Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Supporting Information

Construction of 1,3,4-oxadiazolines bearing CF_3-quaternary center via amino-assisting [3+2] cycloadditions

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1. General information

All the solvents and starting materials were obtained from commercial sources and used without further purification unless otherwise stated. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) were recorded on a Bruker AV 400 (400 MHz) spectrometer with $CDCl_3$ as solvent. Chemical shifts were recorded in parts per million (ppm) relative to tetramethylsilane as an internal reference. All shifts are reported in ppm as downfield from TMS as standard. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), m (multiplet). Coupling constants J are reported in Hz. HRMS were obtained on an VG ZAB-HS mass spectrometer with ESI resource. Melting points were measured on a RY-I apparatus and are reported uncorrected. Column chromatography was performed on silica gel 200-300 mesh. The *ortho*-amino trifluoroacetophenones **1**[1] and hydrazonyl chlorides **2**[2] were prepared according to the known methods.

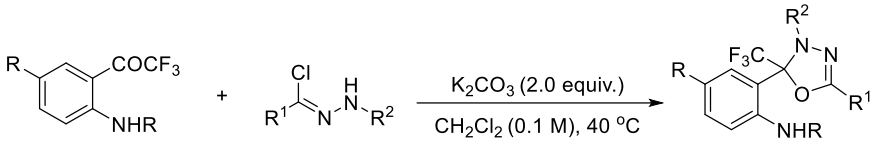
2. References

1. (a) P. Czerwinski and M. Michalak, *J. Org. Chem.,* 2017, **82**, 7980–7997; (b) Y. Sun, Y. Wei and M. Shi, *Org. Chem. Front.,* 2017, **4**, 2392–2402.

2. L. K. B. Garve, M. Petzold, P. G. Jones, and D. B. Werz, *Org. Lett.,* 2016, **18**, 564–567.

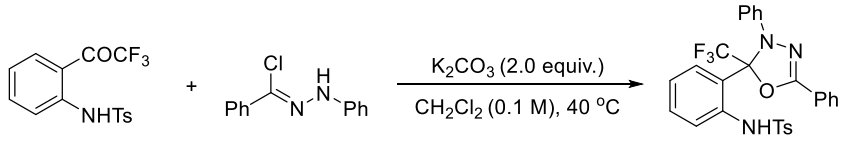
3. General procedures

General procedure for the synthesis of 1,3,4-oxadiazolines 3



The *ortho*-amino trifluoroacetophenones **1** (0.30 mmol), K_2CO_3 (0.60 mmol, 2.0 equiv.) and CH_2Cl_2 (3.0 mL) were added to a 15 mL sealed tube at room temperature. Then hydrazonyl chlorides **2** (0.45 mmol, 1.5 equiv.) was added. This solution was stirred at 40 °C for 8 hours until the complete consumption of the starting materials **1** monitored by TLC. After the removal of the solvent, the residue was purified by flash column chromatography (petroleum ether: EtOAc = 5:1) on silica gel to afford 1,3,4-oxadiazolines **3**.

General procedure for the scale-up experiment



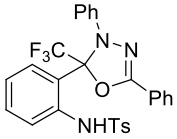
The *ortho*-amino trifluoroacetophenone derivatives **1a** (1.03 g, 3.0 mmol), K_2CO_3 (829 mg, 6.0 mmol, 2.0 equiv.) and CH_2Cl_2 (30 mL) were added to a 100 mL sealed tube at room temperature. Then hydrazonyl chloride **2a** (1.04 g, 4.5 mmol, 1.5 equiv.) was added. This solution was stirred at 40 °C for 8 hours until the complete consumption of the starting material **1a** monitored by TLC. After the removal of the solvent, the residue was purified by flash column chromatography (petroleum ether: EtOAc = 5:1) on silica gel to afford 1,3,4-oxadiazoline **3aa** (1.16 g, 72% yield).

General procedure for the MTT assay

CAL33 grown in logarithmic phase were taken, digested with trypsin to obtain cell suspensions, counted and adjusted to appropriate cell density. 200 μL of cells per well were inoculated in 96-well plates and incubated at 37°C in a humidified 5% CO_2 atmosphere for 24 h. The different compounds were first dissolved in 100% DMSO at 100 mM and then diluted appropriately so that the final concentration of DMSO in cell culture did not exceed 0.1%. Then different compounds were added, all at a concentration of 50 μM, and the corresponding volume of solvent (DMSO) was added to the control group. The incubation was then continued in an incubator at 37°C with 5% CO_2 for another 48h. Briefly, culture medium was added with 5mg/mL 3-(4,5-dimethylthyazol-2-yl)-2,5-diphenyltetrazolium bromide 20 μL and incubated for 4 h at 37 °C. Absorbance was measured at 490 nm in a Varioskan Lux from Bio-Rad using the SkanIt TM software v.6.0 to determine the percentage of cell survival relative to the untreated controls. Cell viability was calculated using the specific application within GraphPath Prism v9.0.1. In addition, cell images for each condition were taken using a ZOE Fluorescent Cell Imager (Bio-Rad Laboratories, Inc., Spain) before the MTT assays.

4. Characterization data

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzene sulfonamide (3aa)



White solid (121.0 mg, 75% yield, m.p. 104-106 °C)

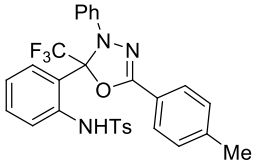
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.6 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.40 (m, 4H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.23 – 7.07 (m, 3H), 7.02 – 6.92 (m, 3H), 6.86 (d, *J* = 8.0 Hz, 2H), 2.23 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 143.8, 140.5, 138.0, 136.3, 132.2, 131.7, 129.5, 129.0, 128.8, 127.1, 127.0, 124.1, 123.6, 123.4, 121.4, 120.1, 117.7, 98.8 (q, *J* = 29.7 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.90 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{23}F_3N_3O_3S$ ($[M+H]^+$): 538.1407; found: 538.1403.

4-Methyl-N-(2-(3-phenyl-5-p-tolyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)benzenesulfonamide (3ab)



White solid (139.0 mg, 84% yield, m.p. 127-129 °C)

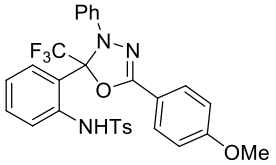
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (t, *J* = 7.8 Hz, 3H), 7.50 (dt, *J* = 8.2, 2.1 Hz, 1H), 7.30 (td, *J* = 8.4, 7.9, 1.4 Hz, 1H), 7.27 – 7.21 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.06 – 6.96 (m, 3H), 6.85 (d, *J* = 7.4 Hz, 1H), 6.83 – 6.78 (m, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 2.31 (s, 3H), 2.12 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 143.8, 142.2, 140.7, 138.0, 136.3, 132.1, 129.5, 129.5, 129.0, 127.2, 127.0, 124.0, 123.2, 121.3, 120.7, 120.2, 117.6, 98.7 (q, *J* = 29.8 Hz), 21.7, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.93(s, 3F).

HRMS (ESI) m/z calcd for $C_{29}H_{25}F_3N_3O_3S$ ($[M+H]^+$): 552.1563; found: 552.1560.

N-(2-(5-(4-methoxyphenyl)-3-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ac)



White solid (115.8 mg, 68% yield, m.p. 138-141 °C)

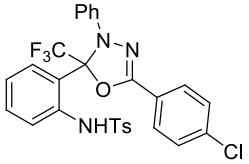
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.72 (d, *J* = 8.5 Hz, 2H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.38 – 7.24 (m, 3H), 7.10 – 6.99 (m, 3H), 6.92 – 6.83 (m, 5H), 6.80 (d, *J* = 8.0 Hz, 2H), 3.75 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 161.3, 152.6, 142.7, 139.7, 136.9, 135.3, 131.0, 128.4, 127.8, 127.7, 126.1, 122.8, 122.0, 120.1, 119.1, 116.5, 114.8, 113.2, 97.5 (q, *J* = 29.7 Hz), 54.4, 20.4.

^{19}F NMR (376 MHz, CDCl$_3$) δ -73.93 (s, 3F).

HRMS (ESI) m/z calcd for $C_{29}H_{25}F_3N_3O_4S$ ([M+H]$^+$): 568.1512; found: 568.1506.

N-(2-(5-(4-chlorophenyl)-3-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ad)



White solid (125.3 mg, 73% yield, m.p. 158-160 °C)

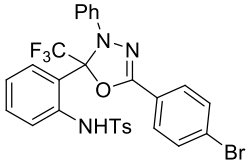
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.57 (t, *J* = 9.8 Hz, 2H), 7.41 – 7.22 (m, 6H), 7.19 – 6.99 (m, 3H), 6.96 – 6.69 (m, 5H), 2.16 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 151.8, 142.8, 139.3, 136.8, 136.6, 135.5, 131.2, 128.5, 128.1, 127.9, 127.8 (q, *J* = 4.2 Hz), 127.1, 126.0, 123.2, 122.4, 121.0, 120.8, 119.4, 116.5, 97.9 (q, *J* = 29.8 Hz), 20.4.

^{19}F NMR (376 MHz, CDCl$_3$) δ -74.11 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}ClF_3N_3O_3S$ ([M+H]$^+$): 572.1017; found: 572.1011.

N-(2-(5-(4-bromophenyl)-3-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ae)



White solid (120.2 mg, 65% yield, m.p. 129-131 °C)

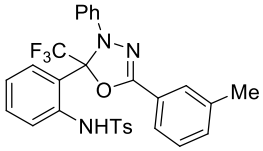
^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 – 7.62 (m, 4H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.49 – 7.41 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.22 – 7.17 (m, 1H), 7.15 (t, *J* = 7.9 Hz, 2H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.93 (t, *J* = 7.6 Hz, 4H), 2.26 (s, 3H).

^{13}C NMR (101 MHz, CDCl$_3$) δ 152.9, 143.9, 140.4, 138.0, 136.6, 132.3, 132.1, 129.6, 129.0, 128.8 (t, *J* = 4.3 Hz), 128.3, 127.0, 126.1, 124.3, 123.5, 122.5, 121.9, 120.5, 117.6, 99.0 (q, *J* = 29.8 Hz), 21.6.

^{19}F NMR (376 MHz, CDCl$_3$) δ -74.11 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}BrF_3N_3O_3S$ ($[M+H]^+$): 616.0512; found: 616.0506.

4-methyl-N-(2-(3-phenyl-5-m-tolyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)benzenesulfonamide (3af)



White solid (137.3 mg, 83% yield, m.p. 112-114 °C)

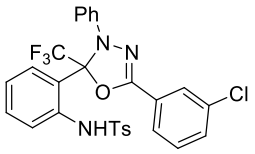
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 1H), 7.65 – 7.48 (m, 3H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.31 – 7.15 (m, 4H), 7.12 – 7.00 (m, 3H), 6.91 – 6.82 (m, 3H), 6.78 (d, *J* = 7.9 Hz, 2H), 2.33 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 143.8, 140.6, 138.7, 138.0, 136.3, 132.5, 132.1, 129.5, 129.0, 129.0, 128.8, 128.7, 127.5, 127.2, 124.2, 124.0, 123.4, 123.3, 121.2, 120.0, 117.7, 98.7 (q, *J* = 29.5 Hz), 21.5, 21.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.88 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}BrF_3N_3O_3S$ ($[M+H]^+$): 552.1563; found: 552.1557.

N-(2-(5-(3-chlorophenyl)-3-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (**3ag**)



White solid (121.8 mg, 71% yield, m.p. 118-121 °C)

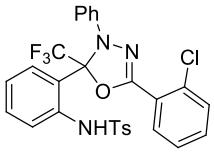
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.73 (m, 3H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.43 – 7.33 (m, 3H), 7.25 – 7.11 (m, 4H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.94 (t, *J* = 7.7 Hz, 4H), 2.27 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.5, 144.0, 140.3, 137.9, 136.4, 134.9, 132.3, 131.6, 130.2, 129.6, 129.1, 128.9 (q, *J* = 4.2 Hz), 127.1, 126.8, 125.3, 125.1, 124.3, 123.6, 121.8, 120.2, 117.7, 99.1 (q, *J* = 29.8 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.99 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}ClF_3N_3O_3S$ ($[M+H]^+$): 572.1017; found: 572.1012.

N-(2-(5-(2-chlorophenyl)-3-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ah)



White solid (106.4 mg, 62% yield, m.p. 105-107 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 24.6, 8.0 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.35 – 7.12 (m, 6H), 7.14 – 6.93 (m, 3H), 6.90 – 6.60 (m, 5H), 2.07 (s, 3H).

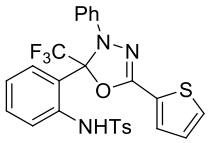
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.5, 143.8, 140.4, 138.0, 136.4, 133.5, 132.2, 132.1, 131.3, 130.8, 129.4, 129.0, 128.9 (d, *J* = 4.4 Hz), 127.0, 126.9, 124.2, 123.5, 122.6, 121.9, 120.3, 117.7, 98.3 (q, *J* =

29.8 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.83 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}ClF_3N_3O_3S$ ($[M+H]^+$): 572.1017; found: 572.1012.

4-methyl-N-(2-(3-phenyl-5-(thiophen-2-yl)-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)benzenesulfonamide (3ai)



Yellow oil (112.5 mg, 69% yield)

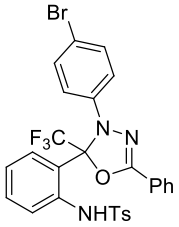
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.63 (dt, *J* = 8.2, 2.1 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.54 – 7.50 (m, 1H), 7.45 – 7.40 (m, 2H), 7.18 – 7.12 (m, 4H), 7.02 – 6.89 (m, 5H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 143.8, 140.4, 138.0, 136.4, 132.2, 130.2, 130.1, 129.5, 129.0, 128.9, 127.9, 127.1, 124.9, 124.1, 123.5, 121.5, 120.0, 117.8, 98.9 (q, *J* = 30.1 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.88 (s, 3F).

HRMS (ESI) m/z calcd for $C_{26}H_{21}F_3N_3O_3S_2$ ($[M+H]^+$): 544.0971; found: 544.0966.

N-(2-(3-(4-bromophenyl)-5-phenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3aj)



White solid (140.6 mg, 76% yield, m.p. 146-148 °C)

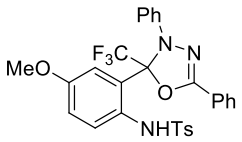
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.54 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.37 (t, *J* = 6.8 Hz, 3H), 7.27 (d, *J* = 7.8 Hz, 2H), 7.20 – 7.06 (m, 4H), 6.80 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 8.4 Hz, 2H), 2.15 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 144.0, 139.6, 137.9, 136.1, 132.4, 131.9, 129.5, 128.9, 128.8 (d, *J* = 4.1 Hz), 127.1, 127.0, 124.2, 123.2, 121.4, 119.6, 118.8, 115.7, 98.5 (q, *J* = 30.1 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.13 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}BrF_3N_3O_3S$ ($[M+H]^+$): 616.0512; found: 616.0506.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-4-methoxyphenyl)-4-methylbenzenesulfonamide (3ba)



White solid (120.9 mg, 71% yield, m.p. 120-123 °C)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 2H), 7.53 (d, *J* = 9.0 Hz, 1H), 7.49 – 7.30 (m, 3H),

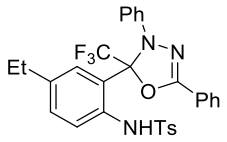
7.26 (d, *J* = 7.9 Hz, 2H), 7.16 – 7.09 (m, 1H), 7.05 (t, *J* = 7.8 Hz, 2H), 6.94 – 6.82 (m, 4H), 6.77 (d, *J* = 8.0 Hz, 2H), 3.68 (s, 3H), 2.13 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.3, 153.5, 143.5, 140.7, 136.8, 131.5, 130.4, 129.5, 129.0, 128.7, 127.1, 127.0, 124.7, 123.8, 123.3, 117.6, 116.1, 115.7 (q, *J* = 4.2 Hz), 98.6 (q, *J* = 29.5 Hz), 55.6, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.10 (s, 3F).

HRMS (ESI) m/z calcd for $C_{29}H_{25}F_3N_3O_4S$ ($[M+H]^+$): 568.1512; found: 568.1508.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-4-ethylphenyl)-4-methylbenzenesulfonamide (3ca)



White solid (129.0 mg, 76% yield, m.p. 138-141 °C)

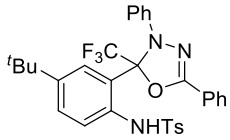
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 2H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.71 – 7.48 (m, 4H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 3H), 6.93 (d, *J* = 7.9 Hz, 2H), 2.71 (q, *J* = 7.9 Hz, 2H), 2.29 (s, 3H), 1.29 (t, *J* = 7.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 143.7, 140.7, 140.2, 136.6, 135.5, 131.6, 131.5, 129.5, 129.0, 128.8, 128.2 (q, *J* = 4.1 Hz), 127.1, 127.0, 123.7, 123.3, 121.9, 120.5, 117.7, 98.9 (q, *J* = 29.7 Hz), 28.3, 21.5, 15.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.80 (s, 3F).

HRMS (ESI) m/z calcd for $C_{30}H_{27}F_3N_3O_3S$ ($[M+H]^+$): 566.1720; found: 566.1715.

N-(4-tert-butyl-2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3da)



White solid (135.4 mg, 76% yield, m.p. 140-142 °C)

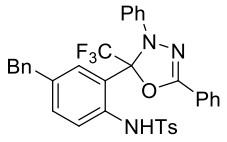
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.3 Hz, 2H), 7.79 – 7.64 (m, 2H), 7.63 – 7.37 (m, 6H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.11 – 6.84 (m, 5H), 2.29 (s, 3H), 1.37 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 147.1, 143.6, 140.8, 136.8, 135.1, 131.6, 129.5, 128.9, 128.8, 127.1, 127.0, 125.9 (d, *J* = 4.3 Hz), 123.7, 123.3, 121.4, 120.0, 117.8, 99.1 (q, *J* = 29.8 Hz), 34.6, 31.2, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.06 (s, 3F).

HRMS (ESI) m/z calcd for $C_{32}H_{31}F_3N_3O_3S$ ($[M+H]^+$): 594.2033; found: 594.2028.

N-(4-benzyl-2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ea)



White solid (167.6 mg, 89% yield, m.p. 118-120 °C)

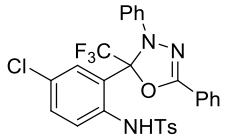
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dt, *J* = 7.0, 1.7 Hz, 2H), 7.75 (dt, *J* = 8.5, 2.1 Hz, 1H), 7.65 – 7.51 (m, 4H), 7.47 (dt, *J* = 8.4, 1.8 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.38 – 7.30 (m, 2H), 7.29 – 7.18 (m, 4H), 7.13 – 7.03 (m, 3H), 6.97 (d, *J* = 8.0 Hz, 2H), 4.07 (s, 2H), 2.31 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 143.8, 140.7, 140.1, 137.3, 136.6, 136.0, 132.5, 131.7, 129.6, 129.4 (q, *J* = 4.0 Hz), 129.0, 128.9, 128.8, 128.8, 127.2, 127.0, 126.6, 123.7, 123.4, 121.9, 120.5, 117.8, 98.9 (q, *J* = 29.8 Hz), 41.3, 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.01(s, 3F).

HRMS (ESI) m/z calcd for $C_{35}H_{29}F_3N_3O_3S$ ($[M+H]^+$): 628.1876; found: 628.1872.

N-(4-chloro-2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3fa)



White solid (125.3 mg, 73% yield, m.p. 104-106 °C)

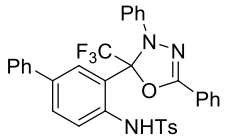
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 2H), 7.77 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.57 (m, 1H), 7.56 – 7.51 (m, 1H), 7.52 – 7.45 (m, 2H), 7.43 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.23 – 7.15 (m, 2H), 7.06 – 7.00 (m, 1H), 6.95 (dd, *J* = 7.6, 1.6 Hz, 2H), 6.87 (d, *J* = 8.1 Hz, 2H), 2.25 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 145.8, 144.0, 140.3, 136.7, 136.0, 132.1, 131.8, 129.6, 129.5, 129.4, 129.1, 128.8, 127.1, 127.0, 123.8, 123.3, 122.6, 121.8, 118.0, 98.3 (q, *J* = 29.9 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.96 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{22}ClF_3N_3O_3S$ ($[M+H]^+$): 572.1017; found: 572.1016.

N-(3-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)biphenyl-4-yl)-4-methylbenzenesulfonamide (3ga)



White solid (132.5 mg, 72% yield, m.p. 168-170 °C)

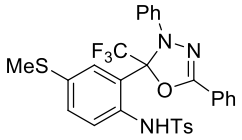
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.71 (m, 4H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.48 – 7.27 (m, 9H), 7.23 (t, *J* = 7.3 Hz, 1H), 7.04 (t, *J* = 7.7 Hz, 2H), 6.95 – 6.82 (m, 3H), 6.75 (d, *J* = 7.9 Hz, 2H), 2.10 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 143.9, 140.6, 139.3, 137.2, 137.0, 136.4, 131.7, 130.6, 129.6, 129.2, 129.1, 128.9, 128.0, 127.5 (t, *J* = 4.3 Hz), 127.2, 127.1, 126.9, 123.6 (d, *J* = 4.3 Hz), 121.8, 120.7, 117.9, 99.0 (q, *J* = 29.6 Hz), 21.6.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.52 (s, 3F).

HRMS (ESI) m/z calcd for $C_{34}H_{27}F_3N_3O_3S$ ($[M+H]^+$): 614.1720; found: 614.1715.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-4-(methylthio)phenyl)-4-methylbenzenesulfonamide (3ha)



Yellow solid (129.6 mg, 74% yield, m.p. 107-109 °C)

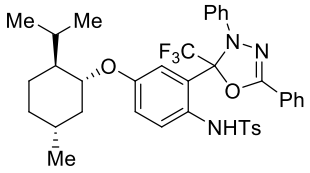
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.85 (m, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.64 – 7.47 (m, 4H), 7.44 – 7.34 (m, 3H), 7.23 (t, *J* = 7.9 Hz, 2H), 7.04 (t, *J* = 7.2 Hz, 3H), 6.92 (d, *J* = 8.0 Hz, 2H), 2.50 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 143.8, 140.5, 136.3, 135.1, 134.7, 131.7, 130.2, 129.6, 129.1, 128.8, 127.1, 127.0, 123.6, 123.5, 122.4, 121.3, 117.9, 98.6 (q, *J* = 29.8 Hz), 21.5, 16.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.65 (s, 3F).

HRMS (ESI) m/z calcd for $C_{29}H_{25}F_3N_3O_3S_2$ ($[M+H]^+$): 584.1284; found: 584.1280.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)-4-((1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy)phenyl)-4-methylbenzenesulfonamide (3ia)



Pale yellow solid (197.2 mg, 95% yield, m.p. 154-156 °C)

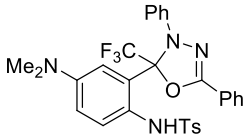
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 2H), 7.71 – 7.36 (m, 5H), 7.24 (d, *J* = 32.6 Hz, 4H), 7.13 – 6.79 (m, 7H), 4.03 (s, 1H), 2.29 (s, 3H), 2.20 – 2.04 (m, 2H), 1.78 (d, *J* = 12.2 Hz, 2H), 1.54 (d, *J* = 31.7 Hz, 2H), 1.24 – 0.91 (m, 9H), 0.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 153.4, 143.5, 140.8, 137.0 (d, *J* = 4.3 Hz), 131.5, 130.1 (d, *J* = 6.8 Hz), 129.5, 128.9 (d, *J* = 2.3 Hz), 128.7, 127.1, 127.0, 124.8 (d, *J* = 3.8 Hz), 123.8 (d, *J* = 2.3 Hz), 123.4 (d, *J* = 11.3 Hz), 123.2, 118.4 (d, *J* = 22.5 Hz), 117.9 (d, *J* = 4.3 Hz), 117.7 (d, *J* = 4.0 Hz), 98.6 (q, *J* = 29.4 Hz), 79.0, 78.9, 48.1, 40.2, 34.4, 31.4, 26.1, 23.6 (d, *J* = 2.4 Hz), 22.2, 21.5, 20.8 (d, *J* = 2.8 Hz), 16.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.27 (s, 3F).

