An Efficient and Highly Regioselective Fluorination of Aziridines Using $BF_3{\cdot}OEt_2$ as Fluorine Source

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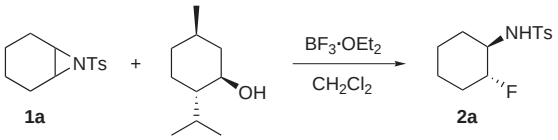
Abstract: β-Fluoro amines were prepared from the reaction of aziridines and boron trifluoride in high regioselectivity and in high yield. All three fluorine atoms of $BF_3{\cdot}OEt_2$ were incorporated into the products when it reacted with aziridines.

Key words: aziridines, fluorination, $BF_3{\cdot}OEt_2$, ring-opening reaction, β-fluoro amine

$BF_3{\cdot}OEt_2$ is one of the most common Lewis acids and widely used as catalyst in numerous organic transformations, such as polymerization, alkylation, isomerization, condensation, and degradation,[1] but is rarely used as fluorine source in fluorination reactions.[2] On the other hand, the introduction of a fluorine atom into organic molecules has received much interest due to the physical and biological properties of fluorine-containing organic molecules.[3] Usually monofluorination is realized using diethylaminosulfurtrifluoride (DAST), tris(diethylamino)sulfonium difluorotrimethylsilicate (TAS-F), complexes of hydrogen fluoride with organic bases as reagents.[4] Recently, a facile ring-opening reaction of aziridines to β-fluoro amines using KF in the presence of Bu_4NHSO_4 was developed in our groups.[5] However, the reaction suffered from low regioselectivity for monosubstituted aziridines. During the course of studies on the transformation of aziridines,[6] we tried to use $BF_3{\cdot}OEt_2$ as the catalyst in the reaction of aziridines. It was surprising to find that ring-opening products of aziridines from fluorine attack were separated in high regioselectivity and in high yield. Additionally, all three fluorine atoms of BF_3 were transformed into the products efficiently.[7] In this letter, we would like to report our preliminary results on the preparation of β-fluoro amines from ring-opening reaction of aziridines using BF_3 as fluorine source.

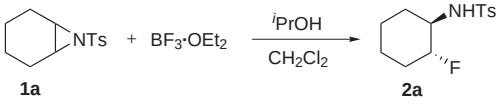
In an attempted ring-opening reaction of aziridine **1a** with (–)-menthol in the presence of 1.0 equivalent $BF_3{\cdot}OEt_2$, the reaction was completed in two hours. However, no corresponding ring-opening product of aziridine from (–)-menthol attack was obtained. Instead, an unexpected β-fluoro amine **2a** was isolated in 63% yield (Scheme 1). In the absence of (–)-menthol, the reaction completed in 48 hours and β-fluoro amine **2a** was also provided in 73% yield. Obviously, BF_3 serves as the reagent to provide the fluoride in this reaction and the alcohol accelerated the reaction. The optimization of the reaction conditions showed that *i*-PrOH is a more efficient additive than MeOH or *t*-BuOH and CH_2Cl_2 is a better solvent among Et_2O, toluene or THF, in which the yield increased to 83%.



Scheme 1

In this reaction, $BF_3{\cdot}OEt_2$ is the only fluorine source. It was noted that there are three fluorine atoms in $BF_3{\cdot}OEt_2$. Then we were interested to know whether the transformation of the second or even the third fluorine atom to aziridine is possible. So various amounts of $BF_3{\cdot}OEt_2$ and *i*-PrOH were used to test the possibility and the results are showed in Table 1.

Table 1 Reaction of Aziridine **1a** with $BF_3{\cdot}OEt_2$ in the Presence of *i*-PrOH under Various Reaction Conditions



Entry	$BF_3{\cdot}OEt_2$ (equiv)	*i*-PrOH (equiv)	Time (h)	Yield (%)[a]
1	1.0	1.0	1	83
2	0.50	0.50	12	80
3	0.40	0.40	26	87
4	0.35	0.35	26	82
5	0.35	0	120	78
6	0.25	0.25	76	63

[a] Isolated yields based on aziridine.

