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HIGHLY SELECTIVE RING OPENING OF EPOXIDES WITH SILICON TETRAFLUORIDE: PREPARATION OF FLUOROHYDRINS

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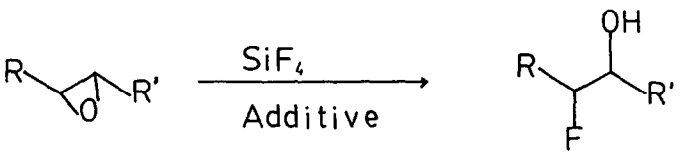
Summary: Regio-, stereo-, and chemoselective transformation of epoxides into fluorohydrins with silicon tetrafluoride is described.

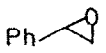
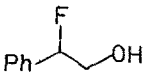
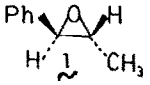
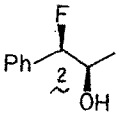
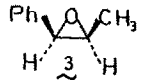
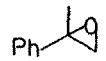
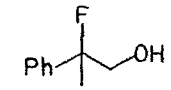
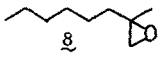
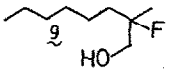
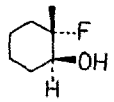
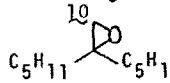
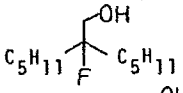
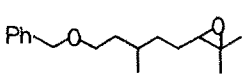
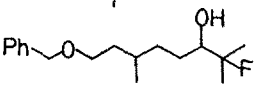
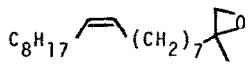
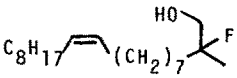
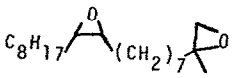
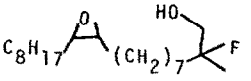
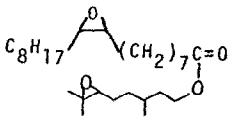
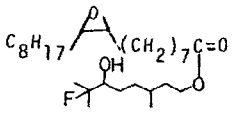
One of the most fundamental but difficult transformations in fluorine chemistry is the opening of epoxides to produce fluorohydrins.[1] The fluorohydrin synthesis has long been applied to the selective introduction of a fluorine atom into certain bioactive moleclules such as steroids,[2] amino acids,[3] carbohydrates,[4] and prostaglandins[5]. Although hydrogen fluoride modified with some Lewis acids or bases has been commonly used for this purpose, most cases require heating at high temperatures for long periods, which often cause byproducts resulted from rearrangements, polymerizations, or hydrofluorination of double bonds and thus decrease regio- and stereoselectivities.[1] We now report a new method for preparation of fluorohydrins in the high selectivities under mild conditions employing silicon tetrafluoride[6] with certain additives, which eliminates the hazards or troubles arising from the HF reagents.



Silicon tetrafluoride has only a few applications in organic synthesis; conversion of ethyl orthoformate to ethyl fluoride at high temperatures[7a] and a catalyst for glycosilation.[7b] We found that treatment of phenyloxirane with SiF_4 in 1,2-dichloroethane at 0 °C~ rt gave 2-fluoro-2-phenylethanol in 62% yield together with rearranged phenylacetaldehyde(>20%).

