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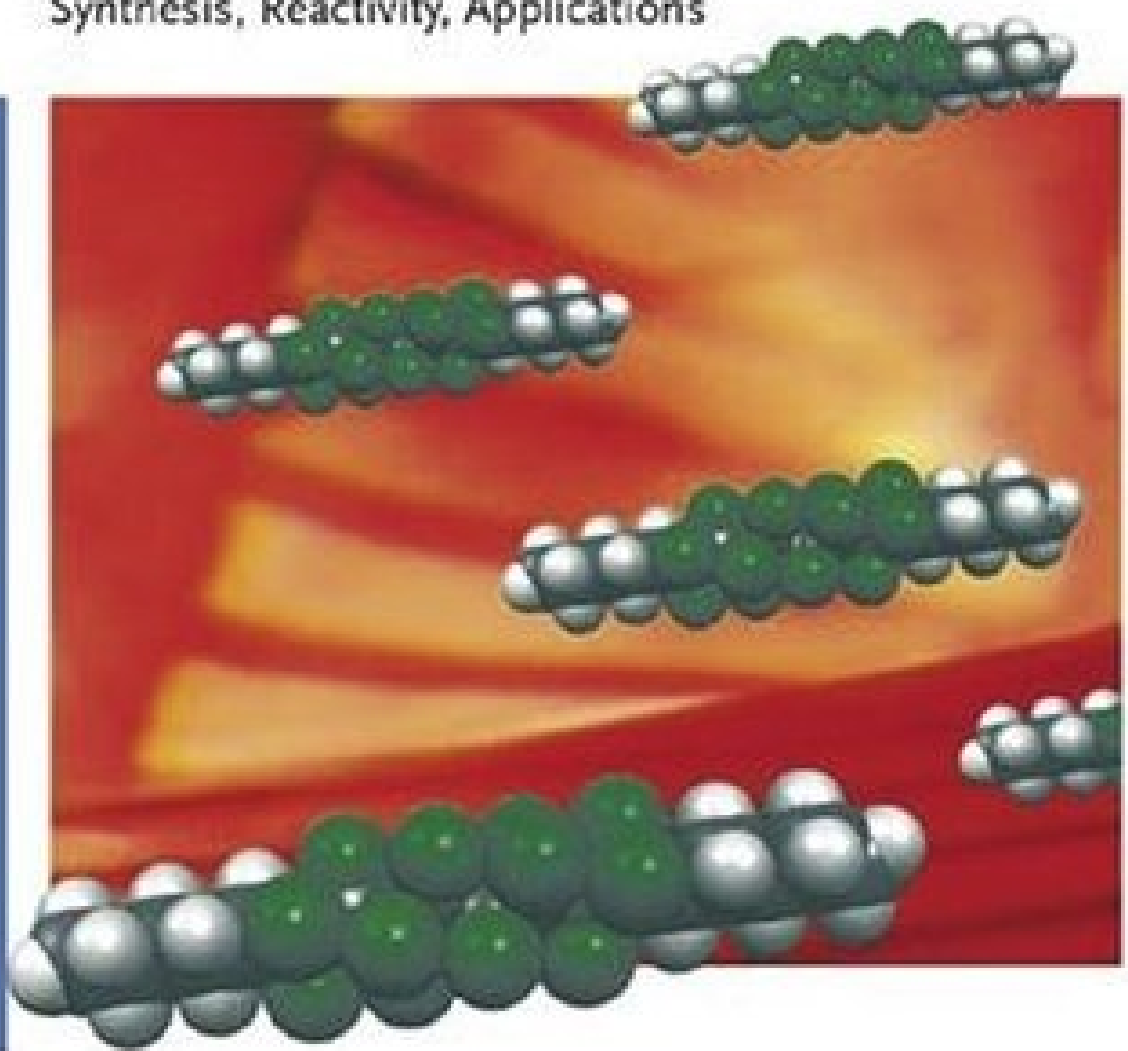
Modern Fluoroorganic Chemistry

Synthesis, Reactivity, Applications



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To Annette and Alexander

"The fury of the chemical world is the element fluorine. It exists peacefully in the company with calcium in fluorspar and also in a few other compounds; but when isolated, as it recently has been, it is a rabid gas that nothing can resist."

Scientific American, April **1888**

"Fluorine leaves nobody indifferent; it inflames emotions be that affections or aversions. As a substituent, it is rarely boring, always good for a surprise, but often completely unpredictable."

M. Schlosser, *Angew. Chem. Int. Ed.* **1998**, *37*, 1496–1513

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Preface

The field of fluoroorganic chemistry has grown tremendously in recent years, and fluorochemicals have permeated nearly every aspect of our daily lives. This book is aimed at the synthetic chemist who wants to gain a deeper understanding of the fascinating implications of including the highly unusual element fluorine in organic compounds.

The idea behind this book was to introduce the reader to a wide range of synthetic methodology, based on the mechanistic background and the unique chemical and physicochemical properties of fluoroorganic compounds. There are quite some barriers to entering the field of preparative fluoroorganic chemistry, many based on unfounded prejudice. To reduce the threshold to practical engagement in fluoroorganic chemistry, I include some representative synthetic procedures which can be performed with relatively standard laboratory equipment.

To point out what can be achieved by introducing fluorine into organic molecules, a whole section of this book is dedicated to selected applications. Naturally, because of the extremely wide range of sometime highly specialized applications, this part had to be limited to examples which have gained particular importance in recent years. Of course, this selection is influenced strongly by the particular "taste" of the author.

I could not have completed this book without help and support from friends and colleagues. I would like to thank my colleagues at Merck KGaA, in particular Detlef Pauluth for his continuous support of my book project, and Matthias Bremer and Oliver Heppert for proof reading and for many good suggestions and ideas how to improve the book. The remaining errors are entirely my fault. G. K. Surya Prakash, Karl O. Christe, and David O'Hagan not only gave valuable advice but also provided me with literature. Gerd-Volker Röschenthaler, Günter Haufe, and Max Lieb introduced me to the fascinating field of fluorine chemistry. Andrew E. Feiring and Barbara Hall helped me to obtain historical photographs. Elke Maase from Wiley–VCH accompanied my work with continuous support and encouragement.

In the last 18 months I have spent most of my free time working on this book and not with my family. I would, therefore, like to dedicate this book to my wife Annette and my son Alexander.

Darmstadt, May 2004 Peer Kirsch

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List of Abbreviations

acac	acetylacetonate ligand
aHF	anhydrous hydrofluoric acid
AIBN	azobis(isobutyronitrile)
AM	active matrix
ASV	"Advanced Super-V"
ATPH	aluminum tri(2,6-bis(*tert*-butyl)-phenoxide
BAST	*N,N*-bis(methoxyethyl)amino sulfur trifluoride
BINOL	1,1′-bis(2-naphthol)
Bop-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BSSE	basis set superposition error
BTF	benzotrifluoride
CFC	chlorofluorocarbon
COD	cyclooctadiene
CSA	camphor sulfonic acid
Cso	camphor sulfonyl protecting group
CVD	chemical vapor deposition
DABCO	diazabicyclooctane
DAST	*N,N*-diethylamino sulfur trifluoride
DBH	1,3-dibromo-5,5-dimethyl hydantoin
DBPO	dibenzoylperoxide
DEAD	diethyl azodicarboxylate
DCC	dicyclohexyl carbodiimide
DEC	*N,N*-diethylcarbamoyl protecting group
DFI	2,2-difluoro-1,3-dimethylimidazolidine
DFT	density functional theory
DIP-Cl	β-chlorodiisopinocampheylborane
DMAc	*N,N*-dimethyl acetamide
DMAP	4-(*N,N*-dimethylamino)pyridine
DME	1,2-dimethoxy ethane
DMF	*N,N*-dimethyl formamide
DMSO	dimethylsulfoxide
DSM	dynamic scattering mode
DTBP	di-*tert*-butyl peroxide
dTMP	deoxythymidine monophosphate
dUMP	deoxyuridine monophosphate
ECF	electrochemical fluorination
ED	effective dose
EPSP	5-enolpyruvylshikimate-3-phosphate
ETFE	poly(ethylene-*co*-tetrafluoroethylene)
FAR	α-fluorinated alkylamine reagents
FDA	fluorodeoxyadenosine
FDG	fluorodeoxyglucose
FITS	perfluoroalkyl phenyl iodonium trifluoromethylsulfonate reagents
FRPSG	fluorous reversed-phase silica gel
FSPE	fluorous solid phase extraction
F-TEDA	*N*-fluoro-*N*′-chloromethyl diazoniabicyclooctane reagents
GWP	global warming potential
HFCF	hydrofluorochlorocarbon
HFC	hydrofluorocarbon
HFP	hexafluoropropene
HMG^+	hexamethyl guanidinium cation
HMPA	hexamethyl phosphoric acid triamide
IPS	in plane switching
ITO	indium tin oxide
LC	lethal concentration
LCD	liquid crystal display
LD	lethal dose
LDA	lithium diisopropylamide
MCPBA	*m*-chloro perbenzoic acid
MEM	methoxymethyl protecting group
MOST	morpholino sulfur trifluoride
MVA	multi-domain vertical alignment

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NAD^+/ NADH	nicotinamide adenine dinucleotide, oxidized/reduced form
$NADP^+$/ NADPH	nicotinamide adenine dinucleotide phosphate, oxidized/reduced form
NBS	*N*-bromo succinimide
NCS	*N*-chloro succinimide
NE	norepinephrine
NFPy	*N*-fluoro pyridinium tetrafluoroborate
NFTh	*N*-fluoro benzene-1,2-sulfonimide
NIS	*N*-iodo succinimide
NLO	non-linear optics
NMP	*N*-methyl pyrrolidone
NPSP	*N*-phenylselenylphthalimide
OD	ornithine decarboxylase
ODP	ozone-depleting potential
PCH	phenylcyclohexane
PCTFE	poly(chlorotrifluoroethylene)
PDA	personal digital assistant
PET	positron emission tomography
PFA	perfluoropolyether
PFC	perfluorocarbon
PFMC	perfluoro(methylcyclohexane)
PFOA	perfluorooctanoic acid
PFOB	perfluoro-*n*-octyl bromide
PI	polyimide
pip^+	1,1,2,2,6,6-hexamethylpiperidinium cation
PLP	pyridoxal phosphate
PNP	purine nucleoside phosphorylase
PPVE	poly(heptafluoropropyl trifluorovinyl ether)
PTC	phase transfer catalysis
PTFE	poly(tetrafluoroethylene) (Teflon)
PVDF	poly(vinylidene difluoride)
PVPHF	poly(vinylpyridine) hydrofluoride
QM/MM	quantum mechanics/molecular mechanics
QSAR	quantitative structure-activity relationship
SAH	*S*-adenosyl homocystein hydrolase
SAM	*S*-adenosyl methionine
SBAH	sodium bis(methoxyethoxy) aluminum hydride
$scCO_2$	supercritical carbon dioxide
SFM	super-fluorinated materials
SPE	solid phase extraction
STN	super-twisted nematic
TADDOL	α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
TAS^+	tris(dimethylamino)sulfonium cation
TASF	tris(dimethylamino)sulfonium difluorotrimethylsiliconate, $(Me_2N)_3S^+\ Me_3SiF_2^-$
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl protecting group
TBS	see TBDMS
TBTU	*O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium tetrafluoroborate
TDAE	tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-tetramethylpiperidine-*N*-oxide
TFT	thin film transistor
THF	1. tetrahydrofurane 2. tetrahydrofolate coenzyme
THP	tetrahydropyranyl protecting group
TIPS	triisopropylsilyl protecting group
TLC	thin layer chromatography
TMS	trimethylsilyl protecting group
TN	twisted nematic
VHR	voltage holding ratio
ZPE	zero point energy

1
Introduction

1.1
Why Organofluorine Chemistry?

Fluorine is the element of extremes, and many fluorinated organic compounds exhibit extreme and sometimes even bizarre behavior. A large number of polymers, liquid crystals, and other advanced materials owe their unique property profile to the influence of fluorinated structures.

Fluoroorganic compounds are almost completely foreign to the biosphere. No central biological processes rely on fluorinated metabolites. Many modern pharmaceuticals and agrochemicals, on the other hand, contain at least one fluorine atom, which usually has a very specific function. Perfluoroalkanes, especially, can be regarded as "orthogonal" to life – they can assume a purely physical function, for example oxygen transport, but are foreign to the living system to such an extent that they are not recognized and are completely ignored by the body.

Although fluorine itself is the most reactive of all elements, some fluoroorganic compounds have chemical inertness like that of the noble gases. They sometimes cause ecological problems not because of their reactivity but because of the lack it, making them persistent in nature on a geological time scale.

All these points render fluoroorganic chemistry a highly unusual and fascinating field [1–13], providing surprises and intellectual stimulation in the whole range of chemistry-related sciences, including theoretical, synthetic, and biomedical chemistry and materials science.

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1.2 History

Because of the hazardous character of hydrofluoric acid and the difficult access to elemental fluorine itself, the development of organofluorine chemistry and the practical use of fluoroorganic compounds started relatively late in the 19th century (Table 1.1). The real breakthrough was the first synthesis of elemental fluorine by H. Moissan in 1886 [1].

Industrial application of fluorinated organic compounds started in the beginning of the 1930s with the introduction of chlorofluorocarbons (CFC) as refrigerants [2]. The major turning point in the history of industrial fluoroorganic chemistry was the beginning of the Manhattan Project for development of nuclear weapons in 1941 [3]. The Manhattan Project triggered the need for highly resistant materials, lubricants, coolants and the development of technology for handling extremely corrosive fluoroinorganic compounds. The consumption of hydrofluoric acid as the main precursor of all these materials soared upward, accordingly, during the 1940s. After 1945, with the beginning of the Cold War, various defense programs provided a constant driving force for further development of the chemistry and use of organofluorine compounds. In the 1950s and 60s more civilian applications of fluorinated pharmaceuticals and materials moved into the forefront [4].

The prediction of the ozone-depleting effect of CFC in 1974 [5] and the subsequent occurrence of the ozone hole over the Antarctic in 1980 enforced a drastic reorientation of industrial fluoroorganic chemistry. With the Montreal protocol in 1987 the phasing-out of most CFC was initiated. Some of these refrigerants and cleaning chemicals could be replaced by other fluorine-containing chemicals (for example hydrofluorocarbons, HFC, and fluorinated ethers) but in general the fluorochemical industry had to refocus on other fields of application, for example fluoropolymers, fluorosurfactants, and fluorinated intermediates for pharmaceuticals and agrochemicals [4]. A major and rapidly growing market segment is fluorine-containing fine chemicals for use as intermediates in pharmaceutical and agrochemistry and in the electronics industry. Another application in which fluorochemicals have started to play an increasingly dominant role in the last

Table 1.1 Dates and historic key events in the development of fluoroorganic chemistry.

Time	*Key Event*
1764	First synthesis of hydrofluoric acid from fluorspar and sulfuric acid by A. S. Marggraf, repeated in 1771 by C. Scheele
1886	First synthesis of elemental fluorine by H. Moissan (Nobel Prize in 1906) by electrolysis of an HF–KF system
1890s	Beginning of halofluorocarbon chemistry by direct fluorination (H. Moissan) and Lewis acid-catalyzed halogen exchange (F. Swarts)
1920s	Access to fluoroarenes by the Balz–Schiemann reaction
1930s	Refrigerants ("Freon", in Germany "Frigen"), fire extinguishing chemicals ("Halon"), aerosol propellants
1940s	Polymers (PTFE = "Teflon"), electrochemical fluorination (H. Simons)
1941–1954	Manhattan Project: highly resistant materials for isotope separation plants, lubricants for gas centrifuges, coolants
1950s	Fluoropharmaceuticals, agrochemicals, artificial blood substitutes, respiratory fluids, chemical weapons
1980s	Gases for plasma etching processes and cleaning fluids for the semiconductor industry
1987	The Montreal Protocol initiates the phasing-out of CFC
1990s	Fluorinated liquid crystals for active matrix liquid crystal displays (AM-LCD)
2000s	Fluorinated photoresists for the manufacture of integrated electronic circuits by 157 nm photolithography

few years is the electronics industry. Relevant compounds include plasma etching gases, cleaning fluids, specialized fluoropolymers, fluorinated photoresists for manufacturing integrated circuits by the currently emerging 157 nm photolithography, and liquid crystals for LCD application.

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1.3 The Basic Materials

Naturally occurring fluorine is composed of the pure $^{19}_{9}F$ isotope. Its relative abundance in the earth crust as a whole is 0.027 % by weight (for comparison, Cl is 0.19 % and Br 6×10^{-4} % by weight). Because of the extremely low solubility (solubility product 1.7×10^{-10} at 298 K) of its most important mineral, fluorspar (CaF_2), the concentration of fluoride in seawater is very low (ca. 1.4 mg L^{-1}) [1].

The most abundant natural sources of fluorine are the minerals fluorspar and cryolith (Na_3AlF_6). Fluoroapatite ($Ca_5(PO_4)_3F$ = "$3Ca_3(PO_4)_2 \cdot CaF_2$") is, with hydroxyapatite ($Ca_5(PO_4)_3OH$), a major component of tooth enamel, giving it its extreme mechanical strength and life-long durability.

Despite of the relatively high abundance of fluorine in the lithosphere, only very few fluoroorganic metabolites have been identified in the biosphere [2]. No central metabolic process depending essentially on fluorine is yet known. It might be speculated that the reason for this unexpected phenomenon is the poor solubility of CaF_2, with Ca^{2+} ions being one of the central components essential for the existence of any living organism. Another reason might also be the very high hydration enthalpy of the small fluoride anion, which limits its nucleophilicity in aqueous media by requiring an energetically demanding dehydration step before any reaction as a nucleophile [2].

1.3.1 Hydrofluoric Acid

Hydrofluoric acid is the most basic common precursor of most fluorochemicals. Aqueous hydrofluoric acid is prepared by reaction of sulfuric acid with fluorspar (CaF_2). Because HF etches glass with formation of silicon tetrafluoride, it must be handled in platinum, lead, copper, Monel (a Cu–Ni alloy developed during the Manhattan Project), or plastic (e. g. polyethylene or PTFE) apparatus. The azeotrope contains 38 % *w*/*w* HF and it is a relatively weak acid (pK_a 3.18, 8 % dissociation), comparable with formic acid. Other physicochemical properties of hydrofluoric acid are listed in Table 1.2.

Anhydrous hydrofluoric acid (aHF) is obtained by heating Fremy's Salt ($KF \cdot HF$) as a liquid, boiling at 19.5 °C. Similar to water, aHF has a liquid range of approximately 100 K and a dielectric constant ε of 83.5 (at 0 °C). Associated by strong hy-

Table 1.2 Physicochemical properties of hydrofluoric acid [3] (the vapor pressure and density correspond to a temperature of 0 °C).

Property	*Anhydrous HF*	*40 % HF/H_2O*
Boiling point (°C)	19.5	111.7
Melting Point (°C)	−83.4	−44.0
HF vapor pressure (Torr)	364	21
Density (g cm^{-3})	1015	1135

drogen bonding, it forms oligomeric $(HF)_n$ chains with a predominant chain length n of nine HF units. In contrast with aqueous HF, pure aHF is a very strong acid, slightly weaker than sulfuric acid. Like water, aHF undergoes autoprotolysis with an ion product $c(FHF^-) \times c(HFH^+)$ of $10^{-10.7}$ at 0 °C. In combination with strong Lewis acids, for example as AsF_5, SbF_5, or SO_3, anhydrous hydrofluoric acid forms some of the strongest known protic acids. The best known example is "magic acid" (FSO_3H–SbF_5) which can protonate and crack paraffins to give *tert*-butyl cations [3]. Apart from its use as a reagent, aHF is also an efficient and electrochemically inert solvent for a variety of inorganic and organic compounds.

The dark side of hydrofluoric acid is its toxicity and corrosiveness. Aqueous and anhydrous HF readily penetrate the skin, and, because of its locally anesthetizing effect, even in very small quantities can cause deep lesions and necroses [4, 5]. An additional health hazard is the systemic toxicity of fluoride ions, which interfere strongly with calcium metabolism. Resorption of HF by skin contact (from a contact area exceeding 160 cm^2), inhalation, or ingestion leads to hypocalcemia with very serious consequences, for example cardiac arrhythmia.

The most effective, specific antidote to HF and inorganic fluorides is calcium gluconate, which acts by precipitating fluoride ions as insoluble CaF_2. After inhalation of HF vapor, treatment of the victim with dexamethasone aerosol is recommended, to prevent pulmonary edema. Even slight contamination with HF must always be taken seriously, and after the necessary first-aid measures a physician should be consulted as soon as possible.

It should also be kept in mind that some inorganic (e. g. CoF_3) and organic fluorinated compounds (e. g. pyridine–HF, $NEt_3 \cdot 3HF$, DAST) can hydrolyze on contact with skin and body fluids, liberating hydrofluoric acid with the same adverse consequences.

Nevertheless, when the necessary, relatively simple precautions are taken [4], hydrofluoric acid and its derivatives can be handled safely and with minimum risk to health.

1.3.2 Fluorine

Despite the ubiquitous occurrence of fluorides in nature, elemental fluorine itself proved to be quite elusive. Because of its very high redox potential (approx. +3 V, depending on the pH of aqueous systems), chemical synthesis from inorganic fluorides was impeded by the lack of a suitable oxidant. Therefore, H. Moissan's first synthesis of fluorine in 1886 by electrolysis of a solution of KF in aHF in a platinum apparatus [6, 7] was a significant scientific breakthrough, and he was awarded the Nobel Prize for chemistry in 1906 for his discovery (Figure 1.1).

Fluorine is a greenish-yellow gas, melting at −219.6 °C and boiling at −188.1 °C. It has a pungent smell reminiscent of a mixture of chlorine and ozone and is perceptible even at a concentration of 10 ppm. It is highly toxic and extremely corrosive, especially toward oxidizable substrates. Most organic compounds spontaneously combust or explode on contact with undiluted fluorine at ambient pres-

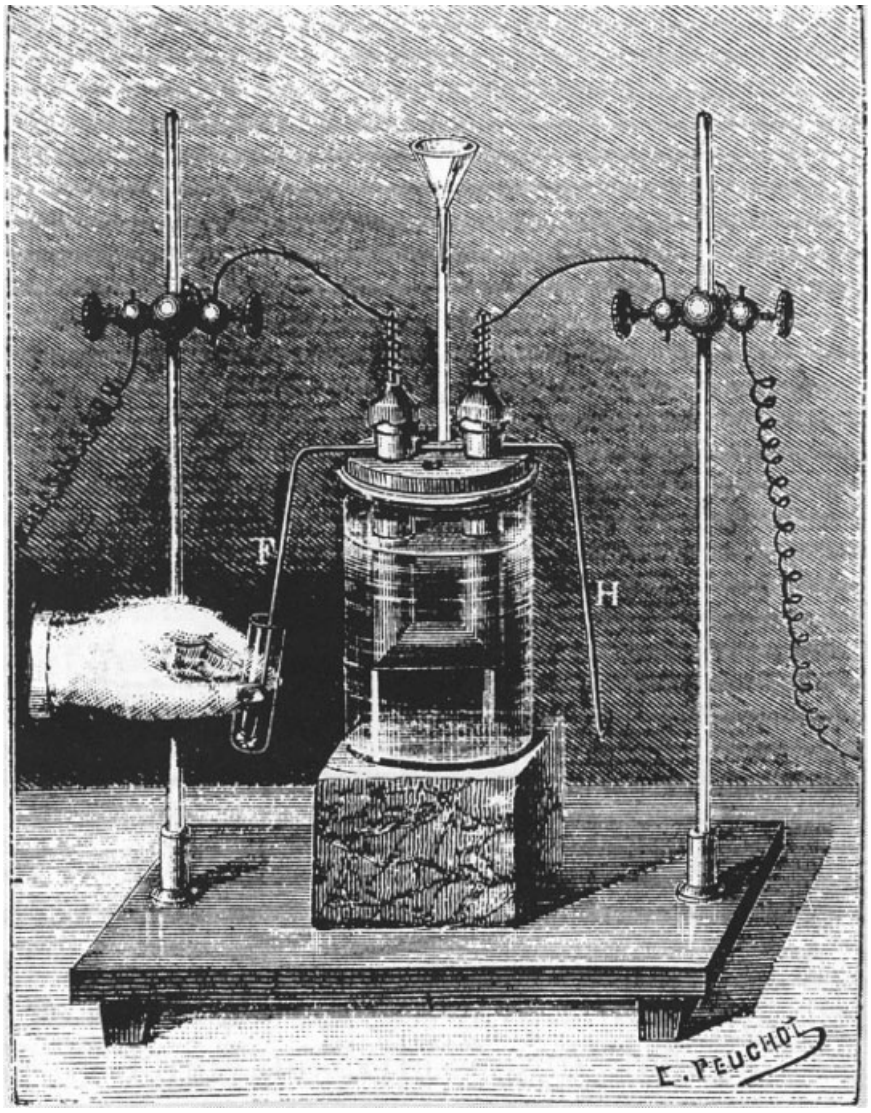

Figure 1.1 The apparatus used by H. Moissan for the first isolation of elemental fluorine by electrolysis of a HF–KF system in 1886 [6].

sure. Because of its high reactivity, fluorine reacts with hot platinum and gold, and even with the noble gases krypton and xenon. In contrast with hydrofluoric acid, dry fluorine gas does not etch glassware. Because of its extreme reactivity and hazardous nature, for many chemical transformations fluorine is diluted with nitrogen (typically 10 % F_2 in N_2). In this form, the gas can be stored without undue risk in passivated steel pressure bottles. Reactions can be conducted either in glassware

or in fluoropolymer (PTFE or PFA) apparatus. If some elementary precautions are taken (for details see Appendix A), reactions with nitrogen-diluted fluorine can be conducted safely in an ordinarily equipped laboratory.

Fluorine owes its unparalleled reactivity, on the one hand, to the ease of its homolytic dissociation into radicals (only 37.8 kcal mol^{-1}, compared with 58.2 kcal mol^{-1} for Cl_2) and, on the other hand, to its very high redox potentials of +3.06 V and +2.87 V, respectively, in acidic and basic aqueous media [8].

Fluorine, as the most electronegative element (electronegativity 3.98) [9], occurs in its compounds exclusively in the oxidation state −1. The high electron affinity (3.448 eV), extreme ionization energy (17.418 eV) and other unique properties of fluorine can be explained by its special location in the periodic system as the first element with p orbitals able to achieve a noble gas electron configuration (Ne) by uptake of one additional electron. For the same reason the fluoride ion is also the smallest (ion radius 133 pm) and least polarizable monoatomic anion. These very unusual characteristics are the reason fluorine or fluorine-containing non-polarizable anions can stabilize many elements in their highest and otherwise inaccessible oxidation states (e. g. IF_7, XeF_6, KrF_2, $O_2^+PtF_6^-$, $N_5^+AsF_6^-$).

A purely chemical synthesis of elemental fluorine was achieved by K. O. Christe in 1986 [10] (Scheme 1.1), just in time for the 100 year anniversary of Moissan's first electrochemical fluorine synthesis. Nevertheless, in his paper Christe remarks that all the basic know-how required for this work had already been available 50 years earlier. The key to his simple method is a displacement reaction between potassium hexafluoropermanganate [11] with the strongly fluorophilic Lewis acid antimony pentafluoride at 150 °C.

$$2\,KMnO_4 + 2\,KF + 10\,HF + 3\,H_2O_2 \xrightarrow[50\%\ aqu.\ HF]{74\%} 2\,\boldsymbol{K_2MnF_6}\downarrow + 8\,H_2O + 3\,O_2$$

$$K_2MnF_6 + 2\,SbF_5 \xrightarrow[150°C]{>40\%} 2\,KSbF_6 + MnF_3 + {}^1/_2\,\boldsymbol{F_2}\uparrow$$

Scheme 1.1 The first "chemical" synthesis of fluorine [10].

Nowadays, industrial fluorine production is based on Moissan's original method [1]. In the so-called "middle-temperature method" a $KF \cdot 2HF$ melt is electrolyzed at 70–130 °C in a steel cell. The steel cell itself is used as cathode; the anodes are specially treated carbon blocks (Söderberg electrodes). The voltage used is 8–12 V per cell [12]. During the cold war the major use of elemental fluorine was in the production of uranium hexafluoride for separation of the ^{235}U isotope. Nowadays, the production of nuclear weapons has moved into the background and a large quantity of fluorine is used for preparation of chemicals for the electronics industry (for example WF_6 for CVD (chemical vapor deposition), SF_6, NF_3, and BrF_3 as etching gases for semiconductor production, and graphite fluorides as cathode materials in primary lithium batteries) and for making polyethylene gasoline tanks inert in the automobile industry.

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1.4 The Unique Properties of Organofluorine Compounds

Fluoroorganic and, especially, perfluorinated compounds are characterized by a unique set of unusual and sometimes extreme physical and chemical properties. These are being utilized for a variety of different applications ranging from pharmaceutical chemistry to materials science [1].

1.4.1 Physical Properties

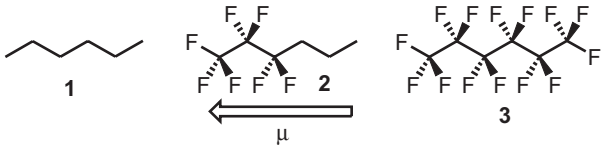
The physical properties of fluoroorganic compounds are governed by two main factors: (1) the combination of high electronegativity with moderate size, and the excellent match between the fluorine 2s or 2p orbitals with the corresponding orbitals of carbon, and (2) the resulting extremely low polarizability of fluorine [2].

Fluorine has the highest electronegativity of all the elements (3.98) [3], rendering the carbon–fluorine bond highly polar with a typical dipole moment of around 1.4 D, depending on the exact chemical environment (Table 1.3). The apparently contradictory observation that perfluorocarbons are among the most *non-polar* solvents in existence (e. g. $\varepsilon = 1.69$ for C_6F_{14} (**3**) compared with 1.89 for C_6H_{14} (**1**); Table 1.4) can be explained by the fact that all local dipole moments within the same molecule cancel each other, leading in total to a non-polar compound. In semi-fluorinated compounds, for example **2**, in which some local dipole moments

Table 1.3 Comparison of the characteristics of the carbon–halogen and carbon–carbon bonds (bond lengths in pm; binding energies in kcal mol^{-1}; electronegativities from Ref. [3]; dipole moments in D; Van der Waals radii in pm from Ref. [4]; atom polarizabilities α in 10^{-24} cm^{-3} from Ref. [5]).

X	*H*	*F*	*Cl*	*Br*	*I*	*C*
Bond length C–X	109	138	177	194	213	–
Binding energy C–X	98.0	115.7	77.2	64.3	50.7	~83
Electronegativity	2.20	3.98	3.16	2.96	2.66	2.55
Dipole moment, μ, C–X	(0.4)	1.41	1.46	1.38	1.19	–
Van der Waals radius	120	147	175	185	198	–
Atom polarizability, α	0.667	0.557	2.18	3.05	4.7	–

Table 1.4 Comparison of selected physicochemical properties of *n*-hexane (**1**) and its perfluorinated (**3**) and semifluorinated (**2**) analogues [2] (boiling point b. p. in °C; heat of vaporization ΔH_v in kcal mol^{-1}; critical temperature T_c in °C; density d^{25} in g cm^{-3}; viscosity η^{25} in cP; surface tension γ^{25} in dyn cm^{-1}; compressibility β in 10^{-6} atm^{-1}; refractive index n_D^{25}; dielectric constant ε).



Property	*1*	*2*	*3*
b. p. (°C)	69	64	57
ΔH_v (kcal mol^{-1})	6.9	7.9	6.7
T_c (°C)	235	200	174
d^{25} (g cm^3)	0.655	1.265	1.672
η^{25} (cP)	0.29	0.48	0.66
γ^{25} (dyn cm^{-1})	17.9	14.3	11.4
β (10^{-6} atm^{-1})	150	198	254
n_D^{25}	1.372	1.190	1.252
ε	1.89	5.99	1.69

are not compensated, the effects of the resulting overall dipole moment is mirrored by their physicochemical properties, especially their heats of vaporization (ΔH_v) and their dielectric constants (ε).

The low polarizability and the slightly larger size of fluorine compared with hydrogen (23 % larger Van der Waals radius) also have consequences for the structure and molecular dynamics of perfluorocarbons. Linear hydrocarbons have a linear zigzag conformation (Figure 1.2). Perfluorocarbons, in contrast, have a helical structure, because of the steric repulsion of the electronically "hard" fluorine substituents bound to carbon atoms in the relative 1,3-positions. Whilst the hydrocarbon backbone has some conformational flexibility, perfluorocarbons are rigid, rod-like molecules. This rigidity can be attributed to repulsive stretching by the 1,3-difluoromethylene groups.

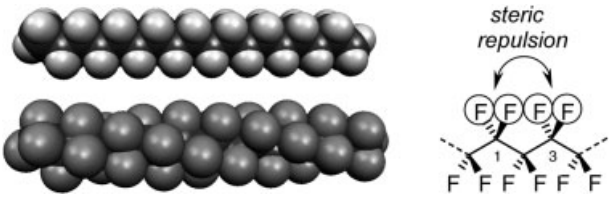


Figure 1.2 The zigzag conformation of octadecane (*above*) compared with the helical perfluorooctadecane (*below*), modeled on the PM3 level of theory [6, 7].

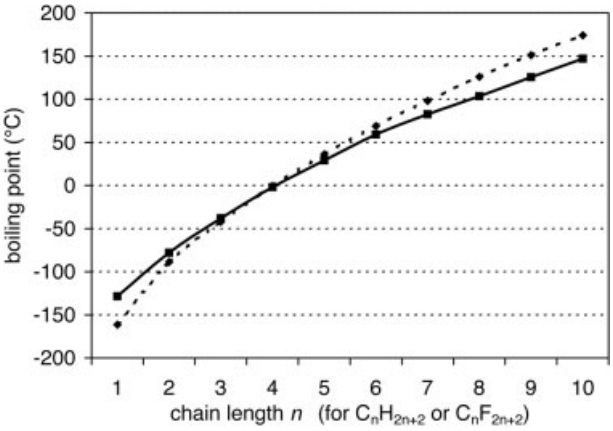


Figure 1.3 The boiling points of homologous alkanes (◆) compared with those of the corresponding perfluoroalkanes (■) [2].

Another consequence of the low polarizability of perfluorocarbons is very weak intermolecular dispersion interactions. A striking characteristic of perfluorocarbons is their very low boiling points, compared with hydrocarbons of similar molecular mass. For example, *n*-hexane and CF_4 have about the same molecular mass (M_r 86 g mol^{-1} and 88 g mol^{-1}, respectively), but the boiling point of CF_4 (b. p. −128 °C) is nearly 200 K lower than for *n*-hexane (b. p. 69 °C). If the homologous hydrocarbons and perfluorocarbons are compared (Figure 1.3) it is apparent they have very similar boiling points, even though the molecular mass of the perfluorocarbons is about four times higher than that of the corresponding hydrocarbons.

In contrast with typical hydrocarbon systems, branching has a negligible effect on the boiling points of perfluorocarbons (Figure 1.4).

Perfluorinated amines, ethers and ketones usually have much lower boiling points than their hydrocarbon analogues.

An interesting fact is that the boiling points of perfluorocarbons are only 25–30 K higher that those of noble gases of similar molecular mass (Kr, M_r 83.8 g mol^{-1}, b. p. −153.4 °C; Xe, M_r 131.3 g mol^{-1}, b. p. −108.1 °C; Rn, M_r 222 g mol^{-1}, b. p.

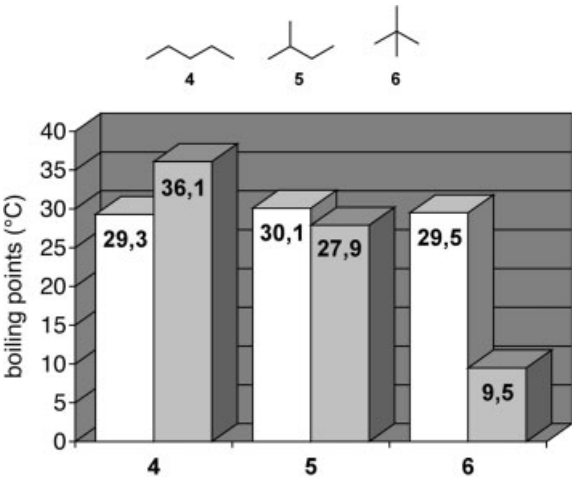


Figure 1.4 Boiling points of linear and branched isomers of perfluoropentane (*white bars*) and pentane (*gray bars*) [2].

−62.1 °C). In other aspects also, for example their limited chemical reactivity, perfluorocarbons resemble the noble gases.

Another consequence of the low polarizability of perfluorocarbons is the occurrence of large miscibility gaps in solvent systems composed of perfluorocarbons and hydrocarbons. The occurrence of a third, "fluorous", liquid phase in addition to the "organic" and "aqueous" phases has been extensively exploited in the convenient and supposedly ecologically benign "fluorous" chemistry, which will be discussed in detail in Chapter 3.

Another very prominent characteristic resulting from their weak intermolecular interaction is the extremely low surface tension (γ) of the perfluoroalkanes. They have the lowest surface tensions of any organic liquids (an example is given in Table 1.4.) and therefore wet almost any surface [2].

Solid perfluorocarbon surfaces also have extremely low surface energies (γ_c). Thus, poly(tetrafluoroethylene) (PTFE, Teflon) has a γ_c value of 18.5 dyn cm^{-1}, which is the reason for the anti-stick and low-friction properties used for frying pans and other applications. That this effect is directly related to the fluorine content becomes obvious on comparison of the surface energies of poly(difluoroethylene) (25 dyn cm^{-1}), poly(fluoroethylene) (28 dyn cm^{-1}), and polyethylene (31 dyn cm^{-1}). If only one fluorine atom in PTFE is replaced by more polarizable chlorine, the surface energy of the resulting poly(chlorotrifluoroethylene) jumps to 31 dyn cm^{-1}, the same value as for polyethylene [8].

The decisive aspect of achieving low surface energies seems to be a surface which is densely covered by fluorine atoms. Accordingly, the lowest surface energies of any material observed are those of fluorinated graphites $(C_2F)_n$ and $(CF)_n$, approximately 6 dyn cm^{-1} [9]. Monolayers of perfluoroalkanoic acids $CF_3(CF_2)_nCOOH$ also have surface energies ranging between 6 and 9 dyn cm^{-1} if $n \geq 6$ [10]. The same effect is observed for alkanoic acids containing only a re-

latively short perfluorinated segment (at least $CF_3(CF_2)_6$) at the end of their alkyl chain, which is then displayed at the surface.

When a hydrophilic functional group is attached to a perfluorocarbon chain the resulting fluorosurfactants (e. g. n-$C_nF_{2n+1}COOLi$, with $n \geq 6$) can reduce the surface tension of water from 72 dyn cm^{-1} to 15–20 dyn cm^{-1} compared to 25–35 dyn cm^{-1} for analogous hydrocarbon surfactants [11].

Most unusual types of surfactant are the so-called diblockamphiphiles $F(CF_2)_m(CH_2)_nH$, which have both hydrocarbon and perfluorocarbon moieties. At the interface between an organic and a "fluorous" phase (e. g. a liquid perfluorocarbon) they show the behavior of typical surfactants [12], for example micelle formation.

Whereas intermolecular interactions between perfluoroalkanes are very weak, quite strong electrostatic interactions are observed for some partially fluorinated hydrocarbons (hydrofluorocarbons, HFC), because of local, non-compensated carbon–fluorine dipole moments. The most pronounced effects of this kind are observed when bonds to fluorine and hydrogen arise from the same carbon atom. In such circumstances the polarized C–H bonds can act as hydrogen-bond donors with the fluorine as the acceptor. The simplest example for this effect is difluoromethane. If the boiling points of methane and the different fluoromethanes are compared (Figure 1.5), the non-polar compounds CH_4 and CF_4 are seen to have the lowest boiling points; the more polar compounds CH_3F and CHF_3 boil at slightly higher temperatures. The maximum is for CH_2F_2, which has the strongest molecular dipole moment and which can – at least in principle – form a three-dimensional hydrogen-bond network similar to that of water with the C–H bonds acting as the hydrogen-bond donors and C–F bonds as the acceptors (Figure 1.6.) [13].

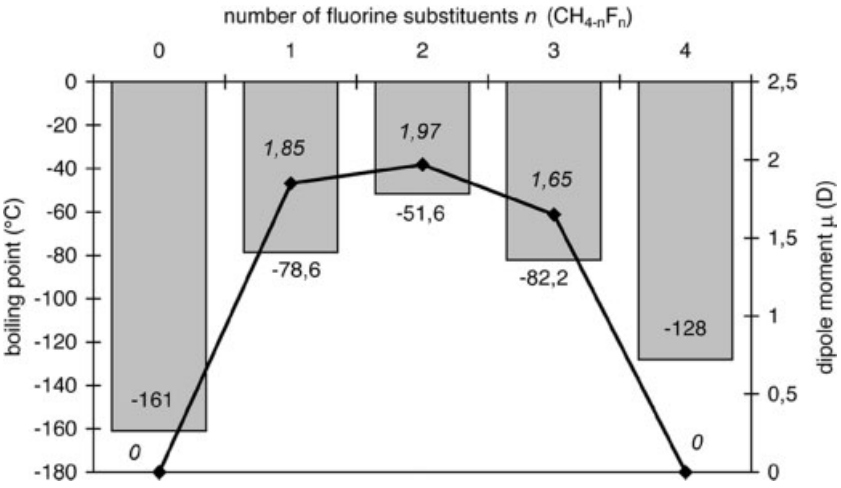


Figure 1.5 Boiling points (°C; *gray bars*) and dipole moments μ (D; ◆, *numerical values in italics*) of methane and the different fluoromethanes $CH_{4-n}F_n$ [2].

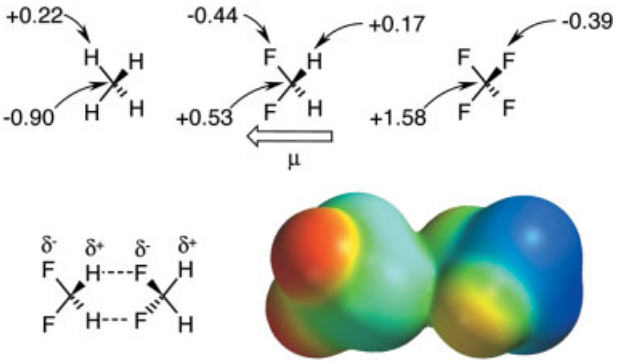


Figure 1.6 *Top*: comparison of the distribution of natural partial charges q (e) on CH_4, CH_2F_2, and CF_4 (MP2/6-31+G** level of theory) [14] and (*below*) the calculated structure (AM1) of a doubly hydrogen-bridged difluoromethane dimer. The electrostatic potential (red denotes negative, blue positive partial charges) is mapped on the electron isodensity surface [7].

A different type of strong electrostatic interaction is observed between arenes and perfluoroarenes (a detailed discussion of this phenomenon can be found in Ref. [15]). Benzene (m. p. 5.5 °C; b. p. 80 °C) and hexafluorobenzene (m. p. 3.9 °C; b. p. 80.5 °C) are known to have very similar phase-transition temperatures. In contrast, an equimolar mixture of both compounds gives a crystalline 1:1 complex melting at 23.7 °C, i. e. ca. 19 K higher than the single components [16]. Different from C_6H_6 and C_6F_6, which crystallize in a edge-to-face, fishbone pattern, $C_6H_6 \cdot C_6F_6$ co-crystals contain both components in alternating, tilted parallel, and approximately centered stacks with an inter-layer distance of ca. 3.4 Å and a centroid–centroid distance of ca. 3.7 Å (Figure 1.7). Neighboring stacks are slightly stabilized by additional lateral C_{aryl}–H · · · F contacts [17].

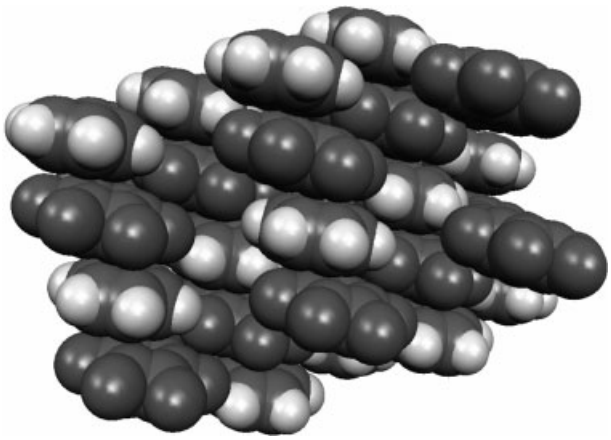


Figure 1.7 X-ray crystal structure of the benzene–hexafluorobenzene 1:1 complex, measured at 30 K in the lowest-temperature modification [17b].

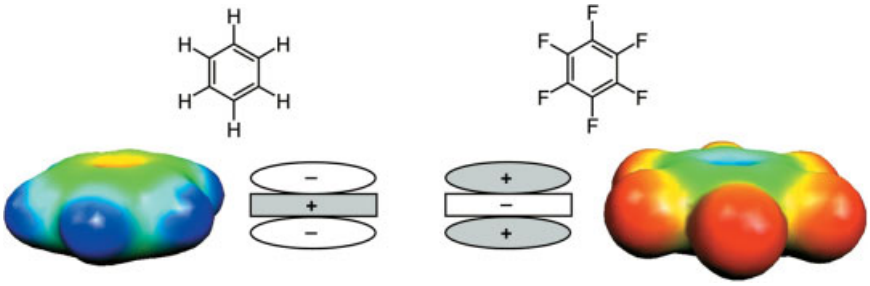


Figure 1.8 Schematic representation of the complementary quadrupole moments of benzene (*left*) (-29.0×10^{-40} C m^{-2}) and hexafluorobenzene (*right*) ($+31.7 \times 10^{-40}$ C m^{-2}) [14]. The color pictures show the electrostatic potentials mapped on the isodensity surfaces (B3LYP/6-31G* level of theory) [7, 14]. In benzene (*far left*) the largest negative charge density (coded in red) is located above and below the plane of the π-system. In contrast, in hexafluorobenzene, these locations carry a positive partial charge (coded in blue).

Similar structures have been observed for a variety of other arene-perfluoroarene complexes [15], indicating that this kind of interaction is a generally occurring phenomenon for this type of structure [18]. Evidence based on structural [17] and spectroscopic data [19], and on quantum chemical calculations [20] (Figure 1.8) indicates, that the observed arene–perfluoroarene interactions are mainly the consequence of strong quadrupolar electrostatic attraction [21].

The usual interactions driving "aromatic stacking forces", for example dispersion interactions with a distance dependence of r^{-6}, seem to play an additional major role in this phenomenon. The occurrence of a charge-transfer complex between electron-rich benzene and electron-deficient hexafluorobenzene can, on the other hand, be excluded by spectroscopic data. The quadrupole moments of benzene (-29.0×10^{-40} C m^{-2}) and hexafluorobenzene ($+31.7 \times 10^{-40}$ C m^{-2}) have a very similar order of magnitude but with their different sign the compounds form a complementary pair, interacting with a distance dependence of r^{-5}. The directionality of the quadrupolar interaction is considered to be the main force driving preference for the sandwich-like arrangement of the complementary arenes in the solid state. Ab-initio and DFT calculations gave estimates between -3.7 and -5.6 kcal mol^{-1} (assuming an inter-planar distance of 3.6 Å) for the interaction

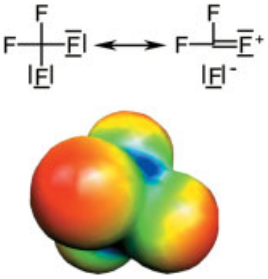


Figure 1.9 Resonance stabilization of the carbon–fluorine bond in tetrafluoromethane, and electrostatic and steric shielding against nucleophilic attack on the central carbon atom. The electrostatic potentials are mapped on the electron isodensity surface (calculation at the MP2/6-31+G* level of theory [7, 14]; red denotes negative, blue positive partial charges).

energy between a parallel, but slightly shifted heterodimer as found in the crystal structure. The interaction within the heterodimer was estimated to be between 1.5 and 3 times stronger than within the corresponding benzene or hexafluorobenzene homodimers. Another interesting result from the calculations is that the contribution of the dispersion interactions to the overall binding energy of the heterodimer is even stronger than that of the electrostatic interaction.

Electrostatic interactions resulting from the polarity of the carbon–fluorine bond play an important role in the binding of fluorinated biologically active compounds to their effectors [22] (discussed in detail in Sections 4.5 and 4.6) and for the mesophase behavior of fluorinated liquid crystals [23] (Section 4.4). The consequences of the low polarizability of perfluorinated molecular substructures have been put into commercial use for chlorofluorocarbon (CFC) refrigerants, fire fighting chemicals, lubricants, polymers with anti-stick and low-friction properties, and fluorosurfactants.

1.4.2 Chemical Properties

The most obvious characteristic of fluoroorganic compounds is the extreme stability of the carbon–fluorine bond. The stability increases with the number of fluorine substituents bound to the same carbon atom. This increase of stability is reflected in the lengths of the C–F bonds in the series CH_3F (140 pm) > CH_2F_2 (137 pm) > CHF_3 (135 pm) > CF_4 (133 pm) (calculation at the MP2/6-31+G** level of theory) [14]. The main reason for this stabilization is the nearly optimum overlap between the fluorine 2s and 2p orbitals and the corresponding orbitals of carbon; this enables the occurrence of dipolar resonance structures for multiply fluorine-substituted carbon (Figure 1.9, see p. 14). The consequences on chemical reactivity of this "self-stabilization" of multiple fluorine substituents on the same carbon atom are discussed in more detail in Section 2.1.3.

In addition to this thermodynamic stabilization, in perfluorocarbons additional kinetic stability is derived from the steric shielding of the central carbon atom by a "coating" of fluorine substituents. The three tightly bound lone electron-pairs per fluorine atom and the negative partial charges are an effective electrostatic and steric shield against any nucleophilic attack targeted against the central carbon atom.

Perfluorocarbons are, therefore, extremely inert against basic hydrolysis. PTFE, for example, can even withstand the action of molten potassium hydroxide. At high temperatures PFC are attacked by strong Lewis acids, for example aluminum chloride. In such reactions decomposition is initiated by the removal of a fluoride ion from the fluorous "protection shield", rendering the resulting carbocation open to nucleophilic attack. Another mode of degradation of perfluorocarbons is by strong reducing agents at elevated temperatures. Thus PFC are decomposed on contact with molten alkali metals and also on contact with iron at 400–500 °C. The latter type of reaction has even been utilized for industrial synthesis of perfluoroarenes by reductive aromatization of perfluorocycloalkanes (Section 2.1.4.).

Table 1.5 Acidities (pK_a) of organic acids in comparison with their fluorinated analogues [25].

Acid	pK_a
CH_3COOH	4.76
CF_3COOH	0.52
C_6H_5COOH	4.21
C_6F_5COOH	1.75
CH_3CH_2OH	15.9
CF_3CH_2OH	12.4
$(CH_3)_2CHOH$	16.1
$(CF_3)_2CHOH$	9.3
$(CH_3)_3COH$	19.0
$(CF_3)_3COH$	5.4
C_6H_5OH	10.0
C_6F_5OH	5.5

Table 1.6 Basicities (pK_b) of organic bases in comparison with their fluorinated analogues [25].

Base	pK_b
$CH_3CH_2NH_2$	3.3
$CF_3CH_2NH_2$	8.1
$C_6H_5NH_2$	9.4
$C_6F_5NH_2$	14.36

Because of its strongly negative inductive effect, fluorine substitution tends to dramatically increase the acidity of organic acids [24, 25] (Table 1.5). For example, the acidity of trifluoroacetic acid ($pK_a = 0.52$) is four orders of magnitude higher than that of acetic acid ($pK_a = 4.76$). Even very weak acids, for example *tert*-butanol ($pK_a = 19.0$), are converted by fluorination into moderately strong acids ($(CF_3)_3COH$, $pK_a = 5.4$).

The inductive effect of fluorination also reduces the basicity of organic bases by approximately the same order of magnitude (Table 1.6). In contrast with basicity, the nucleophilicity of amines is influenced much less by fluorinated substituents.

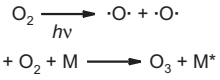
Other effects of fluorine substitution in organic compounds include a strong influence on lipophilicity and the ability of fluorine to participate in hydrogen bonding either as a hydrogen-bond acceptor or as an inductive activator of a hydrogen-bond donor group. This behavior has a substantial effect on the biological activity of fluorochemicals and will be discussed in more detail in Section 4.5.

1.4.3 Ecological Impact

Despite or, better, because of their extreme chemical stability perfluorocarbons and halofluorocarbons have a dramatic impact on the global environment; this was nearly impossible to predict when the substances were first introduced into industrial mass-production and ubiquitous use.

1.4.3.1 Ozone Depletion by Chlorofluorocarbons

Because of their extreme stability against all kinds of aggressive chemical agent, for example radicals, perfluorocarbons and halofluorocarbons are not degraded in the lower layers of the atmosphere as are other pollutants. After several years, or even decades, they finally reach the stratosphere at altitudes of 20 to 40 km [26, 27]. In this layer, under the influence of short-wave UV irradiation, ozone is formed continuously (Scheme 1.2). This stratospheric ozone plays an essential role in preserving life on earth by absorbing the short-wavelength UV which would otherwise lead to an increase of photochemically induced mutations in most life-forms. For humans, over-exposure to short-wave UV irradiation results in a dramatically increased risk of skin cancer. Many crops and other plants also react rather sensitively towards an increase of UV exposure.



Scheme 1.2 Mechanism of the ozone formation in the stratosphere [26]. Dioxygen is photochemically split into atomic oxygen, which adds to another dioxygen molecule. The excess energy from the recombination is carried away by a collision partner (M).

Although CFC are highly stable in the lower atmospheric layers, in the stratosphere they are slowly photolyzed by the ambient short-wavelength UV radiation which also drives ozone formation. The bonds in CFC most susceptible to photolytic dissociation are the carbon–chlorine bonds; chlorine and perfluoroalkyl radicals are liberated. The chlorine radicals react with ozone with formation of oxygen and chlorooxide radicals, which are recycled back to chlorine radicals by reaction with atomic oxygen, nitrous oxide, nitric oxide, or hydroperoxy radicals (Figure 1.10). Chlorine radicals also react with stratospheric methane to give hydrochloric acid, which is rapidly re-oxidized to chlorine by hydroxyl radicals. In summary, stratospheric ozone is depleted, in a catalytic process, faster than it can be replenished by the natural, UV-driven process [27].

It has also been speculated that the concomitantly generated perfluoroalkyl radicals play a minor role in ozone depletion but, in contrast with chlorine, the trifluoromethyl radical, for example, is cleared from the atmosphere relatively quickly via its irreversible conversion to carbonyl difluoride (CF_2O) [28]. Whereas bromine

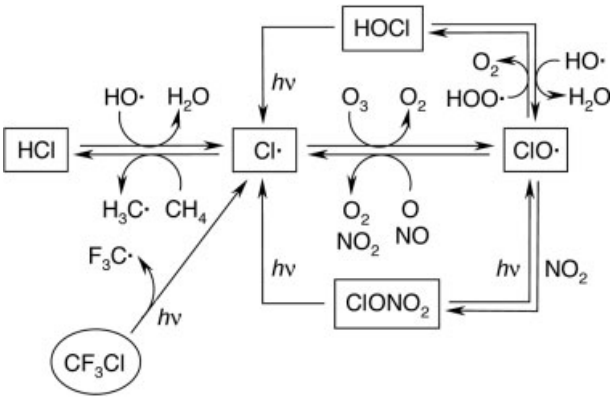


Figure 1.10 Catalytic ozone degradation by CFC in the stratosphere [26].

(arising from bromofluorocarbon-based fire-fighting chemicals, for example CF_2Br_2) has a similar effect to chlorine, fluorine radicals do not contribute very much to ozone depletion, because they are rapidly removed from the catalytic cycle by irreversible formation of highly persistent hydrofluoric acid.

When Molina and Rowland made their prediction in 1974, world production of $CFCl_3$ and CF_2Cl_2 was approximately 0.3 and 0.5 Mton a^{-1}, respectively; fluorocarbon production in the US was growing by 8.7% per year around 1970 [27]. Six years later, and every year since then, the predicted ozone hole was detected over Antarctica, when the chlorine concentration in the same atmospheric layer was approximately 2000 pmol mol^{-1} [29]. After this clear evidence of the deleterious effects of CFC, in 1987 this class of substance and most bromofluorocarbons were banned from further industrial use in the Montreal Protocol (ratified by the first 29 states in 1989). Because of the decade-long lifetime of stratospheric CFC, their phasing-out can be expected to show an effect no earlier than approximately 2040.

Because CFC had many essential functions in all aspects of our daily life (for example refrigerants, foaming agents, or propellants for aerosol cans), subsequent to the Montreal Protocol an intensive search for potential replacements was initiated. CFC replacements so far include hydrofluorocarbons (HFC; for example CF_3CFH_2, marketed as HFC-134a), hydrochlorofluorocarbons (HCFC), and partially fluorinated ethers (for example CH_3OCF_3). These substances are much less stable to attack by radicals in the lower atmosphere and thus cannot reach the stratosphere where they would deplete the ozone layer [30].

1.4.3.2 **Greenhouse Effect**

In addition to their long atmospheric lifetime, fluorocarbons also have strong infrared absorption bands between 1000 and 1400 cm^{-1}, where the atmosphere is relatively transparent. This IR absorption is used for analytical determination of the

Table 1.7 Atmospheric lifetimes (years), global-warming potential (GWP), and ozone-depleting potential (ODP) of different fluorochemicals. The global warming potential of a material is the integrated radiative forcing over 100 years after release of 1 kg divided by the integrated radiative forcing over the same period from release of 1 kg carbon dioxide [29, 31, 32a].

Compound	*Atmospheric Lifetime*	*GWP*	*ODP*
CF_4	50000	5700	–
C_2F_6	10000	11400	–
CF_3Cl (CFC-13)	640	14000	1.0
C_2F_5Cl (CFC-115)	1700	10300	0.6
CF_3Br (Halon 1301)	65	6900	10.0
SF_5CF_3	1000	17500	–
SF_6	3200	22200	–
CHF_3 (HFC-23)	243	14800	–
CH_2FCF_3 (HFC-134a)	13.6	1600	–
$C_4F_9OC_2H_5$ (HFE-7200)	0.77	55	–

concentration of the different organofluorine compounds in the stratosphere. The infrared absorption of CFC is much stronger than that of carbon dioxide, rendering them a potential contributor to global warming (Table 1.7). On the other hand, because of the relative quantities of the different greenhouse gases released into the atmosphere, CFC and related compounds (for example SF_6, used as an insulating gas in high-voltage installations) have a negligible effect on global warming. For example, in 2000 emissions of CO_2 were 200000 times greater than the combined emissions of HFC and PFC [29].

Some of the most potent fluorine-containing greenhouse gases are not produced on purpose but are by-products of industrial processes. Thus trifluoromethane (CHF_3) is a product of over-fluorination during the technical production of HCFC-22 ($CHClF_2$), and CF_4 and C_2F_6 are mostly formed during aluminum production by melt electrolysis of cryolith (Na_3AlF_6). Most of the SF_6 and the similarly greenhouse potent SF_5CF_3 [31] released into the atmosphere are by-products from electrochemical fluorination processes.

Recently it has been proposed to make use of the greenhouse potential of CFC for the "ferraforming" of Mars [32b]. Addition of a four hundreds parts per billion (ppb) to the Martian atmosphere would lead to a 70 K increase of its surface temperature.

1.4.4 Physiological Properties

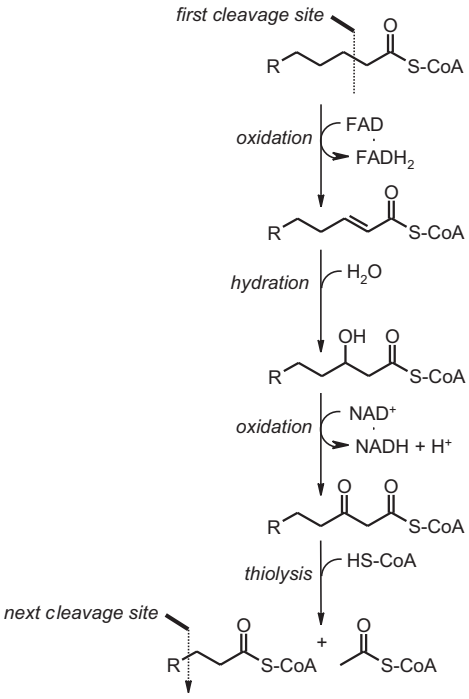
In their interaction with living organisms the behavior of organofluorine compounds is again extreme. Most aliphatic perfluorocarbons (PFC), chlorofluorocarbons (CFC), and related compounds are essentially "ignored" by organisms [33]. Because of their generally low reactivity, comparable to that of the noble gases,

they are not metabolized. Because they are usually quite volatile and do not dissolve readily either in aqueous (e. g. blood) or fatty (e. g. nervous system) compartments of the body, they are usually not even recognized as "foreign" but just exhaled through the lungs. This inertness results in some unique opportunities for medical applications, which will be discussed in detail in Section 4.5.

A very few fluorine-containing substances are, on the other hand, extremely toxic. The most (in)famous of these are fluoroacetic acid (LD_{50} 4.7 mg kg^{-1} in rats, LD_{100} 5 mg kg^{-1} in humans [33] – the doses after which 50 % or 100 %, respectively, of the tested individuals die) and perfluoroisobutene ($LC_{50} < 1$ ppm – the concentration in ambient air for 4 h after which half of the tested individuals die).

Fluoroacetic acid has been identified as the toxic component of the South African plant "*gifblaar*" (*Dichapetalum cymosum*) [34]. Its mechanism of action is based on inhibition of the citric acid cycle, the main source of metabolic energy in all animals [35]. In this cycle, fluoroacetate can replace acetate as a substrate of aconitase, an enzyme complex which usually forms citrate by addition of acetate to α-oxoglutarate. The resulting fluorocitrate is binds tightly to the enzyme, but cannot be further converted to *cis*-aconitate and isocitrate [36], thus inhibiting aconitase.

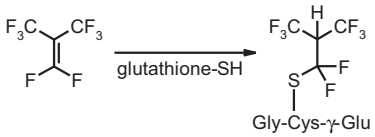
It must also be remembered that some fluoroorganic compounds are, if ingested, degraded to toxic metabolites. This phenomenon occurs with ω-fluoro fatty acids, aldehydes, alcohols, amines, and related compounds – because of metabolic oxidation of fatty acids by step-wise cleavage of C_2 units, ω-fluoro fatty acids with an even number of carbon atoms end up as toxic fluoroacetate (e. g.



Scheme 1.3 The "alternating" toxicity of ω-fluorocarboxylic acids can be explained by the oxidative metabolism of fatty acids in C_2 units. Only if the number of carbon atoms is even the final oxidation product is the highly toxic fluoroacetate [36]. Odd-membered ω-fluoro fatty acids are metabolized to the less toxic 3-fluoropropionate.

$F(CH_2)_{15}COOH$ which has an LD_{50} of 7 mg kg^{-1} in mice). Odd-numbered ω-fluoro fatty acids are metabolized to the less critical 3-fluoropropionate. This phenomenon is known as the "alternating" toxicity of ω-fluoro fatty acids [36] (Scheme 1.3).

Perfluoroisobutene is the most toxic fluorinated compound yet discovered, with an LC_{50} of less than 1 ppm. The reason for its extreme toxicity is not completely understood. The target organs of the compound are the liver and lungs. Inhalation can cause lethal edema even 1–2 days after the end of exposure. Perfluoroisobutene is assumed to add to the thiol group of glutathione (Gly-Cys-γ-Glu), a tripeptide which serves as an ubiquitous intracellular antioxidant and which is also used by the liver to clear toxins and their metabolites as *S*-conjugates by renal excretion (Scheme 1.4). The glutathione–perfluoroisobutene adduct seems to be the real toxin. The toxicity of perfluoroisobutene and other (less toxic) perfluoroolefins is of some practical relevance in daily life, because these compounds can also be formed at high temperatures during pyrolysis of polytetrafluoroethylene (PTFE, Teflon) which is widely used as an anti-stick coating for household appliances.



Scheme 1.4 Formation of the toxic glutathione–perfluorisobutene adduct.

Some widely used fluorotensides have recently become the focus of environmental concerns. Compounds such as perfluorooctyl sulfonic acid and perfluorooctanoic acid (PFOA) have environmental lifetimes on a nearly geological time-scale. Traces of these substances have been found to be present in the remotest locations on earth and the source of the contamination remains unclear. There is not yet much unambiguous evidence of negative physiological effects of these widely used fluorosurfactants, although perfluorooctyl carboxylates have attracted some critical attention as a potential developmental toxin in rats [37]. Some major producers have, therefore, already started to replace these tensides by more readily degradable alternative compounds.

1.4.5
Analysis of Fluorochemicals: ^{19}F NMR Spectroscopy

Naturally and exclusively occurring $^{19}_{9}F$ has a nuclear spin of $\frac{1}{2}$, and NMR sensitivity only 20 % less than ^{1}H. This renders ^{19}F NMR spectroscopy the method of choice for analysis and elucidation of the structure of fluorinated compounds [38, 39] (Figure 1.11). Depending on their chemical environment, the ^{19}F resonances of fluoroorganic and fluoroinorganic compounds cover a range of over 400 ppm and 700 ppm, respectively. $CFCl_3$ is typically used as reference standard.

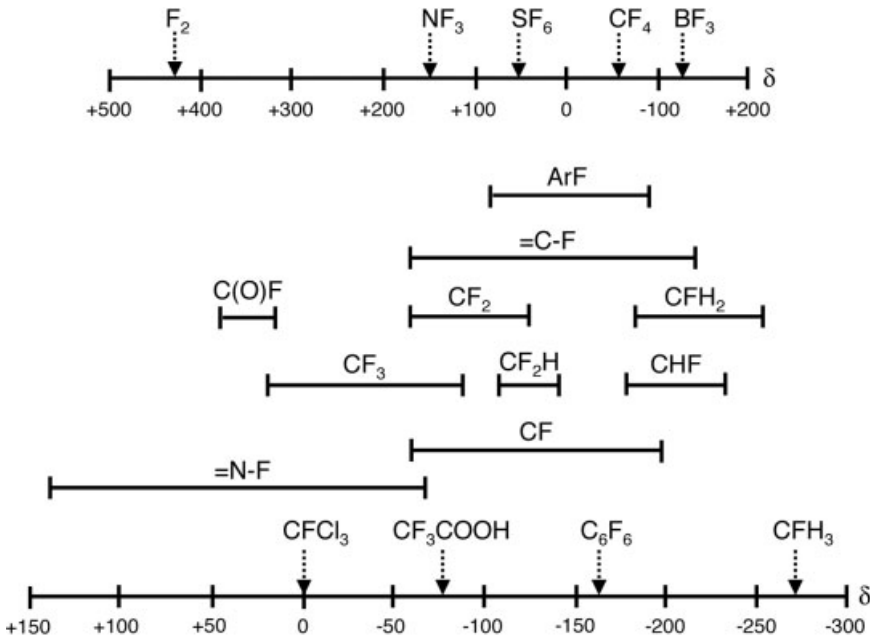


Figure 1.11 ^{19}F chemical shifts for different fluorochemicals and fluorinated fragments [38].

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2
Synthesis of Complex Organofluorine Compounds

2.1
Introduction of Fluorine

2.1.1
Perfluorination and Selective Direct Fluorination

Shortly after their first isolation of elemental fluorine in 1886, Moissan and his coworkers treated several organic substrates with this highly reactive gas. All these experiments, either at room temperature or at liquid nitrogen temperature, resulted in sometimes violent explosions. No major defined reaction products could be isolated.

A plausible, first explanation for these discouraging results was proposed by W. Bockemüller in the 1930s, on the basis of thermochemical considerations. The energy released by formation of the highly stable carbon–fluorine bonds ($\sim$116 kcal mol^{-1}) is considerably greater than the energy needed for dissociation of carbon–carbon ($\sim$83 kcal mol^{-1}) or carbon–hydrogen bonds ($\sim$99 kcal mol^{-1}) [1]. A second problem is the extremely low homolytic dissociation energy of elemental fluorine (only 37 kcal mol^{-1}), which enables ready initiation of uncontrollable radical chain reactions, even at low temperatures and in the absence of light [2].

The first defined fluoroaliphatic compounds obtained by direct fluorination of organic substrates in liquid reaction media were characterized by Bockemüller [3] in the early 1930s and published with his thermochemical analysis. To control the immense reaction enthalpy the fluorine gas was diluted with nitrogen or carbon dioxide. The organic substrate was dissolved in a cooled inert solvent, for example CCl_4 or CF_2Cl_2. A similar line of work was pursued in the United States by L. A. Bigelow [4] who studied the reaction of arenes with fluorine gas.

In an alternative approach, volatile organic substrates were fluorinated in the gas phase on contact with a copper mesh. This work was pioneered by Fredenhagen and Cadenbach in the early 1930s [5] and then continued by Bigelow and Fukuhara [6] as a part of the Manhattan Project (Figure 2.1). Vapor phase fluorination finally enabled the preparation of (relatively) defined polyfluorination products from aliphatic hydrocarbons, benzene, or acetone.

A modern, improved version of this general method, the LaMar (Lagow–Margrave) process, uses a nickel reactor with different temperature zones and silver-

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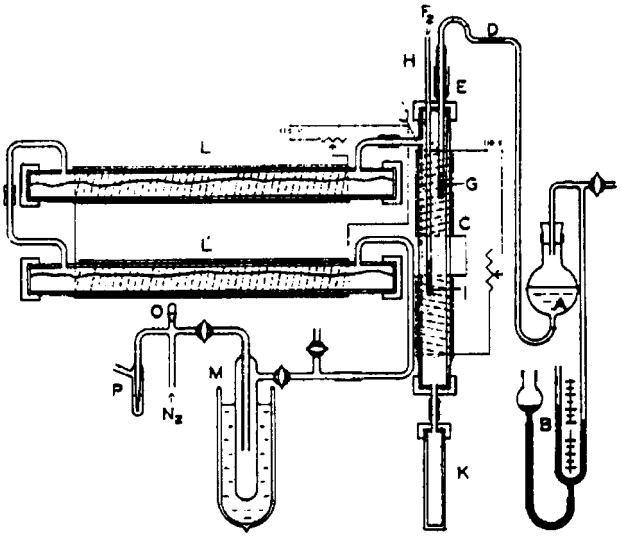
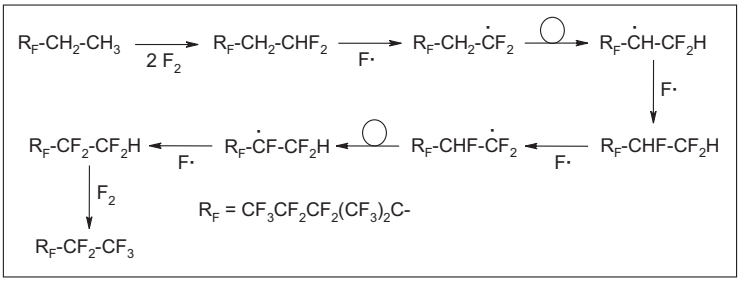
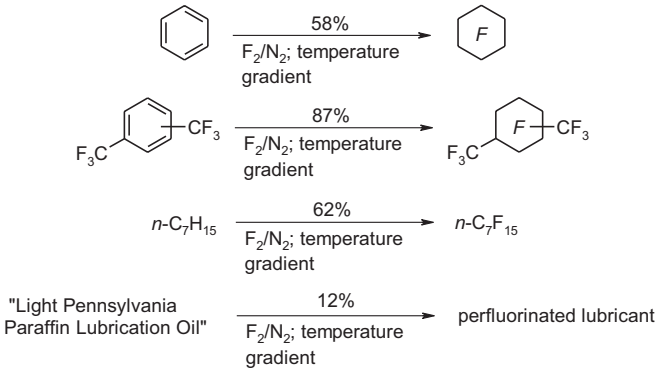


Figure 2.1 Fluorination apparatus used by Bigelow and Fukuhara for perfluorination of a variety of organic substrates (courtesy of the American Chemical Society) [6].

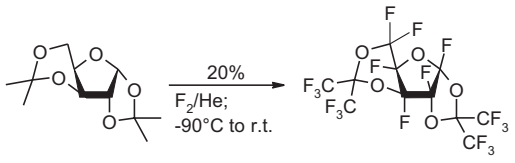




Scheme 2.1 Gas-phase perfluorination of a variety of hydrocarbons by the LaMar process. At the top the proposed mechanism of free radical direct fluorination of alkanes is shown [8].

doped copper filings as a catalytic contact (Scheme 2.1). During the reaction, the concentration of fluorine in proportion to inert gas is slowly increased [7].

Another method used to control the high reaction enthalpy of fluorination is coating of the organic substrate as a thin film on sodium fluoride powder and reaction in a moving bed reactor with fluorine gas, diluted with nitrogen or helium. Slow, stepwise increase of the fluorine concentration also enables clean perfluorination of rather complex substrates [9] (Scheme 2.2).



Scheme 2.2 After adsorption by solid sodium fluoride complex and sensitive organic compounds can be cleanly perfluorinated [9].

The first pure and fully characterized *perfluoro*carbons (PFC) were obtained by the reaction of graphite with fluorine gas, yielding mainly carbon tetrafluoride [10]. An improved procedure, less prone to accidents, was reported by Simons and Block in 1937 – passage of fluorine over graphite impregnated with catalytic amounts of mercuric chloride furnished a mixture of various perfluorocarbons in a controllable and reproducible reaction, proceeding "steadily and without explosions" [11].

The industrial scale procedure probably most important for synthesis of perfluorocarbon-based solvents was developed during the Manhattan Project [12] (Figure 2.2). In the so-called cobalt trifluoride process (recently commercialized by F2 Chemicals as the "Flutec" process) [13] the large fluorination enthalpy is harnessed by dividing the reaction into two less exothermic steps. In the first step, CoF_2 is oxidized with fluorine, at 350 °C, to CoF_3. In the second step, the organic

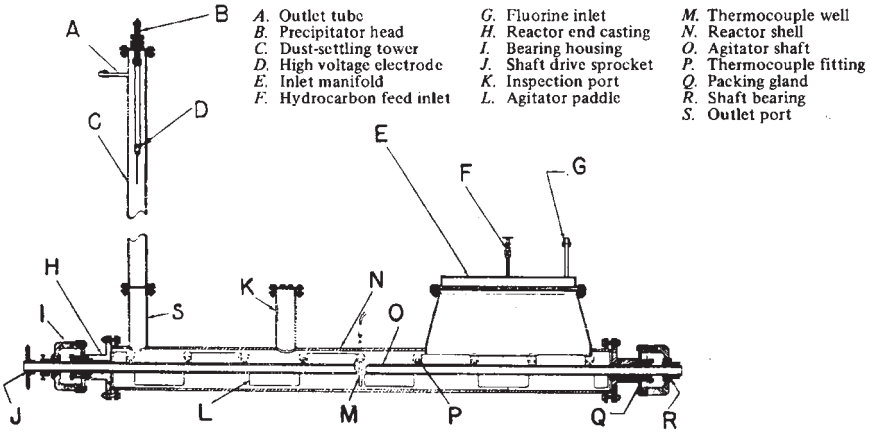
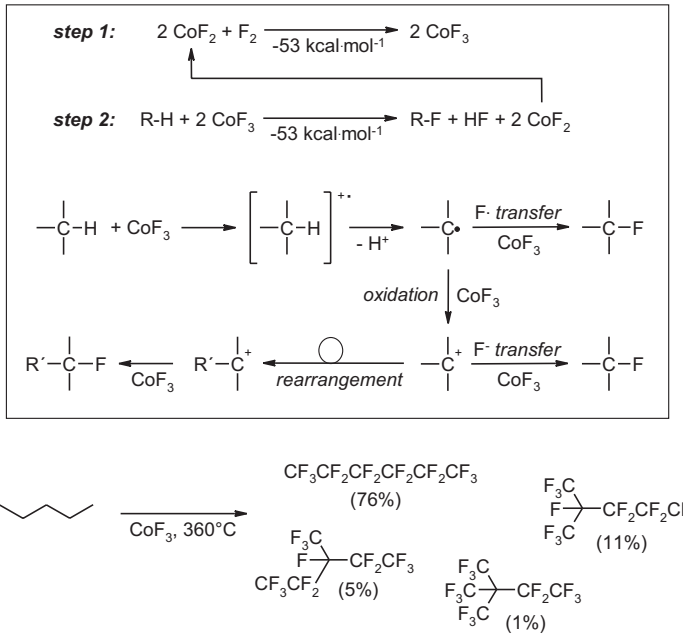


Figure 2.2 Schematic representation of the apparatus used to perform the cobalt trifluoride process (courtesy of the American Chemical Society) [13].

substrate is introduced and fluorinated by the CoF_3 at a suitable temperature. The CoF_2 formed is regenerated (i. e. re-oxidized) to CoF_3 in the next reaction cycle.

The cobalt trifluoride process is of particular value for industrial perfluorination of organic substrates and it is based on the findings by Ruff and coworkers in the 1920s that high-valence metal fluorides such as AgF_2, CoF_3, or MnF_3, are highly effective oxidative fluorination agents. Typical product distributions and the nature of the various rearrangement products indicate that the mechanism of the CoF_3 and related processes involves single-electron transfers and carbocationic intermediates [14] (Scheme 2.3).



Scheme 2.3 Two-step perfluorination of organic substrates by the cobalt trifluoride (Flutec) process. The mechanism is assumed to involve single electron transfers and carbocationic intermediates [8].

Although the cobalt trifluoride process is most suitable for the production of industrial-scale quantities of perfluorocarbons, other high-valence metal fluorides also are attractive additions to the methodology toolbox for selective fluorination on a laboratory scale. K_2PtF_6 was recently used for the selective fluorination of buckminsterfullerene (C_{60}) to the partially fluorinated fluorofullerene $C_{60}F_{18}$ which was not accessible by other methods [15] (Figure 2.3). A major disadvantage of such metal fluorides, with extremely strong oxidizing power, in routine application is, nevertheless, the need to work either with volatile substrates in the gas phase or to use either no solvent at all or anhydrous hydrofluoric acid as the only stable reaction medium.

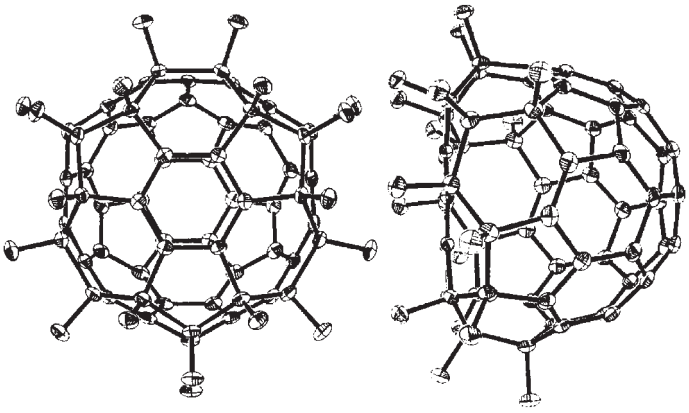
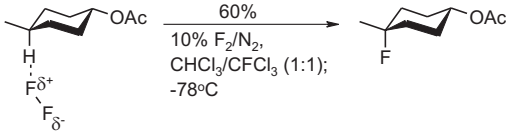


Figure 2.3 X-ray structure of $C_{60}F_{18}$ obtained by selective fluorination of C_{60} with K_2PtF_6 without solvent at 230–330°C [15].

On the laboratory scale, the tendency of elemental fluorine to initiate radical chain reactions resulting in tar formation can be controlled by appropriate choice of solvent. The solvent system $CFCl_3/CHCl_3$, sometimes with additional 10 % ethanol, serves as an effective radical scavenger. The reaction enthalpy is controlled by dilution of the substrate in this solvent, by dilution of the fluorine gas with nitrogen or helium, and by use of a low reaction temperature. Under these conditions, the selective fluorination of cyclohexane derivatives in the tertiary axial position is possible in reasonable yields [16] (Scheme 2.4), supposedly by an electrophilic mechanism.

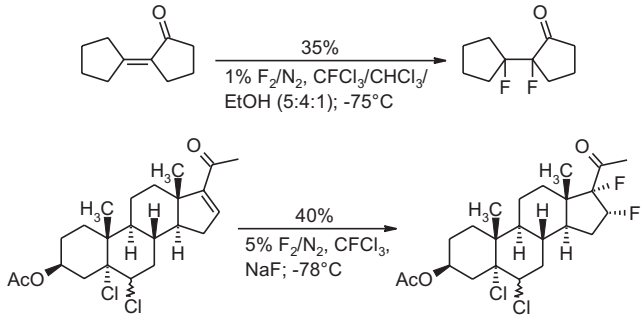


Scheme 2.4 Direct fluorination of aliphatic compounds in the tertiary position by an electrophilic mechanism [16].

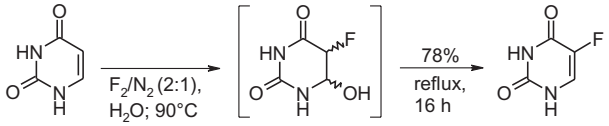
Under similar conditions selective addition of fluorine to double bonds, even with complex organic substrates such as steroids, can also be achieved [17] (Scheme 2.5).

One of the first examples of industrial application of selective direct fluorination was the synthesis of the cytostatic 5-fluorouracil. In the most commonly used process the precursor uracil is treated with nitrogen-diluted fluorine in hot water and the intermediate fluorohydrin is subsequently dehydrated either by heating the aqueous solution to 100 °C or with sulfuric acid [18] (Scheme 2.6.).

During the last few years, especially, there have been great advances in the selective direct fluorination of even sensitive organic substrates. Some of the methods introduced by R. D. Chambers and coworkers are even fulfilling the requirements of robust and reproducible industrial processes, and the resulting products have

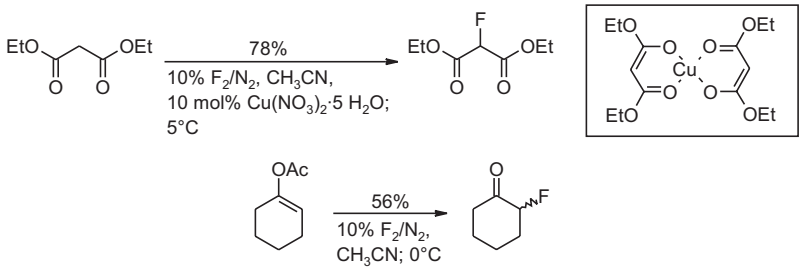


Scheme 2.5 Selective direct fluorination of double bonds in complex organic compounds [17].



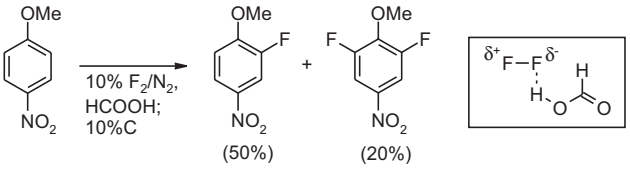
Scheme 2.6 Direct fluorination process for industrial-scale production of 5-fluorouracil [18].

become commercially available. The selective fluorination of β-dicarbonyl derivatives is best achieved in acetonitrile which, because of its stability, is a particularly suitable solvent for direct fluorination. Typical reaction temperatures are conveniently in the range 0 to 5 °C. With dialkyl malonates addition of catalytic amounts of copper(II) nitrate enables selective formation of the *mono*-fluoromalonates almost without difluorinated byproducts [19] (Scheme 2.7). Enol acetates are cleanly converted into the respective α-fluoroketones [20].



Scheme 2.7 Selective direct α-fluorination of carbonyl compounds. Copper salt catalysis supposedly acts via formation of the copper enolate complex [19, 20]. The formation of the corresponding copper complex of monofluoromalonate, the precursor of difluorinated products, is energetically disfavored.

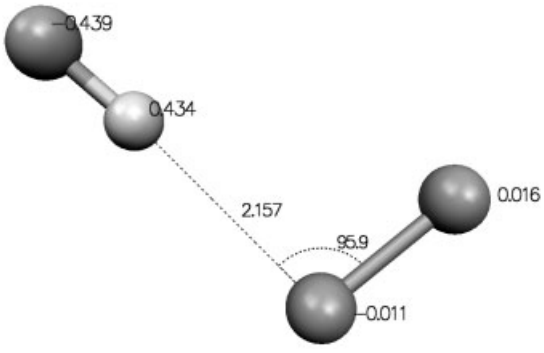
Although clean, direct fluorination of aromatic compounds is possible [21], the selectivity of this process is not yet high enough for commercialization. Arenes are best fluorinated in acidic solvents such as sulfuric acid or formic acid, to obtain an electrophilic mechanism (Scheme 2.8). The main obstacle to large-scale industrial application of the potentially inexpensive direct fluorination of aromatic compounds is the difficult separation of the regioisomers and other by-products with higher or lower fluorine content.



Scheme 2.8 "Electrophilic" direct fluorination of activated arenes in acidic solvents [21].

A more recent approach to the control of the large reaction enthalpies in technical-scale direct fluorination is the use of microreactors [22]. These have three advantages compared with conventional arrangements: (1) the high surface-to-volume ratio for contact between gas and liquid phase is especially advantageous for direct fluorinations, because it enables good mixing of the reactants and good temperature control; (2) because the actual reaction volume is very small, the risk of runaway reactions or explosions is significantly reduced; and (3) the upscale to industrial throughput is conveniently accomplished by the parallel operation of as many microreactors as necessary.

Recent computational studies [23] on the structure and charge distribution of hydrogen bonded F_2 suggest a more differentiated view on the supposedly "electrophilic" mechanism of direct fluorination of aliphatic and aromatic hydrocarbons. *Ab-initio* calculations indicate that even for the complex of F_2 with the extremely strong hydrogen-bond donor HF as a model system, the energy of complex formation is very low – only 0.38 kcal mol^{-1} (MP2/6-31+G**//MP2/6-31+G** level of theory, ZPE and BSSE correction) [24] (Scheme 2.9). Because of the low polarizabil-

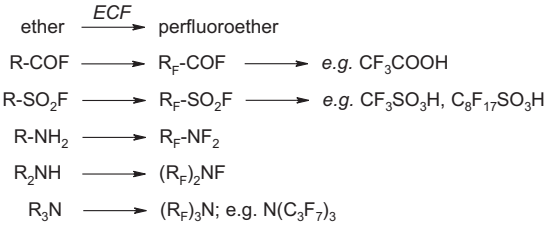


Scheme 2.9 Calculated gas phase structure (MP2/6-31+G**//MP2/6-31+G** level of theory, ZPE and BSSE correction) [23–25] of the $F_2 \cdots HF$ complex, with the length (Å) and angle (°) of the central hydrogen bond and the induced Mulliken partial charges (e). The natural partial charges on the F_2 fluorine atoms are −0.02 e and +0.02 e, respectively. The formation of the complex is slightly exothermic by 0.38 kcal mol^{-1}.

ity of the fluorine molecule only very small partial charges are induced by acceptance of a weak hydrogen bond from HF. This polarization alone (a natural charge of $q_F = +0.02$ e for the more electrophilic fluorine atom) seems to be too small to change the course of direct fluorination reactions from a radical to a polar electrophilic mechanism as proposed by S. Rozen [16] and R. D. Chambers [21a]. Experimentally, the achievement of a "clean" reaction when using polar protic solvents strongly suggests a non-free radical pathway. Theoretically there are clear indications that the proposed electrophilic mechanism involving significant polarization of F_2 either by a C–H bond of the substrate or by a hydrogen bridge-donating solvent has to reconsidered.

2.1.2 Electrochemical Fluorination (ECF)

Another important technical process for production of a variety of perfluorinated organic compounds – electrochemical fluorination (ECF) – was also developed during the Manhattan Project. This process was pioneered by J. H. Simons and coworkers in 1941 but published only after declassification in 1949 [26]. For electrochemical fluorination, the organic substrate is dissolved in anhydrous hydrofluoric acid (aHF) at 0 °C and a current is passed through the solution at a potential of 4.5 to 6 V. Sometimes additives are used to increase the conductivity. In this voltage range, at the nickel anode, where the fluorination occurs, no fluorine gas is evolved, but hydrogen is evolved at the steel cathode, which is usually also the reaction vessel. With increasing fluorination the solubility of the products in aHF decreases and, finally, the perfluorinated products formed at the anode become immiscible with aHF and form a separate phase which is more dense than the solvent. They can, therefore, be easily removed from the bottom of the reaction vessel. Because the process depends crucially on the solubility of the substrate in aHF (which for many organic compounds is typically around 4 % at 0 °C), in contrast to the CoF_3 process, it is applicable only for the perfluorination of functionalized organic compounds such as ethers, amines, carboxylic, and sulfonic acid derivatives. ECF provided, for the first time, at reasonable cost, commercial quantities of the technically important trifluoroacetic acid and trifluoromethyl and perfluorooctyl sulfonic acids (Scheme 2.10).



Scheme 2.10 Technically relevant conversions by the Simons ECF process (R_F = perfluoroalkyl).

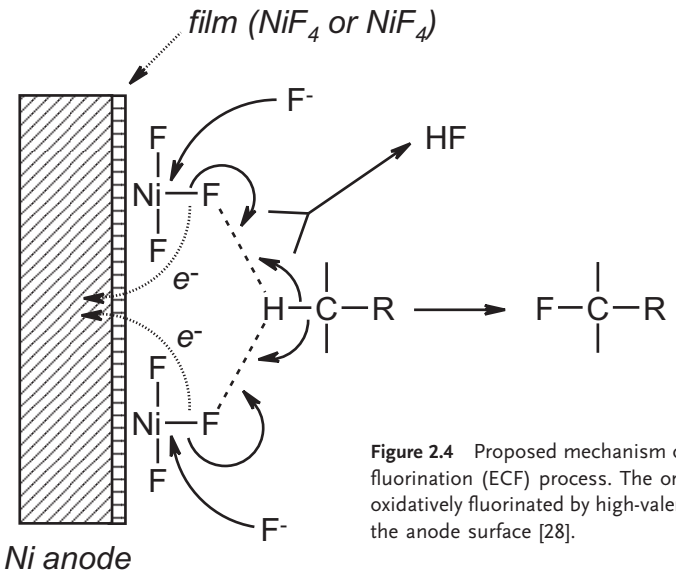


Figure 2.4 Proposed mechanism of the electrochemical fluorination (ECF) process. The organic substrate is oxidatively fluorinated by high-valence nickel fluorides at the anode surface [28].

The Simons ECF process was subsequently developed to an industrial production process by the 3M Company. It currently provides the precursors to the palette of more than 250 large-scale fluorine-containing compounds produced by this company [27]. These products include fluorotensides, fire-fighting chemicals, perfluorinated solvents, and artificial blood substitutes.

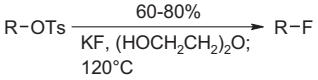
Electrochemical formation of high-valence nickel fluorides with strong fluorinating power at the nickel anode has been discussed as the key to the mechanism of ECF [28] (Figure 2.4). This hypothesis is supported by the findings of N. Bartlett and coworkers that chemically generated NiF_3 and NiF_4 in aHF are also very effective perfluorinating reagents [29].

2.1.3
Nucleophilic Fluorination

For industrial chemistry, the various methods used for nucleophilic fluorination are probably the most important route to fluorinated fine chemicals. In aliphatic nucleophilic substitution (S_N) reactions, fluoride as the leaving group is the most inert halogen (order of nucleofugicity I > Br > Cl > F), because of the very strong carbon–fluorine bond and the high charge density of the liberated fluoride ion. The behavior of the fluoride ion as a nucleophilic species is, however, bizarre – depending on the reaction environment it can act either as an extremely poor nucleophile (in a protic solvent) or as a very powerful nucleophile (in polar aprotic solvents, especially with large lipophilic cations).

2.1.3.1 Finkelstein Exchange

The fact that fluoride is a poor leaving group in aliphatic nucleophilic substitutions and the high volatility of fluoroaliphatic compounds are the keys to the Finkelstein synthesis of alkyl fluorides. An alkyl iodide, bromide, or tosylate is heated in a polar solvent with an alkali fluoride and the volatile alkyl fluoride is removed by distillation during the reaction [30] (Scheme 2.11). For safe handling of primary alkyl fluorides it must be kept in mind that the even-membered compounds of this series are toxic, because they can be oxidatively metabolized to the poisonous fluoroacetate [31].



Scheme 2.11 Finkelstein exchange of tosylates by fluoride. The volatile alkyl fluoride is removed from the reaction mixture by distillation [30].

The nucleophilic reactivity of the alkali metal fluorides decreases in the order CsF > RbF > KF > NaF > LiF, because of the increasing lattice energy of the fluorides with decreasing ion radius of the cation (CsF 177.7 kcal mol^{-1}; RbF 186.4 kcal mol^{-1}; KF 194.0 kcal mol^{-1}; NaF 218.4 kcal mol^{-1}; LiF 247.0 kcal mol^{-1}) [32]. To avoid this problem, crown ethers or phase-transfer catalysts with large, lipophilic cations are often used to render nucleophilic fluorinations more efficient.

