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# Diastereoselective Heterocyclization of Geminal Bromo-Fluoro Arylcyclopropanes by Nitrosonium Tetrafluoroborate: Access to 4-Fluorinated Isoxazolines and Isoxazoles

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ABSTRACT

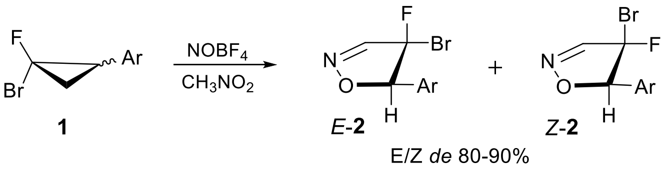
A series of 5-aryl-4-bromo-4-fluoroisoxazolines was synthesized via nitrosation of 2-aryl-1-bromo-1-fluorocyclopropanes with $NOBF_4$. It was shown that the *E*-isomers of the cyclopropanes react highly regio- and diastereoselectively leading exclusively to the *E*-isomers of the isoxazolines. The obtained 5-aryl-4-bromo-4-fluoroisoxazolines were transformed selectively into the corresponding 5-aryl-4-fluoro- or 5-aryl-4-bromoisoxazoles in good yields in the reaction with Lewis acids.

## 1. Introduction

Synthesis of organic compounds possessing a definitely located fluorine atom constitutes a synthetic challenge, which is typically resolved by a systematic search for selective fluorinating reagents. An alternative for this synthetic strategy is the utilization of fluorine-containing synthons/precursors. Fluorocyclopropanes derived from readily accessible fluorocarbenes can be viewed as one of such synthons. A successful example of this approach is the nitrosation of fluorocyclopropanes to afford fluorinated heterocycles. Recent systematic studies of such nitrosations have assisted the development of practical methods for accessing fluoro-isoxazoles, isoxazolines, and pyrimidines. For example, nitrosation of 1-bromo-1-fluorocyclopropanes with the $SO_3$-activated nitrosyl chloride (i.e. nitrosonium chlorosulfate) yields 5-fluoroisoxazoles, which are challenging to obtain.[1] A three-component heterocyclization involving 1-bromo-1-fluorocyclopropanes, nitrosonium tetrafluoroborate, and a molecule of solvent (nitrile) yields previously unknown fluorinated pyrimidine *N*-oxides.[2] In a recent short communication, we disclosed the reaction of 2-aryl-1-bromo-1-fluorocyclopropanes with $NOBF_4$ to afford 5-aryl-4-bromo-4-fluoroisoxazolines.[3] In this paper, we now report our comprehensive study of the mechanism, stereochemistry, and preparative scope of this useful transformation.

## 2. Results and discussion

In a typical procedure, *gem*-bromofluorocyclopropanes **1**, taken as mixtures of *E/Z*-isomers in a ratio of 1:1, were added to 1.1 equiv of $NOBF_4$ in nitromethane at 0°C; after stirring at room temperature for 20 h, isoxazolines **2** were isolated in moderate yields of 33-43%. We have found that under these conditions, the reaction proceeds highly regio- and diastereoselectively, leading predominantly to isoxazolines **2** of *E*-configuration with diastereomeric excess of 80-90% (Scheme 1).



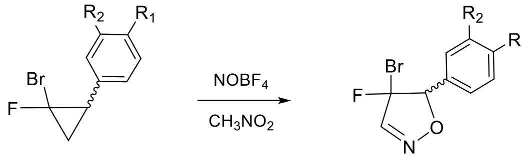
**Scheme 1.**

The products were isolated chromatographically.[4] Their structure and composition were determined by $^1H$, $^{13}C$ and $^{19}F$ NMR spectroscopy, mass-spectrometry and elemental analysis data. The $^1H$ and $^{19}F$ NMR spectra of isoxazolines **2** exhibit doublets at 5.70 and -103.2 ppm, respectively, with the same three-bond coupling of $^3J_{H-F}$ 22.0-22.7 Hz. The signal of HC=N proton appears as a singlet at 7.70 ppm. The $^{13}C$ NMR also showed the expected $^{13}C$-$^{19}F$ coupling with C-4, this appeared as a doublet at 102.8 ppm with a large one-bond coupling ($^1J_{C-F}$ =

271.5 Hz). Carbons C-3 and C-5 appeared both as doublets at 146.4 and 90.6 ppm with smaller two-bond couplings, $^2J_{C\text{-}F}$ = 22.7 and 19.8 Hz, respectively.

To assess the scope and utility of this new bromofluorocyclopropane transformation, we broadened the range of arylcyclopropanes. The results of the nitrosation reaction are given in Table 1.

**Table 1**. Nitrosation of 2-aryl-1-bromo-1-fluorocyclopropanes **1a-g** with nitrosonium tetrafluoroborate: 1.1 eq of $NOBF_4$, $MeNO_2$, 0-20ºC, 24 h, **1a-g** concentration $[C_o]$ = 0.06 mol/L



**1a-g** **2a-g**

| Comp. | $R_1$ | $R_2$ | product | Yield,% |
|---|---|---|---|---|
| **1a** | H | H | **2a** | 38 |
| **1b** | Cl | H | **2b** | 33 |
| **1c** | Br | H | **2c** | 43[a] |
| **1d** | F | H | **2d** | 40[a] |
| **1e** | Me | H | **2e** | 38 |
| **1f** | H | Me | **2f** | 35 |
| **1g** | MeO | H | **2g** | 7[b] |

[a]The resultant mixture contained less than 15% of 3-aryl-5-flioroisoxazole
[b]Attempted reaction with cyclopropane **1g** produced mainly intractable oil even at lower temperatures (-20ºC).

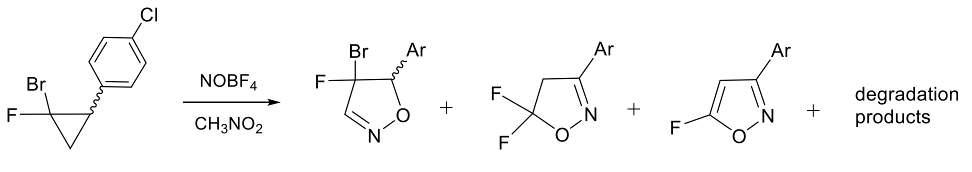
Among the tested compounds only cyclopropanes **1a-g** gave targeted isoxazolines **2a-g**. Instructively, cyclopropanes with an acceptor (Cl, Br or $NO_2$) located in the *meta*-position of the benzene ring were practically unreactive under the same nitrosation reaction conditions. Using an excess of $NOBF_4$ for their case resulted in the formation of complex mixtures of degradation products with only traces of the corresponding isoxazolines and 5-fluoroisoxazoles[1b].

As follows from the Table 1 data, the yields of isoxazolines **2a-g** were less no more than 43%. We should note that the reactivity of $NOBF_4$ toward *gem*-bromofluorocyclopropanes **1a-g** was rather moderate and the reaction times needed for completion of the reaction were typically long. Thus, conversion of cyclopropanes **1a-c** after 1 h of the reaction was about 20% affording isoxazolines **2a-c** as the only product. For longer reaction times, approximately 24 h, cyclopropanes **1a-c** were completely consumed; however, the yields of isoxazolines **2a-c** did not exceed 50%. Moreover, in every case studied, it was apparent from the $^1H$ NMR spectra that at longer times the reaction was complicated due to the formation of by-products. New signals appeared to the left of the HC=N signal (downfield) of isoxazolines (7.70 ppm), indicative of side reactions arising in the system. We also tested an alternative nitrosating reagent, $NaNO_2/CF_3COOH$, which was earlier reported in the syntheses of isoxazolines from arylcyclopropanes.[5] In this case, nitrosation of cyclopropanes **1a-c** also afforded only the *E*-diastereomers of isoxazolines **2a-c**; however, their yields were poor at less than 20%.

Using **1b** as a model compound, we tried to optimize the reaction conditions by varying concentrations, temperatures, and ratios of the initials. For cyclopropane **1b** at concentration of $[C_o]$ = 0.3 mol/L, some degradation products were identified, i.e., 4-chlorobenzoic acid[6] and 4-chlorobenzonitrile (the latter was detected by GC-MS analysis), which were formed in the reaction mixture in amounts comparable with that of isoxazoline **2b** (Table 2, entry 2). Lowering the reaction temperature to 0ºC significantly reduced the reaction rate; however, this did not change the content of the reaction mixture: the starting material **1b**, the corresponding isoxazoline **2b** and degradation products were all present in the resultant mixture after 5 h (Table 2, entry 3). At that, the *E/Z*-isomers ratio of the returned unreacted cyclopropane **1b** was changed after the reaction favoring the Z-isomer (Table 2, entries 3, 5).[7]

Decreasing the concentration of cyclopropane **1b** to $[C_o]$ = 0.01-0.02 mol/L resulted in the appearance of some other products, one of which was determined to be 5,5-difluoroisoxazoline **3b**. This was revealed by the multiplicity observed in the $^1H$, $^{19}F$ and $^{13}C$ NMR spectra, as well as the mass spectrum. Indeed, the $^1H$ and $^{19}F$ NMR spectra of compound **3b** revealed triplets with the same three-bond coupling of $^3J_{H\text{-}F}$ = 14.3 Hz. The $^{13}C$ NMR also showed the expected $^{13}C$-$^{19}F$ coupling, with C-5 appearing as a triplet at 133.0 ppm with a large one-bond coupling ($^1J_{C\text{-}F}$ = 265.4 Hz). Additionally, carbons C-4 and C-3 appeared both as triplets at 41.4 and 158.4 ppm,

**Table 2**. Products of nitrosation of cyclopropane **1b** with $NOBF_4$ in $MeNO_2$ as a function of the reaction duration, temperature, and concentration of **1b**.



