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FLUORINATION METHODS IN DRUG DISCOVERY

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Abstract

Fluorination reactions of medicinal and biologically-active compounds will be discussed. Late stage fluorination strategies of medicinal targets have recently attracted considerable attention on account of the influence that the fluorine atom can impart to targets of medicinal importance, such as a modulation of lipophilicity, electronegativity, basicity and bioavailability, this latter as a consequence of membrane permeability. Therefore, the recourse to late-stage fluorine substitution on compounds with already known and relevant biological activity can provide the pharmaceutical industry with new leads with improved medicinal properties. The fluorination strategies will take into account different fluorinating reagents, nucleophilic, electrophilic and of radical nature. Diverse families of organic compounds such as (hetero)aromatic rings, and aliphatic substrates (sp$^3$, sp$^2$, and sp carbon atoms) will be studied in late-stage fluorination reaction strategies.

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1.-Introduction

There are several recent review articles and comprehensive books that deal with fluorine-containing drugs for human use. The benefits of introducing a fluorine atom into the organic backbone of a pharmacophore is well understood and has been underscored in reports dealing with fluorine in pharmaceuticals and in medicinal chemistry in general. A brief historical overview of fluorine in chemistry and medicinal chemistry has recently been described.

The omniphobicity/lipophilicity and electrostatic interactions can be considered among the most prominent effects. Thus, introducing fluorine into an organic compound can significantly alter its biological properties.

One other subtle but important effect of introducing fluorine into the backbone of a medicinal target is the inflection of acidity and basicity of the parent compound, which can change, inter alia, the binding affinity, and bioavailability. Highly basic groups can have a detrimental effect on the bioavailability of a drug. Thus introducing a fluorine atom next to a basic group can reduce its basicity, enhancing its membrane permeability, and increasing bioavailability. Although the replacement of hydrogen for fluorine does not have a profound steric influence, electrostatic interactions with other groups can change conformations significantly.
The replacement of hydrogen for fluorine on aromatic rings is a well-known strategy to decelerate oxidative metabolic processes by Cytochrome P450 monooxygenases. In this respect, the electron-withdrawing properties of fluorine on aromatic rings, which can slow down hydrolytic metabolism, alter reaction rates and stability of intermediates. Fluorine substitution on aromatic rings is also known to increase binding affinity, as a result of enhancing electrostatic interactions. However, it is difficult to predict the influence of fluorine substitution on the overall profile in a given situation.

As numerous reports attest \(^1\), the number of marketed drugs that contain a fluorine atom has increased rapidly. As of 2009, the FDA had approved >140 fluorine-containing drugs. \(^7\) Many of the approved fluorinated drugs have multibillion dollar revenues, and considered among the most-successful drugs (Figure 1).

![Figure 1. Structures of atorvastatin, fluoxetine and ciprofloxacin](image)

The rapid development of synthetic methodologies in organic fluorine chemistry \(^{1n}\) and the increased understanding of the impact of fluorination on biological properties \(^8\) have made possible the design and synthesis of structurally-diverse and sophisticated drug candidates.

This review article is intended to present new synthetic methodologies \(^9\) for accomplishing fluorination reactions on molecules (drugs/prodrugs) with pharmacological activity. It is not our aim...
to describe, or enumerate fluorine-containing drugs and their mechanism of action.\textsuperscript{1,10} Trifluoromethylation, trifluoromethoxylation, and trifluoromethylthiolation strategies will not be considered in this review.

From the chemistry perspective, fluorinated pharmacologically-active drugs contain the fluorine atom in phenyl rings, heterocyclic rings, steroids and derivatives, for which synthetic late-stage strategies for introducing fluorine can take into account homolytic and \textit{ipso} aromatic substitutions on phenyl and heteroaromatic rings, and substitutions at sp\textsuperscript{3}, sp\textsuperscript{2} C-H bonds in aliphatic compounds.

An area of rapid development is the synthesis of new and improved \textsuperscript{18}F–labeled compounds for applications in positron emission tomography.\textsuperscript{11} This area, deserves particular and detailed attention due to the short half-life of \textsuperscript{18}F (109.8 min) and will not be the subject of this review\textsuperscript{12a,b}, except where traditional and \textsuperscript{18}F protocols overlap.\textsuperscript{15}

2.-Fluorinating Reagents Used in Medicinal Chemistry\textsuperscript{16}

Examples of nucleophilic reagents employed to construct C–F bonds (Figure 2) include diethylaminosulfur trifluoride 1 (DAST)\textsuperscript{17}, 2,2-difluoro-1,3-dimethylimidazolidine 2 (DFI)\textsuperscript{18}, and bis(2-methoxyethyl) aminosulfur trifluoride 3 (Deoxofluor).\textsuperscript{19} Triethylamine trihydrofluoride 4 (TREAT-HF),\textsuperscript{20} has been used as a highly polar fluorinating reagent. More classical fluorinating reagents include CsF used at elevated temperatures in S\textsubscript{N}Ar reactions or anhydrous tetramethyl ammonium fluoride\textsuperscript{21}, AgF, and AgF\textsubscript{2}.
The development of electrophilic fluorinating agents to tame the reactivity of elemental fluorine resulted in a great advancement. A large array of electrophilic reagents bearing a $\text{R}_2\text{N}^+\text{F}$ or $\text{R}_3\text{N}^+\text{F}$ unit has already been developed and commercialized (Figure 3), elaborated from the first such agent, Olah’s reagent (pyridinium poly(hydrogen fluoride) PPHF), $N$-fluoropyridinium triflate 5 (developed by Umemoto), 2,4,6-trimethyl-1-fluoropyridinium triflate 6 (FP-T300), introduced by Shibata. However, the syntheses of all these (commercial) electrophilic reagents require the initial handling of fluorine gas. Among more recent electrophilic reagents are 1-chloromethyl-4-fluoro-1,4-diaza[2.2.2]octane bis(tetrafluoroborate) 7 (Selectfluor), 1-chloromethyl-4-fluoro-1,4-diaza[2.2.2]octane bis(hexafluorophosphat) 8 (FTEDA-PF$_6$), 1-methyl-4-fluoro-1,4-diaza[2.2.2]octane bis(tetrafluoroborate) 9 (Selectfluor II), 1-methyl-4-fluoro-1,4-diaza[2.2.2]octane bis(hexafluorophosphat) 10 (Selectfluor II-PF$_6$), and $N$-fluorobenzenesulfonimide 11 (NFSI) or the methyl analog Me-NFSI 12, or 1-fluoro-4-hydroxy-1,4-diaza[2.2.2]octane bis(tetrafluoroborate) 13 (NFTh), developed by Stavber and fluorobenziodoxole 14 (1-fluoro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxle), reported in 2013 by Togni and Stuart (Figure 3).
Figure 3. Electrophilic fluorinating reagents

Other recently introduced reagents, particularly for deoxyfluorination (Figure 4), include Phenofluor 15, PyFluor 16, and nickel-fluorido complexes 17a and 17b together with (diethylamino)difluorosulphonium tetrafluoroborate 18 (XtalFluor-E). 34.

