**Deployment of small-ring azaheterocycles as building blocks for the synthesis of organofluorine compounds**

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**Abstract:** This Account describes the endeavors made by our group concerning the synthesis of aziridines and azetidin(on)es and their use as novel building blocks for the preparation of nitrogen-containing organofluorine compounds. The majority of contributions comprises the study of fluorinated small-ring substrates, both focusing on their synthesis and their synthetic applicability for further transformations. These investigations revealed a pronounced effect of fluorine on the overall reactivity of small-ring azaheterocycles, often resulting in a different behavior as compared to their nonfluorinated counterparts. In a second part, contributions are covered dealing with the transformation of nonfluorinated small rings into fluorinated target molecules upon treatment with fluorinated reagents.

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**1 Introduction**

During the past decades, fluorine chemistry has gained more and more importance in medicinal chemistry programs,[1](#_ENREF_1) and numerous synthetic methods have thus been developed to incorporate this intriguing halogen atom into organic compounds.[2](#_ENREF_14) Because of the specific properties of fluorine, its introduction has a significant effect on the chemical and biological characteristics of the resulting molecules.[3](#_ENREF_19) Since fluorine is the most electronegative element, the C-F bond is highly polarized, resulting in a very strong bond and an improvement of the overall metabolic stability of the corresponding compounds. Another result of the high electronegativity of fluorine involves its pronounced effect on the acidity and basicity of proximal functional groups. Especially the influence of fluorine atoms on the basicity of nitrogen atoms plays a pivotal role in medicinal chemistry. Furthermore, a reduction in acidity and (mostly) an increase in lipophilicity, due to the presence of fluorine, usually provide a higher bioavailability to these compounds.[4](#_ENREF_21) It is therefore not surprising that nearly 25% of new drugs and agrochemicals contain fluorine in their structure.[1l](#_ENREF_12)

Because of their ring strain and reactivity, aziridines and azetidines constitute versatile building blocks for the preparation of a wide variety of functionalized (a)cyclic amines.[5](#_ENREF_23) As a result, fluorinated small-ring azaheterocycles, which combine a significant inherent reactivity with the beneficial biological properties of fluorine, can be considered as powerful substrates for the synthesis of fluorine-containing nitrogen compounds.

In this Account, an overview of our recent research work concerning the preparation of aziridines and azetidin(on)es is presented, followed by their application in the synthesis of fluorinated acyclic and cyclic target compounds. In a first part, the synthesis and reactivity of fluorine-containing aziridines and azetidines is described, as well as their conversion toward relevant organofluorine compounds. In a second part, the preparation of organofluorine compounds is presented starting from non-fluorinated aziridine and azetidine building blocks. In addition to the results obtained in our research group, a selection of relevant literature contributions will be discussed as well to provide a more comprehensive overview.

**2 Synthesis and reactivity of fluorine-containing aziridines and azetidines**

**2.1 Aziridines**

In the literature, only a limited number of reports on the synthesis of monofluoroaziridines are available, most of which are dealing with the addition of fluorocarbene across imines or with the transfer of a suitable nitrogen source to olefins.[6](#_ENREF_28) On the other hand, intramolecular cyclizations of fluorinated β-haloamines to produce aziridines are far less described. The latter approach involves the synthesis of intermediate β-halogenated amines starting from an appropriate fluorinated building block, followed by intramolecular expulsion of the leaving group toward the corresponding 2-fluoroaziridines. In a first example, 3-aryl-2-fluoroaziridines **4** and **5** have been prepared in a three-step procedure starting from imines **1** or ketones **2** (Scheme 1).[7](#_ENREF_36) On the one hand, α-fluoroimines **3** were acquired via electrophilic fluorination of imines **1** using *N*-fluorobenzenesulfonimide (NFSI) in the presence of K2CO3 and, on the other hand, imination of ketones **2** (R1 = MeO, H; R2 = H; X = Cl, Br) with isopropylamine in the presence of TiCl4 also gave rise to α-fluoroimines **3**. Further elaboration was performed using chlorofluoroimines **3** (X = Cl), because of the higher yields obtained via α-chlorination as compared to α-bromination. Thus, subsequent reduction of chlorofluoroimines **3** with sodium cyanoborohydride in methanol and intramolecular cyclization of the obtained dihaloamines with K2CO3 in DMSO furnished 2-fluoroaziridines **4** and **5**. In some cases, the *cis*- and *trans*-diastereomers could be separated by means of column chromatography. However, *trans*-aziridines **5** appeared to be unstable on silica gel, giving rise to purification problems during chromatography.

**Scheme 1: Synthesis of 3-substituted monofluoroaziridines 4 and 5**



Because of the fact that the above-described methodology could only be successfully applied for the synthesis of 3-aryl-substituted 2-fluoroaziridines, another reaction pathway had to be designed to provide access to 3-nonsubstituted 2-fluoroaziridines (Scheme 2). To that end, treatment of commercially available ethyl chlorofluoroacetate **6** with primary amines afforded the corresponding amides.[8](#_ENREF_37) Then, a variety of reducing agents for the conversion of these amide intermediates into amines **7** were examined. After careful monitoring of the reaction conditions, the desired β,β-dihaloamines **7** were eventually obtained using an excess of borane dimethyl sulfide complex in CH2Cl2 followed by treatment with Pd/C in methanol. The latter procedure was required for the decomposition of the stable amine-borane complex, which was not possible using standard basic or acidic conditions. In order to improve the yields of the obtained amines **7**, analogous reactions using borane in THF or catecholborane in toluene under reflux were examined. Unfortunately, these reaction conditions only resulted in lower yields.

**Scheme 2: Synthesis of 3-nonsubstituted monofluoroaziridines 8**



Due to the presence of the β-chloroamine moiety in amines **7**, these compounds could be further employed for an intramolecular cyclization reaction toward the target 2-fluoroaziridines **8**. Although treatment of the *in situ* formed amines from imines **3** with K2CO3 in DMSO gave rise to ring closure toward aziridines **4** and **5** (Scheme 1), analogous reaction conditions applied to amine **7** (R = Ph) did not result in the corresponding 2-fluoroaziridine **8**. Instead, reaction with K2CO3 in DMSO afforded the fluorinated oxazolidinone **9**, which arose from a nucleophilic attack of the *in situ* created amide across the carbonyl moiety of CO2, followed by ring closure upon expulsion of chloride. In a next step, a variety of bases (KOH in aqueous THF, LDA, or LiHMDS in THF) were evaluated to complete the amine-to-aziridine ring closure. Finally, it was established that treatment of amine **7** with LiHMDS resulted in the highest yields for the synthesis of 2-fluoroaziridines **8**, which were purified by means of column chromatography or via distillation.

In order to further extent the previously described methods for the preparation of monofluoroaziridines, attempts have been made toward the synthesis of analogous 2,2-difluoroaziridines using the same methodologies. In contrast to monofluoroaziridines, the synthesis of 2,2-difluoroaziridines has been scarcely investigated, apart from some trifluorinated and perfluorinated aziridines which have been prepared via transfer of carbenes and nitrenes to specific imines and olefins, respectively.[9](#_ENREF_38)Analogous to the pathway applied for the synthesis of 3-aryl-2-fluoroaziridines **4** and **5**, imines **11** were transformed into 2,2-difluoroaziridines **13** via reduction of the imino moiety followed by intramolecular cyclization (Scheme 3).[7](#_ENREF_36) In concreto, imines **11** were prepared from 2-chloro-2,2-difluoroacetic acid **(10)**, involving a nucleophilic addition of a suitable Grignard reagent and elimination of water, followed by imination with an excess of alkylamine in the presence of TiCl4. Then, α-chloroimines **11** were treated with sodium cyanoborohydride in methanol in the presence of acetic acid, yielding amines **12**.

