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Article

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Deoxofluorination of (Hetero)aromatic Acids

Serhii Trofymchuk,[1] Maksym Bugera,[1,2] Anton A. Klipkov,[1,2] Bohdan Razhyk,[1] Sergey Semenov,[1] Karen Tarasenko,[2,3] Viktoriia S. Starova,[4] Olga A. Zaporozhets,[4] Oksana Y. Tananaiko,[4] Anatoliy N. Alekseenko,[5] Yurii Pustovit,[5] Oleksandr Kiriakov,[1] Igor I. Gerus,[3] Andrei A. Tolmachev[1,4] Pavel K. Mykhailiuk[1,4]*

[1] Enamine Ltd.; Chervonotkatska 78, 02094 Kyiv (Ukraine), www.enamine.net; www.mykhailiukchem.org
[2] V.P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry NAS of Ukraine; Murmanskaya 1, 02094 Kyiv (Ukraine)
[3] UkrOrgSyntez Ltd. (UORSY), 29 Schorsa Str., 01133 Kyiv (Ukraine)
[4] Taras Shevchenko National University of Kyiv; Chemistry Department; Volodymyrska 64, 01601 Kyiv (Ukraine).
[5] Institute of Organic Chemistry NAS of Ukraine, Murmanskaya 5, 02094 Kyiv (Ukraine)

ABSTRACT: Diverse trifluoromethyl-substituted compounds were synthesized by deoxofluorination of cinnamic and (hetero)aromatic carboxylic acids with sulfur tetrafluoride. The obtained products can be used as starting materials in the preparation of novel fluorinated amino acids, anilines and aliphatic amines – valuable building blocks for medicinal chemistry and agrochemistry.

INTRODUCTION

Modern medicinal chemistry and agrochemistry are tightly bound to organofluorine chemistry, because around 20% of all pharmaceuticals and up to 30% of agrochemicals are organic compounds that contain at least one fluorine atom.[1,2] For example, trifluoromethyl-substituted (hetero)aromatic derivatives, that usually posess higher metabolic stability over the non-fluorinated counterparts, comprise to a structure of more than seventy drugs and one hundred agrochemicals (Figure 1).[3] It is no surprise that over the past decade a number of synthetic methods to practically access the trifluoromethyl-substituted organic molecules appeared in the literature.[4]

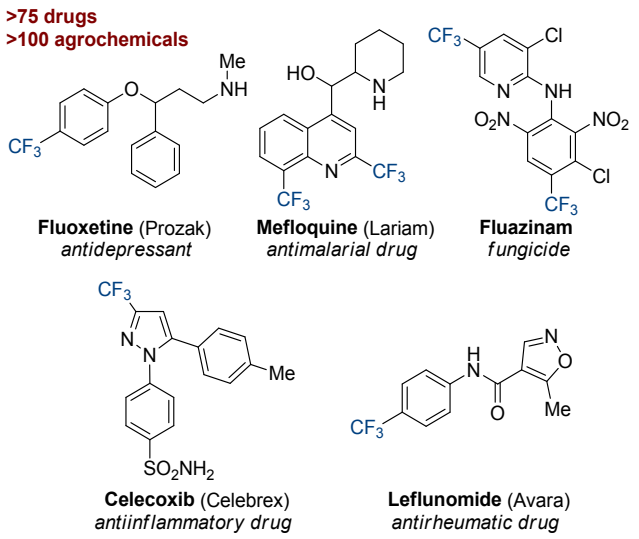
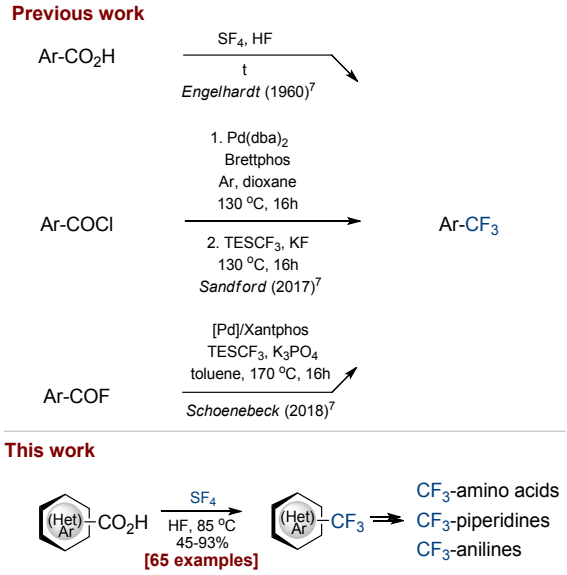


Figure 1. Selected drugs and agrochemicals with the trifluoromethyl-substituted (hetero)aromatic motif.

Carboxylic acids are amongst the most available chemical compounds classes, and it would have been desirable to have a practical method to converting them into the trifluoromethyl-substituted derivatives. Indeed, in 1960, Engelhardt developed deoxofluorination of aromatic acids with sulfur tetrafluoride to obtain the corresponding trifluoromethylated products (Scheme 1).[5] Subsequently, this approach was used by other groups for the synthesis of trifluoromethyl-substituted pyridines,[6] furans,[7] thiazoles, uracils,[8] pyrazoles,[9] quinolones,[10] *etc*.[11] One of the biggest contributions to the field came from the school of Soviet Union chemists led by Yagupolskii.[12] Later, two other methods that proceed via different mechanisms appeared. In particular, in 2017, Sandford developed a decarbonylation of aromatic acyl chlorides with $Pd(dba)_2$/Brettphos.[13] Subsequent coupling of the obtained aryl chlorides with CF_3SiEt_3[14] allowed for the direct one-pot conversion of aromatic acyl chlorides into the trifluoromethylated derivatives. In 2018, Schoenebeck performed a [Pd]-catalyzed decarbonylative coupling of aromatic acyl



Scheme 1. Conversion of (hetero)aromatic carboxylic acids or its derivatives into the trifluoromethyl-substituted compounds.

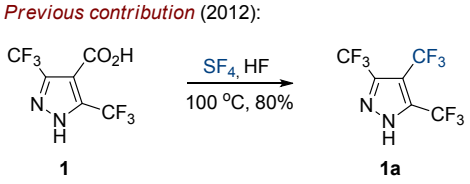
fluorides with CF_3SiEt_3 to obtain the CF_3-substituted products.[15,16] A work of Umemoto, who developed Fluolead reagent for the fluorination of hydroxyl and carbonyl groups, should also be noticed.[17] The authors showed one example of deoxofluorination of benzoic acid into trifluorotoluene. Unfortunately, the scope of this transformation was not further elaborated.

In spite of wide application of the method of Englelhardt during the last century,[18] these days it has become very rare.[19] On the other hand, our research group has been involved in this chemistry for more than a decade already. As a chemical supplier of building blocks, we often receive requests from pharmaceutical and agrochemicals companies for the synthesis of trifluoromethyl-substituted (hetero)aromatic products. From our experience, the deoxofluorination of carboxylic acids with sulfur tetrafluoride is one of the most effective and practical methods to access these compounds on a gram scale. It is undeservedly one of the most underrated reactions today.

Previously, we reported on the deoxofluorination of aliphatic acids with sulfur tetrafluoride.[20] In this manuscript, therefore, we would like to disclose our results on deoxofluorination of (hetero)aromatic and cinnamic acids into the trifluoromethyl-substituted products. This is the first comprehensive study on that transformation in the open literature. In particular, sixty five trifluoromethyl-substituted (hetero)aromatic derivatives were obtained, none of them being synthesized by this method before. We also show here, how the obtained compounds could be used in the preparation of interesting trifluoromethyl-substituted amino acids, anilines and aliphatic amines.

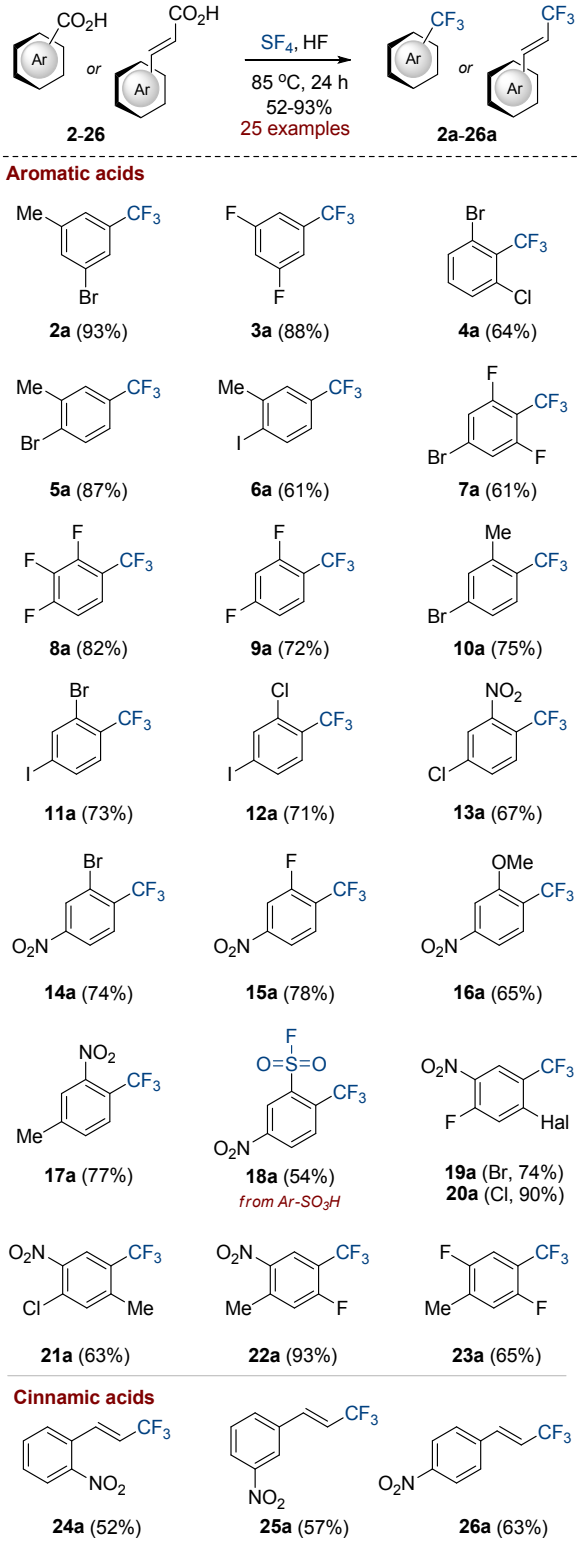
RESULTS AND DISCUSSION

In 2012, we performed deoxofluorination of pyrazole carboxylic acid **1** with sulfur tetrafluoride to obtain tris(trifluoromethyl)pyrazole **1a** (Scheme 2).[9a] Later, compound **1a** was used by Diaz and coworkers as a unique ligand for transition metals.[21] The product was easily obtained on a gram scale, and we became intrigued if we could use the same method for the preparation of other trifluoromethyl-substituted (hetero)aromatic derivatives. As already mentioned before, we often received requests from commercial companies for those molecules, and we needed to elaborate a robust procedure to access them.



