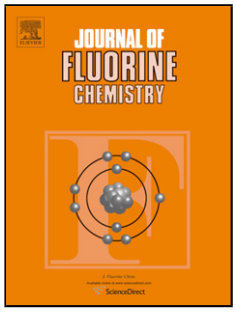

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Author: Zhentong Zhu Yuwei Guo Xiaojun Wang Fanhong Wu Yongming Wu

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Synthesis of Fluorinated 3-Pyrrolines and Pyrroles *via* [3+2] Annulation of N-aryl Fluorinated Imines with Allenoates Catalyzed by Phosphine

Zhentong Zhu[a,b], Yuwei Guo[b,c], Xiaojun Wang[b,c], Fanhong Wu[a,*] and Yongming Wu[b,†]

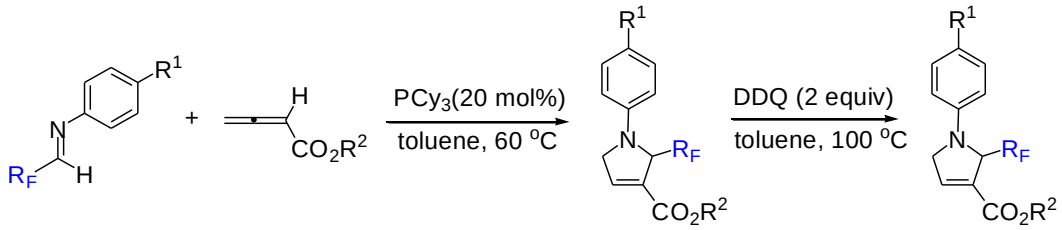
[a] School of Chemical and Environmental Engineering, Shanghai Institute of Technology, 100 Haiquan Road, Shanghai 201418, China.

[b] Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai 200032, China.

[c] Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China.

[*] Corresponding author. Tel.: +86 21 60877230; E-mail address: wfh@sit.edu.cn
[†] Corresponding author. Tel.: +86 21 54925190; fax: +86 21 64166128. E-mail address: ymwu@sioc.ac.cn

Graphical Abstract



1 **2** **3** **5**

R_F=CF_3,CF_2Br,CF_2Cl 20-82% 87-98%

A phosphine-catalyzed [3+2] annulation of *N*-aryl fluorinated imines with allenoates is reported. A series of fluorinated pyrrolines are obtained in moderate yield, which are further transformed to fluorinated pyrroles *via* dehydro-aromatization by DDQ in high to excellent yield.

Highlights

A phosphine-catalyzed [3+2] annulation of *N*-aryl fluorinated imines with allenoates is reported. A series of fluorinated pyrrolines are obtained in moderate yield.

which are further transformed to fluorinated pyrroles *via* dehydro-aromatization by DDQ in high to excellent yield.

The reaction mechanism is also discussed.

Abstract

A phosphine-catalyzed [3+2] annulation of *N*-aryl fluorinated imines with allenoates is reported. A series of fluorinated pyrrolines are obtained in moderate yield, which are further transformed to fluorinated pyrroles *via* dehydro-aromatization by DDQ in high to excellent yield. The reaction mechanism is also discussed.

Keywords: fluorinated pyrrole; fluorinated 3-pyrroline; *N*-aryl fluorinated imines; allenoates; [3+2] annulation

1. Introduction

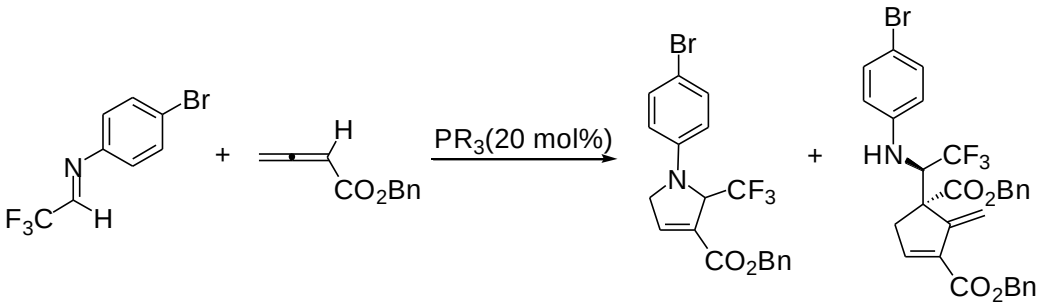
Pyrrolines, pyrroles and their derivatives represent an important class of heterocycles, which are often presented in nature products and therapeutic compounds [1]. Because of their biological properties, many of them have diverse applications such as: cholesterol reducing and anti-inflammatory drugs, etc. [2]. It has been demonstrated that the incorporation of fluorine or fluorinated groups into organic molecules could dramatically alters their chemical and biological properties [3]. An indirect method using fluorinated building blocks plays a significant role in synthesizing fluorinated heterocycles, which has been extensively applied for the synthesis of some drugs and inhibitors [4]. Recently, several research groups have reported methods for the synthesis of fluorinated pyrroline and pyrroles [5-7]. For instance, Rutjes and co-workers described a series of Ru-catalyzed ring-closing metathesis to form pyrroles and 3-pyrrolines [5]. Liu's group explored the silver-catalyzed intramolecular oxidative aminofluorination of allenes [6]. Marquez and co-workers have successfully synthesized the fluorinated 3-pyrrolines by the treatment of Grubbs 2nd generation catalyst and diene [7]. However, the majority of these studies are too much dependent on transition-metal-catalysis. Since Lu's pioneer report of phosphine-catalyzed [3+2] cycloaddition of allenoates and activated alkenes or imines[8], nucleophilic phosphine organocatalysis has become a powerful tool for the construction of carbocycles or heterocycles. . Particularly in heterocycles, it continues to attract great interest for researchers in expanding its scope[9]. Herein, we report a metal-free and facile synthesis of *N*-aryl-2-fluorinated-pyrrolines or pyrroles utilizing Lu's [3+2] cycloaddition reaction.

