


Efficient Synthesis and Ring-Opening Reactions of Monofluorinated Epoxides Derived from α -Fluorosulfoximines

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Abstract: Monofluorinated epoxides were successfully prepared through the *O*-cyclization reaction between α -fluorosulfoximines and ketones. The obtained fluoroepoxides were found to readily undergo an interesting ring-opening process (involving both a C–F bond cleavage and another C–F bond formation) in the presence of titanium tetrafluoride or pyridinium poly(hydrogen fluoride) to afford α -fluorinated ketones. The later process constitutes a formal catalytic 1,2-fluorine shift reaction.

Keywords: epoxides; fluorine; fluorine shift; ring-opening; sulfoximines

Due to the high electronegativity and small size of the fluorine atom, the replacement of hydrogen atom(s) by fluorine in organic compounds often results in a profound change in their physical, chemical and biological properties.^[1] As a consequence, over the past decade, organofluorine compounds have found broad applications in both life sciences and materials science.^[2] To date, many endeavours have been made to develop new efficient synthetic methods for the selective introduction of fluorine atom(s) or fluorinated moieties into organic molecules.^[2] Although epoxides are highly useful building blocks in organic synthesis, the reports on the preparation and synthetic utilizations of monofluorinated epoxides are scarce.^[3–5] Monofluorinated epoxides are usually prepared by the epoxidation of monofluoroolefins,^[3] the treatment of fluorohalohydrins with a base,^[4] or the Darzens reaction between a ketone and dibromo(*tert*-butyldimethylsilyl)fluoromethane^[5] (or ethyl dibromofluoroacetate^[6]).

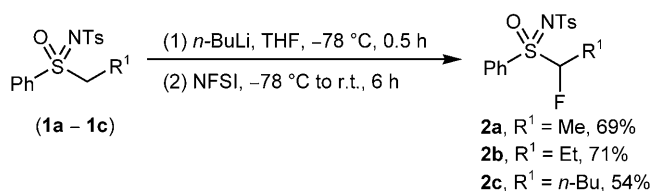
Fluorinated epoxides are known to be relatively unstable, and tend to undergo a variety of ring-opening

reactions with nucleophiles.^[3c,7,9] When monofluoroepoxides were treated with fluoride ion, α -fluorinated carbonyl compounds were obtained through a ring-opening process involving both a C–F bond cleavage and another C–F bond formation.^[3a,8] This type of transformation also proceeded smoothly in the presence of triethylamine-tris(hydrogen fluoride)^[9] or boron trifluoride^[10]. Furthermore, the acid-catalyzed isomerizations of polyfluorinated epoxides into the corresponding ketones have been previously documented.^[7]

As part of our efforts to develop new synthetic approaches for organofluorine compounds,^[11] we recently developed some unique synthetic methods for the preparation of di- and monofluorinated compounds by using fluorinated sulfoximine reagents.^[12,13] In particular, the α -difluoromethylsulfoximine was used as a novel and efficient difluorocarbene reagent,^[12] and the α -fluorosulfoximines could readily react with simple nitrones to give monofluoroalkenes with excellent *Z/E* stereocontrol.^[13] In this paper, we wish to report another interesting synthetic application of fluorinated sulfoximines, that is, the efficient synthesis of α -monofluorinated epoxides derived from α -fluorosulfoximines and ketones, and the subsequent ring-opening reaction of the monofluoroepoxides by using TiF₄ or pyridinium poly(hydrogen fluoride) (Olah's reagent, pyridine-9HF) to afford α -fluoro ketones.

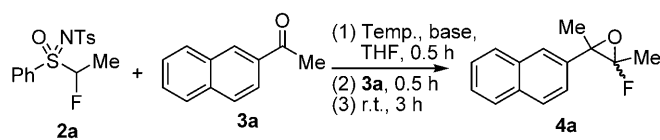
α -Fluorosulfoximines (**2a–2c**) could be readily prepared from non-fluorinated sulfoximines (**1a–1c**) by electrophilic fluorination reactions. When compounds **1a–1c** were treated with *n*-BuLi at -78°C and then reacted with *N*-fluorodibenzene-sulfonylimide (NFSI), the corresponding α -fluorosulfoximines (**2a–2c**) were obtained in 54–71% yields (Scheme 1).

