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Visible-light mediated regioselective (phenylsulfonyl)difluoromethylation of fused imidazoles with iododifluoromethyl phenyl sulfone

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Abstract: A visible-light catalyzed direct and regioselective (phenylsulfonyl)difluoromethylation of imidazo[1,2-*a*]pyridines and benzo[*d*]-imidazo [2,1-*b*]thiazoles with readily available $PhSO_2CF_2I$ under mild conditions was developed. This synthetic methodology enables the introduction of a CF_2SO_2Ph group in an efficient and regioselective reaction through C-H bond functionalization with a broad substrate scope in good to excellent yields.

Keywords: imidazoheterocycles; (phenylsulfonyl) difluoromethylation; photoredox; radical reactions; regioselectivity.

Introduction

The difluoromethyl moiety is one of the key structural units found in pharmaceuticals, agrochemicals and functional materials mainly due to its excellent binding affinity, enhancement of membrane permeability, and high bioavailability [1]. Consequently, extensive efforts have been devoted to the development of methods for selective introduction of difluoromethyl group onto a particular position [2, 3]. Among the various sources of difluorinated moieties, a (phenylsulfonyl)difluoromethyl group ($PhSO_2CF_2$) is appealing because of its versatile functionality that can be further modified into other functionalized fluoroalkyl groups [4, 5]. Miscellaneous methods for the incorporation of $PhSO_2CF_2$ motifs have been extensively investigated over the years. The traditional methods for the synthesis of $PhSO_2CF_2$-containing molecules typically involve nucleophilic addition, coupling of boronic acids and radical addition [6–9]. Alternatively, the direct (phenylsulfonyl) difluoromethylation of C-H bonds appears to be more economical and practical synthetic approach towards $PhSO_2CF_2$-containing heteroarenes. In 2014, Wang and co-workers reported a visible-light photoredox-catalyzed (phenylsulfonyl)difluoromethylation of electron-rich N-, O-, and S-containing heteroarenes with $PhSO_2CF_2I$ [10]. However, these examples are mainly concentrated on pyrroles and indoles. As far as we know, there has been no report on the introduction of a $PhSO_2CF_2$ group at the imidazo[1,2-*a*]pyridine system.

Imidazo[1,2-*a*]pyridines are an important class of heterocycles with unique chemical and biological properties. This fused heterocycle is found in many bioactive natural products, pharmaceuticals and agrochemicals, and many of them exhibit potent biological activities, such as antiviral, antimicrobial, antitumor and anti-inflammatory properties [11–13]. Attention has been paid to the development of efficient methods for the synthesis of imidazopyridine derivatives [14, 15]. In this regard, the functionalization of imidazo[1,2-*a*]pyridine derivatives through transition-metal-catalyzed coupling or the electrophile and radical addition reactions at the 3-position have made significant progress [16]. Various functionalized atoms (C, S, N and Se) have been successfully introduced into the 3-position of imidazo[1,2-*a*]pyridines [17–24]. Recently, we also developed a visible-light-induced radical pathway to introduce a trifluoroethyl group into the imidazo[1,2-*a*]pyridine core at the 3-position [25]. As a continuation of our interest in methodology for the synthesis of fluorinated heterocycles [26–28], we wished to introduce other versatile building blocks into the imidazo[1,2-*a*]pyridine structure with the aim of synthesizing various 3-functionalized imidazo[1,2-*a*] pyridines in a radical fashion. We focused our attention on 3-$PhSO_2CF_2$-containing imidazo[1,2-*a*]pyridine architectures by visible-light photoredox catalysis.