2. Results and discussion

Initially, we choose the allonate **2a** and *N*-aryl trifluoroethylimine **1a,** which was obtained by the condensation of the commercial trifluoroacetaldehyde ethyl hemiacetal with arylamine, as the model substrates to optimize the reaction condition. A couple of phosphines have been screened at room temperature in toluene. As shown in Table 1, phosphines, with relatively low catalytic activity, could generate anticipative products **3a** in moderate yield with incomplete conversion of **1a** (Table 1, entries 1-2, 5-7). Tri(2-furyl)phosphine couldn't promote the forming of desired product **3a** as observed in ^{19}FNMR (Table 1, entry 8), but a small amount of by-product **4a** is formed unexpectedly. Based on Ma's research, we suspect that it is a sequential 3+2/3+2 annulation of two equivalent allenes with imines[10]. Crystal structure of **4a** demonstrates that it is a fluorinated compound of five-membered carbon ring with an exocyclic double bond in only one configuration and the molecular weight is the same as the construction we speculated (S.I. Figure 1). Although application of high-performance phosphine catalyst could result in a good conversion, but the yield is low (Table 1, entries 3-4). Particularly in the presence of PBu_3, the impurities are difficult to separate. Based on the results mentioned above, PCy_3 was found to be the best suitable catalyst for this reaction. Studies of the effects of different temperatures for this reaction indicated that lower temperature of the reaction resulted in good conversion but in a relatively low yield (Table 1, entries 9-11), and high temperature was beneficial to the reaction and more **2a** is required as the temperature increases (Table 1, entries 12-13). Changes of the reaction solvent did not have a significant effect on the yield of **3a** (Table 1, entries 14-16), use of DMF or MeCN as solvent only resulted in a plenty of

impurities under the same condition. Therefore, the optimization conditions were ascertained as PCy_3 (20 mol%) in toluene at 60°C.

Table 1 Optimization of the conditions



1a **2a** **3a** **4a**

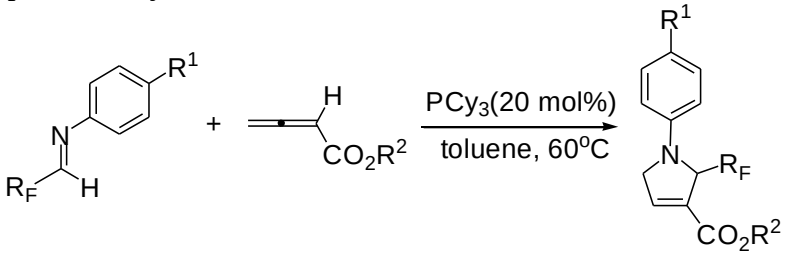
Entry	Cat.	Solvent	Temp.(°C)	Time	Conv.(**1a**, %)[a]	Yield(%)[b] **3a**	**4a**
1	PCy_3	Toluene	rt	24h	81	50	12
2	PPh_3	Toluene	rt	24h	75	48	9
3	PBu_3	Toluene	rt	5h	100	-	-
4	PMe_2Ph	Toluene	rt	5h	100	19	trace
5	PPh_2Me	Toluene	rt	24h	65	40	10
6	PCy_2Ph	Toluene	rt	24h	77	43	13
7	PPh_2Cy	Toluene	rt	24h	64	42	16
8	$P(2\text{-furyl})_3$	Toluene	rt	24h	0	-	-
9	PCy_3	Toluene	10	24h	82	37	13
10	PCy_3	Toluene	0	24h	96	34	14
11	PCy_3	Toluene	-10	24h	92	22	trace
12[c]	PCy_3	Toluene	30	5h	100	60	14
13[d]	PCy_3	Toluene	60	5h	100	82	trace
14[d]	PCy_3	1,4-dioxane	60	5h	100	68	trace
15[d]	PCy_3	p-xylene	60	5h	100	67	trace
16[d]	PCy_3	THF	60	5h	100	72	trace
17[d]	PCy_3	MeCN	60	5h	100	-	-
18[d]	PCy_3	DMF	60	5h	100	-	-

[a] Unless otherwise mentioned, reactions were performed with *N*-aryl trifluoroethylimine **1a** (0.2 mmol), allenoate **2a** (0.22 mmol), solvent (2ml).
[b] Isolated yield caculated on the basis of *N*-aryl trifluoroethylimine.
[c] 1.7 equiv of **2a** were used
[d] 2.0 equiv of **2a** were used.

Following the optimized reaction conditions, the scope of this methodology was further explored. As shown in Table 2, several substrates could be tolerated under the optimized conditions. Electron-withdraw substituents on the benzene ring of the imine

such as bromo, chloro, iodo and trifluoromethyl could provide **3** in moderate to high yields (Table 2, entries 1-4). Meanwhile, electron-donating groups on the benzene ring of the imine sharply decreased the yields and leave a plenty of imines under the reaction system. The replacement of a fluorinated group with a chlrorodifluoromethyl group resulted in a moderate to high yield with a prolonged reaction time (Table 2, entries 7-8). Utilizing a bromodifluoromethyl group as the fluorinated group could only produce a relatively low yield because of the activity of the imine and the steric hindrance of the bromineand require more reaction time (Table 2, entries 5-6). The substrates on the ester group of allenoates such as methyl, ethyl, and tert-butyl also proceeded in good yield (Table 2, entries 11-13).

