FLUORINATED HETEROCYCLIC COMPOUNDS

Synthesis, Chemistry, and Applications

Edited by

VIACHESLAV A. PETROV
DuPont Central Research and Development
Wilmington, DE, USA

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PREFACE

Heterocycles represent a larger group of organic compounds and play an important role in all aspects of pure and applied chemistry. The subgroup of this class called *fluorinated* heterocycles is relatively "young," since the intensive development of the synthetic chemistry of fluorinated heterocycles started only after World War II. Nowadays fluorinated heterocyclic compounds can be found among potent pharmaceuticals, crop protection agents, and products of technical importance. This merging area of organic, heterocyclic, and fluoroorganic chemistry is still rapidly growing and in the past six decades a large number of fluorinated heterocyclic materials have been discovered.

Several books containing sections on chemistry of fluorinated heterocyclic compounds have been published in last fifteen years. A short, nonexhaustive list includes *Organofluorine Chemistry* by T. Hiyama, Springer, 2000; *Modern Fluoroorganic Chemistry* by P. Kirsch, Wiley-VCH, 2004; *Fluorine in Organic Chemistry* by R. Chambers, Blackwell Publishing/CRC Press, 2004; and *Organofluorine Chemistry* by K. Uneyama, Blackwell Publishing, 2006. Some technical applications of selected fluorinated heterocycles were covered in Chapters 10, 11, 13, 15, 19, 21, and 24 of *Organofluorine Chemistry: Principles and Commercial Applications* by R.E. Banks, B.E. Smart, and J.C. Tatlow (Eds.), Plenum Press, published in 1994. Interestingly, so far only one book fully dedicated to the chemistry of fluorinated heterocyclic materials was published (Г. Г. Фурин, "Фторсодержащие Гетероциклические Соединения", Новосибирск, Наука, 2001 (G.G. Furin, *Fluorinated Heterocyclic Compounds*, Novosibirsk, Nauka, 2001)). Unfortunately, this monograph written in Russian language was not translated and due to its relatively small print run (550 prints), it is not readily available to the international chemical community. The list would not be complete without the recently published

book *Fluorinated Heterocycles* by A. Gakh and K. Kirk (Eds.), ACS Symposium Series 1003, American Chemical Society, Washington, DC, 2009, dealing with different aspects of synthetic methodology for the preparation of selected classes of fluorinated heterocycles.

The diversity, complexity, and unique behavior of fluorinated heterocycles combined with a wide range of applications and the fact that a large body of experimental material has to be reviewed make the comprehensive coverage of the subject extremely difficult. As a compromise, it was decided to confine this book to the most representative routes, chemical transformations, and applications of fluorinated heterocycles containing oxygen, nitrogen, and sulfur (and to some extent other elements such as phosphorous and selenium) and also to limit a review of the literature to publications in open rather (than patent) scientific literature. The synthesis and transformations of three- and four-membered heterocycles containing oxygen, nitrogen, and sulfur are covered in Chapters 1 and 2, respectively. Due to a substantial number of publications on the synthesis and chemistry of five-membered heterocycles, it was decided to divide into two groups. The synthesis and chemistry of nitrogen-containing heterocycles are reviewed in Chapter 3; heterocycles containing oxygen, sulfur, and other elements are dealt with in Chapter 4. Data on the synthesis of fluorinated sugars are given in Chapter 5.

A similar approach was used in case of aromatic fluorinated heterocycles. Ring-fluorinated pyridines containing one, two, and three fluorine substituents are reviewed in Chapter 6, while Chapter 7 focuses on the synthesis and typical chemical transformations of aromatic heterocycles containing perfluoroalkyl groups.

Since *perfluorinated* heterocycles have distinct and often unique chemistry, this group was considered as a separate category and data on perfluorinated aromatic and nonaromatic compounds are given in Chapters 8 and 9, respectively. The information on seven-membered and larger ring heterocycles, including perfluorinated crown ethers and polyfluorinated macrocycles, is provided in Chapter 10, which concludes Part I of the book.

Part II contains information on different applications of fluorinated heterocycles. Chapter 11 focuses on the use of fluorinated heterocycles in agricultural products, Chapter 12 summarizes data on pharmaceuticals containing fluorinated heterocycles, and Chapter 13 reviews different aspects of technical applications of fluorinated heterocycles.

This book is intended for advanced students, graduates, and researchers from both academia and industry working in the area of organic, heterocyclic, and fluoroorganic chemistry and looking for a survey on the synthetic methods, chemistry, and applications of major classes of fluorinated heterocycles.

