MARTIN SCHÜLER*[1], PATRICIA ARGIBAY[2]
1. Orgafluor SL, Carrer Baldiri Reixac 4, 08028 Barcelona, Spain
2. Unidad de Química Combinatoria, Carrer Baldiri Reixac 10, 08028 Barcelona, Spain


Martin Schüler

# Crafting Organofluorine

**KEYWORDS: Fluorination, Selectfluor, Deoxofluor, NFSI, DAST, Orgafluor.**

Abstract This communication covers contemporary methodologies to access organofluorine materials which are of growing interest for the materials sciences and life science industries. The orthogonal strategies currently employed in chemical manufacturing are reviewed and challenges faced by the synthetic chemist to introduce fluorine in a regio- and stereospecific manner are examined. Industrial applications involve fluorinating agents that are compatible with a high degree of molecular functionality, affording structurally complex organofluorine compounds in a convenient and economic manner.

## INTRODUCTION

Fluorination has long become a standard tool to increase bioavailability and metabolic stability of biologically active lead structures. The fact that nature has rarely evolved effective mechanisms to incorporate fluorine in biological pathways makes organofluorine compounds generally inert towards enzymatic degradation and only in a few rare cases has the release of fluoride by enzymatic action led to the withdrawal of a new molecular entity from its clinical use (1).


**Figure 1**. New molecular entities containing fluorine registered with the FDA in 2014.

Fluorine is closest to hydrogen in terms of atomic size and while its introduction has only limited impact on the steric properties of an organic molecule, it can strongly affect its electronic properties to modulate the acidity and basicity of neighboring groups, thermal and oxidative stability, its lipophilicity, and molecular conformation (2). As a consequence the pharmacokinetic profile of the biologically active compound can be dramatically altered, a methodology which is increasingly harvested in pharmaceutical development (Figure 1). This trend is clearly evidenced by the almost 30 percent of New Molecular Entities (NME) approved by the FDA in 2014 containing fluorine as an integral part of its molecular structure (3).

Naturally occurring organofluorine compounds are extremely rare and therefore accessible solely by synthetic organic chemistry. However, due to strong inductive and resonance effects of fluorine, conventional synthetic methods are not always applicable to access or transform the fluorinated intermediate along the synthetic route. Whilst the carbon-fluorine bonds are among the strongest covalent bonds known, the high electron affinity of fluorine makes the fluoride ion a highly stable species and thus excellent leaving group, especially in proximity to an acidic proton or an aromatic environment (4). Expertise and a deep understanding of mechanistic foundations, available reagents, and synthesis strategy based on the unique chemical properties of fluorine are therefore essential to obtain organofluorine compounds in the desired quality and quantity in an economical and efficient manner. In addition, fluorinating reagents are often hazardous and typically require special equipment, limiting fluorination technology to only a few specialized companies (5).

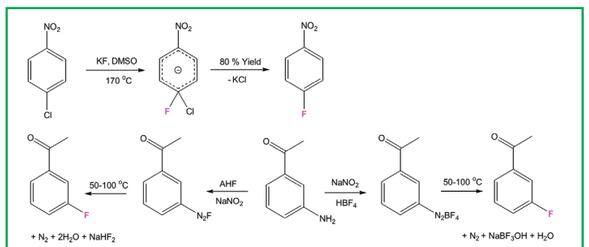


**Figure 2**. Halogen-exchange reaction and Balz-Schiemann reaction involving tetrafluoroboric acid and anhydrous hydrogen fluoride (EP0105641A1).

