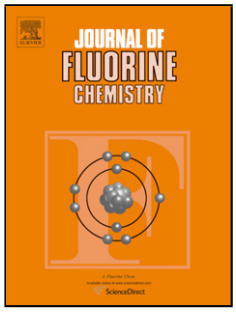


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# Bromofluorination of Unsaturated Compounds using DMPU/HF as a Fluorinating Reagent

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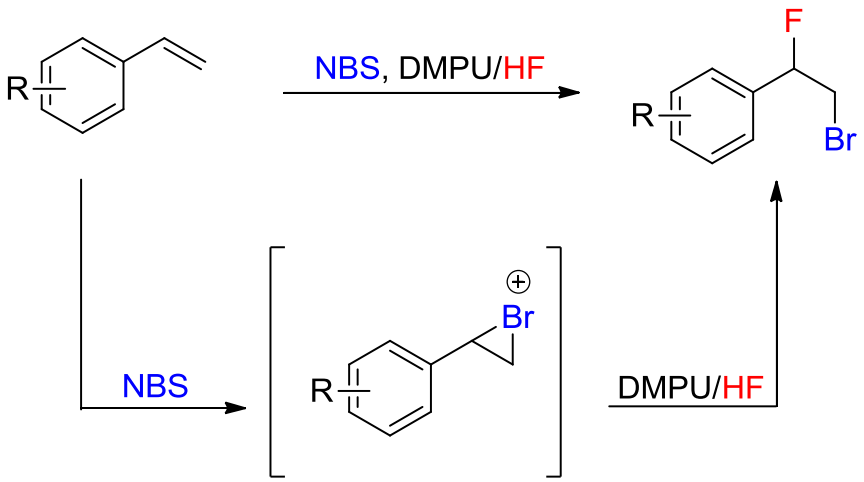
**GRAPHICAL ABSTRACT**



**Highlights**

- Novel nucleophilic fluorinating reagent was used for bromofluorination of alkenes.
- The mechanism relied on the formation of bromonium ion intermediate followed by nucleophilic attack of fluoride.
- Both high yield and regioselectivity were obtained.

**ABSTRACT**

Bromofluorination reactions were performed by treating of a variety of unsaturated compounds with N-bromosuccinimide (NBS) and DMPU/HF as the fluorinating reagent. The DMPU/HF complex showed to be an efficient fluorinating reagent to convert alkenes into their corresponding bromofluoro compounds. It showed to have high reactivity and the process afforded bromofluorinated products with good Markovnikov regioselectivity. These fluorinated compounds are useful starting materials and serve as building blocks for many fluorinated biologically active molecules.

**Keywords:** Bromofluorination, Alkenes, Regioselective, N-bromosuccinimide, DMPU/HF

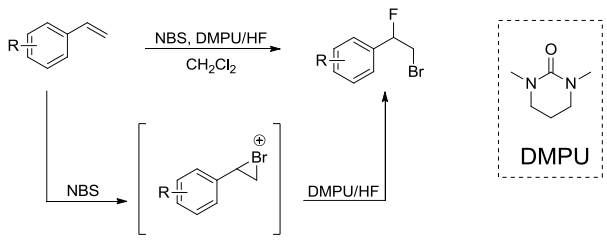
## 1. Introduction

The synthesis of fluorinated organic molecules has gained demand in recent years and has attracted attention from pharmaceutical, chemical and agrochemical industries [1,2]. The incorporation of fluorine into organic compounds is a strategy used to tune the biological properties of molecules as they change their lipophilicity and metabolic activity [3]. One efficient method for the incorporation of fluorine into molecules is the halofluorination of unsaturated compounds. Accordingly, there has been an extensive effort for the development of methodologies and reagents for the effective synthesis of bromofluoro compounds [4,5]. Existing synthetic strategies to effectively pursue bromofluorination of alkenes relied on utilizing different reagents such as tetrabutylammonium bifluoride [6] and $BrF_3$ [7]. It has been shown that the combination N-bromosuccinimide (NBS) and triethylamine trihydrofluoride ($Et_3N$/3HF) was an efficient way of producing bromofluoro compounds from alkenes [8]. In this case, NBS was acting as electrophilic bromine source and $Et_3N$/3HF is the nucleophilic fluorinating specie. An alternative bromonium

ions source was 1,3-dibromo-5,5-dimethylhydantoin [9]. And other HF-based reagents such as pyridine hydrofluoride (Olah's Reagent) [10], potassium fluoride poly(hydrogen fluoride) [11] and tetrabutylphosphonium dihydrogen trifluoride [12] have been used as the nucleophilic source of fluorine.

