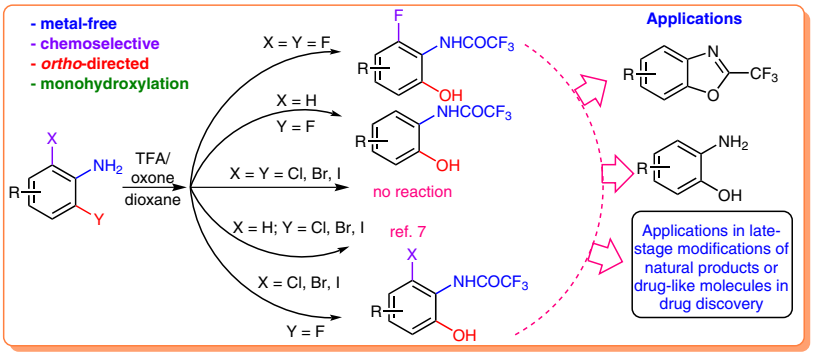
Synlett V. Venkateswarlu et al. Letter

Metal-Free Chemoselective *ortho*-C(sp²)–F Bond Hydroxylation and *N*-Trifluoroacylation of Fluoroarylamines for Domino Synthesis of 2-(*N*-Trifluoroacyl)aminophenols

Vunnam Venkateswarlu[a,b]
Shilpi Balgotra[a,b]
K. A. Aravinda Kumar[a]
Ram A. Vishwakarma[a,b]
Sanghapal D. Sawant*[a,b]

[a] Medicinal Chemistry Division, CSIR-Indian Institute of Integrative Medicine, Canal Road, Jammu-180 001, India
[b] Academy of Scientific and Innovative Research, Anusandhan Bhawan, 2 Rafi Marg, New Delhi 110 001, India
sdsawant@iiim.res.in
sawant.rrl@gmail.com



Received: 31.10.2014
Accepted after revision: 25.02.2015
Published online: 24.03.2015
DOI: 10.1055/s-0034-1379905; Art ID: st-2014-d0907-l

Abstract A novel chemoselective reaction for the formation of C–O bonds by C(sp²)–F bond cleavage and concomitant N-trifluoroacylation of fluoroanilines using trifluoroacetic acid and Oxone® is presented. This domino reaction gives *o*-hydroxy-*N*-trifluoroacetanilides in good yields under metal-free conditions in a single step. Selective *ortho*-directed monohydroxylation and N-trifluoroacylation of 2- and 6-fluoro- or 2,6-difluoro-substituted anilines takes place in this transformation.

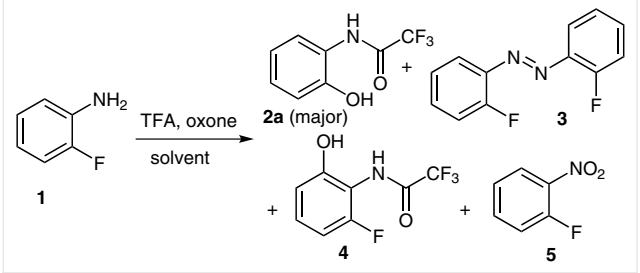
Key words C–F bonds, chemoselective reactions, C–O bonds, fluoroarylamine, hydroxylation

Fluorine forms the strongest single bond to carbon and is very hard to cleave;[1] consequently, chemical modification of such sites in organic fluorocompounds is not an easy task.[2] Nevertheless, several reports relate to C–F bond cleavage for the reduction of fluorocarbons or the transformation of fluorocarbons into partially fluorinated organic molecules.[3]

C–F bond-cleavage reactions, mediated by activation of this bond, can be achieved by using transition-metal species.[4] Cleavage of the C–F bond for the formation of phenol has been little explored, with few reports available on this conversion.[5] Generally, conversions of aryl halides into phenols are limited to iodo-, bromo- and, to some extent, chloro-aromatic substrates through nucleophilic substitution. Many methods have been reported for the generation of phenolic C–O bonds[6] and aromatic hydroxylation is attractive for late-stage oxidative derivatization of aromatic substrates.

