Electronic Supplementary Material (ESI) for ChemComm.

Sequential *Ortho*-/*Meta*-C–H Functionalizations of *N*-Tosyl-Benzamides for the Synthesis of Polyfunctionalized Arenes

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Supporting Information

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1. General information

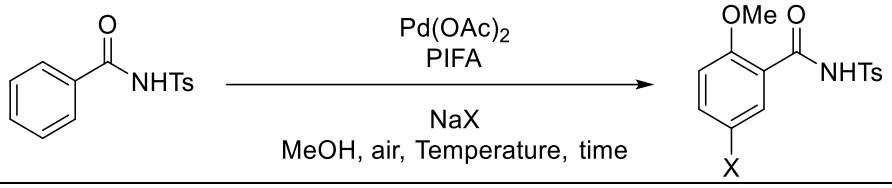
All reactions were carried out using oven-dried glassware and magnetic stirring under air unless otherwise stated. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Analytical thin layer chromatography was performed on silica gel aluminum plates with F-254 indicator and visualized by UV light (254 nm) and/or chemical staining with a *p*-anisaldehyde solution. Purifications were carried on flash column chromatography using 0.040 – 0.063 mm silica or using PTLC (Merck PLC Silica gel 60 F_{254}, 2mm). ^{1}H NMR spectra were recorded on a Bruker DXP 300 MHz spectrometer at 300.1 MHz, ^{13}C NMR spectra at 75.5 MHz, ^{19}F NMR spectra at 282.4 MHz. Chemical shifts (δ) are quoted in parts per millions (ppm) relative to residual solvent peak ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.00 ppm, DMSO-d6: δ_H = 2.50 ppm, δ_C = 39.52 ppm or relative to external $CFCl_3$, δ_F = 0 ppm). Coupling constants (J) are quoted in Hz. The following abbreviations were used to show the multiplicities: s: singlet, br.s: broad singlet, d: doublet, t: triplet, q: quadruplet, dd: doublet of doublet, m: multiplet. High-resolution mass spectrometry (HRMS) was carried out on an electrospray ionization mass spectrometer with a micro-TOF analyzer. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrometer Paragon 100 (ATR). The wave numbers (σ) of recorded IR-signals (ATR) are quoted in cm^{-1}. Melting points were measured on a STUART SMP3 melting point apparatus in open capillaries and were uncorrected.

2. Materials

Anhydrous acetonitrile (CH_3CN), methanol or ethyl acetate were purchased from Acros Organics (Solvents Extra Dry Over Molecular Sieve, AcroSeal®). Toluene and THF were distilled over sodium/benzophenone prior to use. Dichloromethane was distilled over CaH_2 prior to use. Bis-trifluoroacetoxy iodobenzene (PIFA), NaBr, NaCl, CsBr, MeI, DMAP, Et_3N, $Pd(PPh_3)_4$, MeMgBr, $HBF_4.Et_2O$, TFAA, 4-(aminoethyl)benzoic acid hydrochloride and $Pd(OAc)_2$ were purchased from either Fisher Scientific, Sigma Aldrich or Acros Organics. K_2CO_3 and Na_2CO_3 were purchased from Sigma-Aldrich and stored under N_2 atmosphere in a glovebox prior to use. The starting *N*-sulfonylbenzamide derivatives were prepared using sulfonamide derivatives bought from Sigma Aldrich and benzoyl chloride commercially available or made according to the literature procedure.[1] Thianthren oxide (TTO) was prepared following the literature.[2]

3. Optimization studies

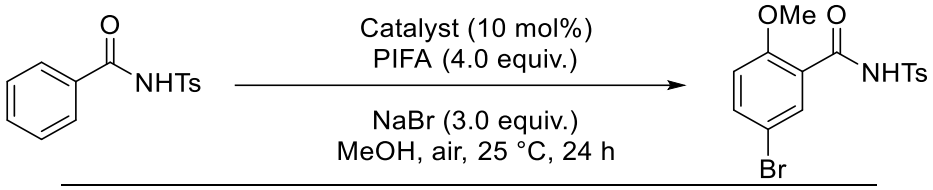
a) Preliminary results



Entry	Catalyst	Oxidant	Halogen salts	Temperature and time	NMR yields[a]
1	$Pd(OAc)_2$ (10 mol%)	PIFA (4.0 equiv.)	NaBr (3.0 equiv.)	25 °C, 24 h	5%
2	$Pd(OAc)_2$ (10 mol%)	PIFA (6.0 equiv.)	NaBr (6.0 equiv.)	25 °C, 24 h	5%
3	$Pd(OAc)_2$ (20 mol%)	PIFA (4.0 equiv.)	NaBr (3.0 equiv.)	25 °C, 24 h	9%
4	**$Pd(OAc)_2$ (10 mol%)**	**PIFA (4.0 equiv.)**	**NaBr (3.0 equiv.)**	**40 °C, 24 h**	**11%**
5	$Pd(OAc)_2$ (10 mol%)	PIFA (4.0 equiv.)	NaBr (3.0 equiv.)	50 °C, 24 h	9%
6	$Pd(OAc)_2$ (10 mol%)	PIFA (4.0 equiv.)	NaBr (3.0 equiv.)	60 °C, 24 h	3%
7	$Pd(OAc)_2$ (10 mol%)	PIFA (4.0 equiv.)	NaI (3.0 equiv.)	25 °C, 24 h	0%

[a] Yields determined by ^{1}H NMR using nitromethane as the internal standard.

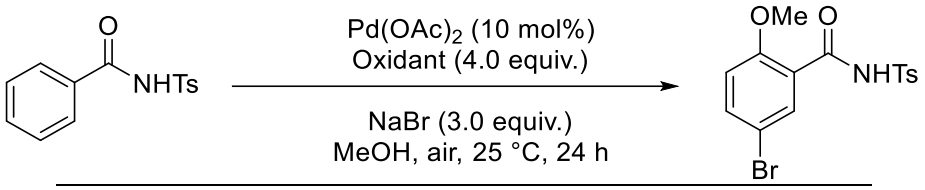
b) Nature of the catalyst



Entry	Catalyst	Yields[a]
1	$Pd(OAc)_2$	5%
2	$Pd(TFA)_2$	7%
3	$PdCl_2$	6%
4	$PdBr_2$	0%
5	$Pd(acac)_2$	0%
6	$PdCl_2(MeCN)_2$	0%

[a] Yields determined by ^{1}H NMR using nitromethane as the internal standard.

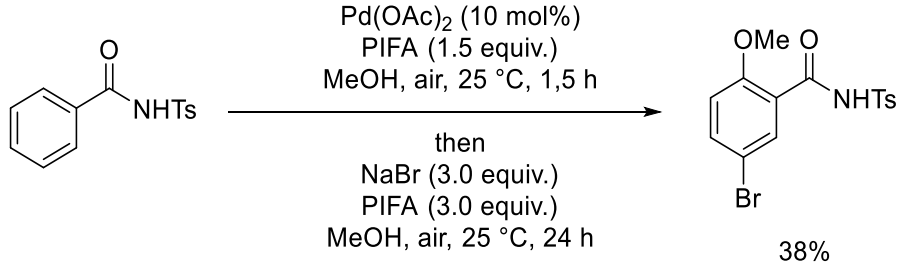
c) Nature of oxidant



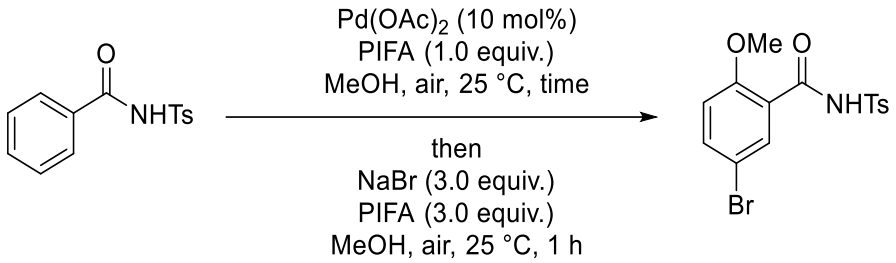
Entry	**Oxidant**	**Yields**[a]
1	PIFA	5%
2	PIDA	0%
3	$K_2S_2O_8$	0%
4	HIO_4	0%
5	Oxone	0%

[a] Yields determined by ^1H NMR using nitromethane as the internal standard.

d) One-pot sequential methoxylation then bromination



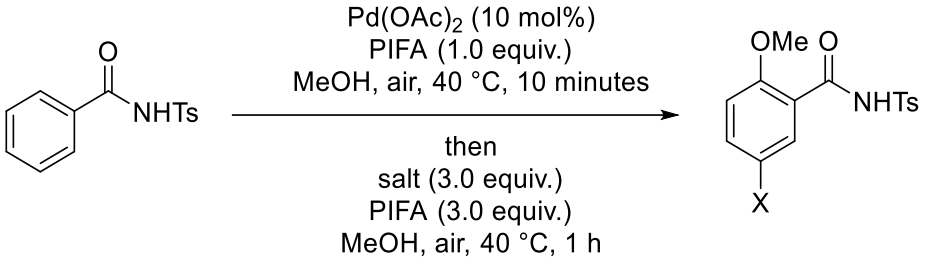
e) Optimization of the reaction time of step 1



Entry	**Time of step 1**	**NMR yield**[a]	**Remarks**
1	90 minutes	42%	38% isolated yield
2	30 minutes	42%	
3	10 minutes	60%	60 % isolated yield
4	1 minutes	14%	
5	10 minutes	47%	1.1 equiv. PIFA and 1.1 equiv. NaBr
6	**10 minutes**	**66%**	Reaction carried out at 40 °C

[a] Yields determined by ^{1}H NMR using nitromethane as the internal standard.

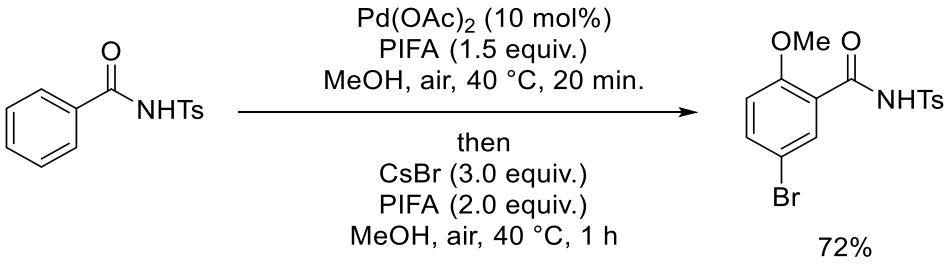
f) Nature of the salt



Entry	**Halogen salt**	**NMR yields**[a]
1	NaBr	66%
2	**KBr**	**70%**
3	LiBr	33%
4	NH_4Br	30%
5	NaCl	50%
6	CsI	44%

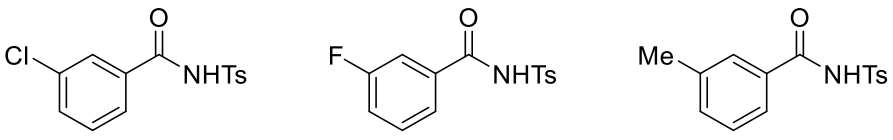
[a] Yields determined by ^1H NMR using nitromethane as the internal standard.

g) Optimal reaction conditions



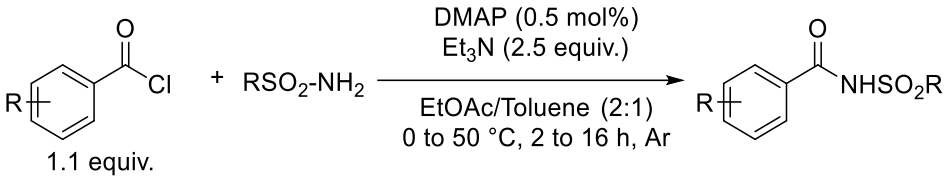
72%

h) Reluctant Substrates



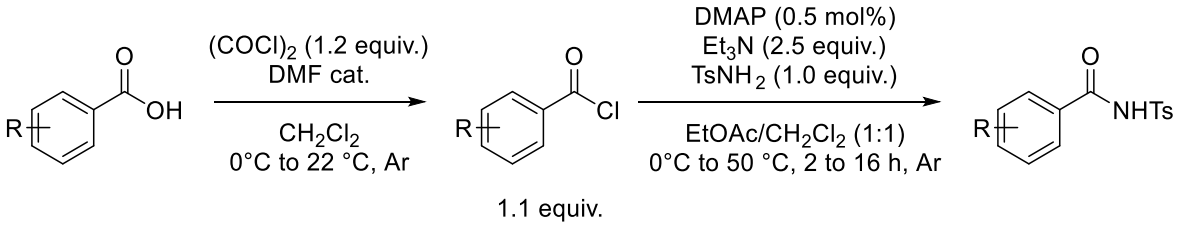
4. General procedures for the synthesis of the starting *N*-arylsulfonamide derivatives.

General procedure A



A round-bottom flask was charged under argon with the sulfonamide (10 mmol, 1.0 equiv.), DMAP (6.1 mg, 0.05 mmol, 0.5 mol%), EtOAc (20 mL) and Et_3N (3.48 mL, 25 mmol, 2.5 equiv.). The mixture was stirred at 0°C for 5 minutes. A solution of commercially available benzoyl chloride (11 mmol, 1.1 equiv.) in Toluene (10 mL) was added at 0 °C slowly. The mixture was then heated up to 50 °C for 2 to 16 h. The reaction mixture was then cooled down to room temperature and HCl 1M (20 mL) was added along with CH_2Cl_2 (40 mL). The aqueous layer was then extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried on $MgSO_4$, filtered, and the solvent was removed under reduced pressure. The crude mixture was then diluted in a minimum of CH_2Cl_2 and the resulting solution was filtered on a silica gel pad to remove an impurity (yellow fraction). The pad was washed 3 times with CH_2Cl_2. The solvent was then evaporated under reduced pressure, and the resulting solid was recrystallized in a minimum amount of hot EtOH.

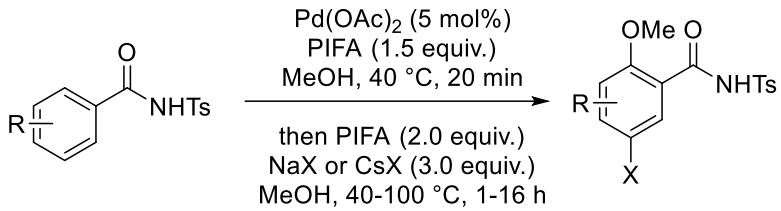
General procedure B



To a solution of benzoic acid (11 mmol, 1.1 equiv.) and a catalytic amount of DMF in dry CH_2Cl_2 (0.2 M) was dropwise added oxalyl chloride (1.03 mL, 12 mmol, 1.2 equiv.) at 0°C under argon. Once the addition completed, the mixture was warmed up to room temperature and the reaction was monitored by TLC. When the starting material was consumed, the solvent was removed under reduced pressure. The crude residue was then dissolved in dry CH_2Cl_2 (2 mL/mmol). The crude mixture was then used directly on the next step without any purification. A round-bottom flask was charged under argon with the *p*-toluenesulfonamide (1.712 g, 10 mmol, 1.0 equiv., 1.0 equiv.), DMAP (6.1 mg, 0.05 mmol, 0.5 mol%), EtOAc (20 mL) and Et_3N (3.48 mL, 25 mmol, 2.5 equiv.). The mixture was stirred at 0°C for 5 minutes. The freshly made solution of benzoyl chloride was added at 0 °C slowly. The mixture was then heated up to 50 °C for 2 to 16 h. The reaction mixture was then cooled down to room temperature and HCl 1M (20 mL) was added along with CH_2Cl_2 (40 mL). The mixture was then extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried on $MgSO_4$, filtered, and evaporated. The crude mixture was then diluted in a minimum of CH_2Cl_2 and the resulting solution was filtered on a silica gel pad to remove an impurity (yellow fraction). The pad was washed 3 times with CH_2Cl_2. The solvent was then evaporated under reduced pressure, and the resulting solid was

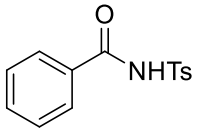
recrystallized in a minimum amount of hot EtOH.

5. General procedure for synthesis of compound 2.



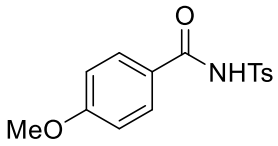
A 10 mL screw-cap tube was loaded with the *N*-arylsulfonamide (0.3 mmol, 1.0 equiv.), PIFA (193.5 mg, 0.45 mmol, 1.5 equiv.), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 0.05 equiv.) and MeOH (3 mL). The tube was screw-capped, and the reaction mixture was stirred at 40 °C for 20 minutes to 1 hour. The cap was then removed and PIFA (258.0 mg, 0.6 mmol, 2.0 equiv.) and NaX or CsX (0.9 mmol, 3.0 equiv.) were added. The tube was screw-capped, and the reaction mixture was then stirred at 40 to 100 °C for 1 to 16 hours. Once the reaction was completed, the reaction mixture was cooled down to room temperature and the solvent was removed under reduced pressure. The crude purified by column chromatograph or was diluted in a minimum amount of CH_2Cl_2 amount and purified on PTLC.

6. Purification and characterization of the starting materials 1.



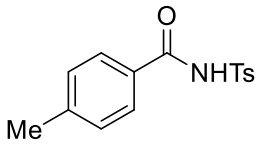
1a

***N*-tosylbenzamide 1a.** Scale = 30 mmol. The reaction was performed following the general procedure A. The product was isolated as a white solid (6.40 g, 23.2 mmol, 78%). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 9.41 (br.s, 1H), 8.05 (d, J = 8.4 Hz, 2H), 7.86 – 7.80 (m, 2H), 7.58 – 7.50 (m, 1H), 7.45 – 7.31 (m, 4H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 164.7, 145.3, 135.5, 133.5, 131.1, 129.7, 128.9, 128.6, 128.0, 21.7. **IR** (neat, cm^{-1}): ν 3307, 1707, 1420, 1333, 1164, 1057, 839, 816, 708, 659, 548. **HRMS** (ESI^-) calcd for $C_{14}H_{12}NO_3S$ *m/z* 274.0538 $[M-H]^-$, Found 274.0538 (Δ -0.7 ppm). **m.p.** 181-182 °C.



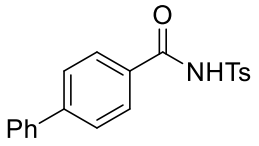
1b

4-Methoxy-*N*-tosylbenzamide 1b. Scale = 10 mmol. The reaction was performed following the general procedure A. The product was isolated along with 9% impurity as a white solid (2.206 g, 7.23 mmol, 72%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.30 (br.s, 1H), 7.92 – 7.83 (m, 4H), 7.42 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 3.80 (s, 3H), 2.38 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 164.6, 163.2, 144.1, 136.8, 130.6, 129.5, 127.8, 123.5, 113.9, 55.6, 21.1. **IR** (neat, cm^{-1}): ν 3230, 1667, 1604, 1436, 1417, 1341, 1163, 1081, 1021, 837, 764, 657, 559. **HRMS** (ESI^-) calcd for $C_{15}H_{14}NO_4S$ *m/z* 304.0644 $[M-H]^-$, Found 304.0632 (Δ -3.9 ppm).



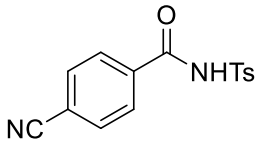
1c

4-Methyl-*N*-tosylbenzamide 1c. Scale = 10 mmol. The reaction was performed following the general procedure A. The product was isolated as a white solid (1.713 g, 5.92 mmol, 59%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.39 (br.s, 1H), 7.89 (d, J = 8.1 Hz, 2H), 7.77 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 7.28 (d, J = 7.28 Hz, 2H), 2.38 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 165.2, 144.2, 143.7, 136.7, 129.5, 129.2, 128.7, 128.5, 127.8, 21.1, 21.1. **IR** (neat, cm^{-1}): ν 3296, 1697, 1422, 1334, 1167, 1068, 894, 828, 817, 744, 657, 562, 543. **HRMS** (ESI^-) calcd for $C_{15}H_{14}NO_3S$ *m/z* 288.0694 $[M-H]^-$, Found 288.0697 (Δ +1.0 ppm). **m.p.** 159-160 °C.



1d

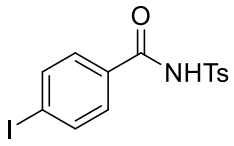
4-Phenyl-*N*-tosylbenzamide 1d. Scale = 10 mmol. The reaction was performed following the general procedure B. The product was isolated as a white solid (2.290 g, 6.52 mmol, 65%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.56 (br.s, 1H), 8.01 – 7.90 (m, 4H), 7.78 (d, J = 8.7 Hz, 2H), 7.75 – 7.69 (m, 2H), 7.52 – 7.37 (m, 5H), 2.39 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ. 165.1, 144.7, 144.3, 138.7, 136.6, 130.2, 129.6, 129.1, 128.5, 127.8, 127.0, 126.8, 21.1. **IR** (neat, cm^{-1}): ν 3287, 1698, 1607, 1425, 1334, 1164, 1060, 837, 816, 739, 663, 541. **HRMS** (ESI-) calcd for $C_{20}H_{16}NO_3S$ *m/z* 350.0851 $[M-H]^-$, Found 350.0851 (Δ 0 ppm). **m.p.** 213-214 °C.



1e

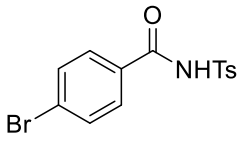
4-Nitrile-*N*-tosylbenzamide 1e. Scale = 10 mmol. The reaction was performed following the general procedure B. The product was isolated as a white solid (1.937 g, 6.45 mmol, 65%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.77 (br.s, 1H), 8.04 – 7.87 (m, 6H), 7.43 (d, J = 8.4 Hz, 2H), 2.38 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ. 164.3, 144.6, 136.2, 135.4, 132.6, 129.7, 129.2, 127.9, 118.0, 115.4, 21.1. **IR** (neat, cm^{-1}): ν 3307, 2236, 1695, 1439, 1342, 1166, 1077, 889, 859, 832, 760, 660, 565, 547. **HRMS** (ESI^-) calcd for $C_{15}H_{11}N_2O_3S$ *m/z* 299.0490 $[M-H]^-$, Found 299.0499 (Δ +3.0 ppm). **m.p.** 217-

218 °C.



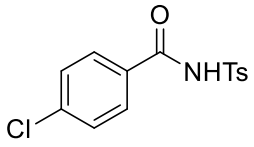
1f

4-Iodo-*N*-tosylbenzamide 1f. Scale = 10 mmol. The reaction was performed following the general procedure B. The product was isolated as a white solid (1.590 g, 3.96 mmol, 40%). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 9.37 (br.s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.7 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 2.44 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 163.8, 145.5, 138.2, 135.2, 130.5, 129.7, 129.2, 128.6, 21.7. **IR** (neat, cm^{-1}): ν 3212, 1698, 1581, 1432, 1330, 1162, 1068, 1002, 827, 749, 659, 562, 545. **HRMS** (ESI$^-$) calcd for $C_{14}H_{11}NO_3SI$ *m/z* 399.9504 [M-H]$^-$, Found 399.9519 (Δ +3.8 ppm). **m.p.** 198-199 °C.



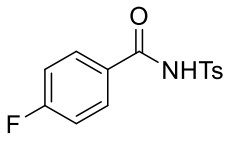
1g

4-Bromo-*N*-tosylbenzamide 1g. Scale = 11 mmol. The reaction was performed following the general procedure B. The product was isolated as a white solid (1.360 g, 3.85 mmol, 35%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.62 (br.s, 1H), 7.90 (d, J = 8.1 Hz, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.1 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 164.5, 144.3, 136.4, 131.6, 130.6, 130.4, 129.5, 127.8, 127.3, 21.0. **IR** (neat, cm^{-1}): ν 3212, 1784, 1699, 1586, 1435, 1334, 1243, 1163, 1069, 1006, 884, 828, 739, 660, 545. **HRMS** (ESI$^-$) calcd for $C_{14}H_{11}NO_3S^{81}Br$ *m/z* 353.9623 [M-H]$^-$, Found 353.9626 (Δ +0.8 ppm). **m.p.** 193-194 °C.