## FLUORINATED ARENES

The fluorine substituent is often attached to an aromatic ring, in order to stabilize the biologically active molecule against oxidative degradation. Since this metabolic process is ubiquitous in living organisms, fluorination represents an effective tool to increase the stability and bioavailability of an biologically active compound. Fluorination of aromatic compounds has been extensively studied and conventional methodology such as halogen exchange and Balz-Schiemann reactions are common in industrial settings (Figure 2). Inexpensive alkali metal fluorides are used to replace aromatic- and heteroaromatic chlorine and -bromine to produce aryl fluorides. Increasing ionic strength of the fluoride salt decreases nucleophilicity and solubility in the reaction medium which often makes potassium fluoride the best compromise between reactivity and cost. In these processes the rate determining step is a nucleophilic addition of fluoride ion, to form the Meisenheimer complex, a mechanism that favors the conversion of aryl chlorides over aryl iodides and bromides (6). Highly polar solvents must be employed to dissolve inorganic fluoride, which in turn reduces its nucleophilicity. Elevated temperatures and prolonged reaction times are often the consequence which in combination with the strongly basic conditions produced by fluoride ion can pose considerable challenges in terms of equipment and process safety. The Balz-Schiemann Reaction is a special case of nucleophilic aromatic fluorination that is preceded by pyrolysis of an aromatic diazonium tetrafluoroborate. The intermediates are generated by action of fluoroboric acid onto their corresponding anilines. Variations involve the use of anhydrous hydrogen fluoride, its pyridine or ammonium complexes, or complexes of borontrifluoride. The hazardous nature of the chemicals involved, lack of reproducibility and the generation of large quantities of undesired waste however limit its suitability for large scale processes.

Moreover the harsh reaction conditions employed in nucleophilic aromatic fluorination are generally incompatible with structural complexity and functionality in the substrate. Therefore fluorine containing aromatic compounds are mostly assembled starting from structurally simple fluorinated building blocks that can be further elaborated by using standard synthetic protocols (Figure 3).

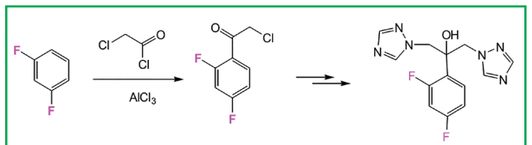


**Figure 3**. Building block approach for the synthesis of fluconazole (WO9703971).

## TRIFLUOROMETHYL

The trifluoromethyl motif is one of the most common structural element amongst fluorine containing pharmaceuticals. The inductive effect of trifluoromethyl is yet stronger than that imparted by a single fluorine substituent and can therefore have a dramatic effect on stability and chemical properties of the molecule. A trifluoromethyl group strongly modulates the lipophilicity of the molecule, thus affecting bioavailability and molecular conformation of the biologically active compound. Several reagents have been developed in recent years that can stabilize an electrophilic and a nucleophilic trifluoromethyl group and allow for its direct and selective introduction into aromatic, aliphatic or heterocyclic structures (7). Such methods are however relatively expensive and thus trifluoromethylated compounds are predominantly constructed by crafting a structurally simple CF3 containg building block into the molecule. A broad variety of building blocks containing aromatic trifluoromethyl are commercialy available, whereas trifluoroacetic acid and its derivatives can serve to assemble trifluoromethylated quinolines, pyridines, pyrimidines, pyrroles,and other heterocycles (Figure 4).

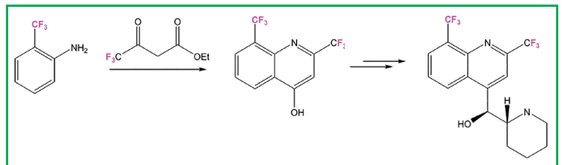

**Figure 4**. Synthesis of Mefloquine involving trifluoromethyl building blocks (US4507482).

Building blocks containing trifluoromethyl can be obtained from a trichloromethyl precursor by action of anhydrous hydrogen fluoride. Alternative methods include the conversion of a carboxylic acid with alkylaminosulfur trifluorides, which are a safer and easier to handle form of the highly toxic gas sulfur tetrafluoride that has been traditionally used for this transformation (8). Hydrogen fluoride is the most basic and common precursor of fluorochemicals and extensively used in our laboratories for solid-phase peptide synthesis (9). The reagent is a low boiling liquid that forms corrosive and toxic hydrofluoric acid upon contact with moisture. Hydrofluoric acid quickly penetrates the living tissue where it strongly interferes with the calcium metabolism, leading to hypocalcemia with very serious health consequences. Also special equipment made of Hastelloy or Teflon must be used as hydrofluoric acid readily attacks glassware through formation of silicon tetrafluoride and leads to corrosion problems in stainless steel (Figure 5).

**Figure 5**. Laboratory setup for handling hydrogen fluoride, from right: HF cylinder, vacuum gauge, HF collection vessel, reaction vessel, calcium oxide trap, vacuum pump (Special reactions laboratory, Parc Científic de Barcelona).

