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Selective Halofluorination Reaction Mediated by Hexafluoropropene-Diethylamine Complex and *N*-Haloimides

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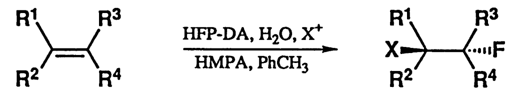
Synopsis. Olefins were halofluorinated with hexafluoropropene–diethylamine and *N*-haloimides in a highly regio- and stereoselective manner.

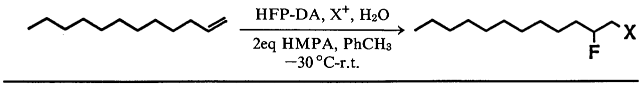
Growing interests in organofluorine chemistry prompt us to develop new methodologies for the introduction of a fluorine atom into molecules in highly selective ways.[1)] For the introduction of a fluorine atom into molecules, halofluorination of olefins is one of the most straightforward ways.[2)] However, there still remain several important problems associated mainly with selectivities of the reaction, the tedious experimental procedures, and the need for the use of special reaction vessels. A non-trivial problem often accompanies halofluorinations, which concerns the use of hydrogen fluoride-a readily available and inexpensive fluoride ion source but the handling holds certain problems,[2a)] and in situ generation of a limited amount of hydrogen fluoride in the reaction medium appears to circumvent some of the problems associated with the conventional halofluorination reactions.

We have now found that the use of hexafluoropropene–diethylamine complex (HFP–DA)[3)] and *N*-haloimides enables us to carry out halofluorination reactions quite readily with high regio-and stereoselectivities in an ordinary glassware vessel (Scheme 1). Initial survey of the hydrogen fluoride sources involves the use of acid fluorides (CH_3COF or CH_3SO_2F)–water or metal fluorides (CsF, KF, CoF_2, CoF_3, SbF_3 or SbF_5)–water, which resulted in utter failure. However, the combined use of HFP–DA complex and water revealed a ready accessibility of a limited amount of hydrogen fluoride, and the halofluorination of 1- dodecene was successfully performed (see Table 1).



Scheme 1.

Table 1. Halofluorination of 1-Dodecene[a)]



Entry	X^+ source (equiv)	H_2O (equiv)	Yield[b)]/%
1	DBH (1.5)[c)]	1.5	41
2	DBH (1.5)	1.5	51
3	DBH (1.7)	1.7	58
4	DBH (2.5)	2.5	64
5	DBH (2.5)	0	17
6	DCH (1.7)	1.7	44
7	NIS (1.7)	1.7	61
8	NIS (2.5)	2.5	78

a) The reaction was carried out at −30 °C—room temp for 24 h. b) Isolated yield. c) In 1,4-dioxane.

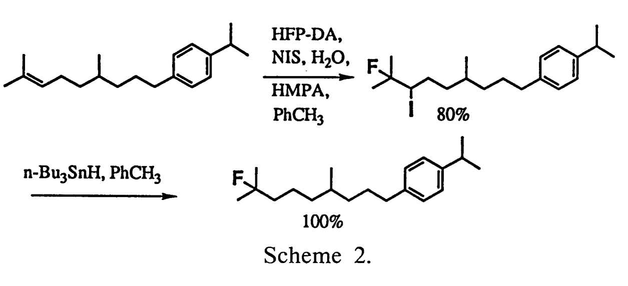
As shown in Table 1, the best result was obtained when the reaction was carried out with HFP–DA (2.0 equiv), *N*-iodosuccinimide (NIS, 2.0—2.5 equiv) or 1,3-dibromo-5,5-dimethylhydantoin (DBH, 2,0—2.5 equiv), H_2O (2.5 equiv) and hexamethylphosphoric triamide (HMPA, 2.0 equiv) in toluene at −30 °C to room temperature, whereas the reaction with 1,3-dichloro-5,5- dimethylhydantoin (DCH) met with moderate success presumably due to the less stable nature of the bridged halonium ion intermediate relative to its iodo or bromo counterpart (see Entries 3, 6, and 7). Under the optimum reaction conditions found for 1-dodecene a variety of olefins were converted into the corresponding halofluorides in good to excellent yields, and Table 2 shows the results.

