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Divergent Rearrangements of Cyclopropyl-Substituted Fluoroepoxides Involving C−F Bond Cleavage and Formation

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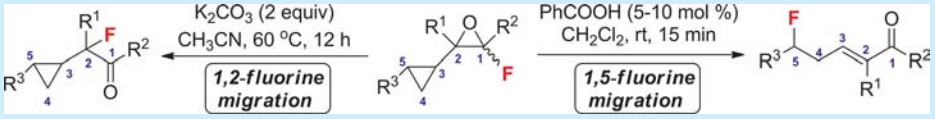
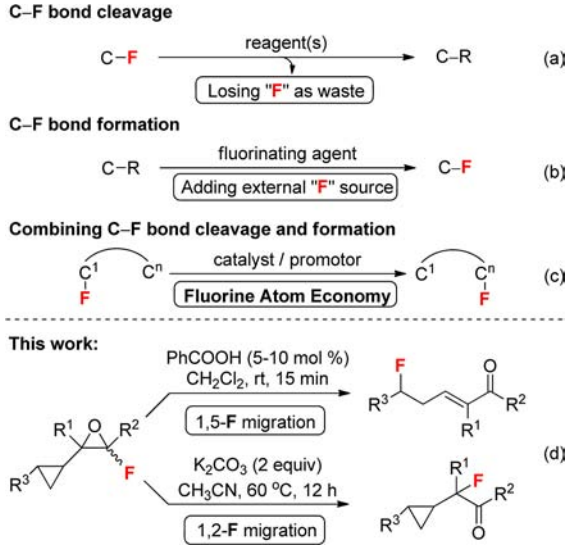
Supporting Information



ABSTRACT: Unprecedented divergent rearrangements of cyclopropyl-substituted fluoroepoxides are reported. In the presence of a catalytic amount of benzoic acid, cyclopropyl-substituted fluoroepoxides efficiently undergo 1,5-fluorine migration. However, when the fluoroepoxides are heated with K_2CO_3 at 60 °C, 1,2-fluorine migration occurs. The 1,5-fluorine migration is believed to proceed via a carbocation intermediate, while the 1,2-fluorine migration may involve a tight ion pair intermediate or proceed via a concerted process.

The carbon−fluorine bond is the strongest single bond that carbon can form, and therefore, the activation and/or functionalization of C−F bonds are challenging tasks that have drawn much attention during the past three decades.[1] In general, the currently known C−F bond activation/functionalization processes often lose the fluorine atom as waste (Scheme 1, eq (a)).[2] On the other hand, despite their rarity in nature,[3] organofluorine compounds play very important roles in pharmaceuticals, agrochemicals, and advanced materials.[4] As a result, selective C−F bond formation has become one of the most desirable reactions in modern organic chemistry (Scheme 1, eq (b)).[5,6] Therefore, the fusion of C−F bond activation/functionalization and C−F bond formation may create a new branch of synthetic organic chemistry. In this context, one would envision that a process that combines C−F bond cleavage and C−F bond formation within one molecule could become a new intriguing protocol for the synthesis of organofluorine compounds (Scheme 1, eq (c)).

Scheme 1. Reactions Involving C−F Bond



Fluorine migration reactions typically involve C−F bond cleavage and C−F bond formation within one molecule without adding external fluorinating agent(s). However, reports on fluorine migration are scarce,[7] and most of these reported methods require harsh reaction conditions[7a−d] and/or specific substrates.[7e,f] Recently, we synthesized fluoroepoxides and transformed them to α-fluorinated ketones in one pot.[8] In this process, we used external fluorinating agents such as TiF_4 or Py·10HF to facilitate the formal 1,2-fluorine migration reaction. To realize a real fluorine migration reaction without adding external fluorinating agents, we conducted extensive screening of reaction conditions (Supporting Information, Tables 1−4) and structural optimization of substrates (Supporting Information, Table 5). Eventually, we realized a real fluorine migration reaction with cyclopropyl-substituted fluoroepoxides. Remarkably, these fluoroepoxides can selectively undergo regioselective 1,2- or 1,5-fluorine migration by changing the acidity of the reaction system (Scheme 1, eq (d)). Although the rearrangement from epoxides to carbonyl compounds has appeared in the literature,[9] to the best of our knowledge, the selective 1,2- and 1,5-divergent rearrangements of epoxides have never been reported.[10]

At the onset of our investigation, we successfully synthesized cyclopropyl-substituted fluoroepoxides from fluorosulfoximines and ketones using an improved procedure.[11] The crude fluoroepoxide **1a** (as a mixture of four diastereomers)[12] was directly used to optimize reaction conditions of rearrangements

