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この研究はフローニン化合物の選択的導入に関するもので、主にフローニン化合物の性質と応用について述べています。
Selective introduction of fluorine atoms to the tert-carbons of functionalized adamantanes by BrF₃

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Abstract
The direct fluorination reaction of the functionalized adamantanes was achieved by using BrF₃. In the reaction with methyl adamantane-1-carboxylate 1 and dimethyl adamantane-1,3-dicarboxylate 3, three and two fluorine atoms, respectively, were introduced selectively to their tert-carbons. On the other hand, in the reactions with 1-acetoxyethyladamantane 5, and 2-adamanetone 9, not only the expected fluorination of their tert-carbons, but also unexpected reactions such as fluorination of carbonyl functionality occurred.

1. Introduction
Adamantane is a simple cage compound consisting of four tert-carbons and six sec-carbon atoms. Bioactive derivatives of adamantane are known, and 1-aminoadamantane (amantadine) and 1-amin-3,5-dimethyladamantane (memantine) have medicinal uses [1]. Introduction of fluorine atoms in bioactive compounds can enhance their activities and reduce undesirable side-effects. Therefore, the synthesis of
fluorinated adamantane derivatives has received significant attention [2]. Recently, we reported the direct fluorination of adamantanes by an electrochemical method [3]. One to three fluorine atoms can be introduced selectively on the tert-carbons of the adamantanes by controlling the conditions, and functional groups such as ester or cyano groups could survive under the conditions. However, a drawback is that special equipment is required for the electrochemical reaction. Therefore, we also studied the fluorination of adamantanes by non-electrochemical methods, and succeeded in the fluorination of adamantanes with IF₅, without the special equipment needed for electrolysis [4]. However, owing to the inherent reactivity of IF₅, only one or two fluorine atoms could be introduced. Moreover, when electron-withdrawing groups were attached on the substrate, fewer (or no) fluorine atoms could be introduced. For example, 1-cyanoadamantane and dimethyl adamantane-1,3-dicarboxylate were inert to IF₅, and only one fluorine atom could be introduced to methyl adamantane-1-carboxylate. For the introduction of more fluorine atoms to adamantane derivatives with low reactivity, a more reactive fluorination reagent than IF₅ is required [5]. Herein, we report the direct fluorination of adamantanes using BrF₃ [6], which is more reactive than IF₅ [8].

2. Results and discussion

Initially, the reaction of methyl adamantane-1-carboxylate 1 with BrF₃ was performed. The reaction proceeded even at -78 °C, and three fluorine atoms were introduced to its tert-carbons (Entry 1 in Table 1). The best result was obtained by performing the reaction using 4 eq of BrF₃ at 0 °C for 3 h, and methyl 3,5,7-trifluoroadamantane-1-carboxylate 2 was obtained in 88% yield (Entry 3). These results demonstrated the higher reactivity of BrF₃ compared to IF₅ in the direct fluorination reaction of the adamantanes.
Table 1

Reaction of methyl adamantane-1-carboxylate 1 with BrF3

<table>
<thead>
<tr>
<th>Entry</th>
<th>BrF3 / 1</th>
<th>Temperature (0 °C)</th>
<th>React time (h)</th>
<th>Yield of 2 (%)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>-78</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>0</td>
<td>2</td>
<td>(88)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>0</td>
<td>3</td>
<td>88 (95)</td>
</tr>
</tbody>
</table>

a Isolation yield based on 1, in parentheses, 19FNMR yield.

Next, we applied BrF3 to the fluorination of dimethyl adamantane-1,3-dicarboxylate 3, which was inert to IF5, and obtained dimethyl 5,7-difluoroadamantane-1,3-dicarboxylate 4 in 86 % yield (Entry 2 in Table 2). Unexpected reactions also occurred during the fluorination reaction using BrF3. When 1-acetoxymethyladamantane 5 was reacted with BrF3 at -78 °C for 0.5 h, two fluorine atoms were selectively introduced and 1-acetoxymethyl-3,5-difluoroadamantane 6 was obtained in 94 % yield (Entry 3). On the other hand, when the reaction was carried out at 0 °C for 6 h, three fluorine atoms were introduced and 1-acetoxymethyl-3,5,7-trifluoroadamantane 7 was obtained in 62 % yield (Entry 4). However, unexpectedly, 1-((1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane 8 was also formed in 14 % yield. Under these conditions, the fluorination of the carbonyl group also occurred [9]. In the reaction with 2-adamantanone 9, a mixture of
tetrafluorinated compounds 10 and 11 was obtained (Entry 5). Rearrangement of the carbonyl group occurred in addition to the fluorination of the carbonyl group and \textit{tert}-carbons [11] (Scheme 1).

