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Fluorinated *N*-[2-(haloalkyl)phenyl]imidoyl chloride, a key intermediate for the synthesis of 2-fluoroalkyl substituted indole derivatives *via* Grignard cyclization process

Zengxue Wang [a], Fenglian Ge [a], Wen Wan [a], Haizhen Jiang [a], Jian Hao [a,b,*]

[a] *Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China*
[b] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

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This paper is dedicated to Prof. Kenji Uneyama in honor of his receiving the 2007 ACS Award for Creative Work in Fluorine Chemistry.

Abstract

Fluorinated *N*-[2-(haloalkyl)phenyl]imidoyl chloride, which was readily available from the corresponding anilines by using Uneyama's one-pot synthesis of fluorinated imidoyl chloride, was found to be a key intermediate for the facile synthesis of 2-fluoroalkyl substituted indole derivatives *via* the Grignard cyclization process. The bromination of 3-methyl group of 3-methyl-2-trifluoromethyl indole with NBS/CCl_4 led to the formation of 3-bromomethyl substituted indole which can be further utilized to synthesize some new and biologically interested indole derivatives.

Keywords: Fluorine-containing indoles; Grignard cyclization; Imidoyl chlorides; Heterocycles

1. Introduction

Fourteen years have been passed since the discovery of one-pot synthesis of trifluoroacetimidoyl halides by Uneyama et al. in 1993 [1]. Fluorinated imidolyl halides became a versatile tool in the synthesis of various and important fluorine-containing molecules, such as fluorinated amino acids, fluorinated heterocycles, etc. [2]. Among those, the fluoroalkyl substituted indole derivatives have received wide attention from either synthetic or pharmaceutical view for long time due to their wide potential bioactivities [3]. The transition metal catalyzed ring closure methodology provides a direct access to the indole ring component with fewer steps and became a key strategy for the synthesis of indole ring system in last 40 years [4]. However, the construction of 2- or 3-fluoroalkyl substituted indole ring system is not well-investigated so far mainly due to the limitation of starting material source [5]. The development of novel and simple approach to synthesize the fluoroalkyl substituted indole derivatives from commercially or rapidly available materials still remains a challenge.

2. Results and discussion

2.1. Grignard cyclization reaction to the synthesis of 2-fluoroalkyl substituted indoles

As previously communicated, the Grignard cyclization reaction of fluoroalkyl substituted *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides, which were rapidly prepared from *o*-bromoalkyl anilines *via* Uneyama's one-pot approach for the synthesis of fluorinated imidoyl halides, provided a facile and efficient approach to access the 2-fluoroalkyl indole ring system [6]. Following on this previous work, this method was found to be also applicable to the Grignard cyclization of using *o*-chloroalkyl substituted imidoyl chloride under same reaction conditions (Scheme 1).

The Grignard cyclization reaction of either fluorinated *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides (**2**) or *N*-[2-(chloroalkyl)phenyl]imidoyl chlorides (**4**) was achieved under normal

* Corresponding author at: Department of Chemistry, Shanghai University, 99 Shangda Road, Shanghai 200444, China. Tel.: +86 21 66133380; fax: +86 21 66133380.
E-mail address: jhao@mail.shu.edu.cn (J. Hao).

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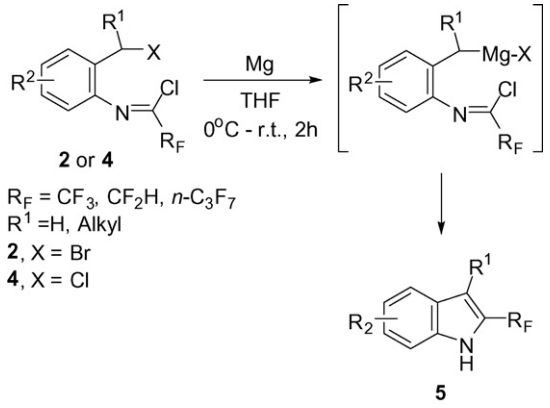


Scheme 1. Grignard cyclization reaction of fluoroalkyl substituted *N*-[2-(haloalkyl)phenyl]imidoyl chlorides.

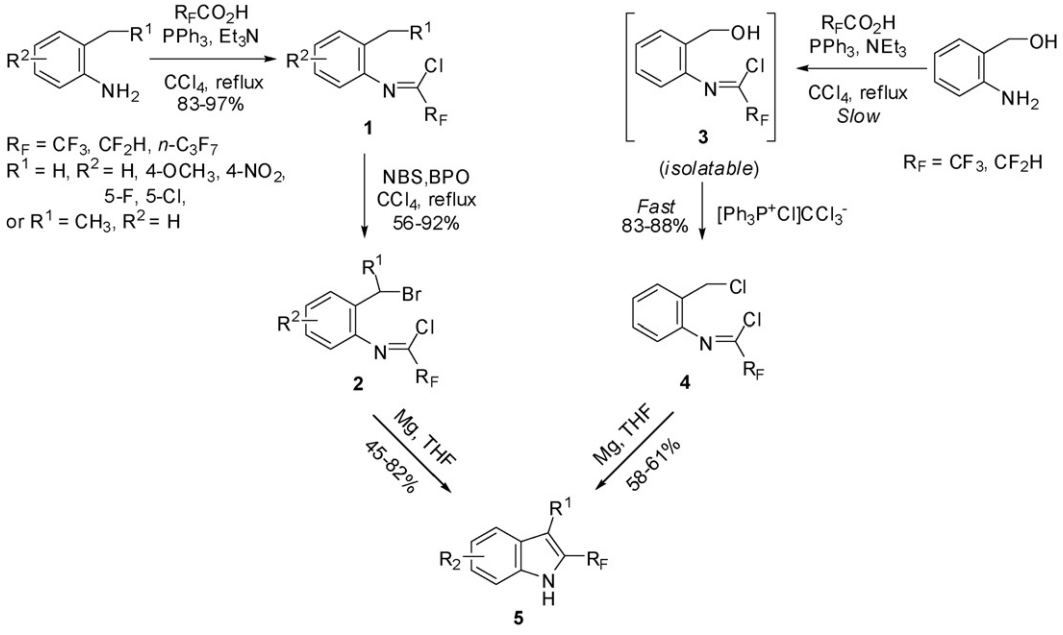
Grignard reaction condition with moderate to good yields. The yields of **5** from cyclization of **2** were found to be greatly affected by the electronic effect of the substituent group R^2 on the benzene ring. Without the substituent group (R^2 = H) or with an electron-donating group, such as a methoxyl group, **5** could be obtained in good yields. With electron negative element, such as F and Cl, the yields of **5** were decreased to the moderate possibly due to the electron-inducing effect of halogens. The electron-withdrawing substituent, such as a nitro group, was found to inhibit the reaction effectively from the generation of Grignard intermediate species and resulted in the recovery of starting material (Table 1). The reaction process of this cyclization was generally clean, no byproduct was detected in reaction mixture in all examined cases. Good yield and simple working-up procedure provides us a possibility to carry out the reactions even in larger scale.

The *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides (**2**) were simply prepared in two steps from *o*-alkylanilines, which were utilized to the synthesis of fluorine-containing imidoyl chlorides (**1**) in the 1st step according to the Uneyama's one-pot approach [1], the subsequent α-bromination at the benzylic position of **1** in the presence of *N*-bromosuccinimide (NBS)/benzoyl peroxide (BPO) resulted in the formation of *N*-[2-(bromoalkyl)phenyl]imidolyl chlorides (**2**) in good to excellent yields (Scheme 2).

Table 1
Synthesis of 2-fluoroalkyl substituted indole derivatives **5** from *o*-alkylanilines[a]

Entry	R_F	R^1	R^2	Yield of **1** (%)	Yield of **2** (%)	Yield of **5** (%)
1	CF_3	H	H	89 (**1a**)	91 (**2a**)	78 (**5a**)
2	CF_3	CH_3	H	86 (**1b**)	92 (**2b**)	82 (**5b**)
3	CF_3	H	4-OCH_3	92 (**1c**)	88 (**2c**)	75 (**5c**)
4	CF_3	H	5-F	97 (**1d**)	82 (**2d**)	62 (**5d**)
5	CF_3	H	5-Cl	97 (**1e**)	68 (**2e**)	45 (**5e**)
6	CF_3	H	4-NO_2	88 (**1f**)	56 (**2f**)	–[b]
7	CF_2H	H	H	83 (**1g**)	85 (**2g**)	77 (**5g**)
8	CF_2H	H	4-OCH_3	90 (**1h**)	82 (**2h**)	78 (**5h**)
9	*n*-C_3F_7	CH_3	H	89 (**1i**)	92 (**2i**)	79 (**5i**)
10	*n*-C_3F_7	H	4-OCH_3	90 (**1j**)	83 (**2j**)	76 (**5j**)

[a] The yields listed in this table are isolated yields.
[b] Recovery of starting material.



Scheme 2. Synthesis of 2-fluoroalkyl substituted indole derivatives from *o*-alkylanilines or (2-aminophenyl)methanol.

Table 2
Synthesis of 2-fluoroalkyl substituted indoles **5** from (2-amino-phenyl)methanol[a]

Entry	R_F	R	Yield of **4** (%)	Yield of **5** (%)
1	CF_3	H	88 (**4a**)	61 (**5a**)
2	CF_2H	H	83 (**4g**)	58 (**5g**)

[a] The yields listed here are isolated yields.

