

Science of Synthesis

**Compounds with One
Carbon–Heteroatom Bond**

Fluorine

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Science of Synthesis

Houben-Weyl Methods of Molecular Transformations

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Volume 34

Fluorine

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of the Editorial Board

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Preface

As our understanding of the natural world increases, we begin to understand complex phenomena at molecular levels. This level of understanding allows for the design of molecular entities for functions ranging from material science to biology. Such design requires synthesis and, as the structures increase in complexity as a necessity for specificity, puts increasing demands on the level of sophistication of the synthetic methods. Such needs stimulate the improvement of existing methods and, more importantly, the development of new methods. As scientists confront the synthetic problems posed by the molecular targets, they require access to a source of reliable synthetic information. Thus, the need for a new, comprehensive, and critical treatment of synthetic chemistry has become apparent. To meet this challenge, an entirely new edition of the esteemed reference work **Houben-Weyl Methods of Organic Chemistry** will be published starting in the year 2000.

To reflect the new broader need and focus, this new edition has a new title, **Science of Synthesis, Houben-Weyl Methods of Molecular Transformations**. **Science of Synthesis** will benefit from more than 90 years of experience and will continue the tradition of excellence in publishing synthetic chemistry reference works. **Science of Synthesis** will be a balanced and critical reference work produced by the collaborative efforts of chemists, from both industry and academia, selected by the editorial board. All published results from journals, books, and patent literature from the early 1800s until the year of publication will be considered by our authors, who are among the leading experts in their field. The 48 volumes of **Science of Synthesis** will provide chemists with the most reliable methods to solve their synthesis problems. **Science of Synthesis** will be updated periodically and will become a prime source of information for chemists in the 21st century.

Science of Synthesis will be organized in a logical hierarchical system based on the target molecule to be synthesized. The critical coverage of methods will be supported by information intended to help the user choose the most suitable method for their application, thus providing a strong foundation from which to develop a successful synthetic route. Within each category of product, illuminating background information such as history, nomenclature, structure, stability, reactivity, properties, safety, and environmental aspects will be discussed along with a detailed selection of reliable methods. Each method and variation will be accompanied by reaction schemes, tables of examples, experimental procedures, and a background discussion of the scope and limitations of the reaction described.

The policy of the editorial board is to make **Science of Synthesis** the ultimate tool for the synthetic chemist in the 21st century.

We would like to thank all of our authors for submitting contributions of such outstanding quality, and, also for the dedication and commitment they have shown throughout the entire editorial process.

The Editorial Board

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Volume Editor's Preface

The chemical and patent literature contains very many monofluorinated compounds; most of them fall outside the scope of this volume because they contain fluorine bound to an aromatic or heteroaromatic nucleus. In these locations, a single fluorine atom can increase bioavailability by increasing hydrophobicity, or block metabolic oxidation; these effects are familiar and much exploited. In the molecules described in this volume, the solitary fluorine atom can modify pK_a (and bioavailability), conformation, molecular recognition (through the modulation of hydrogen bonding networks), and serve as a valuable label for NMR studies *in vivo* and *in vitro*, and all with minimal perturbation of molecular volume. Chemists working at the interface with biomolecular science often use molecules bearing this remarkable atom, either as candidate drug molecules or to gain insight concerning events in enzyme active sites, or when proteins bind to ligands, at the molecular level. Significant gains await other scientists bold enough to consider solving their problems using selectively fluorinated molecules.

Of course, synthesis is a prerequisite and there are aspects of organofluorine chemistry which are distinctly specialized. However, the various contributors to this volume show clearly how the subject has expanded to admit the non-specialist, through the development of methods which deliver valuable compounds via procedures which can be run at normal temperatures and pressures, in conventional laboratory glassware, and with commercial reagents. The synthetic chemistry described in this volume achieves the exchange of many of the most common functional groups for a single C—F bond. Some of the reagents required are relatively hazardous and require careful handling; others are considerably more amenable to general use.

The volume covers the entire landscape of reagents from elemental fluorine and hydrofluoric acid, to transition-metal catalysts which mediate the introduction of fluorine in novel ways. The chemistry often occurs close to, or at, mechanistic borderlines; there is little real physical organic understanding of any of the transformations described in this volume so reaction outcomes can be unpredictable. Despite this potential difficulty, considerable progress has been made and there are many effective and ingenious methods for use in target synthesis. One of the major challenges in this area of chemistry is sustainability; for example, the fluorinated methanes, a well-known class of building block for the synthesis of monofluorinated compounds, are under considerable pressure as known or potential stratospheric ozone depletors. It is likely that other familiar fluorinated starting materials will become progressively less available.

Much of the primary and review literature upon which this volume is based deals with methodology rather than types of target molecules. The organofluorine literature contains relatively few comparisons between methods, which can make route selection rather difficult. Where the literature is sufficiently extensive, individual contributors have been encouraged to compare and contrast the scope and effectiveness of the available methodologies. These comparisons, and the organization of the volume into target classes and types of functional group exchange reaction, will assist experimentalists in planning synthetic campaigns.

I would like to thank all those who have allowed the delivery of the project, the authors who have contributed to the volume, and especially the editorial staff who have realised the transmutation of manuscripts into volume so extremely professionally.

Volume Editor

J. M. Percy

Strathclyde, UK

Volume 34: Fluorine

	Preface	V
	Volume Editor's Preface	VII
	Table of Contents	IX
	Introduction	
	J. M. Percy	1
34.1	Product Class 1: Fluoroalkanes	
	J. M. Percy	11
34.1.1	Synthesis by Substitution of Hydrogen	
	G. Sandford	21
34.1.2	Synthesis by Substitution of Metals	
	V. Gouverneur and M. Tredwell	39
34.1.3	Synthesis by Substitution of Carbon Functionalities	
	M. A. Carroll	49
34.1.4	Synthesis by Substitution of Heteroatoms	57
34.1.4.1	Synthesis by Substitution of a Halogen	
	T. P. Lequeux	57
34.1.4.2	Synthesis by Substitution of Hydroxy Groups in Alcohols	
	K. Dax	71
34.1.4.3	Synthesis by Substitution of Oxygen and Sulfur Functionalities	
	T. P. Lequeux	149
34.1.5	Synthesis by Addition Reactions to Alkenes	
	G. Haufe	169
34.1.6	Synthesis with Retention of the Functional Group	
	T. Yamazaki	225
34.2	Product Class 2: Fluorocyclopropanes	
	J. M. Percy	245
34.3	Product Class 3: (Fluoromethyl)cyclopropanes	
	J. M. Percy	267
34.4	Product Class 4: Fluorocyclobutanes	
	J. M. Percy	271
34.5	Product Class 5: Propargylic Fluorides	
	J. A. L. Miles and J. M. Percy	277

34.6	Product Class 6: Benzylic Fluorides	
	A. Sai Krishna Murthy, R. Tardivel, and R. Grée	295
34.7	Product Class 7: Allylic Fluorides	
	R. Roig and J. M. Percy	319
34.8	Product Class 8: Homoallylic Fluorides	
	J. M. Percy	341
34.9	Product Class 9: β-Fluoro Alcohols	
	G. Haufe	345
34.10	Product Class 10: β-Fluoroamines	
	J. M. Percy	379
	Keyword Index	387
	Author Index	403
	Abbreviations	419