Table 2 Phosphine-catalyzed [3+2] annulation of fluorinated imine **1** and allenoates **2**



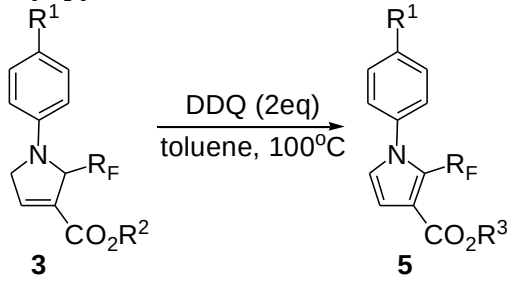
1 **2** **3**

Entry	**1**(R^1,R_F)	**2**(R^2)	Time(h)	Yield(%)[a]
1	**1a**(Br, CF_3)	Bn	5h	**3a**, 82
2	**1b**(Cl, CF_3)	Bn	5h	**3b**, 73
3	**1c**(I, CF_3)	Bn	5h	**3c**, 63
4	**1d**(CF_3, CF_3)	Bn	5h	**3d**, 73
5	**1e**(Br, CF_2Br)	Bn	24h	**3e**, 20
6[b]	**1f**(Br, CF_2Br)	Et	24h	**3f**, 31
7	**1g**(Br, CF_2Cl)	Bn	12h	**3g**, 62
8[b]	**1h**(Br, CF_2Cl)	Et	12h	**3h**, 75
9[b]	**1i**(Br, CF_3)	t-Bu	5h	**3i**, 72
10[b]	**1j**(Br, CF_3)	Et	5h	**3j**, 75
11[b]	**1k**(Br, CF_3)	Me	5h	**3k**, 70

[a] isolated yield
[b] 1.7 equiv of **2** were used

3-pyrrolines can also be used as significant precursor for the synthesis of pyrroles[11]. After investigation of some conditions, the presence of DDQ in 100°C was selected as the best condition in dehydro-aromatization of some pyrrolines **3**, which offered high to excellent yield of pyrroles **5** (Table 3, entries 1-9). The structure of **5i** was confirmed by X-ray crystal diffraction studies (Figure 1).

Table 3 Synthesis of *N*-aryl pyrroles



3 **5**

Entry	**3**(R^1,R^2,R_F)	Time	Yield(%)[a]
1	**3a**(Br, Bn, CF_3)	7h	**5a**, 98
2	**3b**(Cl, Bn, CF_3)	7h	**5b**, 90
3	**3c**(I, Bn, CF_3)	7h	**5c**, 94
4	**3d**(CF_3, Bn, CF_3)	12h	**5d**, 92
5	**3g**(Br, Bn, CF_2Cl)	12h	**5g**, 90
6	**3h**(Br, Et, CF_2Cl)	7h	**5h**, 87
7	**3i**(Br, t-Bu, CF_3)	7h	**5i**, 98
8	**3j**(Br, Et, CF_3)	7h	**5j**, 95
9	**3k**(Br, Me, CF_3)	7h	**5k**, 96

[a] isolated yield

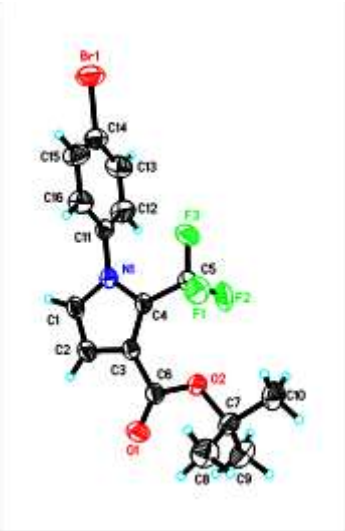
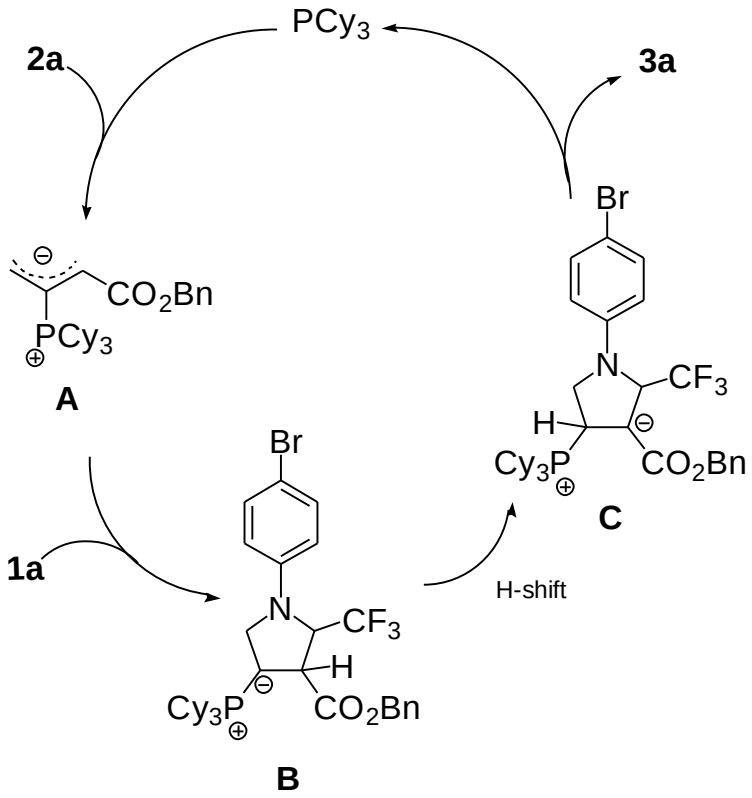


Figure 1 Crystal structure of **5i**

A plausible mechanism has been proposed from the Lu's [3+2] cycloaddition reaction and the strength of analogue products in Yu's study [8][12]. Initially, allenoate **2a** in presence of the phosphine catalyst generates a zwitterionic intermediate **A** which behaves as a 1,3-dipole and undergoes a [3+2] cycloaddition with **1a** to give a phophorus ylieded intermediate **B**. After a proton shift it generates another zwitterionic **C,** and then eliminates the phosphine give rise to the desire product **3a**.



