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One-pot two-step sequential transformation: Highly efficient construction of *o*-2,3,5,6-tetrafluorobenzonitrile substituted oximes ethers

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ABSTRACT

A practical variety of *o*-2,3,5,6-tetrafluorobenzonitrile substituted oximes ethers bearing broad functional groups were synthesized in moderate to good yields. The key highlight of this disclosure involving a one-pot two-step tandem procedure in aqueous media: the in situ formation of aryl aldehydes or ketones oximes followed by the S_NAr reaction with pentafluorobenzonitrile via the high selective C–F bond cleavage.

1. Introduction

Compounds with a polyfluoroarylated moiety are a class of important fluorine-containing species due to their unique chemical and structural properties [1]. Among these polyfluoroarylated compounds, 2,3,5,6-tetrafluorobenzonitrile-derived molecules demonstrate excellent applications in the materials science, pharmaceutical and agricultural. For example, *N*-2,3,5,6-tetrafluorobenzonitrile substituted dihydroquinoline compound **I** possesses good inhibitory activities for many STAT3 target genes in the JAK-STAT (Janus kinase-signal transducers and activators of transcription) pathway [2]. Polyfluoroarylated UA derivatives **II** could inhibit the formation of mammalian poly(ADP-ribose)polymerase 1, which is a nuclear protein involved in a number of cell processes such as transcription, replication, DNA repair, and cell death [3]. Compounds **III** is selected as a kind of good photolabel reagent for photoaffinity labeling (PAL) used in biochemistry and molecular biology to study the proximity of components within biological systems [4] (Fig. 1). Given the importance of polyfluoroarylated skeletons, development of an efficient method to access such valuable molecules is of great synthetic interest.

Recently, the nucleophilic aromatic substitution (S_NAr) reaction has been proved to be a direct and efficient protocol in organic syntheses and many complex molecules are synthesized using this method [5]. As a simple, mild and environmentally benign strategy, the S_NAr reaction has gradually become an outstanding procedure for the creation of polyfluoroarylated compounds utilizing polyfluoroarenes as the starting materials via the C–F bond cleavage with diverse electrophiles [6]. However, up to date, only a limited number of reactions related to pentafluorobenzonitrile for further transformations based on this strategy [7]. For instance, Sandford and coworkers reported an annelation reaction between pentafluorobenzonitrile and *N*-H containing substrates to give a series of ring-fused systems [8]. The Leyve group developed a microwave-assisted fast synthesis of substituted fluorophenyl mono- and diazides by S_NAr to prepare photoaffinity labeling and crosslinking reagents [9]. Although the elegant work has been achieved, most of the present studies are focused on two components reactions for the creation of new bonds, and the

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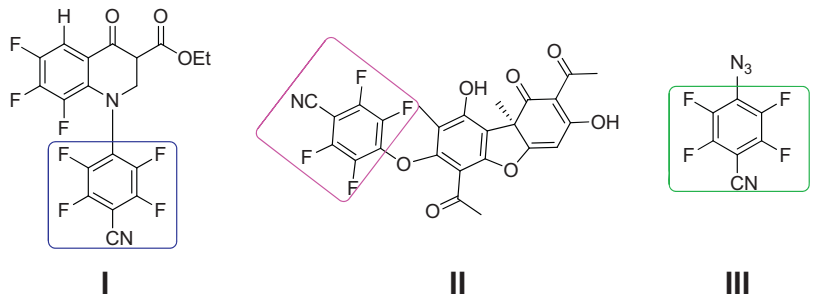


Fig. 1. Three examples of 2,3,5,6-tetrafluorobenzonitrile-containing bioactive and material compounds.

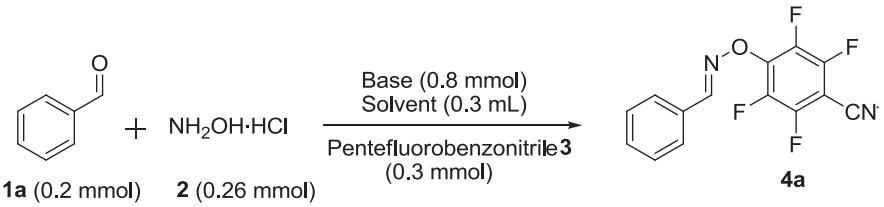
one-pot multi-components reactions involving pentafluorobenzonitrile are still rare. One recent investigation by Cao realized a three components assemble via VNS_{Ar}-S_NAr process fabricated α-*C*-2,3,5,6-tetrafluorobenzonitrile substituted arylacetates in NMP [10]. Consequently, the development of one-pot multi-components reactions for introducing 2,3,5,6-tetrafluorobenzonitrile groups into organic molecules has been the subject of intense research.

Herein, we reported for the first time a one-pot two-step sequential protocol for the construction of *o*-2,3,5,6-tetrafluorobenzonitrile substituted oxime ethers. This method involving the in situ formation of aryl oximes from aldehydes/ketones with hydroxylamine hydrochloride followed by the S_NAr reaction of pentafluorobenzonitrile via the selective C–F bond cleavage. With this strategy, a series of the corresponding products with broad functional groups were furnished in mild to good yields. Furthermore, the procedure was accomplished in aqueous media, which was distinct from the previous reports. Additionally, compared with the present methodologies for the synthesis of *o*-arylated oxime ethers, our method exhibits simple, efficient, and green characteristics.

2. Results and discussion

From the point of synthetic simplicity, one-pot multi-components tandem reaction could provide a far more efficient and straightforward access to the target molecules. In the connection with our study on polyfluoroaryl ethers [11], we envisioned that aryl oximes produced in situ from aldehyde/ketone with hydroxylamine hydrochloride may stereoselectively react with electron-withdrawing group substituted polyfluoroarenes to form C–F functionalized products. Initially, the reaction was treated with **1a** (1.0 equiv), **2** (1.3 equiv), and NaOH (4.0 equiv) in DMF at 70 °C for 8 h. Then followed by the addition of **3** (1.5 equiv) to this mixture and stirred at the same temperature for 6 h. However, to our disappointment, only trace mount of the corresponding product was detected under the primary selected conditions (Table 1, entry 1). We then

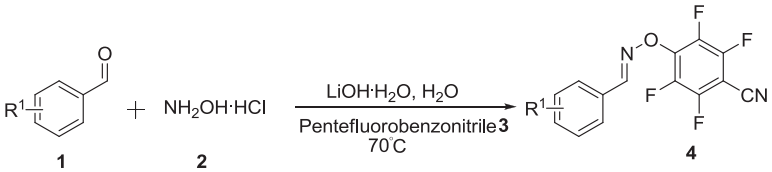
Table 1
Screening of the solvents and bases for the one-pot two-step sequential reaction of benzaldehyde, hydroxylamine hydrochloride, and pentafluorobenzonitrile[a].



