α-Fluorinated Ethers, Thioethers, and Amines: Anomerically Biased Species

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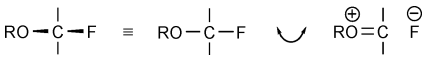
1. Introduction

When asked to draw up a list of textbook substituents, hardly anyone would consider to associate such an "exotic entity" like trifluoromethoxy to the lastingly popular carboxy, acetyl, formyl, nitro, amino, hydroxy, and sulfo groups. There are nevertheless good arguments why a broad coverage of the chemistry, physics, and biology of OCF_3 compounds and congeners appears to be timely.

First of all, their *occurrence* has significantly increased in recent years. Some 30 000 OCF_3-containing structures are presently compiled in chemical databases. They are documented in more than 7 000 literature references. Although most of these are patent applications, there are also close to 500 pertinent research articles published in scientific journals.

What makes the occupation with OCF_3 compounds particularly intriguing is their unique electron distribution. The geminal combination of an alkoxy or aryloxy group with a fluorine atom offers the possibility of bonding/nonbonding resonance which can be formally expressed by the superposition of a covalent and an ionic limiting structure. This phenomenon which reveals itself by a lengthening and weakening of the carbon−halogen bond and a shortening and strengthening of the carbon−oxygen bond is widely known as the generalized *anomeric effect*.[1−3]



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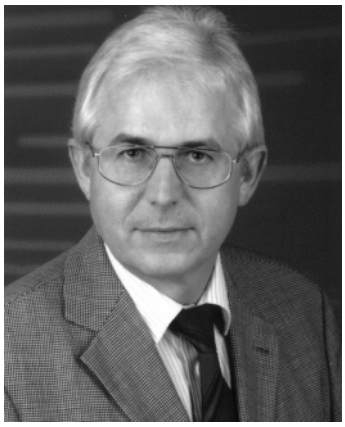
Frédéric Leroux graduated from the University of Konstanz (Germany) in 1993 and received his Ph.D. degree in 1997 after having completed an in-depth investigation of hetero-binuclear transition metal complexes under the supervision of Professor Helmut Fischer. In 1998, he was appointed "Maître-assistant" at the University of Lausanne, and in 2001 "Chargé de cours" at the Ecole Polytechnique Fédérale de Lausanne (EPFL) in the group of Professor Manfred Schlosser. In 2003, he obtained a permanent position at the Centre National de la Recherche Scientifique (CNRS) in France. His research work focuses on the chemistry of polar organometallic compounds oriented toward the synthesis of chiral ligands for the homogeneous and heterogeneous asymmetric catalysis, the synthesis of biologically active compounds, and the preparation of new building blocks.

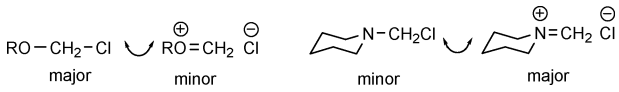


Peter Jeschke received the Ph.D. degree at the University of Halle/Wittenberg (Germany). He then joined the agrochemical research division of the Fahlberg-List Company. After a one-year stay at the Institute of Neurobiology and Brain Research of the German Academy of Sciences, he took a position at the Agricultural Centre of Bayer AG in 1989. Since 2002, he has been Head of Insecticides Chemistry 2 of Bayer CropScience AG at Monheim (Germany). Dr. Jeschke has published over 30 scientific contributions including six review articles and is named as a (co)inventor of 54 patents. His research interests focus on the syntheses of active ingredients in crop protection and include aspects of natural product chemistry.

Obviously, the manifestation of an anomeric effect does not require the presence of three α-fluorine atoms. One or two are perfectly enough. Moreover, the oxygen atom may be replaced by any other donor element, in particular, by sulfur or nitrogen. However, lone-pair lacking substituents such as hydrocarbon residues, sulfonyl, or phosphonyl groups (e.g., as present in α-fluoro- and α,α-difluorophosphonates[4−6]) or halogens do not qualify as promoters of anomeric polarity. Finally, the fluorine acceptor might be replaced by a chlorine or bromine atom. This may, but must not, increase the ionicity to an extreme. *N*-(Chloromethyl)piperidine is a salt-like

Professor Manfred Schlosser carried out his thesis under the supervision of Professor Georg Wittig, receiving his doctorate degree in 1960. After a research year in Brussels and his "Habilitation" in Heidelberg (1966), he accepted the position of a group leader ("Oberarzt") at the German Cancer Research Center in Heidelberg. In 1971, he was appointed as the successor of Professor Jiři Sicher at the University of Lausanne. He has lectured as a visiting professor in Italy (Perugia, Firenze), Germany (Berlin), Hungary (Budapest), USA (San Jose; Santa Barbara), and Japan (Kyoto). His research work is characterized by an intimate interplay between novel mechanistic insight and synthetic applications. He is author or editor of three books in organometallic chemistry, a second edition of the most recent one having been released recently (*Organometallics in Synthesis: A Manual*; Wiley: Chichester, 2002).

compound,[7,8] whereas chloromethyl alkyl ethers[9] still exhibit the characteristics of "typically organic" materials.



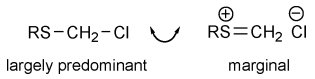
For reasons of thematic coherence, the scope of the present review restricts itself to α-fluorine bearing ethers, sulfides, and amines. The immediately following sections will deal with the preparation and transformation of such substances. The next two chapters summarize structural peculiarities and physicochemical properties. Finally, their utility in material and life sciences will be outlined.

R_2N-CH_2F	$RO-CH_2F$	$RS-CH_2F$
	$RO-CR'F_2$	
R_2N-CXF_2	$RO-CXF_2$	$RS-CXF_2$
R_2N-CF_3	$RO-CF_3$	$RS-CF_3$

[R = alkyl, aryl, acyl; R' = alkyl, aryl; X = OR, Cl, Br; CHF_2, $CClF_2$, $(CF_2)_nCF_3$ (n = 0 - 7)]

α-Fluoroalkyl sulfides are included in this review for comparison with the corresponding ethers. In fact, the two structural families exhibit many similarities. For example, the pK_a values of benzoic acids are almost identical when OCF_3 or SCF_3 serves as a *meta*- or *para*-substituent (see Section 5.3.1). On the other hand, the stereoelectronics of (trifluoromethoxy)-benzene and (trifluoromethylthio)benzene differ markedly (Section 4.1.3). Moreover, the two series distinguish themselves as far as anomeric effects are concerned, which are only marginally sustained by sulfur compounds. The relatively long bond distance between the second row element and carbon weakens

of course double bonds as the one present in the charged limiting structure of α-haloalkyl sulfides.



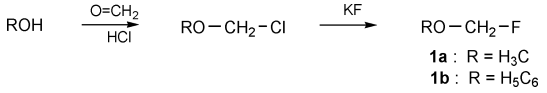
To some extent at least, electron density can nevertheless flow from a neutral sulfur to a positively charged carbon atom. This anomeric bonding/nonbonding resonance (n−σ^* interaction) explains why the S_N1 solvolysis rate of chloromethyl methyl sulfide[10] is increased by many powers of ten when compared with that of 1-chlorobutane, which, moreover, appears to follow a solvent-S_N2 rather than a genuine S_N1 process.[11]

2. Preparation of α-Fluoro Ethers, Sulfides, and Amines

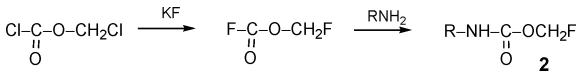
The following survey of synthetic methods does not intend to be exhaustive. To the contrary, the numerous known methods were critically evaluated to highlight just the most general and efficacious ones.

2.1. α-Fluoro Ethers, Carbamates and Esters

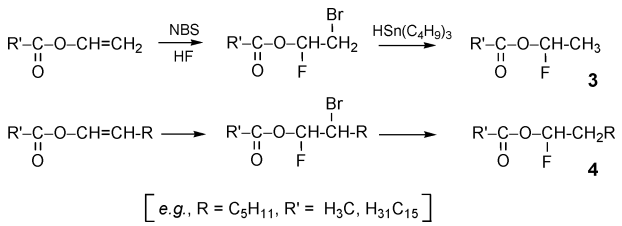
Fluoromethyl methyl ether (**1a**)[12] and fluoromethyl phenyl ether (**1b**)[13] are easily obtained from the chloro analogues by nucleophilic substitution with potassium fluoride. The chloromethyl ethers are readily accessible.[9,14−17]



In the same way, the commercial chloromethyl chloroformate can be converted into the fluoromethyl fluoroformate.[18] When this compound is treated with a primary amine (or imidazole) the corresponding fluoromethyl carbamate **2** is formed.[18]



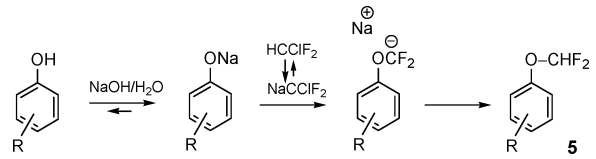
O-Fluoroalkyl carboxylates **3** are readily obtained by the fluoride-catalyzed addition of an acyl fluoride to monomeric formaldehyde dissolved in tetrahydrofuran.[19] In contrast, *O*-α-fluoroethyl and *O*-α-fluoroalkyl carboxylates **3** and **4** are most conveniently prepared by reaction of an *O*-ene-ester with *N*-bromosuccinimide in the presence of hydrogen fluoride followed by reductive debromination using tributyltin hydride.



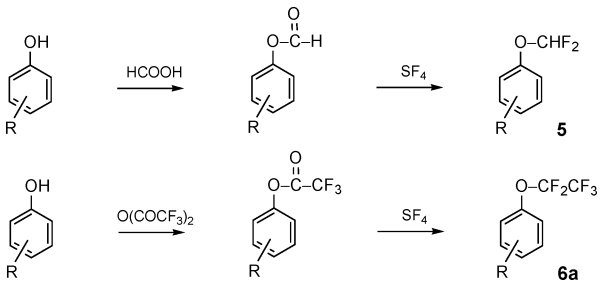
2.2. α,α-Difluoromethyl Ethers

α,α-Difluoroalkyl alkyl ethers or substituted congeners such as the α,α-difluorobenzyl methyl ether have been recently obtained by the fluorodesulfuration of the corresponding thionoesters.[20,21] Bis(2-methoxyethyl)aminosulfur trifluoride has been recommended as the reagent of choice for this purpose.

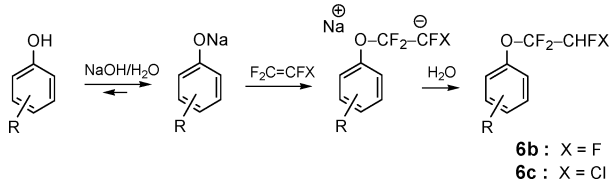
The standard route to difluoromethyl aryl ethers **5** is the reaction of the appropriate phenolate with chlorodifluoromethane in the presence of a base such as sodium hydroxide.[22−24] The method is robust enough to be applied on a technical scale and gives high yields.



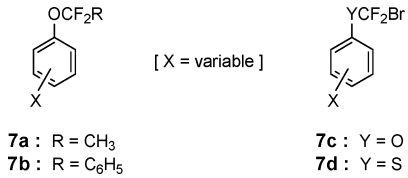
Alternatively, difluoromethyl aryl ethers **5** should also be accessible by sulfur tetrafluoride-mediated fluorodeoxygenation of aryl formates. Although this is a rather expensive and not very expedient route, its extension to aryl trifluoroacetate represents the best entry to pentafluoroethyl aryl ethers **6a**.[25]



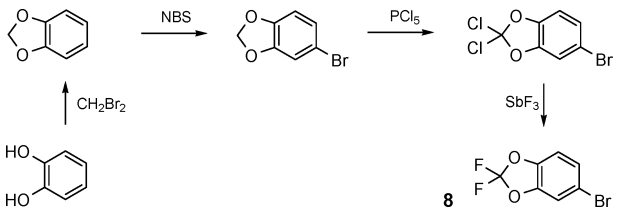
1,1,2,2-Tetrafluoroethyl aryl ethers **6b** can be made more economically by the base-catalyzed addition of phenols to tetrafluoroethylene.[26] Analogously, 2-chloro-1,1,2-trifluoroethyl aryl ethers **6c** are produced from phenols and chlorotrifluoroethylene.[27]



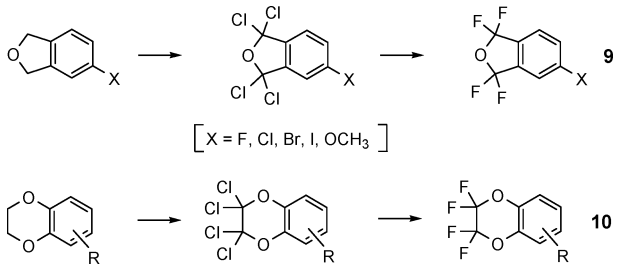
α,α-Difluoroethyl aryl ethers **7a**[28] and α,α-difluorobenzyl aryl ethers **7b**[28,29] can be prepared by oxidative desulfurization−fluorination[28] of the corresponding xanthogenates or from substituted benzaldehydes by fluorination with sulfur tetrafluoride, bromination, and subsequent condensation with phenolate.[29] Bromodifluoromethyl aryl ethers **7c** and thioethers **7d** have been made by condensation of phenolates or thiophenolates with dibromodifluoromethane.[30]



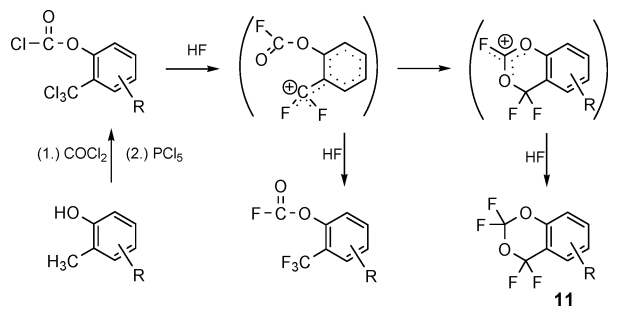
The key step in the preparation of diaryloxydifluoromethanes[31,32] is a chlorine/fluorine exchange usually accomplished with antimony trifluoride. The heavier element is beforehand introduced by radical halogenation. The sequence[33] starting with the conversion of pyrocatechol into 1,3-benzodioxole and the bromination of the latter[34] and leading via 5-bromo-2,2-dichloro-1,3-benzodioxole to 5-bromo-2,2-difluoro-1,3-benzodioxole **8** is representative in this respect.



