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Nucleophilic difluoromethylation of C=N bonds in heterocycles with difluoromethyl silane reagents

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ABSTRACT

An efficient and straightforward nucleophilic difluoromethylation of C=N bonds in heterocycles under the activation of alkylating agents has been developed. Cyclic iminium salts derived from dihydroisoquinolines, quinolines, and pyridines were successfully difluoromethylated with sulfur-based fluoroalkyl silanes affording a series of new difluoromethylated nitrogen-containing heterocyclic compounds.

1. Introduction

Organic compounds possessing both nitrogen and fluorine atoms and especially fluoroalkylated amines have received remarkable attention in bioorganic and medical chemistry research due to profound change of the basicity of the amine functionality, which will enhance the bioavailability of a target molecule.[1] Representative methods for the synthesis of fluoroalkylated amines including multi-step transformation of fluorinated building blocks and fluoroalkylation of C=N bonds.[2] Currently, the fluoroalkylation approach mainly focuses on nucleophilic addition of fluoroalkyl anions to C=N bonds in acyclic systems.[3,4] Considering the wide application of fluorinated heterocycles in drug design, crop protection, and new materials research, the synthesis of fluoroalkylated heterocyclic compounds is of great interest.[5] Among various available synthetic methods, the addition of fluoroalkyl anions to C=N bonds in heterocycles is the most attractive one because of the easy availability of many nucleophilic fluoroalkylating agents. However, the azomethine carbon in a neutral heterocyclic compound is usually not electrophilic enough toward a fluoroalkyl nucleophile. The currently known nucleophilic fluoroalkyl addition to unactivated C=N bonds is limited to strained 3- and 4-memebered heterocycles[6] and perfluorinated six-membered heterocycles.[7] The formation of iminium salts by alkylation or protonation has been widely used in the activation of inert C=N bonds in both acyclic and cyclic systems.[3] In 2007, Makosza and co-workers reported the perfluoromethylation of quinoline and pyridine by formation of their benzylazinium salts.[4a,b] In 2011, Nenajdenko, Röschenthaler and co-workers reported the trifluoromethylation of 5- and 6-memebered cyclic imines with Ruppert–Prakash reagent under acidic conditions.[4e] To the best of our knowledge, there has been no report on the nucleophilic difluoromethylation of C=N bonds in heterocyclic systems.[8] Considering the unique properties of difluoromethylene functionality (CF_2),[9] we have been interested in the introduction of a difluoromethyl group into these heterocyclic systems. In this article, we would like to disclose our success in selective difluoromethylation of C=N bonds in heterocycles including dihydroisoquinolines, quinolines, and pyridines, which affords a series of difluoromethylated tetrahydroisoquinolines, dihydroquinolines, and dihydropyridines.

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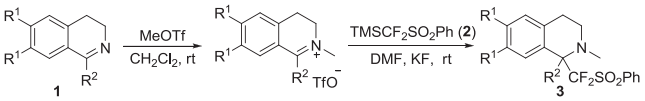
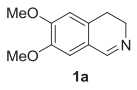
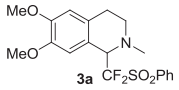
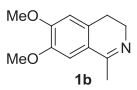
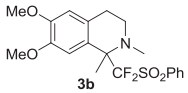
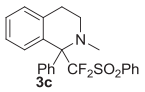
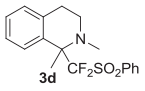
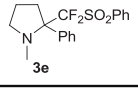
2. Results and discussion

2.1. Nucleophilic fluoroalkylation of dihydroisoquinolines

Firstly, we prepared a series of six-membered cyclic imines **1a–d** using the Bischler-Napieralski cyclization[10] and a five-memebered cyclic imine **1e** by transformation of lactam with PhMgBr under the activation of TMSCl.[11] Thereafter, we investigated the direct nucleophilic difluoromethylation reaction with **1a** as model compound. Among many nucleophilic difluoromethylation reagents, such as $PhSO_2CF_2H$, $PhSO_2CF_2Br$, $TMSCF_2SO_2Ph$, $TMSCF_2SPh$ and $TMSCF_2H$, the sulfur-based silane reagents can be handled under very mild conditions and have been used in the nucleophilic difluoromethylation of aldehydes, ketones, *N*-(*tert*-butylsulfinyl)imines and alkyl halides.[12] With $TMSCF_2SO_2Ph$ (**2**) as the difluoromethylation reagent, it was found that no expected reaction took place between **1a** and **2**. According to Dilman's report, the activation of the imine is a good strategy to enhance the latter's electrophilicity.[3] As an alternative to the reported activation of cyclic imines with Brønsted acid,[4e] we chose the formation of iminium salts by alkylation to activate those imines. Due to the hydroscopic nature of the *N*-(*p*-methoxybenzyl) iminium salts, in our case, we chose methylation strategy using methyl triflate (MeOTf) as efficient methylating agent.[4c] As shown in Table 1, after methylation of the cyclic imines **1** with MeOTf (1.2 equiv) in CH_2Cl_2 and subsequent removal of the solvent, the iminium salt was then treated with **2** (2.0 equiv) in DMF under the initiation of KF (3.0 equiv). All the cyclic aldimines and cyclic ketimines showed high reactivity toward **2**, giving the desired *N*-methyl cyclic amines **3** in modertate to good yields (64–94% yields) after short reaction time (0.5 h). For comparison purpose, the reaction of the methylated **1a** with $PhSO_2CF_2H$ under strong basic conditions was tested,[13a] and it was found that the iminium salt of **1a** (using LiHMDS as a base) decomposed under such conditions, indicating that the fluoroalkyl silanes proved to be the privileged reagents for this fluoroalkylation reaction.

Table 1
Nucleophilic difluoromethylation of dihydroisoquinolines with $TMSCF_2SO_2Ph$ (**2**)

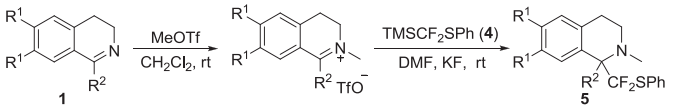


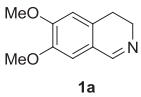
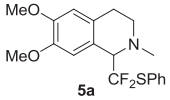
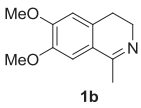
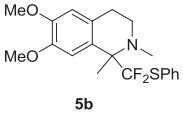
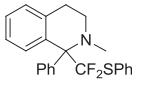
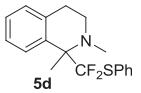
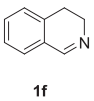
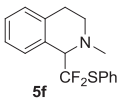
Entry	Substrate	Product	Yield(%)[a]
1	 1a	 3a	94
2	 1b	 3b	80
3	 1c	 3c	68[b]
4	 1d	 3d	64[b]
5	 1e	 3e	90

[a] Isolated yield.
[b] Purified by recrystallization after column chromatography.

Based on the above results, we further investigated the difluoromethylation of the iminium salts of cyclic imines **1** with $TMSCF_2SPh$ (**4**) as the fluoroalkylation reagent. $TMSCF_2SPh$ is also a stable and effective difluoromethylation reagent.[12a,13b] The $PhSCF_2$-containing tetrahydroisoquinolines can not only be transformed into difluoromethylated compounds, but also have the potential to be incorporated into alkenes via radiacal fluoroalkylation.[13b] Under similar reaction conditions, the $PhSCF_2$-substituted cyclic amines **5** were obtained in moderate to good yields (43–94%) (Table 2). However, in most cases, the yields were lower than those for (phenylsulfonyl)difluoromethylation of the iminium salts (as shown in Table 1).

Table 2
Nucleophilic difluoromethylation of dihydroisoquinolines with $TMSCF_2SPh$ (**4**)



Entry	Substrate	Product	Yield(%)[a]
1	 1a	 5a	57
2	 1b	 5b	43
3	 1c	 5c	94
4	 1d	 5d	71
5	 1f	 5f	58

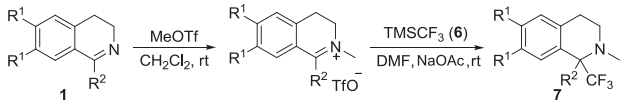
[a] Isolated yield.

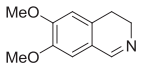
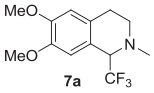
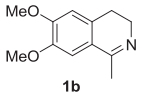
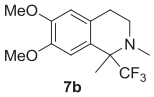
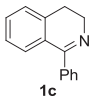
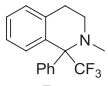
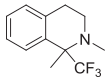
To further extend this fluoroalkylation of iminium salts with other fluoroalkylating agents, we conducted the trifluoromethylation reactions with Ruppert–Prakash reagent ($TMSCF_3$) (**6**).[14] Under similar reaction conditions, the addition products **7** were obtained in moderate to excellent yields (56–99%) (see Table 3).