Entry	Base	Solvent	*T* (°C)	Yield[b] (%)
1	NaOH	DMF	70	Trace
2	NaOH	DMSO	70	Trace
3	NaOH	CH_3CN	70	<10
4	NaOH	CH_3OH	70	43
5	NaOH	THF	70	Trace
6	NaOH	Toluene	70	51
7	NaOH	H_2O	70	69
8	K_2CO_3	H_2O	70	59
9	KOH	H_2O	70	56
10	K_3PO_4	H_2O	70	36
12	$LiOH·H_2O$	H_2O	70	76
13	NaOtBu	H_2O	70	Trace
14	DABCO	H_2O	70	–

[a] *Reaction conditions*: benzaldehyde (0.2 mmol, hydroxylamine hydrochloride (0.26 mmol), base (0.8 mmol), solvent (0.3 mL), 70 °C 8 h, then pentafluorobenzonitrile (0.3 mmol) was added and stirred at 70 °C for 6 h.
[b] Isolated yield.

Table 2
One-pot two-step sequential reaction of aldehydes, hydroxylamine hydrochloride, and pentafluorobenzonitrile.[a]



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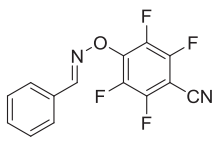
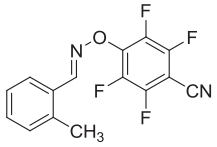
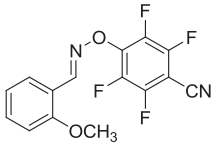


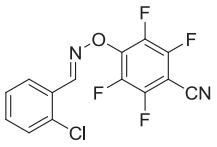
4a, 76%



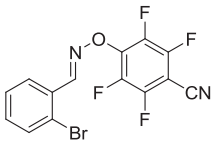
4b, 76%



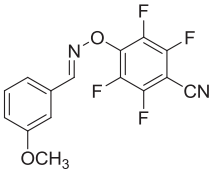
4c, 81%



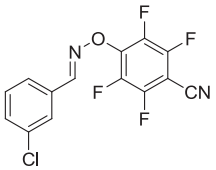
4d, 71%



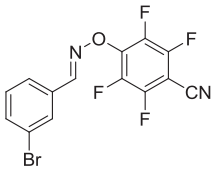
4e, 78%



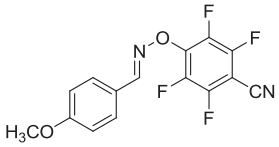
4f, 71%



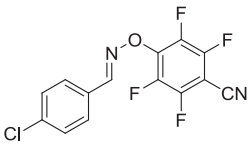
4g, 81%



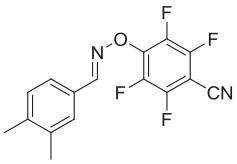
4h, 86%



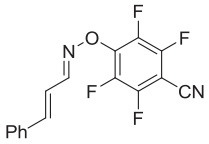
4i, 71%



4j, 67%



4k, 69%



4l, 79%

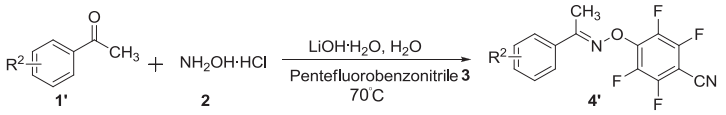
[a] *Reaction conditions*: aldehydes (0.2 mmol, hydroxylamine hydrochloride (0.26 mmol), LiOH·H_2O (0.8 mmol), water (0.3 mL), 70 °C 8 h, then pentafluorobenzonitrile (0.3 mmol) was added and stirred at 70 °C for 6 h. Isolated yields are reported.

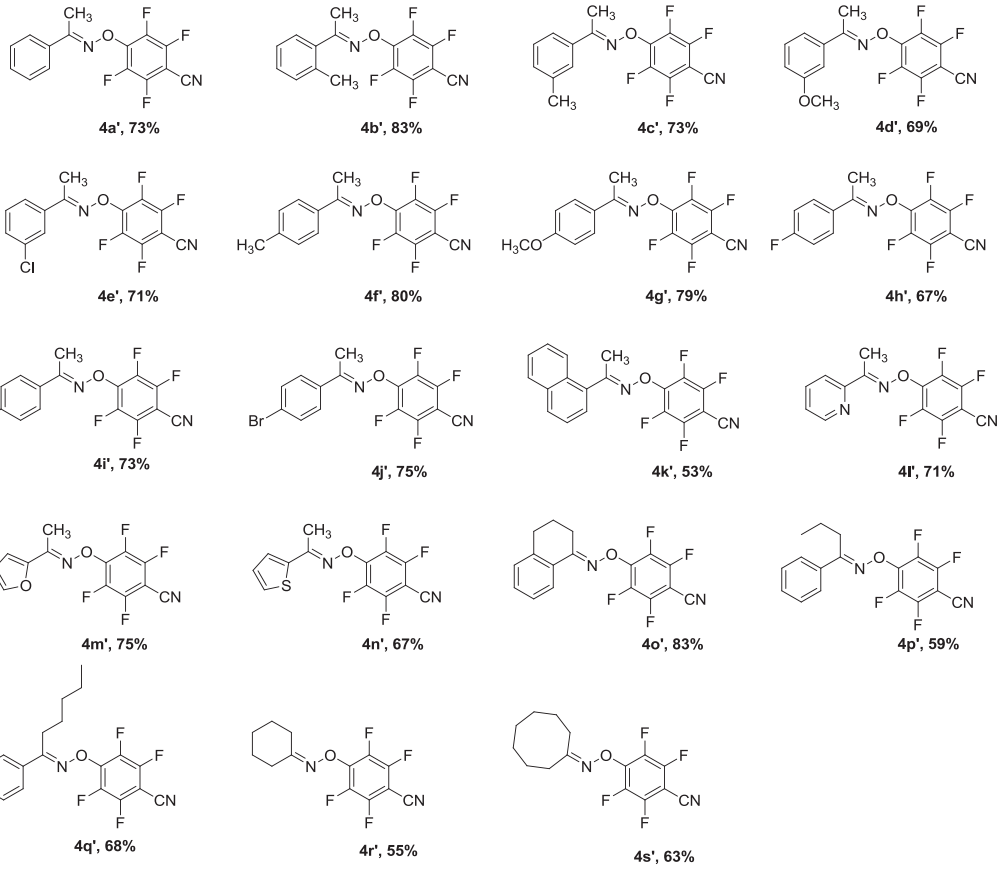
investigated the influence of solvents, and found that only H_2O was critical for the reaction efficiency (Table 1, entry 7). The use of other solvents, such as acetonitrile, methanol, tetrahydrofuran, toluene, and dimethylsulfoxide led to a lower yield or even no product (Table 1, entries 2–6), which was very different from the previous reports. As we all know, water is very green and environmental, and using water as the solvent for the organic synthesis could avoid the employment of some toxic solvents, such as DMF, toluene, etc. Many significant reactions were conducted in aqueous media [12]. Next, a further examination of the bases revealed that only LiOH·H_2O gave the best result and the other inorganic or organic bases were observed to be inferior to LiOH·H_2O. Thus, it illustrated that the solvent and the base played an important role in our one-pot three-component sequential reaction system.

