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## DIASTEREOSELECTIVE SYNTHESIS OF 3-FLUORO-2-SUBSTITUTED PIPERIDINES AND PYRROLIDINES<sup>†</sup>

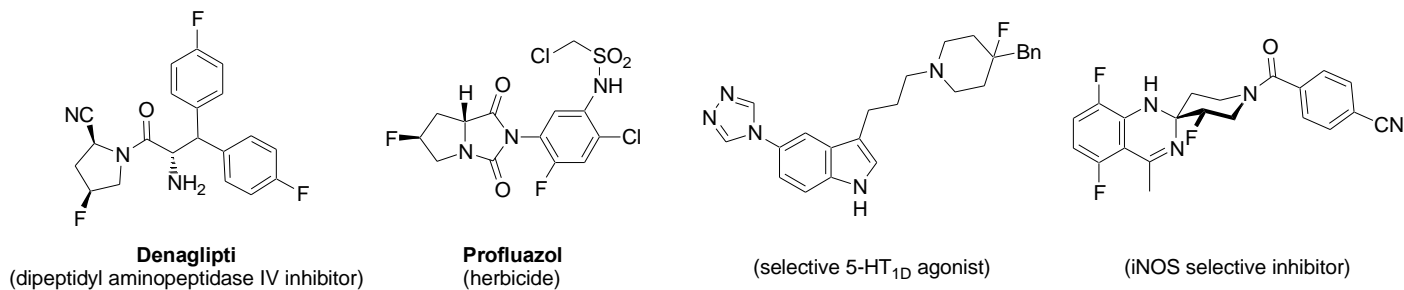
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**Abstract** – A facile procedure for synthesis of *trans*-3-fluoro-2-substituted piperidines by utilizing electrophilic fluorination of cyclic enamines and Lewis acid mediated nucleophilic substitution has been developed. Also, optically active *trans*-2-allyl-3-fluorinated pyrrolidines have been prepared by utilizing nucleophilic fluorination of hydroxyl group of *trans*-hydroxy-L-proline and Lewis acid mediated diastereoselective allylation as key steps.

### INTRODUCTION

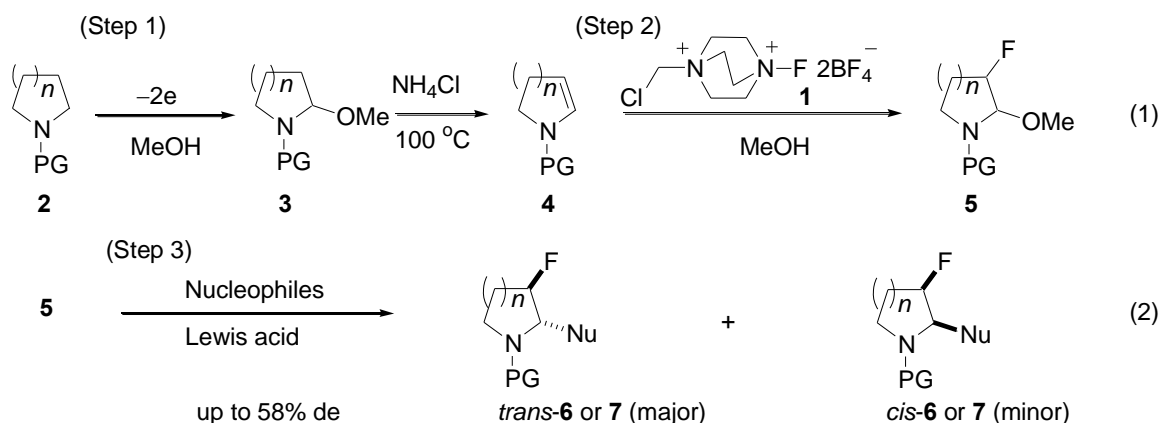
*N*-Heterocycles such as substituted piperidine or pyrrolidines are vast substructures in a great number of biologically active natural products and small molecule pharmaceuticals.<sup>1</sup> Since fluorinated compounds exhibit distinctive biological and physical properties, fluorinated *N*-heterocycles are of great interest in areas such as; material science, agrochemicals, and pharmaceuticals (Figure 1).<sup>2</sup> To date, both electrophilic and nucleophilic fluorination methods have been developed to furnish fluorinated *N*-heterocycles.<sup>3,4</sup>



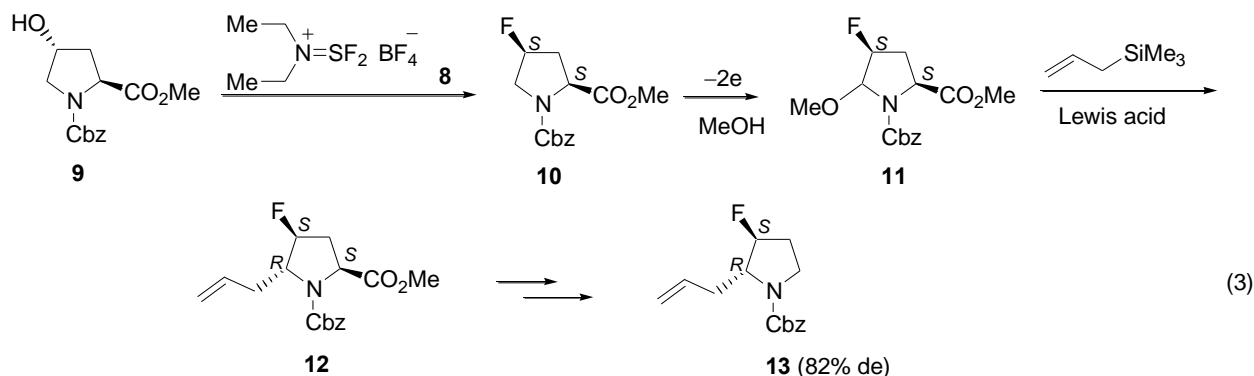
**Figure 1.** Some examples of fluorinated *N*-heterocycles

<sup>†</sup> Dedicated to Professor Dr. Victor Snieckus on his 77<sup>th</sup> birthday.

In addition, the nucleophilic additions to *N*-acyliminium ions are powerful methods for synthesis of biologically active *N*-heterocycles.<sup>5</sup> Also, a large number of methods containing diastereoselective reactions to furnish substituted piperidines and pyrrolidines have been developed.<sup>6</sup> An example of such addition reaction to *N*-acyliminium ion in which a fluorine atom present on the ring influences the stereochemistry of the adducts is uniquely important. Hence the synthesis of stereo defined fluorinated cyclic amine derivatives with nucleophilic addition to *N*-acyliminium ion has not yet been reported. Herein, we describe a facile synthesis using an electrophilic fluorinating reagent Selectfluor<sup>TM</sup> **1**<sup>7</sup> utilizing *N*-acyliminium ion precursors to furnish 3-fluorinated derivatives, where the fluorine atom on the ring influences the diastereoselectivities of adducts. The significance of this method is threefold: (Step 1) Preparation of *N*-protected cyclic enamines **4** from corresponding amines **2** using the electrochemical oxidation method<sup>8</sup> and demethoxylation of **3**.<sup>9</sup> (Step 2) Electrophilic fluorination of **4** using **1**, which is safe, non-toxic, and easy to handle (Eq. 1).<sup>10,11</sup> (Step 3) Lewis acid mediated nucleophilic substitution of **5** to give *trans*-substituted derivatives **6** or **7** (Eq. 2).



