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Oxidation of fluoroalkyl alcohols using sodium hypochlorite pentahydrate [1]

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ABSTRACT

Fluoroalkyl alcohols are effectivity oxidized to the corresponding fluoroalkyl carbonyl compounds by reaction with sodium hypochlorite pentahydrate in acetonitrile in the presence of acid and nitroxyl radical catalysts. Although the reaction proceeded slower under a nitroxyl radical catalyst- free condition, the desired carbonyl compounds were obtained in high yields. For the reaction with fluoroalkyl allylic alcohols, the corresponding α,β-epoxyketone hydrates were obtained in high yields.

1. Introduction

Fluoroalkyl carbonyl compounds, represented by the trifluoromethyl ketones, are very important and attractive building blocks for the syntheses of fluorine-containing organic molecules in several fields of science & industry (medicinal chemistry, pharmaceutical science, material science, agricultural chemistry, etc.) [2]. Several methods of generating fluoroalkyl carbonyl compounds have been developed. Among them, the oxidation of fluoroalkyl alcohols is one of the most useful methods [3].

The secondary fluoroalkyl alcohols are easily prepared by the Ruppert-Prakash reaction {the reaction of aldehydes with trimethylsilylated fluoroalkanes [(trifluoromethyl)trimethylsilane ($TMSCF_3$), (difluoromethyl)trimethylsilane ($TMSCHF_2$), etc.]} [4], however, the fluoroalkyl alcohols are generally hard to be oxidized due to the strong electron withdrawing fluoroalkyl groups. Therefore, very strong oxidants, such as the Dess-Martin reagent [3a,b] or chromium(VI) [3c], are required to obtain the fluoroalkyl ketones from the secondary fluoroalkyl alcohols (Scheme 1). Although these oxidants afford the desired products, the Dess-Martin reagent is expensive and explosive, and chromium(VI) is highly toxic. To overcome these drawbacks of the conventional methods of oxidation of fluoroalkyl alcohols, several new reactions have recently been developed [3d-i].

We have developed the oxidation of alcohols with sodium hypochlorite pentahydrate ($NaOCl{\cdot}5H_2O$) catalyzed by TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) (Scheme 2) [5c,f]. This reaction efficiently provides the corresponding carbonyl compounds in high yields, and the experimental procedure is simple and easy. Moreover, this method is environmentally benign because the postoxidation waste is harmless "table salt" (NaCl) [5,6].

During the course of our study of the oxidation by $NaOCl{\cdot}5H_2O$, we found that secondary alcohols bearing fluoroalkyl groups were efficiently oxidized to the corresponding ketones by $NaOCl{\cdot}5H_2O$ catalyzed by TEMPO [1]. Recently, Leadbeatear and Eddy et al. reported that 2,2,6,6-tetramethylpiperidine-4-acetamido-hydroxyammonium tetrafluoroborate (4-AcO-TEMPOH·BF_4) is a good catalyst for the oxidation of alcohols by $NaOCl{\cdot}5H_2O$ [6d]. Although secondary fluoroalkylalcohols were also effectively oxidized to the corresponding ketones by their method [6d], 4-AcO-TEMPOH·BF_4 is not commercially available and has to be prepared from the relatively expensive 4-AcO--TEMPO. We further examined the oxidation of fluoroalkylalcohols with $NaOCl{\cdot}5H_2O$, and found that commercially available and inexpensive TEMPO is a good catalyst for oxidation of several fluoroalkylalcohols including some primary alcohols. For the secondary fluoroalkylalcohols, $NaOCl{\cdot}5H_2O$ provided the desired ketones under a catalyst-free condition. We also found that fluoroalkyl allylic alcohols afforded the corresponding α,β-epoxyketone hydrates. This article will describe the full details of our results (Scheme 3).

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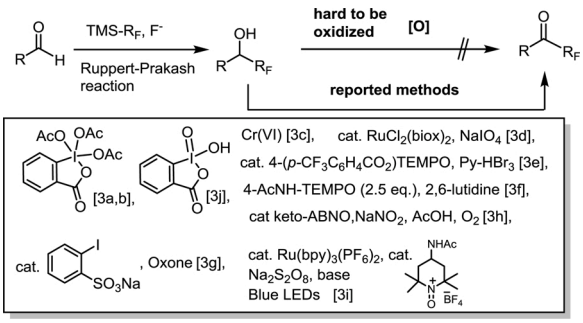
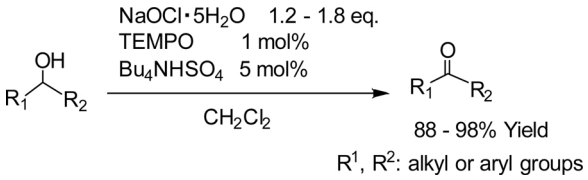
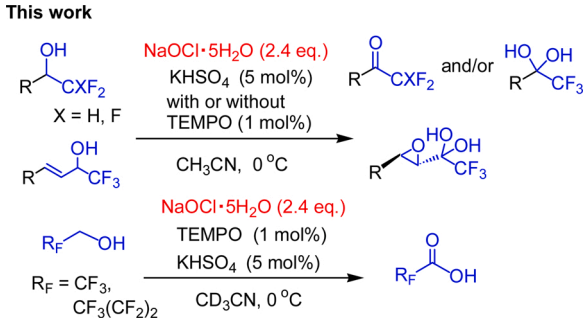


Scheme 1. Oxidation of fluoroalkyl alcohols.



Scheme 2. Oxidation of alcohols with NaOCl·5H$_2$O catalyzed by TEMPO.



Scheme 3. Oxidation of fluoroalkylalcohols using NaOCl·5H$_2$O.

2. Results and discussion

2.1. Examinations of the reaction conditions

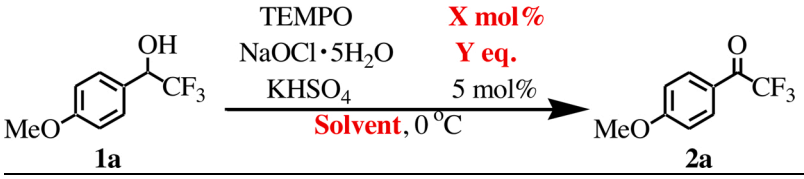
The reaction conditions were evaluated using 1,1,1-trifluoro-2-(4-methoxyphenyl)ethanol (**1a**) as a substrate (Table 1). The reaction of **1a** with NaOCl·5H$_2$O produced the desired ketone (**2a**) in 85 % yield under the standard conditions for the oxidation of non-fluorinated alcohols (1 mol% TEMPO, 2.4 eq NaOCl·5H$_2$O, in dichloromethane) (run 1). The investigation of the solvent effect suggested that several solvents can be used for this oxidation except for acetone (runs 2–8). Acetone rapidly reacted with NaOCl·5H$_2$O, and all of **1a** remained unreacted (run 6). The best solvent for the oxidation of **1a** is acetonitrile (run 8). The reaction of **1a** at room temperature provided some by-products resulting in a decrease in yield (run 9). The use of 1.2 eq. NaOCl·5H$_2$O afforded **2a** in low yield (run 10).

