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Iodofluorination of alkenes using IF$_5$-pyridine-HF

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Abstract: Iodofluorination of alkenes was performed by using IF$_5$-pyridine-HF and a reductant such as KI or Sn powder. The addition of IF to the double bond proceeded with stereo- and regio-selectivity. In the reaction with internal alkenes, the trans-addition product was obtained selectively. With terminal alkenes, the addition took place regioselectively to give I-iodo-2-fluoroalkanes.

Key words: fluorine, addition, stereoselective synthesis, halogenation, alkenes

Iodofluorination of alkenes is a convenient method for the synthesis of organofluorine compounds. Iodofluorination was originally performed by iodine monofluoride generated from I$_2$ and F$_2$ gas. As alternatives to the hazardous F$_2$ gas and I$_2$, reagents for F$^-$ and I$^+$ sources have been used to generate “IF” species for the iodofluorination. However, some of the reagents for the F$^-$ source are still hazardous, while some reagents for I$^+$ source are not readily available. Moreover, the reactivity of the IF species is dependent on the reagents used. Therefore, a more convenient and effective method for the iodofluorination reaction of alkenes is still desired. Recently, we reported a stable fluorinating reagent, IF$_5$-pyridine-HF, and its application to fluorination reactions. During the course of our study on the new fluorination reaction using IF$_5$-pyridine-HF, we found that this reagent can be employed in the iodofluorination of alkenes via reduction with KI or Sn, to obtain the corresponding iodofluoroalkane (Equation 1).

![Equation 1 Iodofluorination of alkenes using IF$_5$-pyridine-HF](image)

Although IF$_5$-pyridine-HF is unreactive to alkenes, IF$_5$ was used for the iodofluorination of alkenes after reduction to IF species. Therefore, in the present study, reductants such as I$_2$, KI, and NaI were used to generate IF species from IF$_5$-pyridine-HF. All the reductants used were found to be effective for the iodofluorination of cyclooctadecene 1a, and 1-fluoro-2-iodocyclooctadecene 2a was obtained in good yield (Table 1).

![Table 1 Iodofluorination of 1a by IF$_5$-pyridine-HF and a reductant](table)

The use of KI was favorable for the reaction of 1a, and 2a was obtained in good yield (Entry 1 in Table 2). In contrast, when KI was used in the reaction of 1-decadiene 1b, 2-fluoro-1-iododecane 2b was formed as the major product, but its regioisomer, 1-fluoro-2-iododecane, was also formed (91:9 ratio). For the reaction of 1b, Sn powder was more suitable, and 2b was selectively formed in 82 % yield (Entry 2). The present iodofluorination reaction proceeded stereoselectively, and 1-fluoro-2-iodocyclohexane 2c was selectively formed from cyclohexene 1c (Entry 3). Furthermore, when trans- and cis-5-decenes (1e and 1f) were used, the corresponding (5S*, 6R*)-5-fluoro-6-iododecane 2e and (5R*, 6R*)-5-fluoro-6-iododecane 2f were selectively formed (Entries 5 and 6). As the reaction proceeded under mild conditions, functional groups such as ester and free hydroxy group were tolerated (Entries 7, 8, 9, and 10). Furthermore, it was possible to distinguish between two double bonds of different reactivities. In the reaction of diene 1i, where one double bond is less reactive than the other due to the electron-withdrawing substituent, the iodofluorination selectively took place at the more reactive double bond (Entry 9). Iodofluorination of electron-deficient alkenes is rare, and there are only a few reported examples. The present iodofluorination is applicable to wide variety of alkenes, including electron-deficient alkenes. When 4-methylpent-3-en-2-one 1j was used in the reaction, the corresponding iodofluorination product 2j was obtained regioselectively (Entry 10).
Table 2  Iodofluorination of alkenes using IF₅-pyridine-HF and a reductant

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkene</th>
<th>Reductant</th>
<th>Product</th>
<th>Yield, %b</th>
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<td>KI</td>
<td><img src="image" alt="2a" /></td>
<td>78</td>
</tr>
<tr>
<td>2c</td>
<td><img src="image" alt="1b" /></td>
<td>Sn</td>
<td><img src="image" alt="2b" /></td>
<td>82</td>
</tr>
<tr>
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<td><img src="image" alt="1c" /></td>
<td>Sn</td>
<td><img src="image" alt="2c" /></td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="1d" /></td>
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<td><img src="image" alt="1e" /></td>
<td>KI</td>
<td><img src="image" alt="2e" /></td>
<td>57</td>
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<td>6</td>
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<tr>
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<td>77</td>
</tr>
<tr>
<td>8c</td>
<td><img src="image" alt="1h" /></td>
<td>Sn</td>
<td><img src="image" alt="2h" /></td>
<td>(86)</td>
</tr>
<tr>
<td>9</td>
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<tr>
<td>10</td>
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<td>KI</td>
<td><img src="image" alt="2j" /></td>
<td>(67)</td>
</tr>
</tbody>
</table>

*aIf otherwise not mentioned, the reaction was carried out at room temperature for 17 h using 1 eq. of IF₅-pyridine-HF and KI as a reductant in CH₂Cl₂.

bIsolated yield based on alkene used. In parentheses, ¹⁹F NMR yield.

c3 eq. of IF₅-pyridine-HF and 2 eq of Sn powder were used.

