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Boron Trifluoride Etherate Functioning as a Fluorine Source in an Iodosobenzene-Mediated Intramolecular Aminofluorination of Homoallylic Amines

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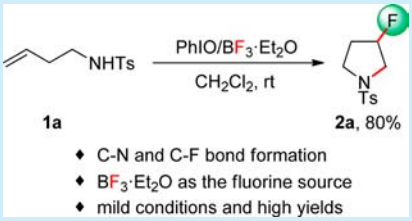
Supporting Information

ABSTRACT: A widely used Lewis acid $BF_3{\cdot}Et_2O$ was shown to be capable of acting as an efficient fluorinating agent in an intramolecular aminofluorination reaction of homoallylic amines to provide 3-fluoropyrrolidines mediated by a commercially available hypervalent iodine(III) reagent PhIO at room temperature. A mechanism involving a carbocation intermediate was proposed on the basis of several experimental evidence.



The introduction of a fluorine atom into organic molecules can greatly change their physical, chemical, and biological properties,[1] which may explain why ca. 40% of agrochemicals and ca. 20% of pharmaceuticals contain at least one fluorine atom.[2] 3-Fluoropyrrolidine, a fluorine-containing five-membered heterocycle, is the key structural unit presenting in the inhibitors of many enzymes (Figure 1, I and II), which are implicated in several diseases including diabetes, cancer, and mood disorders.[3] Some of the molecules bearing a 3-fluoropyrrolidine moiety show good antibacterial activity exemplified as compound III (Figure 1).[4] Usually, the synthesis of 3-fluoropyrrolidine relies on the deoxyfluorination of 3-hydroxypyrrolidine using diethylaminosulfur trifluoride (DAST) or its derivatives,[5] but such a method often suffers from the competing dehydration reaction and rearrangement processes.[5b,c,6] There is another strategy to synthesize 3-fluoropyrrolidine via a heteroannulation reaction of acyclic alkene having an amino functionality, which has, however, received much less attention. The only example following this strategy, with homoallylic amines containing a silyl group as substrates, was reported by Gouverneur et al. in which Selectfluor was employed as the fluorine source compound; however, the yield of silicon-containing 3-fluoropyrrolidines was not satisfactory.[7] It is worth noting that the same heteroannulation strategy has been successfully applied in the synthesis of other important heterocycles including 3-fluoropiperidine,[8a−d] fluorinated spiro-fused oxazoline,[8e] and fluorinated tetrahydrofuroindole[8f] in recent years.

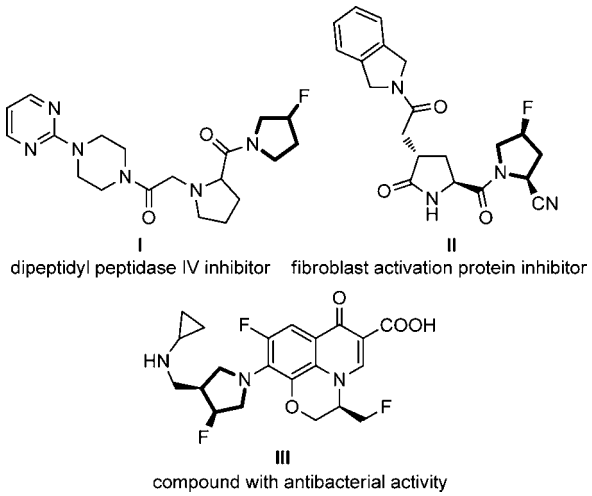


Figure 1. Selected biologically active compounds containing the 3-fluoropyrrolidine moiety.