For the reaction with 0.1 mol% TEMPO, **2a** was obtained in a good yield (84 %), though the reaction proceeded slowly (run 11).

Next, the types of nitroxyl radical catalysts were evaluated in acetonitrile (Table 2). All the catalysts were effective for the oxidation of **1a** with NaOCl·5H$_2$O (runs 1–4). Interestingly, although the reaction rate was slower, **2a** was obtained in a high yield from the reaction with NaOCl·5H$_2$O under a nitroxyl radical-free condition (run 5) [7,8].

For the TEMPO-catalyzed oxidation of ordinary alcohols, [4e, f] NaOCl·5H$_2$O was a far more effective oxidant than the conventional aqueous 13 % NaOCl. A similar result is anticipated for the oxidation of fluoroalkyl secondary alcohols. Thus, the reaction of **1a** with the conventional aqueous 13 % NaOCl proceeded very slowly and the desired **2a** was obtained in a poor yield (Table 3 run 2). In our previous studies of the oxidation using NaOCl as an oxidant, we admitted that the oxidizing ability of NaOCl largely depends on the pH; the main difference between NaOCl·5H$_2$O and the conventional aqueous 13 % NaOCl is their pH (NaOCl·5H$_2$O: 10~11, conventional aqueous 13 % NaOCl: >13). Actually, aqueous NaOCl (pH 10.7) prepared from the conventional aqueous 13 % NaOCl and hydrochloric acid was effective for the oxidation of **1a** (run 5) and exhibited a reactivity similar to the aqueous NaOCl (pH 10.7) prepared from NaOCl·5H$_2$O and water (run 3). On the other hand, aqueous NaOCl (pH 13) prepared from NaOCl·5H$_2$O, water and sodium hydroxide reacted with **1a** very slowly (run 5) as in the case of the conventional aqueous 13 % NaOCl (run 2).

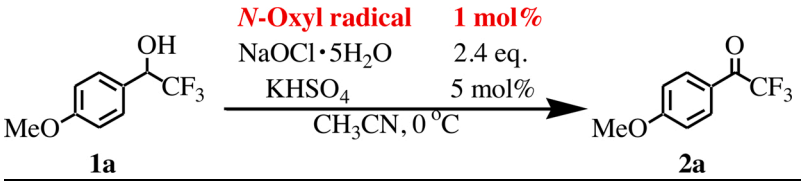
Table 1
Examination of the reaction conditions.



Run	Solvent	TEMPO	NaOCl· 5H$_2$O	Time	Yield (%)[a]
1	CH_2Cl_2	1 mol%	2.4 eq	1 h 15 min	85
2	DCE[b]	1 mol%	2.4 eq	30 min	78
3	Toluene	1 mol%	2.4 eq	30 min	80
4	BTF[c]	1 mol%	2.4 eq	1 h 15 min	80
5	Hexane	1 mol%	2.4 eq	2 h	80
6	Acetone	1 mol%	2.4 eq	2 h	0
7	EtOAc	1 mol%	2.4 eq	1 h 45 min	87
8	**CH_3CN**	**1 mol%**	**2.4 eq**	**15 min**	**99 (81)[d]**
9	CH_3CN	1 mol%	2.4 eq	15 min	85[e]
10	CH_3CN	1 mol%	1.2 eq	1 h	79
11	CH_3CN	0.1 mol%	2.4 eq	1 h 15 min	84

[a] Yields based on ^{19}F NMR spectra of the crude reaction mixture using 4-chlorobenzotrifluoride as the internal standard.
[b] DCE: 1,2-Dichloroethane.
[c] BTF: Benzotrifluoride [(trifluoromethyl)benzene].
[d] The number in parentheses is referred to as the isolated yield.
[e] Reaction at room temperature.

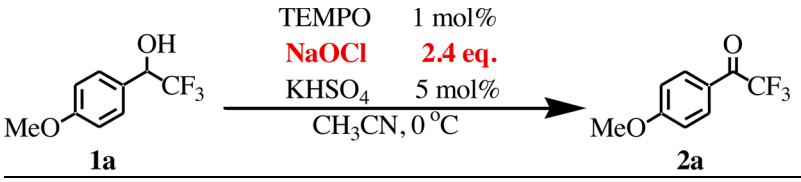
Table 2
Examination of the *N*-oxyl radical.



Run	*N*-oxyl radical	Time	Yield (%)[a]
1	**TEMPO**	**15 min**	**99 (81)**[b]
2	4-Methoxy-TEMPO	30 min	81
3	AZADO	15 min	86
4	keto-ABNO	2 h	85
5	–	**5 h**	**89 (73)**[b]

[a] Yields based on ^{19}F NMR spectra of the crude reaction mixture using 4-chlorobenzotrifluoride as the internal standard.
[b] The numbers in parentheses refer to the isolated yield.

Table 3
Comparison of NaOCl · $5H_2O$ vs. conventional 13 % aq. NaOCl with varying pH.



Run	NaOCl	pH	Additive	Time	Yield(%)[a]
1	**NaOCl· $5H_2O$**	–	–	**20 min**	**99 (81**[b]**)**
2	**13 % NaOCl(aq) [conventional aq. solution]**	**13**	–	**24 h**	**18**[b]
3	13 % NaOCl(aq) [prepared from NaOCl·$5H_2O$]	**10.7**	–	45 min	**quant**
4	13 % NaOCl(aq) [prepared from NaOCl·$5H_2O$]	13	**NaOH**	24 h	37
5	13 % NaOCl(aq) [conventional aq. solution]	**10.7**	**HCl**	45 min	**83**[b]

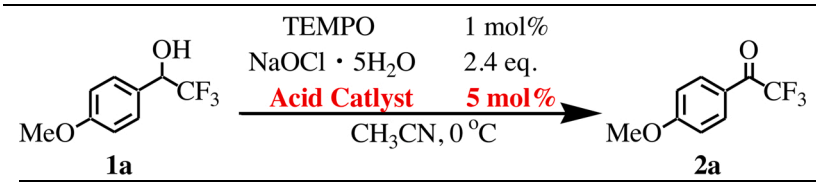
[a] Yields based on ^{19}F NMR ratio.
[b] Isolated yield.