Scheme 1 A plausible mechanism for formation of **3a**

3. Conclusion

In conclusion, we have reported a phosphine-catalyzed [3+2] annulation reaction of fluorinated imines with electron deficient allenoates. The electron-withdraw substituents on the benzene ring of the imines are beneficial to the annulation. Finally, an efficient

dehydro-aromatization can be used to synthesize *N*-aryl pyrroles *via* DDQ with a high to excellent yield.

4. Experimental

4.1 General Information

Unless otherwise stated, all reactions were run in an oven-dried Schlenk tube and magnetic stirring under an atmosphere of nitrogen. ^{1}H NMR spectra were recorded in $CDCl_3$ on an Agilent NMR 400 spectrometer (400 MHz) with TMS as internal standard.^{13}C NMR spectra were taken on a Bruker AM-400 (101 MHz) spectrometer or an Aglilent 400 spectrometer (101 MHz). ^{19}F NMR spectra were taken on an Agilent 400 spectrometer (376 MHz). IR spectra were obtained with a Nicolet AV-360 spectrophotometer. Mass spectra were recorded on Finnigan MAT-8430 mass spectrometer. Solvents were purchased from commercial sources and purified before used by standard procedures. TLC analysis was performed on silica gel plates, column chromatography over silica gel (mesh 300-400) and petroleum ether/ethyl acetate or n-hexane/dichloromethane combination were used as the eluent.

4.2 General procedure for **1** synthesis

For example the procedure for **1c** synthesis: The a solution of 1-ethoxy-2,2,2-trifluoroethanol (7.2g, 50mmol), 4-iodoaniline (9.9g, 45mmol) and catalytic amount of *p*-toluene sulfonic acid (20mg) in toluene (30 mL) was added, then the mixture was heated at 130^{o}C and refluxed for 4h. After completion of reaction as indicated by TLC, the mixture was concentrated in vacuo. Then vacuum distillation to provide the desire product **1c**.

4.2.1 (*E*)-2,2,2-trifluoro-*N*-(4-iodophenyl)ethan-1-imine (**1c**)

White solid, mp: 95-97 ^{o}C, bp: 37-39 ^{o}C, 20 pa; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (q, *J* = 3.4 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (101 MHz,

$CDCl_3$) δ 147.70 (q, *J* = 39.1 Hz), 147.05 (s), 138.61 (s), 122.88 (s), 118.97 (q, *J* = 274.5 Hz), 93.91 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -71.20 (d, *J* = 3.4 Hz); IR (film,cm^{-1}): ν 2912, 1665, 1589, 1479, 1359, 1281, 1139, 1006, 886, 818; HRMS (EI) calcd. For $C_8H_5NF_3I$: 298.9419; Found: 298.9422.

4.2.2 (*E*)-2-bromo-*N*-(4-bromophenyl)-2,2-difluoroethan-1-imine (**1e**)

Yellow liquid, bp: 40-42 ^oC, 20 pa; ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (t, *J* = 5.2 Hz, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.70 (t, *J* = 28.7 Hz), 146.07, 132.66, 122.91, 122.38, 115.26 (t, *J* = 304.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.47 (d, *J* = 5.2 Hz); IR (film,cm^{-1}): ν 2922, 1655, 1582, 1484, 1339, 1240, 1121, 967, 861, 758; HRMS (EI) calcd. For $C_8H_5NF_2Br_2$: 310.8757, Found: 310.8756.

4.2.3 (*E*)-*N*-(4-bromophenyl)-2-chloro-2,2-difluoroethan-1-imine (**1g**)

Colorless liquid, bp: 34-36 ^oC, 20 pa; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (t, *J* = 4.5 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.11 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.83 (t, *J* = 32.1 Hz), 146.28, 132.67, 122.87, 122.38, 122,17 (t, *J* = 290.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.98 (d, *J* = 4.4 Hz); IR (film,cm^{-1}): ν 2920, 1660, 1583, 1484, 1340, 1244, 1071, 984, 827, 775; HRMS (EI) calcd. For $C_8H_5NF_2ClBr$: 226.9262, Found: 266.9260.

4.3 General procedure for **3** synthesis

For example the procedure for **3a** synthesis: In a nitrogen-filled box, a schlenk tube was charged with tricyclohexylphosphine (11.2 mg, 0.04 mmol). Then toluene (2.0 mL), imine (50.4 mg, 0.2 mmol) and 2,3-alleonate (69.6 mg, 0.4 mmol) was added successively and stirred at 60^oC for 5h. After completion of reaction as indicated by TLC, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica (combined solvent ethyl acetate and petrol ether as eluent to provide the desire product **3a**.

4.3.1 benzyl 1-(4-bromophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3a**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 5H), 7.34 (d, *J* = 9.0 Hz, 2H), 7.21 (s, 1H), 6.61 (d, *J* = 8.9 Hz, 2H), 5.40 (p, *J* = 5.1 Hz, 1H), 5.32 – 5.21 (m, 2H), 4.46 (ddd, *J* = 17.3, 5.6, 1.7 Hz, 1H), 4.21 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.52 (s), 144.79 (s), 143.32 (s), 135.22 (s), 132.00 (s), 129.59 (d, *J* = 1.6 Hz), 128.68 (s), 128.57 (s), 128.43(s), 124.98 (q, *J* = 286.8 Hz), 113.98 (d, *J* = 0.9 Hz), 110.49 (s), 67.14 (s), 64.39 (q, *J* = 32.3 Hz), 56.77 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.54 (d, *J* = 4.9 Hz); IR (film,cm^{-1}): ν 2851, 1725, 1594, 1496, 1370, 1255, 1135, 1098, 808, 749; HRMS (EI) calcd. For $C_{19}H_{15}NO_2F_3Br$: 425.0238; Found: 425.0240.

