Supplementary Material

Defluorination of *gem*-difluoromethyl(ene) compounds with calcium salts

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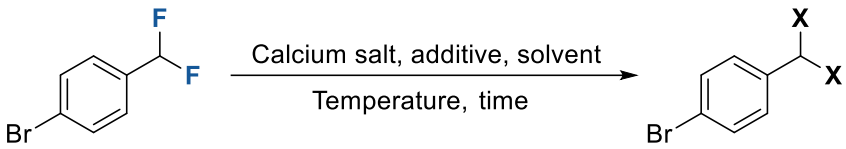
1. Reaction Optimization

1.1 Optimization data of difluoride to dihalide conversion:



A 1.75 ml vial equipped with a stirrer bar was charged with 1-bromo-4-(difluoromethyl)benzene (20.6 mg, 0.1 mmol, 1 equiv.), followed by calcium salt (Table **S1**), solvent (Table **S1** and **S2**) and additive (Table **S3**). The vial was covered with a cap, sealed with Parafilm, and stirred for a given time (Table **S2**) at given temperature (Table **S2**). The solids were then filtered off on a Celite plug using deuterated chloroform, and 4-fluoroanisole, or 2-fluoromesitylene (10 µL), as an internal NMR reference, were added to the filtrate, which was then transferred to an NMR tube for characterisation.

Table **S1.** Condition screening for difluoride to dihalide conversion – solvent and calcium salts

Entry	Salt (equiv.)	Solvent (conc)	Temp (°C)	Time (h)	NMR Yield[a]
S1A	$CaBr_2$ (3)	Hexane (1 M)	rt	16	86%
S1B	$CaBr_2$ (3)	Octane (1 M)	rt	16	89%
S1C	$CaBr_2$ (3)	CH_2Cl_2 (1 M)	rt	16	62%
S1D	$CaBr_2$ (3)	MeCN (1 M)	rt	16	0%
S1E	$CaBr_2$ (3)	THF (1 M)	rt	16	0%
S1F	$CaBr_2$ (3)	DMSO (1 M)	rt	16	0%
S1G	$CaBr_2$ (3)	DMF (1 M)	rt	16	0%
S1H	$CaBr_2$ (3)	MeOH (1 M)	rt	16	0%
S1I	$CaBr_2$ (1)	Hexane (1 M)	rt	16	44%
S1J	$CaBr_2$ (2)	Hexane (1 M)	rt	16	74%
S1K	$CaBr_2$ (4)	Hexane (1 M)	rt	16	94%
S1L	CaI_2 (3)	Hexane (1 M)	rt	16	78%
S1M	CaI_2 (3)	CH_2Cl_2 (1 M)	rt	16	67%
S1N	CaI_2 (3)	MeCN (0.5 M)	rt	16	0%
S1O	CaI_2 (3)	THF (0.5 M)	rt	16	0%
S1P	CaI_2 (3)	DMSO (1 M)	rt	16	0%
S1Q	CaI_2 (3)	DMF (1 M)	rt	16	0%
S1R	CaI_2 (3)	MeOH (1 M)	rt	16	0%
S1S	$Ca(HCO_2)_2$ (3)	Hexane (1 M)	rt	16	0%
S1T	CaO (3)	Hexane (1 M)	rt	16	0%
S1U	$Ca(OMe)_2$ (3)	Hexane (1 M)	rt	16	0%
S1V	$CaCl_2$ (3)	Hexane (1 M)	rt	16	0%
S1W	CaH_2 (3)	Hexane (1 M)	rt	16	0%
S1X	$Ca(OH)_2$ (3)	Hexane (1 M)	rt	16	0%

[a]NMR yield with 4-fluoroanisole used as an internal standard.

Table **S2.** Condition screening for difluoride to dihalide conversion – concentration, reaction time and temperature

Entry	Salt (equiv.)	Solvent (conc)	Temp (°C)	Time (h)	NMR Yield[a]
S1A	$CaBr_2$ (3)	Hexane (1 M)	rt	16	86%
S2A	$CaBr_2$ (3)	Hexane (1 M)	rt	6	66%
S2B	$CaBr_2$ (3)	Hexane (1 M)	rt	18	85%
S2C	$CaBr_2$ (3)	Hexane (1 M)	rt	24	39%
S2D	$CaBr_2$ (3)	Hexane (1 M)	rt	50	81%
S2E	CaI_2 (3)	Hexane (1 M)	rt	16	78%
S2F	CaI_2 (3)	Hexane (1 M)	rt	6	73%
S2G	CaI_2 (3)	Hexane (1 M)	rt	3	68%
S2H	$CaBr_2$ (3)	Hexane (0.5 M)	rt	6	51%
S2I	$CaBr_2$ (3)	Hexane (0.25 M)	rt	6	53%
S2J	$CaBr_2$ (3)	Hexane (0.1 M)	rt	6	7%
S2K	$CaBr_2$ (3)	Hexane (1 M)	40	6	14%
S2L	$CaBr_2$ (3)	Hexane (1 M)	60	6	25%
S2M	$CaBr_2$ (3)	Octane (1 M)	60	6	20%
S2N	$CaBr_2$ (3)	Octane (1 M)	80	6	22%
S2O	$CaBr_2$ (3)	Octane (1 M)	80	3	2%
S2P	$CaBr_2$ (3)	Octane (1 M)	100	6	0%
S2Q	$CaBr_2$ (3)	Octane (1 M)	100	3	2%

[a]NMR yield with 4-fluoroanisole used as an internal standard.

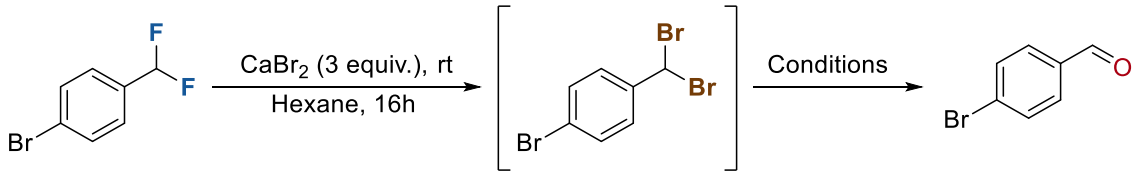
Table **S3.** Condition screening for difluoride to dihalide conversion – additives. MS = molecular sieves; NBS = N-bromosucciniminde

Entry	Salt (equiv.)	Additive (equiv.)	Solvent (conc)	Temp (°C)	Time (h)	NMR Yield[a]
S1A	$CaBr_2$ (3)	-	Hexane (1 M)	rt	16	86%
S3A	$CaBr_2$ (3)	H_2O (3)	Hexane (1 M)	rt	16	16%
S3B	$CaBr_2$ (3)	LiBr (1)	Hexane (1 M)	rt	16	28%
S3C	$CaBr_2$ (3)	TMSBr (0.5)	Hexane (1 M)	rt	16	19%
S3D	$CaBr_2$ (3)	4 Å MS	Hexane (1 M)	rt	16	27%
S3E	$CaBr_2$ (3)	NBS (0.5)	Hexane (1 M)	rt	16	0%
S3F	$CaBr_2$ (3)	Br_2 (0.05)	Hexane (1 M)	rt	16	49%

[a]NMR yield with 4-fluoroanisole used as an internal standard.

1.2. Optimization data of dihalide to aldehyde conversion:

1.2.1 Optimization data of dibromide to aldehyde conversion:



A 1.75 ml vial equipped with a stirrer bar was charged with 1-bromo-4-(difluoromethyl)benzene (20.6 mg, 0.1 mmol, 1 equiv.), followed by calcium bromide (60 mg, 0.3 mmol, 3 equiv.) and hexane (0.1 ml, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred for 16 hours at room temperature. Then, the crude mixture was subjected to one of the methods described below (Table **S**).

Method S4A

Based on a literature procedure,[1] crude sample was diluted with hexane (0.5 ml) and aq. $AgNO_3$ solution was added (1 M, 0.5 ml, 5 equiv.). The reaction was stirred at 60 ^oC for 24 h. The solids were filtered off, and the filtrate was washed with CH_2Cl_2 (3 x 5 ml) followed by water (10 ml). Organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*.

Method S4B

Crude sample was filtered on a Celite pad using CH_2Cl_2 and concentrated until dryness. Then, it was diluted with 0.2 ml of hexane and aq. $AgNO_3$ solution (2.5 M, 0.2 ml, 5 equiv.) was added. The reaction was stirred at room temperature until completion as monitored by TLC. The solids were filtered off on a cotton wool (water and CH_2Cl_2), and the filtrate was washed with DCM (3 x 5 ml) followed by water (10 ml). Organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*.

Method S4C

Crude sample was filtered on a Celite pad using CH_2Cl_2 and concentrated until dryness. Then, it was diluted with hexane (0.5 M) and aq. $AgNO_3$ solution (1 M, 0.5 ml, 5 equiv.) was added. The reaction was stirred at room temperature until completion as monitored by TLC. The solids were filtered off on a cotton wool (water and CH_2Cl_2), and the filtrate was washed with CH_2Cl_2 (3 x 5 ml) followed by water (10 ml). Organic layers were combined, dried over $MgSO_4$, and concentrated *in vacuo*.

Method S4D

Based on a literature procedure,[1] to a crude sample 0.1 ml of water was added followed by 0.9 ml of formic acid (98%). The reaction mixture was heated to 60 ^oC and left to stir until completion as monitored by TLC. The reaction mixture was cooled to room temperature, poured over 5 ml of water and quenched with sodium bicarbonate with the amount needed to achieve a neutral pH of the solution. The mixture was allowed to sit in the separation funnel for a couple of minutes, and then was extracted with CH_2Cl_2 (3 x 5 ml). Combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

Method S4E

Crude sample was filtered on a Celite pad using CH_2Cl_2 and concentrated until dryness. Water (0.1 ml) was added followed by addition of formic acid (0.9 ml). The reaction mixture was stirred at 60 ^oC. After completion as monitored by TLC, the reaction mixture was poured over 5 ml of water and quenched with sodium bicarbonate with the amount needed to achieve a neutral pH of the solution. The mixture was allowed to sit in the separation funnel for a couple of minutes, and then was extracted with CH_2Cl_2 (3 x 5 ml). Combined extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*.

Method S4F

Based on a literature procedure,[2] to a crude sample 1-butyl-3-methylimidazolium tetrafluoroborate (90.4 mg, 0.4 mmol, 4 equiv.) were added followed by water (0.2 ml). The reaction mixture was stirred at 60 ^oC until completion as monitored by TLC. After 4 hours, the reaction mixture was cooled to room temperature, diluted with water (0.5 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The combined organic layers were dried over anhydrous $MgSO_4$and concentrated *in vacuo*.

Method S4G

Based on a literature procedure,[3] to a crude sample CH_2Cl_2 (0.2 ml) along with pyridine (80.9 µL, 2.0 mmol, 20 equiv.) were added and the reaction was stirred at 60 ^oC until completion as monitored by TLC. After 4 hours, the reaction mixture was cooled to room temperature, and poured over ice-cold water (5 ml) followed by extraction with CH_2Cl_2 (3 x 5 ml). Organic layers were combined and washed with water and brine solution, dried over $MgSO_4$ and concentrated *in vacuo*.