With the optimum conditions in hand, we firstly evaluated the substrate scope with respect to the aldehydes. As depicted in Table 2, versatile functional groups such as methyl, dimethyl, methoxyl, chloride and bromide were compatible with the reaction system (Table 2, entries **4b**–**k**), and good results were obtained no matter where the substituted group lay. Not that, the products bearing the chloro or bromo group could easily be further functionalized by transition-metal-catalyzed methods or the other techniques to form new carbon–carbon or carbon–heteroatom bonds (Table 2, entries **4d**, **4e**, **4g**, **4h**, **4j**). In particular, the cinnamaldehyde was also effective for this transformation and generated the corresponding product in a promising yield.

After having screened a range of aldehydes, we subsequently turned our attention to the ketones substrates. As expected, we were pleased to find that the optimal conditions worked well for different types of ketones. A number of the desired products were furnished in acceptable yields regardless of the ketones possessing electron-donating groups or electron-withdrawing groups, indicating that the electronic effects of the substituents had no influence on the effectiveness of the reaction (Table 3, entries **4a′**–**k′**). In addition, the heterocyclic reagents, e.g. 2-acetylpyridine, 2-acetylfuran, and 2-acetyl thiophene were all tolerated, giving rise to the corresponding products in 67–75% yields (Table 3, entries **4l′**–**n′**). The aromatic ketones containing long-chain and cycle were good candidates, too. And they provided the products in mild to good yields (Table 3, entries **4o′**–**q′**). Interestingly, the aliphatic ketones, such as cyclohexanone and cyclooctanone were also suitable in this system, albeit in moderate yields of the products (Table 3, entries **4r′** and **4s′**). Noteworthy, most of the products were new compounds, and they were all characterized by mass spectroscopy, ^{1}H, ^{13}C and ^{19}F NMR spectroscopy (see the Supporting Information).

Table 3
One-pot two-step sequential reaction of ketones, hydroxylamine hydrochloride, and pentafluorobenzonitrile.[a]





[a] *Reaction conditions*: ketones (0.2 mmol, hydroxylamine hydrochloride (0.26 mmol), LiOH·H_2O (0.8 mmol), water (0.3 mL), 70 °C 8 h, then pentafluorobenzonitrile (0.3 mmol) was added and stirred at 70 °C for 6 h. Isolated yields are reported.

3. Conclusions

In conclusion, we have developed a simple and practical method for direct synthesis of *o*-2,3,5,6-tetrafluorobenzonitrile substituted oxime ethers via the selective C–F bond cleavage of pentafluorobenzonitrile. With this strategy, both different types of aldehydes and ketones substrates were employed and a variety of the corresponding products were obtained in good yields. Moreover, the reaction proceeded through a one-pot two-step domino procedure and by using water as the solvent, which may reach to the extent of the green chemistry.

4. Experimental

^{1}H, ^{13}C, ^{19}F NMR were recorded on Varian Mercury Plus 400 instruments at 400 MHz (^{1}H NMR), 100 MHz (^{13}C NMR), as well as 376 MHz (^{19}F NMR). Chemical shifts were reported in ppm down field from internal Me_4Si and external CCl_3F, respectively. Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br (broad). Coupling constants were reported in Hertz (Hz). Tetrahydrofuran (THF) and toluene were distilled from sodium/benzophenone; CH_3CN were distilled from P_2O_5. All purchased reagents were used without further purification. Analytical thin layer chromatography was performed on 0.20 mm Qingdao Haiyang silica gel plates. Silica gel (200–300 mesh) (from Qingdao Haiyang Chem. Company, Ltd.) was used for flash chromatography. Standard reagents and solvents were purified according to known procedures.

4.1. General procedure for the synthesis of the products

Benzaldehyde **1a** (98%, 21.6 mg, 0.2 mmol), hydroxylamine hydrochloride **2** (98%, 18.4 mg, 0.26 mmol), and lithium hydroxide monohydrate (90%, 37.3 mg, 0.8 mmol) were weighed to a sealed Schlenk flask (25 mL), and water (0.3 mL) was added via syringe at room temperature. After that the Schlenk flask was immersed in an oil bath at 70 °C and stirred until the total conversion of

benzaldehyde (by TLC). And then pentafluorobenzonitrile **3** (98%, 59.1 mg, 0.3 mmol) was added to the mixture and the reaction system was stirred at 70 °C until it was completed. Water (5 mL) was added to the Schlenk flask and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, dried with anhydrous magnesium sulfate and then concentrated in vacuo. The residue was purified on silica gel to afford the product **4a** (44.7 mg, 76% yield).

*4.1.1. (E)-4-(Benzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4a**)*

M: 44.7 mg, Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.56 (s, 1H), 7.67 (d, J = 7.1 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.3 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −130.01 to −130.12 (m, 2F), −150.91 to −151.02 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 155.7, 149.1–149.3 (m), 146.4–146.6 (m), 142.6–142.8 (m), 141.7–141.9 (m), 139.1–139.4 (m), 131.9, 129.3, 129.1, 128.0, 107.4 (t, J_{C-F} = 6.0 Hz), 89.0–89.4 (m); IR (KBr) ν (cm^{-1}): 3647.37, 3034.31, 2926.43, 2317.50, 2242.07, 1649.60, 1506.09, 1437.95, 1209.78, 1004.44, 961.24, 894.45, 846.57, 789.55, 693.88, 582.70, 507.86; HRMS (EI) found: m/z 294.0414 [M]; calcd. for $C_{14}H_6F_4N_2O$ 294.0416.

*4.1.2. (E)-2,3,5,6-Tetrafluoro-4-(2-methylbenzylideneaminooxy)benzonitrile(**4b**)*

M: 46.8 mg, Yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.80 (s, 1H), 7.68 (d, J = 7.7 Hz, 1H), 7.41 (t, J = 7.3 Hz, 1H), 7.29 (t, J = 6.4 Hz, 2H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.06 to −133.17 (m, 2F), −150.98 to −151.09 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 155.1, 149.0–149.3 (m), 146.4–146.8 (m), 142.6–142.9 (m), 141.6–141.8 (m), 139.1–139.3 (m), 138.3, 131.5, 131.3, 128.5, 127.6, 126.4, 107.4 (t, J_{C-F} = 4.0 Hz), 89.0–89.2 (m), 20.3; IR (KBr) ν (cm^{-1}): 3740.66, 3674.72, 3648.59, 3620.77, 2960.49, 2928.68, 2361.05, 2243.11, 1698.88, 1648.28, 1501.95, 1436.22, 1128.80, 1005.00, 963.53, 761.75, 670.42, 420.50; HRMS (ESI) found: m/z 309.0646 $[M+H]^+$; calcd. for $C_{15}H_8F_4N_2O$ + H 309.0651.

