Houben–Weyl 34

Methods of Molecular Transformations

Science of Synthesis

Compounds with One Carbon—Heteroatom Bond

Fluorine

Volume Editor
J. M. Percy

Thieme

Science of Synthesis

Science of Synthesis is the authoritative and comprehensive reference work for the entire field of organic and organometallic synthesis.

Science of Synthesis presents the important synthetic methods for all classes of compounds and includes:

- Methods critically evaluated by leading scientists
- Background information and detailed experimental procedures
- Schemes and tables which illustrate the reaction scope

Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Georg Thieme Verlag
Stuttgart · New York

Science of Synthesis

Houben–Weyl Methods of Molecular Transformations

Category 5 **Compounds with One Carbon–Heteroatom Bond**

Volume 34 **Fluorine**

Volume Editor **J. M. Percy**

Responsible Member of the Editorial Board **S. V. Ley**

Authors

M. A. Carroll
K. Dax
V. Gouverneur
R. Grée
G. Haufe
T. P. Lequeux
J. A. L. Miles
J. M. Percy
R. Roig
A. Sai Krishna Murthy
G. Sandford
R. Tardivel
M. Tredwell
T. Yamazaki

2006
Georg Thieme Verlag
Stuttgart · New York

Rüdigerstrasse 14
D-70469 Stuttgart

Printed in Germany

Typesetting: epline, Kirchheim unter Teck
Printing: Gulde Druck, Tübingen
Binding: J. Spinner, Ottersweier

Bibliographic Information published by Die Deutsche Bibliothek

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available on the internet at <http://dnb.ddb.de>

Library of Congress Cataloging in Publication Data

Science of synthesis : **Houben–Weyl** methods of molecular transformations.
p. cm.
Includes bibliographical references and index.
Contents: category 5. Compounds with One Carbon–Heteroatom Bond. v. 34. Fluorine / volume editor, J. M. Percy
ISBN 3-13-118861-8 – ISBN 1-58890-346-X (v. 34)
1. Organic compounds–Synthesis. I. Title: **Houben–Weyl** methods of molecular transformations.
QD262 .S35 2000
547'.2–dc21
00-061560

(**Houben–Weyl methods of organic chemistry**)

British Library Cataloguing in Publication Data

Science of Synthesis : **Houben–Weyl** methods of molecular transformation
Category 5: Compounds with One Carbon–Heteroatom Bond: Vol. 34: Fluorine. – (**Houben–Weyl methods of organic chemistry**)
1. Organic compounds – Synthesis 2. Organic compounds – Laboratory manuals
I. Percy, J. M., II. Carroll, M. A.
547.2

ISBN 3-13-118861-8
ISBN 978-3-13-118861-8
(Georg Thieme Verlag, Stuttgart)
ISBN 1-58890-346-X
(Thieme New York)

Date of publication: December 7, 2005

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.

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 Strathclyde, UK

J. M. Percy

Volume 34: Fluorine

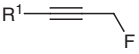
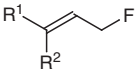
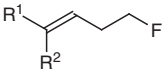
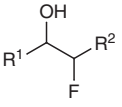
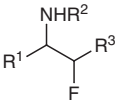
Table of Contents

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

for references see p 9

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.

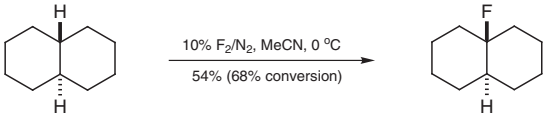
This introduction gives an outline of the individual product classes, together with highlighted synthetic methods. The synthetic chemistry described in this volume achieves the exchange of many of the most common functional groups for a single C—F bond. A significant number of challenges must be met 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 E1/S_N1 and E2/S_N2 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]