$KHSO_4$ might be used as an acid to neutralize NaOCl into HOCl, which is a stronger oxidant. The treatment of **1a** without $KHSO_4$ or with other acids (CF_3CO_2H, CH_3CO_2H) gave **2a** in slightly lower yields (Table 4).

2.2. Reaction of fluoroalkyl secondary alcohols bearing an aromatic substituent catalyzed by TEMPO

Several fluoroalkyl secondary alcohols bearing an aromatic substituent (**1**) were treated with NaOCl·$5H_2O$ (2.4 eq.) and potassium hydrogen sulfate (5 mol%) in acetonitrile in the presence of the TEMPO catalyst at 0 °C (Table 5) [9]. In all cases, the fluorinated alcohols **1** were rapidly oxidized to produce the desired **2** or the corresponding hydrate (*gem*-diol) 2′ in the presence of TEMPO in high yields. The fluorinated alcohols having electron deficient aromatic rings (**1c, 1f**) provided the hydrate (**2′c, 2′f**) as the products (entries 3, 6).

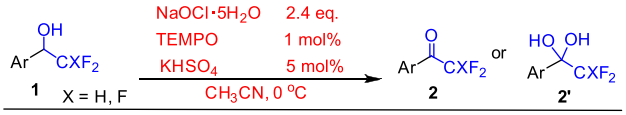
Table 4
Effects of the acid catalyst.

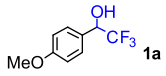
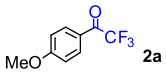
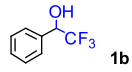
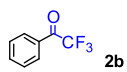
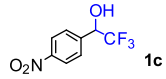
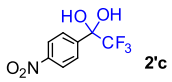
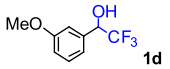
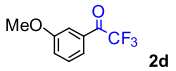
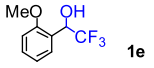
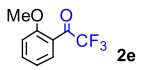
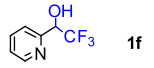
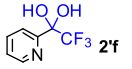
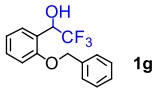
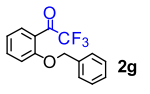
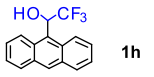
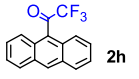
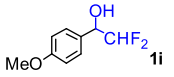
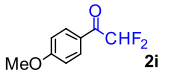


Run	Acid catalyst	Time	Yield(%)[a]
1	**$KHSO_4$**	**20 min**	**99**
2	none	30 min	90
3	CF_3COOH	15 min	80
4	AcOH	20 min	83

[a] Yields based on ^{19}F NMR spectra of the crude reaction mixture using 4-chlorobenzotrifluoride as the internal standard.

Table 5
Oxidation of fluoroalkyl secondary alcohols bearing an aromatic substituent.



Entry	Substrate	Product	Time	Yield (%)[a]
1	 1a	 2a	15 min	81
2	 1b	 2b	25 min	80
3	 1c	 2'c	30 min	91
4	 1d	 2d	20 min	80
5	 1e	 2e	30 min	98
6	 1f	 2'f	30 min	83
7	 1g	 2g	30 min	91
8	 1h	 2h	20 min	74[b]
9	 1i	 2i	25 min	95

[a]Isolated yield.
[b]^{19}F NMR yield using 4-chlorobenzotrifluoride as the internal standard.

2.3. Reaction of fluoroalkyl secondary alcohols bearing an aliphatic substituent

The reaction of fluoroalkyl alcohols bearing an aliphatic substituent with NaOCl·5H$_2$O was then evaluated (Table 6). Unfortunately, fluoroalkyl alcohols having an alkyl group (**1 j, k**) were almost inactive under the standard reaction conditions (entries 1 and 2). An alcohol bearing a cyclopropyl moiety (**1 l**) was efficiently oxidized to afford the desired ketone (**2 l**) without decomposition of the cyclopropane-ring (entry 3). A trifluoromethyl propargyl alcohol (**1 m**) also rapidly reacted with NaOCl·5H$_2$O to provide the corresponding ketone (**2 m**) in 42 % yield, but together with unidentified byproducts (entry 4). In the case of a trifluoromethyl allylic alcohol (**1n**), the epoxyketone hydrate (**3n**) was obtained in 82 %, and formation of the expected enone (**2n**) or enone-hydrate (**2′n**) was not observed (entry 5). The reaction mechanism will be shown later (Scheme 6).

2.4. Reaction of fluoroalkyl secondary alcohols without TEMPO

As shown by run 5 in Table 2, **1a** was oxidized to the ketone (**2a**) by the reaction with NaOCl·5H$_2$O without the TEMPO-catalyst [8]. Therefore, the oxidations of more secondary fluorinated alcohols (**1**) were examined with NaOCl·5H$_2$O and 5 mol% of KHSO$_4$ in CH$_3$CN in the absence of TEMPO (Table 7). Although the reaction rate was slower, the same products (**2** or **3**) were obtained in moderate to high yields.

2.5. Reaction of fluoroalkyl primary alcohols, trifluoroactaldehyde ethylhemiacetal, and hexafluoroisopropanol in acetonitrile-d_3

The oxidations of several other types of fluorinated alcohols were next attempted. The reaction was performed in acetonitrile-d_3 (CD$_3$CN) and analyzed by NMR (Table 8). The reaction of primary alcohols (**1o**, **1p**) provided the corresponding carboxylic acids in good yields. The ethyl hemiacetal of trifluoroacetaldehyde was oxidized to ethyl trifluoroacetate (**2q**) in 77 %. In the case of hexafluoroisopropanol (**1 r**), the desired hydrate of hexafluoroacetone (**2r'**) was obtained in 79 % yield. These results suggested that NaOCl·5H$_2$O is a very good oxidant for the synthesis of perfluoroketones, perfluorocarboxylic acids, and esters of the perfluorocarboxylic acids. Unfortunately, these alcohols (**1o-r**) were completely inert to the reaction with NaOCl·5H$_2$O under the TEMPO-free conditions.