Figure 4. Deoxy-fluorinating reagent 15, PyFluor 16, nickel-fluorido complex 17, and XtalFluor E.
3-New Methods for Monofluorination of Aryl Moieties

There are a large number of drugs and bioactive compounds that possess a fluorine atom appended to an aromatic ring. Among recent fluorophenyl containing drugs are oral epidermal growth factor receptor (EGFR) Gefitinib 19 and Lapatinib 20, together with Vandetanib 21, an antagonist of the vascular endothelial growth factor receptor (VEGFR) and EGFR (Figure 5).

![Figure 5. Structures of Gefitinib 19, Lapatinib 20, and Vandetanib 21](image)

While the vast majority of fluorinated pharmaceuticals are derived from fluoroaryl building blocks, the development of selective fluorination reactions or late-stage fluorination protocols would be beneficial to the syntheses.

3a.- Conversion of C_{Ar}-H into C_{Ar}-F Bonds

Xu and co-workers have developed an ortho C-H bond fluorination of 2-phenoxy pyridine derivatives through a palladium-catalyzed reaction via 6-membered cyclopalladation mode using a removable directing group. This strategy has been applied to the synthesis of 2-phenoxy nicotinic acid derivatives which are antagonists of the P2Y₁₂ receptor, an important target in antiplatelet therapies, Scheme 1.
Scheme 1. *ortho* C-H bond fluorination of 2-phenoxy pyridine derivatives through a palladium-catalysis

The strategy\(^{38}\) utilizes 2-phenoxy pyridines as efficient phenol surrogates to undergo an *ortho* fluorination reaction. This method takes into account the strong coordinating ability of the pyridinyl directing group\(^{40}\) that has been employed before in *ortho*-silylation, -arylation, -borylation, -alkenylation, and acylation reactions.\(^{41}\) The authors also extended the scope of the methodology towards the C-H fluorination of *estrone* derivative 22, as illustrated in Scheme 2 giving the fluorinated derivative 23 in 60% yield.

Scheme 2. C-H fluorination of *estrone* derivative

**3.b.-Conversion of C\(_{Ar}\)-X into C\(_{Ar}\)-F Bonds (X = Cl, Br, I, OT\(_F\), NO\(_2\))**
Transition metal-complexes have been used to prepare fluoroarenes.\textsuperscript{42,35} For instance, the palladium-catalyzed fluorination of aryl triflates bearing electron-withdrawing groups has been undertaken.\textsuperscript{43} The conversion of aryl stannanes\textsuperscript{44,35,45a}, trifluoroborates\textsuperscript{44}, boronic acids\textsuperscript{45c}, and silanes to aryl fluorides through silver or palladium catalysis and an electrophilic fluoride reagent has been reported.\textsuperscript{45}.

Ritter and co-workers\textsuperscript{46} have accomplished the late-stage fluorination of a number of biologically-relevant substrates using a palladium fluoride complex which is easily synthesized from KF and a Pd organo-precursor.\textsuperscript{46} Thus, treatment of the palladium complex 24 with KF affords the palladium fluoride complex 25 in 90% yield within 5 min (Figure 6).\textsuperscript{46}

\begin{center}
\includegraphics[width=0.8\textwidth]{figure6.png}
\end{center}

Figure 6. Synthesis of fluorinating reagent for late-stage fluorination

An application of fluorinating reagent 25 is illustrated in Scheme 3 for the synthesis of fluorodeoxyestrone 27.
Scheme 3. Fluorination of deoxyestrone 26 by reagent 25 (see Figure 6)

This reagent can easily be employed for fluorination with $^{18}$F for PET (positron emission tomography) studies. $^{46}$

Hartwig and collaborators $^{47,35}$ have reported the fluorination of aryl iodides with a simple copper reagent and fluoride source. Reactions of (t-BuCN)$_2$CuOT$_f$ and AgF with a range of aryl iodides are shown in Scheme 4. t-BuCN-ligated CuOT$_f$ was prepared in multi-gram quantities from Cu$_2$O, triflic acid and t-BuCN.

![Scheme 4. Fluorination reaction of iodobenzenes with (t-BuCN)$_2$CuOT$_f$ and AgF](image)

The same combination of (t-BuCN)$_2$CuOT$_f$ and AgF has also been employed by the same authors to achieve fluorination of aryl boronate esters. $^{48}$

More recently, Buchwald and co-workers $^{49}$ have reported the regioselective Pd-catalyzed fluorination of aryl triflates and bromides. The reaction involves the use of a fluorinated ligand in the presence of CsF in toluene or 2-MeTHF as solvent at room temperature. This new Pd-ligand complex (28, Figure 7) enables the fluorination reaction to be undertaken with high regiochemistry,
as opposed to other methods where a regioisomeric mixture of aryl fluorides was obtained. The structure of COD ligand is shown in Figure 7.

![Chemical structure of the COD ligand](image)

Figure 7. Structure of Pd-complex for effecting highly regioselective fluorination of aryl bromides and triflates

The scope of the transformation and application to some biologically-active compounds is illustrated in Scheme 5.49
Scheme 5. Fluorination reaction of aryl triflates and bromides employing CsF or AgF in the presence of Pd-L COD complex (Figure 6) in 2-Me-THF or Toluene

Heteroaryl triflates were also suitable substrates. Notably, XAV939 29\textsuperscript{50,51} a tankyrase inhibitor and potential cancer therapeutic, could be reacted to give the corresponding fluorinated product in excellent yield (Scheme 5), demonstrating the applicability of this method to medicinally-relevant compounds.

A well-known reaction for the industrial preparation of aryl (and heteroaryl) fluorides is the nucleophilic aromatic substitution (S\textsubscript{N}Ar).\textsuperscript{52} This involves the reaction of an electron-deficient (hetero)aryl halide or nitroarene with a nucleophilic fluoride source to generate the corresponding
aryl fluoride. Anhydrous alkali metal fluorides (MF) are most typically employed as the fluoride source (usually CsF). However, these salts are poorly soluble in organic solvents. As a result, high temperatures and long reaction times are necessary to obtain high conversions. These forcing conditions often limit functional group tolerance and lead to the formation of undesired side products.  

Sanford and co-workers have recently introduced the use of anhydrous tetramethyl ammonium fluoride Me₄NF, as fluorinating reagent for halo(hetero)arenes in SNAr reactions. The reactions are carried out in DMF as solvent, at room temperature, and the yields are superior to those obtained when CsF or Bu₄NF is used instead. The authors subjected relevant chloroarenes to the fluorination protocol and the products obtained are illustrated in Scheme 6.