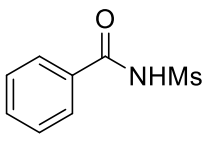
1h

4-Chloro-*N*-tosylbenzamide 1h. Scale = 10 mmol. The reaction was performed following the general procedure B. The product was isolated as a white solid (1.212 g, 3.92 mmol, 39%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.61 (br.s, 1H), 7.93 – 7.85 (m, 4H), 7.54 (d, J = 8.7 Hz, 2H), 7.42 (d, J = 8.4 Hz, 2H), 2.37 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 164.5, 144.4, 138.3, 136.5 130.4, 130.3, 129.6, 128.8, 127.8, 21.1. **IR** (neat, cm^{-1}): ν 3321, 1786, 1697, 1591, 1427, 1336, 1239, 1164, 1059, 1011, 838, 809, 747, 657, 546. **HRMS** (ESI$^-$) calcd for $C_{14}H_{11}NO_3S^{35}Cl$ *m/z* 308.0148 [M-H]$^-$, Found 308.0138 (Δ -3.2 ppm). **m.p.** 196-197 °C.



1i

4-Fluoro-*N*-tosylbenzamide 1i. Scale = 10 mmol. The reaction was performed following the general procedure A. The product was isolated as a white solid (1.53 g, 5.2 mmol, 52%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.55 (brs, 1H), 8.00 – 7.86 (m, 4H), 7.46 –7.39 (m, 2H), 7.36 – 7.26 (m, 2H), 2.38 (s, 3H). **^{19}F NMR** (282.4 MHz, DMSO-d_6) δ -104.6 (s). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 164.9 (d, J = 251.2 Hz), 164.3, 144.3, 136.5, 131.5 (d, J = 9.5 Hz), 129.6, 128.0 (d, J = 2.9 Hz), 127.8, 115.7 (d, J = 22.0 Hz), 21.1. **IR** (neat, cm^{-1}): ν 3281, 1702, 1601, 1433, 1337, 1236, 1166, 1067, 756, 665, 549. **HRMS** (ESI$^-$) calcd for $C_{14}H_{11}NO_3FS$ *m/z* 292.0444 [M-H]$^-$, Found 292.0435 (Δ -3.1 ppm). **m.p.** 165-166 °C.

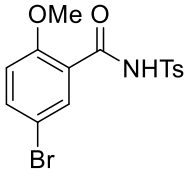


1j

***N*-Mesylbenzamide 1j.** Scale = 20 mmol. The reaction was performed following the general procedure A. The product was isolated as a white solid (2.221 g, 11.15 mmol, 56%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.17 (br.s, 1H), 7.98 – 7.91 (m, 2H), 7.69 – 7.61 (m, 1H), 7.57 – 7.48 (m, 2H), 3.38 (s, 3H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 166.5, 133.3, 131.7, 128.6, 128.5, 41.4. **IR** (neat, cm^{-1}): ν 3233, 1677, 1454, 1436, 1334, 1322, 1164, 1065,

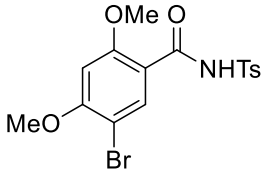
962, 830, 711, 516. **HRMS** (ESI$^-$) calcd for $C_8H_8NO_3S$ *m/z* 198.0225 [M-H]$^-$, Found 198.0217 (Δ -4.0 ppm). **m.p.** 149-150 °C.

7. Purification and characterization of final products 2.



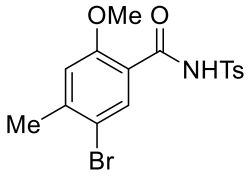
2a

5-bromo-2-methoxy-N-tosylbenzamide 2a. Reaction performed at 40 °C for 20 minutes then 1 hour using CsBr as the salt. The product was purified as a white solid (82.5 mg, 0.215 mmol, 72%) by column chromatography using Petroleum ether/Ethyl acetate/MeOH (17:2:1) as the eluent. (R_f in Petroleum ether/Ethyl acetate/MeOH 17:2:1 = 0.50). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.23 (br.s, 1H), 8.18 (d, *J* = 2.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.60 (dd, *J* = 8.7, 2.7 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 1H), 4.04 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ. 160.9, 156.8, 145.0, 137.5, 135.6, 135.2, 129.5, 128.7, 120.5, 114.4, 113.6, 56.9, 21.7. **IR** (neat, cm^{-1}): *v* 3266, 1682, 1594, 1449, 1342, 1273, 1163, 1017, 854, 811, 522, 536. **HRMS** (ESI$^-$) calcd for $C_{15}H_{13}NO_4S^{81}Br$ *m/z* 383.9728 [M-H]$^-$, Found 383.9714 (Δ -3.6 ppm). **m.p.** 161-162 °C. Note that the reaction was carried out on a 9.08 mmol scale using NaBr as the salt for 30 minutes then 2 hours at 40 °C. The product was obtained by recrystallization in minimum hot EtOH as a white solid (2.12 g, 5.53 mmol, 61%).



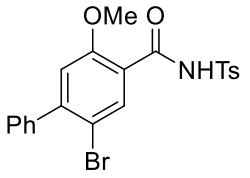
2b

5-Bromo-2,4-dimethoxy-*N*-tosylbenzamide 2b. Reaction performed at 40 °C for 20 minutes then 60 °C for 16 hours using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (64.5 mg, 0.156 mmol, 52%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.45). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.09 (br.s, 1H), 8.21 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 6.44 (s, 1H), 4.06 (s, 3H), 3.95 (s, 3H), 2.42 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.8, 160.8, 158.7, 144.9, 136.7, 135.9, 129.4, 128.7, 112.4, 104.1, 95.7, 56.8, 56.6, 21.7. **IR** (neat, cm^{-1}): *v* 3280, 2923, 1677, 1592, 1427, 1341, 1276, 1163, 848, 817, 531. **HRMS** (ESI$^-$) calcd for $C_{16}H_{15}NO_5S^{81}Br$ *m/z* 413.9834 [M-H]$^-$, Found 413.9823 (Δ -2.7 ppm). **m.p.** 189-190 °C.



2c

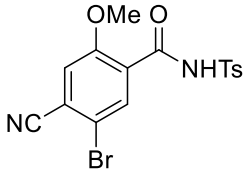
5-Bromo-4-methyl-2-methoxy-*N*-tosylbenzamide 2c. Reaction performed at 40 °C for 20 minutes then 60 °C for 1 hour using NaBr as the salt. The product was purified by PTLC (2 mm) along with 6% of an impurity as a white solid (78.6 mg, 0.198 mmol, 66%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.60). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.21 (br.s, 1H), 8.18 (s, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 6.86 (s, 1H) 4.02 (s, 3H), 2.44 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 161.0, 156.6, 145.7, 144.9, 135.8, 135.8, 129.4, 128.7, 118.0, 116.9, 114.1, 56.7, 23.6, 21.7. **IR** (neat, cm^{-1}): *v* 3281, 1683, 1601, 1426, 1341, 1669, 1158, 1079, 812, 659, 530. **HRMS** (ESI$^-$) calcd for $C_{16}H_{15}NO_4S^{81}Br$ *m/z* 397.9885 [M-H]$^-$, Found 397.9897 (Δ +3.0 ppm). **m.p.** 163-164 °C.



2d

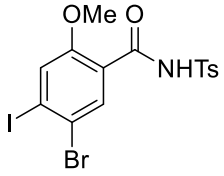
2-Bromo-4-phenyl-5-methoxy-*N*-tosylbenzamide 2d. Reaction performed at 40 °C for 20 minutes then 60 °C for 16 hours using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (78.6 mg, 0.198 mmol, 66%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.72). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.25 (brs, 1H), 8.33 (s, 1H), 8.05 (d, *J* = 8.4 Hz,

2H), 7.48 – 7.32 (m, 7H), 6.95 (s, 1H) 4.04 (s, 3H), 2.44 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.8, 156.5, 148.9, 145.0, 139.7, 136.8, 135.7, 129.5, 128.9, 128.7, 128.6, 128.2, 119.1, 114.7, 56.9, 21.7. One signal for a carbon was overlapped. **IR** (neat, cm^{-1}): *v* 3260, 1674, 1594, 1405, 1346, 1175, 1155, 866, 660, 543. **HRMS** (ESI^-) calcd for $C_{21}H_{17}NO_4S^{81}Br$ *m/z* 460.0041 $[M-H]^-$, Found 460.0046 (Δ +1.1 ppm). **m.p.** 178-179 °C.



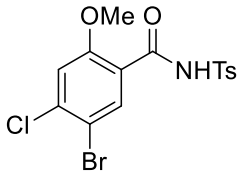
2e

5-Bromo-4-cyano-2-methoxy-*N*-tosylbenzamide 2e. Reaction performed at 40 °C for 1 hour then 100 °C for 16 hours using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (78.5 mg, 0.192 mmol, 64%), using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.40). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.15 (br.s, 1H), 8.16 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.28 – 7.26 (m, 1H), 4.10 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.7, 157.5, 145.3, 135.4, 133.6, 129.6, 128.7, 125.2, 122.9, 117.9, 117.3, 115.3, 57.1, 21.7. **IR** (neat, cm^{-1}): *v* 3277, 2234, 1687, 1423, 1345, 1167, 878, 812, 664, 542. **HRMS** (ESI^-) calcd for $C_{16}H_{13}N_2O_4S$ *m/z* 329.0596 $[M-Br]^+$, Found 329.0585 (Δ -3.3 ppm). **m.p.** 190-191 °C.



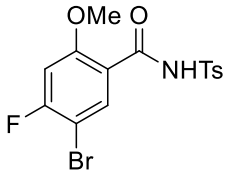
2f

5-Bromo-4-iodo-2-methoxy-*N*-tosylbenzamide 2f. Reaction performed at 40 °C for 20 minutes then 60 °C for 4 hours using NaBr as the salt. The product was purified by PTLC (2 mm) as a pale pink solid (75.5 mg, 0.148 mmol, 49%) using Petroleum ether/Ethyl acetate/MeOH (15:4:1) as the eluent. (R_f in Petroleum ether/Ethyl acetate/MeOH 15:4:1 = 0.57). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.07 (brs, 1H), 8.19 (s, 1H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.47 (s, 1H), 7.35 (d, *J* = 8.1 Hz, 2H), 4.04 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.5, 155.8, 145.2, 135.5, 135.3, 129.5, 128.8, 123.9, 122.5, 108.9, 57.2, 21.7. **IR** (neat, cm^{-1}): *v* 3259, 1695, 1578, 1443, 1341, 1235, 1156, 1079, 1005, 864, 820, 805, 679, 551, 534. **HRMS** (ESI^-) calcd for $C_{15}H_{12}NO_4S^{81}BrI$ *m/z* 509.8695 $[M-H]^-$, Found 509.8689 (Δ -1.2 ppm). **m.p.** 183-184 °C.



2g

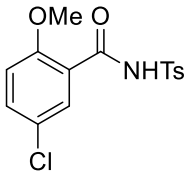
5-Bromo-4-chloro-2-methoxy-*N*-tosylbenzamide 2g. Reaction performed at 40 °C for 20 minutes then 60 °C for 1 hour using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (68.4 mg, 0.164 mmol, 55%) using Petroleum ether/Ethyl acetate/MeOH (15:4:1) as the eluent. (R_f in Petroleum ether/Ethyl acetate/MeOH 15:4:1 = 0.35). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.07 (br.s, 1H), 8.28 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 2H), 7.11 (s, 1H), 4.05 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.2, 156.7, 145.2, 140.9, 137.1, 135.5, 129.5, 128.8, 118.9, 114.9, 114.1, 57.2, 21.7. **IR** (neat, cm^{-1}): *v* 3289, 1679, 1590, 1426, 1341, 1203, 1158, 1080, 803, 660, 543, 527. **HRMS** (ESI^-) calcd for $C_{15}H_{12}NO_4S^{35}Cl^{79}Br$ *m/z* 417.9359 $[M-H]^-$, Found 417.9354 (Δ -1.2 ppm). **m.p.** 174-175 °C.



2h

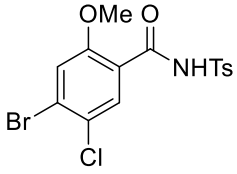
5-Bromo-4-fluoro-2-methoxy-*N*-tosylbenzamide 2h. Reaction performed at 40 °C for 20 minutes then 60 °C for 16 hour using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (87.5 mg, 0.218 mmol, 73%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.35). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.05 (br.s, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 9.6 Hz, 1H), 4.04 (s,

3H), 2.43 (s, 3H). **^{19}F NMR** (282.4 MHz, $CDCl_3$) δ -95.3 (s). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.5 (d, J = 256.3 Hz), 160.2, 158.2 (d, J = 9.6 Hz), 145.1, 137.6 (d, J = 3.1 Hz), 135.6, 129.5, 128.7, 116.6 (d, J = 3.3 Hz), 101.4 (d, J = 21.6 Hz), 101.1 (d, J = 27.2), 57.3, 21.7. **IR** (neat, cm^{-1}): *v*. 3280, 1682, 1604, 1436, 1342, 1282, 1165, 1082, 829, 810, 661, 525. **HRMS** (ESI^-) calcd for $C_{15}H_{12}NO_4FS^{81}Br$ *m/z* 401.9634 $[M-H]^-$, Found 401.9633 (Δ -0.2 ppm). **m.p.** 166-167 °C.



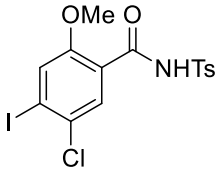
2i

5-Chloro-2-methoxy-*N*-tosylbenzamide 2i. Reaction performed at 40 °C for 20 minutes then 60 °C for 1 hour using NaCl as the salt. The product was purified by column chromatography as a white solid (76.5 mg, 0.226 mmol, 75%) using Petroleum ether/Ethyl acetate/MeOH (15:4:1) as the eluent. (R_f in Petroleum ether/Ethyl acetate/MeOH 15:4:1 = 0.35). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.26 (br.s, 1H), 8.06 – 8.01 (m, 3H), 7.46 (dd, J = 9.0, 2.7 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 4.04 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 161.0, 156.3, 145.0, 135.6, 134.6, 132.3, 129.5, 128.7, 127.3, 120.1, 113.2, 56.9, 21.7. **IR** (neat, cm^{-1}): *v* 3267, 1678, 1443, 1342, 1206, 1163, 1140, 1017, 857, 812, 657, 540, 520. **HRMS** (ESI^-) calcd for $C_{15}H_{13}NO_4S^{35}Cl$ *m/z* 338.0254 $[M-H]^-$, Found 338.0262 (Δ +1.8 ppm). **m.p.** 168-169 °C. Note that a reaction was carried out on a 20 mmol using NaCl as the salt for 30 minutes at 40 °C then 2 hours at 60 °C. The product was obtained by recrystallization in a minimum amount of hot EtOH as a white solid (3.47 g mg, 10.21 mmol, 51%).



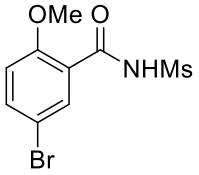
2j

4-Bromo-5-chloro-2-methoxy-*N*-tosylbenzamide 2j. Reaction performed at 40 °C for 20 minutes then 60 °C for 4 hours using NaCl as the salt. The product was purified by PTLC (2 mm) as a white solid (68.0 mg, 0.163 mmol, 54%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.45). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.08 (br.s, 1H), 8.11 (s, 1H), 8.02 (d, J = 8.4, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.28 – 7.24 (m, 1H), 4.05 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.4, 155.8, 145.2, 135.5, 133.4, 129.5, 129.2, 128.8, 128.1, 119.4, 117.4, 57.3, 21.7. **IR** (neat, cm^{-1}): *v* 3293, 1682, 1592, 1429, 1341, 1160, 1082, 1022, 804, 660, 543, 535. **HRMS** (ESI^-) calcd for $C_{15}H_{12}NO_4S^{37}Cl^{81}Br$ *m/z* 417.9338 $[M-H]^-$, Found 417.9333 (Δ -1.2 ppm). **m.p.** 186-187 °C.



2k

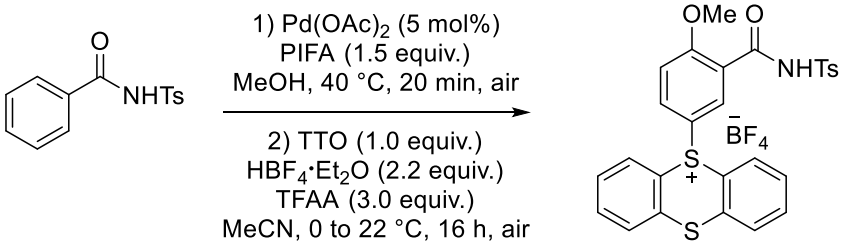
4-iodo-5-chloro-2-methoxy-*N*-tosylbenzamide 2k. Reaction performed at 40 °C for 20 minutes then 60 °C for 16 hours using NaCl as the salt. The product was purified by PTLC (2 mm) as a white solid (79.5 mg, 0.171 mmol, 57%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.50). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.09 (brs, 1H), 8.06 – 8.00 (m, 3H), 7.47 (s, 1H), 7.34 (d, J = 8.1 Hz, 2H), 4.04 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 160.6, 155.2, 145.2, 135.5, 132.4, 131.8, 129.5, 128.7, 123.7, 120.3, 105.6, 57.3, 21.7. **IR** (neat, cm^{-1}): *v* 3278, 1677, 1584, 1427, 1341, 1247, 1160, 1080, 913, 863, 803, 659, 542, 523. **HRMS** (ESI^-) calcd for $C_{15}H_{12}NO_4S^{35}ClI$ *m/z* 465.9191 $[M-H]^-$, Found 465.9187 (Δ -0.9 ppm). **m.p.** 180-181 °C.



2l

5-Bromo-2-methoxy-*N*-(methylsulfonyl)benzamide 2l. Reaction performed at 40 °C for 20 minutes 60 °C for 1 hour using NaBr as the salt. The product was purified by PTLC (2 mm) as a white solid (64.4 mg, 0.210 mmol, 70%) using Petroleum ether/CH_2Cl_2/MeOH (10:9:1) as the eluent. (R_f in Petroleum ether/CH_2Cl_2/MeOH 10:9:1 = 0.4). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.08 (br.s, 1H), 8.28 (br.s, 1H), 7.66 (dd, J = 8.7, 2.7 Hz, 1H), 6.94 (d, J = 9.0 Hz, 1H), 4.03 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.1, 156.9, 137.9, 135.2, 120.2, 114.5, 113.7, 56.9, 41.7. **IR** (neat, cm^{-1}): v 3253, 1680, 1443, 1340, 1272, 1160, 1136, 968, 853, 495. **HRMS** (ESI$^-$) calcd for $C_9H_9NO_4S^{81}Br$ m/z 307.9415 [M-H]$^-$, Found 307.9416 (Δ +0.3 ppm). **m.p.** 123-124°C.

8. Synthesis of compound 3

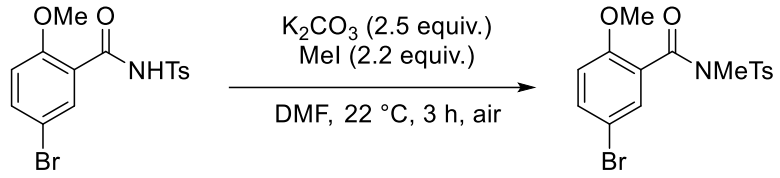


1a **3**, 82%

A 10 mL round bottom flask was loaded under air with **1a** (138 mg, 0.5 mmol, 1.0 equiv.), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 0.05 equiv.), and PIFA (323 mg, 0.75 mmol, 1.5 equiv.). MeOH (5 mL) was added and the reaction was stirred at 40 °C for 20 minutes. The solvent was then evaporated under vacuum and dry MeCN (3 mL) was added. The mixture was then cooled down to 0 °C, TTO (116 mg, 0.5 mmol, 1.0 equiv.) was then added under air followed by HBF_4•Et_2O (150 µL, 1.1 mmol, 2.2 equiv.) and the reaction took a deep purple color. TFAA (278 µL, 2.0 mmol, 4.0 equiv.) was then added and the reaction took a deep blue color purple. The mixture was then stirred at room temperature for 16 h. The reaction was then diluted with CH_2Cl_2 (20 mL) and a saturated aqueous $NaHCO_3$ solution (20 mL) was added. The aqueous layer was then extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were washed with an aqueous $NaBF_4$ solution (5% w/w, 2 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvents were evaporated under reduced pressure. The crude residue was then purified by column flash chromatography using CH_2Cl_2/Methanol (95/5) as the eluent (R_f = 0.1), then dissolved in 3 mL of CH_2Cl_2 followed by 40 mL of Et_2O. A white precipitate was formed, and the suspension was filtered to give the desired product.

2-Methoxy-*N*-tosylbenzamide derived thianthrenium salt 3. The product was isolated as an off-white solid (277 mg, 0.407 mmol, 81%). (R_f in CH_2Cl_2/MeOH 95:5 = 0.1). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 8.39 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 8.1 Hz, 2H), 7.81 – 7.58 (m, 7H), 7.50 – 7.42 (m, 1H), 7.30 – 7.15 (m, 3H), 4.94, (br.s, 1H), 3.96 (s, 3H), 2.36 (s, 3H). **^{19}F NMR** (282.4 MHz, $CDCl_3$) δ -151.1 (s), -151.2 (s). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 161.0, 160.9, 144.9, 136.2, 135.7, 135.0, 134.8, 134.7, 131.4, 130.4, 130.3, 129.5, 128.4, 121.9, 118.6, 115.3, 57.6, 21.5. One signal for a carbon was overlapped. **IR** (neat, cm^{-1}): v 2978, 1688, 1593, 1445, 1282, 1167, 1056, 850, 816, 764, 656, 545. **HRMS** (ESI$^+$) calcd for $C_{27}H_{22}NO_4S_3$ m/z 520.0711 [M-BF_4]$^+$, Found 520.0711 (Δ +0 ppm). **m.p.** 130-131 °C.

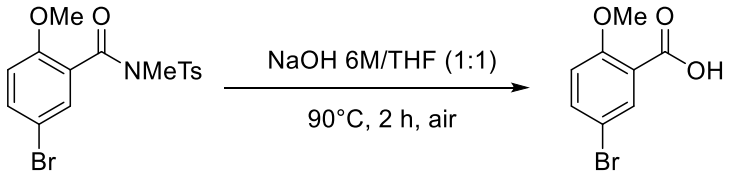
9. Post-functionalization reactions



2a **4**, 70%

A 50 mL round bottom flask was loaded with **2a** (768 mg, 2.0 mmol, 1.0 equiv.), K_2CO_3 (691 mg, 5.0 mmol, 2.5 equiv.) and DMF (10 mL) under air. MeI (274 µL, 4.4 mmol, 2.2 equiv.) was added. The reaction mixture was stirred at room temperature for 3 hours. EtOAc (20 mL) and a saturated solution of NaCl (20 mL) were then added. The aqueous layer was extracted with EtOAc (3×20 mL), the organic layers were washed with distilled water (3×20 mL). The combined organic layers were then dried on $MgSO_4$, filtered on cotton. The solvents were removed under reduced pressure. The product was then recrystallized in a minimum amount of hot ethanol. The solid was then filtered and washed with a minimum amount of ice-cold ethanol to provide the expected compound **4** as a white solid (559 mg, 1,408 mmol, 70%).

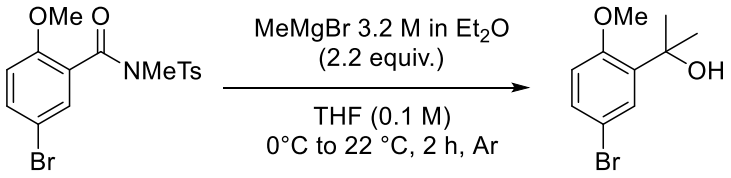
5-Bromo-2-methoxy-*N*-methyl-*N*-tosylbenzamide 4. ^{1}H NMR (300.1 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 2H), 7.45 (dd, J = 9.0, 2.4 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 7.16 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 9.0 Hz, 1H), 3.73 (s, 3H), 3.30 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ. 167.3, 155.0, 145.0, 135.7, 134.3, 130.8, 129.5, 128.1, 126.8, 112.8, 112.5, 55.9, 33.7, 21.7. **IR** (neat, cm^{-1}): *v*. 3010, 2955, 1682, 1594, 1348, 1282, 1163, 1023, 828, 809, 773, 689, 590, 545, 531. **HRMS** (AP^+) calcd for $C_{16}H_{17}NO_4S^{81}Br$ *m/z* 400.0041 $[M+H]^+$, Found 400.0038 (Δ -0.7 ppm). **m.p.** 137-138 °C.