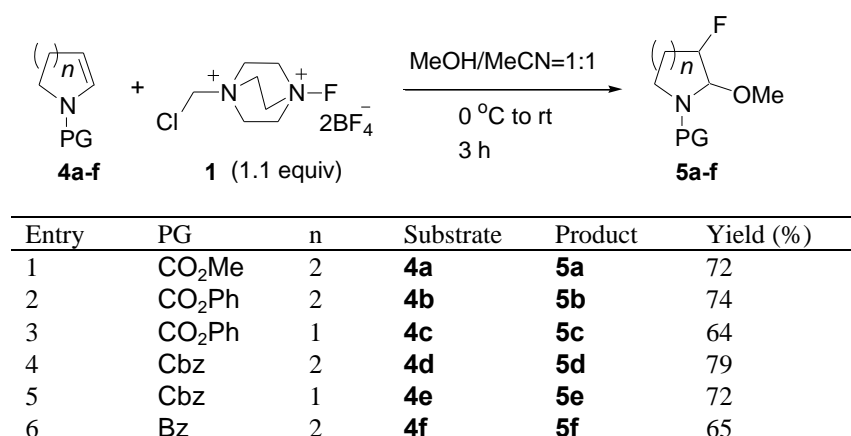
In addition, a nucleophilic fluorination with XtalFluor-E<sup>TM</sup> **8**<sup>12</sup> of *N*-Cbz-*trans*-4-hydroxy-L-prolinate **9** afforded *cis*-fluoro-L-prolinate **10** which was electrochemically transformed into methoxylated derivative **11**. Successive diastereoselective allylation of **11** afforded optically active allylated derivative **12** which was easily transformed into 2*R*-allyl-3*S*-fluoropyrrolidine **13** (Eq. 3).<sup>13</sup>



## RESULTS AND DISCUSSION

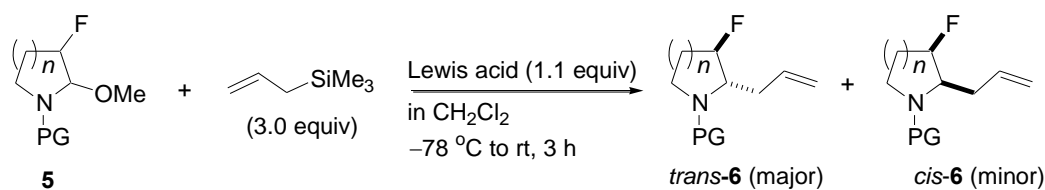
Preparation of *N*-protected enamines **4a-f** from the respective *N*-protected piperidines and pyrrolidines was achieved according to Shono method which consists of electrochemical methoxylation and successive removal of methanol with up to 97% yield.<sup>8,9</sup> Next, electrophilic fluorination of substrates **4a-f** using Selectfluor<sup>TM</sup> **1** afforded 3-fluoro-2-methoxy-*N*-protected piperidine and pyrrolidine derivatives.<sup>7,10</sup> Namely, addition of **1** to a solution of **4** in acetonitrile/methanol gave **5a-f** in good yields (Table 1).

**Table 1.** Fluoromethoxylation of cyclic enamines **4a-f**



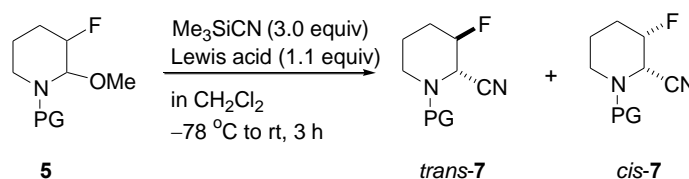
We envisaged that upon treatment of **5** with some Lewis acids, the *N*-acyliminium ions was generated and readily trapped by the carbon nucleophiles resulting to the desired products with fluorine atom influencing the diastereoselectivities.<sup>13,14</sup> To our delight, when compounds **5** were treated with some Lewis acids in CH<sub>2</sub>Cl<sub>2</sub>, the allylation using allyltrimethylsilane proceeded satisfactorily to give allylated products **6** in good yields (Table 2). TiCl<sub>4</sub> or BF<sub>3</sub>·OEt<sub>2</sub> mediated allylation of 3-fluoro-2-methoxy-*N*-methoxycarbonylpiperidine **5a** smoothly proceeded to afford the allylated product **6a** in high yields with moderate diastereoselectivities (entries 1 and 2). For allylation of *N*-phenyloxycarbonylated piperidine **5b**, the higher diastereoselectivity was achieved by using TiCl<sub>4</sub> affording 58% de and 81% yield compared with BF<sub>3</sub>·OEt<sub>2</sub> (entries 3 and 4). Although TiCl<sub>4</sub> did not result to the allylated product for *N*-benzyloxycarbonylated piperidine **5d**, using BF<sub>3</sub>·OEt<sub>2</sub> gave 58% de and 87% yield (entries 6 and 7).<sup>15</sup> On the other hand, SnCl<sub>4</sub> did not lead to any improvement on the de value of **6d** (entry 8). In addition, BF<sub>3</sub>·OEt<sub>2</sub> mediated allylation of pyrrolidine derivatives **5c,e** proceeded to afford substituted products **6c,e** in high yields with low diastereoselectivities (entries 5 and 9).

Next we focused on cyanation of **5**. When compounds **5a,b,d** were treated with trimethylsilyl cyanide in the presence of TiCl<sub>4</sub>, the desired product was formed in high yields and moderate diastereoselectivities as shown in Table 3 (entries 1-3). Also, 2-cyano-3-fluoro-*N*-benzyloxycarbonylpiperidine **7d** was formed with a higher de of 58% and yield of 84% when mediated by BF<sub>3</sub>·OEt<sub>2</sub> as the Lewis acid of choice (entry 4). SnCl<sub>4</sub> did not lead to an improvement of the de and the yield of **7d** (entry 5).

**Table 2.** Synthesis of 2-allyl-3-fluoropiperidine derivatives **6**

Entry	PG	n	Lewis acid	Product	Yield (%)	De (%) <sup>a</sup>
1	CO <sub>2</sub> Me	2	TiCl <sub>4</sub>	<b>6a</b>	89	44
2	CO <sub>2</sub> Me	2	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6a</b>	76	40
3	CO <sub>2</sub> Ph	2	TiCl <sub>4</sub>	<b>6b</b>	81	58
4	CO <sub>2</sub> Ph	2	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6b</b>	69	42
5	CO <sub>2</sub> Ph	1	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6c</b>	82	14
6	Cbz	2	TiCl <sub>4</sub>	<b>6d</b>	0	-
7	Cbz	2	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6d</b>	87	58
8	Cbz	2	SnCl <sub>4</sub>	<b>6d</b>	68	48
9	Cbz	1	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>6e</b>	79	26

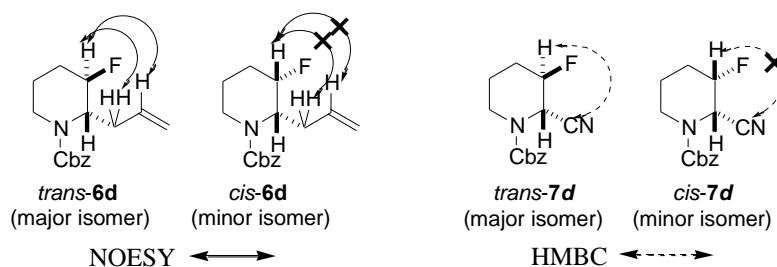
<sup>a</sup> Determined by <sup>1</sup>H NMR and/or <sup>19</sup>F NMR at 50 °C.