**1b** **2b** **3b** **4b**

| entry | [**1**], mol/l | $NOBF_4$, eq | T, ºC | T, h | Reaction mixture content,[a] % | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | **1b** (*Z/E*) | **2b** | **3b** | **4b** | Degrad. products |
| 1 | 0.3 | 1.1 | 0-20 | 3 | 58 (1.6:1.4) | 23 | 3 | - | 16 |
| 2 | 0.3 | 1.1 | 0-20 | 24 | - | 20 | - | 5 | 75 |
| 3 | 0.1 | 1.2 | 0-5 | 5 | 50 (1.4 : 1) | 30 | - | - | 20 |
| 4 | 0.06 | 1.1 | 20 | 24 | - | 35 | 20 | 10 | 35 |
| 5 | 0.02 | 3 | 20 | 3 | 53 (3 : 1) | 27 | 10 | 5 | 5 |
| 6 | 0.01 | 2 | 20 | 48 | 48 (2 : 1) | 34 | 12 | 6 | - |
| 7 | 0.01 | 4 | 20 | 70 | - | 25 | - | 13 | 62 |

[a]Crude reaction mixture products percentage ratio based on $^1H$ NMR

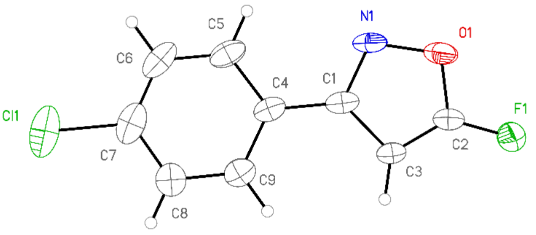


**Figure 1**. ORTEP drawing of one of the two independent molecules of **4b** in the unit cell. Thermal ellipsoids are shown for ρ = 50%.

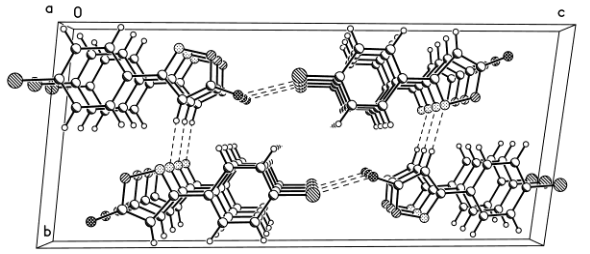
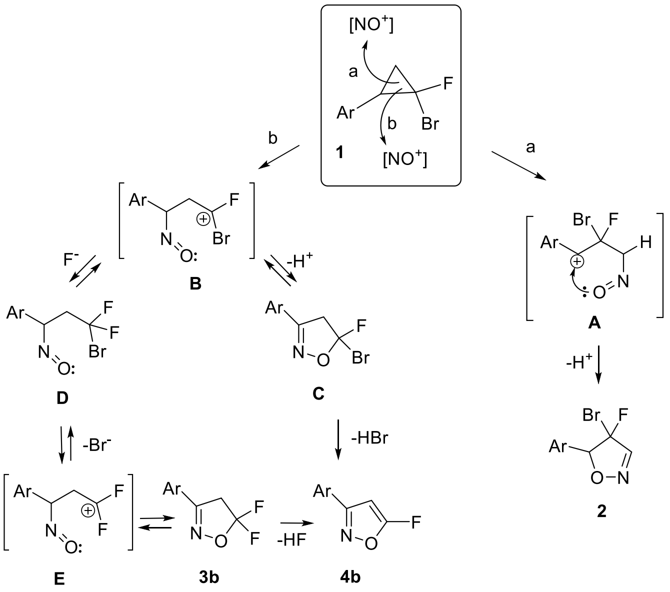


**Figure 2**. Crystal packing of **4b**. Dashed lines show the strongest C-H…N contacts and the halogen bonds Cl…F.

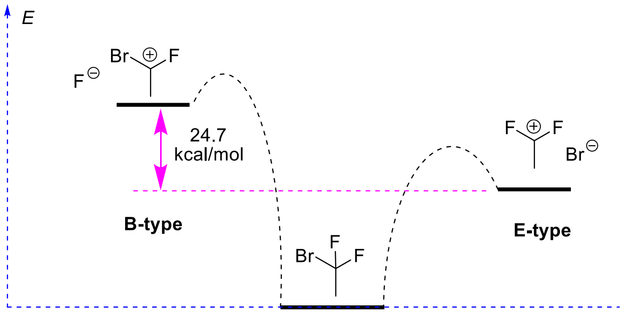
with smaller two- and three-bond couplings, $^2J_{C\text{-}F}$ = 31.7 Hz and $^3J_{C\text{-}F}$ = 2.8 Hz, respectively. The cluster of the molecular ion of **3b** in the mass-chromatogram was presented by two peaks at 217 (100) and 219 (33). The main mode of **3b** fragmentation was the loss of $CH_2$=$CF_2$ fragment. Finally, along with **3b** negligible amounts of 5-fluoroisoxazole **4b** were detected which structure was unambiguously established by X-ray single crystal diffractometry (see Figs. 1, 2).

Experimental observations suggested the following mechanistic rationale for the overall processes shown in Scheme 2. Nitrosonium attack at the methylene group of bromofluorocyclopropane **1** cleaves the C2-C3 bond furnishing benzylic cation **A** (path *a,* the main). Subsequent heterocyclization leads directly to isoxazolines **2**.[8] One more reaction pathway is realized in parallel with path *a* at lower initial concentrations of **1b** ([C$_o$] = 0.01-0.06 mol/L). In these cases the attack of nitrosonium cation is directed also at the benzylic position followed by the C1-C2 bond cleavage to form a competing halogen-stabilized cation **B** (path *b*, the minor one).



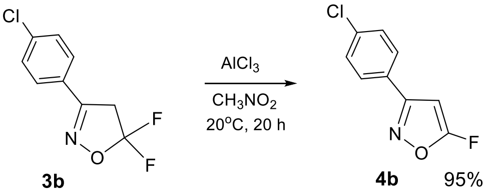
**Scheme 2.** Mechanistic rationale for the main reaction paths in nitrosation of cyclopropanes **1**.

Halogen exchange, as evidenced by the formation of difluoroisoxazoline **3b**, could conceivably be initiated by the fluoride anion captured by cation **B** followed by the loss of the bromide anion to yield **E**.[9] Judging by our PCM (nitromethane) computations at the B3LYP/6-311+G(d,p) level (Scheme 3), ionization of 1-bromo-1,1-difluoroethane as a model compound for probable intermediate **D** produces two competing halogen-stabilized cations of **B**-type and **E**-type, with the latter being almost 25 kcal/mol more stabilized. Kinetically, the bromide departure from **D** to form **E** is also expected to be faster than the departure of the fluoride anion to revert to **B**.



**Scheme 3.** The energetics of ionization of 1-bromo-1,1-difluoroethane assessed at the B3LYP/6-311+G(d,p) level of theory with a PCM model (nitromethane).

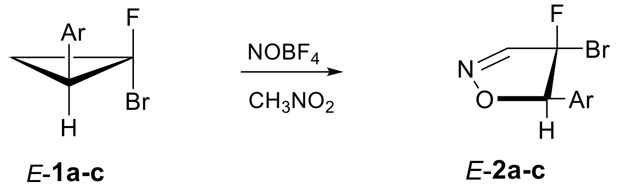
It is conceivable that the formation of 5-fluoroisoxazole **4b** also results from the nitrosation of cyclopropane **1b** at the benzylic position, scission of the C1-C2 bond, and subsequent heterocyclization and aromatization with elimination of HBr, as precedented in the case of nitrosation of dibromocyclopropane[10] and also was demonstrated by our recent results with bromofluorocyclopropanes.[1] However only small quantities of 5-fluoroisoxazole **4b** were observed regardless of the reaction conditions, implying that it is formed independently from the main reaction channel. Furthermore (Table 2), isoxazole **4b** is produced in smaller amounts than isoxazoline **3b**, except for the cases involving high concentration of the starting materials or the 4-fold excess of the nitrosating agent in conjunction with the extended reaction time (Table 2, entries 2 and 7, respectively). We hypothesize that isoxazole **4b** results from dehydrofluorination of isoxazoline **3b**. Experimentally, we confirmed that HF eliminates from **3b** on extended exposure to $AlCl_3$ (Scheme 4).



