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Regioselective Synthesis of Fluorohydrines via S_N2-Type Ring-Opening of Epoxides with Bu₄N⁺-HF₂⁻-KHF₂

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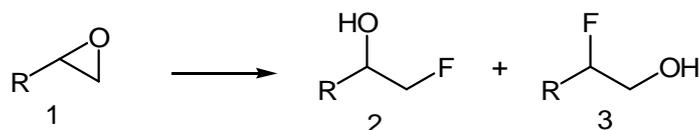
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Abstract: We found that the ring-opening fluorination of terminal epoxides using TBABF-KHF₂ proceeds with high selectivity through the S_N2 mechanism. As TBABF-KHF₂ is easily obtainable, is stable, and can be used in glassware, it can be a useful reagent for 1-fluoro-2-alkanols synthesis from the terminal epoxides.

Key words: epoxides, fluorohydrine, regioselectivity, ring-opening, tetrabutylammonium bifluoride (TBABF)-KHF₂

Ring-opening reaction of epoxides with a fluoride ion has been widely used to prepare organofluorine compounds.¹ Especially, regioselective fluorination of terminal epoxides has attracted much attention because optically active fluorohydrines, expected as building blocks for liquid crystal materials,² can be prepared from easily accessible, optically active terminal epoxides by that method. Though many reagents for regioselective ring-opening fluorination of terminal epoxides **1** have been reported, only a few of them successfully obtained good regioselectivity for 1-fluoro-2-alkanols **2** (Equation 1).



Equation 1

Schlosser et al. attained high regioselectivity (> 90%) for **2** by *i*-Pr₂NEt-HF,³ and Yoshioka et al. succeeded by using PBu₄F(HF)_n.⁴ However, they each showed only one example and the generality of their methods was not confirmed. Furthermore, a drawback of these methods is that the reagents are not easily available. We wish to report here that high regioselectivity (≥ 90%) for **2** was realized by Bu₄N⁺HF₂⁻(TBABF)-KHF₂, prepared from commercially available Bu₄NF (TBAF), aq HF, and KHF₂. The application of TBAF to the reaction with 1-octene oxide (**1a**) resulted in poor selectivity and chemical yield as shown in Table 1, and a

significant amount of Bu_3N was found after the reaction at $100\text{ }^\circ\text{C}$. As the fluoride ion of the TBAF is highly basic, Hofmann-type elimination took place under the reaction conditions and the TBAF decomposed to Bu_3N , butene, and HF .⁵ TBAF- $5\text{H}_2\text{O}$, reported to be less basic than TBAF, also gave a poor result.⁶ On the other hand, TBABF reacted with **1a** at $100\text{ }^\circ\text{C}$ to give **2a** in 78% yield with good regioselectivity (90%).⁷ However, application of longer reaction time or higher reaction temperature ($120\text{ }^\circ\text{C}$) could not improve the yield, and the formation of Bu_3N was observed after the reaction. Though TBABF is stable at below $140\text{ }^\circ\text{C}$, after the reaction with epoxides, it changes to the TBAF. The addition of KHF_2 was found to be effective not only to suppress the formation of Bu_3N but also to improve the yield. In the reaction of **1a** with 3 equivalents of TBABF and 0.3 equivalents of KHF_2 at $120\text{ }^\circ\text{C}$, **2a** was obtained in 92% yield and with good selectivity (91%).⁸ Though TBAF- 2HF (TBATF) also showed high reactivity in the reaction with **1a**, the regioselectivity was less satisfactory.

Table 1 Fluorination of **1a** with Various Reagents

Fluorination ^a reagent	Temp ($^\circ\text{C}$)	Time (h)	Yield (%) ^b
TBAF ^c	rt	24	0
TBAF	100	18	37(84 : 16)
TBAF- $5\text{H}_2\text{O}$	100	18	36 (72 : 28)
TBABF	100	18	78 (90 : 10)
TBABF	120	4	73 (90 : 10)
TBATF	120	4	97 (78 : 22)
TBABF- KHF_2 ^d	120	4	92 (91 : 9)

a) If otherwise not mentioned, fluorination reagent (3 mmol), **1a** (1 mmol) and heptane (0.1 mL) were used.

b) ^{19}F NMR yield using $\text{FCH}_2\text{CH}_2\text{OH}$ as internal standard. In parentheses, ratio of **2a** : **3a** obtained by ^{19}F NMR.

