S_N2[′] Reaction of Allylic Difluorides with Lithium Amides and Thiolates

Maxime Bergeron, David Guyader, and Jean-François Paquin*

Canada Research Chair in Organic and Medicinal Chemistry, Département de chimie, Université Laval, 1045 avenue de la Médecine, Québec, Québec G1V 0A6, Canada

jean-francois.paquin@chm.ulaval.ca

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The synthesis of monofluoroalkenes using an $S_N 2'$ reaction of lithium amides derived from aromatic amines or lithium thiolates with 3,3-difluoropropenes is reported. This transformation features the use of fluoride as a leaving group.

The pursuit of a new means of activating the C–F bond is an active field of research.¹ This strong interest originates from both the fundamental and practical aspects of such transformations. Indeed, the C–F bond is the strongest single carbon–halogen bond² and one of the least reactive carbon–halogen bonds in aliphatic substitution reactions;^{1,3,4} however, its transformation may provide new pathways to fluorinated motifs, privileged scaffolds in pharmaceutical sciences.⁵

We have recently described the activation of allylic fluorides for $S_N 2'$ displacement using organolithium reagents where we postulated that the lithium ion would serve to enhance the leaving group ability of the fluorine atom (Scheme 1A).⁶ Starting from 3,3-difluoropropenes,

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this reaction gave access to monofluoroalkenes, a useful class of organofluorine compounds.^{7,8} We have also reported a palladium-catalyzed allylic amination reaction from 3,3-difluoropropenes as a new access to β -aminofluoroalkenes.⁹ This transformation worked well with secondary and primary aliphatic amines (Scheme 1B).¹⁰ However, under these conditions, the use of aromatic amines led to low conversions (<20%), and further optimization of the reaction conditions was not successful.

In this context, we wondered if lithium amides derived from aromatic amines would react directly with 3,3difluoropropenes. Indeed, while the reaction of lithium amides with 3,3,3-trifluoropropenes is well documented,¹¹

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Scheme 1. (A) Activation of a C–F Bond through a C–F···Li Interaction (B) Synthesis of β -Aminofluoroalkenes from 3,3-Difluoropropenes



this transformation with 3,3-difluoropropenes has not been explored. Overall, this transformation would not only provide a route to β -aminofluoroalkenes that would complement our palladium-catalyzed version, but would also represent an additional example of the use of fluoride as a competent leaving group in substitution reactions.^{1,4} Herein, we report the viability of this concept and also show that it can be extended to *S*-based nucleophiles.

The initial optimization was performed on 3,3-difluoropropene 1, which is readily available from α -tetralone, and the results are reported in Table 1. The first reaction, which was conducted in THF at 0 °C using 3 equiv of the lithium amide, led to complete conversion in 1 h with 81% isolated yield of the β -aminofluoroalkene 2 (entry 1). Attempts to use fewer equivalents of the lithium amide only provided lower conversions and isolated yields (entries 2-3), even if the reactions were conducted at room temperature for a longer period of time (16 h). Switching to hexane as the solvent completely shut down the reaction (entry 4).^{12a} Using Et₂O provided full conversion with a respectable 77% yield; however, some reproducibility problems were encountered with these conditions. Finally, the use of toluene as cosolvent was examined since this solvent has been shown to potentially influence the structure and reactivity of organolithium reagents.¹² Thus, while using Et_2O /toluene (1:1) gave a moderate conversion and a low isolated yield (entry 6), using THF/toluene (1:1) provided, in a reproducible fashion, full conversion and a good isolated yield (entry 7).

The scope of this transformation was next examined using these optimized conditions on various 3,3-difluoropropenes and lithium amides derived from aromatic amines (Table 2). Using 3,3-difluoropropene 1, the use of anilines substituted either on the nitrogen atom (entries 1-3), on the aromatic Table 1. Selected Optimization Results^a



^{*a*} See the Supporting Information for details of the reaction conditions. ^{*b*} Determined by ¹⁹F NMR analysis of the crude mixture. ^{*c*} Yield of isolated **2**. ^{*d*} Estimated by ¹H and ¹⁹F NMR.

ring (entry 4) or a combination of both (entry 5) proceeded well (63-98% yield). The lithium amide derived from indoline could also be used (entry 6). In two cases, low yields were obtained at room temperature (entry 3 and 6); however, running the reaction at 60 °C allowed the isolation of the corresponding products in improved yields. The presence of an extra substituent on the alkene as found on 3,3-difluoropropene 3 considerably reduced the reactivity, and as such, the desired β -aminofluoroalkene 14 was obtained in low yield (entry 7). As conversion of 3 was almost complete (ca. 91%) by ¹⁹F NMR, we imagine that various side-reactions took place, although no specific side-product could be isolated in pure form. Likewise, reaction of 1-indanone-derived 3,3-difluoropropene 4 provided no desired product despite its full conversion (entry 8). In this case, we presume that the methylene protons in 15, which are both benzylic and allylic, can be easily abstracted under the reaction conditions leading again to various side reactions preventing its formation. 1-Benzosuberonederived 3,3-difluoropropene 5 reacted well providing 16 in 57% yield (entry 9). Finally, acyclic 3,3-difluoropropenes 6 and 7 could also be used providing trisubstituted monofluoroalkenes in 60–79% as a mixture of Z/E isomers (entries 10-12). Interestingly, products 17-19 structurally resemble known MAO inhibitors.¹³