We now report a simple approach for the hydroxylation and concomitant N-trifluoroacylation to form *N*-trifluoroacyl-2-aminophenols by nucleophilic substitution of *ortho*-fluoro arylamines by using an oxidative nonmetallic combination of TFA and Oxone®; these products can alternatively be obtained by following a conventional synthetic route using selective N-trifluoroacylation of aminophenols by using a protection/deprotection strategy. To our knowledge, there are no reports on the direct formation of *N*-trifluoroacyl-2-aminophenols from fluoroarylamines. Herein, we report the nucleophilic substitution (S_NAr) of a 2-fluoro-substituent with an OH group to give 2-hydroxy-*N*-trifluoroacylated arylamines in good yields.

We recently reported a selective *ortho*-directed C–H oxygenation of simple anilines, forming *N*-trifloroacylated *o*-hydroxy arylamines.[7] During our studies on conversion of various halo-substituted arylamines, especially fluoro-substituted compounds, using an oxidative mixture of TFA and Oxone, we came across an interesting conversion (Scheme 1; solvent = dioxane). Typically, when 2-fluoro-substituted arylamines were subjected to this oxidation reaction, we could detect the formation of a mixture of products by GC-MS analysis (Figure S1 in the Supporting Information), including *ortho*-hydroxylated *N*-trifluoroacetanilide as a major product, with the fluorine having been replaced by a hy-



Scheme 1 Formation of 2-hydroxy-*N*-trifluoroacetanilide and by-products from 2-fluoroaniline by using TFA and Oxone

Table 1 Screening of Solvents for Formation of 2-Hydroxy-*N*-trifluoroacetanilide from 2-Fluoroaniline (See Scheme 1)

Entry	Solvent	Yield (%)[a]				
		1[b]	**2a**	**3**	**4**	**5**
1	toluene	45	–	55	–	–
2	DMF	20	–	20	–	10
3	MeOH	–	–	90	–	–
4	dioxane	–	67	21	9.2	3.5
5	THF	25	35	–	5	–
6	DMSO	–	–	40	25	15
7	CH_2Cl_2	30	–	–	–	10
8	MeCN	45	10	5	25	8

[a] Isolated yield after column chromatography.
[b] Recovered starting material.

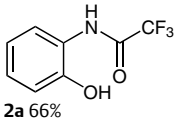
droxyl group. These findings were confirmed by ^{19}F NMR spectroscopic analysis of the product, which revealed that the fluorine peak had disappeared.

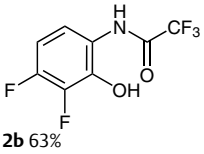
Our studies then continued by screening a range of fluoroaniline substrates to explore the generality of this reaction (Table 1). In all cases, good yields of the respective 2-hydroxy-*N*-trifluoroacyl-arylamine products were obtained. Screening of solvents was carried out and dioxane was found to give the best results (Table 1, entry 4); whereas with DMSO, THF, DMF, acetonitrile, and MeOH, comparatively low or no yields were obtained. Furthermore, the use of 1.2 equivalents of Oxone and more than 2.0 equivalents of TFA led to excellent conversion of substrate **1**, at 90 °C in 2–3 hours. All subsequent reactions were performed under these optimized conditions. A wide range of substituted arylamines underwent reaction smoothly (Table 2).

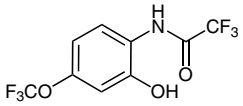
The conversion was found to be very specific for 2- and/or 6-fluoro or 2,6-difluoro-substituted arylamine substrates. No product formation was observed when Cl, Br, or I groups were substituted for fluorine. Some examples of this chemoselective conversion are presented in Table 3.

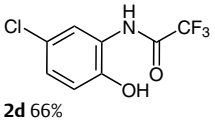
However, in the case of 2,6-disubstituted fluoroaniline, only monohydroxy-*N*-trifluoroacetanilide was obtained, with no dihydroxy product being observed. Furthermore,

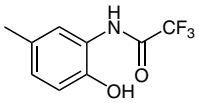
Table 2 Formation of 2-Hydroxy-*N*-trifluoroacetanilide from Fluoroarylamine Substrates[a]