Aromatic, aliphatic, and alicyclic olefins all underwent halofluorination with high regio- and stereoselectivities, where iodofluorination in general showed better yield than the bromo analogue. The fluorine atom was always introduced into the more substituted carbons and the trans orientation of fluorine to the other halogen was usually observed. In particular bromofluorination of (*Z*)-1-phenyl-1-propene is noteworthy; (1*R**, 2*R**)-bromofluoride **2** was formed predominantly in the present case (Entry 15), showing a distinct contrast to the methods reported previously[2l)] in which (1*R**, 2*S**)-isomer **1** is obtained as a sole product. Close examination of the present halofluorination reveals that the reaction proceeds most probably via generation of a limited amount of hydrogen fluoride from HFP–DA complex and H_2O followed by formation of XF species with NIS or DBH as the following equation shows.

$$Et_2NCF_2CHFCF_3 + H_2O \longrightarrow Et_2NCOCHFCF_3 + 2HF$$

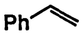
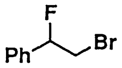
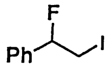
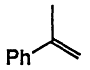
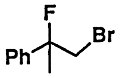
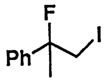
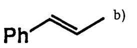
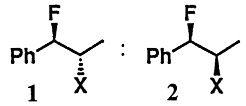
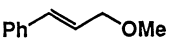
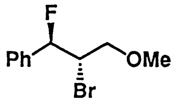
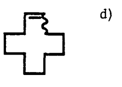
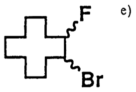
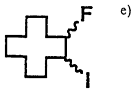
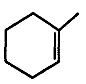
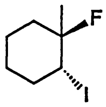
$$HF + X^+ \longrightarrow XF + H^+$$

Application of the present halofluorination reaction to the synthesis of a biologically interesting molecule was readily performed via iodofluorination followed by reduction with *n*-Bu_3SnH in good overall yield. Scheme 2 shows the preparation of a fluorine analogue

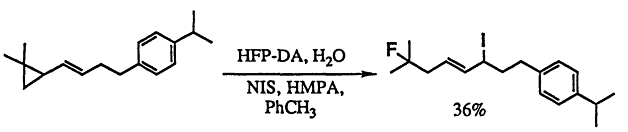


Scheme 2.

Table 2. Halofluorination of Olefins

Entry	Olefin	X^+ source	Product	Yield[a]/%
9		DBH		44
10		NIS		45
11		DBH		70
12		NIS		87
13	 [b]		 **1** : **2**	
		DBH	X=Br (94 : 6)	63
14		NIS	X=I (100 : 0)	93
15	 [c]	DBH	X=Br (17 : 83)	46
16		NIS	X=I (27 : 73)	38
17		DBH		78
18	 [d]	DBH	 [e]	46
19		NIS	 [e]	88
20		NIS		70

a) Isolated yield. b) *E*:*Z*=99 : 1. c) *E*:*Z*=10 : 90. d) A 1 : 1 mixture of (*E*)- and (*Z*)-isomers. e) A 1 : 1 mixture of *cis*- and *trans*-isomers.



Scheme 3.

of a juvenile hormone MV-678.[4]

Halofluorination reaction exercised in the present study provides a ready procedure for the introduction of fluorine into olefins with high regio- and stereoselectivities under mild conditions using a normal glassware apparatus. With slight modification of the substrate[5] the present halofluorination is further applicable to the synthesis of homologous fluorides, as Scheme 3 illustrates.

Experimental

Infrared spectra of neat liquid film samples (unless otherwise noted) were determined on a JASCO IR-810 spectrometer. ^{1}H NMR spectra were taken on a JEOL JNM-RMX60si spectrometer using tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded on a Hitachi R-24F spectrometer using $CFCl_3$ as an internal standard. Mass spectra were taken on a Shimadzu QP 1000 spectrometer. Preparative TLC plates were prepared with Merck Kiesel Gel PF_{254}. Column chromatography was carried out with silica gel (Wakogel C-300).