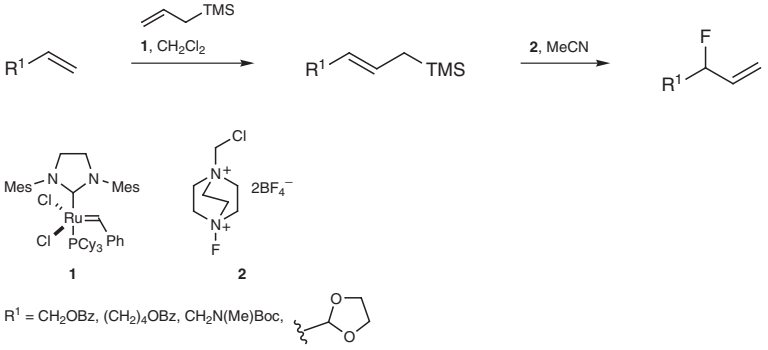


This pattern of reactivity would be consistent with either carbenium ion or free-radical chemistry. The chemistry is believed to be electrophilic in character and displays a selectivity related to carbenium ion stability. The reactions with elemental fluorine represent an extremely cost-effective solution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

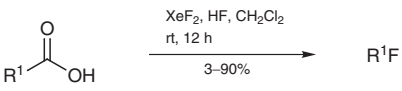
Scheme 2 Efficient Combination of Fluorodesilylation of Allylsilanes with Alkene Cross-Metathesis[3]



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]

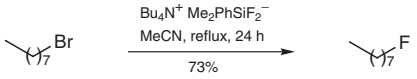


for references see p 9

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•3H_2O) 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]

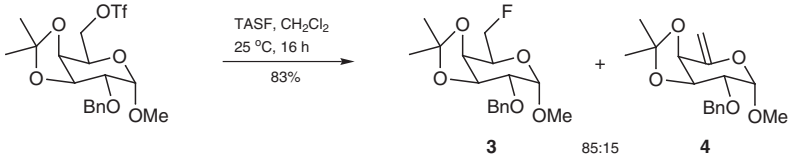
All the tetraalkylammonium fluorides are basic as well as nucleophilic so alkene formation (to varying extents) usually accompanies the nucleophilic introduction of fluorine (E2/S_N2 competition). The crystalline nonhygroscopic silicate reagents developed by DeShong[8] normally yield lower proportions 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 (SF_4, 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**, R^1 = Et), *N*,*N*-bis(2-methoxyethyl)aminosulfur trifluoride [**5**, $R^1 = (CH_2)_2OMe$], Ishikawa's reagent (**6**, $R^1 = CF_3$), Yarovenko reagent (**6**, R^1 = 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

5 **6** **7** **8**

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.

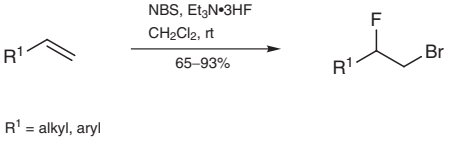
The reagents pioneered by Ishikawa and Yarovenko show good thermal properties, although their use is considerably less common. They can be made relatively easily from amines and perhaloalkenes and can be supplied commercially at scale. The byproducts of their reactions are carboxylic amides, which can 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[difluoro(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]

for references see p 9

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]

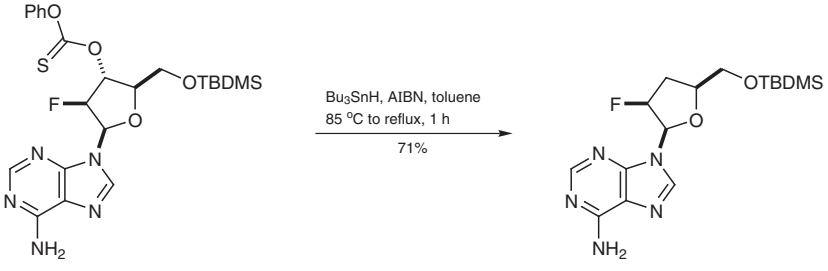
Scheme 7 Bromofluorination of a Terminal Alkene[15]



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]



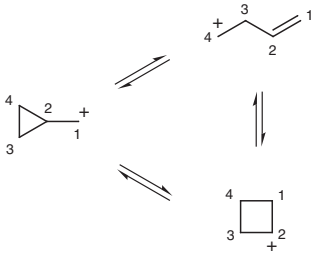
A number of other methods can be used to achieve cleavage of C—X bonds which are β to C—F bonds without loss of the fluorine atom.