![Scheme 6: Fluorination of haloarenes employing Me₄NF in DMF at room temperature (24 h) through a SNAr reaction](image)

As opposed to the observed low reactivity of aryl bromides and iodides in SNAr fluorination reactions, Sanford and co-workers showed that aryl halides (and nitro-arenes) can react with NMe₄F to afford comparable yields of the fluorinated product. The relative rates of substitution were found to be NO₂ ≫ Br > Cl > I ≫ OTf.

Ritter and co-workers have accomplished the deoxy-fluorination of aromatic and heteroaromatic compounds employing Phenofluor 14 as fluorinating reagent. The scope of the transformation is illustrated in Scheme 7.
Scheme 7. Deoxy-fluorination of aromatic compounds

Sulfonamides are well represented in a number of antibacterial, antimigraine, anti-inflammatory and antidiabetic agents as well as diuretics. Gouverneur and colleagues have described an oxidative fluorination protocol of 4-t-butyl-substituted sulfonamides in the presence of PhI(OAc)$_2$ (PIDA) and HF•Pyr as a fluoride source in DCM as solvent (Scheme 8).
Scheme 8. Fluorination reaction of sulfonamides

Arylsulfonamides substituted with either electron withdrawing or releasing groups, afford the respected fluorinated products in similar yields (products 30-33). Aryl rings ortho-substituted with moderate releasing or attracting groups, afford fluorine substituted products in good yields (products 34, 35, 37, 38), as opposed to strong electron donating groups on the aryl moieties, which afford poor yields (product 36).

Interestingly, 3,4-dihydro-2.1-benzothiazine 2,2-dioxide 39 activated with the t-butyl group at C-6 undergoes fluorination with PIDA and 4 eq. of HF-pyridine (Scheme 9). This reaction affords 40 in 83% yield. A control experiment performed with the unsubstituted benzosultam 41 confirms that the presence of the t-butyl group on the substrate is necessary for formation of the desired product.

Scheme 9. Oxidative fluorination of benzosultams 39 and 41

The authors investigated the mechanism of the reaction, and postulated an aryl-stabilized N-sulfonylnitrenium intermediate, which undergoes nucleophilic fluorination. Addition of TFA re-aromatizes the resulting fluorodienimine, with loss of t-butyl cation (Scheme 10).\(^\text{56}\)

Scheme 10. Proposed reaction mechanism for the oxidative fluorination of sulfonamides
4.-Methods for Fluorination of Heteroaromatic Compounds

4.a.- Conversion of C_Het-H into C_Het-F Bonds

4.a.1.- Pyridine, Pyridazine, Pyrazine Derivatives

Hartwig and co-workers\textsuperscript{57} have accomplished the late stage\textsuperscript{36,37} C_Het-H fluorination of a broad range of pyridines, quinolines, pyrazines, pyrimidines, and pyridazines with AgF\textsubscript{2} to afford monofluorinated products (Scheme 11).

\[
\text{R} + \text{AgF}_2 \xrightarrow{\text{MeCN, rt, hr, (0.05 M), (3 equiv)}} \text{R}\text{-Het-F}
\]

Scheme 11. Late stage fluorination reaction of pyridines, quinolines, pyrazines, pyrimidines, and pyridazines with AgF\textsubscript{2}

Benzoyl- and methylacetyloxy-substituted pyridines afford 2-fluorinated products in acceptable yields (products 42 and 45, Scheme 11). Pyridines substituted with chlorine- or methyl groups also afford good product yields (43 and 44). Quinolines, and pyrazine derivatives also render
good yields of ortho-fluorine substituted products (46-49), as is the case for pyrimidine and pyridazine substrates (50-54).

It should be noted that the fluorinated core of pyrazine (49, Scheme 11) has found recent applications in the treatment of influenza virus. For instance, favipiravir (Figure 8) is an antiviral drug that selectively inhibits the RNA-dependent RNA polymerase of influenza virus. Favipiravir is active against a broad range of influenza viruses, including A(H1N1), A(H5N1), and the recently emerged A(H7N9) avian virus. It also inhibits influenza strains resistant to widely used antiviral drugs such as amantadine, rimantadine, and neuraminidase inhibitors and shows a synergistic effect in combination with oseltamivir, thereby enabling influenza treatment options to be expanded.

Figure 8. Structure of favipiravir and related active pyrazine analog

The authors next examined the late-stage fluorination with representative drugs. The fluorination of acetyl-protected tropicamide, an anticholinergic drug containing a base-sensitive acetate and an acidic α-phenyl amide, gave 55 in 70% isolated yield (Figure 9). t-Butyl 4-(3-methyl-2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate, (a 1-(piperidin-4-yl)-1H-imidazo[4,5-b]-pyridin-2-(3H)-one core found in more than 1000 calcitonin gene-related peptide (CGRP) receptor antagonists), afforded 56 in 82% yield. Furthermore, 3-(cyclopropylmethoxy)-N-(2,6-dichlorophenyl)-4-(difluoromethoxy)-N-methylbenzamide reacted to form a 2-fluorinated analog of roflumilast, a drug used to treat chronic obstructive pulmonary disease.
Figure 9. Late stage fluorination to give F-tropicamide 55, F-1000 calcitonin 56, and F-roflumilast 57.

The authors 57 proposed a mechanism that involves initial coordination of AgF₂ to pyridine, followed by addition of the [Ag]-F bond across the π system of the pyridine to form an amido-silver(II)-fluoride complex 58 (Scheme 12). The authors also observed a KIE of 2.9, suggesting that the coordination of pyridine to AgF₂ and the addition step are reversible.

Scheme 12. Proposed reaction mechanism for the synthesis of 2-fluoropyridines with AgF₂

4.a.2.- Pyrrole and Imidazole Derivatives

Fluoro-substituted pyrroles have found important applications in medicinal chemistry. For instance, compound 59 (Figure 10) has potent anti-inflammatory activity and compound 60 has angiotensin II antagonist activity.
Figure 10. Fluoro-pyrroles with biological activity

Nenajdenko and collaborators have recently reviewed the fluorination methods for pyrrole derivatives. 60 N-Fluorodibenzenesulfonimide 11 (NFSI) was also used for the synthesis of 5-fluorocamptothecin 62 – a derivative of the antitumoral and antileukemic quinoline alkaloid 61 isolated from Camptotheca acuminata (Scheme 13). 60

Scheme 13. Synthesis of fluorocamptothecin 62

Albertshofer and Mani 61 have recently accomplished the regioselective electrophilic fluorination of N-1-protected imidazole derivatives by quenching an intermediate lithio-species with NFSI at –78 °C. 62 The transformation is illustrated in Scheme 14.
Scheme 14. Regioselective electrophilic fluorination of N-1-protected imidazolines

5.a.3.-Imidazoheterocyclic Derivatives

Imidazo[1,2-a]pyridines are important structural motifs in medicinal chemistry, such as zolpidem 63 64, alpidem 64 65, minodronic acid 65 66, olprinone 66 67, and zolimidine 67 68 (Figure 11). The fluorination of imidazo[1,2-a]pyridines has recently been accomplished by Sun and co-workers.63

