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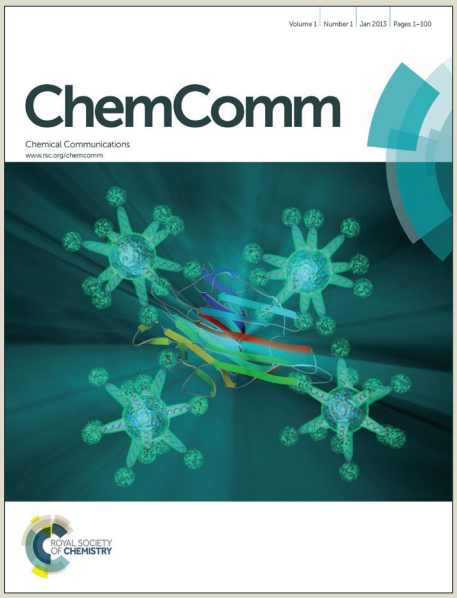

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C-F bond substitution via aziridinium ion intermediates

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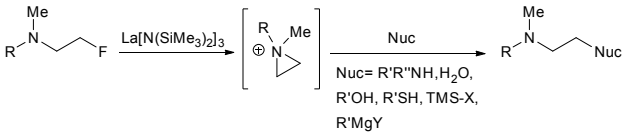
Aliphatic C-F bonds in β-position to a nitrogen undergo extremely fast substitution reactions under the influence of lanthanum *tris*(hexamethyldisilazide). The substitution proceeds via an in situ generated aziridinium ion intermediate, which subsequently ring opens by additon of a nucleophile, yielding various β-substituted amines.

The prospect of utilizing stable aliphatic organofluorides as a novel modular functionality in synthetic chemistry is an engaging task, exploitable thanks to the numerous fluorinating protocols available nowadays.[1] However, aliphatic organofluorides are traditionally considered impractical for chemical transformation, and the challenge of selective activation and transformation under mild conditions can be ascribed to the overall chemical inertness of the C-F bond. Compounds with the possibility of utilizing intramolecular assistance, as shown by Paquin et al., Gouverneur et al. and Hu et al., may overcome the activation energy and contribute to the C-F bond cleavage.[2] In line with this aspect, β-amino fluorides have received little attention and literature reports are scarce.[3] Chong et al. recently reported on a Lewis acid promoted β-haloamine substitution, with one example of fluoride displacement affording only 24% yield, noticeably showing fluoride as a poor leaving group.[4] Concerning the development of new C-F bond cleavage methodology, our group has focused on designing selective substitution of unactivated alkyl fluorides using trivalent lanthanides. Recently we communicated that various lanthanide (III) salts mediates mild and selective substitution of aliphatic fluorides into aliphatic iodides[5] and tertiary amines[6]. In these transformations, we have proposed that a strong lanthanide-fluoride interaction is central in the C-F bond cleavage. Having established these results, we hypothesized that intramolecular amine substitution of β-amino fluorides, with the proper choice of lanthanide (III) reagent, would generate aziridinium ions. Subsequent ring-opening of such reactive intermediates, with various nucleophiles, would give access to a plethora of different β-substituted amines, and it would expand the use of aziridinium ions as key intermediates in organic synthesis (Scheme 1).[7] Herein we present a simple and fast approach to use the C-F bond as a precursor for aziridinium ion formation.



Scheme 1: Schematic picture of in situ aziridinium formation, generated from β-amino fluorides, and the scope of β-subsituted amines formed.

When adding *N*-benzyl-*N*-methyl-2-fluoroethylamine (**1a**) to a mixture of dibutylamine and lanthanum *tris*(hexamethyldisilazide) ($La[N(SiMe_3)_2]_3$) an increase in reaction rate was observed, affording the product in matter of seconds. Close observation of the ^1H NMR spectra revealed an instantaneous formation of an aziridinium ion as a reactive intermediate (Figure 1).[11]