**Table 3.** Synthesis of 2-cyano-3-fluoropiperidine derivatives **7**

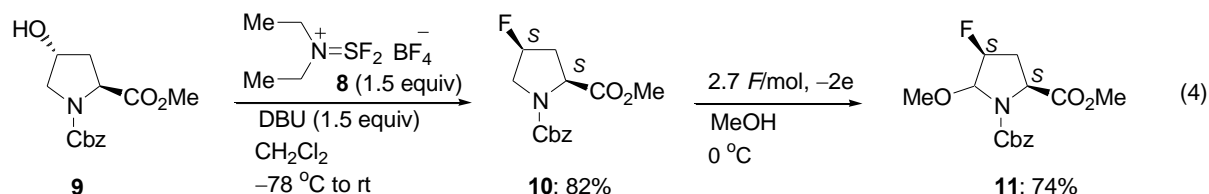
Entry	PG	Lewis acid	Product	Yield (%)	De (%) <sup>a</sup>
1	CO <sub>2</sub> Me	TiCl <sub>4</sub>	<b>7a</b>	89	48
2	CO <sub>2</sub> Ph	TiCl <sub>4</sub>	<b>7b</b>	83	50
3	Cbz	TiCl <sub>4</sub>	<b>7d</b>	76	50
4	Cbz	BF <sub>3</sub> ·OEt <sub>2</sub>	<b>7d</b>	84	58
5	Cbz	SnCl <sub>4</sub>	<b>7d</b>	62	34

<sup>a</sup> Determined by <sup>1</sup>H NMR and/or <sup>19</sup>F NMR at 50 °C.

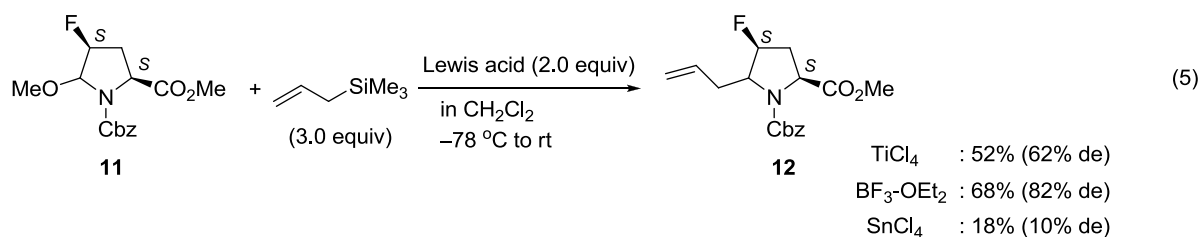
Relative stereoconfigurations for **6** and **7** were speculated by the NOESY studies for **6d** and the HMBC studies<sup>16</sup> for **7d**. Diastereomers of **6d** or **7d** were separable by silica gel PTLC to afford major isomer and minor isomer, respectively. The NOESY spectroscopy for major isomer of **6d** showed correlations, while the NOESY spectroscopy for minor isomer of **6d** did not show the correlation. Accordingly, it was determined that major isomer was *trans*-**6d** and minor isomer was *cis*-**6d**. Similarly separated major isomer for **7d** was determined as *trans* configuration (Figure 2).

**Figure 2.** NOESY for **6d** and HMBC for **7d**

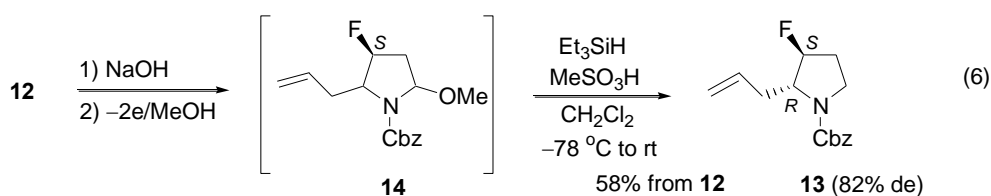
We next focused on the synthesis of optically active 2-allyl-3-fluoropyrrolidine starting from *N*-Cbz-*trans*-4-hydroxy-L-prolinate **9**.<sup>17</sup> Deoxofluorination of **9** was achieved by utilizing XtalFluor-E<sup>TM</sup> **8** as the reagent of choice.<sup>12</sup> The fluorination of the hydroxyl group at the 4-position proceeded in an inversion manner to give the desired compound **10** in 82% yield.<sup>12,18</sup> Electrochemical oxidation of **10** afforded 4-fluoro-5-methoxy-L-proline derivative **11** in 74% yield (Eq. 4).



The allylation of **11** using 2.0 equiv of Lewis acids<sup>19</sup> was successfully achieved affording compound **12** (Eq. 5).<sup>13</sup> In the case of *N*-benzyloxycarbonylprolinate **11**, the allylation mediated by TiCl<sub>4</sub> resulted to good yield and de. Using BF<sub>3</sub>·OEt<sub>2</sub> afforded **12** in higher yield and de (entry 2), while the use of SnCl<sub>4</sub> afforded low yield and de of **12**.



Hydrolysis, successive decarboxylative methoxylation, and reductive demethoxylation<sup>13</sup> of **12** prepared by using BF<sub>3</sub>·OEt<sub>2</sub> proceeded smoothly without purification of intermediate **14** to give 2-allyl-3*S*-fluoropyrrolidine **13** (Eq. 6).



Comparing HPLC pattern of **13** with that of **6e** (*trans/cis*=63:37) showed that the relative stereoconfiguration of **13** was majorly *trans* (82% de) and its absolute stereoconfiguration was 2*R*,3*S*.

## CONCLUSION

In conclusion, a facile procedure for synthesis of *trans*-3-fluoro-2-substituted piperidines and optically active *trans*-2-allyl-3-fluorinated pyrrolidine which can be used as precursors for new drugs in pharmaceuticals has been developed. This was achieved by utilizing facile electrochemical oxidation and electrophilic or nucleophilic fluorination. Additionally, mild conditions and practical convenience will make this method a valuable synthetic tool in organic chemistry.

