Regioselective Fluorohydrin Synthesis from Allylsilanes

A. W. Clover, A. P. Jones, G. W. O'Neil*

Department of Chemistry, Western Washington University, Bellingham, WA 98229 (USA)

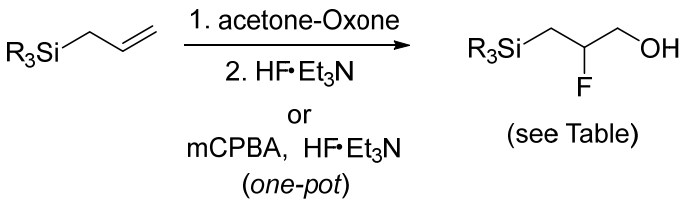
*Corresponding author. Email: oneilg@wwu.edu

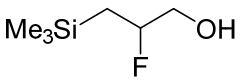
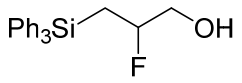
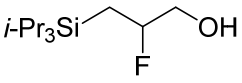
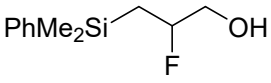
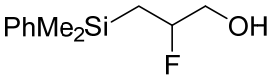
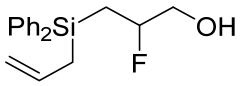
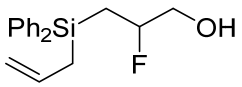
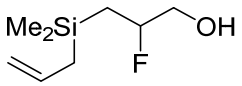
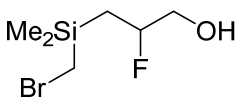
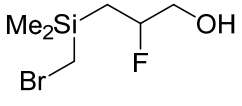
Abstract: Allysilanes can be regioselectively transformed into the corresponding 3-silylfluorohydrin in good yield using a sequence of epoxidation followed by treatment with HF•Et_3N with or without isolation of the intermediate epoxide. Various silicon-substitution is tolerated, resulting in a range of 2-fluoro-3-silylpropan-1ol products from this method. Whereas other fluorohydrin syntheses by epoxide opening using HF•Et_3N generally require more forcing conditions (e.g. higher reaction temperature), opening of allylsilane-derived epoxides with this reagent occurs at room temperature. We attribute this rate acceleration along with the observed regioselectivity to a beta-silyl effect that stabilizes a proposed cationic intermediate. The use of enantioenriched epoxides produces similarly enantioenriched fluorohydrins suggestive of an S_N2-type mechanism.

The introduction of fluorine atoms is an established tool for modulating the physicochemical properties of organic molecules, used widely in the pharmaceutical industry to improve selectivity, potency, and pharmacokinetic properties of active ingredients.[1-7] New methods continue to emerge for the preparation of organofluorine compounds, including both catalytic and enantioselective systems.[8] The ongoing need by drug discovery programs for fluorine-containing building blocks, makes important the development of reliable, scalable, and selective strategies to generate organofluorine chemicals capable of further functionalization.[9,10]

As part of an ongoing program investigating new reactions of allylsilanes,[11-13] we observed that epoxysilanes, prepared by epoxidation of the corresponding allylsilane, are cleanly converted to the corresponding fluorohydrin upon treatment with triethylamine trihydrofluoride (HF•Et_3N; Table 1). Other HF sources such as Olah's reagent (HF•pyridine) resulted in significant decomposition. However, the addition of commercially available HF•Et_3N (ca. 37% HF) to a solution of the epoxysilane in dichloromethane (DCM) at room temperature produced the 2-fluoro-3-silylpropan-1-ols in uniformly high yield and with complete regioselectivity. In a typical experiment, the allylsilane was epoxidized using *in situ*-prepared dimethyldioxirane.[14] This generally gave a sufficiently pure epoxide that could be taken directly into the epoxide opening with HF•Et_3N. An exception was allyltrimethylsilane, where the resulting epoxide proved somewhat volatile, making its isolation challenging. Instead, a one-pot epoxidation/epoxide opening was performed by treatment of allyltrimethylsilane with mCPBA and HF•Et_3N in DCM.[15] Under these conditions, the fluorohydrin was isolated in 65% yield (Entry 1) containing small amounts (~10%) of 1-hydroxy-3-(trimethylsilyl)propan-2-yl 3-chlorobenzoate, resulting from opening of the epoxide by mCPBA-derived 3-chlorobenzoic acid.[16,17] This one-pot procedure also proved effective for less volatile allylsilanes, and in general gave comparable yields to the two-step procedure (e.g. Entries 4 and 5). The reaction was notably slower with the phenyl-substituted epoxysilanes (Entries 2, 4-7), where greater phenyl substitution resulted in longer reaction times. We rationalize this reduced rate as being due to the electron-withdrawing nature of the phenyl groups, thereby reducing the β-silyl effect[18] in stabilizing the proposed cationic intermediate.