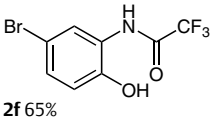

2a 66%

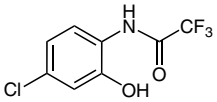

2b 63%

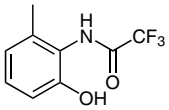

2c 69%

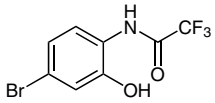

2d 66%

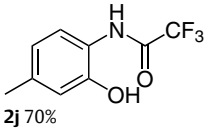

2e 67%

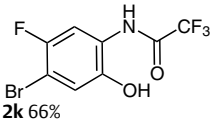

2f 65%

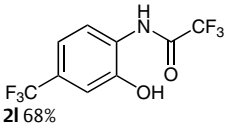

2g 69%

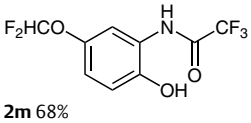

2h 68%

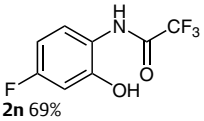

2i 67%

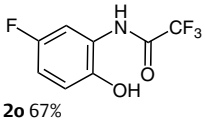

2j 70%

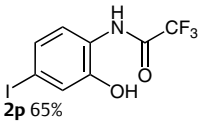

2k 66%

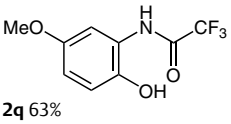

2l 68%

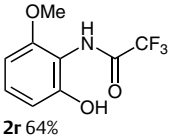

2m 68%


2n 69%


2o 67%

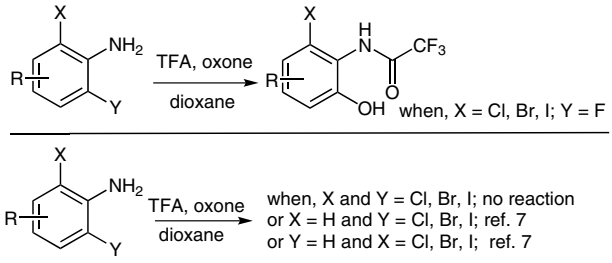

2p 65%

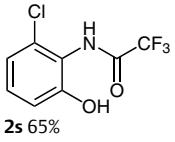
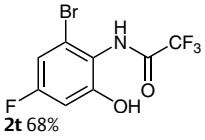
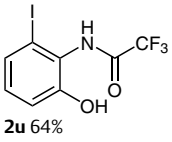
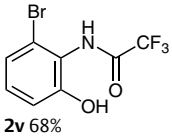

2q 63%


2r 64%

[a] Isolated yield after column chromatography.

Table 3 Screening of Halo-Substituted Arylamine Substrates

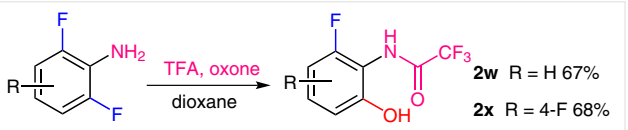


Entry	Y	X	R	Product[a]
1	F	Cl	H	 **2s** 65%
2	Br	Br	H	no reaction
3	F	Br	4-F	 **2t** 68%
4	Cl	Cl	H	no reaction
5	F	I	H	 **2u** 64%
6	I	I	H	no reaction
7	F	Br	H	 **2v** 68%

[a] Isolated yield after column chromatography.

increasing the number of equivalents of TFA and Oxone did not lead to the dihydroxylated product. In the case of 2,6-difluorinated substrates, after initial hydroxylation, the amino group is concomitantly trifluoroacylated. The trifluoroacyl group withdraws electron density from the nitrogen and effectively makes the resulting trifluoroacetamide incapable of participating in the second hydroxylation. A range of 2,6-difluoro-substituted arylamines underwent this reaction smoothly and representative examples are shown in Scheme 2.

When the reaction was conducted with fluorobenzene, conversion into phenol was not observed. Reaction of aniline with TFA simply gave the N-trifluoroacylated product and with Oxone the reaction gave the respective nitrobenzene product. Thus, the approach is very specific to fluoroanilines only.



