



A cooperative allylic fluorination: combination of nucleophilic and electrophilic fluorine sources



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ABSTRACT

A one step, regioselective allylic fluorination of alkenes is reported in which electrophilic and nucleophilic sources of fluorine act synergistically to afford rearranged allylic fluorides over alternative vicinal dihalides. The reaction occurs under exceptionally mild conditions and without need for prefunctionalization or transition metal catalysts. The fluorination of cyclic alkenes and monoterpenes is highlighted, and preliminary mechanistic experiments reveal that dual (radical and ionic) pathways operate simultaneously.

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Introduction

The selective incorporation of fluorine has become a powerful strategy in the optimization of pharmaceuticals,¹ agrochemicals,² and performance materials.³ The unique properties of the fluorine atom make it an ideal bioisostere for hydrogen or oxygen, while imparting a unique set of physical and chemical properties onto the parent molecule.⁴ For instance, substitution of a single C–H bond with fluorine has been shown to enhance membrane permeability, metabolic stability, and binding affinities of potential drug candidates, among other notable features.⁵

In addition, the ¹⁸F radioisotope is ideally suited for use in positron emission tomography (PET) imaging due to its low-energy emission, ease of preparation from [¹⁸O] water, and appreciable half-life.⁶ Accordingly, methods for the direct conversion of C–H to C–F bonds are of high synthetic value. While preparative methods for aryl fluorides⁷ and α -fluorocarbonyl compounds⁸ have advanced dramatically over the last decade, methods for the synthesis of allylic fluorides also remain in considerable demand. The allyl fluoride moiety is found in a variety of medicines and agrochemicals from common insecticides and herbicides to synthetically complex prostanoid analogues (Fig. 1).⁹ In addition to these cases, allylic fluorides serve as versatile building blocks in the construction of various fluorinated compounds.

Of the methods currently available for allylic fluorination, the majority have necessarily involved nucleophilic fluorination

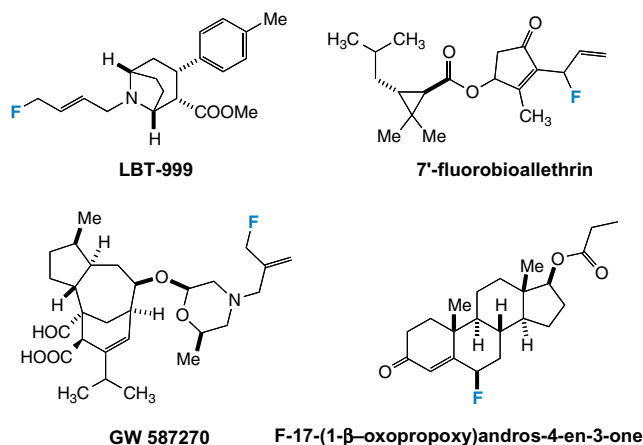
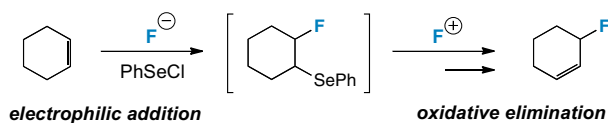


Figure 1. Allylic fluorides in medicine.

mediated by transition metal catalysts.¹⁰ Terminal and electron rich olefins react quite efficiently, whereas cyclic and aliphatic alkenes afford only trace to moderate yields of fluorinated products. It was our interest to devise a complementary system for the fluorination of unactivated cyclic and acyclic olefins under mild conditions in part to address the cyclic olefin problem. Previously, it has been reported that the use of ambiphilic fluorinating agents, or a combination of appropriate electrophilic and nucleophilic sources of fluorine, may be used to afford vicinal difluorides in excellent yields and selectivities from the starting alkene.¹¹

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Scheme 1. Proposed pathway for allylic fluorination.

