Direct nucleophilic difluoromethylation of aromatic isoxazoles activated by electron-withdrawing groups using (difluoromethyl) trimethylsilane

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ABSTRACT

The activation of aromatic diaryl isoxazoles with strong electron-withdrawing groups, such as the nitro, triflyl, and the phenylsulfonyl groups, at the 4-position has enabled the first regio- and diastereoselective difluoromethylation at the 5-position of isoxazoles by nucleophilic addition using (difluoromethyl) trimethylsilane, $\text{Me}_3\text{SiCF}_2\text{H}$, to provide difluoromethylated isoxazolines in good yields. Conjugated styryl-4-nitroisoxazoles were also nicely converted into the corresponding CF_2H adducts with high regio- and excellent diastereoselectivities. Since the trifluoromethylated analogs of the corresponding diaryl-isoxazolines are effective ectoparasitocides, represented by fluralaner, should a series of difluoromethylated isoxazolines be obtained, they would be of great importance as promising drug candidates in this field.

Heterocycles have an extensive history and are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds [1–4]. Man-made fluorinated organic compounds have become a remarkable success in the pharmaceutical industry, despite their relatively young history [5–20]. In this context, fluorinated heterocycles have gained attention as new drug candidates over the past few decades in medicine and agro-chemistry [21–28]. Fluorinated and trifluoromethylated compounds have been well targeted in this research area [5–20, 21–28], and difluoromethylated compounds are next [16, 21–28]. The difluoromethyl (CF_2H) group is known to be isosteric and isopolar to a hydroxy (OH) and thiol (SH) unit. The CF_2H group can also act as a more lipophilic hydrogen donor than OH and NH groups through hydrogen bonding [31–34]. Thus, the difluoromethylation of biologically active molecules is an effective strategy for the design new candidates of pharmaceuticals and agrochemicals [16].

BRAVECTO™ (fluralaner) is a highly potent insect and acarid RDL and GluCl inhibitor that was just recently approved in chewable tablets for dogs against fleas and ticks [35]. A systematically large number of research disclosed that 3,5-diaryl-5-(trifluoromethyl)-2-isoxazoline unit **1** is a key skeleton for its biological activity [36–38]. Since 2010, our group has also made contributions to this fascinating structure by the direct late-stage trifluoromethylation of aromatic isoxazoles with Ruppert–Prakash reagent (trifluoromethyl) trimethylsilane (Me_3SiCF_3) [39–41], and a fluorinated building block strategy based on the use of inexpensive reagents under organocatalysis with an eye on industrial purposes [36–38]. We are now interested in the synthesis of difluoromethyl analogs of this key structure, i.e., 3,5-diaryl-5-(difluoromethyl)-2-isoxazolines **2**. More than 27,000 isoxazolines **1** with a quaternary carbon bearing a CF_3 group at the 5-position have been synthesized and patented [42]; however, common structures bearing a CF_2H group **2** are rare [43] (19 compounds, 4 patents Figure 1).

In this paper, we disclose the first direct difluoromethylation at the 5-position of diaryl-isoxazoles **3** by nucleophilic addition using (difluoromethyl) trimethylsilane ($\text{Me}_3\text{SiCF}_2\text{H}$) in the presence of tetramethylammonium fluoride at room temperature. A series of diaryl-isoxazoles **3** having a nitro ($\text{X} = \text{NO}_2$), triflyl ($\text{X} = \text{SO}_2\text{CF}_3$), or phenylsulfonyl ($\text{X} = \text{SO}_2\text{Ph}$) group at the 4-position are nicely CF_2H -functionalized under the same mild conditions with good to high diastereoselectivity. Nucleophilic difluoromethylation of 1,6-conjugated styryl-4-nitro isoxazoles was also achieved with $\text{Me}_3\text{SiCF}_2\text{H}$ under the same reaction conditions to provide CF_2H -adducts **4**, with high regio- and excellent diastereoselectivities. A wide variety of CF_2H analogs of agrochemically attractive diaryl-isoxazolines **2** and their styryl analogs **4** were synthesized by this method. The nitro group in products **2** ($\text{X} = \text{NO}_2$)

Figure 1. BRAVECTO™, trifluoromethyl-diarylisoxazolines **1** and their difluoromethyl analogs **2**.

can be removed under radical reaction conditions to afford **2** ($X = H$). The patented examples of this skeleton are synthesized by a so-called building block strategy [44–47]; hence, our method is the first example of the synthesis of 3,5-diaryl-5-(difluoromethyl)-2-isoxazolines by a direct difluoromethylation reaction (Figure 2).