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. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. Sn powder of ~45 µm and 99.5 % purity was used. IF₅ in a cylinder was supplied by Daikin industries, Ltd.
Anhydrous HF in a cylider was purchased from Stella Chemifa Corporation. IF₅-pyridine-HF was prepared from IF₅ and pyridine-HF by the previously reported method. Glassware can be used for the reaction, but use of Teflon™ or polyethylene ware is recommended.

### General Procedure of Iodofluorination of Alkenes Using KI as a Reductant

To a CH₂Cl₂ solution (3 mL) of an alkene (0.5 mmol), KI (0.5 mmol) was added at 0 °C, and IF₅-pyridine-HF (161 mg, 0.5 mmol) was added at −5 °C KI (83 mg, 0.5 mmol), and the mixture was stirred at 0 °C for 30 min and at room temperature for 17 h. Then, the mixture was poured into water (20 mL) and aq Na₂S₂O₃ (20 mL) and extracted with ether (20 mL x 3). The combined organic layer was washed with aq Na₂S₂O₃ (20 mL) and aq NaHCO₃ (20 mL), dried over MgSO₄. After concentration, the product was isolated by column chromatography (silica gel).

### General Procedure of Iodofluorination of Alkenes Using Sn powder as a Reductant

To a CH₂Cl₂ solution (3 mL) of an alkene (0.5 mmol) and Sn powder (119 mg, 1.0 mmol), and the mixture was stirred at 0 °C for 30 min and at room temperature for 17 h. The solid part was removed by filtration through a celite, and the filtrate was poured into water (20 mL). The product was extracted with ether (20 mL x 3), and the combined organic layer was washed with aq Na₂S₂O₃ (20 mL) and aq NaHCO₃ (20 mL), dried over MgSO₄. After concentration, the product was isolated by column chromatography (silica gel).

### 1-Fluoro-2-iodocyclohexane (2a)

The reaction was performed using KI as the reductant, and 2a was isolated by column chromatography (silica gel/hexane) in 78 % yield as a colorless liquid.

IR (neat): 3033, 1454, 960, 699 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 4.48-4.31 (m, 2H), 2.41-2.36 (m, 1H), 2.25-2.06 (m, 3H), 1.74 (s, 2H), 1.47-1.27 (m, 2H); 2J_F = 4.7 Hz, 3J_F = 21.9 Hz, 2H, 2J_F = 28.6 Hz.

### 2-Fluoro-1-iodododecane (2b)

The reaction was performed using Sn powder as the reductant, and 2b was isolated by column chromatography (silica gel/hexane) in 82 % yield as a white solid.

Mp. 27-31°C.

IR (KBr): 2923, 1465, 884 cm⁻¹.

### 2a

1F NMR (376 MHz, CDCl₃): δ = –159.2 (brs, 1F)((lit2b. –167.10 (ddd, J₉₋₁₇₇.₄ Hz, 3JC_F = 21.0 Hz), 34.9 (d, 2JC_F = 21.0 Hz), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8 (d, 3JC_F = 4.7 Hz), 22.9, 14.2, 7.26 (d, 2JC_F = 24.8 Hz).

### trans-1-Fluoro-2-iododicyclohexane (2c)

The reaction was performed using Sn powder as the reductant, and 2c was isolated by column chromatography (silica gel/hexane) in 54 % yield as a colorless liquid.

IR (neat): 2941, 1449, 950 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 4.65-4.48 (dm, J = 49.4 Hz, 1H), 4.15-4.09 (m, 1H), 1.96-1.24 (m, 12H), 0.88 (t, J = 7.2 Hz, 6H).

19F NMR (376 MHz, CDCl₃): –168.55 (brs, 1F)(lit2b. –171.5 (m, 1F)).

13C NMR (100 MHz, CDCl₃): 92.8 (d, 1JC_F = 177.4 Hz), 34.7 (d, 2JC_F = 19.0 Hz), 33.4 (d, 3JC_F = 2.9 Hz), 30.4 (d, 4JC_F = 21.9 Hz), 24.4-23.7 (4C), 23.4, 22.3, 22.0, 20.5 (d, 5JC_F = 4.8 Hz).

