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Recent Recent progress on 1,2-hydroxyfluorination of alkenes

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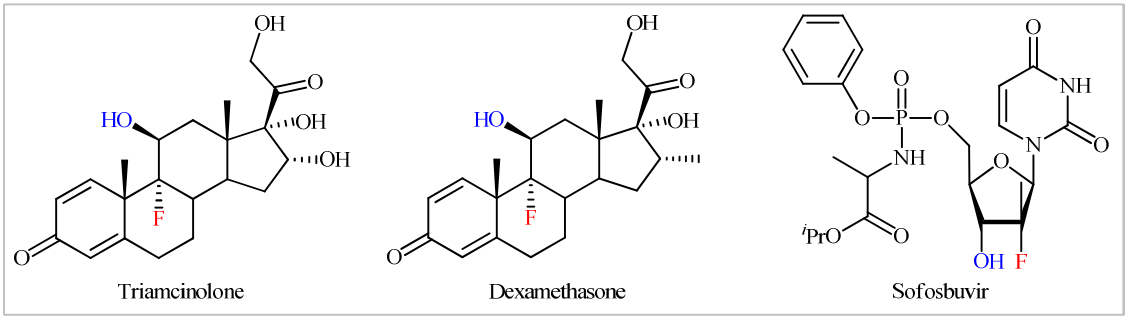
ABSTRACT

The direct fluorinative difunctionalization of alkenes is one of the most convenient platforms to the structurally complex organofluorine compounds from bulk chemicals. Accordingly, tremendous efforts to explore synthetic methodologies in this research area have been documented. In this family of reactions, the direct hydroxyfluorination of simple alkenes has emerged as a sustainable and powerful synthetic strategy for the efficient construction of vicinal fluorohydrins, which are found widespread applications in the fields of human life. The purpose of this review is to provide an overview of the available evidence on the synthesis of vicinal fluorohydrins through the direct hydroxyfluorination of corresponding alkenes. Literature has been surveyed from 1999 to the end of October 2023.

1.Introduction

Fluorinated organic compounds have a broad scope of uses ranging from pharmaceuticals [1] and agrochemicals [2] to materials [3] and PET imaging [4]. Interestingly, nearly 25 % of small molecule drugs in the clinic and 50% of commercially available agrochemicals are fluorine-containing compounds [5, 6]. α-Fluorohydrins, as an important subclass of organofluorine compounds, are not only widely find in a broad range of biologically active molecules (Scheme 1) [7], but also play a pivotal role in organic synthesis, due to their versatile reactivity. General synthetic methods toward vicinal fluorohydrins involve the reduction of α-fluoroketones [8] and ring opening of epoxide [9]. However, these methods suffer from poor availability of starting materials, limited substrate scope, and production of unwanted byproducts, among others. Therefore, the development of efficient and practical strategies for the synthesis of these compounds from simple and readily available starting materials is desirable.



Scheme 1. Selected examples of bioactive molecules containing α-fluorohydrins.

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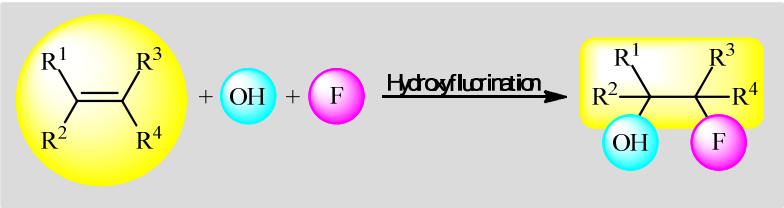


Fig. 1. 1,2-Hydroxyfluorination of alkenes.

Alkenes represent a family of versatile synthetic building blocks in chemical synthesis, owing to their abundance and versatile reactivity [10-15]. Recently, the direct 1,2-difunctionalization of alkenes to incorporate two functional groups across a double bond has emerged as a powerful approach towards the creation of highly substituted, multifunctional, and stereochemically defined products from simple chemical inputs [16-21]. In this regard, following published review articles in organic synthesis [22-24], hydroxyfluorination of alkenes, which installs a hydroxyl group and a fluorine atom in adjacent carbons simultaneously, offers a powerful strategy for the selective synthesis of α-fluorohydrins (Figure 1). Despite the remarkable progress that has been achieved since 1999 in this existing research field, a comprehensive overview on this this hot research topic has not yet been appeared in the literature. This review provides a concise overview of the most important advances and developments of the direct 1,2-hydroxyfluorination of alkenes with particular emphasis on the mechanistic aspects of the reactions