HRMS (ESI) m/z calcd for $C_{38}H_{41}F_3N_3O_4S$ ($[M+H]^+$): 692.2764; found: 692.2759.

N-(4-(dimethylamino)-2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methylbenzenesulfonamide (3ja)



Yellow solid (146.3 mg, 84% yield, m.p. 150-152 °C)

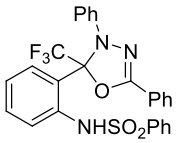
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.76 (m, 2H), 7.56 – 7.40 (m, 4H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.17 – 7.10 (m, 2H), 6.99 – 6.92 (m, 4H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.81 (s, 1H), 6.73 (dd, *J* = 9.1, 2.8 Hz, 1H), 2.95 (s, 6H), 2.24 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 147.8, 143.1, 140.9, 137.4, 131.3, 129.4, 128.9, 128.6, 127.1, 127.0, 125.7, 124.1, 123.9, 122.8, 117.4, 114.9, 112.3 (d, *J* = 5.0 Hz), 98.9 (q, *J* = 29.8 Hz), 40.4, 21.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ -74.08(s, 3F).

HRMS (ESI) m/z calcd for $C_{30}H_{28}F_3N_4O_3S$ ($[M+H]^+$): 581.1829; found: 581.1824.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)benzenesulfonamide (3ka)



White solid (111.5 mg, 71% yield, m.p. 106-108 °C)

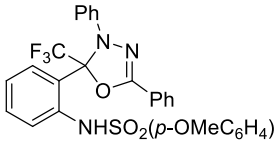
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.90 (m, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.62 – 7.45 (m, 5H), 7.39 (s, 1H), 7.30 – 6.94 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 140.5, 139.3, 137.9, 133.0, 132.2, 131.7, 129.1, 128.9, 128.9, 127.1, 127.1, 124.2, 123.6, 123.5, 121.4, 120.3, 117.7, 98.8 (q, *J* = 29.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$) δ -73.91(s, 3F).

HRMS (ESI) m/z calcd for $C_{27}H_{21}F_3N_3O_3S$ ($[M+H]^+$): 524.1250; found: 524.1245.

N-(2-(3,5-diphenyl-2-(trifluoromethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenyl)-4-methoxybenzenesulfonamide (3la)



White solid (134.5 mg, 81% yield, m.p. 124-126 °C)

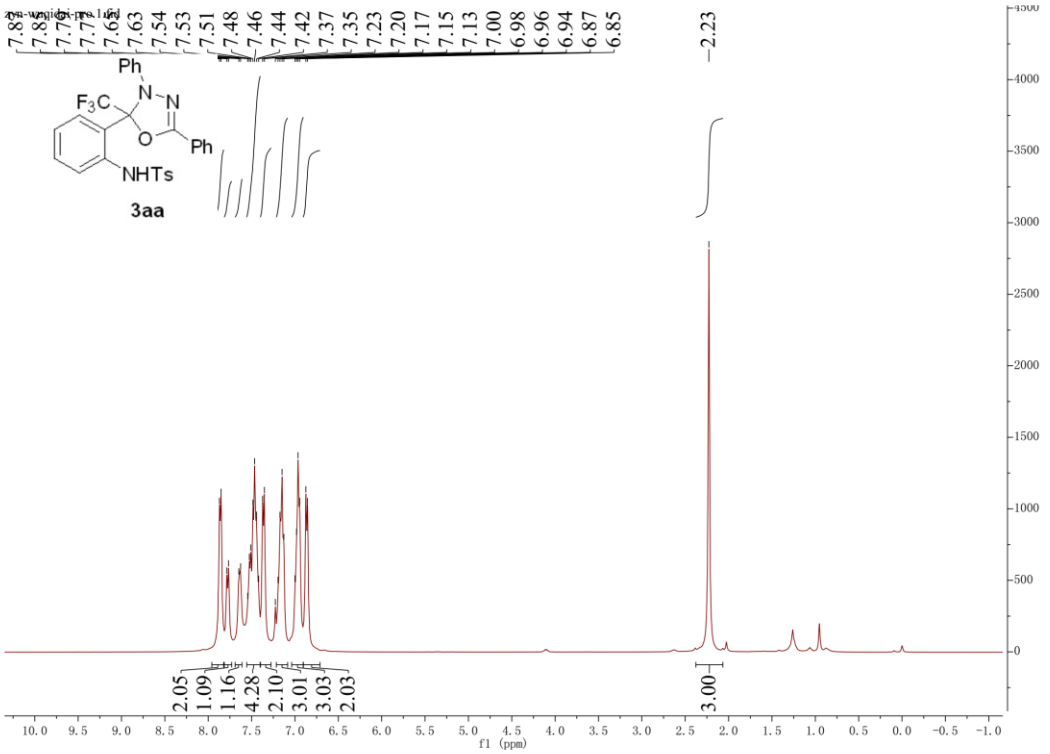
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 0H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.57 – 7.33 (m, 3H), 7.23 – 7.07 (m, 2H), 7.05 – 6.84 (m, 1H), 6.53 (d, *J* = 8.5 Hz, 1H), 3.68 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 153.6, 140.5, 138.1, 132.2, 131.7, 130.7, 129.4, 129.0, 128.9, 127.0, 124.0, 123.5, 123.3, 121.3, 120.0, 117.6, 114.0, 98.8 (q, *J* = 29.7 Hz), 55.5.

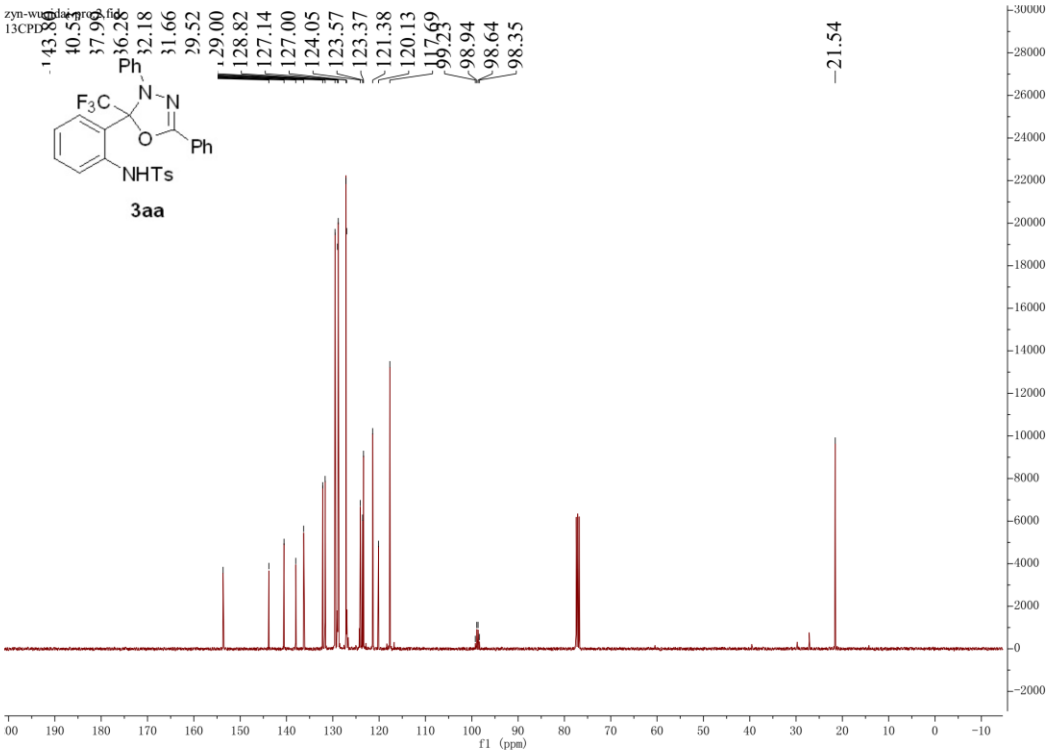
^{19}F NMR (376 MHz, $CDCl_3$) δ -73.89 (s, 3F).

HRMS (ESI) m/z calcd for $C_{28}H_{23}F_3N_3O_4S$ ($[M+H]^+$): 554.1356; found: 554.1353.

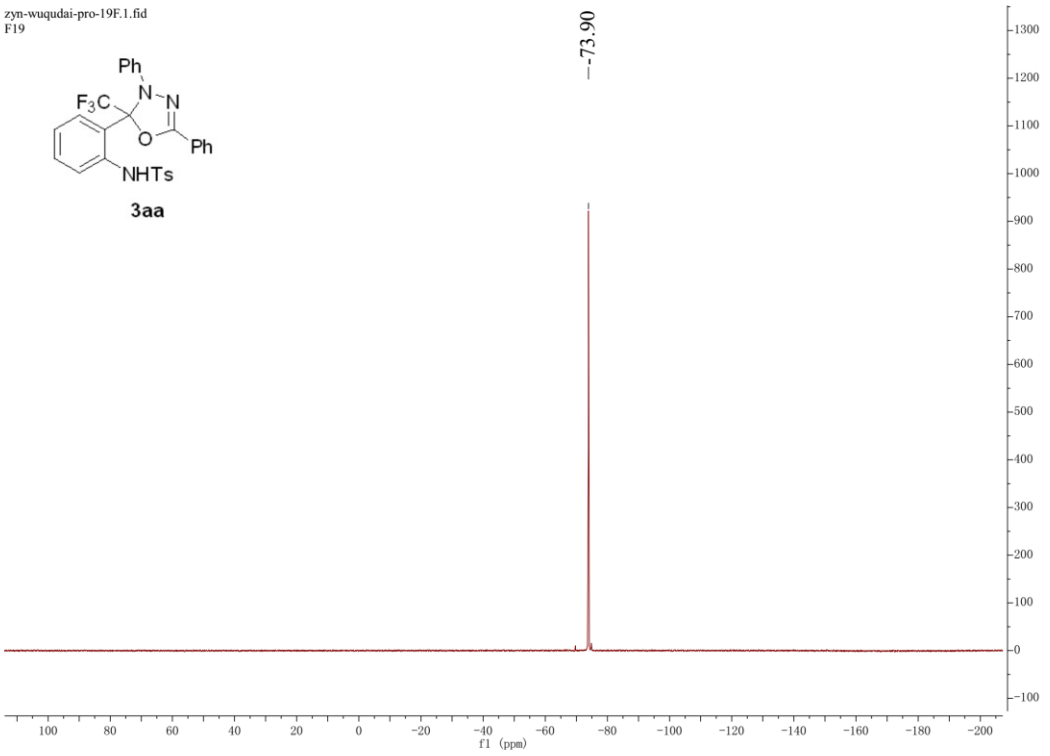
5. NMR spectra of products



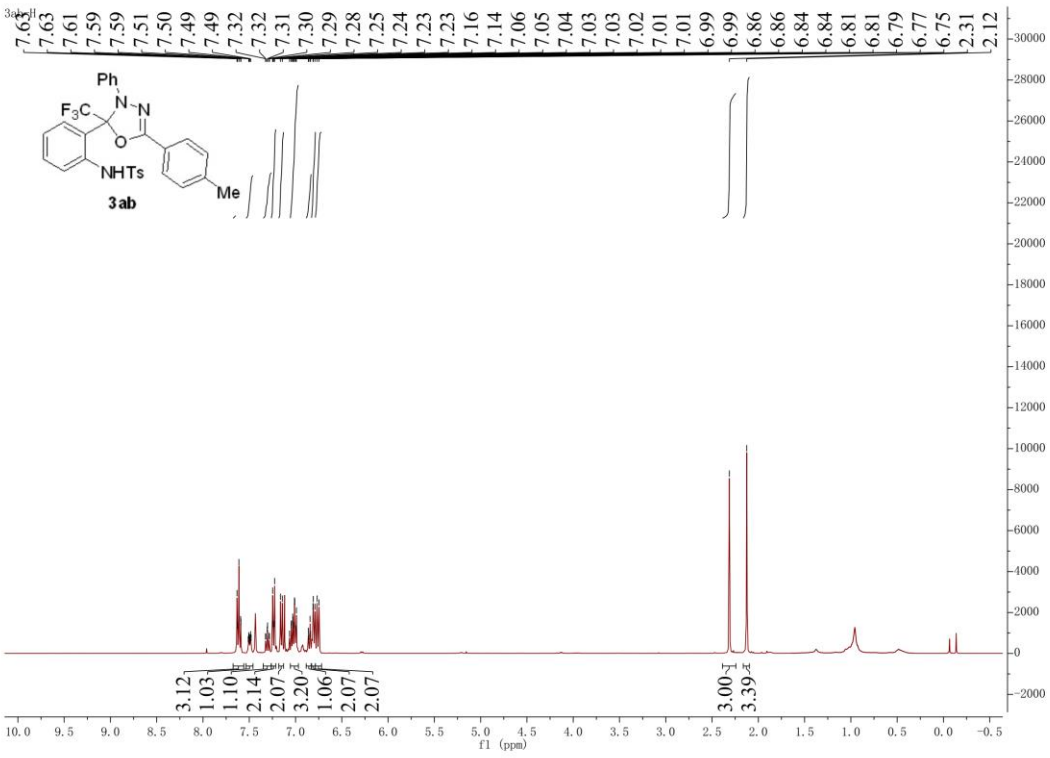
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3aa**



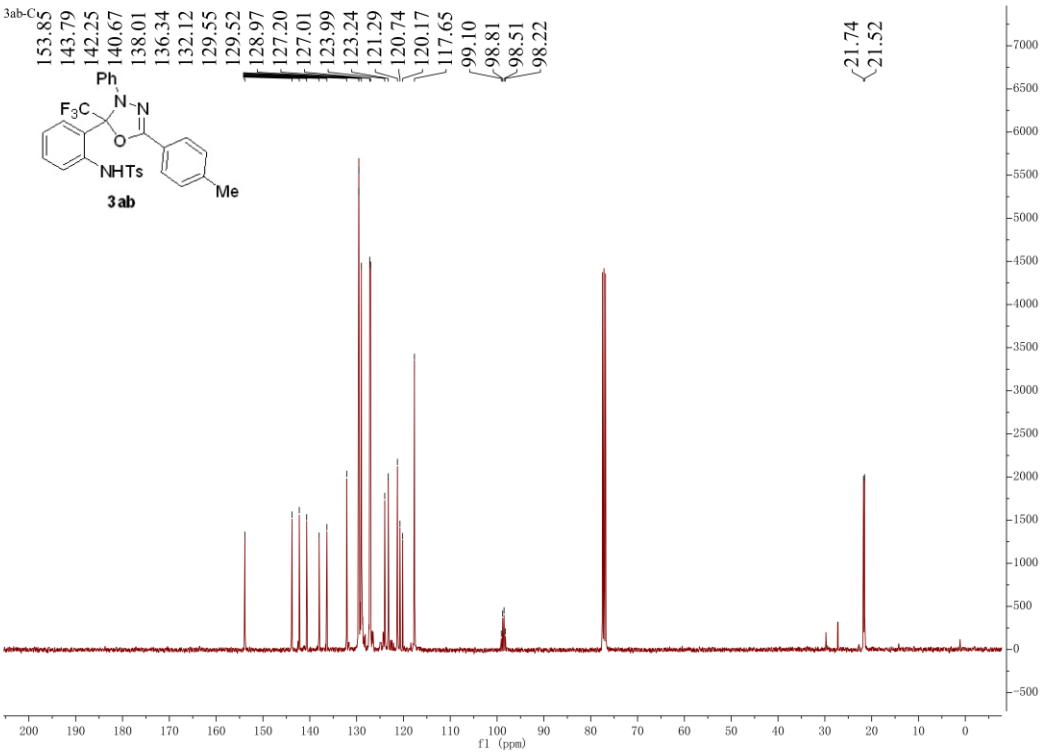
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3aa**



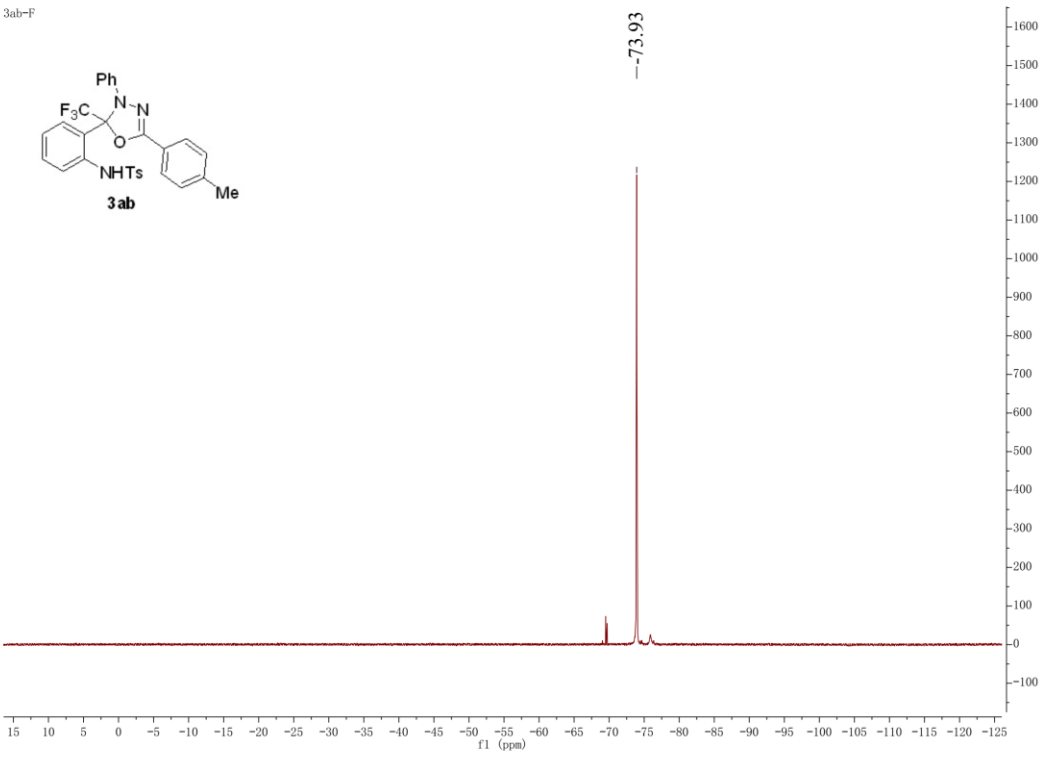
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3aa**



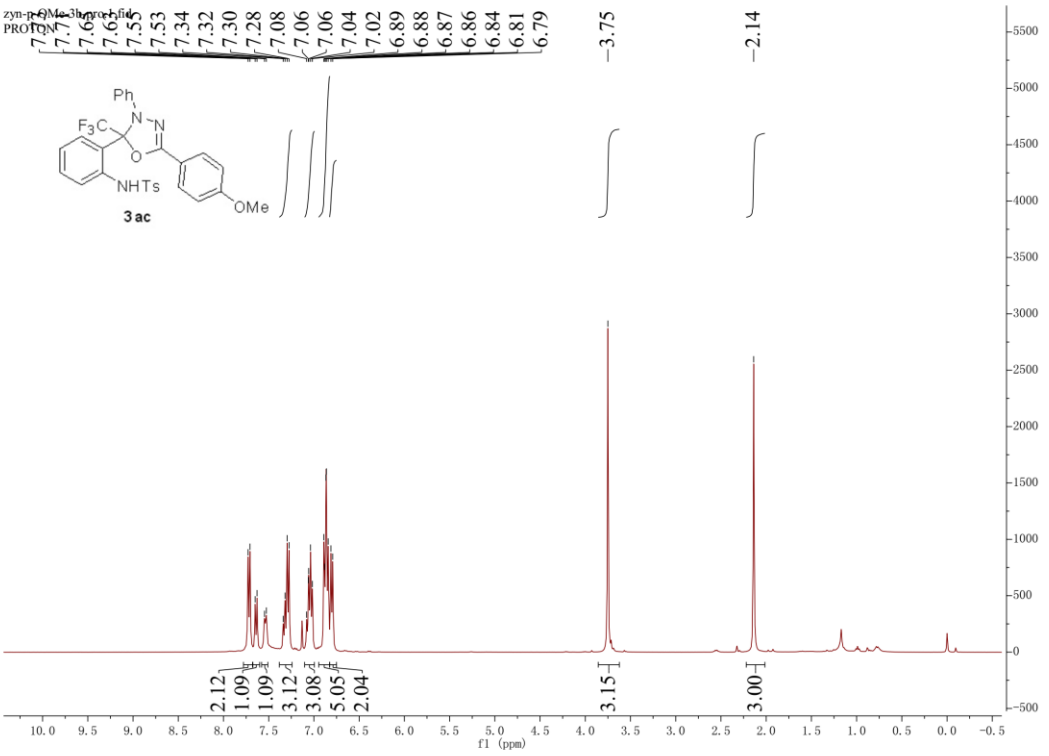
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ab**



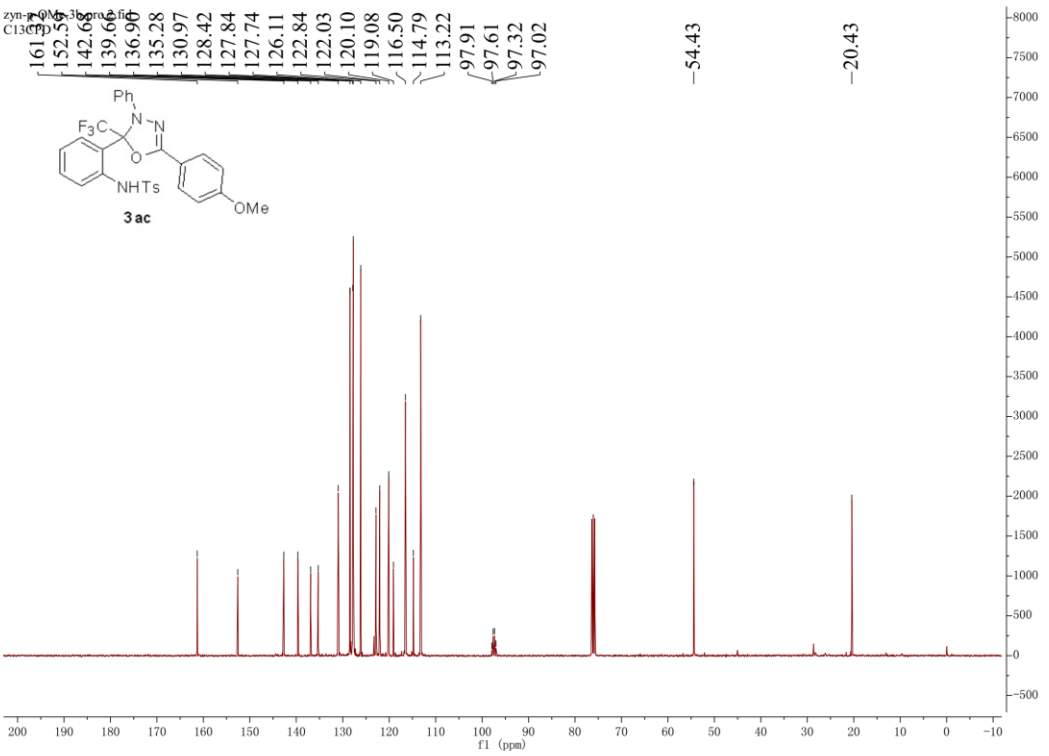
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ab**