## EXPERIMENTAL

**General:** All commercial materials, reagents and solvents, were used without further purification unless otherwise stated. Electrochemical reactions were carried out by the use of DC power supply (GP 050-2) of Takasago Seikakusho in an undivided glass cell by using platinum plate electrodes (10 x 20 mm), graphite electrodes (50 x 12 x 2 mm).  $^1\text{H}$  NMR spectra were measured at 500 and 400 MHz with TMS as an internal standard at 50 °C,  $^{19}\text{F}$  NMR spectra were measured at 376 MHz with  $\text{CFCl}_3$  used as the internal standard at 50 °C.  $^{13}\text{C}$  NMR spectra were measured at 100MHz on JEOL JNM-AL 400MHZ. IR spectra were obtained on Shimadzu FTIR-8100A. High resolution mass spectra were recorded on a JEOL JMS-700N instrument using electron ionization (EI) mass spectrometry. Melting points were measured with micro melting point apparatus (Yanaco). Flash column chromatography was performed using silica gel 60 (230-400 mesh, Nacalai tesque) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck). Specific optical rotations were recorded on JASCO DIP-1000 digital polarimeter.

### *General procedure for the preparation of N-protected enamines 4a-f*

The substrates **4a-i** were prepared from the respective *N*-protected piperidine and pyrrolidines according to previously reported methods.<sup>8,9</sup> Compounds **4a**,<sup>8</sup> **4b**,<sup>20</sup> **4c**,<sup>21</sup> **4d**,<sup>22</sup> **4e**,<sup>9</sup> and **4f**<sup>23</sup> are known compounds and their spectroscopic data is available in literature.

### *General procedure for the fluorination of N-protected enamines 4a-i using Selectfluor*

To the substrates **4a-f** (1.0 mmol) dissolved in 3 mL of MeCN/MeOH (1:1) under a nitrogen atmosphere, Selectfluor (1.1 mmol) was added at 0 °C stirring the mixture for 1 h. The temperature of the mixture was then gradually allowed to rise to room temperature and the reaction was monitored using TLC for over 2 h. Water (5 mL) was added and the mixture extracted using  $\text{CH}_2\text{Cl}_2$  (5 x 10 mL). The combined organic layer was dried by anhydrous  $\text{Na}_2\text{SO}_4$ . The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc 4:1) to give the desired product **5a-f**.

### *3-Fluoro-2-methoxy-N-methoxycarbonylpiperidine (5a)*

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42-1.65 (m, 1H), 1.73-2.03 (m, 3H), 2.85-2.99 (m, 1H), 3.30 and 3.36 (2s, 3H), 3.74 and 3.75 (2s, 3H), 3.81-4.03 (m, 1H), 4.35-4.52 and 4.61 (m and d,  $J=46.4$  Hz, 1H), 5.20-5.55 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.7 and 23.2 (2s), 24.1 and 24.2 (2s), 37.3 and 37.9 (2s), 52.4 and 52.5 (2s), 54.6 and 55.1 (2s), 82.2 and 82.5 (2s), 85.8 and 88.6 (2d,  $J=170.6$  and 183.9 Hz), 156.7 and 155.9 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -191.2 (br s, 0.67F), -183.5 (d,  $J=47.3$  Hz, 0.33F); IR (neat) 2953, 1701, 1440, 1412, 1369, 1261, 1163, 1086, 962, 770  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_8\text{H}_{14}\text{FNO}_3$  [ $\text{M}^+$ ] 191.0958, found 191.0941.

### *3-Fluoro-2-methoxy-N-phenyloxycarbonylpiperidine (5b)*

Mp 76-78 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.52-1.68 (m, 1H), 1.75-2.07 (m, 3H), 3.05 (br s, 1H), 3.31-3.53 (m, 3H), 3.96-4.10 (m, 1H), 4.53 and 4.67 (br d and d,  $J=47.6$  and 47.6 Hz, 1H), 5.51-5.62 (m, 1H), 7.09-7.36 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.82-24.38 (m), 25.50 (br s), 38.19 (br s), 52.75-56.04 (m), 82.98 (br s), 84.88-86.79 (m), 121.06-121.76 (m, 2C), 124.67-125.60 (m), 128.75-129.40 (m, 2C), 150.89-151.35 (m), 153.61 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -191.57 (t,  $J=45.1$  Hz, 0.40F), -183.8 (t,  $J=47.1$  Hz, 0.60F); IR (neat) 2945, 1717, 1495, 1410, 1381, 1369, 1260, 1198, 1161, 1069, 1024, 968, 748  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{FNO}_3$  [ $\text{M}^+$ ] 253.1114, found 253.1127.

**3-Fluoro-2-methoxy-N-phenyloxycarbonylpyrrolidine (5c)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.20-2.31 (m, 2H), 3.48 and 3.58 (2s, 3H), 3.73-3.81 (m, 2H), 4.89-5.04 (m, 1H), 5.24-5.33 (m, 1H), 7.13-7.25 (m, 3H), 7.34-7.38 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.17-29.96 (m), 41.37-46.30 (m), 56.04-57.97 (m), 86.39 (s), 91.49-95.59 (m), 121.92 (br s), 125.87 (s, 2C), 129.66 (s, 2C), 151.01 (2s), 153.02-154.84 (m);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -200.3- -201.5 (m, 0.37F), -186.9- -188.2 (m, 0.63F); IR (neat) 2936, 1721, 1593, 1495, 1456, 1387, 1371, 1204, 1163, 1099, 1042, 957, 731  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{12}\text{H}_{14}\text{FNO}_3$  [ $\text{M}^+$ ] 239.0958, found 239.0958.

**N-Benzoyloxycarbonyl-3-fluoro-2-methoxypiperidine (5d)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.40-1.54 (m, 1H), 1.69-2.05 (m, 3H), 2.89-2.95 (m, 1H), 3.25-3.62 (m, 3H), 3.68-4.00 (m, 1H), 4.33-4.50 and 4.59 (m and d,  $J=48.1$  Hz, 1H), 5.06-5.27 (m, 2H), 5.46 (br s, 1H), 7.23-7.41 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.9 and 23.3 (2s), 24.2 and 24.4 (2s), 37.5 and 38.1 (2s), 54.8 and 55.1 (2s), 67.2 and 67.4 (2s), 82.3 and 82.6 (2s), 85.9 and 88.7 (2s), 127.9 (s), 128.1 (s), 128.0 (s), 128.3 (s), 128.5 and 128.6 (2s), 136.2 and 136.5 (2s), 155.2 and 155.9 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -191.37(s, 0.50F), -183.67 (s, 0.50F); IR (neat) 2947, 1697, 1447, 1418, 1258, 1070, 962  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{14}\text{H}_{18}\text{FNO}_3$  [ $\text{M}^+$ ] 267.1271, found 267.1257.

**N-Benzoyloxycarbonyl-3-fluoro-2-methoxypyrrolidine (5e)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.03-2.15 (m, 2H), 3.18-3.47 (m, 4H), 3.57 (br s, 1H), 4.68-4.88 and 4.81 (m and d,  $J=52.4$  Hz, 1H), 4.95-5.25 (m, 3H), 7.19-7.28 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.82 (s), 41.55 (s), 43.71 and 45.62 (2s), 55.60 and 56.16 (2s), 86.55 (s), 91.65 (s), 127.72-128.58 (m, 5C), 136.19-136.35 (m), 155.17-155.79 (m);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -201.25 and -200.32 (2d,  $J=41.0$ , 51.9 Hz, 0.19F), -188.03 and -187.10 (2s, 0.81F); IR (neat) 2947, 1705, 1449, 1404, 1341, 1279, 1213, 1177, 1096, 1076, 959, 772  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{FNO}_3$  [ $\text{M}^+$ ] 253.1114, found: 253.1120.

