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Hypervalent Iodine/HF Reagents for the Synthesis of 3-Fluoropyrrolidines

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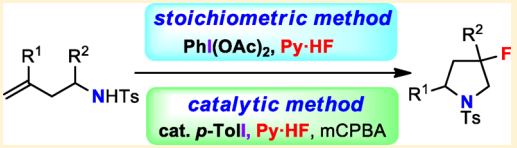
Supporting Information

ABSTRACT: The intramolecular aminofluorination of homoallylamine derivatives using a reagent system of $PhI(OAc)_2$ and Py·HF in CH_2Cl_2 at room temperature for 5 h gave *N*-tosyl-3-fluoropyrrolidines in good to high yields. Furthermore, the catalytic aminofluorination was furnished by the reaction using *p*-iodotoluene as a catalyst in the presence of Py·HF as a fluorine source and mCPBA as a terminal oxidant.



INTRODUCTION

3-Fluoropyrrolidine derivatives are biologically active compounds and have attracted much attention as dipeptidyl peptidase (DPP) IV inhibitors (Figure 1),[1] together with other activities, such as glucokinase activators,[2] prolyl oligopeptidase inhibitors,[3] and purine nucleoside phosphorylase inhibitors.[4]

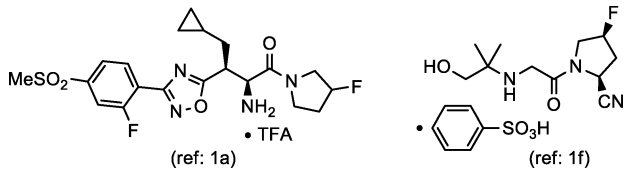
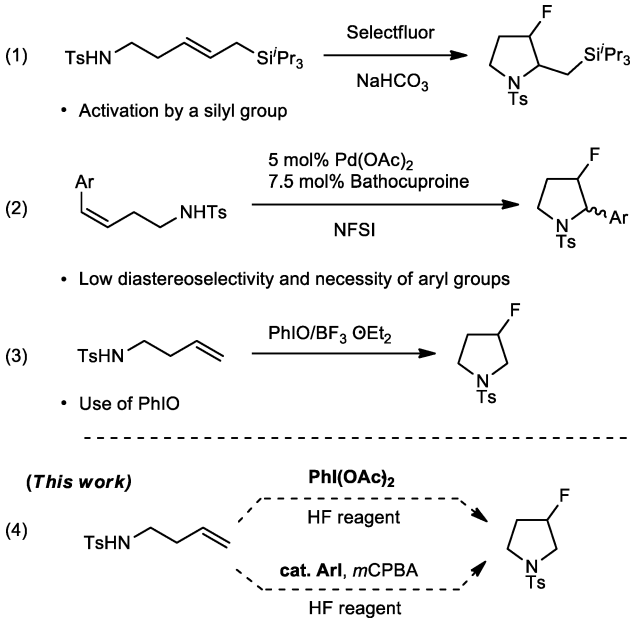


Figure 1. Examples of DPP IV inhibitors bearing 3-fluoropyrrolidine units.

The representative synthetic approach to the 3-fluoropyrrolidines has been performed by fluorination of 3-hydroxylpyrrolidines[5] and pyrrolidines.[6] Although a few reviews on aminofluorination of alkenes have been reported recently,[7] intramolecular aminofluorination is a direct and convenient reaction introducing a fluorine atom to nitrogen-containing heterocycles, which is a highly efficient method for performing the ring-construction and the introduction of fluorine atom at the same time. However, there are few reactions which have reported generation of 3-fluoropyrrolidines until now, and the substrate and the reagent are restricted as shown in Scheme 1. It was reported that intramolecular aminofluorination of homoallylamines activated by silyl groups proceeded in the presence of Selectfluor as a fluorinating agent to give 3-fluoropyrrolidines (eq 1 in Scheme 1).[8] This method needs activation by a silyl group, and significant generation of the byproduct by fluorodesilylation cannot be avoided. Pd-catalyzed intramolecular oxidative aminofluorination of styrene derivatives was achieved using *N*-fluorobenzenesulfonimide (NFSI) as a fluorinating agent to give 3-fluoropyrrolidines (eq 2 in Scheme 1).[9] The diastereoselectivity of the product was

Scheme 1. Intramolecular Aminofluorination Giving 3-Fluoropyrrolidines



low and this reaction could not be applied to an aliphatic homoallylamine. It was also reported that hypervalent iodine-mediated intramolecular aminofluorination of homoallylamines provided 3-fluoropyrrolidines in the presence of BF_3·OEt_2 (eq 3 in Scheme 1).[10] In this article, BF_3·OEt_2 was used as a fluorine source as well as an activating agent of PhIO. However, PhIO is not suitable for long-term preservation, and it may be difficult to use BF_3·OEt_2 as the fluorine source in the catalytic

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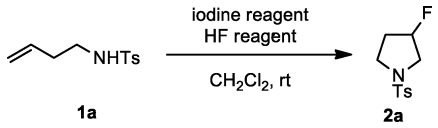
aminofluorination reaction because BF_3·OEt_2 reacts with a terminal oxidant or other reagents.