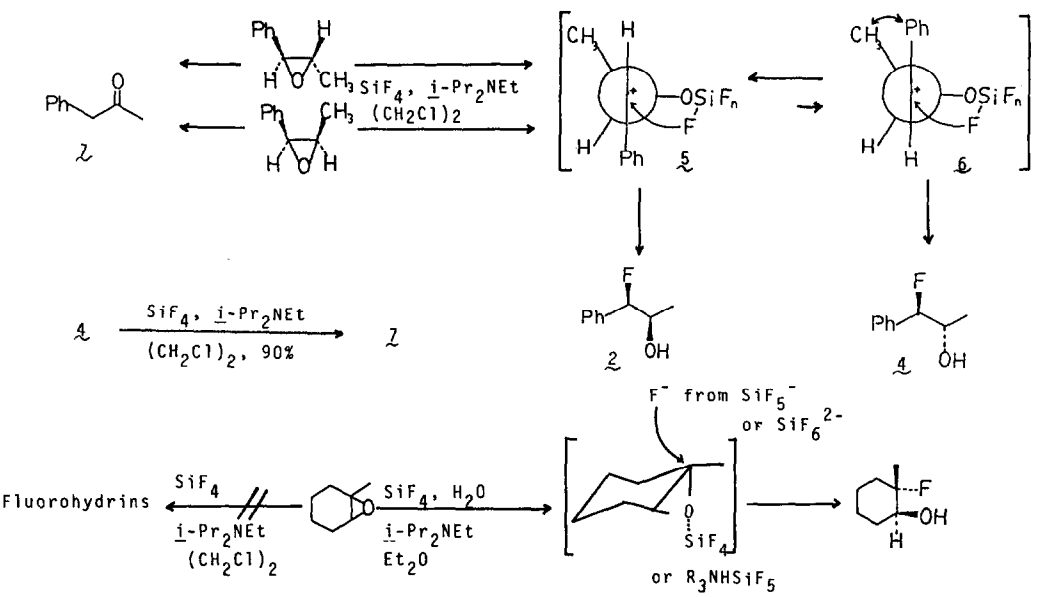
As shown in Table 1, addition of a Lewis base, *e. g.*, diisopropylethylamine, to the reaction media gave the fluorohydrin in 71% yield with a trace of the aldehyde (entry 1). Reaction of aliphatic epoxides with SiF_4-*i*-Pr_2NEt, however, gave no fluorohydrin, and predominantly yielded rearranged products (see footnote h of entry 6). This may be due to the low nucleophilicity of F^- in SiF_4, since addition of tetra-*n*-butylammonium fluoride(1.1~ 1.8 equiv.) or water(2.0~ 4.0 equiv.) distinctly altered the reaction course, and the fluorohydrin was obtained in good yield as a sole product (entries 7 and 8). These results suggest that hypervalent fluorosilane (SiF_5^- or SiF_6^{2-})[8] formed from SiF_4-*n*-Bu_4NF or SiF_4-H_2O would increase the nucleophilicity of fluoride anion and facilitate the opening of epoxides.

Table 1. Reaction of Epoxides with SiF_4[a]

Entry	Epoxide	Solvent	Additive (equiv)	Product[b]	%yield[c]
1		$(CH_2Cl)_2$	i-Pr_2NEt (0.5)		71
2		$(CH_2Cl)_2$	i-Pr_2NEt (0.5)		78[d]
3		$(CH_2Cl)_2$	No	2	31[e]
4	3	$(CH_2Cl)_2$	i-Pr_2NEt (0.5)	2	12[f]
5		$(CH_2Cl)_2$	i-Pr_2NEt (10.0)		58[g]
6		$(CH_2Cl)_2$	i-Pr_2NEt (1.0)		0[h]
7	8	Et_2O	i-Pr_2NEt (1.0) n-Bu_4NF (1.8)	9	70
8	8	Et_2O	i-Pr_2NEt (1.0) H_2O (4.0)	9	69
9		Et_2O	i-Pr_2NEt (1.0) H_2O (4.0)		71
10		Et_2O	i-Pr_2NEt (1.0) H_2O (4.0)		70
11		Et_2O	i-Pr_2NEt (1.0) H_2O (4.0)		91
12		Et_2O	i-Pr_2NEt (1.0) H_2O (4.0)		76
13		Et_2O	i-Pr_2NEt (1.0) n-Bu_4NF (1.4)		59
14		Et_2O	i-Pr_2NEt (1.0) n-Bu_4NF (1.5)		52

[a]The reaction was carried out at 0°C ~ rt for 1 ~ 5 hr under an atmosphere of SiF_4. [b]All the products were characterized by ^1H NMR, ^{19}F NMR, ir, and mass spectra. [c]Isolated yield. [d]1-Phenyl-2-propanone (7) (11%) was formed. [e]7 (39%) was formed. [f]7 (85%) was formed. [g]2-Phenylpropanal (11%) was formed. [h]2-Methyloctanal (32%) was formed.

