

CHEMICAL FLUORINATION OF ORGANIC COMPOUNDS

Vasile DINOIU^{a*}

^aRoumanian Academy, Institute of Organic Chemistry “C. D. Nenitzescu”, Spl. Independentei 202B,
77141 Bucharest, Roumania

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This review covers the recent remarkable advances in chemical fluorination of organic compounds such as olefins, aromatic compounds, carbonyl compounds, heteroatom compounds and heterocycles. Mono-, di- and trifluorination are discussed.

INTRODUCTION

Very few fields in chemistry have shown such a considerable interest as fluoroorganic chemistry. Fluorine is perhaps the element that has experienced the greatest recent interest as pointed out by the exceptionally high number of publications and the high percentage of fluorinated new molecules over recent decades.¹ Today, the significant expansion in the use of fluorinated chemicals has attracted the attention of organic, agricultural, medicinal, and material chemists.²⁻¹⁰ The replacement of hydrogen by fluorine, the most electronegative element, alters sterically and electronically the properties of the molecules, affecting the basicity or acidity of neighboring groups, dipole moment, and overall reactivity and stability. Fluorine is often regarded as an isostere of hydrogen despite the fact that their van der Waals radii are different (1.47 versus 1.20 Å).¹¹ The carbon-fluorine bond length (1.39 Å) is similar to the carbon-oxygen one (1.43 Å), suggesting an isosteric behavior. The high carbon-fluorine bond energy (485.7 kJ/mol)¹² confers relative stability against metabolic transformations. In addition, fluorine can participate in hydrogen bonding interactions with H-C even if hydrogen bonds to C-F are definitely much weaker than those observed to oxygen or nitrogen.^{13,14} Nevertheless, the controversy remains on the existence of hydrogen bonds between the C-F group and -OH or -NH donors.¹⁵⁻¹⁷ With regard to the CF₃ group, its size

(van der Waals volume) is relatively large, between those of the *i*-Pr and the *t*-Bu groups.¹⁸ The CF₃ group has an electronegativity similar to that of oxygen¹⁹ and a large hydrophobic parameter.²⁰ The trifluoromethyl group appears in many biologically active pharmaceutical and agrochemical compounds. The increased lipophilicity and a superior metabolic stability compared to that of the trimethyl analogues, often accounts for an improved activity profile. Higher fluoroalkyl groups, which are the perfluoroalkyl groups, are introduced mainly to increase the lipophilicity, and also in the context of fluorous chemistry.²¹

Partially fluorinated organic compounds are prepared by two different approaches: (i) by insertion of a group already containing C-F bonds into an existing molecule (the building-block approach), or (ii) by creating new C-F bonds by fluorination.

MONOFLUORINATION OF ORGANIC COMPOUNDS

Electrophilic fluorination is one of the most direct methods for selective introduction of fluorine into organic compounds. Elemental fluorine, F₂, itself is one of the most powerful reagents.²² However, fluoroxy compounds, such as CF₃OF²³, FClO₃,²⁴ CF₃COOF,²⁵ CH₃COOF,²⁶ and CsSO₄F²⁷, some of which are generated in situ, are exciting reagents for the introduction of fluorine electrophilically into a wide variety of organic compounds.

* E-mail address: vdinoiu@yahoo.com

The rather hazardous perchloryl fluoride has lost favor to other electrophiles, including xenon difluoride, XeF₂, which has been employed as a particularly interesting and easily handled source of electrophilic fluorine.²⁸

More recently, much attention has been given to new N-F, C-F, or S-F compounds that are generally somewhat less reactive than the fluoroxy reagents described above, but nevertheless they have proved to be particularly useful with a wide range of organic nucleophiles.

DAST (Diethylaminosulfur trifluoride), Et₂NSF₃

DAST (Fig. 1) has proven to be an extremely popular reagent for nucleophilic fluorination, due

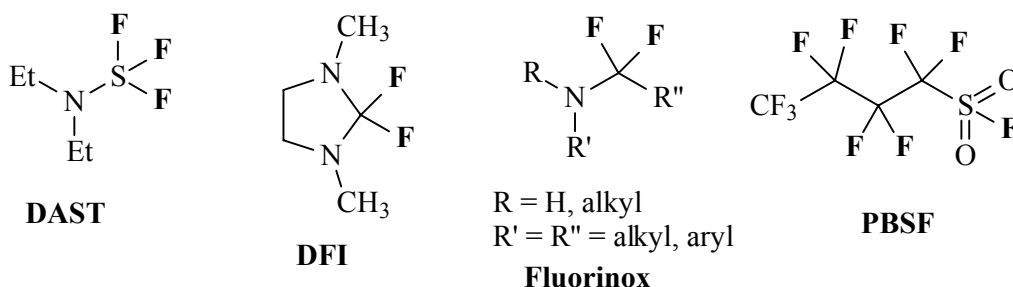
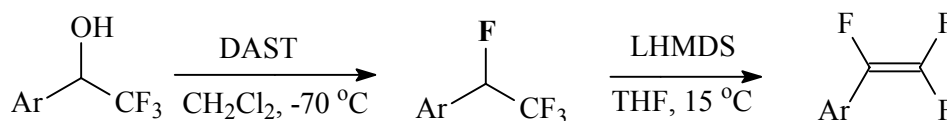


Fig. 1



Scheme 1

Because DAST is made from very toxic and corrosive SF₄ and decomposes spontaneously, new milder and more stable fluorinating reagents were developed. Perfluoro-1-butanefluoride (PBSF) is a nontoxic, easily handled reagent used in the stereoselective substitution of an alcohol by fluorine, on a highly functionalized chiral substrate.

Fluorinox and DFI (Fig. 1), like DAST, exchange fluorine for hydroxyl groups but they are more stable.

DEOXOFLUOR [(CH₃OCH₂CH₂)₂NSF₃]

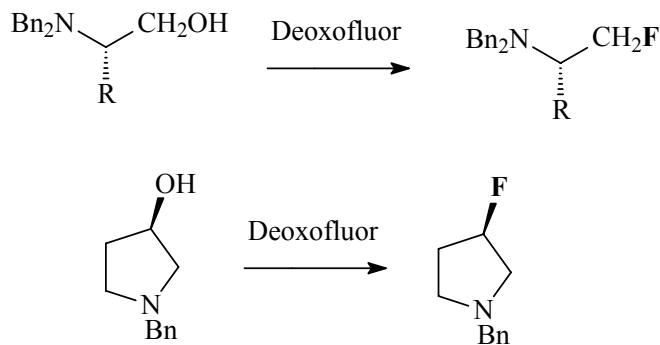
The Deoxo-Fluor™ reagent, (Fig. 2), is a versatile, easy-to-use, nucleophilic fluorinating reagent with enhanced safety features. It rapidly "deoxofluorinates" a wide variety of alcohols, aldehydes, ketones and sulfoxides under mild

to its ease of handling and versatility. It has regularly been employed in selective fluorination of alcohols, carbohydrates, ketones, sulfides, epoxides, thioethers and cyanohydrins. In addition some novel organic cyclizations are possible when DAST was used as a reagent.²⁹ For example, 1,2,2-trifluorostyrene can be synthesized using a sequential reaction on the parent α-(trifluoromethyl)phenylethanol with DAST, followed by dehydrohalogenation with lithium bis(trimethylsilyl)amide (LHMDS). This method achieves the trifluorostyrene without requirement of palladium coupling (Scheme 1).³⁰

conditions to yield the corresponding fluorinated compounds with high efficiency and selectivity. Various fluorinated chiral compounds were synthesized by the reactions of amino alcohols with bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) (Scheme 2).³¹

