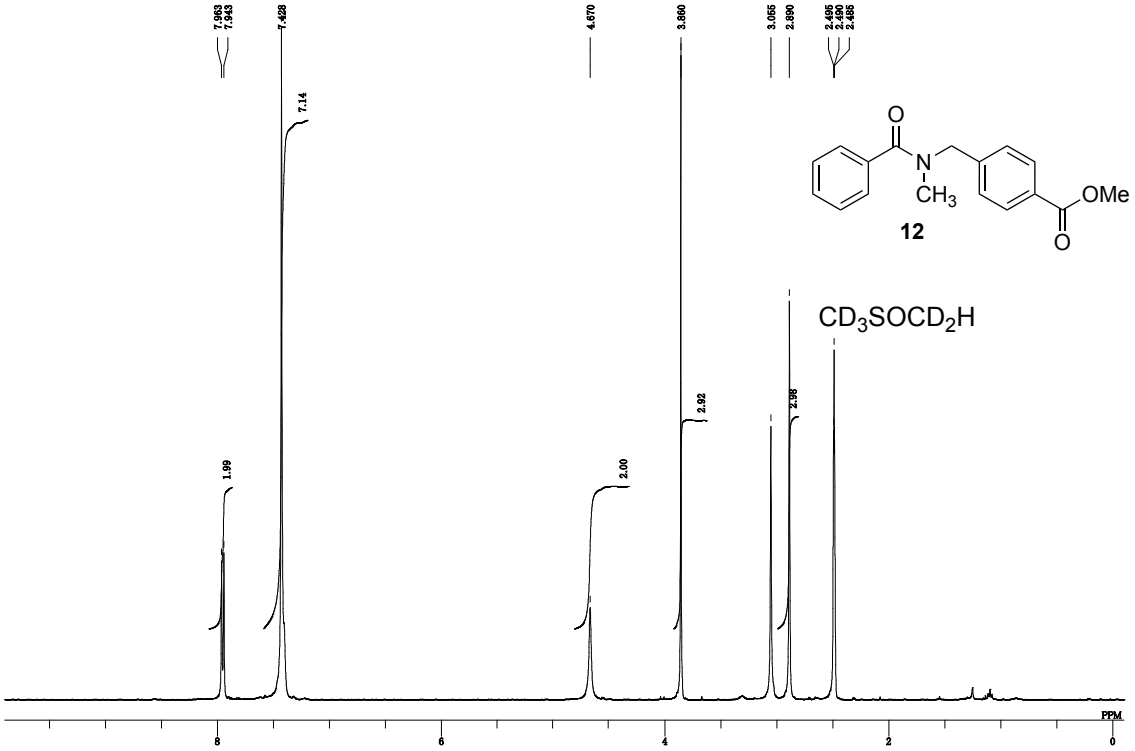
$^{13}C\{^{1}H\}$ NMR (150 MHz, DMSO-d_6) spectrum of **12F**



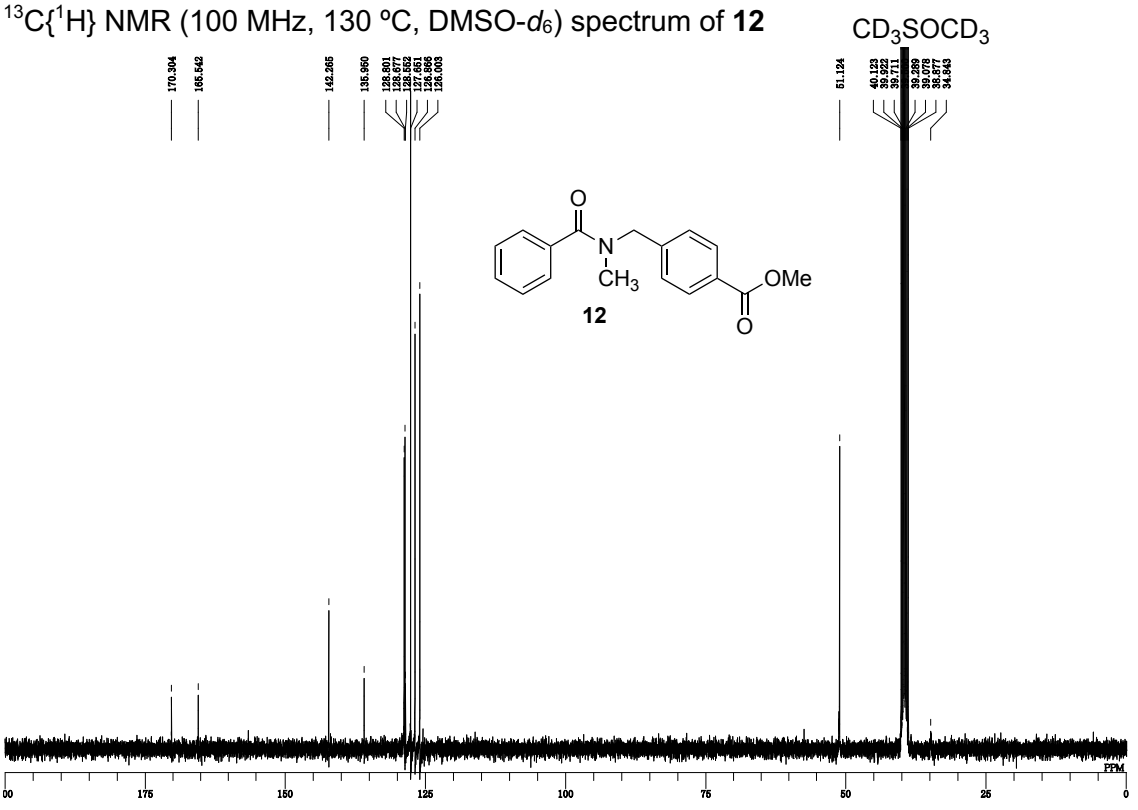
^{19}F NMR (376 MHz, 80 ºC, DMSO-d_6) spectrum of **12F**



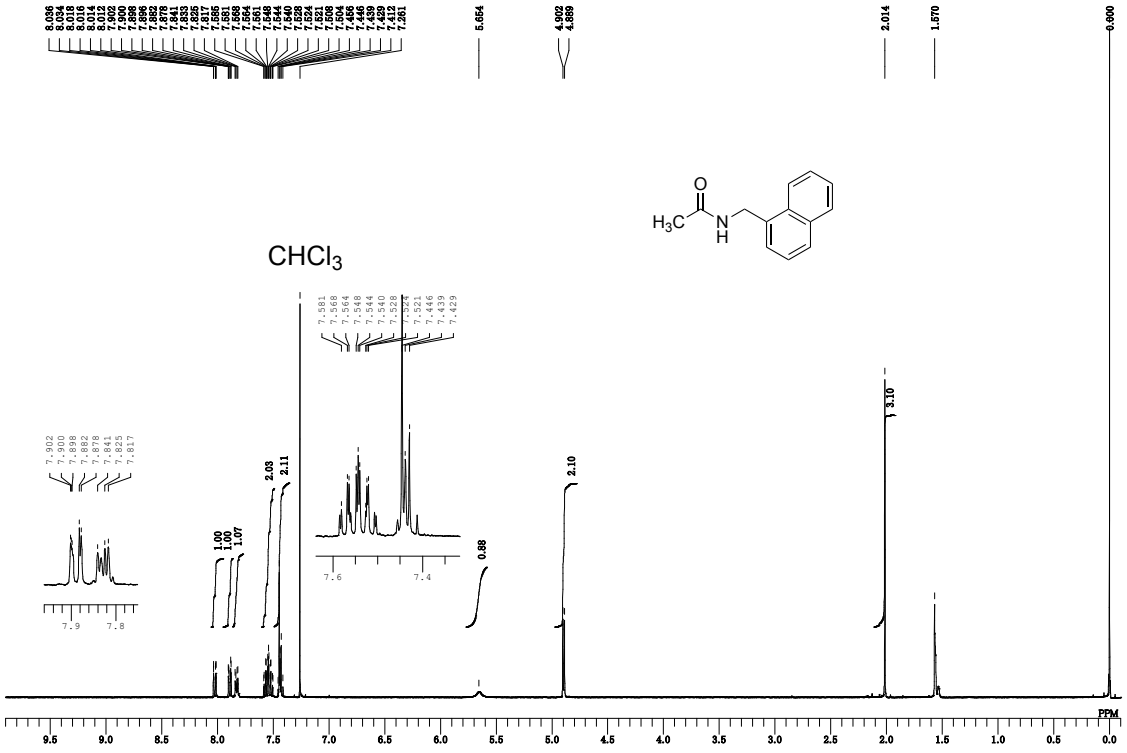
^{1}H NMR (400 MHz, 120 ºC, DMSO-d_6) spectrum of **12**



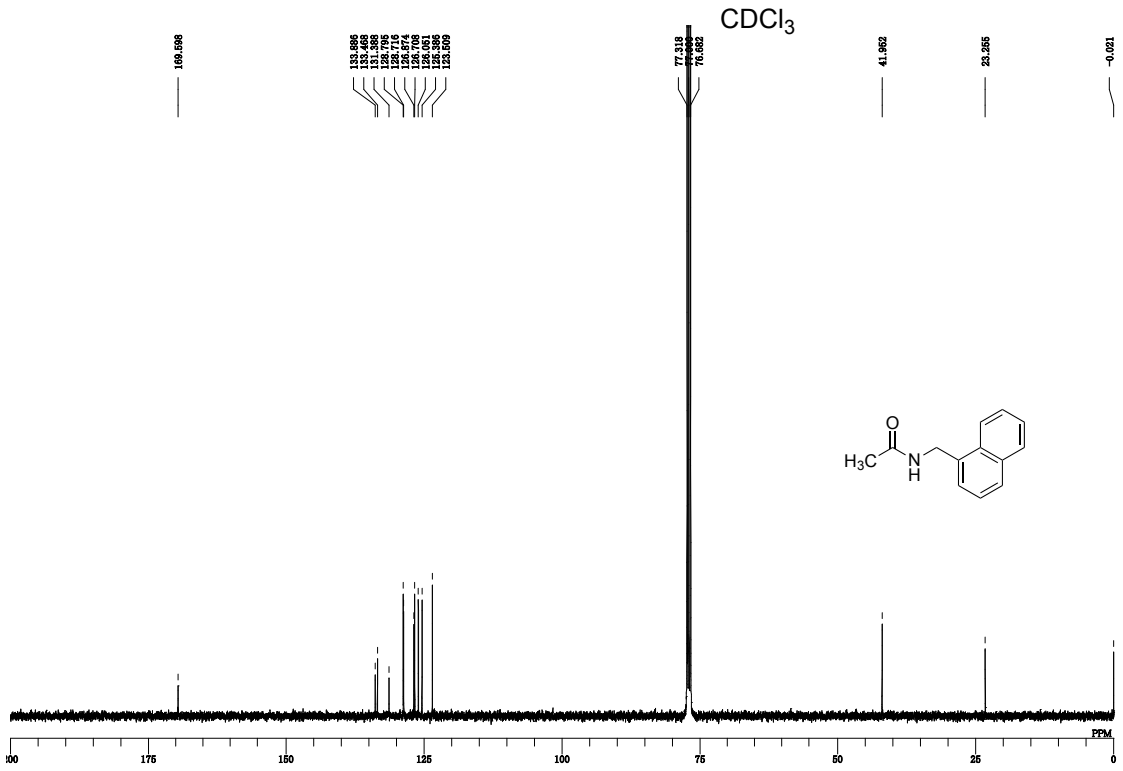
^{13}C{^{1}H} NMR (100 MHz, 130 ºC, DMSO-d_6) spectrum of **12**



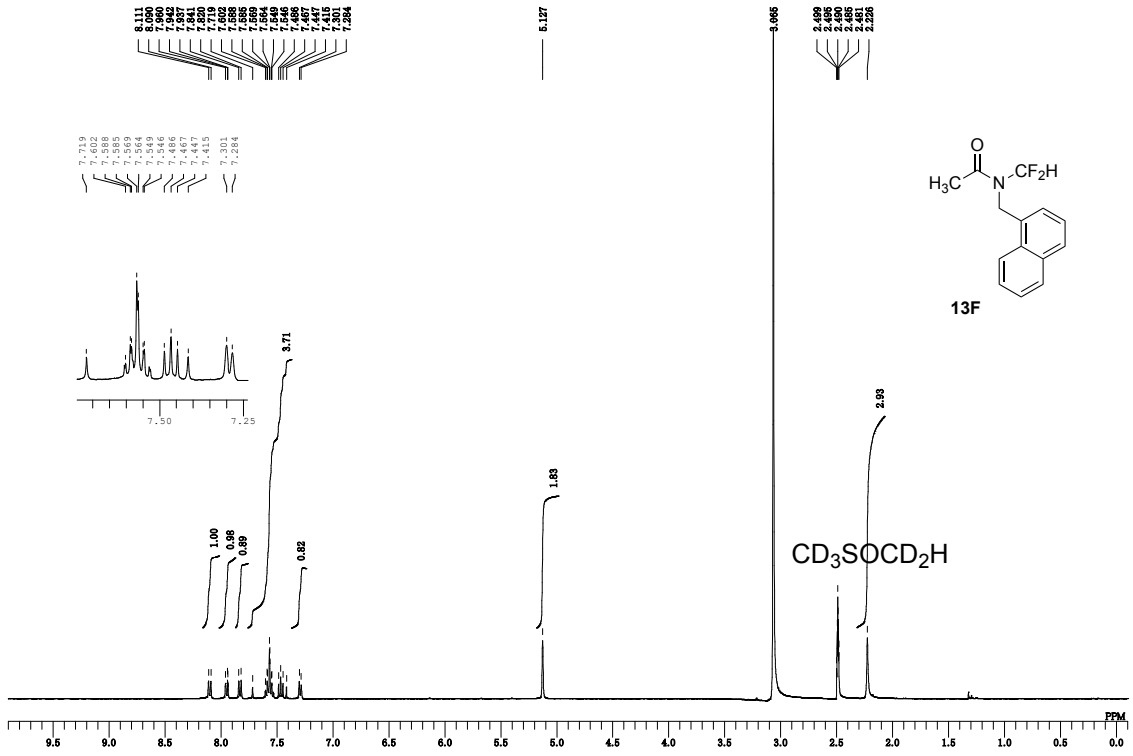
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *N*-(1-Naphthalenylmethyl)acetamide



