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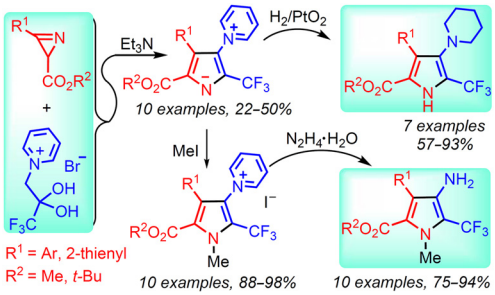
An Azirine Strategy for the Synthesis of Alkyl 4-Amino-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates

Liya D. Funt
Olesya A. Tomashenko
Mikhail S. Novikov
Alexander F. Khlebnikov*

Saint Petersburg State University, Institute of Chemistry,
7/9 Universitetskaya nab., St. Petersburg, 199034,
Russian Federation
a.khlebnikov@spbu.ru



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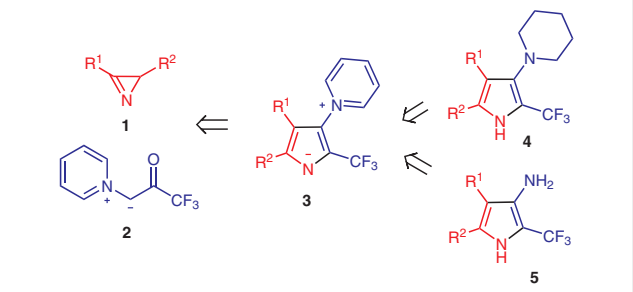
Abstract 1-(3,3,3-Trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide serves as a trifluoromethyl-containing building block for the preparation of trifluoromethyl-substituted aminopyrroles based on the 2*H*-azirine ring expansion strategy. The primary products, 3-aryl-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ides, can be hydrogenated by H_2/PtO_2 to form alkyl 3-aryl-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates and transformed into alkyl 4-amino-3-aryl-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates via methylation/hydrazinolysis.

Key words trifluoromethylpyrrole, aminopyrrole, trifluoromethylated pyridinium ylide, pyridine, piperidine

Functionalized pyrroles are present as a structural motif in a range of natural products and bioactive molecules.[1] They are also versatile building blocks in heterocyclic synthesis and have found applications in the development of new progressive materials that are useful for bioimaging applications and chemosensors.[1,2] Therefore, many synthetic methodologies have been developed for the construction of a variety of substituted pyrroles.[2] In particular, trifluoromethylated pyrroles are privileged structures in medicinal chemistry research due to a remarkable influence of the trifluoromethyl group on many important properties of potential drugs, such as metabolic stability, lipophilicity, and bioavailability.[3,4] There are two main synthetic approaches to trifluoromethylated pyrroles; namely, direct trifluoromethylation of the pyrrole ring[4,5] and cyclizations involving trifluoromethylated building blocks.[5,6] Amino-substituted pyrroles have a wide range of biological activities, and they are also useful as precursors for the preparation of a variety of valuable acyclic and heterocyclic derivatives.[7] Substituted pyrroles containing both the trifluoromethyl and amino groups have, to our knowledge, been previously unknown.

We earlier discovered the reaction of 2*H*-azirines with *N*-phenacylpyridinium ylides,[8] leading to 1-(1*H*-pyrrol-3-yl)pyridinium salts, which formed the basis of a new strategy for the synthesis of heteryl- and amino-substituted pyrroles.[9] The reaction was successfully extended to *N*-phenacylimidazolium,[10] *N*-phenacyl-1,2,4-triazolium ylides[11] and 2-methoxy-2-oxo-1-(pyridin-1-ium-1-yl)ethan-1-ides,[12] to obtain a great variety of pyrrolyl-imidazole and pyrrolyl-triazole dyads, azole betaines, and NHCs. Zincke cleavage[13] of the pyridinium ring in 4-(pyridin-1-ium-1-yl)pyrrol-1-ides and 1-(1*H*-pyrrol-3-yl)pyridinium salts[14] allowed us to synthesize 3-aminopyrrole derivatives. Based on this background, we hypothesized that the reaction of 2*H*-azirines **1** with trifluoromethylated ylide **2**, 3,3,3-trifluoro-2-oxo-1-(pyridin-1-ium-1-yl)propan-1-ide, as a trifluoromethyl-containing building block, could be potentially used for the synthesis of trifluoromethylated pyrroles with N-heterocyclic and amino substituents **3**–**5** (Scheme 1).



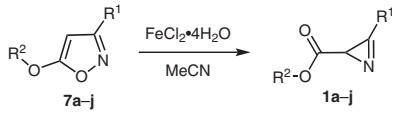
Scheme 1 Retrosynthetic scheme for the synthesis of trifluoromethylated pyrroles with N-heterocyclic and amino substituents

To start with, the simplest substrate 3-phenyl-2*H*-azirine was reacted with 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide (**6**) under the reaction condi-

tions that were successfully used for the preparation of 1-(1*H*-pyrrol-3-yl)pyridinium salts by the reaction of 2*H*-azirines with *N*-phenacylpyridinium ylides.[9] The model reaction was carried out in CH_2Cl_2 at room temperature with 1.1 equivalents of Et_3N as a base and molecular sieves as a supporting dehydrating agent. Monitoring the reaction mixture by ^1H NMR spectroscopy showed that, after 24 hours, the only result of the reaction was partial conversion of salt **6** into the enol form of ylide **2** (ca. 30%). Increasing the temperature led to considerable tarring of the reaction mixture, but still no trace of the target pyrrole was detected. Performing the reaction in CH_3CN, which was the solvent of choice in the case of some substituted azirines,[10–12] at either room temperature of under heating, was also not successful. Similarly, adding $Cu(OAc)_2$ to activate azirine[15] gave no positive result. Thus, the reaction of 3-phenyl-2*H*-azirine with trifluoromethylated ylide **2** did not lead to the target pyrrole under any of the conditions. The reaction with 2,3-diaryl-substituted azirine, 2,3-diphenyl-2*H*-azirine, also failed. The electron-withdrawing character of the CF_3-group means that ylide **2** is less nucleophilic than *N*-phenacylpyridinium ylide, which easily reacted with 3-phenyl-2*H*-azirine and 2,3-diphenyl-2*H*-azirine. We therefore further tested more electrophilic azirines containing an electron-acceptor substituent at the azirine ring. Furthermore, since the preparation of pure ylide **2** from **6** gives **2** in only 22% yield,[16] optimization of the reaction conditions for the synthesis of pyrrole **3a** from azirine **1a** was performed by generation of **2** in situ from **6** by reaction with triethylamine at 20–120 °C in MeCN, MeOH and 1,2-dichloroethane (DCE) (Table 1). Salt **6** did not react with methyl 3-phenyl-2*H*-azirine-2-carboxylate **1a** in MeCN at room temperature, but the reaction slowly proceeded at 80 °C to afford desired pyrrole **3a** in 31% yield (Table 1). The best yield of **3a** could be achieved with MeCN as solvent at 120 °C.

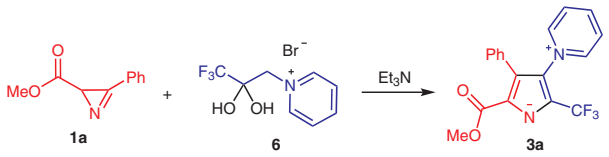
The use of excess Et_3N enhanced tar formation but, on the other hand, with the amount of base less than 1.05 equivalents, full conversion of the starting material could not be achieved.

To evaluate the scope of the reaction, we synthesized alkyl 2*H*-azirine-2-carboxylates **1a–j**, containing various 3-aryl/hetaryl-substituents, by Fe(II)-catalyzed isomerization of the corresponding 5-alkoxyisoxazoles **7a–j** (Scheme 2). Azirines **1a–j** were reacted with pyridinium bromide **6** under the optimal conditions to obtain the corresponding betaines **3a–j** in 22–50% yield (Table 2).



Scheme 2 Synthesis of alkyl 2*H*-azirine-2-carboxylates **1a–j** (R^i see Table 2)

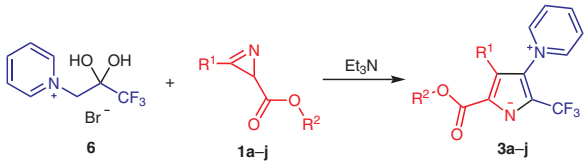
Table 1 Optimization of Reaction Conditions[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield of **3a** (%)[b]
1	MeCN	r.t.	24	0
2	MeCN	80	96	31
3	MeCN	100	48	34
4	MeCN	120	48	42
5	DCE	100	48	0
6	MeOH	100	48	0

[a] A solution of **1a** (1.3 equiv), **6** (1 equiv) and Et_3N (1.05 equiv) in solvent (2 mL) was heated under stirring at the indicated temperature in a screw-cap thick-wall test tube for the period shown; the reaction mixture was cooled, and the product was isolated by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1), the resulting residue was suspended in water, filtered off, and dried under vacuum.
[b] Isolated yields calculated based on bromide **6**.

Table 2 Synthesis of Betaines **3**



Entry	**1**	R^1	R^2	Yield of **3** (%)
1	**1a**	Ph	Me	42
2	**1b**	4-BrC_6H_4	Me	50
3	**1c**	4-$MeOC_6H_4$	Me	22
4	**1d**	4-$NO_2C_6H_4$	Me	45
5	**1e**	2-BrC_6H_4	*t*-Bu	26
6	**1f**	4-MeC_6H_4	Me	32
7	**1g**	3,4-$Me_2C_6H_3$	Me	28
8	**1h**	4-FC_6H_4	Me	33
9	**1i**	Ph	*t*-Bu	35
10	**1j**	2-thienyl	Me	32

Decrease of thermal stability (azirine **1c**) and increase of steric congestion (azirines **1e**, **1g**) of the azirine leads to lower yield of the betaine. Compounds **3a–j** were characterized by standard spectroscopic methods. The structure of **3a** was also confirmed by single-crystal X-ray analysis (Figure 1).[17]

Piperidine is a privileged structural moiety, which is ranked as the most frequently present in FDA-approved drugs.[18] The pyridine substituent in a molecular system can

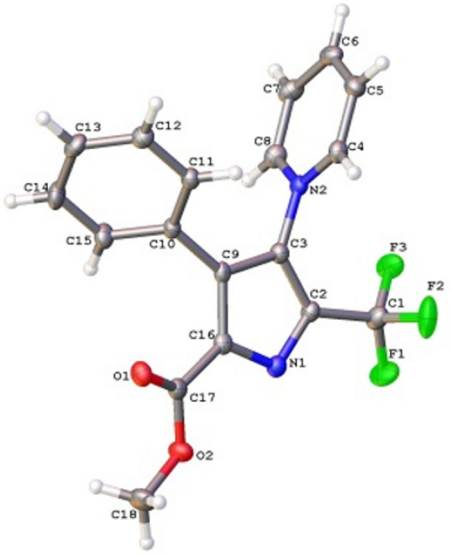
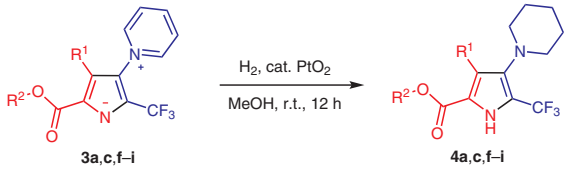


Figure 1 X-ray crystal structure of betaine **3a**

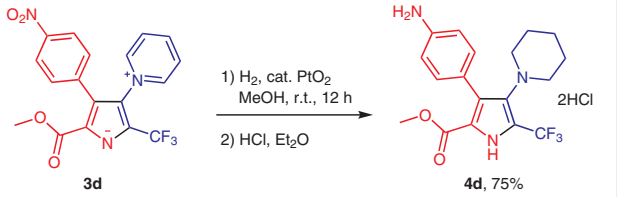
serve as the synthetic equivalent of the piperidine moiety, because it can be selectively hydrogenated when necessary.[9,12,14a] It was found that betaines **3a**, **3c**, and **3f–i** can be hydrogenated at room temperature in MeOH under atmospheric pressure of H_2 in the presence of Adams' catalyst to give the corresponding alkyl 3-aryl-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates **4** in good yields (Table 3). Hydrogenation of compounds **3b**, **3d**, and **3e** under these conditions in addition to the reduction of the pyridinium fragment, leads to substitution of bromine for hydrogen in the 3-(2/4-bromophenyl) moieties (compounds **3b** and **3e**) and reduction of the nitro group in the 3-(4-nitrophenyl) moiety (compound **3d**) to the amino group (Scheme 3).