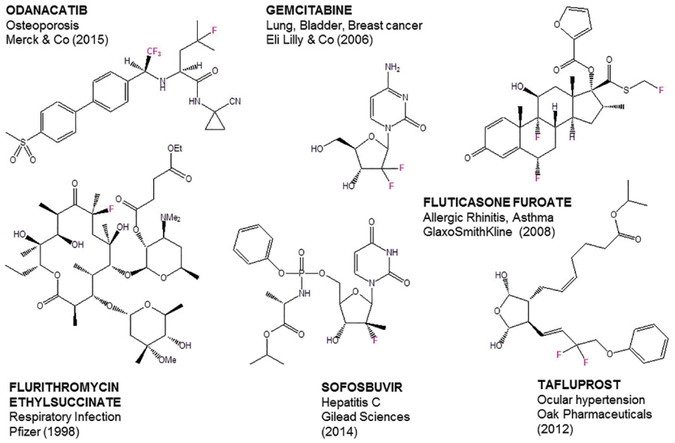


**Figure 6.** Fluorine containing molecular entities approved for medicinal use.

Direct fluorination or trifluoromethylation becomes inevitable when the pronounced inductive effect of fluorine renders the intermediate inept for chemical modification or, when a suitable fluorinated building block is simply not available. This is obviously the case when fluorinated derivatives of natural products such as polyketides, carbohydrates, steroids, alkaloids, and prostaglandins are to be made (Figure 6).

## ELECTROPHILIC FLUORINATION

Direct introduction of fluorine presents considerable synthetic challenges as conventional fluorinating agents are usually aggressive and may give rise to side reactions, with the consequence of reduced yield and low selectivity. This can be particularly costly, not only because of the economic value of the starting material, but also due to the difficulties in separating structurally similar byproducts. Selective and mild fluorinating agents that are compatible with structural complexity in the fluorination process have thus become of great interest in recent years (10). Electrophilic fluorinating agents address the common conflict between reactivity and selectivity. Fluorine is not delivered in form of the basic fluoride ion or highly reactive radical, but as fluoronium ion that formally carries a positive charge and readily reacts with centers of high electron density such as enolates, silyl ethers, double bonds, aromatic- and heteroaromatic structures (11). The most successful reagent of this class is arguably 1-Chloromethyl-4-fluoro-diazoniabiciclo[2.2.2] octane bis(tetrafluorborate), (F-TEDA) , introduced in 1990 under its brand name Selectfluor®. As a safer alternative to toxic and explosive perchloryl fluoride it rapidly becamethe standard fluorinating agent in the manufacturing of 6-fluoroprednisolones such as Fluticasone, Flumethasone, Diflorasone, Halobetasol, Flunisolide which are important anti-asthmatic and anti-inflammatory medicines (Figure 7).

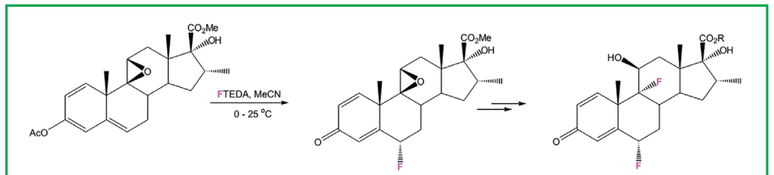


**Figure 7**. Synthesis of 6-fluoroprednisolones involving an electrophilic fluorination step (WO 03047329).

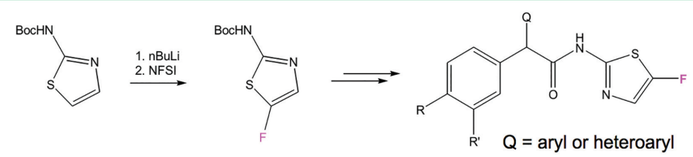


**Figure 8**. Synthesis of fluorothiazoles involving N-fluorosulfonimide (WO2006016174).

Alternative reagents for electrophilic fluorination include N-fluorosulfonimide (NFSI) and N-Fluoropyridines which are less reactive than F-TEDA, yet chemically stable to sustain strongly basic conditions, for instance found in carbanion chemistry (Figure 8). New, innovative fluorination methods based on transition metal chemistry have been developed recently which allow for mild reaction conditions, excellent selectivity, and high atom efficiency (12). It can therefore be expected that these methods will quickly find their way into industrial applications.

