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ARTICLE

Divergent Reactivities in Fluoronation of Allylic Alcohols: Synthesis of *Z*-Fluoroalkenes *via* Carbon-Carbon Bond Cleavage†

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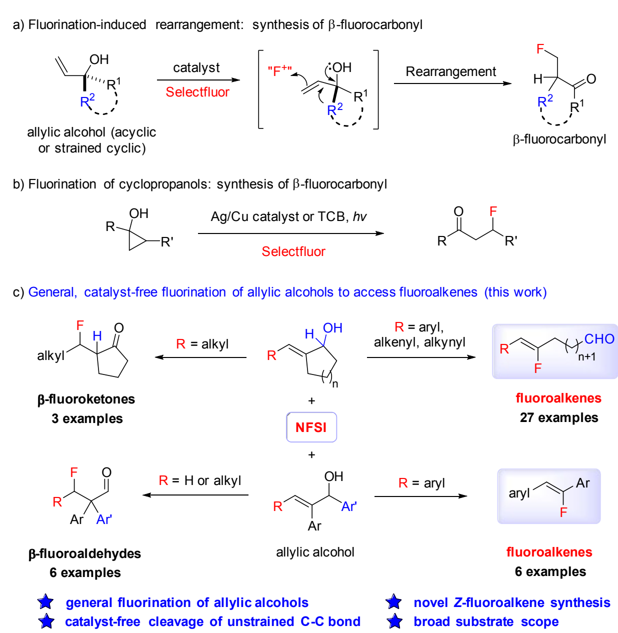
An unconventional cleavage of unstrained carbon-carbon bond in allylic alcohols can be induced by the use of *N*-fluorobenzenesulfonimide (NFSI) under catalyst-free conditions. By using this simple procedure, a wide range of functionalized *Z*-fluoroalkenes can be accessed in high yield and selectivity from cyclic and acyclic allylic alcohols.

Introduction

The incorporation of fluorine in pharmaceuticals and agrochemicals has become a common practice as a consequence of the attractive properties fluorine can confer on them.[1] Accordingly, fluorination chemistry has been extensively explored in the past decades to deliver fluorinated compounds of various substitution patterns.[2] Despite the great progress achieved for catalytic C_{sp3}-F bond formation[3] as well as aryl fluoride synthesis,[4] significant limitations still exist for the preparation of certain structures such as fluoroalkenes that are highly valuable as peptide isosteres and building blocks.[5] The preparation of fluoroalkenes through direct C-F formation requires the use of sensitive organometallic reagents or intermediates (such as alkenyl lithium) and are thus limited in the substrate scope.[6] Alternatively, classical olefination reactions using fluorine-containing reagents have been extensively explored;[7] the control of olefin geometry in these methods, however, has remained an unsolved challenge. Only very recently the synthesis of 1,2-disubstituted *Z*-fluoroalkenes was achieved through catalytic cross metathesis.[8] We present here a highly efficient and operationally simple method that can deliver functionalized trisubstituted *Z*-fluoroalkenes from readily available allylic alcohols with excellent stereoselectivity.

The electrophilic fluorination of enolate intermediates and alkenes has proven to be a highly successful strategy for C-F bond formation.[3] By utilizing allylic alcohols as the substrate, a tandem metal-catalyzed isomerization to the enolate followed by fluorination has been reported to prepare α-fluoroketones.[9] Alternatively, fluorination of the alkene moiety followed by semi-pinacol rearrangement was realized to prepare β-fluoroketones (Scheme 1a).[10] Related to this, the fluorination induced ring opening of cyclopropanols was also reported recently to deliver β-fluoroketones under Ag/Cu or photo-catalysis (Scheme 1b).[11] We have discovered a general and catalyst-free fluorination of allylic alcohols simply by reacting the substrate with commercial NFSI open to air (Scheme 1c). In particular, a conceptually new transformation of allylic alcohols to *Z*-fluoroalkenes was realized through the cleavage of non-activated carbon-carbon bond. It is noteworthy that carbon-carbon bond activation has been actively investigated as a new strategy in organic synthesis, with the majority of the systems involving transition metal-mediated opening of strained C-C bonds.[12] While examples of the activation of unstrained C-C bonds in carbonyl derivatives



Scheme 1. Fluorination of Allylic Alcohols and Cyclopropanols

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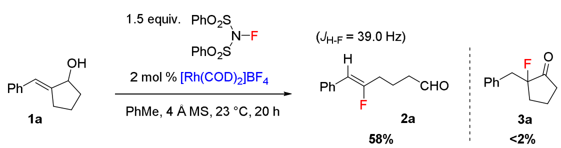
are known under transition metal- or photocatalytic conditions,[13] our method represents an unprecedented reactivity of allylic alcohols, in which the non-activated C-C bond undergoes cleavage induced by NFSI. The stereoselective formation of fluoroalkenes also renders this system a valuable tool in chemical synthesis.