2.2. Nucleophilic difluoromethylation of quinolines and pyridines

Quinoline and pyridine derivatives are usually regarded as unactivated cyclic imines. It is almost impossible to conduct direct nucleophilic fluoroalkylation reaction toward the C=N bonds in these heterocycles.[4a] The nucleophilic addition of trifluoromethyl and perfluoroisopropyl anions to C=N bonds in pyridinium and quinolinium salts was reported by Makosza and co-workers in 2007.[4a,b] The 2-fluoroalkyl 1,2-dihydroazines were oxidized into 2-fluoroalkyl azines after deprotection and aromatization, and therefore, a formal oxidative fluoroalkylation of azines was realized.[4a,b] To further explore the difluoromethylation of C=N bonds in heterocycles, we performed the reaction between *N*-(*p*-

Table 3
Nucleophilic trifluoromethylation of dihydroisoquinolines with $TMSCF_3$ (**6**)



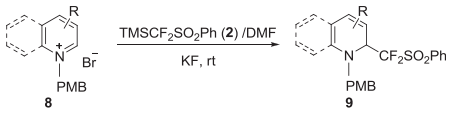
Entry	Substrate	Initiator	Product	Yield(%)[a]
1	 **1a**	NaOAc	 **7a**	81
2	 **1b**	KF	 **7b**	77
3	 **1c**	NaOAc	 **7c**	99
4	 **1d**	NaOAc	 **7d**	56
5	 **1e**	NaOAc	 **7e**	77

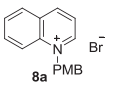
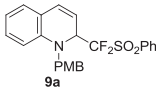
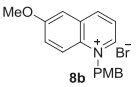
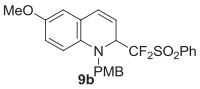
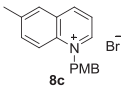
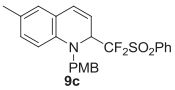
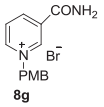
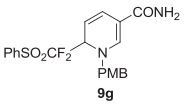
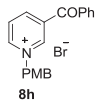
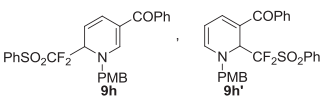
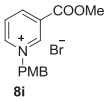
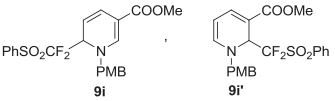
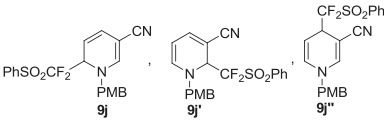
[a] Isolated yield.

methoxybenzyl)quinolinium salt **8a** and **2** in the presence of an initiator at ambient temperature. After a quick screening of the reaction conditions, it was found that the readily available KF was better than tetrabutylammonium triphenyldifluorosilicate (TBAT) as an initiator, and K_2CO_3 can also be used as an initiator (but inferior to KF). The use of 2.0 equiv of **2** was beneficial for the high yield (90%) of **9a** when DMF was used as a solvent. When the reaction was conducted in CH_2Cl_2, only moderate yields were achieved.

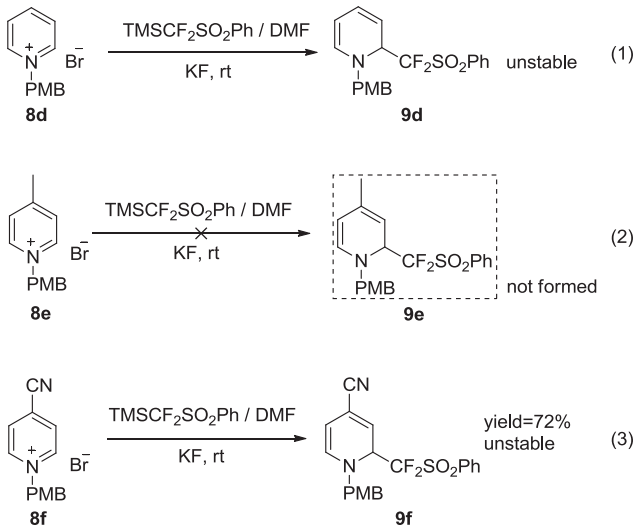
With the optimized reaction conditions established, the difluoromethylation of C=N bonds in a series of heterocycles was investigated (Table 4). It was found that the nucleophilic difluoroalkylation of the quinolinium salts **8a**–**8c** proceeded smoothly and gave the desired product in high yields (86–90%). As for the regioselectivity, the $PhSO_2CF_2$ anion added exclusively at the 2-position of the quinoline ring (entries 1–3). When we invetigated the reactivity of various pyridinium salts, a significant substituent effect was observed. Although the difluoromethylation of simple pyridinium salt **8d** could afford the addition product **9d** in high yield (90% yield according to ^{19}F NMR), **9d** was not stable enough to be isolated by flash column chromatography (Scheme 1, Eq. 1). When the more electron-rich *p*-methyl pyridinium salt **8e** was used, no desired product was formed (Scheme 1, Eq. 2). In the case of the electron-deficient *p*-cyano pyridinium salt **8f**, the expected product **9f** could be isolated in 72% yield. However, we found that compound **9f** readily decomposed in pure form (Scheme 1, Eq. 3). Finally, we found that the pyridinium salts substituted with an electron withdrawing group at the 3-position could give the stable (phenylsulfonyl)difluoromethylated 1,2-dihydropyridines in 40–96% yields (Table 4, entries 4–7). The reaction is of good tolerance to amide, ketone, ester, and nitrile groups. The reaction of 3-benzoylpyridinium salt **8h** (entry 5) was particularly notable as no product resulting from nucleophilic difluoromethylation of carbonyl group was observed. Although the regioselectivity varied with the substituent, the less sterically demanding 6-position always showed higher reactivity. In the case of **8g**, the $PhSO_2CF_2$ anion added exclusively at the 6-position (entry 4), while in the cases of pyridinium salts **8h** and **8i**, the anion added at the 2/6-positions of the pyridine rings (entries 5–6). For pyridinium salt **8j**, the 1,4-addition product **9j″** was also formed in 16% yield (entry 7). In all cases, the regioisomers were readily separated by flash

Table 4
Nucleophilic difluoromethylation of quinolinium and pyridinium salts (**8**) with **2**



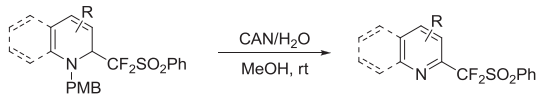
Entry	Substrate	Product	Yield(%)[a]
1	 **8a**	 **9a**	90
2	 **8b**	 **9b**	89
3	 **8c**	 **9c**	86
4	 **8g**	 **9g**	40
5	 **8h**	 **9h** **9h'**	60, 30
6	 **8i**	 **9i** **9i'**	54, 42
7	 **8j**	 **9j** **9j'** **9j''**	44, 32, 16

[a] Isolated yield.

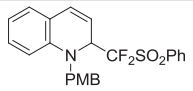
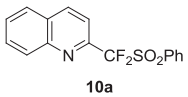
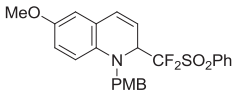
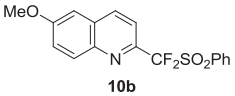
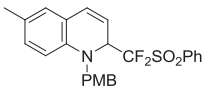
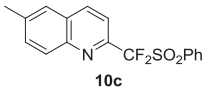
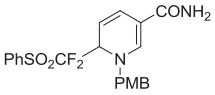
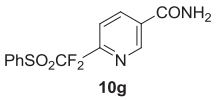
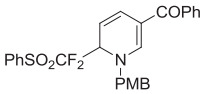
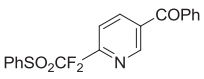
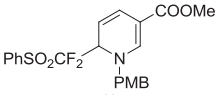
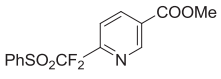
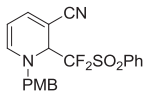
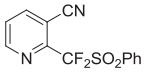


Scheme 1. Substituent effect in difluoromethylation of pyridinium salts.

Table 5
Oxidative aromatization of addition products **9**



9 **10**

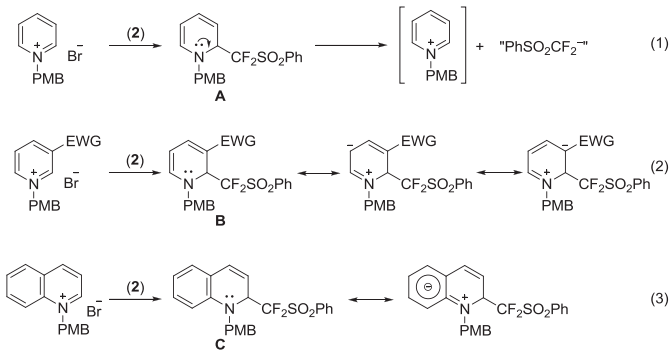
Entry	Substrate	Product	Yield(%)[a]
1	 **9a**	 **10a**	93
2	 **9b**	 **10b**	92
3	 **9c**	 **10c**	89
4	 **9g**	 **10g**	81
5	 **9h**	 **10h**	86
6	 **9i**	 **10i**	95
7	 **9j'**	 **10j'**	83

[a] Isolated yield.

column chromatography. The preference of 1,2-addition over 1.4-addition in these reactions indicated that the $PhSO_2CF_2$ anion is a hard nucleophile. However, by comparing with the regioselectivity observed in the trifluoromethylation of iminium salt **8d** (entry 7, 44/32/16 vs 29/32/0),[4b] it suggests that $PhSO_2CF_2$ anion is a somewhat softer nucleophile than CF_3 anion.

