Organic Process Research & Development **2008,** *12,* 305–321

Reviews

Fluorination in Medicinal Chemistry: Methods, Strategies, and Recent Developments

Kenneth L. Kirk

Laboratory of Bioorganic Chemistry, National Institute Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20892, U.S.A.

Abstract:

Methods for introducing fluorine into organic molecules are reviewed, with an emphasis on preparation of compounds designed for biomedicinal applications. Electrophilic fluorination, nucleophilic fluorination, and enantioselective monofluorination procedures are discussed. This is followed by a review of the development of nucleophilic and electrophilic trifluoromethylation procedures. The final sections highlight recent applications of fluorine chemistry in drug development with selected examples.

1. Introduction

Fluorine is the 13th most abundant element in the earth's crust, where it occurs predominantly in the form of cyrolite, calcium fluorspar, and fluorapatite. Despite this abundance in nature, only 13 naturally occurring organic compounds have been identified, and the majority of these (8) are higher homologues of the most notorious, fluoroacetic acid. The oxidation potential of fluorine precludes the existence of a haloperoxidase capable of oxidative incorporation of fluorine (in contrast to the situation with chlorine, bromine, and iodine), while the poor effective nucleophilicity of fluoride under natural conditions makes introduction of fluorine by nucleophilic substitution unlikely. The special properties of fluorine reflected in the rarity of naturally occurring organic compounds will be discussed in greater depth in the following sections. These same properties impart special advantages to the use of fluorine substitution in drug design. These advantages have stimulated an enormous amount of research directed toward exploiting these properties, and the large inventory of synthetic fluorinated analogues continues to grow. In this report the development of procedures that have greatly facilitated laboratory introduction of fluorine into organic molecules and made this progress possible will be reviewed. This is an extremely broad subject, so emphasis will be placed on the development of fluorinating agents that have found widespread and routine applications. Literature references for more extensive reviews of each of the topics are given in the text. Limitation in space and the author's ability to assemble all relevant material will undoubtedly lead to unfortunate omissions. A tabulation of procedures in the review by Banks and Tatlow published in 1994 reveals the broader scope of fluorination methods and reagents.[1]

Fluorination procedures are conveniently divided into methods that use electrophilic incorporation of fluorine and those that proceed by nucleophilic attack. The use of fluorinated synthons is a third strategy that is used extensively. This will not be reviewed in this report, except for procedures used to introduce the trifluoromethyl group. Electrochemical fluorination will not be covered.

2. Electrophilic Fluorinations

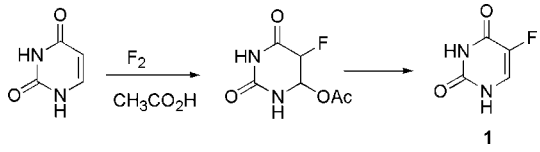
Transfer of "F^+" to an electron-rich center is the fundamental process of electrophilic fluorination. However, the species "F^+" is incapable of independent existence, so considerable ingenuity has been required to design "F^+" equivalents to implement this process. Taming of elemental fluorine and the use of *O*-F and *N*-F reagents were critical to this development. Reviews by Taylor et al.[2] and Purrington et al.[3] provide comprehensive discussions of this material.

2.1. Elemental Fluorine. Elemental fluorine was isolated by Moissan in 1886 in impressive research that earned him the Nobel Prize. The atomic configuration of F [$(He)2s^22p^5$] has an unshielded high nuclear charge that strongly attracts the surrounding electrons. Completion of the neon core [$(He)2s^22p^6$] through formation of F^- or formation of a covalent bond is highly favorable. The low F−F bond energy (36.6 kcal/mol) resulting from strong repulsion of lone pair electrons combined with the high energy of bonds formed with other elements make reactions of elemental fluorine with other elements or compounds extremely exothermic, often explosive. High reactivity, lack of selectivity, toxicity, and risk of free radical initiated runaway reactions were all properties that made working with elemental fluorine a challenge. Nonetheless, elemental fluorine initially was the only reagent available for electrophilic fluorinations and was quite useful, especially for the preparation of fluorocarbons. In addition, subsequent research that focused on strategies to tame elemental fluorine has resulted in the development of many useful reagents that make laboratory electrophilic fluorinations with elemental fluorine or derived reagents quite routine.

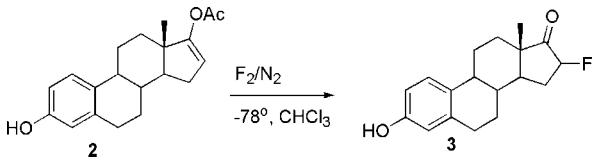
(1) Banks, R. E.; Tatlow, J. C.; Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*, Plenum Press, New York, 1994; pp 25–55..
(2) Taylor, S. D.; Kotoris, C. C.; Hum, G. *Tetrahedron* **1999**, *55*, 12431–12477.
(3) Purrington, S. T.; Kagen, B. S. *Chem. Rev.* **1986**, *86*, 997–1018.

10.1021/op700134j
Published on Web 01/26/2008

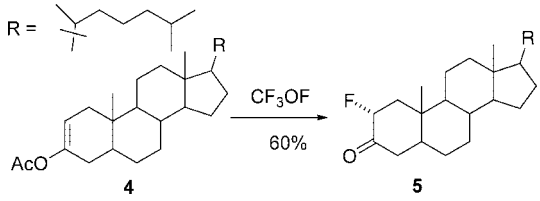
Scheme 1



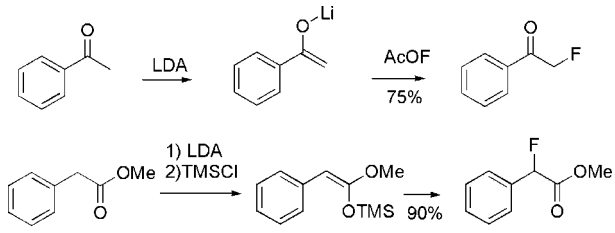
Scheme 2



Scheme 3



Scheme 4



Taming of fluorine was achieved in the 1960s by diluting elemental fluorine with an inert gas such as nitrogen or argon. Such mixtures, now commercially available, greatly expanded the scope of fluorination reactions with elemental fluorine. For more comprehensive discussions, the reviews by Purrington et al.,[3] Moilet,[4] and Sanford[5] are recommended. Early examples of success include the synthesis of 5-fluorouracil (**1**) and related analogues (Scheme 1).[6] Fluorination of the steroid enol acetate **2** to produce the α-fluoroketone **3** provides another typical example (Scheme 2).[7]

2.2. Organofluoroxy Reagents. Many reagents were developed from elemental fluorine that carry out electrophilic fluorinations through nucleophilic attack on fluorine with displacement of a highly electronegative leaving group.[3] An early example, fluoroxytrifluoromethane, was developed extensively by Barton[8] and used effectively for the fluorination of biologically active compounds such as steroids. This is illustrated by the conversion of enol acetate **4** to the 2α-fluorocholestane **5** (Scheme 3). The applications of CF_3OF have been reviewed by Hesse.[9]

Acetyl hypofluorite had been known since 1953, but it was the convenient synthesis developed by Rozen in 1981 that led to the emergence of this reagent as a versatile fluorinating agent.[10] The review by Purrington et al.[3] provides a good overview of reactions. These include aromatic ring fluorination, addition to double bonds, fluorination of lithium enolates,[11] and synthesis of α-fluorocarboxylic acid derivatives from the corresponding acids or esters (examples shown in Scheme 4).[12]

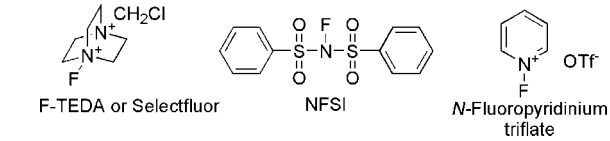


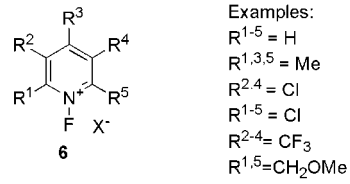
Figure 1. **Examples of commercially available *N*-fluoro electrophilic reagents.**

2.3. Additional Electrophilic Reagents XO-F. Other electrophilic fluorinating agents that were introduced include perchloryl fluoride, xenon difluoride, and others. Many of these are strong oxidizing agents and can present problems related to safety and selectivity.[3]

2.4. *N*-F Reagents. Major progress in the field of electrophilic fluorinating agents came with the advent of *N*-F reagents. The lower electronegativity of nitrogen compared to oxygen and the greater strength of the *N*-F bond compared to the *O*-F bond are factors that decrease the electrophilicity of these reagents and render them stable and convenient to handle. For a review, see Lal et al.[13] Early examples include *N*-fluoropyridinium triflate and derivatives developed by Umemoto,[14] *N*-fluoro-*N*-alkysulfonimides synthesized by Barnette,[15] *N*-fluoroperfluoroalkylsulfonamides developed by DesMarteau,[16] and *N*-fluorobenzenesulfonimide (NFSI) developed by Differding.[17] Several reagents are now commercially available, examples of which are given in Figure 1.[2] These will be discussed in the following sections.

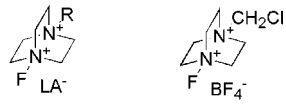
a. N-Fluoropyridinium Triflates. The development of *N*-fluoropyiridinium salts (**6**) as electrophilic fluorinating agents has been explored extensively by Umemoto and co-workers.[14] The key to the successful application of these reagents to fluorination was the discovery that non-nucleophilic counterions were essential to their stability, with triflates being particularly advantageous. The electrophilic fluorinating power of these reagents increases with decreasing electron density of the N^+-F site, and this can be controlled by varying the ring substituents (Figure 2). This provides convenient tuning of the reagents for reactivity and selectivity. These reagents are useful for fluorination of aromatic rings, carbanions, enol ethers, and related substrates. The synthesis of a fluorinated analogue **7** of the

(4) Moilliet, J. S. *J. Fluorine Chem.* **2001**, *109*, 13–17.
(5) Sanford, G. *J. Fluorine Chem.* **2007**, *128*, 90–104.
(6) Cech, D.; Holy, A. *Collect. Czech. Chem. Commun.* **1976**, *41*, 3335–3342.
(7) Patrick, T. B.; Mortezania, R. *J. Org. Chem.* **1988**, *53*, 5153–5155.
(8) Barton, D. H. R.; Ganguly, A. K.; Hesse, R. H.; Loo, S. N.; Pechet, M. M. *Chem. Commun.* **1968**, 806–808.
(9) Hesse, R. H. *Isr. J. Chem.* **1978**, *17*, 60–70.
(10) Lerman, O.; Tor, Y.; Rozen, S. *J. Org. Chem.* **1981**, *46*, 4631–4633.
(11) Rozen, S.; Brand, M. *Synthesis* **1985**, 665–667.
(12) Rozen, S.; Hagooly, A.; Harduf, R. *J. Org. Chem.* **2001**, *66*, 7464–7468.
(13) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737–1756.
(14) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465–4468. Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomia, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563–8575. Umemoto, T.; Tomizawa, G. *J. Org. Chem.* **1995**, *60*, 6563–6570.
(15) Barnette, W. E. *J. Am. Chem. Soc.* **1984**, *106*, 452–454.
(16) Singh, S.; DesMarteau, D. D.; Zuberi, S. S.; Witz, M.; Huang, H.-N. *J. Am. Chem. Soc.* **1987**, *109*, 7194–7196.
(17) Differding, E.; Ofner, H. *Synlett* **1991**, 187–189.