Scheme 2 Monohydroxylation of 2,6-difluoro-substituted arylamines for formation of *ortho*-hydroxy-*N*-trifluoroacetanilides

To investigate mechanistic aspects, we followed the reaction by using LC-MS analytical techniques. Our observations lead us to propose that this reaction follows a similar pathway to that presented in our recent report (Figure 1).[7] Intermediate **6** is formed upon mixing of TFA and Oxone and this is subsequently converted into intermediate **7** by loss of water. The fluoroaniline adds to intermediate **7**, giving unstable intermediates **8** and **9**. During this stage, the electron lone pair on the oxygen atom of the peroxy linkage (intermediate **8**) undergoes nucleophilic attack on the C–F bond and forms the weaker C–O bond in cyclic intermediate **10**, which finally releases $KHSO_4$ and gives the product 2-hydroxy-*N*-trifluoroacetanilide **2a**.[10]

The method has wide applicability and can be an important tool for bringing in functional moieties to fine-tune the physicochemical properties of molecules. The technique could also be useful in late-stage modifications in drug discovery programs. Mostly in various drug discovery programs, at the lead optimization stage, introducing the CF_3 group in a compound is often preferred because it plays an important role in solving issues related to bioavailability or lipophilicity and physicochemical properties.[2b,8,9] The present method can be applied to biologically active small molecules such as sparfloxacin and to natural products, and it can be used as a medicinal chemistry tool. Moreover, this method provides scope and also offers diversity for obtaining 2-aminophenols or CF_3 bearing benzoxazoles derivatives, which are an important class of compounds that are of great utility.

In conclusion, we have presented a new approach for the nucleophilic substitution of a fluoro group with a hydroxyl group selectively at the *ortho*-position and concomitant N-trifluoroacylation of fluoro-substituted anilines. This is an oxidative reaction under metal-free conditions offering good yields of 2-hydroxy-*N*-trifluoroacetanilides. This method is chemoselective and can be applied on all kinds of substrates having 2- or 6-fluoro substitutions offering monohydroxylated products, with tolerance of electron-withdrawing and electron-donating groups. 2,6-Disubstituted fluoroaniline could be converted into the monohydroxylated product selectively.

Acknowledgment

V.V. thanks UGC/CSIR for the award of a Research Fellowship. Funding support from CSIR sponsored BSC0108 project is gratefully acknowledged. IIIM Communication No. IIIM/1623/2013.