Although hypervalent iodine compounds have been widely used in organic synthesis as low toxic, mild, and environmentally benign reagents,[11] the metal-free hypervalent iodine-mediated five-membered ring formation reactions are few. Considering the viewpoint of the high biological activity of pyrrolidines, a simpler and more efficient synthetic method should be developed as a challenging subject. Thus, we envisaged that a fluorinating reagent composed of a hypervalent iodine and HF[12] would be effective for synthesis of 3-fluoropyrrolidines by intramolecular aminofluorination of homoallylamines. In this reagent system, $PhI(OAc)_2$ can be used as a stable hypervalent iodine reagent. More importantly, this reagent system can be extended to a catalytic intramolecular aminofluorination reaction. In this article, we report the hypervalent iodine-mediated intramolecular aminofluorination reactions giving 3-fluoropyrrolidines, which cover from a stoichiometric aminofluorination reaction using a stable $PhI(OAc)_2$ to a catalytic aminofluorination with an iodoarene catalyst.

RESULTS AND DISCUSSION

First, we chose *N*-tosyl-3-butenylamine (**1a**) as a model substrate, $PhI(OAc)_2$ as a hypervalent iodine reagent, and pyridine·HF complex (Py·HF) as a fluorine source. When the fluorination of **1a** was conducted using the Py·HF reagent in the presence of $PhI(OAc)_2$ in CH_2Cl_2 at room temperature for 5 h, *N*-tosyl-3-fluoropyrrolidine (**2a**) was obtained in 75% yield (Table 1, entry 1). Instead of the Py·HF reagent, hydrofluoric

Table 1. Optimization of Fluorination Reactions of 1a[a]



1a 2a

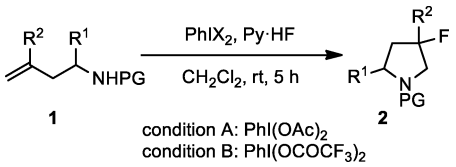
entry	iodine reagent (equiv)	HF reagent (HF equiv)	yield (%)[b]
1	$PhI(OAc)_2$ (1.2)	Py·HF (25)	75
2	$PhI(OAc)_2$ (1.2)	55% HF (25)	52
3	$PhI(OAc)_2$ (1.2)	Et_3N·5HF (25)	38
4	$PhI(OAc)_2$ (1.2)	Et_3N·3HF (25)	trace
5	PhIO (1.2)	Py·HF (25)	76
6	$PhI(OCOCF_3)_2$ (1.2)	Py·HF (25)	76
7	$PhI(OPiv)_2$ (1.2)	Py·HF (25)	82
8	PhI(OH)OTs (1.2)	Py·HF (25)	16
9	$PhI(OAc)_2$ (1.2)	Py·HF (10)	76
10	$PhI(OAc)_2$ (1.35)	Py·HF (10)	94
11	$PhI(OAc)_2$ (1.5)	Py·HF (10)	76

[a]Conditions: **1a** (0.2 mmol), an iodine reagent, a HF reagent, CH_2Cl_2 (0.5 mL), rt, 5 h. [b]Determined by ^{19}F NMR.

acid (55% HF), trietylamine pentahydrofluoride (TEA·5HF) and triethylamine trihydrofluoride (TEA·3HF) were examined as the fluorine source but the yield was not improved (entries 2−4). Screening the hypervalent iodine reagents, almost the same results as the case of $PhI(OAc)_2$ were obtained in the cases of PhIO and $PhI(OCOCF_3)_2$, respectively (entries 5 and 6). The reaction using $PhI(OPiv)_2$ gave the improved yield (82%) of **2a** (entry 7), but the use of Koser's salt (PhI(OH)OTs) resulted in a low yield (entry 8). Although $PhI(OPiv)_2$ was stable and prepared readily from $PhI(OAc)_2$, we have adopted the more economical $PhI(OAc)_2$ for this study. Increasing the amount of Py·HF reagent maintained the yield of **2a** (entry 9), and a slight increment of $PhI(OAc)_2$ increased the yield to 94% (entry 10). However, further increase of $PhI(OAc)_2$ did not improve the yield (entry 11). Therefore, we adopted the condition of entry 10 as an optimal condition.