General Procedure for the Halofluorination of Olefins: The following is a typical experimental procedure. In an ordinary glassware vessel to NIS (562 mg, 2.5 mmol) were added toluene (1.5 ml), HFP-DA (0.87 ml, 2.5 mmol), HMPA (0.35 ml, 2.0 mmol), and H_2O (45 ml, 2.5 mmol) successively at −30 °C, and the mixture was stirred at that temperature for 15 min. A solution of 1-dodecene (169 mg, 1.0 mmol) in toluene (1.5 ml) was added and the reaction mixture was allowed to stand at room temperature for 24 h. The normal workup followed by purification by silica-gel column chromatography gave 2-fluoro-1-iodododecane (245 mg, 78%) as a colorless oil. The spectroscopic properties were identical with the reported data.[2d] IR (neat) 2940, 2860, 1470, 1420, 1380, 1195, 995, 800, 730, and 640 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.68—2.20 (21H, m), 3.22 (2H, dd, J=6.0, 18.0 Hz), 4.43

(1H, dm, J=48.0 Hz); ^{19}F NMR (CCl_4) δ=−173.0 (m).

1-Bromo-2-fluorododecane:2d) IR (neat) 2940, 2860, 1475, 1430, 1385, 1020, 830, 730, 695, and 685 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.67—2.10 (21H, m), 3.40 (2H, dd, J=6.0, 18.0 Hz), 4.53(1H, dm, J=48.0 Hz); ^{19}F NMR (CCl_4) δ=−180.0 (m).

2-Bromo-1-fluoro-1-phenylethane:2i). IR (neat) 3050, 3020, 2950, 2910, 1450, 1400, 1200, 1170, 1050, 955, 760, 740, 690, and 590 cm^{-1}; ^{1}H NMR (CCl_4) δ=3.65 (2H, dd, J=6.0, 21.0 Hz, a signal at δ=3.37 appears as multiplet), 5.50 (1H, dt, J=6.0, 46.0 Hz), 7.30 (5H, s); ^{19}F NMR (CCl_4) δ=−178.0 (m).

1-Fluoro-2-iodo-1-phenylethane:2i) IR (neat) 3050, 3020, 2950, 2910, 1450, 1400, 1200, 1170, 1050, 955, 760, 740, 690, and 570 cm^{-1}; ^{1}H NMR (CCl_4) δ=3.40 (2H, dd, J=6.0, 18.0 Hz, a signal at δ=3.27 appears as multiplet), 5.47 (1H, dt, J=6.0, 46.0 Hz), 7.26 (5H, s); ^{19}F NMR (CCl_4) δ=−170.0 (m).

1-Bromo-2-fluoro-2-phenylpropane:2g) IR (neat) 3060, 3030, 2990, 2930, 1500, 1450, 1380, 1295, 1220, 1180, 1060, 1050, 770, 700, and 595 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.78 (3H, d, J=22.0 Hz), 3.53 (2H, d, J=22.0 Hz, a signal at δ=3.40 appears as doublet, J=2.0 Hz), 7.28 (5H, s); ^{19}F NMR (CCl_4) δ=−151.0 (tq, J=19.0, 19.0 Hz).

1-Iodo-2-fluoro-2-phenylpropane:2i) IR (neat) 3060, 3020, 2980, 2925, 1450, 1380, 1290, 1200, 1170, 1070, 1050, 1030, 760, 750, and 580 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.82 (3H, d, J=22.0 Hz), 3.50 (2H, d, J=20.0 Hz), 7.33 (5H, s); ^{19}F NMR (CCl_4) δ=−145.0 (tq, J=19.0, 19.0 Hz).

(1*R, 2*S**)-2-Bromo-1-fluoro-1-phenylpropane:**2l) IR (neat) 3070, 3030, 2980, 2930, 1455, 1380, 1200, 1020, 970, 760, 700, 665, and 580 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.72 (2H, d, J=7.0 Hz), 3.83—4.67 (1H, m), 5.43 (1H, dd, J=6.0, 46.0 Hz), 7.30 (5H, s); ^{19}F NMR (CCl_4) δ=−182.0 (dd, δ=19.0, 47.0 Hz).