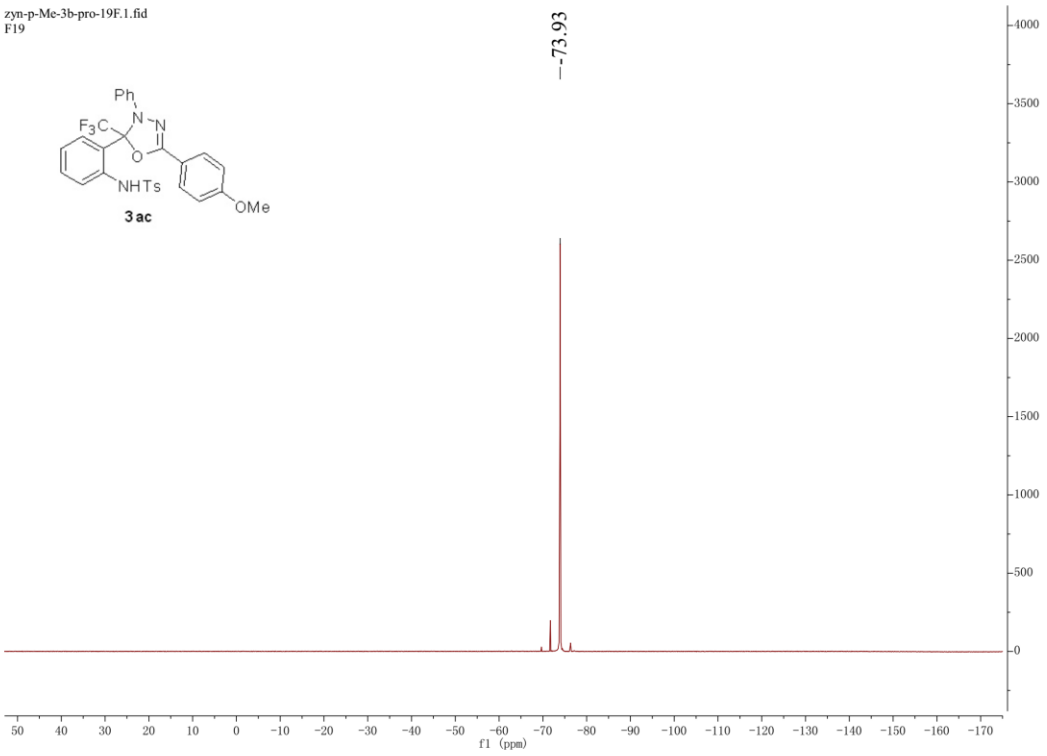
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ab**



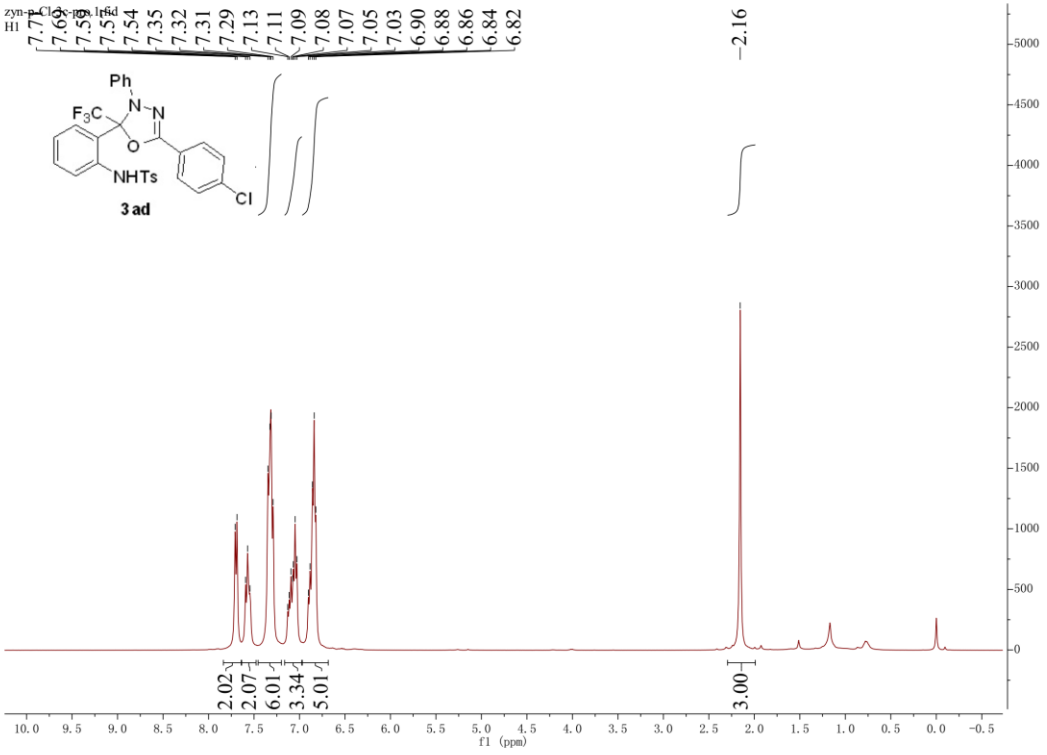
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ac**



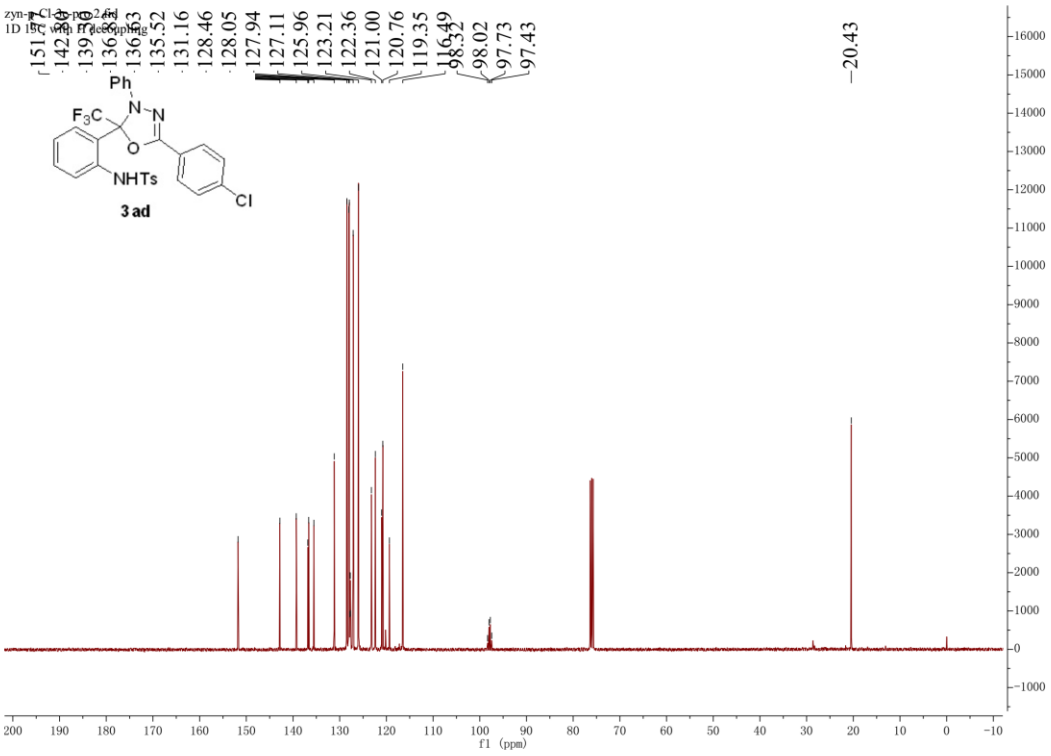
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ac**



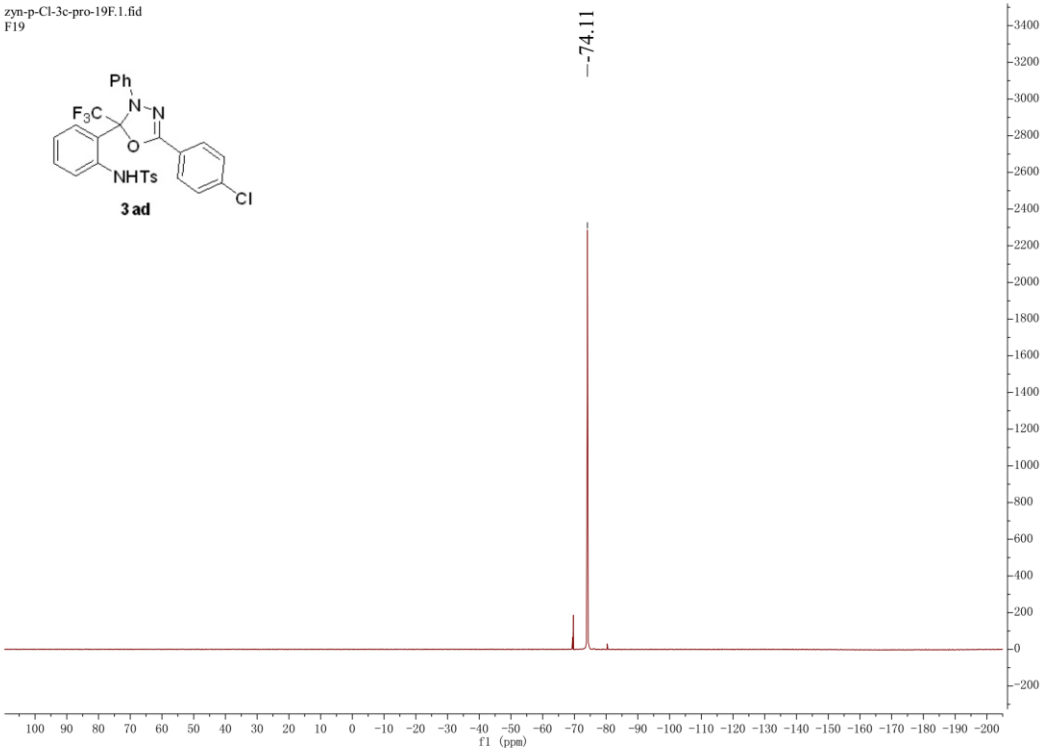
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ac**



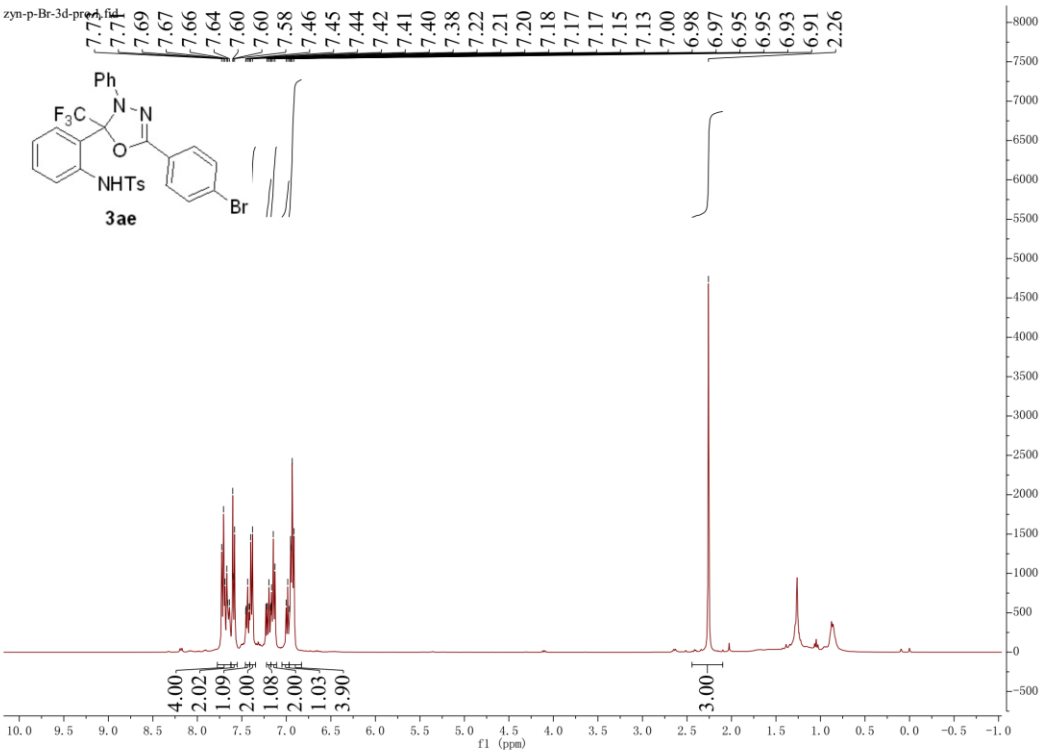
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ad**



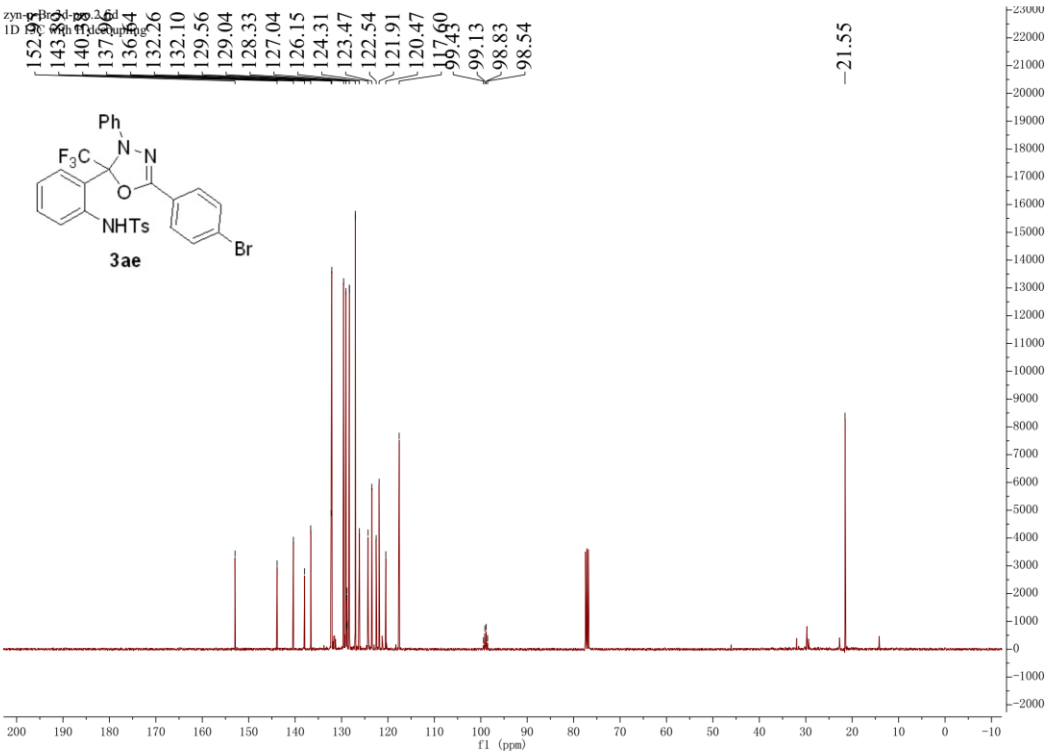
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ad**



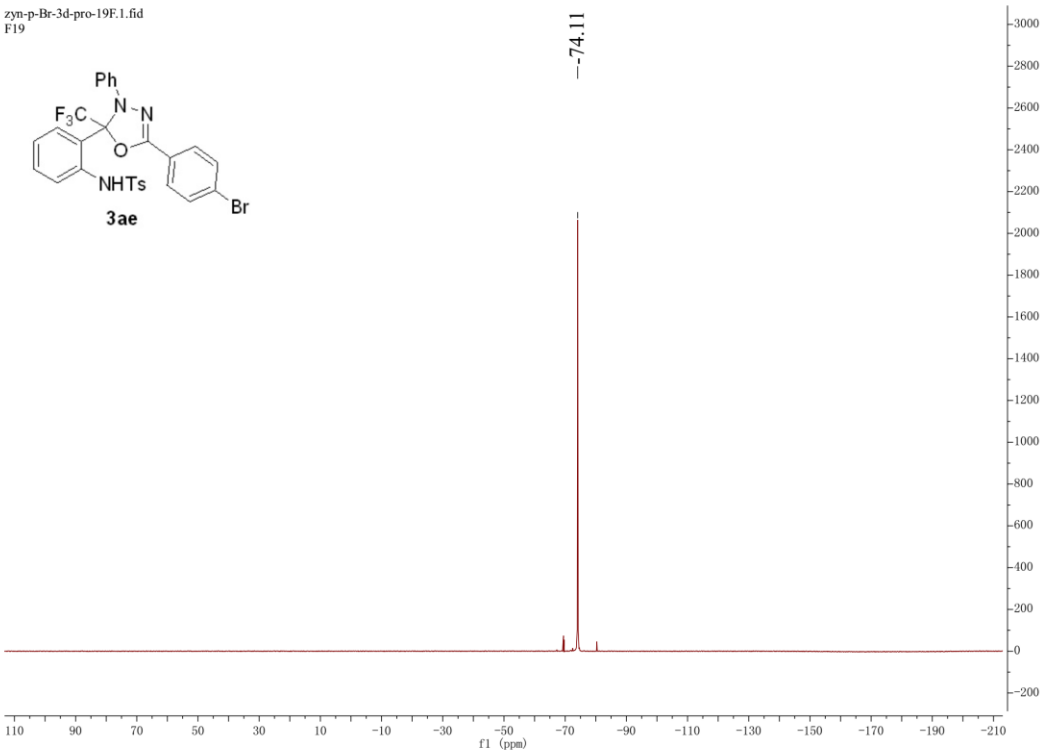
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ad**



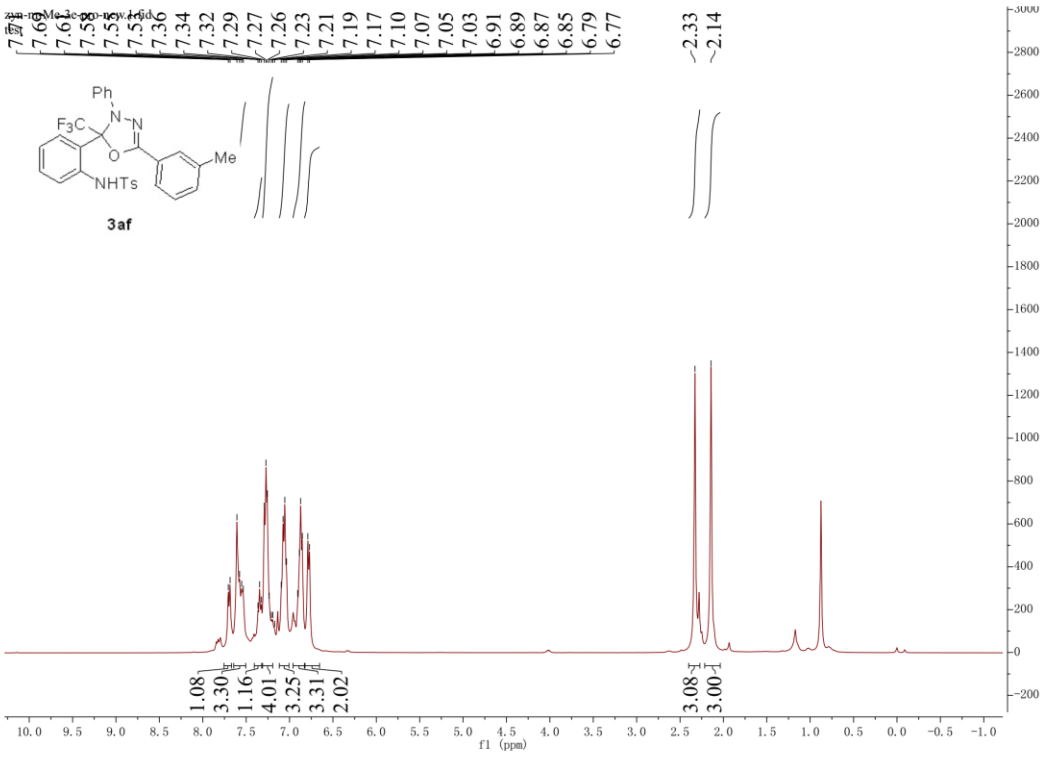
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ae**



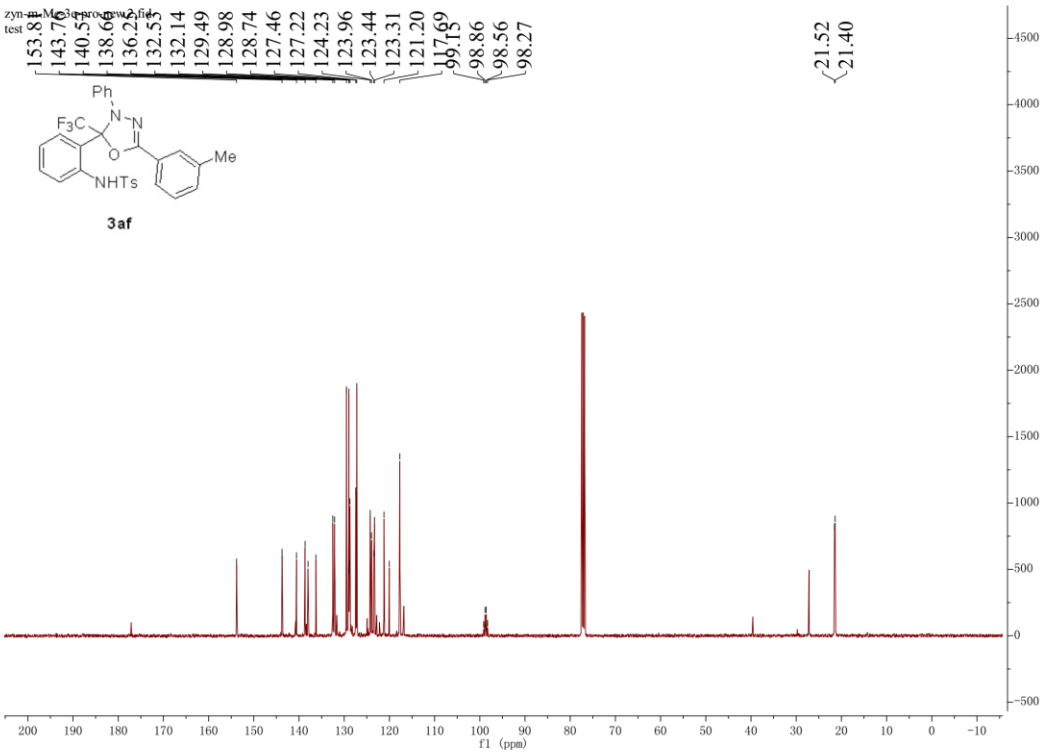
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ae**