Table 3 Synthesis of 4-Piperidinopyrroles **4a**, **4c**, and **4f–i**



3a,**c**,**f–i** **4a**,**c**,**f–i**

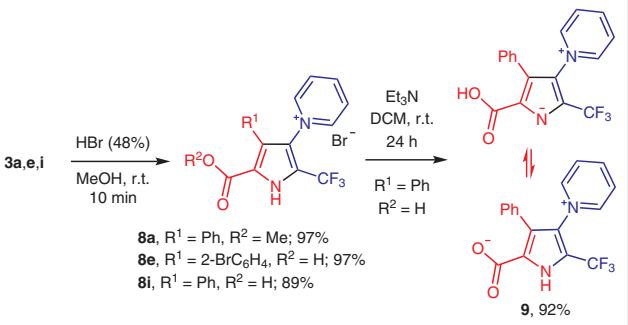
Entry	R^1	R^2	Yield of **4** (%)
1	Ph	Me	**4a**, 71
2	4-$MeOC_6H_4$	Me	**4c**, 74
3	4-MeC_6H_4	Me	**4f**, 57
4	3,4-$Me_2C_6H_3$	Me	**4g**, 62
5	4-FC_6H_4	Me	**4h**, 93
6	Ph	*t*-Bu	**4i**, 72



3d **4d**, 75%

Scheme 3 Reduction of betaine **3d**

Then we tried to transform the pyridinium moiety in compounds **3** to the amino group, but, unexpectedly, the procedure,[14] which was successfully used for the Zincke cleavage of the pyridinio substituent in pyrroles containing no CF_3 group, failed. A complex mixture of unidentified products formed in the reaction of compound **3a** with hydrazine. Earlier we used (1*H*-pyrrol-3-yl)pyridin-1-ium salts as starting materials for the preparation of 3-aminopyrroles by Zincke cleavage, even though this reaction is most likely to proceed through the corresponding betaines formed from the salts in the presence of excess of hydrazine.[14] To check the use of salts for the synthesis of trifluoromethylated NH-pyrroles **5**, we prepared 2-trifluoromethyl-(1*H*-pyrrol-3-yl)pyridin-1-ium bromide **8a** in a nearly quantitative yield by treatment of betaine **3a** with aqueous HBr (Scheme 4).



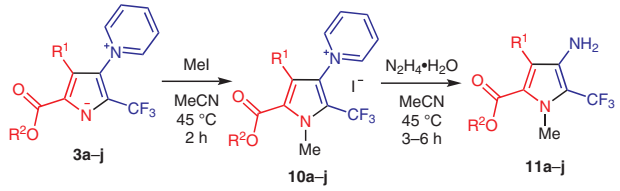
Scheme 4 Synthesis of salts **8a**, **8e**, and **8i**, and betaine **9**

In the case of *tert*-butyl esters **3e** and **3i**, the formation of pyridinium salts under these conditions was accompanied by the HBr-catalyzed hydrolysis of the ester group to give salts **8e** and **8i**. It is interesting that the neutralization of salt **8i** with Et_3N afforded trifluoromethylated betaine **9** in high yield. According to the NMR spectra, the latter exists as a mixture of rapidly interconverting OH and NH tautomers.

However, like with betaine **3a**, the reaction of hydrazine with salt **8a** gave a complex mixture of unidentified products, probably because of the instability of NH-aminopyrrole **5** under the reaction conditions. Therefore, methyl protection of the pyrrole nitrogen was further tried. The starting compounds **3a–j** were N-methylated with methyl iodide to give the corresponding 1-(5-(alkoxycarbonyl)-4-aryl-1-

methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodides **10a–j** in nearly quantitative yields. Hydrazinolysis of the pyridinium moiety in compounds **10a–j** provided the target trifluoromethylated aminopyrroles **11a–j** in good to excellent yields (Table 4).

Table 4 Synthesis of Compounds **10** and **11**



Entry	R^1	R^2	Yield of **10** (%)	Yield of **11** (%)
1	Ph	Me	**10a**, 90	**11a**, 75
2	4-BrC_6H_4	Me	**10b**, 98	**11b**, 97
3	4-MeOC_6H_4	Me	**10c**, 92	**11c**, 81
4	4-$O_2N C_6H_4$	Me	**10d**, 98	**11d**, 90
5	2-BrC_6H_4	*t*-Bu	**10e**, 97	**11e**, 78
6	4-MeC_6H_4	Me	**10f**, 91	**11f**, 93
7	3,4-$Me_2C_6H_3$	Me	**10g**, 96	**11g**, 89
8	4-FC_6H_4	Me	**10h**, 96	**11h**, 94
9	Ph	*t*-Bu	**10i**, 88	**11i**, 76
10	2-thienyl	Me	**10j**, 92	**11j**, 89

In summary, 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide was used as a trifluoromethyl-containing building block for the preparation of trifluoromethyl-substituted aminopyrroles using the 2*H*-azirine ring expansion strategy. The primary products, 3-aryl-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ides, were hydrogenated with hydrogen on Adams' catalyst to give the corresponding alkyl 3-aryl-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates. Hydrogenation of the pyridinium ring in compound **3d**, containing the nitro group in the aryl moiety, under these conditions is accompanied by the reduction of the nitro to amino group. 3-Aryl-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ides were transformed into alkyl 4-amino-3-aryl-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylates through methylation of the pyrrole nitrogen with MeI followed by Zincke cleavage of the pyridinium moiety.

Melting points were determined with a Stuart SMP30 capillary melting-point apparatus. ^{1}H (400 MHz) and ^{13}C (100 or 125 MHz), ^{19}F (376 or 470 MHz) NMR spectra of $CDCl_3$ or DMSO-d_6 solutions were recorded with Bruker Avance III 400 and 500 MHz spectrometers. Chemical shifts (δ) are reported in ppm downfield from TMS (δ = 0.00 ppm). ^{1}H NMR spectra were calibrated according to the residual peak of $CHCl_3$ (δ = 7.26 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C{^{1}H} and ^{13}C DEPT135 were calibrated according to the peak of $CDCl_3$ (δ = 77.00 ppm) or DMSO-d_6 (δ = 39.51 ppm). ^{19}F NMR spectra were calibrated according to a $CFCl_3$ external standard (δ = 0 ppm). Mass spectra were recorded with a Bruker maXis HRMS-ESI-QTOF, electrospray ionization, in positive mode. Thin-layer chromatography (TLC) was conducted on aluminum sheets with 0.2 mm silica gel (fluorescent indicator, Macherey-Nagel) and Macherey-Nagel Silica 60 M was used for column chromatography.

Synthesis of Starting Materials

Preparation of Azirines 1a–j; General Procedure

Iron(II) chloride tetrahydrate (1 mmol, 10 mol%) was added to a stirred solution of 3-aryl-5-alkoxyisoxazole **7a–j** (10 mmol) in MeCN (23 mL) and the resulting mixture was stirred for 2 h under an inert atmosphere at r.t. (monitored by TLC, hexane/EtOAc, 4:1). After completion of the reaction, the solution was filtered through Celite, concentrated in vacuo and the product was purified by flash column chromatography (hexane/EtOAc, 4:1) to give azirines **1a–j**.

Methyl 3-Phenyl-2*H*-azirine-2-carboxylate (1a)

Azirine **1a** was prepared from isoxazole **7a**[19] (1.15 g, 6.57 mmol) and $FeCl_2{\cdot}4H_2O$ (131 mg, 0.66 mmol).

Yield: 1.09 g (95%); colorless solid; mp 76–78 °C (hexane/EtOAc) (Lit.[20] 44–46 °C).

Methyl 3-(4-Bromophenyl)-2*H*-azirine-2-carboxylate (1b)

Azirine **1b** was prepared from isoxazole **7b**[19] (1.0 g, 3.93 mmol) and $FeCl_2{\cdot}4H_2O$ (78 mg, 0.39 mmol).

Yield: 1.0 g (100%); colorless solid; mp 74–75 °C (EtOAc) (Lit.[21] 68.2–68.7 °C).

Methyl 3-(4-Methoxyphenyl)-2*H*-azirine-2-carboxylate (1c)

Azirine **1c** was prepared from isoxazole **7c**[19] (1.2 g, 5.85 mmol) and $FeCl_2{\cdot}4H_2O$ (116 mg, 0.58 mmol).

Yield: 1.07 g (89%); colorless solid; mp 47–48 °C (hexane/EtOAc) (Lit.[22] colorless oil).

Methyl 3-(4-Nitrophenyl)-2*H*-azirine-2-carboxylate (1d)

Azirine **1d** was prepared from isoxazole **7d**[23] (1.3 g, 5.88 mmol) and $FeCl_2{\cdot}4H_2O$ (117 mg, 0.59 mmol).

Yield: 1.28 g (98%); yellow solid; mp 93–95 °C (hexane/EtOAc) (Lit.[24] 96–98 °C).

tert-Butyl 3-(2-Bromophenyl)-2*H*-azirine-2-carboxylate (1e)

3-(2-Bromophenyl)-5-chloroisoxazole

2-Bromo-*N*-hydroxybenzimidoyl chloride[25] (4 g, 0.017 mol, 1 equiv) in 1,1-dichloroethylene (17 mL) and anhydrous 1,2-dichloroethane (32 mL) was slowly added dropwise to a stirred solution of Et_3N (4.31 g, 0.043 mol, 2.5 equiv) in 1,1-dichloroethylene (17 mL) cooled to 0 °C with an ice bath. The reaction mixture was stirred at r.t. overnight and then water (90 mL) was added and the solution was extracted with benzene (2 × 40 mL). The combined organic phases were washed with saturated NH_4Cl (2 × 40 mL), water (2 × 40 mL), and brine (2 × 40 mL), dried over Na_2SO_4, filtered off, concentrated in vacuo and the residue was purified by column chromatography (hexane/EtOAc, 12:1).

