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A facile one-pot synthesis of 2-fluoroalkyl 1,3-imidazolines and 1,3-oxazolines through imidoyl halide intermediates

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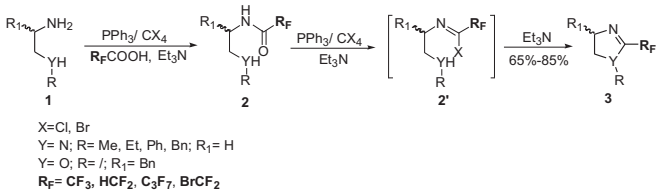
ABSTRACT

A facile one-pot procedure has been developed for the synthesis of 1,3-imidazolines and 1,3-oxazolines bearing fluorinated alkyl groups at the 2-position. The reaction involves the condensation of *N*-monosubstituted ethane-1,2-diamines or 2-aminoethanols with a fluorinated carboxylic acid in the presence of PPh_3/CX_4. The proposed mechanism is that the amide intermediates were initially formed, and then converted to the imidoyl halide intermediates in the presence of PPh_3/CX_4, followed by rapid intramolecular cyclization to 1,3-diazoline products. This protocol allows for the synthesis of 2-bromodifluoromethyl-1,3-imidazoline, a useful CF_2Br-heterocyclic building block, which can be used for the synthesis of *gem*-difluoromethylene linked compounds.

1. Introduction

1,3-Imidazoline and 1,3-oxazoline heterocycles are basic skeletons of many important biologically active compounds, natural products, and organomaterials.[1] It has been reported that their biological activities are greatly enhanced by a substituent at the 2-position,[2] especially 2-fluorinated alkyl groups.[3] Therefore, there has been great interest in developing syntheses of 1,3-diazolines bearing fluorinated alkyl groups at the 2-position. However, only a few examples have been reported for the synthesis of 2-fluoroalkyl-1,3-imidazolines or 2-fluoroalkyl-1,3-oxazolines. These include the reaction of trifluoroacetate with ethane-1,2-diamine, intramolecular cyclization using Ph_3P and *N*-(2-azidoethyl)-trifluoroacetamide, and cyclocondensation of trifluorothioacetamide with ethane-1,2-diamine.[4] Thus, novel and general synthetic methods for 2-fluoroalkyl-1,3-imidazolines or 1,3-oxazolines are highly desirable.

Fluorinated imidoyl halides are sophisticated and multifunctional fluorine-containing building blocks that have versatile applications for the synthesis of biologically interesting fluoroalkyl compounds.[5] Our group has previously reported the synthesis of 2-fluoroalkyl-benzo-1,3-diazoles through fluorinated imidoyl chloride intermediates.[6] In this paper, we report our recent results on the synthesis of 2-fluoroalkyl-1,3-imidazolines and 2-fluoroalkyl-1,3-oxazolines. In refluxing CCl_4 or in toluene at 90 °C in the presence of 3 equiv of CBr_4, Ph_3P, and excess Et_3N, *N*-monosubstituted ethane-1,2-diamines or 2-amino-3-phenylpropanol condense with fluorinated carboxylic acids to generate 2-fluoroalkyl-1,3-imidazolines or 2-fluoroalkyl-1,3-oxazolines, respectively (Scheme 1, Table 1). The reactions were carried out in a one-pot process with good to excellent isolated yields. The postulated mechanism of this tandem process was supported experimentally by isolation of the fluorinated amide intermediates **2**, which then converted to imidoyl halide intermediates **2′** in the presence of PPh_3/CX_4, followed by rapid intramolecular cyclization to the desired products **3**.



Scheme 1. The synthesis of 2-fluoroalkyl substituted 1,3-imidazolines and 1,3-oxazolines.

2. Results and discussion

The reaction of 2-amino-3-phenylpropanol with various non-fluorinated aromatic acids in the presence of PPh_3/CBr_4 or $PPh_3/$

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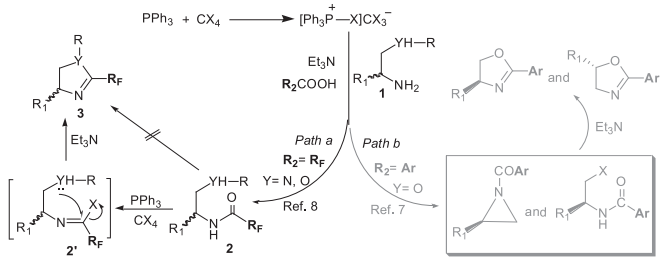
Table 1
Synthesis of 2-fluoroalkyl 1,3-imidazolines and 1,3-oxazolines

