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Nucleophile-Dependent Regioselective Reaction of (*S*)-4-Benzyl-2-Fluoroalkyl-1,3-Oxazolines

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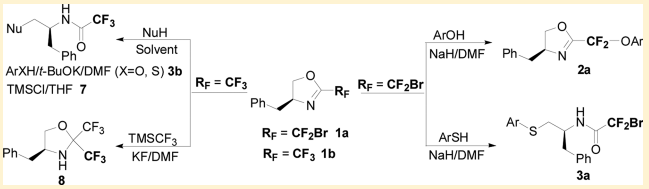
Supporting Information

ABSTRACT: Nucleophile-dependent regioselectivities in the nucleophilic reaction of (*S*)-4-benzyl-2-fluoroalkyl-1,3-oxazoline to different types of fluorinated compounds were investigated experimentally and theoretically. The ring opening of (*S*)-4-benzyl-2-bromodifluoromethyl-1,3-oxazoline by arenethiolates exclusively occurred at the C5 position of the 1,3-oxazoline ring, whereas completely different regioselectivity was observed for a unimolecular radical nucleophilic substitution ($S_{RN}1$) at the terminal bromine atom of the CF_2Br group when arenolates were employed as the nucleophiles. The reaction of (*S*)-4-benzyl-2-trifluoromethyl-1,3-oxazoline with nucleophiles such as arenethiols, arenols, and TMSCl underwent nucleophilic ring opening in a regiospecific way, while the use of $TMSCF_3$ was determined to proceed through nucleophilic addition to the C=N bond.



INTRODUCTION

Heterocycles based on 1,3-oxazolines have received much attention in the past few decades, since they are the core skeletons of many biologically active products and natural products[1] and are of value in organic synthesis.[2] Diverse chemical transformations can be realized using 1,3-oxazoline heterocycles as the synthetic intermediates,[3] including ring-opening[4] and nucleophilic addition reactions[5] and functional group conversion on the 1,3-oxazoline ring. Moreover, regiocontrolled ring-opening reactions of 1,3-oxazoline constitute useful tools for the preparation of carboxamide targets. For example, the ring opening of (*S* or *R*)-4-methyl-2-alkyl-1,3-oxazoline by thiophenol is known as an important process toward the synthesis of biologically significant chiral secondary carboxamides through cleavage of the C5−O1 bond of 1,3-oxazoline.[6] However, in comparison with ring opening at the C5 position, nucleophilic addition to the C=N bond of 1,3-oxazolines has few precedents.[7] Additionally, the regioselectivity between ring opening at C5 and addition to the C=N bond of 1,3-oxazolines is susceptible to several factors such as the substrate, the type of nucleophile, and the solvent.[8] Moreover, fluorinated groups can greatly alter reaction properties.[9] Therefore, the study of the regioselectivity of nucleophilic reactions of chiral 2-fluoroalkyl-1,3-oxazolines comprise a challenging topic for fundamental research. On the other hand, considering the importance of organofluorine compounds in medicines, agricultural chemicals, and electronic materials,[10] the reaction of fluorinated 1,3-oxazolines with different nucleophiles would be intriguing for the formation of various types of fluorinated compounds. Herein, we report our studies on the nucleophilic reaction of chiral 2-trifluoromethyl- and 2-bromodifluoromethyl-1,3-oxazolines, which generates the corresponding biologically significant trifluorinated and *gem*-difluorinated compounds. Specifically, we discovered nucleophile-dependent regioselective reactions of ring opening at the C5 position (path a) vs unimolecular radical nucleophilic substitution ($S_{RN}1$) to the terminal bromine atom of the CF_2Br group (path b) of (*S*)-4-benzyl-2-bromodifluoromethyl-1,3-oxazoline (**1a**) and ring opening through cleavage of the C5−O1 bond (path a) vs nucleophilic addition to the C=N bond (path c) of (*S*)-4-benzyl-2-trifluoromethyl-1,3-oxazoline (**1b**) (Scheme 1).

RESULTS AND DISCUSSION

Our initial experiments on the reaction of 2-bromodifluoromethyl-1,3-oxazoline (**1a**)[11] with phenolate disclosed that a *gem*-difluoromethylene-linked 1,3-oxazoline-contaning phenyl ether (**2aa**) could be obtained exclusively. The reaction was carried out in a 1:1.1:2 **1a**:PhOH:NaH molar ratio in DMF at 80 °C. The results were similar to those of 2-bromodifluoromethylbenzoxazole with arenethiolates and arenolates.[12] This reaction did not undergo ring opening as reported for the reaction of phenylthiolate and 2-alkyl-1,3-oxazoline.[4] Intrigued by this finding, we further explored the reactions of **1a**,**b** with

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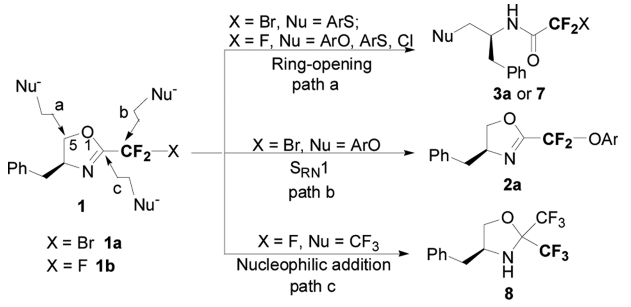
Scheme 1. Selective Reaction of 1 with Different Nucleophiles



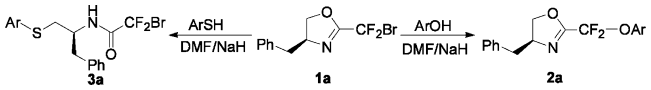
nucleophiles, including other arenols and arenethiols, as well as the reactions of **1b** with TMSCl and $TMSCF_3$.

Under the reaction conditions for phenol (see above), the reactions of other arenols and arenethiols with (*S*)-4-benzyl-2-bromodifluoromethyl-1,3-oxazoline (**1a**) were studied. The results are summarized in Table 1. As expected, the reactions employing arenolates provided *gem*-difluoromethylene-linked phenyl ethers **2a** as the only detectable product in 65−78% isolated yields (Table 1, entries 1−7). The results showed that the reactivity of arenols did not display obvious variation arising from the steric and electronic effects of substituents. The reaction is proposed to undergo a unimolecular radical nucleophilic substitution ($S_{RN}1$) process.[12,13] It is interesting to note that 3-hydroxypyridine could also be employed in this $S_{RN}1$ process and reacted with **1a** to give **2ae** in 73% yield (Table 1, entry 5). This result is distinct from the previous report[12] under similar reaction conditions. In the case of thiophenol under reaction conditions similar to those shown above in a 1:1.1:2 **1a**:PhSH:NaH molar ratio in DMF at 80 °C, the optically active (*S*)-*N*-bromodifluoracyl *β*-thioamide **3ah** was obtained in 79% yield, which was thought to arise from ring opening involving an S_N2-type nucleophilic attack of thiophenolate at the C5 position of **1a**, along with the unexpected **5** (15%) and a small amount of disulfide (Table 1, entry 8, Scheme 2). No *gem*-difluoromethylene-linked product **2a** was detected. However, other arenethiols, such as 4,6-dimethylpyrimidine-2-thiol and benzothiazole-2-thiol, also underwent a ring opening by nucleophilic attack of arenethiolates at the C5 position of the oxazoline ring and led to the formation of the corresponding optically active secondary carboxamides **3a** as the only detectable regioisomer (Table 1, entries 9 and 10).

