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Exploiting a Difference in Leaving Group Ability: An Approach to β-Substituted Monofluoroalkenes Using *gem*-Chlorofluoropropenes

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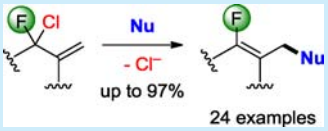
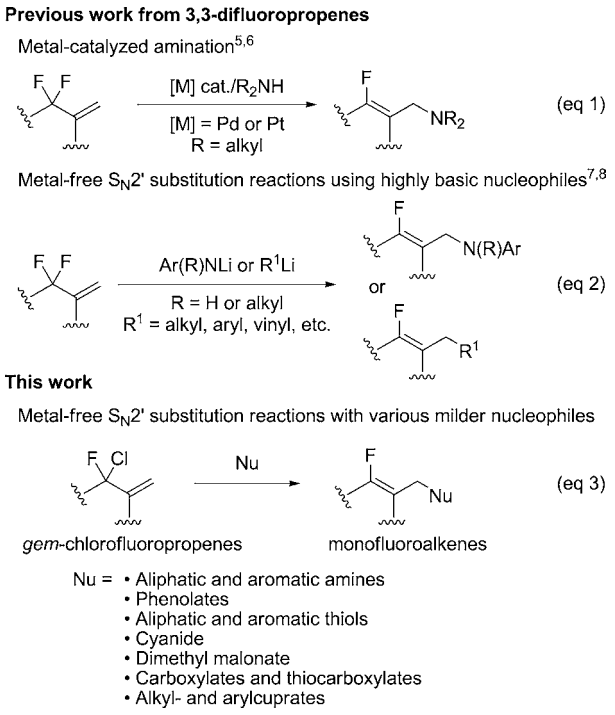
Supporting Information

ABSTRACT: The superior nucleofuge character of chlorine over fluorine was taken advantage of in the selective S_N2' substitution reaction of *gem*-chlorofluoropropenes, allowing for the clean formation of β-substituted monofluoroalkenes under metal-free conditions. Numerous *N*-, *S*-, *O*-, and *C*-nucleophiles behaved nicely in this system. Further synthetic transformations of selected monofluoroalkenes were also accomplished.



Organofluorine compounds occupy a significant place in medicinal chemistry, agrochemistry, and material sciences due to the unique properties of the fluorine atom.[1] It is, therefore, not surprising that considerable effort has been dedicated to the discovery and improvement of methods for the preparation of fluorinated compounds.[2] Over the past years, we have been particularly interested in the synthesis of monofluoroalkenes,[3] a useful enol or amide mimic, from 3,3-difluoropropenes[4] using either transition-metal-catalyzed (Scheme 1, eq 1)[5,6] or metal-free (Scheme 1, eq 2)[7,8] reactions. All of these approaches relied on using one of the fluorine atoms as a leaving group, even though it is generally considered a poor one.[1,9] While these methods provide a convenient access to this important fluorinated motif, they suffer from drawbacks. For instance, the Pd-catalyzed reaction only allowed the use of aliphatic amines (Scheme 1, eq 1, [M] = Pd).[5] Likewise, the Pt-catalyzed reaction only tolerated secondary aliphatic amines, and other nucleophiles behaved poorly (Scheme 1, eq 1, [M] = Pt).[6] Concerning the metal-free approach (Scheme 1, eq 2), only organolithium reagents, lithium thiolates, and lithium anilides performed well. In this case, the high basicity of those reagents considerably limits the functional group tolerance. Considering those issues, we decided to explore a milder and more versatile alternative that would not only solve the concerns raised but also extend the scope in terms of nucleophiles, thus allowing the possibility to prepare more functionalized β-substituted monofluoroalkenes.

Scheme 1. Previous Work and Current Work



To this end, we sought to exploit the difference in leaving group ability between a fluorine and a chlorine in geminal relationship,[1b,10] a phenomenon that has been rarely taken advantage of.[11−19] Herein, we report a convenient approach to β-substituted monofluoroalkenes from *gem*-chlorofluoropropenes exploiting this difference in nucleofuge character (Scheme 1, eq 3).[20] Notably, this transformation provides structurally diverse monofluoroalkenes and is compatible with a wide range of milder nucleophiles, some of which could not be employed using previous methods.

