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Lewis acid-mediated defluorinative [3+2] cycloaddition/aromatization cascade of 2,2-difluoroethanol systems with nitriles

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Abstract: The properties of C-F bonds, including high thermal and chemical stability, make derivatization of organic fluorine-containing compounds by the activation of the C-F bond and subsequent functionalization quite challenging. We herein report a Lewis acid-mediated defluorinative cycloaddition/aromatization cascade of 2,2-difluoroethanols with nitriles as a novel synthetic method for the preparation of 2,4,5-trisubstituted oxazoles. This reaction, which involves cleavage of two C-F bonds and the consecutive formation of C-O and C-N bonds in a one-pot fashion, features a broad substrate scope and moderate to high reaction yields. Mechanistic studies revealed that the reaction is initiated by the Lewis acid-mediated ring closure of the 2,2-difluoroethanol to produce the fluoroepoxide intermediate.

Keywords: Lewis acid; cascade; oxazoles; [3+2] cycloaddition; defluorination

Continued advances in the field of fluoroorganic chemistry are of great importance in both academia and industry. Compared to the large number of C-F bond-forming methodologies that have been developed,[1] C−F bond activation/functionalization protocols[2] that allow the preparation of partially fluorinated or nonfluorinated products from readily available perfluorinated parent compounds are less thoroughly explored, although this trend has begun to change. From the perspective of organic synthesis, selective derivatization of inert C-F bonds in molecules containing other labile functionalities is appealing and may allow the preparation of derivatives with new skeletons or increased structural complexity. In addition, fluorinated organic species can bioaccumulate in food chains and have health concerns[3] due to their high biopersistence resulting from the high bond dissociation energy (BDE) of C-F bonds.[4] All these factors have inspired chemists to develop versatile methods for the transformation of C-F bonds. In the past decade, the selective activation of benzylic and allylic C-F bonds[5] has emerged as a valuable synthetic strategy for the modification of fluorinated compounds. Benzylic and allylic C-F bonds are activated by the adjacent π systems, making their BDEs significantly lower than that of a nonactivated C(sp3)-F bond[4] and therefore making them more susceptible to cleavage. Therefore methodologies taking advantage of transition metals,[5a-b,6] strong main-group Lewis acids,[5d,7] fluorine-hydrogen bonding[2b,8] and organolithium agents[9] have also been developed. Gouverneur and Brown demonstrated, for the first time, that the palladium-catalyzed allylic alkylation of allylic fluorides occurred via C-F displacement.[5a] A short time later, Paquin et al. reported palladium-catalyzed allylic amination reactions of 3,3-difluoropropenes with amines via the activation of allylic C-F bonds,[10] which allowed the efficient synthesis of various β-aminofluoroalkenes (Scheme 1, eq 1). Synthesis of *gem*-difluoroalkenes via S_N2' reaction of organolithium reagents with α-(trifluoromethyl)styrene was reported by Bonnet-Delpon et al. in 1996. [9a] A modified process that utilized 1-trifluoromethylvinylsilane as a CF_2=C-CH_2^+ synthon in the synthesis of functionalized 1,1-difluoro-1-alkenes was subsequently disclosed by Ichikawa.[9b] Recently, analogous transformations via the S_N2' reaction of lithium amides or lithium thiolates with 3,3-difluoropropenes[9c-d] were presented by Paquin et al. (eq 2). The S_N2' reactions of allylic fluorides (vide supra) demonstrated that fluoride behaved as a leaving group. Main-group Lewis acids, including boron-based, aluminum-based