Yield: 3.37 g (77%); pale-yellow solid; mp 44–45 °C (hexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.64 (s, 1 H), 7.30–7.38 (m, 1 H), 7.39–7.45 (m, 1 H), 7.58–7.65 (m, 1 H), 7.66–7.73 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.1 (CH), 122.3 (C), 127.9 (CH), 129.8 (C), 131.3 (CH), 131.7 (CH), 133.9 (CH), 154.4 (C), 164.4 (C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_9H_5BrClNNaO^+$: 279.9135; found: 279.9136.

3-(2-Bromophenyl)-5-(*tert*-butoxy)isoxazole (7e)

*t*BuOK (1.04 g, 9.29 mmol, 1.2 equiv) was added to a stirred solution of 3-(2-bromophenyl)-5-chloroisoxazole (1.93 g, 7.45 mmol, 1 equiv) in anhydrous THF (25 mL) at r.t. After homogenization, the reaction mixture was heated at reflux for 4 h. When the reaction was over (monitored by TLC, hexane/EtOAc, 4:1) water (70 mL) was added and the reaction mixture was extracted with Et_2O (70 mL). The organic phase was washed with water (2 × 50 mL), and saturated NH_4Cl (2 × 50 mL) and again with water (2 × 50 mL), dried over Na_2SO_4, filtered off and concentrated in vacuo.

Yield: 1.84 g (83%); colorless solid; mp 37–38 °C (Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (s, 9 H), 5.79 (s, 1 H), 7.26–7.31 (m, 1 H), 7.35–7.42 (m, 1 H), 7.61–7.72 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.4 (CH_3), 85.2 (C), 86.3 (CH), 122.3 (C), 127.7 (CH), 131.0 (CH), 131.2 (CH), 131.4 (C), 133.7 (CH), 164.1 (C), 171.3 (C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{14}BrNNaO_2^+$: 318.0100; found: 318.0114

Azirine **1e** was prepared from isoxazole **7e** (350 mg, 1.15 mmol) and $FeCl_2{\cdot}4H_2O$ (23 mg, 0.12 mmol).

Yield: 319 mg (94%); colorless solid; mp 77–79 °C (hexane/EtOAc) (Lit.[26] 80–86 °C).

Methyl 3-(4-Methylphenyl)-2*H*-azirine-2-carboxylate (1f)

Azirine **1f** was prepared from isoxazole **7f**[20] (1.30 g, 6.88 mmol) and $FeCl_2{\cdot}4H_2O$ (137 mg, 0.69 mmol).

Yield: 1.26 g (97%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46 (s, 3 H), 2.82 (s, 1 H), 3.73 (s, 3 H), 7.33–7.43 (m, 2 H), 7.72–7.83 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.0 (CH_3), 29.4 (CH_3), 52.3 (CH), 119.5 (C), 130.2 (CH), 130.6 (CH), 145.1 (C), 158.1 (C), 172.3 (C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{11}NNaO_2^+$: 212.0682; found: 212.0682.

Methyl 3-(3,4-Dimethylphenyl)-2*H*-azirine-2-carboxylate (1g)

3-(3,4-Dimethylphenyl)isoxazol-5(4*H*)-one

Hydroxylamine hydrochloride (7.96 g, 0.11 mol, 3 equiv) was added to a suspension of ethyl 3-(3,4-dimethylphenyl)-3-oxopropanoate (8.40 g, 0.038 mol, 1 equiv) in water (25 mL) and the mixture was heated at 100 °C for 5 min. EtOH (ca. 80 mL, to homogenization) was added to the reaction mixture and the solution was heated at reflux for 1 h, then cooled. The precipitate formed was filtered off, washed with cold 50% EtOH and dried to obtain pure product.

Yield: 5.83 g (81%); colorless solid; mp 106–108 °C (hexane/EtOAc).

The compound in DMSO solution is a mixture of two tautomers: 3-(3,4-dimethylphenyl)isoxazol-5(4*H*)-one and 3-(3,4-dimethylphenyl)isoxazol-5-ol in 1:0.8 ratio.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.27 (s, 10.40 H), 4.27 (s, 1.60 H), 5.65 (s, 1 H), 7.20–7.35 (m, 1.80 H), 7.38–7.47 (m, 1.80 H), 7.51 (s, 1.80 H), 12.83 (s, 0.80 H).

The ^{13}C NMR spectrum consisted of very wide signals due to the tautomeric equilibrium.

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{12}NO_2^+$: 190.0863; found: 190.0868.

3-(3,4-Dimethylphenyl)-5-methoxyisoxazole (7g)

A solution of diazomethane [prepared from 1-methyl-1-nitrosourea (9.17 g, 0.089 mol, 3 equiv), potassium hydroxide (17.27 g, 0.31 mol, 10 equiv), H_2O (25 mL) and Et_2O (100 mL)] was added dropwise under stirring to a cold (ice bath) suspension of 3-(3,4-dimethylphenyl)isoxazol-5(4*H*)-one (5.83 g, 0.031 mol, 1 equiv) in Et_2O (30 mL). The resulting mixture was stirred at r.t. for 1 h, unreacted diazomethane was destroyed with AcOH, and the homogeneous solution was concentrated in vacuo. The solid product was recrystallized from MeOH.

Yield: 2.78 g (44%); colorless solid; mp 100–102 °C (MeOH).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H), 2.31 (s, 3 H), 4.03 (s, 3 H), 5.50 (s, 1 H), 7.15–7.23 (m, 1 H), 7.39–7.50 (m, 1 H), 7.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.8 (CH_3), 19.8 (CH_3), 58.9 (CH_3), 75.4 (CH), 124.1 (CH), 127.2 (C), 127.6 (CH), 130.1 (CH), 137.2 (C), 139.0 (C), 164.4 (C), 174.5 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2^+$: 204.1019; found: 204.1025.

Azirine **1g** was prepared from isoxazole **7g** (2.68 g, 0.013 mol) and $FeCl_2{\cdot}4H_2O$ (262 mg, 1.32 mmol).

Yield: 2.50 g (93%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 3 H), 2.35 (s, 3 H), 2.80 (s, 1 H), 3.72 (s, 3 H), 7.29–7.36 (m, 1 H), 7.55–7.61 (m, 1 H), 7.61–7.69 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7 (CH_3), 20.4 (CH_3), 29.4 (CH), 52.3 (CH_3), 119.8 (C), 128.2 (CH), 130.7 (CH), 131.5 (CH), 138.1 (C), 143.9 (C), 158.1 (C), 172.4 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{14}NO_2^+$: 204.1019; found: 204.1009.

Methyl 3-(4-Fluorophenyl)-2*H*-azirine-2-carboxylate (1h)

3-(4-Fluorophenyl)-5-methoxyisoxazole (7h)

A solution of diazomethane [prepared from 1-methyl-1-nitrosourea (7.13 g, 0.069 mol, 4 equiv), potassium hydroxide (9.70 g, 0.17 mol, 10 equiv), H_2O (20 mL) and Et_2O (80 mL)] was added dropwise under stirring to a cold (ice bath) suspension of 3-(4-fluorophenyl)isoxazol-5(4*H*)-one (3.10 g, 0.017 mol, 1 equiv) in Et_2O (20 mL). The resulting mixture was stirred at r.t. for 1 h, unreacted diazomethane was destroyed with AcOH, and the homogeneous solution was concentrated in vacuo. The solid product was recrystallized from MeOH.

Yield: 2.69 g (81%); colorless solid; mp 82–84 °C (hexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.05 (s, 3 H), 5.49 (s, 1 H), 7.06–7.19 (m, 2 H), 7.66–7.81 (m, 2 H).

^{19}F NMR (470 MHz, $CDCl_3$): δ = –110.53.

^{13}C NMR {^{1}H, ^{19}F} (125 MHz, $CDCl_3$): δ = 59.0 (CH_3), 75.5 (CH), 116.0 (CH), 125.9 (C), 128.5 (CH), 163.4 (C), 163.9 (C), 174.7 (C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_8FNNaO_2^+$: 216.0431; found: 216.0424.

Azirine **1h** was prepared from isoxazole **7h** (2.61 g, 0.014 mol) and $FeCl_2·4H_2O$ (270 mg, 1.35 mmol).

Yield: 2.39 g (92%); colorless solid; mp 47–49 °C (hexane/EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (s, 1 H), 3.75 (s, 3 H), 7.20–7.33 (m, 2 H), 7.87–7.96 (m, 2 H).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –102.48.

^{13}C NMR {^{1}H, ^{19}F} (125 MHz, $CDCl_3$): δ = 29.7 (CH), 52.5 (CH_3), 117.0 (CH), 118.7 (C), 133.0 (CH), 157.6 (C), 166.1 (C), 172.0 (C).

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd for $C_{10}H_8FNNaO_2^+$: 216.0431; found: 216.0431.

tert-Butyl 3-Phenyl-2*H*-azirine-2-carboxylate (1i)

Azirine **1i** was prepared from isoxazole **7i**[23] (3.43 g, 0.016 mol) and $FeCl_2·4H_2O$ (315 mg, 1.58 mmol).

Yield: 3.35 g (98%); colorless solid; mp 55–57 °C (hexane/EtOAc) (Lit.[27] 71–72 °C).

Methyl 3-(Thiophen-2-yl)-2*H*-azirine-2-carboxylate (1j)

Azirine **1j** was prepared from isoxazole **7j**[14b] (1.24 g, 6.85 mmol) and $FeCl_2·4H_2O$ (136 mg, 0.69 mmol).

Yield: 1.16 g (94%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.88 (s, 1 H), 3.75 (s, 3 H), 7.23–7.31 (m, 1 H), 7.71 (dd, *J* = 3.8, 1.2 Hz, 1 H), 7.88 (dd, *J* = 5.0, 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.4 (CH), 52.5 (CH_3), 124.7 (C), 128.7 (CH), 135.56 (CH), 135.64 (CH), 151.9 (C), 171.8 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_8H_8NO_2S^+$: 182.0270; found: 182.0275.

Preparation of Betaines 3a–j; Typical Procedure

Methyl 3-phenyl-2*H*-azirine-2-carboxylate **1a** (83 mg, 0.48 mmol, 1.3 equiv) and Et_3N (39 mg, 0.38 mmol, 1.05 equiv) were subsequently added to a stirred suspension of 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (100 mg, 0.37 mmol) in anhydrous MeCN (3 mL). The reaction mixture was heated in a sealed test-tube for 48 h at 120 °C, then concentrated in vacuo and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1). The crude product was suspended in water, filtered off and dried to give compound **3a**.

2-(Methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3a)

Compound **3a** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (100 mg, 0.37 mmol), methyl 3-phenyl-2*H*-azirine-2-carboxylate **1a** (83 mg, 0.48 mmol) and Et_3N (39 mg, 0.38 mmol) and additionally recrystallized from $CHCl_3$.

Yield: 53 mg (42%); beige solid; mp >240 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.56 (s, 3 H), 7.00–7.23 (m, 5 H), 7.96–8.16 (m, 2 H), 8.50–8.68 (m, 1 H), 8.91–9.11 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.54.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.0 (CH_3), 123.1 (C, q, *J* = 262.5 Hz), 123.3 (C, q, *J* = 33.3 Hz), 124.3 (C), 126.2 (CH), 126.3 (C), 126.4 (C), 127.4 (CH), 127.5 (CH), 129.7 (CH), 133.5 (C), 146.2 (CH), 147.4 (CH), 164.3 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{14}F_3N_2O_2^+$: 347.1002; found: 347.1005.