2.6. Reaction of fluoroalkyl alcohols bearing an allylic substituent: Synthesis of 1,1,1-trifluoromethyl α,β-epoxyketone hydrates

As shown in the previous chapter (2–4), the 1,1,1-trifluoromethyl α,β-epoxyketone hydrate (**3′n**) was efficiently obtained from the reaction of the fluorinated allylic alcohol (**1n**) with NaOCl·5H$_2$O catalyzed by TEMPO (Table 6 entry 5) [10]. Since 1,1,1-trifluoromethyl α,β-epoxyketone hydrates (3′) seem to be attractive synthetic building blocks, the generality of this reaction was then evaluated.

Several 1,1,1-trifluoromethyl allylic alcohols (**1n-x**) were treated with NaOCl·5H$_2$O (2.4 eq) in the presence of the TEMPO-catalyst (Table 9). The allylic alcohols having an electron-deficient aromatic ring (**1s-u**) efficiently produced the desired α,β-epoxyketone hydrates (**3′s-u**) in high yields (entries 2–4). In all cases, the corresponding enones or enone hydrates were not obtained at all. Unfortunately, an allylic alcohol having an electron-rich aromatic ring (**1v**) provided a complex mixture (entry 5) affected by the electrophilic chlorination of the aromatic ring.

2.7. Consideration of the reaction mechanism of the reaction of fluoroalkyl alcohols with NaOCl·5H$_2$O

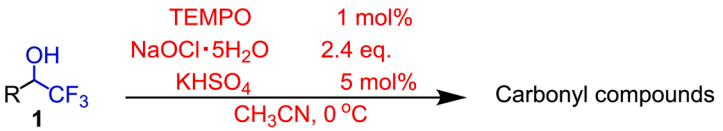
The reaction mechanism of this reaction is almost the same as that of the oxidation of ordinary alcohols with NaOCl·5H$_2$O catalyzed by TEMPO and KHSO$_4$ (Scheme 4). First, hypochloric acid (HOCl) is produced from the reaction of NaOCl·5H$_2$O and KHSO$_4$. HOCl oxidizes TEMPO to produce the active species (**A**) and HCl. The produced HCl then reacts with NaOCl to form HOCl and NaCl. Since the oxidation of alcohols with NaOCl·5H$_2$O/TEMPO/KHSO$_4$ occurs under acidic to neutral conditions, the reaction proceeds via the transition state **B** [11]. The lone pair of the nitrogen atom attacks the hydrogen atom of the hydroxy group in the alcohol, therefore, more acidic fluorinated alcohols are good substrates for this reaction.

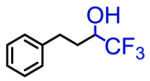
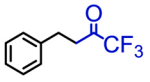
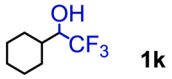
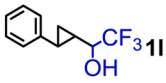
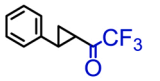
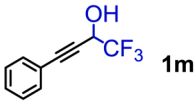
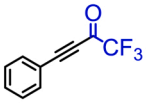
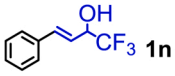
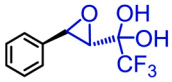
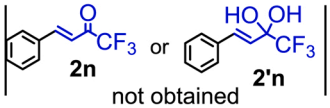
2.8. Consideration of the reaction mechanism of the fluoroalkyl allylic alcohol (1n)

The mechanism of the formation of α,β-epoxyketone hydrate (**3′n**) from **1n** was investigated. The epoxide (**3′n**) might be produced from the corresponding enone (**2n**) which was provided from the oxidation of **1n**. We prepared **2n** according to the literature [3j], and examined the reaction of **2n** with NaOCl·5H$_2$O both in the presence and absence of TEMPO. The corresponding **3′n** was obtained in both cases (Scheme 5) [12].

The plausible mechanism is shown in Scheme 6. The fluorinated allylic alcohol (**1n**) is first oxidized to the corresponding enone (**2n**). Further oxidation of **2n** might produce the epoxyketone, which is isolated as the hydrated form of **3n** (Scheme 6). Although the reactive species is HOCl prepared from NaOCl·5H$_2$O with acid, the lone pair of the nitrogen atom of active formed TEMPO (Scheme 4, A) acts as base to

Table 6
Oxidation of fluoroalkyl secondary alcohols bearing an aliphatic substituent with $NaOCl{\cdot}5H_2O$ catalyzed by TEMPO.



Entry	Substrate	Product	Time	Yield (%)[a]
1	 **1j**	 **2j**	3 h	4[b]
2	 **1k**	—	2 h	0[b]
3	 **1l**	 **2l**	20 min	89
4	 **1m**	 **2m**	15 min	42[b]
5	 **1n**	 **3'n**	20 min	82
		 **2n** or **2'n** not obtained		

[a]Isolated yield.
[b]^{19}F NMR yield using 4-chlorobenzotrifluoride as the internal standard.

react with HOCl providing ClO^-. Therefore, the reaction in the presence of TEMPO catalyst provided the better result in Scheme 4.

Interestingly, the reaction of a non-fluorinated analog (**4**) with $NaOCl{\cdot}5H_2O$ under the same reaction conditions for a longer reaction time (4 h 32 min) only provided the simple enone (**5**) in a lower yield with recovery of the starting material (**4**) (Table 10). The electron withdrawing trifluoromethyl moiety is essential in order to form an α,β-epoxyketone.

3. Conclusion

Several fluoroalkyl alcohols (**1**) are effectively oxidized by the reaction with $NaOCl{\cdot}5H_2O$ catalyzed by TEMPO to afford the corresponding fluoroalkyl ketones and fluoroalkyl carboxylic acid in high yields, except for fluoroalkyl alcohols bearing simple alkyl groups. In the case of the secondary fluoroalkyl alcohols, the desired fluoroalkyl ketones are also obtained in good yields. The α,β-epoxyketones were efficiently obtained by the reaction of fluoroalkyl allylic alcohols with $NaOCl{\cdot}5H_2O$ catalyzed by TEMPO.

4. Experimental section

General Information: All reagents were purchased from Nacalai Tesque, Wako Pure Chemicals Industries, Kanto Kagaku, Kishida Reagents Chemical Co., Tokyo Chemical Industry or Aldrich, and used without any further purification. Most of the starting materials (**1a~i, 1j~n, 1s~x**) were prepared from the reaction of (trimethylsilyl)trifluoromethane [or (trimethylsilyl)difluoromethane] with the corresponding aldehydes according to the literature [13]. For the starting materials in Table 8 (**1o~r**), commercially available reagents were used. Melting points were measured by a Yanaco micro melting point apparatus (MP-J3) and are uncorrected. The NMR spectra were recorded by a JEOL (JNM-EX400) spectrometer as solutions in $CDCl_3$ using TMS, $CFCl_3$ or the residual solvent peak as the internal standard, and the coupling constants (J) are given in hertz (Hz). The IR spectra were recorded using a Jasco IR-8300 FT-IR spectrophotometer. The mass spectra were recorded by a Shimadzu GCMS-QP1100EX spectrometer (EI) or JEOL JMS-T100LC spectrometer (ESI).

