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A new synthesis of 4′-trifluoromethyl-2,2′:6′,2′′-terpyridine

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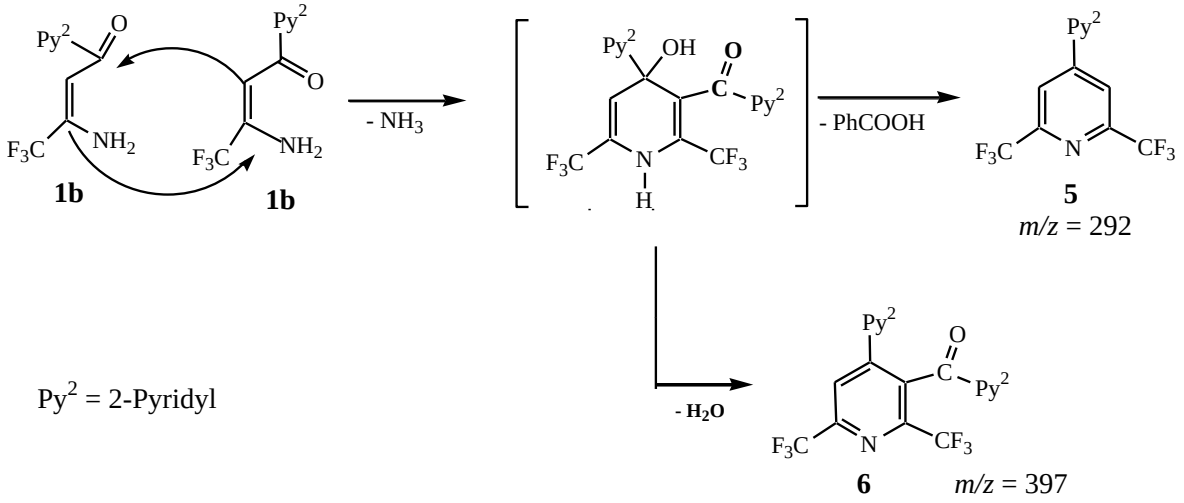
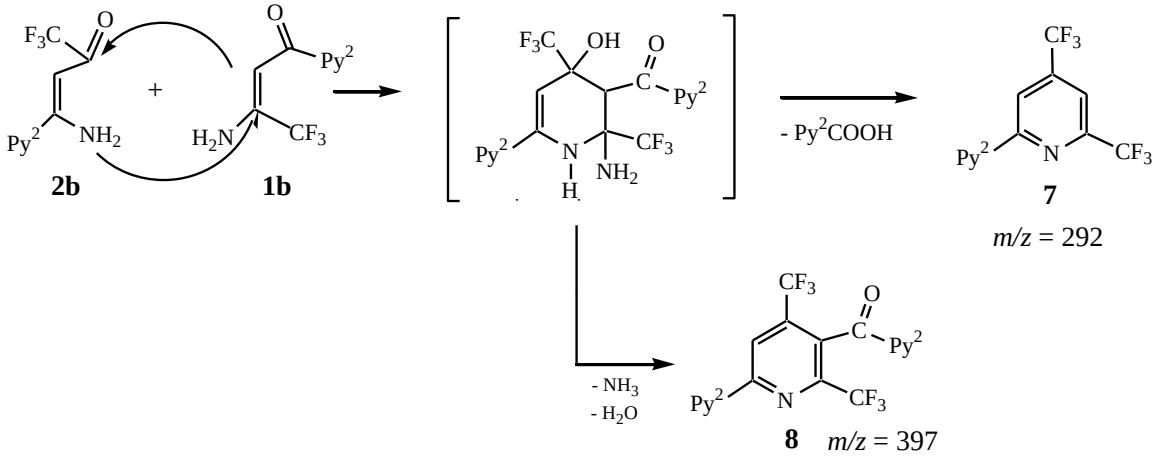
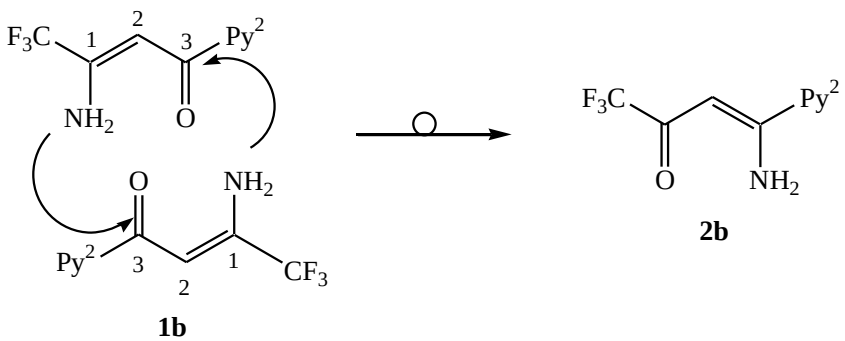


Scheme S1



Scheme S2



Scheme S3 Isomerization of AVK **1b** into AVK **2b**.

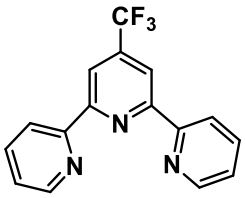
Materials and methods.

Regioisomeric AVKs **1b** and **2b** were obtained by the reaction of lithium (*Z*)-1,1,1-trifluoro-4-oxo-4-(2-pyridyl)but-2-ene-2-olate with ammonium acetate in glacial AcOH. AVK **1b**: mp 103 - 104 °C. AVK **2b**: mp 80 – 81 °C[S1].

The purity of compounds was monitored by TLC on Sorbfil plates (UV-254, eluent $CHCl_3$). Spots on the plates were detected by UV light and a treatment with $Cu(OAc)_2$ aqueous solution. ^1H and ^{13}C spectra were recorded on Bruker DRX-400 and Bruker AVANCE-500 spectrometers using TMS as internal standards. ^{19}F NMR spectra were recorded on Bruker DRX-400 spectrometer in $CDCl_3$ using C_6F_6 as the external standard and converted to the $CFCl_3$ standard by the calculation of $\delta(CFCl_3) = \delta(C_6F_6) - 162{,}93$. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR instrument equipped with attenuated total reflection (ATR) or the diffusion reflection accessory (DRA) units for the 400–4000 cm^{-1} range in solid form. Elemental analysis was carried out using a Perkin Elmer PE 2400 element analyzer. The GC-MS analysis was performed on GC-MS spectrometer Trace GC Ultra DSQ II (USA) with a quartz capillary column Thermo TR-5ms (polydimethylsiloxane, 5 wt % of phenyl groups, 30 m×0.25 mm, film thickness 0.25 μm, Figures S5 – S13) or column HP-5MS 30 m×0.25 mm ID x 0.25 μm (5% phenyl methyl silox, Figures S14 – S27) with a quadrupole mass-spectrometric detector with electron ionization (70 eV). Carrier gas helium, split ratio 1:50, flow through the column 1.0 ml min^{-1}. Scan of the total ionic current in the range 20–1000 Da. The initial column temperature was 40°C (storage 3 min), programming rate was 10 K min^{-1} to 280 °C (storage 30 min). The temperatures of the injector 250°C, of the source 200°C, of the transfer line 200 °C. Solutions of the samples with a concentration of 4-5 mg ml^{-1} were prepared in ethanol.

*Synthesis of 4'-trifluoromethyl-2,2':6',2''-terpyridine **3b** and 6'-trifluoromethyl-2,2':4',2''-terpyridine **4*** A solution of AVKs **1b** and **2b** (0.6 g, 2.7 mmol each) in glacial acetic acid (5 ml) was boiled for 10 hours. The mixture was poured into water, extracted with diethyl ether (3×10 ml). The extract was washed with water (2×10 ml), the solvent was evaporated and residue was chromatographed on a column (eluent dichloromethane). The composition of each fraction was controlled by the GC-MS method. Fractions containing the highest amounts of Tpy **3b** (or Tpy **4**) were combined and further purified by column chromatography and then recrystallized from hexane, to obtain 0.31 g (37%) white crystals of Tpy **3b** and 0.012 g (1.4%) of a light yellow powder Tpy **4**. The solutions remaining after isolation of Tpy **3b** and Tpy **4** were combined, the solvent was evaporated and the residue was analyzed by GC-MS (Figures S9 – S14).

4'-Trifluoromethyl-2,2':6',2''-terpyridine ***3b***

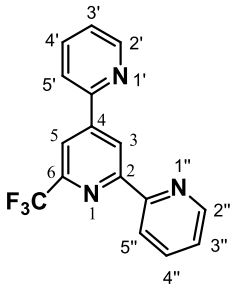


mp 144-145 °C, soluble in dichloromethane, chloroform, diethyl ether, ethyl acetate, acetone; insoluble in water. Found: C 63.77; H 3.38; N 13.96; F 18.95. Calc. for $C_{16}H_{10}F_3N_3$: C 63.79; H 3.35; N 13.95; F 18.92. IR (dra, cm^{-1}): 3091, 3060, 3019, 1587, 1568, 1468, 1448, 1404, 1374, 1265, 1168, 1124, 1091, 1070, 994, 895, 839, 792, 742, 717, 663, 621.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.77 m (2H), 8.74 s (2H), 8.66 d (*J* = 8.3 Hz, 2H), 7.92 td (*J* = 7.8, 1.5 Hz, 2H), 7.42 m (2H). ^{19}F NMR (470.5 MHz, $CDCl_3$), *δ*: -65.81 s (CF_3). ^{13}C NMR ($CDCl_3$) δ_C 116.70 (q, *J* 5.0), 121.37 (s), 123.20 (q, *J* 268.5), 124.49 (s), 137.03 (s), 140.49 (q, *J* 31.2), 149.36 (s), 154.87 (s), 156.78 (s).

GC-MS: τ_R = 24,31. MS (EI) *m/z* (rel. intensity, %) 301 (100.0%) $[M]^+$; 273 (24); 232 (18) $[M\text{-}CF_3]^+$; 223 (16) $[M\text{-}Py^2]^+$; 203 (8) $[M\text{-}Py^2\text{-}HF]^+$; 151 (10); 128 (8); 78 (28) $[Py^2]^+$; 51 (10).

6'-Trifluoromethyl-2,2':4',2''-terpyridine ***4***



mp 119.5-120.5 °C, soluble in dichloromethane, chloroform, diethyl ether, acetone; insoluble in water. Found: C 63.82; H 3.40; N 13.92; F 18.85. Calc. for $C_{16}H_{10}F_3N_3$: C 63.79; H 3.35; N 13.95; F 18.92. IR (dra, cm^{-1}): 2955, 2924, 2853, 1609, 1587, 1559, 1478, 1444, 1425, 1372, 1265, 1232, 1179, 1159, 1124, 1074, 1043, 994, 904, 783, 671, 646, 619.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 – 7.41 m (2H), 7.86 – 7.89 m (2H), 8.04 d (*J* = 7.95, 1H), 8.45 d (*J* = 1.20, 1H,), 8.56 d (*J* = 7.95, 1H), 8.72 d (*J* = 4.80, 1H), 8.80 d (*J* = 4.50, 1H), 9.18 s (1H,). ^{19}F NMR (470.5 MHz, $CDCl_3$), *δ*: - 69.07 s (CF_3).

GC-MS: τ_R = 23,48. MS (EI) *m/z* (rel. intensity, %) 301 (100.0%) $[M]^+$; 273 (24); 261 (4), 232 (18) $[M\text{-}CF_3]^+$; 223 (16) $[M\text{-}Py^2]^+$; 203 (8) $[M\text{-}Py^2\text{-}HF]^+$; 151 (10); 128 (8); 78 (28) $[Py^2]^+$; 51 (10).

Isomerization of AVK ***1b*** *into AVK* ***2b***

The sample of (0.05 g, 0.00023 mol) AVK **1b** was thermostated at 110 °C for 2 hours, analyzed by GC-MS (Figures S17–S21); then this sample was thermostated at 110° C for an additional 8 hours and analyzed by GC-MS (Fig. S15 – S28). *NOTE*. The presence of the Tpy **3b** impurity in this sample (Figures S14–S16) does not interfere with the study of the isomerization process.