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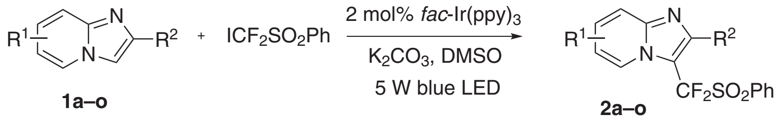
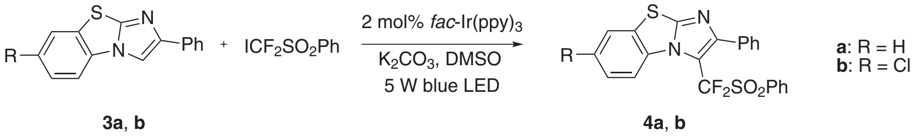


2a: R^1 = H; R^2 = Ph
2b: R^1 = H; R^2 = 4-Me-C_6H_4
2c: R^1 = H; R^2 = 3-Me-C_6H_4
2d: R^1 = H; R^2 = 4-OMe-C_6H_4
2e: R^1 = H; R^2 = 4-Cl-C_6H_4
2f: R^1 = H; R^2 = 4-Br-C_6H_4
2g: R^1 = H; R^2 = 3-Br-C_6H_4
2h: R^1 = H; R^2 = 4-F-C_6H_4
2i: R^1 = H; R^2 = 4-CN-C_6H_4
2j: R^1 = H; R^2 = 4-Ph-C_6H_4
2k: R^1 = 4-Me; R^2 = Ph
2l: R^1 = 5-Me; R^2 = Ph
2m: R^1 = 5-F; R^2 = Ph
2n: R^1 = H; R^2 = 2-naphthyl
2o: R^1 = H; R^2 = Me

Scheme 1 Synthesis of $PhSO_2CF_2$-containing imidazo[1,2-*a*]pyridines.

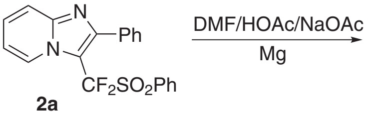


Scheme 2 Regioselective (phenylsulfonyl)difluoromethylation of benzo[*d*]-imidazo[2,1-*b*]thiazoles.

Results and discussion

Our initial investigation focused on the reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and $PhSO_2CF_2I$ (1.5 equiv) under the catalysis of *fac*-Ir(ppy)$_3$ (2 mol%) in DMSO (Scheme 1). The C-3 regioselective (phenylsulfonyl) difluoromethylation reaction proceed smoothly to give the desired product **2a** in 68% yield. When Ru(bpy)$_3$(PF$_6$)$_2$ was used instead of *fac*-Ir(ppy)$_3$, the yield of this reaction was only 40%, and eosin Y was totally inactive. After screening a series of bases, such as Na_2CO_3, K_2CO_3 and KOAc using *fac*-Ir(ppy)$_3$ as the photocatalyst, K_2CO_3 was found to be the best choice and gave 86% yield. Other solvents such as DMF, DCM and acetonitrile were also tested for the (phenylsulfonyl)difluoromethylation reaction of **1a** at room temperature, but they all were less efficient compared with DMSO. Moreover, the reaction was completely inhibited in the absence of the photocatalyst or in the dark. Thus, *fac*-Ir(ppy)$_3$ (2 mol%), $PhSO_2CF_2I$ (1.5 equiv), and K_2CO_3 (1.5 equiv) in DMSO under 5 W blue LED irradiation have been defined as the optimized reaction conditions.

With the optimum conditions in hand, we investigated the scope of this visible-light mediated (phenylsulfonyl)difluoromethylation with diverse imidazopyridines and the results are summarized in Scheme 1. It was found that a variety of imidazo[1,2-*a*]pyridines can be successfully (phenylsulfonyl)difluoromethylated at the C3-position with high selectivity to the desired products in moderate to good yields. We first examined the substituent effect at the 2-arylimidazo[1,2-*a*]pyridines. In general, the reactions of substrates containing electron-donating groups tend to give the desired products in slightly higher yields (85%–91%) than compound **1m** substituted with an electron-withdrawing 5-fluoro atom. Aryl and alkyl substituted substrates are well tolerated in this transformation.