4 **6**, 66%

A 50 mL round bottom flask was loaded under air with **4** (199 mg, 0.5 mmol, 1.0 equiv.), THF (2.5 mL) and an aqueous solution of NaOH 6M (2.5 mL). The reaction mixture was stirred for 2 hours at 90 °C. When the reaction was completed, the reaction was acidified with an aqueous solution of HCl 3M until pH = 1. The aqueous was extracted with EtOAc (3×10 mL). The combined organic layers were combined, dried over $MgSO_4$, filtered through cotton and the solvents were evaporated under reduced pressure. The crude residue was then purified by column chromatography using petroleum ether/ethyl acetate (7:3) as the eluent.

5-Bromo-2-methoxybenzoic acid 6. The product was isolated as a white solid (76.1 mg, 0.33 mmol, 66%). (R_f in Petroleum ether/Ethyl acetate 7:3 = 0.1). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 8.25 (d, J = 2.7 Hz, 1H), 7.65 (dd, J = 8.7, 2.7 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 4.06 (s, 3H). The OH from the carboxylic acid could not be found. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 164.4, 157.2, 137.6, 136.1, 119.3, 114.5, 113.6, 57.0. **IR** (neat, cm^{-1}): ν 2921, 2852, 1541, 1704, 1565, 1486, 1240, 1013, 900, 813, 657. **HRMS** (ESI^-) calcd for $C_8H_6O_3{}^{79}Br$ *m/z* 228.9500 $[M-H]^-$, Found 228.9501 (Δ +0.4 ppm). **m.p.** 130-131 °C.

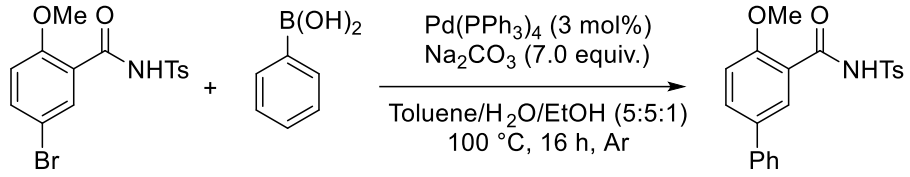


4 **8**, 90%

A 10 mL screw-cap tube was loaded under Argon with **4** (76.8 mg, 0.2 mmol, 1.0 equiv.) and THF (2 mL). A solution of methyl magnesium bromide 3.2 M in diethyl ether (138 µL, 0.44 mmol, 2.2 equiv.) was then added slowly at 0 °C. The reaction mixture was stirred at room temperature for 2 hours under argon. The mixture was then quenched with water (10 mL). The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered through cotton and the solvents were evaporated under reduced pressure. The crude residue was then purified by column chromatography using petroleum ether/ethyl acetate (95/5) as the eluent. The product was obtained as a white solid (44.1 mg, 0.180 mmol, 90%).

2-(5-bromo-2-methoxyphenyl)propan-2-ol 8. (R_f in Petroleum ether/Ethyl acetate 95:5 = 0.23). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 7.38 (d, J = 2.4 Hz, 1H), 7.26 (dd, J = 8.7, 2.4 Hz, 1H), 6.72 (d, J = 8.7 Hz, 1H), 3.81 (s, 3H), 1.51 (s, 6H). The signal from the OH group was not observed. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 155.9, 138.0, 130.6, 128.9, 113.5, 112.9, 72.3, 55.5, 29.4. **IR** (neat, cm^{-1}): ν 3285, 2962, 2934, 1692, 1457, 1360, 1236, 1175, 1072, 871, 809, 626. **HRMS** (AP^+) calcd for $C_{10}H_{12}O^{81}Br$ *m/z* 229.0051 $[M-H_2O]^+$, Found 229.0040 (Δ -4.8 ppm). **m.p.** 72-73 °C.

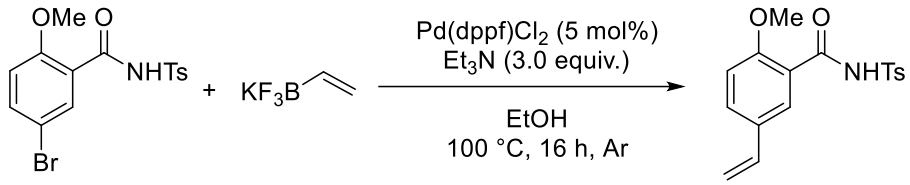
Suzuki coupling



2a **9**, 74%

A 10 mL dried tube was loaded under Argon with **2a** (76.5 mg, 0.2 mmol, 1.0 equiv.), phenylboronic acid (27.9 mg, 0.22 mmol, 1.1 equiv.), Na_2CO_3 (148.4 mg, 1.4 mmol, 7.0 equiv.) and $Pd(PPh_3)_4$ (7.0 mg, 0.006 mmol, 3 mol%) toluene (1 mL), water (1 mL) and 0.2 EtOH (0.2 mL) were added. The mixture was then stirred at 100 °C for 16 h. The reaction was then cooled down to room temperature. CH_2Cl_2 (10 mL) and water (10 mL) were then added. The aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered through cotton and the solvents were evaporated under reduced pressure. The crude residue was then purified on column chromatography (h= 13 cm, w= 1.5 cm) using petroleum ether/ethyl acetate (7:3) as the eluant.

4-methoxy-5-phenyl-*N*-tosylbenzamide 9. The product was obtained as an off-white solid (56.2 mg, 0.147 mmol, 74%). (R_f in Petroleum ether/Ethyl Acetate 7:3 = 0.3). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.39 (br.s, 1H), 8.33 (d, J = 2.4 Hz, 1H), 8.09 – 8.04 (m, 2H), 7.75 (dd, J = 8.7, 2.4 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.44 – 7.29 (m, 5H), 7.08 (d, J = 8.7 Hz, 1H), 4.09 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.2, 157.1, 144.8, 138.9, 135.9, 134.8, 133.3, 131.0, 129.4, 128.8, 128.7, 127.5, 126.6, 118.9, 112.2, 56.7, 21.6. **IR** (neat, cm^{-1}): *v* 3292, 1688, 1442, 1426, 1345, 1267, 1169, 1083, 866, 761, 533. **HRMS** (ESI^-) calcd for $C_{21}H_{18}NO_4S$ *m/z* 380.0957 $[M-H]^-$, Found 380.0954 (Δ -0.8 ppm). **m.p.** 166-167 °C.

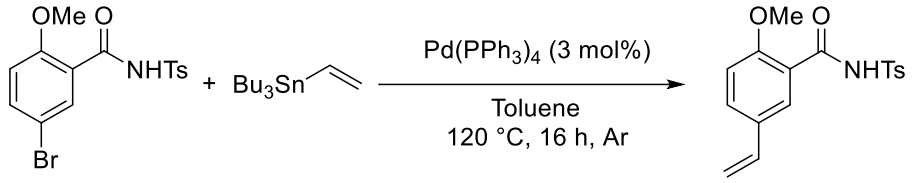


2a (1.1 equiv.) **10**, 62%

A 10 mL dried tube was loaded under Argon with **2a** (114.9 mg, 0.3 mmol, 1.0 equiv.), potassium vinyltrifluoroborate (44.2 mg, 0.33 mmol, 1.1 equiv.), $Pd(dppf)Cl_2$ (11.0 mg, 0.009 mmol, 3 mol%) and EtOH (2 mL). The mixture was then stirred at 100 °C for 16 h. The reaction was then allowed to cool down to room temperature and the crude residue was then purified on column chromatography (h= 11 cm, w= 1.5 cm) using petroleum ether/ethyl acetate (8:2) as the eluant. The product was obtained as a brown solid (62.1 mg, 0.187 mmol, 62%).

2-Methoxy-*N*-tosyl-5-vinylbenzamide 10. (R_f in Petroleum ether/Ethyl acetate 8:2 = 0.27). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.34 (brs, 1H), 8.10 – 8.00 (m, 3H), 7.52 (dd, J = 8.7, 2.4 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.59 (dd, J = 17.7, 11.1 Hz, 1H), 5.65 (d, J = 18.0 Hz, 1H), 5.19 (d, J = 11.1 Hz, 1H), 4.03 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.2, 157.2, 144.8, 135.9, 134.7, 132.4, 131.6, 130.4, 129.4, 128.7, 118.7, 114.1, 111.9, 56.6, 21.7. **IR** (neat, cm^{-1}): *v*. 3264, 2955, 2922, 1685, 1598, 1438, 1343, 1164, 1079, 868, 655, 538. **HRMS** (ESI^-) calcd for $C_{17}H_{16}NO_4S$ *m/z* 330.0800 $[M-H]^-$, Found 330.0788 (Δ -3.6 ppm). **m.p.** 104-105 °C.

Stille coupling

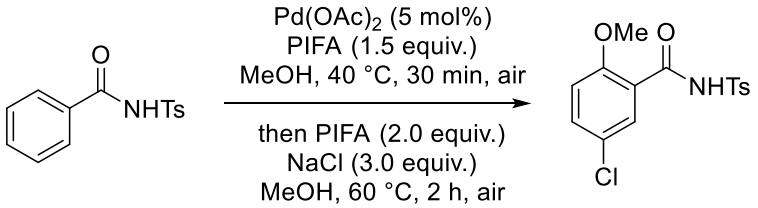


2a (1.0 equiv.) **10**, 95%

A 10 mL dried tube was loaded under Argon with **2a** (153.2 mg, 0.4 mmol, 1.0 equiv.), tributyl(vinyl)stannane (122 µL, 0.4 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (9.2 mg, 0.012 mmol, 3 mol%) and toluene (2 mL). The mixture was then stirred at 120 °C for 16 h. The reaction was then allowed to cool down to room temperature and the crude residue was then purified on column chromatography (h= 15 cm, w= 1.5 cm) using petroleum ether/ethyl acetate (8:2) as the eluant. The product **10** was obtained as a brown solid (126.2 mg, 0.381 mmol, 95%).

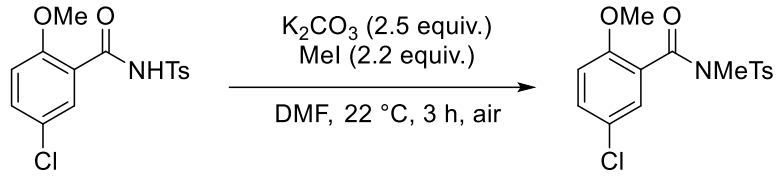
2-Methoxy-*N*-tosyl-5-vinylbenzamide 10. (R_f in Petroleum ether/Ethyl acetate 8:2 = 0.27). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 10.34 (br.s, 1H), 8.10 – 8.00 (m, 3H), 7.52 (dd, J = 8.7, 2.4 Hz, 1H), 7.32 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 8.7 Hz, 1H), 6.59 (dd, J = 17.4, 11.1 Hz, 1H), 5.65 (d, J = 17.7 Hz, 1H), 5.19 (d, J = 11.1 Hz, 1H), 4.03 (s, 3H), 2.41 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 162.2, 157.2, 144.8, 135.9, 134.7, 132.4, 131.6, 130.4, 129.4, 128.7, 118.7, 114.1, 111.9, 56.6, 21.7. **IR** (neat, cm^{-1}): *v*. 3264, 2955, 2922, 1685, 1598, 1438, 1343, 1164, 1079, 868, 655, 538. **HRMS** (ESI^-) calcd for $C_{17}H_{16}NO_4S$ *m/z* 330.0800 $[M-H]^-$, Found 330.0788 (Δ -3.6 ppm). **m.p.** 104-105 °C.

10.Synthesis of the Meglitinide



(20.0 mmol) **2i,** 51%

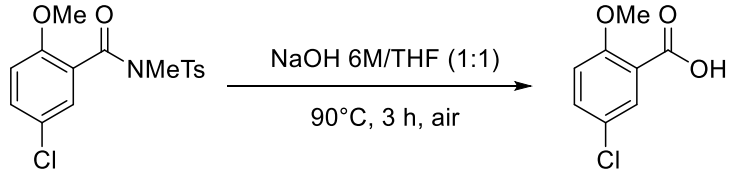
5-Chloro-2-methoxy-N-tosylbenzamide 2i. Reaction performed following the general procedure at 40 °C for 30 minutes then 60 °C for 2 hours using NaCl as the salt on a 20 mmol scale. The product was obtained by recrystallization in minimum amount of hot EtOH as a white solid (3.47 g mg, 10.21 mmol, 51%).



2i **5**, 80%

A 50 mL round bottom flask was loaded under air with **2i** (1.36 g, 4.0 mmol, 1.0 equiv.), K_2CO_3 (1.38 g, 10.0 mmol, 2.5 equiv.) and DMF (16 mL). MeI (548 µL, 8.8 mmol, 2.2 equiv.) was then added. The reaction mixture was stirred at room temperature for 3 hours. 30 mL of EtOAc and 30 mL of a saturated solution of NaCl were then added. The mixture was extracted EtOAc (3×30 mL). The organic layers were combined and washed 3 times with 30 mL of distilled water. The organic layer was then dried on $MgSO_4$, filtered on cotton and the solvents were removed under reduced pressure. The product was then recrystallized in a minimum of hot ethanol. The solid was then filtered and washed with a minimum of ice-cold ethanol.

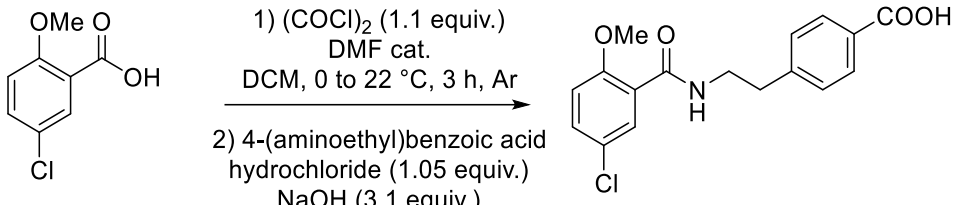
5-Chloro-2-methoxy-*N*-methyl-*N*-tosylbenzamide 5. The product was isolated as a white solid (1.14 g, 3.22 mmol, 80%). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.35–7.28 (m, 3H), 7.05 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 9.0 Hz, 1H), 3.75 (s, 3H), 3.31 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ. 167.4, 154.5, 144.9, 135.7, 131.3, 129.5, 128.1, 128.0, 126.4, 125.5, 112.2, 55.9, 33.6, 21.6. **IR** (neat, cm^{-1}): *v*. 3011, 2956, 1678, 1487, 1348, 1304, 1284, 1161, 1022, 847, 829, 772, 661, 593, 532. **HRMS** (ESI$^+$) calcd for $C_{16}H_{17}NO_4S^{35}Cl$ *m/z* 354.0567 $[M+H]^+$, Found 354.0562 (Δ -1.4 ppm). **m.p.** 128-129 °C.



5 **7**, 78%

A 50 mL round bottom flask was loaded under air with **5** (1.06 g, 3.0 mmol, 1.0 equiv.). THF (15 mL and a solution of NaOH 6M (15 mL) was then added. The reaction mixture was stirred for 3 hours at 90 °C. When the reaction was completed, the reaction was acidified with HCl 3M until pH = 1. The mixture was extracted with EtOAc (3×20 mL). The organic layers were combined, dried over $MgSO_4$, filtered through cotton and the solvents were evaporated under reduced pressure. The crude residue was then purified by column chromatography using petroleum ether/ethyl acetate (7/3) as the eluent.

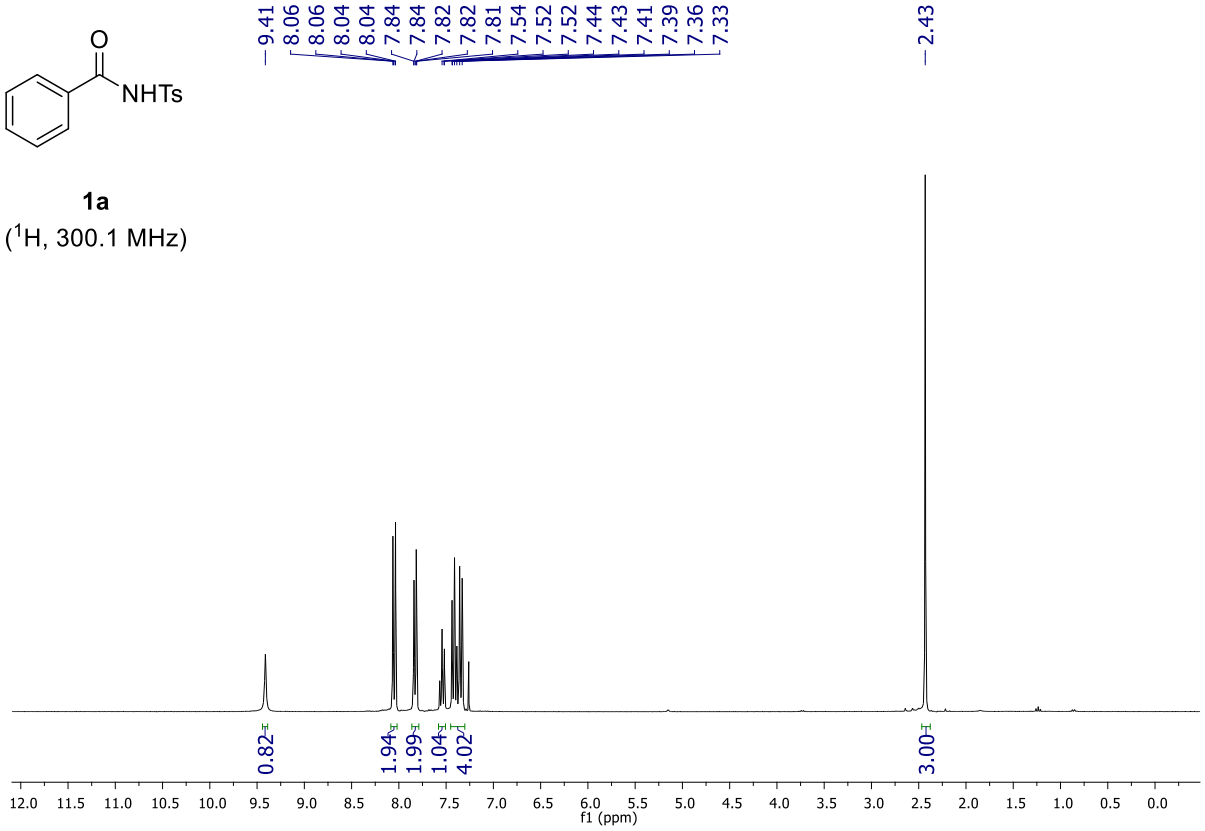
5-Chloro-2-methoxybenzoic acid 7. (R_f in Petroleum ether/Ethyl Acetate 7:3 = 0.1). The product was isolated as a white solid (433 mg, 2.33 mmol, 78%). **^{1}H NMR** (300.1 MHz, $CDCl_3$) δ 8.11 (d, J = 2.7 Hz, 1H), 7.51 (dd, J = 8.7, 2.7 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 4.07 (s, 3H). The OH from the carboxylic acid could not be found. **^{13}C NMR** (75.5 MHz, $CDCl_3$) δ 164.5, 156.6, 134.7, 133.2, 127.5, 119.0, 113.2, 57.1. **IR** (neat, cm^{-1}): *v* 3029, 2947, 1708, 1667, 1601, 1462, 1237, 1012, 813, 682, 645. **HRMS** (ESI$^-$) calcd for $C_8H_6O_3^{35}Cl$ *m/z* 185.0005 $[M-H]^-$, Found 185.0005 (Δ 0 ppm). **m.p.** 82-83 °C.



A 50 mL round bottom flask was loaded under Argon with **7** (219 mg, 1.07 mmol, 1.0 equiv.). CH_2Cl_2 (10 mL) was then added followed by 5 drops of DMF. The mixture was then cooled down to 0 °C and oxalyl chloride (100 µL, 1.18 mmol, 1.1 equiv.) was dropwise added. The reaction mixture was then warmed up to room temperature and stirred for 3 hours. The solvent was then removed under reduced pressure and the crude residue was then diluted in THF (10 mL). NaOH pellets (133 mg, 3.32 mmol, 3.1 equiv.) and the 4-(aminoethyl)benzoic acid hydrochloride (211.7 mg, 1.12 mmol, 1.05 equiv.) were then added and the reaction was stirred at room temperature for 16 hours under Argon. The reaction was then acidified to pH = 1 with an aqueous solution of HCl 1M. EtOAc (10 mL) was added and the mixture was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was then recrystallized in a minimum amount of hot EtOH.

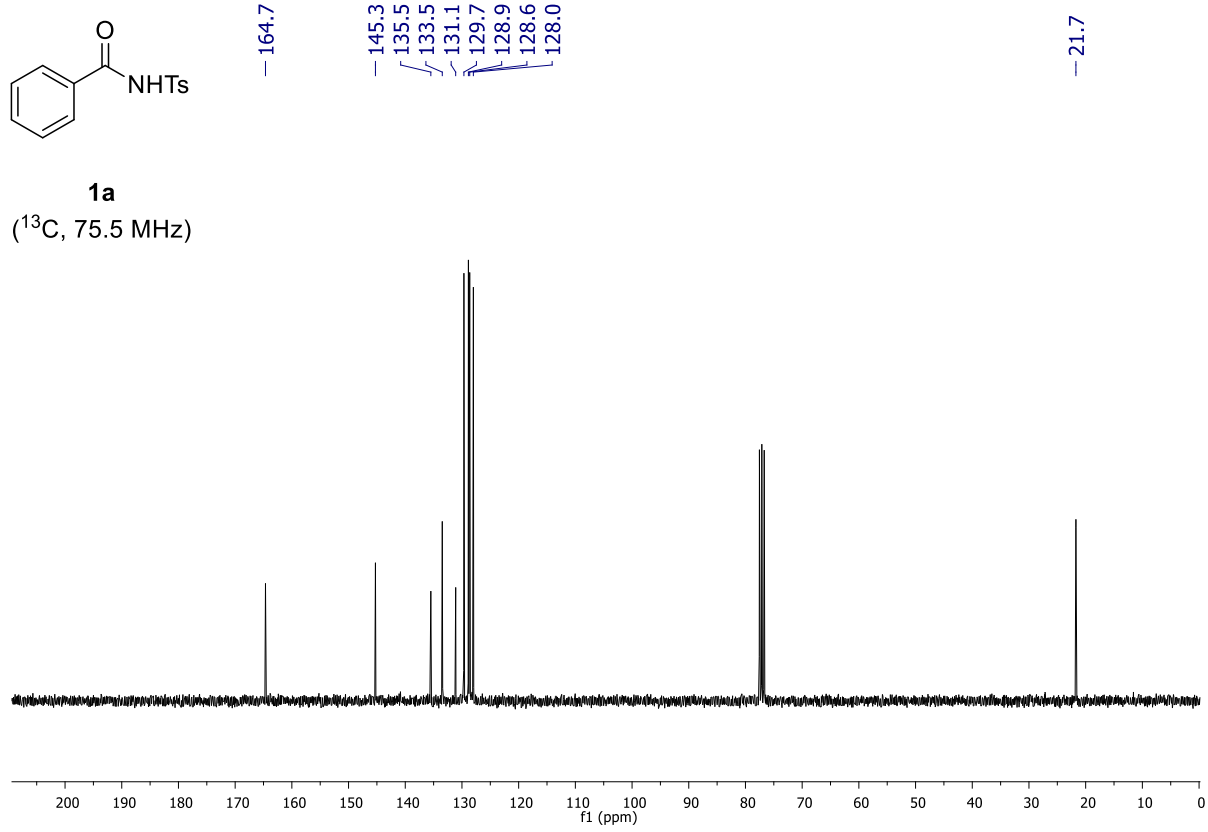
4-(2-(5-chloro-2-methoxybenzamido)ethyl)benzoic acid 11. The product was isolated as a white solid (131 mg, 0.392 mmol, 37%). **^{1}H NMR** (300.1 MHz, DMSO-d_6) δ 12.86 (br.s, 1H), 8.34 – 8.22 (m, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.49 (dd, J = 8.7, 3.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 9.0 Hz, 1H), 3.81 (s, 3H), 3.58 – 3.50 (m, 2H), 2.94 – 2.88 (m, 2H). **^{13}C NMR** (75.5 MHz, DMSO-d_6) δ 167.3, 163.6, 155.7, 144.8, 131.5, 129.5, 129.4, 129.0, 128.8, 124.8, 124.3, 114.1, 56.2, 34.9. One signal for a carbon was overlapped. **IR** (neat, cm^{-1}): ν 3394, 3365, 2946, 1691, 1648, 1610, 1532, 1478, 1291, 1270, 1236, 1016, 810, 765, 676, 524. **HRMS** (ESI$^-$) calcd for $C_{17}H_{15}NO_4{}^{35}Cl$ *m/z* 332.0690 [M-H]$^-$, Found 332.0681 (Δ -2.7 ppm). **m.p.** 180-181 °C.