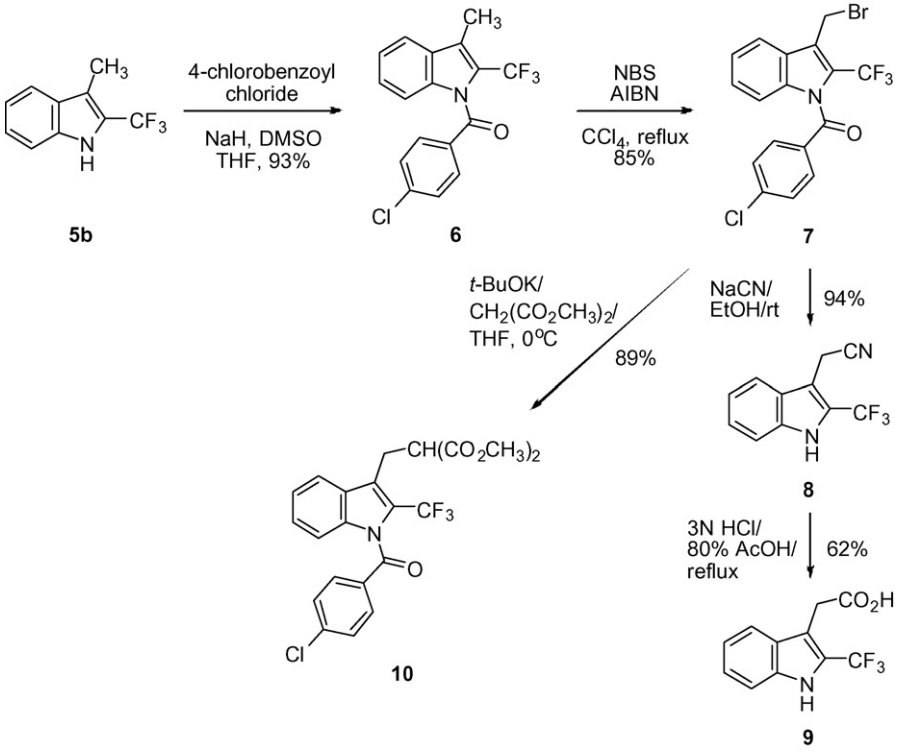
Although *N*-[2-(bromoalkyl)phenyl]imidolyl chlorides (**2**) were generally sensitive to acids, bases, and moisture, **2** can be purified by flash column chromatography on neutral or basic aluminum oxide, or distillation under reduced pressure. The electron-withdrawing substituents such as a nitro group substituted on the benzene ring decreased the yield of bromination reaction (entry 6, Table 1).

The similar reaction condition for the synthesis of **1** in the existence of excess amount of triphenyl-phosphine (6 equiv.) was successfully applied to the preparation of **4a** directly from (2-aminophenyl)methanol in 88% yield in our initial test. The *N*-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride intermediate (**3a**) assumed in Scheme 2 was isolated from reaction mixture as a stable product in 63% yield. During the course of this reaction, **3a** was found to be a major product in the 1st half of reaction time, but with time going, **3a** disappeared quickly, instead, **4a** was formed as a final product. The excess amount of $[Ph_3P^+Cl]CCl_3^-$ intermediate generated during the reaction process was considered to be a chlorinating reagent, and caused the conversion of OH group in **3a** into Cl directly. The Grignard cyclization reaction (GCR) of **4a** also led to the formation of **5a** in 61% yield though the yield obtained from this cyclization was relatively lower than the yield from **2a** (Scheme 2). After that, this method was extended to the synthesis of 2-difluoromethyl indole **5g** in 58% yields (Table 2). As an alternative route, the preparation of **4** and subsequent Grignard cyclization reaction (GCR) of **4** effectively extended the starting material source at least for this synthesis.

2.2. Applications of 3-methyl-2-trifluoromethyl indole (*5b*)

To stretch the applications of 2-fluoroalkyl substituted indoles, the 3-methyl-2-trifluoromethyl indole (**5b**) was selected as a substrate to examine the synthesis of some interested molecules, such as 2-fluoroalkyl substituted new heteroauxin and indomethacin derivatives which are considered to the successful formation of **7** provided us an opportunity to synthesize new fluorine-containing indole derivatives *via* the nucleophilic substitution at 3-bromomethyl position. The nucleophilic substitution with NaCN was examined in EtOH at room temperature, and resulted in the formation of *N*-deprotected product **8** in 94% yield. Deprotection of *N*-chlorobenzoyl group was caused by the attack possibly have the different potential bioactivities comparing with the original one. The protection of nitrogen group in **5b** with 4-chlorobenzoyl chloride under basic condition in DMSO-THF resulted in the formation *N*-4-chlorobenzoyl protected **6** in 93% yield. Subsequential bromination of 3-methyl group of **6** with NBS/AIBN refluxing in CCl_4 led to formation of **7** in 85% yield [7].

The successful formation of **7** provided us an opportunity to synthesize new fluorine-containing indole derivatives *via* the nucleophilic substitution at 3-bromomethyl position. The nucleophilic substitution with NaCN was examined in EtOH



Scheme 3. Applications of 3-methyl-2-trifluoromethyl indole (**5b**).

at room temperature, and resulted in the formation of *N*-deprotected product **8** in 94% yield. Deprotection of *N*-chlorobenzoyl group was caused by the attack of cyanide group. Subsequential hydrolysis of cyanide group of **8** led to the formation of 2-trifluoromethyl substituted heteroauxin **9** in 62% yield, which can possibly be used as a potential new plant growth regulator or herbicide [8]. The bioactivity of **9** is currently under investigation. Meanwhile, **9** can be used as a precursor for the synthesis of 2-trifluoromethyl substituted indomethacin derivatives. The nucleophilic substitution reaction of **7** with malonate carboanion also successfully led to the formation of **10** in 89% yield (Scheme 3).

3. Conclusion

In summary, the biologically interested 2-fluoroalkyl substituted indole derivatives were successfully synthesized *via* the Grignard cyclization reaction of corresponding fluorinated *N*-[2-(haloalkyl)phenyl]imidoyl chlorides without any transition metal catalysts, Each step of this method is suitable for the larger scale preparation. The nucleophilic substitutions of 3-bromomethyl indole derivative (**7**) have been demonstrated as one of the efficient ways to access new generation of interested various fluorine-containing indole derivatives, which may lead to the discovery of new and valuable biologically active molecules.

4. Experimental

4.1. General

THF was distilled under N_2 atmosphere from sodium/benzophenone prior to use. Thin layer chromatography (TLC) was performed on HSGF254 silica gel. All melting points were taken on a WRS-1A or WRS-1B Digital Melting Point Apparatus without correction. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ on a Bruker AV-500 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in ppm relative to internal chloroform (δ 77.0 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from external fluorotrichloro-methane ($CFCl_3$). Coupling constants (J) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartlet; br refers to a broad signal. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer. High resolution mass spectra were recorded on a CONCEPT 1H spectrometer. Elemental analyses were carried out on a VARIO EL111 elemental analyzer.

4.2. General procedure for the synthesis of fluorinated *N*-(2-alkylphenyl)imidoyl chlorides (*1*)

To a 200 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added Ph_3P (34.5 g, 132 mmol), Et_3N (7.3 mL, 53 mmol), CCl_4 (21.1 mL, 220 mmol), and fluorine-containing carboxylic acid (44 mmol) at 0 °C under a nitrogen atmosphere and stirred for 10 min. A solution of *o*-alkylaniline (44 mmol) dissolved in CCl_4 (21.1 mL, 220 mmol) was added dropwise to the reaction mixture. Upon completion of the addition, the reaction mixture was allowed to reflux for 3 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed with PE (3×), the precipitation was removed *via* filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by flash column chromatography (10:1 hexane–EtOAc) or distillation under reduced pressure to yield products **1**.

4.2.1. *N*-(*o*-Tolyl)-2,2,2-trifluoroacetimidoyl chloride (*1a*)

1a was obtained as a yellowish green oil in 89% yield by flash column chromatography on neutral Al_2O_3: bp 56–58 °C/8 mmHg; ^{1}H NMR (500 MHz) δ 7.27–7.16 (m, 3H, Ar–*H*), 6.91 (d, J = 8.0 Hz, 1H, Ar–*H*), 2.17 (s, 3H, Ar–C*H*$_3$); ^{13}C NMR (125 MHz) δ 142.7, 132.4 (q, $^2J_{C-F}$ = 42.4 Hz, *C*–CF_3), 130.8, 129.2, 127.1, 126.4, 118.4, 116.8 (q, $^1J_{C-F}$ = 275.3 Hz, *C*F_3), 17.4 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −71.45 (s, 3F); IR (neat) 3027, 1698 (C=N), 1489, 1291, 1210, 1163, 947, 718 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_7ClF_3N$ [M^+]: 221.0219, Found: 221.0217.

4.2.2. *N*-(2-Ethylphenyl)-2,2,2-trifluoroacetimidoyl chloride (*1b*)

1b was obtained as a yellowish green oil in 86% yield by flash column chromatography on neutral Al_2O_3: bp 54–55 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.31–6.91 (m, 4H, Ar–*H*), 2.53 (q, J = 7.5 Hz, 2H, Ar–C*H*$_2$CH$_3$), 1.15 (t, J = 7.5 Hz, 3H, Ar–CH$_2$C*H*$_3$); ^{13}C NMR (125 MHz) δ 142.1, 135.6, 132.1 (q, $^2J_{C-F}$ = 42.9 Hz, *C*–CF_3), 129.1, 127.4, 126.4, 118.5, 116.8 (q, $^1J_{C-F}$ = 275.4 Hz, *C*F_3), 24.7 (Ar–*C*H$_2$CH$_3$), 14.3 (Ar–CH$_2$*C*H$_3$); ^{19}F NMR (470 MHz) δ −71.51 (s, 3F); IR (neat) 2972, 1699 (C=N), 1487, 1287, 1206, 1164, 948, 766 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_9ClF_3N$ [M^+]: 235.0376, Found: 235.0373.