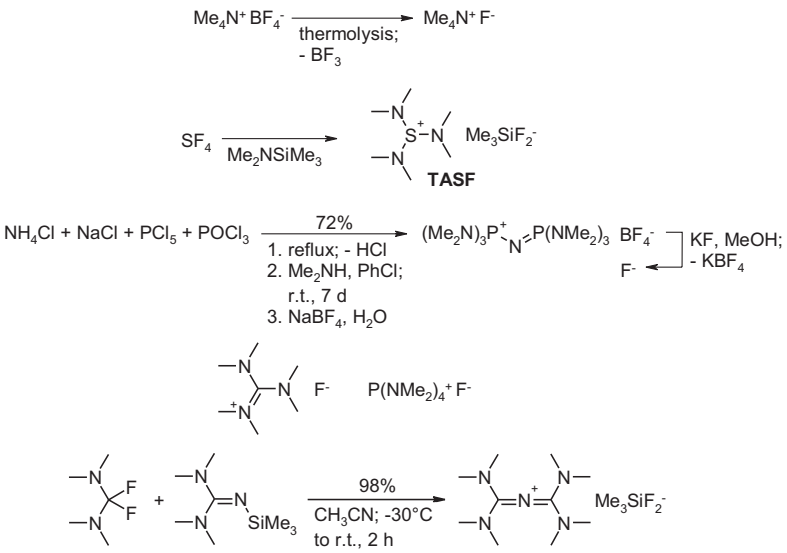
2.1.3.2 "Naked" Fluoride

Generally speaking, the fluoride ion – as it occurs in solutions of alkali fluorides in polar protic solvents – is not a very nucleophilic species. Because of the unique position of fluorine in the periodic system, it is the smallest possible mono-anion with the largest negative charge density. The fluoride ion therefore acts as an extremely strong hydrogen-bond acceptor. This and its low polarizability are the reasons for the relatively moderate nucleophilicity in protic solvents. In contrast, in polar aprotic environments where no potential hydrogen bond donors are available and no close interaction with the cation occurs, fluoride acts as a very potent nucleophile and as a strong base.

Suitable systems are, e. g., fluorides with large organic cations (so-called "naked" fluorides) in polar aprotic solvents such as acetonitrile or DME. The basicity of the "naked" fluoride ion is so large that, in the solid state of the corresponding salts, many usually quite stable organic cations, for example the tetrabutylammonium cation, are decomposed by a deprotonation-induced mechanism. Many crystal structures of fluorides with organic counter-ions show the fluoride ion in close, hydrogen-bonding-like contact with, e. g. dimethylamino groups. Similar interaction and deactivation is the reason for reduced nucleophilicity of such salts in solvents which are usually considered "aprotic" (e. g. acetone). For this reason discussion continues about whether truly "naked" fluorides exist at all.

The quest for naked fluoride has its counterpart on the cationic side with the search for truly uncoordinated lithium cations, which are not deactivated by interactions with solvent or anion and thus limited in their Lewis acidity.

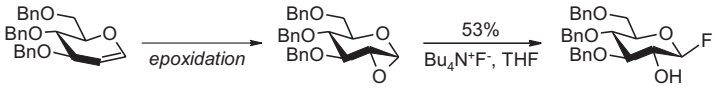
Preparatively, it is sometimes not possible to remove traces of hydrogen-bonded water or alcohols from the fluorides without decomposing the organic cation. Under such conditions the fluoride is generated in the last step of the synthesis by thermolyzing the corresponding tetrafluoroborates (e. g. for $Me_4N^+F^-$). Another stabilization strategy is to use kinetically labile difluorotrimethylsiliconates (e. g. in TASF) or difluorotriphenylstannates [39] as sources of "semi-naked" fluoride ions. A very effective means of increasing the nucleophilicity of "naked" fluorides is efficient charge distribution over a large organic cation, for example tetrakis(dialkylamino)phosphonium or phosphazenium ions (Scheme 2.12).



Scheme 2.12 Sources of "naked" fluorides and some examples of their syntheses (TASF = tris(dimethylamino)sulfonium difluorotrimethylsiliconate) [33–38].

An industrially important application of the lipophilic tetrakis(dimethylamino) phosphonium fluoride is as a phase-transfer catalyst in the Halex process for technical synthesis of fluoroarenes.

In contrast with alkali fluorides, even the moderately active tetrabutylammonium fluoride (TBAF) in THF is an effective reagent for nucleophilic ring opening of epoxides (Scheme 2.13).



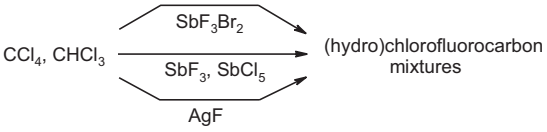
Scheme 2.13 Nucleophilic ring opening of 1,2-anhydro-α-D-hexopyranose derivatives with tetrabutylammonium fluoride (TBAF) [40].

Because of the strong basicity of the fluoride ion, in nucleophilic S_N2 reactions elimination usually occurs as a dominant side-reaction. On the other hand, the basicity of the "naked" fluoride can be used for synthetic purposes, e. g. for deprotonation of phosphonium salts to the corresponding ylides in a system based on potassium fluoride with catalytic amounts of 18-crown-6 in acetonitrile.

2.1.3.3 **Lewis Acid-assisted Fluorination**

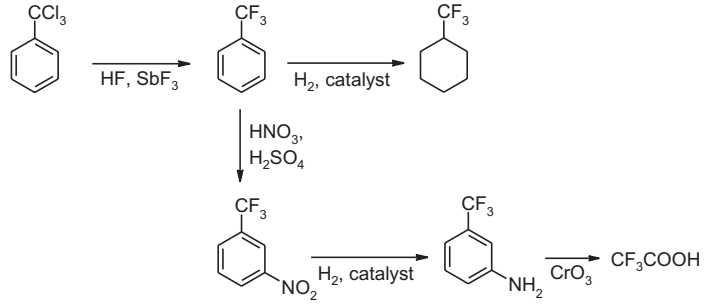
There are two principal ways of increasing the reactivity of the fluoride ion as a nucleophile. The first is to inhibit any deactivating hydrogen bonding or other coordination by choice of a suitable lipophilic counter-ion and reaction medium, rendering the fluoride "naked". The alternative is to increase the nucleofugicity of the leaving groups – in technically relevant cases usually halogen – by activation with Brønsted or Lewis acids. The use of Lewis catalysts increases the reaction rate of nucleophilic exchange dramatically. The thermodynamic direction of the reaction is again determined by the strong carbon–fluorine bond.

The pioneering work in this field was performed by F. Swarts starting from 1892. Treatment of different haloalkanes with HF in the presence of Lewis acids such as SbF_3, SbF_5, AgF, HgF_2, and AlF_3 yielded mixtures of partially and fully fluorinated alkanes, depending on the exact reaction conditions (Scheme 2.14). Stoichiometric amounts of the Lewis catalysts themselves can also serve as the fluoride source [41].



Scheme 2.14 Lewis acid-assisted halogen exchange of chloroalkanes to (hydro)chlorofluorocarbons (CFC and HCFC).

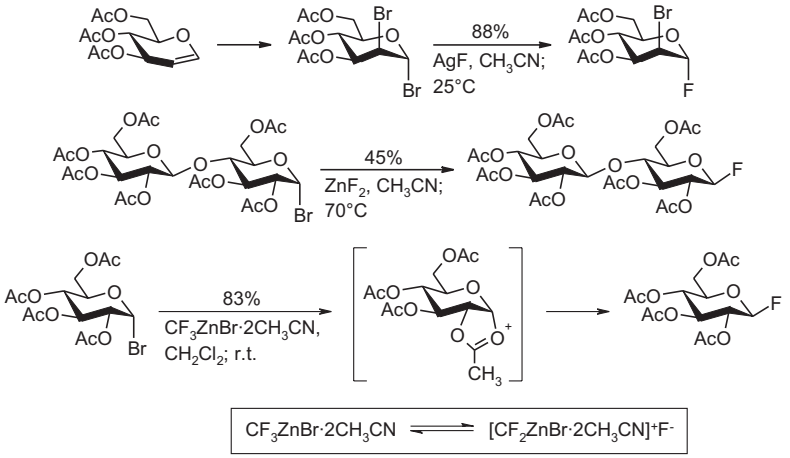
The catalytic halogen exchange works especially well in the benzylic position of aromatic compounds, giving access to a variety of industrially important fluorinated solvents [42, 43] and intermediates [44] (Scheme 2.15).



Scheme 2.15 Catalytic nucleophilic fluorination of benzotrichloride and subsequent synthesis of other fluorinated fine chemicals [44].

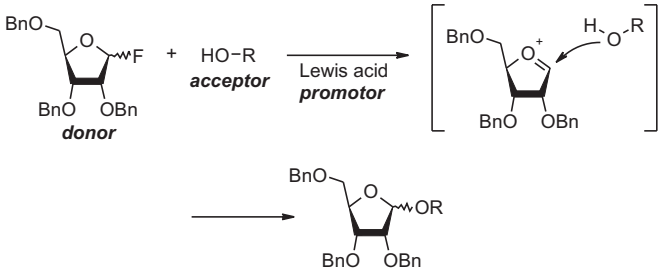
The chemistry developed by Swarts has over many years also been the foundation of the quantitatively most significant branch of industrial fluoroorganic chemistry, the production of chlorofluorocarbon refrigerants ("Freon", in Germany "Frigen") [45] and fire-fighting agents ("Halon"), which started in the 1930s. The most important CFC are Freons 11 ($CFCl_3$), 12 (CF_2Cl_2), 113 ($CF_2ClCFCl_2$), and 114 (CF_2ClCF_2Cl). Later HCFC such as Freon 22 (CHF_2Cl) were also introduced into the market. Typically, these substances were synthesized with anhydrous hydrofluoric acid as the source of fluoride and catalytic amounts of $SbCl_5$ at temperatures below 200 °C. (The nomenclature of CFC is discussed in Section 4.1.).

A newer field of application of Swarts fluorination in carbohydrate chemistry is the synthesis of glycosyl fluorides from the corresponding bromides [46] (Scheme 2.16.).



Scheme 2.16 Synthesis of a variety of glycosyl fluorides by Lewis acid-assisted nucleophilic substitution of the corresponding bromides. The trifluoromethylzinc bromide bis(acetonitrile) complex acts as the fluoride source and electrophilic catalyst at the same time [46].

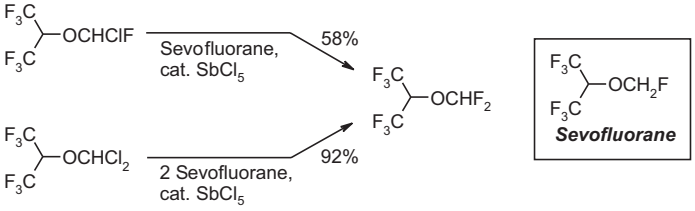
Glycosyl fluorides [47] are among the most versatile building blocks in modern carbohydrate and glycoconjugate chemistry [48]. In glycosylation reactions they serve as the glycosyl donor. A fluoride ion is readily abstracted by "hard" Lewis acids (promoters). The glycosyl acceptor subsequently adds to the resulting resonance-stabilized carbocation intermediate. A large variety of Lewis acids can be used as promoters [49], most commonly $BF_3 \cdot OEt_2$ [50], $SnCl_2$/AgOTf [51], Me_3SiOTf [52], and, more recently, Cp_2HfCl_2/AgOTf [53] (Scheme 2.17).



Scheme 2.17 General mechanism of glycosylation by means of glycosyl fluorides [49].

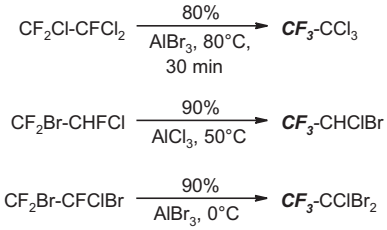
2.1.3.4 The "General Fluorine Effect"

At elevated reaction temperatures Lewis catalysts cause a certain amount of *inter*molecular and *intra*molecular halogen migration. Not only hydrofluoric acid can be used as the fluoride source, but also other fluoroaliphatic compounds, for example fluoromethyl ethers [54] (Scheme 2.18).



Scheme 2.18 Use of Sevofluorane as a fluoride source for the synthesis of inhalation anesthetics [54].

One clear tendency is apparent from the equilibrium product distribution of Lewis acid-induced transfluorination and halogen scrambling: if fluorine can migrate it will always tend to "concentrate" at one carbon atom. Most preferred reaction products are trifluoromethyl derivatives, followed by geminal difluoromethyl derivatives. This thermodynamic product control is often referred to as the "general" fluorine effect (Scheme 2.19).



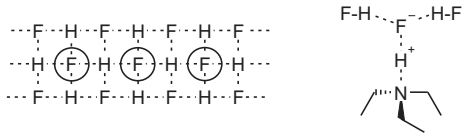
Scheme 2.19 The "general" fluorine effect in Lewis acid-induced halogen scrambling. For example, in the top example the formation of CF_3CCl_3 is energetically preferred by ca 5.6 kcal mol^{-1} (calculation on the B3LYP/6-31G*//B3LYP/6-31G* level of theory) [24].

The reason for this energetic preference for fluorine accumulation at the same sp^3 center is "self-stabilizing" by formation of possible ionic resonance structures, as already discussed in Section 1.4.2.

2.1.3.5 Amine–Hydrogen Fluoride and Ether–Hydrogen Fluoride Reagents

Hydrofluoric acid itself is one of the most hazardous reagents used in fluorine chemistry, possibly more so than elemental fluorine itself. Reasons are the low boiling point of aHF (19.5 °C) and its topical and systemic toxicity in combination with its local anesthetizing effect.

To enable safer and more convenient handling of this reagent of central importance, several attempts have been made to "stabilize" the hydrogen-bonding network of the strongly associated liquid HF by adding hydrogen-bridge acceptors, for example tetraalkyl ureas, amines, or ethers (Scheme 2.20).



Scheme 2.20 Postulated structures of strongly associated amine-HF reagents. *Left*: ^{19}F NMR studies of pyridine·9HF (70 % HF–pyridine) indicate a poly(hydrogen fluoride) network with each fluorine surrounded by four hydrogen atoms [55c]. *Right*: The proposed structure of the complex $NEt_3 \cdot 3HF$ [58].

The first published example of such "tamed hydrofluoric acid" was pyridinium poly(hydrogen fluoride), also known as "Olah's Reagent" [55]. The stoichiometric complex pyridine·9HF containing 70 % HF is a strongly acidic liquid stable up to 55 °C. Like anhydrous HF, pyridine–HF etches glass and is highly toxic but, because of its lower vapor pressure, handling is much safer. It was soon found that by changing the ratio of amine to HF the acidity and nucleophilicity of this and similar reagents could be modified in a wide range. A further improvement of safety and ease of handling was the use of polyvinylpyridine as a solid base [56].

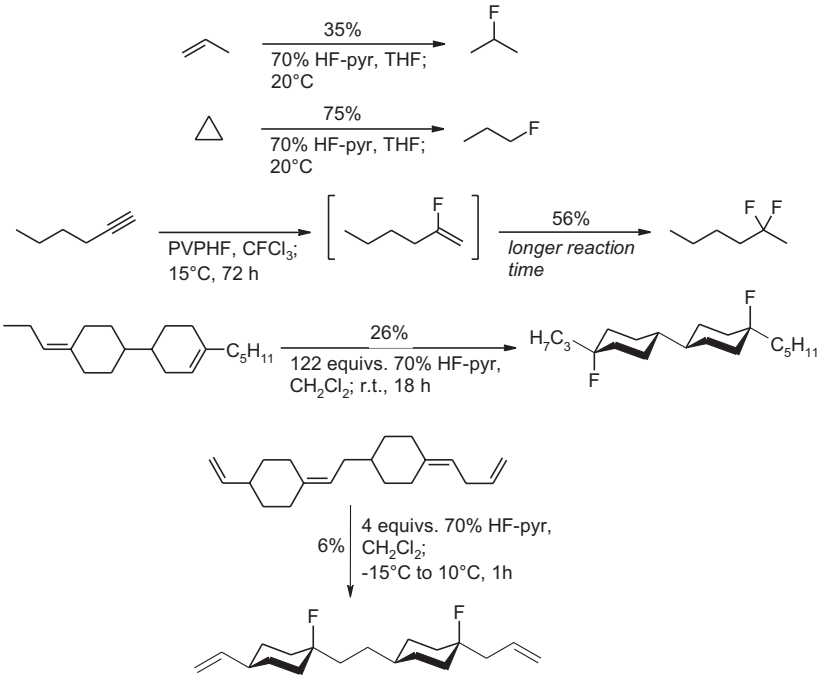
Of course, the general concept works not only with pyridine as a hydrogen bridge acceptor. Other complexes, such as $NEt_3 \cdot 3HF$ [57, 58] and $Bu_4N^+(H_2F_3)^-$ [59] have also found widespread practical application, because they are slightly basic or neutral and have no HF vapor pressure above the liquid. Triethylamine tris(hydrogen fluoride) (b. p. 78 °C without decomposition at 1.5 mbar) does not etch glass and can be handled in ordinary glassware even at elevated temperatures.

A more recent development, more acidic variants of "tamed HF", are HF–dialkyl ether complexes such as $Me_2O \cdot 2HF$ [60].

As a result of these developments, in preparative fluoroorganic chemistry there usually is no longer any need to use anhydrous hydrofluoric acid. This most hazardous reagent can usually be replaced by some kind of "tamed HF" with custom-tailored acidity and nucleophilicity.

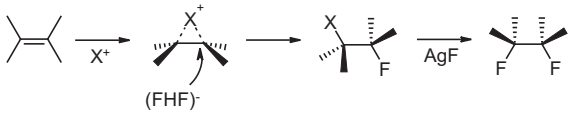
2.1.3.6 Hydrofluorination, Halofluorination, and Epoxide Ring Opening

Many amine–hydrofluoric acid reagents still have sufficient acidity to add to carbon–carbon double and triple bonds to yield hydrofluorination products. Olah's Reagent (70 % HF–pyridine) [55] and its polymer-based analog [56] are especially widely used as less hazardous alternatives to anhydrous hydrofluoric acid. By selection of the right co-solvent it is even possible to modulate the reactivity of 70 % HF–pyridine so that highly selective, partial hydrofluorination of systems with several double bonds becomes feasible [61] (Scheme 2.21).



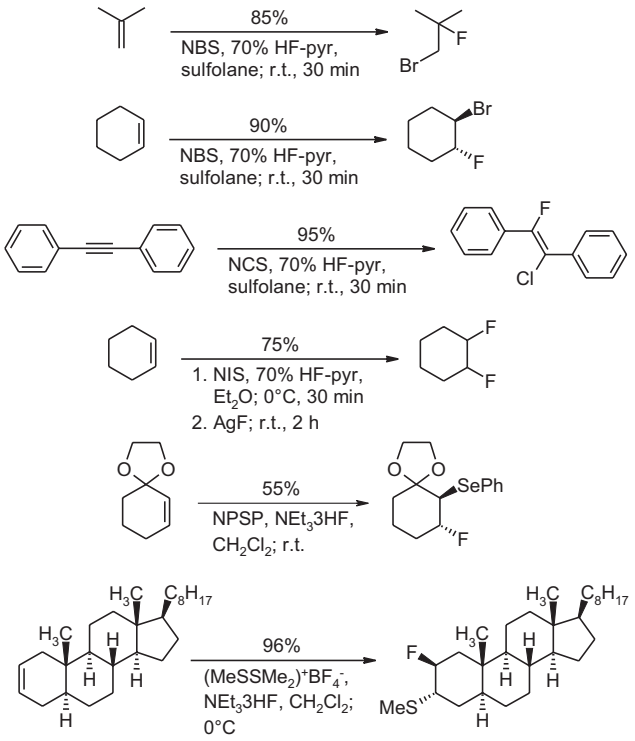
Scheme 2.21 Hydrofluorination of olefins and acetylenes with 70 % HF–pyridine and polyvinylpyridine hydrofluoride (PVPHF) [55a, 56, 61].

For halofluorination of multiple bonds there is no need for a strongly acidic fluorination reagent. Selection of suitable amine–HF reagents therefore becomes broader than for hydrofluorination. There is also a wide choice of electrophiles for initiating the reaction. The acidic 70 % HF–pyridine [55b] or the more neutral $NEt_3 \cdot 3HF$ [62] are most commonly used as fluoride sources. The most common electrophiles are the halogenating reagents NBS and NIS (Scheme 2.22). The trans stereochemistry of the halofluorination product indicates the formation of a three-ring, bridged intermediate which is subsequently opened by attack of a fluoride ion [63]. Occasionally the 1-fluoro-2-haloalkane formed initially is converted *in situ* into the corresponding 1,2-difluoroalkane by further reaction with silver fluoride.



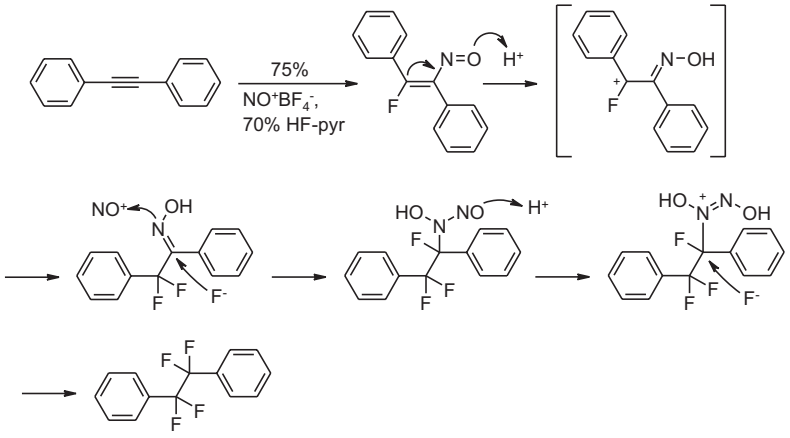
Scheme 2.22 Mechanism of the halofluorination reaction (X^+ = electrophile, e. g. *N*-halogenosuccinimide, $(MeSSMe_2)^+BF_4^-$, NPSP). If the group X is bromine or iodine it can be replaced by fluorine *in situ* with AgF [63–65].

Alternatively, several non-halogen electrophiles, for example dimethyl(methylthio)sulfonium tetrafluoroborate [64] or *N*-phenylselenylphthalimide (NPSP) have been used [65]. The phenylselenyl moiety can be removed later, either by using *m*-chloroperbenzoic acid (MCPBA) to give fluoroalkenes or by radical reduction to furnish the fluoroalkane (Scheme 2.23).



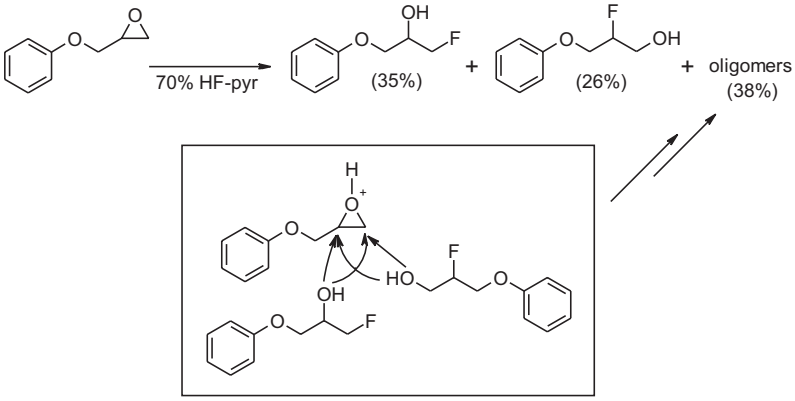
Scheme 2.23 Examples of halofluorinations and mechanistically similar reactions [55b, 62–65].

Another, mechanistically related, reaction is the perfluorination of acetylene derivatives with $NO^+BF_4^-$ in 70 % HF–pyridine [66] (Scheme 2.24).



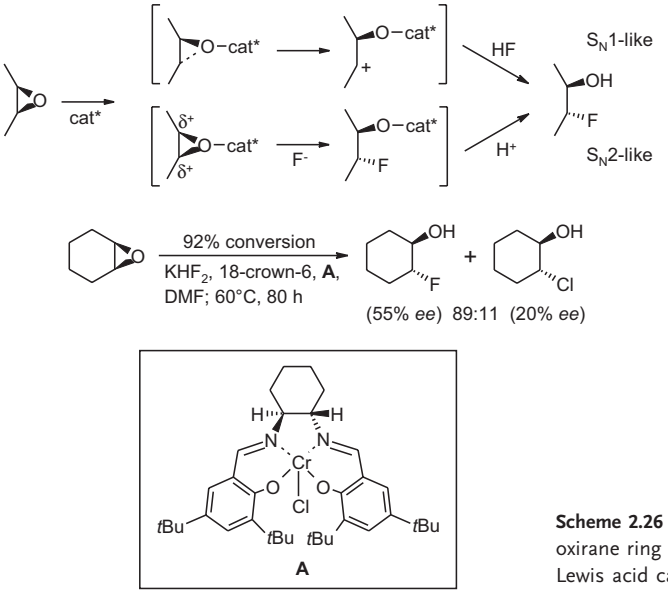
Scheme 2.24 Nitrosonium ion-induced fluorination of tolane derivatives to the corresponding diphenyltetrafluoroethylenes [66].

Opening of epoxides to give *β*-fluoroalcohols can also be achieved by use of amine–HF reagents. Because of the very different acidity and nucleophilicity of the various reagents, the stereoselectivity of the reaction can be modulated [67]. With neutral to basic reagents the ring opening proceeds via nucleophilic attack of a hydrofluoride ion on the more electropositive carbon of the epoxide ring (S_N2-like) [68]. If an acidic complex is used the primary step is protonation of the oxygen, followed by nucleophilic ring opening (S_N1-like) [69] (Scheme 2.25).



Scheme 2.25 Ring opening of oxiranes with the acidic amine–HF reagent 70 % HF–pyr is poorly selective and leads to the formation of oligomeric byproducts [70].

Ring opening with milder but more selective reagents such as $NEt_3 \cdot 3HF$ or KHF_2/18-crown-6 proceeds significantly more slowly but it can be catalyzed by electrophilic transition metal complexes. With a chiral salen catalyst even enantioselective synthesis of chiral fluorohydrins can be achieved [70]. This type of reaction is of enormous interest for enantioselective synthesis of fluoropharmaceutical compounds (Scheme 2.26).



Scheme 2.26 Enantioselective oxirane ring opening with a chiral Lewis acid catalyst (cat*) [70].

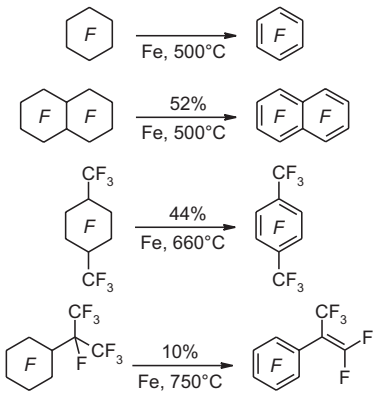
2.1.4 Synthesis and Reactivity of Fluoroaromatic Compounds

2.1.4.1 Synthesis of Fluoroaromatic Compounds

Fluorinated arenes are widely used as precursors for synthesis of agrochemicals and pharmaceuticals [71] with a volume of several thousand tons per year [72]. More than 20 % of the pharmaceuticals currently in clinical testing contain fluorinated aromatic substructures, for some types of agrochemical the proportion is even exceeding 50 % for newly introduced compounds.

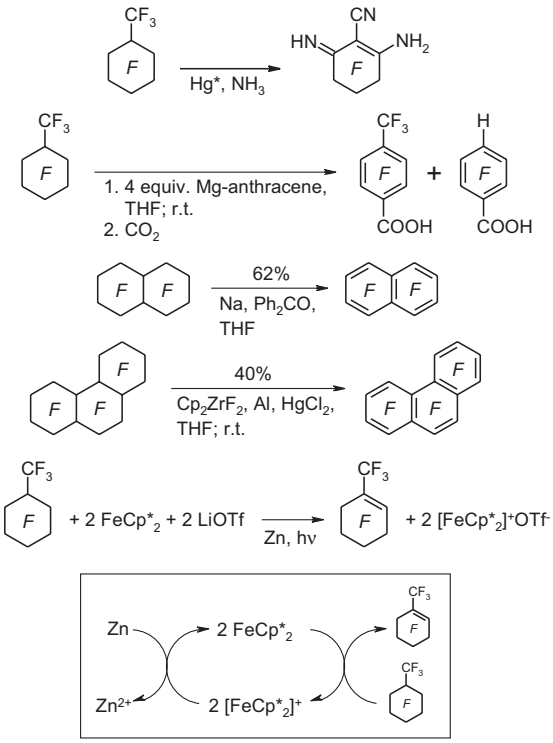
2.1.4.2 Reductive Aromatization

Perfluoroaromatic compounds can be obtained by reductive aromatization of readily accessible perfluorocycloaliphatic precursors [73]. Defluorination can be accomplished by contact with hot (500 °C) iron or iron oxide. After reducing the perfluoroaliphatic compound the metal surface can be regenerated by passage of hydrogen gas. This method has been scaled up to a continuous flow process for industrial synthesis of a variety of perfluorinated aromatic compounds (Scheme 2.27).



Scheme 2.27 Industrial-scale methods for reductive defluorination–aromatization of perfluorocycloaliphatic precursors, which again are accessible by the cobalt trifluoride process [74].

Reductive agents other than iron can also lead to aromatization or partial desaturation of perfluorocycloaliphatic derivatives. Photochemically activated ammonia (NH_3/Hg*) as the reducing agent leads to subsequent aminolysis products [75]. Others are complex catalytic systems which achieve the defluorination even at room temperature [8, 76] (Scheme 2.28).

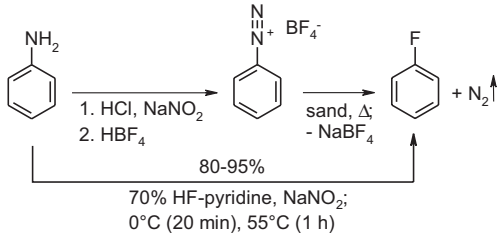


Scheme 2.28 Reductive defluorination–aromatization under milder reaction conditions suitable for laboratory-scale synthesis of perfluoroolefins and related products (Hg* = photochemically excited mercury); Cp* = pentamethylcyclopentadienyl [75, 76].

2.1.4.3 The Balz–Schiemann Reaction

One of the earliest means of introducing fluorine *selectively* into specific positions of aromatic compounds is the Balz–Schiemann reaction [77] which dates back to the 1920s. An isolated arene diazonium tetrafluoroborate is thermolyzed at up to 120 °C to yield the corresponding fluoroaromatic compound. Because of the infamously hazardous nature of isolated diazonium salts the scope of the classical variant of the Balz–Schiemann reaction was limited to the small scale. The high exothermicity of the reaction is most conveniently controlled by diluting the diazonium salt with a solid inert medium such as sea sand. In addition to the danger to the experimenter, the reproducibility of the reaction yield is quite poor.

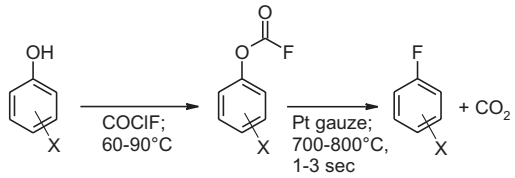
In recent variants, more useful on a technical scale, the diazonium salt is not isolated but generated in situ by treating a solution of a suitable aromatic amine precursor in aqueous hydrofluoric acid or in 70 % HF–pyridine with $NaNO_2$ at 0–5 °C. The resulting diazonium salt solution is subsequently thermolyzed at 55–160 °C [55c, 78, 79] (Scheme 2.29).



Scheme 2.29 Balz–Schiemann fluorination of aryl diazonium tetrafluoroborates. A recent variant works in 70 % HF–pyridine, avoiding isolation of the explosive diazonium salt [77–79].

2.1.4.4 The Fluoroformate Process

An alternative means of technical-scale access to fluoroarenes is the fluoroformate method. Starting from the corresponding phenol a fluoroformate is generated by reaction with carbonyl chloride fluoride and subsequently catalytically decarboxylated to the aryl fluoride, in the gas phase, by contact with hot platinum [80] (Scheme 2.30). A newer, "greener" variant of the fluoroformate process has recently been introduced by Rhodia. In this the fluoroformate is formed by the (catalyzed) reaction of the phenol with CO_2 in HF, and the expensive platinum catalyst is replaced by an aluminum-based material.

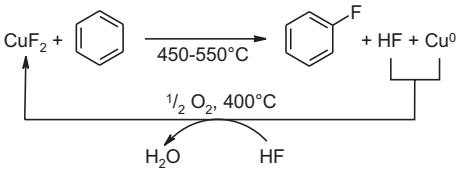


Scheme 2.30 Synthesis of selectively fluorinated aromatic compounds from phenols via the fluoroformate. Under optimized conditions, depending on the nature of the substituents X, the yields are nearly quantitative [80].

2.1.4.5 Transition Metal-assisted Oxidative Fluorination

One of the many drawbacks of the classic Balz–Schiemann synthesis is the generation of large quantities of undesired waste products such as $NaBF_4$, NaCl, or HCl.

A new method, recently developed at DuPont [81], is based on the copper-catalyzed oxidative fluorination of aromatic compounds with hydrofluoric acid in the presence of oxygen (Scheme 2.31).

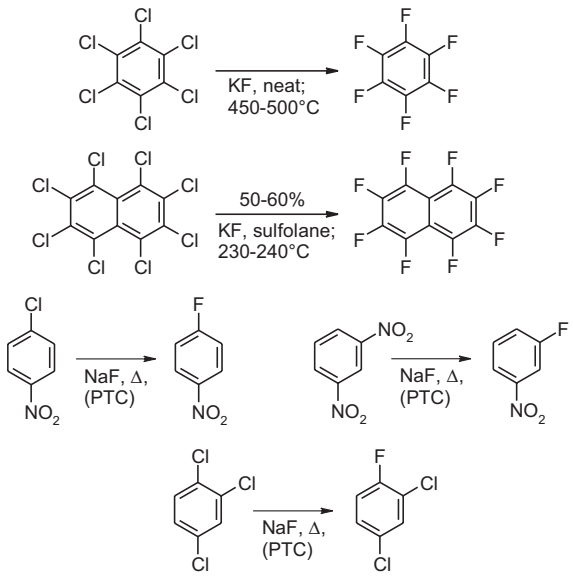


Scheme 2.31 Oxidative fluorination of benzene by CuF_2 which is regenerated by reaction with HF and O_2 at 400 °C [81].

The thermodynamic force driving this process is the formation of water as the only stoichiometric byproduct. The intermediately formed CuF_2 acts as the fluorinating agent at temperatures around 500 °C. The resulting copper is subsequently recycled by reaction with hydrofluoric acid and oxygen at 400 °C. The reaction–regeneration cycles can be repeated without loss of activity of the copper reagent. The same process can also be used for the waste-efficient and cost-effective industrial production of other fluorinated arenes such as fluorotoluenes and difluorobenzenes.

2.1.4.6 **The Halex Process**

The technically most relevant method for synthesis of specifically fluorinated aromatic compounds is the Halex (halogen exchange) process [82]. Aromatic starting materials with electron-withdrawing substituents, for example halogen or, sometimes, nitro groups are treated at moderate to high temperatures with inorganic



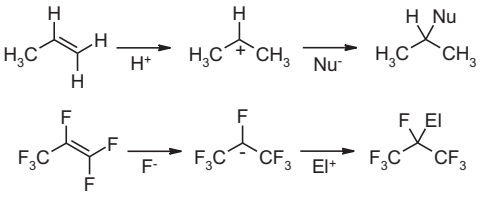
Scheme 2.32 Examples for aromatic Halex fluorinations [83, 84]. Lipophilic phase transfer catalysts (PTC), such as tetrakis(dimethylamino)phosphonium salts [33–38] can increase the efficiency of the exchange reaction dramatically.

fluoride sources to exchange these groups nucleophilically by fluorine. With the aim of increasing the nucleophilicty of the inorganic fluoride and thus also the efficiency of the process, lipophilic phase-transfer catalysts are often used [33–38] (Scheme 2.32).

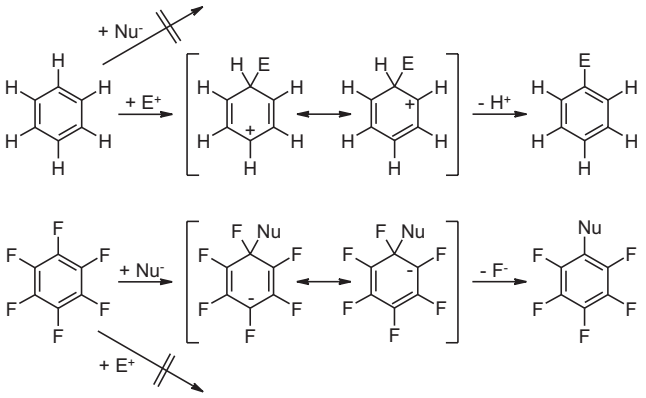
2.1.4.7 Think Negative! – "Orthogonal" Reactivity of Perfluoroaromatic and Perfluoroolefinic Systems

One of the most prominent properties of perfluoroaliphatic compounds is their extreme chemical inertness, which is comparable with that of noble gases. Most unsaturated systems, for example perfluoroolefins and perfluoroarenes, are on the other hand, very reactive species. Although the chemistry of "normal", hydrocarbon-based olefins is governed by their susceptibility toward electrophilic agents, for example protic acids, perfluoroolefins are inert under acidic conditions but react readily with nucleophiles, most notably the fluoride ion. In the same way as the positively charged proton is the key species in olefin chemistry, the negative fluoride ion is its counterpart in perfluoroolefin chemistry (Scheme 2.33).

Analogously, but in contrast with hydrogen-based chemistry, perfluoroolefins tend to add nucleophilic reagents, followed either by quenching of the resulting perfluorocarbanion with a suitable electrophile or by re-aromatization with elimination of a fluoride ion (Scheme 2.34).



Scheme 2.33 Schematic representation of the inversely analogous reactivity of olefins and perfluoroolefins. (Nu^- = nucleophile, El^+ = electrophile.)



Scheme 2.34 Orthogonal reactivity of benzene and hexafluorobenzene toward electrophiles and nucleophiles, respectively.

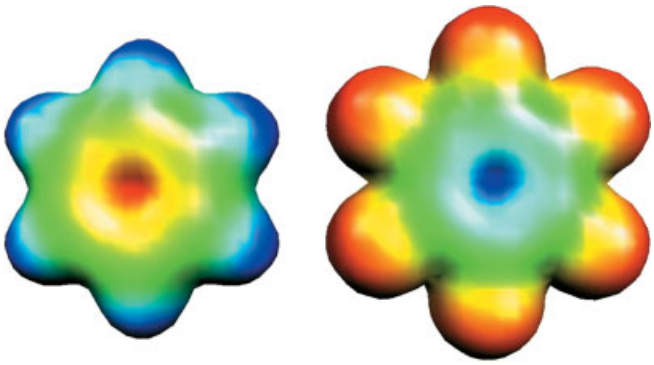
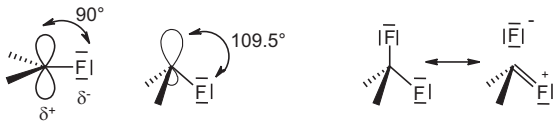


Figure 2.5 Electrostatic potentials (red and blue indicate negative and positive partial charges, respectively) mapped on the electron isodensity surfaces of benzene (*left*) and hexafluorobenzene (*right*) aid visualization of the complementary susceptibility of both compounds toward electrophilic or nucleophilic attack (B3LYP/6-31G* level of theory) [24, 25].

The reason for this "orthogonal" reactivity can be found by comparing the charge distribution in the corresponding species. In "normal" olefinic systems the negative charge density has its maximum in the center of the π-system, rendering it the preferred target of electrophilic attack by positively charged species. In perfluoroolefins the situation is more complex – because of the strong inductive effect of the electronegative fluorine, the negative charge density is concentrated in the periphery surrounding the π-system, making its center, with a positive partial charge, most susceptible toward nucleophilic attack by negatively charged nucleophiles. Population analysis shows natural partial charges $q_C = -0.24$ e and $q_H = +0.24$ e for benzene, in contrast with $q_C = +0.30$ e and $q_F = -0.30$ e for hexafluorobenzene (B3LYP/6-31G* level of theory) [24, 25]. The electrostatic potentials for both compounds are depicted in Figure 2.5.

The π-system is, in addition, destabilized by a repulsive interaction between the lone electron pairs on the fluorine atoms and the π-orbitals on the sp^2 hybridized carbon atoms. Nucleophilic attack on the carbon induces re-hybridization to the sp^3 state, relieving some of this repulsive strain.

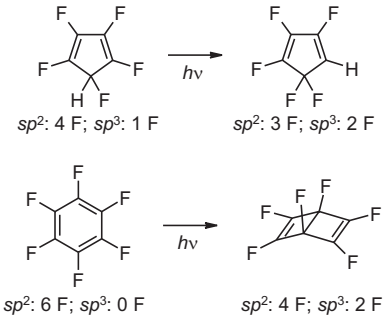
Another contribution to the driving force for nucleophilic addition of fluoride ions is stabilization of the resulting geminal difluoromethylene group by hyperconjugation. This so-called "negative" hyperconjugation can also be regarded as the most important reason for the previously discussed "general" fluorine effect [85] (Scheme 2.35).



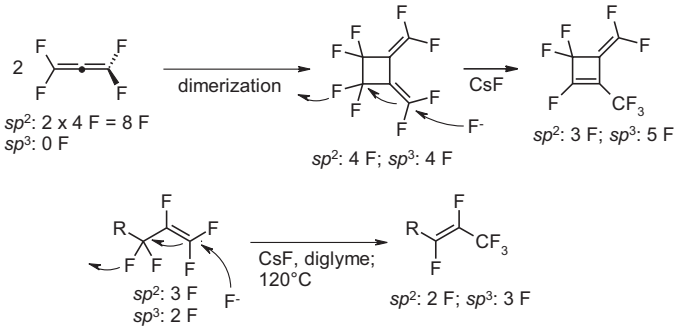
Scheme 2.35 *Left*: repulsive interaction between the fluorine lone electron pairs and the π-orbital on the sp^2 hydridized carbon, release of repulsive strain on the sp^3 carbon. *Right*: stabilization of the geminal difluoromethylene group by "negative" hyperconjugation.

2.1.4.8 **The "Special Fluorine Effect"**

The repulsive destabilization of sp^2-bound fluorine results in peculiar reactivity which has no real counterpart in hydrocarbon chemistry. This quite unique behavior of fluorinated olefins and arenes is summarized under the term "special fluorine effect" (as opposed to the previously discussed "general fluorine effect"). The photochemically induced (Scheme 2.36) or fluoride ion-induced (Scheme 2.37) rearrangements observed can be rationalized as the system trying to reduce the number of energetically unfavorable fluorine atoms bound to sp^2-hybridized carbon.

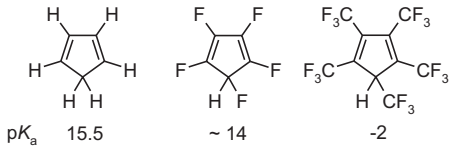


Scheme 2.36 Photochemically induced rearrangements of pentafluorocyclopentadiene [86] and hexafluorobenzene [87] reduce the number of fluorine atoms bound to sp^2-hybridized carbon.



Scheme 2.37 Fluoride ion induced rearrangements of perfluoroolefins leading to a reduced number of fluorine atoms bound to sp^2 carbon (R = $CF_2CF_2CF_2CF_2H$) [88, 89]. The estimated enthalpies of the rearrangements are -5.2 kcal mol^{-1} in the upper scheme and -15.0 kcal mol^{-1} for the lower one (for R = CH_3; calculation on the HF/6-31G*//HF/6-31G* level of theory) [24].

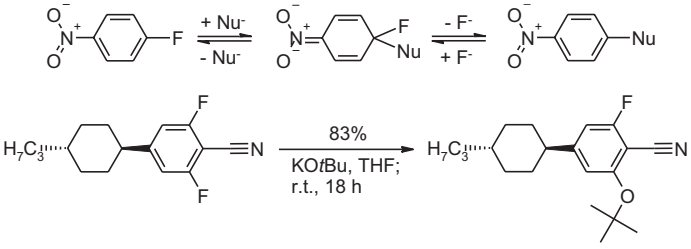
The strong destabilization of sp^2 centers by fluorine is impressively demonstrated by the acidities of different fluorine-containing cyclopentadiene derivatives (Scheme 2.38) – despite the strong, cumulative negative inductive ($-I_\sigma$) effect of five fluorine atoms, the acidity of pentafluorocyclopentadiene [90] is similar to that of cyclopentadiene. The reason for this unexpected behavior is that deprotonation would create one more fluorinated sp^2 center. In contrast, the expected behavior is observed for the pentakis(trifluoromethyl) derivative, which is more acidic by 16 orders of magnitude [91].



Scheme 2.38 Acidities of cyclopentandiene, pentafluorocyclopentadiene [90], and pentakis(trifluoromethyl)cyclopentadiene [91].

2.1.4.9 **Aromatic Nucleophilic Sustitution**

The destabilization of sp^2-bound fluorine by p–π repulsion activates fluorinated aromatic compounds toward nucleophilic attack and subsequent substitution. The susceptibility of the carbon center toward nucleophiles is also enhanced by the negative inductive ($-I_\sigma$) effect of fluorine. In particular, if the aromatic compound is also activated by $-M$ electron-withdrawing substituents, for example a nitro or cyano group, in the *ortho* or *para* positions the fluorine is easily replaced by a variety of nucleophiles even under very mild conditions via a resonance stabilized Meisenheimer complex (Scheme 2.39). The ease of nucleophilic halogen replacement – F > Cl > Br > I – is in the opposite order to that for aliphatic nucleophilic substitution.

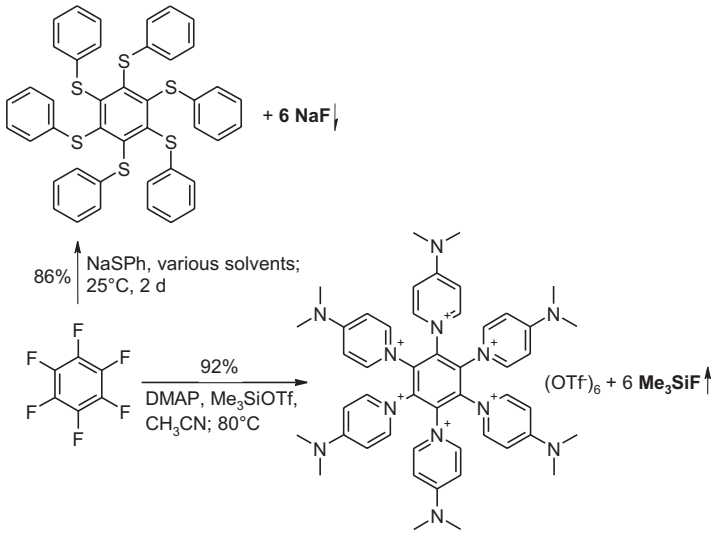


Scheme 2.39 Nucleophilic substitution of aromatic fluorine via a resonance-stabilized Meisenheimer-type complex intermediate [92].

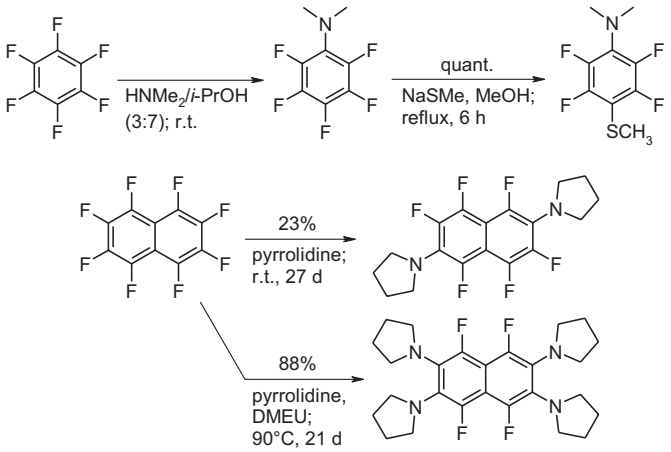
Even if no $-M$ electron-withdrawing substituents are present, however, aromatic fluorine can be replaced. The ease of this replacement increases with the degree of fluorination. Perfluoroaromatic compounds such as hexafluorobenzene or pentafluoropyridine are especially highly reactive toward a variety of nucleophiles (Scheme 2.40).

By analogy with the "hydrocarbon world", high selectivity is also observed in the regiochemistry of the second substitution in perfluoroaromatic compounds (Scheme 2.41). For hexafluorobenzene a second nucleophilic replacement always occurs in the position *para* to the first substituent. A similar, clear preference is also observed for perfluoronaphthalene [95].

Rationalization of the observed selectivity can be based on several considerations [95]. The negative charge of the intermediate adduct (analogous to the σ-complex in electrophilic aromatic substitution) has to be stabilized. This

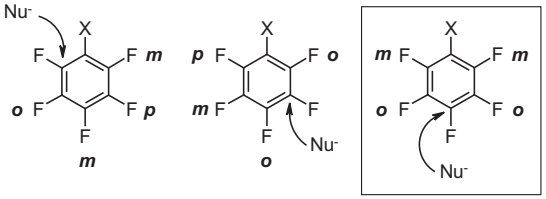


Scheme 2.40 The complete nucleophilic replacement of all fluorine atoms can be driven, e. g., by the strong nucleophilicity of the thiolate anion and the lattice energy of the formed NaF (*above*), [93] or by removal of the competing expelled nucleophilic fluoride with the volatile Me_3SiF (*bottom right*) [94].



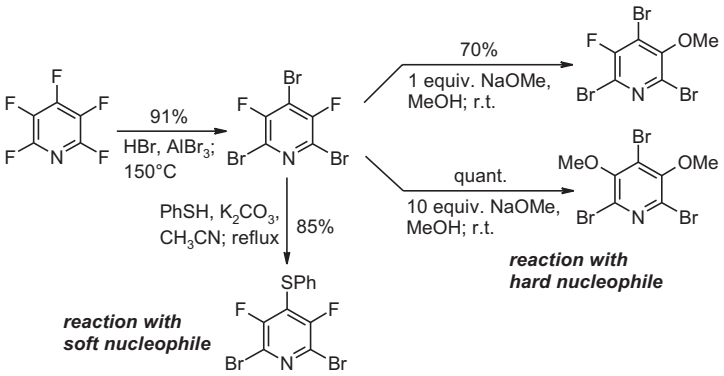
Scheme 2.41 Regioselectivity of the stepwise nucleophilic replacement of fluorine in perfluoroaromatic systems [96–98].

stabilization occurs mostly as a result of the combined inductive effects of the remaining fluorine atoms. This inductive effect must overcompensate the concomitant strongly destabilizing p–π repulsion of the sp^2-bound fluorine atoms which is most significant in the positions *ortho* and *para* to the site of nucleophilic attack. Most effective for overall stabilization of the negatively charged intermediate (Scheme 2.34) is fluorine in the *ortho* position; *meta* fluorine is less effective and fluorine in the *para* position is least effective (Scheme 2.42).



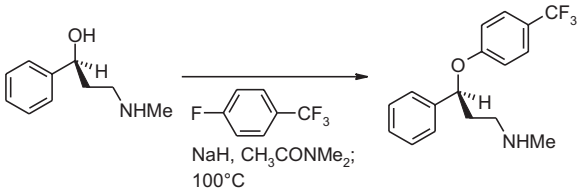
Scheme 2.42 The regioselectivity of a second nucleophilic aromatic substitution in perfluoroaromatic systems. The negatively charged primary addition product is stabilized best by fluorine in the *ortho* position (*o*), second best in the *meta* (*m*), and least in the *para* position (*p*). Only for attack of the nucleophile in the *para* position (*right*) is the complex stabilized by two *ortho* and two *meta* fluorines (Nu^- = nucleophile; X = first substituent, e. g. OMe, NMe_2) [95].

Systematic exploitation of the different susceptibilities of the different positions of perfluoroaromatic compounds can be used as a tool for combinatorial synthesis of (fluoro)aromatic compounds. The feasibility of this concept was recently demonstrated by R. D. Chambers and coworkers who used the pentafluoropyridine system as an example [99] (Scheme 2.43). Further differentiation of the reactivity toward hard and soft nucleophiles was achieved by partial replacement of fluorine by bromine in this system.



Scheme 2.43 A variety of conversions starting from the pentafluoropyridine system as a molecular scaffold, e. g. for combinatorial chemistry [99].

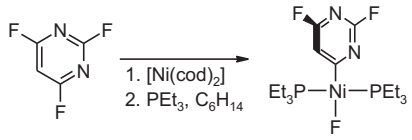
If the reaction temperatures are increased less active aromatic compounds with fewer fluorine atoms or other inductively activating groups can also be used as substrates for nucleophilic replacement of fluorine [100] (Scheme 2.44).

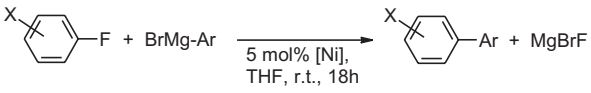


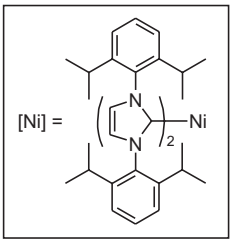
Scheme 2.44 Nucleophilic replacement of fluorine in only partially fluorinated systems is an important tool for synthesis of pharmaceuticals, for example (*S*)-norfluoxetine, a serotonin re-absorption inhibitor [100].

2.1.4.10 **Activation of the Carbon–Fluorine Bond by Transition Metals**

Because of the extraordinary strength of the carbon–fluorine bond, transition metal-mediated activation of fluoroalkanes and arenes is not easy to achieve. Nevertheless, activation of the C–F bond in highly electron-deficient compounds such as 2,4,6-trifluoropyrimidine, pentafluoropyridine, or hexafluorobenzene is possible with stoichiometric amounts of bis(triethylphosphano) nickel(0) [101] (Scheme 2.45). More recently Herrmann and coworkers [102] have described a variant of the Kumada–Corriu cross-coupling reaction [103] between fluorobenzene and aryl Grignard compounds which uses catalytic amounts of nickel carbene complexes. Hammett analysis of the relative kinetic rate constants indicated that the reaction proceeds via initial oxidative addition of the fluoroaromatic reactant to the nickel(0) species.



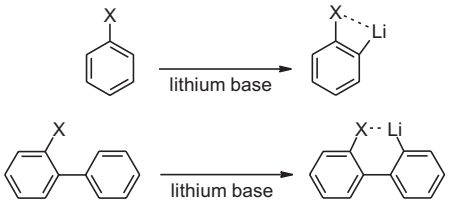




Scheme 2.45 Transition metal-mediated activation of the aromatic carbon–fluorine bond and subsequent reactions. *Above*: stoichiometric reaction of electron-deficient fluoroarenes with Ni(0) complexes [101]. *Below*: Ni(0) carbene-catalyzed Kumada–Corriu coupling between fluoroarenes and aryl Grignard compounds [102].

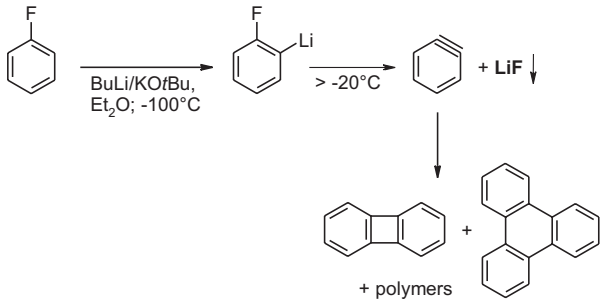
2.1.4.11 Activation of Fluoroaromatic Compounds by *ortho*-Metalation

Inductively electron-withdrawing substituents in aromatic compounds increase the thermodynamic acidity of the other aromatic hydrogen atoms. These hydrogen atoms can be abstracted by strong bases (LDA, BuLi) and "super-bases" (e. g. BuLi/KO*t*Bu) [104], leading to aryl metal compounds. The metal atom – usually lithium – is also stabilized by favorable electrostatic and electron-donating interactions with the lone electron pairs of neighboring groups (Scheme 2.46). The observed *ortho* selectivity of the metalation of suitably substituted aromatic compounds is, therefore, usually kinetically induced [105]. In biphenyl systems, the site-directing effect can also result in clean lithiation at the *ortho* position of the neighboring phenyl ring [106].



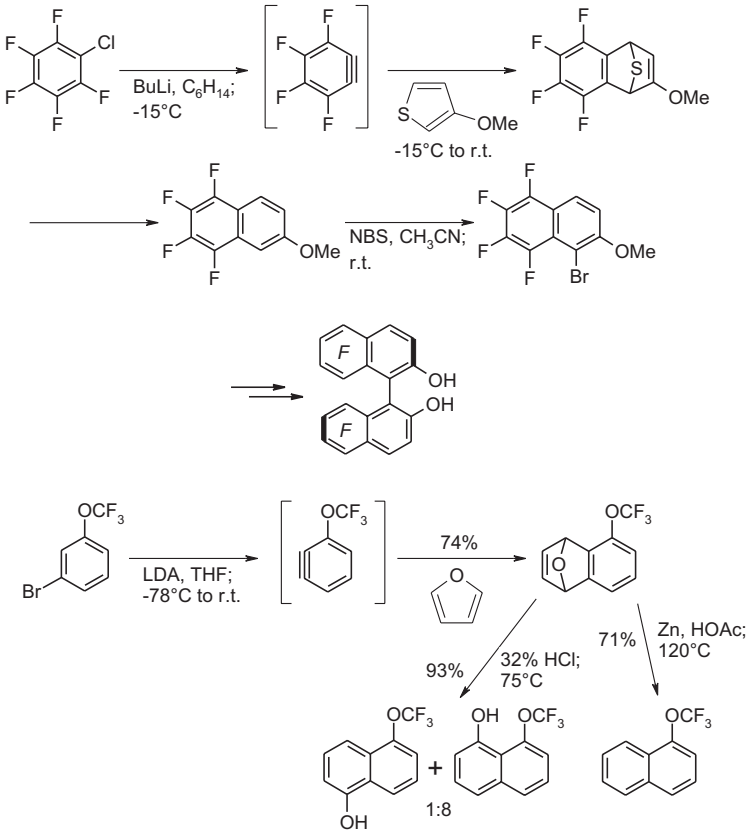
Scheme 2.46 Directed *ortho* lithiation of aromatics carrying an inductively electron-withdrawing substituent (X = CON*i*Pr$_2$, OMe, NMe$_3$, F, OCF$_3$). The reaction product is stabilized by interaction of the lone electron pairs of the group X with the neighboring lithium [104, 106].

Directed *ortho*-metalation is induced, e. g., by diisopropyl amido or alkoxy groups which strongly stabilize the metal–organic species by σ-donation [107]. Fluorine is also highly effective as a strongly *ortho*-directing, acidity-enhancing substituent [108]. Whereas many aryl lithium species are stable up to room temperature and above, *ortho*-fluoro lithio arenes are stable at low temperatures only. If heated above ca −30 °C, they tend to decompose violently to the corresponding aryne and lithium fluoride [109] (Scheme 2.47). The dominant force driving aryne formation is the high lattice energy of lithium fluoride (247 kcal mol^{-1}).



Scheme 2.47 *ortho*-Lithiation of fluorobenzene and subsequent aryne formation with elimination of lithium fluoride.

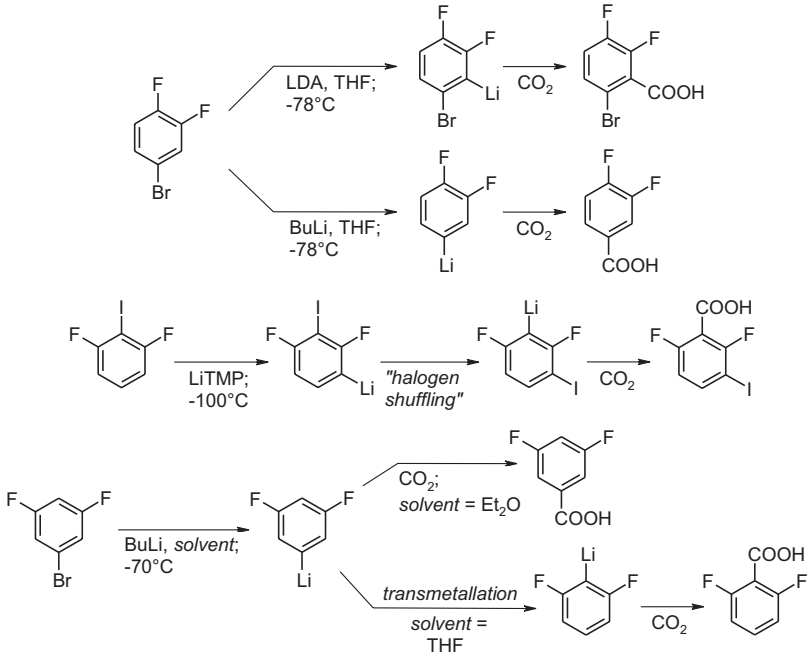
In contrast with being a mere hazard, aryne formation by LiF elimination has been put to synthetic use in the otherwise very difficult preparation of fluorinated naphthalene derivatives [110, 111] (Scheme 2.48).



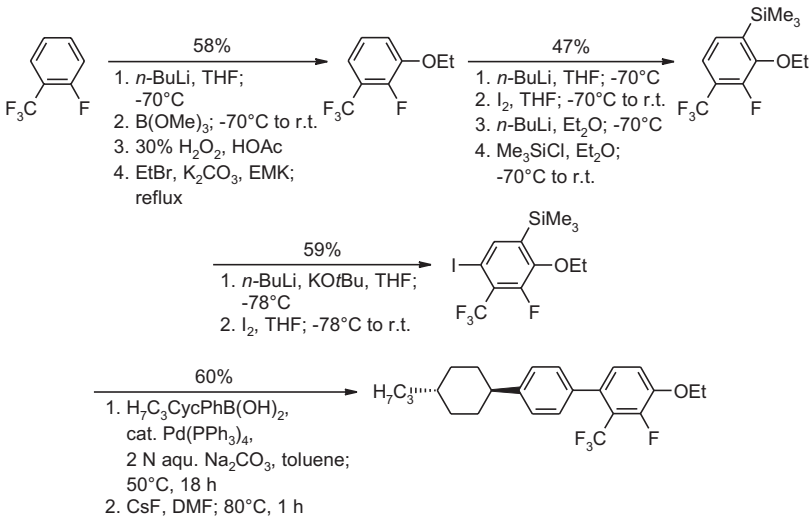
Scheme 2.48 Synthesis of naphthalene derivatives via fluorinated arynes [110, 111].

Ortho-Metalation is a tool of high value not only for derivatization of fluorinated arenes – the aryl lithium species can subsequently be converted into a variety of useful synthetic intermediates. Choice of the right combination of base and solvent enables highly selective derivatization of halogenated arenes; this cannot yet be achieved by any other means [112] (Scheme 2.49).

One complication, which sometimes leads to highly specific but unexpected reaction products, is transmetalation and so-called "halogen shuffling". The primary metalation product with no *ortho*-directing neighbor (or one only) can gain additional stability by transmetalation, leading to a product with two stabilizing *ortho* substituents. This effect is more likely in strongly coordinating solvents, for example THF, and can be suppressed by changing the reaction medium to diethyl ether, which leads to higher aggregation and lower reactivity of the metal organic species [113].



Scheme 2.49 Selective derivatization of fluoroarenes by different base–solvent combinations. If additional stability can be gained, e. g. as a result of two *ortho* fluorines, transmetalation often occurs (*middle* and *bottom*). Occasionally (*bottom*) this can be suppressed by the right choice of reaction solvent [112].



Scheme 2.50 Example of the synthesis of a fluorinated liquid crystal via stepwise derivatization of 2-fluorobenzotrifluoride, making use of a trimethylsilyl-blocked intermediate [114].

Occasionally the order of the *ortho*-directing strength of different substituents does not enable access to the desired substitution pattern by a direct route. In such circumstances a protective group strategy is necessary to temporarily block the most acidic positions of the intermediates. A convenient group for traceless aromatic blocking is the trimethylsilyl group, which is readily removable by use of inorganic fluorides (e. g. cesium fluoride in DMF) [114] (Scheme 2.50).

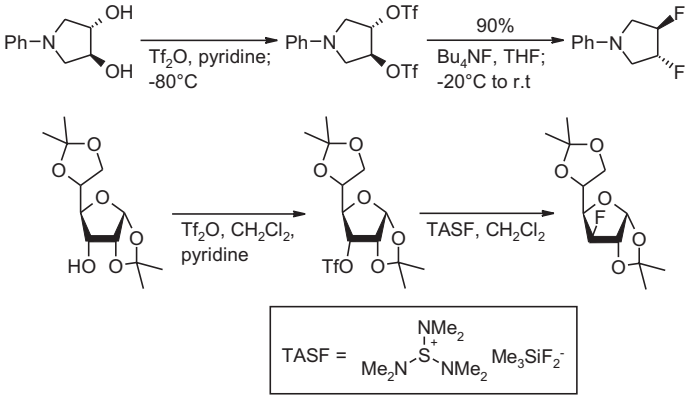
2.1.5 Transformations of Functional Groups

2.1.5.1 Hydroxy into Fluoro

The first unsuccessful attempts to convert alcohols directly into alkylfluorides were documented in 1782, when Scheele treated ethanol with hydrofluoric acid vapor obtained from the reaction of fluorspar (CaF_2) with sulfuric acid [115]. Despite this and other early failures, a variety of successful and convenient strategies designed to solve this general synthetic problem have been developed, especially since the 1920s.

Two-Step Activation–Fluorination

First reports of the activation of alcohols with nucleofugic leaving groups date back to the beginning of the 1800s. In 1835 Dumas and Péligot [116] heated "chauffant doucement", a mixture of dimethyl sulfate and potassium fluoride, to furnish methyl fluoride. Afterwards, the same principal method was used to obtain ethyl fluoride [117] and other alkyl fluorides. Nowadays, activation of alcohols with more nucleofugic leaving groups, for example mesylate, tosylate or triflate, and subsequent nucleophilic S_N2 substitution by fluoride under clean inversion, have become a standard tool, particularly when fluorination with defined stereochemistry is required (Scheme 2.51).

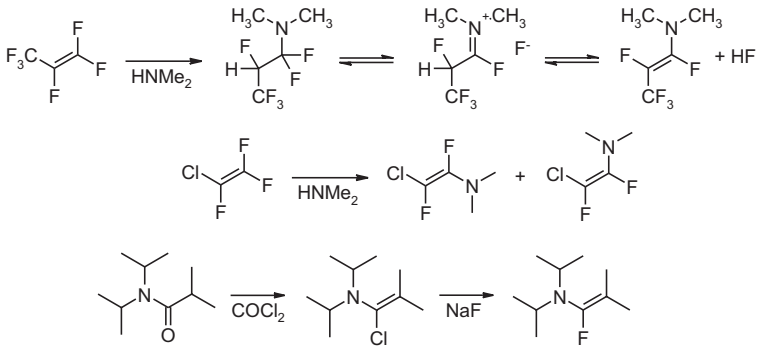


Scheme 2.51 Examples of the activation–fluorination procedure on substrates with stereogenic centers [118, 119].

α,α-Difluoroalkylamine and α-Fluoroenamine Reagents

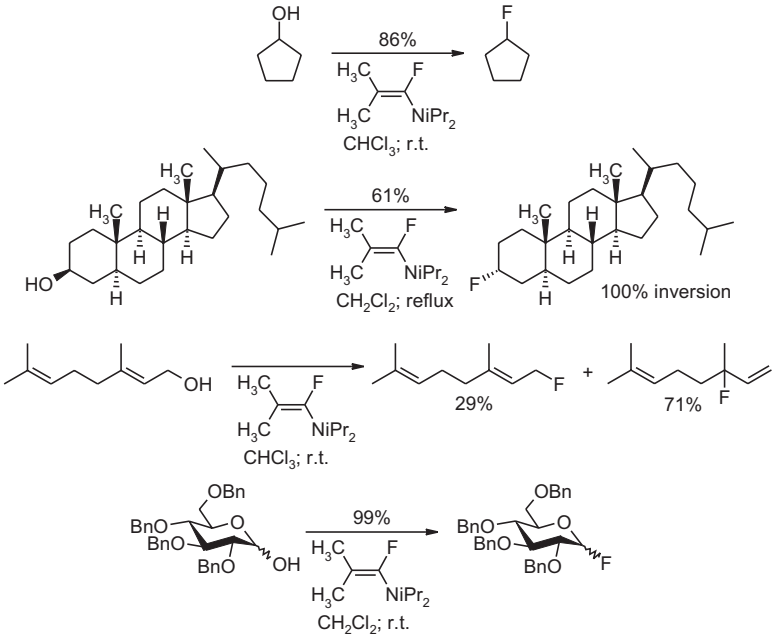
A more convenient approach to the exchange of hydroxy groups by fluorine is one-step activation–substitution – the alcohol is treated with a sufficiently electron-deficient, fluorine-containing reagent which condenses with it, with liberation of a fluoride ion. This ion, in turn, effects nucleophilic replacement of the now present leaving group. Stereochemically, this process results in clean inversion at the carbon center.

The first examples of this kind were the α,α-difluoroalkylamine reagents introduced by Yarovenko [120] and Ishikawa [121]. They are conveniently obtained by reaction of dimethylamine with either chlorotrifluoroethylene or perfluoropropene, respectively, and are quite effective for conversion of aliphatic alcohols to alkyl fluorides (Scheme 2.52). Another useful addition to the methodic toolbox was the more stable α-fluoroenamine reagent introduced by Ghosez and coworkers [122] which enables several highly selective conversions (Scheme 2.53). An advantage of this reagent is that it acts in a neutral reaction medium, thus also enabling transformation of acid-sensitive substrates.

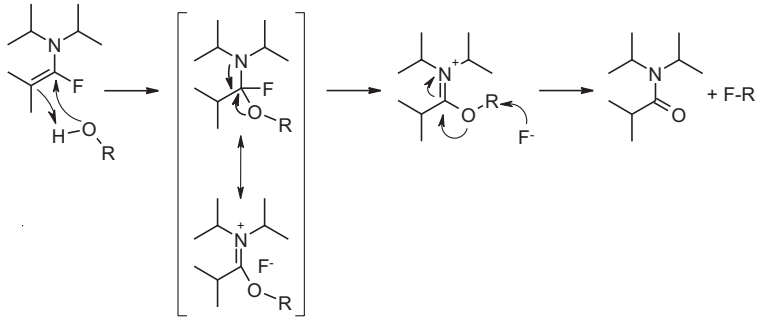


Scheme 2.52 The most usual fluorinated amine reagents and their syntheses. *Top*: the perfluoropropene-based reagent exists as an equilibrium mixture of an α,α-difluoroalkylamine and the two isomeric α-fluoroenamines. *Middle*: The dimethyl(2-chloro-1,2-difluorovinyl)amine reagent has a more defined composition. *Bottom*: Synthesis of an α-fluoroenamine fluorination reagent [120–122].

The mechanism of the primary condensation (Scheme 2.54) is again based on the relative instability of fluorine at sp^2 centers. In α-fluoroenamines the p–π destabilization is even increased by the $+I_\pi$ effect of the π-donating dialkylamino group. Addition of the alcohol coverts the sp^2 center into a very electron-rich sp^3 center and the fluoride ion is expelled, facilitated by the combined π-donation from the dimethylamino and alkoxy groups. The resulting imido ester is, in turn, a nucleofugic leaving group which is replaced by the fluoride ion. The most significant side-reactions with all α-fluoroenamine reagents are elimination and, in allylic systems, rearrangements.

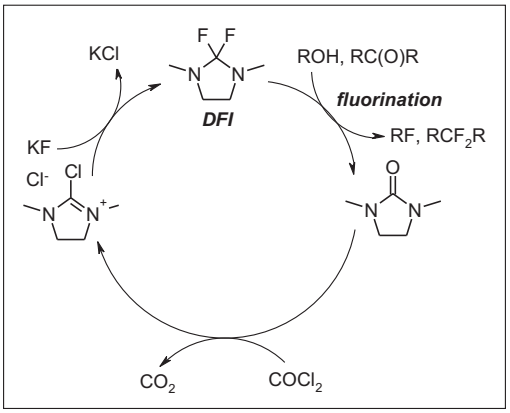


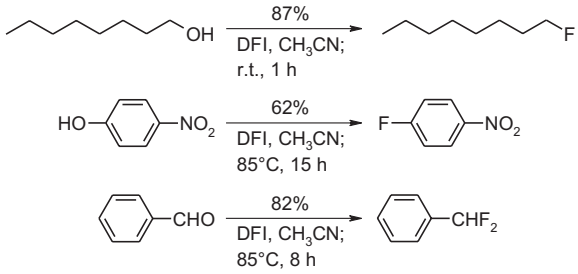
Scheme 2.53 Examples of the fluorination of alcohols with α,α-difluoroalkylamines or α-fluoroenamines. Synthesis of cycloalkyl fluorides, fluorosteroids, fluoroterpenes, and glycosyl fluorides with α-fluoroenamines [122, 123].



Scheme 2.54 Mechanism of activation and reaction of α-fluoroenamine reagents. The S_N2 mechanism of the replacement of the imidoester leaving group by the fluoride ion results in a clean inversion.

A more recent development of the same general type of reagent is 2,2-difluoro-1,3-dimethylimidazolidine (DFI), which is even more reactive, because of the stabilizing effects of two nitrogen atoms at the active center [124] (Scheme 2.55). By reaction with the inexpensive phosgene and subsequent nucleophilic fluorination the reagent can be recycled on an industrial scale.

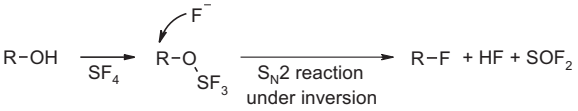




Scheme 2.55 The fluorination reagent 2,2-difluoro-1,3-dimethylimidazolidine (DFI) and its mechanism of activation [124].

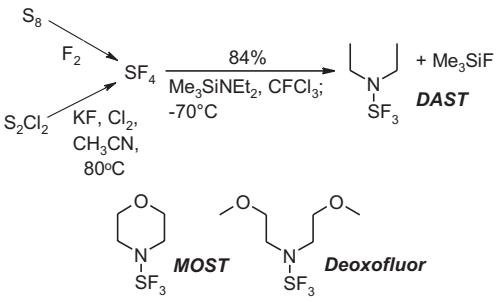
Sulfur Tetrafluoride and DAST

Probably the most versatile reagent for one-step exchange of hydroxy groups by fluorine, and for many other conversions, is sulfur tetrafluoride SF_4 [125]. Sulfur tetrafluoride first converts the alcohol into a covalent intermediate with a nucleofugic group which is subsequently replaced by a liberated fluoride ion, with inversion (S_N2 mechanism). The sulfur tetrafluoride is converted into sulfonyl fluoride, only two fluorine atoms are used for the reaction.



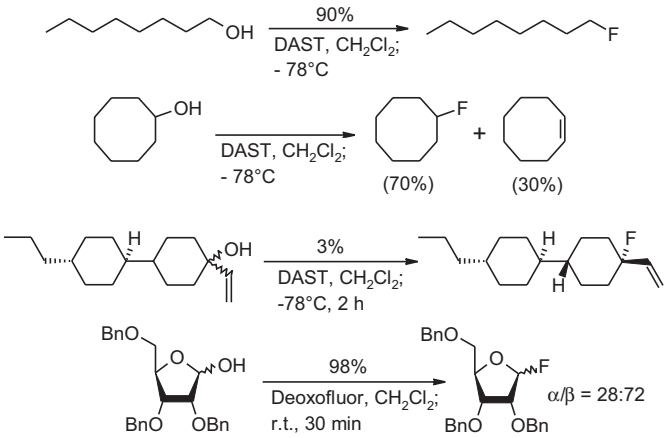
Scheme 2.56 Reaction of alcohols with SF_4 with formation of alkyl fluorides, HF, and sulfonyl fluoride.

Despite its versatility, SF_4 has some major disadvantages. It is a highly toxic gas (m. p. −121 °C, b. p. −38 °C) and must therefore be handled under pressure in an autoclave [126]. In order to overcome these difficulties, less volatile analogs of SF_4 have been synthesized by exchanging one fluorine atom by a dialkylamino group (Scheme 2.57).



Scheme 2.57 Synthesis of diethylamino sulfurtrifluoride (DAST) [127], morpholino sulfurtrifluoride (MOST), and bis(methoxyethylamino) sulfurtrifluoride (BAST; commercialized by Air Products, Inc. under the brand name Deoxofluor) and its analogs.

The reactivity of DAST (b. p. 46–47 °C) [127] is slightly lower than that of SF_4 but its handling in small-scale reactions is much easier (Scheme 2.58). Because of the relative instability of the sulfur–nitrogen bond, DAST can explode violently when heated over ca 50 °C.



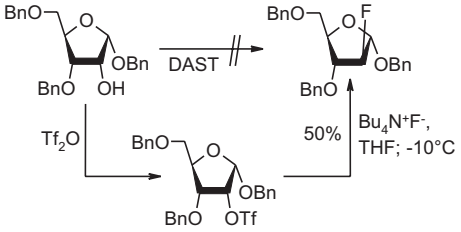
Scheme 2.58 Examples for fluorinations of alcohols with DAST and its analogs [127–129].

Frequently occurring side-reactions are elimination and rearrangements of the carbon skeleton [127], because of the intermediate formation of carbocationic species.

With the aim of obtaining a fluorination reagent which can be safely handled on a larger scale, other derivatives such as the morpholino sulfurtrifluoride (MOST) or the methoxyethyl analog (Deoxofluor) were developed [129]. Deoxofluor also decomposes at elevated temperatures, but it does so without a thermal run-away reaction

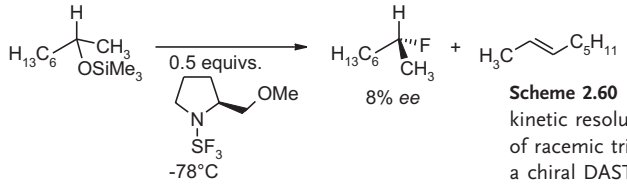
and subsequent explosion. This renders the reagent safe enough for application in the industrial production of fluoropharmaceuticals and advanced materials.

The lower reactivity of DAST and its analogs compared with SF_4 can be attributed to its larger steric requirements and to the less strong inductive effect of the dialkylamino moiety. This is obvious from failed attempts to fluorinate hydroxy groups in sterically crowded positions [130] (Scheme 2.59).



Scheme 2.59 Attempted fluorination of a sterically crowded ribose derivative with DAST, and successful reaction by a two-step activation–fluorination procedure [130].

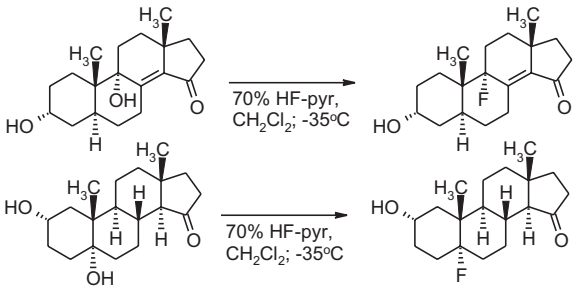
A chiral analog of DAST, (*S*)-2-(methoxymethyl)pyrrolidin-1-ylsulfur trifluoride [131], was prepared and studied to achieve enantioselection in the fluorination of chiral alcohols by double stereodifferentiation (Scheme 2.60). The desired effect was observed, but not to a preparatively useful extent.



Scheme 2.60 Achievement of minor kinetic resolution in the fluorination of racemic trimethylsilyl ethers with a chiral DAST analog [131].

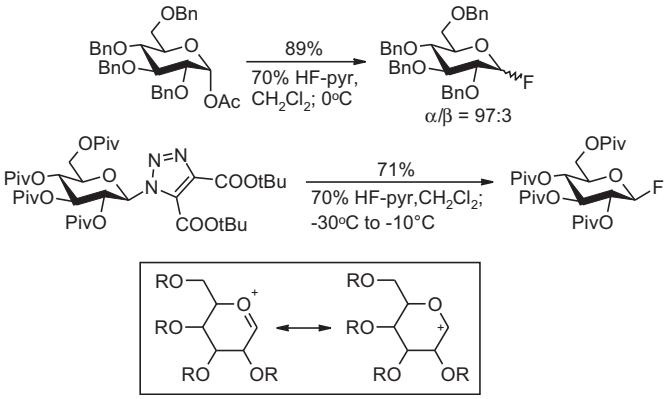
Amine–Hydrogen Fluoride Reagents

For exchange of tertiary alcohols direct fluorination without activation can be achieved by use of aHF or other sources of acidic fluoride (Scheme 2.61). This type of reaction in an acidic medium proceeds via a stabilized carbocation by an S_N1 mechanism. Fluoride addition is often reversible, and the stereochemistry of the reaction is controlled thermodynamically only by the relative free enthalpies of the possible product isomers.



Scheme 2.61 Fluorination of tertiary steroid alcohols with 70 % HF–pyridine [132, 133].

Potential leaving groups other than hydroxy can also be activated with acidic amine–HF complexes, if a sufficiently stabilized carbocation is formed as a reaction intermediate. Thus, glycosyl fluorides can be conveniently prepared from a variety of different glycosidic precursors, because of the stability of the intermediately formed glycosyl cation [134, 135] (Scheme 2.62).

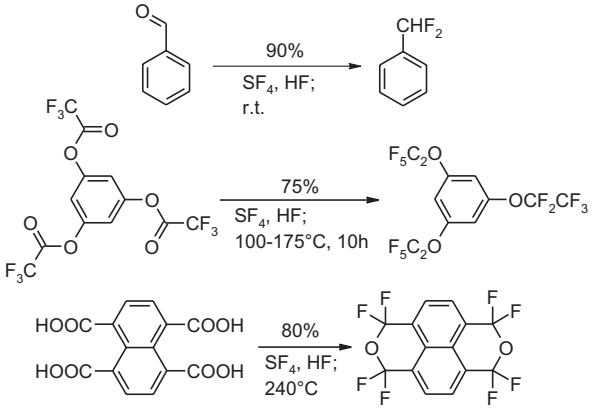


Scheme 2.62 Synthesis of glycosyl fluorides with 70 % HF–pyridine from different activated precursors [134, 135].

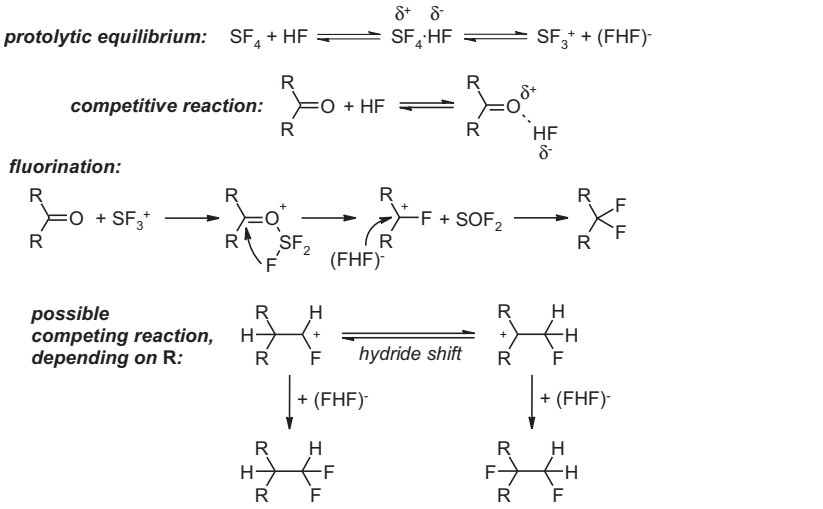
2.1.5.2 Conversion of Carbonyl into *gem*-Difluoromethylene

Sulfur Tetrafluoride and DAST

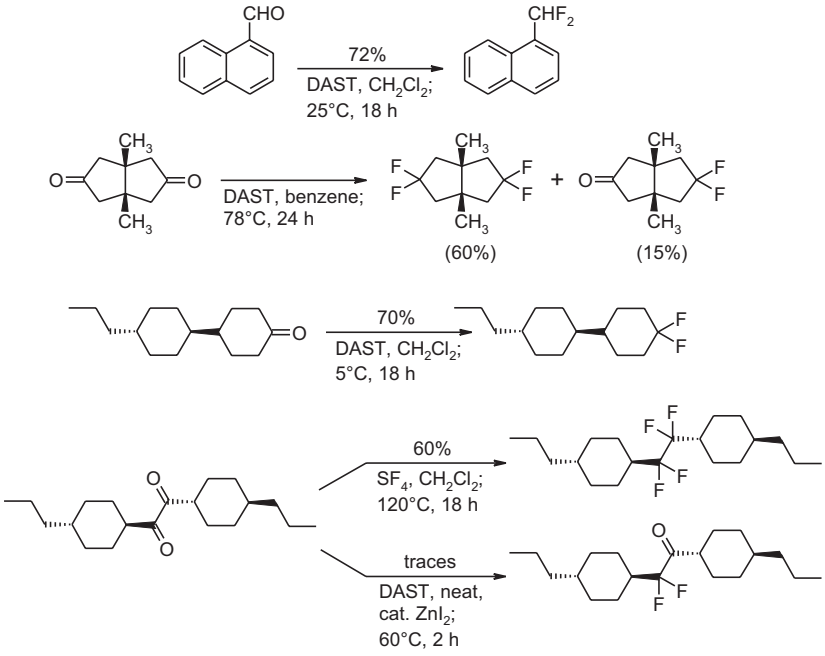
Sulfur tetrafluoride is also the reagent of choice [125] for conversion of aldehydes, ketones and ester carbonyl functions into *gem*-difluoromethylene groups [136] (Scheme 2.63). The reactivity of SF_4 is further enhanced by addition of Lewis acid catalysts (for example BF_3) or simply by conducting the reaction in aHF as solvent.



Scheme 2.63 Reaction of aldehydes, esters, and carboxylic acid anhydrides with SF_4 [125a, 137, 138].



Scheme 2.64 Proposed mechanism for fluorination of carbonyl compounds into the corresponding *gem*-difluoromethylene derivatives [139].



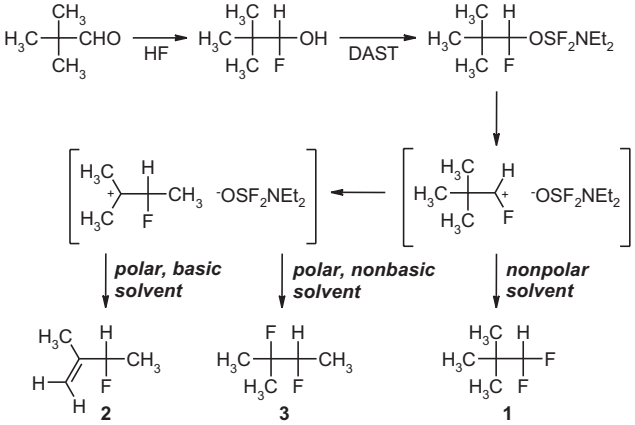
Scheme 2.65 *Above*: Conversion of carbonyl compounds to difluoromethylene derivatives by DAST [127]. *Below*: Limits of the reactivity of DAST compared with SF_4 [140].

On the basis of analysis of typical byproduct spectra W. Dmowski postulated a mechanism for the reaction [139]. In aHF as solvent the SF_3^+ species is generated in a solvolytic equilibrium. The strongly electrophilic SF_3^+ ion adds to the carbonyl oxygen, making the α-carbon atom highly electrophilic. A fluorine atom is then transferred intramolecularly to the carbon and sulfonyl fluoride is expelled. The resulting resonance-stabilized (by π-donation from fluorine lone electron pairs) α-fluoro carbenium ion adds fluoride from ambient $(FHF)^-$ ions (Scheme 2.64). The formation of typical by-products, mostly rearrangement products, can be explained on the basis of this mechanism.

The more convenient reagent DAST can also be used to fluorinate aldehydes and some ketones in high yields (Scheme 2.65). The reaction does not work for sterically hindered ketones or for esters or anhydrides, even under harsh conditions.

As in the fluorination of alcohols, here also the most important side-reactions are elimination and rearrangements. As demonstrated for pivaldehyde as example (Table 2.1), the product distribution depends critically on the choice of a suitable reaction solvent. Non-polar solvents ($CFCl_3$, pentane, or CH_2Cl_2) favor the

Table 2.1 Dependence on the solvent of the mechanism of fluorination of pivaldehyde with DAST and of the formation of side-products [127].

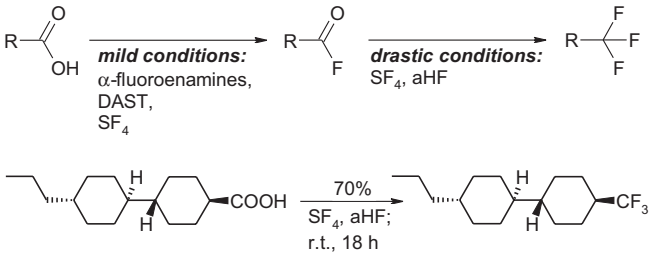


Solvent	*GLC Yield (%)*		
	1	*2*	*3*
CCl_3F	88	2	10
Pentane	87	3	10
$CHCl_3$	72	3	25
CH_2Cl_2	72	2	26
Xylene	64	8	28
THF	65	20	15
Pivaldehyde	60	10	30
Diglyme	30	32	38

formation of the desired fluorides whereas polar solvents (THF or diglyme), which can stabilize cationic intermediates, favor elimination and rearrangement products.

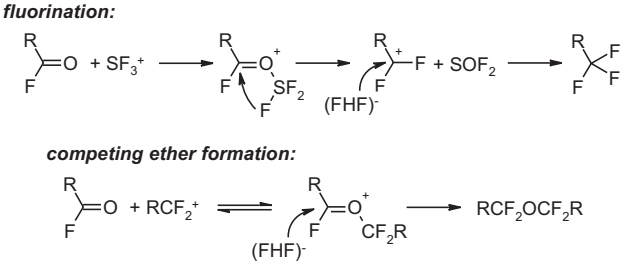
2.1.5.3 Carboxyl into Trifluoromethyl

The conversion of carboxyl groups into trifluoromethyl groups proceeds in two steps. The first step, exchange of the hydroxy group by fluorine, can be accomplished easily by use of less potent fluorination agents such as α-fluoroenamines or DAST. Subsequent conversion of the carboxylic acid fluoride into the trifluoromethyl group requires more drastic conditions and can be achieved only with SF_4. The most convenient procedure is the one-step direct reaction of carboxylic acids with SF_4 in aHF as solvent (Scheme 2.66). For most aliphatic and aromatic carboxylic acids, excellent yields can be obtained even at room temperature or below.



Scheme 2.66 Conversion of carboxylic acids to the corresponding trifluoromethyl compounds by sulfur tetrafluoride [125a, 140].

A major side-reaction of the fluorination of carboxylic acids is the formation of bis(α,α-difluoroalkyl) ethers, presumably (Scheme 2.67) via cationic intermediates.



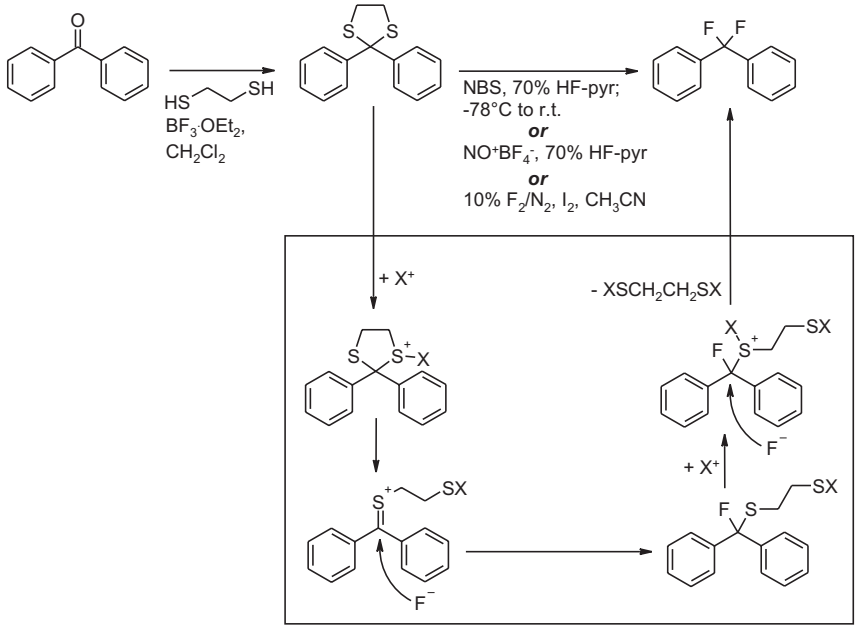
Scheme 2.67 Mechanism of the fluorination of carboxylic acids to trifluoromethyl derivatives, and the competing formation of bis(α,α-difluoroalkyl) ethers [139].