In our previous studies, direct trifluoromethylation into the 5-position of isoxazoles was achieved by using the Ruppert–Prakash reagent, Me_3SiCF_3 [39–41]. Therefore, difluoromethylation with $\text{Me}_3\text{SiCF}_2\text{H}$ instead of Me_3SiCF_3 under the same conditions is an ideal extension of this strategy. However, the use of $\text{Me}_3\text{SiCF}_2\text{H}$ instead of Me_3SiCF_3 is not just a simple extension of direct trifluoromethylation, due to the rather inactive character of $\text{Me}_3\text{SiCF}_2\text{H}$ [48, 49]. According to molecular orbital calculations of (difluoromethyl)- and (trifluoromethyl)fluorotrimethylsilicates reported by Fuchikami et al. [48], the bond order of the $\text{Si-CF}_2\text{H}$ bond (0.436) is significantly higher than that of the Si-CF_3 bond (0.220); eventually, the cleavage of the $\text{Si-CF}_2\text{H}$ bond is more difficult than that of the Si-CF_3 bond. Since Fuchikami's report, difluoromethylsilanes were believed to be not very useful for nucleophilic difluoromethylation until a recent report emerged from Hu et al. in 2011. They developed a Lewis base that could activate the nucleophilic difluoromethylation of various aldehydes, ketones, and imines with $\text{Me}_3\text{SiCF}_2\text{H}$ at room temperature or even at low temperature [49]. Encouraged by their work, combined with the advances of our previous work, we initialized the optimization of the reaction conditions for the difluoromethylation of 4-nitro-3,5-diphenylisoxazole (**3a**), using $\text{Me}_3\text{SiCF}_2\text{H}$.

Figure 2. Two strategies for difluoromethylated isoxazolines **2** and newly obtained difluoromethylated isoxazolines **2** and **4**.

We first attempted difluoromethylation under the previous best conditions for trifluoromethylation of **3a** [39, 40] or 4-triflyl-3,5-diphenylisoxazole (**3f**) [41], however, the results were not satisfactory (Table 1, entries 1 and 2). There was no reaction in the presence of other basic conditions (entries 3–5). Yield improved to 22–33% when phase-transfer catalyst 18-crown-6 (1.5 equiv) was added with potassium acetate and potassium fluoride (entries 6 and 7). Interestingly, ammonium salt tetramethylammonium fluoride (Me_4NF) could cleave the $\text{Si-CF}_2\text{H}$ bond more efficiently. The reaction was attempted using Me_4NF instead of a base, which gave the desired product in 53% yield (entry 8). Extension of the reaction time did not improve product yield (52%, entry 9). Traces of the desired product were detected when other quaternary ammonium salts replaced Me_4NF (entries 10, 11). No effect on product yield (52%) was observed with a catalytic amount of cetyltrimethylammonium bromide (entry 12). Solvent screening did not improve the reaction (entries 13–17), and the best condition was determined to be entry 8, by treating **3a** with $\text{Me}_3\text{SiCF}_2\text{H}$ (2.0 equiv) in N,N -dimethylformide (DMF) in the presence of Me_4NF at room temperature for 4 h, and desired product **2a** was obtained in 53% yield (entry 8). The stereochemistry of **2a** was tentatively assigned according to comparisons with previous results [39, 40, 41], and finally it was clearly determined by X-ray analysis (CCDC 1057178). Assigning the best condition as the standard, we examined the scope of substrates **3** for our difluoromethylation reaction

Table 1. Optimization of reaction conditions.

