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Metal-Free and User-Friendly Regioselective Hydroxyfluorination of Olefins

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Abstract

A simple, user-friendly, metal-free protocol for the regioselective anti-Markovnikov hydrofluorination of olefins using readily available and inexpensive reagents has been developed. This new approach displays a broader scope than previously reported methodologies and has been applied to the late-stage fluorination of a complex molecule, giving rise to a fluorosteroid derivative. The stereochemistry of the process has also been studied in some detail.

Graphical Abstract

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Author Contributions

All authors have given approval to the final version of the manuscript.

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Supporting Information

Experimental procedures, characterization of all new compounds, copies of HPLC chromatograms and NMR spectra (H, C and F; PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

- **Broad scope**
- **Metal-free**
- **Highly selective**
- **Experimental simplicity**
- **Inexpensive reagents**
- **Suitable for late-stage fluorination**

1,2-Difunctionalization of olefins and alkynes has become one of the most powerful strategies for the rapid construction of molecular complexity, since it allows the introduction of two vicinal functional groups at the expense of the π -component of a double or triple bond.¹ Sharpless' asymmetric dihydroxylation or aminohydroxylation reactions are emblematic examples of such processes.² On the other hand, organofluorine compounds have received a great deal of attention by synthetic organic chemists in the last decades.³ The unique physical-chemical properties brought about by the introduction of fluorine in organic molecules and the resulting effect on their corresponding pharmacological profiles,⁴ along with their applications in imaging techniques⁵ or material science,⁶ has propelled the research in this field forward. Among organofluorine compounds, fluorohydrins⁷ stand out as an important subclass with *fludrocortisone* (**1A**) being the first fluorine-containing marketed drug (Figure 1).⁸ In addition to this paradigmatic example, recently reported drugs such as the ocular anti-inflammatory corticosteroid Difluprednate^{9a-c} (**1B**, Sirion 2008) or the anti-hepatitis C agent Sofosbuvir^{9d} (**1C**, Gilead 2013), contain the 1,2-fluorohydrin substructure. Not only steroid and nucleotide analogs, but also alkaloid-derived fluorohydrins have been described.^{9e}

The synthesis of fluorohydrins has mostly relied on the nucleophilic opening of epoxides with several fluoride sources, among which the use of HF-base reagents (e.g. Olah's reagent) is particularly noteworthy.¹⁰ Epoxides, in turn, are usually derived from olefins by means of the well-known Prilezhaev reaction using *m*-CPBA,¹¹ among other methodologies.¹² In view of the wide availability and low cost of olefins, we envisioned that the direct 1,2-difunctionalization of olefins toward the corresponding fluorohydrins would be an ideal synthetic approach for this subclass of biorelevant compounds (Scheme 1).

In spite of its *a priori* simplicity, to the best of our knowledge, only one report studying the compatibility of an electrophilic epoxidating agent (*m*-CPBA) and nucleophilic fluoride source (HBF₄) has been published; although this report is limited to the use of allylic amines as substrates.¹³ On the other hand, most studies of olefin hydrofluorination rely on electrophilic fluorine sources (Selectfluor, NFSI) resulting, in some cases, in the opposite

regioselectivity.¹⁴ Moreover, some of these protocols proceed through radical pathways, and are limited to styrene derivatives because they are able to stabilize the radical intermediate formed upon addition of the hydroxyl radical (Scheme 1, eq. 1).^{14a} In addition, the recent report by Xu and Tang suffers from complex reaction conditions (AgOTf/Sm (OTf)₃, Selectfluor, PhNO₂/H₂O/MeNO₂).

We started our study by optimizing the number of equivalents of both HF and *m*-CPBA (used as received from the commercial source), the HF source, and the delay in HF addition (Table 1, t). Regarding the number of equivalents (Table 1, entries 1–5), an excess of HF·DMPU (*N,N*-Dimethylpropyleneurea or 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) with respect to *m*-CPBA was necessary; we found that the use of 2 and 7 equivalents, respectively, afforded the highest yield (Table 1, entry 5). On the other hand, allowing the olefin to react with *m*-CPBA prior to the addition of HF·DMPU did not lead to any advantage (Table 1, entries 5–8), thus we decided to establish the addition of both reagents from the onset as the optimized conditions seeking maximum practicality (Table 1, entry 8).

In addition, given that only minor differences were observed between HF·DMPU or HF·Py as the fluoride source (Table 1, entries 8 and 10) we decided to continue our study with Olah's reagent, as it is readily available and inexpensive. No reaction took place when HF·TEA was used (Table 1, entry 9). Lastly, the replacement of chloroform by dichloromethane as the reaction solvent made no significant difference to the outcome of the reaction (Table 1, entries 10 and 11). Therefore, the simultaneous addition of two equivalents of *m*-CPBA and seven equivalents of HF·Py to the olefin in DCM at 0 °C, were selected as the optimal reaction conditions.

With the optimized conditions in hand, we investigated the scope and limitations of this highly convenient protocol (Scheme 2). First, styrene derivatives bearing several substituents at the *para* position were evaluated **2a-j** (Scheme 2). To our delight, we found that several electron-withdrawing substituents were well tolerated; affording the corresponding fluorohydrins **3a-g** in moderate to good yields (Scheme 2). On the other hand, electron-donating substituents at the *para* position **2h-j** (Scheme 2) hampered the reaction, possibly due to the diminished electrophilicity of the benzylic carbon (the intermediate epoxide was the main species identified in the crude reaction mixture).¹⁵ This explanation is supported by the moderate yield obtained for the *m*-methoxy substituted substrate **2k**, in which the –I effect of the electronegative oxygen atom overrides its +R effect due to lack of conjugation with the benzylic position (Scheme 2).¹⁶ Next, allylbenzene substrates were tested **2l-n** (Scheme 2).