With the optimized conditions in hand, we next examined the scope of the substrate using $PhI(OAc)_2$ (condition A) or $PhI(OCOCF_3)_2$ (condition B). The results are given in Table 2. Under the condition A, homoallylamines **1b** and **1c**

Table 2. Aminofluorination of Homoallylamine Derivatives[a]



entry	product	condition	yield (%)[b]
1	 **2b**	A	67
2	 **2c**	A	85
3	 **2d**	A	63 (70:30)
4	**2d**	B	69 (70:30)
5	 **2e**	A	62 (80:20)
6	**2e**	B	68 (70:30)
7	 **2f**	A	50 (70:30)
8	**2f**	B	61 (65:35)
9	 **2g**	A	70 (80:20)
10	**2g**	B	60 (80:20)
11	 **2h**	A	69 (70:30)
12	**2h**	B	57 (75:25)
13	 **2i**	A	87

[a]Condition A: 1 (0.4 mmol), $PhI(OAc)_2$ (0.54 mmol), Py·HF (4 mmol HF), and CH_2Cl_2 (1 mL), rt, 5 h. Condition B: $PhI(OCOCF_3)_2$ (0.54 mmol) was used instead of $PhI(OAc)_2$. [b]Yields were determined by ^{19}F NMR. Values in parentheses represent the *cis*:*trans* ratio.

protected with mesyl (Ms) and nosyl (Ns) groups gave the corresponding *N*-mesyl- and *N*-nosyl-3-fluoropyrrolidines (**2b** and **2c**) in 67 and 85% yields, respectively (entries 1 and 2). The similar reaction of *N*-tosyl-2-phenyl-3-butenylamine (**1d**) under the condition A afforded *N*-tosyl-4-fluoro-2-phenylpyrrolidine (**2d**) in 63% yield (entry 3). However, the purification by column chromatography on silica gel resulted in a large loss of the product due to the contamination of AcO-incorporated byproducts. When the reaction of **1d** was conducted under the condition B, the product **2d** was isolated

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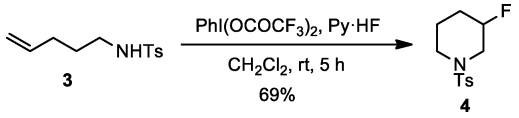
in 69% yield (entry 4). The same situation was observed in the cases of the substrates **1e**−**1h** substituted with *o*-tolyl, *p*-tolyl, ethyl, or isopropyl groups at the 2 position. 2-Substituted 4-fluoropyrrolidines **2d**−**2h** were obtained in 50−70% yields (entries 5−12). Interestingly, sterically unfavorable *cis*-isomers were selectively formed, showing that the *cis*:*trans* ratio was in the range from 65:35 to 80:20. *N*-Tosyl-3-methyl-3-butenylamine (**1i**) also underwent the aminofluorination reaction to afford *N*-tosyl-3-fluoro-3-methylpyrrolidine (**2i**) in 86% yield (entry 13).

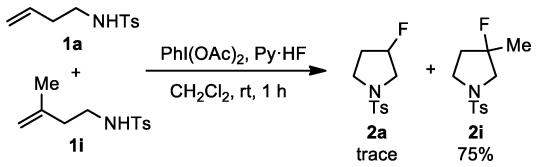
To compare with other reagent systems, we examined the aminofluorination of *N*-tosyl-4-pentenylamine (**3**) using the reagent system of $PhI(OCOCF_3)_2$ and Py·HF. As shown in Scheme 2, six-membered *N*-tosyl-3-fluoropiperidine (**4**) was obtained in 69% yield. The present reagent system provides the same result as the previously reported reagents.[13]

Scheme 2. Aminofluorination of *N*-Tosyl-4-pentenylamine 3



To obtain the information about the reaction mechanism for the intramolecular aminofluorination, we examined the competitive reaction between homoallylamines **1a** and **1i**. An equimolar mixture of **1a** and **1i** was subject to undergo the aminofluorination reaction (Scheme 3). As expected, only the

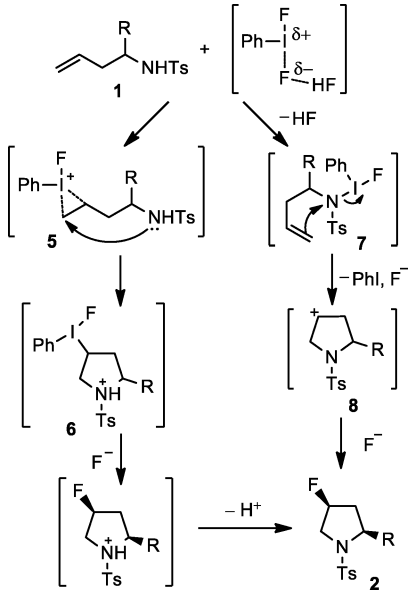
Scheme 3. Competitive Fluorination



reaction of **1i** occurred preferentially and 3-fluoro-3-methylpyrrolidine **2i** was obtained in 75% yield. This result indicates that a hypervalent iodine reagent selectively reacts with the more electron-rich olefinic moiety of **1i** than that of **1a**.