Method S4H

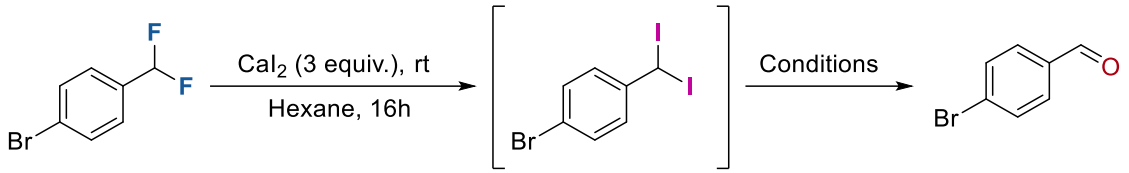
Based on a literature procedure,[4] to a crude sample sodium carbonate (0.1 g) along with water (1 ml) were added. at 60 ^oC until completion as monitored by TLC. After 30 h the sample was cooled to room temperature and transferred to a separatory funnel. The solution was diluted with water (5 ml) and CH_2Cl_2 (5 ml), and the mixture was washed with CH_2Cl_2 (4 x 5 ml). Combined organic layers were then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

Table S4. Conditions screening for dibromide hydrolysis

Method	Aldehyde NMR Yield[a]
S4A	52%
S4B	76%
S4C	30%
S4D	69%
S4E	79%
S4F	31%
S4G	8%
S4H	17%

[a]NMR yield with 4-fluoroanisole used as an internal standard**.**

1.2.2 Optimization data of diiodide to aldehyde conversion:



A 1.75 ml vial equipped with a stirrer bar was charged with 1-bromo-4-(difluoromethyl)benzene (20.6 mg, 0.1 mmol, 1 equiv.), followed by calcium iodide (88.6 mg, 0.3 mmol, 3 equiv.) and hexane (0.1 ml, 1 M). The vial was covered with a cap, sealed with Parafilm, and stirred for 16 hours at room temperature. Then, the crude mixture was subjected to one of the methods described below (Table **S**).

Method S5A

To the crude sample was added water (18 µL, 10 equiv.) and the mixture was stirred for 16h. Then, saturated aqueous sodium thiosulfate solution (0.2 ml) was added in one portion and the reaction was stirred for further 16 h. Next, the mixture was transferred to a separatory funnel and was washed with CH_2Cl_2 (3 x 8 ml). Combined organic layers were then washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Method S5B

To the crude sample was added CH_2Cl_2 (0.1 ml), followed by aq. NaOH solution (1 M, 0.2 ml, 2 equiv.) and the mixture was stirred for 5.5 hours. The reaction mixture was quenched with 1 M aq. HCl solution until the pH = 7 was achieved. Then, the mixture was transferred to a separatory funnel and washed with diethyl ether (3 x 5 ml). Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*.

Method S5C

To the crude sample was added aq. HCl solution (1 M, 0.4 ml, 4 equiv.) and the resulting solution was stirred for 18 hours at 60 ^oC. After that, the reaction mixture was diluted with water (5 ml) and CH_2Cl_2 (5 ml) and transferred to a separatory funnel. Aqueous layer was separated from the organic layer, and the organic layer was washed with CH_2Cl_2 (4 x 5 ml). Combined organic layers were washed with sat. $Na_2S_2O_3$ aq. solution followed by washing with brine. The organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*.

Method S5D

To the crude sample was added aq. HCl solution (1 M, 0.4 ml, 4 equiv.) and the resulting solution was stirred for 18 hours at 100 ^oC. After that, the reaction mixture was diluted with water (5 ml) and CH_2Cl_2 (5 ml) and transferred to a separatory funnel. Aqueous layer was separated from the organic layer, and the organic layer was washed with CH_2Cl_2 (4 x 5 ml). Combined organic layers were washed with sat. $Na_2S_2O_3$ aq. solution followed by washing with brine. The organic layers were then dried over Na_2SO_4 and concentrated *in vacuo*.

Method S5E

Based on a literature procedure,[5] to the crude sample was added $NaHCO_3$ (3 equiv.) in water (0.5 ml, 0.2 M) and the resulting mixture was stirred at 100 ^oC for 37 hours. The sample was then transferred to a separatory funnel, and washed with CH_2Cl_2 (3 x 5 ml). Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*.

Method S5F

The crude sample was filtered on a Celite pad and concentrated, which was followed by addition of water (0.1 ml) and formic acid (0.9 ml). The vial was capped, and secured with parafilm, and then heated to 60 ^{o}C for 1.5-6 h until completion as observed by TLC. The reaction mixture was allowed to cool down to room temperature, and then transferred to a separatory funnel, where it was quenched with saturated aq. $NaHCO_3$ solution until pH 7. Both organic and aqueous layers were washed with sodium thiosulfate 5% aq. solution. The aqueous layer was then washed with CH_2Cl_2 (3 x 6 ml), and the combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

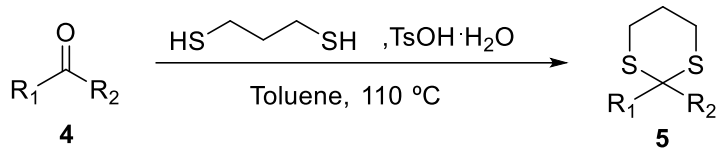
Table S5. Conditions screening for diiodide hydrolysis

Method	Aldehyde NMR Yield[a]
S5A	25%
S5B	2%
S5C	63%
S5D	2%
S5E	24%
S5F	82%

[a]NMR yield with 4-fluoroanisole used as an internal standard**.**

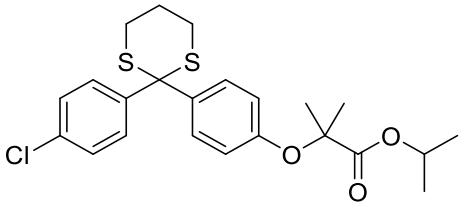
2. Synthesis of Starting Materials

2.1 General procedure for the synthesis of starting thioacetals:



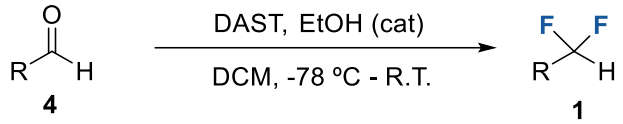
A two-neck round bottom flask was charged with magnetic stirrer bar, ketone (1 equiv.) and anh. toluene (2M) under N_2 atmosphere. Then, propane-1,3-dithiol (1.33 equiv.) was added followed by catalytic *p*-toluenesulfonic acid monohydrate (2%). The mixture was heated at reflux and stirred under N_2 atmosphere for 18 hours. After cool at room temperature, the reaction mixture was concentrated to dryness and purified by means of flash column chromatography on silica gel using mixtures of pentane and ethyl acetate as eluents.

isopropyl 2-(4-(2-(4-chlorophenyl)-1,3-dithian-2-yl)phenoxy)-2-methylpropanoate (5y)



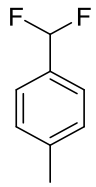
Following the general procedure described above, **5y** (1.273 g, 80% yield) was obtained as a white solid starting from fenofibrate (1.28 g, 3.55 mmol) of X after flash chromatography with 15:1 pentane: ethyl acetate. **M. p.** =82 – 83 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 9.0 Hz, 2H), 5.07 (hept, *J* = 6.3 Hz, 1H), 2.76 – 2.73 (m, 4H), 2.01 – 1.96 (m, 2H), 1.59 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 155.1, 141.3, 135.2, 133.4, 131.0, 130.1, 128.5, 118.2, 79.1, 69.0, 61.8, 29.4, 25.4, 24.4, 21.6. **IR** (neat, cm^{-1}), ν = 2935, 1724, 1503, 1290, 1249, 1180, 1157, 1101, 1013, 793. **HRMS** (ESI) m/z calculated for $C_{23}H_{27}ClO_3S_2$ $[M+Na]^+$ 473.0982, found 473.0988.

2.2 General procedure for the synthesis of starting difluorides:



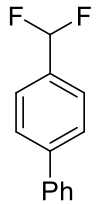
Based on literature procedure[6] a two-neck flame-dried round bottom flask was charged with magnetic stirrer bar, aldehyde **4** (1 equiv.) and anh. CH_2Cl_2 (1M) under N_2 atmosphere. The flask was cooled to -78 °C and diethylaminosulfur trifluoride was added dropwise (1.7 equiv.) followed by catalytic ethanol (10-20 µL). The mixture was allowed to warm to room temperature and stirred under N_2 atmosphere for 18 hours or until completion as monitored by TLC. Remaining diethylaminosulfur trifluoride was quenched by careful addition of sat. Na_2CO_3 aq. solution, and the resulting mixture was stirred at room temperature for 5 minutes, before transferring to a separatory funnel and extracting with CH_2Cl_2 3 times. The combined organic phases were then was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo to afford crude compound **1**, which was purified by column chromatography.

1-(difluoromethyl)-4-methylbenzene (1c)



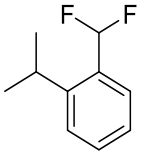
By means of the general procedure described above, **1c** (165 mg, 35% yield) was obtained as a volatile colourless oil starting from 510 mg (4.24 mmol) of **4c** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 6.62 (t, *J* = 56.7 Hz, 1H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.0 (d, *J* = 2.3 Hz), 131.8 (t, *J* = 22.4 Hz), 129.4, 125.6 (t, *J* = 6.0 Hz), 115.1 (t, *J* = 238.0 Hz), 21.5. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.71 (d, *J* = 56.9 Hz). Spectroscopic data are in accordance with those in literature.[7]

4-(difluoromethyl)-1,1'-biphenyl (1d)



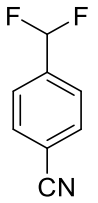
By means of the general procedure described above, **1d** (534 mg, 75% yield) was obtained as a white solid starting from 2 g (10.98 mmol) of **4d** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.70 – 7.67 (m, 2H), 7.62 – 7.58 (m, 4H), 7.50 – 7.46 (m, 2H), 7.42 – 7.38 (m, 1H), 6.71 (t, *J* = 56.5 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.8 (t, *J* = 2.1 Hz), 140.3, 133.3 (t, *J* = 22.5 Hz), 129.1, 128.0, 127.6, 127.4, 126.2 (t, *J* = 6.0 Hz), 114.9 (t, *J* = 238.6 Hz).**^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.34 (d, *J* = 56.7 Hz). Spectroscopic data are in accordance with those in literature.[7]z

1-(difluoromethyl)-2-isopropylbenzene (1e)