The structure of **5** was confirmed by X-ray diffraction studies as well as ^1H NMR, ^{13}C NMR, and ^{19}F NMR analysis. Compound **5** (32% isolated yield) was the only isolated fluorine-containing product, along with a large amount of the disulfide as byproduct with no detectable **3ah** by ^{19}F NMR, when the amount of thiophenol was increased (1:3.1 **1a**:thiophenol molar ratio). The formation of compound **5** is presumed to proceed via the attack of thiophenolate at the C5 position of **1a** to form the ring-opening product bromodifluoromethyl carboxamide (**3ah**), which reacted further with excess thiophenolate via the $S_{RN}1$ reaction pathway on the bromodifluoromethyl group to generate **5** (Scheme 2). This speculation is consistent with the observation that the isolated ring-opening product **3ah** was transformed into **5** in the presence of thiophenol in NaH/DMF at 80 °C (Scheme 2). Surprisingly, other *N*-bromodifluoracyl *β*-thioamides such as **3ai** and **3aj** could not undergo the $S_{RN}1$ reaction with thiophenolate and arenolates. In addition, the $S_{RN}1$ products **2a** could not continue ring-opening reactions with arenols and arenethiols under the same conditions stated above.

The distinction in the reaction of **1a** with arenolates and arenethiolates was attributed to the different nucleophilicities and reducibilities of the nucleophilic anion. The displacement of bromine from **1a** by arenolates via an $S_{RN}1$ mechanism,

Table 1. Reaction of 1a with Arenethiols and Arenols



Entry	ArXH	Time (h)	Product **2** or **3**	Yield (%) [a]
1		9	**2aa**	66
2		11	**2ab**	75
3		4	**2ac**	65
4		10	**2ad**	66
5		11	**2ae**	73
6		10	**2af**	75
7		10	**2ag**	78
8		20	**3ah**	79 [b]
9		12	**3ai**	78
10		16	**3aj**	75

[a]Isolated yield. [b]15% of product **5** and some disulfide observed.

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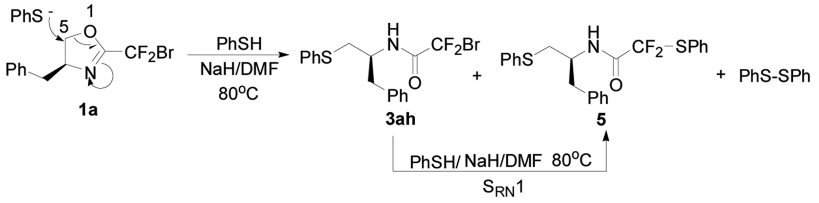
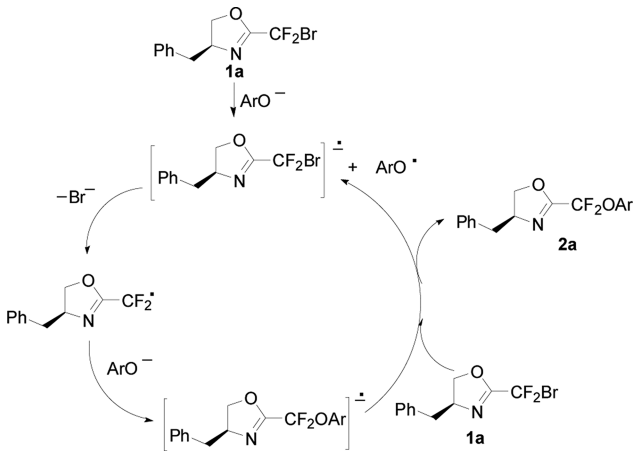
Scheme 2. Formation of Compound 5



rather than the general S_N2 substitution reaction, is possibly due to the relatively high reducibility and low nucleophilicity of arenolates as compared to arenethiolates. This process may involve a transfer of one electron (ET) from arenolate to **1a** to form the radical anion of **1a**, followed by the cleavage of the C–Br bond and departure of the bromide anion to give a free radical species which combined with ArO^-, yielding a new radical anion precursor of **2a**. Afterward, the radical anion precursor of **2a** underwent an intermolecular ET with **1a** to provide the *gem*-difluoromethylene-linked 1,3-oxazoline-contaning aryl ether **2a** as a single regioisomer and radical anion of **1a** which turns on the chain cycling[13] (Scheme 3). The radical

Scheme 3. $S_{RN}1$ Process for 2a

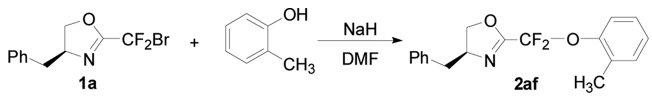


anion of **1a** should be stabilized by delocalization of the extra electron obtained from PhO^- into the conjugated oxazoline moiety, as confirmed by density functional theory (DFT) calculations (Figure S4 in the Supporting Information).

In order to gain deeper insight the mechanism, radical inhibition experiments such as addition of *p*-dinitrobenzene or hydroquinone (HQ) to the reaction mixture, as well as reactions in the dark and at room temperature, were carried out in a 1:1.1 **1a**:2-methylphenol molar ratio. As shown in Table 2, the yield was obviously decreased at room temperature as compared with that at 80 °C (entry 2 vs 1 and 4 vs 3), and the presence of the radical scavenger *p*-dinitrobenzene or free radical inhibitor hydroquinone (HQ) significantly suppressed the reaction (entries 5 and 6). Additionally, the reaction rate in the dark was also slower than that under laboratory illumination during the first 0.25 h. However, when the reaction was run for an additional 2–9 h, similar yields of the product **2af** were obtained in the dark and under laboratory illumination conditions (entry 3 vs 1). All these observations support the $S_{RN}1$ mechanism.

On the other hand, although the reducibility of arenethiolates is somewhat weaker than that of arenolates, their strong

Table 2. Influences of Inhibition Conditions on $S_{RN}1$ Reactions



entry	reaction conditions	temp (°C)	time (h)	yield (%)[a]
1	lab. ill.[b]	80	0.25/2/10	56/78/84
2	lab. ill.	room temp	0.25/10	31/42
3	in dark	80	0.25/2/10	38/75/81
4	in dark	room temp	0.25/10	18/39
5	lab. ill., *p*-DNB (20 mol %)	80	10	62
6	lab. ill., HQ (20 mol %)	80	10	70

[a] ^{19}F NMR yield using benzotrifluoride as an internal standard (1:1 benzotrifluoride:**1a** molar ratio). [b] lab. ill. = laboratory illumination.

nucleophilicity caused the arenethiolates to attack at the C5 position of the 1,3-oxazoline ring to proceed via nucleophilic ring opening.

We also attempted to examine the reaction of 2-trifluoromethyl-1,3-oxazoline (**1b**) with different nucleophiles. Initially, the reactions with arenethiolates and arenolates were carried out with a 1:1.1:2 **1b**:ArXH:NaH molar ratio in DMF at 80 °C as mentioned above. It was found that the reactions yielded the ring-opening products **3b** by nucleophilic attack at the C5 position of 1,3-oxazolines in both cases, which were different from the reaction with **1a**. Arenethiolates only provided the desired ring-opening products **3b** in relatively high yields (Table 4, entries 6 and 7, procedure B), while arenolates showed lower efficiency to give ring-opening products **3b** along with a small amount of trifluoromethylated acetamide product **6** (Table 4, entries 1–5, procedure B). The structure of **6** was confirmed by X-ray diffraction studies, which may arise from nucleophilic attack of hydroxide anion. Thus, further optimization studies were performed to improve the yields of the desired ring-opening products **3b** for the reaction of 2-trifluoromethyl-1,3-oxazoline (**1b**) with phenol as the model substrate. A screen of bases revealed that *t*-BuOK was optimal, which provided a higher yield of the desired product **3ba** and a lower yield of byproduct **6** (Table 3, entries 1–6). The reaction did not work well in THF (Table 3, entries 7 and 17) but became much more efficient in dry DMF (entry 13 vs 11). After scanning of the reactant ratio, an optimal yield of **3ba** (97% ^{19}F NMR yield) was eventually observed when the reaction proceeded in dry DMF at 80 °C for 12 h with a 1.2:1.0:1.1 **1b**:PhOH:*t*-BuOK molar ratio (Table 3, entry 13). The byproduct **6**, which could also be obtained in the absence of PhOH using NaH or *t*-BuOK as base and dry DMF as solvent (entries 18 and 19), was the ring-opening product derived from nucleophilic attack of the hydroxide anion. We reasoned that hydroxide is most likely from the impurities of NaH or *t*-BuOK.