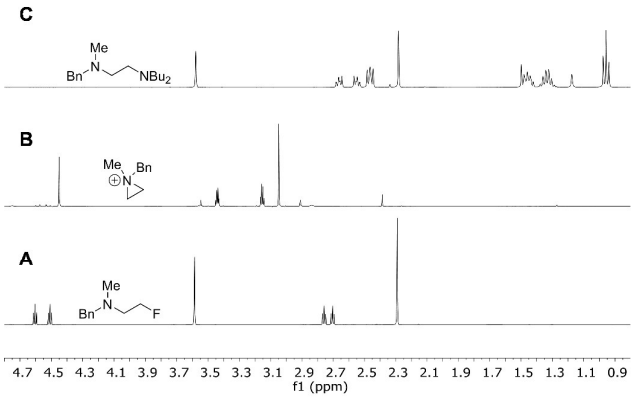


Figure 1: A ^1H NMR overview of the β-amino fluoride C-F bond substitution mediated by $La[N(SiMe_3)_2]_3$. A= *N*-benzyl-*N*-methyl-2-fluoroethylamine (**1a**). B= Aziridinium ion intermediate formed by mixing **1a** with $La[N(SiMe_3)_2]_3$ (1:1). C= *N*1-benzyl-*N*2,*N*2-dibutyl-*N*1-methylethane-1,2-diamine (**2a**).

A higher shift change of approximately 0.9 ppm for the Ph-C$\underline{H}_2$-N- and 0.8 ppm for the -N-C$\underline{H}_3$ protons were observed, simultaneously with a lower shift of 1.1 ppm for the –C$\underline{H}_2$-F protons, clearly indicating that the C-F bond has been cleaved and that a charged intermediate species has been formed (Figure 1B). We believe that the formation of a strong La-F bond is the driving force of the instantaneous ring closure. Furthermore, when adding 1 equivalent of dibutylamine, the aziridinium ion subsequently underwent an

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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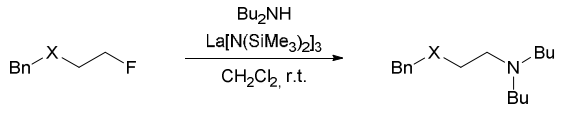
extremely fast nucleophilic ring opening and the β-substituted amine product (**2a**) was obtained after work-up (Figure 1C). It is well known that β-substituted amines with a good leaving group readily undergo transformation into the corresponding aziridines[8] or aziridinium ions.[7,9] However, since aliphatic fluorides are generally not considered a good leaving group, a fluorophilic reagent is needed to activate the C-F bond towards cleavage. To explore this, a range of different Lewis acids ($La[N(SiMe_3)_2]_3$, SmF_3, YbF_3, $AlCl_3$, $MgCl_2$, $SmCl_3$, KBr, $SmBr_3$, AlI_3, LiI, KI, YbI_3, $La(OTf)_3$, $Sm(OTf)_3$, and $Yb(OTf)_3$) were subjected to the reaction between **1a** and benzylmethylamine in dichloromethane (CH_2Cl_2) (see supporting information, SI). In the presence of $La[N(SiMe_3)_2]_3$ the strong C-F bond was cleaved within the matter of seconds. Most of the other Lewis acids did not promote the reaction at all, and the few that did could not compare with $La[N(SiMe_3)_2]_3$ in terms of yield and reactivity. The efficacy of these transformations relies on the nature of the neighbouring group and its distance from the fluorine. In general the presence of a hydroxyl, carboxyl, sulfydryl, primary or secondary amine or a carbanionic carbon in the β-position could act as a neighbouring group to assist in intramolecular substitution.[2,3,4] Different heteroatoms were incorporated to a β-substituted alkyl fluoride to investigate the effect of the neighbouring group (Table 1). Since carbon cannot assist in the substitution of fluoride this substrate was included as a reference (entry 4).

Table 1: The effect of different heteroatoms as neighbouring group participants in the C-F substitution reaction.[a]

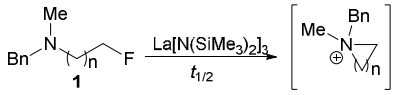


Entry	X	t (min)	yield (%)[b]
1	NMe (**1a**)[c]	1	93 (**2a**)
2	S (**3**)	1	87 (**4**)
3	O (**5a**)[d]	60	89 (**6**)
4	CH_2 (**7**)[d]	60	93 (**8**)