**Scheme 3: Synthesis of 3-substituted difluoroaziridines 13**



In contrast to 2-fluoroaziridines **4** and **5**, which were prepared from the corresponding amines upon treatment with K2CO3, 2,2-difluoroaziridine **13** (R1 = Ph, R2 = *i*Pr) was not formed in that way. Instead, these reaction conditions furnished α,α-difluoroimine **14** via a 1,2-dehydrochlorination and subsequent enamine – imine tautomerization. Treatment of amine **12** (R1 = Ph, R2 = *i*Pr) with KO*t*Bu in THF afforded α,α-difluoroimine **14** as well. However, when the more sterically hindered and stronger base LDA was applied, no imine **14** was observed, but instead an intramolecular cyclization proceeded resulting in the desired 2,2-difluoroaziridines **13**. It was observed that 2,2-difluoro-3-phenylaziridines (R1 = Ph in **13**) were less stable as compared to their 3-alkylated counterparts (R1 = C6H13, C8H17 in **13**). In concreto, 2,2-difluoro-3-phenylaziridines **15** decomposed upon purification by means of column chromatography and, in the presence of moist air, these aziridines **15** underwent a ring opening reaction resulting in amides **16** (Scheme 4). On the other hand, 3-alkyl-2,2-difluoroaziridine **17** (R = C8H17) appeared to be stable but could be forced to undergo a ring-opening reaction upon treatment with aqueous HCl in DMSO. Analogous reaction conditions (aqueous HCl in CH3CN) were applied for the conversion of 2,2-difluoro-3-phenylaziridine **17** (R = Ph) toward the corresponding amide **18** (R = Ph).

**Scheme 4: Reactivity of difluorinated aziridines 15 and 17**



Following the four-step procedure for the synthesis of 2-fluoroaziridines **8** starting from ethyl chlorofluoroacetate **6** as described in Scheme 2, the preparation of 2,2-difluoroaziridines **21** was studied likewise, starting from ethyl chlorodifluoroacetate **19** (Scheme 5).[8](#_ENREF_37) Because this starting material only bears one fluorine atom more than ethyl ester **6**, it was expected that the reaction conditions used for the synthesis of monofluoroaziridines **8** should also be applicable for the synthesis of difluoroaziridines **21**. In that way, nucleophilic addition with a selection of amines across the carbonyl moiety of ethyl ester **19** afforded the corresponding amides. Subsequently, reduction of the obtained amides with borane dimethyl sulfide complex followed by cleavage of the stable borane-amine complexes with Pd/C in methanol furnished the desired amines **20**. Finally, deprotonation with LiHMDS effected an intramolecular cyclization toward 2,2-difluoroaziridines **21**.

**Scheme 5: Synthesis of 3-nonsubstituted difluoroaziridines 21**



After having developed a number of procedures for the synthesis of mono- and difluorinated aziridines via intramolecular cyclization of β-halogenated amines with an appropriate base, a reactivity study was performed to investigate the chemical behavior of the obtained aziridines with respect to nucleophiles. In that way, both 1-benzyl-2,2-difluoroaziridine **22** and 1-benzyl-2-fluoroaziridine **26** were treated with a hydrochloric acid source (Scheme 6). Reaction of difluoroaziridine **22** with aqueous HCl resulted in protonation of the nitrogen atom to generate an aziridinium intermediate. Subsequent chloride-mediated ring opening of this electrophilic speciesat C3 afforded amine **24**, followed by hydrolysis toward amide **25**. Then, monofluoroaziridine **26** was subjected to the same reaction conditions, but this resulted in a low yield of ring opened product **28**. However, treatment of aziridine **26** with gaseous HCl afforded amine **28** in higher yields, obtained via ring opening of aziridinium ion **27** at the 2-position and subsequent basic workup. It was concluded that the regioselectivity of the ring opening process was dependent on the substitution pattern of the aziridine core. Whereas 2,2-difluoroaziridine **22** was attacked at the less hindered carbon atom, ring opening of 2-fluoroaziridine **26** proceeded at the more hindered carbon atom. The difference in regioselectivity for the ring opening of difluorinated versus monofluorinated aziridines was attributed to sterical hindrance exerted by two geminal fluorine atoms on the one hand and the specific electronic properties of one fluorine atom on the other hand.[10](#_ENREF_44)

**Scheme 6: Reactivity of fluorinated aziridines 22 and 26 with respect to HCl**



In order to confirm the difference in regioselectivity of the nucleophilic ring opening of mono- and difluoroaziridines, both aziridines **22** and **26** were treated with sodium methoxide in methanol. In the case of difluoroaziridine **22**, reaction occurred again at the less hindered carbon atom, yielding 2-methoxyacetamide **29** after hydrolysis (Scheme 7). The same reaction conditions were applied for nucleophilic ring opening of monofluoroaziridine **26**. Unfortunately, the result was a complex reaction mixture in which a small amount of 2,2-dimethoxyamine **30** was present. However, heating of aziridine **26** in methanol in a sealed vessel at 100°C afforded the desired 2,2-dimethoxyamine **30**, obtained via regioselective ring opening at the more hindered carbon atom and subsequent substitution of fluoride by methoxide. It should be noted that the reactivity of aziridines can also be influenced by the reaction medium, as the electrophilicity of the aziridine carbon atoms is considerably higher in acidic media because of aziridine protonation at nitrogen, which is not the case in basic media.

**Scheme 7: Reactivity of fluorinated aziridines 22 and 26 toward sodium methoxide and methanol**



Next to the class of mono- and difluoroaziridines, the synthesis and reactivity of trifluoromethylated aziridines has also been the topic of several studies.[9e](#_ENREF_42),[11](#_ENREF_45)A powerful technique for the preparation of compounds containing a CF3-substituent is based on the direct nucleophilic, electrophilic or radical introduction of a CF3-group in a late stage of a synthetic sequence by using trifluoromethylating agents.[12](#_ENREF_63) However, in some cases the use of this strategy seems problematic (issues of selectivity, stability,…),and therefore a building block approach can circumvent these problems by using commercially available CF3-containing starting materials for the synthesis of trifluoromethylated target compounds. In our research group, the latter building block strategy has extensively been employed starting from CF3-carrier reagents for the synthesis of trifluoromethylated aziridines. Herein, a distinction is made between activated and nonactivated trifluoromethylated aziridines, according to whether or not quaternization towards an aziridinium intermediate is required for nucleophilic ring-opening reactions. This classification is intimately related to the nature of the *N*-substituent, i.e. the presence of an electron-withdrawing or an electron-donating group.

In the literature, different methodologies toward the synthesis of nonactivated 2-CF3-aziridines are known. Besides the synthesis of nonactivated trifluoromethyl-substituted aziridines *via* intramolecular substitution, other routes involving carbene addition across imines as substrates,[11a](#_ENREF_45),[11c](#_ENREF_47),[11g](#_ENREF_51),[13](#_ENREF_77) aziridination of a β-(trifluoromethyl)vinyl sulfonium salt,[11m](#_ENREF_57) and late-stage trifluoromethylation[14](#_ENREF_79" \o "Félix, 1994 #117) have also been described. In our research group, the synthesis of nonactivated 2-CF3-aziridines is usually based on the first approach, i.e. intramolecular cyclization of an (*in situ* formed) α-CF3-amine upon expulsion of a good leaving group. In a first example, a new and convenient approach for the synthesis of 1-alkyl-2-(trifluoromethyl)aziridines **33** has been developed starting from 1,1,1-trifluoroacetone **31** (Scheme 8).[15](#_ENREF_80) To that end, condensation of 1,1,1-trifluoroacetone **31** with a suitable primary amine in the presence of TiCl4 resulted in the formation of CF3-imines **34**. These imines **34** were then α-chlorinated using NCS in cyclohexane affording α-chloroimines **35**. Importantly, this reaction was performed in cyclohexane as a more “green” solvent as compared to the carcinogenic carbon tetrachloride (see Scheme 1 and 3), without altering the rate or yield of the reaction. Most α-haloimines via chlorination of imines with *N*-halosuccinimides have been prepared previously in carbon tetrachloride.[16](#_ENREF_81) Because of their hydrolytic instability and high purity (≥90%), these imines **35** were immediately used in the following reaction step. Thus, α-chloroimines **35** were treated with an excess of NaBH4 furnishing β-chloroamines **32**, and in the following step LiHMDS was used to effect ring closure of α-chloroimines **32** toward 2-(trifluoromethyl)aziridines **33**. In order to shorten the synthetic pathway, different reducing agents were also evaluated for the direct cyclization of imines **35** toward aziridines **33**. Unfortunately, all attempts (LiAlH4 or LiBH4 in THF, 0°C to reflux) did not complete the desired amine-to-aziridine ring closure due to the reduced nucleophilicity of the nitrogen atom in amines **32**, which can be explained by the strong electron-withdrawing effect of the trifluoromethyl substituent in the α-position.