**N-Benzoyl-3-fluoro-2-methoxypiperidine (5f)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.45-2.23 (m, 4H), 2.94-3.52 (m, 4H), 4.15-6.10 (m, 3H), 7.39-7.48 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.31 (br s), 24.62-25.03 (m), 36.22 (m), 54.85 and 55.6 (2s), 85.74-88.01 (m),

89.87 (br s), 127.23-127.80 (m, 2C), 128.68-128.89 (m, 2C), 130.03 and 130.42 (2s), 135.55 and 135.76 (2s), 171.65 and 172.38 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -191.24 (br s, 0.29F), -183.23 and -184.09 (2br s, 0.71F); IR (neat) 2945, 1641, 1412, 1352, 1301, 1273, 1069, 1045, 968, 702  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{13}\text{H}_{16}\text{FNO}_2$  [ $\text{M}^+$ ] 237.1165, found 237.1151.

**General procedure for the preparation of 2-allyl-3-fluoro-N-protected cyclic amine derivatives 6a-e**

The substrate compound **5** (1.0 mmol) and allyltrimethylsilane (3.0 mmol) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $-78$  °C, under nitrogen atmosphere. 1M  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  (1.1 mmol) was added dropwise via syringe. The reaction was allowed to warm to room temperature over 3 h, progress monitored by TLC. After completion, the reaction mixture was quenched with (5 mL) of saturated aqueous  $\text{NaHCO}_3$  solution. The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL) and the combined organic layer washed with saturated aqueous  $\text{NaCl}$  (10 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The organic layer was evaporated in vacuo, which was further purified by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) as eluent giving a mixture of diastereoisomers compound **6**.

**2-Allyl-3-fluoro-N-methoxycarbonylpiperidine (6a) (44% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.34-1.52 (m, 1H), 1.58-1.78 (m, 2H), 1.80-1.97 (m, 1H), 2.13-2.39 (m, 2H), 2.68 (td,  $J=13.4, 3.1$  Hz, 0.72H), 2.78-2.83 (m, 0.28H), 3.48-3.72 (m, 3H), 3.87 (d,  $J=12.2$  Hz, 0.72H), 4.01 (d,  $J=9.8$  Hz, 0.28H), 4.45-4.51 (m, 1H), 4.57-4.63 (m, 1H), 4.94-5.05 (m, 2H), 5.61-5.72 (m, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.65 (s), 24.96-25.24 (m), 25.90 (s), 33.63 and 33.72 (2s), 38.09 and 39.15 (2s), 53.01-54.12 (m), 87.98 and 89.74 (2d,  $J=184.0$  and 170.5 Hz), 117.72 and 118.24 (2s), 134.29 and 134.72 (2s), 156.95 and 157.27 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -182.45 (br s, 0.28F), -181.51 (d,  $J=48.8$  Hz, 0.72F); IR (neat) 2953, 1694, 1449, 1408, 1366, 1310, 1190, 1152, 1034, 959, 916, 766  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{10}\text{H}_{16}\text{FNO}_2$  [ $\text{M}^+$ ] 201.1165, found 201.1163.

**2-Allyl-3-fluoro-N-phenyloxycarbonylpiperidine (6b) (58% de)**

Mp 80-81 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.57-1.72 (m, 2H), 1.73-1.91 (m, 1H), 1.87-2.15 (m, 1H), 2.34-2.58 (m, 2H), 4.09 (d,  $J=13.7$  Hz, 0.79H), 4.22 (d,  $J=12.2$  Hz, 0.21H), 4.56-4.87 (m, 2H), 4.99-5.25 (m, 2H), 5.15-5.66 (m, 1H), 5.70-5.95 (m, 1H), 7.01-7.13 (m, 2H), 7.13-7.21 (m, 1H), 7.27-7.39 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.24 (s), 24.79 and 24.57 (2s), 33.24 and 33.33 (2s), 38.08 (br s), 53.84 (br s), 86.72 and 88.71 (2s), 115.73 (s), 118.0 (br s), 119.08 (s), 121.73 (s), 125.15 (s), 129.19 (s), 133.56 (s), 151.61 (s), 154.23 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -178.91 and -179.55 (2b s, 1F); IR (neat) 2949, 1709, 1643, 1593, 1495, 1412, 1356, 1310, 1240, 1196, 1161, 1140, 1040, 1024, 991, 957, 743  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{15}\text{H}_{18}\text{FNO}_2$  [ $\text{M}^+$ ] 263.1322, found 263.1324.

**2-Allyl-3-fluoro-N-phenyloxycarbonylpyrrolidine (6c) (14% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.79-2.67 (m, 4H), 2.81 and 3.42-4.28 (br s and m, 3H), 4.83-5.26 (m,



3H), 5.68-5.87 (m, 1H), 7.06-7.17 (m, 3H), 7.27-7.35 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  28.54-31.62 (m), 35.72 and 36.78 (2br s), 44.65 (s), 62.11 and 63.99 (2br s), 91.86-94.26 (m), 117.88 (s), 118.15 (br s), 121.58 (s), 125.19 (s), 129.11 and 129.19 (2s), 133.48 (br s), 134.14 and 134.16 (2s), 151.33 and 151.35 (2s), 153.09 and 153.17 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -193.17 and -193.84 (2br s, 0.57F), -176.21- -175.20 (m, 0.43F); IR (neat) 2949, 1717, 1641, 1593, 1494, 1389, 1192, 1070, 1022, 918, 754, 739  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{14}\text{H}_{16}\text{FNO}_2$  [ $\text{M}^+$ ] 249.1165, found 249.1162.

**2-Allyl-N-benzyloxycarbonyl-3-fluoropiperidine (6d) (58% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42-1.64 (m, 2H), 1.68-1.83 (m, 1H), 1.88-2.05 (m, 1H), 2.35-2.47 (m, 2H), 2.78 (t,  $J=13.4$  Hz, 0.79H), 2.88 (t,  $J=13.2$  Hz, 0.21H), 4.00 (br d,  $J=13.9$  Hz, 0.79H), 4.14 (br d,  $J=13.2$  Hz, 0.21H), 4.50-4.72 (m, 2H), 4.95-5.20 (m, 4H), 5.62-5.78 (m, 1H), 7.33 (s, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.71 (s), 25.59 and 25.78 (2s), 28.88 (s), 37.96 and 39.01 (2s), 53.67 and 53.92 (2s), 67.46 and 67.64 (2s), 88.25 and 90.06 (2s), 117.63 and 118.11 (2s), 128.1-28.92 (m, 5C), 134.05 and 134.59 (2s), 137.14 and 137.40 (2s), 156.07 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -181.48 (d,  $J=48.9$  Hz, 1F); IR (neat) 2949, 1692, 1423, 1350, 1248, 1148, 1069, 1028, 1001, 959, 733  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{16}\text{H}_{20}\text{FNO}_2$  [ $\text{M}^+$ ] 277.1478, found 277.1458.