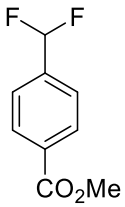
By means of the general procedure described above, **1e** (201 mg, 35% yield) was obtained as a volatile colourless oil starting from 500 mg (3.37 mmol) of **4a** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.8 Hz, 1H), 7.47 – 7.39 (m, 2H), 7.29 – 7.25 (m, 1H), 6.86 (t, *J* = 55.5 Hz, 1H), 3.27 (hept, *J* = 6.9 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.5 (t, *J* = 4.3 Hz), 131.1 (t, J = 1.7 Hz), 131.1 (t, J = 20.7 Hz), 126.2, 126.0, 125.9 (t, *J* = 7.7 Hz), 114.2 (t, *J* = 237.6 Hz), 28.8, 24.2. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.22 (d, *J* = 55.6 Hz). Spectroscopic data are in accordance with those in literature.[8]

4-(difluoromethyl)benzonitrile (1f)



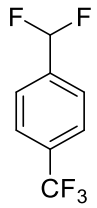
By means of the general procedure described above, **1f** (441.5 mg, 76% yield) was obtained as a colourless oil starting from 500 mg (3.62 mmol) of **4f** (95% purity) after flash chromatography with 20:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H), 6.69 (t, *J* = 55.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.5 (t, *J* = 22.9 Hz), 132.6, 126.4 (t, *J* = 6.1 Hz), 118.0, 114.7, 113.4 (t, *J* = 240.4 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -113.09 (d, *J* = 58.7 Hz). Spectroscopic data are in accordance with those in literature.[9]

methyl 4-(difluoromethyl)benzoate (1g)



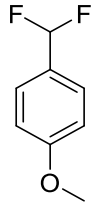
By means of the general procedure described above, **1g** (452 mg, 80% yield) was obtained as a white solid starting from 500 mg (3.04 mmol) of **4g** after flash chromatography with 20:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 2H), 6.67 (t, *J* = 56.1 Hz, 0H), 3.92 (s, 3H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 138.5 (t, *J* = 22.4 Hz), 132.4 (t, *J* = 2.0 Hz), 130.0, 125.7 (t, *J* = 6.0 Hz), 114.1 (t, *J* = 239.6 Hz), 52.4. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -112.26 (d, *J* = 56.5 Hz). Spectroscopic data are in accordance with those in literature.[9]

1-(difluoromethyl)-4-(trifluoromethyl)benzene (1i)



By means of the general procedure described above, **1i** (200.4 mg, 28% yield) was obtained as a volatile colourless oil starting from 637.5 mg (3.65 mmol) of **4i** after flash chromatography with pentane. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 6.70 (t, *J* = 56.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0 (t, *J* = 22.0 Hz), 133.0 (q, *J* = 32.7 Hz), 126.3 (t, *J* = 6.1 Hz), 125.95 (q, *J* = 3.9 Hz), 123.8 (q, *J* = 271.0 Hz), 113.9 (t, *J* = 239.9 Hz).**^{19}F NMR** (376 MHz, $CDCl_3$) δ -63.11, -112.39 (d, *J* = 57.0 Hz). Spectroscopic data are in accordance with those in literature.[9]

1-(difluoromethyl)-4-methoxybenzene (1j)

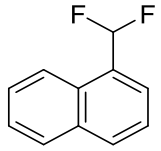


By means of the general procedure described above, **1j** (434 mg, 74% yield) was obtained as a colourlessoil starting from 505 mg (3.71 mmol) of **2j** after flash chromatography with 20:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.61 (t, *J* = 56.7 Hz, 1H), 3.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.5, 127.3 (t, *J* = 5.9 Hz), 126.9 (t, *J* = 22.8 Hz), 115.0 (t, *J* = 237.4 Hz), 114.1, 55.5.**^{19}F NMR** (377 MHz, $CDCl_3$) δ -108.20 (d, *J* = 57.1 Hz). Spectroscopic data are in accordance with those in literature.[10]

5-(difluoromethyl)-1,2,3,4-tetrahydronaphthalene (1k)

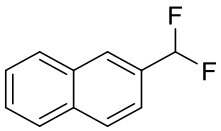
By means of the general procedure described above, **1k** (394 mg, 68% yield) was obtained as colourless oil starting from 527 mg (3.12 mmol) of **4k** (95% purity) after flash chromatography with 40:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35 (q, *J* = 4.6, 4.1 Hz, 1H), 7.18 (d, *J* = 5.3 Hz, 2H), 6.76 (t, *J* = 55.5 Hz, 1H), 2.84 (dt, *J* = 12.4, 5.9 Hz, 5H), 1.92 – 1.76 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.2, 135.3, 132.0, 131.9 (t, *J* = 2.0 Hz), 125.4, 123.2 (t, *J* = 7.9 Hz), 114.3 (t, *J* = 237.7 Hz), 29.9, 25.3, 22.8, 22.5. **^{19}F NMR** (377 MHz, $CDCl_3$) δ -113.60 (d, *J* = 55.8 Hz). IR (thin layer film, cm^{-1}), ν = 2939, 2360, 1462, 1381, 1250, 1104, 1021, 803, 782, 750. **HRMS:** Compound X does not form stable molecular or pseudo-molecular ions in mass spectrometry.

1-(difluoromethyl)naphthalene (1l)



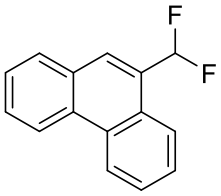
By means of the general procedure described above, **1l** (427 mg, 68% yield) was obtained as a colourless oil starting from 575 mg (3.5 mmol) of **4l** (95% purity) after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 1H), 7.99– 7.91 (m, 2H), 7.70 (dd, *J* = 7.2, 1.4 Hz, 1H), 7.63 – 7.55 (m, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 55.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 133.9, 131.6 (t, *J* = 2.0 Hz), 129.9, 129.7, 128.9, 127.3, 126.5, 124.9 (t, *J* = 8.7 Hz), 124.8, 123.7, 115.6 (t, *J* = 238.3 Hz).**^{19}F NMR** (377 MHz, $CDCl_3$) δ -110.87 (d, *J* = 55.6 Hz). Spectroscopic data are in accordance with those in literature.[11]

2-(difluoromethyl)naphthalene (1m)



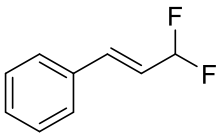
By means of the general procedure described above, **1m** (416 mg, 73% yield) was obtained as a white solid starting from 500 mg (3.20 mmol) of **4m** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 – 7.88 (m, 4H), 7.63 – 7.54 (m, 3H), 6.81 (t, *J* = 56.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 134.4, 132.7, 131.7 (t, *J* = 22.3 Hz), 129.0, 128.7, 128.0, 127.5, 126.9, 126.0 (t, *J* = 7.5 Hz), 122.2 (t, *J* = 4.8 Hz), 115.2 (t, *J* = 238.5 Hz).**^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.80 (d, *J* = 56.7 Hz). Spectroscopic data are in accordance with those in literature.[11]

9-(difluoromethyl)phenanthrene (1n)



By means of the general procedure described above, **1n** (393 mg, 71% yield) was obtained as a white solid starting from 500 mg (2.42 mmol) of **4n** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.74 – 8.71 (m, 1H), 8.66 (d, *J* = 8.3 Hz, 1H), 8.26 – 8.21 (m, 1H), 7.96 (s, 1H), 7.92 (d, *J* = 6.1 Hz, 1H), 7.74 – 7.62 (m, 4H), 7.16 (t, *J* = 55.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.5, 130.9, 130.2, 129.6, 128.4, 128.1 (t, *J* = 20.5 Hz), 128.0 (t, *J* = 2.0 Hz), 127.3, 127.2, 127.2, 126.9 (t, *J* = 9.3 Hz), 124.6 (t, *J* = 2.0 Hz), 123.3, 122.7, 115.8 (t, *J* = 238.6 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -111.67 (d, *J* = 55.2 Hz). Spectroscopic data are in accordance with those in literature.[12]

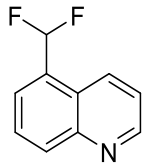
(*E*)-(3,3-difluoroprop-1-en-1-yl)benzene (1o):



By means of the general procedure described above, **1o** (270 mg, 46% yield) was obtained as a colourlessoil starting from 527 mg (3.81 mmol) of **4o** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.45 (m, 2H), 7.43 – 7.37 (m, 3H), 6.93 – 6.88 (m, 1H), 6.42 – 6.13 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.2 (t, *J* = 12.1 Hz), 134.6,

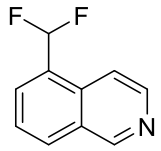
129.5, 128.9, 127.4, 121.1 (t, *J* = 23.9 Hz), 115.6 (t, *J* = 233.6 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -109.48 – 109.71 (m). Spectroscopic data are in accordance with those in literature.[9]

5-(difluoromethyl)quinoline (1q)



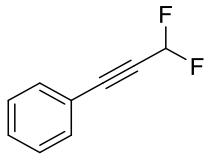
By means of the general procedure described above, **1q** (215 mg, 39% yield) was obtained as a yellow semisolid starting from 485 mg (3.09 mmol) of **4q** after flash chromatography with 2:1 pentane: ethyl acetate.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.02 (d, *J* = 4.4 Hz, 1H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.66 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.59 (d, *J* = 4.4, 1H), 7.16 (t, *J* = 54.8 Hz, 1H).**^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.0, 148.6, 137.80 (t, *J* = 22.0 Hz), 130.5, 130.0, 127.9, 124.2, 123.3, 118.0 (t, *J* = 7.7 Hz), 113.3 (t, *J* = 240.5 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -108.87 (d, *J* = 55.4 Hz). **HRMS** (ESI) m/z calculated for $C_{10}H_7F_2N$ $[M+H]^+$ 180.0619, found 180.0616. **IR** (thin layer film, cm^{-1}), ν = 1507, 1432, 1106, 1079, 1023, 880, 804.

5-(difluoromethyl)isoquinoline (1r):



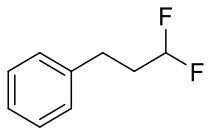
By means of the general procedure described above, **1r** (188 mg, 33% yield) was obtained as a with solid starting from 500 mg (3.18 mmol) of **4r** after flash chromatography with 2:1 pentane: ethyl acetate. **M. p.** = 53 – 54 °C. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.64 (d, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 6.1 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.65 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.09 (t, *J* = 54.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.2, 144.3, 132.5 (t, *J* = 2.6 Hz), 131.1 (t, *J* = 1.9 Hz), 129.0 (t, *J* = 21.5 Hz), 129.0 (t, *J* = 8.3 Hz), 128.8, 126.3, 116.6, 114.7 (t, *J* = 239.1 Hz).^{19}F NMR (376 MHz, $CDCl_3$) δ -111.19 (d, *J* = 55.1 Hz). **HRMS** (ESI) m/z calculated for $C_{10}H_7F_2N$ $[M+H]^+$ 180.0619, found 180.0618. **IR** (neat, cm^{-1}), ν = 1501, 1168, 1100, 1010, 892, 807, 719.