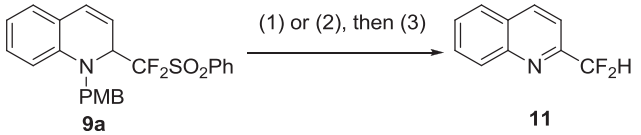
An explanation for the substituent effect on the addition reaction of aziniums and stability of the corresponding dihydroazines is as shown in Scheme 2. As for the simple pyridine iminium salts, such as **8d**, the addition of $PhSO_2CF_2$ anion leads to the dearomatization of pyridine aromatic ring, which could be thermodynamically disfavored. On the other hand, since $PhSO_2CF_2$ anion is a good leaving group, the product **A** readily undergoes decomposition due to its aromatization to pyridinium ring (Scheme 2, Eq. 1). When the 3-position is substituted by an EWG, the nitrogen lone pair could delocalize to the EWG, which reduces the tendency of aromatization; as a result, such addition product is more stable (Scheme 2, Eq. 2). Furthermore, in the case of the quinoline derivatives, although the addition of $PhSO_2CF_2$ anion will lead to the dearomatization of quinoline aromatic ring, in this process a benzene ring still remains, which could stabilize the addition products (Scheme 2, Eq. 3).

The *p*-methoxybenzyl substituent can be readily removed by oxidizing agents, such as DDQ or CAN.[4b] The oxidative deprotection was performed in a mixed solvent system of MeOH/H_2O (v/v=4:1)



Scheme 2. Conjugational stabilization.

at ambient temperature, and 2.5 equiv of CAN was used as an oxidizing agent. The aromatization reaction proceeded in high yield to give a variety of substituted azines **10** containing a (phenylsulfonyl) difluoromethyl group at 2- or 6-position (Table 5). However, these $PhSO_2CF_2$-substituted azines failed to be transformed into the CF_2H-containing azines by reductive desulfonation. When the reductive desulfonation[15] was conducted before oxidative aromatization, 2-(difluoromethyl)quinoline was obtained in moderate yield (Scheme 3).



Scheme 3. Preparation of 2-difluoromethyl quinoline. Conditions: (1) Mg/HOAc/NaOAc, DMF, rt, 66%; (2) Na–Hg, Na_2HPO_4, anhydrous MeOH, −20 °C to 0 °C, 93%; (3) CAN, MeOH/H_2O 4:1, rt, 68%.

3. Conclusion

In conclusion, we have developed an efficient and straightforward nucleophilic difluoromethylation of inert C=N bonds in heterocyclic systemes under the activation of alkylation reagents. Cyclic iminium salts derived from dihydroisoquinolines, quinolines, and pryridines were successfully difluoromethylated with $TMSCF_2SO_2Ph$ and $TMSCF_2SPh$. This research not only extends the synthetic application of sulfur-based fluoroalkyl silanes, but also provides a facile method for the preparation of a series of novel difluoromethylated nitrogen-containing heterocyclic compounds.

4. Experimental section

4.1. General information

All reactions were carried out in oven-dried glassware under a nitrogen atmosphere. DMF was distilled from CaH_2. Other commercially available chemicals were used without further purification. Column chromatography was performed on silica gel 300–400 (0.038–0.048 mm). ^1H, ^{13}C, and ^{19}F NMR spectra were recorded in $CDCl_3$, chemical shifts (δ) are given in parts per million (ppm) and spin–spin coupling constants (J) are given in Hertz (Hz). ^1H NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ δ 7.26. ^{13}C NMR chemical shifts were determined relative to internal TMS at δ 0.0. ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ at δ 0.0. Mass spectra were obtained on a mass spectrometer in the ESI mode. High-resolution mass data were recorded on a high-resolution mass spectrometer in the ESI mode. Melting points are uncorrected.

4.2. Typical procedure for the reaction of cyclic imines 1 with $TMSCF_2SO_2Ph$ (2)

Under a nitrogen atmosphere, into a CH_2Cl_2 (8 mL) solution of cyclic imine **1a** (96 mg, 0.5 mmol) was added MeOTf (0.068 mL, 0.6 mmol) dropwise in 10 min. After the reaction mixture was stirred for 1 h at ambient temperature, the solvent CH_2Cl_2 was gently evaporated and dry DMF (3 mL) and KF (87 mg, 1.5 mmol) were added. Then a DMF (2 mL) solution of $TMSCF_2SO_2Ph$ (**2**) (264 mg, 1.0 mmol) was added to the reaction system dropwise in 10 min. After stirring at ambient temperature for 30 min, the reaction mixture was quenched with a saturated $NaHCO_3$ aqueous solution (20 mL) and extracted with ethyl acetate (3×15 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (15 mL), and dried by anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 3:1) to give **3a** as a pale yellow solid (187 mg, 94%).

*4.2.1. 1-(Difluoro(phenylsulfonyl)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**3a**).* Pale yellow solid. Mp: 150–152 °C. IR (KBr): 3073, 3029, 2955, 2945, 2837, 1612, 1520, 1328, 1257, 1162, 1015, 763, 722, 685, 635, 579, 557 cm^{-1} ^1H NMR: δ 8.00 (d, J=7.8 Hz, 2H), 7.69 (t, J=7.5 Hz, 1H), 7.56 (t, J=7.5 Hz, 2H), 6.72 (d, J=3.6 Hz, 1H), 6.60 (s, 1H), 4.40 (dd, J=24.3 Hz, 7.5 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.78–3.02 (m, 2H), 2.54 (s, 3H), 2.34–2.54 (m, 2H). ^{19}F NMR: δ −95.1 (d, J=238.6 Hz, 1F), −109.6 (dd, J=237.4 Hz, 24.3 Hz, 1F). ^{13}C NMR: δ 149.0, 147.3, 135.8, 134.4, 130.2, 128.8, 128.6, 123.1 (dd, J=298.9 Hz, 290.1 Hz), 118.1, 111.7 (dd, J=6.4 Hz, 2.2 Hz), 111.5, 61.6 (dd, J=23.2 Hz, 18.9 Hz), 55.9, 55.7, 45.2, 42.2, 21.6. MS (ESI, m/z): 398.1 ($[M+H]^+$). Anal. Calcd for $C_{19}H_{21}F_2NO_4S$: C, 57.42; H, 5.33; N, 3.52; Found: C, 57.38; H, 5.32; N, 3.35.

*4.2.2. 1-(Difluoro(phenylsulfonyl)methyl)-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**3b**).* pale yellow solid. Mp: 153–155 °C. IR (KBr): 3008, 2962, 2931, 2836, 1611, 1515, 1327, 1256, 1162, 1093, 981, 867, 760, 723, 686, 597, 568 cm^{-1} ^1H NMR: δ 7.93 (d, J=7.5 Hz, 2H), 7.63 (t, J=7.5 Hz, 1H), 7.52 (t, J=7.5 Hz, 2H), 6.78 (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.79 (s, 3H), 3.00–3.08 (m, 1H), 2.80–2.88 (m, 1H), 2.46–2.60 (m, 2H), 2.46 (s, 3H), 1.81 (s, 3H). ^{19}F NMR: δ −90.5 (d, J=239.4 Hz, 1F), −92.9 (d, J=240.3 Hz, 1F). ^{13}C NMR: δ 148.4, 147.2, 136.6, 134.0, 130.2, 129.0, 128.5, 125.9 (d, J=2.0 Hz), 124.4 (dd, J=302.4 Hz, 300.5 Hz), 111.1, 110.6, 64.7 (dd, J=20.5 Hz, 19.4 Hz), 55.9, 55.6, 48.0 (d, J=5.4 Hz), 37.9, 23.5, 21.1. MS (ESI, m/z): 412.1 ($[M+H]^+$). Anal. Calcd for $C_{20}H_{23}F_2NO_4S$: C, 58.38; H, 5.63; N, 3.40; Found: C, 58.34; H, 5.58; N, 3.16.

*4.2.3. 1-(Difluoro(phenylsulfonyl)methyl)-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**3c**).* White solid. Mp: 177–179 °C. IR (KBr): 3051, 2952, 2813, 1497, 1447, 1348, 1097, 1041, 771, 756, 709, 698, 685, 576, 538, 518 cm^{-1} ^1H NMR: δ 7.87 (d, J=8.1 Hz, 2H), 7.64 (t, J=7.8 Hz, 1H), 7.51 (t, J=7.5 Hz, 2H), 7.21–7.28 (m, 7H), 6.98–7.03 (m, 1H), 6.87–6.91 (m, 1H), 3.61–3.72 (m, 1H), 3.03–3.08 (m, 1H), 2.84 (dt, J=15.6 Hz, 3.0 Hz, 1H), 2.03 (s, 3H). ^{19}F NMR: δ −86.8 (dd, J=232.4 Hz, 3.4 Hz, 1F), −94.0 (d, J=237.2 Hz, 1F). ^{13}C NMR: δ 141.5, 137.6, 136.3, 134.2 (d, J=5.6 Hz), 134.0, 132.0 (d, J=7.3 Hz), 130.3, 128.6, 128.4, 127.9, 127.7, 127.6, 127.1, 125.4, 124.3 (t, J=307.2 Hz), 71.6 (dd, J=20.4 Hz, 16.1 Hz), 49.3, 41.6 (d, J=7.8 Hz), 29.8. MS (ESI, m/z): 414.1 ($[M+H]^+$). Anal. Calcd for $C_{23}H_{21}F_2NO_2S$: C, 66.81; H, 5.12; N, 3.39; Found: C, 66.81; H, 5.17; N, 3.23.