SELECTFLUOR

More recently, much attention has been given to the fluoronitrogen compounds. Selectfluor, 1-chloromethyl-4-fluoro-1, 4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) or F-TEDA (Fig. 2) is a user-friendly, mild, air- and moisture-stable, non-volatile reagent for electrophilic fluorination in one step, with excellent regioselectivity. An example is the regioselective fluorination of pyrimidine bases (Scheme 3).³²



Scheme 2

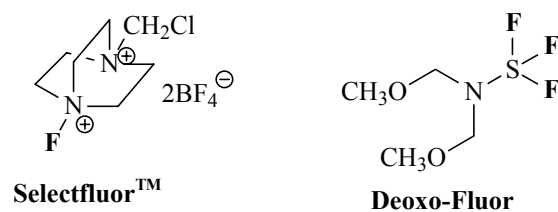
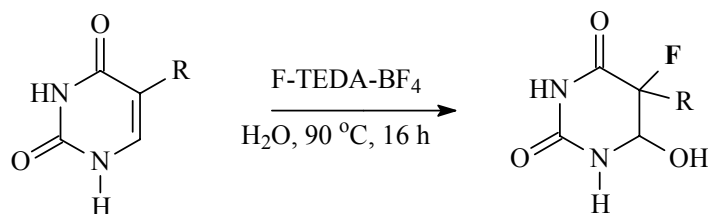


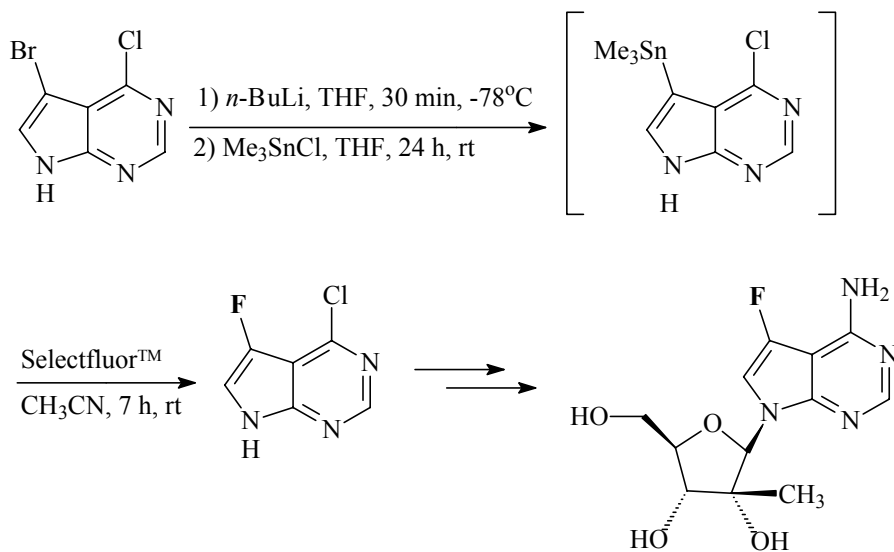
Fig. 2



Scheme 3

Recently, a synthesis of a potent and noncytotoxic nucleoside inhibitor of Hepatitis C virus RNA application was accomplished using

Selectfluor (Scheme 4). This ribonucleoside shows a significantly improved enzymatic stability profile compared to the parent 2'-C-methyladenosine.³³



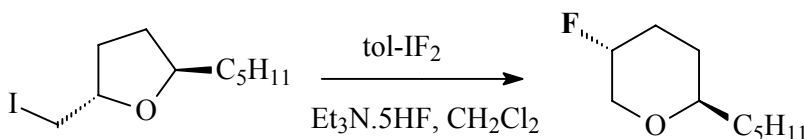
Scheme 4

Selectfluor is considered a good alternative to harsher methods, especially for high-value compounds. The electrophilic reagent acts essentially as a stoichiometric source of F^+ and can fluorinate specific positions in a range of substrates.

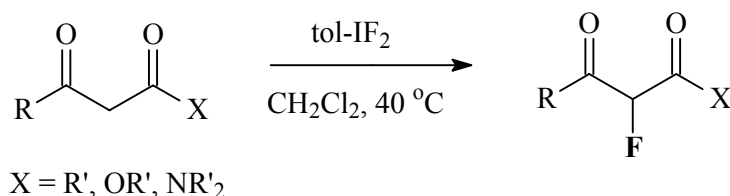
Selectfluor and Deoxo-Fluor were created to deliver fluorine to the pharmaceutical industry through a safe and effective material. Deoxo-Fluor is an easy-to-use, stable liquid that is cost-efficient and more amenable than DAST to large-scale applications. Similarly, Selectfluor consists of thermally stable, free-flowing crystals.

IODOTOLUENE DIFLUORIDE - a new and mild fluorination reagent

Elemental fluorine and many electrophilic fluorinating agents have been used in synthesis;



Scheme 5



Scheme 6

N-FLUOROPYRIDINIUM SALTS

The *N*-fluoropyridinium salts are particularly useful as electrophilic fluorinating agents toward organic compounds in terms of easy handling and variability of fluorinating power and selectivity. This variability makes selective fluorination of a wide range of organic compounds differing in reactivity possible. Three classes of power- and selectivity-variable fluorinating agents, non-counterion-bound *N*-fluoropyridinium salt series, counterion-bound *N*-fluoropyridinium-sulfonate series, and dimeric *N,N'*-difluorobipyridinium salt series, were developed and successfully utilized for selective fluorinations of various substrates.

N-Fluoropyridinium trifluoromethanesulfonate (triflate) and its analogs (Fig. 3) are widely applicable, stable fluorinating agents with varying degrees of power and selectivity in fluorinations.³⁶⁻⁴⁵

however, most of these fluorinating agents are highly aggressive, unstable, and require special equipment and care for safe handling. By contrast, iodotoluene difluoride (tol-IF₂) is easy to handle, and is less toxic than many fluorinating agents.

A new methodology for the synthesis of fluorinated cyclic ethers was recently reported, which utilized tol-IF₂ to achieve a fluorinative ring-expansion of four-, five-, and six-membered rings, an example of which is illustrated below (Scheme 5).³⁴

Selective monofluorination of β -ketoesters, β -ketoamides, and β -diketones takes place without requirement of HF-amine complexes under mild conditions (Scheme 6). The formation of difluoro products were not detected in these reactions.³⁵

The reagents are all stable, crystalline materials and thus can be handled routinely. It should be noticed that the relative stability of the *N*-fluoropyridinium salts decreases with increasing fluorinating power. Examples of fluorinations which illustrate their use are given in Table I. The weakest reagent, **2**, is most suited for fluorinating reactive or easily oxidized compounds, such as carbanions, enamines, and sulfides, whereas the most potent reagents **4** and **5** are preferred for fluorinating alkenes and aromatic rings.

N-Fluoropyridinium triflate shows high regioselectivity in its fluorinations, as evidenced by the results in Scheme 7.⁴⁶ With steroids **6** and **8**, each having two reactive sites, **1** reacts to give exclusively the 6-fluoro steroid **7** and the 16-fluoro steroid **9**, respectively. Thus **1** can distinguish between a conjugated and a nonconjugated vinyl acetate, and between an enol silyl ether and a

conjugated vinyl acetate in its fluorinations. The present procedure for converting estrone enol silyl ether to 16 α -fluoroestrone also shows that **1**

selectively reacts with an enol silyl ether moiety in the presence of an activated aromatic ring.