This book is written by an international team of world-recognized experts in the area of organic and industrial chemistry of fluorine. I would like to thank all contributors for their time and hard work, which made this first book on the chemistry and applications of fluorinated heterocycles possible. I am also indebted to Susan Farmer of Wiley-Blackwell, who came up with the idea of this book, for all her support and encouragement and also to the staff of the editorial office of Wiley-Blackwell for their cooperation and understanding.

This book would not have been possible without the encouragement of my family and I would like to thank Olga, Masha, Alexandra, and Andrew for all their help and continuous support.

February 2009 VIACHESLAV PETROV

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INTRODUCTION: NOMENCLATURE OF POLYFLUORINATED HETEROCYCLES

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There are three types of nomenclature used for heterocyclic compounds.[1] Many heterocycles have *trivial* names, which are based on their occurrence, special properties, or historical reasons such as discovery of particular material. *Systematic* names of heterocyclic compounds derived from the structure of the compound are governed by IUPAC rules, which are divided into two groups: the Hantzsch–Widman and replacement nomenclatures.[1] In this book, we were trying to follow the guidelines for naming the heterocyclic compounds, which are summarized in Chapter 2 of the excellent book *The Chemistry of Heterocycles: Structures, Reactions, and Applications*.[1]

It should be pointed out that currently both trivial and systematic names are commonly used for naming the heterocyclic compounds. For example, an organic chemist will recognize without any difficulty the structures connected to names such as furane, pyrrole, pyrrolidine, pyrazole, imidazole, pyridine, or piperidine, despite the fact that all these names are trivial. On the other hand, the complex heterocycles require more sophisticated approaches in order to avoid ambiguity and correctly translate the chemical structure into the name. For these, compound names are often made using either trivial name (e.g., indazole for benzopyrazole, benzimidazole, indole, and isoindole) or the Hantzsch–Widman nomenclature, for example, 1,2,3- or 1,2,5-oxadiazoles, 1,3-dioxolane, 1,2- or 1,3-dithiolane, and 1,3- or 1,4-dioxane.[1] It should be noted that the Hantzsch–Widman nomenclature treats the unsaturated heterocycle with maximum number of conjugated double bonds as *parent* compound.[1] This adds another layer of complexity, giving rise to names such as

tetrahydrofurane, tetrahydrothiophene, 2,3-dihydropyrrole, or 3,4-dihydrofurane. As it can be seen from the mentioned examples, names of heterocyclic compounds form a separate terminological group and the work with this terminology requires basic knowledge of the "language" used in this area of organic chemistry.

Heterocycles containing limited amount of fluorinated substituents (usually 1–3) can be named using trivial names or conventional nomenclature in combination with indication of the position of fluorinated substituents, for example, 2-fluoro-4-trifluoromethylpyridine. The situation becomes more complicated in case of polyfluorinated and completely fluorinated heterocycles. In case of heterocycles with relatively small number of fluorinated substituents and well-defined structures, Greek or Latin numeral roots can be used.[2] Names such as hexafluoropropene oxide, 2,2-bis (trifluoromethyl)oxirane, 2,2,3,3-tetrafluorooxetane, tetrakis(trifluoromethyl)furane, pentafluoropyridine, tetrafluoropyridazine, tetrafluoropyrimidine, and heptafluoroquinoline are unambiguous and commonly accepted (see Fig. 0.1).

It should be pointed out that for completely fluorinated materials, one could use the so-called perfluoro- or *F*-nomenclature.[2] The prefix perfluoro- or symbol *F*- have the same meaning and combined with trivial or standard systematic name of a heterocycle, it indicates that in parent compound all hydrogens *connected to carbons* were replaced by fluorines. Examples of different names for heterocycles, such as perfluoropropene oxide or *F*-propene oxide, perfluoro-(2,2-dimethyloxirane) or *F*-(2,2-dimethyloxirane), and so on, are shown in Fig. 0.2.

