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Minireview

Organofluorine Molecules | *Very Important Paper* |

VIP

Synthesis of Fluorine-Containing Molecular Entities Through Fluoride Ring Opening of Oxiranes and Aziridines

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Abstract: The current minireview highlights the most relevant methodologies for the creation of fluorinated scaffolds accessed through transformations of three-membered heterocycles (oxiranes and aziridines) involving their opening with various nucleophilic fluorinating agents reported over recent years. The purpose of the review is also to provide an overview of the ring-opening synthetic practices with fluoride towards different functionalized, fluorine-containing scaffolds with the focus on regioselectivity/regiocontrol and enantioselectivity including symmetric or unsymmetric monoheterocycles, cycloalkane-fused oxiranes and aziridines.

Contents

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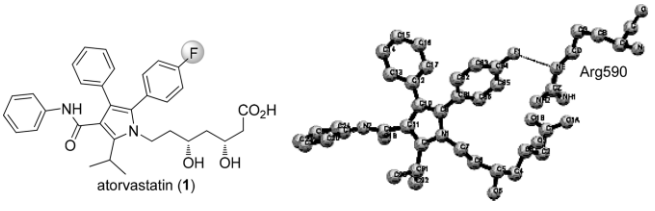
1. Introduction and Aims

The synthesis of organofluorine compounds has become a hot topic in recent decades thanks to their unique properties.[1–4] The highly electronegative fluorine makes the C–F bond strongly polar, enabling dipole–dipole interactions (Scheme 1).[4–8] However, further polarization of this bond is difficult, resulting from the weak hydrogen-bond acceptor quality and polar hydrophobic nature.[5,6,9,10] Electron withdrawal by the fluorine atom can considerably change pK_a values of nearby functional groups which, together with polar hydrophobicity, affects lipophilicity a key pharmaceutical parameter.[4–6,8,9]

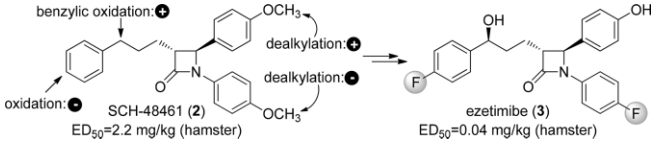


Scheme 1. The drug atorvastatin blocks cholesterol synthesis by inhibiting HMG-CoA reductase. The F atom increases the binding of atorvastatin through an electrostatic $C–F^{\delta-}\cdots N^{\delta+}$ interaction with the side chain of Arg590.

An important aspect of fluorine incorporation is the size of the F atom, which is between that of the H and the OH group. As a result, replacement of hydrogen with fluorine does not have usually a significant steric influence, however stereoelectronic effects can influence conformation.[4–6,8]

Fluorination also influences metabolism, another important pharmaceutical parameter. Because the C–F bond is stronger than the C–H bond, replacement of metabolically labile hydrogens with fluorine increases stability. Fluorine also withdraws

electrons from nearby atoms, deactivating them toward oxidative metabolism (Scheme 2).[4–6,8,9,11]

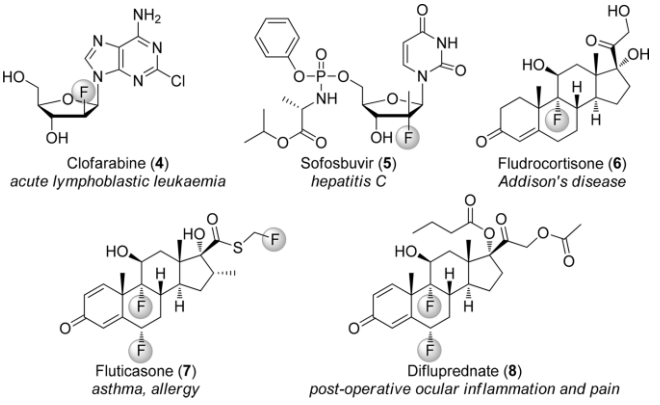


Scheme 2. During the development of ezetimibe, which inhibits cholesterol uptake, fluorination was used to improve metabolic stability.

Thanks to the above advantages, fluorinated drug molecules have become common and in the 2000s the ratio of fluorinated molecules within newly-approved drugs started to increase.[9,11] Incorporation of the ^{18}F atom ($t_{1/2}$ = 110 min) to produce radiopharmaceuticals is also an emerging area.[4,8,12,13]

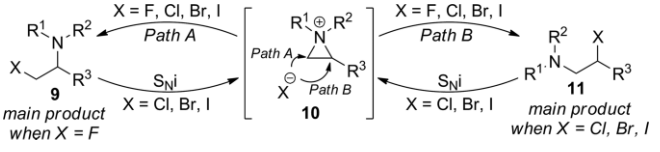
The increasing importance of fluorinated molecules brought about significant development of fluorination techniques in the last decades. Currently, both electrophilic and nucleophilic fluorine sources as well as fluorinated building blocks are available at affordable prices. However, research towards effective, selective, and functional-group tolerant fluorination methods, which can be performed under mild conditions, is still in progress.[1,4]

Thanks to their high ring strain, epoxides are susceptible to ring opening with nucleophiles. Performing this reaction with fluoride sources yields vicinal fluorohydrins.[4,14] It is worth noting that the fluorohydrin motif is present in multiple drugs (Scheme 3) such as Clofarabine (**4**, approved in 2004)[15] and Sofosbuvir (**5**, approved in 2013).[16] In addition, there are a high number of fluorinated steroids like 9α-fluorohydrocortisone (Fludrocortisone, **6**, approved in 1954 as the first fluorine-containing drug),[11] Fluticasone (**7**, approved in 1990),[11] and Difluprednate (**8**, approved in 2008).[17] Although ring opening of oxiranes by fluoride is a well-known reaction,[4,14] the often harsh reaction conditions and selectivity problems or side reaction issues generated considerable need for improvements. Desymmetrization of *meso* epoxides is also an area of interest.[18] Synthesis of PET tracers by ring opening of epoxides with [^{18}F]F^- is a promising area too.[8,13,19–21]



Scheme 3. Approved drugs containing fluorohydrin moieties.

Aziridines have a strained ring similar to that of epoxides. However, ring opening of aziridines with fluoride sources has been investigated to a lesser extent.[14,22] Such reactions yield β-fluoroamines, which are less basic and more lipophilic than their non-fluorinated counterparts,[6,8] making them interesting from the viewpoint of pharmaceutical chemistry. An interesting aspect of these reactions is that, according to experiments with aziridinium ions, they are kinetically controlled. In contrast, ring opening of aziridinium ions with other halides is thermodynamically controlled. The reason of this difference is the leaving group ability of halides: Cl^-, Br^-, and I^- are good leaving groups, enabling equilibration between the products through aziridinium halide **10**. F^-, on the other hand, is a bad leaving group, which inhibits equilibration. As a result, fluoride attack on the sterically less hindered aziridine carbon is favored in simple aziridines (Scheme 4).[23–25] Groups with *–M* effect (activating



Scheme 4. Difference between ring openings of aziridinium ions with various halides. S_Ni reaction required for product equilibration is disabled when X = F, and steric effects inducing the dominance of *Path A* and product **9**. In the cases of other halides, equilibration yields **11** as the most stable product.

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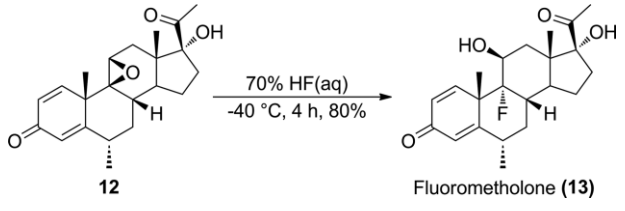
groups) can overrule this behavior, directing F^- to the carbon connected to the activating group.[24] Substituents on the N-atom also influence ring opening reactivity; namely, groups with *–M* effect facilitate fluorination.[26] Development of aziridine ring opening reactions with [^{18}F]F^- to synthesize PET tracers is still in its infancy.[27]

The aim of this review is to survey recent literature with respect to improved or novel methods for the ring opening of oxiranes and aziridines with fluoride. Methods utilizing [^{18}F]F^- are omitted. Within these two main sections, reactions will be grouped according to the applied reagent.

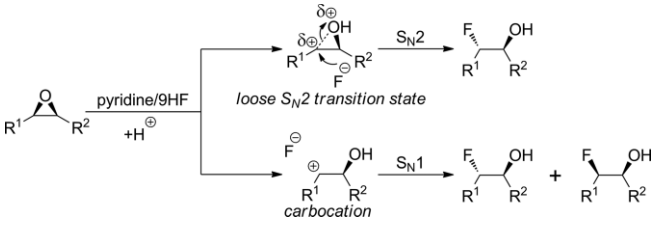
2. Fluoride Ring Opening of Oxiranes

2.1. Ring Opening with Hydrogen Fluoride Solutions

Aqueous HF, although cheap, is an agent used rarely for the ring opening of epoxides with fluoride. In water, fluoride ions are strongly solvated, which greatly reduces their nucleophilicity,[13] and water could also compete as a nucleophile. The acidity of HF can also cause polymerization and side reactions such as rearrangement.[14a] A serious practical disadvantage of HF solutions is their ability to dissolve glass, requiring the use of polymer vessels. Despite these difficulties, literature shows that solutions of HF in water or in organic solvents are quite effective in the fluoride ring opening of rigid, polycyclic steroid epoxides.[14a,28] Accordingly, the only reported case in recent literature where 70 % aqueous HF was used is the synthesis of Fluorometholone or 6α-methyl-9α-fluoro-11β,17α-dihydroxypregna-1,4-diene-3,20-dione (Scheme 5).[29] As expected from an acidic reagent, the epoxide is activated by *O*-protonation, and the fluoride ion attacks the more substituted epoxide carbon (loose S_N2 transition state, see Scheme 6 for details).



Scheme 5. Synthesis of fluorometholone.



Scheme 6. Mechanisms for oxirane ring opening with pyridine/9HF.

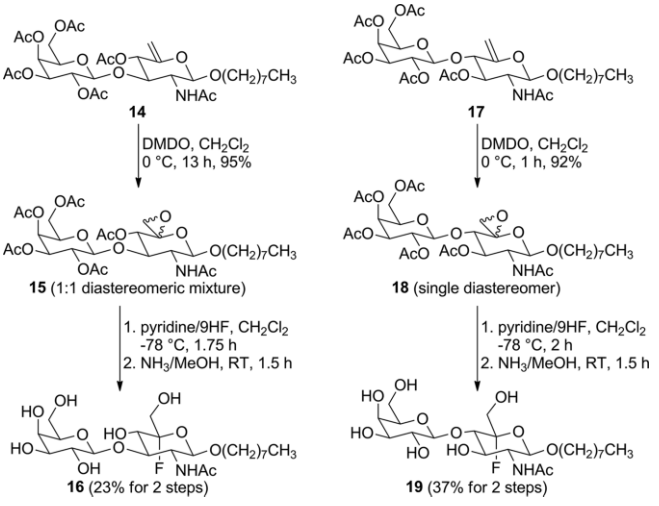
2.2. Ring Opening with Pyridine/9HF

Pyridine/9HF, also known as Olah's reagent (70 % HF/pyridine), is a well-known reagent for the ring opening of epoxides with fluoride. The compound, a commercially available cheap liquid, was developed as a "tamed" version of HF. It is stable up to 55 °C and has lower vapor pressure compared to HF. However, is highly toxic, quite acidic and etches glass. Thanks to its acidic nature, it protonates epoxides to form highly reactive cationic species with considerable positive charge on the oxirane carbon atoms. As a result, ring opening with pyridine/9HF is rapid and has pronounced S_N1 character. Usually, the mechanism proceeds through a loose S_N2 transition state (inversion-like S_N2 coupled with S_N1-like regioselectivity), but S_N1 mechanism is also possible if the substrate can produce stabilized carbocations (Scheme 6). Unfortunately, similar to the case of HF, the high reactivity of protonated epoxides can cause oligomerization or polymerization. The considerable cationic character of the oxirane carbon atoms can result in rearrangements as well. The reason is the low nucleophilicity of Olah's reagent, which increases the lifetime of carbocations (Scheme 9). However, acidity and reactivity can be fine-tuned by addition of pyridine.[4,14a]

The first preparation of diastereomerically and enantiomerically pure vicinal difluoroalkanes was described by Schlosser and co-authors. The two fluorine atoms were introduced by ring opening of an oxirane by addition of hydrogen fluoride followed by treatment of the resulting fluorohydrine with diethylaminosulfur trifluoride.[14b]

Because these reactions have been long known, only a few selected examples will be shown to illustrate the advantages, disadvantages, and selectivity of this reagent appropriately or describe recent developments.

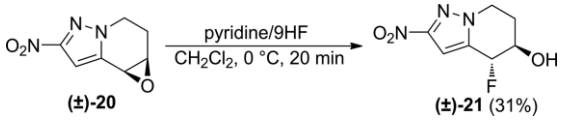
Tara et al. reported the synthesis of glycosides containing 5-fluoro-lactosamine and 5-fluoro-isolactosamine units by a late-stage fluorination approach. Alkenes **14** and **17**, obtained though multistep synthesis involving selenium chemistry, were epoxidized with dimethyldioxirane (DMDO). Compound **15** formed as a 1:1 mixture of diastereomers, while compound **18** was a single product whose stereochemistry was not determined. Treatment of these epoxides with pyridine/9HF followed by removal of the *O*-acetate group with NH_3/MeOH resulted in fluorohydrins **16** and **19** as sole products. As expected, the



Scheme 7. Ring openings of sugar epoxides **15** and **18**.

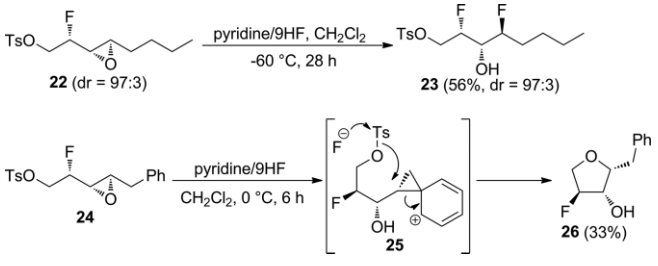
fluoride ion attacked the tertiary carbon instead of the primary one and even at –78 °C the reaction required only 1.75–2 h (Scheme 7).[30]

Twigg et al. described regioselective fluoride ring opening of oxirane **(±)-20**. In this case, both epoxide carbons are secondary, but one of them is benzylic, making it the preferred target of nucleophilic attack (Scheme 8).[31]



Scheme 8. Differentiation between secondary carbons during fluoride ring opening of **(±)-20**.

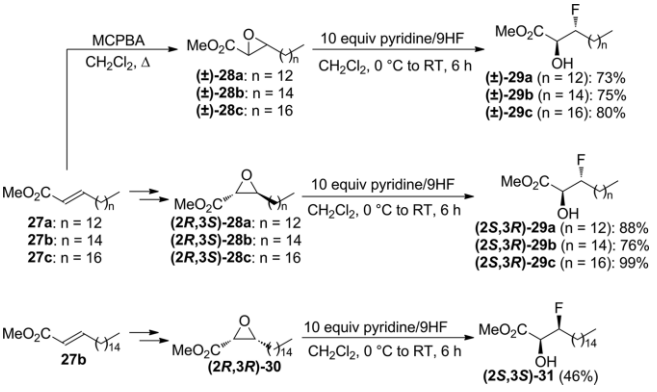
During their synthesis of vicinal trifluorides, O'Hagan and co-workers treated fluorine-containing epoxides **22** and **24** with pyridine/9HF. Although both of their oxirane carbons are secondary, ring opening of epoxides **22** and **24** was regioselective because the high electron withdrawal of fluorine disfavored the formation of a carbocation in β position relative to F. The reaction of **22** delivered desired fluorohydrin **23** whereas ring opening of **24** yielded furan **26** through benzenium ion intermediate **25** (Scheme 9). This is a good example of rearrangement reactions caused by acidity, since performing the reaction with Et_3N/3HF gives the expected fluorohydrin **73** (together with two by-products formed by replacement of TsO with F, see Scheme 22).[32] A similar observation was disclosed by Bykova et al.[33]



Scheme 9. Ring opening of fluorinated epoxides **22** and **24** with pyridine/9HF.

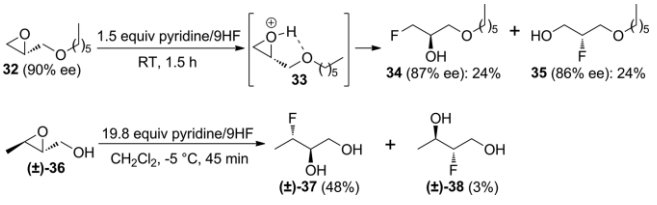
Another example of regioselective oxirane ring opening induced by an electron-withdrawing group was reported by Haufe and co-workers. The reaction of 2,3-epoxyalkanoates with pyridine/9HF resulted in 2-fluoro-3-hydroxyalkanoates selectively, thanks to the *–M* effect of the ester group (Scheme 10).[34]

Other structural factors can also cause regioselective oxirane ring opening. Umezawa et al. observed that during the reaction of pyridine/9HF with epoxy ether **32**, fluoride attack on the primary and secondary carbon has approximately equal chances. The authors explained this finding with a hydrogen bond between the protonated oxirane and the oxygen in the side chain. This directs fluoride to the primary carbon, which is not part of the pseudo five-membered ring, counteracting the expected preference for the secondary carbon.[35] Recently, Fox et al. reported that fluoride ring opening of *trans*-(2,3-epoxy)-butanol **(±)-36** yielded (2*R**,3*S**)-3-fluorobutane-1,2-diol **(±)-37**



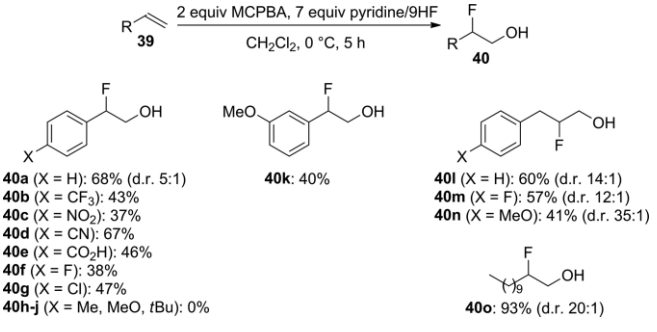
Scheme 10. Regioselective ring opening of 2,3-epoxyalkanoates with pyridine/9HF.

as the main product (Scheme 11). In this case, because both oxirane carbons are secondary, the possible reason of regioselectivity is the aforementioned hydrogen bond directing effect.[36] The regioselective ring opening of a partially saturated anthracenediepoxide, observed by Mehta and Sen, may have a similar origin.[37]



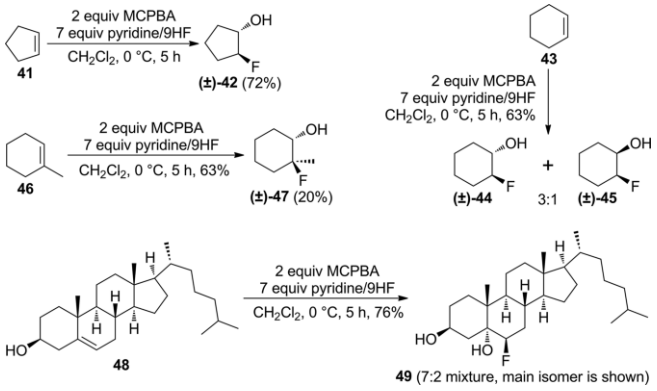
Scheme 11. Effect of hydroxymethyl or alkoxymethyl substituents on the regioselectivity of epoxide ring opening with pyridine/9HF.