6

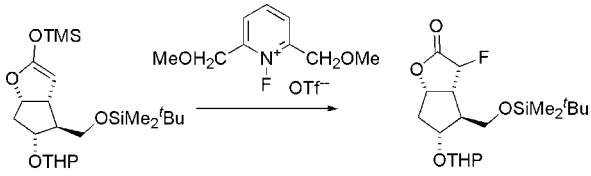
Figure 2. **Power-variable *N*-fluoropyridinium salts.**



F-TEDA-BF_4 **8**

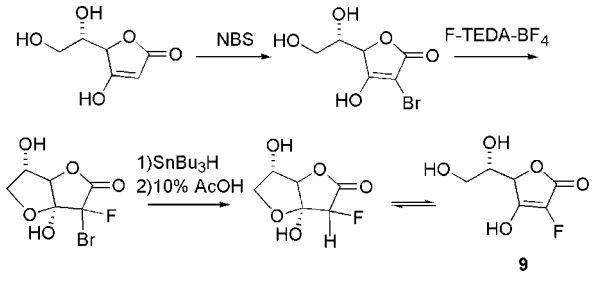
Figure 3. **In a series of *N*-fluoroquinucludinium salts, fluorinating ability increases with increasing electron-withdrawing ability of the R group.**

Scheme 5



7

Scheme 6



9

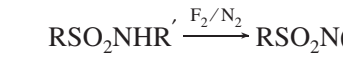
Corey lactone prostaglandin synthetic intermediate provides an example (Scheme 5).

b. Selectfluor and Derivatives. F-TEDA-BF_4 or Selectfluor is an exceptionally stable, user-friendly and versatile electrophilic fluorinating agent that was developed by Banks and coworkers as part of their research on *N*-F chemistry.[18] In a series of *N*-fluoroquinuclidines, the fluorinating power increased with the electron-withdrawing power of the R group (CH_3, C_2H_5, C_8H_7 < CH_2Cl < CF_3CH_2), thus permitting "tunability" in the series (Figure 3). F-TEDA-BF_4 or Selectfluor (R = CH_2Cl) (**8**) is available commercially and has become a very popular reagent with many applications, including fluorination of aryl groups, nucleosides, steroids, carbon−metal bonds, and other substrates.

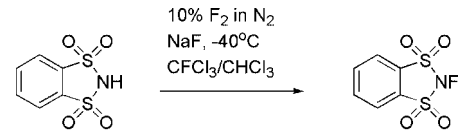
From many available examples, we choose one from our own work. Fluorination of 2-bromo-2-deoxyascorbic acid was a key step in the synthesis of 2-fluoro-2-deoxyascorbic acid (**9**) (Scheme 6).[19]

c. Sulfonyl Derivatives $RSO_2N(F)R'$. In 1984 Barnette demonstrated that *N*-alkyl-*N*-fluorosulfonamides are versatile and effective fluorinating agents.[15] They are readily prepared

Scheme 7.



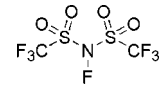
Scheme 8



11

by treatment of the precursor amide with 1 equiv of 1–5% fluorine in nitrogen (Scheme 7). As opposed to the reagents discussed above, the *N*-fluorosulfonamides are neutral *N*-F reagents. Many reagents based on this general structure have enjoyed considerable popularity because they are stable and can be used for a variety of selective fluorination procedures.

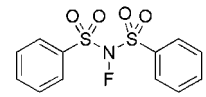
Additional early examples of *N*-F reagents include the perfluoroalkylsulfonamides exemplified by the *N*-fluoro-trifluoromethylsulfonimide **10**, reported by DesMarteau in 1987. These are among the most powerful electrophilic fluorinating reagents known.[16] A disadvantage of compound **10** is that it must be prepared from undiluted elemental fluorine.



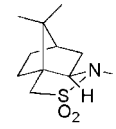
10

In 1991, Davis and Han reported the synthesis of *N*-fluoro-*o*-benzenedisulfonimide (**11**) (NFOBS) as an alternative to *N*-fluoro-*N*-alkylsulfonamides or *N*-fluoropyridinium triflate, reagents that had been ineffective for their research needs (Scheme 8). This proved to be an effective reagent for fluorination of a series of enolates.[20]

N-Fluorobenzenesulfonimide (NFSI) (**12**) was reported by Differding in 1991.[17] This commercially available reagent has become quite popular, having reactivity somewhere between the more powerful DesMarteau reagents and the less powerful alkylsulfonamides. Differding and Lang reported the first enantioselective fluorination reaction using the camphor-derived *N*-fluorosultam **13**.[21] This and related structures will be discussed in greater detail below.



12



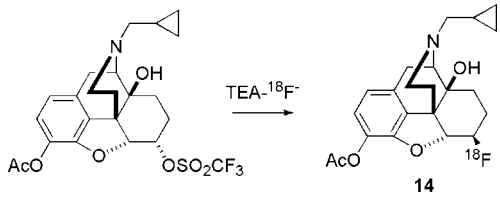
13

3. Nucleophilic Fluorinations

3.1. Direct Displacement with Fluoride. Fluoride is strongly solvated in protic solvents and forms tight ion pairs in most aprotic solvents. Because of this, fluoride is a poor nucleophile in protic solvents, while in aprotic solvents ion pairing must be overcome in order to take advantage of the inherent potent nucleophilicity of the fluoride ion. The latter has been ac-

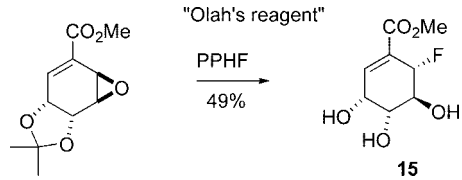
(18) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1–17.
(19) Ge, P.; Kirk, K. L. *J. Org. Chem.* **1997**, *62*, 3340–3343.
(20) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1991**, *32*, 1631–1634.
(21) Differding, E.; Lang, R. W. *Tetrahedron Lett.* **1988**, *29*, 6087–6090.

Scheme 9



14

Scheme 10



15

complished through the use of large sterically demanding cations that reduce ion pairing by delocalizing the positive charge. One such popular reagent is tetrabutyl ammonium fluoride (TBAF).

Nucleophilic fluorination is very important for the labeling of compounds with ^{18}F in the development of PET-scanning agents. The preparation of [^{18}F]fluoride requires the $^{18}O(p,n)^{18}F$ reaction. This provides high specific activity but requires enriched water. Elemental [^{18}F]fluorine, the source of electrophilic [^{18}F]fluorinating agent, is prepared by bombarding neon with deuterons [$^{20}Ne(d,\alpha)^{18}F$]. This process requires addition of carrier F_2 to the neon target and produces a radiotracer with much lower specific activity. Since higher specific activity scanning agents can be prepared using nucleophilic fluorination, much research has been carried out to increase the efficiency of nucleophilic displacement using such reagents as TBAF. An example of a PET-scanning agent prepared by nucleophilic fluorination is [^{18}F]-acetyl-cyclopfoxy (**14**), developed for the study of opiate receptors (Scheme 9).[22] Recently, a procedure for preparing completely anhydrous TBAF reported by DiMagno and co-workers has expanded the scope of this approach to PET-scanning agents.[23]

3.2. HF Reagents. In another approach to nucleophilic fluorination, the corrosive and reactive nature of HF can be tamed to facilitate ease of handling by use of amines [e.g., pyridinium poly(hydrogen fluoride), PPHF, Olah's reagent]. The presence of amines also reduces the nucleophilicity, and an activated substrate is generally required. An example of many applications of these reagents is the epoxide ring opening used in a synthesis of a fluorinated analogue **15** of shikimic acid (Scheme 10).[24]

In epoxide ring opening, the ring strain provides activation for the reaction to proceed. In another strategy, substrates for fluorination are activated by oxidation. The NBS/HF-amine

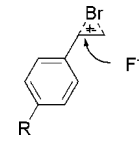


Figure 4. **Markovnikoff addition of F-Br to an olefin.**

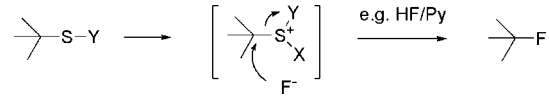
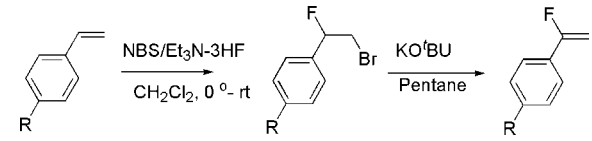
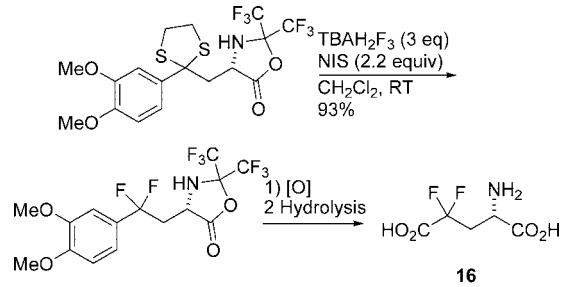


Figure 5. **Mechanism of desulfurization−fluorination.**

Scheme 11



Scheme 12



16

$TBAH_2F_3$ = Tetrabutylammonium dihydrogen trifluoride

addition of F-Br to olefins is an example. This offers a convenient route to fluorinated alkenes (Scheme 11).[25]

The fluoroolefin obtained from the elimination step is available for further elaboration, including a repeat of the fluorination reaction, providing access to many useful fluorinated intermediates. A Markonikoff addition is followed (Figure 4).

Oxidative desulfurization−fluorination has been used extensively in another application of substrate activation. This process has been reviewed recently by Shimizu and Hiyama.[26] A general mechanism is shown in Figure 5. An example of the use of this approach is seen in the desulfurization−fluorination of thio ketals, as applied to the synthesis of γ,γ-difluoroglutamic acid (**16**) (Scheme 12).[26] The conversion of xanthates of primiary alcohols and phenols to trifluormethyl ethers is exemplified by the synthesis of the steroidal trifluoromethyl ether (**17**) (Scheme 13).[27]

3.3. DAST and Relatives. Another approach to increasing the nucleophilicity of fluoride is to pair the hard Lewis base F^- with soft Lewis acids such as late transition metal fluorides (Pd, Sn, Hg), various S-F reagents such as SF_4, DAST, methylDAST (deoxofluor), and BrF_3. The now commercially available DAST, first prepared by Middleton in 1975, has proven to be a valuable and versatile fluorinating reagent.[28] The related bismethoxyethyl derivative (Deoxofluor) was reported

(22) Channing, M. A.; Eckelman, W. C.; Bennett, J. M.; Burke, T. R., Jr.; Rice, K. C. *Int. J. Radiat. Isot.* **1985**, *36*, 429–433. Pert, C. B.; Danke, J. A.; Channing, M. A.; Eckelman, W. C.; Larson, S. M.; Bennett, J. M.; Burke, T. R., Jr.; Rice, K. C. *FEBS* **2001**, *177*, 281–286.

(23) Sun, H.; DiMagno, S. G. *J. Am. Chem. Soc.* **2005**, *127*, 2050–2051. Sun, H.; DiMagno, S. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2720–2725. Sun, H.; DiMagno, S. G. *Chem. Commun.* **2007**, 528–529.

(24) Bowles, S.; Campbell, M. M.; Sainsbury, M.; Davies, G. M. *Tetrahedron Lett.* **1989**, *30*, 3711–3714.

(25) Ernet, T.; Haufe, G. *Tetrahedron Lett.* **1996**, *37*, 7251–7252.

(26) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 214–231.

(27) Kanie, K.; Tanaka, Y.; Suzuki, K.; Kuroboshi, M.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 471–484.

(28) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574–578.