4.2.3. *N*-(4-Methoxy-2-methylphenyl)-2,2,2-trifluoroacetimidoyl chloride (*1c*)

1c was obtained as a light yellow oil in 92% yield by flash column chromatography on basic Al_2O_3: bp 76–78 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.18 (d, J = 8.5 Hz, 1H, Ar–*H*), 6.81 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.77 (dd, J = 8.8, 2.8 Hz, 1H, Ar–*H*), 3.81 (s, 3H, Ar–OC*H*$_3$), 2.23 (s, 3H, Ar–C*H*$_3$); ^{13}C NMR (125 MHz) δ 159.2, 134.7, 134.2, 128.6 (q, $^2J_{C-F}$ = 42.5 Hz, *C*–CF_3), 120.7, 116.9 (q, $^1J_{C-F}$ = 275.0 Hz, *C*F_3), 116.0, 111.3, 55.3 (Ar–O*C*H$_3$), 18.0 (Ar–*C*H$_3$); ^{19}F NMR (470 MHz) δ −71.16 (s, 3F); IR (neat) 2959, 1690 (C=N), 1603, 1496, 1282, 1248, 1158, 927, 800 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_9ClF_3NO$ [M^+]: 251.0325, Found: 251.0323.

4.2.4. *N*-(5-Fluoro-2-methylphenyl)-2,2,2-trifluoroacetimidoyl chloride (*1d*)

1d was obtained as a colorless oil in 97% yield by distillation under reduced pressure: bp 48–49 °C/10 mmHg; ^{1}H NMR (500 MHz) δ 7.21 (dd, J = 8.5, 6.0 Hz, 1H, Ar–*H*), 6.90 (td,

J = 8.5, 2.5 Hz, 1H, Ar–*H*), 6.66 (dd, J = 9.0, 2.5Hz, 1H, Ar–*H*), 2.12 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 161.0 (d, $^1J_{C-F}$ = 243.8 Hz), 143.5 (d, $^3J_{C-F}$ = 8.8 Hz), 133.8 (q, $^2J_{C-F}$ = 42.9 Hz, *C*–CF_3), 131.9 (d, $^3J_{C-F}$ = 8.8 Hz), 124.6 (d, $^4J_{C-F}$ = 3.8 Hz), 116.7 (q, $^1J_{C-F}$ = 275.8 Hz, *C*F_3), 113.6 (d, $^2J_{C-F}$ = 21.2 Hz), 106.0 (d, $^2J_{C-F}$ = 23.8 Hz), 16.7 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −71.56 (s, 3F, C*F*$_3$), −115.6 (q, J = 7.8 Hz, 1F, Ar–*F*); IR (neat) 2931, 1697 (C=N), 1498, 1294, 1217, 1166, 960, 810 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_6ClF_4N$ [M^+]: 239.0125, Found: 239.0128.

4.2.5. *N-(5-Chloro-2-methylphenyl)-2,2,2-trifluoroacetimidoyl chloride (**1e**)*

1e was obtained as a colorless oil in 97% yield by distillation under reduced pressure: bp 66–67 °C/8 mmHg; ^{1}H NMR (500 MHz) δ 7.21–7.15 (m, 2H, Ar–*H*), 6.92 (d, J = 2.0 Hz, 1H, Ar–*H*), 2.13 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 143.6, 133.9 (q, $^2J_{C-F}$ = 42.9 Hz, *C*–CF_3), 131.9, 131.8, 127.4, 126.8, 118.4, 116.7 (q, $^1J_{C-F}$ = 275.8 Hz, *C*F_3), 16.8 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −71.49 (s, 3F); IR (neat) 2928, 1699 (C=N), 1597, 1484, 1288, 1165, 948, 811 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_6Cl_2F_3N$ [M^+]: 254.9829, Found: 254.9833.

4.2.6. *N-(2-Methyl-4-nitrophenyl)-2,2,2-trifluoroacetimidoyl chloride (**1f**)*

1f was obtained as a yellow oil in 88% yield by distillation under reduced pressure: bp 90–92 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 8.19 (d, J = 2.0 Hz, 1H, Ar–*H*), 8.16 (dd, J = 8.8, 2.2 Hz, 1H, Ar–*H*), 6.99 (d, J = 8.5 Hz, 1H, Ar–*H*), 2.26 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 148.2, 146.0, 135.8 (q, $^2J_{C-F}$ = 43.6 Hz, *C*–CF_3), 129.7, 126.1, 122.4, 118.8, 116.4 (q, $^1J_{C-F}$ = 276.0 Hz, *C*F_3), 17.4 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −71.59 (s, 3F); IR (neat) 3105, 1700 (C=N), 1523, 1287, 1212, 1166, 948, 718 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_6ClF_3N_2O_2$ [M^+]: 266.0070, Found: 266.0072.

4.2.7. *N-(o-Tolyl)-2,2-difluoroacetimidoyl chloride (**1g**)*

1g was obtained as a colorless oil in 83% yield by flash column chromatography on neutral Al_2O_3: bp 58–60 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.31–7.19 (m, 3H, Ar–*H*), 6.92 (d, J = 7.5 Hz, 1H, Ar–*H*), 6.32 (t, J_{H-F} = 54.8 Hz, 1H, CF_2H), 2.20 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 143.6, 138.7 (t, $^2J_{C-F}$ = 32.5 Hz, *C*–CF_2H), 130.7, 128.6, 126.5, 126.4, 118.6, 110.3 (t, $^1J_{C-F}$ = 245.6 Hz, *C*F_2H), 17.4 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −118.76 (d, J_{F-H} = 54.5 Hz, 2F); IR (neat) 3026, 1694 (C=N), 1488, 1350, 1169, 1069, 772 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_8ClF_2N$ [M^+]: 203.0313, Found: 203.0311.

4.2.8. *N-(4-Methoxy-2-methylphenyl)-2,2-difluoroacetimidoyl chloride (**1h**)*

1h was obtained as a light yellow oil in 90% yield by distillation under reduced pressure: bp 96–98 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.05 (d, J = 8.5 Hz, 1H, Ar–*H*), 6.80 (d, J = 3.0 Hz, 1H, Ar–*H*), 6.76 (dd, J = 8.8, 2.8 Hz, 1H, Ar–*H*), 6.25 (t, J_{H-F} = 55.0 Hz, 1H, CF_2H), 3.80 (s, 3H, Ar–OCH_3), 2.19 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 158.5, 136.1 (t, $^2J_{C-F}$ = 32.5 Hz, *C*–CF_2H), 136.0, 132.7, 120.5, 116.0, 111.3, 110.7 (t, $^1J_{C-F}$ = 245.0 Hz, *C*F_2H), 55.4 (Ar–O*C*H_3), 18.0 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −118.39 (d, J_{F-H} = 54.5 Hz, 2F); IR (neat) 2957, 1684 (C=N), 1604, 1496, 1249, 1164, 1056, 813 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_{10}ClF_2NO$ [M^+]: 233.0419, Found: 233.0414.

4.2.9. *N-(2-Ethylphenyl)-2,2,3,3,4,4,4-heptafluorobutanimidoyl chloride (**1i**)*

1i was obtained as a colorless oil in 89% yield by flash column chromatography on basic Al_2O_3: bp 66–68 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.31–6.93 (m, 4H, Ar–*H*), 2.53 (q, J = 7.5 Hz, 2H, Ar–CH_2CH$_3$), 1.14 (t, J = 7.5 Hz, 3H, Ar–CH$_2$CH_3); ^{13}C NMR (125 MHz) δ 142.3, 136.0, 132.6 (t, $^2J_{C-F}$ = 31.2 Hz, *C*–C_3F_7), 129.2, 127.6, 126.4, 118.5, 117.7 (qt, $^1J_{C-F}$ = 286.2 Hz, $^2J_{C-F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 109.2 (tt, $^1J_{C-F}$ = 260.0 Hz, $^2J_{C-F}$ = 31.2 Hz, $CF_2CF_2CF_3$), 108.7 (m, $CF_2CF_2CF_3$), 24.7 (Ar–CH_2CH$_3$), 14.2 (Ar–CH$_2$*C*H$_3$); ^{19}F NMR (470 MHz) δ −80.20 (t, J = 9.4 Hz, 3F, $CF_2CF_2CF_3$), −110.76 (q, J = 9.4 Hz, 2F, $CF_2CF_2CF_3$), −125.02 (s, 2F, $CF_2CF_2CF_3$); IR (neat) 2973, 1681 (C=N), 1346, 1236, 1190, 1126, 997, 758 cm^{-1}; HRMS: *m*/*z* calcd for $C_{12}H_9ClF_7N$ [M^+]: 335.0312, Found: 335.0315.