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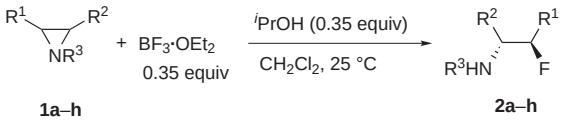
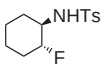
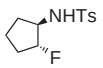
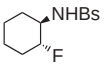
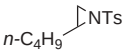
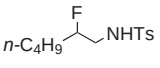
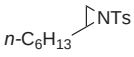
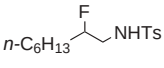
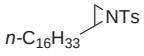
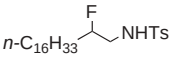
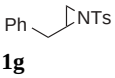
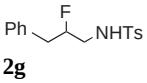
Indeed, all three fluorine atoms can be transformed into the ring-opening product of aziridine as shown in Table 1. When the amount of $BF_3{\cdot}OEt_2$ and *i*-PrOH was decreased to 50 mol% in reaction mentioned above, 80% yield of β-fluoro amine **2a** was obtained after 12 hours (entry 2). Then the amount of both $BF_3{\cdot}OEt_2$ and *i*-PrOH was further reduced to 40 mol%, 35 mol% and 25 mol%, β-fluoro amine **2a** was separated in 87%, 82% and 63% yield, respectively, with longer reaction time (entry 3, 4 and 6). These results suggested that all three fluorine atoms in $BF_3{\cdot}OEt_2$ could be transformed to the ring-opened product of aziridine. It was also noted that the presence of alcohol is important, in the absence of alcohol the reaction needed 120 hours to completion (entry 5).

Table 2 The Ring-Opening of Aziridines with $BF_3{\cdot}OEt_2$ in the Presence of *i*-PrOH



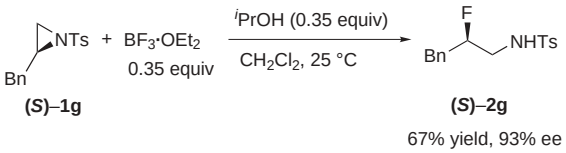
1a–h **2a–h**

Entry	Substrate[a]	Product	Time (h)	Yield (%)[b]
1	 **1a**	 **2a**	26	82
2	 **1b**	 **2b**	20	49
3	 **1c**	 **2c**	25	68
4	 **1d**	 **2d**	19	51
5	 **1e**	 **2e**	23	67
6	 **1f**	 **2f**	36	83
7	 **1g**	 **2g**	28	68

[a] Ts = *p*-$CH_3C_6H_4SO_2$, Bs = $C_6H_5SO_2$.
[b] Isolated yield based on aziridine.

Varies of aziridines were used to test the ability of this fluoride-transfer reaction using $BF_3{\cdot}OEt_2$ as fluorine source and the results are shown in Table 2.[9] It can be seen that all aziridines derived from cyclic and acyclic alkenes with electronic-withdrawing groups on nitrogen are suitable substrates to provide corresponding β-fluoro amines in good to high yield when the reaction proceed using 0.35 equivalents of $BF_3{\cdot}OEt_2$ in the presence of 0.35 equivalents of *i*-PrOH in CH_2Cl_2. The important feature of the reaction is its high regioselectivity. The reaction for all aziridines derived from acyclic alkenes gave only one regioisomer, resulting from fluoride attack at the more substituted carbon atom of the aziridines. This regioselectivity differs not only from that using KF in the presence of Bu_4NHSO_4 reported recently by us,[5] in which two isomers were obtained resulting from the attack of fluoride to both carbons of aziridine ring, but also from that of ring-opening reaction of aziridines using Lewis acid as catalyst.[8] However when non-activated aziridine was used as substrate, reaction didn't occur.

When enantiomerically pure monosubstituted *N*-tosyl-aziridine **(*S*)-1g** prepared by the method of Craig[10] was used as substrate, corresponding product **(*S*)-2g** was obtained without the loss of ee value (Scheme 2). Obviously this procedure provides an easy and simple but efficient way to chiral β-fluoro amine.



(*S*)–1g **(*S*)–2g**

67% yield, 93% ee

Scheme 2

In conclusion, we have demonstrated that BF_3 is a good fluorine source and all three fluorine atoms are used in the facile ring-opening reactions of aziridines to β-fluoro amines. The reactions afforded β-fluoro amines with excellent regioselectivity. Although the detailed reaction mechanism is not clear at moment, the highly regioselectivity of the reaction implies that this fluoride-transfer reaction proceeds in an unusual way. Investigations of the mechanism and the asymmetric version of the reaction are in progress.

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(7) Hu's group reported similar result but only one example was present and 2.0 equiv of $BF_3{\cdot}OEt_2$ was used: Hu, X. E. *Tetrahedron Lett.* **2002**, *43*, 5315.