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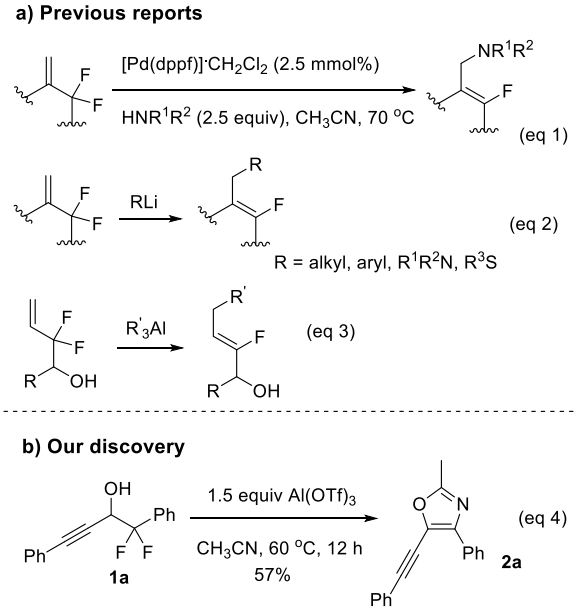
and silicon-based Lewis acids, exhibited high levels of fluorophilicity and could attract aliphatic fluorides. Taguchi and coworkers reported that the reaction of trialkylaluminum reagents with difluorohomoallyl alcohols readily gave (Z)-fluoro-olefins[7a] (eq 3). The presence of a hydroxyl group adjacent to the allylic gem-difluoromethylene moiety and excess trialkylaluminum (3.0 equiv) are essential for reactivity. In the course of our investigations into the synthesis of fluorinated compounds, we serendipitously found that the reaction of 2,2-difluoroethanol substrate **1a** with 1.5 equiv of $Al(OTf)_3$ in CH_3CN did not lead to the expected Meyer-Schuster rearrangement enone product[11] but instead afforded a substantial amount of oxazole **2a** (eq 4). **2a** is composed of 1 molecule of CH_3CN and 1 molecule of **1a** from which 2 molecules of HF have been eliminated. This result suggested that a C-F bond scissoring process was occurring. In this process, the 2,2-difluoroethanol moiety turned out to serve as a synthon for a O-C=C unit. Herein, we disclosed our preliminary investigations regarding the scope and limitations of the title reaction and provided mechanistic insights into the reaction pathway.



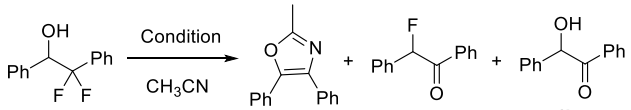
Scheme 1. C-F bond activation reactions.

Our study began by using **1b** as a model substrate because the reaction afforded the corresponding 4,5-diphenyloxazole, which is a common core structure in many bioactive drug molecules.[12] Anhydrous CH_3CN was employed both as the solvent and as a reagent. The efficiency of $Al(OTf)_3$ in the defluorinative cascade reaction of **1b** and CH_3CN was evaluated first. Entry 1 of Table 1 showed that when the reaction was carried out using 1.5 equiv of $Al(OTf)_3$, the anticipated oxazole **2b** was obtained in 65% yield, and compounds **3b** (7%) and **4b** (8%) were obtained as minor products. Further reduction of the loading of $Al(OTf)_3$ to 1.0 equiv and 0.5 equiv resulted in diminished conversions to **2b** (entries 2 and 3). Triflic acid has been reported to promote intra- and intermolecular arylations of trifluoromethylated arenes via C-F bond activation.[13] This inspired us to perform the reaction using 1.5 equiv of triflic acid. As shown in entry 4, triflic acid did not promote the desired reaction, indicating that the defluorinative process is promoted by the direct use of $Al(OTf)_3$ instead of triflic acid, even though triflic acid may be generated in situ via the hydrolysis of $Al(OTf)_3$. A systematic screening of Lewis acids was then carried out. These particular Lewis acids were chosen because they had previously been found to be suitable or potentially suitable for activating C-F bonds.[5d] The use of TiF_4 or $TiCl_4$ led to results comparable to that obtained with $Al(OTf)_3$ (entries 5-7). Changing the Lewis acid to $AlCl_3$ resulted in a dramatic improvement in the yield of **2b** (entry 8); however, an excess of $AlCl_3$ was required (entry 9). To our delight, the use of 1.5 equiv of $BF_3{\cdot}OEt_2$ gave **2b** in 81% yield (entry 10). The yield remained high even when one equivalent or a catalytic amount of $BF_3{\cdot}OEt_2$ was used (entries 11-13). The optimal result was achieved using 0.5 equiv of $BF_3{\cdot}OEt_2$ (entry 12). The reaction was found to be highly sensitive to water: only 32% of **2b** and significant amounts of **3b** and **4b** were obtained when using wet CH_3CN as the solvent (entry 14). Attempts to use other aluminum- and boron-based Lewis acids such as $AlBr_3$, $AlMe_3$, AlF_3, BCl_3 and $B(C_6F_5)_3$ were fruitless; in each case, **1b** was recovered intact or decomposed (entries 15-19). The effect of a strong base, NaH (entry 20),[14] was evaluated, but its use resulted in the recovery of **1b**. The reaction of **1b** with CH_3CN produced two equivalents of HF. Therefore, HF was examined to affect the cycloaddition reaction (entry 21). Compound **1b** in CH_3CN was treated with HF (2.0 equiv) at 45 °C. It was found to remain intact after 12 hours.