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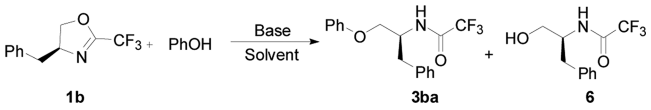
Table 3. Optimization of Ring-Opening Reaction of 1b



1b 3ba 6

entry	base	1b:PhOH:base	solvent	yield of 3ba (%)[a]	yield of 6 (%)[a]
1	NaH	1:1.1:2	DMF	35 (21[b])	28 (22[b])
2	KOH	1:1.1:1.1	DMF	34	22
3	K_2CO_3	1:1.1:1.1	DMF	10	2
4	$NaOCH_3$	1:1.1:1.1	DMF	17	1
5	*t*-BuOK	1:1.1:1.1	DMF	63	10
6		1:1.1:0	DMF	0	0
7	*t*-BuOK	1:1.1:1.1	THF (dry)	0	0
8	*t*-BuOK	1:1:1	DMF	68	9
9	*t*-BuOK	1:1.1:2.2	DMF	78	26
10	*t*-BuOK	1:2:2.2	DMF	78	20
11	*t*-BuOK	1.2:1:1.1	DMF	93	10
12	*t*-BuOK	1.5:1:1.1	DMF	98[c]	13
13	**t-BuOK**	**1.2:1:1.1**	**DMF (dry)**	**97**	**8**
14	*t*-BuOK	1.2:1:1	DMF	70	8
15	NaH	1.2:1:2	DMF	81	21
16	NaH	2:1:2	DMF	74	14
17	NaH	1.2:1:2	THF (dry)	0	0
18	*t*-BuOK	1.2:0:1	DMF (dry)	0	6
19	NaH	1.2:0:2	DMF (dry)	0	29

[a]^{19}F NMR yield using benzotrifluoride as an internal standard (1:1 benzotrifluoride:PhOH molar ratio). [b]Isolated yield based on **1b**. [c]With 20% residual substrate **1b**.

With the optimized reaction conditions in hand, a series of arenethiolates and arenolates were examined in the ring-opening reaction with 2-trifluoromethyl-1,3-oxazoline (**1b**). For procedure A shown in Table 4, the yields of trifluoromethylated acetamide products **3b** were significantly improved. The formation of byproduct **6** was obviously suppressed. However, the reaction with an electron-poor arenolate such as 4-nitrophenol required a long reaction time, and only 47% of conversion of the substrate was observed after 60 h (Table 4, entry 2, procedure A).

When other nucleophiles such as TMSCl and $TMSCF_3$ were applied in the reaction with 2-trifluoromethyl-1,3-oxazoline (**1b**), we found that the reaction with TMSCl still provided the ring-opening product **7** in 77% yield. Remarkably, using $TMSCF_3$ as nucleophile, the product **8** was obtained in 68% yield (Scheme 4). The reaction was proposed to proceed via nucleophilic addition to the C═N bond of 1,3-oxazoline to generate the isolable intermediate **9**, which then converted into product **8** in DMF. The distinction in the reaction of **1b** with $TMSCF_3$ and TMSCl was possibly caused by the different performance of chloride and CF_3 groups. Owing to the difficulty of breaking the Si−CF_3 bond, a catalytic amount of KF was needed as an initiator to cleave the Si−CF_3 bond and generate the CF_3 anion. The addition of the resulting CF_3 anion to the C2 position of 1,3-oxazoline then occurred followed by the attack of N^- at $TMSCF_3$, forming intermediate **9** and the CF_3 anion, which turns on the cycle (Scheme 4).[14] The fiinal deprotection of amine of **9** provided **8**. In contrast, the Si−Cl bond was relatively easily broken, and the electron lone pair on nitrogen attacked TMSCl and broke the Si−Cl bond.[15] The resulting chloride subsequently attacked the C5 position of 1,3-oxazoline, resulting in the formation of ring-opening product **7** (Scheme 4). Surprisingly, when **1a** reacted with $TMSCF_3$ or TMSCl, the reaction results were too complicated to analyze.

To explain the selectivity of the substitution reaction of (*S*)-4-benzyl-2-fluoroalkyl-1,3-oxazolines with PhOH and PhSH as summarized in Scheme 5, DFT calculations were performed at the B3LYP/6-311+G(d)//SDD level of theory.

PhO^- and PhS^- are as known as strong reductants and should be capable of transferring one electron to 1,3-oxazoline **1** (Scheme 3). However, from the electron affinity energies (−154.5 and 1.8 kJ/mol for **1a**,**b**, respectively), it was concluded that 2-bromodifluoromethyl-1,3-oxazoline **1a** could undergo one-electron reduction when reacting with PhO^- or PhS^-, while 2-trifluoromethyl-1,3-oxazoline **1b** could not undergo the same process. **1a** accepted one electron from PhO^-, which led to C−Br bond weakening (the C−Br bond distance stretched from 2.005 Å for **1a** to 2.825 Å for its radical anion; Figure 1), then the C−Br bond is broken to give the free radical, followed by single-electron transfer to form the $S_{RN}1$ product **2aa** (Scheme 3). On the other hand, **1a** had a much lower LUMO energy than **1b** (>50% difference) (Figure 2). Thus, **1a** had a higher tendency to accept an electron from the HOMO of the nonbonding electron pair of PhO^- for the $S_{RN}1$ reaction. However, for **1b** and its hypothetical radical anion, no significant structural changes were observed (Figure 1), indicating that the C−F bond could not be weakened. As **1b** had a relatively high LUMO energy, it could not carry out the $S_{RN}1$ reaction, preferring to execute ring opening.

The reaction of **1a** with PhO^- proceeded by a single-electron transfer to form the $S_{RN}1$ product, while the reaction with PhS^- took place by a ring-opening process. The different behaviors in the two reactions were difficult to legitimately explain using the energies of PhS^- and PhO^- because of their similarity in energies such as the ionization energies and the HOMO energies. Through the study of the reaction mechanism, we found that the reason for the regioselective reaction pathways of **1a** in the presence of PhO^- and PhS^- could be appraised from the reverse reaction. The hypothetical $S_{RN}1$ product **10** could undergo a reverse reaction: **10** had an electron affinity energy of −57.8 kJ/mol and could be readily reduced by PhS^-. Meanwhile, the C−S bond was weakened during this reduction and the length of the C−S bond was stretched from 1.84 to 2.62 Å (Figure 3). Therefore, PhS^- could be substituted by Br^- reversibly to regenerate the bromodifluoromethylated 1,3-oxazoline **1a**. Thus, the ring-opening reaction of **1a** had a priority due to the strong nucleophilicity of PhS^-. However, **2aa** displayed an electron affinity energy of −23.3 kJ/mol and should be difficult to reduce. In addition, the C−O bond was not significantly weakened in the radical anion of **2aa**, which thus did not undergo the reverse reaction.