**Scheme 4.**

In a continued effort to improve the yields of isoxazolines **2** we studied the behavior of each individual cyclopropane diastereomer (*E* and *Z*) under nitrosation conditions. In the case of cyclopropane *Z*-**1b** we obtained ambiguous results using either $NOBF_4$ or $NaNO_2$/$CF_3COOH$ conditions. The reaction proceeded slowly (it takes 20-24 h for consumption of the initial) and produced complex mixture of degradation products and only traces of isoxazolines (<10%, *Z*-**2b** : *E*-**2b** = 1 : 1). On the contrary, the *E*-isomers of cyclopropanes **1a-c** reacted quickly and smoothly with either $NOBF_4$ or $NaNO_2/CF_3COOH$ system resulting in 100% conversion. The reactions proceeded with high regio- and diastereoselectivity leading exclusively to the corresponding 4-bromo-4-fluoroisoxazolines *E*-**2a-c** in good yields (50-73%), Table 3.

**Table 3.** Nitrosation of cyclopropanes *E*-**1a-c**



| Comp | Reagent | $NO^+$, eqv | Solvent | $[C_o]$, mol/L | τ, h | Product | Yield,% |
|---|---|---|---|---|---|---|---|
| ***E*-1a** | $NOBF_4$ | 1.1 | $MeNO_2$ | 0.10[a] | 3 | ***E*-2a** | 73 |
| ***E*-1b** | $NOBF_4$ | 1.1 | $MeNO_2$ | 0.06 | 8 | ***E*-2b** | 60 |
| ***E*-1b** | $NaNO_2$ | 3 | $Ac_fOH$/ $MeNO_2$ | 0.04 | 4 | ***E*-2b** | 60 |
| ***E*-1c** | $NOBF_4$ | 1.2 | $MeNO_2$ | 0.10 | 8 | ***E*-2c** | 50 |
| ***E*-1c** | $NaNO_2$ | 3 | $Ac_fOH$/ $MeNO_2$ | 0.04 | 4 | ***E*-2c** | 56 |

[a]Notice that *E*-**1a** (conc. $[C_o]$ = 0.01 mol/L) reacted with $NOBF_4$ to give the products of benzene ring nitration: *ortho*-nitro *E*-**1h** and *para* -nitro *E*-**1i** were formed in a ratio of ~1 : 1 respectively.

Elucidation of the structure and stereochemistry of isoxazolines **2** was guided by computations of $^1H$ and $^{13}C$ NMR chemical shifts with the recently developed hybrid DFT-parametric *DU8+* method.[10-13] As follows from Fig. 3, mapping the experimental $^{13}C$ NMR chemical shift values (blue) onto the ones calculated with *DU8+* (magenta) for *E*-isomers *E*-**2a-c** produced an excellent match, rmsd ≤ 1.2 ppm, over all 9 carbon atoms. For *Z*-isomers **2a-c,** the rmsd values degraded to > 2.7 ppm. The largest single discrepancy between the calculated and experimental values (i.e. > 7.5 ppm) was due to the carbon bearing the halogen atoms, i.e. C(4). This unambiguously establishes that the major stereoisomers in this reaction possess the *E*-configuration. The rationale of high diastereoselectivity in the nitrosation reaction of arylbromofluorocyclopropanes is under ongoing investigation.

Among the fluorine-containing compounds, isoxazolines and isoxazoles fluorinated at the heterocyclic ring are still underexplored. With isoxazolines **2** in hand, we examined the feasibility of employing these new fluorinated heterocycles as precursors for the synthesis of 4-fluoroisoxazoles. There are very few examples of the synthesis of 4-fluoroisoxazoles in the literature. The first 4-fluoroisoxazoles were synthesized by condensation of 2-fluoro-1,3-propanediones with hydroxylamine hydrochloride[14] or by direct electrophilic fluorination of isoxazole ring with Selectfluor.[15] The reactions were demonstrated on a scarce number of substrates and ensured moderate yields of 4-fluoroisoxazoles. Later, these methods were improved and are presented now by high yielding one-pot cascade fluorination-cyclization[16] or (in reversed order) the cyclization-fluorination processes.[17] The latter approach makes it possible to synthesize 3,5-diaryl-4-fluoroisoxazoles of non-symmetric structures. Another method for the synthesis of non-symmetric 3,5-diaryl-4-fluoroisoxazoles involves treatment of the corresponding arylated 4-fluoro-4-nitroisoxazolines with MeONa in MeOH.[18]

First, we tested several bases for dehydrobromination of **2**. However, the initial studies showed that traditional bases were not suitable in this case. Treating **2b** with $NEt_3$ at ambient temperature afforded starting material. Inducing dehydrobromination of **2b** under more extreme conditions (reflux with $NEt_3$ or treatment with *t*-BuOK/*t*-BuOH at 20 ºC) resulted in a considerable amount of degradation of the starting material: no discernible individual compounds were isolated from the resulting mixtures. It is a well-known fact that the isoxazole ring is vulnerable to nucleophilic ring opening. Often, it is the N-O bond of isoxazoles, which is cleaved in reactions by nucleophiles.[19] Finally we turned to silver nitrate, that is widely used as a promoter and catalyst in organic synthesis.[20] When **2a** was treated with 1 eq of $AgNO_3$ for half an hour in ethanol at ambient temperature, we managed to obtain 4-fluoroisoxazole **5a** as a sole product. However, incomplete conversion (30%) of the starting material was observed. To our delight, the use of 3 eq. of $AgNO_3$ in anhydrous ethanol at 60ºC, gave the desired result: 4-bromo-4-fluoroisoxazolines **2a-g,j** underwent dehydrobromination to afford 4-fluoroisoxazoles **5a-g,j** in good-to-excellent yields, see Table 4. We also found that mercury(I) nitrate, $Hg_2(NO_3)_2$ could be used in place of silver nitrate in these reactions, however this reagent was somewhat less effective.

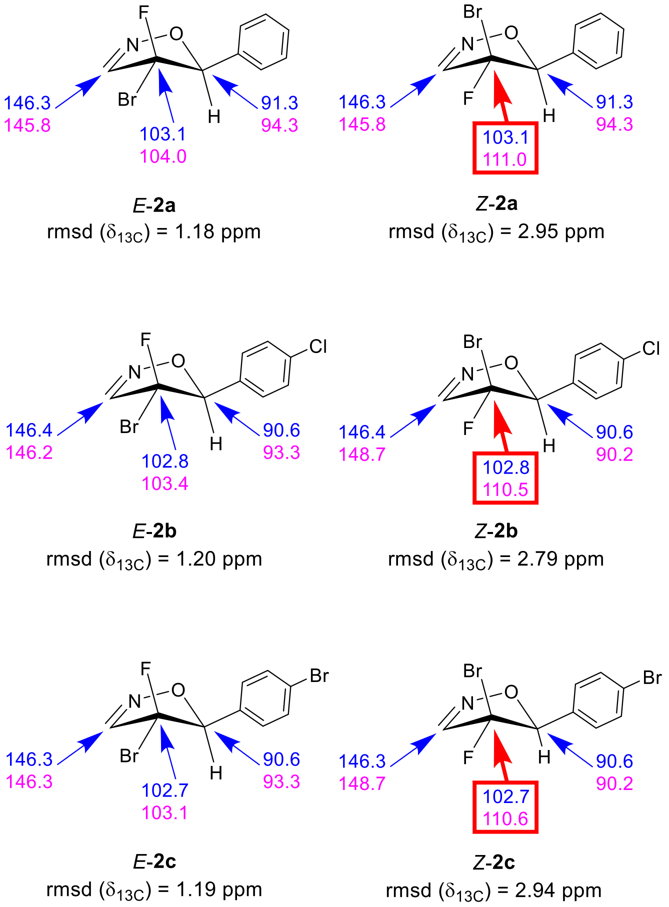
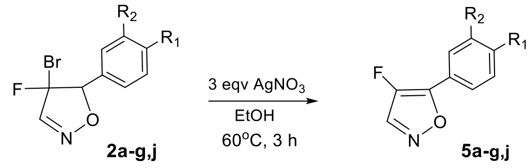


**Figure 3.** Experimental $^{13}C$ NMR chemical shifts (blue) for the major products **2a-c** are compared with the *DU8+* calculated values (magenta) for their respective *E*- and *Z*- isomers revealing a consistently better match (rmsd ≤ 1.2 ppm over 9 carbons) for the *E*-configuration. The largest deviation for the Z-series (>7.5 ppm) is localized at the C(4) carbon bearing the halogens

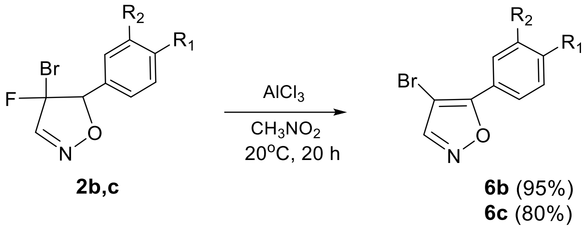
**Table 4**. Silver(I) nitrate assisted dehydrobromination of 4-bromo-4-fluoroisoxazolines **2a-g,j**



| entry | compound | R$_1$ | R$_2$ | product | Yield,% | m.p., ºC |
|---|---|---|---|---|---|---|
| 1 | **2a** | H | H | **5a** | 45 | 31 |
| 2 | **2b** | Cl | H | **5b** | 60 (64[a]) | 95-97 |
| 3 | **2c** | Br | H | **5c** | 82 | 92-93 |
| 4 | **2d** | F | H | **5d** | 76 | 78-80 |
| 5 | **2e** | Me | H | **5e** | 92 | 44-46 |
| 6 | **2f** | H | Me | **5f** | 75 | 35-36 |
| 7 | **2g**[b] | MeO | H | **5g** | 60 | 61-63 |
| 8 | **2j**[b] | MeO | Br | **5j** | 78 | 118-120 |

[a]The reaction was carried out at 20ºC for 20 h. [b]Isoxazolines **2g,j** were obtained via nitrosation of **1g** with nitrosonium chlorosulfate.