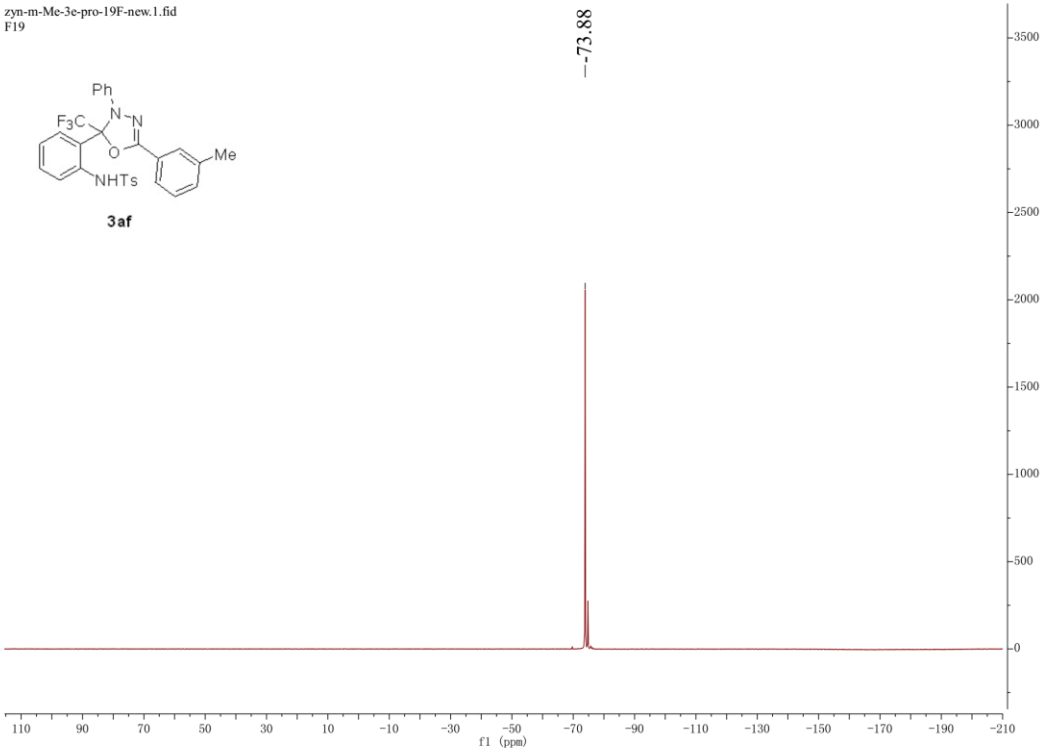
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ae**



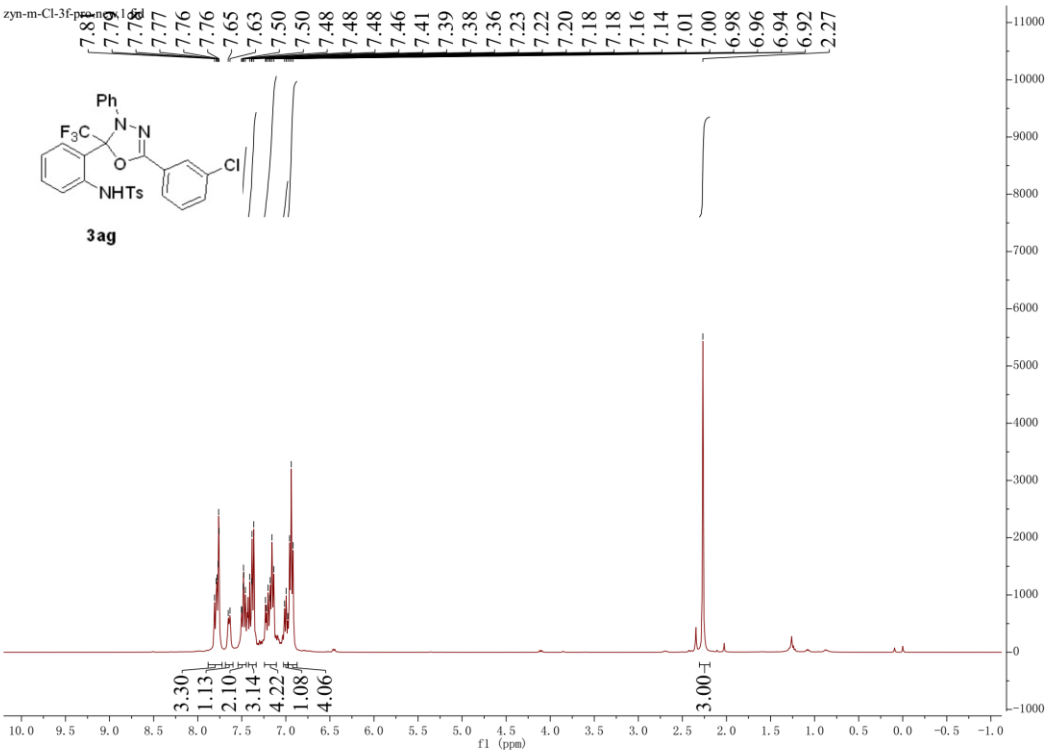
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3af**



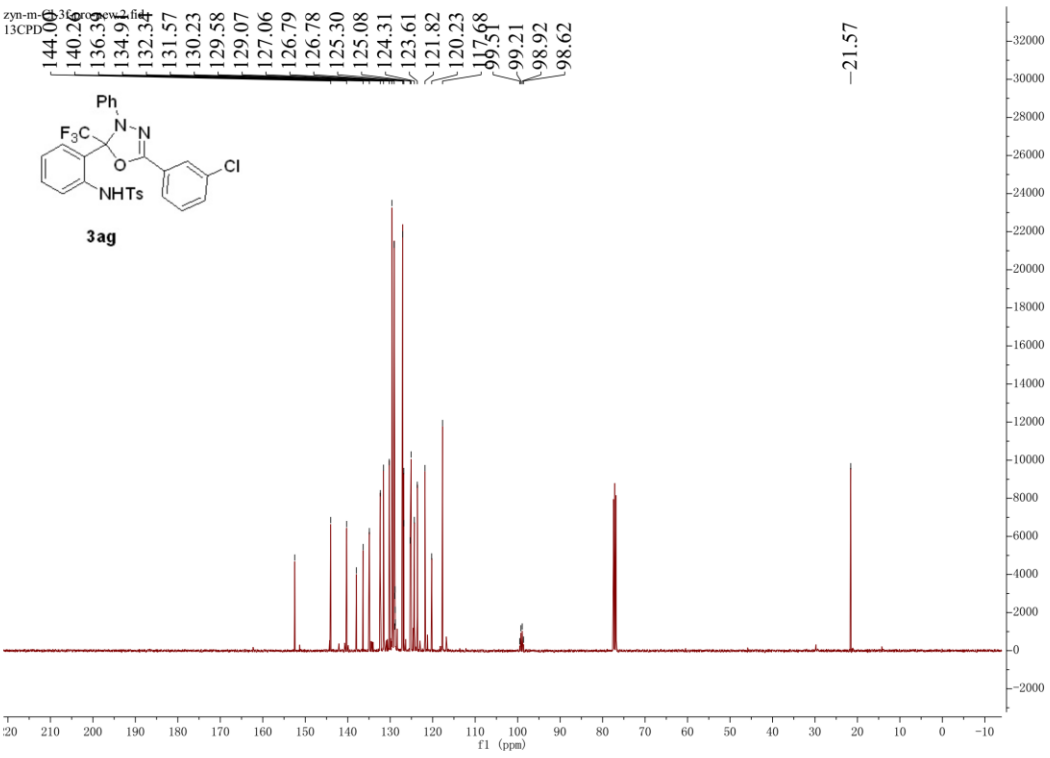
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3af**



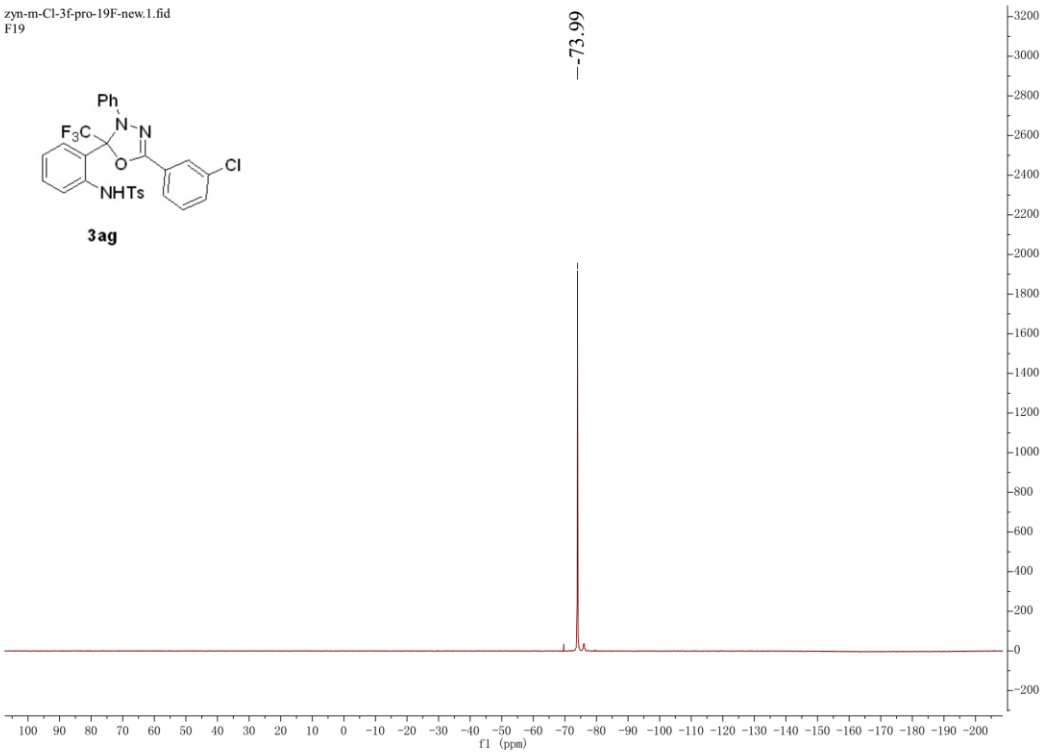
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3af**



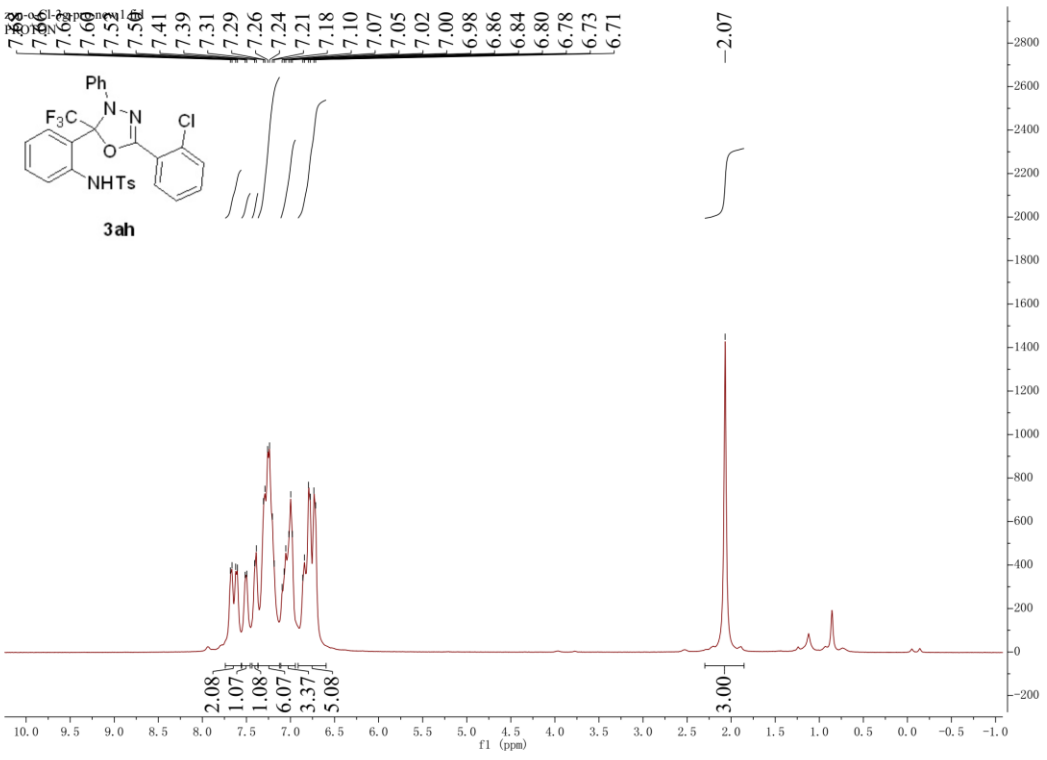
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ag**



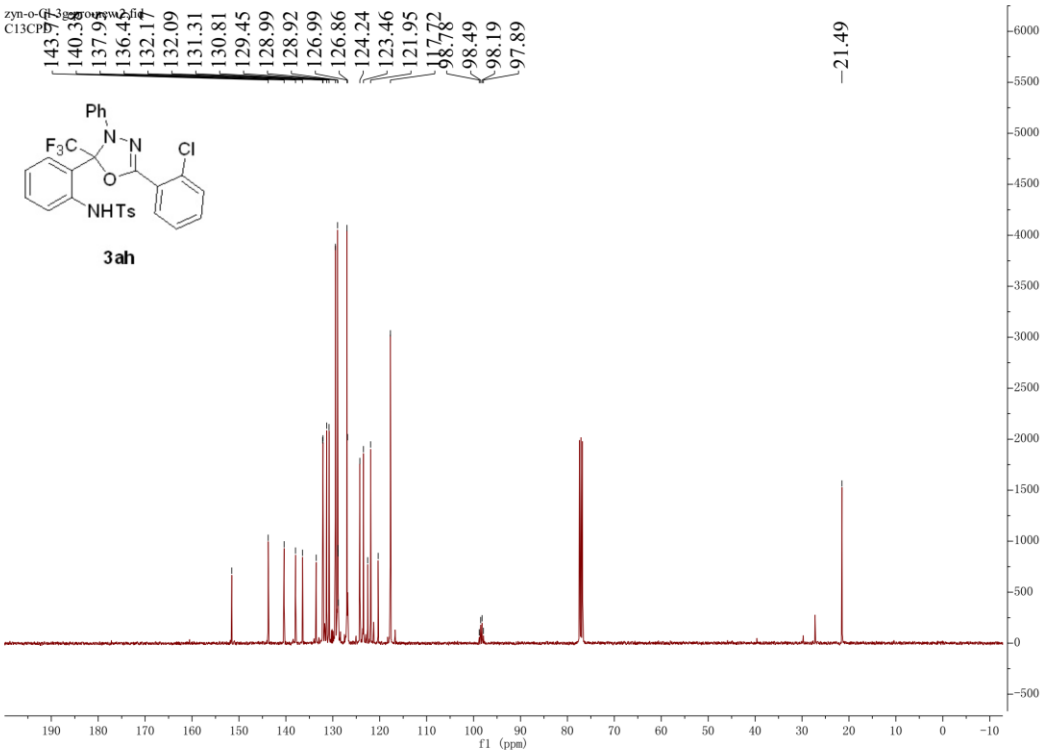
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ag**



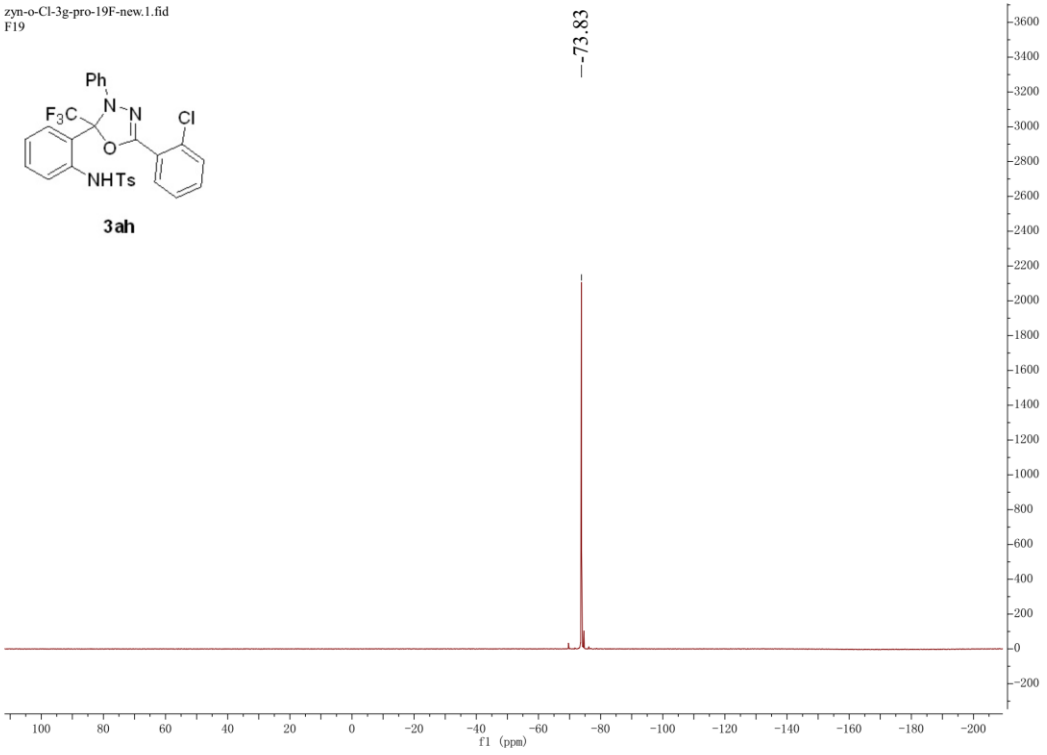
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ag**



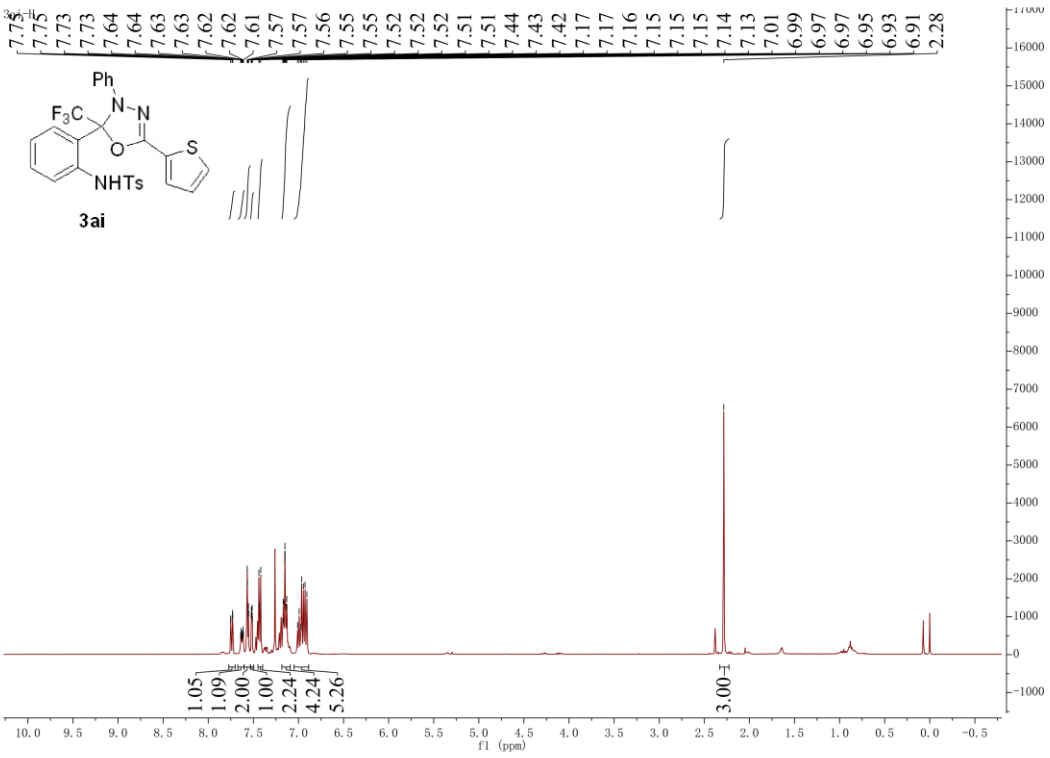
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ah**



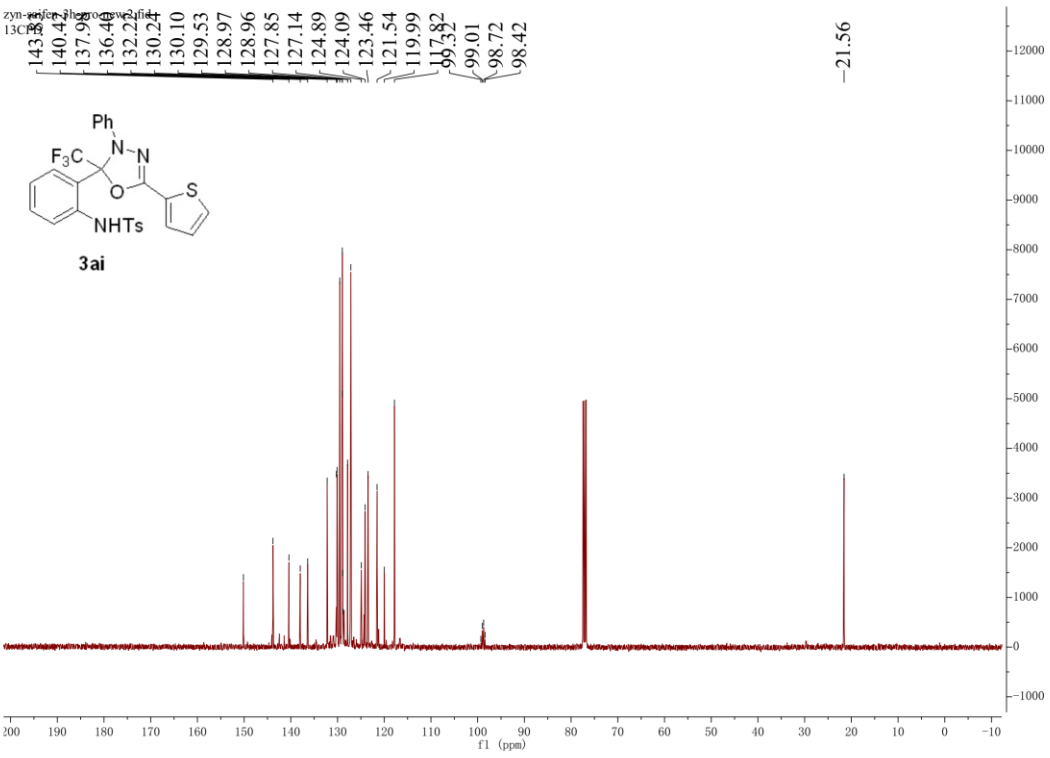
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ah**



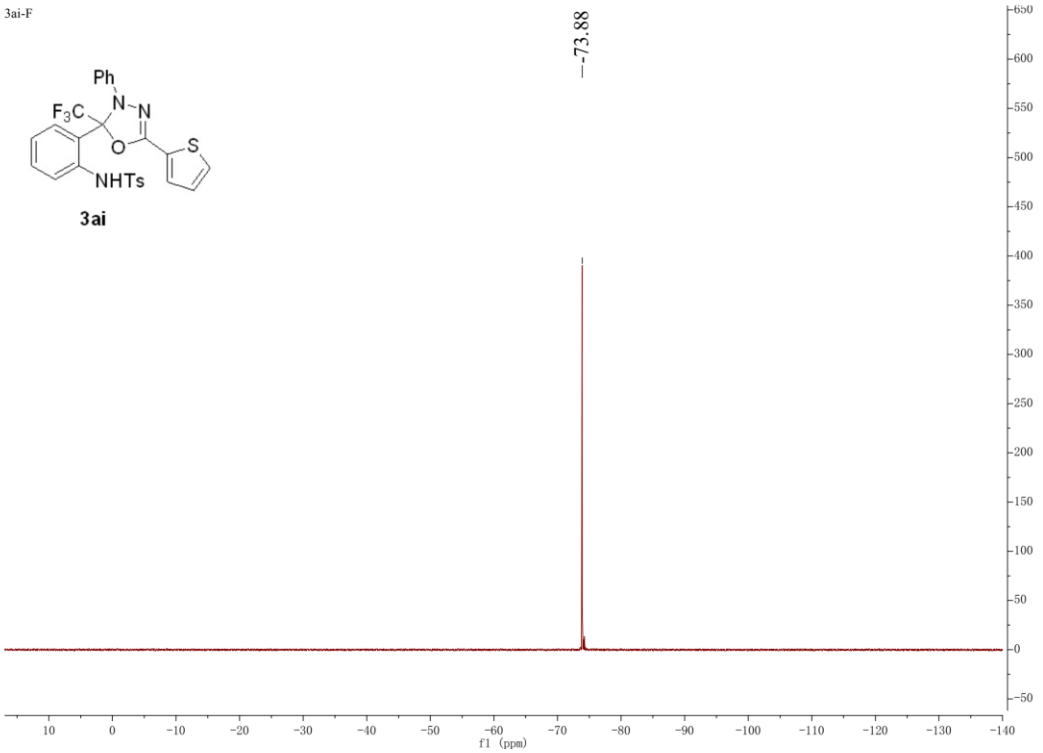
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ah**