(3,3-difluoroprop-1-yn-1-yl)benzene (1s)



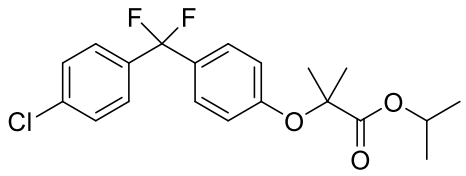
By means of the general procedure described above, **1s** (313 mg, 51% yield) was obtained as a volatile colourless oil starting from 532 mg (4.09 mmol) of **4s** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.54 – 7.51 (m, 2H), 7.45 – 7.41 (m, 1H), 7.39 – 7.35 (m, 2H), 6.42 (t, *J* = 55.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.3 (t, *J* = 2.7 Hz), 130.3, 128.7, 120.0 (d, *J* = 3.3 Hz), 104.4 (t, *J* = 232.0 Hz), 88.6 (t, *J* = 7.3 Hz), 79.9 (t, *J* = 33.9 Hz). **^{19}F NMR** (377 MHz, $CDCl_3$) δ -105.26 (d, *J* = 55.2 Hz). Spectroscopic data are in accordance with those in literature.[9]

(3,3-difluoropropyl)benzene (1t)



By means of the general procedure described above, **1t** (405 mg, 68% yield) was obtained as a colourless oil starting from 509.5 mg (3.8 mmol) of **4t** after flash chromatography with 30:1 pentane: diethyl ether. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.30 (m, 2H), 7.25 – 7.20 (m, 3H), 5.81 (tt, *J* = 56.7, 4.5 Hz, 1H), 2.81 – 2.77 (m, 2H), 2.23 – 2.09 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.0, 128.8, 128.5, 126.5, 116.8 (t, *J* = 239.0 Hz), 35.8 (t, *J* = 21.1 Hz), 28.5 (t, *J* = 6.0 Hz).**^{19}F NMR** (377 MHz, $CDCl_3$) δ -117.13 (dt, *J* = 56.7, 17.1 Hz). Spectroscopic data are in accordance with those in literature.[9]

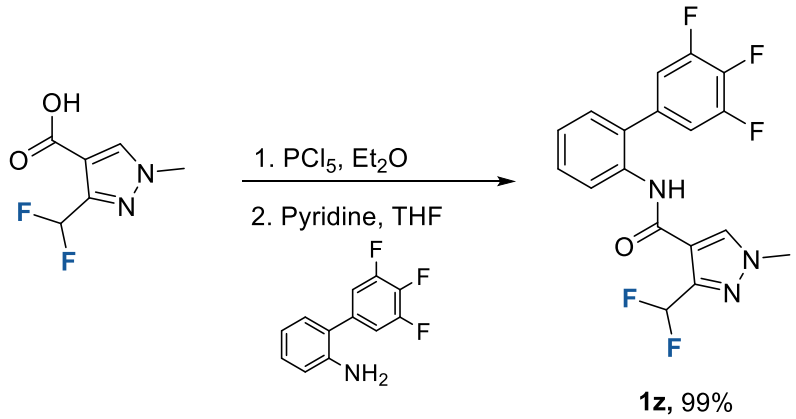
isopropyl 2-(4-((4-chlorophenyl)difluoromethyl)phenoxy)-2-methylpropanoate (1y)



A two-neck round bottom flask was charged with magnetic stirrer bar, fenofibrate (1.28 g, 3.55 mmol) and anh. toluene (2M) under N_2 atmosphere. Then, propane-1,3-dithiol (1.33 equiv.) was added followed by catalytic *p*-toluenesulfonic acid monohydrate (2%). The mixture was heated at reflux and stirred under N_2 atmosphere for 18 hours. After cool at room temperature, the reaction mixture was concentrated to dryness. By means of the general procedure described above, **1y** (386.2 mg, 91% yield) was obtained as a colourless oil starting from 500 mg (1.1 mmol) of **5y** after flash chromatography with 20:1 pentane: ethyl acetate.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 4H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 5.07 (hept, *J* = 6.3 Hz, 1H), 1.61 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.5, 157.15, 136.4 (t, *J* = 29.0 Hz), 130.4 (t, *J* = 29.0 Hz), 128.7, 127.5 (t, *J* = 5.4 Hz), 127.1 (t, *J* = 5.4 Hz), 120.5 (t, *J* = 240.0 Hz), 118.1, 79.4, 69.3, 25.5, 21.7.**^{19}F NMR** (377 MHz, $CDCl_3$) δ -86.87. Spectroscopic data are in accordance with those in literature.[13]

2.3 Synthesis of agrochemicals

Fluxapyroxad (1z)

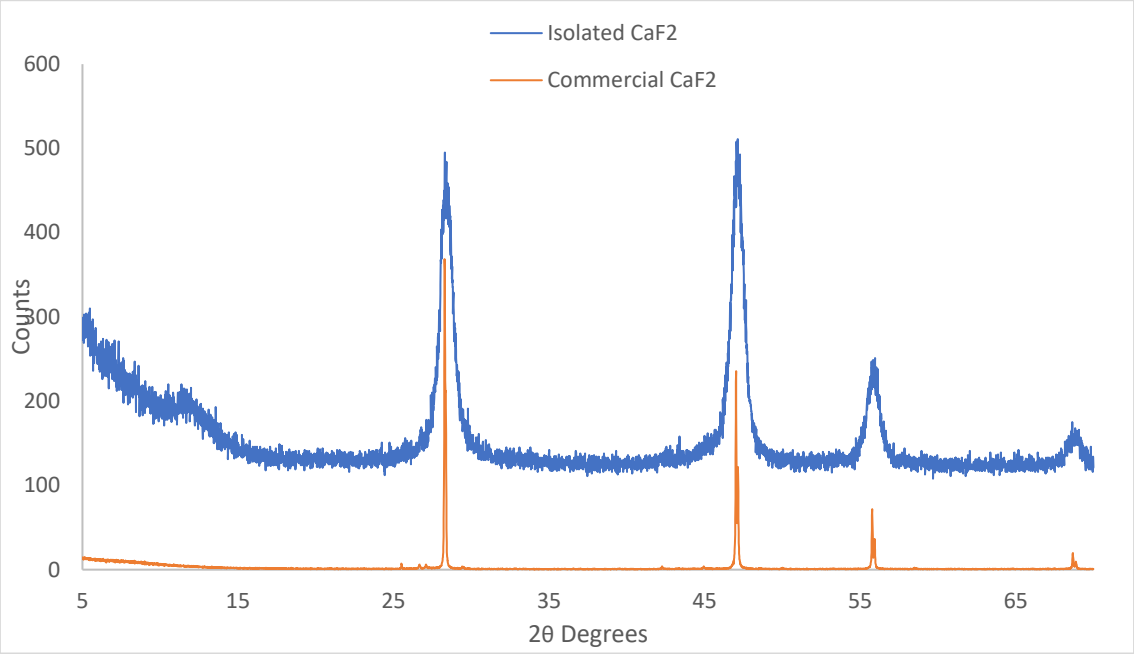


Based on literature procedure,[Error! Bookmark not defined.] suspension of 3-(difluoromethyl)-1-methyl-1 H-pyrazole-4-carboxylic acid (300 mg, 1.7 mmol) and PCl_5 (391 mg, 1.1 equiv.) in anhydrous diethyl ether (6.3 mL, 0.27M) was stirred at room temperature for 3 h under nitrogen atmosphere until. After that, the solvent was evaporated under vacuum and the residue containing the intermediate acyl chloride was then dissolved in anhydrous THF (3.1 mL, 0.55M) and treated with anhydrous pyridine (0.28 mL, 2 equiv.) and 3',4',5'-trifluoro-[1,1'-biphenyl]-2-amine (380 mg, 1 equiv.) under N_2 atmosphere. The resulting mixture was stirred at room temperature for 12 h before dilution with ethyl acetate. The organic layer was sequentially washed with aqueous solution of 3M HCl and saturated $NaHCO_3$ solution. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash column chromatography with 2:1 pentane:ethyl acetate to give fluxapyroxad (643 mg, 99% yield) as a white solid.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.96 (s, 1H), 7.81 (bs, 1H), 7.45 − 7.41 (m, 1H), 7.25 – 7.20 (m, 2H), 7.02 – 6.98 (m, 2H), 6.65 (t, *J* = 54.1 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 151.4 (ddd, *J* = 251.3, 10.0, 4.3 Hz), 142.3 (t, *J* = 29.4 Hz), 139.7 (dt, *J* = 252.4, 15.3 Hz), 136.5, 134.7, 134.2 (td, *J* = 7.9, 4.8 Hz), 131.3, 130.2, 129.4, 125.3, 123.5, 116.8, 113.9 (dd, J = 16.6, 4.6 Hz), 111.8 (t, J = 233.0 Hz), 39.7. **^{19}F NMR** (376 MHz, $CDCl_3$) δ -108.64 (dd, *J* = 54.1, 4.7 Hz, 2F), -133.69 (dd, *J* = 20.5, 7.9 Hz, 2F), -161.48 (tt, *J* = 20.5, 6.5 Hz, 1F). Spectroscopic data are in accordance with those in literature.[9]