*4.2.4. 1-(Difluoro(phenylsulfonyl)methyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**3d**).* White solid. Mp: 119–121 °C. IR (KBr): 3057, 2925, 1597, 1510, 1392, 1260, 1237, 1126, 979, 771 cm^{-1} ^1H NMR: δ 7.94 (d, J=8.1 Hz, 2H), 7.65 (t, J=7.2 Hz, 1H), 7.53 (t, J=7.8 Hz, 2H), 7.34 (d, J=6.3 Hz, 1H), 7.11–7.23 (m, 2H), 7.07 (d, J=12.0 Hz, 1H), 3.03–3.12 (m, 1H), 2.87–2.98 (m, 1H), 2.59–2.67 (m, 2H), 2.49 (s, 3H), 1.84 (s, 3H). ^{19}F NMR: δ −90.4 (d, J=239.7 Hz, 1F), −93.2 (dd, J=239.1 Hz, 8.2 Hz, 1F). ^{13}C NMR: δ 136.6, 136.5, 134.5, 134.1, 130.2, 129.1, 128.5, 127.7, 127.5, 126.2, 124.4 (t, J=302.9 Hz), 64.9 (dd, J=20.5 Hz, 18.6 Hz), 47.9 (d, J=6.0 Hz), 38.0, 24.2, 21.0. MS (ESI, m/z): 352.1 ($[M+H]^+$). HRMS (ESI): calcd for $C_{18}H_{20}F_2NO_2S^+$($[M+H]^+$): 352.1177; Found: 352.1173.

*4.2.5. 2-(Difluoro(phenylsulfonyl)methyl)-1-methyl-2-phenylpyrrolidine (**3e**).* Colorless oil. IR (film): 3063, 2885, 2857, 2810, 1498, 1448, 1342, 1174, 1151, 1107, 1060, 1014, 912, 883, 756, 724, 710, 687, 610, 579, 530 cm^{-1} ^1H NMR: δ 7.91 (d, J=7.5 Hz, 2H), 7.61 (t, J=7.8 Hz, 1H), 7.51 (t, J=7.5 Hz, 2H), 7.15–7.25 (m, 5H), 3.24–3.31 (m, 1H), 3.08–3.18 (m, 1H), 2.94–3.02 (m, 1H), 2.09–2.02 (m, 2H), 2.09 (s, 3H), 1.86–1.95 (m, 1H). ^{19}F NMR: δ −87.6 (d, J=239.4 Hz, 1F), −96.9 (d, J=241.1 Hz, 1F). ^{13}C NMR: δ 140.8 (d, J=3.3 Hz), 136.1, 134.2, 130.0, 128.7, 128.0, 127.1, 126.7 (dd, J=4.1 Hz, 1.9 Hz), 125.8 (dd, J=306.3 Hz, 299.9 Hz), 73.8 (dd, J=21.4 Hz, 17.5 Hz), 55.9, 38.7, 36.1 (dd, J=3.5 Hz, 1.5 Hz), 22.1. MS (ESI, m/z): 352.1 ($[M+H]^+$). HRMS (ESI): calcd for $C_{18}H_{20}F_2NO_2S^+$($[M+H]^+$): 352.1177; Found: 352.1173.

*4.2.6. 1-(Difluoro(phenylthio)methyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5a**).* Pale yellow solid. Mp: 97–99 °C. IR (KBr): 3063, 2997, 2955, 2924, 2835, 2805, 2778, 1610, 1521, 1255, 1232, 1104, 1002, 981, 873, 848, 811, 747, 692, 585, 500 cm^{-1} ^1H NMR: δ 7.58 (d, J=7.5 Hz, 2H), 7.32–7.34 (m, 3H), 6.77 (s, 1H), 6.63 (s, 1H), 4.04 (dd, J=14.7 Hz, 7.8 Hz, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.35–3.43 (m, 1H), 2.78–2.91 (m, 2H), 2.62–2.69 (m, 1H), 2.62 (s, 3H). ^{19}F NMR: δ −70.7 (dd, J=202.5 Hz, 6.5 Hz, 1F), −73.8 (dd, J=202.2 Hz, 14.1 Hz, 1F). ^{13}C NMR: δ 148.4, 147.0, 136.0, 132.3 (dd, J=287.4 Hz, 281.7 Hz), 129.1, 128.6, 128.4, 128.0 (d, J=2.5 Hz), 120.4, 112.0, 111.0, 67.9 (t, J=24.6 Hz), 55.7, 55.6, 47.3 (d, J=3.1 Hz), 43.5, 23.7. MS (ESI, m/z): 366.1 ($[M+H]^+$). HRMS (ESI): calcd for $C_{19}H_{22}F_2NO_2S^+$($[M+H]^+$): 366.1334; Found: 366.1329.

*4.2.7. 1-(Difluoro(phenylthio)methyl)-6,7-dimethoxy-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**5b**).* Pale yellow oil. IR (film): 2997, 2806, 1611, 1516, 1257, 1222, 1064, 1027, 965, 842, 750, 693, 506 cm^{-1} ^1H NMR: δ 7.51 (d, J=7.2 Hz, 2H), 7.26–7.34 (m, 3H), 6.88 (s, 1H), 6.60 (s, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.32–3.36 (m, 1H), 2.72–2.89 (m, 3H), 2.57 (s, 3H), 1.67 (s, 3H). ^{19}F NMR: δ −68.8 (d, J=203.9 Hz, 1F), −73.1 (d, J=203.6 Hz, 1F). ^{13}C NMR: δ 148.1, 146.9, 136.2, 134.9 (t, J=289.9 Hz), 128.94, 128.93, 128.7, 128.5, 126.6, 111.6, 110.8, 65.9 (t, J=22.2 Hz), 55.9, 55.6, 48.4 (d, J=4.5 Hz), 38.7, 25.7, 19.7 (d, J=3.6 Hz). MS (ESI, m/z): 380.1 ($[M+H]^+$). HRMS (ESI): calcd for $C_{20}H_{24}F_2NO_2S^+$($[M+H]^+$): 380.1490; Found: 380.1487.

*4.2.8. 1-(Difluoro(phenylthio)methyl)-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (**5c**).* Orange solid. Mp: 99–101 °C. IR (KBr): 3055, 2941, 2916, 2812, 2710, 1581, 1497, 1475, 1441, 1294, 1132, 1036, 1014, 822, 762, 746, 699, 641, 503 cm^{-1} ^1H NMR: δ 7.13–7.26 (m, 12H), 6.94–6.98 (m, 1H), 6.83–6.89 (m, 1H), 3.32–3.45 (m, 1H), 2.93–3.02 (m, 2H), 2.79 (d, J=16.2 Hz, 1H), 2.16 (s, 3H). ^{19}F NMR: δ −69.5 (d, J=195.4 Hz, 1F), −72.6 (d, J=196.8 Hz, 1F). ^{13}C NMR: δ 141.1, 137.2, 136.7, 134.5 (t, J=285.9 Hz), 132.1, 132.0, 129.4, 129.2, 128.5, 128.2, 127.8, 127.5, 127.1, 126.9, 125.5, 73.3, 49.5, 41.8, 30.4. MS (ESI, m/z): 382.1 ($[M+H]^+$). HRMS (ESI): calcd for $C_{23}H_{22}F_2NS^+$($[M+H]^+$): 382.1436; Found: 382.1439.

*4.2.9. 1-(Difluoro(phenylthio)methyl)-1,2-dimethyl-1,2,3,4-tetrahydroisoquinoline (**5d**).* Pale yellow oil. IR (film): 3062, 2959, 2912, 2857, 2806, 1475, 1441, 1376, 1262, 1064, 1027, 960, 824, 751, 692, 664, 602, 506 cm^{-1} ^1H NMR: δ 7.39 (d, J=6.9 Hz, 2H), 7.31 (d, J=7.5 Hz, 1H), 7.15–7.25 (m, 3H), 7.10 (t, J=7.2 Hz, 2H), 7.03 (d,

J=7.2 Hz, 1H), 3.23–3.33 (m, 1H), 2.74–2.83 (m, 3H), 2.49 (s, 3H), 1.60 (s, 3H). ^{19}F NMR: δ −69.3 (d, J=205.0 Hz, 1F), −73.1 (d, J=202.5 Hz, 1F). ^{13}C NMR: δ 136.5, 136.2, 135.1, 134.8 (t, J=290.0 Hz), 129.0, 128.71, 128.69, 128.6, 128.5, 127.1, 125.8, 66.2 (t, J=22.7 Hz), 48.3 (d, J=4.8 Hz), 38.9, 26.4, 19.5. MS (ESI, m/z): 320.1 ([M+H]$^+$). HRMS (ESI): calcd for $C_{18}H_{20}F_2NS^+$([M+H]$^+$): 320.1279; Found: 320.1282.