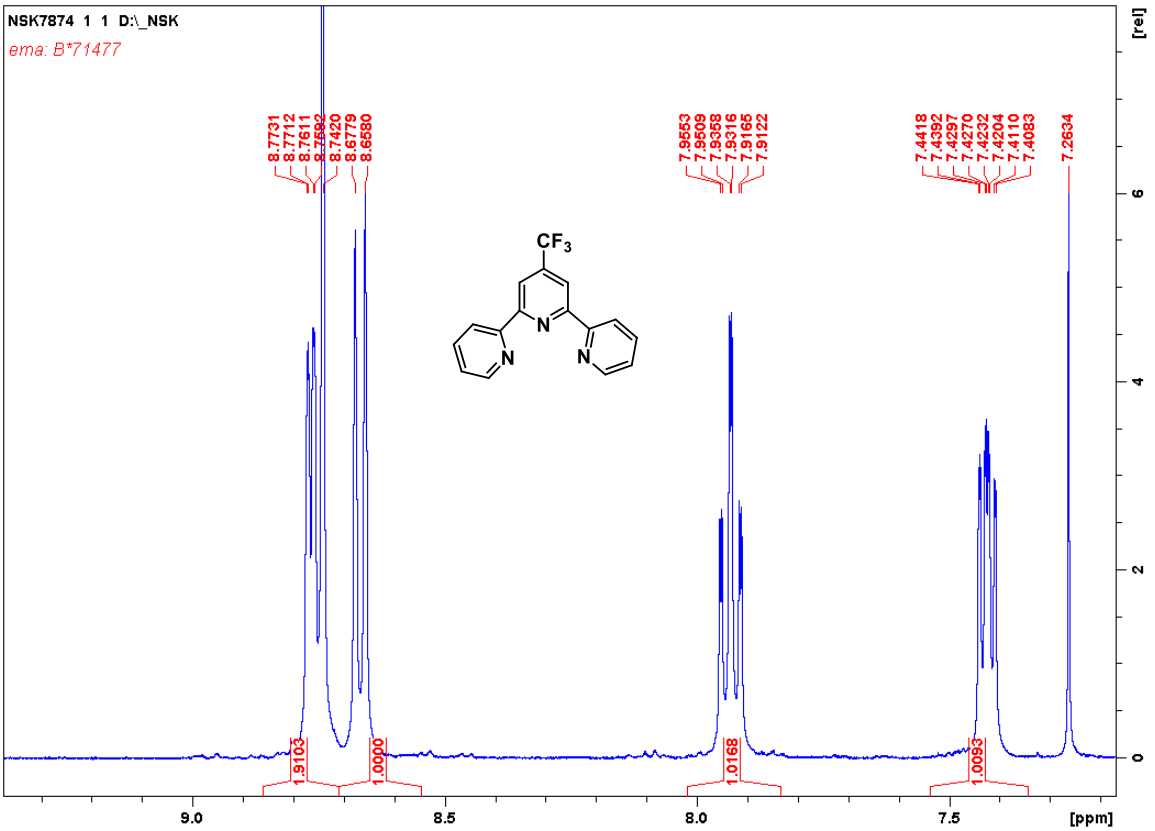


Fig. S1. ^{1}H NMR spectra of Tpy **3b**

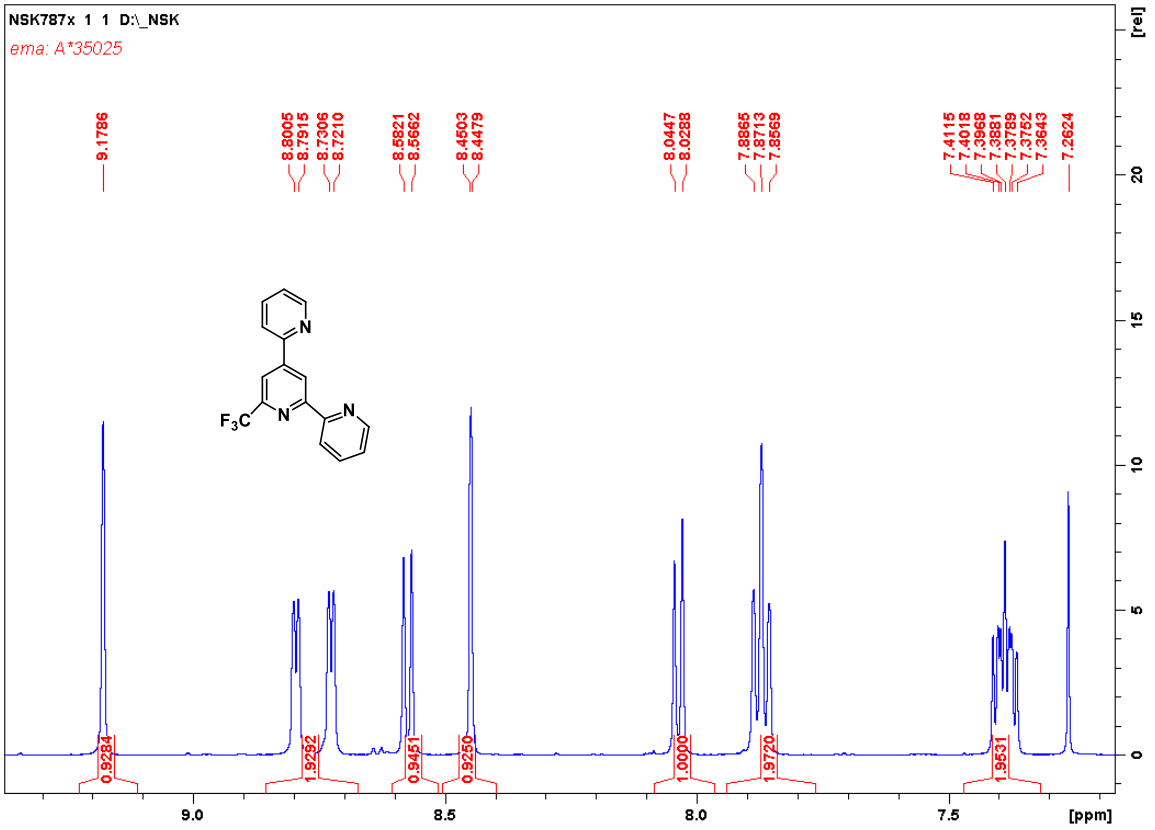


Fig. S2. ^{1}H NMR spectra of Tpy **4**

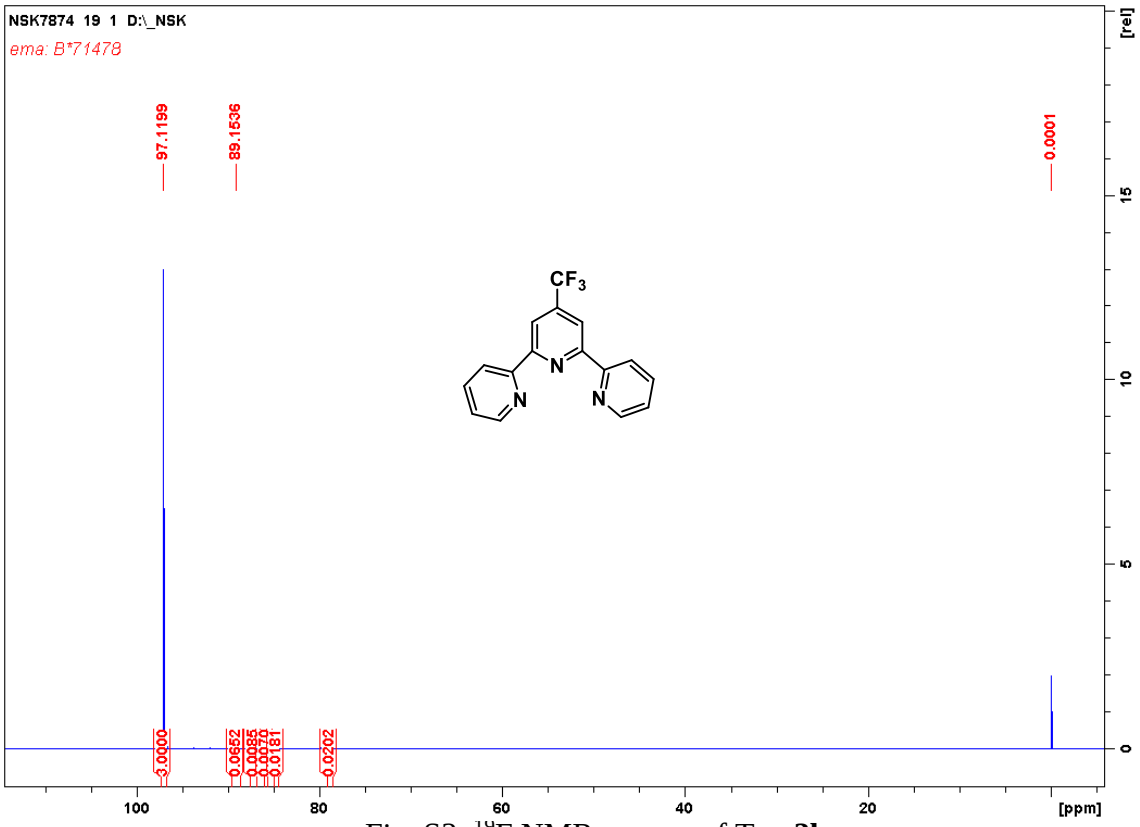


Fig. S3. ^{19}F NMR spectra of Tpy **3b**

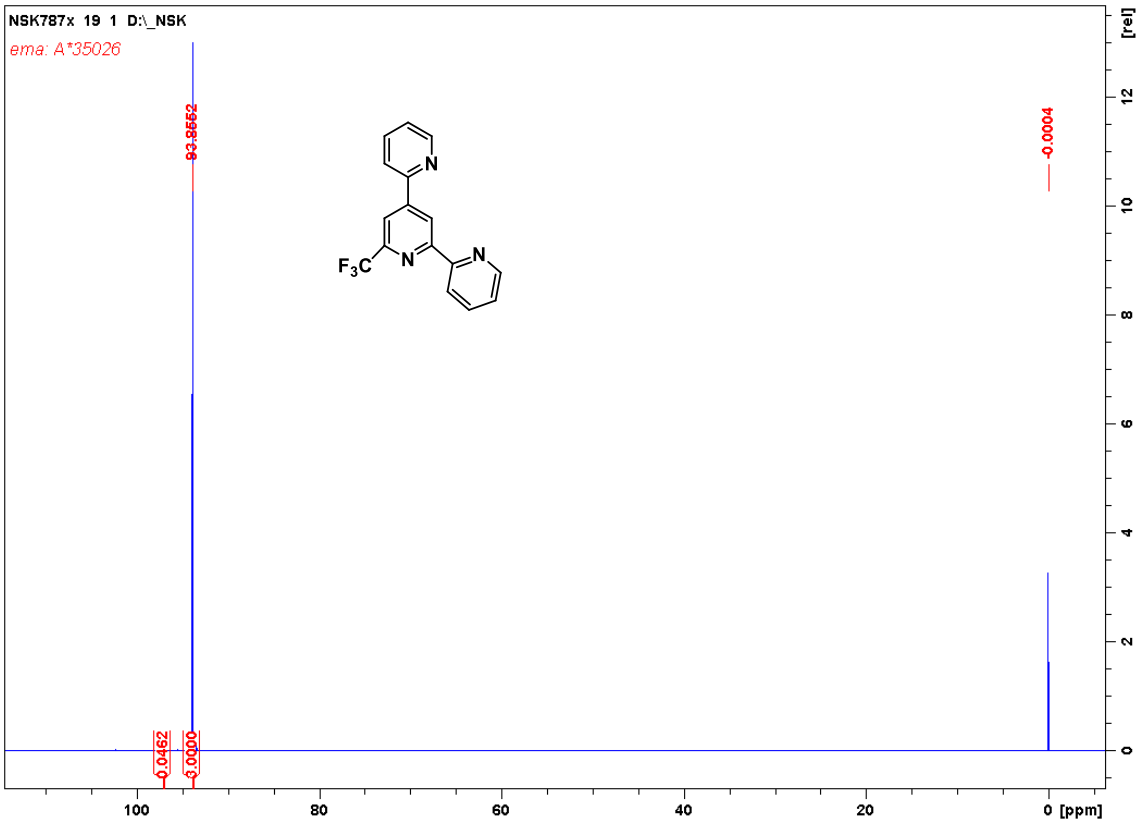


Fig. S4. ^{19}F NMR spectra of Tpy **4**

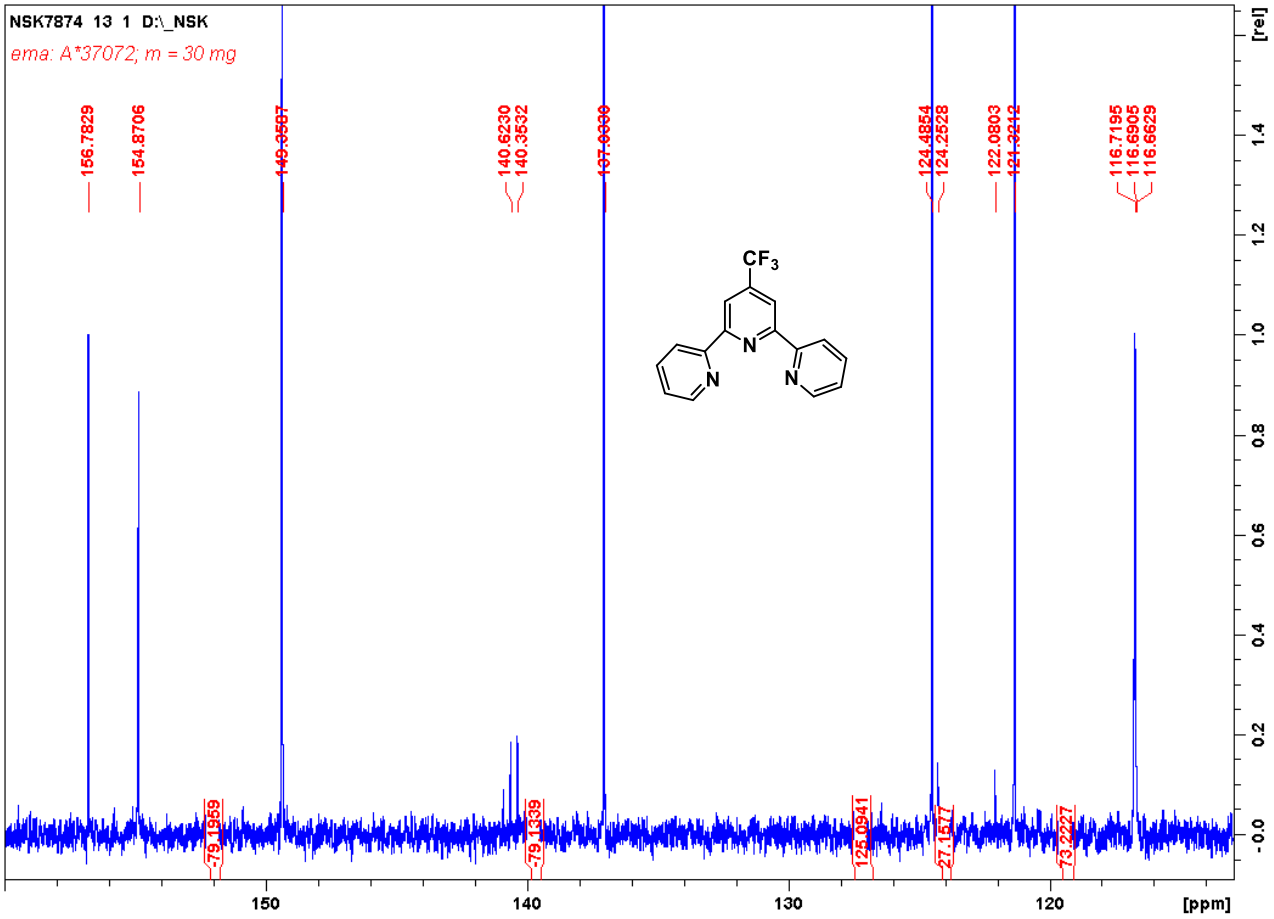
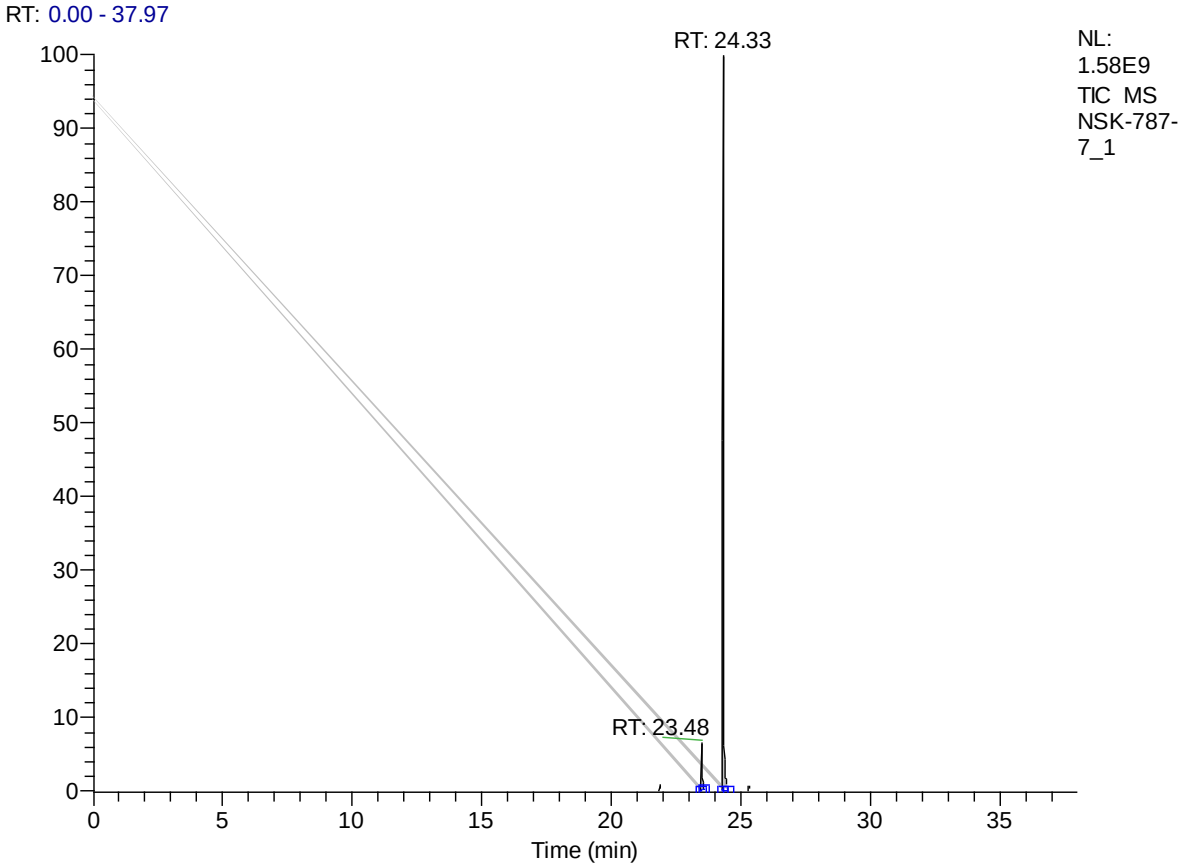


Fig. S5. ^{13}C NMR spectra of Tpy **3b**

Trace GC Ultra DSQ II

Column: Thermo TR-5ms 30 m x 0.25 mm ID x 0.25 μm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 ^{0}C, split, split flow 50 ml/min, split ratio 1:50, col flow 1.0 ml/min