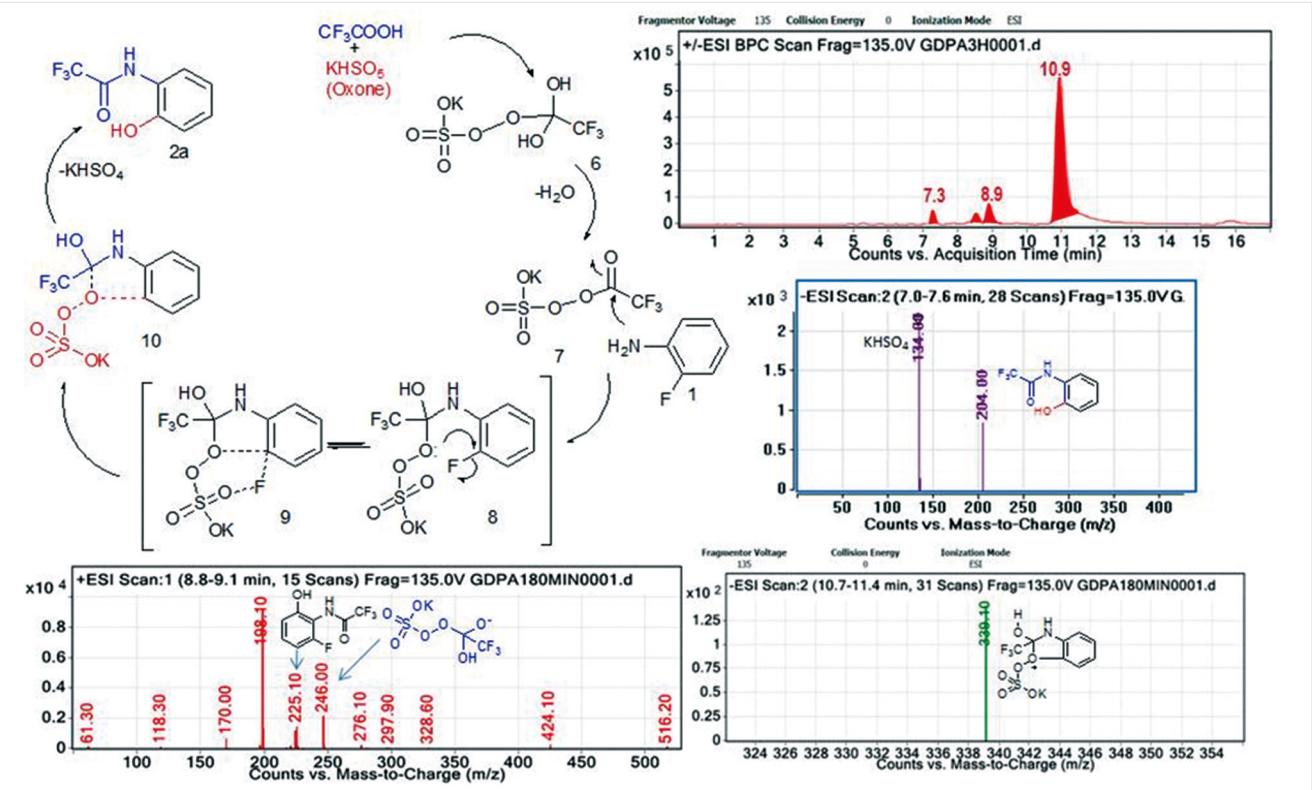


Figure 1 Plausible mechanism for the formation of 2-hydroxy-*N*-trifluoroacetanilide with interpretation of intermediates observed using LC-MS analysis at 30 min reaction time intervals. Mass peaks of intermediate **6** (*m*/*z* 246.00), intermediate **10** (*m*/*z* 339.10), **2a** (*m*/*z* 204.00 [M – H$^+$]), and $KHSO_4$ (*m*/*z* 134.00 [M – H$^+$])

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379905.

References and Notes

(1) (a) Choi, J.; Wang, D. Y.; Kundu, S.; Choliy, Y.; Emge, T. J.; Krogh-Jespersen, K.; Goldman, A. S. *Science* **2011**, *332*, 1545. (b) Arnold, J.; Gianetti, T.; Bergman, R. G. *Chem. Sci.* **2014**, *5*, 2517.
(2) (a) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255. (b) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308.
(3) (a) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (b) Mazurek, U.; Schwarz, H. *Chem. Commun.* **2003**, 1321.
(4) For recent reviews on metal-mediated aliphatic C–F bond activation, see: (a) Cárdenas, D. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 384. (b) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 663. (c) Torrens, H. *Coord. Chem. Rev.* **2005**, *249*, 1957.
(5) (a) Del Mar, E. G.; Barmore, R. M.; Sheehan, D.; Van Wagenen, B. C.; Callahan, J. F.; Keenan, R. M.; Kotecha, N. R.; Lago, M. A.; Southall, L. S.; Thompson, M. *Method of using calcilytic compounds* U. S. Patent 6022894, **2000**; *Chem. Abstr.* **2000**, *132*, 12. (b) Johansson, H.; Cailly, T.; Rojas, A.; Thomsen, B.; Bräuner-Osborne, H.; Pedersen, D. S. *Beilstein J. Org. Chem.* **2013**, *9*, 1383. (c) Rogers, J. F.; Green, D. M. *Tetrahedron Lett.* **2002**, *43*, 3585. (d) Levin, J. I.; Du, M. T. *Synth. Commun.* **2002**, *32*, 1401. (e) Serrano-Plana, J.; Garcia-Bosch, I.; Miyake, R.; Costas, M.; Company, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9608.
(6) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. *J. Am. Chem. Soc.* **2013**, *135*, 5368.
(7) Venkateswarlu, V.; Aravinda Kumar, K. A.; Balgotra, S.; Reddy, G. L.; Srinivas, M.; Vishwakarma, R. A.; Sawant, S. D. *Chem. Eur. J.* **2014**, *20*, 6641.
(8) Filler, R.; Sahu, R. *Future Med. Chem.* **2009**, *1*, 777.
(9) (a) Wong, D. T.; Perry, K. W.; Bymaster, F. P. *Nat. Rev. Drug Discovery* **2005**, *4*, 764. (b) Rabasseda, X.; Sorbera, L. A.; Castaner, J. *Drugs Future* **1999**, *24*, 1057. (c) Wouters, J.; Moureau, F.; Evrard, G.; Koenig, J.-J.; Jegham, S.; George, P.; Durant, F. *Bioorg. Med. Chem.* **1999**, *7*, 1683. (d) Margot, P.; Huggenberger, F.; Amrein, J.; Weiss, B. *BCPC Conf.-Pests. Dis.* **1998**, *2*, 375. (e) Milne, G. W. A. *CRC Handbook of Pesticides*; CRC: Boca Raton, **1995**. (f) Ren, J.; Milton, J.; Weaver, K. L.; Short, S. A.; Stuart, D. I.; Stammers, D. K. *Structure* **2000**, *8*, 1089. (g) Pedersen, O. S.; Pedersen, E. B. *Synthesis* **2000**, 479.
(10) **Synthesis of 2-Hydroxy-*N*-trifluoroacetamides; General Procedure:** A Schlenk tube was charged with Oxone (0.398 g, 0.648 mmol) and trifloroacetic acid (0.099 mL, 1.296 mmol) in anhydrous dioxane (2 mL) under argon. To this mixture was added 2-fluoroaniline (0.06 g, 0.54 mmol), and the reaction mixture was heated to 90 °C under argon until starting material was consumed. As the reaction progressed, the color turned from light red to dark red. The mixture was then cooled to room tempera-