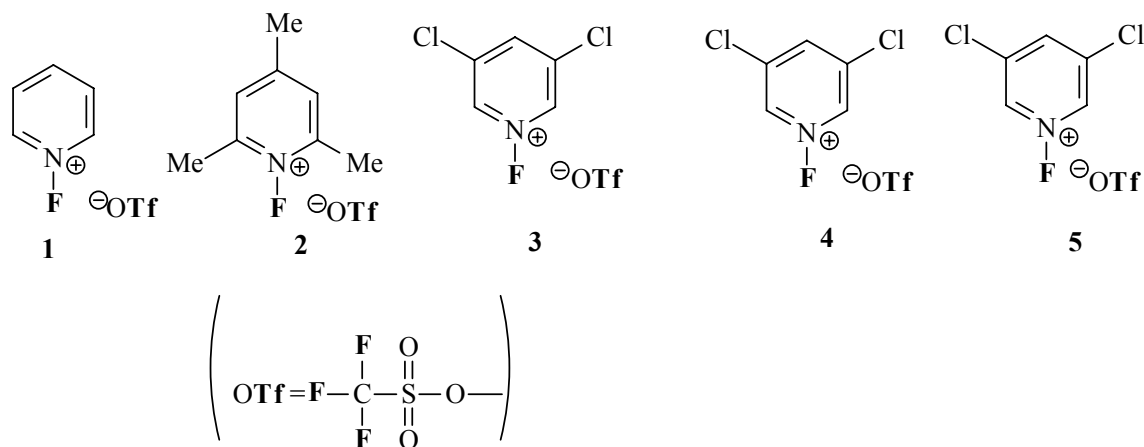
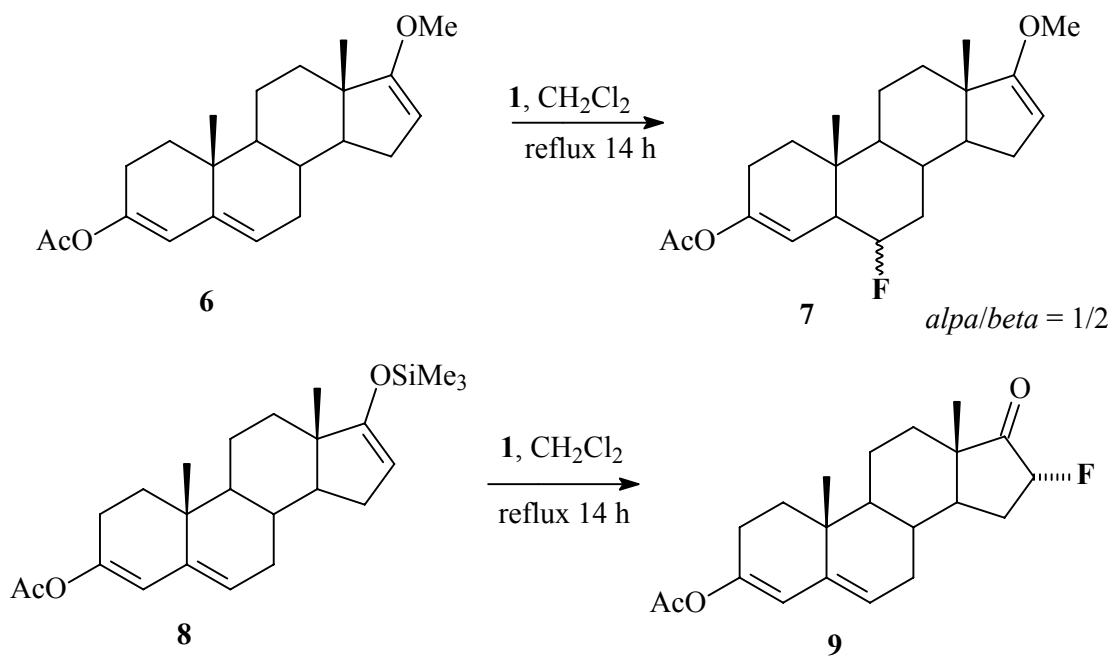


Fig. 3



Scheme 7

HALOGEN EXCHANGE, a selective aliphatic fluorination by in mild conditions

Fluorine–chlorine exchange is the most widely used technology to synthesize fluorinated molecules. When this exchange reaction occurs in an aliphatic molecule or at the benzylic position, anhydrous hydrogen fluoride is the most versatile industrial reagent. The limitation of this technology

comes from the acidity of anhydrous HF. Its use on fragile or functionalized molecules is limited due to formation of cationic intermediates and undesired side reactions. Alternatives to or improved versions of traditional fluorination reagents are being developed by companies with fluorine chemistry expertise. The early fluorinating reagent pyridinium poly(HF), or Olah's reagent, was discovered by Nobel Laureate George A. Olah

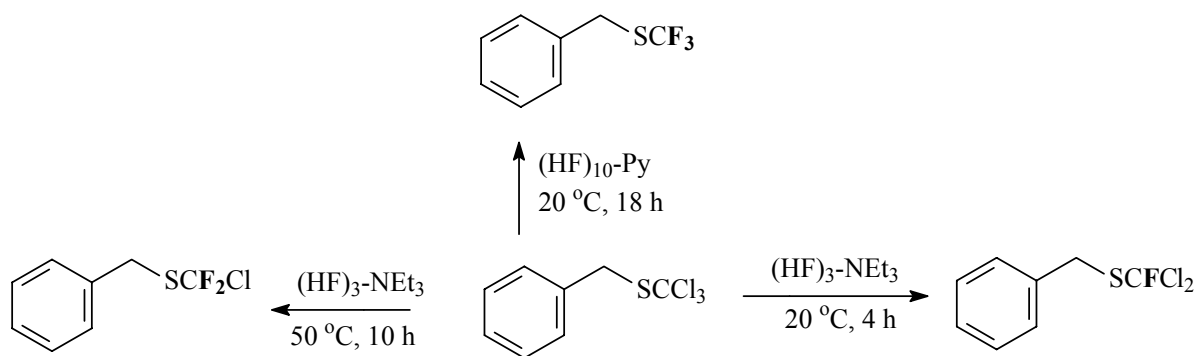
in the late 1970s. Since then, many other nitrogen-based structures have emerged; with the general form R_2N-F or R_3N^+-F , they are often called the N-F or $[N-F]^+$ reagents, respectively.

Daikin Industries offers several derivatized pyridinium compounds in lab and bulk scale, including *N,N'*-difluoro-2,2'-bipyridinium bis(tetrafluoroborate). DuPont makes *N,N*-dimethyl-1,1,2,2-tetrafluoroethylamine (TFEDMA), the dimethylamine adduct of tetrafluoroethylene (TFE), available on a research scale. Mitsui Chemicals, which makes fluorinated materials for electronics applications, also sells 2,2,-difluoro-1,3-dimethylimidazolidine (DFI), which exchanges hydroxyl groups and carbonyls for fluorine, as a low-cost and more stable alternative to DAST.

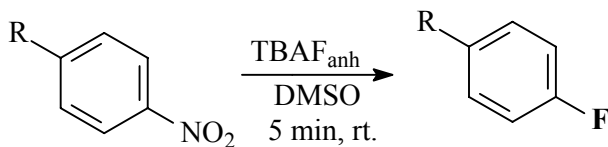
In a paper published in 2006, Laurent Saint-Jalmes⁴⁷ reported new fluorinating reagents based on HF-Base media, in particular $(HF)_{10}$ -pyridine or $(HF)_3$ -triethylamine that allow aliphatic chlorine-fluorine exchanges on acid-sensitive molecules without side reactions involving carbocation intermediates. Depending on the nature (pyridine or triethylamine), stoichiometry of the base and temperature, selective mono-, di-, or tri-chlorine-fluorine exchanges on trichloromethyl groups alpha to sulfur, oxygen and carbon atoms can be obtained. For example the use of $(HF)_{10}$ -pyridine and $(HF)_3$ -triethylamine on trichloromethylbenzyl sulfide **1** give the results shown in Scheme.