With the α -fluorosulfoximines in hand, we next attempted their *O*-cyclization reaction with ketones to afford the monofluorinated epoxides (Table 1). It was found that *n*-BuLi and LDA were more suitable than



Scheme 1. Synthesis of α -fluorosulfoximines **2a–2c** (Ts = *p*-toluenesulfonyl group).

Table 1. Survey of *O*-cyclization reaction conditions.



Entry	Base	Ratio (2a:Base:3a)	Temp [$^{\circ}\text{C}$]	Yield ^[a] [%]
1	<i>n</i> -BuLi	1.3:1.3:1.0	-78	86
2	<i>n</i> -BuLi	1.5:1.5:1.0	-78	94
3	LDA	1.3:1.3:1.0	-78	85
4	NaH	1.3:1.3:1.0	-78	22
5	<i>t</i> -BuOK	1.3:1.3:1.0	-40	21

^[a] Determined by ^{19}F NMR spectroscopy using PhCF_3 as internal standard.

NaH and *t*-BuOK for this addition-elimination reaction; after deprotonation with 1.5 equivalents of *n*-BuLi, compound **2a** was able to react with ketone **3a**, giving the monofluoroepoxide **4a** in 94% yield (Table 1, entry 2).

However, it should be noted that the above-obtained product **4a** was found to be unstable, which decomposed during the purification process using silica gel flash column chromatography. To further evaluate the stability of monofluorinated epoxides, we synthesized a variety of structurally diverse monofluoroepoxides by using the α -fluorosulfoximines and ketones under the optimized reaction conditions (Table 2). Although benzophenone **3b** and ketone **3c** showed good reactivity towards α -fluorosulfoximine **2a**, the corresponding fluoroepoxides **4b** and **4c** could not be obtained after passage through a silica gel column (Table 2, entries 1, 2). Further investigation indicated that the monofluorinated epoxides **4d–4i**, which contain a strong electron-withdrawing substituent on the aryl group, were more stable than **4b** and **4c**, and the two diastereomers of the epoxides were separated by silica gel column chromatography without decomposition (Table 2, entries 3–8). We also noticed that the *n*-butyl group-substituted fluorosulfoximine **2c** can be readily converted to monofluorinated epoxide **4i** in good yield (76%, Table 2, entry 8). These fluoroepoxides (**4d–4i**) were obtained with low diastereoselectivity; however, the two isomers of each product could be separated by column chromatography. It is worth-

Table 2. *O*-Cyclization of ketones with **2**.

(1) $-78\text{ }^{\circ}\text{C}$, *n*-BuLi, THF, 0.5 h
(2) $-78\text{ }^{\circ}\text{C}$, **3**, 0.5 h
(3) r.t., 3 h

Entry	R^1	Substance (3)	Product (4)	Yield ^[a] [%]	d_r ^[b] (<i>cis/trans</i>)
1	Me (2a)	Ph-C(=O)-Ph 3b	Ph-C(O)-C(F)(Me)-Ph 4b	(76) ^[c]	–
2	Me (2a)	Ph-CH2-C(=O)-Ph 3c	Ph-CH2-C(O)-C(F)(Me)-Ph 4c	(80) ^[c]	–
3	Me (2a)	4-NO2-C6H4-C(=O)-Me 3d	4-NO2-C6H4-C(O)-C(F)(Me)-Me 4d	82	50:50
4	Me (2a)	3-NO2-C6H4-C(=O)-Me 3e	3-NO2-C6H4-C(O)-C(F)(Me)-Me 4e	90	41:49
5	Me (2a)	2-NO2-C6H4-C(=O)-Me 3f	2-NO2-C6H4-C(O)-C(F)(Me)-Me 4f	80	49:51
6	Me (2a)	4-Cl-C6H4-C(=O)-Me 3g	4-Cl-C6H4-C(O)-C(F)(Me)-Me 4g	81	43:57
7	Et (2b)	3d	4-NO2-C6H4-C(O)-C(F)(Et)-Me 4h	75	45:55
8	<i>n</i> -Bu (2c)	3d	4-NO2-C6H4-C(O)-C(F)(<i>n</i> -Bu)-Me 4i	76	46:54