Entry	X	Y	R_F	pK_a (R_FCOOH)	R	R_1	Product **3**	Time (h)	Yield[a] (%)
1	Cl	N	CF_3	0.5	H	H	**3a**	12	—[b]
2	Cl/Br	N	CF_3	0.5	Bn	H	**3b**	18/8	85/88[c]
3	Cl	N	CF_3	0.5	Ph	H	**3c**	18	82
4	Cl	N	CF_3	0.5	Et	H	**3d**	3	72
5	Cl	N	CF_3	0.5	Me	H	**3e**	3	65
6	Cl	N	HCF_2	1.3	Bn	H	**3f**	18	81
7	Cl	N	HCF_2	1.3	Ph	H	**3g**	18	77
8	Cl	N	C_3F_7	1.9	Bn	H	**3h**	18	80
9	Cl	N	C_3F_7	1.9	Ph	H	**3i**	18	75
10	Cl	N	$BrCF_2$	0.2	Bn	H	**3j**	18	70
11	Cl	N	$BrCF_2$	0.2	Ph	H	**3k**	18	68
12	Cl	N	CF_3	0.5	*cis* or *trans*-1,2-Diaminocyclohexane		**3l**	120	—[b]
13	Cl/Br	O	CF_3	0.5	—	Bn	**3m**	24/8	63/71[c]
14	Cl/Br	O	$BrCF_2$	0.2	—	Bn	**3n**	24/8	61/73[c]
15	Cl/Br	O	HCF_2	1.3	—	Bn	**3o**	24/10	21/50[c]
16	Cl/Br	O	C_3F_7	1.9	—	Bn	**3p**	24/8	48/61[c]

[a] Isolated yield.
[b] The product was not observed.
[c] The reaction was carried out in toluene with 3 equiv of CBr_4/PPh_3 at 90 °C.

CCl_4 has been demonstrated to proceed through an *N*-aroyl aziridine and a noncyclized amide intermediate (Scheme 2, path b) to provide 4-benzyl-1,3-oxazolines and the isomeric 5-benzyl-1,3-oxazolines.[7] However, when 2-amino-3-phenylpropanol (or *N*-monosubstituted ethane-1,2-diamines) and fluorinated carboxylic acids were used, only 2-fluoroalkyl-4-benzyl-1,3-oxazolines (or 2-fluoroalkyl-1,3-imidazolines) were observed through ^{19}F NMR analysis and isolated. This result revealed that the mechanism of reaction with fluorinated carboxylic acids differs from that of non-fluorinated aromatic acids. In order to study the differing reaction mechanisms, we attempted to capture the reaction intermediates. Fortunately, the amide intermediates **2** were successfully isolated from the reaction mixture of *N*-aryl ethane-1,2-diamines or 2-amino-3-phenylpropanol reacted with the fluorinated carboxylic acids in the presence of PPh_3 and excess Et_3N in refluxing CCl_4 (Table 2). The structure of the amide intermediate **2m** was further confirmed by X-ray diffraction study (Fig. 1). In addition, 2-fluoroalkyl-1,3-diazolines were obtained only when PPh_3 and an excess triethylamine was added to the isolated amide **2** in refluxing CCl_4. On the other hand, the reaction of *N*-aryl ethane-1,2-diamines or 2-amino-3-phenylpropanol with the same equivalent of PPh_3 and excess Et_3N in refluxing CCl_4 provided amide as the only product. Those experimental facts confirmed that the reaction



Scheme 2. Mechanism of formation of 2-fluoroalkyl 1,3-imidazolines and 1,3-oxazolines (**3**).

Table 2
Synthesis of fluorinated amide intermediates **2**

Entry	Y	R_F	R_1	R	Product **2**
1	N	CF_3	H	Bn	**2b**
2	N	HCF_2	H	Bn	**2f**
3	N	HCF_2	H	Ph	**2g**
4	O	CF_3	Bn (*S*)	—	**2m**

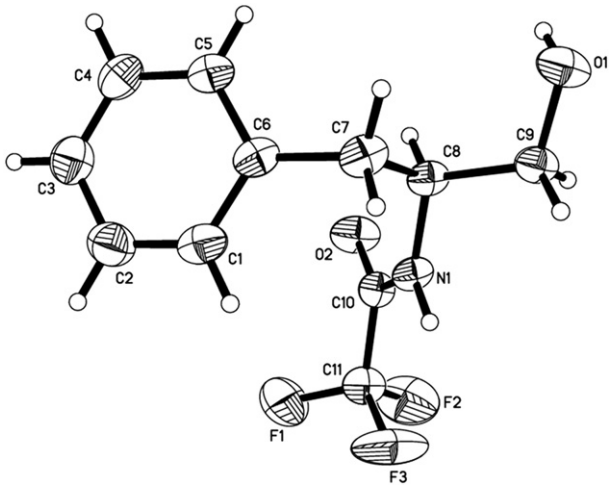
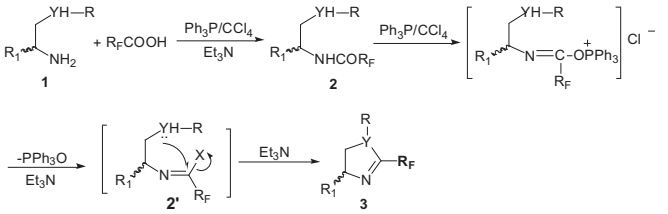