ture and washed with a saturated aqueous sodium bicarbonate. The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried over Na_2SO_4. After filtering and removal of the solvent under reduced pressure in vacuo, the residue was purified by silica gel (100–200 mesh) column chromatography (hexane–EtOAc, 9:1), to afford a pale-brown solid (65%) of 2-hydroxy-*N*-trifluoroacetanilides from 2-fluoroaniline (**2a**).

2-Hydroxy-*N*-trifluoroacetanilides from 2-Fluoroaniline (2a): Pale brown solid; mp 155–156 °C. IR ($CHCl_3$): 3389, 3248, 2923, 2851, 1690, 1597, 1562, 1465, 1194, 1159, 1101, 1041, 851, 749 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.51 (br s, 1 H), 9.94 (br s, 1 H), 7.31 (dd, *J* = 7.8, 1.4 Hz, 1 H), 7.16–7.12 (m, 1 H), 6.94 (d, *J* = 7.1 Hz, 1 H), 6.85–6.81 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.9 (q, *J* = 36 Hz), 151.2, 127.9, 126.3, 122.2, 118.9, 115.9 (q, *J* = 287 Hz), 116.0. ^{19}F NMR (376.50 MHz, CD_3OD): δ = –77.16 (s, 3 F). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_5F_3NO_2$: 204.0275; found: 204.0273.

***N*-(3,4-Difluoro-2-hydroxyphenyl)-2,2,2-trifluoroacetamide (2b):** Brownish semi-solid. ^1H NMR (400 MHz, acetone-d_6): δ = 7.56–7.48 (m, 1 H), 6.89 (ddd, *J* = 10.0, 9.3, 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, CD_3OD): δ = 152.7, 152.3 (d, *J* = 24 Hz), 143.2, 133.8, 120.9, 120.2, 117.3 (d, *J* = 256 Hz), 107.3 (d, *J* = 18.7 Hz). ^{19}F NMR (376 MHz, CD_3OD): δ = –77.03 (s, 3 F), –141.09 (ddd, *J* = 20.3, 10.1, 5.4 Hz, 1 F), –160.66 to –164.19 (m, 1 F). GC-MS: *m*/*z* = 241.2 [M]$^+$.