[a] $La[N(SiMe_3)_2]_3$ (0.176 mmol), CH_2Cl_2 (1.0 mL), Bu_2NH (0.176 mmol), substrate (1.0 M in CH_2Cl_2, 0.160 mmol). [b] Isolated yields are reported. [c] 95% conversion within 10 s measured by GC-FID. [d] Bu_2NH (0.48 mmol)

Replacing the carbon (**7**) for nitrogen (**1a**) or sulphur (**3**) gave a >60 fold increase in reaction rate, clearly showing a neighbouring group effect (entry 1-2, 4). Exchanging for oxygen (**5a**) did not give any observable effect (entry 3). It was also investigated if an amide group in the β-position could assist in the C-F bond cleavage, but only degradation of the substrate was observed under present conditions. As stated, the distance between the functional group and the fluorine will also influence the rate of the reaction. To obtain such an effect, a relative rate study of the ring formation of each charged intermediate were estimated based on the respective half-life-times ($t_{1/2}$) (Table 2).

Table 2: The effect of varying the distance between the neighbouring group and the fluorine in the C-F substitution reaction.[a]



Entry	n	$t_{1/2}$ (s)[b]
1	1 (**1a**)	~4
2	2 (**1b**)	~30
3	3 (**1c**)	<<1
4	4 (**1d**)	~1
5	5 (**1e**)	240

[a] $La[N(SiMe_3)_2]_3$ (0.044 mmol), CH_2Cl_2 (0.25 mL), Bu_2NH (0.044 mmol), (1.0 M in CH_2Cl_2, 0.040 mmol). *n*-Dodecane (0.040 mmol) was added to the reaction as internal standard. [b] Analysed by GC-FID.

The reactivity decreased according to the following order of ring size 5>6>3>4>>7.[3] For β-amino fluoride **1a** a $t_{1/2}$ of 4 s was observed (entry 1). A $t_{1/2}$ of approximately 30 s was observed for the substrate with the nitrogen in γ-position (**1b**, entry 2). For **1c** and **1d**, the 5- and 6-exo-tet ring formation were extremely fast, with $t_{1/2}$ <<1 s and $t_{1/2}$ ~1 s respectively (entry 3-4). Even with the nitrogen in ζ-position (**1e**), 7-exo-tet ring formation was observed, albeit at a lower rate (entry 5). Neither of the charged intermediates of the 5-, 6-, or 7-membered rings (entry 3, 4 and 5) showed any reactivity towards the nucleophilic amine even with prolonged reaction time (24 h). Such charged quaternary amines are known to be very stable, and therefore require harsh conditions to undergo ring opening.[10] The release of the large strain of the 3-membered ring is suggested to be the driving force for fast nucleophilic opening of the aziridinium ion. Despite the synthetic versatility, ring opening of aziridinium ions are not as common than other less reactive three-membered congeners such as aziridines and epoxides.[8,9] However, in our case, activated aziridinium ions are produced in situ which makes it possible to add different nucleophiles directly to the reaction mixture (Table 3). Not only secondary amines, such as dibutylamine and benzylmethylamine, underwent nucleophilic ring-opening of the aziridinium ion, but even morpholine provided the corresponding diamine. The reaction reached full conversion within 1 min, and **2b** was isolated in 93% yield. Even a heteroaromatic secondary amine, such as imidazole, gave clean ring-opening and **2c** was obtained in 81% yield. The nucleophilic amide phthalimide was incorporated, generating **2m** in 78% isolated yield. Thiol and alcohol as nucleophiles gave the corresponding thioether (**2d**) and ether (**2e**) in high to excellent yields within 5 min. In a similar fashion 2-hydroxypyridine, which potentially can react in both its tautomeric forms, only yielded the ether product (**2h**). With water as nucleophile either the β-hydroxy amine (**2f**) or the tridentate ether ligand (**2g**) was obtained in high to moderate yields, with the ratio being dependent on the amount of water and reaction time.

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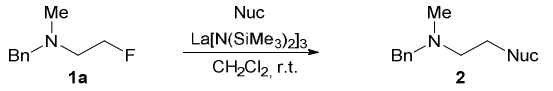
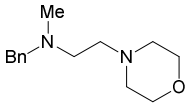
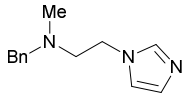
Table 3: Scope of different nucleohphiles.[a]

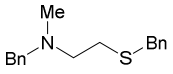




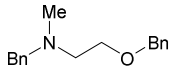
2b (93%, 1 min)
Nuc: morpholine (1.05 equiv.)