Results and discussion

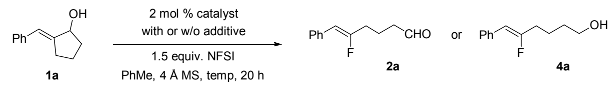
In the past few years, our laboratory has been exploring catalytic enantioselective redox-neutral processes for the preparation of important chiral entities.[14] During our investigation of a Rh-catalyzed isomerization of allylic alcohol **1a** to the corresponding α-benzyl cyclopentanone (Scheme 2),[14e] as a mechanistic probe we attempted the synthesis of **3a** by trapping the proposed enolate intermediate with an electrophilic fluorinating reagent such as NFSI. To our great surprise, none of **3a** could be accessed under this set of conditions and a completely unexpected product **2a** was formed instead. This transformation involves the cleavage of an unstrained carbon-carbon (C-C) bond in a five-membered ring and delivers synthetically versatile fluoroalkene **2a** as a single *Z*-isomer (determined by the $J_{H\text{-}F}$ value as well as 2D NMR; see SI for details). Intrigued by this discovery, we decided to explore this transformation in detail.



Scheme 2. Discovery of fluoroalkene synthesis from allylic alcohol.

As summarized in Table 1, a series of transition metal complexes based on Rh, Ir, Ru, etc were examined first. Interestingly, all these catalysts led to the formation of **2a** in similar yields of 58-60% (entries 1-3). The addition of ligands such as triphenylphosphine had no effect at all (results not shown). When the reaction was carried out by simply mixing **1a** and NFSI at ambient temperature in the absence of any catalyst, a 61% yield was obtained for **2a** (entry 4)! Clearly this intriguing C-C bond cleavage of allylic alcohols proceeds under transition metal-free conditions. The use of other fluorinating reagents such as Selectfluor provided no conversion to **2a** at all (entry 5). The effect of various bases as the additive was examined next, which led to reduced reaction efficiency (e.g., use of K_2CO_3 in entry 6). Considering the important precedent on photo-catalyzed fluorination reactions from the Lectka group,[13b] we tested the effect of light for our reaction. By carrying out the same reaction in the dark. The same reaction efficiency was obtained, thus excluding the possibility of photocatalysis (entry 7). When Ag- or Cu-based salts that are known to promote single electron transfer were examined, no improvement was observed for our reaction either (entries 8-9).[11]

Table 1. Optimization of Fluoroalkene Synthesis.[a]



entry	catalyst	F^+ (equiv.)	T (°C)	Yield (%)[b]
1	$[Rh(cod)_2]BF_4$	NFSI (1.5)	23	58
2	$[Ir(cod)Cl]_2$	NFSI (1.5)	23	60
3	$[RuCl_2$(*p*-cymeme)$]_2$	NFSI (1.5)	23	59
4	/	NFSI (1.5)	23	61
5	/	Selectfluor	23	<5
6	K_2CO_3	NFSI (1.5)	23	55
7	*In dark*	NFSI (1.5)	23	60
8	Ag_2CO_3	NFSI (1.5)	23	54
9	CuCl	NFSI (1.5)	23	50
10	/	NFSI (1.5)	40	66
11	/	NFSI (2.0)	40	70
12	/	NFSI (2.0)	40	**82 (4a)**[c]

[a] The reactions were carried out with 0.2 mmol **1a** and 100 mg 4Å molecular sieve in 2 mL toluene open to air using commercially available NFSI. [b] Isolated yields. [c] The isolated yield of alcohol **4a** after the reduction of aldehyde.