MS transfer line 250 ^{0}C, Ion Source 200 ^{0}C, mass range 20-1000 Da, solvent delay 4.0 min

Sample Name: NSK-787.7
Data File: C:\Xcalibur\data\ labGC\Boltacheva\ NSK-787-7_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 6\12\2018
Vial: 1
Injection Volume (μl): 1.0
Comments: The sample NSK-787.7, c= 4,48 mg ml^{-1} in $CHCl_3$, input 1.0 μl AI/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
23.48	203843050.793	4.64	101861302.664	6.06
24.33	4191617470.649	95.36	1578970172.371	93.94

Fig. S6. Chromatogram of the mixture of Tpy **3b** and Tpy **4**

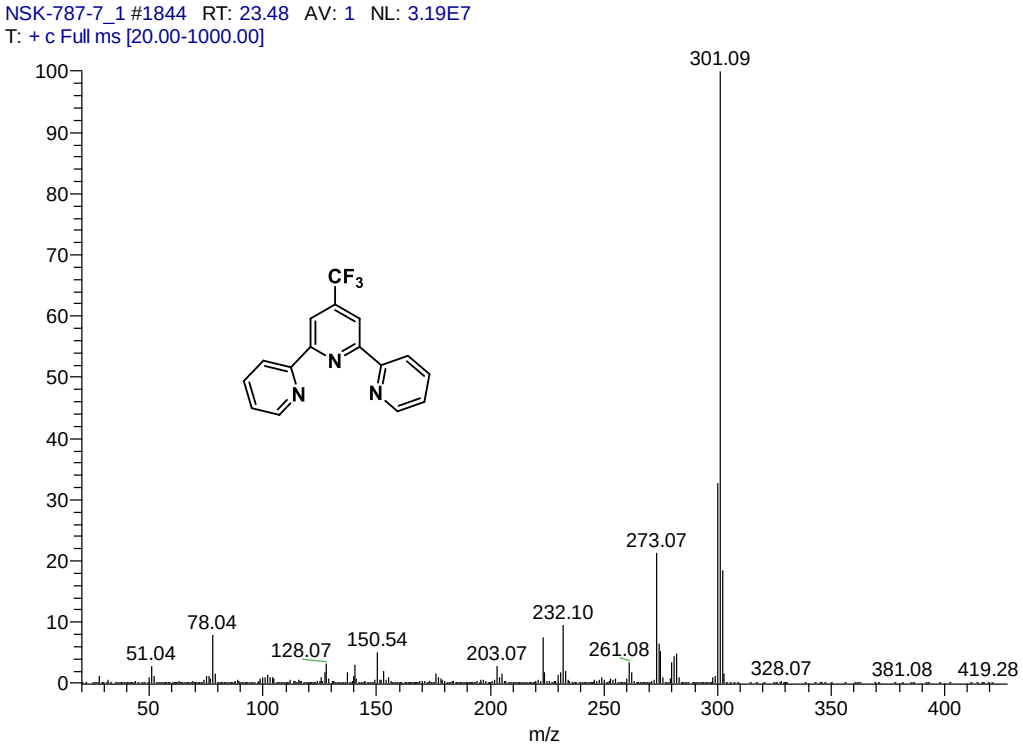


Fig. S7. Mass spectrum of Tpy **3b**

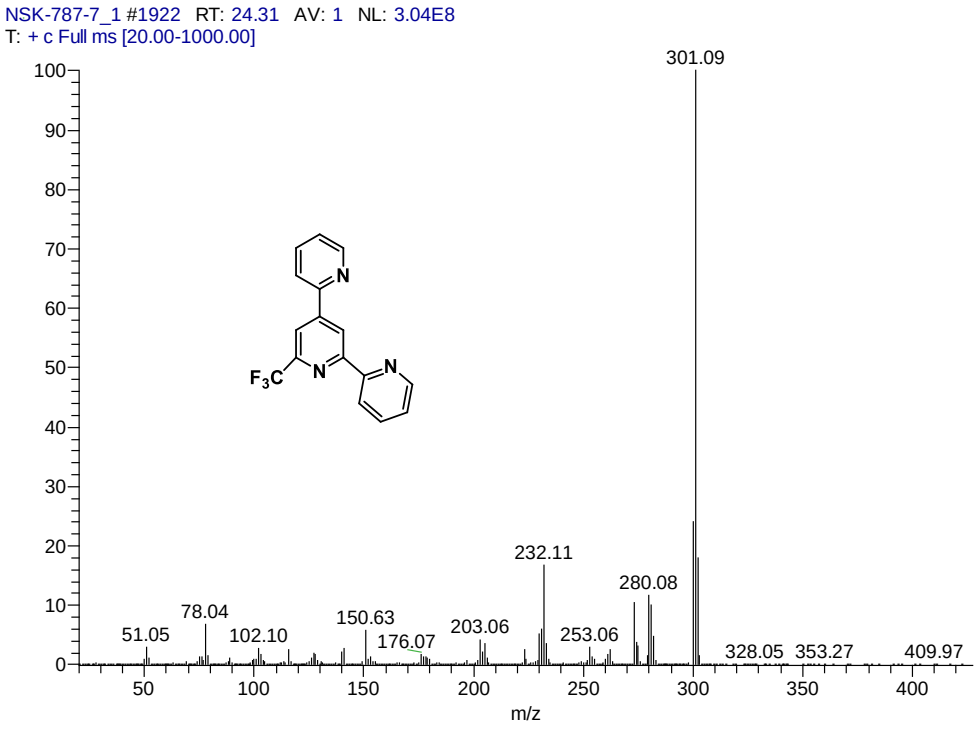
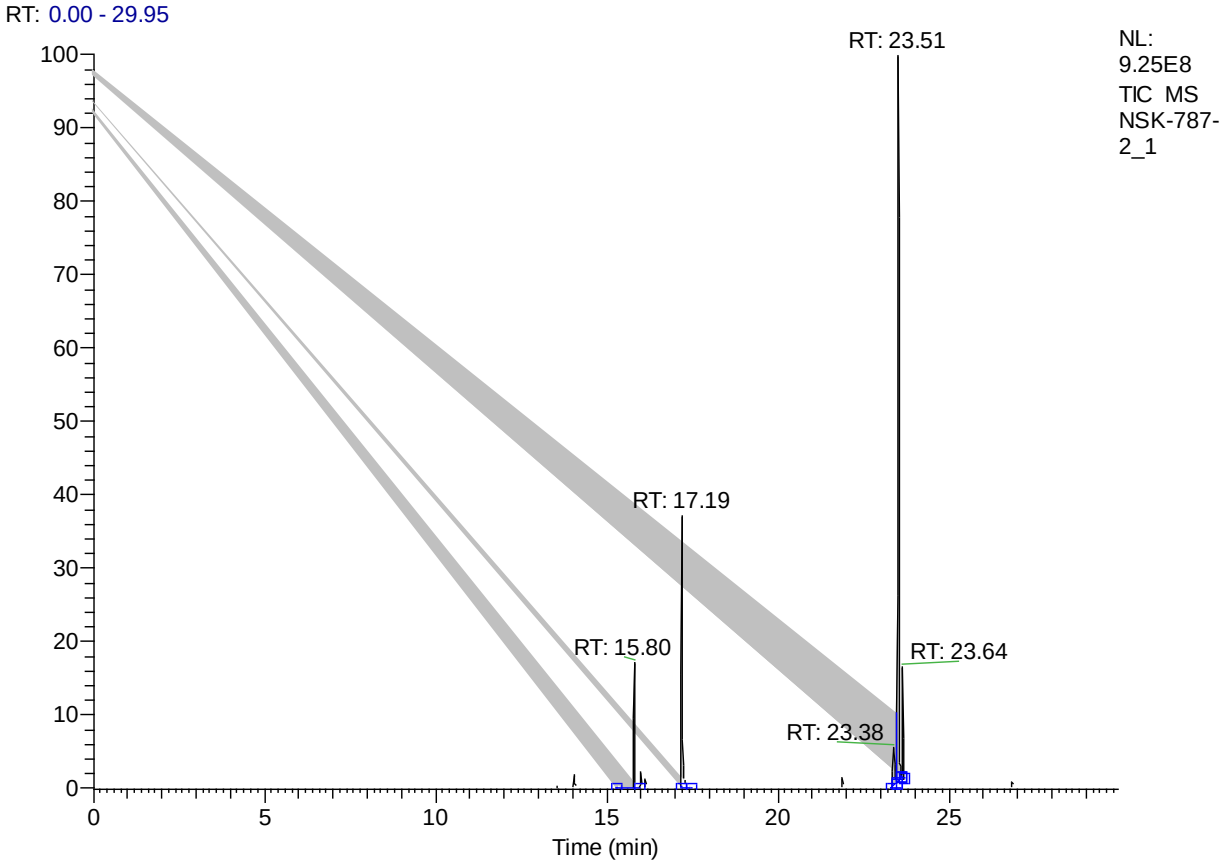