11. NMR spectra



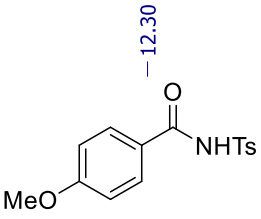
1a

(^{1}H, 300.1 MHz)



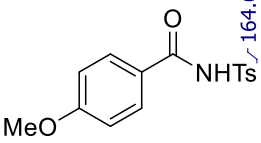
1a

(^{13}C, 75.5 MHz)



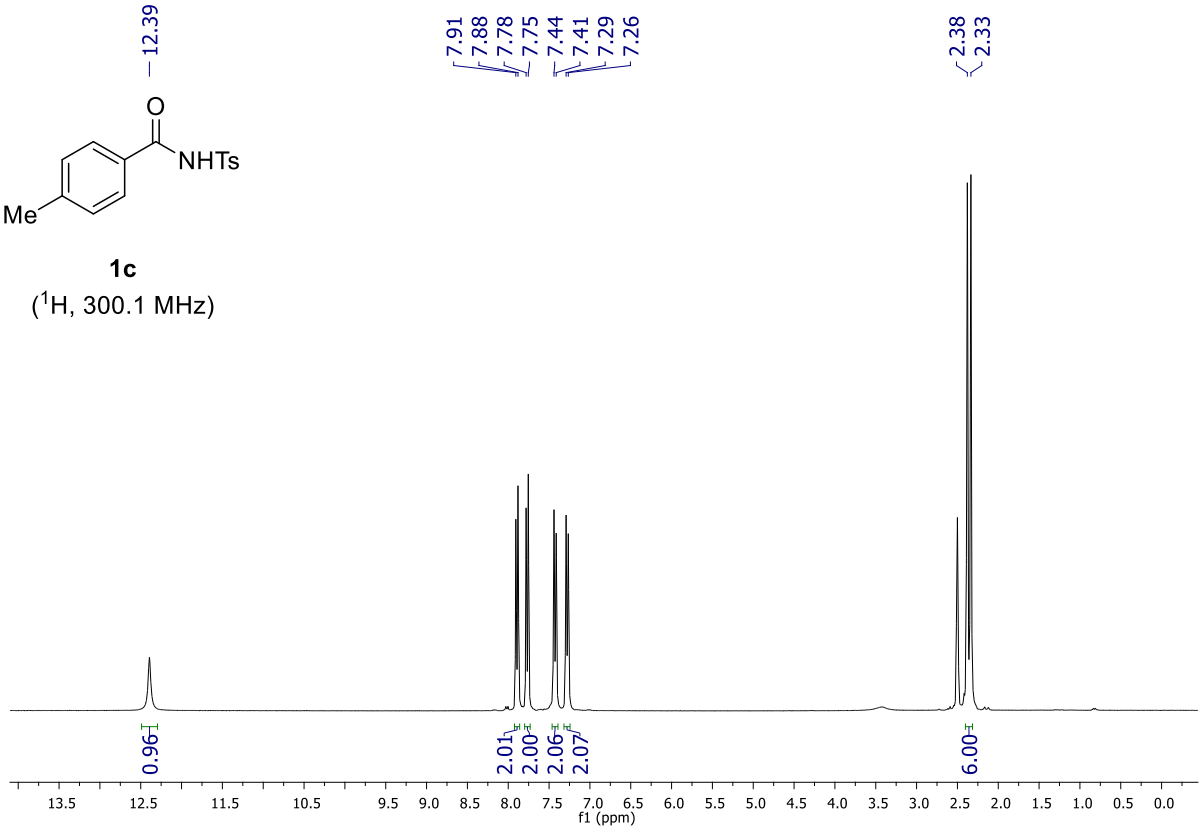
1b

(^{1}H, 300.1 MHz)



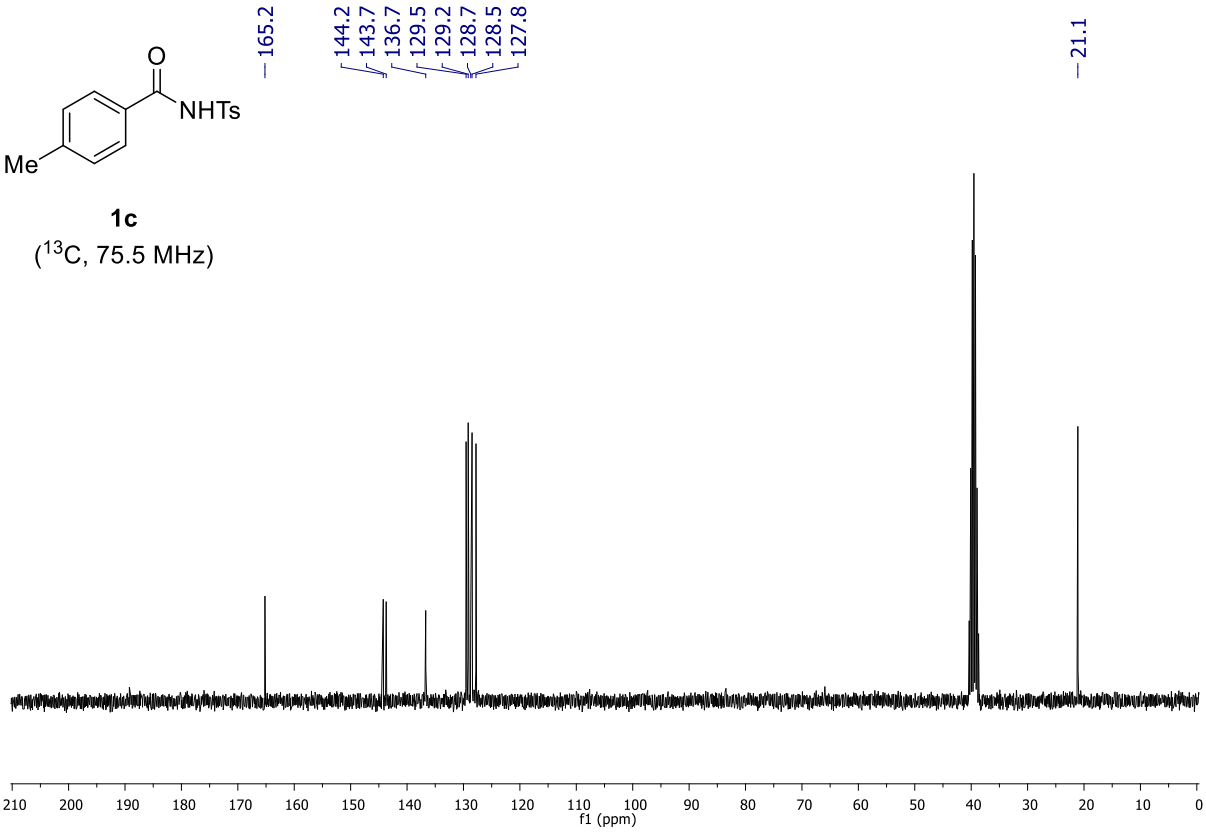
1b

(^{13}C, 75.5 MHz)



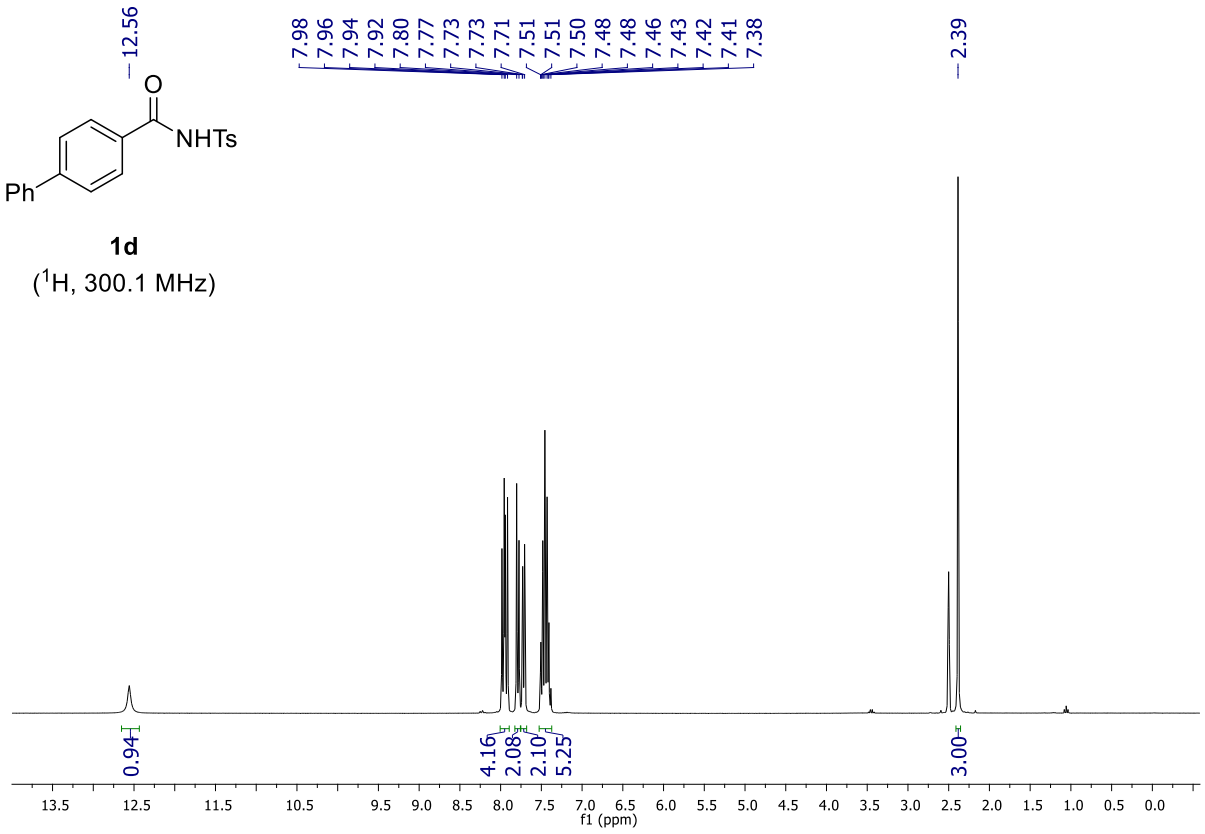
1c

(^{1}H, 300.1 MHz)



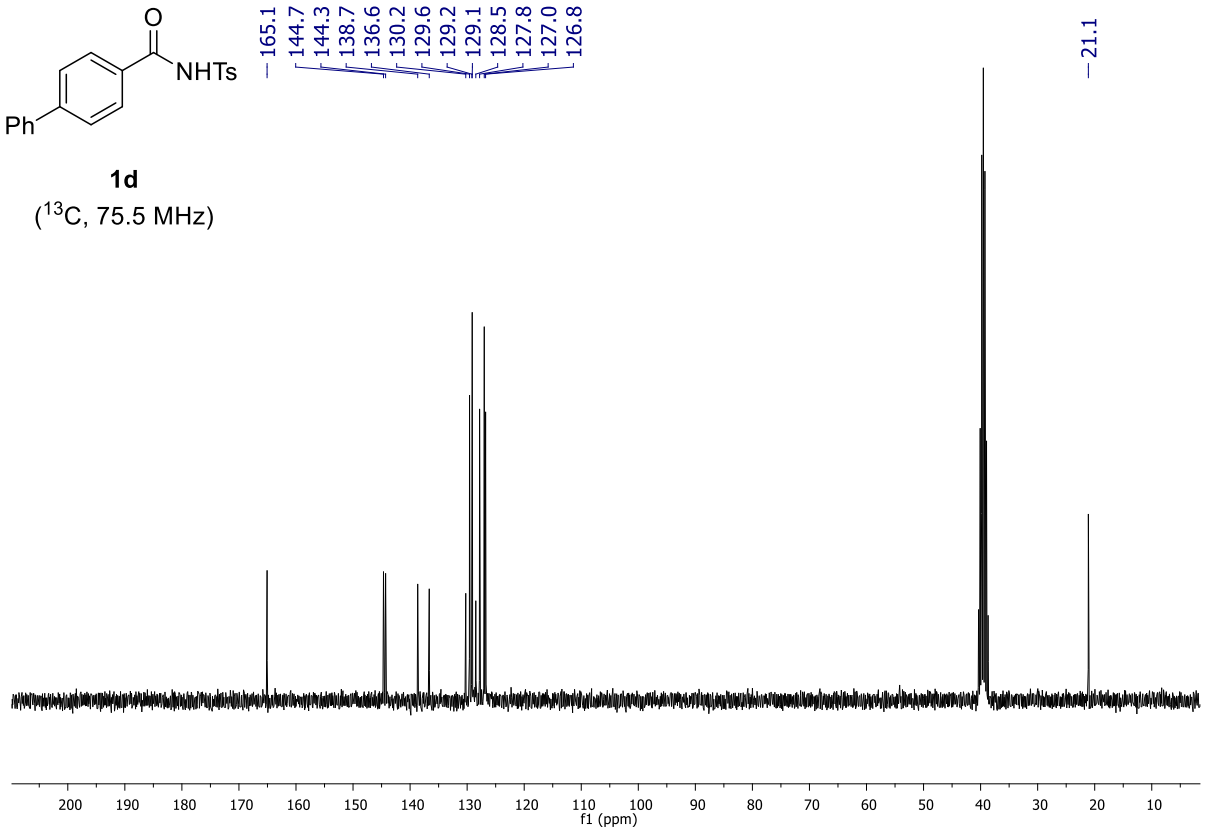
1c

(^{13}C, 75.5 MHz)



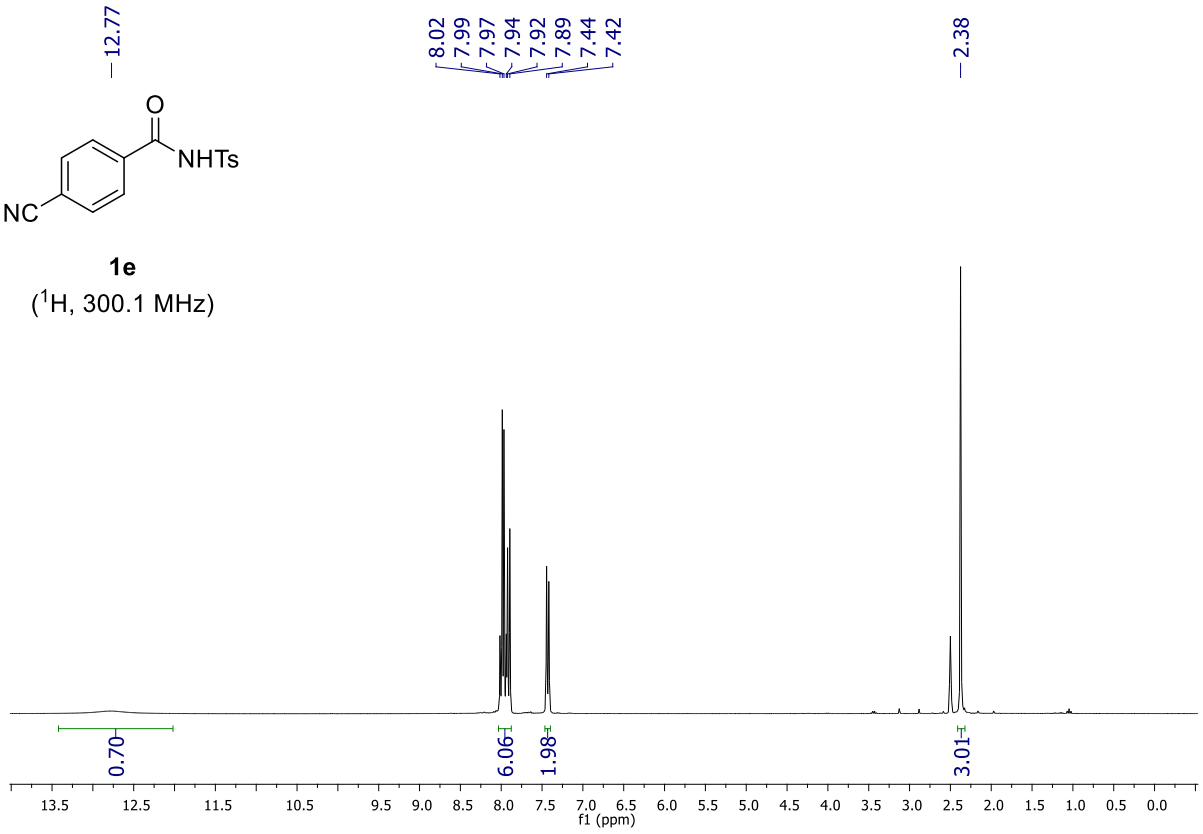
1d

(^{1}H, 300.1 MHz)



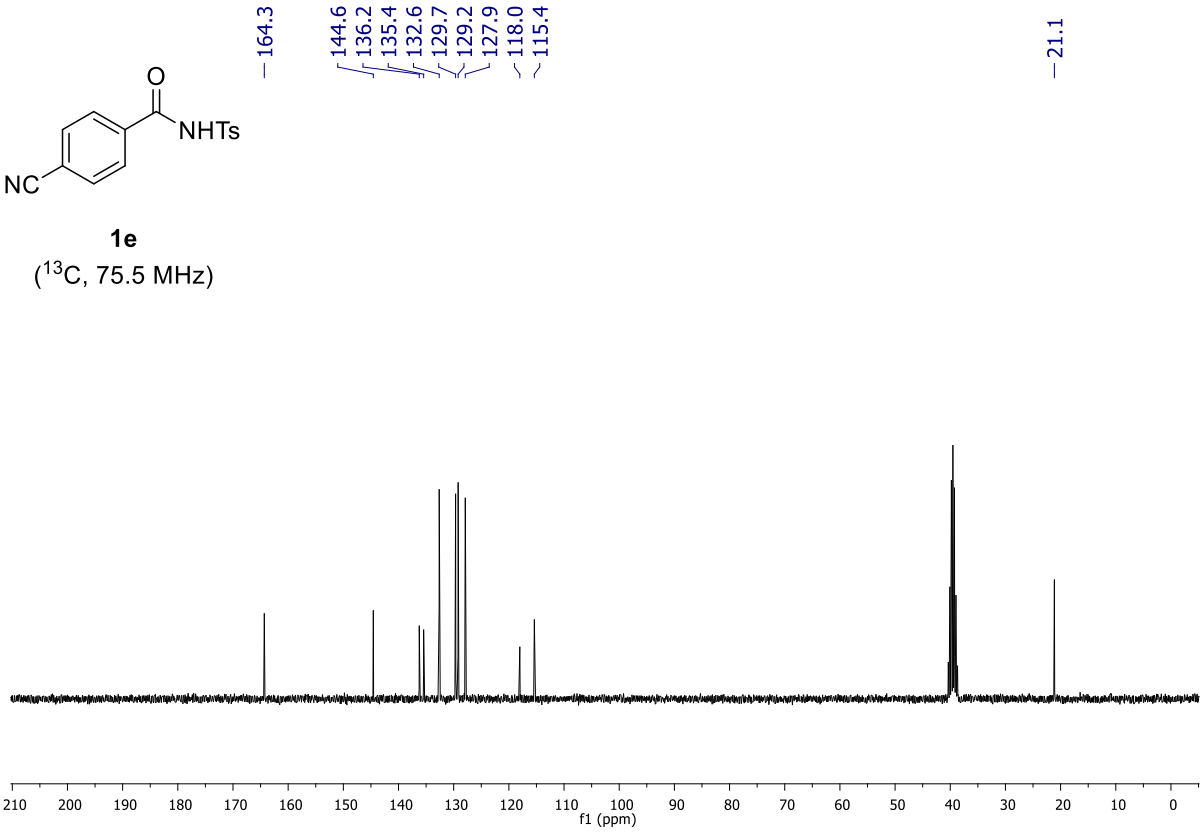
1d

(^{13}C, 75.5 MHz)



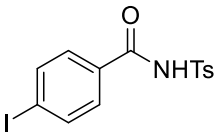
1e

(^{1}H, 300.1 MHz)



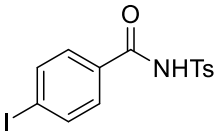
1e

(^{13}C, 75.5 MHz)



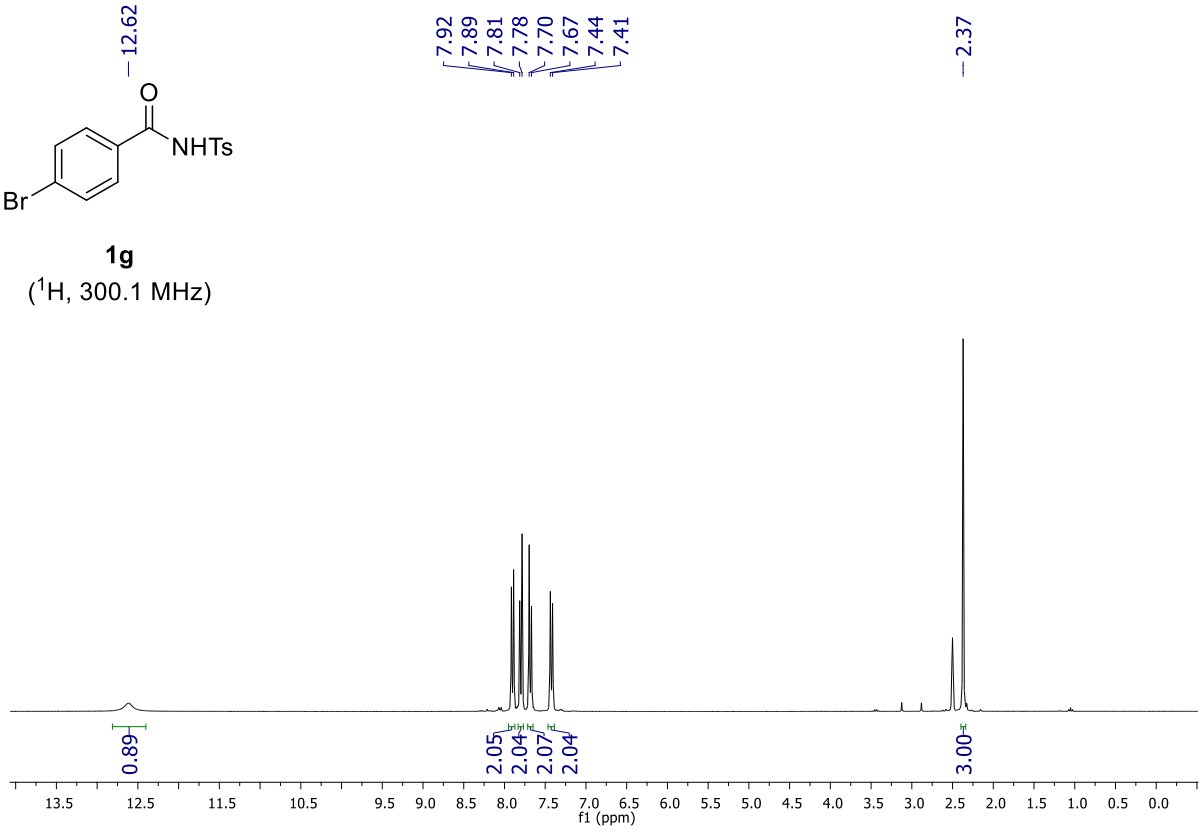
1f

(^{1}H, 300.1 MHz)