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 fluorohalocyclopropanes 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.

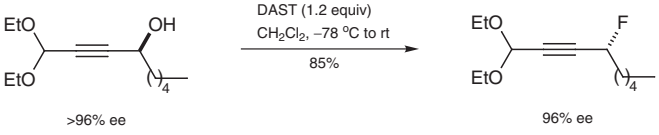
(Fluoromethyl)cyclopropanes (Section 34.3) have a very limited chemistry, as do fluorocyclobutanes (Section 34.4); these two classes are related to each other (and to the homoallylic fluorides of Section 34.8) by a set of carbenium ion interconversions. The electronic properties of substituents exert 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]

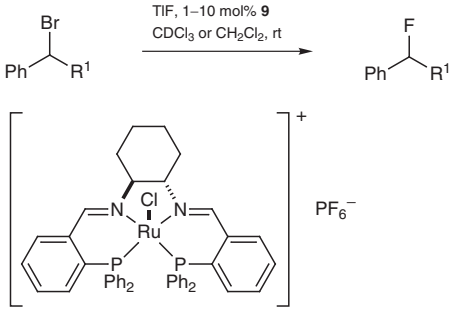
Scheme 10 Fluorination with Inversion of Highly Enantiomerically Enriched Secondary Propargylic Alcohols[19]



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]

for references see p 9

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



9

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.

References

[1] McGhie, S.; Strachan, C.; Aitken, S., *Org. Process Res. Dev.*, (2002) **6**, 898.
[2] Chambers, R. D.; Kenwright, A. M.; Parsons, M.; Sandford, G.; Moilliet, J. S., *J. Chem. Soc., Perkin Trans. 1*, (2002), 2190.
[3] Thibaudeau, S.; Gouverneur, V., *Org. Lett.*, (2003) **5**, 4891.
[4] Patrick, T. B.; Khazaeli, S.; Nadji, S.; Hering-Smith, K.; Reif, D., *J. Org. Chem.*, (1993) **58**, 705.
[5] Dolbier, W. R., Jr.; Alty, A. C.; Phanstiel, O., *J. Am. Chem. Soc.*, (1987) **109**, 3046.
[6] Albanese, D.; Landini, D.; Penso, M., *J. Org. Chem.*, (1998) **63**, 9587.
[7] Christe, K. O.; Wilson, W. W.; Wilson, R. D.; Bau, R.; Feng, J.-a., *J. Am. Chem. Soc.*, (1990) **112**, 7619.
[8] Picher, A. S.; Ammon, H. L.; DeShong, P., *J. Am. Chem. Soc.*, (1995) **117**, 5166.
[9] Sofian, A. S.; Kuan Lee, C., *J. Carbohydr. Chem.*, (2003) **22**, 185.
[10] Hudlicky, M., *Org. React. (N. Y.)*, (1988) **35**, 513.
[11] Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H., *J. Org. Chem.*, (1999) **64**, 7048.
[12] Hayashi, H.; Sonoda, H.; Fukumura, K.; Nagata, T., *Chem. Commun. (Cambridge)*, (2002), 1618.
[13] Kobayashi, S.; Yoneda, A.; Fukuhara, T.; Hara, S., *Tetrahedron*, (2004) **60**, 6923.
[14] Yoneda, N., *Tetrahedron*, (1991) **47**, 5329.
[15] Tranel, F.; Haufe, G., *J. Fluorine Chem.*, (2004) **125**, 1593.
[16] Marquez, V. E.; Tseng, C. K.-H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford, H., Jr.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S., *J. Med. Chem.*, (1990) **33**, 978.
[17] *The Montreal Protocol on Substances that Deplete the Ozone Layer*, United Nations Environment Programme, Nairobi, (2000); pp 41–45.
[18] Olah, G. A.; Reddy, V. P.; Prakash, G. K. S., *Chem. Rev.*, (1992) **92**, 69.
[19] Prakesch, M.; Grée, D.; Grée, R., *J. Org. Chem.*, (2001) **66**, 3146.
[20] Barthazy, P.; Togni, A.; Mezzetti, A., *Organometallics*, (2001) **20**, 3472.