**Scheme 8: Synthesis of 1-alkyl-2-(trifluoromethyl)aziridines 33**



In another article, the synthesis of (2*R*)-2-(trifluoromethyl)aziridine **33** has been reported by reaction of (2*S*)-(trifluoromethyl)oxirane **36** with different primary amines to generate the corresponding β-amino alcohols **37**, and subsequent ring closure with triphenylphosphine dichloride in the presence of triethylamine in an overall yield of 30-66% (Scheme 9).[11i](#_ENREF_53),[11p](#_ENREF_60) However, an important drawback of this procedure involved the high cost of the optically pure starting material. The latter ring closure has also been used by Obijalska et al. to prepare a number of 1-alkyl-2-aryl-2-(trifluoromethyl)aziridines upon treatment of the corresponding amino alcohols with the same reaction conditions as applied for the synthesis of (2*R*)-2-(trifluoromethyl)aziridines **33**.[17](#_ENREF_85) In an alternative slightly different approach, enantiomerically pure (2*S*)-1-benzyl-2-phenyl-2-(trifluoromethyl)aziridine has been prepared *via* intramolecular cyclization of the corresponding *N*-benzylamino alcohol using the Appel reaction conditions.[11f](#_ENREF_50)

**Scheme 9: Synthesis of (2R)-2-(trifluoromethyl)aziridine 33**



Ring opening of 1-alkyl-2-(trifluoromethyl)aziridines **33** by Brønsted acids or by a wide variety of nucleophiles under acid catalysis has extensively been investigated by Katagiri et al.[11k](#_ENREF_55) and Karimova et al.,[11h](#_ENREF_52) resulting in the efficient and regioselective formation of diverse α-CF3-amines **38** (Scheme 10). In contrast, Lewis acid-catalyzed ring opening reactions did not proceed at all, probably due to the low coordinating ability of the lone pair of the nitrogen atom in 2-CF3-aziridines **33**.

**Scheme 10: Brønsted- or acid-catalyzed synthesis of α-CF3-amines 38**



Based on these results, the reactivity of the 2-(trifluoromethyl)aziridines **33** toward different nucleophiles has also been explored in our research group (Scheme 11). At first, 1-benzyl-2-(trifluoromethyl)aziridine **39** was treated with an excess of LiAlH4 to induce ring opening toward the corresponding benzylamine **41**. Unfortunately, no conversion of the substrate was observed, which can be explained by insufficient coordination of the aluminium with the nitrogen atom. The lack of reactivity of aziridine **39** toward LiAlH4 can be attributed to the reduced basicity of the nitrogen atom, and hence the reduced activation of the ring, caused by the strong electron-withdrawing effect of the CF3-group. Moreover, the difficult ring opening of 1-benzyl-2-(trifluoromethyl)aziridine **39** was confirmed by reaction with acetic acid in CH2Cl2, which required heating for a long period (7 days) to obtain complete conversion into 2-benzylamino-3,3,3-trifluoropropyl acetate **42**. In an effort to overcome this difficulty, acetic acid was used as the solvent, which unfortunately appeared to be less successful since more impurities were formed in this way.

Besides protonation of *N*-alkylaziridines **39** toward the corresponding aziridinium salts, *N*-alkylation has also been studied as an alternative activation method in order to induce successful ring opening of 2-CF3-aziridines **39**. As an elegant way to produce trifluoromethylated β-iodoamines, ring opening of 1-alkyl-2-(trifluoromethyl)aziridines **39** was triggered with alkyl iodides. To that end, aziridines **39** had to be reacted with benzyl iodide and methyl iodide under very harsh conditions to obtain complete conversion, which is again a result of the poor reactivity of the nitrogen atom toward electrophiles. In contrast to ring opening of nonactivated 2-alkylaziridines, which are preferentially attacked at the more substituted carbon atom under thermodynamic control,[10](#_ENREF_44),[18](#_ENREF_86) their trifluoromethylated counterparts were regioselectively opened at the less substituted carbon atom, suggesting that this transformation probably occurred under kinetic control caused by the steric and electronic hindrance of the CF3-group with respect to nucleophilic attack. Furthermore, the strong electron-withdrawing property of the CF3-group prevents recyclization of primary β-iodo amines **43** and **44** toward intermediate aziridinium salts **40**, hampering thermodynamic equilibration. In order to extend the regioselective ring opening of 2-(trifluoromethyl)aziridines **39** upon treatment with other halides, these aziridines **39** have also been reacted with benzyl bromide under different reaction conditions. Unfortunately, all of these attempts resulted in incomplete conversions or complex reaction mixtures.

**Scheme 11: Reactivity of 1-alkyl-2-(trifluoromethyl)aziridines 39**



Because iodo atoms are known to be good leaving groups in nucleophilic substitution reactions, attempts have been performed to realize the coupling of 1,1,1-trifluoro-3-iodopropan-2-amines **43** with an aromatic moiety, as an introduction to novel trifluoromethylated amphetamine derivatives. At first, reaction of amines **43** with a Grignard reagent under various conditions (2 equiv of PhMgCl in THF or CH2Cl2 at -78°C, 0°C, rt or reflux) did not afford the desired end product. Furthermore, elimination products were observed at low temperatures (-78°C and 0°C). In another attempt, a Negishi cross-coupling was examined with iodobenzene, but this only resulted in complex reaction mixtures. Eventually, α-trifluoromethyl-β-phenylethylamines **45** were successfully obtained by using a Gilman reagent (in this case lithium diphenylcuprate) (Scheme 12). Also, a direct conversion of aziridines **39** to the corresponding β-phenylethylamines **45** has been evaluated. However, treatment of aziridines **39** with PhLi or Ph2CuLi resulted in the full recovery of the starting material.

**Scheme 12: Synthesis of β-phenylethylamine 45**



In another study, the stereoselective synthesis of *cis*- and *trans*-2-(methyl/phenyl)-3-(trifluoromethyl)aziridines has been accomplished as the 3-substituted counterparts of 2-(trifluoromethyl)aziridines **33**.[19](#_ENREF_87) In this approach, involving a quite similar reaction sequence as compared to the one leading to aziridines **33**, 3-(trifluoromethyl)aziridines **49** and **51** were acquired via imination, α-chlorination and hydride-induced ring closure of commercially available trifluoromethylated ketones **46** (Scheme 13). Depending on the number of chlorine atoms at the α-position of the trifluoromethylated imines **48**, the stereoselectivity of the ring closure could be controlled. On the one hand, the reductive ring closing reaction of dichlorinated imines **48** with LiAlH4 resulted in the formation of *cis*-3-(trifluoromethyl)aziridines **49** in excellent diastereomeric ratios (94-97:3-6), whereas treatment of monochlorinated imines **50** gave rise to *trans*-3-(trifluoromethyl)aziridines **51** in slightly lower diastereomeric excess (22-6:94-78). However, the diastereoselective formation of the *trans* isomers **51** could be enhanced by lowering the reaction temperature to -40°C. It should be noted that the reduction of imines **50** was also tested with NaBH4 using the same reaction conditions as applied in the reaction sequence toward aziridines **33** (Scheme 8). However, this led to elimination of hydrochloric acid and the *in situ* isomerization to a more stable azadiene. Treatment of the same substrate **50** with NaCNBH3 resulted in β-chloroamines, besides aziridines **51** in variable conversion rates (10-93%). The high stereoselectivity obtained for the *cis*-aziridines **49** was explained by the intermediacy of the stereoselective hydride attack of an intermediate azirinium ion.[19-20](#_ENREF_87)

**Scheme 13: Synthesis of cis- and trans-1-alkyl-2-(trifluoromethyl)aziridines 49 and 51**



The difference in stereochemical outcome can be rationalized by considering the reaction mechanism for both ring formations (Scheme 14). In the case of *cis*-3-(trifluoromethyl)aziridines **49**, initial imine reduction and subsequent intramolecular ring closure toward 2-chloroaziridines **53** is followed by expulsion of the second chlorine atom, resulting in azirinium intermediates **54**. Due to their high reactivity, intermediates **54** are immediately attacked by another hydride ion coming in from the opposite side of the CF3-directing group, leading selectively toward *cis*-3-(trifluoromethyl)aziridines **49**. On the other hand, the stereoselective formation of *trans*-3-(trifluoromethyl)aziridines **51** can be explained considering a lithium complex-induced diastereoselective hydride transfer to imines **55**. Under the influence of the R1-substituent (R1 = Me or Ph) the hydride ion will attack from the opposite side of the R1-directing group, leading selectively to anions **56**. Finally, free rotation around the C2-C3 bond allows ring closure via expulsion of chlorine through a SN2 mechanism, resulting in *trans*-aziridines **51**.