Recently, our research group has designed an efficient fluorinating reagent DMPU/HF (DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone); when compared with other commonly used fluorinating reagents such as $Et_3N/3HF$ and Olah's Reagent, DMPU/HF is superior due to the non-nucleophilic, weakly basic and weakly coordinating properties of DMPU. We also demonstrated the synthetic utility and effectiveness of DMPU/HF in some nucleophilic fluorination reactions: the gold-catalyzed hydrofluorination of alkynes [13], fluoro-Prins cyclization reactions [14] and ring-opening fluorination of aziridines [15]. DMPU/HF exhibited high reactivity and selectivity compared with the other aforementioned HF-based reagents. Herein, we report our studies on the bromofluorination of alkenes using DMPU/HF as fluorinating reagent, and described its efficiency to provide products with good regioselectivity.

The strategy for bromofluorination relies on the acid-catalyzed attack of the pi electrons of an alkene to the positive bromine in NBS to form the electrophilic bromonium ion intermediate. Then, the bromonium ion opens by the attack of nucleophilic fluoride to provide the desired product (Scheme 1).

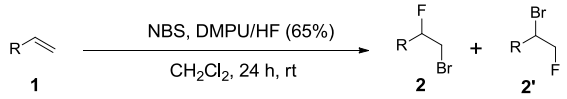


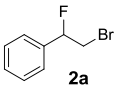
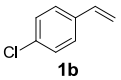
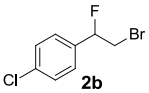
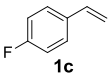
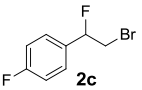
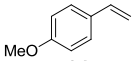
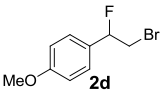
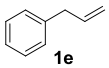
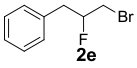
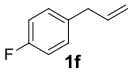
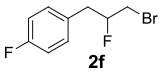
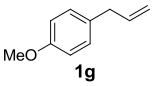
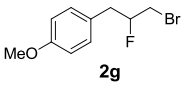
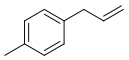
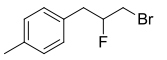
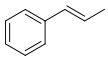
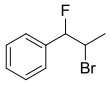
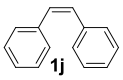
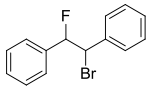

**Scheme 1. Strategy for the bromofluorination of alkenes using NBS and DMPU/HF**

## 2. Results and discussion

A series of alkenes were used to examine the capability of DMPU/HF in producing the corresponding fluorinated products. The results are summarized in Table 1. The products were isolated in good to excellent yields (66-89%) and good regioselectivity. Specifically, alkenes derived from aryl vinyl substituted with halogens and an ether group (compounds **1b-1d**) furnished the corresponding bromofluoro compound when using 7 equivalents of DMPU/HF in the presence of 1.5 equivalents of NBS in $CH_2Cl_2$. In each case, only the Markovnikov regioselective product was obtained, resulting from fluoride attack at the more substituted carbon atom of the bromonium ion intermediate. This strategy was subsequently applied to allylbenzylic compounds substituted with electron-withdrawing and electron-donating groups (compounds **1f-1h**). These substrates generated a mixture of bromofluorinated regioisomers products under these conditions with the Markovnikov product being the major isomer. Furthermore, this reaction appeared to be stereoselective with substrates bearing an internal double bond. In the case of (*E*)-1-phenylpropene **(1i),** the major product observed was *anti*-2-bromo-1-fluoro-1-phenylpropane **(2i)**. In a similar fashion, the treatment of cis-stilbene **(1j)** with NBS followed by DMPU/HF provided *threo*-1-bromo-2-fluoro-1,2-diphenylethane **(2j)** as the sole product.

