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A Novel and Selective Fluoride Opening of Aziridines by XtalFluor-E. Synthesis of Fluorinated Diamino Acid Derivatives

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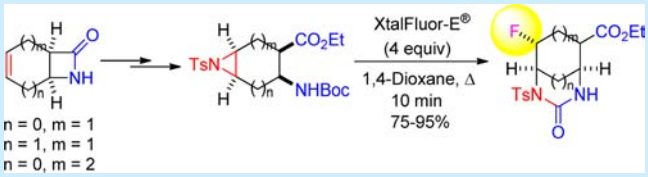
Supporting Information

ABSTRACT: The selective introduction of fluorine onto the skeleton of an aminocyclopentane or cyclohexane carboxylate has been developed through a novel and efficient fluoride opening of an activated aziridine ring with XtalFluor-E. The reaction proceeded through a stereoselective aziridination of the olefinic bond of a bicyclic lactam and regioselective aziridine ring opening with difluorosulfiliminium tetrafluoroborate with the neighboring group assistance of the sulfonamide moiety to yield fluorinated diamino acid derivatives. The method based on the selective aziridine opening by fluoride has been generalized to afford access to mono- or bicyclic fluorinated substances.



The aziridines are an important and valuable class of synthons which undergo ring opening with various nucleophiles to give functionalized amines. They are therefore useful ring systems for the creation of novel functionalities in certain molecules, or for the synthesis of substituted amines, amino alcohols, amino acids, azasugars, natural products, or bioactive compounds. The nucleophilic ring opening of aziridines with carbon, oxygen, sulfur, nitrogen, hydrogen, or halogen (e.g., iodide, bromide or chloride) nucleophiles has been studied extensively and has found broad application in synthetic organic and medicinal chemistry.[1]

In consequence of the considerable importance of fluorinated organic materials in medicinal chemistry and the increasing impact of fluorine-containing organic molecules in drug research (25% of the current pharmaceuticals contain at least one fluorine atom), an ever-increasing number of fluorination methodologies have emerged during the past 20 years, in particular involving the use of safe, commercially available electrophilic or nucleophilic organic fluorinating agents. The most common methods are mainly based on fluorination through an active methylene (electrophilic) by the use of *N*-fluorobenzenesulfonimide (NFSI) or its analogs, Selectfluor, or by leaving group substitution with fluoride, e.g. hydroxy—fluorine, oxo—fluorine interconversion with the application of diethylaminosulfur trifluoride (DAST), *bis*(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor), *N,N*-diethyl-*S,S*-difluorosulfiliminium tetrafluoroborate (XtalFluor-E) or XtalFluor-M (nucleophilic).[2]

Although aziridines are useful precursors in the preparation of a number of functionalized substances, and especially β-fluoroamines, important elements of drug candidates of biological relevance (e.g., antileukemia agents and drugs for the treatment of Alzheimer's disease),[2a,g] there have been few reports relating to the ring opening of aziridines with a fluoride anion. The most important and convenient synthetic approaches for the opening of aziridines with fluoride are the *N*-three-membered ring opening with the HF—pyridine reagent,[3] or reactions with tetrabutylammonium fluoride (TBAF)[4a−c] or TBAF/$NiCl_2$[4d] KF in the presence of Bu_4NHSO_4[5] or BF_3OEt_2.[6] A combination of PhCOF, HFIP (hexafluoroisopropanol), and 1,5-diazabicyclo-[4.3.0]non-5-ene (DBN) was recently described for the *in situ* generation of an HF/amine system in order to achieve the fluorination of aziridines.[7] Both hydroxy—fluorine exchange and the rearrangement of β-amino alcohols with organic aminosulfur trifluorides such as Deoxofluor[8a,b] or DAST[8c] have been carried out through aziridinium ion intermediates to give β-fluoroamines.

We describe here a novel and effective substrate-directed selective synthetic method for the opening of functionalized cyclopentane or cyclohexane-fused activated aziridines through the use of XtalFluor-E. Due to the high biological relevance of five-membered unsaturated cyclic β-amino acids (e.g., cispentacin, icofungipen, oryzoxymycin, etc.), we first selected the fluoride opening of the *N*-three-membered ring of aziridino cycloalkane β-amino esters as a model transformation.[9]

Cyclopentene β-amino ester **2**,[10] derived from bicyclic β-lactam **1**, was transformed by *cis*-selective stereoselective aziridination with chloramine-T and a catalytic amount of phenyltrimethylammonium tribromide (PTAB) to the corre-

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sponding aziridine-fused cyclic amino ester **3** and its stereoisomer **4**.[10a]

Several commercially available fluorinating agents (Figure 1) were used for the fluoride opening of the aziridine framework.