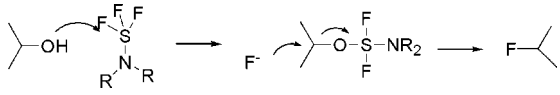
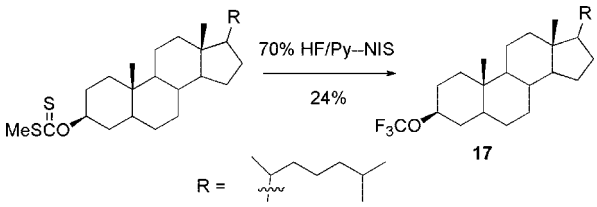


Figure 6. **Mechanism (simplified) of deoxyfluorination by dialkylamino sulfurtrifluorides.**

Scheme 13

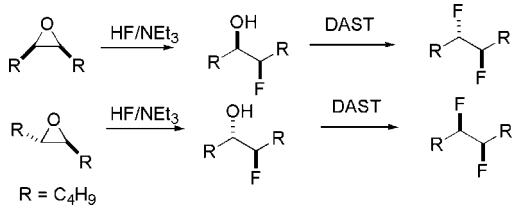


Scheme 14.

$$(Et)_2NSi(Me)_3 + SF_4 \rightarrow \underset{\text{Diethylaminosulfur trifluoride (DAST)}}{Et_2NSF_3} + Me_3SiF$$

$$(MeOCH_2CH_2)_2NSiMe_3 + SF_4 \rightarrow \underset{\text{Deoxofluor}}{(MeOCH_2CH_2)_2NSF_3} + Me_3SiF$$

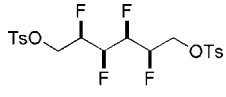
Scheme 15



by Lal in the late 1990s.[29] Both reagents are prepared by reaction of sulfur tetrafluoride with a precursor siliylated amine (Scheme 14). Deoxofluor addresses the issue of the thermal instability of DAST, which has been reported to detonate at temperatures above 90 °C. Stability is ascribed to coordination of the ether oxygen and sulfur.[29,30]

Fluorodeoxygenation of alcohols has been an important application of these reagents. Displacement of fluoride by nucleophilic attack by the hydroxyl group converts the hydroxy functionality into a good leaving group that is displaced by nucleophilic attack by the released fluoride (Figure 6). The fact that the reaction in general occurs with inversion of configuration allows introduction of the C-F bond with stereochemical control. Schlosser and co-workers combined this procedure with epoxide ring opening to prepare vicinal difluorides in a stereospecific manner (Scheme 15).[31]

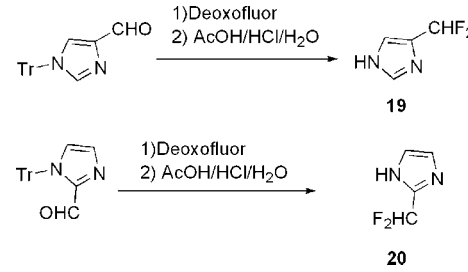
This and related stereoselective nucleophilic reactions were used by O'Hagan and co-workers to prepare the all-*syn* vicinal tetrafluoro motif exemplified in structure **18**.[32]



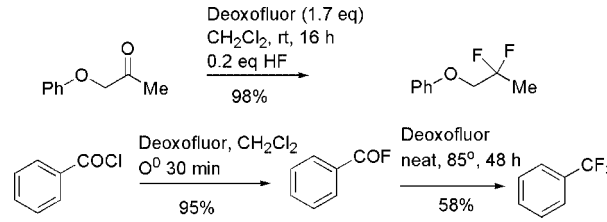
18

The dialkylaminosulfurtrifluoride reagents have been used extensively to convert carbonyl compounds to *gem*-difluoro

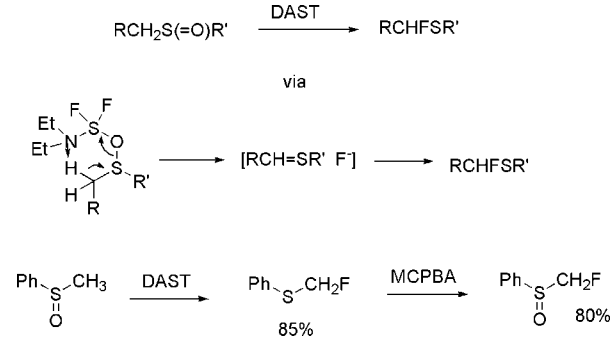
Scheme 16



Scheme 17



Scheme 18



derivatives. Examples include the conversion of imidazole carboxaldehydes to the very reactive difluoromethylene-substituted imidazoles **19** and **20** (Scheme 16).[33]

Lal reported conversions of a series of ketones to difluoromethylene derivatives as well as a procedure for converting carboxylic acids to the trifluoromethyl group (Scheme 17).[29] These are examples of the extensive applications of Deoxofluor that are described in this and subsequent reports from many research groups.[30]

The very interesting fluoropummerer reaction was discovered in the 1980s. In this process, DAST activates a sulfoxide for fragmentation, similar to the Pummerer reaction, and fluoride then attacks the electrophilic intermediate (Scheme 18).[34] Reoxidation of the formed sulfide to sulfoxide generates valuable fluorinated synthons (Scheme 19).[35] The synthesis of

(29) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *J. Chem. Soc., Chem. Commun.* **1999**, 215–216. Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64*, 7048–7054.

(30) Reviewed by Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, *17*, 2561–2578.

(31) Hamatani, T.; Matsubara, S.; Matsuda, H.; Schlosser, M. *Tetrahedron* **1988**, *44*, 2875–2881.

(32) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423.

(33) Dolensky, B.; Kirk, K. L. *Collect. Czech. Chem. Commun.* **2002**, *67*, 1335–1344.

(34) McCarthy, J. R.; Peet, N. P.; LeTourneau, M. E.; Inbasekaran, M. *J. Am. Chem. Soc.* **1985**, *107*, 735–737.

(35) Inbasekaran, M.; Peet, N. P.; McCarthy, J. R.; LeTourneau, M. E. *J. Chem. Soc., Chem. Commun.* **1985**, 678–679.

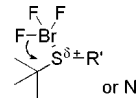
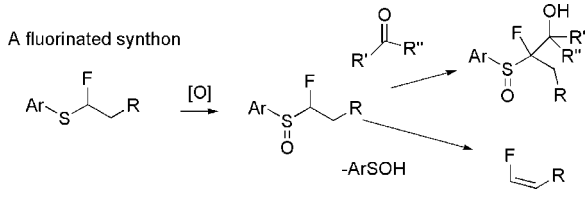
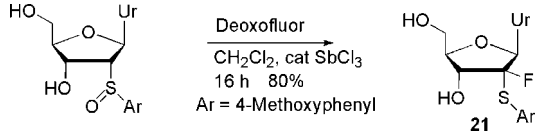


Figure 7. **Delivery of F^- to the electrophilic center by coordination of S and Br.**

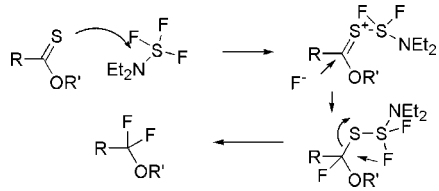
Scheme 19



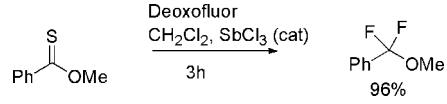
Scheme 20



Scheme 21



Scheme 22



2-fluoronucleoside **21** is one demonstration of the versatility of this reaction (Scheme 20).[29]

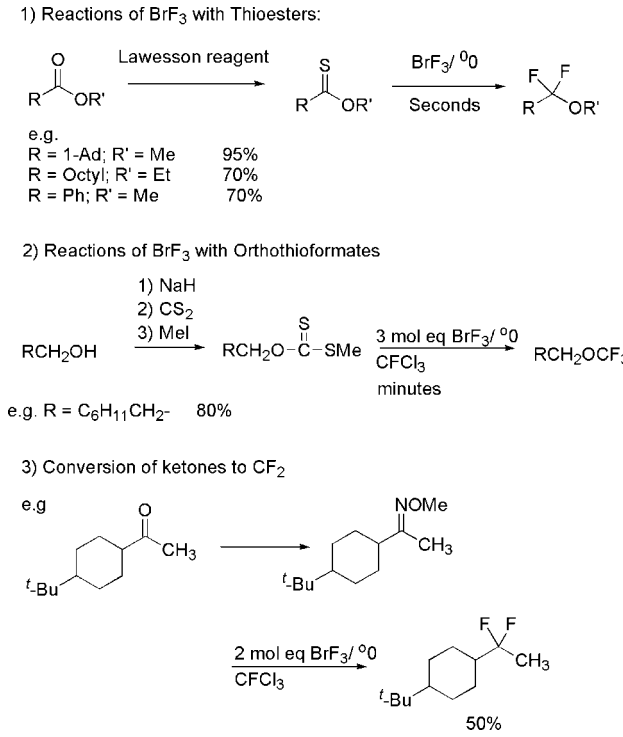
Conversion of esters to α,α-difluoroethers had been difficult; chlorine monofluride, for example, has been used for this transformation, but overfluorination and experimental difficulties were problems to be overcome. Bunnelle et al. found that DAST converts thioesters to these ethers according to the mechanism shown in Scheme 21.[36] Lal et al. describe an even more efficient conversion using Deoxofluor (Scheme 22).[29]

3.4. BrF_3. Commercially available bromine trifluoride undergoes strong and frequently uncontrolled reactions with water and hydroxylic solvents but can be conveniently and safely handled in halogenated solvents. Using these solvents, Rozen extensively studied the chemistry of bromine trifluoride and has developed many very useful transformations (examples shown in Scheme 23).[37]

The mechanism here is reminiscent of DAST and Deoxofluor Pummerer chemistry. The key to the reaction is the interaction of the soft acid Br with the soft base S (or N) positioning the reagent for facile delivery of F^- to the electrophilic center (Figure 7).

3.5. Nucleophilic Fluorination with SbF_5-HF (Super Acid). The vinca alkaloids are important chemotherapeutic agents. As such, structural analogues have been explored in a search for more efficacious compounds. A potent semisynthetic analogue, vinorelbine (**22**), was used by chemists at Pierre Fabre and the University of Poitiers to study super acid-catalyzed functionalization of normally unreactive moieties. This led to the discovery of a remarkable reaction that converts vinorelbine to vinflunine (**23**). The ability of chloromethanes to form highly electrophilic intermediates (CCl_3^+, for example) is an important part of the mechanism. These intermediates generate carbonium ion species that are attacked by nucleophilic fluoride. Although in vitro antitumor activity of vinflunine was lower, in vivo activity was much better, apparently due to decreased drug resistance. Vinflunine is in clinical trials (Scheme 24).[38,39]

Scheme 23



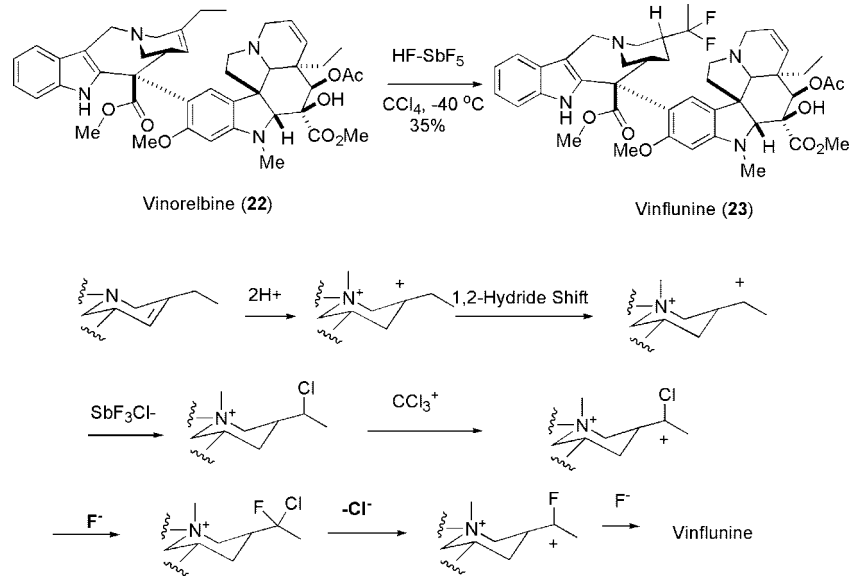
4. Enantioselective Monofluorination

Enantioselective fluorination presents serious challenges. For example, the fluorination reaction should be both chemoselective and regioselective. A particular problem stems from the fact that monofluorinated compounds are more readily deprotonated than nonfluorinated starting materials. Therefore, any reaction that involves carbanion formation or proceeds through an enolate will be problematic.

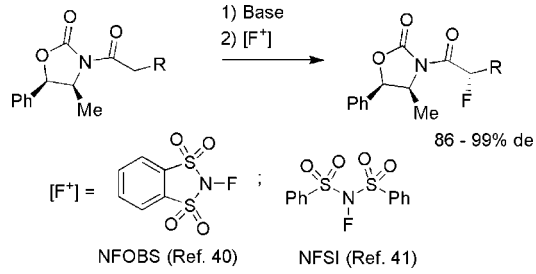
4.1. Substrate Control. Use of chiral auxiliaries, extremely effective for many reaction types, has not been exploited extensively for stereoselective formation of the C-F bond. The necessity for attachment and removal of the chiral auxiliary is a disadvantage. To exemplify this approach, the work of Davis and co-workers can be cited. Diastereoselective fluorinations

(36) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768–770.
(37) Review Rozen, S. *Acc. Chem. Res.* **2005**, *38*, 803–812.
(38) Fahy, J.; Duflos, A.; Ribet, J.-P.; Jacquesy, J.-C.; Berrier, C.; Jouannetaud, M.-P.; Zunino, F. *J. Am. Chem. Soc.* **1997**, *119*, 8576–8577.
(39) Jacquesy, J.-C. *J. Fluorine Chem.* **2006**, *127*, 1484–1487.