Scheme 3 Desulfonylation of **2a**.

Benzo[*d*]-imidazo[2,1-*b*]thiazole derivatives were also successfully applied in the reaction, and the desired products **4a**,**b** were prepared in excellent yield (Scheme 2).

As already mentioned, the CF_2SO_2Ph group is an important motif which can be converted into CF_2H group. The product **2a** in DMF/HOAc/NaOAc, in the presence of Mg, was converted into difluoromethylated imidazo[1,2-*a*] pyridine **5** in 77% yield (Scheme 3).

Conclusions

We described an efficient and general method for the synthesis of $PhSO_2CF_2$-containing imidazo[1,2-*a*]pyridines and benzo[*d*]-imidazo[2,1-*b*]thiazoles using a visible-light-mediated reaction of $PhSO_2CF_2I$ with imidazoheterocycles. The reaction of imidazopyridines is regioselective.

Experimental

All reactions were performed in a 20-mL tube equipped with a rubber septum at room temperature. Photo-irradiation was carried out with a 5 W blue LED. Solvents were purified or dried in a standard manner. ^{1}H NMR (500 MHz), ^{13}C NMR (125 MHz) and ^{19}F NMR (470 MHz) spectra were measured in $CDCl_3$. HR-MS analyses were recorded using ESI technique.

General procedure for the synthesis of $PhSO_2CF_2$-containing imidazo[1,2-*a*]pyridines 2a-o and benzo[*d*]-imidazo[2,1-*b*]thiazoles 4a,b

A mixture of imidazo[1,2-*a*]pyridine **1** or benzo[*d*]-imidazo[2,1-*b*]thiazole **3** (0.30 mmol), ICF_2SO_2Ph (0.45 mmol) and K_2CO_3 (0.45 mmol) in 3.0 mL of DMSO was treated with *fac*-Ir(ppy)$_3$ (0.006 mmol, 2.0 mol%) under N_2 atmosphere. The mixture was stirred at room temperature under 5 W blue LED irradiation for 24 h and then quenched with EtOAc and brine. The aqueous layer was extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate (5:1) as the eluent to give pure product **2**.

3-(Difluoro(phenylsulfonyl)methyl)-2-phenylimidazo[1,2-*a*]pyridine (2a) White solid; mp 135–137°C; yield 86%; ^{1}H NMR: δ 8.71 (d, $J=7.5$ Hz, 1H), 7.99 (d, $J=7.5$ Hz, 2H), 7.73–7.78 (m, 4H), 7.60–7.64 (m, 2H), 7.41–7.46 (m, 4H), 7.01–7.04 (m, 1H); ^{13}C NMR: δ 152.1, 147.5, 135.6, 133.3, 132.8, 130.7, 129.7, 129.5, 128.8, 127.9, 127.7, 127.5 (t, $J=5.0$ Hz), 120.4 (t, $J=285$ Hz), 117.8, 113.7, 106.6 (t, $J=29$ Hz); ^{19}F NMR: δ −97.3 (s, 2 F). ESI-HRMS. Calcd for $C_{20}H_{15}F_2N_2O_2S$, $[M+H]^+$: *m/z* 385.0822. Found: *m/z* 385.0815.

3-(Difluoro(phenylsulfonyl)methyl)-2-(p-tolyl)imidazo[1,2-*a*]pyridine (2b) White solid; mp 122–124°C; yield 90%; ^{1}H NMR: δ 8.70 (d, $J=7.0$ Hz, 1H), 8.00 (d, $J=7.5$ Hz, 2H), 7.74–7.80 (m, 2H), 7.61–7.64 (m, 4H), 7.43 (t, $J=7.5$ Hz, 1H), 7.23 (d, $J=8.0$ Hz, 2H), 7.02 (d, $J=7.0$ Hz, 1H), 2.43(s, 3H); ^{13}C NMR: δ 152.2, 147.4, 138.7, 135.5, 132.9, 130.7, 130.3, 129.5, 129.4, 128.6, 127.6, 127.5 (t, $J=5.5$ Hz), 120.5 (t, $J=285.0$ Hz), 117.7, 113.6, 106.3 (t, $J=29$ Hz), 21.4; ^{19}F NMR: δ −97.3 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{17}F_2N_2O_2S$, $[M+H]^+$: *m/z* 399.0979. Found: *m/z* 399.0987.