4.3.2 benzyl 1-(4-chlorophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3b**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.34 (m, 5H), 7.21 (s, 1H), 7.20 (d, *J* = 9.1 Hz, 2H), 6.64 (d, *J* = 9.0 Hz, 2H), 5.40 (p, *J* = 5.1 Hz, 1H), 5.31 – 5.12 (m, 2H), 4.45 (ddd, *J* = 17.3, 5.6, 1.7 Hz, 1H), 4.20 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.54 (s), 144.38 (s), 143.37 (s), 135.25 (s), 129.59 (d, *J* = 1.6 Hz), 129.13 (s), 128.68 (s), 128.57 (s), 128.43 (s), 125.02 (q, *J* = 286.8 Hz), 123.33 (s), 113.49 (d, *J* = 0.7 Hz), 67.13 (s), 64.45 (q, *J* = 32.3 Hz), 56.84 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.57 (d, *J* = 4.8 Hz); IR (film,cm^{-1}): ν 2846, 1726, 1600, 1499, 1369, 1258, 1135, 1091, 811, 749; HRMS (EI) calcd. For $C_{19}H_{15}NO_2F_3Cl$: 381.0743; Found: 381.0745.

4.3.3 benzyl 1-(4-iodophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3c**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 9.0 Hz, 2H), 7.40 – 7.33 (m, 5H), 7.20 (s, 1H), 6.50 (d, *J* = 8.9 Hz, 2H), 5.39 (p, *J* = 5.1 Hz, 1H), 5.30 – 5.21 (m, 2H), 4.44 (ddd, *J* = 17.3, 5.5, 1.7 Hz, 1H), 4.19 (d, *J* = 17.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.49 (s), 145.37 (s), 143.26 (s), 137.85 (s), 135.18 (s), 129.60 (d, *J* = 1.7 Hz), 128.66 (s), 128.56 (s), 128.43(s), 124.93 (q, *J* = 286.8 Hz), 114.58 (d, *J* = 0.9 Hz), 79.82 (s), 67.15 (s), 64.25 (q, *J* = 32.3 Hz), 56.65 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.52 (d, *J* = 5.1 Hz); IR (film,cm^{-1}): ν 2962, 1724, 1588, 1493, 1370, 1256, 1135, 1095, 806, 750; HRMS (EI) calcd. For $C_{19}H_{15}NO_2F_3I$: 473.0100; Found: 473.0108.

4.3.4 benzyl 2-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3d**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.7 Hz, 2H), 7.41 – 7.34 (m, 5H), 7.22 (s, 1H), 6.76 (d, *J* = 8.6 Hz, 2H), 5.48 (p, *J* = 5.0 Hz, 1H), 5.31 – 5.22 (m, 2H), 4.49 (dd, *J* = 17.0, 5.0 Hz, 1H), 4.28 (d, *J* = 17.1 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.37 (s), 147.99 (s), 143.02 (s), 135.12 (s), 129.63 (d, *J* = 1.5 Hz), 128.66 (s), 128.58 (s), 128.43 (s), 126.60 (q, *J* = 3.8 Hz), 124.87 (q, *J* = 286.6 Hz), 124.65 (q, *J* = 270.3 Hz), 120.26 (q, *J* = 32.8 Hz), 111.89 (d, *J* = 0.9 Hz), 67.21 (s), 64.18 (q, *J* = 32.5 Hz), 56.53 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.30 (s), -72.46 (d, *J* = 4.9 Hz); IR (film,cm^{-1}): ν 2855, 1727, 1617, 1529, 1333, 1255, 1136, 1070, 846, 749; HRMS (EI) calcd. For $C_{20}H_{15}NO_2F_6$: 415.1007; Found: 415.1002.

4.3.5 benzyl 2-(bromodifluoromethyl)-1-(4-bromophenyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3e**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 5H), 7.33 (d, *J* = 9.1 Hz, 2H), 7.23 (s, 1H), 6.63 (d, *J* = 7.9 Hz, 2H), 5.39 (s, 1H), 5.28 – 5.22 (m, 2H), 4.54 (ddd, *J* = 17.3, 5.3, 1.4 Hz, 1H), 4.16 (d, *J* = 17.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.66 (s), 144.75 (s), 143.51 (s), 135.19 (s), 131.92 (s), 131.03 (t, *J* = 303.5 Hz), 130.91 (d, *J* = 3.9 Hz), 128.64 (s), 128.53 (s), 128.41 (s), 114.24 (s), 110.62 (s), 69.07 (dd, *J* = 29.5, 27.5 Hz), 67.12 (s), 57.28 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -46.69 (dd, *J* = 162.8, 2.6 Hz), -47.68 (d, *J* = 162.8 Hz); IR (film,cm^{-1}): ν 2921, 1724, 1593, 1494, 1367, 1247, 1100, 1010, 809, 753; HRMS (EI) calcd. For $C_{19}H_{15}NO_2F_2Br_2$: 484.9438; Found: 484.9445.

4.3.6 ethyl 2-(bromodifluoromethyl)-1-(4-bromophenyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3f**)

White solid, mp: 95-97 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.1 Hz, 2H), 7.19 (s, 1H), 6.65 (d, *J* = 7.9 Hz, 2H), 5.38 (t, *J* = 3.9 Hz, 1H), 4.54 (ddd, *J* = 17.2, 5.3, 1.3 Hz, 1H), 4.34 – 4.21 (m, 2H), 4.17 (d, *J* = 17.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.79 (s), 144.75 (s), 142.81 (s), 131.93 (s), 131.81 (d, *J* = 5.7 Hz), 127.08 (t, *J* = 320.8 Hz), 114.33 (d, *J* = 2.5 Hz), 110.69 (s), 70.38 (dd, *J* = 28.3,

24.2 Hz), 61.36 (s), 57.50 (s), 14.13 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -46.61 (dd, *J* = 162.6, 2.4 Hz), -47.73 (d, *J* = 162.6 Hz); IR (film,cm^{-1}): ν 2989,1715, 1590, 1492, 1367, 1249, 1113, 999, 806, 759; HRMS (EI) calcd. For $C_{14}H_{13}NO_2F_2Br_2$: 422.9281; Found: 422.9276.