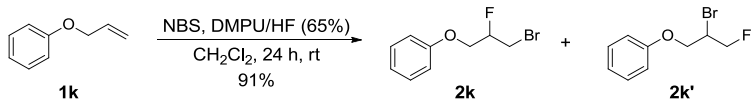
**Table 1. Bromofluorination of alkenes.**



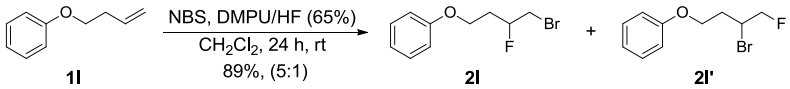

| entry | substrate | major product | yield | ratio (**2**:**2'**) |
|---|---|---|---|---|
| 1 |  **1a** |  **2a** | 89% | — |
| 2 |  **1b** |  **2b** | 87% | — |
| 3 |  **1c** |  **2c** | 87% | — |
| 4 |  **1d** |  **2d** | 86% | — |
| 5 |  **1e** |  **2e** | 82% | 11:1 |
| 6 |  **1f** |  **2f** | 87% | 11:1 |
| 7 |  **1g** |  **2g** | 86% | 9:1 |
| 8 |  **1h** |  **2h** | 84% | >20:1 |
| 9 |  **1i** |  **2i** | 79% | — |
| 10 |  **1j** |  **2j** | 66% | — |

Next, we turned our attention to the bromofluorination of phenyl ether derivatives. We wanted to compare the regioselectivity of our fluorinated reagent with $Et_3N/3HF$ and Olah's reagent. Specifically, the reaction of allyphenyl ether with NBS followed by DMPU/HF provided a mixture of the Markovnikov product and its regioisomer in a 1.1:1, 2.2:1 and 5:1 ratio in the presence of $Et_3N/3HF$, Olah's reagent and DMPU/HF, respectively (Scheme 2). Additionally, the treatment of homoallylphenyl ether with DMPU/HF reagent gave a 5:1 ratio of the Markovnikov product and its regioisomer (Scheme 3). Lastly, when ((3-methylbut-3-en-1-yl)oxy)benzene was reacted with

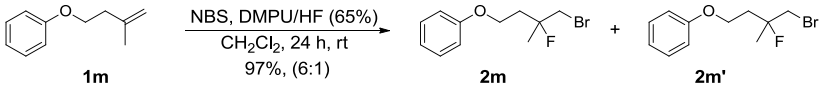
NBS and DMPU/HF it provided 97% yield of 6:1 mixture of the bromofluoride products (Scheme 4). All the regioisomers ratios were calculated after $^{19}F$ NMR analysis of the crude reaction mixture.




**Scheme 2. Bromofluorination reaction of allylphenyl ether.**




**Scheme 3. Bromofluorination of homoallylphenyl ether.**




**Scheme 4. Bromofluorination phenyl ether derivative.**

## 3. Conclusions

In summary, we have demonstrated the utility of DMPU/HF as a fluorinating reagent to generate vicinal bromofluoro products from a broad scope of alkenes. This strategy is effective and afforded products in good yields and with good regioselectivity.

## 4. Experimental

### 4.1 Materials and methods

NMR spectra were recorded on a Varian 400 MR system (400 MHz) with automated sampling, locking, shimming, and tuning. The DMPU/HF reagent was prepared by condensing gaseous HF dispensed from a PTFE manifold into a cooled PTFE cylinder that contained pre-weighted DMPU.

HDPE vials and bottles purchased from VWR. All operations involving HF were conducted in a well-ventilated fume hood.

### 4.2 General experimental procedure

The reaction was performed in a plastic vial. A mixture of NBS (53.4 mg, 0.3 mmol) and alkene (0.20 mmol) in $CH_2Cl_2$ (1 mL) was treated with DMPU/HF (41.2 μL, 1.4 mmol) and stirred for 24 h at room temperature. Next, water (2 mL) was added and the resultant mixture was extracted with $CH_2Cl_2$ (3 × 2 mL). The organic layer was dried over $Na_2SO_4$ and concentrated under reduced pressure. $SiO_2$ flash chromatography (9:1 hexanes/EtOAc) afforded the bromofluoride compounds as mixtures of regioisomers in some cases.