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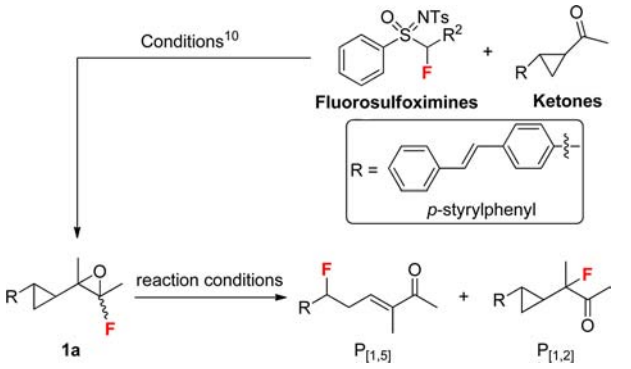
owing to the instability of **1a** during the purification process.[8] The results are summarized in Table 1. The fluoroepoxide **1a** showed good stability in CH_3CN solution when no additive was added (Table 1, entry 1). However, an acid dramatically promoted the rearrangement reaction, and all of the four diastereomers of **1a** can readily undergo the rearrangement. When benzoic acid (5 mol %) was added as a catalyst, the crude **1a** was consumed completely within 15 min and was mainly converted to 1,5-fluorine migration product (the ratio of 1,5- and 1,2-migration products $P_{[1,5]}$:$P_{[1,2]}$ = 69:31) (Table 1, entry 2). It seems that dichloromethane (DCM) was a better solvent for the 1,5-fluorine migration, and the ratio ($P_{[1,5]}$:$P_{[1,2]}$) increased to 95:5, with the yield of $P_{[1,5]}$ being improved to 70% (Table 1, entry 3). However, the reaction became less efficient when we changed the reaction parameters such as catalyst loading (Table 1, entries 4 and 5), temperature (Table 1, entry 6), reaction time (Table 1, entry 7), and concentration (Table 1, entry 8). To our surprise, **1a** was also able to undergo a thermal rearrangement even in the absence of an acid catalyst ($P_{[1,5]}$:$P_{[1,2]}$ = 78:22) (Table 1, entry 9). When we changed the solvent to CH_3CN, the regioselectivity of the reaction was also changed, with the major product being $P_{[1,2]}$ ($P_{[1,5]}$:$P_{[1,2]}$ = 48:52, yield of $P_{[1,2]}$ = 27%) (Table 1, entry 10). When triethylamine was added (2.0 equiv) to the reaction system, the product ratio ($P_{[1,5]}$:$P_{[1,2]}$) was remarkably improved to 5:95, and the yield of $P_{[1,2]}$ increased to 54% (Table 1, entry 11). It seems that K_2CO_3 was a better additive than NEt_3 ($P_{[1,5]}$:$P_{[1,2]}$ = 3:97, yield ($P_{[1,2]}$) = 60%) (Table 1, entry 12). Decreasing the reaction temperature to 60 °C could make the thermal rearrangement more efficient ($P_{[1,5]}$:$P_{[1,2]}$ = 1:99, yield ($P_{[1,2]}$) = 65%) (Table 1, entry 13). However, further lowering the reaction temperature to 50 °C resulted in an incomplete reaction (Table 1, entry 14). Finally, we chose the reaction conditions of entry 3 in Table 1 as standard for 1,5-fluorine migration reaction, and those of entry 13 in Table 1 were selected as standard for 1,2-fluorine migration reaction.

Table 1. Survey of Reaction Conditions of the Divergent Rearrangements[a]



entry	additive	solvent	temp (°C)	time	$P_{[1,5]}/P_{[1,2]}$[b]	yield[c] (%)
1	Null	CH_3CN	rt	0.5 h		NR
2	PhCOOH (5 mol %)	CH_3CN	rt	15 min	69:31	ND
3	**PhCOOH (5 mol %)**	**CH_2Cl_2**	**rt**	**15 min**	**95:5**	**70**
4	PhCOOH (10 mol %)	CH_2Cl_2	rt	15 min	93:7	62
5	PhCOOH (20 mol %)	CH_2Cl_2	rt	15 min	93:7	55
6	PhCOOH (5 mol %)	CH_2Cl_2	0 °C	15 min	90:10	41
7	PhCOOH (5 mol %)	CH_2Cl_2	rt	3 h	92:8	62
8[d]	PhCOOH (5 mol %)	CH_2Cl_2	rt	15 min	91:9	64
9	Null	DCE	80 °C	2h	78:22	ND
10	Null	CH_3CN	80 °C	4 h	48:52	27
11	NEt_3 (2.0 equiv)	CH_3CN	80 °C	4 h	5:95	54
12	K_2CO_3 (2.0 equiv)	CH_3CN	80 °C	4 h	3:97	60
13	**K_2CO_3 (2.0 equiv)**	**CH_3CN**	**60 °C**	**12 h**	**1:99**	**65**
14	K_2CO_3 (2.0 equiv)	CH_3CN	50 °C	12 h	2:98	34[e]