The reactivity was initially investigated using chlorofluoropropene **1**, which was easily obtained from 1-tetralone in three steps (α-fluorination using Selectfluor, α-chlorination using *N*-chlorosuccinimide, and Peterson olefination),[21] and morpholine as the nucleophile. After some optimization, it was found that the desired β-aminomonofluoroalkene **2a** could be obtained in 96% isolated yield (Scheme 2). This result compared favorably with the 72% and 68% yields achieved in the Pd- and Pt-catalyzed transformations, respectively (i.e., Scheme 1, eq 1).[5a,6]

Delighted with this initial result, we began exploring the use of other nucleophiles and found that a variety could be employed successfully upon slight modifications of reaction

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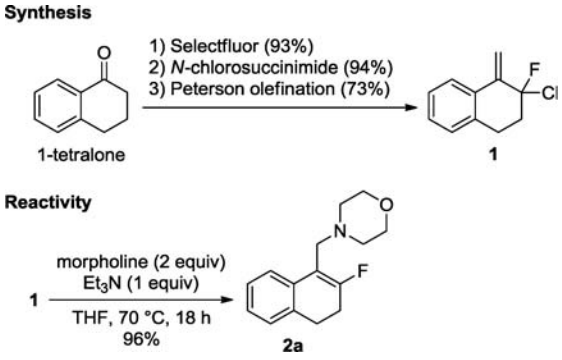
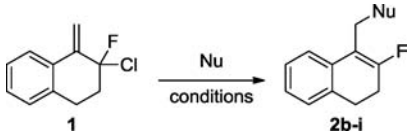
Scheme 2. Synthesis and Reactivity of Chlorofluoropropene 1 with Morpholine



conditions (Table 1). For instance, the use of sodium phenolate provided the monofluoroalkene **2b** in 80% yield (Table 1, entry 1). Notably, a phenolic nucleophile did not work with 3,3-difluoropropenes (i.e., Scheme 1, eq 2),[8] where an elimination side reaction was predominant. Sulfur-based nucleophiles, such as an alkyl- and an arylthiolate, as well as a thiocarboxylate, all behaved nicely (Table 1, entries 2−4), and the desired products **2c−e** could be obtained in very good to excellent yields.[22] The use of cyanide (Table 1, entry 5) as the nucleophile provided the β-cyanomonofluoroalkene **2f** in 96% yield. Interestingly, the nitrile functionality opens the door to further transformations (vide infra). Dimethyl malonate reacted well, and the monofluoroalkene **2g** was produced in 82% yield (Table 1, entry 6). Phenyl cuprate (generated in situ from the corresponding Grignard reagent and copper(I) bromide dimethyl sulfide complex)[23] was a suitable nucleophile, and the monofluoroalkene **2h** was obtained in 95% yield, which compares favorably with the 80% obtained using highly basic phenyllithium with a 3,3-difluoropropene (i.e., Scheme 1, eq 2).[7] At that point, despite extensive optimization, the use of either sodium methoxide (an alkoxide), sodium acetate (a carboxylate), or *N*-methylaniline (an aromatic amine) did not provide the desired product in satisfactory yields (not shown in Table 1). Finally, iodide could be used successfully as a nucleophile to provide the β-iodomonofluoroalkene **2i** in good NMR yield (Table 1, entry 8). While the isolation of the product did not prove possible, its clean formation, as shown by NMR, provided an opportunity to use it as an intermediate to promote substitution with reluctant nucleophiles (Scheme 3).