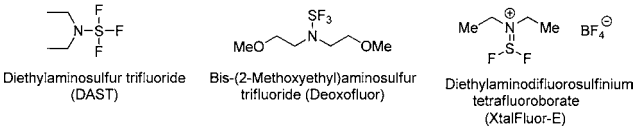


Figure 1. Some commercially available fluorinating agents used in this work.

First, aziridine derivative **3** was subjected to fluoride opening with DAST as the fluoride source. The reaction was accomplished in several common solvents, such as CH_2Cl_2, THF, 1,4-dioxane, or PhMe, at different temperatures. In refluxing dioxane, a fluorinated compound was isolated as the sole product in a yield of 5% after 30 min and was identified by bidimensional NMR analysis and X-ray crystallography (Figure 2, Scheme 1) as **5**; this was formed through intramolecular

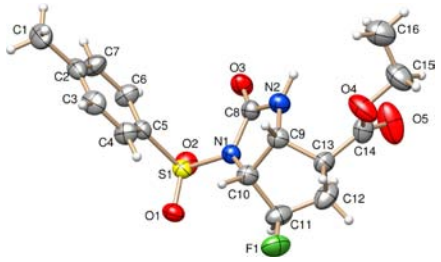
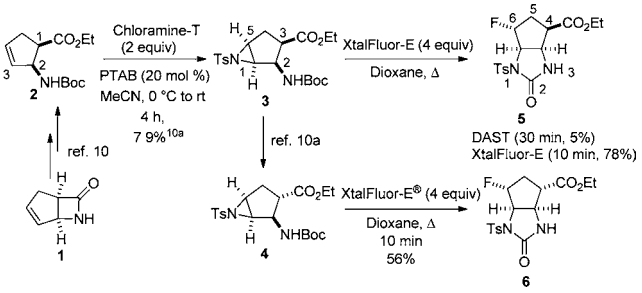


Figure 2. Structure of compound **5** revealed by X-ray diffraction analysis.

Scheme 1. Fluorination of Aziridine Stereoisomers 3 and 4



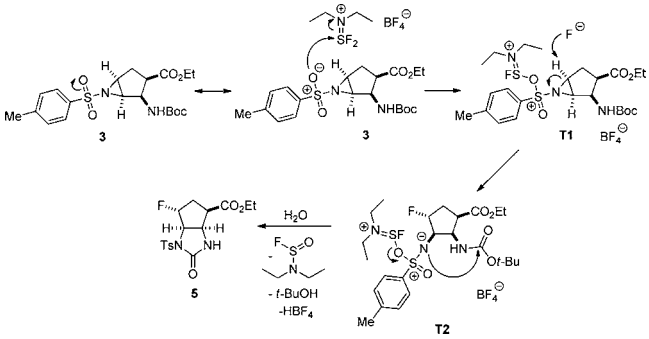
cyclization involving formation of a bicyclic compound containing an imidazolidinone ring, with a fluorine atom on C-6. Since DAST is unstable at higher temperatures, prolonged refluxing did not result in an increase of yield: only unreacted starting material was detected on TLC. In further preliminary experiments with 50% Deoxofluor solution in THF, aziridine opening was not observed in different solvents or various temperatures.

Aminodifluorosulfinium salts are significantly more stable fluorinating agents than DAST or Deoxofluor. For example, in contrast with DAST or Deoxofluor, XtalFluor-E (diethylaminodifluorosulfiliminium tetrafluoroborate) is a solid, more easily handled, and a thermally stable reagent.[11] We found that the transformation of aziridino amino ester **3** with 4 equiv of XtalFluor-E in refluxing dioxane during 10 min afforded **5** as a single product, which was isolated in 78% yield after workup and column chromatography (Scheme 1, Figure 2). It is noteworthy that variation of the concentration of the solvent did not significantly influence the yield of the transformation.

Under the same conditions as those for the *cis* counterpart **3**, the *trans* derivative **4**[10a] readily underwent aziridine opening with XtalFluor-E in refluxing dioxane for 10 min to furnish bicyclic fluorinated ester **6** regioselectively (Scheme 1). A probable explanation for the regioselectivity of the aziridine ring opening by the attack of fluoride at C-5 (in **3** or **4**) might be attributed to electronic factors. The electron-withdrawing effect of the *N*-atom of the carbamate will generate an electron deficiency at C-5 in **3** or **4**, and the fluoride will therefore attack this position; however, the elucidation of the regioselectivity requires further investigation (for a similar nucleophilic ring opening, see ref 10).