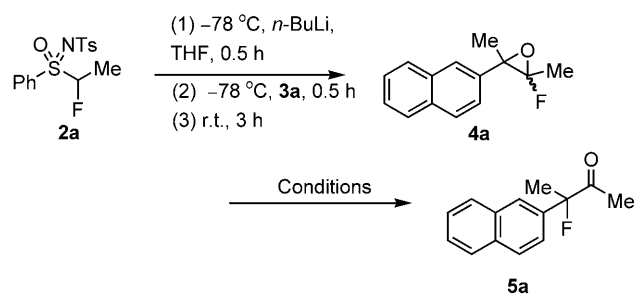
^[a] Isolated yield.

^[b] The two isomers can be separated by column chromatography.

^[c] Determined by ^{19}F NMR spectroscopy.

while to mention that the current epoxide formation reaction with α -fluorosulfoximines were not only successfully applied to a variety of acyclic ketones (see Table 1, Table 2 and Table 4), it can also be extended to cyclic ketones such as 1-tetralone (the reaction between **2a** and 1-tetralone gave the corresponding fluorinated epoxide in 60% yield, determined by ^{19}F NMR). However, a similar reaction between fluorosulfoximine **2a** and aldehydes (such as benzaldehyde) only gave a complex reaction mixture.

Considering that the monofluoroepoxides could be conveniently prepared by addition-elimination reactions between fluorosulfoximines and ketones, we then examined their ring-opening reactions to give α -fluorinated carbonyl compounds. By using the monofluoroepoxide **4a** as a model compound,^[14] the ring-opening reaction was assessed by tuning the reaction parameters such as additive, solvent, temperature and reaction time (Table 3). After the *O*-cyclization reaction, the resulting crude product **4a** was obtained by

Table 3. Survey of ring opening reaction conditions.

Entry ^[a]	Additive	Equiv.	Solvent	Temp. [°C]	Time [h]	Yield ^[b] [%]
1	–	–	CH ₂ Cl ₂	50	3	0
2	–	–	THF	60	3	0
3	H ₂ SO ₄ ^[c]	2.0	CHCl ₃	r.t.	3	0
4	BF ₃ ·Et ₂ O	2.0	CH ₂ Cl ₂	50	3	0
5	TBAF	2.0	THF	50	3	0
6	SbF ₃	0.3	CH ₂ Cl ₂	r.t.	4	trace
7	TiF ₄	0.2	CH ₃ CN	60	18	trace
8	TiF ₄	0.2	DMF	60	18	0
9	TiF ₄	0.3	CH ₂ Cl ₂	60	4	48
10	TiF ₄	0.1	THF	60	48	33 ^[d]
11	TiF ₄	0.2	THF	60	18	67
12	TiF ₄	0.3	THF	60	18	77
13 ^[e]	TiF ₄	0.4	THF	60	24	90
14 ^[f]	pyridine-9 HF	65.0	THF	60	4	80

^[a] For entries 1, 3 and 4–8, the starting material **4a** was mostly unreacted. For entries 3 and 4, **4a** was consumed to give a complex product mixture.

^[b] Two steps, isolated yield of **5a**.

^[c] H₂SO₄ (10%) was used.

^[d] Determined by ¹⁹F NMR spectroscopy.

^[e] Method A.