Table of Contents

	Introduction	
	J. M. Percy	
	Introduction	1
34.1	Product Class 1: Fluoroalkanes	
	J. M. Percy	
34.1	Product Class 1: Fluoroalkanes	11
34.1.1	Synthesis by Substitution of Hydrogen	
	G. Sandford	
34.1.1	Synthesis by Substitution of Hydrogen	21
34.1.1.1	Method 1: Direct Fluorination with Elemental Fluorine	21
34.1.1.2	Method 2: Reaction with Selectfluor	29
34.1.1.3	Method 3: Reaction with Xenon Difluoride	32
34.1.1.4	Method 4: Reaction with Organic Hypofluorites	33
34.1.1.5	Method 5: Reaction with Cesium Fluoroxysulfate	35
34.1.1.6	Method 6: Reaction with Hydrogen Fluoride/Pyridine and Nitrosonium Tetrafluoroborate	37
34.1.2	Synthesis by Substitution of Metals	
	V. Gouverneur and M. Tredwell	
34.1.2	Synthesis by Substitution of Metals	39
34.1.2.1	Method 1: Synthesis from Organosilanes	40
34.1.2.2	Method 2: Synthesis from an Organothallium Compound	42
34.1.2.3	Method 3: Synthesis from Organomercury Compounds	43
34.1.2.4	Method 4: Synthesis from Organomagnesium Compounds	44
34.1.2.5	Method 5: Synthesis from Organolithium Compounds	45
34.1.2.5.1	Variation 1: Using Molecular Fluorine	45
34.1.2.5.2	Variation 2: Using Perchloryl Fluoride	46
34.1.3	Synthesis by Substitution of Carbon Functionalities	
	M. A. Carroll	
34.1.3	Synthesis by Substitution of Carbon Functionalities	49
34.1.3.1	Method 1: Synthesis from Alkanecarboxylates Using Fluorine	49
34.1.3.2	Method 2: Synthesis from Alkanecarboxylic Acids	50
34.1.3.2.1	Variation 1: Using Titanium(IV) Oxide/Silver(I) Fluoride	50
34.1.3.2.2	Variation 2: Using Xenon Difluoride	51
34.1.3.2.3	Variation 3: Using Bromine Trifluoride	53
34.1.3.2.4	Variation 4: Using Triethylamine Trihydrofluoride	54
34.1.3.3	Method 3: Synthesis from Cyclopropanes	54

34.1.4	Synthesis by Substitution of Heteroatoms		
34.1.4.1	Synthesis by Substitution of a Halogen		
	T. P. Lequeux		
<hr/>			
34.1.4.1	Synthesis by Substitution of a Halogen	57
34.1.4.1.1	Method 1: Substitution of Primary Halides	57
34.1.4.1.1.1	Variation 1: Using Metal Fluorides	57
34.1.4.1.1.2	Variation 2: Using Hydrogen Fluoride Complexes	60
34.1.4.1.1.3	Variation 3: Using Tetraalkylammonium Fluorides	61
34.1.4.1.1.4	Variation 4: Using Fluorosilicate Derivatives	62
34.1.4.1.2	Method 2: Substitution of Secondary Halides	62
34.1.4.1.2.1	Variation 1: Using Metal Fluorides	63
34.1.4.1.2.2	Variation 2: Using Hydrogen Fluoride Complexes	65
34.1.4.1.3	Method 3: Substitution of Tertiary Halides	66
34.1.4.1.3.1	Variation 1: Using Metal Fluorides	66
34.1.4.1.3.2	Variation 2: Using Base-Hydrogen Fluoride Complexes	67
34.1.4.1.3.3	Variation 3: Using Silver(I) Tetrafluoroborate	67
34.1.4.1.3.4	Variation 4: Using Ruthenium Complexes	68
34.1.4.2	Synthesis by Substitution of Hydroxy Groups in Alcohols		
	K. Dax		
<hr/>			
34.1.4.2	Synthesis by Substitution of Hydroxy Groups in Alcohols	71
34.1.4.2.1	Method 1: Reaction with Fluoro- λ^4 -sulfanes	72
34.1.4.2.1.1	Variation 1: With <i>N,N</i> -Diethylaminosulfur Trifluoride	76
34.1.4.2.1.2	Variation 2: With <i>N,N</i> -Bis(2-methoxyethyl)aminosulfur Trifluoride (Deoxo-Fluor)	108
34.1.4.2.1.3	Variation 3: With Morpholinosulfur Trifluoride	111
34.1.4.2.1.4	Variation 4: With <i>N,N</i> -Dimethylaminosulfur Trifluoride	113
34.1.4.2.1.5	Variation 5: With Other Dialkylaminofluoro- λ^4 -sulfanes	113
34.1.4.2.1.6	Variation 6: With Sulfur Tetrafluoride	114
34.1.4.2.1.7	Variation 7: With Alkoxy-sulfur Trifluorides	116
34.1.4.2.2	Method 2: Reaction with Selenium Tetrafluoride	117
34.1.4.2.3	Method 3: Reaction with Fluorophosphoranes	118
34.1.4.2.3.1	Variation 1: With Difluoro(triphenyl)phosphorane	119
34.1.4.2.3.2	Variation 2: With Trifluoro(diphenyl)phosphorane	119
34.1.4.2.3.3	Variation 3: With Tetrafluoro(phenyl)phosphorane	119
34.1.4.2.4	Method 4: Reaction with Fluoroalkylamine Reagents	121
34.1.4.2.4.1	Variation 1: With 2-Chloro- <i>N,N</i> -diethyl-1,1,2-trifluoroethylamine (Yarovenko Reagent)	122
34.1.4.2.4.2	Variation 2: With <i>N,N</i> -Diethyl-1,1,2,3,3,3-hexafluoropropylamine (Ishikawa Reagent)	124
34.1.4.2.4.3	Variation 3: With <i>N,N</i> -Diethyl(trifluoromethyl)amine	125
34.1.4.2.4.4	Variation 4: With 1,1-Difluoro- <i>N,N</i> -dimethyl-1-phenylmethanamine	126
34.1.4.2.4.5	Variation 5: With <i>N,N</i> -Dimethyl(1,1,2,2-tetrafluoroethyl)amine	126
34.1.4.2.4.6	Variation 6: With <i>N,N</i> -Diethyl-1,1-difluoro-1-(3-tolyl)methanamine	127
34.1.4.2.4.7	Variation 7: With 2,2-Difluoro-1,3-dimethylimidazolidine	129