4.2.10. *N-(4-Methoxy-2-methylphenyl)-2,2,3,3,4,4,4-heptafluorobutanimidoyl chloride (**1j**)*

1j was obtained as a yellow oil in 90% yield by distillation under reduced pressure: bp 92–93 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.25 (d, J = 9.0 Hz, 1H, Ar–*H*), 6.82 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.78 (dd, J = 8.8, 2.8 Hz, 1H, Ar–*H*), 3.82 (s, 3H, Ar–OCH_3), 2.23 (s, 3H, Ar–CH_3); ^{13}C NMR (125 MHz) δ 159.5, 135.1, 134.9, 128.7 (t, $^2J_{C-F}$ = 31.9 Hz, *C*–C_3F_7), 120.8, 117.8 (qt, $^1J_{C-F}$ = 286.2 Hz, $^2J_{C-F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 116.0, 111.3, 109.3 (tt, $^1J_{C-F}$ = 260.0 Hz, $^2J_{C-F}$ = 30.0 Hz, $CF_2CF_2CF_3$), 108.8 (m, $CF_2CF_2CF_3$), 55.2 (Ar–O*C*H_3), 18.0 (Ar–*C*H_3); ^{19}F NMR (470 MHz) δ −80.25 (t, J = 9.4 Hz, 3F, $CF_2CF_2CF_3$), −110.30 (q, J = 9.4 Hz, 2F, $CF_2CF_2CF_3$), −125.03 (s, 2F, $CF_2CF_2CF_3$); IR (neat) 2959, 1682 (C=N), 1603, 1496, 1235, 1124, 994, 849, 737 cm^{-1}; HRMS: *m*/*z* calcd for $C_{12}H_9ClF_7NO$ [M^+]: 351.0261, Found: 351.0264.

4.3. *General procedure for the synthesis of fluorinated N-[2-(bromoalkyl)phenyl]imidoyl chlorides (**2**)*

To a 200 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added fluorinated *N*-2-arylimidoyl chloride **1** (46 mmol), *N*-bromosuccinimide (8.6 g, 48 mmol), benzoyl peroxide (0.6 g, 2.3 mmol), and anhydrous CCl_4 (80 mL) under a nitrogen atmosphere. This reaction mixture was stirred and heated to reflux for 2–5 h (monitored by TLC). After cooling, the precipitation was removed *via* filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by flash column chromatography (10:1 hexane–EtOAc) or distillation under reduced pressure to yield products **2**.

4.3.1. N-[2-(Bromomethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride (**2a**)

2a was obtained as a colorless oil in 91% yield by flash column chromatography on neutral Al_2O_3: bp 91–93 °C/8 mmHg; ^{1}H NMR (500 MHz) δ 7.49–7.26 (m, 3H, Ar–*H*), 7.01 (d, J = 8.0 Hz, 1H, Ar–*H*), 4.43 (s, 2H, Ar–CH_2Br); ^{13}C NMR (125 MHz) δ 142.6, 134.3 (q, $^2J_{C-F}$ = 43.3 Hz, *C*–CF_3), 130.5, 129.9, 129.4, 127.7, 119.4, 116.7 (q, $^1J_{C-F}$ = 276.0 Hz, *C*F_3), 28.8 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −71.64 (s, 3F); IR (neat) 3075, 1697 (C=N), 1488, 1285, 1166, 953, 762 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_6BrClF_3N$ [M^+]: 298.9324, Found: 298.9321.

4.3.2. N-[2-(1-Bromoethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride (**2b**)

2b was obtained as a colorless oil in 92% yield by flash column chromatography on neutral Al_2O_3: bp 90–92 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.63 (dd, J = 7.5, 2.0 Hz, 1H, Ar–*H*), 7.39–7.31 (m, 2H, Ar–*H*), 6.96 (dd, J = 7.5, 1.2 Hz, 1H, Ar–*H*), 5.29 (q, J = 7.0 Hz, 1H, Ar–C*H*BrCH_3), 2.04 (d, J = 7.0 Hz, 3H, Ar–CHBrCH_3); ^{13}C NMR (125 MHz) δ 141.2, 134.9, 134.1 (q, $^2J_{C-F}$ = 42.9 Hz, *C*–CF_3), 128.9, 127.8, 126.9, 119.2, 116.8 (q, $^1J_{C-F}$ = 275.8 Hz, *C*F_3), 43.1 (Ar–*C*HBrCH_3), 25.1 (Ar–CHBr*C*H_3); ^{19}F NMR (470 MHz) δ −71.59 (s, 3F); IR (neat) 2980, 1697 (C=N), 1486, 1288, 1209, 1165, 951, 765 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_8BrClF_3N$ [M^+]: 312.9481, Found: 312.9479.

4.3.3. N-[2-(Bromomethyl)-4-methoxyphenyl]-2,2,2-trifluoroacetimidoyl chloride (**2c**)

2c was obtained as a yellow oil in 88% yield by flash column chromatography on basic Al_2O_3: bp 108–110 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.25 (d, J = 9.0 Hz, 1H, Ar–*H*), 7.00 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.91 (dd, J = 8.8, 2.8 Hz, 1H, Ar–*H*), 4.48 (s, 2H, Ar–CH_2Br), 3.84 (s, 3H, Ar–OCH_3); ^{13}C NMR (125 MHz) δ 159.4, 134.3, 134.0, 130.7 (q, $^2J_{C-F}$ = 42.5 Hz, *C*–CF_3), 121.5, 116.9 (q, $^1J_{C-F}$ = 275.0 Hz, *C*F_3), 115.5, 114.6, 55.6 (Ar–O*C*H_3), 28.9 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −71.36 (s, 3F); IR (neat) 2965, 1693 (C=N), 1603, 1495, 1284, 1161, 1036, 936, 729 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_8BrClF_3NO$ [M^+]: 328.9430, Found: 328.9435.

4.3.4. N-[2-(Bromomethyl)-5-fluorophenyl]-2,2,2-trifluoroacetimidoyl chloride (**2d**)

2d was obtained as a colorless oil in 82% yield by distillation under reduced pressure: bp 84–86 °C/10 mmHg; ^{1}H NMR (500 MHz) δ 7.43 (dd, J = 8.8, 5.8 Hz, 1H, Ar–*H*), 6.99 (td, J = 8.5, 2.5 Hz, 1H, Ar–*H*), 6.75 (dd, J = 9.0, 2.5 Hz, 1H, Ar–*H*), 4.39 (s, 2H, Ar–CH_2Br); ^{13}C NMR (125 MHz) δ 162.6 (d, $^1J_{C-F}$ = 250.0 Hz), 143.9 (d, $^3J_{C-F}$ = 8.8 Hz), 135.9 (q, $^2J_{C-F}$ = 43.3 Hz, *C*–CF_3), 132.1 (d, $^3J_{C-F}$ = 10.0 Hz), 125.8 (d, $^4J_{C-F}$ = 3.8 Hz), 116.6 (q, $^1J_{C-F}$ = 275.8 Hz, *C*F_3), 114.4 (d, $^2J_{C-F}$ = 21.2 Hz), 107.1 (d, $^2J_{C-F}$ = 25.0 Hz), 28.0 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −71.73 (s, 3F, CF_3), −109.8 (q, J = 7.8 Hz, 1F, Ar–*F*); IR (neat) 2976, 1694 (C=N), 1608, 1497, 1292, 1167, 972, 713 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_5BrClF_4N$ [M^+]: 316.9230, Found: 316.9232.

4.3.5. N-[2-(Bromomethyl)-5-chlorophenyl]-2,2,2-trifluoroacetimidoyl chloride (**2e**)

2e was obtained as colorless oil in 68% yield by distillation under reduced pressure: bp 96–98 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.39 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.26 (dd, J = 8.2, 2.2 Hz, 1H, Ar–*H*), 7.00 (d, J = 2.0 Hz, 1H, Ar–*H*), 4.37 (s, 2H, Ar–CH_2Br); ^{13}C NMR (125 MHz) δ 143.5, 135.9 (q, $^2J_{C-F}$ = 43.3 Hz, *C*–CF_3), 135.0, 131.6, 128.3, 127.6, 119.4, 116.6 (q, $^1J_{C-F}$ = 276.2 Hz, *C*F_3), 27.8 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −71.70 (s, 3F); IR (neat) 2973, 1702 (C=N), 1483, 1288, 1227, 1167, 953, 822 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_5BrCl_2F_3N$ [M^+]: 332.8935, Found: 332.8931.

4.3.6. N-[2-(Bromomethyl)-4-nitrophenyl]-2,2,2-trifluoroacetimidoyl chloride (**2f**)

2f was obtained as a white solid in 56% yield by flash column chromatography on neutral Al_2O_3, after the mixture under stirring for 4–5 h: mp 97–98 °C; ^{1}H NMR (500 MHz) δ 8.37 (d, J = 2.5 Hz, 1H, Ar–*H*), 8.29 (dd, J = 8.8, 2.2 Hz, 1H, Ar–*H*), 7.10 (d, J = 9.0 Hz, 1H, Ar–*H*), 4.43 (s, 2H, Ar–CH_2Br); ^{13}C NMR (125 MHz) δ 148.1, 146.3, 137.9 (q, $^2J_{C-F}$ = 43.8 Hz, *C*–CF_3), 130.7, 125.9, 125.0, 120.1, 116.5 (q, $^1J_{C-F}$ = 276.2 Hz, *C*F_3), 26.9 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −71.74 (s, 3F); IR (neat) 3068, 1706 (C=N), 1518, 1286, 1162, 949, 720 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_5BrClF_3N_2O_2$ [M^+]: 343.9175, Found: 343.9172.