2.1.5.4 **Oxidative Fluorodesulfuration**

A very generally applicable method for converting a variety of different functional groups into their partially or fully fluorinated analogs is the oxidative fluorodesulfuration of thiocarbonyl compounds, dithiolanes, dithianes, and dithianylium salts. The principal method was initially discovered in the 1970s [141, 142]; since the beginning of the 1990s it has been systematically developed into a valuable tool for fluoroorganic synthesis [143–147].

The general concept is that sulfur is introduced into the organic substrate as a direct synthetic precursor of fluorine. The sulfur compound is then treated with a thiophilic, "soft" electrophilic oxidant, for example electrophilic halogenation agents (NBS, NIS, DBH, Br_2, SO_2Cl_2 [148], F_2 [149], IF_5 [150], BrF_3 [151], 4-$MePhIF_2$ [152], or nitrosyl cations ($NO^+BF_4^-$) [146] in the presence of a fluoride source (50 % or 70 % HF–pyridine [143], HF–melamine [144], $NEt_3 \cdot 3HF$) [147]. The chemical oxidant can also be replaced by electrochemical oxidation [153, 154]. The sulfur species is thus activated by *S*-halogenation into a nucleofugic leaving group, which is substituted by fluoride. The fluorodesulfuration of thiocarbonyl compounds is supposed to follow a similar principal pathway.

The mechanism as depicted in Scheme 2.68 [142] is tentative, derived and made plausible by molecular modeling and by analysis of the complete product spectrum, including side-reactions. The extruded sulfur species cannot be expected to be stable in the presence of a substantial excess of oxidant and the typical subsequent aqueous work-up conditions.

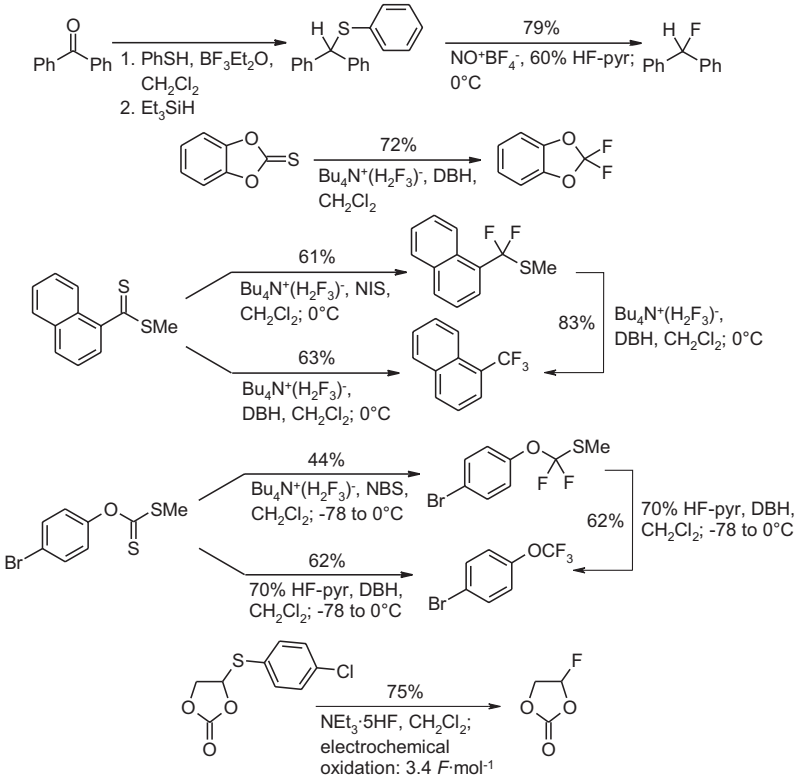


Scheme 2.68 Proposed mechanism of oxidative fluorodesulfuration of dithiolanes [142] (X^+ stands for electrophilic bromine "Br^+", iodine "I^+", or the nitrosyl cation, NO^+).

From the viewpoint of "atom economy" [155], dithiolane or dithiane fluorodesulfuration chemistry suffers from a drawback – as a result of oxidation of the sulfurous protecting (and activating) group a relatively large part (by molecular mass) of the starting material is lost and cannot be recovered or recycled.

Many varieties of fluorodesulfuration of protected (or activated) carbonyl compounds are known. Some contain an intermediate reductive step, leading to a *mono*-fluoromethylene instead of a *gem*-difluoromethylene group [146].

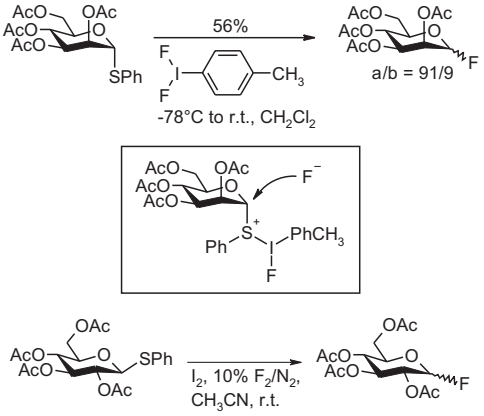
It has been demonstrated several times that different sulfur species (thiocarbonyl or thioether) can be selectively oxidized by careful choice of thiophilic oxidant and the acidity of the reaction medium. In thioesters or xanthogenates the thiocarbonyl group is fluorodesulfurated in neutral to mildly acidic medium ($Bu_4N^+(H_2F_3)^-$) with a relatively mild oxidant (NIS) whereas oxidation of the remaining α-difluorothioether requires a strongly acidic medium (70% HF–pyridine) and a more powerful oxidant (DBH) (Scheme 2.69). It seems that after oxidation of the thiocarbonyl group the resulting *gem*-difluoromethylene moiety deactivates the remaining sulfur against further thiophilic attack.



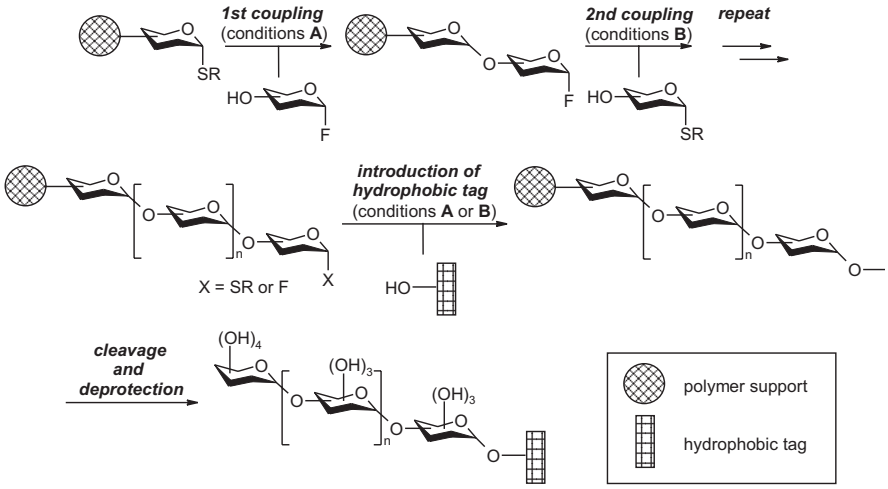
Scheme 2.69 Examples of the versatility of the different varieties of fluorodesulfuration reactions [146, 154, 156, 157].

In carbohydrate chemistry fluorodesulfuration has become a convenient tool for switching between different, "orthogonal" modes of glycosidic activation [158] (Scheme 2.70).

Orthogonal glycosidic activation is essentially based on application of Pearson's HSAB concept [159]. Under typical conditions for activation of thioglycosides into glycosyl donors with "soft" Lewis acids (e. g. MeOTf/MeSSMe system, with $MeSSMe_2^+$ as the activating species) glycosyl fluorides are inert. On the other hand, activation of glycosyl fluorides with "hard" Lewis acids (e. g. the Cp_2HfCl_2/AgOTf system, with Cp_2HfCl^+ as the activating species) does not affect thiogylcosides present in the same reaction mixture (Scheme 2.71). Orthogonal glycosidic activation is an important step in the direction of automated oligoglycoside synthesis [160].

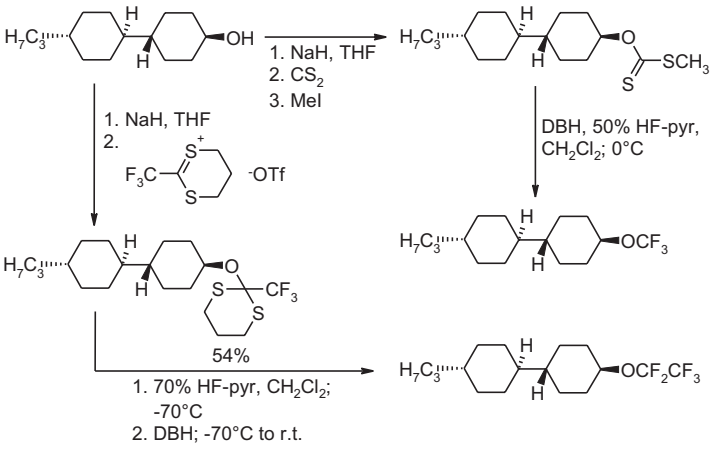


Scheme 2.70 Syntheses of glycosyl fluorides from thioglycosides by oxidative fluorodesulfuration [145, 152].



Scheme 2.71 Principle of "orthogonal" glycosidic activation on a polymer (e. g. polyethylene glycol) support. To facilitate purification, a hydrophobic tag (e. g. 2-(trimethylsilyl)ethyl) is introduced [158]. Conditions **A** are for thioglycoside activation, conditions **B** for activation of glycosyl fluorides.

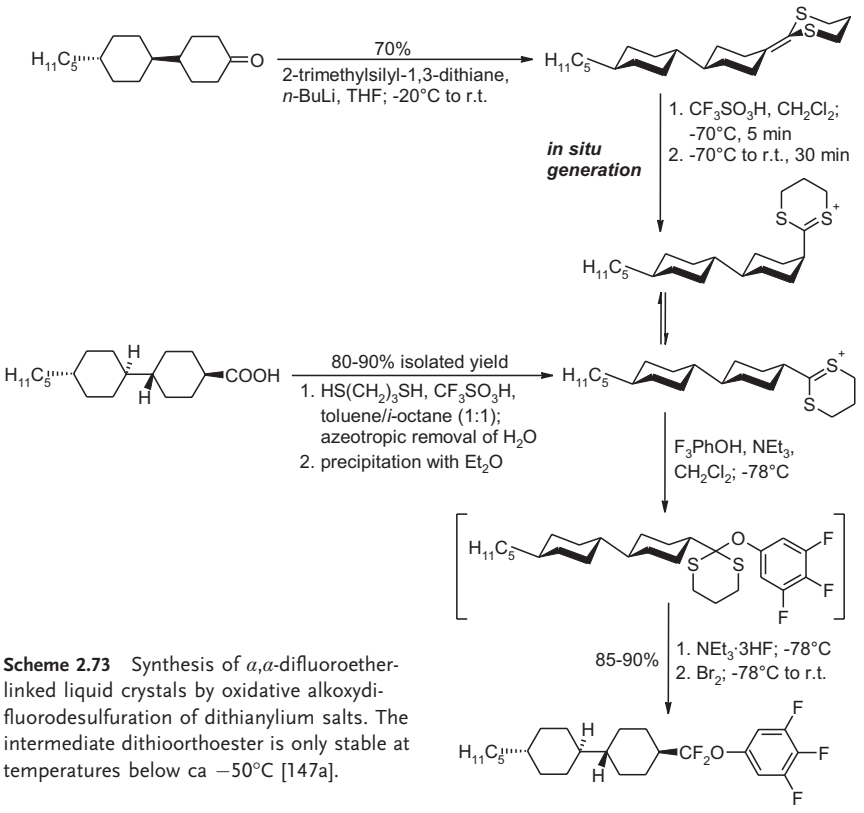
Since the late 1990s, fluorodesulfuration has gained importance as a valuable synthetic tool, especially for preparation of liquid crystals [161, 162]. The methodology enables convenient access to aliphatic trifluoromethyl ethers and, more recently, to *α,α*-difluoroalkyl [147a] and perfluoroalkyl ethers also [163] (Scheme 2.72).



Scheme 2.72 Synthesis of liquid crystals by oxidative fluorodesulfuration of xanthogenates (*above*) [162], and by the oxidative alkoxydifluorodesulfuration of dithianylium salts (*below*) [163].

The alkoxydifluorodesulfuration of dithianylium salts [164] has some very special advantages compared with other known fluorodesulfuration routes via thionoesters [147]. (1) Dithianylium salts are easily accessible. They can be either prepared from carboxylic acids or acid chlorides [165] and isolated by simple precipitation as stable, crystalline solids. (2) Many aliphatic thionoesters (as the alternative substrate for oxidative fluorodesulfuration) are unstable and tend to eliminate the corresponding alkoxy moiety, forming even more unstable thioketenes. (3) Typical liquid crystalline mesogenic core structures are based on *trans*-1,4-cyclohexane substructures. Making use of the reversibility of the formation of aliphatic dithianylium salts the thermodynamically preferred *trans*-4-alkylcyclohexyl dithianylium salts can be conveniently obtained by protonation and subsequent equilibration of the corresponding ketenedithioketals. The *in situ* formation of dithianylium salts by protonation of ketenedithioketals is also quite useful for generation of simple 2-alkyl-1,3-dithianylium salts which do not crystallize.

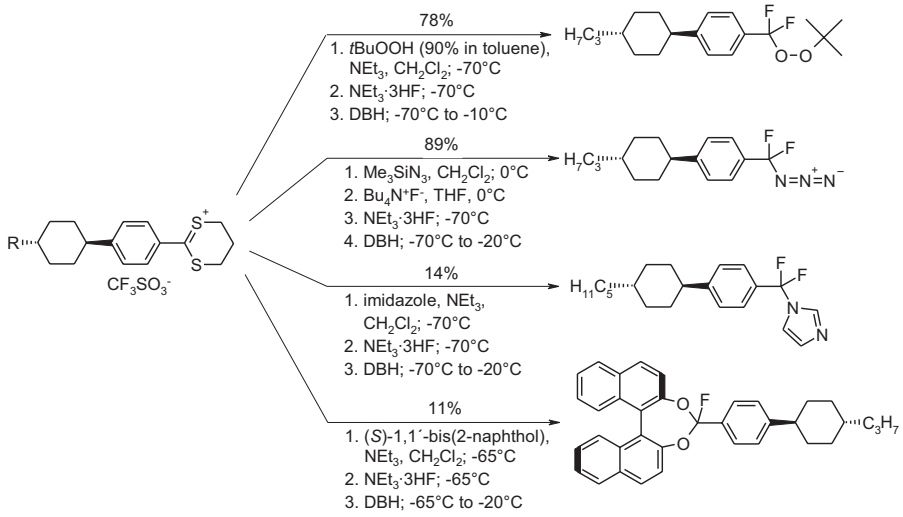
Mechanistically the only difference from the chemistry depicted in Scheme 2.68 is the formation of a dithioorthoester as the central sulfur-containing intermediate; if this is generated from strongly electron-deficient perfluoroalkyl dithianylium salts (Scheme 2.73) it can be isolated at room temperature. For alkyl or aryl dithianylium salts with less fluorination the dithioorthoester is a labile intermediate which is only stable at low temperatures (up to ca. −50 °C). This intermediate is subsequently fluorodesulfurated to yield the corresponding *α,α*-difluoroether.



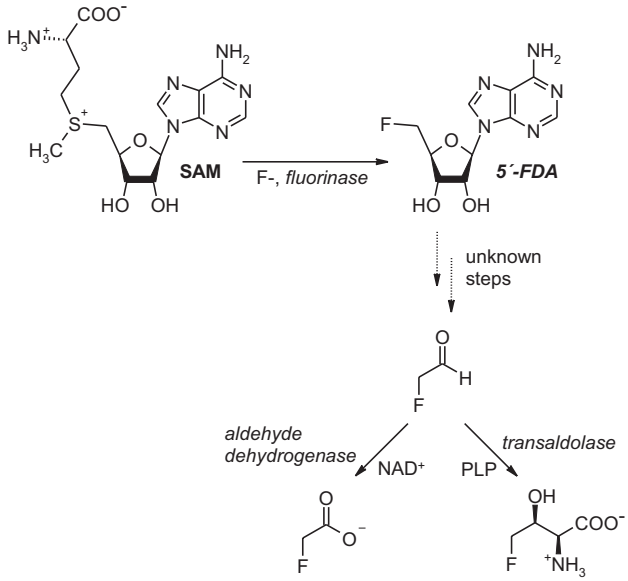
Scheme 2.73 Synthesis of α,α-difluoroether-linked liquid crystals by oxidative alkoxydi-fluorodesulfuration of dithianylium salts. The intermediate dithioorthoester is only stable at temperatures below ca −50°C [147a].

Dithianylium salts in combination with oxidative fluorodesulfuration chemistry are also useful reagents for synthesis of *gem*-difluoromethylene analogs of carboxylic acid derivatives other than esters. If the fluorodesulfuration is conducted in the presence of other *O*- or *N*-nucleophiles the corresponding α,α-difluoroalkyl compounds are obtained in reasonable to good yields (Scheme 2.74).

O'Hagan and coworkers recently found that fluorodesulfuration is not only a versatile tool for the synthetic organic chemist but also – in a non-oxidative variant – so far the only known pathway in nature for enzymatic incorporation of inorganic fluoride ions into secondary metabolites [166] (Scheme 2.75). As the key step of this enzymatic reaction sequence a trialkylsulfonium ion (SAM) reacts with inorganic fluoride in a nucleophilic replacement with methionine as the leaving group.



Scheme 2.74 Fluorodesulfuration of dithianylium salts in the presence of different *O*- and *N*-nucleophiles enables convenient access to a variety of α,α-difluoroalkylated products (R = *n*-C_3H_7 or *n*-C_5H_{11}) [147b].



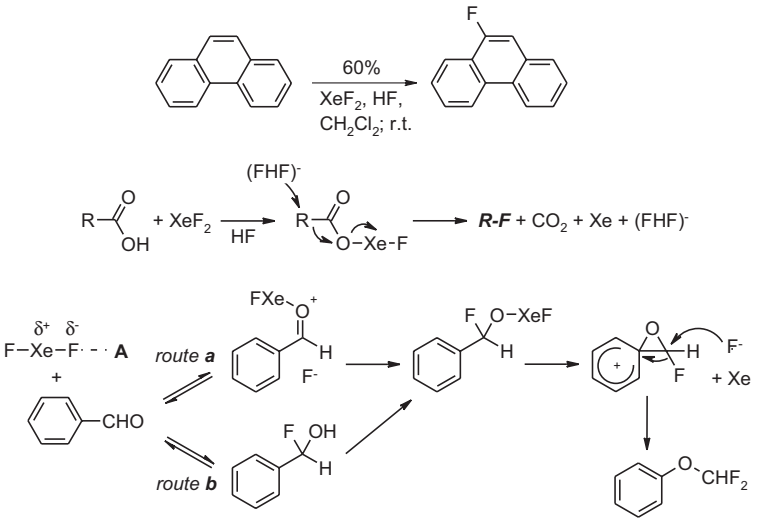
Scheme 2.75 Biological fluorodesulfuration and subsequent enzymatic conversions (SAM = *S*-adenosyl methionine, 5′-FDA = 5′-fluorodesoxyadenosine, NAD^+ = nicotinamide adenine dinucleotide, PLP = pyridoxal phosphate) [166].

2.1.6 "Electrophilic" Fluorination

The discovery of Fried and coworkers [167] in the 1950s that incorporation of fluorine substituents into 9α-fluorocortisone acetate dramatically increased its therapeutic effect provided a strong stimulus for interest in fluorinated pharmaceuticals. One valuable component still missing from the toolbox of methods in organofluorine chemistry was a generally applicable method for electrophilic fluorination of sensitive organic substrates under mild conditions.

2.1.6.1 Xenon Difluoride

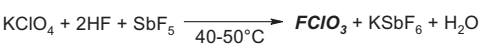
One of the first reagents used for electrophilic fluorination was xenon difluoride (XeF_2) [168], a solid which is easy to handle and which can be used in solvents which are relatively inert toward oxidation, for example acetonitrile and dichloromethane. The reactivity is mostly determined by its strong oxidizing power, rendering its mode of action more oxidative than electrophilic fluorination. With XeF_2 not only are typical "electrophilic" fluorinations of aromatic compounds possible but also the Hunsdiecker-like fluorodecarboxylation of carboxylic acids and fluorinative rearrangements of carbonyl compounds to difluoromethyl ethers [169–171] (Scheme 2.76.).



Scheme 2.76 Fluorination reactions with xenon difluoride (**A** = catalytic amount of SiF_4 as a Lewis acid) [169–171].

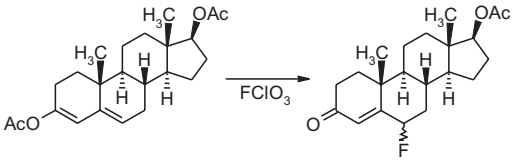
2.1.6.2 Perchloryl Fluoride and Hypofluorides

The first electrophilic fluorination reagent with industrial relevance was perchloryl fluoride $FClO_3$ [172] (Scheme 2.77) a gas (m. p. −147.8 °C, b. p. −46.7 °C) which is thermally stable up to 500 °C [173]. It was used commercially from the beginning of the 1960s for production of fluoropharmaceuticals, in particular fluorosteroids.



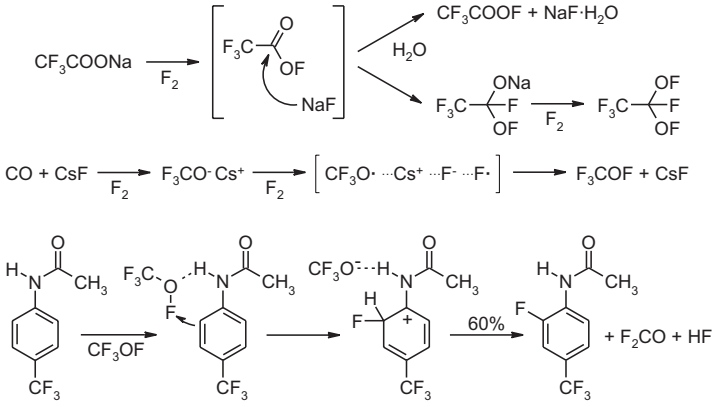
Scheme 2.77 Synthesis of perchloryl fluoride [173].

$FClO_3$ owes its reactivity to the fluorine bound to a strongly electronegative chlorine in its highest oxidation state. Although $FClO_3$ enables selective synthesis of complex organic compounds such as fluorocorticoids (Scheme 2.78), its high oxidation potential in combination with organic solvents poses a constant threat of explosion. On contact with alcohols, in particular, the extremely shock-sensitive alkyl perchlorates are formed.



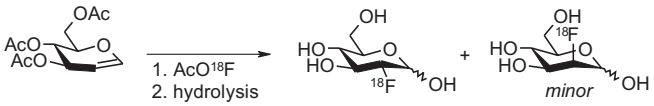
Scheme 2.78 Synthesis of fluorosteroids by electrophilic fluorination with perchloryl fluoride.

Another class of powerful electrophilic fluorination reagents, which are slightly less risky to use, are the hypofluorites or "*OF*"-reagents, with fluorine activated by electronegative oxygen groups [174]. The most prominent examples of these hypofluorites are CH_3COOF (m. p. −96 °C, b. p. ~53 °C) [175], CF_3COOF [176], and CF_3OF [177] (Scheme 2.79) all highly toxic low-boiling liquids or gases at room temperature. In addition to their toxicity the hypofluorites tend to detonate in contact with organic solvents and are therefore not safe enough for industrial use.



Scheme 2.79 Representative syntheses of a variety of *OF*-reagents and the mechanism proposed for the selective electrophilic *ortho* fluorination of aromatic acetamides [178].

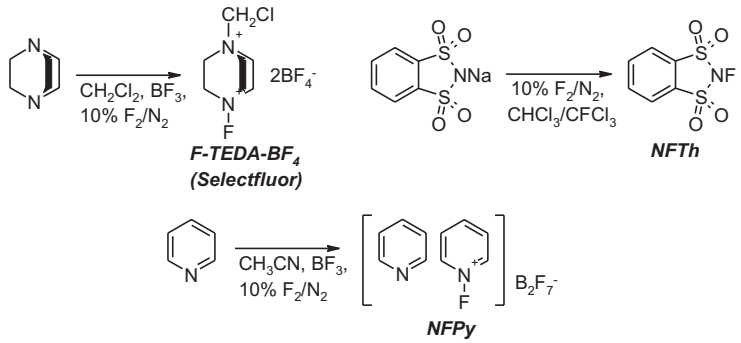
Acetyl hypofluorite has achieved particular importance as a fluorinating agent for rapid synthesis of positron-emitting ^{18}F radiopharmaceuticals and diagnostics with a half-life of 109.7 min (Scheme 2.80). The compound is readily available by the "dry column" method, i. e. by passing gaseous F_2 or $^{18}F^{19}F$ through a column packed with solvated KOAc · 2HOAc [179].



Scheme 2.80 Synthesis of [^{18}F]2-fluorodeoxyglucose [180].

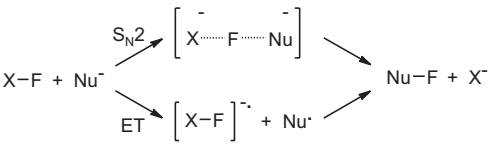
2.1.6.3 *"NF"*-Reagents

Toward the end of the 1980s the intensive search for less hazardous electrophilic fluorination agents produced a number of different sub-classes of so-called "*NF*"-reagents [181–183] (Scheme 2.81). The concept underlying these reagents is based on work dating back to the late 1950s when the synthetic potential of *N*-fluoroamines such as perfluoro-*N*-fluoropiperidine [184] or, later, NF_4^+ and N_2F^+ was explored [185]. The *NF*-reagents derive their fluorinating power from fluorine bound to electronegative nitrogen, occasionally additionally activated either by strongly electron-withdrawing groups such as carbonyl or sulfonyl or by non-stabilized positive charges in the same molecule. The great advantage of all these *NF*-reagents compared with the previous generation of electrophilic fluorination reagents is that most are solid, involatile compounds which are not explosive. The commercial availability of reagents such as those depicted in Scheme 2.81 triggered an avalanche of experimental work on electrophilic fluorination in subsequent years [186].

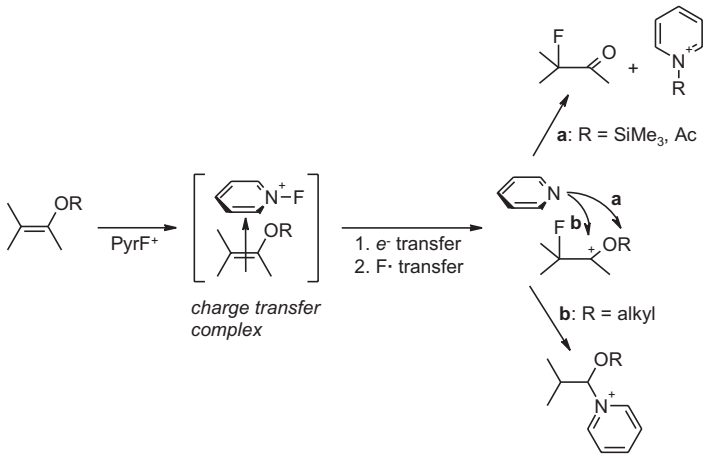


Scheme 2.81 The most important classes of commercially available electrophilic fluorination reagents of the *NF*-type and their syntheses [186].

The mechanism of electrophilic fluorination (real electrophilic "F^+" transfer vs. a two-step single electron/fluorine radical transfer; Scheme 2.82) has been a matter of controversy for some time [187]. There is, however, a general consensus that the high enthalpy of formation of the F^+ cation in the gas phase (420 kcal mol^{-1}) precludes a truly "electrophilic" mechanism. A mechanism proceeding via a pure S_N2 pathway at the electrophilic fluorine also seems unlikely [187b]. Detailed studies of product distribution for *NF*-type reagents under different reaction conditions indicate a two-step mechanism via an electron transfer with subsequent fluorine radical transfer [183b] (Scheme 2.83).

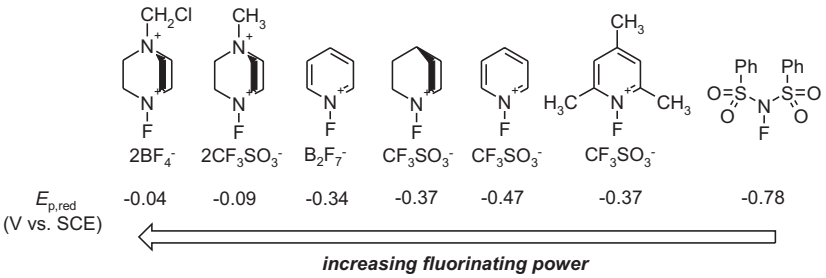


Scheme 2.82 Possible mechanisms for electrophilic fluorination – two-step electron transfer/fluorine radical transfer or S_N2 nucleophilic substitution mechanism [187].



Scheme 2.83 Proposed mechanism of electrophilic fluorination with *N*-fluoropyridinium salts [183b].

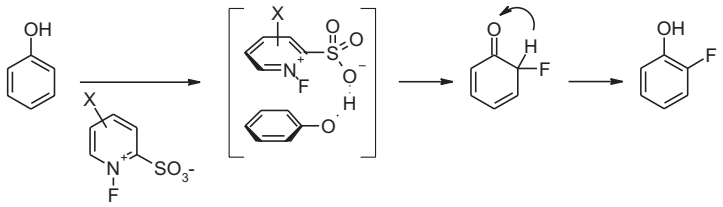
Additional evidence for the two-step oxidation–fluorination mechanism is the correlation observed between the fluorinating "power" and the first reduction potential of different *NF*-reagents. Systematic studies by cyclic voltammetry [188] (Scheme 2.84) reflect not only the different reactivity ranges of the classes of *NF*-reagent but also that additional modulation of the fluorinating power can be achieved by suitable substitution of the basic structures with electron-donating or withdrawing groups.



Scheme 2.84 Reduction peak potentials of different electrophilic fluorination reagents: $E_{p,red}$ in V relative to the standard calomel electrode; 1–5 mM in CH_3CN/0.1 M $Bu_4N^+BF_4^-$ or $CF_3SO_3^-$ [188b].

Newer QM/MM simulations of the electrophilic fluorination of a malonate coordinated to a titanium center with a simplified Selectfluor (F-TEDA) analog [189] throw a new light on the electron transfer/fluorine transfer mechanism. During the approach of the electrophilic fluorine toward the carbon nucleophile an electron is transferred from the nucleophile to Selectfluor, then fluorine is transferred to the nucleophile. Interestingly, the transition state for transfer of the fluorine radical is formed only if a polar solvent (acetonitrile) is used. If the simulation is carried out *in vacuo*, the reaction stops after the initial electron transfer.

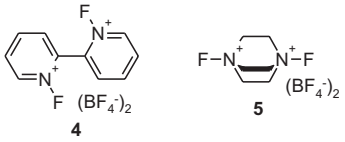
In addition to modulation of the general reactivity by choice of substituents with different electron demand, Umemoto and coworkers described a method of increasing the selectivity of the fluorination, particularly for phenols and aromatic urethanes in the *ortho*-position [183b, 190]. In the reaction of *N*-fluoropyridinium-2-sulfonate the electrophilic fluorine is supposedly directed by a combination of $\pi \cdots \pi$ donor–acceptor interaction and electrostatic (hydrogen) bonding to a specific position (Scheme 2.85).



Scheme 2.85 Directed *ortho*-fluorination of phenols by *N*-fluoropyridinium-2-sulfonates [190].

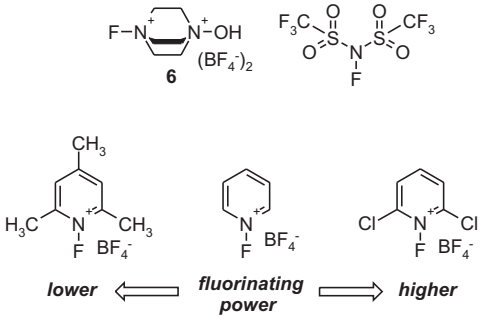
A major drawback so far for all *NF*-reagents is their relatively high molecular weight and their low content of "active" fluorine. For example, for Selectfluor the ratio of active fluorine to the molecular weight is only 5.4 %, for NFTh it is 8.0 %, and for NFPy 6.0 %. This issue was addressed by synthesis of more "compact" fluorination reagents [191]. One approach towards this goal was to link two or more pyridinium units to a single molecule (**4**, commercialized as Synfluor).

Another approach, introducing two nitrogen–fluorine bonds to the same diazabicyclooctane (DABCO) system (**5**) [192], yielded a system with significantly improved fluorination power. Unfortunately, in this system only one fluorine is reactive in fluorination; the other merely modulates its reactivity by means of its positive charge in close vicinity to the reactive center (Scheme 2.86).



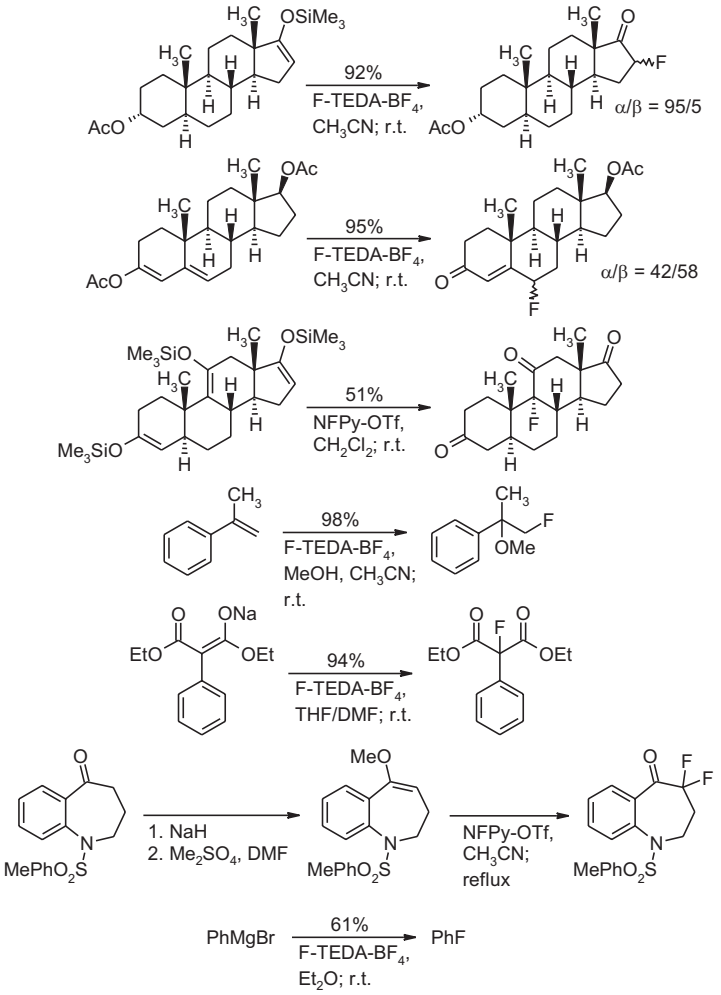
Scheme 2.86 Electrophilic fluorination reagents with an improved ratio of electrophilic fluorine to molecular weight. The respective ratios are: **4** 11.2%, **5** theoretically 12.8%, but only one fluorine is reactive, therefore actually only 6.4% "active" fluorine [191, 192].

A similar reactivity-enhancing effect was achieved by use of the *N*-hydroxy analog (**6**) of Selectfluor [193], commercialized under the name Accufluor. In addition, a number of other derivatives of the fluorinating agents with up- or down-tuned reactivity are available (Scheme 2.87). The tuning is usually achieved by selection of more or less electronegative substituents on the basic structures DABCO, pyridine, or sulfonimide [194].



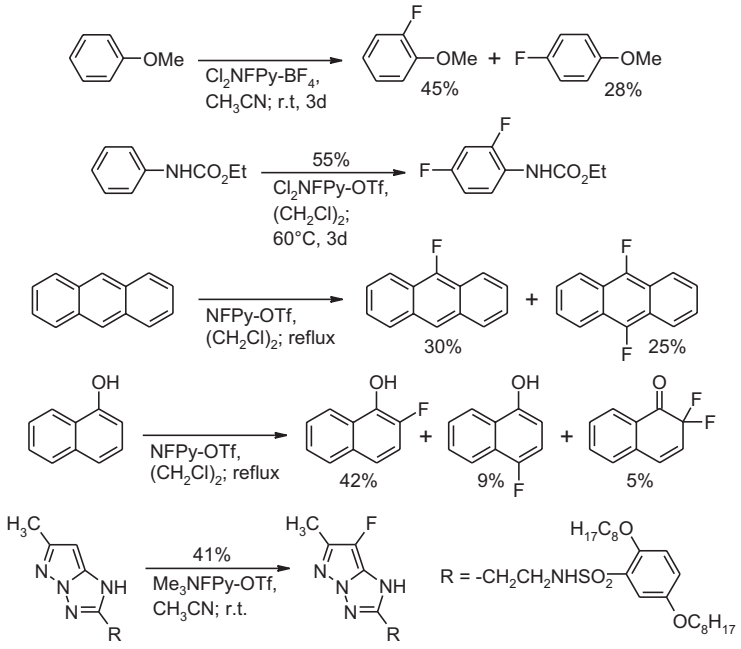
Scheme 2.87 *NF*-reagents with up- or down-tuned reactivity.

The range of possible fluorination reactions on electron-rich double bonds, enolates, and enol ethers, with Selectfluor (F-TEDA-BF_4) as example, is depicted in Scheme 2.88. Yields from the fluorination of unstabilized carbanions, for example phenyl magnesium bromide, are usually relatively low, mostly because of competing oxidation side-reactions.



Scheme 2.88 Reaction of a variety of substrates with the different *NF*-reagents [183b, 195, 196].

Although electrophilic fluorination of aromatic compounds can be achieved by use of a wide range of different *NF*-reagents (Scheme 2.89), lack of sufficient selectivity in the fluorination and difficulty of separating the fluoro isomers, because of their very similar boiling points, remains a problem. For this reason, electrophilic fluorination of aromatic compounds, either with *NF*-reagents or with elemental fluorine, is used only in few special cases. For production-scale synthesis Halex and Balz–Schiemann chemistry remain unrivaled.



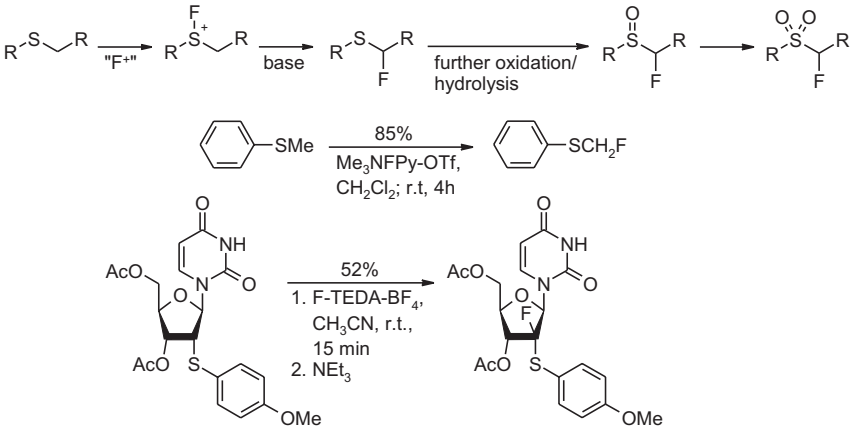
Scheme 2.89 Electrophilic fluorination of aromatic compounds [183b, 190, 197, 198].

Reaction of thioethers with one equivalent of *NF*-reagent results in the formation of *α*-fluorothioethers via a fluoro-Pummerer rearrangement [199] (Scheme 2.90). With appropriate excesses *α*-fluorosulfoxides and sulfones are obtained [200]. The thiophenyl group can also be used as a subsequently removable directing function for site-selective fluorination of natural products [201].

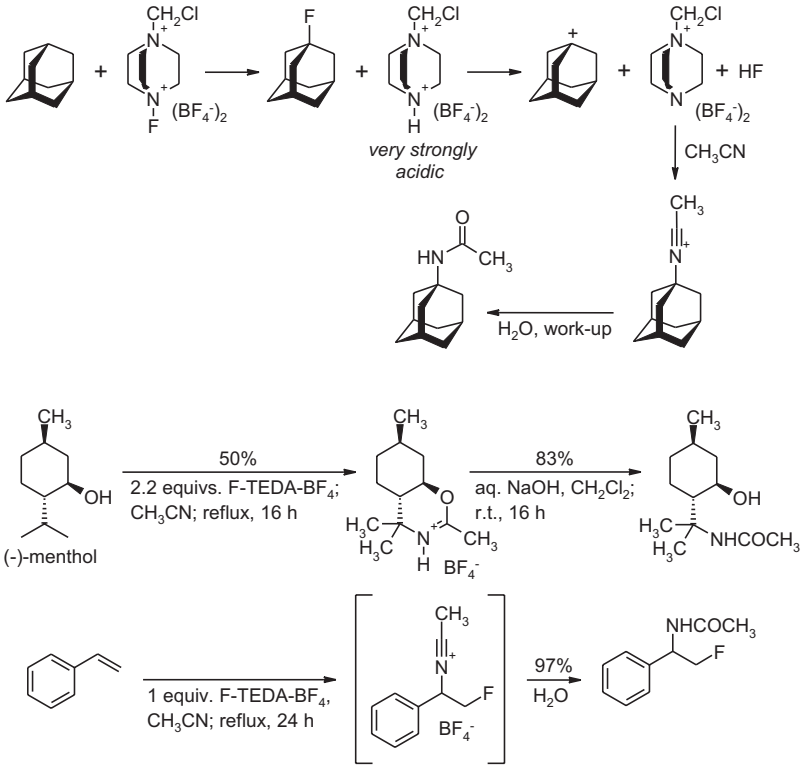
It was also found recently that direct selective substitution of aliphatic hydrocarbons via a supposedly electrophilic mechanism can be achieved by use of F-TEDA-BF_4 [202]. Depending on the exact reaction conditions, either alkyl fluorides or Ritter-type products are obtained (Scheme 2.91). Relatively short reaction times favor the formation of the fluorides, longer heating with F-TEDA-BF_4 in acetonitrile favors the formation of acetamides, especially in the presence of additional $BF_3 \cdot OEt_2$ as Lewis acid catalyst [203].

Although enantioselective electrophilic fluorination can be achieved by use of a variety of chiral *NF*-reagents [204], enantiomeric excesses *(ee)* are only moderate and far lower than expected for "real" electrophilic addition. It might be speculated that the reason lies in the specific mechanism of electrophilic fluorination in general – the electron-transfer which presumably precedes fluorine transfer results in a short-lived radical intermediate which is configurationally unstable and can racemize.

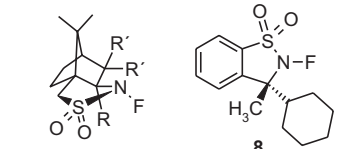
Chiral reagents of the first generation are *N*-fluorosultams, derived either from camphorsultam or from sulfonylcarboximide (Scheme 2.92).



Scheme 2.90 α-Fluorination of thioethers with *NF*-reagents [199–201].

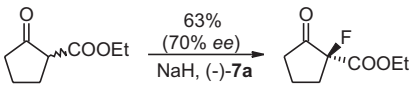


Scheme 2.91 Aliphatic fluorination and Ritter-type reactions of *NF*-reagents in acetonitrile [202, 203].



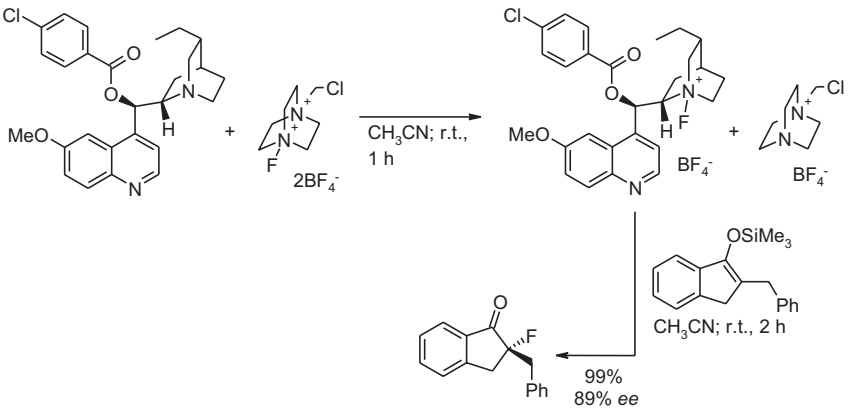
7a: R, R′ = H
7b: R = CH_3, R′ = H
7c: R = H, R′ = Cl
7d: R = H, R′= OCH_3

8



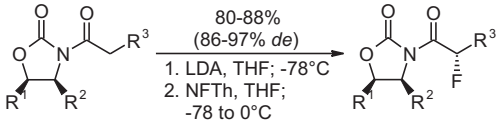
Scheme 2.92 Uncharged chiral electrophilic fluorination reagents of the first generation: *N*-fluoro camphorsultams **7a**–**7d** [181a] and *N*-fluorosultam **8** [205].

Newer approaches make use of derivatives of quinuclidine alkaloids, such as quinine. The quinine derivative is first converted into the fluorination reagent by Selectfluor, in one-pot procedure, and in a second step reacted with the desired substrate (Scheme 2.93). The enantiomeric excesses achieved with this type of reagent are higher than for the *N*-fluoroimides but still below those of other enantioselective reactions.



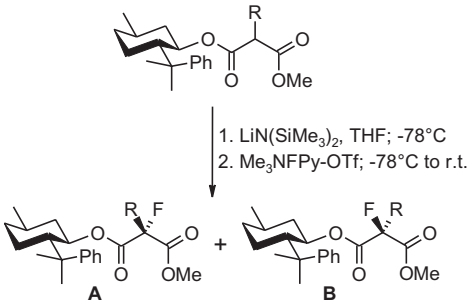
Scheme 2.93 Enantioselective electrophilic fluorination of silyl enol ethers by *N*-fluorodihydroquinine 4-chlorobenzoate. The enantioselective fluorination reagent is generated *in situ* from F-TEDA-BF_4 (Selectfluor) and dihydroquinine 4-chlorobenzoate [206].

A different approach to enantioselective electrophilic fluorination is the use of chiral auxiliary groups on the substrate; this converts the problem into a diastereoselective fluorination. The ground-breaking work in this field was done since 1992 by the Davis group [207], by fluorination of imide enolates modified by Evans' oxazolidinone chiral auxiliary [208] using *N*-fluoro-*o*-benzenedisulfonimide (NFTh) as the electrophilic fluorination agent (Scheme 2.94).



Scheme 2.94 Synthesis of α-fluorocarbonyl compounds by use of Evans' oxazolidinone as chiral auxiliary (R^1 = H, Ph; R^2 = CH_3, *i*-Pr; R^3 = *n*-Bu, *t*-Bu, Bn, Ph) [207, 208].

Table 2.2 Use of menthol derivatives as chiral auxiliaries [209].



R	***A*:*B***
Me	3.8:1
Et	1:2
Pr	1:2
CH_2Ph	1:1.6

Menthol derivatives are also an inexpensive means of obtaining diastereoselection during electrophilic fluorination [209]. Depending on the size of the substituents at the nucleophilic center, the stereoselectivity not only changes but can be completely inverted (Table 2.2).

Yet another example of diastereoselective electrophilic fluorination was observed on the route to fluorinated prostaglandin analogs [210]. In this reaction the concave shape and large size of a tetrahydropyranyl protecting group impedes attack of the fluorinating agent from the concave side of the molecule (Figure 2.6).

A newer approach toward the enantioselective electrophilic fluorination of β-ketoesters is based on enolization of the substrate under neutral conditions by coordination to a chiral titanium catalyst [211]. The catalyst, a chiral titanium TADDOLato complex (TADDOL = $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) [212, 213], coordinates to the β-ketoester, enolizes it, and thus renders it susceptible to electrophilic fluorination (Scheme 2.95). One face of the prochiral enolate substructure is covered by a bulky naphthyl substituent from the TADDOL ligand, impeding electrophilic attack of F-TEDA.

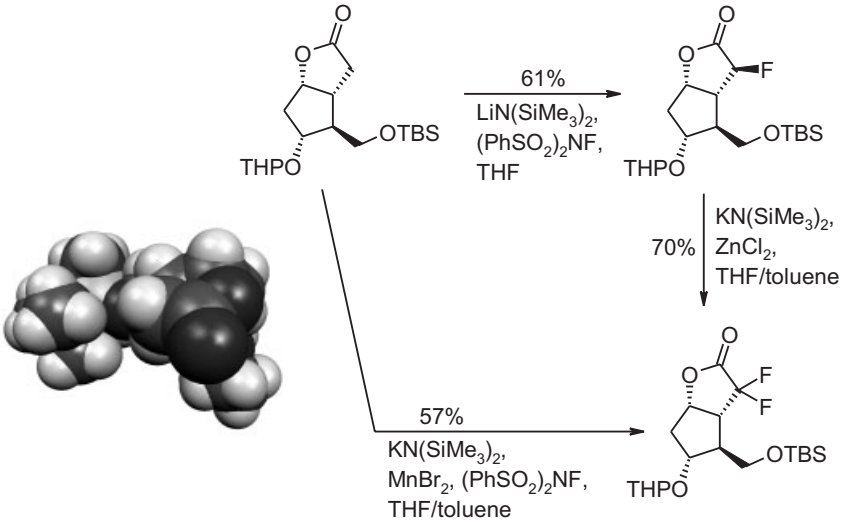
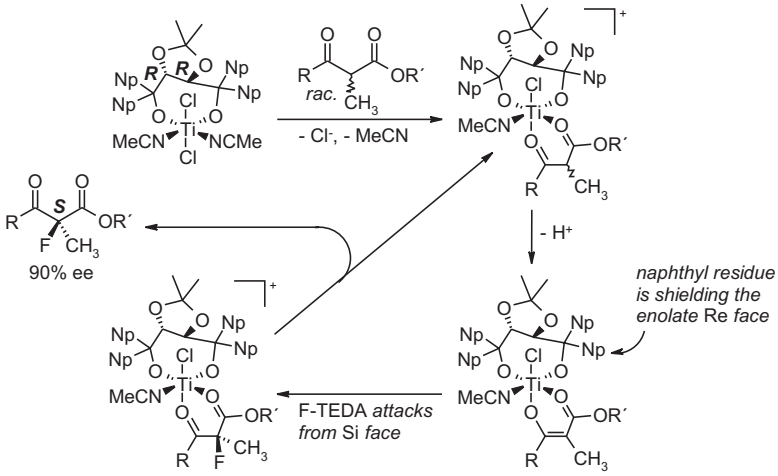


Figure 2.6 Diastereodirection of the fluorination site by neighboring chiral centers [210].



Scheme 2.95 Asymmetric electrophilic fluorination of β-ketoesters, catalyzed by chiral titanium TADDOL complexes (Np = 1-naphthyl, R = Et, R′ = 2,4,6-(iPr)$_3$C$_6$H$_2$-CH$_2$) [211].

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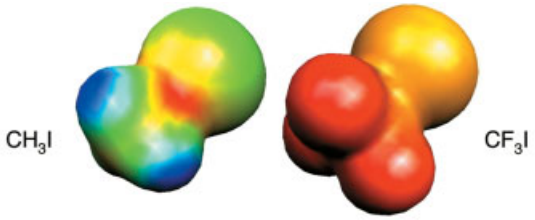
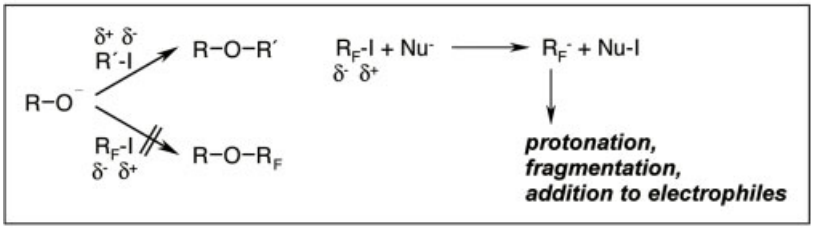
2.2
Perfluoroalkylation

2.2.1
Radical Perfluoroalkylation

Whereas haloalkanes are widely used for the electrophilic alkylation of a broad variety of nucleophiles, perfluoroalkyl bromides or iodides do not act analogously as electrophilic perfluoroalkylation reagents (Figure 2.7). For example, the reaction of perfluoroalkyl iodides with aliphatic alcoholates does not yield the expected alkyl perfluoroalkyl ether (analogous to the Williamson ether synthesis) but mostly the hydrofluorocarbon resulting from the reduction of the iodide [1]. In contrast, perfluoroalkyl iodides and bromides have been used as preparatively useful electrophilic iodination or bromination reagents [2].

The reason for this – at first glance – unexpected behavior is inversion of the electrostatic partial charges (compared, e. g., with the corresponding iodoalkanes) by the negative inductive effect of the perfluoroalkyl moiety. Nevertheless, in the presence of some classes of nucleophile, for example thiolates, resonance-stabilized carbanions, or enamines, the behavior of perfluoroalkyl halides is sometimes puz-





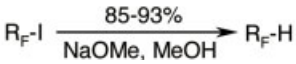
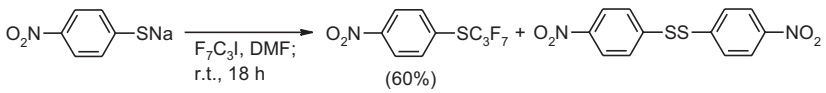


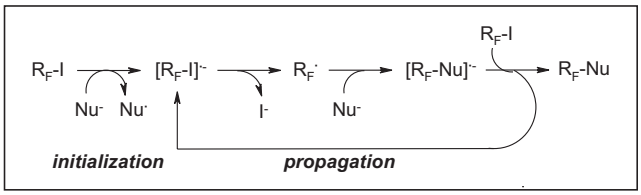
Figure 2.7 *Above*: The inverted electrophilic reactivity of alkyl halides compared with that of perfluoroalkyl halides. *Below*: Electrostatic potentials (red, negative; blue, positive partial charges) mapped on the electron isodensity surfaces of CH_3I (*left*) and CF_3I (*right*). The natural partial charges of CH_3I are $q_C = -0.84$ e, $q_H = +0.26$ e, $q_I = +0.07$ e, and of CF_3I $q_C = +0.93$ e, $q_F = -0.34$ e, $q_I = 0.09$ e (B3LYP/6-31G*(C,H,F),LANL2DZ(I)//AM1 level of theory) [3, 4].



Scheme 2.96 The reactivity of some oxidizable nucleophiles toward perfluoroalkyl halides suggests an electron-transfer initiated mechanism [5].

zling and superficially reminiscent of electrophilic reactivity (Scheme 2.96). This kind of reactivity strongly depends on the solvent, on irradiation with light, or the presence of redox shuttles, for example methyl viologen.

A closer look at the optimum reaction conditions and at the byproduct spectrum reveals that the observed reactivity can most probably be attributed to a chain reaction involving electrochemically generated and regenerated perfluoroalkyl radicals [6] (Scheme 2.97). In contrast to alkyl radicals, perfluoroalkyl radicals are rather electrophilic in nature. Therefore, the radical pathway sometimes mimics the outcome of a nucleophilic substitution on a perfluoroalkyl bromide or iodide.



$$n\text{-}F_{13}C_6I + Na^+ Me_2C{=}NO_2^- \xrightarrow[h\nu,\ DMF;\ r.t,\ 3\ h]{89\%} n\text{-}F_{13}C_6Me_2CNO_2 + NaI$$

Scheme 2.97 The mechanism of the perfluoroalkylation of oxidizable nucleophiles (e. g. $Nu^- = [Me_2CNO_2]^-$) by perfluoroalkyl halides mimics an electrophilic pathway, i. e. nucleophilic substitution (S_N) of the halide [7].

2.2.1.1 Structure, Properties, and Reactivity of Perfluoroalkyl Radicals

Thermodynamically, perfluoroalkyl radicals are not generally more stable or they are even more destabilized than alkyl radicals. Nevertheless, several factors can dramatically stabilize perfluoroalkyl radicals *kinetically*.

Termination of a perfluoroalkyl radical is possible only either (1) by dimerization, or (2) by radical transfer involving either the cleavage of a carbon–carbon bond or of the very stable carbon–fluorine bond. The second option requires relatively high activation energies because of the strengths of the bonds (e. g. the carbon–fluorine bond) which would have to be cleaved. The first option is the most common pathway for termination, especially of primary perfluoroalkyl radicals, which are often used for synthetic purposes. Nevertheless, for secondary and most pronounced for tertiary radicals very long lifetimes can be observed, because the carbon-centered radical is shielded by a "protective" shell of sterically demanding fluorine atoms. This effectively inhibits dimerization and disproportionation by radical transfer. The most famous of these highly persistent perfluoroalkyl radicals are Scherer's radicals **11** and **12** [8] (Figure 2.8). The radical **11** has a half life of 1 h at 100 °C for β-scission to the olefin isomers **13** and **14** and trifluoromethyl radicals. This fragmentation can be used as a preparative source of $CF_3\cdot$ radicals – if perfluoroolefins **9** or **10** are heated in the presence of **11**, their reaction with the *in-situ*-generated $CF_3\cdot$ yields the even more stable radical **12**, which does not react with 100 % fluorine gas at 1.3 bar at room temperature even after 300 h.

The structure and reactivity of perfluoroalkyl radicals is determined by the complex interplay between the strong σ-acceptor effect and the π-donating effect of fluorine. Whereas the methyl radical is planar, fluorinated methyl radicals are pyramidal [9]. The pyramidalization and inversion barriers increase with increasing fluorination [10]. The calculated inversion barriers are ~1, 7, and 25 kcal mol^{-1} for $CH_2F\cdot$, $CHF_2\cdot$, and $CF_3\cdot$, respectively [11].

The reactivity of perfluoroalkyl radicals can be summarized again under the motto "Think Negative!". As a kind of starting point, the absolute electronegativities (as a measure of reactivity) [12] of the methyl and trifluoromethyl radicals

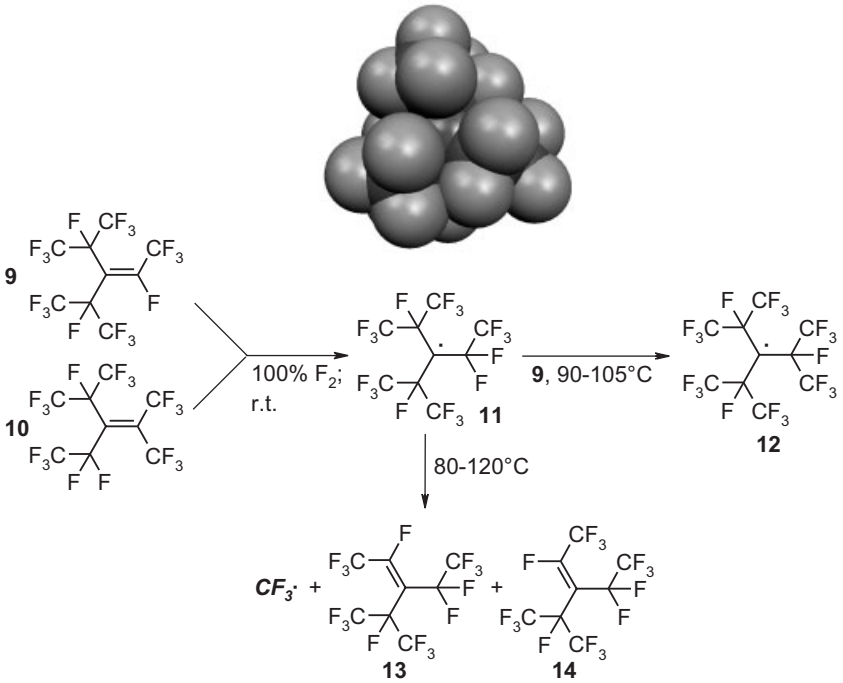


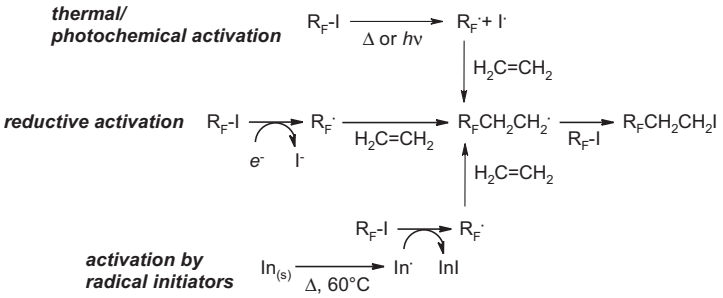
Figure 2.8 Synthesis of Scherer's sterically highly hindered, extremely persistent perfluoroalkyl radicals **11** and **12**. The AM1 model (*above*) indicates the bulky structure of **11** [8].

does not differ very much. Whilst the *nucleophilicity* of alkyl radicals increases from primary to tertiary, for their perfluorinated analogs the opposite is observed – their *electrophilicity* increases from the primary to tertiary radicals.

2.2.1.2 **Preparatively Useful Reactions of Perfluoroalkyl Radicals**

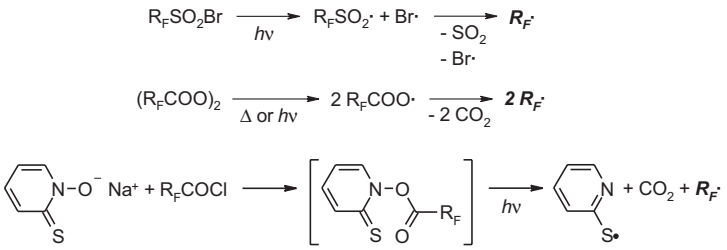
To make preparative use of perfluoroalkyl radicals they must first be generated by a method which does not interfere with other functional groups present in the reaction system. Because of their predominantly electrophilic nature, the most important reaction partners for these radicals are either highly polarizable ("soft") σ-electron systems (for example thiolates, selenides or phosphites) or, preferably, electron-rich π-systems (for example olefins and some aromatic compounds).

The most convenient sources of perfluoroalkyl radicals are perfluoroalkyl halides, from which the corresponding radicals can be generated photochemically or electrochemically [13]. Although electrochemical activation can be achieved either by oxidation or by reduction, e. g. of perfluoroalkyl iodides, the most popular method of activation is reduction (Scheme 2.98). The reductive radical generation can also be initiated photochemically via auxiliary radical sources, such as silanes or stannanes.



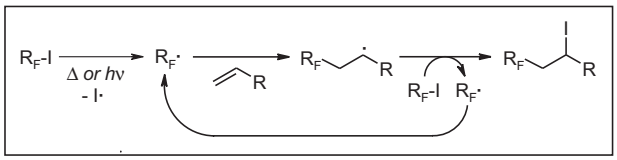
Scheme 2.98 Activation mechanisms of radical chain reactions starting from perfluoroalkyl iodides.

Other pathways of radical generation involve thermal or photochemical fragmentation of perfluoroacyl peroxides [14] or photochemical fragmentation of perfluoroalkylsulfonyl bromides [15]. The *in situ* formation of Barton esters from perfluoroacyl chlorides and thiopyridone-*N*-oxide has also been used as a convenient source of radicals [16] (Scheme 2.99).



Scheme 2.99 Other commonly used methods for generation of perfluoroalkyl radicals [14–16]. The activation energy of perfluorodiacyl peroxide fragmentation is approximately 24 kcal mol^{-1}, resulting in a half-life at room temperature of ca. 5 h.

As early as the 1940s Emeleus and Haszeldine [17] discovered that perfluoroalkyl iodides are not only cleaved into perfluoroalkyl radicals by light but also that they add readily to a variety of olefins to yield telomers and 1:1 adducts [18]. This kind of radical chain reaction can also be initiated by high temperatures (Scheme 2.100). The addition of perfluoroalkyl iodides to olefins is a very important method for synthesis of partially fluorinated alkanes, polymers, oligomers, and their derivatives [19]. The synthesis of some perfluoroalkyl aromatic compounds can also be achieved [20].



$CF_3I + CH_2{=}CH_2 \xrightarrow[250°C,\ 48\ h]{} CF_3CH_2CH_2I\ (75\%) + \text{higher telomers}\ (25\%)$

$CF_3I + CH_2{=}CHCH_3 \xrightarrow[h\nu]{98\%} CF_3CH_2CHICH_3$

$n\text{-}F_7C_3I + CH_2{=}CHCOOEt \xrightarrow[h\nu,\ 254\ nm,\ 24\ h]{100\%} n\text{-}F_7C_3\text{-}CH_2CHICOOEt$

$CF_3I + n\ CF_2{=}CF_2 \xrightarrow{h\nu} CF_3(CF_2CF_2)_nI$

ratio = 10 : 1 94% (n=1), 4% (n=2)
5 : 1 81% (n=1)
1 : 1 16% (n=1), 10% (n=2), 5% (n=3), 63% (n>3)
10 : 1 mixture with n=10~20

$n\text{-}F_{15}C_7I +$  $\xrightarrow[250°C,\ 15\ h]{62\%}$ 

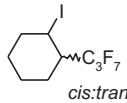
$CF_3I +$  $\xrightarrow[h\nu,\ Hg,\ 100\ h]{65\%}$ 

Scheme 2.100 Photo-initiated and thermally initiated radical additions of perfluoroalkyl iodides and bromides to olefins and aromatic compounds [11].

Inspired by M. S. Kharash's work on radical addition of CCl_4 to olefins [21], the same methodology was applied to perfluoroalkyl halides [13]. It was found that the addition of these compounds to olefins could be achieved with higher selectivity and at lower temperatures in the presence of radical initiators [22] (Scheme 2.101).

$n\text{-}F_{13}C_6I + CH_2{=}CHOAc \xrightarrow[AIBN;\ 80°C,\ 1\ h]{91\%} n\text{-}F_{13}C_6\text{-}CH_2CHIOAc$

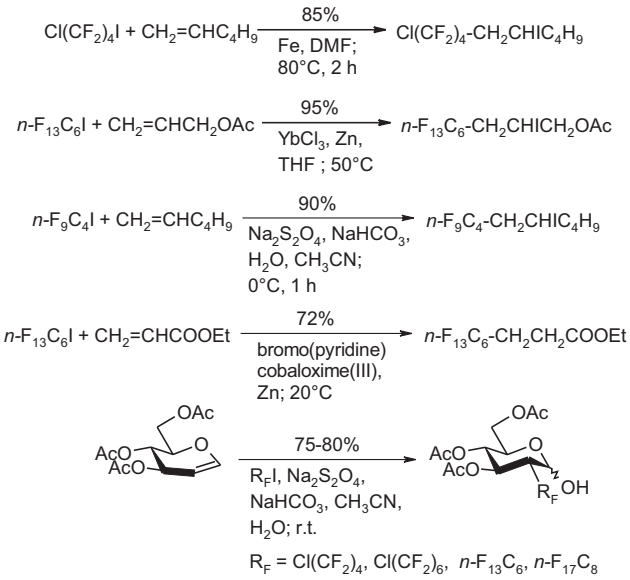
$n\text{-}F_{13}C_6I + CH_2{=}CH_2CHOAc \xrightarrow[DBP;\ 89°C,\ 1\ h]{94\%} n\text{-}F_{13}C_6\text{-}CH_2CH_2CHIOAc$

$n\text{-}F_7C_3I +$  $\xrightarrow[AIBN;\ 68°C,\ 21\ h]{80\%}$ 

cis:trans = 1:1

Scheme 2.101 Free radical additions of perfluoroalkyl iodides to a variety of olefins [11].

The method of perfluoroalkylation which, especially on the laboratory scale, has many practical advantages, is the reductively initiated radical addition of perfluoroalkyl iodides to olefins (Scheme 2.102). A large variety of reducing agents has been used for the initiation; examples include metals for heterogeneous reactions and also low valence metal salts or dithionites [23] for homogeneous reactions [11]. By use of special reducing agent systems in combination with electron-deficient olefins the *hydro*perfluoroalkylation products are obtained in high yields [24].

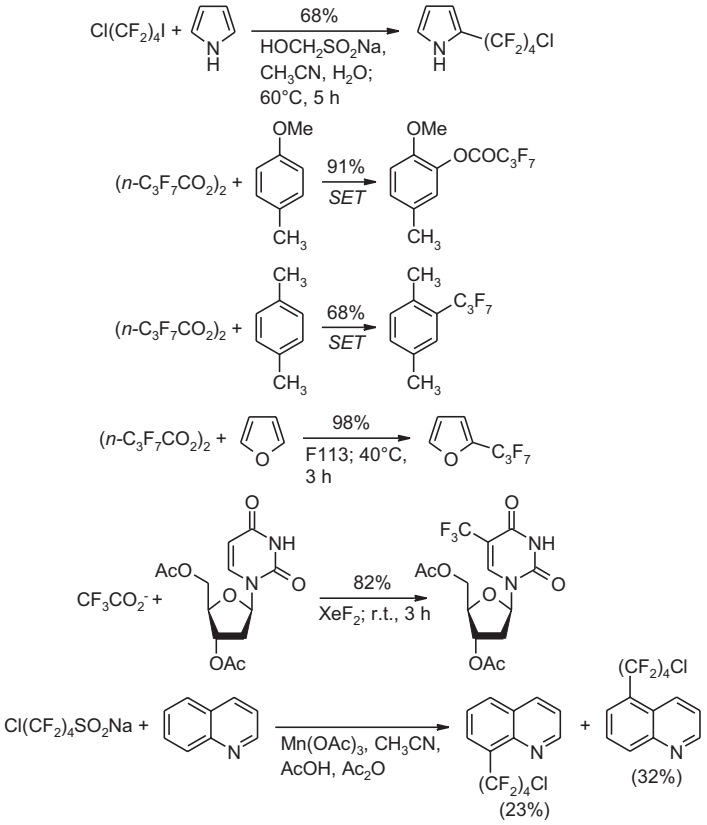


Scheme 2.102 Reductively initiated additions of perfluoroalkyl iodides to olefins [11, 25].

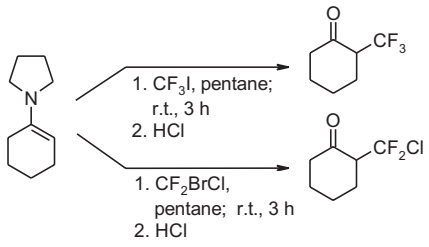
Reactions with reductively and oxidatively generated [26] perfluoroalkyl radicals have also been successfully used for perfluoroalkylation of aromatic compounds (Scheme 2.103). For the reductive initiation, the single electron transfer (SET) necessary for formation of the radical anion priming the reaction sequence can be provided either by a reductive reagent (for example $HOCH_2SO_2Na$) [27] or by an electron-rich aromatic substrate itself [28]. The oxidatively induced variant enables the perfluoroalkylation of more electron-deficient aromatic substrates, for example quinoline.

Resonance-stabilized carbanions, for example enamines [29], are good substrates for the SET-induced radical perfluoroalkylation (Scheme 2.104).

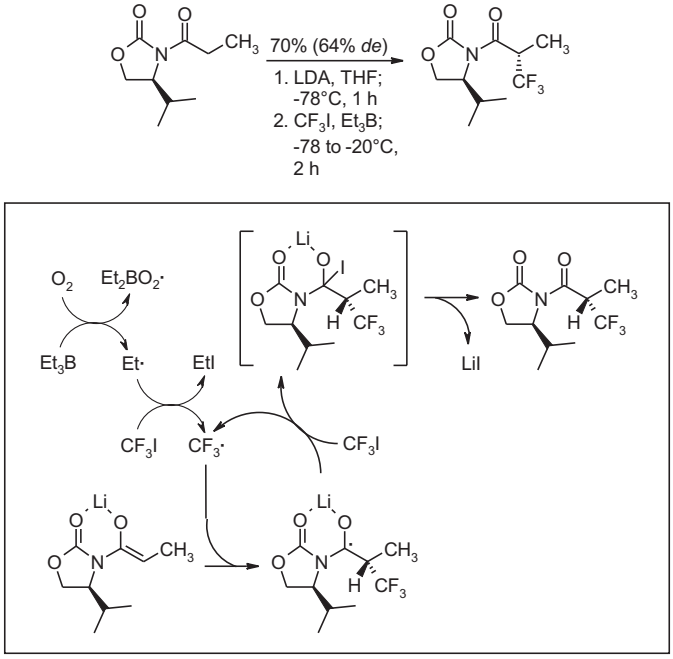
With non-stabilized enolates the radical reaction does not occur spontaneously but can be effectively initiated by triethylborane. The use of a chiral auxiliary group on the enolate leads to perfluoroalkylation products with reasonably good diastereomeric excesses (Scheme 2.105).



Scheme 2.103 Reductively and oxidatively induced radical perfluoroalkylation of a variety of aromatic and heterocyclic compounds [11].



Scheme 2.104 Perfluoroalkylation of enamines with perfluoroalkyl iodides [29].

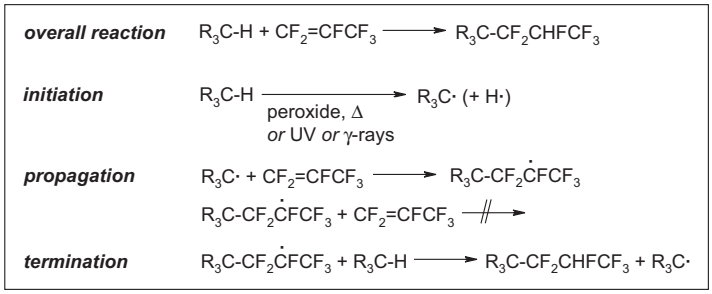


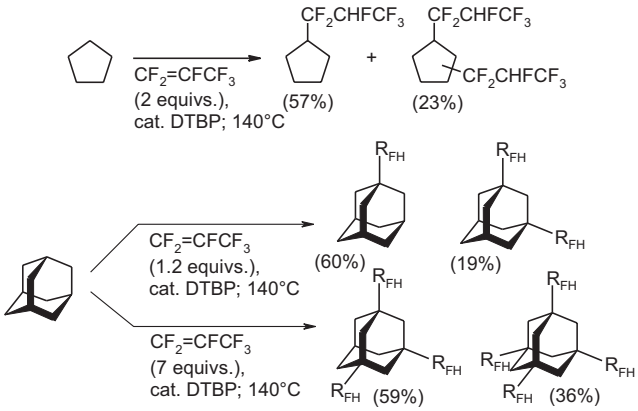
Scheme 2.105 Enantioselective perfluoroalkylation [30] using perfluoroalkyl halides with chiral auxiliary groups [31].

2.2.1.3 **"Inverse" Radical Addition of Alkyl Radicals to Perfluoroolefins**

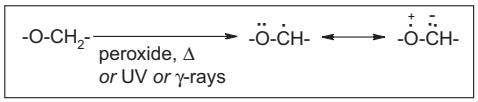
The "inverse" addition of nucleophilic alkyl radicals to electrophilic, highly fluorinated olefins was the subject of a detailed study by the Chambers and Sandford group [32]. Alkyl radicals can be generated directly from alkanes either with initiators (such as DBPO) or by γ-irradiation. Via the chain transfer mechanism outlined in Scheme 2.106 they add smoothly to fluoroolefins such as perfluoropropene or pentafluoropropene. For aliphatic systems with primary, secondary, and tertiary hydrogen substituents, especially, reasonably high regioselectivity of the (per)fluoroalkylation can be achieved by choice of reactant stoichiometry and reaction temperature. In practice, the most important prerequisite for this type of reaction is complete removal of oxygen from the reaction mixture, because oxygen inhibits the radical chain propagation even at very low concentrations.

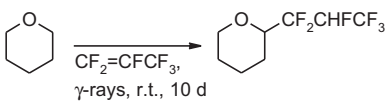
Under the same conditions, radicals are formed not only from saturated hydrocarbons but even more readily from ethers, in which the radical site is resonance stabilized. Thus, ethers also are readily perfluoroalkylated by fluoroolefins under radical-generation conditions (Scheme 2.107).





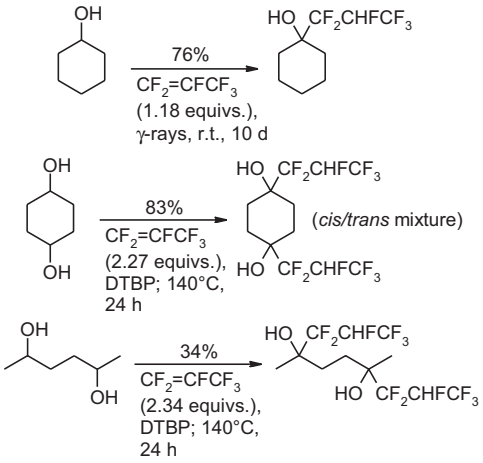
Scheme 2.106 Examples of the addition of alkyl radicals to highly fluorinated olefins ($R_{FH} = CF_2CHFCF_3$) (*below*), and the mechanism of the radical chain reaction (*above*) [32a].





Scheme 2.107 Resonance stabilization of α-oxaalkyl radicals (*above*), and radical addition of ethers to highly fluorinated olefins initiated by γ-irradiation (*below*) [32a].

Even easier is the α-fluoroalkylation of alcohols [32b]. The α-hydroxyalkyl radicals are also resonance-stabilized. Because of their nucleophilicity, they are highly reactive towards perfluoropropene and have the right reactivity for the radical chain propagation step (Scheme 2.108).



Scheme 2.108 Addition of α-hydroxyalkyl radicals to perfluoropropene [32b].

2.2.2
Nucleophilic Perfluoroalkylation

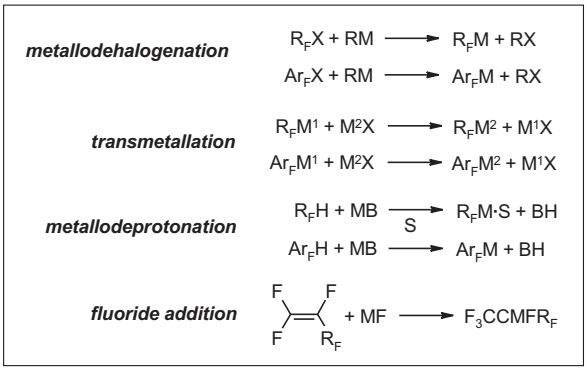
For medium-scale synthesis of fine chemicals and pharmaceuticals, especially, a variety of methods for nucleophilic perfluoroalkylation have assumed an important role. For nucleophilic perfluoroalkylation, either perfluoroalkyl carbanions, "carbanionoid", or perfluoroalkyl metal species must be generated, stabilized, and reacted with suitable electrophiles [33].

2.2.2.1 Properties, Stability, and Reactivity of Fluorinated Carbanions

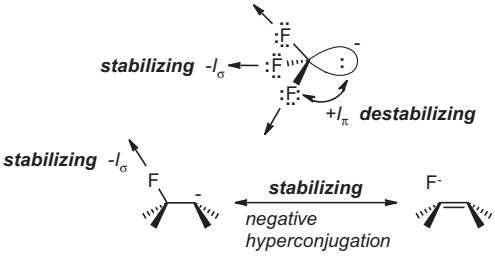
Perfluoroalkyl anions can, in principle, be generated by the same methods as "normal" alkyl or aryl anions – either by deprotonation of a suitable CH-acidic precursor by a strong base or by reductive halogen (usually iodine or bromine) metal exchange (Scheme 2.109). Another method – unique to the "perfluoro world" – is addition of fluoride ions or other anions to perfluoroolefins.

All perfluoroalkyl carbanions are stabilized by the negative inductive effect ($-I_\sigma$) of their fluoro substituents. At the same time, α-fluoro carbanions are destabilized by electronic p–π repulsion of the lone electron pairs of the fluorine and at the anionic center ($+I_\pi$ effect). This is reflected in the relatively weak acidity of CHF_3 in comparison with the other haloforms – the pK_a values of the various trihalomethanes are: CHF_3 30.5, $CHCl_3$ 22.4, $CHBr_3$ 22.7, and CH_4 68–70 [34].

In contrast, for β-fluoro carbanions, negative hyperconjugation [35] has a stabilizing effect. For example, in the perfluoro-*tert*-butyl anion the negative charge is not centered completely at the carbon atom, but comparably high partial charges are located on all the β-fluorine atoms [33] (Scheme 2.110).



Scheme 2.109 Principal methods for generation of fluorinated carbanions and perfluoroalkyl metal compounds (R_F = (per)fluoroalkyl, Ar_F = (per)fluoroaryl, M = metal, X = halogen, B = base, S = solvent). The particularly unstable trifluoromethyl anion can be stabilized by formation of an adduct with a suitable solvent, for example DMF, which itself acts as a "CF_3^-" source in a haloform-like reaction (*bottom*).

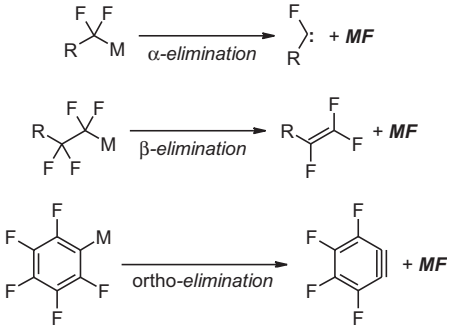


Scheme 2.110 Effects stabilizing and destabilizing carbanions: α-fluorocarbanions (*above*) are stabilized by $-I_\sigma$ and destabilized by $+I_\pi$ effects; β-fluorocarbanions (*below*) are also stabilized by the $-I_\sigma$ effect, but additional stabilization is derived from negative hyperconjugation.

2.2.2.2 Perfluoroalkyl Metal Compounds

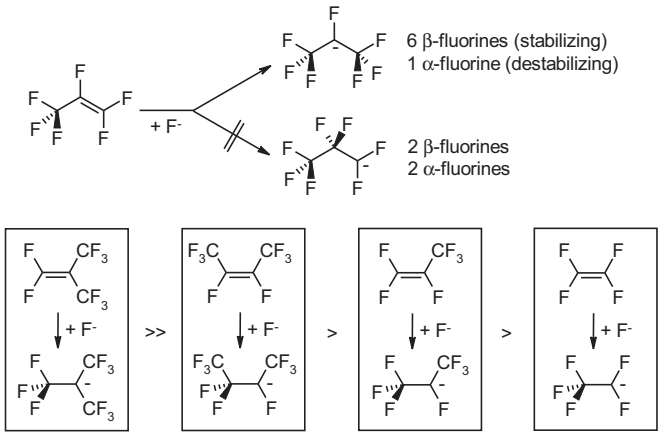
If the carbanion is not in a "free" state but bound to a metal which is also a "hard" Lewis acid, for example lithium or magnesium, the potential liberation of the huge lattice energies (e. g. 247 kcal mol^{-1} for LiF) strongly favors fragmentation of the perfluoroalkyl or perfluoroaryl metal compound (Scheme 2.111). If β-fluorine atoms are available, β-fluoride elimination occurs, leaving a terminal perfluoroolefin. If only α-fluorine is available, such as in CF_3Li (which has never been unambiguously observed), α-fluoride elimination results in the formation of difluorocar-

benes. Perfluoro*aryl* lithium species fragment also at low temperatures (typically from −40 to −20 °C, depending on the substitution) in a sometimes violently exothermic reaction, giving the corresponding arynes and lithium fluoride (see also Section 2.1.4).



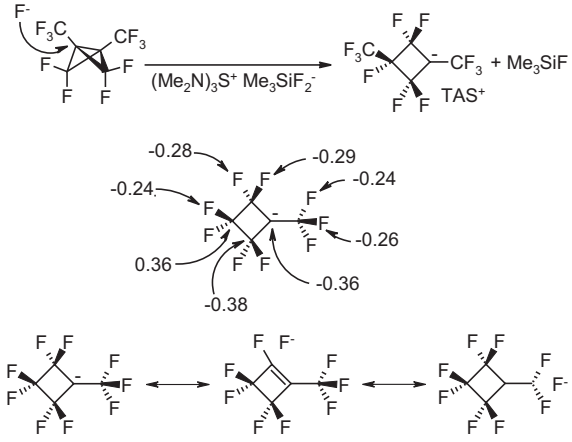
Scheme 2.111 Fragmentation pathways for different types of fluorocarbon metal compound.

As already discussed in Section 2.1.4, addition of fluoride to perfluoroolefins is very much favored, because conversion of fluorine-substituted sp^2 centers into sp^3 carbon results in a relief of strain from p–π repulsion. Addition to perfluoropropylene and other perfluoroolefins is highly regioselective – the anion with the largest number of carbon atoms bound to the negatively charged carbon center is always formed. This reactivity can be regarded as the "negative" but analogous version of Markownikov's rules for the hydrohalogenation of olefins (with protonation of the olefin as the preceding step). The reason for this phenomenon is the additional gain in stabilization of the negative charge by negative hyperconjugation for each newly created adjoining perfluoroalkyl group (Scheme 2.112).



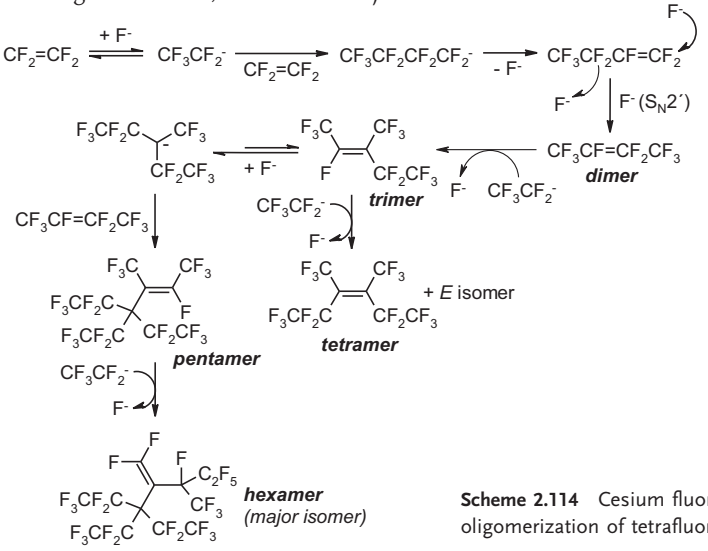
Scheme 2.112 The regioselectivity of fluoride addition and the relative stabilities of the carbanions derived from different perfluoroolefins are governed by the number of β-fluorine substituents which can stabilize the negative charge by their combined $-I_\sigma$ effects and by negative hyperconjugation.

Clear experimental evidence of "negative" hyperconjugation was obtained from X-ray structure analysis of the perfluoro-1,3-dimethylcyclobutanide anion [36]. The anionic center and the cyclobutane ring are *planar*, and the observed bond lengths are indicating a strong contribution of negative hyperconjugation. The fact that the same principal structure had been predicted by *ab-initio* computational methods [37] for a model compound (Scheme 2.113) strongly supports the value of this general methodology as a tool for understanding and elucidating the very special reactivity and structure in fluoroorganic chemistry.



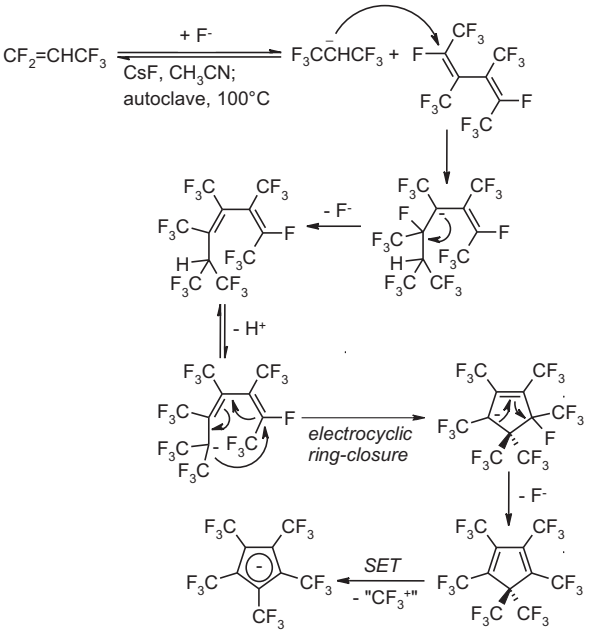
Scheme 2.113 Synthesis and structure of TAS^+ (tris(dimethylamino)sulfonium) perfluoro-1,3-cyclobutanide (*top*). Calculated Mulliken partial charges *q* (e) for a related model anion (*middle*) suggest negative hyperconjugation (*bottom*) [37].

Not only fluoride ions add readily to perfluoroolefins, but also carbanions themselves. Treatment of perfluoroolefins with catalytic amounts of CsF yields sometimes complex mixtures of various oligomers (the "negative" counterpart of cationic oligomerization; Scheme 2.114).



Scheme 2.114 Cesium fluoride-catalyzed oligomerization of tetrafluoroethylene [38].

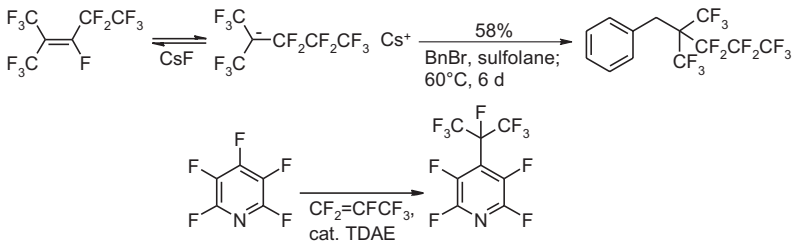
On the other hand, the example of the pentakis(trifluoromethyl)cyclopentadienide anion demonstrates impressively that this type of reaction can also be employed highly selectively to supplant a previous complex multi-step synthesis [39] by a one-pot procedure [40] (Scheme 2.115).



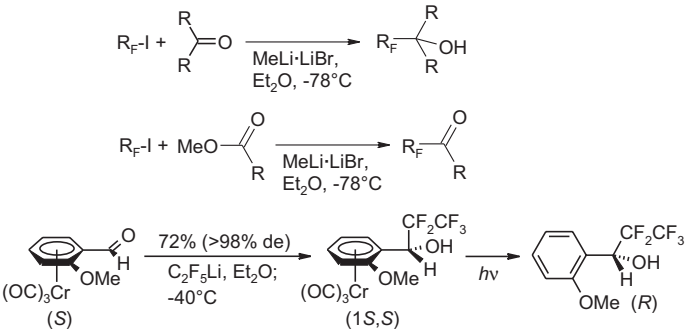
Scheme 2.115 One-pot synthesis of cesium pentakis(trifluoromethyl)cyclopentadienide by fluoride addition-induced intramolecular cyclization [40]. The ring-closure is supposed to proceed by an electrocyclic mechanism, and final loss of a "CF_3^+" fragment involves a single electron transfer (SET), possibly from the solvent, under the quite energetic reaction conditions [41].

Perfluoroalkyl carbanions generated by addition of fluoride to perfluoroolefins can also be used preparatively for selective introduction of perfluoroalkyl groups by aliphatic [42] or aromatic nucleophilic substitution of suitable substrates. Because for aromatic substrates the nucleofugic leaving group is typically fluoride, the reaction can be performed with a catalytic quantity of fluoride. This catalyst can be introduced either as an inorganic fluoride (CsF) or generated in a preceding electrochemical reaction by reduction–defluorination of the perfluoroolefin itself [43] (Scheme 2.116).

Higher homologues of perfluoro*alkyl* lithium compounds are usually generated at very low temperatures (−78 °C or below) in situ and directly reacted with a suitable electrophile, often a carbonyl compound, for example an aldehyde, ketone [45], or ester [46] (Scheme 2.117). If this carbonyl compound is chiral, reasonable diastereomeric excesses can be obtained [47]. The corresponding trifluoromethyl lithium (CF_3Li) is still unknown, because of its immediate α-elimination with difluorocar-



Scheme 2.116 Nucleophilic perfluoroalkylation of aliphatic or aromatic substrates by perfluoroalkyl anions generated by fluoride addition [43, 44] (TDAE = tetrakis(diurethylamino)ethylene).



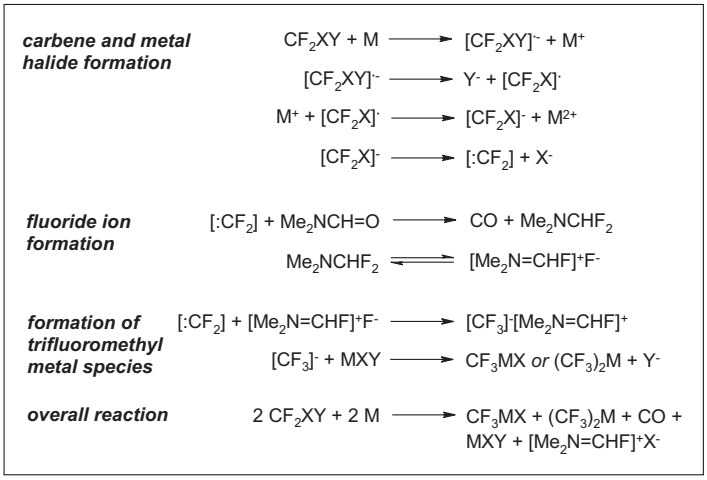
Scheme 2.117 Generation and *in-situ* reaction of perfluoroalkyl lithium species [47].

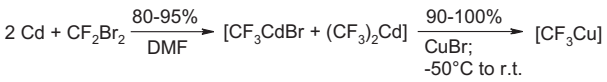
bene formation. The analogous magnesium (Grignard) species CF_3MgX has been prepared but is too unstable even at very low temperatures to be of any synthetic use.