Trichloromethylbenzyl sulfide **1** is totally fluorinated at 20 °C in 18 h in $(HF)_{10}$ -pyridine (40 molar equivalents of HF) and leads to trifluoromethylbenzyl sulfide **2** with 94% selectivity (¹⁹F NMR assay) and 85% isolated yield. Surprisingly $(HF)_3$ -triethylamine (50 molar equivalents of HF) leads to selective fluorination on trichloromethylbenzyl sulfide **1** through exchange of one or two chlorine atoms depending on the temperature; at 20 °C in 4 h monofluorodichlorobenzyl sulfide **3** is obtained with 90% selectivity, at 50 °C in 10 h difluorochlorobenzyl sulfide **4** is obtained with 88% selectivity (Scheme 8). These results are in accordance with the lower acidity of $(HF)_3$ -triethylamine compared to $(HF)_{10}$ -pyridine; the less acidic is the medium of fluorination the lower is the rate of chlorine-fluorine exchange.

Recently, chemistry Professor Stephen G. DiMugno at the University of Nebraska, Lincoln, USA, has used tetrabutylammonium fluoride (TBAF) for Halex and fluorodenitration reactions.⁴⁸ His group found that anhydrous TBAF_{anh} in dimethylsulfoxide works well under mild conditions as a fluorinating reagent for activated ring systems (Scheme 9). The results suggest that ion pairing and solvation are the factors that limit the impressive nucleophilicity of the fluoride ion under conditions typically employed for nucleophilic aromatic substitution.



Scheme 8

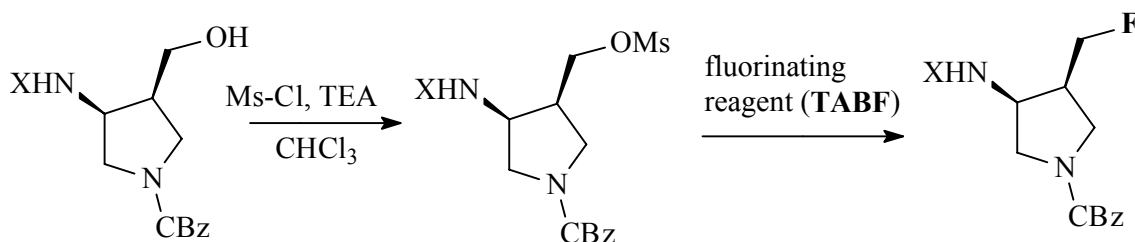
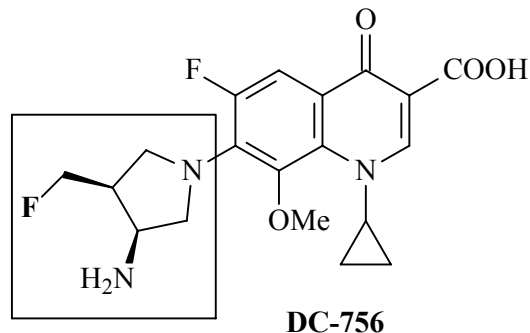


R = COOEt, CN, CF₃, F, H, Me

Scheme 9

In 2005, Satoshi Takei from Daiichi Pharmaceutical Company, Research Center, presented at ACS Meeting, San Diego, California, March 13-17, an interesting fluorination with TBAF as fluorinating reagent in synthesis of DC-

756, a new potent quinolone antibacterial agent.⁴⁹ The synthesis of DC-756 required the development of the preparation of the key building block pyrrolidine. Carbamateon 3-amino group was suitable for fluorination by TBAF (Scheme 10).



Scheme 10

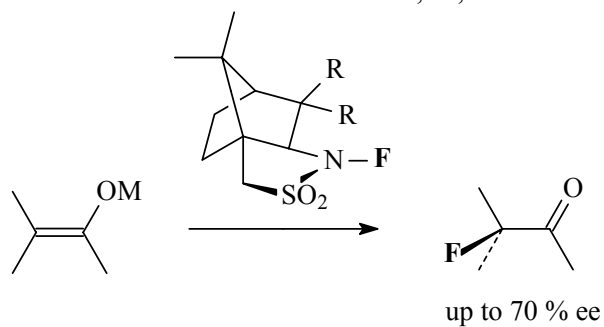
ELECTROPHILIC ENANTIOSELECTIVE FLUORINATION

An important part of the advances in fluorination of organic compounds was the development of the enantioselective fluorination reactions, especially those that proceed by electrophilic mechanisms.

Since the initial report over 10 years ago of the first examples of enantioselective halogenating reagents crystalline, optically pure *N*-fluoro sultams, these have been studied extensively. An asymmetric fluorination of enolates⁵⁰ is presented in Scheme 11.

non racemic *N*-Fluoro-2,10-Camphorsultams

R = R = H, Cl, OMe



Asymmetric Fluorination of Enolates with Nonracemic *N*-Fluoro-2,10-Camphorsultams

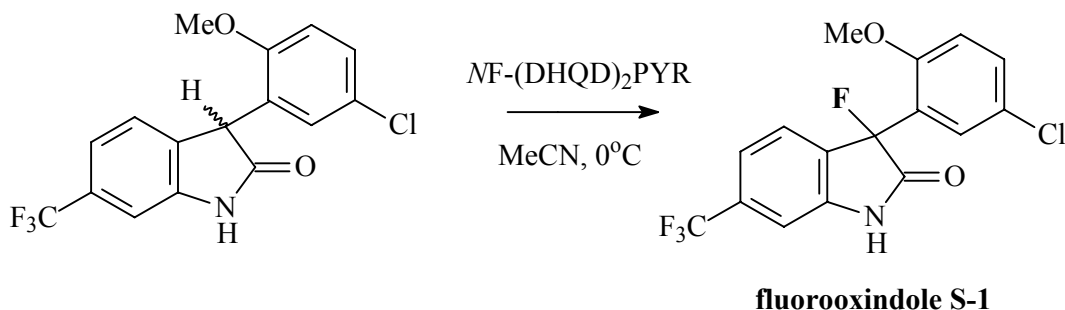
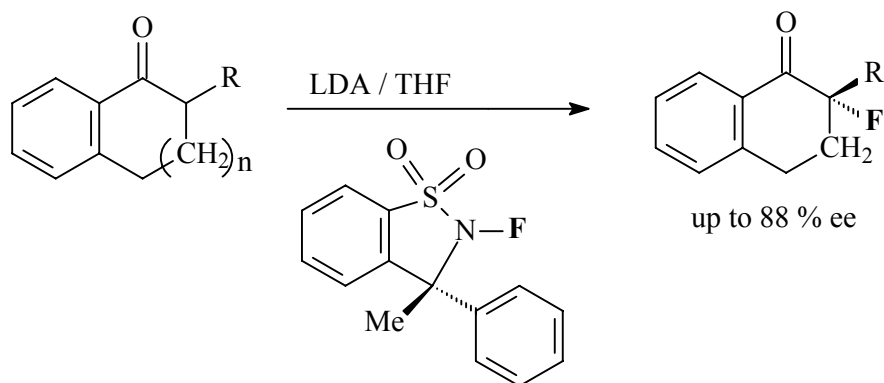
Scheme 11