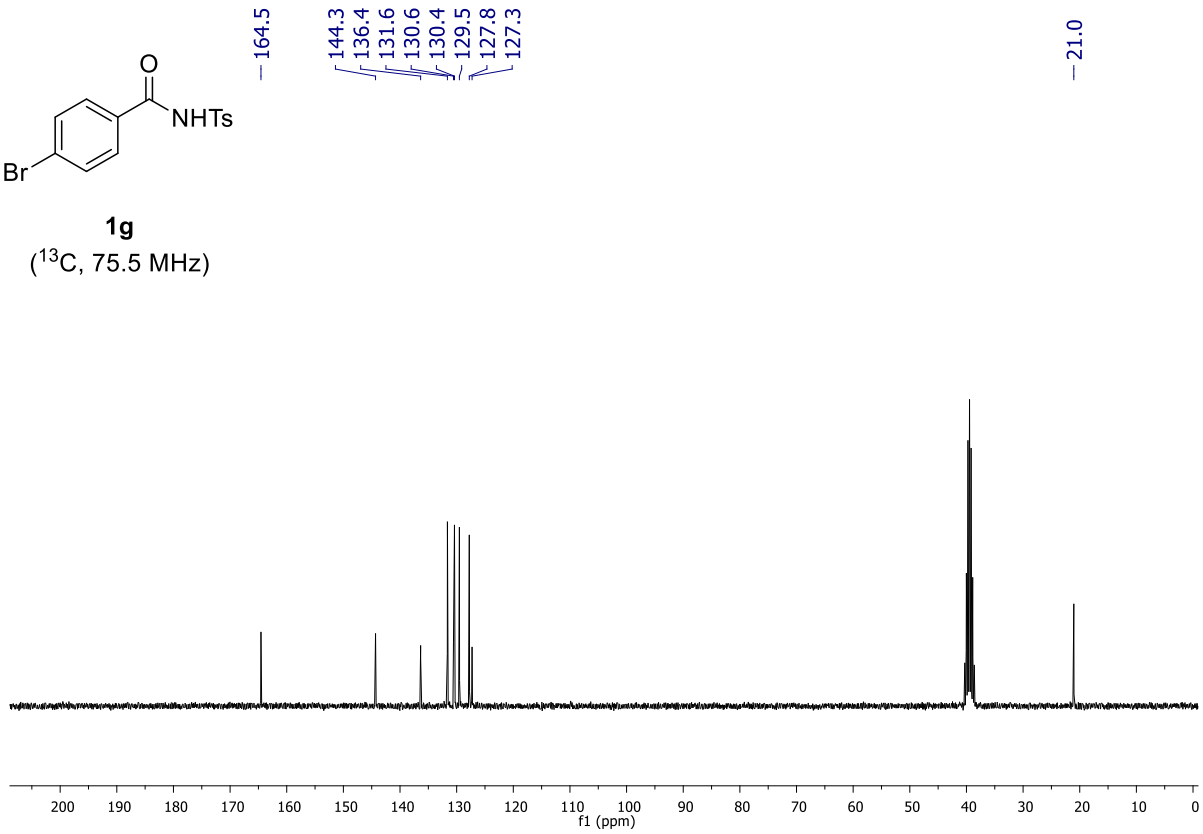
1f

(^{13}C, 75.5 MHz)



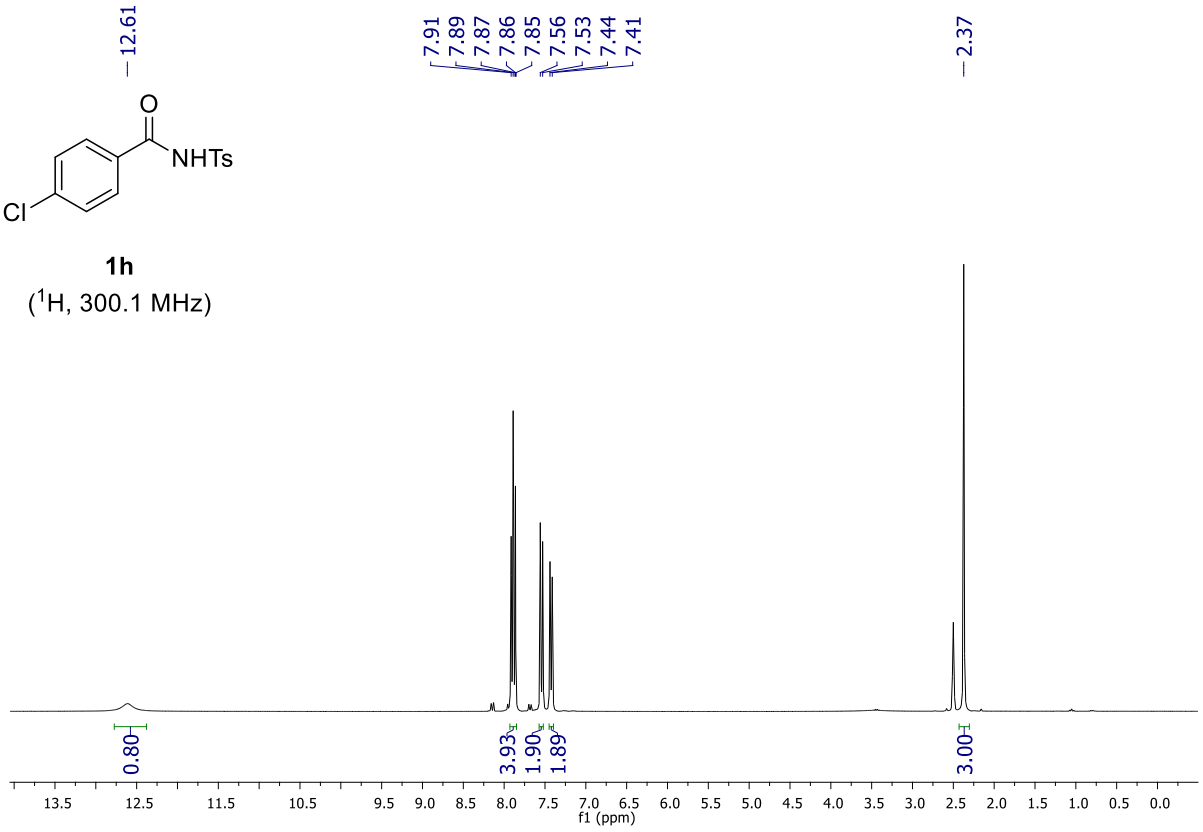
1g

(^{1}H, 300.1 MHz)



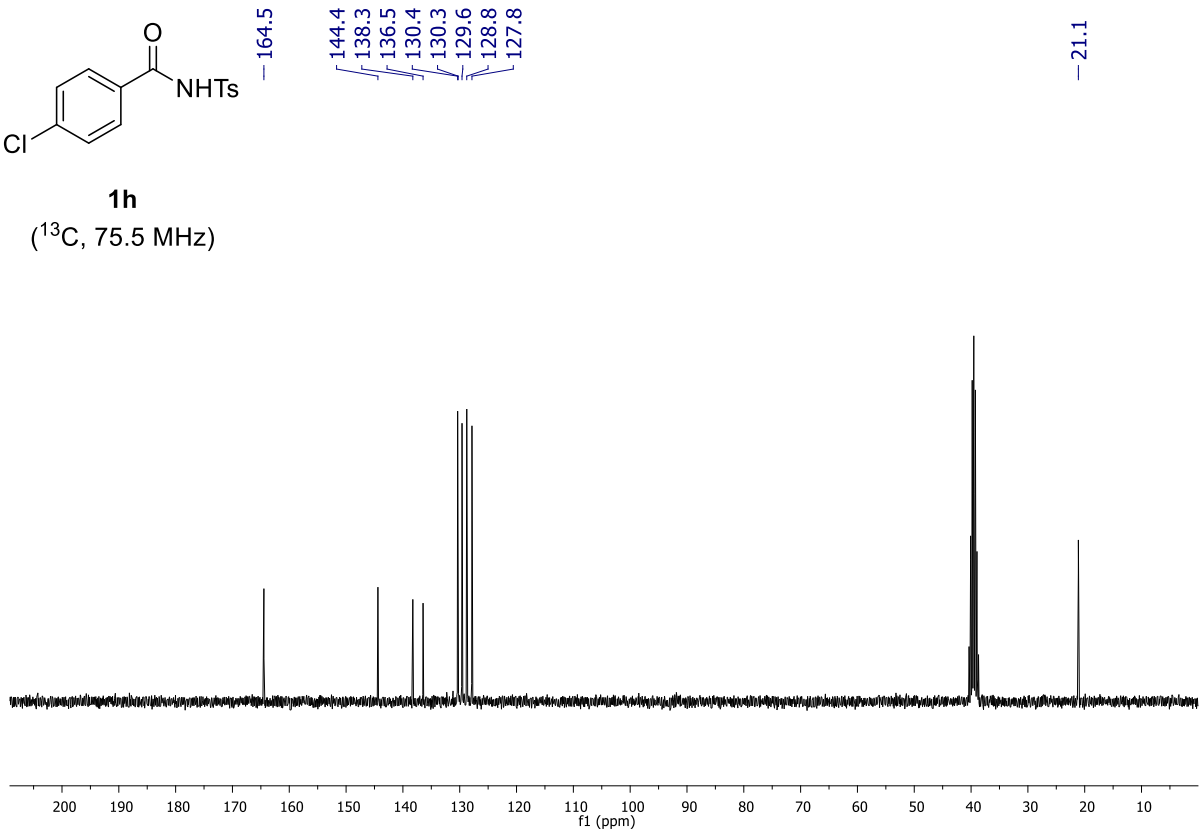
1g

(^{13}C, 75.5 MHz)



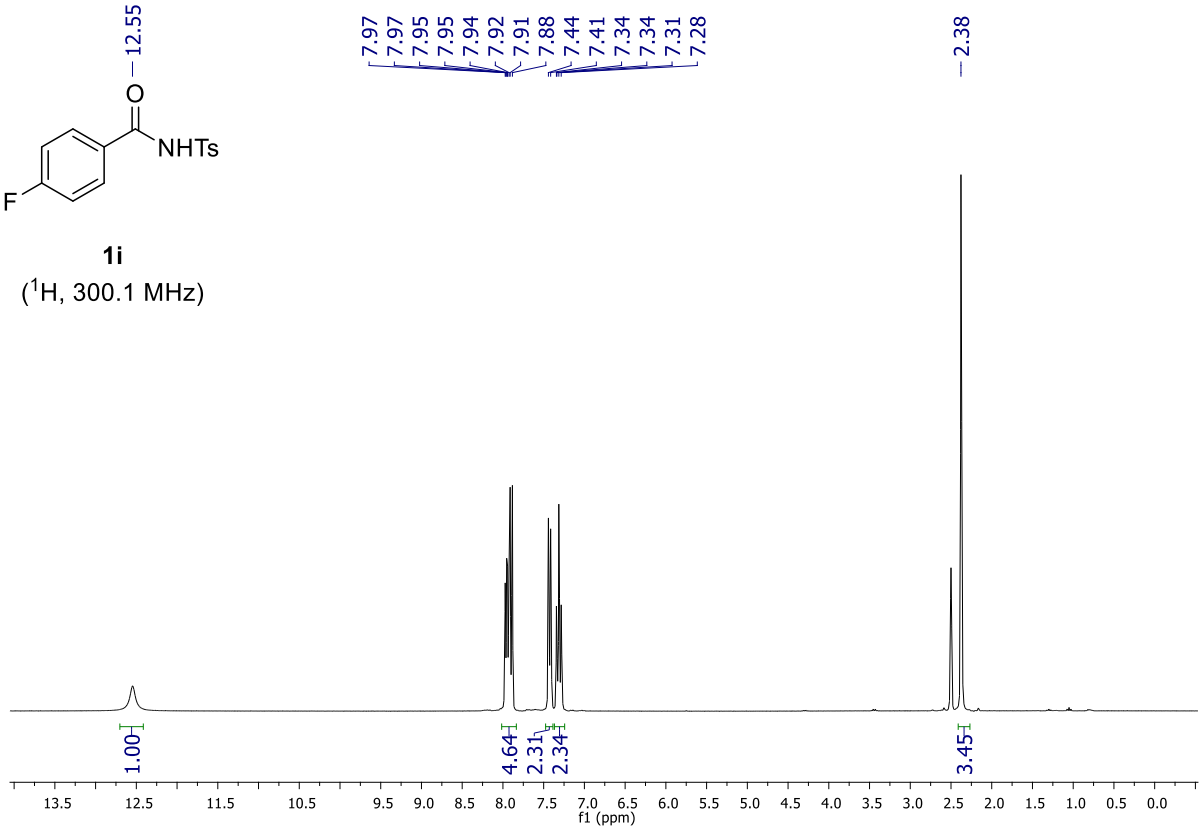
1h

(^{1}H, 300.1 MHz)



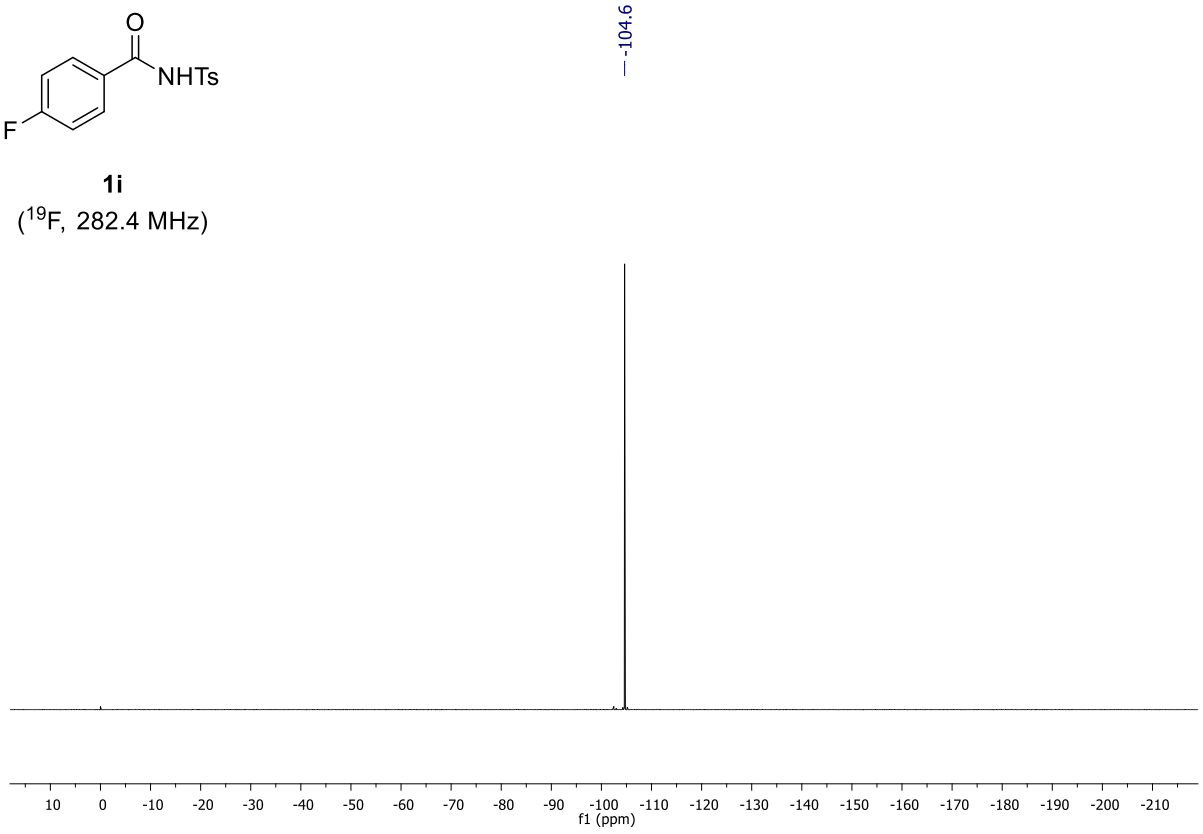
1h

(^{13}C, 75.5 MHz)



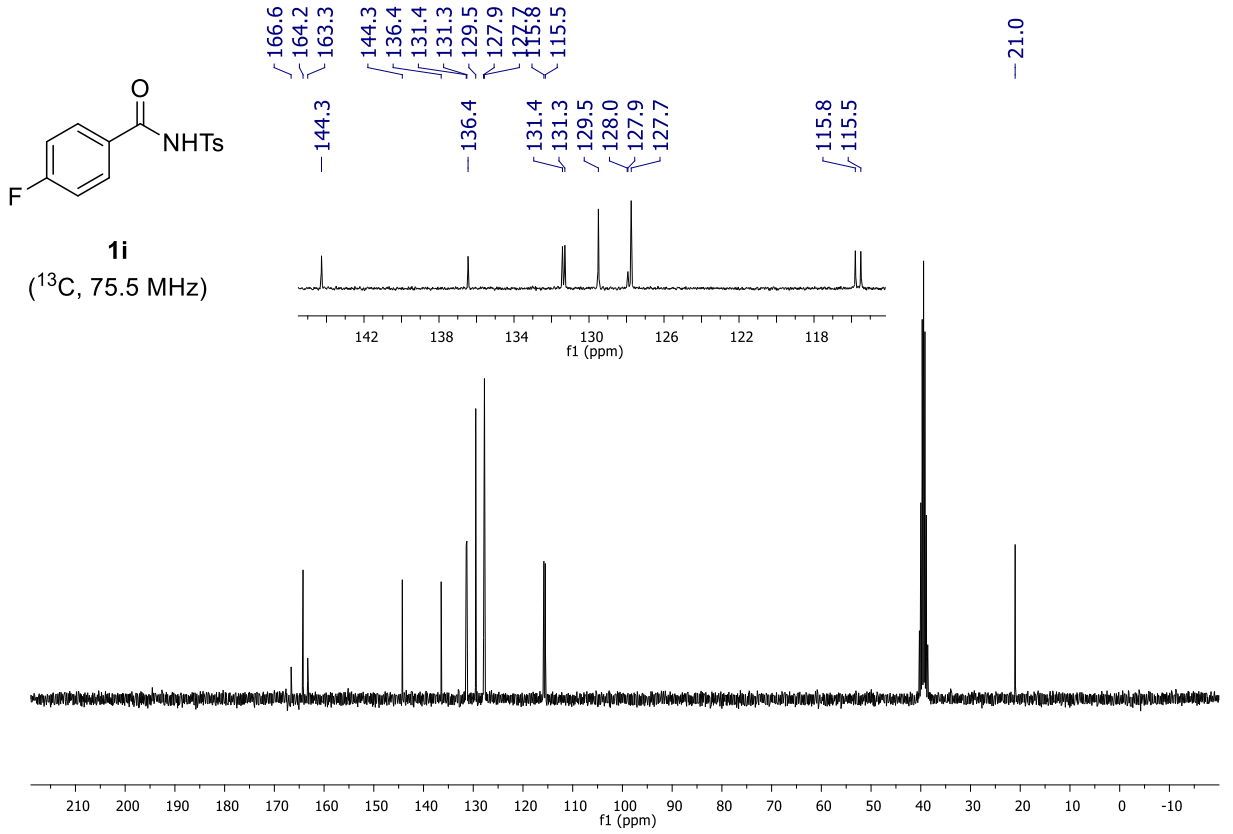
1i

(^{1}H, 300.1 MHz)



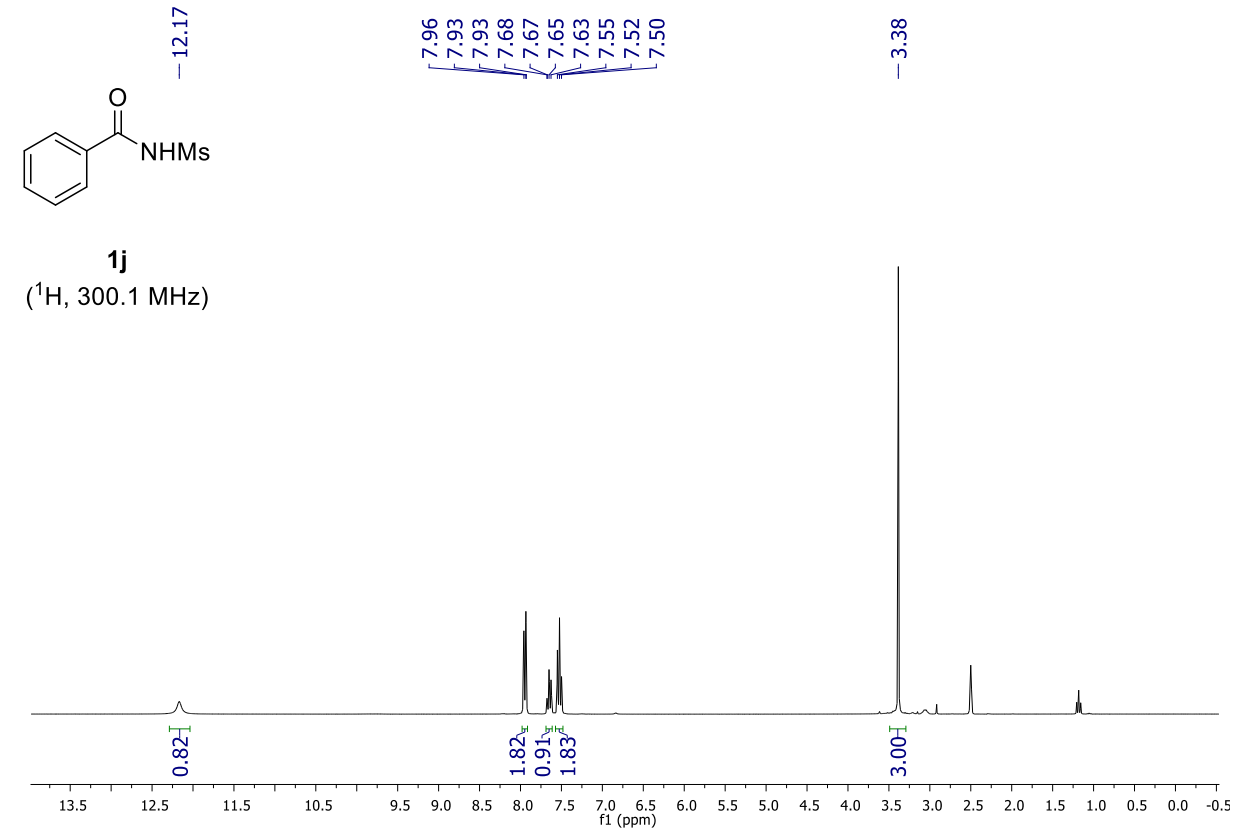
1i

(^{19}F, 282.4 MHz)



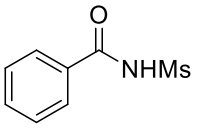
1i

(^{13}C, 75.5 MHz)



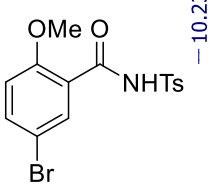
1j

(^{1}H, 300.1 MHz)



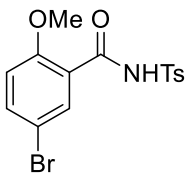
1j

(^{13}C, 75.5 MHz)



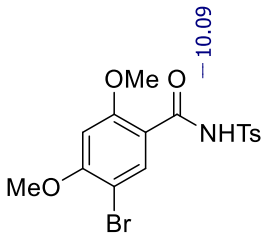
2a

(^{1}H, 300.1 MHz)