^[f] Method B.

extraction, drying over MgSO₄ and evaporation of the solvent without further purification. Thereafter, the epoxide **4a** was heated in CH₂Cl₂ or THF without other additive, however, the thermal fluorine shift reaction did not occur (Table 3, entries 1, 2). Furthermore, in the presence of H₂SO₄, BF₃·Et₂O or TBAF, the reaction was unsuccessful and no desired product **5a** was detected (Table 3, entries 3–5). When a catalytic amount of SbF₃ or TiF₄ was added to the reaction mixture, we obtained a trace amount of α -fluorinated ketone **5a** (Table 3, entries 6, 7). Thereafter, various solvents and the amount of TiF₄ were examined. The best product yield (90%, two steps from **2a**) was obtained when 0.4 equivalent of TiF₄ was used as an additive by using THF as a solvent, and the mixture was heated at 60 °C for 24 h (Method A, Table 3, entry 13). The other method of transforming the monofluoroepoxide **4a** to the α -fluorinated ketone **5a**

by simple treatment with pyridine-9HF (Olah's reagent) was also explored. When pyridine-9HF (65.0 equiv. of HF) was added to the crude product **4a**, derived from the reaction mixture of the fluorosulfoximine **2a** and ketone **3a**, the corresponding product **5a** was obtained with good yield (Method B, Table 3, entry 14).

With these two optimized reaction conditions (Methods A and B), we then examined the substrate scope of this ring opening reaction. As shown in Table 4, the first *O*-cyclization reactions were carried out under standard conditions (Table 1, entry 2), and the yields of monofluoroepoxides are shown in the parentheses, which were determined by ¹⁹F NMR spectroscopy. It was found that a variety of structurally diverse ketones showed high reactivity with the α -fluorosulfoximines **2a–2c** to afford the corresponding monofluoroepoxides (Table 4, entries 1–17). However, the phenyl-substituted α -fluorosulfoximines **2d** gave a low yield (30%, Table 4, entry 18). When aryl-substituted epoxides, derived from aryl ketones (**3a**, **3h**, **3k–3n**), were treated by TiF₄ or pyridine-9HF reagent (Method A or B), α -fluorinated ketones were obtained in good isolated yields (Table 4, entries 1–4, 9–18). However, the monofluoroepoxides bearing three alkyl groups (derived from ketone **3i** and **3j**) showed lower reactivity with both methods A and B (Table 4, entries 5–8). Furthermore, the ring-opening reactions with *n*-butyl- and phenyl-substituted monofluoroepoxides proceeded smoothly with Method A or B (Table 4, entries 17, 18).

We also extended this ring-opening reaction to produce α -chlorinated ketone **6** (Scheme 2). When monofluoroepoxides **4a** was used to react with 4.0 equivalents of TiCl₄, the corresponding α -chlorinated ketone **6** was obtained in 82% yield after 2 steps.

Although a detailed investigation is needed to get insight into the mechanism of the current interesting formal 1,2-fluorine shift reaction, we propose that it may proceed through a Lewis acid- or Brønsted acid-mediated 1,2-fluorine shift^[18] process *via* transition states **7A** or **7B**, respectively (Scheme 3). A coordination of the Lewis acid or Brønsted acid on the oxygen atom of **4** may facilitate the fluoride ion to attack the α -carbon atom and the subsequent C–F bond cleavage. Although Elkik and co-workers reported the thermal rearrangement of 2-fluoroepoxides leading to α -fluorocarbonyl compounds,^[10] a direct 1,2-fluorine shift mechanism appears to be unlikely for the transformation from **2** to **5** (see Table 3, entries 1–8 and Scheme 2). It should be noted that similar ring-opening reactions with α -nitro- or chloro-substituted epoxides have been reported, and in those cases, both nitro and chlorine act as leaving groups during the acid-mediated ring-opening process.^[15–17]

In summary, we have demonstrated an efficient *O*-cyclization reaction between α -fluorosulfoximines and

Table 4. Ring-opening reactions of monofluoroepoxides.