### 1-Fluoro-2-ido-1-phenylethane (2d)

The reaction was performed using KI as the reductant, and the yield of 2d was determined to be 52% by 19F NMR using fluorobenzene as an internal standard, and pure 2d was isolated by column chromatography (silica gel/hexane).

IR (neat): 3033, 1454, 960, 699 cm⁻¹.

1H NMR (400 MHz, CDCl₃): 4.65-4.48 (dm, J = 49.4 Hz, 1H), 4.15-4.09 (m, 1H), 1.96-1.24 (m, 12H), 0.88 (t, J = 7.2 Hz, 6H).

19F NMR (376 MHz, CDCl₃): –159.2 (brs, 1F)((lit2b. –167.10 (ddd, J₉₋₁₇₇.₄ Hz, 3JC_F = 21.0 Hz), 34.9 (d, 2JC_F = 21.0 Hz), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8 (d, 3JC_F = 4.7 Hz), 22.9, 14.2, 7.26 (d, 2JC_F = 24.8 Hz).

### 2d

19F NMR (376 MHz, CDCl₃): –159.2 (brs, 1F)((lit2b. –167.10 (ddd, J₉₋₁₇₇.₄ Hz, 3JC_F = 21.0 Hz), 34.9 (d, 2JC_F = 21.0 Hz), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8 (d, 3JC_F = 4.7 Hz), 22.9, 14.2, 7.26 (d, 2JC_F = 24.8 Hz).

### (5S*, 6R*)-5-Fluoro-6-iododecane (2e)

The reaction was performed using KI as the reductant, and 2a was isolated by column chromatography (silica gel/hexane) in 57 % yield as a colorless liquid.

IR (neat): 2957, 1466 cm⁻¹.

1H NMR (400 MHz, CDCl₃): δ = 7.44-7.34 (m, 5H), 5.55 (dd, J = 47.6, 7.6, 5.6 Hz, 1H), 3.54-3.43 (m, 2H); 19F NMR (376 MHz, CDCl₃): δ = –166.6 to –166.9 (m, 1F)(lit2b. –167.10 (ddd, J₉₋₁₇₇.₄ Hz, 3JC_F = 21.0 Hz), 129.5, 129.0 (2C), 125.9 (d, 2JC_F = 6.6 Hz, 2C), 93.4 (d, 3JC_F = 180.2 Hz), 7.7 (d, 4JC_F = 28.6 Hz).

19F NMR (376 MHz, CDCl₃): δ = –166.6 to –166.9 (m, 1F)(lit2b. –167.10 (ddd, J₉₋₁₇₇.₄ Hz, 3JC_F = 21.0 Hz), 129.5, 129.0 (2C), 125.9 (d, 2JC_F = 6.6 Hz, 2C), 93.4 (d, 3JC_F = 180.2 Hz), 7.7 (d, 4JC_F = 28.6 Hz).

1H NMR (400 MHz, CDCl₃): δ = 4.53-4.36 (dm, J = 49.4 Hz, 1H), 3.35-3.27 (m, 2H), 1.77-1.69 (m, 2H), 1.44-1.27 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H).

C NMR (100 MHz, CDCl₃): δ = –171.40 to –171.76 (m, 1F) ((lit2a. –171.5 (m, 1F)).
4.8 Hz), 33.8 (d, $J_{CF} = 21.1$ Hz), 31.9, 27.4 (d, $J_{CF} = 1.9$ Hz), 22.8, 22.2, 14.3 (2C).

(5R*, 6R*)-5-Fluoro-6-iododecane (2f)
The reaction was performed using KI as the reductant, and 2f was isolated by column chromatography (silica gel/hexane) as a white solid. IR (KBr): 3304 (-OH), 2921, 1467, 1070 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 4.14-3.99$ (m, 2H), 1.99-1.28 (m, 12H), 0.93 (t, $J = 7.2$ Hz, 6H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = –171.4$ to –171.8 (m, 1F).

13C NMR (100 MHz, CDCl$_3$): $\delta = 95.1$ (d, $J_{CF} = 179.3$ Hz), 38.8 (d, $J_{CF} = 22.0$ Hz), 36.1, 34.1 (d, $J_{CF} = 20.0$ Hz), 31.8, 27.3 (d, $J_{CF} = 3.8$ Hz), 22.5, 22.0, 14.1, 14.0.

HRMS (EI) Calcd for C$_{10}$H$_{20}$FI 286.05908, found 286.05937.

13C NMR (100 MHz, CDCl$_3$): $\delta = 3.8$ Hz), 22.5, 22.0, 14.1, 14.0.

HRMS (EI) Calcd for C$_{10}$H$_{20}$FI 286.05908, found 286.05937.

Methyl 2-Fluoro-1-iodoundecanoate (2g)
The reaction was performed using Sn powder as the reductant, and 2g was isolated by column chromatography (silica gel/hexane-ether) in 82 % yield as a white solid.