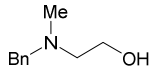
2c (81%, 60 min)
Nuc: imidazole (1.5 equiv.)



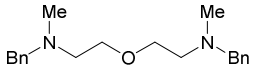
2d (96%, 5 min)
Nuc: BnSH (1.1 equiv.)



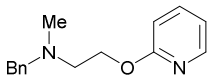
2e (72%, 5 min)[b]
Nuc: BnOH (3.0 equiv.)



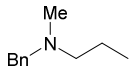
2f (70%, 60 min)
Nuc: H_2O (1.1 equiv.)



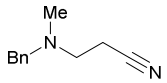
2g (61%, 1 min)
Nuc: H_2O (100 equiv.)



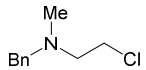
2h (69%, 60 min)
Nuc: 2-hydroxypyridine (1.5 equiv.)



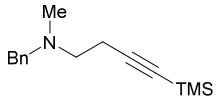
2i (87%, 60 min)[b]
Nuc: MeMgCl
(1.1 equiv.)



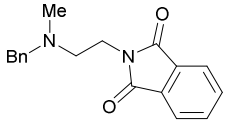
2j (89%, 5 min)
Nuc: TMS-CN
(1.1 equiv.)



2k (78%, 1 min)
Nuc: TMS-Cl
(3.0 equiv.)



2l (71%, 5 min)[b]
Nuc: TMS-ethynyl (3.0 equiv.)

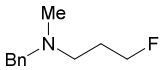
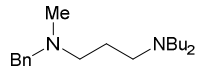
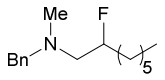
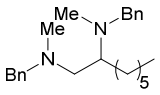
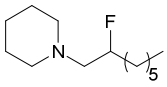
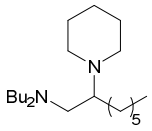
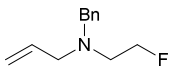
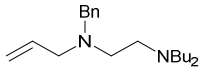
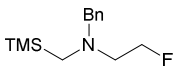
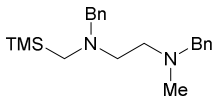
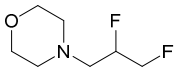
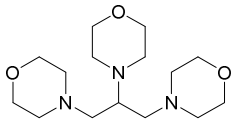


2m (78%, 120 min)
Nuc: phthalimide (1.5 equiv.)

[a] $La[N(SiMe_3)_2]_3$ (0.20 mmol), CH_2Cl_2 (1.25 mL), **1a** (1.0 M in CH_2Cl_2, 0.20 mmol). Isolated yields are reported. [b] Run in Et_2O (1.25 mL)

With this methodology it was even possible to achieve C-C bond formation utilizing Grignard reagent (MeMgCl, **2i**), ethynyltrimethylsilane (**2l**), or TMS-CN (**2j**), all isolated in high yields. Noteworthy, in the case of **2l** the TMS group is not cleaved. A halogen exchange was accomplished by utilizing TMS-Cl as nucleophile, and the corresponding β-chloro amine (**2k**) was obtained within 1 min in high yield. The β-chloro amine (**2k**) was in turn subjected to the same conditions as **1a** (Table 1, entry 1), and only 10% conversion into product **2a** was observed within 1 min. Thus, the β-chloro amine is much less reactive then the corresponding β-fluoro amine (**1a**). The scope of the reaction was further elaborated by its application on other β-amino alkyl fluorides (Table 4). As presented in the literature, the azetidinium ion is less reactive towards nucleophiles then the corresponding aziridinium ion.[11] The nucleophilic ring opening of **1b** was a bit slower and full conversion into product (**2n**) was reached only after several hours.

Table 4: Scope of different β-amino fluorides.