CONCLUSION

In conclusion, the reactions of (*S*)-4-benzyl-2-fluoroalkyl-1,3-oxazolines (**1**) with different nucleophiles were studied. (*S*)-4-Benzyl-2-bromodifluoromethyl-1,3-oxazoline (**1a**) reacted with arenethiols to provide biologically interesting, optically active fluoromethylated secondary carboxamides through a nucleophilic ring-opening process at the C5 position of 1,3-oxazoline, while when arenols were used as the nucleophiles, *gem*-difluoromethylene-linked, 1,3-oxazoline-contaning phenyl

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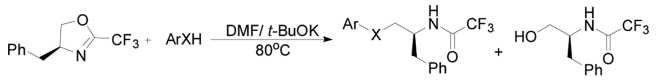
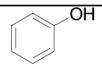
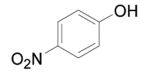
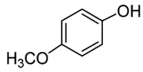
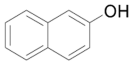
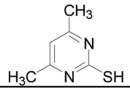
Table 4. Reaction of 1b with Arenethiols and Arenols

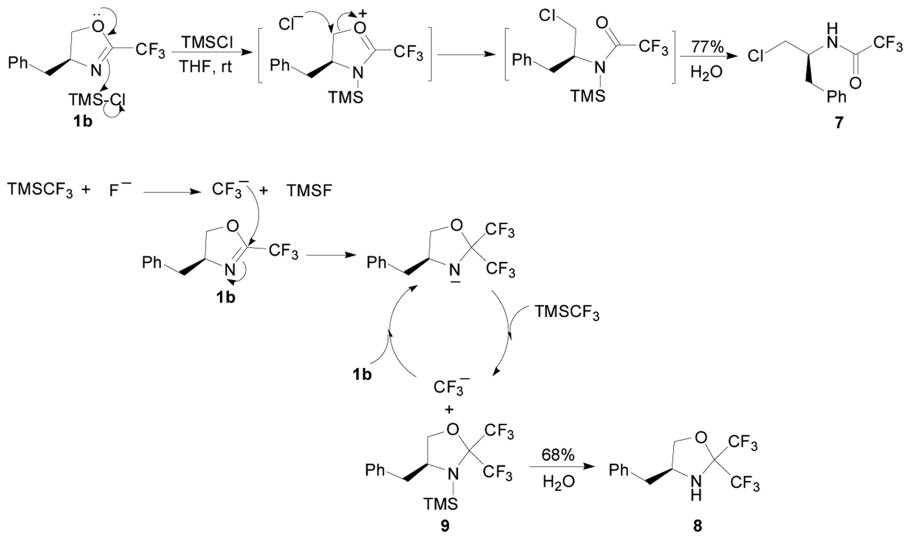


1b 3b 6

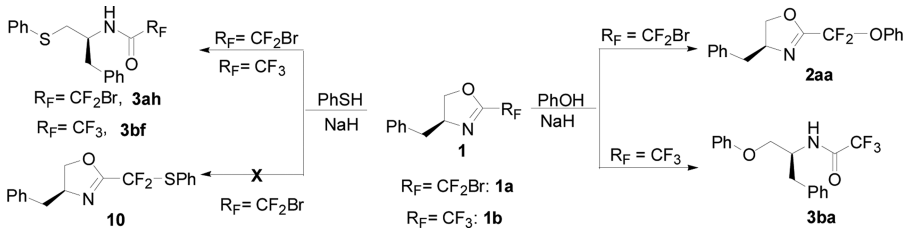
Entry	ArXH	Procedure [a]	Time (h)	Product **3b**	Yield of **3b** (%) [b]	Yield of **6** (%) [b]
1		A	12	**3ba**	90	6
		B	18		20	22
2		A	60	**3bb**	32 [c]	6
		B	45		5 [c]	26
3		A	11	**3bc**	80	4
		B	16		28	19
4		A	11	**3bd**	78	5
		B	20		19	18
5		A	14	**3be**	78 [c]	4
		B	20		12 [c]	21
6		A	8	**3bf**	86	trace
		B	8		46	0
7		A	10	**3bg**	78	5
		B	12		58	0

[a]Procedure A: 1.2:1.0:1.1 **1b**:PhXH:*t*-BuOK reactant molar ratio. Procedure B: 1:1.1:2 **1b**:ArXH:NaH reactant molar ratio. [b]Isolated yield in procedure A based on PhXH; isolated yield in procedure B based on **1b**. [c]With residue of **1b**.

Scheme 4. Selective Reactions of 1b



Scheme 5. Reaction of 1 with Phenol and Thiophenol



ethers **2** as the only regioisomer were obtained via a unimolecular radical nucleophilic substitution reaction ($S_{RN}1$) with the terminal bromine atom of the CF_2Br group. The reaction of (*S*)-4-benzyl-2-trifluoromethyl-1,3-oxazoline (**1b**)

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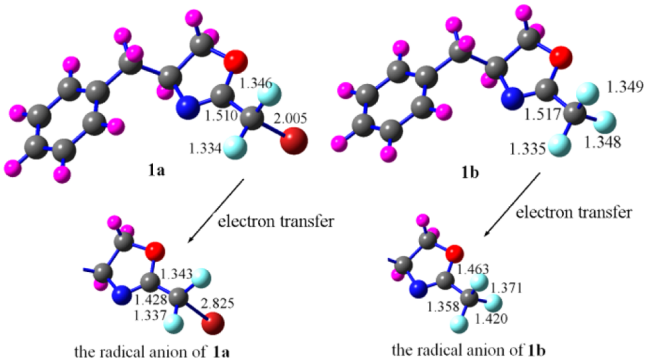

Figure 1. Bond length changes during the electron affinity reactions: gray, C; blue, N; red, O; light blue, F; purple, H; brown, Br.

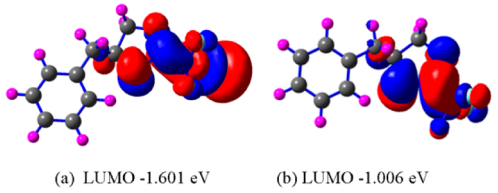

Figure 2. LUMO shapes and energies of **1a** (a) and **1b** (b).

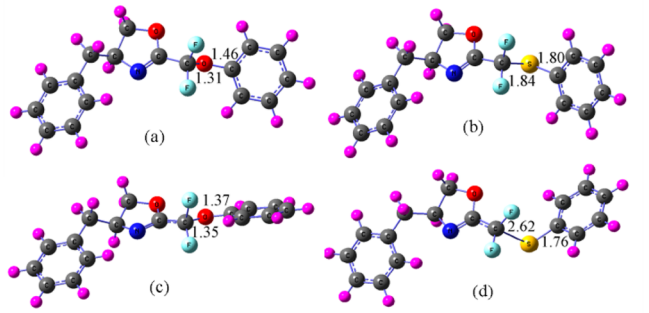

Figure 3. Optimized structures for (a) **2aa**, (b) **10**, (c) the radical anion of **2aa**, and (d) the radical anion of **10**: gray, C; blue, N; red, O; light blue, F; purple, H; yellow, S; brown, Br.

with arenethiols, arenols, and TMSCl was a ring-opening pathway through cleavage of the C5−O1 bond, while the use of $TMSCF_3$ was determined to proceed by nucleophilic addition to the C═N bond to form the product **8**. Selective reactions of (*S*)-4-benzyl-2-bromodifluoromethyl-1,3-oxazoline (**1a**) and (*S*)-4-benzyl-2-trifluoromethyl-1,3-oxazoline (**1b**) with phenol and thiophenol were explained by using density functional theory (DFT) calculations.

EXPERIMENTAL SECTION

General Methods. *General Comments.* ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on 500 MHz spectrometers. Chemical shifts for ^{1}H NMR spectra are reported in ppm 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 ($CFCl_3$). Infrared spectra (IR) were recorded with KBr pellets. Silica gel (200−400 mesh) was used for flash column chromatography. Melting points are uncorrected. Optical rotations were recorded on a highly sensitive polarimeter with a 200 mm cell. High-resolution mass spectrometry (HRMS) was conducted by TOF MS with electron impact (EI) ionization at 70 eV. Mass spectra were obtained using EI. DFT calculations were carried out at the B3LYP/6-311+G(d)//SDD level of theory as implemented in the program suite of GAUSSIAN 2003.