\[
\begin{align*}
\text{9} & \xrightarrow{\text{BrF}_3} \begin{array}{c}
\text{O} \\
\text{F} \\
\Theta
\end{array} \\
\begin{array}{c}
\text{O} \\
\text{F} \\
\Theta
\end{array} & \rightarrow \begin{array}{c}
\text{O} \\
\text{F} \\
\Theta
\end{array}
\end{align*}
\]  

\textbf{Scheme 1.} Plausible mechanism for the formation of 10 and 11

These unexpected reactions were due to the high reactivity of BrF$_3$, and were not observed in the case of IF$_5$. 

4
Table 2

Reaction of functionalized adamantanes with BrF$_3$ $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Adamantane</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)$^b$</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0 °C, 2 h</td>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>0 °C, 6 h</td>
<td>4</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>-78 °C, 0.5 h</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>0 °C, 6 h</td>
<td>7</td>
<td>62$^c$</td>
</tr>
<tr>
<td>5</td>
<td>9</td>
<td>0 °C, 6 h</td>
<td>10, 11</td>
<td>67</td>
</tr>
</tbody>
</table>

$^a$If otherwise not mentioned, the reaction was carried out in CH$_2$Cl$_2$ using 4 eq of BrF$_3$.

$^b$Isolated yield based on 1 used. In parentheses, $^{19}$F NMR yield.
1-(1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane 8 was also formed in 14% yield.

3. Conclusion

Various functionalized adamantanes were reacted with BrF₃, and two to three fluorine atoms were introduced selectively on their tert-carbons. Even when less reactive substrates such as methyl adamantane-1-carboxylate 1 or dimethyl adamantane-1,3-dicarboxylate 3, were used, multiple fluorine atoms were introduced to their tert-carbons. On the other hand, in the reaction of 1-acetoxymethyladamantane 5 and 2-adamantanone 9, unexpected reactions occurred, such as the fluorination of carbonyl group, and rearrangement.

4. Experimental

4.1. General

The melting points were measured with a Yanagimoto micro melting-point apparatus. The IR spectra were recorded using a JASCO FT/IR-410. The ¹H NMR (400 MHz) spectra, ¹⁹F NMR (376 MHz) spectra, and ¹³C NMR (100 MHz) were recorded in CDCl₃ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, is referred to TMS (¹H, ¹³C) and CFCl₃ (¹⁹F), respectively. BrF₃ in a cylinder was purchased from Galaxy Chemicals, LLC and used without purification. BrF₃ was transferred from cylinder to a
Teflon™ bottle through a Teflon™ tube using nitrogen pressure, and a small quantity of BrF₃ in a small Teflon bottle was kept in a freezer [12]. It decomposes in air by humidity emitting HF fume and was handled in a bench hood with rubber-gloved hands under atmosphere of nitrogen. It is highly reactive and a special care is required for its use. BrF₃ is stable in glasswear but the reaction was carried out in a centrifuge tube of Teflon™ FEP with a tight screw cap because generation of HF occurs during the reaction.

4.2. Fluorination of adamantane derivatives by BrF₃.

**Methyl 3,5,7-trifluoroadamantane-1-carboxylate (2):** To a CH₂Cl₂ solution (1.5 mL) of BrF₃ (378 mg, 2.76 mmol) in a Teflon™ FEP reactor, methyl adamantane-1-carboxylate (134mg, 0.69 mmol) in CH₂Cl₂ (0.8 mL) was added at -78 °C through a Teflon™ cannula and the mixture was stirred at 0 °C for 2h. Then the mixture was cooled to -78 °C again, and 2mL of Me₃SiCl was added slowly to decompose the excess of BrF₃. The mixture was brought up to room temperature and neutralized with aq NaHCO₃. The mixture was extracted with CH₂Cl₂ (20 mL X 3) and the combined organic phase was washed with aq Na₂S₂O₃ and dried over MgSO₄. After concentration under reduced pressure, 2 was isolated by column chromatography (silica gel, hexane-ether) in 88 % yield. mp 109–112 °C (sealed tube) (lit.[2] 108.5-110 °C); IR (KBr) 2958, 1737, 1339, 1259, 1226, 964 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.74 (s, 3H), 2.16–1.99 (m, 12H); ¹⁹F NMR (376 MHz, CDCl₃) δ -144.00 (s, 3F); ¹³C NMR (100MHz, CDCl₃) δ 173.4 (q, ⁴J_C-F = 3.4 Hz), 91.7 (dt, ¹J_C-F = 191.2, ³J_C-F = 15.3 Hz, 3C), 52.6, 46.6-46.0 (m, 3C), 43.2 (q, ³J_C-F = 11.8 Hz), 42.1-41.7 (m, 3C); HRMS (EI) calcd for C₁₂H₁₅O₂F₃ 248.1024, found 248.1013.

