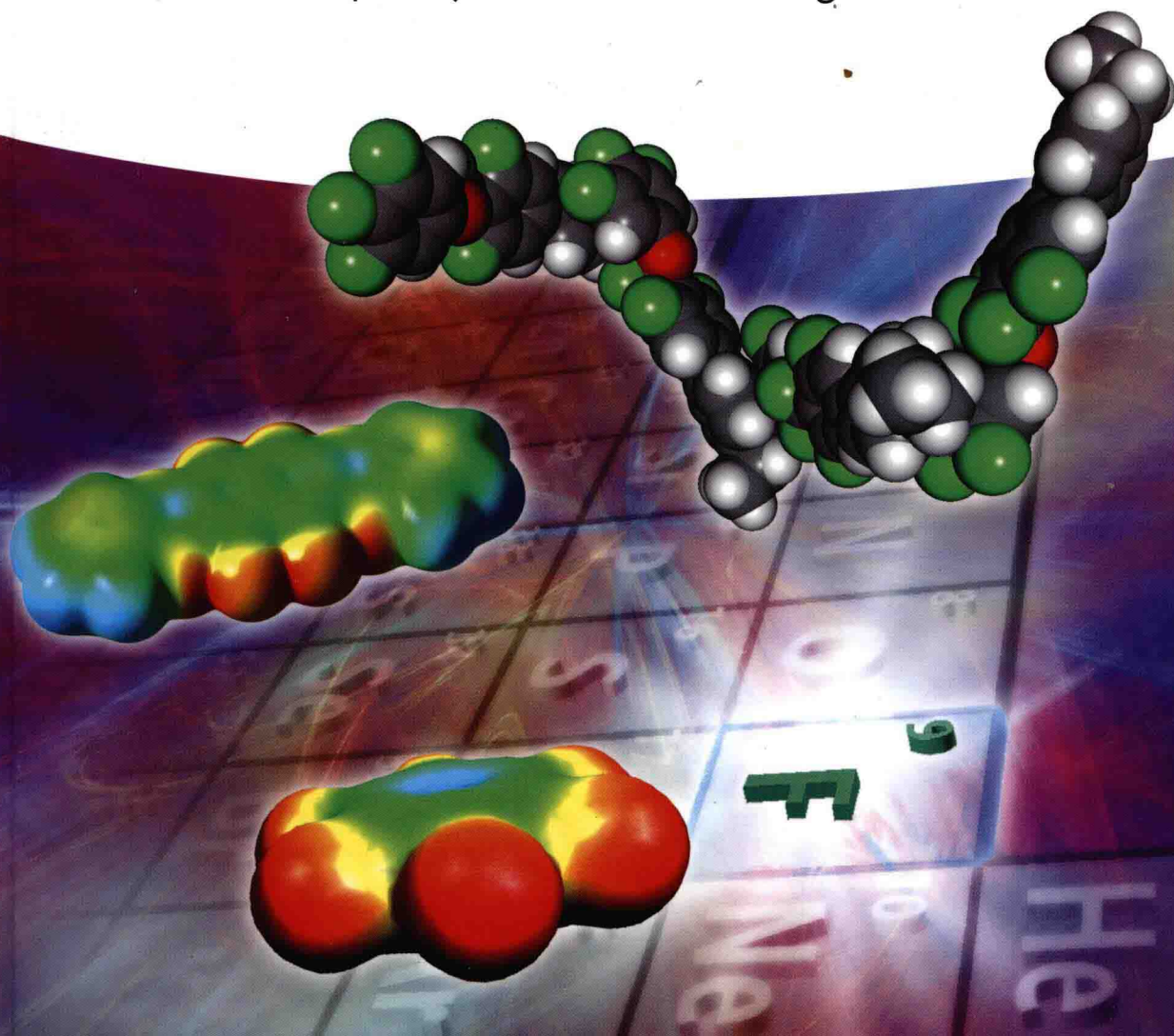


Peer Kirsch

Modern Fluoroorganic Chemistry

Synthesis, Reactivity, Applications

Second, Completely Revised and Enlarged Edition

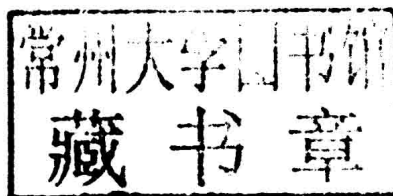


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To Annette and Alexander

“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.