Finally, Sedgwick et al. reported a one-pot epoxidation/fluoride ring opening process of terminal or cyclic alkenes, utilizing 3-chloroperbenzoic acid (MCPBA) and pyridine/9HF. Their results are summarized in Scheme 12 and Scheme 13. In the case of styrenes, electron-withdrawing substituents on the aromatic ring were well tolerated, but electron-donating substituents stopped the reaction mostly at the epoxide stage. Similarly, cyclohexene afforded better results than the more electron rich 1-methylcyclohexene. In allylbenzenes, where the olefinic bond and the benzene ring are not conjugated, substituents of the phenyl group had much less effect. The usefulness of this reaction was also demonstrated by the smooth transformation of cholesterol. Experiments with stilbenes suggested that ring

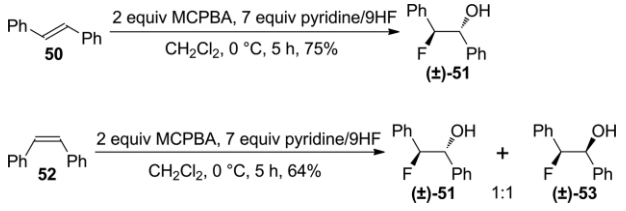


Scheme 12. One-pot epoxidation/fluoride ring opening of terminal alkenes.

opening of styrene oxides takes place with S_N1 mechanism (Scheme 14), which was indicated by the observed major *ee* loss in the reactions of enantiopure styrene oxide with different amine/HF reagents. However, ring opening of enantioenriched dodec-1-ene oxide proceeded without loss of *ee* (S_N2 mechanism), hinting that development of an asymmetric version of this process is possible.[38]



Scheme 13. One-pot epoxidation/fluoride ring opening of cyclic alkenes.

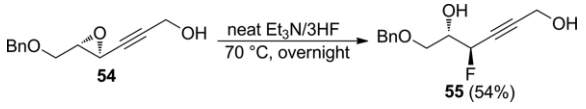


Scheme 14. Some mechanistic insights into the mechanism of olefin fluorohydroxylation.

2.3. Ring Opening with $Et_3N/3HF$

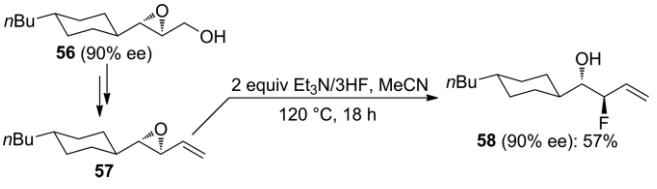
Triethylamine trihydrofluoride is a cheap, commercially available liquid. Similar to pyridine/9HF, it is a "tamed" version of HF and a well-known reagent for oxirane ring opening with fluoride. However, compared to Olah's reagent, $Et_3N/3HF$ is more stable: it can be used in standard borosilicate glassware up to 150 °C without etching. It is also considerably less acidic and more nucleophilic. As a consequence, it does not protonate the epoxide and ring opening with $Et_3N/3HF$, in most cases, is an S_N2 process. Thanks to this mechanism, oligomerization or rearrangement occurs only rarely. However, it has a disadvantage: the lack of epoxide protonation seriously slows down the ring opening process, requiring the use of neat $Et_3N/3HF$ (supported by the low cost of the reagent) or high temperature.[4,14] Similar to ***Section 2.2***, because $Et_3N/3HF$ is widely used for oxirane ring opening with fluoride, only selected examples will be shown to illustrate the advantages, disadvantages, and selectivity of this reagent. A recently developed Rh-catalyzed method[39] will be discussed together with processes catalyzed by other transition metals in ***Section 2.6***. Oxirane ring opening with $Et_3N/3HF$ and XtalFluor-E[40] will be discussed in ***Section 2.8*** together with the use of other deoxyfluorinating reagents.

Chen et al. used fluorohydrin **55** for the construction of γ-monofluorinated goniothalamin analogues. Compound **55** was obtained by the reaction of epoxide **54** and $Et_3N/3HF$ in a completely regio- and stereoselective manner. It was attributed by the authors to the higher positive charge on the carbon connected to the electron-withdrawing alkynyl group (Scheme 15).[41]

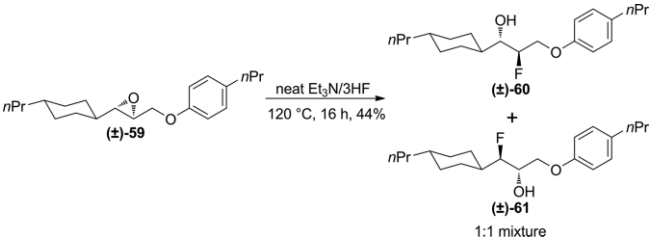


Scheme 15. Regio- and stereoselective ring opening of alkynyl-substituted epoxide **54**.

During their attempts to synthesize multivicinal hexafluoroalkanes, O'Hagan and co-workers reacted epoxide **57**, dissolved in MeCN, with $Et_3N/3HF$ in a Teflon-lined steel bomb (Scheme 16). Similar to the above case, the fluoride attacked the epoxide carbon that connected to an unsaturated C atom.[42] Interestingly, Al-Maharik et al. reported that ring opening of epoxide **(±)-59** is not regioselective (Scheme 17),[43] excluding the possibility that steric hindrance caused by the large cyclohexyl group directs the F^- ion to attack the allylic carbon in epoxide **57**.

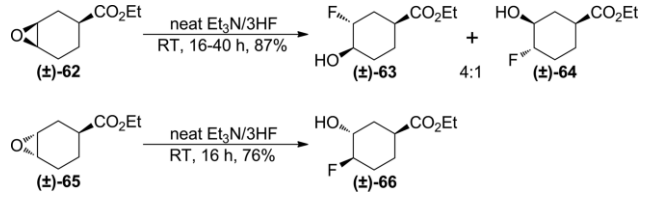


Scheme 16. Regio- and stereoselective ring opening of vinyl-substituted epoxide **57**.



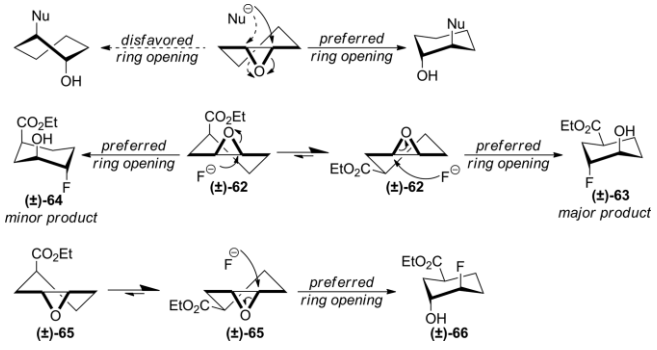
Scheme 17. Nonselective ring opening of cyclohexyl-substituted oxirane **(±)-59**.

Goss et al. described ring openings of two bicyclic oxiranes. With **(±)-65**, the process was completely stereo- and regioselective. Transformation of epoxide **(±)-62**, in turn, was less selective and a 4:1 mixture of fluorohydrins was formed (Scheme 18). Separation of the products succeeded only after their transformation to tetrahydropyranyl ethers.[44] Interestingly, Remete et al. reported the isolation of **(±)-63** as the sole product after treatment of epoxide **(±)-62** with XtalFluor-E and $Et_3N/3HF$ in 1,4-dioxane at reflux temperature, work-up, and column chromatography (Scheme 61).[40]



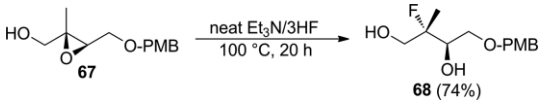
Scheme 18. Ring openings of epoxycyclohexane derivatives with Et_3N/3HF.

The reason for this selectivity (Fürst–Plattner rule) lies in the conformations of cyclohexene oxides and cyclohexanes. In the case of epoxycyclohexane derivatives, two half-chair conformers are in equilibrium with each other, and the pseudoequatorial position of the substituents is favored, shifting the equilibrium. When a given conformer undergoes ring opening, the preferred result is that when the product is formed directly in its lowest energy chair conformation (the other possible ring opening yields a product in the higher energy twist-boat conformation). The results for **(±)-62** and **(±)-65** are shown in Scheme 19.



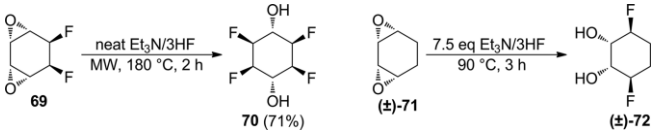
Scheme 19. The connection of oxirane ring opening selectivity and conformations in the case of epoxycyclohexanes.

As a rare example, Marquez and co-workers presented that the reaction of epoxide **67** with Et_3N/3HF has S_N1-like regioselectivity, although the stereochemical outcome is inversion (Scheme 20).[45]



Scheme 20. Reaction of compound **67** with a tertiary oxirane carbon having some S_N1 character.

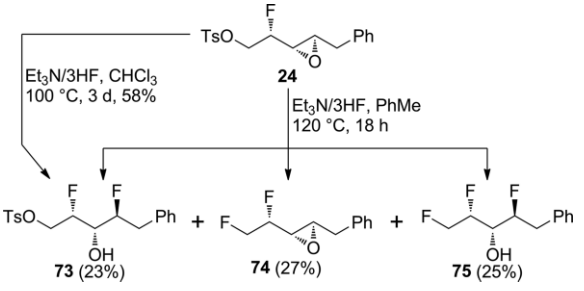
In the case of highly substituted epoxides, steric hindrance can necessitate unusually strong conditions. During their synthesis of *all-cis* 1,2,3,4,5,6-hexafluorocyclohexane, O'Hagan and co-workers had to use 180 °C (MW heating) to open difluorinated diepoxycyclohexane **69** (Scheme 21).[46] Ring opening of



Scheme 21. Regioselective ring opening of diepoxycyclohexanes.

the related diepoxide **(±)-71** was much easier and had different regioselectivity (Scheme 21; the product was used without further purification).[47]

As already mentioned in Section 2.2 (Scheme 9), ring opening of epoxide **24** with pyridine/9HF yielded furan **26** through benzenium ion intermediate **25** thanks to the acidity of that reagent. O'Hagan and co-workers performed the reaction with Et_3N/3HF as well, resulting in the expected fluorohydrin **73** in 23 % yield together with two by-products formed by replacement of TsO with F (Scheme 22). The optimal conversion and selectivity was achieved by performing the reaction in $CHCl_3$ in an autoclave and compound **73** was obtained in 58 % yield.[32] Another recent example, when treatment of an epoxide with pyridine/9HF led to rearrangement, while treatment of the same epoxide with Et_3N/3HF did not, was reported by Bykova et al.[33]



Scheme 22. Reaction of epoxide **24** with Et_3N/3HF proceeds without rearrangement, in contrast with pyridine/9HF.

2.4. Ring Opening with Alkali and Tetraalkylammonium Hydrofluorides

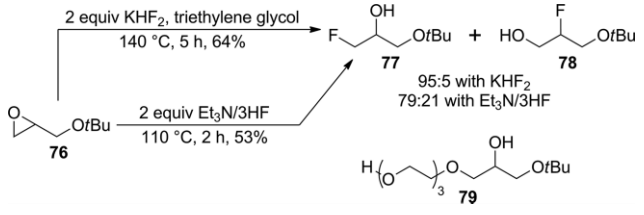
Potassium hydrogen difluoride (KHF_2) is another common reagent for fluoride ring opening of oxiranes. The compound is an inexpensive solid; however, it etches glass and has solubility issues in organic solvents. Even in polar organic solvents (where KHF_2 is usually applied), the compound is mostly suspended, not dissolved. In such environment, KHF_2 is less acidic and more nucleophilic than Et_3N/3HF, resulting in more pronounced S_N2 mechanism. It also necessitates the use of high temperature to achieve ring opening, since oxirane activation is absent. Usual solvents compatible with these conditions are DMF (aprotic) or ethylene glycol and its oligomers (protic). Notably, this method is suitable for large-scale reactions. However, when the reaction is performed in alcohols, a common side reaction is nucleophilic attack of the alcohol on the substrate (facilitated by the basicity of F^- ions).[14]

Another solution of the solubility issues is the use of hydrofluorides with an organic cation. Tetrabutylammonium dihydrogen trifluoride ($nBu_4N^+H_2F_3^-$) is one of the most common choices. This compound is liquid at room temperature, soluble in organic solvents, commercially available but more expensive than KHF_2. Although it can be used in itself, a more common and economical solution is the application of sub-stoichiometric amounts of $nBu_4N^+H_2F_3^-$ together with excess KHF_2. In this case, the tetrabutylammonium ion acts as a solid–liquid phase-

transfer catalyst to facilitate the entry of HF_2^- ions from the suspended KHF_2 into the solvent, which regenerates the consumed $nBu_4N^+H_2F_3^-$. This method was varied greatly (e.g., solvent, quantities of the two fluoride sources, or replacement of $nBu_4N^+H_2F_3^-$ with other tetrabutylammonium fluorides), but elevated temperatures are still required. Harsh reaction conditions can be avoided by using $nBu_4N^+H_2F_3^-$ together with a Lewis acid, which activates the epoxide. This accelerates the reaction and enables the use of mild conditions, but also shifts the mechanism towards S_N1.[14]

In this section, some recent examples for KHF_2-mediated ring openings will be shown first to illustrate the S_N2 selectivity and the required forcing conditions. Then, examples utilizing different amounts of KHF_2 and $nBu_4N^+H_2F_3^-$ will be discussed, followed by cases where other tetraalkylammonium fluorides were used together with KHF_2. Finally, the method utilizing Lewis acid will be described.

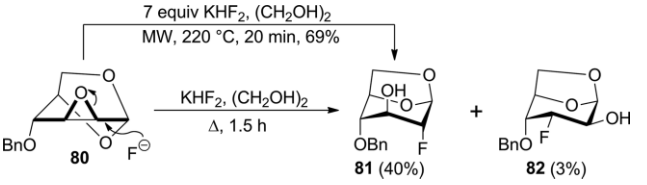
During their attempts towards a building block for *Carmegliptin*, Zutter and co-workers reported ring opening of racemic *tert*-butyl glycidyl ether **76** with KHF_2. Typically, such reactions required heating at 140 °C in triethylene glycol. After workup, distillation resulted in a 95:5 mixture of fluorohydrins in 64 % yield showing the S_N2 selectivity. The main side product was compound **(±)-79** (≈ 20 %) originating from the nucleophilic attack of the solvent. It is worth mentioning that the reaction was performed with 75 kg substrate, emphasizing the scale-up opportunities of this ring opening method. Smaller-scale experiments showed that utilizing neat $Et_3N/3HF$ gives a 79:21 mixture of fluorohydrins in 53 % yield supporting the stronger S_N2 character of the KHF_2 ring opening (Scheme 23).[48]



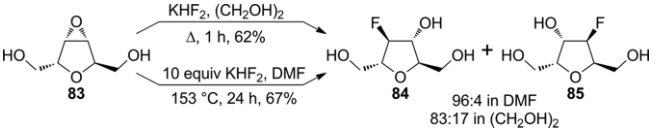
Scheme 23. Ring opening of racemic glycidyl ether **76** with KHF_2.

The use of microwave heating instead of conventional heating enables the reaching of higher temperatures, which often accelerates reactions or improves their yield. Viuff et al. found that compared to the original report by Pacák et al.,[49] ring opening of sugar-derived epoxide **80** with KHF_2 provides higher yield and better selectivity when microwave heating is applied (Scheme 24).[50] The reason apart from the selectivity of this reaction is that the substrate is a bridged, rigidified epoxycyclohexane, which prefers to open directly into a chair conformer (see Scheme 19 and related discussion about the Fürst–Plattner rule).

An interesting example for the use of DMF instead of oligoethylene glycols was found by West and co-workers. Ring opening of sugar-derived epoxide **83** had similar yields in both DMF and ethylene glycol, but the regioselectivity in DMF was much better (Scheme 25).[51]

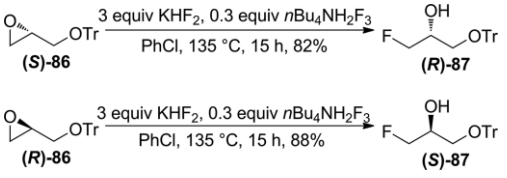


Scheme 24. Original and improved ring openings of Černý epoxide **80**. Only the direction of the preferred oxirane ring opening is shown.



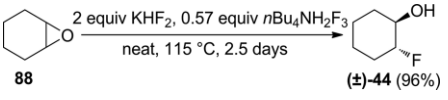
Scheme 25. Regioselectivity of KHF_2 ring opening of epoxide **83** in DMF and ethylene glycol.

A good example for using a catalytic amount of $nBu_4N^+H_2F_3$ with KHF_2 was reported by Baszczyński et al. Ring opening of enantiopure trityl glycidyl ethers **(*S*)-86** and **(*R*)-86** with this reagent combination in chlorobenzene at 135 °C proceeded with complete S_N2 regio- and stereoselectivity, giving products **(*R*)-87** and **(*S*)-87** in high yields (Scheme 26).[52]



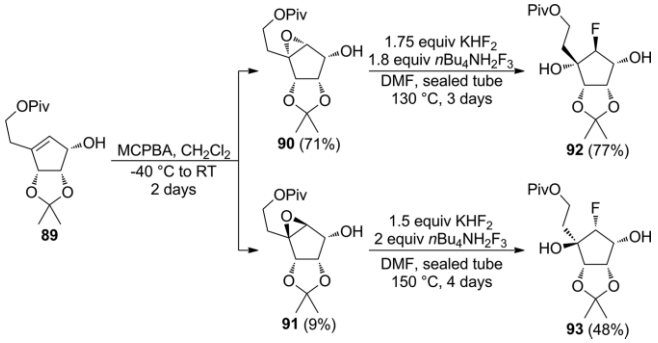
Scheme 26. Ring opening of enantiopure glycidyl ethers under solid–liquid phase transfer conditions.

For the above method, the presence of a solvent is not necessary if the reaction mixture is liquid at the reaction temperature. Graton et al. described ring opening of cyclohexene oxide **88** under these conditions in almost quantitative yield (Scheme 27). The reaction proceeded with inversion at the epoxide carbon.[53]



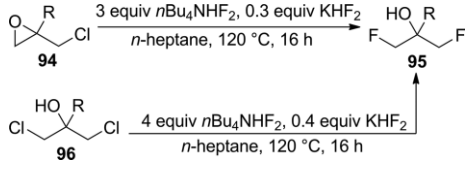
Scheme 27. Ring opening of cyclohexene oxide with $nBu_4N^+H_2F_3^-$ and KHF_2 without solvent.

Interestingly, Jeong and co-workers used comparable amounts of the two fluoride sources for the ring opening of stereoisomeric epoxycyclopentane derivatives **90** and **91**. The reaction required prolonged heating in DMF and showed complete S_N2 stereo- and regio-selectivity (Scheme 28). The obtained fluorohydrins were transformed into fluorinated homoneplanocin A.[54]

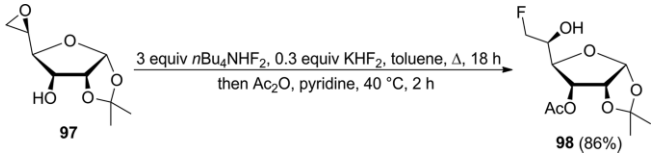


Scheme 28. Ring opening of epoxycyclopentane derivatives **90** and **91** with excess $nBu_4NH_2F_3$ and excess KHF_2.

Akiyama et al. replaced $nBu_4N^+H_2F_3^-$ with $nBu_4N^+HF_2^-$. This reagent has to be prepared from commercially available tetrabutylammonium fluoride and aqueous HF solution, and the product requires extensive drying prior to use. Strangely, they used it in excess together with a sub-stoichiometric amount of KHF_2, completely opposing the classical method (which utilizes excess KHF_2 as a cheap HF source and a small amount of tetrabutylammonium salt as phase-transfer catalyst).[55] Haufe et al. applied this method to synthesize 2-substituted 1,3-difluoropropan-2-ols **95** from epichlorohydrin derivatives **94** or 2-substituted 1,3-dichloropropan-2-ols **96** (Scheme 29). It is worth noting that the aliphatic Cl is replaced by F during fluoride ring opening of compounds **94**. Because treatment of substrates **96** under similar conditions results in the same product,[56] it was concluded that the basicity of fluoride ions enables ring closing of the chlorohydrin moiety to oxirane, which then undergoes ring opening with fluoride. (The bad leaving group nature of F^- ions hinders base-promoted transformation of fluorohydrins to epoxides.) Wanek and co-workers used the same reagent combination for the ring opening of sugar-derived epoxide **97** but under reflux conditions in toluene (Scheme 30).[57]

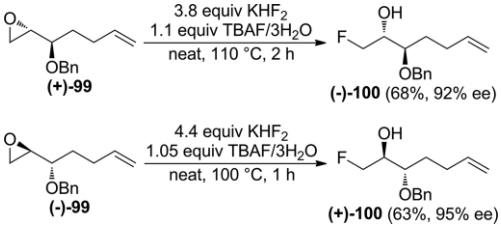


Scheme 29. Ring opening of epichlorohydrin derivatives with nBu_4NHF_2 in the presence of a small amount of KHF_2.