34.1.4.2.4.8	Variation 8:	With Other Fluoroalkylamine Reagents	130
34.1.4.2.5	Method 5:	Reaction with Perfluorocyclobutane Ylides	132
34.1.4.2.6	Method 6:	Reaction with Perfluoro(2-methylpent-2-ene)	133
34.1.4.2.7	Method 7:	One-Pot Versions of the Sulfonate Displacement Route Using Alkane- or Arenesulfonyl Fluorides	134
34.1.4.2.8	Method 8:	Reaction with Hydrogen Fluoride	137
34.1.4.2.8.1	Variation 1:	In Combination with Organic Bases (Amines or Ethers)	138
34.1.4.3	Synthesis by Substitution of Oxygen and Sulfur Functionalities T. P. Lequeux		
34.1.4.3	Synthesis by Substitution of Oxygen and Sulfur Functionalities		149
34.1.4.3.1	Method 1:	Substitution of Trifluoromethanesulfonates and Imidazolesulfonates	149
34.1.4.3.1.1	Variation 1:	Using Difluorosilicate Derivatives	149
34.1.4.3.1.2	Variation 2:	Using Tetrabutylammonium Fluoride	150
34.1.4.3.1.3	Variation 3:	Using Base-Hydrogen Fluoride Complexes	152
34.1.4.3.2	Method 2:	Substitution of Cyclic Sulfates	153
34.1.4.3.2.1	Variation 1:	Using Ammonium Fluoride	153
34.1.4.3.2.2	Variation 2:	Using Tetrabutylammonium Fluoride for the Substitution of Cyclic Sulfamates	155
34.1.4.3.3	Method 3:	Substitution of Carboxylic Esters and Cyclic Carbonates	156
34.1.4.3.4	Method 4:	Substitution of <i>O,S</i> -Dialkyl Dithiocarbonates	157
34.1.4.3.5	Method 5:	Substitution of Primary Sulfonates	159
34.1.4.3.5.1	Variation 1:	Using Potassium Fluoride	159
34.1.4.3.5.2	Variation 2:	Using an Ionic Liquid and Cesium Fluoride	160
34.1.4.3.5.3	Variation 3:	Using Ammonium Fluorides under High Pressure	160
34.1.4.3.5.4	Variation 4:	Using Ammonium Fluorides or Hydrogen Difluorides	161
34.1.4.3.5.5	Variation 5:	Using Difluorosilicate Derivatives	162
34.1.4.3.6	Method 6:	Substitution of Secondary Sulfonates	163
34.1.4.3.6.1	Variation 1:	Using Potassium Fluoride	163
34.1.4.3.6.2	Variation 2:	Using Ammonium Fluorides	164
34.1.4.3.6.3	Variation 3:	Using Reagents Containing Hydrogen Fluoride	164
34.1.4.3.7	Method 7:	Substitution of Sulfides	165
34.1.5	Synthesis by Addition Reactions to Alkenes G. Haufe		
34.1.5	Synthesis by Addition Reactions to Alkenes		169
34.1.5.1	Vicinal Chlorofluoroalkanes from Alkenes		171
34.1.5.1.1	Method 1:	Synthesis Using <i>N</i> -Chloro Imides and a Fluoride Source	172
34.1.5.1.1.1	Variation 1:	Using <i>N</i> -Chlorosuccinimide or <i>N</i> -Chlorosaccharin, and Hydrogen Fluoride/Pyridine	172
34.1.5.1.1.2	Variation 2:	Using <i>N</i> -Chlorosuccinimide and Triethylamine Trihydrofluoride	174
34.1.5.1.1.3	Variation 3:	Using Hexachloromelamine and Anhydrous Hydrogen Fluoride	175
34.1.5.1.2	Method 2:	Synthesis Using Chlorine and Silver(I) Fluoride	177
34.1.5.1.3	Method 3:	Synthesis Using Alkyl Hypochlorites and Boron Trifluoride	178

34.1.5.2	Vicinal Bromofluoroalkanes from Alkenes	179
34.1.5.2.1	Method 1: Synthesis Using <i>N</i> -Bromo Imides and a Fluoride Source	179
34.1.5.2.1.1	Variation 1: Using <i>N</i> -Bromosuccinimide and Anhydrous Hydrogen Fluoride in Coordinating Solvents	179
34.1.5.2.1.2	Variation 2: Using <i>N</i> -Bromosuccinimide or 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione, and Hydrogen Fluoride/Pyridine or Polymer-Supported Hydrogen Fluoride/Pyridine	181
34.1.5.2.1.3	Variation 3: Using <i>N</i> -Bromosuccinimide or 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione, and Triethylamine Trihydrofluoride or a Related Amine–Hydrogen Fluoride Reagent	184
34.1.5.2.1.4	Variation 4: <i>N</i> -Bromosuccinimide or 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione, and Tetrabutylammonium and Tetrabutylphosphonium Hydrogen Fluorides	187
34.1.5.2.1.5	Variation 5: 1,3-Dibromo-5,5-dimethylimidazolidine-2,4-dione and Metal Fluoride–Hydrogen Fluoride Salts	189
34.1.5.2.2	Method 2: Synthesis Using Bromine Monofluoride Prepared In Situ	190
34.1.5.2.2.1	Variation 1: Preparation from Bromine and Fluorine	190
34.1.5.2.2.2	Variation 2: Preparation from Bromine and Silver(I) Fluoride	192
34.1.5.2.3	Method 3: Synthesis Using Other Fluoride Sources	193
34.1.5.3	Vicinal Fluoroiodoalkanes from Alkenes	194
34.1.5.3.1	Method 1: Reaction with Iodine Monofluoride Prepared In Situ	194
34.1.5.3.1.1	Variation 1: Prepared from Iodine and Fluorine	194
34.1.5.3.1.2	Variation 2: Prepared from Iodine and Metal Fluorides	196
34.1.5.3.2	Method 2: Reaction with <i>N</i> -Iodosuccinimide and Hydrogen Fluoride	197
34.1.5.3.2.1	Variation 1: In Coordinating Solvents	197
34.1.5.3.2.2	Variation 2: In Water with Phase-Transfer Catalysis	198
34.1.5.3.2.3	Variation 3: Using Hydrogen Fluoride/Pyridine	200
34.1.5.3.2.4	Variation 4: Using Polymer-Supported Hydrogen Fluoride/Pyridine	200
34.1.5.3.2.5	Variation 5: Using Triethylamine Trihydrofluoride	201
34.1.5.3.2.6	Variation 6: Using Metal Fluoride–Hydrogen Fluoride Salts	202
34.1.5.3.2.7	Variation 7: Using Ammonium Hydrogen Fluorides	203
34.1.5.3.2.8	Variation 8: Using Tetrabutylphosphonium Hydrogen Fluorides	204
34.1.5.3.2.9	Variation 9: Using Hexafluoropropene/Diethylamine Complex	205
34.1.5.3.3	Method 3: Reaction with Iodonium Equivalents Other Than Iodine or <i>N</i> -Iodosuccinimide and a Fluoride Source	206
34.1.5.4	Vicinal Fluoro(sulfanyl)alkanes	207
34.1.5.4.1	Method 1: Fluorosulfanylation of Alkenes	208
34.1.5.4.1.1	Variation 1: Using Dimethyl(methylsulfanyl)sulfonium Tetrafluoroborate and Triethylamine Trihydrofluoride	208
34.1.5.4.1.2	Variation 2: Using Benzenesulfonyl Chloride and Silver(I) Fluoride	210
34.1.5.4.1.3	Variation 3: Using <i>N</i> -(Phenylsulfanyl)phthalimide and Hydrogen Fluoride/Pyridine	211
34.1.5.4.1.4	Variation 4: Using Trifluoromethanesulfonyl Fluoride	212
34.1.5.5	Vicinal Fluoro(selanyl)alkanes	213
34.1.5.5.1	Method 1: Synthesis Using Benzeneselenenyl Bromide or Chloride and Silver(I) Fluoride	213