In fluorination reactions, the choice of fluorine source compounds is the key issue. The last four decades saw the emergence of mild organic fluorinating agents such as DAST and its derivatives,[5f,6] *N*-fluorobenzenesulfonimide (NFSI),[9] Selectfluor,[10] and PhenoFluor,[11] which have been successfully used in deoxyfluorination,[6,11] electrophilic fluorination,[9,10,12] radical fluorination,[13] and transition-metal-catalyzed fluorination reaction.[12c,14] Compared with traditional fluorinating agents including molecular fluorine, sulfur tetrafluoride, these organo-fluorinating agents were relatively stable and easily handled, which resulted in their broad application in fluorination reactions; however, there are still some issues needed to be addressed. For example, DAST, Selectfluor, and NFSI are expensive and show poor atom economy in fluorination reactions. DAST is also sensitive to moisture. Our goal is to develop an efficient and operationally simple aminofluorination reaction in which a readily available, cheap, and easily handled fluorine source compound is employed. It

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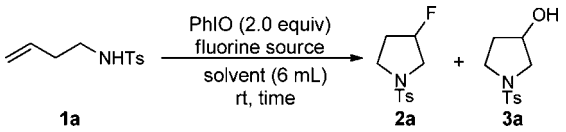
was reported that $BF_3{\cdot}Et_2O$, a widely used Lewis acid, could act as the fluorine source in the epoxide ring-opening reaction,[15] Prins reaction,[16] and carbofluorination reaction.[17] In addition, $BF_3{\cdot}Et_2O$ together with toxic $Pb(OAc)_4$ could also realize aromatic fluorination reaction.[18] Herein, as part of our continuing research on the new synthetic applications of a commercially available hypervalent iodine(III) reagent iodosobenzene (PhIO),[19] we first disclosed a metal-free oxidative transformation to provide 3-fluoropyrrolidines with $BF_3{\cdot}Et_2O$ as the fluorine source and PhIO as the oxidant.

At the beginning of the reaction, the model substrate *N*-(but-3-en-1-yl)-4-methylbenzenesulfonamide (**1a**) was treated with 2.0 equiv of PhIO and 4.0 equiv of $BF_3{\cdot}Et_2O$ in dichloromethane at room temperature. After 2.5 h, it was found that the desired cyclic product **2a** could be obtained in 81% yield along with a trace amount of hydroxylated product **3a** being formed (Table 1, entry 1). When $BF_3{\cdot}Et_2O$ was replaced by other

Table 1. Optimization of the Reaction Conditions[a]



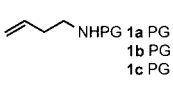
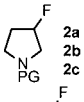
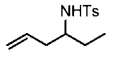
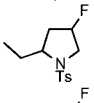
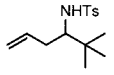
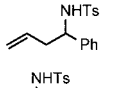
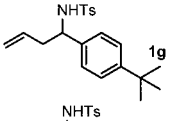
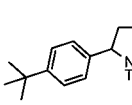
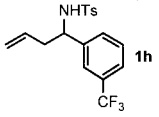
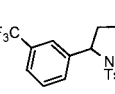
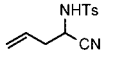
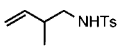
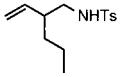
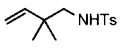
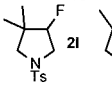
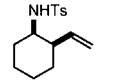
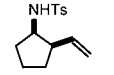
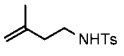
1a **2a** **3a**