3-(Difluoro(phenylsulfonyl)methyl)-2-(m-tolyl)imidazo[1,2-*a*]pyridine (2c) White solid; mp 117–118°C; yield 85%; ^{1}H NMR: δ 8.69 (d, $J=7.0$ Hz, 1H), 7.95 (d, $J=8.0$ Hz, 2H), 7.72–7.78 (m, 2H), 7.58–7.61 (m, 2H), 7.50 (d, $J=7.5$ Hz, 1H), 7.46 (s, 1H), 7.40–7.44 (m, 1H), 7.28 (t, $J=8.0$ Hz, 1H), 7.21 (d, $J=7.5$ Hz, 1H), 6.99–7.02 (m, 1H), 2.40 (s, 3H); ^{13}C NMR: δ 152.2, 147.4, 137.4, 135.5, 133.3, 132.9, 130.6, 130.3, 129.6, 127.7, 127.5 (t, $J=5.0$ Hz), 126.8, 120.4 (t, $J=285.0$ Hz), 117.8, 113.7, 106.6 (t, $J=29.3$ Hz), 21.4; ^{19}F NMR: δ −97.2 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{17}F_2N_2O_2S$, $[M+H]^+$: *m/z* 399.0979. Found: *m/z* 399.0974.

3-(Difluoro(phenylsulfonyl)methyl)-2-(4-methoxyphenyl)-imidazo[1,2-*a*]pyridine (2d) White solid; mp 115–117°C; yield 91%; ^{1}H NMR: δ 8.67 (d, $J=7.0$ Hz, 1H), 7.98 (d, $J=7.5$ Hz, 2H), 7.71–7.78 (m, 2H), 7.67 (d, $J=8.0$ Hz, 2H), 7.61 (t, $J=8.0$ Hz, 2H), 7.40 (d, $J=7.0$ Hz, 1H), 6.98 (t, $J=7.0$ Hz, 1H), 6.93 (d, $J=8.0$ Hz, 2H), 3.86 (s, 3H); ^{13}C NMR: δ 160.2, 152.0, 147.4, 135.5, 132.9, 131.0, 130.7, 129.5, 127.6, 127.5 (t, $J=5.0$ Hz), 120.5 (t, $J=285$ Hz), 117.7, 113.6, 113.4, 106.1 (t, $J=29$ Hz), 55.3; ^{19}F NMR: δ −97.5 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{17}F_2N_2O_3S$, $[M+H]^+$: *m/z* 415.0923. Found: *m/z* 415.0916.

2-(4-Chlorophenyl)-3-(difluoro(phenylsulfonyl)methyl)imidazo-[1,2-*a*]pyridine (2e) White solid ; mp 131–133°C; yield 73%; ^{1}H NMR: δ 8.67 (d, $J=7.0$ Hz, 1H), 7.99 (d, $J=7.5$ Hz, 2H), 7.76 (d, $J=7.5$ Hz, 1H), 7.69–7.73 (m, 3H), 7.61 (t, $J=8.0$ Hz, 2H), 7.38–7.43 (m, 3H), 7.00 (t, $J=7.0$ Hz, 1H); ^{13}C NMR: δ, 150.9, 147.5, 135.6, 135.1, 132.8, 131.8, 131.0, 130.7, 129.5, 128.1, 127.8, 127.5 (t, $J=8.8$ Hz), 120.3 (t, $J=285$ Hz), 117.8, 113.9, 106.8 (t, $J=32$ Hz); ^{19}F NMR: δ −97.4 (s, 2 F). ESI-HRMS. Calcd for $C_{20}H_{14}ClF_2N_2O_2S$, $[M+H]^+$: *m/z* 419.0432. Found: *m/z* 419.0421.