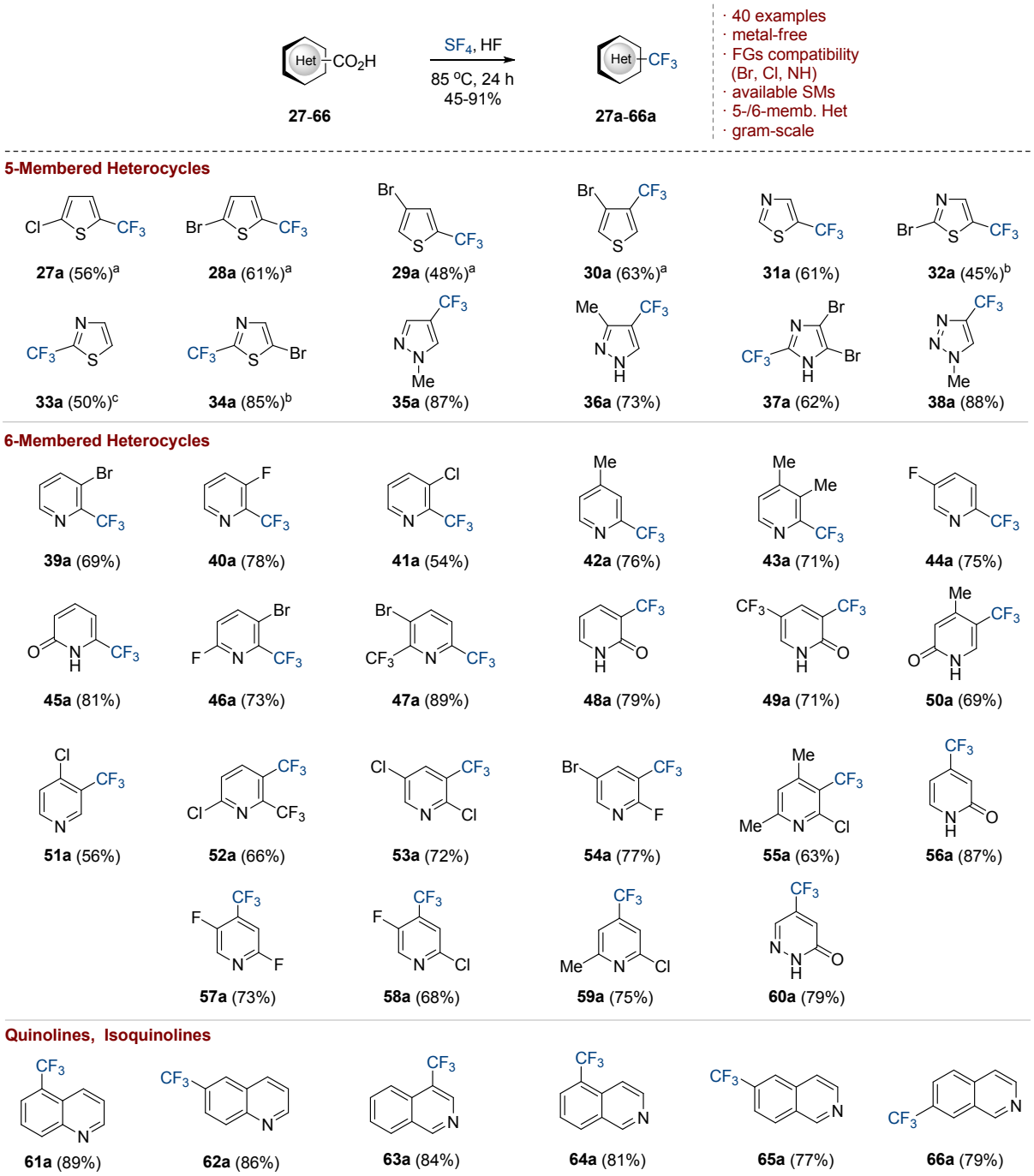
Scheme 2. Synthesis of pyrazole **1a** – a ligand for transition metals.[9a]

Scope. After some experimentation, we found that for aromatic substrates, the reaction temperature could be safely reduced to 85-90 °C. Luckily, we could deoxofluorinate diverse aromatic acids **2-23** into the needed trifluoromethyl-substituted products **2a-23a** in 54-93% yield after a distillation (Scheme 3). The reaction had a good functional group tolerance: aromatic fluorine (**3a**, **7a-9a**, *etc*), chlorine (**4a**, **12a**, **13a**, *etc*), bromine (**2a**, **4a**, **5a**, *etc*) and iodine atoms (**6a**, **11a**, **12a**), ether (**16a**) and nitro



Scheme 3. Scope of deoxofluorination of aromatic and cinnamic acids with SF_4. *Reaction conditions*: (i) carboxylic acid (1.0 equiv), SF_4 (3.0 equiv), hydrogen fluoride, 85 °C, 24 h; (ii) work up; (iii) distillation.

(**13a-17a** *etc*) groups were compatible with the reaction conditions. Three peculiarities are additionally worth mentioning. First, deoxofluorination of the carboxylic acid with a sulfonic group (**18**) afforded the trifluoromethyl-substituted sulfonyl fluoride **18a** in 54% yield – a class of building blocks especially



Scheme 4. Scope of fluorination of heterocyclic acids with sulfur tetrafluoride. *Reaction conditions*: (i) heterocyclic acid (1.0 equiv), sulfur tetrafluoride (3.0 equiv), hydrogen fluoride, 85 °C, 24 h; (ii) work up; (iii) distillation. [a]The reaction was performed at 115 °C for three days. [b]The reaction was performed at 45 °C for two days. [c]The reaction was performed at 75 °C for four days.

popular these days in medicinal chemistry.[22] Second, deoxofluorination of nitro cinnamic acids **24-26** was also accomplished to obtain the trifluoromethylated styrenes **24a-26a** in 52-63% yield. Previously this transformation was reported via radical processes only.[23] Third, the method was efficient for converting the hindered 1,1'-disubstituted benzoic acids **4**, **7** into the corresponding trifluoromethyl-substituted derivatives **4a**, **7a**.

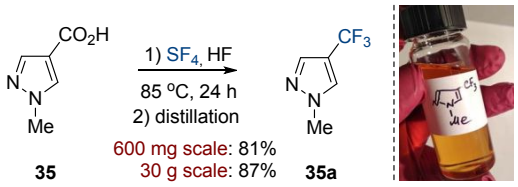
Next, we studied a scope of heterocyclic acids (Scheme 4). Various five-membered heterocycles - thiophenes (**27-30**), thiazoles (**31-34**), pyrazoles (**35**, **36**), imidazoles (**37**) and triazoles (**38**), - gave the needed trifluoromethylated products **27a-38a** in 45-88% yield after a distillation. Notably, deoxofluorination of thiophenes **27-30** under the standard conditions (85 °C, 24 h) afforded products **27a-30a** in only 5-10% yield. However, performing the reaction at higher temperature (115 °C) without hydrogen fluoride gave the needed products in 48-63% yield. Reaction of thiazole **33** with hydrogen fluoride at high temperature led to partial decarboxylation. Therefore, we performed a two-step sequence: first, we added sulfur tetrafluoride to thiazole **33** at room temperature, to generate the

corresponding acyl fluoride, and then performed the deoxofluorination at lower temperature (75 °C) to obtain the needed product **33a** in 50% yield. Pyridines and pyridones **39-59** as well as diazinone **60** were also transformed into the trifluoromethyl-substituted compounds **39a-60a** in 54-89% yield. Finally, quinolines and isoquinolines **61-66** also provided the needed CF_3-substituted derivatives **61a-66a** in 77-89% yield.

It is important to mention that in spite of previous literature precedents on deoxofluorination of (hetero)aromatic acids,[5-12] none of products **2a-65a** synthesized here, was ever obtained by this method before. It seems that even today, after almost sixty years since the discovery, this powerful synthetic strategy has not realized its full potential yet.

Practical aspects. From the practical standpoint, the reaction was performed in a Hastelloy autoclave using hydrogen fluoride as a solvent. After heating the reaction mixture at 85 °C for one day, the reaction was cooled to a room temperature, and the gaseous products were vented off into an aqueous solution of sodium hydroxide. The reaction mixture was then poured into an ice followed by a standard work up. We purified all crude products by simple distillation. The reaction also produced ca. 10% of the dimeric side product RCF_2OCF_2R that remained in the residue after distillation, and we did not isolate it in the pure state.[24] Most of syntheses were performed on a gram scale, but also can be realized on a milligram amount. For example, the synthesis of compound **35a** was performed on 600 mg (81% yield) and 30 g scale (87% yield). On a large scale the yields were higher, because the distillation procedure was technically easier to do (Scheme 5).

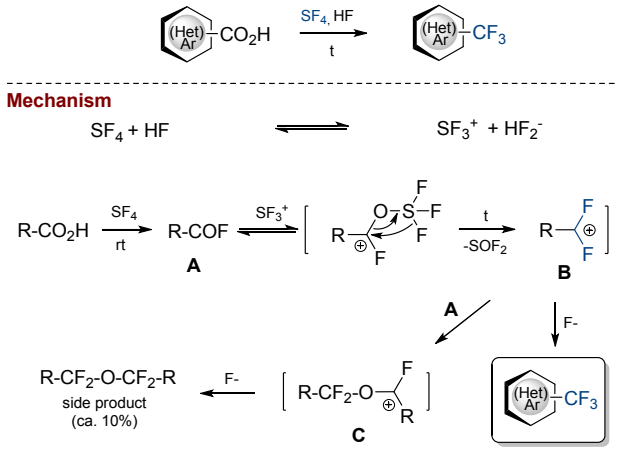
Caution! Sulfur tetrafluoride (SF_4) and hydrogen fluoride (HF) are toxic. Special care and an additional technical training must be taken before working with them.



Scheme 5. Synthesis of pyrazole **35a** on different scale.

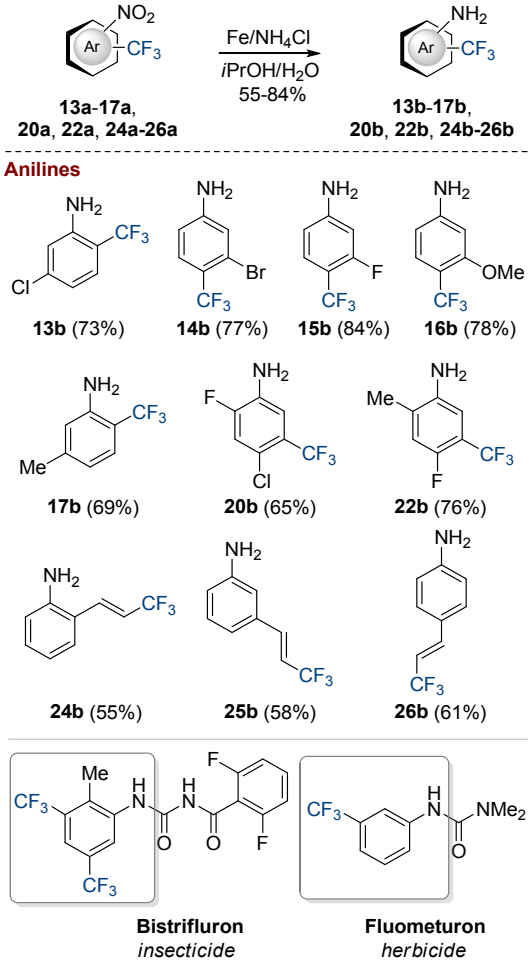
Mechanism. Mechanistically, hydrogen fluoride plays two roles in the reaction: as a solvent and as an "activator" for sulfur tetrafluoride.[25] First, sulfur tetrafluoride reacts with a carboxylic acid to rapidly give acyl fluoride **A** (Scheme 6). This step is fast and already proceeds at 0 °C or below. The next step is rate-limiting and requires a heating. Sulfur tetrafluoride reversibly reacts with hydrogen fluoride to give an active SF_3^+ intermediate. Next, SF_3^+ cation reacts with acyl fluoride (**A**) to form the difluoromethyl cation (**B**). The latter either reacts with hydrodifluoride anion to give the target CF_3-substituted product; or with another molecule of acyl fluoride to form the side dimeric product $(RCF_2)_2O$ via intermediate **C** (Scheme 6).

Practical application. Many trifluoromethyl-substituted products highlighted at Schemes 3 and 4 contain bromine/iodine or activated chlorine/fluorine atoms, and therefore are of practical interest for both metal-mediated cross-coupling reactions (Br, I) and SNAr2 nucleophilic substitutions (Cl, F). But we also



Scheme 6. Mechanism of fluorination of (hetero)aromatic acids with sulfur tetrafluoride in hydrogen fluoride.

additionally wanted to demonstrate their high utility as starting materials for further synthesis of trifluoromethyl-substituted aliphatic and aromatic derivatives.