As mentioned above, we managed to eliminate hydrogen fluoride from isoxazoline **3b** by reacting it with AlCl$_3$. To probe if AlCl$_3$ is capable of eliminating HF from bromo-fluorides **2**, we subjected isoxazolines **2b,c** to similar reaction conditions, i.e. AlCl$_3$ in nitromethane (Scheme 5). To our satisfaction, isoxazolines **2b,c** were smoothly and selectively converted into the corresponding 5-aryl-4-bromoisoxazoles **6b,c**. These two last reactions nicely illustrate Pearson's hard and soft acid/base principle: silver nitrate as a soft Lewis acid coordinates to the bromine atom (soft base). In contrast, the hard Lewis acid, AlCl$_3$, reacts with the fluorine atom (hard base).



**Scheme 5.**

## 3. Conclusions

We investigated the reaction of aryl-bromofluorocyclopropanes with nitrosating reagents (NOBF$_4$ and NaNO$_2$/CF$_3$COOH) in nitromethane and demonstrated that the outcome of this process largely depends on the *E/Z*-configuration of the starting material. Having established that the *E*-isomers are considerably more reactive producing 5-aryl-4-bromo-4-fluoroisoxazolines of *E*-configuration in good yields, we developed this reaction into a new synthetic approach to 4-bromo-4-fluoroisoxazolines. We have also demonstrated that synthesized 5-aryl-4-bromo-4-fluoroisoxazolines can be smoothly dehydrohalogenated with Lewis acids in agreement with Pearson's concept. 5-Aryl-4-fluoroisoxazoles were obtained in good yields and high regioselectivity by reacting with soft Lewis acids: silver(I) or mercury(I) nitrates. On the contrary, the reaction of 5-aryl-4-bromo-4-fluoroisoxazolines with AlCl$_3$, a hard Lewis acid, afforded 5-aryl-4-bromoisoxazoles in good yields.

## 4. Experimental

The $^1$H, $^{13}$C, and $^{19}$F spectra of compounds in CDCl$_3$ were registered using Bruker Avance-400 and Agilent 400-MR spectrometers with working frequencies of 400.13, 100.67, and 376.29 MHz, respectively (internal standards were HMDS for $^1$H and $^{13}$C, and CFCl$_3$ for $^{19}$F). Chemical shifts were measured with an accuracy of 0.01 ppm, spin-spin coupling constants were measured with an accuracy of 0.1 Hz. Mass spectra were recorded using a Thermo Scientific TSQ 8000 gas chromatograph-mass spectrometer (capillary chromatographic column SPB™-5 (15 m x 0.25 mm), the gas carrier was helium, with a gas flow rate at 1 mL min$^{-1}$). The ionization method was electron impact (electron energy was 70 eV). Temperature conditions were 70 ºC (2 min), heating at a rate of 20 ºC min$^{-1}$ and maintained at 280 ºC (5 min). HRMS measurements were performed with an electrospray ionization (ESI) instrument using a time-of-flight (TOF) detector. The melting points of the obtained compounds were measured using a Mel-TempII instrument and were not corrected. The course of the reaction and the purity of the products were monitored by TLC on Silufol-UV plates ($\lambda$ = 240 cm$^{-1}$). The initial cyclopropanes were synthesized according to the known procedure.[21] The *anti*- and *syn*-diastereomers **1a-c** were separated by column chromatography on silica gel (40 x 100 mesh), eluent – light petroleum ether.

### *E-/Z*-2-aryl-1-bromo-1-fluorocyclopropanes

***E*-1-bromo-1-flouro-2-phenylcyclopropane** (*E*-**1a**) colorless liquid; $d_H$ (400 MHz, CDCl$_3$) 7.27-7.45 (5H, m, Ph), 2.81 (1H, ddd, $^3J_{HH}$ 8.4, $^3J_{HH}$ 11.0, $^3J_{HF}$ 2.4 Hz, CH), 1.92 (1H, dt, $J$ 8.4, $^3J_{HF}$ 17.2 Hz, CH$_2$), 1.85 (1H, ddd, $J$ 8.4, 9.0, 11.0 Hz, CH$_2$); $d_C$ (101 MHz, CDCl$_3$) 133.6 (C$_{Ph}$), 128.5 (2CH$_{Ph}$), 128.4 (2CH$_{Ph}$), 127.4 (CH$_{Ph}$), 80.5 (d, $^1J_{CF}$ 302.0 Hz, Br$\underline{C}$F), 33.3 (d, $^2J_{CF}$ 10.4 Hz, $\underline{C}$HPh), 22.7 (d, $^2J_{CF}$ 10.4 Hz, CH$_2$); $d_F$ (376 MHz, CDCl$_3$) -146.53 – -146.37 (1F, m).

***E*-1-bromo-2-(4-chlorophenyl)-1-fluorocyclopropane** (*E*-**1b**) colorless liquid; $d_H$ (400 MHz, CDCl$_3$) 7.33 (2H, d, $^3J$ 8.5 Hz, CH$_{Ar}$), 7.20 (2H, d, $^3J$ 8.5 Hz, CH$_{Ar}$), 2.76 (1H, ddd, $^3J_{HH}$ 8.7, 10.8, $^3J_{HF}$ 2.5 Hz, C$\underline{H}$Ar), 1.81-1.90 (2H, m, CH$_2$); $d_C$ (101 MHz, CDCl$_3$) 133.3 (C$_{Ar}$), 132.1 (C$_{Ar}$), 129.7 (2CH$_{Ar}$), 128.7 (2CH$_{Ar}$), 80.0 (d, $^1J_{CF}$ 302.0 Hz, Br$\underline{C}$F), 32.6 (d, $^2J_{CF}$ 10.4 Hz, $\underline{C}$HAr), 22.8 (d, $^2J_{CF}$ 10.4 Hz, CH$_2$); $d_F$ (376 MHz, CDCl$_3$) -146.47 – -146.39 (1F, ddd, $^3J_{HF}$ 2.5, 11.0, 15.4 Hz).

***Z*-1-bromo-2-(4-chlorophenyl)-1-fluorocyclopropane** (*Z*-**1b**) colorless liquid; $d_H$ (400 MHz, CDCl$_3$) 7.33 (2H, d, $^3J$ 8.4 Hz, CH$_{Ar}$), 7.15 (2H, d, $^3J$ 8.4 Hz, CH$_{Ar}$), 2.76 (1H, ddd, $^3J_{HF}$ 17.8, $^3J_{HH}$ 11.6, $^3J_{HH}$ 8.1 Hz, C$\underline{H}$Ar), 2.06 (1H, ddd, $^3J_{HF}$ 16.9, $^3J_{HH}$ 11.6, $^2J_{HH}$ 8.0 Hz, CH$_2$), 1.65 (1H, pseudo-q, $J$ 8.0 Hz, CH$_2$); $d_C$ (101 MHz, CDCl$_3$) 134.0 (C$_{Ar}$), 133.4 (C$_{Ar}$), 129.9 (2CH$_{Ar}$), 128.6 (2CH$_{Ar}$), 85.6 (d, $^1J_{CF}$ 302.0 Hz, Br$\underline{C}$F), 29.9 (d, $^2J_{CF}$ 11.2 Hz, $\underline{C}$HAr), 22.1 (d, $^2J_{CF}$ 11.2 Hz, CH$_2$); $d_F$ (376 MHz, CDCl$_3$) -125.45 (1F, pseudo-td, $^3J_{HF}$ 17.7, 6.8 Hz).