To further optimize the reaction, the loading of NFSI and the reaction temperature were varied. The use of 2.0 equiv. of NFSI at 40 °C proved to be the optimal (entries 10-11). Overall, a simple and effective procedure that involves a simple mixing of the substrate and NFSI with gentle heating proved to be the most effective. Finally, a more convenient procedure was adopted that included an *in situ* reduction of **2a** using $NaBH_4$; the corresponding primary alcohol **4a** could be isolated in a high yield of 82% (entry 12). The scale-up of this reaction proved to be straightforward as well. A similar yield of 78% was obtained for **4a** on a 5 mmol scale (Scheme 3).

With the optimal conditions in hand, we moved on to explore the scope of this ring-opening fluorination reaction. For the ring-opening of cyclopentanols (n = 1), various substituted aryl groups can be well-tolerated (Scheme 3a). A wide range of fluoroalkenes bearing electron-deficient (**4b**-**4e**), electron-neutral (**4f-g**) and electron-rich (**4h**) substitutions at the *para*-position of the arene were prepared in good to excellent yield. Reactive functionalities such as ester or cyano groups could be well tolerated to produce (**4i**-**4j**) in good yield as a single isomer. *Meta*-substituted arenes such as **4k** worked out similarly well. For *ortho*-substituted substrates (**4l**-**4n**), only moderate yields were obtained probably due to steric hindrance of these substrates. Naphthyl- and heterocycle-substituted fluoro-alkenes (**4o**-**4r**) could also be prepared in reasonable yields. While alkyl-substituted allylic alcohols failed to produce the desired products, alkenyl- and alkynyl-substituted substrates underwent fluorination smoothly to produce fluoro-substituted diene **4s** and enyne **4t**. Such highly functionalized fluoroalkenes are accessed for the first time and could prove highly valuable as building blocks in chemical synthesis.

In addition to cyclopentanols, this fluorination method is also applicable to the opening of different sized rings, including 4, 6, 7, and 8-membered substrates (Scheme 3b). In this way a series of fluoroalkenes bearing a formyl or alcohol functionality in different distances can be accessed

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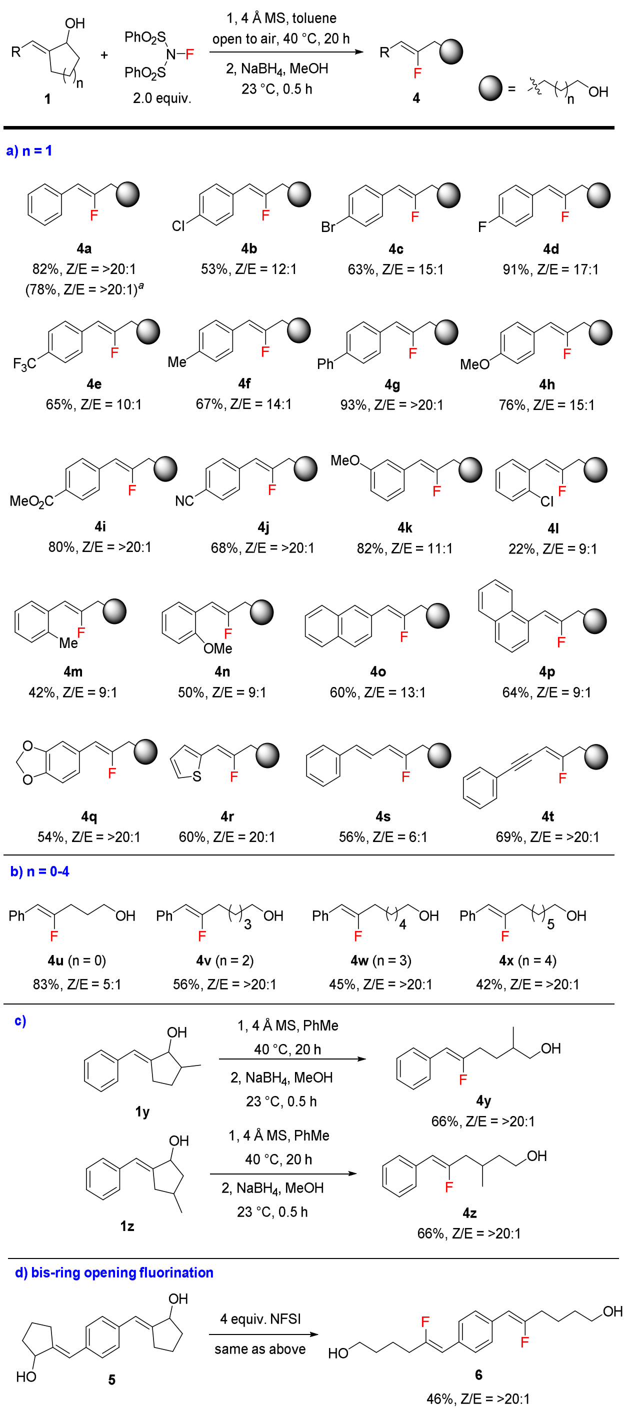
conveniently, although the efficiency gradually drops for longer tethers (**4u-4x**). In addition to the generation of simple linear products, substitution at different positions in the cycloalkanol substrates (such as **1y** and **1z**) was well-tolerated to produce α- or β-branched fluoroalkene-containing alcohols **4y** and **4z** with excellent *Z*-selectivity (Scheme 3c).

