Synthetic Methods

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The Use of Fluoride as a Leaving Group: S_N2' Displacement of a C−F Bond on 3,3-Difluoropropenes with Organolithium Reagents To Give Direct Access to Monofluoroalkenes**

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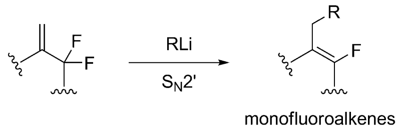
The C−F bond is the strongest single carbon–halogen bond (DH_{298} CH_3−F = 115 kcal mol^{-1} compared to DH_{298} CH_3−I = 57.6 kcal mol^{-1}).[1] As a result, as well as for other reasons, fluoride has the worst leaving group ability of the halogen series (nucleofuge ability: $I^- > Br^- > Cl^- \gg F^-$). It is therefore not surprising that reactions involving nucleophilic displacement of a C_{sp^3}−F bond are not common.[2,3] To compensate for the lack of reactivity, the use of transition metals to catalyze or mediate the activation and/or harsh conditions have emerged as viable solutions.[2a] Interestingly, geminal trifluoro allylic compounds, that is, trifluoromethylated alkenes or 3,3,3-trifluoropropenes react directly under mild conditions and without the use of transition metals with hard and soft nucleophiles to generate 3-substituted-1,1-difluoroalkenes via, in most cases, an S_N2' pathway.[2a,4,5] This increase in reactivity has been postulated to the fact that a trifluoromethyl group attached to an alkene lowers the LUMO of the bond, arising from both the inductive electron-withdrawing effect of the trifluoromethyl group ($\sigma_I = 0.38$) and its electron-withdrawing resonance effect ($\sigma_R = 0.16$), and therefore accelerates nucleophilic addition to the double bond.[4] These inductive and resonance effects are less important in 3,3-difluoropropenes ($\sigma_I = 0.29$, $\sigma_R = 0.03$) and 3-fluoropropenes ($\sigma_I = 0.15$, $\sigma_R = -0.04$),[4] and as such, similar reaction with 3,3-difluoropropenes are scarce and, aside from metal-catalyzed transformations,[6,7c] are limited to the addition of soft nucleophiles such as organocopper and aluminum-based reagents, or reduction using organocopper-, samarium diiodide- or N-hetereocyclic carbene-mediated transformation.[8] In addition, the presence of a free alcohol group in close proximity is necessary for reactivity in a few cases. In line with our efforts to design new synthetic methods for the preparation of monofluoroalkenes,[7] we wondered if the addition of hard nucleophiles such as organolithium reagents would proceed on 3,3-difluoropropenes. This method would provide a simple and straightforward approach to this pharmaceutically important fluorinated motif (Scheme 1).[9]

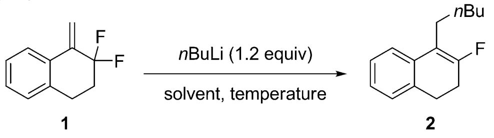


Scheme 1. S_N2' reaction of 3,3-difluoropropenes with organolithium reagents.

Herein, we report our initial studies on the S_N2' displacement of C−F bonds on 3,3-difluoropropene compounds with various organolithium reagents. Notably, this transformation occurs without nearby directing groups and preliminary results support the importance of a fluorine–lithium interaction in activating the C−F bond. Finally, this transformation represents the first example of the addition of hard nucleophiles to 3,3-difluoropropenes.

Initial reactions were performed on 3,3-difluoropropene **1** derived from α-tetralone and are reported in Table 1. When **1** was treated with *n*BuLi at −78 °C, full conversion was observed and the desired product **2** was isolated in 97% yield. The reaction could also be carried out at higher temperature with comparable results (Table 1, entries 2 and 3). Tetrahydrofuran could be replaced by Et_2O or hexanes without affecting the reaction (compare Table 1, entries 5 and

Table 1: Initial results for the S_N2' reaction of *n*-butyllithium with 3,3-difluoropropene **1**.[a]



Entry	Solvent	T [°C]	Conv. [%][b]	Yield [%][c]
1	THF	−78	100	97
2	THF	0	100	78
3	THF	21	100	80
4	Et_2O	−78	56	–
5	Et_2O	0	100	77
6	hexanes	−78	0	0
7	hexanes	0	95	77

[a] See the Supporting Information for details of the reaction conditions. [b] Determined by ^{19}F NMR spectroscopic analysis of the crude mixture. [c] Yield of isolated **2**. THF = tetrahydrofuran.