The present intramolecular aminofluorination reaction may proceed by the mechanism shown in Scheme 4. In the mechanism via bridged iodonium intermediate **5**,[12f,14] difluoroiodobenzene formed in situ is activated by HF and then attacks the double bond of homoallylamines **1** to generate bridged iodonium salts **5**. Attacking the terminal carbon by the nucleophilic nitrogen atom, the bridged iodonium salts **5** undergo the ring-opening to afford five-membered pyrrolidines **6**, which are subject to S_N 2-type substitution by fluoride ion. Finally, 3-fluoropyrrolidines **2** are formed by deprotonation. However, we could not discard another mechanism via an aminofluoroiodonium intermediate.[7a,13a,b] In this mechanism, the difluoroidobenzene reacts at the tosylamio group to generate the aminofluoroiodonium intermediate **7**. Then, the intermediate **7** reacts with the double bond to generate carbocation **8**, which is attacked by fluoride ion to give **2**. If the rate-determining step is the intramolecular cyclization of **7** to **8**, the high reactivity of **1i** satisfies with the result of the competitive reaction. The preferential formation of the *cis* isomer of **2** in the case of 2-substituted homoallylamines **1d**-**1i** may be explained by the preferential formation of the sterically

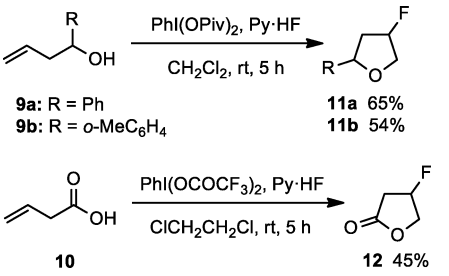
Scheme 4. Possible Mechanism for Intramolecular Aminofluorination



favored *trans* isomer of **6** or the neighboring group participation of the tosyl group in the cation **8**.

To extend the scope of substrates and get more information about the mechanism, we further studied the fluorocyclization of homoallylalcohols **9** and 3-butenoic acid (**10**), as shown in Scheme 5. The fluorination reaction of homoallylalcohols **9** was

Scheme 5. Fluorocyclization of 9 and 11



conducted using the reagent system of $PhI(OPiv)_2$ and Py·HF in CH_2Cl_2. As expected, fluorinated tetrahydrofuran derivatives **11** were obtained in 54−65% yields as a mixture of *cis* and *trans* isomers. Similarly, butenoic acid **10** underwent the fluorocyclization to give fluorinated butyrolactone **12** in 45% yield. These results are consistent with those from the reaction with (difluoroiodo)toluene,[15] suggesting that the oxygen part acts as the nucleophilic site in the fluorocyclization process. Namely, the behavior of **9** and **10** is similar to that of homoallylamines **1**. Consequently, these results support the mechanism via bridged iodonium intermediates **5** and also improve the usefulness of this method.

The catalytic use of reagents is one of significant reactions with respect to the guiding principle of Green Chemistry.[16] In the stoichiometric aminofluorination of homoallylamines **1** using the $PhI(OAc)_2$/Py·HF reagent, iodobenzene is produced as the byproduct. If the generated iodobenzene would be reoxidized to iodosylbenzene, the iodosylbenzene could be converted into difluoroiodobenzene and participate again into the aminofluorination reaction. Thus, we examined the catalytic

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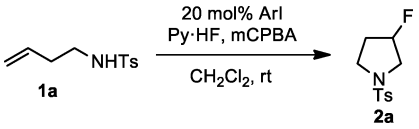
aminofluorination of homoallylamines using iodoarene catalysts.