Preface to the Second Edition

Within the few years since the first edition, the landscape of fluorine chemistry has changed dramatically: it is no longer the domain of a highly specialized (and often quite courageous) community, but the field has attracted the attention of mainstream organic and bioorganic chemists. The value of fluorine substitution in bioactive compounds and other functional materials has been widely recognized beyond the boundaries of the traditional fluorine chemistry community. Consequently, the variety of available synthetic methodology has exploded. A review with a reasonable degree of completeness has become impossible, and even the selection of the most significant developments is a very difficult task.

The scope of this book is not to offer a complete review of available methods, but to provide an introduction and a representative overview over the rapidly evolving field for the interested newcomer. It should be used as an entry point for a detailed in-depth study, but it is not intended as a stand-alone encyclopedia of fluorine chemistry. Therefore, there are many omissions, and the selection of the most interesting new developments has often been a matter of taste of the author.

The focus of the second edition is application fields where fluorine is essential for function, and also the chemistry needed to access such compounds. This applies not only to the material sciences but of course also to the biomedical field. On the synthetic side, the most remarkable new development is a huge variety of transition metal-catalyzed methods for the introduction of fluorine and fluorinated groups.

From the conceptual side, the author's choice of the most important new developments has been covered. From the application side, two new areas have been added: fluorinated dyes as one of the first areas of the industrial application of fluorine chemistry was recognized as a gap in the previous edition. In the last 10 years, the field of organic electronics has developed tremendously, and also here fluorine chemistry has found a very specific range of applications. A short review of the role and function of fluorine chemistry in this rapidly developing field has been added.

The author would like to thank the friends and colleagues who have provided their help and valuable input during the update of the text. In particular,

Matthias Bremer, Alois Haas, Ingo Krossing, David O'Hagan, Gerd Röschenhaler, Georg Schulz, Peter and Marina Wanczek, John Welch, and Yurii Yagupolskii supported my project with information and critical discussions. From Wiley-VCH, Anne Brennführer and Lesley Belfit provided me with steady support and encouragement. Most of all, I owe my gratitude to my wife Annette and my son Alexander, who received much less attention than they deserved and who provided an environment where I could make the time for writing a book on top of many other things.

Seeheim-Jugenheim
January 2013

Peer Kirsch

Preface to the First Edition

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 Rösenthaller, 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

Abbreviations

acac	Acetylacetonate ligand
aHF	Anhydrous hydrofluoric acid
AIBN	Azobis(isobutyronitrile)
AM	Active matrix
ASV	“Advanced super-V”
ATPH	Aluminum tri[2,6-bis(<i>tert</i> -butyl)phenoxide]
BAST	<i>N,N</i> -Bis(methoxyethyl)amino sulfur trifluoride
BINOL	1,1'-Bi-2-naphthol
Boc	<i>tert</i> -Butoxycarbonyl protecting group
Bop-Cl	Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BSSE	Basis set superposition error
BTF	Benzotrifluoride
CFC	Chlorofluorocarbon
COD	Cyclooctadiene
CSA	Camphorsulfonic acid
Cso	Camphorsulfonyl protecting group
CVD	Chemical vapor deposition
cVHP	Chicken villin headpiece subdomain
DABCO	Diazabicyclooctane
DAM	Di(<i>p</i> -anisyl)methyl protecting group
DAST	<i>N,N</i> -Diethylamino sulfur trifluoride
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DBPO	Dibenzoyl peroxide
DEAD	Diethyl azodicarboxylate
DCC	Dicyclohexylcarbodiimide
DCEH	Dicarboxyethoxyhydrazine
DEC	<i>N,N</i> -Diethylcarbamoyl protecting group
DFI	2,2-Difluoro-1,3-dimethylimidazolidine
DFT	Density functional theory
DIP-Cl	β -Chlorodiisopinocampheylborane
DMAc	<i>N,N</i> -Dimethylacetamide
DMAP	4-(<i>N,N</i> -Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMS	Dimethyl sulfide
DMSO	Dimethyl sulfoxide
DSM	Dynamic scattering mode