2-(4-Bromophenyl)-3-(difluoro(phenylsulfonyl)methyl)imidazo-[1,2-*a*]pyridine (2f) White solid; mp 139–140°C; yield 70%; ^{1}H NMR: δ 8.67 (d, $J=7.0$ Hz, 1H), 8.00 (d, $J=7.5$ Hz, 2H), 7.72–7.80 (m, 2H), 7.61–76.5 (m, 4H), 7.54 (d, $J=7.5$ Hz, 2H), 7.44 (t, $J=7.5$ Hz, 1H), 7.02 (d, $J=7.0$ Hz, 1H); ^{13}C NMR: δ 150.9, 147.5, 135.7, 132.7, 132.2, 131.5, 131.3, 130.7, 129.6, 127.9, 127.5 (t, $J=9.1$ Hz), 123.4, 120.3 (t, $J=285$ Hz), 117.8, 113.9, 106.7 (t, $J=29$ Hz); ^{19}F NMR: δ −97.4 (s, 2 F). ESI-HRMS. Calcd for $C_{20}H_{14}BrF_2N_2O_2S$, $[M+H]^+$: *m/z* 462.9927. Found: *m/z* 462.9938.

2-(3-Bromophenyl)-3-(difluoro(phenylsulfonyl)methyl)imidazo-[1,2-*a*]pyridine (2g) White solid; mp 122–124°C; yield 68%; ^{1}H NMR: δ 8.70 (d, $J=7.0$ Hz, 1H), 7.96 (d, $J=7.5$ Hz, 2H), 7.79–7.82 (m, 2H), 7.75 (d, $J=8.0$ Hz, 1H), 7.69 (d, $J=7.5$ Hz, 1H), 7.60–7.64 (m, 2H), 7.53–7.55 (m, 1H), 7.44–7.48 (m, 1H), 7.27–7.0 (m, 1H), 7.03–7.07 (m, 1H); ^{13}C NMR: δ, 150.2, 147.4, 135.8, 135.1, 132.6, 132.5, 131.8, 130.7, 129.6, 129.4, 128.4, 128.0, 127.5 (t, $J=5.0$ Hz), 121.9, 120.2 (t, $J=285$ Hz), 117.9, 114.1, 107.0 (t, $J=29$ Hz); ^{19}F NMR: δ −97.5 (s, 2 F). ESI-HRMS. Calcd for $[M+H]^+$ $C_{20}H_{14}BrF_2N_2O_2S$, $[M+H]^+$: *m/z* 462.9927. Found: *m/z* 462.9920.

3-(Difluoro(phenylsulfonyl)methyl)-2-(4-fluorophenyl)imidazo-[1,2-*a*]pyridine (2h) White solid; mp 102–104°C; yield 73%; ^{1}H NMR: δ 8.67 (d, $J=7.0$ Hz, 1H), 7.98 (d, $J=8.0$ Hz, 2H), 7.71–7.77 (m, 4H), 7.60 (t, $J=8.0$ Hz, 2H), 7.41 (t, $J=7.0$ Hz, 1H), 7.09 (t, $J=7.5$ Hz, 2H), 6.99 (d, $J=7.5$ Hz, 1H); ^{13}C NMR: δ 163.4 (d, $J=247$ Hz), 151.1, 147.4, 135.6, 132.9, 131.6 (d, $J=8.3$ Hz), 130.7, 129.5, 129.4, 127.8, 127.5 (t, $J=6.0$ Hz), 120.4 (t, $J=285$ Hz), 117.8, 114.9 (d, $J=21$ Hz), 113.8, 106.6 (t, $J=29$ Hz); ^{19}F NMR: δ −97.4 (s, 2 F), −112.7(s, 1 F). ESI-HRMS. Calcd for $C_{20}H_{14}F_3N_2O_2S$, $[M+H]^+$: *m/z* 403.0728. Found: *m/z* 403.0730.