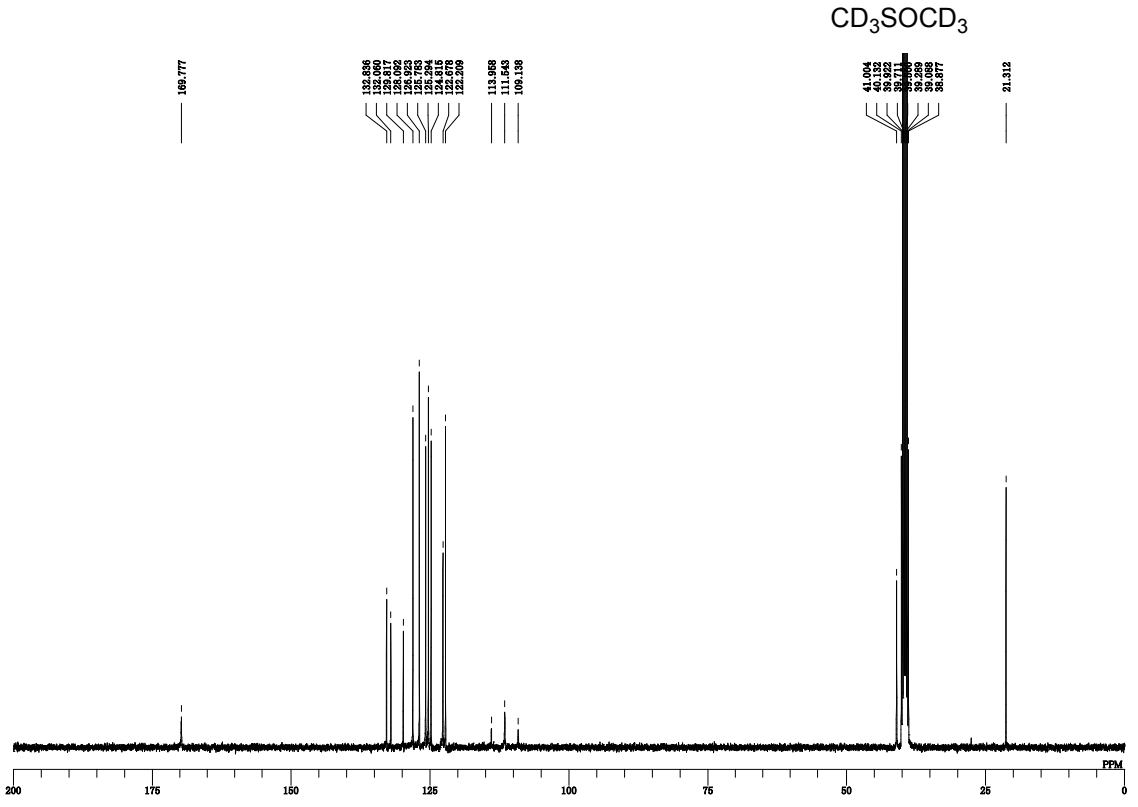
^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) spectrum of *N*-(1-Naphthalenylmethyl)acetamide



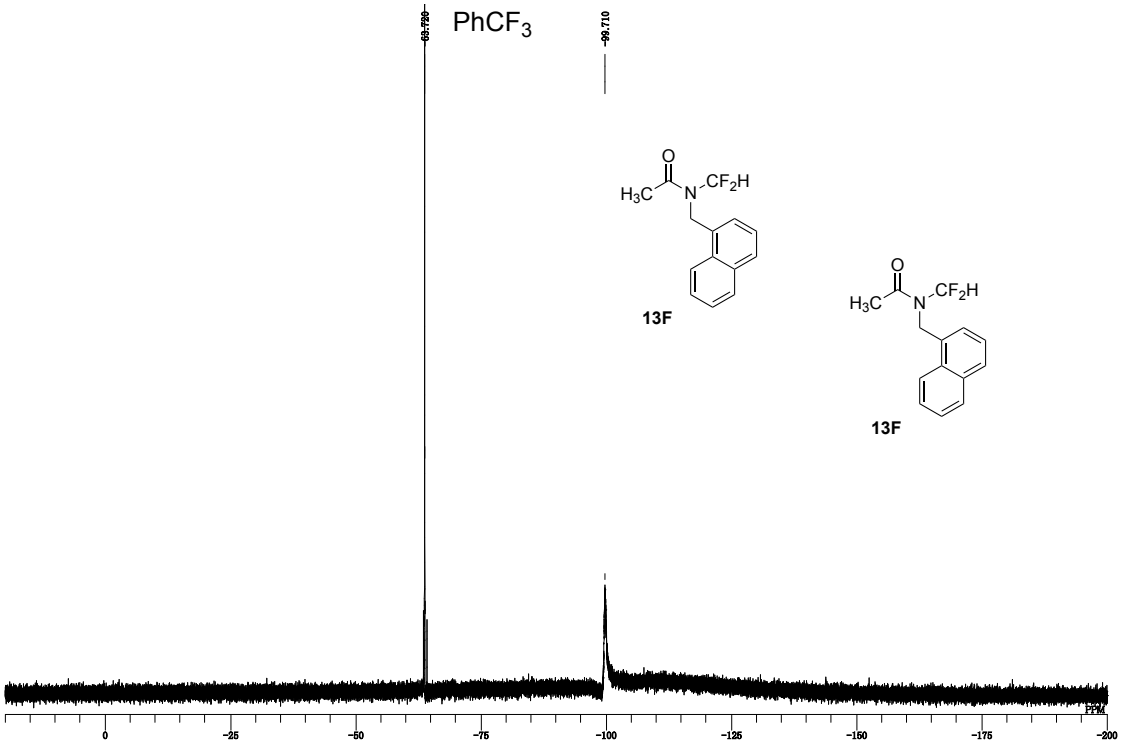
^{1}H NMR (400 MHz, 80 ºC, DMSO-d_6) spectrum of **13F**



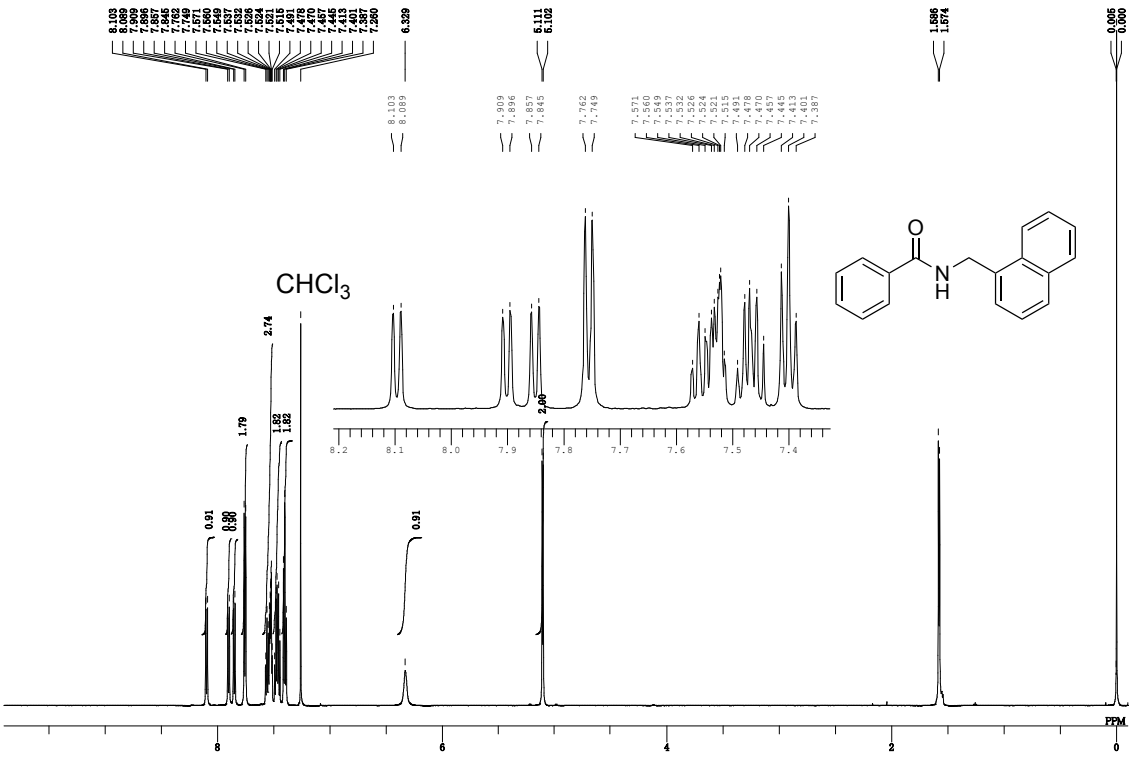
^{13}C{^{1}H} NMR (100 MHz, 95 ºC, DMSO-d_6) spectrum of **13F**.



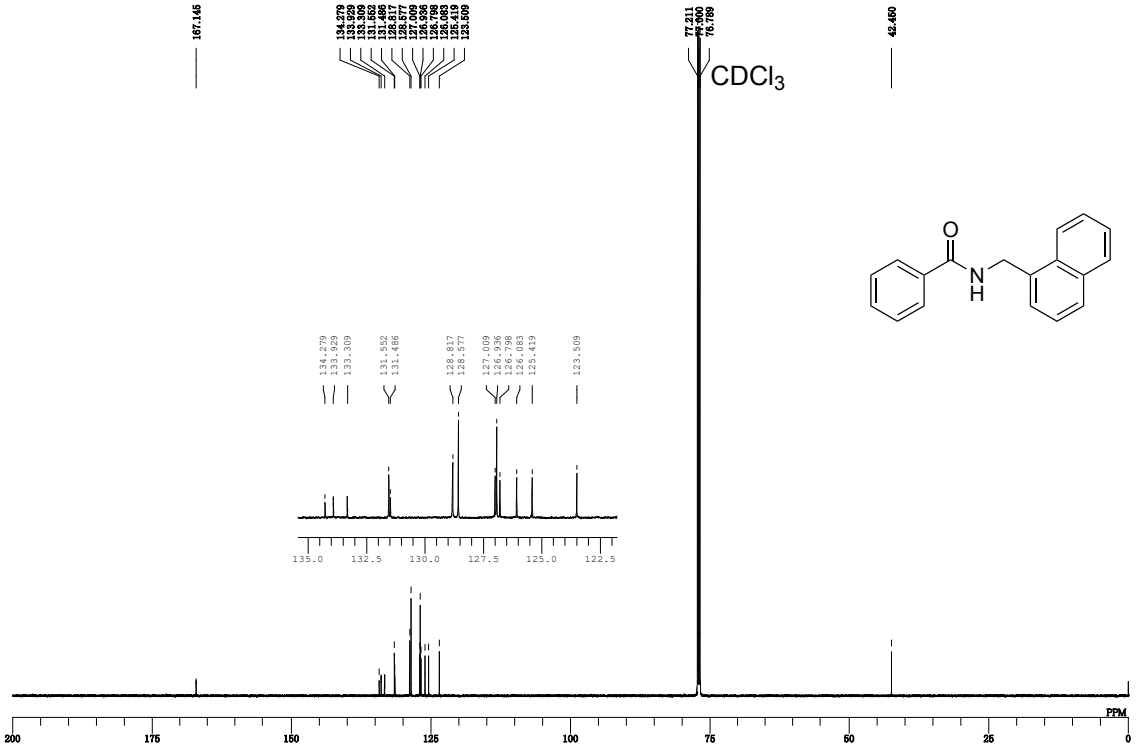
^{19}F NMR (376 MHz, 130 ºC, DMSO-d_6) spectrum of **13F**



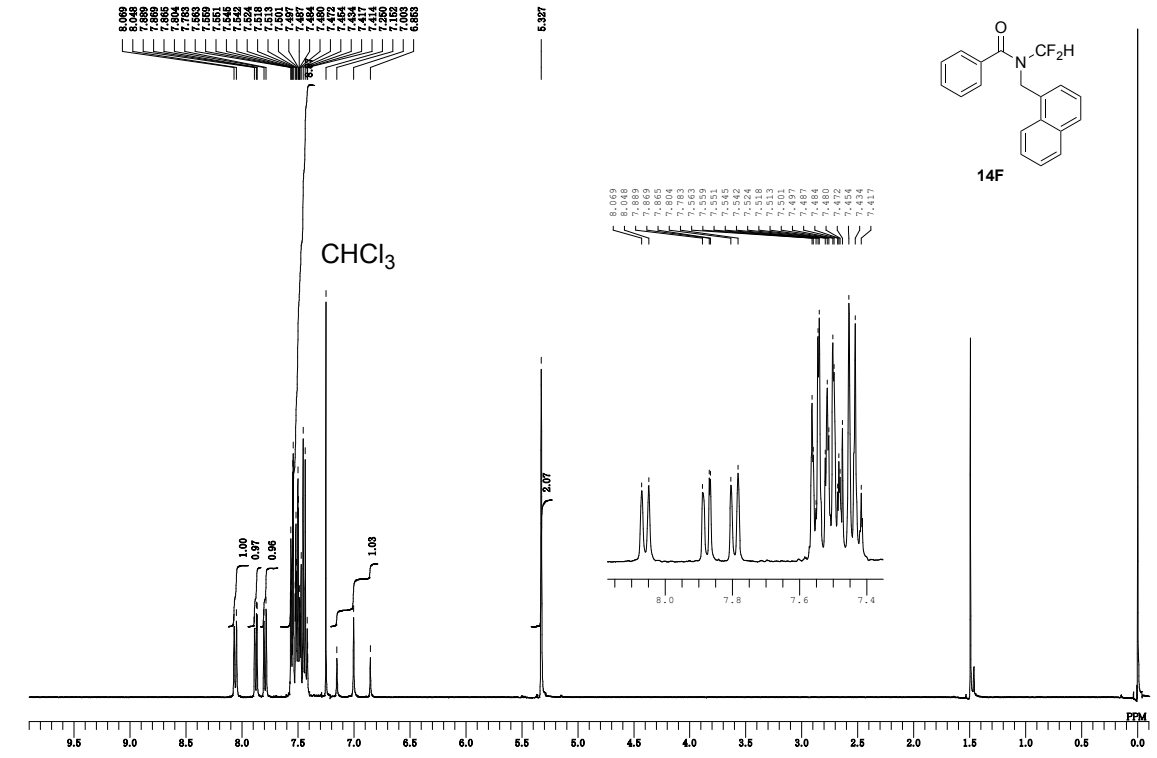
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of *N*-(1-Naphthalenylmethyl)benzamide