entry	fluorine source (equiv)	solvent	time (h)	yield[b] (%) 2a	3a
1	$BF_3{\cdot}Et_2O$ (4.0)	CH_2Cl_2	2.5	81	5
2[c]	AlF_3 (4.0)	CH_2Cl_2	24	0	0
3[d]	FeF_3 (4.0)	CH_2Cl_2	24	0	0
4[d]	CsF (4.0)	CH_2Cl_2	24	0	0
5[c]	SbF_3 (4.0)	CH_2Cl_2	24	0	0
6[e]	AgF (4.0)	CH_2Cl_2	24	0	0
7	$BF_3{\cdot}THF$ (4.0)	CH_2Cl_2	4	71	10
8	$BF_3{\cdot}Et_2O$ (4.0)	1,4-dioxane	4	22	8
9[f]	$BF_3{\cdot}Et_2O$ (4.0)	EtOAc	0.25	30	18
10[g]	$BF_3{\cdot}Et_2O$ (4.0)	CH_3CN	2	0	0
11[h]	$BF_3{\cdot}Et_2O$ (4.0)	*n*-PrOH	24	0	0
12	$BF_3{\cdot}Et_2O$ (4.0)	HFIP	2	45	8
13[i]	$BF_3{\cdot}Et_2O$ (4.0)	CH_3COOH	2	8	0
14	$BF_3{\cdot}Et_2O$ (4.0)	$ClCH_2CH_2Cl$	1.5	72	4
15[j]	$BF_3{\cdot}Et_2O$ (4.0)	$CHCl_3$	12	58	8
16	$BF_3{\cdot}Et_2O$ (3.0)	CH_2Cl_2	3	81	6
17	$BF_3{\cdot}Et_2O$ (2.0)	CH_2Cl_2	4	81	6
18	$BF_3{\cdot}Et_2O$ (1.0)	CH_2Cl_2	4	80	7
19[k]	$BF_3{\cdot}Et_2O$ (0.5)	CH_2Cl_2	24	5	0
20[l]	$BF_3{\cdot}Et_2O$ (1.0)	CH_2Cl_2	15	79	6

[a]The reaction was conducted using 0.2 mmol of **1a**. [b]Isolated yield. [c]The recovery of **1a** was 91%. [d]The recovery of **1a** was 93%. [e]The recovery of **1a** was 92%. [f]1-Tosylpyrrolidin-3-yl acetate (**3b**) was provided in 34% yield. [g]**3c** (a Ritter product, vide infra) was afforded in 41% yield. [h]The recovery of **1a** was 95%. [i]**3b** was provided in 80% yield. [j]The conversion of **1a** was 72%. [k]The recovery of **1a** was 88%. [l]1.5 equiv of PhIO was used.

fluorine-containing compounds such as AlF_3, FeF_3, CsF, SbF_3, and AgF, no reaction occurred and the starting material **1a** was almost recovered (entries 2−6). When $BF_3{\cdot}THF$ was used, the desired product **2a** was obtained in 71% yield, a little lower than the yield of $BF_3{\cdot}Et_2O$ (entry 7). The use of EtOAc as the solvent led to 30% of the desired product **2a** as well as 34% of 1-tosylpyrrolidin-3-yl acetate (**3b**) (entry 9). When CH_3CN was used, no desired product **2a** was formed, whereas *N*-(1-tosylpyrrolidin-3-yl)acetamide (**3c**, a Ritter product, vide infra)

Table 2. Substrate Scope of Intramolecular Aminofluorination Reaction Using $BF_3{\cdot}Et_2O$ as the Fluorine Source[a]

entry	substrate	time (h)	product	yield (%)[b]
1	 **1a** PG = Ts	4	 **2a** PG = Ts	80
2	**1b** PG = Ns	3.5	**2b** PG = Ns	80
3	**1c** PG = Bs	5	**2c** PG = Bs	78
4	 **1d**	2	 **2d**	87 (4.3:1)
5	 **1e**	2	 **2e**	82 (6.0:1)
6	 **1f**	2	 **2f**	88 (5.5:1) 76, 1g scale
7	 **1g**	2.5	 **2g**	82 (5.0:1)
8	 **1h**	15	 **2h**	84 (4.7:1)
9	 **1i**	24	 **2i**	52 (1.1:1)[c]
10	 **1j**	6	 **2j**	70 (3.4:1)
11	 **1k**	12	 **2k**	64 (1.9:1)
12	 **1l**	24	 **2l** **3l**	32 (**2l**) 14 (**3l**)
13	 **1m**	2	 **2m**	45 (5.8:1)
14	 **1n**	6	 **2n**	42 (9.3:1)
15	 **1o**	1.5	 **2o**	43

[a]The reaction was conducted on a 0.2 mmol scale. [b]Isolated yield; the numbers in the parentheses are the diastereomeric ratio (*cis*/*trans*) determined by ^{19}F NMR analysis. [c]2.0 equiv of $BF_3{\cdot}Et_2O$ was used.