Further purification of a mixture of *cis*- and *trans*-**6d** by PTLC afforded *cis*-**6d** and *trans*-**6d**.

***cis*-2-Allyl-N-benzyloxycarbonyl-3-fluoropiperidine (*cis*-6d) (less polar)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.44-1.62 (m, 1H), 1.69-1.85 (m, 2H), 1.89-2.05 (m, 1H), 2.35-2.45 (m, 2H), 2.88 (t,  $J=13.4$  Hz, 1H), 4.14 (d,  $J=13.7$  Hz, 1H), 4.52-4.71 (m, 2H), 5.09 (br s, 1H), 4.99-5.03 (m, 1H), 5.10-5.17 (m, 2H), 5.7 (d,  $J=7.3$  Hz, 1H), 7.27-7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.66 and 23.76 (2s), 24.82 and 25.04 (2s), 28.88 (s), 37.96 (s), 53.67 and 53.92 (2s), 67.46 and 67.64 (2s), 88.25 and 90.06 (2s), 117.63 and 118.11 (2s), 128.15-128.86 (m, 5C), 134.05 and 134.59 (2s), 137.14 and 137.40 (2s), 156.07 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -180.78 (d,  $J=45.7$  Hz, 1F).

***trans*-2-Allyl-N-benzyloxycarbonyl-3-fluoropiperidine (*trans*-6d) (polar)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49-1.64 (m, 2H), 1.72-1.83 (m, 1H), 1.88-2.00 (m, 1H), 2.34-2.44 (m, 2H), 2.77 (t,  $J=13.3$  Hz, 1H), 3.99 (d,  $J=13.7$  Hz, 1H), 4.55 (dt,  $J=10.9, 5.3$  Hz, 1H), 4.51-4.59 (m, 1H), 4.61-4.70 (m, 1H), 4.98 (d,  $J=10.0$  Hz, 1H), 5.06 (d,  $J=17.3$  Hz, 1H), 5.09-5.16 (m, 2H), 5.70 (d,  $J=7.32$  Hz, 1H), 7.33 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  23.71 (s), 25.68 (s), 28.88 (s), 37.96 (s), 53.67 and 53.92 (2s), 67.46 and 67.64 (2s), 88.25 and 90.06 (2s), 117.63 and 118.11 (2s), 126.11-130.61 (m, 5C), 133.10 (s), 136.36 (s), 156.07 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -181.52 (d,  $J=48.9$  Hz, 1F).

**2-Allyl-N-benzyloxycarbonyl-3-fluoropyrrolidine (6e) (26% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.62-2.40 (m, 4H), 3.16-4.10 (m, 3H), 4.83 (dd,  $J=52.4, 2.2$  Hz, 0.63H), 4.87 (dd,  $J=52.8, 2.8$  Hz, 0.37H), 4.96 and 5.00 (2d,  $J=3.4$  and  $3.4$  Hz, 1H), 5.02-5.11 (m, 1H), 5.12-5.21

(m, 2H), 5.62-5.92 (m, 1H), 7.27-7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.02 and 30.05 (2br s), 31.08 and 31.30 (2s), 44.50 and 44.52 (2s), 61.53 and 63.69 (2br s), 66.88 (s), 90.34 and 91.86 (2s), 117.60 (s), 117.96 (s), 127.78 (s), 127.89 and 127.95 (2s), 128.42 and 128.44 (2s), 133.55 (s), 134.29 and 134.31 (2s), 136.79 (s), 154.57 and 154.68 (2s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -186.96 and -187.89 (2br s, 0.63F), -176.07 and -175.46 (2br s, 0.37F); IR (neat) 2953, 1701, 1447, 1406, 1340, 1279, 1211, 1179, 1098, 1078, 1053, 959, 735  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{15}\text{H}_{18}\text{FNO}_2$  [ $\text{M}^+$ ] 263.1322, found 263.1313. HPLC YMC-Pack SIL column; 150 mm x 4.6 mm $\phi$ ; *n*-hexane/2-propanol 50:1, wavelength 254 nm, flow rate: 1.0 mL/min, retention time: 3.8 min (37%), 5.6 min (63%).

**General procedure for the preparation of 2-cyano-3-fluoro-*N*-protected cyclic amine derivatives 7a-d**

The substrate compound **5** (1.0 mmol) and trimethylsilyl cyanide (3.0 mmol) were dissolved in dry  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $-78^\circ\text{C}$ , under nitrogen atmosphere. 1M  $\text{TiCl}_4$  in  $\text{CH}_2\text{Cl}_2$  (1.1 mmol) was added dropwise via syringe. The reaction was allowed to warm to room temperature, then quenched with saturated aqueous  $\text{NaHCO}_3$  (5 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL) and the combined organic layer washed with saturated aqueous  $\text{NaCl}$  (10 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The organic layer was evaporated in vacuo, which was further purified by column chromatography on silica gel (*n*-hexane/EtOAc 8:1) as eluent giving a mixture of diastereoisomers compound **7**. The same procedure was repeated for  $\text{BF}_3\cdot\text{OEt}_2$  and  $\text{SnCl}_4$ .

**2-Cyano-3-fluoro-*N*-methyloxycarbonylpiperidine (7a) (48% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.51-1.54 (m, 1H), 1.83-1.92 (m, 2H), 2.10-2.30 (m, 1H), 2.96 (td,  $J=13.4, 2.7$  Hz, 0.74H), 3.05 (br t,  $J=13.4$  Hz, 0.26H), 3.77 (s, 3H), 4.06 (br d,  $J=12.9$  Hz, 0.74H), 4.19 (br d,  $J=11.2$  Hz, 0.26H), 4.42-4.60 (m, 0.74H), 4.85 (br d,  $J=46.2$  Hz, 0.26H), 5.43 and 5.53 (2br s, 1H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  22.31 (s), 25.45 and 27.00 (2s), 40.34 (s), 48.33 and 48.61 (2s), 53.45 (s), 85.80 and 87.63 (2s), 114.21 (s), 154.86 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -186.45 (br s, 0.26F), -178.76 (d,  $J=47.3$  Hz, 0.74F); IR (neat) 2959, 1707, 1447, 1404, 1366, 1306, 1261, 1202, 1109, 1042, 980, 932, 903, 869, 733, 702  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_8\text{H}_{11}\text{FN}_2\text{O}_2$  [ $\text{M}^+$ ] 186.0805, found 186.0802.