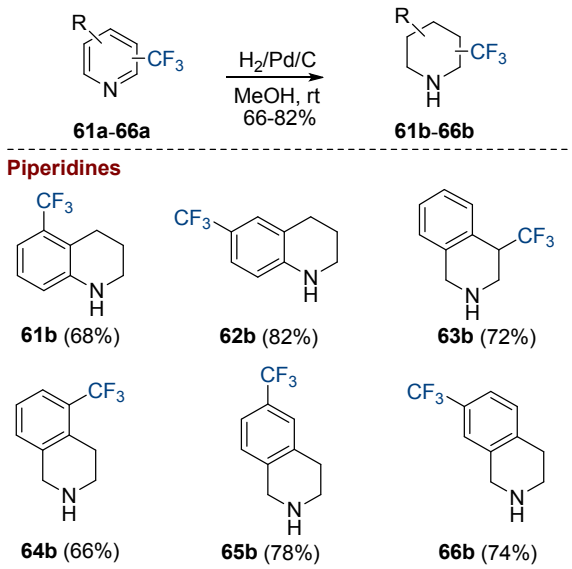


Scheme 7. Synthesis of trifluoromethyl-substituted anilines **13b-17b**, **20b**, **22b** and **24b-26b**. Bistrifluron, Fluometuron: derivatives of trifluoromethyl-substituted anilines in argochemistry.

In particular, reduction of the nitro group in aromatic compounds **13a-17a**, **20a**, **22a** and **24a-26a** with iron dust,

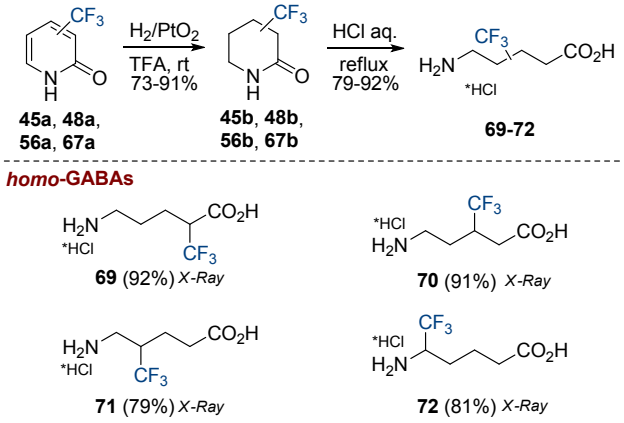
ammonium chloride in isopropanol/water mixture gave unique trifluoromethyl-substituted anilines **13b-17b**, **20b**, **22b** and **24b-26b** in 55-84% yield – molecules with high potential for agrochemistry (Figure 1, Scheme 7).

Selective hydrogenation of pyridine ring in quinolines and isoquinolines **61a-66a** at 150 bar using 10% Pd/C as a catalyst in methanol gave the benzo-annulated trifluoromethyl-substituted pyperidines **61b-66b** in 66-82% yield – interesting building blocks for medicinal chemistry (Scheme 8).[26]



Scheme 8. Synthesis of trifluoromethyl-substituted benzo-annulated piperidines **61b-66b**.

Finally, we synthesized and characterized all four regioisomers of trifluoromethyl-substituted 5-aminovaleric acid (*homo*-GABA, **68**) analogues **69-72** (Scheme 9). Hydrogenation of pyridones **45a**, **48a**, **56a** and **67a** in trifluoroacetic acid at room temperature using PtO_2 as a catalyst gave piperidones **45b**, **48b**, **56b**, **67b**. Hydrolysis of latters in aqueous hydrochloric acid under a prolonged heating provided four fluorinated acids **69***HCl-**72***HCl.

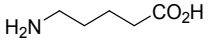
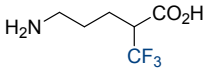
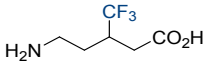
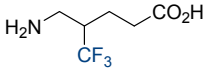
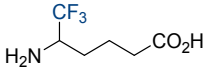


Scheme 9. Synthesis of trifluoromethyl-substituted amino acids **69-72** (substituted analogues of *homo*-GABA).

We studied also an influence of the trifluoromethyl moiety on the acidity/basicity of functional groups, and the conformation of *homo*-GABA.[27] pK_a values of the functional groups in compounds **68-72** were determined by potentiometric titration (please, see SI for details). Indeed, placing the trifluoromethyl substituent at the α-position to the carboxylic group in **68** - compound **69**, - increased its acidity by almost two orders of magnitude: pK_a (CO_2H) = 2.5 (**69**) *vs* 4.2 (**68**). As expected the trifluoromethyl substituents at β-position of homo-GABA - amino acid **70**, - had much lower effect on the acidity of the carboxylic group: pK_a (CO_2H) = 3.6 (**70**) *vs* 4.2 (**68**). The trifluoromethyl group at the γ-(**71**) and δ-(**72**) positions of homo-GABA had a minor effect on the acidity of the carboxyl group: pK_a (CO_2H) = 4.0 (**71**) *vs* 4.1 (**72**) *vs* 4.2 (**68**) (Table 1).

The trifluoromethyl substituent had also a dramatic effect on the basicity of the amino function in compound **68**. Amino acid **72** was almost four magnitudes of order less basic than homo-GABA: pK_a (NH_3^+): = 6.7 (**72**) *vs* 10.8 (**68**).[28]Amino group in **71** was ca. one magnitude of order less basic than that in homo-GABA: pK_a (NH_3^+): = 9.5 (**71**) *vs* 10.8 (**68**). The trifluoromethyl substituent in amino acids **69** and **70** only slightly decreased the basicity of the amino group: pK_a (NH_3^+): = 10.4 (**70**) *vs* 10.5 (**69**) *vs* 10.8 (**68**) (Table 1).

Table 1. Experimental pK_a values for amino acids **68-72**.

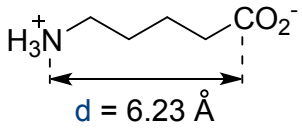
Amino acid		pK_a(CO_2H)	pK_a(NH_3^+)
68 (*homo-GABA*)		4.2	10.8
69*HCl		2.5	10.5
70*HCl		3.6	10.4
71*HCl		4.0	9.5
72*HCl		4.1	6.7

To study an effect of the trifluoromethyl group on the conformation of *homo*-GABA, we obtained single crystals of amino acids **69***HCl-**72***HCl suitable for X-Ray analysis.[29] X-Ray structure of homo-GABA (**68**) was already reported in the literature so that we could use this data.[30] In the crystal state, compound **68** adopted an extended linear conformation, with the distance, d = 6.23 Å between amino and carboxyl groups (Table 2). Intriguingly, all four amino acids **69***HCl-**72***HCl possessed different conformations (Table 2). In molecules **69** and **72**, for example, the bulky trifluoromethyl group acted as a conformational "anchor" – it occupied the terminus of the extended conformation, pushing the carboxyl (**69**) or the amino group (**72**) away from the zig-zag chain. Similar effect was observed in molecules **70** and **71**, where the trifluoromethyl substituent also occupied the terminus of the zig-zag conformation. Not surprisingly, that in all four molecules **69***HCl-**72***HCl the distance (d) was different: 5.25 Å (**69**); 4.23 Å (**70**); 5.12 Å (**71**) and 5.38 Å (**72**). Moreover, it significantly

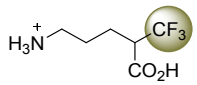
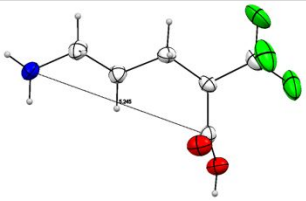
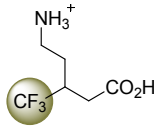
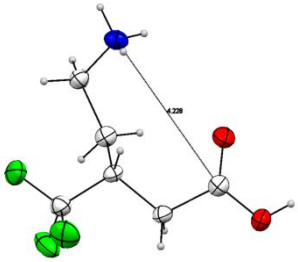
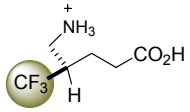
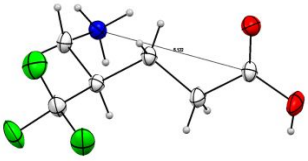
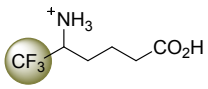
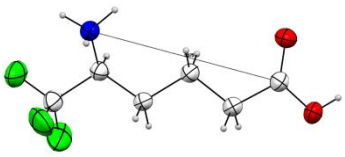
deviated from d = 6.23 Å in the parent amino acid *homo*-GABA (**68**).

As a brief summary, in isomeric amino acids **69***HCl-**72***HCl, the trifluoromethyl group tuned both the electronic properties and the molecular conformation of compounds. First, due to (*–I*)-inductive effect, it altered the acidity/basicity of amino and carboxyl groups. Second, as a bulky substituent - "anchor," - it defined the conformation of all four molecules, occurring at the terminus of the zig-zag chain. As a result all five compounds, - *homo*-GABA (**68**) and its isomeric trifluoromethyl-substituted analogues **69-72**, - have completely different acidity/basicity of functional groups and the conformation in the crystal phase. It is beyond the scope of this work, but we expect that five amino acids **69-72** will have different affinity to GABA receptors.

Table 2. X-Ray crystal structure, and the representative conformation of amino acids **68-72**. Distance, d (Å) between amino and carboxyl groups in the crystal state is shown. The N, C, F, O-atoms are shown at 30% thermal ellipsoid % probability. Distance (d) between carboxyl and amino groups is shown.



68 (*homo-GABA*)

Conformation, distance (d, Å)	X-Ray
 d = 5.25 Å **69**	
 d = 4.23 Å **70**	
 d = 5.12 Å **71**	
 d = 5.38 Å **72**	

CONCLUSIONS

In 1960, Engelhardt developed deoxofluorination of aromatic acids with sulfur tetrafluoride.[5] Even though many research groups subsequently extended this approach onto heterocyclic acids,[6-12] these days it remains mostly in the shadow. In this work, therefore, we disclosed our results over the past ten years on the deoxofluorination of cinnamic and (hetero)aromatic carboxylic acids with sulfur tetrafluoride. In particular, the synthesis of sixty five trifluoromethyl-substituted products is described here on a gram scale. These compounds were further used as starting materials to obtain unique building blocks for medicinal chemistry and agrochemistry - trifluoromethylated anilines, piperidines and amino acids.[31,32] We hope that after the current study, chemists will keep in mind this approach when planning the synthesis of trifluoromethyl-substituted molecules.

EXPERIMENTAL SECTION

General. All chemicals were provided by Enamine Ltd. (www.enamine.net). Autoclaves were provided by UOSLab (en.uoslab.com). All solvents were treated according standard methods. Product purification was performed using distillation. TLC-characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh).^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H-NMR spectra were recorded at 400 or 500 MHz (Varian); ^{19}F-NMR spectra were recorded at 376 MHz (Varian) and ^{13}C NMR spectra were recorded at 100, 126 or 151 MHz (Varian). ^{1}H-NMR chemical shifts are reported downfield from $CDCl_3$ (δ = 7.26 ppm), D_2O (δ = 4.79 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C-NMR chemical shifts for ^{13}C-NMR are reported relative to the central $CDCl_3$ (δ = 77.16 ppm) or DMSO-d_6 (δ = 39.52 ppm). Coupling constants are given in Hz. MS analysis was performed on an LCMS instrument with chemical ionization or GCMS with electrospray ionization. High-resolution mass spectra (HRMS) were recorded on an Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments.