Figure 11. Therapeutic drugs containing the imidazo[1,2-a]pyridine nucleus

The authors 63 undertook a late-stage fluorination of the imidazo[1,2-a]pyridine core by employing Selectfluor as the fluorinating reagent, DMAP as a base in a mixture of CHCl₃:H₂O (3:1) starting the reaction at 0 °C for 2 h and then, allowing to reach room temperature (12 hour reaction). Some examples of this transformation are shown in Scheme 15.
Imidazopyridines with electron releasing groups such as OMe proceeded in good yields (compound 69). Aryl-substituted imidazopyridines with halogen atoms on the aryl ring, also gave good yields of 3-fluorinated imidazo[1,2-a]pyridine derivatives (compounds 70-73). Notably, the antiulcer drug Zolimidine 67 was fluorinated in 87% yield to afford 3-fluoro-2-(4-(methylsulfonyl)phenyl)imidazo[1,2-a]pyridine 74. Halogenated imidazo[1,2-a]pyridines also afford good yields of 3-fluoro-substituted compounds (78 and 79).

Next, the authors explored the scope of imidazo-heterocycles such as those shown in Scheme 16, obtaining the respective fluoro-substituted compounds in excellent yields. 2-Phenylimidazo[1,2-a]pyrimidine 80 affords 71% yield of 3-fluoro-2-phenylimidazo[1,2-a]pyrimidine.

Scheme 15. Monofluorination of aryl-substituted imidazo[1,2-a]pyridines
81, whereas 2-phenylbenzo[d]imidazo[2,1-b]thiazole 82 affords the 3-fluoro-substituted analog 83 in 63% yield (Scheme 16). The reaction mechanism is depicted in Scheme 19.

Scheme 16. Fluorination of imidazo heterocyclic derivatives

![Scheme 16](image)

Scheme 17. Proposed reaction mechanism for the 3-fluorination of imidazo[1,2-a]pyridines

Taking into account literature precedent, the reaction proceeds through an electrophilic fluorination mechanism (Scheme 17). Initially, reaction of imidazo[1,2-a]pyridine 84 with Selectfluor 7 yields the unstable 3-fluorinated cation 85, followed by addition of water to form 86. Deprotonation follows to generate intermediate 87, and then a proton is abstracted by DMAP to furnish the monofluorinated product 88.
4.a.4.-Isoxazolinone Cores

The fluorination of oxygen- and sulfur-containing heterocycles has recently been reviewed by O’Sullivan and co-workers.\textsuperscript{70} Isoxazolinone cores are widespread components in numerous biological important molecules such as those depicted in Figure 12.

Figure 12. Representative isoxazolinone cores in pharmaceutical drugs 89 and 90 are of natural origin; 91 and 92 are of non-natural origin

The fluorination of isoxazolinone cores has recently been developed by Wang and co-workers.\textsuperscript{71} The authors\textsuperscript{71} have accomplished the stereoselective fluorination through the use of an asymmetric catalyst 93 (a \textit{bis}-cinchona alkaloid\textsuperscript{72}), NFSI as fluorinating agent, in the presence of K$_3$PO$_4$, in CHCl$_3$ at -50 °C. Yields of 4-fluorinated product range from 78 to 93% with enantiomeric excess ranging from 73-83% (Scheme 18).
Scheme 18. Stereoselective fluorination of isoxazolinones

4.a.5.-Synthesis of Benzoxazine Cores

Benzoxazines are present in bioactive compounds, such as the anxiolytic and anticonvulsant drug *etifoxine* 100,74,73, or progesterone receptor agonists 101 (Figure 13).

![Bioactive compounds 100 and 101 containing the 4H-3,1-benzoxazine core](image)

The fluorination of 4H-3,1-benzoxazine core has been developed by Guo and co-workers,73 through electrophilic fluorocyclization75 of styryl amides. The optimal conditions used Selectfluor reagent, in MeCN at room temperature under atmosphere of nitrogen. The scope of the transformation is illustrated in Scheme 19.
Scheme 19. Synthesis of fluorinated 4H-3,1-benzoxazine cores from styryl-amide precursors

4.b.-Conversion of C\text{Het}-X into C\text{Het}-F Bonds (X = Cl, Br, I, OH, OT\text{f}, NO\text{2})

4.b.1.-Pyridine, Pyridazine, Pyrazine, Imidazole and Triazole Derivatives

As mentioned in Section 3a, Sanford and co-workers \textsuperscript{53b} developed anhydrous Me\textsubscript{4}NF for S\text{N}Ar fluorination of appropriate halo-precursors (Cl, Br, I). These conditions have been extended to halo-(hetero)aromatic starting materials (Figure 14). Pyridines with electron withdrawing groups yield fluoro-substituted products \textbf{103-105} in good yields. Chloroquinoline, chloroisouquinoline, chloropyridazine and chloropyrazine substrates also undergo room-temperature fluorination to form fluorinated products \textbf{106-110}, respectively, in excellent yields. The high-yielding synthesis of 8-(benzyloxy)-2-fluoroquinoline \textbf{107} is particularly noteworthy, as \textsuperscript{18}F-\textbf{107} has been used for the PET imaging of amyloid plaques. \textsuperscript{76,77}
Figure 14. S$_N$Ar fluorination of chloropyridine, isoquinoline, chloropyridazine and chloropyrazine substrates with Me$_4$NF

Ritter and co-workers$^{31c}$ have accomplished the deoxy-fluorination of heteroaromatic compounds employing Phenofluor 15 as fluorinating reagent. The scope of the transformation is illustrated in Scheme 20.
Scheme 20. Scope of the deoxyfluorination reaction of quinolines, isoquinolines, pyrazines and pyrimidine derivatives with Phenofluor

Quinolines, isoquinolines, quinoxaline and pyrimidine starting materials gave good yields of fluorine-substituted products, whereas pyridine and quinazoline starting materials afforded lower yields of the desired products (Scheme 20).

*Terconazole 118, fluconazole 119, cyproconazole 120, and triazolam 121* (Figure 15) are representative of marketed drugs containing a triazole.78

![Figure 15. Triazoles in clinical use](image)

The fluorination of triazole nuclei has recently been carried out by Chu and co-workers79, starting from 5-iodotriazole, and employing AgF (5 equiv), TMEDA (tetramethyl ethylene diamine, 0.2 equiv), in toluene at 110 °C for 20 h.79 The scope of the reaction is illustrated in Figure 16.
Figure 16. Scope of the fluorination of triazole derivatives

1,4-Disubstituted triazoles afford good yields of 5-fluorotriazole derivatives 122 and 123. Triazoles substituted with methylpyridine, n-heptyl, methylnaphthalene at the 1-position (and a phenyl group at the 4-position) also afford good yields of 5-fluorotriazole derivatives (products 124-126).