4-(3-(Difluoro(phenylsulfonyl)methyl)imidazo[1,2-*a*]pyridin-2-yl)-benzonitrile (2i) White solid; mp 139–141°C; yield 62%; ^{1}H NMR: δ 8.68 (d, $J=7.0$ Hz, 1H), 8.02 (d, $J=7.5$ Hz, 2H), 7.92 (d, $J=8.0$ Hz, 2H), 7.79 (t, $J=8.0$ Hz, 1H), 7.71–7.77 (m, 3H), 7.64 (t, $J=7.5$ Hz, 2H), 7.45 (t, $J=7.5$ Hz, 1H), 7.04 (t, $J=7.0$ Hz, 1H); ^{13}C NMR: δ 149.9, 147.7, 137.9, 135.8, 132.6, 131.7, 130.8, 130.5, 129.6, 128.2, 127.5 (t, $J=4.8$ Hz), 120.2 (t, $J=285$ Hz), 118.7, 118.1, 114.2, 112.7, 107.3 (t, $J=29$ Hz); ^{19}F NMR: δ −97.3 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{14}F_2N_3O_2S$, $[M+H]^+$: *m/z* 410.0775. Found: *m/z* 410.0768.

2-([Biphenyl]-4-yl)-3-(difluoro(phenylsulfonyl)methyl)imidazo-[1,2-*a*]pyridine (2j) White solid; mp 143–145°C; yield 81%; ^{1}H NMR: δ 8.69 (d, $J=7.0$ Hz, 1H), 8.00 (d, $J=7.5$ Hz, 2H), 7.81 (d, $J=8.0$ Hz, 2H), 7.74 (d, $J=8.0$ Hz, 2H), 7.64–7.67 (m, 4H), 7.59 (d, $J=7.5$ Hz, 2H), 7.46 (t, $J=7.5$ Hz, 2H), 7.41 (t, $J=8.0$ Hz, 1H), 7.6 (t, $J=7.5$ Hz, 1H), 7.00 (d, $J=7.0$ Hz, 1H); ^{13}C NMR: δ 151.8, 147.5, 141.5, 140.7, 135.6, 132.8, 132.2, 130.7, 130.1, 129.5, 128.8, 127.8, 127.6 (t, $J=8.9$ Hz), 127.2, 126.6, 120.5 (t, $J=285$ Hz), 117.8, 113.8, 106.6 (t, $J=29$ Hz); ^{19}F NMR: δ −97.2 (s, 2 F). ESI-HRMS. Calcd for $C_{26}H_{19}F_2N_2O_2S$, $[M+H]^+$: *m/z* 461.1135. Found: *m/z* 461.1124.

3-(Difluoro(phenylsulfonyl)methyl)-7-methyl-2-phenylimidazo[1,2-*a*]pyridine (2k) White solid; mp 132–133°C; yield 75%; ^{1}H NMR: δ 8.55 (d, J = 7.0 Hz, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.75 (t, J = 7.5 Hz, 1H), 7.65–7.67 (m, 2H), 7.59 (t, J = 7.5 Hz, 2H), 7.47 (s, 1H), 7.37–7.39 (m, 3H), 6.83–6.85 (m, 1H), 2.47 (s, 3H); ^{13}C NMR: δ 152.1, 147.9, 139.1, 135.5, 132.9, 130.6, 129.6, 129.5, 128.7, 127.8, 126.6 (t, J = 4.9 Hz), 120.4 (t, J = 289 Hz), 116.3, 116.2, 106.9 (t, J = 29 Hz), 21.4; ^{19}F NMR: δ −97.2 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{17}F_2N_2O_2S$, $[M+H]^+$: *m/z* 399.0979. Found: *m/z* 399.0984.