**Scheme 14: Reaction mechanism for the synthesis of cis-aziridines 49 and trans-aziridines 51**



Furthermore, a reactivity study has been performed with emphasis on *N*-protonation and *N*-alkylation for the activation of 3-(trifluoromethyl)aziridines **49** and **51**. Acidic activation of *cis*- and *trans*-aziridines **49** and **51** and consecutive smooth ring opening by water, methanol and bromide resulted in *syn*- and *anti*-β-amino alcohols **57** and **58**, β-amino ethers **59** and **60**, β-bromo amines **61** and **62**, respectively (Scheme 15). Thus, ring opening of *cis*- and *trans*-aziridines **49** and **51** proceeded regioselectively at the less hindered carbon atom, which is in line with the nucleophilic ring opening of 2-(trifluoromethyl)aziridines **39** (Scheme 11). Furthermore, this ring transformation occurred in a stereocontrolled way, implying that the reaction obeys an SN2 mechanism. Additional proof for this mechanism has been reported by means of the stereocontrolled ring opening of *cis*- and *trans*-alkyl 1-benzyl-3-(trifluoromethyl)aziridine-2-carboxylates upon treatment with acids or sulfur nucleophiles under acidic catalysis, giving rise to *cis*- and *trans*-β-amino esters, respectively.[11c](#_ENREF_47),[11d](#_ENREF_48)

**Scheme 15: Acid-mediated ring opening of trifluoromethylated aziridines 49 and 51**



In the same study, β-amino alcohols **57** and **58** were further treated with glyoxal toward *trans*- and *cis*-morpholinones **63** and **64** (Scheme 16). Unfortunately, these morpholinones **63** and **64** were obtained in low yields, probably due to the reduced nucleophilic character of the nitrogen atom caused by the strong electron-withdrawing effect of the trifluoromethyl substituent. On the other hand, this electronic effect has also been shown to have a positive side, as hydrogenation of β-amino ethers **59** and **60** over Pd(OH)2/C toward primary amines **65** and **66** proceeded very efficiently (Scheme 16).

**Scheme 16: Synthesis of morpholinones 63 and 64 and debenzylated trifluoromethylated primary amines 65 and 66**



Besides acid-catalyzed ring opening reactions with nucleophiles, activation of aziridines **49** and **51** via *N*-alkylation and consecutive ring opening has been examined as well. Analogous to the ring opening of 1-alkyl-2-(trifluoromethyl)aziridines **36**, ring opening of aziridines **49** and **51** was also evaluated with alkyl halides. However, treatment of aziridines **49** and **51** with various electrophiles (BnBr, BnI, MeI) resulted in either complex reaction mixtures or in the recovery of starting material.Finally, ring opening of 2-phenyl-substituted aziridines **49** and **51** with benzylamine and thiophenol was effectuated after activation with Me3OBF4, affording tertiary methylamines **67, 68** and **69, 70** in quite low yields (Scheme 17). Ring opening provoked by aziridine *N*-alkylation seemed to be more sluggish, giving rise to side products. Whereas the deployment of thiophenol as a nucleophile also resulted in nonmethylated secondary amines **71** and **72**, ring opening of aziridines **49** and **51** induced by benzylamine did not furnish these *N*-demethylated products. Nonetheless, these ring transformations again proceeded in a regio- and stereoselective way, providing access to a wide range of interesting trifluoromethylated functionalized β-amines. The employment of Me3OBF4 as a reagent for the activation of nonactivated CF3-aziridines has also been evaluated by Katagiri et al.[11k](#_ENREF_55) In their work, (*S*)-1-benzyl-2-(trifluoromethyl)aziridine was methylated using Me3OBF4, followed by ring opening of the intermediate aziridinium salt by phosphorus, oxygen, nitrogen and carbon nucleophiles, affording the corresponding α-CF3-amines.

**Scheme 17: Synthesis of trifluoromethylamines 67-72**



Based on the above-mentioned results regarding nucleophilic ring opening of nonactivated 2-(trifluoromethyl)aziridines **36**, **49** and **51**, it can be concluded that activation of the aziridine moiety is required prior to ring opening. In order to study the difference in ring opening aptitude between activated and nonactivated CF3-aziridines, research has also been performed within our research group concerning the synthesis and reactivity of activated CF3-aziridines. The first report on the displacement of the protecting group of nonactivated CF3-aziridines to produce their activated counterparts has been elaborated by Rinaudo et al. Herein, reductive *N*-benzyl deprotection of *cis*-ethyl 1-benzyl-2-(trifluoromethyl)aziridine-3-carboxylate resulted in the corresponding *NH*-aziridine, which was converted into different activated *cis*-aziridines in the presence of benzyl chloroformate, *p*-toluenesulfonyl chloride or 4-nitrobenzenesulfonyl chloride.[11n](#_ENREF_58)

As an introduction to activated 2-(trifluoromethyl)aziridines, the synthesis of *N*-tosyl-protected trifluoromethylated aziridines **73** and **74** has been explored by us as well, starting from nonactivated *N*-benzylaziridines **49** and **51** (Scheme 18) and using the same synthetic strategy as applied by Rinaudo et al. In that respect, initial removal of the *N*-benzyl group was achieved upon hydrogenation over Pd(OH)2/C, followed by subsequent trapping of the corresponding free amines with tosyl chloride. Hydrogenation has also been tested on 2-phenyl-substituted aziridines **49** and **51**, but this resulted in a ring opening product. Consequently, *N*-tosyl aziridines **73** and **74** were subjected to nucleophilic ring opening upon treatment with thiophenol, affording *syn*- and *anti*-*N*-tosyl-1,1,1-trifluoro-3-(phenylthio)butan-2-amines **75** and **76** in excellent yields (99-100%), corroborating the assumption that activated aziridines **73** and **74** are very prone to undergo ring opening. Efforts have also been made to effect detosylation of the obtained β-amino thioethers **75** and **76**. Unfortunately, treatment of compound **75** with sulfuric acid or heating in the presence of Mg in methanol gave rise to complex reaction mixtures or full recovery of the starting material, respectively.

**Scheme 18: Synthesis of 1-tosyl-2-(trifluoromethyl)aziridines 73 and 74 and subsequent ring opening toward tosylamines 75 and 76**



Because *N*-tosyl-protected trifluoromethylated aziridines **73** and **74** had shown their high susceptibility to nucleophilic ring opening reactions, in contrast to their nonactivated counterparts **49** and **51**, synthetic pathways for the preparation of other classes of activated 2-(trifluoromethyl)aziridines have been developed as well. In a first approach, 1-tosyl-2-(trifluoromethyl)aziridine **79** was prepared in a two-step procedure, involving a chemoselective tosylation of commercially available aminopropanol **77**, followed by a Mitsunobu-type cyclization (Scheme 19).[21](#_ENREF_89)

**Scheme 19: Synthesis of 1-tosyl-2-(trifluoromethyl)aziridine 79**



This approach had been based on work performed by Uneyama and co-workers.[11p](#_ENREF_60) In their strategy, optically pure (2*S*)-2-(trifluoromethyl)oxirane **36** was treated with an excess of aqueous ammonia followed by ditosylation, resulting in the ditosylate **80**. Intramolecular SN2-substitution of this ditosylate **80** yielded enantiopure (*R*)-1-tosyl-2-(trifluoromethyl)aziridine **79** in an overall yield of 31% (route a, Scheme 20). Later, an improved method for the preparation of aziridine **79** with an increased overall yield of 61% has been developed by the same group (route b, Scheme 20).[11j](#_ENREF_54) Herein, the direct ring opening reaction of oxirane **36** with *p*-toluenesulfonamide under Lewis acid catalysis afforded β-hydroxysulfonamide **78**, which was converted into the desired 2-CF3-aziridine **79** by an intramolecular Mitsunobu reaction.