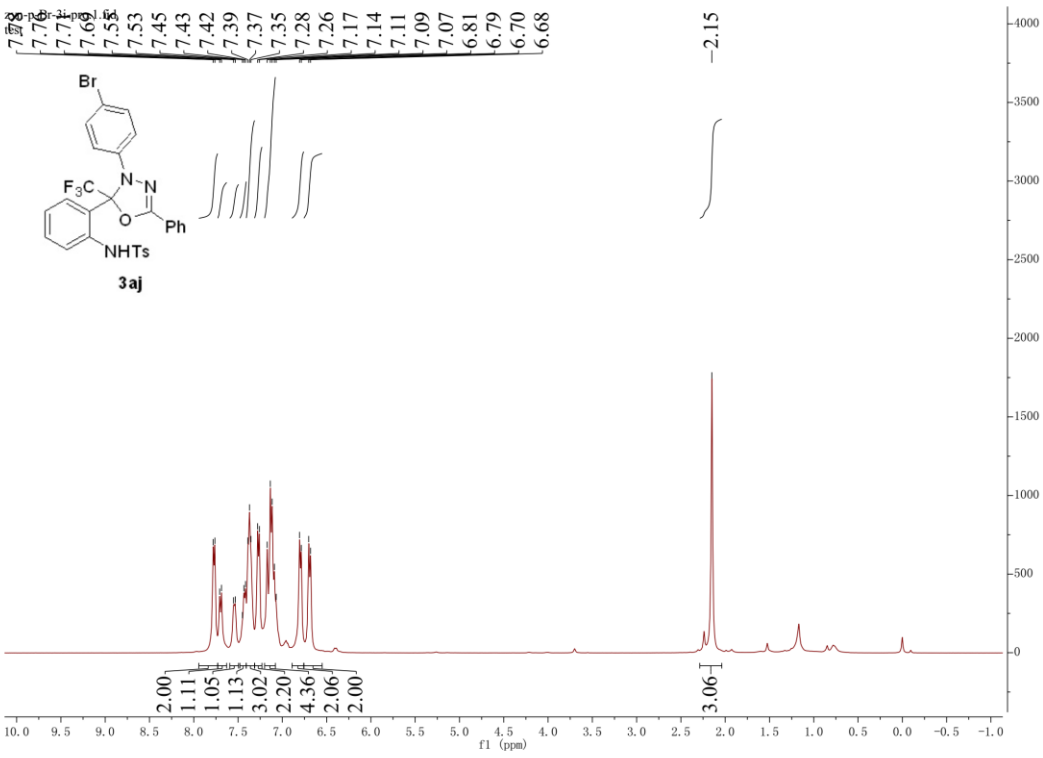
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ai**



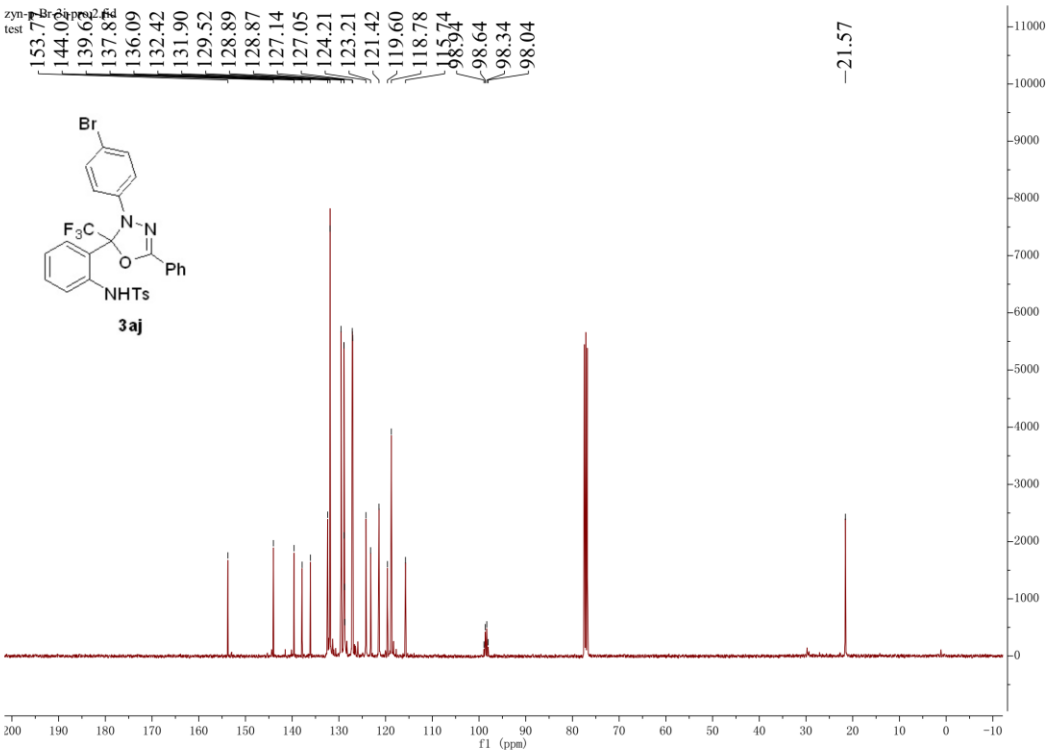
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ai**



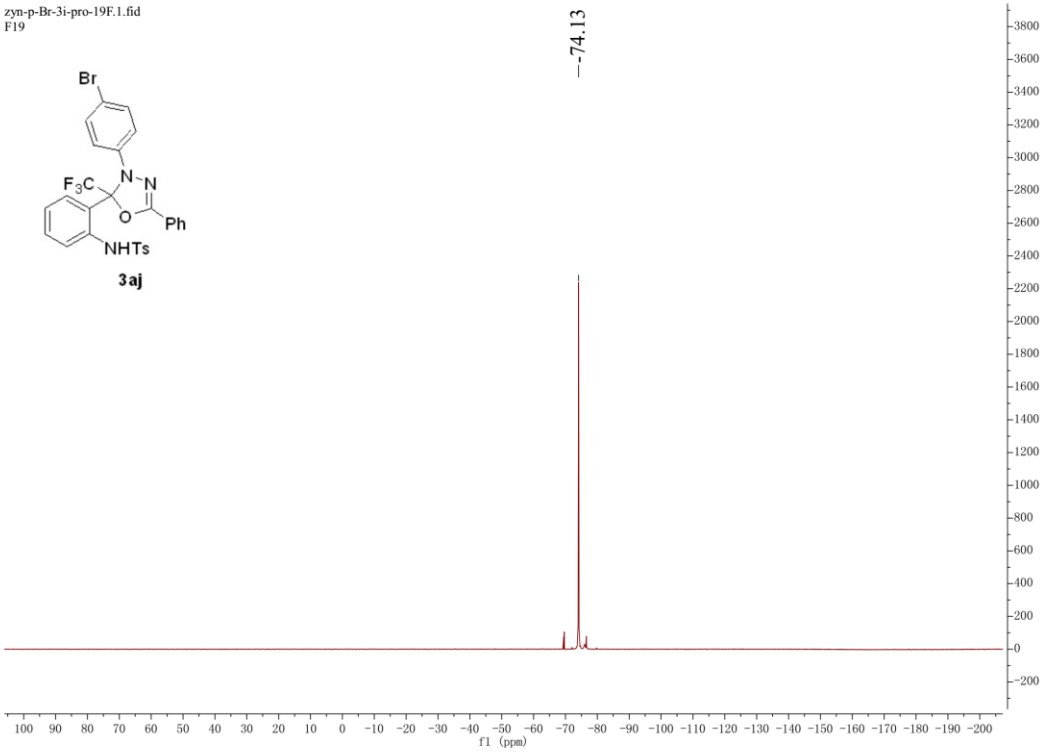
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ai**



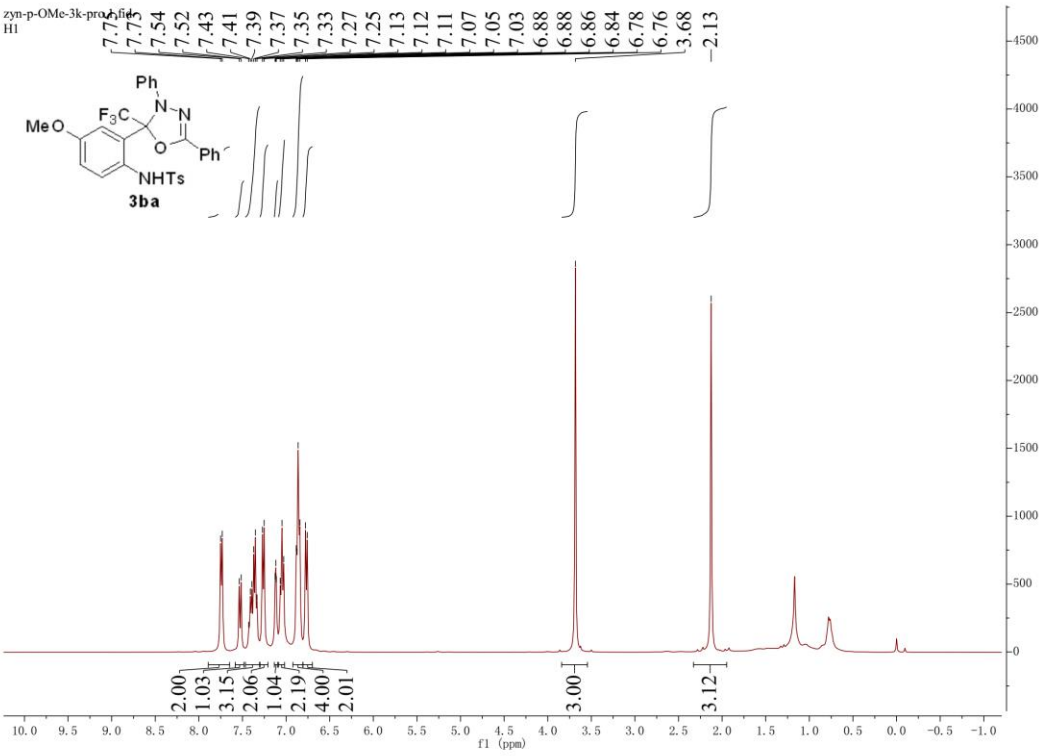
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3aj**



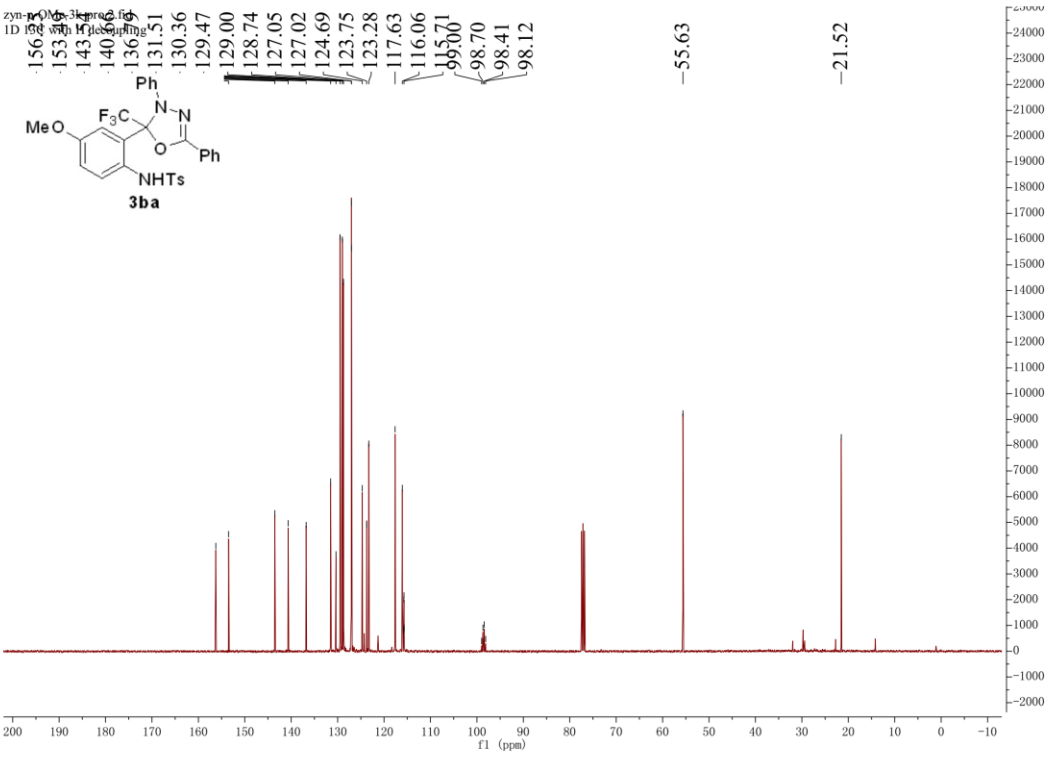
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3aj**



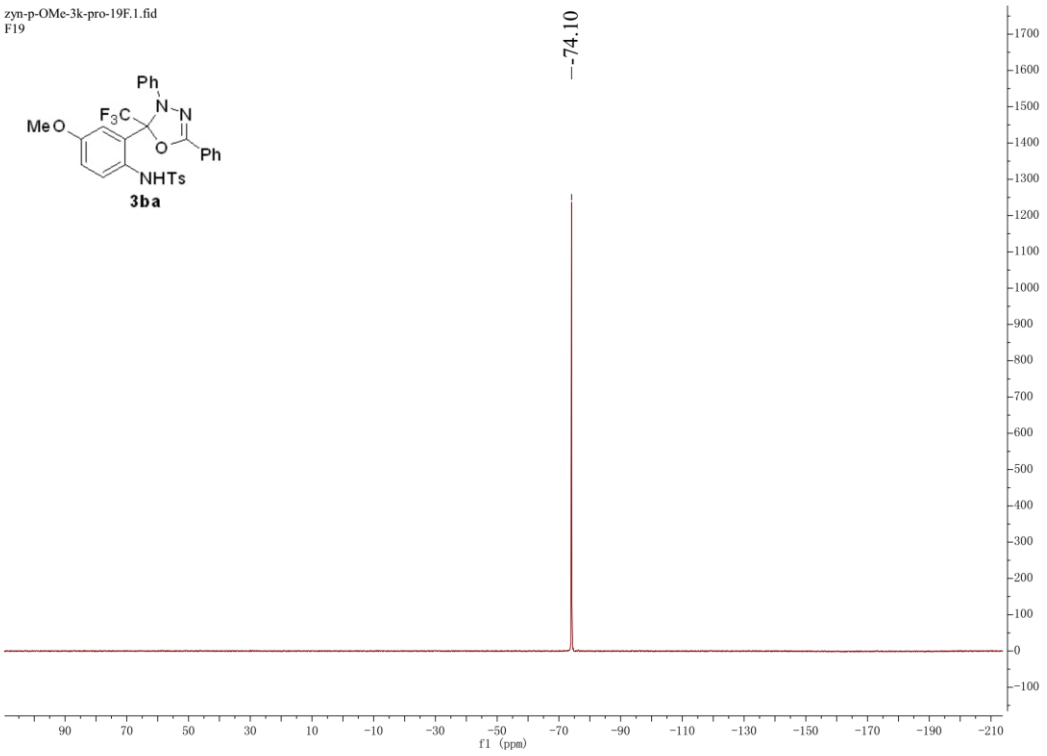
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3aj**



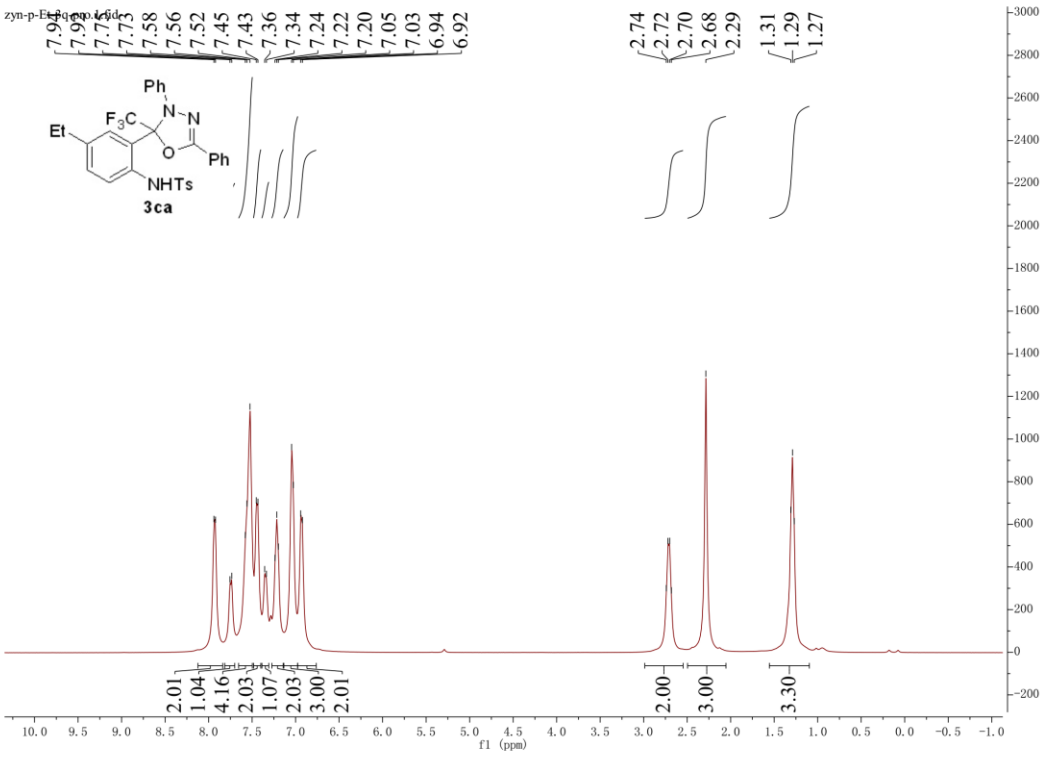
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ba**



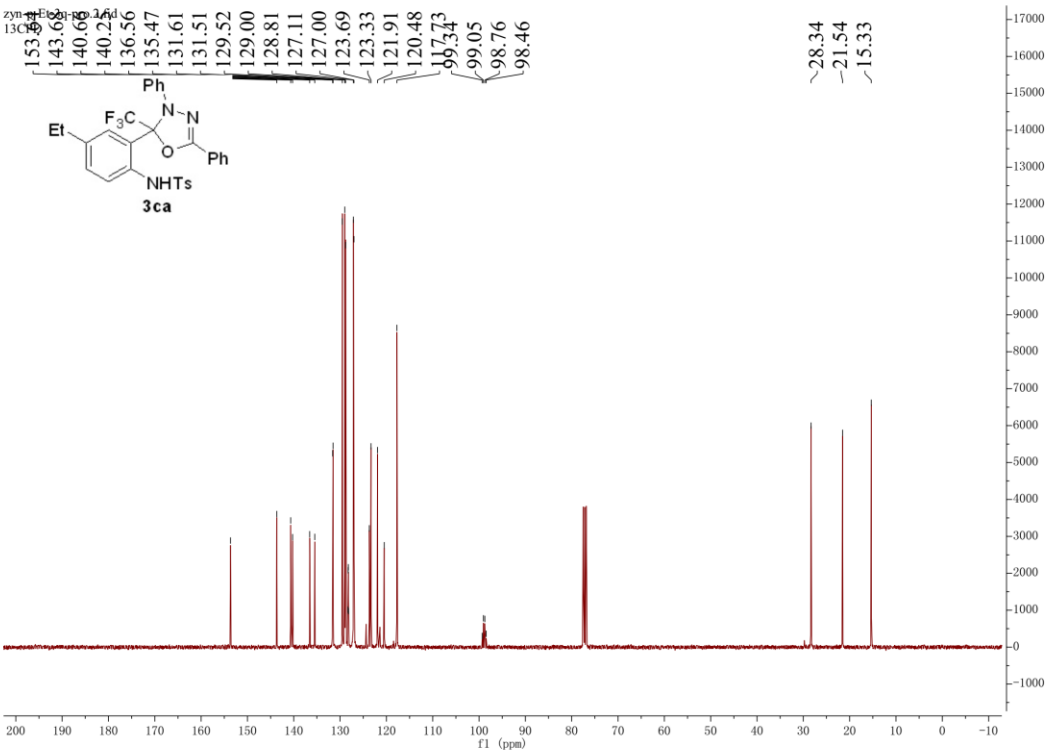
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ba**



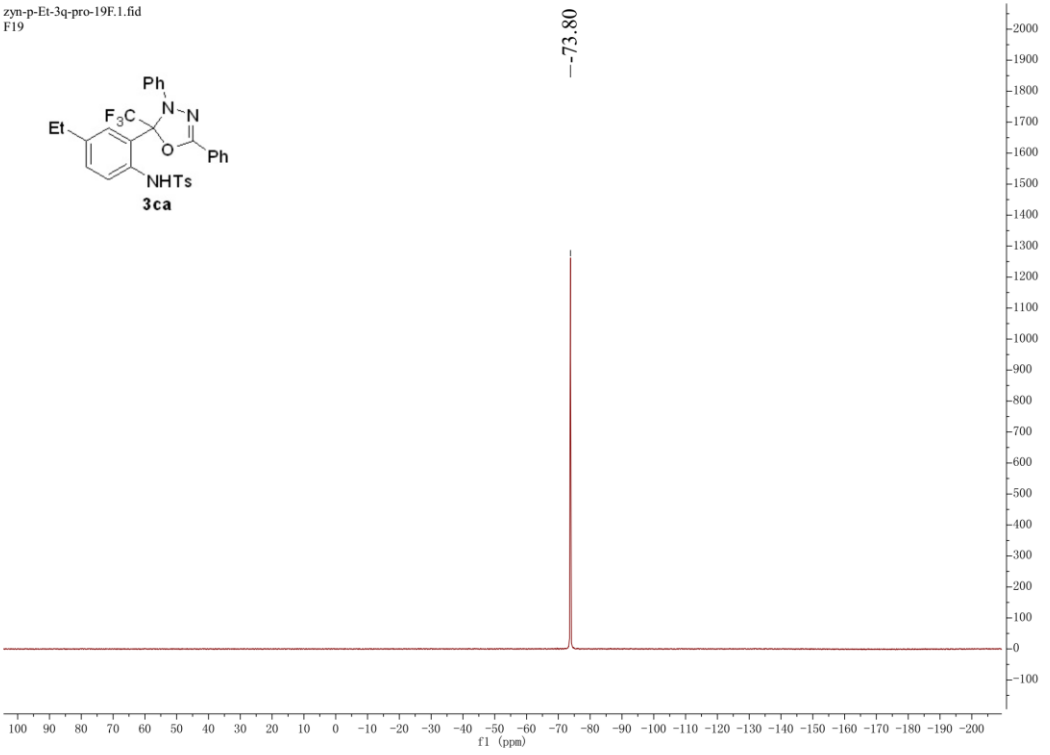
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ba**



