DOI: 10.1002/adsc.201000499

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

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Received: June 28, 2010; Published online: October 26, 2010

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201000499.

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

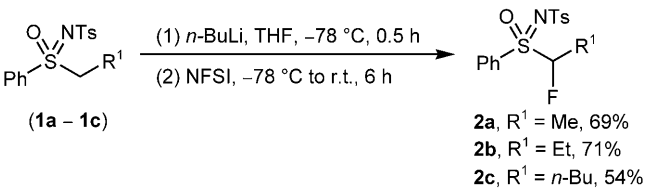
Due to the high electronegativity and small size of the fluorine atom, the replacement of hydrogen atom(s) by fluorine in organic compounds often results in a profound change in their physical, chemical and biological properties.[1] As a consequence, over the past decade, organofluorine compounds have 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*-butyldimethylsililyl)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]. Futhermore, 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 TiF_4 or pyridinium poly(hydrogen fluoride) (Olah's reagent, pyridine-9 HF) to afford α-fluoro ketones.

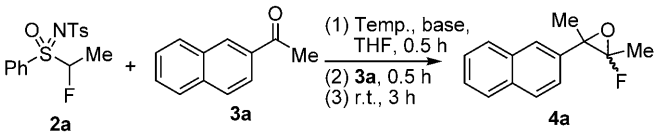
α-Fluorosulfoximines (**2a**–**2c**) could be readily prepared from non-fluorinated sulfoximines (**1a**–**1c**) by electrophilic fluorination reactions. When compounds **1a**–**1c** were treated with *n*-BuLi at −78 °C and then reacted with *N*-fluorodibenzenesulfonimide (NFSI), the corresponding α-fluorosulfoximines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



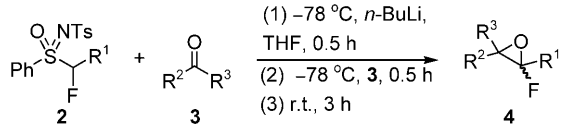
Entry	Base	Ratio (**2a**:Base:**3a**)	Temp [°C]	Yield[a] [%]
1	*n*-BuLi	1.3:1.3:1.0	−78	86
2	*n*-BuLi	1.5:1.5:1.0	−78	94
3	LDA	1.3:1.3:1.0	−78	85
4	NaH	1.3:1.3:1.0	−78	22
5	*t*-BuOK	1.3:1.3:1.0	−40	21

[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 worthwhile 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.

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

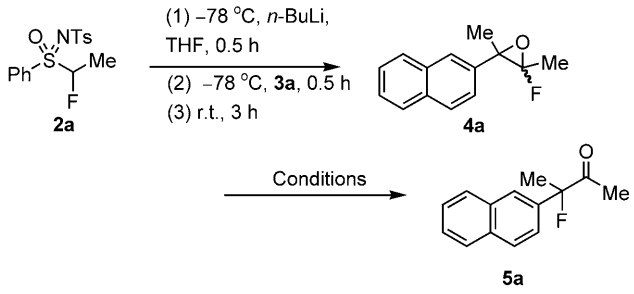


Entry	R^1	Substance (**3**)	Product (**4**)	Yield[a] [%]	*dr*[b] (*cis*/*trans*)
1	Me (**2a**)	**3b**	**4b**	(76)[c]	–
2	Me (**2a**)	**3c**	**4c**	(80)[c]	–
3	Me (**2a**)	**3d**	**4d**	82	50:50
4	Me (**2a**)	**3e**	**4e**	90	41:49
5	Me (**2a**)	**3f**	**4f**	80	49:51
6	Me (**2a**)	**3g**	**4g**	81	43:57
7	Et (**2b**)	**3d**	**4h**	75	45:55
8	*n*-Bu (**2c**)	**3d**	**4i**	76	46:54

[a] Isolated yield.
[b] The two isomers can be separated by column chromatography.
[c] Determined by ^{19}F NMR spectroscopy.

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.