First, we studied the aminofluorination reaction of **1a** using *p*-iodotoluene (20 mol%) as a catalyst in the presence of Py·HF (10 equiv of HF) as a fluorine source and mCPBA (2 equiv) as a terminal oxidant. The results are given in Table 3. The

Table 3. Catalytic Aminofluorination of Homoallylamines 1a[a]



entry	ArI	Py·HF (equiv of HF)	mCPBA (equiv)	time (h)	yield (%)[b]
1	*p*-TolI	10	2	8	50
2	*p*-TolI	15	2	8	63
3	*p*-TolI	20	2	8	82
4	*p*-TolI	25	2	8	71
5	PhI	20	2	8	54
6	*o*-TolI	20	2	8	59
7	*o*-AnI	20	2	8	42
8	*p*-AnI	20	2	8	48
9	2,6-$(MeO)_2C_6H_3I$	20	2	8	46
10	2,4,6-$Me_3C_6H_2I$	20	2	8	52
11	*p*-TolI	20	1	2	74

[a]Conditions: **1a** (0.2 mmol), ArI (0.04 mmol), Py·HF, mCPBA, CH_2Cl_2 (0.5 mL), rt. [b]Yield was determined by ^{19}F NMR.

reaction of **1a** in CH_2Cl_2 at room temperature for 8 h gave 3-fluoropyrrolidine **2a** in 50% yield (entry 1). Increasing the amount of Py·HF (entries 2−4), the reaction using 4 equiv of HF gave the highest yield (82%) of **2a** (entry 3). Although we screened other iodoarenes (entries 5−10), the yield of **2a** was not improved. Even though the amount of mCPBA was decreased to 1 equiv, the product was obtained in a reasonable yield (74%) (entry 11). Accordingly, we further examined the scope of the substrate using the conditions of entry 11, Table 3.

We examined several homoallylamines **1** for catalytic aminofluorination using *p*-iodotoluene. The results are given in Table 4. The substrates **1** employed in the catalytic aminofluorination afforded products **2** in good to high yields. This indicates that the aminofluorination of **1** also proceeds catalytically.

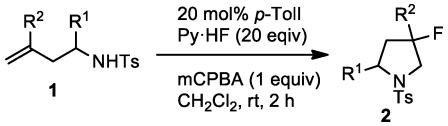
CONCLUSION

In summary, we have demonstrated that hypervalent iodine-mediated intramolecular aminofluorination of homoallylamine derivatives **1** proceeds efficiently to give 3-fluoropyrrolidine derivatives **2**. This reaction takes place both with a stoichiometric $PhI(OAc)_2$/Py·HF reagent and with a catalytic amount of *p*-iodotoluene, and provides an efficient method for synthesis of 3-fluoropyrolidine derivatives. The present method is applied to fluorocyclization of the substrates with oxygen nucleophiles, such as homoallylalcohols **9** and butenoic acid **10**.

EXPERIMENTAL SECTION

General Procedure for Fluorination of Homoallylamines 1 with $PhI(OAc)_2$/Py·HF Reagent: Condition A. To a Teflon test tube were placed $PhI(OAc)_2$ (174 mg, 0.54 mmol), Py·HF reagent (115 mg, 4 mmol), and CH_2Cl_2 (0.5 mL). After stirring for 15 min,

Table 4. Scope of Substrates for Catalytic Aminofluorination[a]



entry	product	yield (%)
1	 **2a**	74
2	 **2d**	71 (*cis*:*trans* = 65:35)
3	 **2g**	78 (*cis*:*trans* = 70:30)
4	 **2h**	86 (*cis*:*trans* = 70:30)
5	 **2i**	60

[a]Conditions: **1** (0.4 mmol), ArI (0.08 mmol), Py·HF (HF, 8 mmol), mCPBA (0.4 mmol), CH_2Cl_2 (1 mL), rt, 2 h.

homoallylamine **1** (0.4 mmol) and CH_2Cl_2 (0.5 mL) were added, and the mixture was stirred for 5 h at room temperature. After completion of the reaction, the yield of product **2** was determined by ^{19}F NMR using fluorobenzene as an internal standard. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL × 3). The organic phase was dried over anhydrous Na_2SO_4 and concentrated by a Rotary evaporator. The product **2** was purified by column chromatography on silica gel with hexane/EtOAc (70:30).

Condition B. The fluorination reaction of **1** was carried out in the same procedure as the condition A except for using $PhI(OCOCF_3)_2$ (232 mg, 0.54 mmol) instead of $PhI(OAc)_2$.

*3-Fluoro-1-[(4-methylphenyl)sulfonyl]pyrrolidine (**2a**).*[10] Under the condition A using 0.2 mmol of **1a** (Table 1, entry 10), the product was isolated by column chromatography to give 37.5 mg (77%) of **2a** as colorless solid, mp 101.3−103.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.86−2.01 (m, 1H), 2.08−2.18 (m, 1H), 2.43 (s, 3H), 3.24−3.30 (m, 1H), 3.48−3.57 (m, 3H), 5.14 (d, J = 52 Hz, 1H), 7.33 (d, J = 8 Hz, 2H), 7.72 (d, J = 8 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 21.5, 32.5 (d, J = 22 Hz), 45.8, 54.3 (d, J = 23 Hz), 92.2 (d, J = 177 Hz), 127.5, 129.7, 133.6, 143.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −175.8.