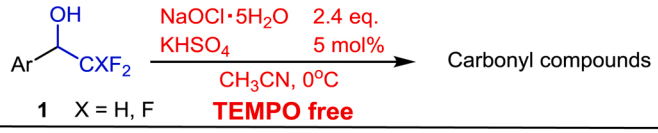
4.1. Standard experimental procedure for the oxidation of fluorine-containing alcohols using $NaOCl{\cdot}5H_2O$ catalyzed by TEMPO

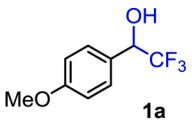
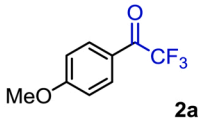
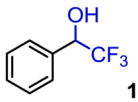
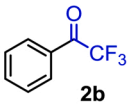
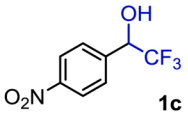
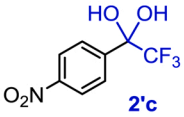
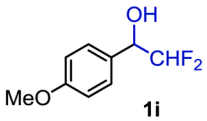
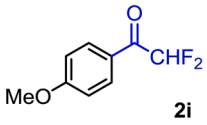
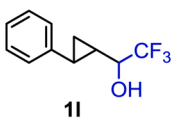
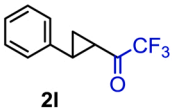
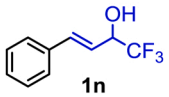
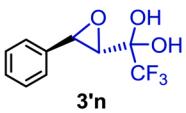
Potassium hydrogen sulfate (6.7 mg, 0.05 mmol) and TEMPO (1.7 mg, 0.01 mmol) were added to a stirred solution of a fluoroalkyl alcohol (**1**) (1.0 mmol) in acetonitrile (5 mL) at room temperature, and the resulting mixture was cooled to 0 °C. Sodium hypochlorite pentahydrate (395 mg, 2.4 mmol) was then added to the reaction mixture, stirred under the same conditions, and monitored by TLC. After the starting material (**1**) had been consumed, water (5 mL) was added, and the resulting mixture was extracted with ethyl acetate (20 mL×3). The combined organic extract was washed with brine (50 mL), dried over sodium sulfate, and evaporated. The ^{19}F-NMR yields were calculated by using 4-chlorobenzotrifluoride as the internal standard. The crude product was purified by silica-gel column chromatography using hexane/ethyl acetate as the eluent to provide the fluoroalkyl ketone (**2**).

4.2. Standard experimental procedure for the oxidation of fluorine-containing alcohols using $NaOCl{\cdot}5H_2O$ without the TEMPO catalyst

Potassium hydrogen sulfate (13.7 mg, 0.10 mmol) was added to a stirred solution of a fluoroalkyl alcohol (**1**) (2.0 mmol) in acetonitrile (5 mL) at room temperature, and the resulting mixture was cooled to 0 °C. Sodium hypochlorite pentahydrate (791 mg, 4.8 mmol) was added to the reaction mixture, stirred under the same conditions, and

Table 7
Oxidation of fluoroalkyl secondary alcohols with NaOCl·5H$_2$O without TEMPO-catalyst.



Entry	Substrate	Product	Time	Yield (%)[a]
1	 **1a**	 **2a**	5 h	77
2	 **1b**	 **2b**	21 h 40 min	92
3	 **1c**	 **2'c**	1 h 25 min	83
4	 **1i**	 **2i**	5 h	85
5	 **1l**	 **2l**	5 h	87
6	 **1n**	 **3'n**	3 h 20 min	60

[a]Isolated yield.

monitored by TLC. After the starting material (**1**) had been consumed, water (5 mL) was added, and the resulting mixture was extracted with ethyl acetate (20 mL×3). The combined organic extract was washed with brine (50 mL), dried over sodium sulfate, and evaporated. The residue was purified by silica-gel column chromatography using hexane/ethyl acetate as the eluent to produce the fluoroalkyl ketone (**2**).

4.3. 2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-one (2a) [14]

Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 3.89 (3H, s), 7.00 (2H, apparent doublet, J = 8.8 Hz), 8.06 (2H, apparent doublet, J = 8.8 Hz).
^{13}C NMR ($CDCl_3$) δ: 55.6, 114.4, 115.4 (q, J = 291.3 Hz), 122.7, 132.7, 165.4, 178.7 (q, J = 34.4 Hz).
^{19}F NMR ($CDCl_3$) δ: -71.48 (s).

4.4. 2,2,2-Trifluoro-1-phenylethan-1-one (2b) [15]

Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 7.55 (2H, apparent triplet, J = 7.2 Hz), 7.72 (1H, apparent triplet, J = 8.0 Hz), 8.09 (2H, apparent doublet, J = 8.8 Hz).
^{13}C NMR ($CDCl_3$) δ: 116.67 (q, J = 291.7 Hz), 129.06, 129.90, 130.06, 135.49, 181.05 (t, J = 35.2 Hz).
^{19}F NMR ($CDCl_3$) δ: -71.23 (s).

4.5. 2,2,2-Trifluoro-1-(4-nitrophenyl)ethane-1,1-diol (2'c) [16]

Pale yellow crystals.
mp: 80–82 ℃ (lit. 79–80 ℃ [16])
^{1}H NMR (CD_3OD) δ: 7.90 (2H, dd, J = 22.0, 8.8 Hz), 8.23 (2H, m).
^{13}C NMR(CD_3OD) δ: 95.84 (q, J = 31.7 Hz), 122.20 (q, J = 287.6 Hz), 122.72, 129.02, 141.17, 148.27.
^{19}F NMR(CD_3OD) δ: -82.98 (s).