Fig. S8. Mass spectrum of Tpy **4**

Trace GC Ultra DSQ II

Column: Thermo TR-5ms 30 m x 0.25 mm ID x 0.25 μm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 ^{0}C, split, split flow 50 ml/min, split ratio 1:50, col flow 1.0 ml/min
MS transfer line 250 ^{0}C, Ion Source 200 ^{0}C, mass range 20-1000 Da, solvent delay 4.0 min

Sample Name: NSK-787.2
Data File: C:\Xcalibur\data\ labGC\Boltacheva\ NSK-787-2_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 29\11\2018
Vial: 1
Injection Volume (μl): 1.0
Comments: The sample NSK-787.2; 23.6 mg in 4 ml $CHCl_3$, input 1.0 μl AI/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
15.80	267231918.971	7.65	157273248.720	9.83
17.19	807948796.944	23.14	342167744.119	21.38
23.38	163581243.378	4.68	48395615.709	3.02
23.51	2008498458.491	57.51	910185609.399	56.88
23.64	245028368.516	7.02	142284507.135	8.89

Fig. S9. Chromatogram of the mass remaining after the isolation of Tpy **3b** and Tpy **4**.

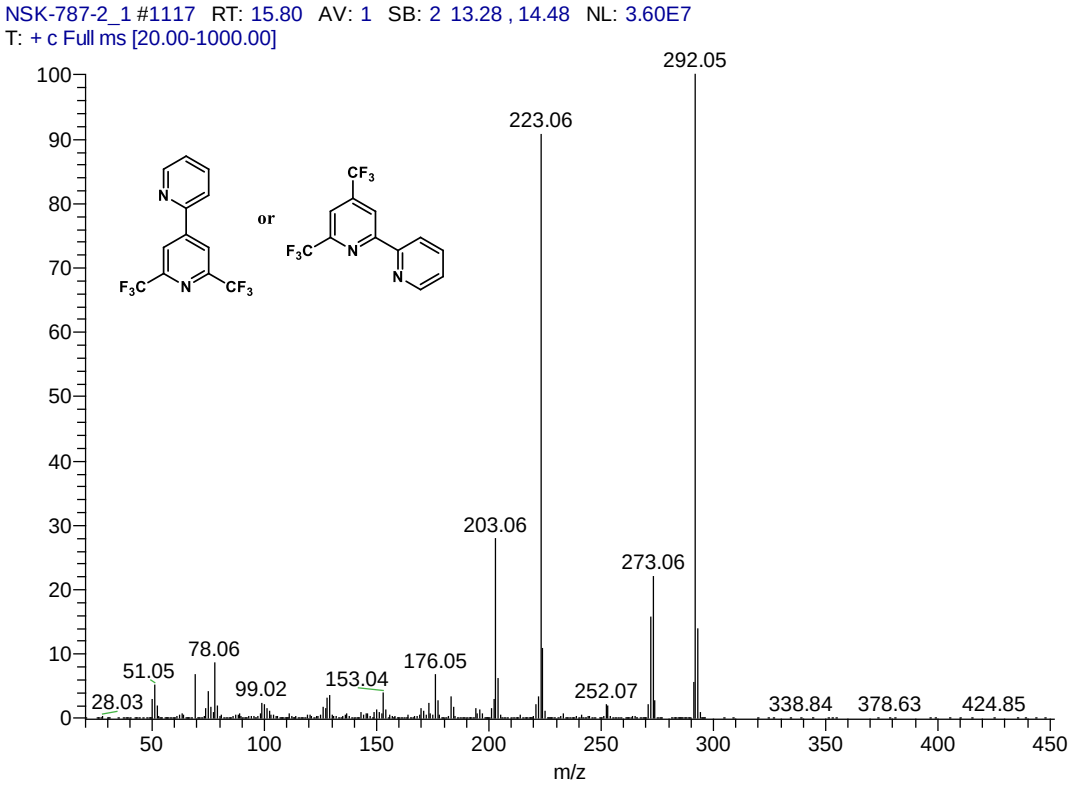


Fig.S10. Mass spectrum of 2,6-di(trifluoromethyl)-4-(2-pyridyl)pyridine **5** or 2-(2-pyridyl)-4,6-di(trifluoromethyl)pyridine **7**

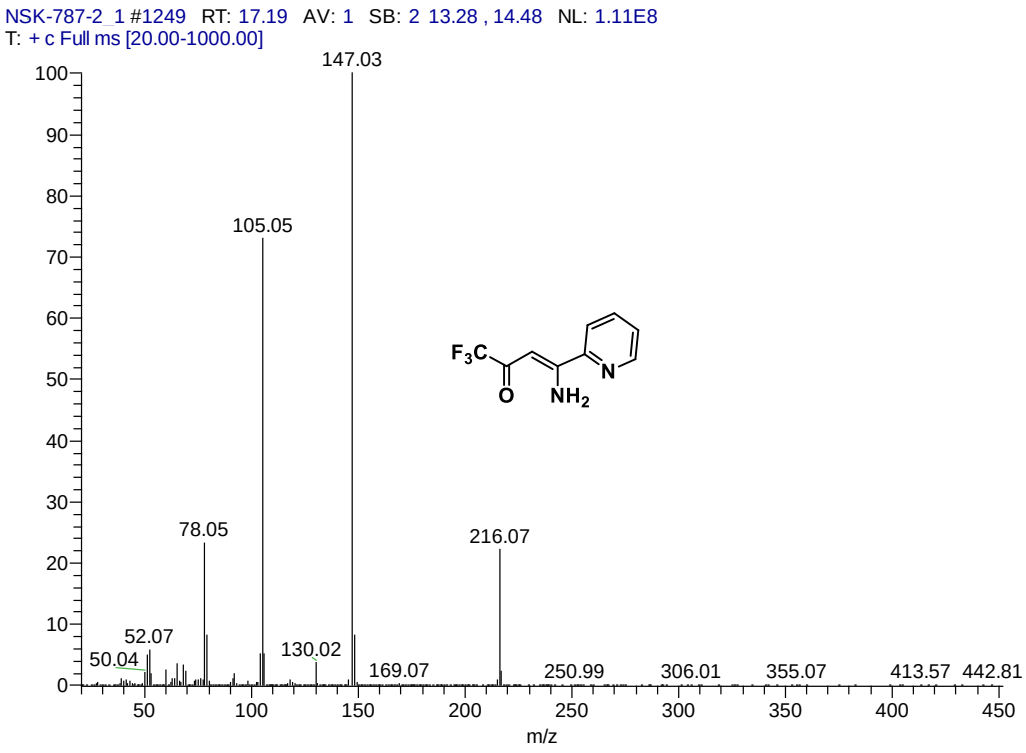


Fig.S11. Mass spectrum of AVK **2b**[S1]