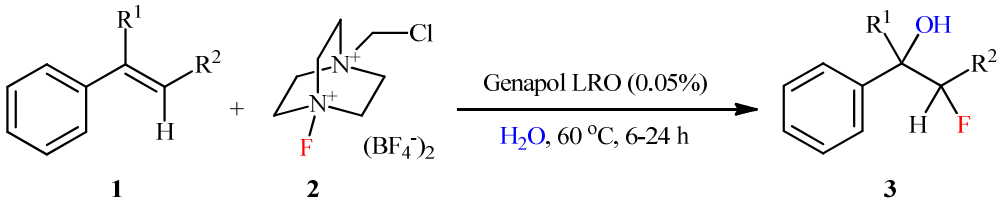
2. Hydroxyfluorination of alkenes

After pioneering work by Shimizu's research group on the high yielding synthesis of 2-((benzoyloxy)methyl)-6-fluoro-5-hydroxytetrahydro-2*H*-pyran-3,4-diyl dibenzoate through the regioselective hydroxyfluorination of corresponding glycal-tribenzoate with $PhI(OAc)_2$-SiF_4 and water as the fluorine and hydroxyl sources, respectively [25], the first general report on the direct hydroxyfluorination of alkenes was published by Stavber and co-workers in 2004 [26]. In this study, five 2-fluoro-1-phenylethanols **3** were selectively synthesized through the treatment of various styrene derivatives **1** with selectfluor **2** (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), or F-TEDA) in the presence of only 0.05% of Genapol LRO as a surfactant in water at 60 ^{o}C (Scheme 2). The optimized protocol tolerated both terminal and internal styrenes derivatives and provided the target 2-fluoro-1-phenylethanols in high yields and outstanding regioselectivities in which the hydroxyl group selectively attached to the carbon atom adjacent to the phenyl ring. The authors also evaluated the stereochemistry of their difunctionalization reaction using (*E*)- and (*Z*)-1,2-diphenylethene as the model substrates under the identical conditions. In the case of the (*E*)-isomer, the formation of the *erythro* stereoisomer was found to be predominant, while complete lack of stereoselectivity of the addition process was observed when the (*Z*)-isomer. Two years later, Vincent and co-workers successfully applied a similar principle to the hydroxyfluorination of phosphonylated *exo*-glycals [27].

In 2010, Chang and colleagues demonstrated the similar hydroxyfluorination under catalyst- and additive-free conditions [28]. The transformation was performed in a 10:1 mixture of MeCN and H_2O at reflux temperature by using 1.1 equiv, of selectfluor. Under these conditions several 1,1-diaryl-2,2-dialkyl-ethenes **4** carrying various substituents were converted to the corresponding 2-fluoro-2,2-dialkyl-1,1-diaryl-ethene-1-ols **5** in good to excellent yields, ranging from 61% to 93%, within 1-4 h (Scheme 3). Intriguingly, when water was replaced with alcohols, the respective fluoroalkoxide products were obtained in good yields. Of note, when the standard system was applied for *endo*-olefins, the corresponding monofluorinated allylic compounds were obtained in moderate yields without any of hydroxyfluorinated product formation

Later, microwave assisted version of this transformation was disclosed by Kumar *et al* [29], who realized that the treatment of phenyl substituted alkenes **6** with selectfluor in binary solvent MeCN/H_2O (5:1) under microwave radiations afforded the corresponding fluorohydrins **7** in high to near quantitative yields within minutes (Scheme 4). Although various mono-, 1,1-di, 1,2-di, tri-, and four-substituted alkenes were investigated, compatibility of any common functional group was not investigated in this study.

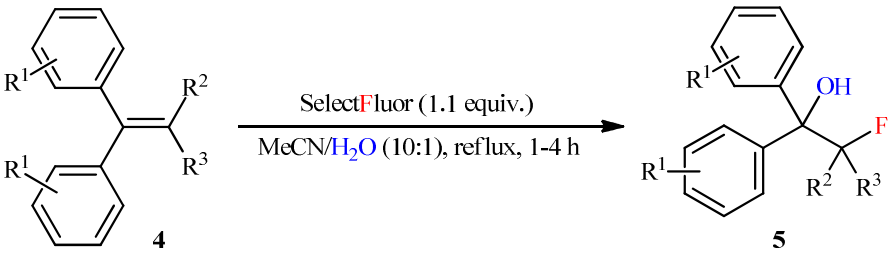
Drawing inspiration from these works, in 2012, Davies and co-workers disclosed the use of commercially available low-cost tetrafluoroboric acid diethyl ether complex ($HBF_4{\cdot}OEt_2$) as an alternative fluorinating reagent in hydroxyfluorination reactions [30].



R^1= H, Me, Ph
R^2= H, Me, F

5 examples (84-86%)

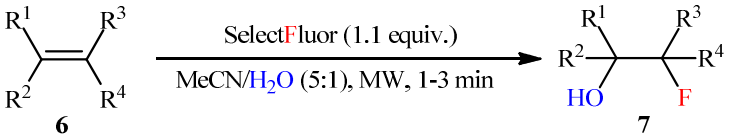
Scheme 2. Stavber's synthesis of 2-fluoro-1-phenylethanols **3**.



R^1= H, 4-OMe, 4-F
R^2= Me
R^3= Me
$R^2 + R^3$= $-(CH_2)_4-$, $-(CH_2)_5-$, $-(CH_2)_2O(CH_2)_2-$, $-(CH_2)_2NMs(CH_2)_2-$, $-(CH_2)_2NBs(CH_2)_2-$, $-(CH_2)_2NTs(CH_2)_2-$, $-CH_2NBs(CH_2)_3-$

14 examples (61-93%)

Scheme 3. Chang's synthesis of 2-fluoro-2,2-dialkyl-1,1-diaryl-ethene-1-ols **5**.