4.3.7. N-[2-(Bromomethyl)phenyl]-2,2-difluoroacetimidoyl chloride (**2g**)

2g was obtained as a white solid in 85% yield by flash column chromatography on neutral Al_2O_3: mp 115–117 °C; ^{1}H NMR (500 MHz) δ 7.45–7.23 (m, 3H, Ar–*H*), 6.97 (d, J = 7.5 Hz, 1H, Ar–*H*), 6.31 (t, J_{H-F} = 54.5 Hz, 1H, CF_2H), 4.40 (s, 2H, Ar–CH_2Br); ^{13}C NMR (125 MHz) δ 143.4, 140.4 (t, $^2J_{C-F}$ = 32.8 Hz, *C*–CF_2H), 130.4, 130.2, 129.4, 127.1, 119.5, 110.2 (t, $^1J_{C-F}$ = 245.9 Hz, *C*F_2H), 29.0 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −119.02 (d, J_{F-H} = 54.5 Hz, 2F); IR (neat) 2925, 1691 (C=N), 1488, 1350, 1170, 1070, 779, 608 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_7BrClF_2N$ [M^+]: 280.9418, Found: 280.9425.

4.3.8. N-[2-(Bromomethyl)-4-methoxyphenyl]-2,2-difluoroacetimidoyl chloride (**2h**)

2h was obtained as a yellow oil in 82% yield by distillation under reduced pressure: bp 136–138 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.16 (d, J = 9.0 Hz, 1H, Ar–*H*), 6.99 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.90 (dd, J = 9.0, 2.5 Hz, 1H, Ar–*H*), 6.29 (t, J_{H-F} = 55.0 Hz, 1H, CF_2H), 4.44 (s, 2H, Ar–CH_2Br), 3.83 (s, 3H, Ar–OCH_3); ^{13}C NMR (125 MHz) δ 158.8, 137.7 (t, $^2J_{C-F}$ = 33.8 Hz, *C*–CF_2H), 135.4, 132.7, 121.5, 115.4, 114.6, 110.5 (t, $^1J_{C-F}$ = 245.6 Hz, *C*F_2H), 55.5 (Ar–O*C*H_3), 29.1 (Ar–*C*H_2Br); ^{19}F NMR (470 MHz) δ −118.60 (d, J_{F-H} = 54.5 Hz, 2F); IR (neat) 2965, 1684 (C=N), 1604, 1496, 1215, 1163, 1067, 821 cm^{-1} HRMS: *m*/*z* calcd for $C_{10}H_9BrClF_2NO$ [M^+]: 310.9524, Found: 310.9521.

*4.3.9. N-[2-(1-Bromoethyl)phenyl]-2,2,3,3,4,4,4-heptafluorobutanimidoyl chloride (**2i**)*

2i was obtained as a light yellow oil in 92% yield by distillation under reduced pressure: bp 94–95 °C/9 mmHg; ^{1}H NMR (500 MHz) δ 7.66 (d, J = 7.5 Hz, 1H, Ar–*H*), 7.36 (m, 2H, Ar–*H*), 6.97 (d, J = 7.5 Hz, 1H, Ar–*H*), 5.27 (q, J = 7.0 Hz, 1H, Ar–C*H*BrCH$_3$), 2.04 (d, J = 7.0 Hz, 3H, Ar–CHBrC*H*$_3$); ^{13}C NMR (125 MHz) δ 141.3, 135.2, 134.8 (t, $^2J_{C–F}$ = 31.2 Hz, *C*–C$_3$F$_7$), 128.8, 128.0, 127.0, 119.0, 117.7 (qt, $^1J_{C–F}$ = 286.2 Hz, $^2J_{C–F}$ = 33.8 Hz, CF$_2$CF$_2$*C*F$_3$), 109.3 (tt, $^1J_{C–F}$ = 260.0 Hz, $^2J_{C–F}$ = 31.2 Hz, *C*F$_2$CF$_2$CF$_3$), 108.7 (m, CF$_2$*C*F$_2$CF$_3$), 42.6 (Ar–*C*HBrCH$_3$), 25.1 (Ar–CHBr*C*H$_3$); ^{19}F NMR (470 MHz) δ −80.18 (t, J = 9.4 Hz, 3F, CF$_2$CF$_2$C*F*$_3$), −111.02 (q, J = 9.4 Hz, 2F, C*F*$_2$CF$_2$CF$_3$), −124.88 (s, 2F, CF$_2$C*F*$_2$CF$_3$); IR (neat) 2981, 1679 (C=N), 1348, 1237, 1127, 998, 761 cm^{-1}; HRMS: *m/z* calcd for C$_{12}$H$_8$BrClF$_7$N [M^+]: 412.9417, Found: 412.9427.

*4.3.10. N-[2-(Bromomethyl)-4-methoxyphenyl]-2,2,3,3,4,4,4-heptafluorobutanimidoyl chloride (**2j**)*

2j was obtained as a yellow oil in 83% yield by distillation under reduced pressure: bp 122–124 °C/10 mmHg; ^{1}H NMR (500 MHz) δ 7.31 (d, J = 9.0 Hz, 1H, Ar–*H*), 7.02 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.91 (dd, J = 8.8, 2.8 Hz, 1H, Ar–*H*), 4.47 (s, 2H, Ar–C*H*$_2$Br), 3.84 (s, 3H, Ar–OC*H*$_3$); ^{13}C NMR (125 MHz) δ 159.8, 134.6, 134.4, 131.1 (t, $^2J_{C–F}$ = 31.9 Hz, *C*–C$_3$F$_7$), 121.7, 117.7 (qt, $^1J_{C–F}$ = 286.2 Hz, $^2J_{C–F}$ = 33.8 Hz, CF$_2$CF$_2$*C*F$_3$), 115.7, 114.6, 109.4 (tt, $^1J_{C–F}$ = 260.0 Hz, $^2J_{C–F}$ = 30.0 Hz, *C*F$_2$CF$_2$CF$_3$), 108.7 (m, CF$_2$*C*F$_2$CF$_3$), 55.6 (Ar–OCH$_3$), 28.7 (Ar–CH$_2$Br); ^{19}F NMR (470 MHz) δ −80.26 (t, J = 9.4 Hz, 3F, CF$_2$CF$_2$C*F*$_3$), −110.53 (q, J = 9.4 Hz, 2F, C*F*$_2$CF$_2$CF$_3$), −124.93 (s, 2F, CF$_2$C*F*$_2$CF$_3$); IR (neat) 2965, 1681 (C=N), 1603, 1495, 1238, 1126, 996, 738 cm^{-1} HRMS: *m/z* calcd for C$_{12}$H$_8$BrClF$_7$NO [M^+]: 428.9366, Found: 428.9363.

*4.4. General procedure for the synthesis of N-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride (**3a**)*

To a 500 mL three-necked round bottom flask equipped with condenser and magnetic stir bar was added Ph$_3$P (69.0 g, 264 mmol), Et$_3$N (7.3 mL, 53 mmol), CCl$_4$ (80 mL), and TFA (3.4 mL, 44 mmol) at 0 °C under a nitrogen atmosphere and stirred for 10 min. A solution of (2-aminophenyl)methanol (5.4 g, 44 mmol) dissolved in CCl$_4$ (15 mL) was added dropwise to the reaction mixture. Upon completion of the addition, the reaction mixture was allowed to reflux for 2 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed with PE (3×), the precipitation was removed *via* filtration. The combined filtrate was concentrated by rotary evaporator. The residue was then purified by flash column chromatography (10:1 hexane–EtOAc) to yield **3a** as the white powder (6.6 g, 27.8 mmol, 63%): mp 100–101 °C; ^{1}H NMR (500 MHz) δ 8.45 (br, 1H, O*H*), 7.91 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.45 (td, J = 8.0, 1.5 Hz, 1H, Ar–*H*), 7.37 (dd, J = 7.5, 1.5 Hz, 1H, Ar–*H*), 7.27 (td, J = 7.5, 1.0 Hz, 1H, Ar–*H*), 4.63 (s, 2H, Ar–C*H*$_2$OH); ^{13}C NMR (125 MHz) δ 155.2 (q, $^2J_{C–F}$ = 37.5 Hz, *C*–CF$_3$), 133.8, 130.4, 130.3, 128.7, 127.1, 124.3, 115.8 (q, $^1J_{C–F}$ = 286.7 Hz, *C*F$_3$), 43.6 (Ar–*C*H$_2$OH); ^{19}F NMR (470 MHz) δ −75.86 (s, 3F); IR (neat) 3268 (OH), 3078, 1709 (C=N), 1546, 1253, 1187, 723 cm^{-1}; HRMS: *m/z* calcd for C$_9$H$_7$ClF$_3$NO [M^+]: 237.0168, Found: 237.0165.

*4.5. General procedure for the synthesis of fluorinated N-[2-(chloroalkyl)phenyl]imidoyl chlorides (**4**)*

Compounds **4** were obtained by flash column chromatography (10:1 hexane–EtOAc) on neutral Al$_2$O$_3$ after refluxing for 3 h under the same procedure described above for **3a**.

*4.5.1. N-[2-(Chloromethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride (**4a**)*

4a was obtained as a yellowish green oil in 88% yield: bp 102–104 °C/12 mmHg; ^{1}H NMR (500 MHz) δ 7.48 (dd, J = 7.5, 1.0 Hz, 1H, Ar–*H*), 7.41 (td, J = 7.8, 1.2 Hz, 1H, Ar–*H*), 7.30 (td, J = 7.5, 1.5 Hz, 1H, Ar–*H*), 7.02 (dd, J = 8.0, 1.0 Hz, 1H, Ar–*H*), 4.53 (s, 2H, Ar–C*H*$_2$Cl); ^{13}C NMR (125 MHz) δ 142.5, 134.4 (q, $^2J_{C–F}$ = 42.9 Hz, *C*–CF$_3$), 130.2, 129.5, 129.4, 127.6, 119.1, 116.7 (q, $^1J_{C–F}$ = 276.0 Hz, *C*F$_3$), 42.1 (Ar–*C*H$_2$Cl); ^{19}F NMR (470 MHz) δ −71.64 (s, 3F); IR (neat) 2964, 1697 (C=N), 1287, 1210, 1166, 952, 762 cm^{-1}; HRMS: *m/z* calcd for C$_9$H$_6$Cl$_2$F$_3$N [M^+]: 254.9829, Found: 254.9827.