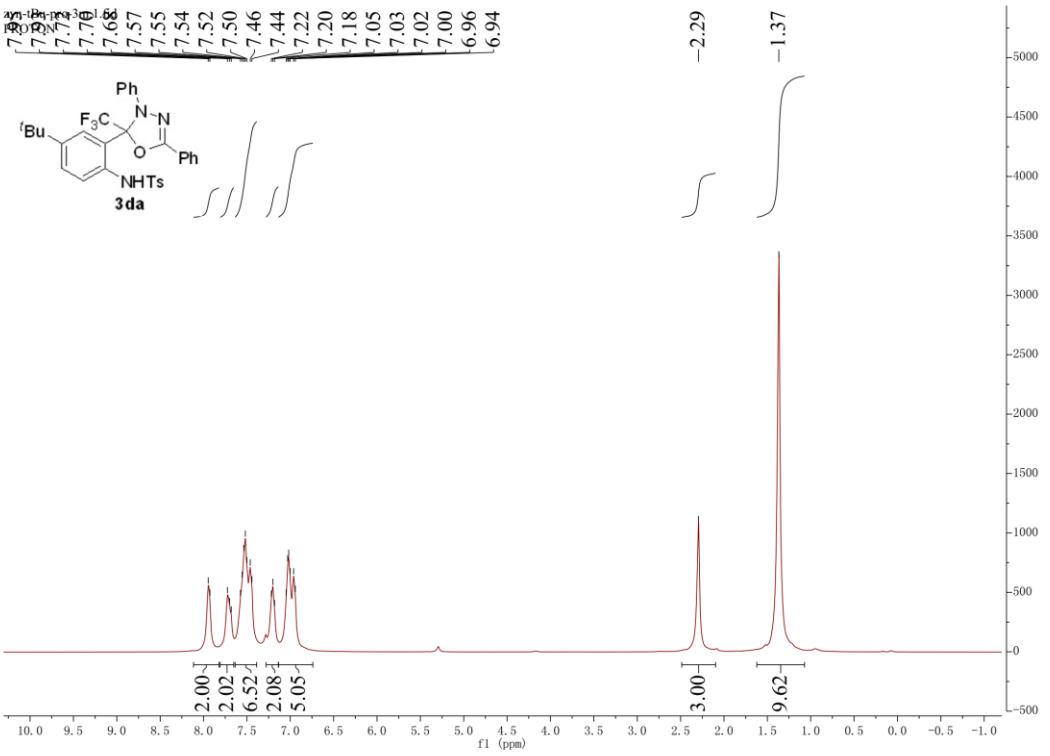
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ca**



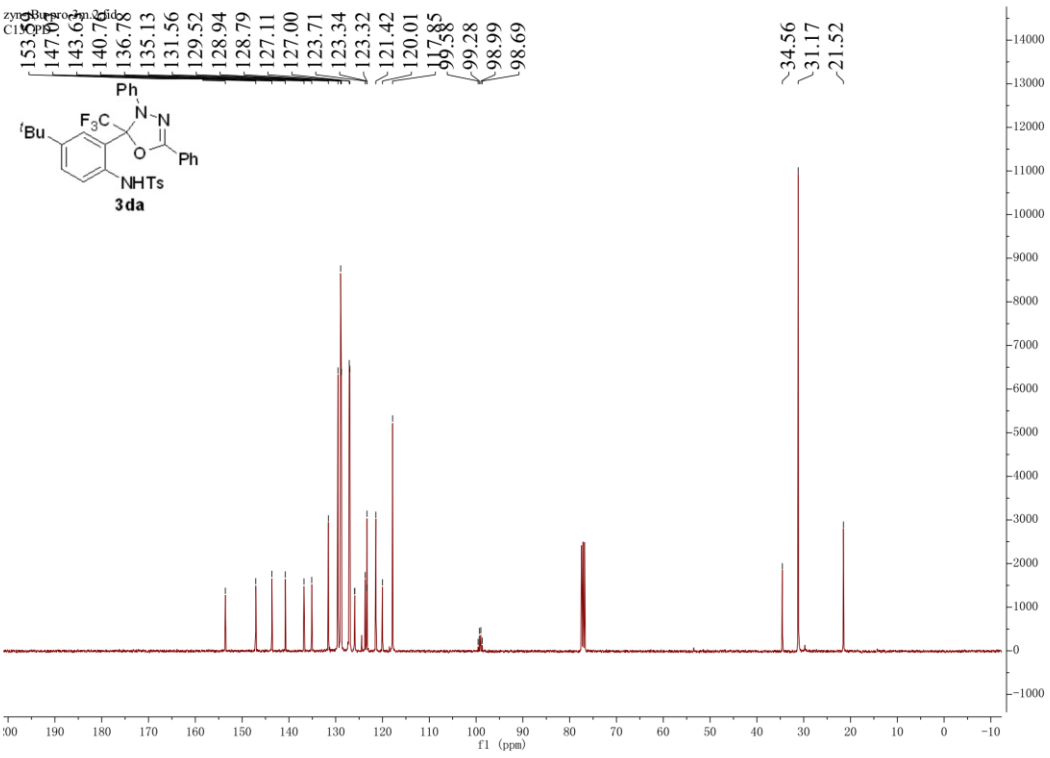
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ca**



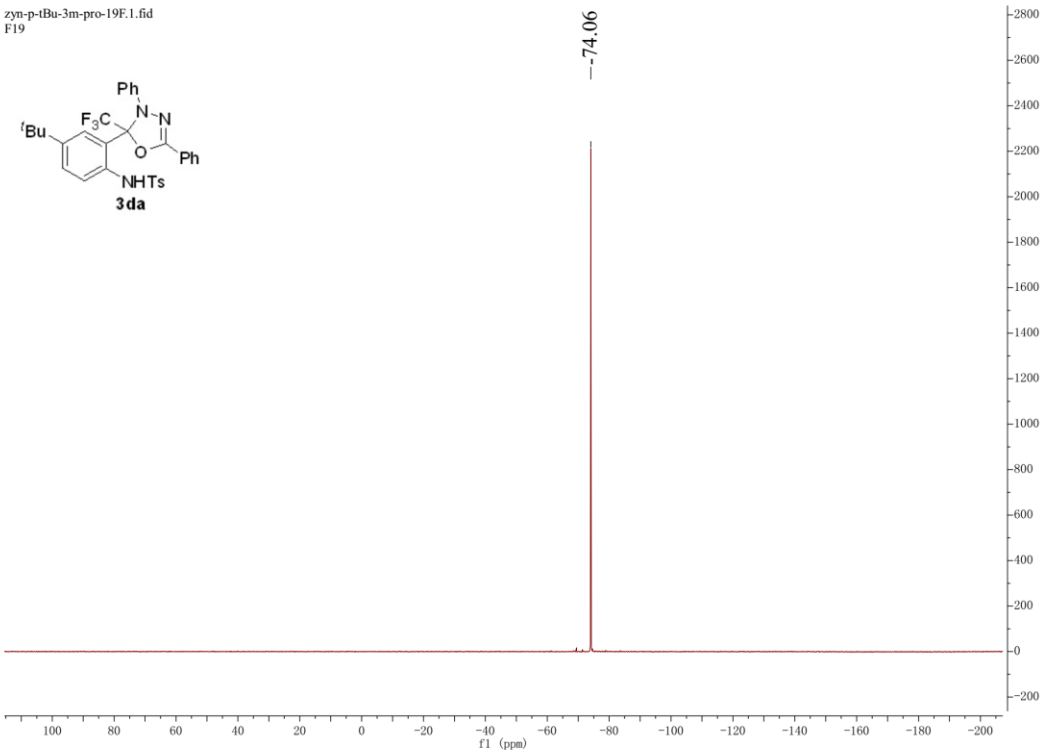
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ca**



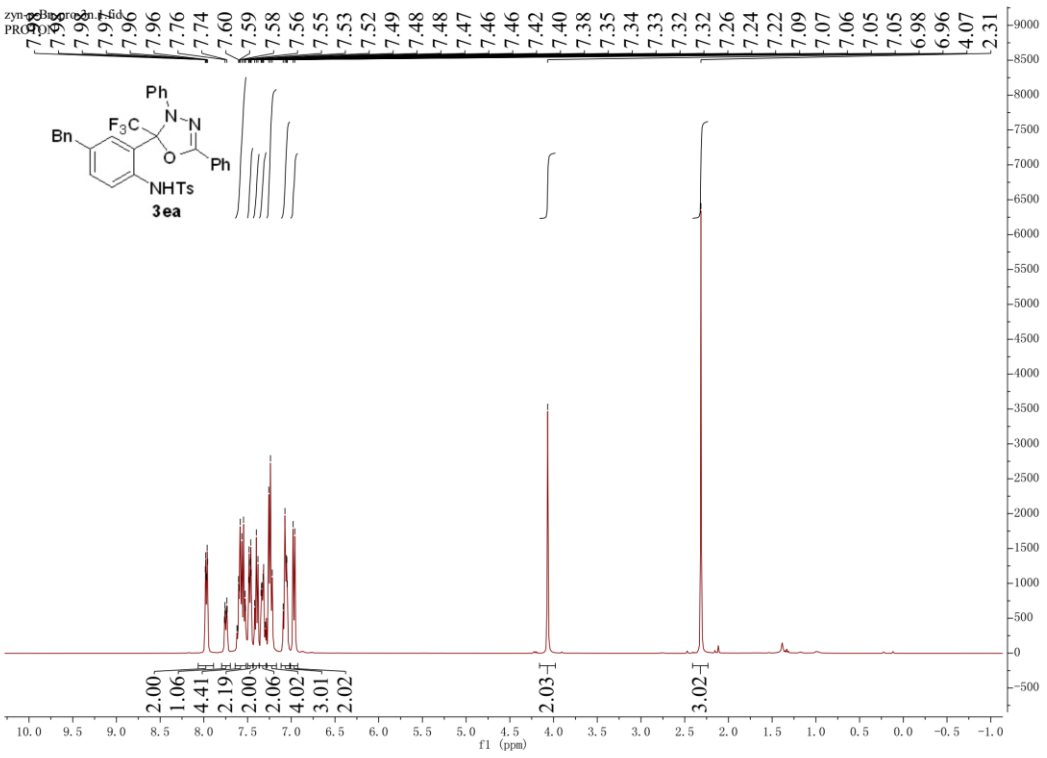
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3da**



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



^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3da**



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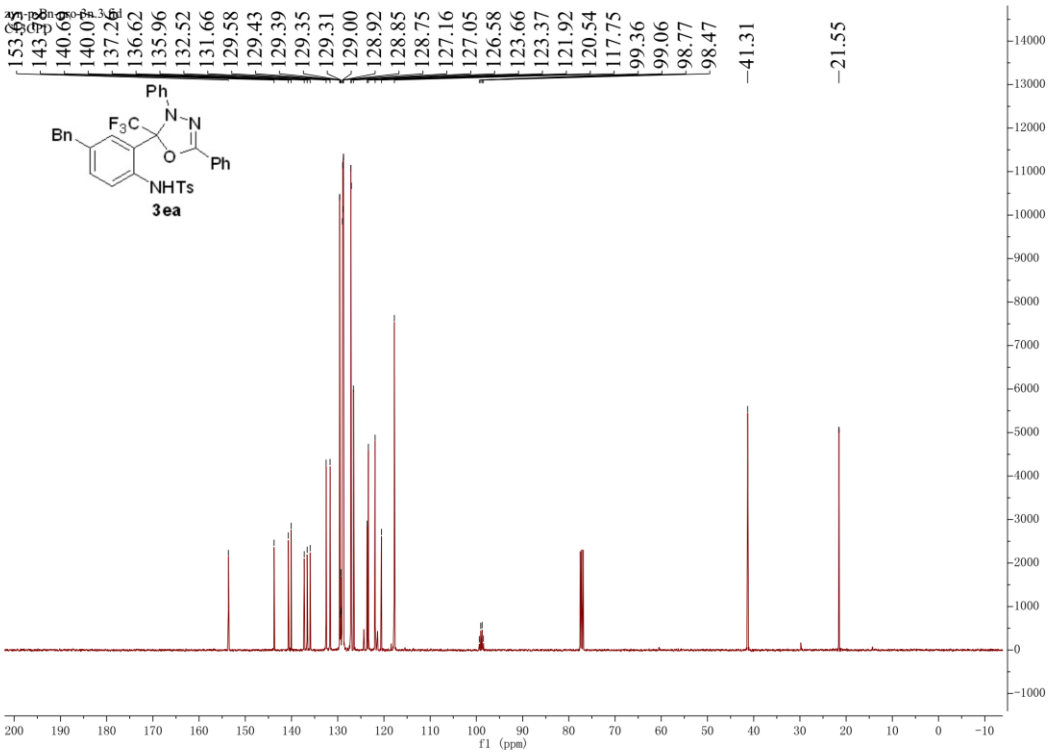
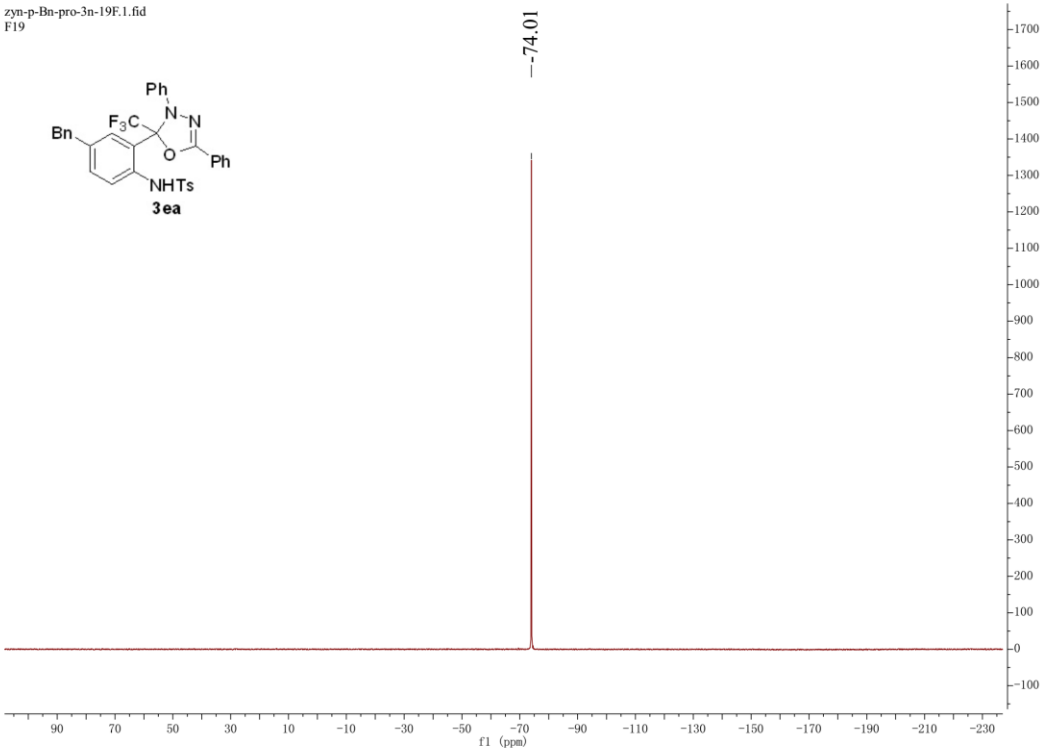


^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ea**



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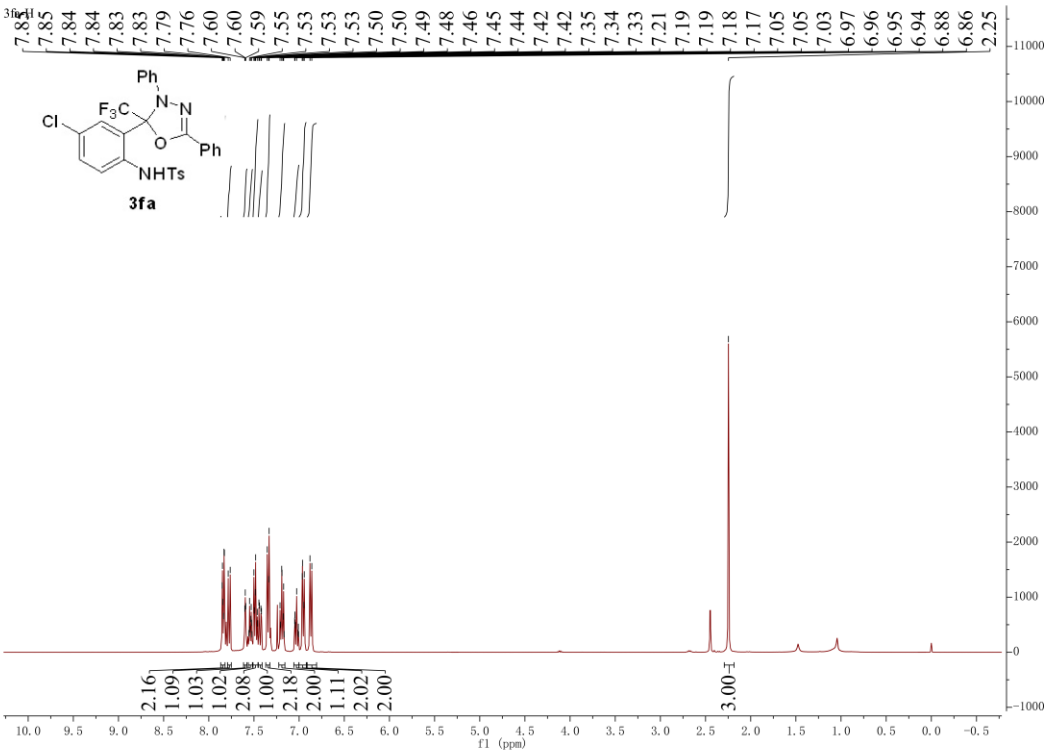
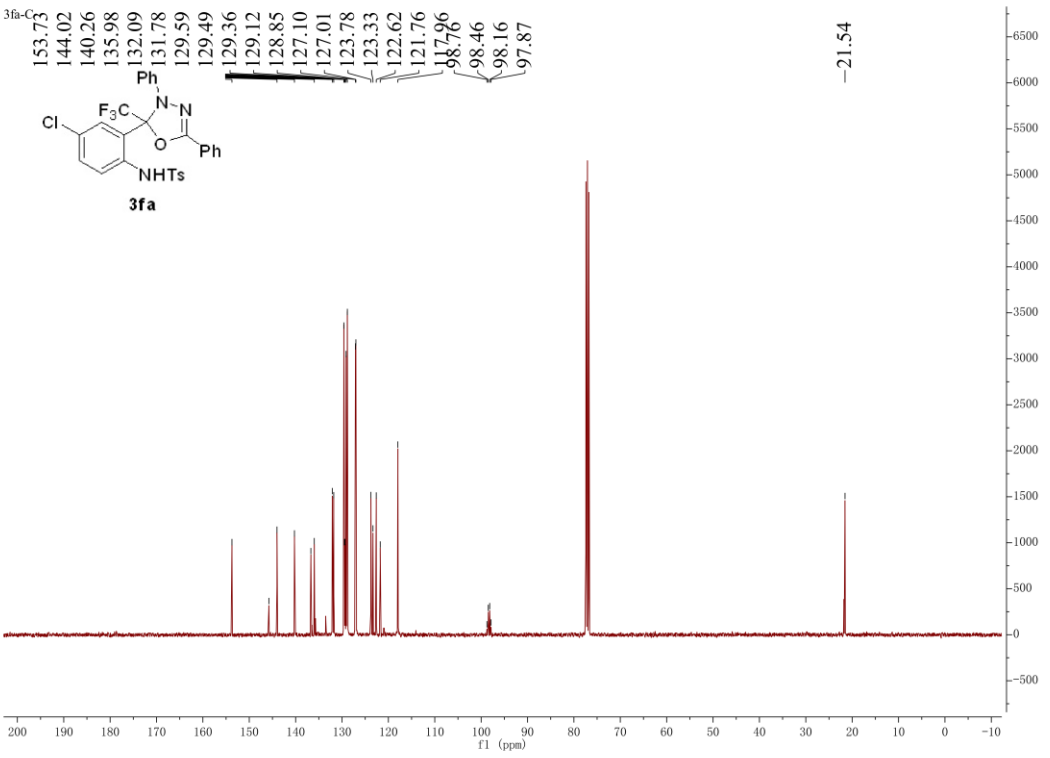
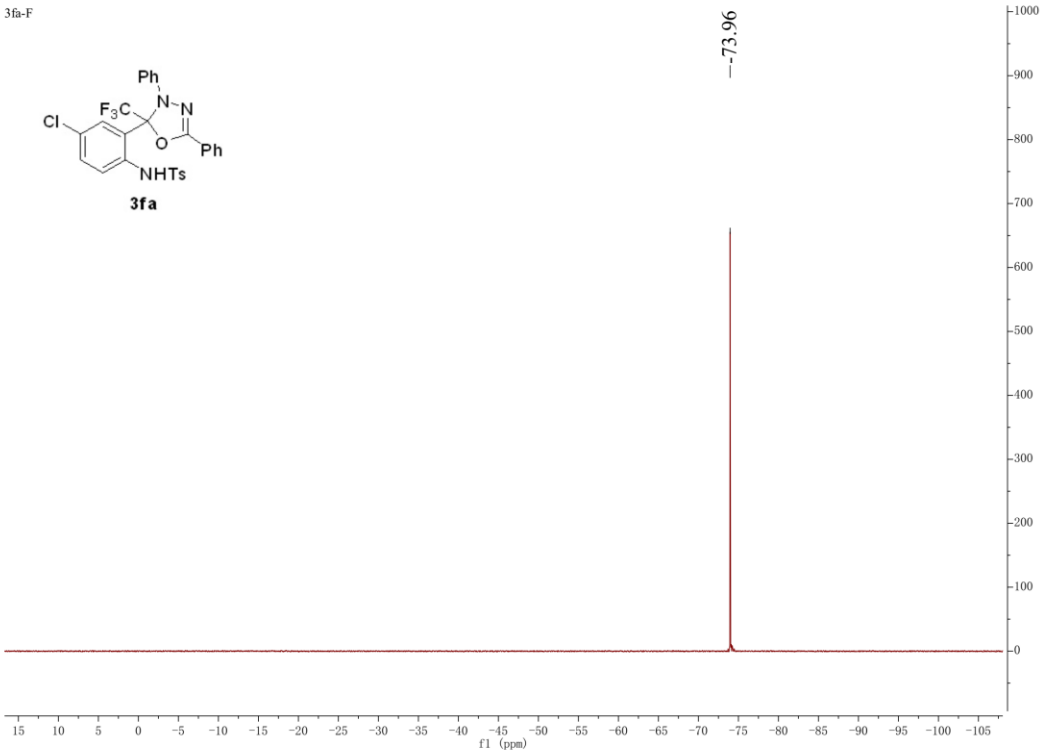