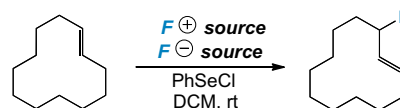
We envisaged a bicomponent system utilizing both fluorination strategies in which electrophilic addition is accompanied by an oxidative elimination rather than nucleophilic trapping with fluoride to yield allylic products instead of a vicinal dihalide. Toward this effort, it is well documented that PhSeF, generated *in situ* by the reaction of phenylselenenyl chloride with silver(I) fluoride, adds regioselectively to alkenes to afford β -fluoro phenylselenides.¹² Moreover, electrophilic N–F reagents have been shown to oxidize both sulfur and selenium efficiently, often promoting their substitution or elimination with various nucleophiles and bases.¹³ We surmised that the combination of PhSeF and an appropriate N–F reagent could be used in tandem to yield allylic fluorides from alkenes in a single reaction. It was our idea to employ a tandem fluoroselenation–deselenation process mediated by phenylselenium fluoride and an electrophilic fluorinating agent, N-fluoropyridinium tetrafluoroborate (NFPy·BF₄), for the allylic fluorination of alkenes in a single reaction vessel without need for purification of the intermediate β -fluoroselenide (Scheme 1). This method proved not only to be fairly general in scope, but highlights the ability of both nucleophilic and electrophilic sources of fluorine to operate synergistically to afford a rearranged allylic fluoride over the alternative vicinal difluoride.

Until recently, the synthesis of allylic fluorides has often relied heavily on the dehydroxylation of alcohols with (diethylamino)sulfur trifluoride¹⁴ or nucleophilic fluorination of preassembled allylic halides,¹⁵ *p*-nitrobenzoates,¹⁶ trichloroacetimidates,¹⁷ and phosphorothioates¹⁸ catalyzed by an array of transition metals, most notably Pd, Ir, and Cu. However, these and corresponding methods often suffer from poor regioselectivity and narrow substrate scope, especially in the way of unactivated or *sp*³-rich cyclic alkenes. Earlier this year, Doyle et al. reported the first account of a direct allylic C–H fluorination of olefins using an electrophilic Pd(II)-sulfoxide catalyst, benzoquinone as oxidant, the Lewis acid (salen)CrCl, and Et₃N·3HF as a stoichiometric fluoride source.¹⁹ Recently, our lab has undertaken an interest in the design of novel C–H to C–F bond-forming reactions. Most notably, we and others have developed methods for the direct fluorination of aliphatic²⁰ and benzylic²¹ C–H bonds employing common, naturally abundant metals, photocatalysis,²² and oxidative free radicals.²³ We ventured that the identification of a system involving a main group element for allylic fluorination could prove advantageous for cyclic substrates, complementing transition metal catalysis or older stoichiometric methods. A while ago, we envisioned a convenient method involving selenium as a viable alternative. Synthetically, selenium reagents have found widespread applications in a variety of oxidative C–H reactions, in particular those involving allylic hydrogen atoms. For example, C–H hydroxylation²⁴ using stoichiometric SeO₂, selenation with (PhSe)₂,²⁵ and halogenations²⁶ as well as aminations²⁷ by catalytic PhSeCl have been reported.

Results and discussion

To begin our studies, we selected the aliphatic alkene cyclododecene as a prototypical substrate. During our initial screening, we surveyed a number of electrophilic N–F reagents for reactivity including N-fluorobenzenesulfonamide (NFSI), Selectfluor, *p*-toluenesulfonyl fluoride (TsF), and N-fluoropyridinium tetrafluoroborate in combination with cyclododecene, PhSeCl, and silver(I)

Table 1
Screening of reaction conditions



F [⊖]	F [⊕] source	Yield (%)
NEt ₃ ·3HF	Selectfluor	0
Py·HF	Selectfluor	0
TBAF	Selectfluor	0
Xtalfluor	Selectfluor	0
DAST	Selectfluor	14
AgF	Selectfluor	27
AgF	NFSI	0
AgF	TsF	0
AgF	NFPy·BF ₄	71

Reactions were performed with PhSeCl (1.2 equiv), F⁺ (2.2 equiv) and F[−] (3.0 equiv) in CH₂Cl₂ (3 ml) over 24 h. Yields were determined by ¹⁹F NMR using 3-chlorobenzotrifluoride as an internal standard.

fluoride in CH₂Cl₂ (Table 1). Among these reagents, NFPy·BF₄ performed most admirably, yielding 1-fluoro-2-cyclododecene in 71% yield after 24 h.