Entry	R ¹	Substance (3)	Product (5)	Method	Yield [%] (4) ^[c] 5 ^[d]
1	Me	2-Naphth-3-one	2-Naphth-3-yl methyl ketone	A	(94) 90
2	Me (2a)	2-Naphth-3-one	2-Naphth-3-yl methyl ketone	B	(94) 80
3	Me (2a)	<i>p</i> -MeOPh-3-one	<i>p</i> -MeOPh-3-yl methyl ketone	A	(86) 67
4	Me (2a)	<i>p</i> -MeOPh-3-one	<i>p</i> -MeOPh-3-yl methyl ketone	B	(89) 82
5	Me (2a)	Ph-3-one	Ph-3-yl methyl ketone	A	(96) 20
6	Me (2a)	Ph-3-one	Ph-3-yl methyl ketone	B	(95) 48
7	Me (2a)	Ph-3-one	Ph-3-yl methyl ketone	A	(93) 31
8	Me (2a)	Ph-3-one	Ph-3-yl methyl ketone	B	(96) 54
9	Et (2b)	3a	2-Naphth-3-yl ethyl ketone	B	(80) 77
10	Me (2a)	3k, R' = Ph	5f, R' = Ph	A	(88) 80
11	Me (2a)	3l, R' = Me	5g, R' = Me	B	(90) 83
12	Me (2a)	3l, R' = Me	5g, R' = Me	A	(90) 75
13	Me (2a)	3m, R' = Cl	5h, R' = Cl	B ^[e]	(83) 65
14	Me (2a)	3m, R' = Cl	5h, R' = Cl	A ^[f]	(84) 60
15	Me (2a)	3n, R' = MeO	5i, R' = MeO	B ^[e]	(87) 60
16	Et (2b)	3k	5j, R ¹ = Et	A	(72) 70
17	<i>n</i> -Bu (2c)	3k	5k, R ¹ = <i>n</i> -Bu	A	(75) 68
18	Ph (2d)	3k	5l, R ¹ = Ph	B	(30) 28

[a] Method A: TiF₄ (0.4 equiv.), THF, 60 °C, 24 h, THF.

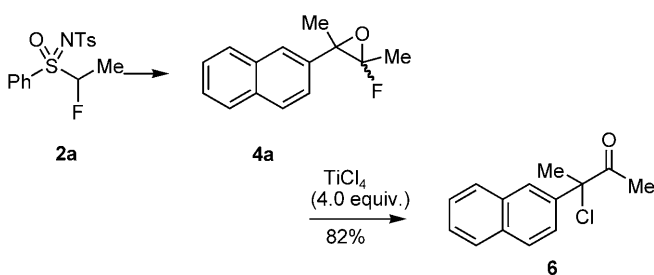
[b] Method B: pyridine-9HF (65.0 equiv.), 60 °C, 4 h, THF.

[c] Yields of monofluoroepoxides **4** are shown in the parentheses, which were determined by ¹⁹F NMR spectroscopy.

[d] Two steps, isolated yield of product **5**.

[e] Additional pyridine-9HF (40.0 equiv.) was added after 4 h, then stirring for 3 h.

[f] Additional 0.6 equiv. of TiF₄ was added after 24 h, then stirring for 42 h.

**Scheme 2.** Synthesis of α -chlorinated ketone **6**.

ketones to afford monofluorinated epoxides, and the subsequent ring-opening/formal catalytic 1,2-fluorine shift reaction of monofluoroepoxides was also developed by simply treatment of catalytic amount of TiF₄ or pyridine-9HF reagent. Not only do our results present a useful method for the synthesis of monofluoroepoxides and α -fluorinated ketones, they also provide another important synthetic aspect of fluorinated sulfoximine chemistry and fluorine shift reactions are currently underway in our laboratory.