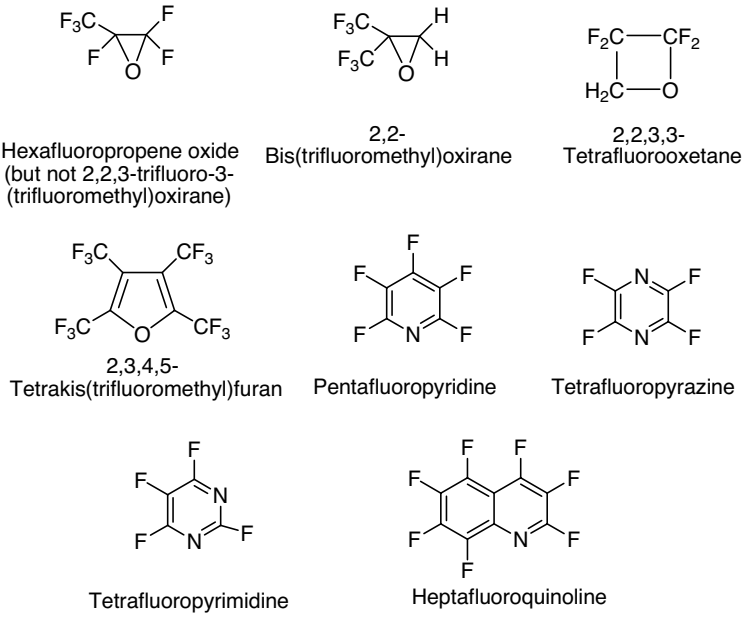

FIGURE 0.1 Nomenclature of polyfluorinated heterocycles.

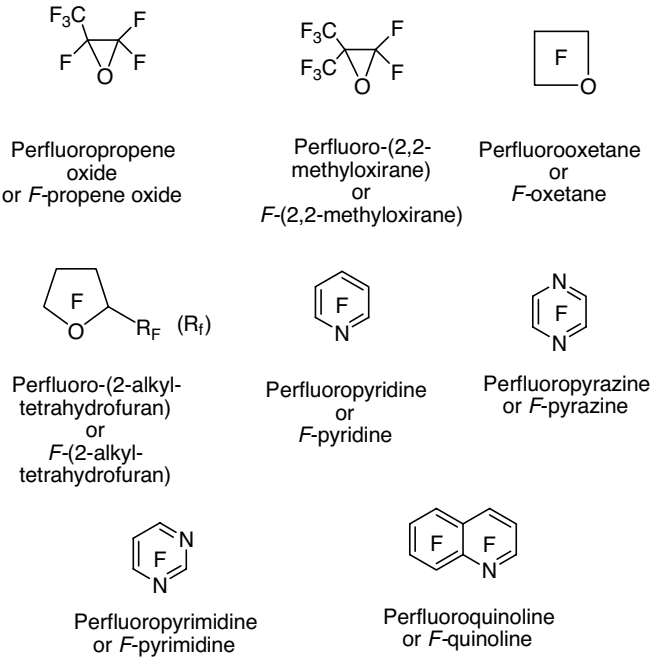

FIGURE 0.2 Examples of perfluoro- and *F*-nomenclatures of fluorinated heterocycles.

It should also be pointed out that the symbol "F" placed in the center of the heterocycle has the same meaning and denotes perfluorinated compound (see Fig. 0.2).[2]

Perfluoro- or *F*-nomenclatures are extremely convenient for the heterocyclic systems containing a large number of fluorines or perfluoroalkyl substituents. For example, listing all positions of 12 fluorine substituents in *F*-thiepane (see Fig. 0.3) makes systematic name of this compound long and cumbersome.

It should also be pointed out that the symbols R_F or Ar_F are also often used and they usually refer to monovalent perfluoroalkyl or perfluoroaryl group.[2] Despite the fact that R_F or Ar_F are recommended abbreviation of the corresponding groups, nowadays in scientific literature, symbols R_f or Ar_f are also used as equivalent of perfluoroalkyl or perfluoroaryl groups, respectively. In this book, both types of abbreviations can be found, although we were trying to adhere to original R_F or Ar_F abbreviations.

It is noteworthy that the case of cyclic polyfluorinated amines is special. Since the prefix perfluoro- is used to show the substitution of all hydrogens in the molecule with exception of those whose replacement affects the functionality,[2] the name perfluoropiperidine should be used for the compound containing NH group, but not for *N*-fluoroamine, which should be called perfluoro-*N*-fluoropiperidine (Fig. 0.3).

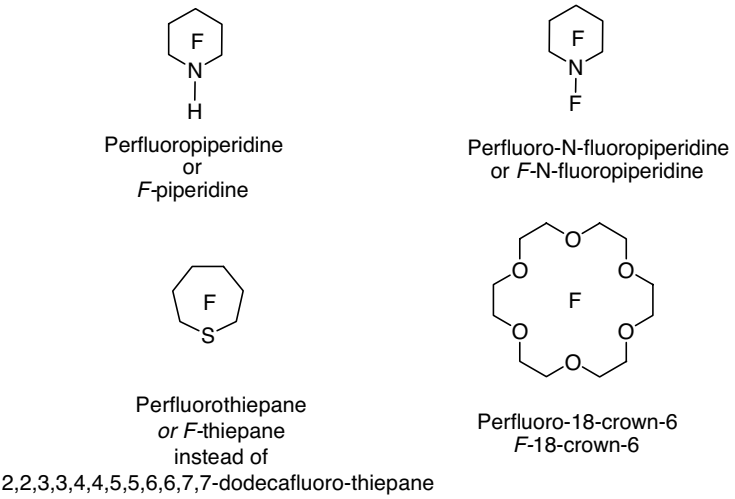

FIGURE 0.3 Examples of nomenclature for perfluorinated heterocycles.