The scope of this reaction was then examined first under the optimal conditions (condition A). Derivatives **1b-p** were synthesized by varying the R^1 and R^2 functionalities attached to the difluoroethanol moiety. When R^1 was a methyl, *n*-butyl, phenylethynyl, (2-chlorophenyl)ethynyl or 2-furyl group and R^2 was a phenyl group, the yields were generally moderate to good, as exemplified by **2a** and **2c-f**. The lower yield in the case of **2f** could be attributed to the instability of the furan ring under acidic conditions. Notably, the reaction of a substrate bearing a sterically demanding 1-naphthyl moiety at

R^1 gave oxazole **2g** in good yield. When R^2 was a hydrogen and R^1 was a phenyl group with either electron-withdrawing or electron-donating substituents, the reaction proceeded smoothly to give **2h-k** in good yields regardless of the electronic demands of the phenyl group. However, when styryl- and 5-benzyl-2-furyl-substituted substrates were subjected to reaction condition A, short reaction times (*ca.* 10 mins) and trace amounts of products **2l** (13%) and **2m** (9%) were obtained. Tuning the reaction conditions for these two substrates showed that the use of 1.5 equiv of $Al(OTf)_3$ (condition B) provided greater yields of the desired oxazoles. When R^1 was 2-pyridyl, no reaction was observed conceivably because the nitrogen-based heteroaromatic group was not compatible with the Lewis acid catalyst. The identity of the nitrile was then varied to investigate the scope of the formation of 2-substituted oxazole. Initially, the effects of the solvent and the nitrile loading were briefly examined using **1b** and benzonitrile as model substrates (Supporting information, Table S1). CH_2Cl_2 was superior to other solvents, provided **5a** in 63% yield and was thus selected as the solvent of choice. THF, 1,4-dioxane and toluene were found to be unsuitable for this reaction due to reduced reaction rates and product yields. In addition, the amount of nitrile can be reduced to 1.5 equiv without a reduction in yield. The optimal conditions are delineated as condition C.

Table 1. Optimization of Reaction Conditions.[a]