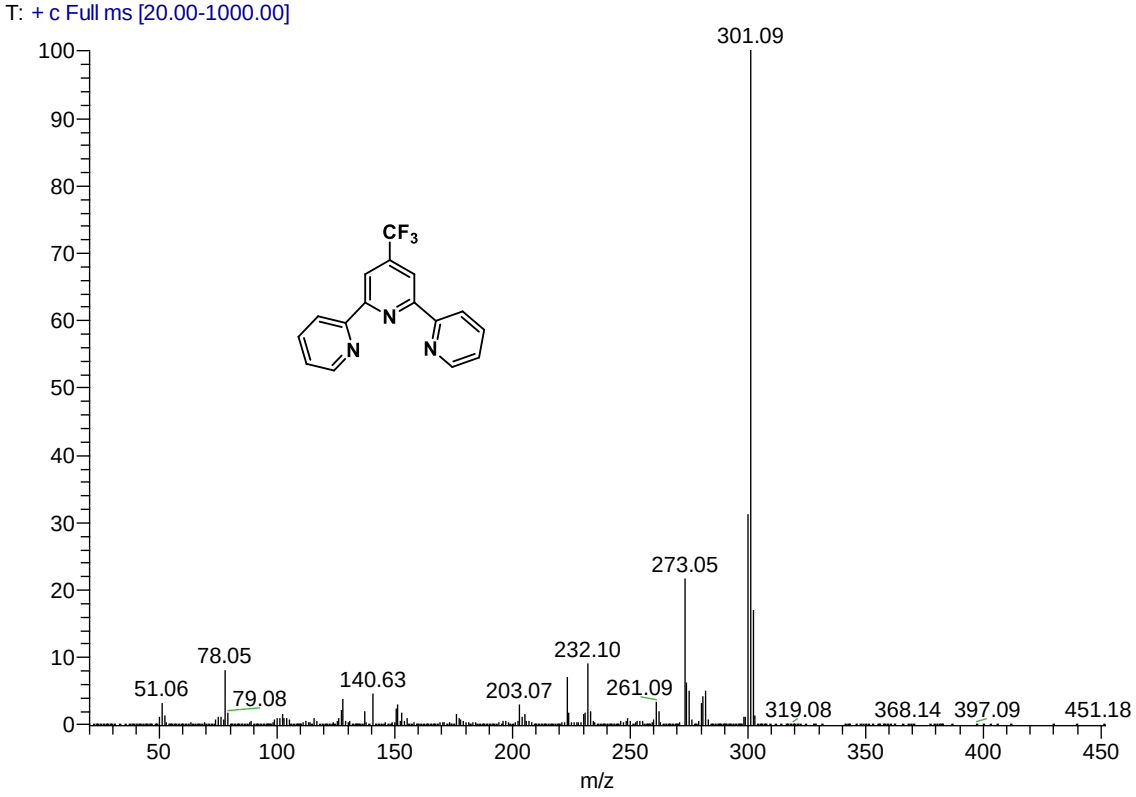


Fig.S12. Mass spectrum of Tpy **3b**

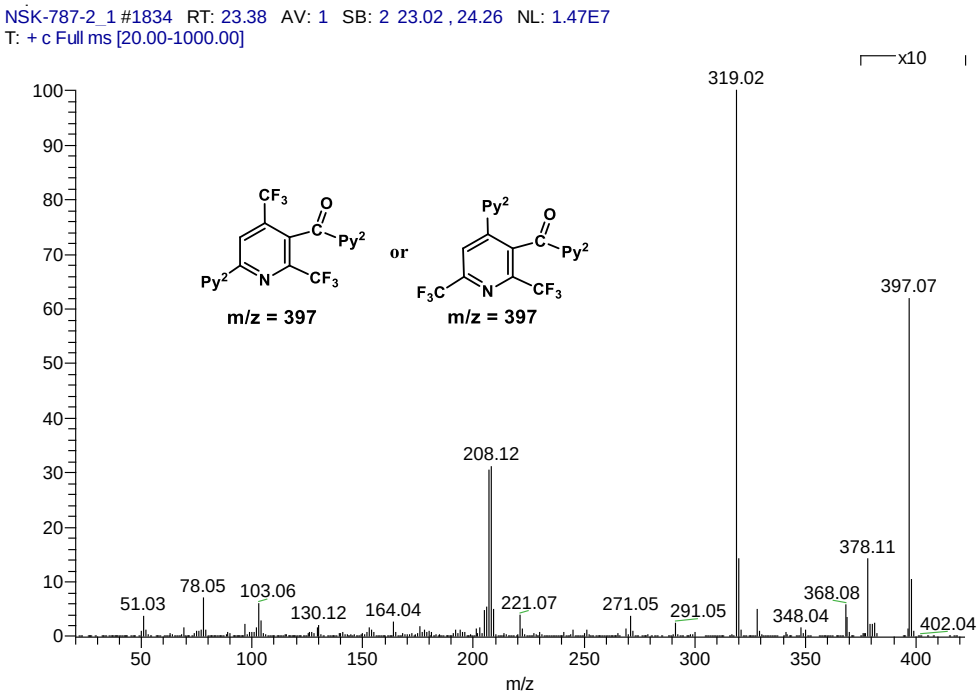


Fig.S13. Mass spectrum of compounds **6** or **8**

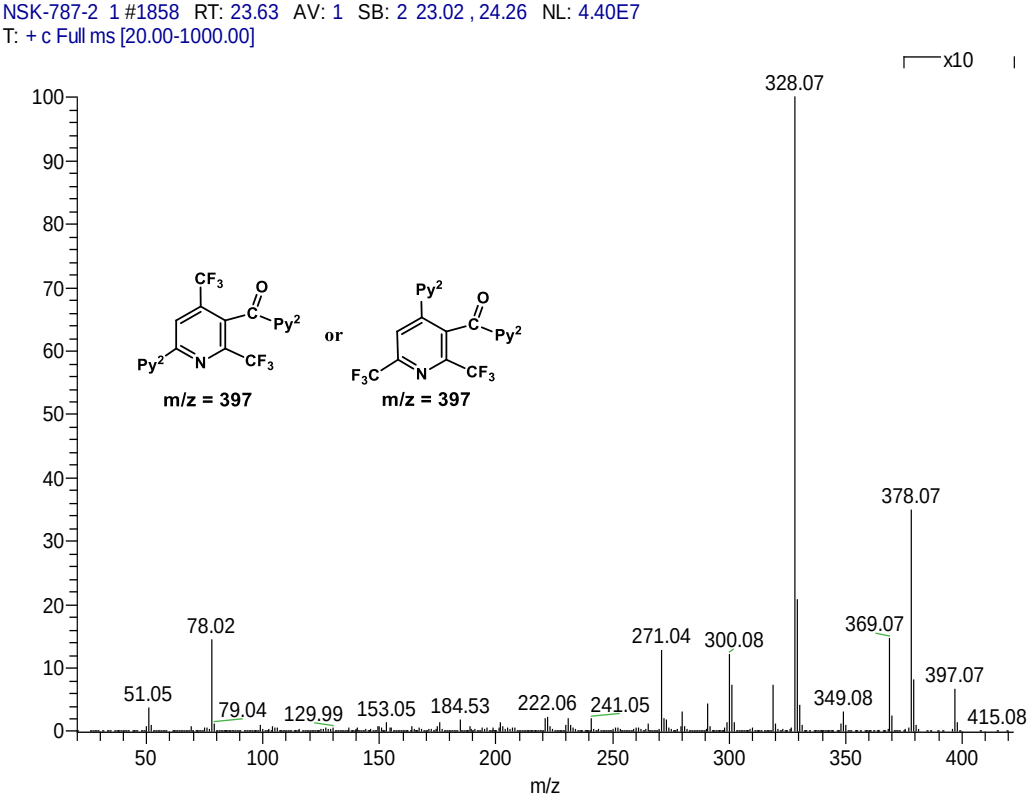
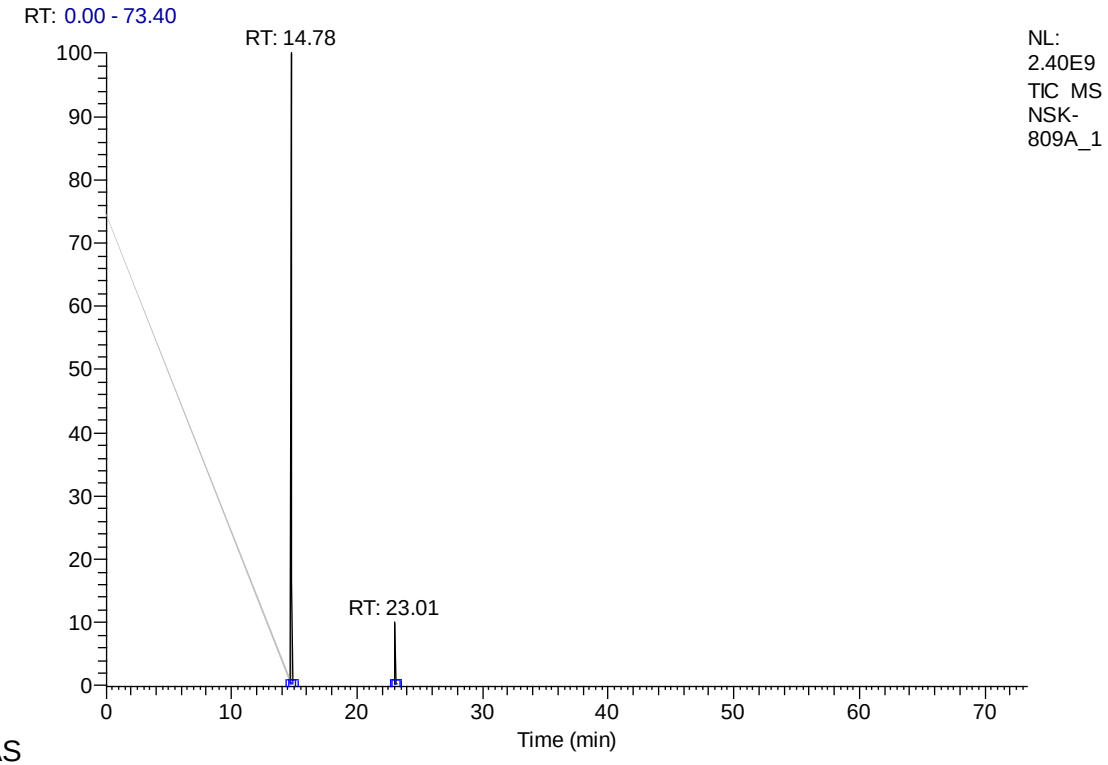


Fig.S14. Mass spectrum of compounds **6** or **8**

Trace GC Ultra DSQ II
Column: HP-5MS 30 m x 0.25 mm ID x 0.25 μm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 ^{0}C, split, split flow 50 ml/min, split ratio 1:50, col flow 1.0 ml/min
MS transfer line 250 ^{0}C, Ion Source 200 ^{0}C, mass range 20-1000 Da, solvent delay 4.0 min

Sample Name: NSK-809A
Data File: C:\Xcalibur\data\ labGC\IBoltacheva\NSK-809A_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 21\02\2020
Vial: 1
Injection Volume (μl): 1.0
Comments: The sample NSK-809A in $CHCl_3$, c= 4.86 mg/ml, input 1.0 μl



AI/AS

PEAK LIST

Apex RT	Area	%Area	Height	%Height
14.78	6485910780.991	93.17	2395497802.335	91.18
23.01	475412914.815	6.83	231681606.000	8.82

Fig.S15. Chromatogram of the initial sample of AVK **1b** (with an admixture of Tpy **3b**)

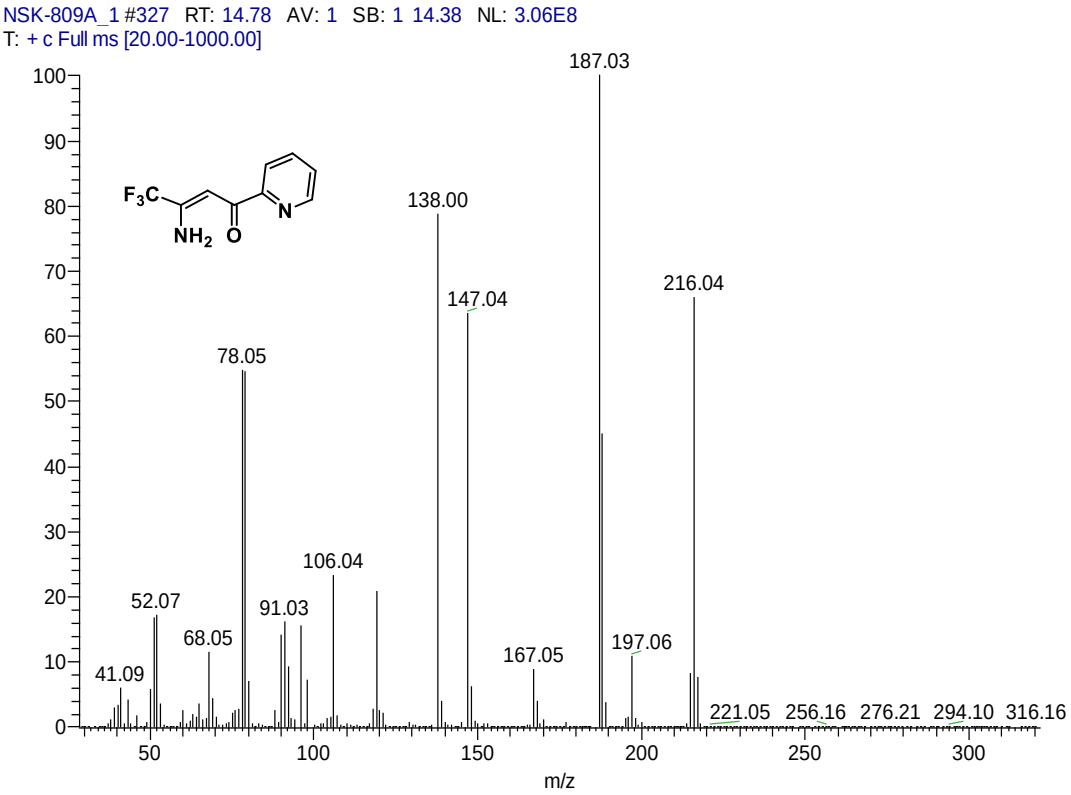


Fig. S16. Mass spectrum of AVK **1b** [S1]