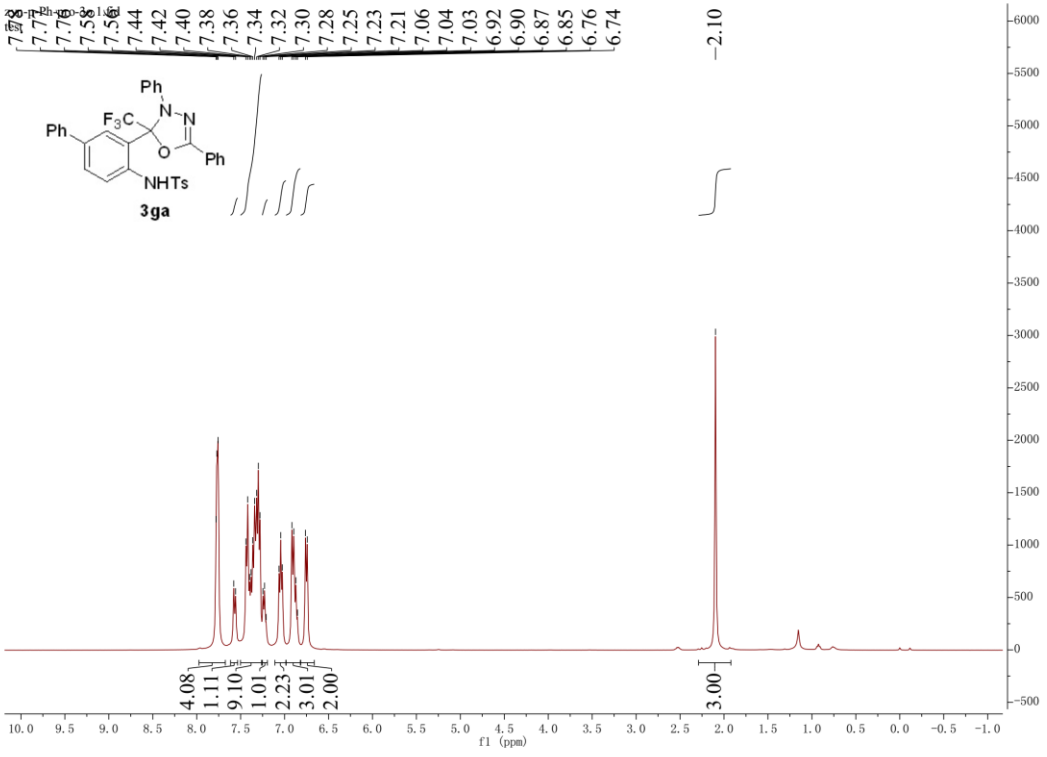
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3fa**



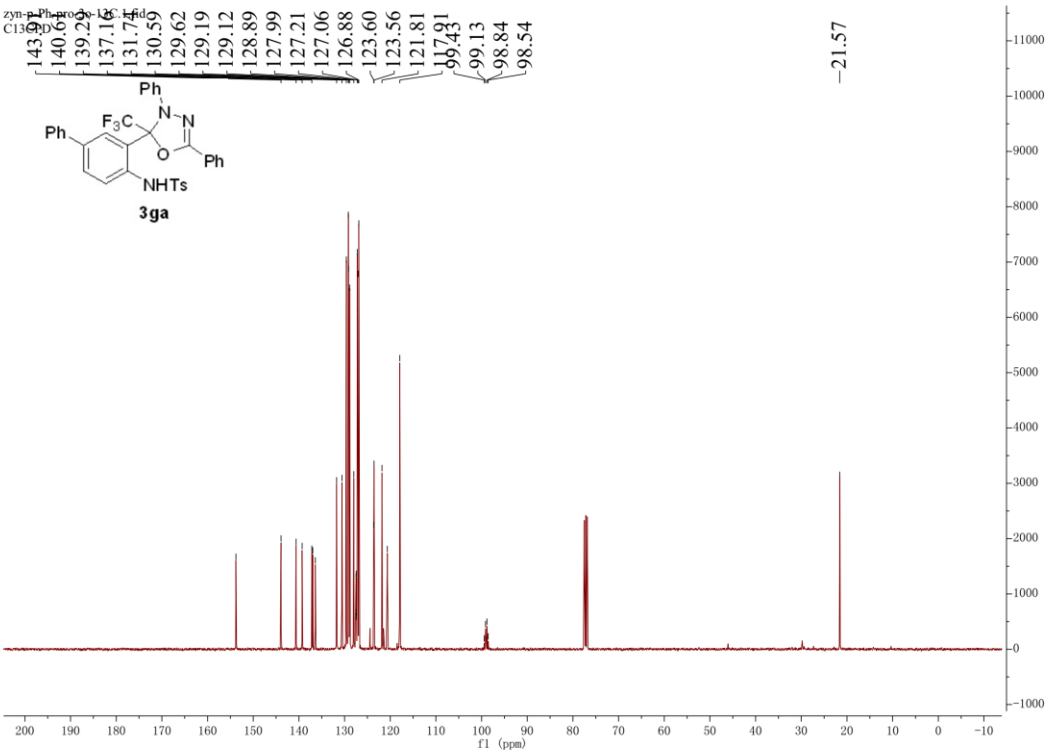
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3fa**



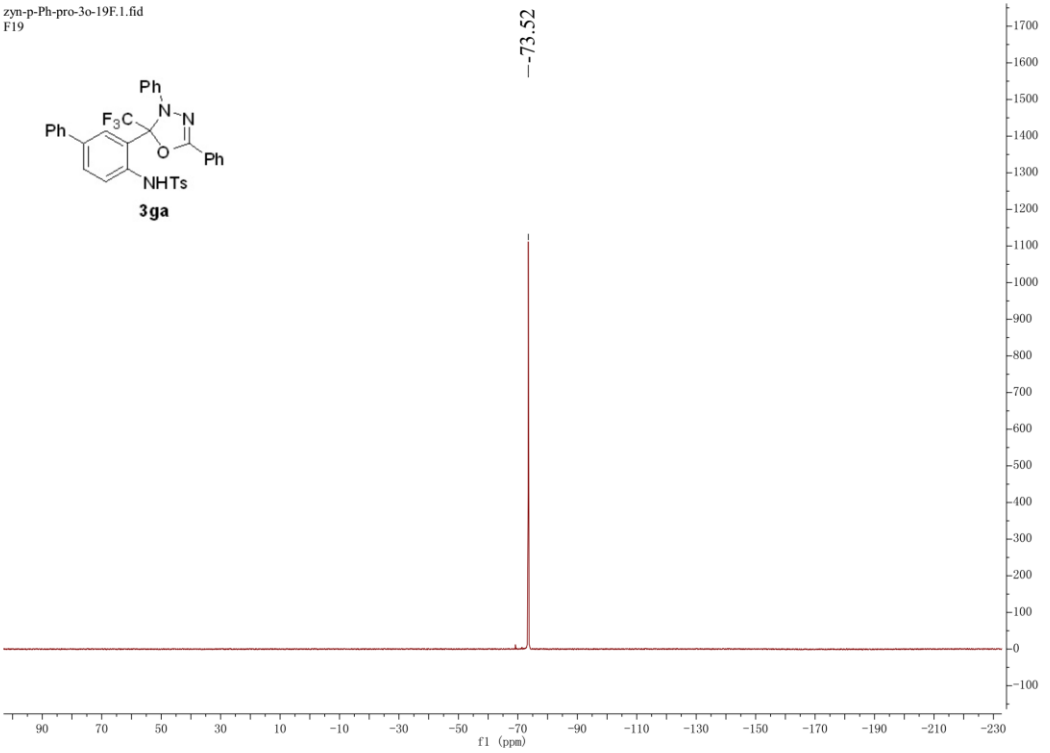
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3fa**



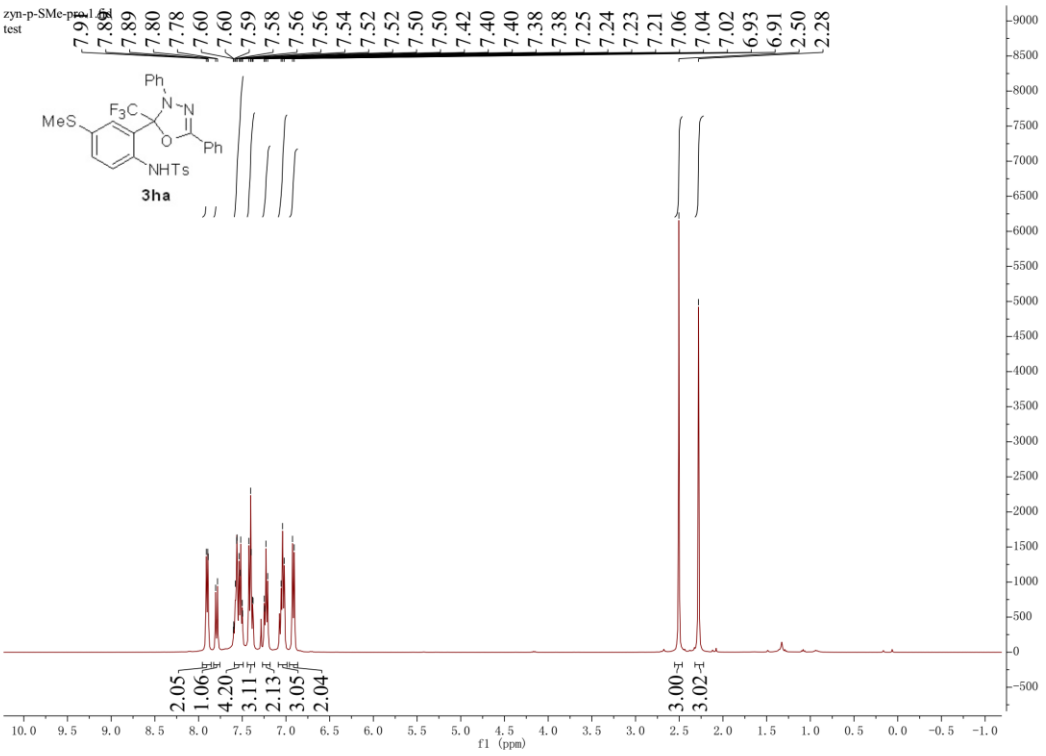
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ga**



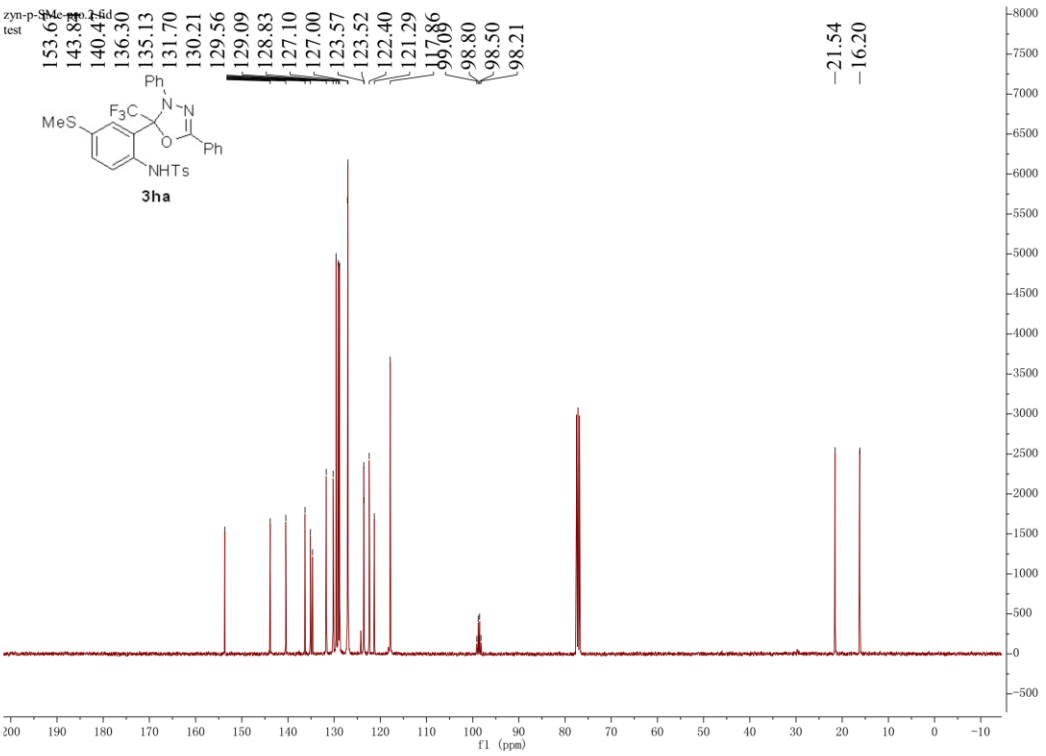
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ga**



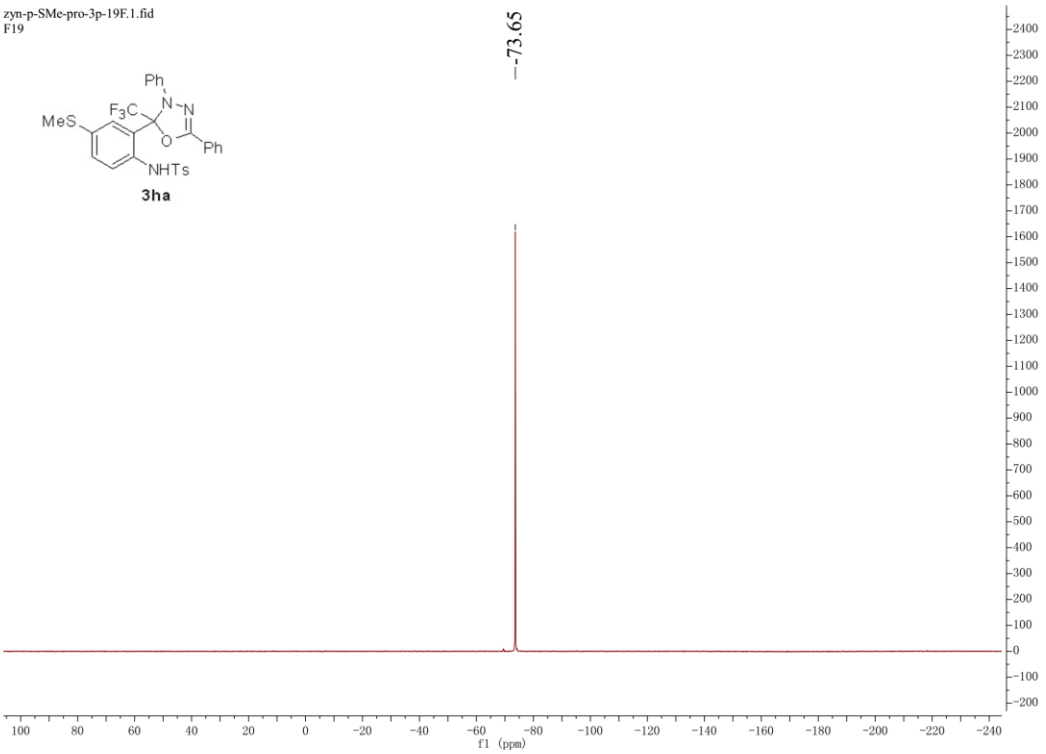
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ga**



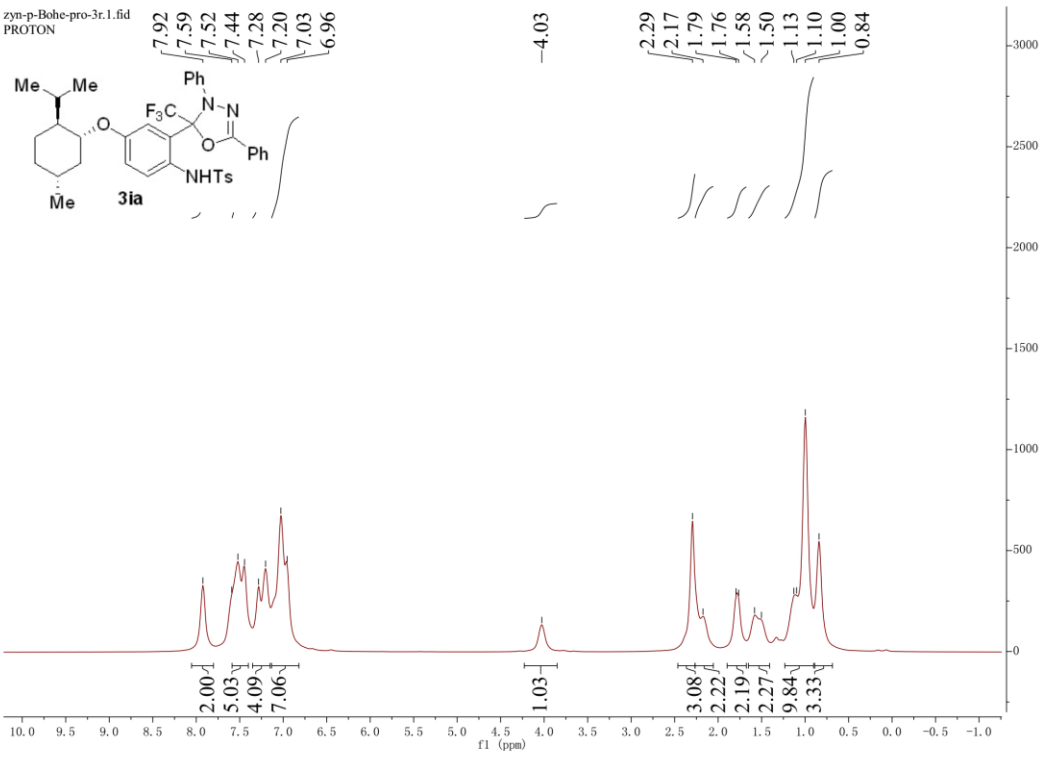
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ha**



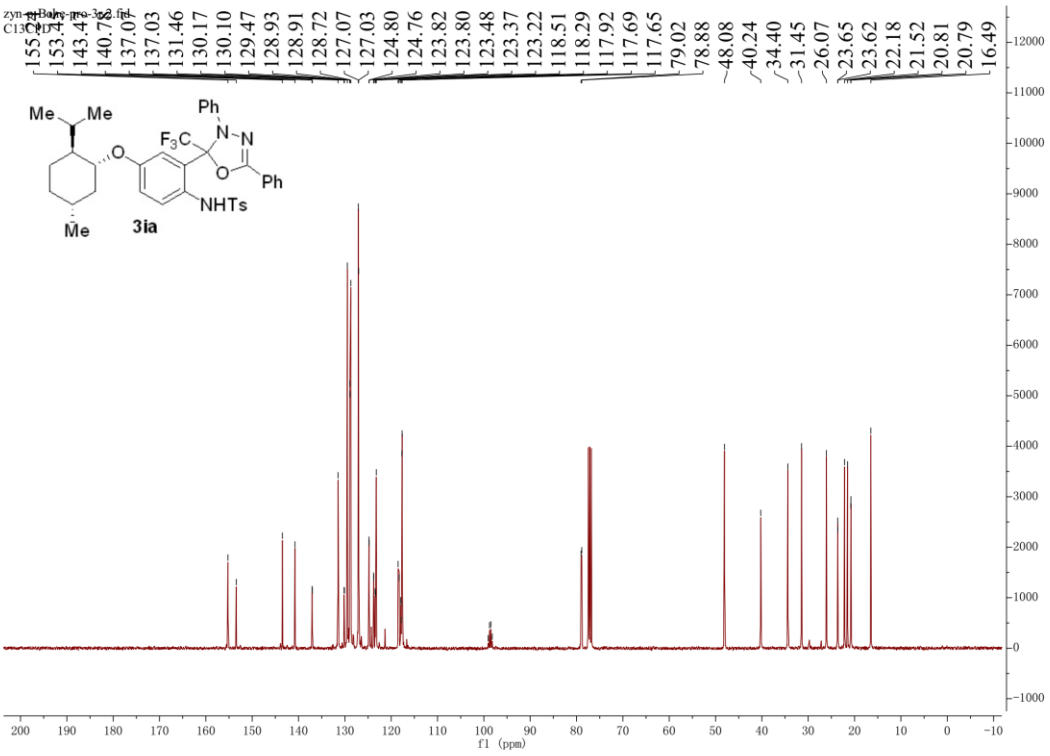
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ha**



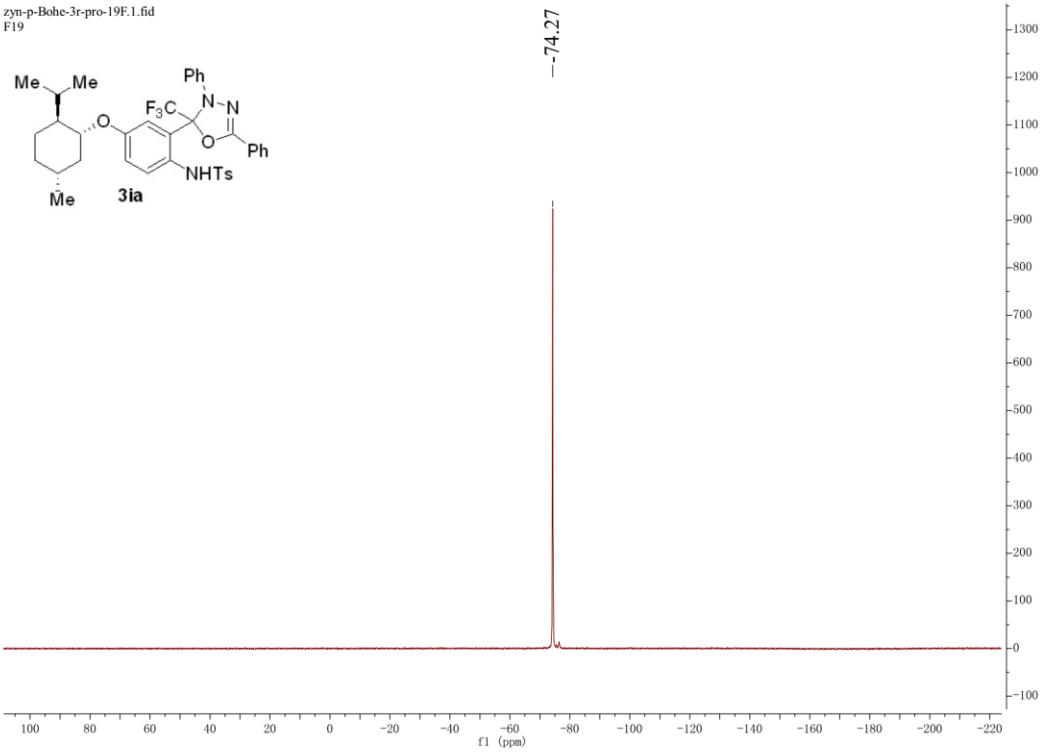
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ha**



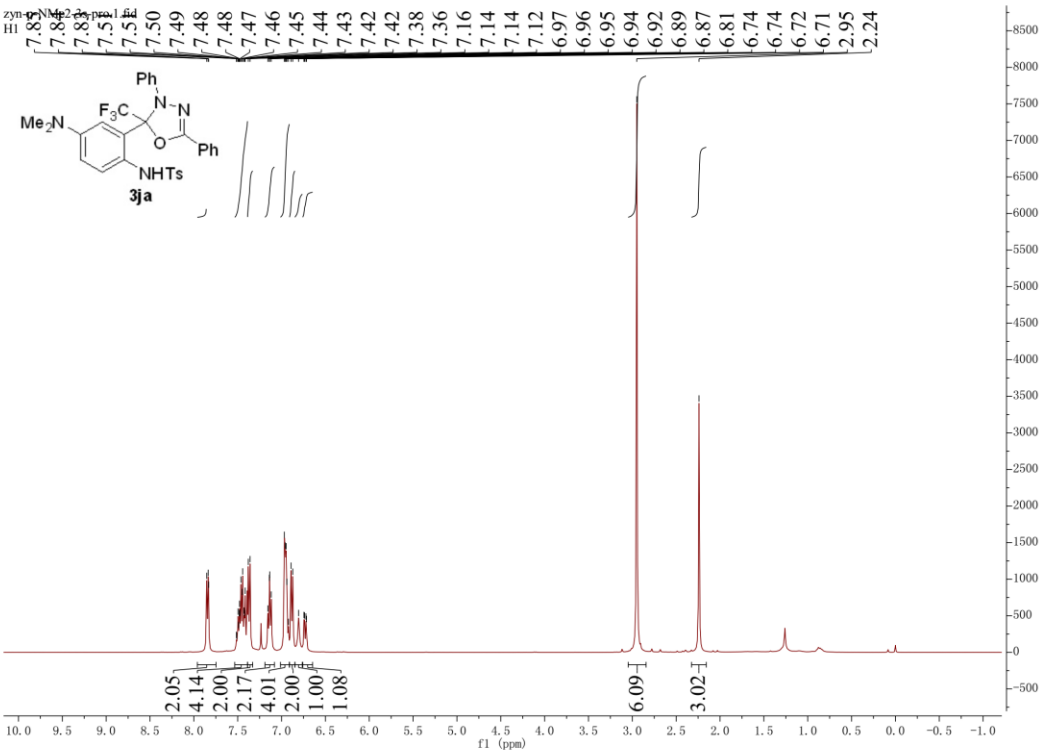
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ia**