3-(4-Bromophenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3b)

Compound **3b** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (111 mg, 0.40 mmol), methyl 3-(4-bromophenyl)-2*H*-azirine-2-carboxylate **1b** (135 mg, 0.53 mmol) and Et_3N (43 mg, 0.42 mmol).

Yield: 86 mg (50%); beige solid; mp >240 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.57 (s, 3 H), 6.93–7.10 (m, 2 H), 7.28–7.44 (m, 2 H), 8.00–8.18 (m, 2 H), 8.52–8.71 (m, 1 H), 8.93–9.12 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.63.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.0 (CH_3), 119.6 (C), 123.0 (C, q, *J* = 268.2 Hz), 123.7 (C, q, *J* = 34.8 Hz), 124.1 (C), 124.9 (C), 126.6 (C), 127.6 (CH), 130.4 (CH), 131.8 (CH), 132.9 (C), 146.3 (CH), 147.3 (CH), 164.3 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}BrF_3N_2O_2^+$: 425.0107; found: 425.0125.

2-(Methoxycarbonyl)-3-(4-methoxyphenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3c)

Compound **3c** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (214 mg, 0.79 mmol), methyl 3-(4-methoxyphenyl)-2*H*-azirine-2-carboxylate **1c** (210 mg, 1.02 mmol) and Et_3N (87 mg, 0.86 mmol).

Yield: 65 mg (22%); beige solid; mp >220 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.56 (s, 3 H), 3.68 (s, 3 H), 6.68–6.77 (m, 2 H), 6.94–7.04 (m, 2 H), 8.03–8.12 (m, 2 H), 8.54–8.65 (m, 1 H), 8.94–9.06 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.48.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 49.9 (CH_3), 54.8 (CH_3), 113.0 (CH), 123.16 (C, q, *J* = 268.2 Hz), 123.23 (C, q, *J* = 33.3 Hz), 124.3 (C), 125.6 (C), 126.0 (C), 126.5 (C), 127.4 (CH), 130.8 (CH), 146.0 (CH), 147.4 (CH), 157.7 (C), 164.3 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_3^+$: 377.1108; found: 377.1114.

2-(Methoxycarbonyl)-3-(4-nitrophenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3d)

Compound **3d** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (200 mg, 0.73 mmol), methyl 3-(4-nitrophenyl)-2*H*-azirine-2-carboxylate **1d** (209 mg, 0.95 mmol) and Et_3N (78 mg, 0.77 mmol).

Yield: 128 mg (45%); beige solid; mp >200 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.60 (s, 3 H), 7.25–7.43 (m, 2 H), 7.98–8.07 (m, 2 H), 8.08–8.17 (m, 2 H), 8.55–8.74 (m, 1 H), 8.98–9.17 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –52.07.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.2 (CH_3), 122.7 (CH), 122.9 (C, q, *J* = 266.7 Hz), 124.0 (C), 124.2 (C), 124.3 (C, q, *J* = 35.2 Hz), 127.2 (C), 127.7 (CH), 130.8 (CH), 141.1 (C), 145.6 (C), 146.5 (CH), 147.3 (CH, m), 164.2 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{13}F_3N_3O_4^+$: 392.0853; found: 392.0859.

3-(2-Bromophenyl)-2-(*tert*-butoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3e)

Compound **3e** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (250 mg, 0.92 mmol), *tert*-butyl 3-(2-bromophenyl)-2*H*-azirine-2-carboxylate **1e** (352 mg, 1.19 mmol) and Et_3N (97 mg, 0.96 mmol).

Yield: 111 mg (26%); beige solid; mp 208–210 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 9 H), 7.07–7.14 (m, 1 H), 7.19–7.25 (m, 1 H), 7.26–7.31 (m, 1 H), 7.45–7.54 (m, 1 H), 8.02–8.12 (m, 2 H), 8.52–8.61 (m, 1 H), 8.82–9.00 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.29.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.6 (CH_3), 77.3 (C), 122.6 (C, q, J = 30.0 Hz), 123.1 (C, q, J = 265.4 Hz), 123.6 (C), 124.2 (C), 124.9 (C), 126.8 (CH), 127.5 (CH), 128.6 (CH), 128.9 (C), 131.6 (CH), 132.2 (CH), 135.8 (C), 146.2 (CH), 146.8 (CH), 162.7 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{21}H_{19}BrF_3N_2O_2^+$: 467.0577; found: 467.0596.

2-(Methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-3-(*p*-tolyl)-5-(trifluoromethyl)pyrrol-1-ide (3f)

Compound **3f** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (300 mg, 1.10 mmol), methyl 3-(*p*-tolyl)-2*H*-azirine-2-carboxylate **1f** (270 mg, 1.43 mmol) and Et_3N (117 mg, 1.15 mmol).

Yield: 126 mg (32%); beige solid; mp >260 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.21 (s, 3 H), 3.55 (s, 3 H), 6.83–7.07 (m, 4 H), 7.98–8.19 (m, 2 H), 8.48–8.69 (m, 1 H), 8.88–9.12 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.49.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.6 (CH_3), 49.9 (CH_3), 123.2 (C, q, J = 266.6 Hz), 123.4 (C, q, J = 34.8 Hz), 124.4 (C), 126.2 (C), 126.6 (C), 127.4 (CH), 128.2 (CH), 129.5 (CH), 130.6 (C), 135.2 (C), 146.1 (CH), 147.4 (CH), 164.4 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2^+$: 361.1158; found: 361.1155.

3-(3,4-Dimethylphenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3g)

Compound **3g** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (300 mg, 1.10 mmol), methyl 3-(3,4-dimethylphenyl)-2*H*-azirine-2-carboxylate **3g** (290 mg, 1.43 mmol) and Et_3N (117 mg, 1.15 mmol) and additionally recrystallized from $CHCl_3$.

Yield: 115 mg (28%); beige solid; mp >230 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.07 (s, 3 H), 2.12 (s, 3 H), 3.56 (s, 3 H), 6.67–7.77 (m, 1 H), 6.84–6.93 (m, 2 H), 8.00–8.15 (m, 2 H), 8.49–8.70 (m, 1 H), 8.82–9.11 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.49.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 18.9 (CH_3), 19.3 (CH_3), 50.0 (CH_3), 123.1 (C, q, J = 266.6 Hz), 123.2 (C, q, J = 35.8 Hz), 124.3 (C), 126.3 (C), 126.4 (C), 126.8 (CH), 127.4 (CH), 128.7 (CH), 130.8 (C), 131.0 (CH), 134.0 (C), 135.0 (C), 146.1 (CH), 147.4 (CH), 164.3 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{20}H_{18}F_3N_2O_2^+$: 375.1315; found: 375.1329.

3-(4-Fluorophenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3h)

Compound **3h** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (400 mg, 1.47 mmol), methyl 3-(4-fluorophenyl)-2*H*-azirine-2-carboxylate **1h** (368 mg, 1.90 mmol) and Et_3N (155 mg, 1.54 mmol).

Yield: 175 mg (33%); beige solid; mp >210 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.56 (s, 3 H), 6.90–7.04 (m, 2 H), 7.06–7.16 (m, 2 H), 8.02–8.14 (m, 2 H), 8.51–8.68 (m, 1 H), 8.94–9.10 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –116.42, 56.60.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 50.0 (CH_3), 114.3 (CH, d, J = 21.2 Hz), 121.1 (C, q, J = 266.6 Hz), 123.3 (C, q, J = 33.8 Hz), 124.4 (C), 125.2 (C), 126.6 (C), 127.5 (CH), 129.9 (C, d, J = 2.8 Hz), 131.6 (CH, d, J = 8.0 Hz), 146.2 (CH), 147.3 (CH), 160.9 (C, d, J = 242.9 Hz), 164.2 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{18}H_{13}F_4N_2O_2^+$: 365.0908; found: 365.0924.

2-(*tert*-Butoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide (3i)

Compound **3i** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (590 mg, 2.16 mmol), *tert*-butyl 3-phenyl-2*H*-azirine-2-carboxylate **1i** (610 mg, 2.81 mmol) and Et_3N (229 mg, 2.27 mmol).

Yield: 293 mg (35%); beige solid; mp 241–243 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (s, 9 H), 7.02–7.20 (m, 5 H), 7.98–8.12 (m, 2 H), 8.46–8.66 (m, 1 H), 8.82–9.12 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.30.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.8 (CH_3), 77.4 (C), 122.9 (C, q, J = 35.0 Hz), 123.3 (C, q, J = 266.3 Hz), 124.0 (C), 125.7 (C), 125.9 (CH), 127.3 (CH), 127.4 (CH), 128.6 (C), 129.8 (CH), 134.5 (C), 145.9 (CH), 147.3 (CH), 165.3 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{21}H_{20}F_3N_2O_2^+$: 389.1471; found: 389.1475.

2-(Methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-3-(thiophen-2-yl)-5-(trifluoromethyl)pyrrol-1-ide (3j)

Compound **3j** was prepared according to the typical procedure from 1-(3,3,3-trifluoro-2,2-dihydroxypropyl)pyridin-1-ium bromide **6** (300 mg, 1.10 mmol), methyl 3-(thiophen-2-yl)-2*H*-azirine-2-carboxylate **1j** (259 mg, 1.43 mmol) and Et_3N (116 mg, 1.15 mmol).

Yield: 125 mg (32%); beige solid; mp > 220 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.61 (s, 3 H), 6.75–6.84 (m, 1 H), 6.85–6.93 (m, 1 H), 7.27–7.41 (m, 1 H), 8.06–8.20 (m, 2 H), 8.58–8.72 (m, 1 H), 8.92–9.22 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.93.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 50.2 (CH_3), 118.0 (C), 122.9 (C, q, J = 268.4 Hz), 123.8 (C, q, J = 35.3 Hz), 124.7 (C), 125.7 (CH), 126.6 (CH), 127.0 (CH), 127.5 (C), 127.6 (CH), 133.9 (C), 146.6 (CH), 147.6 (CH), 164.1 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{16}H_{12}F_3N_2O_2S^+$: 353.0566; found: 353.0582.

Catalytic Hydrogenation of Betaines 3; Typical Procedure

A suspension of 2-(methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3a** (51 mg, 0.15 mmol) and PtO_2 (3 mg, 10 mol%) in MeOH (2 mL) was stirred at r.t. in a hydrogen at-

mosphere overnight (monitored by TLC). The resulting solution was filtered from PtO_2, concentrated in vacuo and purified by column chromatography on silica gel (CH_2Cl_2).

Methyl 3-Phenyl-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4a)

Compound **4a** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3a** (51 mg, 0.15 mmol) and PtO_2 (3 mg, 10 mol%).