*4.1.3. (E)-2,3,5,6-Tetrafluoro-4-(2-methoxybenzylideneaminooxy)benzonitrile (**4c**)*

M: 52.5 mg, Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.95 (s, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.00 (dd, J = 14.1, 7.8 Hz, 2H), 3.92 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.28 to −133.39 (m, 2F), −150.95 to −151.06 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 158.4, 151.8, 149.0–149.2 (m), 146.4–146.7 (m), 142.8–143.1 (m), 141.6–141.8 (m), 139.0–139.3 (m), 133.3, 127.1, 120.0, 117.7, 111.4, 107.5 (t, J_{C-F} = 4.0 Hz), 88.6–89.0 (m), 55.7; IR (KBr) ν (cm^{-1}): 3451.14, 2965.62, 2847.84, 2240.79, 1647.17, 1600.17, 1500.60, 1436.13, 1289.31, 1253.31, 1155.78, 1129.92, 1047.32, 1005.66, 965.19, 759.99, 587.42; HRMS (EI) found: m/z 304.0453 [M−HF]; calcd. for $C_{15}H_8F_4N_2O_2$ − HF 304.0460.

*4.1.4. (E)-4-(2-Chlorobenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4d**)*

M: 46.7 mg, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 9.00 (s, 1H), 7.89 (d, J = 7.9 Hz, 1H), 7.46 (q, J = 8.1 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.83 to −132.94 (m, 2F), −150.95 to −151.06 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 152.8, 149.0–149.3 (m), 146.4–146.6 (m), 142.4–142.6 (m), 141.6–141.8 (m), 139.1–139.3 (m), 135.0, 132.8, 130.2, 127.8, 127.3, 127.2, 107.3 (t, J_{C-F} = 4.0 Hz), 89.3–89.6 (m); IR (KBr) ν (cm^{-1}): 3449.20, 2929.25, 2243.58, 1646.05, 1493.31, 1433.29, 1207.72, 1131.24, 1005.08, 966.51, 764.45, 587.61, 481.23; HRMS (EI) found: m/z 307.9967 [M−HF]; calcd. for $C_{14}H_5ClF_4N_2O$ − HF 307.9964.

*4.1.5. (E)-4-(2-Bromobenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4e**)*

M: 58.2 mg, Yield: 78%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.97 (s, 1H), 7.92–7.84 (m, 1H), 7.69–7.63 (m, 1H), 7.38 (p, J = 7.1 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.83 to −132.94 (m, 2F), −150.95 to −151.06 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 155.0, 149.0–149.2 (m), 146.4–146.6 (m), 142.4–142.6 (m), 141.6–141.9 (m), 139.0–139.3 (m), 133.5, 133.0, 128.9, 128.2, 127.9, 124.8, 107.3 (t, J_{C-F} = 4.0 Hz), 89.3–89.6 (m); IR (KBr) ν (cm^{-1}): 3450.98, 2926.98, 2854.48, 2245.04, 1645.44, 1589.51, 1498.85, 1431.96, 1130.07, 964.76, 900.27, 762.71, 587.40; HRMS (ESI) found: m/z 372.9594 $[M+H]^+$; calcd. for $C_{14}H_5BrF_4N_2O$ + H 372.9599.

*4.1.6. (E)-2,3,5,6-Tetrafluoro-4-(3-methoxybenzylideneaminooxy)benzonitrile (**4f**)*

M: 46.0 mg, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.52 (s, 1H), 7.38 (t, J = 8.1 Hz, 1H), 7.24–7.18 (m, 2H), 7.06 (dd, J = 8.2, 2.1 Hz, 1H), 3.86 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.05 to −133.16 (m, 2F), −150.89 to −151.00 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 160.0, 155.5, 149.0–149.2 (m), 146.4–146.7 (m), 142.6–142.8 (m), 141.7–141.9 (m), 139.1–139.4 (m), 130.5, 130.1, 121.2, 118.2, 112.0, 107.4 (t, J_{C-F} = 4.0 Hz), 89.1–89.4 (m), 55.4; IR (KBr) ν (cm^{-1}): 3448.87, 2969.51, 2920.18, 2239.29, 1647.85, 1610.17, 1572.56, 1485.28, 1437.88, 1270.99, 1131.07, 1010.82, 969.88, 921.53, 859.15, 684.75, 569.94; HRMS (EI) found: m/z 304.0453 [M−HF]; calcd. for $C_{15}H_8F_4N_2O_2$ − HF 304.0460.

*4.1.7. (E)-4-(3-Chlorobenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4g**)*

M: 53.2 mg, Yield: 81%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.51 (s, 1H), 7.68 (s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.78 to −132.89 (m, 2F), −150.86 to −150.97 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 154.3, 149.0–149.2 (m), 146.4–146.8 (m), 142.3–142.5 (m), 141.7–142.0 (m), 139.1–139.4 (m), 135.3, 131.8, 131.0, 130.4, 127.6, 107.3 (t, J_{C-F} = 3.0 Hz), 89.4–89.7 (m); IR (KBr) ν (cm^{-1}): 3454.35, 2926.21, 2244.09, 1646.50, 1564.54, 1500.48, 1435.64, 1344.21, 1208.58, 1131.11, 1044.53, 963.48, 788.80, 720.73, 683.16, 586.28; HRMS (EI) found: m/z 307.9967 [M−HF]; calcd. for $C_{14}H_5ClF_4N_2O$ − HF 37.9964.

*4.1.8. (E)-4-(3-Bromobenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4h**)*

M: 64.2 mg, Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.50 (s, 1H), 7.83 (s, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.9 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.74 to −132.85 (m, 2F), −150.82 to −150.93 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 154.2, 149.0–149.2 (m), 146.4–146.6 (m), 142.3–142.6 (m), 141.7–142.0 (m), 139.2–139.4 (m), 134.8, 131.2, 130.6, 126.8, 127.6, 123.2, 107.3 (t, J_{C-F} = 3.0 Hz), 89.4–89.8 (m); IR (KBr) ν (cm^{-1}): 3734.48, 3651.58, 3061.64, 2961.74, 2244.81, 1648.76, 1555.61, 1490.11, 1436.91, 1206.99, 1128.10, 1009.39, 965.89, 907.19, 868.30, 743.99, 682.58, 471.61, 426.33; HRMS (ESI) found: m/z 372.9594 $[M+H]^+$; calcd. for $C_{14}H_5BrF_4N_2O$ + H 372.9599.