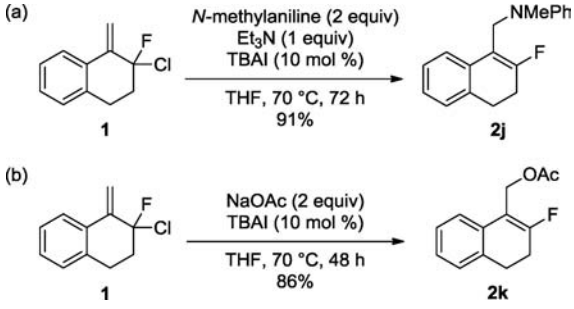
Table 1. Reactivity of Chlorofluoropropene 1 with Various Nucleophiles[a]



entry	2, Nu	conditions	yield (%)
1	**2b**, OPh	NaOPh, THF, 70 °C, 72 h	80
2	**2c**, SPh	NaSPh, THF, rt, 1 h	97
3	**2d**, $S(CH_2)_9CH_3$	$NaS(CH_2)_9CH_3$, THF, rt, 1 h	90
4	**2e**, SAc	KSAc, THF, 70 °C, 18 h	84
5	**2f**, CN	KCN, DMF, rt, 24 h	96
6	**2g**, $CH(CO_2Me)_2$	$NaCH(CO_2Me)_2$, CH_3CN 70 °C, 18 h	82
7	**2h**, Ph	PhMgBr, CuBr·SMe_2, THF, 50 °C, 18 h	95
8	**2i**, I	NaI, acetone, 60 °C, 18 h	74[b]

[a]See the Supporting Information for the detailed experimental procedures. [b]NMR yield estimated using 2-fluoro-4-nitrotoluene as the internal standard.

Scheme 3. Reaction of 1 with (a) *N*-Methylaniline and (b) Sodium Acetate in the Presence of a Catalytic Amount of Iodide



Indeed, using either *N*-methylaniline or sodium acetate in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) provided the desired monofluoroalkenes **2j** and **2k** in 91% and 86% yield, respectively, thus further expanding the scope to carboxylates and aromatic amines as suitable nucleophiles for this transformation.

The reactivity of analogues of successful *N*-, *S*-, *O*-, and *C*-nucleophiles was next assessed (Scheme 4). Functionalized secondary amines such as L-proline methyl ester and 2-(methylamino)ethanol reacted well with **1** and provided the desired products **2l** and **2m** in 85% and 64% yield, respectively. Notably, in the latter case, protection of the alcohol was not necessary. An excellent yield of **2n** was obtained with *n*-butylamine (a primary amine) from **1** as long as an excess of the nucleophile was used to avoid a mixture of mono- and dialkylated products. Interestingly, L-cysteine methyl ester reacted with **1** and provided the *S*-alkylation product **2o** in 70% yield without any need for the protection of the nitrogen. Using estrone as a source of a functionalized phenolate provided product **2p** in 78% yield. Other chlorofluoropropenes could also be utilized. For instance, the chlorofluoropropene derived from 1-indanone **4** reacted with an aliphatic amine, *N*-methylbenzylamine, to provide monofluoroalkene **9** in 78% yield. Similarly, when the chlorofluoropropene obtained from 4-chromanone **6** was used, reaction with indoline, an aromatic amine, afforded monofluoroalkene **10** in 61% yield. In addition, monofluoroalkene **11** was isolated in 61% yield after exposure of the chlorofluoropropene prepared from 4,4-dimethyl-2-cyclohexen-1-one (**6**) to sodium thiophenolate. Finally, acyclic chlorofluoropropenes could also be used, as exemplified by the transformations of chlorofluoropropenes **7** and **8** into monofluoroalkenes **12a,b** and **13a,b**, respectively, which were obtained in good to excellent yields as a mixture of diastereoisomers. Interestingly, when **7** was used with either morpholine **12a** or sodium thiophenolate **12b** as the nucleophile, the *E*/*Z* selectivity could be modestly modulated by changing the solvent. In both cases, the use of DMF, a more polar solvent, favored the *E*-isomer as the major one, while the use of a less polar solvent (i.e., toluene or THF) produced the opposite *Z*-isomer as the major isomer.[24,25] The reason behind the change in selectivity is not clear at the moment, and further studies to understand this are in progress.