Fluorinated aryl lithium compounds, on the other hand, are of high synthetic value, as already discussed in Section 2.1.4. Although the *ortho*-fluoroaryl lithium species (because they are typically obtained by *ortho*-metalation) must be handled at temperatures below −40 °C, other fluoroaryl lithium and magnesium compounds can also be prepared at higher temperature, because they cannot undergo spontaneous, explosive *ortho*-elimination of thermodynamically highly stable metal fluorides to give the corresponding arynes.

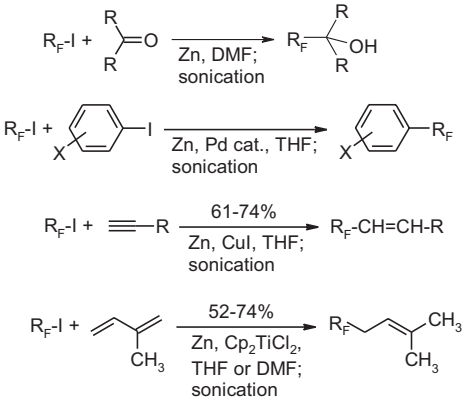
If the metal is a "soft" Lewis acid, for example zinc, cadmium, or copper, the corresponding perfluoroalkyl metal compounds are stabilized by the more covalent character of the metal–carbon bond (Scheme 2.118). The copper(I) compounds, in particular, can be readily isolated, handled, and reacted even at elevated temperatures.

The less stable trifluoromethyl zinc compounds [48] can be used as a source of nucleophilic trifluoromethyl fragments either in the isolated form or generated in situ by sonication of perfluoroalkyl iodides with zinc in DMF or THF. Zinc perfluoroorganyls find application in Barbier-type reactions [49], palladium-catalyzed cross-coupling reactions [50], or hydroperfluoroalkylations of acetylenes or olefins [51] (Scheme 2.119).





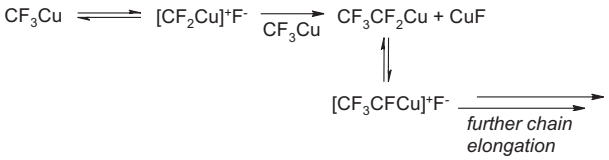
Scheme 2.118 Mechanism of the synthesis of trifluoromethyl zinc and cadmium reagents (*top*: X, Y = Br, Cl; M = Zn, Cd), and the preparation of trifluoromethyl copper(I) by *in situ* transmetalation (*bottom*).



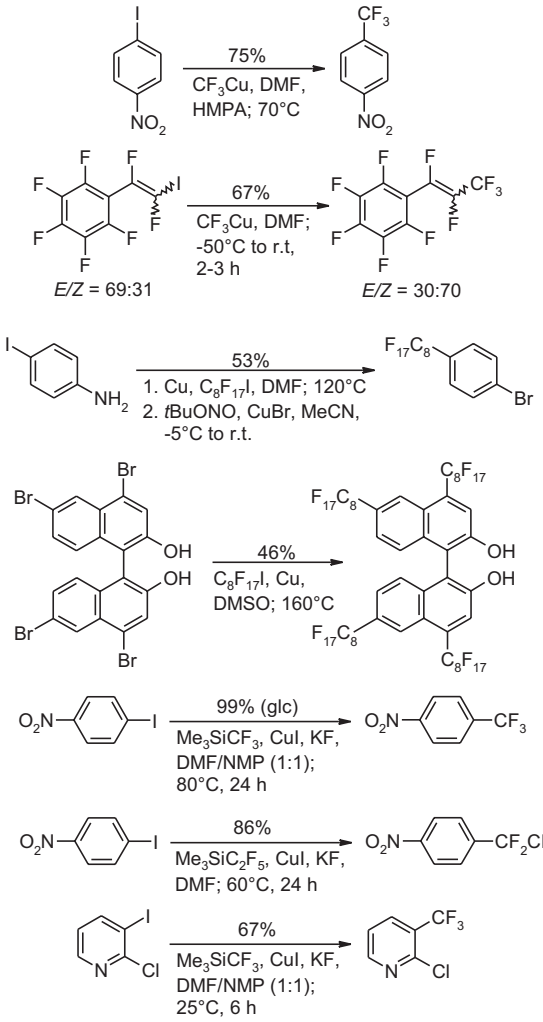
Scheme 2.119 Synthetic use of perfluoroalkyl zinc reagents – generated *in situ* by sonication – for various types of reaction [51].

In contrast, trifluoromethyl copper(I) can be generated and reacted, e. g. by thermal decarboxylation of trifluoroacetates in the presence of copper(I) salts at 150 °C, or by reaction of copper powder with perfluoroalkyl iodides. Nevertheless, even for the outwardly stable CF_3Cu there is evidence of a solvent- and temperature-dependent equilibrium between the trifluoromethyl copper(I) species and a difluorocar-

bene copper(I) fluoride complex. This equilibrium can be used for stepwise building of longer chain perfluoroalkyl copper(I) complexes by a difluorocarbene insertion mechanism (Scheme 2.120). The reaction can be blocked if CF_3Cu is stabilized by addition of stoichiometric amounts of HMPA.



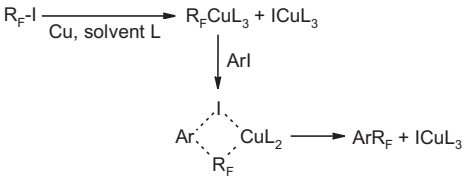
Scheme 2.120 Elongation of perfluoroalkyl copper(I) compounds by a carbene insertion mechanism [52].



Scheme 2.121 Cross-coupling of perfluoroalkyl copper(I) and aryl halides or perfluoroiodo olefins [52–54]. The CF_3Cu used for the upper two reactions was generated by metathesis of trifluoromethyl cadmium and copper(I) salts.

The most common use of perfluoroalkyl copper reagents is cross-coupling with aryl bromides or iodides to give the corresponding perfluoroalkyl arenes. A complication, especially for copper-mediated trifluoromethylation, is the concomitant formation of perfluoroethyl derivatives, which are difficult to remove during work-up and purification. The reason for this ubiquitous impurity is the above mentioned carbene insertion equilibrium; this can sometimes be suppressed by optimization of the solvent (e. g. addition of HMPA) and use of lower reaction temperatures. Especially mild reaction conditions are achieved by using Me_3SiCF_3 [2c] as the primary source of the nucleophilic trifluoromethyl group in combination with potassium fluoride and cuprous iodide for the *in-situ* formation of $CuCF_3$ [53] in a mixture of DMF and NMP. The same method (using $Me_3SiC_2F_5$) has also been successfully applied to the pentafluoroethylation of aryl iodides (Scheme 2.121).

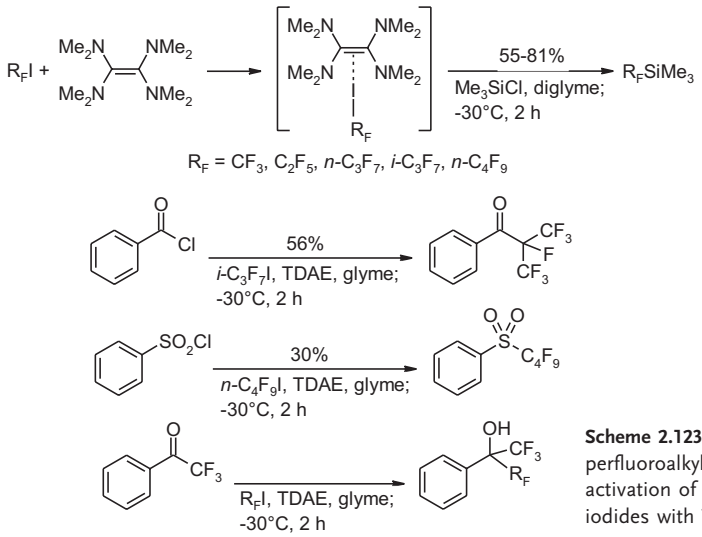
The mechanism of the copper-mediated cross-coupling of iodoarenes and perfluoroalkyl iodides is supposed to be similar to that of related reactions involving the interaction of halogenoarenes with cuprous salts of organic nucleophilic anions (for example CuCN) [55] (Scheme 2.122). First a solvated perfluoroalkyl copper(I) complex is formed. This then coordinates to the iodoarene followed by exchange of ligands [56]. Several electron-transfer steps are probably involved in this process. The efficiency of the reaction depends critically on the solvating power of the solvent for the copper(I) complex – DMF, pyridine. and DMSO give the highest yields. Because the complex is not sensitive to hydrolysis, the reaction also tolerates the presence of free carboxyl, amino, or hydroxy groups. The order of reactivity of the halogens as the aromatic leaving groups is I > Br >> Cl.



Scheme 2.122 Proposed mechanism for the copper-mediated coupling between perfluoroalkyl iodides and iodoarenes [56].

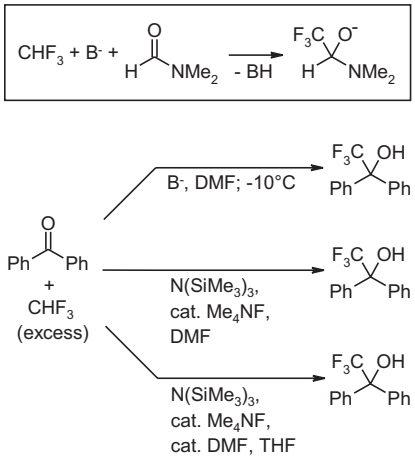
"Metal-free" alternatives to the reductive nucleophilic activation of perfluoroalkyl iodides have been described by G. Pawelke [57] and V. A. Petrov [58]. If perfluoroalkyl iodides are treated at low temperatures with the organic reducing agent TDAE, the resulting "R_F^-"-like species (presumably a charge-transfer complex $R_FI\cdots TDAE$) can be trapped with a variety of nucleophiles, for example Me_3SiCl, yielding Ruppert's Reagent Me_3SiCF_3 [2c], or carbonyl compounds, yielding the corresponding alcohols (Scheme 2.123).

Probably the most efficient way to generate CF_3^- from the view point of atom economy is deprotonation of inexpensive CHF_3 with a strong base [59]. Unfortunately, this route poses two problems. First, the low boiling point of fluoroform (−82.2 °C) creates – at least on the laboratory scale – the practical problem of handling a gas. The second problem is the need to trap and stabilize the trifluoromethyl anion immediately after its generation, to suppress fragmentation. This second complication, in particular, impeded the apparently straightforward preparative



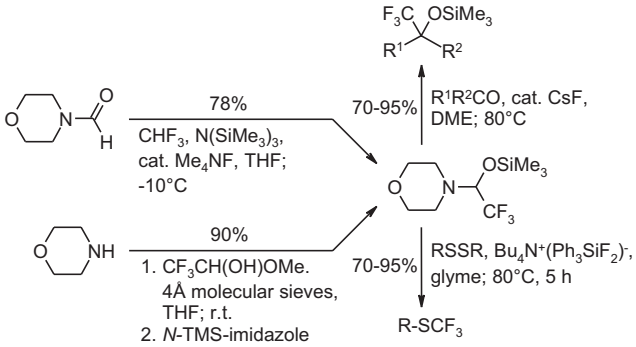
Scheme 2.123 Nucleophilic perfluoroalkylation by reductive activation of perfluoroalkyl iodides with TDAE [57, 58].

use of CHF_3 for several years [60]. Persistent work on this challenging subject [61] showed that if DMF is used as solvent in combination with a strong base (KO*t*Bu, $KN(SiMe_3)_2$, DMSO/KH), CF_3^- is trapped by the DMF and the resulting stable hemiaminolate can be used as a reservoir of nucleophilic trifluoromethide anion [62] (Scheme 2.124).



Scheme 2.124 Syntheses making use of CHF_3 in combination with DMF as a source of nucleophilic "CF_3^-" [59]. The yields for different base systems B^- are: KO*t*Bu 95 %, $KN(SiMe_3)_2$ 79 %, $N(SiMe_3)_3$ (1.5 equiv.)/Me_4NF (1.5 equiv.) 72 %.

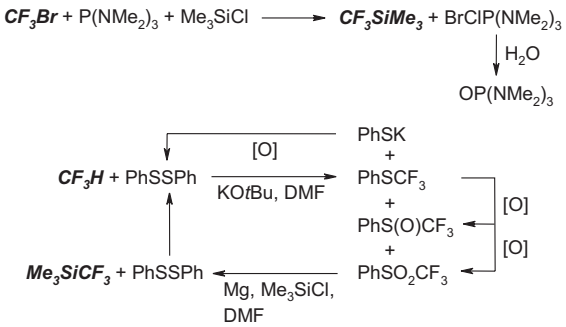
This CHF_3/DMF methodology was recently extended by the addition of related hemiaminals (readily accessible by reaction of fluoral methylhemiacetal with morpholine or *N*-benzylpiperazine) which are useful, stable, and inexpensive starting materials for a variety of fluoroorganic compounds [63] (Scheme 2.125).



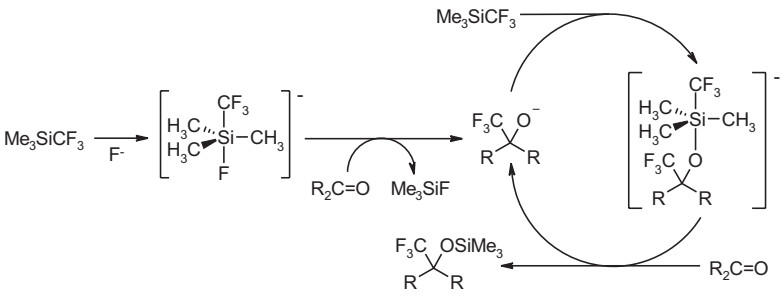
Scheme 2.125 Synthesis of trifluoroacetaldehyde hemiaminal derivatives and their use as nucleophilic trifluoromethylation reagents (TMS = trimethylsilyl) [59].

2.2.2.3 **Perfluoroalkyl Silanes**

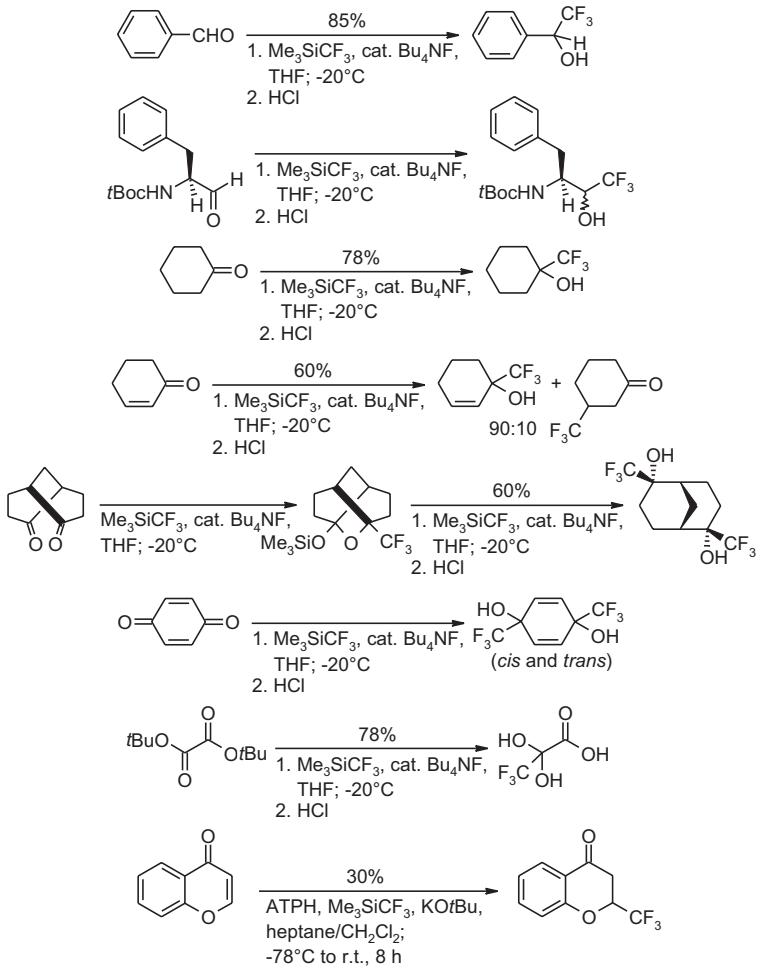
In the last few years, Me_3SiCF_3 and its higher perfluoroalkyl homologues have become probably the most popular nucleophilic perfluoroalkylation reagents [64]. Me_3SiCF_3, sometimes called Ruppert's Reagent, was first synthesized by I. Ruppert and coworkers in 1984 [2c] but its extraordinary value as a nucleophilic trifluoromethylation reagent was recognized and systematically developed by G. K. S. Prakash and coworkers [65]. The substance class owes its attraction to its stability, ease of its handling (b. p. 54–55 °C for Me_3SiCF_3), and the versatility of the reactions which can be achieved highly conveniently. Me_3SiCF_3 can be prepared by reaction of CF_3I or CF_3Br with Me_3SiCl in the presence of a variety of reducing agents, for example $P(NMe_2)_3$ [66], TDAE [57, 58], or aluminum [67]. The synthesis of CF_3Br by electrochemical reduction in the presence of Me_3SiCl has also been reported [68] (Scheme 2.126).



Scheme 2.126 Preparation of trifluoromethyltrimethyl silane (Me_3SiCF_3, Ruppert's Reagent). Ruppert's original method [2c] (*above*) leads, after aqueous work-up, to the formation of stoichiometric amounts of the carcinogenic HMPA ($OP(NMe_2)_3$). In addition, ozone-depleting CF_3Br is used as the starting material. A recent method (*below*), with potential for technical upscale, utilizes the inexpensive CHF_3 and depends on a catalytic cycle initiated by diphenyldisulfide [69].



Scheme 2.127 Mechanism of the nucleophilic trifluoromethylation of carbonyl compounds by Me_3SiCF_3 [59, 65].

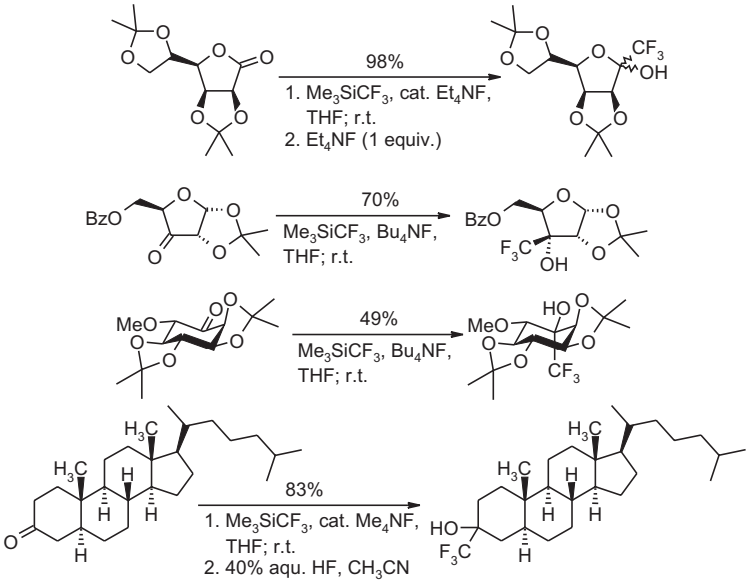


Scheme 2.128 Reaction of Me_3SiCF_3 with a variety of carbonyl compounds (ATPH = aluminum tri(2,6-bis(*tert*-butyl)phenoxide) [64b, 65, 73].

Under catalysis by fluoride ions, *tert*-butylate or other Lewis bases [70], Me_3SiCF_3 can transfer "CF_3^-" equivalents in high yields to a large variety of electrophilic substrates. The mechanism of this transfer involves the formation of "carbanionoid" alkoxy trimethyl trifluoromethyl siliconate species, which add their trifluoromethyl moiety to carbonyl groups in a self-activating chain reaction which is initiated by a small amount of fluoride ions (5–10 mol%) [65] (Scheme 2.127). Some of the intermediate siliconate species have been isolated and characterized either by NMR or X-ray crystallography [71, 72]. Remarkably, in contrast with most other organosilicon reagents the addition reaction cannot be initiated by Lewis acid catalysts.

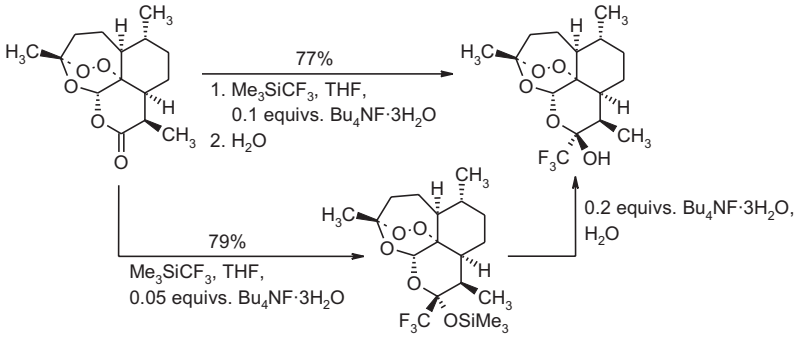
Nucleophilic addition of the trifluoromethyl group to aldehydes, ketones and other carbonyl compounds leads primarily to the corresponding trimethylsilyl ether; this must subsequently be hydrolyzed to the alcohol. Because typical reaction conditions are very mild, the method is widely applicable, even for sensitive substrates. In contrast with most other methods, fluoride-induced perfluoroalkylation via silicon compounds also works for enolizable carbonyl compounds. With α,β-unsaturated substrates 1,2-addition directly to the carbonyl group is strongly preferred [64b]. If the oxygen is coordinated to a bulky Lewis acid, for example aluminum tri(2,6-bis(*tert*-butyl)phenoxide (ATPH), the 1,4-addition products are obtained selectively [73f] (Scheme 2.128).

Since the original report on the utility of Me_3SiCF_3 in 1989 [65], the general method has been widely used for synthesis of trifluoromethylated analogs of a variety of natural products, for example carbohydrates, nucleotides [74], and steroids (Scheme 2.129).



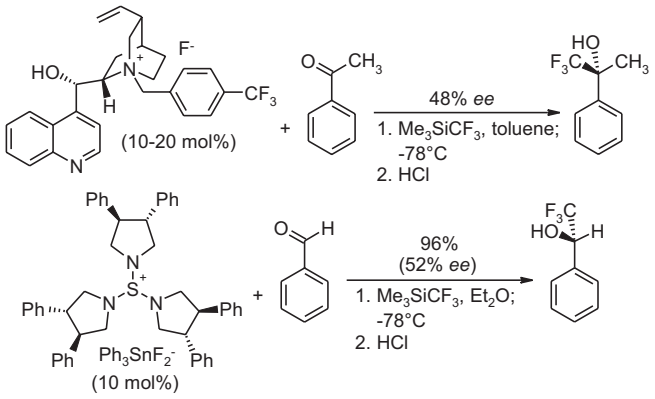
Scheme 2.129 Use of Me_3SiCF_3 for the synthesis of carbohydrate analogs and steroids containing a trifluoromethyl group [75].

Another recent application of the reagent, in the pharmaceutical chemistry, is the trifluoromethylation of the antimalarial compound artemisinin, with the aim of improving the pharmacological profile of the natural compound [76] (Scheme 2.130).



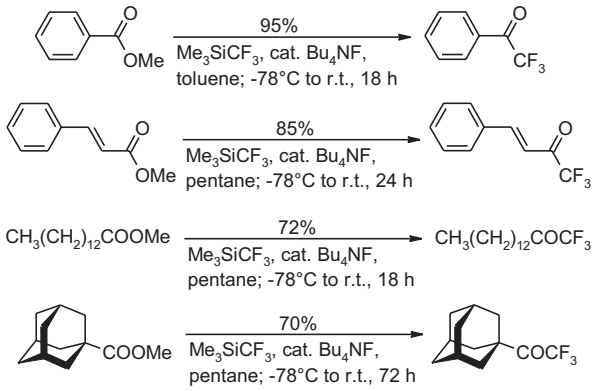
Scheme 2.130 Nucleophilic trifluoromethylation of artemisinin to the β-trimethylsilyl ether as the kinetic primary product and the α-trifluoromethyl hemiketal as the thermodynamic final product after desilylation [76].

Use of chiral fluoride sources at low reaction temperatures opens – at least in principle – a route to enantioselective nucleophilic trifluoromethylation of prochiral carbonyl compounds [77, 78] (Scheme 2.131). Enantiomeric excesses obtained so far by this method are, however, low to moderate only.



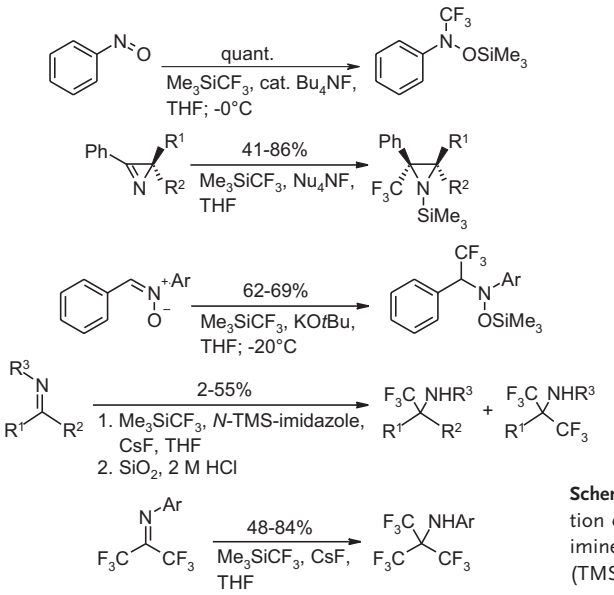
Scheme 2.131 Enantioselective nucleophilic trifluoromethylation of prochiral carbonyl compounds with chiral fluoride sources [78].

If – instead of the usual polar ether – a non-polar solvent such as toluene, pentane, or dichloromethane is used as the reaction medium, clean conversion of a large variety (aromatic, aliphatic, non-enolizable, and enolizable) of esters to the corresponding trifluoromethyl ketones can be achieved [79] (Scheme 2.132).



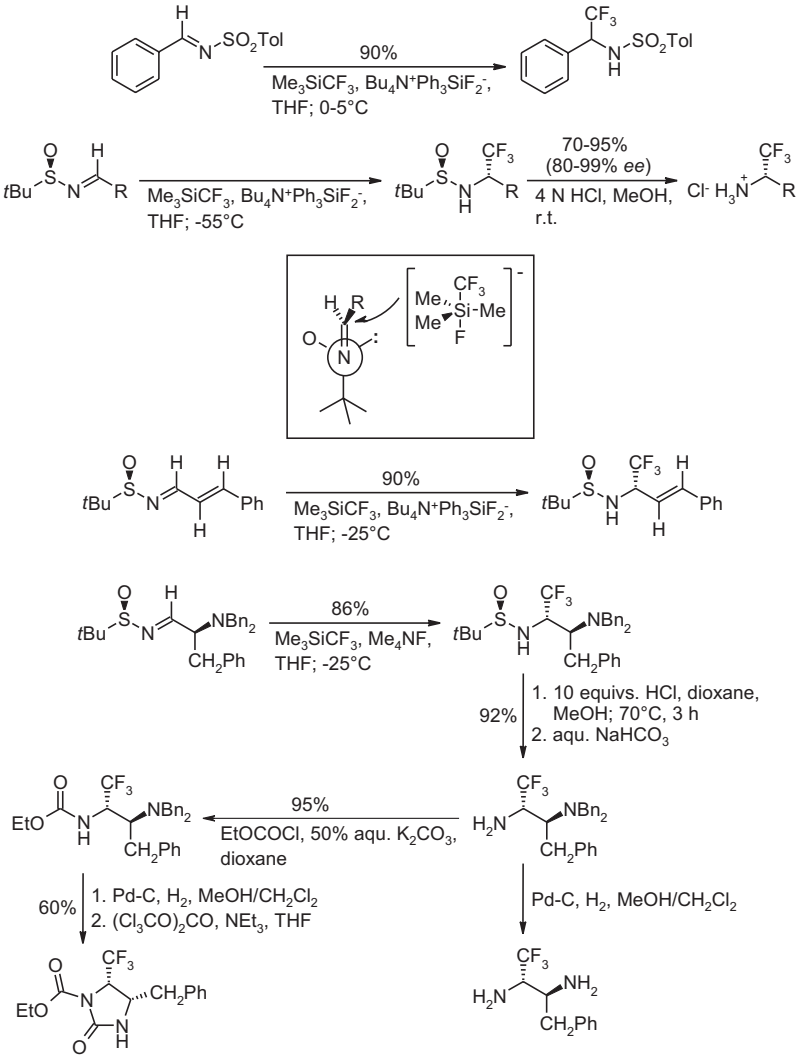
Scheme 2.132 Preparation of trifluoromethyl ketones from esters with Me_3SiCF_3 [79].

Although most carbonyl compounds are sufficiently electrophilic to be reactive toward Me_3SiCF_3, most nitrogen electrophiles have to be activated in some way to make them susceptible toward nucleophilic attack. Nitrosobenzene, the most simple heteroanalogous "carbonyl" compound, smoothly adds Ruppert's reagent to yield a product which is analogous to the normal carbonyl addition product [80]. Imines, on the other hand, are generally not reactive under the same conditions. They must be activated either by steric strain, for example the aziridines [81], or by electron-withdrawing substituents at the nitrogen (for example nitrones) [82] or at the electrophilic carbon center [83]. Non-activated imines might also be reacted in low to moderate yields by use of *N*-trimethylsilylimidazole as an additional activator [84] (Scheme 2.133).



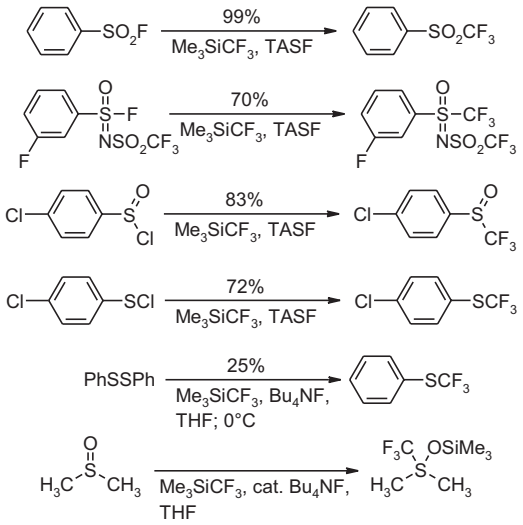
Scheme 2.133 Trifluoromethylation of nitrogen electrophiles, imines, and related compounds (TMS = trimethylsilyl) [80–84].

Reversible activation of an imine is achieved by use of the tosyl group, which can be removed after trifluoromethylation to furnish α-trifluoromethylamines [85]. The *N*-sulfenyl group also leads to sufficient activation of the imino moiety. Thus, via the readily available chiral *N*-sulfenimines stereoselective trifluoromethylation is possible with high diastereoselectivity. The resulting sulfenamines can be hydrolyzed and converted to chiral amines carrying a trifluoromethyl group; these are of growing interest as intermediates for pharmaceutical chemistry [86] (Scheme 2.134).



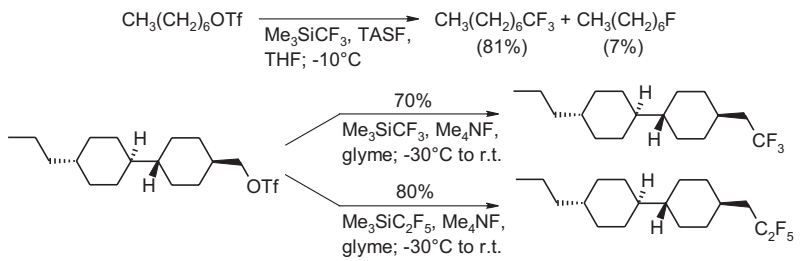
Scheme 2.134 Nucleophilic trifluoromethylation of *N*-tosyl aldimines and chiral sulfinimines [85, 86]. The mechanistic rationalization of the observed stereoselectivity of the addition to chiral sulfinimines is sketched in a box.

By use of a similar synthetic procedure Me_3SiCF_3 can also be employed as a reagent for nucleophilic trifluoromethylation of a variety of sulfur electrophiles (Scheme 2.135). The other way around, Prakash and coworkers demonstrated, that trifuoromethyl sulfones can also be used as a source of nucleophilic "CF_3^-" equivalents when they are treated with alcoholates [69]



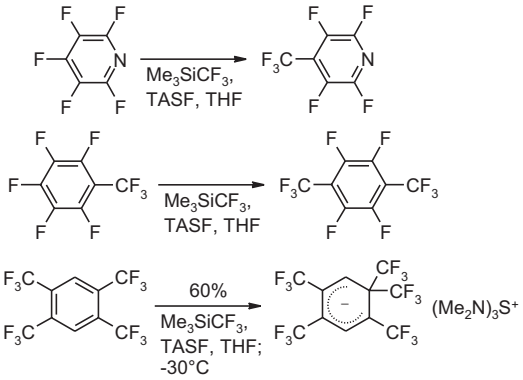
Scheme 2.135 Reaction of Me_3SiCF_3 with sulfur electrophiles [87–89].

If equimolar quantities of tetramethylammonium fluoride and a threefold excess of Me_3SiCF_3 or its homologues are used the perfluoroalkyltrimethyl silane acts as an effective source of nucleophilic perfluoroalkyl equivalents for nucleophilic substitution of aliphatic triflates [90] (Scheme 2.136). This method enables the simple synthesis of partially fluorinated alkane structures which are of interest in the chemistry of liquid crystals and other functional materials.



Scheme 2.136 Perfluoroalkylation with Me_3SiCF_3 and its homologue $Me_3SiC_2F_5$ by nucleophilic substitution of alkyl triflates (glyme = ethyleneglycol dimethyl ether) [90].

A similar method of activation of the perfluoroalkyl silane is used for nucleophilic addition or substitution of trifluoromethyl moieties to obtain electron-deficient fluorinated aromatic compounds [91] (Scheme 2.137).



Scheme 2.137 Aromatic nucleophilic substitution and *ipso*-addition with a variety of "R_F^-" sources [91].

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2.2.3
"Electrophilic" Perfluoroalkylation

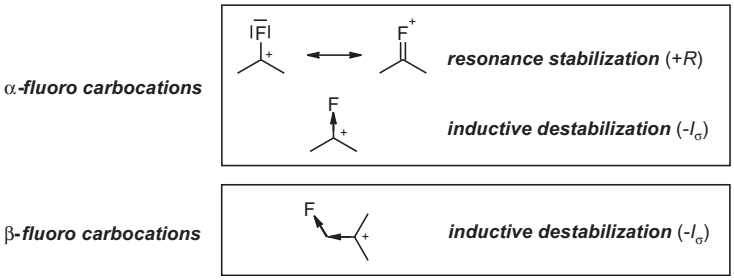
As already discussed in Section 2.2.1, perfluoroalkyl halides do not act as effective electrophilic perfluoroalkylation reagents, as might be expected by analogy with the reactivity of alkyl halides. Even if some "electrophilic" perfluoroalkylation reactivity is mimicked with some especially suitable (i. e. easily oxidizable) substrates by an electron-transfer-induced radical mechanism, the practical usefulness of this reaction pathway is limited to very few examples.

2.2.3.1 Properties and Stability of Fluorinated Carbocations

The stability of fluorinated carbocations [1] is determined by a delicate equilibrium between inductive destabilization and mesomeric stabilization of the positive charge. α-Fluoro substituents stabilize the positively charged carbon by π-donation

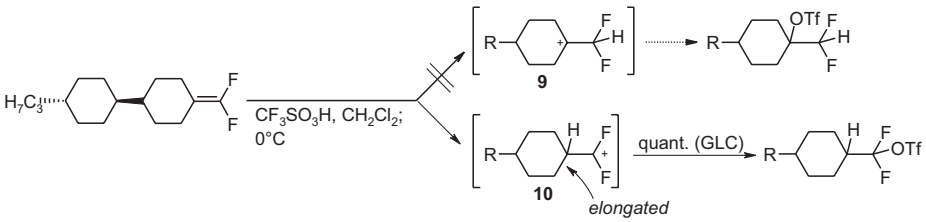
(+*R*) from their lone electron pairs. The charge is, on the other hand, destabilized by the negative inductive ($-I_\sigma$) effects from α-fluorine.

Fluorine substitution in the position β to the positive carbon exerts a strongly destabilizing inductive ($-I_\sigma$) effect only (Scheme 2.138).



Scheme 2.138 Stabilizing and destabilizing effects for fluorinated carbocations.

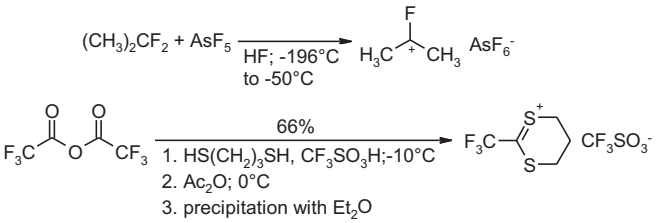
The strongly stabilizing effect of α-fluorine on carbocations is well demonstrated by the reactivity of *exo*-difluoromethylene cyclohexane toward triflic acid. Initial protonation of the double bond forms only the cyclohexyldifluoromethyl cation, in contrast with the usually observed high stability of trialkyl carbocations. Molecular modeling (B3LYP/6-31G*//B3LYP/6-31G* level of theory) indicates stabilization of 3.3 kcal mol^{-1} in favor of the former cation [2]. In this case cation **9** is stabilized by $+I_\sigma$ effects from the alkyl substituents and some hyperconjugation from the α-C–H bonds. It is, on the other hand, inductively destabilized ($-I_\sigma$) by the two β-fluorines. The cation **10** is stabilized by π-donation (+*R*) from two α-fluorines, by σ-donation ($+I_\sigma$) from the cyclohexyl group and also by hyperconjugation from one of the α,β-C–C bonds in the cyclohexane. The hyperconjugation is also reflected by the unusually long C–C bond (163 pm; B3LYP/6-31G*) (Scheme 2.139).



Scheme 2.139 The reactivity of *exo*-difluoromethylene cyclohexane derivatives toward triflic acid nicely illustrates the strongly stabilizing effect of α-fluoro substituents on carbocations [2]. The elongated C–C bond mirrors the contribution of C–C hyperconjugation to the stabilization of the cation **10**.

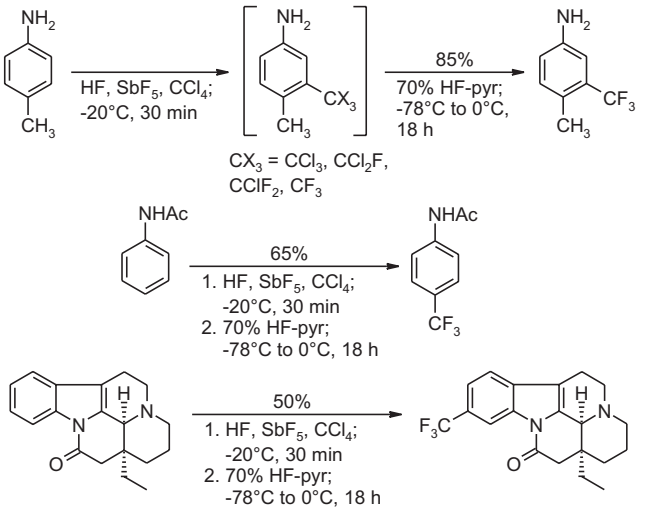
Because of their strong inductive destabilization, few salts of α- or β-fluorocarbenium ions have been isolated and characterized. Despite persistent attempts to isolate salts of the CF_3^+ cation, this most simple α-fluorocarbenium ion has so far only been subject of numerous theoretical studies [3]. Recently, the more stable dimethylfluorocarbenium ion, in the form of its hexafluoroarsenate salt ($Me_2CF^+AsF_6^-$), has been characterized by X-ray crystallography [4].

For β-fluorocarbenium ions also, very few examples have been isolated as their salts and fully characterized; all were additionally stabilized either by bonding to a metal center [5] or by α-substitution with stabilizing heteroatoms such as sulfur [6, 7] (Scheme 2.140).



Scheme 2.140 Representative examples of α- and β-fluorocarbenium salts which have been isolated and fully characterized [4, 7].

Although free trifluoromethyl cation salts have not yet been isolated and characterized, it is possible to generate a mixture of chlorofluoromethyl cations ($CF_xCl_{3-x}^+$) *in situ* from carbon tetrachloride and strong Lewis acids [8]. These systems can be used for electrophilic trihalomethylation of electron-rich aromatic substrates. The remaining chlorine substituents are substituted by fluorine with 70 % HF–pyridine (Scheme 2.141).

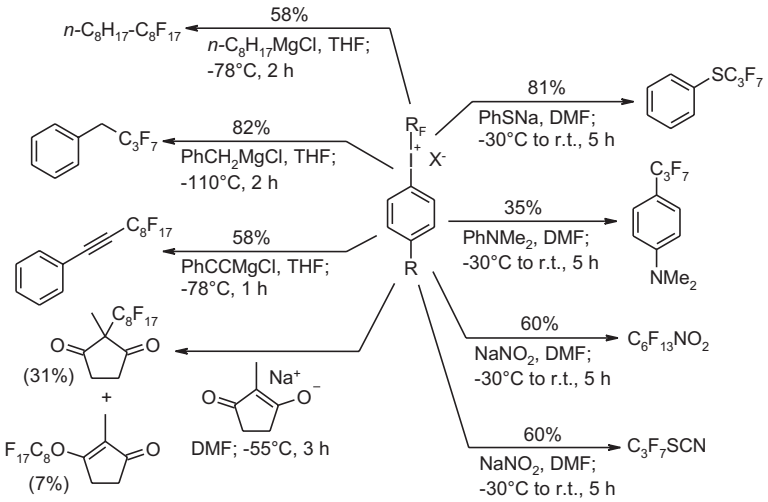


Scheme 2.141 Electrophilic trifluoromethylation of activated aromatic substrates by an HF/CCl_4/SbF_5 system and subsequent treatment with 70 % HF–pyridine [8].

2.2.3.2 Aryl Perfluoroalkyl Iodonium Salts

Because of their extremely high group electronegativity (e. g. 3.45 for the CF_3 group, compared with only 3.0 for chlorine) [9], perfluoroalkyl groups cannot be expected to be transferred by a truly electrophilic mechanism from their corresponding halides to non-oxidizable nucleophiles. If, on the other hand, the group electronegativity of the leaving group X of a potential perfluoroalkylation reagent R_FX is increased until it matches or exceeds this high value for R_F, then a process at least similar to electrophilic perfluoroalkylation becomes feasible [10].

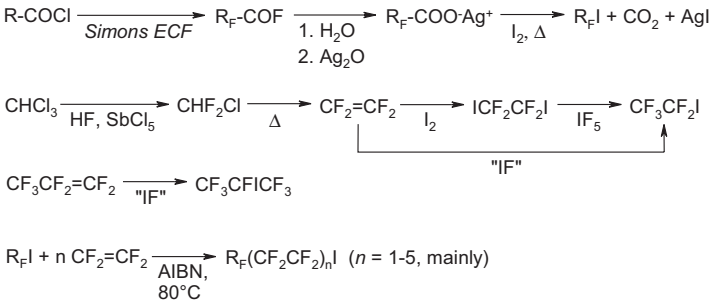
This general concept was used by Yagupolskii and coworkers [11], when they achieved for the first time electrophilic perfluoroalkylation of a variety of nucleophiles using aryl perfluoroalkyl iodonium chlorides as reagent. Later, the corresponding tetrafluoroborates were reported to be even more reactive [12]. Similar reactivity is observed for the corresponding triflates (also known as FITS reagents, perfluoroalkyl phenyl iodonium trifluoromethanesulfonates) introduced by T. Umemoto's group [13] (Scheme 2.142).



Scheme 2.142 Examples of the reactivity of aryl perfluoroalkyl iodonium reagents (reactions on the *left*: R = H, X = OTf; *right*: R = CH_3, X = Cl) [10].

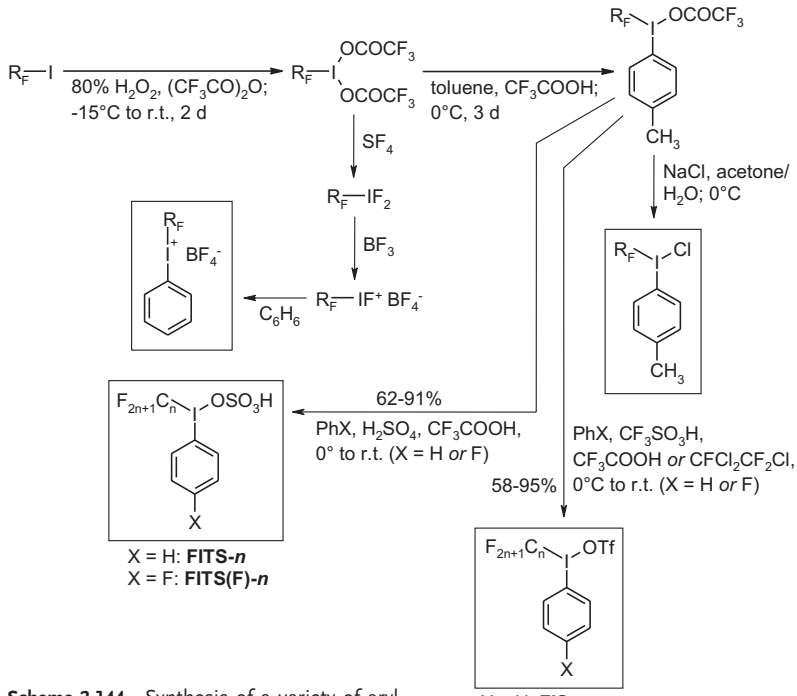
Starting materials for the synthesis of all perfluoroalkyl iodonium reagents are the perfluoroalkyl iodides, which themselves play a central role as building blocks in fluoroorganic chemistry. The iodides are available either by pyrolysis of the silver salts of perfluoroalkyl carboxylic acids in the presence on iodine [14] or – on a more technical scale – by iodofluorination of tetrafluoroethylene [15] with the iodine–IF_5 system [16] and subsequent radical telomerization of tetrafluoroethylene with the resulting intermediate perfluoroalkyl iodides [17] (Scheme 2.143).

The perfluoroalkyl iodides are subsequently oxidized to the bis(trifluoroacetates) or to the difluoroiodides, which again are reacted with a suitable arene in an elec-



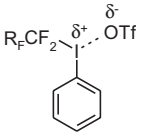
Scheme 2.143 Synthesis of perfluoroalkyl iodides by the Hunsdiecker route (*top*), based on the electrochemical fluorination of carboxylic acid derivatives ($R_F = CF_3{\sim}(CF_2)_9CF_3$) and the industrial telomerization route (*bottom*) based on tetrafluoroethylene as the central intermediate.

trophilic substitution. The resulting intermediates are converted into the chlorides or tetrafluoroborates (Yagupolskii's reagents) or into triflates or hydrogen sulfates (Umemoto's reagents). The covalent or ionic character of the different iodonium salts depends strongly on the electronegativity and nucleofugicity of the counterion X^- (Scheme 2.144).



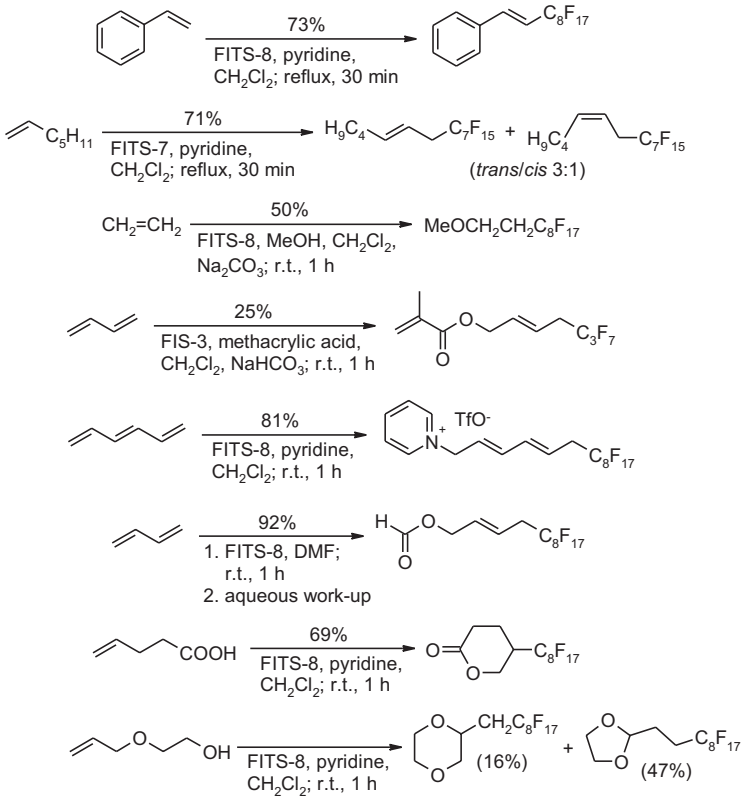
Scheme 2.144 Synthesis of a variety of aryl perfluoroalkyl iodonium salts [10].

According to the ^{19}F NMR chemical shifts of the α-CF_2 group, the ionic character of the iodine–X bond increases for substituents X in the order Cl < OSO_2CH_3 < OSO_3H < OTf. Even for the most electronegative triflate group the I–OTf bond is strongly polarized but not really ionic in nature [13c] (Scheme 2.145).



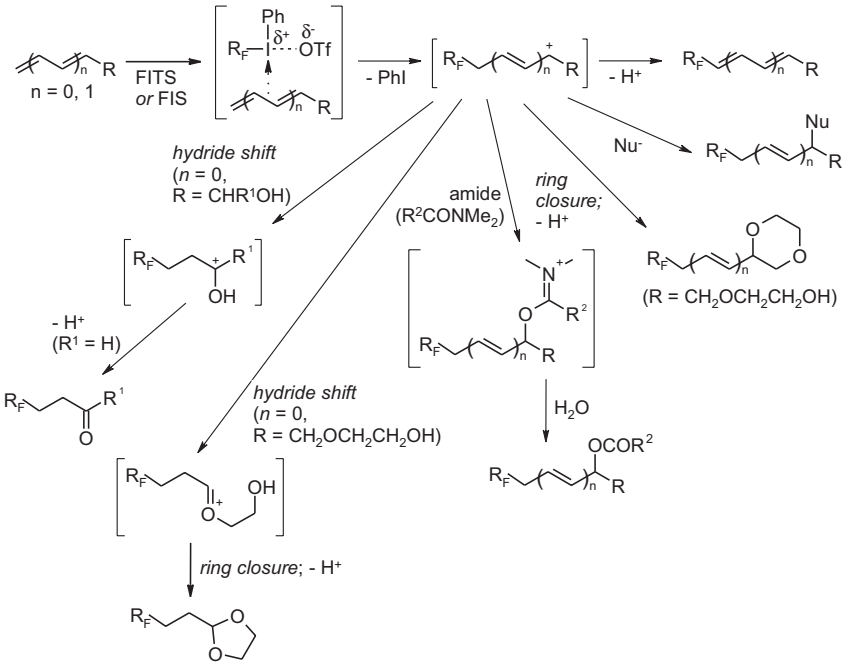
Scheme 2.145 For aryl perfluoroalkyliodonium reagents – even for the triflates – the iodine–counterion bond is strongly polarized but not completely ionic [13c].

Interestingly, the most basic of the iodonium reagents, aryl trifluoromethyl iodonium salts, are still unknown. They cannot be prepared by the methods outlined in Scheme 2.144. The presumed reason for this unexpected fact is the low stability of the carbon–iodine bond of their potential synthetic precursors CF_3IF_2 or CF_3IO, compared with their analogs with two or more carbon atoms in the perfluoroalkyl chain [18].



Scheme 2.146 Examples of the electrophilic perfluoroalkylation of olefins with FITS reagents [19].

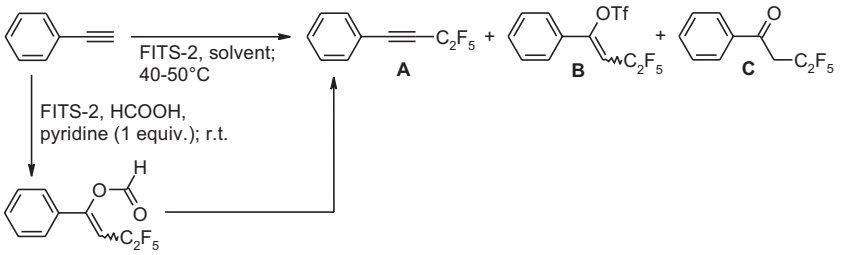
In addition to the arenes, enolates, and other nucleophiles depicted in Scheme 2.142, FITS reagents are also reactive in the perfluoroalkylation of unactivated alkenes, alkadienes [19], and acetylenes [20] (Scheme 2.146). In contrast with olefin perfluoroalkylation by means of perfluoroalkyl bromides or iodides (Section 2.2.1), this reaction does not follow a free radical mechanism but proceeds via cationic intermediates which can be either trapped by addition of nucleophiles or nucleophilic solvents or quenched by β-deprotonation with a base (Scheme 2.147).



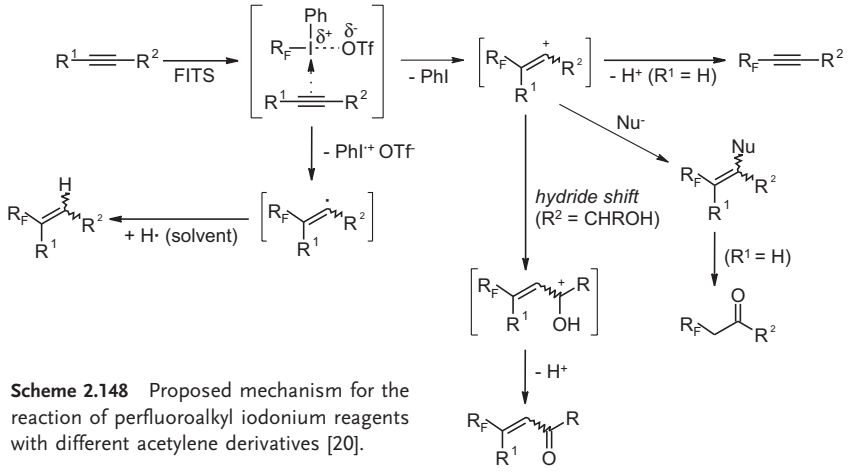
Scheme 2.147 Ionic mechanism of the reaction of FITS and related reagents with olefins [10].

A mechanism taking either an ionic or a radical path, depending on the solvent, is assumed for the reaction of perfluoroalkyl iodonium reagents with acetylenes [20], leading to a variety of addition or substitution products (Table 2.3 and Scheme 2.148).

Table 2.3 Reaction of phenylacetylene with the FITS-2 reagent in different solvents with or without addition of pyridine as a base [20].



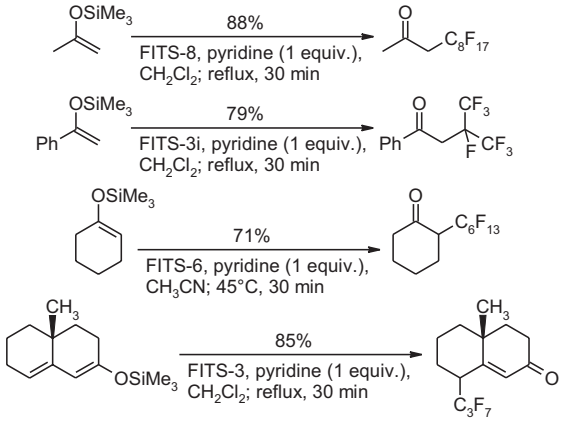
Solvent	*Additive*	*A*	*B*	*C*
CH_2Cl_2	Pyridine	47	36	4
CH_2Cl_2	–	15	31	51
DMF	–	45	0	0
MeOH	–	100	0	0
HCOOH	–	4	0	86



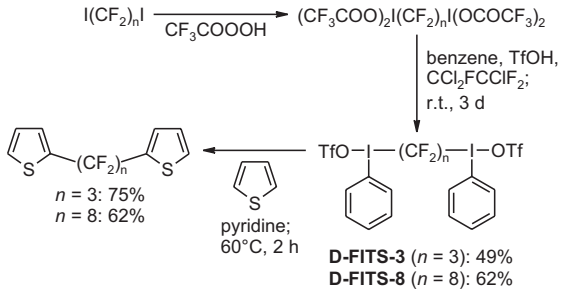
Scheme 2.148 Proposed mechanism for the reaction of perfluoroalkyl iodonium reagents with different acetylene derivatives [20].

Of special importance for introduction of perfluoroalkyl groups into pharmaceuticals and for synthesis of perfluoroalkylated analogs of natural products is the reaction of FITS reagents with silyl enol ethers, leading to α-perfluoroalkyl carbonyl compounds [21] (Scheme 2.149).

Perfluoroalkyl iodonium salts are also available as bivalent perfluoroalkylation reagents enabling the introduction of bridging perfluoroalkylene groups between nucleophilic precursors in one synthetic step [22] (Scheme 2.150).

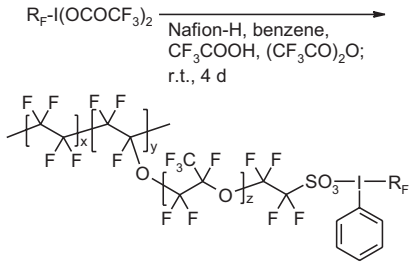


Scheme 2.149 Perfluoroalkylation of silyl enol ethers with different FITS reagents [21].



Scheme 2.150 Synthesis and preparative use of perfluoroalkylene FITS reagents [22].

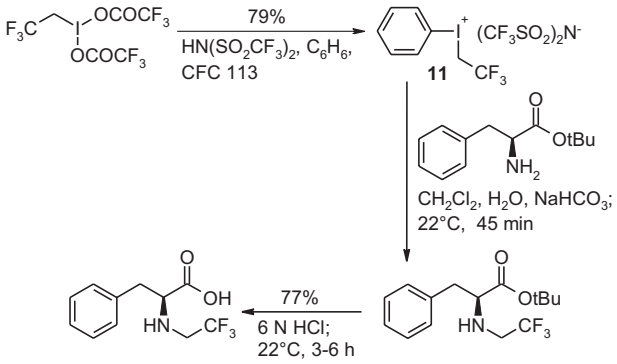
The synthesis of FITS reagents poses two principal difficulties: (1) isolation of the FITS reagent from the reaction mixture often requires repeated yield-reducing recrystallization steps; and (2) recovery of the expensive triflic acid obtained during the synthesis is difficult. A solution to these problems was found in the immobilization of the reagents [23] by means of a solid analog of triflic acid – Nafion-H resin [24] (Scheme 2.151).



Scheme 2.151 A Nafion-based polymeric version of FITS facilitates work-up of the reaction mixtures after electrophilic perfluoroalkylation. The effective concentrations of perfluoroalkyl groups of different chain lengths are approximately 0.4 mmol g^{-1} [23].

Highly effective electrophilic trifluoroethylation and 1*H*,1*H*-perfluoroalkylation reagents are available by means of a similar iodonium-based concept, either as

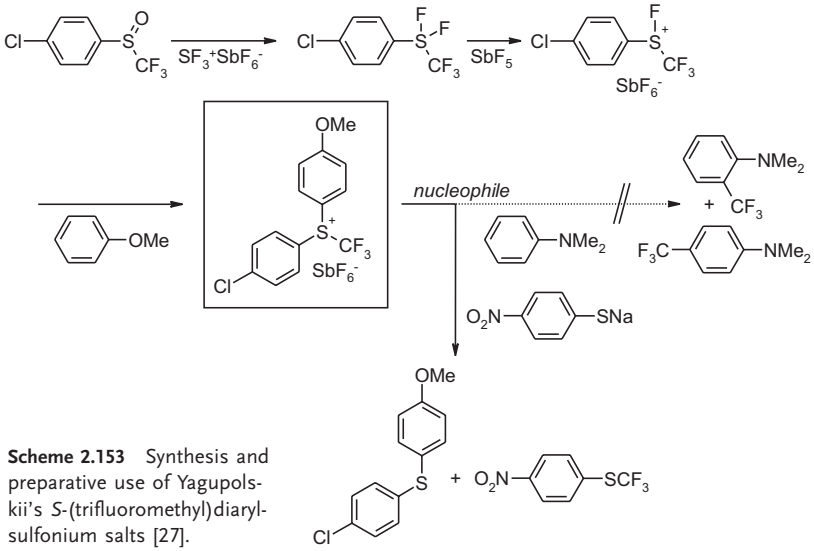
the triflates [25] or as the more hydrolytically stable triflimides [26]. Because of its resistance to hydrolysis, triflimide **11** can even be employed in aqueous reaction media, rendering it an interesting tool for biochemical applications [26c] (Scheme 2.152).



Scheme 2.152 Example of the synthesis of an aryl 1*H*,1*H*-perfluoroalkyl iodonium triflimide (**11**) which is sufficiently hydrolytically stable to electrophilically trifluoroethylate amino acids in an aqueous medium [26]. The *N*-trifluoroethyl substructure element has recently gained importance in medicinal chemistry as a means of blocking the oxidative metabolism of pharmaceuticals via the nitrogen site.

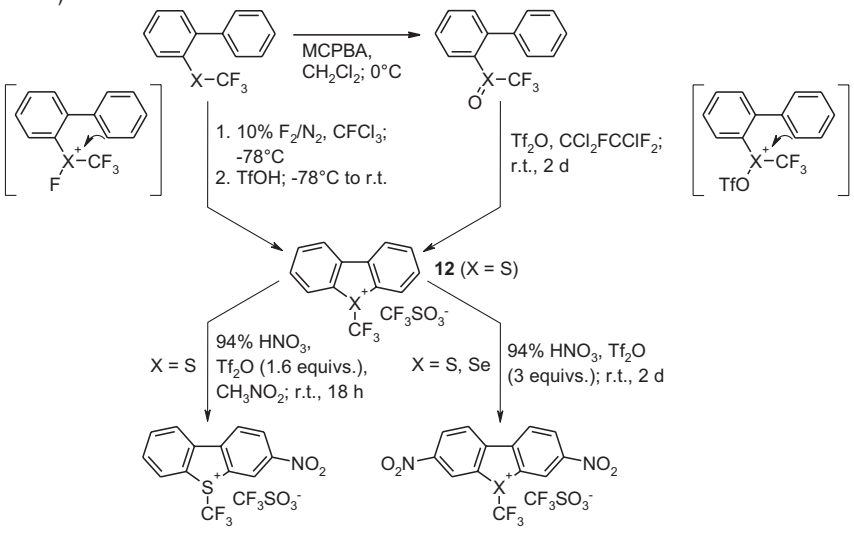
2.2.3.3 **Perfluoroalkyl Sulfonium, Selenonium, Telluronium, and Oxonium Salts**

A completely different class of electrophilic perfluorination reagents, the trifluoromethyldiaryl sulfonium salts, were introduced by Yagupolskii and coworkers [27] in 1984 (Scheme 2.153).

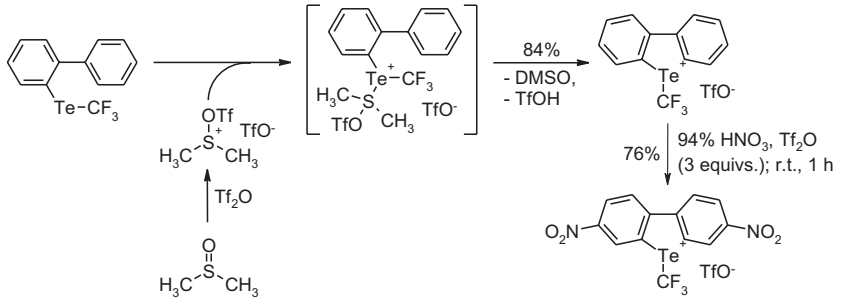


Scheme 2.153 Synthesis and preparative use of Yagupolskii's *S*-(trifluoromethyl)diarylsulfonium salts [27].

The first generation of sulfonium-based trifluoromethylation reagent (Scheme 2.153) was very effective for trifluoromethylation of thiolates (e. g. sodium 4-nitrothiophenolate) but they failed to trifluoromethylate electron-rich aromatic substrates such as *N*,*N*-dimethylaniline, even at elevated temperatures. Taking the step from an open diarylsulfonium to a cyclic dibenzothiophenium system, Umemoto and coworkers, at the beginning of the 1990s, developed a class of reagent with significantly larger trifluoromethylation power [28]. The concept was subsequently extended to trifluoromethyl dibenzoselenophenium, dibenzotellurophenium, and even dibenzofuranium systems, furnishing a whole range of power-variable electrophilic trifluoromethylation reagents (Schemes 2.154 and 2.155).

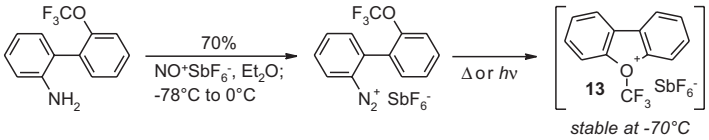


Scheme 2.154 Synthesis of trifluoromethyldibenzothiophenium and -selenophenium triflates (X = S, Se) and their subsequent nitration [28b]. On the *extreme left* and the *extreme right*, the reactive sulfonium intermediates for both synthesis routes are depicted undergoing ring-closure by intramolecular electrophilic substitution.



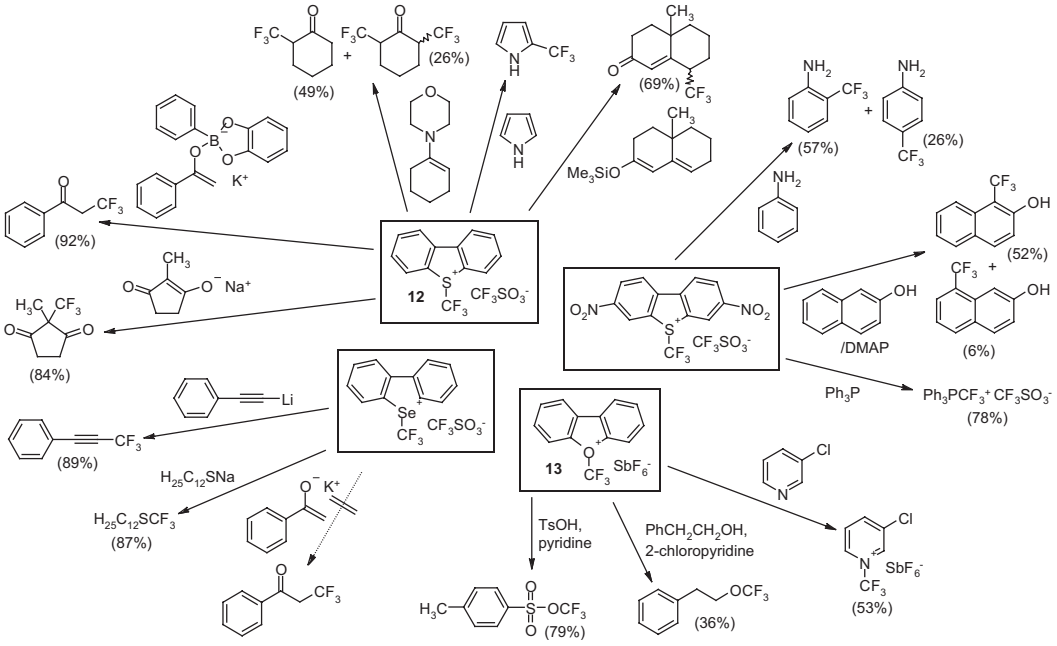
Scheme 2.155 Synthesis of trifluoromethyl dibenzotellurophenonium-based reagents. Here, the cyclization reaction is initiated by the electrophilic attack of pre-generated sulfonium species on the trifluoromethyltelluride moiety [28b].

Umemoto's series of reagents is based on leaving groups with different electronegativity. This variation is caused, on the one hand, by the different chalconium centers and, on the other hand by mono- or dinitration. The mildest trifluoroalkylating reagents are the telluronium systems, which are able to trifluoromethylate very "soft" and polarizable nucleophiles. The most reactive species is the dibenzofuranium system **13** which has to be generated *in situ* from a diazonium salt precursor (Scheme 2.156). This system trifluoromethylates even very "hard" nucleophiles, for example aliphatic alcohols or *p*-toluenesulfonic acid. Within the different classes of onium reagents their trifluoromethylating power can be up-tuned stepwise by mono- or dinitration.



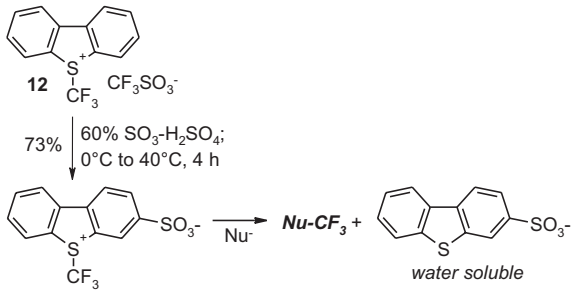
Scheme 2.156 Synthesis of Umemoto's most reactive trifluoromethylating reagent, the dibenzofuranium system **13**, which is generated *in situ* from the more stable diazonium salt precursor [10, 29].

In the same way as for the FITS reagents, the basic concept for the dibenzothiopenium reagents has been successfully extended to the electrophilic transfer of longer perfluoroalkyl chains [29].

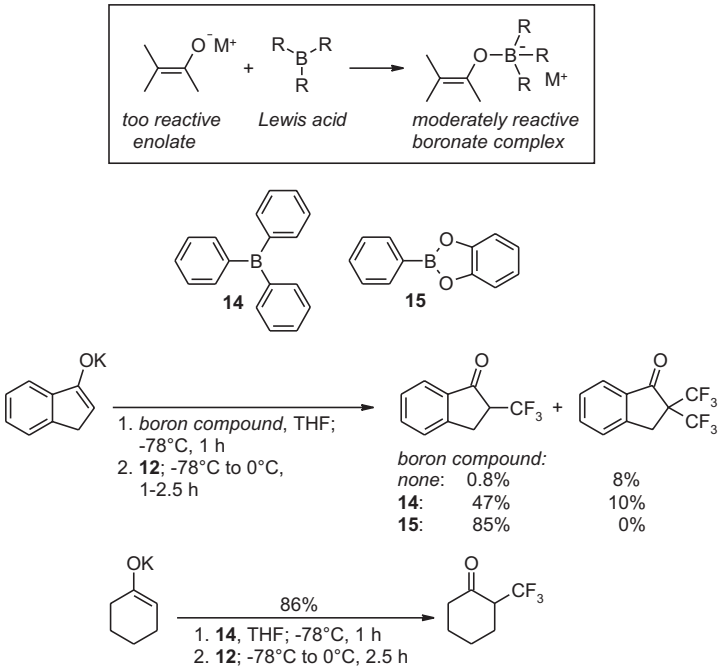


Scheme 2.157 Examples of applications of different types of Umemoto's reagent [29].

Umemoto's reagents are soluble and stable in a variety of polar solvents, for example DMSO, DMF, acetonitrile, THF, or CH_2Cl_2. A side product of the trifluoromethylation of any nucleophile is the formation of one equivalent of dibenzofuran, which is sometimes difficult to separate from the desired reaction product. To facilitate the work-up, zwitterionic dibenzothiophenium sulfonates were designed. Here, the side product is dibenzothiophene sulfonic acid, which can be conveniently removed from the reaction mixture by extraction with aqueous base [30] (Scheme 2.158).



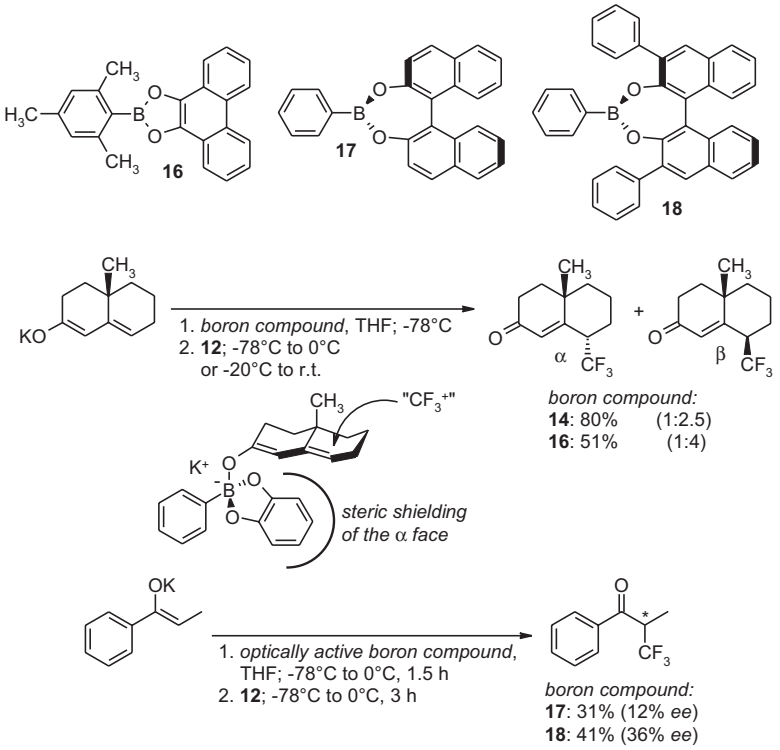
Scheme 2.158 Trifluoromethylation with sulfonated Umemoto's reagents facilitate work-up of the reaction mixtures [30].



Scheme 2.159 α-Trifluoromethylation of carbonyl compounds via boronate complexes of the enolates [31].

Although most nucleophiles, ranging from very "soft" (e. g. thiolates) to quite "hard" (e. g. aliphatic alcohols) can be trifluoromethylated by one of Umemoto's onium reagents with matching reactivity, most early attempts at the synthetically important α-trifluoromethylation of carbonyl compounds via their alkali enolates failed (see also Scheme 2.157). These problems arose, presumably, because the reactivity of the enolates was too high, because of the delocalization of the negative charge. It was found that the excess reactivity could be moderated by addition of the enolate to a variety of benzene boronic esters and other organoboron compounds [31] (Scheme 2.159).

Sterically demanding boronic esters can be used to achieve diastereoselective trifluoromethylation of steroid substructures (Scheme 2.160). Chiral boronates act as effective auxiliaries for the enantioselective trifluoromethylation.

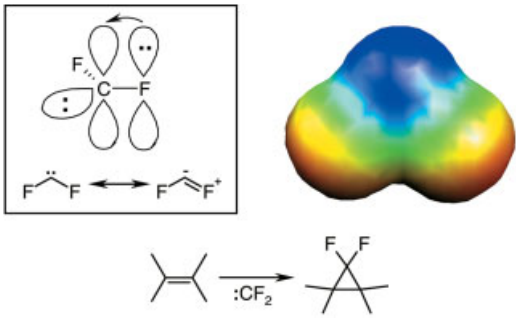


Scheme 2.160 Stereo- and enantioselective trifluoromethylations using bulky or chiral organoboron auxiliaries [31].

The mechanism of electrophilic trifluoromethylation with Umemoto's reagents is supposed to proceed via a charge-transfer complex between the onium salt and the nucleophilic substrate. The geometry of this charge-transfer complex finally governs the selectivity of the reaction, e. g. the preference for *ortho* or *para* trifluoromethylation of aniline. The exact mechanism of the transfer of the trifluoromethyl group from the onium system to the nucleophile has still to be elucidated in detail. Nevertheless, a nucleophilic S_N2 substitution at the CF_3 carbon can be ruled out for steric reasons [10], leaving mechanistic alternatives similar to those discussed for electrophilic fluorination or for the reactivity of FITS reagents.

2.2.4
Difluorocarbene and Fluorinated Cyclopropanes

The reactive species of choice for the synthesis of fluorinated cyclopropane derivatives are fluorinated carbenes [32] (Scheme 2.161). That most extensively used preparatively is difluorocarbene.

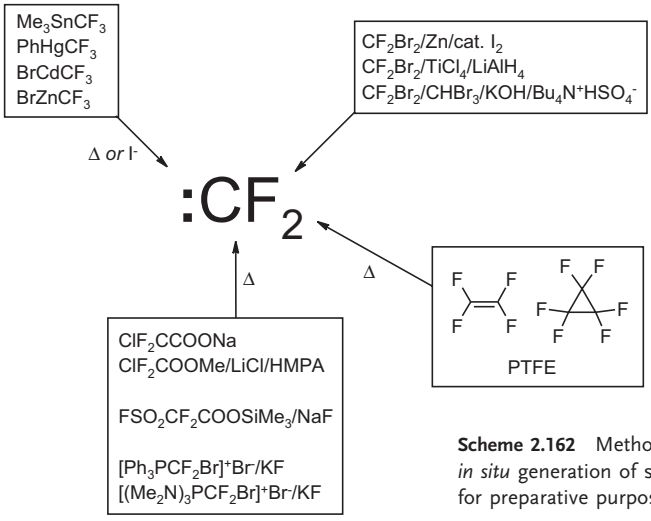


Scheme 2.161 Despite the resonance stabilization of singlet difluorocarbene by π-donation ($+R$) (*box*) from the α-fluorine atom, the carbon atom still has quite a large positive natural charge q_C of $+0.84$ e ($q_F = -0.42$ e), rendering the species moderately electrophilic (geometry optimization at the MP2/6-311+G* level of theory, electrostatic potential mapped on electron isodensity surface; blue and red denote positive and negative partial charges, respectively) [33, 34]. Difluorocarbene reacts readily with electron-rich olefins to yield *gem*-difluorocyclopropanes.

Despite the negative inductive effect of fluorine, because of its electronegativity, α-fluorinated carbenes are stabilized in their singlet state by π-donation from the fluorine to the carbon. This combination of destabilizing and stabilizing effects renders difluorocarbene a moderately electrophilic species [35].

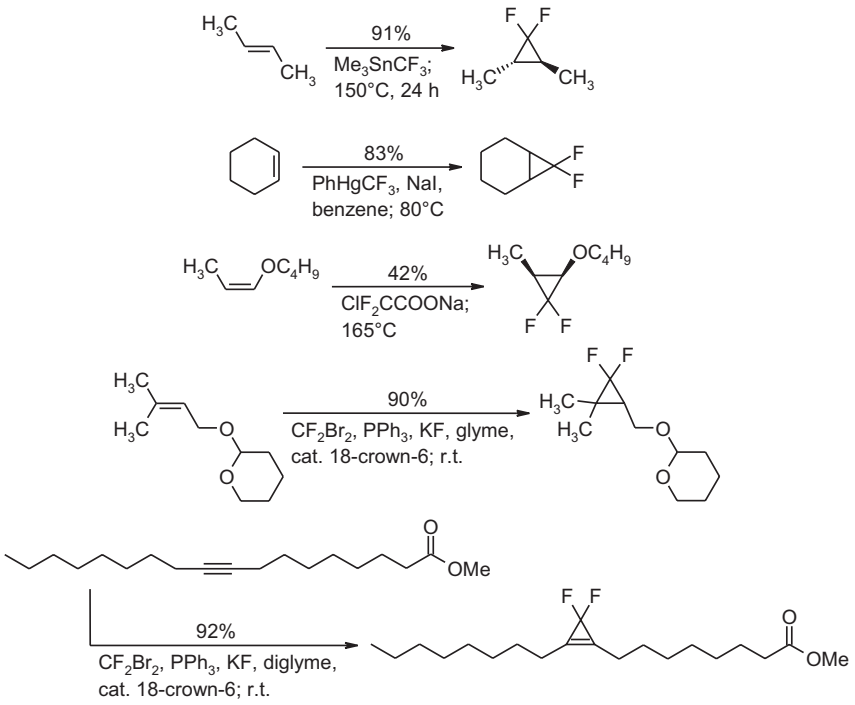
Several strategies are used for generation of difluorocarbene *in situ* for synthetic purposes. (1) The fragmentation of tin [36], mercury [37], cadmium or zinc trifluoromethyl [38] compounds works very reliably, but with the need to handle highly toxic (with the exception of zinc) heavy metal derivatives. (2) A very convenient method is the thermal fragmentation of alkali salts of halodifluoroacetic acids [39]. This second method has the disadvantage of requiring relatively high reaction temperatures which might not be compatible with a sensitive substrate for difluorocyclopropanation. A related, milder, variant of this type of reaction is the base- or fluoride-induced fragmentation of derivatives of fluorosulfonyldifluoroacetic acid (e. g. the $FSO_2CF_2COOSiMe_3/NaF$ system) [40], an intermediate from the technical production of Nafion resin. Another, widely used related fragmentation method is based on the thermolysis of halodifluoromethyl phosphonium salts [41]. (3) The third general method for generation of difluorocarbene is reduction of dihalodifluoromethanes by a variety of reducing agents [42].

In addition, difluorocarbene can be generated by thermolysis of a variety of perfluorocarbons (e. g. PTFE, tetrafluoroethylene, or perfluorocyclopropane) and HCFC (tetrafluoroethylene is technically produced by thermal elimination of hydrochloric acid from $CHClF_2$ via difluorocarbene as an intermediate) [32a] (Scheme 2.162).



Scheme 2.162 Methods commonly used for *in situ* generation of singlet difluorocarbene for preparative purposes [32a].

Difluorocarbene reacts readily with electron-rich olefins, giving the corresponding *gem*-difluorocyclopropanes, whereas its reactivity toward electron deficient olefins is much lower [43] (Scheme 2.163).

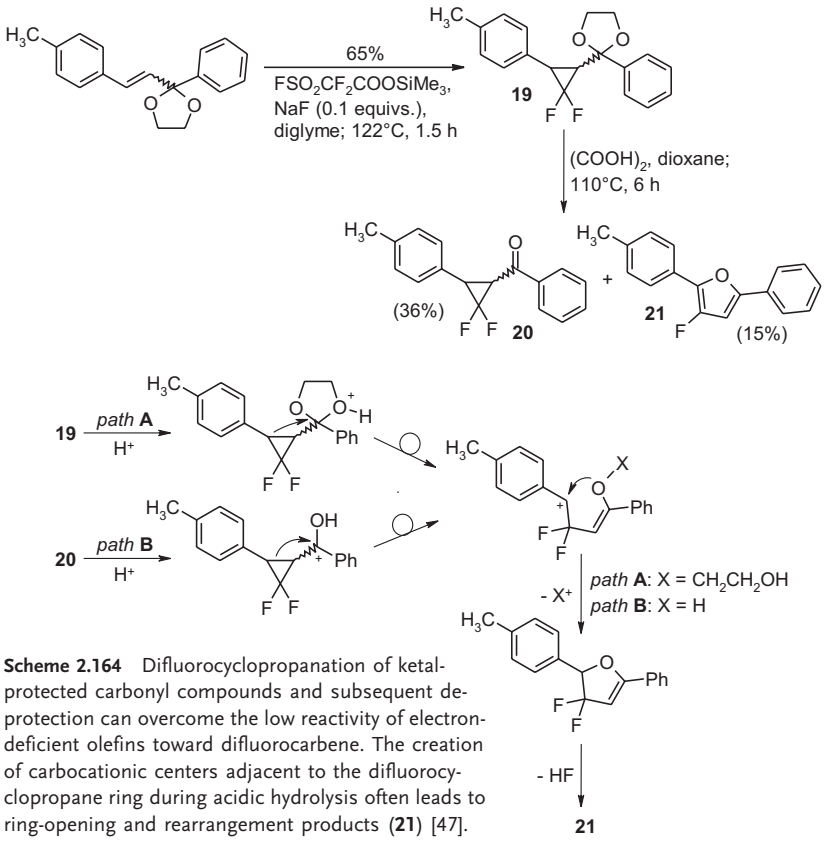


Scheme 2.163 Examples of the difluorocyclopropanation of olefins and acetylenes [37, 39a, 41c, 41d, 44, 45].

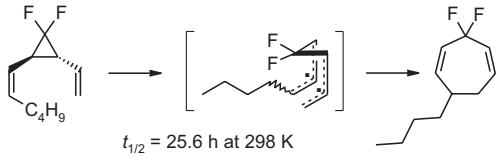
Using the difluorocarbene precursor $FSO_2CF_2COOSiMe_3$ [46] it was possible to difluorocyclopropanate even the relatively electron-deficient *n*-butyl acrylate in 73 % yield. Unfortunately, this reaction works with a quite limited number of electron-poor substrates only. Electron-withdrawing carbonyl groups must, therefore, usually be protected as less electronegative ketals during the difluorocyclopropanation step [47] (Scheme 2.164).

In a quite elegant reaction sequence, difluorocyclopropanation has been used as the initial step for subsequent [3,3]-sigmatropic rearrangement, leading finally to difluoroheptatrienes [43] which are not readily accessible by other means (Scheme 2.165).

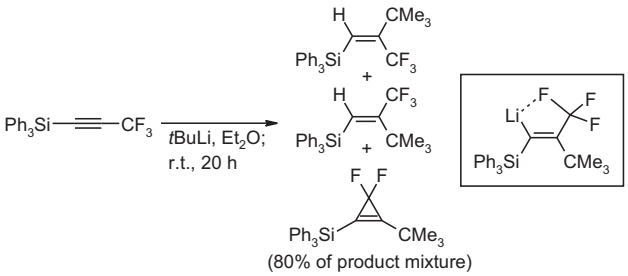
A recently published, alternative method for obtaining difluorocyclopropenes (Scheme 2.166) does not depend on addition of difluoromethylene [48]. Mechanistically, the reaction is initiated by addition of the sterically demanding *tert*-butyl group to the acetylene carbon adjacent to the trifluoromethyl group. The resulting vinyl lithium species has very close contact between lithium and one fluorine atom of the trifluoromethyl group, facilitating extrusion of lithium fluoride. As for many other examples, here also the driving force of the reaction is the formation of lithium fluoride with its high lattice energy.



Scheme 2.164 Difluorocyclopropanation of ketal-protected carbonyl compounds and subsequent deprotection can overcome the low reactivity of electron-deficient olefins toward difluorocarbene. The creation of carbocationic centers adjacent to the difluorocyclopropane ring during acidic hydrolysis often leads to ring-opening and rearrangement products (**21**) [47].



Scheme 2.165 Synthesis of a fluorinated natural product analog via sigmatropic rearrangement of a divinyl *gem*-difluorocyclopropane [43].



Scheme 2.166 Addition of sterically demanding *tert*-butyl lithium to trifluoromethyl acetylene derivatives leads to difluorocyclopropenes [48]. The driving force of the cyclization reaction is energetically favorable extrusion of lithium fluoride from the vinyl lithium intermediate.

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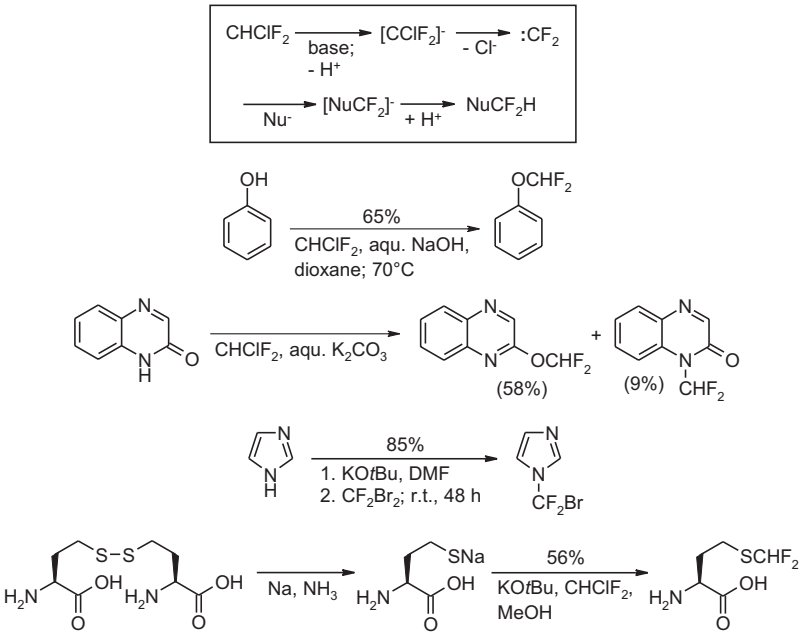
2.3
Selected Fluorinated Structures and Reaction Types

2.3.1
Difluoromethylation and Halodifluoromethylation

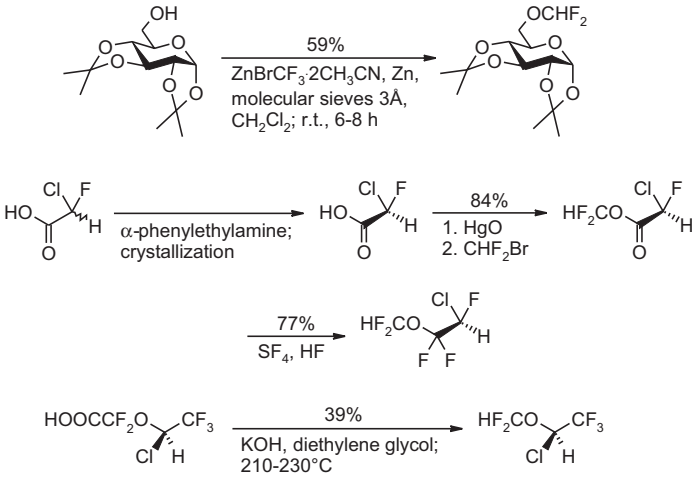
Compounds carrying a difluoromethoxy group as a substituent play an important role in pharmaceutical chemistry [1] and in liquid crystals for display applications [2]. Although most of these substances have an aromatic difluoromethoxy group, aliphatic difluoromethyl ethers also have important applications, e. g. as anesthetics [3].

Aromatic difluoromethyl ethers are conveniently synthesized by reaction of phenolates with $CHClF_2$ [4]. Although this is superficially similar to simple nucleophilic substitution of chlorine by the phenolate, the conversion in fact proceeds via difluorocarbene as the reactive, electrophilic species [5] (Scheme 2.167). Analogous difluoromethylation products are also obtained from other nucleophiles [6].



Scheme 2.167. Electrophilic difluoromethylation of *O*-, *N*-, and *S*-nucleophiles [4a, 4b, 6].

The difluoromethylation of aliphatic alcohols is also possible, in principle, but the resulting difluoroethers often tend to undergo acid-catalyzed hydrolysis to the corresponding formates. They are only stable if the corresponding alcohol is sufficiently acidic, i. e. if it carries electron-withdrawing substituents. *O*-Difluoromethylated carbohydrates have been reported [7]. In contrast, some highly fluorinated alkyl difluoromethyl ethers can be synthesized under quite drastic conditions (Scheme 2.168), and because of their extreme stability they can be used as inhalation anesthetics [3, 8].

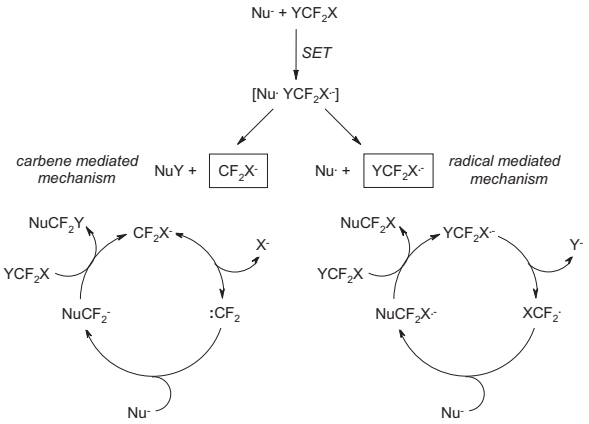


Scheme 2.168 Synthesis of aliphatic difluoromethyl ethers [3, 7a, 8].

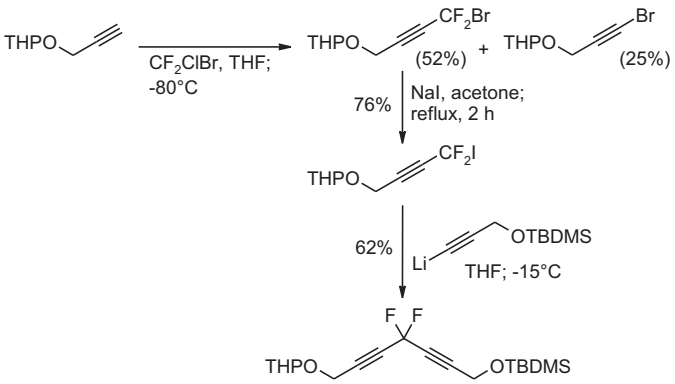
Another, related type of reaction is the halodifluoromethylation of nucleophiles by dihalodifluoromethanes (e. g. CF_2Br_2) [9]. This reaction is always initiated by a single electron transfer from the nucleophile to the CF_2XY species (X and Y denote halogens other than fluorine). The subsequent fate of the resulting radical ion pair depends on the ability of the nucleophile to form a stabilized radical, and also on the choice of solvent [10]. For phenoxides [4a, 5, 11] and thiophenoxides [4c, 11a] a reaction pathway via difluorocarbene is usually preferred whereas enamines and ynamines are halodifluoromethylated by a radical chain mechanism (see also Section 2.2.1) [12] (Scheme 2.169).

Bromodifluoromethylation of *C*-nucleophiles which are not resonance stabilized is supposed to proceed via the carbene mechanism (Scheme 2.170). A typical by-product of this reaction is the brominated nucleophile [13].