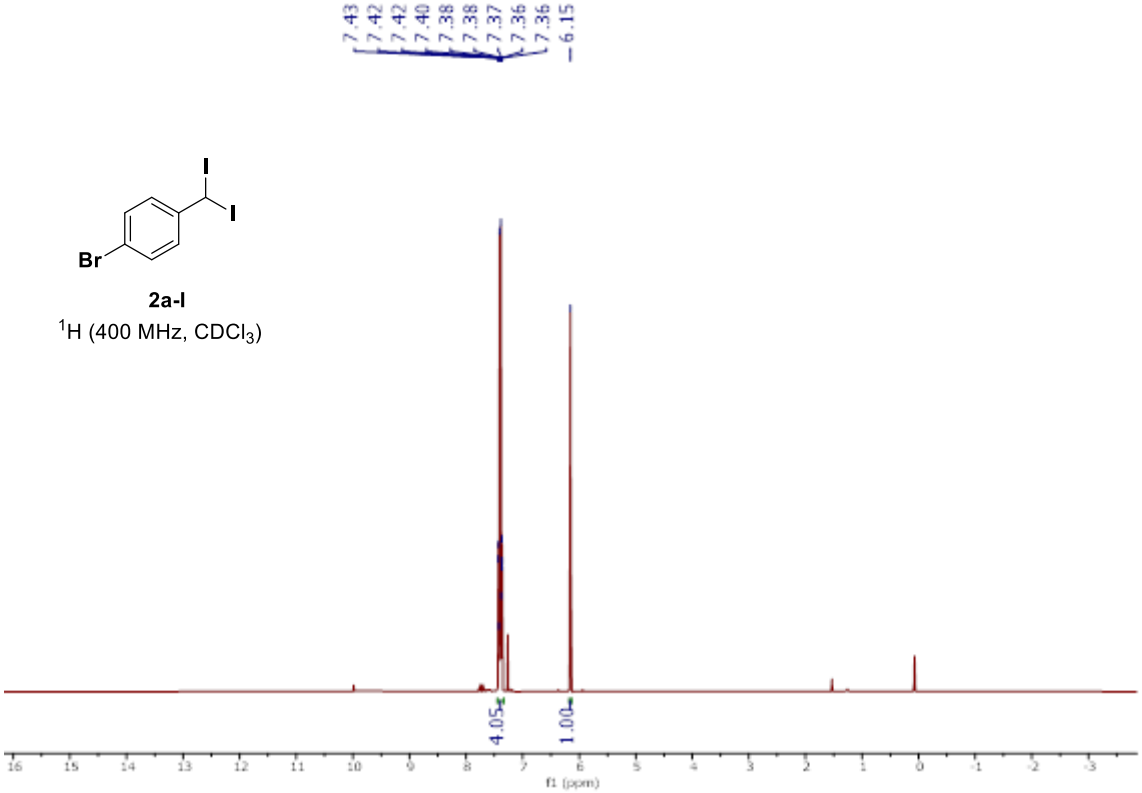
3. Reference

1. Harvey, R. G.; Dai, Q.; Ran, C.; Penning, T. M. *J. Org. Chem.* **2004**, *69*, 2024.
2. Lemos, A.; Gomes, A. S.; Loureiro, J. B.; Brandão, P.; Palmeira, A.; Pinto, M. M. M.; Saraiva, L.; Sousa, M. E. *Molecules* **2019**, *24*, 1975.
3. Augustine, J. K.; Naik, Y. A.; Mandal, A. B.; Chowdappa, N.; Praveen, V. B. *Tetrahedron* **2008**, *64*, 688.
4. Le Bourdonnec, B.; El Kouhen, R.; Lunzer, M. M.; Law, P. Y.; Loh, H. H.; Portoghese, P. S. *J. Med. Chem.* **2000**, *43*, 2489.
5. Langer, O.; Dollé, F.; Valette, H.; Halldin, C.; Vaufrey, F.; Fuseau, C.; Coulon, C.; Ottaviani, M.; Någren, K.; Bottlaender, M.; et al. *Bioorg. Med. Chem.* **2001**, *9*, 677.
6. Verhoog, S.; Pfeifer, L.; Khotavivattana, T.; Calderwood, S.; Collier, T. L.; Wheelhouse, K.; Tredwell, M.; Gouverneur, V. *Synlett* **2016**, *27*, 25.
7. Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524.
8. Ge, S.; Wojciech Chaładaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149.
9. Su, Y. -H.; Chiang, L. -W.; Jeng, K. -C.; Huang, H. -L.; Chen, J. -T.; Lin, W. -J.; Huang, C. -W.; Yu, C. -S. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1320.
10. Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett*. **2014**, *16*, 5984.
11. C. Lu, H. Lu, J. Wu, H. C. Shen, T. Hu, Y. Gu, Q. Shen, *J. Org. Chem*. **2018**, *83*, 1077.
12. Motohashi, H.; Mikami, K. *Org. Lett*. **2018**, *20*, 5340.
13. Bai, H.; Hong, J.; Cai, L.; Wei, H.; Liu, X.; Zheng, X. World Intellectual Property Organization WO2013159724A1, 2013; *Chem. Abstr.* **2013**, 159, 638907.

4. Copy of Powder XRD Spectrum of Isolated CaF_2

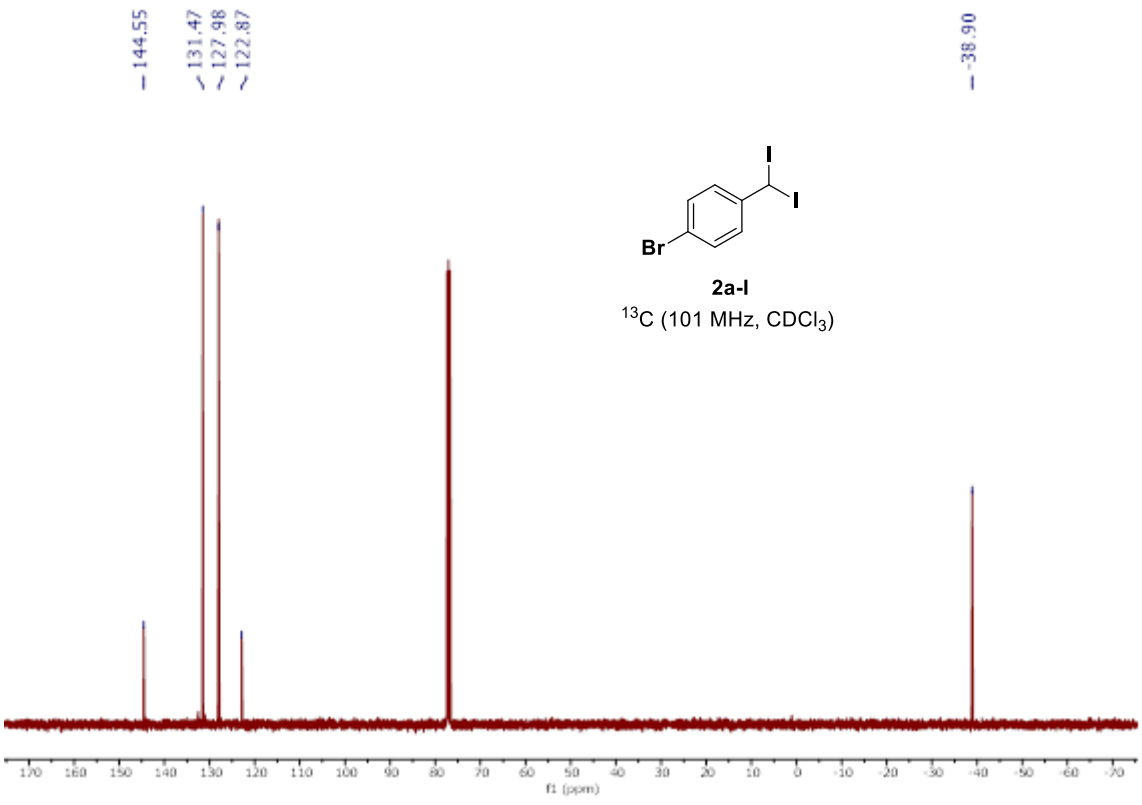


5. Copies of NMR Spectra



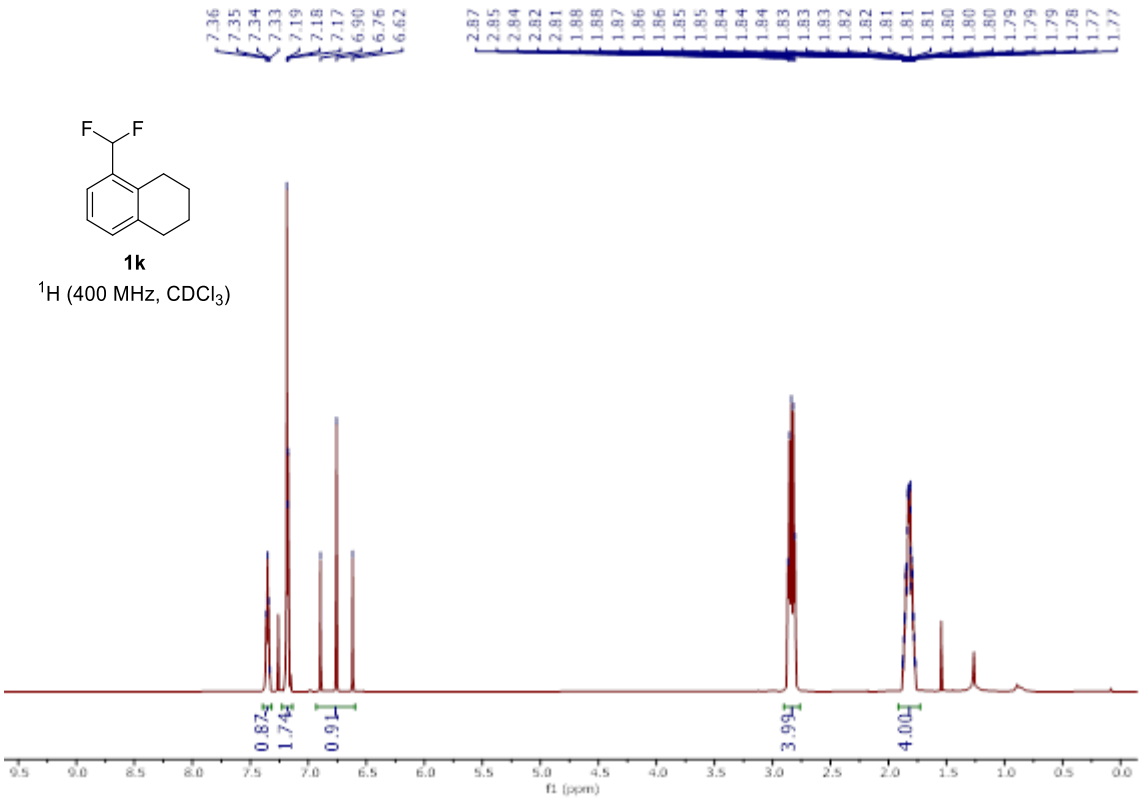
2a-I

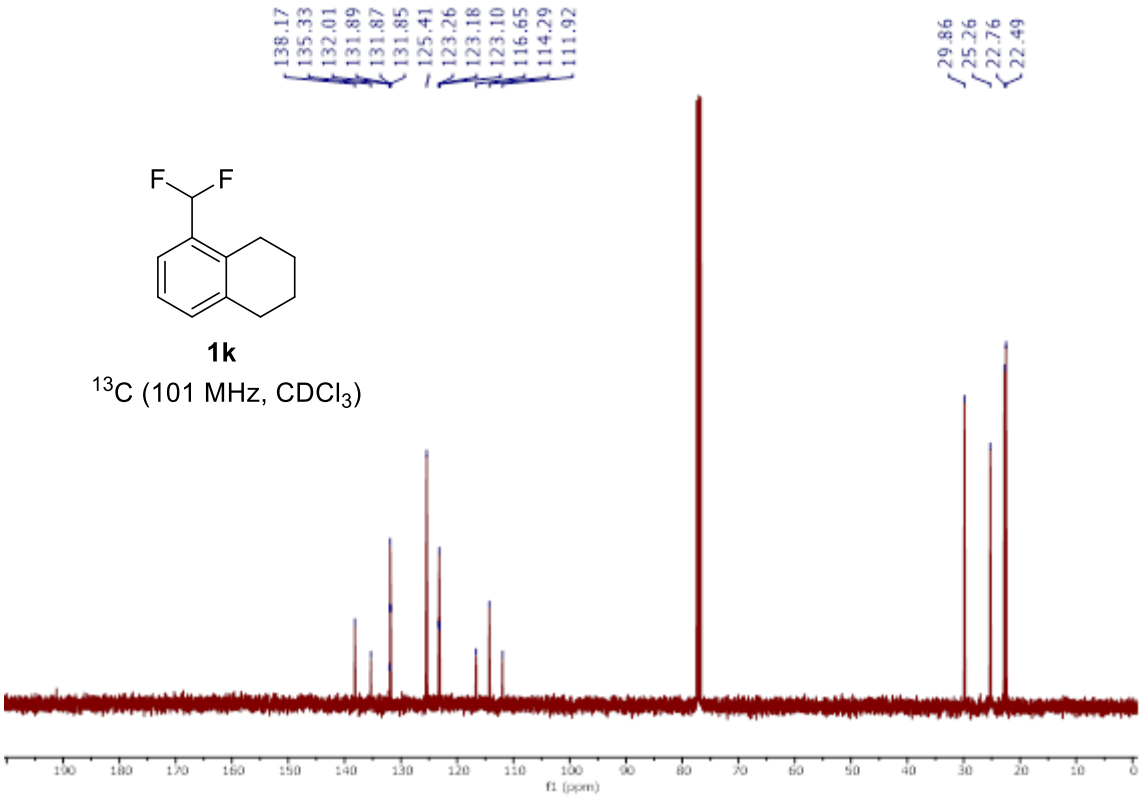
^{1}H (400 MHz, $CDCl_3$)