**Dimethyl 5,7-difluoroadamantane-1,3-dicarboxylate (4):** mp 87–89 °C (sealed tube);
IR (KBr) 2960, 1738, 1435, 1275 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.72 (s, 6H), 2.12 (t, J = 5.3 Hz, 2H), 2.05–1.97 (m, 8H), 1.93 (brs, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –140.21 (s, 3F); ¹³C NMR (100MHz, CDCl₃) δ 173.9 (t, 1.2J_C,F = 2.6 Hz, 2C), 92.4 (dd, 1.3J_C,F = 189.1, 3J_C,F = 14.3 Hz, 2C), 52.4 (2C), 46.7 (t, 2J_C,F = 19.3 Hz), 45.0 (t, 3J_C,F = 11.0 Hz, 2C), 42.2 (t, 3J_C,F = 6.0 Hz, 2C), 42.0 (t, 3J_C,F = 5.9 Hz, 2C), 38.3 (t, 4J_C,F = 2.0 Hz); HRMS (EI) calcd for C₁₄H₁₈O₄F₂, 288.1173, found 288.1183.

1-(Acetoxymethyl)-3,5-difluoroadamantane (6): IR (neat) 2949, 1741, 1243 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.86 (s, 2H), 2.49 (brs, 1H), 2.10 (brs, 2H), 2.08 (s, 3H), 1.83–1.65 (m, 8H), 1.43(brs, 2H); ¹⁹F NMR (376 MHz, CDCl₃) δ –137.54 (s, 2F); ¹³C NMR (100MHz, CDCl₃) δ 170.9, 93.0 (dd, 1J_C,F = 188.1, 3J_C,F = 13.6 Hz, 2C), 71.1 (t, 4J_C,F = 1.9 Hz), 47.5 (t, 2J_C,F = 19.0 Hz), 43.3 (t, 4J_C,F = 5.5 Hz), 43.1 (t, 4J_C,F = 5.6 Hz), 40.8 (t, 4J_C,F = 5.4 Hz), 40.6 (t, 4J_C,F = 5.4 Hz), 39.2 (t, 3J_C,F = 10.3 Hz), 36.6 (t, 4J_C,F = 2.1 Hz), 30.4 (t, 3J_C,F = 10.6 Hz), 20.7; HRMS (EI) calcd for C₁₃H₁₈O₂F₂ 244.1275, found 244.1285.

1-(Acetoxymethyl)-3,5,7-trifluoroadamantane (7): mp 58–63 °C (sealed tube); IR (KBr) 2947, 1749, 1336, 1237, 1217, 1024 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.94 (s, 2H), 2.16–2.08 (m, 6H), 2.10 (s, 3H), 1.69 (brs, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ –144.07 (s, 3F); ¹³C NMR (100MHz, CDCl₃) δ 170.7, 92.0 (dt, 1J_C,F = 190.5, 3J_C,F = 15.0 Hz, 3C), 70.2 (q, 4J_C,F = 2.1 Hz), 46.7–46.2 (m, 3C), 42.4–42.1 (m, 3C), 37.0 (q, 3J_C,F = 11.4 Hz), 20.7; HRMS (EI) calcd for C₁₃H₁₇O₂F₃ 262.1181, found 262.1167.