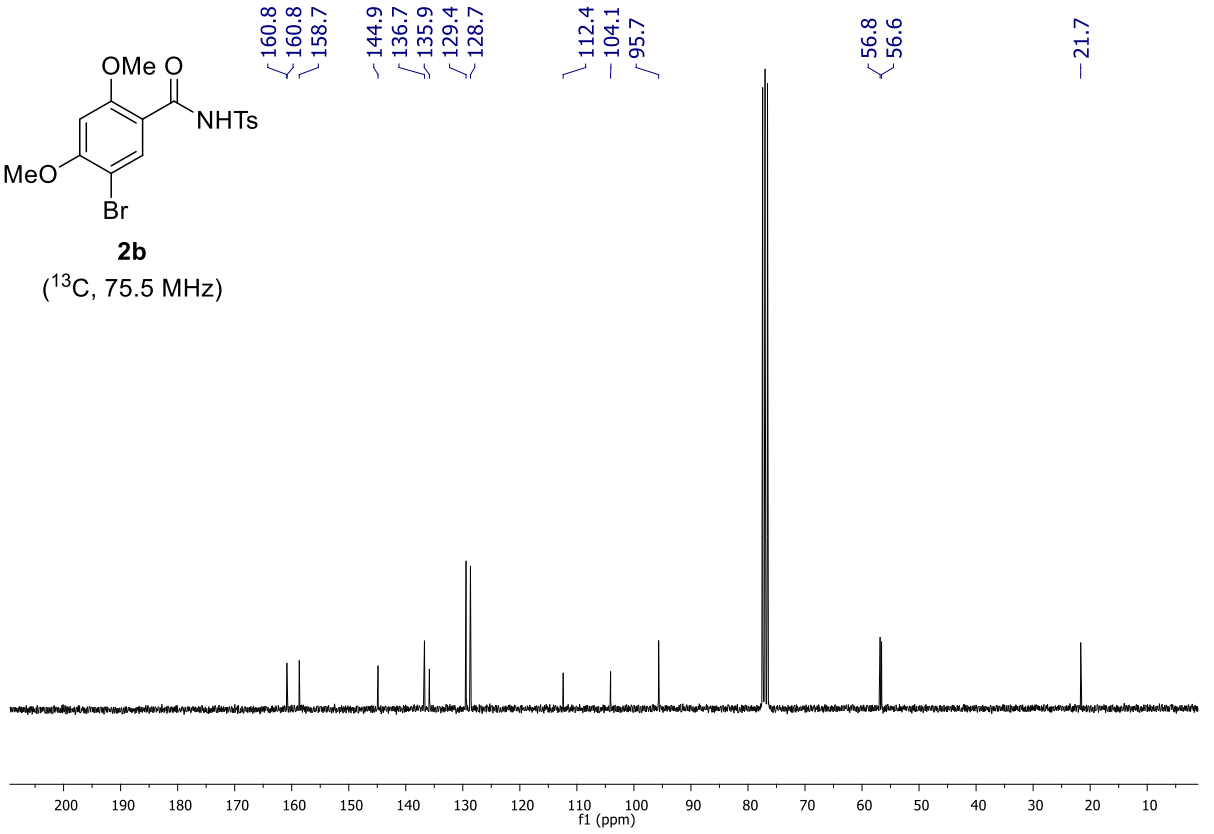
2a

(^{13}C, 75.5 MHz)



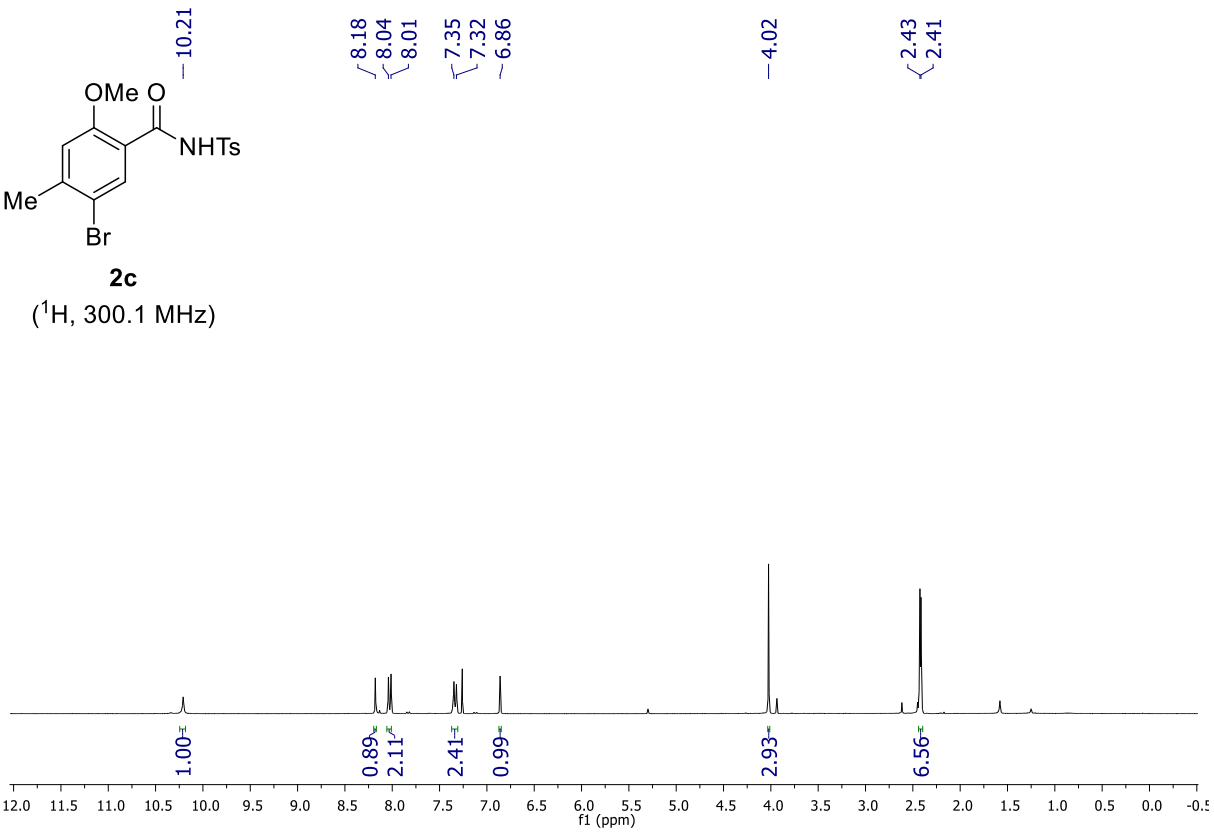
2b

(^{1}H, 300.1 MHz)



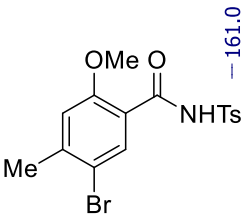
2b

(^{13}C, 75.5 MHz)



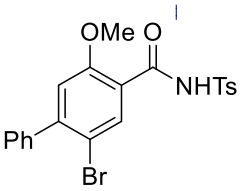
2c

(^{1}H, 300.1 MHz)



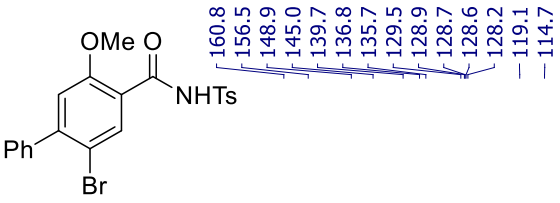
2c

(^{13}C, 75.5 MHz)



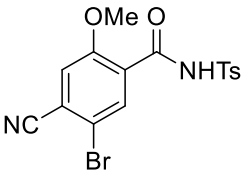
2d

(^{1}H, 300.1 MHz)



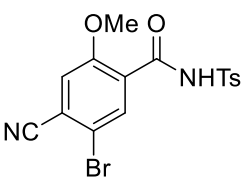
2d

(^{13}C, 75.5 MHz)



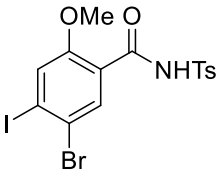
2e

(^{1}H, 300.1 MHz)



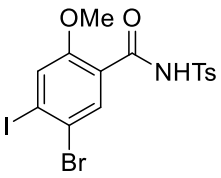
2e

(^{13}C, 75.5 MHz)

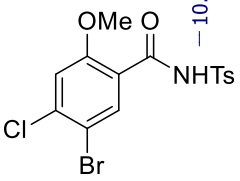


2f

(^{1}H, 300.1 MHz)

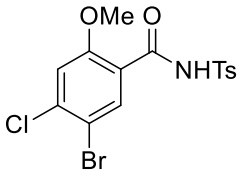


2f



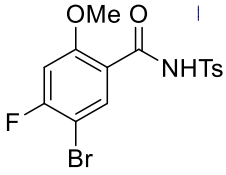
2g

(^{1}H, 300.1 MHz)



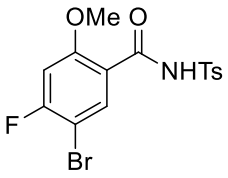
2g

(^{13}C, 75.5 MHz)



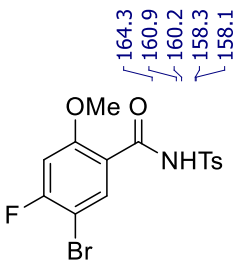
2h

(^{1}H, 300.1 MHz)



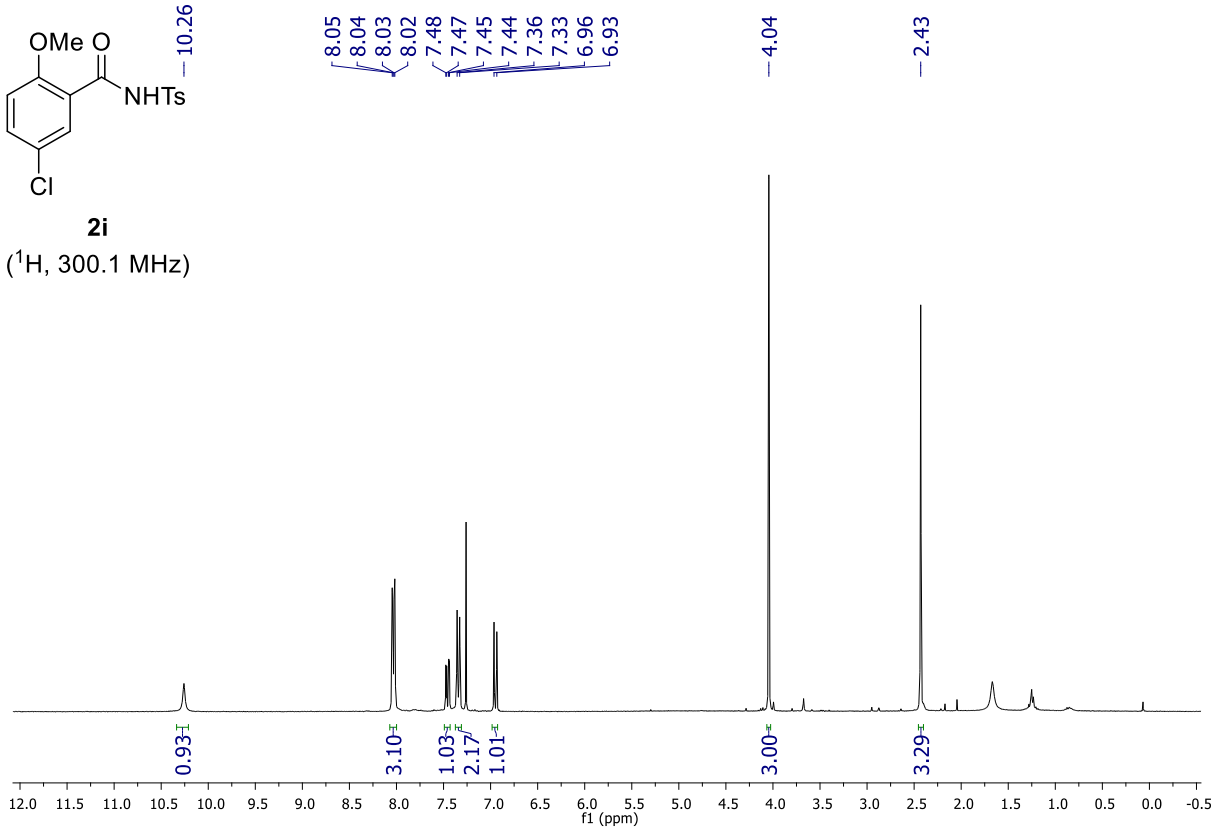
2h

(^{19}F, 282.4 MHz)



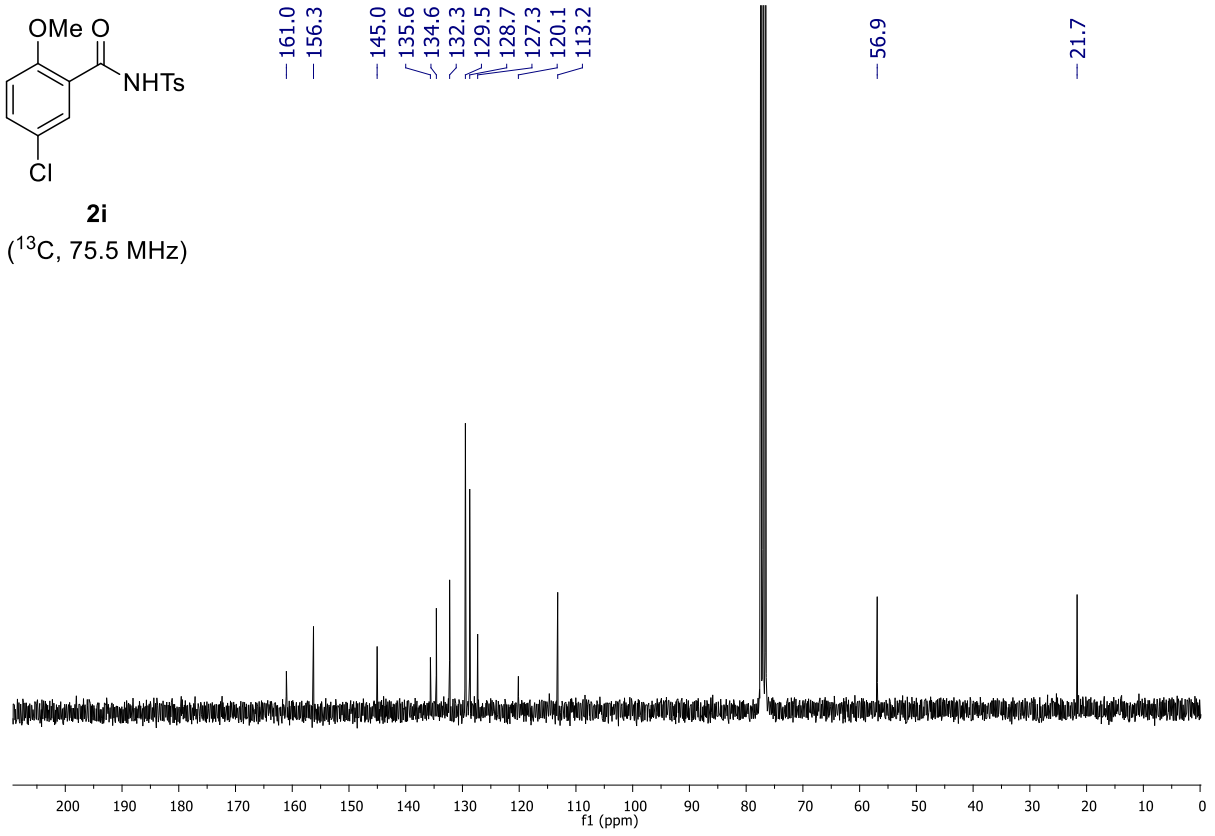
2h

(^{13}C, 75.5 MHz)



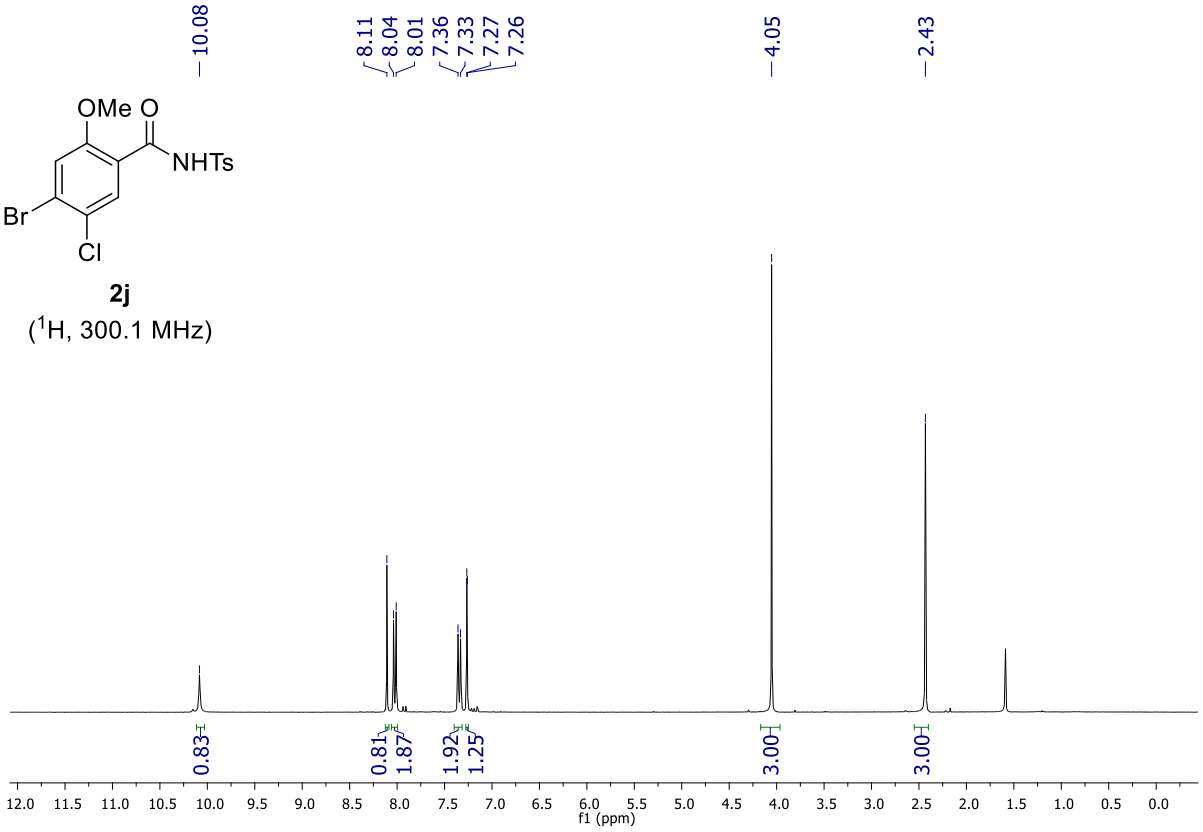
2i

(^{1}H, 300.1 MHz)



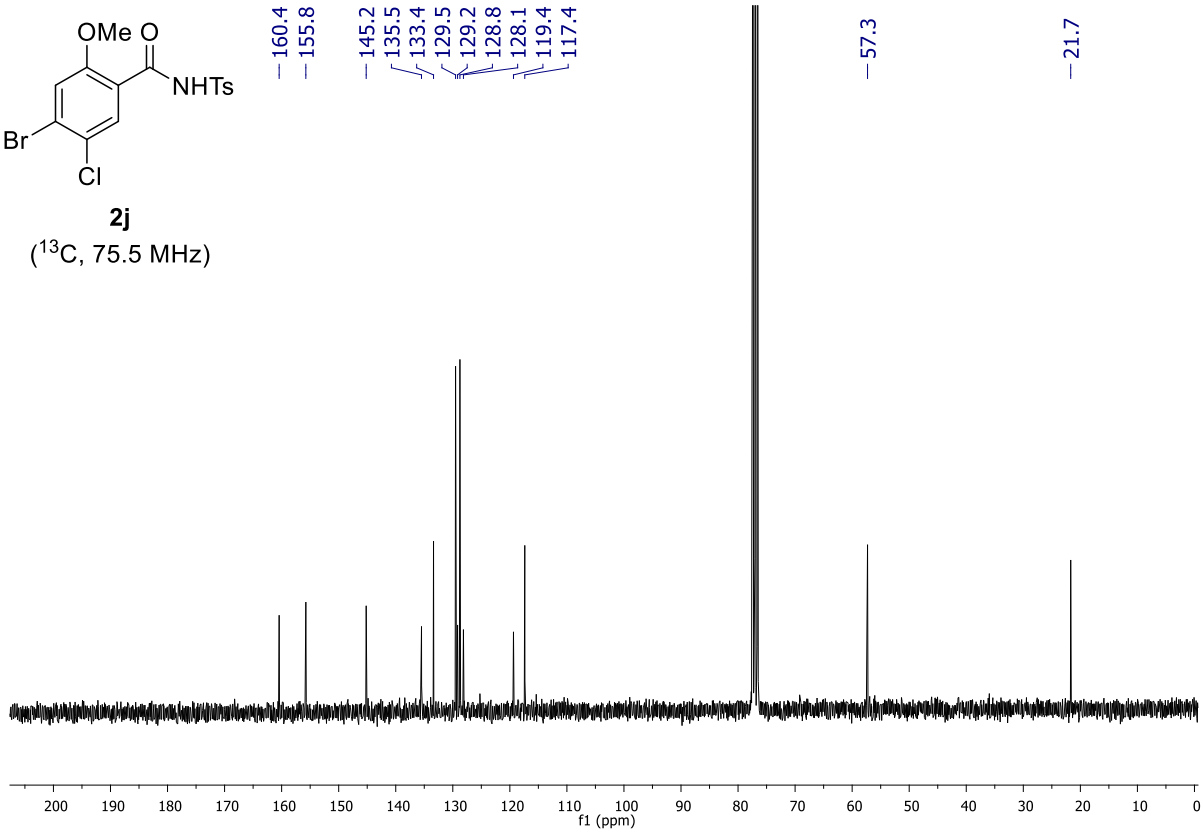
2i

(^{13}C, 75.5 MHz)



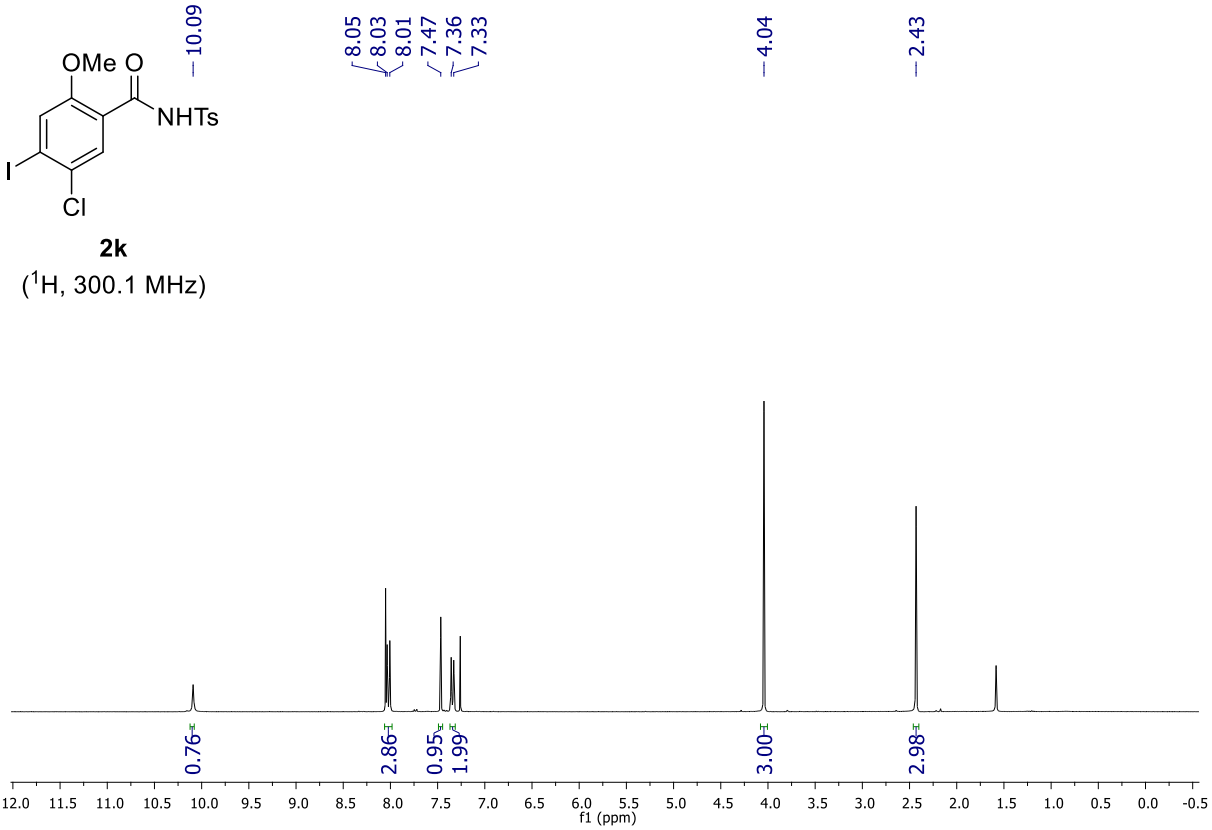
2j

(^{1}H, 300.1 MHz)