was afforded in 41% yield (entry 10), indicating that a carbocation intermediate was involved in the reaction. Polar protic solvents like hexafluoro-2-propanol (HFIP) gave 45% of the desired product **2a** (entry 12). The employment of $ClCH_2CH_2Cl$ and $CHCl_3$ did not show superior results compared with that in CH_2Cl_2, producing **2a** in 72% and 58% yields, respectively (entries 14 and 15). Further investigation of the amount of $BF_3{\cdot}Et_2O$ and PhIO revealed that 1.0 equiv of $BF_3{\cdot}Et_2O$, and 2.0 equiv of PhIO was enough for the present reaction, giving **2a** in 80% yield within 4 h (entry 18). We also tried Gouverneur's conditions (1.1 equiv of Selectfluor, 1.1 equiv of $NaHCO_3$, CH_3CN, rt, 48 h),[7] but the aminofluorination reaction did not occur since **1a** was recovered in 95% yield.

After having optimized the reaction conditions, the substrate scope was investigated (Table 2). When the *N*-protecting group

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was tuned to *p*-nitrobenzenesulfonyl (Ns) or benzenesulfonyl (Bs), the intramolecular aminofluorination reaction was run smoothly, giving the corresponding 3-fluoropyrrolidine derivatives **2b** and **2c** in 80% and 78% yields, respectively (Table 2, entries 2 and 3). When ethyl, *tert*-butyl, phenyl, *p*-(*tert*-butyl)phenyl, or *m*-trifluoromethylphenyl group was attached to the α-carbon of the amino group, the desired products **2d**−**h** could be obtained in 82−88% yields, while the diastereomeric ratio (*cis*/*trans*) varied from 4.3:1 to 6.0:1 (entries 4−8). Notably, the gram-scale reaction of **1f** could also give **2f** in 76% yield. For the substrate **1i** with a cyano group at the α-carbon of the amino group, the aminofluorination reaction gave 52% yield of the desired product (entry 9), which might have potential utility in the synthesis of a fibroblast activation protein inhibitor compound II (Figure 1) and 3-fluorinated proline derivatives. When a methyl or *n*-propyl group was attached to the allylic position, the desired products **2j,k** could be obtained in 70% and 64% yields with moderate diastereoselectivity (entries 10 and 11). As for the substrate **1l** bearing two methyl groups at the allylic position, the desired aminofluorinated product **2l** was only obtained in 32% yield while dihydropyrrole product **3l** was formed in 14% yield, which came from a methyl shift process (entry 12, vide infra). The reaction of aminoalkene **1m**, in which the C−C double bond and the amino group were attached to a six-membered ring with a *cis* configuration afforded bicyclic product **2m** in 45% yield with a diastereomeric ratio (*cis*/*trans*) of 5.8:1 (entry 13). For a 1,1-disubstituted olefin **1o**, the aminofluorination reaction proceeded smoothly to produce **2o** in 43% yield (entry 15). The configuration of major isomers of products exemplified as **2e** was confirmed to be *cis* by their X-ray diffraction analysis (Figure 2) and NMR spectra (for details, see the Supporting Information).

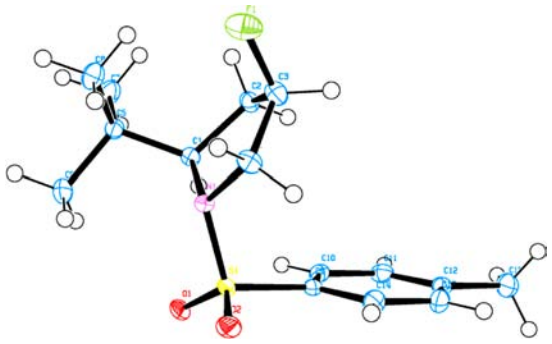
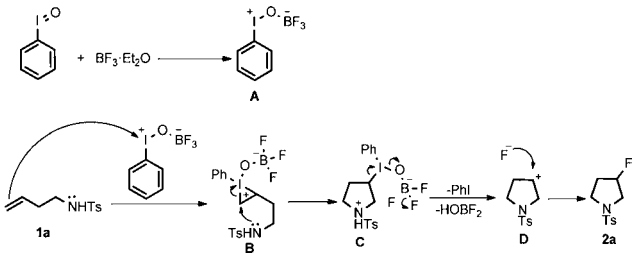


Figure 2. X-ray single-crystal structure of the *cis* isomer of **2e**.