3-(Difluoro(phenylsulfonyl)methyl)-6-methyl-2-phenylimidazo[1,2-*a*]pyridine (2l) White solid; mp 113–115°C; yield 81%; ^{1}H NMR: δ 8.45 (s, 1H), 7.98 (d, J = 8.0 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.60–7.68 (m, 5H), 7.39–7.41 (m, 3H), 7.28 (d, J = 7.5 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR: δ 151.8, 146.5, 135.5, 133.4, 132.9, 130.8, 130.7, 129.6, 129.5, 128.7, 127.8, 125.1 (t, J = 8.9Hz), 123.6, 120.4 (t, J = 285 Hz), 117.0, 106.3 (t, J = 29 Hz), 18.6; ^{19}F NMR: δ −97.2 (s, 2 F). ESI-HRMS. Calcd for $C_{21}H_{17}F_2N_2O_2S$, $[M+H]^+$: *m/z* 399.0979. Found: *m/z* 399.0968.

3-(Difluoro(phenylsulfonyl)methyl)-6-fluoro-2-phenylimidazo[1,2-*a*]pyridine (2m) White solid; mp 122–124°C; yield 63%; ^{1}H NMR: δ 8.66 (s, 1H), 7.74–7.81 (m, 4H), 7.62–7.66 (m, 4H), 7.40–7.45 (m, 3H), 7.35 (t, J = 8.0 Hz, 1H); ^{13}C NMR: δ 153.5 (d, J = 237 Hz), 152.9, 145.1, 135.7, 132.9, 132.6, 130.7, 129.6, 128.9, 127.9, 120.1 (t, J = 285.0 Hz), 119.7 (d, J = 25 Hz), 118.1 (d, J = 8.3 Hz), 114.8 (d, J = 43 Hz), 108.1 (t, J = 30 Hz); ^{19}F NMR: δ −98.1 (s, 2 F), −137.2 (s, 1 F). ESI-HRMS. Calcd for $C_{20}H_{14}F_3N_2O_2S$, $[M+H]^+$: *m/z* 403.0728. Found: *m/z* 403.0718.

3-(Difluoro(phenylsulfonyl)methyl)-2-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine (2n) White solid; mp 120–121°C; yield 76%; ^{1}H NMR: δ 8.75 (d, J = 7.0 Hz, 1H), 8.24 (s, 1H), 8.00 (d, J = 8.0 Hz, 2H), 7.88–7.95 (m, 4H), 7.74–7.81 (m, 2H), 7.54–7.61 (m, 4H), 7.47 (t, J = 8.0 Hz, 1H), 7.05 (t, J = 7.0 Hz, 1H); ^{13}C NMR: δ 152.1, 147.6, 135.6, 133.4, 132.9, 132.8, 130.7, 129.5, 128.6, 127.8, 127.7, 127.6, 127.4, 127.2, 126.5, 126.1, 120.5 (t, J = 289 Hz), 117.8, 113.8, 106.9 (t, J = 29 Hz); ^{19}F NMR: δ −97.2 (s, 2 F). ESI-HRMS. Calcd for $C_{24}H_{17}F_2N_2O_2S$, $[M+H]^+$: *m/z* 435.0979. Found: *m/z* 435.0971.

3-(Difluoro(phenylsulfonyl)methyl)-2-methylimidazo[1,2-*a*]pyridine (2o) White solid; mp 104–105°C; yield 88%; ^{1}H NMR: δ 8.65 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.65(d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.41–7.44 (m, 1H), 7.23–7.20 (m, 1H), 6.87–6.85 (m, 1H), 2.48 (s, 3H); ^{13}C NMR: δ 149.2, 146.7, 135.7, 132.4, 130.7, 129.6, 128.3, 126.7 (t, J = 5.4 Hz), 120.3 (t, J = 284 Hz), 116.9, 113.8, 107.1 (t, J = 30 Hz), 14.8; ^{19}F NMR: δ −100.1 (s, 2 F). ESI-HRMS. Calcd for $C_{15}H_{13}F_2N_2O_2S$, $[M+H]^+$: *m/z* 323.0661. Found: *m/z* 323.0665.