1-((1,1-difluoroethoxy)methyl)-3,5,7-trifluoroadamantane (8): IR (neat) 2964, 1336, 1027 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.67 (s, 2H), 2.15-2.04 (m, 6H), 1.75 (t, J = 13.3 Hz, 3H), 1.69 (brs, 6H); ¹⁹F NMR (376 MHz, CDCl₃) δ –69.92 (q, J = 13.3 Hz, 2F), –144.07 (s, 3F); ¹³C NMR (100MHz, CDCl₃) δ 124.8 (t, 1J_C,F = 260.6 Hz), 92.1 (dt,
$^1J_{CF} = 191.6$, $^3J_{CF} = 3.2$ Hz, 3C), 69.2–69.0 (m), 47.0–46.2 (m, 3C), 42.5–42.2 (m, 3C), 37.1 (t, $^4J_{CF} = 11.5$ Hz), 22.5 (t, $^2J_{CF} = 32.6$ Hz); HRMS (EI) calcd for C$_{13}$H$_7$F$_3$O 284.11996, found 284.11940.

1,5,5,8-Tetrafluoro-4-oxatricyclo[4.3.1.13,8]undecane (10): mp 102–104 °C, IR (KBr) 2965, 1389, 1116 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.59 (s, 1H), 2.79 (brs, 1H), 2.31–2.25 (m, 4H), 2.18–2.04 (m, 2H), 2.03–2.00 (m, 2H), 1.91 (brs, 2H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –57.71 (s, 2F) –135.66 (s, 2F); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 128.2 (t, $^1J_{CF} = 248.2$ Hz), 93.0 (dd, $^1J_{CF} = 185.9$ Hz, $^3J_{CF} = 13.2$ Hz, 2C), 71.6–71.2 (m), 47.1 (t, $^3J_{CF} = 18.8$ Hz), 41.2–40.8 (m, 2C), 36.4–35.5 (m, 2C), 34.5–34.2 (m); HRMS (EI) calcd for C$_{10}$H$_{12}$F$_4$O 224.08243, found 224.08195.

1,3,5,5-Tetrafluoro-4-oxatricyclo[4.3.1.13,8]undecane (11): mp 85–87 °C, IR (KBr) 2961, 1371, 1111 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.77 (brs, 1H), 2.59–2.50 (m, 2H), 2.37–2.21 (m, 3H), 2.10–2.02 (m, 2H), 1.96–1.89 (m, 3H), 1.72–1.68 (m, 1H); $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ –59.87 (d, $J = 166.3$ Hz, 1F), –63.34 (d, $J = 166.3$ Hz, 1F), –95.10 (d, $J = 9.0$ Hz, 1F), –135.99 (s, 1F); $^{13}$C NMR (100MHz, CDCl$_3$) $\delta$ 124.4 (dt, $^3J_{CF} = 11.5$ Hz, $^1J_{CF} = 254.2$ Hz), 114.3 (dt, $^1J_{CF} = 217.0$ Hz, $^3J_{CF} = 15.3$ Hz), 90.2 (dd, $^1J_{CF} = 184.1$ Hz, $^3J_{CF} = 14.3$ Hz), 46.6 (dt, $^4J_{CF} = 2.9$ Hz, $^3J_{CF} = 23.8$ Hz), 40.6–40.1 (m, 2C), 39.8 (dt, $^3J_{CF} = 12.2$ Hz, $^2J_{CF} = 30.5$ Hz), 35.3–35.0 (m), 28.8 (dd, $^3J_{CF} = 12.4$ Hz, $^2J_{CF} = 10.5$ Hz), 28.2 (brd, $^4J_{CF} = 6.9$ Hz); HRMS (EI) calcd for C$_{10}$H$_{12}$F$_4$O 224.08243, found 224.08157.

Acknowledgment
We are grateful to prof. Hermann-Josef Frohn (University of Duisburg-Essen, Germany)
for his kind advice on the handling of BrF$_3$.

References


[6] Previously, the reaction of 1-cyano adamantane with BrF$_3$ was reported to give 3,5-difluoroadamantane [7].


[9] Conversion of an ester group to a difluoromethylene ether was previously reported by the reaction of $\alpha$-cyano esters with BrF$_3$ [7][10].

A similar fluorination reaction accompanying the rearrangement was reported in the reaction of a trivalent bromine reagent with benzaldehyde, see: M. Ochiai, A. Yoshimura, M. M. Hoque, T. Okubo, M. Saito, K. Miyamoto, Org. Lett. 13 (2011) 5568-5571.

BrF₃ can be stored in a cylinder at room temperature under complete blocking of humidity.