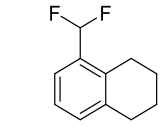


2a-I

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


F
F
1k
^{1}H (400 MHz, CDCl$_3$)
0.87
1.74
0.91
3.99
4.00
f1 (ppm)


F
F
1k
^{13}C (101 MHz, CDCl$_3$)
f1 (ppm)

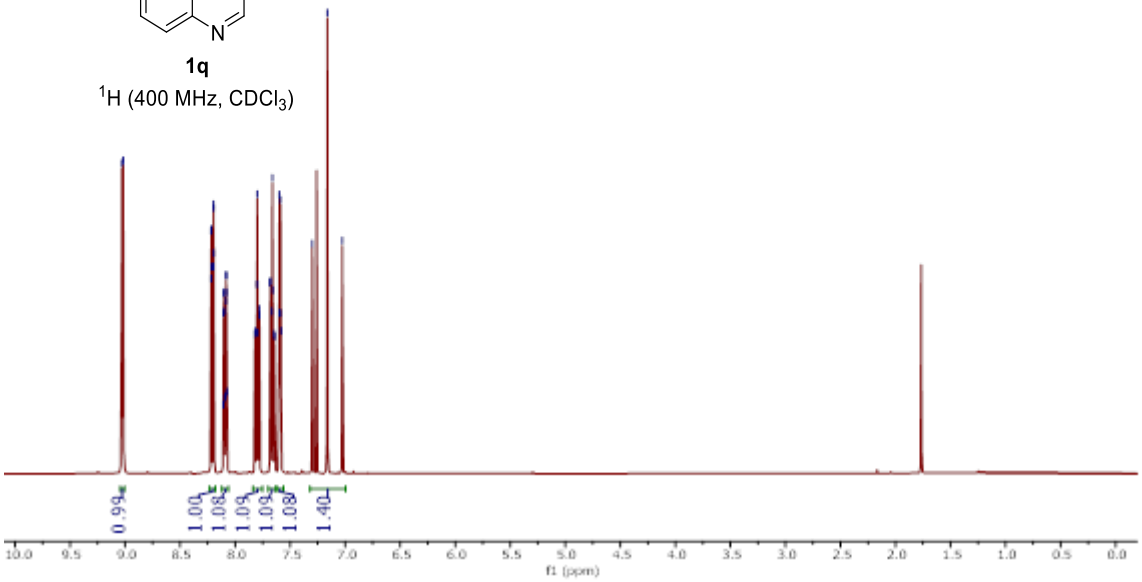


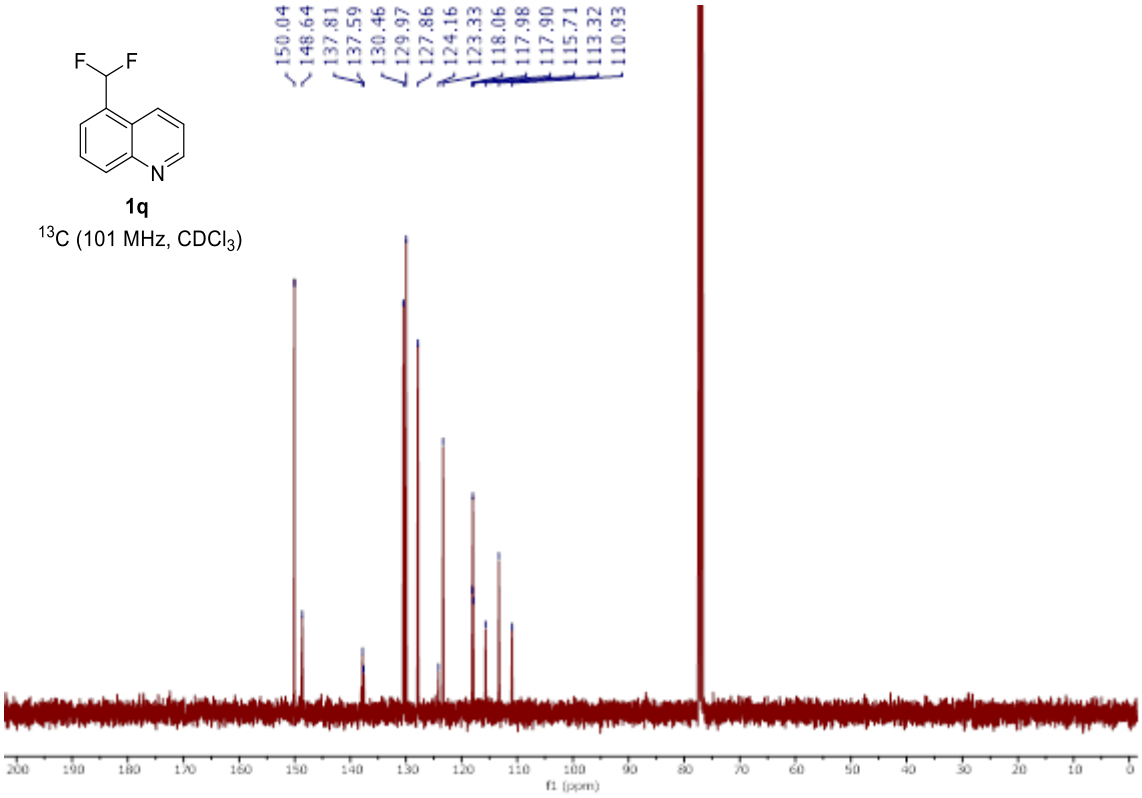
1k

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

1q

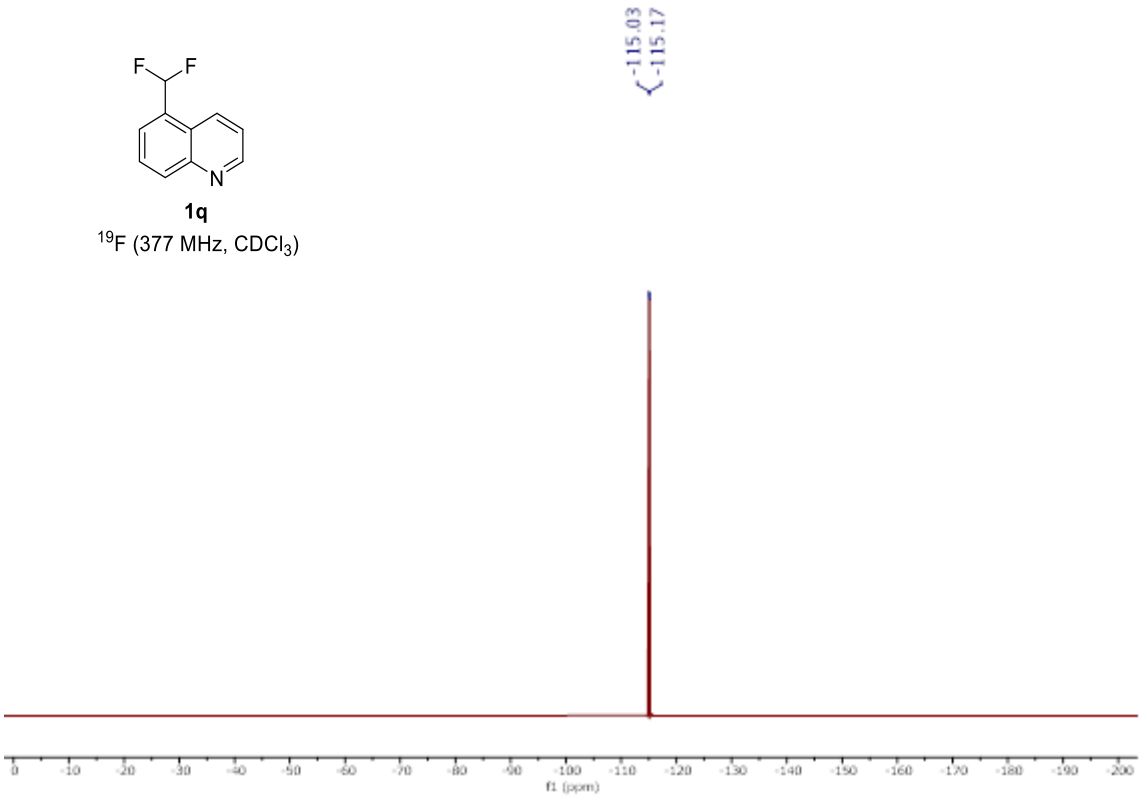
^{1}H (400 MHz, $CDCl_3$)