Due to overlap between perfluoro- and heterocycle nomenclatures, some names may be rather complicated and contradictory, such as *perfluoro*(*tetrahydro*furane), for the compound that has no single hydrogen in the molecule!

For the same reason naming of perfluorinated, nonaromatic derivatives may be difficult and in this case, replacement nomenclature is used, despite the fact that this it is recommended by IUPAC for use with larger ring heterocycles. The use of replacement nomenclature allows simplifying the process and shortening some names of heterocycles. For example, in case of two compounds shown in Fig. 0.4, perfluoro-1-azacyclopentene-1 and perfluoro-1-azacyclohexene-1 names are often used instead of perfluoro-3,4-dihydro-*2H*-pyrrole and perfluoro-2,3,4,5-tetrahydropyridine in scientific literature.

In this book, although we were trying to follow recommendations given in Refs 1 and 2, due to complexity of the subject it was difficult to keep it consistent, so the reader of the book should be prepared to find all types of nomenclatures and names of polyfluorinated heterocyclic compounds used in practice.

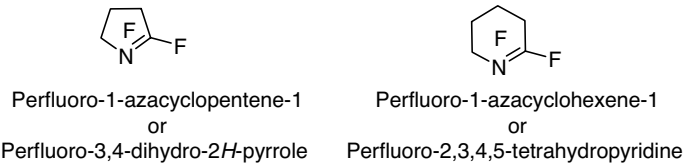

FIGURE 0.4 Examples of replacement and systematic nomenclatures for naming the perfluorinated nonaromatic compounds.

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PART I

SYNTHESIS AND CHEMISTRY OF FLUORINATED HETEROCYCLES

1

FLUORINATED THREE-MEMBERED RING HETEROCYCLES

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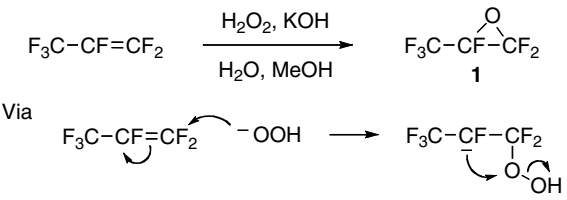
1.1 FLUOROOXIRANES[1–4]

1.1.1 Synthesis

Highly fluorinated oxiranes contrast sharply with their hydrocarbon counterparts with regard to both methods for their synthesis and chemical reactivity. Hydrocarbon-derived oxiranes are normally prepared by cyclization of an alcohol with a leaving group on the β-carbon or by electrophilic epoxidation of an alkene, but perfluoro- and halofluorooxiranes are usually synthesized via nucleophilic attack on the corresponding alkene. For example, hydrogen peroxide and aqueous alkali with a water-miscible cosolvent or phase-transfer agent have been used to prepare hexafluoropropylene oxide (HFPO, **1**).[5] Hydroperoxide anion adds to C1 of the alkene, and the resulting carbanionic center attacks at oxygen, breaking the weak O–O bond and expelling the hydroxide ion.



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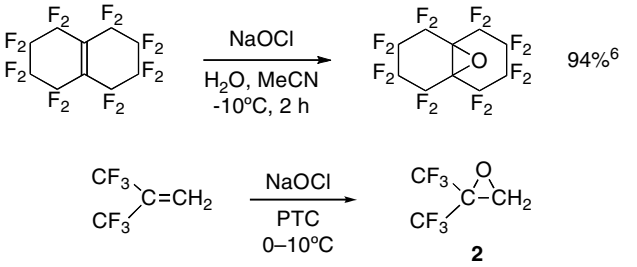
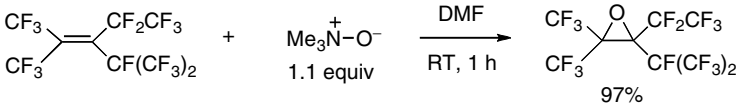
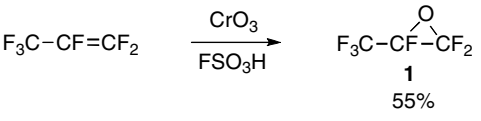
Yields are often higher with sodium hypochlorite, which reacts analogously to hydrogen peroxide, with expulsion of chloride ion. The oxidation of *cis*- and *trans*-perfluoroalkenes proceeds stereospecifically with retention of configuration.[2] 2,2-Bis (trifluoromethyl)ethylene is oxidized to **2** in 65–75% yield by sodium hypochlorite with phase-transfer catalysis (PTC) using Aliquat®-336.[7]