**Scheme 20: Synthesis of (R)-1-tosyl-2-(trifluoromethyl)aziridine 79 starting from (S)-2-trifluoromethyloxirane 36**



In the previously mentioned studies, trifluoromethylated aziridines have been applied as electrophiles in ring opening reactions, whether or not in the presence of a reagent for aziridine activation. In the case of 1-tosyl-2-(trifluoromethyl)aziridine **79**, however, the *C*-alkylation aptitude has also been evaluated, bearing in mind the fact that enantiomerically pure *N*-tosylated 2-(trifluoromethyl)aziridine **79** had already proven to be susceptible to deprotonation with organolithium bases at the C2-position by Yamauchi et al., followed by coupling with a diverse range of electrophiles as depicted in Scheme 21.[11p](#_ENREF_60),[11q](#_ENREF_61) Reaction of the *in situ* created aziridin-2-yl anion **81** was mainly performed with a variety of carbonyl electrophiles such as aldehydes, ketones and acid chlorides toward (*S*)-2,2-disubstituted aziridines **82** in good to high yields. However, reaction with the less electrophilic benzyl bromide only resulted in a low yield of 13%.

**Scheme 21: Deprotonation of (R)-1-tosyl-2-(trifluoromethyl)aziridine 79 and subsequent coupling with different electrophiles**



As a consequence, research has been performed within our research group in order to extend the scope of these *C*-alkylation reactions. To that end, racemic aziridine **79** was treated with the strong base *n*BuLi, creating an aziridin-2-yl anion which was subsequently trapped with a suitable alkyl iodide (MeI, Cl(CH2)3I, Cl(CH2)4I) affording 2-methylaziridine **83** and 2-(ω-chloroalkyl)aziridines **84** depending on the electrophile used (Scheme 22). Thorough investigation of the reaction conditions revealed that this *C*-alkylation is extremely temperature dependent, and a very low temperature of -100°C was required to effect deprotonation and to stabilize the *in situ* created aziridin-2-yl anion. Furthermore, the use of an equimolar amount of HMPA appeared to be necessary to induce efficient reaction with the dihalogenated electrophiles. Besides the mentioned alkylation reactions, *C*-acylation and *C*-allylation of aziridine **79** has also been evaluated applying the same reaction conditions as for the synthesis of 2-(ω-chloroalkyl)aziridines **84**,but these attempts only resulted in complex reaction mixtures. Due to the presence of a good terminal leaving group in the side chain of aziridines **84**, a ring transformation of these aziridines could be established upon treatment with a variety of nucleophiles, affording a library of functionalized 2-(trifluoromethyl)pyrrolidines **85** and -piperidines **86**. From a mechanistic point of view, pyrrolidines **85** and piperidines **86** were acquired via initial nucleophilic attack at the less hindered carbon atom of aziridines **84**, followed by ring closure upon expulsion of the terminal chloride atom. These aziridine-to-pyrrolidine and aziridine-to-piperidine ring transformations clearly indicated the regioselective nucleophilic attack at trifluoromethylated aziridines, caused by the steric hindrance and electronic effect exerted by the trifluoromethyl substituent. Surprisingly, treatment of 2-(4-chorobutyl)aziridine **84** (n = 2) with isoalkylamines in acetonitrile also resulted in the formation of 3-(trifluoromethyl)azepanes **87**, besides the expected 2-isoalkylaminomethyl-1-tosyl-2-(trifluoromethyl)piperidines **86**. Although detosylation of β-amino thioethers **75** and **76** could not be attained, removal of the *N*-protecting group of 2-(trifluoromethyl)pyrrolidine **85** (Nu = OMe) was successfully achieved upon treatment with concentrated sulfuric acid, yielding pyrrolidine oxalic acid complex **88**.

**Scheme 22: Synthesis of 2-(trifluoromethyl)pyrrolidines 85 and 88, 2-(trifluoromethyl)piperidines 86 and 3-(trifluoromethyl)azepanes 87**



Ring expansion of 1-tosyl-2-(trifluoromethyl)aziridine **79** appears to be quite rare in the literature, as only one other approach has been reported so far, pointing to the chemical importance of the above-mentioned ring transformation. In that particular study, reaction of aziridine **79** with various aldehydes **89** in the presence of a catalytic amount of silver hexafluoroantimonate (AgSbF6) provided 2-substituted *cis*-1-tosyl-4-(trifluoromethyl)oxazolidines **90** with excellent regio- and stereoselectivity (Scheme 23).[11l](#_ENREF_56)

**Scheme 23: Synthesis of oxazolidinones 90 starting from 1-tosyl-2-(trifluoromethyl)aziridine 79**



A second route toward the synthesis of activated trifluoromethylated aziridines partially relied on a previously mentioned strategy, i.e. transformation of a nonactivated toward an activated 2-(trifluoromethyl)aziridine (see Scheme 18). In concreto, initial imination of hemiacetal **91** with benzylamine, followed by aziridination with ethyl diazoacetate and subsequent reduction of the ester moiety furnished *cis*-2-hydroxymethyl-3-(trifluoromethyl)aziridine **92** (Scheme 24).[22](#_ENREF_90) Then, following the same strategy as applied for the synthesis of aziridines **73** and **74** (Scheme 18), *N*-benzyl-protected aziridine **92** was converted into *N*-tosyl-protected aziridine **93** via initial debenzylation followed by tosylation. It should be mentioned that the aziridine ring formation in this approach was accomplished via addition of a carbene across a trifluoromethylated imine, in line with the strategy developed by Fioravanti et al. in which aziridine formation occurred via nitrene addition across a trifluoromethylated olefin.[11e](#_ENREF_49)

**Scheme 24: Synthesis of 1-tosyl-3-(trifluoromethyl)aziridine 93**



In a next phase, the reactivity profile of functionalized aziridine **93** was explored toward different types of aromatic sulfur and oxygen nucleophiles. Reaction of aziridine **93** with thiophenols afforded the corresponding *cis*-2-arylthiomethyl-1-tosyl-3-(trifluoromethyl)aziridines **94**, as expected (Scheme 25). Reaction of aziridine **93** with an excess of arenethiol at reflux furnished the corresponding ring opened sulfonamides **96**, showing that a subequimolar amount of arenethiol (0.9 equiv), as well as a low reaction temperature was required to avoid ring opening of the formed 2-(arylthiomethyl)aziridines **94**. Surprisingly, treatment of aziridine **93** with the oxygen analogues of arenethiols did not result in the anticipated aziridine systems but in *cis*-3-aryloxy-1-tosyl-2-(trifluoromethyl)azetidines **95**. Furthermore, an elevated temperature and pressure was required for the conversion of the starting material with phenols, in contrast to the reaction performed with arenethiols. This difference in chemoselectivity could be explained considering the HSAB (Hard Soft Acid Base) concept, although other factors could be involved as well.

**Scheme 25: Reactivity of 1-tosyl-3-(trifluoromethyl)aziridine 93 toward aromatic S- and O-nucleophiles**



From a mechanistic point of view, sulfur nucleophiles selectively attacked the exocyclic methylene carbon, which resulted in the direct displacement of the tosylate group toward the corresponding *cis*-3-CF3-aziridines **94** (route a, Scheme 26), whereas oxygen nucleophiles affected ring opening of the aziridine ring in a regio- and stereoselective manner at the C2-position followed by expulsion of the tosyl group, affording *cis*-2-(trifluoromethyl)azetidines **95** as the final products (route b, Scheme 26). The observed regioselectivity again confirmed the strong electronic and steric effect of the trifluoromethyl substituent, giving rise to a favored ring opening at the non-CF3-substituted side.