Fig. 1. X-ray diffraction of the amide intermediate **2m**.

proceeded through the other intermediate besides the amide intermediate **2**, which was deduced to be imidoyl halide intermediate **2′** according to Uneyama's research.[8] The final products **3** could be from imidoyl halide **2′** rapid intramolecular cyclization (Scheme 2, path a). The selective formation of imidoyl halide intermediate in Path a or *N*-aroyl aziridine and noncyclised amide intermediate in Path b could depend on the acidity of carboxylic acid. Because of high acidity of fluorinated carboxylic acids (pK_a 0.2–1.9), amidation of the amino group of 2-amino-3-phenylpropanol or *N*-aryl ethane-1,2-diamines was easier than halogenation of hydroxyl or amino group in the presence of PPh_3/CX_4.[9] This made it much easier to form the amide intermediate **2** rather than *N*-aroyl aziridine or noncyclised amide. On the other hand, due to the strong electron withdrawing effect of fluoroalkyl group, this amide may preferentially give the imidoyl halide **2′** through the conversion of the imino alcohol of the amide tautomer in the presence of PPh_3/CX_4 (Scheme 3) rather than the direct formation of five-membered 1,3-diazolines from amide intermediate **2** intramolecular cyclization. Owing to the electrophilicity of the C=N double bond and the nucleophilicity of the *N*-substituted amino group or hydroxyl group, the imidoyl halide easily undergo the intramolecular cyclization to form the desired imidazolines or oxazolines **3** (Scheme 3).



Scheme 3. The formation of the imidoyl halide intermediate **2′**.

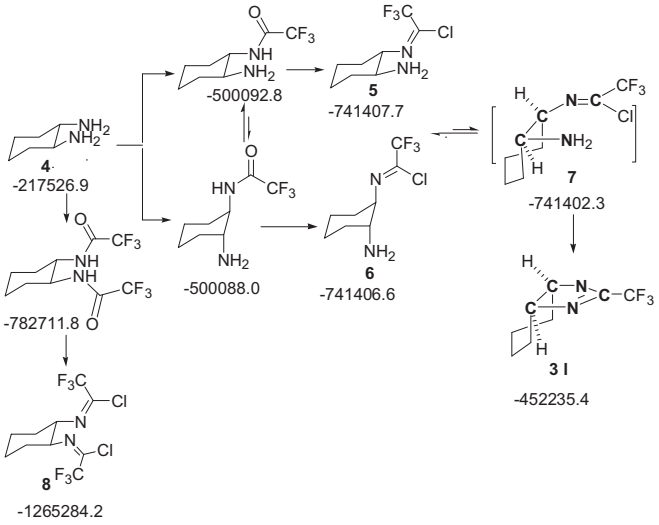
This transformation was initially carried out in refluxing CCl_4. It was later found that the reaction proceeded even faster and with higher isolated yields by heating in toluene with only 3 equiv of CBr_4.