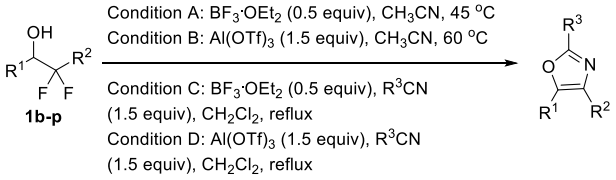
1b **2b** **3b** **4b**

Entry	Regent (equiv)	Temp [°C]	Time	Yield [%][b] 2b	3b	4b
1	$Al(OTf)_3$ (1.5)	60	8 h	65	7	8
2	$Al(OTf)_3$ (1.0)	60	18 h	49	6	7
3	$Al(OTf)_3$ (0.5)	60	30 h	29	8	9
4	TfOH (1.5)	60	20 h	NR		
5	TiF_4 (1.5)	60	12 h	59	8	7
6	TiF_4 (0.5)	60	20 h	37	6	8
7	$TiCl_4$ (1.5)	60	8 h	51	0	0
8	$AlCl_3$ (1.5)	60	8 h	84	5	5
9	$AlCl_3$ (0.5)	60	20 h	29	7	12
10	$BF_3{\cdot}OEt_2$ (1.5)	45	4 h	81	0	4
11	$BF_3{\cdot}OEt_2$ (1.0)	45	6 h	82	0	5
12	$BF_3{\cdot}OEt_2$ (0.5)	45	8 h	80	0	4
13	$BF_3{\cdot}OEt_2$ (0.25)	45	15 h	59	0	15
14[c]	$BF_3{\cdot}OEt_2$ (1.5)	45	8 h	32	5	33
15	$AlBr_3$ (1.5)	rt	3 h	Mess		
16	$AlMe_3$ (1.5)	0	3 h	Mess		
17	AlF_3 (1.5)	45	12 h	NR		
18	BCl_3 (1.5)	45	12 h	NR		
19	$B(C_6F_5)_3$ (1.5)	45	12 h	NR		
20	NaH (1.5)	rt	12 h	NR		
21	HF (2.0)	45	12 h	NR		

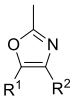
[a] All reactions (except entry 14) were performed under the standard reaction conditions: substrate **1a** (142 mg, 0.60 mmol) and anhydrous acetonitrile (2 mL).
[b] Isolated yields after silica gel chromatography.
[c] Commercial reagent-grade CH_3CN was used directly without predrying treatment.

Under these conditions, the reaction of **1b** with various nitriles gave rise to **5a-l**, which have aryl, alkyl and alkenyl substituents or linear alkyl chains with terminal cyano or chloro groups at C-2, in moderate to good yields (Table 2). Notably, oxazole **5h**, an intermediate in the synthesis of the NSAID drug oxaprozin,[12] was produced in 81% yield. Other structurally diverse difluoroethanol compounds were subjected to the reaction with different nitriles and provided the corresponding desired oxazoles **6a-f**, **7a-b**, **8a-b** and **9** in moderate to good yields.

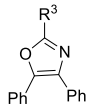
Table 2. Reaction Scope and Limitations.[a]



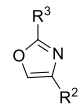
1b-p



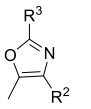
2a R^1 = phenylethynyl, R^2 = C_6H_5, 74%[b]
2c R^1 = CH_3, R^2 = C_6H_5, 77%[b]
2d R^1 = *n*-Bu, R^2 = C_6H_5, 82%[b]
2e R^1 = (2-chlorophenyl)ethynyl, R^2 = C_6H_5, 68%[b]
2f R^1 = 2-furyl, R^2 = C_6H_5, 41%[b]
2g R^1 = 1-hexyn-1-yl, R^2 = 1-naphthyl, 79%[b]
2h R^1 = H, R^2 = C_6H_5, 83%[b]
2i R^1 = H, R^2 = 4-$CO_2EtC_6H_4$, 73%[b]
2j R^1 = H, R^2 = 2-ClC_6H_4, 69%[b]
2k R^1 = H, R^2 = 4-$OMeC_6H_4$, 71%[b]
2l R^1 = H, R^2 = styryl, 83%[c]
2m R^1 = H, R^2 = 5-benzyl-2-furyl, 57%[c]
2n R^1 = C_6H_5, R^2 = 2-pyridyl, 0%[b,d]



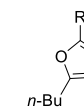
5a R^3 = C_6H_5, 63%[e]
5b R^3 = 4-FC_6H_4, 70%[e]
5c R^3 = 4-ClC_6H_4, 67%[e]
5d R^3 = 4-BrC_6H_4, 63%[e]
5e R^3 = 4-$OMeC_6H_4$, 77%[e]
5f R^3 = 2-$NO_2C_6H_4$, 46%[e]
5g R^3 = -$(CH_2)_4CN$, 71%[e]
5h R^3 = -$(CH_2)_2CO_2Me$, 81%[e]
5i R^3 = -$(CH_2)_2Cl$, 73%[e]
5j R^3 = 3-thienyl, 59%[e]
5k R^3 = *t*-Bu, 46%[e]
5l R^3 = prop-1-enyl, 53%[e]