**Scheme 26: Reaction mechanism for the synthesis of aziridines 94 and azetidines 95 starting from 1-tosyl-3-(trifluoromethyl)aziridine 93**



This remarkable difference in reactivity has been further explored by using (thio)phenols with an additional nucleophilic group to affect ring expansion toward heterobicyclic systems via a domino ring opening-cyclization sequence. At first, treatment of aziridine **93** with a number of substituted thiophenols has been performed affording heterobicyclics **98** (Scheme 27). Taking into account the reactivity of aziridine **93** toward sulfur nucleophiles, the formation of aziridine **100** was assumed to occur first prior to intramolecular ring opening at the C2 position of the aziridine core by the additional heteroatom (Y in compound **100**). However, by appling 2-mercaptophenol, the initial ring opening by the oxygen atom toward sulfonamide **100** and consecutive expulsion of the tosyl group by the sulfur atom could not be excluded. For the reaction of aziridine **93** with 2-aminoarenethiols, heating at elevated temperatures appeared to be necessary to obtain a complete conversion toward 2,3-dihydrobenzofused thiomorpholines **98** (Y = N). Furthermore, the use of an excess of 2-aminothiophenol resulted in the partial formation of the corresponding ring opened product, again confirming that excess sulfur nucleophiles could elicit ring opening of the aziridine moiety. In a second part, the deployment of phenols with an additional nucleophilic substituent was evaluated as well. It was found that the oxygen atom first attacked the aziridine ring at the C2-position through an SN2-type approach resulting in ring opened intermediate **101**, followed by ring formation upon attack by the other heteroatom (Y in **101**).

**Scheme 27: Synthesis of heterobicyclics 98 and 95**



The regioselective ring opening at the non-CF3-substituted side of activated 2-(trifluoromethyl)aziridines has also been observed by Grellepois et al. and Rinaudo et al. when trifluoromethyl-substituted aziridines **102** were treated with a variety of oxygen and nitrogen nucleophiles (Scheme 28).[11f](#_ENREF_50),[11n](#_ENREF_58) However, in the case of 2-phenyl-1-tosylaziridine **102**, reaction under acidic conditions (aq. HClO4) provided ring opening at the more hindered carbon atom furnishing the corresponding amine **104** (R2 = Ph) with complete regioselectivity. This unusual outcome could be explained by the delocalization property of the phenyl group.

**Scheme 28: Nucleophilic ring opening of activated CF3-aziridines 102**



In addition, Katagiri et al. have also reported on the nucleophile-induced ring opening of 2-CF3-aziridines.[11j](#_ENREF_54) Treatment of ethyl 1-tosyl-2-(trifluoromethyl)aziridine-2-carboxylate **106** with a range of nucleophiles resulted in a library of α-CF3-sulfonamides **107**, as depicted in Scheme 29. Deprotection of the *N*-tosyl group was successfully attained by reaction with concentrated sulfuric acid, providing α-(trifluoromethyl)amines **111** in good yields (40-86%). Sulfonamide **108** was obtained by a zinc-mediated debromination of β-bromo amine **107** (Nu = Br) and was converted into amine **110** upon treatment with sulfuric acid. In addition, the synthesis of 5-(trifluoromethyl)pyrrolidin-2-one **109** was accomplished *via* hydrolysis and subsequent ring closure of amine **107** [Nu = CH2(COOMe)2]. Finally, removal of the *N*-tosyl group in pyrrolidin-2-one **109** afforded the free pyrrolidin-2-one **112** in an excellent yield of 92%.

**Scheme 29: Synthesis of α-CF3-amines starting from ethyl 1-tosyl-2-(trifluoromethyl)aziridine-2-carboxylate 106**



**2.2 Azetidines**

In contrast to aziridines, whose applicability as versatile building blocks has amply been proven by means of a variety of ring opening and ring transformation reactions,[5a](#_ENREF_23),[5b](#_ENREF_24),[5d](#_ENREF_26),[5e](#_ENREF_27),[23](#_ENREF_91) the class of their higher homologues, azetidines, has received considerably less attention in the chemical literature.[24](#_ENREF_97)Until a few years ago, the synthesis and reactivity of fluorinated azetidines had only been scarcely described in the literature. Apart from a few 3-fluoroazetidines, most attention went to 3-chloro- and 3-bromoazetidines.[25](#_ENREF_103) However, during the last years the chemistry of fluorine-containing azetidines has been gradually developed, partly due to a contribution by our research group. To that end, a number of mono- and difluorinated azetidines has been prepared starting from nonfluorinated substrates. On the other hand, a new synthetic protocol has been elaborated for the synthesis of 2-(trifluoromethyl)azetidines, starting from a trifluoromethylated CF3-carrier agent, followed by a study of their reactivity profile regarding ring transformation reactions.

At first, different routes have been developed for the synthesis of a variety of 3-fluoroazetidines. Herein, bromofluorination of a suitable *N*-propenylimine followed by ring closure upon expulsion of bromide is applied. In a first sequence, nonactivated 3-fluoroazetidines **114** were prepared in a three-step procedure starting from aldehydes **113**, involving imination, regiospecific bromofluorination and final ring closure (Scheme 30).[26](#_ENREF_104) This methodology has also been evaluated for the synthesis of 3-bromo-3-fluoroazetidines (R2 = Br in **114**). Unfortunately, the second step appeared to be unsuccessful and resulted in the recovery of the corresponding benzaldehydes due to hydrolysis during aqueous workup. Furthermore, the bromofluorination step was not regiospecific in all cases, as treatment of ketimine **115** with NBS and Et3N·3HF and subsequent reductive ring closure resulted in the formation of two isomeric structures **116** and **117** in a 1:3 ratio (Scheme 31). Analogs of 2-(fluoromethyl)aziridine **116** are almost unknown, apart from some single examples, pointing to the chemical relevance of this type of ring formation.[27](#_ENREF_105)

**Scheme 30: Synthesis of monofluoroazetidines 114**



**Scheme 31: Synthesis of 2-(fluoromethyl)aziridine 116 and 3-fluoroazetidine 117**



This approach has also been applied toward the preparation of *N*-diphenylmethyl-protected 3-aryl-3-fluoroazetidines **119**, although by means of slightly different reaction conditions (Scheme 32).[28](#_ENREF_108) Herein, transamination of propenylamines **118** was followed by a bromofluorination reaction upon treatment with NBS and Et3N·3HF. Consecutive reduction resulted in the partial formation (50-100%) of azetidines **119**. In the case of the 2-phenyl intermediate complete ring closure was accomplished by reaction with K2CO3.

**Scheme 32: Synthesis of 3-fluoroazetidines 119**



With the β-fluorinated azetidines **119** in hand, attempts have been made for the preparation of the corresponding β-fluorinated amino acids, bearing in mind the biological utility of these scaffolds. First, the *O*-protecting group in 3-(4-methoxyphenoxymethyl)azetidine **119** was removed upon oxidation with CAN (Scheme 33). Then, several reaction conditions were tested to oxidize the hydroxymethyl moiety of **120** to the corresponding carboxylic acid. However, all attempts failed, probably due to the basic amino group present in azetidine **120**. Therefore, the nitrogen atom was made less basic through replacement of the *N*-alkyl protecting group by a *N*-alkoxycarbonyl protecting group, affording *N*-(ethoxycarbonyl)azetidine **123**. However, it was found that cleavage of the *N*-alkyl substituent in **119** followed by *N*-Boc protection resulted in higher yields of *N*-(*tert*-butoxycarbonyl)azetidines **121**. Removal of the *O*-protecting group within azetidine **121** (R = 4-MeOC6H4OCH2) by reaction with CAN afforded 3-(hydroxymethyl)azetidine **124**. Due to the electron-withdrawing Boc group on the azetidine core, rendering the nitrogen atom less basic, azetidine **124** became accessible to oxidation to generate β-fluorinated carboxylic acid **125** upon treatment with NaIO4 in the presence of a catalytic amount of RuCl3.3H2O. In a final experiment, the free 3-fluoroazetidines **122** were obtained as well, isolated as their hydrochlorides and trifluoroacetates.