*4.1.9. (E)-2,3,5,6-Tetrafluoro-4-(4-methoxybenzylideneaminooxy)benzonitrile (**4i**)*

M: 46.0 mg, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.49 (s, 1H), 7.61 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.22 to −133.32 (m, 2F), −150.99 to −151.10 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 162.6, 155.1, 149.0–149.3 (m), 146.4–146.6 (m), 142.8–142.9 (m), 141.6–141.9 (m), 139.1–139.3 (m), 130.0, 121.6, 114.6, 107.5 (t, J_{C-F} = 3.0 Hz), 88.7–89.1 (m), 55.4; IR (KBr) ν (cm^{-1}): 3736.13,

3647.09, 2967.49, 2928.18, 2850.30, 2240.84, 1649.55, 1603.64, 1503.92, 1438.43, 1356.83, 1307.06, 1254.14, 1172.54, 1129.44, 1005.09, 968.10, 900.19, 836.53, 531.28; HRMS (EI) found: *m/z* 304.0453 [M−HF]; calcd. for $C_{15}H_8F_4N_2O_2$ − HF 304.0460.

*4.1.10. (E)-4-(4-Chlorobenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4j**)*

M: 44.0 mg, Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.53 (s, 1H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.45 (d, *J* = 8.3 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.87 to −132.97 (m, 2F), −150.93 to −151.03 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 154.4, 149.0–149.2 (m), 146.4–146.6 (m), 142.4–142.6 (m), 141.7–141.9 (m), 139.1–139.4 (m), 138.1, 129.5, 129.2, 127.7, 107.3 (t, J_{C-F} = 3.0 Hz), 89.2–89.6 (m); IR (KBr) ν (cm^{-1}): 3448.27, 2924.46, 2239.90, 1645.37, 1592.06, 1484.88, 1435.21, 1400.78, 1209.85, 1153.91, 11,227.59, 1008.29, 968.36, 900.32, 832.50, 515.98; HRMS (EI) found: *m/z* 307.9967 [M−HF]; calcd. for $C_{14}H_5ClF_4N_2O$ − HF 307.9964.

*4.1.11. (E)-4-(3,4-Dmethylbenzylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4k**)*

M: 44.5 mg, Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.49 (s, 1H), 7.44 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 2.33 (d, *J* = 5.4 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.18 to −133.28 (m, 2F), −150.91 to −151.01 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 155.7, 149.0–149.2 (m), 146.4–146.6 (m), 142.6–143.0 (m), 141.7–141.9 (m), 141.3, 139.1–139.4 (m), 137.6, 130.3, 128.8, 126.7, 125.9, 107.4 (t, J_{C-F} = 3.5 Hz), 88.9–89.1 (m), 19.9, 19.6; IR (KBr) ν (cm^{-1}): 3654.50, 2954.65, 2925.69, 2239.65, 1648.40, 1503.25, 1438.25, 1346.61, 1152.60, 1130.03, 1006.61, 968.65, 937.55, 889.98, 828.56, 801.60, 710.61, 573.01, 473.00, 441.90; HRMS (ESI) found: *m/z* 323.0802 [M+H]$^+$; calcd. for $C_{16}H_{10}F_4N_2O$ + H 323.0807.

*4.1.12. 2,3,5,6-Tetrafluoro-4-((E)-((E)-3-phenylallylidene)aminooxy)benzonitrile (**4l**)*

M: 50.6 mg, Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.34 (d, *J* = 9.9 Hz, 1H), 7.52 (d, *J* = 5.9 Hz, 2H), 7.42 (d, *J* = 5.9 Hz, 3H), 7.08 (d, *J* = 16.0 Hz, 1H), 6.85 (dd, *J* = 15.9, 10.0 Hz, 1H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.00 to −133.10 (m, 2F), −150.99 to −151.09 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 157.1, 149.0–149.2 (m), 146.4–146.6 (m), 143.9, 142.5–142.7 (m), 141.7–141.9 (m), 139.1–139.4 (m), 135.0, 130.0, 129.0, 127.5, 118.6, 107.4 (t, J_{C-F} = 3.0 Hz), 89.0–89.5 (m); IR (KBr) ν (cm^{-1}): 3646.79, 2922.70, 2853.16, 2241.50, 1647.00, 1580.07, 1502.02, 1438.71, 1368.41, 1166.93, 1121.84, 1004.54, 964.72, 878.29, 787.57, 753.51, 690.90, 512.31, 420.79; HRMS (ESI) found: *m/z* 321.0646 [M+H]$^+$; calcd. for $C_{16}H_8F_4N_2O$ + H 321.0651.

*4.1.13. (E)-2,3,5,6-Tetrafluoro-4-(1-phenylethylideneaminooxy)benzonitrile (**4a′**)*

M: 45.0 mg, Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.70 (d, *J* = 6.9 Hz, 2H), 7.52–7.42 (m, 3H), 2.55 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.23 to −133.34 (m, 2F), −151.12 to −151.23 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 162.4, 149.0–149.2 (m), 146.4–146.7 (m), 143.0–143.3 (m), 141.8–142.0 (m), 139.2–139.5 (m), 133.8, 130.8, 128.8, 126.7, 107.6 (t, J_{C-F} = 4.5 Hz), 88.7–89.1 (m), 13.6; IR (KBr) ν (cm^{-1}): 3728.25, 3646.25, 2961.55, 2243.01, 1647.23, 1491.14, 1436.35, 1305.61, 1137.14, 998.97, 960.27, 877.38, 761.44, 693.24, 564.79, 418.71; HRMS (ESI) found: *m/z* 309.0646 [M+H]$^+$; calcd. for $C_{15}H_8F_4N_2O$ + H 309.0651.

*4.1.14. (E)-2,3,5,6-Tetrafluoro-4-(1-o-tolylethylideneaminooxy)benzonitrile (**4b′**)*

M: 53.5 mg, Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.35 (dd, *J* = 9.2, 4.4 Hz, 1H), 7.31–7.23 (m, 3H), 2.50 (s, 3H), 2.43 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.34 to −133.45 (m, 2F), −151.09 to −151.20 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 166.1, 148.9–149.2 (m), 146.4–146.6 (m), 143.0–143.1 (m), 142.0–142.2 (m), 139.4–139.7 (m), 135.9, 134.5, 131.0, 129.7, 128.1, 126.1, 107.5 (t, J_{C-F} = 3.0 Hz), 88.9–89.1 (m), 19.9, 17.3; IR (KBr) ν (cm^{-1}): 3741.41, 3676.61, 3648.97, 3621.28, 2959.88, 2927.10, 2361.14, 1649.80, 1505.84, 1369.87, 1264.09, 1156.19, 985.70, 798.78, 672.06, 420.52; HRMS (ESI) found: *m/z* 323.0802 [M+H]$^+$; calcd. for $C_{16}H_{10}F_4N_2O$ + H 323.0807.