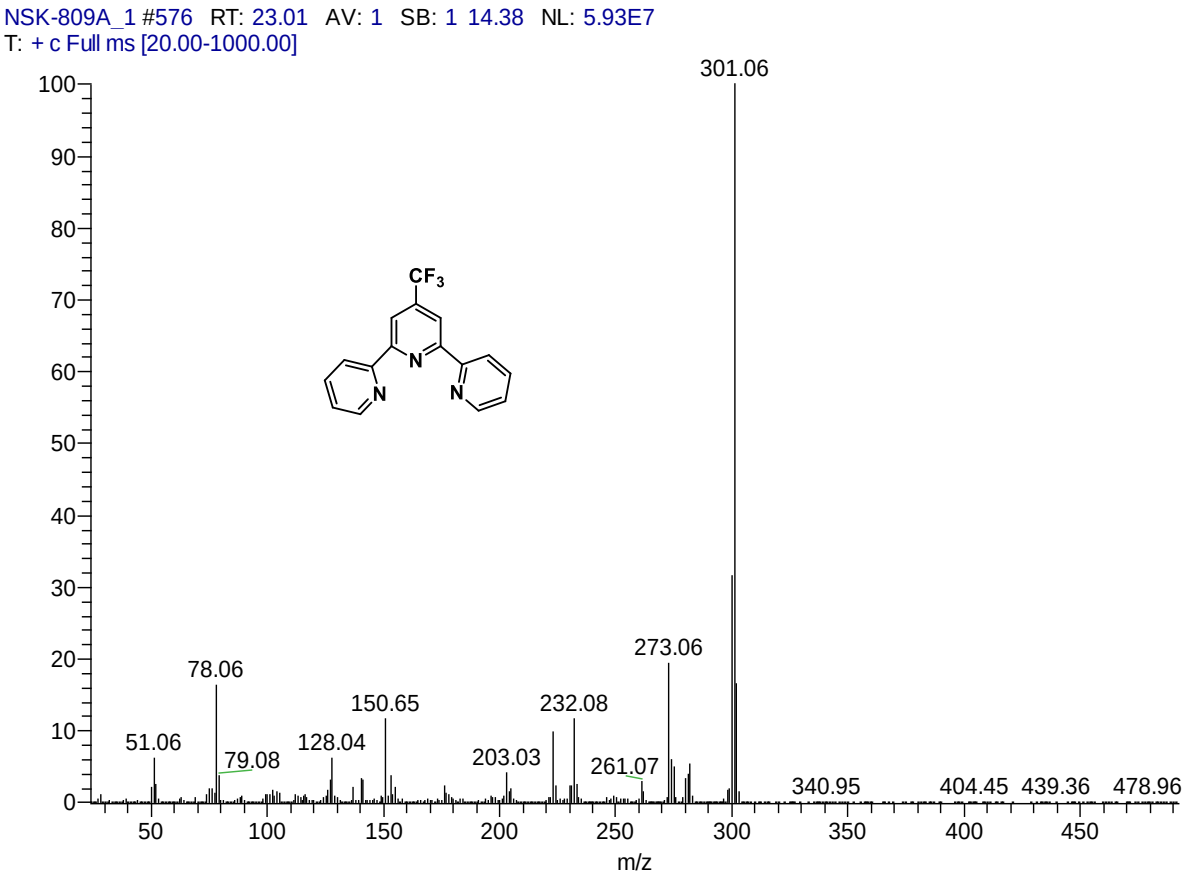
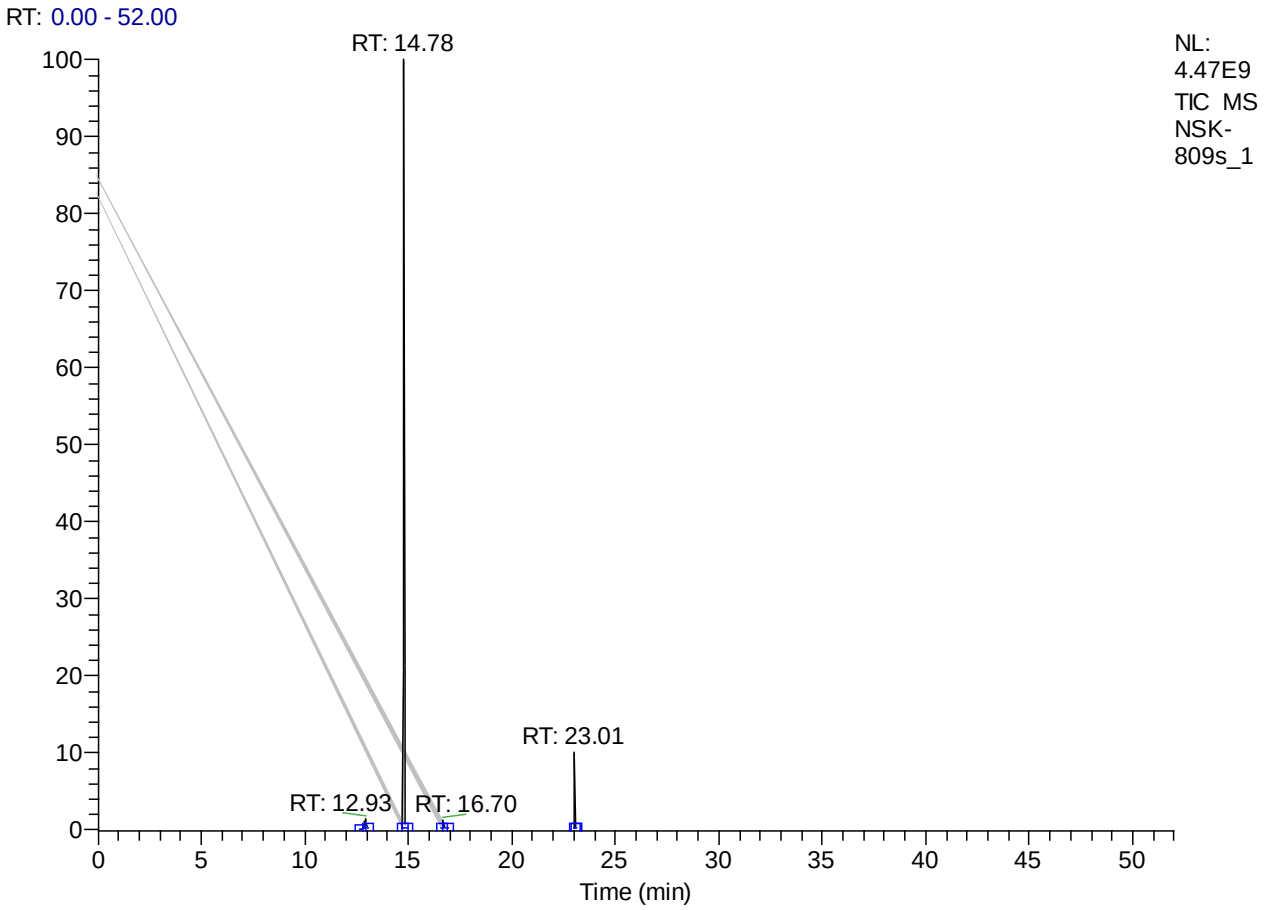


Fig. S17. Mass spectrum of Tpy **3b**

Trace GC Ultra DSQ II
Column: HP-5MS 30 m x 0.25 mm ID x 0.25 μm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 ^{0}C, split, split flow 30 ml/min, split ratio 1:30, col flow 1.0 ml/min
MS transfer line 250 ^{0}C, Ion Source 200 ^{0}C, mass range 20-1000 Da, solvent delay 4.0 min

Sample Name: NSK-809s
Data File: C:\Xcalibur\data\ labGC\IBoltacheva\NSK-809s_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 03\03\2020
Vial: 1
Injection Volume (μl): 1.0
Comments: The sample NSK-809s in $CHCl_3$, c= 4.98 mg/ml, input 1.0 μl AI/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
12.93	326726681.538	2.32	56382535.014	1.13
14.78	12676902775.386	90.09	4458790197.271	89.09
16.70	137900147.721	0.98	49313876.104	0.99
23.01	930566685.848	6.61	440599254.631	8.80

Fig. S18. Chromatogram of the thermostating products of the sample AVK **1b** at 110°C for 2 hours

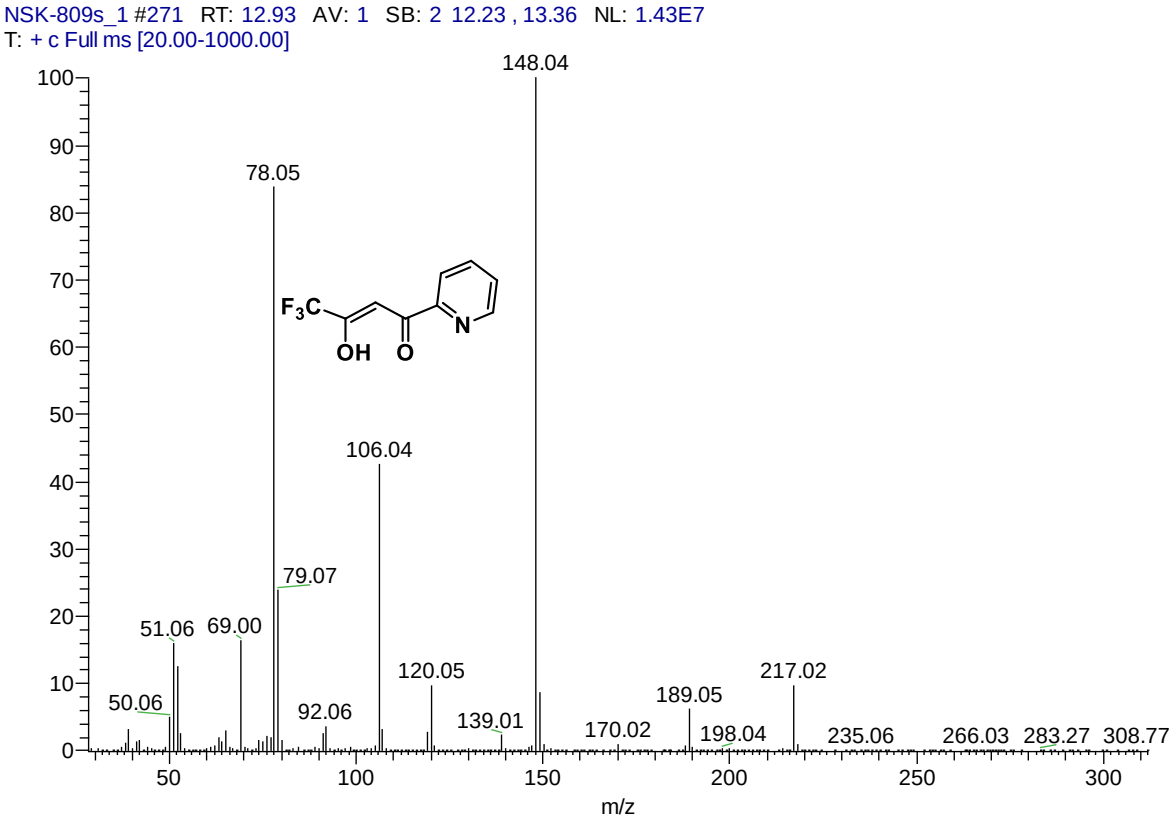


Fig. S19. Mass spectrum of 4,4,4-trifluoro-3-hydroxy-1-(2-pyridyl)but-2-en-1-one – hydrolysis product of AVK **1b** and/or AVK **2b**

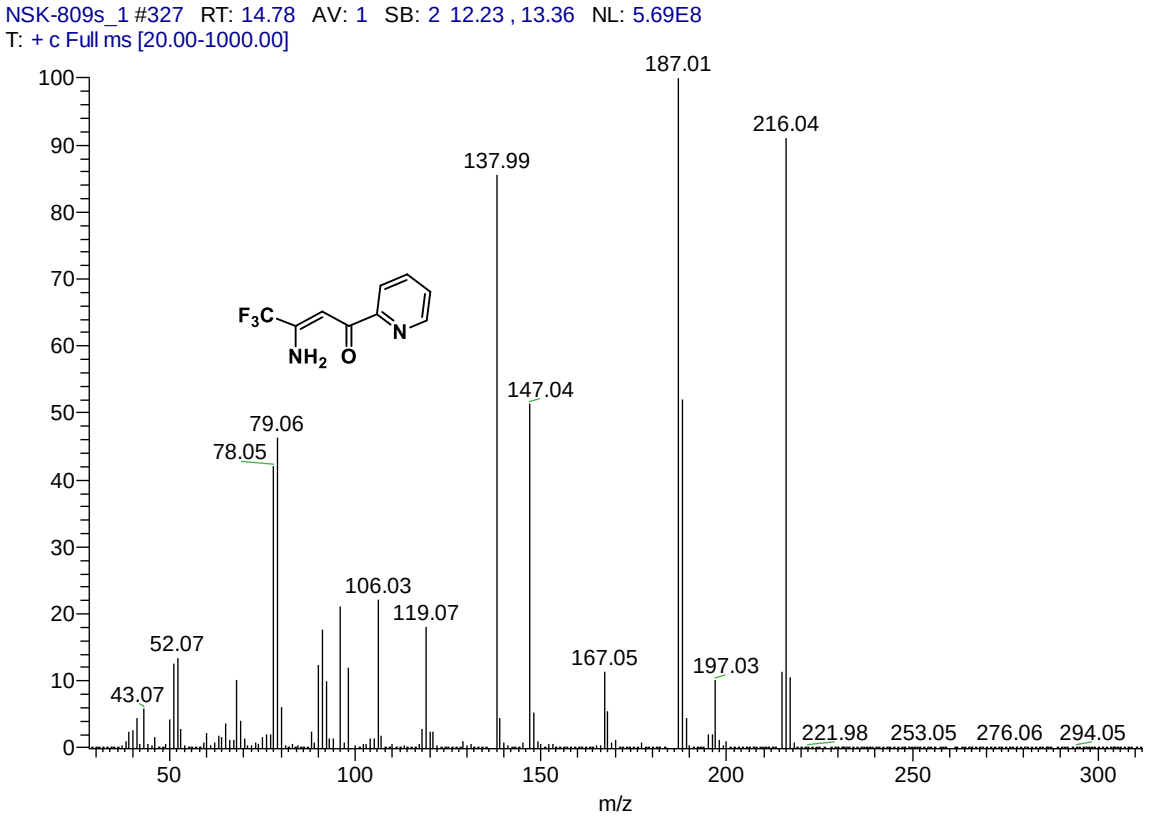


Fig. S20. Mass spectrum of AVK **1b**[S1]