When (*S*)-2-amino-3-phenylpropanol was the substrate, 2-fluoroalkyl-4-benzyl-1,3-oxazolines were successfully obtained as the only product after being treated with 3 equiv of CBr_4, Ph_3P, and excess Et_3N in toluene at 90 °C (entries 13–16, Table 1). *N*-Monosubstituted ethane-1,2-diamines smoothly underwent the transformation. When *N*-substituted groups were donor groups with little steric hindrance (such as *N*-methyl or *N*-ethyl), the reaction proceeded more rapidly (Table 1, entries 4 and 5). The formation of the amide and the imidoyl chloride and subsequent cyclization reaction happened almost simultaneously according to TLC analysis, so the corresponding amide intermediates were not isolated. In contrast, when aryl groups are attached to the nitrogen atom, *N*-(2-phenylamino-ethyl)-acetamide (**2g**) was formed in the first 1–2 h, which could be isolated by column chromatography, and subsequently converted slowly to the imidazoline in the following 9–10 h. This synthetic methodology was suitable for a series of *N*-monosubstituted ethylenediamines for the preparation of 2-fluoroalkyl imidazolines in good yield (Table 2). However, ethane-1,2-diamine failed to generate the expected 2-trifluoromethyl-imidazoline (Table 1, entry 1). According to ^{19}F NMR studies, the chemical shift was only −75.66 ppm after stirring for 12 h. This suggests that both amino groups may form amides (**2a**). Unfortunately, we were unable to obtain this amide (**2a**). 2-Trifluoromethyl-imidazoline **3a** was also not observed. The free rotation about the C–C single bond of ethane-1,2-diamine may be the reason for without any **3a**. The two amino groups of ethane-1,2-diamine will be most stable in a staggered conformation, and formation of an amide or imidoyl chloride on one end should not sterically hinder reaction at the other end. However, 1,2-diaminobenzene has two amino groups constrained in close proximity and steric hindrance prevents the formation of an imidoyl chloride on both amino groups. Thus, it can be successfully converted to 2-trifluoromethyl-benzimidazole under the same reaction conditions, as shown in our previous research.[7] To our surprise, *cis* or *trans*-1,2-diaminocyclohexane, whose amino groups are also held in close proximity, failed to produce the expected product, even after a reaction time of 120 h. Although ^{19}F NMR suggested the ready formation of the amide, the amide intermediate failed to be isolated and the expected product was not observed. Therefore, the $B_3LYP/6\text{-}31G$ (d) calculation method was used to calculate the static energy of the reactants and products of the reaction with *trans*-1,2-diaminocyclohexane through thermodynamic analysis in order to help explain why the reaction had failed. The formation of imidoyl chlorides (**8**), (**5**) or (**6**) is facile due to their lower static energy than *trans*-1,2-diaminocyclohexane (Table 3, Scheme 4). However, if 1,3-imidazoline (**3l**) was to be formed, the five atoms must be in the same plane (Scheme 4), thus distorting the conformation of the cyclohexane ring. This is shown in conformation **7**, whose formation is more difficult because of the higher static energy (−741402.3 kcal/mol). Moreover, even if conformation **7** is present in the reaction system, it would be difficult to form the intramolecular cyclic product **3l** due to its much higher energy. This could explain why the intramolecular cyclic product **3l** was difficult to formation.

Table 3
The static energy of the conformations

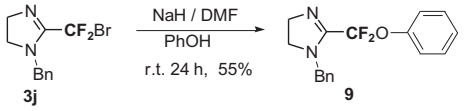
Entry	Conformation	The static energy (kcal/mol)[a]
1	**4**	−217526.9
2	**5**	−741407.7
3	**6**	−741406.6
4	**7**	−741402.3
5	**8**	−1265284.2
6	**3l**	−452235.4

[a] Calculation method: $B_3LYP/6\text{-}31G$ (d).



Scheme 4. Postulated conformation of cyclohexane amide and imidoyl chlorides.

Introduction of a *gem*-difluoromethylene moiety into organic molecules has been shown to enhance potential biological activities as the CF_2 group can confer types of compounds unique polarity and activity.[10] In order to synthesize *gem*-difluoromethylene linked molecules, 2-bromodifluoromethyl-1,3-imidazoline, readily available using our method (entry 10), was tentatively reacted with phenol in the presence of NaH/DMF through a typical SET mechanism.[10d] This reaction yielded the *gem*-difluoromethylene linked compound **9** in 55% yield (Scheme 5). The application of 2-bromodifluoromethyl-1,3-imidazoline to other types of reactions is being explored.



Scheme 5. Reaction of 2-bromodifluoromethyl 1,3-imidazoline with sodium phenolate.

3. Conclusion

In summary, 2-fluoroalkyl-imidazolines and 2-fluoroalkyl-oxazolines were successfully prepared from *N*-monosubstituted 1,2-diamines or 2-aminoethanol and the fluorinated carboxylic acids in the presence of PPh_3/CX_4 using a convenient one-pot synthesis. The reaction mechanism is proposed to go through amide intermediates, then converted to imidoyl halide intermediates, followed by rapid intramolecular cyclization to 2-fluoroalkyl-1,3-diazolines. In addition, 2-bromodifluoromethyl-1,3-imidazoline,

which is readily available using our method, was successfully used in the synthesis of *gem*-difluoromethylene linked compounds to be used in biological studies.

4. Experimental section

4.1. General

Reactions were generally carried out under nitrogen in an appropriate round-bottom flask with magnetic stirring. Thin layer chromatography (TLC) was performed on silica gel. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million downfield from TMS, chemical shifts for ^{13}C NMR spectra are reported in ppm relative to internal chloroform (δ 77.2 ppm for ^{13}C), and chemical shifts for ^{19}F NMR spectra are reported in ppm downfield from internal fluorotrichloromethane ($CFCl_3$). Coupling constants (J) are given in Hertz (Hz). The terms m, s, d, t, q refer to multiplet, singlet, doublet, triplet, quartet; br refers to a broad signal. Infrared spectra (IR) were recorded on an FT-IR spectrometer and absorbance frequencies are given at maximum intensity in cm^{-1}. Mass spectra were obtained using ESI. High resolution mass spectra were obtained using EI at 70 eV.