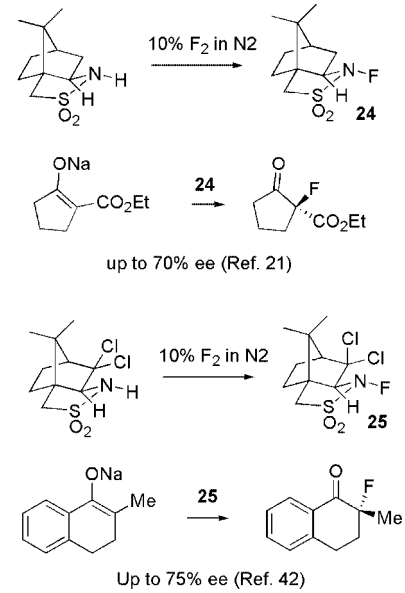
Scheme 24



Scheme 25



Scheme 26



of chiral oxazolidinone-derived enolates were achieved using NFOBS and NFSI as electrophilic fluorinating agents (Scheme 25).[40,41]

Not to be included in this discussion are the many reports of substrate-controlled diastereoselective fluorination reactions wherein asymmetry is naturally resident in the substrate. Several examples have been cited above, such as the synthesis of 6-α-fluorocholestane (**5**) using trifluoromethyl hypofluorite (Scheme 3).[9]

4.2. Reagent Control. *4.2.1. Chiral Sultams.* In contrast to the limited use of chiral auxiliaries, reagent control has been studied extensively. For example, Differding[21] and Davis[42] each employed chiral *N*-fluorosutams (**24** and **25**, respectively) to carry out enantioselective fluorination of preformed enolates. The reagents can be made by fluorination of precursors with dilute elemental fluorine. Applications with tetrasubstituted cyclic enolates avoid the problems of product epimerization as well as that of establishing enolate geometry. Fairly good enantioselection has been achieved (Scheme 26).

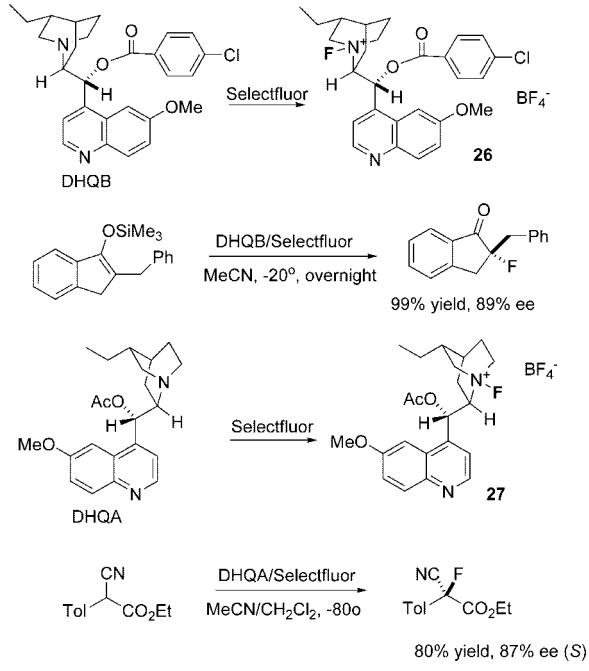
4.2.2. Cinchona Alkaloids. Takeuchi and co-workers developed interesting new chiral *N*-F reagents by treating cinchona alkaloids with Selectfluor. Fluorine is transferred to a chiral alkaloid in situ to produce chiral N-F reagents, for example, **26** and **27**, which effect fluorinations of enolates with good enantioselectivity (Scheme 27). Attempts to make this a catalytic process—less than stoichiometric quantities of alkalod in the presence of selectfluor—were unsuccessful. Such a catalytic process is thwarted by the fact that selectfluor can fluorinate the enolate directly, bypassing the *N*-fluoro alkaloid, to give racemic product.[43]

4.3. Catalyst Control. Major recent progress has been made in the area of catalyst-controlled enantioselective monofluorination, including reactions mediated by both metal and organocatalysts. Recent reviews provide good in-depth discussions of these developments.[44,45]

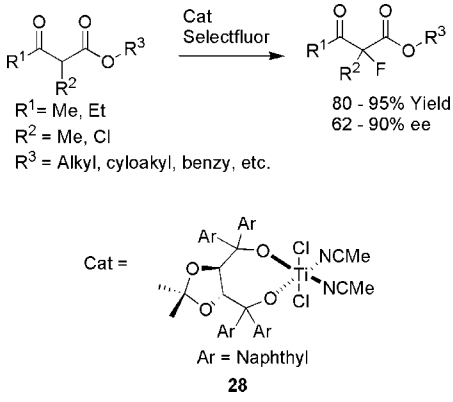
4.3.1. Metal-Mediated Catalyst Control. The first success in catalyst control of enantioselectivity in electrophilic fluorina-

(40) Davis, F. A.; Han, W. *Tetrahedron Lett.* **1992**, *33*, 1153–1156.
(41) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135–6138.
(42) Davis, F. A.; Zhou, P.; Murphy, C. K. *Tetrahedron Lett.* **1993**, *34*, 3971–3974. Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. J. *J. Org. Chem.* **1998**, *63*, 2273–2280.
(43) Shibata, N.; Suzuki, E.; Takeuchi, Y. *J. Am. Chem. Soc.* **2000**, *122*, 10728–10729.
(44) Bobbio, C.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 2065–2075.
(45) Pihko, P. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 544–547.

Scheme 27



Scheme 28



tions seems to be the work reported by Hintermann and Togni.[46] The TADDOL-modified titanium complex **28** was used to catalyze the enantioselective fluorination of branched β-keto esters (Scheme 28).

The steric bulk of the catalyst promotes *si* facial attack of the enolate that is complexed to the catalyst through two-point binding (Figure 8). This process is limited to branched keto esters since these titanium catalysts otherwise could promote enolization of the products.

Sodeoka and colleagues used the concept of 1,3-dicarbonyl two-point binding using palladium-based complexes **29** derived from homochiral bis(phosphanes) to carry out enantioselective fluorinations of branched β-keto esters (Scheme 29). NFSI was

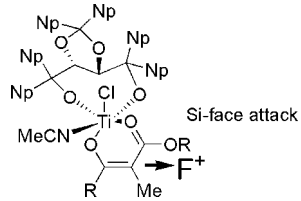
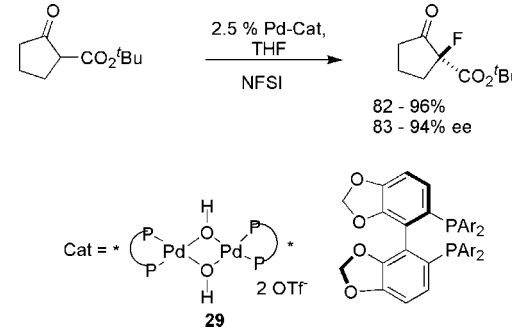
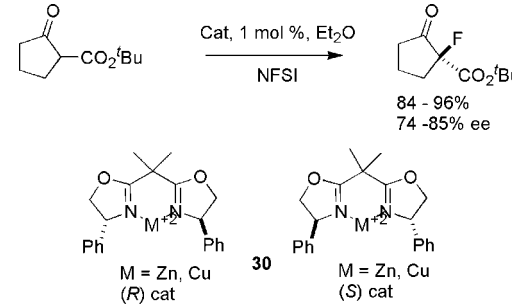


***Figure 8. si*-Facial reaction of enolate with electrophilic fluorinating agent influenced by steric bulk of metal–ligands.**

Scheme 29



Scheme 30



the superior fluorinating agent, and excellent enantioselection was achieved. Congestion of one face of the enolate by steric interaction with the ester group of the catalyst was proposed as an important influence on the direction of fluorination.[47]

Ma and Cahard used *C*2-symmetric bis(oxazoline) (Phebox) metal complexes **30** to direct enantioslective fluorinations (Scheme 30). Excellent results were achieved using NFSI. The presence of hexafluoroisopropyl alcohol improved the enantioselection.[48]

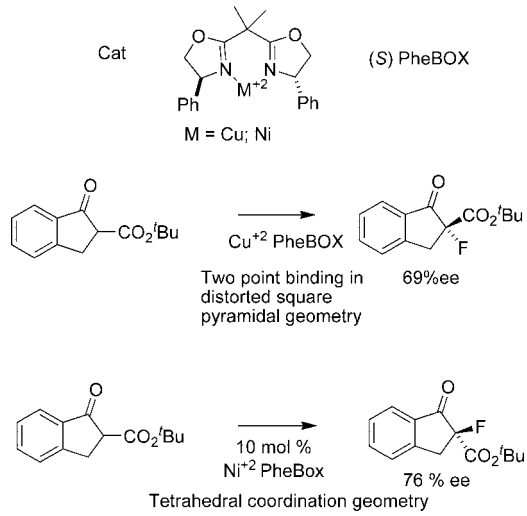
Shibata and co-workers carried out similar reactions with Phebox catalysts and made the interesting observation that the sense of enantioselection could be reversed by changing the metal used (Scheme 31). This apparently reflects a difference in coordination geometry.[49]

Two syntheses of MaxiPost (**31**), a potassium channel opener, are appropriate examples to illustrate practical results of this catalytic approach to enantioselective fluorinations (Scheme 32). The *S*-enantiomer of this oxindol consistently gives a more robust response and has been developed as BMS-204352. The Sodeoka and Shibata groups both have used metal-mediated catalytic enantioselective fluorinations to provide new routes to the *S*-enantiomer of this drug.[50,51]

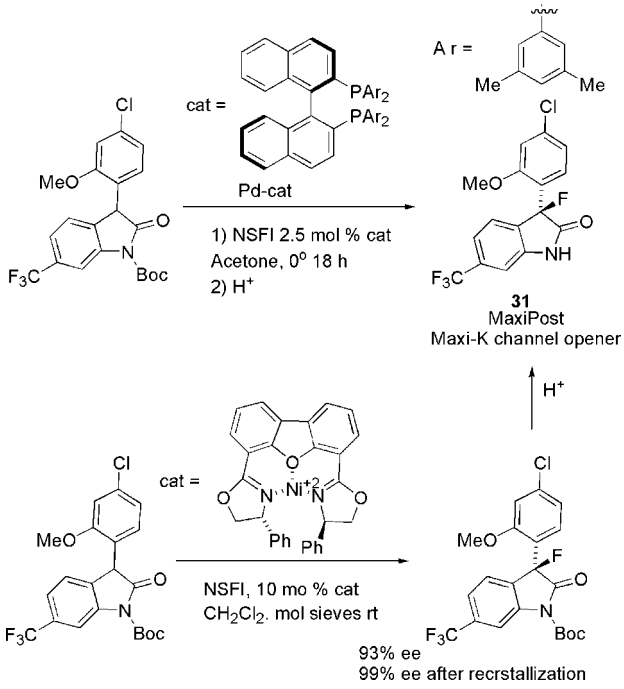
4.3.2. Organocatalysts. In 1971 researchers at Scherring reported that *S*-Proline could catalyze enantioselective intramolecular aldol condensations (the Hajos−Parrish−Eder−Sauer−

(46) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *124*, 4359–4362.
(47) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, N. *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531.
(48) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007–1011.
(49) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, *10*, 1703–1706.
(50) Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165.
(51) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakmura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204–4207.

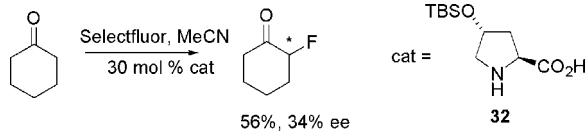
Scheme 31



Scheme 32



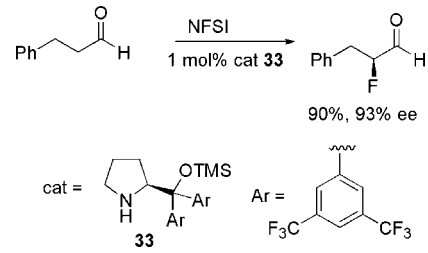
Scheme 33



Wiechert reaction).[52] The real progress in the area of organocatalysts, however, has been relatively recent, but it has been impressive. It is not surprising that, just as enantioselective organocatalysis is very efficient for such processes as the aldol reaction, similar investigations of fluorinations have been intense. Much work has been concentrated on the use of eneamine and imminium intermediates derived from carbonyl groups and chiral amines.

(52) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496–497.
(53) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991–993.