Note that the use of other nucleophilic fluoride sources failed to give any appreciable amount of the fluorinated product. Unsurprisingly, in the absence of AgF, NFPy·BF₄, or PhSeCl, no fluorinated products were observed. Attempts to optimize our system found that use of AgF (3.0 equiv), PhSeCl (1.2 equiv) and non-substituted NFPy·BF₄ (2.2 equiv) in DCM provided the best results. Moving forward, we decided to screen a host of alkenes to assess the scope of our reaction. Gratifyingly, cyclic, branched, and linear alkenes were found to possess requisite reactivity, affording fluorinated products in good to excellent yields and in outstanding regioselectivity (Table 2). Of importance: (1) fluorination occurs at the most substituted carbon of the alkene; (2) allylic fluorides are favored over vinylic fluorides; (3) monofluorination is preferred (of particular significance in the case of diene **5**); (4) the formation of rearranged products is minimal despite the possible participation of carbocations.

In addition to these findings, we also discovered that conjugated alkenes, **9** and **11**, proved less amenable to deselenation, instead affording β -fluorophenylselenides predominantly. In such instances, we screened a host of conditions in the way of temperature, additive bases, Lewis acid catalysts, and co-oxidants in the hope of improving conversions to the appropriate allylic fluorides. Unfortunately, altering the reaction conditions resulted in either diminished yields or the appearance of several unidentifiable byproducts.

Investigating further, we next examined monoterpenes as potential candidates for allylic fluorination. Isoprene-derived substrates are often valuable precursors in the biosynthesis of other, higher-order products and have found considerable applications as both flavor additives and fragrance enhancers.²⁸ We found that reaction of the hemiterpene **6** under standard fluorination conditions afforded the tertiary fluoride **6b** in 55% yield by ¹⁹F NMR. Fortuitously, phthalimide **8** and biologically active citronellol benzoate **10** performed equally as well.

Unfortunately, the tertiary fluorides **6b**, **8b**, and **10b** proved difficult to isolate by conventional methods (column chromatography on silica gel or Florisil); polymerization and/or decomposition was observed. Nevertheless, the reaction proceeded with excellent regioselectivity.²⁹ In the case of **9** and **11**, diminished yields of **9b** and **11b** may likewise be attributed to the instability of allylbenzyl fluorides based on the literature precedent.²⁸

Table 2
Survey of allylic fluorinated substrates and products

Entry	Substrate	Allylic-H	AgF / PhSeCl (3:1.2 equiv) NFPy·BF ₄ (2.2 equiv) DCM, rt	Allylic-F	Product	Yield (%)
1		1a			1b	66 ^b
2		2a			2b	68 ^b
3		3a			3b	67 ^b
4		4a			4b	70 ^a
5		5a			5b	37 ^b (19.2:1)
6		6a			6b	55 ^b
7		7a			7b	47 ^a
8		8a			8b	71 ^a
9		9a			9b	15 ^b
10		10a			10b	68 ^b
11		11a			11b	24 ^b

All reactions were performed under an inert atmosphere of N₂ and stirred for 24 h.

^a Isolated as the major fluorinated product.

^b Yield based on ¹⁹F NMR using 3-chlorobenzotrifluoride as an internal standard.

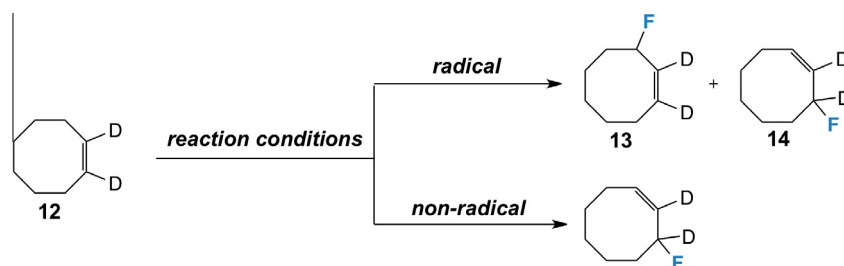
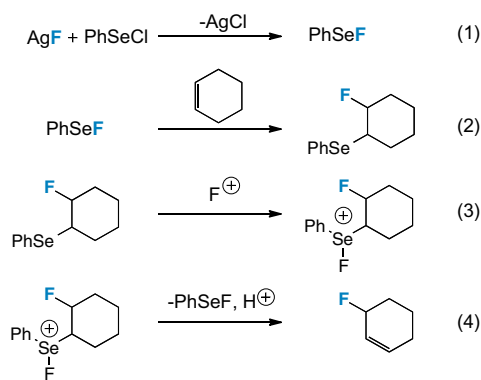


Figure 2. Isotopic labeling study.