CCDC 861104 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

4.2. General procedure for 1,3-diazolines

4.2.1. Former procedure. A 200-ml three-necked flask equipped with a condenser was charged with Ph_3P (34.5 g, 132 mmol), Et_3N (excess), CCl_4 (21.1 ml, 220 mmol), and fluorinated carboxylic acid (44 mmol) at 0 °C under nitrogen. After the solution was stirred for about 10 min (ice water bath), a solution of substrate **1** (53 mmol) in CCl_4 (21.1 ml, 220 mmol) was added dropwise. The mixture was refluxed under stirring for 3–18 h. The solvent was evaporated under reduced pressure, and the residue was diluted with petroleum ether (60–90 °C) and filtered. The residual solid Ph_3PO and $Et_3N{\cdot}HCl$ was washed with petroleum ether three times. The filtrate was concentrated, and the residue was purified by column chromatography to obtain the product **3**. When *N*-benzylethylenediamine and *N*-phenylethylenediamine were employed as the substrates **1** in this reaction, amides **2** could be isolated after stirring for 1–2 h.

4.2.2. Optimal procedure. A 200-ml three-necked flask equipped with a condenser was charged with Ph_3P (2.20 g, 8.4 mmol), Et_3N (0.85 g, 8.4 mmol), CBr_4 (16.8 g, 8.4 mmol), the substrate **1** (3.3 mmol), and fluorinated carboxylic acid (2.8 mmol) in toluene (15.0 ml) under a nitrogen atmosphere. After the solution was stirred for about 10 min at room temperature, the mixture was heated to 90 °C by for 1–3 h with stirring. The solvent was evaporated under reduced pressure, and the residue was diluted with petroleum ether (60–90 °C) and filtered. The residual solid Ph_3PO and $Et_3N{\cdot}HCl$ was washed with petroleum ether three times. The filtrate was concentrated, and the residue was purified by column chromatography to obtain product **3**.

*4.2.3. N-(2-Benzylamino-ethyl)-2,2,2-trifluoroacetamide(**2b**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 8.04 (m, 1H), 7.35–7.22 (m, 5H), 3.71 (s, 2H), 3.31 (dd, J=6.0, 5.5 Hz, 2H), 2.74 (t, J=6.0 Hz, 2H), 1.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4 (q, $^{2}J_{C-F}$=36.7 Hz), 139.8, 128.4, 128.0, 127.6, 116.0 (q, $^{1}J_{C-F}$=285.6 Hz), 53.2, 46.9, 39.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.85 (s); IR (KBr, cm^{-1}) 3407, 3109, 3081, 1716, 1531, 1186, 762, 721, 697.

*4.2.4. N-(2-Benzylamino-ethyl)-2,2-difluoroacetamide (**2f**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.37–7.25 (m, 6H), 5.90 (t, $^{2}J_{H-F}$=54.5 Hz, 1H), 3.80 (s, 2H), 3.40 (dd, J=5.0, 5.0 Hz, 2H), 2.82 (t, J=5.0 Hz, 2H), 1.98 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (t, $^{2}J_{C-F}$=24.4 Hz), 139.8, 128.7, 128.3, 127.4, 108.7 (t, $^{1}J_{C-F}$=250.3 Hz), 53.4, 47.2, 38.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.36 (d, $^{2}J_{H-F}$=54.4 Hz). IR (KBr, cm^{-1}) 3416, 3104, 3067, 1693, 1605, 1132, 767, 713, 689.

*4.2.5. 2,2-Difluoro-N-(2-phenylamino-ethyl)-acetamide (**2g**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.22–7.18 (m, 2H), 7.09 (s, 1H), 6.77–6.62 (m, 3H), 5.87 (t, $^{2}J_{H-F}$=54.3 Hz, 1H), 3.98 (br, 1H), 3.54 (dd, J=6.0, 5.5 Hz 2H), 3.32 (t, J=6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4 (t, $^{2}J_{C-F}$=25.0 Hz), 147.7, 129.5, 118.1, 113.0, 108.5 (t, $^{1}J_{C-F}$=250.0 Hz), 43.2; 39.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −126.34 (d, $^{2}J_{H-F}$=54.3 Hz). IR (KBr, cm^{-1}) 3405, 3031, 1706, 1601, 1127, 785, 716, 692.