Caution! Sulfur tetrafluoride (SF_4) and hydrogen fluoride (HF) are highly toxic. Special care and an additional technical training must be taken before working with them.[33,34]

General procedure A (2a as an example)

1-Bromo-3-methyl-5-(trifluoromethyl)benzene (2a). Compound **2** (21.5 g, 0.1 mol, 1 equiv) was placed in 500 mL autoclave made of Hastelloy nickel alloy. The reaction vessel was cooled down by liquid nitrogen and anhydrous HF (17.2 mL, 0.8 mL for 1 g of acid) was added. Then SF_4 (32.4 g, 0.3 mol, 3 equiv) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. It was then heated at 85 °C in oil bath for 24 h. The autoclave was allowed to cool down to a room temperature, and the gaseous products were vented off into a trap with aqueous solution of NaOH (1M). The residue was poured onto a suspension of $NaHCO_3$ and ice (500 g) (for products with no basic centers, just ice can be used) extracted with MTBE, and an organic extract was washed with saturated aq. $NaHCO_3$ (500 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under

reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 22.2 g, 93%, yellow oil, b.p. 85 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.51 (s, 1H), 7.36 (s, 1H), 2.40 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 141.1, 135.6, 132.3 (q, *J* = 32.6 Hz), 125.7 (q, *J* = 3.8 Hz), 124.8 (q, *J* = 3.6 Hz), 123.4 (q, *J* = 272.9 Hz), 122.6, 21.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (s). GCMS (*m/z*): 239 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9680.

1,3-Difluoro-5-(trifluoromethyl)benzene (3a): yield: 16 g, 88%, colorless oil, b.p. 75 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 5.2 Hz, 2H), 7.01 (t, *J* = 8.6 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.1 (dd, *J* = 251.7, 12.2 Hz), 134.2 – 133.3 (m), 126.2 – 119.4, 109.6 – 109.2 (m), 109.2 – 108.9 (m), 107.7 (t, *J* = 24.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.6 (s, 3F), -107.7 (s, 2F). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4F_5$, 183.0233; found 183.0230.

1-Bromo-3-chloro-2-(trifluoromethyl)benzene (4a): yield: 16.45 g, 64%, yellow oil, b.p. 82 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 134.8, 134.5, 132.7, 131.5, 127.8 (q, *J* = 30.6 Hz), 122.5 (q, *J* = 276.5 Hz), 121.8 (d, *J* = 1.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.4 (s). GCMS (*m/z*): 259 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4BrClF_3$, 258.9137; found 258.9139.

1-Bromo-2-methyl-4-(trifluoromethyl)benzene (5a): yield: 20.8 g, 87%, colorless oil, b.p. 67 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 1H), 7.48 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 1H), 2.46 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.1, 133.0, 129.9 (q, *J* = 32.6 Hz), 128.9, 127.6 (q, *J* = 3.5 Hz), 124.2 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 272.3 Hz), 23.1. GCMS (*m/z*): 239 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9681.

1-Iodo-2-methyl-4-(trifluoromethyl)benzene (6a): yield: 17.4 g, 61%, pink oil, b.p. 90 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.2 Hz, 1H), 7.47 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 2.49 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 142.6, 139.6, 130.8 (q, *J* = 32.6 Hz), 126.2 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 272.2 Hz), 124.1 (q, *J* = 3.7 Hz), 105.4, 28.33 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 (s). GCMS (*m/z*): 286 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7F_3I$, 286.9545; found 286.9541.

5-Bromo-1,3-difluoro-2-(trifluoromethyl)benzene (7a): yield: 15.9 g, 61%, colorless oil, , b.p. 60 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 1H), 7.19 (s, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.0 (d, *J* = 263.5 Hz), 160.0 (d, *J* = 263.9 Hz), 127.1 (t, *J* = 12.2 Hz), 121.5 (q, *J* = 273.4 Hz), 117.0 (d, *J* = 3.7 Hz), 116.8 (d, *J* = 3.7 Hz), 107.7 – 107.3 (m). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.0 (t, *J* = 22.6 Hz, 3F), -109.5 (dd, *J* = 45.6, 23.0 Hz, 2F). GCMS (*m/z*): 261 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_3BrF_5$, 260.9338; found 260.9342.

1,2,3-Trifluoro-4-(trifluoromethyl)benzene (8a): yield: 16.4 g, 82%, colorless oil, b.p. 77 °C, 760 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.34 (m, 1H), 7.14 – 7.05 (m, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 153.8 (dd, *J* = 257.2, 13.7 Hz), 149.7 (dd, *J* = 262.0, 17.0 Hz), 140.6 (dt, *J* = 254.6, 14.9 Hz), 121.9 (q, *J* = 272.5 Hz), 121.7 – 121.1 (m), 117.1 – 115.8 (m), 112.5 (dd, *J* = 18.4, 4.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.4 (d, *J* = 13.2 Hz, 3F), -127.2 – -127.4 (m, 1F), -134.5 – -135.0 (m, 1F), -157.9 (t, *J* = 20.7 Hz, 1F). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_3F_6$, 201.0139; found 201.0139.

2,4-Difluoro-1-(trifluoromethyl)benzene (9a): yield: 13.1 g, 72%, colorless oil, b.p. 85 °C, 760 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 14.7, 8.1 Hz, 1H), 7.03 – 6.89 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.4 (dd, *J* = 254.8, 11.4 Hz), 160.7 (ddd, *J* = 259.2, 12.7, 1.8 Hz), 129.2 – 128.5 (m), 122.5 (q, *J* = 271.5 Hz), 115.8 – 114.3 (m), 111.7 (dd, *J* = 22.0, 3.8 Hz), 105.7 (dd, *J* = 25.6, 24.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.5 (d, *J* = 13.2 Hz, 3F), -103.4 (d, *J* = 11.7 Hz, 1F), -110.0 (dt, *J* = 25.8, 12.8 Hz, 1F). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4F_5$, 183.0233; found 183.0235.

4-Bromo-2-methyl-1-(trifluoromethyl)benzene (10a): yield 17.85 g, 75%, colorless oil, b.p. 95 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.36 (m, 3H), 2.46 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.0 (d, *J* = 1.6 Hz), 134.9, 129.1, 128.1 (q, *J* = 30.5 Hz), 127.5 (q, *J* = 5.6 Hz), 126.2, 124.4 (q, *J* = 273.5 Hz), 19.3 (d, *J* = 2.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2 (s). GCMS (*m/z*): 239 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_8H_7BrF_3$, 238.9683; found 238.9688.

2-Bromo-4-iodo-1-(trifluoromethyl)benzene (11a): yield: 18.25 g, 73%, olive oil, b.p. 36 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.14 (m, 1H), 7.69-7.82 (m, 1H), 7.31-7.45 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.2, 136.7, 130.1 (q, *J* = 31.8 Hz), 129.0 (q, *J* = 5.2 Hz), 123.0 (q, *J* = 273.3 Hz), 121.0, 98.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 (s). GCMS (*m/z*): 250 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4BrF_3I$, 350.8493; found 350.8495.

2-Chloro-4-iodo-1-(trifluoromethyl)benzene (12a): yield: 21.7 g, 71%, yellow oil, b.p. 56 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.0, 136.2, 133.3, 128.7 (q, *J* = 5.3 Hz), 128.3 (q, *J* = 31.8 Hz), 122.9 (q, *J* = 273.2 Hz), 98.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.4 (s). GCMS (*m/z*): 306 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4ClF_3I$, 306.8998; found 306.8994.

4-Chloro-2-nitro-1-(trifluoromethyl)benzene (13a): yield: 15.1 g, 67%, yellow oil, b.p. 72 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, DMSO-d_6) δ 148.0, 138.8, 133.4, 130.3 – 129.4 (m), 125.4, 120.9 – 119.3 (m). ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.5 (s). GCMS (*m/z*): 225 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4ClF_3NO_2$, 225.9883; found 225.9888.

2-Bromo-4-nitro-1-(trifluoromethyl)benzene (14a): yield: 20 g, 74%, orange oil, b.p. 91 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.6 (s, 1H), 8.3 (d, *J* = 8.4 Hz, 1H), 7.9 (d, *J* = 8.6 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.0, 135.8 (q, *J* = 32.2 Hz), 130.1, 129.1 (q, *J* = 5.4 Hz), 122.3, 122.1 (q, *J* = 274.5 Hz), 121.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.7 (s). GCMS (*m/z*): 270 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_7H_4BrF_3NO_2$, 269.9378; found 269.9378.

2-Fluoro-4-nitro-1-(trifluoromethyl)benzene (15a): yield: 16.3 g, 78%, yellow oil, b.p. 64 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 9.7 Hz, 1H), 7.86 (t, *J* = 7.7 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.8 (d, *J* = 262.2 Hz), 151.3, 128.7 (d, *J* = 4.5 Hz), 124.7 – 124.1 (m), 121.6 (q, *J* = 273.6 Hz), 119.4 (d, *J* = 4.2 Hz), 113.1 (d, *J* = 25.7

Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 (d, *J* = 13.2 Hz, 3F), -109.2 (dd, *J* = 26.9, 13.7 Hz, 1F). GCMS (*m/z*): 209 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_4F_4NO_2$, 210.0178; found 210.0174.

2-Methoxy-4-nitro-1-(trifluoromethyl)benzene (16a): yield: 14.35 g, 65%, yellow solid, m.p. 35 °C, b.p. 68 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.6 Hz, 1H), 7.85 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 4.03 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.4, 151.4, 128.3 (q, *J* = 5.2 Hz), 124.5 (q, *J* = 31.8 Hz), 122.6 (q, *J* = 273.3 Hz), 115.1, 107.2, 56.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8 (s). GCMS (*m/z*): 221 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_7F_3NO_3$, 222.0378; found 222.0382.

4-Methyl-2-nitro-1-(trifluoromethyl)benzene (17a): yield: 15.8 g, 77%, yellow oil, b.p. 58 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.65 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 2.51 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.2, 144.6, 133.1, 127.9 (q, *J* = 5.1 Hz), 125.5, 122.3 (q, *J* = 272.6 Hz), 120.8 (q, *J* = 34.2 Hz), 21.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.3 (s). GCMS (*m/z*): 205 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_7F_3NO_2$, 206.0429; found 206.0425.

5-Nitro-2-(trifluoromethyl)benzenesulfonyl fluoride (18a): yield: 14.74 g, 54%, grey solid, m.p. 56-58 °C, b.p. 91 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.74 (d, *J* = 8.4 Hz, 1H), 8.26 (d, *J* = 8.6 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.8, 134.6 (q, *J* = 35.5 Hz), 134.0 (d, *J* = 30.8 Hz), 131.1 (q, *J* = 5.8 Hz), 130.1, 127.8, 121.1 (q, *J* = 275.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ 65.71 (q, *J* = 13.4 Hz, 1F), -59.45 (d, *J* = 13.4 Hz, 3F). GCMS (*m/z*): 273 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_4F_4NO_4S$, 273.9797; found 273.9791.

1-Bromo-5-fluoro-4-nitro-2-(trifluoromethyl)benzene (19a): yield: 21.2 g, 74%, yellow solid, 82-84 °C, b.p. 82 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 7.1 Hz, 1H), 7.74 (d, *J* = 9.4 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.5 (d, *J* = 275.4 Hz), 136.0 – 135.8 (m), 128.0 – 127.5 (m), 126.3 – 126.0 (m), 125.9, 125.7, 121.6 (q, *J* = 273.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 (s, 3F), -110.0 (s, 1F). GCMS (*m/z*): 287 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_3BrF_4NO_2$, 287.9283; found 287.9289.

1-Chloro-5-fluoro-4-nitro-2-(trifluoromethyl)benzene (20a): yield: 21.9 g, 90%, yellow solid, m.p. 46 °C, b.p. 93 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 7.4 Hz, 1H), 7.54 (d, *J* = 9.8 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.5 – 155.3 (m), 140.1 (d, *J* = 10.5 Hz), 135.5, 126.2 – 126.1 (m), 122.4, 122.3, 121.4 (q, *J* = 273.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (s, 3F), -109.4 (s, 1F). GCMS (*m/z*): 243 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_3ClF_4NO_2$, 243.9788; found 243.9788.