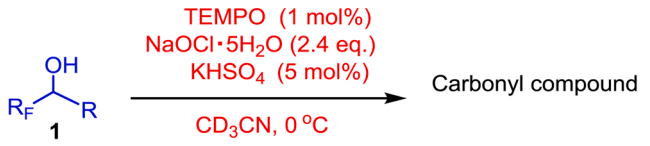
4.6. 2,2,2-Trifluoro-1-(3-methoxyphenyl)ethan-1-one (2d)[14]

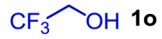
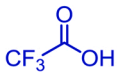
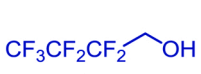
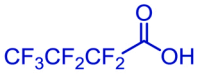
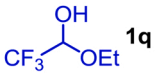
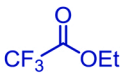
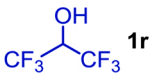
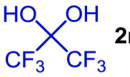
Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 3.88 (3H, s), 7.26 (1H, m), 7.46 (1H, t, J = 7.8 Hz), 7.57 (1H, s), 7.67 (1H, d, J = 7.8 Hz).
^{13}C NMR ($CDCl_3$) δ: 55.52, 113.97, 116.64 (q, J = 291.4 Hz), 122.26, 122.72, 130.10, 131.07, 159.98, 180.54 (q, J = 34.5 Hz).
^{19}F NMR ($CDCl_3$) δ: -71.73 (s).

4.7. 2,2,2-Trifluoro-1-(2-methoxyphenyl)ethan-1-one (2e) [14]

Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 3.91 (3H, s), 7.04 (2H, m), 7.59 (2H, m), 7.68 (1H, d, J = 8.0 Hz).
^{13}C NMR ($CDCl_3$) δ: 56.24, 112.07, 116.23 (q, J = 291.3 Hz), 120.66, 121.67, 131.30, 135.29, 159.82, 183.12 (q, J = 36.2 Hz).

Table 8
Oxidations of several other types of fluorinated alcohols.



Entry	Substrate	Product	Time	Yield (%)[a]
1	 **1o**	 **2o**	25 min	77[b]
2	 **1p**	 **2p**	1 h	71[b]
3	 **1q**	 **2q**	30 min	77
4	 **1r**	 **2r'**	30 min	79

[a]^{19}F-NMR yield using 4-chlorobenzotrifluoride as the internal standard.
[b]Containing the corresponding sodium salt.

^{19}F NMR ($CDCl_3$) δ: -74.97 (s).

4.8. 2,2,2-Trifluoro-1-(pyridine-2-yl)ethane-1,1-diol (2'f) [17]

Pale yellow crystals
mp: 63–65 °C (lit. 64–66 °C [17])
^{1}H NMR ($CDCl_3$) δ: 7.45 (1H, m), 6.xx (2H, s), 7.75 (1H, dd, J = 7.7, 0.78 Hz), 7.88 (1H, td, J = 7.7, 1.2 Hz), 8.6 (1H, m).
^{13}C NMR ($CDCl_3$) δ: 95.14 (q, J = 32.6 Hz), 123.96 (q, J = 286.6 Hz), 125.08, 128.72, 137.99, 147.48, 152.17.
^{19}F NMR ($CDCl_3$) δ: -83.18 (s).

4.9. 2,2,2-Trifluoro-1-[2-(benzyloxy)oxy)phenyl]ethan-1-one (2g)

Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 5.10 (2H, s), 6.96–7.02 (2H, m), 7.28–7.50 (6H, m), 7.47 (1H, t, J = 7.2 Hz), 7.65 (1H, d, J = 8.0 Hz).
^{13}C NMR ($CDCl_3$) δ: 70.91, 113.51, 116.45 (q, J = 291.4 Hz), 121.03, 122.07, 127.45, 128.33, 128.77, 129.11, 131.49, 135.92, 135.95, 183.29 (q, J = 36.4 Hz).
^{19}F NMR ($CDCl_3$) δ: -74.03 (s).
IR (neat) cm^{-1}: 3070, 3038, 2933, 2879, 1712, 1597, 1490, 1453, 1276, 1175, 1011, 940, 752, 700, 667, 526.
MS (EI) (m/z): 280 (M^+).
HRMS (ESI) calcd for $C_{15}H_{11}F_3O_2Na$ [$(M+Na)^+$], 303.0603, found : 303.0603.

4.10. 1-(9-Anthracenyl-)2,2,2-trifluoroethan-1-one (2h) [18]

Yellow crystals.
mp: 80–82 °C (lit. 81–84 °C [18])
^{1}H NMR ($CDCl_3$) δ: 7.45–7.58 (4H, m), 7.74 (2H, d, J = 8.4 Hz), 8.06 (2H, d, J = 8.4 Hz), 8.59 (1H, s).
^{13}C NMR ($CDCl_3$) δ: 116.00 (q, J = 293.4 Hz), 123.85, 125.86, 127.31, 127.85, 128.72, 128.94, 130.68, 130.92, 191.10 (q, J = 38.3 Hz).
^{19}F NMR ($CDCl_3$) δ: -76.49 (s).

4.11. 2,2-Difluoro-1-(4-methoxyphenyl)ethan-1-one (2i) [19]

Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 3.88 (3H, s), 6.24 (1H, t, J = 53.6 Hz), 6.98 (2H, d, J = 8.7 Hz), 8.05 (2H, d, J = 8.7 Hz).
^{13}C NMR ($CDCl_3$) δ: 55.3, 111.0 (t, J = 253.0 Hz), 114.1, 124.3, 131.8, 164.8, 185.7 (t, J = 24.8 Hz).
^{19}F NMR ($CDCl_3$) δ: -121.98 (d, J = 57.6 Hz).

4.12. 1,1,1-Trifluoro-4-phenylbutan-2-one (2j) [20]

It could not be isolated due to small amount.
The ^{19}F-NMR peak of this crude product was identical to that in the literature. [20]
^{19}F NMR ($CDCl_3$) δ: -79.767 (s).

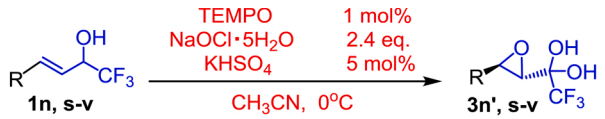
4.13. 2,2,2-Trifluoro-1-(2-phenylcyclopropyl)ethan-1-one (2l) [3h]

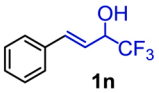
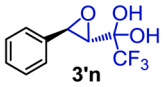
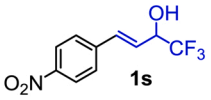
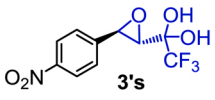
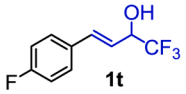
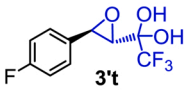
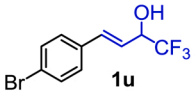
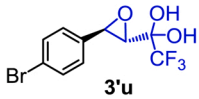
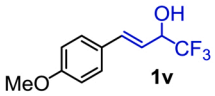
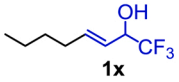
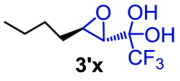
Pale yellow oil.
^{1}H NMR ($CDCl_3$) δ: 1.72–1.75 (1H, m), 2.74–2.81 (1H, m), 2.49–2.53 (1H, m), 2.74–2.81 (1H, m), 7.13–7.15 (2H, m), 7.25–7.34 (3H, m).
^{13}C NMR ($CDCl_3$) δ: 20.75, 27.23, 32.72, 114.33 (q, J = 290.4 Hz), 126.44, 127.40, 128.73, 138.16, 189.45 (q, J = 36.4 Hz).
^{19}F NMR ($CDCl_3$) δ: -79.19 (s).