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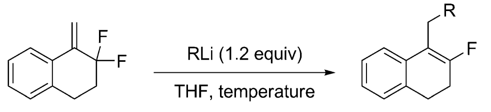
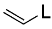
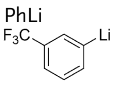
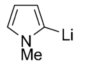
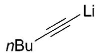
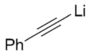
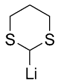
7) although good conversions were only observed at 0 °C. The possibility of using various solvents is important because commercially available or synthetically prepared organolithium reagents are often sold or prepared specifically in one of these three solvents.[10]

We next examined the scope of organolithium reagents (Table 2). Various alkyl lithium reagents (Table 2, entries 1–3) could be used including *tert*-butyllithium, which readily added at −78 °C. An sp^2-based organolithium could also be added such as vinyllithium, phenyllithium, and (3-trifluoromethyl)-phenyllithium (Table 2, entries 4–6). In the case of the lithium reagent derived from *N*-methylpyrrole, a higher temperature was required to achieve a good yield (Table 2, entry 7). Even less-nucleophilic lithiated alkynes could react with **1** although a higher temperature was required (Table 2, entries 8 and 9) and led, in the case of phenylacetylene, to a low yield of the desired product **3i**. Interestingly, 2-lithio-1,3-dithiane added smoothly to **1** in good yield (Table 2, entry 10). Finally, reduction of **1** was possible using $LiAlH_4$ or $LiEt_3BH$ and furnished the same product **3k** in 97 % and 73 % yield, respectively (Table 2, entries 11 and 12).

Table 2: Scope of organolithium reagents.[a]



1 **3a-k**

Entry	RLi	*T* [°C]	Product **3**	Yield [%][b]
1	MeLi	21	**3a**	82
2	*s*BuLi	0	**3b**	76
3	*t*BuLi	−78	**3c**	79
4		−78→21	**3d**	61
5	PhLi	21	**3e**	80
6[c]		21	**3f**	76
7[d]		66	**3g**	72
8		66	**3h**	78
9		66	**3i**	30
10[d]		0	**3j**	73
11[e]	$LiAlH_4$ (R=H)	0	**3k**	97
12[d]	$LiEt_3BH$ (R=H)	0	**3k**	73

[a] See the Supporting Information for details of the reaction conditions. [b] Yields after purification by flash chromatography. [c] Reaction was performed in Et_2O. [d] Performed with 3.0 equivalents of the organolithium reagent [e] Performed with 2 equivalents of $LiAlH_4$.

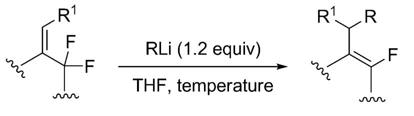
In terms of substrate, a variety of 3,3-difluoropropenes, as shown in Table 3, could be used. These included cyclic (Table 3, entries 1–7) or acyclic (Table 3, entries 8–14) substrates, thus allowing the preparation of structurally diverse tri- or tetrasubstituted monofluoroalkene compounds. Notably, a number of functional groups can be tolerated and included an alcohol (Table 3, entry 8), a carboxylic acid (Table 3, entry 12), a Boc-protected amine (Table 3, entry 13), or an aryl chloride (Table 3, entry 14). The reactivity of 3,3-difluoropropene **4c** derived from 2,2-difluoro-1-indanone is interesting. Although its reduction using $LiAlH_4$ proceeded well (Table 3, entry 3), when treated with MeLi, full conversion was observed but monofluoroalkene **5d** was isolated in low yield (35 %) along with a number of unidentified side products (Table 3, entry 4). We hypothesized that the methylene protons in **5c**, which are both benzylic and allylic, can be easily abstracted under the reaction conditions leading to various side reactions. Based on these observations, we envisioned an alternative route to monofluoroalkene **5d** based on the reduction of 3,3-difluoropropene **4d**. As expected, this reduction worked well and furnished **5d** in 76 % yield, thus demonstrating that for some problematic substrates, alternative synthetic routes may be available (Table 3, entry 5).