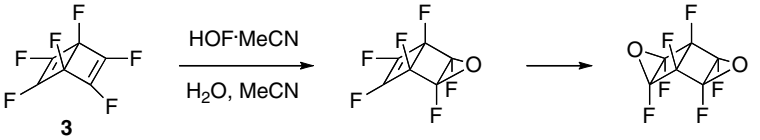


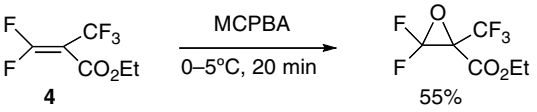
Another nucleophilic reagent that is effective with tri- and tetrasubstituted perfluoroalkenes is trimethylamine oxide. Attack by the oxygen atom is followed by elimination of trimethylamine. The amine oxide can be used catalytically as well as stoichiometrically, as *m*-chloroperbenzoic acid (MCPBA) or urea/hydrogen peroxide reoxidizes the amine.[8]



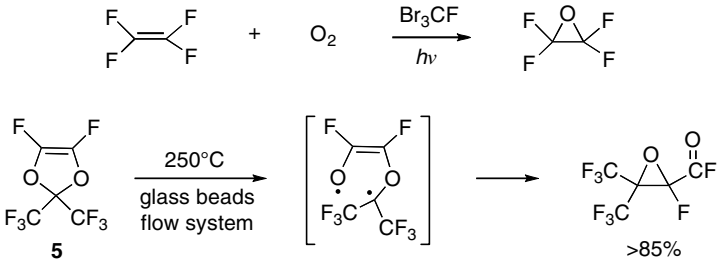
Though it requires vigorous conditions and is less common than nucleophilic epoxidation, electrophilic epoxidation of a perfluoroalkene is possible with the potent combination of chromic oxide and fluorosulfonic acid, providing another route to hexafluoropropylene oxide (**1**).[9] As a further example of electrophilic attack, hexafluoro Dewar benzene (**3**) is transformed into either a mono- or a diepoxide by the powerful hypofluorous acid–acetonitrile complex.[10] The fact that the much weaker electrophile MCPBA readily epoxides such electron-deficient alkenes as ethyl pentafluoromethacrylate (**4**)[11] suggests that it actually reacts via nucleophilic attack at the β-carbon.





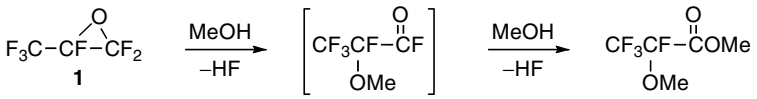


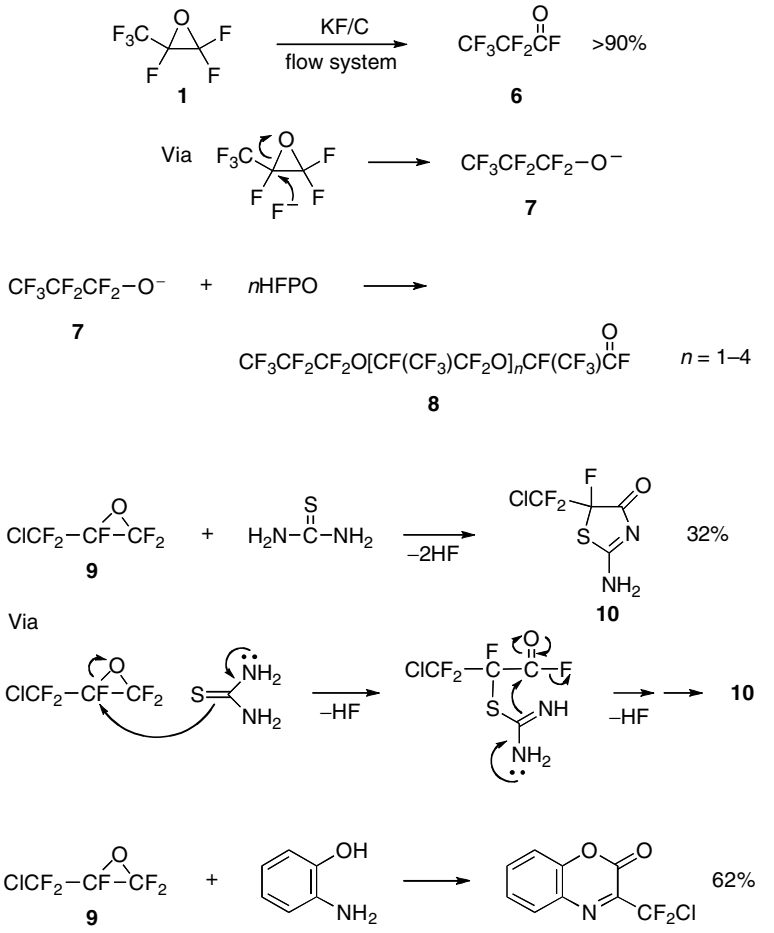
Oxirane formation can also occur via free radical mechanisms, as in the reaction of certain fluoroalkenes with oxygen. Under pressure at elevated temperatures, oxygen alone can suffice, but activation is frequently provided in the form of radical initiators (e.g., tribromofluoromethane) and ultraviolet light.[12] Thermolysis of dioxole **5**, comonomer from which DuPont's Teflon-AF® is made, offers an unusual route to an oxirane. Rearrangement of the heterocycle presumably takes place via a biradical intermediate.[13]