Scheme 34



Enders and Hüttl reported the first direct organocatalytic fluorination of aldehydes and ketones. Silylated hydroxy prolines (e.g., **32**) proved to be the best of several catalysts studied (Scheme 33), although enantioselectivities were low (<35%).[53]

Later work in the laboratories of Jørgensen, [54] Barbas, [55] and MacMillan[56] revealed that the choice of fluorinating agent was crucial. Enolization of the product also must be suppressed. With a low loading of catalyst **33** Jørgensen achieved >90% conversion in highly enantioselective fluorination of aldehydes, along with suppression of difluorination and racemization (Scheme 34).[54] The catalyst directs *si*-facial attack through steric blocking of the *re* face of the intermediate enamine **34**. In addition, this same steric congestion blocks water-mediated enolization of the flluorinated intermediate **35**, thereby favoring product formation over re-enolzition and formation of the difluoro analogue (Figure 9).

Barbas and co-workers obtained excellent yields and enantioselectivities using the imidizoldone *R*-**36** (Scheme 35).[55] Beeson and MacMillan also demonstrated the power of this catalytic system with enolizable aldehydes. Using *S*-**36** as catalyst, such sensitive compounds as phenylacetaldehyde were fluorinated in excellent chemical and optical yields (Scheme 36).[56] The product aldehydes could be reduced to the more stable alcohols for convenience of isolation

4.3.3. Phase Transfer Catalysis. Kim and Park used phase transfer methodology mediated by the cinchona alkaloid **37** to

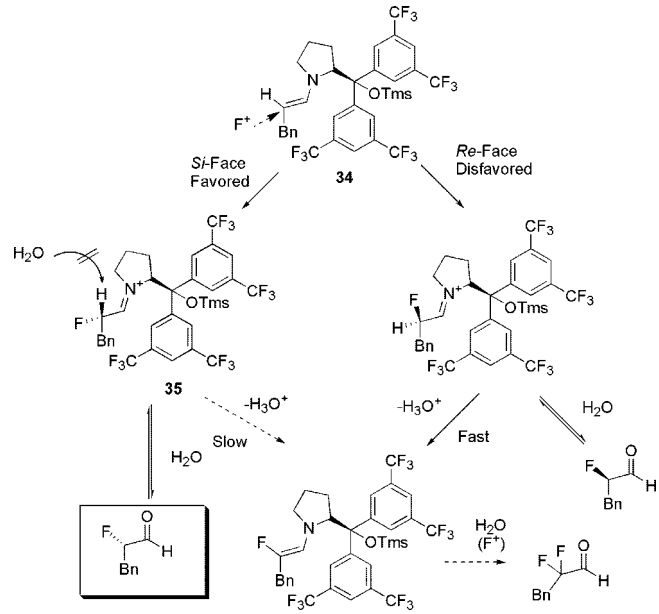
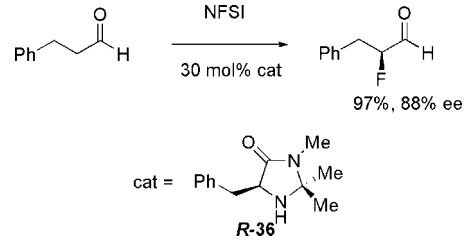
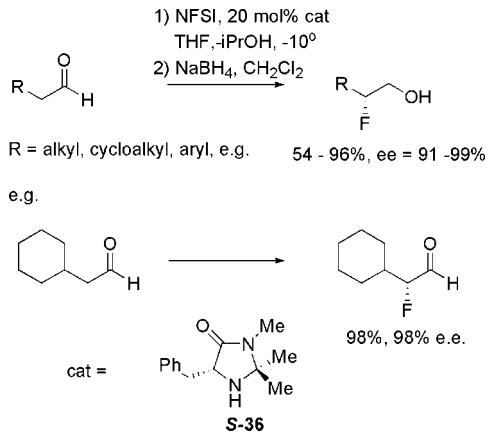


Figure 9. **Steric congestion favors *si*-facial attack on the eneamine and blocks enolization of the fluorinated intermediate.**

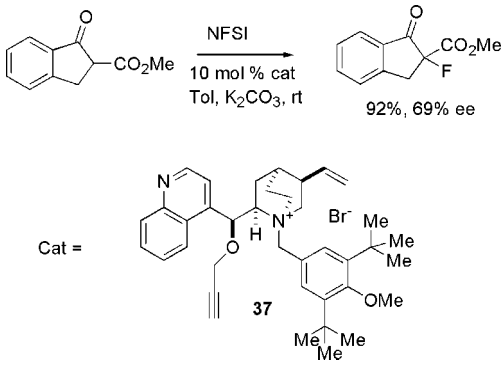
Scheme 35



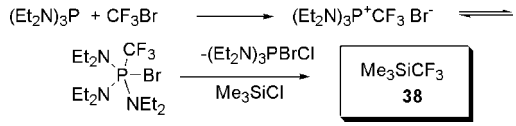
Scheme 36



Scheme 37



Scheme 38



catalyze enantioselective fluorinations. This is more correctly considered to be a process involving chiral coordination of a metal catalyst (Scheme 37).[57]

5. Trifluoromethylation

Introduction of a trifluoromethyl group is increasingly used as a strategy to alter properties of a molecule for improvement of therapeutic potential. Increased lipophilicity and increased metabolic stability are effects of this substitution that can be

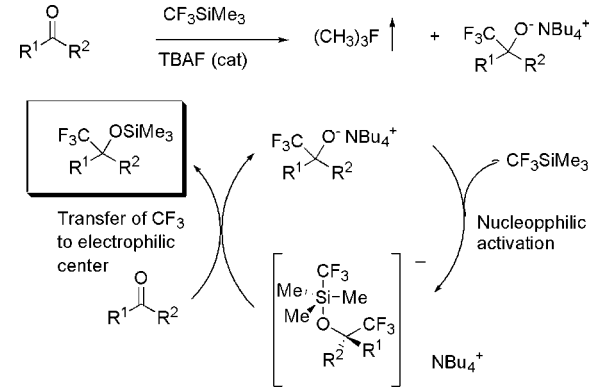
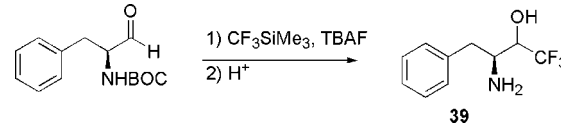


Figure 10. **Transfer of a CF_3 group from Rupert's reagent to a carbonyl group catalyzed by fluoride.**

Scheme 39



exploited. In this discussion, two fundamental approaches to the introduction of the trifluoromethyl group will be considered. Thus, similar to monofluorination procedures, nucleophilic and electrophilic procedures will be reviewed. The use of organometallic reagents such as those based on CF_3Cu will not be discussed.[58]

5.1. Nucleophilic Trifluoromethylation with Organosilicon Reagents. Trifluoromethyl trimethylsilane (Rupert's reagent, **38**) was synthesized in 1984 by the three-component reaction shown in scheme 38.[59] Applications of this reagent have been studied extensively by Prakash and co-workers.[60]

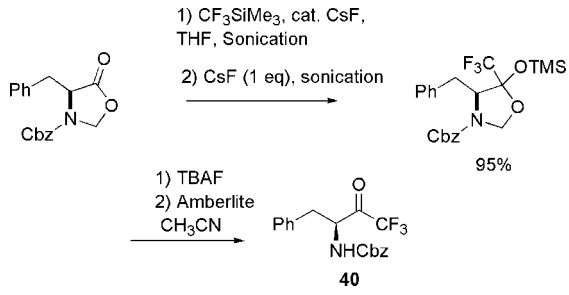
Trifluoromethylation is based on the susceptibility of silicon to nucleophilic attack, particularly by fluoride. This triggers transfer of the CF_3 moiety to an available electrophile. For example, the sequence shown in Figure 10 is initiated by catalytic fluoride in the presence of a carbonyl substrate. This nucleophilic activation of the silicone center allows transfer of the trifluoromethyl group to an electrophilic center, in this case the carbonyl group. Only a catalytic amount of the initial nucleophile is required, since attack of trifluoromethyl group generates another nucleophile. The sequence takes advantage of the high oxo- and fluorofilicities of silicone.[60]

Reactions with aldehydes provide a convenient route to trifluoromethyl carbinols. Skiles and co-workers used this procedure to prepare a trifluormethylated building block **39** for the synthesis of trifluoromethyl-containing tripeptide derivatives. These were studied as inhibitors of human leukocyte elastase (HLE) (Scheme 39).[61]

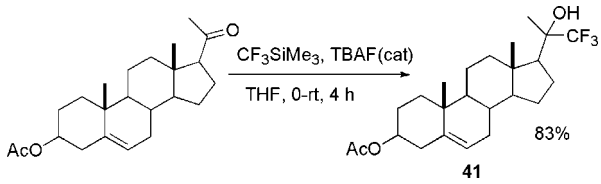
Walters and co-workers developed an alternative route to trifluoromethyl ketone intermediates that were used in their

(54) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706.
(55) Steiner, D. D.; Mase, N.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710.
(56) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.
(57) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545–547.
(58) Yang, J.-J.; Kirchmeier, R. L.; Shreeve, J. M. *J. Org. Chem.* **1998**, *63*, 2656–2660.
(59) Rupert, I.; Schlich, K.; Volbach, W. *Tetrahedron Lett.* **1984**, *25*, 2195–2918.
(60) Review Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757–786. Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613–7632.
(61) Skiles, J. W.; Fuchs, V.; Miao, C.; Sorcek, R.; Grozinger, K. G.; Mauldin, S. C.; Vitous, J.; Mui, P. W.; Jacober, S.; Chow, G.; Matteo, M.; Skoog, M.; Weldon, S. M.; Possanza, G.; Keirns, J.; Letta, G.; Rosenthal, A. S. *J. Med. Chem.* **1992**, *35*, 641–662.

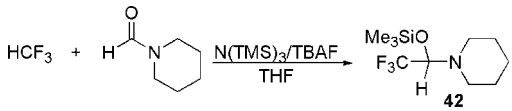
Scheme 40



Scheme 41



Scheme 42



Source of CF_3^- stable enough to be stored and sold

synthesis of metallo-β-lactamase inhibitors. Nucleophilic addition of CF_3^- to aldehydes followed by oxidation to the ketone was found to give mixed results. However, reaction of CF_3SiMe_3 with an oxazolidinone followed by desilylation and ring opening of the initial trifluoromethyl adduct gave the ketone **40** in good yield (Scheme 40).[62]

Reactions with ketones provide a convenient route to secondary trifluoromethyl carbinols, as illustrated by the reaction with the steroidal ketone **41** (Scheme 41).[63]

Other reagents have recently been developed. One important point is the fact that bromotrifluoromethane is now banned for environmental reasons. Langlois and co-workers recently reported the *N*-formylpiperidine adduct **42** as a stable source of nucleophilic CF_3 prepared from trifluoromethane (Scheme 42).[64]

5.2. Electrophilic Trifluoromethylation. As discussed above, Umemoto and co-workers developed tunable electrophilic fluorinating agents based on pyridinium fluorides. This group also prepared a series of power-variable trifluoromethylating agents (**43**–**47**). These are effective for transfer of the CF_3 group to carbanions, enolates, enol ethers, and other electron-rich species (Figure 11).[65]

Shreeve and co-workers have also prepared a series of power-variable electrophilic trifluoromethylating agents (**48**–**50**) that are easily synthesized. Trifluoromethyl thiobenzene, obtained from trifluoromethylthiocopper and iodobenzene, was condensed with aromatic substrates by the action of triflic anhydride (Figure 12). The reactivity of the resulting trifluoromethylsulfonium derivative increases with the electronegativity of the aromatic ring substituent.[58] These are versatile reagents, for example, allowing direct trifluoromethylation of electron-rich aromatic systems (Figure 12).