Scheme 3. Scope of Fluorination-Induced Ring Opening of Cyclic Allylic Alcohols

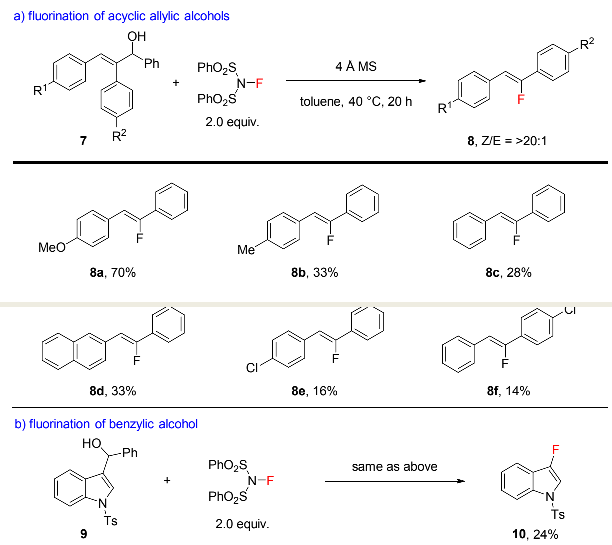


See SI for detailed procedure. The product *Z*/*E* ratios were determined by crude NMR. All yields are isolated yields. [a] 5 mmol scale reaction

Finally, a double fluorination of bis-allylic alcohol **5** also worked out smoothly to produce bis-fluoroalkene **6** in moderate yield as a single isomer (Scheme 3d). This transformation, however, failed to produce ketone products by the reaction of tertiary allylic alcohols related to **1a**. Although tertiary alcohols are more popular substrates in carbon-carbon bond activation, in our case the more serious steric hindrance in these substrates are likely the culprit for this lack of reactivity.

The success of the opening of large-ring substrates suggested that acyclic substrates might undergo similar transformation as well. Substituted acyclic allylic alcohols were examined next. As shown in Scheme 4a, this type of substrates underwent the same C-C bond cleavage to produce trisubstituted fluoroalkenes,[7,8] while producing benzaldehyde as the side product. It is noteworthy the alternative semi-pinacol rearrangement product (Scheme 1b) was not observed at all. The efficiency of this process, however, leaves much room for further optimization. While **8a** bearing an electron-rich aryl substituent was obtained in a good yield of 70%, most fluoroalkenes were produced in yields ranging from 14-33%. The stereoselectivity of this process, however, is uniformly high to produce the fluoroalkenes as a single *Z*-isomer. Related fluoroalkenes of the same substitution pattern have been popular targets in medicinal chemistry[15] and our method represents an alternative method for their synthesis with unparalleled stereoselectivity.

In addition, this fluorination of allylic alcohols can be extended to benzylic alcohols (Scheme 4b). A proof-of-principle reaction involves the fluorination of indole-substituted benzylic alcohol **9**, which produced 3-fluoroindole **10** in 24% yield. This greatly expanded the scope of this fluorination method and further application is currently under investigation.