*4.5.2. N-[2-(Chloromethyl)phenyl]-2,2-difluoroacetimidoyl chloride (**4g**)*

4g was obtained as a colorless oil in 83% yield: mp 122–124 °C/14 mmHg; ^{1}H NMR (500 MHz) δ 7.44 (dd, J = 7.8, 1.2 Hz, 1H, Ar–*H*), 7.37 (td, J = 7.8, 1.5 Hz, 1H, Ar–*H*), 7.25 (td, J = 7.5, 1.0 Hz, 1H, Ar–*H*), 6.96 (dd, J = 7.8, 0.8 Hz, 1H, Ar–*H*), 6.28 (t, $J_{H–F}$ = 54.5 Hz, 1H, CF$_2$*H*), 4.49 (s, 2H, Ar–C*H*$_2$Cl); ^{13}C NMR (125 MHz) δ 143.5, 140.7 (t, $^2J_{C–F}$ = 33.1 Hz, *C*–CF$_2$H), 130.4, 129.6, 129.1, 127.2, 119.6, 110.3 (t, $^1J_{C–F}$ = 246.2 Hz, *C*F$_2$H), 42.4 (Ar–*C*H$_2$Cl); ^{19}F NMR (470 MHz) δ −119.00 (d, $J_{F–H}$ = 51.7 Hz, 2F); IR (neat) 2964, 1691 (C=N), 1488, 1350, 1169, 1068, 765, 676 cm^{-1}; HRMS: *m/z* calcd for C$_9$H$_7$Cl$_2$F$_2$N [M^+]: 236.9924, Found: 236.9925.

*4.6. General procedure for the synthesis of 2-fluoroalkyl substituted indoles (**5**)*

To a frame-dried 100 mL three-necked round bottom flask equipped with magnetic stir bar was added magnesium ribbon (0.3 g, 12.1 mmol) and THF (25 mL) under a nitrogen atmosphere. A solution of appropriate fluorinated *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides **2** or fluorinated *N*-[2-(chloroalkyl)phenyl]imidoyl chloride **4** (10.1 mmol) dissolved in THF (6 mL) was added dropwise at 0 °C. The reaction started within a few minutes. After addition, the reaction mixture was stirred for 2 h at 0 °C (monitored by TLC). Upon completion of the addition, the reaction mixture was quenched with 10 mL sat. solution of NH$_4$Cl and extracted with EtOAc

(15 mL, 3×). The combined organic layer was washed with brine, dried over Mg_2SO_4, concentrated by rotary evaporator. The residue was then purified by column chromatography (20:1 hexane–EtOAc) on neutral Al_2O_3 to offer the products **5**.

*4.6.1. 2-Trifluoromethylindole (**5a**)*

5a was obtained as a light yellow solid in 78% yield from **2a**, and 61% yield from **4a**: mp 107–108 °C; ^{1}H NMR (500 MHz) δ 8.30 (br, 1H, N*H*), 7.68 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.40 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.32 (t, J = 7.5 Hz, 1H, Ar–*H*), 7.20 (t, J = 7.5 Hz, 1H, Ar–*H*), 6.92 (s, 1H, C*H*=C–CF_3); ^{13}C NMR (125 MHz) δ 136.1, 126.6, 125.7 (q, $^2J_{C-F}$ = 38.8 Hz, *C*–CF_3), 124.8, 122.1, 121.2 (q, $^1J_{C-F}$ = 266.2 Hz, *C*F_3), 121.1, 111.7, 104.3 (q, $^3J_{C-F}$ = 3.3 Hz, *C*H=C–CF_3); ^{19}F NMR (470 MHz) δ −60.50 (s, 3F); IR (neat) 3389 (NH), 2921, 1375, 1306, 1168, 1103, 940, 818, 754 cm^{-1}; Anal. Calcd for $C_9H_6F_3N$: C, 58.38; H, 3.27; N, 7.57. Found: C, 58.39; H, 3.32; N, 7.55. HRMS: *m*/*z* calcd for $C_9H_6F_3N$ [M^+]: 185.0452, Found: 185.0452.

*4.6.2. 3-Methyl-2-trifluoromethylindole (**5b**)*

5b was obtained as a yellow solid in 82% yield using 1.5 equiv. of magnesium ribbon: mp 73–74 °C; ^{1}H NMR (500 MHz) δ 8.16 (br, 1H, N*H*) 7.64 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.38 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.32 (t, J = 7.7 Hz, 1H, Ar–*H*), 7.19 (t, J = 7.5 Hz, 1H, Ar–*H*), 2.44 (q, J = 1.7 Hz, 3H, C*H*$_3$–C=C–CF_3); ^{13}C NMR (125 MHz) δ 135.2, 128.1, 124.8, 122.1 (q, $^1J_{C-F}$ = 266.3 Hz, *C*F_3), 121.6 (q, $^2J_{C-F}$ = 36.7 Hz, *C*–CF_3), 120.4, 120.1, 114.1 (q, $^3J_{C-F}$ = 2.9 Hz, CH_3–*C*=C–CF_3), 111.6, 8.3 (*C*H_3–C=C–CF_3); ^{19}F NMR (470 MHz) δ −58.61 (s, 3F); IR (neat) 3393 (NH), 2925, 1454, 1321, 1263, 1166, 1116, 756 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_8F_3N$ [M^+]: 199.0609, Found: 199.0610.

*4.6.3. 5-Methoxy-2-trifluoromethyl indole (**5c**)*

5c was obtained as a light yellow solid in 75% yield: mp 50–51 °C; ^{1}H NMR (500 MHz) δ 8.30 (br, 1H, N*H*), 7.32 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.10 (d, J = 2.5 Hz, 1H, Ar–*H*), 7.00 (dd, J = 9.0, 2.5 Hz, 1H, Ar–*H*), 6.85 (s, 1H, C*H*=C–CF_3), 3.86 (s, 3H, Ar–O*CH*$_3$); ^{13}C NMR (125 MHz) δ 154.8, 131.3, 127.1, 126.2 (q, $^2J_{C-F}$ = 38.4 Hz, *C*–CF_3), 121.2 (q, $^1J_{C-F}$ = 265.9 Hz, *C*F_3), 115.7, 112.6, 103.8 (q, $^3J_{C-F}$ = 3.3 Hz, *C*H=C–CF_3), 102.8, 55.7 (Ar–O*C*H$_3$); ^{19}F NMR (470 MHz) δ −60.45 (s, 3F); IR (neat) 3402 (NH), 2949, 1559, 1461, 1224, 1174, 1117, 801 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_8F_3NO$ [M^+]: 215.0558, Found: 215.0557.

*4.6.4. 6-Fluoro-2-trifluoromethylindole (**5d**)*

5d was obtained as a yellow viscous liquid in 62% yield: mp 126 °C (dec.); ^{1}H NMR (500 MHz) δ 8.40 (br, 1H, N*H*), 7.58 (dd, J = 8.8, 5.2 Hz, 1H, Ar–*H*), 7.06 (dd, J = 9.0, 1.8 Hz, 1H, Ar–*H*), 6.96 (td, J = 9.0, 2.2 Hz, 1H, Ar–*H*), 6.88 (s, 1H, C*H*=C–CF_3); ^{13}C NMR (125 MHz) δ 161.2 (d, $^1J_{C-F}$ = 240.0 Hz), 136.2 (d, $^3J_{C-F}$ = 12.5 Hz), 126.2 (q, $^2J_{C-F}$ = 39.2 Hz, *C*–CF_3), 123.2 (d, $^3J_{C-F}$ = 10.0 Hz), 123.1, 121.0 (q, $^1J_{C-F}$ = 265.8 Hz, *C*F_3), 110.4 (d, $^2J_{C-F}$ = 25.0 Hz), 104.4 (q, $^3J_{C-F}$ = 3.3 Hz, *C*H=C–CF_3), 97.9 (d, $^2J_{C-F}$ = 26.2 Hz); ^{19}F NMR (470 MHz) δ −60.66 (s, 3F, C*F*$_3$), −116.7 (m, 1F, Ar–*F*); IR (neat) 3463 (NH), 2929, 1567, 1323, 1258, 1174, 835 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_5F_4N$ [M^+]: 203.0358, Found: 203.0361.

*4.6.5. 6-Chloro-2-trifluoromethylindole (**5e**)*

5e was obtained as a yellow viscous liquid in 45% yield, using 1.5 equiv. of magnesium ribbon: mp 145 °C (dec.); ^{1}H NMR (500 MHz) δ 8.41 (br, 1H, N*H*), 7.59 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.43–7.16 (m, 2H, Ar–*H*), 6.91 (s, 1H, C*H*=C–CF_3); ^{13}C NMR (125 MHz) δ 136.4, 130.7, 126.4 (q, $^2J_{C-F}$ = 38.8 Hz, *C*–CF_3), 125.1, 123.0, 122.1, 120.9 (q, $^1J_{C-F}$ = 266.3 Hz, *C*F_3), 111.6, 104.3 (q, $^3J_{C-F}$ = 3.5 Hz, *C*H=C–CF_3); ^{19}F NMR (470 MHz) δ −60.71 (s, 3F); IR (neat) 3425 (NH), 1554, 1417, 1356, 1313, 1125, 922, 826 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_5ClF_3N$ [M^+]: 219.0063, Found: 219.0059.