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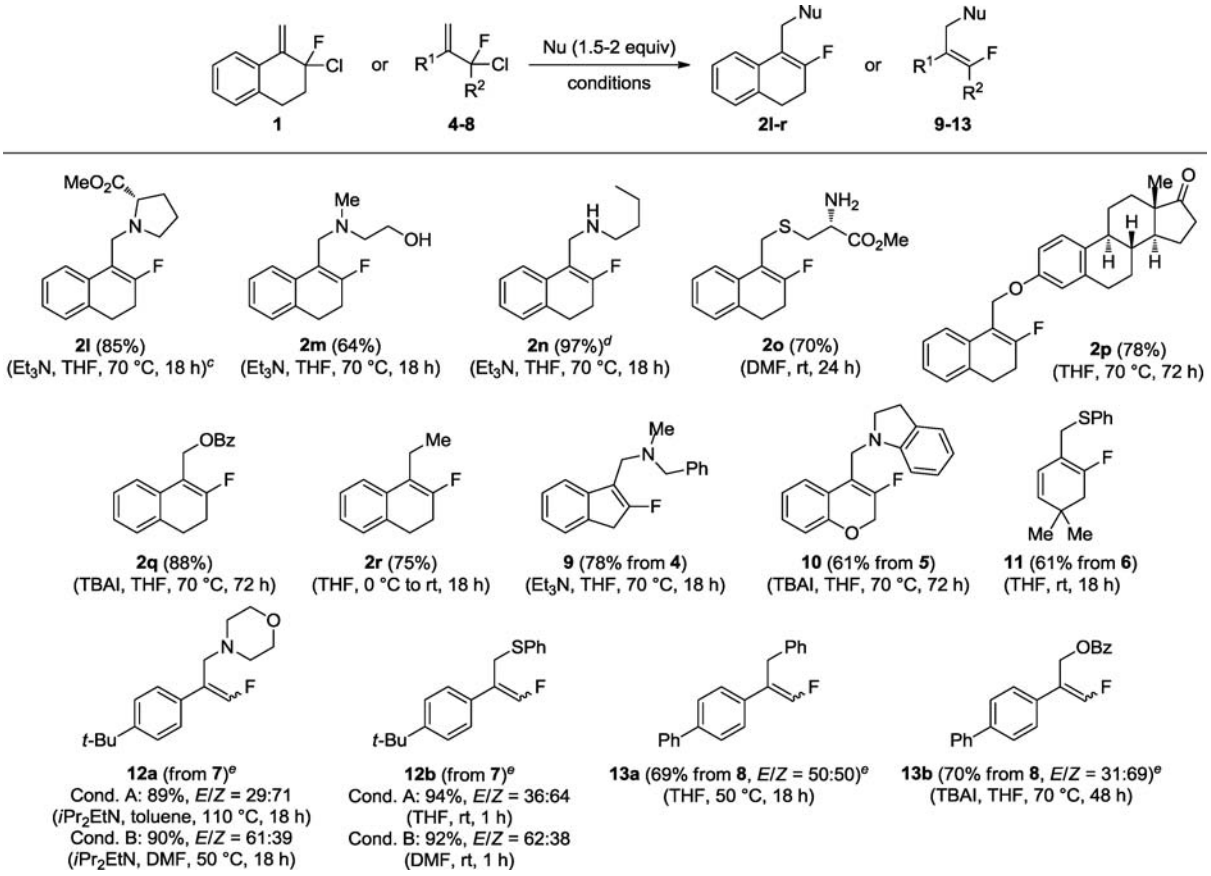
Scheme 4. Reaction of Cyclic and Acylic Chlorofluoropropenes with Various *N*-, *S*-, *O*-, and *C*-Nucleophiles[a,b]