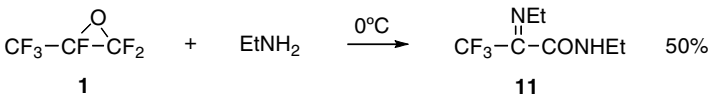
1.1.2 Reactions with Nucleophiles

Fluorooxiranes are easily ring opened by nucleophiles. Treatment of HFPO (**1**) with methanol, for example, affords methyl 2-methoxytetrafluoropropionate (96% yield) via the acid fluoride.[14] Nucleophilic attack on HFPO nearly always takes place at C3, the more hindered carbon, a surprising result for an S_N2 reaction.[3] This may be attributable at least in part to stabilization by negative hyperconjugation of the developing oxyanion in the ring-opening transition state. Both the X-ray structure and calculations show that this effect is very large in the trifluoromethoxide ion.[15] Passed over KF/activated carbon, HFPO is isomerized in excellent yield to perfluoropropionyl fluoride (**6**).[16] However, reaction of **1** with CsF in tetraglyme results in oligomerization.[17] The intermediate perfluoropropoxide ion (**7**) attacks another molecule of HFPO, and the process repeats itself to afford oligomers terminating as acyl fluorides (**8**). Fluorodecarbonylation of **8** produces the inert Krytox® fluids, which are useful as vacuum pump oils.[18] Thiourea behaves as a bifunctional nucleophile in its reaction with oxirane **9**, giving thiazolidinone **10**, with initial attack again at the more substituted carbon. 2-Aminophenol reacts with **9** in analogous fashion.[19]

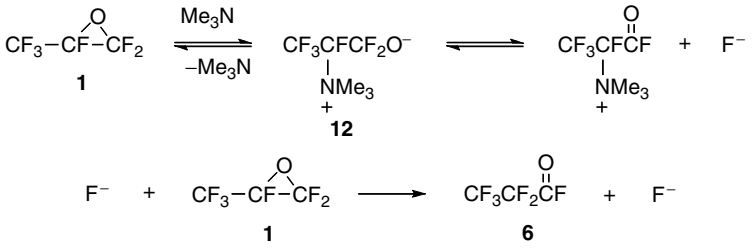




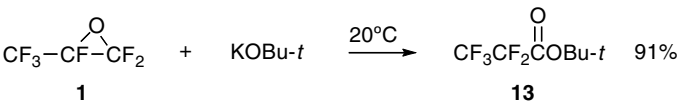
The primary amine ethylamine attacks at C3 of HFPO (**1**) to yield an acyl fluoride that reacts further to afford iminoamide **11**,[14] but the tertiary amine trimethylamine isomerizes **1** to perfluoropropionyl fluoride (**6**) almost quantitatively (30 h, 100°C).[20]



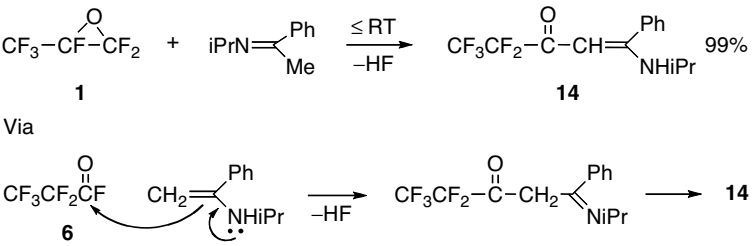
The mechanism shown below, in which the 3° amine just functions as an initiator, differs from others proposed in the literature[20,21] by avoiding unlikely substitution steps. Alternatively, fluoride migration may occur in the betaine **12** with expulsion of trimethylamine, yielding **6** directly.[14]