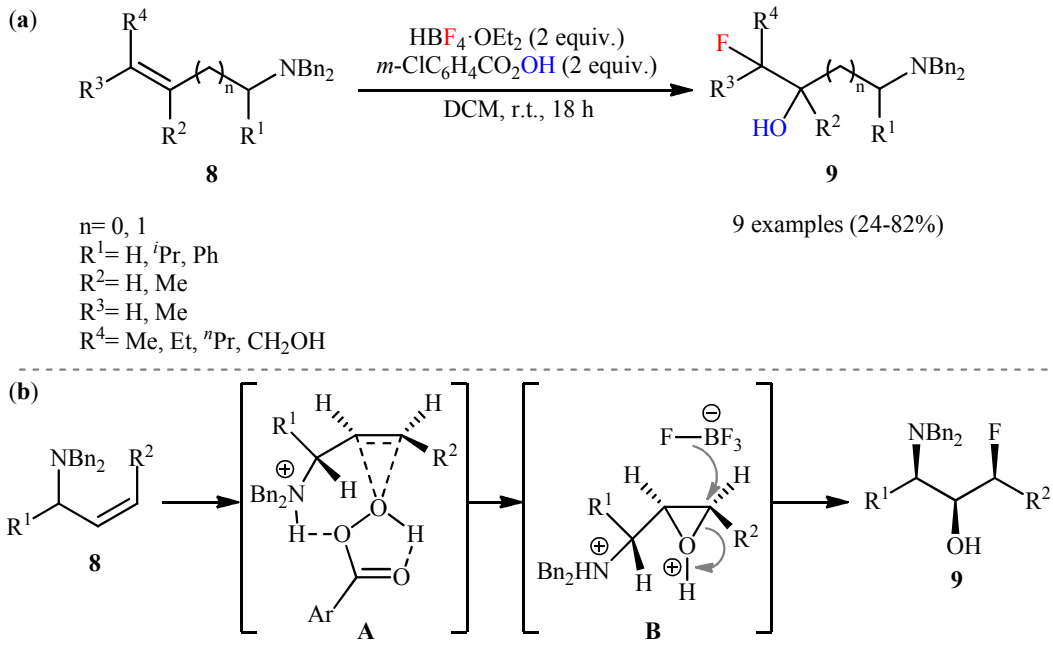


R^1= Ph, 1-naphthyl
R^2= H, Ph
R^3= H, Ph, 1-naphthyl
R^4= H, Ph

6 examples (85-98%)

Scheme 4. Kumar's synthesis of α-fluorohydrins **7**.

In this investigation, nine diastereoisomeric amino fluorohydrins **9** were synthesized in relatively poor to high yields by sequential treatment of (homo)allylic amines **8** with 2 equiv of *meta*-chloroperbenzoic acid (*m*-CPBA) followed by $HBF_4 \cdot OEt_2$ at room temperature in DCM (Scheme 5a). According to the authors proposed mechanism (Scheme 5b), this transformation proceeds through the epoxidation of C-C double bond of alkenes **8** *via* oxidation with peroxy acid, which is followed by regioselective and stereospecific epoxide ring-opening by transfer of fluoride from a $BF4^-$ ion (an S_N2-type process at the carbon atom distal to the ammonium moiety). A promising contribution to this field was reported by Toste and co-workers in 2012 [31], when enamides **10** were converted to the corresponding *N*-(2-fluoro-1-hydroxyethyl) amides **11** through a doubly axially chiral phosphoric acid-catalyzed hydroxyfluorination with selectfluor and water under ambient conditions. As shown in Scheme 6, this reaction tolerated both aromatic and aliphatic substituted enamides, and gave the final products in moderate to high yields and excellent diastereo-selectivities. It should be mentioned that only the (*Z*)-enamides gave high diastereo- and enantioselectivities under these reaction conditions.

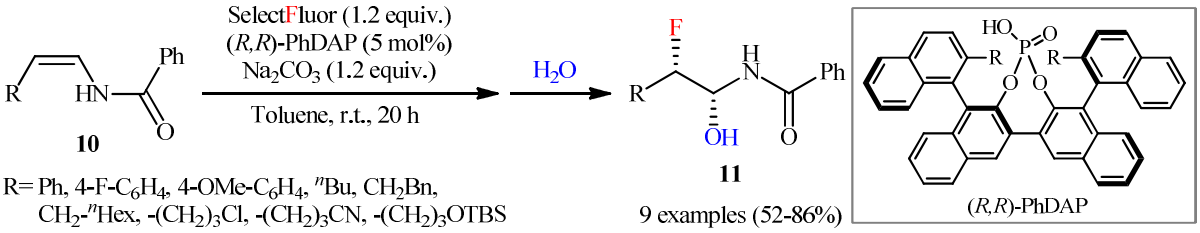


Scheme 5. (a) Diastereodivergent hydroxyfluorination of (homo)allylic amines **8** employing the merge of $HBF_4{\cdot}OEt_2$ and *m*-CPBA) at room temperature; (b) Mechanism proposed to explain the formation of diastereoisomeric amino fluorohydrins **9**.

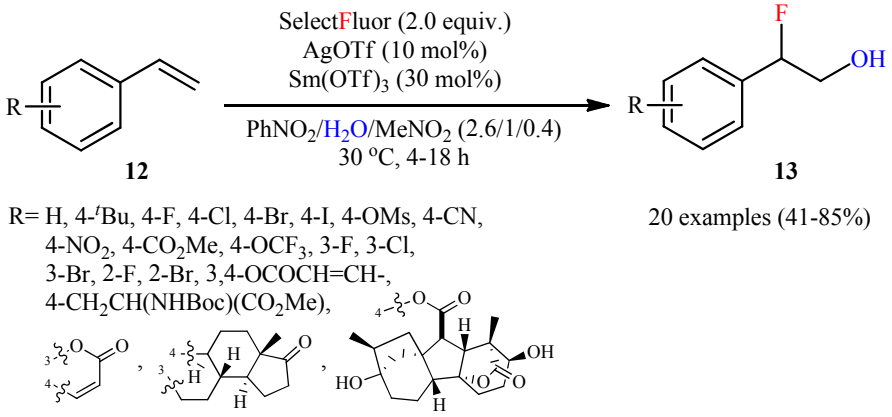
Notably, when the reaction was carried out in the presence of alcohols, alcohol addition was observed rather than hydration. They also explored substrates that would generate a chiral quaternary fluorine stereocenter, specifically the benzoyl enamide derived from 2-phenylpropionaldehyde.