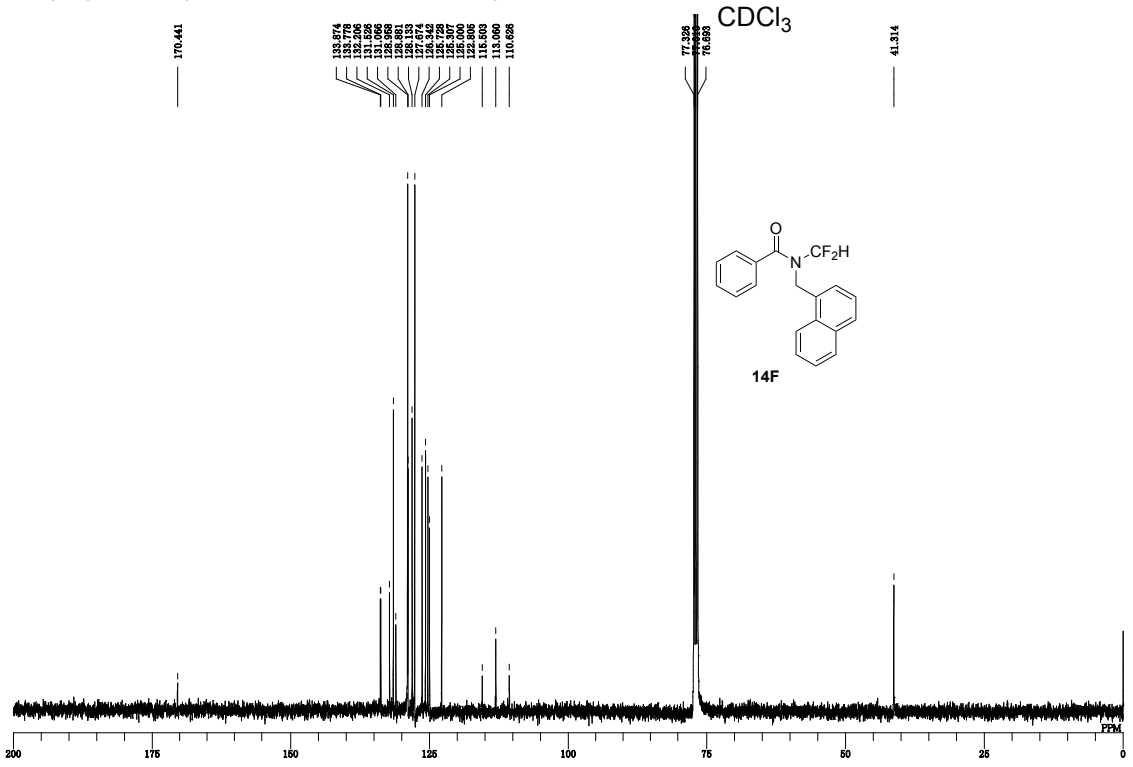
$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of *N*-(1-Naphthalenylmethyl)benzamide



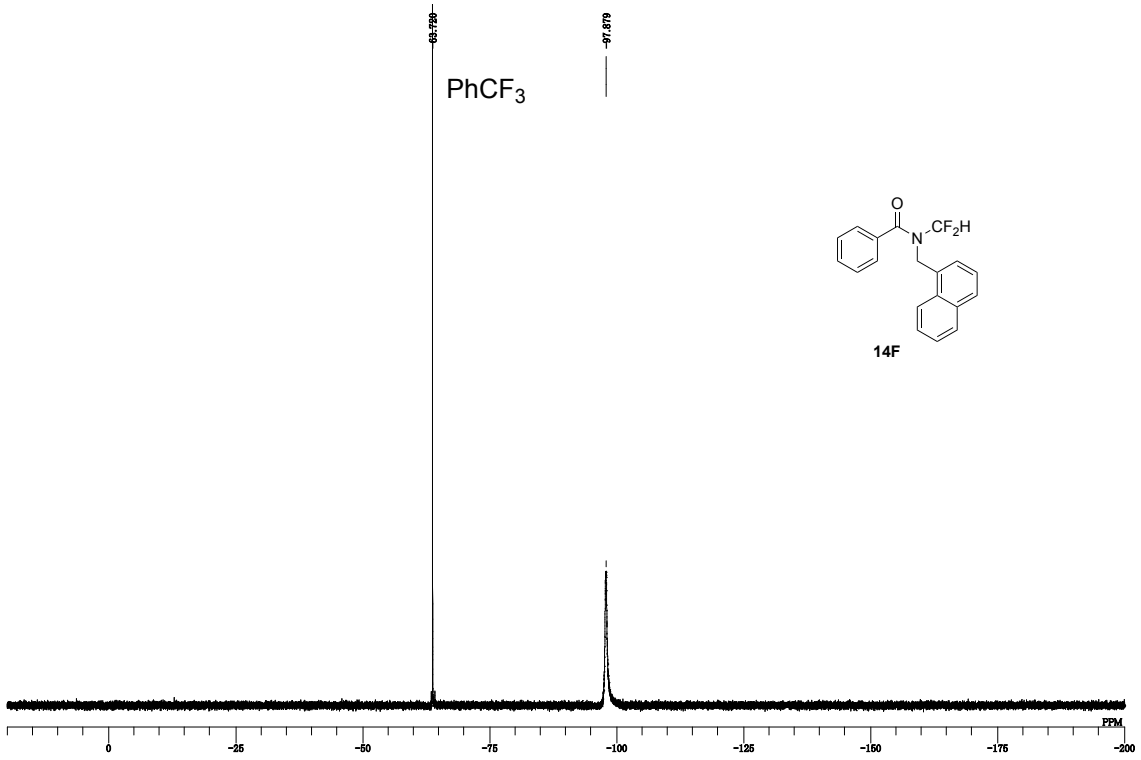
^{1}H NMR (400 MHz, 40 ºC, $CDCl_3$) spectrum of **14F**



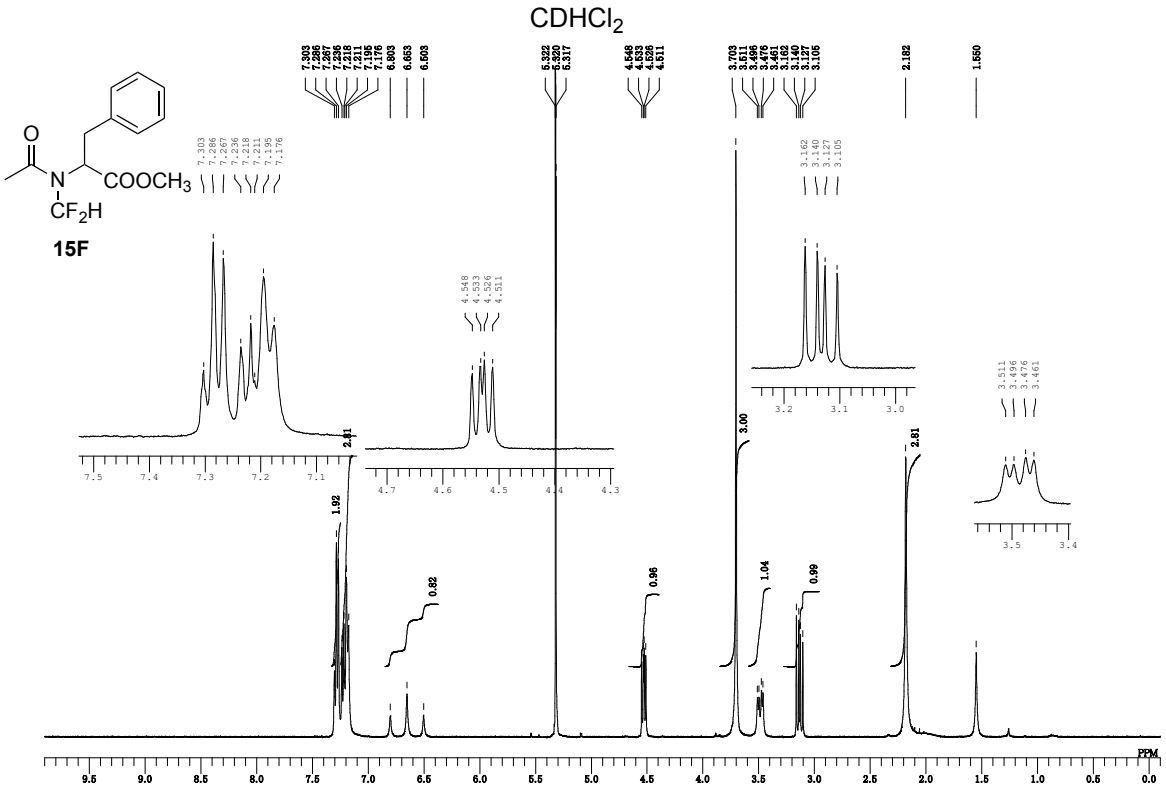
$^{13}C\{^{1}H\}$ NMR (100 MHz, 40 ºC, $CDCl_3$) spectrum of **14F**



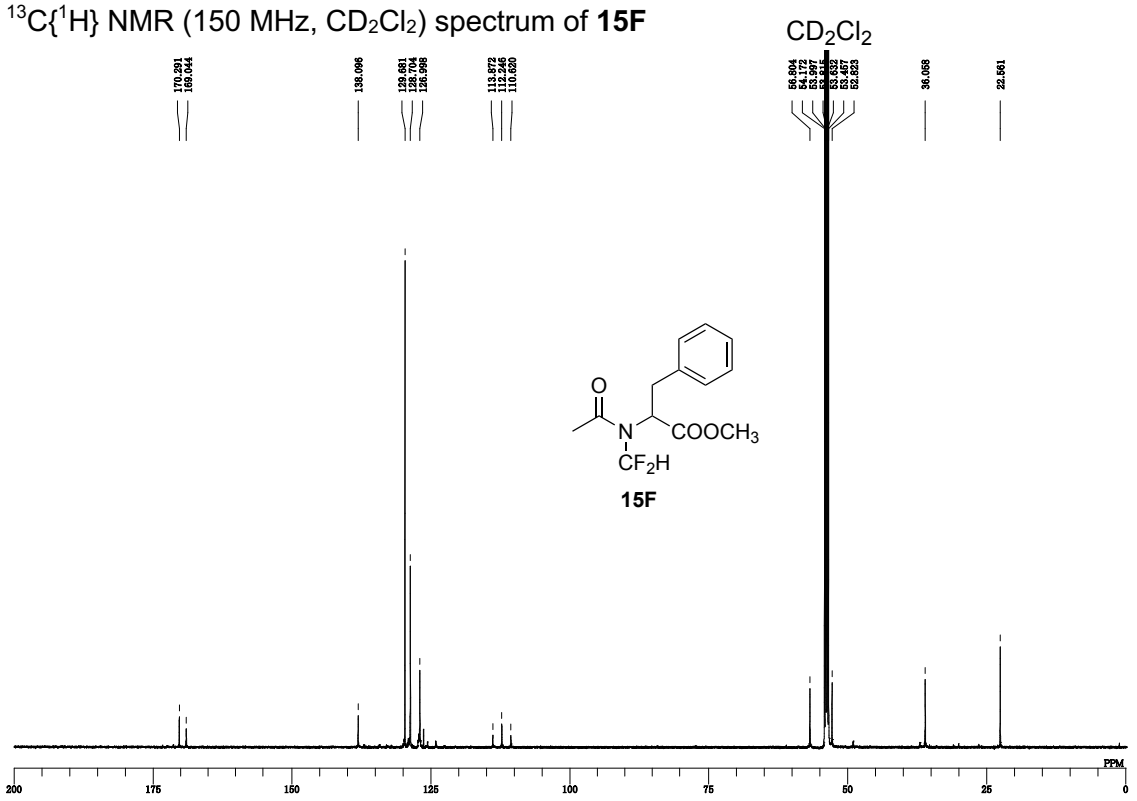
^{19}F NMR (376 MHz, 40 ºC, $CDCl_3$) spectrum of **14F**



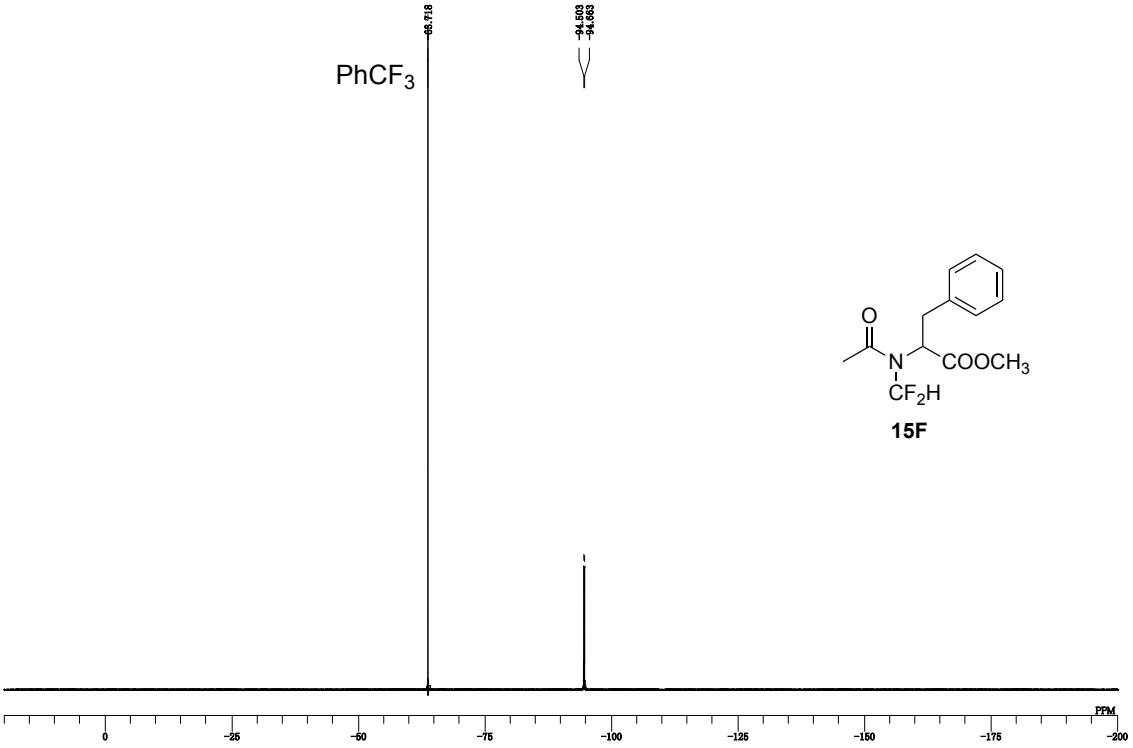
^{1}H NMR (400 MHz, 20 ºC, CD_2Cl_2) spectrum of **15F**