34.1.5.5.2	Method 2: Synthesis Using <i>N</i> -(Phenylselanyl)phthalimide and Triethylamine Trihydrofluoride	214
34.1.5.5.3	Method 3: Synthesis Using Diphenyl Diselenide and Xenon Difluoride ...	216
34.1.5.6	Vicinal Nitro- and Nitriminofluoroalkanes	218
34.1.5.6.1	Method 1: Nitrofluorination of Alkenes	218
34.1.5.6.2	Method 2: Nitriminofluorination of Alkenes	219
34.1.6	Synthesis with Retention of the Functional Group T. Yamazaki	
<hr/>		
34.1.6	Synthesis with Retention of the Functional Group	225
34.1.6.1	Method 1: α -Functional Group Elimination	225
34.1.6.1.1	Variation 1: Free-Radical-Mediated Dehalogenation with Tributyltin Hydride	225
34.1.6.1.2	Variation 2: Ring Expansion with Dehalogenation Mediated by Palladium Oxide or Acid	228
34.1.6.1.3	Variation 3: By Desulfonylation	230
34.1.6.1.4	Variation 4: By Denitration	230
34.1.6.2	Method 2: β -Functional Group Elimination	231
34.1.6.2.1	Variation 1: By Dehalogenation	231
34.1.6.2.2	Variation 2: By Ionic Deoxygenation	232
34.1.6.2.3	Variation 3: By Radical Deoxygenation	233
34.1.6.2.4	Variation 4: By Deselenation	235
34.1.6.3	Method 3: Hydrogenation of Unsaturated Compounds Containing Fluorine	236
34.1.6.3.1	Variation 1: Hydrogenation of Vinylic Fluorides	236
34.1.6.3.2	Variation 2: Hydrogenation of Allylic and Propargylic Fluorides	238
34.1.6.3.3	Variation 3: Reduction of Fluorinated Arenes	240
34.2	Product Class 2: Fluorocyclopropanes J. M. Percy	
<hr/>		
34.2	Product Class 2: Fluorocyclopropanes	245
34.2.1	Synthesis of Product Class 2	246
34.2.1.1	Method 1: Radical Dechlorination of Chlorofluorocyclopropanes Using Tributyltin Hydride	246
34.2.1.2	Method 2: Debromination of Bromofluorocyclopropanes with Zinc Powder	247
34.2.1.3	Method 3: Carbene and Carbenoid Additions to Fluoroalkenes	248
34.2.1.3.1	Variation 1: Simmons–Smith Reaction of Fluoroallylic Alcohols Using a Zinc/Copper Couple	249
34.2.1.3.2	Variation 2: Diastereoselective Simmons–Smith Reaction Using Diethylzinc(II)/Diiodomethane	250
34.2.1.3.3	Variation 3: Addition of Diazoacetic Esters to Fluoroalkenes	251
34.2.1.3.4	Variation 4: Diastereoselective Addition of Diazoacetic Esters to Fluoroalkenes	251

34.2.1.3.5	Variation 5:	Addition of Diazomethane to Ethyl (2 <i>E</i>)-3-Fluoro-2-phenylacrylate with Adduct Photolysis	252
34.2.1.3.6	Variation 6:	Intramolecular Carbenoid Addition to an Ethyl (2 <i>Z</i>)-2-Fluoroalk-2-enoate	253
34.2.1.4	Method 4:	Fluorohalocyclopropanes via Fluorohalocarbene Addition to Alkenes	253
34.2.1.4.1	Variation 1:	Phase-Transfer-Catalyzed Formation of Chlorofluorocyclopropanes	254
34.2.1.4.2	Variation 2:	Titanium-Mediated Formation of Chlorofluorocyclopropanes	255
34.2.1.4.3	Variation 3:	Generation of Chlorofluorocyclopropanes from Methyl Dichlorofluoroacetate	256
34.2.1.4.4	Variation 4:	Bromofluorocarbene Addition to Alkenes Using Phase-Transfer Catalysis	257
34.2.1.5	Method 5:	Direct Fluorocarbene Addition to Alkenes	257
34.2.1.6	Method 6:	Intermolecular Addition of Fluoroiodoacetate to Alkenes and Subsequent Anionic Cyclization	260
34.2.1.7	Method 7:	Fluorination of Cyclopropanes and Their Conjugate Bases	261
34.2.1.7.1	Variation 1:	Electrophilic Fluorination of Methylene-cyclopropane Carboxylate Esters with <i>N</i> -Fluorobis(phenylsulfonyl)amine	261
34.3	Product Class 3: (Fluoromethyl)cyclopropanes		
	J. M. Percy		
34.3	Product Class 3: (Fluoromethyl)cyclopropanes		
34.3.1	Synthesis of Product Class 3		
34.3.1.1	Method 1:	Fluorodehydroxylation of Cyclopropylmethanol with <i>N,N</i> -Diethylaminosulfur Trifluoride	267
34.3.1.2	Method 2:	In Situ Formation and Fluoride Ion Displacement of a Cyclopropylmethyl 4-Toluenesulfonate	268
34.3.1.3	Method 3:	Ring Contraction of Cyclobutanols	268
34.3.1.4	Method 4:	Transannular Epoxide Opening with Trimethylamine Trihydrofluoride	269
34.4	Product Class 4: Fluorocyclobutanes		
	J. M. Percy		
34.4	Product Class 4: Fluorocyclobutanes		
34.4.1	Synthesis of Product Class 4		
34.4.1.1	Method 1:	Fluorodehydroxylation of Cyclobutanols by Reaction with <i>N,N</i> -Diethylaminosulfur Trifluoride	272
34.4.1.2	Method 2:	Reaction of Halocyclobutanes with Fluorinating Agents	273
34.4.1.2.1	Variation 1:	Reaction of Iodocubane with Xenon Difluoride	273
34.4.1.3	Method 3:	Reaction of (Iodomethyl)cyclopropane with Xenon Difluoride	274
34.4.1.4	Method 4:	Addition of Iodine Fluoride to Methylene-cyclobutanes	274

34.5	Product Class 5: Propargylic Fluorides	
	J. A. L. Miles and J. M. Percy	
<hr/>		
34.5	Product Class 5: Propargylic Fluorides	277
34.5.1	Synthesis of Product Class 5	277
34.5.1.1	Method 1: Nucleophilic Substitution of Propargylic Alcohols with 1-Fluoro- <i>N,N</i> -diisopropyl-2-methylprop-1-en-1-amine	277
34.5.1.2	Method 2: Nucleophilic Substitution of Silyl Ethers with Piperidinosulfur Trifluoride	278
34.5.1.3	Method 3: Reaction of Prop-2-yn-1-ol with 2-Chloro- <i>N,N</i> -diethyl-1,1,2-trifluoroethanamine	280
34.5.1.4	Method 4: Nucleophilic Substitution with Tetrabutylammonium Fluoride	281
34.5.1.5	Method 5: Ring Opening of Oxetanes Using Silicon Tetrafluoride	282
34.5.1.6	Method 6: Nucleophilic Substitution Using Sulfur Tetrafluoride	282
34.5.1.7	Method 7: Nucleophilic Substitution of Propargylic Alcohols with <i>N,N</i> -Diethylaminosulfur Trifluoride	283
34.5.1.7.1	Variation 1: Inverse Addition of a Propargylic Alcohol Precursor to a Cold Solution of <i>N,N</i> -Diethylaminosulfur Trifluoride without Low Temperature Quenching	284
34.5.1.7.2	Variation 2: Inverse Addition of a Propargylic Alcohol Precursor to a Cold Solution of <i>N,N</i> -Diethylaminosulfur Trifluoride with Low Temperature Quenching	286
34.5.1.7.3	Variation 3: From Propargylic Alcohols by Inverse Addition to a Cooled Solution of <i>N,N</i> -Diethylaminosulfur Trifluoride	287
34.5.1.7.4	Variation 4: From Hexacarbonyldicobalt-Protected Propargylic Alcohols	288
34.5.1.8	Method 8: Synthesis From 3-Substituted 1,1,3-Tribromo-1-fluoropropanes via (Alk-1-ynyl)fluorocarbenes	291
34.6	Product Class 6: Benzylic Fluorides	
	A. Sai Krishna Murthy, R. Tardivel, and R. Grée	
<hr/>		
34.6	Product Class 6: Benzylic Fluorides	295
34.6.1	Synthesis of Product Class 6	295
34.6.1.1	Nucleophilic Fluorination	295
34.6.1.1.1	Method 1: Dehydrofluorination	295
34.6.1.1.1.1	Variation 1: Electrochemical Methods	295
34.6.1.1.1.2	Variation 2: Photochemical Methods	300
34.6.1.1.2	Method 2: Dehydroxyfluorination	300
34.6.1.1.2.1	Variation 1: With <i>N,N</i> -Diethylaminosulfur Trifluoride and Related Reagents	301
34.6.1.1.2.2	Variation 2: With Nonfluorobutanesulfonyl Fluoride with a Trialkylamine Trihydrofluoride and a Base	304
34.6.1.1.2.3	Variation 3: With Fluoroalkylamines and Related Reagents	304
34.6.1.1.2.4	Variation 4: Fluorination with Rearrangement	305
34.6.1.1.3	Method 3: Desulfurative Fluorinations	307
34.6.1.1.4	Method 4: Halogen-Exchange Reactions	307
34.6.1.1.5	Method 5: Nucleophilic Substitutions	311