*Procedure a for the Synthesis of Compounds **2**, **3**, **5**, and **6**.* A 25 mL, three-necked, round-bottom flask was charged with NaH (2 mmol, 60% weight) and 10 mL of dry DMF under a nitrogen atmosphere. To the stirred suspension was added the arenethiol or arenol (1.1 mmol). Hydrogen gas was evolved, and the flask became warm. After the mixture was stirred for 30 min, a clear solution was obtained. Then the substrate **1** (1 mmol) in 5 mL of DMF was added dropwise, and the solution was stirred at 80 °C for 8−45 h. The mixture was poured into 5 mL of ice water and then extracted three times with 10 mL portions of ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation at reduced pressure. The residue was then purified by column chromatography (2:1 petroleum ether:ethyl acetate) on basic aluminum oxide to offer the products **2**, **3**, **5**, and **6.**

Optimal procedure for the synthesis of products **3b**: to a stirred suspension of *t*-BuOK (0.054 g, 0.480 mmol) and the arenethiol or arenol (0.437 mmol) in 2 mL of dry DMF under nitrogen atmosphere was added dropwise the substrate **1b** (0.120 g, 0.524 mmol) in 1 mL of DMF. Then the solution was stirred at 80 °C. With reference to the separation processes described above, the products **3b** were obtained.

*(S)-4-Benzyl-2-(difluorophenoxymethyl)-4,5-dihydrooxazole (**2aa**):* colorless oil; yield 0.20 g, 68%; $[\alpha]_D^{25}$ = −20.6° (*c* = 1.36, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 7.33−7.14 (m, 10H), 4.55−4.49 (m, 1H), 4.32 (t, *J* = 9.0 Hz, 1H), 4.12 (t, *J* = 8.5 Hz, 1H), 3.12 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.65 (dd, *J* = 14.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.4 (t, $^2J_{C-F}$ = 38.8 Hz), 149.5, 136.7, 129.5, 129.2, 128.6, 126.8, 126.3, 121.9, 115.2 (t, $^1J_{C-F}$ = 261.3 Hz,), 73.4, 67.5, 40.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.69 (s, 2F); IR (KBr, cm^{-1}) ν 3065, 3029, 2925, 1687, 1492, 1393, 1197, 1109, 741, 701; HRMS (EI TOF) calcd for (M^+) $C_{17}H_{15}F_2NO_2$ 303.1071, found 303.1073.

*(S)-4-Benzyl-2-(difluoro(4-nitrophenoxy)methyl)-4,5-dihydrooxazole (**2ab**):* yellow oil; yield 0.26 g, 76%; $[\alpha]_D^{25}$ = −18.6° (*c* = 0.54, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 8.28 (td, *J* = 9.5, 2.5 Hz, 2H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.34 (t, *J* = 7.0 Hz, 2H), 7.29−7.27 (m, 1H), 7.22 (d, *J* = 7.0 Hz, 2H), 4.68−4.62 (m, 1H), 4.48 (t, *J* = 9.0 Hz, 1H), 4.26 (t, *J* = 8.0 Hz, 1H), 3.21 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.79 (dd, *J* = 14.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (t, $^2J_{C-F}$ = 37.5 Hz), 154.4, 145.5, 136.6, 129.3, 128.8, 127.1, 125.6, 121.8, 115.2 (t, $^1J_{C-F}$ = 265.0 Hz), 73.8, 67.7, 40.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.37 (d, *J* = 10.2, 2F); IR (KBr, cm^{-1}) ν 3043, 2930, 1688, 1476, 1375, 1235, 1109, 969, 705. Anal. Calcd for $C_{17}H_{14}F_2N_2O_4$ (348.09): C, 58.62; H, 4.05; N, 8.04. Found: C, 58.66; H, 3.98; N, 8.01

*(S)-4-Benzyl-2-(difluoro(4-methoxyphenoxy)methyl)-4,5-dihydrooxazole (**2ac**):* colorless oil; yield 0.22 g, 65%; $[\alpha]_D^{25}$ = −14.6° (*c* = 0.86, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 7.31 (t, *J* = 7.5 Hz, 2H), 7.25−7.18 (m, 5H), 6.88−6.84 (m, 2H), 4.59−4.53 (m, 1H), 4.37 (t, *J* = 9.0 Hz, 1H), 4.17 (t, *J* = 8.0 Hz, 1H), 3.75 (s, 3H), 3.16 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.70 (dd, *J* = 14.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 157.4 (t, $^2J_{C-F}$ = 38.8 Hz), 142.6, 136.8, 129.1, 128.6, 126.7, 123.2, 115.2 (t, $^1J_{C-F}$ = 260.0 Hz), 114.3, 73.3, 67.4, 55.4, 40.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.94 (s, 2F); IR (KBr, cm^{-1}) ν 3050, 2936, 1678, 1485, 1385, 1208, 1088, 950, 696. Anal. Calcd for $C_{18}H_{17}F_2NO_3$ (333.11): C, 64.86; H, 5.14; N, 4.20. Found: C, 64.92; H, 5.11; N, 4.24.

*(S)-4-Benzyl-2-(difluoro(naphthalen-2-yloxy)methyl)-4,5-dihydrooxazole (**2ad**):* yellow oil; yield 0.23 g, 66%; $[\alpha]_D^{25}$ = −9.3° (*c* = 1.39, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 7.85−7.81 (m, 3H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.53−7.47 (m, 2H), 7.38 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 2H), 7.25−7.22 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 2H), 4.63−4.57 (m, 1H), 4.42 (t, *J* = 9.0 Hz, 1H), 4.21 (t, *J* = 8.0 Hz, 1H), 3.19 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.68 (dd, *J* = 14.0, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6 (t, $^2J_{C-F}$ = 38.8 Hz), 147.2, 136.8, 133.7, 131.6, 129.7, 129.3, 128.8, 127.8, 127.8, 126.9, 126.1, 121.3, 119.0, 115.5 (t, $^1J_{C-F}$ = 261.3 Hz), 73.6, 67.7, 40.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.62 (s, 2F); IR (KBr, cm^{-1}) ν 3023, 2968, 1697, 1456, 1398, 1275, 1088, 926, 712. Anal. Calcd for $C_{21}H_{17}F_2NO_2$

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(353.12): C, 71.38; H, 4.85; N, 3.96. Found: C, 71.43; H, 4.81; N, 3.98.

*(S)-3-((4-Benzyl-4,5-dihydrooxazol-2-yl)difluoromethoxy)pyridine (**2ae**):* yellow oil; yield 0.22 g, 73%; $[\alpha]_D^{25}$ = −10.6° (*c* = 1.20, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 8.53 (m, 2H), 7.58 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.32−7.28 (m, 3H), 7.24−7.21 (m, 1H), 7.18 (d, *J* = 7.1 Hz, 2H), 4.62−4.56 (m, 1H), 4.41 (t, *J* = 8.5 Hz, 1H), 4.20 (t, *J* = 8.0 Hz, 1H), 3.17 (dd, *J* = 14.0, 5.5 Hz, 1H), 2.71 (dd, *J* = 14.0, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0 (t, $^2J_{C-F}$ = 38.8 Hz), 147.6, 143.9, 136.6, 129.4, 129.3, 128.8, 126.9, 124.1, 115.2 (t, $^1J_{C-F}$ = 263.8 Hz), 73.7, 67.6, 40.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −72.06 (s, 2F); IR (KBr, cm^{-1}) ν 3035, 2916, 1665, 1477, 1385, 1289, 1075, 981, 696; HRMS (EI TOF) calcd for (M^+) $C_{16}H_{14}F_2N_2O_2$ 304.1023, found 304.1021.

*(S)-4-Benzyl-2-(difluoro(o-tolyloxy)methyl)-4,5-dihydrooxazole (**2af**):* colorless oil; yield 0.24 g, 75%; $[\alpha]_D^{25}$ = −25.4° (*c* = 1.38, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 7.35−7.32 (m, 2H), 7.30−7.24 (m, 3H), 7.24−7.16 (m, 4H), 4.64−4.58 (m, 1H), 4.41 (t, *J* = 9.0 Hz, 1H), 4.21 (t, *J* = 8.0 Hz, 1H), 3.20 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.74 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7 (t, $^2J_{C-F}$ = 39.2 Hz), 148.1, 136.9, 131.7, 131.4, 128.7, 126.9, 126.8, 122.2, 115.5 (t, $^1J_{C-F}$ = 262.7 Hz), 73.5, 67.6, 40.9, 16.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −71.10 (dd, *J* = 183.4, 152.8 Hz, 2F); IR (KBr, cm^{-1}) ν 3063, 3029, 2929, 1685, 1494, 1393, 1172, 1120, 749, 702. Anal. Calcd for $C_{18}H_{17}F_2NO_2$ (317.12): C, 68.13; H, 5.40; N, 4.41. Found: C, 68.07; H, 5.34; N, 4.37.