(8) For recent review on nucleophilic ring-opening of aziridines see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(9) **General Procedure of the Reaction of Aziridine 1 with $BF_3{\cdot}OEt_2$ in the Presence of Alcohol**: To a stirred solution of aziridine **1** (0.5 mmol) and alcohol in corresponding solvent (2.0 mL) was added $BF_3{\cdot}OEt_2$ (0.6 mmol) under argon. The resulting mixture was stirred at 25 °C till complete consumption of substrate (monitored by TLC). The reaction mixture was quenched with 5 mL of sat. NH_4Cl aq solution. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layer was dried over anhyd Na_2SO_4. The solvent was removed in vacuum and the crude product was purified by flash column chromatography on silica gel to provide corresponding β-fluoro amines.[5] The analytical data of some products are shown below:

***N*-(2-Fluorohexyl)-4-methylbenzenesulfonamide (2d)**: 51% yield; white solid; mp 62–63 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.27–1.63 (m, 6 H), 2.44 (s, 3 H), 2.93–3.08 (m, 1 H), 3.20–3.31 (m, 1 H), 4.43 and 4.60 (double multiplet, $^2J_{H\text{-}F}$ = 51.0 Hz, 1 H), 4.78 (dd, *J* = 4.8, 7.2 Hz, 1 H), 7.32 (d, *J* = 7.8 Hz, 2 H), 7.75 (d, *J* = 8.7 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C, CF_3COOH): δ = –186.4 (m). MS (EI): *m/z* (%) = 273 (1.63)(M^+), 184 (80), 155 (100), 91 (85). IR (film): 3279, 1599, 1496 cm^{-1}.

***N*-(2-Fluorooctyl)-4-methylbenzenesulfonamide (2e)**: 67% yield; white solid; mp 72–73 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, *J* = 6.9 Hz, 3 H), 1.25–1.60 (m, 10 H), 2.44 (s, 3 H), 2.94–3.09 (m, 1 H), 3.21–3.32 (m, 1 H), 4.43 and 4.59 (double multiplet, $^2J_{H\text{-}F}$ = 48.6 Hz, 1 H), 4.75 (dd, *J* = 4.8, 7.5 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.75 (d, *J* = 8.4 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C, CF_3COOH): δ = –173.9 (m). MS (EI): *m/z* (%) = 301 (1.19) [M^+], 184 (99), 155 (100), 146 (12), 91 (95). IR (film): 3276, 1600, 1324, 1160 cm^{-1}. Anal. Calcd for $C_{15}H_{24}FNO_2S$: C, 59.77; H, 8.03; N, 4.65. Found: C, 59.73; H, 7.97; N, 4.54.

***N*-(2-Fluorooctadecyl)-4-methylbenzenesulfon-amide (2f)**: 83% yield; white solid; mp 82–83 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 0.88 (t, *J* = 6.6 Hz, 3 H), 1.25–1.58 (m, 30 H), 2.44 (s, 3 H), 2.93–3.08 (m, 1 H), 3.13–3.31 (m, 1 H), 4.42 and 4.58 (double multiplet, $^2J_{H\text{-}F}$ = 49.2 Hz, 1 H), 4.71 (dd, *J* = 4.8, 7.8 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 7.74 (d, *J* = 8.1 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C, CF_3COOH): δ = –186.6 (m). MS (EI): *m/z* (%) = 441 (1.14) [M^+], 286 (35), 184 (100), 155 (59), 91 (37). IR (film): 3290, 1927, 1600, 1334, 1163 cm^{-1}. Anal. Calcd for $C_{25}H_{44}FNO_2S$: C, 67.98; H, 10.04; N, 3.17. Found: C, 68.23; H, 9.85; N: 3.20.

(*S*)-*N*-(2-Fluoro-3-phenylpropyl)-4-methylbenzene-sulfonamide (2g): 68% yield; white solid; mp 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 2.43 (s, 3 H), 2.84–3.27 (m, 4 H), 4.59–4.83 (m, 1 H), 4.75–4.83 (m, 1 H), 7.14 (d, *J* = 6.6 Hz, 2 H), 7.25–7.32 (m, 5 H), 7.71 (d, *J* = 8.1 Hz, 2 H). ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C, CF_3COOH): δ = –184.5 (m). MS (EI): *m/z* (%) = 308 (0.64) [M + 1]$^+$, 132 (100), 155 (41), 91 (94). IR (film): 3284, 1928, 1598, 1315, 1162 cm^{-1}. Anal. Calcd for $C_{16}H_{18}FNO_2S$: C, 62.52; H, 5.90; N, 4.56. Found: C, 656; H, 6.08; N: 4.52.

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