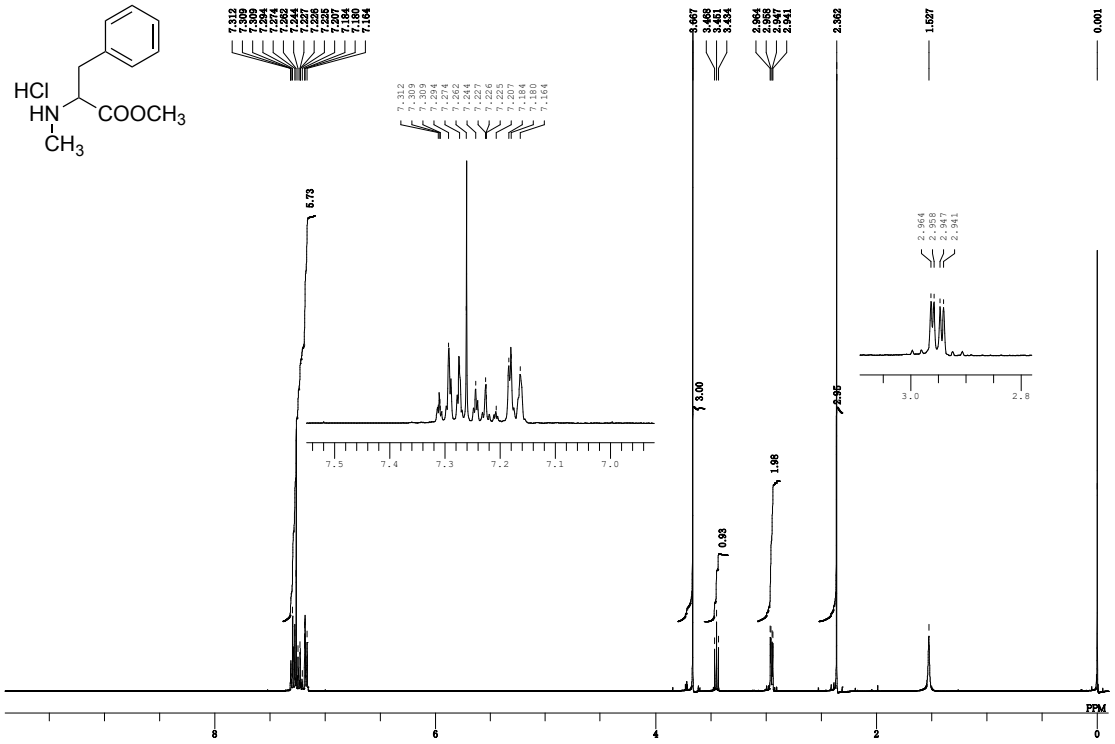
^{13}C{^{1}H} NMR (150 MHz, CD_2Cl_2) spectrum of **15F**



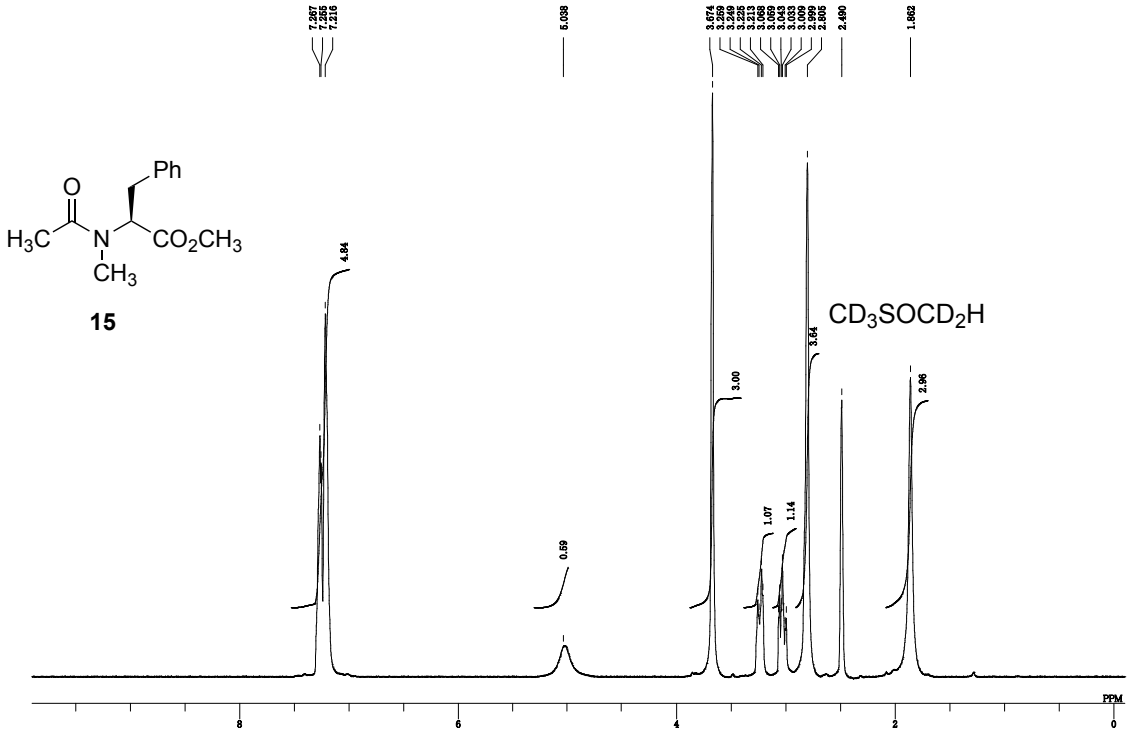
^{19}F NMR (376 MHz, CD_2Cl_2) spectrum of **15F**



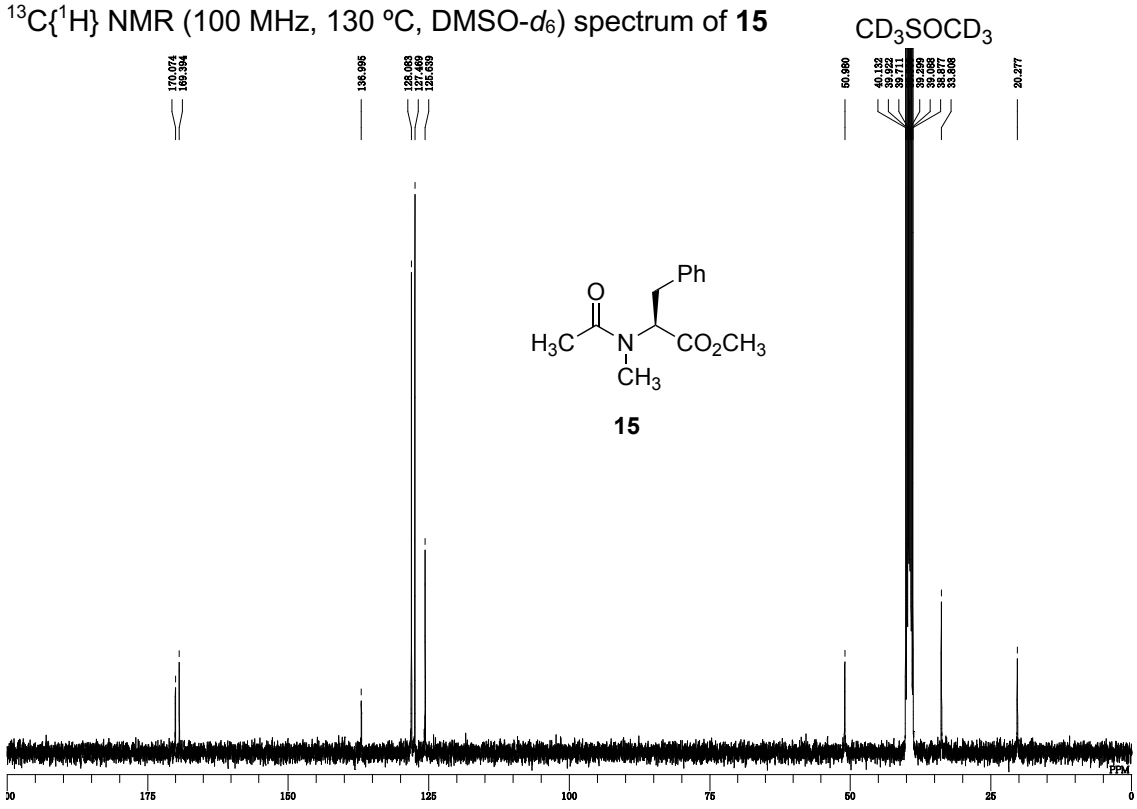
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of *N*-Methyl-L-phenylalanine methyl ester hydrochloride



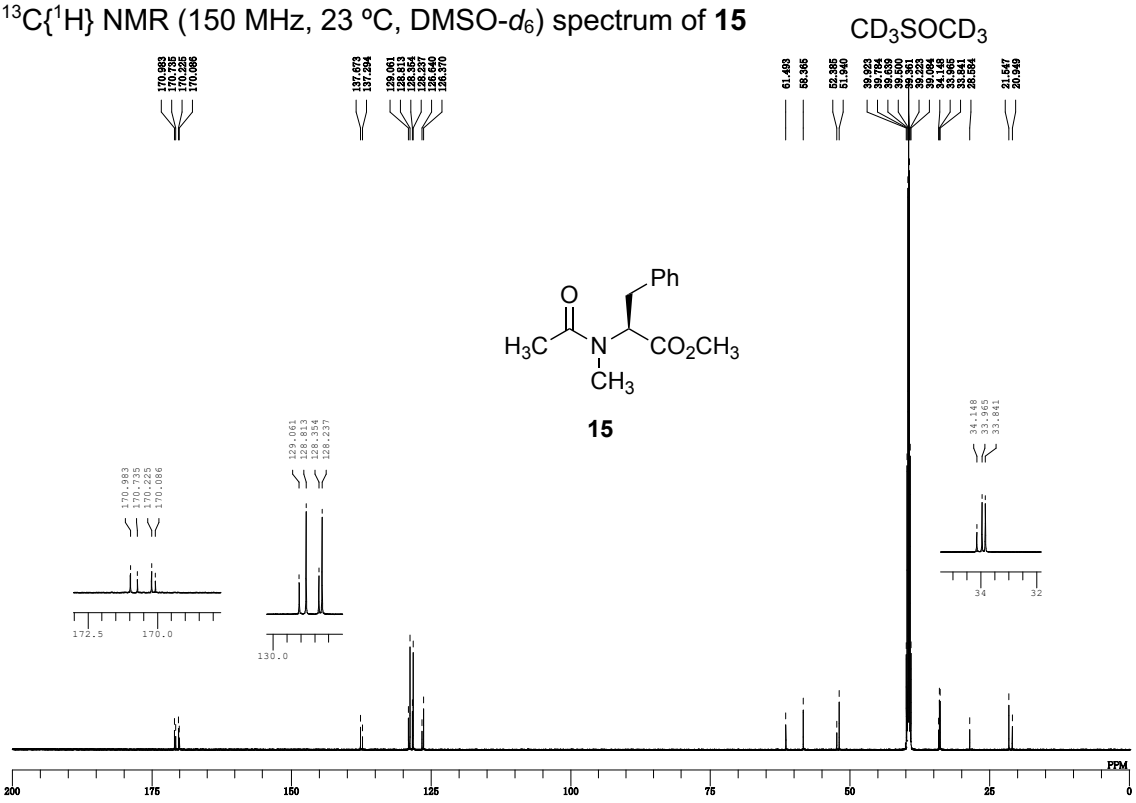
^{1}H NMR (400 MHz, 130 ºC, DMSO-d_6) spectrum of **15**



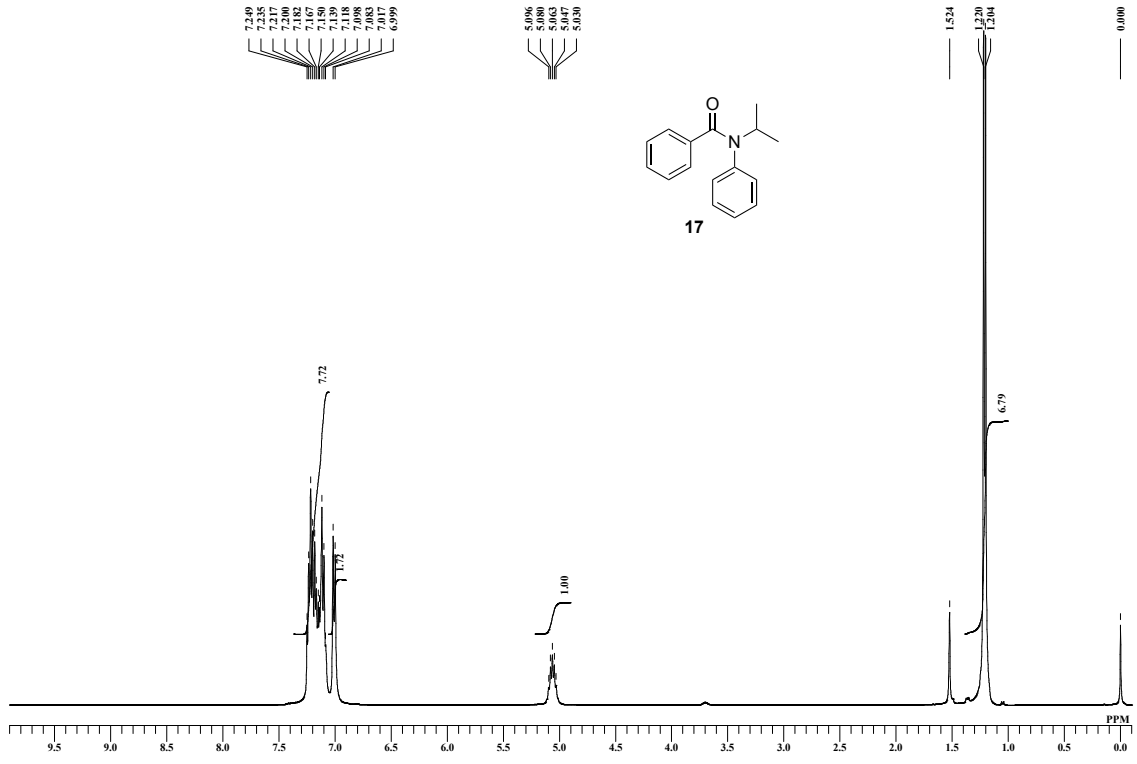
^{13}C{^{1}H} NMR (100 MHz, 130 ºC, DMSO-d_6) spectrum of **15**