Scheme 4. Scope of Fluorination of Acyclic Allylic and Benzylic Alcohols

It is worth noting that an aryl (or sp^2-hybridized) substituent on the alkene moiety of the allylic alcohol

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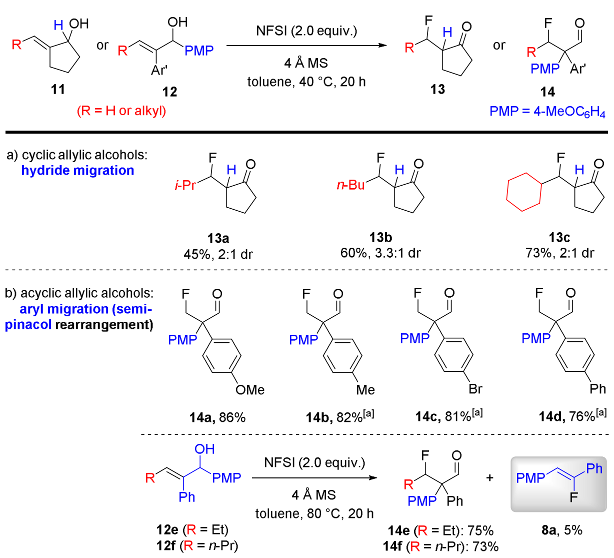
substrates is required for the synthesis of fluoroalkenes as shown in scheme 3 and 4. When allylic alcohols bearing an alkyl substituent were examined (**11** or **12**), an intriguing, complete switch of reactivity was observed (Scheme 5). In the case of cyclopentanols **11**, fluorination under identical conditions led to the formation of β-fluoroketones **13a-c** in moderate to good yields, which should be formed via β-fluorination followed by a hydride migration. In contrast, the acyclic allylic alcohols **12** underwent β-fluorination followed by a more classical semi-pinacol rearrangement to deliver β-fluoroaldehydes **14a-f** in uniformly good yield.[10] While these β-fluoroketones **13** and **14** are valuable compounds for their own sake, their synthesis also provided important insight for the mechanism of this catalyst-free fluorination of allylic alcohols. More intriguingly, a small amount of fluoroalkene **8a** was obtained during the synthesis of **14e** and **14f**. The formation of **8a** from **12**, a formally cleavage of the alkene moiety of the substrate, led us to hypothesize the involvement of a key oxetane intermediate in the fluoroalkene synthesis.

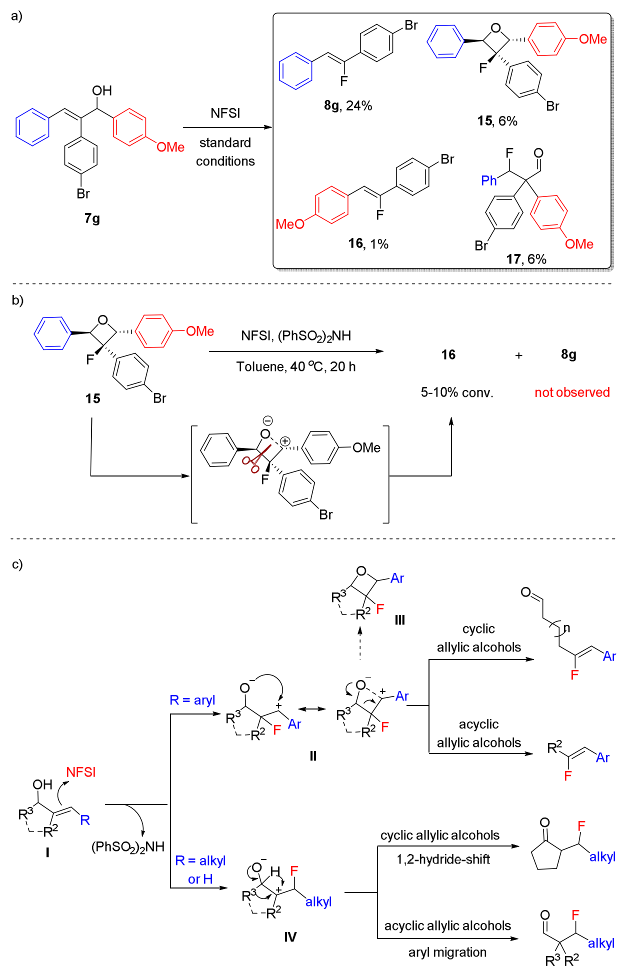


See SI for detailed procedure. The product d.r. ratios were determined by crude NMR. All yields are isolated yields. [a]The reaction was carried out at 80 °C.

Scheme 5. Fluorination of alkyl-substituted allylic alcohols.