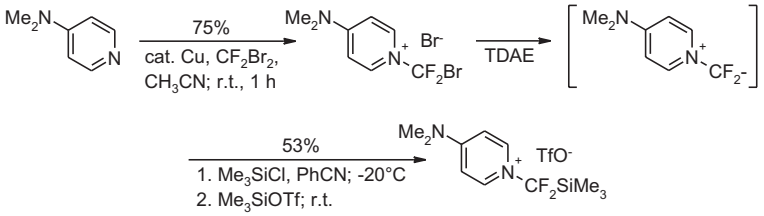
The initial reduction step does not necessarily rely on the nucleophilic substrate as the reducing agent. It can also be induced by addition of catalytic amounts of copper as an auxiliary reducing agent [14] (Scheme 2.171). The whole reaction sequence follows supposedly an $S_{RN}1$ mechanism [15].



Scheme 2.169 The different possible mechanistic pathways for the halodifluorination of different substrates [9, 10].



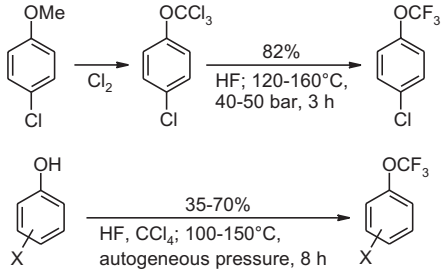
Scheme 2.170 Synthetic steps towards *gem*-difluoromethylene analogs of arachidonic acid via bromodifluoromethylation of *C*-nucleophiles [13].



Scheme 2.171 Bromodifluorination of *N*-nucleophiles (4-(*N*,*N*-dimethylamino)pyridine, DMAP) under the action of electrocatalysis by copper and subsequent reduction by TDAE (tetrakis(dimethylamino)ethylene) to a nitrogen ylide, which is formally an adduct of DMAP, to difluorocarbene [6a, 16].

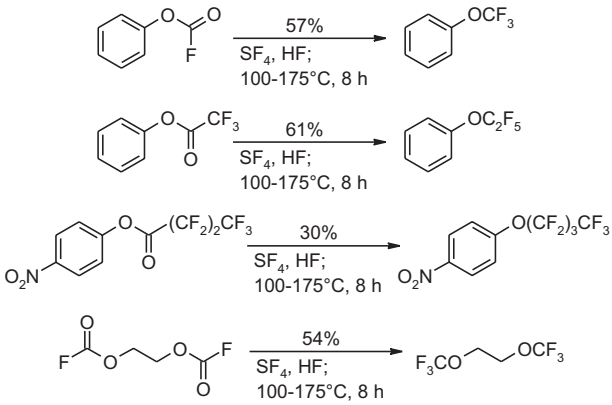
2.3.2 The Perfluoroalkoxy Group

Perfluoroalkoxy groups and, especially, the trifluoromethoxy group, are commonly used as structural elements in pharmaceuticals (Section 4.5) and organic materials (Section 4.4). Aromatic and aliphatic perfluoroalkoxy groups are conveniently accessible via fluorodesulfuration chemistry (see also Section 2.1.5.4). Nevertheless, the technically important trifluoromethoxy arenes, in particular, are produced on a larger scale by a different method, based on chlorine–fluorine exchange with hydrofluoric acid [17] (Scheme 2.172).



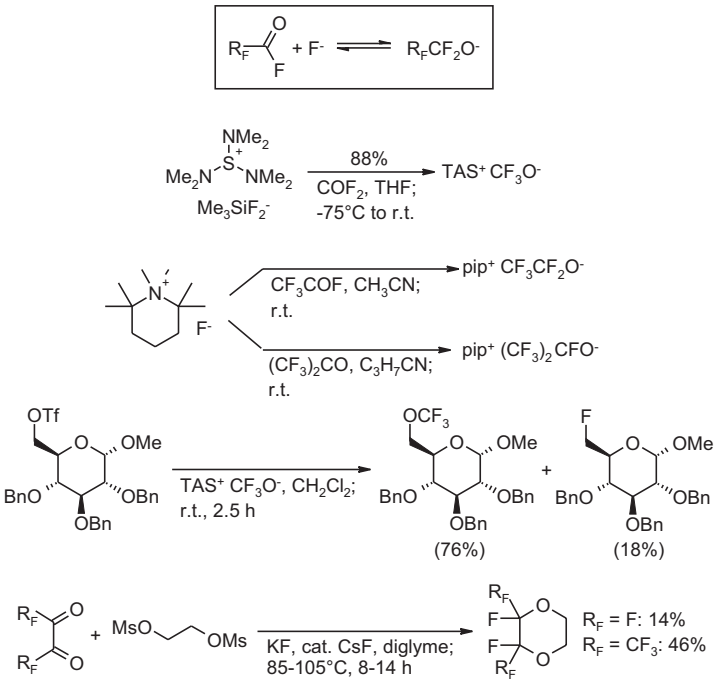
Scheme 2.172 Technical syntheses of trifluoromethoxy arenes via the trichloromethoxy derivative or directly from the phenol [17] (X denotes 3- or 4-NO_2, 4-Cl, 2,4-Cl_2, 3-CF_3, 4-NH_2, 2-F, 4-OH).

The fluorination of perfluoroacyloxy arenes with sulfur tetrafluoride to the corresponding perfluoroalkoxy arenes affords access to a larger structural variety [18]. For less sensitive structures, this method can also be extended to the synthesis of alkyl perfluoroalkyl ethers [19] (Scheme 2.173).



Scheme 2.173 Synthesis of aromatic and aliphatic perfluoroalkyl ethers via the fluorination of the corresponding perfluoroalkanoates with SF_4 [18a, 19a].

Even if perfluoroalkoxide anions are usually poor nucleophiles, they can be used for nucleophilic perfluoroalkoxylation of some aliphatic substrates [20]. The perfluoroalkoxide anion is stable in the presence of relatively large cations, for example K^+, Rb^+, Cs^+ [21], tris(dimethylamino)sulfonium (TAS^+) [22], 1,1,2,2,6,6-hexamethylpiperidinium (pip^+) [23], or hexamethylguanidinium HMG^+) [24] cations (Scheme 2.174). Under the conditions of most nucleophilic exchange reactions



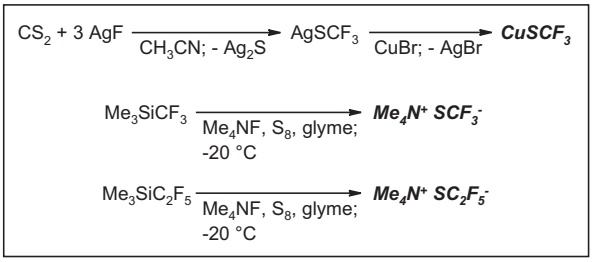
Scheme 2.174 Generation of perfluoroalkoxide anions and their use to generate aliphatic perfluoroalkyl ethers by nucleophilic substitution of a suitable leaving group (TAS^+ = tris(dimethylamino)sulfonium; pip^+ = 1,1,2,2,6,6-hexamethylpiperidinium) [20, 22, 23, 25b].

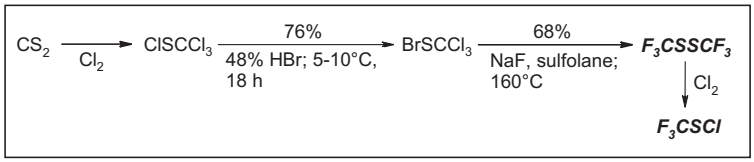
the anion exists in an equilibrium with perfluorocarboxylic acid fluoride and a fluoride anion [25]. Nucleophilic perfluoroalkoxylation, therefore, always competes with fluorination.

2.3.3
The Perfluoroalkylthio Group and Sulfur-based Super-electron-withdrawing Groups

The trifluoromethylthio group is a widely used structural motif in agrochemicals, because it induces an exceptionally large lipophilicity ($\pi_p = +1.44$) [26]. Its analogs with sulfur in higher oxidation states, for example the trifluoromethylsulfonyl group and fluorinated sulfimide- and sulfoximide-based structures are among the strongest known electron-withdrawing substituents. All these sulfur-based structures are very resistant to acidic hydrolysis.

The trifluoromethylthio group can be generated either from the corresponding thiols [27], rhodanides [28] or disulfides, or by reaction of nucleophilic [29] or electrophilic SCF_3-transfer reagents with suitable aromatic, aromatic, or olefin substrates [30] (Schemes 2.175 and 2.176).





Scheme 2.175 Syntheses of the most important nucleophilic (*top*) and electrophilic (*bottom*) perfluoroalkylthio transfer reagents [29a, 29b, 31].

Organic perfluoroalkylthio derivatives can be oxidized to the sulfoxides [37] and sulfones [30a, 34] by a variety of methods (Scheme 2.177). Compared with non-fluorinated thioethers the SR_F derivatives are less susceptible to oxidation. Thus, more energetic reaction conditions must be chosen.

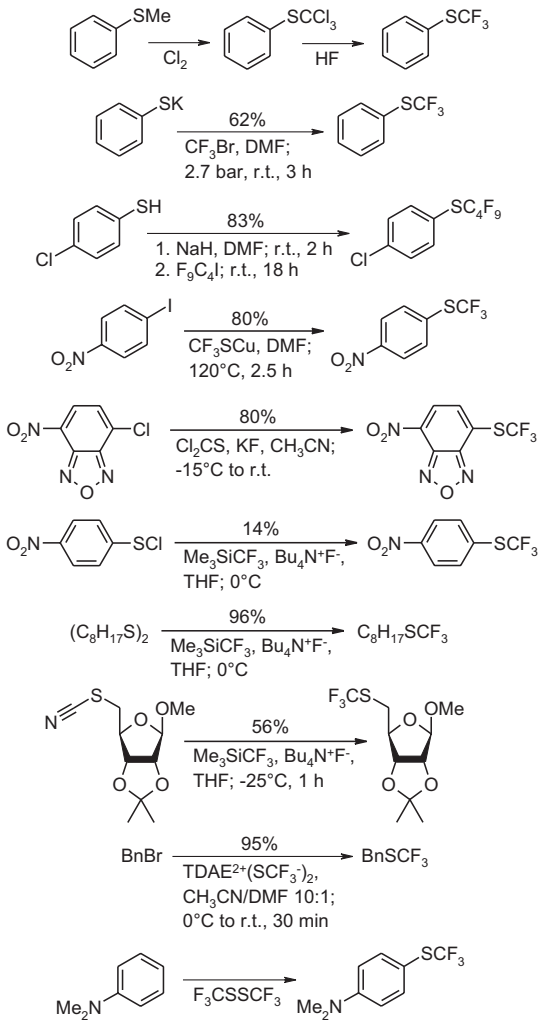
An alternative route to aromatic trifluoromethylsulfonyl and sulfinyl compounds is based on the nucleophilic trifluoromethylation of sulfonyl or sulfinyl halides with Me_3SiCF_3 [38] (Scheme 2.178).

One entrance into the chemistry of sulfimide-based functional groups is electrophilic activation of the corresponding sulfoxides with triflic anhydride and subsequent reaction of the resulting sulfonium salts with trifluoromethane sulfonamide [39] (Scheme 2.179). The other entrance is oxidative imination of a sulfoxide then trifluoromethanesulfonylation of the resulting imidosulfone [40].

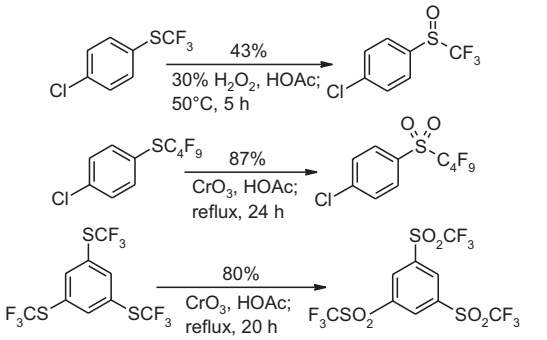
A third method is based on oxidative amination of diaryl disulfides with *N,N*-dichlorotrifluoromethane sulfonamide, leading to imidosulfinyl chlorides (Scheme 2.180).

2.3.4
The Pentafluorosulfuranyl Group and Related Structures

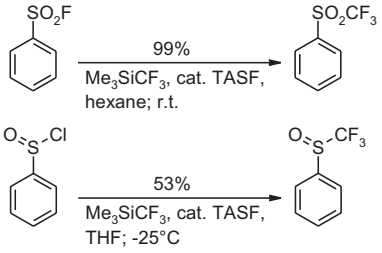
Another sulfur-based, strongly polar functional group is the pentafluorosulfuranyl group [42]. Within a few years after the initial synthesis and characterization of a variety of aromatic [43] and aliphatic [44] SF_5 derivatives at the beginning of the 1960s, interest in this unusual group vanished almost completely, with very few exceptions [45], partly because of inconvenient synthetic access to this class of substance and partly because of unfounded prejudice regarding the hydrolytic stability of the pentafluorosulfuranyl group.



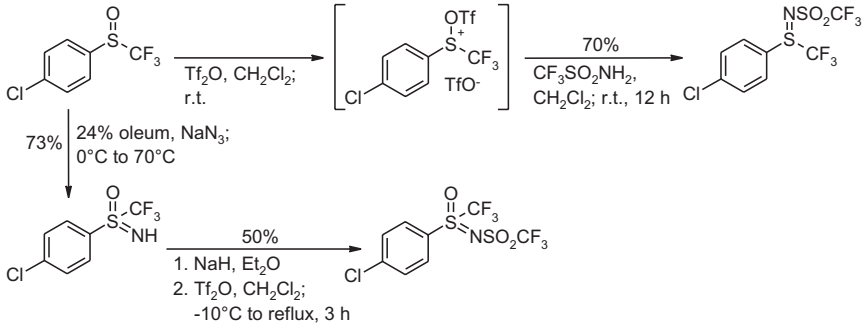
Scheme 2.176 Syntheses of different perfluoroalkylthio arenes [28a, 29c, 30c, 32–36].



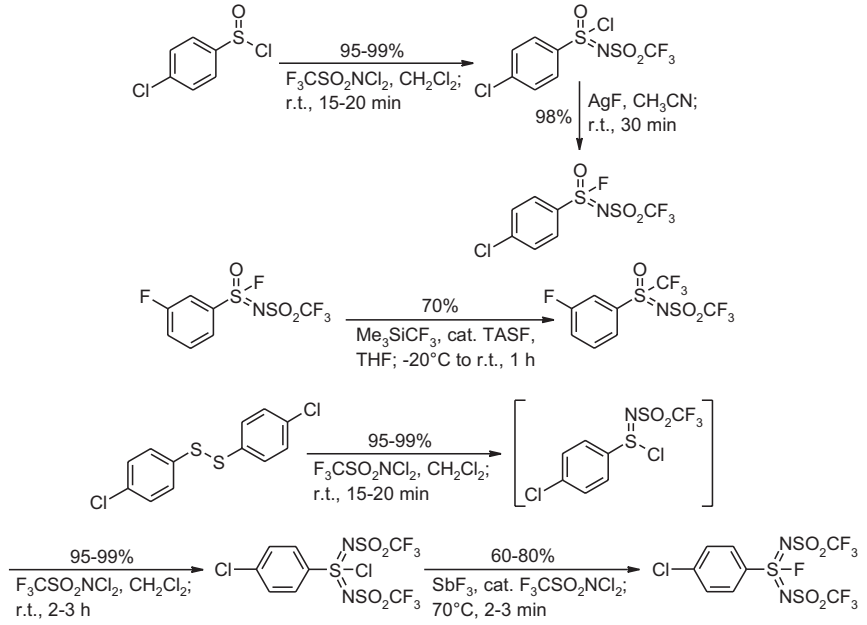
Scheme 2.177 Synthesis of perfluoroalkylsulfinyl (SOR_F) and perfluoroalkylsulfonyl (SO_2R_F) derivatives [30a, 34, 37].



Scheme 2.178 Conversion of sulfonyl and sulfinyl halides to the corresponding trifluoromethyl sulfones and sulfoxides by nucleophilic trifluoromethylation [38].



Scheme 2.179 Syntheses of some sulfur imide-based super-electron-withdrawing substituents via the sulfoxides [38b, 39, 40].

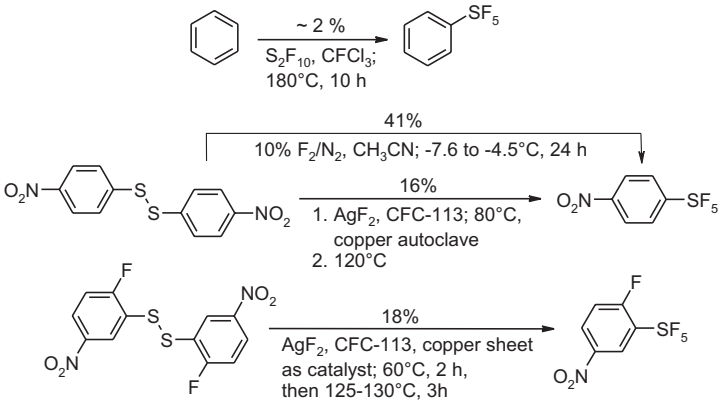


Scheme 2.180 Syntheses of some sulfur imide-based super-electron-withdrawing substituents via oxidation by *N*,*N*-dichlorotrifluoromethane sulfonamide [38b, 41].

The exploration of this functional group was resumed when, toward the end of the 1990s, the first commercial quantities of *o*- and *m*-nitropentafluorosulfuranylbenzene became available from a direct fluorination process [46]. Because of its strong polarity and high lipophilicity, the pentafluorosulfuranyl group is an interesting structural motif not only for design of bioactive compounds [47] but also for organic functional materials, for example polymers [45b–d] or liquid crystals [49].

The first practicable synthesis of aromatic pentafluorosulfuranyl derivatives was introduced by W. A. Sheppard [50] in 1960 [43a]. It was based on the stepwise oxidative fluorination of diaryldisulfides with AgF_2, via the trifluorosulfanyl arenes [51], to the corresponding pentafluorosulfuranyl compounds [43b]. This early synthesis suffered from relatively low yields and sometimes bad reproducibility. Then J. S. Thrasher and coworkers [45b–d, 48] found that the autoclave material used by Sheppard, copper, acts as a catalyst in the conversion. Copper and some other metals are supposed to facilitate the fluorination reaction via formation of metal thiolate intermediates.

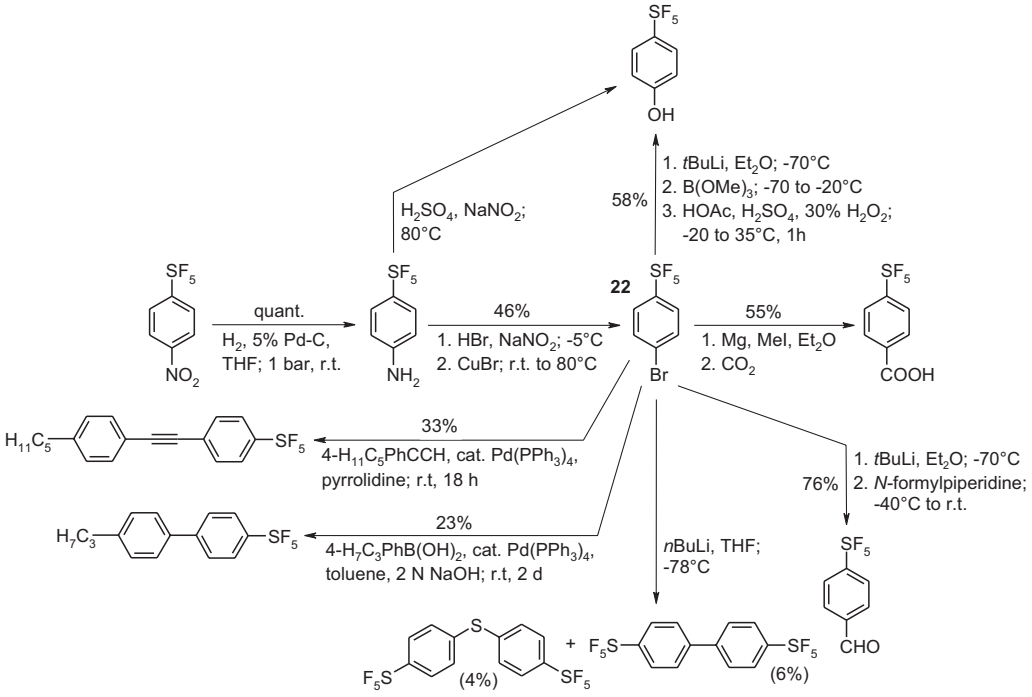
The breakthrough in the commercialization of pentafluorosulfuranyl arenes came in 1996 with the introduction of a new, very reliable synthetic procedure based on direct fluorination of bis(nitrophenyl)disulfides [46c] (Scheme 2.181). This sudden, convenient access to larger quantities of this class of substance triggered renewed interest in exploration of the chemical properties of SF_5 compounds, especially their hydrolytic stability.



Scheme 2.181 Different syntheses of pentafluorosulfuranyl arenes [43b, 43d, 46c, 46d, 48]. The commercial process for the synthesis of *m*- and *p*-nitropentafluorosulfuranyl benzene is based on direct fluorination of the corresponding disulfides.

It has been known since Sheppard's original work [43b] that the hydrolytic stability of aromatic pentafluorosulfuranyl groups equals or exceeds that of trifluoromethyl groups (Scheme 2.182); this is considered sufficiently stable for ubiquitous use as a structural motif in medicinal chemistry. Aromatic SF_5 derivatives tolerate

attack by strong Brønstedt acids and bases, and they are stable under the conditions used for different nickel-, palladium-, or platinum-catalyzed hydrogenation reactions or carbon–carbon coupling reactions [49, 52].

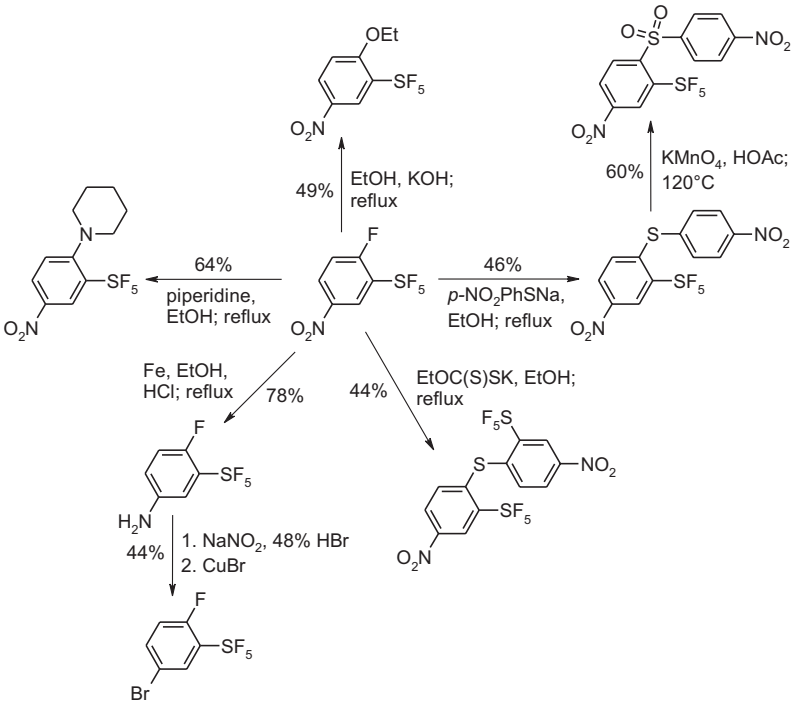


Scheme 2.182 Examples of conversions of 4-nitropentafluorosulfuranylbenzene demonstrate the stability of the aromatic pentafluorosulfuranyl group, which is comparable with that of the trifluoromethyl function [43b, 49a]. The Achilles' heel of the SF_5 group is its susceptibility toward reduction by some organometallic species, for example *n*-butyllithium in THF.

Like their trifluoromethyl analogs they are sensitive toward strong Lewis acids [53]. The real Achilles' heel of the SF_5 group, which distinguishes it from the trifluoromethyl function, is its susceptibility toward reduction by some organometallic reagents. Sheppard observed that *p*-bromopentafluorosulfuranyl benzene (**22**) could not be converted directly into the Grignard compound with magnesium metal, but only under the catalytic action of methyl magnesium iodide [43b]. Attempts to lithiate the bromoarene **22** with *n*-butyllithium in THF at −78°C also resulted merely in the immediate formation of a variety of reduction products. When, on the other hand, *tert*-butyllithium in diethyl ether at −78°C was used instead, the compound was cleanly lithiated and could be used for many different transformations [49a].

Sheppard was unable to convert *o*-nitrophenyl sulfurtrifluoride into the corresponding SF_5 derivative in the same manner as for the *m*- and *p*-nitrophenyl deri-

vatives. He explained this as a consequence of the bulkiness of the pentafluorosulfuranyl group, which interacts sterically with the *ortho*-nitro function [43b]. *ortho*-Substituted pentafluorosulfuranyl benzenes are still unknown and it has been speculated they are generally unstable. Recently, Thrasher and coworkers demonstrated not only that *ortho*-fluorinated aromatic disulfides cannot be fluorinated by AgF_2 to the *o*-fluoro pentafluorosulfuranyl arene but also that the *ortho*-fluorine can be replaced by a variety of nucleophiles without any evidence that the resulting substitution products are in any way susceptible to hydrolysis [48] (Scheme 2.183).



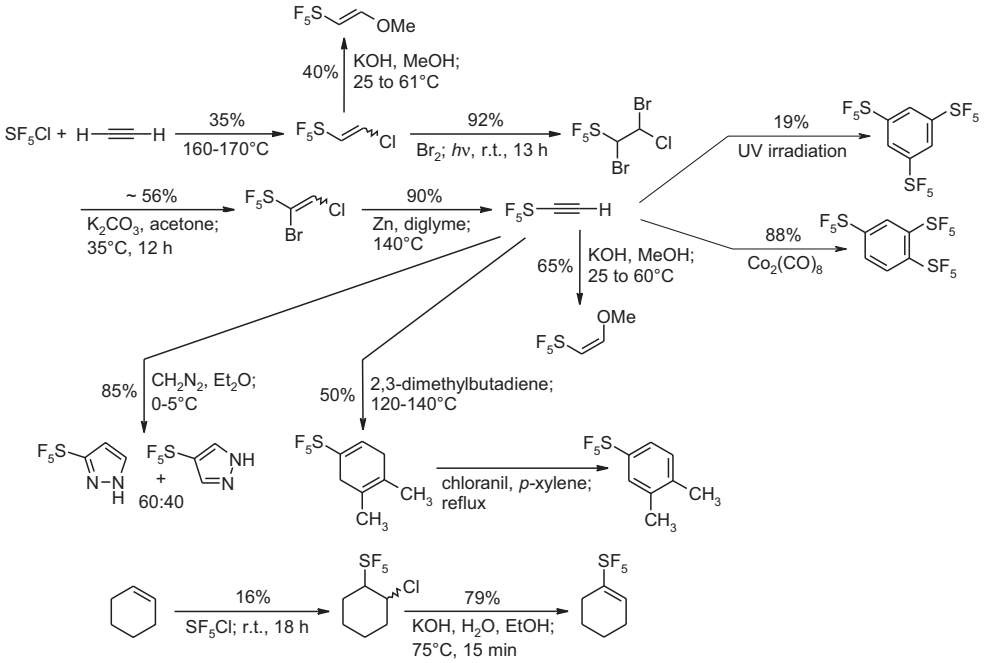
Scheme 2.183 Conversions of 1-fluoro-4-nitro-2-pentafluorosulfuranylbenzene into other functionalized derivatives demonstrate the hydrolytic stability of the pentafluorosulfuranyl group even in the presence of bulky *ortho*-substituents [48].

Electronically, the SF_5 group can be regarded as a "super-trifluoromethyl" group. It has inductive and resonance effects [54] ($\sigma_I = 0.55$, $\sigma_R = 0.11$) which are analogous to but significantly stronger than those of CF_3 ($\sigma_I = 0.39$, $\sigma_R = 0.12$) [43c].

The electronegativity of the SF_5 group is 3.62 [55], compared to 3.45 for CF_3 [56]. A particular attractive property in the design of functional organic materials, for example liquid crystals, is the strong dipole moment which can be achieved by use of the SF_5 group. For example, the dipole moment of pentafluorosulfuranyl benzene ($PhSF_5$) is 3.44 D (25 °C) [43c] compared with only 2.6 D for benzotrifluoride ($PhCF_3$) [57].

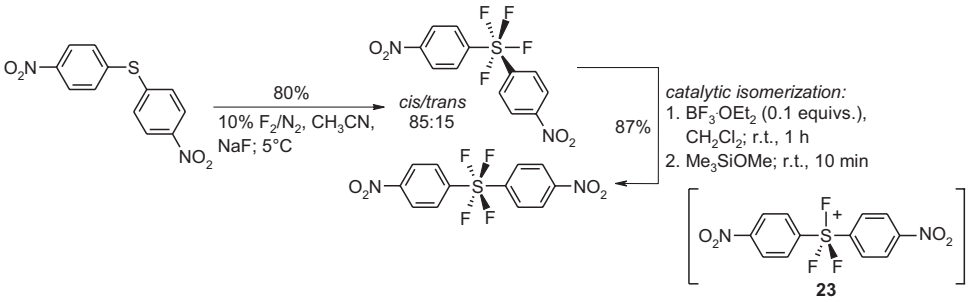
Since the 1950s perfluoroaliphatic SF_5 compounds have been made by a variety of methods, including fluorination with cobalt trifluoride and direct and electrochemical fluorination [42a]. Selective introduction of a pentafluorosulfuranyl group into more complex aliphatic compounds, on the other hand, remains still a challenge.

Most syntheses of aliphatic pentafluorosulfuranyl derivatives are based on radical addition of SF_5X (X = Cl, Br) to olefins (Scheme 2.184). The general reactivity of SF_5X is very similar to that of perfluoroalkyl iodides and bromides and the stability of the resulting adducts is comparable with that of their perfluoroalkyl analogs [44, 58]. Nevertheless, because access to SF_5Cl and SF_5Br is difficult, the chemistry and the physicochemical properties of aliphatic SF_5 derivatives are relatively unexplored.



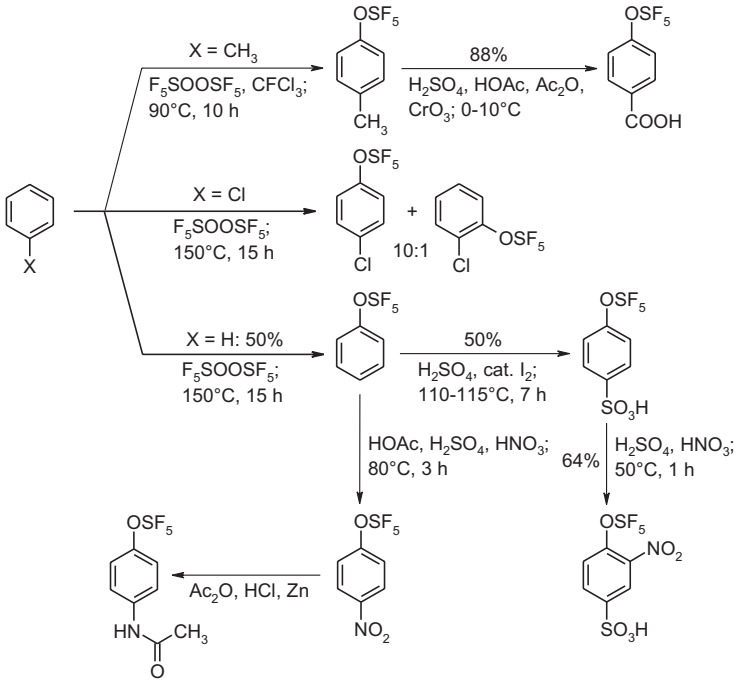
Scheme 2.184 Examples of syntheses of some non-aromatic pentafluorosulfuranyl derivatives [44, 58].

Arenes bridged by a tetrafluorosulfuranyl group are accessible by the same principal method as pentafluorosulfuranyl compounds [59] (Scheme 2.185). Direct fluorination of the corresponding diaryl sulfides with 10% fluorine in nitrogen yields mixtures of the *cis* and *trans* isomers. The aromatic moieties must be deactivated, by electron-withdrawing substituents, against the attack by fluorine. Because diaryl trifluorosulfuranonium cations (**23**) are resonance-stabilized, the *cis* isomer can be easily isomerized into the thermodynamically more stable *trans* isomer by the action of a catalytic amount of a fluorophilic Lewis acid.



Scheme 2.185 Synthesis of the isomeric bis(4-nitrophenyl)tetrafluorosulfuranes and subsequent catalytic isomerization to the energetically preferred *trans* isomer [59].

The pentafluorosulfuranyloxy group can be regarded as a sulfur based analog of the trifluoromethoxy group. Aromatic pentafluorosulfuranyloxy compounds are highly stable toward hydrolysis, similar to their pentafluorosulfuranyl analogs, because of kinetic stabilization by the five fluorine atoms shielding the central sulfur against nucleophilic attack. The substance class is accessible by high-temperature reaction between arenes and bis(pentafluorosulfuranyl)peroxide (F_5SOOSF_5) [60], a thermally stable compound (b. p. 49°C) [61] (Scheme 2.186). Because access to



Scheme 2.186 Synthesis of a variety of pentafluorosulfuranyloxybenzene derivatives [61].

F_5SOOSF_5 is difficult, after the initial publication in 1962 this chemistry has, unfortunately, not been explored further. Physicochemical studies on *p*-pentafluorosulfuranyloxybenzoic acid ($pK_a = 5.04$; for comparison, benzoic acid 5.68, *p*-nitrobenzoic acid 4.55) show the *p*-OSF_5 group has a relatively large σ_{para} value of +0.44 (for comparison, *p*-F +0.062, *p*-COOEt +0.45), indicating a strong inductive electron-withdrawing (-*I*) effect.

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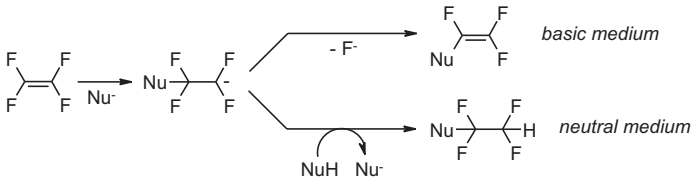
2.4
The Chemistry of Highly Fluorinated Olefins

Fluorinated olefins are particularly useful and versatile, both as synthons and in materials science [1]. The sections which follow give examples of the chemistry of these compounds, but do not claim to be even close to completeness. The aim is merely to introduce the synthetic opportunities and potential applications of these structurally interesting compounds.

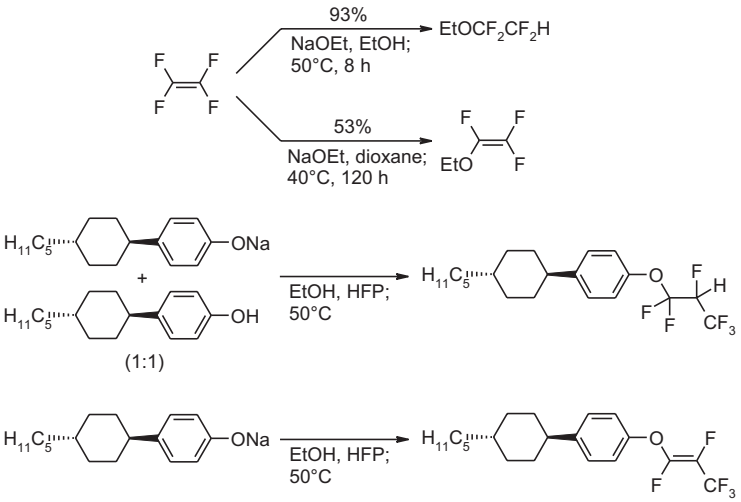
2.4.1
Fluorinated Polymethines

The chemistry of fluorinated olefins is dominated by nucleophilic addition and substitution reactions (Section 2.1.4). Depending on the acidity or basicity of the reaction medium, after a primary addition step the resulting anion is either quenched by protonation or by β-elimination of fluoride (Scheme 2.187).

On reaction with basic nucleophiles, for example organometallic species or alcoholates, substitution products are obtained [2]. With only mildly basic to neutral nucleophiles, such as phenolate/phenol mixtures, on the other hand, addition products predominate [3] (Scheme 2.188).

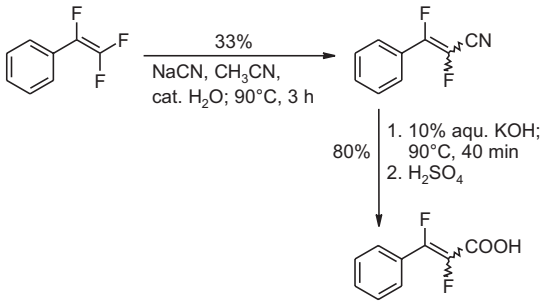


Scheme 2.187 Different pathways for reaction of tetrafluoroethylene with nucleophiles.



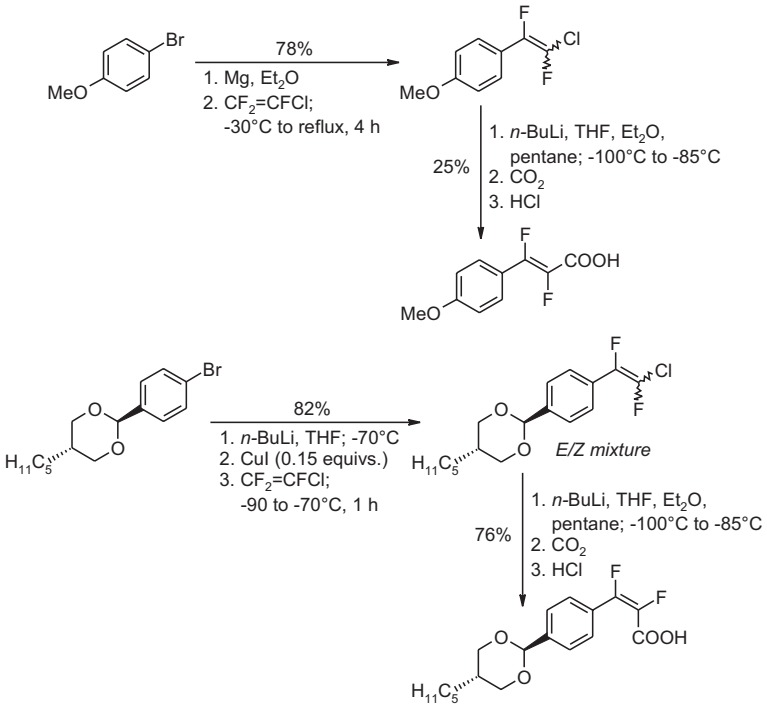
Scheme 2.188 Use of perfluoropropene for the fluoroalkylation or fluoroalkenylation of alcohols and phenols (HFP = hexafluoropropene) [2–4].

This kind of chemistry is not limited to tetrafluoroethylene but it can be extended to systems with a lower fluorine content, on the one hand [5], and to conjugated polyfluoromethine compounds on the other hand [6, 7] (Scheme 2.189).



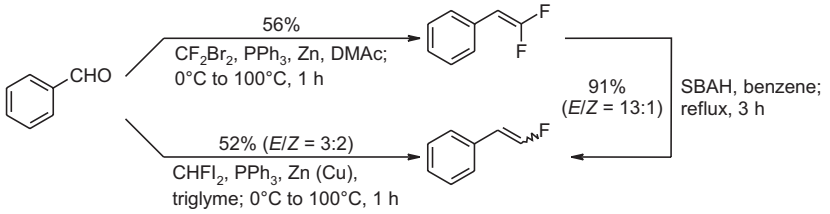
Scheme 2.189 Synthesis of α,β-difluorocinnamonitriles [5] and subsequent hydrolysis to the isomeric α,β-difluorocinnamic acids.

Use of chlorotrifluoroethylene as a central scaffold enables stepwise synthesis of, e. g., α,β-difluorocinnamic acids, by nucleophilic substitution by an aryl Grignard species, followed by organometallic activation of the chlorine and subsequent quenching with a suitable electrophile (Scheme 2.190). The initial nucleophilic substitution step with Grignard or organolithium nucleophiles often takes several hours at room temperature for completion [8]. When catalytic quantities of CuI are added the reaction is complete after only a few minutes at −70°C [9]. The reason for this dramatic acceleration of the rate of reaction is, presumably, formation of diaryl cuprate species which act as very "soft" and more reactive nucleophiles, in contrast with the "hard" organolithium or magnesium nucleophiles.



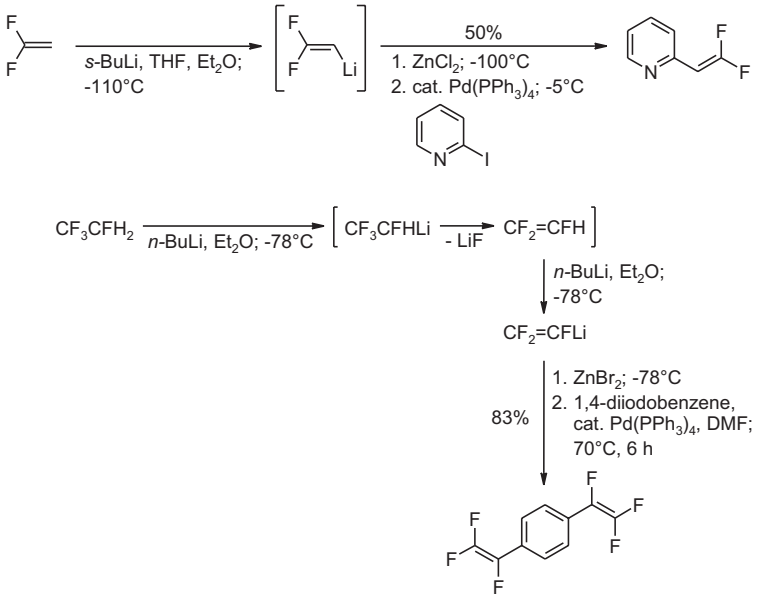
Scheme 2.190 Synthesis of substituted α,β-difluorocinnamic acids [8–10].

Many methods are used for preparation of fluoroolefin precursors [11]. One of these strategies is based on Wittig-like metathesis reactions between carbonyl compounds and α-fluoroalkyl phosphoranes [12] (Scheme 2.191).



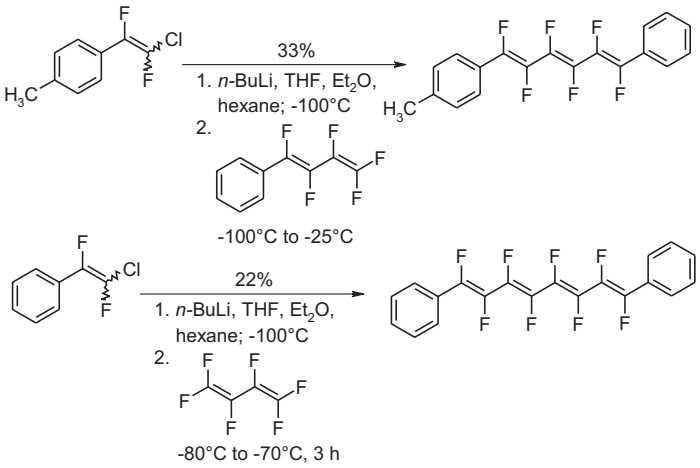
Scheme 2.191 Synthesis of fluoro and difluoro olefins by metathesis of carbonyl compounds with fluoroalkyl phosphoranes (SBAH = sodium bis(methoxyethoxy)aluminum hydride) [12d].

Another principal method is the fluorovinylation of suitable precursors by transition metal-catalyzed carbon–carbon coupling reactions [13]. Activated fluorovinyl species can be conveniently generated *in situ* from commonly used hydrofluorocarbons, for example HFC-134a [14] (Scheme 2.192). Fluorinated vinyl zinc halides are often used for the coupling reactions, but other activated species, for example stannanes [15] or boronates [16], have also been applied successfully.



Scheme 2.192 Examples of the coupling of fluorinated vinyl species to other building blocks via transition metal catalysis [13e, 14, 17].

Another method for homologation of conjugated fluorinated polyenes is based on nucleophilic replacement of fluoride from fluoroolefins [7, 18] (Scheme 2.193).



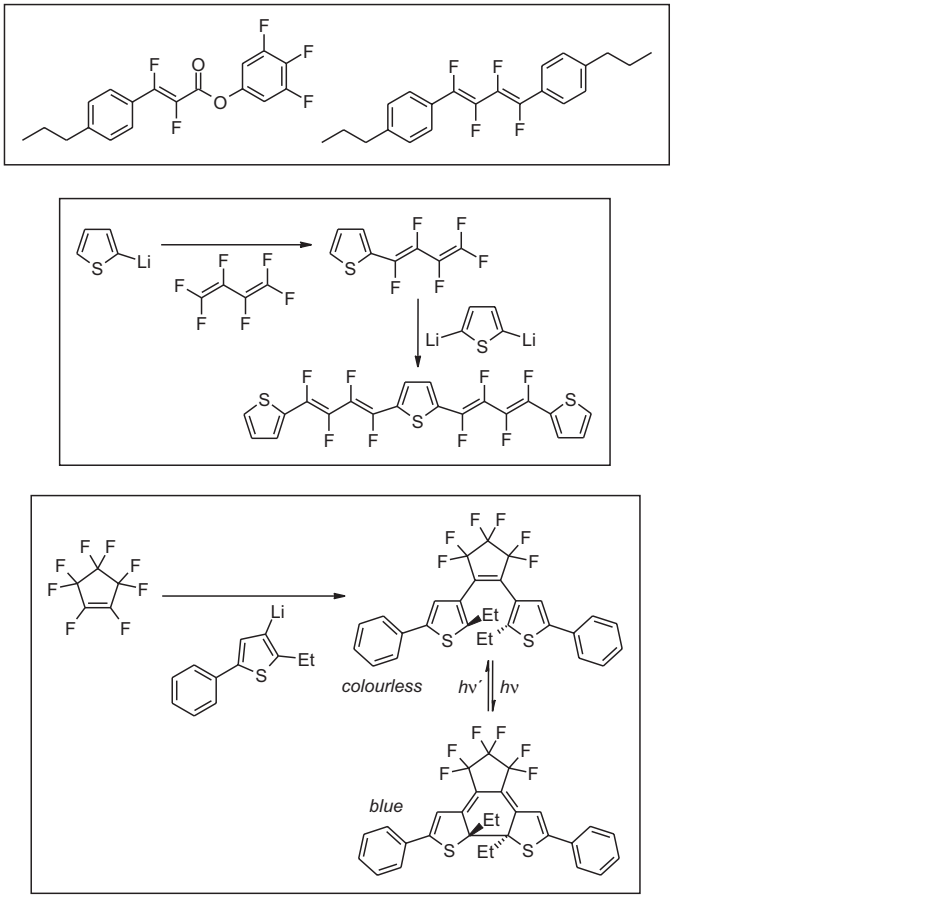
Scheme 2.193 Homologation of fluorinated polyenes by nucleophilic replacement of fluorine by lithium organyls [7, 19].

The ease of structural modification of fluorinated olefins makes them an interesting structural scaffold for design of functional materials such as liquid crystals [10, 20, 21], compounds for non-linear optics (NLO) [22], or media for holographic data storage [23] (Scheme 2.194).

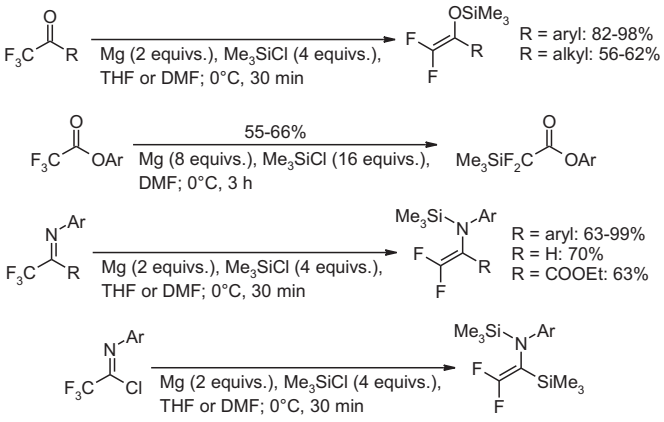
2.4.2
Fluorinated Enol Ethers as Synthetic Building Blocks

Difluoroenol ethers are synthetically equivalent to nucleophilic *gem*-difluoromethylene building blocks [24] which can be derivatized in their α-positions by a wide range of structures [25]. Similarly to their non-fluorinated analogs, they react with a variety of different electrophiles or radicals [26] and afford particularly convenient access to fluorinated analogs of natural products and other bioactive compounds.

Compounds carrying a trifluoroacetyl group, for example trifluoromethyl ketones and esters of trifluoroacetic acid, can be converted into the corresponding trimethylsilyl difluoroenol ethers [27] or into trimethylsilyldifluoroacetic acid esters [28] by reduction with magnesium metal in the presence of Me_3SiCl (Scheme 2.195). These readily accessible species are synthetically very useful as nucleophilic difluoromethylene equivalents. The same type of chemistry [29] can also be extended to trifluoromethyl imines [30].

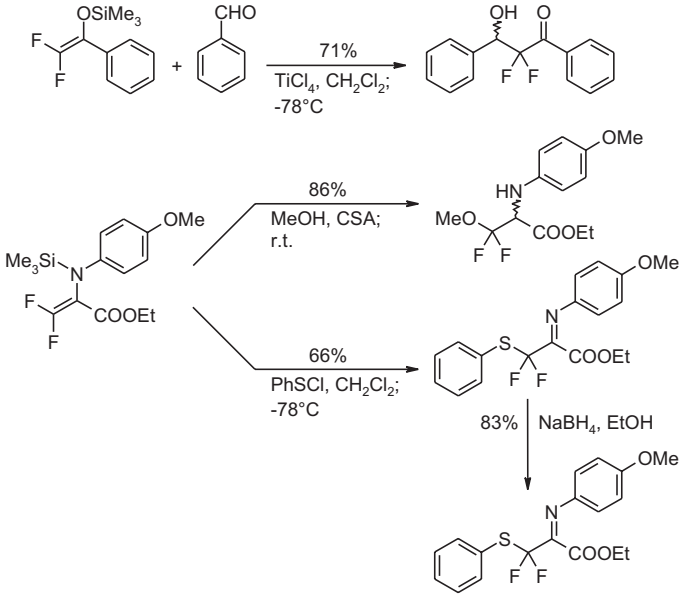


Scheme 2.194 Examples of the use of fluoroolefins as liquid crystals (*top*) [10, 21], NLO compounds (*middle*) [22], and photochromic materials for holographic data storage (*bottom*) [23].

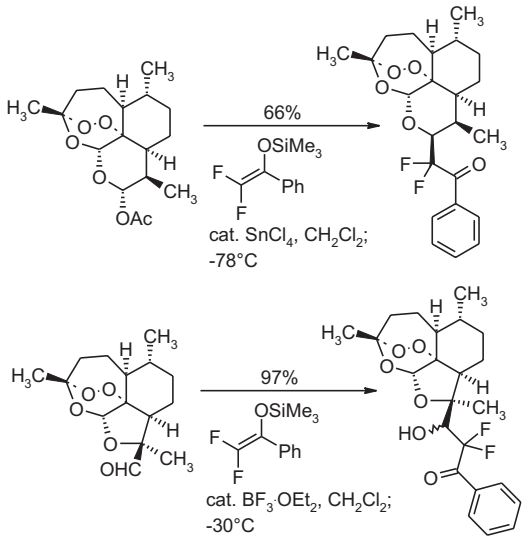


Scheme 2.195 Magnesium metal-promoted activation of trifluoroacetyl groups [27–30].

Trimethylsilyl difluoroenol ethers and their imine analogs react with a variety of different electrophiles [29] (Schemes 2.196 and 2.197). They have, for example, been used for the synthesis of fluorinated amino acids [30] and anti-malarials [31].

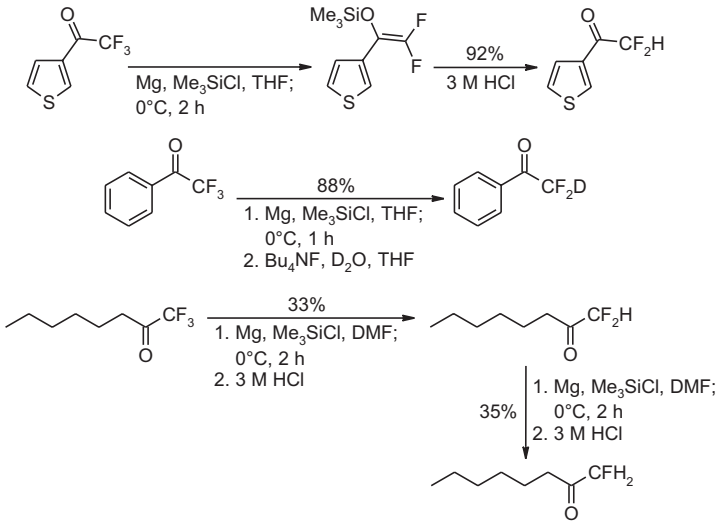


Scheme 2.196 Examples of reactions with silyl difluoroenolates and difluoroenamines (CSA = camphorsulfonic acid) [27, 30].



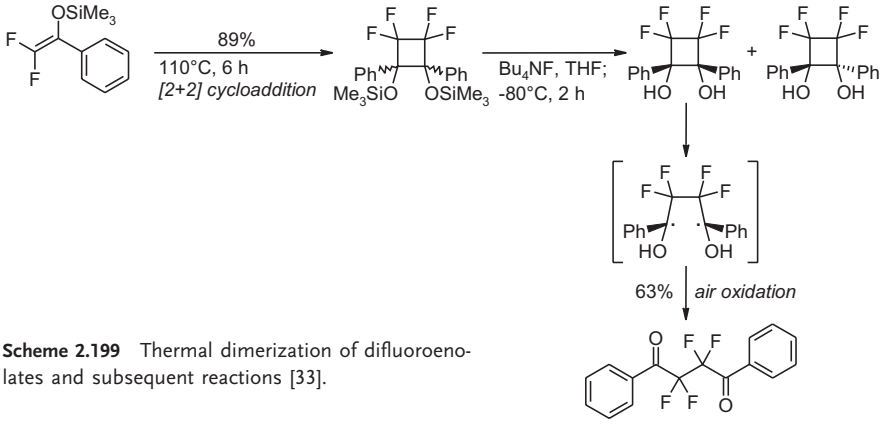
Scheme 2.197 Synthesis of a difluoromethylene ketone-derivatized artemisinine by use of a difluoroenol silyl ether [31].

Also difluoromethyl ketones can be reduced by magnesium to the corresponding fluorenol ethers [32]. Thus, by application of one or two sequential reduction–desilylation steps, trifluoromethyl ketones can be converted into difluoromethyl and fluoromethyl ketones (Scheme 2.198). Deuterodesilylation instead of the usual protodesilylation enables convenient access to deuterated analogs of these compounds.



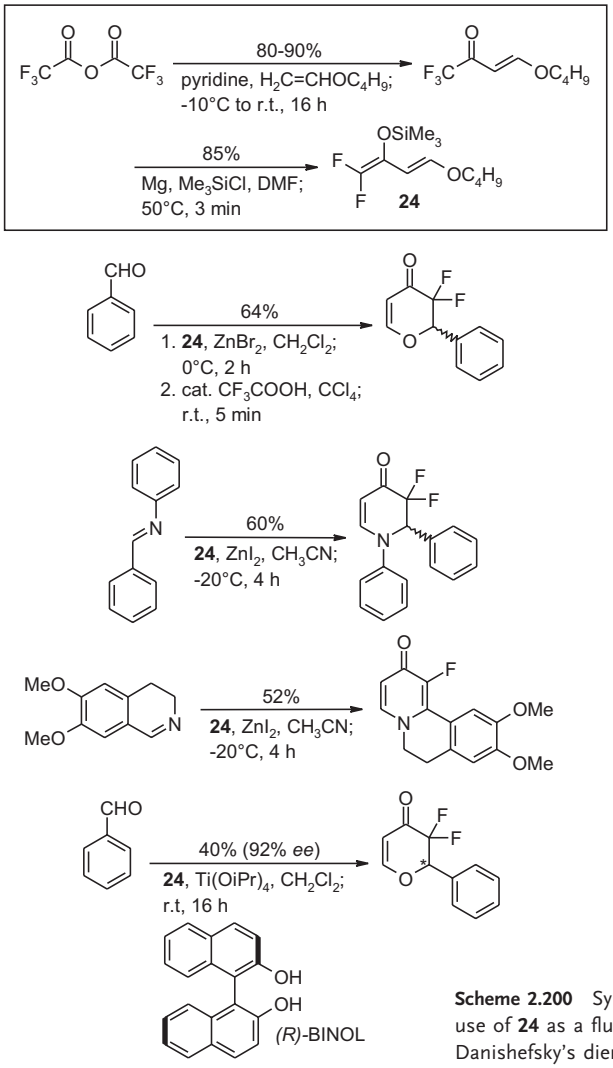
Scheme 2.198 Synthesis of fluoromethyl and difluoromethyl ketones by stepwise reduction of trifluoromethyl ketones with magnesium [32]. This method also enables the simple preparation of deuterated analogs.

Trimethylsilyl enol ethers can be thermally dimerized to the corresponding silyl-protected tetrafluorocyclobutanediols [33]. If these intermediates are desilylated by use of TBAF the resulting trans diol is stable whereas the cis diol undergoes clean conversion to the 2,2,3,3-tetrafluorobutane-1,4-dione (Scheme 2.199). Ring opening is assumed to proceed via a diradical which is oxidized by ambient air to the diketone.



Scheme 2.199 Thermal dimerization of difluoroenolates and subsequent reactions [33].

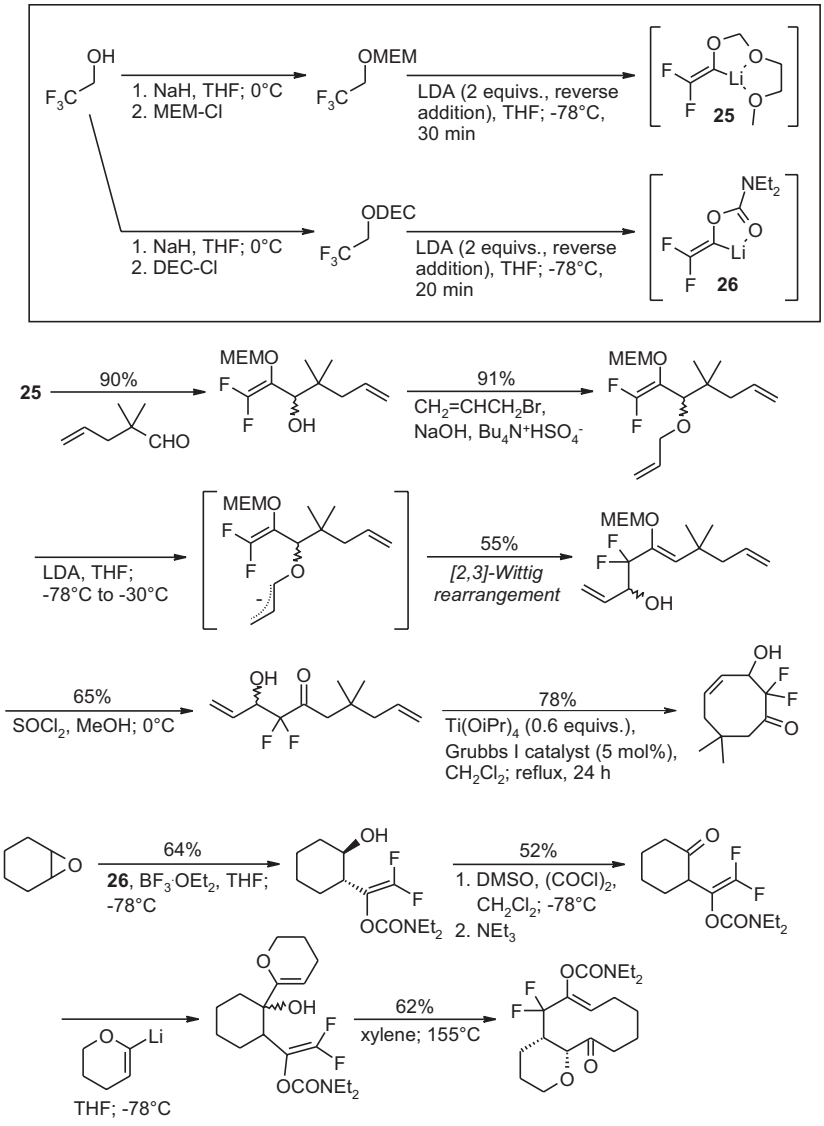
Reaction of trifluoromethyl vinyl ketones with magnesium/Me_3SiCl leads to a difluoro analog of Danishefsky's diene (**24**) [34] (Scheme 2.200) which is a useful building block for synthesis of fluorinated heterocycles [35].



Scheme 2.200 Synthesis and preparative use of **24** as a fluorinated analog [29, 35] of Danishefsky's diene [34].

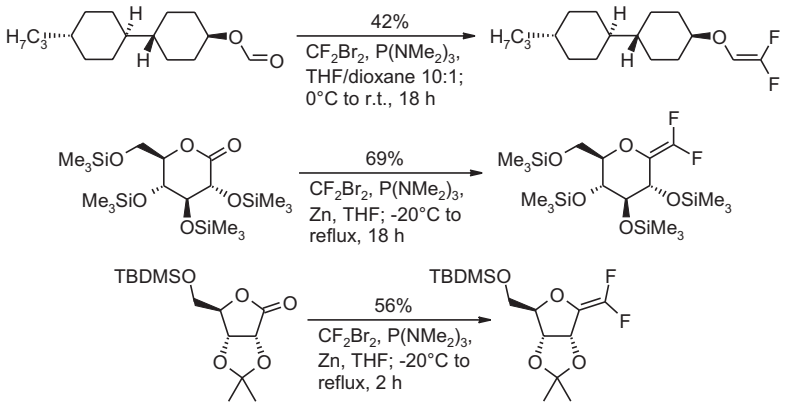
Another inexpensive and readily accessible precursor to difluoroenol ethers is trifluoroethanol. Several *O*-substituted derivatives of trifluoroethanol have been converted into 1-lithio 2,2-difluoroenolates by elimination of hydrogen fluoride and subsequent metalation with LDA [36]. These building blocks have the advantage

that they are bivalent two-carbon units which can either be reacted sequentially with two different electrophiles or reacted first with an electrophile and then in an electrocyclic reaction (Scheme 2.201).



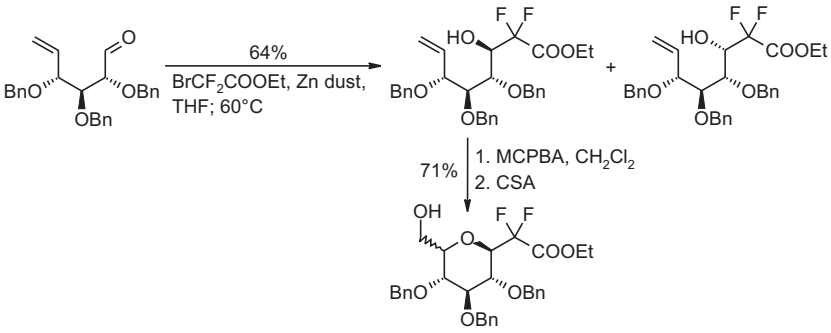
Scheme 2.201 Preparation of two different 1-lithio-2,2-difluoroenolates [36] **25** and **26** (*box*), and examples for their preparative use (MEM = 2-methoxyethoxymethyl; DEC = *N,N*-diethylcarbamoyl) [37].

Difluoroenol ethers are also available from esters and lactones by a Wittig-like reaction with $CF_2Br_2/P(NMe_2)_3$ in the presence of a reducing agent [38, 39] (Scheme 2.202).

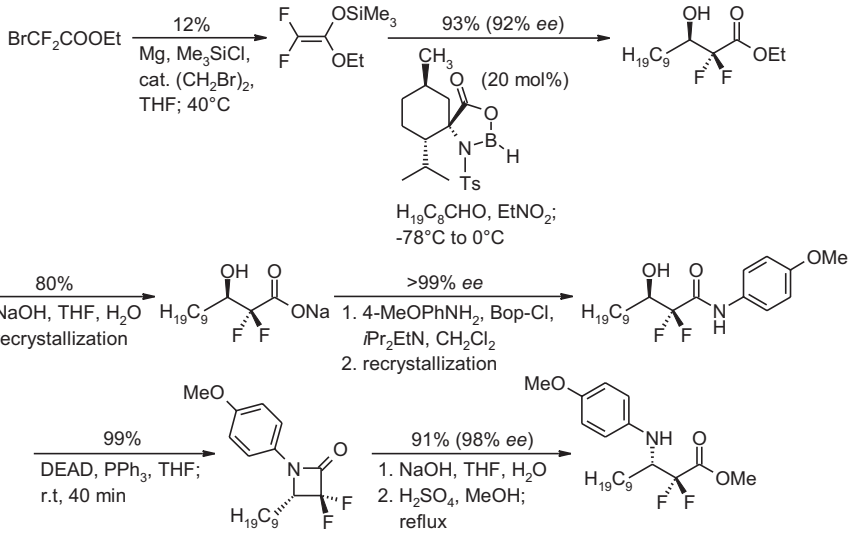


Scheme 2.202 Synthesis of difluoroenol ethers from esters and lactones [38, 39].

Difluoroester enolates are available by reduction of halodifluoroacetates with zinc metal [40]. Although the reaction of *O*-trimethylsilyl difluoroesterenolates with carbonyl compounds leads to the same reaction products as the analogous Reformatsky reaction [41] (Scheme 2.203), use of chiral catalysts results in additions with much greater enantioselectivity [42] (Scheme 2.204).

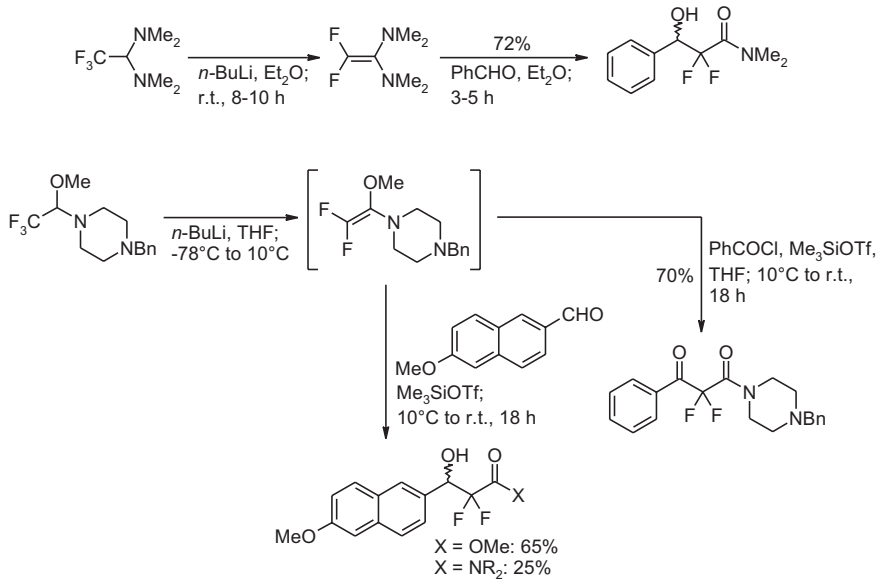


Scheme 2.203 Example of the synthesis of *gem*-difluorinated carbohydrate analogs via a Reformatsky reaction with ethyl bromodifluoroacetate [41c].



Scheme 2.204 Examples of the use of halodifluoroacetates for generation of *O*-trimethylsilyl difluoroesterenolates (DEAD = diethyl azodicarboxylate) [40a, 42].

A type of building block with similar reactivity is obtained by elimination of HF from aminals [43] or hemiaminals [44] of trifluoroacetaldehyde [45] (Scheme 2.205).



Scheme 2.205 Examples of the preparative use of difluoroketene aminals (*above*) [43] and hemiaminals (*below*) [45].

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3
Fluorous Chemistry

In most chemical syntheses the work-up procedure after the reaction itself is the most tedious and time-consuming step. Side-products, excess reagents, and solvents must be removed. If an expensive catalyst is used there is a strong incentive to recover and recycle it. In addition to economic aspects, especially in the design of large-scale industrial processes, ecological considerations, for example resource-saving use of reagents and solvents, have gained increasing importance.

The unique properties of highly fluorinated and perfluorinated ("fluorous") solvents and reagents open several routes to a solution of these problems and to a sustainable "green" chemistry [1-5]. These properties include their very temperature-dependent miscibility with typical hydrocarbons, their non-toxicity, and their extreme chemical inertness.

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3.1
Fluorous Biphase Catalysis

Most perfluoroaliphatic solvents are not miscible with hydrocarbon solvents at room temperature. At elevated temperatures, however, a homogeneous system is formed, which separates again on cooling. This strongly temperature-dependent and reversible miscibility gap is well demonstrated by the phase diagram of the perfluoro(methylcyclohexane)/benzene system depicted in Figure 3.1.

Reagents with very high fluorine content (>60 % fluorine by weight) tend to dissolve well in fluorous solvents. In a biphasic fluorocarbon–hydrocarbon system they have a strong preference for the fluorous phase. Thus, by simple temperature cycling, such a solvent system can be reversibly switched between a biphasic and a homogeneous state. In the biphasic state, fluorous reagents are exclusively present

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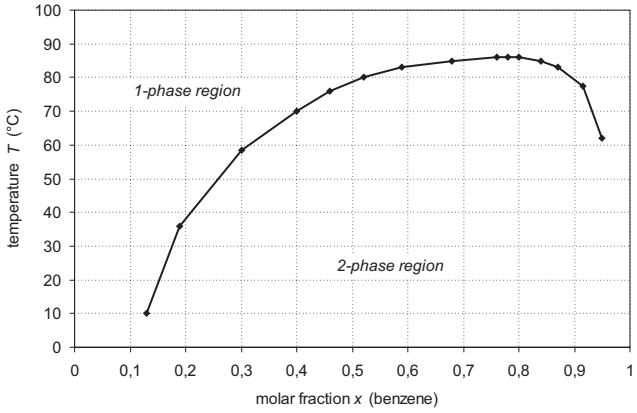
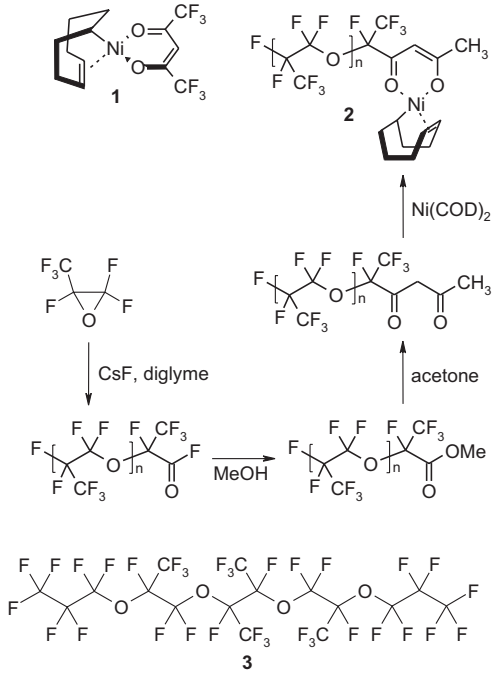


Figure 3.1 Phase diagram of the perfluoro(methylcyclohexane)/benzene system (x denotes the molar fraction of benzene; T_c is the critical temperature from which complete miscibility occurs [1, 2].

in the perfluorocarbon phase and can be separated from reaction mixture by simple means.

The effects of "fluorous" solvents and reagents have been utilized since the beginning of the 1990s. The first practical applications were the immobilization and recovery of expensive or toxic catalysts [3] and the use of chemically inert fluorocarbons to stabilize reactive intermediates [4] (Scheme 3.1).



Scheme 3.1 Catalysts for olefin dimerization – standard nickel catalyst **1** and its fluorous analog **2** (n = 3–5). In a Hostinert 216 (**3**)/toluene biphasic system the catalyst stays in the fluorous phase [5] whereas the product dissolves preferably in toluene [4].

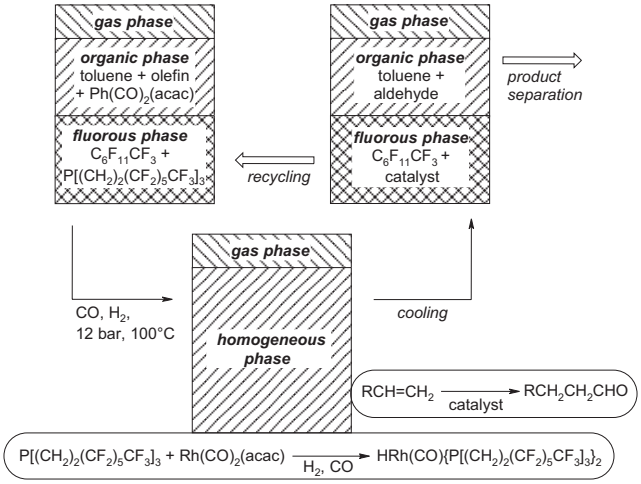
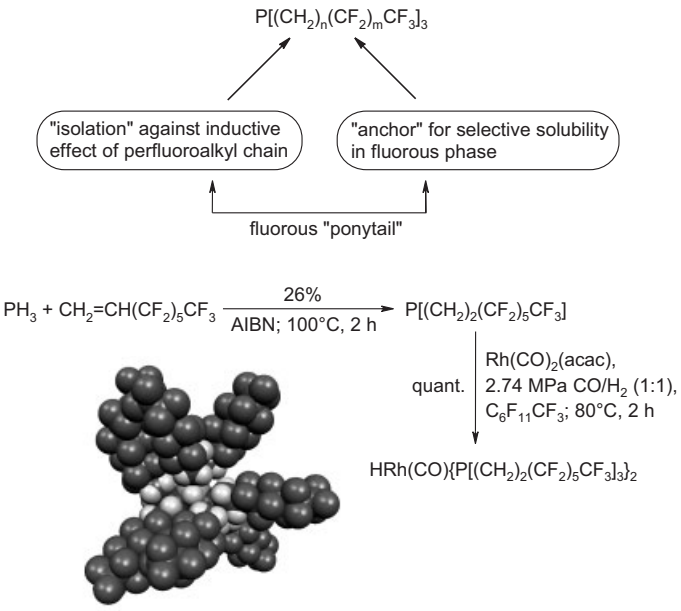


Figure 3.2 Principle of the Union Carbide hydroformylation process [7]. The reactands, precatalyst, and fluorous ligand in a fluorocarbon–hydrocarbon system are heated under carbon monoxide and hydrogen pressure to enable the catalyzed reaction in a homogeneous phase. On cooling the system separates and the expensive catalyst can be separated and re-used with the fluorous phase.

The real breakthrough in the fluorous biphase concept [6] came in 1994 when I. T. Horváth and J. Rábai described a novel catalytic hydroformylation process based on a fluorous solvent in combination with a fluorous catalyst [7] (Figure 3.2). The solvent system was perfluoro(methylcyclohexane)/toluene, and a fluorous rhodium catalyst was constituted *in situ* from $Rh(CO)_2(acac)$ and a phosphane ligand containing long perfluoroalkyl chains (often referred to as "ponytails"). The two-phase system is heated to 100 °C, under pressure, with the olefin, carbon monoxide, and hydrogen, forming a homogeneous phase in which hydroformylation occurs. On cooling the product separates with the organic phase as the upper layer and the catalyst retained in the fluorous phase (lower layer). For the next cycle new toluene and olefin are added and the procedure is repeated with only negligible leaching of the expensive rhodium catalyst into the organic product phase.

Several factors must be taken into account in the design of the fluorous phosphane ligand [8] (Scheme 3.2). (1) The fluorine content of the ligand should be >60 % of the molecular weight. (2) To shield the phosphorus center from the inductive effects of the perfluoroalkyl groups ("ponytails"), an isolating alkylene segment $(CH_2)_n$ has to be inserted. (3) If the fluorous chain $(CF_2)_mCF_3$ is too long the solubility of the ligand in the organic and fluorous phases will be too low. Because the ethylene bridge ($n = 2$) has been identified as the optimum isolating group, the best compromise between fluorophilicity and general solubility is the perfluorohexyl chain ($m = 5$).



Scheme 3.2 Design and synthesis of the fluorous phosphane ligands and the catalyst for fluorous biphasic hydroformylation [8].

The temperature-dependent miscibility of fluorous biphasic systems [1] can be predicted by use of the Hildebrand–Scratchard or regular solution theory [2, 9]. According to this theory the critical temperature (T_c), above which the two liquids of a biphasic system mix in all ratios is close to the phase-separation temperature of a biphasic system consisting of equal volumes of each phase:

$$T_c \approx \frac{K(v_1 + v_2)}{4R} \tag{1}$$

$$K = (\delta_1 - \delta_2)^2 \tag{2}$$

where R is the universal gas constant, and v_i the molar volume. The variable K (J m^{-3}) is a measure of the interaction energy between unlike molecules relative to that between similar molecules. The weaker the interaction between two unlike molecules, the higher the value of K. Large values of K correspond to a high critical temperature T_c, i. e. to low miscibility of the biphasic system.

$$\delta_i = \sqrt{\frac{\Delta H_i^v}{v_i}} \tag{3}$$

The Hildebrand parameter δ_i ($Mpa^{0.5}$) of a solvent is defined by Eq. (3) as a function of the enthalpy of vaporization (ΔH_i^v) and the molar volume (v_i). From Eqs (1) and (2) it can be calculated that two liquids are miscible at room temperature when $|\delta_1 - \delta_2|$ is less than ca 7 $Mpa^{0.5}$ for an average molar volume of 100 mL. The Hildebrand parameters, δ_i, are very low for typical fluorous solvents (ranging from 12.1 for perfluorohexane to 12.7 for perfluorotributylamine), intermediate for organic solvents (*n*-hexane 14.9, toluene 18.2, dichloromethane 19.8, acetonitrile 24.3), and high for hydrophilic solvents (methanol 29.7, ethylene glycol 34.9, water 48.0). Of special usefulness for fluorous biphasic separations are organic solvents with a Hildebrand parameter of approximately 18 $Mpa^{0.5}$, because these result in phase separation at room temperature. Supercritical carbon dioxide with a pressure-dependent δ-value between fluorous and organic solvents ($\delta(scCO_2) = 18.2\ Mpa^{0.5} \times \rho_{sc}/\rho_{liq}$) dissolves many fluorous compounds in sufficient concentrations to be useful as a "green" reaction medium [10].

A similar quantitative theory enabling prediction of the fluorophilicity f_i (a substance is considered fluorophilic if $f_i > 0$) or the fluorous partition coefficients P_i for fluorous reagents [11] is, unfortunately, not available.

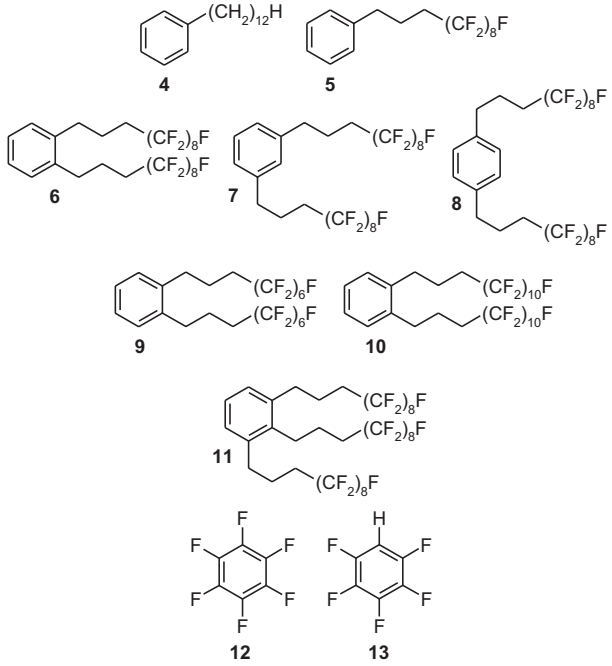
$$f_i = \ln P_i = \ln\left[\frac{c_i(C_6F_{11}CF_3)}{c_i(C_6H_5CH_3)}\right];\ T = 298\ K \tag{4}$$

Nevertheless, for general design of fluorous compounds some rules have been derived by combination of empirical and computational methods (QSAR, neural network simulation) [12]. These rules are illustrated by the data in Table 3.1 and can be summarized as follows:

- *Rule 1*: The fluorine content must be at least 60 % by molecular weight.
- *Rule 2*: The longer the fluorous ponytail, the higher the partition coefficient, and the lower the absolute solubility in both phases. On the other hand, an increase in the proportion of "anti-fluorous" (fluorophobic) [13, 14] domains in the molecule increases the absolute solubility in the organic phase.
- *Rule 3*: Increasing the number of fluorous ponytails leads to an increase in the partition coefficient while retaining acceptable solubility in the fluorous phase [15].
- *Rule 4*: The number of "anti-fluorous" functional groups capable of attractive intermolecular interactions, via electrostatic forces, hydrogen bonds, or dispersion interactions must be minimized [16]. An example of such an "anti-fluorous" effect is the low fluorophilicity of hexafluorobenzene (**12**) and pentafluorobenzene (**13**) despite their high relative fluorine content. Both compounds can participate in specific electrostatic interactions with electron-rich hydrocarbons, for example the toluene component of the biphasic test mixture.

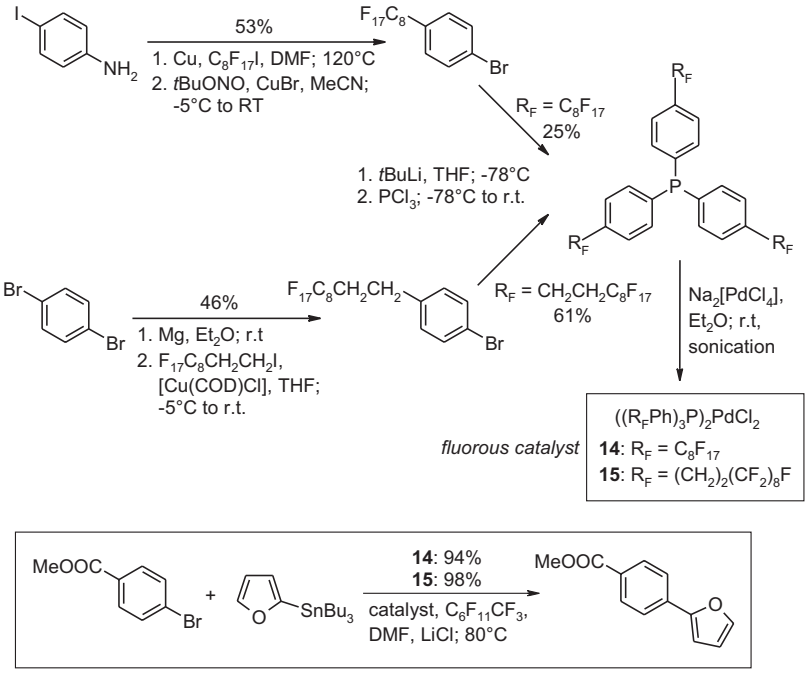
The effect of structure (linear or branched, incorporation of heteroatoms, etc.) and conformational flexibility or rigidity of the fluorous ponytail on the partition coefficients has not yet been studied in detail.

Table 3.1 Partition coefficients (P_i) at $T = 24\,°C$ in the perfluoro(methylcyclohexane)/toluene system, fluorophilicity parameters (f_i), and fluorine content (fluorine as a percentage of molecular weight) of a variety of fluorinated and non-fluorinated compounds (data modified or calculated from Ref. [17]).



Compound	P_i	f_i	*Fluorine Content*
4	0.10	−2.31	0
5	0.98	−0.02	60
6	10.36	2.34	64
7	9.75	2.28	64
8	10.24	2.33	64
9	2.80	1.03	62
10	37.46	3.62	67
11	>3000	>8	66
12	0.39	−0.94	61
13	0.29	−1.24	57

After publication of details of the biphasic catalytic hydroformylation system in 1994 many applications of the same concept were found. A variety of fluorous triaryl phosphane ligands was synthesized to enable recycling of precious transition metal catalysts [10b, 18] (Scheme 3.3).

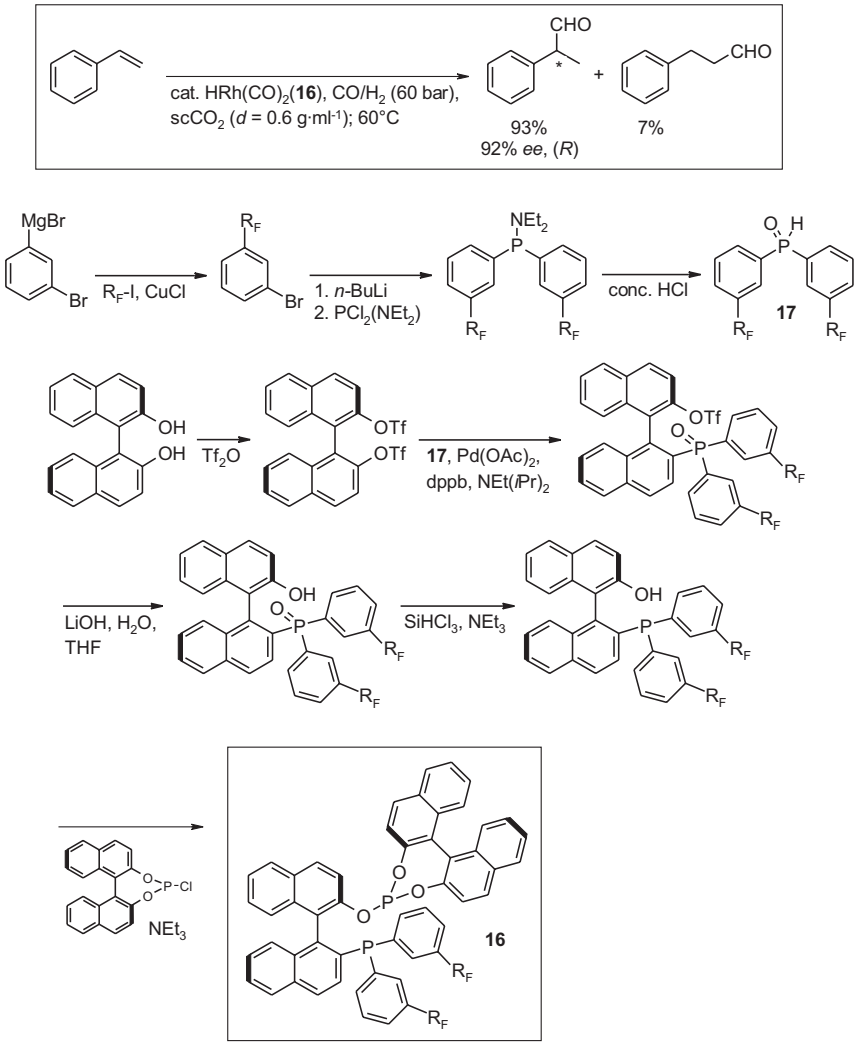


Scheme 3.3 One example of the synthesis of a fluorous phosphane ligand and one of the variety of reactions catalyzed by fluorous transition metal complexes [18g].

Because of their high solubility in supercritical carbon dioxide ($scCO_2$), similar fluorous catalyst systems have also been successfully used for enantioselective hydroformylation of olefins in this environmentally benign reaction medium [19] (Scheme 3.4).

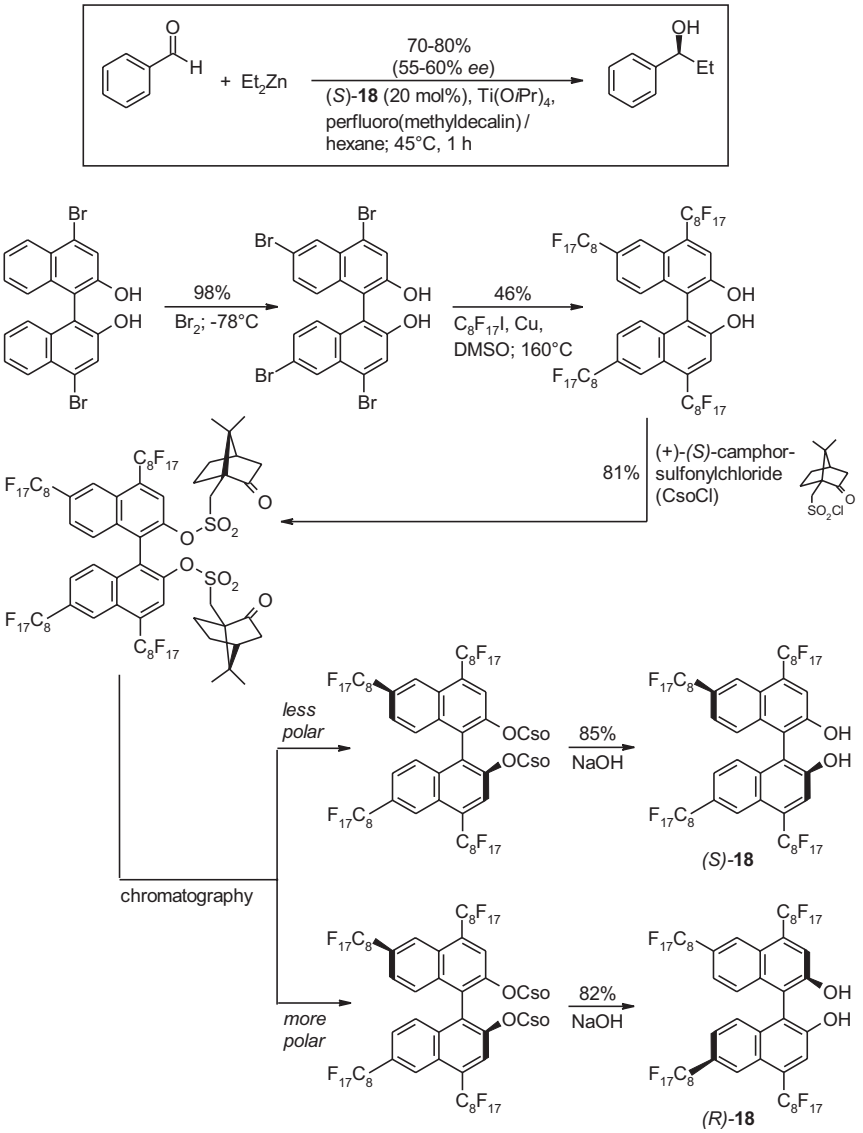
Fluorous chiral binaphthol ligands have been used for enantioselective addition of diethyl zinc to aldehydes in a biphasic system [20] (Scheme 3.5).

Lanthanoid salts with non-coordinating anions carrying long perfluoroalkyl chains, $Yb[C(SO_2C_8F_{17})_3]_3$ (**19**) and $Sc[C(SO_2C_8F_{17})_3]_3$ (**20**), have been successfully used as Lewis catalysts for *O*-acylations, Friedel–Crafts, Diels–Alder, and Mukayama aldol reactions in fluorous biphasic media [21] (Scheme 3.6). In these reactions the fluorous medium avoids deactivation of the Lewis acid by solvent coordination. The catalyst can also be recycled and reused.



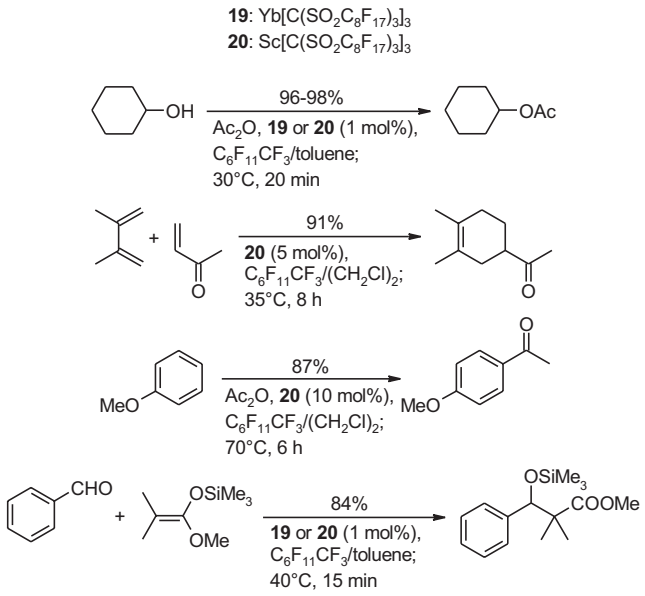
Scheme 3.4 Synthesis of the chiral fluorous (*R*,*S*)-3-H^{2}F^6-Binaphos (**16**) ligand for the rhodium-catalyzed enantioselective hydroformylation of olefins in supercritical carbon dioxide ($scCO_2$) [19] ($R_F = (CH_2)_2(CF_2)_6F$).