DTBP	Di- <i>tert</i> -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
FET	Field effect transistor
FFS	Fringe field switching
FITS	Perfluoroalkyl phenyl iodonium trifluoromethylsulfonate reagents
FRPSG	Fluorous reversed-phase silica gel
FSPE	Fluorous solid-phase extraction
F-TEDA	<i>N</i> -Fluoro- <i>N'</i> -chloromethyldiazoniabicyclooctane reagents
GWP	Global warming potential
HFCF	Hydrofluorocarbon
HFC	Hydrofluorocarbon
HFP	Hexafluoropropene
HMG ⁺	Hexamethylguanidinium cation
HMPA	Hexamethylphosphoric acid triamide
HSAB	Hard and soft acids and bases (Pearson concept)
IPS	In-plane switching
ITO	Indium tin oxide
LC	1. Liquid crystal 2. Lethal concentration
LCD	Liquid crystal display
LD	Lethal dose
LDA	Lithium diisopropylamide
MCPBA	<i>m</i> -Chloroperbenzoic acid
MEM	Methoxyethoxymethyl protecting group
MOM	Methoxymethyl protecting group
MOST	Morpholino sulfur trifluoride
MVA	Multi-domain vertical alignment
NAD ⁺ /NADH	Nicotinamide adenine dinucleotide, oxidized/reduced form
NADP ⁺ /NADPH	Nicotinamide adenine dinucleotide phosphate, oxidized/reduced form
NBS	<i>N</i> -Bromosuccinimide
NCS	<i>N</i> -Chlorosuccinimide
NE	Norepinephrine
NFPy	<i>N</i> -Fluoropyridinium tetrafluoroborate
NFTh	<i>N</i> -Fluoro- <i>o</i> -benzenedisulfonimide
NIS	<i>N</i> -Iodosuccinimide
NLO	Nonlinear optics
NMP	<i>N</i> -Methylpyrrolidone
NPSP	<i>N</i> -Phenylselenylphthalimide

OD	Ornithine decarboxylase
ODP	Ozone-depleting potential
OFET	Organic field effect transistor
OLED	Organic light-emitting diode
OPV	Organic photovoltaics
OTFT	Organic thin-film transistor
PCH	Phenylcyclohexane
PCTFE	Polychlorotrifluoroethylene
PDA	Personal digital assistant
PET	1. Positron emission tomography 2. Poly(ethylene terephthalate)
PFA	Perfluoropolyether
PFC	Perfluorocarbon
PFMC	Perfluoro(methylcyclohexane)
PFOA	Perfluorooctanoic acid
PFOB	Perfluoro- <i>n</i> -octyl bromide
PFOS	Perfluorooctylsulfonic acid
phen	Phenanthroline
PI	Polyimide
PIDA	Phenyliodonium diacetate
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	Polytetrafluoroethylene (Teflon TM)
PVDF	Poly(vinylidene difluoride)
PVPHF	Poly(vinylpyridine) hydrofluoride
P3DT	Poly(3-dodecylthiophene)
QM/MM	Quantum mechanics/molecular mechanics
QSAR	Quantitative structure–activity relationships
SAH	S-Adenosylhomocysteine hydrolase
SAM	1. S-Adenosylmethionine 2. Self-assembled monolayer
SBAH	Sodium bis(methoxyethoxy)aluminum hydride
scCO ₂	Supercritical carbon dioxide
SFC	Supercritical fluid chromatography
SET	Single electron transfer
SFM	Superfluorinated material
SPE	Solid-phase extraction
STN	Super-twisted nematic
TADDOL	$\alpha,\alpha,\alpha',\alpha'$ -Tetraaryl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol
TAS ⁺	Tris(dimethylamino)sulfonium cation
TASF	Tris(dimethylamino)sulfonium difluorotrimethylsiliconate, (Me ₂ N) ₃ S ⁺ Me ₃ SiF ₂ [−]
TBAF	Tetrabutylammonium fluoride
TBDMS	<i>tert</i> -Butyldimethylsilyl protecting group
TBS	See TBDMS

TBTU	O-(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TDAE	Tetrakis(dimethylamino)ethylene
TEMPO	2,2,6,6-Tetramethylpiperidine- <i>N</i> -oxide
TFT	Thin film transistor
THF	1. Tetrahydrofuran 2. Tetrahydrofolate coenzyme
THP	Tetrahydropyranyl protecting group
TIPS	Triisopropylsilyl protecting group
TLC	Thin-layer chromatography
TMS	Trimethylsilyl protecting group
TN	Twisted nematic
TPP	Triphenylphosphine
TPPO	Triphenylphosphine oxide
TR	Trypanothione reductase
VHR	Voltage holding ratio
ZPE	Zero point energy

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