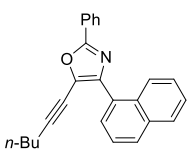
6a R^2 = C_6H_5, R^3 = C_6H_5, 76%[e]
6b R^2 = 4-$CO_2EtC_6H_4$, R^3 = 4-FC_6H_4, 74%[e]
6c R^2 = 4-$CO_2EtC_6H_4$, R^3 = -$(CH_2)_4CN$, 81%[e]
6d R^2 = 4-$CO_2EtC_6H_4$, R^3 = 3-thienyl, 71%[e]
6e R^2 = styryl, R^3 = C_6H_5, 51%[f]
6f R^2 = styryl, R^3 = -$(CH_2)_2Cl$, 53%[f]



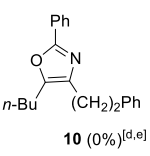
7a R^2 = C_6H_5, R^3 = C_6H_5, 83%[e]
7b R^2 = C_6H_5, R^3 = 4-$OMeC_6H_4$, 86%[e]



8a R^3 = -$(CH_2)_2CO_2Me$, 71%[e]
8b R^3 = C_6H_5, 64%[e]



9 (62%)[e]



10 (0%)[d,e]

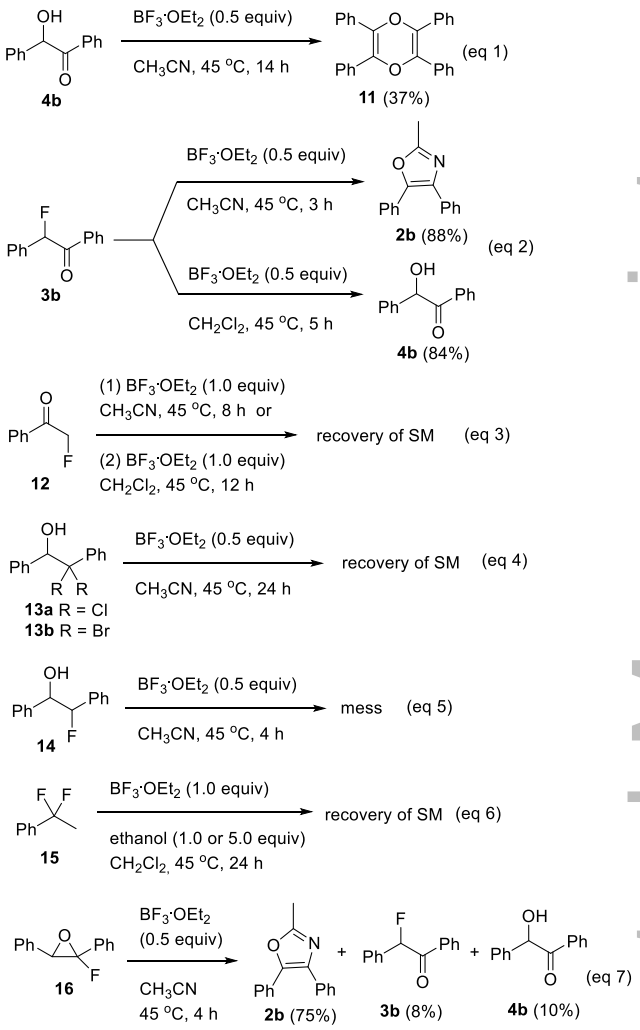
[a] Isolated yields after silica gel chromatography.
[b] The reactions were performed under condition A.
[c] The reactions were performed under condition B.
[d] Starting substrates were recovered intact.

[e] The reactions were performed under condition C.
[f] The reactions were performed under condition D.