4.3.7 benzyl 1-(4-bromophenyl)-2-(chlorodifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3g**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.34 (m, 5H), 7.32 (d, *J* = 9.1 Hz, 2H), 7.21 (s, 1H), 6.63 (d, *J* = 8.7 Hz, 2H), 5.52 (s, 1H), 5.29 – 5.21 (m, 2H), 4.49 (ddd, *J* = 17.3, 5.4, 1.6 Hz, 1H), 4.17 (d, *J* = 17.3 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.67 (s), 144.76 (s), 143.51 (s), 135.20 (s), 131.94 (s), 131.02 (dd, *J* = 307.9, 299.2 Hz), 130.92 (d, *J* = 1.0 Hz), 128.65 (s), 128.55 (s), 128.43 (s), 114.24 (d, *J* = 1.0 Hz), 110.64 (s), 69.09 (dd, *J* = 29.5, 27.6 Hz), 67.13 (s), 57.29 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.65 (dd, *J* = 164.9, 3.1 Hz), -55.17 (dd, *J* = 164.8, 2.2 Hz), -55.17 (dd, *J* = 164.8, 2.2 Hz); IR (film,cm^{-1}): ν 2918, 1724, 1594, 1495, 1368, 1247, 1100, 1021, 809, 755; HRMS (EI) calcd. For $C_{19}H_{15}NO_2F_2ClBr$: 440.9943; Found: 440.9939.

4.3.8 ethyl 1-(4-bromophenyl)-2-(chlorodifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3h**)

Yellow solid, mp: 69-70^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.0 Hz, 2H), 7.17 (s, 1H), 6.64 (d, *J* = 8.7 Hz, 2H), 5.50 (s, 1H), 4.49 (ddd, *J* = 17.2, 5.3, 1.5 Hz, 1H), 4.32 – 4.22 (m, 2H), 4.18 (d, *J* = 17.2 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.86 (s), 144.83 (s), 142.77 (s), 131.92 (s), 131.26 (d, *J* = 3.6 Hz), 131.07 (t, *J* = 304.5 Hz), 114.24 (s), 110.57 (s), 69.11 (dd, *J* = 29.6, 27.2 Hz), 61.34 (s), 57.27 (s), 14.12 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.61 (dd, *J* = 164.7, 2.9 Hz), -55.20 (d, *J* = 164.7 Hz); IR (film,cm^{-1}): ν 2982, 1725, 1593, 1495, 1368, 1250, 1101,1019, 809, 758; HRMS (EI) calcd. For $C_{14}H_{13}NO_2F_2ClBr$: 378.9786; Found: 378.9782.

4.3.9 *tert*-butyl 1-(4-bromophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-

carboxylate (**3i**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.0 Hz, 2H), 7.06 (s, 1H), 6.59 (d, *J* = 8.8 Hz, 2H), 5.33 – 5.24 (m, 1H), 4.41 (ddd, *J* = 16.9, 5.5, 1.5 Hz, 1H), 4.16 (d, *J* = 16.8 Hz, 1H), 1.51 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.94 (s), 144.93 (s), 141.41 (s), 131.94 (s), 131.44 (d, *J* = 1.5 Hz), 126.44 (t, *J* = 286.8 Hz), 113.90 (d, *J* = 0.9 Hz), 110.29 (s), 82.26 (s), 64.55 (q, *J* = 32.1 Hz), 56.61 (s), 27.95 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.31 (d, *J* = 5.2 Hz); IR (film,cm^{-1}): ν 2980, 1719, 1595, 1496, 1368, 1255, 1166, 1099, 809, 756; HRMS (EI) calcd. For $C_{16}H_{17}NO_2F_3Br$: 391.0395; Found: 391.0398.

4.3.10 ethyl 1-(4-bromophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3j**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.0 Hz, 2H), 7.15 (s, 1H), 6.60 (d, *J* = 8.8 Hz, 2H), 5.41 – 5.33 (m, 1H), 4.44 (ddd, *J* = 17.1, 5.5, 1.4 Hz, 1H), 4.33 – 4.23 (m, 2H), 4.19 (d, *J* = 17.1 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.68 (s), 144.84 (s), 142.51 (s), 131.98 (s), 129.96 (d, *J* = 1.7 Hz), 124.95 (q, *J* = 286.7 Hz), 113.95 (d, *J* = 1.0 Hz), 110.43 (s), 64.41 (q, *J* = 32.2 Hz), 61.33 (s), 56.74 (s), 14.10 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -72.60 (d, *J* = 5.1 Hz); IR (film,cm^{-1}): ν 2983, 1725, 1594, 1496, 1370, 1253, 1135, 1017, 808, 751; HRMS (EI) calcd. For $C_{14}H_{13}NO_2F_3Br$: 363.0082; Found: 363.0074.

4.3.11 methyl 1-(4-bromophenyl)-2-(trifluoromethyl)-2,5-dihydro-1*H*-pyrrole-3-carboxylate (**3k**)

Yellow solid, mp: 77-78^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 9.1 Hz, 2H), 7.16 (s, 1H), 6.60 (d, *J* = 8.9 Hz, 2H), 5.38 (p, *J* = 5.2 Hz, 1H), 4.44 (ddd, *J* = 17.2, 5.6, 1.7 Hz, 1H), 4.19 (d, *J* = 17.2 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.10 (s), 144.79 (s), 142.85 (s), 131.98 (s), 129.54 (d, *J* = 1.7 Hz), 124.91 (q, *J* = 286.6 Hz), 113.94 (d, *J* = 0.9 Hz), 110.45 (s), 64.37 (q, *J* = 32.3 Hz), 56.75 (s), 52.23 (s);

^{19}F NMR (376 MHz, $CDCl_3$) δ -72.72 (d, *J* = 5.0 Hz); IR (film,cm^{-1}): ν 2921, 1727, 1595, 1496, 1362, 1251, 1163, 1099, 982, 847, 813, 752; HRMS (EI) calcd. For $C_{13}H_{11}NO_2F_3Br$: 348.9925; Found: 348.9928.