34.6.1.2	Electrophilic Fluorination	313
34.6.1.2.1	Method 1: Fluorination of Alkylbenzenes with Cesium Fluoroxy sulfate ..	313
34.6.1.3	C—C Bond Formation of Fluorinated Compounds	314
34.6.1.3.1	Method 1: Transition-Metal-Catalyzed Reactions	314
34.6.1.3.2	Method 2: Cycloadditions to Vinylic Fluorides	315
34.7	Product Class 7: Allylic Fluorides R. Roig and J. M. Percy	
<hr/>		
34.7	Product Class 7: Allylic Fluorides	319
34.7.1	Product Subclass 1: Allyl Fluorides	319
34.7.1.1	Synthesis of Product Subclass 1	319
34.7.1.1.1	Method 1: Deoxofluorination of Allylic Alcohols with <i>N,N</i> -Diethylaminosulfur Trifluoride	319
34.7.1.1.1.1	Variation 1: Deoxofluorination of Allylic Alcohols with Bis(dialkylamino)sulfur Difluorides	322
34.7.1.1.2	Method 2: Addition to α -Fluoroalkynes	323
34.7.1.1.3	Method 3: Electrophilic Fluorination of Alkenes	325
34.7.1.1.3.1	Variation 1: Electrophilic Fluorination of Alkenes with Acetyl Hypofluorite	325
34.7.1.1.3.2	Variation 2: Electrophilic Fluorination of Activated Alkenes with Elemental Fluorine	326
34.7.1.1.3.3	Variation 3: Electrophilic Fluorination of Alkenes with <i>N</i> -Fluoropyridinium Salts	327
34.7.1.1.4	Method 4: Nucleophilic Substitution of Allylic Halides	328
34.7.1.1.4.1	Variation 1: Nucleophilic Substitution of Allylic Halides with Tetraethylammonium Fluoride	328
34.7.1.1.4.2	Variation 2: Heterogeneous Fluorination of Allylic Halides by the Combination of Lead(II) Fluoride and a Sodium Salt	329
34.7.1.1.4.3	Variation 3: A Facile Method for the Fluorination of Phenyl Thioethers via Sulfonium Salts Using Cesium Fluoride	330
34.7.1.1.5	Method 5: Fluoroalkenylation of 1,3-Bis(<i>tert</i> -butyldimethylsilyl) Ethers	331
34.7.1.1.6	Method 6: Oxidative Elimination of β -Fluoro Selenides	332
34.7.1.1.7	Methods 7: Additional Methods	332
34.7.2	Product Subclass 2: α-Fluoroallyl- and 3-Fluoroalk-1-enylphosphonate Esters	333
34.7.2.1	Synthesis of Product Subclass 2	334
34.7.2.1.1	Method 1: Deoxofluorination of α -Hydroxyallylphosphonate Esters with <i>N,N</i> -Diethylaminosulfur Trifluoride	334
34.7.2.1.2	Method 2: Coupling of α -Fluoro Phosphonate Esters with Vinylic Halides	334
34.7.2.1.3	Method 3: Catalytic Hydrogenation of α -Fluoropropargylphosphonate Esters	335
34.7.3	Product Subclass 3: γ-Fluoro α,β-Unsaturated Esters	337
34.7.3.1	Synthesis of Product Subclass 3	337
34.7.3.1.1	Method 1: Horner–Emmons Condensation of α -Fluoro Aldehydes and Ketones	337

34.8	Product Class 8: Homoallylic Fluorides J. M. Percy	
<hr/>		
34.8	Product Class 8: Homoallylic Fluorides	341
34.8.1	Synthesis of Product Class 8	341
34.8.1.1	Method 1: Ring Opening of Cyclopropylmethanols with a Fluoride Ion Source	341
34.9	Product Class 9: β-Fluoro Alcohols G. Haufe	
<hr/>		
34.9	Product Class 9: β-Fluoro Alcohols	345
34.9.1	Synthesis of Product Class 9	345
34.9.1.1	Method 1: Synthesis Using Hydrogen Fluoride	348
34.9.1.1.1	Variation 1: Aqueous Hydrogen Fluoride	348
34.9.1.1.2	Variation 2: Anhydrous Hydrogen Fluoride in Coordinating Solvents	349
34.9.1.1.3	Variation 3: Anhydrous Hydrogen Fluoride in the Presence of Lewis Acids	350
34.9.1.2	Method 2: Synthesis Using Metal Fluorides and Metal Hydrogen Fluorides	351
34.9.1.2.1	Variation 1: Alkali Metal Hydrogen Fluorides in Coordinating Solvents	351
34.9.1.2.2	Variation 2: Potassium Hydrogen Difluoride or Silver(I) Fluoride in the Presence of a Chiral Lewis Acid	355
34.9.1.3	Method 3: Synthesis Using Alkylammonium and Alkylphosphonium Fluorides	357
34.9.1.3.1	Variation 1: Tetrabutylammonium and Tetrabutylphosphonium Fluorides	357
34.9.1.3.2	Variation 2: Tetraethylammonium Fluorides	360
34.9.1.4	Method 4: Synthesis Using Amine Polyhydrofluorides	361
34.9.1.4.1	Variation 1: Hydrogen Fluoride/Pyridine	362
34.9.1.4.2	Variation 2: Alkylamine Hydrofluorides	367
34.9.1.5	Method 5: Synthesis Using Boron Trifluoride–Diethyl Ether Complex	374
34.10	Product Class 10: β-Fluoroamines J. M. Percy	
<hr/>		
34.10	Product Class 10: β-Fluoroamines	379
34.10.1	Synthesis of Product Class 10	379
34.10.1.1	Method 1: Reduction of β -Fluoro Azides	379
34.10.1.2	Method 2: Displacement of β -Fluoro 4-Toluenesulfonates by Amines	380
34.10.1.3	Method 3: Ring Opening of Aziridines with Hydrogen Fluoride Equivalents	381
34.10.1.3.1	Variation 1: Ring Opening of Aziridines by Fluoride Ion	382
34.10.1.3.2	Variation 2: Ring Opening of Azabicyclo[1.1.0]butanes with Hydrogen Fluoride/Pyridine	383
34.10.4	Method 4: Ring Opening of Cyclic Sulfamates with Fluoride Ion	384





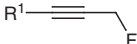

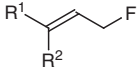
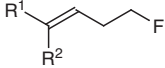
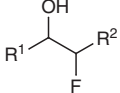
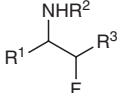
Keyword Index	387
Author Index	403
Abbreviations	419

Introduction

J. M. Percy

This volume covers the synthesis of compounds containing a single fluorine atom bonded to an sp^3 carbon, excluding α -fluorocarbonyl compounds {aldehydes, ketones, and acids and their derivatives (covered in *Science of Synthesis*, Volumes 25, 26, and 20, respectively) and 1,1-dihalides [including geminal difluorides (Volume 29)]}. The volume content is organized firstly according to the different classes of fluorinated molecule, and then by the methods of synthesis. The distribution of content is shown in Table 1, along with the appropriate section number.