*4.2.10. 1-(Difluoro(phenylthio)methyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**5f**).* Pale yellow solid. Mp: 87–89 °C. IR (KBr): 3018, 2960, 2947, 2814, 1473, 1442, 1263, 1105, 1031, 992, 813, 801, 759, 744, 693, 658, 504 cm^{-1} ^{1}H NMR: δ 7.48 (d, J=6.6 Hz, 2H), 7.07–7.27 (m, 7H), 4.04 (dd, J=13.8 Hz, 7.5 Hz, 1H), 3.32–3.34 (m, 1H), 2.69–2.87 (m, 3H), 2.58 (s, 3H). ^{19}F NMR: δ −71.0 (dd, J=203.6 Hz, 7.1 Hz, 1F), −74.4 (dd, J=201.6 Hz, 13.3 Hz, 1F). ^{13}C NMR: δ 136.5, 136.2, 132.2 (dd, J=287.2 Hz, 282.5 Hz), 129.7, 129.2, 129.1, 128.7, 128.6, 128.0, 127.7, 125.9, 68.5 (t, J=24.4 Hz), 47.9, 44.0, 25.0. MS (ESI, m/z): 306.0 ([M+H]$^+$). HRMS (ESI): calcd for $C_{17}H_{18}F_2NS^+$([M+H]$^+$): 306.1123; Found: 306.1120.

*4.2.11. 6,7-Dimethoxy-2-methyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**7a**).* Colorless oil. IR (film): 3001, 2951, 2913, 2864, 2837, 2804, 1612, 1521, 1467, 1339, 1268, 1232, 1147, 1114, 1011, 850, 807, 780, 709, 653 cm^{-1} ^{1}H NMR: δ 6.71 (s, 1H), 6.64 (s, 1H), 3.97 (q, J=7.5 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.18–3.25 (m, 1H), 2.72–2.78 (m, 2H), 2.64 (s, 3H), 2.56–2.64 (m, 1H). ^{19}F NMR: δ −73.6 (d, J=5.1 Hz, 3F). ^{13}C NMR: δ 148.8, 147.2, 129.7, 126.1 (q, J=282.5 Hz), 119.6, 112.1, 111.0, 64.3 (q, J=27.1 Hz), 56.0, 55.8, 49.5, 45.0, 26.9. MS (ESI, m/z): 276.0 ([M+H]$^+$). HRMS (ESI): calcd for $C_{13}H_{17}F_3NO_2^+$([M+H]$^+$): 276.1206; Found: 276.1204.

*4.2.12. 6,7-Dimethoxy-1,2-dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**7b**).* White solid. Mp: 61–63 °C. IR (KBr): 3002, 2954, 2802, 1613, 1521, 1466, 1261, 1141, 1109, 1002, 870, 805, 774, 723 cm^{-1} ^{1}H NMR: δ 6.89 (s, 1H), 6.57 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.18–3.23 (m, 1H), 2.68–2.88 (m, 3H), 2.62 (s, 3H), 1.64 (s, 3H). ^{19}F NMR: δ −71.7 (s, 3F). ^{13}C NMR: δ 148.5, 146.9, 129.4, 127.9 (q, J=290.7 Hz), 125.5, 111.4, 111.0, 62.2 (q, J=23.3 Hz), 56.1, 55.7, 48.4, 39.7, 28.0, 19.9. MS (ESI, m/z): 290.1 ([M+H]$^+$). HRMS (ESI): calcd for $C_{14}H_{19}F_3NO_2^+$([M+H]$^+$): 290.1362; Found: 290.1360.

*4.2.13. 2-Methyl-1-phenyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**7c**).* Pale yellow oil. IR (film): 3064, 3029, 2962, 2865, 2809, 1496, 1452, 1260, 1148, 1035, 928, 793, 764, 741, 699, 661 cm^{-1} ^{1}H NMR: δ 7.16–7.22 (m, 5H), 7.05–7.10 (m, 2H), 6.89 (t, J=6.9 Hz, 1H), 6.75 (d, J=7.8 Hz, 1H), 2.94–3.10 (m, 2H), 2.84–2.92 (m, 2H), 2.12 (s, 3H). ^{19}F NMR: δ −66.6 (s, 3F). ^{13}C NMR: δ 140.5, 136.9, 135.1, 131.3, 128.8, 128.1, 127.8, 127.5, 127.44 (q, J=290.7 Hz), 127.43, 125.5, 70.6 (q, J=23.7 Hz), 48.4, 41.2, 29.8. MS (ESI, m/z): 292.1 ([M+H]$^+$). HRMS (ESI): calcd for $C_{17}H_{17}F_3N^+$([M+H]$^+$): 292.1308; Found: 292.1307.

*4.2.14. 1,2-Dimethyl-1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline (**7d**).* Pale yellow oil. IR (film): 3011, 2926, 2866, 1454, 1380, 1280, 1246, 1172, 1145, 1123, 1089, 1061, 898, 759, 739, 733, 715, 652, 612 cm^{-1} ^{1}H NMR: δ 7.36 (d, J=4.2 Hz, 1H), 7.11–7.14 (m, 2H), 7.02–7.04 (m, 1H), 3.12–3.15 (m, 1H), 2.72–2.88 (m, 3H), 2.55 (s, 3H), 1.58 (s, 3H). ^{19}F NMR: δ −71.8 (s, 3F). ^{13}C NMR: δ 136.7, 133.9, 120.1, 128.1 (q, J=2.2 Hz), 127.9 (q, J=290.8 Hz), 127.5, 125.8, 62.6 (q, J=23.3 Hz), 48.3, 39.7, 28.6, 19.7. MS (ESI, m/z): 230.1 ([M+H]$^+$). HRMS (ESI): calcd for $C_{12}H_{15}F_3N^+$([M+H]$^+$): 230.1151; Found: 230.1153.

*4.2.15. 1-Methyl-2-phenyl-2-(trifluoromethyl)pyrrolidine (**7e**).* Colorless oil. IR (film): 3063, 2964, 2856, 2808, 1494, 1448, 1262, 1147, 1093, 906, 806, 759, 726, 700, 520 cm^{-1} ^{1}H NMR: δ 7.44 (d, J=7.8 Hz, 2H), 7.16–7.28 (m, 3H), 2.94–3.08 (m, 2H), 2.42–2.52 (m, 1H), 2.33 (s, 3H), 1.96–2.06 (m, 1H), 1.77–1.82 (m, 2H). ^{19}F NMR: δ −68.3 (s, 3F). ^{13}C NMR: δ 140.3, 128.5 (q, J=290.4 Hz), 128.2, 127.3, 126.9 (q, J=2.3 Hz), 71.5 (q, J=23.9 Hz), 55.3, 38.3, 35.6, 22.7. MS (ESI, m/z): 230.1 ([M+H]$^+$). HRMS (ESI): calcd for $C_{12}H_{15}F_3N^+$([M+H]$^+$): 230.1151; Found: 230.1153.

4.3. Typical procedure for the reaction of quinolinium or pyridinium salts 8 with $TMSCF_2SO_2Ph$ (2)

Under a nitrogen atmosphere, into a mixture of iminium salt **8a** (165 mg, 0.5 mmol), KF(87 mg, 1.5 mmol) was added dry DMF (2 mL). After the addition of a DMF (2 mL) solution of $TMSCF_2SO_2Ph$ (264 mg, 1.0 mmol) dropwise in 10 min, the reaction mixture was stirred for 1 h at ambient temperature. Then the reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (20 mL), and extracted with ethyl acetate (3×15 mL). The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution (15 mL), and dried with anhydrous Na_2SO_4. After the removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 20:1) to give **9a** as a white solid (199 mg, 90%).

*4.3.1. 2-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,2-dihydroquinoline (**9a**).* White solid. Mp: 131–133 °C. IR (KBr): 3026, 2956, 2839, 1597, 1514, 1492, 1335, 1251, 1137, 815, 749, 683, 619 cm^{-1} ^{1}H NMR: δ 7.92 (d, J=7.5 Hz, 2H), 7.72 (t, J=7.5 Hz, 1H), 7.57 (t, J=7.5 Hz, 2H), 7.17 (d, J=8.7 Hz, 2H), 7.00–7.08 (m, 2H), 6.83 (d, J=9.0 Hz, 2H), 6.76 (d, J=9.6 Hz, 1H), 6.66–6.72 (m, 2H), 5.82 (dd, J=9.6 Hz, 6.9 Hz, 1H), 5.05–5.16 (m, 1H), 4.86 (d, J=15.6 Hz, 1H), 4.47 (d, J=15.9 Hz, 1H), 3.78 (s, 3H). ^{19}F NMR: δ −108.2 (dd, J=232.1 Hz, 7.9 Hz, 1F), −112.1 (dd, J=231.3 Hz, 16.4 Hz, 1F). ^{13}C NMR: δ 159.0, 143.1, 135.2, 133.1, 130.8, 130.4, 129.24, 129.17, 128.9, 128.6, 127.5, 122.6, 122.3 (t, J=298.3 Hz), 118.4, 115.1(d, J=3.3 Hz), 114.1, 113.8, 57.8 (dd, J=20.9 Hz, 18.7 Hz), 55.2, 55.0 (d, J=3.1 Hz). MS (ESI, m/z): 442.0 ([M+H]$^+$). Anal. Calcd for $C_{24}H_{21}F_2NO_3S$: C, 65.29; H, 4.79; N, 3.17; Found: C, 65.22; H, 5.08; N, 3.13.