We then studied the halogen-atom effects. We first examined whether or not two fluorine atoms were required for the reaction to occur by using 3-fluoropropene **6** with *n*BuLi (Scheme 2).[11] The reaction of **6** proceeded smoothly and **7** was isolated in good yield, thus indicating that the two fluorine atoms are not essential for reactivity. We next examined the reactivity of 3-chloro-3-fluoropropene **8** under identical conditions. Interestingly, the monofluoroalkene **2** was isolated as the major product (65 %) while the monochloroalkene **9** was only isolated in 18 % yield. In this case, nucleofuge ability seems to be the controlling factor. Finally, reaction of **10**, the chloro analogue of **1**, led to the isolation of a moderate 38 % yield of **9** along with a number of unidentified products.

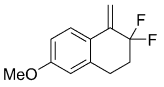
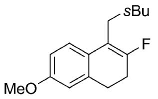
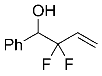
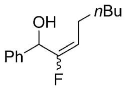
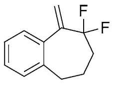
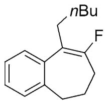
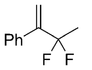
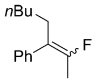
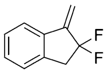
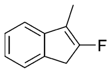
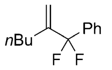
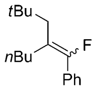
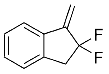
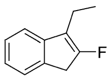
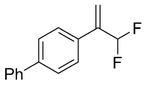
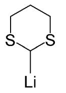
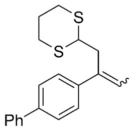
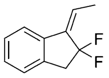
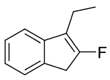
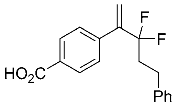
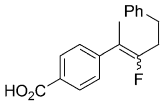
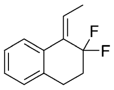
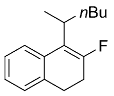
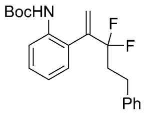
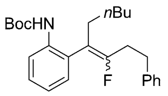
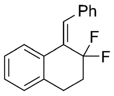
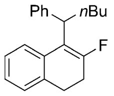
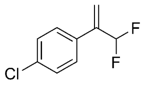
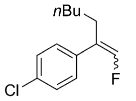
With respect to the mechanism, the reaction between organolithium reagents and 3,3-difluoropropenes would proceed through an S_N2'-type pathway where one of the fluorine atoms would act as a leaving group (Scheme 3). Even though fluoride is generally regarded as a poor leaving group,[2b] we propose that in this case, the increase in nucleofuge ability comes from a C−F···Li interaction. Indeed, upon addition of the organolithium reagent to the 3,3-difluoropropene **11**, the lithium atom[12] would interact with the carbon-bound fluorine atom. The lithium atom is classified as a hard atom while the neutral fluorine atom in a C−F bond is also a hard and effective donor and thus, both should associate strongly. Such chelation of the lithium atom by a carbon-bound fluorine atom has been proposed to be a key factor in some reactions.[4,13,14] Although double chelation as in **12a** would be energetically favored,[13b] reaction would most likely proceed via **12b** as exemplified by the successful reaction of **6** (Scheme 2) where only one C−F···Li interaction was possible. In addition, the fact that the fluoride would be released as LiF would compensate for its basicity and would also serve as a driving force for its departure.

Finally, to further probe the effect of the lithium, two additional experiments were performed (Scheme 4). First, the reaction of two *n*-butylmetal reagents with **1** was explored. While *n*BuZnCl gave no product (0 % conversion), the use of *n*BuMgBr only gave 37 % yield of **2** along with the starting material **1**. The reactivity observed for the different counterion correlates with the strength of the M−F bond.[15] Indeed, the Li−F bond (138 kcal mol^{-1}) is stronger than a Mg−F bond

Table 3: Scope of 3,3-difluoropropene compounds.[a]