Table 1 Classes of Compounds Covered in Volume 34

Product Class and Method	Structural Formula	Section
fluoroalkanes		
by substitution of hydrogen		34.1.1
by substitution of metals		34.1.2
by substitution of carbon functionalities		34.1.3
by substitution of a halogen		34.1.4.1
by substitution of hydroxy groups in alcohols		34.1.4.2
by substitution of oxygen and sulfur functionalities		34.1.4.3
by addition reactions to alkenes		34.1.5
by retention of the functional group		34.1.6
fluorocyclopropanes		34.2
(fluoromethyl)cyclopropanes		34.3
fluorocyclobutanes		34.4
propargylic fluorides		34.5
benzylic fluorides		34.6
allylic fluorides		34.7
homoallylic fluorides		34.8
β -fluoro alcohols		34.9
β -fluoroamines		34.10

References to reviews on the different classes of compounds are given wherever possible, but much of the literature upon which this volume is based deals with methodology rather than type of target molecule. The organofluorine literature contains relatively few comparisons between methods, which can make route selection rather difficult. Where the literature is sufficiently extensive, individual contributors have been encouraged to compare and contrast the scope and effectiveness of the available methodologies. Selected compound data (^{19}F NMR chemical shifts) and experimental details have been reported as fully as possible. In some cases, the original reports of important methodologies contain minimal detail. The material covered in the volume is selective in some chapters and more exhaustive in others, reflecting the fact that there are very few ways of making some of the subclasses of molecule described.

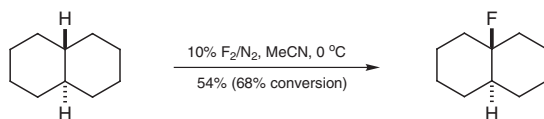
This introduction gives an outline of the individual product classes, together with highlighted synthetic methods. The synthetic chemistry described in this volume achieves the exchange of many of the most common functional groups for a single C—F bond. A significant number of challenges must be met in order to achieve accurate and efficient formation of a C—F bond to an sp^3 carbon. Some of the reagents required are relatively hazardous and require careful handling. Electron demand may be high in some of the reactions, and relatively basic reagents may be required in others, so the chemistry often occurs close to, or at, the $\text{E1}/\text{S}_{\text{N}}1$ and $\text{E2}/\text{S}_{\text{N}}2$ borderlines. Despite these difficulties, considerable progress has been made and there are many effective and ingenious methods for use in target synthesis. However, there is little real physical organic understanding of any of the transformations described in this volume; predictability of outcome may therefore be lacking.

The costs of the reagents used vary widely, from intrinsically inexpensive species such as hydrofluoric acid or elemental fluorine, which are used on an industrial scale,^[1] to the considerably more costly and exotic xenon difluoride, which is a laboratory reagent for demanding and specialized applications only. A number of commercial electrophilic fluorinating agents are becoming widely used but these are moderately costly, with clear potential for use in the synthesis of pharmaceutical agents, but perhaps beyond the acceptable cost constraints of the synthesis of agrochemicals.

The volumes of *Houben–Weyl* which cover organofluorine chemistry (Volumes E 10a–c) and a number of other reviews, organize their extensive material by type of fluorinating agent rather than by class of product or transformation. This introduction will take the latter approach and attempt to show how synthetic strategy is served by the various types of fluorinating agent, or indeed, fluorinated building blocks.

The most atom-direct method for the synthesis of simple fluoroalkanes, which involves the exchange of sp^3 C—H bonds for their C—F counterparts, is described in Section 34.1.1. The reaction has been achieved with both elemental fluorine and Selectfluor, suggesting strong parallels between the way in which these reagents react (although there are some significant differences between outcomes with the two reagents). Fluorination of C—H bonds occurs most easily at more substituted sites; selective fluorination of *trans*-Decalin occurs (Scheme 1) with elemental fluorine.^[2]

Scheme 1 Selective Fluorination of *trans*-Decalin with Elemental Fluorine^[2]

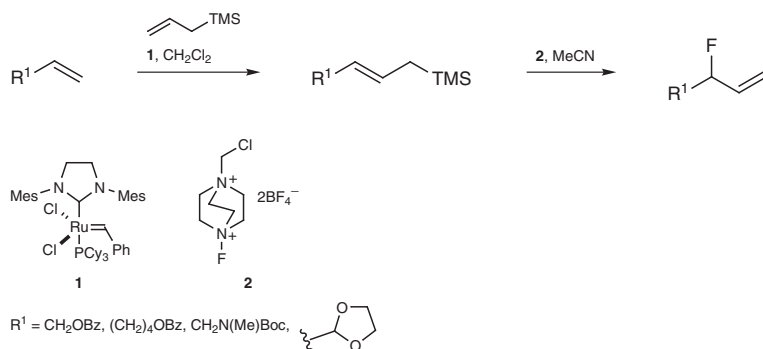


This pattern of reactivity would be consistent with either carbenium ion or free-radical chemistry. The chemistry is believed to be electrophilic in character and displays a selectivity related to carbenium ion stability. The reactions with elemental fluorine represent an extremely cost-effective solution in cases where the locus for fluorination is a tertiary

site. Electron-withdrawing substituents, if close to the fluorination site, will lower reaction rates strongly. However, fluorination has been shown to occur smoothly at more remote sites. Of course, one of those additional functional groups may serve as a locus for the efficient introduction of fluorine via different methodology so the direct fluorination may complement other methods. Elemental fluorine is not the only reagent capable of carrying out this type of transformation: Selectfluor, xenon difluoride, trifluoromethyl hypofluorite, and cesium fluoroxysulfate may also be used for direct replacement of C—H bonds by C—F bonds.

The reaction of electrophilic fluorinating agents with simple σ -organometallic reagents (Grignard, organolithium species) remains an area where there are relatively few useful reactions (Section 34.1.2). Elemental fluorine and perchloryl fluoride have been used as sources of electrophilic fluorine for a very limited range of organometallic nucleophiles. Perchloryl fluoride is available commercially, but is very reactive, and impurities present in some samples of the reagent can lead to violent reactions. The C—F bond can be relatively vulnerable in the presence of highly reactive (and basic) organometallic reagents. The risk of elimination and alkene formation accompanies the exposure of any alkyl halide to basic organometallic reagents. However, upon exposure to Selectfluor (**2**), organosilanes (and allylsilanes in particular, formed using ruthenium complex **1**) undergo smooth fluorination with loss of silicon to afford allylic fluorides (Scheme 2).^[3]

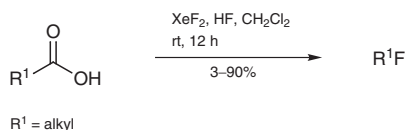
Scheme 2 Efficient Combination of Fluorodesilylation of Allylsilanes with Alkene Cross-Metathesis^[3]



The procedures are simple and high yielding in many cases, and represent the only really general and effective reactions of electrophilic fluorinating agents with organometallic reagents. The ease of synthesis of substituted allylsilanes via alkene cross-metathesis chemistry makes this approach a particularly valuable one (see Section 34.7 for other approaches to allylic fluorides). Alkene reduction without defluorination delivers the fluoroalkanes. The latter approach to fluoroalkane synthesis, in which other functionalities are removed from the vicinity of a C—F bond, is reviewed in Section 34.1.6.