Entry	Base	Additive ^b	Solvent	Yield (%) ^a
1	NaOAc	$[\text{CH}_3(\text{CH}_2)_{15}\text{N}(\text{CH}_3)_3]\text{Br}$ (30 mol%)	DMF	24
2	KOAc	—	DMSO	NR ^b
3	<i>t</i> BuOK	—	DMF	NR ^b
4	KOAc	—	DMF	NR ^b
5	KOH	—	DMF	NR ^b
6	KOAc	18-crown-6 (1.5 equiv)	DMF	22
7	KF	18-crown-6 (1.5 equiv)	DMF	33
8	Me_4NF	—	DMF	53
9 ^c	Me_4NF	—	DMF	52
10	$\text{Et}_4\text{NF} \cdot \text{H}_2\text{O}$	—	DMF	trace ^b
11	$n\text{Bu}_4\text{NF} \cdot \text{H}_2\text{O}$	—	DMF	trace ^b
12	Me_4NF	$[\text{CH}_3(\text{CH}_2)_{15}\text{N}(\text{CH}_3)_3]\text{Br}$ (30 mol%)	DMF	52
13	Me_4NF	—	THF	trace ^b
14	Me_4NF	—	NMP	NR ^b
15	Me_4NF	—	DMSO	trace ^b
16	Me_4NF	—	DMA	11
17	Me_4NF	—	DMI	NR ^b

^aThe yield of isolated product.

^bDetermined by ^{19}F NMR analysis of the crude reaction mixture.

^cReaction ran for 48 h.

in order to establish the generality of the process. A series of 3,5-diaryl-4-nitro-isoxazole **3** with different substituents at aromatic rings, including electron-donating and electron-withdrawing groups, were converted into corresponding difluoromethylated adducts smoothly in moderate yields with good to excellent diastereoselectivities (d.r. = 85:15–97:3, Table 2, **2a–2e**). It should be noted that isoxazoles having a different electron-withdrawing group at the 4-position, SO_2CF_3 and SO_2Ph , i.e., 3,5-diphenyl-4-(trifluoromethanesulfonyl)isoxazole **3f** and 3,5-diphenyl-4-(phenylsulfonyl)isoxazole **3g**, were also suitable substrates for this transformation, affording difluoromethylated adducts **2f** and **2g** in moderate yields but rather low diastereoselectivities.

We next investigated the difluoromethylation of 4-nitro-5-styrylisoxazoles **5**. These compounds are flexible building blocks that bear a number of different functionalities [50–66]. Generally, 4-nitro-5-styrylisoxazoles **5** have two electrophilic centres, both of which can be attacked by nucleophiles [50–66]. Although the addition of carbon nucleophiles at the 4-position of **5** is rare, according to our previous work [39, 40], nucleophilic trifluoromethylation to conjugated alkenes with Me_3SiCF_3 fundamentally occurs exclusively by a 1,2-addition, and not a 1,4-addition. These results indicate that the addition of an aromatic isoxazole ring at the 5-position is specific to the trifluoromethylation reaction. In this work, we investigated the nucleophilic difluoromethylation of various 4-nitro-5-styrylisoxazoles **5** under the same reaction conditions to afford 1,2-addition difluoromethylated compounds as main products, while a very small amount of the 1,4-addition of

Table 2. Stereoselective difluoromethylation of 3,5-diarylisoxazole **3** by nucleophilic difluoromethylation.^a

^aYield of the isolated products.

Table 3. Regio- and diastereoselective difluoromethylation of 4-nitro-5-styrylisoxazoles by nucleophilic addition.^a

^aYield of the isolated products.

difluoromethylated compound was observed (less than 10% of all difluoromethylated products) (Table 3). 3-Methyl-5-difluoromethyl-5-styrylisoxazoles were obtained with complete diastereoselectivity as single isomers (**4a–4e**). Moderate yields were obtained when R^1 was an electron-rich aromatic ring or a non-substrate benzene ring (**4a–4c**). When R^1 was an electron-poor aromatic ring, lower yields of corresponding products were obtained (**4d** and **4e**). 3-Aryl-5-styrylisoxazoles were next investigated for the difluoromethylation and gave the corresponding products smoothly as single isomers (**4f** and **4g**).