In these cases, the introduction of a fluorine atom at the *para* position resulted in a somewhat diminished regioselectivity, while a *para*-methoxy substituent improved the regioselectivity, although at the expense of chemical yield. Aliphatic unfunctionalized substrates, both cyclic and linear, also afforded the corresponding fluorohydrins in good to excellent yields **3o-r** (Scheme 2). Regarding the substitution pattern, a dramatic drop in chemical yield was observed when switching from cyclohexene to 1-methylcyclohexene **3q** vs **3r** (Scheme 2), while the reaction with 1,2-dimethylcyclohexene did not afford the desired product. Finally,

in order to study the suitability of this new methodology for the late-stage functionalization of complex organic molecules, cholesterol **2s** produced the corresponding fluorohydrin **3s** in high yield and with high regio- and diastereoselectivity (Scheme 2).¹⁷ The latter result showcases the amenability of our approach for late-stage fluorination of complex natural products and pharmaceuticals.

Recently, we reported the HF·DMPU-mediated ring opening of aziridines in detail.¹⁸ From this study, we concluded that the stereochemical outcome of this reaction was more complex than anticipated. Therefore, we investigated the stereochemical aspects of our new protocol, namely, its double stereospecificity. We selected *cis*- and *trans*-stilbene (*cis*-**2t** and *trans*-**2t**) as model substrates (Scheme 3). Unexpectedly, although *trans*-**2t** afforded exclusively the *anti*-**3t** product, *cis*-**2t** furnished a 1:1 mixture of *syn*- and *anti*-**3t** using our optimal conditions. We suspect this result is due to the ring opening of strained *cis*epoxide intermediate *cis*-**It**, resulting in the stabilized benzylic carbocation **IIIt** (Scheme 3). The lack of stereoselectivity observed suggests that the α stereocenter is unable to direct the nucleophilic attack by the fluoride anion.

These results made us question whether the ring opening of the intermediate epoxide could have proceeded with erosion of optical purity if the starting material was enantiomerically enriched, which was similar to our observations with aziridines.¹⁸ Hence, commercially available (*R*)-styrene oxide was subjected to a nucleophilic ring opening with HF·Py under identical conditions to the one-pot procedure (Table 2, entry 1). Indeed, a major loss of optical purity was observed (> 99 % to 15% ee). The use of the more acidic HF·DMPU gave rise to a higher degree of racemization (Table 2, entry 2). Furthermore, the use of an external base did not improve the optical purity of the product to a satisfactory degree (Table 2, entries 3 and 4).

The stabilization of the benzylic carbocation again explains the aforementioned results. Thus, in order to find further support to this assumption, enantiomerically enriched (*S*)-1-dodecene oxide (*S*)-**Io** was synthesized, according to a reported procedure¹⁹ and was subjected to nucleophilic ring opening with HF·Py (Scheme 4). To our satisfaction, an improved 76% ee was obtained, demonstrating complete conservation of the optical purity. These results must be taken into account to develop an enantioselective version of this hydrofluorination reaction.²⁰

In conclusion, we have developed a convenient and user-friendly hydrofluorination of olefins that uses readily available, inexpensive reagents (*m*-CPBA and HF·Py) and mild reaction conditions (CH₂Cl₂, 0 °C, under air). The reaction has shown good functional group tolerance and is suitable for the late-stage fluorination of complex organic molecules bearing a double bond. An additional benefit of our one-pot protocol is the stereospecific nature of the two processes, namely *syn* epoxidation and *anti* epoxide opening, as well as from extremely practical and economical reaction conditions. The development of an asymmetric version of this methodology is currently under study in our laboratories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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1A, Fludrocortisone

1B, Difluprednate

1C, Sofosbuvir

Figure 1.

Biorelevant compounds containing the 1,2-fluorohydrin subunit.

Previous work^{14a}

This work

Scheme 1.

1,2-Difunctionalization approach towards fluorohydrins.

^a Isolated yields ^b Diastereomeric ratio in parentheses, when observed ^c 3:1 mixture of cis/trans isomers

Scheme 2.
Scope and limitations.^{a,b}

Scheme 3.
Stereochemical outcome with stilbenes.

Scheme 4.
Ring opening of enantioenriched 10.

Table 1.

Optimization of the reaction conditions.

entry	n	m	t (h)	HF·base	solvent	(%) ^{a,b}
1	1.1	2.2	1	HF·DMPU	CHCl ₃	32
2	1.2	2.4	1	HF·DMPU	CHCl ₃	44
3	1.5	3	1	HF·DMPU	CHCl ₃	48
4	2	4	1	HF·DMPU	CHCl ₃	55
5	2	7	1	HF·DMPU	CHCl ₃	76
6	2	7	4	HF·DMPU	CHCl ₃	77
7	2	7	0.5	HF·DMPU	CHCl ₃	75
8	2	7	0	HF·DMPU	CHCl ₃	75
9	2	7	0	HF·TEA	CHCl ₃	NR
10	2	7	0	HF·Py	CHCl ₃	74
11	2	7	0	HF·Py	CH ₂ Cl ₂	75

^aNMR yield.^bMinor amounts (ca. 5%) of the product arising from the nucleophilic ring-opening by 3-chlorobenzoic acid were observed in the crude reaction mixture.

Table 2.

Ring-opening of enantioenriched Ia.

entry	HF·amine	base	ee % ^a
1	HF·Py	-	15
2	HF·DMPU	-	10
3	HF·DMPU	Et ₃ N	20
4	HF·DMPU	Py	11

^aDetermined by HPLC