2a **4a** **5a**

Entry[a]	Additive	Equiv.	Sovent	Temp. [°C]	Time [h]	Yield[b] [%]
1	–	–	CH_2Cl_2	50	3	0
2	–	–	THF	60	3	0
3	H_2SO_4[c]	2.0	$CHCl_3$	r.t.	3	0
4	$BF_3{\cdot}Et_2O$	2.0	CH_2Cl_2	50	3	0
5	TBAF	2.0	THF	50	3	0
6	SbF_3	0.3	CH_2Cl_2	r.t.	4	trace
7	TiF_4	0.2	CH_3CN	60	18	trace
8	TiF_4	0.2	DMF	60	18	0
9	TiF_4	0.3	CH_2Cl_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] H_2SO_4 (10%) was used.
[d] Determined by ^{19}F NMR spectroscopy.
[e] Method A.
[f] Method B.

extraction, drying over $MgSO_4$ and evaporation of the solvent without further purification. Thereafter, the epoxide **4a** was heated in CH_2Cl_2 or THF without other additive, however, the thermal fluorine shift reaction did not occur (Table 3, entries 1, 2). Furthermore, in the presence of H_2SO_4, $BF_3{\cdot}Et_2O$ or TBAF, the reaction was unsuccessful and no desired product **5a** was detected (Table 3, entries 3–5). When a catalytic amount of SbF_3 or TiF_4 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 TiF_4 were examined. The best product yield (90%, two steps from **2a**) was obtained when 0.4 equivalent of TiF_4 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-9 HF (Olah's reagent) was also explored. When pyridine-9 HF (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).

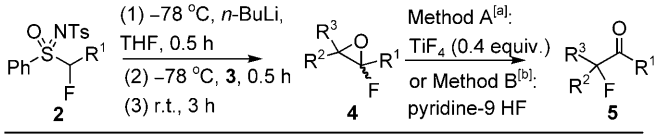
With these two optimized reaction conditions (Methods A and B), we then examined the substrate scope of this ring opening reaction. As shown in Table 4, the first *O*-cyclization reactions were carried out under standard conditions (Table 1, entry 2), and the yields of monofluoroepoxides are shown in the parentheses, which were determined by ^{19}F 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 TiF_4 or pyridine-9 HF 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 $TiCl_4$, the corresponding α-chlorinated ketone **6** was obtained in 82% yield after 2 steps.

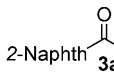
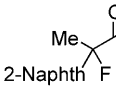
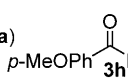
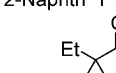
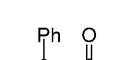
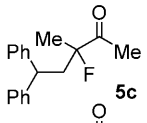
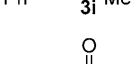
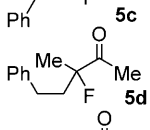
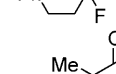
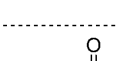
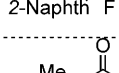
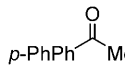
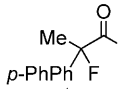
Although a detailed investigation is needed to get insight into the mechanism of the current interesting formal 1,2-fluorine shift reaction, we propose that it may proceed through a Lewis acid- or Brønsted acid-mediated 1,2-fluorine shift[18] process *via* transition states **7A** or **7B**, respectively (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

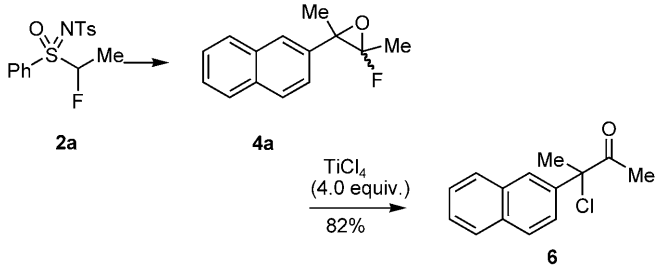
Table 4. Ring-opening reactions of monofluoroepoxides.