In a rather limited number of cases, fluorination can be triggered by decarboxylation in a Hunsdiecker-type reaction (Section 34.1.3), or by the removal of other types of carbon-based functional group. The reagents used for this type of transformation include elemental fluorine, xenon difluoride,^[4] and bromine trifluoride; this type of transformation is shown in Scheme 3.

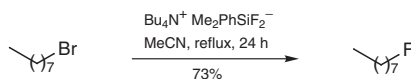
Scheme 3 Fluorination Triggered by Decarboxylation^[4]



Substitution reactions that exchange carbon—heteroatom bonds for C—F bonds (Section 34.1.4) are significantly more common, and make up the bulk of our synthetic capability. The direct displacement of other halogens can be carried out with a wide range of fluoride sources. These are very simple reactions in principle (Section 34.1.4.1); however, they raise a number of issues. There are many sources of fluoride ion, ranging from the ubiquitous to the exotic (and extremely costly). Many of the simple metal fluorides have high lattice energies and low solubility in organic solvents. Species such as ethylene glycol or diglyme, or dipolar aprotic solvents, are often used as solvents for reactions with potassium fluoride and related salts. Considerable effort has been expended in developing soluble and anhydrous fluoride ion sources which can be used in lower boiling solvents under milder conditions. Some species such as tetrabutylammonium fluoride are extremely well-known as reagents for C—F bond formation (in addition to their use for the removal of trialkylsilyl protecting groups). Several forms of tetrabutylammonium fluoride are commercially available including a trihydrate (TBAF•3H₂O) and an “anhydrous” reagent which is supplied as a solution in tetrahydrofuran. Tetrabutylammonium fluoride is extremely hygroscopic, and the water content of the “anhydrous” reagent may be significant. Drying of the reagent must be undertaken with considerable care; exposure to a combination of reduced pressure and even very modest temperatures (>40 °C)^[5] results in elimination of hydrogen fluoride and modification of the chemistry. It has been shown that small amounts of water in tetrabutylammonium fluoride solutions may help the reagent to carry out nucleophilic transformations more effectively.^[6] Tetramethylammonium fluoride is reported to be easier to obtain in an anhydrous state; it is hygroscopic but can be dried effectively.^[7]

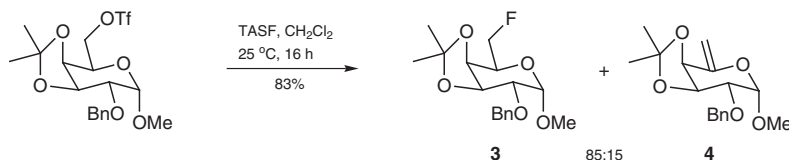
All the tetraalkylammonium fluorides are basic as well as nucleophilic so alkene formation (to varying extents) usually accompanies the nucleophilic introduction of fluorine (E2/S_N2 competition). The crystalline nonhygroscopic silicate reagents developed by DeShong^[8] normally yield lower proportions of E2 products than reagents such as tetrabutylammonium fluoride, but they are less reactive and must be used in excess if good conversions are to be secured. Scheme 4 shows a transformation using a DeShong reagent, which is typical of the reactions described in Section 3.1.4.1.

Scheme 4 Efficient Fluorodebromination Using a Nonhygroscopic Silicate Reagent^[8]



Similar concerns apply to the displacements of alkanesulfonates (Section 34.1.4.3) and a very limited number of sulfur functionalities. The highly expensive and moisture-sensitive reagent tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TASF) is often considered to be the least basic and most nucleophilic fluoride source available. Scheme 5 shows a typical application in which a valuable sugar is efficiently transformed to a fluoride **3**, along with the formation of a significant quantity of elimination product **4**.^[9]

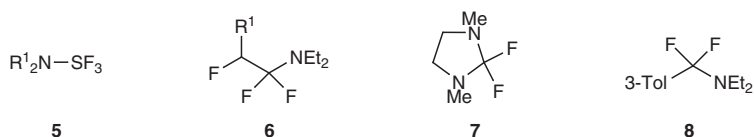
Scheme 5 Substitution of a Trifluoromethanesulfonate with Tris(dimethylamino)sulfur (Trimethylsilyl)difluoride^[9]



The investigator must assess the ease of separation of the alkene from the fluoride (and the haloalkane in the case of procedures which do not run to complete conversion) and undertake cost/benefit analysis before selecting an appropriate fluoride source.

The direct fluorodehydroxylation of alcohols remains a reaction of great strategic importance (Section 34.1.4.2) because the hydroxy group serves not only as a locus for fluorine introduction but also as a site for fragment assembly through C—C bond formation. Many reagents can carry out the exchange of C—OH for C—F in one pot, although they differ widely in terms of ease of handling. Hydrofluoric acid can bring about the conversion when the alcohol is highly substituted (and can lead to a highly stabilized carbenium ion), but *N,N*-diethylaminosulfur trifluoride (DAST) and related reagents^[10] may be required for less substituted alcohols. The original reagent introduced for this conversion (SF₄, which is a gas and must be used in an autoclave) has been largely superseded, and *N,N*-diethylaminosulfur trifluoride is unpopular for scale-up, because of the highly exothermic decomposition which it undergoes at relatively modest temperatures. More recent derivatives such as Deoxo-Fluor [*N,N*-bis(2-methoxyethyl)aminosulfur trifluoride, BAST]^[11] retain the mode of operation of *N,N*-diethylaminosulfur trifluoride, while improving on the thermal properties. Unfortunately, some chemical reactivity was lost when the structure was optimized for thermal properties. Scheme 6 shows the structures of some of the most widely used fluorodehydroxylation reagents: *N,N*-diethylaminosulfur trifluoride (**5**, R¹ = Et), *N,N*-bis(2-methoxyethyl)aminosulfur trifluoride [**5**, R¹ = (CH₂)₂OMe], Ishikawa's reagent (**6**, R¹ = CF₃), Yarovenko reagent (**6**, R¹ = Cl), 2,2-difluoro-1,3-dimethylimidazolidine (DFI, **7**), and *N,N*-diethyldifluoro(3-tolyl)methylamine (DFMBA, **8**).

Scheme 6 Fluorodehydroxylation Reagents in General Use



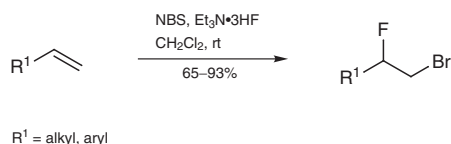
The mechanism of action of these and related reagents remains a subject of contention, in the absence of any quantitative mechanistic work. While there are hundreds of reaction yields reported in the literature, there seem to be no measured reaction rates, and this hinders the prediction of reaction outcomes. The *N,N*-dialkylaminosulfur trifluorides show a very wide tolerance of substrate reactivities but their reactions often involve the development of significant partial positive charge (carbenium ion character). This can lead to the activation of pathways involving group shifts, elimination, and neighboring-group participation, and the formation of unexpected or undesired products.

The reagents pioneered by Ishikawa and Yarovenko show good thermal properties, although their use is considerably less common. They can be made relatively easily from amines and perhaloalkenes and can be supplied commercially at scale. The byproducts of their reactions are carboxylic amides, which can sometimes be separated from reaction products by distillation (of the product from the amide in simple cases) but must often be removed by chromatography. They appear to be generally less reactive than *N,N*-diethylaminosulfur trifluoride and congeners.