***E*-1-bromo-2-(4-bromophenyl)-1-fluorocyclopropane** (*E*-**1c**) colorless liquid; $d_H$ (400 MHz, CDCl$_3$) 7.47 (2H, d, $^3J$ 8.3 Hz, CH$_{Ar}$), 7.13 (2H, d, $^3J$ 8.3 Hz, CH$_{Ar}$), 2.73 (1H, pseudo-td, $J$ 10.0, $^3J_{HF}$ 2.0 Hz, C$\underline{H}$Ar), 1.81 - 1.90 (2H, m, CH$_2$); $d_C$ (101 MHz, CDCl$_3$) 132.6 (d, $^3J_{CF}$ 1.9 Hz, C(1)$_{Ar}$), 131.6 (2CH$_{Ar}$), 130.0 (d, $^4J_{CF}$ 1.5 Hz, 2CH$_{Ar}$), 121.3 (CBr), 79.8 (d, $^1J_{CF}$ 301.7 Hz, Br$\underline{C}$F), 32.6 (d, $^2J_{CF}$ 10.7 Hz, $\underline{C}$HAr), 22.8 (d, $^2J_{CF}$ 10.7 Hz, $\underline{C}$H$_2$); $d_F$ (376 MHz, CDCl$_3$) -146.45 – -146.33 (1F, ddd, $^3J_{HF}$ 2.0, 11.6, 15.0 Hz).

***E*-1-bromo-1-fluoro-2-(2-nitrophenyl)cyclopropane** (*E*-**1h**) colorless liquid; $d_H$ (400 MHz, CDCl$_3$) 8.02 (1H, dd, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.2 Hz, CH$_{Ar}$), 7.59 (1H, td, $^3J_{HH}$ 7.9, $^4J_{HH}$ 1.2 Hz, CH$_{Ar}$), 7.46 (1H, t, $^3J_{HH}$ 7.9 Hz, CH$_{Ar}$), 7.42 (1H, d, $^3J_{HH}$ 7.9 Hz, CH$_{Ar}$), 3.19 (1H, pseudo-t, $J$ 9.8 Hz, ArC$\underline{H}$), 1.88-1.95 (1H, m, CH$_2$), 1.83 (1H, pseudo-dt, $^3J_{HF}$ 17.6, $^3J_{HH}$ 8.6 Hz, CH$_2$); d$_F$ (376 MHz, CDCl$_3$) -143.64 (1F, ddd, $^3J_{HF}$ 2.0, 9.0, 17.6 Hz).

***E*-1-bromo-1-fluoro-2-(4-nitrophenyl)cyclopropane** (***E*-1i**) colorless liquid; d$_H$ (400 MHz, CDCl$_3$) 8.20 (2H, d, $^3J_{HH}$ 8.7 Hz, CH$_{Ar}$), 7.41 (2H, d, $^3J_{HH}$ 8.7 Hz, CH$_{Ar}$), 2.85 (1H, pseudo-td, $J$ 9.5, $^3J_{HF}$ 2.2 Hz, ArC$\underline{H}$), 1.96-2.05 (2H, m, CH$_2$).[22]

**General Procedure for Synthesis of Isoxazolines 2a-g.** To 1.1 mmole of NOBF$_4$ in 15 mL of nitromethane 1.0 mmole of 2-aryl-1-bromo-1-fluorocyclopropane **1** was added under stirring at 0ºC. The reaction mixture was brought to ambient temperature and stirring was continued until the disappearance of **1** (monitored by TLC). Reaction was quenched with saturated Na$_2$CO$_3$, the organic layer was separated, and the water layer was additionally shaked with dichloromethane (2 x 25 mL). Combined organic layers were dried over anhydrous Na$_2$SO$_4$, solvent was evaporated under reduced pressure and the residue was chromatographed on a slurry-packed Silica Gel column, EtOAc-petroleum ether, 1:20). Isoxazolines **2a-c** were described previously.[3]

***E*-4-Bromo-4-fluoro-5-(4-fluorophenyl)isoxazoline** (***E*-2d**) was obtained from 300 mg (1.29 mmol) of 1-bromo-1-flouro-2-(4-fluorophenyl)cyclopropane **1d** as light-yellow oil (135 mg, 40%). d$_H$ (400 MHz, CDCl$_3$) 7.70 (1H, s, HC=N), 7.40 (2H, dd, $^3J_{HH}$ 8.5, $J_{HF}$ 5.3 Hz, CH$_{Ar}$), 7.13 (2H, pseudo-t, $J$ 8.5 Hz, CH$_{Ar}$), 5.74 (1H, d, $^3J_{HF}$ 22.7 Hz, HC-O); d$_C$ (101 MHz, CDCl$_3$) 163.6 (d, $^1J_{CF}$ 249.0 Hz, C$_{Ar}$F), 146.4 (d, $^2J_{CF}$ 22.5 Hz, HC=N), 129.6 (d, $^3J_{CF}$ 8.8 Hz, 2CH$_{Ar}$), 124.8 (dd, $J_{CF}$ 5.2, $J_{CF}$ 3.6 Hz, C(1)$_{Ar}$), 115.9 (d, $^2J_{CF}$ 21.7 Hz, 2CH$_{Ar}$), 102.8 (d, $^1J_{CF}$ 272.2 Hz, BrCF), 90.7 (d, $^2J_{CF}$ 19.3 Hz, HC$_{is}$-O); d$_F$ (376 MHz, CDCl$_3$) -103.2 (1F, d, $^3J_{HF}$ 22.7 Hz, C(4)$_{is}$F), -111.2 (1F, pseudo-tt, $J_{HF}$ 8.5, 5.3 Hz, C$_{Ar}$F); GC-MS (EI, 70 eV): $m/z$ ($I_{rel}$, %): cluster 261 (25), 263 (23) [$M$]$^+$; cluster 218 (37), 220 (36) [$M$-HCNO]$^+$; 182 (32) [$M$-Br]$^+$; 165 (30) [$M$-Br-OH]$^+$; 155 (32) [$M$-Br-HCN]$^+$; 151 (70) [$M$-Br-HNO]$^+$; 127 (100) [FC$_6$H$_4$CHF]$^+$; 123 (65) [FC$_6$H$_4$C=O]$^+$; 108 (50) [C$_6$H$_4$CHF]$^+$; 95 (48) [FC$_6$H$_4$]$^+$; 75 (25). Anal. Calcd (%) for C$_9$H$_6$BrF$_2$NO: C 41.25, H 2.31, N 5.35, found: C 41.11, H 2.15, N 5.43.

***E*-4-Bromo-4-fluoro-5-(4-methylphenyl)isoxazoline** (***E*-2e**) was obtained from 480 mg (2.10 mmol) of 1-bromo-1-flouro-2-(4-methylphenyl)cyclopropane **1e** as light-yellow oil (205 mg, 38%). d$_H$ (400 MHz, CDCl$_3$) 7.69 (1H, s, HC=N), 7.32 (2H, d, $^3J$ 7.9 Hz, CH$_{Ar}$), 7.26 (2H, d, $^3J$ 7.9 Hz, CH$_{Ar}$), 5.75 (1H, d, $^3J_{HF}$ 22.7 Hz, HC-O), 2.40 (3H, s, CH$_3$); d$_C$ (101 MHz, CDCl$_3$) 146.4 (d, $^2J_{CF}$ 22.5 Hz, HC=N), 139.9 (C$_{Ar}$Me), 129.5 (2CH$_{Ar}$), 127.7 (2CH$_{Ar}$), 126.0 (d, $^3J_{CF}$ 5.6 Hz, C(1)$_{Ar}$), 103.1 (d, $^1J_{CF}$ 271.4 Hz, BrCF), 91.3 (d, $^2J_{CF}$ 19.3 Hz, HC$_{is}$-O), 21.4 (CH$_3$); d$_F$ (376 MHz, CDCl$_3$) -103.0 (1F, d, $^3J_{HF}$ 22.7 Hz, C(4)$_{is}$F). HRMS (ESI): $m/z$ calcd for C$_{10}$H$_9$BrFNO+H$^+$: 257.9924, 259.9904 [$M$+H]$^+$, found: 257.9919, 259.9900.

***E*-4-Bromo-4-fluoro-5-(3-methylphenyl)isoxazoline** (***E*-2f**) was obtained from 1192 mg (5.20 mmol) of 1-bromo-1-flouro-2-(3-methylphenyl)cyclopropane **1f** as light-yellow oil (509 mg, 35%).

d$_H$ (400 MHz, CDCl$_3$) 7.69 (1H, s, HC=N), 7.34 (1H, t, $^3J$ 8.1 Hz, CH$_{Ar}$), 7.21-7.26 (3H, m, CH$_{Ar}$), 5.77 (1H, d, $^3J_{HF}$ 21.8 Hz, HC-O), 2.41 (3H, s, CH$_3$); d$_C$ (101 MHz, CDCl$_3$) 146.3 (d, $^2J_{CF}$ 24.9 Hz, HC=N), 138.6 (C$_{Ar}$Me), 130.6 (CH$_{Ar}$), 129.1 (d, $^3J_{CF}$ 4.8 Hz, C(1)$_{Ar}$), 128.6 (CH$_{Ar}$), 128.2 (CH$_{Ar}$), 124.8 (CH$_{Ar}$), 103.2 (d, $^1J_{CF}$ 272.2 Hz, BrCF), 91.3 (d, $^2J_{CF}$ 20.1 Hz, HC$_{is}$-O), 21.4 (CH$_3$); d$_F$ (376 MHz, CDCl$_3$) -103.2 (1F, d, $^3J_{HF}$ 21.8 Hz, C(4)$_{is}$F); GC-MS (EI, 70eV): $m/z$ ($I_{rel}$, %): cluster 257 (44), 259 (39) [$M^+$]; cluster 214 (27), 216 (27) [$M$ -HCNO]$^+$; 178 (100) [$M$ -Br]$^+$; 161 (82) [$M$ -Br-OH]$^+$; 151 (44) [$M$ -Br-HCN]$^+$; 135 (20) [$M$ -Br-HCNO]$^+$; 133 (50); 123 (84) [MeC$_6$H$_4$CHF]$^+$; 119 (66) [MeC$_6$H$_4$C=O]$^+$; 91 (67) [MeC$_6$H$_4$]$^+$. Anal. Calcd for C$_{10}$H$_9$BrFNO: C 46.54, H 3.51, N 5.43, found: C 46.62, H 3.64, N 5.50.

