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An expeditious synthesis of 4-fluoropiperidines via aza-Prins cyclization

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ABSTRACT

The reaction of aldehydes with *N*-tosyl homoallylamine in the presence of a solution of tetrafluoroboric acid-diethyl ether complex in dichloromethane at ambient temperature gave the 4-fluoropiperidines in good yields and with high cis-selectivity. This aza-Prins-type cyclization has a wide scope and the use of $HBF_4{\cdot}OEt_2$ makes this procedure simple, convenient, and cost-effective for the preparation of 4-fluoropiperidines.

The synthesis of cyclic and acyclic fluoro-organics has received considerable attention from the pharmaceutical industry.[1] The substitution of hydrogen or hydroxyl with fluorine is a widely used strategy for modification and/or enhancement of biological activity. The introduction of fluorine onto an organic molecule often alters the lipophilicity and chemical reactivity.[1] Therefore, we have investigated the synthesis of 4-fluoro-substituted piperidines, as they are structural components in one of our research projects in bio-organic and medicinal chemistry. The aza-Prins cyclization is one of the simple and direct methods for the preparation of 2,4-di- and 2,4,6-trisubstituted piperidines.[2] The use of the aza-silyl-Prins reaction has also recently been reported for the synthesis of *trans*-2,6-disubstituted dihydropyridine derivatives.[3] Several 4-fluoropiperidine derivatives have already demonstrated interesting biological properties (Fig. 1).[4] However, only a few methods are reported for the synthesis of fluoro-substituted piperidines using fluorinated ionic liquids or super acid media.[5] Therefore, the use of simple, convenient, and cost-effective fluorinating agents would certainly extend the scope of aza-Prins cyclization.

As a continuation of our research program on Prins cyclization,[2c,d,6] we report herein a novel method for the synthesis of 4-fluoropiperidines from aldehydes and *N*-tosyl homoallylamine (2) by means of aza-Prins cyclization using a solution of tetrafluoroboric acid-diethyl ether complex in dichloromethane under mild conditions. We initially attempted the coupling of benzaldehyde with *N*-tosyl homoallylamine in the presence of 1.2 equiv of $HBF_4{\cdot}OEt_2$ in dichloromethane at room temperature. The reaction was complete in 2 h and the corresponding 4-fluoro-2-phenylpiperidine **3a** was obtained in 90% yield with cis-selectivity (Scheme 1).[5]

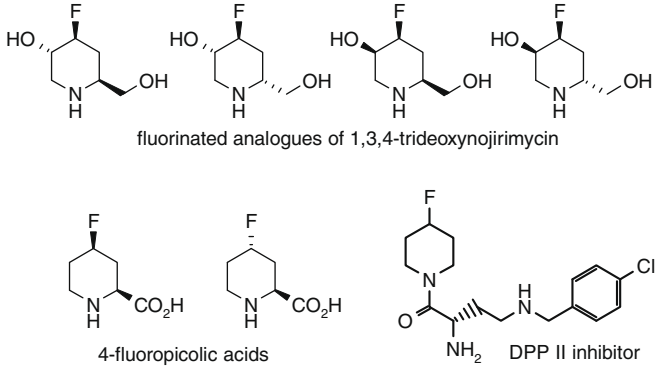
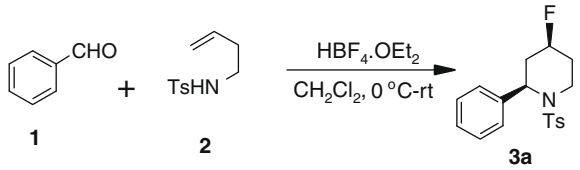


Figure 1. Some biologically active 4-fluoropiperidine derivatives.



Scheme 1. Preparation of 4-fluoropiperidine **3a**.