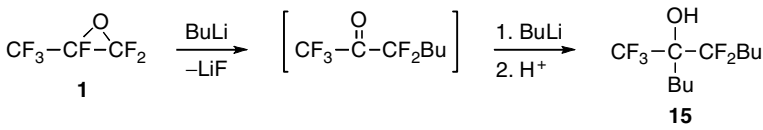
t-Butoxide reacts with HFPO (**1**) to give *t*-butyl perfluoropropionate (**13**).[22] Probably the reaction proceeds by butoxide attacking in the usual way to generate a little acyl fluoride and fluoride ion. Because the butoxide is too hindered to compete for **1** with fluoride, the fluoride ion then catalyzes isomerization of the rest of the HFPO to acyl fluoride **6**, which reacts with *t*-butoxide to give the ester **13**.



The reaction of **1** with an imine to give vinylogous amide **14**[23] can be interpreted similarly. Isomerization of **1** to **6** by fluoride ion is followed by attack on **6** of the enamine tautomer of the imine.

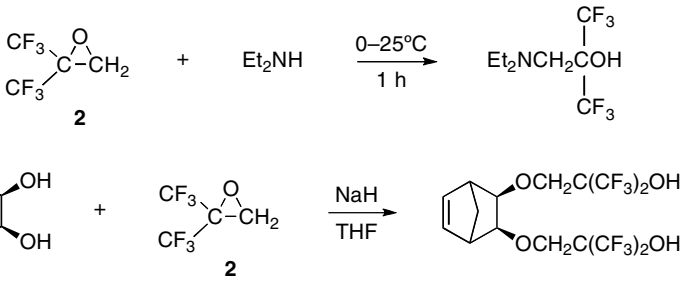


Finally, butyllithium is a rare example of a nucleophilic reagent that attacks at C2 of HFPO, leading after workup to tertiary alcohol **15**.[4]



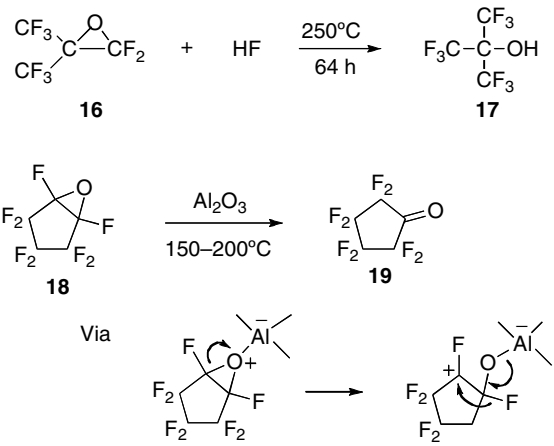
In contrast to HFPO, 2,2-bis(trifluoromethyl)oxirane (**2**) ring opens with oxygen, nitrogen, sulfur, and carbon nucleophiles at the less hindered carbon, yielding tertiary alcohols.[24,25] With diethylamine, for example, **2** affords an aminoalcohol in 83% yield. Oxirane **2** played an important role in the development of monomers from which to build highly transparent, yet readily alkali-soluble photoresist copolymers

for use in semiconductor photolithography at 157 and 193 nm.[26] One such monomer was prepared by ring opening of **2** with a norbornene diol.

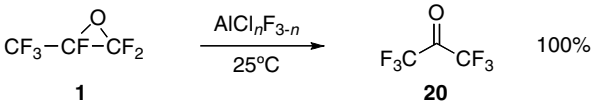


1.1.3 Reactions with Electrophiles

Hydrogen fluoride opens oxirane **16** under very vigorous conditions to give perfluoro-*t*-butanol (**17**).[27] However, Lewis acids isomerize perfluorooxiranes to carbonyl compounds, as illustrated by the transformation of perfluorocyclopentene oxide (**18**) into perfluorocyclopentanone (**19**) over alumina.[28]