**Scheme 33: Reactivity of 3-fluoroazetidines 119**



Besides *N*-Boc-protected 3-fluoroazetidines **121, 124** and **125**, another 3-fluoroazetidine with the same protecting group has been prepared as well. In that respect, *N*-Boc-protected 3-fluoroazetidine **127** was attained in a four-step procedure (Scheme 34).[29](#_ENREF_109) To that end, azide substitution of 2-methyl-2-propenyl chloride **126** and subsequent bromofluorination and hydrogenation in the presence of Boc2O gave rise to 1-Boc-3-bromo-2-fluoro-2-methylpropylamine intermediate, which was finally subjected to NaH-induced ring closure resulting in the desired *N*-Boc-protected 3-fluoroazetidine **127**.

**Scheme 34: Synthesis of 3-methyl-3-fluoroazetidine 127**



Next to the synthesis of monofluorinated azetidines, the preparation of 3,3-difluoroazetidines has been accomplished as well. In contrast to the synthesis of 2-fluoroazetidines, which were obtained via a bromofluorination of a suitable *N*-propenylimine and a subsequent ring closure, 3,3-difluoroazetidines have been obtained via a crucial Reformatsky-type reaction.[30](#_ENREF_110) To that end, a variety of imines **128** were treated with ethyl bromodifluoroacetate, yielding difluorinated β-lactams **129** (Scheme 35). In the case of *N*-(2-methylpropylidene)-2-propenyl-1-amine **128** (R1 = allyl, R2 = *i*Pr), reaction with ethyl bromodifluoroacetate also furnished a small amount (5%) of ethyl 3-allylamino-2,2-difluoro-4-methylpentanoate due to incomplete ring closure. In a next step, azetidin-2-one **129** (R1 = 4-MeOC6H4CH2, R2 = Ph) was debenzylated upon treatment with CAN. Then, *N*-functionalization of the free *NH*-β-lactam **130** was evaluated by reaction with two alkyl bromides, affording *N*-alkylated β-lactams **131**. In the case of 1-bromobutane, harder reaction conditions were required to complete the reaction. In a final step, azetidinones **129** and **130** were reduced with *in situ* prepared monochloroalane (AlH2Cl), efficiently resulting in 3,3-difluoroazetidines **132**.

**Scheme 35: Synthesis of 3,3-difluoroazetidines 132**



Elaborating on the earlier described protocols for the synthesis of different classes of trifluoromethylated aziridines, additional research has been performed by us concerning the preparation of their higher homologues, 2-(trifluoromethyl)azetidines, again exploiting a building block approach.[31](#_ENREF_111) Moreover, the reactivity profile of these four-membered rings toward a variety of nucleophiles has been explored in order to study possible similarities or discrepancies with their three-membered counterparts. Importantly, it should be mentioned that, apart from this study, no further information concerning the reactivity profile of 2-(trifluoromethyl)azetidines is available in the literature.

The synthesis of 2-(trifluoromethyl)azetidines **137** was achieved through a four-step procedure starting from ethyl 4,4,4-trifluoroacetoacetate **133** involving imination, hydride reduction, chlorination, and base-induced ring closure (Scheme 36). However, this protocol was not as straightforward as it seemed. Firstly, different reducing agents had to be tested for the conversion of enamines **134** into the corresponding amino alcohols **135**. Whereas the use of LiAlH4 resulted in full recovery of the starting material, treatment of enamine **134** (R = Bn) with NaBH4 in methanol only gave rise to the partial formation (75-83%) of the desired amino alcohol **135** (R = Bn). Secondly, the tosylate group as an alternative for the chloride atom in 4-chloroamine **136** (R = Bn) was evaluated as well. However, due to the low yield of the tosylation reaction, the initial approach using thionyl chloride was preferred. Finally, different bases (Et3N, NaH, LiHMDS) were investigated for the ring-closing reaction of amine **136** (R = Bn) toward the desired 2-CF3-azetidine **137** (R = Bn). Unfortunately, no reaction occurred when Et3N or NaH were used, not even after prolonged reaction times of 24 to 64 hours. Therefore, based on previous results obtained for the synthesis of 2-CF3-aziridines, a stronger base such as LiHMDS was required due to the reduced nucleophilicity of the nitrogen atom, caused by the strong electron-withdrawing effect of the trifluoromethyl substituent at the α-position.

**Scheme 36: Synthesis of 2-(trifluoromethyl)azetidines 137**



In the next phase of this study, the reactivity of 2-(trifluoromethyl)azetidines **137** toward a variety of nucleophiles was examined (Scheme 37). In a first section, azetidinium ion formation was achieved via *N*-protonation upon prolonged dissolution in concentrated hydrochloric acid or hydrobromic acid at high temperature in a pressure vial, yielding 4-halobutan-2-amines **139** after regioselective ring opening by the halide (Cl-, Br-) at the less hindered C4 position. The use of these strong acids and harsh reaction conditions appeared to be necessary to achieve full conversion. Heating of 4-methylbenzyl-2-(trifluoromethyl)azetidine **137** (R1 = 4-MeC6H4CH2) in 50% aqueous solution of sulfuric acid confirmed the negative effect of a trifluoromethyl group on nucleophilic ring opening reactions, as only 43% conversion toward the corresponding amino alcohol after 14 days was achieved.

Next to *N*-protonation, *N*-acylation has also been evaluated to effect activation of 2-(trifluoromethyl)azetidines **137**. To that end, a selection of 2-(trifluoromethyl)azetidines **137** was treated with acetylchloride and methyl chloroformate resulting in amides **140** (R3 = Me) and carbamates **140** (R3 = OMe). Due to the steric and electronic effects of the trifluoromethyl substituent in azetidines **137**, nucleophilic attack again proceeded regioselectively at the less hindered side of the azetidine core. Carbamates **140** (R3 = OMe) underwent upon heating and microwave irradiation ring closure to the interesting CF3-substituted 1,3-oxazinan-2-ones **141**.

In a next part of this study, a regioselective ring opening of 2-CF3-azetidines **137** was accomplished by *N*-alkylation to produce transient quaternary ammonium salts **138**. In that respect, azetidines **137** were subjected to benzyl iodide affording γ-iodoamines **142** through regioselective ring opening at the less hindered carbon atom, as could be expected from the results of the alkyl iodide-induced ring opening of their smaller counterparts, 2-(trifluoromethyl)aziridines **39** (Scheme 11). Next to alkylation by benzyl iodide, azetidines **137** were also activated with Me3OBF4. Afterwards, the *in situ* created azetidinium salts **138** (R2 = Me) were treated with a variety of oxygen, nitrogen, carbon, and sulfur nucleophiles, yielding a library of α-(trifluoromethyl)amines **143** through regioselective ring opening at C4.

**Scheme 37: Reactivity of 2-(trifluoromethyl)azetidines 137**



Taking the above-mentioned results concerning the ring opening of 2-(trifluoromethyl)azetidines **137** into account, it can be concluded that attack by any nucleophile always proceeds regioselectively at the less hindered position, independent of the type of activation and the nature of the nucleophile involved. Furthermore, in all of the performed experiments, nucleophilic ring opening of the *in situ* created azetidinium ions **138** gave always rise to primary ring opening products, pointing to a kinetically controlled reaction pathway. This stands in sharp contrast to nucleophilic attack across their non-fluorinated analogues, in which ring opening occurs at the substituted azetidine carbon atom under thermodynamic control, as has been demonstrated in the same study.[31](#_ENREF_111) As a consequence, the reactivity profile of azetidines containing an alkyl group (e.g. CH3) instead of a trifluoromethyl group is completely different, which can be attributed to the strong electron-withdrawing property of the CF3-substituent. This conclusion is completely in line with the chemistry of trifluoromethylated aziridines and underlines again the pronounced effect of introducing a CF3-group.