Substrate	conditions	product
 **1b**[b]	Bu_2NH, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2n** (90%, 180 min)
 **1f**[a]	BnMeNH, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2o** (75%, 5 min)
 **1g**[a]	Bu_2NH, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2p** (81%, 5 min)
 **1h**[b,c]	Bu_2NH, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2q** (89%, 5 min)
 **1i**[b]	BnMeNH, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2r** (90%, 5 min)
 **1j**[d]	morpholine, $La[N(SiMe_3)_2]_3$, CH_2Cl_2, r.t.	 **2s** (51%, 180 min)

[a] $La[N(SiMe_3)_2]_3$ (0.176 mmol), CH_2Cl_2 (1.0 mL), substrate (1.0 M in CH_2Cl_2, 0.16 mmol), nucleophile (0.176 mmol). Isolated yields are reported. [b] $La[N(SiMe_3)_2]_3$ (0.20 mmol), CH_2Cl_2 (1.25 mL), substrate (1.0 M in CH_2Cl_2, 0.20 mmol), nucleophile (0.22 mmol). Isolated yields are reported. [c] Bu_2NH (0.60 mmol). [d] $La[N(SiMe_3)_2]_3$ (0.40 mmol), CH_2Cl_2 (1.25 mL), substrate (1.0 M in CH_2Cl_2, 0.20 mmol), morpholine (0.42 mmol).

Assistance from neighbouring groups allowed secondary alkyl fluorides (**1f**-**g**) to easily be cleaved within 5 minutes. The corresponding diamines were isolated in high yield (**2o**-**p**). Non-symmetric aziridinium ions are generated from secondary alkyl fluorides, and different isomeric products can be obtained in the nucleophilic ring opening. In the examples displayed herein, **2p** was obtained in high regioselectivity (see SI for NMR). Thus, the substitution predominantly occurs on the unsubstituted carbon of the corresponding aziridinium ion intermediate.[7,9,11] Furthermore, even vicinal fluorides (**1j** yielding **2s**) were substituted with the assistance of a neighbouring group. Of the two possible charged intermediates, the aziridinium ion was the major one, while the

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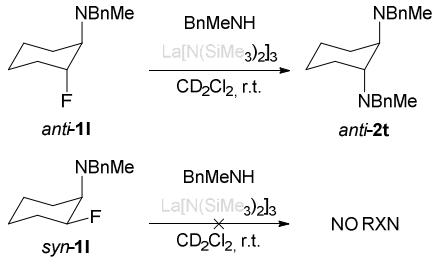
azetidinium ion was minor one. Allylbenzylamine (**1h**) and *N*-[(trimethylsilyl)methyl]benzylamine (**1i**), which both are capable of rearrangement,[12] yielded the corresponding diamines (**2q** and **2r** respectively) within 5 min, indicating an extremely fast and selective activation and substitution of the β-alkyl fluoride. Compound **1k**, with a trifluoromethyl group in the α-position, was unreactive, resulting from a shorter and stronger C-F bond as more fluorines are added to the carbon.[13] No substitution of the secondary fluoride took place in **5b**, due to lack of neighbouring group assistance from the oxygen.

5b **1k**

It is well established that the formation and ring opening of an aziridinium ion proceeds via an S_N2 pathway.[4,7,9] Accordingly, double inversion of *anti*-**1l** afforded *anti*-**2t**, while *syn*-**1l** did not react at all (Scheme 2).



Scheme 2: Investigating the stereochemical outcome of the substitution. $La[N(SiMe_3)_2]_3$ (0.080 mmol), CD_2Cl_2 (0.5 mL), substrate (1.0 M in CD_2Cl_2, 0.080 mmol) BnMeNH (0.080 mmol). Analysed by ^{1}H-NMR.

The results communicated herein shows that the seemingly inactive C-F bond should under these conditions be considered a very reactive functional group. Thus, a combination of a chelating group (N or S) in close proximity to fluorine enables selective and fast ring formation by instantaneous C-F bond cleavage mediated by $La[N(SiMe_3)_2]_3$. Subsequent ring opening of these 3-membered intermediates by various nucleophiles generated novel β-substituted amines. Overall, our findings present a distinct and mild methodology for C-F bond activation of several β-amino fluorides. Not only does this approach of activation illustrate the convenience of utilizing aziridinium ions as reactive intermediates, but it also enables the usage of fluorine as a novel and interesting modular functionality. In the laboratory we are currently exploring the usage of β-amino fluorides in complex structures as well as developing methodology for catalytic lanthanide mediated C/F substitution.

Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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