Disadvantages of this "classic" fluorous biphase catalysis are the high price and the large global warming potential of the perfluoroalkane solvent, even if it can be reused several times. Gladysz and coworkers reported a system making use of the extreme temperature-dependence of the solubility of fluorous trialkylphosphanes in organic solvents [22] (Figure 3.3). For example, the solubility of the fluorous



Scheme 3.5 Enantioselective carbon–carbon bond formation in a fluorous biphasic system (*top*), and synthesis of the fluorous BINOL catalyst **18** (*bottom*) (Cso = camphorsulfonyl) [20].

phosphane $P[(CH_2)_2(CF_2)_8F]$ (**21**) in octane is 150-fold higher at 100 °C than at 20 °C. After catalyzing the addition of an alcohol to methyl propiolate in a simple hydrocarbon solvent, the phosphane catalyst can be nearly quantitatively removed from the reaction mixture simply by cooling to −20 °C and decanting from the waxy solid.



Scheme 3.6 Reactions in fluorous biphasic media catalyzed by fluorous lanthanoid-based Lewis acids [21].

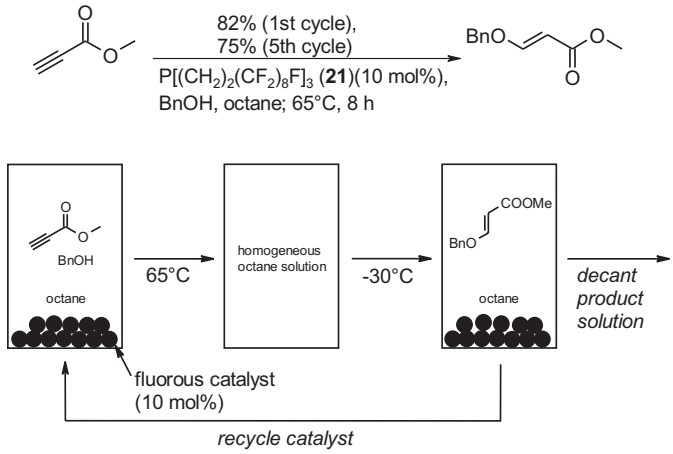
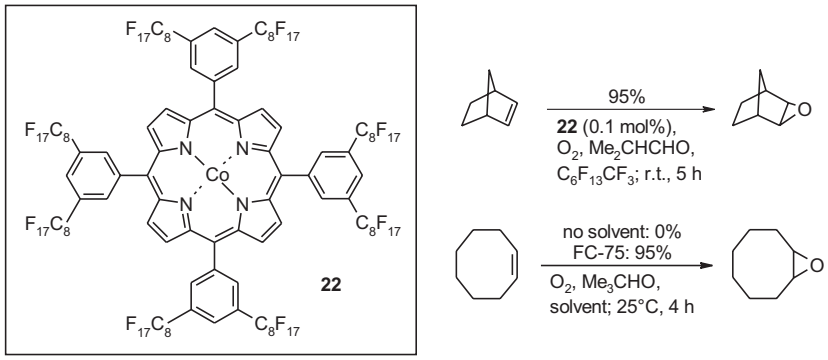


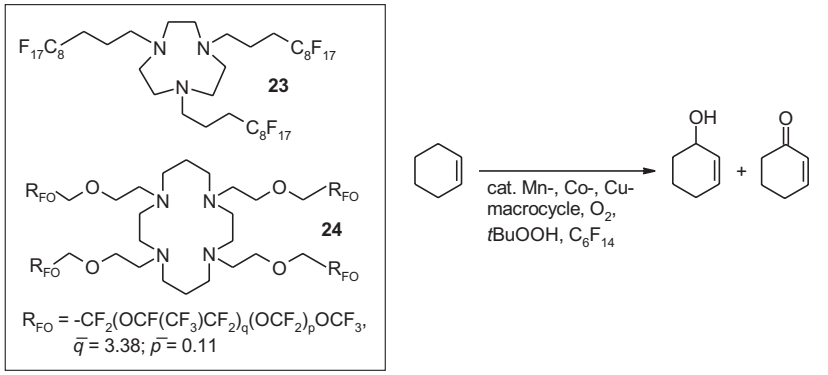
Figure 3.3 Catalysis with a fluorous phosphane catalyst (**21**) in a homogeneous hydrocarbon solvent. Because of the very different solubility of **21** in hot and cold octane, the catalyst can be quantitatively precipitated from the reaction mixture by simple cooling to −30 °C (the lower scheme was re-drawn from Ref. [22]).

For typical fluorous biphase catalysis the most important aspect is the simple recycling and re-use of the catalyst. Fluorous solvents have one special advantage over hydrocarbon solvents, however. Their very high oxygen dissolving capacity, combined with their extreme resistance to oxidative decomposition makes perfluorocarbons in combination with fluorous catalysts the optimum choice for oxidation reactions. Thus, the biomimetic oxidation of olefins with molecular oxygen and 2-methylpropanal as a co-reductand has been achieved with a fluorous cobalt porphyrin catalyst (**22**) [23], and also even without catalyst [24] (Scheme 3.7).

Similar results have been obtained with manganese, cobalt, and copper complexes of fluorous aza-crown ethers (**23**, **24**) [25] (Scheme 3.8).

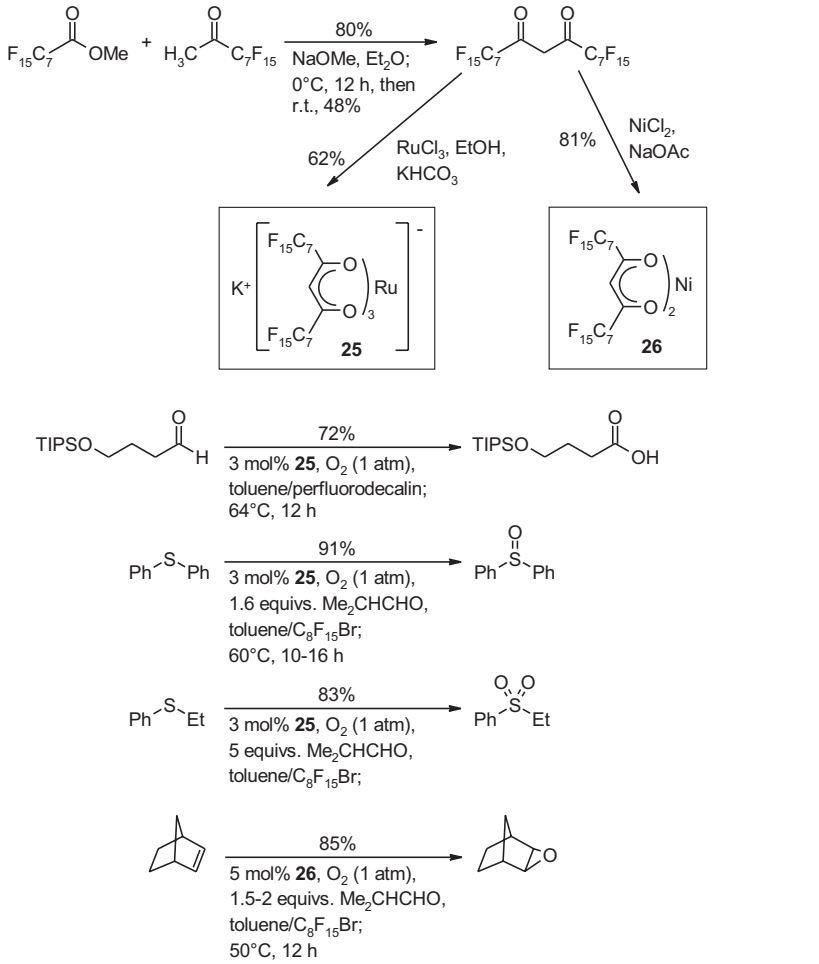


Scheme 3.7 Catalyzed and uncatalyzed biomimetic oxidations in fluorous solvents (FC-75 consists mainly of perfluoro *n*-butyltetrahydrofuran, b. p. 102 °C, commercially available from 3M) [23, 24].



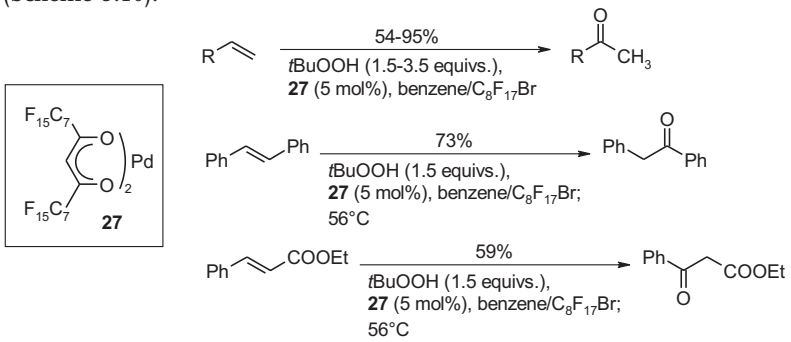
Scheme 3.8 Oxidation of cyclohexene with molecular oxygen catalyzed by transition metal complexes of fluorous macrocycles (**23**, **24**) in perfluorohexane as solvent [25].

A variety of different substrates can also be oxidized by molecular oxygen in the presence of fluorous ruthenium or nickel β-diketonates in fluorous solvents [26] (Scheme 3.9).



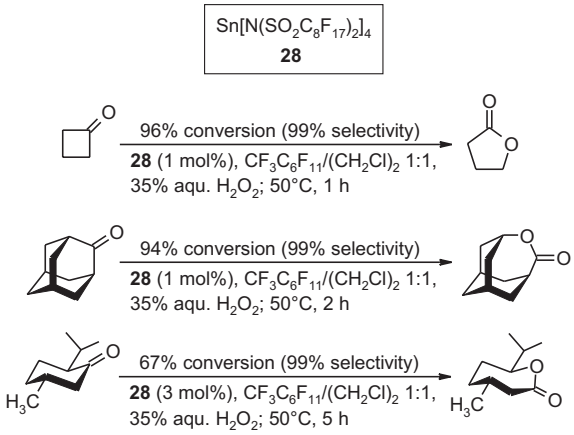
Scheme 3.9 Oxidations with molecular oxygen, catalyzed by fluorous ruthenium and nickel β-diketonates (**25**, **26**) [26].

Similar, fluorous palladium β-diketonate complexes (**27**) have been employed for Wacker oxidation of olefins to the corresponding ketones in a biphasic system [27] (Scheme 3.10).



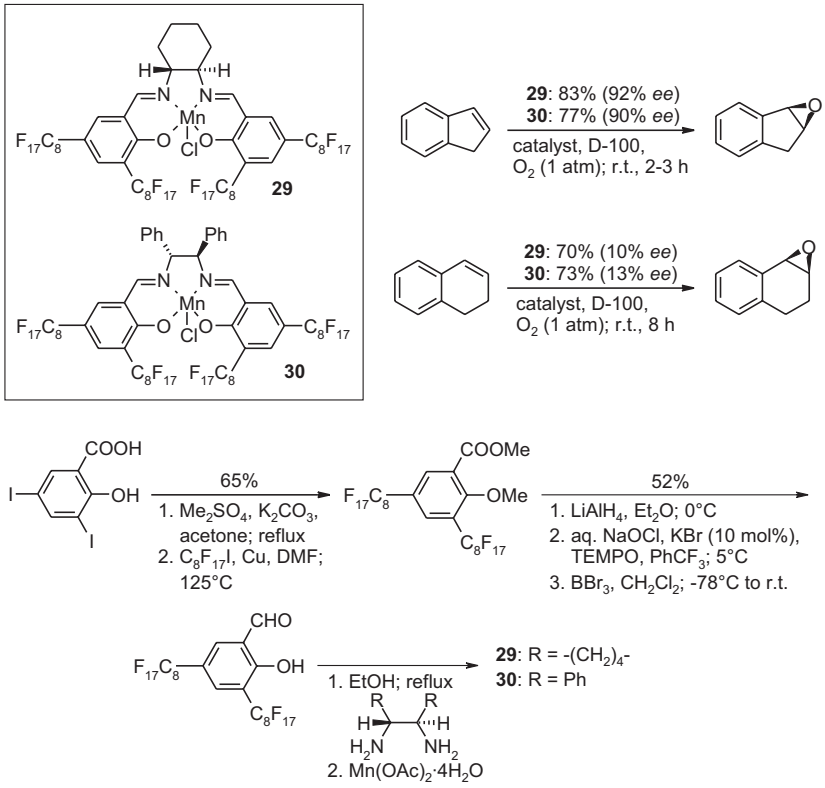
Scheme 3.10 Wacker oxidation of olefins with a fluorous Pd(II) catalyst (**27**) in a biphasic system [27].

Another industrially important oxidation reaction, the Baeyer–Villiger oxidation [28] of ketones to esters by 35 % aqueous hydrogen peroxide as oxidant, can also be advantageously conducted in a fluorous biphasic medium [29]. When the recyclable fluorous Lewis acidic tin(IV) complex (**28**) is used as catalyst very high selectivity of conversion of ketones to the corresponding esters or lactones is achieved (Scheme 3.11).



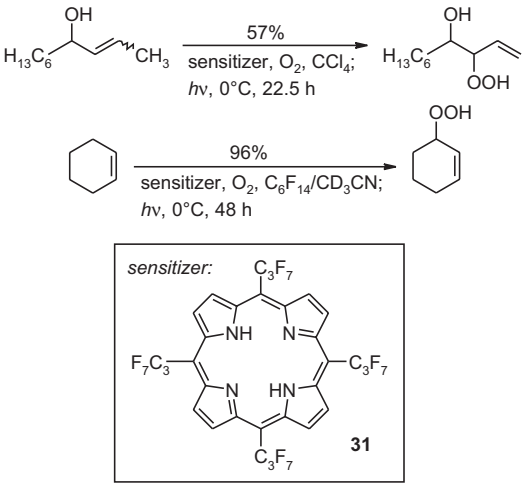
Scheme 3.11 Baeyer–Villiger oxidation of ketones to the corresponding lactones. The oxidations were conducted in a fluorous biphasic medium in the presence of the fluorous tin(IV) complex **28** as Lewis acid catalyst. The selectivity is defined as the ratio of the quantity of lactone formed to that of ketone used [29].

The use of fluorous chiral manganese salene (Jacobsen–Katsuki) catalysts (**29**, **30**) [30] in combination with different oxidants enables enantioselective epoxidation of olefins [31] in high yields and with moderate to high enantiomeric excess (Scheme 3.12).



Scheme 3.12 Enantioselective epoxidation of olefins with fluorous Jacobsen–Katsuki catalysts **29** and **30** (*above*) [31a], and the synthesis of these catalysts (*below*) (D-100 consists mainly of *n*-perfluorooctane, b. p. 100 °C, and is commercially available from Ausimont).

Because of the inertness of perfluorohexane and of 5,10,15,20-tetrakis(perfluoropropyl)porphyrin (**31**) as sensitizer, the photocatalyic oxidation of allyl alcohols and cyclohexene with singlet oxygen ($^1O_2$) can be achieved with negligible degradation of the porphyrin catalyst [32] (Scheme 3.13). In perfluorohexane singlet oxygen has the relatively long lifetime of ~100 ms whereas the lifetime in acetonitrile is only 54.4 μs [33]. In contrast, if "non-fluorous" tetraphenylporphyrin is used instead of its fluorous analog the catalyst is rapidly destroyed by oxidation.



Scheme 3.13 Photosensitized oxidation of allylic alcohols and cyclohexene with singlet oxygen ($^1O_2$) in the presence of a fluorous porphyrin sensitizer (**31**) [32a].

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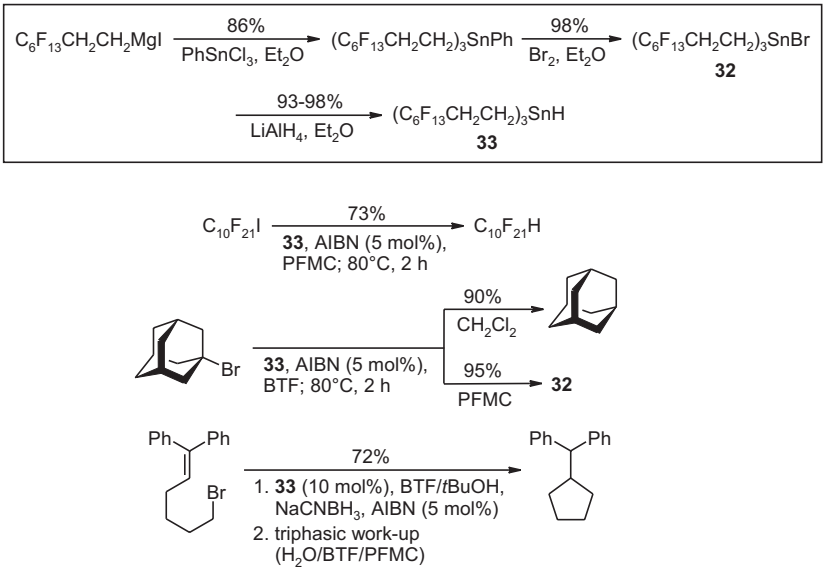
3.2
Fluorous Synthesis and Combinatorial Chemistry

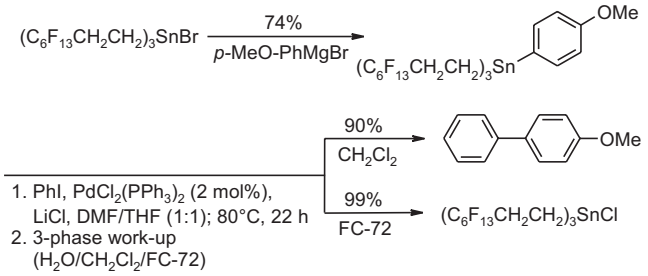
3.2.1
Fluorous Synthesis

Fluorous solvents and biphasic systems have advantages not only for catalytic processes but also for classic organic synthesis. Since the mid-1990s several synthetic procedures have been published which make use of fluorous reagents which facilitate either work-up or recycling, particularly of toxic compounds. One of the first examples, combining both of these advantages, was the introduction of fluorous tin halides [1] and hydrides [2] by Curran and coworkers [3] (Scheme 3.14). Fluorous tin halides can be reduced to the corresponding hydrides, which are the reagents of choice for radical hydrodehalogenations. After the reaction the reagent used, again a fluorous tin halide, can be recovered readily by extraction with a perfluorocarbon solvent.



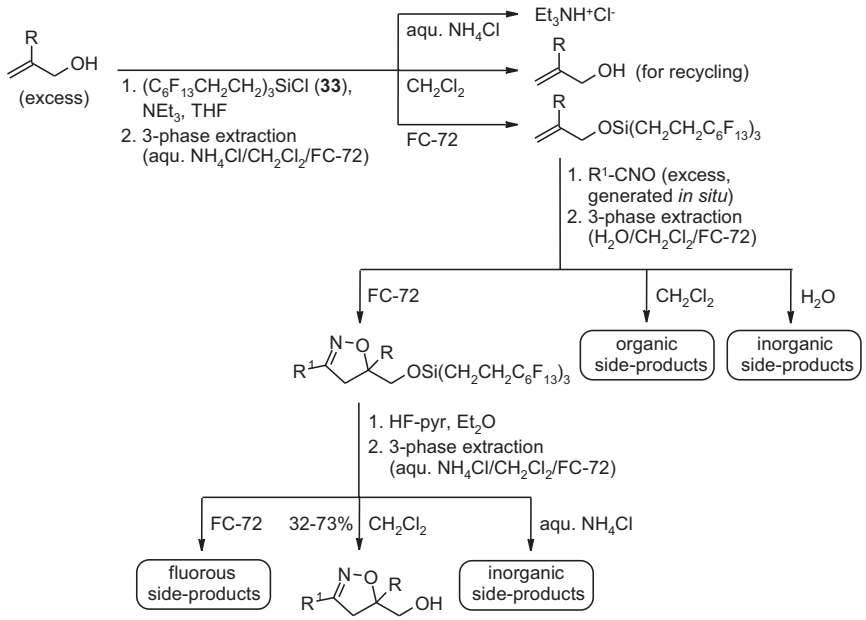
Scheme 3.14 Examples of radical reductions by the fluorous tin hydride reagent **33**. The reagent can be removed from the reaction mixture by organic–fluorous liquid–liquid extraction [2a, 3].

The fluorous tin halides are also of use as precursors for the trialkylstannyl activating group which is required for the Stille coupling [4]. Here a trialkylstannyl arene (typically tributylstannyl) is cross-coupled with a bromoarene in the presence of a palladium catalyst. The major obstacle to large-scale application of the Stille reaction is the toxicity of the auxiliary organotin reagents. If a fluorous version of the trialkylstannyl residue is used instead, the organotin byproducts can be easily recovered by means of a reaction work-up with an organic–aqueous–fluorous three-phase extraction procedure [1a, 1d] (Scheme 3.15). Purification of the biaryl reaction product is also significantly simplified by this procedure, because separation of organotin compounds from other substances is notoriously difficult.



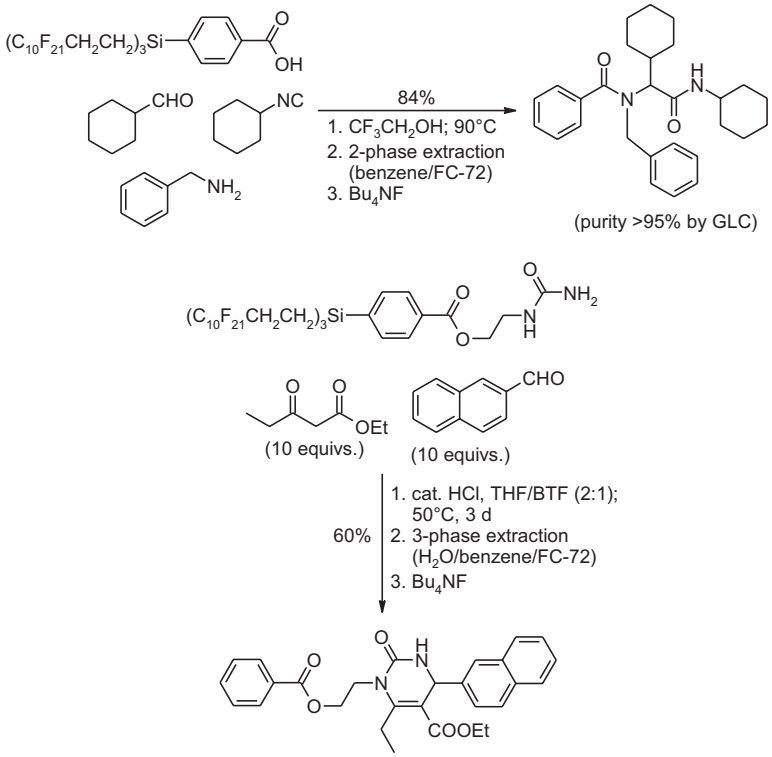
Scheme 3.15 Stille coupling with a fluorous trialkyltin arene component [1a]. Triphasic work-up enables convenient removal (and possible subsequent recycling) of toxic organotin side-products (FC-72 consists mostly of isomers of C_6F_{14}, b. p. 56 °C, and is commercially available from 3M).

Fluorous trialkyl silyl protecting groups have also been used to simplify the purification of complex reaction mixtures [5] (Scheme 3.16). Separation of the reaction products can be achieved by means of a simple three-phase extraction (aqueous/organic/fluorous) instead of the usual chromatography. In this respect, the concept of using fluorous protecting groups has some parallels with the solid-phase-supported chemistry which also was primarily developed to simplify multiple work-up operations.



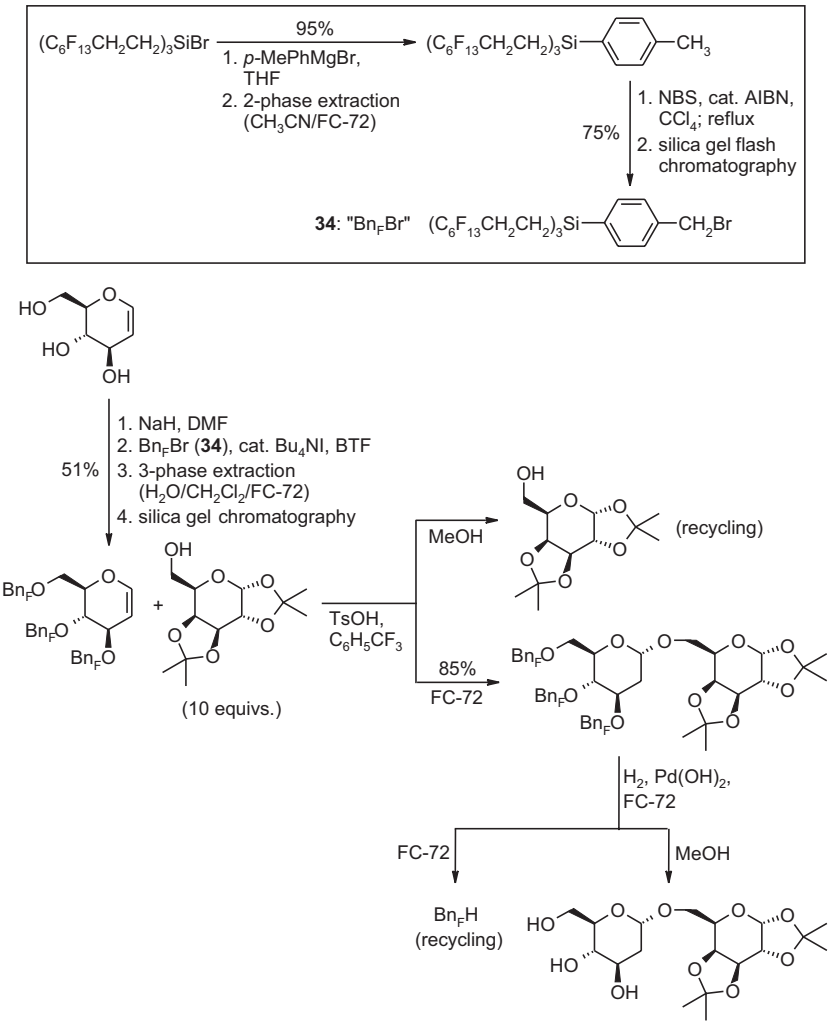
Scheme 3.16 Simplification of product purification after 1,3-dipolar cycloaddition by use of fluorous silyl protecting groups (R = H, CH_3; R^1 = CH_3, C_3H_7, Ph) [5]. The nitrile oxide (R^1-CNO) is generated *in situ* by either the Huisgen or Mukaiyama method [6].

Another example of the advantages of fluorous markers for facilitating product purification are multi-component reactions such as the Ugi [7] or Biginelli reactions [8] (Scheme 3.17). Fluorous tagging of one component and use of the other components in large excess drives the reaction to completion and enables separation of the desired fluorous condensation product from side-products and remaining other reagents by simple two- or three-phase liquid–liquid extractions [5]. In the final reaction step the fluorous silyl group is removed by treatment with tetrabutylammonium fluoride (TBAF). The product is thus obtained in high purity, requiring no chromatographic purification of any of the intermediates.



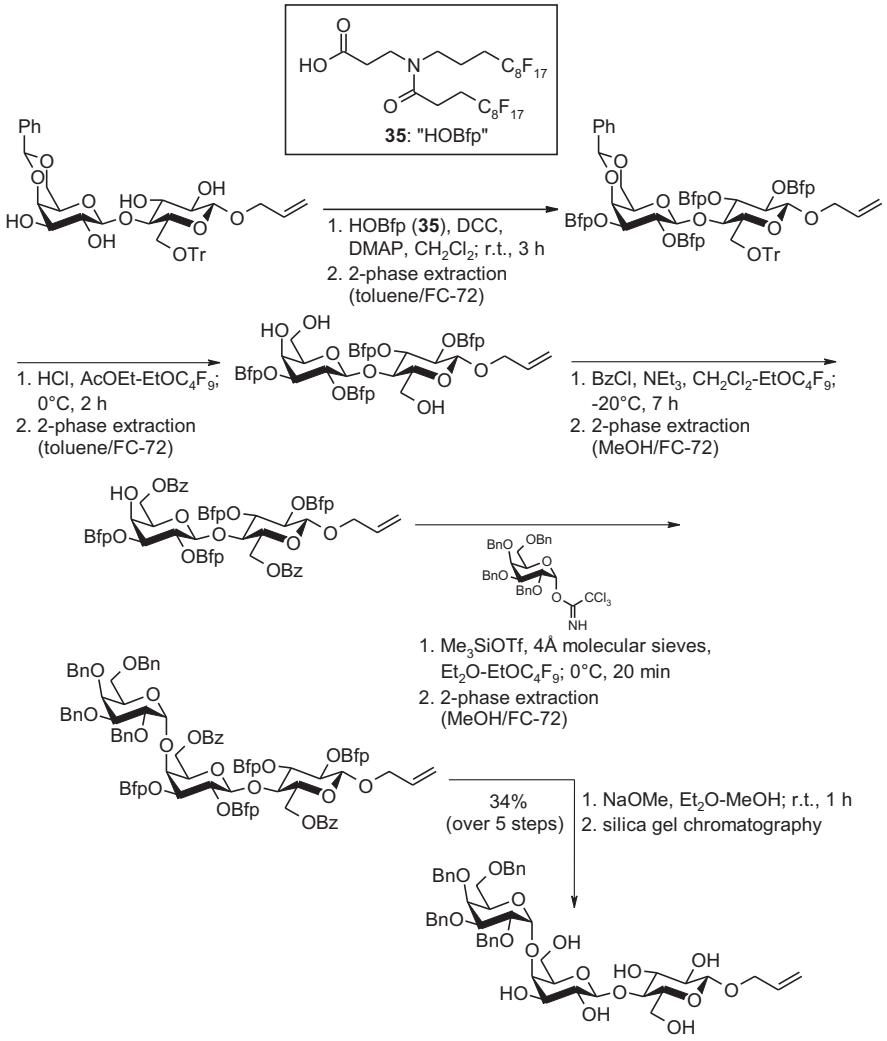
Scheme 3.17 Fluorous variants of the Ugi (*above*) and Biginelli multi-component reactions (*below*) enable the purification of the primary fluorous condensation products (not shown in this scheme) by simple two- or three-phase extraction, followed by "traceless" cleavage of the fluorous silyl tag with TBAF [5].

Formation of glycosidic linkages can be achieved by a variety of different methods [9]. In principle, for most of these methods the yield of the glycosidation product can be optimized by using a large excess of either the glycosyl donor or the acceptor component. Nevertheless, this approach is not often chosen, because of the resulting separation problems or the difficult accessibility of the excess component. Again the use of fluorous auxiliary groups offers an elegant solution to this dilemma. Because carbohydrate chemistry is highly dependent on protecting group methodology, the use of modified fluorous protecting groups, for example a fluorous benzyl group, enables simple separation and purification of the desired glycosylation product, and the fluorous protecting reagent (**34**) can even be recycled for repeated use [10] (Scheme 3.18).



Scheme 3.18 Synthesis (*box*) and use of a fluorous benzyl protective group ($Bn_F = (C_6F_{13}CH_2CH_2)_3SiPhCH_2$) in carbohydrate chemistry [10a]. The Bn_F protecting group enables the use and subsequent clean separation of excess glycosyl acceptor for a glycal-based glycosylation procedure [11].

A related strategy was used for synthesis of a more complex carbohydrate, the trisaccharide moiety of globotriaosyl ceramide (Gb3) [10b] (Scheme 3.19). In this reaction an acyl-based fluorous protecting group was used to facilitate the intermediate purification steps in a similar way as can be achieved by solid phase carbohydrate chemistry [12].



Scheme 3.19 Synthesis of a precursor of the trisaccharide moiety of globotriaosyl ceramide (Gb3) [10b] using a fluorous acyl protecting group (Bfp) ($EtOC_4F_9$ is commercially available from 3M under the brand name Novec HFE-7200).

3.2.2
Separation on Fluorous Stationary Phases

To make effective use of fluorous biphasic systems, the fluorous phase may also be a stationary phase. Fluorous compounds or compounds carrying fluorous "ponytails" have high affinity for "fluorous reversed-phase" silica gel [1c, 13] which has been modified by means of a fluorous silane [14]. This effect has been used to achieve convenient isolation and purification of a variety of compounds with high fluorine content, first by simple solid-phase extraction (SPE) [15] and later by chromatography with a mobile phase based on a fluorophilicity gradient [16].

In fluorous solid phase extraction (FSPE; Figure 3.4), a reaction mixture containing organic and fluorous components is placed on a fluorous silica gel column in a "fluorophobic" solvent, for example acetonitrile, methanol or a methanol–water mixture. Then, with a fluorophobic mobile phase, first the organic compounds are eluted while the fluorous compounds remain adsorbed by the solid phase. In the second step a "fluorophilic" solvent such as THF, diethyl ether, or benzotrifluoride (BTF) is used to elute the fluorous compounds.

If, instead of two-solvent FSPE, a gradient leading from a fluorophobic solvent to a fluorophilic solvent is used, real chromatography becomes possible on fluorous reversed-phase silica gel (Figure 3.5). Although "ordinary" organic compounds cannot be separated by fluorous chromatography, for substances with perfluoroalkyl substituents of different lengths very efficient separations can be achieved. Within the same class of substance elution occurs in order of the fluorine content of the analyte. This rule cannot, however, be generalized, because other factors such as polarity and structural features also have a significant effect on retention times [17].

3.2.3
Fluorous Concepts in Combinatorial Chemistry

Fluorous chromatography is a simple means of separating different perfluoralkyl homologs of structurally similar compounds and a unique opportunity for combinatorial chemistry.

One of several different approaches [18] to the preparation of larger compound libraries for medicinal chemistry or materials science is parallel mixture synthesis in solution. Here, a library of m somehow "labeled", structurally similar, starting materials (S) is mixed, and then subjected to a number (n) of synthetic steps. So far, this approach is highly economic and time-saving – $m \times n$ reaction steps have been condensed into only n, in addition to the initial m labeling procedures. The problem starts with the de-mixing of the labeled products. For "conventional" labels (such as fluorophors) in combination with standard or reversed-phase chromatography the retention times of the products depend mostly on their polarity and on sometimes subtle differences between their molecular structures. Therefore, even if all products can be separated, considerable efforts must subsequently be made to correlate the isolated fractions with the desired structures within the library. Because of these difficulties, for conventional solution-phase-mixture syntheses the problem has often been circumvented by directly subjecting "organized" mixtures to biological assays in a so-called deconvolution process [19].

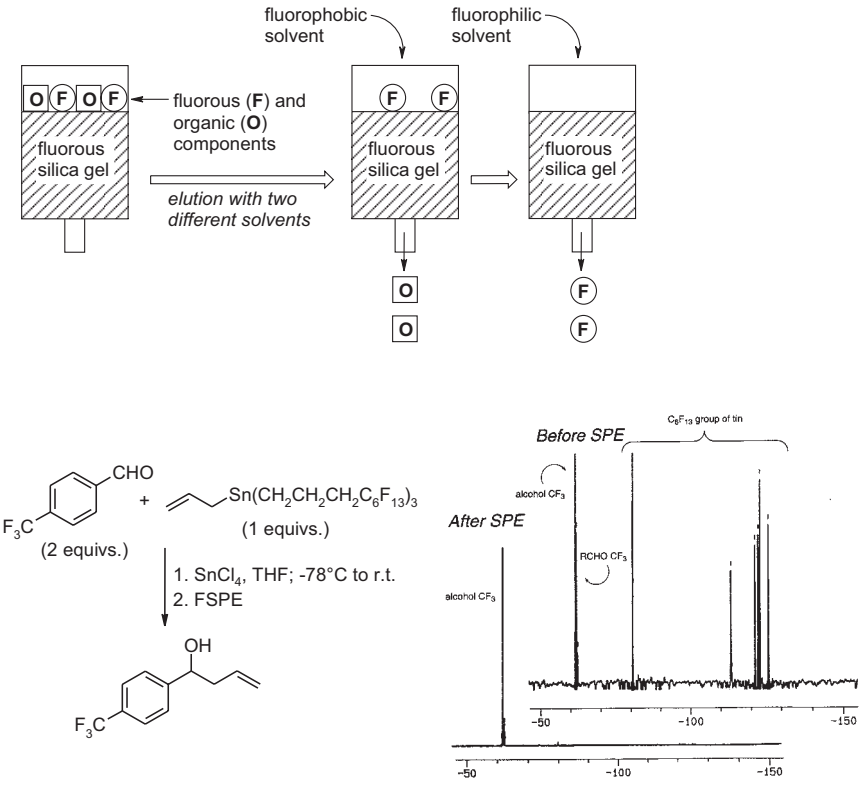


Figure 3.4 The principle of fluorous solid-phase extraction (FSPE). Allylation of 4-trifluoromethylbenzaldehyde with a fluorous allyl tin reagent and subsequent work-up of the reaction mixture by FSPE. To the *right* of the reaction scheme the ^{19}F NMR spectra of the reaction mixture before and after FSPE purification are shown (figure modified from Ref. [16], courtesy of Thieme Verlag).

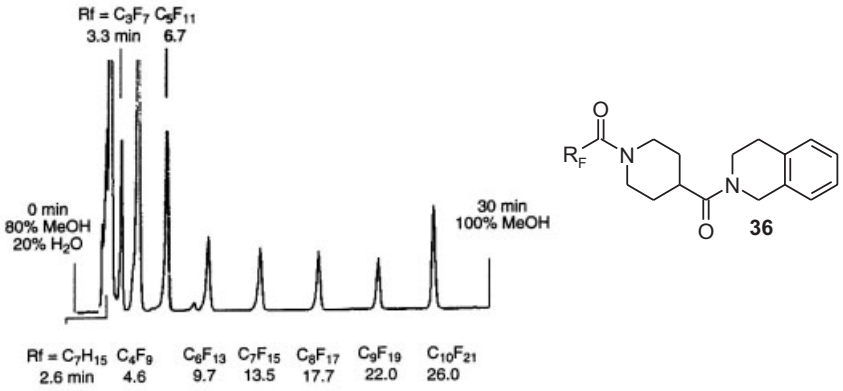


Figure 3.5 Separation of a mixture of amides (**36**) carrying different perfluoroalkanoyl substituents on a Fluofix 120E column (figure modified from Ref. [16], courtesy of Thieme Verlag). A gradient from MeOH/H_2O 80:20 (highly fluorophobic) to MeOH (slightly fluorophilic) was used as mobile phase.

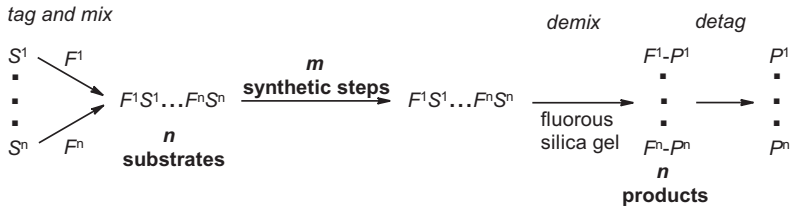
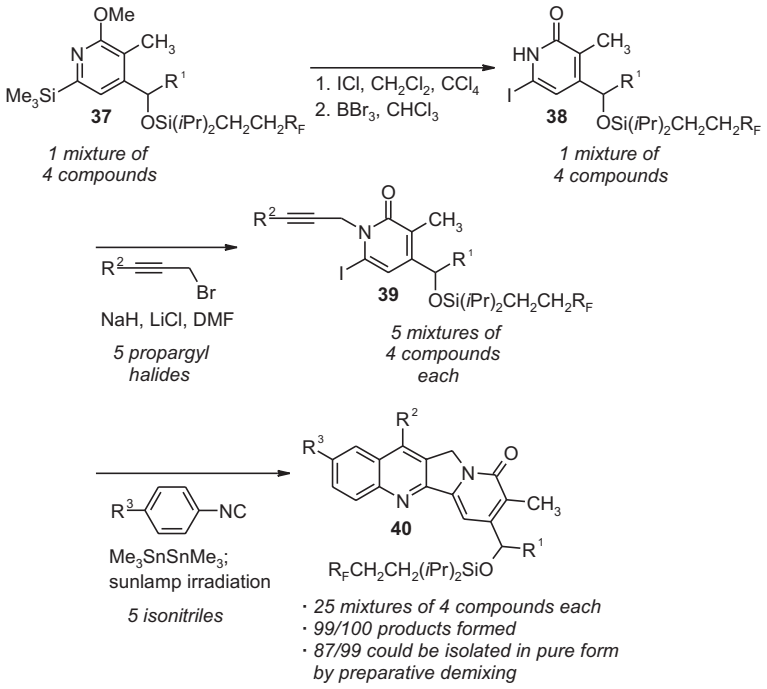


Figure 3.6 Schematic representation of the principle of fluorous mixture synthesis [17, 20]. By this scheme $m \times n$ reaction steps can be performed in parallel by means of m synthetic steps plus n tagging and n detagging procedures.



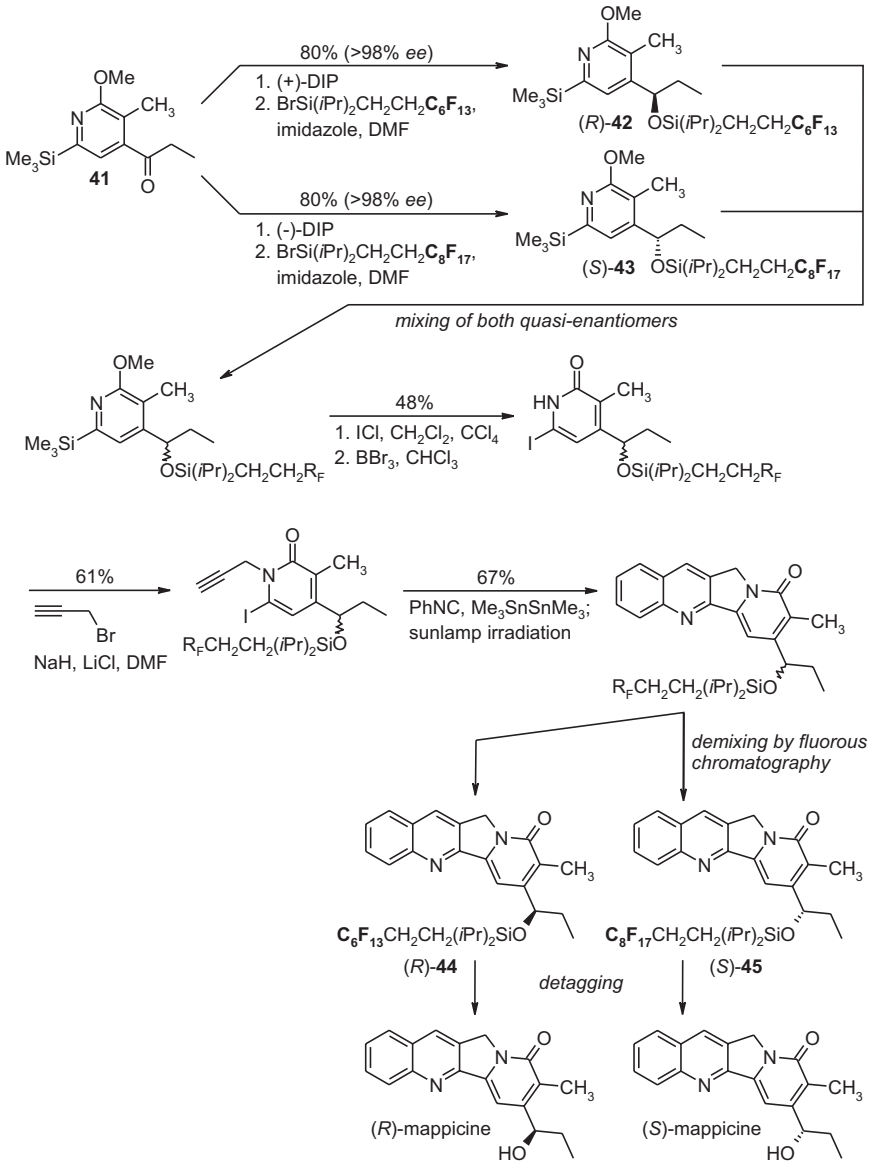
Scheme 3.20 Fluorous mixture synthesis of 100 mappicine analogues [20]. The coding scheme for the substituents R_F, R^1, R^2, and R^3 is: R^1, R_F = Pr, C_4F_9; Et, C_6F_{13}; *i*Pr, C_8F_7; $CH_2CH_2C_6H_{11}$, $C_{10}F_{21}$; R^2 = H, Me, Et, C_5H_{11}, Si(*i*Pr)Me_2; R^3 = H, F, Me, OMe, CF_3. The mixture of **37** (four compounds) was converted into four compounds of **38**, which were split and reacted with five propargyl bromides. The resulting five mixtures (each containing four different propargyl amines **39**) were split and reacted with five isonitriles, giving five mixtures containing 20 different tagged, racemic mappicines **40**, each. Demixing was achieved on a preparative Fluofix 120E column with the gradient: 0 to 30 min, 80 % MeOH/H_2O to 100 % MeOH; 30 to 40 min, 100 % MeOH to 90 % MeOH/10 % THF.

The combination of fluorous synthesis with fluorous chromatography offers an elegant solution to this labeling problem (Figure 3.6). If the starting library (S^n) is tagged with different fluorous labels (F^n) of different lengths, after mixing and conducting the series of synthetic conversions demixing of the labeled product library ($F^n - P^n$) can be conveniently achieved by fluorous chromatography. As an additional advantage, for smaller libraries the identity of the isolated labeled compounds can be derived from the order of elution, which is far more strongly related to the length of the fluorous alkyl label than to other structural characteristics.

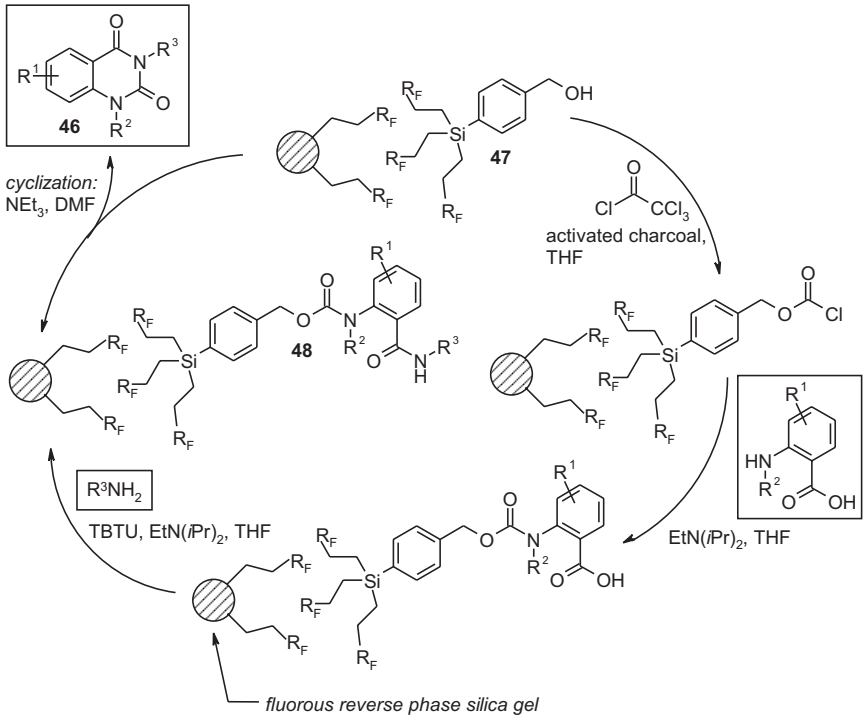
This concept of fluorous mixture synthesis has been used and extended for the preparation of compound libraries of interest in medicinal chemistry [17, 20–22]. The introduction of additional substituent groups in combination with the discriminating perfluoroalkyl labels during the synthetic sequence enables convenient preparation and subsequent separation of relatively large libraries. For the library of 100 mappicine derivatives outlined in Scheme 3.20, 300 reactions would be required for the conventional, sequential approach. By application of fluorous mixture synthesis this was condensed into 26 steps. In addition, four tagging and 100 detagging operations are required to obtain the full, unprotected 100-member library from unprotected starting materials.

A similar approach of "fluorous quasi-racemic synthesis" [20] was used to synthesize both enantiomers of mappicine at the same time in a "coded" mixture. The pyridine derivative **41** was split, and the carbonyl group was reduced enantioselectively by (+)- and (-)-DIP-Cl, respectively. The resulting enantiomerically pure alcohols were subsequently derivatized – the (*R*) enantiomer with $BrSi(i\text{Pr})_2CH_2CH_2C_6F_{13}$ to yield (*R*)-**42** and the (*S*) enantiomer with $BrSi(i\text{Pr})_2CH_2CH_2C_8F_{17}$ to yield the quasi-enantiomer (*S*)-**43**. The mixture of both quasi-enantiomers was then subjected to the reaction sequence leading to the fluorous mappicines (*R*)-**44** and (*S*)-**45**. These were separated by fluorous chromatography and deprotected to yield the two mappicine enantiomers (Scheme 3.21).

A recent example of the parallel synthesis of different quinazoline-2,4-dione derivatives (**46**) demonstrates how to combine the advantages of fluorous synthesis with those of solid-phase chemistry without using expensive perfluorinated solvents [22] (Scheme 3.22). In the beginning, a fluorous benzyl alcohol (**47**) is adsorbed on fluorous reversed-phase silica gel (FRPSG). Then, in a sequence of splits and reactions, the linker group, which remains bound to the FRPSG by fluorophilic interactions, is converted into a library of differently substituted carboxamidourethanes (**48**). These are cyclized and the liberated quinazoline-2,4-diones (**46**) are eluted from the support with the fluorophobic solvents water and CH_3CN/H_2O 4:1, leaving the fluorous benzyl alcohol adsorbed by the fluorous phase to be re-used in another reaction cycle.

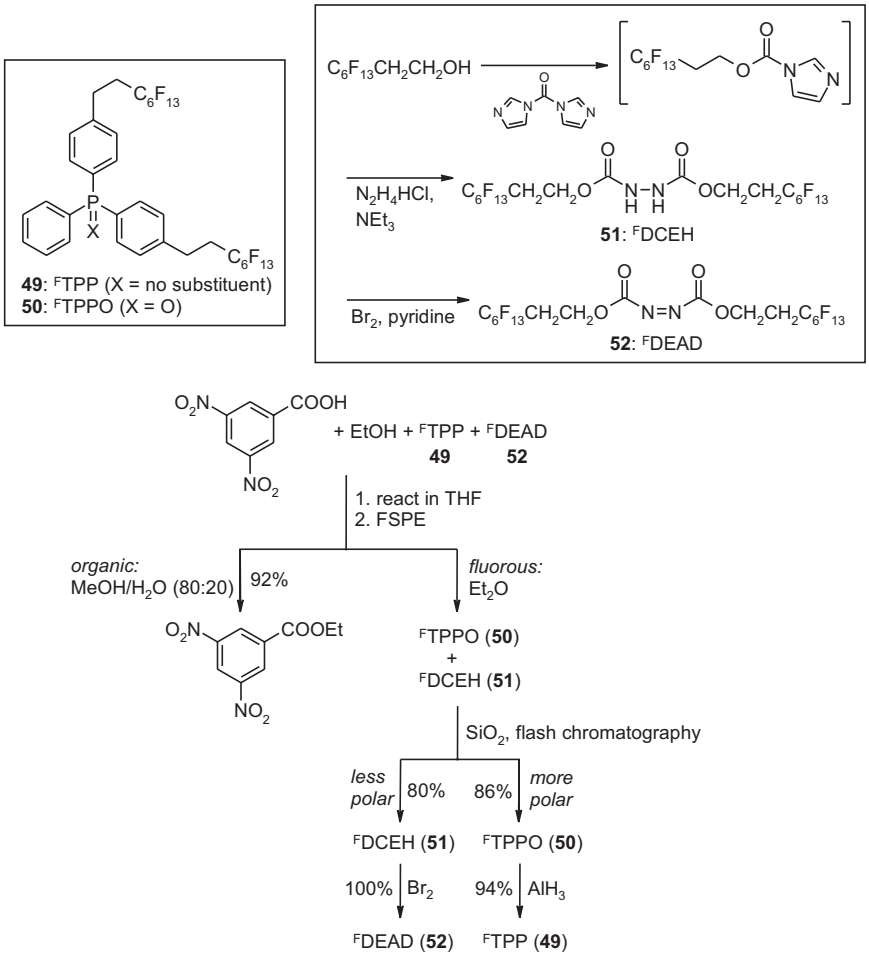


Scheme 3.21 "Fluorous quasi-racemic synthesis" of both enantiomers of mappicine [20]. (DIP = diisopinocampheylborane; R_F is either C_6F_{13} or C_8F_{17}).

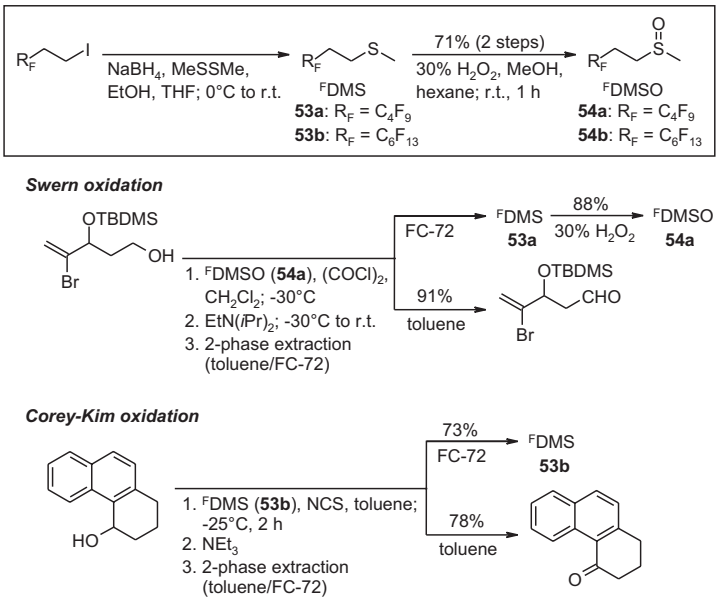


Scheme 3.22 Fluorous synthesis of a library of substituted quinazoline-2,4-diones (**46**) [22]. The key to this approach is a fluorous benzyloxycarbonyl group on which the target molecules are stepwise constructed and which keeps the different synthetic intermediates bound to fluorous reversed-phase silica gel (FRPSG) during the purification cycles. The structural diversity of the target compound library (**46**) is introduced by the different anthranilic acid derivatives and primary amines (*in boxes*) (TBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate).

In the last few years fluorous combinatorial chemistry has been extended and augmented by other fluorous techniques developed by analogy with established methods in solid-phase-supported synthesis. Use of fluorous condensation reagents for the Mitsunobu reaction [23] enables easy removal of all condensation reagents except the coupled starting materials after the reaction [24] (Scheme 3.23). A fluorous variant of the Swern [25] and Corey–Kim oxidations [26] enables handling of stoichiometric quantities of malodorous dimethyl sulfide to be avoided [27] (Scheme 3.24).

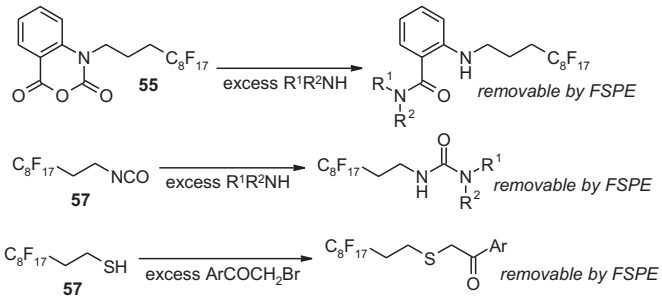


Scheme 3.23 The Mitsunobu reaction with fluorous condensation reagents [24] enables the simple purification of the reaction product and recycling of the reagents ^{F}TPP (**49**) and ^{F}DEAD (**52**). (^{F}TPP = fluorous triphenylphosphine; ^{F}TPPO = fluorous triphenylphosphine oxide; ^{F}DEAD = fluorous diethyl diazodicarboxylate; ^{F}DCEH = fluorous dicarboxyethoxyhydrazine).



Scheme 3.24 Fluorous variants of the Swern and Corey–Kim oxidations of alcohols to the corresponding aldehydes or ketones [27] (^{F}DMS = fluorous dimethyl sulfide; ^{F}DMSO = fluorous dimethylsulfoxide).

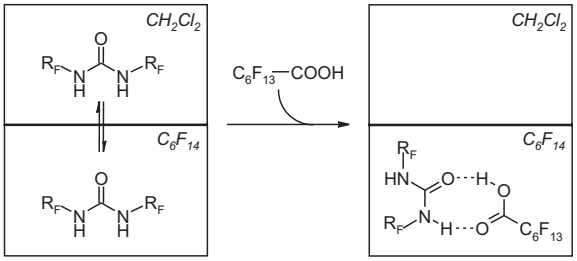
Fluorous scavengers facilitate removal of excess reagents from complex reaction mixtures [28] (Scheme 3.25). Thus, the fluorous anhydrides **55** and isocyanates **56** enable the removal of excess amine reagents. Several custom-tailored fluorous scavengers with complementary reactivity are available for removal of other reactive species.



Scheme 3.25 Examples of fluorous scavengers enabling simple removal of excess reagents from complex reaction mixtures [28].

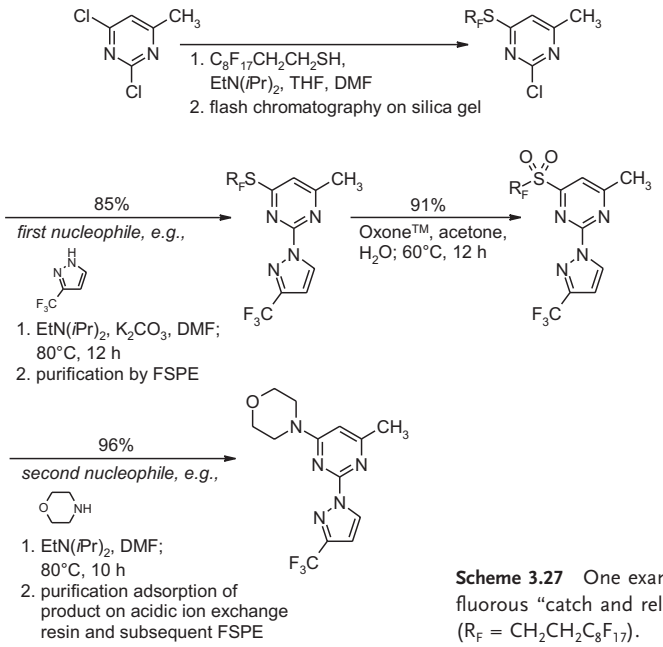
Fluorous scavengers do not necessarily need to form a covalent bond with the species they have to remove into the fluorous phase. For example, "lightly" fluorous *N,N′*-dialkyl ureas can bind to perfluorocarboxylic acids by hydrogen

bonding [29]. Although the urea is partly dissolved in the organic phase, the resulting complex has a significantly increased fluorophilicity and is found exclusively in the fluorous phase (Scheme 3.26).



Scheme 3.26 "Lightly" fluorous *N,N'*-dialkyl urea ($R_F = C_6F_{13}$) has a relatively low partition coefficient of 30:70 in a C_6F_{14}/CH_2Cl_2 biphasic system. After addition of perfluoroheptanoic acid, the partition coefficient of the resulting hydrogen bonded complex is 99:1, and the urea is completely removed from the organic into the fluorous phase [29].

By analogy with similar concepts in use in solid-phase combinatorial chemistry, several examples for fluorous "catch and release" tags have been described by Zhang and coworkers [30] (Scheme 3.27). These functionalities first act as a fluorophilic auxiliary during a multi-step synthesis, simplifying purification of the intermediates. In the last reaction step the tag is replaced by another reactive agent, thus releasing the target compound while simultaneously enabling a further increase of the molecular diversity of combinatorial libraries.



Scheme 3.27 One example of the use of fluorous "catch and release" tags [30b] ($R_F = CH_2CH_2C_8F_{17}$).

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4
Applications of Organofluorine Compounds

4.1
Halofluorocarbons, Hydrofluorocarbons and Related Compounds

The first and economically most significant class of organofluorine compound produced on a technical scale were the various chlorofluorocarbons (CFC; Table 4.1) [1]. Initially they were used as refrigerants in cooling and air conditioning equipment. Later they also found wide application as propellants for aerosol cans and foaming agents in the production of heat-insulating polymer formulations. The unique usefulness of CFC was recognized for the first time in 1928 by T. Midgley at the Frigidaire Corporation [2, 3]. The special properties which made this substance class so attractive for many applications were their high volatility and their lack of chemical reactivity, which rendered them non-toxic and non-flammable. The first domestic refrigerator containing a CFC appeared in 1933. At the peak of their industrial use CFC were produced on a scale of approximately one million tons per year.

Table 4.1 Properties and technical applications of some (hydro)halofluorocarbons [1] (b.p. in °C).

Compound	*b. p.*	*Applications*
HFC-23 (CHF_3)	−81	Azeotrope with CFC-13 in biomedical freezers
CFC-13 ($CClF_3$)	−82	See above
HFC-22 ($CHClF_2$)	−41	Room air-conditioning, supermarket freezers, industrial refrigeration, Japanese domestic refrigerators; tetrafluoroethylene feed stock; polystyrene foam blowing
CFC-12 (CCl_2F_2)	−30	Domestic refrigeration, automobile air-conditioning, supermarket fresh food stores, industrial air conditioning, hot climate air-conditioning; medical aerosols
CFC-11 (CCl_3F)	24	Water chiller air-conditioning systems; polyurethane foam blowing; medical aerosols
Halon 1211 ($CBrClF_2$)	− 4	Fire extinguishers
Halon 2402 ($CBrF_2CBrF_2$)	47	Fire extinguishers
CFC-113 (CCl_2FCClF_2)	48	Train switch gear coolant; solvent; chlorotrifluoroethene feed stock
HFC-134a (CF_3CH_2F)	−27	Domestic refrigeration, automobile air-conditioning, supermarket fresh food stores, hot climate air-conditioning; insulating foam blowing; metered dose inhalers; solvent for flavor and fragrance extraction

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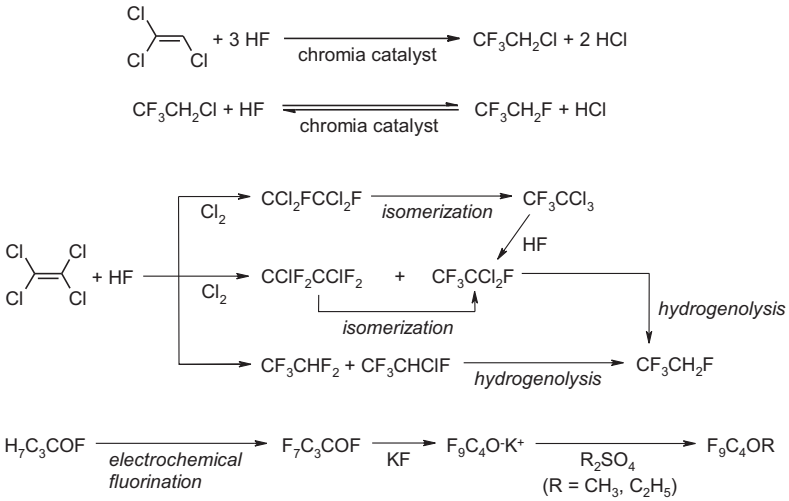
The economically most important of these so-called "Freons" (in Germany "Frigens") were Freon 11 ($CFCl_3$), Freon 12 (CF_2Cl_2), Freon 113 ($CF_2ClCFCl_2$), and Freon 114 (CF_2ClCF_2Cl) and the hydrochlorofluorocarbon (HCFC) Freon 22 (HCFC-22, CHF_2Cl). The numbering system used for CFC and HCFC is based on a three-digit number. The last digit denotes the number of fluorine atoms, the second last the number of hydrogen atoms minus one. The first digit denotes the number of carbon atoms minus one. For methane derivatives this digit is zero and is therefore omitted. All remaining atoms are assumed to be chlorine [4].

Bromofluorocarbons such as CF_3Br and CF_2Br_2, the so-called "Halons", have been widely used until recently as fire-extinguishing chemicals. For Halons a different five-digit coding scheme is used. Here, the five digits stand for the number of C, F, Cl, Br and I atoms – in exactly this order. Accordingly, Halon 1211 corresponds to CF_2ClBr. Halons are particularly useful as fire-extinguishing chemicals, because they are non-toxic and non-flammable. The homolytic carbon–bromine bond dissociation energy (64.3 kcal mol^{-1}) is low enough to start at relatively moderate temperatures, drawing heat from a fire as a result of its endothermicity.

Since the Montreal protocol in 1987 the use of ozone-depleting CFC and related compounds has been severely restricted, and they are currently being phased out. Because these compounds have such unique properties and are almost irreplaceable for many applications, much effort has been devoted to finding non-ozone-depleting replacements with significantly shorter atmospheric lifetimes (Scheme 4.1).

Most of these alternatives are hydrofluorocarbons (HFC) and fluorinated ethers, for example E143a (CF_3OCH_3), E134 (CHF_2OCHF_2), and E125 (CF_3OCHF_2) for use as refrigerants and foam blowing applications and $C_4F_9OCH_3$ and $C_4F_9OC_2H_5$ as replacements for the solvent CFC-113 (CCl_2FCClF_2).



Scheme 4.1 Typical technical syntheses of some (hydro)halofluorocarbons and fluorinated ethers as non-ozone-depleting CFC replacements [1].

The main synthetic route to CFC, HCFC and Halons is the Swarts fluorination. Technically this is often achieved by reaction of a chlorinated or brominated precursor with anhydrous hydrofluoric acid in the presence of a solid Lewis acid catalyst, for example chromia. Other important reactions are Lewis acid-catalyzed halogen isomerization and hydrogenolysis of chlorine or bromine.

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4.2
Polymers and Lubricants

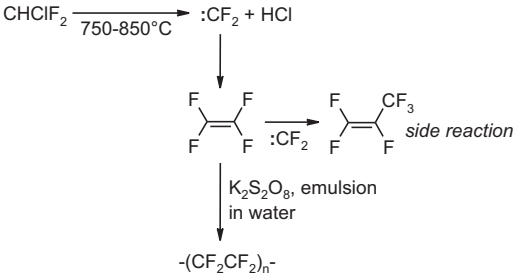
Fluoropolymers are still one of the largest scale applications of fluororganic compounds [1]. This field began with the serendipitous discovery of poly(tetrafluoroethylene) (PTFE, or Teflon) by R. J. Plunkett at DuPont in 1938 (Figure 4.1). When

Figure 4.1 R. J. Plunkett (*right*) with a cut cylinder of polymerized tetrafluoroethylene (courtesy of the Hagley Museum and Library, Wilmington, DE, USA).

he cut open a cylinder of tetrafluoroethylene when it mysteriously lost its pressure but kept its weight he found a white powder with most unusual properties, making it the most widely used fluoropolymer.

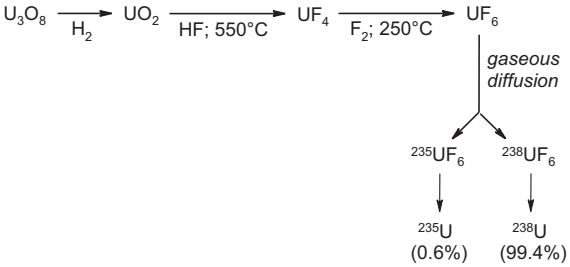
PTFE is extremely chemically stable against a variety of the most aggressive reagents, for example elemental fluorine, uranium hexafluoride, molten alkali metal hydroxides, and hot mineral acids. As a structural material it retains its function from near absolute zero to 260 °C. In addition it has, like the perfluoroalkanes, very low surface energy, leading to unusually advantageous low friction and anti-stick properties. One of the first popular applications of PTFE was as a lining for anti-stick frying pans. More recently, very thin fibers produced by fibrillation of a stretched PTFE sheet have found use in special performance garments under the brand name "Goretex". Goretex garments protect the wearer against liquid water while being permeable to water vapor from perspiration.

Low molecular mass PTFE (3000 to 50000 Dalton), obtained by polymerization in the presence of a chain-transfer reagent such as methylcyclohexane, or by γ-irradiation of high molecular mass PTFE, is used as highly effective lubricants which are extremely resistant to chemical degradation [3] (Scheme 4.2).



Scheme 4.2 Technical synthesis of tetrafluoroethylene by thermal fragmentation of $CHClF_2$. In a side reaction difluorocarbene is inserted into a carbon–fluorine bond of tetrafluoroethylene to give perfluoropropene. Radical polymerization in aqueous emulsion at 10–70 bar is initiated by peroxides, and the polymer is obtained as a powder.

During the Manhattan Project, directed toward construction of the first nuclear weapons [4], a strong need arose for materials, lubricants, and cooling fluids resistant to attack by the extremely aggressive uranium hexafluoride (UF_6) (Scheme 4.3).



Scheme 4.3 Synthesis of the volatile uranium compound UF_6, which is used for the separation of 0.6 % ^{235}U from the major isotope ^{238}U by gaseous diffusion. Only ^{235}U can be used for nuclear weapons because – in contrast with ^{238}U – it is fissible in a fast neutron-initiated chain reaction [4].

Figure 4.2 The K-25 facility in Oak Ridge (*left*) where uranium isotopes were separated by gaseous diffusion of UF_6. The atomic bomb which destroyed Hiroshima on August 6, 1945 (*right*), was based on ^{235}U from this facility (courtesy of the Manhattan Project Heritage Preservation Association) [5].

The volatile UF_6 (sublimation at 65 °C) was, and remains, the key material for separation of 0.6 % ^{235}U from the major uranium isotope ^{238}U (Figure 4.2). The reactivity of UF_6 is comparable to that of elemental fluorine, and it oxidizes most metals immediately and reacts violently with conventional organic materials. When the first large-scale separation of the uranium isotopes was achieved in a gaseous diffusion plant in 1943, PTFE seals in combination with compressed nickel powder diffusion barriers played a crucial role in this success. After the explosion of the first atomic bomb based on ^{235}U over Hiroshima on August 6, 1945, the atomic weapons programs in the West and the Eastern Bloc became one of the dominant forces driving the development of industrial fluorine chemistry.

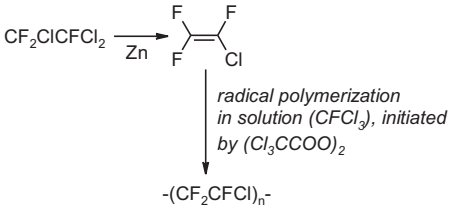
Besides its many highly desirable properties, PTFE also has some major disadvantages. First, because of its very high melt viscosity, it cannot be processed by extrusion like other polymers. It must be formed into blocks by sintering PTFE powder under pressure (100–400 bar, 365–385 °C). These blocks are subsequently cut mechanically into their final shape. For chemical labware made from PTFE by this method a resulting major disadvantage is the opaqueness of the vessels. Another problem with the labware is the extremely low thermal conductivity of PTFE. This cost-intensive procedure is similar to the processing of some high melting metals or ceramics. Melt-processable varieties of PTFE were subsequently obtained by copolymerization with 5 % perfluoropropene, which disrupts the high crystallinity of PTFE.

A second problem is the tendency of PTFE to creep under applied pressure, which limits the mechanic stability of PTFE devices. This can be overcome to some extent by blending PTFE with filler materials, such as glass or carbon. Also the otherwise highly advantageous anti-stick properties of PTFE cause pro-

blems during the manufacture of devices – usually, the material cannot be attached to metal surfaces, no conventional adhesives stick to it. For the PTFE coating of frying pans a layer of specially treated aluminum is used to connect the metal to the anti-stick layer.

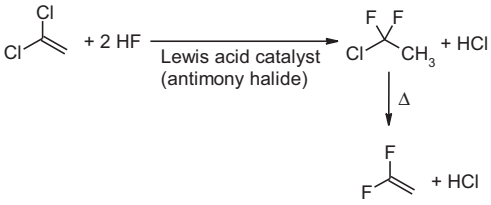
Polymers with elastomeric properties have been obtained since the 1960s by copolymerization of tetrafluoroethylene with trifluorovinyl ethers such as heptafluoropropyl trifluorovinyl ether (PPVE). These so-called second-generation fluoropolymers combine high thermal and chemical resistance with elasticity and are used for coatings, seals, and other parts which can be produced by conventional extrusion and molding processes.

An early alternative to PTFE was poly(chlorotrifluoroethylene) (PCTFE), which was invented in 1941 by W. T. Miller at Cornell University (Scheme 4.4). In contrast with PTFE, this material can be extruded at 250–300 °C. Depending on molecular mass PCTFE has applications as a thermoplastic or a lubricant.



Scheme 4.4 Synthesis of poly(chlorotrifluoroethylene) (PCTFE).

Another widely used fluoropolymer with highly advantageous properties is poly(difluoroethylene) (poly(vinylidene difluoride); PVDF) (Scheme 4.5). In quantities produced PVDF is second only to PTFE, because it can be processed not only into dimensionally stable mechanical components but also into transparent films with very good light transmittance. This and its high UV resistance makes it excellently suitable as a cover for solar collectors (as a flexible and low-weight glass replacement) and as component for formulation of high-performance paints and other coatings.



Scheme 4.5 Synthesis of the PVDF monomer 1,1-difluoroethylene.

PVDF is not solely of interest as a structural material. Oriented films have piezoelectric properties which are used for highly sensitive microphones, acoustic transmitters, and military applications. The piezoelectric characteristics of PVDF can be even improved by copolymerization with small quantities of other monomers which enhance its elastomeric properties.

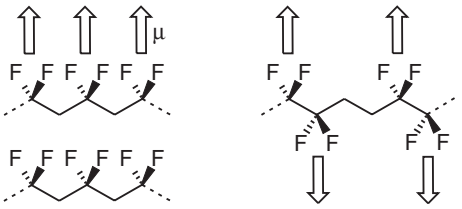
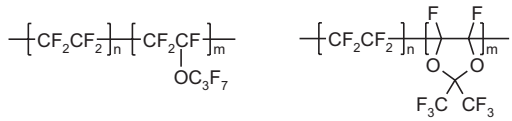


Figure 4.3 Piezoelectric poly(vinylidene difluoride) PVDF and its non-piezoelectric isomer, poly(ethylene-*co*-tetrafluoroethylene) (ETFE) [6].

The interesting dielectric properties of PVDF can be explained by its pattern of fluorination. In the stretched polymer with its zigzag conformation all *gem*-difluoromethylene groups are oriented to one side, perpendicular to the polymer backbone. Because of this alignment, the dipole moments of the carbon–fluorine bonds are additive; they also couple with the dipoles of neighboring polymer strands (Figure 4.3). In contrast, the isomeric poly(ethylene-*co*-tetrafluoroethylene) (ETFE) cannot adopt such a polar conformation because each local dipole moment is compensated by the adjacent *gem*-difluoromethylene group pointing in the opposite direction.

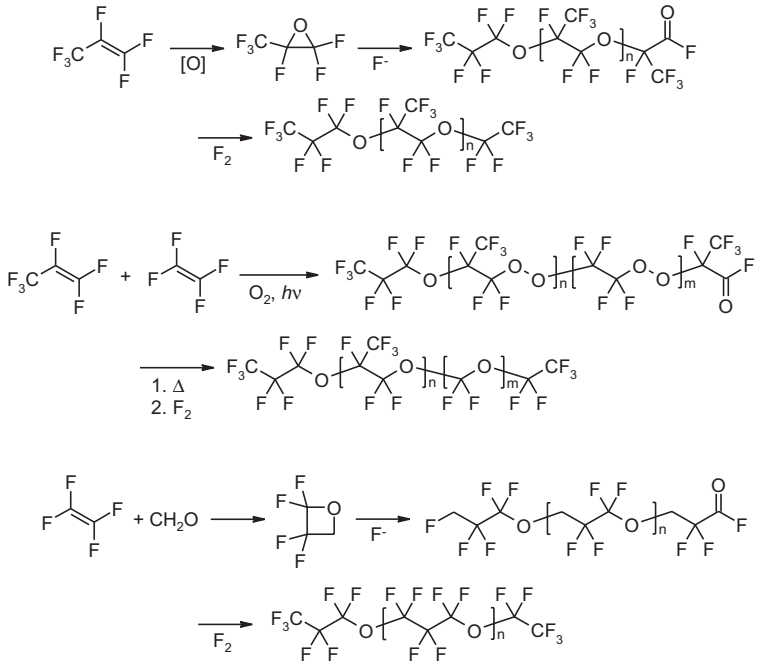
Other types of perfluorinated polymer include ether structures. The monomers of these materials, third-generation fluoropolymers, are trifluoroenol ethers and cyclic difluoroendiol ethers. Perfluoropolyethers (PFA) are readily processable and, because of their transparency, they are often used for chemical apparatus if aggressive reagents are involved. Another application of PFA is as sample vessels for ion analysis (Scheme 4.6).



Scheme 4.6 Examples of perfluorinated polyethers: PFA (*left*) is used for labware in analytical chemistry, Teflon AF (*right*) has special applications in the manufacture of electronic circuits.

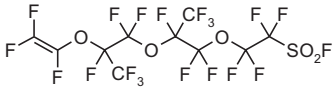
Perfluoroether oligomers are used as the structural basis for most fluorinated lubricants [3] (Scheme 4.7). These materials have, like perfluoroalkanes, very low surface energies and friction coefficients [7] but do not usually have better lubricant characteristics than their hydrocarbon analogs. Their advantage compared with those much cheaper (typically by a factor of fifty) compounds is their extreme resistance toward chemical degradation (especially oxidation to carboxylic acids), their extremely low vapor pressure and their non-miscibility with organic solvents. Perfluoropolyethers have therefore become the lubricants of choice for vacuum pumps used to evacuate microchip plasma etching chambers, in which corrosive gases, for example hydrogen fluoride or silicon tetrafluoride, are generated. Their very low vapor pressure, which, at a given viscosity, is much lower than

for analogous hydrocarbon lubricants, renders perfluoropolyethers the ideal lubricant for mechanical devices used in spacecraft. For example during the Giotto mission to Halley's comet some critical mechanical components moving perpetually in the high vacuum of space were lubricated with perfluoropolyethers.



Scheme 4.7 Syntheses of typical perfluorinated polyether lubricants [1].

Perfluorinated polyethers have also gained importance as actively functional materials. Ionic polymer membranes (e. g. DuPont's "Nafion") based on sulfonic acid-derivatized perfluoropolyethers have been used for nearly 30 years as ion-conducting membranes in chloralkali electrolysis cells, replacing the large amounts of toxic mercury used until then in the classic Castner–Kellner cells (Scheme 4.8.). One of the earliest applications of Nafion was as a membrane in the hydrogen–oxygen fuel cells which powered the Apollo spacecraft carrying the first men to the moon.



Scheme 4.8 Nafion is produced by copolymerization of a fluorosulfonylated trifluoroenol ether with tetrafluoroethylene then hydrolysis to the sulfonic acid.

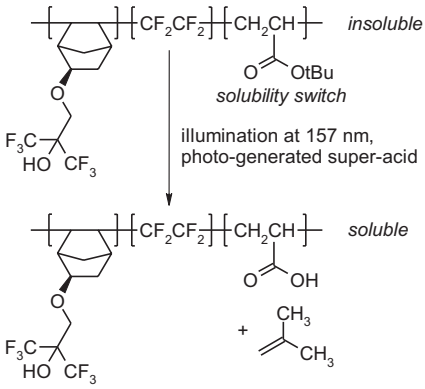
Nafion can be regarded as a polymeric analog of trifluoromethane sulfonic acid and was therefore the first solid super-acid.

The electronics industry currently has to achieve the transition from 248 nm (KrF excimer laser) to 193 nm (ArF excimer laser) technology for photolithographic patterning processes for the mass production in the electronic circuitry. The next step, already in preparation, is down to 157 nm (F_2 laser) [8]. Patterns with a resolution of approximately 120 nm can currently be achieved. It is expected that from 157-nm technology the resolution will be pushed down to 50 nm in 2009. The 157 nm technology will be firmly based on inorganic and organic fluorine chemistry; the best known optical material for lithographic lenses in this short wavelength range is calcium fluoride (CaF_2).

A major challenge is the design of photoresists which are highly transparent in the 157 nm region [9]. In the photolithographic process, the complex patterns on a chip are obtained by passing light of a given wavelength through a mask containing the pattern on to wafer substrate which is covered by a thin layer of a photoresist. In a "positive" working resist, the incident light causes chemical transformation in the illuminated areas which render them more soluble than the untreated photoresist. After irradiation the exposed parts of the photoresist can be washed away with a suitable solvent. The wafer with the patterned photoresist layer is now subjected to an ion-etching process, which selectively ablates the uncovered areas of the wafer substrate. After removal of the remaining photoresist, the pattern of the mask has been transferred to the wafer. A complex sequence of several of these patterning processes is used to mass-produce all kinds of electronic integrated circuit. Modern optics enables reduction of the dimensions of the patterned structures to approximately half the wavelength of the illuminating light source.

Photoresists have to meet, among others (for a more detailed discussion see Ref. [9]), the following requirements at least: (1) They need functionality for image formation and subsequent selective dissolution. (2) The transparency at the imaging wavelength must be high enough to enable complete penetration through the photoresist layer. (3) The non-illuminated photoresist remaining after dissolution must be resistant to the etching process.

Current photoresists cannot be used for 157 nm technology, mainly because their transmittance at 157 nm is too low. Although materials with aromatic substructures are quite useful for the 248-nm process, only purely aliphatic polymers are employed in the current 193 nm technology. For an illuminating wavelength of 157 nm, even the absorptivity of most aliphatic compounds is too high. Therefore, only partially fluorinated polymers with absorption characteristics carefully optimized by experiment [10] and molecular modeling [11] can be used. The "solubility switch" after illumination is usually achieved by addition of a photo-activatable super-acid (e. g. a diaryl iodonium hexafluoroantimonate) [12], which typically cleaves an acid-labile *tert*-butyl ester in the polymer (Scheme 4.9).



Scheme 4.9 Candidate for a 157 nm photoresist [9]. The perfluoroisopropanol moiety enhances transparency and general solubility. The *tert*-butyl ester group serves as the acid-labile solubility switch which can be activated by photo-generated super-acid.

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4.3
Applications in Electronics Industry

In addition to polymers there are many other applications of low-molecular-mass fluorochemicals in the electronics industry. Some typical applications of perfluoroalkanes and ethers are listed in Table 4.2.

An important field of application of fluorinated gases such as CF_4, $CClF_3$, CHF_3, and C_2F_6 is the plasma-etching process during fabrication of microchips [1, 2]. Like all chemicals involved in semiconductor manufacturing processes, etching gases must be extremely pure, to avoid changing the carefully adjusted electronic characteristics of the semiconductors.

A problem with the first generation of liquid etching agents was the inability to etch straight, perpendicular walls into silicon wafers. Because of their surface tension their etching rate depends strongly on the exact geometric environment and on the nature of the adjoining contact surfaces.

In the anisotropic plasma etching process, in contrast, straight features can be obtained by exposing the masked wafer to a plasma created by electrical discharges in a perfluorocarbon atmosphere, because the etching rate is highly dependent on the direction relative to the crystallographic lattice axes of the substrate (Figure 4.4). This plasma contains, among a variety of charged species, excited fluorine atoms which can ablate, e. g., silicon as volatile silicon tetrafluoride (SiF_4). For the very small features achievable by 193 nm and 157 nm photolithography, especially, plasma etching has become indispensable.

For production of micro-mechanic devices etching paths parallel to the wafer substrate surface are often required. Bromine trifluoride (BrF_3) is used for this special kind of anisotropic etching. Because of the extreme reactivity of this compound, electrical excitation and plasma formation is not necessary.

Table 4.2 Applications of perfluorinated fluids in electronics manufacturing processes [1].

Application	*Properties Exploited*	*Fluid Type*
Shock testing of microchips	Inertness towards encapsulating resins, wide liquid range	Perfluorinated cyclic ethers
Vapor-phase soldering of printed circuit boards	Thermal stability, inertness toward encapsulating resins	Perfluorophenanthrene
Cooling super-computers	Inertness toward resins, good heat-transfer properties	Perfluorocarbons
Tracer for gas emissions	Very high sensitivity electron-capture detectors toward CFC	Perfluorocyclohexanes
Solvent mixtures with alcohols and hydrocarbons to replace CFC-113 for cleaning microchips	Non-flammability	Perfluorocarbons

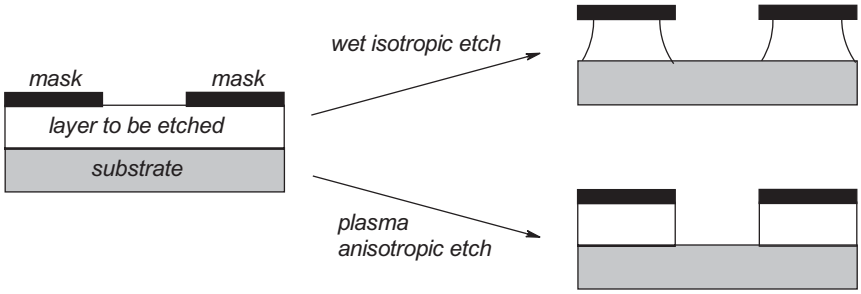

Figure 4.4 Comparison of the anisotropic etching process with liquid and gaseous (plasma) etching agents.

A typical microchip manufacturing process also contains several chemical vapor deposition (CVD) steps, to apply different functional layers to the silicon wafer substrate. These layers of metal (e. g. tungsten) or dielectrics (SiO_2, Si_2N_3, various doped oxides, silicon oxynitride) are deposited from reactive, gaseous, chemical precursors, for example SiH_4, tetraethoxysilane or tungsten hexafluoride (WF_6). After each of these deposition steps the residues from the CVD chemicals must be removed from the internal surface of the vacuum chamber. Historically this was done by taking the chamber off-line and cleaning manually with wet chemicals. Because this down-time was expensive in terms of the high cost of extremely capital intensive wafer fabrication facilities (FAB), deposition chambers are nowadays cleaned by means of a plasma of different fluorochemicals. In the same way as for plasma etching, the active species in this "dry" chamber-cleaning process [3] are excited fluorine atoms which carry the residues away as volatile fluorides. Typical chamber cleaning gases are NF_3 [4] and, more recently, the less hazardous C_2F_6, C_3F_8 and the mixtures CF_4/O_2 and C_2F_6/O_2 [5].

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4.4
Liquid Crystals for Active Matrix Liquid Crystal Displays

4.4.1
Calamitic Liquid Crystals: A Short Introduction

As early as 1888 the Austrian botanist F. Reinitzer [1] found that cholesteryl benzoate, if heated above its melting point, 146.6 °C, forms a milky, iridescent fluid with some of the typical characteristics of a liquid and some of a crystal [2]. On further heating above 180.6 °C a clear melt is obtained. On cooling the effect was found to be reversible.

The subsequently so-called "mesophase" combines its fluidity with some typical anisotropic properties of the solid, crystalline state, for example birefringence. In the years which followed this phenomenon became the subject of intensive study [3] and it was found that many compounds with rod-like molecular geometry formed "liquid crystalline" phases [4].

The structurally most simple of these calamitic mesophases is the nematic phase. The nematic mesophase can be understood as a one-dimensionally ordered elastic fluid in which the molecules are orientationally ordered but in which there is no long-range positional ordering of the molecules. The rod-like molecules tend to align parallel to each other with their long axes all pointing roughly in the same direction [5] (Figure 4.5). In addition to the nematic phase some substances form smectic mesophases in which the molecules are ordered in a layer structure underlying the directional order. The geometries of the different types of smectic phase

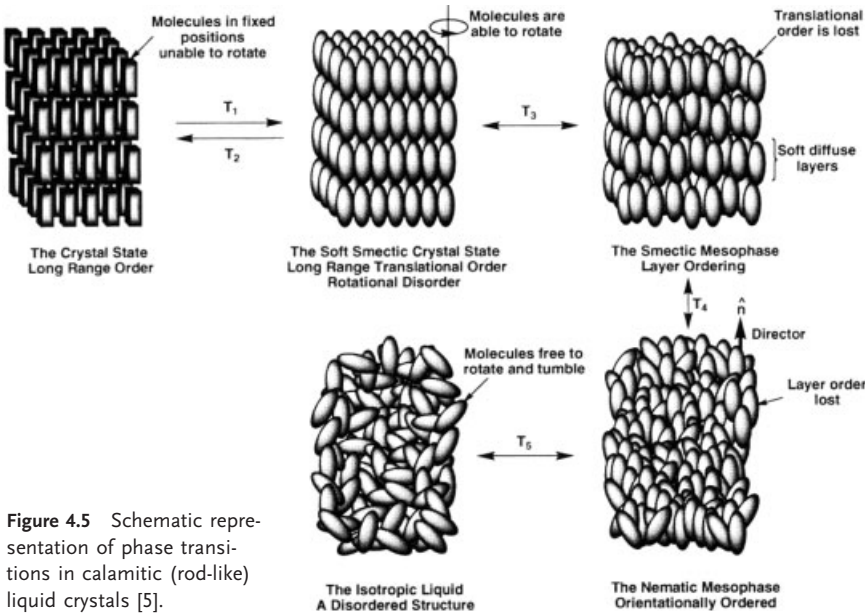


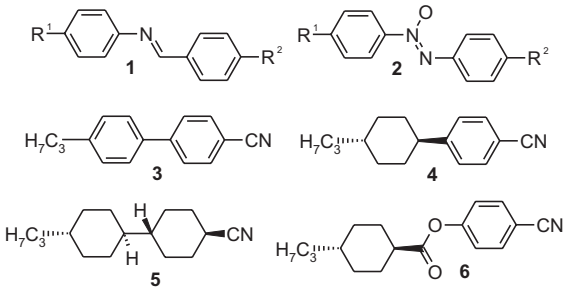
Figure 4.5 Schematic representation of phase transitions in calamitic (rod-like) liquid crystals [5].

are defined by the tilt orientational ordering of the long axes of the molecules relative to the layer planes.

4.4.2 Functioning of Active Matrix LCD

After Reinitzer's discovery nearly 80 years were to pass until the first successful attempts to use liquid crystals in the design of electrically switchable displays. The first prototypes of liquid crystal displays (LCD), reported by the Radio Corporation of America (RCA) in the 1960s [6], were based on the dynamic scattering mode (DSM). This mode is based on a cell containing a uniformly oriented nematic liquid crystal layer which is doped with a conducting salt. If a voltage is applied migrating ions cause director fluctuations in the normally transparent layer, resulting in scattering of light. A DSM display suffers from slow response times and rapid electrochemical degradation; this limits its lifetime and its commercial attractiveness. In addition to these inherent problems the liquid crystalline material used for this application was derived either from aromatic azomethines (**1**), which are highly sensitive to hydrolysis, or from azoxy compounds (**2**) [7], which suffer from photochemical lability.

The broad application of liquid crystal displays became feasible as a result of two, nearly simultaneous, groundbreaking innovations – the invention of the twisted nematic (TN) cell by M. Schadt and W. Helfrich [8] in 1971 and the discovery of the cyanobiphenyls (**3**) by G. W. Gray and coworkers [9] in the beginning of the 1970s. A further decisive development on the materials side were the cyanophenylcyclohexanes (**4**, PCH), reported in 1977 by R. Eidenschink and coworkers [10]. By making use of the melting point depression of mixtures of alkyl homologs of these and structurally similar substance classes (**5**, **6**) [11], it finally became possible to provide nematic materials for TN displays with a broad operating temperature range and almost unlimited lifetime (Scheme 4.10).



Scheme 4.10 Examples of liquid crystals of the first (**1**, **2**) and second (**3**–**6**) generation (R = alkyl).

In a liquid crystal cell based on the TN mode, a homogeneously aligned layer of a nematic liquid crystalline material with positive dielectric anisotropy ($\Delta\varepsilon$), helically twisted by 90°, is placed in an ITO-lined glass cell between crossed polarizers

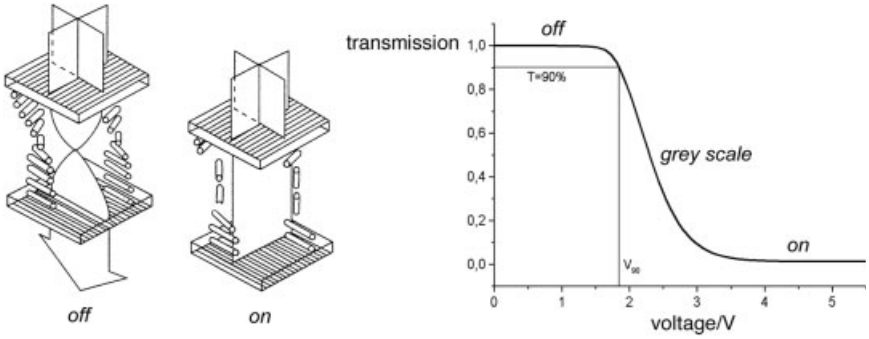


Figure 4.6 Working principle of a twisted nematic (TN) cell in the "normally white" configuration (*left*), and the change of transmission with increasing applied voltage (*right*). In the cell configuration sketched above the threshold voltage (V_{th}) for the electrooptical response corresponds to approximately V_{90} for 90 % of maximum transmission.

(Figure 4.6). The orientation of the liquid crystal is achieved by means of an alignment layer of directionally rubbed polyimide within the cell [12]. To ensure homogeneous handedness of the helical structure and thus to avoid the formation of domains in the display, a small amount (up to 0.1 %) of a chiral dopant is added to the liquid crystal material [13]. In the off-state the incoming light is polarized and the plane of polarization of the light passing through the liquid crystal layer is rotated by 90° and thus able to exit the second polarizer. If a voltage is applied the liquid crystal helix is deformed and the incident light cannot pass the crossed polarizers. Thus, in the off-state the cell, which is illuminated from the back, appears white; in the on-state it is black. A gray-scale can be achieved by applying a voltage between the threshold voltage (V_{th}) and the saturation voltage.