*(S)-4-Benzyl-2-((2,6-dimethylphenoxy)difluoromethyl)-4,5-dihydrooxazole (**2ag**):* colorless oil; yield 0.26 g, 78%; $[\alpha]_D^{25}$ = −9.5° (*c* = 1.20, $CHCl_3$); ^{1}H NMR (500 MH_Z, $CDCl_3$) δ 7.35 (t, *J* = 7.5 Hz, 2H), 7.26 (dd, *J* = 18.8, 7.3 Hz, 3H), 7.0 (s, 3H), 4.67−4.61 (m, 1H), 4.42 (t, *J* = 9.0 Hz, 1H), 4.22 (t, *J* = 8.0 Hz, 1H), 3.22 (dd, *J* = 14.0, 5.3 Hz, 1H), 2.78 (dd, *J* = 14.0, 8.5 Hz, 1H), 2.40 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9 (t, $^2J_{C-F}$ = 39.3 Hz), 146.9, 136.9, 132.8, 129.4, 128.7, 126.9, 126.5, 116.2 (t, $^1J_{C-F}$ = 264.2 Hz), 73.5, 67.5, 40.9, 17.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ −69.82 (dd, *J* = 164.5, 152.9 Hz, 2F); IR (KBr, cm^{-1}) ν 3063, 3028, 2931, 1686, 1474, 1390, 1160, 1113, 773, 702. Anal. Calcd for $C_{19}H_{19}F_2NO_2$ (317.12): C, 68.87; H, 5.78; N, 4.23. Found: C, 68.84; H, 5.71; N, 4.21.

*(S)-N-(1-Benzyl-2-phenylsulfanylethyl)-2-bromo-2,2-difluoroacetamide (**3ah**):* pale yellow solid; mp 118.6−119.5 °C; yield 0.32 g, 79%; $[\alpha]_D^{25}$ = +25.1° (*c* = 1.21, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.37 (m, 2H), 7.33−7.29 (m, 4H), 7.27−7.22 (m, 2H), 7.17−7.15 (m, 2H), 6.30 (d, *J* = 7.5 Hz, 1H), 4.37−4.30 (m, 1H), 3.14−3.06 (m, 2H), 3.01 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (t, $^2J_{C-F}$ = 27.5 Hz), 136.2, 134.9, 130.2, 129.4, 128.8, 127.1, 127.1, 111.5 (t, $^1J_{C-F}$ = 315.0 Hz), 51.3, 38.7, 37.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.74 (s, 2F); IR (KBr, cm^{-1}) ν 3382, 3049, 2942, 1669, 1527, 1441, 1276, 1078, 970, 715; HRMS (EI TOF) calcd for (M^+) $C_{17}H_{16}BrF_2NOS$ 399.0104, found 399.0101.

*(S)-N-(1-Benzyl-2-phenylsulfanylethyl)-2,2-difluoro-2-phenylsulfanylacetamide (**5**):* pale yellow solid; mp 97.0−97.6 °C; yield 0.064 g, 15%; $[\alpha]_D^{25}$ = +11.5° (*c* = 1.14, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.0 Hz, 2H), 7.45−7.42 (m, 1H), 7.38−7.35 (m, 4H), 7.32−7.21 (m, 6H), 7.11 (d, *J* = 7.0 Hz, 2H), 6.28 (d, *J* = 8.0 Hz, 1H), 4.31−4.24 (m, 1H), 3.01−2.84 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ161.1 (t, $^2J_{C-F}$ = 27.5 Hz), 136.8, 136.4, 135.1, 130.6, 130.0, 129.5, 129.4, 129.3, 128.8, 127.1, 126.9, 125.0, 122.3 (t, $^1J_{C-F}$ = 287.5 Hz), 50.7, 38.4, 36.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −82.46 (s, 2F); IR (KBr, cm^{-1}) ν 3412, 3060, 3028, 2951, 1676, 1540, 1478, 1441, 1214, 1059, 987; HRMS (EI TOF) calcd for (M^+) $C_{23}H_{21}F_2NOS_2$ 429.1033, found 429.1032. Anal. Calcd for $C_{23}H_{21}F_2NOS_2$ (429.55): C, 64.31; H, 4.93; N, 3.26. Found: C, 64.16; H, 5.018; N, 3.207.

*(S)-N-[1-Benzyl-2-(4,6-dimethylpyrimidin-2-ylsulfanyl)ethyl]-2-bromo-2,2-difluoro-acetamide (**3ai**):* white solid; mp 145.3−146.0 °C; yield 0.34 g, 78%; $[\alpha]_D^{25}$ = −33.5° (*c* = 1.15, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (d, *J* = 5.5 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.0 Hz, 2H), 7.27 (t, *J* = 7.0 Hz, 3H), 6.76 (s, 1H), 4.36−4.29 (m, 1H), 3.36 (dd, *J* = 10.0, 5.0 Hz, 1H), 3.22 (dd, *J* = 13.5, 4.0 Hz, 1H), 3.17 (dd, *J* = 15.0, 3.5 Hz, 1H), 2.94 (dd, *J* = 13.5, 8.5 Hz, 1H), 2.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 167.5, 160.0 (t, $^2J_{C-F}$ = 26.3 Hz), 136.6, 129.8, 128.7, 127.0, 116.5, 111.8 (t, $^1J_{C-F}$ = 315.0 Hz), 54.5, 39.6, 32.7, 23.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.63 (dd, 2F); IR (KBr, cm^{-1}) ν 3364, 3084, 3028, 2924, 1699, 1584, 1265, 1115, 964. Anal. Calcd for $C_{17}H_{18}BrF_2N_3OS$ (429.03): C, 47.45; H, 4.22; N, 9.77. Found: C, 47.67; H, 4.21; N, 9.77.

*(S)-N-[2-(Benzothiazol-2-ylsulfanyl)-1-benzylethyl]-2-bromo-2,2-difluoroacetamide (**3aj**):* pale yellow solid; mp 134.3−135.4 °C; yield 70.34 g, 5%; $[\alpha]_D^{25}$ = −36.9° (*c* = 1.11, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.40 (d, *J* = 6.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.49−7.46 (m, 1H), 7.38−7.28 (m, 6H), 4.48−4.42 (m, 1H), 3.43 (d, *J* = 6.0 Hz, 2H), 3.35 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.95 (dd, *J* = 13.5, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 160.3 (t, $^2J_{C-F}$ = 27.5 Hz), 152.1, 136.7, 135.5, 129.5, 128.9, 127.1, 126.6, 125.0, 121.4, 121.2, 111.9 (t, $^1J_{C-F}$ = 315.0 Hz), 53.8, 39.1, 35.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −60.27 (s, 2F); IR (KBr, cm^{-1}) ν 3359, 3064, 3029, 2928, 1697, 1547, 1426, 1134, 1080, 958, 751, 698. Anal. Calcd for $C_{18}H_{15}BrF_2N_2OS_2$ (455.97): C, 47.27; H, 3.31; N, 6.13; Found: C, 47.19; H, 3.27; N, 6.15.