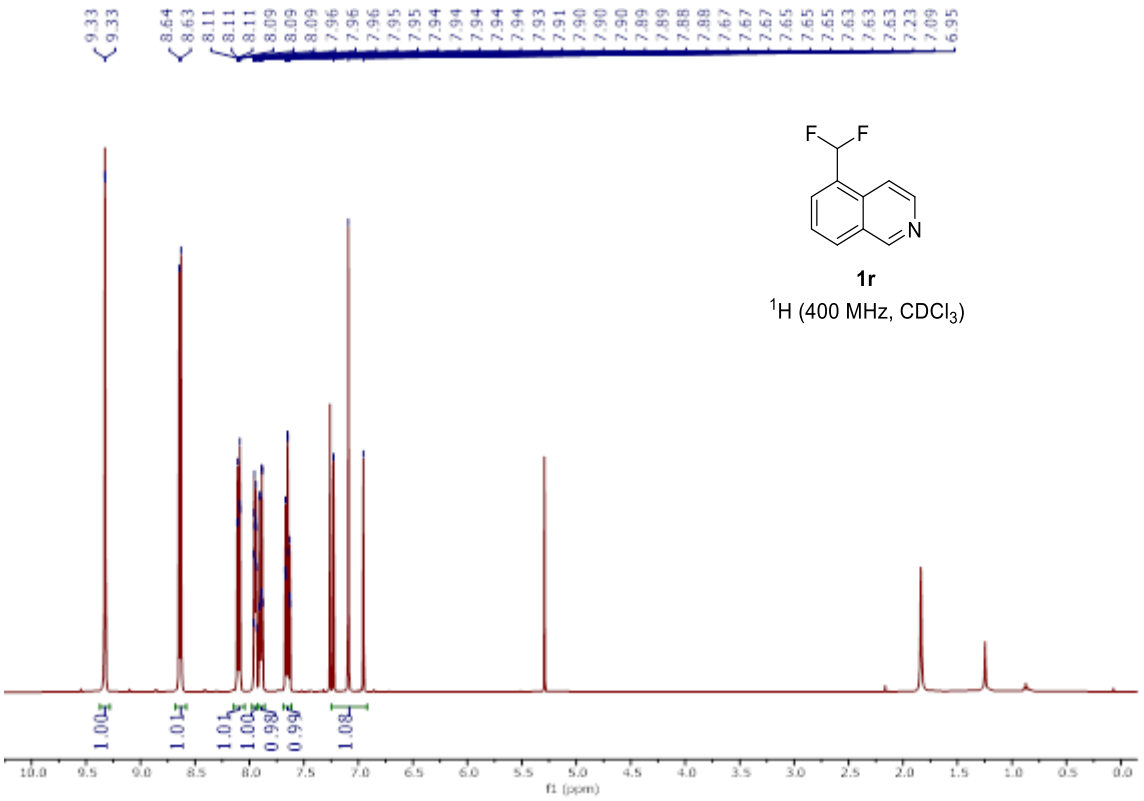
1q

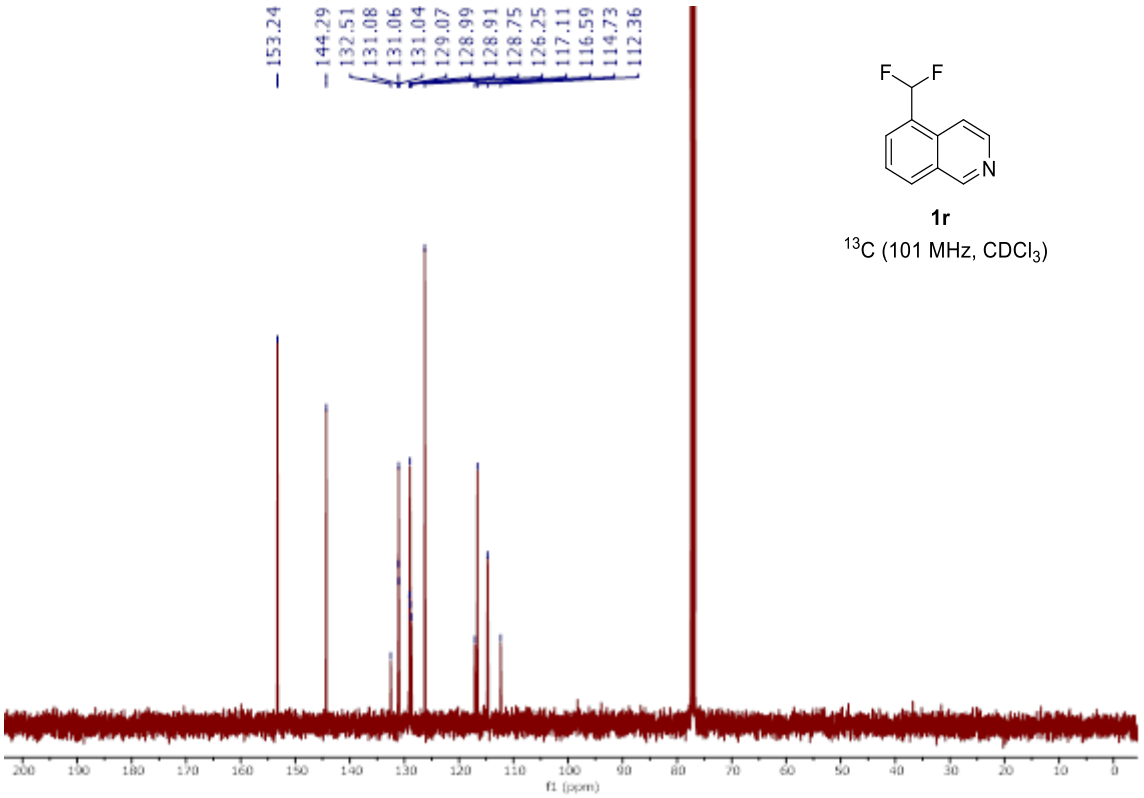
^{13}C (101 MHz, $CDCl_3$)

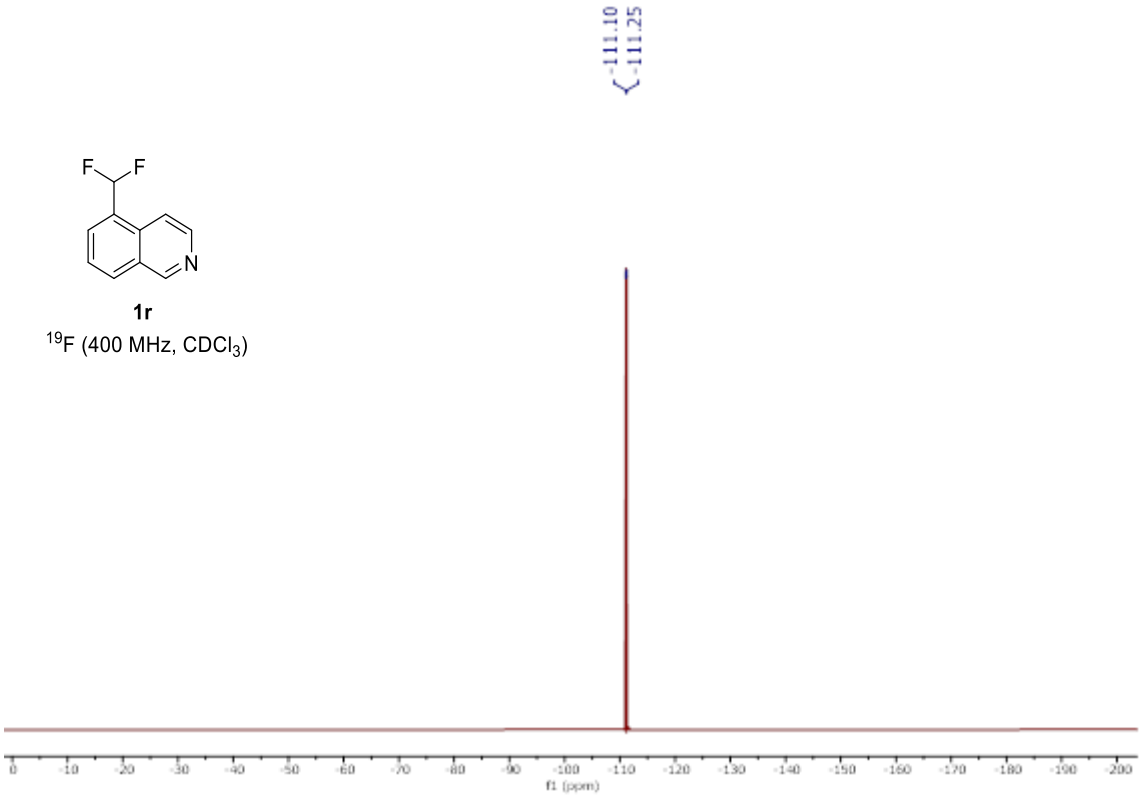


1q

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

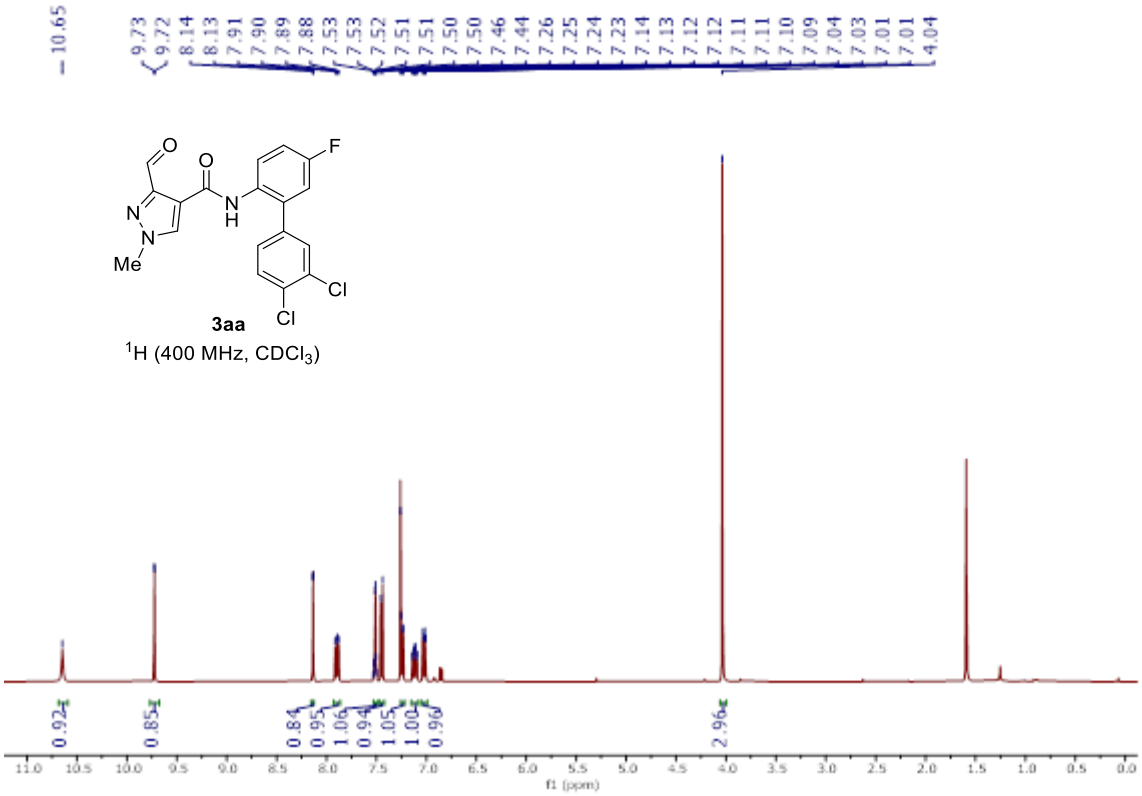

F
F
N
1r
^{1}H (400 MHz, $CDCl_3$)


F
F
N
1r
^{13}C (101 MHz, $CDCl_3$)