***E*-4-Bromo-4-fluoro-5-(4-methoxyphenyl)isoxazoline** (***E*-2g**) was obtained from 450 mg (1.83 mmol) of 1-bromo-1-flouro-2-(4-methoxylphenyl)cyclopropane **1g** as light-yellow oil (35 mg, 7%). d$_H$ (400 MHz, CDCl$_3$) 7.70 (1H, s, HC=N), 7.33 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 6.96 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 5.71 (1H, d, $^3J_{HF}$ 23.4 Hz, HC-O), 3.83 (3H, s, OMe); d$_C$ (101 MHz, CDCl$_3$) 160.8 ($\underline{C}_{Ar}$OMe), 146.5 (d, $^2J_{CF}$ 23.3 Hz, HC=N), 129.3 (2CH$_{Ar}$), 120.8 (d, $^3J_{CF}$ 5.6 Hz, C(1)$_{Ar}$), 114.2 (2CH$_{Ar}$), 103.0 (d, $^1J_{CF}$ 270.6 Hz, BrCF), 91.3 (d, $^2J_{CF}$ 19.3 Hz, HC$_{is}$-O), 55.3 (MeO); d$_F$ (376 MHz, CDCl$_3$) -103.0 (1F, d, $^3J_{HF}$ 23.4 Hz, C(4)$_{is}$F); GC-MS (EI, 70 eV): $m/z$ ($I_{rel}$, %): cluster 273 (39), 275 (37) [$M^+$]; cluster 230 (41), 232 (41) [$M$ -HCNO]$^+$; cluster 215 (14), 217 (15) [$M$ -HCNO-Me]$^+$; 177 (28) [$M$ -Br-OH]$^+$; 167 (69) [$M$ -Br-HCN]$^+$; 139 (100) [MeOC$_6$H$_4$CHF]$^+$; 137 (38); 136 (92); 135 (65) [MeOC$_6$H$_4$C=O]$^+$; 107 (25) [MeOC$_6$H$_4$]$^+$. Anal. Calcd for C$_{10}$H$_9$BrFNO$_2$: C 43.82, H 3.31, N 5.11, found: C 43.86, H 3.51, N 4.79.

***Z*-4-Bromo-5-(4-chlorophenyl)-4-fluoroisoxazoline** (***Z*-2b**) characterized from mixture with ***E*-2b**. d$_H$ (400 MHz, CDCl$_3$) 7.73 (1H, s, HC=N), 7.45 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 7.32 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 5.53 (1H, d, $^3J_{HF}$ 26.9 Hz, HCO). GC-MS (EI, 70 eV): $m/z$ ($I_{rel}$, %): cluster 277 (8), 279 (11), 281 (3) [M$^+$]; cluster 234 (12), 236 (15), 238 (4) [M$^+$ − HCNO]; cluster 198 (12), 200 (4) [M$^+$ − Br]; cluster 171 (20), 173 (7) [M$^+$ − Br − HCN]; cluster 143 (100), 145 (32) [ClC$_6$H$_4$CHF]$^+$; cluster 139 (90), 141 (30) [ClC$_6$H$_4$CO]$^+$; cluster 111 (70), 113 (23) [ClC$_6$H$_4$]$^+$; 75 (85), 50 (75).

**3-(4-Chlorophenyl)-5,5-difluoroisoxazoline** (**3b**) yellowish liquid; d$_H$ (400 MHz, CDCl$_3$) 7.57 (2H, d, $^3J$ 8.5 Hz, CH$_{Ar}$), 7.44 (2H, d, $^3J$ 8.5 Hz, CH$_{Ar}$), 3.75 (2H, t, $^3J_{HF}$ 14.3 Hz, CH$_2$); d$_C$ (101 MHz, CDCl$_3$) 158.4 (t, $^3J_{CF}$ 3.2 Hz, C=N), 137.9 (CCl), 133.1 (t, $^1J_{CF}$ 265.0 Hz, O-CF$_2$), 129.5 (2CH$_{Ar}$), 127.8 (2CH$_{Ar}$), 126.0 (C(1)$_{Ar}$), 41.4 (t, $^2J_{CF}$ 31.7 Hz, CH$_2$); d$_F$ (376 MHz, CDCl$_3$) -67.8 (2F, t, $^3J_{HF}$ 14.3 Hz, CF$_2$); GC-MS (EI, 70 eV) $m/z$ ($I_{rel}$, %): cluster 217 (100), 219 (32) [$M^+$]; cluster 197 (3), 199(1) [$M$ -HF]$^+$; cluster 187 (5), 189 (1.7) [$M$ -NO]$^+$; cluster 169 (10), 171 (3) [$M$ -HF-CO]$^+$; cluster 153 (42), 155 (12) [$M$ - CH$_2$CF$_2$]$^+$; cluster 125 (17), 127 (5); cluster 111 (25), 113 (8) [ClC$_6$H$_4$]$^+$; 90 (25); 75 (30)

**3-(4-Chlorophenyl)-5-fluoroisoxazole** (**4b**), colorless crystals. m.p. 62-64ºC; d$_H$ (400 MHz, CDCl$_3$) 7.71 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 7.47 (2H, d, $^3J$ 8.7 Hz, CH$_{Ar}$), 5.87 (1H, d, $^3J_{HF}$ 7.5 Hz, C(4)$_{is}$H); d$_C$ (101 MHz, CDCl$_3$) 170.1 (d, $^1J_{CF}$ 295.7 Hz, =CFO), 164.1 (d, $^3J_{CF}$ 5.9 Hz, C=N), 136.8 (CCl), 129.3 (2CH$_{Ar}$), 127.7 (2CH$_{Ar}$), 127.1 (C$_{Ar}$), 77.5 (d, $^2J_{CF}$ 17.6 Hz, C(4)$_{is}$H); d$_F$ (376 MHz, CDCl$_3$) -103.1 (1F, d, $^3J$ 7.5 Hz, OCF); GC-MS (EI, 70 eV) $m/z$ ($I_{rel}$, %): cluster 197 (7), 199 (2) [$M^+$]; cluster 169 (42), 171 (14) [$M$ -CO]$^+$; cluster 142 (78), 144 (23) [$M$ -CO-HCN]$^+$ = [ClC$_6$H$_4$CF]$^+$; 134 (40) [$M$ -CO-Cl]$^+$, cluster 111 (9), 113 (3) [C$_6$H$_4$Cl]$^+$; 107 (100) [C$_6$H$_4$CF]$^+$; 102 (8) [C$_6$H$_4$CN]$^+$; 75 (23) [C$_6$H$_3$]$^+$; 50 (8). HRMS (ESI) $m/z$ calcd for C$_9$H$_5$ClFNO+H$^+$: 198.0116, 200.0087 [M+H]$^+$, found: 198.0114, 200.0082. The structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC), deposition number 1893335.

**General Procedure for Synthesis of 3-Aryl-4-fluoroisoxazoles 5a-g,j.** Isoxazoline **2** (1 eq) was dissolved in 5 ml of absolute ethanol. Then AgNO$_3$ (3 eq) was added to the solution. The mixture was heated in a water bath (60ºC) for 3 h. After completion of the reaction (TLC control), the precipitate ($AgBr$, $Ag$ and $AgNO_3$) was filtered off, the mother liquor was evaporated and the crude product was purified by recrystallization from ethanol.