In an effort to better understand the limitation in the fluorination of acyclic allylic alcohols, the reaction of **7g** was carried out in a larger scale and the product mixture was analyzed carefully (Scheme 6a). In addition to the desired fluoroalkene **8g**, β-fluoroaldehyde **17** was isolated in a low yield, indicating that two fluorination pathways were in competition. More interestingly, a small amount of oxetane **15** and the alternative *Z*-fluoroalkene **16** were also isolated, which could be linked to the formation of **8a** from fluorination of **12e**/**12f** as shown in scheme 5.

When oxetane **15** was subjected to the fluorination conditions (scheme. 6b), however, only a slow conversion to **16** was observed; no formation of **8g** could be detected. We hypothesized that the conversion of **15** to **16** likely proceeded through a zwitterionic intermediate and the carbocation is formed preferentially on the more electron-rich benzylic position, which explained why **8g** was not formed. This observation also indicated that oxetane is likely a side reaction pathway in the fluoroalkene synthesis instead of being an intermediate for the formation of **8g** or other fluoroalkenes shown in scheme 4.



Scheme 6 Preliminary mechanistic studies and the proposed reaction pathway.

Based on the above observations and taken all the types of fluorination products into consideration, we propose the general mechanism for fluorination of allylic alcohols using NFSI shown in scheme 6c. For the substrates bearing an aryl substituent (or alkenyl, alkynyl as in **5s** and **5t**), the electrophilic fluorination generates a zwitterion **II**, in which the formation of a more stable benzylic carbocation serves as the driving force for this regio-selectivity. Fragmentation of **II** then leads to the formation of fluoroalkenes. Oxetane formation (**III**) is a side pathway from this reaction, which could undergo fragmentation through zwitterion **II** or the alternative species to deliver the more electron-rich fluoroalkene product (e.g., **16**).[16] For the substrates bearing an alkyl substituent, on the other hand, the electrophilic fluorination takes place at the β-position to generate zwitterion **IV**. Again the stability of carbocation is likely the determining factor. A migration (either

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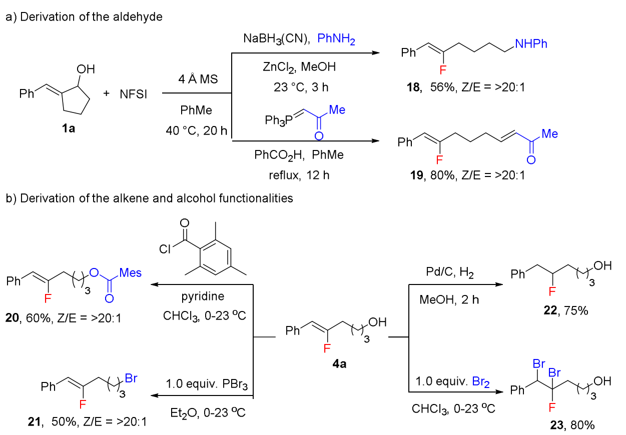
a hydride or aryl group) will then follow to deliver the more traditional β-fluorocarbonyl products.

The products from this reaction can be used as versatile building blocks to prepare various organofluorine compounds (scheme 7). In addition to the reduction of **2a** to yield alcohol **4a**, reductive amination or Wittig olefination of **2a** worked out smoothly in one-pot with fluorination to yield amine **18** or enone **19** in good yield (Scheme 7a). The alcohol functionality in **4a** could also be converted to ester or bromide functionalities as in **20** and **21** without optimization (Scheme 7b). More importantly, the fluoroalkene moiety has proven to be a synthetically versatile building block to access a diverse range of fluoro-containing compounds.[17] As representative examples, hydrogenation and dibromination of **4a** were carried out to produce alkyl fluoride **22** and multiple-halogen-containing **23**.



Scheme 7 Derivatization of Fluoroalkenes.

Conclusions

We have discovered a general fluorination of allylic alcohols and in particular, a conceptually new and practical method to access functionalized *Z*-fluoroalkenes with good to excellent geometry control. This operationally simple procedure involves the reaction of readily available allylic alcohols and NFSI open to air with gentle heating to produce the versatile functionalized fluoroalkenes. Current efforts in our laboratory are focused on the application of this method to the preparation of other valuable fluorinated compounds.

Acknowledgements

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