*4.1.15. (E)-2,3,5,6-Tetrafluoro-4-(1-m-tolylethylideneaminooxy)benzonitrile (**4c′**)*

M: 47.1 mg, Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.49 (d, *J* = 12.2 Hz, 2H), 7.32 (dt, *J* = 16.1, 5.8 Hz, 2H), 2.53 (s, 3H), 2.42 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.29 to −133.40 (m, 2F), −151.09 to −151.20 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 162.6, 149.0–149.2 (m), 146.4–146.7 (m), 143.0–143.3 (m), 141.8–142.1 (m), 139.3–139.5 (m), 138.6, 133.8, 131.6, 128.7, 127.2, 123.9, 107.5 (t, J_{C-F} = 3.5 Hz), 88.9–89.1 (m), 21.4, 13.7; IR (KBr) ν (cm^{-1}): 3453.34, 2929.22, 2858.83, 2239.51, 1645.51, 1500.05, 1437.19, 1373.83, 1325.91, 1154.37, 1130.68, 1005.57, 892.91, 791.37, 696.23; HRMS (ESI) found: *m/z* 323.0802 [M+H]$^+$; calcd. for $C_{16}H_{10}F_4N_2O$ + H 323.0807.

*4.1.16. (E)-2,3,5,6-Tetrafluoro-4-(1-(3-methoxyphenyl)ethylideneaminooxy)benzonitrile (**4d′**)*

M: 46.7 mg, Yield: 69%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.37 (t, *J* = 7.9 Hz, 1H), 7.28–7.21 (m, 2H), 7.03 (dd, *J* = 8.1, 1.9 Hz, 1H), 3.86 (s, 3H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.23 to −133.34 (m, 2F), −151.13 to −151.24 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 162.3, 159.8, 149.0–149.3 (m), 146.4–146.6 (m), 142.9–143.1 (m), 141.8–142.0 (m), 139.3–139.5 (m), 135.1, 129.8, 119.2, 116.5, 112.1, 107.5 (t, J_{C-F} = 3.5 Hz), 88.6–89.2 (m), 55.4, 13.7; IR (KBr) ν (cm^{-1}): 3735.88, 3647.03, 3022.28, 2975.87, 1649.15, 1573.15, 1488.43, 1370.48, 1287.53, 1225.96, 1177.10, 1006.65, 889.84, 784.71, 694.65, 571.98, 419.13; HRMS (EI) found: *m/z* 338.0689 [M]; calcd. for $C_{16}H_{10}F_4N_2O_2$ 338.0678.

*4.1.17. (E)-4-(1-(3-Chlorophenyl)ethylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4e′**)*

M: 48.7 mg, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.69 (s, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −132.98 to −133.09 (m, 2F), −151.08 to −151.19 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 161.2, 149.0–149.2 (m), 146.4–146.7 (m), 142.8–143.0 (m), 141.8–142.0 (m), 139.3–139.5 (m), 135.6, 14.9, 130.8, 130.0, 126.8, 124.9, 107.4 (t, J_{C-F} = 3.0 Hz), 89.0–89.5 (m), 13.7; IR (KBr) ν (cm^{-1}): 3740.46, 3064.45, 2924.29, 2856.12, 2361.16, 2241.52, 1641.23, 1558.44, 1488.39, 1438.69, 1372.39, 1297.00, 1154.08, 1125.88, 964.07, 892.17, 831.05, 797.72, 718.80, 685.58, 477.13, 422.07; HRMS (ESI) found: *m/z* 343.0256 [M+H]$^+$; calcd. for $C_{15}H_7ClF_4N_2O$ + H 343.0261.

*4.1.18. (E)-2,3,5,6-Tetrafluoro-4-(1-p-tolylethylideneaminooxy)benzonitrile (**4f′**)*

M: 51.6 mg, Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 2.52 (s, 3H), 2.42 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.42 to −133.53 (m, 2F), −151.20 to −151.31 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 162.3, 149.0–149.2 (m), 146.4–146.7 (m), 143.1–143.3 (m), 141.8–142.0 (m), 141.2, 139.2–139.5 (m), 130.9, 129.5, 126.6, 107.5 (t, J_{C-F} = 3.0 Hz), 88.7–88.8 (m), 21.3, 13.5; IR (KBr) ν (cm^{-1}): 3449.82, 2935.02, 2861.25, 2238.87, 1646.26, 1500.22, 1438.26, 1128.68, 1001.90, 874.56, 820.20, 560.80; HRMS (ESI) found: *m/z* 323.0802 [M+H]$^+$; calcd. for $C_{16}H_{10}F_4N_2O$ + H 323.0807.

*4.1.19. (E)-2,3,5,6-Tetrafluoro-4-(1-(4-methoxyphenyl)ethylideneaminooxy)benzonitrile (**4g′**)*

M: 53.4 mg, Yield: 79%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.66 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H), 2.51 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.41 to −133.52 (m, 2F), −151.21 to −151.32 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 161.8, 161.7, 149.0–149.3 (m), 146.4–146.7 (m), 143.2–143.3 (m), 141.7–142.0 (m), 139.3–139.4 (m), 128.2, 126.0, 114.2, 107.6 (t, J_{C-F} = 3.5 Hz), 88.5–88.8 (m), 55.4, 13.4; IR (KBr) ν (cm^{-1}): 3488.67, 3132.43, 2964.59, 2929.54, 2238.99, 1648.24, 1501.67, 1435.14, 1401.23, 1153.77, 1129.75, 1002.72, 960.98, 820.76, 781.83, 562.16, 506.98, 419.21; HRMS (EI) found: m/z 338.0689 [M]; calcd. for $C_{16}H_{10}F_4N_2O_2$ 338.0678.

*4.1.20. (E)-2,3,5,6-Tetrafluoro-4-(1-(4-fluorophenyl)ethylideneaminooxy)benzonitrile (**4h′**)*

M: 43.7 mg, Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.71 (dd, J = 8.6, 5.4 Hz, 2H), 7.13 (t, J = 8.6 Hz, 2H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −109.17 to −109.25 (m, F), −133.26 to −133.37 (m, 2F), −151.25 to −151.36 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 164.4 (d, $^1J_{C-F}$ = 228 Hz), 161.3, 149.0–149.2 (m), 146.4–146.7 (m), 142.9–143.2 (m), 141.8–142.0 (m), 139.2–139.4 (m), 129.9 (d, $^4J_{C-F}$ = 4.0 Hz), 128.8 (d, $^3J_{C-F}$ = 9.0 Hz), 115.9 (d, $^2J_{C-F}$ = 22.0 Hz), 107.4 (t, J_{C-F} = 2.5 Hz), 88.8–89.2 (m), 13.5; IR (KBr) ν (cm^{-1}): 3073.40, 2933.53, 2859.42, 2243.27, 1646.85, 1598.31, 1501.41, 1438.10, 1373.92, 1304.46, 1230.81, 1156.57, 1128.31, 1007.38, 963.60, 888.92, 845.09, 558.71; HRMS (EI) found: m/z 326.0485 [M]; calcd. for $C_{15}H_7F_5N_2O$ 326.0479.