*4.2.6. 2,2,2-Trifluoro-N-(1-hydroxymethyl-2-phenyl-ethyl)-acetamide (**2m**).* White solid; mp 172.3–176.0 °C. $[\alpha]_D^{25}$ −18.1 (*c* 2.021, acetone); ^{1}H NMR (500 Hz, $CDCl_3$) δ 7.34–7.21 (m, 5H), 6.61 (br, 1H), 4.27–4.21 (m, 1H), 3.74–3.67 (m, 2H), 2.92–2.99 (m, 2H), 1.71 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 156.4 (q, $^{2}J_{C-F}$=35.0 Hz), 138.8, 129.4, 128.6, 126.6, 116.4 (q, $^{1}J_{C-F}$=287.5 Hz), 62.8, 54.4, 36.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.89 (s). IR (KBr, cm^{-1}) 3511, 3109, 3063, 1699, 1561, 1225, 1207, 1179, 877, 755, 699, 681.

*4.2.7. N-Benzyl-2-trifluoromethylimidazoline (**3b**).* Yellow oil; 88%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.38–7.25 (m, 5H), 4.39 (s, 2H), 3.87 (t, J=10.5 Hz, 2H), 3.35 (t, J=10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8 (q, $^{2}J_{C-F}$=34.4 Hz), 136.3, 128.9, 128.0, 127.8, 118.3 (q, $^{1}J_{C-F}$=273.1 Hz), 53.1, 51.0, 50.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −66.75 (s); IR (KBr, cm^{-1}) 3032, 2934, 2872, 1628, 1193, 1150, 742, 700; ESI-MS: m/z=229 $[M+1]^+$.

*4.2.8. N-Phenyl-2-trifluoromethylimidazoline (**3c**).* Yellow oil; 82%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.38–7.21 (m, 5H), 4.06–3.94 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (q, $^{2}J_{C-F}$=35.6 Hz), 140.0, 129.5, 127.3, 125.7, 118.0 (q, $^{1}J_{C-F}$=273.8 Hz), 55.6, 53.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −64.83 (s); IR (KBr, cm^{-1}) 3061, 2944, 2875, 1630, 1597, 1497, 1289, 1199, 1148, 764, 697; ESI-MS: m/z=215 $[M+1]^+$.

*4.2.9. N-Ethyl-2-trifluoromethylimidazoline (**3d**).* Yellow oil; 72%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.88 (t, J=10.0 Hz, 2H), 3.52 (t, J=10.0 Hz, 2H), 3.29 (q, J=6.4 Hz, 2H), 1.18 (t, J=6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7 (q, $^{2}J_{C-F}$=35.0 Hz), 118.0 (q, $^{1}J_{C-F}$=273.1 Hz), 52.7, 50.0, 46.0, 13.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −67.59 (s); IR (KBr, cm^{-1}): 2973, 2936, 2877, 1694, 1186, 1148; ESI-MS: m/z=167 $[M+1]^+$.

*4.2.10. N-Methyl-2-trifluoromethylimidazoline (**3e**).* Yellow oil; 65%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 3.87 (t, J=10.3 Hz, 2H), 3.48 (t, J=10.3 Hz, 2H), 2.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5 (q, $^{2}J_{C-F}$=35.6 Hz), 117.4 (q, $^{1}J_{C-F}$=261.3 Hz), 53.4, 50.8, 46.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −64.67 (s); IR (KBr, cm^{-1}) 2970, 2937, 1690, 1208, 1190, 1149, 1116; ESI-MS: m/z=153 $[M+1]^+$.

*4.2.11. N-Benzyl-2-difluoromethylimidazoline (**3f**).* Yellow oil; 81%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.36–7.24 (m, 5H), 6.32 (t, $^{2}J_{H-F}$=53.0 Hz, 1H), 4.44 (s, 2H), 3.79 (t, J=10.3 Hz, 2H), 3.27 (t, J=10.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5 (t, $^{2}J_{C-F}$=25.0 Hz), 136.8, 128.5, 128.1, 127.2, 110.7 (t, $^{1}J_{C-F}$=240.0 Hz),

53.3, 50.5, 50.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −120.47 (d, $^2J_{H-F}$=53.0 Hz); IR (KBr, cm^{-1}) 3064, 3030, 2940, 2869, 1698, 1623, 1280, 1109, 1054, 739, 700; HRMS calcd for (M^+) $C_{11}H_{12}F_2N_2$: 210.0969, found 210.0973.

*4.2.12. N-Phenyl-2-difluoromethylimidazoline (**3g**).* Yellow oil; 77%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.65–7.13(m, 5H), 6.23 (t, $^2J_{H-F}$=53.0 Hz, 1H), 4.08–3.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (t, $^2J_{C-F}$=24.4 Hz), 139.8, 129.4, 127.3, 123.4, 108.7 (t, $^1J_{C-F}$=240.6 Hz), 55.8; 53.7, ^{19}F NMR (470 MHz, $CDCl_3$) δ −119.50 (d, $^2J_{H-F}$=53.0 Hz); IR (KBr, cm^{-1}) 3058, 2946, 2873, 1697, 1600, 1499, 1120, 1059, 696; ESI-MS: *m*/*z*=197 [M+1]$^+$.