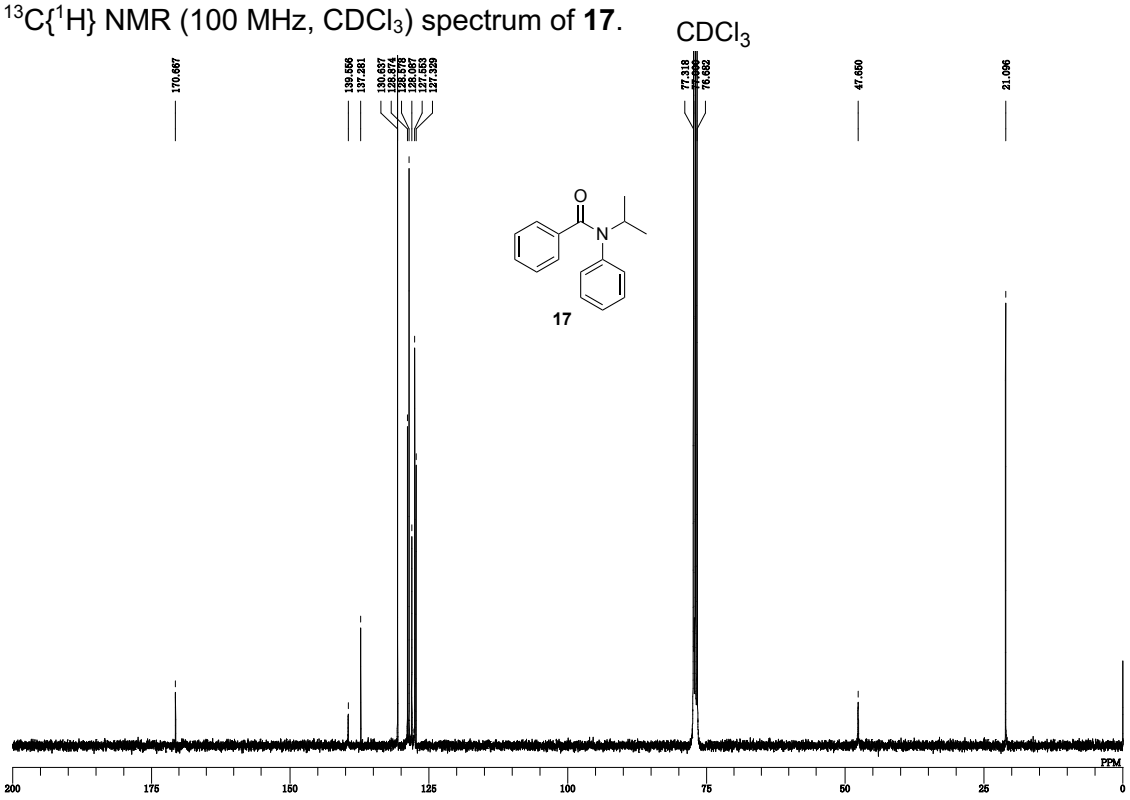
$^{13}C\{^{1}H\}$ NMR (150 MHz, 23 ºC, DMSO-d_6) spectrum of **15**



^{1}H NMR (400 MHz, 50 ºC, $CDCl_3$) spectrum of **17**.



$^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) spectrum of **17**.



6, DFT calculations

All calculations were performed using the Gaussian16 suite (Rev C. 01).[13] Relaxed scans of the dihedral angle, (O=)C–N–CF_2–H, were conducted at 5-degree intervals ranging from the most stable conformer at the M06-2X_6311(d,p) level with SMD (CH_2Cl_2) solvation at 213K. If a large change in energy occurred due to rotation of the N–Ph bond, another scan was performed in the reverse direction. NBO calculations were performed using the NBO 7.0 program[14] with the optimized structure. NCI plot analysis was performed by Multiwfn 3.8[15] and visualized by VMD 1.9.[16]

2 (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

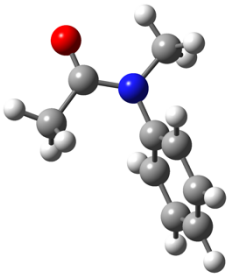
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –479.500392

Sum of electronic and thermal energies = –479.310404

Sum of electronic and thermal enthalpies = –479.309730

Sum of electronic and thermal free energies = –479.340188



O	3.185336	-0.172568	0.111467
N	1.040182	0.497293	0.178396
C	1.500558	1.874791	0.354968
C	2.003495	-0.463970	0.020107
C	-0.358377	0.250379	0.064828
C	-2.467423	0.695126	-1.018384
H	-3.035936	1.212156	-1.782644
C	-3.103473	-0.190964	-0.152936
C	-1.098286	0.913471	-0.914919
H	-0.594104	1.592567	-1.593831
C	1.563956	-1.877782	-0.286894
H	2.418606	-2.395047	-0.718781
H	1.274822	-2.392326	0.631938
C	-2.365322	-0.847180	0.827543
H	-2.855626	-1.528354	1.513264
C	-0.998422	-0.618915	0.946875
H	-0.423053	-1.105077	1.726035
H	0.719702	-1.912314	-0.975549
H	-4.169575	-0.364569	-0.238875
H	1.969045	2.255277	-0.556361
H	0.647842	2.498945	0.613561
H	2.234974	1.913929	1.159580

2 (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

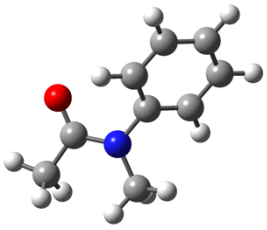
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –479.498834

Sum of electronic and thermal energies = –479.308720

Sum of electronic and thermal enthalpies = –479.308045

Sum of electronic and thermal free energies = –479.337452



O	1.558665	-1.654288	-0.591782

N	1.000161	0.398591	0.220514	H	3.557710	0.752861	-0.698996
C	1.434072	1.753798	0.563922	C	-2.339953	-1.229871	0.442180
C	1.903696	-0.555381	-0.197765	H	-2.769147	-2.163760	0.786746
C	-0.399700	0.163107	0.103293	C	-0.967883	-1.036171	0.541085
C	-2.597881	0.959342	-0.511982	H	-0.333863	-1.809059	0.951848
H	-3.224123	1.742154	-0.924168	H	3.686346	-0.012695	0.888043
C	-3.162615	-0.236260	-0.082942	H	-4.232376	-0.393058	-0.154096
C	-1.223785	1.159387	-0.423694	H	1.628720	2.363584	-0.323115
H	-0.790752	2.089962	-0.771505	H	2.335149	1.716060	1.172766
C	3.364020	-0.167096	-0.144312	H	0.653124	2.229386	1.154643
H	3.935798	-0.983490	-0.579090				

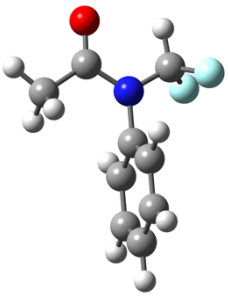
2F (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –677.993281

Sum of electronic and thermal energies = –677.817564



Sum of electronic and thermal enthalpies = –677.816889

Sum of electronic and thermal free energies = –677.850521

F	1.160804	-1.933111	1.084172	C	1.553343	-1.201993	0.002995
F	1.163972	-1.933885	-1.078916	H	2.632419	-1.092732	0.004472
O	2.903603	1.153399	-0.005540	C	-1.211623	0.057952	1.211319
N	0.913546	0.058501	0.001813	H	-0.652046	0.052040	2.139547
C	1.694080	1.213492	-0.002702	C	-2.602337	0.059902	1.207430
C	-0.524593	0.068274	0.001311	H	-3.143234	0.055317	2.146172
				C	-3.295874	0.064967	0.000292
				H	-4.379618	0.066662	-0.000092
				C	0.934617	2.511744	-0.003600
				H	1.656249	3.325020	-0.002457
				H	0.292879	2.581490	0.876848
				H	0.296231	2.581563	-0.886520
				C	-1.210768	0.062917	-1.209218
				H	-0.650541	0.060692	-2.137092
				C	-2.601478	0.065070	-1.206362
				H	-3.141686	0.064520	-2.14551

2F (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

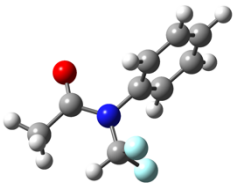
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –777.236802

Sum of electronic and thermal energies = –677.990029

Sum of electronic and thermal enthalpies = –677.813957

Sum of electronic and thermal free energies = –677.846067



F	-1.061696	-2.179430	0.251698
F	-0.875231	-1.012817	2.063246
O	-0.685502	2.009974	-1.069636
N	-0.684325	0.057509	0.059201
C	-1.327971	1.163604	-0.494212
C	0.749702	-0.040434	-0.038033
C	-1.344182	-0.956233	0.782977
H	-2.419836	-0.826202	0.809513
C	1.317684	-0.775809	-1.071608
H	0.674638	-1.259203	-1.797515
C	2.702497	-0.876065	-1.156681
H	3.152048	-1.447491	-1.960036
C	3.506689	-0.243242	-0.213274
H	4.585333	-0.322143	-0.282284
C	-2.826819	1.243059	-0.345770
H	-3.154077	2.155109	-0.838660
H	-3.116847	1.276531	0.706334
H	-3.313911	0.384753	-0.812892
C	1.545029	0.593296	0.910170
H	1.075457	1.159729	1.705879
C	2.928597	0.491562	0.818509
H	3.554340	0.984651	1.552922

3 (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

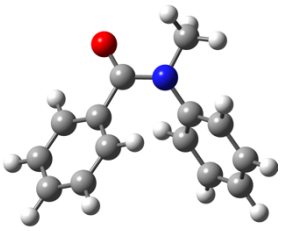
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –671.211321

Sum of electronic and thermal energies = –670.966367

Sum of electronic and thermal enthalpies = –670.965692

Sum of electronic and thermal free energies = –671.000231



C	-1.247945	-0.451238	1.189878
C	-1.958005	-1.631886	1.382786
C	-2.897362	-2.047066	0.444355
C	-3.124389	-1.276162	-0.693429
C	-2.406044	-0.104904	-0.899839
C	-1.459141	0.305297	0.038620
N	-0.735118	1.516591	-0.180884
C	0.618159	1.631077	0.005480
C	1.465367	0.394472	-0.106958
C	1.219823	-0.603037	-1.051797
C	2.085292	-1.685713	-1.158218
C	3.189485	-1.784258	-0.315517
C	3.440621	-0.785934	0.621611
C	2.588304	0.307956	0.715284
O	1.139444	2.715456	0.208532
C	-1.500258	2.764692	-0.189797
H	-0.525423	-0.116176	1.925567
H	-1.782195	-2.221112	2.275159
H	-3.452719	-2.964431	0.599527
H	-3.855170	-1.593056	-1.428257
H	-2.561883	0.489665	-1.793383
H	0.362150	-0.530065	-1.710350
H	1.897493	-2.453138	-1.899874
H	3.856880	-2.634674	-0.394339
H	4.303483	-0.855638	1.273531
H	2.783860	1.103386	1.424816
H	-0.984957	3.501725	-0.802756
H	-2.487571	2.570662	-0.603716
H	-1.606413	3.162465	0.823950

3 (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

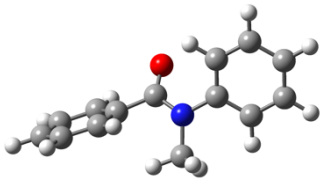
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –671.206652

Sum of electronic and thermal energies = –670.961276

Sum of electronic and thermal enthalpies = –670.960601

Sum of electronic and thermal free energies = –670.994995



C	8.266967	4.681937	9.435407
C	7.311896	5.638873	9.742443

C	5.995739	5.495934	9.305162
C	5.650037	4.381835	8.553155
C	6.601239	3.411635	8.243605
C	7.917098	3.551271	8.687119
N	8.913286	2.597359	8.330291
C	9.834895	2.195591	9.280294
C	11.048446	1.447256	8.803539
C	11.784159	1.877657	7.698297
C	12.969606	1.234823	7.360528
C	13.416319	0.153550	8.115881
C	12.686493	-0.272399	9.222364
C	11.512891	0.383693	9.575471
O	9.725697	2.464430	10.461099
C	8.673785	1.810732	7.118055
H	9.286926	4.805748	9.773758
H	7.600935	6.508359	10.321572
H	5.253979	6.248310	9.545107
H	4.633024	4.255608	8.200163
H	6.305036	2.550997	7.658518
H	11.433954	2.720786	7.111871
H	13.544946	1.578598	6.509009
H	14.336481	-0.351719	7.846136
H	13.036244	-1.109288	9.815323
H	10.949886	0.078550	10.449927
H	7.854589	1.102676	7.267155
H	8.422307	2.480325	6.294600
H	9.559992	1.244548	6.854055

3F (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

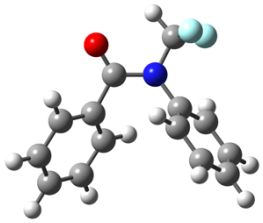
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –869.701587

Sum of electronic and thermal energies = –869.470593

Sum of electronic and thermal enthalpies = –869.469918

Sum of electronic and thermal free energies = –869.506932



F	2.606483	-1.738426	0.966159
F	2.882109	-1.345729	-1.144894
O	-0.476240	-2.721622	0.265059
N	0.835296	-0.932874	-0.244369
C	1.077388	0.462174	0.020690
C	-0.397023	-1.541139	0.001587
C	-1.616807	-0.682879	-0.109600
C	1.972957	-1.786822	-0.239783
H	1.697056	-2.812447	-0.457787
C	-1.750902	0.300022	-1.091372
H	-0.940776	0.494419	-1.783748
C	-2.675511	-0.955783	0.756399
H	-2.564548	-1.737911	1.498232
C	0.782805	0.981020	1.278045
H	0.373758	0.329638	2.042738
C	-2.938611	1.014010	-1.193867
H	-3.047396	1.768572	-1.963731
C	-3.984630	0.761025	-0.310144
H	-4.905255	1.327919	-0.385815
C	-3.852937	-0.223949	0.665015

H	-4.668568	-0.425703	1.349058
C	1.622735	1.269719	-0.972918
H	1.842253	0.846052	-1.945158
C	1.862715	2.612618	-0.704389
H	2.285421	3.245610	-1.475468
C	1.551810	3.143993	0.544259
H	1.733027	4.193008	0.746536
C	1.010580	2.328329	1.533650
H	0.773133	2.737303	2.508424

3F(trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

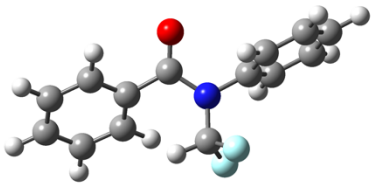
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –869.699277