[a]General reaction conditions: crude **1a** (0.2 mmol) was dissolved in solvent (3 mL) and stirred with additives under N_2 atmosphere at the indicated temperature for the indicated time. [b]The value of ($P_{[1,5]}$:$P_{[1,2]}$) was detected by ^{19}FNMR. [c]Yield was of the major product (two steps' total yield, calculated from ketones) and detected by ^{19}F NMR using $PhS(NTs)(O)CFH_2$ as internal standard. [d]Using CH_2Cl_2 (6 mL) as solvent. [e]There were 31% fluoroepoxides unreacted. NR = no reaction. ND = not determined. DCE = 1,2-dichloroethane.

With optimized reaction conditions in hand, we next examined the substrate scope of 1,5-fluorine migration reaction. The results are summarized in Scheme 2.[13] All isolated yields of products (**2a**–**h**) refer to the overall yields for two steps starting from ketones. The PhCOOH-catalyzed 1,5-fluorine migration was amenable to structurally diverse cyclopropyl-substituted fluoroepoxides. When R^1 was changed from phenyl (**2a**) to 1-naphthyl (**2b**), 2-naphthyl (**2c**), or 4-*tert*-butylphenyl (**2d**), the reaction showed good efficiency (46–64% yields) and excellent regioselectivity ($P_{[1,5]}$:$P_{[1,2]}$ ≥ 90:10). However, when R^1 = styryl (**2e**), the 1,5-migration became less efficient (34% yield) due to the decreased regioselectivity ($P_{[1,5]}$:$P_{[1,2]}$ = 73:27). When R^1 was an alkyl group (**2f**), the reaction was still effective (yield of $P_{[1,5]}$ = 49%; $P_{[1,5]}$:$P_{[1,2]}$ = 85:15). When we changed R^2 from methyl to ethyl (**2g**), the reaction exhibited slightly increased regioselectivity ($P_{[1,5]}$:$P_{[1,2]}$ = 96:4) and decreased efficiency (39% yield). Furthermore, when R^3 = ethyl group (**2h**), the efficiency of the reaction was only moderate (34% yield; $P_{[1,5]}$:$P_{[1,2]}$ = 87:13).

Next, we examined the substrate scope of the 1,2-fluorine migration reaction. The results are summarized in Scheme 3.[14] Compared to 1,5-fluorine migration, the thermal 1,2-fluorine migration exhibited higher regioselectivity and efficiency in the cases of all cyclopropyl-substituted fluoroepoxides that we investigated. When R^1 = phenyl (**3a**), 1-naphthyl (**3b**), 2-naphthyl (**3c**), styryl (**3e**), or alkyl (**3f**) group, the reaction proceeded smoothly to give 1,2-migration products in 51–74% yields and with excellent regioselectivity ($P_{[1,2]}$:$P_{[1,5]}$ ≥ 98:2). When R^2 = ethyl (**3h**), the product yield was moderate (47% yield) but with high regioselectivity ($P_{[1,2]}$:$P_{[1,5]}$ = 98:2).

To gain more insight into these unusual 1,5- and 1,2-divergent rearrangements of cyclopropyl-substituted fluoroepoxides, we carried out several experiments to probe the reaction mechanism. As shown in Scheme 4, $P_{[1,5]}$ (**2a**) and $P_{[1,2]}$ (**3a**) were not able to transform between each other under the aforementioned reaction conditions (Scheme 4, eqs a and b), which suggests that the formations of $P_{[1,5]}$ (**2a**) and $P_{[1,2]}$ (**3a**) should proceed through two different pathways. When we added water (1 mL) into the thermal rearrangement reaction system, we isolated two major products **3a** (16%) and **4a**