The aziridine ring opening of bicyclic compound **3** with XtalFluor-E, followed by intramolecular ring closure to give fluorinated ester **5** containing an imidazolidinone ring system, is a rather unusual process. Thus, we assumed that it can be interpreted in terms of relatively simple steps. The activated aziridine, involving sulfonamide group assistance, plays a crucial role in the process. First, it is presumed that the partially negatively polarized O atom of sulfonamide **3** attacks the sulfur atom of Xtal-Fluor E to form adduct **T1**, with the concomitant generation of a fluoride anion. Through a regioselective nucleophilic aziridine opening, the latter fluoride leads to aziridine-opened intermediate **T2**, which undergoes an intramolecular nucleophilic acyl substitution step on the Boc carbonyl C atom to produce the imidazolidinone ring, with simultaneous reformation of the *N*-tosyl moiety, giving rise to fluorinated product **5** (Scheme 2). Transformations analogous to the S_N2-

Scheme 2. Supposed Route to Fluorinated Imidazolidinone Ester Derivative 5



type ring opening (**T1** to **T2**) of bicyclic aziridines with fluoride (generated as presented in the Introduction) proceeded with a similar mechanism, giving rise to *trans*-β-fluoramines.[5,6c,7] It is noteworthy that *N,N*-diethylsulfamoyl fluoride was earlier recognized as a side product in deoxofluorination reactions with XtalFluor-E.[11a]

Another cyclopentene amino ester **8** of value as a precursor of bioactive products,[12] derived from Vince's lactam, was subjected to aziridination with chloramine-T to result *cis*-stereoselectively in aziridino γ-amino ester **9**. Fluorination of compound **9** with XtalFluor-E proceeded through regioselective aziridine opening, with concomitant intramolecular ring closure, to afford fluorinated ester **10** (Scheme 3). In order to extend the above method to the preparation of novel cyclic fluorinated amino acid derivatives, the fluorination of several cyclohexene 2-amino ester stereo- and regioisomers **11**, **14**, **17**, and **20**[13] was investigated.

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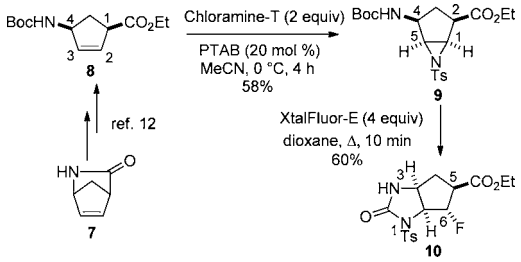
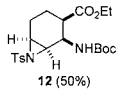
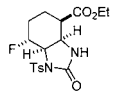
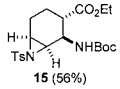
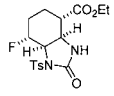
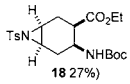
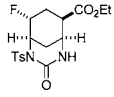
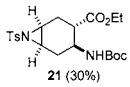
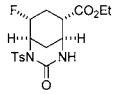
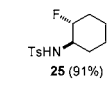
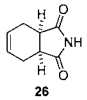
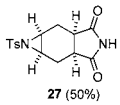
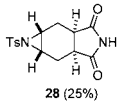
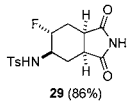
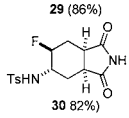
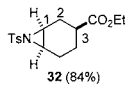
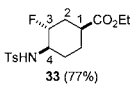
Scheme 3. Synthesis and Fluorination of Aziridine 9



With chloramine-T and PTAB, these compounds readily underwent 100% *cis*-stereoselective transformation to the corresponding aziridine-fused bicyclic products **12**, **15**, **18**, and **21** (Table 1).

Table 1. Fluorination of Bi- And Tricyclic Aziridines (Ratio of 27/28 = 2:1)

entry	amino ester	aziridine (yield)	product (yield)
1	 **11**	 **12** (50%)	 **13** (75%)
2	 **14**	 **15** (56%)	 **16** (70%)
3	 **17**	 **18** 27%)	 **19** (95%)
4	 **20**	 **21** (30%)	 **22** (75%)
5	 **23**	 **24** (60%)	 **25** (91%)
6	 **26**	 **27** (50%)  **28** (25%)	 **29** (86%)  **30** 82%)
7	 **31**	 **32** (84%)	 **33** (77%)

Analogously to the five-membered counterparts **3**, **4**, and **9**, on reaction with XtalFluor-E (4 equiv), in refluxing dioxane, after 10 min these six-membered aziridino esters led regioselectively to the corresponding bicyclic fluorinated esters in good yields through aziridine opening of **13**, **16**, **19**, and **22** (Table 1).

As this fluoride opening of bicyclic aziridines is a convenient method for the selective introduction of a fluorine atom onto the skeleton of an organic molecule, we considered the potential generalization of the above synthetic route by extending it to relatively simple bicyclic or tricyclic fused symmetrical aziridines.