Experimental Section

Typical Procedure for *O*-Cyclization Reactions of α -Fluorosulfoximines and Ketones

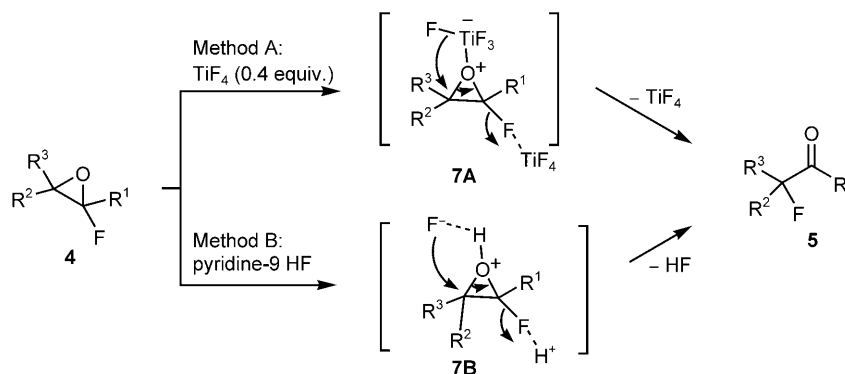
Under an N₂ atmosphere, *n*-BuLi (0.23 mL, 1.6 M, 1.5 equiv.) was added *via* a needle to the solution of α -fluorosulfoximine **2a** (124 mg, 0.36 mmol, 1.5 equiv.) in dry THF (4 mL) at -78 °C, then the mixture was stirred for 30 min, followed by addition of a solution of **3d** (40 mg, 0.24 mmol, 1.0 equiv.) in THF (1 mL). The temperature was maintained for 0.5 h at -78 °C, then the dry-ice bath was removed. After stirring for 3 h at room temperature, the reaction was quenched by adding an excess amount of H₂O, followed by extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous MgSO₄. After the solution had been filtered and the solvent evaporated under vacuum, the residue was subjected to silica gel column chromatography using petroleum ether as eluent to give product **4d** [yield: 82%, *cis*-**4d** (21 mg), *trans*-**4d** (21 mg)].

cis-**4d**: white solid; mp 54–55 °C. IR (film): $\nu = 1606, 1523, 1350, 1191, 1115, 840, 758$ cm⁻¹; ¹H NMR: $\delta = 8.17$ (d, $J = 9.3$ Hz, 2H), 7.43 (d, $J = 8.7$ Hz, 2H), 1.74 (s, 3H), 1.36 (d, $J = 16.5$ Hz, 3H); ¹⁹F NMR: $\delta = -123.9$ (q, $J = 16.6$ Hz, 1F); ¹³C NMR: $\delta = 147.8, 145.5, 127.0, 124.0, 99.4$ (d, $J = 266.5$ Hz), 66.5 (d, $J = 19.3$ Hz), 18.8, 16.1 (d, $J = 32.8$ Hz); MS (EI): m/z (%) = 211 (M⁺, 2.12), 149 (100.00); HR-MS (EI): $m/z = 211.0648$, calcd. for C₁₀H₁₀NO₃F: 211.0645.

trans-**4d**: white solid; mp 87–88 °C. IR (film): $\nu = 1603, 1523, 1350, 1187, 1112, 860, 706, 572$ cm⁻¹; ¹H NMR: $\delta = 8.24$ (d, $J = 8.1$ Hz, 2H), 7.59 (d, $J = 8.7$ Hz, 2H), 1.86 (d, $J = 16.5$ Hz, 3H), 1.71 (s, 3H); ¹⁹F NMR: $\delta = -125.2$ (q, $J = 16.6$ Hz, 1F); ¹³C NMR: $\delta = 147.6, 144.6, 127.6, 123.4, 98.6$ (d, $J = 261.3$ Hz), 65.8 (d, $J = 20.1$ Hz), 19.5, 16.2 (d, $J = 33.5$ Hz); MS (EI): m/z (%) = 211 (M⁺, 3.50), 149 (100.00); HR-MS (EI): $m/z = 211.0647$, calcd. for C₁₀H₁₀NO₃F: 211.0645.