4.3.12 dibenzyl (*S*)-1-((*R*)-1-((4-bromophenyl)amino)-2,2,2-trifluoroethyl)-2-methylenecyclopen -t-3-ene-1,3-dicarboxylate (**4a**)

Yellow solid, mp: 122-124^{o}C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 7H), 7.19 (d, *J* = 8.7 Hz, 2H), 7.14 – 7.06 (m, 3H), 6.50 (d, *J* = 8.7 Hz, 2H), 6.15 (s, 1H), 5.49 (s, 1H), 5.21 (q, *J* = 12.4 Hz, 2H), 5.05 (d, *J* = 11.9 Hz, 1H), 4.91 (d, *J* = 11.9 Hz, 1H), 4.59 (td, *J* = 14.1, 7.0 Hz, 1H), 3.98 (d, *J* = 10.9 Hz, 1H), 3.49 (dd, *J* = 19.9, 1.8 Hz, 1H), 2.86 (dd, *J* = 19.9, 2.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.67 (s), 162.67 (s), 146.90 (s), 145.18 (s), 144.84 (s), 135.71 (s), 134.61 (s), 133.78 (s), 132.10 (s), 131.79 (s), 128.63 (s), 128.61 (s), 128.34 (s), 128.23 (s), 127.75 (s), 125.34 (q, *J* = 286.9 Hz), 115.58 (s), 112.85 (s), 111.29 (s), 68.34 (s), 66.38 (s), 60.52 (q, *J* = 26.9 Hz), 58.72 (s), 35.83 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.01 (d, *J* = 7.1 Hz); IR (film,cm^{-1}): ν 3389, 3033, 1723, 1594, 1490, 1343, 1240,1174, 908, 814, 749; HRMS (EI) calcd. For $C_{30}H_{25}NO_4F_3Br$: 599.0919, Found: 599.0914.

4.4 General procedure for **5** synthesis

For example the procedure for **5a** synthesis: In a nitrogen-filled box, a schlenk tube was charged with **3a** (42.5 mg, 0.1 mmol) and DDQ (45.4mg, 0.2mmol) in toluene (2.0 mL). The reaction mixture was stirred at 100^{o}C for 7h. After completion of reaction as indicated by TLC, the mixture was concentrated in vacuo. The residue was purified by column chromatography on silica (combined solvent ethyl acetate and petrol ether as eluent) to provide the desire product **5a**.

4.4.1 benzyl 1-(4-bromophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5a**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.5 Hz, 2H), 7.47 – 7.30 (m, 5H), 7.21 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 2.9 Hz, 1H), 6.74 (d, *J* = 3.0 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.67 (s), 138.19 (s), 135.86 (s), 132.41 (s), 128.53 (s),128.24 (s), 128.20 (s), 127.74 (d, *J* = 0.5 Hz), 126.12 (d, *J* = 1.2 Hz), 123.11 (s), 122.75 (q, *J*= 38.9 Hz), 120.20 (q, *J*= 270.3 Hz), 119.59 (q, *J* = 1.6 Hz), 112.32 (s), 66.68 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.16 (s); IR (film, cm^{-1}): ν 3034, 2956, 1728, 1554, 1495, 1455, 1265, 1188, 1130, 1016, 834, 787; HRMS (EI) calcd. For $C_{19}H_{13}NO_2F_3Br$: 423.0082; Found: 423.0086.

4.4.2 benzyl 1-(4-chlorophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5b**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.42 – 7.29 (m, 5H), 7.25 (d, *J* = 8.9 Hz, 2H), 6.76 (d, *J* = 3.0 Hz, 1H), 6.73 (d, *J* = 3.0 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.68 (s), 137.66 (s), 135.85 (s), 135.12 (s), 129.40 (s), 128.51 (s), 128.22 (s), 128.18 (s), 127.45 (d, *J* = 0.8 Hz), 126.14 (d, *J* = 1.3 Hz), 122.80 (dd, *J* = 77.6, 38.9 Hz), 120.18 (q, *J* = 270.0 Hz), 119.54 (d, *J* = 2.0 Hz), 112.27 (s), 66.67 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.16 (s); IR (film, cm^{-1}): ν 3034, 2959, 1727, 1553,1499, 1435, 1264, 1188, 1130, 1018, 837, 743; HRMS (EI) calcd. For $C_{19}H_{13}NO_2F_3Cl$: 379.0587; Found: 379.0595.

4.4.3 benzyl 1-(4-iodophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5c**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.7 Hz, 2H), 7.49 – 7.27 (m, 5H), 7.06 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 3.0 Hz, 1H), 6.72 (d, *J* = 3.0 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (101MHz, $CDCl_3$) δ 162.67 (s), 138.90 (s), 138.39 (s), 135.84 (s), 128.52 (s), 128.23 (s), 128.18 (s), 127.89 (d, *J* = 0.9 Hz), 126.05 (d, *J* = 1.4 Hz), 122.70 (q, *J* = 39.0 Hz), 120.17 (q, *J* = 270.0 Hz), 119.61 (d, *J* = 2.0 Hz), 112.33 (s), 94.55 (s), 66.68 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.11 (s); IR(film,cm^{-1}): ν 3033, 2946, 1726, 1553, 1493, 1436, 1264, 1187, 1130, 1013, 830, 743; HRMS (EI) calcd. For $C_{19}H_{13}NO_2F_3I$: 470.9943, Found:470.9944.