The observed stereochemistry of the epoxide ring-opening is noteworthy (entries 2 and 3): Both 1 and 3 gave *syn*-fluorohydrin, whereas *i*-$Pr_2NH.3HF$[9] gave the *anti*-isomer from the *trans*-epoxide 1. In contrast to 1, 1-methylcyclohexene oxide 10 gave the *trans*-fluorohydrin 11 in good yield (entry 9). These may be explained as follows: In the cases with entries 2, 3, and 4 which were conducted in the absence of H_2O or *n*-Bu_4NF, the reactions proceeded via the intermediate carbonium ion 5 stabilized with a phenyl group and the subsequent intramolecular fluorination gave the *syn*-fluorohydrin 2. Although the formation of the *anti*-isomer 4 via the intermediate 6 is also possible, the steric repulsion between phenyl and methyl groups may make 6 unfavoured. Furthermore, the *anti*-isomer 4 prepared by Aranda's method[9] gave the rearranged ketone 7 upon treatment with SiF_4-*i*-Pr_2NEt in $(CH_2Cl)_2$, which also accounts for the absence of 4, even if formed initially in the present system. The low yield of 2 from 3 is due to the rapid rearrangement to the ketone 7 (see footnotes e and f of entries 3 and 4, respectively).[10] On the other hand, the reaction course was changed by the presence of H_2O or *n*-Bu_4NF by which hypervalent fluorosilanes are formed. For example, reaction of 1 with SiF_4-H_2O or SiF_4-*n*-Bu_4NF gave a mixture of 2 (*syn*) and 4 (*anti*) in ca. 1:1 ratio in 30~35% yield. In the case of 10, SiF_4-*i*-Pr_2NEt treatment gave no fluorohydrin and the presence of H_2O was crucial for opening of the oxirane ring. Therefore, it is reasonable to assume that the *trans*-opening of 10 was caused by the activation of the oxirane ring with SiF_4 or $[R_3NHSiF_5]$ followed by the intermolecular attack of hypervalent fluorosilanes.[11]



Regio-, and chemoselectivities are also noteworthy: In all the available examples a fluorine atom was regiospecifically introduced to the more substituted carbons. Olefins, ethers, and 1,2-disubstituted aliphatic oxiranes were intact under the present reaction conditions (entries 11~14). In addition, monosubstituted aliphatic oxiranes, *e. g.*, *n*-hexyloxirane and *n*-dodecyloxirane, gave no fluorohydrins but resulted in polymeric products.

The present fluorohydrin formation from oxiranes mediated by silicon tetrafluoride has the following advantages over the existing methodologies: The reaction can be operated in usual glass reaction vessels for a short period of time at low temperatures with high regio- stereo- and chemoselectivities, which will offer diverse potentials in a selective fluorinarion.

The following is a typical experimental procedure: Into a 30 ml round-bottomed flask equipped with a balloon filled with SiF_4 (Ca. 100 ml: Although approximately 12 ml of the gas is sufficient on the present scale, the reaction was most conveniently run under an excess SiF_4) were added ether (3 ml), diisopropylamine (87 μl, 0.5 mmol), and water (36 μl, 2.0 mmol) successively. To it was added a solution of 8-benzyloxy-2,6-dimethyl-2,3-epoxyoctane (131 mg, 0.5 mmol) in ether (2 ml) at 0 °C and the mixture was stirred at that temperature for 1 hr. Aqueous KF solution (5 ml) was added and the normal workup gave 8-benzyloxy-2,6-dimethyl-2-fluorooctan-3-ol (129 mg, 91% yield) as a colorless oil.

References and Notes

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(11) **2**, **4**, and **11** gave the following spectra. **2**: ^{1}H NMR ($CDCl_3$) δ 1.05 (d, 3 H, J = 6.3 Hz), 2.76 (brs, 1 H), 4.06 (ddt, 1 H, J = 14.0, 7.3, and 7.3 Hz), 5.14 (dd, 1 H, J = 47.7 and 7.0 Hz), 7.30 (s, 5 H); ^{19}F NMR ($CDCl_3/CFCl_3$) -183 ppm. **4**: ^{1}H NMR ($CDCl_3$) δ 1.19 (dd, 3 H, J = 7.2 and 2.9 Hz), 2.42 (brs, 1 H), 3.68-4.24 (m, 1 H), 5.26 (dd, 1 H, J = 46.8 and 5.4 Hz), 7.32 (s, 5 H); ^{19}F NMR ($CDCl_3/CFCl_3$) -192 ppm. **11**: ^{1}H NMR ($CDCl_3$) δ 1.12-2.08 (m, 11 H, including a doublet at δ = 1.36 J = 23.3 Hz), 2.20 (brs, 1 H), 3.54-3.92 (m, 1 H); ^{19}F NMR ($CDCl_3/CFCl_3$) -143 ppm.

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