The structurally related 1,1,3,3-tetrafluoro-2-benzofurans[35] **9** (1,1,3,3-tetrafluorophthalanes) and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxines[36] **10** are made analogously. The readily available precursor 2-benzofurans and 2,3-dihydro-1,4-benzodioxines are perchlorinated at the heterocyclic ring before being subjected to the chlorine/fluorine displacement reaction. Tetrafluoro-2-benzofurans **9** are also obtained when phthalic acids are heated in the presence of sulfur tetrafluoride.[37]

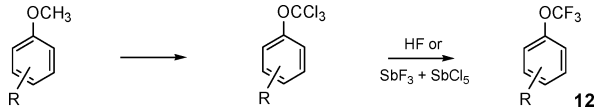


The isomeric 2,2,4,4-tetrafluoro-2*H*,4*H*-dihydro-1,3-benzodioxines **11** are formed in high yields along with 2-(trifluoromethyl)aryl fluoroformates as byproducts when 2-(trichloromethyl)aryl fluoroformates or chloroformates are dissolved in an excess of anhydrous hydrogen fluoride, and the mixture is kept 0.5−6 h in the temperature range between 20 and 60 °C.[38] The immediate precursor to the exchange-coupled cyclization stage is a 2-(fluorocarbonyloxy)benzyl cation that benefits from the extra stabilization[39] provided by the two α-fluorine atoms. The required 2-(trichloromethyl)phenyl chloroformate intermediate and congeners are obtained by the consecutive treatment of *o*-cresol with phosgene and phosphorus pentachloride.[40]

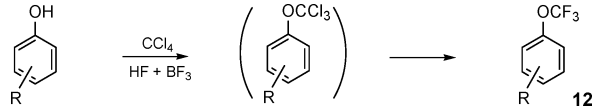


2.3. Trifluoromethyl Aryl Ethers

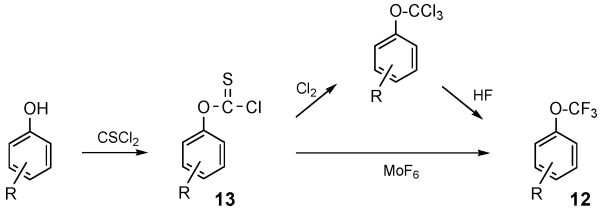
The chlorination/exchange sequence is also routinely used for the preparation of trifluoromethoxy-substituted arenes **12**. The displacement of the heavier halogen by the lighter halogen can again be brought about with anhydrous hydrogen fluoride[41] or with antimony trifluoride in the presence of antimony pentachloride.[42−44] The side chain chlorination works well, when phosphorus pentachloride is employed at 200 °C[32,42] or, with elemental chlorine, photostimulated in refluxing tetrachloromethane.[45] However, halogen attack on the phenyl ring can never be ruled out definitively.[16] By the way, (trifluoromethoxy)-arenes may in turn be transformed to the trichloro analogues just by treating them with aluminum trichloride.[46]



The scheme described above can be simplified by producing the trichloromethyl aryl ethers without isolation and through in situ conversion into the final trifluoromethyl aryl ethers **12**. To this end, the phenol is heated together with tetrachloromethane, anhydrous hydrogen fluoride, and catalytic amounts of boron trifluoride up to 150 °C.[47]



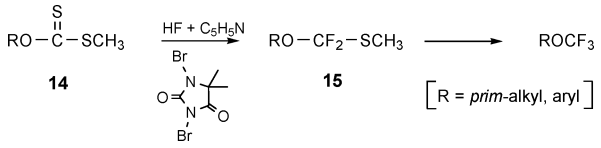
Using elemental chlorine, the readily accessible, although highly toxic aryl chlorothionoformates **13** can be cleanly converted into trichloromethyl aryl ethers, the precursors to trifluoromethyl aryl ethers **12**. [25,43] Moreover, they afford directly the latter compounds when treated with molybdenum hexafluoride.[48]



The chlorination/exchange sequence is well compatible with substrates carrying electron-withdrawing groups as these confine the menace of ring chlorination. A greater substituent tolerance is exhibited by the other standard method, the reaction of aryl formates with sulfur tetrafluoride.[25,43] The (trifluoromethoxy)arenes **12** are obtained in yields ranging from 9 to 81%.[25,43]

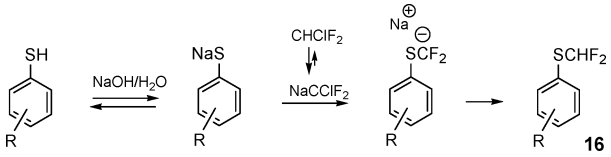
Recently, a new method of fluorodesulfurization has been disclosed.[49,50] When dithiocarbonates (**14**, xanthogenates) are exposed to a huge excess of hydrogen fluoride-pyridine and 1,3-dibromo-5,5-dimethylhydantoin, trifluoromethyl ethers form in moderate-to-excellent yields. Under modified reaction conditions, the transient monothioacetals **15** can be

isolated, although in poor yields. What makes this procedure attractive is its applicability to the conversion of aliphatic alcohols into trifluoromethyl alkyl ethers provided that the alcohol is a simple primary rather than a benzylic, secondary, or tertiary one (in which case the reaction fails). Alkyl trifluoromethyl ethers, still a rarity, have so far been prepared by the reaction of alkyl fluoroformates with sulfur tetrafluoride,[51] the trifluoromethyl transfer from *O*-(trifluoromethyl)dibenzofuranium tetrafluoroborate,[52] and the addition of trifluoromethyl hypofluorite ($FOCF_3$) to olefins.[53]

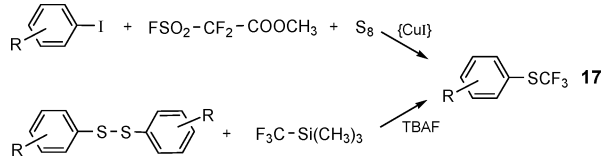


2.4. α,α-Difluoromethyl Sulfides and Trifluoromethyl Sulfides

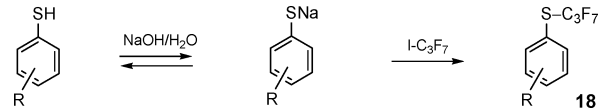
In a similar manner as described above for phenols, thiophenols react in the presence of sodium hydroxide with chlorodifluoromethane to give difluoromethyl aryl sulfides[24] (**16**). There is general agreement about the intermediacy of chlorodifluoromethylsodium and difluorocarbene.



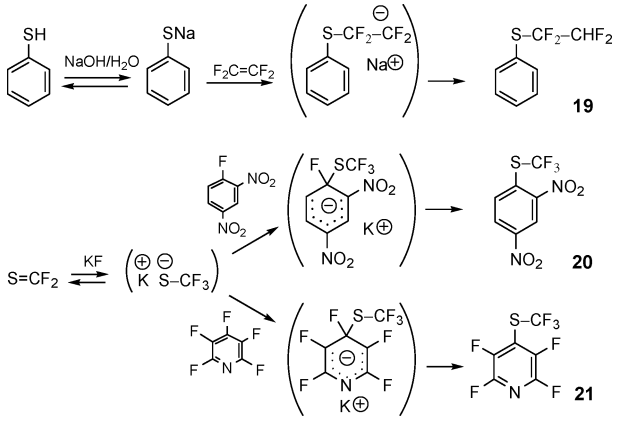
Trifluoromethyl phenyl sulfide and ring-substituted analogues **17** are readily made from iodo- or bromoarenes, methyl difluoro(fluorosulfonyl)acetate, and elemental sulfur in the presence of cuprous iodide in hexamethylphosphoric triamide (HMPA) or *N*-methylpyrrolidone (NMP).[54] Alternatively, trifluoromethyl aryl sulfides and even trifluoromethyl *prim*- or *sec*-alkyl sulfides can be obtained by the reaction between the corresponding disulfide and trimethyl(trifluoromethyl)silane in tetrahydrofuran at 0 °C using tetrabutylammonium fluoride (TBAF) as a promoter.[55]



The base-promoted condensation of thiophenols with 1-iodoheptafluoropropane affords heptafluoropropyl aryl sulfides **18**.[56] At first sight, this reaction appears to testify the exceptionally high nucleophilicity of thiolates. However, in reality it proceeds as a single electron-transfer triggered radical anion/radical ($S_{RN}1$) process.

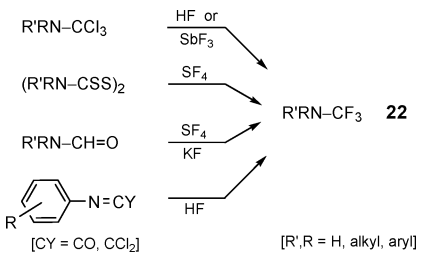


The extraordinary thiolate nucleophilicity explains the success of two other transformations. If a suitable base is present, thiophenols add to tetrafluoroethylene under very mild conditions, thus affording 1,1,2,2-tetrafluoroethyl aryl sulfides (**19**).[26] Furthermore, electron-deficient arenes and heterocycles such as 1-fluoro-2,4-dinitrobenzene and pentafluoropyridine undergo nucleophilic aromatic substitution with in situ generated potassium trifluoromethylthiolate to give, for example, trifluoromethyl 2,4-dinitrophenyl sulfide (**20**) and trifluoromethyl 2,3,5,6-tetrafluoropyrid-4-yl sulfide (**21**).[57]



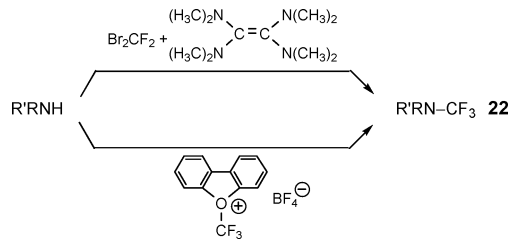
2.5. (Trifluoromethyl)amines

There are numerous possibilities to produce *N*-trifluoromethyl-substituted amines **22**. Besides the classical method of chlorine/fluorine exchange with hydrogen fluoride or antimony trifluoride applied to *N*-(trichloromethyl)amines,[58] bis(dialkylthioxocarbamoyl) disulfides (tetraalkylthiuram disulfides) and sulfur tetrafluoride,[59] *N*,*N*-dialkylformamides and sulfur tetrafluoride in the presence of potassium fluoride[60] and arylisocyanates[61] or phosgene arylimines[61] with hydrogen fluoride all afford *N*-(trifluoromethyl)-amines in acceptable-to-high yields. The electrochemical fluorination[62] of *N*-methylamines is an industrially attractive process whenever it can be conducted site selectively.

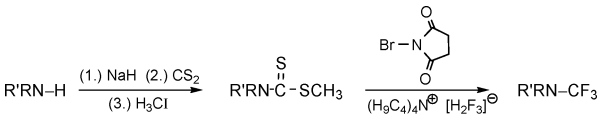


Less frequently employed is the reaction of secondary amines with dibromodifluoromethane in the presence of tetrakis(dimethylamino)ethylene[63] or with

O-(trifluoromethyl)dibenzofuranylium tetrafluoroborate.[64]



Recently, a new method was suggested that also starts from secondary amines but passes through dithiocarbamates as the crucial intermediates. Their oxidative fluorodesulfurization with excess *N*-bromosuccinimide and tetrabutylammonium dihydrogen trifluoride gives the products **22** in good-to-excellent yields.[65]



By virtue of its trivalency, nitrogen can entertain a single bond to an alkyl or aryl substituent on one side and a double bond to an alkylidene group on the other, thus forming an imine (Schiff base). Numerous *N*-trifluoromethyl-bearing imines are known indeed, although no universal method for their synthesis exists. In general, their preparation relies on the use of highly reactive N-CF_3 species such as trifluoronitrosomethane,[66] difluoromethylene-*N*-(trifluoromethyl)-amine,[67] bis(trifluoromethyl)methylene-*N*-(trifluoromethyl)amine,[68] tetrafluoroethylidene-*N*-(trifluoromethyl)amine,[69] hexafluoropropylidene-*N*-(trifluoromethyl)amine,[69] 2,2-bis(trifluoromethyl)tetrafluoropropylidine-*N*-(trifluoromethyl)amine,[69] and trifluoromethylisocyanide.[70]

3. Reactivity

The first part of this section will briefly summarize all standard transformations based on the S_N2 scheme or involving radical or cationic intermediates. The generation of organometallic derivatives from (difluoromethyl)arenes and (trifluoromethyl)arenes and the interception of such species will be dealt with subsequently.

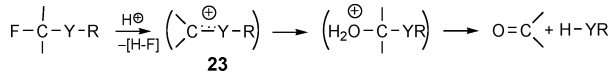
3.1. Hydrolysis, Redox Processes, and Electrophilic Aromatic Substitution

Most of the systematic investigations quoted in this subsection deal with (difluoromethyl)arenes and (trifluoromethyl)arenes. The findings also should nevertheless apply *grano cum salis* to α-fluorinated sulfides and amines.

3.1.1. Hydrolysis

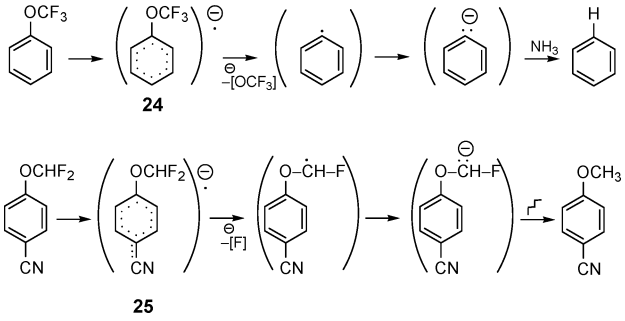
α-Alkoxy substituents are known to enhance the nucleofugal mobility of the leaving group of alkyl halides.[13,71] Thus, α-fluoromethyl phenyl ether should be labile in the presence of nucleophiles including alkaline solutions. On the other hand, difluoromethyl and trifluoromethyl ethers become progressively inert against the action of bases as halogens generally retard nucleophilic substitutions occurring in their vicinity.[72]

Electron-donors such as alkoxy (aryloxy), alkylthio (arylthio), and dialkylamino groups effectively stabilize adjacent carbenium ions **23** and thus immensely facilitate S_N1 processes.[73,74] Consequently, α-fluorinated ethers, thioethers, and amines must be and are sensitive toward Brønsted and Lewis acids. As fluorine can also share nonbonding electrons with a positively charged center,[75−78] one might expect the lability to increase with the number of α-fluorine atoms. However, the hydride affinity does not grow monotonically in the series methyl, fluoromethyl, difluoromethyl, and trifluoromethyl cation but diminishes upon introduction of the third fluorine atom.[79] Therefore, α-mono-, -di-, and -trifluorinated ethers are all similarly and pronouncedly vulnerable toward acids and, as a corollary, autocatalytically destructive hydrolysis.



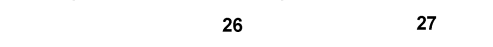
3.1.2. Reduction and Reductive OC–Bond Cleavage

Electrochemical reduction[80] in liquid ammonia converts (trifluoromethoxy)benzene into benzene and the trifluoromethoxy anion, the ultimate fate of which remains a matter of speculation. Radical anions such as species **24** presumably act as the first intermediates. However, they may be channelled into another mode of decomposition. This is evidenced by 4-(difluoromethoxy)benzonitrile, which, via the radical anion **25**, loses consecutively both fluorine atoms to give 4-methoxy benzonitrile.[80]



3.1.3. Oxidation

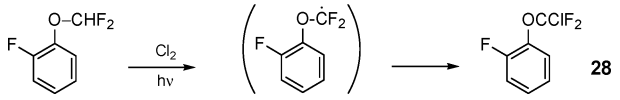
Trifluoromethyl ethers and *N*-(trifluoromethyl)-amines appear to be quite stable toward oxidative stress. In contrast, trifluoromethyl sulfides readily undergo oxygenation to the corresponding sulfoxides[81] **26** and sulfones[82] **27**.



3.1.4. Radical Chlorination

Photochlorination of (difluoromethyl)arenes, such as difluoromethyl 2-fluorophenyl ether, affords the corresponding (chlorodifluoromethoxy)arenes (e.g.,

28). The latter compounds resemble (trifluoromethoxy)-arenes in several respects.[83]



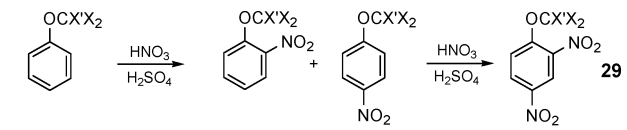
3.1.5. Electrophilic Aromatic Substitution

Systematic studies have focused on the nitration of difluoromethyl and trifluoromethyl ethers. In both cases, one has to navigate between the *Scylla* of the desired substitution and the *Charybdis* of the detrimental hydrolysis to the phenol that invariably sets in if the acid is too concentrated (>50%) or the temperature is raised beyond a safe threshold (50 °C).

Whereas anisole proves far more reactive,[84] (difluoromethoxy)benzene and (trifluoromethoxy)benzene undergo nitration considerably (up to 5 times) more slowly than benzene. However, not even trace amounts of *meta* isomers have ever been detected in the last two cases. This means an omnipresent inductive electron-withdrawing effect compromises the attack of the electrophile. This retarding influence is counterbalanced, to some extent at least, by the capacity of the ether oxygen to act through resonance as an electron donor. Such antagonistic behavior is well-known for chloro and bromo substituents.

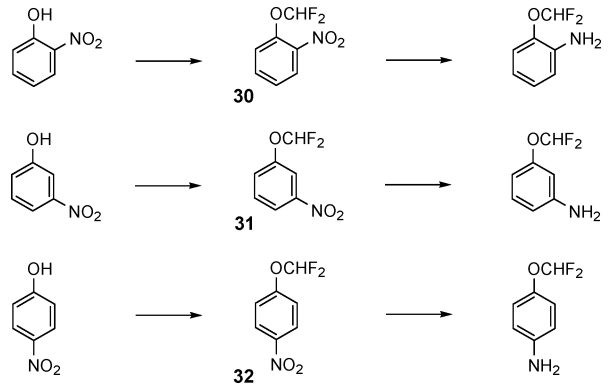
When the nitration is carried out under standard conditions (i.e., with concentrated nitric and sulfuric acids in the presence or absence of glacial acetic acid), the ortho/para distribution alters drastically with the number of fluorine atoms in the ether part. The ortho/para ratio of 1:1.3 as reported for anisole[85] decreases to 1:2.6 for (difluoromethoxy)benzene[86] and 1:9 in the case of (trifluoromethoxy)benzene.[87] Apparently, the proximity of a O-CF and the NO_2 dipole, inevitable if the electrophile docks at the ortho position, is energetically detrimental. It is quite instructive to break down the relative reactivities and the regioselectivities in partial rate factors.[84] One finds for (trifluoromethoxy)benzene, relative to benzene (≡ 1.00) after statistic correction, $o_f^{OCF_3}$ 0.065, $m_f^{OCF_3}$ < 0.01, and $p_f^{OCF_3}$ 1.04.

At temperatures in the range of 25−50 °C, double nitration can be achieved. The resulting 2,4-dinitrophenyl ethers **29** are isolated in moderate-to-excellent yield (**29a**: 90%;[88] **29b**: 91%;[86] **29c**: 50%[25]). It is plausible to suppose that the ortho-mononitro derivatives of the α-fluorinated ethers are more rapidly consumed than their para isomers in such secondary reactions.