*3-Fluoro-1-(methylsulfonyl)pyrrolidine (**2b**).* Under the condition A (Table 2, entry 1), the product was isolated by column chromatography to give 42.1 mg (63%) of **2b** as colorless solid, mp 102.4−103.6 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.99−2.19 (m, 1H), 2.29−2.39 (m, 1H), 2.86 (s, 3H), 3.38−3.69 (m, 4H), 5.27 (d, J = 52 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 33.1 (d, J = 22 Hz), 34.7, 46.2, 54.9 (d, J = 23 Hz), 92.9 (d, J = 177 Hz). ^{19}F NMR (376 MHz, $CDCl_3$): δ = −176.8. HRMS (EI-EB): m/z $[M]^+$ calcd for $C_5H_{10}FNO_2S$: 167.0416; found: 167.0415.

*3-Fluoro1-[(2-nitrophenyl)sulfonyl]pyrrolidine (**2c**).* Under the condition A (Table 2, entry 2), the product was isolated by column chromatography to give 93.3 mg (85%) of **2c** as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.97−2.18 (m, 1H), 2.30−2.32 (m, 1H), 3.52−3.83 (m, 4H), 5.26 (d, J = 52 Hz, 1H), 7.63 (d, J = 7.2 Hz, 1H), 7.72−7.69 (m, 2H), 8.01 (d, J = 6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 32.6 (d, J = 22 Hz), 45.9, 54.2 (d, J = 24 Hz), 92.1 (d, J = 178 Hz), 123.96, 124.0, 130.3, 131.7, 133.7,148.2. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −177.0. HRMS (EI-EB): m/z $[M]^+$ calcd for $C_{10}H_{11}FN_2O_4S$: 274.0424; found: 274.0424.

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*4-Fluoro-2-phenyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (**2d**).*[10] Under the condition B (Table 2, entry 4), the product was isolated by column chromatography to give 88.2 mg (69%) of **2d** as a mixture of *cis* and *trans* isomers, colorless solid, mp 103.9−106.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.18−2.26 (m, 1H), 2.37 (s, 3H), 3.54−3.65 (m, 1H), 3.80−3.89 (m, 1H), 4.88−4.91 (m, 1H), 5.11 (d, J = 53 Hz, 1H), 7.18−7.94 (m, 7H), 7.59 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 21.5, 41.5 (d, J = 21 Hz), 55.4 (d, J = 24 Hz), 62.2, 92.0 (d, J = 180 Hz), 126.6, 127.2, 127.5, 128.2, 129.6, 134.5, 141.8, 143.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −172.5, −177.7.

*4-Fluoro-2-(2-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-pyrrolidine (**2e**).* Under the condition B (Table 2, entry 6), the product was isolated by column chromatography to give 78.7 mg (59%) of **2e** as a mixture of *cis* and *trans* isomers, colorless solid, mp 160.1−162.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06−2.15 (m, 1H), 2.31−2.48 (m, 7H), 3.59−3.72 (m, 1H), 3.93 (dd, J = 12, 21 Hz, 1H), 5.10−5.22 (m, 2H), 7.09−7.10 (m, 3H), 7.25 (d, J = 8 Hz, 2H), 7.40 (d, J = 6 Hz, 1H), 7.62 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 19.4, 21.5, 40.6 (d, J = 20 Hz), 55.4 (d, J = 24 Hz), 59.1, 92.1 (d, J = 180 Hz), 126.0, 126.4, 127.0, 127.5, 129.6, 130.1, 133.54, 134.7, 140.1, 143.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −172.6, −177.8. HRMS (EI-EB): m/z [M]$^+$ calcd for $C_{18}H_{20}FNO_2S$: 333.1199; found: 333.1200.