2 4 5

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

[a] Method A: TiF_4 (0.4 equiv.), THF, 60 °C, 24 h, THF.
[b] Method B: pyridine-9 HF (65.0 equiv.), 60 °C, 4 h, THF.
[c] Yields of monofluorooxiranes **4** are shown in the parentheses, which were determined by ^{19}F NMR spectroscopy.
[d] Two steps, isolated yield of product **5**.
[e] Additional pyridine-9 HF (40.0 equiv.) was added after 4 h, then stirring for 3 h.
[f] Additional 0.6 equiv. of TiF_4 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 TiF_4 or pyridine-9 HF 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 sulfoximines.[12,13] Further explorations 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

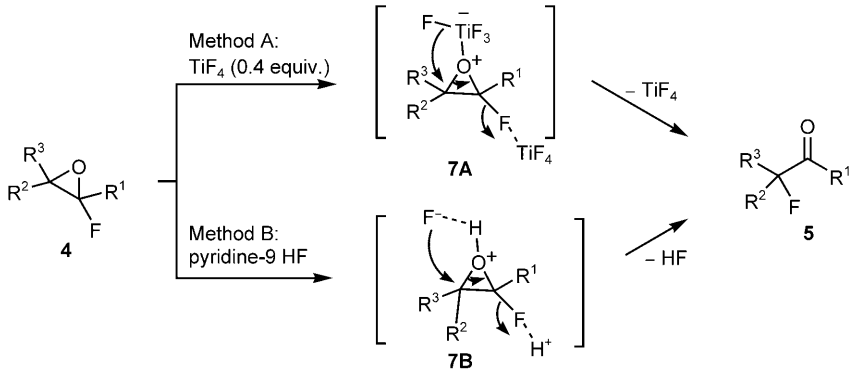
Under an N_2 atmosphere, *n*-BuLi (0.23 mL, 1.6 M, 1.5 equiv.) was added *via* a needle to the solution of α-fluorosulfoximine **2a** (124 mg, 0.36 mmol, 1.5 equiv.) in dry THF (4 mL) at −78 °C, then the mixture was stirred for 30 min, followed by addition of a solution of **3d** (40 mg, 0.24 mmol, 1.0 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 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 **4d** [yield: 82%, *cis*-**4d** (21 mg), *trans*-**4d** (21 mg)].

cis-**4d**; white solid; mp 54–55 °C). IR (film): ν = 1606, 1523, 1350, 1191, 1115, 840, 758 cm^{-1}; ^1H NMR: δ = 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); ^{19}F NMR: δ = −123.9 (q, J = 16.6 Hz, 1F); ^{13}C NMR: δ = 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 $C_{10}H_{10}NO_3F$: 211.0645.

trans-**4d**: white solid; mp 87–88 °C. IR (film): ν = 1603, 1523, 1350, 1187, 1112, 860, 706, 572 cm^{-1}; ^1H NMR: δ = 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); ^{19}F NMR: δ = −125.2 (q, J = 16.6 Hz, 1F); ^{13}C NMR: δ = 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 $C_{10}H_{10}NO_3F$: 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 ^{19}F NMR spectroscopy. Therefore, the reaction was quenched by adding an excess amount of H_2O, 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 cm^{-1}; ^1H NMR: $\delta = 7.84$–7.73 (m, 4H), 7.43–7.40 (m, 3H), 2.17 (d, $J = 5.1$ Hz, 3H), 1.78 (d, $J = 22.8$ Hz, 3H); ^{19}F NMR: $\delta = -154.1$–154.3 (m, 1F); ^{13}C NMR: $\delta = 207.2$ (d, $J = 30.6$ Hz), 136.2 (d, $J = 22.2$ Hz), 132.9, 128.6, 128.3, 127.7, 126.6, 123.3, 123.2, 121.9, 121.8 100.8 (d, $J = 183.6$ Hz), 24.6, 24.1 (d, $J = 24.1$ Hz); MS (EI): m/z (%) = 216 (M^+, 13.28), 173 (100.00). HR-MS (EI): $m/z = 216.0951$, calcd. for $C_{14}H_{13}OF$: 216.0950.

Acknowledgements

Support of our work by the National Natural Science Foundation of China (20772144, 20825209, 20832008) and the Chinese Academy of Sciences (Hundreds-Talent Program and Knowledge Innovation Program) is gratefully acknowledged.

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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-9 HF (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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[18] For the term of "1,2-fluorine shift", see ref.[7a], page 263.