In 2017, Tang and co-workers developed a unique silver-catalyzed hydroxyfluorination of styrene derivatives **12** with selectfluor and H_2O [32]. The reaction was carried out in the presence of $SmOTf_3$/AgOTf combination as the catalytic system in $PhNO_2/H_2O/CH_3NO_2$ (2.6/1/0.4) under mild condition, tolerated various important functional groups (*e.g.*, F, Cl, Br, I, OMs, CN, NO_2, CO_2Me, OCF_3) and afforded the corresponding vicinal fluorohydrins **13** in moderate to high yields and exclusive anti-Markovnikov-type regioselectivity, in which the hydroxyl group exclusively added to the less sterically hindered end of the double bond (Scheme 7). Noteworthy, other simple silver salts such as $AgNO_3$, AgO_2CPh, Ag_2CO_3, AgF, Ag_2SO_4, $AgSbF_6$, $AgBF_4$, and Ag_2O were also found to catalyze this hydroxyfluorination reaction, albeit with reduced efficiencies. In this report, several control experiments, such as radical-trapping, isotope-labelling, DFT calculation and others, were conducted for the insight of the reaction mechanism, which suggested that a radical chain or a single-electron transfer (SET) mechanism may be operating (Scheme 8). As shown in Scheme 2, initially, coordination of $(H_2O)Ag(I)$ with styrene **12** leads to the formation of the complex **A** that, after oxidation with selectfluor provides Ag(II) intermediate **B** and TEDA radical cation (Scheme 2, path a). Subsequently, oxidation of the ligated styrene with the Ag(II) intermediate **B** results in the formation of styrene radical cation **C**. Next, the reaction of newly formed radical cation **C** with the OTf- and H2O affords benzylic radical intermediate **D**, which after abstraction of fluorine from selecfluor provides the final product **13** and TEDA radical. In another possibility, TEDA radical cation can also oxidize the Ag(I) complex **A** to continue the catalytic cycle (Scheme 2, path b). Notably, the oxidation of complex **A** by TEDA radical cation requires 5.8 kcal/mol less energy barrier than the oxidation of this complex by selecfluor, which suggests that the catalytic cycle should prefer to continue along pathway b after it starts along pathway a.

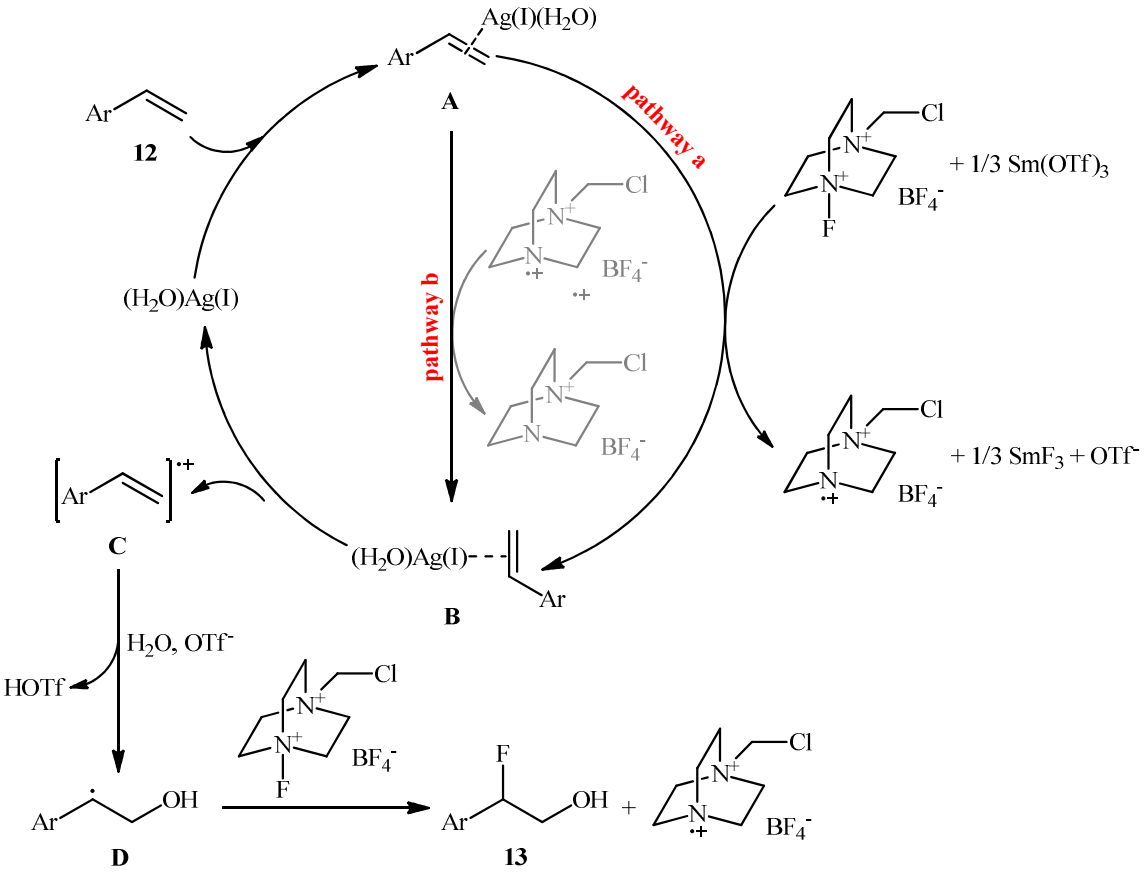
Subsequently, Arcadi and co-workers investigated the regio- and chemo-selective synthesis of 4-fluoromethyl-4-hydroxy-oxazolidinones through a domino 5-*exo-dig* aminocylization– hydroxyfluorination sequence [33].