*4-Fluoro-2-(4-methylphenyl)-1-[(4-methylphenyl)sulfonyl]-pyrrolidine (**2f**).* Under the condition B (Table 2, entry 8), the product was isolated by column chromatography to give 56.0 mg (42%) of **2f** as a mixture of *cis* and *trans* isomers, colorless solid, mp 93.6−95.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91−2.55 (m, 8H), 3.54−3.99 (m, 2H), 4.63−4.86 (m, 1H), 5.03−5.20 (m, 1H), 7.08−7.15 (m, 2H), 7.21−7.29 (m, 4H), 7.60−7.65 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz): δ = 21.0, 21.1, 21.4, 21,5, 41.1 (d, J = 21 Hz), 44.0 (d, J = 21 Hz), 55.4 (d, J = 24 Hz), 56.0 (d, J = 22 Hz), 62.0, 62.3, 91.1 (d, J = 178 Hz), 91.9 (d, J = 180 Hz), 126.3, 126.5, 127.5, 127.7, 128.9, 129.2, 129.3, 129.5, 134.3, 134.6, 136.8, 137.2, 138.4, 138.9, 143.4, 143.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −172.6, −177.6. HRMS (EI-EB): m/z [M]$^+$ calcd for $C_{18}H_{20}FNO_2S$: 333.1199; found: 333.1200.

*2-Ethyl-4-fluoro-1-tosylpyrrolidine (**2g**).*[10] Under the condition B (Table 2, entry 10), the product was isolated by column chromatography to give 65.1 mg (60%) of **2g** as a mixture of *cis* and *trans* isomers, yellow viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88−0.95 (m, 3H), 1.62−1.79 (m, 2H), 1.89−2.16 (m, 2H), 2.43 (s, 3H), 3.37−3.50 (m, 1H), 3.61−3.75 (m, 2H), 4.94−5.10 (m, 1H), 7.29−7.33 (m, 2H), 7.70−7.72 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 9.2, 10.6, 21.4, 28.4, 29.0, 36.1 (d, J = 20 Hz), 38.2 (d, J = 22 Hz), 54.6 (d, J = 25 Hz), 55.6 (d, J = 23 Hz), 60.1, 61.4, 91.2 (d, J = 178 Hz), 92.4 (d, J = 179 Hz), 127.4, 127.7, 129.4, 129.7, 134.6, 134.8, 143.4, 143.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −171.7, −177.2.

*4-Fluoro-2-(1-methylethyl)-1-[(4-methylphenyl)sulfonyl]-pyrrolidine (**2h**).* Under the condition B (Table 2, entry 12), the product was isolated by column chromatography to give 47.9 mg (42%) of **2h** as a mixture of *cis* and *trans* isomers, colorless solid, mp 87.7−89.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d, J = 8 Hz, 3H), 1.0 (d, J = 8 Hz, 3H), 1.53−1.66 (m, 1H), 1.94−2.14 (m, 1H), 2.43 (s, 3H), 3.49−3.66 (m, 3H), 4.89 (d, J = 55 Hz, 1H), 7.32 (d, J = 8 Hz, 2H), 7.70 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 17.6, 20.1, 21.5, 31.3, 33.7 (d, J = 20 Hz), 54.6 (d, J = 26 Hz), 65.6, 91.7 (d, J = 180 Hz), 127.5, 129.8, 134.7, 143.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −171.5, −176.6. HRMS (EI-EB): m/z [M]$^+$ calcd for $C_{14}H_{20}FNO_2S$: 285.1199; found: 285.1198.

*3-Fluoro-3-methyl-1-[(4-methylphenyl)sulfonyl]pyrrolidine (**2i**).*[10] Under the condition A (Table 2, entry 13), the product was isolated by column chromatography to give 88.5 mg (86%) of **2i** as colorless solid, mp 103.2−104.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (d, J = 22 Hz, 3H), 1.76−1.93 (m, 1H), 2.04−2.13 (m, 1H), 2.43 (s, 3H), 3.26−3.37 (m, 2H), 3.46−3.58 (m, 2H), 7.33 (d, J = 8 Hz, 2H), 7.71 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 21.4, 21.7 (d, J = 26 Hz), 37.5 (d, J = 23 Hz), 46.8, 58.2 (d, J = 26 Hz), 100.2 (d, J = 175 Hz), 127.4, 129.58, 133.4, 143.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −141.2.

*3-Fluoro-1-[(4-methylphenyl)sulfonyl]pyperidine (**4**).*[17] Under the condition B (Scheme 2), the product was isolated by column chromatography to give 71.0 mg (69%) of **4** as colorless solid, mp 93.4−95.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57−1.67 (m, 2H), 1.77−1.87 (m, 2H), 2.44 (s, 3H), 2.86−2.90 (m, 1H), 2.95−3.02 (m, 1H), 3.13−3.15 (m, 1H), 3.35−3.43 (m, 1H), 4.59−4.72 (m, 1H), 7.33 (d, J = 8 Hz, 2H), 7.66 (d, J = 8 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 21.6 (d, J = 6 Hz), 21.9, 29.7 (d, J = 19 Hz), 46.1, 50.0 (d, J = 27 Hz), 86.4 (d, J = 175 Hz), 128.0, 130.1, 133.8, 144.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −182.9.