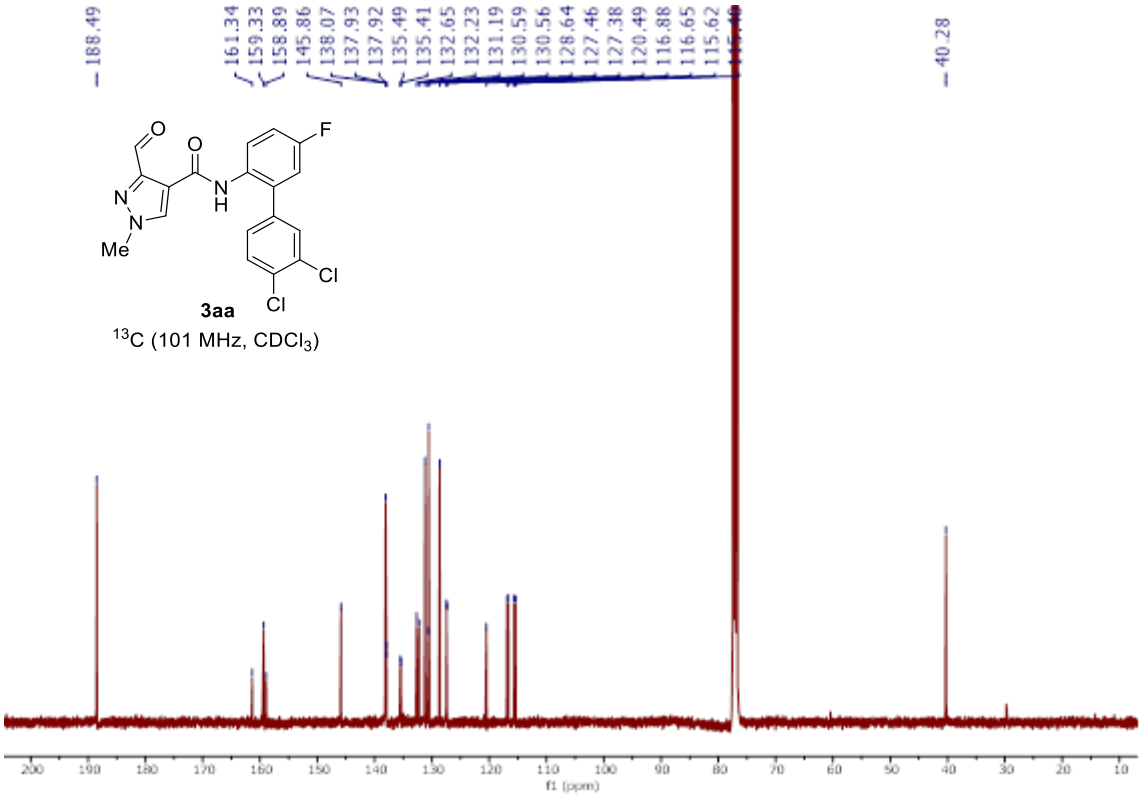
1r

^{19}F (400 MHz, $CDCl_3$)



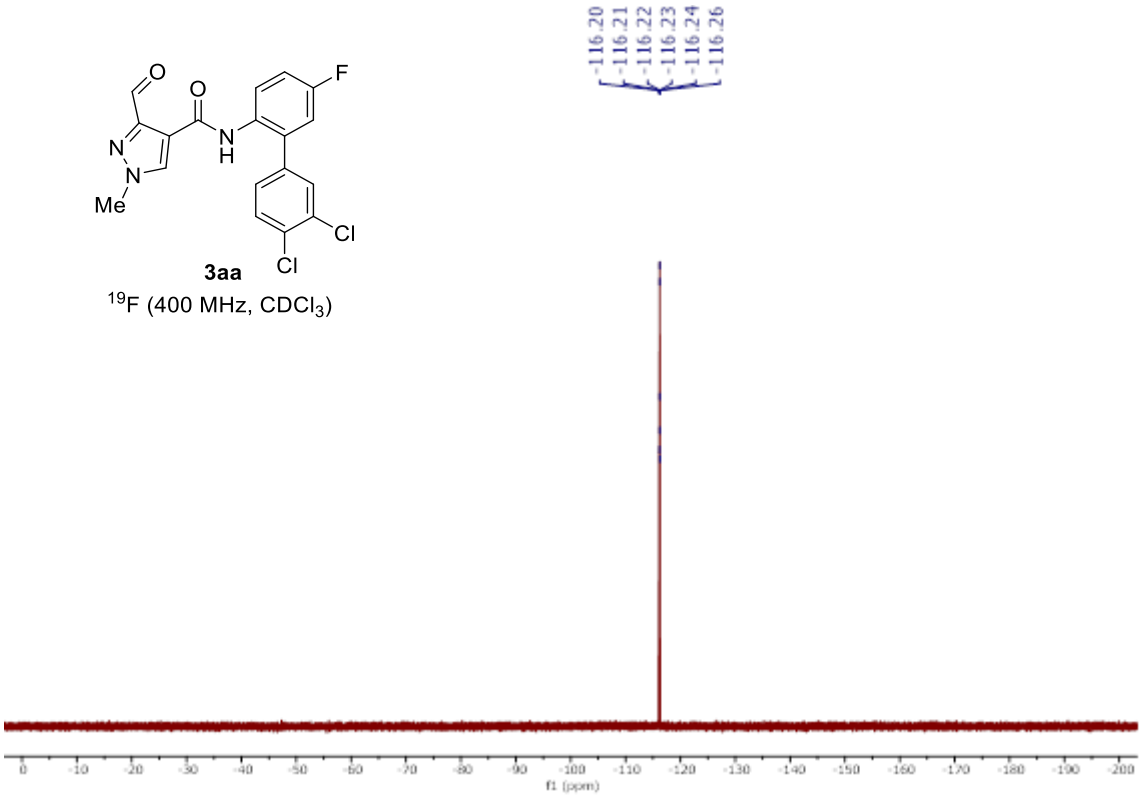
3aa

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



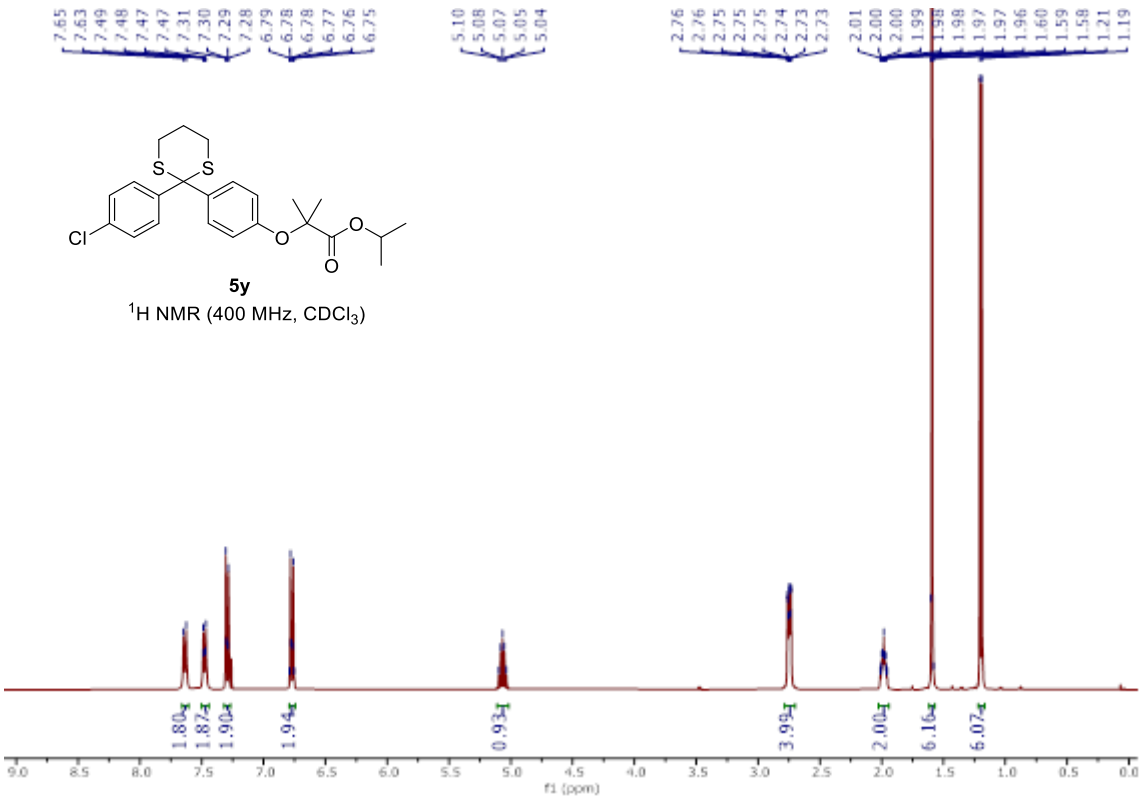
3aa

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



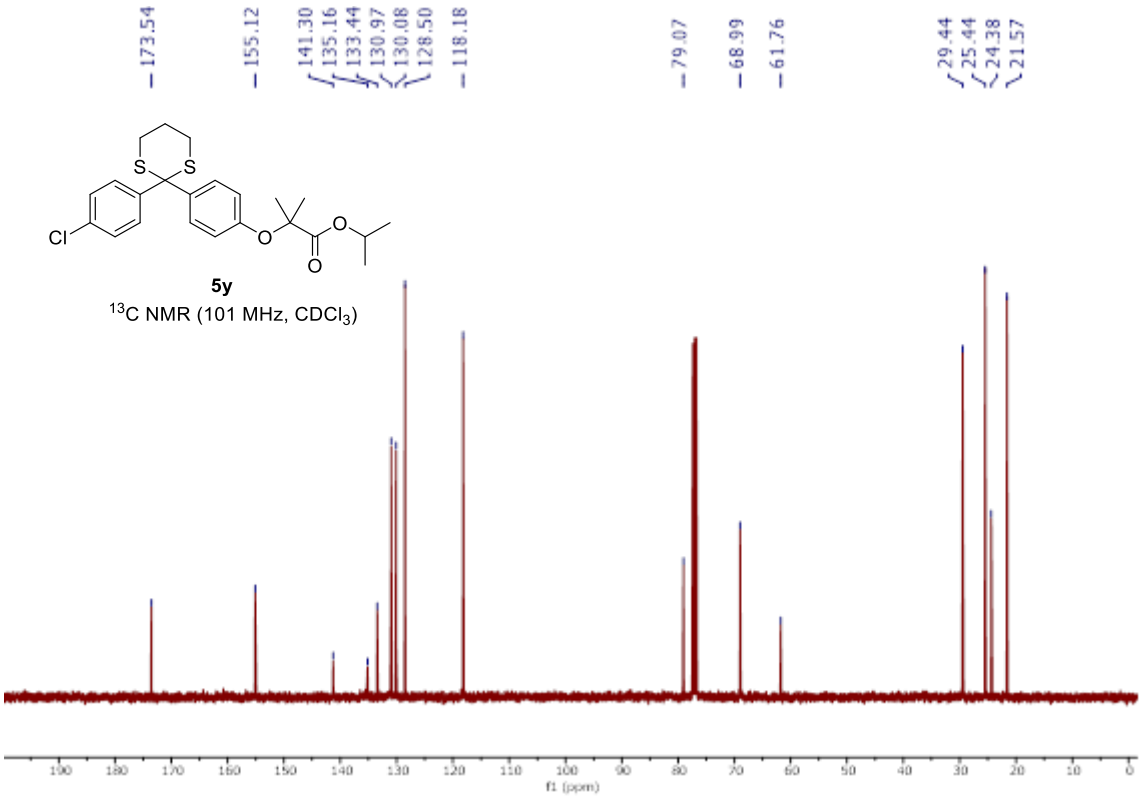
3aa

^{19}F (400 MHz, $CDCl_3$)



5y

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



5y

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