*4.3.2. 2-(Difluoro(phenylsulfonyl)methyl)-6-methoxy-1-(4-methoxybenzyl)-1,2-dihydroquinoline (**9b**).* Pale yellow solid. Mp: 117–119 °C. IR (KBr): 2950, 2892, 2833, 1612, 1515, 1498, 1336, 1247, 1147, 1030, 800, 717, 596, 530 cm^{-1} ^{1}H NMR: δ 7.85 (d, J=7.8 Hz, 2H), 7.65 (t, J=6.9 Hz, 1H), 7.50 (t, J=7.2 Hz, 2H), 7.08 (d, J=8.4 Hz, 2H), 6.74 (d, J=8.1 Hz, 2H), 6.64 (d, J=9.3 Hz, 1H), 6.50–6.60 (m, 3H), 5.77 (dd, J=9.0 Hz, 5.7 Hz, 1H), 4.93–5.04 (m, 1H), 4.70 (d, J=15.9 Hz, 1H), 4.35 (d, J=15.9 Hz, 1H), 3.70 (s, 3H), 3.65 (s, 3H). ^{19}F NMR: δ −106.6 (dd, J=230.7 Hz, 8.8 Hz, 1F), −111.6 (dd, J=231.0 Hz, 18.1 Hz, 1F). ^{13}C NMR: δ 158.9, 152.3, 137.1, 135.1, 133.2, 130.6, 130.4, 129.2, 129.1, 128.6, 123.5, 122.3 (t, J=295.5 Hz), 116.2 (d, J=3.0 Hz), 115.2, 114.8, 114.0, 112.6, 59.7(dd, J=21.6 Hz, 18.6 Hz), 55.7 (d, J=3.0 Hz), 55.5, 55.1. MS (ESI, m/z): 472.0 ([M+H]$^+$). Anal. Calcd for $C_{25}H_{23}F_2NO_4S$: C, 63.68; H, 4.92; N, 2.97; Found: C, 63.56; H, 4.94; N, 3.04.

*4.3.3. 2-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-6-methyl-1,2-dihydroquinoline (**9c**).* White solid. Mp: 151–153 °C. IR (KBr): 1637, 1613, 1515, 1501, 1332, 1249, 1148, 1101, 809, 716, 608 cm^{-1} ^{1}H NMR: δ 7.92 (d, J=8.1 Hz, 2H), 7.72 (t, J=8.1 Hz, 1H), 7.57 (t, J=7.2 Hz, 2H), 7.16 (d, J=7.5 Hz, 2H), 6.81–6.88 (m, 4H), 6.72 (d, J=10.2 Hz, 1H), 6.58 (d, J=8.1 Hz, 1H), 5.78–5.83 (m, 1H), 5.03–5.13 (m, 1H), 4.83 (d, J=16.2 Hz, 1H), 4.44 (d, J=15.3 Hz, 1H), 3.78 (s, 3H), 2.20 (s, 3H). ^{19}F NMR: δ −106.3 (dd, J=230.4 Hz, 7.6 Hz, 1F), −111.7 (dd, J=230.4 Hz, 17.2 Hz, 1F). ^{13}C NMR: δ 158.9, 140.8, 135.1, 133.1, 130.8, 130.4, 129.8, 129.1, 128.6, 128.0, 127.4, 122.5, 122.3 (t, J=295.5 Hz), 115.1 (d, J=3.7 Hz), 114.0, 113.8, 57.9 (dd, J=20.8 Hz, 18.6 Hz), 55.2, 55.1, 20.3. MS (ESI, m/z): 456.0 ([M+H]$^+$). Anal. Calcd

for $C_{25}H_{23}F_2NO_3S$: C, 65.92; H, 5.09; N, 3.07; Found: C, 66.02; H, 5.05; N, 3.15.

*4.3.4. 6-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,6-dihydropyridine-3-carboxamide (**9g**).* Pale yellow solid. Mp: 142–144 °C. IR (KBr): 3419, 3177, 1655, 1558, 1381, 1252, 1146, 825, 716, 584 cm^{-1} ^1H NMR: δ 7.96 (d, J=8.1 Hz, 2H), 7.78 (t, J=7.5 Hz, 1H), 7.63 (t, J=7.2 Hz, 2H), 7.47 (s, 1H), 7.18 (d, J=8.7 Hz, 2H), 6.89 (d, J=9.0 Hz, 2H), 6.56 (d, J=9.0 Hz, 1H), 5.26 (s, 2H), 5.06–5.20 (m, 2H), 4.60 (d, J=15.0 Hz, 1H), 4.50 (d, J=15.0 Hz, 1H), 3.81 (s, 3H). ^{19}F NMR: δ −108.2 (dd, J=232.1 Hz, 7.9 Hz, 1F), −112.1 (dd, J=231.3 Hz, 16.4 Hz, 1F). ^{13}C NMR: δ 168.0, 159.6, 144.3, 135.5, 132.6, 130.5, 129.3, 129.0, 127.5, 126.2, 121.0 (t, J=296.3 Hz), 114.4, 103.8, 103.5, 59.4 (d, J=2.9 Hz), 56.5 (dd, J=22.3 Hz, 17.9 Hz), 55.2. MS (ESI, m/z): 435.1 ($[M+H]^+$). Anal. Calcd for $C_{21}H_{20}F_2N_2O_4S$: C, 58.06; H, 4.64; N, 6.45; Found: C, 58.20; H, 4.95; N, 6.38.

*4.3.5. (6-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,6-dihydropyridin-3-yl)(phenyl)methanone (**9h**).* Yellow solid. Mp: 39–42 °C. IR (KBr): 3063, 2837, 1612, 1561, 1513, 1327, 1251, 1149, 1106, 1029, 909, 816, 712 cm^{-1} ^1H NMR: δ 8.00 (d, J=8.4 Hz, 2H), 7.80 (t, J=6.6 Hz, 1H), 7.65 (t, J=6.6 Hz, 2H), 7.58 (d, J=9.9 Hz, 2H), 7.37–7.50 (m, 3H), 7.26 (s, 1H), 7.14 (d, J=7.5 Hz, 2H), 7.08 (d, J=8.7 Hz, 1H), 6.88 (d, J=6.9 Hz, 2H), 5.12–5.25 (m, 2H), 4.70 (d, J=15.0 Hz, 1H), 4.46 (d, J=15.3 Hz, 1H), 3.80 (s, 3H). ^{19}F NMR: δ −108.4 (dd, J=234.7 Hz, 9.0 Hz, 1F), −110.4 (dd, J=234.9 Hz, 15.0 Hz, 1F). ^{13}C NMR: δ 190.9, 159.8, 150.6, 139.4, 135.6, 132.6, 130.7, 130.6, 129.4, 129.0, 128.7, 128.1, 127.4, 126.8, 120.9 (t, J=295.5 Hz), 114.5, 111.7, 104.6, 59.7, 57.1 (dd, J=23.1 Hz, 19.4 Hz), 55.3. MS (ESI, m/z): 518.0 ($[M+Na]^+$). HRMS (ESI): calcd for $C_{27}H_{24}NO_4F_2S^+$($[M+H]^+$): 496.1389; Found: 496.1391.

*4.3.6. (2-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,2-dihydropyridin-3-yl)(phenyl)methanone (**9h'**).* Yellow solid. Mp 124–126 °C. IR (KBr): 3079, 2936, 2835, 1622, 1499, 1344, 1245, 1150, 1108, 928, 844, 723, 594 cm^{-1} ^1H NMR: δ 7.98 (d, J=7.5 Hz, 2H), 7.71 (t, J=7.2 Hz, 1H), 7.55–7.63 (m, 4H), 7.35–7.44 (m, 3H), 7.16 (d, J=8.1 Hz, 2H), 7.04 (d, J=6.6 Hz, 1H), 6.86 (d, J=7.5 Hz, 2H), 6.68 (d, J=6.6 Hz, 1H), 6.38 (dd, J=18.3 Hz, 7.5 Hz, 1H), 5.20 (t, J=6.3 Hz, 1H), 4.79 (d, J=15.3 Hz, 1H), 4.64 (d, J=15.0 Hz, 1H), 3.78 (s, 3H). ^{19}F NMR: δ −108.2 (dd, J=239.2 Hz, 7.3 Hz, 1F), −112.2 (dd, J=239.5 Hz, 18.6 Hz, 1F). ^{13}C NMR: δ 193.8, 159.4, 143.0, 140.9, 138.9, 135.2, 133.1, 130.8, 130.6, 129.1, 128.9, 128.6, 128.2, 128.0, 121.3 (dd, J=300.7 Hz, 292.5 Hz), 114.3, 110.2, 98.7, 59.4, 56.5 (dd, J=26.8 Hz, 20.1 Hz), 55.2. MS (ESI, m/z): 496.1 ($[M+H]^+$). Anal. Calcd for $C_{27}H_{23}F_2NO_4S$: C, 65.44; H, 4.68; N, 2.83; Found: C, 65.21; H, 4.62; N, 2.89.