Again, when R^2 is a styryl group (**6e** and **6f**), $Al(OTf)_3$ (condition D) was used instead of $BF_3{\cdot}OEt_2$ (condition C). The steric demands of R^3 had a substantial effect on the defluorinative reaction, as evidenced by the more moderate yields of **5f** and **5k**. In addition, the R^1 functionality had no significant influence on the reaction. The cascade reactions were highly regioselective since no possible regioisomers were obtained. At the outset of the current study, we envisioned that 2,2-difuoroethanol compounds with activated allylic or benzylic C-F bonds were required for the reaction; this assumption was verified by the fact that when R^2 was a saturated alkyl chain, the desired oxazole product **10** was not isolated, and the starting material was recovered intact.

To probe the possible intermediate, a brief ^{19}F NMR reaction monitoring study (Supporting information, Fig. S1) was carried out. Reactions with **1b** (1.0 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv) and anhydrous acetonitrile (6.0 equiv) were performed using $CDCl_3$ as the solvent in NMR tubes. Upon treatment with $BF_3{\cdot}OEt_2$, compound **1b** was readily converted to compound **3b** and fluoro derivatives with ^{19}F signals at δ = -117 and -150 ppm. Efforts to isolate these intermediates by column chromatography were unsuccessful. These fluoro intermediates were tentatively assigned as a mixture of *cis*- and *trans*-2-fluoro-2,3-diphenyloxiranes by comparison of their spectral features with those of authentic compounds.[15]

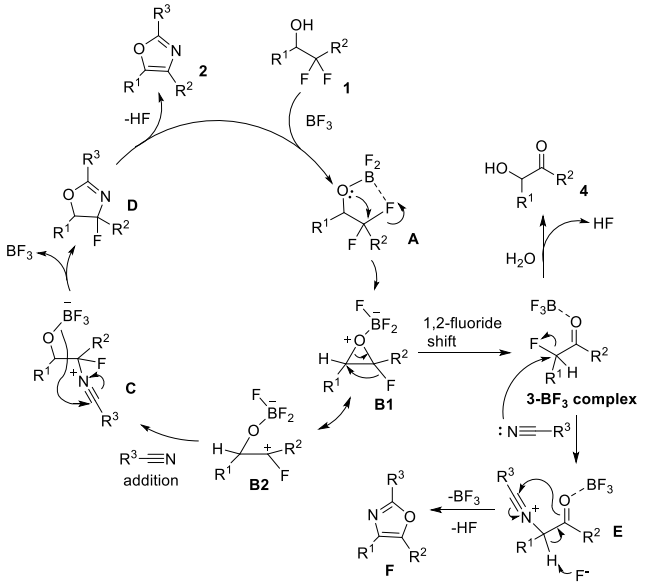
Following the NMR studies, control experiments were carried out to further elucidate the mechanistic pathway. As shown in eq 1 of Scheme 2, the reaction of **4b** with $BF_3{\cdot}OEt_2$ in CH_3CN produced bisdioxetanes **11**, which implied that formation of the oxazole product did not proceed via the known acid-promoted condensation of bezoin and acetonitrile.[16] **3b** was converted to **2b** by treatment with 0.5 equiv of $BF_3{\cdot}OEt_2$ in CH_3CN. When the solvent was changed from CH_3CN to CH_2Cl_2 with the same reactant and catalyst, the reaction produced **4b** in 84% yield (eq 2). However, the reaction of **12** with $BF_3{\cdot}OEt_2$ (1.0 equiv) did not proceed in either CH_3CN or CH_2Cl_2, and the starting materials were recovered intact (eq 3). For comparison, compounds **13a** and **13b**, the chlorinated and brominated analogs of **1b**, were subjected to the $BF_3{\cdot}OEt_2$-catalyzed conditions; both were recovered intact after 24 h (eq 4). Under similar conditions, the reaction of monofluorinated compound **14**[17] gave complex results (eq 5). When 1.0 equiv of $BF_3{\cdot}OEt_2$ was used, the defluorinative reactions of **15** with ethanol (1.0 equiv or 5.0 equiv) did not occur, implying that a hydroxyl group in close proximity is necessary for the activation of the difluoromethylene moiety. To confirm the fluoroepoxide intermediate, *trans*-2-fluoro-2,3-diphenyloxirane **16**,[15] was subjected to the $BF_3{\cdot}OEt_2$-catalyzed conditions. The reaction successfully delivered **2b**, **3b** and **4b**, which provided solid support for our previous assignment.