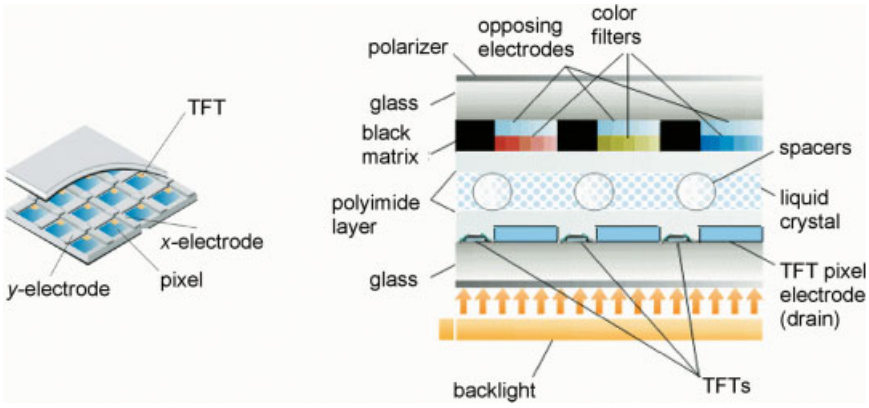


Figure 4.7 Set-up of a typical active matrix LCD: "Exploded" view of twelve pixels (*left*) and cross-section of three sub-pixels in the basic colors (*right*) (PI = polyimide, TFT = thin film transistor). The spacers are used to adjust the cell gap to typically 5–6 µm.

The first TN-LCD were simple, directly addressed segment displays as still used, e. g., for wrist watches. When attempts were made to increase the information content of the displays by time-sequential addressing in rows and lines (multiplexing) the limits of the TN cell were soon met. At higher multiplex ratios [14] contrast loss occurred, because of ever shorter addressing times. The development of the supertwisted nematic (STN) cell in 1984 [15] pushed the practicable limit to higher multiplex ratios, but it did not lead to a general solution of the problem.

Even by the end of the 1960s the first commercial LCD still based on the dynamic scattering mode (DSM) had faced the same principal problem of addressability at higher multiplex ratios. As a solution, the use of an "active matrix" of a thin film transistor (TFT) in combination with a voltage holding capacitor for each pixel was proposed [16] (Figure 4.7, see p. 217). In the long term the DSM mode itself did not prove feasible, but the general idea of active matrix addressing was intensively re-evaluated during the 1980s for TN displays, to enable precise control of the applied voltage, and thus the optical transmission, for each pixel separately. Full color capability is achieved by dividing each pixel into three sub-pixels, in combination with color filters for the three basic colors [17].

These efforts resulted in the first prototype of a 3-inch (7.5 cm diagonal) TFT display presented by Sharp in 1986. Because the manufacturing process of the TFT arrays is highly complex and expensive in terms of financial investment and human resources, the larger scale production of AM-LCD for use in notebook computers only started in 1989 [18].

The major drawback of the first AM-LCD was the strong dependence of the contrast on the viewing angle, resulting in gray-scale inversion and color shift when looking at the display from other than an approximately perpendicular direction. This problem was solved for the "classic" TN-TFT design by using birefringent compensation films, sometimes in combination with multi-domain technology [19]. In recent years technological diversification has been targeted at further improvement of the performance of active matrix-addressed LCD. The in-plane-switching (IPS) mode [20], the multi-domain vertical alignment (MVA) LCD mode [21], and the technically related ASV mode [22] have succeeded in increasing the viewing angle to 170°, in reducing the switching time to less than 15 ms, and in dramatically improving the contrast ratio to as high as 500:1 for the newest generation of LCD TV.

Currently, innovation in LCD technology is driven predominantly by multimedia and LCD TV applications, which require displays able to show high quality moving pictures. The time span between two video frames at a rate of 25 per second (PAL standard) is 16.7 ms. This means that for a video compatible LCD a switching time below ca 15 ms has become an absolute necessity.

4.4.2.1 **The Physical Properties of Nematic Liquid Crystals**

For each particular application and for each display mode a nematic material with custom-tailored physical properties [23] is required. The most application-relevant of these properties are the temperature range of the nematic phase (i. e. the tem-

perature range between the melting point and the clearing temperature T_{NI}), the dielectric anisotropy $\Delta\varepsilon$, the birefringence Δn, the rotational viscosity γ_1, and the elastic constants K_1, K_2 and K_3.

Although the dielectric and optical anisotropies $\Delta\varepsilon$ and Δn are properties of the condensed nematic phase, they can be related to the physical properties of single molecules. This is of great importance for the targeted, rational design of liquid crystalline materials.

To respond to an applied electric field, the liquid crystal must exhibit dielectric anisotropy ($\Delta\varepsilon = \varepsilon_{\parallel} - \varepsilon_{\perp}$), defined as the difference between the dielectric constant parallel and perpendicular to the director $(\hat{n})$ of the nematic phase. The relationship between $\Delta\varepsilon$ on a supramolecular level and the physical characteristics of the single molecules is described by the Maier–Meier formula (Eq. 1):

$$\Delta\varepsilon = \frac{NhF}{\varepsilon_0}\left\{\Delta\alpha - F\frac{\mu^2}{2k_B T}(1 - 3\cos^2\beta)\right\}S \tag{1}$$

where k_B denotes the Boltzmann constant, S the Saupe orientational order parameter of the nematic phase, F the reaction field factor where $F = \dfrac{1}{1 - f\alpha}$ and $f = \dfrac{\varepsilon - 1}{2\pi\varepsilon_0 a^3(2\varepsilon + 1)}$, and h the cavity factor, where $h = \dfrac{3\varepsilon}{2\varepsilon + 1}$. For ε the *macroscopic* dielectric constant is used [24].

The dielectric anisotropy is proportional to the square of the molecular dipole moment, μ, and is a function of the orientation of this dipole relative to the nematic direction, described by the angle β. For the practical design of calamitic liquid crystals, the director $(\hat{n})$ is usually approximated by the orientation of the long axis of the rod-like liquid-crystal molecules. If the dipole moment is exactly parallel to the long molecular axis ($\beta = 0°$) it has the greatest effect on the dielectric anisotropy of the material. If the dipole moment is perpendicular to the long axis ($\beta = 90°$), $\Delta\varepsilon$ becomes negative. In between, at the magic angle $\beta = 54.7°$, $\Delta\varepsilon$ passes through a minimum determined by the very small value of the anisotropy of the polarizability ($\Delta\alpha$). The dielectric anisotropy is the decisive factor affecting the threshold voltage V_{th} of the electrooptical response and consequently also the operating voltage of the driving circuitry of an LCD.

The birefringence ($\Delta n = n_e - n_o = n_{\parallel} - n_{\perp}$) of a nematic liquid crystal is correlated with the anisotropy of the molecular polarizability ($\Delta\alpha = \alpha_{\parallel} - \alpha_{\perp} = \alpha_{xx} - (\alpha_{yy} + \alpha_{zz})/2$), with the xx-axis corresponding to the long molecular axis [25]:

$$\frac{n_e^2 - 1}{n^2 + 2} = \frac{N}{3\varepsilon_0}\left(\alpha + \frac{2\Delta\alpha S}{3}\right);\ \frac{n_o^2 - 1}{n^2 + 2} = \frac{N}{3\varepsilon_0}\left(\alpha - \frac{\Delta\alpha S}{3}\right);\ n^2 = \frac{n_e^2 + 2n_o^2}{3} \tag{2}$$

The switching time τ of a TN cell depends mostly on the rotational viscosity γ_1, which can be influenced by molecular design, and on the elastic splay constant K_1; the correlation of K_1 with molecular structure remains quite elusive.

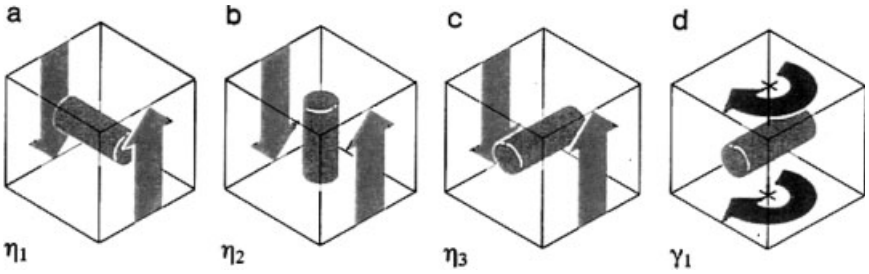


Figure 4.8 The corresponding shear and rotational flow profiles for the anisotropic Miesowicz viscosity terms η_1, η_2, and η_3 [26], and the rotational viscosity γ_1, relative to an isolated liquid crystal molecule. In the design of TN LCD γ_1 is of predominant importance, because it is proportional to the switching time of the display [27].

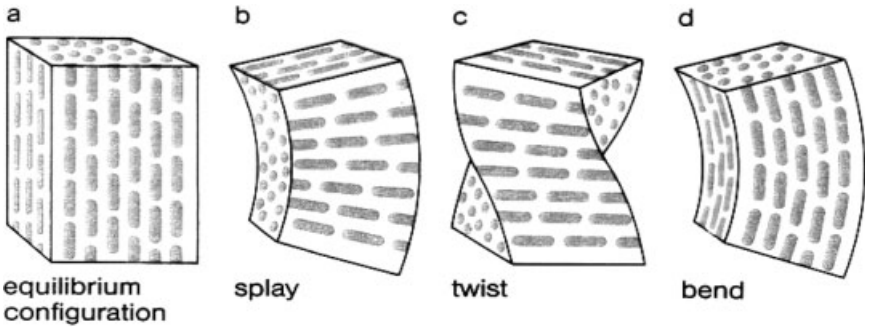


Figure 4.9 Elastic deformations of calamitic, rod-like liquid crystals in the nematic phase. The corresponding elastic elasticity constants are K_1 (splay), K_2 (twist), and K_3 (bend). K_1 has the largest influence on the threshold voltage, V_{th}, of TN cells [23f].

Due to the clear correlation between molecular properties which can be calculated by computational methods and the physical properties of the nematic phase, the dielectric anisotropy ($\Delta\varepsilon$) and the birefringence (Δn) can be predicted with reasonable accuracy by molecular modeling [28]. On the other hand, the viscoelastic terms γ_1 and K_1, K_2, K_3 are currently not really predictable, even if some recent results based on neural networks [3b], Monte Carlo simulations [29] and molecular mechanics approaches [30] give rise to some careful optimism (Figures 4.8 and 4.9).

The relationship between the physical properties of liquid crystalline materials and LCD performance is summarized in Table 4.3.

A prerequisite for experimental determination of the anisotropic electrooptic properties ($\Delta\varepsilon$, Δn) is the occurrence of a nematic phase with a defined order parameter S [4]. As single substances, many commercially used "liquid crystalline" materials have either no mesophase or a smectic phase only. As components of nematic basic mixtures on the other hand, they behave like typical liquid crystals,

contributing with their molecular anisotropies to the overall anisotropy of the mixture. To obtain for all potentially interesting substances a uniform and comparable set of characterization properties for application-oriented evaluation so-called "virtual" properties are used. These are derived by extrapolation of the properties of a defined solution of the material of interest in a standardized nematic host mixture. The change of the order parameter induced by addition of the analyte is taken into account for the extrapolation procedure [31a]. Usually, the values for $\Delta\varepsilon$, Δn and γ_1 are measured by this procedure. In addition, for the characterization profile a "virtual" clearing point (T_{NI}) is also cited.

With currently existing liquid crystalline single materials, simultaneous optimization of all these properties for one specific application cannot be achieved. Therefore, commercial liquid crystals are typically mixtures of 5–15 substances. Usually, these complex mixtures are based on different alkyl homologs of the same basic structure [32] (Figure 4.10).

In addition to these properties another set of application-relevant properties is used to characterize the "reliability" of a liquid crystalline single substance or a mixture. The different LCD manufacturers define these properties differently,

Table 4.3 Relationship between the physical properties of nematic liquid crystals and the corresponding application-relevant display properties.

Liquid Crystal	*Display Properties*
Nematic phase range	Operating temperature range (typically −30 °C to 90 °C)
Dielectric anisotropy ($\Delta\varepsilon$)	Operating voltage and maximum achievable integration density (miniaturization) of the driving circuits; large impact on manufacturing costs
Birefringence (Δn)	Cell gap (typically 4.5–6 μm)
Rotational viscosity (γ_1)	Switching time ($\tau_{on} + \tau_{off}$), below 16.7 ms for video applications
Elastic constants (K_1, K_2, K_3)	Operating voltage for display panel

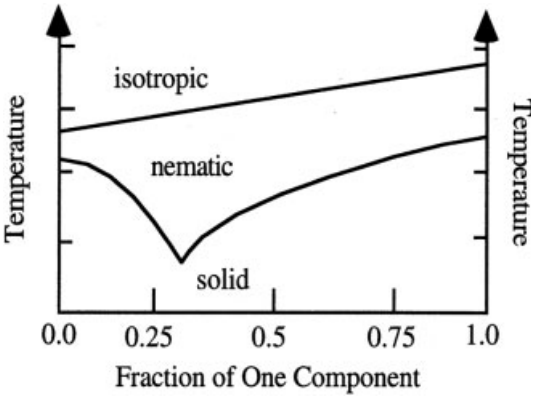


Figure 4.10 Typical phase diagram of a binary mixture of nematic liquid crystals. By use of "eutectic blocks" of structurally similar compounds (e. g. alkyl homologs), the nematic phase range is extended to lower temperatures [32].

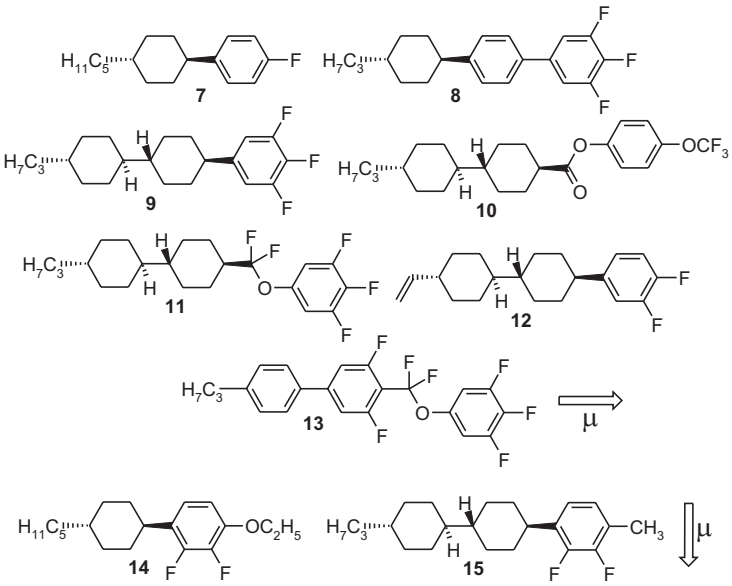
but usually they are centered around the chemical long-term stability under thermal, oxidative, and photochemical stress, the specific resistivity, and the voltage-holding ratio (VHR) [33]. The voltage holding ratio is defined as the ratio of voltage applied to a pixel at the end and at the beginning of a given time span. If the specific resistivity or the VHR of a liquid crystal too low, this results in visible flicker or contrast loss of the display. The reliability of the liquid crystal therefore has a decisive impact on the production yield and costs for the LCD manufacturer (Table 4.4).

Table 4.4 The most important active matrix (AM) LCD technologies and requirements for the corresponding liquid crystalline materials.

Technology	*Applications*	*Material Requirements*	*Characteristics*
Standard AM-LCD (5 V/4 V driver)	PC monitors, notebook PC, flat-panel TV	$\Delta\varepsilon \approx 4–8$ $\Delta n \approx 0.085–0.10$ $T_{NI} \approx 80–120\,°C$	Well-established technology; use of birefringent compensation films for improvement of dependence of contrast on viewing angle
AM-LCD with low threshold voltage (3.3 V/2.5 V driver)	Notebook PC, personal digital assistants (PDA), viewfinder for digital cameras	$\Delta\varepsilon \approx 10–12$ $\Delta n \approx 0.085–0.10$ $T_{NI} \approx 70–80\,°C$	Cheaper and more compact driving circuitry required than for standard AM-LCD; low power consumption; better miniaturization achievable; material very sensitive to ionic impurities
Reflective/transflective AM-LCD	Video games ("Gameboy"), sub-notebook PC, PDA	$\Delta\varepsilon \approx 4–8$ $\Delta n \approx 0.06–0.08$ $T_{NI} \approx 80–90\,°C$	Requires no backlight and only one polarizer, therefore reduction of power consumption by 70–90 %; high brightness and contrast difficult to achieve
In plane switching (IPS)	PC monitors, flat panel TV	$\Delta\varepsilon \approx 10–12$ $\Delta n \approx 0.075–0.09$ $T_{NI} \approx 70–85\,°C$	Very wide viewing angle and brilliant picture
Multi domain vertical alignment (MVA), advanced super view (ASV)	PC monitors, flat panel TV	$\Delta\varepsilon \approx -3–-5$ $\Delta n \approx 0.08–0.09$ $T_{NI} \approx 70–80\,°C$	Very wide viewing angle and brilliant picture; high contrast; fast switching ($<$15 ms)

4.4.3 Why Fluorinated Liquid Crystals?

Fluorochemicals, in general, have the disadvantage of relatively high price and, often, synthetic access is quite challenging. Nevertheless, most liquid crystalline single materials nowadays in use for active matrix LCD technology contain fluorine, either as a part of a polar group or within the mesogenic core structure [31] (Scheme 4.11). There are many good reasons to make use of the unique properties of fluorinated substructures for design of liquid crystals and these far outweigh the economic and synthetic disadvantages.



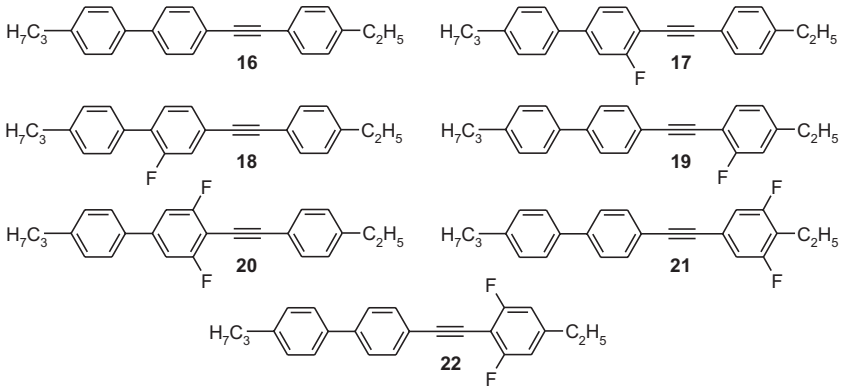
Scheme 4.11 Examples of typical super-fluorinated materials (SFM) used in the current generation of active matrix LCD. The liquid crystals **7**–**13** have positive dielectric anisotropy, compounds **14** and **15** have negative dielectric anisotropy. The approximate orientation of the molecular dipole moment for the two classes of material is indicated by arrows.

4.4.3.1 Improved Mesophase Behavior by Lateral Fluorination

Some of the reasons for the preference for fluorinated liquid crystals date back to the beginnings of LCD technology, others have gained paramount importance since the introduction of active matrix LCD in 1989.

Lateral fluorination of aromatic substructures in the mesogenic core structure of liquid crystals often results in significant broadening of the nematic phase range, a decrease in the melting point, and improved solubility. A less welcome side-effect of lateral fluorination is a drop in the clearing temperature compared with the non-fluorinated analog. Clearing point depression as a result of lateral fluorination was observed as early as the 1950s by G. W. Gray and coworkers [34]; more beneficial

Table 4.5 Mesophase sequences of differently fluorinated analogs of the liquid crystal **16** [41].



Compound	*Mesophase Sequence*
16	C 171 $S_?$ (160) N 217 I
17	C 118 N 189 I
18	C 104 N 164 I
19	C 125 N 195 I
20	C 125 N 164 I
21	C 111 S_B 149 S_A 168 I
22	C 69 N 175 I

effects, for example suppression of smectic phases, were not recognized until the beginning of the 1980s [35]. Subsequently, data on suitable, already existing compounds [36] were reviewed, systematically interpreted [37], and the effect was systematically explored by targeted synthesis of new materials [38]. In parallel, some theoretical explanations were also offered [39].

The strong effect on the mesophase sequence of lateral mono- and difluorination at different sites of an aromatic mesogenic core structure is illustrated by the data in Table 4.5 [40]. The relatively moderate mesogenic properties of material **14** were dramatically improved by introduction of two lateral fluorine substituents in the liquid crystal **22**. Unfortunately, this target was achieved only by a purely empirical trial-and-error process requiring a tremendous amount of synthetic work.

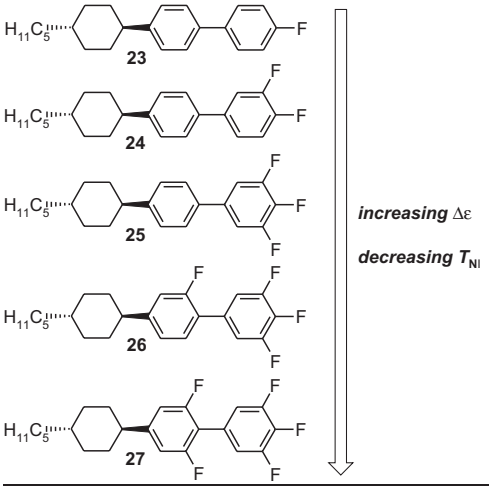
The decrease of the clearing point induced by lateral fluorination can be understood in terms of reduction of the length-to-breadth ratio of the liquid crystal molecule caused by any lateral substituent. As rule of thumb, for most compounds a decrease of the clearing temperature of 30–40 K is observed for each lateral fluorine atom.

4.4.3.2 Fluorinated Polar Groups

Another reason to make use of fluorinated substructures in the design of liquid crystals is the strong polarity of the carbon–fluorine bond, as a result of the large difference between the electronegativities of carbon (2.5) and fluorine (4.0). By analogy with nitrile-based liquid crystals, the most simple SFM (super-fluorinated materials) carry one terminal fluorine substituent on an aromatic moiety. For a typical phenylcyclohexane-based mesogenic core structure, this results in a $\Delta\varepsilon$ of ca 4. The dielectric anisotropy is increased if one or two additional fluorine substituents are introduced *ortho* to the terminal group (Table 4.6). For larger systems with three or more phenylene moieties in their mesogenic core structure a further increase of the dielectric anisotropy is achieved by using the additional rings as a scaffold for attachment of further lateral fluorine substituents.

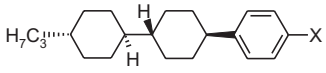
As an alternative to *ortho* fluorination, the dielectric anisotropy can be increased by making use of the cumulative effect of several carbon–fluorine bonds in a more complex fluorinated terminal group, for example CF_3, $OCHF_2$, or OCF_3. By analogy, other element–fluorine bonds can also be employed (Table 4.7). The pentafluorosulfuranyl (SF_5) group is, currently, the most effective polarity-inducing functionality still compatible with active matrix technology. From its effects the SF_5 group can be regarded as a "super-trifluoromethyl" group.

Table 4.6 The increase of the dielectric anisotropy by stepwise lateral fluorination is accompanied by a drop of the virtual clearing points ($T_{NI,virt}$) [41].



Compound	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
23	C 102 N 153.9 I	150.7	4.2
24	C 55 N 105.4 I	107.0	6.3
25	C 25 N 54.8 I	66.0	11.7
26	C 63 N (37.0) I	36.9	14.6
27	C 114 I	2.0	19.1

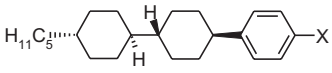
Table 4.7 The effects of different fluorinated polar groups on the same basic structure (**28**–**32**) in comparison with the corresponding nitrile-substituted liquid crystal **33** [41].



28-33

Compound	*X*	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
28	F	C 90 N 158.3 I	158.3	3.0
29	$OCHF_2$	C 52 S_B 69 N 173.6 I	163.2	5.2
30	OCF_3	C 39 $S_?$ 70 N 154.7 I	147.3	6.9
31	CF_3	C 133 I	112.2	9.5
32	SF_5	C 121 I	95.5	11.6
33	CN	C 75 N 241.7 I	226.8	14.8

Table 4.8 The effects of longer terminal perfluoroalkyl groups on the mesophase sequence and dielectric anisotropy of the phenylbicyclohexanes **34**–**36**. The values for $T_{NI,virt}$ and $\Delta\varepsilon$ were obtained by extrapolation from the Merck mixture ZLI-4792. The data denoted [a] were extrapolated from ZLI-1132 [41].



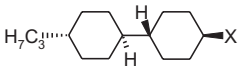
34-36

Compound	*X*	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
34	CF_3	C 143 $S_?$ 109 N 122.9 I	100.0	9.1[a]
35	C_2F_5	C 89 N (88.6) I	116.1	6.3[a]
36	C_3F_7	C 127 N (126) I	110.8	7.5

In contrast with the obvious expectation the use of longer terminal perfluoroalkyl homologs of the terminal CF_3 or OCF_3 group does not usually result in a further increase of $\Delta\varepsilon$ (Table 4.8). Long perfluoroalkyl moieties occasionally induce smectic mesophases and often reduce the solubility of the material.

For LCD applications requiring low birefringence, polar materials based on a bicyclohexyl structure are used (Table 4.9). Although most liquid crystals of this type have a strong tendency to form smectic phases, they have become indispensable as components of liquid crystal mixtures for all kinds of reflective or transflective LCD for battery-powered devices with low energy consumption. In the same way as for phenylcyclohexane-based liquid crystals the first generation of these materials derived its dielectric anisotropy from a terminal nitrile group (**5**). Since the introduction of active matrix technology nitriles have fallen out of favor for several reasons and nowadays the trifluoromethyl derivative **37** is usually used in commercial liquid crystal mixtures, although other chain perfluoroalkyl and perfluoroalkoxy derivatives have also been synthesized and evaluated for their practical usefulness.

Table 4.9 Bicyclohexyl-based liquid crystals **5** and **37–41** with polar substituents [41].

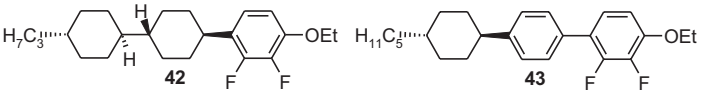


5, **37-41**

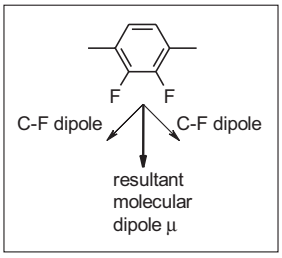
Compound	*X*	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
5	CN	C 59 S_B (53) N 82.1 I	19.9	9.4
37	CF_3	C 19 S_H (8) S_B? 41 I	−44.4	6.8
38	C_2F_5	C 10 $S_?$ (1) N (1.7) I	−24.1	5.8
39	C_3F_7	C 22 S_B 77 I	39.5	6.8
40	OCF_3	C 32 I	−29.7	9.0
41	OC_2F_5	C 43 S_B (43) I	−0.6	7.8

If the molecular dipole moment is oriented perpendicularly to the long molecular axis, a material with negative $\Delta\varepsilon$ is obtained [31b]. For steric reasons simple lateral monofluorination of an aromatic moiety within the mesogenic core structure does not result in a perpendicular orientation of the molecular dipole moment. This can be achieved only by pair-wise lateral difluorination, which results in mutual cancellation of the respective longitudinal components of the dipole moment vector leaving only the perpendicular contribution. Examples of the most commonly used dielectrically negative materials based on this concept are listed in Table 4.10.

Table 4.10 Examples for the most commonly used dielectrically negative liquid crystals deriving their dipole moment from lateral difluorination. The virtual clearing points $T_{NI,virt}$ are extrapolated from the Merck mixture ZLI-4792, $\Delta\varepsilon$ from ZLI-2857 [41].

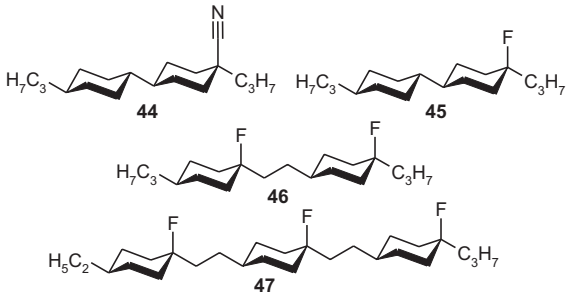


42 **43**



Compound	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
14	C 49 N (12.9) I	16.5	−6.2
15	C 67 N 145.3 I	139.0	−2.7
42	C 79 S_B (78) N 184.5 I	175.4	−5.9
43	C 74 S_A 86 N 170.7 I	190.6	−5.3

Table 4.11 Dielectrically negative liquid crystals with their polar groups attached to the tertiary axial sites of cyclohexane subunits. The virtual clearing points $T_{NI,virt}$ are extrapolated from the Merck mixture ZLI-4792, $\Delta\varepsilon$ from ZLI-2857 [41].



Compound	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$
44	C 34 N (19) I	−13.5	−8.3
45	C 75 S_B 94 I	79.6	−2.2
46	C 78 S_B 105 I	76.5	−4.6
47	C > 120, dec.	–	–

Also, the tertiary axial positions of a bicyclohexyl-based mesogenic core structure are highly suitable as a molecular scaffold for perpendicular orientation of polar groups. Linking cyclohexylene subunits via ethylene chains even enables construction of liquid crystals with strongly negative $\Delta\varepsilon$ from repeating units with the same orientation of the polar groups (Table 4.11). Because of the low solubility of **47**, this concept could be verified experimentally for up to two repeated units only (**46**).

4.4.3.3 **Improved Reliability**

Shortly after the commercial introduction of the first active matrix LCD in 1989 it became clear that cyano-based liquid crystals of the second generation (e. g. **3**–**6**) cannot be used for this application. Even after extensive purification, the voltage holding ratio of this type of material is too low. The stringent reliability requirements could, on the other hand, be easily fulfilled with "super-fluorinated" materials (SFM), such as those depicted in Scheme 4.11. For this reason – with in-plane switching (IPS) technology as the only exception – only SFM are currently used in AM-LCD.

The reason for the very different reliability properties of cyano materials and SFM is assumed to be the different kind of interaction of ionic trace impurities with these two types of liquid crystal.

From the perspective of electrical engineering each pixel of an AM-LCD can be regarded as a capacitor with the liquid crystal as the dielectric medium. At the start of each frame cycle this capacitor is charged, and must keep this charge and the corresponding voltage constant until the end of the cycle. If the applied voltage

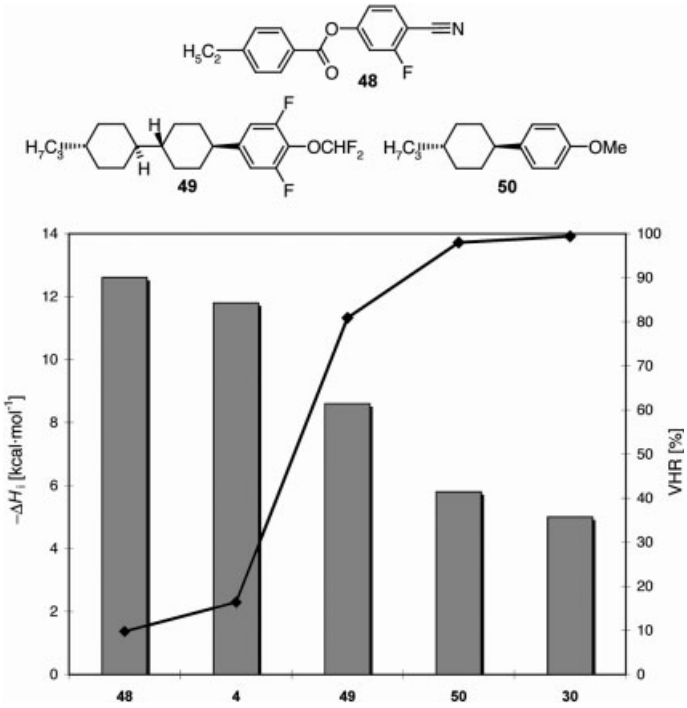


Figure 4.11 Relationship between the calculated heat of interaction (*gray bars*, $-\Delta H_i$ in kcal mol^{-1}) for different types of liquid crystal and a "sparkle" (calculated at the AM1 level of theory with MOPAC 6.0) and the measured voltage holding ratio (*diamonds*, VHR in %) [42].

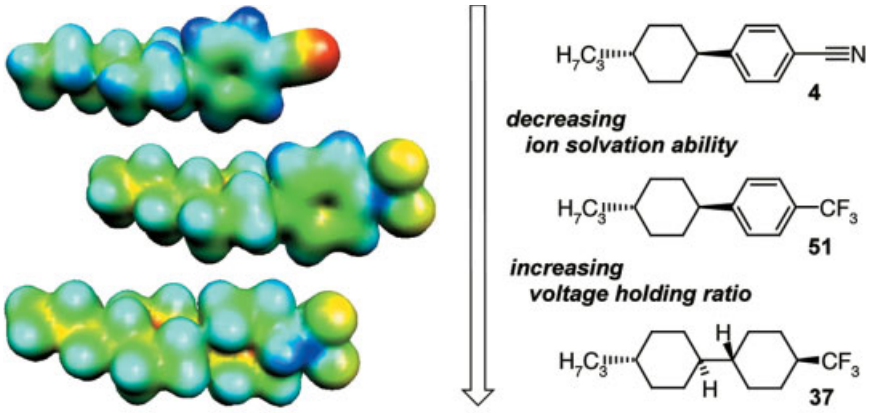


Figure 4.12 Increasing evenness of electrostatic charge distribution (red and blue denote and positive partial charges, respectively; B3LYP/6-31G*//AM1 level of theory) [43, 44] minimizes the ability of fluorinated polar liquid crystals to solvate ionic impurities by local electrostatic interactions.

drops during the frame cycle, because of migration of ionic impurities through the liquid crystal, the transmission varies, which manifests itself in contrast loss or inhomogeneity, or in visible flicker.

The tendency of ions to migrate through the liquid crystal layer depends on the strength of the interaction between the material and, especially, cations. If the interaction is strong, the cations are solvated or incorporated into coordination complexes and thus mobilized. If the solvating power of the liquid crystal is low the ions remain bound to the polar polyimide alignment layer and other peripheral materials and cannot traverse the cell gap and discharge the pixel.

By means of a combination of experimental results and molecular modeling it was found that the cyano group of older materials effectively solvates a variety of cations whereas the interaction of fluorinated polar groups of typical SFM with ionic impurities is much weaker. A semi-quantitative measure of the strength of this interaction with liquid crystals – and thus the voltage holding ratio – can be obtained by molecular modeling of a simple model system consisting of the liquid crystal in question and a so-called "sparkle", a model cation with a fixed radius carrying a positive charge but having no electronic orbitals [42] (Figure 4.11, see p. 229).

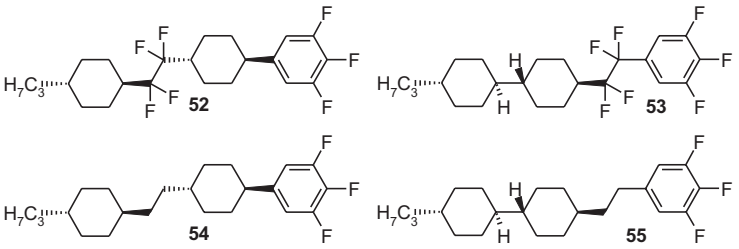
Another, more qualitative, picture of potential coordination sites can be obtained by graphical representation of the electrostatic potential surfaces of liquid crystals. The more homogeneous the distribution of partial charges the lower the ability to form cationic complexes by local electrostatic interactions (Figure 4.12, see p. 229). An even charge distribution correlates reasonably well with a high voltage holding ratio of a material.

4.4.3.4 **Fluorinated Bridge Structures**

The mesophase sequence of liquid crystals is favorably influenced not only by lateral fluorination but, to an even greater extent, by insertion of highly fluorinated bridging groups into the mesogenic core structure. The full extent of this effect was recognized relatively late in the 1990s, primarily because of the synthetic hurdles which had to be overcome to enable a full-scale investigation of this subject. Extension of commonly used liquid crystalline basic structures by tetrafluoroethylene (CF_2CF_2) [45] and difluorooxymethylene (CF_2O) [46] bridges have a dramatic influence on the clearing point, mesophase sequence, and rotational viscosity (γ_1) of these materials.

The tetrafluoroethylene bridge, if inserted between two cyclohexylene subunits (**52**), increases the clearing point (real and virtual) of a liquid crystal by 50–70 K. On the other hand, the bridge leads to an increase of γ_1 and occasionally induces smectic phases. If inserted between a cyclohexylene and a phenylene moiety (**53**) the clearing point is increased by only 15–20 K but the rotational viscosity is even lower than for the directly linked reference compound **9**. These quite dramatic effects can be clearly attributed to the presence of fluorine in the bridge – no significant improvement of mesogenic properties is observed for analogous materials containing non-fluorinated ethylene bridges (**54** and **55**) (Table 4.12).

Table 4.12 Comparison of liquid crystals containing a tetrafluoroethylene bridge in their mesogenic core structure (**52**, **53**) with their ethylene-bridged (**54**, **55**) and directly linked (**9**) analogs [41].



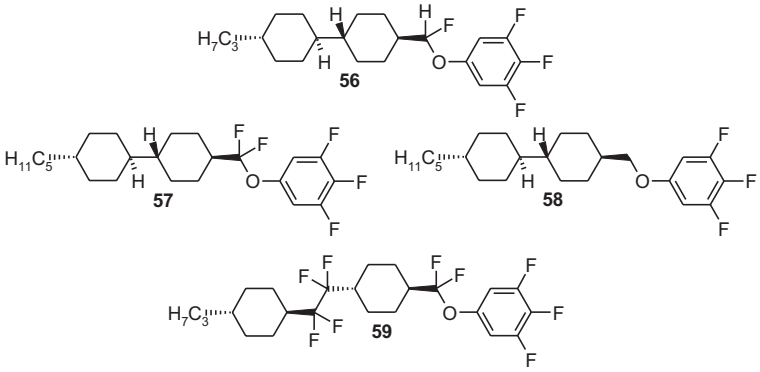
Compound	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$	γ_1
52	C 70 S_G 95 S_B 102 N 168.6 I	74.7	9.7	269
53	C 74 S_B 102 N 114.9 I	91.5	8.1	150
9	C 66 N 94.1 I	74.7	9.7	171
54	C 45 N 82.8 I	66.6	9.4	212
55	C 35 S_B 42 N 100.8	84.2	9.3	207

Insertion of a difluorooxymethylene bridge between cyclohexylene and a phenylene moieties (**11**) also results in an increase of the clearing temperature by 10–15 K. In contrast with the tetrafluoroethylene bridge no smectic phases are induced and the nematic phase range compared with the reference material **9** is even significantly broadened. At the same time the rotational viscosity is strongly reduced. In addition, the inherent dipole moment of the difluorooxymethylene substructure reinforces the dipole moments of the terminal fluorine atoms and increases the dielectric anisotropy. In the same way as for the tetrafluoroethylene-linked materials, both fluorine substituents in the bridge are essential for the excellent property profiles of **11** (propyl homologue) and **57** (pentyl homologue). The loss of even one fluorine atom from the bridge (**11** → **56**) results in reduction of the clearing point by ca 15 K, a decrease of $\Delta\varepsilon$, and a sharp increase of the rotational viscosity γ_1. Omitting both fluorine substituents from the bridge (**57** → **58**) results in a similar loss of the advantageous properties.

If both bridge elements CF_2CF_2 and CF_2O are introduced at the same time in their most effective positions within the mesogenic core structure (**59**) the difluorooxymethylene group compensates some of the negative side-effects of the tetrafluoroethylene bridge, for example the relatively high melting point of **52** [47]. The success of this concept indicates that different structural features within a liquid crystalline structure can be used relatively independently to influence and optimize the physical characteristics of the material (Table 4.13).

Explanation of the dramatic effects on physical properties of perfluorinated bridges in contrast with hydrocarbon-based bridges probably lies in the larger van der Waals radius (147 pm compared with 120 pm for hydrogen, i. e. fluorine is 23 % larger than hydrogen) and the low polarizability of fluorine. Molecular

Table 4.13 Examples of liquid crystals containing difluorooxymethylene (**11**, **57**), monofluorooxymethylene (**56**), and oxymethylene bridges (**58**), and a combination of two different fluorinated bridges (**59**) [41].



Compound	*Mesophase Sequence*	$T_{NI,virt}$	$\Delta\varepsilon$	γ_1
11	C44 N 105.3 I	91.5	10.5	145
56	C 43 N 88.0 I	75.6	8.0	~300
57	C 59 N 112.1	99.3	9.5	184
58	C 73 N 87.9 I	77.1	7.5	328
59	C 49 S_B 115 N 165.4 I	128.0	9.4	250

modeling indicates there is close contact between all fluorine atoms of the tetrafluoroethylene bridge and the secondary equatorial and axial and the tertiary axial hydrogen atoms of both adjoining cyclohexane rings. The fluorine atoms of the difluorooxymethylene bridge are also very close to the cyclohexane and phenyl hydrogens. Because of the low polarizability of fluorine this results in strong repulsion and conformational "stretching" of the bridges (Figure 4.13). This, in turn, leads to rigidification of the bridges, rendering liquid crystal conformers with a bent shape energetically disfavored.

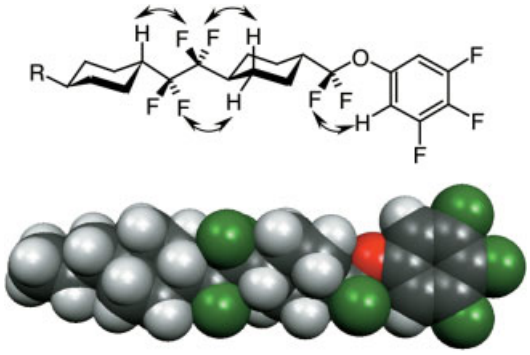
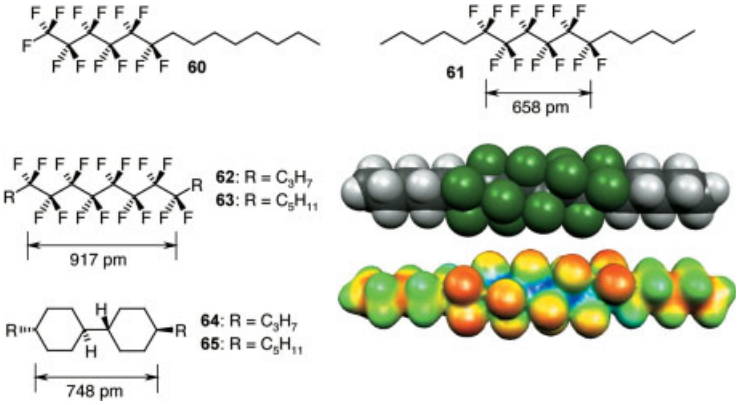


Figure 4.13 The key to an understanding the "fluorine effect" observed in liquid crystals with perfluorinated bridges in their mesogenic core structure lies in the steric repulsion between fluorine and hydrogen in neighboring rings.

If pushed to an extreme the perfluorinated bridge concept can be used to obtain liquid crystals with no cyclic moieties in their mesogenic core structure [48]. Since the beginning of the 1980s it has been known that semi-fluorinated *n*-alkanes, so-called "diblock" compounds, $F(CF_2)_n(CH_2)_mH$, form smectic phases [49], because of microphase separation as a result of separate, layer-like aggregation of the hydrocarbon and fluorocarbon moieties. Nevertheless, if introduced into a nematic host mixture, even small quantities of these diblocks cause gelation of the mixture. Their solubility is also limited to a few percent by weight.

If the mesogenic core structure of a liquid crystal is replaced by a rigid perfluoroalkylene segment of similar length, a liquid crystal is obtained which has physical characteristics very similar to those of typical dialkyl bicyclohexyls. Like the "diblocks" (e. g. **60**), some of these materials have a smectic phase but, unlike these, they behave in a nematic host mixture in the same way as a nematic liquid crystalline single material with low rotational viscosity. Comparison of the "diblock" **60** with compound **62** shows that, despite the same length of the carbon backbone (C_{14}), the mesogenic properties (for example the virtual clearing point $T_{NI,virt}$) of **62** are much more "liquid crystal-like" (Table 4.14).

Table 4.14 Structure (*top*) and physical properties [41] (*table below*) of semi-fluorinated *n*-alkanes (**60**–**63**) and the homologous dialkyl bicyclohexyl liquid crystals **64** and **65** from which they are structurally derived. The spacefill model of **63** shows the helical conformation of the central perfluoroalkylene segment in contrast with the pentyl side-chains with their typical hydrocarbon zigzag conformation. The differences in charge distribution (red and blue denote negative and positive partial charges, respectively) are visualized by mapping of the electrostatic potential on to the electron density of **63** (B3LYP/6-31G*//PM3 level of theory) [44, 50].



Compound	*Mesophase Sequence*	$T_{NI,virt}$	γ_1
60	T_g −42 S_B −8 I	−104.6	–
61	C 28 I	−71.1	35
62	C 5 $S_?$ 25 I	−27.8	31
63	C 44 I	−20.2	54
64	C 65 S_B 83 I	69.1	29
65	C 41 S_B 114 I	77.0	–

4.4.4 Conclusion and Outlook

In recent years devices based on liquid crystal displays have become an inseparable part of our daily life. Flat panel LCD-TV, PC monitors, notebook computers, cellular phones, and PDA would not exist without fluorine-containing liquid crystals. The use of fluorinated substructures, supported by computational methods and the development of novel preparative methods, enables targeted design and synthesis of new materials with a broad range of custom-tailored properties.

Several different AM-LCD technologies currently compete on the market. This race will probably be decided economically by the cost of mass production and technically by the ability to achieve the very fast switching time required for LCD-TV, the major economic driving force coming to the LCD market. Use of the unique properties of fluoroorganic materials will most probably play a decisive role in this development.

Nematic materials are only one member of a large family of a variety of structurally different compounds forming liquid crystalline mesophases. Although only nematics have yet found really widespread use, mostly for display applications, some structurally highly diverse smectic phases also have unique electrooptical characteristics, for example ferroelectricity or antiferroelectricity, which can be modulated by selective fluorination [5, 51]. For 20 years intensive effort has been devoted to making practical use of these phenomena.

It is impossible to predict which type of mesogen will win the race to become "ultimate" LCD technology. But it is a safe bet to assume that fluorinated substructures will play a predominant role.

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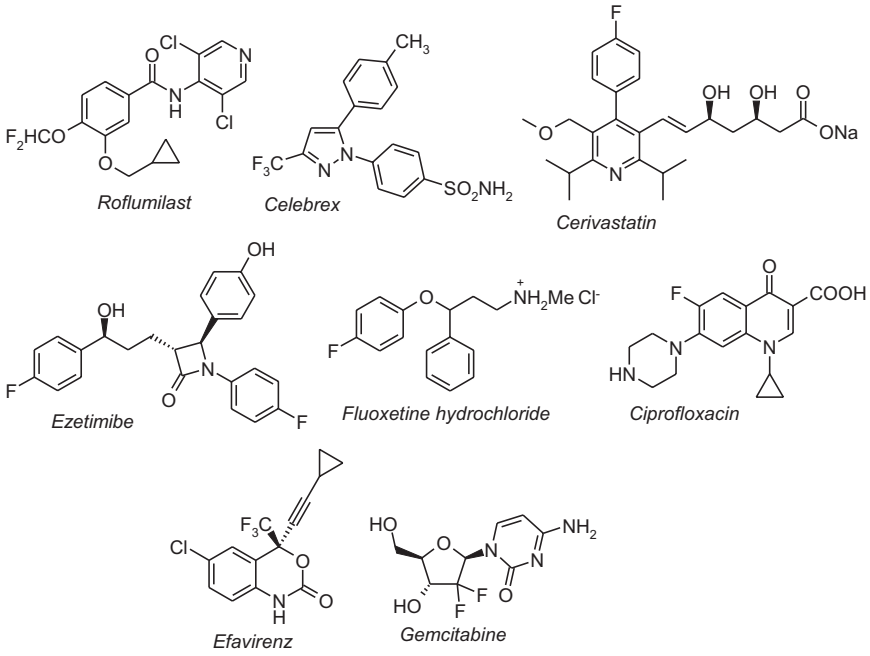
4.5
Pharmaceuticals and Other Biomedical Applications

There are many very different but highly specific reasons to make use of fluorinated substructures in medicinal chemistry [1]. Depending on the field of application, the strategies used to utilize effectively the unique properties of fluorine are quite diverse (Scheme 4.12). The action of most "normal" pharmaceuticals [2] is based on highly specific interaction with target structures in the organism and sometimes also on specific metabolic conversions. In these compounds the degree of fluorination is usually quite low, and a few fluorine substituents or fluorinated groups only are selectively introduced into the active structure, each with its specific purpose [3].



Scheme 4.12 Examples of fluorine-containing pharmaceuticals: non-steroidal anti-inflammatory drugs (Roflumilast, Celebrex), modulators of cholesterol metabolism (Cerivastatin, Ezetimibe), anti-depressants (Fluoxetine), antibiotics (Ciprofloxazin), and anti-virals (Efavirenz, Gemcitabine) [2].

There is also, in contrast, a fundamentally different type of application, including inhalation anesthetics [4], X-ray and ultrasound contrast agents [5], blood replacements, and respiratory fluids. Here, the active compound does not participate in any biochemical conversions. With the possible exception of inhalation anesthetics, its action is based on a rather unspecific physical effect. Such compounds are often applied in extremely large doses (tens of grams per treatment) and they are designed such that, ideally, they leave the organism through the lungs or skin. Such compounds are highly fluorinated or even perfluorinated, to achieve total chemical inertness.

4.5.1 Why Fluorinated Pharmaceuticals?

The similarity in size makes fluorine an obvious candidate to replace hydrogen, often without significant disruption of the molecular geometry and shape [6]. Because fluorine is so strongly electronegative, however, it has a dramatic effect on the electronic properties of the basic compound. On a molecular level this enables modulation of the lipophilicity profile, of electrostatic interactions with the target structure, and inhibition of some metabolic pathways [7]. On the physiological level, better bioavailability, increased selectivity for the target organs, and – in general – a far lower effective dose than for analogous non-fluorinated pharmaceuticals can be achieved.

A unique mechanism-based mode of action ("suicide inhibition") for some fluoropharmaceuticals involves direct chemical reaction of a fluorinated substructure with the target protein.

4.5.2 Lipophilicity and Substituent Effects

Every substituent has a particular steric and electronic influence on its scaffolding main structure. These substituent effects can be condensed into a set of physicochemical terms. The most important of these translate the steric interaction of the substituent with its immediate environment [8], its interaction with different types of solvent system (the lipophilicity log P or π describe the distribution in an *n*-octanol/water system) [9], and its electronic influence on the reactivity (σ) of the basic structure into the quantitative language of thermodynamics.

Substituent effects usually have a large impact on the biological activity of organic compounds. Lipophilicity (π) decisively affects the resorption of pharmaceuticals, their ability to reach their target organs, and their final distribution in the different compartments of the living organism. For example, drugs targeting the central nervous system, for example antidepressants, must have specific lipophilicity to be able to pass the blood–brain barrier.

The Hammett constant, σ, can describe the influence of a functional group on the acidity or basicity of a neighboring site, as already discussed in Section 1.4.2. It determines the distribution of partial charges over the surface of a biologically active molecule, modulating its binding behavior toward a target structure.

Table 4.15 Comparison of Hammett constants (σ) and lipophilicity increments (π) for a variety of fluorinated and non-fluorinated functional groups [10, 12, 13].

Substituent X	σ_m	σ_p	σ_I	σ_R	π_p
tert-Bu	−0.10	−0.20	–	–	+1.68
CH_3	−0.07	−0.17	–	–	+0.56
H	0	0	–	–	0
OCH_3	+0.12	−0.27	–	–	−0.04
OH	+0.12	−0.37	–	–	–
F	+0.34	+0.06	–	–	+0.14
Cl	+0.37	+0.23	–	–	+0.71
$COCH_3$	+0.38	+0.50	–	–	–
OCF_3	+0.38	+0.35	–	–	+1.04
Br	+0.39	+0.23	–	–	–
CF_3	+0.41	+0.53	+0.39	+0.12	+0.88
SCF_3	+0.44	+0.48	+0.41	+0.07	+1.44
CN	+0.56	+0.66	–	–	–
SF_5	+0.61	+0.68	+0.55	+0.11	+1.23
OSF_5	–	+0.44	–	–	–
NO_2	+0.71	+0.78	–	–	−0.28
$SOCF_3$	+0.77	+0.85	+0.69	+0.16	–
SO_2CF_3	+1.01	+1.17	+0.84	+0.34	+0.55
$S(CF_3)=NSO_2CF_3$	+1.27	+1.39	+1.15	+0.24	–
$SO(CF_3)=NSO_2CF_3$	+1.36	+1.55	+1.17	+0.38	–
$SF(=NSO_2CF_3)_2$	–	+1.78	+1.37	+0.41	–

In addition, substituent properties can be used systematically to find quantitative structure–activity relationships (QSAR) during lead optimization in structures of pharmaceutical interest [10, 11].

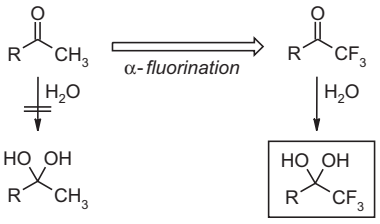
The physicochemical effects of fluorine-containing substituents are among the most extreme (Table 4.15). Thus, the SCF_3 group is, despite its relatively high polarity ($\sigma_p = +0.48$), one of the most lipophilic functions ($\pi_p = +1.44$), far exceeding that of fluorine ($\sigma_p = +0.06$) and chlorine ($\sigma_p = +0.23$). Also the SF_5 group has a remarkable combination of high lipophilicity ($\pi_p = +1.23$) and high polarity ($\sigma_p = +0.68$; for comparison, for the cyano group $\sigma_p = +0.66$ only). The substituents with the strongest known electron-withdrawing effects are the highly fluorinated sulfimides (e. g., $SF(NSO_2CF_3)_2$, for which $\sigma_p = +1.78$).

Sterically, the smallest substituent is fluorine itself with a van der Waals radius only slightly (ca. 23 %) larger than for hydrogen (F 147 pm, H 120 pm) [14]. The steric demand of the trifluoromethyl group, also commonly used in pharmaceuticals, is comparable with that of the isopropyl group. Nevertheless, such simplistic comparisons between the "size" of hydrocarbon and fluorocarbon substituents must be made with care, because of sometimes fundamental differences in the mode of their specific intermolecular and intramolecular steric interactions [6]. It must always be kept in mind that the predominant features of fluorine and fluorine-containing groups are their strong electronegativity and their extremely low polarizability. Thus, depending on the interaction partner, steric interactions can be

dominated either by the attractive complementary distribution of partial charges (e. g. hydrogen bonding to fluorine and fluorine–halogen interactions) or by the strong electrostatic repulsion of tightly bound lone electron pairs in steric fluorine–fluorine interactions.

Even if it might superficially seem logical, it cannot be concluded that fluorinated substituents *always* increase the lipophilicity of organic compounds. This is only true for fluorine itself and for perfluorinated groups in which the local carbon–fluorine dipole moments mostly compensate each other (e. g. CF_3, C_2F_5). Accordingly, lipophilicity is *increased* by aromatic fluorination, by fluorination adjacent to atoms engaged in π electron systems, and by perfluorination of alkyl chains [15].

On the other hand, in ω-fluoroalkyl groups (with one uncompensated C–F dipole moment) fluorination usually *reduces* lipophilicity. Another important instance of fluorine substitution reducing lipophilicity is in compounds with α-fluorocarbonyl groups. In these fluorination can increase the electrophilicity of the carbonyl carbon atom to such an extent that the formation of stable, polar hydrates occurs; this again reduces the lipophilicity significantly (Scheme 4.13). In α-fluorocarboxylic acids and fluorinated phenols the lipophilicity is also reduced by the increased ionization constant which results from the negative inductive ($-I_\sigma$) effect of fluorine [16].

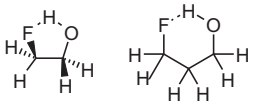


Scheme 4.13 α-Fluorination of carbonyl compounds reduces lipophilicity, because stable hydrophilic hydrates (*box*) can be formed.

4.5.3
Hydrogen Bonding and Electrostatic Interactions

The propensity of highly electronegative fluorine to act as an hydrogen bond acceptor can be used as a means to stabilize some conformations by intramolecular hydrogen bridging. The simplest example of this type of effect is 2-fluoroethanol, which is fixed in its *gauche* conformation in the vapor phase and in the liquid state (Scheme 4.14). This is at least partially because of an internal hydrogen bond [17] which contributes approximately 2 kcal mol^{-1} to conformational stabilization [18]. The rest of the stabilization of the sterically unfavorable *gauche* conformation can be attributed to stereoelectronic effects ("*gauche* effect") which will be discussed in detail in Section 4.5.4. A similar effect is observed for 3-fluoropropanol, but to a far lesser extent [19]. Here, the stabilization is based solely on intramolecular hydrogen bridging, without any contribution from stereoelectronic effects.

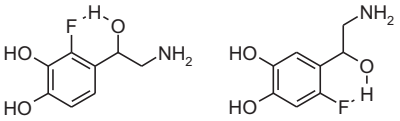
There are numerous examples of hydrogen bonds involving fluorine [20]; the strength of these interactions depends very much on the exact chemical environ-



Scheme 4.14 Conformational stabilization of *gauche* 2-fluoroethanol and 3-fluoropropanol by internal hydrogen bonding [17, 19]. The *gauche* conformation 2-fluoroethanol is further stabilized by the stereoelectronic "*gauche* effect".

ment and is therefore difficult to predict quantitatively. Typically, the strength of an C–F · · · H–O hydrogen bond is approximately 2.4 kcal mol^{-1}, about half that of the average O · · · H hydrogen bond [15].

One example of the relevance of this in pharmaceutical chemistry are the two isomers 2-fluoro (2-F-NE) and 6-fluoronorepinephrine (6-F-NE) [21]. The modes of binding of these two different fluorinated isomers to their receptor are, unexpectedly, fundamentally different – 6-F-NE has agonistic α-adrenergic activity whereas 2-F-NE acts as a β-agonist. This can be explained by the stabilization of two different preferred conformations by internal hydrogen bridges between the aliphatic hydroxy group and the aromatic fluorine (Scheme 4.15).



Scheme 4.15 Intramolecular hydrogen bridges with fluorine as the acceptor stabilize two different conformations of 2-fluoro- and 6-fluoronorepinephrine (2-F-NE and 6-F-NE, respectively), inducing different kinds of biological activity [21].

Two other examples in which the stabilization of specific conformations by intramolecular hydrogen bonding are prerequisite for biological activity are illustrated in Scheme 4.16 [22].

Fluorine substitution on aromatic substructures renders the remaining aromatic hydrogen substituents more acidic so their capacity to act as hydrogen bridge donors is enhanced. Not only can lone electron pairs act as hydrogen bridge acceptors but electron-rich aromatic π electron systems also. The resulting attractive CH/π interaction [23] has been used systematically to strengthen the binding of a fluor-

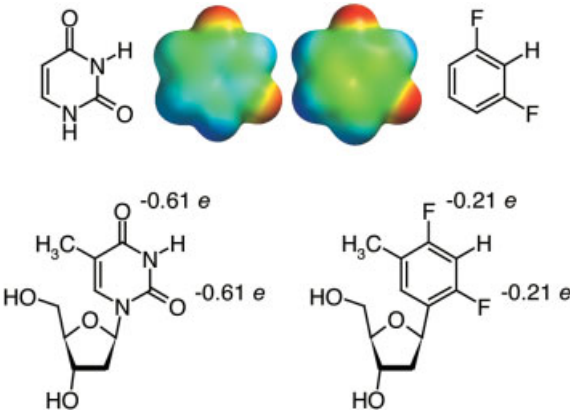
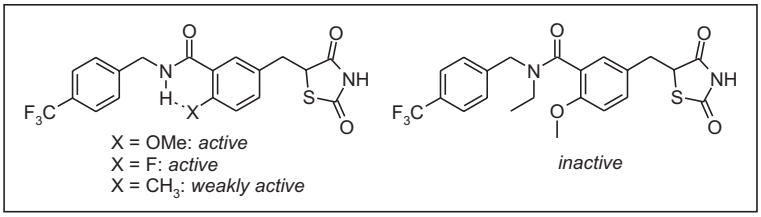
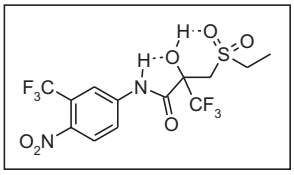


Figure 4.15 Uracil and its fluorinated carbocyclic analog 1,3-difluorobenzene (*above*) have a similar distribution profile of partial charges *q* (mapped on the electron density surface; blue and red denote negative and positive partial charges, respectively; B3LYP/6-31G* level of theory) [30] but the absolute values for, e. g., the 2,4-difluorotoluene analog (*lower right*) are significantly smaller than for deoxythymidine (*lower left*), [31].





Scheme 4.16 The antihyperglycemic activity of the substance class depicted in the *upper box* depends crucially on the capacity to stabilize its preferred conformation by forming an intramolecular hydrogen bond between the amide hydrogen and a suitable acceptor X on the central aromatic moiety [22a]. The antiandrogenic activity of the compound in the *lower box* is based on stabilization of one conformer by two intramolecular hydrogen bonds [22b]. The trifluoromethyl group renders the α-hydroxy function a better hydrogen bridge donor and acceptor at the same time.

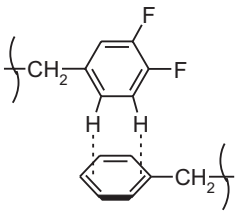


Figure 4.14 Enhancement of the binding of a 3,4-difluorophenylalanine-containing peptide to its receptor by an edge-to-face CH/π interaction [24].

ine-modified heptapeptide to its receptor by edge-to-face interactions [24] (Figure 4.14).

The double helix of DNA [25] and the more complex tertiary structures of RNA [26] are linked together by hydrogen bridges between pairs of nucleobases (approx. 0.5–1.8 kcal mol^{-1} per Watson–Crick base pair) [27] and by hydrophobic "stacking forces". Fluorinated carbocyclic analogs of these nucleobases have been used to study and elucidate the factors underlying base pairing, replication, and the interaction of the bases with proteins such as DNA polymerases [28].

In these pseudo-bases [29] fluorine mimics the electronegative carbonyl oxygen, which normally acts as the hydrogen-bridge acceptor. The steric dimensions of fluorine are similar to those of oxygen and its high electronegativity results in a comparable distribution of partial charges in the analog, although their absolute values are significantly smaller. Fluorine substitution also increases the acidity of the remaining aromatic hydrogen atoms, rendering them potential hydrogen bond donors. Thus, the fluorinated carbocyclic pseudo-bases are supposed to act not only as steric but also as functional mimics of the real bases, although the contribution of hydrogen bridging to base pairing is significantly weaker (Figure 4.15, see p. 241).

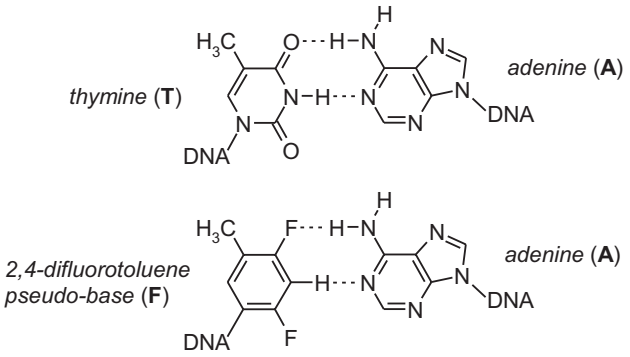


Figure 4.16 Watson–Crick pairing between thymine (T) and adenine (A) (*above*) and the supposed, much weaker pairing of a 2,4-difluorotoluene pseudo-base (F) with adenine (A) (*below*).

The motivation behind studies of these supposedly "non-polar" pseudo-bases is to determine the relative contributions of hydrogen bonding and stacking interactions as forces driving the formation of the double helix. Weakening the contribution of electrostatic hydrogen bridging in a defined manner without changing the shape and general charge distribution of the "bases" was thought likely to be a key to the separation of the two effects [32] (Figure 4.16). Although the subject is still a matter of some controversy [33], results so far indicate that approximately half of the stabilization of the DNA double helix results from π-stacking effects. The contribution of dipole moments seems to be based less on direct attraction between permanent dipoles (for example inter-strand directional hydrogen bonding) than on intra-strand dispersive induced-dipole interactions [32b, 34].

4.5.4
Stereoelectronic Effects and Conformation

Fluorine substituents effect the conformation of organic compounds as a result not only of their steric requirements but also their electronic properties, particularly their strong electronegativity. Similar effects are known for other electronegative heteroatoms, for example oxygen or nitrogen. A well-known example of such stereoelectronic effects is the "anomeric effect" in the conformation of carbohydrates [35]. With an electron-withdrawing oxygen or fluorine substituent (X) in the anomeric position axial orientation of the substituent X is strongly preferred to equatorial orientation [36, 37]. This stabilization, by approximately 6 kcal mol^{-1}, occurs because of energetically favorable n–σ^* overlap between the ring oxygen axial lone electron pair (n) and the anti-bonding σ^* orbital of the C–X bond (Figure 4.17).

A related stereoelectronic effect with particular relevance to fluoroaliphatic compounds is the "*gauche* effect" [38]. Contrary to expectations based solely on the steric repulsion of fluorine, 1,2-difluoroethane prefers the *gauche* rather than anti-parallel alignment of the fluorine substituents, by 0.5–0.9 kcal mol^{-1} [39]. The same is observed for related compounds in which one fluorine atom is replaced

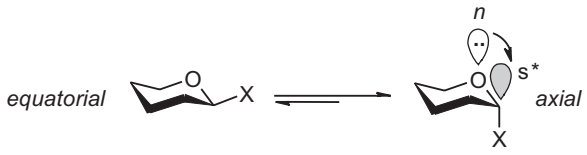


Figure 4.17 The anomeric effect in carbohydrates leads to energetic preference of the electronegative substituent (X = OH, F) in the axial orientation by ca. 6 kcal mol^{-1} [36], because of stabilizing *n*–σ^* overlap. With X in the sterically more favorable equatorial position this overlap is not possible.

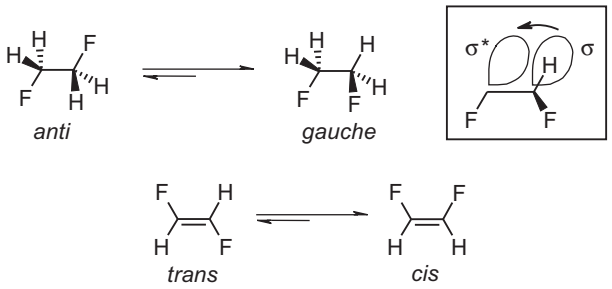


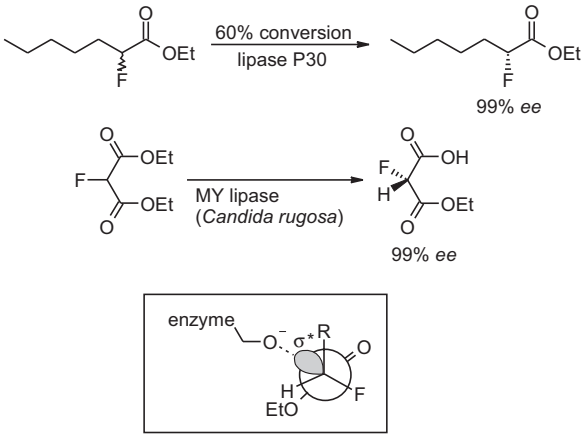
Figure 4.18 1,2-Difluoroethane energetically prefers the *gauche* conformation (*above*) by 0.5–0.9 kcal mol^{-1}, because this enables stabilizing overlap of the electron-rich carbon–hydrogen σ bond and the antibonding σ^* orbital of a neighboring carbon–fluorine bond (*box*). In 1,2-difluoroethylene (*below*) the *cis* isomer is preferred to the *trans* isomer by 1–2 kcal mol^{-1}.

by another electronegative substituent [40]. Depending on this substituent in compounds of the type FCH_2CH_2X, stabilization of up to 1.8 kcal mol^{-1} is obtained, e. g. for X = $NHCOCH_3$ [41]. Similar to the anomeric effect the force driving stabilization of the sterically disfavored *gauche* conformation is assumed to be the σ–σ^* overlap of an electron-rich C–H σ bond with the neighboring C–F anti-bonding σ^* orbital.

Similarly, in 1,2-difluoroethylene, the *cis* isomer is energetically preferred to the *trans* isomer by 1–2 kcal mol^{-1} (Figure 4.18). Among the different explanations of this "*cis* effect" [42] differences in the distortion of the central carbon–carbon bond in the two isomers have been discussed [43]. The extent of energetic stabilization by the *cis* and *gauche* effects increases with the substituent electronegativity.

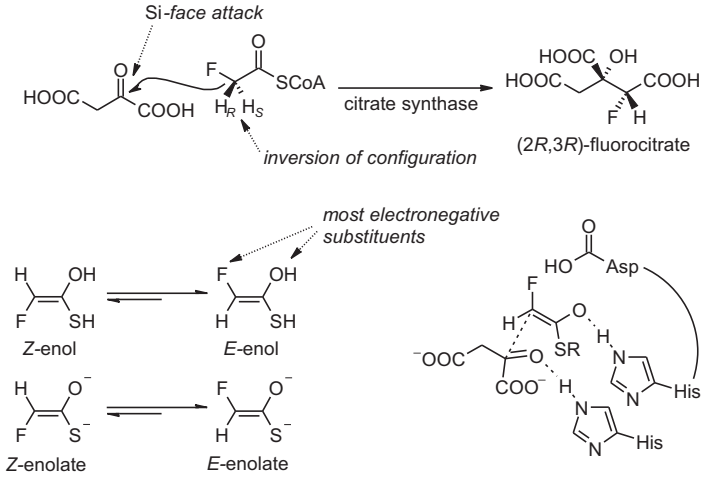
Another stereoelectronic effect induced by electronegative substituents is the "Anh–Eisenstein effect" [44] (Scheme 4.17) which can be of particular importance to the stereochemical outcome of enzymatic reactions involving fluorinated substrates [45]. In α-fluorocarbonyl compounds nucleophilic attack of the carbonyl group occurs preferentially *anti* to the fluorine substituent [46]. The resulting, unusually high stereospecificity, e. g. in some enzymatic reactions of fluorinated substrates [45], cannot be explained by the slightly different steric demands of hydrogen and fluorine alone.

The *cis* effect can also determine the stereochemistry of enzymatic reactions. The most prominent example is the metabolism of toxic fluoroacetate in the Krebs



Scheme 4.17 Anh–Eisenstein stabilization [44] of transition states with the fluorine substituent *anti* to the attacking nucleophile (*box*) induces high stereospecificity in many enzymatic reactions involving α-fluorocarbonyl substrates [45]. Entrance of the nucleophile is guided by a favorable interaction with the anti-binding σ^* orbital of the carbon–fluorine bond.

cycle [47]. The activated thioester derivative of fluoroacetate, fluoroacetyl-CoA, is added to oxaloacetate by the enzyme citrate synthase, generating exclusively the (2*R*,3*R*)-fluorocitrate stereoisomer [48]. It is the formation of this compound which is responsible for the extreme toxicity of fluoroacetate [49], which inhibits aconitase, the next enzymatic "station" in the Krebs cycle, and also impedes citrate transport across mitochondrial membranes. The selective formation of only one stereoisomer of fluorocitrate, despite the rather small steric difference between hydrogen and fluorine, can be explained conclusively in terms of the *cis* effect acting on the difluoro thioesterenolate intermediate (Scheme 4.18).

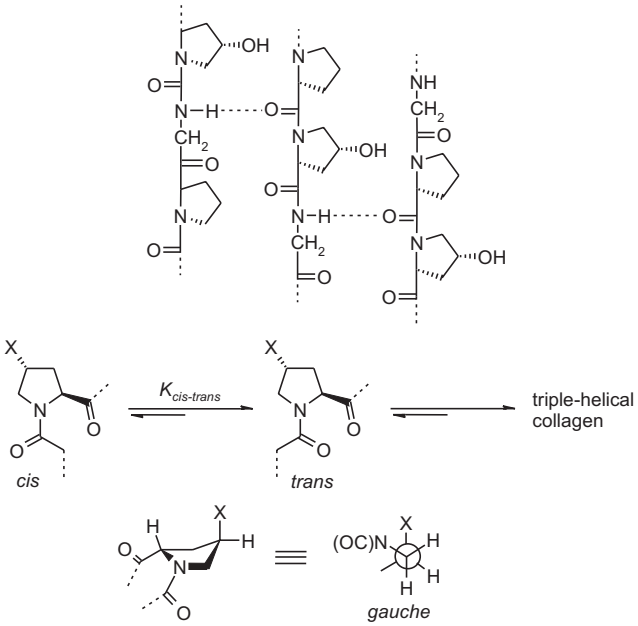


Scheme 4.18 Effect of the different stabilities of fluorothioester enolates (*cis* effect) on the stereochemical course of the citrate synthase reaction on fluoroacetyl-CoA [36]. In the active site of the enzyme, the enolate is assumed to be bound as the more stable *E* isomer, with the most electronegative substituents in their relative *cis* configuration.

One impressive example of the systematic use of stereoelectronic effects to design biologically relevant molecules is a "hyperstable" collagen mimic [50] which owes its unusual stability mostly to the *gauche* effect induced by fluorine.

Collagen is a fibrous protein, a copolymer consisting of approximately 300 Gly-Xxx-Yyy triplets, where Xxx is often an L-proline (Pro) residue and Yyy often a 4-(*R*)-hydroxy-L-proline (Hyp) residue. Three of these polymer strands together form a tight-wound triple helix, and the triple helices are further organized into fibrils of great tensile strength. Collagen of different composition and cross-linking provides bone, tendons, cartilage, ligaments, and skin with their extreme mechanical durability.

The triple helix is predominantly held together by inter-strand hydrogen bridges between the backbone amide N–H and carbonyl groups. The question asked was whether the Hyp hydroxy groups contributed to the stability of the triple helix by acting as an additional hydrogen bond donor or merely by affecting the conformation of the Hyp pyrrolidine substructure (Scheme 4.19).



Scheme 4.19 The collagen triple helix (*top*) is stabilized by inter-strand hydrogen bridges between the peptide links of the backbone. Additional stabilization of the required *trans* proline substructures (*middle and below*) can be derived from the gauche effect of strongly electronegative substituents X, for example hydroxy or fluorine, together with the electron-withdrawing amide group (X = H: Pro, X = OH: Hyp, X = F: Flp) [50b, 51].

When hydroxy was exchanged with fluorine, which cannot act as a hydrogen bridge donor, the stability of the triple helix was found to be dramatically increased. For the 30-mer $(Pro\text{-}Xxx\text{-}Gly)_{10}$ as model compound replacement of Xxx by Hyp

against the reference Xxx = Pro increased the stability by ca 6.5 kcal mol^{-1}. Replacement of Xxx = Pro by its fluoro analog 4-(*R*)-fluoro-L-proline (Flp) stabilized the helix by 11–12 kcal mol^{-1} [50b]. This clearly indicates, that the helix stabilization by Hyp is not due to hydrogen bonding but predominantly to stereoelectronic effects.

The *gauche* effect exerted by fluorine (or by the hydroxy group in natural Hyp) and the electron-withdrawing amide group stabilize a conformation of the pyrrolidine ring which favors the triple-helical arrangement. In addition, the inductive effect of fluorine stabilizes the *trans* isomer of Flp, which is prerequisite for helix formation.

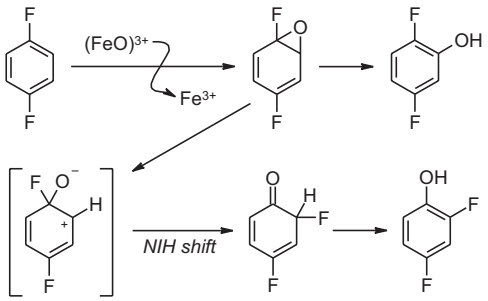
Similar stereoelectronic effects strongly influence the favored conformations of nucleosidic ribose and deoxyribose derivatives [40].

4.5.5
Metabolic Stabilization and Modulation of Reaction Centers

A factor limiting the clinical usefulness of many pharmaceuticals is their too rapid metabolic degradation. In the best case this leads to low effectiveness and puts a heavy load on the liver and kidneys. In other cases the drug seems to fulfill is purpose effectively but it cannot be used clinically because of the formation of toxic or mutagenic metabolites [7].

The key to many of these degradation processes is oxidative metabolism by the cytochrome P450 enzyme family [10]. Cytochrome P450 oxidation is most easy for electron-rich π-electron systems, for example aromatic moieties or olefinic substructures, from which epoxides are generated. These epoxides are often potent electrophiles, intercalating into DNA and reacting with all kinds of nucleophile, for example nucleobases, amines, or thiols. Metabolic processes like this are the reason for the mutagenicity of many polycyclic arenes.

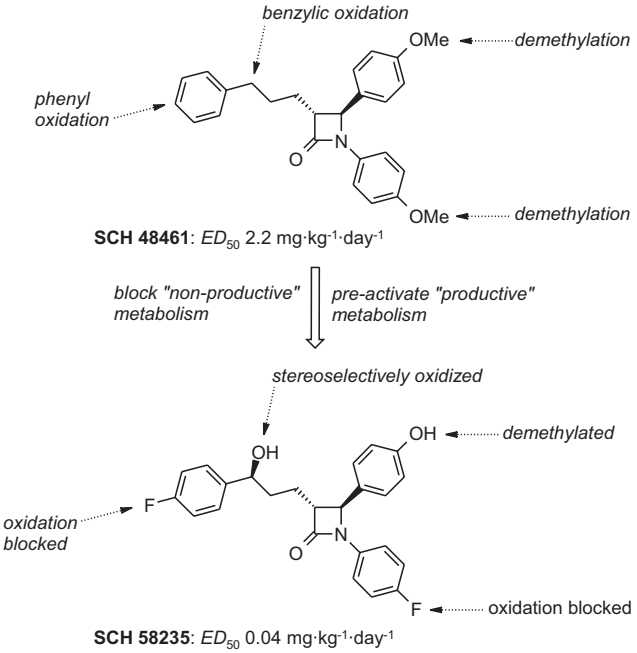
During oxidation of haloarenes 1,2 migration of the halogen, leaving a phenolic hydroxy group at the original position of the halogen, the so-called NIH shift, often occurs [7, 52] (Scheme 4.20).



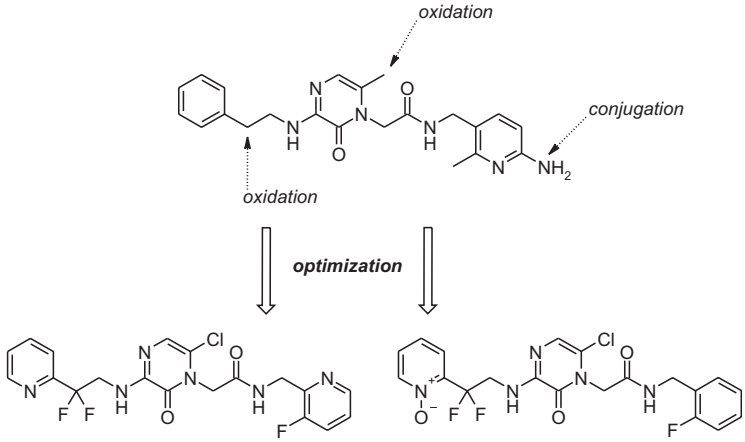
Scheme 4.20 Oxidation of aromatic substructures leads, via an electrophilic epoxide, to the formation of phenols. The so-called NIH shift in haloarenes involves 1,2 migration of the halogen substituent [52].

Other types of P450-mediated metabolic processes are the oxidative hydroxylation of aliphatic compounds with labile hydrogen substituents and oxidative demethylations of aromatic methoxy groups or methylamines.

By using fluorination as a tool for rational drug design it is possible to block undesired metabolic pathways selectively, leading to deactivation and leaving only those pathways resulting in the desired biological activation of a prodrug [53] (Schemes 4.21 and 4.22).



Scheme 4.21 Blocking of unproductive metabolic pathways by fluorination as a design tool for an orally active inhibitor of cholesterol absorption [53a]. The result of this rational approach (SCH 58235) is 50 times more active than the conceptual starting compound SCH 48461. (ED_{50} refers to reduction of liver cholesterol esters in hamsters).

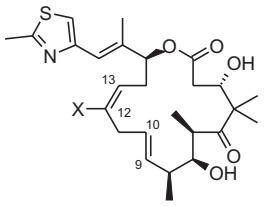


Scheme 4.22 Metabolism-directed optimization of orally bioavailable thrombin inhibitors. Among other modifications, selective fluorination starting from the first lead structure (*top*) results in compounds with dramatically improved effectiveness [53b, c].

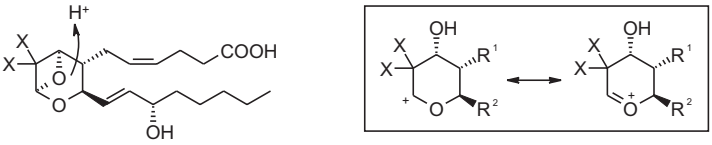
A recent example of selective blocking of oxidative degradation is the rational design of a fluorine-containing analog of the tumor suppressor epothilone [54]. The susceptibility of an olefinic substructure to oxidation was reduced by simply exchanging a methyl substituent (X) by a more electron-withdrawing trifluoromethyl group (Scheme 4.23).

Many other metabolic degradation pathways are either initiated by reactions involving generation of transient carbocations or pass through a transition state with highly positive charge density on a carbon center. Reactions in this category are the acidic hydrolysis of acetals, aminals, or enol ethers, and the oxidation of alcohols to ketones via a hydride-transfer mechanism.

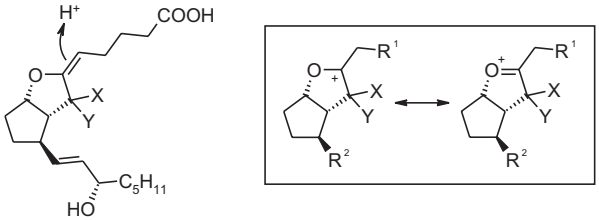
Different kinds of hydrolytic metabolism are relevant to the deactivation of, e. g. thromboxane A_2 [55] (Scheme 4.24), prostacyclin [56] (Scheme 4.25), and many nucleoside-based pharmaceuticals [57]. The first step of the metabolic deactivation of cortisol is oxidation of the 11β hydroxy group to a carbonyl function, presumably by a reaction mechanism involving hydride transfer [58] (Scheme 4.26).



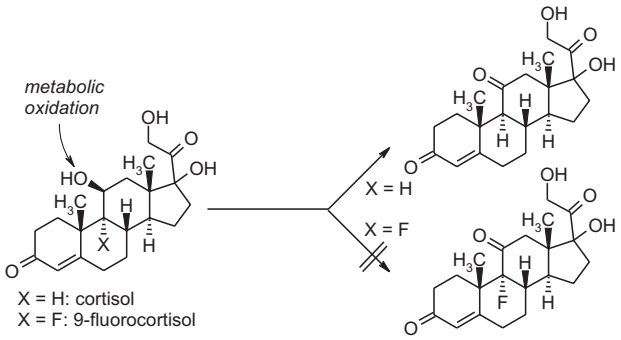
Scheme 4.23 The trifluoromethyl derivative (X = CF_3) of an epothilone analog (X = CH_3) has highly specific tumor-suppression activity with reduced non-specific side-effects [54]. The side-effects can be attributed to oxidative degradation, starting at the C12–C13 double bond, which is inhibited by introduction of a trifluoromethyl group.



Scheme 4.24 Metabolic hydrolysis of the difluorinated analog (X = F) of thromboxane A_2 (X = H) is a factor of 10^8 slower than for thromboxane A_2 itself. This inhibition is because of destabilization of the carbocationic intermediate of the hydrolysis (*box*) by β-fluorination [55].



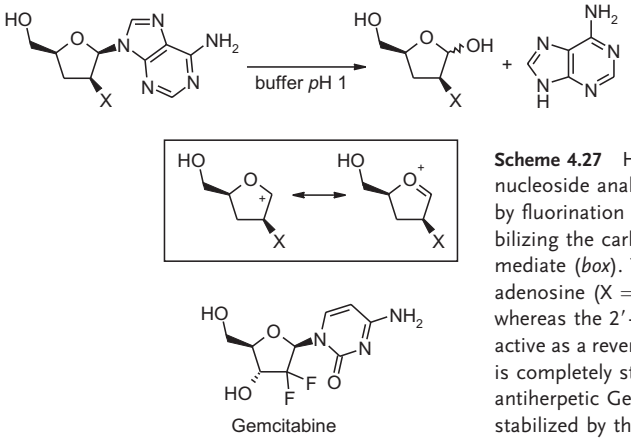
Scheme 4.25 The metabolic lifetime of difluorodidehydroprostacyclin (X = Y = F) and fluorodehydroprostacyclin (X = F, Y = H) is 150 times longer than for prostacyclin (X = Y = H). The cation formed by initial protonation of the double bond (*box*) is destabilized by β-fluorination [56].



Scheme 4.26 Deactivation of cortisol by oxidation of the 11β hydroxy group can be blocked by introduction of fluorine in the 9α position. During the oxidation process the C11 carbon atom supposedly assumes a positive partial charge which is destabilized by the fluorine substitution [58].

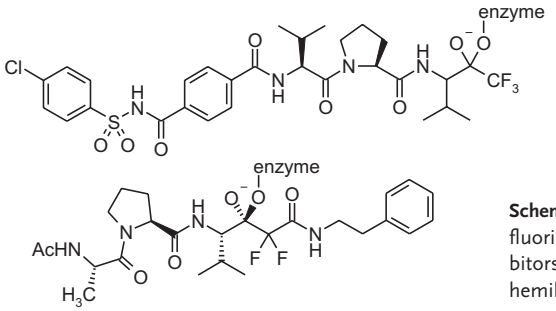
Inhibition of such a pathway can be achieved by fluorination of the position β to the carbon center where the positive charge occurs. β-Fluorination usually destabilizes carbocations because of the strong inductive ($-I_\sigma$) effect of fluorine (Section 2.2.3).

Many anti-cancer and antiviral drugs are derivatives of nucleosides and target DNA or RNA biosynthesis. Nucleosides and their derivatives are then activated by metabolic phosphorylation in the 5′-position. These drugs are, on the other hand, also deactivated by desamination, either hydrolytically or by enzymes such as PNP (purine nucleoside phosphorylase) [59]. This reaction proceeds via an S_N1 mechanism passing through a carbocationic intermediate. The hydrolysis and the PNP-catalyzed reaction can be blocked by mono- or difluorination in the 2′-position (Scheme 4.27), destabilizing the carbocation inductively. In addition, the orientation of the fluorine substituent (ribose or arabinose analog) enables control of the conformation of the furan ring via the *gauche* effect.



Scheme 4.27 Hydrolytic deamination of nucleoside analogs (*top*) can be blocked by fluorination in the 2′-position, destabilizing the carbocationic reaction intermediate (*box*). The half-life of dideoxyadenosine (X = H) at pH 1 is 35 s whereas the 2′-fluoro analog (X = F, active as a reverse transcriptase inhibitor) is completely stable for 20 days [59]. The antiherpetic Gemcitabine (*bottom*) is stabilized by the same principle.

Examples of specific fluorination not primarily affecting metabolism but enabling a unique mode of action by modulating the electrophilicity of a neighboring reaction site are protease inhibitors containing trifluoroacetyl groups or α,α-difluoroketone substructures [60]. This type of reversible inhibitor forms covalent hemiketals of their electrophilic α-fluorinated carbonyl groups with hydroxyl groups of the target protein (Scheme 4.28).



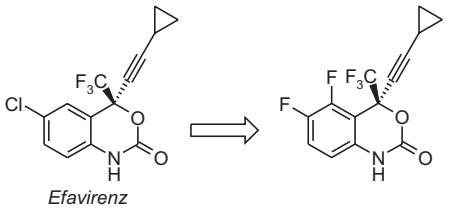
Scheme 4.28 Irreversible binding of α-fluorinated ketone-based protease inhibitors to their target enzyme via a hemiketal [60].

4.5.6
Bioisosteric Mimicking

Some groups which are either metabolically unstable or which are degraded to toxic metabolites can be "mimicked" by fluorine-containing analogs. These "bioisosteric" replacements not only mimic the geometry of another function but can also model the polarity and electrostatic charge distribution of the "original". Typically, the biological target structures cannot discriminate between the congener and the bioisosteric mimic.

For example, a typical replacement of aromatic nitro groups is 1,2-difluoro substitution, resulting in a very similar electrostatic charge distribution. The biological activity of an α_{1a} adrenoreceptor-selective antagonist in which this nitro-difluoro exchange was performed remained virtually unchanged [61] (Figure 4.19).

Another example for the bioisosteric equivalence of aromatic bulky polar substituents (in this case chlorine) and *ortho* difluorination is a second generation analog of the anti-HIV drug Efavirenz. The difluoro analog acts as a reverse transcriptase inhibitor with a different pattern of resistance [62] (Scheme 4.29).



Scheme 4.29 Replacement of bulky chlorine by *ortho* difluoro substitution gives rise to the second generation of Efavirenz-based anti-HIV drugs, acting by inhibition of reverse transcriptase [62].

Aromatic chlorine can also be bioisosterically replaced by a trifluoromethoxy group, which serves as a kind of "pseudohalogen" [63] (Figure 4.20).

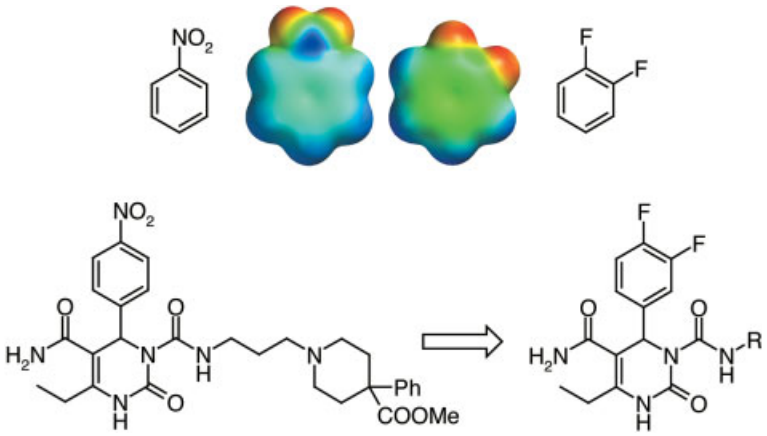


Figure 4.19 Mapping of the electrostatic potential on the electron isodensity surface (red and blue denote negative and positive partial charges, respectively; B3LYP/6-31G*//AM1 level of theory) [30] indicates the electrostatic similarity of 4-nitrophenyl and 3,4-difluorophenyl residue (*top*). Replacement of a nitro group by *ortho* difluoro substitution in pharmaceuticals results in comparable biological activity but far greater metabolic stability and reduced toxicity (*bottom*) [61].

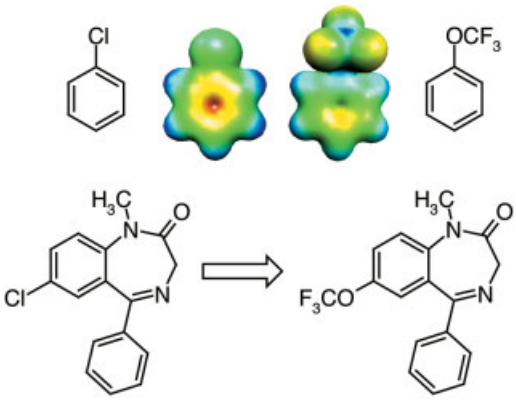


Figure 4.20 Replacement of chlorine by the bioisosteric "pseudohalogen" trifluoromethoxy group leaves the biological activity of diazepam (Valium; *lower left*) virtually unchanged [63]. Mapping of the electrostatic potential (*above*: red and blue denote negative and positive partial charges, respectively; AM1//B3LYP/6-31G* level of theory) [30] on the electron isodensity surface shows the similarity of chlorobenzene and trifluoromethoxybenzene, although the OCF_3 group is sterically more demanding.