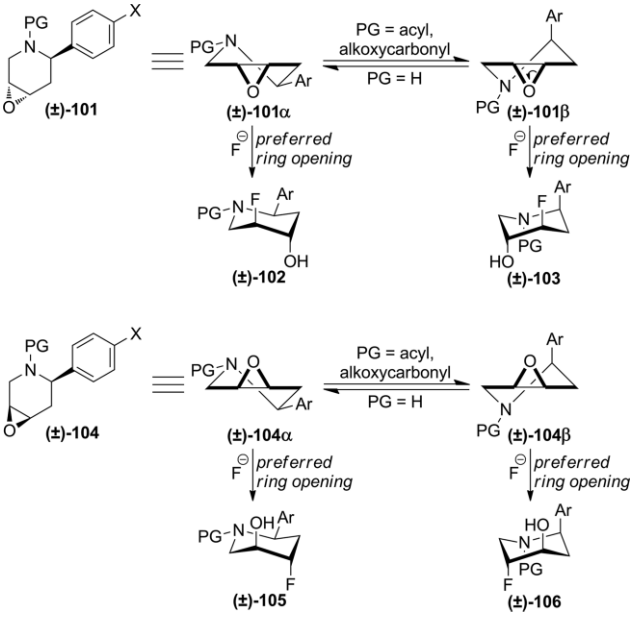
Scheme 30. Fluoride ring opening of sugar-derived epoxide **97** with a slightly modified version of the method by Akiyama et al.

Percy et al. reported that fluoride ring opening of epoxide **(+)-99** is quite difficult. The reaction failed with $nBu_4N^+H_2F_3^-$ or using a catalytic amount of $nBu_4N^+H_2F_3^-/KHF_2$, and had low yield with nBu_4NF (TBAF). Applying KHF_2 in ethylene glycol mostly resulted in ring opening by the conjugate base of the solvent. However, the authors succeeded with a new method using TBAF/$3H_2O$ and KHF_2 at 110 °C without any solvent (in fact, in a molten salt mixture). The reaction was completely regioselective with the fluoride attacking only the less substituted carbon (Scheme 31). The authors successfully applied the reaction to enantiomeric **(–)-99** too. Importantly, TBAF/$3H_2O$ is commercially available and not expensive.[58]



Scheme 31. Ring opening of epoxide **99** enantiomers with neat TBAF/$3H_2O$/KHF_2 system.

This new method was used by Hu and co-workers during their studies on the regioselectivity of the fluoride ring opening of epoxypiperidines **(±)-101** and **(±)-104**. Compounds with acyl or alkoxycarbonyl protecting groups on the N-atom favor conformation **(±)-101β** or **(±)-104β** because of allylic 1,3 strain, while in the case of PG = H conformation **(±)-101α** or **(±)-104α** is preferred (Scheme 32). Initial condition screening with oxirane **(±)-101aa** showed that the conditions of Percy et al.[58] were the most advantageous (Scheme 33). Because purification of **(±)-101aa** was problematic due to its high polarity and chemical instability, the use of Fmoc-protected epoxypiperidines was attempted. Fluoride ions are basic enough to deprotect compounds **(±)-101a**–**d** before oxirane ring opening, providing the desired products **(±)-102a**–**d** as single isomers in ≈ 50 % yields after the one-pot reaction. Then, in order to reverse the regioselectivity, compounds with PG = Boc were sub-

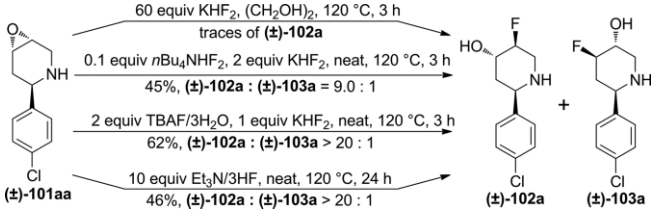


Scheme 32. Regioselectivity during ring opening reactions of epoxypiperidine derivatives.

Table 1. Fluoride ring opening of epoxypiperidines **(±)-101** and **(±)-104** with different *N*-protecting groups and transformation of bromohydrins **(±)-107a**–**d**. Reaction conditions: 2 equiv. TBAF•3H_2O, 1 equiv. KHF_2, neat, 3 h, temperature specified in the table. Isolated yields are given; the product ratios were determined by $^{19}F\{^1H\}$ NMR.

Substrate Number	PG	X	Reaction temperature	Products Number	PG	X	Yield	Ratio
(±)-101a	Fmoc	Cl	120 °C	**(±)-102a**	H	Cl	50 %	> 20:1
(±)-101b	Fmoc	H	120 °C	**(±)-102b**	H	H	52 %	> 20:1
(±)-101c	Fmoc	Me	120 °C	**(±)-102c**	H	Me	54 %	> 20:1
(±)-101d	Fmoc	OMe	120 °C	**(±)-102d**	H	OMe	51 %	> 20:1
(±)-101e	Boc	Cl	120 °C	**(±)-102e**	Boc	Cl	15 %	1:4.9
				(±)-103e	Boc	Cl	68 %	
(±)-101f	Boc	H	120 °C	**(±)-102f**	Boc	H	13 %	1:5.0
				(±)-103f	Boc	H	69 %	
(±)-101g	Boc	Me	120 °C	**(±)-102g**	Boc	Me	18 %	1:3.6
				(±)-103g	Boc	Me	69 %	
(±)-101h	Boc	OMe	120 °C	**(±)-102h**	Boc	OMe	16 %	1:3.8
				(±)-103h	Boc	OMe	64 %	
(±)-104aa	H	Cl	90 °C	**(±)-105a**	H	Cl	64 %	> 20:1
(±)-104e	Boc	Cl	90 °C	**(±)-105e**	Boc	Cl	46 %	1.3:1
				(±)-106e	Boc	Cl	36 %	
(±)-104f	Boc	H	90 °C	**(±)-105f**	Boc	H	46 %	1.2:1
				(±)-106f	Boc	H	38 %	
(±)-104g	Boc	Me	90 °C	**(±)-105g**	Boc	Me	41 %	1.2:1
				(±)-106g	Boc	Me	35 %	
(±)-104h	Boc	OMe	90 °C	**(±)-105h**	Boc	OMe	42 %	1.2:1
				(±)-106h	Boc	OMe	36 %	
(±)-104i	Cbz	Me	90 °C	**(±)-105i**	Cbz	Me	46 %	1.3:1
				(±)-106i	Cbz	Me	35 %	
(±)-104j	CO_2Et	Me	90 °C	**(±)-105j**	CO_2Et	Me	46 %	1.4:1
				(±)-106j	CO_2Et	Me	32 %	

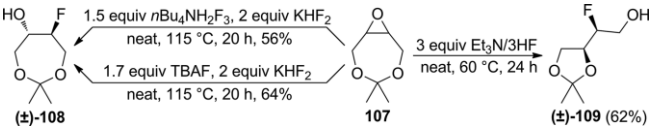
jected to these reaction conditions. Ring opening of epoxides **(±)-101e**–**h** was regioselective, while reactions of epoxides **(±)-104e**–**h** showed very little selectivity. Changing the *N*-protecting group to Cbz or CO_2Et [compounds **(±)-104i**–**j**] did not improve selectivity. These results are summarized in Table 1.[59]



Scheme 33. Initial condition screening for the fluoride ring opening of oxirane **(±)-101aa**. Isolated yields are given, product ratios were determined by $^{19}F\{^1H\}$ NMR.

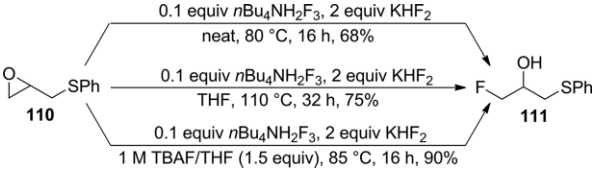
Yan et al. reported that the TBAF/3H_2O/KHF_2 method is superior to Et_3N/3HF or nBu_4NHF_2/KHF_2 for the ring opening of several sugar-derived epoxides.[60] Szpera et al. had similar findings for ring opening of epoxy acetal **107**. Notably, product **(±)-108** is quite acid-sensitive and treatment of substrate **107** with Et_3N/3HF not only opens the oxirane ring but then causes the rearrangement of the acetal moiety as well (Scheme 34).[61]

Hanamoto and co-workers showed that ring opening of epoxy sulfide **110** with a catalytic amount of $nBu_4N^+H_2F_3^-$ and excess KHF_2 is more effective in the presence of excess TBAF (Scheme 35). These conditions are similar to the method of Percy et al.[58] but TBAF was used as its THF solution (which is



Scheme 34. Fluoride ring openings of epoxy acetal **107**.

also commercially available) instead of its hydrate. Note that in this system three fluoride sources are present instead of two. The reaction was performed in a sealed tube, that is the reaction mixture is a THF solution despite the high temperature used.[62]



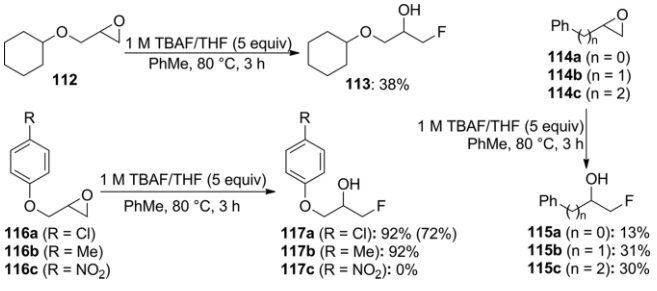
Scheme 35. Ring opening of racemic epoxy sulfide **110** under reaction conditions based on $nBu_4N^+H_2F_3^-$/KHF_2. The reactions were performed in a sealed tube, and GC–MS yields were given.

2.5. Ring Opening with Tetrabutylammonium Fluoride (TBAF)

nBu_4NF is available at affordable prices as its solid trihydrate or as a THF solution (which also contains some water). Because attempts to dry hydrated TBAF cause E2 elimination (nBu_4NF

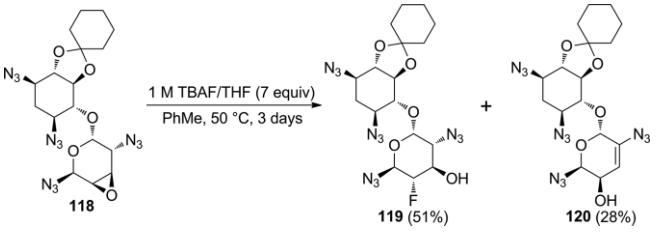
→ nBu$_3$N + but-1-ene + HF; HF forms HF_2^- ions with the fluoride present), obtaining truly anhydrous nBu$_4$NF is difficult.[63] The presence of water is important because it solvates F^- ions greatly decreasing their basicity and nucleophilicity. Still, commercially available TBAF sources are amongst the most nucleophilic (and basic) fluoride sources. This nucleophilicity enables epoxide ring opening via a pure S_N2 mechanism, but the high basicity of F^- ions makes elimination a common side reaction during this process.[4] This may be the reason, why the application of TBAF for oxirane ring opening was not too common,[14] and the substrates were mostly epoxides of terminal olefins or oxiranes with two secondary carbons in their three-membered ring.

Application of TBAF became more common after the report of Chung and co-workers in 2007. These authors were interested in the incorporation of ^{18}F into organic molecules, and because the most available ^{18}F-containing compounds are metal [^{18}F]fluorides and tetrabutylammonium [^{18}F]fluoride, they studied ring opening of various epoxides (mainly glycidyl ethers) with 1 M TBAF/THF solution. They found that the reaction was the most efficient in toluene at 80 °C. Under these conditions, cyclohexyl glycidyl ether **112**, styrene oxide **114a**, 2-benzyloxirane **114b**, and 1,2-epoxy-4-phenylbutane **114c** showed low reactivity, while aryl glycidyl ethers **116** gave high yields of fluorohydrins (except **116c**, which was transformed into 4-nitrophenol). In every case, only terminally fluorinated products were obtained (Scheme 36).[64]



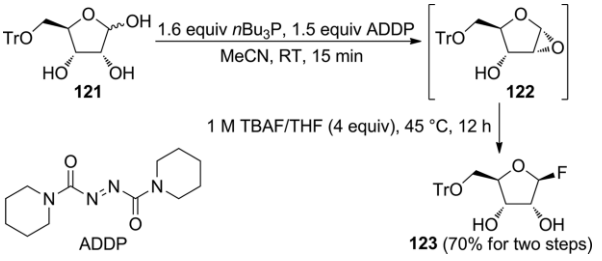
Scheme 36. Ring opening of various terminal epoxides with TBAF/THF. Yields in parentheses are isolated yields, other yields were determined by ^{19}F-NMR. Compound **115b** was formed together with 3-phenylpropane-1,2-diol and 3-phenylprop-2-en-1-ol.

One of the earliest uses of TBAF for oxirane ring opening was the transformation of sugar-derived epoxides.[65] Amongst recent examples, Hanessian et al. reported that ring opening of neamine derivative **118** not only produced desired fluorohydrin **119**, but elimination product **120** was also present (Scheme 37).



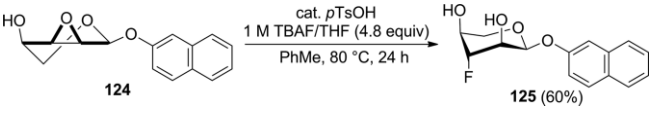
Scheme 37. Ring opening of neamine derivative **118** with TBAF.

This is a good example of side reactions caused by the basicity of TBAF.[66] Possibly, the *–M* effect of the azide ion helps deprotonation. In contrast, the transformation of anhydrosugar **122**, presented by Hocek and co-workers, was clean and efficient (Scheme 38). Because attempts to isolate epoxide **122** by column chromatography failed, the reaction mixture containing **122** was subjected to TBAF bringing about a one-pot two-step process.[67]



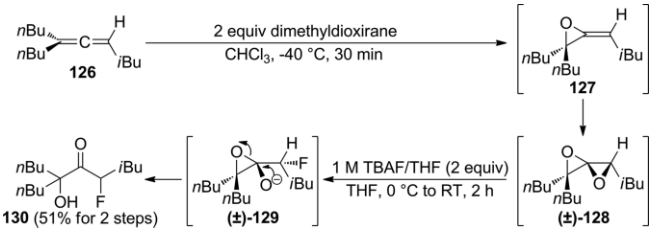
Scheme 38. Reaction of 1,2-anhydro-5-*O*-trityl-α-D-ribofuranose with TBAF.

The ring opening of anhydrosugar **124** with TBAF was found by Willén et al. to take place only in the presence of a catalytic amount of *p*TsOH (Scheme 39). Treatment with TBAF in the absence of acid, or utilizing Et_3N/3HF or Et_3N/2HF resulted in neither fluorination nor glycoside cleavage. Unfortunately, separation of the starting material and the product was unsuccessful.[68]



Scheme 39. Ring opening of anhydrosugar **124** with TBAF and acid catalysis.

Another very early example of using TBAF for oxirane ring opening was the transformation of allene oxides, formed in situ from a suitable epoxide precursor, to α-fluoroketones.[69] Sharma et al. reported that TBAF ring opening of a similar substrate, allene dioxide **(±)-128** gave α-fluoro-α′-hydroxy ketone **130**. Spirodiepoxide **(±)-128** was obtained by oxidizing allene **126** with dimethyldioxirane in $CHCl_3$ (Scheme 40).[70]

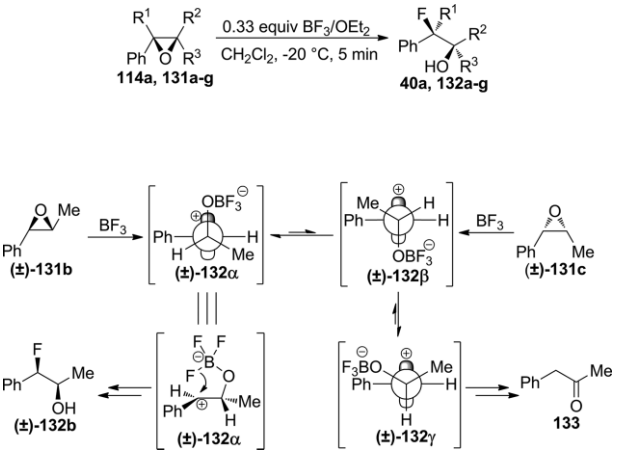


Scheme 40. TBAF ring opening of spirodiepoxide **(±)-128**.

2.6. Ring Opening with Boron Trifluoride Etherate (BF_3/OEt_2), Pinacolatoboron Fluoride, and Fluoroboric Acid Etherate (HBF_4/OEt_2)

Boron trifluoride etherate (BF_3/OEt_2) is a cheap, commercially available liquid (pure BF_3 is a gas with a boiling point of –100.3 °C). Together with anhydrous HF, it was one of the first

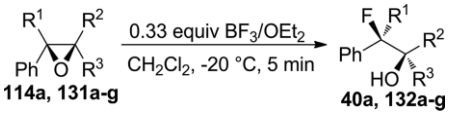
reagents utilized for the fluoride ring opening of oxiranes. BF_3 activates epoxides through coordination, which increases the partial positive charge on the oxirane carbons. Unfortunately, these activated epoxides often polymerize or undergo rearrangement through alkyl or hydride shift making fluorohydrin formation ineffective or completely suppressed. The reaction pathway can be influenced by appropriate solvent selection. In apolar, non-coordinative solvents like arenes or CH_2Cl_2, rearrangement reactions are preferred and rapid reactions (sometimes 2–5 minutes) can still result in fluorohydrins in good or acceptable yields. The use of a coordinating (co)solvent, such as Et_2O creates a Lewis basic environment, which prefers fluorohydrin formation presumably by attenuation of S_N1-like character during the ring opening step. However, because the substrate and the solvent compete for BF_3, the concentration of the activated epoxide is lower and, consequently, the reaction slows down considerably. Fine-tuning the amount of BF_3 can also help, since the excess reagent often favors rearrangement over fluoride ring opening. The success of these factors, however, depends mostly on the structure of the substrate. There are well-established reactions like the transformation of certain steroid epoxides to fluorohydrins, but the relationship between the structure of the starting compound and the outcome of the reaction is not completely understood yet. Together with the development of new, more reliable reagents such as amine hydrofluorides, the above problems made the use of BF_3 for fluoride ring opening disfavored.[71] There are also some difficulties to interpret the reaction mechanism. Unpurified BF_3/OEt_2 contains HBF_4/OEt_2 impurities and the presence of fluoride donor BF_4^- may contribute to the success of the reaction. Indeed, ring opening fluorination of 5,6-epoxysteroids with a 1:1 mixture of BF_3/OEt_2 and HBF_4/OEt_2 is more effective than using BF_3/OEt_2 alone. The stereochemistry of the fluorohydrin product is substrate-dependent too: epoxides with aryl or heteroatom substituent can form stabilized carbocations, often enabling fluoride attack from the side of the epoxide oxygen (see Scheme 41). In the case of other epoxides, fluoride attack mostly proceeds with inversion at the epoxide carbon.[71]



Scheme 41. Reactions of *cis*- and *trans*-β-methylstyrene oxide with BF_3/OEt_2. From **(±)-131b**, mainly **(±)-132b** (83 %) was formed with fluoride transfer. **(±)-131c** gave mainly **133** by [1,2]-H-atom shift.

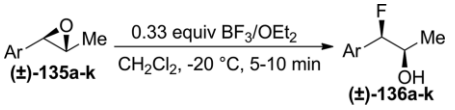
There is only a single recent report utilizing BF_3/OEt_2 for the transformation of oxiranes into fluorohydrins. Cresswell et al. reported stereo- and regio-selective fluoride ring opening of various aryl-substituted epoxides (Table 2, Table 3, and Table 4), and determined the substrate requirements of a successful reaction. First of all, if the initial conformation of the carbocation intermediate (which is ideal for fluorohydrin formation) is sterically disfavored, a conformational change occurs, and the new conformer mainly reacts with a H-shift (Scheme 41). This suggests that the intramolecular fluoride transfer is relatively slow. Furthermore, even if the above requirement is met, too high stabilization of the carbocation enables a conformational change and side reactions will dominate, while insufficient stabilization, which hinders carbocation formation, also leads to side reactions (Table 3). If that substituent has high migratory aptitude, it will migrate to the carbenium ion before fluorination can take place (Table 4). Notably, the reaction required only 0.33 equiv. BF_3 (all 3 fluorines were transferred to the oxir-

Table 2. Reactions of substituted phenyloxiranes with BF_3/OEt_2. Yields in parentheses were determined by ^{19}F-NMR; other yields are isolated ones. Yields of other products are omitted.