Scheme 2. Investigations on the activation of the C-F bond.

Based on the above observations, a plausible reaction mechanism was proposed and outlined in Scheme 3 by using $BF_3{\cdot}OEt_2$ as specific Lewis acid. The reaction of compound **1** with $BF_3{\cdot}OEt_2$ results in the formation of difluoroalkoxyborane **A**, which can undergo ring formation to afford BF_3-expoxide complex **B1**. The epoxide ring closure is believed to proceed via a five-membered ring transition state in which intramolecular coordination of the fluorine atom to a boron center facilitates the C-F bond cleavage. Heterolytic C-O bond cleavage of **B1** preferably produces the more stable dipolar intermediate **B2** which is stabilized by the adjacent π system and α-fluorine atom.[18] The nucleophilic

addition of the nitrile group to the carbocationic center of **B2** affords **C**, which could then undergo C-C bond rotation and intramolecular cyclization to produce oxazoline **D**.[19] Finally, aromatization of oxazoline **D** to oxazole **2** would occur via the loss of HF. In addition, **B1** can undergo a 1,2-fluoride shift[20,21] and C=O bond formation to afford the **3**-BF_3 complex. The C-F bond of **3** can be activated by the coordination of a fluorine atom to the boron center of BF_3. Subsequent nucleophilic substitution of the α-fluorine atom of **3** for H_2O produces **4**. Although in our study the cascade reactions produce oxazole compounds with high regioselectivity, an analogous substitution of compound **3** with nitrile group give oxazole **E**, which in turn can undergo a cyclization process to generate **E** cannot be ruled out as the cause of the formation of 4,5-diphenyloxazole **5a-l**.



Scheme 3. Proposed reaction mechanism.

In conclusion, we have developed an unpresented Lewis acid-mediated defluorinative [3+2] annulation/aromatization cascade in which the 1,3-zwitterionic nature of the 2,2-difluoroethanol moiety was unveiled in situ by an appropriate Lewis acid, which allowed this moiety to function as a synthon for the O-C=C unit in the [3+2] cycloaddition. This transformation represented a rare case of sequential C-N and C-O bond formation via C-F bond breaking. We believe that this study is a valuable addition to the field of C-F bond activation.

Experimental Section

General procedure for the synthesis of oxazole compounds

The general procedure is illustrated immediately below with compound **2b** as a specific example. A solution of compound **1b** (142 mg, 0.60 mmol) and $BF_3{\cdot}OEt_2$ (43 mg, 0.30 mmol) in CH_3CN (2 mL) was heated at 45 °C under argon for 8 hours. Then water (2 mL) and saturated Na_2CO_3 solution (1 mL) was added to quench the reaction at 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (3x3 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silical gel with EtOAc/*n*-hexane (1:10) to afford compound **2b** (114 mg, 80% yield) as colorless oil and compound **4b** (5 mg, 4% yield) as white solid (mp = 132.0–134.0 °C).

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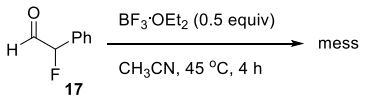
[21] Intermediate **B1** (R^1 = H and R^2 = phenyl) could also undergo a 1,2-hydride shift to provide 2-fluoro-2-phenylethanal **17**, which in turn underwent cycloaddition with CH_3CN to provide oxazole product. To verify the possibility, **17** was submitted to the $BF_3{\cdot}OEt_2$-catalyzed conditions. However, as shown below, the reaction gave messy results.



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Lewis acid-mediated defluorinative [3+2] cycloaddition/aromatization cascade of 2,2-difluoroethanol systems with nitriles

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