**4-Fluoro-5-phenylisoxazole** (**5a**) was obtained from 103 mg (0.49 mmol) of 4-bromo-4-fluoro-5-phenylisoxazoline **2a** as light-yellow solid (32 mg 45%). m.p. 31ºC. $d_H$ (400 MHz, $CDCl_3$) 8.38 (1H, d, $^3J_{HF}$ 4.2 Hz, HC=N), 7.83 (2H, d, $^3J$ 7.7 Hz, $CH_{Ar}$), 7.43-7.52 (3H, m, $CH_{Ar}$); $d_C$ (101 MHz, $CDCl_3$) 152.6 (d, $^2J_{CF}$ 17.7 Hz, C-O), 143.1 (d, $^2J_{CF}$ 17.7 Hz, HC=N), 142.7 (d, $^1J_{CF}$ 256.2 Hz, $C(4)_{is}F$), 130.2 ($CH_{Ar}$), 129.1 ($2CH_{Ar}$), 125.6 (d, $^3J_{CF}$ 4.8 Hz, $C(1)_{Ar}$), 125.3 (d, $^4J_{CF}$ 4.8 Hz, $2CH_{Ar}$); $d_F$ (376 MHz, $CDCl_3$) -179.7 (1F, d, $^3J_{HF}$ 4.2 Hz, $C(4)_{is}F$); GC-MS (EI, 70 eV): *m/z* ($I_{rel}$, %): 163 (41) [$M^+$]; 108 (27) $[PhCF]^+$; 105 (65) $[PhC{=}O]^+$; 77 (100) [$Ph^+$]. HRMS (ESI) calcd for $C_9H_6FNO+H^+$: 163.0428 $[M{+}H]^+$, found: 163.0431.

**5-(4-Chlorophenyl)-4-fluoroisoxazole** (**5b**) was obtained from 262 mg (0.94 mmol) of 4-bromo-5-(4-chlorophenyl)-4-fluoroisoxazoline **2b** as light-yellow solid (110 mg, 60%). m.p. 95-97ºC. $d_H$ (400 MHz, $CDCl_3$) 8.38 (1H, d, $^3J_{HF}$ 4.2 Hz, HC=N), 7.72 (2H, d, $^3J$ 8.6 Hz, $CH_{Ar}$), 7.45 (2H, d, $^3J$ 8.6 Hz, $CH_{Ar}$); $d_C$ (101 MHz, $CDCl_3$) 151.6 (d, $^2J_{CF}$ 17.7 Hz, C-O), 143.1 (d, $^2J_{CF}$ 16.9 Hz, HC=N), 142.8 (d, $^1J_{CF}$ 257.0 Hz, $C(4)_{is}F$), 136.2 (CCl), 129.4 ($2CH_{Ar}$), 126.5 (d, $^4J_{CF}$ 5.6 Hz, $2CH_{Ar}$), 124.0 (d, $^3J_{CF}$ 4.8 Hz, $C(1)_{Ar}$); $d_F$ (376 MHz, $CDCl_3$) -178.8 (1F, d, $^3J_{HF}$ 4.2 Hz, $C(4)_{is}F$); GC-MS (EI, 70 eV): m/z ($I_{rel}$, %): cluster 197 (70), 199 (23) [$M^+$]; cluster 139 (100), 141 (33) $[ClC_6H_4C{=}O]^+$; 134 (39) $[M\text{-}Cl\text{-}CO]^+$; cluster 111 (55), 113 (18) $[ClC_6H_4]^+$; 107 (15); 75 (28) $[C_6H_3]^+$. HRMS (ESI) calcd for $C_9H_5ClFNO+H^+$: 198.0116 $[M{+}H]^+$, found: 198.0114.

**5-(4-Bromophenyl)-4-fluoroisoxazole** (**5c**) was obtained from 223 mg (0.71 mmol) of 4-bromo-5-(4-bromophenyl)-4-fluoroisoxazoline **2c** as light-yellow solid (142 mg, 82%). m.p. 92-93ºC. $d_H$ (400 MHz, $CDCl_3$) 8.38 (1H, d, $^3J_{HF}$ 4.2 Hz, HC=N), 7.66 (2H, d, $^3J$ 8.5 Hz, $CH_{Ar}$), 7.62 (2H, d, $^3J$ 8.5 Hz, $CH_{Ar}$); $d_C$ (101 MHz, $CDCl_3$) 151.7 (d, $^2J_{CF}$ 18.5 Hz, C-O), 143.2 (d, $^2J_{CF}$ 16.9 Hz, HC=N), 142.8 (d, $^1J_{CF}$ 257.8 Hz, $C(4)_{is}F$), 132.4 ($2CH_{Ar}$), 126.7 (d, $^4J_{CF}$ 4.8 Hz, $2CH_{Ar}$), 124.6 (CBr), 124.4 (d, $^3J_{CF}$ 5.6 Hz, $C(1)_{Ar}$); $d_F$ (376 MHz, $CDCl_3$) -178.6 (1F, d, $^3J_{HF}$ 3.4 Hz, $C(4)_{is}F$); GC-MS (EI, 70 eV): *m/z* ($I_{rel}$, %): cluster 241 (96), 243 (88) [$M^+$]; cluster 183 (100), 185 (98) $[BrC_6H_4CO]^+$; 155 (62), 157 (57) $[BrC_6H_4^+]$; 134 ((88) $[M\text{-}Br\text{-}CO]^+$; 107 (36); 76 (41); 75 (41). Anal. Calcd for $C_9H_5BrFNO$: C 44.66, H 2.08, N 5.79, found: C 44.57, H 2.08, N 5.85.

**4-Fluoro-5-(4-fluorophenyl)isoxazole** (**5d**) was obtained from 150 mg (0.64 mmol) of 4-bromo-4-fluoro-5-(4-fluorophenyl)isoxazoline **2d** as light-yellow solid (73 mg, 76%). m.p. 78-80ºC. $d_H$ (400 MHz, $CDCl_3$) 8.38 (1H, d, $^3J_{HF}$ 4.3 Hz, HC=N), 7.83 (2H, dd, $^3J_{HH}$ 8.9, $^3J_{HF}$ 5.1 Hz, $CH_{Ar}$), 7.21 (2H, pseudo-t, $J$ 8.6 Hz, $CH_{Ar}$); $d_C$ (101 MHz, $CDCl_3$) 163.5 (dd, $^1J_{CF}$ 251.5 Hz, $J_{CF}$ 2.0 Hz, $C_{Ar}F$), 151.8 (d, $^2J_{CF}$ 17.5 Hz, C-O), 143.0 (d, $^2J_{CF}$ 17.5 Hz, HC=N), 142.3 (d, $^1J_{CF}$ 255.7 Hz, $C(4)_{is}F$), 127.4 (dd, $^3J_{CF}$ 8.6 Hz, $^4J_{CF}$ 4.7 Hz, $2CH_{Ar}$), 121.9 (dd, $^3J_{CF}$ 5.1, $^4J_{CF}$ 3.5 Hz, $C(1)_{Ar}$), 116.4 (d, $^2J_{CF}$ 22.2 Hz, $2CH_{Ar}$); $d_F$ (376 MHz, $CDCl_3$) -108.9 (1F, m, $C_{Ar}F$), -180.2 (d, $^3J_{HF}$ 3.8 Hz, 1F, $C(4)_{is}F$); GC-MS (EI, 70 eV): *m/z* ($I_{rel}$, %): 181 (1) [$M^+$]; 153 (50) $[M\text{-}CO]^+$; 126 (100) $[FC_6H_4CF]^+$; 125 (27); 107 (17) $[C_6H_4CF]^+$. Anal. Calcd for $C_9H_5F_2NO$: C 59.68, H 2.78, N 7.73, found: C 59.35, H 2.54, N 7.39.

**4-Fluoro-5-(4-methylphenyl)isoxazole** (**5e**) was obtained from 104 mg (0.40 mmol) of 4-bromo-4-fluoro-5-(4-methylphenyl)isoxazoline **2e** as light-yellow solid (65 mg, 92%), m.p. 44-46ºC. $d_H$ (400 MHz, $CDCl_3$) 8.43 (1H, d, $^3J_{HF}$ 4.2 Hz, HC=N), 7.70 (2H, d, $^3J$ 8.2 Hz, $CH_{Ar}$), 7.30 (2H, d, $^3J$ 8.2 Hz, $CH_{Ar}$), 2.41 (3H, s, Me); $d_C$ (101 MHz, $CDCl_3$) 153.4 (d, $^2J_{CF}$ 17.7 Hz, C-O), 143.3 (d, $^2J_{CF}$ 17.8 Hz, HC=N), 142.2 (d, $^1J_{CF}$ 254.7 Hz, $C(4)_{is}F$), 141.0 (CMe), 129.8 ($2CH_{Ar}$), 125.4 (d, $^4J_{CF}$ 4.8 Hz, $2CH_{Ar}$), 122.5 (d, $^3J_{CF}$ 4.8 Hz, $C(1)_{Ar}$), 21.6 (Me); $d_F$ (376 MHz, $CDCl_3$) -180.3 (1F, d, $^3J_{HF}$ 4.2 Hz, $C(4)_{is}F$). Anal. Calcd for $C_{10}H_8FNO$: C 67.79, H 4.55, N 7.91, found: C 67.34, H 4.10, N 7.93.