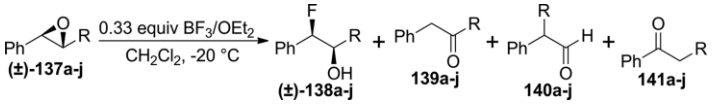
Epoxide Number	R^1	R^2	R^3	Fluorohydrin product Number	Yield
(±)-114a	H	H	H	**(±)-40a**	(8 %)
(±)-131a	Me	H	H	**(±)-132a**	0 %
(±)-131b	H	Me	H	**(±)-132b**	83 %
***(R,R)*-131b** (≈ 90 % *ee*)	H	Me	H	***(R,R)*-132b**	81 % (92 % *ee*)
(±)-131c	H	H	Me	**(±)-132b** (R^2 = Me, R^1 = R^3 = H)	(5 %)
(±)-131d	Me	H	Me	**(±)-132d**	(13 %)
(±)-131e	Me	Me	H	**(±)-132e**	0 %
(±)-131f	H	Me	Me	**(±)-132f**	0 %
(±)-131g	Me	Me	Me	**(±)-132g**	8 %

Table 3. Reactions of BF_3/OEt_2 with *trans*-2-methyl-3-aryloxiranes. Only isolated yields are given. With epoxide **(±)-135k** the reaction was incomplete and gave a mixture of products including the desired fluorohydrin; however, **(±)-136k** was not obtained in pure form. Products other than fluorohydrins are omitted.



Epoxide Number	*dr*	Ar	σ^+ (X)	Reaction time	Fluorohydrin Number	Yield
(±)-135a	> 99:1	*p*-$MeOC_6H_4$	–0.78	5 min	**(±)-136a**	0 %
(±)-135b	90:10	*p*-MeC_6H_4	–0.31	5 min	**(±)-136b**	0 %
(±)-135c	98:2	*p*-PhC_6H_4	–0.18	5 min	**(±)-136c**	0 %
(±)-135d	94:6	*p*-FC_6H_4	–0.07	5 min	**(±)-136d**	76 %
(±)-135e	93:7	*m*-$MeOC_6H_4$	+0.05	5 min	**(±)-136e**	81 %
(±)-135f	94:6	*p*-ClC_6H_4	+0.11	10 min	**(±)-136f**	76 %
(±)-135g	94:6	*p*-BrC_6H_4	+0.15	10 min	**(±)-136g**	78 %
(±)-135h	95:5	*m*-FC_6H_4	+0.35	10 min	**(±)-136h**	67 %
(±)-135i	92:8	*m*-ClC_6H_4	+0.40	10 min	**(±)-136i**	64 %
(±)-135j	91:9	*m*-BrC_6H_4	+0.41	10 min	**(±)-136j**	67 %
(±)-135k	94:6	*p*-$CF_3C_6H_4$	+0.61	10 min	**(±)-136k**	0 %

Table 4. Reactions of $BF_3{\cdot}OEt_2$ with *trans*-substituted phenyloxiranes. Reaction time was 5 min [except **(±)-137h** where 30 min was required]. Product ratios were determined by NMR analysis of the crude product mixture.



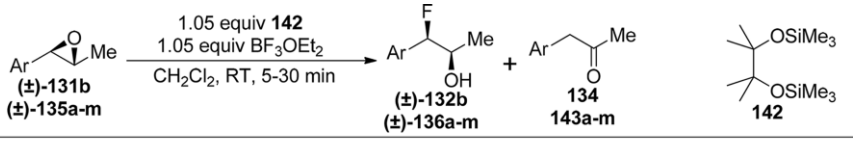
Epoxide Number	R	Isolated product yields **(±)-138**	**139**	**140**	**141**	Product ratio
(±)-137a	CH_2Cl	70 %	0 %	0 %	0 %	78:22:0:0
(±)-137b	CH_2Br	72 %	21 %	0 %	0 %	78:22:0:0
(±)-137c	CH_2N_3	65 %	0 %	0 %	0 %	92:8:0:0
(±)-137d	$CH_2OTBDMS$	31 %	0 %	41 %	0 %	35:10:55:0
(±)-137e	CH_2OTs	84 %	16 %	0 %	0 %	84:16:0:0
(±)-137f	CH_2CH_2OTs	85 %	0 %	0 %	0 %	94:6:0:0
(±)-137g	COPh	42 %	0 %	0 %	not given	69:0:0:31
(±)-137h	CO_2Me	65 %	0 %	0 %	0 %	100:0:0:0
(±)-137i	SO_2Ph	0 %	0 %	91 %	0 %	0:0:100:0
(±)-137j	Ph	0 %	0 %	80 %	0 %	0:0:100:0

ane) and thanks to the CH_2Cl_2 solvent the reaction was rapid (5–10 min at –20 °C).[72]

Later, Cresswell et al. showed that decreasing the Lewis acidity of boron (by replacing fluorides with alkoxides) makes the boron fluoride moiety of **(±)-133** and similar intermediates better fluoride donors, widening the substrate scope of the above reaction. Their best results were achieved with pinacolatoboron fluoride, which had to be prepared in situ because its isolation with distillation failed. Usually, 1.05 equiv. BF_3/OEt_2 was added to a solution of 1.05 equiv. bis(*O*-trimethylsilyl)pinacol **142** in CH_2Cl_2 followed by transferring the resulting solution to a solution of 1.0 equiv. epoxide in CH_2Cl_2 (Table 5). Compared to BF_3, the new method works with *trans*-β-methylstyrene oxide derivatives carrying a moderately activating group on the aromatic ring [substrates **(±)-135b**–**c** and **(±)-135m**], but still fails when a strongly activating or deactivating group is present [substrates **(±)-135a**,**l** and **(±)-135k**]. The mechanism is mostly the same S_N1 as with BF_3 (see Scheme 41), but in the cases of epoxides **(±)-135h**–**j** the small *dr* loss suggests that an S_N2-like pathway is also involved.[73]

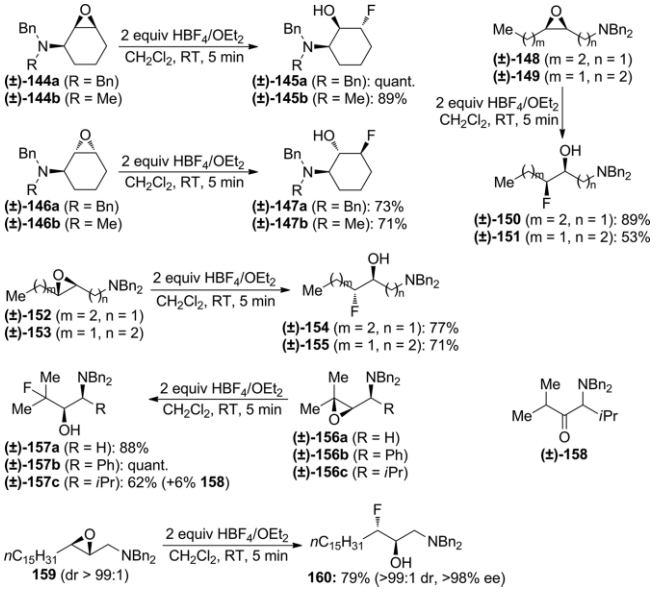
The possible role of HBF_4/OEt_2 impurities in BF_3/OEt_2 in fluoride ring openings and the low cost of liquid HBF_4/OEt_2 directed some attention to this reagent. Although the nucleophilicity of the BF_4^- anion is extremely low, numerous reactions are known in organic chemistry, where it transfers fluoride ion to highly reactive cationic intermediates. However, since this reagent is quite acidic, when used with epoxides, there is a high probability of polymerization and rearrangement side reactions. Cresswell et al. solved this problem by using epoxyamines as substrates. These are protonated on their nitrogen by excess reagent, and the resulting cations repel each other, suppressing polymerization and enabling oxirane ring opening with BF_4^-. The reaction was stereoselective, but in contrast to experiences with $BF_3{\cdot}OEt_2$,[72] it took place with inversion at carbon (S_N2 mechanism). Furthermore, the reaction was also regioselective, because the strong inductive electron withdrawal of the

Table 5. Ring opening of *trans*-2-methyl-3-aryloxiranes with pinacolatoboron fluoride. Only isolated yields are given. Some ketones were not isolated (see an * instead of yield). With epoxide **(±)-135k** no reaction occurred. Product ratios were determined by NMR analysis of the crude product mixtures. Reactions which worked with both BF_3 and pinacolatoboron fluoride are shaded darker grey. Reactions which worked only with pinacolatoboron fluoride are shaded light grey. Results of all other reactions are not shaded.



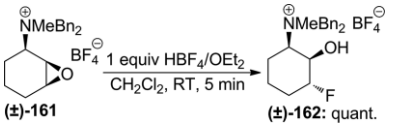
Epoxide				Time	Fluorohydrin			Ketone		Product
Number	Ar	σ+	dr	(min)	Number	%	dr	Number	%	ratio
(±)-135a	*p*-$MeOC_6H_4$	-0.78	96:4	5	**(±)-136a**	–	–	**143a**	69%	0:100
(±)-135l	*p*-$PhOC_6H_4$	-0.50	96:4	5	**(±)-136l**	–	–	**143l**	78%	0:100
(±)-135b	*p*-MeC_6H_4	-0.31	90:10	5	**(±)-136b**	59%	>95:5	**143b**	*	77:23
(±)-135c	*p*-PhC_6H_4	-0.18	98:2	5	**(±)-136c**	53%	>95:5	**143c**	25%	70:30
(±)-135m	2-naphthyl	-0.13	96:4	5	**(±)-136m**	56%	>95:5	**143m**	22%	73:27
(±)-135d	*p*-FC_6H_4	-0.07	94:6	5	**(±)-136d**	52%	>95:5	**143d**	10%	77:23
(±)-131b	Ph	0.00	>99:1	5	**(±)-132b**	63%	98:2	**134**	*	81:19
(±)-135e	*m*-$MeOC_6H_4$	+0.05	93:7	5	**(±)-136e**	54%	>95:5	**143e**	*	66:34
(±)-135f	*p*-ClC_6H_4	+0.11	94:6	10	**(±)-136f**	57%	>95:5	**143f**	27%	68:32
(±)-135g	*p*-BrC_6H_4	+0.15	94:6	10	**(±)-136g**	54%	>95:5	**143g**	31%	62:38
(±)-135h	*m*-FC_6H_4	+0.35	95:5	15	**(±)-136h**	55%	90:10	**143h**	22%	72:28
(±)-135i	*m*-ClC_6H_4	+0.40	92:8	15	**(±)-136i**	56%	89:11	**143i**	23%	74:26
(±)-135j	*m*-BrC_6H_4	+0.41	91:9	15	**(±)-136j**	51%	88:12	**143j**	20%	71:29
(±)-135k	*p*-$CF_3C_6H_4$	+0.61	94:6	30	**(±)-136k**	–	–	**143k**	–	–

ammonium ion destabilizes the late transition state directing fluoride attack to the distal oxirane carbon. Epoxides of both allylic and homoallylic amines were transformed quickly and efficiently to fluorohydrins by this method (Scheme 42).[74]

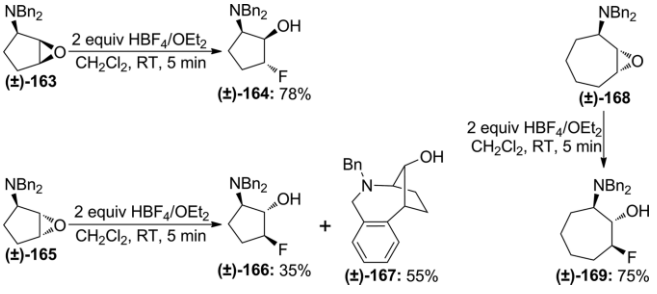


Scheme 42. Ring opening of epoxyamines with HBF_4/OEt_2. Transformation of **(±)-156c** yielded an 83:17 mixture of **(±)-157c** and **158** because [1,2]-H-atom shift competed with S_N2 of fluoride.

Later, Cresswell et al. provided an insight into the reaction mechanism of the above transformation. Treatment of quaternary ammonium fluoroborate **(±)-161** with 1 equiv. *N*,*N*-dibenzyl-*N*-cyclohexylammonium tetrafluoroborate resulted in no reaction, while addition of 1 equiv. HBF_4/OEt_2 gave fluorohydrin **(±)-162** in quantitative yield (Scheme 43). This shows that ring opening of epoxyammonium ion intermediates by BF_4^- requires protonation of the epoxide oxygen, that is, a second equivalent of HBF_4 is also involved. They also transformed 2,3-epoxycycloalkylamines with five- or seven-membered carbocycles into fluorohydrins efficiently. The only exception is **(±)-165** where the arene ring of the *N*-benzyl group competed with fluoride as nucleophile (Scheme 44). Taking into account that epoxid-



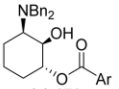
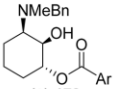
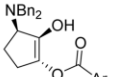
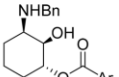
Scheme 43. Insight into the reaction mechanism of epoxyamine ring opening with HBF_4/OEt_2. Both the starting material and the product had > 99:1 *dr*.

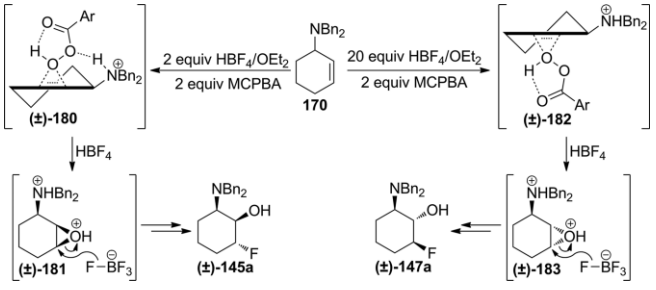


Scheme 44. Transformation of 2,3-epoxycycloalkylamines into fluorohydrins with HBF_4/OEt_2. Every starting materials and products had > 99:1 *dr*.

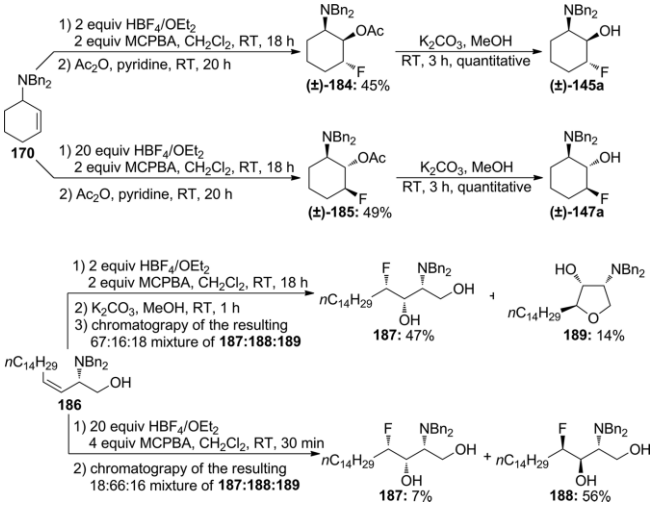
ation of ammonium salts formed from allylic amines with strong Brønsted acids is *cis* selective (ammonium-directed olefinic oxidation), one-pot epoxidation/oxirane ring opening was attempted. The combination of MCPBA and HBF_4/OEt_2 successfully transformed allylic amines into fluorohydrins, and the ratio of fluorohydrins (Table 6) depended on the amount of HBF_4. When larger excess (up to 20–30 equiv.) was used, MCPBA was also protonated and the resulting electrostatic repulsion with the ammonium ion interfered with the hydrogen bond directing effect. Namely, the increasing ratio of *trans* epoxidation to the fluorohydrin product resulting from the *trans* epoxide, sometimes completely reversed selectivity (Scheme 45 and Scheme 46). Isolation of the main product was often difficult (Scheme 46). Other results of the one-pot method can be found in Scheme 47.[75]

Table 6. One-pot epoxidation/oxirane ring opening of different allylic cycloalkeneamines. Conditions: HBF_4/OEt_2 (amount given in the table), then MCPBA (2 equiv.), RT, 18 h. Product ratios were determined by NMR analysis of the crude product mixture. Ar = 3-ClC_6H_4.

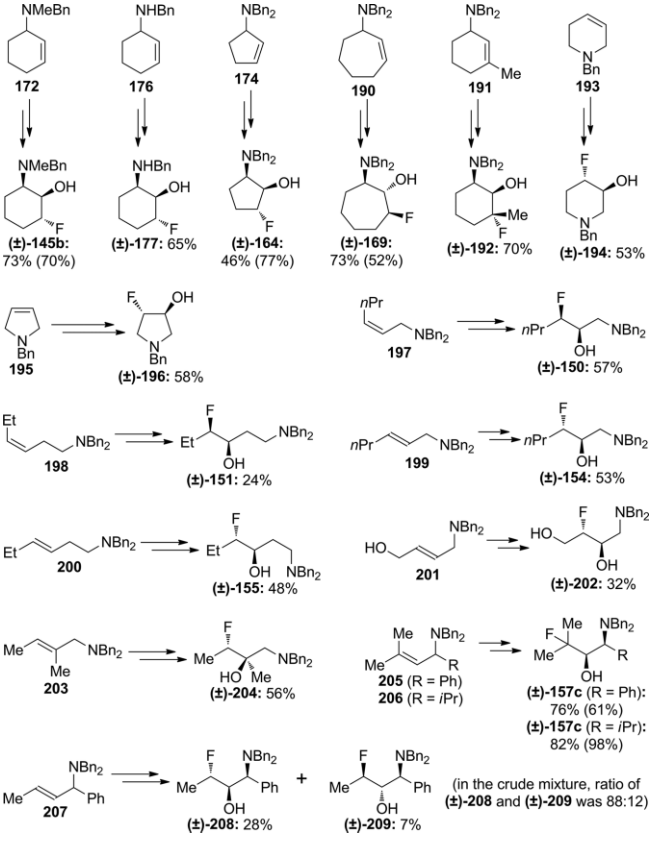
Substrate	Products	Amount of	Product	HBF_4×OEt_2	ratio
 170	 (±)-145a	 (±)-147a	 (±)-171	2 equiv	85:3:12
				5 equiv	43:48:9
				10 equiv	26:70:4
				20 equiv	16:84:0
				30 equiv	10:90:0
 172	 (±)-145b	 (±)-147b	 (±)-173	2 equiv	85:3:12
				5 equiv	68:25:7
				10 equiv	46:50:4
				20 equiv	35:63:2
 174	 (±)-164	 (±)-166	 (±)-175	2 equiv	74:0:26
				5 equiv	71:4:25
				10 equiv	73:9:18
				20 equiv	71:16:13
 176	 (±)-177	 (±)-178	 (±)-179	2 equiv	90:0:10
				5 equiv	86:5:9
				10 equiv	82:11:7
				20 equiv	77:17:6



Scheme 45. Connection between the regioselectivity and the HBF_4 equivalents in the case of allylamine **170**. Compound **172** behaved similarly, while the effect was much weaker during transformation of **174** and **176**. Ar = 3-ClC_6H_4.



Scheme 46. Reversing regioselectivity during one-pot epoxidation/oxirane ring opening of allylic amines. Every compound had > 99:1 *dr*. Product ratios were determined by NMR analysis of the crude product mixture.



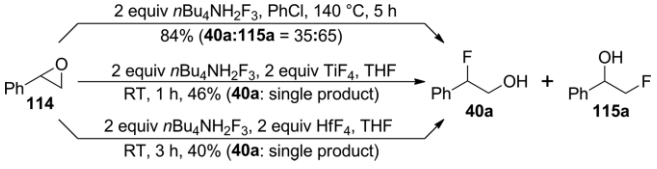
Scheme 47. Other results obtained by utilizing the one-pot method with (homo)allylic amines. Only isolated yields are given. Yields in parentheses are overall yields of the sequential method (ammonium-directed epoxidation, then treatment of the epoxide with HBF_4/OEt_2). General reaction conditions: 2 equiv. HBF_4/OEt_2, 2 equiv. MCPBA, CH_2Cl_2, RT, 18 h; then K_2CO_3, MeOH, RT, 1 h. Exceptions: compounds **195** and **201** (10 equiv. HBF_4/OEt_2 was applied), and compounds **206** and **207** (the first step was 30 min rather than 18 h). Compound **(±)-192** had 95:5 *dr*, every other compound had > 99:1 *dr*.