For this, we selected cyclohexene **23** and *cis*-1,2,3,6-tetrahydrophthalimide **26** as unsaturated mono- and bicyclic compounds. Cyclohexene underwent facile aziridination to the corresponding aziridino cyclohexane (**24**), the treatment of which with XtalFluor-E in refluxing dioxane for 10 min furnished the aziridine ring-opened compound **25**.[4b,5] Aziridination of *cis*-tetrahydrophthalimide **26** under the conditions used in the previous cases afforded aziridine-fused derivatives **27** and **28** in 2:1 ratio, the major product being the *cis* derivative **27** (Figure 3).

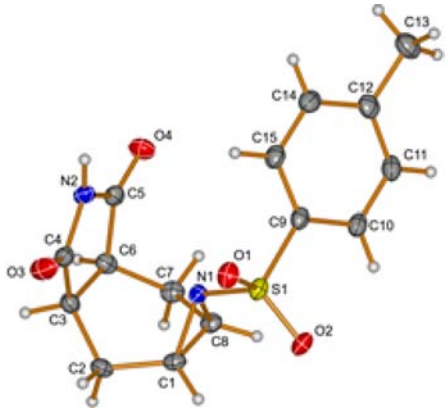
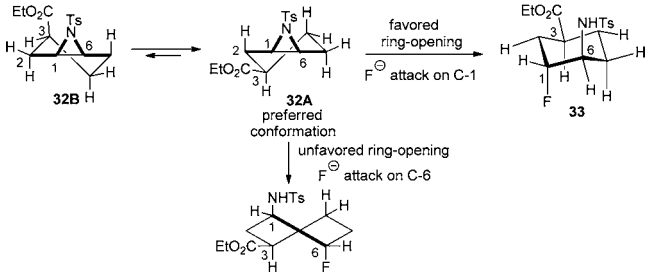


Figure 3. Structure of compound **27** revealed by X-ray diffraction analysis.

Both **27** and **28** participated in fluorination under the described conditions to give the corresponding fluorinated aziridine-opened compounds **29** and **30** (Table 1). Similarly, the monosubstituted cyclohexene **31** stereoselectively furnished aziridine ester **32**, which on treatment with XtalFluor-E in refluxing dioxane for 10 min gave rise regioselectively to compound **33** (determined by 2D NMR analyses) in a yield of 77% (Table 1). The regioselectivity of the aziridine opening in **32** is determined by the preferred diaxial chair conformational arrangement (in contrast with the unfavorable twisted chair arrangement) in the three-membered ring opening, which results from the attack of the fluoride at C-1 in compound **32**. The preferred conformational arrangement of compound **32** (**32A**) (Scheme 4) undergoes ring opening on fluoride attack at C-1,

Scheme 4. Formation of Compound 33



leading to compound **33** through the favored diaxial chair conformation. In contrast, a fluoride attack on C-6 would lead to an unfavorable twisted chair diaxial arrangement (Scheme 4).

In order to supplement our work and demonstrate the utility and high importance of aziridine opening with fluoride, we attempted to achieve the detosylation of fluorinated sulfonamides. As model compounds, we selected fluorine-containing esters **19** and **33**. A number of literature methods are available for

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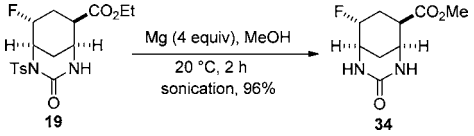
detosylations (see Supporting Information, refs 14−24). Attempts at detosylation in the case of ester **33** were performed under several conditions, but without success to provide the desired deprotected derivative. After several experimental investigations on ester **19** (such as Bu_3SnH/AIBN in PhMe, SmI_2 in THF, TMSI in MeCN, TBAF in THF, Li or Na with naphthalene in DME) without success in obtaining the desired deprotected derivative. It was found that sonication in the presence of 4 equiv of Mg turnings in dry MeOH furnished after 2 h the detosylated product **34**, but with concomitant transesterification (Scheme 5) (see Supporting Information, ref 25). It is noteworthy that when the same reaction was attempted in EtOH, no conversion was obeserved; only starting material was recovered.

Scheme 5. Formation of 34 by Detosylation of Compound 19



In conclusion we have described a novel and efficient generalized approach for the fluoride opening of aziridines for the introduction of a fluorine atom into an organic molecule. The fluoride opening was performed with activated aziridines with XtalFluor-E in refluxing dioxane for 10 min. The reaction proceeded selectively with several bicyclic or tricyclic aziridine derivatives, the ring opening with difluorosulfiniminium tetrafluoroborate occurring with the intramolecular assistance of the sulfonamide moiety. Further applications of this methodology are currently being studied in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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