*(S)-2,2,2-Trifluoro-N-(1-phenoxy-3-phenylpropan-2-yl)acetamide (**3ba**):* white solid; mp 124.7−126.2 °C; yield 0.13^A/0.064^B g, 90/20%; $[\alpha]_D^{25}$ = −18.7° (*c* = 2.00, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 7.24−7.22 (m, 2H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.93−6.91 (m, 2H), 6.78 (d, *J* = 7.5 Hz, 1H), 4.55−4.49 (m, 1H), 4.00−3.94 (m, 2H), 3.09 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.1, 156.9 (q, $^2J_{C-F}$ = 36.3 Hz), 136.4, 129.7, 129.4, 128.9, 127.2, 121.8, 115.8 (q, $^1J_{C-F}$ = 286.3 Hz), 114.6, 66.6, 51.0, 36.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.83 (s, 3F); IR (KBr, cm^{-1}) ν 3318, 3106, 2911, 1706, 1589, 1560, 1246, 1208, 1179, 880, 754, 703, Anal. Calcd for $C_{17}H_{16}F_3NO_2$ (323.11): C, 63.15; H, 4.99; N, 4.33. Found: C, 63.07; H, 4.86; N, 4.22.

*(S)- N-[1-Benzyl-2-(4-nitrophenoxy)ethyl]-2,2,2-trifluoroacetamide (**3bb**):* pale yellow solid; mp 183.2−184.3 °C; yield 0.052^A/0.018^B g, 32/5%; $[\alpha]_D^{25}$ = −4.4° (*c* = 1.10, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24−8.21 (m, 2H), 7.34−7.27 (m, 3H), 7.19−7.17 (m, 2H), 6.98−6.95 (m, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 4.60−4.54 (m, 1H), 4.11−4.03 (m, 2H), 3.13−3.05 (m, 2H); ^{13}C NMR (125 MHz, CD_3COCD_3) δ 164.3, 157.2 (q, $^2J_{C-F}$ = 36.3 Hz), 142.4, 138.0, 129.8, 129.0, 127.2, 126.3, 116.7 (q, $^1J_{C-F}$ = 286.3 Hz), 115.5, 69.6, 51.9, 36.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.82 (s, 3F); IR (KBr, cm^{-1}) ν 3311, 3121, 2923, 1700, 1593, 1562, 1503, 1332, 1264, 1179, 884, 756, 701. Anal. Calcd for $C_{17}H_{15}F_3N_2O_4$ (368.09): C, 55.44; H, 4.11; N, 7.61. Found: C, 55.38; H, 4.03; N, 7.57.

*(S)- N-[1-Benzyl-2-(4-methoxyphenoxy)ethyl]-2,2,2-trifluoroacetamide (**3bc**):* white solid; mp 145.3−146.0 °C; yield 0.12^A/0.098^B g, 80/28%; $[\alpha]_D^{25}$ = −16.6° (*c* = 2.01, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.22 (m, 5H), 6.87−6.85 (m, 4H), 6.83 (s, 1H), 4.51−4.46 (m, 1H), 3.94−3.88 (m, 2H), 3.78 (s, 3H), 3.08 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.9 (q, $^2J_{C-F}$ = 36.3 Hz), 154.6, 152.3, 136.5, 129.4, 128.9, 127.2, 115.9 (q, $^1J_{C-F}$ = 286.3 Hz), 115.7, 114.9, 67.5, 55.8, 51.1, 36.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.83 (s, 3F); IR (KBr, cm^{-1}) ν 3357, 3146, 2925, 1696, 1550, 1514, 1352, 1255, 1240, 1174, 910, 827, 768, 720, 694. Anal. Calcd for $C_{18}H_{18}F_3NO_3$ (353.12): C, 61.19; H, 5.13; N, 3.96. Found: C, 61.11; H, 5.06; N, 3.84.

*(S)-N-[1-Benzyl-2-(naphthalen-2-yloxy)ethyl]-2,2,2-trifluoroacetamide (**3bd**):* white solid; mp 127.3−129.0 °C; yield 0.13^A/0.07^B g, 78/19%; $[\alpha]_D^{25}$ = −14.8° (*c* = 1.02, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83−7.81 (m, 2H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.51−7.47 (m, 1H), 7.42−7.39 (m, 1H), 7.35−7.22 (m, 6H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 4.63−4.57 (m, 1H), 4.11−4.06 (m, 2H), 3.14 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0 (q, $^2J_{C-F}$ = 36.3 Hz), 156.1, 136.4, 134.5, 129.9, 129.4, 129.0, 127.8, 127.2, 127.0, 126.9, 124.2, 118.5, 115.9 (q, $^1J_{C-F}$ = 286.3 Hz), 107.2, 66.7, 51.0, 37.0; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.75 (s, 3F); IR (KBr, cm^{-1}) ν 3420, 3102, 2927, 1704, 1557, 1259, 1176, 875, 837, 759, 744, 701. Anal. Calcd for $C_{21}H_{18}F_3NO_2$ (373.12): C, 67.55; H, 4.86; N, 3.75. Found: C, 67.48; H, 4.79; N, 3.71.

*(S)-N-[1-Benzyl-2-(pyridin-3-yloxy)ethyl]-2,2,2-trifluoroacetamide (**3be**):* white solid; mp 134.2−136.3 °C; yield 0.11^A/0.038^B g, 78/12%; $[\alpha]_D^{25}$ = −5.4° (*c* = 0.91, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ

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8.31 (d, J = 3.0 Hz, 1H), 8.24 (d, J = 4.5 Hz, 1H), 7.32−7.14 (m, 8H), 4.57−4.51 (m, 1H), 4.05−3.97 (m, 2H), 3.09 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1 (q, $^2J_{C-F}$ = 37.5 Hz), 154.5, 143.0, 138.1, 136.2, 129.3, 129.1, 127.4, 124.2, 121.2, 115.9 (q, $^1J_{C-F}$ = 286.3 Hz), 67.2, 50.9, 36.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.71 (s, 3F); IR (KBr, cm^{-1}) ν 3390, 3034, 2929, 1704, 1575, 1475, 1287, 1112, 1054, 883, 798, 703, 613; HRMS (EI TOF) calcd for (M^+) $C_{16}H_{15}F_3N_2O_2$ 324.1086, found 324.1085.

*(S)-N-(1-Benzyl-2-phenylsulfanylethyl)-2,2,2-trifluoroacetamide (**3bf**):* pale yellow solid; mp 48.1−49.6 °C; yield 0.13^A/0.16^B g, 89/46%; mp 48.1−49.6 °C; $[\alpha]_D^{25}$ = +6.6° (c = 1.05, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.36 (m, 2H), 7.33−7.24 (m, 6H), 7.23−7.14 (m, 2H), 6.48 (s, 1H), 4.39−4.32 (m, 1H), 3.16 (dd, J = 14.5, 7.5 Hz, 2H), 3.08 (dd, J = 12.0, 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (q, $^2J_{C-F}$ = 37.5 Hz), 136.2, 134.8, 130.3, 129.4, 129.3, 128.9, 127.3, 127.2, 115.7 (q, $^1J_{C-F}$ = 286.3 Hz), 51.2, 42.4, 38.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.99 (s, 3F); IR (KBr, cm^{-1}) ν 3367, 3041, 2933, 1670, 1543, 1429, 1266, 1078, 968, 701. Anal. Calcd for $C_{17}H_{16}F_3NOS$ (339.09): C, 60.16; H, 4.75; N, 4.13. Found: C, 60.06; H, 4.68; N, 4.10.

*(S)- N-[1-Benzyl-2-(4,6-dimethylpyrimidin-2-ylsulfanyl)ethyl]-2,2,2-trifluoroacetamide (**3bg**):* white solid; mp 149.3−151.0 °C; yield 0.13^A/0.26^B g, 78/58%; $[\alpha]_D^{25}$ = +42.2° (c = 2.55, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, J = 5.5 Hz, 1H), 7.37−7.27 (m, 5H), 6.77 (s, 1H), 4.40−4.33 (m, 1H), 3.34 (dd, J = 9.5, 15.0 Hz, 1H), 3.24 (td, J = 3.5, 13.5 Hz, 2H), 2.96 (dd, J = 8.5, 13.5 Hz, 1H), 2.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 167.6, 157.2 (q, $^2J_{C-F}$ = 36.3 Hz), 136.7, 129.7, 128.8, 127.1, 116.6, 116.0 (q, $^1J_{C-F}$ = 286.3 Hz), 54.4, 39.4, 32.8, 29.8, 23.7; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.88 (s, 3F); IR (KBr, cm^{-1}) ν 3399, 3110, 2925, 1703, 1587, 1563, 1534, 1341, 1264, 1223, 1183, 880, 752, 724, 700. Anal. Calcd for $C_{17}H_{18}F_3N_3OS$ (369.11): C, 55.27; H, 4.91; N, 11.38. Found: C, 55.17; H, 4.87; N, 11.25.