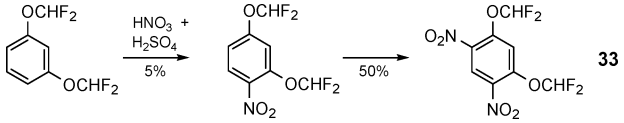


a : X' = X = H	43 : 57
b : X' = H, X = F	28 : 72
c : X' = X = F	10 : 90

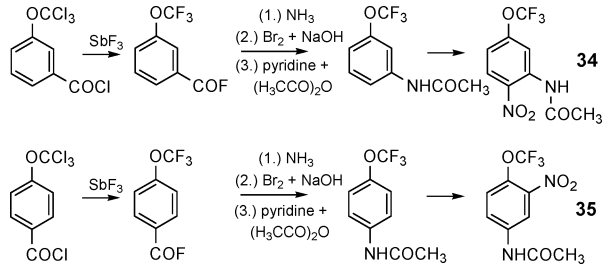
1-Difluoromethoxy-4-nitrobenzene can be separated from the reaction mixture by fractional crystallization (mp 33−35 °C) and 1-trifluoromethoxy-4-nitrobenzene by distillation (bp 82 °C/10 mmHg). It is more convenient, however, to prepare each regioisomer separately from the respective nitrophenols. The nitro compounds **30**−**32** can then be reduced to the anilines, and the latter can be further elaborated by applying well-established diazonium salt chemistry.[86]



Electronic and steric hindrance impedes substitution at double-ortho positions. 1,3-Bis(difluoromethoxy)benzene gives 1-nitro-2,4-bis(difluoromethoxy)benzene at 0 °C and 1,5-dinitro-2,4-bis(difluoromethoxy)-benzene (**33**) at 50 °C.[86]



The para-directing effect of a trifluoromethoxy group surpasses even that of an amide function. *N*-Acetyl-3-(trifluoromethoxy)aniline is nitrated mainly at the 6-position (product **34**; 20%) and to a minor extent (10%) at the 4-position.[32] The *N*-acetyl-4-(trifluoromethoxy)aniline reacts at the 3-position (again meta with respect to the nitrogen function and ortho with respect to to the trifluoromethoxy group!). The *N*-acetyl-4-trifluoromethoxy-3-nitroaniline (**35**; 94%) thus produced can be converted, after deacetylation, by the Gattermann−Sandmeyer method into the 1-trifluoromethoxy-4-iodo-2-nitrobenzene. This compound can be reduced to the 2-(trifluoromethoxy)-aniline in a single operational step by catalytic hydrogenation.[32]



The pronounced preference for *para* substitution of (difluoromethoxy)benzene,[89] (trifluoromethoxy)-benzene[87,89,90] and (trifluoromethyl)thiobenzene[90] holds for most electrophilic aromatic substitutions, in particular sulfonation,[89] bromination,[87] chloromethylation[91] and acylation.[87,90] Unless the *para* position is occupied, *ortho* isomers are formed only in small

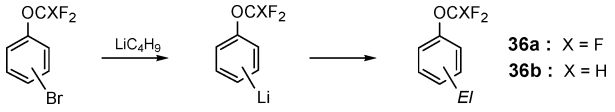
amounts (≤ 10%), if at all.[87] Attack at the *meta* position has so far been observed only with the isopropylation and ethylation of (trifluoromethoxy)-benzene (to the extent of 9 and 31%, respectively).[87]

3.2. Organometallic Reactions

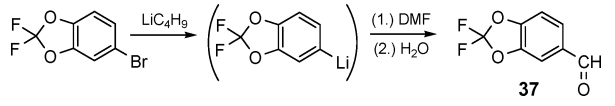
Aromatic difluoromethyl and trifluoromethyl ethers are generally made from the corresponding phenols that are respectively treated with chlorodifluoromethane in the presence of sodium hydroxide or methylated and photochlorinated before being subjected to the halogen displacement with hydrogen fluoride or antimony trifluoride (see above). The structural proliferation of a substrate already containing a $OCHF_2$ or OCF_3 substituent was so far confined to the nitration/reduction/diazotation/substitution sequence. A very versatile new option has been recently developed on the basis of synthesis-oriented organometallic chemistry. The metal is introduced into substrate in general by either one of two favorite methods, the permutational interconversion of halogen against metal or hydrogen against metal. Once the metal is attached, it ensures versatility and product flexibility. This means that it can be replaced by any of the dozens, if not hundreds, of eligible electrophiles.

3.2.1. Halogen/Metal Permutation

The three isomeric bromo(trifluoromethoxy)benzenes and bromo(difluoromethoxy) benzenes being commercial, one needs simply to treat them with butyllithium in diethyl ether at, respectively, −75 °C[92] and −100 °C[93] to generate the corresponding aryllithium species. The latter can be trapped by a variety of electrophiles *El*-X, thus furnishing a diversity of new products **36** such as phenols, benzyl alcohols, 2-aryl ethanols, aldehydes, carboxylic acids, ethyl 2-aryl-2-oxoacetates, ethyl 3-aryl-3-oxopropionates, and nitriles.[94] Because of the lability of the (difluoromethyl)phenyllithiums, the yields of derivatives **36b** (X = H, *El* = e.g., COOH) obtained from such intermediates are only moderate (40−50%).[93]

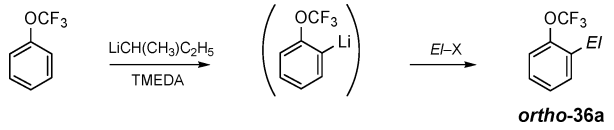


Bromo-2,2-difluoro-1,3-benzodioxole is the first substrate in the area of α-fluorinated ethers and acetals for which a halogen/metal permutation has been reported. Upon consecutive treatment with butyllithium, *N*,*N*-dimethylformamide (DMF), and water, 2,2-difluoro-1,3-benzodioxole-5-carbaldehyde (**37**) has been obtained in 68% yield. [33]



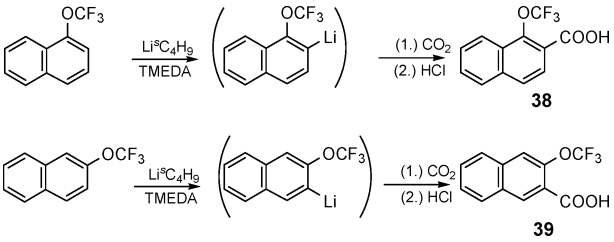
3.2.2. Hydrogen/Metal Permutation ("Metalation")

1-Bromo-2-(trifluoromethoxy)benzene is more than a hundred times more expensive than (trifluoromethoxy)benzene itself. Therefore, it is very fortunate that (trifluoromethoxy)benzene reacts with *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine ("TMEDA") smoothly under hydrogen/metal permutation ("metalation").[92] The ortholithiated species (*ortho*-**36a**) thus generated can be trapped by the same variety of electrophiles already specified in the preceding paragraph.[94]

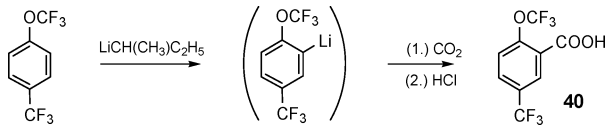


4-(Trifluoromethoxy)biphenyl was metalated using the superbasic LIC−KOR[95−97] mixed metal reagent made by combining butyllithium (LIC) with potassium *tert*-butoxide (KOR) in tetrahydrofuran in the temperature range between −105 and −120 °C. Upon trapping with molecular iodine, 3-iodo-4-(trifluoromethoxy)biphenyl was isolated in 90% yield.[98]

Under the same conditions as employed with (trifluoromethoxy)benzene, 1-(trifluoromethoxy)naphthalene[99] and 2-(trifluoromethoxy)naphthalene[99] undergo selective lithiation at the 2- and 3-position, respectively.[100] The interception with dry ice affords regioisomerically uncontaminated 1-(trifluoromethoxy)naphthalene-2-carboxylic acid (**38**, 80%) and 2-(trifluoromethoxy)naphthalene-3-carboxylic acid (**39**, 87%).[100]

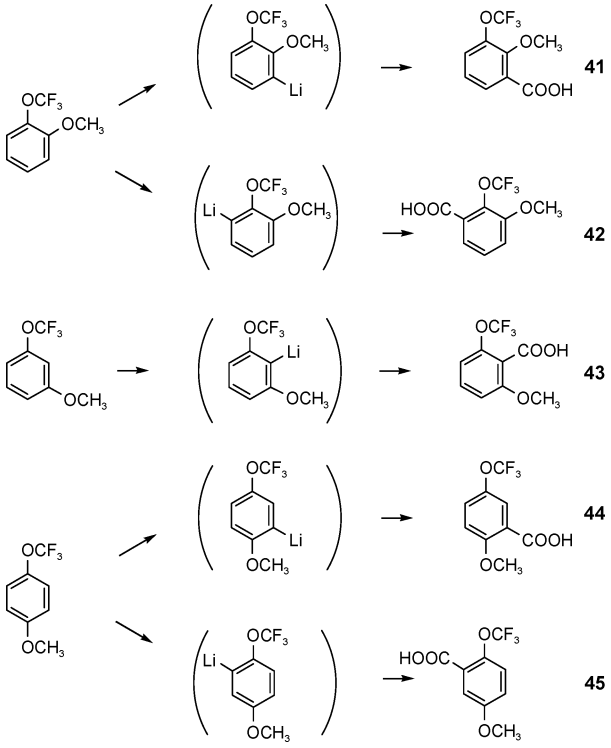


The situation gets intriguing when two activating groups occupy 1,2- or 1,4-positions and thus compete with each other for ortho-directing dominance. Both the trifluoromethyl and the trifluoromethoxy group are strongly electron-withdrawing, and both have a far-reaching activating effect.[99] If the contest between these two substituents in 1-trifluoromethoxy-4-(trifluoromethyl)benzene ends in favor of the OCF_3 substituent, as shown by the formation of 2-trifluoromethoxy-5-(trifluoromethyl)benzoic acid (**40**, 81%) after lithiation and carboxylation,[100b] this outcome may have to be imputed to steric congestion rather than electronic guidance.

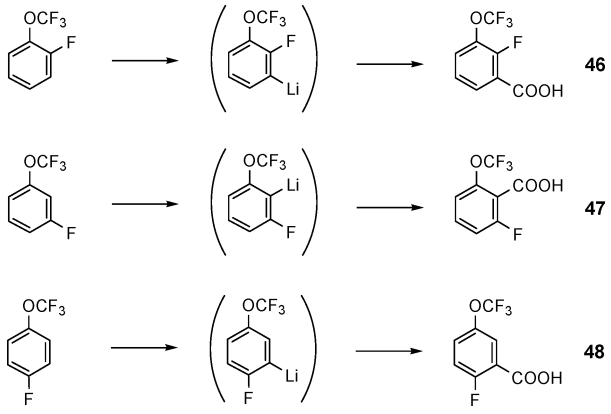


Due to powerful π-polarization,[99] trifluoromethoxy acidifies not only ortho but also meta and para positions strongly. Therefore, metalation of 2- and 4-(trifluoromethoxy)anisole occurs preferentially or exclusively at the methoxy-neighboring position as demonstrated by the formation of the acids **41** and **44** with 80 and 100% regioselectivity, respectively.[100b]

However, proton abstraction at the trifluoromethoxy-adjacent sites, leading to acids **42** and **45**, becomes dominant or at least concomitant (regioselectivities of 91 and 50%, respectively) when *sec*-butyllithium in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) is employed.[100b] 3-(Trifluoromethoxy)anisole undergoes deprotonation and carboxylation (to afford acid **43**) always at the doubly activated 2-position of course.[100b]

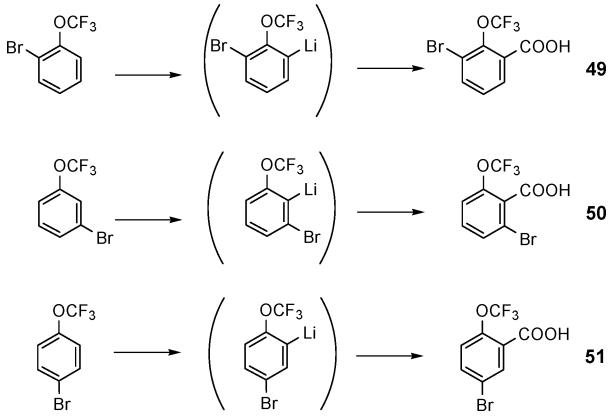


With fluoro(trifluoromethoxy)benzenes as the substrates, no regiochemical ambiguity is encountered. Regardless of whether butyllithium is used as the base in the absence or the presence of potassium *tert*-butoxide, the fluorine-adjacent 6- or 2-positions always are metalated.[100b] Lowering the reaction temperature from −75 °C to −100 °C improves the yields of the acids **46**−**48** (73−79% rather than 51−57%).[100b]



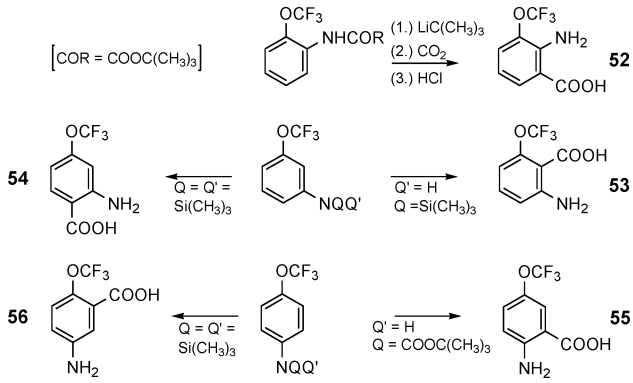
Lithium diisopropylamide is sufficiently basic to deprotonate 1,2-difluoro-3-(trifluoromethoxy)benzene at the fluorine-adjacent 6-position. The resulting organolithium species can be converted into the corresponding boronic acid, which may be used for the synthesis of light-emitting diode materials by Suzuki coupling.[101]

In contrast, bromo(trifluoromethoxy)benzenes are attacked at −100 °C by bases such as LIDA at a position next to the oxygen substituent. Upon subsequent carboxylation, the ortho, meta, and para isomers are converted into the acids **49**−**51** (73−90%).[99] However, under conditions of reversible lithiation, protons are abstracted also from bromine-adjacent and OCF_3-remote positions of the ortho and para isomer.



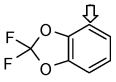
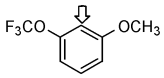
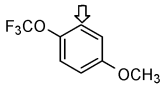
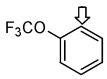
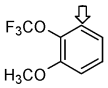
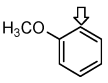
At temperatures above −75 °C, lithium bromide elimination generates didehydro(trifluoromethoxy)-benzenes ("arynes"). These short-lived species can be trapped with furan to form the corresponding Diels−Alder cycloadducts (see 3.3.3).[99]

Trifluoromethoxy-substituted anilines require protection of the amino function. Thus, the *tert*-butoxycarbonyl ("BOC") derivatized ortho isomer gives the 3-(trifluoromethoxy)anthranilic acid (**52**, 73%) after the consecutive treatment with *tert*-butyllithium, dry ice, and an acid.[102] In the same way, the para isomer affords the acid **55** in 78% overall yield.[102] However, a similar reaction sequence accomplished with the 3-trifluoromethoxy-*N*-(trimethylsilyl)aniline provides the acid **53** (33%) and with 3- and 4-trifluoromethoxy-*N*,*N*-bis(trimethylsilyl)aniline the acids **54** (69%) and **56** (48%).[102]

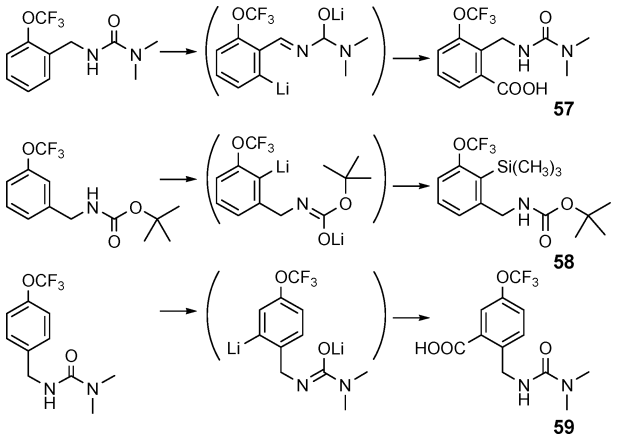


The *N*-(*N*′,*N*′-dimethylcarbamoyl) protected 2- and 4-(trifluoromethoxy)benzylamines react with *tert*-butyllithium and *sec*-butyllithium, respectively, in tetrahydrofuran at −75 °C to give, after carboxylation, the acids **57** (71%) and **59** (84%).[100] Optimum

Table 1. Metalation of OCF_3- and OCF_2O-Substituted Arenes with *sec*-butyllithium in Tetrahydrofuran at −75 °C: Rates (k_{rel}) Relative to (Trifluoromethoxy)-benzene[103]

substrate	k_{rel}
	5.4×10^3
	1.8×10^3
	3.3×10^2
	3.6×10^1
	1.6×10^1
	7.4×10^0
	3.3×10^0
	$\equiv 1.0 \times 10^0$