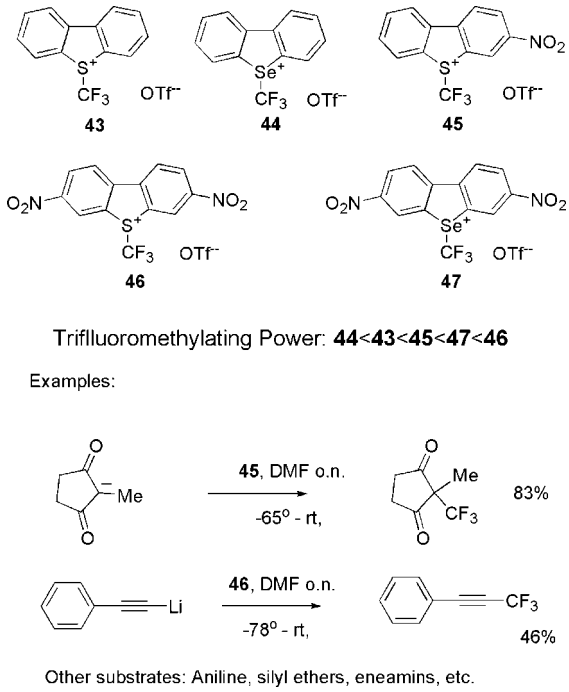


Figure 11. **Examples of power-variable electrophilic trifluormethylating agents and reactions with carbanions.**

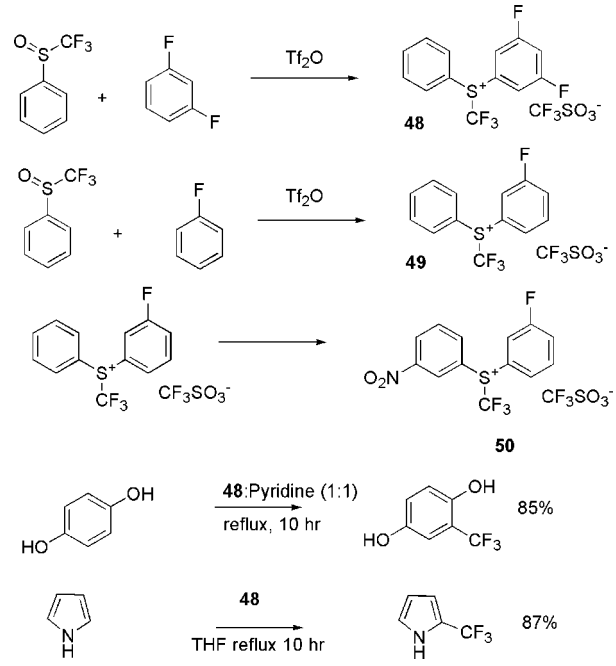


Figure 12. **Additional power-variable electrophilic trifluoromethylating agents and examples of reactions.**

6. Fluorinated Synthons

Although this topic will not be covered in this review, it is appropriate to recognize the importance of the use of fluorinated synthons in synthetic fluorine chemistry. Introduction of a fluorinated moiety into a synthetic sequence at an early or late stage is an important approach to fluorinated molecules, and

(62) Walter, M. W.; Adlington, R. M.; Baldwin, J. E.; Chuhan, J.; Schofield, C. J. *Tetrahedron Lett.* **1995**, *36*, 7761–7764. Walter, M. W.; Felici, A.; Galleni, M.; Soto, R. P.; Adlington, R. M.; Baldwin, J. E.; Frère, J.-M.; Gololobov, M.; Schofield, C. J. *Biorg. Med. Chem. Lett.* **1996**, *6*, 2455–2458.
(63) Wang, Z.; Ruan, B. J. *J. Fluorine Chem.* **1994**, *69*, 1–3.
(64) Billard, T.; Bruns, S.; Langlois, B. R. *Org. Lett.* **2000**, *2*, 2101–2103.

many versatile fluorinated synthons are available. This approach may imply "normal" organic chemistry, but the presence of fluorine often changes the chemical behavior relative to the nonfluorinated species and interesting and sometimes frustrating chemistry can emerge.[66]

7. Fluorine in Medicinal Chemistry

With the increased armamentarium of fluorinating agents, the access to fluorinated compounds is much facilitated. In the next sections, some of the biochemical rationales that have been used will be discussed briefly. There are recent reviews that cover this material more thoroughly.[67–70]

7.1. Orthogonal Reactivity of Hydrogen and Fluorine. In contrast to relatively minor differences in steric parameters between the C-H and C-F bonds, the reactivities of either positively or negatively hydrogen or fluorine are markedly different. Thus, heterolytic cleavage of the C-H bond to form H^+ is a frequent occurrence in reaction mechanisms. In contrast, "F^+" is not capable of independent existence. Similarly, F^- is a good leaving group, loss of which can result from the presence of an adjacent negative charge, especially if this is assisted by hydrogen bonding. In contrast, loss of H^- represents a very energetic process. Many enzyme–inhibitors have been designed by taking advantage of this orthogonal reactivity.

7.1.1. Electronic effect: H^+ vs F^+. An example of exploitation of fluorine as a "deceptor" is found in the mechanism of action of 5-fluorouracil (5-FU), one of the first successful applications of fluorine in drug design. 5-FU inhibits the conversion of deoxyuridine monophosphate (dUMP) to thymidylate by a process involving suicide synthesis (formation of 5-flouro-dUMP) followed by a "catch and trap" mechanism. A final step in the synthesis of thymidylate is loss of the 5-proton with elimination of tetrahydrofolate from the enzyme–substrate−cofactor ternary complex. Fluorine situated on the 5-position cannot be lost as "F^+" so the enzyme is captured and biosynthesis of thymidylate is blocked (Figure 13).[71]

In an important post-transcriptional modification, (cytosine-5)-methyltransferase catalyzes the methylation of deoxycytidine residues in DNA. A catalytic SH residue of the enzyme adds to the 6-position of the pyrimidine, and a methyl group is transferred to the 5-position from *S*-adenosyl methionine. Inhibition of this enzyme by oligonucleotides containing 5-fluoro-2-deoxycytidine can again be attributed to a catch and trap mechanism, based on the inability to release F^+ along the reaction pathway (Figure 14).[72,73]

7.1.2. Electronic Effect: H^- vs F^-. Loss of fluoride by E2 elimination has been the basis for the development of

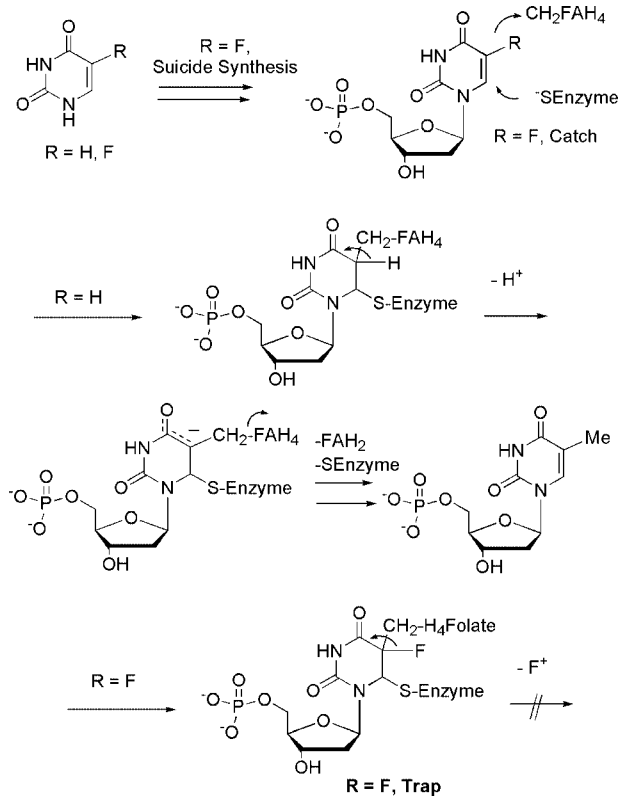


Figure 13. **Inhibition of thymidylate synthetase by 5-fluorouracil by suicide synthesis followed by irreversible formation of a ternary complex (catch and trap).**

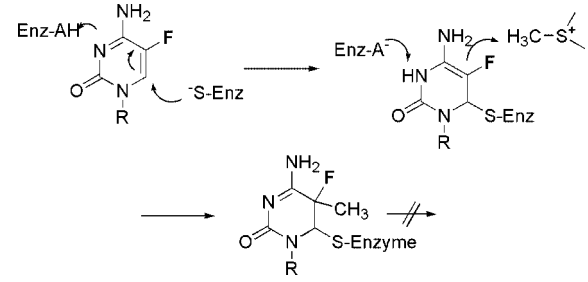


Figure 14. **Inhibition of (cytosine-5)-methyltransferase by 5-fluoro-2-deoxycytidine involves irreversible formation of covalently bound enzyme.**

a large number of mechanism-based enzyme inhibitors. A major subset of these inhibitors is based on the mechanisms of pyridoxal phosphate (PLP)-dependent enzyme-catalyzed reactions. PLP is initially attached to the enzyme through a Schiff base linkage to an ϵ-amino group of an active site lysine. In the presence of amine substrate, a transimination occurs to produce a PLP−substrate Schiff base complex, a structure that can lead to a stabilized carbanion equivalent by breaking one of the bonds to the α-carbon. Labilization of this α-position leads to the tautomerization and other events necessary for the enzyme reaction to proceed (aldolization, transamination, decarboxylation, racemization, etc.). However, a fluorine atom placed next to this developing negative charge can suffer elimination to produce a reaction

(65) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579–3582.
(66) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.;ACS Symposium Series 911; American Chemical Society: Washington, DC, 2005.
(67) Kirk, K. L. *Curr. Top. Med. Chem.* **2006**, *6*, 1447–1456.
(68) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.
(69) Isanbor, C.; O'Hagan, D. *J. Fluorine Chem.* **2006**, *127*, 303–319.
(70) Bégué, J.-P.; Bonnet-Delpon, D. *J. Fluorine Chem.* **2006**, *127*, 992–1012.
(71) Reviewed by: Santi, D. V.; Pogolotti, A. L.; Newman, E. M.; Wataya, Y. In *Biomedicinal Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo, Elsevier Biomedical: Amsterdam, 1982; pp 123–142..
(72) Osterman, D. G.; DePillis, G. D.; Wu, J. C.; Matsuda, A.; Santi, D. V. *Biochemistry* **1988**, *27*, 5204–5210.
(73) Chen, L.; MacMillan, A. M.; Chang, W.; Ezaz-Nikpay, K.; Lane, W. S.; Verdine, G. L. *Biochemistry* **1991**, *30*, 11018–11025.

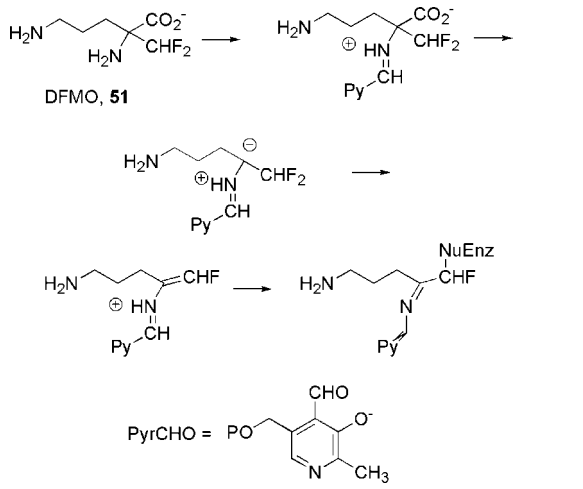


Figure 15. **DFMO (Eflornithine), an irreversible inhibitor of PLP-dependent ornithine decarboxylase.**

intermediate that is subject to attack by an enzyme active site nucleophile, an attack that can lead to irreversible inhibition. An example of this mechanism of inhibition is shown for difluoromethylene ornithine (DFMO) (**51**) (Figure 15). This was developed as an inhibitor of ornithine decarboxylase as a strategy to block polyamine biosynthesis.[74] Despite early promise as an anticancer agent from in vitro studies, subsequent in vivo studies failed to show sustained antitumor effects, showing chemostatic rather than chemotoxic effects.[75] DFMO is an effective drug for the treatment of African sleeping sickness.