**2-Cyano-3-fluoro-*N*-phenyloxycarbonylpiperidine (7b) (50% de)**

Mp  $79-81^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.55-1.70 (m, 1H), 1.90-2.05 (m, 2H), 2.15-2.35 (m, 1H), 3.12 and 3.20 (2br s, 1H), 4.22 and 4.34 (2d,  $J=12.9$  and 13.9 Hz, 1H), 4.54-4.72 (m, 0.75H), 4.93 (d,  $J=45.4$  Hz, 0.25H), 5.56 (d,  $J=10.4$  Hz, 0.25H), 5.65 (d,  $J=5.6$  Hz, 0.75H), 7.10-7.17 (m, 2H), 7.22-7.29 (m, 1H), 7.36-7.33 (m, 2H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  25.46 and 25.66 (2s), 27.03 and 27.21 (2s), 41.11 (br s), 48.72 (br s), 84.69 and 86.56 (2s), 114.39 (s), 121.43-121.77 (m, 2C), 125.97-126.25 (m), 129.46-129.72 (m, 2C), 151.06 and 151.19 (2s), 152.04 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -186.20 and -186.19 (2s, 0.25F), -179.65 (br d,  $J=45.6$  Hz, 0.75F); IR (neat) 2959, 1717, 1593, 1494, 1456, 1408, 1348, 1252, 1196, 1070, 1026,

974, 872, 733  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{13}\text{H}_{13}\text{FN}_2\text{O}_2$  [ $\text{M}^+$ ] 248.0961, found 248.0960.

***N*-Benzyloxycarbonyl-2-cyano-3-fluoropiperidine (7d) (50% de)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.43-2.04 (m, 4H), 3.08 (t,  $J=13.5$  Hz, 0.25H), 3.16 (t,  $J=10.8$  Hz, 0.75H), 3.83 (d,  $J=12.9$  Hz, 0.25H), 3.94 (d,  $J=12.5$  Hz, 0.75H), 4.45-4.55 (m, 0.25H), 4.66 (d,  $J=46.8$  Hz, 0.75H), 5.14 (s, 2H), 5.77 (d,  $J=2.8$  Hz, 0.75H), 5.91 (s, 0.25H), 7.34 (s, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.60 (s), 22.81 and 23.73 (2s), 37.93 (s), 38.59 (s), 67.55 and 67.69 (2s), 85.85 and 87.56 (2s), 127.98 (s, 2C), 128.07 (s), 128.23 and 128.31 (2s), 128.64 (s, 2C), 136.32 and 136.43 (2s), 154.89 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -189.83 (t,  $J=48.8$  Hz, 0.75F), -183.46 (d,  $J=44.3$  Hz, 0.25F); IR (neat) 2959, 1701, 1414, 1344, 1312, 1254, 1155, 1047, 974, 874, 731  $\text{cm}^{-1}$ . HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{14}\text{H}_{15}\text{FN}_2\text{O}_2$  [ $\text{M}^+$ ] 262.1118, found 262.1120.

Further purification of a mixture of *cis*- and *trans*-**7d** by PTLC afforded *cis*-**7d** and *trans*-**7d**.

***cis*-N-Benzyloxycarbonyl-2-cyano-3-fluoropiperidine (cis-7d) (less polar)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.42-1.61 (m, 1H), 1.76-1.95 (m, 2H), 2.09-2.27 (m, 1H), 2.97 (td,  $J=13.3, 2.7$  Hz, 1H), 4.09 (br d,  $J=13.2$  Hz, 1H), 4.42-4.60 (m, 1 H), 5.17 (s, 2H), 5.55 (br s, 1H), 7.32-7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  19.62 (s), 27.76 (s), 35.45 (s), 39.30 (s), 58.08 and 58.63 (2s), 67.87 (s), 87.57 (s), 118.62 (s), 128.49 (s, 2C), 128.60 (s), 129.16 (s), 134.37 and 137.76 (2s), 156.79 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -183.40 (d,  $J=47.0$  Hz, 1F).

***trans*-N-Benzyloxycarbonyl-2-cyano-3-fluoropiperidine (trans-7d) (polar)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.49-1.59 (m, 2H), 1.87-2.04 (m, 2H), 3.07 (t,  $J=12.5$  Hz, 1H), 4.21 (br d,  $J=12.2$  Hz, 1H), 4.86 (d,  $J=45.4$  Hz, 1H), 5.20 (s, 2H), 5.47 (br s, 1H), 7.35 (s, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  18.29 (s), 20.78-26.17 (m, 2C), 28.54-28.97 (m), 35.65-40.83 (m), 67.01-67.52 (m), 85.56 (s), 125.31-131.34 (m, 5C), 133.93-138.02 (m), 152.89-157.42 (m);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -188.84 (d,  $J=47.3$  Hz, 1F).

**Preparation of methyl *N*-benzyloxycarbonyl-*cis*-4-fluoro-*L*-prolinate (10)**

*N*-Benzyloxycarbonyl-*trans*-4-hydroxy-*L*-prolinate (**9**) was prepared from *trans*-4-hydroxy-*L*-proline according to literature method in quantitative yield.<sup>17,24</sup> Compound **9** was transformed into *N*-benzyloxycarbonyl-*cis*-4-fluoro-*L*-prolinate **10** according to literature method using XtalFluor-E **8** in 82% yield.<sup>25</sup>

**Methyl *N*-benzyloxycarbonyl-*cis*-4-fluoro-*L*-prolinate (10)**

$[\alpha]_{\text{D}}^{27}$  -45.0 (c 1.78,  $\text{CH}_2\text{Cl}_2$ ).

**Procedure for electrochemical oxidation of 10**

The substrate (1.0mmol) and  $\text{Et}_4\text{NBF}_4$  (0.1 mmol) were placed in a beaker type cell containing a stirring bar. MeOH and MeCN (1:4) were added and the mixture stirred at 0 °C. The graphite anode and platinum cathodes were fitted and 2.7  $\text{Fmol}^{-1}$  of current was passed through. The reaction mixture was evaporated

to eliminate methanol. Water was added and the mixture was then extracted with EtOAc and the combined organic layer dried using anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed in vacuo and the resulting concentrate purified by silica gel chromatography to afford 4-fluoro-5-methoxy-L-prolinate **11** in 74% yield.

**Methyl (2S,4S)-N-benzyloxycarbonyl-4-fluoro-5-methoxy-L-prolinate (11)**

Yellow oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.23-2.46 (m, 1H), 2.52 (dd,  $J=18.7, 15.0$  Hz, 1H), 3.27-3.95 (m, 6H), 4.50-4.66 (m, 1H), 5.14 (t,  $J=4.3$  Hz, 1H), 5.16-5.23 (m, 2H), 5.27 (t,  $J=4.3$  Hz, 1H), 7.19-7.35 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.32 and 29.67 (2s), 36.34-37.87 (m), 51.80 (s), 52.29-53.83 (m), 57.63 and 57.83 (2s), 67.32 and 67.54 (2s), 91.08 and 92.32 (2d,  $J=356.2$  and  $356.0$  Hz), 127.93-128.82 (m, 5C), 136.55 (s), 154.57 (br s), 171.73 (br s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -173.68 (br s, 1F); IR (neat) 2955, 1755, 1703, 1414, 1348, 1263, 1206, 1167, 1113, 1003, 957, 916, 735  $\text{cm}^{-1}$ ; HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{15}\text{H}_{18}\text{FNO}_5$  [ $\text{M}^+$ ] 311.1169, found; 305.1167.