*4.2.13. N-Benzyl-2-perfluoropropylimidazoline (**3h**).* Yellow oil; 80%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.38–7.25 (m, 5H), 4.42 (s, 2H), 3.91 (t, *J*=10.5 Hz, 2H), 3.33 (t, *J*=10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.2 (t, $^2J_{C-F}$=26.3 Hz), 136.5, 128.9, 127.9, 127.7, 117.9 (q, t, $^1J_{C-F}$=286.3 Hz, $^2J_{C-F}$=33.7 Hz), 113.3 (t, t, $^1J_{C-F}$=255.6 Hz, $^2J_{C-F}$=31.3 Hz), 108.9 (t, t, q, $^1J_{C-F}$=228.8 Hz, $^2J_{C-F}$=35.0 Hz, $^2J_{C-F}$=31.3 Hz), 53.5, 51.6, 51.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.05 (t, *J*=11.8 Hz), −112.05 (q, *J*=11.8 Hz), −125.65 (s); IR (KBr, cm^{-1}) 3063, 3031, 2850, 1627, 1560, 1187, 1147, 743, 700; ESI-MS: *m*/*z*=329 [M+1]$^+$.

*4.2.14. N-Phenyl-2-perfluoropropylimidazoline (**3i**).* Yellow oil; 75%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.36–7.19 (m, 5H), 4.04 (t, *J*=10.3 Hz, 2H), 3.85 (t, *J*=10.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3 (t, $^2J_{C-F}$=25.0 Hz), 141.0, 129.4, 127.5, 126.6, 117.8 (q, t, $^1J_{C-F}$=286.3 Hz, $^2J_{C-F}$=33.8 Hz), 110.9 (t, t, $^1J_{C-F}$=257.5 Hz, $^2J_{C-F}$=31.3 Hz), 108.4 (t, t, q, $^1J_{C-F}$=267.5 Hz, $^2J_{C-F}$=35.0 Hz, $^2J_{C-F}$=33.8 Hz), 56.3, 53.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −80.12 (t, *J*=9.4 Hz), −109.96 (q, *J*=9.4 Hz), −125.24 (s); IR (KBr, cm^{-1}) 3064, 2972, 2876, 1623, 1596, 1267, 1230, 1121, 698. ESI-MS: *m*/*z*=315 [M+1]$^+$.

*4.2.15. N-Benzyl-2-bromodifluoromethylimidazoline (**3j**).* Yellow oil; 70%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.38–7.29 (m, 5H), 4.47 (s, 2H), 3.87 (t, *J*=10.3 Hz, 2H), 3.36 (t, *J*=10.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (t, $^2J_{C-F}$=25.6 Hz), 136.6, 129.0, 128.0, 127.8, 111.7 (t, $^1J_{C-F}$=301.9 Hz), 52.8, 51.7, 51.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ −51.29 (s); IR (KBr, cm^{-1}): 3061, 3031, 2944, 2866, 1614, 1148, 1119, 998, 698; ESI-MS: *m*/*z*=289 [M+1]$^+$.

*4.2.16. N-Phenyl-2-bromodifluoromethylimidazoline (**3k**).* Yellow oil; 68%; ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.40–7.27 (m, 5H), 4.07–3.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8 (t, $^2J_{C-F}$=26.3 Hz), 140.5, 129.5, 127.7, 127.2, 111.7 (t, $^1J_{C-F}$=303.8 Hz), 56.8, 52.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −48.46 (s); IR (KBr, cm^{-1}): 3043, 2975, 2872, 1615, 1591, 1495, 1287, 1147, 699; ESI-MS: *m*/*z*=275 [M+1]$^+$.

*4.2.17. (S)-2-Trifluoromethyl-4-benzyl-1,3-oxazoline (**3m**).* Yellow oil; 71%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.18 (m, 5H), 4.63–4.56 (m, 1H), 4.42 (t, *J*=9.0 Hz, 1H), 4.21 (t, *J*=8.0 Hz, 1H), 3.15 (dd, *J*=14.0, 5.5 Hz, 1H), 2.76 (dd, *J*=14.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3 (dd, $^2J_{C-F}$=40.0 Hz), 136.5, 129.3, 128.8, 127.1, 116.5 (q, $^1J_{C-F}$=273.0 Hz), 73.8, 67.7, 40.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ −70.28 (s, 3F). IR (KBr): *v* 3023, 2925, 1666, 1379, 1215, 1093, 741, 701. HRMS calcd for (M^+) $C_{11}H_{10}F_3NO$: 229.0714, found 229.0714.