*4.6.6. 2-Difluoromethylindole (**5g**)*

5g was obtained as a yellow solid in 77% yield from **2g**, and 58% yield from **4g**: mp 56–58 °C; ^{1}H NMR (500 MHz) δ 8.33 (br, 1H, N*H*), 7.65 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.36 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.28 (t, J = 7.5 Hz, 1H, Ar–*H*), 7.16 (t, J = 7.5 Hz, 1H, Ar–*H*), 6.79 (t, J_{H-F} = 54.5 Hz, 1H, CF_2H), 6.73 (d, J_{H-F} = 2.0 Hz, 1H, C*H*=C–CF_2H); ^{13}C NMR (125 MHz) δ 136.2, 130.0 (t, $^2J_{C-F}$ = 24.2 Hz, *C*–CF_2H), 126.9, 124.1, 121.6, 120.6, 111.6, 110.5 (t, $^1J_{C-F}$ = 233.4 Hz, *C*F_2H), 103.9 (t, $^3J_{C-F}$ = 6.9 Hz, *C*H=C–CF_2H); ^{19}F NMR (470 MHz) δ −109.83 (d, J_{F-H} = 54.9 Hz, 2F); IR (neat) 3395 (NH), 2924, 1621, 1371, 1069, 1015, 810, 750 cm^{-1}; HRMS: *m*/*z* calcd for $C_9H_7F_2N$ [M^+]: 167.0547, Found: 167.0547.

*4.6.7. 2-Difluoromethyl-5-methoxyindole (**5h**)*

5h was obtained as a yellow solid in 78% yield, using 1.5 equiv. of magnesium ribbon: mp 76–78 °C; ^{1}H NMR (500 MHz) δ 8.33 (br, 1H, N*H*), 7.24 (d, J = 9.0 Hz, 1H, Ar–*H*), 7.08 (d, J = 2.5 Hz, 1H, Ar–*H*), 6.95 (dd, J = 9.0, 2.5 Hz, 1H, Ar–*H*), 6.77 (t, J_{H-F} = 55.0 Hz, 1H, CF_2H), 6.66 (d, J = 2.0 Hz, 1H, C*H*=C–CF_2H), 3.84 (s, 3H, Ar–O*CH*$_3$); ^{13}C NMR (125 MHz) δ 154.6, 131.5, 130.6 (t, $^2J_{C-F}$ = 24.2 Hz, *C*–CF_2H), 127.4, 114.8, 112.4, 110.4 (t, $^1J_{C-F}$ = 233.8 Hz, *C*F_2H), 103.6 (t, $^3J_{C-F}$ = 6.8 Hz, *C*H=C–CF_2H), 102.7, 55.7 (Ar–O*C*H$_3$); ^{19}F NMR (470 MHz) δ −109.8 (d, J_{F-H} = 55.0 Hz, 2F); IR (neat) 3459 (NH), 2959, 1561, 1456, 1206, 1173, 1070, 983, 809 cm^{-1}; HRMS: *m*/*z* calcd for $C_{10}H_9F_2NO$ [M^+]: 197.0652, Found: 197.0654.

*4.6.8. 3-Methyl-2-perfluoropropylindole (**5i**)*

5i was obtained as a light yellow solid in 79% yield, using 1.5 equiv. of magnesium ribbon: mp 73–75 °C; ^{1}H NMR (500 MHz) δ 8.18 (br, 1H, N*H*), 7.67 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.41 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.35 (m, 1H, Ar–*H*), 7.22 (m, 1H, Ar–*H*), 2.45 (t, J = 2.2 Hz, 3H, C*H*$_3$–C=C–C_3F_7); ^{13}C NMR (125 MHz) δ 136.0, 128.3, 124.9, 120.4, 120.1, 119.3 (t, $^2J_{C-F}$ = 28.1 Hz. *C*–C_3F_7), 118.0 (qt, $^1J_{C-F}$ = 286.2 Hz, $^2J_{C-F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 116.6 (t, $^3J_{C-F}$ = 3.8 Hz, CH_3–*C*=C–C_3F_7), 114.1 (tt, $^1J_{C-F}$ = 253.1 Hz, $^2J_{C-F}$ = 31.9 Hz, $CF_2CF_2CF_3$), 111.5, 109.2 (m, $CF_2CF_2CF_3$), 8.5 (q, J = 2.1 Hz, *C*H_3–C=C–C_3F_7); ^{19}F NMR (470 MHz) δ −80.26 (t,

J = 9.4 Hz, 3F, $CF_2CF_2CF_3$), −109.60 (q, J = 9.4 Hz, 2F, $CF_2CF_2CF_3$), −126.66 (s, 2F, $CF_2CF_2CF_3$); IR (neat) 3387 (NH), 2928, 1343, 1225, 1112, 903, 748 cm^{-1}; Anal. Calcd for $C_{12}H_8F_7N$: C, 48.17; H, 2.70; N, 4.68. Found: C, 48.20; H, 2.77; N, 4.64. HRMS: m/z calcd for $C_{12}H_8F_7N$ [M^+]: 299.0545, Found: 299.0548.

4.6.9. 5-Methoxy-2-perfluoropropylindole (**5j**)

5j was obtained as a light yellow solid in 76% yield, using 1.5 equiv. of magnesium ribbon: mp 44–46 °C; ^{1}H NMR (500 MHz) δ 8.54 (br, 1H, N*H*), 7.27 (d, J = 9.0 Hz, 1H, Ar–*H*), 7.10 (d, J = 2.0 Hz, 1H, Ar–*H*), 6.99 (dd, J = 8.8, 2.3 Hz, 1H, Ar–*H*), 6.87 (s, 1H, C*H*=C–C_3F_7), 3.84 (s, 3H, Ar–OC*H*$_3$); ^{13}C NMR (125 MHz) δ 155.0, 132.0, 127.5, 124.4 (t, $^2J_{C-F}$ = 29.4 Hz, *C*–C_3F_7), 118.0 (qt, $^1J_{C-F}$ = 286.2 Hz, $^2J_{C-F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 116.1, 112.8 (tt, $^1J_{C-F}$ = 251.9 Hz, $^2J_{C-F}$ = 31.2 Hz, $CF_2CF_2CF_3$), 112.7, 108.8 (m, CF_2CF_2–CF_3), 106.0 (t, ^3J = 5.0 Hz, *C*H=C–C_3F_7), 102.7, 55.8 (Ar–O*C*H$_3$); ^{19}F NMR (470 MHz) δ −80.20 (t, J = 9.4 Hz, 3F, $CF_2CF_2CF_3$), −109.47 (q, J = 9.4 Hz, 2F, $CF_2CF_2CF_3$), −126.70 (s, 2F, $CF_2CF_2CF_3$); IR (neat) 3308 (NH), 2953, 1548, 1459, 1343, 1222, 1180, 976, 792 cm^{-1}; HRMS: m/z calcd for $C_{12}H_8F_7NO$ [M^+]: 315.0494, Found: 315.0496.

4.7. General procedure for the synthesis of 2-trifluoromethylindole derivatives (**6**–**10**)

4.7.1. (4-Chloro-phenyl)[3-methyl-2-(trifluoromethyl)-1H-indol-1-yl]-methanone (**6**)

To a flame-dried 100 mL there-necked flask was added a solution of dimsylsodium [prepared from 0.84 g (21 mmol) of NaH (60% dispersion in oil) and Me_2SO (8.5 mL)] under a nitrogen atmosphere. A solution of 3-methyl-2-trifluoromethylindole **5b** (3.98 g, 20 mmol) in THF (15 mL) was added dropwise to the reaction mixture at 0 °C. After addition, the mixture was warmed up to r.t. and continually stirred at r.t. for 1 h. A solution of 4-chlorobenzoyl chloride (3.25 g, 21 mmol) in THF (20 mL) was then added dropwise to reaction mixture at 0 °C. The reaction mixture was stirred at r.t. for additional 2 h (monitored by TLC). Once it completed, the reaction mixture was poured into ice water and extracted with EtOAc (15 mL, 3×). The combined organic layer was washed with brine, dried over Mg_2SO_4, and concentrated by rotary evaporator. The residue was then purified by column chromatography (20:1 hexane–EtOAc) on neutral Al_2O_3 to offer a colorless crystal (6.27 g, 18.6 mmol, 93%): mp 115–116 °C; ^{1}H NMR (500 MHz) δ 7.78 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.64 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.50 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.28–7.18 (m, 2H, Ar–*H*), 6.79 (d, J = 8.5 Hz, 1H, Ar–*H*), 2.51 (q, J = 2.33 Hz, 3H, C*H*$_3$–C=C–CF_3); ^{13}C NMR (125 MHz) δ 167.5, 140.6, 136.6, 132.4, 131.7 (2 carbons), 129.4 (2 carbons), 128.8, 126.4, 124.5 (q, $^2J_{C-F}$ = 36.3 Hz, *C*–CF_3), 123.2 (q, $^3J_{C-F}$ = 2.9 Hz, CH_3–*C*=C–CF_3), 122.9, 121.6 (q, $^1J_{C-F}$ = 268.3 Hz, *C*F_3), 120.5, 113.6, 9.3 (q, $^4J_{C-F}$ = 2.1 Hz, *C*H_3–C=C–CF_3); ^{19}F NMR (470 MHz) δ −54.36 (s, 3F); IR (neat) 3065, 1701 (C=O), 1591, 1403, 1274, 1161, 1122, 856, 748 cm^{-1}; HRMS: m/z calcd for $C_{17}H_{11}ClF_3NO$ [M^+]: 337.0481, Found: 337.0477.