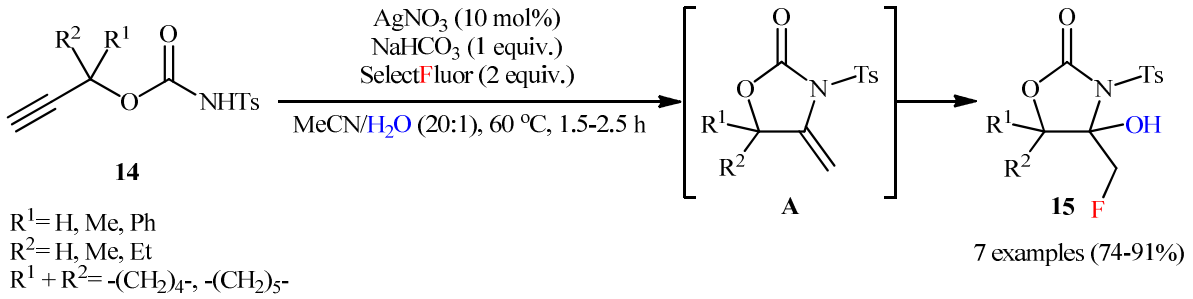
Scheme 6. Doubly axially chiral phosphoric acid-catalyzed hydroxyfluorination of enamides **10**.



Scheme 7. Ag-catalyzed anti-Markovnikov-type hydroxyfluorination of styrenes **12** developed by Tang.

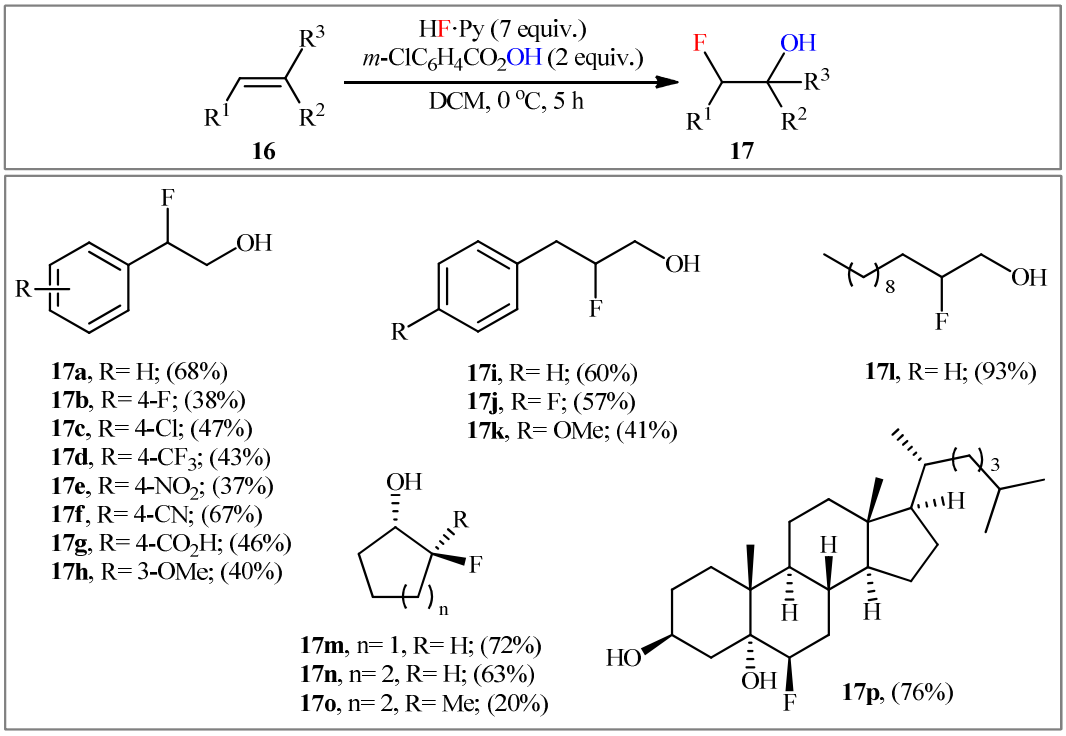


Scheme 8. Mechanism proposed to explain the formation of vicinal fluorohydrins **13**.