*(S)-N-(1-Benzyl-2-hydroxyethyl)-2,2,2-trifluoroacetamide (**6**):* white solid; mp 172.3−173.0 °C; $[\alpha]_D^{25}$ = −18.1° (c = 2.02, acetone); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34−7.31 (m, 2H), 7.28−7.25 (m, 1H), 7.23−7.21 (m, 2H), 6.61 (s, 1H), 4.27−4.21 (m, 1H), 3.74−3.67 (m, 2H), 2.99−2.92 (m, 2H), 1.71 (s, 1H); ^{13}C NMR (125 MHz, DMSO) δ 156.4 (q, $^2J_{C-F}$ = 36.3 Hz), 138.8, 129.4, 128.6, 126.6, 116.4 (q, $^1J_{C-F}$ = 286.3 Hz), 62.8, 54.4, 36.3; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.90 (s, 3F); IR (KBr, cm^{-1}) ν 3400, 3109, 2936, 1699, 1561, 1225, 1207, 1179, 877, 751, 727, 701. Anal. Calcd for $C_{11}H_{12}F_3NO_2$ (247.08): C, 53.44; H, 4.89; N, 5.67. Found: C, 53.37; H, 4.82; N, 5.49.

*Procedure for the Synthesis of **7**.* A 25 mL, three-necked, round-bottom flask was charged with THF (2 mL) and the substrate **1b** (0.88 mmol) under a nitrogen atmosphere. To the stirred suspension was added TMSCl (3.14 mmol). This mixture was stirred at room temperature for 2 h and was then poured into 5 mL of water and extracted three times with 10 mL portions of ethyl acetate. The combined organic layers were washed with saturated brine and then were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation at reduced pressure after filtering. The residue was then purified by column chromatography (20:1 petroleum ether:ethyl acetate) to yield 178 mg of the product **7.**

*N-((S)-3-Chloro-1-phenylpropan-2-yl)-2,2,2-trifluoroacetamide (**7**):* white solid; mp 89−90 °C; yield 0.18 g, 77%; $[\alpha]_D^{25}$ = −1.6° (c = 0.90, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.33 (m, 2H), 7.30−7.23 (m, 3H), 6.53 (s, 1H), 4.50−4.45 (m, 1H), 3.68 (dd, J = 11.5, 4.0 Hz, 1H), 3.56 (dd, J = 11.5, 3.5 Hz, 1H), 3.04−2.96 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7 (q, $^2J_{C-F}$ = 36.8 Hz), 135.6, 129.2, 129.0, 127.4, 115.6 (q, $^1J_{C-F}$ = 286.0 Hz), 51.5, 45.4, 37.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.91 (s, 3F); IR (KBr, cm^{-1}) ν 3301, 3074, 1701, 1606, 1495, 1227, 1175, 754, 699; MS (EI) m/z (%) 265(1) (M^+), 154 (15) (M^+ − H_2NCOCF_3), 152 (46) (M^+ − H_2NCOCF_3), 91 (100) ($PhCH_2$). Anal. Calcd for $C_{11}H_{11}ClF_3NO$ (265.05): C, 49.73; H, 4.17; N, 5.27. Found: C, 49.63; H, 4.09; N, 5.24.

*Procedure for the Synthesis of **8**.* A 25 mL, three-necked, round-bottom flask was charged with KF (0.2 mmol), and then the substrate **1b** (0.8 mmol) in 2 mL of dry DMF was added under a nitrogen atmosphere. To the stirred suspension was added $TMSCF_3$ (2.0 mmol), and then the mixture was stirred at room temperature for 1 h. The mixture was poured into 5 mL of water and then extracted three times with 10 mL portions of ethyl acetate. The combined organic layers were washed with saturated brine and then were dried over anhydrous $MgSO_4$ and concentrated by rotary evaporation at reduced pressure. The residue was then purified by column chromatography (petroleum ether) to yield 162 mg of the product **8.**

*(S)-4-Benzyl-2,2-bis(trifluoromethyl)oxazolidine (**8**):* yellow oil; yield 0.16 g, 70%; $[\alpha]_D^{25}$ = −2.2° (c = 0.82, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 2H), 4.26 (dd, J = 7.0 Hz, J = 6.8 Hz, 1H), 3.93−3.86 (m, 1H), 3.81 (dd, J = 7.1 Hz, J = 8.0 Hz, 1H), 2.93 (dd, J = 7.0, 13.5 Hz, 1H), 2.82 (dd, J = 6.5, 13.5 Hz, 1H), 2.67 (d, J = 6.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.2, 128.9, 128.8, 127.0, 122.1 (q, $^1J_{C-F}$ = 288.3 Hz), 121.9 (q, $^1J_{C-F}$ = 287.1 Hz), 91.5−92.5 (m), 74.3, 58.8, 39.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ −79.61 (q, J = 8.5 Hz, 3F), −79.77 (q, J = 8.5 Hz, 3F); IR (KBr, cm^{-1}) ν 3382, 3031, 1604, 1498, 1216, 1131, 757, 702. Anal. Calcd for $C_{12}H_{11}F_6NO$ (299.07): C, 48.17; H, 3.71; N, 4.68. Found: C, 48.01; H, 3.65; N, 4.53.

*Procedure for the Synthesis of **9**.* A 25 mL, three-necked, round-bottom flask was charged with KF (0.2 mmol), and then a mixture of the substrate **1b** (0.8 mmol) and $TMSCF_3$ (2.0 mmol) in 2 mL of superdry DMF was added under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then was concentrated by rotary evaporation at reduced pressure. The residue was then purified by column chromatography to offer the intermediate **9.**

*(S)-N-Trimethylsilanyl-4-benzyl-2,2-bis(trifluoromethyl)-oxazolidine (**9**):* pale yellow solid; mp 41−43 °C; $[\alpha]_D^{25}$ = −12.3° (c = 1.20, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (t, J = 7.0 Hz, 2H), 7.28 (dd, J = 7.0, 6.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 2H), 4.03 (d, J = 8.0 Hz, 1H), 3.95−3.93 (m, 1H), 3.86 (t, J = 7.0 Hz, 1H), 3.00 (d, J = 13.5 Hz, 1H), 2.80 (t, J = 13.0 Hz, 1H), 0.40 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 129.1, 128.9, 126.8, 122.5 (q, $^1J_{C-F}$ = 291.3 Hz), 121.8 (q, $^1J_{C-F}$ = 286.3 Hz), 94.2−93.7 (m), 71.0, 63.3, 41.7, 1.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −75.14 (q, J = 8.9 Hz, 3F), −76.47 (q, J = 8.9 Hz, 3F); IR (KBr, cm^{-1}) ν 3031, 1604, 1496, 1208, 1136, 843, 746, 702. Anal. Calcd for $C_{15}H_{19}F_6NOSi$ (371.11): C, 48.51; H, 5.16; N, 3.77. Found: C, 48.48; H, 5.13; N, 3.69.

■ ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and CIF files giving experimental details, characterization data (including ^{1}H, ^{13}C, and ^{19}F NMR spectra) for the compounds synthesized, information of single-crystal XRD, and information and the results of the theoretical calculations. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 876227 also contains supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, U.K. (fax: +44 1223 336033).

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Notes

The authors declare no competing financial interest.

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