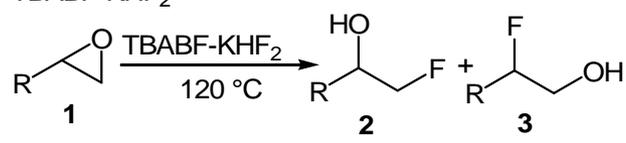
c) 3 mL of 1 M THF solution of TBAF was used.

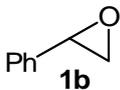
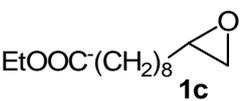
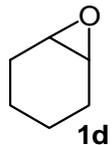
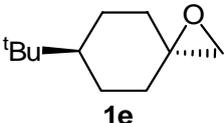
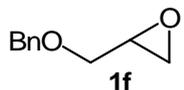
d) TBABF(3 mmol), KHF_2 (0.3 mmol) and heptane (0.1 ml) were used.

The generality of our method for the selective formation of the terminal fluorides **2** was shown in the reaction with various terminal epoxides (Table 2). Even in the reaction with styrene oxide (**1b**), which is apt to give $\text{S}_{\text{N}}1$ product **3b**,^{9a, 10} $\text{S}_{\text{N}}2$ product **2b** was obtained with good selectivity. Sattler and Haufe reported that in the reaction of $\text{Et}_3\text{N-nHF}$ reagents with ethyl 10,11-epoxy undecanoate (**1c**), the isolation of the corresponding fluorohydrine

products from the amine mixtures was difficult.¹⁰ In the reaction of **1c** with TBABF-KHF₂, the fluorohydrine **2c** was obtained in good yield and with high selectivity. From 1-oxaspiro[2,5]octane derivative **1e** and glycidol derivative **1f**, **2e** and **2f** were exclusively obtained.

Table 2 Fluorination of Various Epoxides with TBABF-KHF₂^a



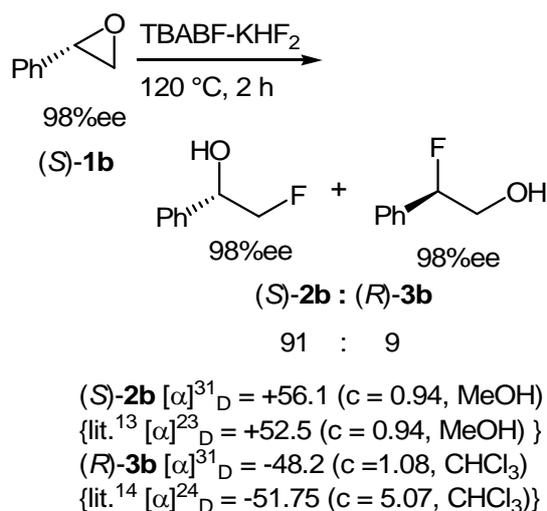
Substrate	Time (h)	Yield of 2 (%) ^b	2 : 3 ^c
 1b	2	86 (68)	90 : 10
 1c	6	86 (65)	90 : 10
 1d	4	71	—
 1e	4	75 (74)	>99 : <1
 1f	4	92 (72)	98 : 2

a) 3 equivalents of TBABF, 0.3 equivalents of KHF₂, and 0.1 mL of heptane were used to **1** (1 mmol).

b) ¹⁹F NMR yield using FCH₂CH₂OH as an internal standard, in parentheses, isolated yield based on **1**.

c) Determined by ¹⁹F NMR.

TBABF-KHF₂ is applicable to the synthesis of optically active fluorohydrines, and (*S*)-1-fluoro-2-phenyl-2-ethanol of 98%ee was obtained in 90% yield from commercially available (*S*)-(-)-styrene oxide (98%ee) as shown in Scheme 1.¹¹ Interestingly, the minor product, 2-phenyl-2-fluoroethanol (**3b**), also kept the optical purity of the starting epoxide. Therefore, both **2b** and **3b** were formed via the S_N2 mechanism without racemization.¹²