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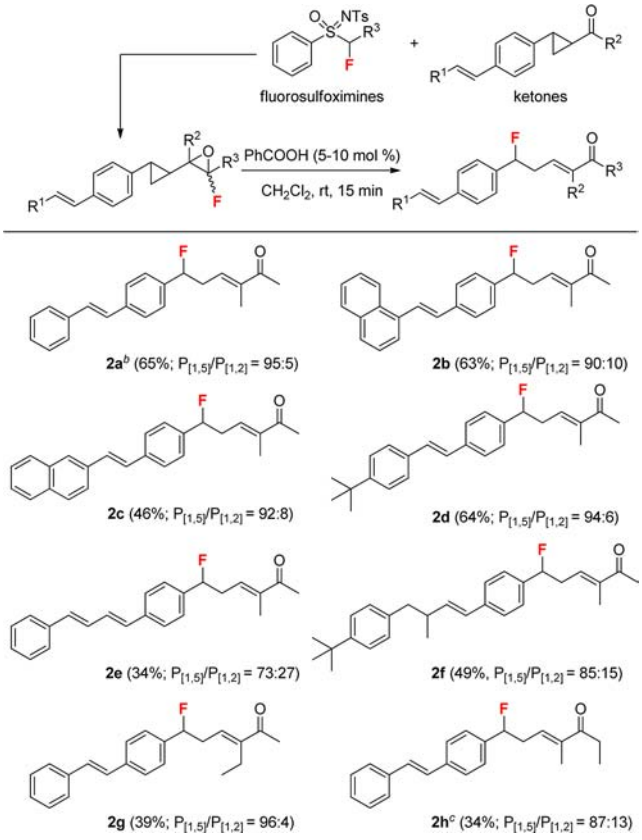
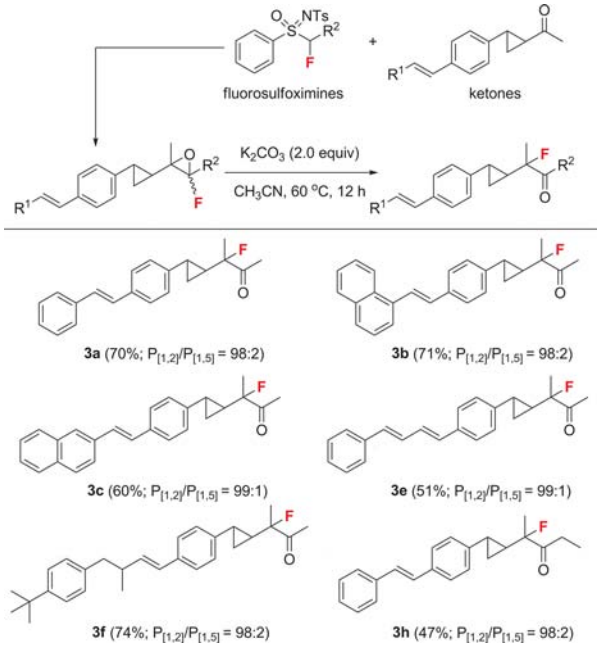
Scheme 2. PhCOOH-Catalyzed 1,5-Fluorine Migration with Cyclopropyl-Substituted Fluoroepoxides[a]



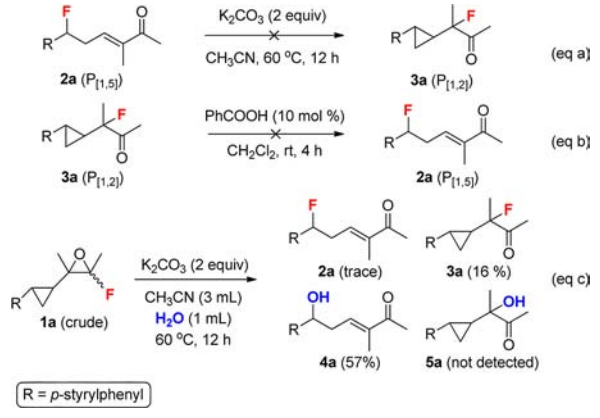
[a]General conditions: a crude fluoroepoxide[12] (0.2 mmol) and PhCOOH (1.2 mg, 0.01 mmol, 5 mol %) were dissolved in CH_2Cl_2 (3 mL) and stirred at room temperature for 15 min. Yields refer to isolated $P_{[1,5]}$ (two steps' total yield, caculated from ketones). [b]The elimination byproduct **6a** was also isolated. [c]PhCOOH (2.4 mg, 0.02 mmol, 10 mol %).

Scheme 3. Thermal 1,2-Fluorine Migration with Cyclopropyl-Substituted Fluoroepoxides[a]



[a]General conditions: a crude fluoroepoxide[12] (0.2 mmol) was dissolved in CH_3CN (3 mL) and stirred with K_2CO_3 (55 mg, 0.4 mmol) at 60 °C for 12 h. Yields refer to isolated $P_{[1,2]}$ (two steps' total yields caclulated from ketones).