## NUCLEOPHILIC FLUORINATION

Nucleophilic fluorination is often the method of choice to access aliphatic or alicyclic fluorine (13). The displacement by fluoride at sp3 hybridized carbon requires an excellent leaving group since fluoride ion is only a moderate nucleophile. Halogens are usually not reactive, unless in allylic and benzylic substrates. The conversion of a hydroxyl group into trifluoromethanesulfonates or methanesulfonates provides a sufficiently reactive leaving group that can be displaced by nucleophilic fluoride, often in form of an ammonium or phosphonate salt which exhibit good solubility in organic solvents. The nucleophilic displacement of a leaving group by fluoride at sp3 hybridized carbon is usually impaired by undesired side reactions such as β-elimination or hydroxylation, a consequence of the basicity of fluoride in nonpolar solvents. In protic solvents, on the other hand, hydrogen bonds strongly decrease the nucleophilicity of fluoride with negative effects on reaction rate and selectivity. The combination of high basicity and strong hydrogen bonding makes fluoride a challenging nucleophile for displacement reactions.

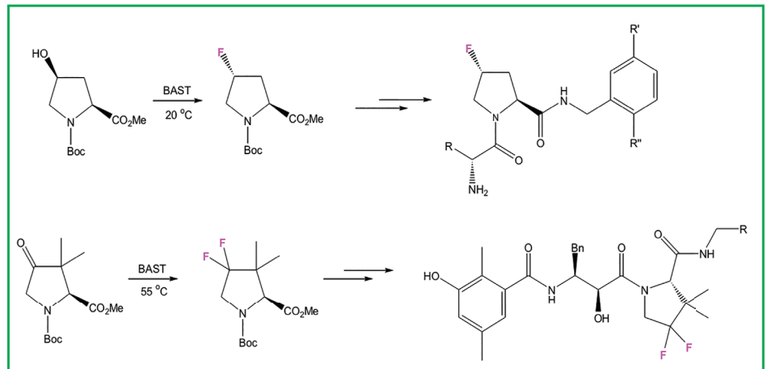


**Figure 9**. Stereoselective nucleophilic fuorination of 4-hydroxyproline (WO2004/032834) and 3,3-dimethyl-4-oxo-proline with alkylaminosulfur trifluoride (WO2005/054187).

Alkylaminosulfur trifluorides such as diethylaminosulfur trifluoride (DAST) and bis(2-methoxyethyl)aminosulfur trifluoride (BAST), provide an alternative for the direct conversion of hydroxyl to form the carbon-fluorine bond. The deoxofluorination proceed under neutral to weakly acidic conditions, often at ambient temperature and most conveniently as a one-step process. In our laboratories we have obtained good yields with structurally diverse starting materials such as primary, secondary, tertiary, allylic, and benzylic alcohols, aldehydes and ketones, carboxylic acids, epoxides, and carbohydrates. The conversion of secondary alcohols is generally stereospecific, and thus suitable to generate a chiral carbon-fluorine bond in a direct and efficient manner (Figure 9). The reaction of alkylaminosulfur trifluorides with aldehydes and ketones provides for germinal difluoro compounds at elevated temperatures and in presence of an activator in form of a Lewis- or Bronsted acid (14). BAST, which is widely known under its commercial name DeoxofluorTM, , has the higher onset of thermal decomposition and uniform heat flow compared to DAST and is therefore the more suitable reagent for such transformations (15).

## CONCLUSION

The development of new fluorinating agents and technologies has sparked the interest of pharmaceuticals and agrochemicals producers, and demands for custom syntheses and fluorinated building blocks will continue to grow as customers find it easier to explore having fluorine in their molecules. However, the regio- and stereoselective introduction of fluorine into organic molecules continues to be a challenge as fluorination methods often lack generality and predictability. To ensure cost and time efficiency in providing tailor-made organofluorine compounds, technological input is paramount and remains a key argument for outsourcing fluorination processes to companies with expertise in this arena.

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