Finally, we decided to undertake some preliminary mechanistic experiments. A reasonable place to start would be to assess the involvement of radicals—or equally likely—the participation of ionic intermediates (Fig. 2). In doing so, we sought the use of a vicinal dideuterated cycloalkene, *d*₂-1,2-cyclooctene **12**, as a mechanistic probe. If the reaction was to involve allylic radicals, we should

obtain a mixture of labeled fluorides **13** and **14**. In contrast, if the reaction proceeds by a purely electrophilic pathway, that is, involving the formation of ionic intermediates, only **14** is expected. The identity of these products may readily be determined from a combination of ²H NMR and ¹⁹F NMR analyses. Experimentally, subjecting of **12** to our reaction conditions provided a mixture of



Scheme 2. Tentative mechanism for the ionic component of allylic fluorination.

fluoroalkenes **13** and **14** in a ~1:4 ratio suggesting the formation of radicals during the reaction. Perhaps the participation of radicals may be used to explain products such as **5b**, as they are unlikely to be formed from a solely electrophilic pathway. For example, hydrogen atom abstraction from diene **5** to furnish the putative allylic radical followed by trapping with fluorine could conceivably lead to a mixture of allylic fluorides. We postulate that the formation of radicals may be due to a high-valent silver fluoride generated *in situ*, as they are known to participate in radical-based fluorinations.³⁰ In the presence of only silver(II) fluoride, we found that trace quantities of **3b** could be prepared from the starting alkene; further investigation regarding this finding will be conducted in the near future.

As a final point of interest, we wanted to examine if β -fluoroselenides could be directly converted to allylic fluorides through reaction with NFPy-BF₄, perhaps offering an explanation for the noted preference of **14** in our labeling study. To do so, β -fluoroselenide, (2-fluorocyclooctyl) (phenyl)selenane was first prepared *in situ* by the reaction of *cis*-cyclooctene with silver(I) fluoride (3.0 equiv) and phenylselenenyl chloride (1.2 equiv) in CH₂Cl₂. After stirring for 1 h, a crude ¹⁹F NMR of the reaction mixture was obtained followed by the addition of NFPy-BF₄ (2.2 equiv). At this point, the reaction mixture was stirred for an additional 1 h, after which a second ¹⁹F NMR spectrum was collected. Upon analysis, we found that after 1 h, in the absence of our electrophilic fluorinating reagent, no allylic products were evident. Instead, *exclusive* formation of the fluoroselenide was observed in 12% yield. However, the inclusion of NFPy-BF₄ resulted in a mixture of allylic fluoride (8%), fluoroselenide (36%) along with a considerable buildup of HF. Clearly, NFPy-BF₄ is needed for product formation. In line with our findings, we propose the following tentative mechanism for the preponderant ionic pathway of the reaction (Scheme 2): (1) *in situ* formation of phenylselenium fluoride (PhSeF); (2) electrophilic addition of PhSeF to the alkene; (3) oxidation of selenium by NFPy-BF₄; and (4) elimination of phenylselenium fluoride to give the allylic fluoride.

Conclusion

A mild, cooperative protocol for the regioselective allylic fluorination of alkenes has been developed utilizing both electrophilic and nucleophilic sources of fluorine. This new system provides ready access to allylic fluorides over a precedent background vicinal difluoride. Preliminary mechanistic evidence suggests the involvement of both carbocations and radicals in the reaction, although their exact roles are not yet known. Continued efforts to discern the precise mechanism of this new reaction will be made, in addition to the search for new applications of our system

to chemical synthesis and the construction of complex fluorinated molecules.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2014.05.093>.

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