Yield: 37 mg (71%); colorless solid; mp 182–184 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23–1.37 (m, 6 H), 2.60–2.71 (m, 4 H), 3.59 (s, 3 H), 7.14–7.46 (m, 5 H), 12.52 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.08.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5 (CH_2), 26.0 (CH_2), 51.2 (CH_3), 53.0 (CH_2), 116.0 (C, q, *J* = 37.5 Hz), 119.0 (C, q, *J* = 1.8 Hz), 121.0 (C, q, *J* = 268.4 Hz), 126.9 (CH), 127.2 (CH), 127.9 (C), 130.5 (CH), 133.7 (C), 138.2 (C, q, *J* = 2.2 Hz), 160.2 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}F_3N_2O_2^+$: 353.1471; found: 353.1483.

Methyl 3-(4-Methoxyphenyl)-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4c)

Compound **4c** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3c** (57 mg, 0.15 mmol) and PtO_2 (3 mg, 10 mol%).

Yield: 42 mg (73%); colorless solid; mp 144–146 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.26–1.39 (m, 6 H), 2.62–2.69 (m, 4 H), 3.60 (s, 3 H), 3.78 (s, 3 H), 6.86–6.96 (m, 2 H), 7.18–7.26 (m, 2 H), 12.43 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.03.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.6 (CH_2), 26.1 (CH_2), 51.2 (CH_3), 52.9 (CH_2), 54.9 (CH_3), 112.7 (CH), 116.0 (C, q, *J* = 37.4 Hz), 119.0 (C, q, *J* = 1.7 Hz), 121.1 (C, q, *J* = 268.3 Hz), 125.7 (C), 127.6 (C), 131.6 (CH), 138.2 (C, q, *J* = 2.2 Hz), 158.2 (C), 160.3 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}F_3N_2O_3^+$: 383.1577; found: 383.1586.

Methyl 3-(4-Aminophenyl)-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate dihydrochloride (4d)

Compound **4d** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-(4-nitrophenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3d** (50 mg, 0.13 mmol) and PtO_2 (3 mg, 10 mol%). Due to low stability of the resulting amine it was dissolved in EtOAc, treated with sat. HCl solution in Et_2O, and the precipitate formed was filtered off, washed and dried.

Yield: 42 mg (75%); colorless solid; mp >210 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25–1.39 (m, 6 H), 2.63–2.70 (m, 4 H), 3.61 (s, 3 H), 7.33–7.39 (m, 2 H), 7.40–7.47 (m, 2 H), 10.19 (s, 1 H), 12.63 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –55.97.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5 (CH_2), 26.1 (CH_2), 51.3 (CH_3), 52.9 (CH_2), 116.2 (C, q, *J* = 37.8 Hz), 119.1 (C, q, *J* = 1.7 Hz), 121.0 (C, q, *J* = 268.6 Hz), 122.2 (CH), 126.6 (C), 130.6 (C), 131.8 (CH), 133.6 (C), 138.1 (C, q, *J* = 2.0 Hz), 160.0 (C).

HRMS-ESI: *m*/*z* [M – 2HCl + H]$^+$ calcd for $C_{18}H_{21}F_3N_3O_2^+$: 368.1580; found: 368.1594.

Methyl 4-(Piperidin-1-yl)-3-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4f)

Compound **4f** was prepared according to the typical procedure from 2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-3-(*p*-tolyl)-5-(trifluoromethyl)pyrrol-1-ide **3f** (91 mg, 0.25 mmol) and PtO_2 (6 mg, 10 mol%).

Yield: 53 mg (57%); colorless solid; mp 172–173 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.25–1.39 (m, 6 H), 2.35 (s, 3 H), 2.61–2.69 (m, 4 H), 3.60 (s, 3 H), 7.14–7.22 (m, 4 H), 12.47 (s, 1 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.09.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 20.9 (CH_3), 23.6 (CH_2), 26.1 (CH_2), 51.2 (CH_3), 53.0 (CH_2), 116.0 (C, q, *J* = 37.3 Hz), 119.0 (C, q, *J* = 1.9 Hz), 121.0 (C, q, *J* = 268.2 Hz), 127.8 (CH), 127.8 (C), 130.4 (CH), 130.7 (C), 135.9 (C), 138.2 (C, q, *J* = 2.4 Hz), 160.2 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}F_3N_2O_2^+$: 367.1628; found: 367.1618.

Methyl 3-(3,4-Dimethylphenyl)-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4g)

Compound **4g** was prepared according to the typical procedure from 3-(3,4-dimethylphenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3g** (76 mg, 0.20 mmol) and PtO_2 (5 mg, 10 mol%).

Yield: 48 mg (62%); colorless solid; mp 181–183 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.24–1.40 (m, 6 H), 2.23 (s, 3 H), 2.25 (s, 3 H), 2.62–2.70 (m, 4 H), 3.60 (s, 3 H), 6.98–7.05 (m, 1 H), 7.06–7.14 (m, 2 H), 12.43 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.09.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1 (CH_3), 19.3 (CH_3), 23.6 (CH_2), 26.1 (CH_2), 51.1 (CH_3), 52.9 (CH_2), 115.9 (C, q, *J* = 37.4 Hz), 118.9 (C, q, *J* = 1.5 Hz), 121.0 (C, q, *J* = 268.5 Hz), 127.88 (CH), 127.92 (C), 128.4 (CH), 130.9 (C), 131.6 (CH), 134.57 (C), 134.62 (C), 131.2 (C, q, *J* = 2.1 Hz), 160.2 (C).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{24}F_3N_2O_2^+$: 381.1784; found: 381.1797.

Methyl 3-(4-Fluorophenyl)-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4h)

Compound **4h** was prepared according to the typical procedure from 3-(4-fluorophenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3h** (40 mg, 0.11 mmol) and PtO_2 (2 mg, 10 mol%).

Yield: 38 mg (93%); colorless solid; mp 192–194 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23–1.40 (m, 6 H), 2.62–2.71 (m, 4 H), 3.60 (s, 3 H), 7.06–7.29 (m, 2 H), 7.30–7.42 (m, 2 H), 12.57 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –115.68, –55.99.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5 (CH_2), 26.0 (CH_2), 51.2 (CH_3), 52.9 (CH_2), 114.1 (CH, d, *J* = 21.3 Hz), 166.0 (C, q, *J* = 37.6 Hz), 119.1 (C), 121.0 (C, q, *J* = 268.4 Hz), 126.7 (C), 129.9 (C, d, *J* = 3.2 Hz), 132.5 (CH, d, *J* = 8.0 Hz), 138.1 (C, q, *J* = 2.1 Hz), 160.1 (C), 161.4 (C, d, *J* = 243.4 Hz).

HRMS-ESI: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{19}F_4N_2O_2^+$: 371.1377; found: 371.1383.

tert-Butyl 3-Phenyl-4-(piperidin-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (4i)

Compound **4i** was prepared according to the typical procedure from 2-(*tert*-butoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3i** (60 mg, 0.15 mmol) and PtO_2 (4 mg, 10 mol%).

Yield: 44 mg (72%); colorless solid; mp 151–153 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.18 (s, 9 H), 1.22–1.28 (m, 2 H), 1.29–1.37 (m, 4 H), 2.60–2.69 (m, 4 H), 7.23–7.40 (m, 5 H), 12.36 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.20.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.5 (CH_2), 26.1 (CH_2), 27.4 (CH_3), 53.2 (CH_2), 80.3 (C), 115.6 (C, q, J = 37.1 Hz), 121.0 (C, q, J = 1.8 Hz), 121.1 (C, q, J = 268.3 Hz), 126.6 (CH), 127.1 (CH), 127.3 (C), 130.5 (CH), 134.6 (H), 138.1 (C, q, J = 2.1 Hz), 159.6 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{21}H_{26}F_3N_2O_2^+$: 395.1941; found: 395.1938.

1-(5-(Methoxycarbonyl)-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Bromide (8a)

HBr (48%, 1 mL) was added to a solution of 2-(methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3a** (30 mg, 0.087 mmol) in MeOH (2 mL). The reaction mixture was stirred for 10 minutes, concentrated in vacuo, washed with Et_2O and dried.

Yield: 37 mg (97%); gray solid; mp 200–202 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.74 (s, 3 H), 7.16–7.23 (m, 2 H), 7.25–7.32 (m, 3 H), 8.20–8.32 (m, 2 H), 8.74–8.83 (m, 1 H), 9.23–9.35 (m, 2 H), 14.56 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –57.07.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.2 (CH_3), 117.5 (C, q, J = 39.8 Hz), 119.34 (C, q, J = 269.5 Hz), 120.7 (C, q, J = 1.0 Hz), 126.0 (C, q, J = 2.2 Hz), 126.4 (C), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.6 (C), 129.6 (CH), 147.4 (CH), 148.8 (CH), 159.6 (C).

HRMS-ESI: m/z [M – Br]$^+$ calcd for $C_{18}H_{14}F_3N_2O_2^+$: 347.1002; found: 347.1017.

1-(4-(2-Bromophenyl)-5-carboxy-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Bromide (8e)

HBr (48%, 1 mL) was added to a solution of 3-(2-bromophenyl)-2-(*tert*-butoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3e** (80 mg, 0.17 mmol) in MeOH (2 mL). The reaction mixture was stirred for 10 minutes, concentrated in vacuo, washed with Et_2O and dried.

Yield: 83 mg (99%); gray solid; mp 274–276 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.21–7.29 (m, 1 H), 7.31–7.38 (m, 1 H), 7.40–7.48 (m, 1 H), 7.54–7.63 (m, 1 H), 8.19–8.34 (m, 2 H), 8.67–8.86 (m, 1 H), 9.06–9.42 (m, 2 H), 13.59 (s, 1 H), 14.62 (s, 1 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.90.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 116.9 (C, q, J = 39.9 Hz), 119.4 (C, q, J = 269.5 Hz), 123.1 (C), 123.8 (C), 124.3 (C), 125.7 (C, q, J = 1.5 Hz), 127.6 (CH), 128.3 (CH), 130.2 (C), 130.8 (CH), 132.2 (CH), 132.3 (CH), 147.2 (CH), 149.0 (CH), 160.3 (C).

HRMS-ESI: m/z [M – Br]$^+$ calcd for $C_{17}H_{11}BrF_3N_2O_2^+$: 410.9951; found: 410.9968.

1-(5-Carboxy-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Bromide (8i)

HBr (48%, 1 mL) was added to a solution of 2-(*tert*-butoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3i** (67 mg, 0.17 mmol) in MeOH (2 mL). The reaction mixture was stirred for 10 minutes, concentrated in vacuo, washed with CH_2Cl_2 and dried.

Yield: 63 mg (89%); gray solid; mp 259–261 °C (MeOH).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.17–7.23 (m, 2 H), 7.24–7.32 (m, 3 H), 8.20–8.31 (m, 2 H), 8.72–8.82 (m, 1 H), 9.24–9.35 (m, 2 H), 13.52 (s, 1 H), 14.38 (s, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –57.00.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 116.9 (C, q, J = 39.6 Hz), 119.5 (C, q, J = 269.2 Hz), 122.0 (C), 125.9 (C), 126.0 (C, q, J = 1.7 Hz), 128.1 (CH), 128.3 (CH), 128.3 (CH), 129.0 (C), 129.8 (CH), 147.5 (CH), 148.7 (CH), 160.6 (C).

HRMS-ESI: m/z [M – Br]$^+$ calcd for $C_{17}H_{12}F_3N_2O_2^+$: 333.0845; found: 333.0862.