Scheme 9. Silver-catalyzed 5-*exo-dig* aminocylization/hydroxyfluorination of propargylic carbamates

Along this line, Fustero's research group developed a metal-free and user-friendly method for regioselective hydroxyfluorination of alkenes employing *m*-CPBA as an electrophilic epoxidating agent and Olah′s reagent (HF·Pyridine) as a nucleophilic fluorinating agent [34]. Various aliphatic unfunctionalized alkenes (both cyclic and linear), styrene derivatives, and allylbenzenes **16** slowly reacted with these reagents to afford the corresponding hydrofluorinated products **17** in good yields when running the reaction in DCM at 0 °C (Scheme 10). Notably, cholesterol **16p** was also effectively converted to the corresponding fluorohydrin **17p** in high yield and with high regio- and diastereoselectivity under the standard conditions, indicating the suitability of this new methodology for the late-stage functionalization of complex organic molecules. The authors investigated the stereochemical aspects of their methodology using *cis*- and *trans*-stilbene as model substrates. Unexpectedly, the *trans*-stilbene was stereospecifically transformed to the corresponding *anti*-product and *cis*-stilbene furnished a 1:1 mixture of *syn*- and *anti*-products under the identical conditions. They explained this observation by the ring opening of strained *cis*-epoxide intermediate, leading to the formation of the stabilized benzylic carbocation intermediate.



Scheme 10. Fustero's synthesis of vicinal fluorohydrins **17**.

In 2018, this hydroxyfluorination chemistry was successfully extended to *gem*-difluoroalkenes by Hu and co-workers [35]. They showed that in the absence of any catalyst or additive in MeCN at room temperature, various *gem*-difluorostyrenes **18** was selectively hydroxyfluorinated with selectfluor/$H_2{}^{18}O$ and afforded the corresponding α-CF_3 alcohols **19** in moderate to excellent yields (Scheme 11). The results indicated that both tri-substituted and tetra-substituted *gem*-difluorostyrenes were compatible with this protocol. The reaction, however, appears to be limited to electron-rich *gem*-difluorostyrenes. A gem-difluoroalkene without aryl substituent was also examined, and no desired product was detected. In order to demonstrate the synthetic utility of this protocol, the authors successfully applied their mythology to the functionalization of difluorovinyl derivative of Fenofibrate, a lipid-lowering agent. Noteworthy, besides $H_2{}^{18}O$, other nucleophiles such as primary and secondary alcohols, MeCN, acetic acid and DMF were also suitable nucleophiles in this hydroxyfluorination reaction.

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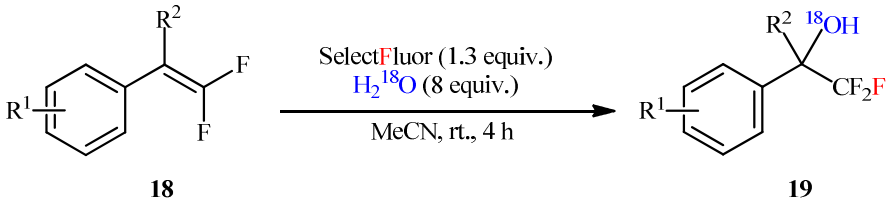


R^1= H, 4-^{t}Bu, 4-Ph, 4-OMe, 4-OBn, 4-OTs, 4-O$(CH_2)_2$OTs, 2-OMe, 3,4-$(CH{=}CH)_2$-, 3,4-OCH_2O-
R^2= H, Me, Et, Ph, 4-OMe-C_6H_4

15 examples (50-99%)

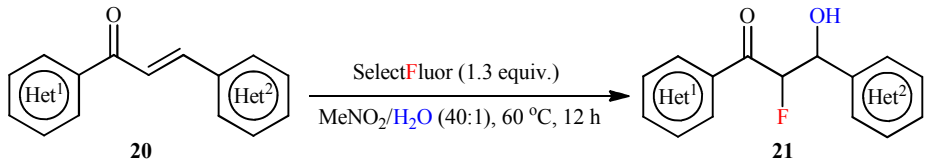
Scheme 11. Synthesis of ^{18}O labeled α-CF_3 alcohols **19** through the direct hydroxyfluorination of *gem*-difluorostyrenes **18**.

Recently, Li's group developed the regioselective hydroxyfluorination of *α*,*β*-unsaturated ketones **20** under catalyst- and additive-free conditions (Scheme 12) [36]. Selectfluor as the oxidant and fluorine source could work well in MeCN/H_2O (40:1) to give *α*-fluorohydrins **21** in 45–81% yields. The reaction has a relatively wide substrate scope, and most products have been synthesized without diastereomers. Interestingly, when the same reaction was performed using 1.2 equiv. selectfluor and 1.0 equiv. H_2O, the corresponding α-fluoroamides were obtained in acceptable yields through the Ritter reaction. In addition, when the loading of selectfluor was increased from 1.2 equivalent to 3.0 equivalent, the α-difluoro-*β*-amidation was obtained in fair yields. After a series of mechanistic investigations, it was confirmed that this difunctionalization reaction most likely proceeds *via* a radical pathway as depicted in Scheme 13.

Very recently, Rong's research group reported their results on the selectfluor-promoted vicinal fluorohydroxylation of *para*-quinone methides **22** [37]. Optimal condition for this reaction was the combination of selectfluor (2.5 equiv.) as a fluorine source, water (1.0 equiv.) as the source of hydroxyl group, and 4 Å molecular sieves as an additive in $MeNO_2$. The reaction proceeded cleanly at ambient temperature and the target vicinal fluorohydrins **23** were obtained in good to high yields (Scheme 14). Interestingly, in the absence of 4 Å molecular sieves, instead of fluorohydrins, ketone- and ether-type products were achieved, and their structures are highly controlled by the electronic properties of the substituents. The results demonstrated that the pore size of the molecular sieve had also an important impact on the reaction outcome, and a small pore size molecular sieve (3 Å Ms) did not match the reaction.