Mp. 35-39 °C.

IR (KBr): 2924, 1736 (C=O), 1437, 1173 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 4.52-4.36$ (dm, $J = 48.5$ Hz, 1H), 3.67 (s, 3H), 3.37-3.24 (m, 2H), 2.32 (t, $J = 7.4$ Hz, 2H), 1.78-1.61 (m, 4H), 1.46-1.30 (m, 10H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = –171.4$ to –171.8 (m, 1F).

13C NMR (100 MHz, CDCl$_3$): $\delta = 174.4, 92.3$ (d, $J_{CF} = 177.4$ Hz), 51.6, 34.8 (d, $J_{CF} = 21.0$ Hz), 34.2, 29.3, 29.2 (2C), 29.1, 25.0, 24.7 (d, $J_{CF} = 3.8$ Hz), 7.2 (d, $J_{CF} = 24.8$ Hz).

11-Fluoro-10-iodoundecan-1-ol (2h)
The reaction was performed using Sn powder as the reductant, and the yield of 2h was determined to be 86 % by $^{19}$F NMR using fluorobenzene as an internal standard. Pure 2h was isolated by column chromatography (silica gel/hexane-ether) as a white solid.

Mp. 48-50 °C.

IR (KBr): 3304 (-OH), 2921, 1467, 1070 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 4.54-4.37$ (dm, $J = 48.0$ Hz, 1H), 3.64 (t, $J = 6.6$ Hz, 2H), 3.37-3.24 (m, 2H), 1.79-1.30 (m, 16H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = –170.9$ to –171.2 (m, 1F).

13C NMR (100 MHz, CDCl$_3$): $\delta = 92.3$ (d, $J_{CF} = 177.4$ Hz), 63.1, 34.9 (d, $J_{CF} = 21.0$ Hz), 32.8, 29.5, 29.4 (2C), 29.3, 25.8, 24.8 (d, $J_{CF} = 4.8$ Hz), 7.22 (d, $J_{CF} = 25.7$ Hz).

(5)-Ethyl 7-fluoro-6-iodo-3,7-dimethyloct-2-enoate (2i)
The reaction was performed using KI as the reductant, and 2i was isolated by column chromatography (silica gel/hexane-ether) in 67 % yield as a colorless liquid.

IR (KBr): 3304 (-OH), 2921, 1467, 1070 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 5.73$ (s, 1H), 4.15 (q, $J = 7.2$ Hz, 2H), 3.98-3.92 (m, 1H), 2.53-2.46 (m, 1H), 2.26-2.16 (m, 1H), 2.16 (s, 3H), 2.04-1.93 (m, 1H), 1.90-1.79 (m, 1H), 1.60 (d, $J = 15.2$ Hz, 3H), 1.55 (d, $J = 15.2$ Hz, 3H), 1.28 (t, $J = 14.4$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = –133.6$ (brs, 1F).

13C NMR (100 MHz, CDCl$_3$): $\delta = 166.9, 157.8, 117.1, 96.4$ (d, $J_{CF} = 173.6$ Hz), 59.9, 42.7 (d, $J_{CF} = 24.8$ Hz), 41.1, 32.6 (d, $J_{CF} = 3.8$ Hz), 27.6 (d, $J_{CF} = 24.8$ Hz), 23.7 (d, $J_{CF} = 24.8$ Hz), 19.0, 14.6.

HRMS (EI) Calcd for C$_{12}$H$_{20}$O$_3$FNa 365.03842, found 365.03894.

4-Fluoro-3-iodo-4-methylpentan-2-one (2j)
The reaction was performed using KI as the reductant, and the yield of 2j was determined to be 67 % by $^{19}$F NMR using fluorobenzene as an internal standard and pure 2j was isolated by column chromatography (silica gel/hexane-ether) as a colorless liquid.

IR (KBr): 3304 (-OH), 2921, 1467, 1070 cm$^{-1}$.

1H NMR (400 MHz, CDCl$_3$): $\delta = 4.64$ (d, $J = 14.8$ Hz, 1H), 2.64 (s, 3H), 1.64 (d, $J = 12.0$ Hz, 3H), 1.59 (d, $J = 10.8$ Hz, 3H).

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta = –130.8$ (brs, 1F).

13C NMR (100 MHz, CDCl$_3$): $\delta = 201.5, 93.9$ (d, $J_{CF} = 177.3$ Hz), 41.0 (d, $J_{CF} = 23.9$ Hz), 28.2 (d, $J_{CF} = 3.8$ Hz), 25.8 (d, $J_{CF} = 22.9$ Hz), 25.7 (d, $J_{CF} = 23.8$ Hz).

HRMS (EI) Calcd for C$_{12}$H$_{10}$OFI 243.97604, found 243.97507.

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References