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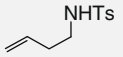
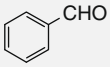
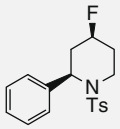
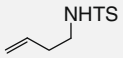
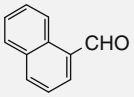
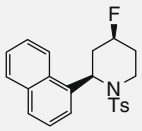
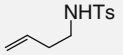
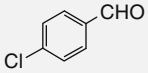
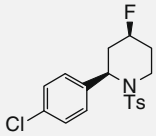
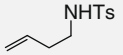
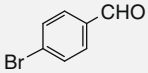
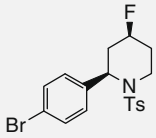
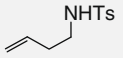
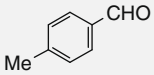
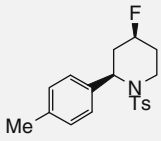
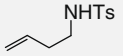
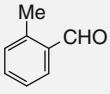
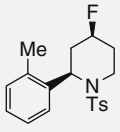
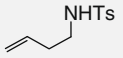
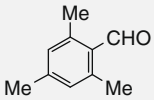
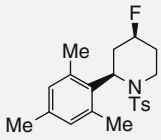
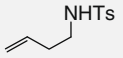
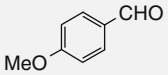
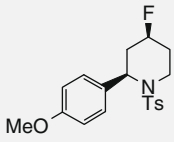
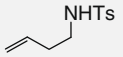
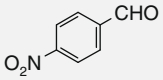
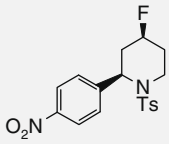
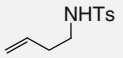
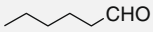
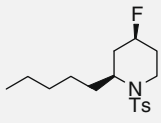
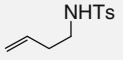
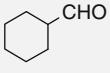
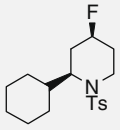
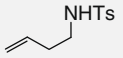
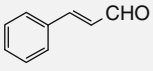
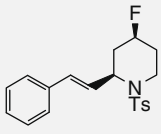
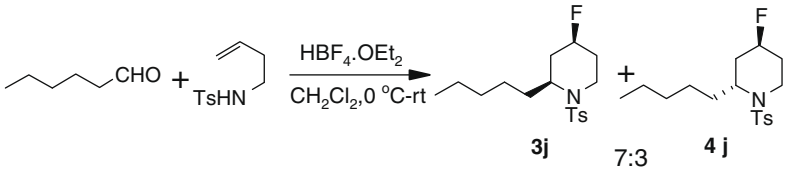
Table 1
$HBF_4{\cdot}OEt_2$-promoted synthesis of 4-fluoropiperidines

Entry	Homoallyl amine	Aldehyde	Arylpiperidine[a]	Time (h)	Yield (%) (cis/trans)[b]
a				2.0	90
b				2.5	85
c				3.0	88
d				3.0	87
e				2.5	85
f				3.5	80
g				4.0	68
h				3.0	74
i				4.0	72
j				1.5	91 (7:3)
k				1.0	93 (7:3)
l				3.0	81 (8:2)

[a] All products were characterized by ^1H NMR, IR and mass spectroscopy.
[b] Inseparable mixture of isomers. Ratio was determined by ^{19}F NMR spectroscopy.



Scheme 2. Preparation of 4-fluoropiperidine **3j** and **4j**.

It is interesting to mention that cis-selectivity[5a,c] was observed in fluoride induced aza-Prins cyclization whereas trans-selectivity was reported in aza-Prins cyclization using other nucleophiles.[2] Encouraged by this result, we extended this process to various aldehydes. Interestingly, aromatic aldehydes such as 1-naphthaldehyde, *p*-chlorobenzaldehyde, *p*-bromobenzaldehyde, *p*-methylbenzaldehyde, *o*-methylbenzaldehyde, 2,4,6-trimethylbenzal dehyde, *p*-methoxybenzaldehyde, and *p*-nitrobenzaldehyde underwent smooth coupling with *N*-tosyl homoallylamine to give the corresponding 2,4-disubstituted piperidines in good yields (Table 1, entries **b–i**). In all cases, the reactions proceeded well at room temperature with high *cis*-selectivity. We next studied the reactivity of aliphatic aldehydes, such as *n*-hexanal and cyclohexanecarboxaldehyde which gave *cis* and *trans* piperidines in a 7:3 ratio as an inseparable mixture (entries **j–k**, Table 1, Scheme 2). Furthermore, acid sensitive *trans*-cinnamaldehyde also participated effectively in this reaction (Table 1, entry **m**).