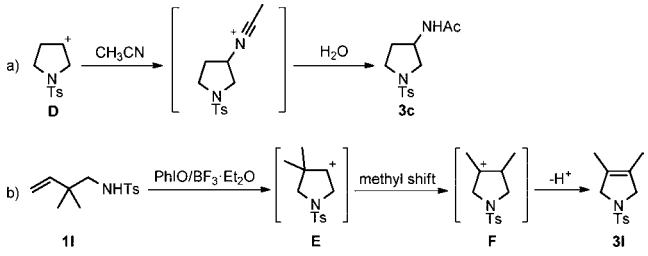
Scheme 1. Proposed Mechanism for the Intramolecular Aminofluorination Reaction



A mechanism for the present intramolecular aminofluorination reaction was proposed (Scheme 1). First, PhIO was activated by $BF_3{\cdot}Et_2O$ to form the iodine(III) intermediate **A**, which reacted with **1a** to give an iodonium intermediate **B**, followed by the intramolecularly nucleophilic attack of the amino group to generate an intermediate **C**. Then the hypervalent iodine(III) intermediate **C** underwent reductive elimination to afford a cyclic carbocation intermediate **D**. Subsequently, this carbocation combined with fluoride ion generated in situ to provide the product **2a**. In the present intramolecular aminofluorination reaction, $BF_3{\cdot}Et_2O$ played dual roles; i.e., it activated iodosobenzene and more significantly acted as the fluorine source.

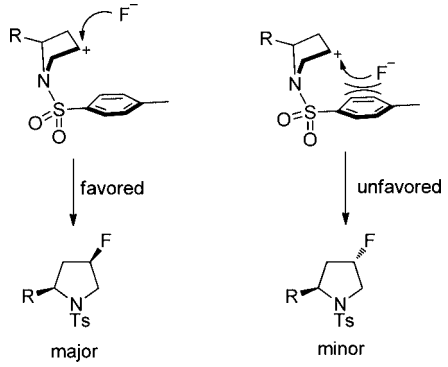
Evidence was obtained to support the above mechanism. When **1a** reacted with PhIO in the presence of $BF_3{\cdot}Et_2O$ in CH_3CN, a Ritter product **3c** was formed (Table 1, entry 10), indicating that the presence of a carbocation intermediate (Scheme 2a).[20] Moreover, when **1l** was treated with a PhIO/$BF_3{\cdot}Et_2O$ system, 14% of **3l** was afforded. It was believed that the formation of **3l** would result from the rearrangement of the key carbocation intermediate **E** (Scheme 2b).

Scheme 2. Explanation of the Formation of 3c and 3l



Owing to the steric hindrance of the Ts group, one side of the pyrrolidine ring was blocked. Thus, the attack of fluoride ion from the opposite side of the pyrrolidine ring was favored, which could account for the observed diastereoselectivity (Scheme 3).

Scheme 3. Explanation of the Diastereoselectivity Observed



In summary, we have developed a mild and efficient intramolecular aminofluorination reaction of homoallylic amines to provide 3-fluoropyrrolidines in which a commonly used Lewis acid $BF_3{\cdot}Et_2O$ was utilized as the fluorine source with PhIO as the oxidant. It was the first time that $BF_3{\cdot}Et_2O$ acting as the fluorine source in a metal-free oxidative transformation was disclosed. Considering the mild reaction conditions, simple operation, and high yields, this method represented an attractive way to synthesize 3-fluoropyrrolidines. Moreover, the present work inspired us to explore more use of safe, readily available, cheap, and easily handled fluorine-

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containing compounds as the fluorine source in other oxidation reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization of new compounds, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra, HRMS, and crystallgraphic data. 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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