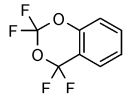
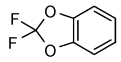
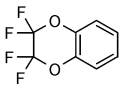
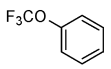
results are obtained with the meta isomer when BOC protected. Simultaneous treatment ("in situ trapping") with LIDA and chlorotrimethylsilane gave the final product **58** (78%).[100]



The quantitative effect of a trifluoromethoxy group on metalation rates is not always easily predictable (Table 1). *sec*-Butyllithium reacts with (trifluoromethoxy)benzene 16 times faster than with anisole but only half as rapidly as with fluorobenzene.[103] A trifluoromethoxy group enhances the kinetic acidity of anisole by a factor of 3 if in the ortho position, 300 if in the para position, and almost 2000 if in the meta position.[103]

The almost 1000-fold rate difference between 1,3-benzodioxole and its 2,2-difluorinated congener (Table 1) is striking. 2,2,4,4-Tetrafluoro-2,4-dihydro-1,3-benzodioxine and 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxine exhibit similar reactivity (Table 2).[100] All these relative rates have been determined by kinetic competition experiments.[104,105]

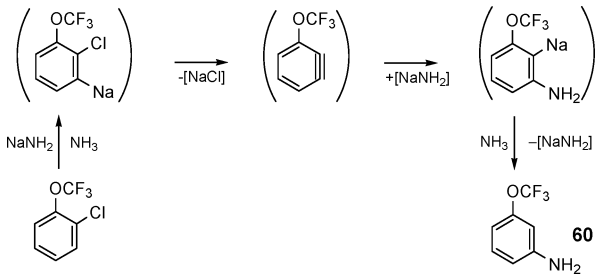
Table 2. Metalation of OCF_2-Incorporating Heterocycles with *sec*-butyllithium in Tetrahydrofuran at −75 °C: Rates (k_{rel}) Relative to (Trifluoromethoxy)benzene[100]

substrate	k_{rel}
	9.2×10^3
	5.4×10^3
	5.0×10^3
	1.0×10^0

Phenyl trifluoromethyl sulfide was found to react with methyllithium under displacement of the CF_3 group providing thioanisole in 70% yield.[106] When employing *tert*-butyllithium again no metalation was achieved but rather formation of *tert*-butyl phenyl sulfide in 67% yield.[107] With lithium 2,2,6,6-tetramethylpiperidide in the presence of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDTA) and potassium *tert*-butoxide ("Faigl mix")[108] decomposition occurred.[107]

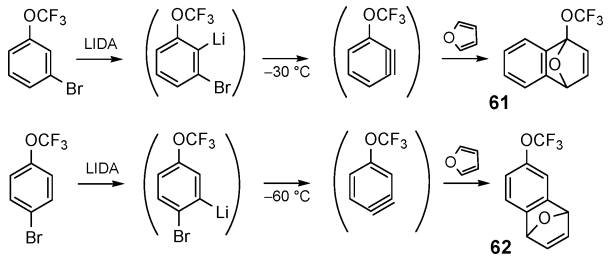
3.2.3. Aryne Intermediates by Metal Halide Elimination

Once a given temperature threshold is passed any *ortho*-haloarylmetal decomposes into metal halide and an "aryne" (1,2-didehydroarene), which may be trapped by a nucleophile. This reaction mode enables, for example, the large-scale preparation of 3-(trifluoromethoxy)aniline (**60**) from 1-chloro-2-(trifluoromethoxy)benzene.[109]



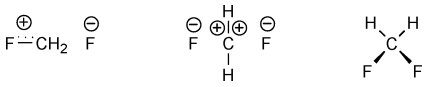
When treated with LIDA in the presence of furan at temperatures above −30 °C and −60 °C, respectively, 1-bromo-3- and −4-(trifluoromethoxy)benzene set free, respectively, 3- and 4-trifluoromethoxy-1,2-didehydrobenzene, which can be instantaneously trapped in a Diels−Alder cycloaddition reaction.[99] The cycloadducts **61** (74%) and **62** (70%) are readily deoxygenated to afford 1- and 2-(trifluoromethoxy)-

naphthalene or converted into bromonaphthols by consecutive bromination, dehydrobromination, and acid-catalyzed isomerization.[99]



4. Structure

As pointed out in the introduction, the *anomeric effect* is a characteristic feature of all compounds carrying a resonance-active electron-donor and an electron-acceptor in geminal positions. Substances having two identical substituents such as difluoromethane do not fall in this category. Their exceptional stability can be accounted for without resorting to anomeric interactions[110] either by referring to an electrostatic model[111] or, in an intuitively more appealing way, on the basis of the attractive and repulsive forces emanating from σ-polarized bonds in terms of the Gillespie−Nyholm formalism.[112,113]

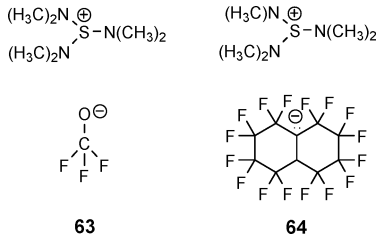


Structural investigations of α-fluorinated ethers and amines have been conducted with crystalline samples using X-ray diffraction and in the gas-phase relying on electron diffraction or microwave, infrared, and Raman spectroscopy. In many cases, the experimental work has been complemented by force field and ab initio calculations. Other studies, mainly by nuclear magnetic resonance, are scarce.

4.1. Crystallography

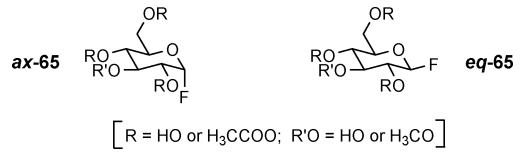
The crystal structure of the "exotic" bis(trifluoromethyl) trioxide [*O*,*O*′′-bis(trifluoromethyl)trioxane] has been published in addition to its gas-phase geometry.[114] However, the bulk of systematic investigations focuses on α-fluoropyranoses and α-di- or polyfluorinated 1,3-benzodioxoles or dihydrobenzodioxines.

As one would expect, the anomeric effect reveals itself by a lengthening of the acceptor bond and a shortening of the donor bond. The differences are nevertheless small at least as far as the carbon−fluorine bond is concerned, which in general is elongated by just two hundreds of an Å. In contrast, anomerically active carbon−oxygen bonds may shrink by almost one tenth of an Å. The stable tris(dimethylamino)sulfonium (TAS) trifluoromethoxide **63**[115] represents an extreme case. The oxido center being an exceptionally powerful donor atom, the three carbon−fluorine bonds are stretched by approximately 0.07 Å and the carbon−oxygen bond contracted by 0.09 Å relative to trifluoromethanol[115] and by 0.21 Å relative to methanol.[116] The electronically equivalent TAS perfluorocarbanion ion pair **64** also exhibits unusual bonding patterns.[117]

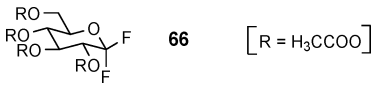


4.1.1. α-Fluoropyranoses

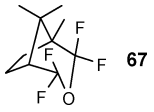
^{13}C NMR spectroscopy reveals differences that may be taken as a first evidence for anomeric effects in the α-fluoropyranose series. 1-Fluorotetrahydropyran-2,3,4,6-tetraol, its O^2,O^3,O^6-triacetoxy-O^4-methyl derivative and other analogues ***ax*-65** and ***eq*-65**[118] have, by some 10 Hz, a smaller one-bond ^{13}C−^{19}F coupling constant than their β-epimers, findings that at first sight appear to be in conflict with the concept of anomeric bond weakening. However, the paradox can be reconciled. The sign of $^1J_{^{13}C,^{19}F}$ being negative, the axial C,F couplings have in fact a less positive value than the equatorial ones.[118]



The geminally 2,2-difluorinated 3,4,5,6-tetraacetyl-2-desoxy glucopyranose (**66**)[119] exhibits unequivocally nonidentical C−F bond lengths, according to crystallography.[120] The difference of 1.5 hundredth of an Å falls in the expected range.[120]



A few naked fluoropyranes have also been reported. The most remarkable model compound outside the sugar family is that of the 2,2,4,4-tetrafluoro-1,8,8-trimethyl-3-oxybicyclo[3.2.1]octane (**67**).[121] Unfortunately, no crystal structure is yet available.

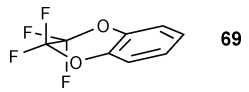


4.1.2. α-Fluorinated 1,3-Benzodioxoles and Dihydrobenzodioxines

The flatness of the benzodioxole ring skeleton forces the geminal pair of fluorine atoms at the 2-position into a perfectly eclipsed array with the lone pairs of the oxygen atoms. The resulting *syn*-periplanar anomeric effect lengthens the CF bond only slightly from 1.325 Å (typical for a gauche interaction of a CF entity with a lone pair; see below) to 1.335 Å

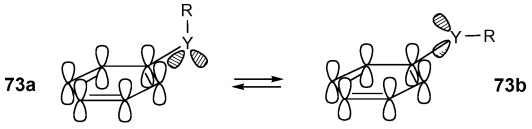
as found in both the 2,2-difluoro-1,3-benzodioxole-4- and -5-carboxylic acid (**68a** and **68b**).[120]

In contrast, the 2,2,3,3-tetrafluoro-2,3-dihydro-1,4-benzodioxine derivative **69** occupies a half-chair conformation and clearly shows differences between quasi-axial and quasi-equatorial fluorine atoms. The average bond lengths of 1.355 and 1.330 Å differ significantly.[120]



4.1.3. Aromatic Trifluoromethyl Ethers and Sulfides

An in-depth search by Roche researchers in the Cambridge Structural Database unearthed six trifluoromethoxy-substituted and one trifluoromethylthio-substituted model compounds. In a single case, the confirmation was found to be skew (dihedral angle C=C/OCF_3: 36°). In all other cases, the OCF_3 proved to adopt a virtually orthogonal orientation **73a** as long as at least one ortho position remained unoccupied.[122,123] This is in striking contrast to the behavior of the fluorine-free analogues. Anisole, *prim*-alkoxy arenes, and (trifluorothio)benzene revealed themselves as virtually coplanar molecular entities **73b** (having dihedral angles of <10°).[122,123]

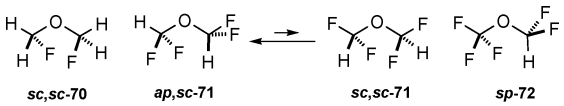


[YR = OCH_3, OCF_3, SCF_3 *etc.*]

4.2. Gas Phase Behavior: Ground-State Structures

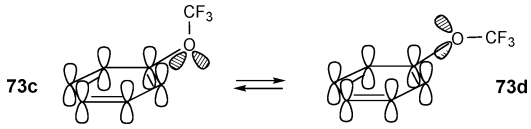
According to an electron diffraction study, tris(trifluoromethyl)amine is nearly flat (∠CNC 117.9°; ∠FCF 108.3°).[124] This implies a negligibly small barrier to pyramidal inversion. Bis(trifluoromethyl) oxide is all-staggered. The experimentally determined ∠COC angle of 119.1°[125] is well reproduced by ab initio calculations (∠118.9°).[126]

Bis(fluoromethyl) ether exists in a dissymmetrical, doubly *syn*-clinal (***sc,sc*-70**) conformation.[127] A predominant *anti*-periplanar/*syn*-clinal conformation (***ap,sc*-71**) for bis(difluoromethyl) ether is accompanied by a minor proportion (about 20%) of a chiral, doubly *syn*-clinal (***sc,sc*-71**) form.[127] Difluoromethyl trifluoromethyl ether favors a *syn*-periplanar (***sp*-72**) conformation.[127]

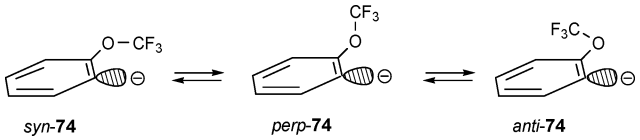


4.3. Conformational Preferences and Mobility

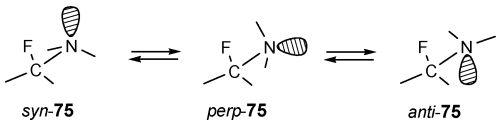
As already suggested by crystallography,[122,123] the OCF_3 group in (trifluoromethoxy)benzene tends to adopt a perpendicular position (**73c**) with respect to the aromatic ring, whereas the methoxy group of anisole seeks the in-plane orientation. These divergent conformational preferences have been confirmed by electron diffraction, microwave, matrix infrared, and Raman methods.[128,129] However, it is not yet clear whether the perpendicular form is the exclusive or only the preponderant conformer. Quantum chemical calculations[128−130] are not really conclusive in this respect. Unlike the MP2/6−311(2d) basis set that favors the perpendicular conformer (**73c**), the B3LYP algorithm puts it at equal energy as the coplanar structure (**73d**) and the HF/3-21G* approximation predicts a skew geometry.[128] Accordingly, the barriers to torsional isomerization vary between 0.0 and 2.8 kcal/mol depending on the computational method applied.[129,131,132]



The *ortho*-(trifluoromethoxy)benzenide ion (**74**) has been evaluated at the MP2(fc)/6-311+G**//HF/6-31+G* level of theory. Most conformers were found to populate a flat valley that extends from the *syn*-periplanar to the perpendicular arrangement, and only thereafter the free energy rises slowly to attain a 1.7 kcal/mol maximum at the *anti*-periplanar state.[130,133]

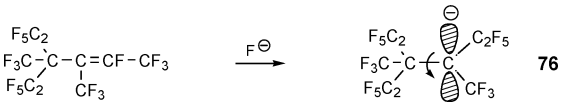


A landmark article published in 1990 probed theoretically the free energy and geometry of fluoromethylamine (**75**) as a function of the C−F/N-lone pair dihedral angle.[134] The anti-periplanar (180°) conformer which had the longest C−F (1.410 Å) and the shortest C−N bond proved to be electronically stabilized by as much as 7.5 kcal/mol. The syn-periplanar isomer, which suffers from imperfect orbital overlap and, in addition, repulsive eclipsing interactions, benefits from only 1.5 kcal/mol of anomeric resonance energy.[134] Such theoretical investigations of the torsional energies associated with anomerically biases substrates were extended in several directions.[135]



The carbanion **76** can be readily generated by fluoride addition to the so-called "tetrafluoroethylene pentamer". Being isoelectronic with tris(perfluoroalkyl)amines (see above), its negatively charged carbon can be safely assumed to be planarized. To overcome the steric hindrance and to promote the rotation between the carbanion center and the ter-

tiary perfluoroalkyl substituent, an activation energy of some 10 kcal/mol is required as monitored by variable-temperature nuclear magnetic resonance spectroscopy.[136]



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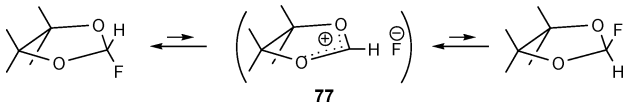
While the anomeric effect can be conceived as an incipient ionization it may develop into a real one. According to dynamic nuclear magnetic resonance studies, the halogen atom of 2-fluoro-4,4,5,5-tetramethyl-1,3-dioxole switches rapidly from one face of the ring to the opposite one. The pronounced solvent polarity effect on the positional exchange rate, in nitroethane 30000 times faster than in tetrahydrofuran, lends support to the alleged intermediacy of a dioxonium-carbenium fluoride ion pair **77**.[137]



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5. Properties

This Chapter will be kept concise as all properties-related issues have been authoritatively reviewed by B. E. Smart.[138,139] Thus, we can content ourselves with throwing a few glimpses on special topics.

5.1. Boiling and Melting Ranges of Polyfluoro Ethers

The boiling points of chloromethanes increase with the molecular mass: methane −164 °C, chloromethane −24 °C, dichloromethane +40 °C, trichloromethane (chloroform) +62 °C, and tetrachloromethane +77 °C. In contrast, the boiling points of fluoromethanes increase only when the first and second halogen is introduced but decrease upon the third and fourth substitution: methane −164 °C, fluoromethane −78 °C, difluoromethane −52 °C, trifluoromethane (fluoroform) −84 °C, tetrafluoromethane −129 °C. In general, the replacement of a hydrogen by a fluoro-atom in a dihalomethane or trihalomethane lowers the boiling point by approximately 40 °C. The high volatility of Freon-type halofluorohydrocarbons causes much environmental concern as they enter in the stratosphere where their dissociation products trigger ozone-depleting processes.