3. Hydroxyfluorination of allenes

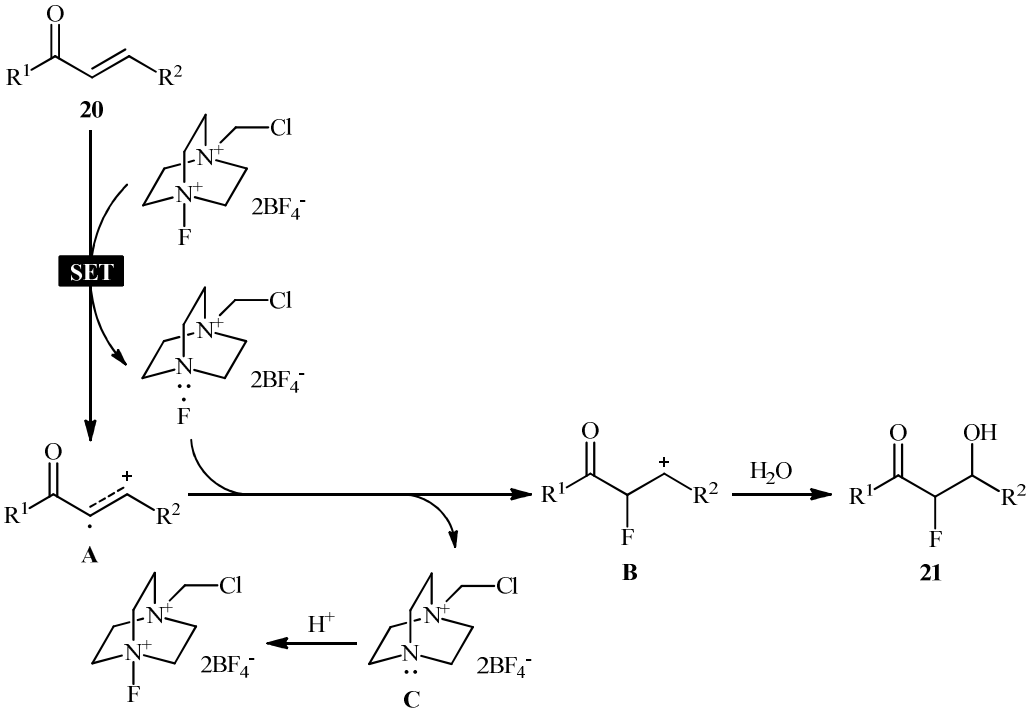
Compared to alkenes, hydroxyfluorination of allenes is much less studied; in fact, only two examples of such a reaction were reported in the literature thus far. In 2008, Fu and Ma along with their co-workers described one of the earliest regioselective hydroxyfluorination of allenes **24** by employing selectfluor and water as fluorine and hydroxyl sources, respectively, providing an efficient approach for the synthesis of fluorinated allylic alcohols **25** (Scheme 15) [38]. The reaction was successfully applied to various mono-substituted and 1,1-disubstituted aryl allenes. However, geminal bisalkyl-substituted allenes did not respond to the reaction, which indicated the importance of the aryl group in this transformation. Generally, 1,1-disubstituted allenes provided better yields than mono-substituted ones. Interestingly, in all cases, hydroxyl group was exclusively added at the more



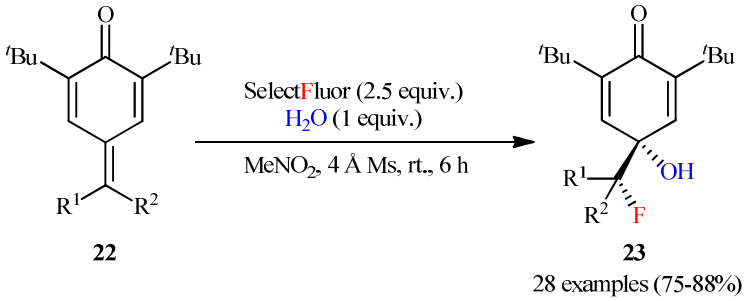
(Het)Ar[1]= Ph, 4-OMe-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 2-thienyl, 2-furyl
(Het)Ar[2]= Ph, 4-Me-C_6H_4, 4-OMe-C_6H_4, 4-F-C_6H_4, 4-Br-C_6H_4, 3-Me-C_6H_4, 2-Cl, 2-Br, 2-thienyl

14 examples (45-81%)

Scheme 12. Hydroxyfluorination of α,β-unsaturated ketones **20** reported by Li.



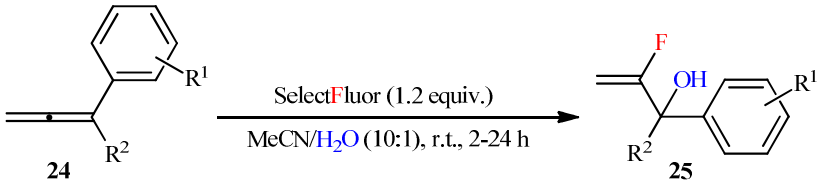
Scheme 13. Proposed mechanism for the reaction in Scheme 12.