Apart from the above-described protocol toward the synthesis of nonactivated 2-CF3-azetidines **137** (Scheme 36) and their subsequent ring opening resulting in a library of α-CF3-amines **139-143** (Scheme 37), only one more approach toward the preparation of nonactivated 2-(trifluoromethyl)azetidines has been reported in the literature by Ngoc Tam et al. In that strategy, chiral imine **144** was converted into diastereomerically pure 2-CF3-azetidin-3-ol **145** in a five-step procedure, involving addition of vinylmagnesium bromide across a chiral CF3-aldimine, methoxycarbonylation with dimethyl carbonate in the presence of InCl2, bromination of the double bond, deprotection using KO*t*Bu and final ring expansion upon heating in isopropanol (Scheme 38).[32](#_ENREF_112) In contrast, the synthesis of activated 2-(trifluoromethyl)azetidines has been studied to a slightly larger extent. In a first approach, *N*-Boc-protected 2-CF3-azetidines **146** have been prepared in a four-step procedure starting from commercially available 3,3,3-trifluoroalanine (**145**) and were further converted into a number of diastereomerically pure 2-CF3-azetidine derivatives (Scheme 39).[33](#_ENREF_113) A second methodology, involving a four-step synthesis starting from *N*-benzyloxycarbonyl-protected imine **148** derived from ethyl trifluoropyruvate, resulted in a *N*-benzyloxycarbonyl-substituted azetidine **149** in an overall yield of 65% (Scheme 40).[34](#_ENREF_114) Finally, two other approaches toward activated 2-CF3-azetidines have been based on either a cycloaddition reaction of a perfluorinated imine and an alkene to give 2,2-bis-(trifluoromethyl)azetidines[35](#_ENREF_115)a,b or a cycloaddition reaction of a CF3-imine and an alkene to afford polysubstituted azetidines.[35](#_ENREF_115)c Recently, a new synthesis of enantiopure (2*R*)-2-(trifluoromethyl)azetidine-2-carboxylic acid (**151**) has been reported through elaboration of bicyclic CF3-substituted oxazolidine **150** (Scheme 41).[36](#_ENREF_117)

**Scheme 38: Synthesis of 2-CF3-azetidinol 145 starting from chiral imine 144**



**Scheme 39: Synthesis of 2-CF3-azetidine 147 starting from 3,3,3-trifluoroalanine 146**



**Scheme 40: Synthesis of 2-CF3-azetidine 149 starting from imine 148**



**Scheme 41: Synthesis of azetidine-2-carboxylic acid 151 starting from CF3-substituted oxazolidine 150**



**3 Synthesis of fluorine-containing nitrogen compounds starting from nonfluorinated aziridines and azetidines**

**3.1 Aziridines**

The synthesis of fluorinated amines starting from aziridines bearing no fluorine atom has been studied to a limited extent by our research group. In that respect, the only research performed on nonfluorinated aziridines involved the systematic study of halide-induced ring opening of 2-substituted aziridinium salts. To that end, a variety of nonactivated 2-(aryloxymethyl)aziridines **152**[10](#_ENREF_44) and 2-(alkanoyloxymethyl)aziridines **152**[37](#_ENREF_118) were treated with an alkyl bromide furnishing β-bromo amines **153** (Scheme 42). Subsequent reaction with TBAF afforded a mixture of primary fluorides **154** as the major constituents (42-86%) and secondary fluorides **155** as the minor compounds (8-28%). From a mechanistic point of view, *N*-alkylation of the starting material **152** affects the activation of aziridines **152** toward the intermediate aziridinium bromides **156**, which are then opened exclusively at the more hindered carbon atom by bromide under thermodynamic control. Subsequent heating resulted in the formation of the intermediate aziridinium ions **156**, which were then preferentially attacked by fluoride at the less hindered carbon atom of the aziridine ring. Recyclization toward aziridinium salts **156** upon expulsion of fluoride did not occur due to the low leaving group capacity of fluoride as compared to the other halides (iodide, bromide and chloride in descending order). Furthermore, the choice of the fluoride source seemed also important, since the use of potassium fluoride resulted in full recovery of β-bromo amines **153**. Variation in the amount of utilized TBAF only had a small influence on the ratio of the major versus the minor isomer.

**Scheme 42: Regioselective ring opening of aziridines 152 with TBAF**



To study the possible effect of the substrate on the halide-dependent regioselective ring opening of aziridines, chiral aziridines **157** have been subjected to tetrabutylammonium fluoride after activation with MeOTf (Scheme 43).[10](#_ENREF_44) Whereas ring opening of the methoxymethyl derivative **158** (R = CH2OMe) mainly produced the expected primary fluoride **159**, the reaction of 2-(ethoxycarbonyl)aziridinium salt **158** (R = CO2Et) with TBAF afforded only the corresponding secondary fluoride **160**, which demonstrates the substrate-dependency of this regioselective ring opening. Due to the presence of an ester group in compound **158** (R = CO2Et), the more substituted carbon atom is more electrophilic, favoring nucleophilic attack at this position.

**Scheme 43: Ring opening of chiral aziridine 157 with TBAF**



These experimental data have also been supported by computational studies, which revealed that the reaction outcome of ring opening reactions of nonactivated aziridines with alkyl halides was mainly dependent on the halide.[10](#_ENREF_44),[38](#_ENREF_119) Whereas chloride-, bromide-, or iodide-induced ring opening was mediated by product stability through thermodynamic control affording secondary halides, ring opening of the same aziridinium salts with fluoride was shown to be dictated by kinetic control (steric interactions) giving rise to primary fluorides as the main constituents.

**3.2 Azetidines**

Next to aziridines, nonfluorinated azetidines have also been applied for the synthesis of organofluorine compounds. In a first approach, ring transformation of 2-(2-bromoethyl)azetidines **161** has been performed upon treatment with tetramethylammonium fluoride (TMAF) affording *cis*-4-fluoro-5,5-dimethylpiperidines **163** (Scheme 44).[39](#_ENREF_120) From a mechanistic point of view, the observed *cis*-stereochemistry of piperidines **163** was rationalized considering the intramolecular displacement of bromide by the nucleophilic nitrogen lone pair of azetidines **161** toward bicyclic azetidinium intermediates **162**.[40](#_ENREF_121) Consecutive ring opening of these highly reactive intermediates **162** at the bridgehead carbon atom by fluoride in a SN2 fashion resulted in the thermodynamically more favored piperidines **163**. In contrast to the previous section regarding the nucleophilic ring opening of aziridines **152** by TBAF, TMAF had to be used in this case because of the decomposition of TBAF at elevated temperatures. Besides the main formation of piperidines, small amounts of piperidine enol ethers were also observed, most probably as a result from a fluoride-induced dehydrobromination of the bromine analogues of piperidines **163**.

**Scheme 44: Synthesis of 3-fluoropiperidines 163**



In a second approach, starting from another class of nonfluorinated azetidines, the synthesis of monofluorinated morpholin-3-ones **166**, **168** and **169** has successfully been accomplished (Scheme 45).[41](#_ENREF_122) To that end, β-lactams **164** were converted into 2-hydroxy-1,4-oxazin-3-ones **165** through a peculiar NaIO4-induced ring transformation. Selective deoxyfluorination of 1,4-oxazin-3-ones **165** was achieved upon treatment with Morph-DAST, affording 2-fluoro-1,4-oxazin-3-ones **166**. In addition, *O*-alkylation with benzoyl chloride and subsequent regioselective bromofluorination resulted in a diastereomeric mixture of 2-benzoyloxy-6-bromo-5-fluoromorpholin-3-ones **168** and **169** through *anti*-addition across the C–C double bond. Based on the experimental coupling pattern in the 13C NMR spectra, the regioselectivity was unambiguously assigned, pointing to the *N*-acyliminium ion character of the intermediates **170** during the bromofluorination.

**Scheme 45: Synthesis of 2-fluoro-1,4-oxazin-3-ones 166 and 5-fluoromorpholin-3-ones 168 and 169**



**4 Conclusions and outlook**

In this Account, an overview was presented dealing with the preparation and consecutive application of small-ring azaheterocycles for the synthesis of a wide variety of organofluorine compounds. Bearing in mind the above-mentioned protocols for the synthesis of (fluorinated) aziridines and azetidines and the exploration of their reactivity, it is clear that both the synthesis of small-ring azaheterocycles and their ring transformation toward different target compounds can be dramatically altered upon fluorine introduction. On the other hand, careful deployment of (fluorinated) small-ring azaheterocycles, based on a good knowledge of their chemical reactivity, provides a powerful approach toward a broad range of valuable fluorinated target compounds, and further endeavors in that direction are certainly expected to have a considerable impact on the field of fluorine chemistry in the near future. It is evident that asymmetric versions of all the above-described racemic approaches can be developed in future work if the synthesis of chiral target compounds is desired.

**5 References**

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