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Halofluorination of Alkenes Using Tetrabutylammonium Dihydrogentrifluoride

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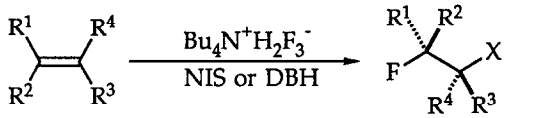
Regio-, stereo-, and chemoselective halofluorination of alkenes is achieved using N-haloamides and tetrabutylammonium dihydrogentrifluoride, and the resulting F-I adducts were successfully converted into fluoroalkenes under dehydroiodination with 1,8-diazabicyclo[5.4.0]undec-7-ene.

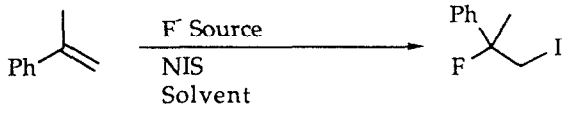
Since a variety of monofluoro compounds often exhibit remarkable biological activities, lots of synthetic methods have been developed.[1] Of these, halofluorination of unsaturated carbon-carbon bonds is one of the most important and convenient reactions for introducing fluorine into organic molecules.[2,3] This reaction is usually carried out with halonium fluoride (XF: X = Cl, Br, I)[4] or with a combined reagent system consisting of a fluoride ion source and a halonium source (*e.g. N*-haloamides).[5] In the latter, metal fluoride such as AgF, anhydrous HF, its precursors, or $(HF)_n$(amine) are employed as the fluoride ion source.[5] Some of these are, however, expensive or highly toxic. We report here that tetrabutylammonium dihydrogentrifluoride ($TBAH_2F_3$)[6,7] can be used as the fluoride ion source for halofluorination of olefins under highly regio-, stereo-, and chemoselective control. The reagent does not corrode common glass flasks and thus allows us to carry out experiments without special care.



(X = I or Br)

On treating 2-phenylpropene (118 mg, 1 mmol) with $TBAH_2F_3$ (1.5 mmol) and *N*-iodosuccinimide (NIS, 1.5 mmol) in dichloromethane (1.5 mL) at 0 °C, we obtained 1-iodo-2-fluoro-2-phenylpropane in 92% yield (entry 1, Table 1). The results summarized in Table 1 clearly show that chlorinated hydrocarbon solvents are effective enough to complete the reaction within 2 h (entries 1-3). Acetonitrile or 1,2-dimethoxyethane required slightly longer reaction time (entries 4 and 5). Tetrabutylammonium hydrogendifluoride used as the fluoride ion source in 1,2-dichloroethane gave the same product in a comparable yield only after warming the reaction mixture at room temperature overnight (entry 6). Tetrabutylammonium fluoride was much less effective (entry 7).

Table 1. Iodofluorination of 2-phenylpropene[a]



Entry	F⁻ Source	Solvent	Conditions	Isolated Yield/%
1	$Bu_4NH_2F_3$	CH_2Cl_2	0 °C, 1 h	92
2	$Bu_4NH_2F_3$	$(CH_2Cl)_2$	0 °C, 1 h	90
3	$Bu_4NH_2F_3$	$CHCl_3$	0 °C, 1.5 h	90
4	$Bu_4NH_2F_3$	CH_3CN	0 °C, 5 h	87
5	$Bu_4NH_2F_3$	$(MeOCH_2)_2$	0 °C, 5 h	83
6	Bu_4NHF_2	$(CH_2Cl)_2$	0 °C, 5 h; rt, 13 h	83
7	Bu_4NF	$(CH_2Cl)_2$	0 °C, 5 h; rt, 13 h	11

a) The alkene was allowed to react with NIS (1.5 mmol) and a fluoride ion source (1.5 mmol) in the solvent (1.5 mL).

The best reaction conditions were applied to various olefins, and the results are summarized in Table 2. The iodofluorination is applicable to olefins having alkyl and/or aromatic substituent(s), and the F-I adducts were isolated in good to excellent yields. However, dimethyl fumarate did not undergo the reaction. It should be noted that such an acid-sensitive group as oxirane is tolerant of the reaction conditions (entry 9). Fluorine is always introduced at the olefin carbon which is more substituted by an electron-donating group and can stabilize the transient positive charge more efficiently. The stereochemistry of the addition of F and I is *anti* (entries 13, 17, 18, and 19) for all the olefins tested.