Sum of electronic and thermal energies = –869.468209

Sum of electronic and thermal enthalpies = –869.467534

Sum of electronic and thermal free energies = –869.504555



F	0.895389	1.311844	-2.052694
F	0.326809	2.396183	-0.269667
O	-0.172268	-1.966725	0.511356
N	0.397539	0.110636	-0.190620
C	1.796527	-0.133651	0.058047
C	-0.530903	-0.862805	0.172099
C	-1.979150	-0.479500	0.178289
C	0.078399	1.248714	-0.968324
H	-0.952531	1.251881	-1.304607
C	-2.906767	-1.437007	-0.232716
H	-2.553662	-2.393239	-0.600369
C	-2.416477	0.744316	0.688451
H	-1.699280	1.478530	1.039608
C	2.511186	-0.986612	-0.776044
H	2.006599	-1.469394	-1.604477
C	-4.265544	-1.157110	-0.169490
H	-4.984621	-1.895290	-0.504019
C	-4.701800	0.066759	0.332697
H	-5.762667	0.280915	0.389973
C	-3.778582	1.012119	0.769294
H	-4.117094	1.957262	1.176515
C	2.411815	0.504460	1.127925
H	1.830934	1.161902	1.763938
C	3.765678	0.284623	1.365791
H	4.252303	0.779685	2.197671
C	4.487993	-0.570116	0.539878
H	5.541212	-0.742324	0.728403
C	3.860680	-1.206259	-0.529232
H	4.423596	-1.872006	-1.172589

4 (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

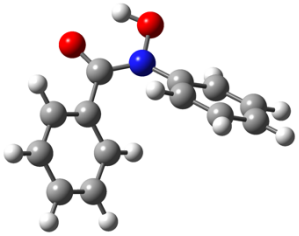
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –707.072526

Sum of electronic and thermal energies = –706.852213

Sum of electronic and thermal enthalpies = –706.851538

Sum of electronic and thermal free energies = –706.885881



O	1.582939	30.423484	3.523593
H	0.774032	30.824482	3.881806
O	0.323411	28.807116	5.119990
C	4.298890	31.051932	4.127455
H	4.169374	30.766233	3.090626
N	2.241467	29.881485	4.618748
C	2.248009	28.148838	6.351957
C	3.351086	30.652899	5.069032
C	1.508031	28.965655	5.341019
C	3.482182	31.025568	6.405273
H	2.726255	30.742137	7.127846
C	1.546693	27.727476	7.481088
H	0.514542	28.033098	7.606336
C	3.568127	27.740882	6.154864
H	4.105686	28.046630	5.264467
C	2.173400	26.927403	8.428679
H	1.631753	26.611399	9.312332
C	3.493315	26.527766	8.236985
H	3.980812	25.898919	8.972978
C	4.590068	31.766983	6.802476
H	4.695015	32.049563	7.843282
C	4.185929	26.927048	7.096593
H	5.207619	26.602335	6.939540
C	5.543703	32.162541	5.870276
H	6.400082	32.747749	6.183406
C	5.388476	31.812232	4.530949
H	6.123505	32.123646	3.798206

4 (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

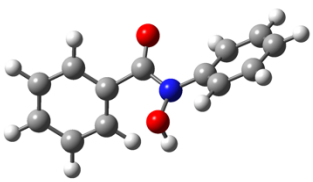
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –707.072321

Sum of electronic and thermal energies = –706.852014

Sum of electronic and thermal enthalpies = –706.851340

Sum of electronic and thermal free energies = –706.885701



C	0.033205	6.626381	14.314985
H	-0.655492	7.225442	13.731290
O	-0.976393	5.391419	11.906779
H	-1.626352	6.107633	11.966113
O	2.408882	6.022419	11.753133
C	0.251109	5.960136	9.963698
C	1.956952	5.173356	14.449652
H	2.754568	4.635917	13.950506
C	1.183437	6.823295	7.920948
H	1.866792	7.497361	7.417764

C	0.823372	5.860895	16.460208
H	0.733309	5.843480	17.540132
C	-0.512796	5.123471	7.840117
H	-1.156598	4.459117	7.275517
N	0.169811	5.974713	11.385188
C	1.286967	5.957157	12.208272
C	-0.069803	6.612361	15.700351
H	-0.847620	7.188238	16.187654
C	1.126840	6.828665	9.308378
H	1.755866	7.495774	9.880859
C	1.044860	5.899861	13.685489
C	1.836350	5.140929	15.833942
H	2.537017	4.561152	16.422961
C	0.367086	5.972865	7.179304
H	0.413931	5.977476	6.096935
C	-0.574989	5.110057	9.229713
H	-1.258208	4.448730	9.744512

15 (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

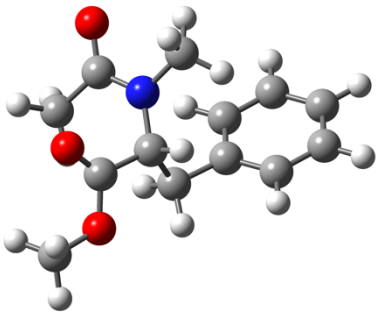
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –785.966870

Sum of electronic and thermal energies = –785.671640

Sum of electronic and thermal enthalpies = –785.670965

Sum of electronic and thermal free energies = –785.711139



O	8.902238	4.629554	10.085429
O	9.741503	4.943131	8.036181
O	8.105722	7.874969	5.964467
N	7.356101	6.156114	7.213453
C	8.091482	7.291770	7.038744
C	7.383290	5.326637	8.406368
H	6.961620	4.359058	8.110286
C	6.584635	5.670961	6.073856
H	6.227070	6.519901	5.495117
C	8.814918	4.967642	8.800735
C	4.163072	5.015986	9.107992
H	4.453431	4.069814	9.554902
C	5.085238	6.063116	9.062872
C	6.497080	5.859774	9.552085
H	6.514165	5.133270	10.365225
H	6.898636	6.800406	9.934128
C	4.698203	7.275676	8.489225
H	5.407820	8.096576	8.450274
C	2.882443	5.173528	8.586240
H	2.176485	4.351946	8.630691
C	10.201130	4.208587	10.529634
H	10.522315	3.328055	9.973115
H	10.088854	3.973367	11.584488
H	10.923107	5.013826	10.392221
C	3.418924	7.437012	7.965745
H	3.133072	8.384108	7.522399
C	2.508583	6.384516	8.010143
H	1.512022	6.509035	7.602534
C	8.893345	7.856901	8.192446

H	9.949449	7.787978	7.925523
H	8.749570	7.386775	9.161919
H	8.635447	8.913823	8.273691
H	5.730104	5.100689	6.438227
H	7.196276	5.034604	5.425939

15 (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

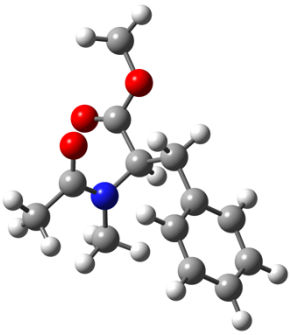
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –785.971922

Sum of electronic and thermal energies = –785.676624

Sum of electronic and thermal enthalpies = –785.675949

Sum of electronic and thermal free energies = –785.715142



O	9.043025	4.750106	10.029441
O	9.656477	4.421798	7.904315
O	8.838701	7.359800	8.128894
N	7.404977	5.937894	7.141403
C	8.184247	7.052094	7.139194
C	7.397179	5.127316	8.350882
H	6.916850	4.179123	8.087485
C	6.632317	5.458221	6.005525
H	6.478978	6.253070	5.280133
C	8.832212	4.750530	8.715340
C	4.183683	5.139805	9.110249
H	4.397037	4.174467	9.559735
C	5.196542	6.098251	9.035403
C	6.595895	5.776637	9.493353
H	6.570792	5.082366	10.334596
H	7.115584	6.680683	9.811389
C	4.905337	7.337436	8.460423
H	5.684412	8.092117	8.406934
C	2.910224	5.409144	8.617097
H	2.133901	4.655440	8.686244
C	10.368112	4.390791	10.439339
H	10.608494	3.380266	10.107883
H	10.366781	4.444899	11.524917
H	11.090432	5.094023	10.023735
C	3.633991	7.610253	7.964046
H	3.423266	8.577577	7.521957
C	2.633196	6.644837	8.038532
H	1.642176	6.856238	7.653783
C	8.209080	7.892768	5.884885
H	8.915033	8.704586	6.043804
H	7.220342	8.308610	5.677139
H	8.518534	7.302996	5.019873
H	5.650900	5.126409	6.351474
H	7.138928	4.620275	5.516366

15F (cis)

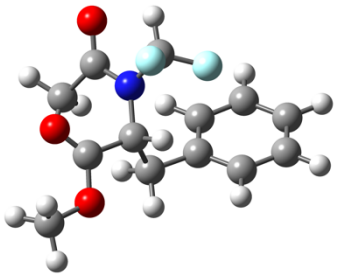
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –984.460448

Sum of electronic and thermal energies = –984.178735

Sum of electronic and thermal enthalpies = –984.178060

Sum of electronic and thermal free energies = –984.219264



F	5.653259	5.033400	6.198345
F	7.647139	4.284187	5.829773
O	8.839312	4.352485	9.982526
O	9.808730	5.199583	8.151768
O	8.067805	7.860240	5.873391
N	7.408084	6.118590	7.164686
C	8.012147	7.359751	6.976491
C	7.402924	5.347117	8.402806
H	6.938095	4.386616	8.156506
C	6.940822	5.438920	6.016086
H	7.012186	6.058548	5.130482
C	8.829188	4.981136	8.811214
C	4.193742	5.125520	9.208554
H	4.489004	4.193736	9.681367
C	5.126573	6.155951	9.083814
C	6.549928	5.953571	9.537282
H	6.581291	5.251373	10.371097
H	6.979909	6.894306	9.880870
C	4.735789	7.347679	8.472474
H	5.454211	8.155056	8.369640
C	2.896468	5.281579	8.731204
H	2.181667	4.473386	8.836438
C	10.125870	3.903826	10.438197
H	10.550741	3.197835	9.724653
H	9.945753	3.418801	11.393596
H	10.797852	4.753218	10.560657
C	3.438762	7.508503	7.994894
H	3.149288	8.440258	7.522466
C	2.516445	6.473875	8.121050
H	1.506114	6.596740	7.748352
C	8.534879	8.094515	8.183517
H	9.310969	8.772177	7.832646
H	8.938560	7.457374	8.965137
H	7.720888	8.691801	8.602994

15F (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

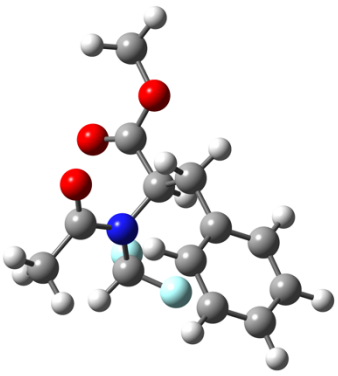
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –984.464839

Sum of electronic and thermal energies = –984.183174

Sum of electronic and thermal enthalpies = –984.182499

Sum of electronic and thermal free energies = –984.223097



F	5.546532	4.964603	6.215094
F	7.480257	4.153378	5.697118
O	9.008725	4.611490	10.021668
O	9.746571	4.709998	7.912115
O	8.608798	7.541987	8.107983
N	7.397656	5.927208	7.123286
C	8.054546	7.146659	7.103743
C	7.412293	5.145639	8.357137
H	6.949192	4.181781	8.122535
C	6.839468	5.325110	5.979807
H	6.873150	5.964371	5.105105
C	8.862168	4.820253	8.716000
C	4.193420	5.175606	9.115583
H	4.406812	4.198873	9.539279
C	5.208260	6.131239	9.054064
C	6.607293	5.795268	9.499842
H	6.580618	5.083640	10.325705
H	7.128650	6.689896	9.838414
C	4.920559	7.383481	8.508294
H	5.701603	8.137258	8.467093
C	2.919806	5.459928	8.633846
H	2.141357	4.707322	8.688451
C	10.331246	4.251703	10.445699
H	10.643062	3.324889	9.963778
H	10.269299	4.119312	11.522530
H	11.032977	5.048537	10.198666
C	3.647516	7.672612	8.025667
H	3.438197	8.650186	7.606150
C	2.644441	6.709119	8.083997
H	1.652553	6.931705	7.707871
C	8.030237	7.946334	5.826935
H	8.537948	8.887768	6.021697
H	7.004552	8.143255	5.507647
H	8.550237	7.416692	5.025800

17 (cis)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

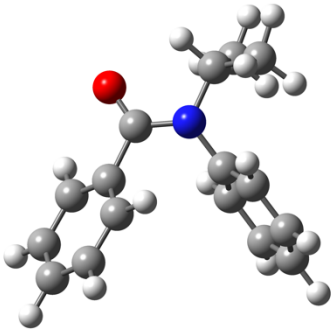
Number of imaginary frequencies: 0

SCF Done: E(RM062X) = –749.824558

Sum of electronic and thermal energies = –749.521451

Sum of electronic and thermal enthalpies = –749.520776

Sum of electronic and thermal free energies = –749.557916



C	1.787037	-1.637534	-0.420610
C	3.120168	0.778490	-0.769521
C	1.138058	-0.567536	-1.035411
C	3.095103	-1.493546	0.030534
C	3.764634	-0.286719	-0.145619
C	1.808614	0.642045	-1.210411
N	-0.214608	-0.719529	-1.488961
C	-1.204189	-1.109340	-0.618126
O	-2.221457	-1.668654	-0.994238
H	1.257105	-2.575296	-0.290526
H	3.635350	1.722429	-0.903763

H	3.590247	-2.326030	0.516468
H	4.784136	-0.174838	0.204313
H	1.291888	1.474360	-1.673441
C	-0.433970	-1.039858	-2.923429
C	0.007827	-2.468545	-3.229424
H	-0.231564	-2.718844	-4.265658
H	1.087597	-2.578314	-3.094512
H	-0.505480	-3.177744	-2.576728
H	-1.512541	-0.970758	-3.057679
C	0.238559	-0.032007	-3.845540
H	1.327831	-0.098425	-3.796495
H	-0.064243	-0.245552	-4.873063
H	-0.064154	0.989392	-3.605677
C	-1.026528	-0.787891	0.840840
C	-0.538039	0.441664	1.284339
C	-1.458427	-1.736111	1.767823
C	-0.468600	0.710570	2.646675
H	-0.227098	1.192377	0.567859
C	-1.367310	-1.474010	3.129863
H	-1.862749	-2.676223	1.410906
C	-0.871867	-0.249886	3.570648
H	-0.099593	1.670990	2.987001
H	-1.689085	-2.220727	3.846307
H	-0.806685	-0.041336	4.632301