In conclusion, the activation of aromatic isoxazoles with a strong electron-withdrawing group at the 4-position has resulted in the realization of the first diastereoselective difluoromethylation at the 5-position of isoxazoles **3** by nucleophilic addition using $\text{Me}_3\text{SiCF}_2\text{H}$. Regio- and diastereoselective difluoromethylation by nucleophilic addition was also achieved in the reaction with 1,6-conjugated styryl-4-nitroisoxazoles **4** under the same reaction conditions. Notably, a strong electron-withdrawing group at the 4-position is essential for this addition. No reaction was

Figure 3. Removal of the NO_2 group of **2a** to **6**.

observed without the use of non-substituted 3,5-diphenyl isoxazole as substrate under the same reaction conditions. The nitro group of **2a** was easily removed under radical reduction conditions to provide **6** in 96% yield (Figure 3). Therefore, this method provides a new series of highly functionalized 5-difluoromethyl-2-isoxazoline derivatives that may be attractive candidates for agrochemicals. The biological activities of selected 5-(difluoromethyl)-2-isoxazoline derivatives **2** and asymmetric variants of this method are now under consideration.

EXPERIMENTAL SECTION

All reagents were used as received from commercial sources, unless specified otherwise, or prepared as described in the literature. Reactions requiring anhydrous conditions were performed in oven-dried glassware under a positive pressure of nitrogen in glove box. Reaction mixtures were stirred magnetically. Solvents were transferred via syringe and were introduced into the reaction vessels through a rubber septum. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or KMnO_4 in water/heat. Column chromatography was carried out on a column packed with silica gel 60 N spherical neutral size 63–210 μm . The ^1H -NMR (300 MHz) and ^{19}F -NMR (282.3 MHz) spectra were recorded on a Varian Mercury 300. The ^{13}C -NMR (150.9 MHz) was recorded on a Bruker Avance 600. Chemical shifts (δ) are reported in parts per million and coupling constants (J) are in hertz. Mass spectra were recorded on a SHIMADZU LCMS-2020. All the isoxazole substrates (**3** and **5**) were prepared according to the literature procedure [39, 40, 67].

General procedure for the difluoromethylation of 4-nitroisoxazoles: in a flame dried test tube, 4-nitroisoxazole **3** or **5** (0.2 mmol) and Me_4NF (0.3 mmol) added in glove box. DMF (2.0 mL) and $\text{Me}_3\text{SiCF}_2\text{H}$ (0.4 mmol) was added in the mixture. After stirring at room temperature for 4.0 h, 1N HCl aq. was added to the reaction mixture and stirred for 30 minutes. After dilution with water, the whole reaction mixture was extracted with AcOEt. The combined organic phase was washed successively with water and saturated brine, and then dried over anhydrous Na_2SO_4 . The solution was filtered and the solvent was removed under reduced pressure. The crude product was further purified by silica gel column chromatography or prepared TLC to give **2a–g** and **4a–g**.

5-(difluoromethyl)-4-nitro-3,5-diphenyl-4,5-dihydroisoxazole (**2a**): Following the general procedure, **2a** was isolated (33.7 mg, 53%) as a yellow solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.95 (t, J = 54.9 Hz, 1H), 6.62 (s, 1H), 7.43–7.75 (m, 10H); ^{19}F NMR (282 MHz, CDCl_3) δ –128.52 (ddd, J = 505.6 Hz, 282.0 Hz, 53.6 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.86, 131.94, 130.36, 129.57, 129.12, 126.80, 126.53, 125.97, 113.82 (t, J = 254.6 Hz), 92.90, 92.05 (t, J = 21.4 Hz); MS (ESI, m/z) 317 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{16}\text{H}_{12}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 341.0714, Found: 341.0712.

5-(difluoromethyl)-5-(naphthalen-2-yl)-4-nitro-3-phenyl-4,5-dihydroisoxazole (**2b**): following the general procedure, **2b** was isolated (36.1 mg, 49%) as a yellow solid. ^1H NMR (CDCl_3 , 300 MHz) δ 6.02 (t, J = 55.5 Hz, 1H), 6.70 (s, 1H), 7.44–8.15 (m, 12H); ^{19}F NMR (282 MHz, CDCl_3) δ –128.10 (ddd, J = 515.5 Hz, 283.1 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.98, 133.78, 132.89, 131.97, 129.59, 129.07, 128.82, 127.82, 127.71, 127.08, 126.83, 125.98, 122.80, 113.99 (t, J = 239.6 Hz), 92.98, 92.255 (t, J = 21.0 Hz); MS (ESI, m/z) 367 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 391.0870, Found: 391.0898.