Later developments include the geminally difluorinated imidazolidine reagent **7** (DFI)^[12] and the difluorinated *N,N*-dialkylbenzylamine **8** (DFMBA). The former shows a very useful reactivity profile and has the distinct advantage that it is generated using an inorganic fluoride rather than being derived from sulfur tetrafluoride. The byproduct from the reagent is the solvent 1,3-dimethylimidazolidin-2-one (DMI). *N,N*-Diethyl[di-fluoro(3-tolyl)methyl]amine (**8**) has been developed into a useful fluorinating agent that can be used to achieve rapid and efficient fluorination under microwave conditions.^[13]

Halofluorination, as well as nitrofluorination, fluorosufanylation, and fluoroselanylation of alkenes provide extremely valuable routes to a wide range of monofluoro compounds (Section 34.1.5). Although the simplest route to fluoroalkanes from alkenes would appear to involve hydrofluorination, halofluorination, nitrofluorination, fluorosufanylation, and fluoroselanylation usually permit the efficient conversion of an alkene into a fluoroalkane more readily than does the addition of hydrogen fluoride. These reagents can be generated in situ from readily available electrophiles (e.g., *N*-bromosuccinimide) and convenient hydrogen fluoride equivalents^[14] (e.g., triethylamine trihydrofluoride); they react with a very wide range of alkenes, often very efficiently. An example is shown in Scheme 7.^[15]

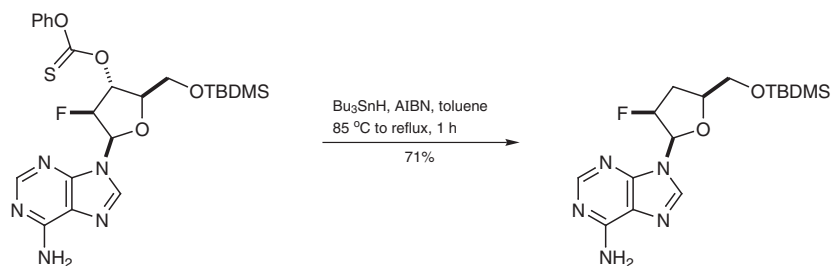
Scheme 7 Bromofluorination of a Terminal Alkene^[15]



Alkenes deactivated by π -acceptor groups often undergo addition reactions of this type. The regiochemistry of all the transformations of this type is usually highly predictable: the $X^{\delta+}$ atom or group adds in such a way that the least destabilized carbenium ion is generated (and subsequently trapped by fluoride anion). Bridged (bromonium, episulfonium) ions are formed and intercepted by fluoride ion. The chalcogenide electrophiles allow a valuable strategic connection with allylic fluorides through thermal sulfoxide or selenoxide elimination (Section 34.7).

Dehalogenation can be carried out β to C—F bonds without loss of the fluorine atom (Section 34.1.6). These reactions pass through free-radical intermediates; the high homolytic strength of the C—F bond ensures its integrity throughout processes of this type. The addition of XF to an alkene, followed by reductive C—X bond cleavage is a useful but relatively underexplored strategy for fluoroalkane synthesis. Other transformations which convert an already monofluorinated molecule containing other functional groups into a fluoroalkane are discussed in Section 34.1.6. The reductive cleavage of derivatives of β -fluorohydrins (via Barton–McCombie reactions) is probably the most commonly used reaction of this type, particularly for the synthesis of fluorinated nucleosides. Scheme 8 shows a typical example of this type of transformation.^[16]

Scheme 8 Free-Radical Deoxygenation of a Fluorinated Nucleoside^[16]



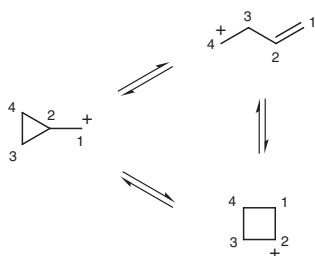
A number of other methods can be used to achieve cleavage of C—X bonds which are β to C—F bonds without loss of the fluorine atom.

Fluorocyclopropanes have a much less well developed chemistry than their difluorinated congeners, with fewer applications and methods for synthesis. Section 34.2 describes this class and the available synthetic routes, which rely upon halomethane starting materials. One of the major challenges in this area of chemistry is sustainability; the fluorinated methanes are under considerable pressure as known or potential stratospher-

ic ozone depletors.^[17] Traditional methods of synthesis involve the preparation of fluoro-halocyclopropanes and then cleavage of the carbon—halogen bond leaving the C—F bond intact, although the formation of fluorocyclopropane directly from diiodofluoromethane has also been achieved. There are also methods based on carbene additions to fluoroalkenes and electrophilic fluorinations of certain methylenecyclopropane carboxylates.

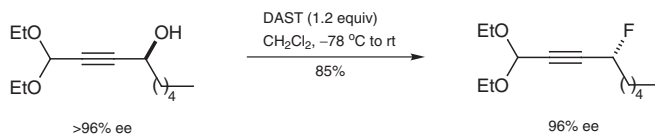
(Fluoromethyl)cyclopropanes (Section 34.3) have a very limited chemistry, as do fluorocyclobutanes (Section 34.4); these two classes are related to each other (and to the homoallylic fluorides of Section 34.8) by a set of carbenium ion interconversions. The electronic properties of substituents exert a major influence over the way in which the three reactive intermediates of Scheme 9 partition; therefore, each of these classes of compound may be approached from a number of different directions.^[18]

Scheme 9 The Cyclopropylmethyl Carbocation Triad^[18]

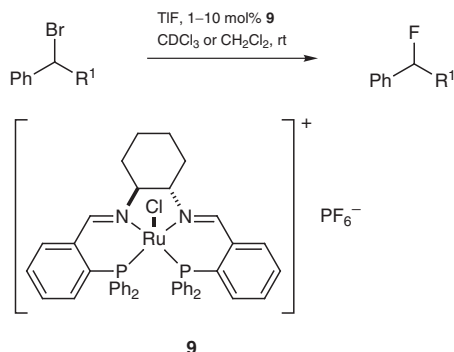


Given the enormous synthetic utility of propargyl species in general, it is perhaps surprising that there are relatively few methods for synthesizing propargylic fluorides (Section 34.5). The direct conversion of propargylic alcohols with *N,N*-diethylaminosulfur trifluoride represents probably the only general method of synthesis; it has been applied very successfully to the stereochemically accurate fluorination, with inversion, of highly enantiomerically enriched secondary propargylic alcohols, as shown in Scheme 10.^[19]

Scheme 10 Fluorination with Inversion of Highly Enantiomerically Enriched Secondary Propargylic Alcohols^[19]



Benzylic fluorides can be synthesized using the methods described in Sections 34.1.4.1–34.1.4.3, but there are also more specialized methods which are discussed in Section 34.6, including the fluorination shown in Scheme 11, which is catalyzed by chiral cationic ruthenium complex **9**.^[20]

Scheme 11 Transition-Metal-Catalyzed Fluorination of a Benzylic Halide^[20]

These results, along with others, may introduce strategically novel methods for controlling absolute configuration at fluorinated benzylic centers.

Allylic fluorides are described in Section 34.7; fluorodehydroxylation with *N,N*-diethylaminosulfur trifluoride is less effective for substrates of this type because allylic rearrangements occur readily when electron demand is high. Other nucleophilic fluorinations are possible; the reader is also referred to Section 34.1.2 if a nonterminal allylic fluoride is sought.

Sections 34.9 and 34.10 deal with the valuable β -fluoro alcohol and β -fluoroamine targets, for which the synthesis by ring opening of epoxides and aziridines, respectively, with amine–hydrogen fluoride adducts is described extensively (for the former at least). The chemistry in Section 34.9 links with Section 34.1.6 through free-radical and related deoxygenation methodologies.

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