Thus unprecedented enantiomeric excesses up to 70% are observed when various prochiral metal enolates are fluorinated by using these new reagents. These initial efforts revealed several limitations in both the chemical yields and enantioselectivities of the fluorinated products using these first-generation chiral reagents. Recent advances in methodology of electrophilic enantioselective fluorinations have led to significant improvements over the past few years, and now enantioselectivities of 90% ee have been reached. In 1999, Takeuchi et al. used *N*-Fluoro-3-cyclohexyl-3-methyl-2,3-dihydrobenzo[1,2-*d*]isothiazole 1,1-Dioxide as an efficient agent for electrophilic asymmetric fluorination of enolates (Scheme 12).⁵¹

In the last years, reactions in which chiral stoichiometric reagents generated stereogenic

centers in achiral substrates were performed. More recently, transition-metal catalysts and organocatalysts have emerged for enantioselective reactions.⁵²

In 2003, the first practical application of enantioselective fluorination systems for the synthesis of chiral medically important fluorinated compounds was reported by Japanese chemists.⁵³ They synthesized fluorooxindole **S-1** using as catalyst *NF*-(DHQD)₂PYR and tests for treatment of acute ischemic stroke are currently in progress. Fluorination occurred to produce **S-1** with 84% ee, and recrystallization produced enantiomerically pure (>99% ee) product (Scheme 13). (**S-1**) is a chiral, nonracemic compound, a key structural feature of which is the fluorine atom bonded to the asymmetric quaternary carbon center at C3 in the oxindole ring.



Antonio Togni and his group⁵⁴ (the Swiss Federal Institute of Technology, Zurich) achieved the first catalytic enantioselective electrophilic fluorination. They found that Selectfluor in the presence of titanium complexes can fluorinate β -ketoesters in high yield and with high enantiomeric excess. They found that Selectfluor

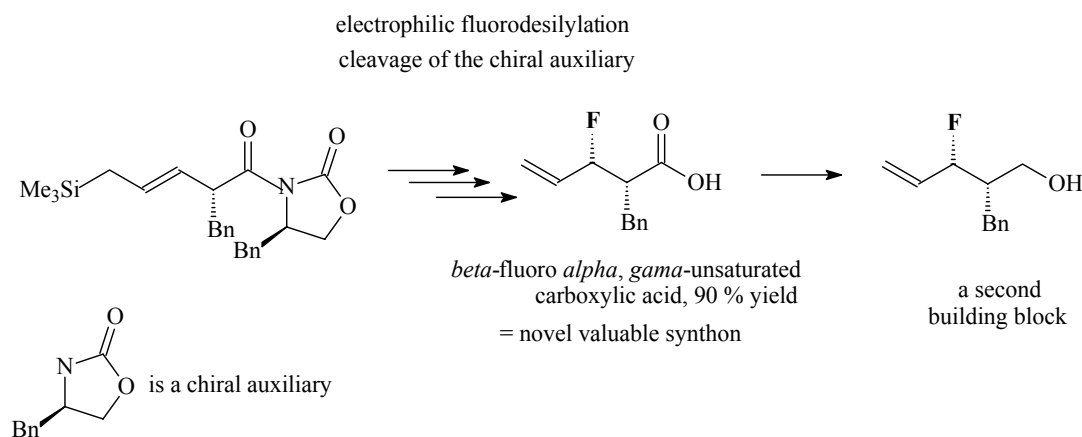
in the presence of titanium complexes can fluorinate β -ketoesters in high yield and with high enantiomeric excess. Solvias now has rights to this technology. Since then, other transition-metal catalyst/fluorinating reagent combinations were used, as palladium, nickel or zinc complexes. Despite these successes, catalytic enantioselective

fluorination has been limited to 1,3-dicarbonyls and β -ketophosphonates; the substrate scope is still quite limited, with carbonyls being needed to coordinate to the metal catalysts. Few synthetic routes have been developed for the preparation of homochiral fluorinated building blocks other than α -fluorinated carbonyl compounds.

V. Gouverneur et al.⁵⁵ used fluorodesilylation with Selectfluor of acyclic homochiral allylsilanes to produce enantiopure β -fluorinated- α -substituted carboxylic acids with an allylic monofluorinated stereogenic center (Scheme 14).

To obtain a chiral center bearing a CF_3 moiety, the nucleophilic addition to a trifluoromethylcarbonyl

group was used. Good results have been obtained using chiral substrates and the trifluoromethylating reagent $\text{CF}_3\text{Si}(\text{CH}_3)_3$, or TMS-CF_3 . Commonly called Ruppert's reagent, (prepared by Ingo Ruppert and coworkers in 1984 at University of Bonn, Germany, and now call as Ruppert-Prakash reagent, after G. K. Surya Prakash⁵⁶ at the (University of Southern California) who found its utility as a stable source of the nucleophilic trifluoromethyl anion. Since 1989, TMS-CF_3 , trifluoroacetamides⁵⁷ and hypervalent iodine reagents (Fig. 4) have been widely used for the trifluoromethylation of carbonyl compounds and other substrates.



Scheme 14

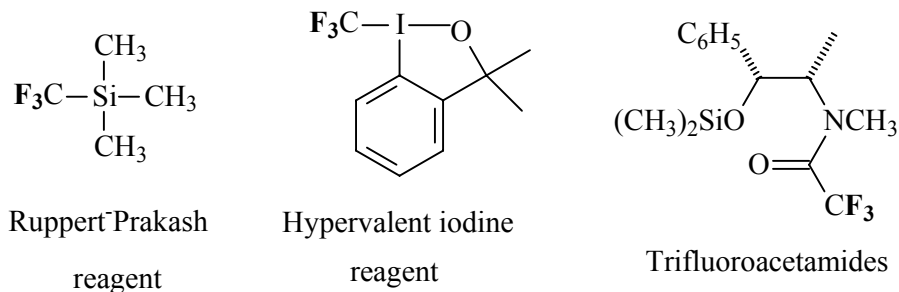


Fig. 4

DIFLUORINATION

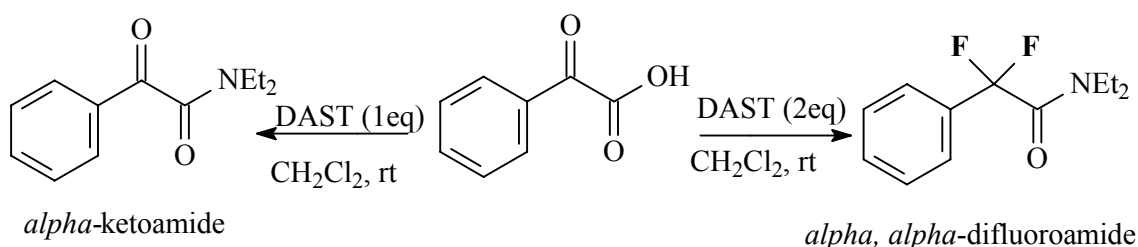
Selective introduction of difluoromethyl group (CF_2H) into organic molecules is of great importance due to its ability to contribute special biological properties to those molecules. CF_2H functionality has been known to be isosteric and isopolar to hydroxyl (OH) group and behaves as a hydrogen donor through hydrogen bonding.⁵⁸⁻⁶² Moreover, CF_2H group has similar high lipophilicity

as the trifluoromethyl group, which is useful in applications where a more lipophilic hydrogen bond donor other than OH is required.⁶⁰ As a result, CF_2H group has been frequently incorporated into various biologically active compounds (such as enzyme inhibitors,⁶³ sugars,⁶⁴ pesticides,⁶⁵ and herbicides⁶⁶) and materials (such as liquid crystals⁶⁷ and fluoropolymers⁶⁸). Many CF_2H -containing compounds have also been used as anesthetics, including well-known desflurane and isoflurane.⁶⁹