5-(4-chlorophenyl)-5-(difluoromethyl)-4-nitro-3-phenyl-4,5-dihydroisoxazole (**2c**): following the general procedure, **2c** was isolated (33.1 mg, 47%) as a yellow solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.92 (t, J = 54.9 Hz, 1H), 6.58 (s, 1H), 7.40–7.73 (m, 9H); ^{19}F NMR (282 MHz, CDCl_3) δ –128.36 (ddd, J = 498.9 Hz, 284.0 Hz, 53.6 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.88, 136.85, 132.09, 129.62, 129.44, 128.05, 126.81, 125.76, 113.53 (t, J = 254.9 Hz), 92.90, 91.64 (t, J = 20.8 Hz); MS (ESI, m/z) 351 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{16}\text{H}_{11}\text{N}_2\text{O}_3\text{ClF}_2+\text{Na}]^+$: 375.0324, Found: 375.0330.

5-(difluoromethyl)-4-nitro-3-phenyl-5-(*m*-tolyl)-4,5-dihydroisoxazole (**2d**): following the general procedure, **2d** was isolated (33.9 mg, 51%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ 2.38 (s, 3H), 5.93 (t, J = 55.5 Hz, 1H), 6.58 (s, 1H), 7.22–7.74 (m, 9H); ^{19}F NMR (282 MHz, CDCl_3) δ –128.53 (ddd, J = 508.4 Hz, 282.0 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.85, 138.99, 131.90, 131.11, 129.56, 128.96, 126.79, 126.02, 123.50, 113.89 (t, J = 255.2 Hz), 92.89, 92.09 (t, J = 21.3 Hz), 21.67; MS (ESI, m/z) 331 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 355.0870, Found: 355.0876.

3-(4-bromophenyl)-5-(3-chlorophenyl)-5-(difluoromethyl)-4-nitro-4,5-dihydroisoxazole (**2e**): following the general procedure, **2e** was isolated (43.2 mg, 50%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.94 (t, J = 54.3 Hz, 1H), 6.57 (s, 1H), 7.35–7.68 (m, 8H); ^{19}F NMR (282 MHz, CDCl_3) δ –128.53 (ddd, J = 597.6 Hz, 284.0 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.17, 135.41, 132.94, 130.80, 130.44, 128.14, 126.79, 124.62, 113.43 (t, J = 254.9 Hz), 92.61, 91.69 (t, J = 21.4 Hz); MS (ESI, m/z) 431 $[\text{M-H}]^-$.

5-(difluoromethyl)-3,5-diphenyl-4-((trifluoromethyl)sulfonyl)-4,5-dihydroisoxazole (**2f**): following the general procedure, **2f** was isolated (32.4 mg, 40%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.53 (s, 0.44H), 5.63 (s, 0.56H), 5.87 (t, J = 55.8 Hz, 0.56H), 6.85 (t, J = 55.2 Hz, 0.44H), 7.38–7.76 (m, 10H); ^{19}F NMR (282 MHz, CDCl_3) δ –73.03, –73.55, –123.00 (ddd, J = 900.4 Hz, 295.0 Hz, 53.3 Hz, 2F), –127.18 (ddd, J = 384.9 Hz, 280.9 Hz, 55.3 Hz, 2F); MS (ESI, m/z) 404 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{17}\text{H}_{12}\text{NO}_3\text{F}_5+\text{Na}]^+$: 428.0356, Found: 428.0355. ^{13}C NMR is too complicated to be analyzed.