17 (trans)

M062X _6311(d, p), SMD(CH_2Cl_2), 213 K

Number of imaginary frequencies: 0

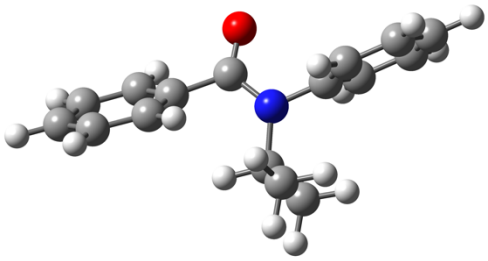
SCF Done: E(RM062X) = –749.820101

Sum of electronic and thermal energies = –749.517055

Sum of electronic and thermal enthalpies = –749.516381

Sum of electronic and thermal free energies = –749.553804

C	1.970085	-1.943461	-0.711936
C	2.677688	0.702460	-0.218004
C	1.062061	-0.920220	-0.966270
C	3.237712	-1.641313	-0.220709
C	3.593260	-0.319380	0.024187
C	1.413208	0.404204	-0.711834
N	-0.236349	-1.245284	-1.489985
C	-1.284504	-1.198416	-0.608385
O	-1.155563	-0.807131	0.539946



H	1.676383	-2.970496	-0.896519
H	2.947824	1.733034	-0.019305
H	3.943057	-2.440643	-0.025819
H	4.579047	-0.084517	0.408430
H	0.690231	1.190314	-0.896126
C	-0.380759	-1.304224	-2.964983
C	0.409173	-2.464875	-3.560396
H	0.198877	-2.536310	-4.630002
H	1.484450	-2.311993	-3.438854
H	0.135687	-3.411708	-3.089972

H	-1.438699	-1.467257	-3.157125	C	-4.049607	-3.417120	-1.990106
C	0.008273	0.022832	-3.613788	H	-1.903072	-3.533598	-1.928462
H	1.075333	0.226692	-3.497849	C	-5.024597	-1.421414	-1.051410
H	-0.213024	-0.022289	-4.682607	H	-3.630006	-0.006900	-0.215598
H	-0.557369	0.850362	-3.179485	C	-5.172710	-2.654829	-1.680112
C	-2.627972	-1.700205	-1.065644	H	-4.163208	-4.384875	-2.464379
C	-2.778691	-2.939090	-1.690030	H	-5.897712	-0.829620	-0.802657
C	-3.755871	-0.952662	-0.729874	H	-6.162304	-3.025206	-1.921412

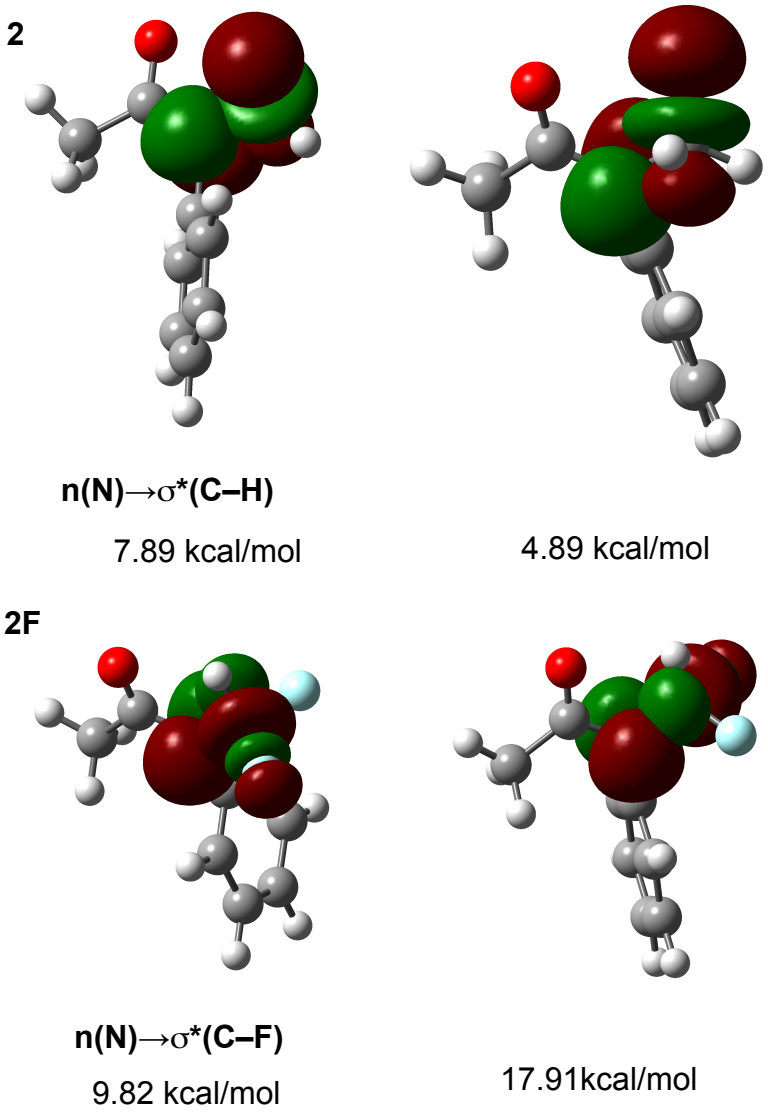
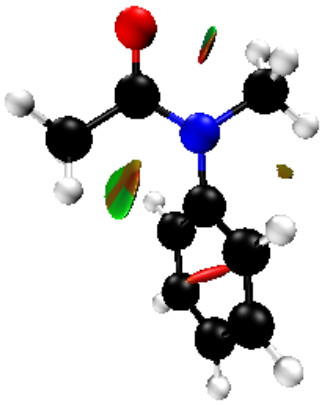
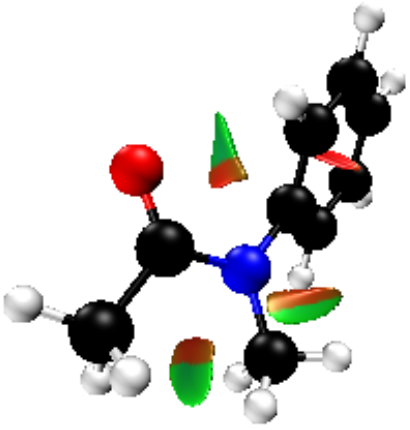


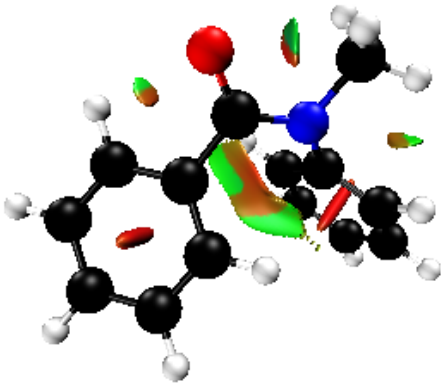
Figure S69. NBO interactions of *n*(N)→σ*(C–H) of **2** and **2F** with isovalues 0.05.



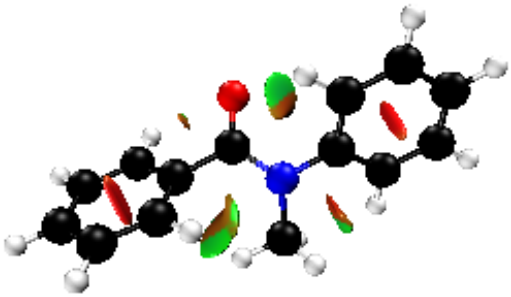
2 (cis)



2 (trans)

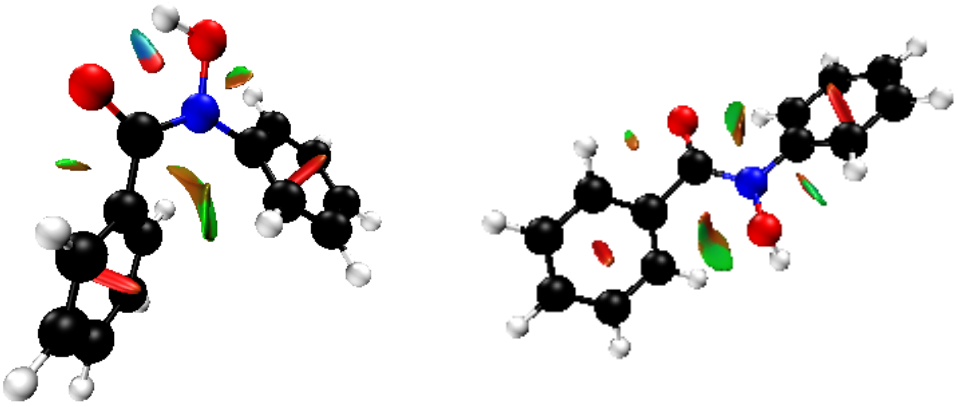


3 (cis)



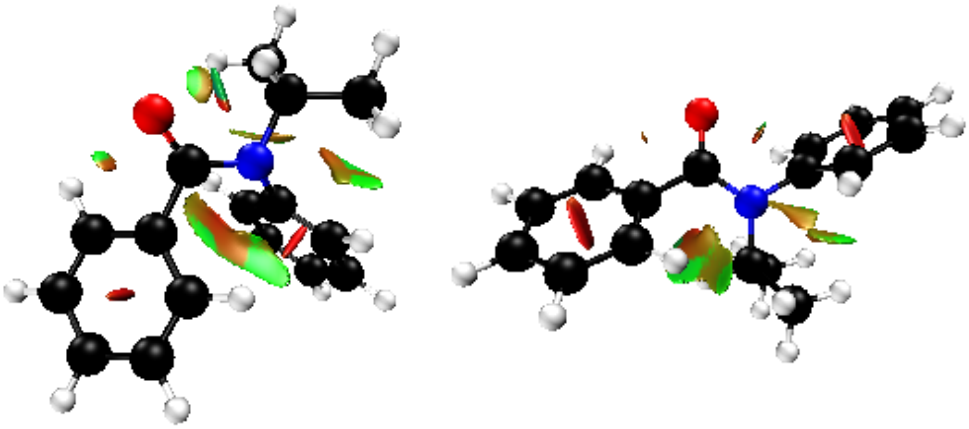
3 (trans)

Figure S70. NCI plot of **2** and **3**.



4 (cis) **4** (trans)

Figure S71. NCI plot of **4**.



17 (cis) **17** (trans)

Figure S72. NCI plot of **17**.

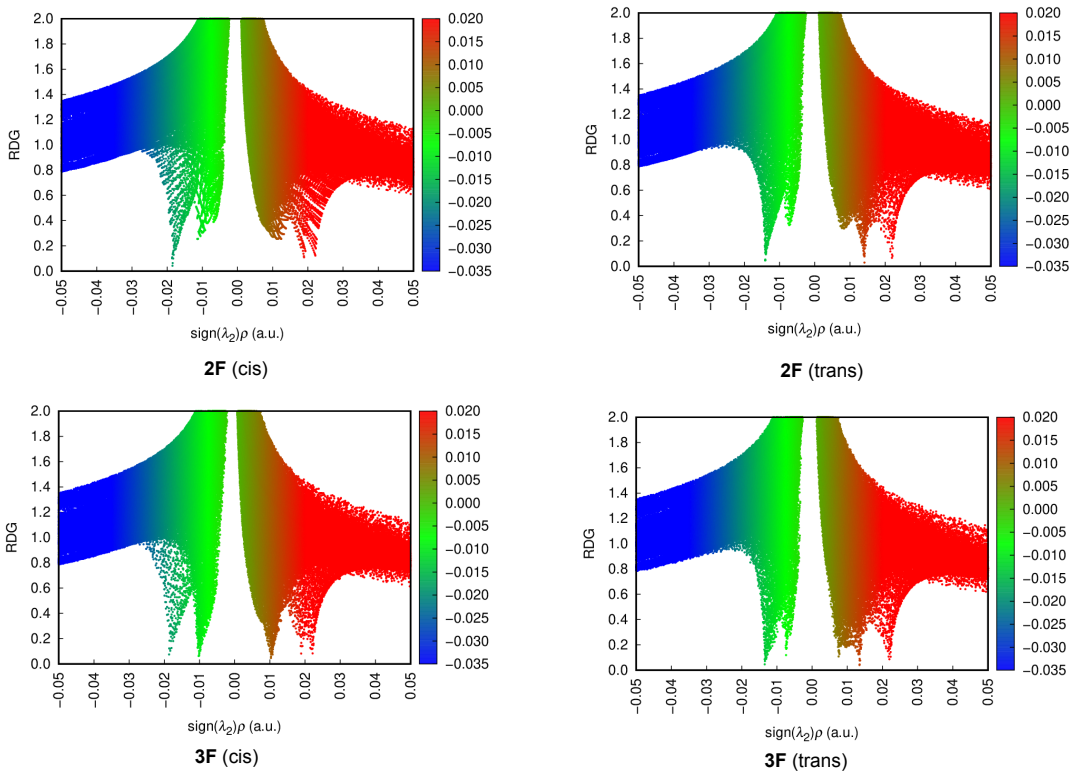


Figure S73. RDG Scattered plot of *N*-CF_2H anilides **2F** and **3F**.