Nucleophilic displacement of fluoride also has been the basis of enzyme inhibitor design. For example, fluoromethyl ketone-containing peptides have been prepared as irreversible cysteine protease inhibitors based on S_N2 displacement of fluoride. This topic has been reviewed recently.[76] In another example, S_NAr displacement of fluoride from a pentafluorophenyl group in the anticancer agent T138067 (**52**) leads to irreversible inhibition of tubulin (Scheme 43).[77]

7.2. Effects of Fluorine Substitution on Adjacent Functional Groups. *7.2.1. Increased Hydrolytic Stability of Acid-Labile Groups.* The inductive effect of a β-fluorine substituent greatly destabilizes a developing positive charge. For this reason a reaction that proceeds through a carbocation intermediate can be substantially inhibited by selective introduction of fluorine. There are many examples of stabilization of otherwise acid-labile biologically active molecules by this strategy. Included is development of orally active 2′-β-fluoro-dideoxyadenosine (F-ara-ddA) (DDA)[78] and similar fluorinated nucleosides that resist the action of stomach acid. Stabilization of enol ethers and oxetanes is found in the examples of fluorinated prostacycline inhibitors **53** and**54** and the thromboxane derivative **55** (Figure 16).[79,80]

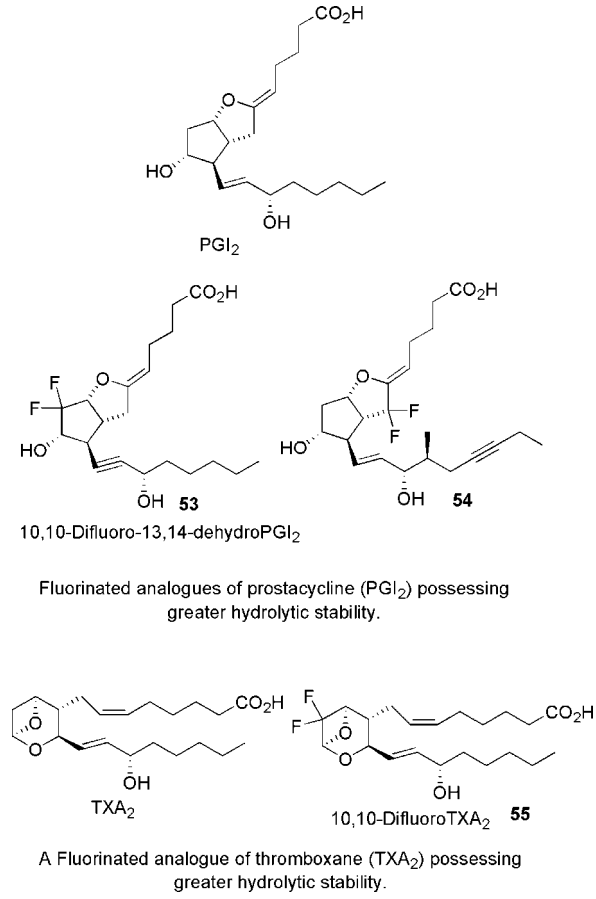
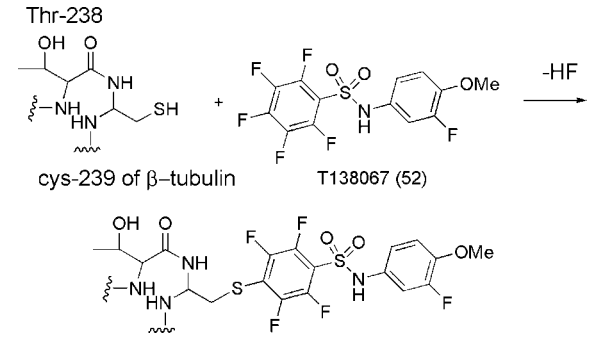


Figure 16. **Examples of fluorinated prostanoids having increased hydrolytic stability.**

Scheme 43



7.2.2. Enhancement of Electrophilicity in Enzyme Inhibitors. Fluorine will increase the electrophilicity of adjacent functional groups. This has been used extensively to design inhibitors of proteolytic enzymes. Early work was based on the so-called statine strategy. A microbially produced pentapetide, pepstatin **56**, is a potent general inhibitor of aspartyl proteases. A

(74) Metcalf, B. W.; Bey, P.; Danzin, C.; Jung, M. J.; Casara, P.; Vevert, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 2551–2553.
(75) Wallace, H. M.; Fraser, A. V.; Hughes, A. *Biochem. J.* **2003**, *376*, 1–14.
(76) Sani, M.; Sinisi, R.; Viani, F. *Curr. Top. Med. Chem.* **2006**, *6*, 1545–1566.
(77) Shan, B.; Medina, J. C.; Santha, E.; Frankmoelle, W. P.; Chou, T.-C.; Learned, R. M.; Narbut, M. R.; Stott, D.; Wu, P.; Jaen, J. C.; Rosen, T.; Timmermans, P. B. M. W. M.; Beckmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 5686–5691.
(78) Marquez, V. E.; Tseng, C. K.-H.; Kelley, J. A.; Mitsuya, H.; Broder, S.; Roth, J. S.; Driscoll, J. S. *Biochem. Pharmacol.* **1987**, *36*, 2719–2722.
(79) Morinelli, T. A.; Okwu, A. K.; Mais, D. E.; Halushka, P. V.; John, V.; Chen, C.-K.; Fried, J. *Proc. Natl. Acad. Sci. U.S.A.* **1989**, *86*, 5600–5604.
(80) For a review, see: Matsumura, Y.; Nakano, T.; Asai, T.; Morizawa, Y. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.;ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; pp 83–94..

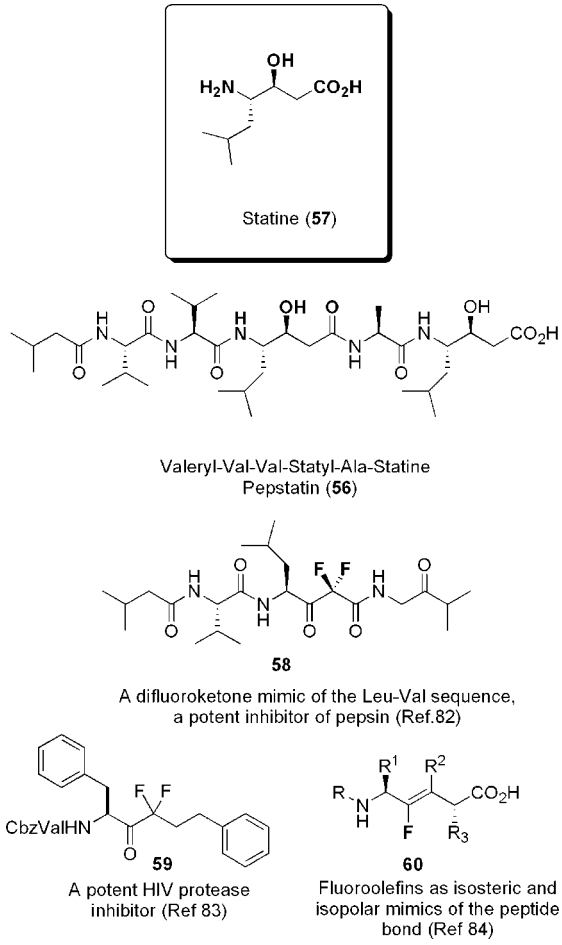


Figure 17. **Fluorinated isosteres of amide linkages as inhibitors of proteolytic enzymes.**

comparison of the structures of statine **57**, a unique residue in pepstatin, and the tetrahedral intermediate that would be formed during the pepsin-catalyzed cleavage of the Leu-Val sequence of peptides suggested that pepstatin and other statine-containing peptides could function as transition state analogue inhibitors of aspartyl proteases.[81] Subsequent work produced difluoroketone-containing analogues that either become hydrated and serve as mimics of the tetrahedral intermediate or are subject to attack by an active site nucleophile of proteases. Pepsin inhibitors, for example, **58**, represent early examples of many such inhibitors for a wide range of applications.[76,82] HIV protease inhibitors, for example, **59**, were later developed,[83] and other fluorine-based mimics of the scissile bonds were produced, including fluoroolefins such as **60**, as exemplified by the work of Allmendinger and co-workers (Figure 17).[84]

7.3. CFH and CF_2 as Replacements for O. Research reported by Blackburn and co-workers in the 1980s revealed the advantages of replacement of oxygen with fluoromethylene or difluoromethylene groups in the design of hydrolytically

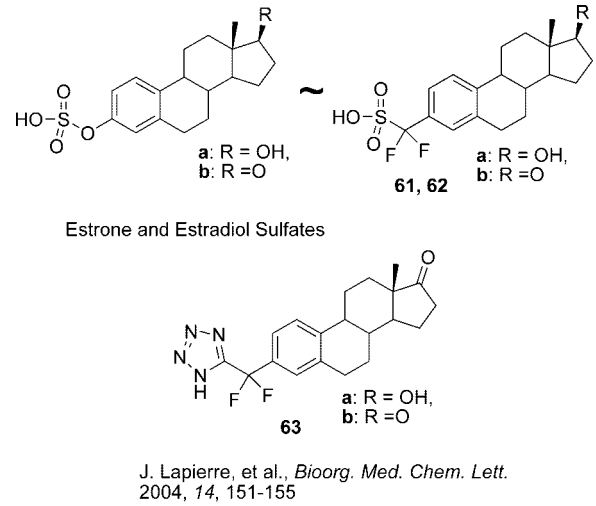


Figure 18. **Difluorophospnonates as isosteric and isopolar analogues of biologically important phosphate esters.**

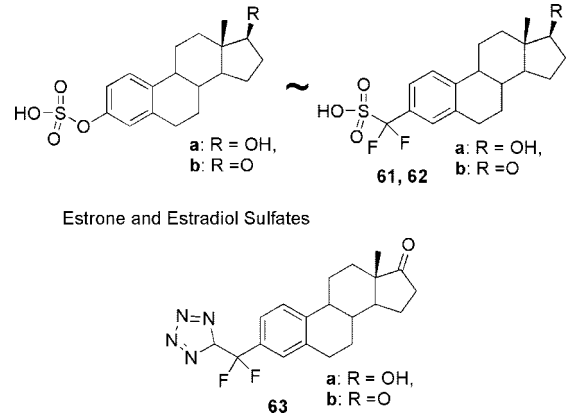


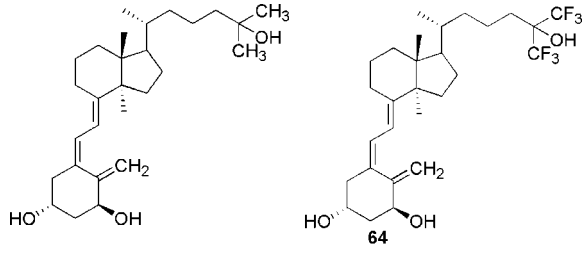
Figure 19. **Difluoromethylene as a replacement for oxygen in hydrolytically stable sulfate ester isosters.**

stable analogues of phosphate esters.[85] This approach has been applied to sugar phosphates, nucleosides, phosphoserine,[86] phosphoenolpruvate,[87] phosphotyrosine,[88] and others (Figure 18). A recent review has been published with an emphasis on α-monofluoroalkylphosphonates.[89]

There is evidence that stored steroid sulfates, through the action of steroid sulfatases, can function as a reservoir of steroids that produce estrogens in breast tumors. Taylor and co-workers have prepared estrone and estradiol sulfate analogues in which the sulfate ester was replaced by α,α-difluoromethylenesulfanate or α,α-difluoromethylene tetrazole group (**61** and **62**) (Figure 19).[90] The fluorinated analogues were more potent inhibitors of steroid sulfatases than their nonfluorinated sulfanate, and the tetrazole inhibitor **63** had an affinity for steroid sulfatase comparable to the natural substrate.

(81) Marciniszyn, J., Jr.; Hartsuck, J. A.; Tang, J. *J. Biol. Chem.* **1976**, *251*, 7088–7094.
(82) Gelb, M. H.; Svaren, J. P.; Abeles, R. H. *Biochemistry* **1985**, *24*, 1813–1817.
(83) Sham, H. L.; Betebenner, D. A.; Wideburg, N. E.; Kemph, D. J.; Plattner, J. J.; Norbeck, D. W. *J. Fluorine Chem.* **1995**, *73*, 221–224.
(84) Allmendinger, T.; Furet, P.; Hungerbühler, E. *Tetrahedron Lett.* **1990**, *31*, 7297–7300.
(85) Blackburn, B. M.; Perree, T. D.; Rashid, A.; Bisbal, C.; Lebleu, B. *Chem. Scr.* **1986**, *26*, 21–24.
(86) Berkowitz, D. B.; Shen, Q.; Maeng, J.-H. *Tetrahedron. Lett.* **1994**, *35*, 6445–6448. Otaka, A.; Miyoshi, K.; Burke, T. R.; Roller, P. P.; Kubota, H.; Tamamura, H.; Fujii, N. *Tetrahedron Lett.* **1995**, *36*, 927–930.
(87) Phillion, D. P.; Cleary, D. G. *J. Org. Chem.* **1992**, *57*, 2763–2764.
(88) Burke, T. R., Jr. *Current Topics Med. Chem.* **2006**, *14*, 1465–1471. Smyth, M. S.; Burke, T. R. *Tetrahedron Lett.* **1994**, *35*, 551–554.
(89) Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13–33.
(90) Lapierre, J.; Ahmed, V.; Chen, M.-J.; Ispahany, M.; Guillemette, J. G.; Taylor, S. D. *Biorg. Med. Chem. Lett.* **2004**, *14*, 151–155.