3-Phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (9)

Et_3N (28 mg, 0.28 mmol, 2 equiv) was added to a solution of 1-(5-carboxy-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium bromide **7i** (57 mg, 0.14 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 24 h, filtered off, washed with CH_2Cl_2 and dried.

Yield: 42 mg (92%); colorless solid; mp 221–223 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04–7.20 (m, 5 H), 7.99–8.17 (m, 2 H), 8.54–8.67 (m, 1 H), 8.95–9.11 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.36.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 122.1 (C, q, J = 35.4 Hz), 123.0 (C, q, J = 268.1 Hz), 124.7 (C, q, J = 1.5 Hz), 125.2 (C), 126.2 (CH), 127.4 (C), 127.5 (CH), 127.5 (CH), 129.7 (CH), 133.5 (C), 146.3 (CH), 147.4 (CH), 164.5 (C).

HRMS-ESI: m/z [M – Br]$^+$ calcd for $C_{17}H_{12}F_3N_2O_2^+$: 333.0845; found: 333.0831.

***N*-Methylation of Betaines 3a–j; Typical Procedure**

MeI (156 mg, 1.09 mmol, 10 equiv) was added to a solution of 2-(methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3a** (38 mg, 0.11 mmol) in MeCN (3 mL) and the reaction mixture was stirred for 2 h at 45 °C. The resulting mixture was concentrated in vacuo to obtain pure solid product **10a**.

1-(5-(Methoxycarbonyl)-1-methyl-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10a)

Compound **9a** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3a** (38 mg, 0.11 mmol) and MeI (156 mg, 1.09 mmol).

Yield: 48 mg (90%); orange solid; mp 151–153 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.63 (s, 3 H), 4.11 (s, 3 H), 7.06–7.18 (m, 2 H), 7.25–7.34 (m, 3 H), 8.20–8.32 (m, 2 H), 8.72–8.85 (m, 1 H), 9.23–9.41 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.70.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 36.0 (CH_3, q, J = 1.6 Hz), 52.3 (CH_3), 118.4 (C, q, J = 37.5 Hz), 119.5 (C, q, J = 270.0 Hz), 123.3 (C, q, J = 1.6 Hz), 126.0 (C, q, J = 1.4 Hz), 126.4 (C), 128.3 (CH), 128.3 (CH), 128.5 (CH), 128.8 (C), 129.3 (CH), 147.4 (CH), 148.9 (CH), 159.8 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{19}H_{16}F_3N_2O_2^+$: 361.1158; found: 361.1171.

1-(4-(4-Bromophenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10b)

Compound **10b** was prepared according to the typical procedure from 3-(4-bromophenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3b** (49 mg, 0.12 mmol) and MeI (164 mg, 1.15 mmol).

Yield: 64 mg (98%); orange solid; mp 100–102 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.66 (s, 3 H), 4.11 (s, 3 H), 7.07–7.15 (m, 2 H), 7.47–7.54 (m, 2 H), 8.23–8.32 (m, 2 H), 8.74–8.90 (m, 1 H), 9.23–9.35 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.73.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1 (CH_3, q, *J* = 2.4 Hz), 52.4 (CH_3), 118.6 (C, q, *J* = 37.3 Hz), 119.4 (C, q, *J* = 268.4 Hz), 122.1 (C), 123.3 (C, q, *J* = 1.7 Hz), 125.2 (C), 125.8 (C, q, *J* = 2.3 Hz), 128.1 (C), 128.4 (CH), 131.3 (CH), 131.5 (CH), 147.4 (CH), 149.0 (CH), 159.7 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{19}H_{15}BrF_3N_2O_2^+$: 439.0264; found: 439.0264.

1-(5-(Methoxycarbonyl)-4-(4-methoxyphenyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10c)

Compound **10c** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-(4-methoxyphenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3c** (38 mg, 0.10 mmol) and MeI (142 mg, 1.00 mmol).

Yield: 47 mg (92%); orange solid; mp 85–87 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.65 (s, 3 H), 3.70 (s, 3 H), 4.09 (s, 3 H), 6.79–6.86 (m, 2 H), 7.01–7.09 (m, 2 H), 8.22–8.31 (m, 2 H), 8.75–8.83 (m, 1 H), 9.24–9.32 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.67.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.0 (CH_3, q, *J* = 2.2 Hz), 52.3 (CH_3), 55.0 (CH_3), 113.7 (CH), 118.3 (C, q, *J* = 37.5 Hz), 119.5 (C, q, *J* = 270.0 Hz), 120.5 (C), 123.3 (C, q, *J* = 2.4 Hz), 126.1 (C, q, *J* = 1.9 Hz), 126.2 (C), 128.3 (CH), 130.6 (CH), 147.5 (CH), 148.8 (CH), 159.1 (C), 159.9 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{20}H_{18}F_3N_2O_3^+$: 391.1264; found: 391.1258.

1-(5-(Methoxycarbonyl)-1-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10d)

Compound **10d** was prepared according to the typical procedure from 2-(methoxycarbonyl)-3-(4-nitrophenyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3d** (33 mg, 0.084 mmol) and MeI (120 mg, 0.84 mmol).

Yield: 44 mg (98%); orange solid; mp 84–86 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.65 (s, 3 H), 4.14 (s, 3 H), 7.40–7.51 (m, 2 H), 8.09–8.20 (m, 2 H), 8.23–8.33 (m, 2 H), 8.74–8.96 (m, 1 H), 9.25–9.39 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.80.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.2 (CH_3, q, *J* = 2.3 Hz), 52.5 (CH_3), 119.0 (C, q, *J* = 37.4 Hz), 119.3 (C, q, *J* = 268.5 Hz), 123.3 (CH), 123.5 (C), 124.5 (C), 125.7 (C, q, *J* = 1.9 Hz), 128.5 (CH), 131.0 (CH), 135.9 (C), 147.29 (C), 147.33 (CH), 149.1 (CH), 159.4 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{19}H_{15}F_3N_3O_4^+$: 406.1009; found: 406.0995.

1-(4-(2-Bromophenyl)-5-(*tert*-butoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10e)

Compound **10e** was prepared according to the typical procedure from 3-(2-bromophenyl)-2-(*tert*-butoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3e** (27 mg, 0.058 mmol) and MeI (82 mg, 0.58 mmol).

Yield: 34 mg (97%); ochre solid; mp 178–180 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 9 H), 4.16 (s, 3 H), 7.23–7.32 (m, 1 H), 7.33–7.44 (m, 2 H), 7.58–7.66 (m, 1 H), 8.17–8.36 (m, 2 H), 8.70–8.86 (m, 1 H), 9.07–9.22 (m, 1 H), 9.25–9.47 (m, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.65.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.0 (CH_3), 34.9 (C, q, *J* = 2.0 Hz), 82.5 (C), 118.4 (C, q, *J* = 37.8 Hz), 119.4 (C, q, *J* = 270.2 Hz), 123.7 (C), 124.4 (C, q, *J* = 1.9 Hz), 125.0 (C), 125.6 (C, q, *J* = 1.7 Hz), 127.6 (CH), 128.3 (CH), 128.4 (CH), 130.7 (C), 130.8 (CH), 131.8 (CH), 132.2 (CH), 147.08 (CH), 147.10 (CH), 149.2 (CH), 158.0 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{22}H_{21}BrF_3N_2O_2^+$: 481.0733; found: 481.0750.

1-(5-(Methoxycarbonyl)-1-methyl-4-(*p*-tolyl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10f)

Compound **10f** was prepared according to the typical procedure from 2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-3-(*p*-tolyl)-5-(trifluoromethyl)pyrrol-1-ide **3f** (40 mg, 0.11 mmol) and MeI (162 mg, 1.14 mmol).

Yield: 51 mg (91%); yellow solid; mp 63–65 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 3.64 (s, 3 H), 4.09 (s, 3 H), 6.95–7.05 (m, 2 H), 7.05–7.15 (m, 2 H), 8.19–8.34 (m, 2 H), 8.72–8.89 (m, 1 H), 9.20–9.39 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.68.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.7 (CH_3), 35.0 (CH_3, q, *J* = 2.1 Hz), 52.3 (CH_3), 118.4 (C, q, *J* = 37.2 Hz), 119.5 (C, q, *J* = 268.4 Hz), 123.3 (C, q, *J* = 1.9 Hz), 125.7 (C), 126.0 (C, q, *J* = 1.7 Hz), 126.3 (C), 128.3 (CH), 128.9 (CH), 129.1 (CH), 137.8 (C), 147.5 (CH), 148.9 (CH), 159.9 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{20}H_{18}F_3N_2O_2^+$: 375.1315; found: 375.1332.

1-(4-(3,4-Dimethylphenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10g)

Compound **10g** was prepared according to the typical procedure from 3-(3,4-dimethylphenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3g** (52 mg, 0.14 mmol) and MeI (197 mg, 1.39 mmol).

Yield: 69 mg (96%); yellow solid; mp 191–193 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.10 (s, 3 H), 2.14 (s, 3 H), 3.65 (s, 3 H), 4.08 (s, 3 H), 6.76–6.84 (m, 1 H), 6.85–6.94 (m, 1 H), 6.97–7.06 (m, 1 H), 8.21–8.32 (m, 2 H), 8.73–8.84 (m, 1 H), 9.23–9.35 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.67.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 19.0 (CH_3), 19.2 (CH_3), 35.0 (CH_3, q, *J* = 2.3 Hz), 52.3 (CH_3), 118.3 (C, q, *J* = 37.2 Hz), 119.5 (C, q, *J* = 270.1 Hz), 123.3 (C, q, *J* = 1.6 Hz), 125.9 (C, q, *J* = 1.2 Hz), 126.0 (C), 126.2 (C), 126.5 (CH), 128.3 (CH), 129.4 (CH), 130.1 (CH), 136.1 (C), 136.6 (C), 147.5 (CH), 148.9 (CH), 160.0 (C).

HRMS-ESI: *m*/*z* [M – I]$^+$ calcd for $C_{21}H_{20}F_3N_2O_2^+$: 389.1471; found: 389.1489.

1-(4-(4-Fluorophenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10h)

Compound **10h** was prepared according to the typical procedure from 3-(4-fluorophenyl)-2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3h** (81 mg, 0.22 mmol) and MeI (316 mg, 2.22 mmol).

Yield: 108 mg (96%); yellow solid; mp 46–48 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.64 (s, 3 H), 4.12 (s, 3 H), 7.07–7.16 (m, 2 H), 7.17–7.27 (m, 2 H), 8.21–8.33 (m, 2 H), 8.73–8.87 (m, 1 H), 9.22–9.35 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –112.96, –56.71.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1 (CH_3, q, J = 2.3 Hz), 52.3 (CH_3), 115.2 (CH, d, J = 21.8 Hz), 118.5 (C, q, J = 37.5 Hz), 119.4 (C, q, J = 268.5 Hz), 123.3 (C, q, J = 1.7 Hz), 125.1 (C, d, J = 3.1 Hz), 125.6 (C), 126.0 (C, q, J = 2.1 Hz), 128.3 (CH), 131.6 (CH, d, J = 8.5 Hz), 147.4 (CH), 148.9 (CH), 159.7 (C), 161.9 (C, d, J = 245.9 Hz).