*4.2.18. (S)-2-(Bromodifluoromethyl)-4-benzyl-1,3-oxazoline (**3n**).* Yellow oil; 73%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.20 (m, 5H), 4.67–4.60 (m, 1H), 4.47 (t, *J*=9.0 Hz, 1H), 4.27 (t, *J*=8.5 Hz, 1H), 3.17 (dd, *J*=14.0, 5.0 Hz, 1H), 2.80 (dd, *J*=14.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (t, $^2J_{C-F}$=30.0 Hz), 136.5, 129.4, 128.9, 127.1, 109.1 (t, $^1J_{C-F}$=303.0 Hz), 74.1, 67.7, 40.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ −55.27 (q, 2F); IR (KBr): *v* 3028, 2928, 1670, 1398, 1276, 1094, 754, 697. HRMS calcd for (M^+) $C_{11}H_{10}BrF_2NO$: 288.9914, found 288.9915.

*4.2.19. (S)-2-Difluoromethyl-4-benzyl-1,3-oxazoline (**3o**).* Yellow oil; 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34–7.21 (m, 5H), 6.22 (t, *J*=52.5 Hz, 1H), 4.57–4.51 (m, 1H), 4.38 (t, *J*=9.0 Hz, 1H), 4.15 (t, *J*=8.0 Hz, 1H), 3.13 (dd, *J*=6.0, 14.0 Hz, 1H), 2.75 (dd, *J*=8.0, 14.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0 (t, $^2J_{C-F}$=27.5 Hz), 137.0, 129.2, 128.7, 126.9, 107.2 (t, $^1J_{C-F}$=240.0 Hz), 73.1, 67.4, 41.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ −124.20 (d, *J*=52.0 Hz); IR (KBr): *v* 3039, 2944, 1676, 1412, 1231, 1104, 755, 696. HRMS calcd for (M^+) $C_{11}H_{11}F_2NO$: 211.0809, found 211.0813.

*4.2.20. (S)-4-Benzyl-2-(perfluoropropyl)-1,3-oxazoline (**3p**).* Yellow oil; 61%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33–7.18 (m, 5H), 4.66–4.60 (m, 1H), 4.43 (t, *J*=8.5 Hz, 1H), 4.22 (t, *J*=8.5 Hz, 1H), 3.17 (dd, *J*=14.0, 5.5 Hz, 1H), 2.76 (dd, *J*=14.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.4 (t, $^2J_{C-F}$=27.5 Hz), 136.5, 129.4, 128.8, 127.0, 117.6 (q, t, $^1J_{C-F}$=285.0 Hz, $^2J_{C-F}$=33.8 Hz), 109.1 (t, t, $^1J_{C-F}$=256.0 Hz, $^2J_{C-F}$=31.0 Hz), 108.4 (t, t, q, $^1J_{C-F}$=268.8 Hz, $^2J_{C-F}$=31.3 Hz, $^2J_{C-F}$=33.8 Hz), 73.7, 68.0, 40.7; ^{19}F NMR (470 MHz, $CDCl_3$): δ −80.68 (t, *J*=9.4 Hz), −116.70 (m), −127.14 (s); IR (KBr): *v* 3021, 2918, 1669, 1396, 1256, 1084, 731, 693. HRMS calcd for (M^+) $C_{13}H_{10}F_7NO$: 329.0651, found 329.0648.

4.3. *N*-Benzyl-2-difluoro(phenoxy)methylimidazoline (7)

A 25 ml, three-necked, round-bottom flask protected by nitrogen was charged with 99.7 mg (4.2 mmol) of NaH (60%) and 10 ml of dry DMF. To the stirred suspension was added 4.2 mmol phenol. Hydrogen gas was evolved and the flask became warm. After stirring for 20 min, a clear solution was obtained. Then 200 mg (0.70 mmol) of **3j** was added all at once, and the solution was allowed to stir at the room temperature for the 24 h. The mixture was poured into 15 ml of ice water, and then extracted three times with 10 ml portions of $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation at reduced pressure. Compound **7** was obtained as a yellow oil in 55% yield and by column chromatography (2/1 petroleum ether/ethyl acetate) on basic aluminum oxide: ^{1}H NMR (500 MHz, $CDCl_3$, ppm) δ 7.36–6.85 (m, 10H), 4.57 (s, 2H), 3.90 (t, *J*=10.3 Hz, 2H), 3.39 (t, *J*=10.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3 (t, $^2J_{C-F}$=35.0 Hz), 149.6, 136.7, 129.8, 129.6, 128. 9, 127.9, 126.3, 121.7, 116.7 (t, $^1J_{C-F}$=263.8 Hz), 52.3, 51.2, 50.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.23 (s); IR (KBr, cm^{-1}) 3064, 2942, 2870, 1623, 1593, 1493, 1199, 1070, 741, 694; HRMS calcd for (M^+) $C_{17}H_{16}F_2N_2O$: 302.1231, found 302.1239.

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Supplementary data

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