5-(difluoromethyl)-3,5-diphenyl-4-(phenylsulfonyl)-4,5-dihydroisoxazole (**2g**): following the general procedure, **2g** was isolated (34.7 mg, 42%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.52 (t, J = 51.0 Hz, 0.78H), 5.70 (t, J = 55.2 Hz,

0.22H), 7.03–7.78 (m, 15H); ^{19}F NMR (282 MHz, CDCl_3) δ –121.86 (ddd, J = 1305.4 Hz, 298.9 Hz, 53.3 Hz, 2F), –128.29 (ddd, J = 480.0 Hz, 280.0 Hz, 55.3 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 155.96, 137.15, 134.28, 131.13, 129.62, 129.10, 128.85, 128.73, 128.20, 128.01, 127.99, 114.16 (t, J = 255.5 Hz), 90.64 (t, J = 20.4 Hz), 72.36; MS (ESI, m/z) 412 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{22}\text{H}_{17}\text{NO}_3\text{F}_2+\text{Na}]^+$: 436.0795, Found: 436.0799.

5-(difluoromethyl)-3-methyl-4-nitro-5-styryl-4,5-dihydroisoxazole (**4a**): following the general procedure, **4a** was isolated (25.4 mg, 45%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ 2.16 (s, 3H), 5.85 (t, J = 55.8 Hz, 1H), 5.89 (s, 1H), 6.56 (dd, J = 292.8 Hz, 16.2 Hz, 2H), 7.34–7.36 (m, 5H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.72 (ddd, J = 833.3 Hz, 285.1 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 149.89, 137.93, 134.75, 129.47, 128.92, 127.39, 114.58, 113.72 (t, J = 256.5 Hz), 94.48, 89.22 (t, J = 23.2 Hz), 12.05; MS (ESI, m/z) 281 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{13}\text{H}_{12}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 305.0714, Found: 305.0710.

5-(difluoromethyl)-3-methyl-5-(4-methylstyryl)-4-nitro-4,5-dihydroisoxazole (**4b**): Following the general procedure, **4b** was isolated (27.8 mg, 47%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 2.08 (s, 3H), 2.27 (s, 3H), 5.80 (t, J = 55.8 Hz, 1H), 6.40 (s, 1H), 6.41 (dd, J = 298.2 Hz, 15.6 Hz, 2H), 7.05–7.18 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.29 (ddd, J = 803.4 Hz, 285.1 Hz, 53.3 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 149.86, 139.63, 137.76, 132.00, 129.60, 127.31, 113.46 (t, J = 256.5 Hz), 113.39, 112.08, 94.46, 89.28 (t, J = 22.9 Hz), 21.46, 12.05; MS (ESI, m/z) 295 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 319.0870, Found: 319.0885.

5-(difluoromethyl)-3-methyl-5-(2-(naphthalen-1-yl)vinyl)-4-nitro-4,5-dihydroisoxazole (**4c**): Following the general procedure, **4c** was isolated (28.6 mg, 43%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ 2.20 (s, 3H), 5.95 (t, J = 58.5 Hz, 1H), 6.12 (s, 1H), 7.44–8.02 (m, 9H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.79 (ddd, J = 866.0 Hz, 285.9 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 149.94, 135.92, 133.60, 132.77, 131.20, 129.71, 128.70, 126.81, 126.30, 125.61, 124.79, 123.69, 117.87, 113.70 (t, J = 255.9 Hz), 94.64, 89.33 (t, J = 23.2 Hz), 12.08; MS (ESI, m/z) 331 $[\text{M-H}]^-$; HRMS calc'd for $[\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 355.0870, Found: 355.0868.

5-(4-chlorostyryl)-5-(difluoromethyl)-3-methyl-4-nitro-4,5-dihydroisoxazole (**4d**): following the general procedure, **4d** was isolated (17.7 mg, 28%) as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz) δ 2.16 (s, 3H), 5.84 (t, J = 54.3 Hz, 1H), 5.89 (s, 1H), 6.53 (dd, J = 285.6 Hz, 15.9 Hz, 2H), 7.30–7.38 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.67 (ddd, J = 843.2 Hz, 285.9 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 149.92, 136.68, 135.36, 133.21, 129.16, 128.60, 115.26, 113.56 (t, J = 252.9 Hz), 94.48, 89.10 (t, J = 23.2 Hz), 12.03; MS (ESI, m/z) 315 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_3\text{ClF}_2+\text{Na}]^+$: 339.0324, Found: 339.0328.