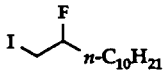
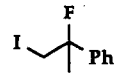
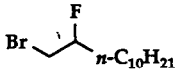
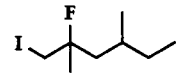
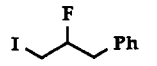
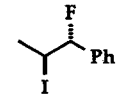
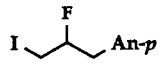
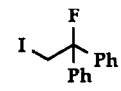
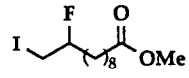
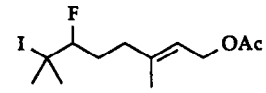
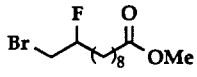
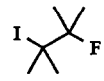
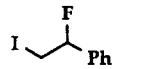
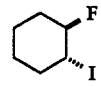
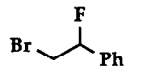
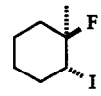
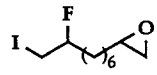
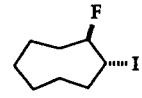
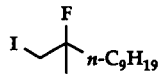
Bromofluorination of alkenes could also be done under the similar conditions by use of 1,3-dibromo-5,5-dimethylhydantoin (DBH, 1.5 mol for 1 mol of the alkene) (entries 2, 6, and 8). Chlorofluorination with *N*-chlorosuccinimide as a chlorinating reagent, however, did not occur at all, and starting alkenes were recovered totally unchanged.

Alkynes were not halofluorinated: Internal alkynes were recovered unchanged and terminal alkynes gave 1-haloalkynes (1-iodo-1-octyne (56%) and 1-iodo-2-phenylethyne (93%) were obtained from the corresponding acetylenes).

When F-I adducts thus obtained were treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 2 mol) in dichloromethane at room temperature, dehydroiodination readily occurred to give vinyl fluorides in excellent yields.[8] Hereby, contamination of 1-fluoro-1-alkenes and/or 1-alkynes was not observed.[9] As both F-I addition and H-I elimination proceed in *anti* mode, (*E*)-1-phenylpropene was converted into (*E*)-1-fluoro-1-phenylpropene by the two-step procedure.

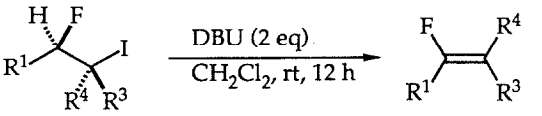
In summary, we have demonstrated that $TBAH_2F_3$ is an efficient fluoride ion source for highly regio-, stereo-, and chemoselective halofluorination of alkenes. The reagent allows us to effect the reaction in an ordinary glassware. Moreover, the halofluorination products are easily

Table 2. Halofluorination of Alkenes[a]

Entry	Product	Cond.	Yield[b] (%)	Entry	Product	Cond.	Yield[b] (%)
1		0 °C, 1 h	87	11		0 °C, 1 h	92
2		0 °C, 5 h; rt, 13 h	82	12		0 °C, 1 h	87
3		0 °C, 2 h	83	13		0 °C, 2 h	82
4		0 °C, 2 h	83	14		0 °C, 2 h	67
5		0 °C, 1 h	83	15		0 °C, 1 h	88
6		0 °C, 5 h; rt, 13 h	85	16		0 °C, 1 h	76
7		0 °C, 1 h	86	17		0 °C, 2 h	60
8		0 °C, 5 h; rt, 13 h	85	18		0 °C, 1.5 h	85
9		0 °C, 2 h	64[c]	19		0 °C, 1 h	78
10		0 °C, 1.5 h	94				

a) An alkene was allowed to react with NIS or DBH (1.5 mmol) and $TBAH_2F_3$ (1.5 mmol) in CH_2Cl_2 (1.5 mL).
b) Isolated yields are given.
c) The starting material (21%) was recovered.

transformed to vinyl fluorides. Study on the reactivity of $TBAH_2F_3$ and its synthetic application as a new fluorinating agent is in progress in our laboratory.



$R^1 = n\text{-}C_{10}H_{21}$, $R^3 = R^4 = H$, 92%
$R^1 = Ph$, $R^3 = Me$, $R^4 = H$, 93%
$R^1 = p\text{-}MeOC_6H_4CH_2$, $R^3 = R^4 = H$, 88%
$R^1 = p\text{-}BrC_6H_4CH_2$, $R^3 = R^4 = H$, 90%

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