*4.3.7. Methyl 6-(difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,6-dihydropyridine-3-carboxylate (**9i**).* White solid. Mp: 130–132 °C. IR (KBr): 1695, 1637, 1570, 1513, 1342, 1305, 1153, 1107, 1091, 1023, 832, 719, 596 cm^{-1} ^1H NMR: δ 7.96 (d, J=7.8 Hz, 2H), 7.78 (t, J=7.8 Hz, 1H), 7.63 (t, J=8.1 Hz, 2H), 7.52 (s, 1H), 7.18 (d, J=8.1 Hz, 2H), 6.90 (d, J=8.4 Hz, 2H), 6.78 (d, J=9.0 Hz, 1H), 5.03–5.19 (m, 2H), 4.63 (d, J=15.3 Hz, 1H), 4.50 (d, J=15.0 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H). ^{19}F NMR: δ −109.1 (dd, J=230.9 Hz, 7.9 Hz, 1F), −112.2 (dd, J=233.2 Hz, 14.4 Hz, 1F). ^{13}C NMR: δ 166.3, 159.7, 146.4, 135.5, 132.7, 130.6, 129.3, 129.0, 127.4, 127.2, 121.0 (t, J=296.3 Hz), 114.5, 103.3, 101.6, 59.5 (d, J=3.0 Hz), 56.8 (dd, J=23.8 Hz, 18.6 Hz), 55.3, 50.9. MS (ESI, m/z): 450.0 ($[M+H]^+$). Anal. Calcd for $C_{22}H_{21}F_2NO_5S$: C, 58.79; H, 4.71; N, 3.12; Found: C, 58.88; H, 4.76; N, 3.31.

*4.3.8. Methyl 2-(difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,2-dihydropyridine-3-carboxylate (**9i'**).* Yellow oil. IR (film): 3005, 2953, 2840, 1695, 1612, 1514, 1345, 1253, 1155, 1090, 1008, 819, 740, 686, 594 cm^{-1} ^1H NMR: δ 7.98 (d, J=7.8 Hz, 2H), 7.74 (t, J=7.5 Hz, 1H), 7.59 (t, J=7.5 Hz, 2H), 7.40 (d, J=7.2 Hz, 1H), 7.15 (d, J=7.2 Hz, 2H), 6.86 (d, J=6.9 Hz, 2H), 6.63 (d, J=6.6 Hz, 1H), 5.93 (dd, J=19.5 Hz, 6.9 Hz, 1H), 5.22 (t, J=7.2 Hz, 1H), 4.77 (d, J=15.3 Hz, 1H), 4.58 (d, J=15.9 Hz, 1H), 3.79 (s, 3H), 3.70 (s, 3H). ^{19}F NMR: δ −108.7 (dd, J=239.7 Hz, 5.1 Hz, 1F), −113.4 (dd, J=237.7 Hz, 19.2 Hz, 1F). ^{13}C NMR: δ 166.2, 159.4, 142.3, 138.1, 135.3, 130.7, 130.6, 129.2, 128.8, 128.7, 121.4 (dd, J=302.3 Hz, 293.3 Hz), 114.3, 100.0, 98.8, 59.2, 56.6 (dd, J=26.8 Hz, 18.6 Hz), 55.3 (d, J=5.2 Hz), 51.5. MS (ESI, m/z): 450.0 ($[M+H]^+$). HRMS (ESI): calcd for $C_{22}H_{22}F_2NO_5S^+$($[M+H]^+$): 450.1181; Found: 450.118.

*4.3.9. 6-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,6-dihydropyridine-3-carbonitrile (**9j**).* Yellow solid. Mp: 95–97 °C. IR (KBr): 3044, 2838, 2206, 1635, 1567, 1516, 1334, 1152, 1101, 1032, 817, 719, 681, 609, 591 cm^{-1} ^1H NMR: δ 7.97 (d, J=7.8 Hz, 2H), 7.80 (t, J=8.1 Hz, 1H), 7.65 (t, J=6.3 Hz, 2H), 7.18 (d, J=6.9 Hz, 2H), 7.02 (s, 1H), 6.92 (d, J=6.9 Hz, 2H), 6.28 (d, J=9.3 Hz, 1H), 5.09–5.22 (m, 2H), 4.56 (d, J=14.7 Hz, 1H), 4.47 (d, J=15.0 Hz, 1H), 3.83 (s, 3H). ^{19}F NMR: δ −108.7 (dd, J=232.1 Hz, 8.5 Hz, 1F), −111.9 (dd, J=233.0 Hz, 13.6 Hz, 1F). ^{13}C NMR: δ 159.9, 147.3, 135.7, 132.4, 130.6, 129.4, 129.3, 126.51, 126.45, 120.6 (t, J=296.3 Hz), 119.6, 114.6, 104.9, 82.1, 59.6 (d, J=3.0 Hz), 56.4 (dd, J=23.9 Hz, 19.4 Hz), 55.3. MS (ESI, m/z): 439.1 ($[M+Na]^+$). HRMS (ESI): calcd for $C_{21}H_{19}F_2N_2O_3S^+$($[M+H]^+$): 417.1079; Found: 417.1085.

*4.3.10. 2-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,2-dihydropyridine-3-carbonitrile (**9j'**).* Yellow solid. Mp: 116–118 °C. IR (KBr): 2951, 2839, 2194, 1612, 1512, 1352, 1247, 1152, 1102, 1008, 713, 611, 547 cm^{-1} ^1H NMR: δ 7.98 (d, J=7.5 Hz, 2H), 7.78 (t, J=7.8 Hz, 1H), 7.63 (t, J=7.8 Hz, 2H), 7.19 (d, J=8.7 Hz, 2H), 6.98 (d, J=4.8 Hz, 1H), 6.91 (d, J=8.4 Hz, 2H), 6.70 (d, J=6.9 Hz, 1H), 5.32 (dd, J=19.8 Hz, 6.9 Hz, 1H), 5.20 (t, J=6.9 Hz, 1H), 4.76 (d, J=15.0 Hz, 1H), 4.52 (d, J=15.3 Hz, 1H), 3.82 (s, 3H). ^{19}F NMR: δ −107.3 (dd, J=243.1 Hz, 5.9 Hz, 1F), −114.8 (dd, J=239.1 Hz, 19.5 Hz, 1F). ^{13}C NMR: δ 159.7, 142.6 (d, J=4.5 Hz), 135.7, 132.4, 130.7, 129.4, 128.9, 127.8, 120.5 (dd, J=303.7 Hz, 291.8 Hz), 118.9, 114.5, 98.7, 79.4, 59.1, 57.3 (dd, J=27.6 Hz, 20.1 Hz), 55.3. MS (ESI, m/z): 439.1 ($[M+Na]^+$). HRMS (ESI): calcd for $C_{21}H_{19}F_2N_2O_3S^+$($[M+H]^+$): 417.1079; Found: 417.1089.

*4.3.11. 4-(Difluoro(phenylsulfonyl)methyl)-1-(4-methoxybenzyl)-1,4-dihydropyridine-3-carbonitrile (**9j''**).* White solid. Mp: 158–160 °C. IR (film): 2191, 1672, 1579, 1514, 1409, 1338, 1255, 1152, 1099, 1034, 821, 714, 610, 542 cm^{-1} ^1H NMR: δ 7.98 (d, J=7.8 Hz, 2H), 7.76 (t, J=7.5 Hz, 1H), 7.62 (t, J=7.5 Hz, 2H), 7.11 (d, J=8.7 Hz, 2H), 6.91 (s, 1H), 6.90 (d, J=8.4 Hz, 2H), 6.19 (d, J=7.8 Hz, 1H), 5.09 (dd, J=7.5 Hz, 4.5 Hz, 1H), 4.37–4.47 (m, 1H), 4.37 (s, 2H), 3.81 (s, 3H). ^{19}F NMR: δ −103.8 (d, J=229.0 Hz, 1F), −112.6 (dd, J=230.4 Hz, 24.0 Hz, 1F). ^{13}C NMR: δ 159.7, 145.8, 135.4, 132.9, 131.8, 130.5, 129.3, 128.7, 127.0, 120.8 (t, J=295.5 Hz), 120.0, 114.5, 96.8 (d, J=6.0 Hz), 71.8, 57.4, 55.3, 37.7 (t, J=21.6 Hz). MS (ESI, m/z): 439.1 ($[M+Na]^+$). HRMS (ESI): calcd for $C_{21}H_{18}F_2N_2O_3SNa^+$($[M+Na]^+$): 439.0898; Found: 439.0900.