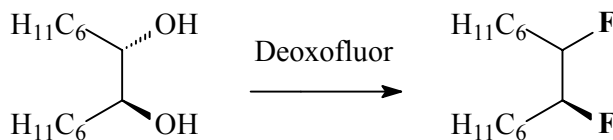
Several methods have been developed for the preparation of CF_2H -containing compounds, including the deoxofluorination of aldehydes using SF_4 , DAST, or SeF_4 ,⁷⁰ nucleophilic fluorination of *gem*-bistriflates using TBAF,⁷² fluorination of 1,2- or 1,3-dithianes using BrF_3 and other in situ-generated halogen fluorides,^{62,72} addition of CF_2Br_2 into double bonds,⁷³ $\text{S}_{\text{RN}}1$ reaction between a nucleophile and CF_2HCl ,⁷⁴ and hydrogenation of terminal 1,1-difluoroalkenes.⁷⁵ Nucleophilic introduction of a CF_2H building block into carbonyl compounds has been reported, using (difluoromethyl)dimethylphenylsilane,⁷⁶ (chlorodifluoromethyl)trimethylsilane,⁶⁰ or difluoromethyl phenyl sulfone⁷⁷ as the CF_2H precursor.

Some recent difluorinations are presented below.

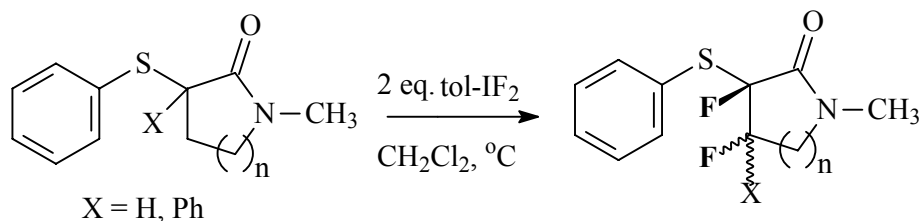
The synthesis of α, α -difluoroamides via direct fluorination was recently reported using DAST as the fluorinating reagent in a one-pot reaction



Scheme 15



Scheme 16



Scheme 17

Difluoromethyl Phenyl Sulfone ($\text{PhSO}_2\text{CF}_2\text{H}$). In 2003, Prakash, Hu and Olah (Loker Hydrocarbon Research Institute and Department of Chemistry, University of Southern California, Los Angeles, USA), reported the preparation of difluoromethylsilanes via the magnesium metal-

(Scheme 15) to give the corresponding difluoro compound; decreasing the molar ratio of DAST to substrate resulted in the formation of the respective α -ketoamide.⁷⁸

Various fluorinated chiral compounds were synthesized using bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor) as a nucleophilic fluorinating reagent; reaction with diols in methylene chloride at room temperature led to the formation of the corresponding fluoro derivatives in good yields (Scheme 16).⁷⁹

Iodotoluene difluoride (tol-IF_2). Treatment of phenylsulfanylated lactams with one equivalent of iodotoluene difluoride (tol-IF_2) results in the unsaturated heterocycle in moderate to good yields. When two equivalents of the reagent were used, the lactams were fluorinated in the α - and β -positions resulting in the diastereomeric difluoride (Scheme 17).⁸⁰

mediated reductive difluoromethylation of chlorotrialkylsilanes using difluoromethyl phenyl sulfone ($\text{PhSO}_2\text{CF}_2\text{H}$) as difluorinating agent.⁸¹

In the next two years (2004-2005), Prakash, Olah and Hu^{82, 83} reported a facile and efficient nucleophilic difluoromethylation of primary alkyl

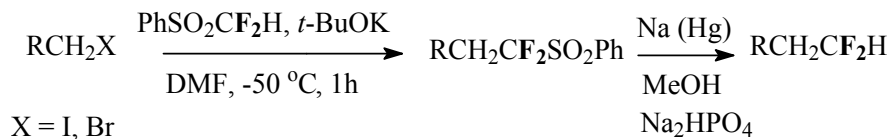
halides (Scheme 18)⁸² and carbonyl compounds.⁸³ that has been disclosed through a novel nucleophilic substitution-reductive desulfonylation strategy, using difluoromethyl phenyl sulfone as a difluoromethyl anion ("CF₂H⁻") equivalent. This new synthetic methodology possesses many advantages, including convenience, cost, and efficiency, and promises to be a highly useful synthetic tool for many other potential applications.

J. Hu and C. Ni⁸⁴ reported the nucleophilic (phenylsulfonyl)difluoromethylation of (R)-(N-tert-butylsulfinyl)aldimines with difluoromethyl phenyl sulfone yielding the corresponding chiral α -difluoromethyl amines in excellent yields and with high diastereoselectivity (dr > 99%).

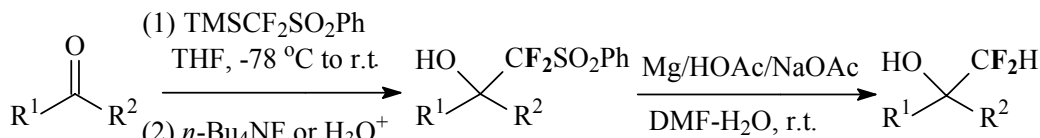
The two Chinese researchers reported also a new nucleophilic difluoromethylation chemistry using fluoride-induced (phenylsulfonyl)

difluoromethylation with TMSCF₂SO₂Ph followed by the magnesium-metal-mediated desulfonylation. This methodology is compatible with both enolizable and non-enolizable aldehydes and ketones and has special advantage in the case of enolizable aldehydes. The new efficient desulfonylation method is considered to be environmentally benign due to the absence of mercury (Scheme 19).⁸⁵

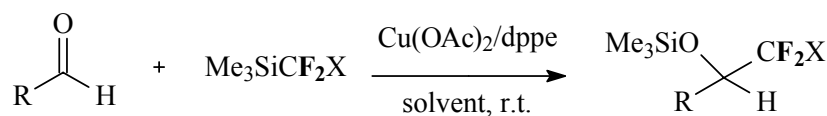
Just recently, the first Lewis acid-catalyzed trifluoromethylation reactions of aldehydes with Me₃SiCF₃ under TiF₄/DMF, Ti(O^{*i*}Pr)₄/DMF and Cu(OAc)₂/dppp/toluene conditions are described by Shibata et al.⁸⁶ They have successfully applied this methodology to the difluoromethylation of aldehydes using Me₃SiCF₂SePh, Me₃SiCF₂P(O)OEt₂ and Me₃SiCF₂SPh (Scheme 20).



Scheme 18



Scheme 19



Scheme 20

NUCLEOPHILIC TRIFLUOROMETHYLATION REACTIONS

In 1989 Prakash and co-workers showed the trifluoromethylating properties of (TMS)CF₃ and the utilization of this compound as a nucleophilic trifluoromethylating agent has rapidly become the method of choice.⁸⁷⁻⁹² (TMS)CF₃ was used as a precursor to the trifluoromethide anion, which was liberated by activation with a fluoride source (nucleophilic initiator). Most commonly, tetraalkylammonium fluorides are used as initiators.