Table 1. Fluorohydrin synthesis from allylsilanes.



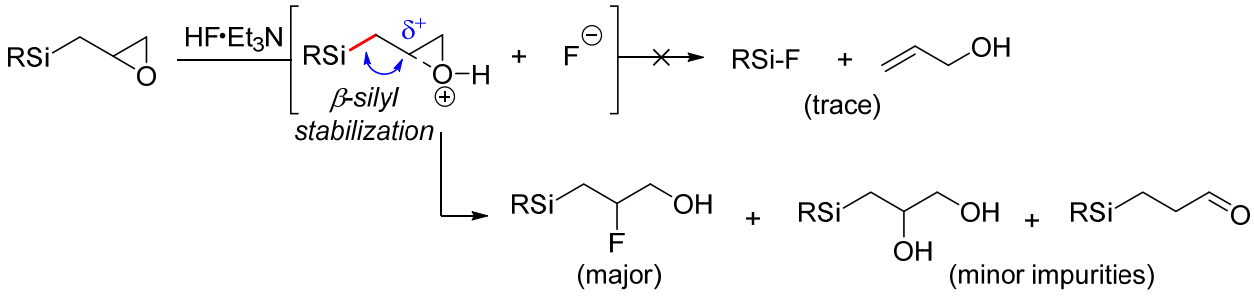
Entry	Conditions	Fluorohydrin	Yield (%)
1.	B		65
2.	A		65
3.	A		92
4.	A		72
5.	B		60
6.	A		41
7.	B		53
8.	B		56
9.	A		60
10.	B		37

Notes for Table: Conditions (**A**): 1. Allylsilane (1.0 mmol), tetrabutyl ammonium hydrogen sulfate (TBAHS) (4 mol%), acetone (30 mmol), K_2CO_3 (0.1 M) (0.2 mmol), MeCN:DMM (2:1) (8 mL), oxone (3 mmol), and K_2CO_3 (13.3 mmol), room temperature; 2. Epoxysilane (1 equiv),

HF•Et_3N (5 equiv), DCM (0.05-0.1 M), room temperature. (**B**): Allylsilane (1 equiv), mCPBA (1.3 equiv), HF•Et_3N (5-7 equiv), DCM (0.05-0.1 M) (C): Yields listed are isolated yields of the fluorohydrin from the starting allylsilane.

There are a few noteworthy aspects of this transformation. First, at the outset we were concerned about competing formation of allyl alcohol and a corresponding fluorosilane, driven by formation of a stable Si-F bond (Scheme 2).[19] By ^{1}H NMR analysis of the crude product mixtures, however, very little allyl alcohol was produced from any of the silanes tested. Other minor byproducts observed were small amounts of the corresponding diol **1** and aldehyde **2**, the latter presumably via a Meinwald-type rearrangement.[20,21] Second, this fluoride opening of epoxysilanes occurs at room temperature. Other reports of fluorohydrin synthesis by epoxide opening with HF•Et_3N generally require heating in order to achieve high conversion.[22] We attribute the rate acceleration, along with control of regioselectivity, to the beta-silyl effect, similar to rate enhancements observed for other reactions involving cationic intermediates with a silicon group at the β-position.[23]

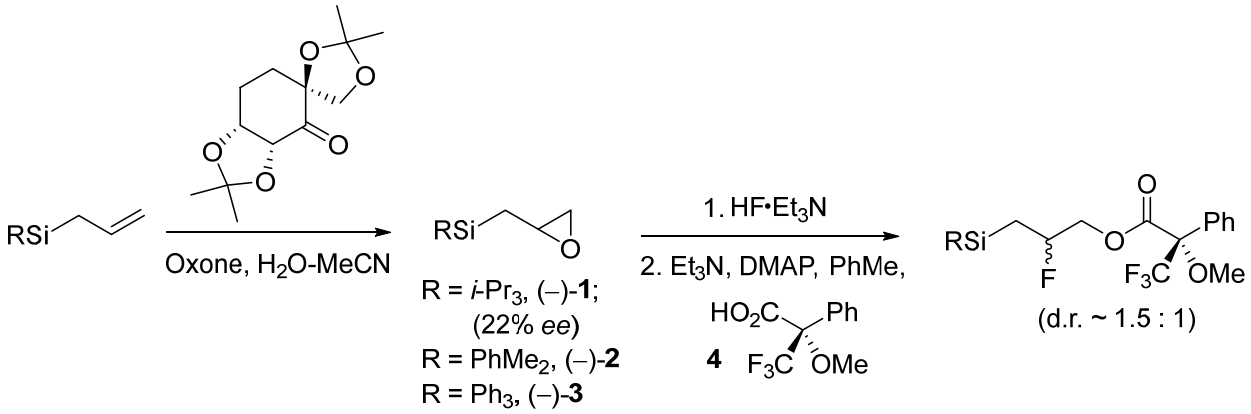
Scheme 2. Explanation of regioselectivity observed and structures of byproducts.