1-Chloro-5-methyl-2-nitro-4-(trifluoromethyl)benzene (21a): yield: 15 g, 63%, yellow oil, b.p. 69 °C, 0.1 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.52 (s, 1H), 2.56 (s, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 145.3, 143.5, 135.5, 130.9, 128.8 (q, *J* = 32.6 Hz), 124.0 (q, *J* = 6.2 Hz), 122.9 (q, *J* = 273.7 Hz), 19.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.8 (s). GCMS (*m/z*): 239 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_6ClF_3NO_2$, 240.0039; found 240.0043.

1-Fluoro-5-methyl-4-nitro-2-(trifluoromethyl)benzene (22a): yield: 20.7 g, 93%, yellow oil, b.p. 58 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, *J* = 6.5 Hz, 1H), 7.22 (d, *J* = 10.2 Hz, 1H), 2.70 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.3 (d, *J* = 265.6 Hz), 141.8 (d, *J* = 9.8 Hz), 125.3 – 125.0 (m), 121.5 (q, *J* = 272.4 Hz), 121.4, 121.3, 117.9 – 117.2 (m), 21.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.2 (d, *J* = 11.7 Hz, 3F), -106.7 (q, *J* = 14.4 Hz, 1F). GCMS (*m/z*): 223 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_6F_4NO_2$, 224.0335; found 224.0337.

1,4-Difluoro-2-methyl-5-(trifluoromethyl)benzene (23a): yield: 12.7 g, 65%, colorless oil, b.p. 71 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 8.5, 6.1 Hz, 1H), 7.03 (dd, *J* = 9.9, 6.0 Hz, 1H), 2.32 (s, 3H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 156.6 (d, *J* = 240.3 Hz), 156.4 – 154.4 (m), 131.7 (dd, *J* = 20.1, 9.1 Hz), 122.1 (q, *J* = 271.9 Hz), 119.6 (d, *J* = 5.5 Hz), 119.5 (d, *J* = 5.5 Hz), 114.1 – 113.1 (m), 14.9 (d, *J* = 3.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.9 (d, *J* = 14.8 Hz, 3F), -121.5 – -121.9 (m, 2F). GCMS (*m/z*): 196 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_6F_5$, 197.0390; found 197.0398.

1-Nitro-2-(3,3,3-trifluoroprop-1-en-1-yl)benzene (24a): yield: 11.3 g, 52%, yellow solid, b.p. 98 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 7.9 Hz, 1H), 7.76 – 7.65 (m, 2H), 7.63 – 7.53 (m, 2H), 6.23 – 6.08 (m, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 148.1, 134.4 (q, *J* = 7.0 Hz), 134.0, 130.5, 129.9, 129.4, 125.2, 122.8 (q, *J* = 269.6 Hz), 120.7 (q, *J* = 34.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.1 (s). GCMS (*m/z*): 217 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_7F_3NO_2$, 218.0429; found 218.0430.

1-Nitro-3-(3,3,3-trifluoroprop-1-en-1-yl)benzene (25a): yield: 12.4 g, 57%, brown solid, m.p. 40 °C, b.p. 65 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 7.23 (dd, *J* = 16.2, 1.8 Hz, 1H), 6.37 (dq, *J* = 16.1, 6.3 Hz, 1H). ^{13}C {^{1}H} (126 MHz, $CDCl_3$) δ 148.9, 135.6 (q, *J* = 6.7 Hz), 135.3, 133.4, 130.2, 124.6, 123.1 (q, *J* = 269.4 Hz), 122.3, 119.2 (q, *J* = 34.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.35 (s), -64.36 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_7F_3NO_2$, 218.0429; found 218.0437.

1-Nitro-4-(3,3,3-trifluoroprop-1-en-1-yl)benzene (26a): yield: 13.7 g, 63%, yellow solid, m.p. 98 °C, b.p. 50 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.6 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 16.3 Hz, 1H), 6.42 – 6.30 (m, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.7, 139.6, 135.6 (q, *J* = 6.7 Hz), 128.5, 124.4, 123.0 (q, *J* = 269.5 Hz), 120.2 (q, *J* = 34.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.5 (s). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_7F_3NO_2$, 218.0429; found 218.0432.

General procedure B for the synthesis of 27a-30a (27a as an example)

2-Chloro-5-(trifluoromethyl)thiophene (27a). Compound **27** (16.25 g, 0.1 mol, 1 equiv) was placed in 280 mL autoclave made of Hastelloy nickel alloy. The reaction vessel was cooled down by liquid nitrogen, and then SF_4 (32.4 g, 0.3 mol, 3 equiv) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. It was then heated at 115 °C in oil bath for 3 d. The autoclave was allowed to cool down to a room temperature, and the gaseous products were vented off into a trap with aqueous solution of NaOH (1M). The residue was poured onto aq NH_4OH (25%) and extracted with CH_2Cl_2, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 10.4 g, 56%, colorless oil, b.p. 52 °C, 15 mmHg. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.23 (d, *J* = 2.9 Hz, 1H), 6.91 (d, *J* = 3.6 Hz, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 137.5 – 131.2 (m), 129.7 (q, *J* = 39.3 Hz), 128.3 (dd, *J* = 8.1, 4.0 Hz), 126.2, 121.8 (q, *J* = 269.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.4 (s). GCMS (*m/z*): 186 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_3ClF_3S$, 186.9596; found 186.9599.

2-Bromo-5-(trifluoromethyl)thiophene (28a): yield: 14.1 g, 61%, colorless oil, b.p. 48 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.19 (m, 1H), 7.04 (d, *J* = 3.5 Hz, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 132.7 (q, *J* = 39.2 Hz), 130.0, 129.1 (q, *J* = 3.9 Hz), 121.8 (q, *J* = 269.0 Hz), 117.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.3 (s). GCMS (*m/z*): 231 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_3BrF_3S$, 230.9091; found 230.9092.

4-Bromo-2-(trifluoromethyl)thiophene (29a): yield: 11.1 g, 48%, colorless oil, b.p. 63 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 1.4 Hz, 1H), 7.38 (s, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 132.8 (q, *J* = 39.6 Hz), 131.4 (q, *J* = 3.7 Hz), 126.3, 121.7 (q, *J* = 269.3 Hz), 110.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.6 (s). GCMS (*m/z*): 231 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_3BrF_3S$, 230.9091; found 230.9093.

3-Bromo-4-(trifluoromethyl)thiophene (30a): yield: 14.6 g, 63%, colorless oil, b.p. 84 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 3.0 Hz, 1H), 7.38 (d, *J* = 2.7 Hz, 1H). ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 131.1 (q, *J* = 35.2 Hz), 128.9 (q, *J* = 5.2 Hz), 126.6, 121.3 (q, *J* = 270.5 Hz), 107.6 (d, *J* = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2 (s). GCMS (*m/z*): 231 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_3BrF_3S$, 230.9091; found 230.9089.

5-(Trifluoromethyl)thiazole (31a): yield: 9.3 g, 61%, colorless oil, b.p. 55 °C, 15 mmHg ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1H), 8.23 (s, 1H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 156.1, 144.7, 127.6 – 127.0 (m), 122.2 (q, *J* = 268.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -54.6 (s). GCMS (*m/z*): 153 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_3F_3NS$, 153.9938; found 153.9936.

General procedure C for the synthesis of 32a and 34a (32a as an example).

2-Bromo-5-(trifluoromethyl)thiazole (32a). Compound **32** (20.8 g, 0.1 mol, 1 equiv) was placed in 500 mL autoclave made of Hastelloy nickel alloy. The reaction vessel was cooled down by liquid nitrogen and anhydrous HF (16.6 mL, 1 mol, 10 equiv) was added. Then SF_4 (32.4 g, 0.3 mol, 3 equiv) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. It was then heated at 45 °C in oil bath for 48 h. The autoclave was allowed to cool down to a room temperature, and the gaseous products were vented off into a trap with aqueous solution of NaOH (1M). The residue was poured onto ice, dissolved in CH_2Cl_2, and washed with saturated aq. $NaHCO_3$ (500 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 10.4 g, 45%, colorless oil, b.p. 84 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 143.8 (q, *J* = 4.0 Hz), 140.4, 130.6 (q, *J* = 39.2 Hz), 121.1 (q, *J* = 269.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.5 (s). GCMS (*m/z*): 232 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_2BrF_3NS$, 231.9043; found 231.9045.

2-(Trifluoromethyl)thiazole (33a). Compound **33** (12.9 g, 0.1 mol, 1 equiv) was placed in 280 mL autoclave made of Hastelloy nickel alloy. The reaction vessel was cooled down by liquid nitrogen and SF_4 (16.2 g, 0.15 mol, 1.5 equiv) was condensed into a reaction vessel. Cooling bath was removed, and the mixture was allowed to warm up to a room temperature. The gaseous products were vented off into a trap with aqueous solution of NaOH (1M) and anhydrous HF (2.1 mL, 0.1 mol, 1 equiv) was added. Then SF_4 (21.6 g, 0.2 mol, 2 equiv) was condensed into a reaction vessel. It was then heated at 75 °C in oil bath for 4 d. The autoclave was allowed to cool down to a room temperature, and the gaseous products were vented off into a trap with aqueous solution of NaOH (1M). The residue was poured onto aq. NH_4OH (25%) and extracted with Et_2O, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product. The final product was purified by distillation. Yield: 7.65 g, 50%, colorless oil, b.p. 88 °C, 760 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.61 (d, *J* = 2.9 Hz, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 156.1 (q, *J* = 40.7 Hz), 144.2, 122.8, 120.0 (q, *J* = 271.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.3 (s). GCMS (*m/z*): 153 (M). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_3F_3NS$, 153.9938; found 153.9938.

5-Bromo-2-(trifluoromethyl)thiazole (34a): yield: 19.7 g, 85%, colorless oil, b.p. 55 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 157.7 – 156.1 (m), 145.3, 119.2 (q, *J* = 272.4 Hz), 114.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_2BrF_3NS$, 231.9043; found 231.9046.

1-Methyl-4-(trifluoromethyl)-1H-pyrazole (35a): yield: 13.1 g, 87%, colorless oil, b.p. 42 °C, 15 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.63 (s, 1H), 3.92 (s, 3H). ^{13}C {^1H} NMR (101 MHz, $CDCl_3$) δ 137.1 (d, *J* = 2.7 Hz), 129.3 (d, *J* = 3.2 Hz), 122.7 (q, *J* = 265.6 Hz), 113.9 (q, *J* = 38.4 Hz), 39.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -56.9 (s). LCMS (*m/z*): 151 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_6F_3N_2$, 151.0483; found 151.0489.

3-Methyl-4-(trifluoromethyl)-1H-pyrazole (36a): yield: 13.05 g, 87%, white solid, m.p. 97-99 °C, b.p. 51 °C, 1 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 11.43 (br s, 1H), 7.75 (s, 1H), 2.44 (s, 3H). ^{13}C {^1H} NMR (151 MHz, $CDCl_3$) δ 142.3, 134.5 (d, *J* = 3.2 Hz), 123.3 (q, *J* = 266.0 Hz), 111.2 (q, *J* = 37.7 Hz), 10.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.4 (s). LCMS (*m/z*): 151 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_5H_6F_3N_2$, 151.0483; found 151.0478.

4,5-Dibromo-2-(trifluoromethyl)-1H-imidazole (37a): yield: 18.1 g, 62%, brown solid, m.p. 127-129 °C, b.p. 92 °C, 0.1 mmHg. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 5.42 (br s, 1H). ^{13}C {^1H} NMR (126 MHz, $CDCl_3$) δ 128.3 (q, *J* = 41.1 Hz), 120.2(q, *J* = 268.7 Hz), 118.7 (d, *J* = 8.9 Hz), 106.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s). LCMS (*m/z*): 295 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_4H_2Br_2F_3N_2$, 292.8537; found 292.8530.

1-Methyl-4-(trifluoromethyl)-1H-1,2,3-triazole (38a): yield: 13.29 g, 88%, yellow solid, m.p. 77-79 °C, b.p. 74 °C, 15 mmHg. ^1H NMR (400 MHz, DMSO-d_6) δ 8.83 (s, 1H), 4.13 (s, 3H). ^{13}C {^1H} NMR (101 MHz, DMSO-d_6) δ 136.7 (q, *J* = 38.2 Hz), 126.3,

120.9 (q, J = 266.9 Hz), 36.9. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.2 (s). LCMS (*m/z*): 152 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_4H_5F_3N_3$, 152.0436; found 152.0431.