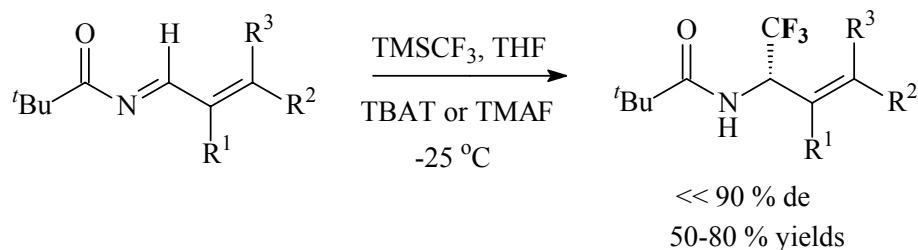
In 2001, G. K. Surya Prakash, Mihirbaran Mandal and George A. Olah reported the first examples of chiral trifluoromethylated allylic amines.⁹³ The trifluoromethide ion generated in situ from TMSCF₃ and TBAT (tetrabutylammonium triphenyldifluorosilicate), as well as TMAF (tetramethylammonium fluoride), adds to the α , β -unsaturated *N*-tert-butanesulfinimines exclusively in a 1,2 fashion with high diastereoselectivities (Scheme 21).

Since the late 1990s, a series of nucleophilic trifluoromethylation methods, employing

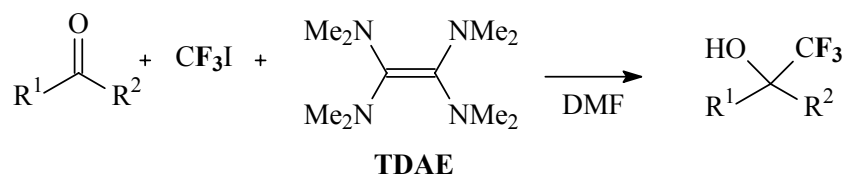
fluoroform, fluoral, and trifluoroacetic and trifluoromethanesulfinic acid derivatives, as well as CF_3I and tetrakis(dimethylamino)ethylene (TDAE) have been developed. In 2001, Dolbier's group⁹⁴ from the University of Florida reported the method of using TDAE and CF_3I in an effort to develop a reagent that would be easy to use (Scheme 22).

In a convenient and efficient procedure, the nucleophilic trifluoromethylation of aldehydes with sodium trifluoroacetate was reported by Ying Chang and Chung Cai, using copper halides as the catalyst (Scheme 23).⁹⁵

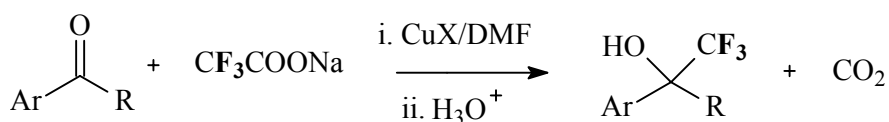
In 2006, B. Langlois et al.⁹⁶ reported the using of β -fluoroalkylated enones as dienophiles in Diels-Alder cycloadditions (Scheme 24).



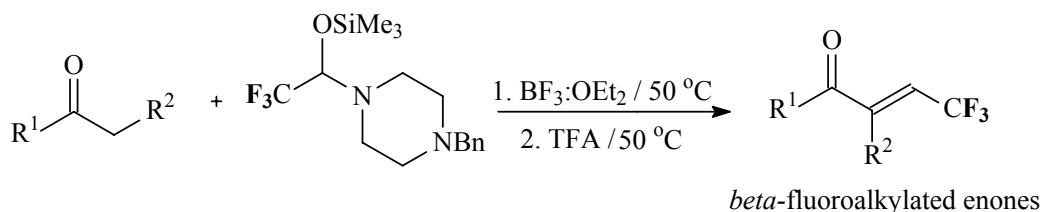
Scheme 21



Scheme 22



Scheme 23



Scheme 24

FLUORINATED HETEROCYCLES

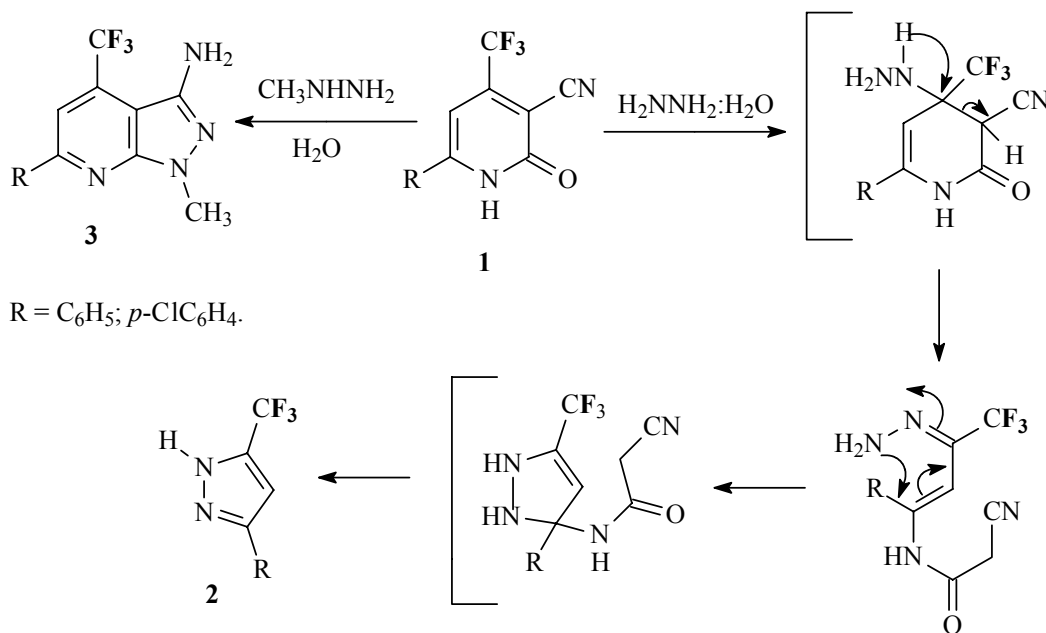
A strategically positioned fluorine in heterocyclic compounds, especially those containing trifluoromethyl groups plays an important role in medicines and agrochemicals. Specifically, the fluorinated pyrazoles have been shown to possess high biological activities as herbicides, fungicides, insecticides, analgesics, antipyretics and antiinflammatories.

Krishnaiah and B. Narsaiah reported a new synthetic methodology for the formation of trifluoromethyl substituted pyrazoles.⁹⁷ The 3-cyano-4-trifluoromethyl-6-phenyl 2(1H) pyridones (**1**) on reaction with hydrazine hydrate, gave exclusively in 5-trifluoromethyl-3-substituted pyrazoles (**2**) through a novel method. A possible mechanistic pathway for change in the site of

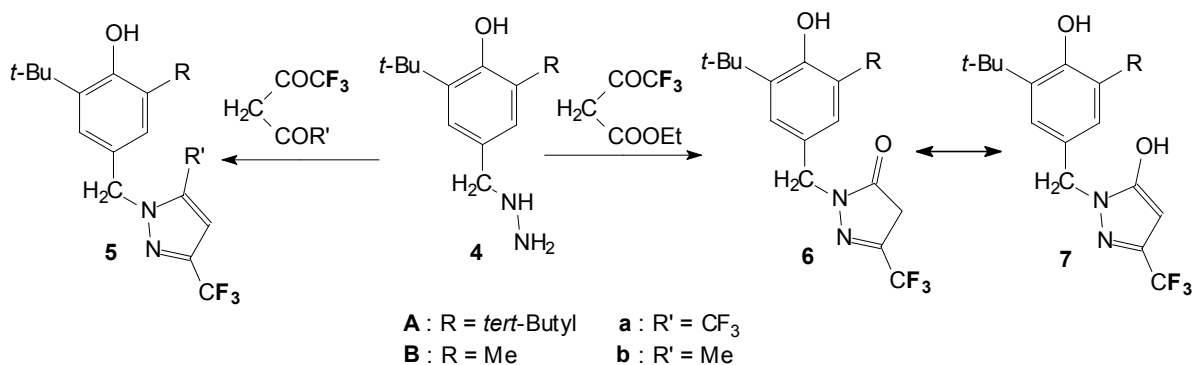
nucleophilic attack due to the CF₃ group in 2(1H) pyridones is described (Scheme 25).