In order to probe the mechanism of this transformation, epoxysilanes **1-3** were prepared in enantioenriched form by Shi epoxidation[24] of the corresponding allylsilanes (Scheme 3). Like we observed for the racemic sequence, when using allyltriphenylsilane the Shi epoxidation was slower than the other differently substituted allylsilanes. Nonetheless, good yields of

triphenylsilyl epoxide **5** could be achieved using a slightly more concentrated reaction mixture and extended reaction times. A comparison of the measured optical activity for triisopropyl silyl epoxide **1** with that previously reported,[24] indicated **1** was obtained as a 62:38 mixture of enantiomers (22% *ee*), in line with previously obtained values for the same transformation.[24] Treatment of **1**-**3** with HF•Et_3N followed by esterification with (*S*)-methoxy-α-(trifluoromethyl)phenylacetic acid (**4**) allowed for an assessment of fluorohydrin enantiopurity by ^{1}H NMR analysis. In this way, the enantiopurity of all three silyl fluorohydrins was determined to be ~1.5:1, indicating the enantiopurity of the starting epoxide was retained and epoxide opening occurred via an S_N2-type process.

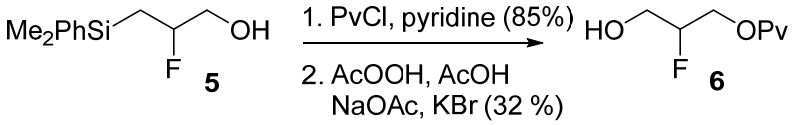
Scheme 3. Preparation of enantioenriched epoxysilanes and their corresponding fluorohydrin with assessment of fluorohydrin enantiopurity by conversion to the Mosher ester derivative.



The fluorohydrin products obtained from this sequence are unique in that they contain two functional group handles (i.e. an alcohol and silyl group), facilitating their incorporation into more complex structures. For instance, acylation of the alcohol in **5** with pivaloyl chloride (PvCl) followed by Tamao-Fleming oxidation[25,26] gave the differentiated 2-flouro-1,3-propanediol **6** (Scheme 4). Compounds of this type have proven to be useful tools to study enzymatic reactions

involving glycerol,[27,28] as well as a starting point to access fluorinated carbohydrate analogues of medicinal value.[29]

Scheme 4. Synthesis of an end-group differentiated fluoroglycerol analogue.



In summary, various allylsilanes can be converted to the corresponding 3-silylfluorohydrins in good yield and excellent regioselectivity by epoxidation followed by epoxide opening with HF•Et_3N. Compared with other fluorohydrin syntheses by epoxide opening with HF•Et_3N, formation of these silicon-substituted fluorohydrins occurs more readily (e.g. room temperature within one hour) and higher regioselectivity that we attribute to a beta-silyl effect. Reactions tended to be slower with phenyl-substituted silanes, which could be due to the electron-withdrawing nature of this group. Extended reaction times, however, allowed for these products to be successfully obtained in similarly high yield to other 3-silylfluorohydrins with differing substituents on silicon. Volatility of some intermediate epoxysilanes prompted us to investigate a one-pot epoxidation/epoxide opening reaction using a combination of mCPBA and HF•Et_3N. Yields for this one-pot procedure were generally in the same range as the overall yield from a two-step process involving epoxidation with *in situ* generated oxone followed by treatment with HF•Et_3N. However, the use of mCPBA generally gave small amounts of the 3-chlorobenzoate adduct resulting from 3-chlorobenzoic acid epoxide opening. For this reason, our preferred method for substrates with suitably low volatility remains the two-step sequence. Our efforts are currently focused on further transformations of these compounds to access valuable fluorine- and/or silicon-containing synthetic intermediates.

References

(1) Shah, P.; Westwell, A. D. *J. Enz. Inhib. Med. Chem*. **2007**, *22*, 527-540.

(2) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev*. **2008**, *37*, 320−330.

(3) Wang, J.; Sanchez-Rosello, M.; Acena, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev*. **2014**, *114*, 2432−2506.

(4) Swallow, S. Fluorine in medicinal chemistry. *Prog. Med. Chem*. **2015**, *54*, 65−133.