3-Bromo-2-(trifluoromethyl)pyridine (39a): yield: 17.66 g, 69%, beige solid, m.p. 41-43 °C, b.p. 81 °C, 15 mmHg ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 3.5 Hz, 1H), 8.07 (d, J = 8.0 Hz, 1H), 7.37 (dd, J = 7.4, 4.6 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.3, 146.3 (q, J = 34.2 Hz), 143.2, 127.5, 121.2 (q, J = 275.1 Hz), 118.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.7 (s). GCMS (*m/z*): 256 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_4BrF_3N$, 225.9479; found 225.9472.

3-Fluoro-2-(trifluoromethyl)pyridine (40a): yield: 12.87 g, 78%, colorless oil, b.p. 122 °C, 760 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.0 Hz, 1H), 7.65 – 7.51 (m, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 157.3 (d, J = 268.3 Hz), 145.1 (d, J = 5.3 Hz), 136.3 (dd, J = 35.7, 11.3 Hz), 128.6 (d, J = 4.2 Hz), 125.7, 125.6, 120.9 (qd, J = 274.3, 4.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.2 (d, J = 15.4 Hz, 3F), -122.16 (q, 1F). GCMS (*m/z*): 165 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_4F_4N$, 166.0280; found 166.0282.

3-Chloro-2-(trifluoromethyl)pyridine (41a): yield: 9.77 g, 54%, beige solid, m.p. 55-56 °C, b.p. 79 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 4.4 Hz, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.47 (dd, J = 8.1, 4.6 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 146.9, 144.9 (q), 139.8, 130.7, 127.4, 121.1 (q, J = 275.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.8 (s). GCMS (*m/z*): 181 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_4ClF_3N$, 181.9984; found 181.9987.

4-Methyl-2-(trifluoromethyl)pyridine (42a): yield: 12.24 g, 76%, brown oil, b.p. 48 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.8 Hz, 1H), 7.49 (s, 1H), 7.29 (d, J = 4.6 Hz, 1H), 2.44 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.9, 149.2, 148.3 (q, J = 34.2 Hz), 127.3, 121.8 (q, J = 274.1 Hz), 121.4 (q, J = 2.6 Hz), 21.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.6 (s). LCMS (*m/z*): 162 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_7F_3N$, 162.0531; found 162.0531.

3,4-Dimethyl-2-(trifluoromethyl)pyridine (43a): yield: 12.43 g, 71%, grey solid, m.p. 51-52 °C, b.p. 71 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 4.5 Hz, 1H), 7.24 (d, J = 4.5 Hz, 1H), 2.37 (s, 3H), 2.35 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.8, 146.0 (q, J = 31.8 Hz), 145.9, 131.7, 127.8, 122.7 (q, J = 275.6 Hz), 19.9, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.6 (s). GCMS (*m/z*): 175 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_9F_3N$, 176.0687; found 176.0687.

5-Fluoro-2-(trifluoromethyl)pyridine (44a): yield: 12.37 g, 75%, colorless oil, b.p. 105 °C, 760 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 2.2 Hz, 1H), 7.73 (dd, J = 8.6, 4.1 Hz, 1H), 7.57 (td, J = 8.4, 2.4 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.8 (d, J = 262.2 Hz), 144.5 (qd, J = 35.5, 4.0 Hz), 139.0 (d, J = 25.1 Hz), 124.0 (d, J = 19.1 Hz), 122.3 (q, J = 2.7 Hz), 121.3 (q, J = 273.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.8 (s, 3F), -121.5 (s, 1F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_4F_4N$, 166.0280; found 166.0285.

6-(Trifluoromethyl)pyridin-2(1H)-one (45a): yield: 13.20 g, 81%, white solid, b.p. 61 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.80 (br s, 1H), 7.68 (t, J = 7.9 Hz, 1H), 6.99 (d, J = 7.0 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.8, 140.9, 140.6 (q, J = 35.5 Hz), 120.6 (q, J = 274.0 Hz), 119.4, 109.8 (q, J = 4.2 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.0 (s). LCMS (*m/z*): 162 $(M-H)^-$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_5F_3NO$, 164.0323; found 164.0325.

3-Bromo-6-fluoro-2-(trifluoromethyl)pyridine (46a): yield: 17.74 g, 73%, colorless oil, b.p. 76 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (t, J = 7.2 Hz, 1H), 7.07 (dd, J = 8.5, 3.5 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.1 (d, J = 245.6 Hz), 148.2 (d, J = 7.5 Hz), 144.56– 143.8 (m), 120.3 (q, J = 275.6 Hz), 114.6 (d, J = 37.8 Hz), 114.1 (d, J = 4.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.9 (s, 3F), -68.0 (s, 1F). GCMS (*m/z*): 243 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_2BrF_5N$, 261.9291; found 261.9293.

3-Bromo-2,6-bis(trifluoromethyl)pyridine (47a): yield: 26.17 g, 89%, yellow oil, b.p. 59 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.3 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 146.8 (q, J = 35.6 Hz), 146.3 (q, J = 37.1 Hz), 144.9, 124.2, 121.6, 120.8 (q, J = 274.5 Hz), 120.5 (q, J = 276.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -67.0 (s, 3F), -68.4 (s, 3F). GCMS (*m/z*): 294 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_2BrF_5N$, 261.9291; found 261.9289.

3-(Trifluoromethyl)pyridin-2(1H)-one (48a): yield: 12.88 g, 79%, yellow solid, b.p. 64 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.42 (br s, 1H), 7.87 (d, J = 6.9 Hz, 1H), 7.66 (d, J = 6.0 Hz, 1H), 6.39 (t, J = 6.7 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.6, 140.8 (q, J = 5.4 Hz), 139.3, 122.8 (q, J = 271.4 Hz), 120.4 (q, J = 31.5 Hz), 105.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -66.2 (s). LCMS (*m/z*): 162 $(M-H)^-$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_5F_3NO$, 164.0323; found 164.0328.

3,5-Bis(trifluoromethyl)pyridin-2(1H)-one (49a): yield: 16.4 g, 71%, white solid, m.p. 145-147 °C, b.p. 79 °C, 15 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.03 (br s, 1H), 8.29 (s, 1H), 8.11 (s, 1H). ^{13}C {^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.0, 141.0 (d, J = 4.5 Hz), 136.2, 123.2 (q, J = 269.7 Hz), 122.3 (q, J = 271.5 Hz), 119.0 (q, J = 31.0 Hz), 105.9 (q, J = 35.9 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.5 (s, 3F), -65.2 (s, 3F). LCMS (*m/z*): 232 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_4F_6NO$, 232.0197; found 232.0199.

4-Methyl-5-(trifluoromethyl)pyridin-2(1H)-one (50a): yield: 12.21 g, 69%, yellow solid, m.p. 182-183 °C, b.p. 65 °C, 1 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (s, 1H), 7.77 (s, 1H), 6.34 (s, 1H), 2.20 (s, 3H). ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 161.9, 147.6, 135.9 (q, J = 6.9 Hz), 124.2 (q, J = 270.2 Hz), 120.8, 107.1 (q, J = 31.6 Hz), 18.6 (d, J = 1.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -59.7 (s). LCMS (*m/z*): 178 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_7F_3NO$, 178.0480; found 178.0483.

4-Chloro-3-(trifluoromethyl)pyridine (51a): yield: 10.14 g, 56%, yellow oil, b.p. 68 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.68 (d, J = 4.7 Hz, 1H), 7.48 (d, J = 5.1 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.8, 148.4 (q, J = 5.7 Hz), 142.9, 126.0, 122.5 (q, J = 273.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (s). GCMS (*m/z*): 181 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_4ClF_3N$, 181.9984; found 181.9984.

6-Chloro-2,3-bis(trifluoromethyl)pyridine (52a): yield: 16.43 g, 66%, colorless oil, b.p. 58 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.4 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.2, 146.0 (q, J = 37.9 Hz),

139.0 (q, J = 5.4 Hz), 127.6, 124.4 (q, J = 35.7 Hz), 122.0 (q, J = 273.8 Hz), 119.9 (q, J = 275.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.0 (q, J = 12.2 Hz, 3F), -65.1 (q, J = 12.2 Hz. 3F). GCMS (*m/z*): 249 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_3ClF_6N$, 249.9858; found 249.9861.

2,5-Dichloro-3-(trifluoromethyl)pyridine (53a): yield: 15.48 g, 72%, colorless oil, b.p. 84 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, J = 1.6 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.2, 147.0, 136.5 (q, J = 5.0 Hz), 131.0, 126.4 (q, J = 33.9 Hz), 121.5 (q, J = 273.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.5 (s). GCMS (*m/z*): 215 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_3Cl_2F_3N$, 215.9595; found 215.9591.

5-Bromo-2-fluoro-3-(trifluoromethyl)pyridine (54a): yield: 18.71 g, 77%, colorless oil, b.p. 66 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.15 (dd, J = 7.8, 1.9 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.8 (d, J = 247.1 Hz), 152.3 (d, J = 15.3 Hz), 140.9, 121.0 (dq, J = 272.8, 6.1 Hz), 116.4 (d, J = 5.2 Hz), 115.9 – 114.4 (m). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.3 (d, J = 11.4 Hz, 3F), -69.1 (d, J = 10.8 Hz, 1F). GCMS (*m/z*): 243 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_3BrF_4N$, 243.9385; found 243.9387.

2-Chloro-4,6-dimethyl-3-(trifluoromethyl)pyridine (55a): yield: 13.17 g, 63%, yellow solid, b.p. 62 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 2.53 – 2.44 (m, 6H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.3, 150.2, 149.2 (d, J = 1.6 Hz), 125.8, 123.9 (q, J = 274.7 Hz), 121.3 (q, J = 31.4 Hz), 23.9, 21.6 (q, J = 4.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -55.9 (s). GCMS (*m/z*): 209 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_8ClF_3N$, 210.0297; found 210.0297.

4-(Trifluoromethyl)pyridin-2(1H)-one (56a): yield: 14.18 g, 87%, yellow solid, m.p. 160-161 °C, b.p. 62 °C, 1 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (br s, 1H), 7.64 (d, J = 6.7 Hz, 1H), 6.68 (s, 1H), 6.37 (d, J = 6.7 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 161.5, 140.8 (q, J = 32.6 Hz), 138.5, 122.4 (q, J = 274.0 Hz), 117.2 (q, J = 4.3 Hz), 99.8 (d, J = 2.6 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -66.0 (s). LCMS (*m/z*): 164 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_5F_3NO$, 164.0323; found 164.0325.

2,5-Difluoro-4-(trifluoromethyl)pyridine (57a): yield: 13.36 g, 73%, colorless oil, b.p. 48 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.19 (t, J = 3.8 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.0 (d, J = 239.5 Hz), 153.7 (d, J = 261.5 Hz), 137.3 (dd, J = 26.8, 15.8 Hz), 131.0 – 130.5 (m), 120.6 (q, J = 272.8 Hz), 107.8 (dq, J = 44.2, 4.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.0 (d, J = 12.9 Hz, 3F), -69.3(d, J = 29.5 Hz, 1F), -134.8 (dt, J = 27.1, 13.1 Hz 1F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_3F_5N$, 184.0186; found 184.0189.

2-Chloro-5-fluoro-4-(trifluoromethyl)pyridine (58a): yield: 13.52 g, 68%, colorless oil, b.p. 79 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.56 (d, J = 4.8 Hz, 1H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 154.9 (d, J = 264.4 Hz), 147.1 (d, J = 3.9 Hz), 139.8 (d, J = 25.3 Hz), 128.6 (qd, J = 35.3, 12.2 Hz), 121.8 (q, J = 4.3 Hz), 120.7 (q, J = 274.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.7 (d, J = 12.3 Hz, 3F), -132.3 (q, J = 12.3 Hz, 1F). GCMS (*m/z*): 199 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_6H_3ClF_4N$, 199.9890; found 199.9892.