It is important to mention that no *N*-tosyl deprotection was observed during the aza-Prins-cyclization. In the absence of tetrafluoroboric acid-diethyl ether, no aza-Prins-cyclization was observed even in refluxing dichloromethane. Furthermore, substituted homoallylamines failed to undergo aza-Prins cyclization under the present reaction conditions. As solvent, dichloromethane gave the best results. In all cases, the reactions proceeded rapidly at room temperature under mild conditions. The reactions were clean and the products were obtained in excellent yields and with good to high diastereoselectivity as determined from the NMR spectra of the crude products. Only a single diastereoisomer was obtained from aromatic aldehydes, the structure of which was confirmed by NMR and also by comparison with authentic samples.[5]

The structure of **3b** shown in Figure 2 was deduced from the NMR data, where the two substituents, fluoro and aryl groups are cis to each other. The coupling constants observed for J_{H-F}, J_{Ha-Ha}, J_{Ha-He} are 48.9, 10.0, 4.0 Hz, respectively, which clearly indicates that both fluoro and aryl substituents are in equatorial position as depicted in Figure 2.

The nature of the substituents on the aromatic ring shows some effect on this conversion. It should be noted that aliphatic, simple aromatic and moderately activated aldehydes such as chloro-, bromo- or methyl-substituted benzaldehyde gave higher yields of products compared to strongly activated or deactivated aldehydes. However, aliphatic aldehydes gave the products with less selectivity (7:3) compared to aromatic aldehydes as reported previously.[7] Furthermore, we have screened the efficiency of various fluorinating agents such as $HBF_4{\cdot}OEt_2$, HF/pyridine, HF/Et_3N, and (diethylamino)sulfur trifluoride. Of these, $HBF_4{\cdot}OEt_2$ was found to give the best conversions with similar stereoselectivity. It is interesting to note that $BF_3{\cdot}OEt_2$ has already been reported as a fluorinating agent.[8] The scope and generality of this process is illustrated in Table 1.[9]

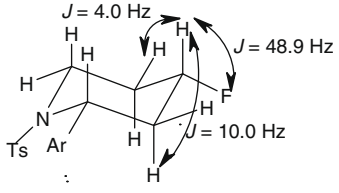


Figure 2. Characteristic *J* values of product **3b**.

In summary, a solution of tetrafluoroboric acid-diethyl ether complex in dichloromethane has proved to be a useful and novel reagent for the aza-Prins-cyclization to produce 2,4-disubstituted piperidines in good yields in short reaction times. The experimental procedure is simple, convenient and the reaction conditions are amenable to scale-up. This method provides an easy access to 4-fluoropiperidines with diverse chemical structures for biological evaluation.