(5) Gillis, E. P.; Eastman, K. J.; Hill, M. D.; Donnelly, D. J.; Meanwell, N. A. *J. Med. Chem*. **2015**, *58*, 8315−8359.

(6) Zhou, Y.; Wang, J.; Gu, Z.; Wang, S.; Zhu, W.; Acena, J. L.; Soloshonok, V. A.; Izawa, K.; Liu, H. *Chem. Rev*. **2016**, *116*, 422−518.

(7) Mei, H.; Han, J.; Fustero, S.; Medio-Simon, M.; Sedgwick, D. M.; Santi, C.; Ruzziconi, R.; Soloshonok, V. A. *Chem. - Eur. J.* **2019**, 25, 11797-11819.

(8) Yang, X.; Wu, T.; Phipps, R. J., Toste, F. D. *Chem. Rev*. **2015**, *115*, 826−870.

(9) Caron, S. *Org. Process Res. Dev*. **2020**, *24*, 470−480.

(10) Britton, R.; Gouverneur, V.; Lin, J-H.; Meanwell, M.; Ni, C.; Pupo, G.; Xiao, J-C.; Hu, J. *Nat. Rev*. **2021**, 1:47 doi.org/10.1038/.

(11) O'Neil, G. W.; Cummins, E. J. "Iodine-mediated rearrangements of diallylsilanes" *Tetrahedron Lett.* **2017**, *58*, 3406-3409.

(12) Spaltenstein, P.; Cummins, E. J.; Yokuda, K-M.; Kowalczyk, T.; Clark, T. B.; O'Neil, G. W. *J. Org. Chem.* **2019**, *84*, 4421–4428.

(13) Fomina, I. A.; Myers, C. R.; Soumis, C. L. M.; Scheuermann, M. L.; McCarty, J.; Clark, T. B.; O'Neil, G. W. *Heterocycles* **2022**, *104*, DOI: 10.3987/COM-22-14735.

(14) Frohn, M.; Wang, Z-X.; Shi, Y. *J. Org. Chem*. **1998**, *63*, 6425–6426.

(15) Sedgwick, D. M.; López, I.; Román, R.; Kobayashi, N.; Okoromoba, O. E.; Xu, B.; Hammond, G. B.; Barrio, P.; Fustero, S. *Org. Lett*. **2018**, *20*, 2338–2341.

(16) Badali, F.; Karalis, A.; Tham, W. Y.; White, J. M. *Aust. J. Chem*. **1996**, *49*, 1293-1299.

(17) Badali, F.; Issa, W.; Pool, B.; White, J. M. *J. Organomet. Chem.* **1999**, *575*, 251-260.

(18) For reviews see: (a) Lambert, J. B. *Tetrahedron* **1990**, *46*, 2677-2689. (b) Roberts, D. D.; McLaughlin, M. G. *Adv. Synth. Catal*. **2022**, *364*, 2307-2332.

(19) Walsh, R. *Acc. Chem. Res.* **1981**, *14*, 246-252.

(20) Rickborn, B. Acid-catalyzed Rearrangements of Epoxides. In: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., **1991**; pp 733– 775.

(21) Wang, Z. Meinwald Rearrangement. In: *Comprehensive Organic Name Reactions and Reagents*; Wiley: Hoboken, NJ, **2010**; pp 1880– 1882.

(22) Remete, A. M.; Kiss, L. *Eur. J. Org. Chem*. **2019**, 5574–5602.

(23) For a recent review see: Roberts, D. D.; McLaughlin, M. G. *Adv. Synth. Cat*. **2022**, *364*, 2307-2332.

(24) Wang, Z-X.; Tu, Y.; Frohn, M.; Zhang, J-R.; Shi, Y. J. *Am. Chem. Soc*. **1997**, *119*, 11224-11235.

(25) Fleming, I. *J. Chem. Soc. Perkin Trans 1* **1995**, 317-337.

(26) Ibrahim, S. M. S.; Banerjee, K.; Slater, K. A.; Friestad, G. K. A Tamao–Fleming Oxidation Route to Dipeptides Bearing N,O-Acetal Functionality. *Tetrahedron Lett*. **2017**, *58*, 4864–4866.

(27) Eisenthal, R.; Harrison, R.; Lloyd, W. J.; Taylor, N. F. *Chem. Commun*. **1970**, 1507-1508.

(28) Li, Y.; Yao, Y.; Yu, L.; Tian, C.; Dong, M. *Chem. Commun*. **2022**, *58*, 2738-2741.

(29) Linclau, B.; Ardá, A.; Reichardt, N-C.; Sollogoub, M.; Unione, L.; Vincent, S. P.; Jiménez-Barbero, J. *Chem. Soc. Rev*., **2020**, *49*, 3863-3888.