2-Chloro-6-methyl-4-(trifluoromethyl)pyridine (59a): yield: 14.63 g, 75%, colorless oil, b.p. 72 °C, 15 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.29 (s, 1H), 2.62 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.3, 151.7, 141.3 (q, J = 34.2 Hz), 122.3 (q, J = 273.6 Hz), 117.8 (q, J = 3.2 Hz), 117.6 (q, J = 3.6 Hz), 24.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.3 (s). GCMS (*m/z*): 195 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_6ClF_3N$, 196.0141; found 196.0139.

5-(Trifluoromethyl)pyridazin-3(2H)-one (60a): yield: 12.96 g, 79%, beige solid, m.p. 108-109 °C, b.p. 59 °C, 1 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (br s, 1H), 8.21 (d, J = 1.4 Hz, 1H), 7.39 (s, 1H). ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 159.4, 133.1 (q, J = 33.5 Hz), 131.6 (d, J = 2.6 Hz), 128.1 (q, J = 4.2 Hz), 122.3 (t, J = 274.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -65.2 (s). LCMS (*m/z*): 165 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_5H_4F_3N_2O$, 165.0276; found 165.0273.

5-(Trifluoromethyl)quinolone (61a): yield: 17.53 g, 89%, colorless oil, b.p. 74 °C, 5 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (d, J = 3.4 Hz, 1H), 8.50 (d, J = 8.6 Hz, 1H), 8.30 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.75 (t, J = 7.9 Hz, 1H), 7.53 (dd, J = 8.7, 4.2 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.15 (s), 148.47 (s), 134.42 (s), 132.72 (s), 127.95 (s), 126.50 (q, J = 30.8 Hz), 125.30 (q, J = 5.6 Hz), 124.58 (s), 122.44 (s), 122.08 (d, J = 273.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.7 (s). GCMS (*m/z*): 197 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0533.

6-(Trifluoromethyl)quinolone (62a): yield: 16.94 g, 86%, white solid, m.p. 39-41 °C, b.p. 69 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (d, J = 3.1 Hz, 1H), 8.23 (t, J = 9.3 Hz, 2H), 8.14 (s, 1H), 7.88 (dd, J = 8.7, 1.2 Hz, 1H), 7.50 (dd, J = 8.3, 4.2 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.6, 149.3, 137.0, 130.9, 128.7 (q, J = 32.6 Hz), 127.4, 125.9 (q, J = 4.3 Hz), 125.3 (q, J = 2.9 Hz), 124.1 (q, J = 272.2 Hz), 122.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s). GCMS (*m/z*): 197 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0535.

4-(Trifluoromethyl)isoquinoline (63a): yield: 16.55 g, 84%, colorless oil, b.p. 62 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.86 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.2 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H). ^{13}C {^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.1, 141.2 (q, J = 6.5 Hz), 132.3, 131.6, 128.6, 128.5, 128.3, 124.5 (q, J = 273.5 Hz), 123.5, 120.4 (q, J = 30.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.7 (s). LCMS (*m/z*): 198 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0529.

5-(Trifluoromethyl)isoquinoline (64a): yield: 15.96 g, 81%, white solid, b.p. 65 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.66 (d, J = 6.1 Hz, 1H), 8.16 (d, J = 8.2 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.94 (d, J = 4.9 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.3, 144.8, 132.4, 132.0, 128.9 (q, J = 5.4 Hz), 125.9, 125.7 (q, J = 31.0 Hz), 124.2 (q, J = 273.4 Hz), 117.0 (d, J = 1.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.8 (s). LCMS (*m/z*): 198 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0528.

6-(Trifluoromethyl)isoquinoline (65a): yield: 15.17 g, 77%, white solid, m.p. 35-36 °C, b.p. 53 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.65 (d, J = 5.7 Hz, 1H), 8.14 (s,

1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 5.7 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.7, 144.5, 135.0, 132.2 (q, *J* = 32.6 Hz), 129.5, 129.0, 124.5 (q, *J* = 4.4 Hz), 123.8 (d, *J* = 272.7 Hz), 123.2 (q, *J* = 2.9 Hz), 121.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.5 (s). LCMS (*m/z*): 198 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0534.

7-(Trifluoromethyl)isoquinoline (66a): yield: 15.56 g, 79%, beige solid, m.p. 38-39 °C, b.p. 49 °C, 0.1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.35 (s, 1H), 8.66 (d, *J* = 5.7 Hz, 1H), 8.28 (s, 1H), 7.94 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.71 (d, *J* = 5.7 Hz, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 153.4, 145.2, 137.2, 129.4 (q, *J* = 32.7 Hz), 128.0, 127.5, 126.1 (q, *J* = 2.8 Hz), 125.7 (q, *J* = 4.4 Hz), 123.9 (q, *J* = 272.4 Hz), 120.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2 (s). LCMS (*m/z*): 198 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{10}H_7F_3N$, 198.0531; found 198.0531.

General procedure for reduction for the synthesis of 13b-17b, 20b, 22b and 24b-26b (13b as an example).

5-Chloro-2-(trifluoromethyl)aniline (13b). To a 500 mL three necked flask carrying a mechanical stirrer, thermometer pocket was charged i-PrOH (200 mL) followed by **13a** (10 g, 0.044 mol, 1 equiv), ammonium chloride (0.89 g, 0.016 mol), water (8.9 mL) and con. HCl (0.9 mL). The mixture was heated at reflux and carefully iron powder (8.9 g, 0.159 mol, 3.6 equiv) was added in portions. TLC shows completion of the reaction, the reaction mixture was filtered throught celite. The filtrate was concentrated, diluted with EtOAc and a solution of $NaHCO_3$. The organic layer was separated and addionally washed with brine, dried over Na_2SO_4, filtered and concentrated under a reduced pressure to afford the desired product. Yield: 6.26 g, 73%, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 8.9 Hz, 1H), 6.77 – 6.69 (m, 2H), 2.41 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 145.7, 138.9, 128.1 (q, *J* = 5.2 Hz), 124.8 (q, *J* = 271.8 Hz), 117.9, 116.8, 112.4 (q, *J* = 30.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1 (s). GCMS (*m/z*): 195 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_6ClF_3N$, 196.0141; found 196.0143.

3-Bromo-4-(trifluoromethyl)aniline (14b): yield: 8.1 g, 77%, brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5 Hz, 1H), 6.95 (d, *J* = 1.8 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 4.00 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.2, 129.0 (q, *J* = 5.4 Hz), 123.7 (q, *J* = 271.3 Hz), 121.1, 120.1, 119.5 (q, *J* = 31.6 Hz), 112.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.2 (s). LCMS (*m/z*): 240 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_6BrF_3N$, 239.9636; found 239.9639.

3-Fluoro-4-(trifluoromethyl)aniline (15b): yield: 6.6 g, 84%, white solid, m.p. 55-56 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (t, *J* = 8.4 Hz, 1H), 6.45 – 6.37 (m, 2H), 4.06 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.3 (d, *J* = 252.7 Hz), 151.7 (d, *J* = 11.2 Hz), 128.4– 128.2 (m), 123.5 (q, *J* = 270.3 Hz), 109.7 (d, *J* = 2.4 Hz), 108.2 – 107.2 (m), 102.1 (d, *J* = 23.8 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ -65.1 (d, *J* = 12.3 Hz, 3F), -119.6 (q, *J* = 12.3 Hz, 1F). GCMS (*m/z*): 179 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_6F_4N$, 180.0436; found 180.0432.

3-Methoxy-4-(trifluoromethyl)aniline (16b): yield: 6.56 g, 78%, yellow solid, m.p. 46-48 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.5 Hz, 1H), 6.27 – 6.18 (m, 2H), 3.96 (br s, 2H), 3.83 (s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.1, 151.3, 128.5 (q, *J* = 5.2 Hz), 124.5 (q, *J* = 270.5 Hz), 108.7 (q, *J* = 31.5 Hz), 105.8, 98.4, 55.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.1 (s). LCMS (*m/z*): 192 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_9F_3NO$, 192.0636; found 192.0632.

5-Methyl-2-(trifluoromethyl)aniline (17b): yield: 5.3 g, 69%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.0 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.56 (s, 1H), 3.97 (br s, 2H), 2.29 (s, 3H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.5, 143.5, 126.6 (q, *J* = 5.1 Hz), 125.4 (d, *J* = 271.6 Hz), 118.9, 117.7, 111.5 (q, *J* = 30.1 Hz), 21.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6 (s). LCMS (*m/z*): 176 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_9F_3N$, 176.0687; found 176.0684.

4-Chloro-2-fluoro-5-(trifluoromethyl)aniline (20b): yield: 6.1 g, 65%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 10.4 Hz, 1H), 7.08 (d, *J* = 8.8 Hz, 1H), 3.89 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 152.3 (d, *J* = 248.2 Hz), 133.6 (d, *J* = 13.2 Hz), 124.9 (qd, *J* = 31.4, 3.5 Hz), 122.8 (q, *J* = 272.9 Hz), 120.6 (d, *J* = 9.2 Hz), 118.7 (d, *J* = 22.7 Hz), 115.34 (p, *J* = 5.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5 (s, 3F), -128.8 (s, 1F). GCMS (*m/z*): 213 (M). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_7H_5ClF_4N$, 214.0047; found 214.0045.

4-Fluoro-2-methyl-5-(trifluoromethyl)aniline hydrochloride (22b): yield: 6.45 g, 76%, beige solid, m.p. 218-219 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 3H), 7.76 (d, *J* = 6.6 Hz, 1H), 7.50 (s, 1H), 2.40 (s, 3H). ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 156.1 (d, *J* = 252.7 Hz), 138.7, 130.9, 122.3 (q, *J* = 271.6 Hz), 119.8, 119.6 (d, *J* = 21.8 Hz), 114.4 (qd, *J* = 34.0, 13.5 Hz), 17.5. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.54 (d, *J* = 13.5 Hz), -120.77 (s). LCMS (*m/z*): 194 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_8H_8F_4N$, 194.0593; found 194.0598.

2-(3,3,3-Trifluoroprop-1-en-1-yl)aniline (24b): yield: 4.5 g, 55%, white solid, m.p. 52-54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.14 (m, 3H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 8.0 Hz, 1H), 6.27 – 5.91 (m, 1H), 3.85 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 144.9, 133.5 (q, *J* = 6.8 Hz), 131.1, 128.1, 123.8 (q, *J* = 269.1 Hz), 119.6, 119.4, 117.0, 116.8 (q, *J* = 33.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.7 (s). LCMS (*m/z*): 188 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9F_3N$, 188.0687; found 188.0687.

3-(3,3,3-Trifluoroprop-1-en-1-yl)aniline (25b): yield: 4.77 g, 58%, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 1H), 7.06 (dd, *J* = 16.1, 1.7 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.75 (s, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 6.25 – 6.07 (m, 1H), 3.71 (br s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.0, 138.0 (q, *J* = 6.8 Hz), 134.6, 130.0, 123.8 (q, *J* = 268.8 Hz), 118.2, 116.9, 115.8 (q, *J* = 33.7 Hz), 113.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.8 (s). LCMS (*m/z*): 188 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9F_3N$, 188.0687; found 188.0689.

4-(3,3,3-Trifluoroprop-1-en-1-yl)aniline (26b): yield: 5.02 g, 61%, yellow solid, m.p. 84-85 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.3 Hz, 2H), 7.01 (dd, *J* = 16.1, 1.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 2H), 6.05 – 5.87 (m, *J* = 13.3, 6.6 Hz, 1H), 3.82 (br s, 2H). ^{13}C {^{1}H} NMR (151 MHz, $CDCl_3$) δ 148.3, 137.6 (q, *J* = 6.9 Hz), 129.2, 124.4 (q, *J* = 268.3 Hz), 123.8, 115.0, 111.7 (q, *J* = 33.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (s). LCMS (*m/z*): 188 $(M+H)^+$. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_9H_9F_3N$, 188.0687; found 188.0685.