5.-Methods for Fluorination of Sugars and Nucleobase Derivatives

Fluorination also has long been recognized in nucleoside chemistry, and the synthetic origin can be traced back to a report by Fox and co-workers. The replacement of the 2′ or 3′ hydroxyl groups of a nucleoside with a fluorine atom causes only a minor change in the overall structure, but profoundly affects the stereoelectronic properties of the sugar moiety. Such dominating effects can control the conformational equilibria and lock the sugar ring into either a North, 127 (C3′-endo pucker) or a South, 128 (C2′-endo pucker) conformation, that can stabilize the glycosidic bond toward hydrolysis, and can also modulate the octanol/water partition coefficient (Log P) (Figure 17). 85
A recent finding\(^5\) has shown that compounds that mimic the C3\(^\prime\)-(F) endo pucker of the native acyl adenylate intermediate\(^6\) exhibit greater biological activity than compounds that adopt the C2\(^\prime\)-endo pucker, thus establishing a strong relationship between bioactivity and conformation for inhibitors of the nucleoside antibiotic 5\(^\prime\)-O-[N-(salicyl)sulfamoyl]-adenosine, which is a prototype for a new class of antibiotics that targets iron acquisition through inhibition of aryl acid adenylating enzymes\(^5\).

The introduction of a fluorine atom into a piperidine can also alter the \(pK_a\) significantly, resulting in an improvement to oral bioavailability.\(^86\) For instance, the 3-piperidinylindole derivative \textbf{129} (Figure 18) binds to the human 5-HT\(_{2A}\) serotonin receptor, and was targeted as a promising antipsychotic drug lead.\(^87\) However, the bioavailability of \textbf{129} was limited due to the basicity of the secondary amine group (positively charged at physiological pH). This inconvenience has been overcome by introducing a fluorine atom onto the piperidine ring (\textbf{130}, Figure 18), reducing the basicity of the secondary amine by nearly two orders of magnitude, resulting in a marked betterment.

**Figure 17.** North \textbf{127} (C3\(^\prime\)- endo pucker) or a South, \textbf{128} (C2\(^\prime\)-endo pucker) conformations of carbohydrates
of the oral bioavailability. The bioavailability (and 5-HT$_{2A}$ binding affinity) could be further improved by the introduction of a second fluorine atom, this time onto the indole moiety (131, Figure 18); this further improvement in bioavailability was attributed to deceleration of the metabolic degradation.$^{86a}$

![Fluorination Improves Bioavailability](image)

Figure 18. Fluorination improves the bioavailability of 3-piperidinylindole derivatives 129-130 by reducing the basicity of the secondary amine

Shaw and collaborators$^{30b}$ achieved the enantioselective fluorination reaction of piperidinones taking advantage of the methodology reported by MacMillan$^{86b}$, which uses a modified cinchona alkaloid catalyst. The authors found that primary chiral amines are superior as chiral inductors than secondary amines. Thus (R)-1-(2-methoxyphenyl)ethanamine is able to induce a high $ee$, as shown in Scheme 21. On the other hand, (R)-2-amino-1,1,2-triphenylethanol affords the opposite enantiomer with high $ee$, albeit lower yields (Scheme 21). With these catalysts, similar yields are obtained to those for the quinine derivatives shown in Figure 19.
Scheme 21. Enantioselective fluorination of piperidinone

Figure 19. Structure of cinchona alkaloid-derived catalysts

The triphenylethanolamine catalyst shows the highest level of $ee$ of all the commercial catalysts, which is in line with the observation that increasing the steric environment around the amine improves the $ee$; however, the conversions are low, which may also be a result of the sterically encumbered environment of the catalyst. The authors also confirmed that when carrying out the reaction at 0 °C, the amount of catalyst could be reduced from the original 20 to 10% without any drop in yield or $ee$. When NFSI is replaced by Selectfluor as fluorinating reagent, the reaction failed to yield any fluorinated product. The refinements in the reaction allowed the procedure to be scaled-up to produce 23g of enantiopure 1-Boc-3S-fluoro-4R-piperidinol.
Iminosugars can competitively bind to glycosidase enzymes because of their structural resemblance to the terminal sugar moiety of natural substrates. As a consequence, iminosugars show great promise for the treatment of a variety of diseases including diabetes, viral infection, bacterial infection, and lysosomal storage disorders.  

*Miglitol* (132, Figure 20) is an orally-available drug used for the treatment of type II diabetes (Merck). The fluorinated analogue 133 (Figure 20) is particularly worthy of note, since this compound is five times more potent than the existing drug 132, and exhibits no toxicity in human cells.

![ Structures of Miglitol and fluorinated analog](image)

**Figure 20.** Structures of *Miglitol* and fluorinated analog

A general strategy for the synthesis of fluorinated *N*-heterocycles is the deoxy-fluorination method using reagents illustrated in Figure 4. 31b C2′, C3′, and C5′-Fluoronucleosides have been synthesized with the use of Selectfluor 90 and NFSI, and some selected examples with Selectfluor are shown in Scheme 22. It should be noted that there are also numerous approaches for fluorination of nucleosides that involve readily prepared fluorinated building blocks 91 that will not be discussed.
There has been a recent review article on the synthesis of fluorinated nucleoside derivatives, where the sugar moiety can be fluorinated through the use of DAST, Selectfluor, or FClO$_3$, etc.

Fluorinated nucleosides have found an array of applications in medicinal chemistry. 2,2'-Difluorocytidine 134 (gemcitabine) belongs to the most widespread applied therapeutics in combination with radiotherapy, against a number of cancers (Figure 21).
Figure 21. Structures of fluorinated nucleobase and nucleosides currently employed in medicinal chemistry

The synthesis of *gemcitabine* 134 has been revisited and improved recently.\textsuperscript{93,94} *Sofosbuvir* 135 (Figure 21) has been approved as a therapeutic agent for the treatment of hepatitis C. Among other fluorinated nucleosides with antiviral activity, are: FddC 136 (2',3'-dideoxy-2'-fluorocytosine)\textsuperscript{95} and FLT 137 (3'-fluoro-3'-deoxythymidine)\textsuperscript{96} which inhibit the HIV reverse transcriptase. In addition, there is one other nucleoside fluorinated at the 2'-position of the sugar moiety approved by the FDA for the treatment of cancer: *clofarabine* 138 (2-chloro-2'-deoxy-2'-fluoroarabinoadenosine)\textsuperscript{97} which is used clinically for the treatment of leukemia in children.

Ferrero and co-workers\textsuperscript{98} have recently studied the synthesis of fluorinated azanucleosides and investigated their biological activity against HIV-1\textsubscript{LAI} using 3'-azido-3'-deoxythymidine (AZT, *zidovudine*) as a reference in an assay with human peripheral blood mononuclear cell (PBM). The representative compounds are illustrated in Figure 22. Compounds 139-141 show modest activity when compared to AZT.
Zajc and co-workers\textsuperscript{99} have come up with a straightforward method for the introduction of a fluorine atom into the 8-position of ribonucleosides via metation-electrophilic fluorination under heterogeneous reaction conditions. The scope of the transformation is illustrated in Scheme 23.
Scheme 23. Fluorination of ribonucleosides and 2’-deoxyribonucleosides

Fluorinated nucleosides 143-147 formed through an S_N process were obtained with all the substrates. The presence of the secondary products 148-151 suggests an ET (electron transfer) process. Thus, a competing nucleophilic substitution reaction and an ET process results in the
mixture of observed products. In the case of ribonucleosides, it is likely that the SN reaction is slower due to steric reasons.