Whenever fluorine raises the boiling range this can be attributed to an increased dipole moment. However, this effect is generally overridden by the poor polarizability of organofluorine compounds. Polarizability expressed by the molar refraction R does indeed correlate linearly with the boiling points within the dihalomethanes, trihalomethanes, and tetrahalomethanes series.[140]

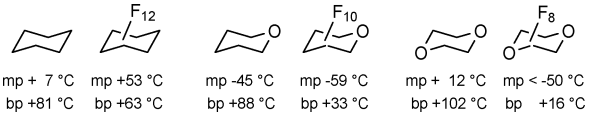
Fluorine tends to increase volatilities also in the aromatic series. Difluoromethyl phenyl ether[22] and trifluoromethyl phenyl ether[25] distill at lower temperatures (139 and 106 °C, respectively) than anisole (155 °C). Unfortunately, the boiling point of fluoromethyl phenyl ether[13,141] has never been reported.

Table 3. Lipophilicity Increments π as Assessed for Monosubstituted Benzenes H_5C_6-X[149]

substituent	π	substituent	π
X = H	0.00	X = CH_3	0.56
X = F	0.14	X = CF_3	0.88
X = Cl	0.71	X = OCF_3	1.04
X = Br	0.86	X = SCF_3	1.44
X = I	1.12	X = SF_5	1.23

The case of so-called "aromatic-dimers" has raised much attention and profound discussion.[142] For example, both benzene and hexafluorobenzene freeze in the temperature range between 5 and 6 °C. However, their 1:1 mixture melts around +24 °C.[143,144] Such arene-stacking phenomena have led to the design of nonpolar DNA mimics.[145,146]

Packing forces appear to affect also fluorinated aliphatic compounds considerably. Whereas perfluorination increases the melting point of cyclohexane by 44 °C, it lowers that of tetrahydropyran by 14 °C and that of 1,4-dioxane by more than 50 °C.[147,148]



5.2. Lipophilicity

Lipophilicity is a key parameter that governs the absorption and transport, hence, the bioavailability, of drugs and crop-protecting chemicals. Fluorine substitution is the magic tool for fine-tuning the positioning of bioactive substances between aqueous and fatty media. Its poor polarizability plays again a crucial role for the phase behavior.

While both trifluoromethyl and trifluoromethoxy substituents invariably boost the lipophilicity (Table 3), single fluorine atoms may alter this parameter in either direction. If the halogen occupies a vicinal or homovicinal position with respect to a hydroxy, alkoxy, or carbonyl oxygen atom, it enhances the solvation energy in water more than in organic solvents (such as 1-octanol or chloroform) and hence lowers the lipophilicity.[122] Conversely, a fluorine atom placed in the vicinity of a basic nitrogen center will diminish the donor capacity of the latter and, as a corollary, cause a strong lg$D$ (lg$P$) increase.[122]

5.3. Acidifying Effect of a Trifluoromethoxy Substituent

Because of the presence of three halogen atoms, a trifluoromethoxy group is of course predestined to act as a electron-withdrawing substituent. On the other hand, the oxygen atom can mobilize its lone pairs and thus facilitate electrophilic aromatic substitutions at ortho and, in particular, para positions (see Section 3.1.5.). Therefore, it is intriguing to determine how trifluoromethoxy and related groups modulate the acidity of a few prominent structural families.

5.3.1. Benzoic Acids

The pK_a measurement of Yagupolskii,[150,151] Sheppard,[152,153] and collaborators provided consistent results (Table 4). Ranked in comparison with other

Table 4. pK_a Values of *meta*- and *para*-Monosubstituted Benzoic Acids X-C_6H_4-COOH[150−154]

substituent X	pK_a^{meta}	pK_a^{para}
H	5.7	5.7
F	3.9	4.1
Cl	3.8	4.1
Br	3.8	4.0
CF_3	5.2	5.2
CH_3	4.1	4.5
OCF_3	5.2	5.2
OCF_2CHF_2	5.2	5.3
SCH_3	5.6	5.7
SCF_3	5.1	5.0
SCF_2CHF_2	5.2	5.0
SO_2CH_3	3.5	3.6
SO_2CF_3	4.5	4.3
NO_2	3.5	3.4

Table 5. pK_a Values of *meta*- and *para*-monosubstituted Phenols X-C_6H_4-OH[152−154,157]

substituent X	pK_a^{meta}	pK_a^{para}
H	9.9	9.9
F	9.3	9.8
Cl	8.2	8.2
Br	8.9	8.2
CF_3	9.0	8.8
OCH_3	9.7	10.2
OCF_3	9.0	9.4
OCF_2CF_3	9.0	9.3
SCH_3	9.0	8.7
SCF_3	9.1	8.8
SCF_2CHF_2	9.1	8.9
SO_2CH_3	8.6	8.4
SO_2CF_3	7.9	6.8
NO_2	8.4	7.1

standard substituents, trifluoromethoxy reveals itself as being moderately electron-withdrawing. It resembles a chlorine atom also in this respect.

The acidity of (trifluoromethoxy)benzoic acids carrying an extra fluoro, trifluoromethyl, or methoxy substituent can be estimated by summing up the individual incremental contributions of each atom or group.[155] This confirms the hypothesis[156] that the effects of first-row elements (and only of those) are additive.

5.3.2. Phenols

The pK_a measurements accomplished in the phenol series essentially parallel the data collected in the benzoic acid series (Table 5). Again, a trifluoromethoxy substituent located at the meta- or para-position lowers the pK_a values by 0.5−1.0 units. The new feature is the through-resonance extending from the hydroxy function to the para position, which, depending on the nature of the substituent, may be more acidified than the meta position despite the increased distance.

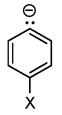
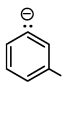
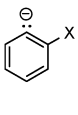
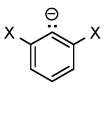
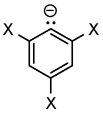
5.3.3. Anilinium Salts

Whereas phenols are considerably less acidic than benzoic acids, anilinium salts are slightly more acidic (Table 6). Moreover, substituent effects are more pronounced than in the former series (as evidenced by Hammett ρ constants of 2.11, 1.0 and 2.77).[158] Particularly noteworthy is how the OCF_3-acidifying effect is diminished when the substituent is moved from the meta to the para position but strengthened in the case of a SCF_3 group (Table 6).

Table 6. pK_a Values of *meta*- and *para*-monosubstituted Anilinium Salts[153,154,159]

substituent X	pK_a^{meta}	pK_a^{para}
H	4.6	4.6
F	3.5	4.7
Cl	3.5	4.1
Br	3.5	3.9
CF_3	3.5	2.5
OCH_3	4.2	5.3
OCF_3	3.3	3.8
OCF_2CHF_2	3.4	4.0
OCF_2CF_3	3.2	3.8
SCH_3	4.0	4.4
SCF_3	3.3	2.8
SCF_2CHF_2	3.4	2.9
SO_2CH_3	2.6	1.4
SO_2CF_3	1.8	0.0
NO_2	2.5	1.0

Table 7. MP-2 ab Initio Proton Affinities of Trifluoromethoxy-Substituted Benzenides Relative to the Phenyl Anion[a]

X					
OCH_3	+0.5	−1.4	−9.2	−20.2	−20.1
OCF_3	−9.5	−10.9	−16.8	−35.7	−46.0
CF_3	−10.1	−10.7	−13.7	−27.6	−38.5

[a] ΔH^{Prot} 400.0; all numbers in kcal/mol.[133]

5.3.4. Aromatic Hydrocarbons

Attempts to measure the gas-phase acidity of (trifluoromethoxy)benzene were hampered by the propensity of this substrate to fragment by setting free difluorocarbene. However, ab initio calculations[133] have unveiled the exceptionally powerful electron-withdrawing effect of the OCF_3 unit. In fact, it stabilizes an *ortho*-benzenide anion not only far better than a methoxy but even more strongly than a trifluoromethyl group (Table 7). Its charge-attenuating effect is long-ranging, leveling off only moderately when the substituent is shifted from the ortho through the meta to the para position of the carbanion (Table 7). When two or three trifluoromethoxy groups are present in the same molecule, their individual contributions to the overall acidity are essentially additive (Table 7).[133]

6. Applications

Trifluoromethoxy groups and related entities hold a considerable promise for the fine-tuning of technical and biological properties. For reasons of space, only three economically important areas of applications will be covered. Specialized reviews should be consulted for other prominent topics such as polyfluorinated anesthetics, blood surrogates,[160] fluids, propellants, fire extinguishers, and polymers.[161−163]

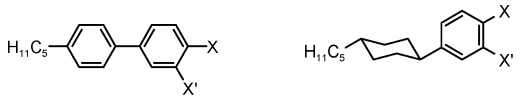
6.1. Electrooptical Displays

Liquid crystals are hybrids placed in the no-man's-land between the crystalline phase and the isotropic

phase. Although they are fluids, they are anisotropic due to intermolecular interactions. Depending on the specific nature of these long-range ordering effects one distinguishes numerous subcategories of mesophases, the most prominent being nematic (threadlike) and smectic (soap-like).[164,165] Nematic liquid crystals serve as the basis of most current liquid crystal displays (LCDs). Their molecular shape is typically rodlike.

The technical progress was breathtaking in the three past decades. Starting with early unsophisticated LCD designs, the evolution advanced to modern active matrix addressed and eventually plasma addressed displays (the latter making flat television screens of more than 1-m diagonal width feasible). In parallel, the material requirements were continuously raised. The specifications that have nowadays to be met include a wide nematic meso phase temperature range (extending, e.g., from −40 to +110 °C) and, as a corollary, a high clearing temperature (for the nematic → isotropic transition), a birefrincence Δn falling in narrowly defined limits (to secure an optimal contrast ratio), high dielectric anisotropy $\Delta\epsilon$ (to reduce the driving voltages to further miniaturize the electronic components and at the same time lower the power consumption, a goal that can be potentiated by implementing reflective devices), to diminish the rotational viscosity (to shorten the switching time to <20 ms), to control the elastic constants (to minimize "splay" deformation) and, last but not least, to safeguard the so-called "reliability" criteria of the material (chemical and photochemical robustness; voltage holding ratio; residual direct current; resistivity; ion density).[166] To solve such a multidimensional task, usually 10 to 15 or even more molecular entities are mixed to an LCD cocktail.

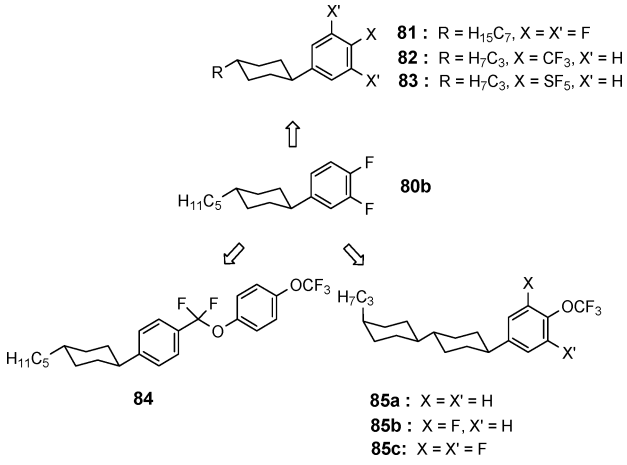
New electrooptical materials are developed guided by a blend of an empirical trial-and-error and a rational approach relying on proven principles such as polar substituents and polarizability. Fluorine compounds marked the breakthrough in the entire field.[166−169] Almost isosteric with hydrogen,[170,171] the smallest halogen causes as a substituent a minimum of perturbation in size but exerts a pronounced influence on physical parameters such as dipole moments or permittivity.[172] When in the early eighties the LCD specialists abandoned twisted nematic (TN) phases in favor of super-twisted (STN) ones, they switched from cyano compounds (e.g., **78a**−**b**, X = CN, X′ = H) to mono- and difluoro analogues (**79a**−**b** and **80a**−**b**, X = F, X′ = H, and X = X′ = F, respectively).[166]



78a : X = CN, X' = H
79a : X = F, X' = H
80a : X = X' = F

78b : X = CN, X' = H
79b : X = CN, X' = H
80b : X = X' = F

Subsequent work led from the difluoro model **80b** to the trifluoro analogues **81** and to the trifluoromethyl- and pentasulfuranyl-substituted derivatives **82** and **83** all recognized later to be blind alleys. In contrast, difluoromethoxy and trifluoromethoxy bearing structures, such as **84** and **85a**−**c**, were found to exhibit quite attractive property profiles. Together with the 3,4-difluorophenyl-based materials, they play today a central role in commercial active matrix displays.[166]



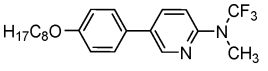
81 : R = $H_{15}C_7$, X = X' = F
82 : R = H_7C_3, X = CF_3, X' = H
83 : R = H_7C_3, X = SF_5, X' = H

80b

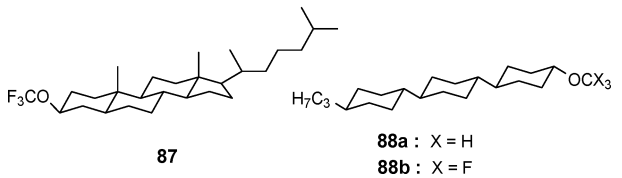
84

85a : X = X' = H
85b : X = F, X' = H
85c: X = X' = F

The most recent progress was achieved in the field of LED (light-emitting diode) additives. Thus, 2-methyl(trifluoromethyl)amino-5-(4-octyloxyphenyl)-pyridine **86**, when compared to the fluorine-free analogue, was found to improve both the range of the smectic phase of a ferroelectric liquid crystal host and its speed of response to an electric field.[173,174] 3β-(Trifluromethoxy)cholestane **87** revealed itself as an excellent dopant for STN (super-twisted nematic, for passive matrixes) and TFT-TN (thin film transistor twisted nematic, for active matrixes) type liquid crystal displays.[173] Particularly noteworthy is the comparison between the methoxy ether **88a** and its trifluoro analogue **88b**. Whereas the parent compound **88a** exhibited only S_B phase behavior in a narrow temperature range, congener **88b** produced an N phase in the entire temperature range from 157 to 189 °C and, in addition, also qualified as a superb LC additive.[173]



86

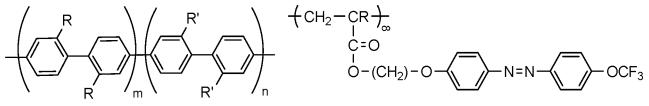


87

88a : X = H
88b : X = F

Present research efforts appear to be focused on the synthesis of novel low-molecular compounds. The potential of polymeric liquid crystals and the modulation of their properties by trifluoromethyl and trifluoromethoxy substituents deserves nevertheless to be mentioned in this context. The *p*-polyphenylene rigid-rod models[175] **89** and the polyacrylates[176] **90** having dangling 4-(trifluoromethoxy)-

azobenzene side chains are typical examples for such development.



89a : R = R' = CF_3
89b : R = CF_3, R' = OCF_3
89c : R = R' = OCF_3

90 : R = H, CH_3; n = 2 - 6

6.2. Agrochemicals

The past 30 years have witnessed a period of significant expansion in the use of fluorinated compounds in the field of agrochemicals research and development. These efforts also comprised the introduction of (difluoromethoxy)- or (trifluoromethoxy)-aryl fragments and other anomerically biased structures into crop protection products. What makes the (trifluoromethoxy)aryl substructure attractive is its ability to improve the membrane permeability of the compounds in which it is embedded. The raw material for such products, (trifluoromethoxy)benzene, is produced today on an industrial scale.

The successful utilization of the special α-fluorinated ethers, thioethers, and amines in the design of active ingredients for modern agrochemicals is testified by various commercial products in all the major areas of crop protection, in particular, insecticides, fungicides, plant growth regulators, and herbicides. The biochemical targets are generally well-known:

(i) Voltage-gated sodium channel modulators; γ-aminobutyric acid (GABA) *receptor/chloride ionophore complexes*, *chitin biosynthesis pathways*, and *mitochondrial electron transport of complex I* for the insecticides

(ii) *Sterol biosynthesis*; *respiratory chain/succinate dehydrogenase (SD)*; *germination* and *hyphal growth*; *protein kinase* for the fungicides

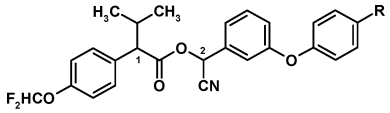
(iii) *Gibberellin biosynthesis pathway* for the plant growth regulators

(iv) *Acetolactate synthase (ALS)* and *protoporphyrinogen IX oxidase (PPO)* for the herbicides.

6.2.1. Insecticides

Voltage-Gated Sodium Channel (vgSCh) Modulators. The *vgSCh*s,[177] integral transmembrane proteins, trigger action potentials in nerve, muscle, and other excitable cells. Therefore, the *vgSCh* is the target for the action of many neurotoxins and some commercially important classes of insecticides such as pyrethroid insecticides, which keep the sodium channels open.[178]

Besides natural pyrethrins, 37 ester and three nonester type pyrethroids are currently registered worldwide.[179] To get mite-active derivatives, further simplification of the pyrethroid basic structure and incorporation of α-fluorinated ether substituents such as $OCHF_2$ or $OCBrF_2$ was found to be essential. Miticide activity of noncyclopropane-type pyrethroidssuch as compounds **91a**,**b** and **92a**−**c** is governed by not only direct toxic action, but also augmented by their effects on behavior, reproduction, and development of the mites.[180] The irritant and repellent properties of these pyrethroids (**91** and **92a**) play a significant role in their miticide action.