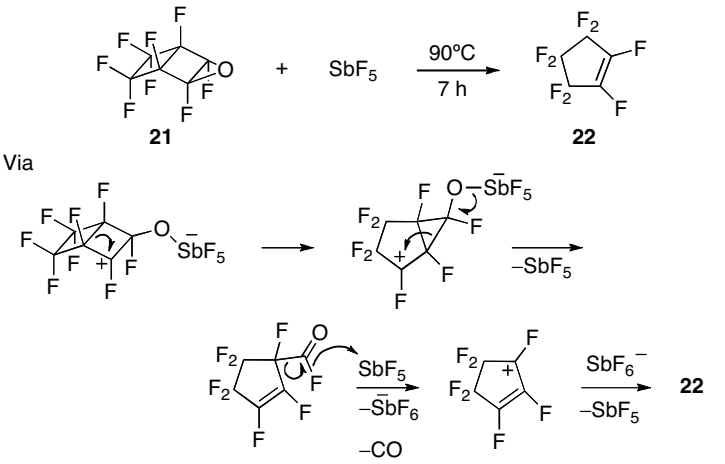


In similar fashion and in contrast to its isomerization by fluoride ion and other bases to perfluoropropionyl fluoride (**6**), HFPO is transformed by Lewis acids such as antimony pentafluoride[29,30] or aluminum chlorofluoride[31] into another isomer, hexafluoroacetone (**20**).

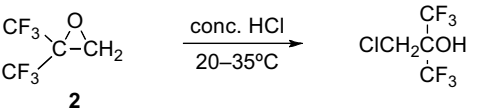


Treatment of the bicyclohexene oxide **21** with antimony pentafluoride yielded perfluorocyclopentene (**22**) instead of the expected bicyclic ketone.[10] Presumably

ring strain is responsible for inducing rearrangement of the initially formed carbocation, then ring opening and decarbonylation ensue.

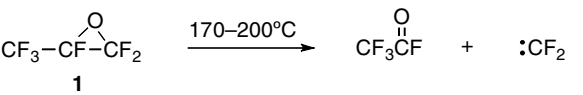


As would be expected, 2,2-bis(trifluoromethyl)oxirane (**2**) is more easily attacked by electrophiles than its perfluorinated counterpart.[24] It readily undergoes ring opening with concentrated hydrochloric acid to give a chlorohydrin in 88% yield.

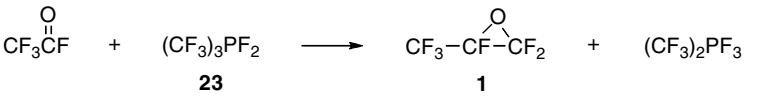


1.1.4 Difluorocarbene Chemistry

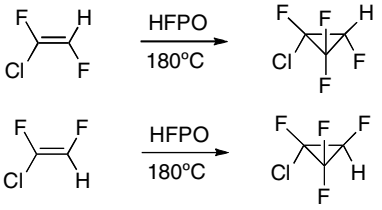
HFPO (**1**) is an excellent source of difluorocarbene, superior to hexafluorocyclopropane because it decomposes at lower temperatures.[3] It fragments into the carbene and trifluoroacetyl fluoride with a half-life of 169 min at 190°C, as determined by gas-phase NMR.[32] In the absence of a carbene trap, hexafluorocyclopropane and the acyl fluoride are the main products of HFPO decomposition at 200°C.[33]



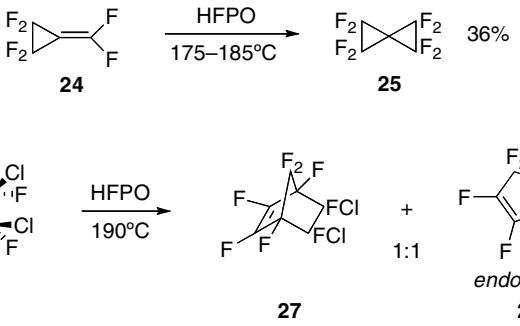
The reaction has been shown to be reversible. When trifluoroacetyl fluoride is heated at 130°C with difluorotris(trifluoromethyl)phosphorane (**23**), a lower temperature source of difluorocarbene, HFPO is formed.[34]



Generated from HFPO, difluorocarbene reacts with a wide variety of unsaturated compounds, both fluorinated and unfluorinated. It can react stereospecifically, as illustrated with the chloro-1,2-difluoroethylenes.[33]



The highly strained perfluorospiropentane (**25**) has been prepared by the reaction of perfluoromethylenecyclopropane (**24**) with HFPO.[35] Cyclohexadiene **26** reacted with HFPO to give in 50% yield a norbornene (**27**) and stereoisomeric bicyclo[3.2.0] heptanes (**28**), all products of vinylcyclopropane rearrangement of the initial cyclopropane adducts.[36]



The carbene is also capable of adding to some carbonyl groups to give oxiranes such as **29** from perfluorocyclobutanone.[37] Hexafluorothioacetone reacts analogously to yield thiirane **30**,[38] and an imine reacts with HFPO to afford aziridine **31**.[39]