3-(Difluoro(phenylsulfonyl)methyl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (4a) White solid; mp 173–175°C; yield 87%; ^{1}H NMR: δ 8.24 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 7.5 Hz, 2H), 7.73–7.76 (m, 2H), 7.52–7.62 (m, 5H), 7.43 (t, J = 7.5 Hz, 1H), 7.35–7.38 (m, 3H); ^{13}C NMR: δ 154.3, 152.7, 135.6, 133.2, 132.9, 132.7, 130.7, 129.9, 129.7, 129.5, 128.7, 127.7, 126.5, 125.6, 124.0, 120.1 (t, J = 285 Hz), 111.7 (t, J = 8.3 Hz), 109.9 (t, J = 31.0 Hz); ^{19}F NMR: δ −92.4. ESI-HRMS. Calcd for $C_{22}H_{15}F_2N_2O_2S_2$, $[M+H]^+$: *m/z* 441.0543. Found: *m/z* 441.0548.

7-Chloro-3-(difluoro(phenylsulfonyl)methyl)-2-phenylbenzo[*d*]imidazo[2,1-*b*]thiazole (4b) White solid; mp 158–160°C; yield 84%; ^{1}H NMR: δ 8.16 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 7.5 Hz, 2H), 7.64 (t, J = 7.5 Hz, 1H), 7.35 (s, 1H), 7.59–7.65 (m, 4H), 7.54 (d, J = 7.5 Hz, 1H), 7.33–7.38 (m, 3H); ^{13}C NMR: δ 154.4, 152.3, 135.7, 133.0, 132.6, 131.5, 131.4, 130.7, 129.7, 129.6, 129.5, 128.9, 127.8, 126.9, 123.6, 120.0 (t, J = 285 Hz), 117.8 (t, J = 8.5 Hz), 110.0 (t, J = 31 Hz); ^{19}F NMR: δ −92.8. ESI-HRMS. Calcd for $C_{22}H_{14}ClF_2N_2O_2S_2$, $[M+H]^+$: *m/z* 475.0153. Found: *m/z* 475.0167.

Desulfonylation of compound 2a to 3-(difluoromethyl)-2-phenylimidazo[1,2-*a*]pyridine (5)

A mixture in a 10-mL flask containing compound **2a** (77 mg, 0.2 mmol), DMF (2 mL), a buffer solution of HOAc/NaOAc (1:1, 8 mol/L, 2 mL) and magnesium turnings (96 mg, 4 mmol) was stirred at room temperature for 6 h and then quenched with water. The mixture was extracted with Et_2O, and the extract was dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with petroleum ether/ethyl acetate (10:1) to furnish pure product **5**: White solid; mp 105–107°C; yield 77%; ^{1}H NMR: δ 8.14 (d, J = 7.0 Hz, 1H), 7.96–7.00 (m, 2H), 7.88 (s, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.46 (t, J = 8.0 Hz, 2H), 7.34–7.37 (m, 1H), 7.18–7.21 (m, 1H), 6.80 (dt, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H); ^{13}C NMR: δ 147.6, 146.6, 133.6, 129.8, 128.7, 128.1, 127.9, 125.4, 124.3 (t, J = 5.5 Hz), 113.5, 111.9 (t, J = 30 Hz), 111.5 (t, J = 246 Hz); ^{19}F NMR: δ −98.4. ESI-HRMS. Calcd for $C_{14}H_{11}F_2N_2$, $[M+H]^+$: *m/z* 245.0885. Found: *m/z* 245.0891.

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