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Iodofluorination of alkenes using IF₅-pyridine-HF

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Abstract: Iodofluorination of alkenes was performed by using IF₅-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 1-iodo-2-fluoroalkanes.

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

Iodofluorination of alkenes is a convenient method for the synthesis of organofluorine compounds¹. Iodofluorination was originally performed by iodine monofluoride generated from I₂ and F₂ gas². As alternatives to the hazardous F₂ gas and I₂, reagents for F⁻ and I⁺ sources have been used to generate "IF" species for the iodofluorination². 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^{1b}. Therefore, a more convenient and effective method for the iodofluorination reaction of alkenes is still desired. Recently, we reported a stable fluorinating reagent, IF₅-pyridine-HF, and its application to fluorination reactions³. During the course of our study on the new fluorination reaction using IF₅-pyridine-HF, we found that this reagent can be employed in the iodofluorination of alkene **1** via reduction with KI or Sn, to obtain the corresponding iodoalkane **2** (Equation 1).

Equation 1 Iodofluorination of alkenes using IF₅-pyridine-HF

Although IF₅-pyridine-HF is unreactive to alkenes, IF₅ was used for the iodofluorination of alkenes after reduction to IF species⁴. Therefore, in the present study, reductants such as I₂, KI, and NaI were used to generate IF species from IF₅-pyridine-HF. All the reductants used were found to be effective for the iodofluorination of cyclododecene **1a**, and 1-fluoro-2-iodocyclododecene **2a** was obtained in good yield (Table 1).

Table 1 Iodofluorination of **1a** by IF₅-pyridine-HF and a reductant^a

Entry	Reductant	Yield % ^b
1	I ₂	78
2	KI	78
3	NaI	78

^aThe reaction was carried out at room temperature for 17 h using 1 eq. of IF₅-pyridine-HF and reductant in CH₂Cl₂.

^bIsolated yield based on **1a**.

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-dodecene **1b**, 2-fluoro-1-iodododecene **2b** was formed as the major product, but its regioisomer, 1-fluoro-2-iodododecene, 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 *trans*-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 (5*S**, 6*R**)-5-fluoro-6-iododecane **2e** and (5*R**, 6*R**)-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^{2c,2m}. 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^a

Entry	Alkene	Reductant	Product	Yield, % ^b
1	1a	KI	2a	78
2 ^c	1b	Sn	2b	82
3 ^c	1c	Sn	2c	54
4	1d	KI	2d	(52)
5	1e	KI	2e	57
6	1f	KI	2f	58
7 ^c	1g	Sn	2g	77
8 ^c	1h	Sn	2h	(86)
9	1i	KI	2i	67
10	1j	KI	2j	(67)

^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.

^c 3 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 cyclidizer was purchased from Stella Chemifa Corporation. IF₅-pyridine-HF was prepared from IF₅ and pyridine-HF by the previously reported method³. 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) and IF₅-pyridine-HF (161 mg, 0.5 mmol) was added at 0 °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 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 IF₅-pyridine-HF (321 mg, 1.0 mmol) was added at 0 °C 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. Then, 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-iodocyclododecane (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): 2926, 1469, 997 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ = 4.48-4.31 (m, 2H), 2.03-1.34 (m, 20H);

¹⁹F NMR (376 MHz, CDCl₃): -168.55 (brs, 1F)(lit^{2s}. -169.5));

¹³C NMR (100 MHz, CDCl₃): 92.8 (d, ¹J_{C-F} = 178.3 Hz), 34.7 (d, ²J_{C-F} = 19.0 Hz), 33.4 (d, ³J_{C-F} = 2.9 Hz), 30.4 (d, ²J_{C-F} = 21.9 Hz), 24.4-23.7 (4C), 23.4, 22.3, 22.0, 20.5 (d, ³J_{C-F} = 4.8 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.

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).

¹⁹F NMR (376 MHz, CDCl₃): δ = -171.40 to -171.76 (m, 1F) ((lit^{2a}. -171.5 (m, 1F)).

¹³C NMR (100 MHz, CDCl₃): δ = 92.3 (d, ¹J_{C-F} = 177.4 Hz), 34.9 (d, ²J_{C-F} = 21.0 Hz), 32.0, 29.7, 29.6, 29.5, 29.4, 29.3, 24.8 (d, ³J_{C-F} = 4.7 Hz), 22.9, 14.2, 7.26 (d, ²J_{C-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), 2.41-2.36 (m, 1H), 2.25-2.16 (m, 1H), 2.00-1.82 (m, 2H), 1.64-1.55 (m, 2H), 1.47-1.27 (m, 2H);

¹⁹F NMR (376 MHz, CDCl₃): -159.2 (brs, 1F)((lit^{2b}. -160.0 (dm, *J* = 48 Hz));