HRMS-ESI: m/z [M – I]$^+$ calcd for $C_{19}H_{15}F_4N_2O_2^+$: 379.1064; found: 379.1059.

1-(5-(*tert*-Butoxycarbonyl)-1-methyl-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium Iodide (10i)

Compound **10i** was prepared according to the typical procedure from 2-(*tert*-butoxycarbonyl)-3-phenyl-4-(pyridin-1-ium-1-yl)-5-(trifluoromethyl)pyrrol-1-ide **3i** (54 mg, 0.14 mmol) and MeI (198 mg, 1.40 mmol).

Yield: 65 mg (88%); ochre solid; mp 174–176 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.17 (s, 9 H), 4.10 (s, 3 H), 7.14–7.21 (m, 2 H), 7.27–7.35 (m, 3 H), 8.20–8.30 (m, 2 H), 8.71–8.82 (m, 1 H), 9.22–9.37 (m, 2 H).

^{19}F NMR (470 MHz, DMSO-d_6): δ = –56.70.

^{13}C NMR (125 MHz, DMSO-d_6): δ = 27.1 (CH_3), 34.7 (CH_3, q, J = 1.6 Hz), 82.7 (C), 118.0 (C, q, J = 37.5 Hz), 119.5 (C, q, J = 269.9 Hz), 124.4 (C, q, J = 2.2 Hz), 125.9 (C, q, J = 1.6 Hz), 126.3 (C), 128.21 (CH), 128.25 (CH), 128.3 (CH), 129.37 (C), 129.43 (CH), 147.3 (CH), 148.8 (CH), 158.5 (C).

HRMS-ESI: m/z [M – I]$^+$ calcd for $C_{22}H_{22}F_3N_2O_2^+$: 403.1628; found: 403.1636.

1-(5-(Methoxycarbonyl)-1-methyl-4-(thiophen-2-yl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide (10j)

Compound **10j** was prepared according to the typical procedure from 2-(methoxycarbonyl)-4-(pyridin-1-ium-1-yl)-3-(thiophen-2-yl)-5-(trifluoromethyl)pyrrol-1-ide **3j** (38 mg, 0.11 mmol) and MeI (152 mg, 1.07 mmol).

Yield: 49 mg (92%); brown solid; mp 58–60 °C (MeCN).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.74 (s, 3 H), 4.08 (s, 3 H), 6.82–7.06 (m, 2 H), 7.46–7.67 (m, 1 H), 8.18–8.45 (m, 2 H), 8.70–8.96 (m, 1 H), 9.21–9.48 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –56.89.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 35.1 (CH_3), 52.6 (CH_3), 118.7 (C, q, J = 37.2 Hz), 118.8 (C), 119.3 (C, q, J = 270.1 Hz), 124.3 (C), 126.2 (C), 127.3 (CH), 127.7 (C), 128.4 (CH), 128.7 (CH), 129.4 (CH), 147.6 (CH), 149.1 (CH), 159.6 (C).

HRMS-ESI: m/z [M – I]$^+$ calcd for $C_{17}H_{14}F_3N_2O_2S^+$: 367.0723; found: 367.0723.

Synthesis of 3-Amino-2-trifluoromethyl-pyrroles 11a–j; Typical Procedure

Hydrazine hydrate (38 mg, 0.76 mmol, 10 equiv) was added to a solution of 1-(5-(methoxycarbonyl)-1-methyl-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10a** (37 mg, 0.076 mmol) in MeCN (2 mL) and the reaction mixture was stirred for 3–6 h at 45 °C (monitored by TLC). After completion of the reaction the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (CH_2Cl_2) to give **11a**.

Methyl 4-Amino-1-methyl-3-phenyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11a)

Compound **11a** was prepared according to the typical procedure from 1-(5-(methoxycarbonyl)-1-methyl-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10a** (37 mg, 0.076 mmol) and $N_2H_4{\cdot}H_2O$ (38 mg, 0.76 mmol).

Yield: 17 mg (75%); colorless solid; mp 46–48 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.51 (s, 3 H), 3.77 (s, 3 H), 4.01 (s, 2 H), 7.17–7.24 (m, 2 H), 7.30–7.36 (m, 1 H), 7.37–7.43 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.66.

^{13}C NMR (100 MHZ, DMSO-d_6): δ = 33.20 (CH_3, q, J = 2.4 Hz), 51.3 (CH_3), 106.7 (C, q, J = 35.8 Hz), 118.6 (C), 122.6 (C, q, J = 2.3 Hz), 122.6 (C, q, J = 267.3 Hz), 127.0 (CH), 128.2 (CH), 129.7 (CH), 132.5 (C), 133.2 (C, q, J = 2.1 Hz), 161.0 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_{14}F_3N_2O_2^+$: 299.1002; found: 299.1016.

Methyl 4-Amino-3-(4-bromophenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11b)

Compound **11b** was prepared according to the typical procedure from 1-(4-(4-bromophenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10b** (55 mg, 0.097 mmol) and $N_2H_4{\cdot}H_2O$ (49 mg, 0.97 mmol).

Yield: 35 mg (97%); colorless solid; mp 101–103 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.54 (s, 3 H), 3.77 (s, 3 H), 4.10 (s, 2 H), 7.11–7.22 (m, 2 H), 7.52–7.63 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.66.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.3 (CH_3, q, J = 2.4 Hz), 51.4 (CH_3), 106.7 (C, q, J = 35.8 Hz), 117.3 (C), 120.3 (C), 122.5 (C, q, J = 2.4 Hz), 122.5 (C, q, J = 267.2 Hz), 131.1 (CH), 131.9 (C), 132.1 (CH), 133.2 (C, q, J = 1.9 Hz), 160.8 (C).

HRMS-ESI: m/z [M + H]$^+$ 377.0107 calcd for $C_{14}H_{13}BrF_3N_2O_2^+$: 377.0107; found: 377.0121.

Methyl 4-Amino-3-(4-methoxyphenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11c)

Compound **11c** was prepared according to the typical procedure from 1-(5-(methoxycarbonyl)-4-(4-methoxyphenyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10c** (36 mg, 0.069 mmol) and $N_2H_4{\cdot}H_2O$ (35 mg, 0.69 mmol).

Yield: 18 mg (81%); colorless oil.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.53 (s, 3 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 3.97 (s, 2 H), 6.89–7.03 (m, 2 H), 7.07–7.22 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.64.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.2 (CH_3, q, J = 2.3 Hz), 51.3 (CH_3), 55.0 (CH_3), 106.6 (C, q, J = 36.0 Hz), 113.7 (CH), 118.4 (C), 122.6 (C, q, J = 2.3 Hz), 122.6 (C, q, J = 267.2 Hz), 124.4 (C), 131.0 (CH), 133.3 (C, q, J = 2.2 Hz), 158.2 (C), 161.0 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{15}H_{16}F_3N_2O_3^+$: 329.1108; found: 329.1116.

Methyl 4-Amino-1-methyl-3-(4-nitrophenyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11d)

Compound **11d** was prepared according to the typical procedure from 1-(5-(methoxycarbonyl)-1-methyl-4-(4-nitrophenyl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10d** (38 mg, 0.071 mmol) and $N_2H_4{\cdot}H_2O$ (35 mg, 0.71 mmol).

Yield: 22 mg (90%); yellow solid; mp 128–130 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.54 (s, 3 H), 3.80 (s, 3 H), 4.27 (s, 2 H), 7.48–7.55 (m, 2 H), 8.19–8.29 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.70.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.4 (CH_3, q, J = 2.4 Hz), 51.5 (CH_3), 106.9 (C, q, J = 35.9 Hz), 116.4 (C), 122.5 (C, q, J = 267.4 Hz), 122.7 (C, q, J = 2.3 Hz), 123.2 (CH), 131.2 (CH), 133.4 (C, q, J = 2.2 Hz), 140.2 (C), 146.1 (C), 160.5 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_{13}F_3N_3O_4^+$: 344.0853; found: 344.0860.

***tert*-Butyl 4-Amino-3-(2-bromophenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11e)**

Compound **11e** was prepared according to the typical procedure from 1-(4-(2-bromophenyl)-5-(*tert*-butoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10e** (40 mg, 0.066 mmol) and $N_2H_4{\cdot}H_2O$ (33 mg, 0.66 mmol).

Yield: 21 mg (78%); colorless solid; mp 103–105 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09 (s, 9 H), 3.81 (s, 3 H), 3.89 (s, 2 H), 7.21–7.26 (m, 1 H), 7.27–7.33 (m, 1 H), 7.39–7.45 (m, 1 H), 7.66–7.73 (m, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.51.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.2 (CH_3), 32.9 (CH_3, q, J = 2.3 Hz), 80.5 (C), 106.3 (C, q, J = 36.0 Hz), 117.8 (C), 122.6 (C, q, J = 267.2 Hz), 123.5 (C, q, J = 2.2 Hz), 125.1 (C), 127.6 (CH), 129.2 (CH), 132.2 (CH), 132.3 (CH), 133.2 (C, q, J = 1.8 Hz), 134.7 (C), 159.3 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{17}H_{19}BrF_3N_2O_2^+$: 419.0577; found: 419.0561.

Methyl 4-Amino-1-methyl-3-(*p*-tolyl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11f)

Compound **11f** was prepared according to the typical procedure from 1-(5-(methoxycarbonyl)-1-methyl-4-(*p*-tolyl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10f** (37 mg, 0.074 mmol) and $N_2H_4{\cdot}H_2O$ (37 mg, 0.74 mmol).

Yield: 21 mg (93%); colorless solid; mp 70–71 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.33 (s, 3 H), 3.52 (s, 3 H), 3.76 (s, 3 H), 3.98 (s, 2 H), 7.04–7.14 (m, 2 H), 7.16–7.26 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.64.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.8 (CH_3), 33.2 (CH_3, q, J = 2.4 Hz), 51.3 (CH_3), 106.6 (C, q, J = 36.0 Hz), 118.5 (C), 122.6 (C, q, J = 267.1 Hz), 122.6 (C, q, J = 2.4 Hz), 128.8 (CH), 129.4 (C), 129.6 (CH), 133.2 (C, q, J = 2.0 Hz), 136.1 (C), 161.0 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{15}H_{16}F_3N_2O_2^+$: 313.1158; found: 313.1150.

Methyl 4-Amino-3-(3,4-dimethylphenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11g)

Compound **11g** was prepared according to the typical procedure from 1-(4-(3,4-dimethylphenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10g** (45 mg, 0.087 mmol) and $N_2H_4{\cdot}H_2O$ (44 mg, 0.87 mmol).

Yield: 25 mg (89%); colorless solid; mp 79–81 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.23 (s, 3 H), 2.24 (s, 3 H), 3.52 (s, 3 H), 3.75 (s, 3 H), 3.97 (s, 2 H), 6.86–6.93 (m, 1 H), 6.95–7.01 (m, 1 H), 7.11–7.20 (m, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.63.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.1 (CH_3), 19.3 (CH_3), 33.2 (CH_3, q, J = 2.3 Hz), 51.3 (CH_3), 106.5 (C, q, J = 36.0 Hz), 118.6 (C), 122.6 (C, q, J = 267.3 Hz), 122.6 (C, q, J = 2.2 Hz), 121.7 (CH), 129.3 (CH), 129.8 (C), 130.6 (CH), 133.2 (C, q, J = 1.9 Hz), 134.8 (C), 135.9 (C), 161.1 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{16}H_{18}F_3N_2O_2^+$: 327.1315; found: 327.1329.