4.4.4 benzyl 2-(trifluoromethyl)-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-3-carboxylate (**5d**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 7.43 – 7.29 (m, 5H), 6.79 (d, *J* = 3.0 Hz, 1H), 6.77 (d, *J* = 3.0 Hz, 1H), 5.33 (s, 2H); ^{13}C NMR (101MHz, $CDCl_3$) δ 162.58 (s), 142.08 (s), 135.78 (s), 131.28 (q, *J* = 33.2 Hz), 128.53 (s), 128.25 (s), 128.22 (s), 126.62 (d, *J* = 0.8 Hz), 126.47 (q, *J* = 3.7 Hz), 126.03 (s), 123.49 (q, *J* = 272.5 Hz), 122.79 (q, *J* = 39.0 Hz), 120.14 (q, *J* = 270.0 Hz), 120.02 (d, *J* = 2.0 Hz), 112.58 (s), 66.75 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.00 (s), -62.71 (s); IR(film,cm^{-1}): ν 3036, 2960, 1728, 1522, 1481, 1437, 1266, 1189, 1130, 1064, 851, 746; HRMS (EI) calcd. For $C_{20}H_{13}NO_2F_6$: 413.0850, Found: 413.0854.

4.4.5 benzyl 1-(4-bromophenyl)-2-(chlorodifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5g**)

Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.29 (m, 5H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 3.0 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 5.32 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.72 (s), 138.31 (d, *J* = 1.4 Hz), 135.83 (s), 132.30 (s), 128.49 (s), 128.31 (s), 128.23 (t, *J* = 34.8 Hz), 128.17 (s), 128.15 (t, *J* = 1.1 Hz), 125.82 (s), 123.12 (s), 121.13 (t, *J* = 289.2 Hz), 117.80 (t, *J* = 1.9 Hz), 112.21 (s), 66.65 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.54 (s); IR (film,cm^{-1}): ν 3071, 2924, 1719, 1552, 1493, 1435, 1261, 1177, 1099, 1027, 883, 742; HRMS (EI) calcd. For $C_{19}H_{13}NO_2F_2ClBr$: 438.9786, Found: 438.9782.

4.4.6 ethyl 1-(4-bromophenyl)-2-(chlorodifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5h**)

Yellow solid, mp: 128-129 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 6.70 (d, *J* = 2.9 Hz, 1H), 6.67 (d, *J* = 3.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.08 (s), 138.38

(s), 132.28 (s), 128.15 (s), 127.56 (t, *J* = 31.0 Hz), 125.79 (s), 123.05 (s), 121.21 (t, *J* = 287.7 Hz), 118.33 (s), 112.00 (s), 60.89 (s), 14.10 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -41.34 (s); IR (film,cm^{-1}): ν 2961, 2854, 1728, 1549, 1494, 1461, 1260, 1178, 1095, 1016, 881, 800; HRMS (EI) calcd. For $C_{14}H_{11}NO_2F_2ClBr$: 376.9630, Found: 377.9636.

4.4.7 *tert*-butyl 1-(4-bromophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5i**)

Yellow solid, mp: 70-72 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (d, *J* = 8.7 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 2.9 Hz, 1H), 6.68 (d, *J* = 2.9 Hz, 1H), 1.55 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.47 (s), 138.41 (s), 132.35 (s), 127.69 (s), 125.86 (s), 122.87 (s), 122.07 (s), 122.00 (q, *J* = 2.1 Hz), 120.33 (q, *J* = 269.7 Hz), 112.10 (s), 81.49 (s), 27.99 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -52.72 (s);IR (film,cm^{-1}): ν 3130, 2918, 1685, 1542, 1496, 1435, 1277, 1200, 1147, 1015, 833, 753; HRMS (EI) calcd. For $C_{16}H_{15}NO_2F_3Br$: 389.0238, Found: 389.0237.

4.4.8 ethyl 1-(4-bromophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5j**)

Yellow solid, mp: 105-107 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.74 – 6.71 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.00 (d, *J* = 0.6 Hz), 138.24 (s), 132.36 (s), 127.73 (d, *J* = 0.9 Hz), 126.03 (d, *J* = 1.4 Hz), 123.02(s), 122.45 (q, *J* = 38.0 Hz), 120.20 (q, *J* = 269.9 Hz), 120.09 (q, *J* = 2.0 Hz), 112.09 (s), 60.89 (s), 14.08 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.14 (d, *J* = 3.1 Hz); IR (film,cm^{-1}): ν 3128, 2991, 1721, 1561, 1494, 1434, 1248, 1188, 1127, 1037, 838, 755; HRMS (EI) calcd. For $C_{14}H_{11}NO_2F_3Br$: 360.9925, Found: 360.9919.

4.4.9 methyl 1-(4-bromophenyl)-2-(trifluoromethyl)-1*H*-pyrrole-3-carboxylate (**5k**)

Yellow solid, mp: 62-64 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 8.6 Hz, 2H), 6.72 (dd, *J* = 6.5, 3.0 Hz, 2H), 3.86 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.35 (s), 138.18 (s), 132.38 (s), 127.73 (s), 126.08 (d, *J* = 1.4 Hz), 123.07 (s), 122.63 (q, *J* = 38.8 Hz), 120.15 (q, *J* = 269.8 Hz), 119.55 (q, *J* = 1.8 Hz), 112.10 (s), 51.96 (s); ^{19}F NMR (376 MHz, $CDCl_3$) δ -53.36 (s); IR (film,cm^{-1}): ν 3130, 2951, 1724, 1555, 1494, 1434, 1250, 1200, 1131, 1030, 860, 750; HRMS (EI) calcd. For $C_{13}H_9NO_2F_3Br$: 346.9769, Found: 346.9761.

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