(1*R, 2*R**)-2-Bromo-1-fluoro-1-phenylpropane:**2l) IR (neat) 3070, 3000, 2920, 2850, 1450, 1000, 600, and 540 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.55 (2H, d, J=7.0 Hz), 3.73—4.67 (1H, m), 5.30 (1H, dd, J=6.0, 46.0 Hz), 7.30 (5H, s); ^{19}F NMR (CCl_4) δ=−176.0 (dd, J=19.0, 47.0 Hz).

(1*R, 2*S**)-1-Fluor-2-iodo-1-phenylpropane:**2l) IR (neat) 3060, 3030, 2970, 2920, 1500, 1450, 1380, 1160, 1150, 1060, 1010, 960, 760, and 700 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.92 (2H, d, J=7.0 Hz), 3.93—4.77 (1H, m), 5.50 (1H, dd, J=6.0, 47.0 Hz), 7.30 (5H, s);^{19}F NMR (CCl_4) δ=−176.0 (dd, J=19.0, 47.0 Hz).

(1*R, 2*R**)-1-Fluoro-2-iodo-1-pheylpropane:**2l) IR (neat) 3060, 3020, 2970, 2910, 1500, 1450, and 760 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.83 (2H, d, J=7.0 Hz), 3.87—4.72 (1H, m), 5.22(1H, dd, J=6.0, 46.0 Hz), 7.32 (5H, s); ^{19}F NMR (CCl_4)δ=−169.0 (dd, J=19.0, 47.0 Hz).

(1*R, 2*S**)-2-Bromo-1-fluoro-3-methoxy-1-phenylpropane:**2l) IR (neat) 3050, 3020, 2980, 2920, 2810, 1460, 1190, 1120, 1010, 960, 760, 700, 590, and 530 cm^{-1}; ^{1}H NMR (CCl_4) δ=3.33 (3H, s), 4.07—4.57 (1H, m), 5.56 (1H, dd, J=6.0, 46.0 Hz), 7.27 (5H, s);^{19}F NMR (CCl_4) δ=−178.0 (dd, J=18.0, 46.0 Hz) MS m/z (rel intensity in %) 227 (M$^+$−19, 3), 226 (M$^+$−20, 3), 184 (24), 182 (27), 166 (12), 147 (23), 135 (94), 115 (60), 109 (100).

1-Bromo-2-fluorocyclododecane:2g) IR (neat) 2950, 2850, 1470, 1440, and 1000 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.07—2.40 (20H, m), 3.83—5.30 (2H, m);^{19}F NMR (CCl_4) δ=−183 (m), −186 (m).

2-Fluoro-1-iodocyclododecane:2g) IR (neat) 3060, 3045, 2980, 2825, 1460, 1210, 1085, 960, 760, and 700, cm^{-1}; ^{1}H NMR (CCl_4)δ=1.07—2.30 (20H, m), 3.63—4.97 (2H, m); ^{19}F NMR (CCl_4) δ=−173 (m), 179 (m).

(1*R, 2*R**)-1-Fluoro-2-iodo-1-methylcyclohexane:**2h) ^{1}H NMR (CCl_4) 1.20—2.60 (8H, m), 1.52 (3H, d, J=22.0 Hz), 4.10—4.53 (1H, m); ^{19}F NMR (CCl_4) δ=−140.0 (m).

2-Fluoro-9-(*p*-isopropylphenyl)-2,6-dimethylnonane: IR (neat) 3020, 2950, 2850, 2820, 1510, 1460, 1370, 1250, 880, 840, and 760 cm^{-1}; ^{1}H NMR (CCl_4) δ=0.33—2.00 (25H, m), 2.30—3.10 (4H, m), 7.00 (4H, s);^{19}F NMR (CCl_4) δ=−141 (m); MS m/z (rel intensity in %) 273 (M$^+$−19, 3), 272(20), 201 (2), 187 (9), 159 (13), 147 (15), 146 (100), 145 (11), 133 (59), 132 (35), 131 (50).

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