2.7. Ring Opening with Transition Metal Catalysis

Transition metal salts can influence oxirane ring opening in multiple ways. First of all, as Lewis acids, they can activate the oxirane with coordination increasing its reactivity (the side effect is increased S_N1 character of the ring opening).[76,77] Opening new reaction pathways is possible too.[39] Finally, chiral

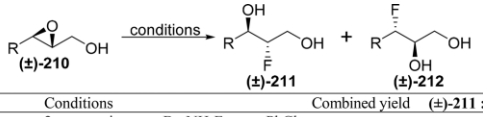
metal complexes enable enantioselective desymmetrization of *meso* epoxides.[18,78,79,80]

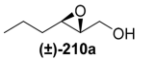
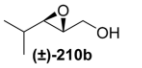
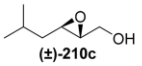
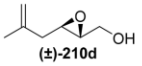
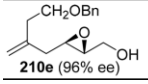
Mikami et al. reported a good example of the effect of coordination. Oxirane ring opening with $nBu_4N^+H_2F_3^-$ was successfully accelerated by addition of Lewis acids (the most effective ones were TiF_4 and HfF_4). As shown with styrene oxide, the reaction mechanism shifted towards S_N1 (Scheme 48). In the case of aliphatic epoxy alcohols **(±)-210a–c** with only secondary oxirane carbons (Table 7), the reaction proceeded with inversion and the regioselectivity was influenced by both nearby C=C bonds and the Lewis acid itself. Namely, the smaller Ti^{IV} preferred the formation of **(±)-212a–c**, which are capable of forming a 5-membered chelate ring with the metal. The larger Hf^{IV}, in turn, promoted formation of **(±)-211a–c**, which can form a 6-membered chelate ring with the metal (Scheme 49).[76] Mikami and co-workers used the same method for the ring opening of epoxy alcohol **210e** in order to achieve maximum selectivity towards product **211e** (Table 7, last line).[77]



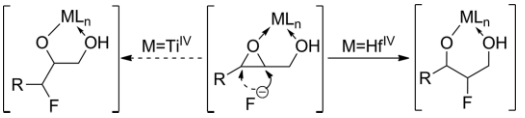
Scheme 48. Ring opening of styrene oxide with $nBu_4N^+H_2F_3^-$ with or without Lewis acids. Yields and product ratios were determined by ^{19}F-NMR.

Table 7. Ring opening of epoxy alcohols with $nBu_4N^+H_2F_3^-$ with or without Lewis acids. Product ratios and most of the yields were determined by ^{19}F-NMR (isolated yields are noted).



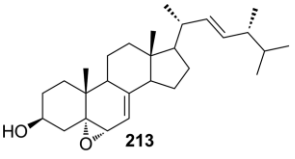
Substrate	Conditions	Combined yield	(±)-211 : (±)-212
 (±)-210a	2 equiv $nBu_4NH_2F_3$, PhCl 140 °C, 18 h	90%	21 : 79
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv TiF_4 CH_2Cl_2, RT, 4 h	92%	11 : 89
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv TiF_4 THF, RT, 4 h	74%	39 : 61
 (±)-210b	2 equiv $nBu_4NH_2F_3$, PhCl 140 °C, 24 h	69%	33 : 67
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv TiF_4 CH_2Cl_2, RT, 4 h	74%	20 : 80
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv TiF_4 THF, RT, 24 h	76%	63 : 37
 (±)-210c	2 equiv $nBu_4NH_2F_3$, PhCl 140 °C, 24 h	57%	13 : 87
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv TiF_4 CH_2Cl_2, RT, 6 h	56%	14 : 86
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv HfF_4 THF, RT, 6 h	71%	39 : 61
 (±)-210d	$nBu_4NH_2F_3$, PhCl, 140 °C, 20 h	60%	39 : 61
	$nBu_4NH_2F_3$, TiF_4 PhCl, RT, 8 h	86% (isolated)	66 : 34
	1.1 equiv $nBu_4NH_2F_3$, 1.1 equiv HfF_4 THF, RT, 8 h	74%	74 : 26
 **210e** (96% ee)	1 equiv $nBu_4NH_2F_3$, 1 equiv HfF_4 THF, 0 °C to RT, 24 h	94% (isolated)	78 : 22 (non-racemic)

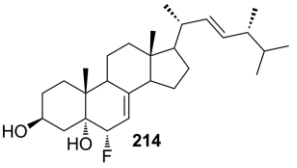
Another example where the transition metal mainly acted as a Lewis acid was described by Kasai et al. Fluoride ring opening of ergosterol-derived epoxide **213** with Et_3N/3HF had elimination and stereoselectivity issues, presumably because of allyl cation intermediate **217**. Consequently, combinations of common fluoride sources with TiF_4 were tested. The best fluorohydrin yield was achieved when tetrabutylammonium difluorotriphenylsilicate ($nBu_4N^+[Ph_3SiF_2]^-$) was used as fluoride source (Table 8). The observed selectivity towards *syn*-fluorohydrin formation suggests internal fluoride ion delivery within an oxirane intermediate activated by titanium fluoride (Scheme 50). The fluorohydrin was easily transformed into the desired 6-fluoroergosterol.[81]

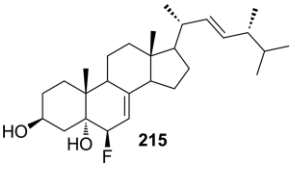


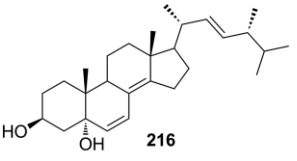
Scheme 49. Reason of different regioselectivity with Ti^{IV} and Hf^{IV} during fluoride ring opening of epoxy alcohols.

Table 8. Fluoride ring opening of ergosterol-derived epoxide **213** under different conditions. Product ratio was determined by ^1H-NMR of the crude product.

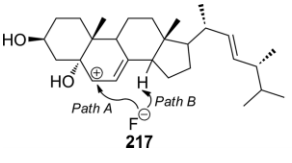


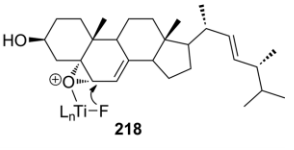






Substrate	Condition	**214/215/216** ratio	Isolated yields
213	Et_3N/3HF, CH_2Cl_2, 0 °C, 1 h	15:10:75	–
213	TiF_4, TBAF, THF, 0 °C to RT, 9 h	12:22:66	–
213	TiF_4, $(Me_2N)_3S^+Me_3SiF_2^-$, CH_2Cl_2, –50 °C to –30 °C, 2 h	19:15:66	–
213	TiF_4, $nBu_4N^+Ph_3SiF_2^-$, THF, 0 °C to RT, 2 days	17:14:69	–
213	TiF_4, $nBu_4N^+Ph_3SiF_2^-$, CH_2Cl_2, 0 °C, 40 min	43:0:57	**214**: 38 % **216**: 45 %



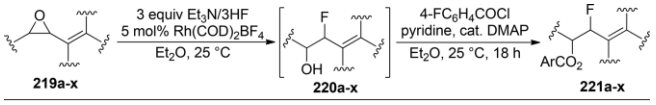


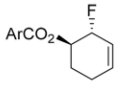
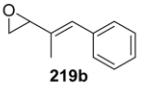
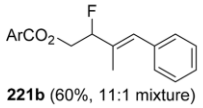
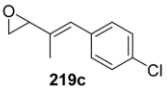
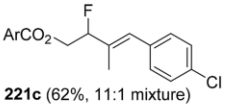
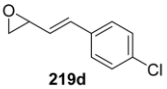
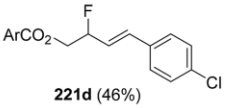
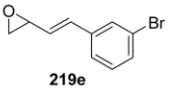
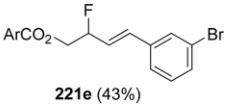
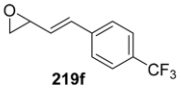
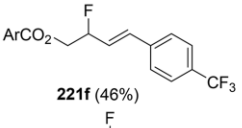
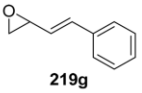
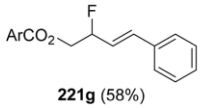
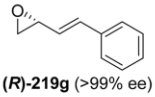
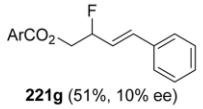
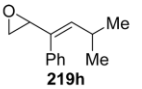
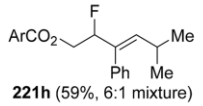
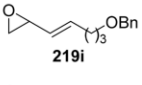
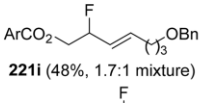
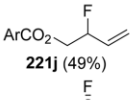
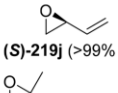
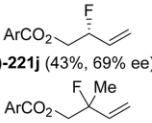
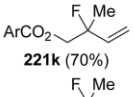
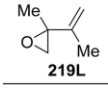
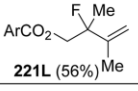
Scheme 50. Intermediates during fluoride ring opening of oxirane **213**. On the left side, *Path A* results in the formation of fluorohydrins **214** and **215**, while *Path B* leads to elimination product **216**.

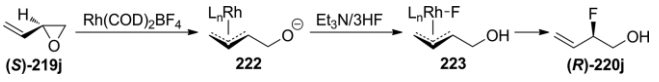
An example for new reaction pathways is the Rh-catalyzed regioselective opening of vinyl epoxides reported by Nguyen and co-workers. Based on their previous results with Ir-catalyzed fluorination of allylic trichloroacetimidates, vinyl epoxide **219a** was treated with fluoride sources in the presence of Ir or Rh complexes. After some optimization, ^{19}F NMR showed that the combination of 5 mol-% $Rh(COD)_2BF_4$ and 3 equiv. Et_3N/3HF in THF or Et_2O provides the best fluorohydrin yield. Et_2O

was selected as the solvent, because it formed a biphasic reaction mixture, eliminating the need for an aqueous workup. The process was then extended to a range of vinyl epoxides (Table 9). The fluorohydrins were isolated as their 4-fluorobenzoates. The reaction showed high selectivity towards 1,2-fluorohydrin formation (although 1,4-fluorohydrins also formed in some cases). Experiments with enantiopure substrates showed that the reaction proceeds mostly with inversion, but there is a substrate-dependent extent of racemization. Because saturated epoxides (styrene oxide, epoxycyclohexane) remained unchanged under the reaction conditions even after 18 h, the Rh complex is not acting as a Lewis acid. The authors suggested that the transformation proceeds through a π-allylrhodium intermediate, and metal-coordinated fluoride attacks the more substituted carbon of the allylic system (Scheme 51).[39]

Table 9. Rh-catalyzed regioselective opening of vinyl epoxides. ^{19}F-NMR yields were obtained by analysis of the crude reaction mixture using $PhCF_3$ as an internal standard. Ar = 4-fluorophenyl. When mixtures were formed, the minor component was the 1,4-fluorohydrin.

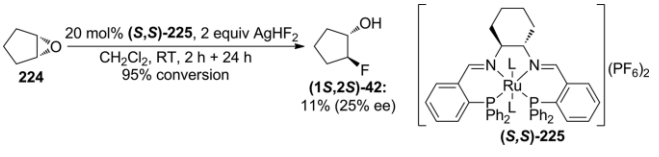


Substrate	Time	^{19}F-NMR yield of fluorohydrins	Final product with isolated yield
 **219a**	0.5 h	89%	 **221a** (79%)
 **219b**	1 h	82%	 **221b** (60%, 11:1 mixture)
 **219c**	1 h	76%	 **221c** (62%, 11:1 mixture)
 **219d**	1 h	64%	 **221d** (46%)
 **219e**	1 h	63%	 **221e** (43%)
 **219f**	4 h	50%	 **221f** (46%)
 **219g**	1 h	69%	 **221g** (58%)
 **(*R*)-219g** (>99% ee)	1 h	–	 **221g** (51%, 10% ee)
 **219h**	10 h	73%	 **221h** (59%, 6:1 mixture)
 **219i**	3 h	61%	 **221i** (48%, 1.7:1 mixture)
 **219j**	1 h	50%	 **221j** (49%)
 **(*S*)-219j** (>99% ee)	1 h	–	 **(*R*)-221j** (43%, 69% ee)
 **219k**	0.5 h	80%	 **221k** (70%)
 **219L**	0.5 h	65%	 **221L** (56%)



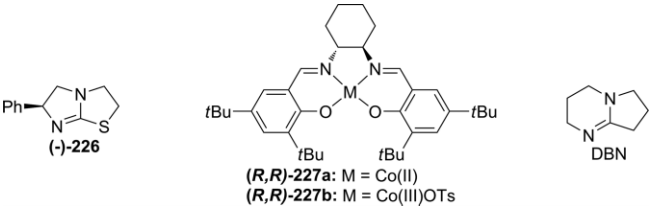
Scheme 51. Mechanism of Rh-catalyzed regioselective opening of vinyl epoxides.

Enantioselective desymmetrization of *meso* epoxides was first reported by Bruns and Haufe, who utilized the chromium chloride complex of (*S*,*S*)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamine together with a fluoride source (initially KHF_2/18-crown-6, later AgF was also used).[82] Unfortunately, a large amount of metal complex (50–100 mol-%) was required. Althaus et al. tried to develop a catalytic version of this process, and treatment of cyclopentene oxide **224** with $[Ru(OEt_2)_2PNNP](PF_6)_2$ **(*S*,*S*)-225** and $AgHF_2$ resulted in fluorohydrin **(1*S*,2*S*)-42** in low yield and *ee* (Scheme 52). This was caused by extensive polymerization, despite the fact that **224** was added via over 2 h. The epoxide of *cis*-stilbene **52**, however, rearranged to diphenylacetaldehyde, which was oxidatively α-fluorinated under these conditions.[78]



Scheme 52. Enantioselective desymmetrization of epoxide **224** with Ru catalyst **(*S*,*S*)-225** and $AgHF_2$.

Kalow and Doyle showed that the combination of 2 equiv. benzoyl fluoride, 4 equiv. of hexafluoroisopropyl alcohol, and 20 mol-% 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) slowly generates DBN/$(HF)_n$ adducts enabling effective fluoride ring opening of cyclohexene oxide. Replacement of achiral DBN with similar but chiral (–)-tetramisole **(–)-226** (Scheme 53) induced enantio-

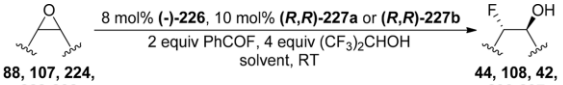


Scheme 53. Compounds utilized for the enantioselective fluoride ring opening of *meso* epoxides.

selectivity only when achiral or chiral Co-salen complexes were also added. Chiral complex **(*R*,*R*)-227a** (Scheme 53) was capable of inducing enantioselectivity even in the presence of DBN, although the process was improved when **(–)-226** was used. After further optimization, enantioselective desymmetrization of various *meso* epoxides was efficiently achieved with the combination of 10 mol-% **(*R*,*R*)-227a** or **(*R*,*R*)-227b** with 8 mol-% **(–)-226** (Table 10). This fluorinating system was also capable of enantioselective fluoride ring opening of terminal oxiranes with S_N2 regioselectivity (Table 11).[79]

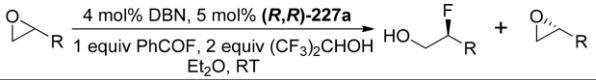
Later, Kalow and Doyle performed a detailed study of this reaction. It was determined that the epoxide coordinates to a fluoride-bridged dimer Co(salen) complex, then interaction with the amine causes dissociation. The results are an amine–Co(salen)–bifluoride complex and an epoxide–Co(salen) complex, and the former transfers F^- ion to the oxirane. Taking these into account, dimeric catalyst **(*R*,*R*,*R*,*R*)-243** (Scheme 54) was synthesized. The new metal complex showed superior reactivity and enantioselectivity (Table 12, Scheme 55). Note that compound **(*S*)-251** represents the "cold" version of the PET radiotracer fluoromisonidazole.[80]

Table 10. Enantioselective desymmetrization of *meso* epoxides with chiral metal complexes and (–)-tetramisole. Only isolated yields are given.

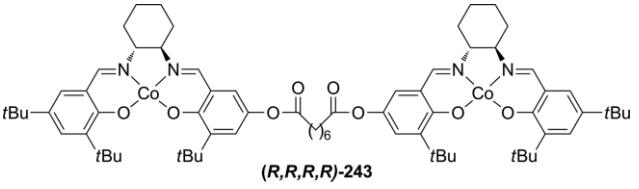


Epoxide	Metal catalyst	Solvent	Reaction time	Product	
				Structure	Yield and ee
88	**(*R*,*R*)-227b**	*t*-amyl alcohol	24 h	**(1*S*,2*S*)-44**	65% yield 93% ee
107	**(*R*,*R*)-227a**	*t*BuOMe	120 h	**(5*S*,6*S*)-108**	55% yield 58% ee
224	**(*R*,*R*)-227a**	Et_2O	72 h	**(1*S*,2*S*)-42**	77% yield 85% ee
229	**(*R*,*R*)-227a**	*t*BuOMe	72 h	**(1*S*,2*S*)-234**	82% yield 90% ee
230	**(*R*,*R*)-227a**	*t*BuOMe	72 h	**(1*S*,8*S*)-235**	87% yield 95% ee
231 (dr 10:1)	**(*R*,*R*)-227a**	*t*-amyl alcohol	120 h	(1*S*,2*S*,4*R*,5*S*)-**236**	75% yield 90% ee
232	**(*R*,*R*)-227a**	*t*BuOMe	120 h	**(1*S*,3*S*,4*S*)-237**	88% yield 86% ee
233	**(*R*,*R*)-227a**	*t*-amyl alcohol	120 h	**(3*S*,4*S*)-238**	84% yield 80% ee

Table 11. Kinetic resolution of terminal epoxides with **(*R*,*R*)-227a** and DBN. Reaction of **239** was conducted with 1.6 mol-% DBN and 2 mol-% **(*R*,*R*)-227a**, with the product isolated as the TBDPS ether. Only isolated yields are given.

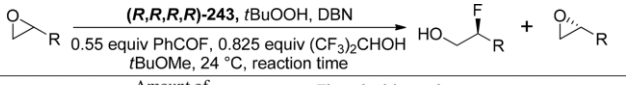


Epoxide	Reaction time	Fluorohydrin product		k_{rel}
		Structure	Yield and ee	
114	10 h	**(*S*)-115a**	44% yield 99% ee	>300
239	30 h	**(*S*)-240**	36% yield 99% ee	>300
241	24 h	**(*R*)-242**	44% yield 98% ee	32

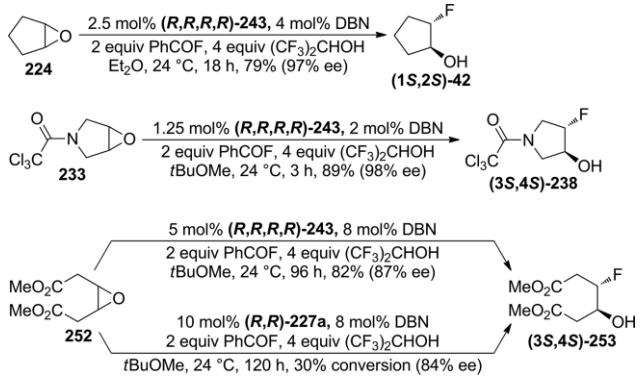


Scheme 54. Structure of chiral dimeric Co(salen) catalyst **(*R*,*R*,*R*,*R*)-243**.

Table 12. Kinetic resolution of terminal epoxides catalyzed by **(*R*,*R*,*R*,*R*)-243**. Reactions of **114**, **244**, and **245** were performed with 0.45 equiv. PhCOF. Relative to **(*R*,*R*,*R*,*R*)-243**, 1.6 equiv. DBN and 2 equiv. of *t*BuOOH were used. Only isolated yields are given. The last column contains the lower bound for the selectivity factor.