V. Dinou⁹⁸ reported the synthesis of new CF₃-containing pyrazole and pyrazol-5-one derivatives, using the building block method, by reaction of 3,5-Dialkyl-4-hydroxybenzylhydrazine **4** with hexafluoroacetylacetone and trifluoroacetylacetone yielding the pyrazoles **5** bearing trifluoromethyl and/or methyl substituents in positions 3 and 5. The same hydrazine derivatives **4** afforded with trifluoroacetoacetic acid ethyl ester the pyrazol-5-one, which might have the tautomeric structures **6** or **7** (Scheme 26)

The synthesis by Duff formylation of a series of fluorinated benzaldehydes and their use in the Wittig synthesis of fluoro-substituted stilbenes (a series of fluorinated analogues of the anticancer drugs) is described by Lawrence et al.⁹⁹ (Scheme 27).



Scheme 25

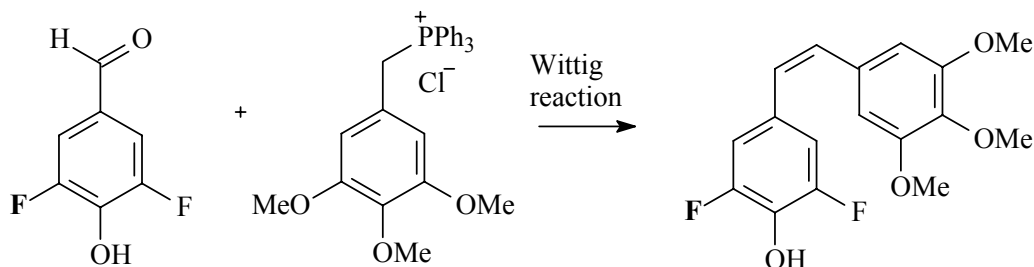


Scheme 26

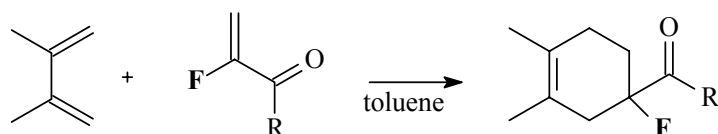
[4+2]-Cycloadditions of cyclopentadiene with the monofluorinated dienophiles are *exo*-selective and yield cycloadducts (Scheme 28).¹⁰⁰

In 2006, V. Dinoiu¹⁰¹ reported the conversion of the perfluoroester (heptafluorobutanoic acid) into new pyridazin-3-ones and α,β -unsaturated lactams, as mixtures of diastereomers (Scheme 29). The

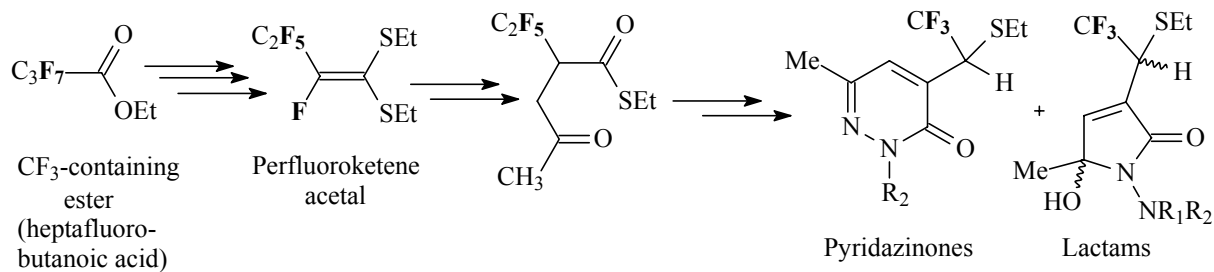
building block method was used to obtain the corresponding CF_3 -containing heterocycle derivatives in seven reaction steps, and a possible reaction mechanism was discussed. Starting from perfluoroester, it was synthesized perfluoroketene dithioacetal that is an excellent building block for the synthesis of new fluorinated heterocycles.¹⁰²



Scheme 27



Scheme 28



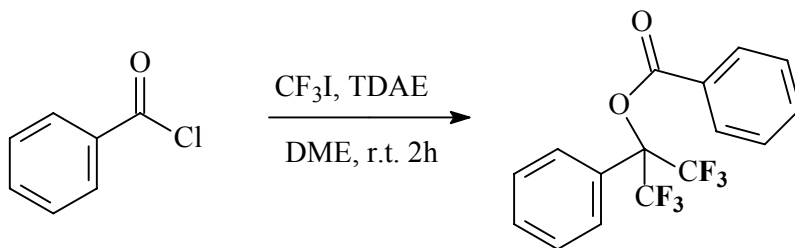
Scheme 29

HIGHER FLUORINATION

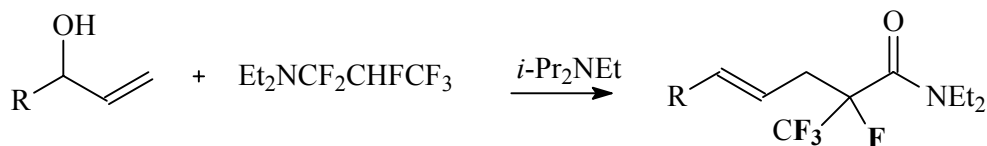
A chemoselective bis-trifluoromethylation of acyl chlorides using the $\text{CF}_3\text{I}/\text{TDAE}$ -derived nucleophilic trifluoromethyl anion reagent was reported by Dolbier Jr. et al.¹⁰³ An ester product was obtained with very high yields by sequential

nucleophilic bis-trifluoromethylation, followed by acylation of the resultant alcoholate (Scheme 30).

N,N-Diethyl-1,1,2,3,3,3-hexafluoropropylamine ($\text{Et}_2\text{NCF}_2\text{CHFCF}_3$), known as Ishikaya's reagent, displayed the ability to insert a fluoro(trifluoromethyl)methylene moiety in unsaturated alcohols (Scheme 31).¹⁰⁴



Scheme 30



Scheme 31

CONCLUSIONS

The development of new fluorination reactions is expected to increase the availability of fluorine-containing structures and spark the interest of drug and agrochemical producers. As customers find it easier to explore having fluorine in their molecules, fine chemicals manufacturers hope demand for custom syntheses and building blocks will grow.

Fluorine chemistry has an important role to play in clean technology, both in catalyst and solvent replacement technologies. Fluorine is a very light element and provides excellent value in terms of activity-per-gram. It is also recognised that fluorochemicals are frequently more effective and are required in smaller quantities than non-fluorinated compounds-in the case of fluorine, 'less is more'. High effect, low dosage fluorinated formulations allow reductions in the use of materials and energy all along the production chain: less non-renewable feedstocks are consumed, transport and packaging is reduced, and the quantity of post-consumer waste is minimised.

Even though fluorochemicals have also been involved in some of the more negative aspects of the chemical industry, fluorine-containing compounds have a great potential for clean synthesis, and utilisation of the high activity that fluorinated groups can impart molecules may help to reduce the quantities required of certain classes of chemicals that are used in the biosphere, including pesticides and pharmaceuticals.

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