***N*-(5-Chloro-2-hydroxyphenyl)-2,2,2-trifluoroacetamide (2d):** Brownish solid; mp 190–191 °C. IR ($CHCl_3$): 3391, 2922, 2852, 1688, 1597, 1158, 1047, 871 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 9.97 (s, 1 H), 9.45 (s, 1 H), 7.98 (d, *J* = 2.4 Hz, 1 H), 7.14 (dd, *J* = 8.7, 2.5 Hz, 1 H), 7.03 (d, *J* = 8.7 Hz, 1 H). ^{13}C NMR (101 MHz, acetone-d_6): δ = 155.6 (d, *J* = 37.6 Hz), 148.2, 127.2, 125.6, 124.4, 123.1, 117.5, 116.8 (q, *J* = 286 Hz). ^{19}F NMR (376 MHz, acetone-d_6): δ = 101.19 (s). GC-MS: *m*/*z* = 239.2 [M]$^+$.

***N*-(4-Bromo-2,3-difluoro-6-hydroxyphenyl)-2,2,2-trifluoroacetamide (2k):** Pale brown solid; 187–188 °C. IR ($CHCl_3$): 3391, 2924, 1690, 1594, 1429, 1255, 1122, 1020, 868 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 7.92 (d, *J* = 10.0 Hz, 1 H), 7.25 (d, *J* = 6.4 Hz, 1 H), 3.04 (s, 1 H), 2.98 (s, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1, 151.7, 146.0, 124.9, 119.8, 116.7 (q, *J* = 285 Hz), 111.1 (d, *J* = 35 Hz), 105.1 (d, *J* = 27.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.68 (s), –119.92 (d, *J* = 6.8 Hz). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_3BrF_4NO_2$: 299.9285; found: 299.9284.

2,2,2-Trifluoro-*N*-(5-fluoro-2-hydroxyphenyl)acetamide (2o): Light-brown solid; mp 192–195 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.94 (s, 1 H), 8.80 (s, 1 H), 7.99 (dd, *J* = 9.4, 2.0 Hz, 1 H), 6.91 (dd, *J* = 8.4, 5.0 Hz, 1 H), 6.76 (t, *J* = 7.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$ + acetone-d_6): δ = 157.4, 154.5 (dd, *J* = 72.0, 34.5 Hz), 142.3, 124.7 (d, *J* = 11.5 Hz), 115.7 (d, *J* = 286 Hz), 115.5, 112.1 (d, *J* = 23.3 Hz), 108.1 (d, *J* = 29.3 Hz). ^{19}F NMR (376 MHz, CD_3OD): δ = –77.23 (s), –122.99 to –128.86 (m). GC-MS: *m*/*z* = 223.2 [M]$^+$.

2,2,2-Trifluoro-*N*-(2-hydroxy-5-methoxyphenyl)acetamide (2q): Brown solid; mp 168–169 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.45 (s, 1 H), 7.68 (d, *J* = 2.2 Hz, 1 H), 6.84 (d, *J* = 8.7 Hz, 1 H), 6.68 (d, *J* = 2.6 Hz, 1 H), 5.53 (s, 1 H), 3.78 (s, 3 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.61. ^{13}C NMR (101 MHz, CD_3OD): δ = 154.2, 143.9, 124.9, 118.8, 117.0, 116.0, 113.5, 110.0, 56.2. ESI-MS: *m*/*z* = 234 [M – H]$^+$.

2,2,2-Trifluoro-*N*-(2-hydroxy-6-methoxyphenyl)acetamide (2r): Brown solid; mp 221–222 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 6.99 (dd, *J* = 21.3, 7.8 Hz, 1 H), 6.17 (s, 1 H), 3.91 (s, 3 H). ^{19}F NMR (376.50 MHz, $CDCl_3$): δ = –75.41 (s, 3 F). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 145.6, 126.7, 125.8, 121.2, 120.8, 111.1, 96.4, 55.7. MS (ESI): *m*/*z* = 234 [M – H]$^+$.

***N*-(2-Chloro-6-hydroxyphenyl)-2,2,2-trifluoroacetamide (2s):** Reddish brown solid; mp 225–226 °C. IR ($CHCl_3$): 3388, 3220, 2920, 2853, 1687, 1565, 1419, 1199, 1154, 1018, 850 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 8.09 (d, *J* = 8.9 Hz, 1 H), 7.52 (s, 1 H), 6.96 (s, 1 H), 6.80 (dd, *J* = 9.0, 2.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 130.9, 128.8, 125.2, 125.1, 123.4, 116.4, 114.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.74. HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_4ClF_3NO_2$: 237.9893; found: 237.9883.