28 examples (75-88%)

R[1]= H, Me
R[2]= Me, Et, ^{t}Bu, -CH=CHPh, Ph, 4-Me-C_6H_4, 4-^{i}Pr-C_6H_4, 4-OMe-C_6H_4, 4-OEt-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 4-Br-C_6H_4, 4-CF_3-C_6H_4, 4-NO_2-C_6H_4, 4-CN-C_6H_4, 3-OMe-C_6H_4, 3-Br-C_6H_4, 2-Me-C_6H_4, 2-OMe-C_6H_4, 2-Cl-C_6H_4, 2-Br-C_6H_4, 3,4-Me_2-C_6H_3, 3,4-Cl_2-C_6H_3, 2,5-Cl_2-C_6H_3, 2-OMe-5-Br-C_6H_3, 2-Br-4-Me-C_6H_3, 2-Br-4-Cl-C_6H_3, 2-Br-5-Cl-C_6H_3, 2-naphthyl, 2-pyridyl, 2-quinolinyl, 2-(6-Br)-pyridyl

Scheme 14. Selectfluor-promoted fluorohydroxylation of *para*-quinone methides **22**.

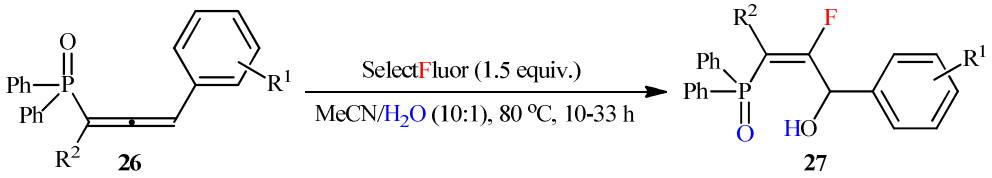


R^1= H, 4-Me, 4-F, 3-Me, 3-CF_3, 2-Me
R^2= H, Et, ^{n}Bu, ^{n}Hex, Ph

12 examples (37-78%)

Scheme 15. Fu-Ma's synthesis of fluorinated allylic alcohols **25**.

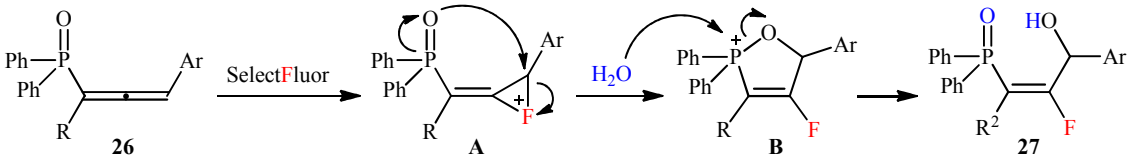
Subsequently, the same research group provided further examples of fluorinated allylic alcohols synthesis directly from the corresponding allenes employing their original procedure [39]. Thus, they showed that in the presence of over stoichiometric amounts of selectfluor in binary solvent MeCN/H2O with ratio 10:1 at 80 oC, a library of 3-aryl substituted 1,2-propadienyl diphenyl phosphine oxides 26 underwent regio- and stereo-selective hydroxyfluorination to afford the desired (E)-(2-fluoro-3-hydroxy-3-arylprop-1-en-1-yl)diphenylphosphine oxides 27 in moderate yields and excellent regio- and (E)-selectivities (Scheme 16). Interestingly, in the reaction of 3-(4-methoxyphenyl)-1,2-propadienyl diphenyl phosphine oxide, further fluorination on the electron-rich phenyl ring was also observed. According to the authors, the (E)-stereoselectivity is controlled by the phosphine oxide functionality. The mechanism proposed by the authors for this transformation is depicted in Scheme 17, and starts with the interaction of the relatively electron-rich carbon-carbon double bond in allene 26 with F, leading to the formation of fluoronium ion A, which subsequently converts to a five-membered cyclic intermediate B via neighboring group participation of the oxygen atom of the diphenyl phosphine oxide functionality. Finally, nucleophilic attack of water molecule to the positively charged phosphorous atom affords the expected product 27 through the cleavage of the P–O bond.



R^1= H, 4-Me, 4-F, 4-Cl, 4-NO_2, 3-Cl, 2-Cl
R^2= H, ^{n}Bu, Ph

12 examples (33-72%)

Scheme 16. Regio- and (*E*)-selectivities hydroxyfluorination of allenes **26** by using selectfluor in MeCN/H_2O.



Scheme 17. Mechanistic explanation of the synthesis of fluorinated allylic alcohols **27**.

4. Conclusion

The direct difunctionalization of alkenes has emerged as a robust and powerful tool to enrich the molecular complexity within a single click. This transformation allows simultaneous installation of two new functional groups across the double bond of abundant and easily accessible alkenes to rapidly construct complex molecules in one step with minimal generation of waste. In this context, several strategies have been developed for direct hydroxyfluorination of alkenes, which allow highly efficient and rapid access to the biologically and synthetically important vicinal fluorohydrins. As illustrated, this page of fluorohydrin synthesis is compatible with all four kinds of mono-, di-, tri-, and tetra-substituted alkenes. It is interesting to note that water was used as the source of hydroxyl group in most of the reports covered in this review. However, the fluorine source is severely limited to the use of selectfluor. Although this reagent is a

very effective, safe, non-toxic, and easy to handle source of electrophilic fluorine, applicability of other common fluorinating agents such as NaF, *N*-fluoro-*o*-benzenedisulfonimide (NFOBS), and *N*-fluorobenzenesulfonimide (NFSI) should also explored in this difunctionalization reaction.

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