Acknowledgements

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9. *General procedure*: To a mixture of *N*-tosylhomoallylic amine (1.0 equiv), aldehyde (1.0 equiv) in dichoromethane (3 mL) was added tetrafluoroboric acid-diethyl ether (1.2 equiv) at 0 °C. The temperature was slowly brought to rt. The reaction mixture was stirred at room temperature for a specified amount of time (Table 1). After completion of the reaction as indicated by TLC, the reaction mixture was extracted with ethylacetate (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Removal of the solvent followed by purification on silica gel (Merck, 60–120 mesh, ethyl acetate–hexane, 0.5–9.5) gave the pure 4-fluoro tetrahydropyridine. The products thus obtained were characterized by IR, NMR and mass spectroscopy. The spectral data were found to be consistent with authentic samples. Spectral data of representative examples **3b:** *cis*-4-Fluoro-2-(naphthalen-2-yl)-1-tosylpiperidine: Liquid, IR (KBr): ν_{max} 3055, 2928, 2856, 1595, 1449, 1343, 1305, 1281, 1197, 1153, 1121, 1092, 1014, 986, 935, 863, 816, 759, 724 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.81–7.78 (m, 2H), 7.76 (d, 2H, J = 8.3 Hz), 7.74–7.68 (m, 1H), 7.64–7.62 (m, 1H), 7.48–7.39 (m, 3H), 7.29 (d, 2H, J = 8.3 Hz), 5.60–5.50 (m, 1H), 4.73–4.54 (dtt, 1H, $J_{H,F}$ = 48.9 Hz, J_{Ha-Ha} = 10.0 Hz, J_{Ha-He} = 4.0 Hz), 4.04–3.95 (m, 1H), 3.10–2.99 (m, 1H), 2.81–2.72 (m, 1H), 2.45 (s, 3H), 1.90–1.81 (m, 1H), 1.80–1.72 (m, 1H), 1.55–1.41 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 137.8, 135.1, 133.1, 129.8, 128.7, 127.8, 127.4, 126.9, 126.2, 126.1, 125.3, 124.4, 86.6 (d, J = 173.4 Hz), 55.6 (d, J = 11.0 Hz), 39.9 (d, J = 11.0 Hz), 33.5 (d, J = 19.8 Hz), 31.0 (d, J = 19.8 Hz), 21.5 ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −99.4 ppm. MS: m/z = 383 $[M]^+$. HRMS calcd for $C_{22}H_{22}FNO_2S$: 383.1355. Found: 383.1359. Compound **3e:** *cis*-4-Fluoro-2-*p*-tolyl-1-tosylpiperidine: Liquid, IR (KBr): ν_{max} 3029, 2925, 2872, 1597, 1511, 1453, 1339, 1158, 1093, 1015, 989, 933, 816, 737 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, 2H, J = 8.1 Hz), 7.25 (d, 2H, J = 8.1 Hz), 7.15 (d, 2H, J = 7.9 Hz), 7.07 (d, 2H, J = 7.9 Hz), 5.37–5.26 (m, 1H), 4.70–4.39 (dtt, 1H, $J_{H,F}$ = 48.7 Hz, J_{Ha-Ha} = 10.0 Hz, J_{Ha-He} = 4.0 Hz), 3.97–3.81 (m, 1H), 3.02–2.87 (m, 1H), 2.64–2.49 (m, 1H), 2.37 (s, 3H), 2.25 (s, 3H), 1.83–1.69 (m, 1H), 1.67–1.56 (m, 1H), 1.41–1.28 (m, 1H) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.4, 137.9, 137.0, 134.6, 129.8, 129.5, 126.9, 126.3, 86.7 (d, J = 174.0 Hz), 55.3 (d, J = 13.2 Hz), 39.8 (d, J = 12.0 Hz), 33.5 (d, J = 19.2 Hz), 31.0 (d, J = 18.6 Hz), 21.5, 20.8 ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ -99.4 ppm. MS: m/z = 347 $[M]^+$. HRMS calcd for $C_{19}H_{22}FNO_2S$: 347.1355. Found: 347.1346. Compound **3j:** *cis*-4-Fluoro-2-pentyl-1-tosylpiperidine: Liquid, IR (KBr): ν_{max} 2924, 2854, 1598, 1461, 1374, 1339, 1158, 1090, 1001, 926, 815, 710 cm^{-1}. ^1H NMR (500 MHz, CDCl3): δ 7.71 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.3 Hz), 4.84–4.52 (dtt, 1H, $J_{H,F}$ = 48.3 Hz, J_{Ha-Ha} = 10.0 Hz, J_{Ha-He} = 4.0 Hz), 4.19–4.10 (m, 1H), 4.01–3.86 (m, 1H), 3.07–2.97 (m, 1H), 2.42 (s, 3H), 2.01–1.80 (m, 2H), 1.75–1.11 (m, 10H), 0.87 (t, 3H, J = 6.7 Hz) ppm. ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.0, 138.2, 129.7, 126.8, 86.9 (d, J = 173.4 Hz), 53.6 (d, J = 11.0 Hz), 38.7 (d, J = 11.0 Hz), 34.1 (d, J = 17.5 Hz), 31.7, 31.2 (d, J = 17.6 Hz), 31.0, 26.3, 26.0, 21.4, 13.9 ppm. ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −100.2 ppm. MS: m/z = 327 $[M]^+$. HRMS calcd for $C_{17}H_{26}FNO_2S$: 327.1668. Found: 327.1676. Compound **4j:** *trans*-4-Fluoro-2-pentyl-1-tosylpiperidine: ^{19}F NMR (376.3 MHz, $CDCl_3$): δ −104.3 ppm.