Typical Procedure for Ring-Opening Reactions of Monofluoroepoxides

Method A: The crude product **4a** (without purification by silica gel column chromatography) was prepared by the *O*-cyclization reaction between α -fluorosulfoximine **2a** and ketone **3a** under the above-mentioned reaction conditions. The product yield of **4a** was 94%, which was determined by ¹⁹F NMR spectroscopy. Therefore, the reaction was quenched by adding an excess amount of H₂O, followed by



Scheme 3. Proposed reaction mechanism.

extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous MgSO_4 . After the solution had been filtered and the solvent evaporated under vacuum, crude product **4a** was then obtained.

Under an N_2 atmosphere, TiF_4 (0.4 equiv.) was added to the solution of the epoxide **4a** in dry THF (5 mL). After stirring for 24 h at 60°C , the reaction was quenched by adding an excess amount of H_2O , followed by extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous MgSO_4 . After the solution had been filtered and the solvent evaporated under vacuum, the residue was subjected to silica gel column chromatography using petroleum ether as eluent to give product **5a** as a colorless liquid; yield: 90%.

Method B: The crude product **4a** (without purification by silica gel column chromatography) was prepared by the *O*-cyclization reaction between α -fluorosulfoximine **2a** and ketone **3a** under the above-mentioned reaction conditions. The product yield of **4a** was 94%, which was determined by ^{19}F NMR spectroscopy. Therefore, the reaction was quenched by adding excess amount of H_2O , followed by extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous MgSO_4 . After the solution had been filtered and the solvent evaporated under vacuum, crude product **4a** was then obtained.

Pyridine-9-HF reagent (ca. 65.0 equiv. of HF) was slowly added to the reaction mixture. After stirring for 4 h at 60°C , the reaction was quenched by adding an excess amount of H_2O , followed by extraction with diethyl ether. The organic phase was washed with brine and then dried over anhydrous MgSO_4 . After the solution had been filtered and the solvent evaporated under vacuum, the residue was subjected to silica gel column chromatography using petroleum ether as eluent to give product **5a** as a colorless liquid; yield: 80%. IR (film): $\nu=3061, 1726, 1508, 1356, 1126, 1108, 820, 747\text{ cm}^{-1}$; ^1H NMR: $\delta=7.84\text{--}7.73$ (m, 4H), $7.43\text{--}7.40$ (m, 3H), 2.17 (d, $J=5.1\text{ Hz}$, 3H), 1.78 (d, $J=22.8\text{ Hz}$, 3H); ^{19}F NMR: $\delta=-154.1\text{--}154.3$ (m, 1F); ^{13}C NMR: $\delta=207.2$ (d, $J=30.6\text{ Hz}$), 136.2 (d, $J=22.2\text{ Hz}$), $132.9, 128.6, 128.3, 127.7, 126.6, 123.3, 123.2, 121.9, 121.8, 100.8$ (d, $J=183.6\text{ Hz}$), $24.6, 24.1$ (d, $J=24.1\text{ Hz}$); MS (EI): m/z (%) = 216 (M^+ , 13.28), 173 (100.00). HR-MS (EI): $m/z=216.0951$, calcd. for $\text{C}_{14}\text{H}_{13}\text{OF}$: 216.0950.

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- [14] The reason of choosing **4a** as a model compound to study the ring-opening reaction is that compound **4a** possesses reasonably good stability in solution, and more importantly, **4a** can undergo ring-opening reaction under acid catalysis. As a comparison, when a more stable fluoroepoxide **4d** was subjected to pyridine-9HF (similar to the reaction condition described in Table 3, entry 14), the corresponding ketone product was obtained in only 20% yield.
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