4.14. 1,1,1-Trifluoro-4-phenylbut-3-yn-2-one (2m) [21]

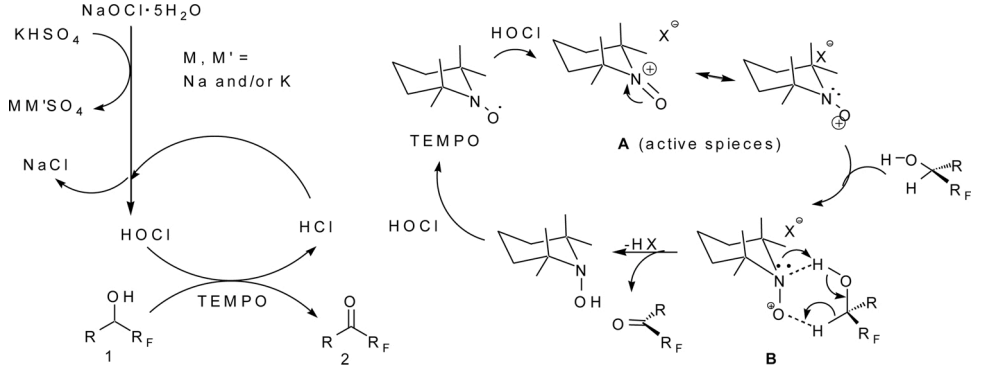
The ^{1}H-, ^{13}C- and ^{19}F-NMR peaks of this crude product were identical to those in the literature [21]. The product decomposed during silica-gel column chromatography.
^{1}H NMR ($CDCl_3$) δ: 7.42−1.66 (5H, m).
^{13}C NMR ($CDCl_3$) δ: 83.36, 100.52, 113.41 (q, J = 288.4 Hz), 118.06, 128.92, 132.51, 133.93, 166.92 (q, J = 42.1 Hz).
^{19}F NMR ($CDCl_3$) δ: -78.29 (s).

Table 9
Synthesis of 1,1,1-trifluoro-α,β-epoxyketone hydrates.

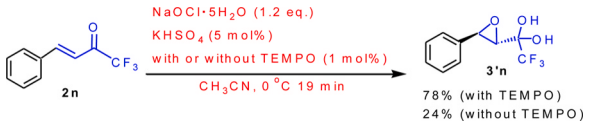


Entry	Substrate	Product	Time	Yield (%)[a]
1	 1n	 3'n	20 min	82
2	 1s	 3's	30 min	80
3	 1t	 3't	15 min	89
4	 1u	 3'u	48 min	49 (65[b])
5	 1v	Complex mixture	30 min	—
6	 1x	 3'x	20 min	60

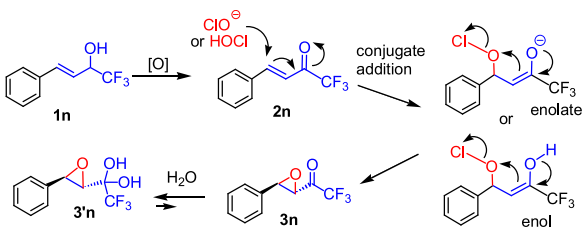
[a]Isolated yield.
[b]^{19}F-NMR yield using 4-chlorobenzotrifluoride as the internal standard.



Scheme 4. Plausible reaction mechanism.

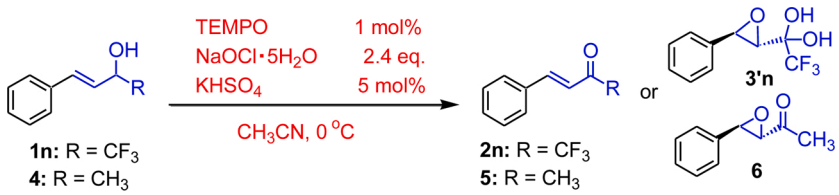


Scheme 5. Reaction of **2n** with NaOCl.



Scheme 6. Reaction mechanism of epoxidation of **2n** with NaOCl.

Table 10
Comparison of the fluorinated allylic alcohol (**1n**) vs the non-fluorinated allylic alcohol (**4**).



Entry	R	Time	Staring Material **1n** or **4** (%)[a]	Enone **2n** or **5** (%)[a]	α,β-epoxyketone **3′n** or **6** (%)[a]
1	CF_3	27 min	0	0	89
2	CH_3	4 h 32 min	83	17	0

[a] Isolated yield.

4.15. 2,2,2-Trifluoro-1-[(2RS, 3SR)-3-phenyloxiranyl]ethenone-1,1-diol (3n) [22]

Colorless crystals, mp: 139–140 °C (lit.130–140 °C [22])

^{1}H NMR ($CDCl_3$) δ: 3.48 (1H, d, J = 1.4 Hz), 4.03 (1H, d, J = 1.4 Hz), 4.20–4.26 (2H, br), 7.29–7.41 (5H, m)

^{13}C NMR ($CDCl_3$) δ: 55.40, 60.43, 92.25 (q, J = 32.6 Hz), 121.76 (q, J = 287.5 Hz), 125.74, 128.69, 128.95, 134.36.

^{19}F NMR ($CDCl_3$) δ: -84.83 (s).

4.16. Standard experimental procedure for the oxidation of fluorine-containing alcohols using NaOCl·5H$_2$O catalyzed by TEMPO in CD$_3$CN

Potassium hydrogen sulfate (6.7 mg, 0.05 mmol), TEMPO (1.7 mg, 0.01 mmol), and 4-chlorobenzotrifluoride (134.5 μL, 1.00 mmol, as the internal standard) were added to a stirred solution of a fluoroalkyl alcohol (**1**) (1.00 mmol) in CD_3CN (5 mL) at room temperature, and the resulting mixture was cooled to 0 °C. Sodium hypochlorite pentahydrate (395 mg, 2.4 mmol) was then added to the reaction mixture and stirred under the same conditions. Part of the reaction solution (0.4 mL) was collected, the ^{19}F NMR was measured, and the yield of **2** was calculated.