As a new family of anti-HIV compounds, emtricitabine FTC 152 (4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one) and racivir RCV 153 (4-amino-5-fluoro-1-[(2S,5R)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one) (Phase II), contain a F atom. Figure 23 illustrates their structures.  

![Figure 23. Structures of Emtricitabine and Racivir](image)

**6.- Fluorination of sp³ Carbon Atoms**

**6.a.- Fluorination of benzylic positions**

Methods for the fluorination of benzylic carbon atoms have been recently reviewed by Hurley and co-workers.  

The beneficial properties of benzyl fluorides in lead optimization have motivated an intense research activity in late stage fluorination of benzylic positions. Britton and colleagues have reported a late-stage fluorination of benzylic positions employing NFSI using either a decatungstate photocatalyst or AIBN-initiation.

They applied the method to the synthesis of fluorinated ibuprofen, as shown in Scheme 24.
Scheme 24. Fluorination of ibuprofen methyl ester

Scheme 25. Photocatalytic mechanism for the late-stage fluorination of benzylic positions

The mechanism for the photocatalytic reactions is illustrated in Scheme 25. Irradiation of photocatalyst tetrabutyl ammonium decatungstate (TBADT) produces an excited species (W*) that abstracts a H atom from a benzylic position, producing a benzylic radical 154. Radical 154 abstracts a fluorine atom from NFSI, producing the fluorination at the benzylic position and bis(benzenesulfonimide) radical 155. Radical 155 accepts a H atom from 156, regenerating TBADT and closing the photocatalytic cycle.

Groves and co-workers \(^{105}\) have developed a manganese-catalyzed oxidative C-H fluorination reaction of benzylic position and applied the fluorination strategy to medicinal targets and compounds with biological activity such as *ibuprofen* and *vitamin E*. The general strategy involves the use of a manganese-salen complex 157 (Scheme 26), triethylamine trihydrofluoride (TREAT-HF, Figure 3) or AgF, in MeCN as solvent. Interestingly, no fluorination of the aryl moiety is encountered.
From Scheme 26 it can be observed that F-ibuprofen methyl ester 158 is obtained in 55% yield, and the F-vitamine E 159 analog in 53% yield.

The authors proposed a mechanism for the above reaction, as illustrated in Scheme 27. The starting [MnIII(salen)F] or [MnIII(salen)F2]− catalyst, formed in situ, is oxidized to [MnV(O)(salen)F], which then abstracts a hydrogen atom from the substrate, forming the benzyl radical and a manganese(IV) species (Scheme 27). Then, the formed radical reacts with the [MnIV(salen)F2] complex, yielding the fluorinated products, regenerating the MnIII catalyst. An important kinetic isotope effect (5.6 ± 0.6) was observed for a 1:1 mixture of ethylbenzene and ethylbenzene-d10 as the substrate. The relatively low enantioselectivities observed (Scheme 26) are probably due to a very early transition state for the fluorine transfer step and a linear Mn–F–C geometry. However, the fact that the asymmetric Mn catalyst can lead to a good stereoinduction, provides strong evidence for a manganese-bound fluorine source in the fluorine transfer step.
Scheme 27. Proposed mechanism for the catalyzed benzylic fluorination

Xu and co-workers \(^{106a}\) have recently developed a fluorination method for benzylic positions (and β-carbonyl compounds, \textit{vide infra}) employing 15 mol% of Pd(OAc)\(_2\), NFSI as fluorinating agent, Ag\(_2\)O, and pivalic acid in chlorobenzene as solvent at 90 °C. The scope of the transformation is illustrated in Scheme 28.

Scheme 28. Palladium-mediated benzylic fluorination reaction
The 8-aminquinoline-derived auxiliary is acting as a directing group for the β-fluorination of the amide group. 106a Fluorination of benzenepropanamide derivative gave good yields of product 160 (Scheme 28). The authors 106a examined additional substrates bearing halogen substituents such as o-Cl, p-F, and 2,4-diCl. All of them gave similar yields of products 161-163. Starting materials containing electron-withdrawing substituent including m-NO2, m-CF3, or electron releasing m-OCH3 also render a good yield of fluorinated product under the reaction conditions (products 164-166, respectively).

6.b.-Fluorination of Steroids 106b and Prostaglandine Derivatives

Fludrocortisone 167 107 was one of the first fluorinated pharmaceutical drug to be developed (Figure 24). A more recent variety is fluticasone propionate 168, an antiinflammatory steroidal drug used to treat a variety of conditions.

![Structure of Fludrocortisone](image1)

![Structure of Fluticasone Propionate](image2)

Figure 24. Structure of fludrocortisone 167. Structure of fluticasone propionate 168

Fluticasone propionate 168 can be applied to treat inflammation associated with dermatoses and psoriasis. 108
Lee and co-workers have recently employed NFSI for the fluorination pathway of \textit{betulinic acid} derivative 169\textsuperscript{109}, according to Scheme 29. \textit{Betulinic acid} derivatives 169 possess potent anti-HIV activity.

Scheme 29. Fluorination step in the synthesis of \textit{betulinic acid} derivative 169, with potent anti HIV activity.

Steroids have recently been reported to undergo a deoxy-fluorination reaction with PyFluor with high diastereoselectivity, as illustrated in Scheme 30.\textsuperscript{32}

Scheme 30. Deoxyfluorination of steroid derivatives employing PyFluor.
A laboratory-devised fluoro pyridinium 171 has been employed for the fluorination of an analog 172 of Corey lactone prostaglandin synthetic intermediate, as illustrated in Scheme 31.

Scheme 31. Fluorination of Corey lactone prostaglandin synthetic intermediate 172

A fluorinated prostaglandin currently employed in the treatment of glaucoma is tafluprost 173 (Figure 25). This prostanoid is a very potent intraocular pressure-lowering agent as a result of FP-receptor agonist activity.110

Figure 25. Structure of tafluprost 173, a fluorinated prostanoid with FP-receptor agonist activity

The synthesis of tafluprost 173 has been achieved 111 by fluorination of a lactone prostaglandin derivative 174, as illustrated in Scheme 32.
The synthesis of tafluprost was started from the Corey aldehyde 174, which was converted to enone 176 by Horner–Emmons reaction with phosphonate 175. The fluorination reaction of enone 176 with morpholinosulfur trifluoride 177 in CHCl₃ at 30–40 °C for 82 h and successive deprotection of the benzoyl group with potassium carbonate in MeOH gave geminal difluoride 178 in 71% yield. Reduction of lactone 178 with iBu₂AlH in THF–toluene at -78 °C and ulterior Wittig reaction with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide (179) and reactions using potassium bis(trimethylsilyl)amide or sodium bis(trimethylsilyl)amide as the base in THF at 0 °C, afforded product 173 with the Z/E stereoselectivity in a 99:1 ratio. The Wittig reaction and successive esterification of the crude acid treated with isopropyl iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in acetone gave the desired 15-deoxy-15,15-difluoro-PGF2a isopropyl ester 173 (tafluprost) in 72% yield.