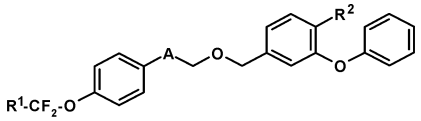


91a : R = H Flucythrinate
91b : R = Br Flubrocythrinate

Flucythrinate (**91a:** Payoff, Cybolt, Cythrin),[181] a mixture of diastereomers (the most active having 1*S*,2*S*-configuration), has contact and stomach action, suppresses phytophagous mites, and is highly active against ticks but not against spider mites. It controls a wide range of sucking insect pests and beetles, particularly on cotton, and lepidoptera, homoptera, and coleptera in pome and stone fruit orchards. Effective dosages are 25−150 g a.i./ha depending upon pest, population pressure, crop, and frequency of treatment.

In 1992, the optically active flubrocythrinate (**91b:** ZXI 8901, lubrocythrinate)[182] also called *"Zhong-Xi bromofluoropyrethrin"* was launched. As a pesticide of high efficacy, low mammalian toxicity, and a broad activity spectrum against insects and mites, it is useful to protect cotton, vegetables, top fruit, tea, wheat, and other crops against destructive insects and mites such as aphids, bollworm, and red spider mites. In addition, compound **91b** is active against eggs and larvae and has residual activity lasting more than three weeks.

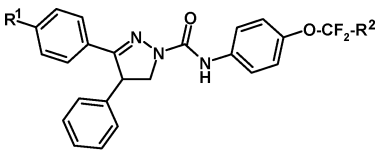
The nonester pyrethroid Fubfenprox (**92a:** MTI-732, Prene EL, Cyprene EL, Sirbon Anniverse)[183] shows contact activity as a broad spectrum acaricide and is knockdown active. It controls all stages of red spider mites, fruit tree red mites, two-spotted spider mites, and rust mites, including the hatching stage of eggs, on citrus fruit, vines, vegetables, tea, and ornamentals.



92a: A = CMe_2, R^1 = Br, R^2 = H Fubfenprox
92b: A = CHCyclopropyl, R^1, R^2 = F F 1327
92c: A = $SiMe_3$, R^1, R^2 = H SSI-117

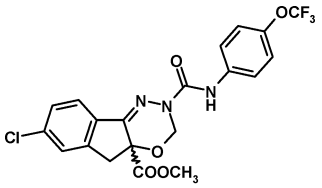
Pyrazoline carboxamides with α-fluoroalkoxy substituents at one of the aryl rings, such as compounds **93a** and **93b**, developed by Philips Duphar in the 1970s,[184] exhibit pesticidal activity against arthropods. On the other hand, compound **93c** shows activity against a wide range of lepidoptera, coleoptera, hemiptera, and diptera pests. The further

development of all these pyrazolines has nevertheless been discontinued.



93a : R^1 = Cl, R^2 = F
93b : R^1 = Cl, R^2 = CHF_2
93c : R^1 = CHF_2, R^2 = F

Finally, the proinsecticide Indoxacarb (**94:** DPX-MP062, Steward, Avaunt, Tornado, Avantar)[185] belonging to the 1,3,4-oxadiazine family was disclosed in the late 1980s and early 1990s. The commercial product **94** contains the inactive (*R*)-enantiomer (DPX-KN 127) and the active (*S*)-enantiomer (DPX-KN 128) in the ratio of 25:75. Like the pyrazolines **93a**−**c**, it blocks the sodium channels.[186]

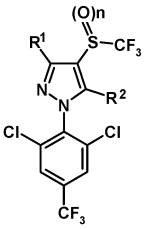


94 Indoxacarb
(S) > (R) enantiomer

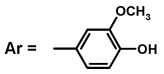
Indoxacarb (**94**) shows contact and ingestion activity and is effective in controlling populations of lepidopteran pests in various crops such as cotton, vegetables, and fruit as well as in viticulture. Furthermore, it has larvicidal and ovicidal activity and shows an excellent knockdown activity, while preserving beneficial insects and mites. Because of a different binding site, no cross-resistance with pyrethroids has been observed.

Inhibitors of the γ-Aminobutyric Acid (GABA) Receptor/Chloride Ionophore Complex. The GABA receptor/chloride ionophore complex has been the focus of intense interest as a target of insecticidal action and its role in resistance as well.[187] The GABA-gated chloride channels are located in the insect central nervous system (CNS) and also in peripheral nerves where they mediate the proper integration of neuronal activity and muscle relaxation by inhibitory actions.[188]

One of the most important noncompetitive GABA antagonists in insects belong to the arylaminopyrazole class represented by the trifluoromethylsulfoxide-containing Fipronil (**95a:** Regent, Prince, Texas, Metis)[189] launched in 1993 by Rhone-Poulenc. This compound either acts by interacting with an allosteric binding site or by irreversible binding[190] and has a wide margin of safety because it exhibits little activity at the corresponding mammalian channel.[191] Fipronil (**95a**) is a broad spectrum insecticide active by contact and ingestion. It is systemic in plants and is highly active against lepidopterous larvae and numerous soil and foliar insects from the orders coleoptera, diptera, hemiptera, and lepidoptera as well as grasshoppers and termites. Furthermore, compound **95a** is used in rice seedling boxes in Japan to control brown planthoppers, stem borers, and leafrollers. In addition, compound **95a** is also used as a household insecticide (Maxforce) and was launched in 1994 for veterinary use (Frontline, Topline) as a fast-acting topical flea/tick adulticide[192] for dogs and cats that has rapidly attained a leading position in world sales for this market.

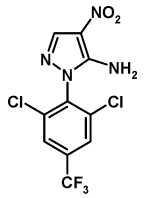


95a : n = 1, R^1 = CN, R^2 = NH_2 Fipronil
95b : n = 2, R^1 = CN, R^2 = NH_2
95c : n = 0, R^1 = CN, R^2 = N=CH-Ar Vaniliprole
95d : n = 0, R^1 = H, R^2 = NH_2 JKU 0422



The trifluoromethylsulfoxide group in the pyrazole **95a** can undergo cytochrome P450-catalyzed oxidation in insects to yield the corresponding trifluoromethyl sulfone metabolite **95b**. The latter is slightly more toxic and 2−6-fold more active on the receptor.[193]

Consequently, this conversion of the proinsecticide **95a** could confer negative cross-resistance in insect strains having elevatated cytochrome P450 detoxification activity. Azomethine formation with the phenylpyrazole amino group leads to vaniliprole (**95c**; Evaluation), another derivative of the precursor **95a**. The trifluoromethylsulfoxide group is a remarkable trigger for insecticidal activity (*"indication shift"*). This is shown for the arylaminopyrazole **95d** (JKU 0422) and its herbicidal active nitro derivative **96**.[194]



96

Insect Growth Regulants (IGRs). Over the past three decades, the benzoylphenyl ureas have been developed and used as commercial IGRs. They act on insects of various orders by inhibiting chitin biosynthesis,[195] thereby causing abnormal endocuticular deposition and abortive molting.[196]

Up to now 10 benzoylphenyl ureas have been commercialized or are in late-stage development. Early studies on structure/activity relationships (SAR) of benzoylphenyl ureas reflected little scope for variation of substituents at the benzoyl ring. Only derivatives with at least one *ortho*-substituent (Hal or R^1) retained insecticidal activity. Such an *ortho*-

Table 8. Physical Properties of Phenylbenzoyl Urea Insecticides 97a−e

cpd no.	common name	m.p. (°C)	log $K_{O/W}$	vapor pressure (Pa) at 25 °C	water solubility (mg /L) at 25 °C
97a	triflumuron	195	4.91	5×10^{-8}	0.025
97b	hexaflumuron	202−205	5.7	5.9×10^{-9}	0.027[a]
97c	lufenuron	174.1	5.1	$< 4 \times 10^{-6}$	< 0.06
97d	novaluron	176−179	5.3	$< 5 \times 10^{-4}$	0.053
97e	noviflumuron	156−157	4.94	2.2×10^{-10}	0.194[b]

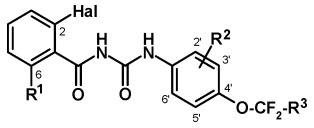
[a] At 18 °C. [b] 20 °C.

Table 9. Use of Phenylbenzoyl Urea Insecticides 97a−e

		agricultural[a]			
cpd no.	trade names[a]	crops	pests	public health[a]	animal health[a]
97a	Alsystin		Lepidoptera, psyllidae, diptera, coleoptera		
	Baycidal			cock-roaches	
	Staricide				fleas
97b	Consult, Ridel, Trueno, Readle, Recruit, Consul	fruits, potatoes, rice, vegatables, cotton, forestry	larvae of isoptera, lepidoptera, coleoptera		
	Sentricon			termites	
97c	Match, Sorba, Lusty, Axor	fruits, cotton, maize, citrus, vegtables	larvae of lepidoptera, coleoptera, white fly, rust mites		
	Program				preadult fleas in dogs and cats
97d	Rimon, Galaxy Pedestal, Counter EC	fruits, cotton, cabbages, tomatoes, ornamentals	coleoptera, homoptera, diptera, lepidoptera		
97e	Recruit III			termites, ants, cockroaches, fleas	

[a] Selection.

substituent (R^1) can be methyl, OCF_3, or OC_2F_5 and lead to active derivatives. However, all commercialized products have ortho-halogen substituents and the insecticidal activity generally follows in the order (Hal, R^1): 2,6-F_2 > 2-Cl,6-H > 2,6-Cl_2.



Among the ureas currently on the market, only the triflumuron (**97a:** Hal = Cl; R^1 = H)[197] does not have the 2,6-difluoro substituent pattern (Hal, R^1 = F). The arylamino part is much more prone to variation. However, for optimum activity the aryl ring has to be substituted by electron-withdrawing groups such as halogen, halogenalkyl, or α-fluoroalkoxy (see Table 8).

The intense search for potent benzoylphenyl ureas provided further compounds containing a α-fluoroalkoxy residue in the 4′-position such as hexaflumuron (**97b:** Hal, R^1 = F; R^2 = 3′,5′-Cl_2; R^3 = CHF_2),[198] lufenuron (**97c:** Hal, R^1 = F; R^2 = 3′,6′-Cl_2; R^3 = CHF−CF_3),[199] novaluron (**97d:** Hal, R^1 = F; R^2 = 3′-Cl; R^3 = CHF−OCF_3),[200] and noviflumuron (**97e:** Hal, R^1 = F; R^2 = 3′,5′-Cl_2, 6′−F; R^3 = CHF−CF_3).[201] They are all far more potent than diflubenzuron against various agricultural pests.[202]

Taken all together, the phenylbenzoyl ureas **97a−e** show an impressively large pesticidal spectrum (see Table 9). Compound **97a** has a broad insecticidal activity against biting insects such as *Spodoptera frugiperda* down to 0.064 ppm and against *Phaedon cochleariae* down to 8 ppm.[203] The phenylbenzoyl urea **97b** is used as a systemic insecticide and larvicide with stomach and some contact action. It has a fast knockdown activity and used to control broad spectrum of insects, especially against major *Heliothis* species. It is particularly active against young larvae and shows also strong ovicidal activity due to its ability to penetrate egg shells. This is most noticeable on newly laid eggs. The product **97b** also suppresses fecundity in adult females. The phenylbenzoyl urea **97c** acts more by ingestion than by contact. It demonstrates activity against larval and nymphal stages of arthropods, rust mites on citrus, and citrus whitefly. The product is not plant-systemic but has some translaminar activity against *Spodoptera littoralis* on cotton leaves. The product has a veterinary use against preadult fleas such as *Ctenocephalides felis* and *Ctenocephalides canis* in dogs and cats. The lipophilicity of **97c** leads to its deposition in adipose tissues of animals from where it is slowly released into the bloodstream. This permits effective blood concentrations to be maintained throughout the recommended oral dosing interval of one month. Compound **97d** is applied as a foliar spray broad-spectrum phenylbenzoyl urea, and it acts from both ingestion and contact. The compound is a powerful suppressor of lepidopteran larvae such as *S. littoralis*, *Spodoptera exigua*, *Spodoptera frugiperda*, *Helicoverpa armigera*, and *Tuta absoluta*, all species being known pests in corn, cotton, and vegetables. It also efficiently controls whiteflies and leafminers. Furthermore, no cross-resistance has been noted between

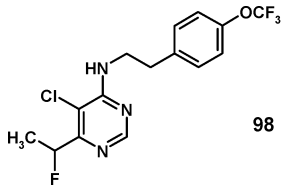
Table 10. Physical Properties of Phenylpyrrole Fungicides 102a,b

cpd no.	m.p. (°C)	log $P_{O/W}$	vapor pressure (Pa) at 25 °C	water solubility (mg /L) at 25 °C	light stability $t_{1/2}$ [h]	thermal stability
102a	144.9−151.1	3.86	1.1×10^{-5}	4.8	48.0	up to 250 °C
102b	199.8	4.12	3.9×10^{-7}	1.8	24.9	up to 250 °C

97d and other phenylbenzoyl urea IGRs used against *Bemisia tabaci*, *Spodoptera* spp. and *Leptinotarsa*. Total larval mortality was obtained at a concentration of 1 mg a.i./l.[200] Compound **97e** is an insecticide especially active against hymenoptera, e.g., ants, cockroaches, fleas, and termites.

Because of their nontoxicity to vertebrates, the phenylbenzoyl ureas **97a**−**c** and **97e** are also used in veterinary medicine (**97a:** Staricide, **97c:** Program) and in the home (**97a:** Baycidal, **97e:** Recruit III) against animal and human health pests such as fleas, ticks, and cockroaches.

Inhibitors of the Mitochondrial Electron Transport of Complex I. Several inhibitors of the mitochondrial electron transport of complex I (NADH dehydrogenase) are described as so-called METI acaricides. Flufenerim (**98:** UR-50701, Fluimfen)[204] a racemic novel pyrimidineamine is under development at Ube Industries with activity against aphids and whitefly. This product contains a novel (trifluoromethoxy)phenethylamino group and is structurally closely related to the acaricide pyrimidifen.

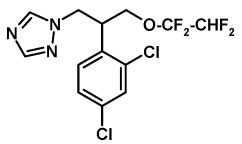


98 Flufenerim

6.2.2. Fungicides

Sterol Biosynthesis Inhibitors (SBIs) and Demethylation Inhibitors (DMIs). The triazole fungicides represent one of the most important chemical groups of widely used agrochemicals. The main mode of action is the inhibition of the cytochrome P450-dependent C_{14}-demethylation of lanosterol, an intermediate in the sterol biosynthetic pathway of fungi.[205]

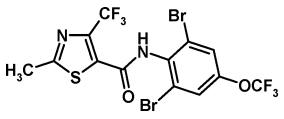
The number of DMIs introduced over the past three decades exceeds around 30 commercial products. Among the azole derivatives launched in the span between 1974 and 1994, almost a fifth (18.5%) had fluorine or fluorine-containing substituents.[206] However, tetraconazole (**99:** Eminent, Lospel, Domark)[207] is the only azole fungicide that contains a fluoroalkoxy residue as a side chain.



99 Tetraconazole

The (*R*)−(+)-enantiomer is more fungitoxic than the (*S*)−(−)-enantiomer, but the product is commercialized as the racemic mixture. The excellent performance of curative and protective foliar treatments of this systemic DMI fungicide made it possible to control *Erysiphe* spp. at exceptionally low dosages (cereals, 125 g a.i./ha) as well as a number of diseases such as *Puccinia* spp., *Podosphaera* spp. (apple, 2.5 g a.i./ha), *Venturia* spp. and *Unicinula* spp. (grapes 25−40 g a.i./ha). It has also translaminar activity. In official trials, **99** showed no phytotoxicity to target crops.

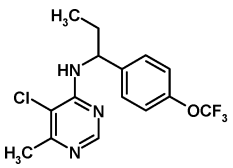
Inhibitors of the Respiratory Chain and Succinate Dehydrogenase (SD). Succinate dehydrogenase is a membrane-bound enzyme that catalyzes the oxidation of succinic acid to fumaric acid. Effects of carboxamides on complex II have been investigated intensively. Following the introduction of carboxin in the 1960s,[208] a range of related compounds has been described,[209] more recent examples including the OCF_3-containing thifluzamide (**100:** MON 24000, Greatum, Greatam, Pulsor, Baton).[210]



100 Thifluzamide

Thifluzamide (**100**) is effective as a fungicide for foliar and seed treatment to control a wide range of basidomycete disease. Control of *Rhizoctonia* sheath blight in rice is achieved through application to seedling boxes and paddy water surface (400−600 g a.i./ha). In peanuts, early season applications of **100** provide season-long suppression of *Corticium rolfsii* and *Rhizoctonia* limb rot. In potatoes, **100** controls both the stem canker and black scurf phases of *Rhizoctonia solani*.