Scheme 44



7.4. Fluorine Substitution To Block Metabolism. Control of oxidative metabolism by fluorine substitution has become a very important strategy in drug development. Chemical intuition and experience can aid in the decision as to where fluorine substitution may serve a desired purpose. In addition, likely sites of metabolism of molecules by cytochrome P450 enzymes can now be predicted by computational methods.[91]

7.4.1. Aliphatic C-F Substitution. The high bond energy and heat of formation of the C-O bond and H-O bond relative to the F-O bond essentially excludes oxidative attack at fluorine. In addition, field effects retard oxidation of C-H bonds adjacent to CF_3 and perfluoro groups. An example of increased metabolic stability of a fluorinated analogue is found in the development of falicalcitral (**64**), a metabolically stabilized analogue of vitamin D_3 marketed in 2001 for the treatment of hyperthyroidism. In this case, C-24 hydroxylation is blocked by the presence of trifluoromethyl substituents (Scheme 44).[92]

7.4.2. Aromatic C-F Substitution. As shown by the early work of Kaufmann, fluorine substitution will greatly retard oxidation of an aromatic ring, if not invariably block it.[93] There exist many published examples of the successful use of this strategy. The development of ezitimibe (**65**), a recently licensed drug used to block cholesterol absorption, offers a good example. In optimization studies involving synthesis of a series of phenolic azetidinones, it was determined that metabolic oxidation at certain positions of **66** enhanced cholesterol lowering activity whereas oxidation at other positions decreased activity. Selective substitution of fluorine was used to block unwanted metabolic oxidation, and the drug ezetimibe was produced (Figure 20). Administration of Ezetimibe together with statins results in dramatic lowering of serum cholesterol. Ezetimibe was licensed in 2002.[94]

7.5. Effect of Fluorine Substitution on Conformation. Discussion continues on the ability of covalently bound fluorine to function as a hydrogen bond acceptor. Several analyses of this issue suggest that such hydrogen bonds are, at best, rare and quite weak,[95] although stabilization of conformations through intramolecular hydrogen bonds have been invoked to rationalize increased activity of fluorinated analogues.[96]

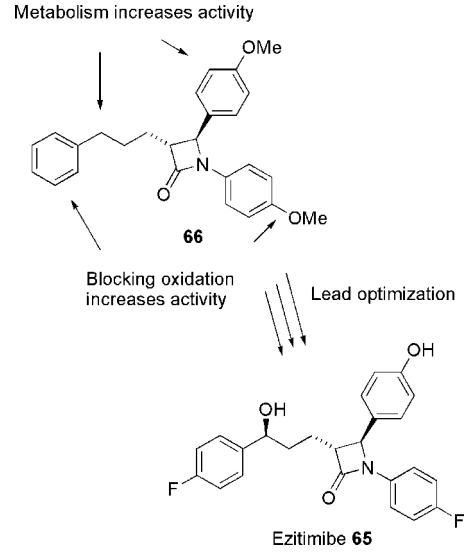


Figure 20. **Selective fluorination in the development of the cholesterol transport inhibitor, Ezetimibe.**

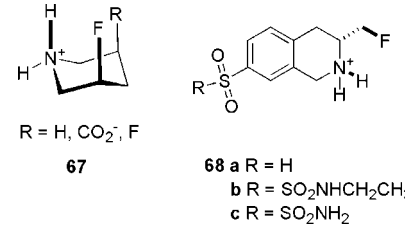


Figure 21. **Conformational effects of the C-F bond interacting with the $^{+}$H-N dipole.**

The C-F bond has a permanent dipole that can exert a localized effect on conformational equilibria. Snyder and co-workers have reported that the 3-fluoropiperidines (**67**) (R = H, CO_2^-, F) prefer axial to equatorial orientation by a 96–100:1 ratio as a result of attractive interactions between appropriately situated C-F and $^{+}$H-N dipoles.[97] This observation was extended to include the flexible 1,2,3,4-tetrahydroisoquinolines (THIQ) **68a,b** that contain a freely rotatable exocyclic fluoromethylene group (Figure 21). Grunewald and co-workers have used the 3-fluoromethyl-tetrahydroisoquinoline motif in the development of potent inhibitors of phenethanolamine *N*-methyltransferase (PNMT) that possess low affinity for the α_2-adrenergic receptor.[98] Conformational analysis of *R*-**68c** in the neutral form shows the global minimum to exist in which the 3-fluoromethyl group is equatorial and the THIQ nitrogen lone pair is axial, similar to that found in the protonated piperidinium system in the previous studies. Docking experiments with *R*-**68b** indicate it exists in this same conformation when bound to the active site of PNMT.

Fluorine substitution on the glycon can alter the conformation of nucleosides. Barchi and co-workers have carried out conformational analyses on the complete series of 2′- and

(91) Cruciani, G.; Carosati, E.; De Boeck, B.; Ethirajulu, K.; Mackie, C.; Howe, T.; Vianello, R. *J. Med. Chem.* **2005**, *48*, 6970–6979.
(92) Tanaka, Y.; DeLuca, H. F.; Kobayashi, Y.; Ikekawa, N. *Arch. Biochem. Biophys.* **1984**, *229*, 348–354.
(93) Kaufman, S. *Biochem. Biophys. Acta* **1961**, *51*, 619–621.
(94) Clader, J. W. *J. Med. Chem.* **2004**, *47*, 1–9.
(95) Dunitz, J. D.; Taylor, R. *Chem. Eur. J.* **1997**, *3*, 89–98.
(96) Nomura, M.; Kinoshita, S.; Satoh, H.; Maeda, T.; Murakami, K.; Tsunoda, M.; Miyachi, H.; Awano, K. *Biorg. Med. Chem. Lett.* **1999**, *9*, 533–538.
(97) Synder, J. P.; Chandrakumar, N. S.; Sato, H.; Lankin, D. C. *J. Am. Chem. Soc.* **2000**, *122*, 544–545.
(98) Grunewald, G. L.; Romero, F. A.; Criscione, K. R. *J. Med. Chem.* **2005**, *48*, 1806–1812.

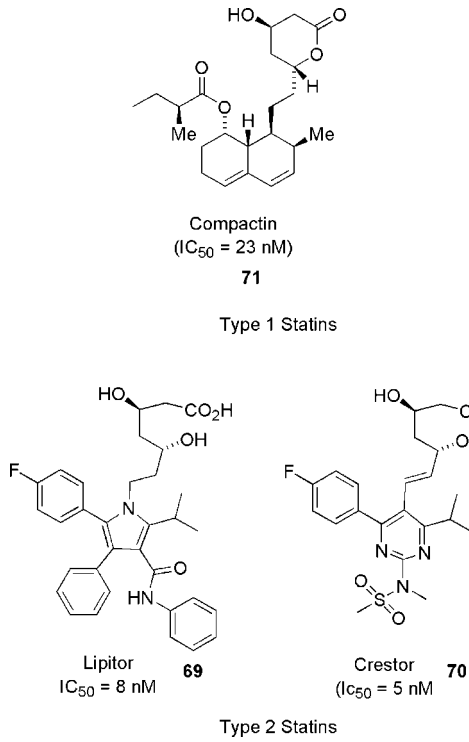
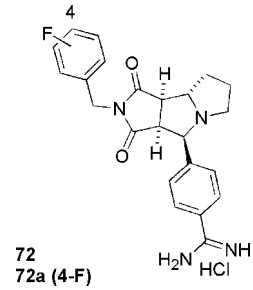


Figure 22. **A *p*-fluorophenyl group is an important structural feature of type 2 statins.**

3′-monofluorinated dideoxyuridines and provide a thorough discussion of the effects of fluorine substitution on north and south (N/S) puckering equilibria.[99]

7.6. Intermolecular Effects of Fluorine Substitution. Noncovalent intermolecular interactions of the C-F bond can play an important part in affinity of a drug with a macromolecular recognition site and much is now being revealed about such interactions through X-ray crystallography and other analytical techniques. For example, in second generation type 2 statins [exemplified by Lipitor (**69**) and Crestar (**70**)], the presence of a 4-fluorophenyl group results in increased affinities for HMG-CoA reductase as compared to affinities of type 1 statins [e.g., Compactin (**71**)] (Figure 22). An X-ray structure of lipitor cocrystallized with HMG-CoA reductase revealed that the guanidinium group of the enzyme stacks on the fluorophenyl group, with polar interactions between the arginine ϵ-nitrogens and the fluorine atom.[100]

Favorable interactions of the C-F moiety with strong H-bond donors (N-H of backbone amide bonds, His side chains, OH groups from Tyr, Ser, and bound water) have been reported in the literature. Favorable interactions also can be formed between C-F and lipophilic side chains such as aromatic residues present as Phe. In addition, aromatic C-F can affect aromatic–aromatic interactions through alterations of the electronic characteristics of the aromatic rings. In one example of research designed to study intermolecular interactions of the C-F bond, Müller, Diederich and co-workers examined a series of fluorinated thrombin inhibitors **72** in which fluorine atoms were systematically placed at all positions of the benzyl group (termed a fluorine scan) known to reach into the D-pocket of the active site. The 4-fluorobenzyl derivative **72a** was significantly more active than the nonfluorinated or other fluorinated congeners. X-ray crystal structure analysis of the inhibitor-protein complex showed favorable interactions of the C-F bond with the backbone Asn98 involving C-F···H-C_α–C=O and C-F···C=O attractions.[101]



Recently, fluorophilic effects such as the above have been described in terms of polar hydrophobicity.[102] Stabilization of C-F dipoles in the preorganized protein receptor and a gain in entropy resulting from desolvation of the ligand are two factors that are predicted to enhance affinity significantly. As an alternative explanation of the relative affinities of the thrombin inhibitors in the above example, nonfavorable interactions of the 2- and 3-fluoro derivatives would be compensated by the increased hydrophobic surface area of the molecule that provides a driving force for binding, resulting in little change in K_i. In the 4-fluoro derivative, the dipolar hydrophobic effect is augmented by a favorable weak C-F···C=O interaction. A recent review on the importance of weak interactions of the aromatic C-F bond has been published.[103]

As noted above, several analyses suggest that hydrogen bonds with the C-F bond as acceptor are, at best, rare and quite weak.[95] On the other hand, a recent analysis of all proteins contained in the protein data bank that had been crystallized with fluorinated ligands indicated that in 18% of the complexes fluorine participated in weak hydrogen bonds.[104]

7.7. Summary. This section has given a very brief overview of selected rational approaches to the exploitation of fluorine substitution in drug design. With the advent of such empirical tools as high throughput screening, combinatorial and parallel syntheses, and the abundant array of new reagents for introduction of fluorine, a more general strategy has evolved. Thus, incorporation of fluorine into a molecule is now a frequently used strategy in lead optimization. This of course will be done with some prior knowledge of possible effects, but the results of such substitution clearly are not predictable with a high degree of certainty. In fact, the results of evaluation of new fluorinated biologically active compounds are adding

(99) Barchi, J. J., Jr.; Jeong, L.-S.; Siddiqui, M. A.; Marquez, V. E. *J. Biochem. Biophys. Methods* **1997**, *34*, 11–29.
(100) Istvan, E. S.; Deisenhofer, J. *Science* **2001**, *292*, 1160–1164.
(101) Olsen, J. A.; Banner, D. W.; Seiler, P.; Wagner, B.; Tschopp, T.; Obst-Sander, U.; Kansy, M.; Müller, K.; Diedrich, F. A. *ChemBioChem* **2004**, *5*, 666–675.
(102) Biffinger, J. C.; Kim, H. W.; DiMagno, S. G. *ChemBioChem* **2004**, *5*, 622–627.

greatly to the knowledge of how fluorine can affect biological properties. Thus, there is a synergistic relationship between the chemistry and biology of fluorinated molecules.

8. Final Comments

The role of fluorine in drug development and design continues to expand. The pressure to develop new methods for introduction of fluorine into organic molecules has led to many procedures that are simple, convenient, and versatile. This has increased the availability of fluorinated analogues for expanded biological evaluation. In this review, the attempt has been made to highlight both aspects of this broad area.

(103) DiMagno, S.; Sun, H. *Curr. Top. Med. Chem.* **2006**, *6*, 1473–1482.
(104) Carosati, E.; Sciabola, S.; Cruciani, G. *J. Med. Chem.* **2004**, *47*, 5114–5125.

Acknowledgment

This project was supported by the intramural research funds of NIDDK, NIH.

Received for review June 14, 2007.

OP700134J