6.c.- Fluorination of terpene-derivatives
Tang and collaborators\textsuperscript{112} have recently reported a new methodology to carry out the fluorination of sp\textsuperscript{3} carbon atoms of biological relevant substrates. The fluorination of \textit{sclareolide} \textbf{180}, a sesquiterpene lactone used as supplement in weight loss therapy, has been accomplished through the use of radical initiator K\textsubscript{2}S\textsubscript{2}O\textsubscript{8}, Selectfluor II (Figure 3), in MeCN/H\textsubscript{2}O mixtures, according to Scheme 33. Fluorination does not take place at the two methine positions due to steric hindrance. Instead, the regioselective fluorination takes place at the C-2 methylene position, which has less steric impediment.

![Scheme 33. Late-stage fluorination of \textit{sclareolide} \textbf{180}](image)

Also, the fluorination of \textit{gibberellic}-derivative GA \textbf{181} \textsuperscript{112} (a diterpene, that stimulates the cells of germinating seeds to produce mRNA molecules that code for hydrolytic enzymes), can give 42\% yield of fluorinated product \textbf{182} (Scheme 34).

![Scheme 34. Late stage fluorination of \textit{gibberellic} \textbf{181} derivative](image)

In \textit{gibberellic} \textbf{181}, fluorination at the C16 methine position occurs as the major product due to a more electron-rich and less steric hindered site compared to the other tertiary C–H bonds.  \textsuperscript{112}
With an ester derivative of the anticancer drug taxol 183 (Scheme 35), fluorination takes place with 4.0 equiv. of K₂S₂O₈ and 2.5 equiv. of Selectfluor II (PF₆) to furnish the fluorinated product 184 in 33% isolated yield. The selective and late-stage fluorination occurred at the methine position on the side chain due to the steric hindrance and deactivation of the other available tertiary C–H bonds on the rings. It is also noteworthy that the alkene and free hydroxyl groups were not fluorinated under the reaction conditions.

![Scheme 35. Late stage fluorination of taxol derivative 183](image)

The proposed mechanism for all the transformations in Schemes 33-35 is depicted below in Scheme 36.

![Scheme 36. Proposed reaction mechanism for the radical fluorination of sp³ C atoms with Selectfluor](image)

It is accepted that peroxydisulfate anion decomposes into the sulfate radical anion which oxidizes an aliphatic C-H bond into a carbon radical 186 (Scheme 36), ensuing electrophilic fluorination. Otherwise, Selectfluor is also known to fluorinate alkyl radicals 186 to form C-F bonds.
7.d. Fluorination of sp³ carbon atoms by photocatalysis

DiRocco and Britton have reported the photocatalytic fluorination of sp³ carbon atoms to be applied the methodology to the synthesis of odanacatib, used in the treatment for osteoporosis and bone metastasis. Compound 189 is an inhibitor of cathepsin K, an enzyme involved in bone resorption. The sodium salt of decatungsten is able to catalyze the fluorination of salts of leucine methyl ester in the presence of NFSI. The large scale production of odanacatib was carried out in a flow photoreactor while irradiating at 365 nm (Scheme 37).

Scheme 37. Fluorination of leucine methyl ester towards the synthesis of odanacatib

The mechanism of the reaction is depicted in Scheme 25 (vide supra).

6.e. Fluorination at the α-Carbonyl Positions and β-Carbonyl Positions
Shibata and colleagues have recently shown that the fluorinating reagent \( N\)-fluoromethanesulfonimide (\( F-N(SO_2Me)_2 \), Me-NFSI, Figure 3) is a better fluorinating reagent for methane groups than NFSI. The authors compared a set of fluorination reactions of methane positions with Me-NFSI and NFSI and demonstrated improved scope and higher yields with the former. They have applied the new reagent to the fluorination reaction of \( \beta \)-keto-esters 190, as illustrated in Scheme 38.

![Scheme 38: Fluorination reaction of \( \beta \)-keto-esters with Me-NFSI](image)

<table>
<thead>
<tr>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>Me-NFSI (1.2 equiv)</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>MeOH, RT</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>92% (in THF)</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>90%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>98%</td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>H</td>
<td>66%</td>
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<td></td>
</tr>
<tr>
<td>Me</td>
<td>R^3 = H</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

Scheme 38. Fluorination reaction of \( \beta \)-keto-esters with Me-NFSI

The enantioselective incorporation of fluorine atoms into organic substrates was pioneered by Shibata and co-workers. The authors employed combinations of cinchona alkaloids and NFSI or Selectfluor as fluorinating reagents. Shaw and collaborators have accomplished the enantioselctive fluorination of piperidinones in good yields and excellent ee\(^{86b,30b} \) (vide supra, Scheme 21, section 5) based on the studies of MacMillan and collaborators.

The enantioselective incorporation of fluoroacetate into organic molecules is a prevailing matter. Acetate is one of the most fundamental building blocks in nature and organic synthesis, from which numerous natural products and medicinally important compounds, such as polyketides and statins are formed. Saadi and Wennmers have very recently employed the fluoromalonic acid.
hemi-thioethers 191 (F-MAHTs, Figure 26) as equivalents of activated fluoroacetate. This F-MAHTs 191 is the fluorinated versions of nature’s acetate building blocks.

Figure 26. Structure of racemic fluoromalonic acid hemi-thioethers F-MAHTs 191, and catalyst 192 (a quinidine-urea catalyst) and its enantiomer 193

F-MAHT 191 in the presence of catalyst 192 or 193 (Figure 26) together with 4-dimethylaminopyridine (DMAP) increased the enantioselectivity towards the synthesis of F-MAHTs (Scheme 39).

Scheme 39. Aldehydes and their decarboxylative aldol reaction of F-MAHTs

In this respect, the authors 119 were able to synthesize fluorinated atorvastatin 194 120 in good yields and with 99% enantiomeric excess, as shown in Scheme 40.
Scheme 40. Synthesis of enantioselective fluorinated atorvastatin 194

Sanford and co-workers\textsuperscript{121} have recently reported a stereoselective fluorination strategy to achieve the synthesis of chiral fluorolactam building blocks (196, Figure 27) towards the synthesis of potential pre-clinical candidate spleen tyrosine kinase inhibitors Syk 195.\textsuperscript{122}

Figure 27. Spleen tyrosine kinase inhibitors Syk, and chiral fluorolactam building blocks B

Fluoromalonate ester 197 (Scheme 41) is synthesized in high yield through direct fluorination reaction of dimethyl malonate ester using fluorine gas, catalyzed by copper nitrate in MeCN solution. Michael addition of acrylonitrile to fluoromalonate 197 affords the desired nitrile 198 in 90% yield.
Ulterior reduction of the nitrile group of 198 by hydrogen over palladium and subsequent base-catalyzed ring closure yielded racemic fluorolactam 199 (Scheme 41).