*4.1.21. (E)-4-(1-(4-Chlorophenyl)ethylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4i′**)*

M: 50.0 mg, Yield: 73%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.65 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 2.53 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.15 to −133.26 (m, 2F), −151.18 to −151.29 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 161.3, 149.0–149.2 (m), 146.4–146.7 (m), 142.9–143.1 (m), 141.8–142.0 (m), 139.2–139.4 (m), 137.1, 132.2, 129.0, 128.0, 107.4 (t, J_{C-F} = 3.0 Hz), 88.9–89.3 (m), 13.4; IR (KBr) ν (cm^{-1}): 3449.36, 2934.05, 2860.68, 2241.28, 1647.75, 1591.66, 1497.41, 1437.88, 1400.91, 1155.89, 1128.95, 1007.80, 837.87, 799.52, 558.75; HRMS (ESI) found: m/z 343.0256 [M+H]$^+$; calcd. for $C_{15}H_7ClF_4N_2O$ + H 343.0261.

*4.1.22. (E)-4-(1-(4-Bromophenyl)ethylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4j′**)*

M: 58.1 mg, Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.59 (d, J = 7.2 Hz, 4H), 2.52 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.08 to −133.19 (m, 2F), −151.15 to −151.26 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 161.8, 161.7, 149.0–149.3 (m), 146.4–146.7 (m), 143.2–143.3 (m), 141.7–142.0 (m), 139.3–139.4 (m), 128.2, 126.0, 114.2, 107.6 (t, J_{C-F} = 3.5 Hz), 88.5–88.8 (m), 55.4, 13.4; IR (KBr) ν (cm^{-1}): 3442.83, 2934.09, 2860.37, 2238.77, 1645.97, 1587.10, 1496.16, 1435.77, 1395.00, 1153.84, 1127.95, 1067.90, 1005.37, 961.90, 831.47, 558.10; HRMS (ESI) found: m/z 386.9751 [M+H]$^+$; calcd. for $C_{15}H_7BrF_4N_2O$ + H 386.9756.

*4.1.23. (E)-2,3,5,6-Tetrafluoro-4-(1-(naphthalen-1-yl)ethylideneaminooxy)benzonitrile (**4k′**)*

M: 38.0 mg, Yield: 53%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.06 (d, J = 8.2 Hz, 1H), 7.95 (dd, J = 13.1, 6.3 Hz, 2H), 7.60 (dd, J = 16.0, 7.6 Hz, 2H), 7.54 (d, J = 4.3 Hz, 2H), 2.68 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.14 to −133.25 (m, 2F), −150.94 to −151.05 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 164.8, 149.0–149.2 (m), 146.4–146.6 (m), 142.9–143.2 (m), 142.0–142.3 (m), 139.5–139.7 (m), 133.9, 132.4, 130.4, 128.7, 127.2, 126.5, 126.4, 125.1, 124.7, 107.5 (t, J_{C-F} = 3.5 Hz), 89.1–89.4 (m), 18.2; IR (KBr) ν (cm^{-1}): 3643.64, 2956.96, 2924.59, 2853.33, 2238.33, 1651.20, 1503.81, 1434.54, 1343.79, 1271.29, 1156.61, 1137.97, 984.07, 799.17, 766.03, 600.39, 419.23; HRMS (ESI) found: m/z 359.0802 [M+H]$^+$; calcd. for $C_{19}H_{10}F_4N_2O$ + H 359.0807.

*4.1.24. (E)-2,3,5,6-Tetrafluoro-4-(1-(pyridin-2-yl)ethylideneaminooxy)benzonitrile (**4l′**)*

M: 43.9 mg, Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 8.69 (d, J = 3.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.44–7.33 (m, 1H), 2.64 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.07 to −133.18 (m, 2F), −151.12 to −151.22 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 163.3, 151.8, 149.4, 149.0–149.4 (m), 146.4–146.6 (m), 142.9–143.1 (m), 141.8–141.9 (m), 139.2–139.4 (m), 136.6, 125.1, 121.4, 107.5 (t, J_{C-F} = 3.0 Hz), 89.0–89.3 (m), 12.1; IR (KBr) ν (cm^{-1}): 3714.63, 3677.07, 3649.27, 3621.97, 2361.24, 2243.17, 1647.66, 1559.09, 1504.95, 1433.53, 1366.68, 1129.68, 1010.94, 974.14, 890.98, 783.71, 678.09, 571.95, 398.57; HRMS (ESI) found: m/z 310.0598 [M+H]$^+$; calcd. for $C_{14}H_7F_4N_3O$ + H 310.0603.

*4.1.25. (E)-2,3,5,6-Tetrafluoro-4-(1-(furan-2-yl)ethylideneaminooxy)benzonitrile (**4m′**)*

M: 44.7 mg, Yield: 75%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.56 (s, 1H), 6.89 (d, J = 3.4 Hz, 1H), 6.54 (dd, J = 3.1, 1.6 Hz, 1H), 2.47 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.11 to −133.22 (m, 2F), −150.91 to −151.02 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 153.9, 149.0–149.2 (m), 147.2, 146.3–146.6 (m), 145.3, 142.7–143.0 (m), 142.1–142.3 (m), 139.5–139.7 (m), 113.4, 111.8, 107.4 (t, J_{C-F} = 3.5 Hz), 89.2–89.6 (m), 12.4; IR (KBr) ν (cm^{-1}): 3159.07, 3115.71, 2240.60, 1649.00, 1591.01, 1499.72, 1437.91, 1308.37, 1174.68, 1129.05, 1009.13, 966.99, 885.11, 723.65, 595.36, 425.24; HRMS (ESI) found: m/z 299.0438 [M+H]$^+$; calcd. for $C_{13}H_6F_4N_2O_2$ + H 299.0443.

*4.1.26. (E)-2,3,5,6-Tetrafluoro-4-(1-(thiophen-2-yl)ethylideneaminooxy)benzonitrile (**4n′**)*

M: 42.1 mg, Yield: 67%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.45 (d, J = 5.6 Hz, 2H), 7.12 (s, 1H), 2.56 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.07 to −133.25 (m, 2F), −151.16 to −151.27 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 157.8, 149.0–149.3 (m), 146.4–146.7 (m), 142.7–143.0 (m), 141.8–142.0 (m), 139.2–139.4 (m), 129.4, 129.2, 127.4, 126.4, 107.5 (t, J_{C-F} = 2.5 Hz), 88.9–89.2 (m), 13.7; IR (KBr) ν (cm^{-1}): 3646.03, 2932.61, 2317.30, 2242.63, 1646.97, 1497.29, 1435.81, 1302.86, 1130.85, 997.81, 959.81, 867.98, 784.40, 717.29, 419.41; HRMS (ESI) found: m/z 315.0210 [M+H]$^+$; calcd. for $C_{13}H_6F_4N_2OS$ + H 315.0215.