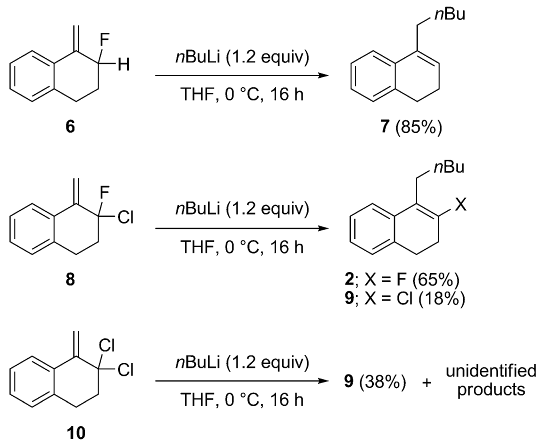
4a-l **5a-m**

No.	Substrate	RLi	T [°C]	Product	Yield [%][b]	No.	Substrate	RLi	T [°C]	Product	Yield [%][b]
1[c]	 **4a**	*s*BuLi	66	 **5a**	71	8	 **4g**	*n*BuLi	0→21	 **5g** (*E*/*Z*=60:40)	73
2	 **4b**	*n*BuLi	0→21	 **5b**	88	9	 **4h**	*n*BuLi	0→21	 **5h** (*E*/*Z*=52:48)	86
3	 **4c**	$LiAlH_4$ (R=H)	0	 **5c**	90	10	 **4i**	*t*BuLi	21	 **5i** (71:29)	87[e]
4	 **4c**	MeLi	0→21	 **5d**	35	11	 **4j**		0	 **5j** (74:26)	76[e]
5	 **4d**	$LiAlH_4$ (R=H)	21	 **5d**	76	12	 **4k**	$LiEt_3BH$ (R=H)	21	 **5k** (71:29)	83[e,f]
6	 **4e**	*n*BuLi	0→21	 **5e**	74	13	 **4l**	*n*BuLi	−78	 **5l** (*E*/*Z*=68:32)	66
7[d]	 **4f**	*n*BuLi	21	 **5f**	41	14	 **4m**	*n*BuLi	−78→21	 **5m** (72:28)	88[e]

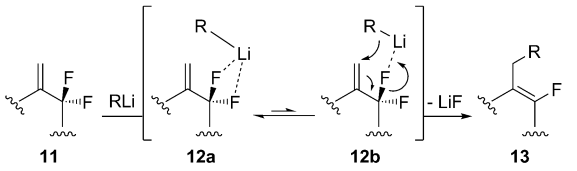
[a] See the Supporting Information for details of the reaction conditions. [b] Yields after purification by flash chromatography. [c] Reaction was performed in hexanes. [d] 3 equivalents of *n*BuLi was used. [e] *E* and *Z* configuration could not be assigned unambiguously. [f] Yield of the isolated methyl ester from **4k**, see the Supporting Information for details. Boc = *tert*-butoxycarbonyl.

(111 kcal mol^{-1}) or a Zn−F bond (87 kcal mol^{-1}), both of which are not able to activate the C−F bond as much as a lithium atom.[4] Second, reaction of **1** with PhLi in the presence of lithium selective [12]crown-4[16,17] resulted in no reaction, thus again suggesting a key role for the lithium atom in increasing the nucleofuge ability of fluoride.

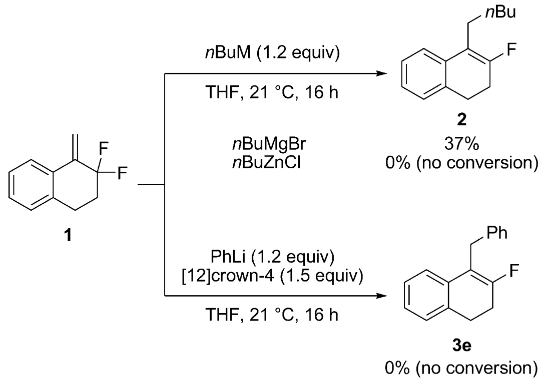
In conclusion, we have reported the S_N2' displacement of C−F bonds on 3,3-difluoropropenes with organolithium reagents as a new approach to monofluoroalkenes. Not only do our results present a practical synthetic method for the preparation of monofluoroalkene compounds, an important fluorinated motif, but they also demonstrate the ability of fluoride to act as a competent leaving group in nucleophilic substitution reactions. Preliminary results support the importance of the fluorine–lithium interaction in activating the C−F bond. Further exploration of this phenomenon and its extension to other synthetically useful systems are currently underway in our laboratory.



Scheme 2. Halogen atom effects.



Scheme 3. Proposed mechanism.



Scheme 4. Probing the importance of the C−F···Li interaction.

Experimental Section

Typical procedure: A solution of *n*BuLi (2.6 M in hexanes, 0.33 mmol) was slowly added to a solution of **1** (50 mg, 0.28 mmol) in THF (2.5 mL) at −78 °C. The mixture was stirred for 2 h before being quenched with drops of water. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with Et_2O (3×). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The resulting colorless liquid **2** (59 mg, 97%) was characterized without further purification.

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