4.17. Trifluoroacetic acid (2o) [23]

The ^{19}F-NMR peaks of this sample were identical to those of commercial reagents.

^{19}F NMR (CD_3CN) δ: -75.3∼ -75.4 (br).

4.18. 2,2-3,3,4,4,4-Heptafluorobutylic acid (2p) [23]

The ^{19}F-NMR peaks of this sample were identical to those of commercial reagents.

^{19}F NMR (CD_3CN) δ: -62.22 (3F, t, J = 8.7 Hz).−117.44 (2F, q, J = 8.7 Hz), -126.82 (2F, brs).

4.19. Ethyl trifluoroacetate (2q) [23]

The ^{1}H-, ^{13}C- and ^{19}F-NMR peaks of this sample were identical to those of commercial reagent.

^{1}H NMR (CD_3CN) δ: 1.32 (3H, t, J = 8.0 Hz), 4.39 (2H, q, J = 7.2 Hz).

^{13}C NMR (CD_3CN) δ: 13.91, 65.58, 115.28 (q, J = 284.7 Hz), 157.92 (q, J = 41.2 Hz).

^{19}F NMR (CD_3CN) δ: -75.2 (s).

4.20. 1,1,1,3,3,3-Hexafluoro-2,2-propanediol (2′r) [24]

The ^{19}F-NMR peak of this sample was similar to that (measured in $CDCl_3$) reported in the literature. [24]

^{19}F NMR (CD_3CN) δ: -82.4 (s)

4.21. Standard experimental procedure for the synthesis of 1,1,1-trifluoromethyl−α,β−epoxyketone hydrates

The 1,1,1-trifluoromethyl−α,β−epoxyketone hydrates were synthesized according to the same procedure for the oxidation of fluorine-containing alcohols using NaOCl·5H$_2$O catalyzed by TEMPO.

4.22. 2,2,2-Trifluoro-1-[(2RS, 3SR)-3-(4-nitrophenyl)oxiranyl]ethane-1,1-diol (3′s)

Pale yellow crystals. mp: 79-82 °C

^{1}H NMR (Acetone-d$_6$) δ: 3.03 (1H, s), 3.46 (1H, d, J = 1.8 Hz), 4.27 (1H, d, J = 1.8 Hz), 6.40 (1H, brd, J = 6.4 Hz), 7.65 (2H, d, J = 9.0 Hz), 8.26 (2H, d, J = 9.0 Hz).

^{13}C NMR (Acetone-d$_6$) δ: 53.79, 61.81, 91.73 (q, J = 31.6 Hz), 124.06 (q, J = 287.5 Hz), 124.36, 127.81, 144.53, 148.86.

^{19}F NMR(Acetone-d$_6$) δ: -83.65 (3F, s).

IR (neat) cm^{-1}: 3445, 3084, 2990, 1605, 1525, 1346, 1165, 1116, 1036, 908, 849, 721, 514, 453

MS (EI) (m/z): 261 [(M--H_2O)$^+$]

HRMS (ESI) calcd for $C_{10}H_6F_3NO_4Na$ [(M+Na--H_2O) $^+$], 284.0141, found: 284.0138.

4.23. 1-[(2RS, 3SR)-3-(4-Fluorophenyl)oxiranyl]-2,2,2-trifluoroethane-1,1-diol (3′t) [22]

Colorless crystals. mp: 76–78 °C (lit. 79–81 °C [22]).

^{1}H NMR ($CDCl_3$) δ: 3.43 (1H, d, J = 1.60 Hz), 3.71 (1H, br), 3.91 (1H, br), 3.99 (1H, d, J = 1.60 Hz), 7.05-7.12 (2H, m), 7.25-7.33(2H, m).

^{13}C NMR ($CDCl_3$,) δ: 55.03, 59.73, 90.83 (q, J = 33.1 Hz), 115.83 (d, J = 21.1 Hz), 122.29 (q, J = 285.6 Hz), 127.65 (d, J = 8.5 Hz), 129.98 (d, J = 2.8 Hz), 163.20 (d, J = 248.2 Hz).

^{19}F NMR ($CDCl_3$) δ: -84.81 (3F, s), -112.75-112.68 (1F, m).

4.24. 1-[(2RS, 3SR)-3–(4-Bromophenyl)oxiranyl]-2,2,2-trifluoroethane-1,1-diol (3′u) [22]

Colorless crystals. mp: 76–78 °C (lit. 77–78 °C [22])

^{1}H NMR ($CDCl_3$) δ: 3.40 (1H, d, J = 1.8 Hz), 3.96 (1H, d, J= 1.8 Hz), 7.1 8 (2H, d, J = 8.4 Hz). 7.52 (2H, d, J = 8.4Hz).

^{13}C NMR ($CDCl_3$) δ: 54.95. 59.78, 90.80 (d, J = 32.9 Hz), 122.28 (q, J = 286.6 Hz), 123.11, 127.43, 131.93, 133.39.

^{19}F NMR($CDCl_3$) δ: -84.83 (s)

4.25. 1-[(2RS, 3SR)-3-Butyloxiranyl]-2,2,2-trifluoroethane-1,1-diol (3′x)

Pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 0.92 (3H, t, J = 5.2 Hz), 1.36–1.74 (6H, m), 3.05 (1H, td, J = 5.7, 2.2 Hz), 3.14 (1H, d, J = 2.2 Hz).

^{13}C NMR ($CDCl_3$) δ: 13.81, 22.26, 27.55, 30.50, 56.02, 56.61, 90.86

(q, J = 32.6 Hz), 122.42 (q, J = 286.2 Hz).

^{19}F NMR ($CDCl_3$) δ: -84.86 (s).

IR (neat) cm^{-1}: 3365, 2348, 1450, 1259, 1187, 1110, 1066, 984, 913, 850, 722, 590.

HRMS (ESI) calcd for $C_8H_{11}F_3O_2$ [(M-H_2O) $^+$], 197.1767, found: 197.1761.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

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[9] In the cases of 1a, b, f, similar results were reported by Leadbeatera and Eddya [6d].

[10] Although the α,β-epoxyketone hydrate **3'n** was produced from the reaction of 1n with NaOCl·5H_2O in the absence of the TEMPO-catalyst, the reaction proceeded slower and the yield of **3'n** was lower (Table 7, entry 6). The TEMPO-free condition is not attractive as a synthetic method of α,β-epoxyketones (**3**).

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