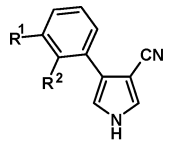
Inhibitors of Germination and Hyphal Growth. Diflumetorim (**101:** Pyricut, Piricat)[211] has protectant activity and is a nonsystemic aminopyridazine fungicide for the control of powdery mildew and rust (*Puccinia horiana*) in small-grain cereals, and for use in horticulture on ornamentals. The product inhibits fungal growth from germination to formation of conidiophores. It is active against fungi resistant to SBIs, dithiocarbamates, benzimidazoles, quinoxalines, and antibiotics.



101 Diflumetorim

Inhibitors of Protein Kinase. Fenpiclonil (**102a**)[212] and its difluoromethylendioxo analogue, Fludioxonil (**102b**: CBA 173506, Saphire, Maxim, Celest, Wispect),[213] are two nonsystemic phenylpyrrole fungicides (see Table 10) active against a wide range of both cereal and noncereal crop diseases.

Their development is an example of the optimization of the natural antibiotic pyrrolnitrin, first isolated from *Pseudomonas pyrrocinia*.[214]



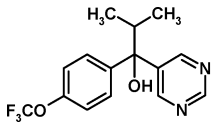
102a : R^1, R^2 = Cl Fenpiclonil
102b : R^1, R^2 = O-CF_2-O Fludioxonil

Their penetration behavior at the surface of the leaves after foliar application and at the outside surface of the seed after seed treatment accounts for their strong protective activity. Especially pyrrole **102b** exhibits a high efficacy as a cereal seed treatment. It controls seed- and soil-borne diseases and gives particularly good control of *Fusarium roseum* and *Gerlachia nivalis* in small-grain cereals. Applied as foliar fungicide, compound **102b** provides high levels of *Botrytis* control in various crops (grapes, 500 g a.i./ha).

Biochemical studies revealed that compound **102a** and **102b** inhibit a protein kinase (PK-III) potentially involved in the osmosensing signal transduction pathway.[215] This underlined the value of their use in antiresistance strategies.[216]

6.2.3. Plant Growth Regulators

Reduction of Internode Elongation − Inhibition of Gibberillin Biosynthesis. Some of the triazoles, but especially their bioisosteric pyrimidine analogues such as flurprimidol (**103:** Cutless, Greenfield, Topflor),[217] exhibit PGR activity in a wide range of mono- and dicotyledonous species by reducing internodal elongation through interaction with the gibberillin biosynthesis pathway.[218]



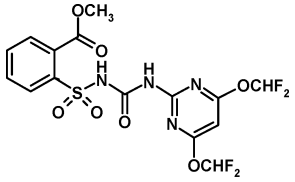
103 Flurprimidol

The racemic product **103** has systemic activity, being translocated in the xylem to the actively growing shoots and leaves. The compound is used to suppress unwanted growth in ornamentals and enhance the quality of ornamentals, trees, turfgrass, and certain speciality food crops. Its application in some flowering plants encourages darker green foliage and more inflorescences.

6.2.4. Herbicides

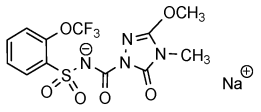
Inhibitors of Acetolactate Synthase (ALS). ALS is a key enzyme within the biosynthesis of branched amino acids such as leucine, isoleucine, or valine.[219] Sulfonylureas are generally extremely potent inhibitors of this enzyme,[220] regardless of the plant source, so that differential sensitivities at the target site play only a little role in the selectivity of these highly efficacious herbicides. The sulfonylureas represent a large and very successful class of selective herbicides[221] originally discovered by DuPont. Although up to now nearly 24% of the sulfonylureas launched so far contain fluorine, only two of them contain a OCF_3 or $OCHF_2$ residue.

Primisulfuron-methyl (**104:** Beacon, Tell, Rifle)[222] is a selective systemic fluorosulfonylurea herbicide, acting by inhibitition of branched-chain amino acids. Compound **104** is absorbed through the roots and leaves, with rapid translocation both acropetally and basipetally. It is employed for post-emergence control or suppression of certain problem grass-weeds including shatter cane, sorghum weeds (*Sorghum bicolor, Sorghum almum, Sorghum halepense*), johnsonsgrass, quack grass, and many broadleaf weeds in maize (20−40 g a.i./ha). Because of the two $OCHF_2$ residues, compound **104** is deactivated by hydroxylation of the phenyl and pyrimidyl moieties followed by hydrolysis or conjugation.

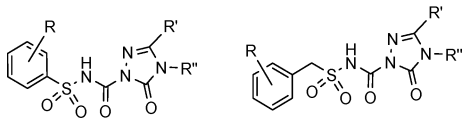


104 Primisulfuron-methyl

The exchange of the *ortho*-$COOCH_3$ by the *ortho*-OCF_3 residue in the sulfonylaryl unit of propoxycarbazone-sodium[223] led to the systemic flucarbazone-sodium herbicide (**105:** Everest, Vulcano),[224] which provides excellent activity against grass weeds and several important broadleaf weeds when applied post-emergence to wheat. In field experiments, the cyclic fluorinated sulfonylurea herbicide **105** has demonstrated strong and consistent activity against wild oat and green foxtail. At the suggested use rate of 30 g a.i./ha, both weeds are selectively controlled in wheat. During optimization of the sulfonyl component the sulfonylaryl **106** showed superior activity compared with the corresponding sulfonylmethylaryl (**107**: position of R = 2 ≫ 3 and 4; R = 2-OCF_3, cereal selectivity). A paricularly good activity and cereal selectivity was identified for the OCF_3 derivative.



105 Flucarbazone-sodium



106 **107**

Inhibitors of of the Protoporphyrinogen IX Oxidase (PPO). PPO inhibitors has a complex mechanism of action that has been reviewed recently.[225] PPO, which is localized in the chloroplast and mitochondrial membranes, catalyzes the conversion of protoporphyrinogen IX to protoporphyrin IX. Many inhibitors mimic the hydrophobic region of protoporphyrinogen IX. New PPO inhibitors with even higher mimicry to protoporphyrinogen IX have

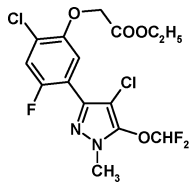
Table 11. α-Fluorinated (Thio)ethers Used as Anesthetics 110a−h

cpd no.	α-fluorinated thio(ethers)	boiling point (°C)[a]	common names	brand names[b]
110a	$F_2HC-O-CHFCF_3$	12.4 ± 25.0	desflurane	Suprane
110b	$F_2HC-O-CHClCF_3$	48.5 ± 0.0	isoflurane	Forane
110c	$FH_2C-O-CH(CF_3)_2$	49.5 ± 25.0	sevoflurane	Sevofrane
110d	$F_2HC-O-CF_2-CHFCl$	59.9 ± 25.0	enflurane	Ethrane
110e	$F_2HC-O-CHF-CF_2-CHF_2$	60.9 ± 25.0	BAX 3224	Synthane
110f	$H_3C-O-CF_2-CHFBr$	87.0 ± 25.0	roflurane	DA 893
110g	$H_3C-O-CF_2-CHCl_2$	105.0 ± 0.0	methoxyflurane	Pentrane
110h	$H_3C-S-CF_2-CHCl_2$	147.4 ± 25.0	thiomethoxyflurane	

[a] 760 Torr. [b] Selection.

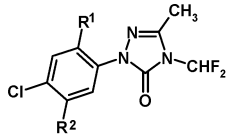
been developed, one set of products resembles three of the pyrrole rings,[226] whereas another set mimics both the hydrophobic and hydrophilic region of protoporphyrinogen IX.[227]

One subclass is the phenylpyrazoles such as the $OCHF_2$-containing pyraflufen-ethyl (**108:** ET-751, Ecopart).[228] This compound is a post-emergence contact herbicide for the control of broadleaf weeds, including cleavers (*Galium aparine*), in cereals and cotton, which also shows excellent crop selectivity for wheat and barley. It is rapidly absorbed by the foliage of broadleaf weeds, resulting in necrosis and desiccation.



108 Pyraflufen-ethyl

The second subclass is the triazolinones with the members sulfentrazone (**109a:** Authority, Boral, Capaz, Spartan)[229] and carfentrazone-ethyl (**109b:** Aim, Platform, Shark, Aurora),[230] both containing the special α-fluorinated amine substitution. Sulfentrazone (**109a**) is a systemic pre- and post-emergence herbicide, which is absorbed by roots and foliage and controls annual broad-leaved and some grass weeds (velvet leaf, barnyard grass, and green foxtail) in cotton and soybeans (430−500 g a.i./ha). Carfentrazone (**109b**) is a selective post-emergence contact herbicide for control of broad-leaved weeds in maize (15−30 g a.i. /ha) and rice (30−40 g a.i./ha) and is absorbed by the leaves.



109a: R^1 = Cl, R^2= NH-SO_2-CH_3, Sulfentrazone

109b: R^1 = F, R^2= CH_2-CHCl-COOH, Carfentrazone-ethyl

6.3. Pharmaceuticals

There has also been an enormous increase in the use of fluorine-containing compounds in the medicinal field. For example, nine of the 31 new chemical entities approved in 2002 contained one or several fluorine atoms.

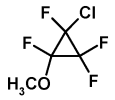
In the 1950s and 1960s, the successful development of α-fluorinated ethers and thioethers as volatile, nontoxic, nonexplosive, and fast-acting inhalation anaesthetics was quickly followed by applications of antiinflammatory agents. Numerous new α-fluorine-containing compounds have been prepared, clinically evaluated, and in many cases marketed as drugs with enhanced effectiveness, often coupled with diminished side effects. Today, significant application areas for α-fluorinated ether, thioether and amine analgesics, anesthetics, cardiovascular drugs, respiratory drugs, psychopharmacologic drugs, neurologic drugs, gastrointestinal drugs, and antiinfective therapeutics.

6.3.1. Anesthetic Drugs

Investigations of the anesthetic properties of α-fluorinated ethers were undertaken on the rational basis that replacement of the hydrogen atom in already known "anesthetic molecules" by fluorine should result in derivatives having improved thermal stabilities relative to the inhalation anesthetics in common use at that time (cyclopropane and ether), like the haloether anesthetic fluoroxene (Fluoromar, $F_3C-H_2C-O-CH=CH_2$; boiling point: 43.0 ± 25.0 °C). Metabolic stability is a desirable feature since the possibility exists that in vivo decomposition may produce toxic effects. Therefore, numerous analogues[231] were prepared and evaluated (see Table 11).

To extend the investigations to five-membered ring systems containing two oxygen atoms, Bagnall and co-workers synthesized a series of fluorinated 1,3-dioxolanes.[232] Some of these compounds, e.g., **110a−b**, have meanwhile largely replaced fluoroxene in its clinical use. Although almost structurally identical to other **110b**, the replacement of chlorine by fluorine gives **110a** an improved pharmacokinetic profile. It is less soluble in blood and tissue and produces a fast onset action and a more rapid recovery from anesthesia. Because six of the seven fluorine atoms in **110c** are magnetically identical, this drug is a good candidate for in vivo magnetic resonance imaging.[233] The basic concept that anesthetic activity is related to the colligative properties of compounds rather than to any specific structural features suggested that anesthetic potency might be encountered in α-fluorinated compounds of widely different structures. Therefore, cyclic α-fluorinated ether structures, like the cyclopropane aliflurane[234] (**111**) (26-P) and the dioxolane dioxychlorane[235] (**112**) are also described as useful anesthetics. Many anesthetics currently

used are powerful positive allosteric modulators of $GABA_A$.[236]



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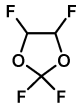
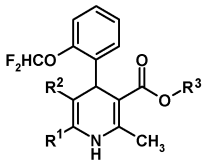


112

6.3.2. Cardiovascular Drugs

Antihypertensive Drugs. 1,4-Dihydro-pyridines containing an $OCHF_2$ group like riodipine (**113a:** Foridon, Phoridone, Riosedyl) are known as Ca^{2+} antagonists. They show antihypertensive and anti-anginal effects.[237]

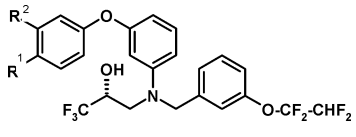


113a : $R^1 = CH_3$, $R^2 = COOCH_3$, $R^3 = CH_3$ Riodipine

113b : $R^1,R^2 = -CH_2-O-CO-$, $R^3 = C_2H_5$ CGP 28392

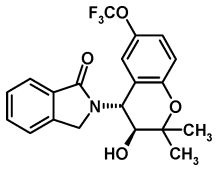
On the other hand, the analogue **113b** (CGP 28392) is described as a Ca^{2+} channel agonist and induce long-term opening of Ca^{2+} channels from purified rat muscle transverse tubules (*t*-tubules) incorporated into planar phospholipid bilayers.[238]

Atherosclerosis Agents. Coronary heart disease has been for some time the leading cause of death in the Western world. Several compounds have been reported to be potent **c**hoesterol **e**ster **t**ransfer **p**rotein (CETP) inhibitors and thus to affect cellular lipids. The OCF_2CHF_2 compound **114a** (SC-795) is a potent CETP inhibitor with an IC_{50} of 20 nM in buffer and 600 nM in the presence of human serum.[239] Recently, the asymmetric synthesis of the *R*(+)-enantiomeric 4-chloro-ethylphenoxy analogue **114b** was described.[240] Compound **114b** shows strong increased inhibitory activity of CETP in buffer (IC_{50} = 0.77 nM, 59 nM in human serum).



114a : $R^1 = H$, $R^2 = H$
114b : $R^1 = Cl$, $R^2 = CH_2CH_3$

Potassium Channel Activators. A potassium channel opener has been considered as a vasorelaxing agent working through hyperpolarization of vascular smooth muscle cells. The cardioprotective celikalim (**115**: WAY-120491)[241] is a putative K^+ channel activator that has been shown to lower blood pressure in animal models and humans.[242]

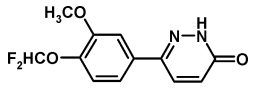


115 Celikalim

Furthermore, **115** is a potent K^+ channel opener in dog and human airway smooth muscles.[243] Celikalim (**115**) elicits renal effects through an ATP-sensitive K^+ channel in the renal vasculatures and renal tubules, and the renal effect of **115** may not be altered in hyperconjugation.[244]

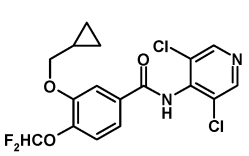
6.3.3. Respiratory Drugs

Asthma Therapy. Cyclic nucleotide phosphodiesterase (PDEs) constitute a broad family of enzymes responsible for the hydrolysis and consequent deactivation of the second messengers cAMP and cGMP.[245] The cAMP specific PDE4 isoenzymes,[246] encoded by four genes (A−D), are particularly abundant in inflammatory and immune cells and in airway smooth muscle.[247] The first crystal structure of the PDE4D catalytic domain and the bronchospasmolytic zardaverine (**116**: BY 290) as inhibitor has been recently published.[248]

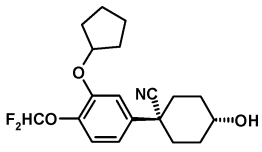


116 Zardaverine

Zardaverine (**116**), a mixed PDE3/4 inhibitor, binds in a highly conserved pocket that includes the catalytic metal binding site and fills only a portion of the active site pocket. It was found that more selective PDE4 inhibitors such as roflumilast (**117**: BY 217)[249] have additional functional groups that can utilize the remaining empty space for increased binding energy and selectivity. Roflumirast (**117**) is a specific PDE4 inhibitor being developed for the potential treatment of asthma and chronic obstructive pulmonary disease (COPD).[250] Selective PDE4 inhibitors were compared for their abilities to suppress superoxide anion production from guinea pig eosinophils, to inhibit the catalytic activity of human $PDE4_A$, and to bind to the high-affinity site.[251] The novel cyanocyclohexane **118** was the most potent compound in these three assays measuring 0.045, 0.02, and 0.025 μM, respectively.



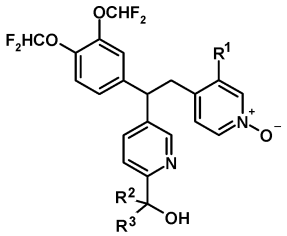
117 Roflumilast



118

Stabilization of CDP840 toward metabolism through replacing the alkoxy groups by $OCHF_2$, and oxidation of the pyridine to the *N*-oxide led to a novel series of triarylethane derivatives of general structure **119**,

bearing a 3,4-bis(difluoromethoxy)phenyl unit and a 2-pyridine-methanol residue **119a** (L-791,943).[252] The evaluation of the SAR in this series led to the identification of the diastereomeric **119c**, which gives highly selective inhibition of phosphodiesterase type 4A (PDE4A) (IC_{50} = 2.0 nM) but without inhibition of other PDE isoforms at up 5.0 μM.[253,254] In monkeys, **119c** displayed good bioavailability (73%), a shorter half-life than **119a**, and a low liability for emesis (10 mg/kg p.o.).