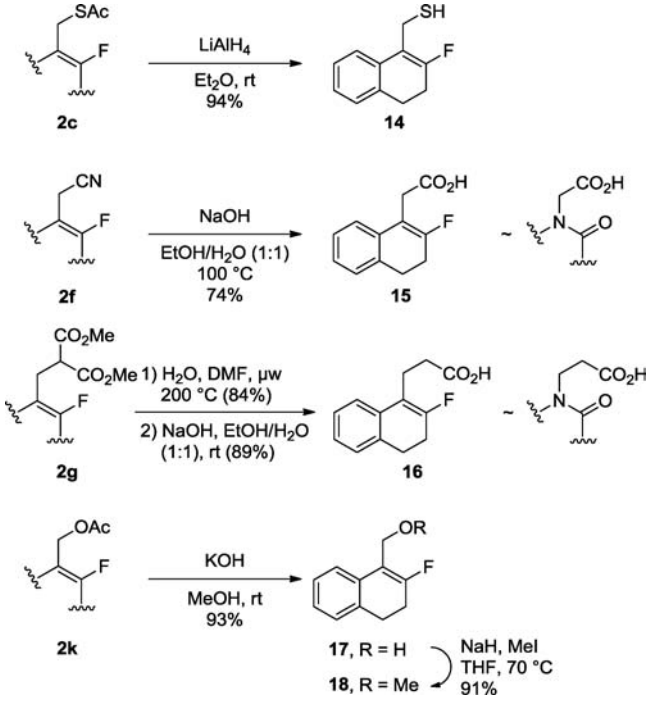


[a]See the Supporting Information for the detailed experimental procedures. [b]Isolated yield. [c]5 equiv of the nucleophile was used. [d]10 equiv of the nucleophile was used. [e]Isolated as a mixture of stereoisomers; *E*/*Z* ratio estimated by ^{1}H or ^{19}F NMR.

Finally, to further extend the utility of this new approach, we investigated potential transformations of the monofluoroalkenes generated (Scheme 5). For instance, reduction of the thioester moiety of **2c** with $LiAlH_4$ provided an excellent yield of *β*-mercaptomonofluoroalkene **14**.[22] Hydrolysis of nitrile **2f** under basic conditions gave acid **15** in 74% yield. As monofluoroalkenes can be seen as amide mimics,[3] this particular product resembles an amide bond between a glycine and an *N*-substituted amino acid. Likewise, a two-step decarboalkoxylation[25]/hydrolysis sequence of malonate **2g** provided acid **16**, which in this case, corresponds to an amide bond between a *β*-glycine and an *N*-substituted amino acid. Finally, deprotection of the acetate of **2k** through methanolysis led to the alcohol **17**,[22c,26] which could be methylated to provide methyl ether **18**. Thus, even if, at this time, preparation of **18** directly from **1** using methoxide as the nucleophile is not possible, this short and high-yielding three-step procedure provides an alternative route to *β*-alkyloxymonofluoroalkenes.

In conclusion, we have reported the preparation of *β*-substituted monofluorolalkenes through allylic substitution of *gem*-chlorofluoropropenes. This strategy relies on the difference in leaving group ability between chlorine and fluorine atoms bonded to the same carbon atom. As neither a transition metal nor a highly basic nucleophile is required in this reaction, a broader range of nucleophiles was shown to be compatible as compared to our previous work. Overall, this new approach allows the preparation of structurally diverse monofluoroal-

Scheme 5. Synthetic Transformation of Some Monofluoroalkenes Obtained



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kenes, potentially useful fluorinated building blocks for medicinal chemistry efforts, in good to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00590.

Detailed experimental procedures and full spectroscopic data for all new compounds (PDF)

Crystallographic data of (*E*)-**12a**·HCl (CIF)

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Notes

The authors declare no competing financial interest.

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(20) To the best of our knowledge, only one example of such a reaction with highly basic nucleophiles has been reported before; however, a mixture of substitution products resulting from the departure of either the fluoride or the chloride was observed; see ref 7. for details.

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(23) A stoichiometric amount of copper salt was used since **1** decomposed rapidly in the presence of Grignard reagents.

(24) Stereochemistry of **12a** was confirmed by XRD analysis of (***E***)-**12a·HCl** (CCDC 1451457). Stereochemistry of compounds **12b**, **13a**, and **13b** was attributed by examination of the ^{1}H, ^{19}F, and ^{13}C NMR spectra.

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