Scheme 4. Probing the Reaction Mechanism[19]



(57%) (Scheme 4, eq c). The formation of **4a** suggests that water could compete with fluoride ion to capture the reaction intermediate, and therefore, the formation of the $P_{[1,5]}$ (**2a**) might involve a carbocation intermediate. The fact that **5a**[15] was not formed during the reaction indicates that the formation of $P_{[1,2]}$ (**3a**) might proceed via a tight ion pair intermediate[16] or through a concerted process.[7e,f,17,18]

Based on these experimental results, we propose a reaction mechanism for these novel 1,5- and 1,2-divergent rearrangements (Scheme 5). When **1a** is treated with an acid, it mainly undergoes 1,5-fluorine migration to give $P_{[1,5]}$ (**2a**). The acid activates the epoxide to form a carbocation intermediate **A**. Owing to the high ring strain of cyclopropyl group, **A** undergoes ring-opening to form carbocation **B**. Intermediate **B** could either be captured by a fluoride ion to give $P_{[1,5]}$ (**2a**) or eliminate a proton to afford **6a**. On the other hand, when **1a** is heated with a base at 60 °C, it mainly undergoes 1,2-fluorine migration to form $P_{[1,2]}$ (**3a**). The 1,2-migration may involve a tight ion pair intermediate or pass through a concerted mechanism,[20] and in this process, the addition of a base presumably inhibits the acid-catalyzed 1,5-migration.

In summary, we have reported the first 1,5- and 1,2-divergent rearrangements of the cyclopropyl-substituted fluoroepoxides. In the presence of a catalytic amount of benzoic acid, the cyclopropyl-substituted fluoroepoxides undergo 1,5-fluorine migration. On the other hand, when treated with K_2CO_3 at 60 °C in acetonitrile, fluoroepoxides undergo an efficient 1,2-fluorine migration. The 1,5-fluorine migration is believed to proceed via a carbocation intermediate, while the 1,2-fluorine migration may involve a tight ion pair intermediate or proceed through a concerted process. These interesting transformations, combining the C−F bond cleavage and formation within one molecule without adding external fluorinating agent(s), provide a proof of concept for the efficient fluorine migration under mild reaction conditions. These results promise to trigger further development of more practically useful fluorine migration reactions. Further exploration in this direction is currently underway in our laboratory.

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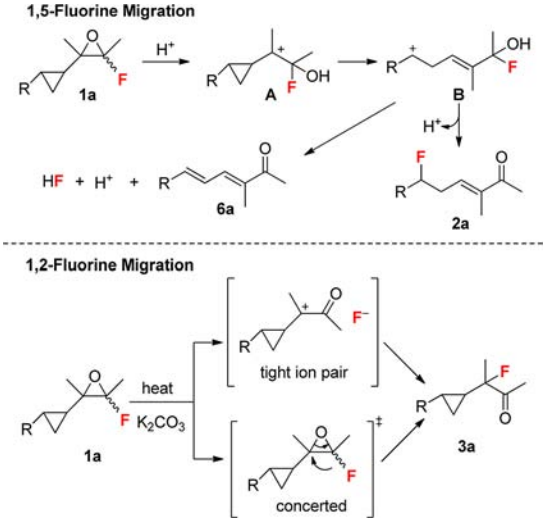
Scheme 5. Proposed Reaction Mechanism for the 1,5-and 1,2-Divergent Rearrangements



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) The preparative method for cyclopropyl-substituted fluoroepoxide **1a** is an improved version of the one reported in ref 8. The experimental details are described in the Supporting Information.

(12) A crude fluoroepoxide contains four diastereomers, and the ratio was determined by ^{19}F NMR (see the Supporting Information).

(13) Based on the NOE experiment of **2d**, the configuration of the newly formed double bond in $P_{[1,5]}$ is assigned as the *E*-configuration. For details, see the Supporting Information.

(14) $P_{[1,2]}$ is a pair of diastereomers. The dr for the product is detected by ^{19}F NMR, which is shown in the Supporting Information.

(15) We synthesized **5a** through another route, and **5a** showed good stability under the reaction conditions as shown in eq (c) of Scheme 4. For details, see the Supporting Information.

(16) The thermal rearrangement of cloroepoxides passed through a tight ion pair mechanism: McDonald, R. N.; Steppel, R. N. *J. Am. Chem. Soc.* **1970**, *92*, 5664.

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(19) For more experiments probing the rearrangement mechanism, see the Supporting Information.

(20) We thank one of the reviewers for raising a point that it is also possible that 1,2-migration proceeds through the following transition state.