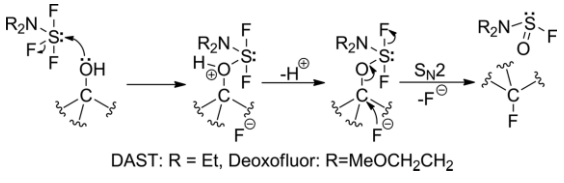
Epoxide	Amount of **(*R*,*R*,*R*,*R*)-243**	Reaction time	Fluorohydrin product		s
			Structure	Yield and ee	
114	0.125 mol%	3.5 h	**(*S*)-115a**	42% yield 98% ee	211
241	0.25 mol%	4 h	**(*R*)-242**	44% yield 96% ee	112
244	0.125 mol%	2 h	**(*S*)-40f**	42% yield 98% ee	211
245	0.125 mol%	2 h	**(*S*)-40d**	43% yield 99% ee	449
246	0.25 mol%	3 h	**(*S*)-249**	44% yield 90% ee	40
247	0.5 mol%	2 h	**(*S*)-250**	45% yield 98% ee	245
248	1.25 mol%	5 min	**(*S*)-251**	40% yield 93% ee	–



Scheme 55. Enantioselective desymmetrization of *meso* epoxides catalyzed by **(*R*,*R*,*R*,*R*)-243**. Only isolated yields are given.

2.8. Ring Opening with Deoxyfluorinating Reagents

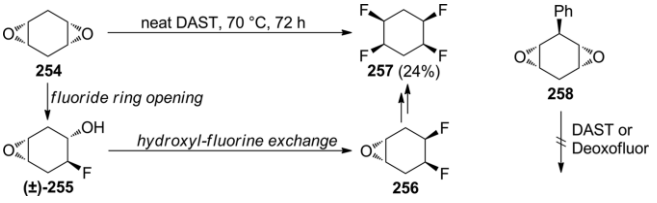
Deoxyfluorinating reagents can exchange OH groups with F or transform carbonyl groups to difluoromethylene moiety. The most commonly used deoxyfluorinating reagents contain S–F bonds [Et_2NSF_3: DAST, $(MeOCH_2CH_2)_2NSF_3$: Deoxofluor, $Et_2N{=}SF_2^+BF_4^-$: XtalFluor-E]. The mechanism of OH→F exchange is shown in Scheme 56: the reagent transforms the OH group into a good leaving group, and the F^- ion formed during this step substitutes the leaving group. The carbonyl→CF_2 transformation requires catalytic amounts of HF, which forms a geminal fluorohydrin intermediate with the oxo compound, and then the hydroxyl group of this intermediate is exchanged to fluorine.



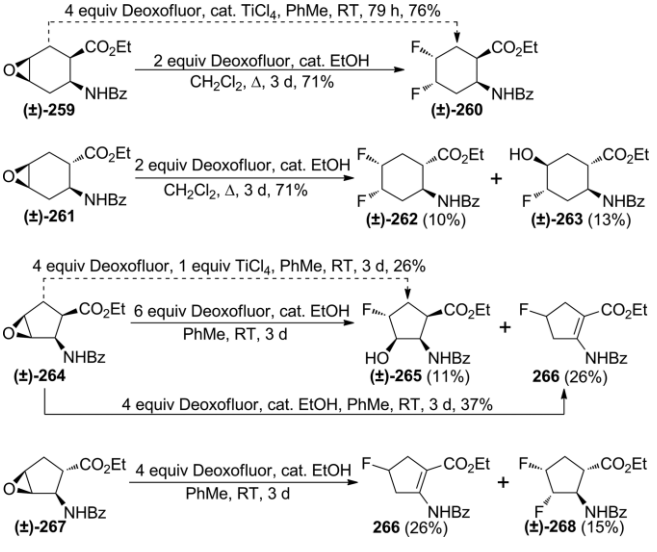
Scheme 56. Deoxyfluorination: mechanism of the OH→F exchange. The last step is usually an S_N2 process; however, S_N1 is possible too if the substrate can form a stabilized carbocation.

Despite the widespread use of these reagents for the above transformation, their use in the literature for the ring opening of oxiranes is scarce. Although Hudlický reported the ability of DAST to transform epoxides into vicinal difluorides as early as 1987,[83] the next report of utilizing this reaction was published in 2012, when O'Hagan and co-workers transformed the *cis* diepoxide of 1,4-cyclohexadiene into all-*syn*-1,2,4,5-tetrafluorocyclohexane (Scheme 57).[84] The stereospecific incorporation of fluorine atoms agrees well with the mechanism suggested by Hudlický, where the fluoride ions open the heteroring with inversion at carbon, and then the OH group of the resulting *anti*-fluorohydrin intermediate is exchanged to F, again with inversion (Scheme 57).[83] Interestingly, O'Hagan and co-workers later found that analogous treatment of epoxide **258** (phenyl-substituted **254**) did not generate clean products.[85]

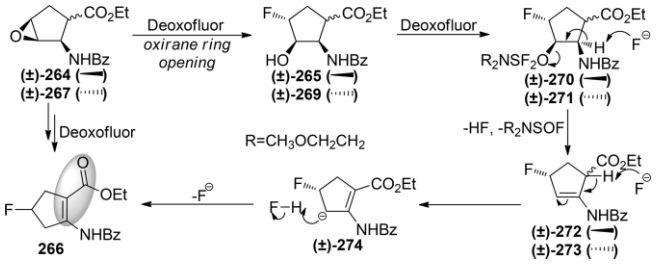
Remete et al. utilized Deoxofluor (a thermally more stable analogue of DAST) for the transformation of epoxides derived from cyclic β-aminoesters to fluorinated compounds. The conditions required for successful fluorination and the actual outcome were greatly substrate-dependent. Initially, catalytic EtOH was added to the reaction mixtures because its reaction with Deoxofluor generates HF facilitating the reaction by electrophilic activation of the oxirane. In the case of compounds **(±)-259** and **(±)-261** with cyclohexane skeleton, reflux in CH_2Cl_2 was the most effective. In the case of compounds **(±)-264** and **(±)-267** with cyclopentane skeleton, stirring in toluene at room temperature was the most efficient. However, even under identical conditions, these epimeric pairs of epoxides afforded different results (Scheme 58). Apart from the desired difluorinated compounds **(±)-260**, **(±)-262**, and **(±)-268**, fluorohydrin intermediates **(±)-263** and **(±)-266** were also isolated, as well as unsaturated product **266**. The latter is possibly formed from fluorohydrins **(±)-265** and **(±)-269** by E2 elimination and isomerization (the last step is driven by extension of conjugation), although **(±)-269** was not detected in the reaction mixtures (Scheme 59). Transformation of **(±)-259** and **(±)-264** was also successful with $TiCl_4$ as electrophilic activating agent instead of EtOH when toluene was used as solvent (Scheme 58, dashed arrows).[86] Later, Remete et al. used the EtOH-catalyzed method on oxiranes **(±)-62**, **(±)-65** and **(±)-276**. Compound **(±)-65** did not give any identifiable product, but the other two oxiranes were successfully transformed into vicinal difluorides (Scheme 60).[40]



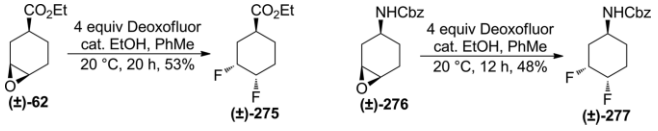
Scheme 57. Substrate-dependent ring opening of diepoxycyclohexane derivatives with DAST. It is worth noting that DAST is unstable at 70 °C and is potentially explosive.



Scheme 58. Transformation of epoxidized cyclic β-aminoesters to fluorinated compounds with Deoxofluor. Formation of **(±)-263** is in agreement with the Fürst–Plattner rule.

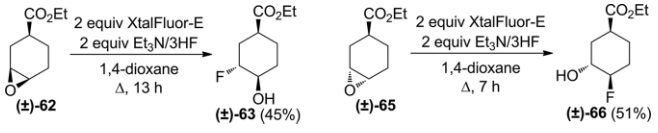


Scheme 59. Formation mechanism of **266** with the conjugated double bonds highlighted. Fluorohydrin **(±)-266** was isolated too, but **(±)-269** was not detected in the reaction mixtures.



Scheme 60. Transformation of functionalized bicyclic oxiranes into vicinal difluorides with Deoxofluor. The reaction failed with **(±)-65** [the C1-epimer of **(±)-62**].

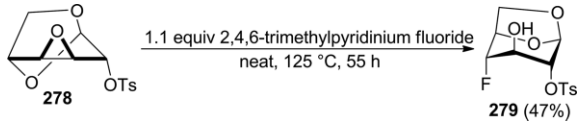
Remete et al. also attempted the transformation of bicyclic oxiranes with XtalFluor-E into fluorinated compounds. With epoxidized β-aminoesters, participation of the NHBz group induced cyclization to non-fluorinated dihydrooxazole derivatives.[86] However, treatment of epimeric oxiranes **(±)-62** and **(±)-65** with XtalFluor-E and Et_3N/3HF yielded fluorohydrins **(±)-63** and **(±)-66**, respectively (Scheme 61). The selectivity of the ring opening followed the Fürst–Plattner rule. Strangely, reaction of epoxyamine **(±)-276** with XtalFluor-E and Et_3N/3HF did not afford any identifiable product.



Scheme 61. Transformation of bicyclic oxiranes into fluorohydrins with XtalFluor-E and Et_3N/3HF.

2.9. Miscellaneous Reactions for Fluoride Ring Opening of Oxiranes

Markina and Voznyi reported that epoxide **278** can be transformed into fluorohydrin **279** efficiently with molten 2,4,6-trimethylpyridin/HF (Scheme 62). Again, this regioselectivity is in agreement with the Fürst–Plattner rule. The use of KHF_2 in boiling ethylene glycol replaced the TsO group with F too (5 % yield of difluoride), while treatment with 25 % HF/dioxane gave **279** only in 2 % yield.[87]



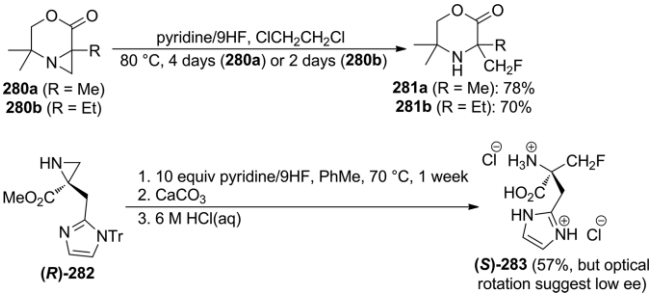
Scheme 62. Ring opening of oxirane **278** with molten 2,4,6-trimethylpyridin/HF.

3. Fluoride Ring Opening of Aziridines

3.1. Ring Opening with Pyridine/9HF

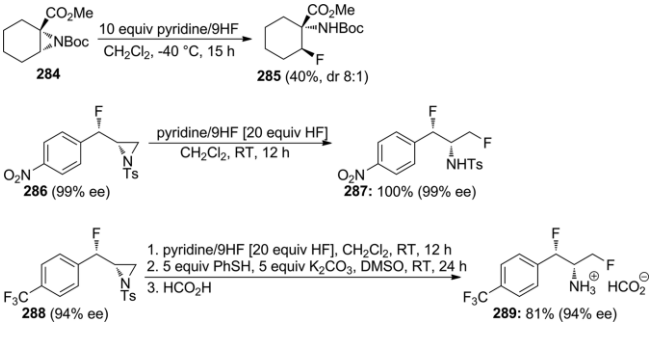
The ability of pyridine/9HF to perform fluoride ring opening of aziridines has been long known.[14] As a result, only selected examples will be shown to appropriately illustrate reaction conditions and selectivities. Important properties of the reagent were described in ***Section 2.2***.

Ring opening of bicyclic aziridine **280a** was shown by McNally et al. to preferentially occur at the less substituted carbon, despite the presence of an activating ester group on the tertiary carbon.[88] Later, Nappi et al. transformed aziridine **280b** similarly.[89] Considine et al. experienced the same regioselectivity when **(*R*)-282** was subjected to Olah's reagent (Scheme 63). Unfortunately, the process was accompanied by extensive racemization, as evidenced by the optical rotation of the product α-fluoromethylhistidine dihydrochloride **(*S*)-283**.[90]



Scheme 63. Regioselective ring opening of *N*-unactivated aziridines with a tertiary carbon connected to an activating group and a primary carbon.

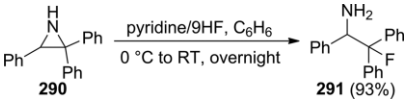
Gilmour and co-workers reported that ring opening of *N*-activated aziridine **284** also occurs at the less substituted carbon, despite the ester group on the tertiary carbon.[91] The reaction proceeded with inversion at carbon. *N*-Activated aziridines **286** and **288** with a primary and a secondary carbon also preferred the attack by fluoride at the less hindered carbon, as reported by Mennie et al.[92] In contrast with the experiences of Considine et al., these reactions preserved the *ee* of the starting compound (Scheme 64). It is also worth noting that the *N*-activating group enabled much milder reaction conditions compared to those shown Scheme 63.



Scheme 64. Regio- and stereoselective ring opening of *N*-activated aziridines with pyridine/9HF.

Cheng and co-workers described that treatment of 2,2,3-triphenylaziridine **290** with pyridine/9HF results in the more sub-

stituted fluoride **291** (Scheme 65).[93] Possibly, the aziridine is activated by protonation and the two phenyl groups can stabilize the positive charge quite efficiently on the adjacent carbon (loose S_N2 transition state or even S_N1 mechanism).

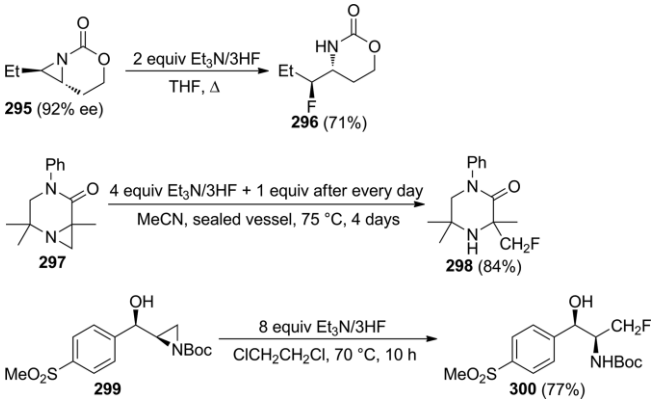


Scheme 65. Ring opening of aziridine **290** with S_N1-like regioselectivity.

3.2. Ring Opening with $Et_3N/3HF$

Utilizing triethylamine trihydrofluoride (for properties, see ***Section 2.3***) for aziridine ring opening is a rather new method. The first report about the use of $Et_3N/3HF$ for aziridine ring opening, was published by Park et al. in 2014. They subjected chiral aziridines **292a**–**h** to $Et_3N/3HF$ and obtained mixtures of the two ring-opened products in ratios depending on the R group (Table 13).[94]

Since that time, only three other cases have been reported. In 2017, Schomaker and co-workers disclosed the stereo- and regio-selective transformation of compound **295** into fluorinated amine **296** with $Et_3N/3HF$. The starting material was prepared by silver-catalyzed chemo- and enantioselective intramolecular aziridination.[95] Then, Alanine et al. reported the regioselective ring opening of aziridine **297** in 2018. This heterocycle was obtained by Pd-catalyzed C–H aziridination of a 3,3,5,5-tetramethylpiperazin-2-one.[96] Finally, Zou et al. described in 2018 a new chemoenzymatic route to florfenicol, an antibiotic, which is widely used in veterinary medicine. Fluorine introduction was accomplished by regioselective aziridine ring opening of **299** (Scheme 66). Notably, the use of more acidic reagents like pyridine/9HF and the HF complex of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (HF-DMPU) led to no reaction.[97]



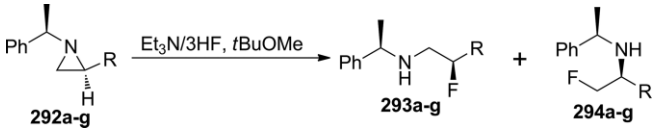
Scheme 66. Ring opening of aziridines with $Et_3N/3HF$.

3.3. Ring Opening with Other "Tamed HF" Reagents

Kalow et al. utilized their strategy of slowly generating an amine/HF reagent by the DBN-catalyzed reaction of 1,1,1,3,3,3-hexafluoroisopropyl alcohol and benzoyl fluoride for the ring opening of aziridines too. At first, *N*-substituted cyclohexene imines were tested (Table 14), then the substrate scope was extended to other bicyclic and monocyclic aziridines (Scheme 67). The reactions taking place with inversion at carbon were effective and usually fast. In the case of chiral aziridine **311**, *ee* was preserved. The use of polypropylene vessels was preferred since this in situ generated amine/HF reagent may be acidic enough to attack glass. Despite this acidity, acid-sensitive substrates like **301a** were also transformed efficiently and the yield was only slightly lower in glassware. *N*-Tosylaziridine **301k** showed greatly decreased reactivity, complementary to ring opening with metal fluorides. The method was capable of diastereoselective ring opening too when a chiral auxiliary was attached to the nitrogen [compound **(*S*)-301L**, Scheme 67].[98]

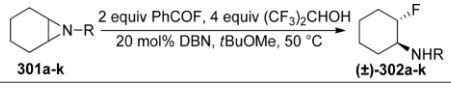
Hammond and co-workers recently developed a new HF-based reagent, HF/DMPU [DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone], which contains 65 wt.-% hydrogen fluoride. Because DMPU, as an urea derivative, is less basic then pyridine or Et_3N, the new reagent is more acidic. It is also more compatible with transition metals, since DMPU is only weakly coordinating.[99] Okoromoba et al. utilized this reagent for the ring opening of *N*-tosylaziridines. Control experiments with compound **316a** showed that HF/DMPU offers higher yield and selectivity than pyridine/9HF (Scheme 68). Transformation of

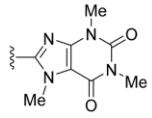
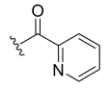
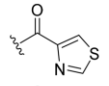
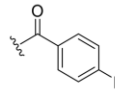
Table 13. Ring opening of chiral aziridines **292a**–**h** with $Et_3N/3HF$. Isolated yields are given.

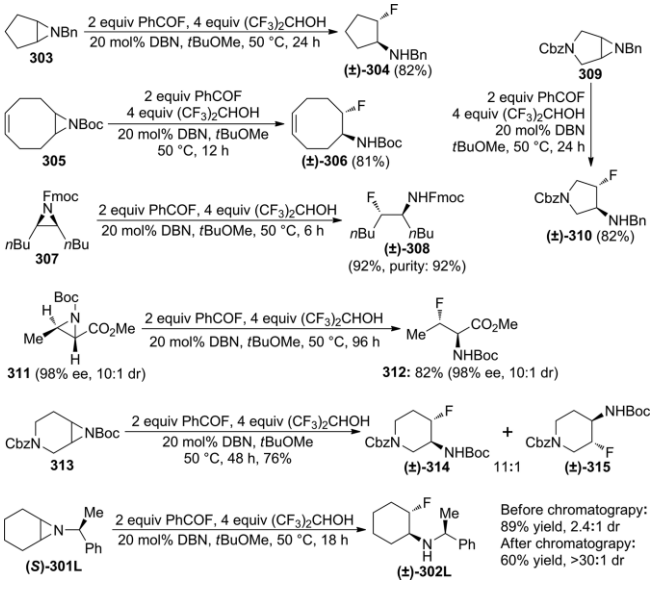


Aziridine	R	Amount of $Et_3N/3HF$	Temperature	Time	Yield	Ratio of **293** and **294**
292a	CO_2Et	6 equiv	75 °C	48 h	51 %	34:66
292b	$CONH_2$	3 equiv	75 °C	60 h	77 %	63:37
292c	CH_2OMe	5 equiv	75 °C	36 h	62 %	32:68
292d	CH_2OBn	5 equiv	75 °C	24 h	54 %	35:65
292e	(*Z*)-CH=CH-Me	3 equiv	50 °C	7 h	71 %	91:9
292f	(*Z*)-CH=CH-Et	4 equiv	50 °C	15 h	61 %	95:5
292g	(*E*)-CH=CH-CO_2Et	4 equiv	60 °C	5 h	73 %	66:34

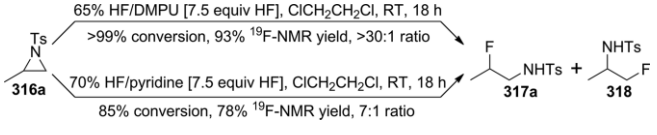
Table 14. Ring opening of *N*-substituted cyclohexene imines **301a**–**k** with in situ generated amine/HF reagent. Reactions were performed in sealed polypropylene vial unless noted otherwise. Only isolated yields are given.