4.4. Typical procedure for the oxidative deprotection/aromatization of addition product 9 to form 10

Into a MeOH (8 mL) solution of the addition product **9a** (221 mg, 0.5 mmol) was added a water (2 mL) solution of CAN (685 mg, 1.25 mmol) dropwise in 10 min. After stirring overnight at ambient temperature, a saturated $NaHCO_3$ aqueous solution (20 mL) was added to quench the reaction and extracted with ethyl acetate (3×15 mL). The combined organic phase was washed with saturated $NaHCO_3$ aquaous solution (15 mL), and dried with anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (petroleum ether/ethyl acetate, 4:1) to give **10a** as a white solid (148 mg, 93%).

*4.4.1. 2-(Difluoro(phenylsulfonyl)methyl)quinoline (**10a**).* Colorless solid. Mp: 141–143 °C. IR (KBr): 1583, 1449, 1346, 1308, 1170, 1124, 1098, 977, 821, 757, 719, 587 cm^{-1} ^1H NMR: δ 8.36 (d, J=8.1 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 8.04 (d, J=8.1 Hz, 2H), 7.86–7.93 (m, 2H), 7.76–7.83 (m, 2H), 7.60–7.70 (m, 3H). ^{19}F NMR: δ -104.8 (s, 2F). ^{13}C NMR: δ 147.4, 146.2 (t, J=23.1 Hz), 137.4, 135.4, 132.8, 131.0, 130.6, 130.2, 129.2, 128.7, 127.6, 119.4 (t, J=3.0 Hz), 119.2 (t, J=286.6 Hz). MS (ESI, m/z): 320.0 ($[M+H]^+$). Anal. Calcd for $C_{16}H_{11}F_2NO_2S$: C, 60.18; H, 3.47; N, 4.39; Found: C, 60.10; H, 3.51; N, 4.45.

*4.4.2. 2-(Difluoro(phenylsulfonyl)methyl)-6-methoxyquinoline (**10b**).* White solid. Mp: 143–145 °C. IR (film): 1623, 1500, 1484, 1344, 1232, 1170, 1097, 843, 722, 604 cm^{-1} ^1H NMR: δ 8.22 (d, J=8.4 Hz, 1H), 8.02–8.07 (m, 3H), 7.75–7.83 (m, 2H), 7.61 (t, J=8.1 Hz, 2H), 7.43 (dd, J=9.0 Hz, 3.0 Hz, 1H), 7.12 (s, 1H), 3.96 (s, 3H). ^{19}F NMR: δ −104.6 (s, 2F). ^{13}C NMR: δ 159.4, 143.7, 143.4 (t, J=23.3 Hz), 135.8, 135.3, 132.9, 131.6, 130.9, 130.2, 129.2, 123.8, 119.8, 119.4 (t, J=286.6 Hz), 104.6, 55.6. MS (ESI, m/z): 350.0 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{13}F_2NO_3S$: C, 58.45; H, 3.75; N, 4.01; Found: C, 58.51; H, 3.89; N, 4.02.

*4.4.3. 2-(Difluoro(phenylsulfonyl)methyl)-6-methylquinoline (**10c**).* White solid. Mp: 166–168 °C. IR (KBr): 1449, 1348, 1172, 1127, 1098, 981, 840, 723, 683, 590, 534 cm^{-1} ^1H NMR: δ 8.15 (d, J=8.7 Hz, 1H), 7.93–7.98 (m, 3H), 7.66–7.75 (m, 2H), 7.50–7.56 (m, 4H), 2.48 (s, 3H). ^{19}F NMR: δ −104.8 (s, 2F). ^{13}C NMR: δ 146.1, 145.2 (t, J=23.1 Hz), 139.0, 136.6, 135.4, 133.0, 132.9, 131.0, 129.8, 129.2, 128.9, 126.4, 119.5 (t, J=3.0 Hz), 119.3 (t, J=287.4 Hz), 21.7. MS (ESI, m/z): 333.9 ($[M+H]^+$). Anal. Calcd for $C_{17}H_{13}F_2NO_2S$: C, 61.25; H, 3.93; N, 4.20; Found: C, 61.19; H, 4.14; N, 4.22.

*4.4.4. 6-(Difluoro(phenylsulfonyl)methyl)nicotinamide (**10g**).* White solid. Mp: 228–230 °C. IR (KBr): 3407, 3194, 1687, 1624, 1398, 1351, 1164, 1098, 1075, 715, 688, 594, 543 cm^{-1} ^1H NMR (DMSO-d_6): δ 9.14 (s, 1H), 8.49 (d, J=7.8 Hz, 1H), 8.42 (s, 1H), 7.92–8.01 (m, 5H), 7.77–7.82 (m, 2H). ^{19}F NMR (DMSO-d_6): δ −104.6 (s, 2F). ^{13}C NMR (DMSO-d_6): δ 165.7, 149.2, 147.5 (t, J=23.1 Hz), 137.3, 136.8, 133.0, 132.0, 130.9, 130.4, 123.8, 119.2 (t, J=285.9 Hz). MS (ESI, m/z): 334.9 ($[M+Na]^+$). HRMS (ESI): calcd for $C_{13}H_{11}F_2N_2O_3S^+$($[M+H]^+$): 313.0453; Found: 313.0463.

*4.4.5. (6-(Difluoro(phenylsulfonyl)methyl)pyridin-3-yl)(phenyl) methanone (**10h**).* White solid. Mp: 134–136 °C. IR (film): 1652, 1587, 1449, 1348, 1285, 1171, 1102, 923, 711, 599, 544 cm^{-1} ^1H NMR: δ 9.10 (s, 1H), 8.29 (d, J=8.7 Hz, 1H), 8.07 (d, J=8.1 Hz, 2H), 7.98 (d, J=7.8 Hz, 1H), 7.80–7.86 (m, 3H), 7.64–7.69 (m, 3H), 7.55 (t, J=6.9 Hz, 2H). ^{19}F NMR: δ -104.9 (s, 2F). ^{13}C NMR: δ 193.5, 150.5, 149.0 (t, J=23.1 Hz), 138.1, 135.9, 135.7, 135.4, 133.7, 132.5, 131.0, 130.0, 129.4, 128.8, 123.5 (t, J=3.8 Hz), 118.8 (t, J=287.3 Hz). MS (ESI, m/z): 374.0 ($[M+H]^+$). Anal. Calcd for $C_{19}H_{13}F_2NO_3S$: C, 61.12; H, 3.51; N, 3.75; Found: C, 61.18; H, 3.54; N, 3.87.

*4.4.6. Methyl 6-(difluoro(phenylsulfonyl)methyl)nicotinate (**10i**).* White solid. Mp: 145–146 °C. IR (KBr): 1732, 1595, 1343, 1282, 1118, 1021, 734, 601, 543 cm^{-1} ^1H NMR: δ 9.32 (s, 1H), 8.51 (d, J=8.1 Hz, 1H), 8.03 (d, J=7.2 Hz, 2H), 7.92 (d, J=8.4 Hz, 1H), 7.81 (t, J=7.5 Hz, 1H), 7.65 (t, J=8.1 Hz, 2H), 4.01 (s, 3H). ^{19}F NMR: δ -105.3 (s, 2F). ^{13}C NMR: δ 164.6, 150.8, 149.8 (t, J=23.1 Hz), 138.3, 135.7, 132.5, 131.0, 129.4, 128.4, 123.5 (t, J=3.7 Hz), 118.8 (t, J=287.3 Hz), 52.9. MS (ESI, m/z): 327.9 ($[M+H]^+$). Anal. Calcd for $C_{14}H_{11}F_2NO_4S$: C, 51.37; H, 3.39; N, 4.28; Found: C, 51.52; H, 3.64; N, 4.34.

*4.4.7. 2-(Difluoro(phenylsulfonyl)methyl)nicotinonitrile (**10j**').* White solid. Mp: 180–182 °C. IR (KBr): 3094, 2234, 1579, 1448, 1344, 1168, 1116, 819, 712, 599 cm^{-1} ^1H NMR: δ 8.91 (d, J=5.1 Hz, 1H), 8.15 (d, J=8.4 Hz, 1H), 8.03 (d, J=7.8 Hz, 2H), 7.77 (t, J=7.5 Hz, 1H), 7.59–7.65 (m, 3H). ^{19}F NMR: δ −101.6 (s, 2F). ^{13}C NMR: δ 152.2, 148.0 (t, J=23.1 Hz), 142.6, 136.0, 131.9, 131.1, 129.6, 125.9, 118.3 (t, J=289.6 Hz), 114.1, 110.8. MS (ESI, m/z): 294.9 ($[M+H]^+$). Anal. Calcd for $C_{14}H_{11}F_2NO_4S$: C, 53.06; H, 2.74; N, 9.52; Found: C, 53.09; H, 3.01; N, 9.72.

*4.4.8. 2-(Difluoromethyl)quinoline (**11**).*[16] Pale yellow oil. ^1H NMR: δ 8.24 (d, J=8.7 Hz, 1H), 8.08 (d, J=8.4 Hz, 1H), 7.80 (d, J=8.1 Hz, 1H), 7.64–7.74 (m, 2H), 7.56 (t, J=7.2 Hz, 1H), 6.72 (t, J=55.5 Hz, 1H). ^{19}F NMR: δ −114.6 (d, J=55.6 Hz, 2F). MS (EI, m/z, %): 179.0 (M^+, 100.00).

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