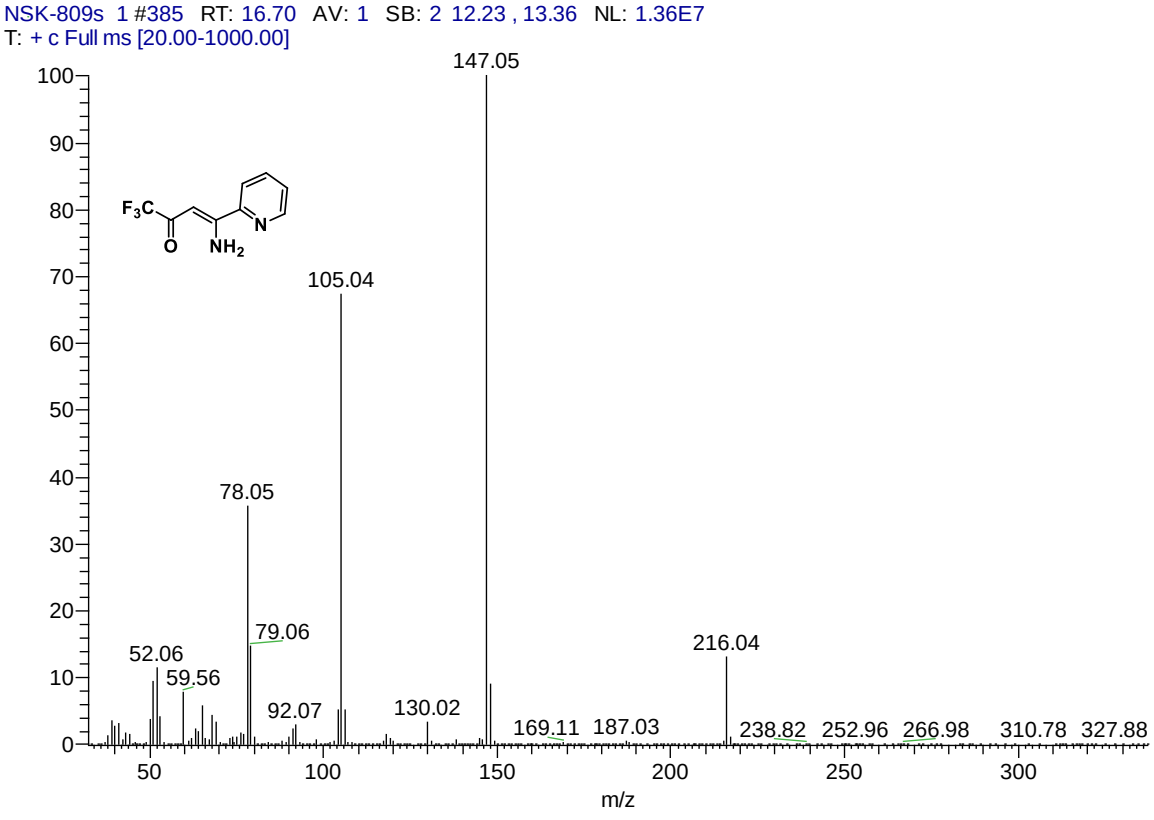


Fig. S21. Mass spectrum of AVK **2b**[S1]

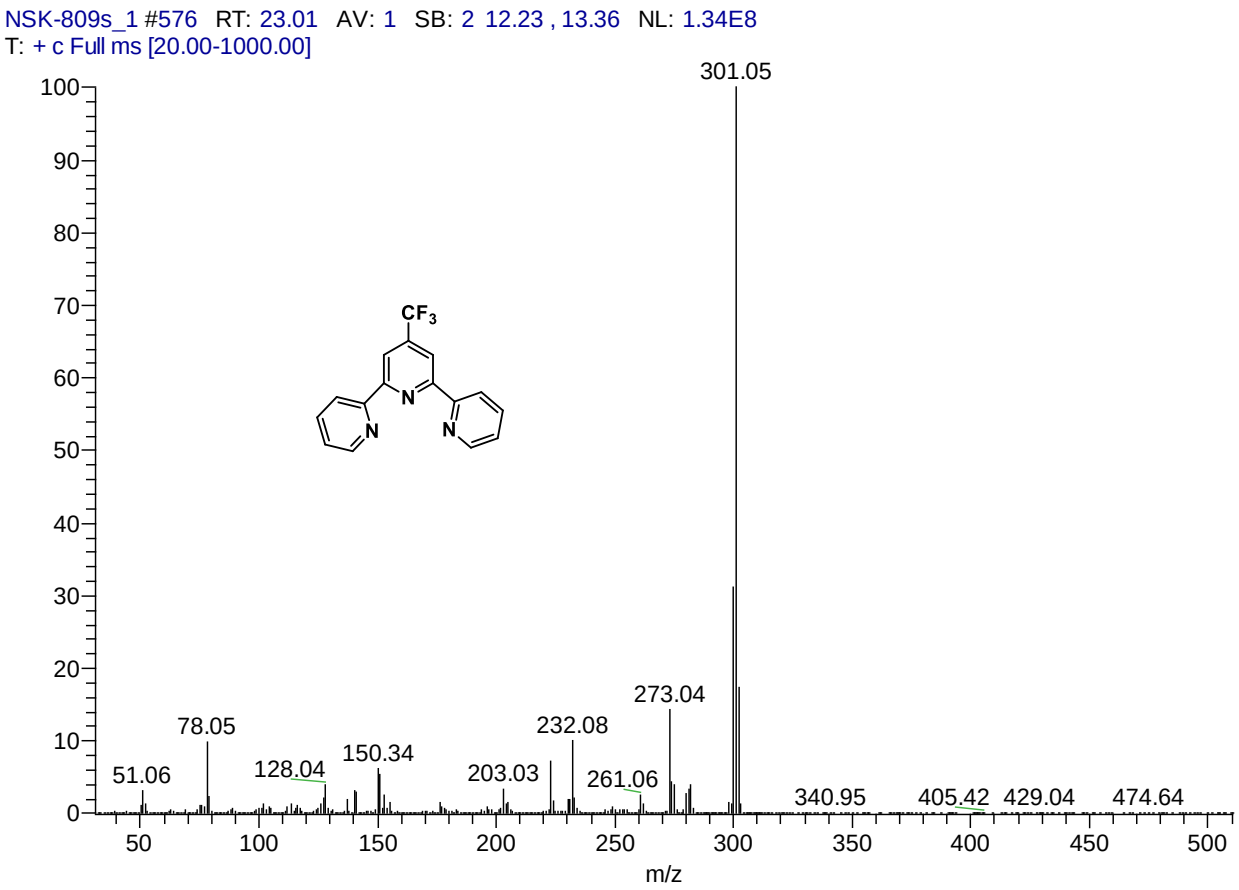
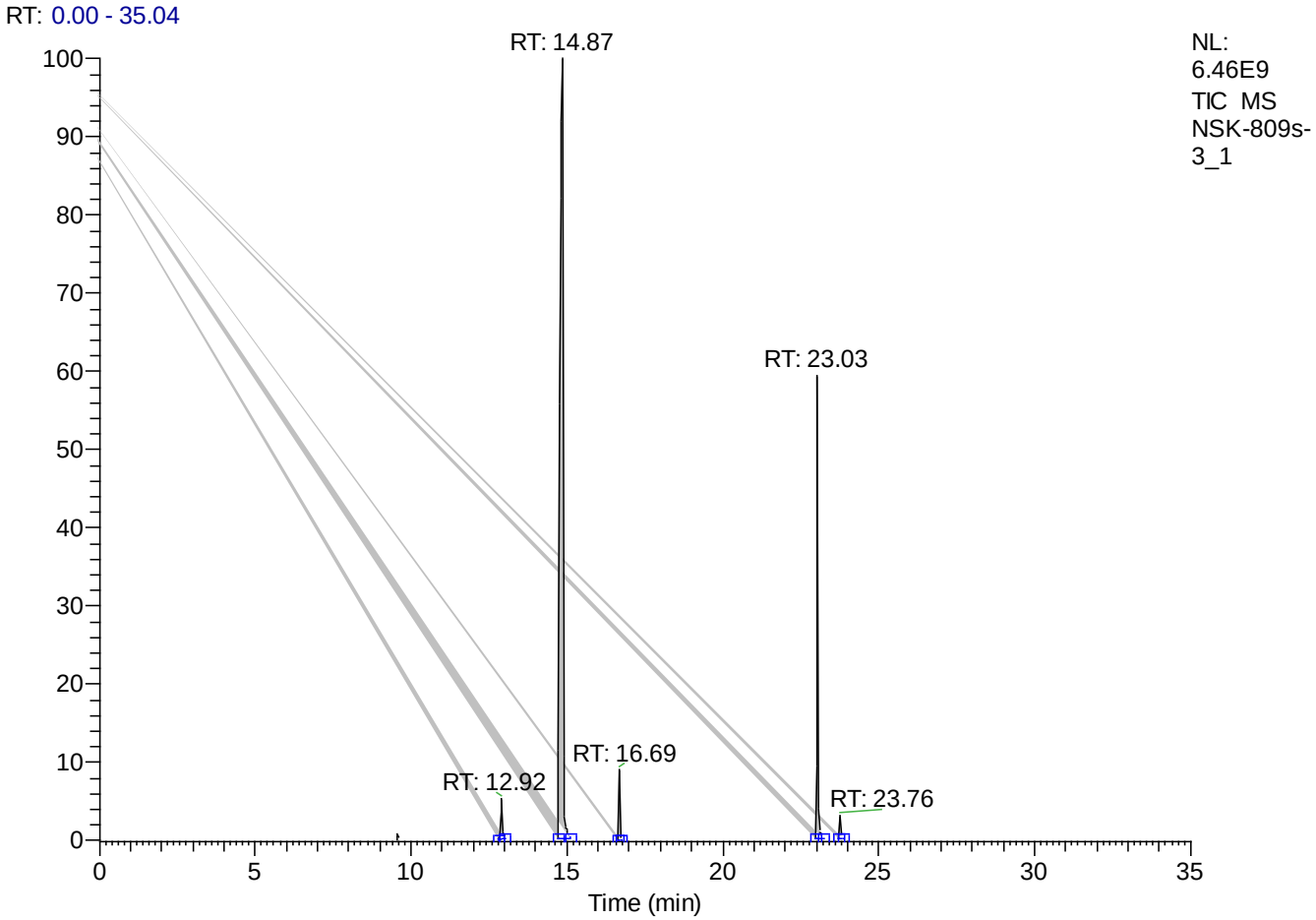


Fig. S22. Mass spectrum of Tpy **3b**

Trace GC Ultra DSQ II

Column: HP-5MS 30 m x 0.25 mm ID x 0.25 μm (5% phenyl methyl silox)
Method: **solv_contr-EI-AOC.meth**
Tkol 40/3/10/280 Tinl 250 ^{0}C, split, split flow 50 ml/min, split ratio 1:50, col flow 1.0 ml/min
MS transfer line 250 ^{0}C, Ion Source 200 ^{0}C, mass range 20-1000 Da, solvent delay 3.0 min

Sample Name: NSK-809s-3
Data File: C:\Xcalibur\data\ labGC\IBoltacheva\NSK-809s-3_1.RAW
Instrument Method: C:\Xcalibur\methods\solv_cont-EI-AOC.meth
Acq: 07\05\2020
Vial: 1
Injection Volume (μl): 1.0
Comments: The sample NSK-809s-3 + 3ml $CHCl_3$, input 1.0 μl AI/AS



PEAK LIST

Apex RT	Area	%Area	Height	%Height
12.92	1376977387.191	2.35	328022816.717	2.88
14.87	45908967923.999	78.20	6450979029.700	56.64
16.69	1282395687.777	2.18	579424707.871	5.09
23.03	9680434570.350	16.49	3835031623.209	33.67
23.76	454995076.157	0.78	196194348.383	1.72

Fig. S23. Chromatogram of the thermostating products of the sample AVK **1b** at 110°C for 10 hours

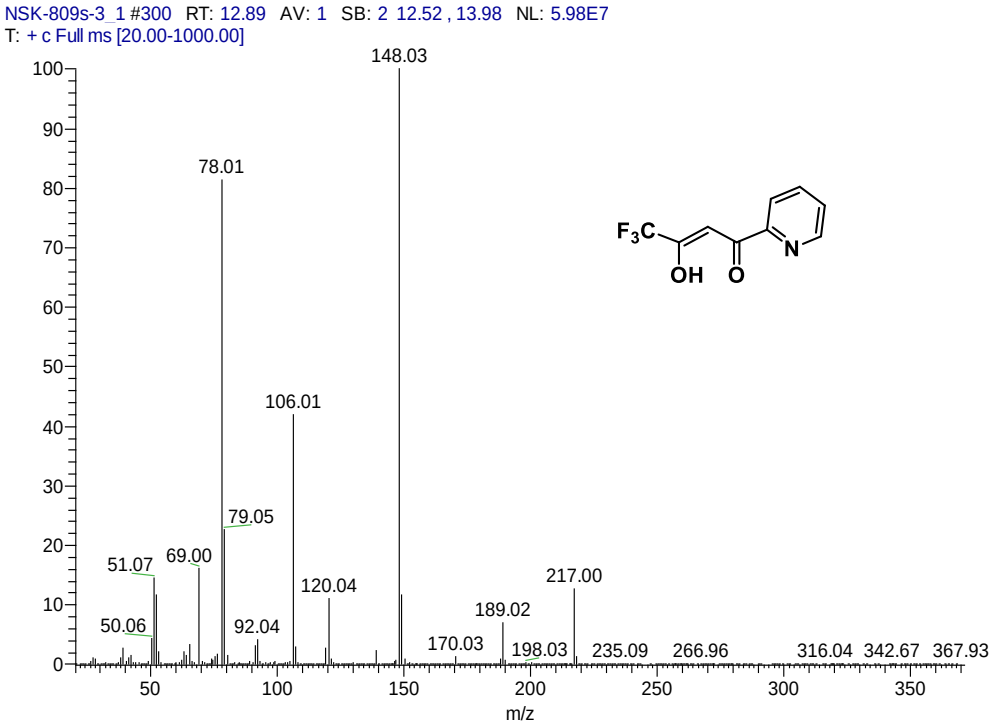


Fig. S24. Mass spectrum of 4,4,4-trifluoro-3-hydroxy-1-(2-pyridyl)but-2-en-1-one – hydrolysis product of AVK **1b** and/or AVK **2b**