Aziridine		Product	Reaction time	Yield	Notes
Number	R				
301a	Boc	**(±)-302a**	1 h	92%	Performed in glassware.
301b	Cbz	**(±)-302b**	4 h	82%	–
301c	Bn	**(±)-302c**	18 h	87%	–
301d		**(±)-302d**	16 h	76%	Product had 95% purity.
301e	2-MeO-C_6H_4	**(±)-302e**	30 h	74%	–
301a		**(±)-302f**	72 h	92%	Cyclopentyl methyl ether was used as solvent.
301g	Bz	**(±)-302g**	3 h	64%	Oxazoline byproduct: 24%.
301h		**(±)-302h**	8 h	81%	Product had 95% purity.
301i		**(±)-302i**	24 h	77%	–
301j		**(±)-302j**	3 h	80%	–
301k	Ts	**(±)-302k**	48 h	46%	Unreacted **301k**: 48%

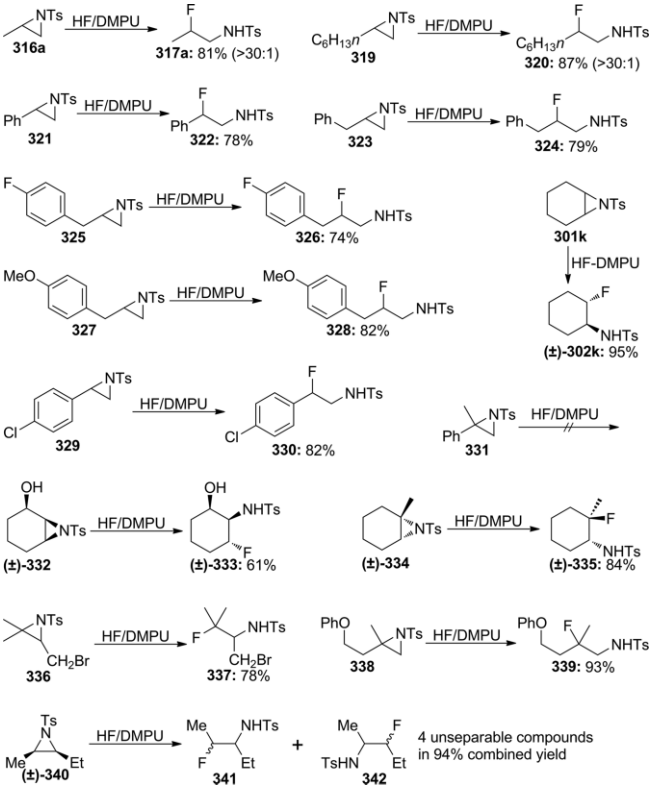


Scheme 67. Ring opening of aziridines with in situ generated amine/HF reagent.

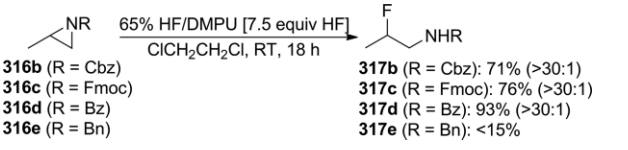


Scheme 68. Comparison of 65 % HF/DMPU and 70 % HF/pyridine.

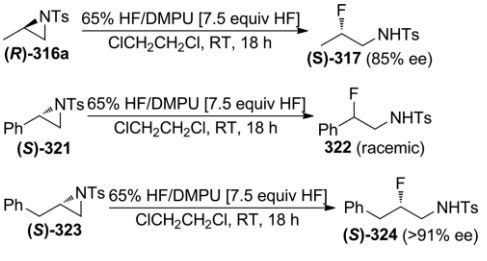
other *N*-tosylaziridines was also efficient (Scheme 69). Replacement of the Ts group with Cbz, Fmoc or Bz was tolerated, but *N*-benzylaziridine **316e** showed insufficient reactivity (Scheme 70). The reactions had S_N1 regioselectivity, but experiments with bicyclic or enantiopure aziridines (Scheme 71) showed that the reaction mostly proceeds with inversion at carbon. This suggests that the aziridine is protonated, increas-



Scheme 69. Fluoride ring opening of racemic *N*-tosylaziridines with 65 % HF/DMPU. Reaction conditions: 65 % HF/DMPU [7.5 equiv. HF], $ClCH_2CH_2Cl$, RT, 18 h. Isolated yields are given. Only major regioisomers are presented. Regioisomeric ratios given in parentheses were determined by ^{19}F-NMR.

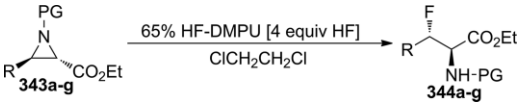


Scheme 70. Effect on the *N*-protecting group on the reactivity of aziridines **316b**–**e** with 65 % HF/DMPU. Only major regioisomers are presented. Regioisomeric ratios given in parentheses were determined by ^{19}F-NMR.



Scheme 71. Fluoride ring opening of enantiopure *N*-tosylaziridines with 65 % HF/DMPU.

Table 15. Fluoride ring opening of various enantiopure aziridinecarboxylates with 65 % HF/DMPU. The reactions were performed in polyethylene vials. Isolated yields are given. In the case of **343a**, 10 equiv. HF was added as 65 % HF/DMPU.



PG	R	Aziridine	Temperature	Time	Product	Yield
Cbz	CO_2Et	**343a**	0 °C to RT	48 h	**344a**	24 %
Boc	(*E*)-CH=CH-CO_2Me	**343b**	0 °C	30 min	**344b**	32 %
Cbz	(*E*)-CH=CH-CO_2Me	**343c**	0 °C	1 h	**344c**	43 %
Ts	(*E*)-CH=CH-CO_2Me	**343d**	0 °C to RT	1 h	**344d**	48 %
Boc	(*E*)-CH=CH-CN	**343e**	0 °C	30 min	**344e**	21 %
Cbz	(*E*)-CH=CH-CN	**343f**	0 °C	1 h	**344f**	45 %
Ts	(*E*)-CH=CH-CN	**343g**	0 °C to RT	1 h	**344g**	37 %

ing partial positive charge at the aziridine carbons and forcing the reaction to proceed in an usual way through a loose S_N2 transition state. Exceptions are compound **321** where the Ph group enables formation of a free carbocation and compound **323** where participation of the Ph group yields a phenonium-ion-like transition structure and retention as the overall stereochemical outcome (Scheme 71). Importantly, compared to pyridine•9HF, the higher acidity of HF-DMPU results in more S_N1 character and improved regioselectivity.[100]

For the fluoride ring opening of various enantiopure aziridinecarboxylates, Alluri and Riss also utilized 65 % HF/DMPU (Table 15). Ring opening of aziridinedicarboxylate **343a** was quite sluggish, in contrast to reactions of **343b**–**g**. In general, aziridines protected as *N*-Ts and *N*-Cbz derivatives gave better yields than *N*-Boc-protected ones.[26]

3.4. Ring Opening with Alkali and Tetraalkylammonium Hydrofluorides

Although using alkali and tetraalkylammonium hydrofluorides for the ring opening of aziridines is not completely unknown[14,101] (see, for example, the work of Kroutil et al.[102]), no recent reference was found with respect to the utilization of tetraalkylammonium hydrofluorides for the ring opening of aziridines and only a single example was found, where KHF_2 was used. Shibata and co-workers reported successful ring opening of bicyclic *N*-sulfonylaziridines with different potassium fluorides (KF, KF/2H_2O or KHF_2) in ionic liquid [bmim][BF_4], which served as both solvent and phase-transfer catalyst (Table 16). KF/2H_2O was effective enough to transform reactive oxiranes into fluorinated amines, but less reactive oxiranes performed better when KHF_2 was used. *N*-Nosylaziridines gave better yields than their *N*-tosyl analogues.[101]

3.5. Ring Opening with Tetrabutylammonium Fluoride (TBAF)

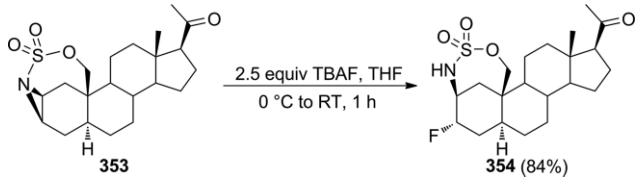
The ability of TBAF (for properties, see ***Section 2.5***) to open aziridine rings has been long known.[22] Since it is a highly nucleophilic fluorinating agent, which does not activate the substrate, and reactions follow the S_N2 mechanism. It is most effective on aziridines activated by an electron-withdrawing group on their nitrogen.[26,98] Together with pyridine/9HF, it is amongst the most commonly utilized reagents for aziridine ring opening. As a result, only selected examples will be shown, which illustrate reaction conditions and selectivities well, or are interesting from a synthetic view of point.

Durán et al. performed successful ring opening of steroid aziridine **353** with TBAF (Scheme 72). The regioselectivity of the reaction follows the Fürst–Plattner rule. The starting aziridine was prepared by Cu-catalyzed intramolecular aziridination of an unsaturated steroid sulfamate precursor. In addition, the reaction left the sulfonyl group attached to the nitrogen intact, contributing to the success of the ring opening step.[103]

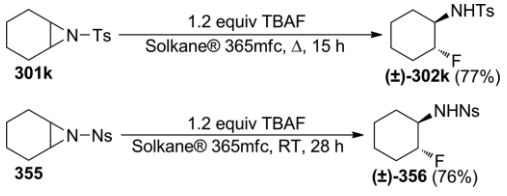
Shibata and co-workers reported successful ring opening of *N*-sulfonylcyclohexeneimines with TBAF in Solkane® 365mfc or 1,1,1,3,3-pentafluorobutane (Scheme 73). The results were comparable to the ones achieved with potassium fluorides in ionic liquid (see Table 16). Importantly, Solkane® 365mfc is a non-toxic, chemically stable hydrofluorocarbon solvent with low flammability. It is readily recovered by distillation (b.p. 40 °C), and can be considered to be a green solvent.[104]

During their synthetic work towards spisulosine and its analogues, Malik et al. reported ring opening of enantioenriched bicyclic aziridine **357** with TBAF (Scheme 74). The starting compound was prepared from a sulfamate by an enantioselective version of the Cu-catalyzed intramolecular aziridination.[105]

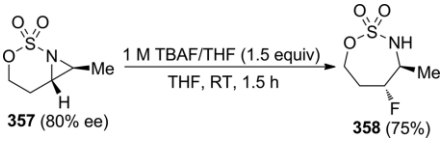
Hajra and co-workers presented stereocontrolled nucleophilic fluorination of spiroaziridine oxindoles at their tertiary sp^3 carbon with TBAF. During the initial optimizing experiments, both pyridine/9HF and TBAF gave good yields, but experiments with enantiopure **(*S*)-361a** showed complete racemization with HF/pyridine. TBAF, on the other hand, yielded enantiopure product **(*S*)-362a** with retention on carbon (Scheme 75). The authors explained this by anchimeric assistance of the oxygen or the nitrogen of the oxindole ring. This was supported by subjecting **(*S*)-321** to ring opening under these reaction conditions, which showed the opposite regioselectivity (F^- attacked mainly the less substituted carbon, see Scheme 76). The reactions were performed on other spiroaziridine oxindoles too (Table 17), showing that the electron-donating substituent on the oxindole nitrogen is necessary to achieve ring opening with TBAF. Substrates which did not react with TBAF can still be



Scheme 72. Stereo- and regio-selective ring opening of steroid aziridine **353** with TBAF.

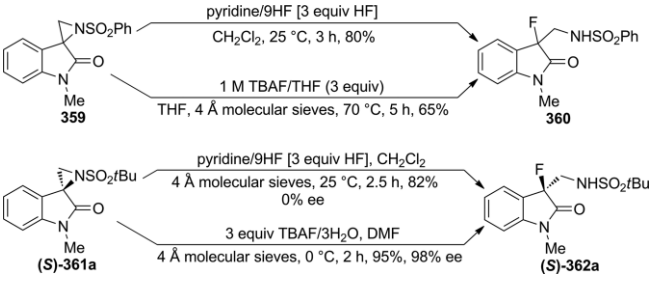


Scheme 73. Ring opening of *N*-sulfonylcyclohexeneimines with TBAF in Solkane® 365mfc.

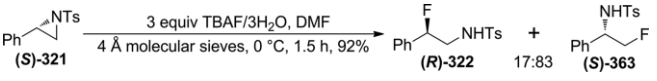


Scheme 74. Regio- and stereoselective ring opening of bicyclic aziridine **357** with TBAF.

opened with pyridine/9HF, but at the cost of their *ee* [and in the case of Boc-protected **(*S*)-361r**, the Boc group is lost too; see Scheme 77].[106]



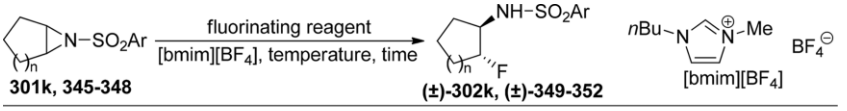
Scheme 75. Fluoride ring opening of spiroaziridine oxindoles.



Scheme 76. Fluoride ring opening of spiroaziridine oxindoles. All compounds had > 99 % *ee*.

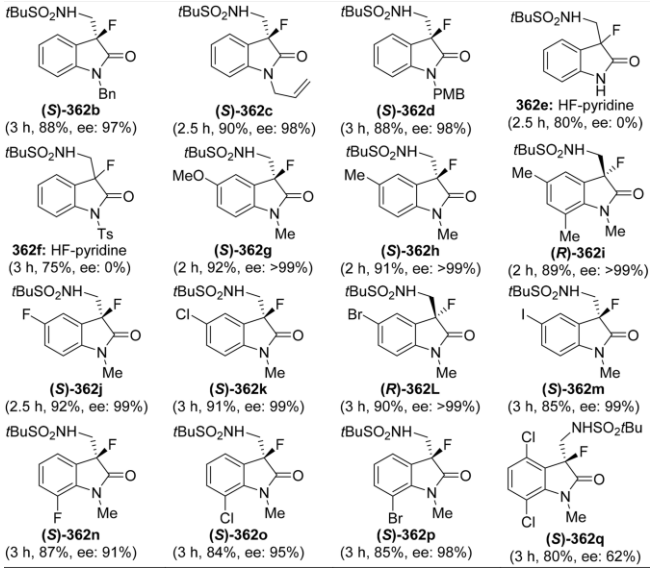
In 2008, a new TBAF-based reagent was reported: tetrabutylammonium tetra(*tert*-butyl alcohol) or TBAF(*t*BuOH)$_4$. The new reagent can be prepared easily in 92 % yield from hydrated TBAF by heating it in *t*BuOH/hexane to 90 °C, followed by recrystallization at RT. It is anhydrous and less hygroscopic then TBAF. Although the solvation of F^- ion by *t*BuOH decreases its reactivity compared to commercial TBAF sources (especially at RT), the lack of water means that no OH^- is present, which could compete with F^- during the nucleophilic attack resulting in by-products. Compared to anhydrous TBAF (prepared in situ from C_6F_6 with $nBu_4N^+CN^-$), the new reagent is much less basic thanks to solvation of F^- ion, helping to avoid elimination side reactions. TBAF(*t*BuOH)$_4$ was found to be the most efficient in polar solvents (protic or aprotic, depending on the reaction).[107]

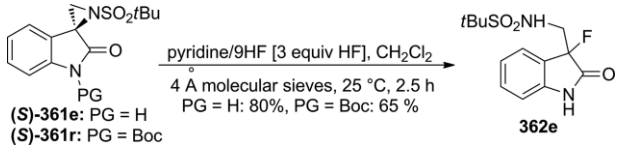
Table 16. Ring opening of bicyclic aziridines with potassium fluorides in an ionic liquid.



Substrate	Fluorinating reagent		Temperature	Time	Product	Isolated yield
	Type	Amount				
NTs **301k**	KF	5 equiv	60 °C	24 h	NHTs F **(±)-302k**	53%
	$KF/2H_2O$	5 equiv	40 °C	24 h		96%
NTs **345**	$KF/2H_2O$	5 equiv	80 °C	24 h	NHTs F **(±)-349**	18%
	KHF_2	5 equiv	80 °C	24 h		59%
NNs **346**	$KF/2H_2O$	5 equiv	60 °C	2 h	NHNs F **(±)-350**	85%
NTs **347**	$KF/2H_2O$	5 equiv	80 °C	24 h	NHTs F **(±)-351**	no reaction
	KHF_2	10 equiv	80 °C	120 h		52%
NNs **348**	$KF/2H_2O$	5 equiv	60 °C	2 h	NHNs F **(±)-352**	70%

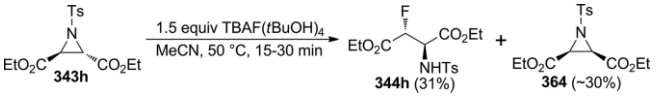
Table 17. Stereocontrolled nucleophilic fluorination of spiroaziridine oxindoles with TBAF. Reaction conditions: 3 equiv. TBAF/3H_2O, DMF, 4 Å molecular sieves, 0 °C. In the case of **(*S*)-361e**–**f**, TBAF resulted in no reaction, so results with pyridine/9HF [3 equiv. HF], CH_2Cl_2, 4 Å molecular sieves, 25 °C are shown instead. Most reactions started with the *S* enantiomer of the corresponding **361**, but **(*R*)-362i**,**L** were synthesized from **(*R*)-361i**,**L**. Reaction time is given together with the yield and the enantiomeric excess. PMB: 4-methoxybenzyl.





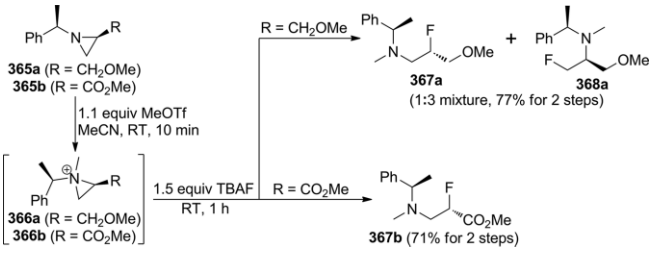
Scheme 77. Synthesis of **362e** from **(*S*)-361e** and **(*S*)-361r**.

Alluri and Riss utilized this new reagent for the ring opening on different *N*-protected enantiopure aziridinedicarboxylates, but only tosylated compound **343h** reacted under the applied conditions (Scheme 78).[26]



Scheme 78. Ring opening of (2*S*,3*S*)-aziridinedicarboxylate **343h** with TBAF(*t*BuOH)$_4$. The basicity of F^- enabled formation of achiral by-product **364** by epimerization.

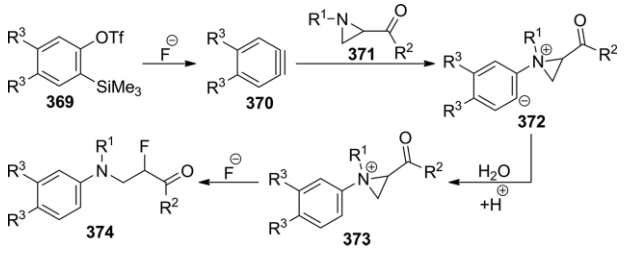
During their studies of the regioselectivity of aziridine/aziridinium ion ring opening with different nucleophiles, D'hooghe et al. activated chiral aziridines **365a**,**b** with MeOTf in MeCN. This reagent produced aziridinium triflates **366a**,**b**, which were stable in the resulting MeCN solutions. Nucleophiles were added to these solutions without isolation or purification of the aziridinium salt intermediate. Reactions of **366a**,**b** with TBAF had rather different regioselectivity (Scheme 79). On the one hand, compound **366a** was preferentially attacked by the F^- ion at the less substituted aziridine carbon, which is a result of kinetic control according to theoretical calculations. On the other hand, transformation of aziridinium ion **366b** was completely regioselective, only the aziridine carbon adjacent to the ester group was attacked by the F^- ion. This was accounted for by the activating effect of the carboxylate group.[24]



Scheme 79. Regioselectivity of aziridinium ion ring opening with TBAF.