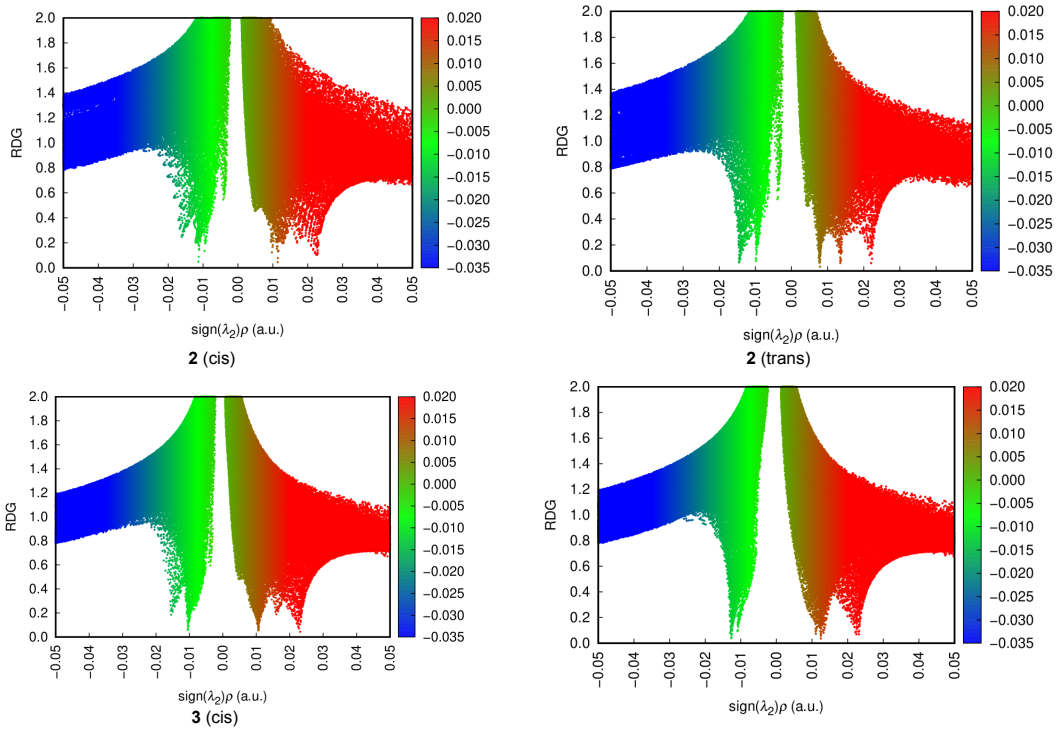


Figure S74. RDG Scattered plot of *N*-CH_3 anilides **2** and **3**.

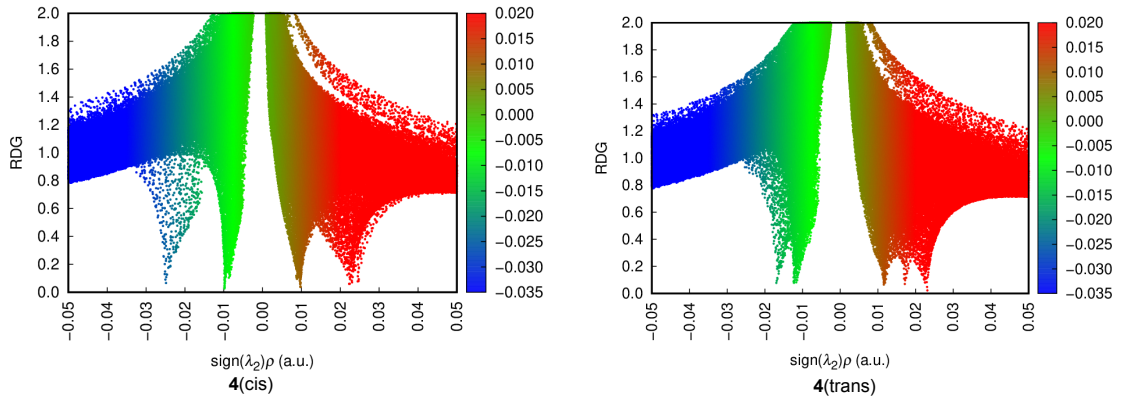


Figure S75. RDG Scattered plot of *N*-OH amides **4**.

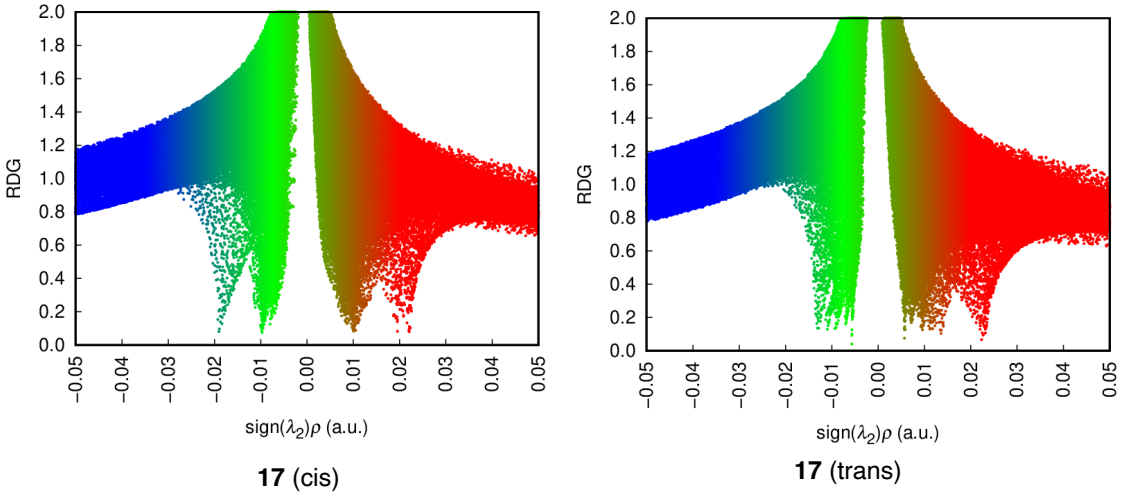


Figure S76. RDG Scattered plot of *N*-isopropyl benzanilide **17**.

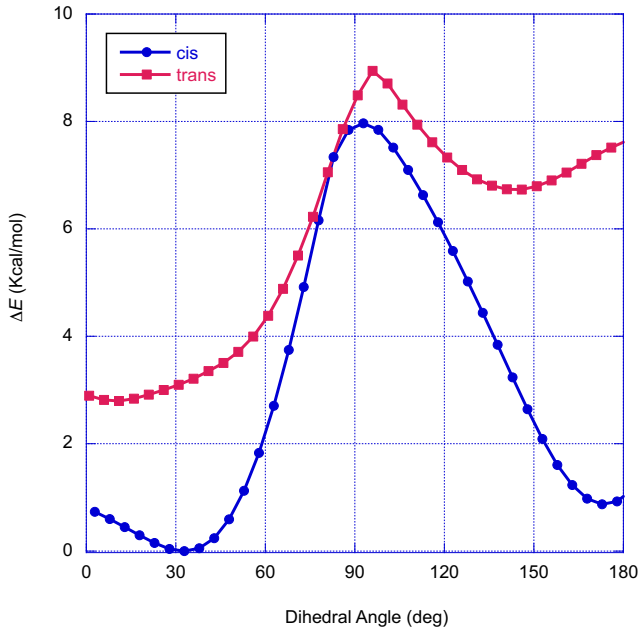
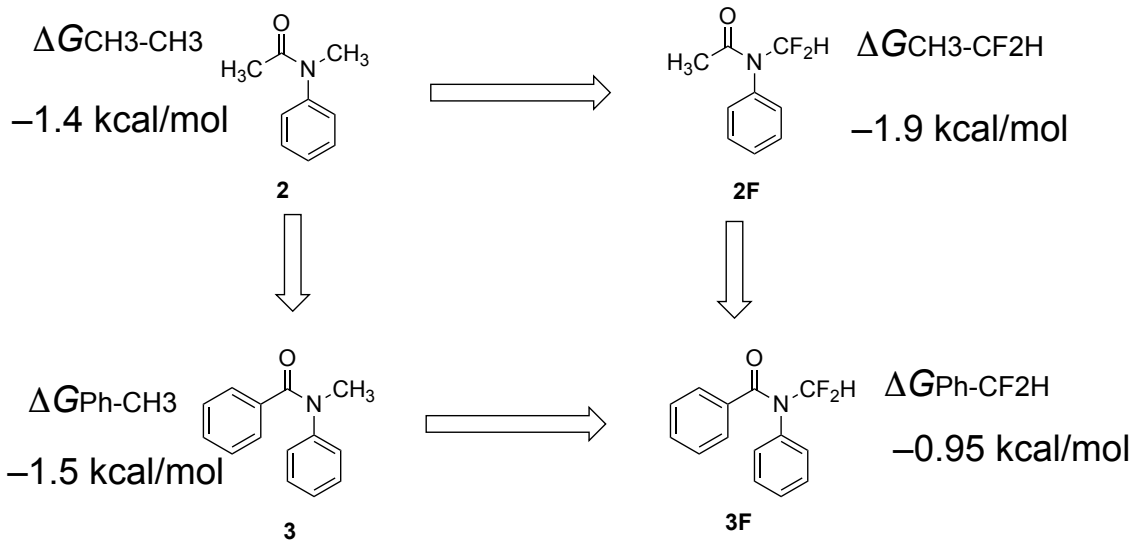


Figure S77. Scanning profile of (O=)C–N–C(CH_3)$_2$–H angle of **17** at the M06-2X/6-311(d,p) SMD (CH_2Cl_2) level at 213 K.

	Acetanilide		Benzanilide								Acetbenzylamide		Benzobenzylamide		Naphthalene		Ac-Phe-OCH_3		*N*-*i*Pr Anilide	
Cmpd	**2**	**2F**	**3**	**3F**	**6F**	**7F**	**8F**	**9F**	**10H**	**10F**	**11**	**11F**	**12**	**12F**	**13F**	**14F**	**15**	**15F**	**16**	**17**
Cis/trans	96/4[a]	99/1	98/2 [a]	90/10[b]	96/4[b]	94/6[b]	89/11[b]	90/10[b]	90/10[a]	82/18[b]	32/68	50/50	46/54	6/94	73/27	7/93[b]	19/81	5/95	2/98	4/94
ΔG^{o}_{216K} (kcal/mol)	-1.4[a] (233K)	-1.9	-1.5 (193K)	-0.95	-1.26	-1.07	-0.84	-0.96	-1.05 (236K)	-0.65	0.33	-0.006	0.07	1.19	-0.42	1.13	0.61	1.25	-1.8	-1.2
Chart	Ref.17	S10	Ref.18	S20	S22	S25	S28	S31	Ref.2	S33	S40	S36	S47	S43	S51	S55	S61	S57	Ref.19	S64
ΔG^{o}_{calc} (kcal/mol)	-1.7	-2.8	-3.3	-1.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	2.5	2.4	N/A	-2.6

Table S5. Summary of energy differences observed in VT-NMR experiments (in CD_2Cl_2, 216 K) and DFT calculations (M06-2X/6-311(d,p) SMD (CH_2Cl_2) level at 213 K).

[a] See references. [b] Determined by ^{19}F NMR.

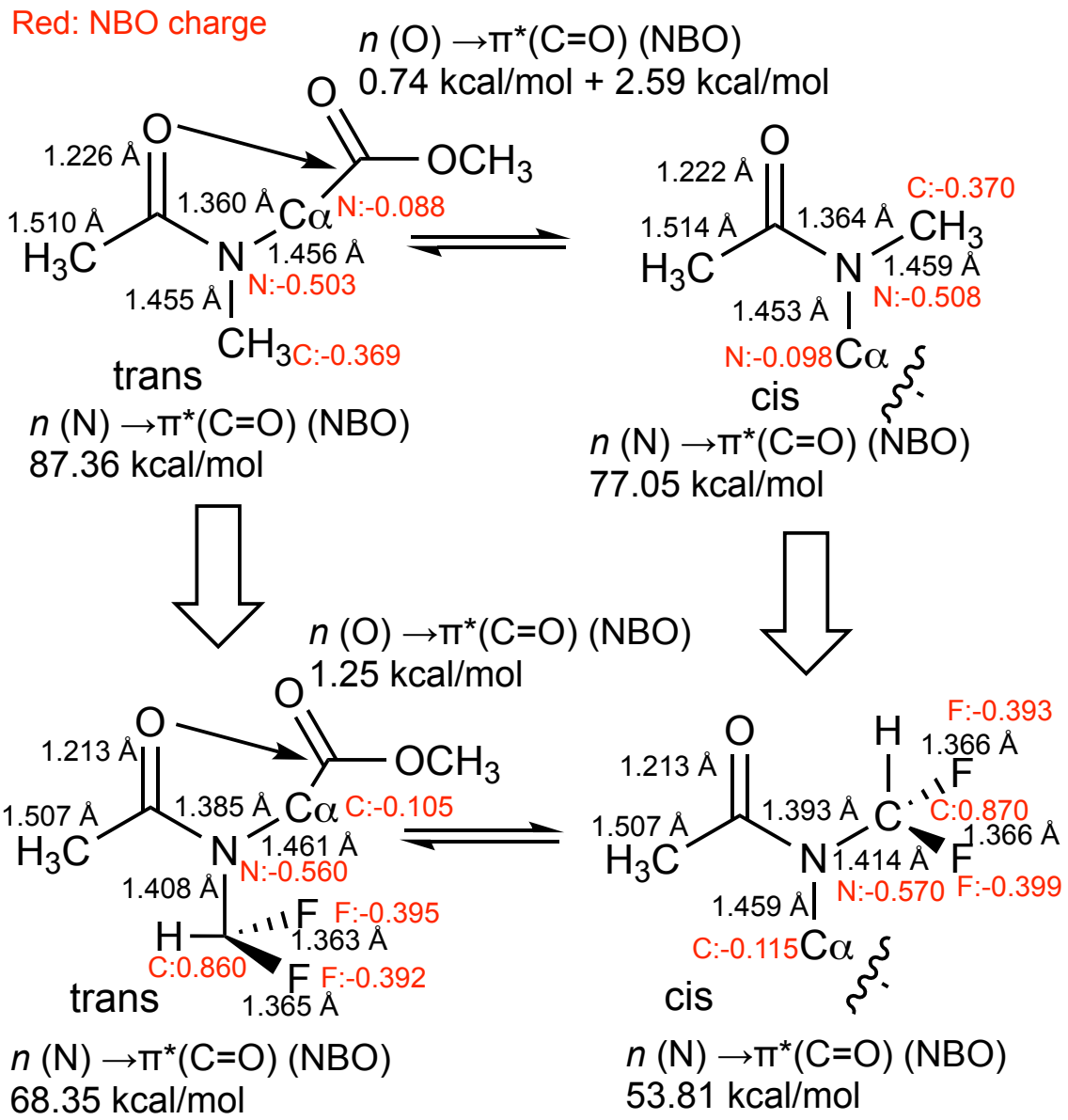


$$\Delta\Delta G_{\text{Ph-CF2H}} = \Delta G_{\text{Ph-CF2H}} - \Delta G_{\text{CH3-CF2H}} - \Delta G_{\text{Ph-CH3}} + \Delta G_{\text{CH3-CH3}}$$

$$= -0.95 - (-1.9) - (-1.5) + (-1.4) \quad \text{(kcal/mol)}$$

$$= 1.05 \text{ (kcal/mol)}$$

Scheme S1. Estimation of the Ph-CF_2H interaction energy.



Scheme S2. DFT optimized bond lengths and NBO amide resonance energies.

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