***N*-(2-Bromo-4-fluoro-6-hydroxyphenyl)-2,2,2-trifluoroacetamide (2t):** Reddish brown solid; mp 195–196 °C. IR ($CHCl_3$): 3293, 2923, 2852, 1730, 1432, 1152, 1118, 857 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.32 (s, 1 H), 7.81 (s, 1 H), 7.02 (dd, *J* = 7.3, 2.7 Hz, 1 H), 6.82 (dd, *J* = 9.5, 2.6 Hz, 1 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.1, 161.1, 156.3 (d, *J* = 38.6 Hz), 152.0 (d, *J* = 13.3 Hz), 117.9 (d, *J* = 12.7 Hz), 115.5 (q, *J* = 285 Hz), 112.86 (d, *J* = 26.4 Hz), 107.62 (d, *J* = 24.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.54 (s, 3 F), –110.09 (dd, *J* = 9.3, 7.4 Hz, 1 F). GC-MS: *m*/*z* = 301.2 [M]$^+$, 303.2 [M$^+$ + 2] (1:1 ratio).

2,2,2-Trifluoro-*N*-(2-hydroxy-6-iodophenyl)acetamide (2u): Light-brown solid; mp 232–233 °C. ^1H NMR (400 MHz, CD_3OD): δ = 7.27 (dd, *J* = 7.4, 1.6 Hz, 1 H), 6.89–6.76 (m, 2 H). ^{13}C NMR (125 MHz, CD_3OD + acetone-d_6): δ = 157.5 (q, *J* = 36.2 Hz), 155.5, 132.0, 130.9, 125.9, 118.9, 117.5, 100.9. ^{19}F NMR (376 MHz, CD_3OD): δ = –76.60 (s). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_4F_3INO_2$: 329.9245; found: 329.9239.

***N*-(2-Bromo-6-hydroxyphenyl)-2,2,2-trifluoroacetamide (2v):** Light-brown solid; mp 315–316 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 7.68 (d, *J* = 6.0 Hz, 1 H), 7.38 (d, *J* = 40.4 Hz, 1 H), 7.20–7.01 (m, 1 H), 6.81 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (q, *J* = 38 Hz), 151.1, 134.1, 130.0, 128.2, 125.6, 119.8 (q, *J* = 277 Hz), 119.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –75.66 (s). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_4BrF_3NO_2$: 283.9365; found: 283.9534.

2,2,2-Trifluoro-*N*-(2-fluoro-6-hydroxyphenyl)acetamide (2w): Light-brown solid; mp 155–156 °C. IR ($CHCl_3$): 3436, 2918, 1619, 1474, 1383, 1200, 1158, 1021, 785 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.20 (dd, *J* = 14.9, 7.6 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.77 (t, *J* = 9.1 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.4 (q, *J* = 39 Hz), 153.9, 150.6, 128.9, 115.6 (q, *J* = 285 Hz), 116.0, 112.1, 112.0, 107.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.51 (s, 3 F), –125.35 (d, *J* = 7.9 Hz, 1 F). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_4F_4NO_2$: 222.0187; found: 272.0178.

***N*-(2,4-Difluoro-6-hydroxyphenyl)-2,2,2-trifluoroacetamide (2x):** Light-brown solid; mp 195–196 °C. IR ($CHCl_3$): 436, 2923, 2852, 1619, 1452, 1384, 1240, 1157, 1054, 1021, 840 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 6.62–6.49 (m, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.1 (d, *J* = 15.7 Hz), 161.4–160.2 (m), 157.2–154.4 (m), 152.1 (dd, *J* = 14.6, 4.1 Hz), 115.5 (q, *J* = 287.1 Hz), 102.7 (dd, *J* = 25.0, 3.3 Hz), 96.6 (dd, *J* = 27.5, 24.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.5 (s), –109.4 (ddd, *J* = 710.6, 163.3, 9.1 Hz), –120.6 (d, *J* = 6.6 Hz). HRMS (ESI): *m*/*z* [M – H^+]$^-$ calcd for $C_8H_3F_5NO_2$: 240.0065; found: 240.0084.