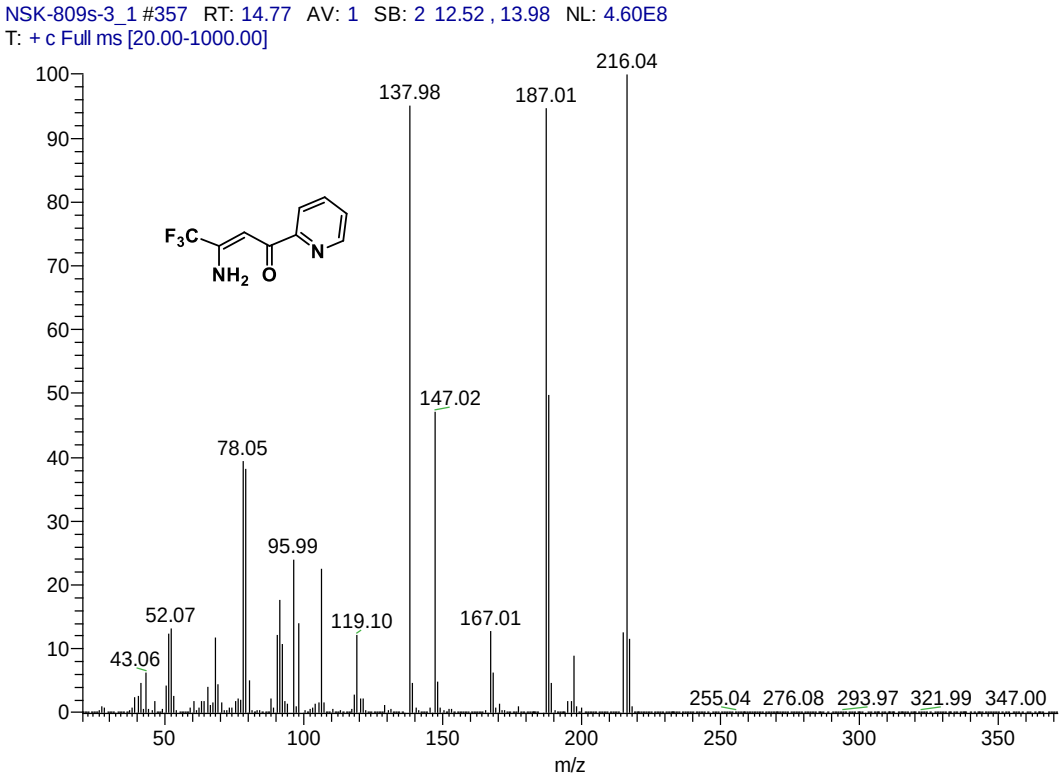


Fig. S25. Mass spectrum of AVK **1b**[S1]

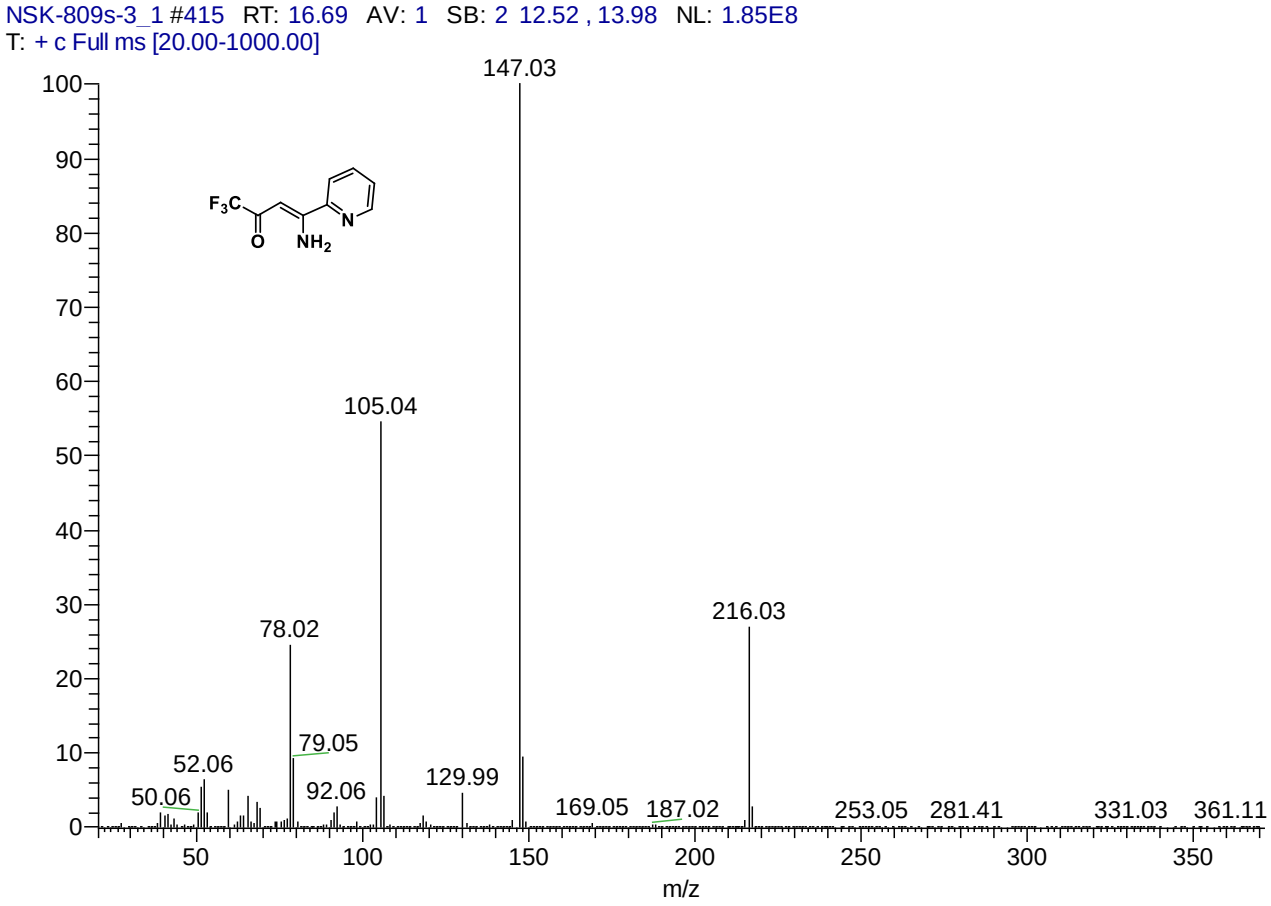


Fig. S26. Mass spectrum of AVK **2b**[S1]

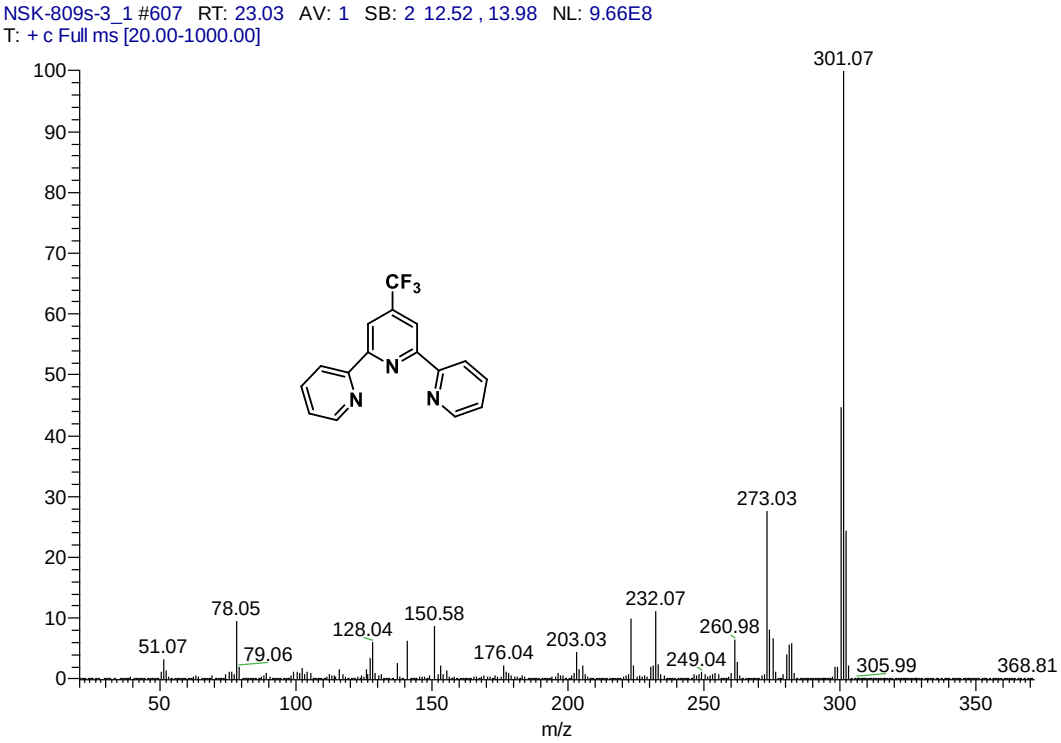


Fig. S27. Mass spectrum of Tpy **3b**

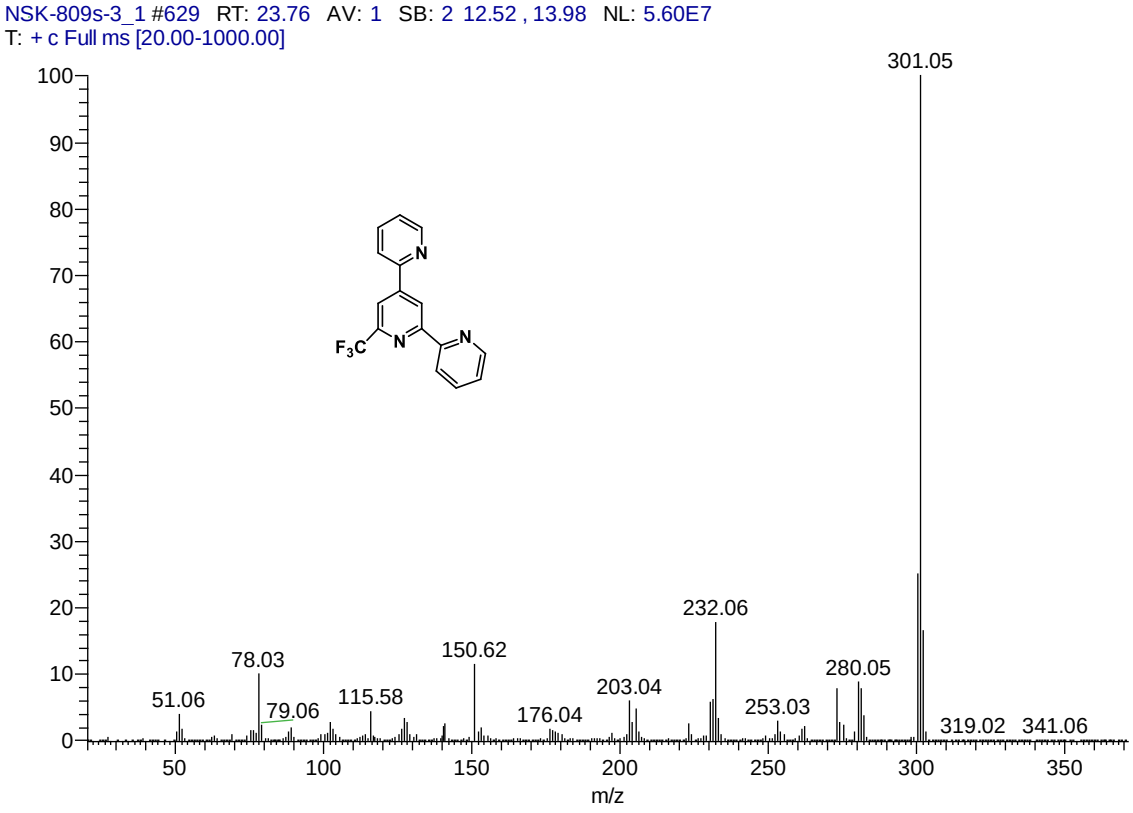


Fig. S28. Mass spectrum of Tpy **4**

References

S1. P. A. Slepukhin, N. S. Boltacheva, M. G. Pervova, V. I. Filyakova and V. N. Charushin, *Russ. Chem. Bull., Int. Ed.*, 2020, **69**, 2355 (*Izv. Akad. Nauk, Ser. Khim.*, 2020, 2355).