General procedure for reduction for the synthesis of 61b-66b (61b as an example)

5-(Trifluoromethyl)-1,2,3,4-tetrahydroquinoline (61b). Compound **61a** (10 g, 0.05 mol, 1 equiv) was dissolved in 150 mL of MeOH and 1 g of 10%-Pd/C was added to the mixture. The mixture was hydrogenated under 150 bar during 24 h. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The crude residue was purified by distillation under high vacuum to afford the final pure compound. Yield: 6.84 g, 68%, colorless oil, b.p. 66 °C, 1 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.99 (t, J = 7.9 Hz, 1H), 6.73 (d, J = 7.6 Hz, 1H), 6.69 (d, J = 8.1 Hz, 1H), 6.13 (br s, 1H), 3.26 – 3.13 (m, 2H), 2.75 (t, J = 6.0 Hz, 2H), 1.87 – 1.72 (m, 2H). ^{13}C {^{1}H} NMR (151 MHz, DMSO-d_6) δ 146.5, 127.4 (q, J = 28.2 Hz), 126.4, 124.9 (q, J = 274.0 Hz), 117.5, 116.9, 111.8 (q, J = 6.1 Hz), 23.2, 20.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -60.1 (s). LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0844.

6-(Trifluoromethyl)-1,2,3,4-tetrahydroquinoline (62b): yield: 8.24 g, 82%, yellow oil, b.p. 72 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.13 (m, 2H), 6.45 (d, J = 8.8 Hz, 1H), 3.91 (br s, 1H), 3.34 (t, J = 5.5 Hz, 1H), 2.77 (t, J = 6.3 Hz, 2H), 1.94 (dt, J = 12.0, 6.1 Hz, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 147.4, 127.4 (q, J = 270.1 Hz), 126.6 (q, J = 3.7 Hz), 124.2 (q, J = 3.6 Hz), 120.7, 118.2 (q, J = 32.5 Hz), 113.2, 41.8, 27.1, 21.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.4 (s). LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0841.

4-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (63b): yield: 7.23 g, 72%, colorless oil, b.p. 64 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.5 Hz, 1H), 7.25 (t, J = 7.7 Hz, 1H), 7.20 (t, J = 7.3 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 4.08 – 3.93 (m, 2H), 3.55 (dd, J = 14.2, 2.2 Hz, 1H), 3.38 – 3.25 (m, 1H), 3.24 – 3.11 (m, 1H), 1.87 (s, 2H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.6, 131.0, 128.2, 127.6, 126.50, 126.47, 124.9 (q, J = 280.9 Hz), 47.8, 43.2 (q, J = 2.7 Hz), 40.4 (q, J = 24.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -68.1 (s). LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0840.

5-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (64b): yield: 6.63 g, 66%, white solid, m.p. 31-32 °C, b.p. 55 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, J = 7.1 Hz, 1H), 7.24 – 7.13 (m, 2H), 4.07 (s, 2H), 3.15 (t, J = 5.9 Hz, 2H), 2.95 (t, J = 5.5 Hz, 2H), 1.79 (s, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 137.6, 133.8, 130.2, 129.1 (q, J = 29.2 Hz), 125.5, 124.7 (q, J = 274.1 Hz), 124.0 (q, J = 5.9 Hz), 48.9, 43.5, 26.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -61.9 (s). LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0844.

6-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (65b): yield: 7.84 g, 78%, colorless oil, b.p. 58 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 2H), 7.10 (d, J = 7.7 Hz, 1H), 4.04 (s, 2H), 3.15 (t, J = 5.9 Hz, 2H), 2.83 (t, J = 5.8 Hz, 2H), 1.83 (s, 1H). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 140.1, 135.7, 128.5 (q, J = 32.2 Hz), 126.8, 126.3 (q, J = 3.8 Hz), 124.4 (q, J = 271.8 Hz), 122.6 (q, J = 3.7 Hz), 48.4, 43.7, 29.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s). LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0840.

7-(Trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (66b): yield: 7.44 g, 74%, yellow solid, m.p. 35-37 °C, b.p. 67 °C, 1 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 7.9 Hz, 1H), 7.24 (s, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.02 (s, 2H), 3.13 (t, J = 5.9 Hz, 2H), 2.82 (t, J = 5.6 Hz, 2H), 1.85 (s, 1H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.9 (s). ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 139.1, 136.7, 129.9, 128.2 (q, J = 32.2 Hz), 126.6 (q, J = 272.0 Hz), 123.3 (q, J = 3.8 Hz), 122.8 (q, J = 3.7 Hz), 48.3, 43.7, 29.3. LCMS (*m/z*): 202 (M+H)$^+$. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{10}H_{11}F_3N$, 202.0844; found 202.0839.

General procedure for pyridine hydrogenation. Synthesis of compounds 45b, 48b, 56b, 67b.

Corresponding pyridine (0.01 mol) was dissolved in 10 mL of TFA and mixed with PtO_2 (83 mg, 5 wt%) and was hydrogenated under 1 atm at ambient temperature until the calculated amount of hydrogen was consumed. Reaction mixture was filtered, and the filtrate was concentrated under reduced pressure, treated with a 10% K_2CO_3 (100 mL) solution and filtered. Solid residue was washed with water (3 × 100 mL) and dried at ambient temperature to yield: crude product which was further crystallized from benzene.

6-(Trifluoromethyl)piperidin-2-one (45b): yield: 1.64 g, 98%, white solid, m.p. 123-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68-1.96 (m, 4H), 2.14-2.24 (m, 2H), 4.08 (m, 1H), 8.07 (br. s, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 18.1, 20.9, 31.4, 52.6 (q, J = 27 Hz), 125.9 (q, J = 299 Hz), 171.6. ^{19}F NMR (376 MHz, DMSO-d_6) δ -76.1 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_9F_3NO$, 168.0636; found 168.0631.

3-(Trifluoromethyl)piperidin-2-one (48b): yield: 1.52 g, 91%, white solid, m.p. 108-109 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.68-1.74 (m, 2H), 1.78-2.10 (m, 2H), 3.14 (br. s, 2H), 3.31-3.40 (m, 1H), 7.87 (br. s, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 20.3, 21.4 (q, J = 2 Hz), 41.0, 44.4 (q, J = 25 Hz), 126.0 (q, J = 278 Hz), 164.1 (q, J = 2 Hz). ^{19}F NMR (376 MHz, DMSO-d_6): δ -66.4 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_9F_3NO$, 168.0636; found 168.0638.

4-(Trifluoromethyl)piperidin-2-one (56b): yield: 1.2 g, 72%, white solid, m.p. 118-119 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55-1.97 (m, 2H), 2.10-2.37 (m, 2H), 2.62-2.99 (m, 1H), 3.11-3.20 (m, 2H), 7.73 (br. s, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 21.2 (q, J = 2 Hz), 30.0 (q, J = 2 Hz), 36.4 (q, J = 28 Hz), 39.2, 127.3 (q, J = 278 Hz), 167.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -73.2 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_9F_3NO$, 168.0636; found 168.0640.

5-(Trifluoromethyl)piperidin-2-one (67b): yield: 1.49 g, 89%, white solid, m.p. 142-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70-1.99 (m, 2H), 2.24-2.32 (m, 2H), 2.84 (br. s, 1H), 3.14-3.32 (m, 2H), 7.62 (br. s, 1H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 19.8, 29.3, 36.6 (q, J = 27 Hz), 39.4 (q, J = 27 Hz), 127.3 (q, J = 298 Hz), 169.7. ^{19}F NMR (376 MHz, DMSO-d_6) δ -71.4 (s). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_6H_9F_3NO$, 168.0636; found 168.0632.

General procedure for piperidone hydrolysis: Synthesis of amino acids 69-71. Corresponding piperidone (0.01 mol) was dissolved in 10 mL of concentrated HCl and was heated at reflux for 16 h. The reaction mixture was concentrated under reduced

pressure and the solid residue was crystallized from acetone/benzene.

5-Amino-2-(trifluoromethyl)pentanoic acid hydrochloride (69): yield: 2.11 g, 95%, white solid, m.p. 153-155 °C. ^{1}H NMR (400 MHz, D_2O) δ 1.72-2.00 (m, 4H), 2.39-2.44 (m, 2H), 4.06 (m, 1H). ^{13}C {^{1}H} NMR (100 MHz, D_2O) δ 19.4, 25.5, 32.7, 52.2 (q, J = 31 Hz), 123.7 (q, J = 284 Hz), 177.4. ^{19}F NMR (376 MHz, D_2O) δ -77.7 (d, $^3J_{HF}$ = 7 Hz, CF_3), -75.0 (d, $^3J_{HF}$ = 7 Hz, CF_3). Anal. calcd for $C_6H_{11}ClF_3NO_2$: C, 32.52; H, 5.00; Cl, 16.00; N, 6.32. Found: C, 32.38; H, 5.17; Cl, 16.17; N, 6.05.

5-Amino-3-(trifluoromethyl)pentanoic acid hydrochloride (70): yield: 2.11 g, 95%, white solid, m.p. 144-146 °C. ^{1}H NMR (400 MHz, D_2O) δ 1.76-2.04 (m, 2H), 2.55 (t, J = 7.53 Hz, 2H,), 2.65-2.70 (m, 1H), 3.10-3.17 (m, 2H). ^{13}C {^{1}H} NMR (100 MHz, D_2O) δ 20.7, 30.4, 37.4, 40.1 (q, J = 28 Hz), 126.9 (q, J = 271 Hz), 176.8. ^{19}F NMR (376 MHz, D_2O) δ -70.5 (d, J = 8 Hz). Anal. calcd for $C_6H_{11}ClF_3NO_2$: C, 32.52; H, 5.00; Cl, 16.00; N, 6.32. Found: C, 32.41; H, 4.85; Cl, 15.90; N, 6.59.

5-Amino-4-(trifluoromethyl)pentanoic acid hydrochloride (71): yield: 1.82 g, 82%, white solid, m.p. 151-152 °C. ^{1}H NMR (400 MHz, D_2O) δ 1.63-1.84 (m, 2H), 2.31-2.53 (m, 2H), 2.63 (br. s, 1H), 2.87 (br. s, 2H). ^{13}C {^{1}H} NMR (100 MHz, D_2O): δ 25.6, 32.5, 36.8 (m), 37.0, 127.1 (q, J= 284 Hz), 174.7. ^{19}F NMR (376 MHz, D_2O): δ = -71.7 (d, J = 8 Hz). Anal. calcd for $C_6H_{11}ClF_3NO_2$: C, 32.52; H, 5.00; Cl, 16.00; N, 6.32. Found: C, 32.67; H, 4.87; Cl, 15.88; N, 6.22.

5-Amino-5-(trifluoromethyl)pentanoic acid hydrochloride (72): yield: 1.84 g, 83%, white solid, m.p. 78-80 °C. ^{1}H NMR (400 MHz, D_2O) δ 1.73-1.91 (m, 4H), 2.98 (br. s, 2H), 3.38 (q, J = 7 Hz, 1H). ^{3}C {^{1}H} NMR (100 MHz, D_2O) δ 22.6, 24.0, 38.9, 49.0 (q, J = 27 Hz), 124.7 (q, J = 239 Hz), 171.1. ^{19}F NMR (376 MHz, D_2O) δ -69.0 (d, J = 8 Hz). Anal. calcd for $C_6H_{11}ClF_3NO_2$: C, 32.52; H, 5.00; Cl, 16.00; N, 6.32. Found: C, 32.37; H, 5.15; Cl, 15.79; N, 6.45.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra of new and known compounds, pKa and pI determination, CIF files and photos.

AUTHOR INFORMATION

Corresponding Author

E-mail: Pavel.Mykhailiuk@gmail.com

www.mykhailiuk.org, www.enamine.net

Notes

Conflict of interests: PM is an employee of a chemical supplier Enamine.

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