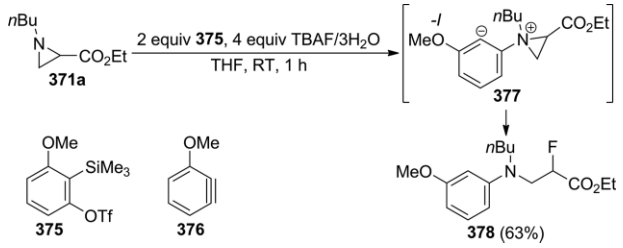
With the aim of obtaining α-fluoro-β-amino acids, Tang et al. activated aziridinecarboxylates by *N*-arylation with dehydrobenzenes in the presence of fluoride as nucleophile. Since dehydrobenzenes can be generated from 2-(trimethylsilyl)phenyl triflates with fluoride, a one-pot reaction seemed plausible. Experiments with fluoride sources showed that the presence of water greatly improves the yield, presumably by protonating the zwitterionic intermediate thereby inhibiting some possible side reactions. Consequently, cheap TBAF/3H_2O was utilized. Ring opening of *N*-arylaziridinium carboxylates was completely regioselective, similar to compound **366b** (see Scheme 79). Table 18 shows the complete reaction mechanism and summarizes results with symmetrical dehydrobenzenes. In the case of unsymmetrical dehydrobenzene **376** (obtained from precursor **375**), its reaction with aziridine **371a** showed the expected regioselectivity. That is, nucleophilic attack on the further carbon of the C≡C bond is preferred and, therefore, the

Table 18. One-pot synthesis of α-fluoro-β-amino acids from dehydrobenzene precursor **369**, aziridine **371** and TBAF/3H_2O. Reaction conditions: racemic aziridine **371** was treated with 2 equiv. aryne precursor **369** and 4 equiv. TBAF/3H_2O in THF at RT for 1 hour.



Aziridine	R^1	R^2	Aryne precursor	R^3	Product	Isolated yield
371a	*n*Bu	OEt	**369a**	H	**374a**	83 %
371b	*n*Bu	OMe	**369a**	H	**374b**	73 %
371c	*n*Bu	O*i*Pr	**369a**	H	**374c**	90 %
371d	*n*Bu	O*t*Bu	**369a**	H	**374d**	65 %
371e	cyclohexyl	OEt	**369a**	H	**374e**	90 %
371f	*i*Pr	OEt	**369a**	H	**374f**	92 %
371g	*t*Bu	OEt	**369a**	H	**374g**	82 %
371h	Bn	OEt	**369a**	H	**374h**	88 %
371i	4-methoxybenzyl	OEt	**369a**	H	**374i**	84 %
371a	*n*Bu	OEt	**369b**	Me	**374j**	86 %
371k	*n*Bu	Me	**369a**	H	**374k**	57 %
371L	Bn	Me	**369a**	H	**374L**	60 %
371k	*n*Bu	Me	**369b**	Me	**374m**	53 %

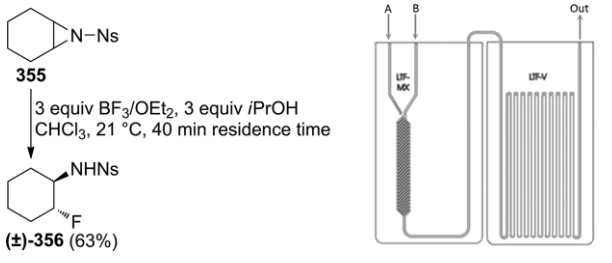
negative charge will be formed closer to the MeO group which stabilizes it by *–I* effect, yielding **378** as the single product (Scheme 80).[108]



Scheme 80. Reaction of asymmetric dehydrobenzene **376** with aziridine **371a** and fluoride ions.

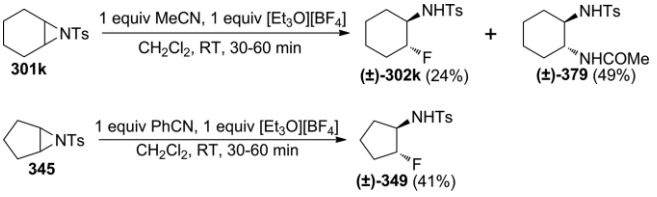
3.6. Ring Opening with Boron Trifluoride Etherate (BF_3/OEt_2) and Related Reagents

Although ring opening of aziridines with BF_3/OEt_2 is not unknown,[22] this reaction is rarely applied. Possibly, the strong Lewis acidic nature of BF_3 can cause various side reactions like rearrangements (see *Section 2.6*). As a result, there is only a single use of this reaction published recently. Hsueh et al. successfully transformed *N*-nosylcyclohexene imine **355** with BF_3/OEt_2 into *trans*-fluorohydrin **(±)-356** utilizing flow chemistry. The reaction (Scheme 81) was performed in a two-input microreactor with 2.0 mL total reaction volume at 21 °C with 40 min residence time (*Solution A*: 0.5 mmol aziridine in 2.0 mL of $CHCl_3$; *Solution B*: 1.5 mmol BF_3/OEt_2 and 1.5 mmol *i*PrOH in 2.0 mL of $CHCl_3$). Using a BF_3/*i*PrOH system for aziridine ring opening with fluoride was reported first by Ding et al.[109] The presence of *i*PrOH greatly accelerates the ring opening, whereas other alcohols were less effective. Interestingly, the original procedure used 0.35 equiv. BF_3 and 0.35 equiv. *i*PrOH, while Hsueh et al. used 3 equiv. BF_3 and 3 equiv. *i*PrOH. After work-up and chromatography, product **(±)-356** was obtained in 63 % yield. Synthesis of aziridine **355** was also possible utilizing flow methods.[110]



Scheme 81. Aziridine ring opening with BF_3/*i*PrOH in a flow system.

The ability of HBF_4/OEt_2 for oxirane ring opening was discussed in ***Section 2.6***. A slightly similar reaction was reported by Singh and co-workers. During their studies of Lewis-acid-catalyzed formal [3+2] cycloaddition of aziridines and nitriles, formation of fluorohydrins was observed in the case of some aziridine + nitrile combinations when $Et_3O^+BF_4^-$ was used as catalyst (Scheme 82).[111]

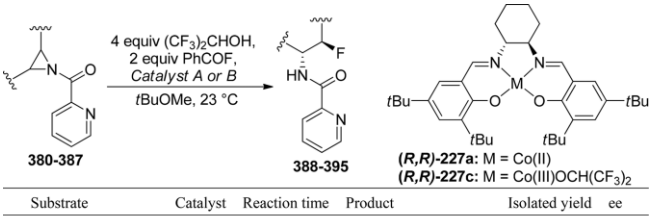


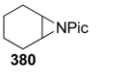
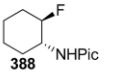
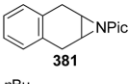
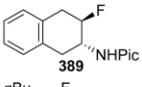
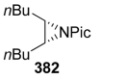
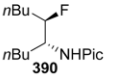
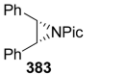
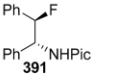
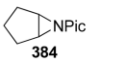
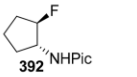
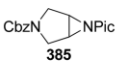
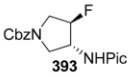
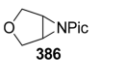
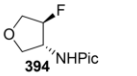
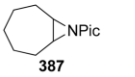
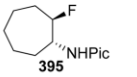
Scheme 82. Accidental ring opening of *N*-tosylaziridines with triethyloxonium fluoroborate.

3.7. Ring Opening with Transition Metal Catalysis

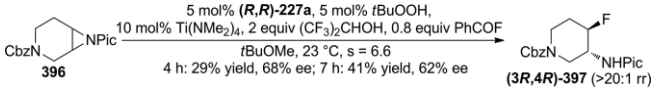
Despite the possible advantages of transition metal catalysis (for example, new reaction pathways or enantioselective reactions), there is only one recent example where transition metal catalysis is utilized for the fluoride ring opening of aziridines. After successfully using their slow in situ fluoride generation method for aziridine ring opening,[98] Kalow and Doyle attempted to develop an enantioselective version. Similar to their method for the enantioselective ring opening of oxiranes with fluoride,[79,80] a chiral Co(salen) complex was chosen as catalyst. However, because Co(salen) Lewis acids are ineffective for the

Table 19. Transition-metal-catalyzed enantioselective desymmetrization of *meso* aziridines. Pic = picolinoyl. *Catalyst A*: 5 mol-% **(*R*,*R*)-227a**, 5 mol-% *t*BuOOH, 10 mol-% $Ti(NMe_2)_4$. *Catalyst B*: **(*R*,*R*)-227c**·$(CF_3)_2CHOH$, 10 mol-% $Ti(NMe_2)_4$.



Substrate	Catalyst	Reaction time	Product	Isolated yield	ee
 380	A	24 h	 388	93%	84%
 381	A	24 h	 389	66%	80%
 382	B	48 h	 390	75%	63%
 383	B	48 h	 391	51%	48%
 384	A	24 h	 392	46%	56%
 385	B	96 h	 393	48%	75%
 386	B	96 h	 394	27%	32%
 387	B	48 h	 395	33%	12%

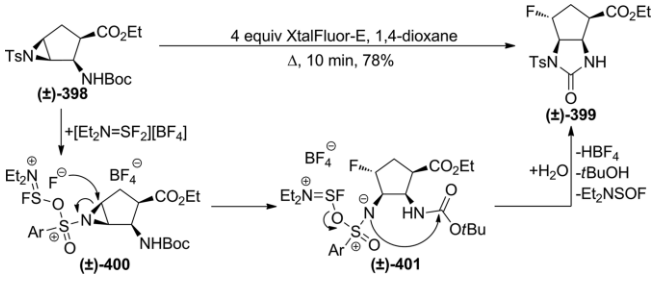
activation of protected aziridines, an achiral Lewis acid cocatalyst was added and the research focused on aziridine substrates with a chelating *N*-protecting group. Optimization showed that picolinamide-protected *meso* aziridines are efficiently transformed into β-fluoroamides even in the absence of achiral Lewis acid cocatalyst, but good enantioselectivity was only achieved when an oxophilic cocatalyst was present. For reactive substrates, the most effective condition was 5 mol-% **(*R*,*R*)-227a**, 5 mol-% *t*BuOOH, and 10 mol-% $Ti(NMe_2)_4$ with 2 equiv. PhCOF and 4 equiv. $(CF_3)_2CHOH$–*t*BuOOH quickly oxidizes the Co^{II} complex to the catalytically active Co^{III} complex. For substrates requiring extended reaction times, the use of 5 mol-% **(*R*,*R*)-227c**·$(CF_3)_2CHOH$ instead of 5 mol-% **(*R*,*R*)-227a** and 5 mol-% *t*BuOOH gave better results (Table 19). Monocyclic aziridines and aziridines fused to five- or six-membered rings were transformed efficiently. THF-fused aziridine **386** and cycloheptane-fused aziridine **387** gave poor results (they were mainly transformed into oxazolines by intramolecular nucleophilic attack). In the case of *cis*-diphenyl aziridine **383**, cationic rearrangements occurred with somewhat depressed yield and enantioselectivity. With slight modifications, the reaction was capable of efficient kinetic resolution of piperidine derivative **396** (Scheme 83).[112]



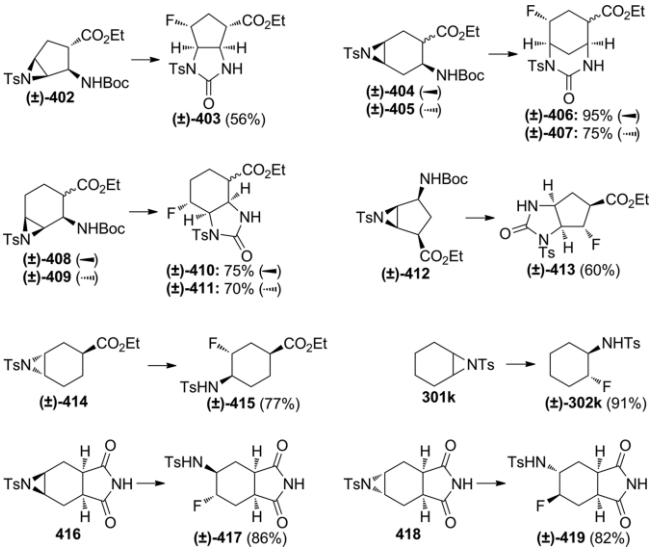
Scheme 83. Kinetic resolution of aziridine **396** by transition-metal-catalyzed enantioselective ring opening with fluoride.

3.8. Ring Opening with Deoxyfluorinating Reagents

Utilization of deoxyfluorinating reagents for fluoride ring opening of aziridines is a rather new approach. In 2015, Nonn et al. reported successful ring opening of *N*-tosylaziridine **398**, derived from a cyclopentene β-amino ester, with XtalFluor-E ($[Et_2N{=}SF_2][BF_4]$). Due to the presence of the NHBoc group, initial aziridine ring opening to intermediate **(±)-401** was followed by formation of an imidazolidinone ring (Scheme 84). This fast and efficient reaction also worked well with other *N*-tosylaziridines derived from unsaturated cyclic β- and γ-amino esters. It was also extended to less-functionalized *N*-tosylaziridines, where the lack of the NHBoc group resulted only in aziridine ring opening (Scheme 85).[113]



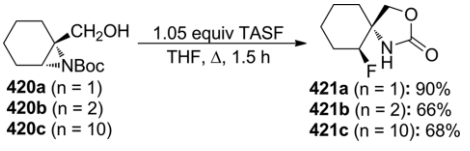
Scheme 84. Mechanism of aziridine ring opening with XtalFluor-E. Ar = 4-toluyl.



Scheme 85. Ring opening of aziridines with XtalFluor-E. Reaction conditions: 4 equiv. XtalFluor-E, 1,4-dioxane, under reflux for 10 minutes.

3.9. Miscellaneous Reactions for Fluoride Ring Opening of Aziridines

Gilmour and co-workers used tris(dimethylamino)sulfonium difluorotrimethylsilicate {TASF, $[(Me_2N)_3S]^+[Me_3SiF_2]^-$} as fluoride source for the ring opening of *N*-Boc-activated hydroxymethyl-substituted chiral aziridines **420a**–**c**. After aziridine ring opening with fluoride, the CH_2OH group participated in subsequent cyclization to provide oxazolidin-2-ones **421a**–**c** (Scheme 86).[91]

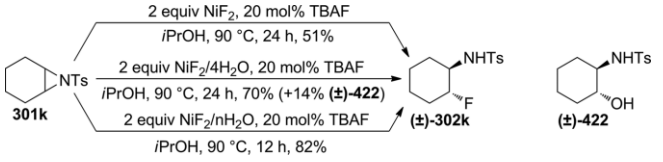


Scheme 86. Ring opening of chiral aziridine alcohols **420a**–**c** with TASF.

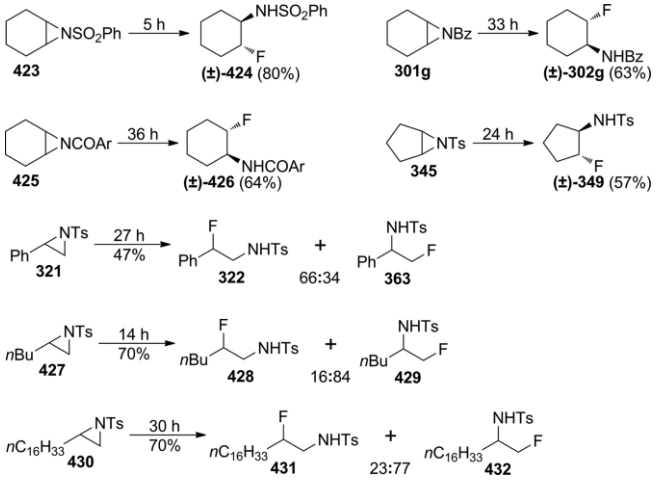
Zhang et al. reported that ring opening of aziridine **301k** can be accomplished by heating to 90 °C in *i*PrOH with 2 equiv. nickel(II) fluoride in the presence of 20 mol-% TBAF (Scheme 87). $NiF_2/4H_2O$ gave more β-fluoroamine than anhydrous NiF_2, but it also produced some β-amino alcohol **(±)-422** through ring opening with water. Partially dried NiF_2 (NiF_2/nH_2O) produced the best results and the presence of TBAF was crucial to achieve successful transformations. The method worked well with other *N*-activated aziridines too, although monosubstituted aziridines tended to form product mixtures (Scheme 88).[114]

Ji et al. activated chiral aziridine **433** by intramolecular ring closure to form aziridinium tosylate **434**. Salt **434** was stable in MeCN and studying the selectivity of its ring opening reactions with different nucleophiles showed that in contrast with other halides, fluoride ion produced both possible ring opening products (Scheme 89).[25]

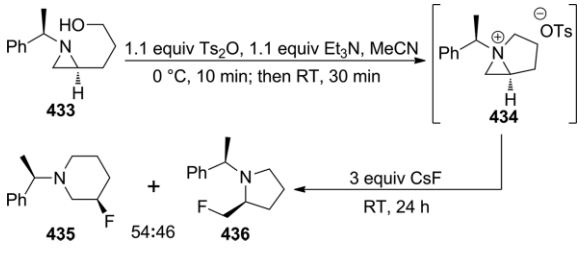
Bower and co-workers successfully opened bicyclic aziridine **437** with phenylacetyl fluoride (Scheme 90). The reagent acti-



Scheme 87. Transformation of aziridine **301k** into fluorinated amine and fluorohydrin by treatment with TBAF/NiF_2 systems.

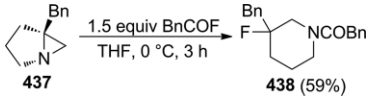


Scheme 88. Fluoride ring opening of *N*-activated aziridines with TBAF/NiF_2/nH_2O. Reaction conditions: 2 equiv. NiF_2/nH_2O, 20 mol-% TBAF, *i*PrOH, 90 °C, time noted on the arrow. Ar = 4-chlorophenyl. Regioisomeric ratios were determined by ^{1}H-NMR.



Scheme 89. Ring opening of enantiopure aziridinium ion **434** with CsF.

vated the substrate as an *N*-acylaziridinium salt, which then underwent ring opening with the fluoride formed during the activation process.[115]



Scheme 90. Aziridine ring opening with an acyl fluoride.

4. Conclusion and Outlook

Organofluorine chemistry represents an expanding area in drug research and synthetic chemistry and it has raised increasing interest over the past decade. It is expected that fluorinated small-molecular entities (azaheterocycles, functionalized alicycles, amino acids, etc.) as interesting scaffolds or building blocks will be of high importance in drug research in years to come. Accordingly, their syntheses and the development of novel synthetic methods towards these derivatives have currently become a hot topic in synthetic chemistry. Among the synthetic protocols towards fluorine-containing derivatives, the formation of small heterocycles (aziridines and oxiranes) followed by their opening with fluoride is considered to be highly applicable procedures in view of selectivity, stereocontrol, and creation of novel functional groups still representing main challenges in organic chemistry.

During the last decade, there has been considerable development in the area of oxirane and aziridine ring opening with fluoride. Various methods are available to transform oxiranes into fluorohydrins through mechanisms ranging from S_N2 to S_N1. TBAF and HBF_4/OEt_2 turned out to be potent agents for oxirane ring opening with F^- (note that HBF_4/OEt_2 only works efficiently with epoxyamines). One-pot epoxidation/fluoride ring opening protocols (overall reaction: olefin fluorohydroxylation) were also developed. Transition-metal-catalyzed methods for enantioselective oxirane ring opening were significantly improved by utilizing Co(salen) complexes with HF formed slowly in situ.

Aziridine ring opening with fluoride was originally a less studied topic, but now a number of methods are available for the ring opening of different aziridines with fluoride. The theoretical background of the regioselectivity of these reactions was also explored. Ring opening of *N*-activated aziridines was originally performed with TBAF, pyridine/9HF or metal (hydro)fluorides. Other reagents discovered recently are Et_3N/3HF, HF/DMPU, XtalFluor-E and (with the exception of *N*-tosylaziridines) slowly in situ formed DBN/$(HF)_n$. Aziridines with a chelating *N*-activating group can also be subjected to transition-metal-catalyzed enantioselective ring opening. Transformation of *N*-unactivated aziridines to β-fluoroamines was originally accomplished with pyridine/9HF (under more forcing conditions than analogous reaction of *N*-activated aziridines). Now, Et_3N/3HF (under more forcing conditions) and DBN/$(HF)_n$ slowly formed in situ can also be utilized. Some interesting *N*-activation methods (dehydrobenzene or acyl fluoride) were also reported.

There is still room for development, especially gaps to fill in the area of transition-metal-catalyzed processes. A synthetically interesting aspect of these reactions is the possibility of new reaction pathways, where the transition metal exerts a strong influence on regio- and stereoselectivity, such as the Rh-catalyzed ring opening of vinyl oxiranes. It is also worthwhile to note that there are only a few methods for the ring opening of *N*-unactivated aziridines with fluoride, and none of these is enantioselective.

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Keywords: Fluorination · Oxiranes · Aziridines · Ring opening · Selectivity

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