Methyl 4-Amino-3-(4-fluorophenyl)-1-methyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11h)

Compound **11h** was prepared according to the typical procedure from 1-(4-(4-fluorophenyl)-5-(methoxycarbonyl)-1-methyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10h** (67 mg, 0.13 mmol) and $N_2H_4{\cdot}H_2O$ (66 mg, 1.32 mmol).

Yield: 39 mg (94%); colorless solid; mp 99–101 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.52 (s, 3 H), 3.78 (s, 3 H), 4.05 (s, 2 H), 7.10–7.37 (m, 4 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –115.53, –53.67.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.3 (CH_3, q, J = 2.4 Hz), 51.3 (CH_3), 106.7 (C, q, J = 35.9 Hz), 115.0 (CH, d, J = 21.3 Hz), 117.6 (C), 122.6 (C, q, J = 267.2 Hz), 122.6 (C, q, J = 2.3 Hz), 128.8 (C, d, J = 3.2 Hz), 131.9 (CH, d, J = 8.3 Hz), 133.4 (C, q, J = 1.5 Hz), 160.8 (C), 161.3 (C, d, J = 243.4 Hz).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{14}H_{13}F_4N_2O_2^+$: 317.0908; found: 317.0922.

***tert*-Butyl 4-Amino-1-methyl-3-phenyl-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11i)**

Compound **11i** was prepared according to the typical procedure from 1-(5-(*tert*-butoxycarbonyl)-1-methyl-4-phenyl-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10i** (39 mg, 0.074 mmol) and $N_2H_4{\cdot}H_2O$ (37 mg, 0.74 mmol).

Yield: 19 mg (76%): colorless solid; mp 52–54 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.14 (s, 9 H), 3.75 (s, 3 H), 3.93 (s, 2 H), 7.15–7.22 (m, 2 H), 7.31–7.37 (m, 1 H), 7.38–7.45 (m, 2 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.55.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 27.4 (CH_3), 33.1 (CH_3, q, J = 2.5 Hz), 81.1 (C), 106.2 (C, q, J = 35.9 Hz), 118.6 (C), 122.9 (C, q, J = 267.1 Hz), 124.2 (C, q, J = 2.5 Hz), 127.1 (CH), 128.4 (CH), 130.2 (CH), 133.3 (C, q, J = 1.6 Hz), 133.3 (C), 160.0 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{17}H_{20}F_3N_2O_2^+$: 341.1471; found: 341.1481.

Methyl 4-Amino-1-methyl-3-(thiophen-2-yl)-5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate (11j)

Compound **11j** was prepared according to the typical procedure from 1-(5-(methoxycarbonyl)-1-methyl-4-(thiophen-2-yl)-2-(trifluoromethyl)-1*H*-pyrrol-3-yl)pyridin-1-ium iodide **10j** (30 mg, 0.061 mmol) and $N_2H_4{\cdot}H_2O$ (30 mg, 0.61 mmol).

Yield: 16 mg (89%); colorless solid; mp 63–65 °C (CH_2Cl_2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.60 (s, 3 H), 3.75 (s, 3 H), 4.18 (s, 2 H), 6.97–7.02 (m, 1 H), 7.09–7.14 (m, 1 H), 7.51–7.54 (m, 1 H).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –53.77.

^{13}C NMR (100 MHz, DMSO-d_6): δ = 33.4 (CH_3, q, J = 2.7 Hz), 51.6 (CH_3), 106.3 (C, q, J = 36.3 Hz), 110.3 (C), 122.4 (C, q, J = 267.1 Hz), 123.6 (C, q, J = 2.6 Hz), 126.6 (CH), 127.2 (CH), 127.7 (CH), 132.5 (C), 134.1 (C, q, J = 1.8 Hz), 160.7 (C).

HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{12}H_{12}F_3N_2O_2S^+$: 305.0566; found: 305.0575.

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Supporting Information

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References

(1) For a recent review, see: (a) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. *RSC Adv.* **2015**, *5*, 15233. (b) Clive, D. L. J.; Cheng, P. *Tetrahedron* **2013**, *69*, 5067. (c) Wu, Y.-J. *Heterocycles and Medicine: A Survey of Heterocyclic Drugs Approved by U.S. FDA from 2000 to Present*, In *Progress in Heterocyclic Chemistry*; Gribble, G. W.; Joule, J. A., Ed.; Elsevier: Oxford, **2012**, 1–54. (d) Shinohara, K.-I.; Bando, T.; Sugiyama, H. *Anti-Cancer Drugs* **2010**, *21*, 228. (e) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. *Chem. Rev.* **2010**, *110*, 6595. (f) Young, I. S.; Thornton, P. D.; Thompson, A. *Nat. Prod. Rep.* **2010**, *27*, 1801.

(2) For a recent review, see: (a) Olivier, W. J.; Smith, J. A.; Bissember, A. C. *Org. Biomol. Chem.* **2018**, *16*, 1216. (b) Trofimov, B. A.; Mikhaleva, A. I.; Schmidt, E. Yu.; Sobenina, L. N. *Chemistry of Pyrroles* **2014**, 398. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633. (d) Yurovskaya, M. A.; Alekseyev, R. S. *Chem. Heterocycl. Compd.* **2014**, *49*, 1400. (e) Sobenina, L. N.; Tomilin, D. N.; Trofimov, B. A. *Russ. Chem. Rev.* **2014**, *83*, 475.

(3) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320.

(4) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, **2013**, 379.

(5) Nenajdenko, V.; Muzalevskiy, V. M.; Serdyuk, O. V. *Chemistry of Fluorinated Pyrroles*, In *Fluorine in Heterocyclic Chemistry*; Nenajdenko, V., Ed.; Springer: Switzerland, **2014**, 55–116.

(6) For recent examples, see: (a) Sommer, H.; Braun, M.; Schröder, B.; Kirschning, A. *Synlett* **2018**, *29*, 121. (b) Rahmani, F.; Darehkordi, A. *Synlett* **2017**, *28*, 1224. (c) Huang, C.; Zeng, Y.; Cheng, H.; Hu, A.; Liu, L.; Xiao, Y.; Zhang, J. *Org. Lett.* **2017**, *19*, 4968.

(7) Cirrincione, G.; Almerico, A. M.; Aiello, E.; Dattolo, G. *Aminopyrroles*, In *Chemistry of Heterocyclic Compounds, Pyrroles, Pt. 2*; Jones, R. A., Ed.; John Wiley & Sons, Inc: Chichester, **1992**, 299–523.

(8) Jacobs, J.; Van Hende, E.; Claessens, S.; De Kimpe, N. *Curr. Org. Chem.* **2011**, *15*, 1340.

(9) Khlebnikov, A. F.; Golovkina, M. V.; Novikov, M. S.; Yufit, D. S. *Org. Lett.* **2012**, *14*, 3768.

(10) (a) Khlebnikov, A. F.; Tomashenko, O. A.; Funt, L. D.; Novikov, M. S. *Org. Biomol. Chem.* **2014**, *12*, 6598. (b) Galenko, E. E.; Tomashenko, O. A.; Khlebnikov, A. F.; Novikov, M. S. *Beilstein J. Org. Chem.* **2015**, *11*, 1732. (c) Tomashenko, O. A.; Novikov, M. S.; Khlebnikov, A. F. *J. Org. Chem.* **2017**, *82*, 616.

(11) (a) Funt, L. D.; Tomashenko, O. A.; Khlebnikov, A. F.; Novikov, M. S.; Ivanov, Yu. A. *J. Org. Chem.* **2016**, *81*, 11210. (b) Funt, L. D.; Tomashenko, O. A.; Mosiagin, I. P.; Novikov, M. S.; Khlebnikov, A. F. *J. Org. Chem.* **2017**, *82*, 7583.

(12) Funt, L. D.; Novikov, M. S.; Starova, G. L.; Khlebnikov, A. F. *Tetrahedron* **2018**, *74*, 2466.

(13) (a) Zincke, T.; Heuser, G.; Möller, W. *Justus Liebigs Ann. Chem.* **1904**, *333*, 296. (b) Zincke, T. *Justus Liebigs Ann. Chem.* **1904**, *330*, 361. (c) Zincke, T.; Wurker, W. *Justus Liebigs Ann. Chem.* **1905**, *338*, 107.

(14) (a) Galenko, E. E.; Tomashenko, O. A.; Khlebnikov, A. F.; Novikov, M. S. *Org. Biomol. Chem.* **2015**, *13*, 9825. (b) Galenko, E. E.; Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Shakirova, J. R. *J. Org. Chem.* **2016**, *81*, 8495. (c) Galenko, E. E.; Galenko, A. V.; Novikov, M. S.; Khlebnikov, A. F.; Kudryavtsev, I. V.; Terpilowski, M. A.; Serebriakova, M. K.; Trulioff, A. S.; Goncharov, N. V. *ChemistrySelect* **2017**, *2*, 7508.

(15) Galenko, A. V.; Khlebnikov, A. F.; Novikov, M. S.; Avdontseva, M. S. *Tetrahedron* **2015**, *71*, 1940.

(16) Wittmann, H.; Ziegler, E.; Peters, K.; Peters, E. M.; von Schnering, H. G. *Monatsh. Chem.* **1983**, *114*, 1097.

(17) CCDC 1826517 (**3a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

(18) Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem.* **2014**, *57*, 10257.

(19) Smetanin, I. A.; Novikov, M. S.; Agafonova, A. V.; Rostovskii, N. V.; Khlebnikov, A. F.; Kudryavtsev, I. V.; Terpilowski, M. A.; Serebriakova, M. K.; Trulioff, A. S.; Goncharov, N. V. *Org. Biomol. Chem.* **2016**, *14*, 4479.

(20) Rostovskii, N. V.; Agafonova, A. V.; Smetanin, I. A.; Novikov, M. S.; Khlebnikov, A. F.; Ruvinskaya, J. O.; Starova, G. L. *Synthesis* **2017**, *49*, 4478.

(21) An, D.; Guan, X.; Guan, R.; Jin, L.; Zhang, G.; Zhang, S. *Chem. Commun.* **2016**, 11211.

(22) Loy, N. S. I.; Singh, A.; Xu, X.; Park, C.-M. *Angew. Chem. Int. Ed.* **2013**, *52*, 2212.

(23) Rostovskii, N. V.; Ruvinskaya, J. O.; Novikov, M. S.; Khlebnikov, A. F.; Smetanin, I. A.; Agafonova, A. V. *J. Org. Chem.* **2017**, *82*, 256.

(24) Ruvinskaya, J. O.; Rostovskii, N. V.; Filippov, I. P.; Khlebnikov, A. F.; Novikov, M. S. *Org. Biomol. Chem.* **2018**, *16*, 38.

(25) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 1180.
(26) Zhao, Y.-Z.; Yang, H.-B.; Tang, X.-Y.; Shi, M. *Chem. Eur. J.* **2015**, *21*, 3562.
(27) Sakai, T.; Liu, Y.; Ohta, H.; Korenaga, T.; Ema, T. *J. Org. Chem.* **2005**, *70*, 1369.