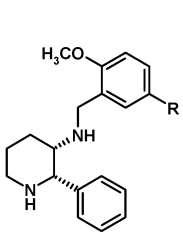
119a : R^1 = H; R^2, R^3 = CF_3 L-791,943
119b : R^1 = CH_3 ; R^2, R^3 = CF_3
119c : R^1 = H; R^2 = CH_3, R^3 = Ph

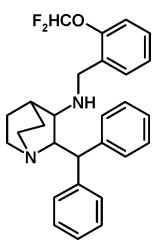
It exhibits excellent in vitro activity (HWB IC_{50} = 0.16 μM), desirable pharmacokinetic parameters, and good efficacy in guinea pig models of ovalbumin-induced bronchoconstriction (0.3 mg/kg i.p.) and in the sheep model of ascaris-induced bronchoconstriction (0.5 mg/kg i.v.) for 4 days.

The potencies of Roflumilast (**117**) and **119b** were determined in human and guinea pig whole blood by qPCR. The latter was more potent than **119b**.[255]

6.3.4. Psychopharmacologic Drugs

Anxiolytics. During the past decade, the search and development of small molecules as antagonists at the neurokinin-1 (NK_1) receptor represent an important opportunity to further explore novel therapeutic agents. The OCF_3-containing piperidine **120b** (CP-122,721), designed to improve the oral activity of the parent compound **120a** (CP-99,994), proved to be 400-fold more potent orally than **120a** in a study monitoring inhibition of aerosolized capsaicin-induced lung plasma extravasation in the guinea pig.[256] Recently, the $OCHF_2$ derivative **121** of the NK_1 receptor antagonist ezlopitant[257] was specifically claimed for treatment of a large number of therapeutic indications such as pain, anxiety, and HIV infection.



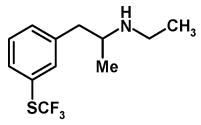


120a : R = H (CP-99,994)
120b : R = OCF_3 (CP-122,721)

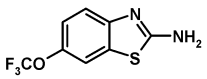
121

6.3.5. Neurologic Drugs

Anorexia Nervosa. Certain *meta*-F_3CS-substituted 2-phenylethylamines such as the (+)-enantiomer tiflorex[258] (**122**) and its racemate flutiorex[259] (SL 72340) show efficacy against anorexia nervosa.



122

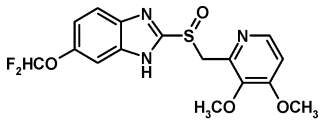


123 Riluzole, Rhone-Poulenc Rorer

Treatment of Amyotropic Lateral Sclerosis. Riluzole (**123**: Rilutek),[260] a OCF_3-substituted 2-aminobenzothiazole, is known to affect motor neurons by at least three mechanisms, including inhibition of glutamate release, inhibition of postsynaptic events following glutamate receptor stimulation, and stabilization of *vgSChs*. It is the first drug approved for treatment of amyotropic lateral sclerosis.

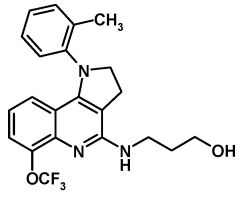
6.3.6. Gastrointestinal Drugs

Antiulcer Drugs. Substituted benzimidazoles such as omeprazole, lansoprasole, rabeprazole (all non-α-fluorinated ethers) and the pH-selective (−)-pantoprazole (**124**: pantoprazole sodium, Rifun, Pantozol, Pantec)[261] are known as gastric proton pump inhibitors (PPIs).[262] All PPIs accumulate in the acidic space of the secreting parietal cell, where their active forms create disulfide bonds with key cysteines of the H^+, K^+-ATPase. (−)-Pantoprazole **(124)**, an irreversible proton pump inhibitor, reached its first market worldwide for acute treatment of gastric and duodenal ulcers and gastroesophageal reflux disease. This profile is different to other PPIs and is likely related to the unique binding of **124** to cysteine 882, a binding site that is buried deep within the membrane domain of the pump and may therefore be inaccessible to reducing agents. Thus, **124** is a valuable alternative to other PPIs in the treatment of acid-related disorders. Furthermore, the PPIs were found to have in vitro activity against three different isolates of *Plasmodium falciparum*.[263]



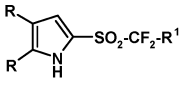
124 (-)-Pantoprazole

Recently, the effect of novel quinoline derivatives of type **125** (AU-006) was described.[264] The quinoline **125** prevented gastric lesions induced by 95% ethanol when given orally (30−300 mg/kg). Its protective effect against gastric lesions was not affected by an NO synthase inhibitor.



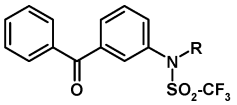
125

Agents for Antiinflammatory Bowel Disease. A series of 4,5-diaryl-2-(substituted thio)-1*H*-imidazoles, such as the 1,1,2,2-tetrafluoro-ethyl-sulfonyl-containing triflamizole (**126a**: EN-350),[265] was described as antiinflammatory and analgesic agents (e.g., antirheumatic).[266] On the other hand, for the F_3CSO_2 derivate **126b** lethal effects of arachidonate-induced platelet aggregation were reported.



126a : R = 4-F-phenyl, $R^1 = CHF_2$
126b : R = 4-H_3CO-phenyl, R^1 = F

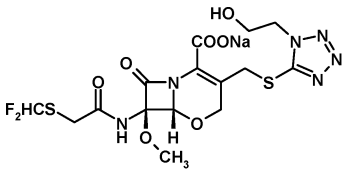
Triflumidate (**127a**: BA 4223, MBR 4223) exhibits a significant antiinflammatory activity. It is about equipotent with aspirin in inhibiting carrageenin-induced edema and was 5 times less potent than phenylbutazone in the adjuvant arthritis assay. A probable metabolite of **127a**, the *N*-decarbethoxy derivative **127b**, is also active.[267]



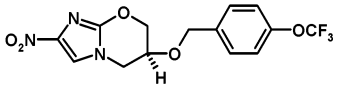
127a : R = $COOC_2H_5$ Triflumidate
127b : R = H

6.3.7. Antiinfective Therapy

Antibiotics. Flomoxef sodium (**128**: Flumarin, 6315-S) is a $SCHF_2$-substituted β-lactamase-resistant oxacephalosporin antibiotic from Shionogi.[268] It shows no disulfiram-like reaction in either rats or humans. The antibacterial activity and its stability to β-lactamases, its toxicity and pharmacokinetics in humans are described in different reviews.[269,270] The antimycobacterial activity and in vitro activity against *Helicobacter pylori* and toxicology of **129** (PA-824) were reported.

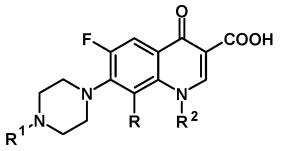


128



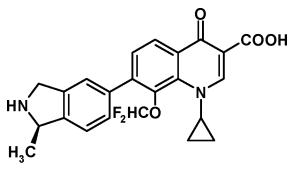
129

Antiviral Drugs. Recent studies in anti-HIV chemotherapy have produced stunning progress in a relatively short period of time.[271] The anti-HIV-1 activities and pharmacokinetics of a series of aryl-piperazinyl fluoroquinolones **130** are reported.[272] The SAR study revealed that the substituent at the C-8 position of **130** plays an important role in anti-HIV-1 activities. Hydrophobicity of the substituent at this position seems to be one of the key factors for antiviral activity. Thus, the inhibitory effect can be further enhanced by substitution of the methoxy group hydrogens in compound **130a** ($IC_{50} = 1.8 \pm 0.6$ μM; $CC_{50} = 26 \pm 2$ μM) with fluorine atoms. Finally, the $OCHF_2$ analogue **130b** ($IC_{50} = 0.25 \pm 0.04$ μM; $CC_{50} = 15 \pm 2$ μM) was found to be the most active in this series of congeners.[273] Compound **130c** has been shown to inhibit replication of herpes viruses, including human cytomegalovirus, varicella-zoster virus, and herpes simplex virus types 1 and 2, which are important opportunistic pathogens in AIDS patients.[274] However, in this case the introduction of a OCF_3 group at the C-8 position proved to be superior (**130d:** $IC_{50} = 0.11$ μM; $CC_{50} = 0.75$ μM) to that of a $OCHF_2$ group (**130c**: $IC_{50} = 0.22$ μM; $CC_{50} = 8.3$ μM) to achieve higher anti-HIV-activity.[275]



130a R = pyrid-2-yl, $R^1 = OCH_3$, R^2 = cyclopropyl
130b R = pyrid-2-yl, $R^1 = OCHF_2$, R^2 = cyclopropyl
130c R = 2-H_3CO-phenyl, $R^1 = OCHF_2$, $R^2 = C_2H_5$
130d R = 2-H_3CO-phenyl, $R^1 = CF_3$, $R^2 = C_2H_5$

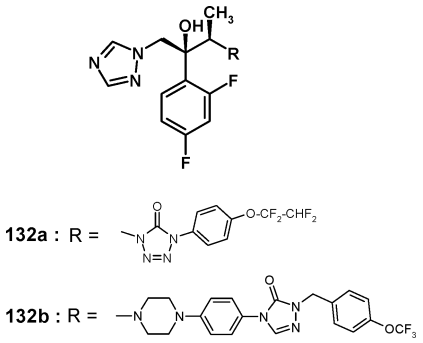
The new des-6-fluoro-quinolone garenoxacin (**131:** T-3811), a DNA topoisomerase ATP hydrolyzing inhibitor, is currently in phase III clinical tests. Garenoxacin (**131**) is a quinolone that demonstrates activity against a wide range of Gram-positive and Gram-negative bacterial pathogens such as *Escherichia coli* ($MIC_{50} = 0.03$ μg/mL), *Enterococcus* spp. ($MIC_{50} = 0.25$ μg/mL), and *Pseudomonas aeruginosa* ($MIC_{50} = 1$ μg/mL).[276]



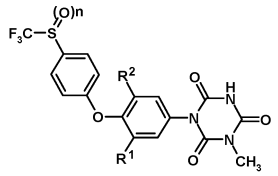
131 Garenoxacin

Antifungal Agents. Systemic fungal infections of immunocompromized hosts continue to be a major problem in infectious disease chemotherapy. Several reports appeared on the synthesis and evaluation of novel azoles with activity against Fluconazole resistant *Candida albicans* and *Aspergillus*. Thus, the tetrazolone[277] **132a** was reported to have efficacies in animal models comparable or superior to fluconazole. The novel broad spectrum agent **132b** contains the 4-piperazinyl-phenyl-triazolone side chain com-

mon to itraconazole and posaconazole and displays similar potency and spectrum as the latter.[278]



Treatment of Protozoal Diseases. The 1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione toltrazuril (**133a:** Baycox, Hycox, Maxicox), containing a *para*-SCF_3-phenoxy group, is a prophylactic and chemotherapeutic coccidiocide for use against parasitic protozoa in numerous species of poultry, e.g., chicken and turkey, exposed to coccidia. It is active against coccidia of the genera *Eimeria*, *Isospora, Toxoplasma, Sarcocystis*, and *Hepatozoon*.[279] The toltrazuril sulfone metabolite ponazuril (**133c**: Bay-Vi 9143, Marquis) shows efficacy in inhibiting merozoite production of *Sarcocystis neurona* in cell cultures. Therefore, compound **133c** may have promise as a therapeutic agent in the treatment of *Sarcocystis neurona* induced equine protozoal myeloencephalitis (EPM) in horses.[280] Finally, the toltrazuril sulfoxide **133b** is further metabolized by rat liver microsomes to the corresponding sulfone **133c**. The reaction is mediated by various cytochromes P450, the most active being cytochrome P450 3A.[281] Extended investigations demonstrated efficacy against all intracellular development stages. The 1,3,5-triazinetrione **133d** (Bay Vg 7183) is effective against mammalian coccidia such as *Eimeria falciformis* (mouse) or *Eimeria contorta* (rat). It is active both on schizonts and gamonts. This explains the high efficacy of single doses (0.25−10 mg/kg).[282]



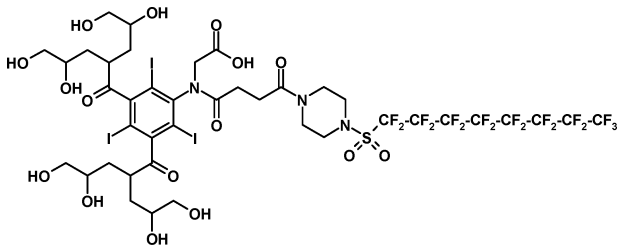
133a: n = 0; $R^1 = CH_3$, $R^2 = H$ Toltrazuril
133b: n = 1; $R^1 = CH_3$, $R^2 = H$
133c: n = 2; $R^1 = CH_3$, $R^2 = H$ Ponazuril
133d: n = 2; R^1, $R^2 = Cl$

6.3.8. Miscellaneous Clinical Applications

Plasma Volume Expander. The perfluorotripropylamine perfluamine (**134**: Fluosol DA) acts as a so-called plasma volume expander, an oxygen-carrying agent for erythrocyte substitution (blood substitute).[283]

$N(CF_2\text{-}CF_2\text{-}CF_3)_3$ **134**

Diagnostic Agents. A contrast agent for use in X-ray or magnetic resonance-based diagnostics is compound **135**, characterized by a low critical micelle concentration (CMC = 5.4 μM).[284]



135

7. Outlook

"Fluorine leaves nobody indifferent.... As a substituent it is rarely boring, but always good for a surprise.... Apparently the smallest halogen emits several kinds of electronic effects which...may counterbalance or amplify each other."[285] An in-depth analysis of why organic fluorine is so special and often behaves as the "odd man out" has recently traced back some of its most characteristic features to the poor molecular polarizability of organofluorine compounds, the lowest relative to the molecular volume among all standard element derivatives.[286] The present review portraying α-fluorinated ethers, thioethers, and amines has introduced as an additional factor of complexity the anomeric effect and thus pushed the door open to the bonding/nonbonding continuum.

To get immersed in organofluorine chemistry entails the challenge to compile better experimental results, computational data, and intellectual arguments until one has established a sufficiently large and solid basis to rationalize all observations made and to foresee the outcome of new reactions or assays. However, product-oriented chemistry cannot delay its day-to-day business until the moment when the ultimate degree of theoretical sophistication and parametrization has been attained and the crucial technical or biological benchmarks such as surface tension, wettability, polymer elasticity, dielectrical anisotropy, acidity, lipophilicity, metabolic stability, and target binding can be predicted with numerical reliability.

Therefore, fluorine will continue to be exploited on the basis of empirical knowledge. In the life science field, one employs single fluorine atoms, difluoromethylene units, and trifluoromethyl or trifluoromethoxy groups to tailor pK_a values,[285] to foster cell penetration by improving the passive permeation through the blood/brain barrier and all kinds of biological membranes,[286] to help accumulate substances in tissues, and to enhance the substrate binding to protein-type receptors by making use of the "polar hydrophobic effect".[287] All this contributes to the critical "bioavailability" of therapeutically active compounds.

There are well-tried recipes to confer metabolic stability to biologically active compounds. For example, the introduction of a fluorine substituent in the para position of a phenyl ring is known to retard the cytochrome P-450-mediated oxidation of the arene unit. On the other hand, metabolic lability can

be a blessing in itself. Unlike the closely related lead compound prosulfuron (see 6.2.4), the post-emergent herbicide primisulfuron-methyl exterminates the weed in corn (maize) fields without harming the crop. The two difluoromethoxy groups attached to the pyrimidine ring offer the possibility to the plant, but not the weed, to detoxify itself in the course of a few hours by oxidative degradation, the $OCHF_2$ substituents thus acting as a specific metabolic breakseal.[288]

A particularly intriguing subject is the role of fluorine as a mimic. The isosteric relationship between fluorine and oxygen (van der Waals radii of 1.47 and 1.52 Å, respectively) is often emphasized. However, unlike the hydroxy group, organic fluorine is a very poor hydrogen bond acceptor[286] and no hydrogen bond donor at all. Thus, the replacement of a hydroxy group by a fluorine atom may totally perturb the interaction pattern. On the other hand, fluorine and hydrogen, both monovalent elements, are sufficiently similar in size (van der Waals radii of 1.47 and 1.20 Å, respectively) to be able to imitate each other (except in rare cases such as the deplanarization of biphenyls by introduction of halogen atoms in the ortho positions of biphenyls[289,290]). In general, fluorine should prove practically isosteric with hydrogen as far as substrate-enzyme and agonist-receptor recognition is concerned. Fluorinated pheromones may even serve to confuse insects and disrupt their mating.[291] Anyway, we have no choice. "There is no other element that can pose as hydrogen except fluorine. Therefore let us do our best to exploit cunningly the similarities and dissimilarities of these unlike twins."[171]

In other words, fluorine will remain an important tool to modulate the properties of biologically active substances. α-Fluorinated ethers, thioethers, and amines will without doubt claim a major role in the future evolution of the field.

8. Acknowledgment

This work was financially supported by the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Bern (Grant 20-55'303-98), and the Bundesamt für Bildung und Wissenschaft, Bern (Grant 97.0083 linked to the TMR project FMRXCT-970129).

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