*Fluorination of Homoallylalcohols **9** and Butenoic Acid **10**.* To a Teflon test tube were placed PhI(OPiv)$_2$ (548.5 mg, 1.35 mmol), Py·HF reagent (286 mg, 10 mmol), and CH_2Cl_2 (0.5 mL). After stirring for 15 min, **9** (1 mmol) and CH_2Cl_2 (0.5 mL) were added, and the mixture was stirred for 5 h at room temperature. After completion of the reaction, the yield of product **11** or **12** was determined by ^{19}F NMR using fluorobenzene as an internal standard. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL × 3). The organic phase was dried over anhydrous Na_2SO_4 and concentrated by a Rotary evaporator. The product was purified by column chromatography on silica gel with hexane/EtOAc (70:30). In the case of 3-butenoic acid (**10**), the reaction of **10** (86.1 mg, 1 mmol) in 1,2-dichloroethane (1 mL) was conducted using Py·HF reagent (583.5 mg, 20 mmol), PhI(OCOCF$_3$)$_2$ (580.5 mg, 1.35 mmol) at 60 °C for 17 h.

*4-Fluoro-2-phenyltetrahydrofuran (**11a**).* The product **11a** (108 mg, 65%) was obtained as a mixture of *cis* and *trans* isomers, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85−2.24 (m, 1H), 2.55−2.74 (m, 1H), 3.71−4.39 (m, 2H), 4.88−5.43 (m, 2H), 7.26−7.38 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 41.4 (d, J = 22 Hz), 42.1 (d, J = 21 Hz), 74.0 (d, J = 24 Hz), 74.1 (d, J = 23 Hz), 79.5, 80.4, 94.0 (d, J = 178 Hz), 94.4 (d, J = 176 Hz), 125.7, 126.1, 127.6, 127.7, 128.40, 128.45, 141.2, 141.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −174.1, −171.6. HRMS (EI-EB): m/z [M]$^+$ calcd for $C_{10}H_{11}FO$: 166.0794; found: 166.9794.

*4-Fluoro-2-(2-methylphenyl)tetrahydrofuran (**11b**).* The product **11b** (97.3 mg, 54%) was obtained as a mixture of *cis* and *trans* isomers, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.73−2.10 (m), 2.29 (s), 2.32 (s), 3.76−4.43 (m), 5.03−5.43 (m), 7.11−7.20 (m), 7.42−7.55 (m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 19.0, 19.1, 40.3 (d, J = 22 Hz), 40.9 (d, J = 21 Hz), 73.7 (d, J = 24 Hz), 73.9 (d, J = 24 Hz), 76.8, 77.5, 94.0 (d, J = 179 Hz), 94.5 (d, J = 176 Hz), 124.4, 125.1, 126.17, 126.21, 127.2, 127.3, 130.0, 130.3, 134.1, 134.6, 139.5, 140.0. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −173.9, −171.3. HRMS (EI-EB): m/z [M]$^+$ calcd for $C_{11}H_{13}FO$: 180.0950; found: 180.0950.

*4-Fluorodihydro-2(3H)-furanone (**12**).*[15] The product **12** (46.8 mg, 45%) was obtained as pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.76 (s, 1H), 2.83 (s, 1H), 4.44 (ddd, J = 3, 12, 35 Hz, 1H), 4.58 (dd, J = 12, 24 Hz, 1H), 5.41 (dd, J = 3, 54 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 35.3 (d, J = 24 Hz), 73.5 (d, J = 26 Hz), 88.5 (d, J = 180 Hz), 173.9. ^{19}F NMR (376 MHz, $CDCl_3$): δ = −176.3.

Representative Procedure for Catalytic Fluorination of Homoallylamines 1 with *p*-Iodotoluene/mCPBA/Py·HF Reagent. To a Teflon test tube were placed *p*-iodotoluene (17.4 mg, 0.08 mmol), mCPBA (98.8 mg, 0.4 mmol), Py·HF reagent (229 mg, 8 mmol), and CH_2Cl_2 (0.5 mL). After stirring for 15 min, homoallylamine **1** (0.4 mmol) and CH_2Cl_2 (0.5 mL) were added, and the mixture was stirred for 2 h at room temperature. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (10 mL × 3). The organic phase was dried over anhydrous Na_2SO_4 and concentrated by a rotary evaporator. The product **2** was purified by column chromatography on silica gel with hexane/EtOAc (70:30).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01266.

^{1}H and ^{13}C NMR spectra of products **2**, **11**, **4**, and **12** (PDF)

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Notes

The authors declare no competing financial interest.

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