**4-Fluoro-5-(3-methylphenyl)isoxazole** (**5f**) was obtained from 141 mg (0.55 mmol) of 4-bromo-4-fluoro-5-(3-methylphenyl)isoxazoline **2f** as yellow solid (72 mg, 75%). m.p. 35-36ºC. $d_H$ (400 MHz, $CDCl_3$) 8.37 (1H, d, $^3J$ 4.2 Hz, HC=N), 7.64 (1H, s, $CH_{Ar}$), 7.63 (1H, d, $^3J$ 7.7 Hz, $CH_{Ar}$), 7.39 (1H, t, $^3J$ 7.7 Hz), 7.27 (1H, d, $^3J$ 7.7 Hz, $CH_{Ar}$), 2.43 (3H, s, Me); $d_C$ (101 MHz, $CDCl_3$) 153.4 (d, $^2J_{CF}$ 18.5 Hz, C-O), 143.3 (d, $^2J_{CF}$ 17.7 Hz, HC=N), 142.6 (d, $^1J_{CF}$ 256.2 Hz, $C(4)_{is}F$), 139.0 (CMe), 131.4 ($CH_{Ar}$), 129.0 ($CH_{Ar}$), 125.9 (d, $^4J_{CF}$ 4.8 Hz, $CH_{Ar}$), 125.1 (d, $^3J_{CF}$ 4.8 Hz, $C(1)_{Ar}$), 122.6 (d, $^4J_{CF}$ 4.8 Hz, $CH_{Ar}$), 21.4 (Me); $d_F$ (376 MHz, $CDCl_3$) -179.7 (1F, m, $C(4)_{is}F$); GC-MS (EI, 70 eV), *m/z* ($I_{rel}$, %): 177 (84) [$M^+$]; 148 (17); 119 (100) $[MeC_6H_4C{=}O]^+$; 91 (63) $[MeC_6H_4]^+$. Anal. calcd for $C_{10}H_8FNO$: C 67.79; H 4.55; N 7.91. found: C 67.57; H 4.53; N 7.91.

**4-Fluoro-5-(4-methoxyphenyl)isoxazole** (**5g**) was obtained from 90 mg (0.33 mmol) of 4-bromo-4-fluoro-5-(4-methoxyphenyl)isoxazoline **2g** as yellow solid (38 mg, 60%). m.p. 61-63ºC $d_H$ (400 MHz, $CDCl_3$) 8.34 (1H, d, $^3J$ 4.2 Hz, HC=N), 7.76 (2H, d, $^3J$ 8.9 Hz, $CH_{Ar}$), 7.02 (2H, d, $^3J$ 8.9 Hz, $CH_{Ar}$), 3.87 (3H, s, OMe); $d_C$ (101 MHz, $CDCl_3$) 161.0 (COMe), 152.8 (d, $^2J_{CF}$ 18.5 Hz, C-O), 142.9 (d, $^2J_{CF}$ 16.9 Hz, HC=N), 141.7 (d, $^1J_{CF}$ 253.8 Hz, $C(4)_{is}F$), 127.0 (d, $^4J_{CF}$ 4.8 Hz, $2CH_{Ar}$), 118.4 (d, $^3J_{CF}$ 5.6 Hz, $C(1)_{Ar}$), 114.5 ($2CH_{Ar}$), 55.4 (OMe); $d_F$ (376 MHz, $CDCl_3$) -181.8 (1F, d, $^3J_{HF}$ 4.2 Hz, $C(4)_{is}F$); GC-MS (EI, 70 eV): *m/z* ($I_{rel}$, %): 193 (65) [$M^+$], 178 (15) $[M\text{-}Me]^+$; 150 (28) $[M\text{-}Me\text{-}CO]^+$; 135 (100) $[MeOC_6H_4C{=}O]^+$; 107 (30) $[MeOC_6H_4]^+$; 92 (38) $[O\text{-}C_6H_4]^+$; 77 (30) [$Ph^+$]. HRMS (ESI) *m/z* calcd for $C_{10}H_8FNO_2+H^+$: 194.0612 $[M{+}H]^+$, found: 194.0613.

**5-(3-Bromo-4-methoxyphenyl)-4-fluoroisoxazole** (**5j**) was obtained from 54 mg (0.15 mmol) of 4-bromo-5-(3-bromo-4-methoxyphenyl)-4-fluoroisoxazoline **2j** as white solid (32 mg, 78%). m.p. 118-120ºC $d_H$ (400 MHz, $CDCl_3$) 8.37 (1H, d, $^3J_{HF}$ 4.2 Hz, HC=N), 8.02 (1H, d, $^4J$ 2.0 Hz, $CH_{Ar}$), 7.75 (1H, dd, $^3J$ 8.7, $^4J$ 2.0 Hz, $CH_{Ar}$), 7.02 (1H, d, $^3J$ 8.7 Hz, $CH_{Ar}$), 3.97 (3H, s, OMe); $d_C$ (101 MHz, $CDCl_3$) 157.2 (C-OMe), 151.4 (d, $^2J_{CF}$ 18.5 Hz, C-O), 143.0 (d, $^2J_{CF}$ 16.9 Hz, HC=N), 142.0 (d, $^1J_{CF}$ 256.2 Hz, $C(4)_{is}F$), 130.3 (d, $^4J_{CF}$ 4.8 Hz, $CH_{Ar}$), 125.9 (d, $^4J_{CF}$ 4.8 Hz, $CH_{Ar}$), 119.5 (d, $^3J_{CF}$ 5.6 Hz, $C(1)_{Ar}$), 112.5 (CBr), 112.1 ($CH_{Ar}$), 56.4 (OMe); $d_F$ (376 MHz, $CDCl_3$) -180.4 (1F, d, $^3J_{HF}$ 4.1 Hz, $C(4)_{is}F$); GC-MS (EI, 70 eV): *m/z* ($I_{rel}$, %): cluster 271 (75), 273 (76) [$M^+$]; cluster 256 (25), 258 (24) $[M\text{ - }Me]^+$; cluster 228 (22), 230 (22) $[M\text{-}Me\text{-}CO]^+$; cluster 213 (98), 215 (100) $[MeO(Br)C_6H_3C{=}O]^+$; cluster 185 (21), 187 (20) $[MeOC_6H_3Br]^+$; cluster 170 (32), 172 (31) $[OC_6H_3Br]^+$; 164 (28) $[M\text{-}Br\text{-}CO]^+$; cluster 155 (21), 157 (22) $[C_6H_4Br]^+$; cluster 142 (13), 144 (13); 137 (28); 121 (28); 119 (24); 107 (31); 94 (30); 76 (26); 75 (41); 74 (39); 63 (95). Anal. calcd for $C_{10}H_7BrFNO_2$: C 44.15, H 2.59, N 5.15, found: C 44.29, H 2.44, N 4.77.

**General Procedure for Dehydrofluorination of Isoxazolines (2b,c and 3b).** Isoxazoline (1 eq) was dissolved in nitromethane, conc. = 0.2 *M*. To this solution, 2 eq of $AlCl_3$ was added and the reaction mixture was stirred at 20ºC for 20h. After that, the reaction mixture was poured into water, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layers were dried over anhydrous $Na_2SO_4$ and the solvent was removed under reduced pressure. The collected residue was pure 5-aryl-4-bromoisoxazoles **6b,c** or 5-fluoroisoxazole **4b** in the case of initials **2b,c** and **3b**, respectively.

**4-Bromo-5-(4-chlorophenyl)isoxazole** (**6b**) was obtained from 20.0 mg (0.072 mmol) of 4-bromo-5-(4-chlorophenyl)-4-fluoroisoxazoline **2b** as light-yellow solid (17.5 mg, 95%). m.p. 90ºC. d$_H$ (400 MHz, CDCl$_3$) 8.30 (1H, s, HC=N), 7.99 (2H, d, $^3J$ 8.8 Hz, CH$_{Ar}$), 7.49 (2H, d, $^3J$ 8.8 Hz, CH$_{Ar}$); d$_C$ (101 MHz, CDCl$_3$) 163.4 (C-O), 153.2 (HC=N), 136.9 (CCl), 129.3 (2CH$_{Ar}$), 128.1 (2CH$_{Ar}$), 124.8 (C(1)$_{Ar}$), 88.9 (C(4)$_{is}$Br).

**4-Bromo-5-(4-bromophenyl)isoxazole** (**6c**) was obtained from 20.0 mg (0.062 mmol) of 4-bromo-5-(4-bromophenyl)-4-fluoroisoxazoline **2c** as light-yellow solid (15.0 mg, 80%). m.p. 115ºC. d$_H$ (400 MHz, CDCl$_3$) 8.30 (1H, s, HC=N), 7.92 (2H, d, $^3J$ 8.6 Hz, CH$_{Ar}$), 7.65 (2H, d, $^3J$ 8.6 Hz, CH$_{Ar}$); d$_C$ (101 MHz, CDCl$_3$) 163.4 (C-O), 153.2 (HC=N), 132.2 (2CH$_{Ar}$), 128.2 (2CH$_{Ar}$), 125.24 (CBr or C(1)$_{Ar}$), 125.19 (CBr or C(1)$_{Ar}$), 88.9 (C(4)$_{is}$Br).

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