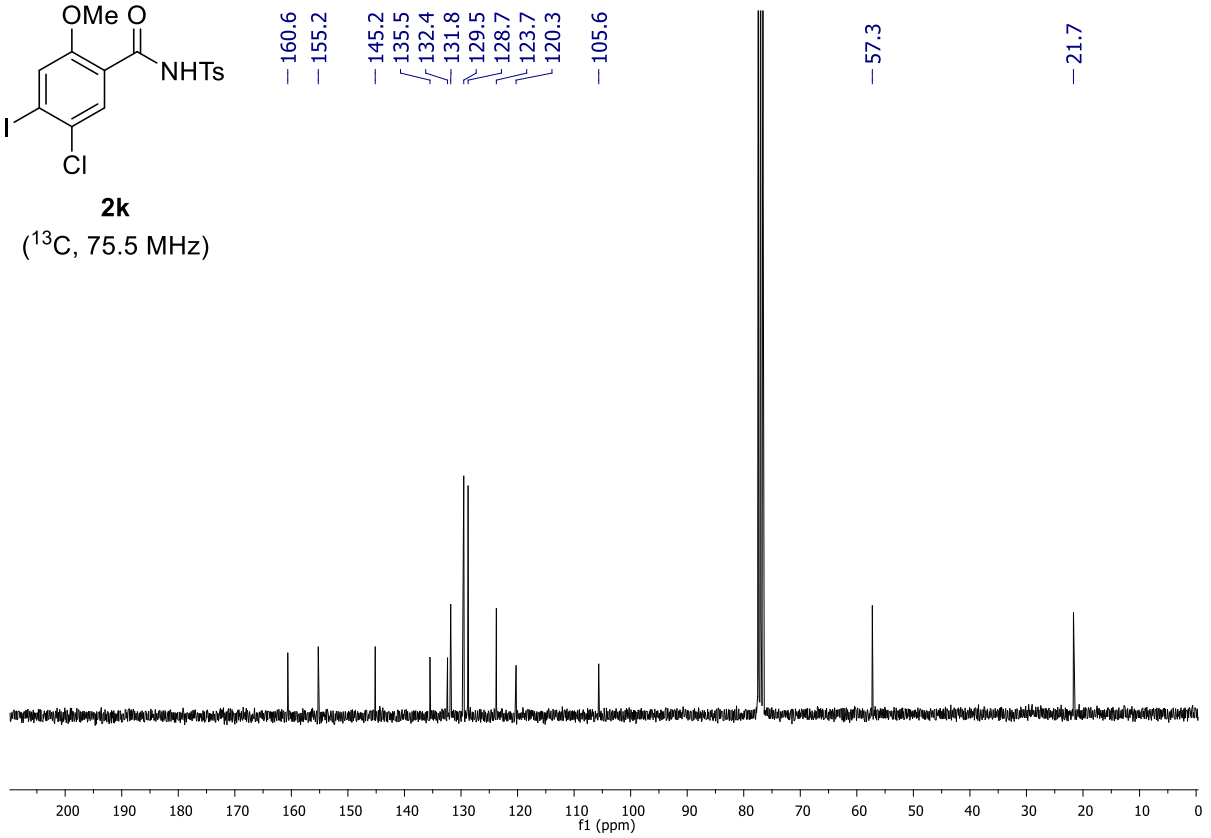
2j

(^{13}C, 75.5 MHz)



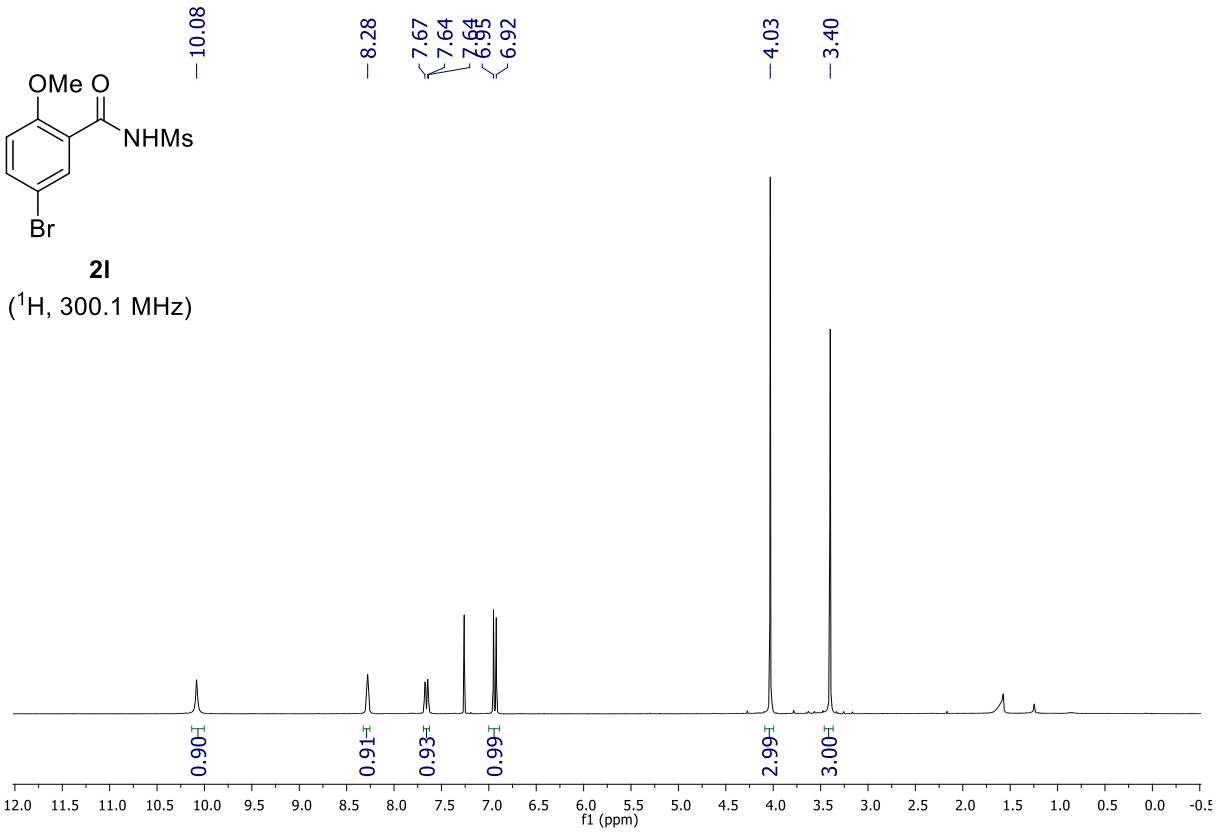
2k

(^{1}H, 300.1 MHz)



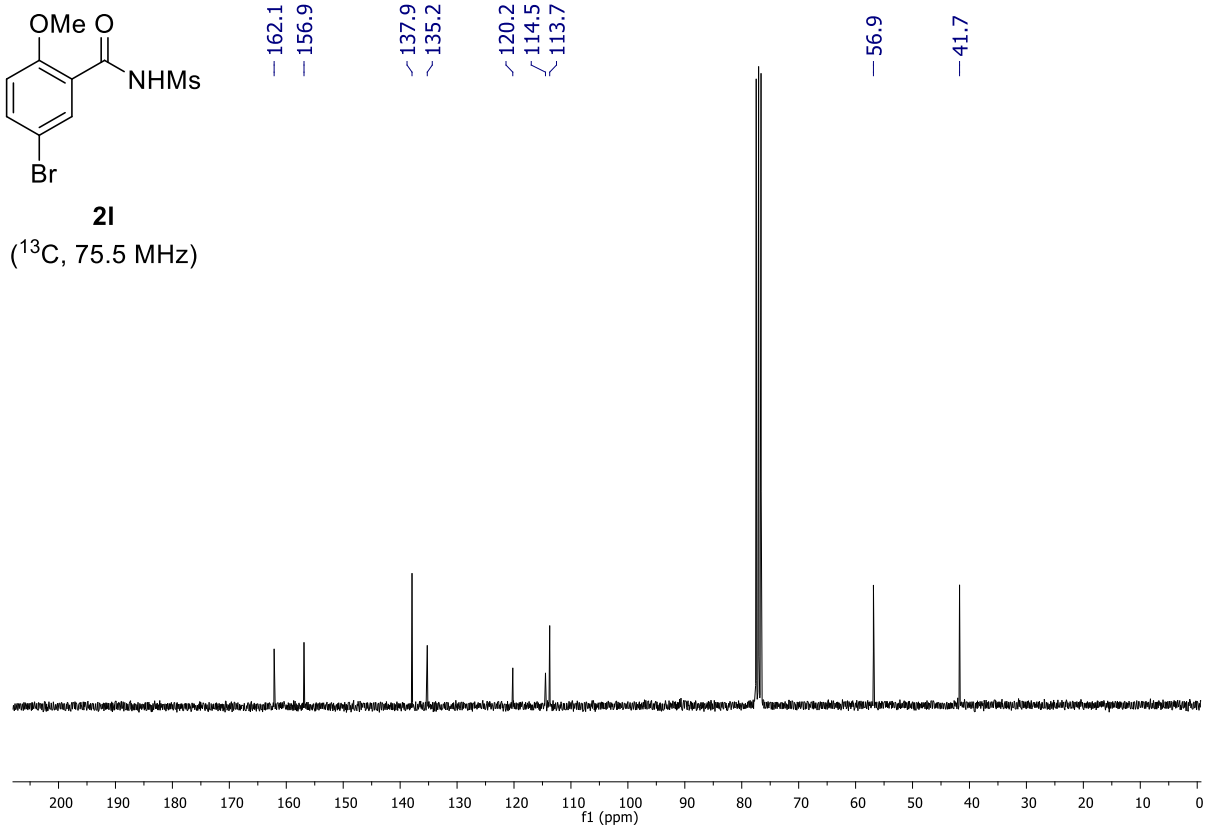
2k

(^{13}C, 75.5 MHz)



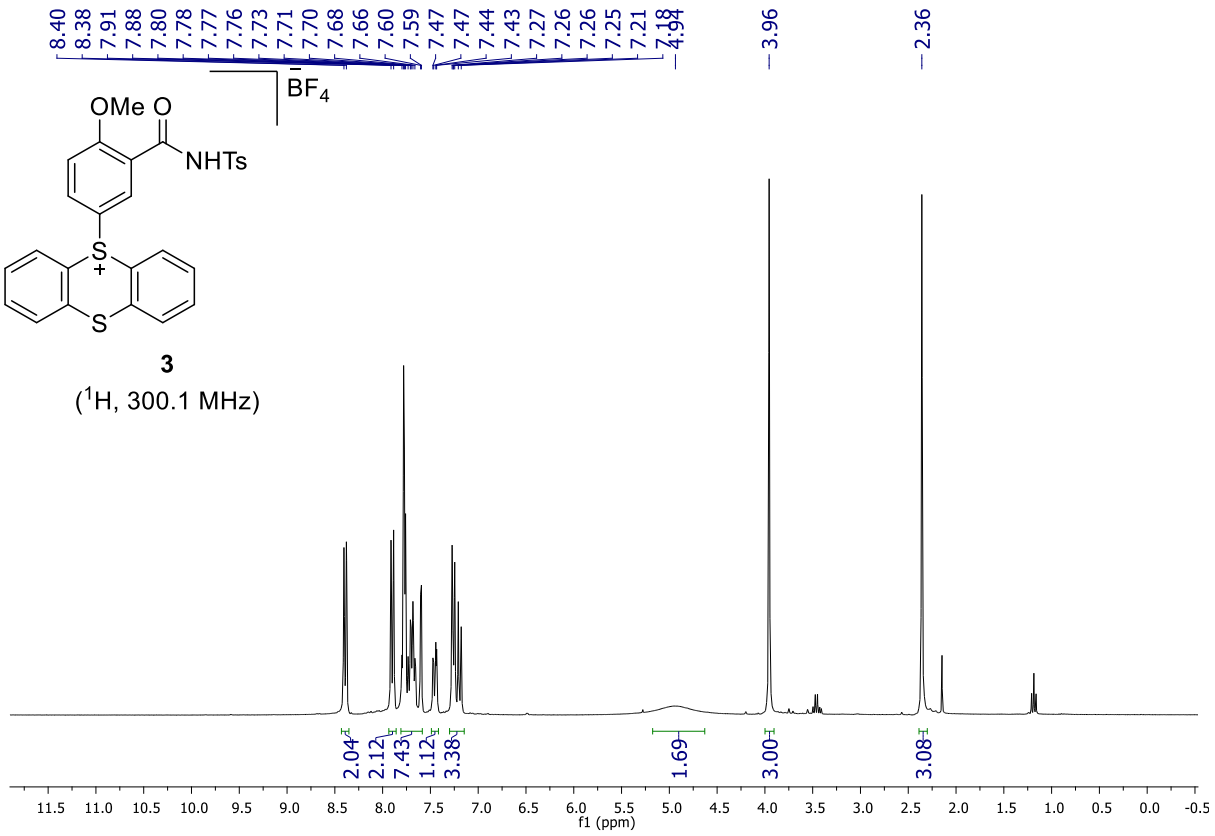
2l

(^{1}H, 300.1 MHz)



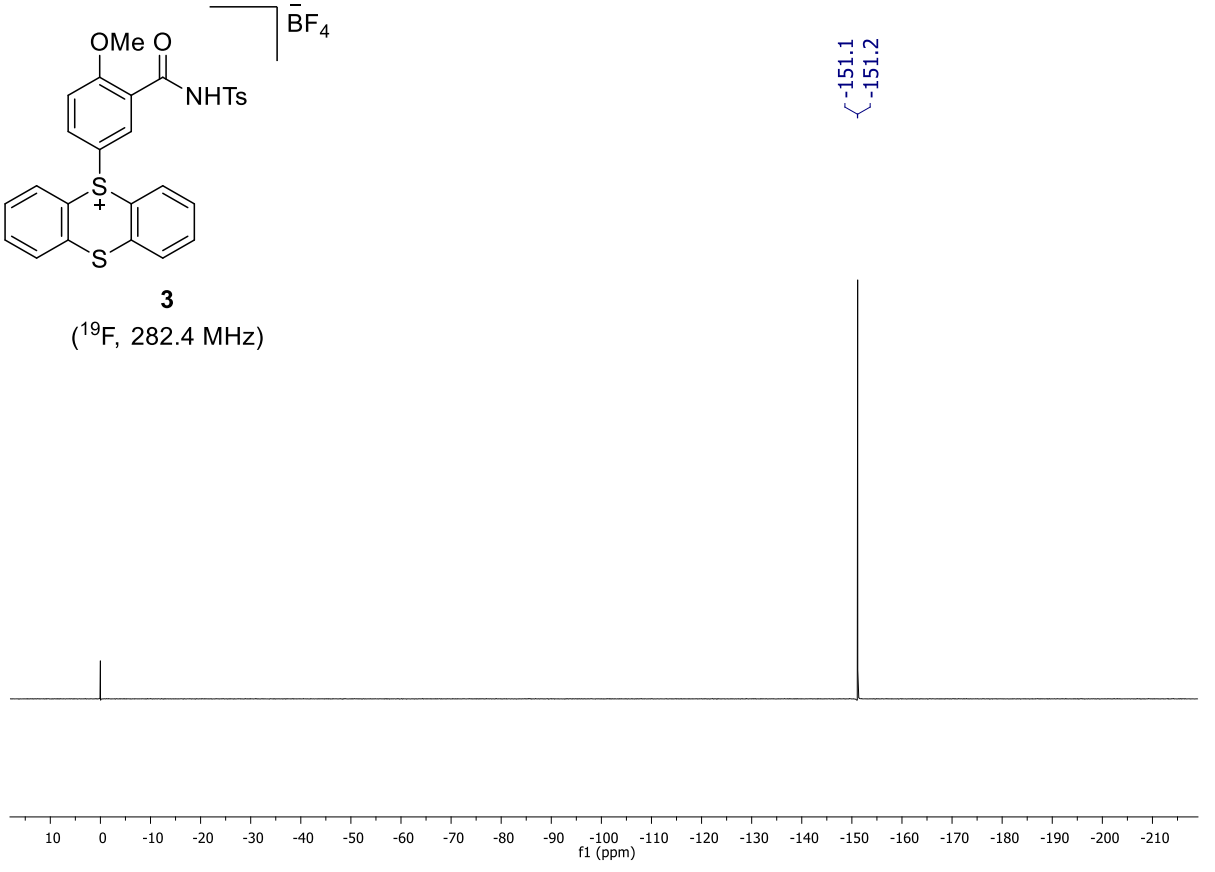
2l

(^{13}C, 75.5 MHz)



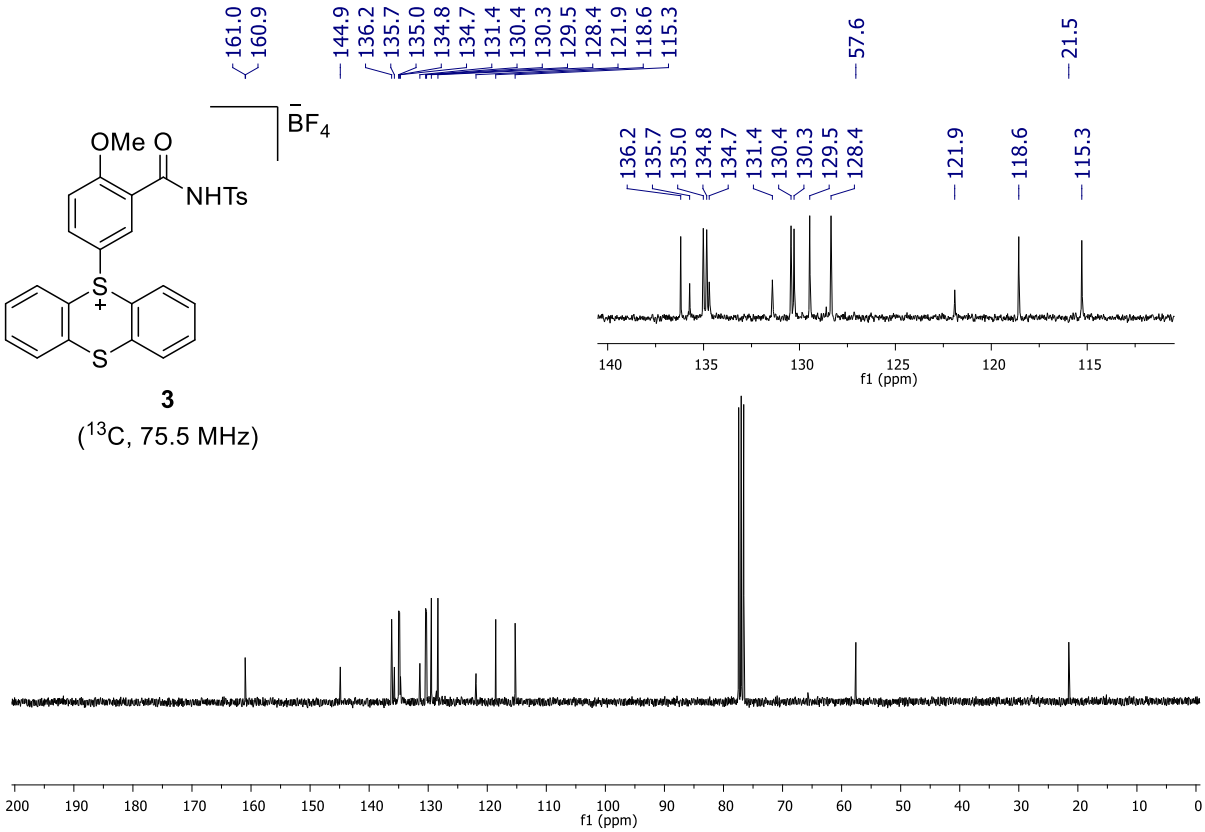
3

(^{1}H, 300.1 MHz)



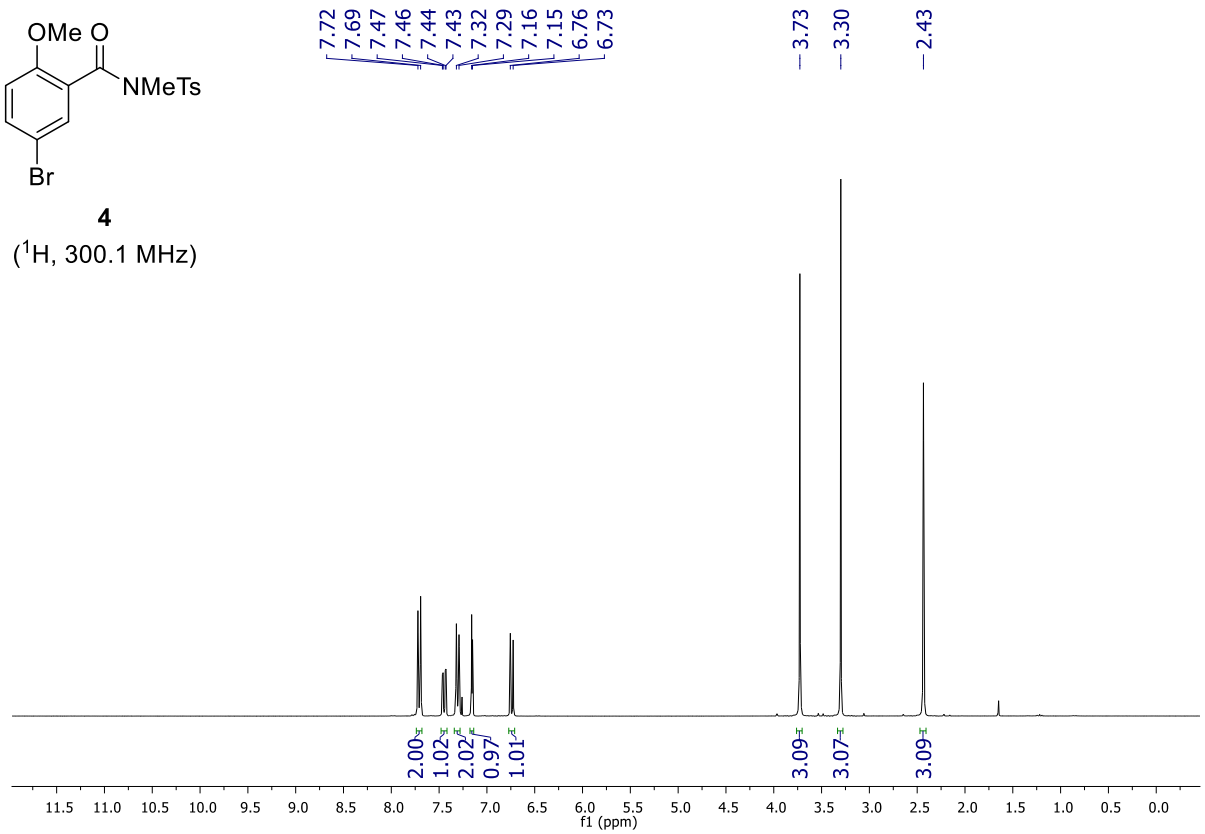
3

(^{19}F, 282.4 MHz)



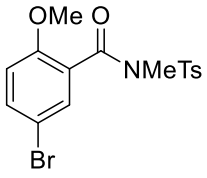
3

(^{13}C, 75.5 MHz)



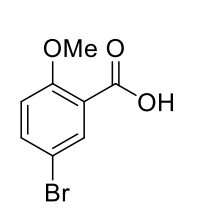
4

(^{1}H, 300.1 MHz)



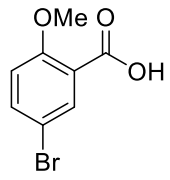
4

(^{13}C, 75.5 MHz)