This transformation was also explored using lithium amides derived from aliphatic amines using 3,3-difluoropropene 1 (Scheme 2). The results varied greatly depending on the amine used. Indeed, morpholine performed well with an isolated yield of 91%, while *N*-methylbenzylamine and pyrrolidine provided the corresponding monofluoroalkenes in 62 and 28% yield, respectively. Those results confirm the complementarity between our two approaches for the synthesis of β -aminofluoroalkenes. Indeed, for aromatic amines, $S_N 2'$ addition of their lithium amides,

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			R
		ArNHR (2 equiv) <i>n</i> -BuLi (2 equiv)	R ¹ _{vu} N Ar
	vî ↓F	THF/toluene (1/1), 21 °C	°√ ↓
	1, 3-7		8-19
entry	substrate	product	yield $(\%)^b$
1	F 1	N(Me)Ph	79
2		F 9	98
3		N(allyl)Ph F 10	$74^{c} (43)^{d}$
4		NHAr F 11 (Ar = 4-MeO-Ph)	64
5		12 (Ar = 2-Cl-Ph)	63
6			$64^{c} (32)^{d}$
7		NHAr F 14 (Ar = 4-MeOPh)	39
8	F 4	15 (Ar = 4-MeOPh)	0
9	5	F 16 (Ar = 4-MeOPh)	57
10		.F CI	60 (67/33) ^e
11		ArHN CI 18 (Ar = 4-CI-Ph)	75 (<i>Z</i> / <i>E</i> = 53/47)
12	Ph F	F Ph(Bn)N Ph Ph	79 (83/17) ^e

Table 2. $S_N 2'$ Reaction of Lithium Amides Derived from Aromatic Amines^{*a*}

^{*a*} See the Supporting Information for details of the reaction conditions. ^{*b*} Yield after purification by flash chromatography. ^{*c*} Reaction was performed at 60 °C. ^{*d*} NMR yield for the reaction conducted at 21 °C. ^{*e*} *E* and *Z* configuration could not be assigned unambiguously.

(14) For example, with substrate 1, reaction of pyrrolidine under the Pd conditions (ref 10a) allowed the isolation of product 22 in 64% (as opposed to 28% with its lithium amide). Likewise, reaction of the same substrate with *N*-methylaniline under the Pd conditions gave 8 in < 3% yield instead of 79% using its lithium amide (Table 2, entry 1).

as reported herein, is preferred, whereas for aliphatic amines, the Pd-catalyzed version^{10a} is ideal.¹⁴





Another complementary aspect of the present transformation is the possibility of synthesizing monofluoroalkenes bearing a primary amine, especially since the use of aqueous ammonia¹⁵ as nucleophile in the palladiumcatalyzed version failed. While initial experiments with LiNH₂ (2 equiv, THF, 21 °C, 16 h) were not successful, the use of benzophenone imine, which has been reported as a synthetic equivalent to ammonia,¹⁶ provided encouraging results. Indeed, reaction of 3,3-difluoropropene **1** with a combination of benzophenone imine and *n*-BuLi under the standard conditions furnished, after an acidic workup, the primary amine **23** in 53% for the two steps (Scheme 3).



We next explored the possibility of preparing β -mercaptomonofluoroalkenes (Scheme 4).¹⁷ Thus, performing the reaction with lithium benzenethiolate or lithium 4-methoxybenzenethiolate provided the desired monofluoroalkenes **24**¹⁸ and **25** in 87 and 63% yield, respectively. Good yields were also observed for *n*-butylthiol (70%) and *t*-butylthiol (94%). Unfortunately, investigations using other substrates revealed a narrower scope compared to lithium amides derived from aromatic amines.¹⁹ Finally, this transformation could not be extended to *O*-based nucleophiles. Indeed, using lithium phenoxide or lithium methoxide gave little or no conversion, and no product was observed in both cases.

At the moment, we believe that the transformation reported herein proceeds through a mechanism similar to

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⁽¹⁹⁾ See the Supporting Information for details.

Scheme 4. $S_N 2'$ Reaction of Lithium Thiolates with 3,3-Difluoropropene 1



the reaction of organolithium reagents with 3,3-difluoropropenes (Scheme 1A).⁶ This is evidenced by the fact that not only do reactions occur under comparable conditions, but also both transformations share analogous reactivity profiles in terms of substrate scope and the requirement for the use of lithium-based nucleophiles.¹⁹

In conclusion, we have reported the synthesis of β -aminofluoroalkenes using a S_N2' reaction of lithium amides derived from aromatic amines with 3,3-difluoropropenes.

The use of lithium thiolates as nucleophiles was also presented. Overall, this transformation represents one of the rare cases where fluoride acts as a competent leaving group in a nucleophilic substitution reaction.

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Supporting Information Available. General experimental procedures, specific details of representative reactions, and the isolation and spectroscopic information of the new compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.