*4.1.27. (E)-4-(3,4-Dihydronaphthalen-1(2H)-ylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4o′**)*

M: 55.5 mg, Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.94 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.3 Hz, 1H), 7.26 (dd, J = 14.4, 6.7 Hz, 2H), 3.07 (t, J = 6.6 Hz, 2H), 2.90–2.82 (m, 2H), 2.04–1.94 (m, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.46 to −133.56 (m, 2F), −151.28 to −151.39 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 161.2, 149.0–149.3 (m), 146.4–146.7 (m), 143.2–143.6 (m), 141.8–142.0 (m), 140.8, 139.2–139.4 (m), 130.9, 128.9, 128.0, 126.7, 125.0, 107.6 (t, J_{C-F} = 3.0 Hz), 88.5–89.8 (m), 29.5, 24.7, 21.1; IR (KBr) ν (cm^{-1}): 3450.25, 2936.36, 2870.30, 2240.93, 1646.92, 1498.13, 1437.77, 1329.37, 1153.28, 1122.09, 1004.67, 963.00, 730.33, 557.02; HRMS (ESI) found: m/z 335.0802 [M+H]$^+$; calcd. for $C_{17}H_{10}F_4N_2O$ + H 335.0807.

*4.1.28. (E)-2,3,5,6-Tetrafluoro-4-(1-phenylbutylideneaminooxy)benzonitrile (**4p′**)*

M: 39.7 mg, Yield: 59%; ^{1}H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.67 (d, J = 7.1 Hz, 2H), 7.46 (d, J = 7.6 Hz, 3H), 3.05–2.95 (m, 2H), 1.76 (dt, J = 22.6, 7.5 Hz, 2H), 1.06 (dd, J = 13.2, 5.9 Hz, 3H); ^{19}F NMR

(376 MHz, $CDCl_3$) [ppm] δ −133.33 to −133.44 (m, 2F), −151.07 to −151.18 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 166.2, 149.0–149.3 (m), 146.4–146.7 (m), 143.1–143.3 (m), 141.9–142.2 (m), 139.3–139.6 (m), 133.1, 130.7, 128.8, 127.0, 107.5 (t, J_{C-F} = 2.5 Hz), 88.7–89.0 (m), 29.4, 20.1, 14.0; IR (KBr) ν (cm^{-1}): 3739.93, 3674.52, 3647.50, 3619.36, 3132.02, 2964.92, 2928.46, 2360.89, 2238.23, 1648.50, 1503.92, 1398.76, 1260.05, 1152.86, 1001.12, 799.70, 755.95, 693.61, 420.52; HRMS (ESI) found: *m*/*z* 337.0959 $[M+H]^+$; calcd. for $C_{17}H_{12}F_4N_2O$ + H 337.0964.

*4.1.29. (E)-2,3,5,6-Tetrafluoro-4-(1-phenylhexylideneaminooxy)benzonitrile (**4q′**)*

M: 49.5 mg, Yield: 68%; ^1H NMR (400 MHz, $CDCl_3$) [ppm] δ 7.68 (d, *J* = 6.9 Hz, 2H), 7.53–7.39 (m, 3H), 3.05–2.96 (m, 2H), 1.72 (dq, *J* = 22.9, 7.7 Hz, 2H), 1.42 (ddd, *J* = 20.6, 10.9, 4.8 Hz, 4H), 0.93 (t, *J* = 6.9 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.36 to −133.47 (m, 2F), −151.10 to −151.21 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 166.3, 149.0–149.2 (m), 146.4–146.7 (m), 143.1–143.4 (m), 141.9–142.1 (m), 139.4–139.6 (m), 133.1, 130.7, 128.8, 127.0, 107.5 (t, J_{C-F} = 3.0 Hz), 88.7–89.0 (m), 31.7, 27.6, 26.3, 22.2, 13.8; IR (KBr) ν (cm^{-1}): 3475.28, 2958.75, 2925.57, 2855.18, 2240.53, 2219.94, 1645.58, 1501.15, 1462.98, 1261.13, 1133.27, 1096.64, 1003.66, 961.24, 799.82, 694.87, 421.14; HRMS (ESI) found: *m*/*z* 365.1275 $[M+H]^+$; calcd. for $C_{19}H_{16}F_4N_2O$ + H 365.1277.

*4.1.30. 4-(Cyclohexylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4r′**)*

M: 31.5 mg, Yield: 55%; ^1H NMR (400 MHz, $CDCl_3$) [ppm] δ 2.72 (t, *J* = 6.4 Hz, 2H), 2.38–2.28 (m, 2H), 1.83–1.75 (m, 4H), 1.69 (d, *J* = 4.6 Hz, 2H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.68 to −133.79 (m, 2F), −151.22 to −151.33 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 167.9, 148.9–149.2 (m), 146.4–146.6 (m), 143.2–143.4 (m), 141.9–142.2 (m), 139.4–139.7 (m), 107.6 (t, J_{C-F} = 3.0 Hz), 88.3–88.6 (m), 31.4, 26.8, 26.0, 25.7, 25.3; IR (KBr) ν (cm^{-1}): 3740.24, 3675.49, 3648.35, 3620.91, 2932.74, 2860.89, 2360.70, 1741.34, 1700.08, 1647.94, 1554.17, 1503.67, 1259.14, 1000.79, 798.07, 671.91, 420.38; HRMS (ESI) found: *m*/*z* 287.0802 $[M+H]^+$; calcd. for $C_{13}H_{10}F_4N_2O$ + H 287.0807.

*4.1.31. 4-(Cyclooctylideneaminooxy)-2,3,5,6-tetrafluorobenzonitrile (**4s′**)*

M: 39.6 mg, Yield: 63%; ^1H NMR (400 MHz, $CDCl_3$) [ppm] δ 2.70–2.62 (m, 2H), 2.44–2.36 (m, 2H), 1.95–1.80 (m, 4H), 1.63–1.52 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) [ppm] δ −133.68 to −133.80 (m, 2F), −151.29 to −151.40 (m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) [ppm] δ 171.6, 149.0–149.2 (m), 146.4–146.6 (m), 143.3–143.5 (m), 142.0–142.3 (m), 139.5–139.8 (m), 107.6 (t, J_{C-F} = 3.5 Hz), 88.4–88.6 (m), 32.7, 27.9, 27.2, 26.0, 25.3, 25.1, 23.8; IR (KBr) ν (cm^{-1}): 3615.24, 2933.64, 2861.94, 1645.79, 1498.56, 1436.39, 1401.76, 1131.89, 998.99, 957.89, 859.59, 810.55, 772.82, 730.21, 420.65; HRMS (ESI) found: *m*/*z* 315.1115 $[M+H]^+$; calcd. for $C_{15}H_{14}F_4N_2O$ + H 315.1120.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2014.06.011.

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