5-(4-bromostyryl)-5-(difluoromethyl)-3-methyl-4-nitro-4,5-dihydroisoxazole (**4e**): following the general procedure, **4e**

was isolated (21.7 mg, 30%) as a yellow solid. ^1H NMR (CDCl_3 , 300 MHz) δ 2.17 (s, 3H), 5.84 (t, J = 55.2 Hz, 1H), 5.89 (s, 1H), 6.53 (dd, J = 275.7 Hz, 16.2 Hz, 2H), 7.22–7.48 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.69 (ddd, J = 855.9 Hz, 285.9 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 149.92, 136.76, 133.64, 132.12, 128.85, 123.61, 115.38, 113.54 (t, J = 254.0 Hz), 94.48, 89.11 (t, J = 23.1 Hz), 12.03; MS (ESI, m/z) 359 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{13}\text{H}_{11}\text{N}_2\text{O}_3\text{BrF}_2+\text{Na}]^+$: 382.9819, Found: 382.9802.

5-(difluoromethyl)-4-nitro-3-phenyl-5-styryl-4,5-dihydroisoxazole (**4f**): following the general procedure, **4f** was isolated (35.1 mg, 51%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.92 (t, J = 56.1 Hz, 1H), 6.42 (s, 1H), 6.66 (dd, J = 290.1 Hz, 16.2 Hz, 2H), 7.33–7.71 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.24 (ddd, J = 813.6 Hz, 285.1 Hz, 53.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.34, 138.44, 134.71, 131.84, 129.56, 129.53, 128.94, 127.42, 126.76, 126.23, 114.11, 113.70 (t, J = 253.1 Hz), 92.18, 90.47 (t, J = 21.9 Hz); MS (ESI, m/z) 343 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 367.0870, Found: 367.0873.

5-(difluoromethyl)-5-(4-methylstyryl)-4-nitro-3-phenyl-4,5-dihydroisoxazole (**4g**): following the general procedure, **4g** was isolated (33.7 mg, 47%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 5.92 (t, J = 56.1 Hz, 1H), 6.42 (s, 1H), 6.66 (dd, J = 290.1 Hz, 16.2 Hz, 2H), 7.33–7.71 (m, 4H); ^{19}F NMR (282 MHz, CDCl_3) δ –130.28 (ddd, J = 802.6 Hz, 285.1 Hz, 54.4 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 152.32, 139.72, 138.27, 131.97, 131.80, 129.61, 129.51, 127.35, 126.74, 126.28, 113.76 (t, J = 257.4 Hz), 112.92, 92.17, 90.54 (t, J = 21.3 Hz), 21.46; MS (ESI, m/z) 357 $[\text{M-H}]^-$ HRMS calc'd for $[\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_3\text{F}_2+\text{Na}]^+$: 381.1027, Found: 381.1025.

Procedure for denitration of **2a**

To a stirred solution of **2a** (31.8 mg, 0.10 mmol) in benzene (2.0 mL) were successively added AIBN (8.2 mg, 0.050 mmol, 0.5 equiv) and $n\text{Bu}_3\text{SnH}$ (40.4 μL , 0.150 mmol, 1.5 equiv), and the whole mixture was heated under reflux for 2 h. After cooling down to room temperature, the solution was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (n -hexane/ethyl acetate = 95/5) to give **6** (26.2 mg, 96%) as a white solid. ^1H NMR (CDCl_3 , 300 MHz) δ 3.82 (dd, J = 124.8 Hz, 16.8 Hz, 2H), 5.91 (t, J = 55.2 Hz, 1H), 7.36–7.70 (m, 10H); ^{19}F NMR (282 MHz, CDCl_3) δ –129.10 (ddd, J = 371.1 Hz, 281.2 Hz, 55.3 Hz, 2F); ^{13}C NMR (150.9 MHz, CDCl_3) δ 156.46, 137.52 (d, J = 2.8 Hz), 130.73, 129.04, 128.95, 128.83, 128.73, 126.94, 126.48, 114.63 (t, J = 251.6 Hz), 88.46 (t, J = 22.5 Hz), 41.77; MS (ESI, m/z) 274 $[\text{M}+\text{H}]^+$ HRMS calc'd for $[\text{C}_{16}\text{H}_{14}\text{NOF}_2]^+$: 274.1043, Found: 274.1045.

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COMPETING INTERESTS

The authors declare no competing interests.

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