**(2-bromo-1-fluoroethyl)benzene (2a).** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.50 (m, 5H), 5.60 (dd, *J* = 47.1, 7.8, 4.1 Hz, 1H), 3.66 (ddd, *J* = 15.3, 11.3, 7.8 Hz,1H), 3.58 (ddd, *J* = 26.0, 11.3, 4.2Hz, 1H), $^{19}$F NMR (376 MHz, $CDCl_3$) δ -175.0 (m), Colorless oil.

**1-(2-Bromo-1-fluoroethyl)-4-chlorobenzene (2b).** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41 (dm, 7.3Hz, 2H), 7.32 (dm, 7.3Hz, 2H), 5.62 (ddd, *J* = 46.6, 7.3, 4.5 Hz, 1H), 3.68 (ddd, *J* = 16.3, 11.3, 7.3 Hz,1H), 3.61 (ddd, *J* = 24.4, 11.3, 4.4Hz, 1H), $^{19}$F NMR (376 MHz, $CDCl_3$) δ -174.5 (m), Yellow oil.

**1-(2-Bromo-1-fluoroethyl)-4-Fluorobenzene (2c).** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 2H), 7.09 (m, 2H), 5.62 (ddd, *J* = 46.6, 7.3, 4.5 Hz, 1H), 3.68 (ddd, *J* = 16.3, 11.3, 7.3 Hz,1H), 3.63 (m, 2H), $^{19}$F NMR (376 MHz, $CDCl_3$) δ -112.0 (m), -171.6 (m). Yellow oil.

**1-(2-bromo-1-fluoroethyl)-4-methoxybenzene (2d).** $^{19}$F NMR yield, $^{19}$F NMR (376 MHz, $CDCl_3$) δ -171.2 (m), Yellow oil.

**(3-Bromo-2-fluoropropyl)benzene (2e).** $^{19}$F NMR yield. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -175.4 (m), Yellow oil.

**1-(3-bromo-2-fluoropropyl)-4-fluorobenzene (2f).** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.4, 5.5 Hz, 2H), 7.01 (t, *J* = 8.7 Hz, 2H), 4.93 – 4.70 (m, 1H), 3.53 – 3.33 (m, 2H), 3.17 – 2.99 (m, 2H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -115.5 (td, *J* = 8.7, 4.3 Hz), -175.5 (m), Yellow oil.

**1-(3-bromo-2-fluoropropyl)-4-methoxybenzene (2g).** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.90 – 4.69 (m, 1H), 3.78 (s, 3H), 3.54 – 3.33 (m, 2H), 3.02 (dd, *J* = 20.7, 6.1 Hz, 2H); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -175.5 (m), Yellow oil.

**1-(3-bromo-2-fluoropropyl)-4-methylbenzene (2h).** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.13 (m, 4H), 4.73 – 4.9 (m, 1H), 3.54 – 3.34 (m, 2H), 3.05 (dd, *J* = 20.6, 6.2 Hz, 2H), 2.33 (s, 3H); $^{19}$F NMR (376 MHz, $CDCl_3$) δ -175.32 (ddt, *J* = 47.2, 38.7, 20.4 Hz), Yellow oil.

**(2-bromo-1-fluoropropyl)benzene (2i).** $^{19}$F NMR (376 MHz, $CDCl_3$) δ -177. 9 (m), Yellow oil.

**(1-bromo-2-fluoroethane-1,2-diyl)dibenzene (2j).** $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.84 (dd, *J* = 46.0, 6.7 Hz, 1H), 5.12 (dd, *J* = 15.0, 6.6 Hz, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ -169. 8 (m), Yellow oil.

**(3-Bromo-2-fluoropropoxy)benzene (2k).** $^{19}$F NMR yield of regioisomer mixtures. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -183.7 (m, **2k**), -217.1 (m, **2k'**).

**(4-Bromo-3-fluorobutoxy)benzene (2l).** $^{19}$F NMR yield of regioisomer mixtures. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -181.0 (m, **2l**), -211.2 (m, **2l'**).

**(4-Bromo-3-fluoro-3-methylbutoxy)benzene (2m).** $^{19}$F NMR yield of regioisomer mixtures. $^{19}$F NMR (376 MHz, $CDCl_3$) δ -144.7 (m, **2m**), -137.97 (m, **2m'**)

**Acknowledgements**

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