¹³C NMR (100 MHz, CDCl₃): 95.0 (d, ¹J_{C-F} = 182.1 Hz), 36.8, 31.6(d, ²J_{C-F} = 19.1 Hz), 31.2 (d, ²J_{C-F} = 19.0 Hz), 26.5, 23.2 (d, ³J_{C-F} = 9.6 Hz)

1-Fluoro-2-iodo-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): δ = 7.44-7.34 (m, 5H), 5.55 (ddd, *J* = 47.6, 7.6, 5.6 Hz, 1H), 3.54-3.43 (m, 2H);

¹⁹F NMR (376 MHz): δ = -166.6 to -166.9 (m, 1F)(lit^{2b}. -167.10 (ddd, *J* = 40.8, 24.2, 16.6 Hz));

¹³C NMR (100 MHz): δ = 138.2 (d, ²J_{C-F} = 21.0 Hz), 129.5, 129.0 (2C), 125.9 (d, ³J_{C-F} = 6.6 Hz, 2C), 93.4 (d, ¹J_{C-F} = 180.2 Hz), 7.7 (d, ²J_{C-F} = 28.6 Hz).

(5S*, 6R*)-5-Fluoro-6-iodododecane (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 = 4.42-4.11 (dm, *J* = 48.4 Hz, 1H), 4.16-4.11 (m, 1H), 1.96-1.24 (m, 12H), 0.93 (t, *J* = 7.2 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃): δ = -173.3 to -173.6 (m, 1F)(lit^{2d}. -174.05 to -174.37 (m, 1F))

¹³C NMR (100 MHz, CDCl₃): δ = 96.0 (d, ¹J_{C-F} = 177.2 Hz), 38.5 (d, ²J_{C-F} = 21.0 Hz), 34.8 (d, ³J_{C-F} =

4.8 Hz), 33.8 (d, $^2J_{C-F}$ = 21.1 Hz), 31.9, 27.4 (d, $^3J_{C-F}$ = 1.9 Hz), 22.8, 22.2, 14.3 (2C).

(5*R**, 6*R**)-5-Fluoro-6-iododecane (**2f**)

The reaction was performed using KI as the reductant, and **2f** was isolated by column chromatography (silica gel/hexane) in 58 % yield as a colorless liquid.

IR (neat): 2957, 1465 cm⁻¹;

¹H NMR (400 MHz, CDCl₃): δ = 4.14-3.99 (m, 2H), 1.99-1.28 (m, 12H), 0.93 (t, J = 7.2 Hz, 6H).

¹⁹F NMR (376 MHz, CDCl₃): δ = -176.1 to -176.2 (m, 1F).

¹³C NMR (100 MHz, CDCl₃): δ = 95.1 (d, $^1J_{C-F}$ = 179.3 Hz), 38.8 (d, $^2J_{C-F}$ = 22.0 Hz), 36.1, 34.1 (d, $^2J_{C-F}$ = 20.0 Hz), 31.8, 27.3 (d, $^3J_{C-F}$ = 3.8 Hz), 22.5, 22.0, 14.1, 14.0.

HRMS (EI) Calcd for C₁₀H₂₀FI 286.05937, found 286.05908.

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, CDCl₃): δ = 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).

¹⁹F NMR (376 MHz, CDCl₃): δ = -171.4 to -171.8 (m, 1F) (lit²¹. -171.3 (m))

¹³C NMR (100 MHz, CDCl₃): δ = 174.4, 92.3 (d, $^1J_{C-F}$ = 177.4 Hz), 51.6, 34.8 (d, $^2J_{C-F}$ = 21.0 Hz), 34.2, 29.3, 29.2 (2C), 29.1, 25.0, 24.7 (d, $^3J_{C-F}$ = 3.8 Hz), 7.2 (d, $^2J_{C-F}$ = 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 ¹⁹F 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, CDCl₃): δ = 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).

¹⁹F NMR (376 MHz, CDCl₃): δ = -170.9 to -171.2 (m, 1F) (lit²¹. -171.2 to -171.6 (m, 1F)).

¹³C NMR (100 MHz, CDCl₃): δ = 92.3 (d, $^1J_{C-F}$ = 177.4 Hz), 63.1, 34.9 (d, $^2J_{C-F}$ = 21.0 Hz), 32.8, 29.5, 29.4 (2C), 29.3, 25.8, 24.8 (d, $^3J_{C-F}$ = 4.8 Hz), 7.22 (d, $^2J_{C-F}$ = 25.7 Hz).

(*E*)-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 (neat) 2983, 1715 (C=O), 1650, 1225, 1147 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 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);

¹⁹F NMR (376 MHz, CDCl₃): δ = -133.6 (brs, 1F);

¹³C NMR (100 MHz, CDCl₃): δ = 166.9, 157.8, 117.1, 96.4 (d, $^1J_{C-F}$ = 173.6 Hz), 59.9, 42.7 (d, $^2J_{C-F}$ = 24.8 Hz), 41.1, 32.6 (d, $^3J_{C-F}$ = 3.8 Hz), 27.6 (d, $^2J_{C-F}$ = 24.8 Hz), 23.7 (d, $^2J_{C-F}$ = 24.8 Hz), 19.0, 14.6.