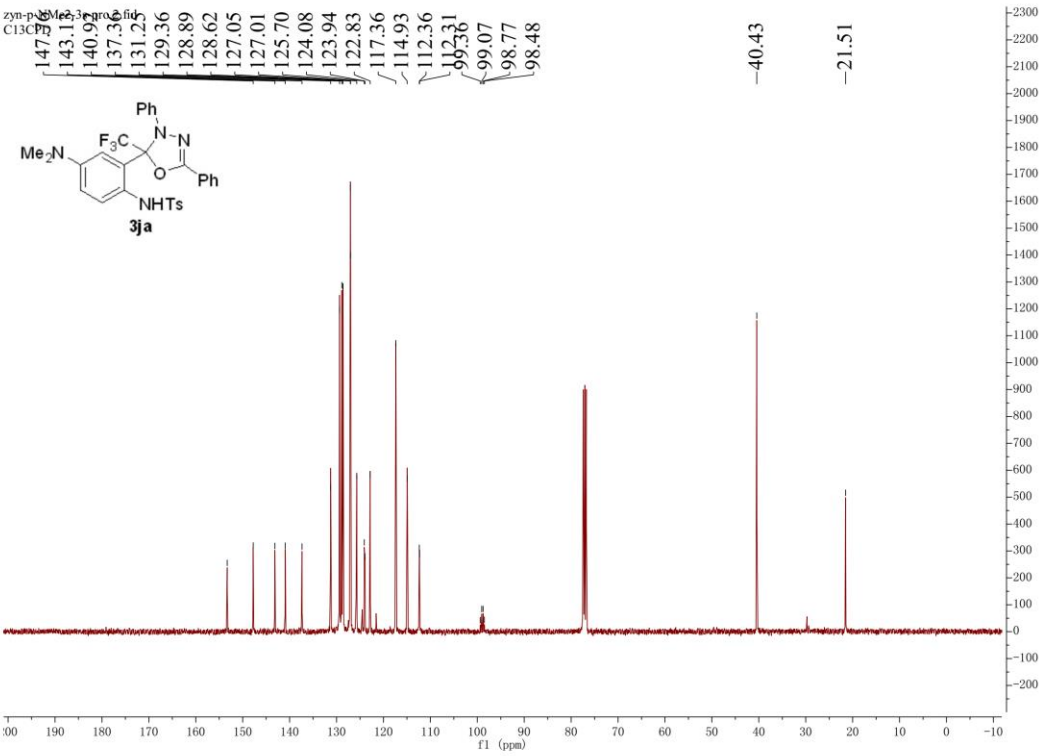
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ia**



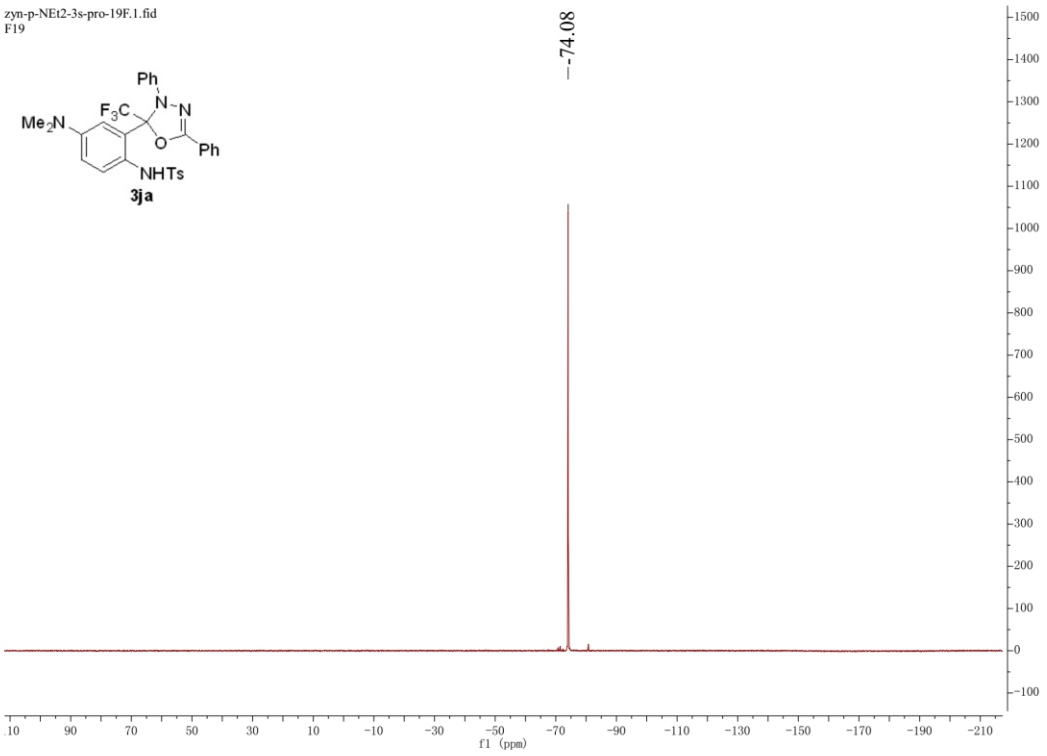
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ia**



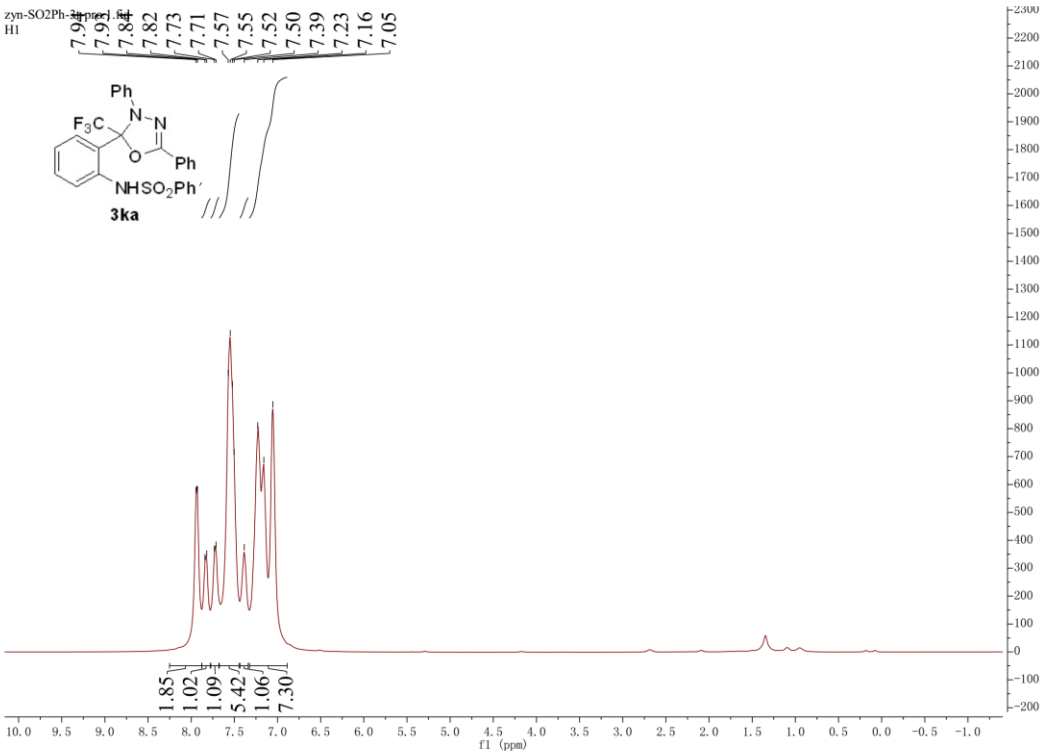
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ja**



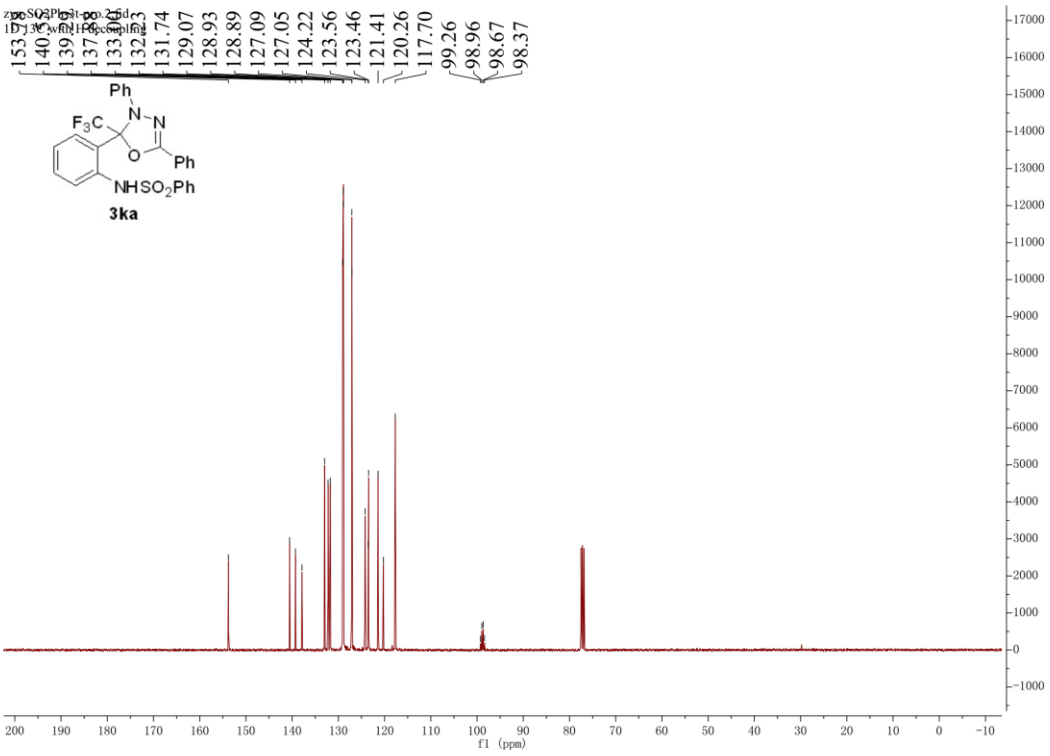
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ja**



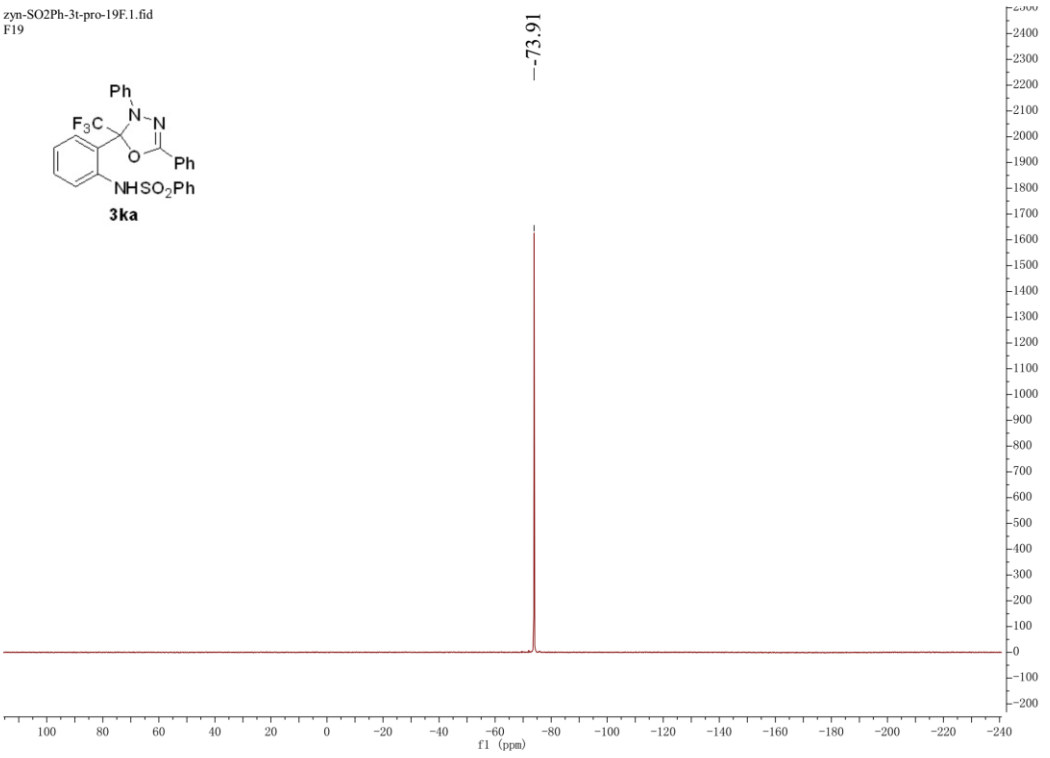
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ja**



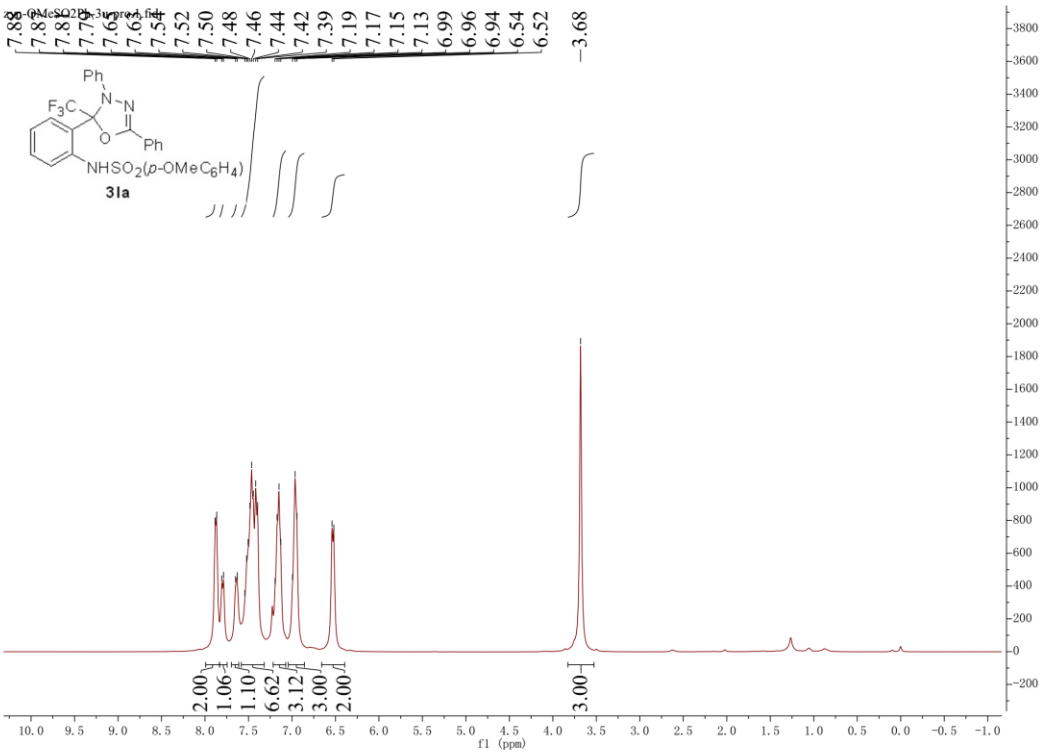
^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3ka**



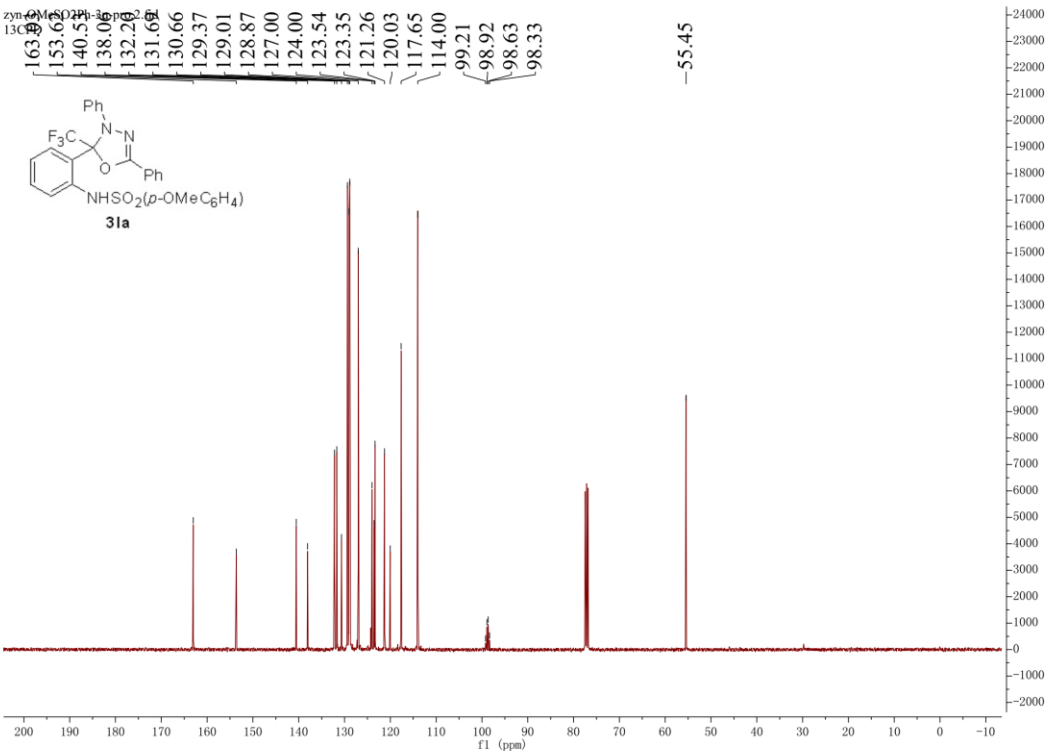
^{13}C NMR spectra (101 MHz, $CDCl_3$) of **3ka**



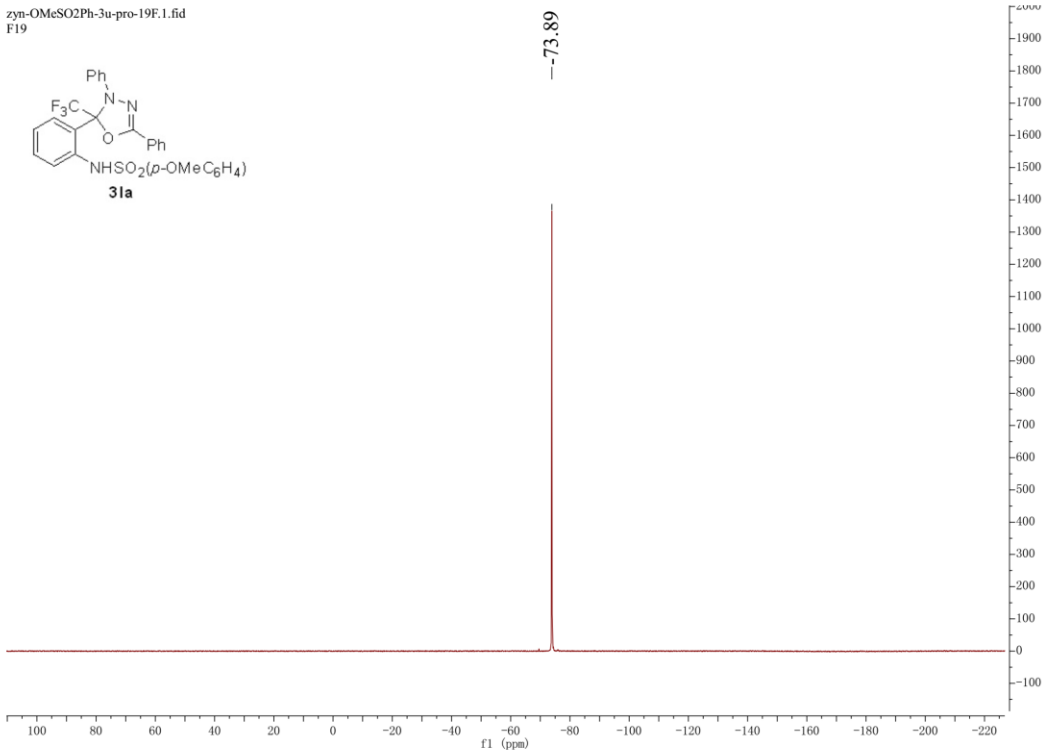
^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3ka**



^{1}H NMR spectra (400 MHz, $CDCl_3$) of **3la**



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



^{19}F NMR spectra (376 MHz, $CDCl_3$) of **3la**

6.X-ray crystal structure of 3ab

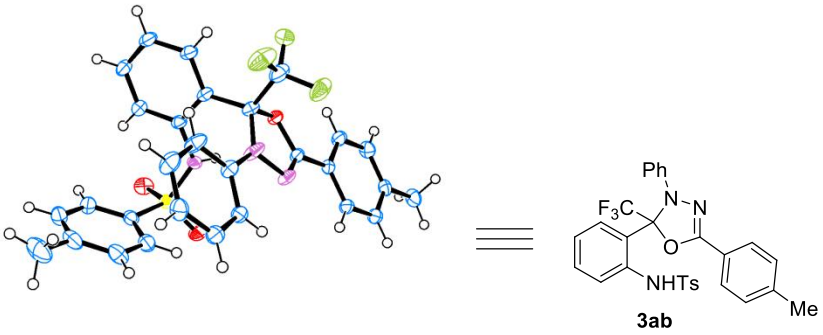


Figure S1. ORTEP diagram of **3ab** (CCDC: 2084149). Thermal ellipsoids are shown at the 50% probability level.

Method of crystallization: A solution of **3ab** in n-hexane/CH_2Cl_2 (2:1) was added to a 10 mL vial. The vial was closed with parafilm and poked a few of holes with a needle on the parafilm to slowly evaporation of solvent.

The X-ray intensity data was measured on a Rigaku 007 Saturn 70 single crystal diffractometer.

Table S1. Crystal data and structure refinement for **3ab**.

Identification code	**3ab**
Empirical formula	$C_{29}H_{24}F_3N_3O_3S$
Formula weight	551.57

Temperature/K	113.15
Crystal system	triclinic
Space group	P-1
a/Å	9.2123(3)
b/Å	13.9474(6)
c/Å	20.6800(7)
α/°	100.472(3)
β/°	92.038(3)
γ/°	92.699(3)
Volume/Å^3	2607.33(17)
Z	4
ρ_{calc}g/cm^3	1.405
μ/mm^{-1}	0.183
F(000)	1144.0
Crystal size/mm^3	0.23 × 0.2 × 0.17
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection/°	3.88 to 62.33
Index ranges	-13 ≤ h ≤ 13, -19 ≤ k ≤ 19, -29 ≤ l ≤ 28
Reflections collected	29273
Independent reflections	15051 [R_{int} = 0.0541, R_{sigma} = 0.0756]
Data/restraints/parameters	15051/0/708
Goodness-of-fit on F^2	1.032
Final R indexes [I>=2σ (I)]	R_1 = 0.0624, wR_2 = 0.1567
Final R indexes [all data]	R_1 = 0.0862, wR_2 = 0.1799
Largest diff. peak/hole / e Å^{-3}	0.63/-0.88