Scheme 1

References

- (1) (a) Mascaretti, O. A. *Aldrichimica Acta*, **1993**, *26*, 47. (b) Bonini, C.; Righi, G. *Synthesis*, **1994**, 225, and the references are cited therein.
- (2) Umezawa, J.; Takahashi, O.; Furuhashi, K.; Nohira, H. *Tetrahedron Asymmetry*, **1993**, *4*, 2053.
- (3) Suga, H.; Hamatani, T.; Schlosser, M. *Tetrahedron*, **1990**, *46*, 4247.
- (4) Seto, H.; Qian, Z.; Yoshioka, H.; Uchibori, Y.; Umeno, M. *Chem. Lett.*, **1991**, 1185.
- (5) (a) Landini, D.; Maia, A.; Rampoldi, A. *J. Org. Chem.*, **1989**, *54*, 328. (b) Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J. *J. Am. Chem. Soc.*, **1990**, *112*, 7619.
- (6) Albanese, D.; Landini, D.; Penso, M. *J. Org. Chem.* **1998**, *63*, 9587.
- (7) TBABF was previously used for the halogen exchange fluorination reaction in polar solvents, see: (a) Bosch, P.; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *Tetrahedron Lett.*, **1987**, *28*, 4733. (b) Moughamir, K.; Atmani, A.; Mestdagh, H.; Rolando, C.; Francesch, C. *Tetrahedron Lett.*, **1998**, *39*, 7305.
- (8) The generated TBAF must be converted to the stable TBABF again by KHF₂ before the decomposition to Bu₃N.⁹ As KHF₂ is slightly soluble in the reaction mixture, further addition of KHF₂ was not effective.
- (9) (a) Landini, D.; Penso, M. *Tetrahedron Lett.*, **1990**, *31*, 7209. (b) Landini, D.; Albanese, D.; Penso, M. *Tetrahedron*, **1992**, *48*, 4163.
- (10) Sattler, A.; Haufe, G. *J. Fluorine Chem.*, **1994**, *69*, 185.
- (11) Enantiomeric excess values of $(S)\text{-2b}$ and $(R)\text{-3b}$ were determined from ¹⁹F NMR after

conversion to MTPA esters.

- (12) The representative procedure for **2a** is as follows: To a 1 M THF solution of TBAF (30 mL, 30 mmol) in a glass vessel was added 46% aq HF (1.3 g, 30 mmol) and the volatile part was removed by evaporator to give a crude TBABF. The crude TBABF, containing a little water, is storable in a glass bottle.¹⁵ The crude TBABF (845 mg, 3 mmol) and KHF₂ (24 mg, 0.3 mmol) were put in a glass vessel and water was completely removed (for 15 min at 100 °C and 0.55 mmHg). After cooling to room temperature, heptane (0.1 mL)¹⁶ and **1a** (1 mmol) were added. The mixture was kept at 120 °C for 4 h and then cooled to room temperature again. To the reaction mixture, 2 mL of water was added and the mixture was extracted with ether (2 mL x 3). NMR yield and the product ratio were determined from ¹⁹F NMR using FCH₂CH₂OH as an internal standard. Isolation was carried out by column chromatography (silica gel/hexane-ether) after concentration. **2a**: IR (film) 3390, 2930, 1460 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.50-4.20 (m, 2H), 3.89-3.86 (m, 1H), 2.00 (s, 1H), 1.48-1.43 (m, 3H), 1.33-1.28 (m, 7H), 0.89 (t, 3H, *J* = 7.0 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -228.81 (dt, *J* = 18.3, 47.7 Hz, 1F); **3a**: IR (film) 3365, 2930, 1466 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.58 (dm, *J* = 50.3 Hz, 1H), 3.79-3.61 (m, 2H), 1.88 (t, *J* = 6.3 Hz, 1H), 1.75-1.30 (m, 12H), 0.89 (t, 3H, *J* = 6.8 Hz); ¹⁹F NMR (376 MHz, CDCl₃) δ -190.03 - -190.42 (m, 1F).
- (13) Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. *J. Org. Chem.*, **2000**, *65*, 157.
- (14) Takano, S.; Yanase, M.; Ogasawara, K. *Chem. Lett.*, **1989**, 1689.
- (15) Complete removal of water gave pure TBABF as a highly viscous liquid¹⁷ which is difficult to handle. Therefore, it is better to store the crude TBABF and to remove the water completely just before use. TBABF is commercially available and TBABF obtained from Tokyo Kasei Kogyo Co., Ltd. showed the same reactivity.
- (16) Heptane was used to wash the substrates attached on the wall of the vessel during the reaction, and in a larger-scale experiment, the solvent is not necessary.
- (17) Spectra data of TBABF thus prepared coincided with the reported ones; ¹⁹F NMR (CD₂Cl₂, -80 °C) δ -151.5 (d, *J*_{HF} = 123.0 Hz), lit.¹⁹ (CD₂Cl₂, -80 °C) δ -147.5 (d, *J*_{HF} = 123.3 Hz).
- (18) Camps, F.; Chamorro, E.; Casol, V.; Guerrero, A. *J. Org. Chem.*, **1989**, *54*, 4294.
- (19) Sharma, R. K.; Fry, J. L. *J. Org. Chem.*, **1983**, *48*, 2112.