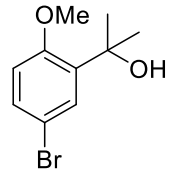
6

(^{1}H, 300.1 MHz)



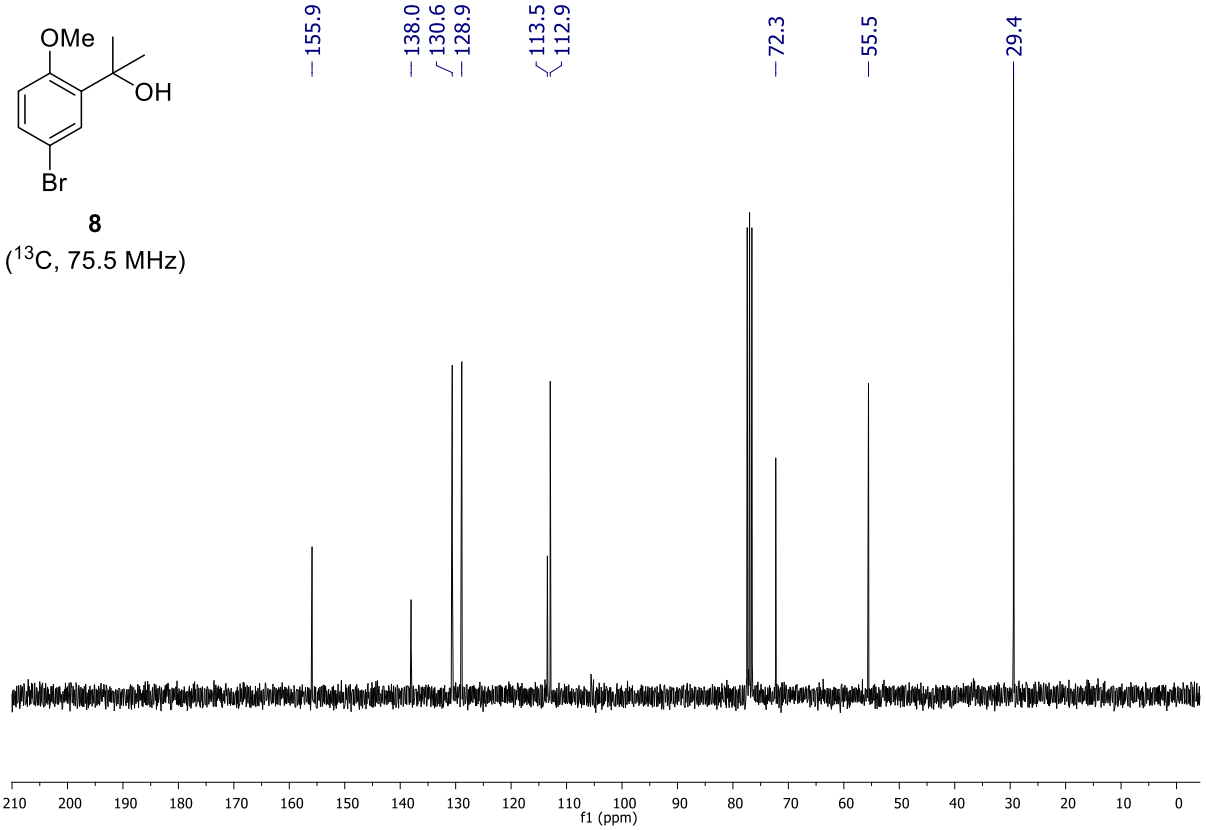
6

(^{13}C, 75.5 MHz)



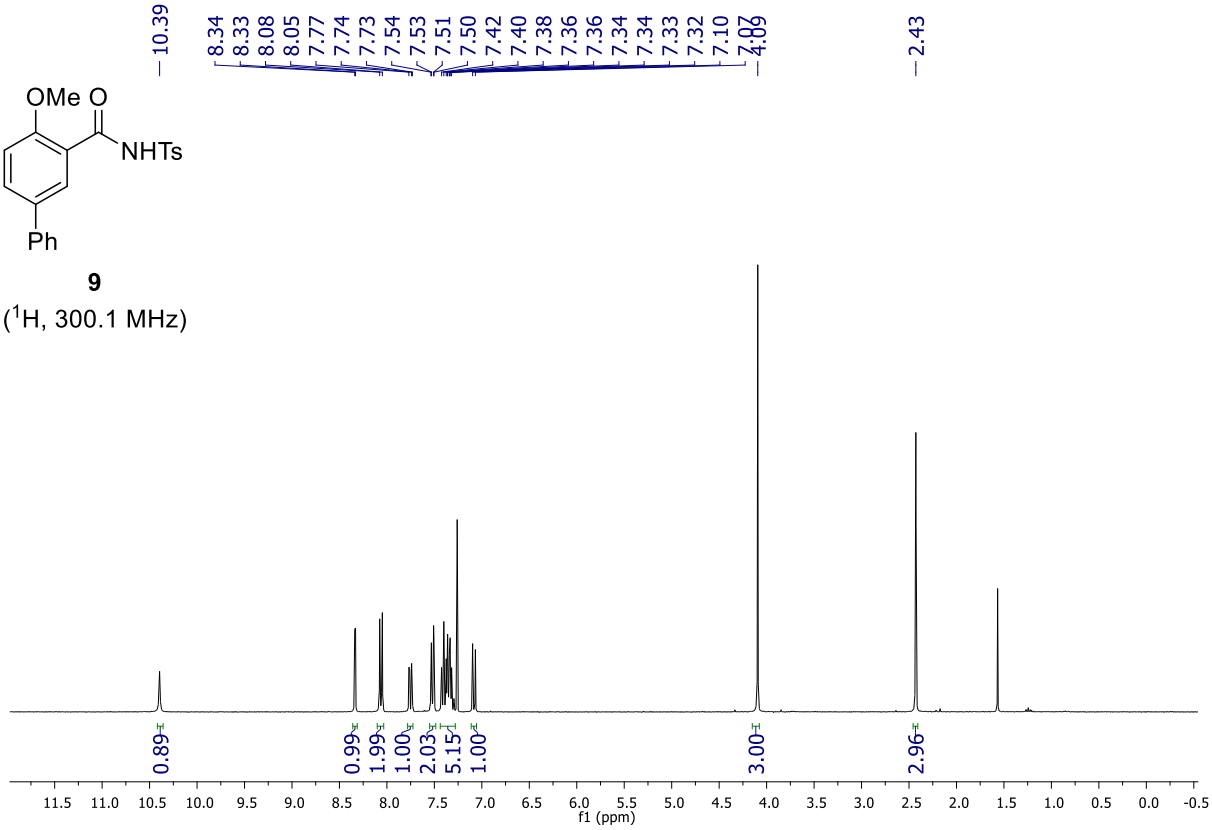
8

(^{1}H, 300.1 MHz)



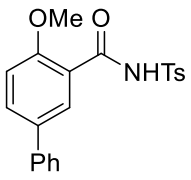
8

(^{13}C, 75.5 MHz)



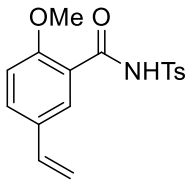
9

(^{1}H, 300.1 MHz)



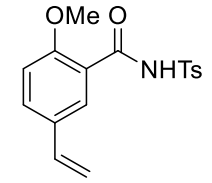
9

(^{13}C, 75.5 MHz)



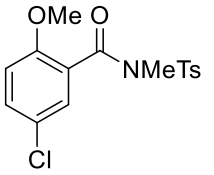
10

(^{1}H, 300.1 MHz)



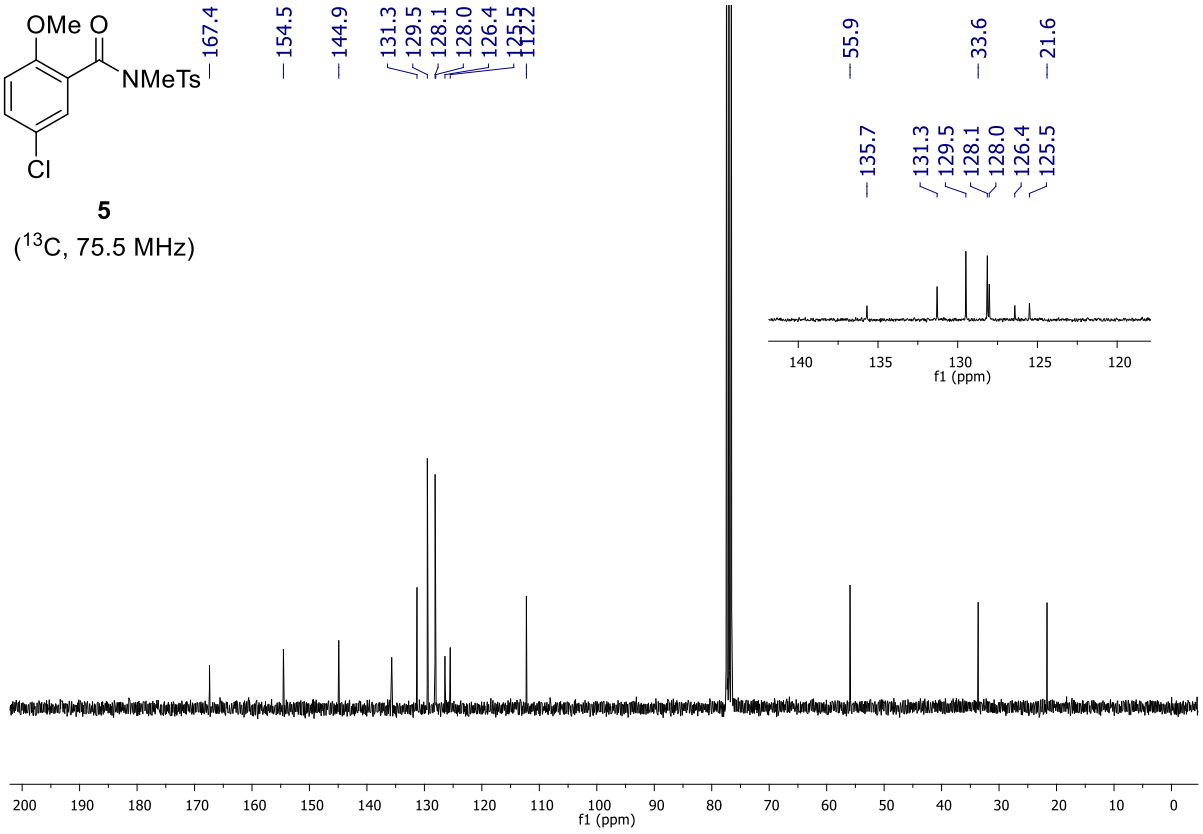
10

(^{13}C, 75.5 MHz)



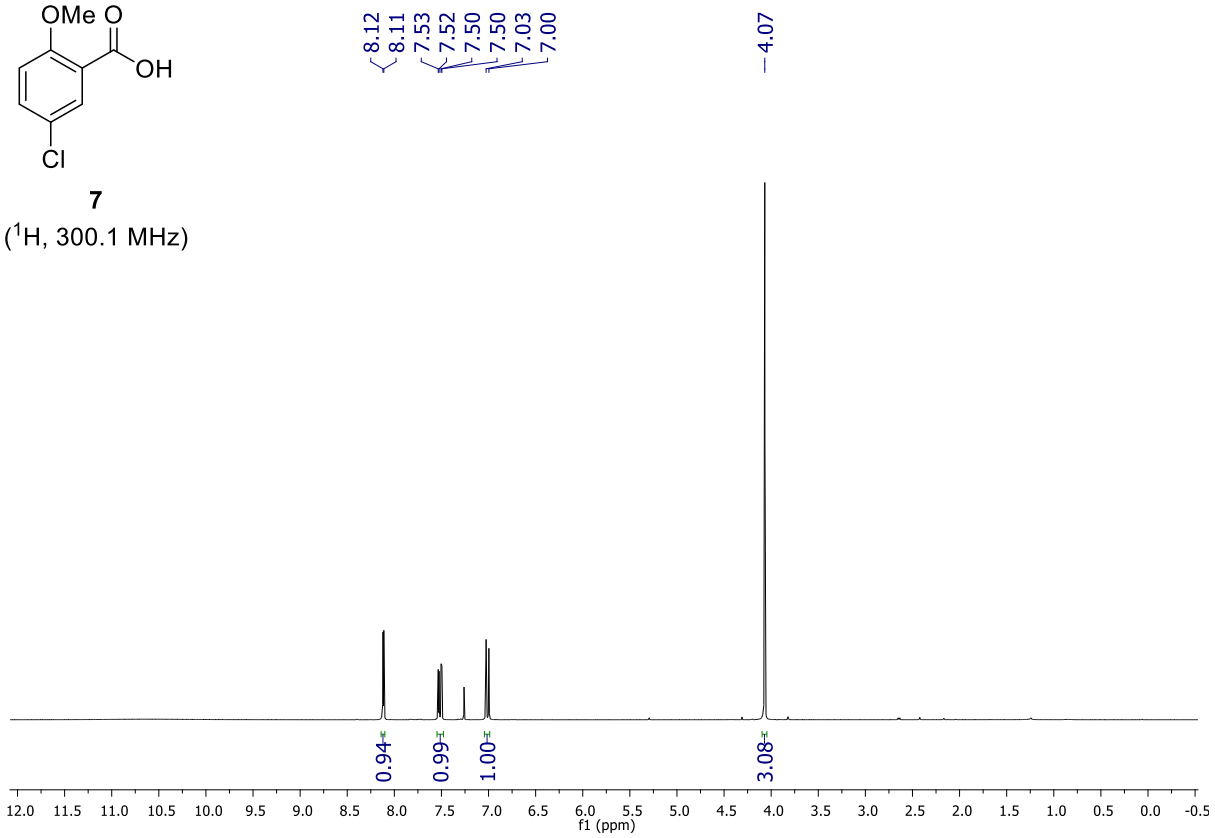
5

(^{1}H, 300.1 MHz)



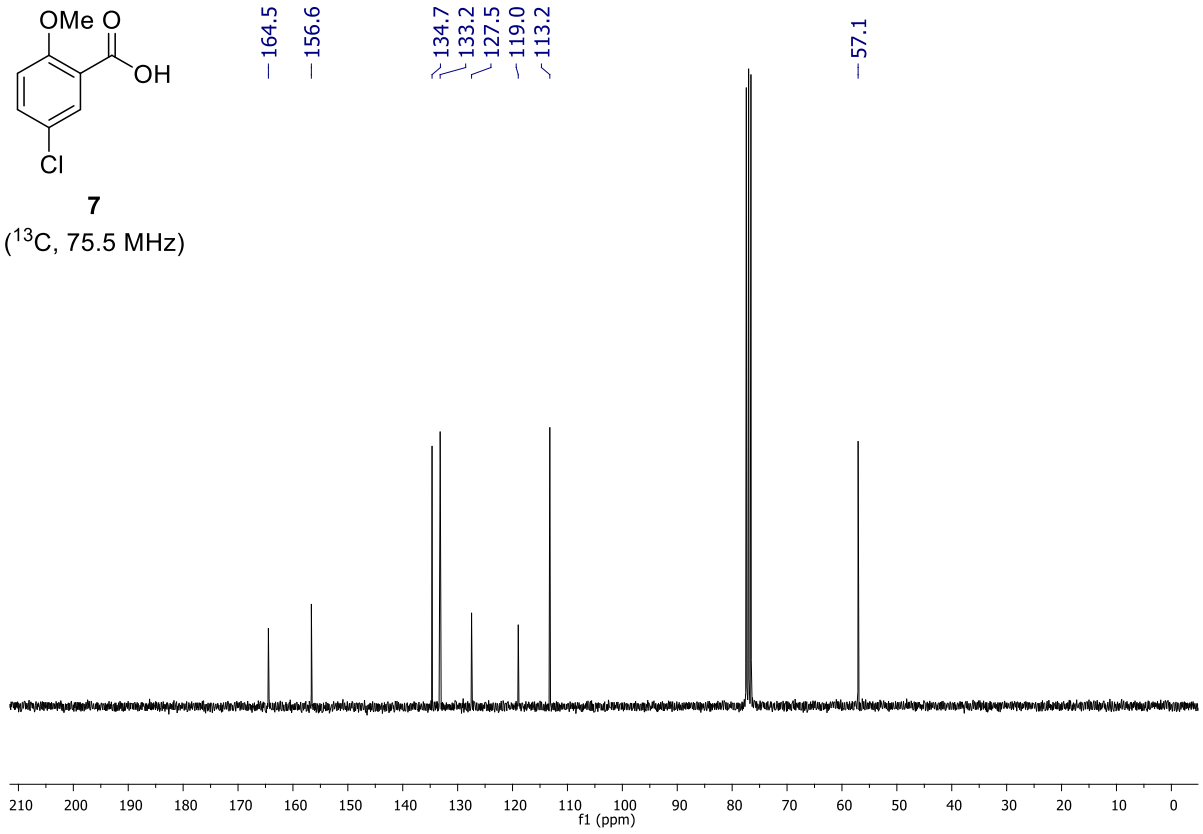
5

(^{13}C, 75.5 MHz)



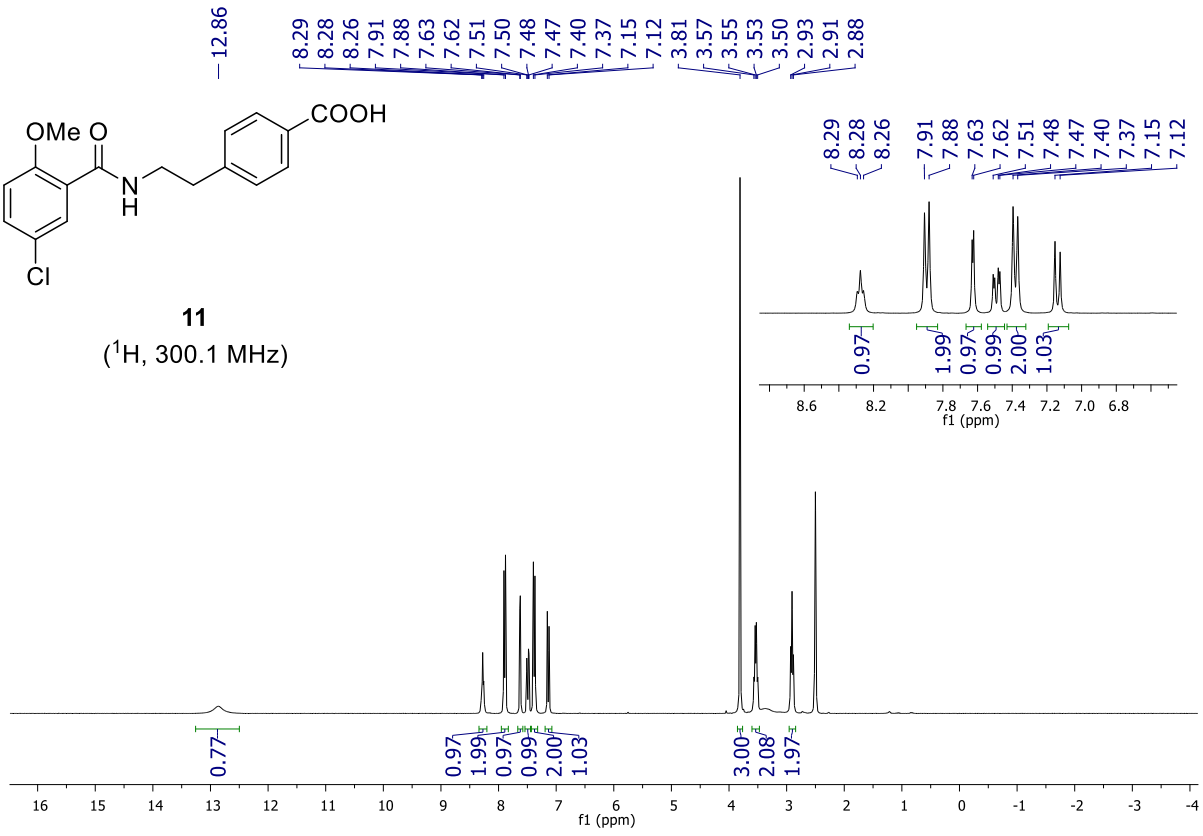
7

(^{1}H, 300.1 MHz)



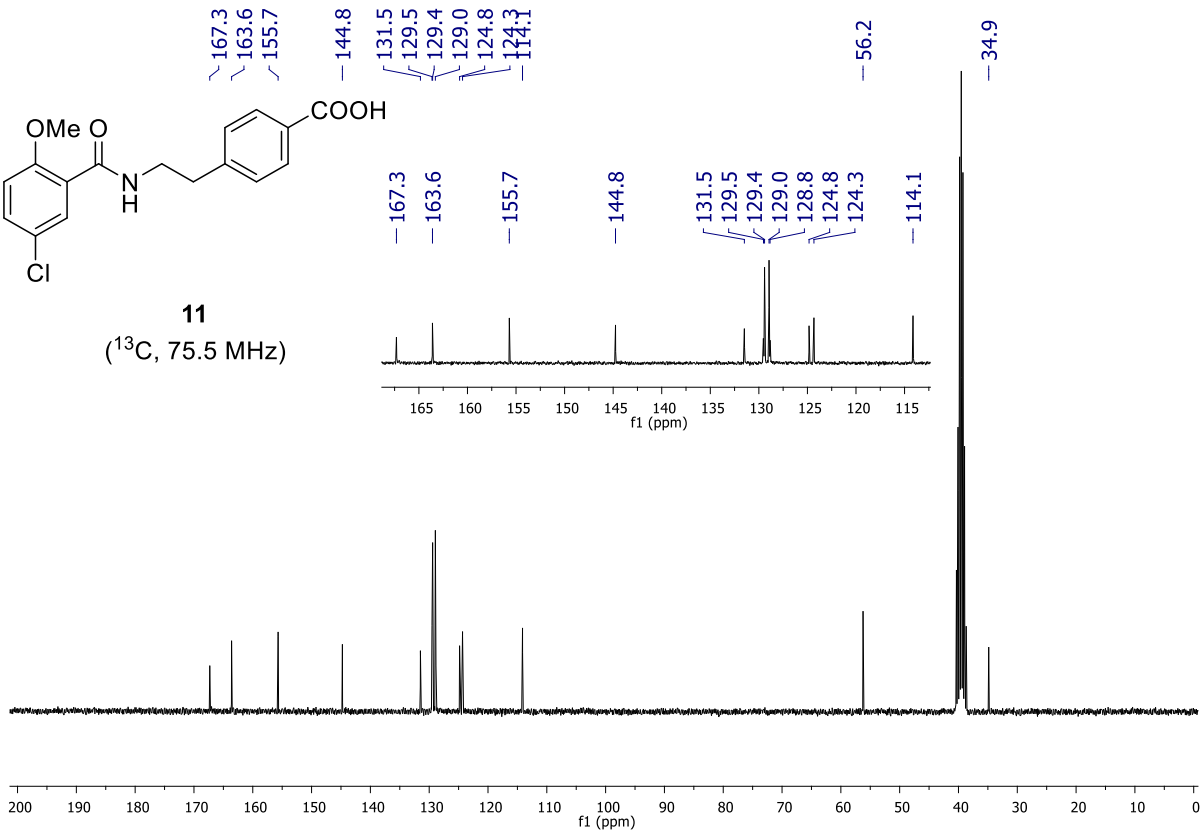
7

(^{13}C, 75.5 MHz)



11

(^{1}H, 300.1 MHz)


167.3
163.6
155.7
144.8
131.5
129.5
129.4
129.0
124.8
124.3
114.1
56.2
34.9
COOH
OMe O
N
H
Cl
11
(13C, 75.5 MHz)
f1 (ppm)
f1 (ppm)

12. References

(1) Péron, F.; Fossey, C.; Sopkova-de Oliveira Santos, J.; Cailly, T.; Fabis, F. Room-Temperature ortho -Alkoxylation and -Halogenation of N -Tosylbenzamides by Using Palladium(II)-Catalyzed C-H Activation. *Chem. Eur. J.* **2014**, *20*, 7507 – 7513.
(2) Berfer, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. Site-selective and versatile aromatic C-H functionalization by thianthrenation. *Nature* **2019**, *567*, 223 – 228.