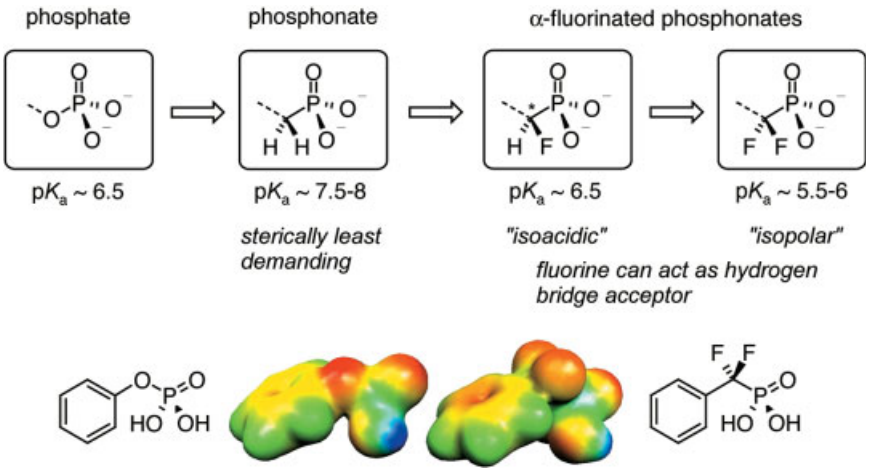


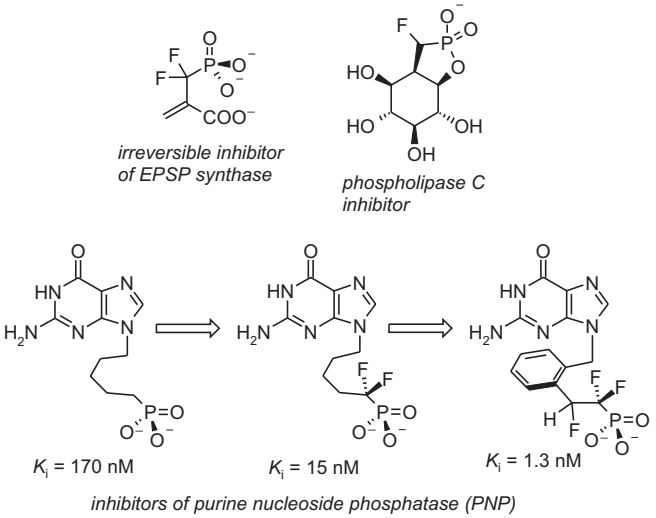
Figure 4.21 Phosphates, which are sensitive to hydrolysis and enzymatic degradation, can be replaced by the corresponding bioisosteric methylphosphonates and their mono- and difluorinated analogs [65]. The acidity of the phosphate group (second pK_a) is best matched by "isoacidic" α-fluoromethylphosphonates, the polarity by "isopolar" α,α-difluoromethylphosphonates.

A substance class of particular importance as intermediates in most central metabolic processes and also as chemical messengers in many signal cascades are organophosphates [64]. Despite of their pivotal biochemical role they are often only short-lived species which are rapidly hydrolyzed either spontaneously or by ubiquitous phosphatases. To make use of phosphates as bioactive compounds of pharmaceutical interest, the hydrolytically labile phosphate bond has to be stabilized [65].

A well-established stable class of phosphate analogs are the alkyl phosphonates, in which a methylene group replaces oxygen [66]. Although the methylene group is sterically only slightly more demanding than oxygen, the acidity (in particular, the second pK_a) of the phosphonate analog is significantly lower than for monophosphates. The polarity of the oxygen bridge, also, is not matched by its methylene replacement [65].

Blackburn [67] and McKenna [68] therefore suggested that α-fluorination would lead to better phosphate mimics: α-fluoromethylphosphonates, in particular, would match the second pK_a of a phosphate group ("isoacidic"), whereas α,α-difluoromethylphosphonates would better match the electrostatic potential surface of the bridge ("isopolar") (Figure 4.21). In contrast with the methylphosphonate congener the α-fluorinated phosphonates [69] can also act as hydrogen-bridge acceptors [36, 5, 70].

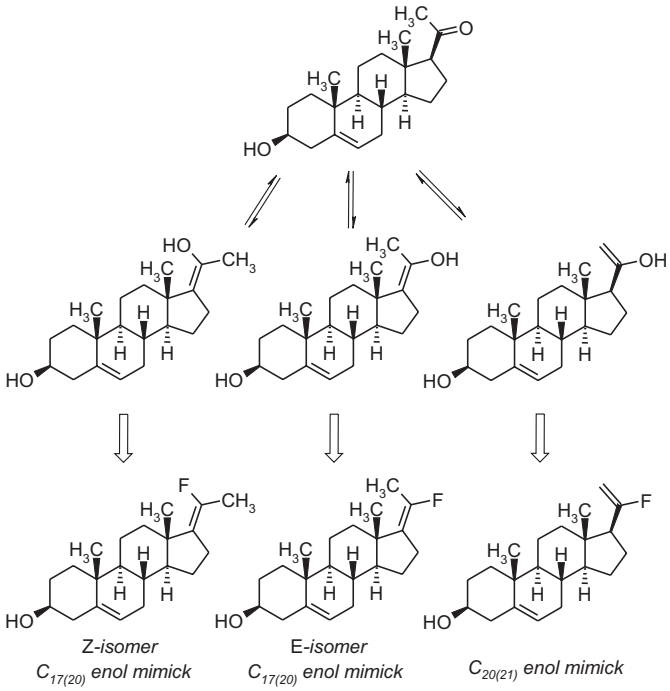
The concept is not limited to analogs of simple linear organophosphates (e. g. phosphoenol pyruvate analog as inhibitor of 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase [71]) but can be extended to cyclic phosphates (e. g. cyclic phosphoinositol analog as a phospholipase C inhibitor [72]) and transition state analogs (e. g. purine nucleoside phosphorylase (PNP) inhibitor [73]) (Scheme 4.30).



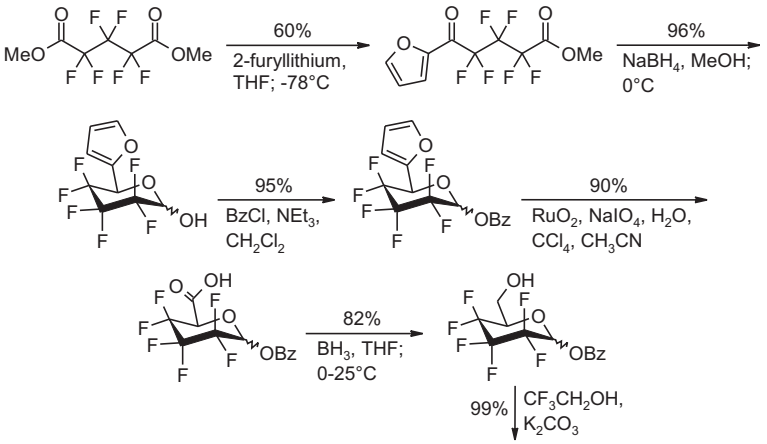
Scheme 4.30 Fluoromethyl phosphonate analogs of phosphoenol pyruvate (irreversible inhibitor of 5-enolpyruvylshikimate-3-phosphate (EPSP) synthase) [71], of cyclic inositol phosphate (lipolipase C inhibitor) [72], and of the transition state of the purine nucleoside phosphorylase (PNP) reaction [73].

Reactive intermediates which are not stable under physiological conditions can also be mimicked by fluorine-based bioisosteric groups. Thus, fluorovinyl derivatives have been successfully used to mimic the enol form of a steroidal ketone, rendering the resulting pregnenolone derivatives (*Z* and *E* isomers) powerful inhibitors of steroid $C_{17(20)}$ lyase [74]. The compounds depicted in Scheme 4.31 target prostate cancer by blocking androgen biosynthesis.

An extreme example of bioisosteric mimicking is replacement of nearly all hydrogen atoms and hydroxy groups by fluorine at the same time. The heavily fluorinated glucose analog depicted in Scheme 4.32 [75] illustrates the concept of "polar hydrophobicity". It has a markedly less polarizability and higher lipophilicity than glucose while retaining shape and electrostatic charge distribution. The "somewhat volatile, sweet-smelling crystalline material" (unfortunately, there is no comment on the taste) obviously shares some characteristics with glucose. It is transported across erythrocyte membranes significantly faster than glucose, indicating high affinity for the glucose-specific transporter protein.



Scheme 4.31 Fluoroolefins, mimicking the different enol forms of pregnenolone, are potential drugs against prostate cancer [74]. Their mechanism of action is based on inhibition of steroid $C_{17(20)}$ lyase, which converts the C_{21}-progestins into C_{19}-androgens.



Scheme 4.32 A heavily fluorinated analog of glucose (*box*), with fluorine mimicking hydrogen and hydroxyl groups at the same time, is recognized by the glucose transport mechanism across erythrocyte membranes [75].

4.5.7
Mechanism-based "Suicide" Inhibition

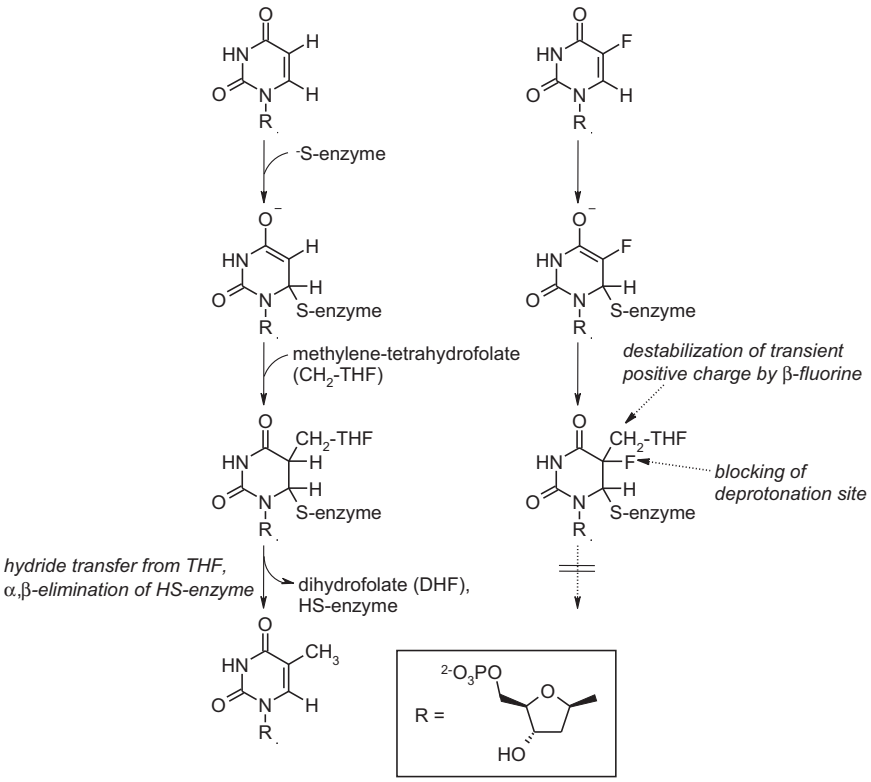
For all the enzyme inhibitors discussed so far, fluorine influences the mechanism of inhibition either by mimicking other functional groups or by influencing the conformation of the inhibitor by stereoelectronic effects.

Many aspects of the reactivity of fluorine can be considered as "orthogonal" to those of hydrogen. Whereas in "organohydrogen" chemistry the (positively charged) proton is a key species and many different reaction types involve proton transfer steps, in organofluorine chemistry everything depends on the negatively charged fluoride ion. Together with the similar steric behavior of hydrogen and fluorine this fundamental difference in reactivity can be used to design very different types of enzyme inhibitor. The mode of action of these generally irreversible inhibitors uses the mechanism of the enzymatic reaction, and the compounds resulting from this concept are sometimes called "suicide inhibitors" [3, 76].

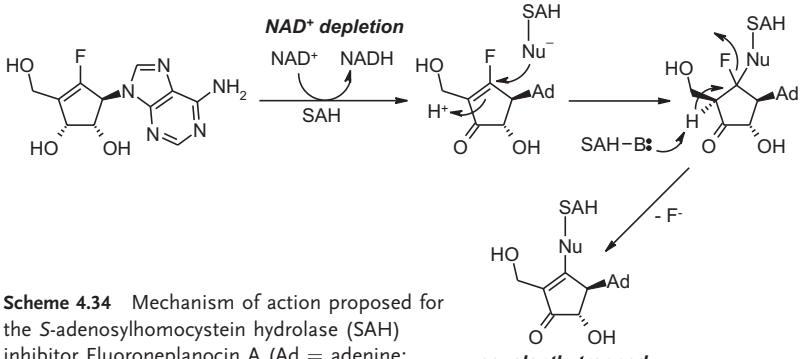
The best-known example of this type of inhibition is 5-fluorouracil, a rather old cytostatic agent. Fluorouracil is first converted metabolically into the corresponding phosphodeoxyriboside. This, in turn, blocks DNA biosynthesis by inhibiting thymidylate synthase, an enzyme which methylates deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP), one of the four building blocks of DNA [77].

During the enzymatic reaction on the fluorinated pseudosubstrate (Scheme 4.33), the 5-fluorodeoxyuridine inhibitor is first processed just like the natural substrate (dUMP) and is bound covalently to the coenzyme tetrahydrofolate (THF) and to the enzyme via a thiol residue. The two final partial steps, separation of the substrate, coenzyme, and enzyme, are blocked by the fluorine substituent in 5-fluoro-dUMP. These steps consist of hydride transfer from the THF coenzyme and separation of the covalent bond between the enzyme and the substrate by elimination. Hydride transfer from THF to the methylene group is supposed to involve transient build-up of a positive partial charge on the reaction center, which is destabilized by the β-fluorine substituent. Elimination of the enzyme thiol group from the natural substrate involves deprotonation in the uracil 5-position. In 5-fluorouracil this cannot occur, because fluorine could be eliminated as a fluoride anion only. The enzyme is thus "committing suicide" by partially processing the inhibitor. Several anti-cancer and antiviral drugs derived from uracil act by deactivating tymidylate synthase by a related mechanism [1, 78].

Another nucleoside-derived mechanism-based enzyme inhibitor is Fluoroneplanocin A [79]. This compound is of interest as a broad-spectrum antiviral drug which acts by irreversible inhibition of *S*-adenosylhomocystein hydrolase (SAH). In a first enzymatic reaction step the 3′-hydroxy group of the inhibitor is oxidized to the corresponding ketone (Scheme 4.34). This leads to depletion of the biochemical oxidizer nicotinamide adenine dinucleotide (NAD^+). In the next step a nucleophilic residue of the enzyme undergoes Michael addition to the β-fluoro α,β-unsaturated ketone moiety. This is followed by fluoride elimination and thus the inhibitor stays covalently trapped in the active site and disables the enzyme permanently.

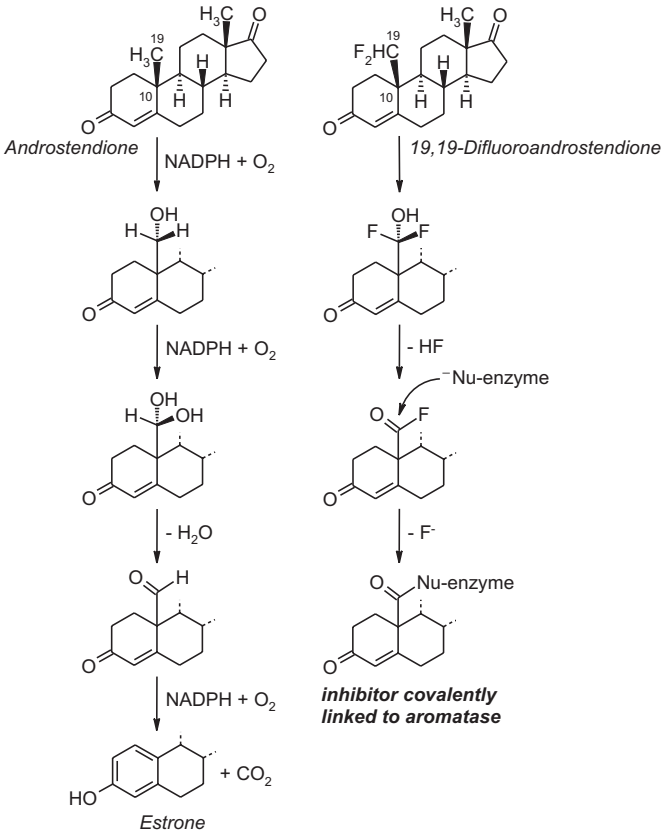


Scheme 4.33 Mechanism of the "suicide inhibition" of tymidylate synthase by 5-fluorouracil. The reaction pathway with the natural substrate (dUMP) is depicted on the left, the analogous sequence with 5-fluoro-dUMP on the right. The key to the irreversible blocking of the enzyme reaction site is the inability of fluorine to functionally replace hydrogen in proton-transfer reactions, for example the β-elimination liberating the enzyme thiolate group [10]. In addition, the transient positive charge on the methylene group during hydride transfer is destabilized by the β-fluorine.



Scheme 4.34 Mechanism of action proposed for the *S*-adenosylhomocystein hydrolase (SAH) inhibitor Fluoroneplanocin A (Ad = adenine; Nu = nucleophilic group) [79].

Estrogen synthase is one of the key enzymes in the conversion of androgens to estrogens [3] and is, therefore, an important drug target. Mechanistically, estrogen synthase oxidizes the C19 methyl group on the A ring of androstendione stepwise to the corresponding carboxylic acid, which decarboxylates on aromatization of the A ring to the corresponding phenol which is characteristic of the estrogens (Scheme 4.35).

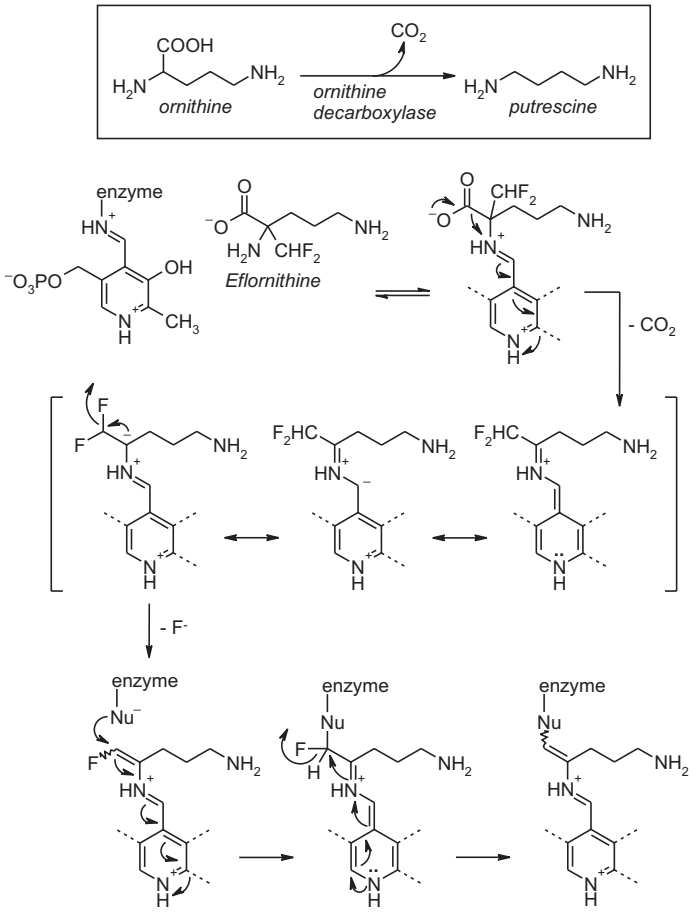


Scheme 4.35 Mechanism of action of the irreversible estrogen synthetase inhibitor 19,19-difluoroandrostendione (*right*) [3, 80] compared with the normal course of the aromatase reaction (*left*) (Nu = nucleophilic group).

The enzyme is irreversibly inhibited by the difluoromethyl analog of androstendione. The mechanism postulated for the inhibition involves oxidation of the difluoromethyl group and subsequent elimination of hydrofluoric acid. The resulting carbonyl fluoride binds covalently to a nucleophilic group of the enzyme, disabling it permanently [80].

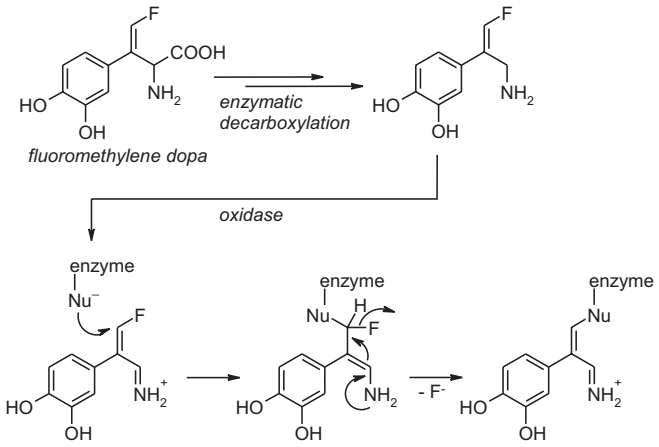
Many fluorinated, mechanism-based inhibitors are amino acid derivatives [3, 81]. These target enzymes involved in amino acid metabolism, for example decarboxylases, transaminases or monoamine oxidases.

The antiprotozoal drug Eflornithine is used to treat African sleeping sickness. The difluoromethyl analog of the natural substrate ornithine acts as a mechanism-based inhibitor of ornithine decarboxylase (OD). The final stage of the process is formation of a covalently bound complex with the enzyme and the coenzyme pyridoxal phosphate (PLP) [10] (Scheme 4.36).



Scheme 4.36 The antiprotozoal drug Eflornithine acts by inhibiting ornithine decarboxylase (OD) (*box*), forming covalent bonds to the enzyme and to the cofactor pyridoxal phosphate (PLP; Nu = nucleophilic group) [10].

Another type of fluorinated amino acid analogs are the β-fluoromethylene derivatives of the acids [3]. For example, fluoromethylene dopa is metabolized to the corresponding dopamine derivative, which is a powerful inhibitor of monoamine oxidase and thus of interest for treatment of Parkinson's disease (Scheme 4.37).

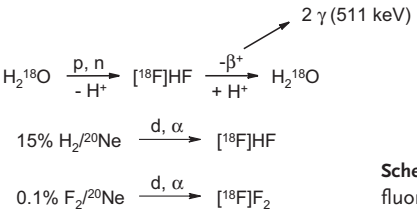


Scheme 4.37 Mechanism of action of fluoromethylene dopa, a mechanism-based inhibitor of monoamine oxidase [3] (Nu = nucleophilic group).

4.5.8
Fluorinated Radiopharmaceuticals

The capacity of fluorine to mimic elements such as hydrogen or oxygen also makes it of interest for use in medicinal diagnostics. In the body many fluorinated metabolites and pharmaceuticals take the same transport and processing pathways as their congeners. If fluorine is used as a marker in a medical imaging processes it is possible to gain insight in the fate of metabolites with high spatial resolution. Particularly useful for imaging purposes is the artificial isotope fluorine-18 (^{18}F), which can be introduced into a variety of organic substrates [82].

Fluorine-18 is a positron (β^+) emitter with a half-life of 109.7 min. The emitted positron disintegrates very quickly on contact with ambient electrons, resulting in emission of two energetic (511 keV) γ photons in directions exactly 180° apart. The isotope can be produced in a cyclotron either as elemental $[^{18}F]F_2$ for electrophilic reactions or as nucleophilic $[^{18}F]F^-$ or [^{18}F]HF [83] (Scheme 4.38).



Scheme 4.38 Methods for generation of ^{18}F-labeled fluoride or hydrogen fluoride [83].

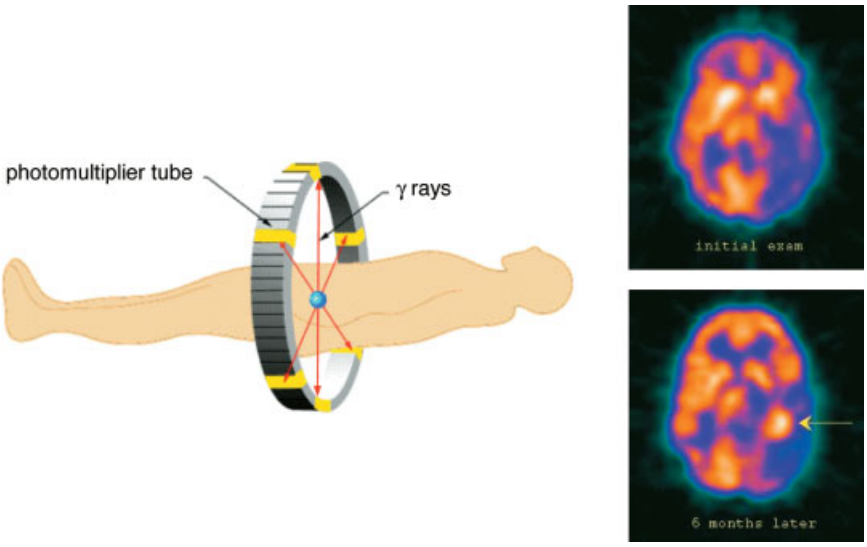
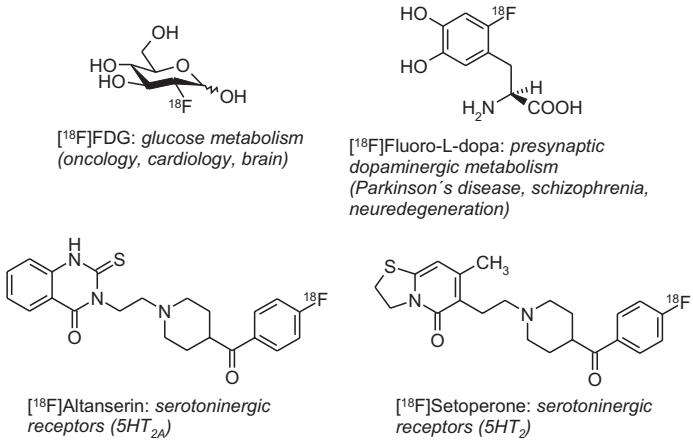


Figure 4.22 The working principle of positron emission tomography (PET) is based on the β^+ decay of ^{18}F-labeled diagnostics, for example [^{18}F]2-fluorodeoxyglucose ([^{18}F]FDG) [85]. The γ photon pairs resulting from positron–electron annihilation are detected (*left*) and enable spatial resolution of the sites where the labeled diagnostics and their congeners are predominantly processed. [^{18}F]FDG is particularly useful for identification of metabolically active areas with high glucose turnover, for example brain tumors (*right*). The two PET scans show a healthy brain (*above*) and a newly developed tumor (*below, arrow*; courtesy of Hamamatsu Photonics).

Because of the very short half-life of fluorine-18 the synthetic steps for introduction of the isotope into organic substrates must be kept simple and fast. The ^{18}F-labeled diagnostics are prepared immediately before use. Their main field of application is medical diagnostics and elucidation of metabolic pathways by positron emission tomography (PET) [84] (Figure 4.22).

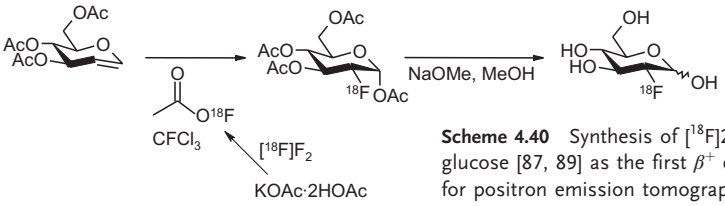
Positron emission tomography (PET) enables identification of metabolically active sites with high spatial resolution. The method is particularly valuable for diagnosis of cancer and diseases of the brain, for example Parkinson's and Alzheimer's disease. Areas with high glucose metabolism, for example tumor tissue, are best visualized with [^{18}F]FDG. The method is sensitive enough to locate the most active areas of the brain during specific cognitive tasks. In brains with Alzheimer's disease large areas with diminished glucose turnover can be detected.

Other ^{18}F-labeled tracers, for example different fluorinated dopamine derivatives, enable, e. g., very differentiated diagnosis of Parkinson's disease [86]. Fluorine-18-derivatized diagnostics have also been used to trace the metabolic pathway of drugs through the body in clinical tests. The radiation dose to which the test person is subjected is in the same range as, e. g., that used for a stomach X-ray examination. Examples of ^{18}F-labeled radiopharmaceuticals and their target sites and applications are illustrated in Scheme 4.39.

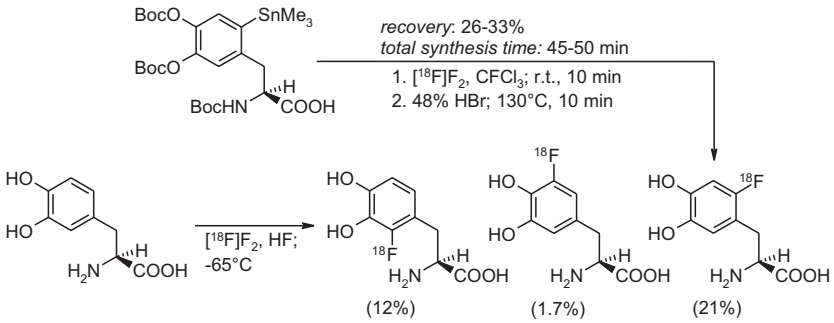


Scheme 4.39 Examples of ^{18}F-labeled radiopharmaceuticals and their target sites and applications [82].

Time-consuming work-up procedures must be avoided in the synthesis of ^{18}F labeled diagnostics, but essentially the usual fluorination methods are used. [^{18}F]FDG can be prepared by electrophilic fluorination of a glycal with [^{18}F]acetyl hypofluorite [87] (Scheme 4.40). This reagent again is produced by reaction of ^{18}F labeled fluorine gas with KOAc·2HOAc [88]. The synthesis of other [^{18}F]fluorodopa isomers is illustrated in Scheme 4.41.



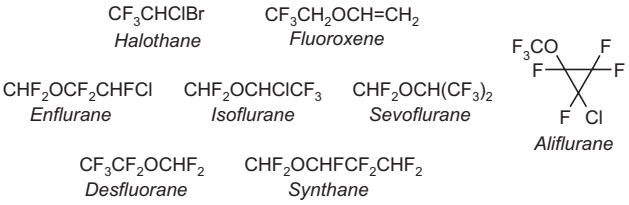
Scheme 4.40 Synthesis of [^{18}F]2-fluorodeoxyglucose [87, 89] as the first β^+ emitter for positron emission tomography (PET) [84].



Scheme 4.41 Synthesis of different [^{18}F]fluorodopa isomers [90] used for diagnosis of brain disorders, for example Parkinson's disease.

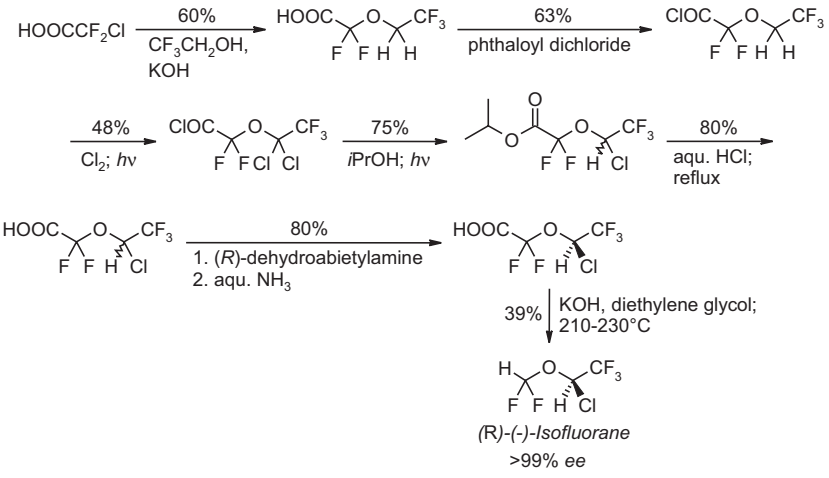
4.5.9
Inhalation Anesthetics

Halofluorocarbons and highly fluorinated ethers have been used as inhalation anesthetics for many years [91]. The first anesthetic of this type was Halothane which was introduced clinically in 1956 [92]. An excellent anesthetic with few unwanted side-effects, Halothane has the particular advantages of high chemical stability and non-flammability. Several alternative heavily fluorinated inhalation anesthetics have subsequently been introduced [93] (Scheme 4.42).



Scheme 4.42 Examples of inhalation anesthetics [94].

The molecular mechanism of action of inhalation anesthetics remains a matter of controversy. The classical view is that narcosis is induced by an unspecific disruption of cell membrane lipids by insertion of the lipophilic anesthetic [95]. Studies of enantiomerically pure analogs of several of the compounds depicted in Scheme 4.42 [96] have, however, revealed clear differences between the effects of enantiomers [97] (Scheme 4.43). There is also a growing body of evidence that the anesthetic effect is at least partly because of specific interaction with proteins [98], for example potassium ion channels and central nicotinic acetylcholine receptors [99].

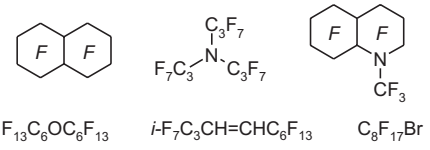


Scheme 4.43 Synthesis of enantiomerically pure (*R*)-(−)-isofluorane [100].

During surgery the anesthetic must be administered in quantities of tens of grams or more. To put no additional load on an organism already stressed by surgery and narcosis the anesthetic should, ideally, not be metabolized at all and be excreted solely by exhalation. One advantage of fluorinated anesthetics compared with older compounds, for example diethyl ether, is their general metabolic inertness. Nevertheless, in the years after their clinical introduction some fluorinated anesthetics have been found, rarely, to cause nephrotoxicity or hepatotoxicity [7], mostly as a result of the formation of toxic metabolites. For example, a significant portion of the administered dose of methoxyfluorane is metabolized to oxalate and fluoride. Most degradation of the anesthetics is done by the cytochrome P450 system and involves oxidative and reductive steps [101].

4.5.10
Blood Substitutes and Respiratory Fluids

Their pronounced ability to dissolve molecular oxygen in combination with their non-toxicity and complete physiological inertness makes perfluorocarbon fluids attractive for applications as respiratory fluids and as components of artificial blood substitutes [102] (Scheme 4.44). Many perfluorocarbons and perfluorinated amines can dissolve up to 40–50 % *v*/*v* oxygen at 1 atm and 37 °C. It has been speculated that this unusual oxygen-dissolving capacity is related to the molecular shape and the occurrence of "cavities" in perfluorocarbon fluids [103].



Scheme 4.44 Compounds used as respiratory fluids (e. g. perfluorodecalin) or as components of artificial blood substitute mixtures [102a].

Perfluorocarbon-based blood substitutes are, typically, a stable emulsion of perfluorocarbons, perfluorotrialkylamines, phospholipids, electrolytes, and water [102a]. During major surgery the blood of the patient is exchanged for the perfluorocarbon substitute. After the operation the stored blood can be reperfused. These temporary blood substitutes provide the body with oxygen during surgery, but – of course –are unable to assume the numerous other functions of natural blood. The fluorocarbon components of the artificial blood are excreted, mostly via the lungs, over a period of days or weeks, depending on their volatility [104, 105] (Figure 4.23).

Pure perfluorocarbon and perfluoroether fluids have also been investigated as liquid oxygenation media for diving operations at great depths, i. e. in a high-pressure environment [106]. By breathing oxygen-saturated perfluorocarbons the diver can avoid complications such as decompression sickness [107]. The concept has been investigated since the 1960s and was recently popularized in the movie *The Abyss* [108]. A major practical disadvantage of breathing perfluorocarbons during

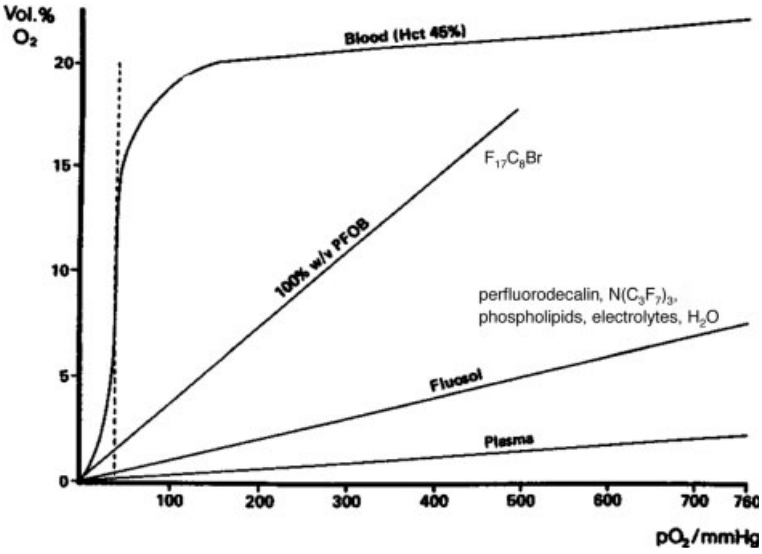


Figure 4.23 Oxygen-carrying capacity of human blood in comparison with pure perfluoro-*n*-octyl bromide (PFOB) and the blood substitute Fluosol [105] (graph modified from Ref. [102]).

prolonged stays in the hypothermic (ca 4 °C) deep-sea is the heat lost by the body because of the good heat-carrying capacity of these fluids [109].

4.5.11
Contrast Media and Medical Diagnostics

In the same way as for anesthetics applied doses of contrast media are in the ten-gram range. Again, because of their physiological inertness, perfluorocarbons have substantial advantages when applied in medical diagnostics. Emulsions of compounds containing heavy atoms, for example perfluoro-*n*-octyl bromide (PFOB), have been used as contrast agents for X-ray imaging of soft tissues, for example the lungs or gastrointestinal tract [110]. PFOB has also been used for ^{19}F NMR imaging of different types of tissue [111].

A newer application of pure perfluorocarbons with relatively low boiling points is as contrast agents for medical ultrasound examination of the circulatory system [112]. Making the ultrasound imaging technique available for examination of, in particular, the cardiovascular system and other soft tissues is highly important, because ultrasound technology is far more widespread and less expensive than other imaging equipment.

Ultrasound imaging is based on reflection of the sound waves (1–3 MHz) at the borders between areas with different acoustic impedance, which is determined by the speed of propagation of sound and the density of the tissue. Because the interfaces between blood and other soft tissues, for example the heart or liver, do not

usually reflect sound very well, the quality of pictures obtained by standard ultrasound imaging is not sufficient for many diagnostic purposes. The acoustic impedance of blood can be changed dramatically by introduction of gaseous microbubbles into the bloodstream. Lower molecular weight perfluorocarbons are particularly suitable for use as the medium for such microbubbles [112b]. They form rather stable bubbles because they are completely insoluble in blood plasma and the vapor pressure in the microbubbles at body temperature is high enough to balance the blood pressure. In addition, they are not metabolized and are completely cleared from the body by exhalation within a few minutes.

Perfluorocarbon-based ultrasound contrast agents, for example C_3F_8, C_4F_{10}, or C_5F_{12}, are injected typically as stabilized microemulsions [113] which have to be activated before use. The amount of perfluorocarbon which must be administered for one examination of a 70-kg person is approximately 50 μL.

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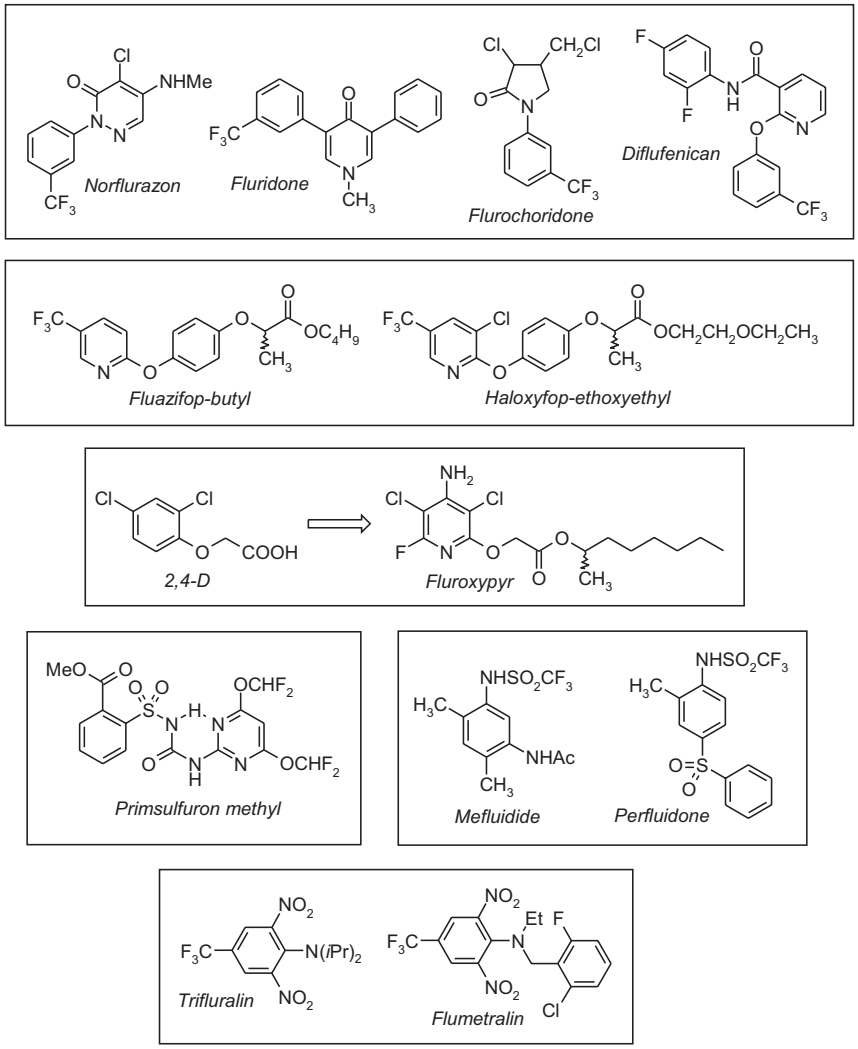
4.6
Agricultural Chemistry

A recent market study has shown that the share of fluorine-containing compounds for crop protection has grown from 9 % in 1988 to 17 % in 1999 [1, 2]. For special applications, for example herbicides (Scheme 4.45) and insecticides (Scheme 4.47), this figure had even reached around 40 %. The higher price of fluorinated compounds is outweighed by often dramatically increased effectiveness – the absolute quantity of newly developed agricultural chemicals which has to be released into the environment is reduced.

Herbicides have several different mechanisms of action. Carotenoid biosynthesis inhibitors (Norflurazon, Fluridone, Flurochoridone, Diflufenican) block the formation of antioxidants which protect the photosynthetic apparatus in plants [3]. Plants treated with this class of substance are bleached and become unable to photosynthesize [4].

Aryloxyphenoxypropionates have selective activity against different grass species [5]. This class of substance inhibits fatty acid biosynthesis. The first example of this type of compound was Diclofop-methyl, which is structurally derived



Scheme 4.45 Different types of fluorine-containing herbicide. From *top* to *bottom*: carotenoid biosynthesis inhibitors, aryloxyphenoxypropionates, pyridyloxyacetic acids, sulfonylureas, trifluoromethane sulfonanilides, benzylamine derivatives [3–14].

from 2,4-dichlorophenol. Introduction of a heterocyclic nitrogen atom and a trifluromethyl group resulted in strongly increased effectiveness (Fluazifop-butyl, Haloxyfop-ethoxyethyl) [6].

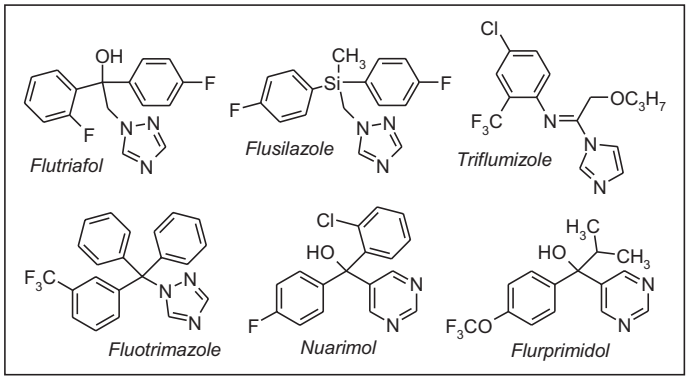
Pyridyloxyacetic acid derivatives (e. g. Fluroxypyr) [7] are structurally related to the "classic" 2,4-D [8]. They have a similar mechanism of action but can also control weed species which are resistant to 2,4-D.

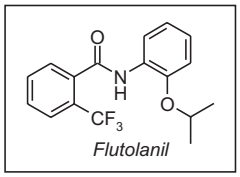
One of the most effective classes of herbicide are the sulfonylureas. They are applied in quantities of no more than a few grams per hectare. The action of sulfonylureas is based on inhibition of acetolactate synthase (ALS) [9]. The fluorine-containing derivative Primsulfuron methyl has selectivity in the cultivation of maize [10].

Another, older, class of herbicide (Mefluidide and Perfluidone) is based on a trifluoromethane sulfonanilide substructure [11].

One of the commercially most successful fluorine-containing herbicides is Trifluralin [12, 13]. Acting by inhibition of root and shoot growth of seedlings immediately after germination it is used as a preplanting herbicide for selective control of annual grasses and broadleaf weeds in cotton and other crops. A newer development is the structurally related Flumetralin [14], which is used to control suckers on tobacco.

Many fungicides [15] act by inhibiting sterol biosynthesis. More specifically, they block the C-14α demethylation step in ergosterol biosynthesis [16]. In many of these compounds (Flutriafol [17], Flusilazole [18], Triflumizole [19], Fluotri-





Scheme 4.46 Different examples of fluorinated fungicides: (*top*) sterol biosynthesis inhibitors and (*bottom*) a benzamide-based compound [15–22].

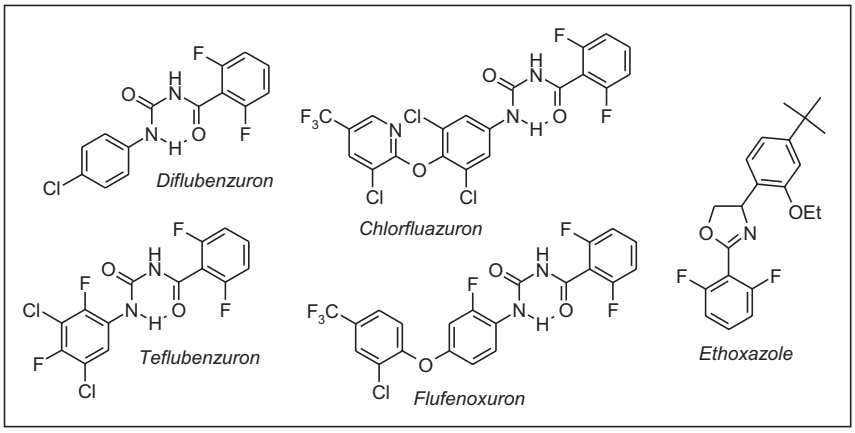
mazole [20], Nuarimol, Flurprimidol [21]) fluorine is essential for their high level of effectiveness (Scheme 4.46).

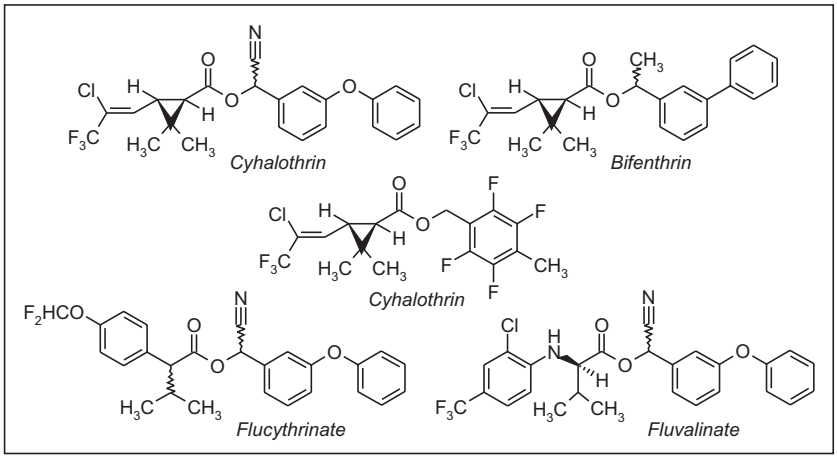
A different type of fungicide for use on rice, cereals, and vegetables is Flutolanil [22], which is based on a benzamide substructure with a trifluoromethyl substituent.

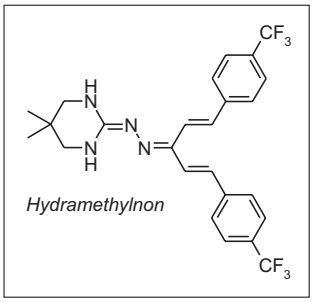
The growth of insects can be controlled by the disruption of the molting process by inhibiting chitin biosynthesis [23, 24]. Since the mid-1970s several fluorinated

benzoylureas (Diflubenzuron, Chlorfluazuron, Teflubenzuron, Fluphenoxuron) acting by this mechanism have been introduced commercially [25].

Perhaps the most important class of insecticide is the pyrethroids [23, 26]. Originally, this class of substance was isolated from the plant species *Chrysanthemum cinerariafolium*, but the natural products were not sufficiently stable for commercial







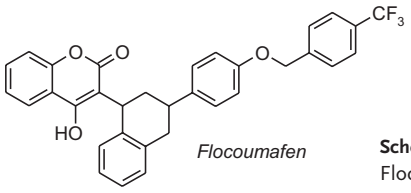
Scheme 4.47 Examples of the different types of fluorinated insecticide. From *top* to *bottom*: benzoylureas [25], pyrethroids [23, 26–28], aminoguanidines [29].

use. Systematic optimization of the basic structure led to several, sometimes highly fluorinated analogs (Cyhalotrin, Bifenthrin, Tefluthrin) [27]. It was found that introduction of one vinylic trifluoromethyl group, especially, dramatically enhanced activity. Later a different type of very active pyrethroid-derived structure was identified (Flucythrinate, Fluvalinate) [28] which does not contain a cyclopropane moiety.

The fluorinated compound Hydramethylnon [29] is used specifically for control of ants.

Different types of fluorinated insecticide are illustrated in Scheme 4.47.

Fluorinated compounds have also found occasional application as rodenticides. Flocoumafen (Scheme 4.48) is an anti-coagulant which is effective against rats which are resistant to other coumarin derivatives [30].



Flocoumafen

Scheme 4.48 The fluorine-containing rodenticide Flocoumafen [30].

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Appendix

A.
Typical Synthetic Procedures

The following examples of synthetic procedures were selected to give an overview of different aspects of preparative fluoroorganic chemistry. The procedures were taken from the original literature with only minimal modification, where necessary. Occasionally general comments and recommendations for possible safety precautions have been added.

A.1
Selective Direct Fluorination

A.1.1 General Remarks

Fluorine diluted with nitrogen [1] (5 % and 10 % *v*/*v* F_2 in N_2) is commercially available in bottles with special valves. For direct fluorination with dry fluorine glassware can, in principle, be used. Because glass-etching hydrogen fluoride is often formed as a by-product of the fluorination reaction, the use of resistant fluoropolymers is recommended for the reaction vessel and tubing. Because of its transparency and plasticity, PFA is a particularly useful material. Because even diluted fluorine can react violently with many organic compounds, care must be taken to avoid even traces of standard glassware lubricants in the apparatus. Special fluorine-resistant lubricants are commercially available. Especially toward the end of fluorination reactions, larger quantities of unreacted fluorine might pass through the apparatus. To destroy this excess fluorine scrubbers containing soda lime or a mixture of aluminum oxide and granulated charcoal are recommended.

Fluorine is a highly reactive and toxic gas and should be handled only under a well-ventilated hood, with protective goggles and gloves. Even low concentrations can be detected by its characteristic smell. Exposure to fluorine, even at low concentrations, carries a significant health risk. Even after apparently minor body contact with fluorine gas competent medical help should be sought immediately.

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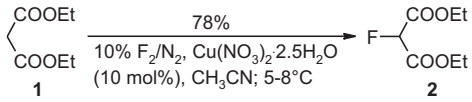
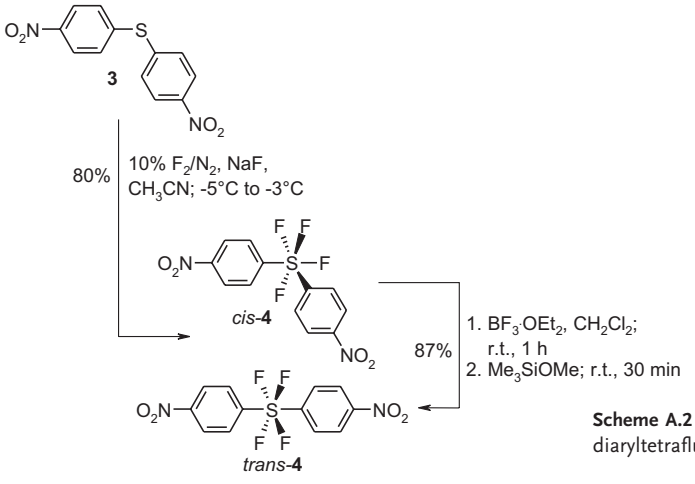
A.1.2 Fluorination of Diethyl Malonate (1) to Diethyl Fluoromalonate (2)



Scheme A.1 Selective direct monofluorination of malonates, catalyzed by copper salts [2].

A glass reaction vessel fitted with a PTFE-coated mechanical stirrer, an FEP thermocouple well, an FEP gas delivery tube, and an exit tube to a scrubber filled with soda lime was charged with diethyl malonate (3.2 g, 20 mmol), $Cu(NO_3)_2{\cdot}2.5H_2O$ (460 mg, 2.0 mmol), and acetonitrile (50 mL) before being cooled to 5–8 °C. The vessel was purged with nitrogen and then fluorine diluted to 10 % *v*/*v* with nitrogen was passed through the stirred solution at a rate of 16 mmol h^{-1} for 4 h. When the fluorine supply had been turned off, the reaction vessel was purged with nitrogen. The reaction mixture was then poured into water and extracted with CH_2Cl_2. A weighed amount of trifluoromethyl benzene was added to the extracts and their ^{19}F NMR spectrum was then measured. The dried extracts were evaporated and the residue was analyzed by GLC and/or ^1H NMR. From this information, the amount of substrate converted (conversion) and the yield of the product, based on the amount of substrate converted, were calculated. A sample of pure product was obtained by preparative scale GC. The diethyl fluoromalonate **2** was obtained in 78 % yield with a conversion of 100 % [2]. ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.41$ (t, $J = 7.1$ Hz, 6H), 4.4 (q, $J = 7.2$ Hz, 4H), 5.36 (d, $J_{HF} = 48.3$ Hz, 1H); ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -196.5$ (d, $J_{HF} = 48.3$ Hz).

A.1.3 Synthesis of Bis(4-nitrophenyl)tetrafluorosulfurane (4) (Isomer Mixture 15 % *trans*/85 % *cis*)



Scheme A.2 Synthesis of diaryltetrafluorosulfuranes [3].

A suspension of bis(4-nitrophenyl)sulfide (**3**) (20 g, 72 mmol) and NaF (60 g; dried *in vacuo* at 250 °C for 18 h) in dry acetonitrile (500 mL) was cooled to −5 °C. A stream of 10 % *v*/*v* fluorine in nitrogen was bubbled through the mixture with vigorous stirring, keeping the temperature between −5 and −3 °C until completion of the reaction, as indicated by GC–MS. (The reaction was conducted in a PFA apparatus. Excess fluorine was absorbed in a scrubber charged with aluminum oxide and granulated charcoal.) After purging of the suspension with nitrogen the solvent was removed under reduced pressure. The solid residue, consisting mainly of NaF, product, and bis(4-nitrophenyl)sulfone, was extracted with hot $CHCl_3$ (5 × 200 mL). The combined extracts were filtered and evaporated to 250 mL. After crystallization for 18 h at −20 °C the crude product was isolated by filtration. A second recrystallization from acetonitrile yielded 20 g (80 %) of yellow crystals, consisting of a mixture of 15 % *trans*-**4** [3] and 85 % *cis*-**4**; m. p. >180 °C, dec.; correct elemental analysis.

A.1.4 **Isomerization to *trans*-4**

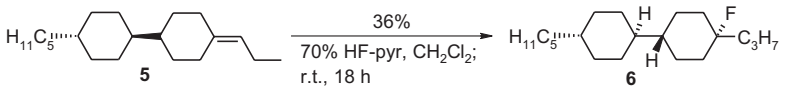
The isomer mixture (*trans*/*cis*-**4** 15:85) (60 g, 0.17 mol) was suspended in dry CH_2Cl_2 (1.8 L) and treated at room temperature with $BF_3{\cdot}Et_2O$ (2.61 mL, 17 mmol) for 60 min. After addition of $MeOSiMe_3$ (6 mL, 44 mmol) the suspension was stirred for a further 30 min and then evaporated to dryness. The crude product was recrystallized twice from acetonitrile. Yield: 52 g (87 %) *trans*-**4**, pale yellow needles [3]; m. p. 249 °C, dec.; ^{1}H NMR (300 MHz, d_6-DMSO, 303 K): $\delta = 8.31$ (d, 4H, $J = 12$ Hz), 8.42 (d, 4H, $J = 12$ Hz); ^{19}F NMR (280 MHz, $CDCl_3$, 303 K): $\delta = 48.1$ (s); MS (EI): $m/z = 352$ [M^+], 333 [M^+-F], 192 [$O_2NPhSF_2^+$], 146 [$PhSF_2^+$], 141 [O_2NPhF^+], 111 [$OPhF^+$], 95 (100 %)[PhF^+].

A.2
Hydrofluorination and Halofluorination

A.2.1 **General Remarks**

When handling 70 % HF–pyridine, skin contact and inhalation of fumes must be avoided. Experiments should be conducted under a well-ventilated hood and protective goggles and gloves should be used. Competent medical care must be sought immediately even after apparently minor contamination. After skin contact, as a first aid measure, immediate and thorough rinsing with water and subsequent treatment with calcium gluconate gel are recommended [4]. Triethylamine tris(hydrofluoride) is less corrosive than 70 % HF–pyridine but the same safety precautions must be applied. In contrast with 70 % HF–pyridine, $NEt_3{\cdot}3HF$ does not attack borosilicate glassware.

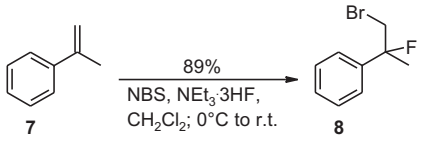
A.2.2 **Synthesis of the liquid crystal 6**



Scheme A.3 Hydrofluorination of olefins [5].

In a PTFE flask a solution of **5** (100 g, 0.36 mol) in CH_2Cl_2 (200 mL) was treated with 70 % HF–pyridine (36.3 mL, 1.45 mol) and stirred at room temperature for 18 h. The mixture was poured on to ice (300 g) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed until neutral with saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After addition of pyridine (1 % *v*/*v*), the solution was evaporated to dryness yielding 98 g crude hydrofluorination product. The crude product was filtered over silica gel (*n*-heptane/pyridine 99:1) and crystallized from the same solvent at −20 °C to furnish **6** (38.4 g, 36 % [5]; mesophase sequence [6]: C 52 S_B 109 I; ^{1}H NMR (500 MHz, $CDCl_3$, 303 K): δ = 0.85–1.56 (m, 34H), 1.70–1.75 (m, 2H), 1.86–1.92 (mc, 1H); ^{19}F NMR (280 MHz, $CDCl_3$, 303 K): δ = −160.4 (mc); MS (EI): m/z = 276 (M^+−HF).

A.2.3 **Synthesis of 8**

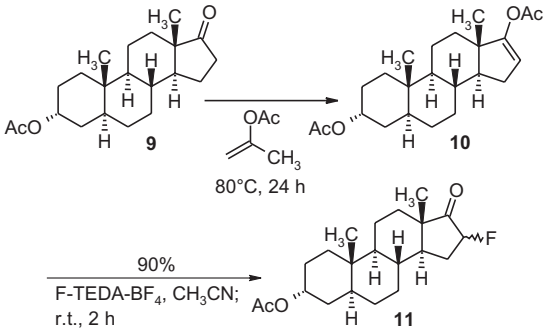


Scheme A.4 Bromofluorination of olefins [7].

A magnetically stirred mixture of α-methylstyrene (**7**) (7.1 g, 60 mmol), $NEt_3 \cdot 3HF$ (14.7 mL, 90 mmol), and CH_2Cl_2 (60 mL) in a 250-mL, single-necked, round-bottomed flask was treated with NBS (11.8 g, 66 mmol) at 0 °C. After 15 min, the bath was removed, and stirring was continued at room temperature for 5 h. The reaction mixture was poured into ice–water (1000 mL), made slightly basic with aqueous 28 % ammonia, and extracted with dichloromethane (4 × 150 mL). The combined extracts were washed with 0.1 M HCl (2 × 150 mL) and 5 % $NaHCO_3$ solution (2 × 150 mL) and then dried over $MgSO_4$. After removal of the solvent by rotary evaporation, the crude product was distilled to give the product **8** [7]: 11.6 g (89 %); b. p. 50–52 °C/0.15 mmHg; n_D^{20} 1.5370.

A.3
Electrophilic Fluorination with F-TEDA-BF_4 (Selectfluor)

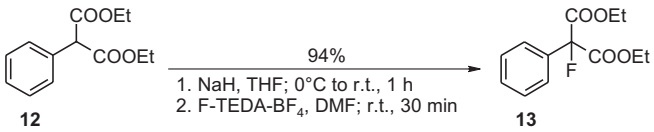
A.3.1 Synthesis of the Fluorosteroid 11



Scheme A.5 Electrophilic fluorination of steroids [8].

A solution of 3β-acetoxyandrosterone (**9**) (0.5 g, 1.52 mmol) in isopropenyl acetate (5.0 mL) was heated at 80 °C for 24 h under N_2. The reaction was cooled and quenched by addition of 200 µL triethylamine. The solvent was removed by distillation *in vacuo* (0.1 mmHg), and the residue (**10**) was dissolved into acetonitrile (25 mL). F-TEDA-BF_4 (537 mg, 1.52 mmol) was added and the reaction was monitored by TLC (ethyl acetate/hexane 1:4). After 2 h the solution was poured into ethyl acetate (25 mL), washed with water (3 × 25 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Flash chromatography of the residue on silica gel (ethyl acetate/hexane 1:4) afforded 474 mg (90 %) of 3β-acetoxy-16-fluoroandrostrone (**11**) ($\alpha/\beta \approx$ 94:6), which had spectroscopic properties consistent with those reported in the literature [9].

A.3.2 Synthesis of Diethyl Fluorophenylmalonate (13)



Scheme A.6 Electrophilic fluorination of malonates [8].

A solution of diethyl phenylmalonate (**12**) (1 mmol) in THF (50 mL) was added to an oil-free suspension of NaH (40 mg of 60 %, 24 mg, 1 mmol) in THF (5.0 mL) under N_2 at 0 °C. The solution was stirred at 0 °C for 30 min and then at room temperature for 1 h. The sodium salt was diluted with DMF (2.0 mL) and F-TEDA-BF_4 (354 mg) was added. After being stirred for 30 min at room temperature the mixture was poured into Et_2O, washed with 5 % H_2SO_4 (10 mL) and

saturated $NaHCO_3$ (10 mL), dried ($MgSO_4$), filtered, and evaporated *in vacuo*. Purification by flash chromatography on silica gel afforded the pure product **13** (94 %) [10].

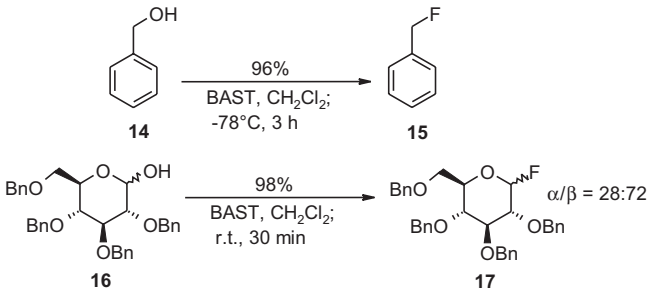
A.4
Fluorinations with DAST and BAST (Deoxofluor)

A.4.1 General Remarks

Because DAST (diethylaminosulfur trifluoride) and BAST (bis(2-methoxyethyl) aminosulfur trifluoride; commercialized as Deoxofluor) hydrolyze readily, giving HF, similar precautions must be taken as for handling hydrofluoric acid and its amine complexes [4]. Because neat DAST tends to explode if heated above 40–50 °C, safety screens are recommended if DAST is heated. For reactions or more inert substrates, requiring higher temperatures, BAST (Deoxofluor) was developed as a safer alternative, because it decomposes on heating only slowly and without detonation [11].

In the fluorination reactions described in Sections A.4.2 and A.4.3 BAST may be replaced by DAST with similar results.

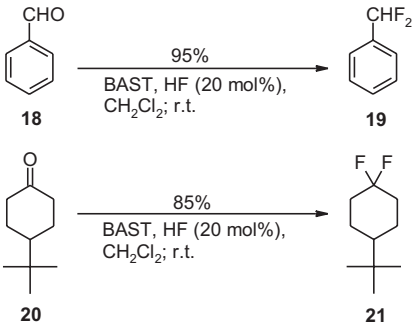
A.4.2 General Procedure for Fluorination of Alcohols



Scheme A.7 Fluorination of alcohols with BAST (Deoxofluor) [11].

The alcohol (10 mmol) in dry CH_2Cl_2 (3.0 mL) was added at −78 °C (for benzyl alcohol **14**) or at room temperature (for protected glucose **16**), under N_2, to a solution of BAST (2.43 g, 11 mmol) in CH_2Cl_2 (2.0 mL) in a 50-mL, three-neck flask equipped with a N_2 inlet tube, septum, and a magnetic stirring bar. The reaction was monitored by GC–MS for disappearance of the starting material. On completion the solution was poured into saturated $NaHCO_3$ (25 mL) and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3 × 15 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Flash chromatography on silica gel in hexanes/ethyl acetate afforded the pure products: benzyl fluoride **15** (1.05 g, 96 %); fluoroglucoside **17** (5.32 g, 98 %, α/β = 28:72) [11].

A.4.3 General Procedure for Fluorination of Aldehydes and Ketones



Scheme A.8 Fluorination of aldehydes and ketones with BAST (Deoxofluor) [11].

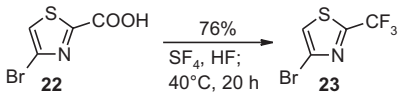
A solution of the aldehyde **18** or ketone **20** (10 mmol) in CH_2Cl_2 (3.0 mL), in a 25-mL PTFE bottle equipped with a N_2 inlet tube and stirring bar, was treated with a solution of BAST (3.76 g, 17 mmol) in CH_2Cl_2 (2.0 mL) at room temperature. Ethanol (92 mg, 116 µL, 2 mmol) was added (for *in situ* generation of catalytic quantities of HF) and the mixture was stirred at room temperature. The progress of the reaction was monitored by GC–MS. On completion the solution was poured into saturated $NaHCO_3$ and after CO_2 evolution ceased it was extracted into CH_2Cl_2 (3×15 mL), dried (Na_2SO_4), filtered, and evaporated *in vacuo*. Flash chromatography on silica gel in hexanes/Et_2O afforded the pure products: benzal fluoride **19** (1.22 g, 95 %); 1,1-difluoro-4-*tert*-butylcyclohexane **21** (1.50 g, 85 %) [11].

A.5
Fluorination of a Carboxylic Acid with Sulfur Tetrafluoride

A.5.1 General Remarks

Sulfur tetrafluoride is a hazardous and highly toxic gas [4], in some aspects comparable with phosgene [12]. For reactions with SF_4 with or without HF autoclaves made from Hastelloy C with Monel 400 piping and valves are recommended [13]. When handling SF_4 sufficient ventilation must be provided and protective goggles and gloves should be worn. On autoclave depressurization, excess SF_4 and HF should be scrubbed with potassium hydroxide solution.

A.5.2 Synthesis of 4-Bromo-2-(trifluoromethyl)thiazole (23)

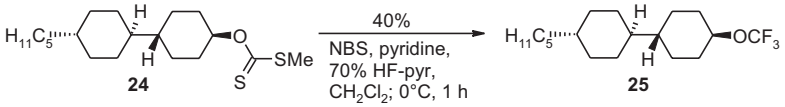


Scheme A.9 Conversion of a carboxyl group to a trifluoromethyl group by sulfur tetrafluoride [14].

A 300-mL autoclave was charged with acid **22** (0.1 mol), evacuated, cooled to −60 °C, and subsequently charged with HF (30 g) and SF_4 (33 g, 0.3 mol). The reaction was heated to 40 °C for 20 h with stirring at 400–600 rpm. The volatile compounds were then vented and the reaction was diluted with ether (100 mL). The organic solution was stored over NaF as a precaution and was later washed with water (1 × 200 mL) and 10 % NaOH (1 × 200 mL), and distilled to give 18.4 g (76 %) pure **23** [14]; b. p. 101–105 °C/150 mmHg; ^{1}H NMR ($CDCl_3$): $\delta = 7.46$ (s, 1H); ^{19}F NMR ($CDCl_3$): $\delta = -66.5$.

A.6 Generation of a Trifluoromethoxy Group by Oxidative Fluorodesulfuration of a Xanthogenate

A.6.1 Synthesis of the Liquid Crystal 25



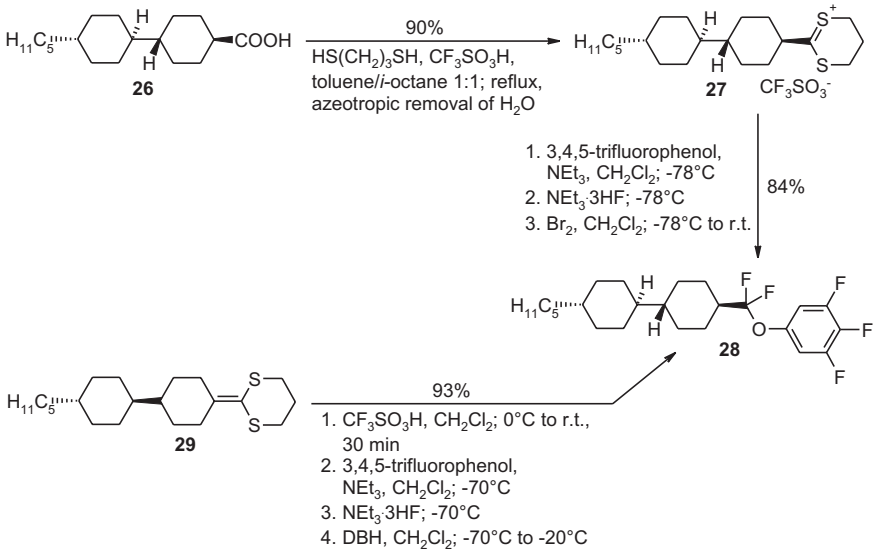
Scheme A.10 Synthesis of trifluoromethyl ethers from xanthogenates [15].

To a suspension of NBS (5.0 mmol) and CH_2Cl_2 (2.5 mL) in an oven-dried polypropylene round-bottom tube equipped with a rubber septum and a PTFE-coated magnetic stirring bar, were added dropwise pyridine (0.46 mL) and, subsequently, 70 % HF–pyridine (1.0 mL, 40 mmol HF) at −42 °C (cooled by means of a CCl_4/dry ice bath) under an argon atmosphere. The resulting mixture was stirred at room temperature for 5 min and then cooled to 0 °C. A solution of the xanthogenate **24** (1.0 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise to the suspension at 0 °C to give a dark-red mixture. This was stirred at 0 °C for 1 h, diluted carefully with Et_2O (5.0 mL), and quenched with ice-cold buffer solution (pH 10, $NaHCO_3$, $NaHSO_3$, and NaOH). The pH of the mixture was adjusted to 10 by careful addition of ice-cold 10 % aqueous NaOH solution and extracted with Et_2O; the aqueous phase was extracted with Et_2O three times. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash column chromatography (silica gel; cyclohexane) afforded 40 % trifluoromethyl ether **25** [15]; m. p. 30.8–31.1 °C; b. p. 160 °C/0.4 mmHg; $R_F = 0.91$ (silica gel; hexane); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 0.75$–1.92 (m, 19H), 0.87

(t, $J = 7$ Hz, 3H), 2.00–2.28 (m, 4H), 4.07 (tt, $J = 5$ Hz, $J = 11$ Hz, 1H); ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -58.0$ (s, 3F).

A.7
Oxidative Alkoxydifluorodesulfuration of Dithianylium Salts

A.7.1 Dithianylium Triflate 27



Scheme A.11 Synthesis of α,α-difluoro ethers via dithianylium salts [16].

To a suspension of **26** (250 g, 0.89 mol) in a mixture of toluene (250 mL) and iso-octane (250 mL), 1,3-propanedithiol (125 g, 1.16 mol) was added. The milky suspension was heated to 50 °C and trifluoromethanesulfonic acid (173 g, 1.16 mol) was added within 30 min (slightly exothermic). The resulting solution was heated to 102–104 °C and reaction water (28 mL) was removed azeotropically within 4 h. The solution was cooled to 90 °C and methyl *tert*-butyl ether (1000 mL) was added within 45 min at 90–70 °C. The suspension was cooled to 0 °C and filtered under a dry nitrogen atmosphere. The crystals were washed with methyl *tert*-butyl ether (4 × 250 mL) and dried *in vacuo* to yield **27** (402 g, 90 %) as pinkish crystals. The purity was estimated by ^{1}H NMR to be ca 95 %, sufficient for further reactions [16]. Slow decomposition starting from 90–100 °C; ^{1}H NMR (250 MHz, $CDCl_3$, 303 K): $\delta = 1.35–0.75$ (m, 21H), 2.03–1.60 (m, 4H), 2.17 (d, $J = 10$ Hz, 2H), 2.60–2.45 (m, 2H), 3.15–2.95 (m, 2H), 3.75 (t, $J = 5$ Hz, 4H); ^{13}C NMR (60 MHz, $CDCl_3$, 303 K): $\delta = 14.5, 17.3, 23.1, 27.1, 29.5, 30.3, 32.5, 33.8, 35.5, 37.7, 38.1, 42.3, 43.2, 53.5, 57.2, 121.1$ (q, $CF_3SO_3^-$), 203.4 (–S–C=S$^+$–); MS (EI): m/z (%) = 352 [$M^+ - CF_3SO_3H$] (100 %).

A.7.2 Synthesis of 28 from the Dithianylium salt 27

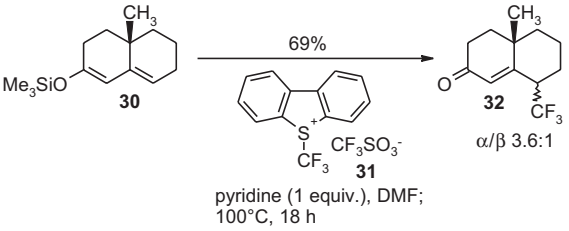
A solution of 3,4,5-trifluorophenol (10 g, 68 mmol) in a mixture of triethylamine (7.33 g, 72 mmol) and CH_2Cl_2 (90 mL) was cooled to −70 °C and a solution of **27** (30.9 g, 62 mmol) in CH_2Cl_2 (85 mL) was then added within 45 min at the same temperature. After stirring for 1 h, $NEt_3{\cdot}3HF$ (50 mL, 310 mmol) was added over 5 min. Then, over a period of 1 h, a solution of bromine (49.5 g, 310 mmol) in CH_2Cl_2 (20 g) was added at −70 °C. The mixture was stirred for one more hour at −70 °C and then left to warm to 0 °C. The solution was poured into a mixture of 32 % aqueous NaOH (107 g) and ice (200 g). The pH was adjusted to 5 to 8 by addition of ca. 28 g 32 % aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 (50 mL), and the combined organic extracts were filtered through celite (2.5 g), washed with water, and evaporated to dryness. The residue was dissolved in *n*-heptane (60 mL), stirred for 30 min with silica gel (5.0 g), filtered, and evaporated to dryness. The crude product was chromatographed with *n*-heptane on silica gel to yield 22.8 g (84 %) **28** as a nematic oil which slowly crystallized (purity 99.2 %, verified by GLC and HPLC) [16]. Further purification was accomplished by recrystallization from *n*-heptane at −20 °C (purity >99.9 %; GLC and HPLC); mesophase sequence [6]: C 59 N 112.1 I; ^{1}H NMR (250 MHz, $CDCl_3$, 303 K): δ = 1.38–0.80 (m, 27H), 2.08–1.65 (m, 4H), 6.82 (mc, 2H, ar-2,6-*H*); ^{19}F NMR (280 MHz, $CDCl_3$, 303 K): δ = −79.3 (d, J = 8.4 Hz, 2F, C*F*$_2$O), −133.8 (mc, 2F, ar-3,5-*F*), −165.3 (mc, 1F, ar-4-*F*); MS (EI): m/z (%) = 432 [M^+] (25), 284 [$M^+ - F_3PhOH$] (50).

A.7.3 Synthesis of 28 from the Ketenedithioketal 29

To a solution of **29** [17] (1.00 g, 2.84 mmol) in CH_2Cl_2 (15 mL) trifluoromethanesulfonic acid (0.25 mL, 2.84 mmol) was added dropwise at 0 °C. The cooling bath was removed and the mixture was stirred for 30 min at room temperature. It was then cooled to −70 °C and solutions of 90 % 3,4,5-trifluorophenol in toluene (0.70 g, 4.25 mmol) and triethylamine (0.71 mL, 5.10 mmol) in CH_2Cl_2 (3.0 mL) were added. After stirring for 1 h at −70 °C, $NEt_3{\cdot}3HF$ (2.29 mL, 14.2 mmol) was added. After 5 min a suspension of DBH (4.05 g, 14.2 mmol) in CH_2Cl_2 (15 mL) was added in portions over a time period of 30 min. After stirring for an additional 60 min the mixture was left to warm to −20 °C and then poured into ice-cold 1 M aqueous NaOH (50 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were stirred for 15 min with celite (5.0 g), filtered, washed with brine (2 × 30 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was dissolved in *n*-hexane and filtered through a short silica gel column. Yield: 1.14 g (93 %) of **28**, containing 96.9 % *trans–trans* and 2.2 % *trans–cis* isomer (GLC). Further purification to >99.8 % (GLC) of *trans–trans*-**28** [16] was accomplished by crystallization from *n*-heptane at −20 °C.

A.8
Electrophilic Trifluoromethylation with Umemoto's Reagents

A.8.1 Trifluoromethylation of the Trimethylsilyl Dienol Ether 30



Scheme A.12 Electrophilic trifluoromethylation with Umemoto's reagent [18].

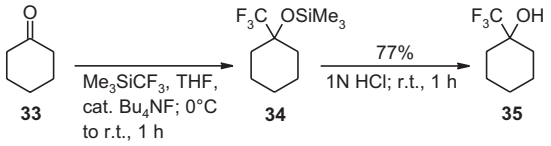
Under an argon atmosphere *S*-(trifluoromethyl)dibenzothiophenium triflate (**31**) (1.0 mmol) was added to a stirred solution of **30** (1.0 mmol) and pyridine (1.0 mmol) in DMF (6 mL). The mixture was heated to 100 °C for 18 h then subjected to aqueous work-up by the usual methods [18], yielding a mixture of α- and β-**32** (69 %; α/β 3.6:1) as an oil; IR (neat): 1681 cm^{-1} (C=O); MS (EI): m/z (%) = 232 [M^+].

α-**32**: ^{1}H NMR ($CDCl_3$): δ = 1.26 (s, 3H), 2.25–2.20 (m, 1H), 2.50 (ddd, 1H, J = 16.8 Hz, J = 12.6 Hz, J = 6.3 Hz), 3.05 (m, 1H), 6.01 (m, 1H); ^{19}F NMR ($CDCl_3$): δ = −68.38 (dd, J = 8.2 Hz, J = 2.2 Hz).

β-**32**: ^{1}H NMR ($CDCl_3$): δ = 1.29 (s, 3H), 2.20–2.15 (m, 1H), 2.65 (ddd, 1H, J = 17.8 Hz, J = 15.0 Hz, J = 5.1 Hz), 3.05 (m, 1H), 5.89 (s, 1H); ^{19}F NMR ($CDCl_3$): δ = −66.44 (d, J = 11.5 Hz).

A.9
Nucleophilic Trifluoromethylation with Me_3SiCF_3

A.9.1 Nucleophilic Trifluoromethylation of Ketone 33



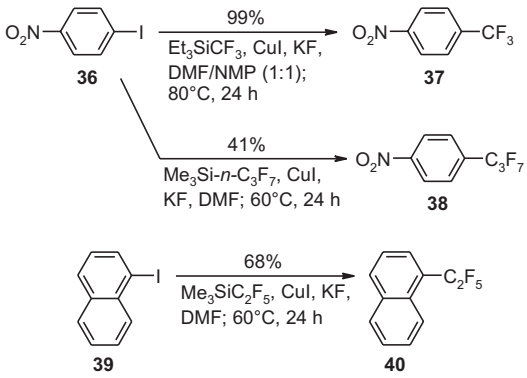
Scheme A.13 Nucleophilic trifluoromethylation of ketones [19].

A mixture of **33** (10 mmol), Me_3SiCF_3 (12 mmol), and THF (25 mL) cooled to 0 °C in an ice bath was treated with tetrabutylammonium fluoride (20 mg). Instantaneously a yellow color developed with initial evolution of fluorotrimethylsilane. The mixture was then brought to ambient temperature and stirred. After 1 h the

intermediate trimethylsilyl ether **34** was hydrolyzed by addition of 1 M HCl and stirring for 1 h. (For some carbonyl compounds, for example benzophenone, acidic hydrolysis of the intermediate trimethylsilyl ethers is difficult. For these, fluoride-induced hydrolysis in an cesium fluoride/methanol system under reflux is often more successful.) Isolation of **35** [19] was achieved by aqueous work-up by the usual methods; 77 % yield, m. p. 59–61 °C, b. p. 72–73 °C/40 mmHg; ^{19}F NMR: $\delta = -86.0$ (s); MS (EI): m/z (%) = 168 [M^+] (0.1), 83 (100).

A.10
Copper-mediated Aromatic Perfluoroalkylation

A.10.1 Copper-mediated Trifluoromethylation of 36 Using Silane Reagents

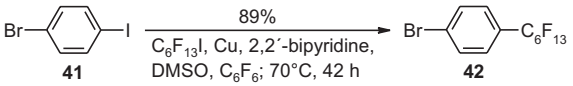


Scheme A.14 Copper-mediated perfluoroalkylation of iodoarenes by perfluoroalkyl silane reagents [20].

A mixture of **36** (0.5 mmol), Et_3SiCF_3 (0.6 mmol), CuI (0.75 mmol), KF (0.6 mmol), and DMF/NMP (1:1) (1 mL) was heated in a sealed Pyrex tube to 80 °C for 24 h. After cooling the tube was opened with the usual safety precautions and the contents were subjected to an aqueous work-up. Compound **37** was obtained in 99 % yield with minimal contamination by its pentafluoroethyl analog [20].

Similar results can be achieved by use of Me_3SiCF_3 (Ruppert's Reagent) [21]. When $Me_3SiC_2F_5$ or Me_3Si-n-C_3F_7 are used instead (in DMF at 60 °C for 24 h), the pentafluoroethyl (**40**) or perfluoropropyl arenes (**38**) are obtained in reasonable to good yields [20].

A.10.2 **Copper-mediated Perfluoroalkylation of Aryl Iodide 41**



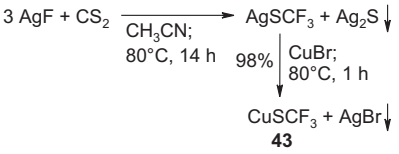
Scheme A.15 Copper-mediated perfluoroalkylation of iodoarenes by perfluoroalkyl iodides [22].

A solution of $C_6F_{13}I$ (18.78 g, 42 mmol) in hexafluorobenzene (40 mL) was added dropwise over 3 h to a stirred mixture of **41** (11.91 g, 42 mmol), copper powder (5.88 g, 92 mmol), 2,2′-bipyridine (0.46 g, 2.95 mmol), DMSO (40 mL), and C_6F_6 (60 mL) at 70 °C. The mixture was subsequently stirred at 70 °C for 72 h then poured into a beaker containing dichloromethane (100 mL) and water (100 mL). After filtering the organic layer was separated, washed with water (3 × 50 mL), and dried over $CaCl_2$ and $MgSO_4$. After concentration to 30 mL the crude product was extracted into perfluoro-1,3-dimethylcyclohexane (3 × 20 mL) and the solvent was removed *in vacuo*. Distillation *in vacuo* using a Kugelrohr apparatus gave the product **42** as a colorless liquid (17.0 g, 89 %) [22]; b. p. 80–96 °C/0.02 mmHg; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.5$ (d, $J = 8.5$ Hz, 2H), 7.7 (d, $J = 9$ Hz, 2H); ^{19}F NMR (235 MHz, $CDCl_3$): $\delta = -81.3$ (t, $J = 10$ Hz, 3F), −111.4 (t, $J = 14$ Hz, 2F), −121.9 (m, 2F), −122.4 (m, 2F), −123.3 (m, 2F), −126.6 (m, 2F) ; MS (EI): m/z (%) = 474/476 [M^+] (18), 455/457 (5), 205/207 (100), 126 (30), 69 (9).

A.11
Copper-mediated Introduction of the Trifluoromethylthio Group

A.11.1 **Preparation of Trifluoromethylthio Copper Reagent 43**

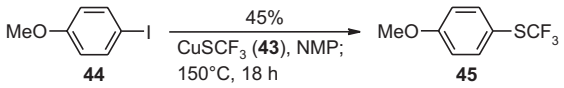
Silver fluoride (15 g, 0.12 mol), carbon disulfide (15 mL), and acetonitrile (100 mL)



Scheme A.16 Preparation of the trifluoromethylthio copper(I) reagent [23].

were placed in a 3-neck 250-mL flask fitted with overhead stirrer and condenser. The mixture was stirred for 14 h at 80 °C (oil bath) then the condenser's position was altered to enable removal of any remaining carbon disulfide by distillation. Copper(I) bromide (5.69 g, 40 mmol) was then added and the mixture was left stirring for a further 1 h. The black precipitate formed was removed by filtration and the acetonitrile was removed under reduced pressure to yield **43** as a white/gray solid (6.6 g, 98 %) [23]. (^{19}F NMR showed this to be mainly $CuCSF_3$ with slight contamination by HF_2^- species.)

A.11.2 Reaction of $CuSCF_3$ with 4-Iodoanisole (44)

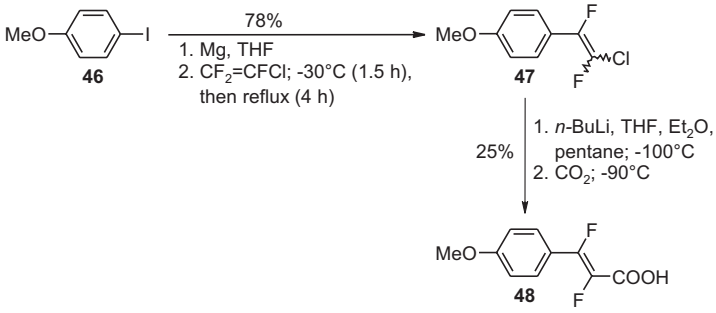


Scheme A.17 Introduction of the trifluoromethylthio group using $CuSCF_3$ [23].

Trifluoromethylthio copper(I) (**43**) (0.47 g, 2 mmol), 4-iodoanisole (**44**) (1.55 g, 10 mmol), and NMP (10 mL) were placed in a 25-mL round-bottom flask and heated at 150 °C for 18 h. The resulting black solution was left to cool. Water was then added and the organic products were extracted twice into diethyl ether. The ether extracts were combined and washed three times with water. The ether was removed by rotary evaporation to yield 0.21 g product **45** (45 %) [23]; ^{19}F NMR ($CDCl_3$): $\delta = -44.4$ (s); MS (EI): m/z (%) = 208 [M^+] (60), 139 (100).

A.12
Substitution Reactions on Fluoroolefins and Fluoroarenes

A.12.1 Preparation of α,β-Difluoro-β-chlorostyrenes (47)



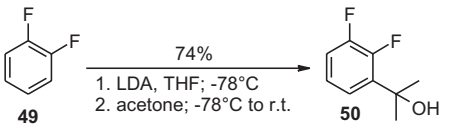
Scheme A.18 Synthesis of α,β-difluorocinnamic acids [24].

A sample of chlorotrifluoroethylene (23.3 g, 200 mmol) was condensed at −30 °C into a solution of *p*-anisyl magnesium bromide (prepared from **46** (23.5 g, 126 mmol) with magnesium in THF by the usual methods) (126 mmol) in THF (150 mL). The solution was stirred for 1.5 h at −30 °C and then boiled for 4 h with a reflux condenser packed with dry ice. The mixture was filtered and the filtrate was treated with hydrochloric acid and ice, extracted with ether, washed with water and 5 % Na_2CO_3, and dried. Yield: 24 g (78 %) of **47** [24] as an isomer mixture with a *cis*/*trans* ratio of ca. 1:3 (J_{FF} ca. 9–12 Hz for the *cis* and 126–127 Hz for the *trans* isomer); b. p. 115–116 °C/15 mmHg; n_D^{25} 1.5399.

A.12.2 **Preparation of α,β-Difluorocinnamic Acid 48**

A solution of styrene **47** (4.1 g, 20 mmol) in a mixture of THF (9 mL), diethyl ether (5 mL), and pentane (5 mL) was cooled to −100 °C and a 1 M solution of *n*-butyl lithium in diethyl ether (20 mL), cooled to −90 to −100 °C, added during a period of 30 min. The mixture was stirred for 1 h at −85 to −90 °C and poured on to a mixture of diethyl ether and dry ice. The acid was extracted from the ether with 10 % Na_2CO_3 and the soda extracts were washed with ether, filtered, and acidified with 15 % HCl. The product was removed by filtration, washed with water, dried, and recrystallized from benzene. Yield: 1.1 g (25 %) of **48** [24]; m. p. 185–187 °C.

A.12.3 ***Ortho*-Metalation of 1,2-Difluorobenzene (49) with LDA [25] (Scheme A.19)**



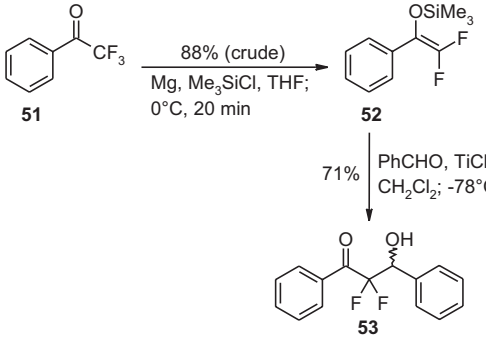
49 **50**

Scheme A.19 Derivatization of 1,2-difluorobenzene via *ortho*-metalation [25].

n-Butyllithium in hexane (32.5 mL, 52 mmol) was added in portions to dry diisopropylamine (7.3 mL) in dry THF at 0 °C under nitrogen. The mixture was stirred at 0 °C for 15 min then cooled to −78 °C. 1,2-Difluorobenzene (**49**) (5.3 mL, 52 mmol) was added in portions to this mixture. After being stirred for 30 min acetone (4 × 5 mL) was added and the mixture was left to warm to room temperature. (**Caution**: Lithiated *ortho*-fluoroarene intermediates should never be allowed to warm to above −40 to −30 °C! The compounds tend to eliminate LiF in a highly exothermic and often violent reaction.) The product was poured into 1 M HCl (200 mL) and extracted with diethyl ether (100 mL); the ether solution was washed with water (200 mL) and dried ($MgSO_4$). The solvent was removed by rotary evaporation and the crude yellow product was distilled under reduced pressure and subsequently further purified by column chromatography (silica gel; CH_2Cl_2) to give **50** as a colorless oil (6.9 g, 74 %) [25]; b. p. 80–82 °C/5.0 mmHg; MS (EI): m/z = 172 [M^+], 157 [M^+-CH_3].

A.13
Reactions with Difluoroenolates

A.13.1 Preparation of the Trimethylsilyl Difluoroenol Ether 52



Scheme A.20 Reaction of trimethylsilyl difluoroenol ethers with aldehydes [26].

A mixture of Me_3SiCl (2.6 g, 24 mmol) and Mg (290 mg, 12 mmol) in freshly distilled THF (24 mL) was cooled to 0 °C under an argon atmosphere and trifluoroacetophenone (**51**) (1.04 g, 6.0 mmol) was added dropwise; the mixture was then stirred for additional 20 min. After evaporation of most of the THF, hexane (20 mL) was added to the residue and the resulting salt was filtered and the filtrate was concentrated to give 1.21 g (ca 88 %) crude **52** (purity, determined by GLC, >95 %) [26].

A.13.2 Addition of 52 to Carbonyl Compounds

A solution of crude **52** (1.21 g, 0.53 mmol) and benzaldehyde (1.27 g, 12 mmol) in CH_2Cl_2 (10 mL) was cooled to −78 °C and a solution of $TiCl_4$ (6 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was then quenched with aqueous NH_4Cl and the organic layer was washed with brine and dried over $MgSO_4$. Purification of the product by chromatography (silica gel; hexane/ethyl acetate 5 :1) provided **53** (1.18 g, 71 % based on **51**) as a colorless oil [26].

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6 C = crystalline, S_B = smectic B, N = nematic, I = isotropic. The transition temperatures are cited in °C.
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