HRMS (EI) Calcd for C₁₂H₂₀O₂FINa 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 ¹⁹F NMR using fluorobenzene as an internal standard and pure **2j** was isolated by column chromatography (silica gel/hexane-ether) as a colorless liquid.

IR (neat) 2987, 1705 (C=O), 1358 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 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).

¹⁹F NMR (376 MHz, CDCl₃): δ = -130.8 (brs, 1F).

¹³C NMR (100 MHz, CDCl₃): δ = 201.5, 93.9 (d, $^1J_{C-F}$ = 177.3 Hz), 41.0 (d, $^2J_{C-F}$ = 23.9 Hz), 28.2 (d, $^3J_{C-F}$ = 3.8 Hz), 25.8 (d, $^2J_{C-F}$ = 22.9 Hz), 25.7 (d, $^2J_{C-F}$ = 23.8 Hz).

HRMS (EI) Calcd for C₆H₁₀OFI 243.97604, found 234.97507.

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References

- (1) As for the review articles of iodofluorination reaction, see: (a) Rozen, S. In *Fluorine-Containing Reagents*; Paquette, L. A., Ed.; Wiley: Chichester, **2007**, 336. (b) Shellhamer, D. F.; Heasley, V. L. In *Advances in Organic synthesis*; Laali, K. K., Ed.; Bentham Science Publication LTD: Hilversum, **2006**, 43. (c) Hiyama, T. In *Organofluorine Compounds*; Yamamoto, H., Ed.; Springer: Heidelberg, **2000**, 56.
- (2) (a) Walkowiak, J.; Marciniak, B.; Koroniak, H. *J. Fluorine Chem.* **2012**, *143*, 287. (b) Crespo, L. T. C.; Ribeiro, R. S.; Mattos, M. C. S.; Esteves, P. M. *Synthesis* **2010**, 2379. (c) Nagura, H.; Kuribayashi, S.; Ishiguro, Y.; Inagi, S.; Fuchigami, T. *Tetrahedron* **2010**, *66*, 183. (d) Conte, P.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* **2006**, *47*, 273. (e) Shimizu, M.; Okamura, M.; Fujisawa, T. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2596. (f) Yoshino, H.; Matsumoto, K.; Hagiwara, R.; Ito, Y.; Oshima, K.; Matsubara, S. *J. Fluorine Chem.* **2006**, *127*, 29. (g) Yoshino, H.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2005**, *126*, 121. (h) Yoshino, H.; Matsubara, S.; Oshima, K.; Matsumoto, K.; Hagiwara, R.; Ito, Y. *J. Fluorine Chem.* **2004**, *125*, 455. (i) Kobayashi, S.; Sawaguchi, M.; Ayuba, S.; Fukuhara, T.; Hara, S. *Synlett* **2001**, 1938. (j) Shellhamer, D. F.; Jones, B. C.; Pettus, B. J.; Pettus, T. L.; Stringer, J. M.; Heasley, V. L. *J. Fluorine Chem.* **1998**, *88*, 37. (k) Tamura, M.; Shibakami, M.; Sekiya, A.; *Synthesis* **1995**, 515. (l) Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1799. (m) Barluenga, J.; Campos, P. J.; González, J. M. Suárez, J. L., Asensio, G. *J. Org. Chem.* **1991**, *56*, 2234. (n) Kuroboshi, M.; Hiyama, T. *Synlett* **1991**, 185. (o) Kuroboshi, M.; Hiyama, T.; *Tetrahedron Lett.* **1991**, *32*, 1215. (p) Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* **1990**, *31*, 3167. (q) Chamorro, F. C. E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* **1989**, *54*, 4294. (r) Evans, R. D.; Schauble, J. H. *Synthesis*, **1987**, 551. (s) Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* **1987**, 562. (t) Barluenga, J. González, J. M.; Campos, P. J.; Asensio, G. *Angew. Chem. Int. Ed.* **1985**, *24*, 319. (u) Rozen, S.; Brand, M. *J. Org. Chem.* **1985**, *50*, 3342. (v) Rozen, S.; Brand, M. *Tetrahedron Lett.* **1980**, *21*, 4543.
- (3) (a) Hara, S.; Monoi, M.; Umemura, R.; Fuse, C. *Tetrahedron* **2012**, *68*, 10145. (b) Kunigami, M.; Hara, S. *J. Fluorine Chem.* **2014**, *167*, 101.
- (4) Chambers, R. D.; Cooper, J. A.; Copin, E.; Sandford, G. *Chem. Commun.* **2001**, 2428.