**Preparation of methyl N-benzyloxycarbonyl -5-allyl-4-fluoro-L-prolinate (12)**

To a mixture of **11** (1.0 mmol) and allyltrimethylsilane (3.0 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (3 mL) was added dropwise  $\text{BF}_3 \cdot \text{OEt}_2$  (2.0 mmol) at  $-78$  °C under nitrogen atmosphere. The reaction was allowed to warm to room temperature over 12 h. The reaction mixture was quenched with saturated aqueous  $\text{NaHCO}_3$  (5 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3 x 5 mL) and the combined organic layer washed with saturated aqueous NaCl (10 mL) and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . The organic layer was evaporated in vacuo, which was further purified by column chromatography on silica gel (*n*-hexane/EtOAc 2:1) as eluent giving **12**.

**Methyl (2S,4S)-5-allyl-N-benzyloxycarbonyl-4-fluoro-L-prolinate (12)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.94-3.00 (m, 4H), 3.41-4.20 (m, 4H), 4.44-4.65 (m, 1H), 4.97-5.25 (m, 3H), 5.18 (d,  $J=11.8$  Hz, 1H), 5.35 (d,  $J=13.4$  Hz, 1H), 5.68-5.90 (m, 1H), 7.22-7.47 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.66 and 31.76 (2s), 51.48 and 51.78 (2s), 52.10 (s), 58.17 (s), 67.17 (s), 69.67-70.19 (m), 109.73-110.75 (m), 116.82-121.24 (m), 127.43-128.89 (m, 5C), 134.10 (s), 136.50 (s), 160.84 (s), 171.85 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$  -173.63 (br s, 1F); IR (neat) 2953, 1757, 1709, 1436, 1354, 1213, 1175, 957, 756  $\text{cm}^{-1}$ ; HR-MS [EI (+)]:  $m/z$  calcd for  $\text{C}_{17}\text{H}_{20}\text{FNO}_4$  [ $\text{M}^+$ ] 322.1376, found; 322.1361.

**Demethoxycarbonylation of 12**

2N NaOH (1mmol) was added to a solution of **12** (1.0 mmol) in MeOH (10 mL) and the mixture refluxed for 2 h. MeOH was removed in vacuo and the pH was adjusted to 1 with 3N HCl. The resulting suspension was extracted using EtOAc (3x 5 mL). The combined organic layer was dried using anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated to give the corresponding acid which was further dissolved in MeOH (7 mL). The resulting mixture was placed in a beaker type cell stirring at 0 °C. Then graphite anode and

platinum cathode were fitted and 2,6-lutidine (1.2 mmol) was added and a constant current of  $2.0 \text{ Fmol}^{-1}$  was passed through. The solvent was evaporated followed by addition of aqueous NaCl (7 mL). The mixture was extracted with EtOAc 3 times and the combined organic layer dried over anhydrous  $\text{MgSO}_4$  and filtered. The solvent was removed under vacuo to give the corresponding methoxylated compound **14**. Triethylsilane (0.75 mmol) was added to a stirred solution of **14** (0.50 mmol) dissolved in dry  $\text{CH}_2\text{Cl}_2$  (3 mL) at  $-78^\circ\text{C}$  under nitrogen atmosphere. The reaction was allowed to warm to  $0^\circ\text{C}$  for 1 h. Methanesulfonic acid (0.60 mmol) was then added drop wise and the mixture was stirred over 30 min at room temperature. Water (20 mL) was added and the solution was extracted with  $\text{CHCl}_3$  (3 x 10 mL). The combined organic layer was dried over anhydrous  $\text{MgSO}_4$  and filtered. The organic layer was evaporated in vacuo and the concentrate was purified by using silica-gel column chromatography (*n*-hexane/EtOAc 2:1) as eluent giving **13** in 58% yield.

**(2R,3S)-2-Allyl-N-benzyloxycarbonyl-3-fluoropyrrolidine (13)**

Colorless oil;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.94-2.90 (m, 4H), 3.25-4.10 (m, 3H), 4.81-4.88 (m, 1H), 4.94-5.50 (m, 4H), 5.62-5.92 (m, 1H), 7.32-7.38 (m, 5H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  29.28 and 30.05 (2br s), 31.52 (s), 44.51 and 44.53 (2s), 61.55 and 63.02 (2br d), 66.91 (s), 89.91-92.87 (m), 117.59 (s), 117.93 (s), 127.80 (s), 127.90 and 127.95 (2s), 128.42 (s), 133.33 (br s), 134.32 (s), 136.81 (s), 154.90 (s);  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ )  $\delta$   $-187.61$  and  $-186.68$  (2br s); IR (neat) 2953, 1701, 1447, 1406, 1340, 1279, 1211, 1179, 1098, 1078, 1053, 959,  $735 \text{ cm}^{-1}$ ; HR-MS [EI (+)]: *m/z* calcd for  $\text{C}_{15}\text{H}_{18}\text{FNO}_2$  [ $\text{M}^+$ ] 263.1322, found 263.1313. HPLC YMC-Pack SIL column; 150 mm x 4.6 mm $\phi$ ; *n*-hexane/2-propanol 50:1, wavelength 254 nm, flow rate: 1.0 mL/min, retention time: 3.8 min (2*S*, 9%), 5.6 min (2*R*, 91%).

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15. BF<sub>3</sub>·OEt<sub>2</sub> mediated allylation of 3-chloro-2-methoxy-*N*-benzyloxycarbonylpiperidine gave 2-allyl-3-chloro-*N*-benzyloxypiperidine in 87% de and 74% yield.  
**2-Allyl-3-chloro-*N*-benzyloxypiperidine**: Colorless oil; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.45-1.51 (m, 1 H), 1.90-1.99 (m, 1H), 2.03-2.09 (m, 2H), 2.29-2.34 (m, 1H), 2.39-2.46 (m, 1H), 2.87 (br t, *J*=13.2 Hz, 1H), 4.15-4.21 (m, 2H), 4.57 (br t, *J*=7.7 Hz, 1H), 5.03-5.10 (m, 2H), 5.15 (s, 2H), 5.65-5.78 (m, 1H), 7.28-7.35 (m, 5H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 18.99 (s), 27.13 (s), 34.81 (s), 38.64 (s), 53.32 (s), 57.41 and 57.95 (2s), 67.18 (s), 117.87 (s), 127.72, 127.84 and 128.40 (3s, 5C), 133.60 (s), 136.98 (s), 155.99 (s); IR (neat) 2951, 1692, 1423, 1348, 1246, 1186, 1123, 1026, 916, 733 cm<sup>-1</sup>. HR-MS [EI (+)]: *m/z* calcd for C<sub>16</sub>H<sub>20</sub>ClNO<sub>2</sub> [M<sup>+</sup>] 293.1183, found; 293.1174. HPLC YMC-Pack SIL column; 150 mm x 4.6 mmφ; *n*-hexane/2-propanol 50:1, wavelength 254 nm, flow rate: 1.0 mL/min, retention time: 2.7 min (6.3%), 3.5 min (93.7%).
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