4.7.2. [3-(Bromomethyl)-2-(trifluoromethyl)-1H-indol-1-yl](4-chlorophenyl)methanone (**7**)

To a flame-dried 100 mL two-necked flask was charged with **6** (3.64 g, 10.8 mmol), *N*-bromosuccinimide (2.30 g, 12.9 mmol), 2,2′-Azobisisobutyronitrile (0.18 g, 1.1 mmol), and anhydrous CCl_4 (50 mL) under a nitrogen atmosphere. The reaction mixture was refluxed for 5 h (monitored by TLC). Once it completed, the reaction mixture was filtered. The precipitation was washed with hot CCl_4 (20 mL, 2×). The combined organic layer was concentrated by rotary evaporator. The residue was purified by column chromatography (20:1 hexane–EtOAc) on neutral Al_2O_3 to offer a colorless crystal (3.82 g, 9.2 mmol, 85%): mp 153 °C (dec.); ^{1}H NMR (500 MHz) δ 7.79 (d, J = 8.5 Hz, 3H, Ar–*H*), 7.51 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.33 (t, J = 7.5 Hz, 1H, Ar–*H*), 7.25 (t, J = 7.5 Hz, 1H, Ar–*H*), 6.82 (d, J = 8.5 Hz, 1H, Ar–*H*), 4.82 (s, 2H, C*H*$_2$Br–C=C–CF_3); ^{13}C NMR (125 MHz) δ 167.1, 141.3, 136.7, 131.9 (2 carbons), 131.6, 129.6 (2 carbons), 126.9, 126.4, 124.9 (q, $^2J_{C-F}$ = 37.5 Hz, *C*–CF_3), 123.4, 121.9 (q, $^3J_{C-F}$ = 2.1 Hz, CH_2Br–*C*=C–CF_3), 120.9 (q, $^1J_{C-F}$ = 268.7 Hz, *C*F_3), 120.6, 113.7, 29.7 (*C*H_2Br–C=C–CF_3); ^{19}F NMR (470 MHz) δ −54.75 (s, 3F); IR (neat) 2922, 1711 (C=O), 1593, 1333, 1161, 1136, 750 cm^{-1}; HRMS: m/z calcd for $C_{17}H_{10}BrClF_3NO$ [M^+]: 414.9586, Found: 414.9588.

4.7.3. 2-Trifluoromethylindole-3-acetonitrile (**8**)

To a flame-dried 150 mL two-necked flask was charged with a solution of NaCN (0.18 g, 3.67 mmol) in EtOH (50 mL). A solution of **7** (1.02 g, 2.45 mmol) in EtOH (10 mL) was added dropwise at 0 °C. After addition, the reaction mixture was stirred at r.t. for 6 h (monitored by TLC). Once it completed, the mixture was directly extracted with EtOAc (20 mL, 2×). The combined organic layer was washed with brine, dried over Mg_2SO_4, and concentrated by rotary evaporator. The residue was then purified by column chromatography (4:1 hexane–EtOAc) to offer a white solid (0.52 g, 2.32 mmol, 94%): mp 106–108 °C; ^{1}H NMR (500 MHz) δ 8.51 (br, 1H, N*H*), 7.80 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.46 (d, J = 8.5 Hz, 1H, Ar–*H*), 7.43–7.28 (m, 2H, Ar–*H*), 3.98 (s, 2H, C*H*$_2$CN); ^{13}C NMR (125 MHz) δ 135.1, 125.8, 125.5, 122.8 (q, $^2J_{C-F}$ = 37.5 Hz, *C*–CF_3), 121.6, 121.2 (q, $^1J_{C-F}$ = 267.1 Hz, *C*F_3), 119.3, 116.9 (*C*≡N), 112.2, 105.3, 12.6 (*C*H_2CN); ^{19}F NMR (470 MHz) δ −58.42 (s, 3F); IR (neat) 3298 (NH), 2920, 2261 (C≡N), 1596, 1463, 1331, 1369, 1167, 1120, 748 cm^{-1}; Anal. Calcd for $C_{11}H_7F_3N_2$: C, 58.93; H, 3.15; N, 12.50. Found: C, 58.94; H, 3.19; N, 12.56. HRMS: m/z calcd for $C_{11}H_7F_3N_2$ [M^+]: 224.0561, Found: 224.0559.

4.7.4. 2-Trifluoromethylindole-3-acetic acid (**9**)

To a 50 mL two-necked flask was charged with a solution of **8** (100 mg, 0.45 mmol in 25 mL 80% AcOH and 1.7 mL 3N HCl), and stirred at r.t. for 10 min. After that, the reaction mixture was allowed to reflux under stirring for 2 weeks (monitored by TLC). Once it completed, the reaction mixture was cooled down to r.t., and treated with sat. solution of $NaHCO_3$ to adjust pH 4. The reaction mixture then was extracted with EtOAc (10 mL, 3×). The combined organic

layer was washed with brine, dried over Mg_2SO_4, and concentrated by rotary evaporator. The residue was purified by column chromatography (2:1 hexane–EtOAc) to offer a yellow solid (68 mg, 0.28 mmol, 62%): mp 111–113 °C; ^{1}H NMR (500 MHz) δ 8.47 (br, 1H, N*H*), 7.64 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.38 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.34–7.18 (m, 2H, Ar–*H*), 3.94 (s, 2H,CH_2CO_2H); ^{13}C NMR (125 MHz) δ 176.4 (*C*=O), 135.1, 127.2, 125.2, 123.0 (q, $^2J_{C-F}$ = 37.1 Hz, *C*–CF_3), 121.6 (q, $^1J_{C-F}$ = 267.1 Hz, *C*F_3), 121.2, 120.1, 111.9, 109.7 (q, $^3J_{C-F}$ = 2.7 Hz, *C*=C–CF_3), 29.5 (*C*H_2CO_2H); ^{19}F NMR (470 MHz) δ −58.50 (s, 3F); IR (neat) 3415 (NH), 3500–2500 (COOH), 1714 (C=O), 1597, 1260, 1165, 1114, 802 cm^{-1}; HRMS: *m*/*z* calcd for $C_{11}H_8F_3NO_2$ [M^+]: 243.0507, Found: 243.0503.

*4.7.5. Dimethyl-2-{[1-(4-chlorobenzoyl)-2-(trifluoromethyl)indol-3-yl]methyl}malonate (**10**)*

To a flame-dried 50-mL there-necked flask was charged with a solution of *t*-BuOK (118 mg, 1.05 mmol) in THF (15 mL) under a nitrogen atmosphere. The solution was then cooled to 0 °C. A solution of $CH_2(COOCH_3)_2$ (138 mg, 1.05 mmol) in THF (2 mL) was added dropwise. Upon completion of the addition, a solution of **7** (0.42 g, 1.01 mmol) in THF (2 mL) was added slowly over a period of 20–30 min and stirred at 0 °C for additional 4 h (monitored by TLC). The reaction mixture was quenched with 10 mL sat. solution of NH_4Cl, extracted with EtOAc (10 mL, 3×). The combined organic layer was washed with brine, dried over Mg_2SO_4, and concentrated by rotary evaporator. The residue was purified by column chromatography (4:1 hexane–EtOAc) to offer a white solid (420 mg, 0.90 mmol, 89%): mp 127–128 °C; ^{1}H NMR (500 MHz) δ 7.76 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.71 (d, J = 8.0 Hz, 1H, Ar–*H*), 7.51 (d, J = 8.5 Hz, 2H, Ar–*H*), 7.27 (t, J = 7.5 Hz, 1H, Ar–*H*), 7.22 (t, J = 7.5 Hz, 1H, Ar–*H*), 6.81 (d, J = 8.5 Hz, 1H, Ar–*H*), 3.79 (t, J = 7.5 Hz, 1H, C*H*$(CO_2CH_3)_2$), 3.70 (s, 6H, OCH_3), 3.61 (d, J = 7.5 Hz, 2H, CH_2CH$(CO_2CH_3)_2$); ^{13}C NMR (125 MHz) δ 168.8 (2 carbons, O=*C*–OCH_3), 167.3 (O=*C*–N), 140.9, 136.5, 132.0, 131.8 (2 carbons), 129.4 (2 carbons), 127.5, 126.6, 124.8 (q, $^2J_{C-F}$ = 37.5 Hz, *C*–CF_3), 123.1, 122.5 (q, $^3J_{C-F}$ = 2.5 Hz, *C*=C–CF_3), 121.2 (q, $^1J_{C-F}$ = 268.3 Hz, *C*F_3), 120.7, 113.6, 52.7 (2 carbons, O*C*H_3), 52.2 (*C*H$(CO_2CH_3)_2$), 23.5 (*C*H_2CH$(CO_2CH_3)_2$); ^{19}F NMR (470 MHz) δ −54.60 (s, 3F); IR (neat) 2953, 1740 (*O*=*C*–OCH_3), 1701 (*O*=*C*–N), 1589, 1288, 1271, 1130, 1036, 753 cm^{-1}; HRMS: *m*/*z* calcd for$C_{22}H_{17}ClF_3NO_5$ [M^+]: 467.0747, Found: 467.0749.

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