![Scheme 41. Synthesis of racemic fluoromalonate 199](image)

The authors used CAL-B 10 000 (a recombinant Candida Antartica Lipase B that is commercially available and used to catalyze a range of biotransformations) to give the desired fluorolactam 200 in > 99% e.e. (Scheme 42).

![Scheme 42. Synthesis of enantioselective fluorolactam 200 employing Candida Antartica Lipase B](image)

More recently, Stuart and co-workers have come up with a fluorination method of 1,3-dicarbonyl compounds employing fluoroiodane 14, according to Scheme 43.
Scheme 43. Fluorination of 1,3-dicarbonyl compounds with 1-fluoro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole 14

In a disconnected approach, De Kimpe and co-workers\textsuperscript{124,125} have employed ethylbenzoyl fluoroacetate 201 for the construction of 4-fluoropyrazolones 202 and their ulterior reduction to 3-hydroxy-4-fluoropyrazoles 203, according to Scheme 44. Such pyrazole cores are present in numerous pharmacologically-active compounds.

Scheme 44. Synthesis of 3-hydroxy-4-fluoropyrazole derivatives

Britton and co-workers have prepared a range of flavone derivatives in order to evaluate their potential as anti-prostate cancer agents\textsuperscript{126} through $\alpha$-fluorination of 1,3-dicarbonyl derivatives. They successfully incorporated fluorine into 204 using NFSI, affording fluorinated adduct 206 in 37% yield (Scheme 45). Acidification of 205 led to spontaneous cyclisation and elimination of water to furnish fluoroflavone 206 in excellent yield.
Scheme 45. Fluorinated adduct 206 with anti-prostate cancer activity

A recent method for the enantioselective $\alpha$-fluorination of carbonyl compounds (aldehydes) has been developed by Sun and coworkers. The authors used the Bode catalyst 207 (Scheme 46), NFSI as both fluorinating and oxidizing agent, $\text{K}_2\text{CO}_3$ as the base, in CHCl$_3$ at room temperature.

- **R CO$_2$R'**
- **F**
- **NFSI** (3 equiv), R'OH (1.1 equiv)
- CHCl$_3$, RT, 48 h

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph CO$_2$Me</td>
<td>63%, 93% ee</td>
<td></td>
</tr>
<tr>
<td>Ph CO$_2$Me</td>
<td>65%, 93% ee</td>
<td></td>
</tr>
<tr>
<td>Ph CO$_2$Me</td>
<td>65%, 94% ee</td>
<td></td>
</tr>
<tr>
<td>Ph CO$_2$Me</td>
<td>75%, 94% ee</td>
<td></td>
</tr>
<tr>
<td>Ph CO$_2$Me</td>
<td>62%, 95% ee</td>
<td></td>
</tr>
<tr>
<td>Ph CO$_2$Me</td>
<td>63%, 93% ee</td>
<td></td>
</tr>
</tbody>
</table>
Scheme 46. Scope of the enantioselective α-fluorination of aldehydes

Heterocycles, such as the easily oxidizable pyridine and thiophene, were also compatible with the strongly oxidative reaction conditions.\textsuperscript{127} The authors\textsuperscript{127} also applied the strategy to the synthesis of α-fluoroamides and thioesters, starting with aldehydes and making them react with nucleophiles such as amines and thiols.

Statines, or β-hydroxy-γ-amino acids, are important components of several key peptides. These peptides usually function as protease inhibitors and therefore are relevant substrates for the treatment of various diseases including cancer (cathepsin D), Alzheimer’s disease (cathepsin D, BACE, α-secretase), hypertension (renin), AIDS (HIV protease), and malaria (plasmepsins).\textsuperscript{128} As a result, the synthesis of both natural statines and their analogues has been a subject of intense interest. Hunter and coworkers\textsuperscript{129} have designed a diastereoselective synthesis of 2-(R) and 2-(S) fluorostatines represented in Scheme 47.
Scheme 47. Diastereoselective fluorination of protected statines

The reaction started with protected leucine, and the fluorination took place from chiral aldehyde 208 (Scheme 47) employing NFSI as fluorinating reagent, organocatalysts 209 (i.e.: (R)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine, (R)-209 and (S)-2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine, (S)-209) in methyl t-butyl ether as solvent (MTBE), and further reduction with NaBH₄. The (R)-209 organocatalyst afforded the highest diastereoselective ratios of protected fluoro-statine. Deprotection took place with HCl.²⁹

Xu and coworkers¹⁰⁶ have developed a protocol for introducing a fluorine atom into the β-position of carbonyl compounds. They employed catalyst Pd(OAc)₂, NFSI as fluorinating source,
pivalic acid, in chlorobenzene as solvent at 80 °C. The scope of the transformation is depicted in Scheme 48.

Scheme 48. Scope of the synthesis of fluorinated of β-carbonyl compounds

The proposed mechanism is illustrated in Scheme 49.

Scheme 49. Proposed reaction mechanism for the synthesis of fluorinated of β-carbonyl compounds
The first step involves the formation of the cyclopalladated intermediate \( \text{210} \) (Scheme 49) to afford the [5,5]-fused bicyclic. Then, Pd\( ^{\text{II}} \) is oxidized into a Pd\( ^{\text{IV}} \) intermediate by NFSI and Ag\(_2\)O. The role of PivOH in this reaction is presumably to help reductive elimination of strong metal–fluorine bond by replacing the N(SO\(_2\)Ph)\(_2\) ligand on Pd\( ^{\text{IV}} \) complex or to help regenerate the active catalyst by replacing the N(SO\(_2\)Ph)\(_2\) ligand on Pd\( ^{\text{II}} \). Finally, reductive elimination of \( \text{211} \) forms the fluorination product \( \text{212} \) with ulterior regeneration of Pd\( ^{\text{II}} \).

Thus this \( \beta\)(\( sp^3\))-H fluorination of carbonyl compound derivatives such as carboxylic acids can provide a new method for the introduction of fluorine atom into a drug candidate which is of great value for SAR studies.\(^{\text{1f,n}}\)

6.f.-Synthesis of \( \alpha\)- and \( \beta\)-Fluoroamine Cores with Pharmacological Activity

The rationale behind the special treatment in fluorinating techniques for amines is the decrease in their basicity upon introducing a vicinal fluorine atom, and modulation of physicochemical characteristics, such as Log P. Incorporation of the fluorine substituent at a late stage of the transformation is also desirable.\(^{\text{130}}\).

Chen and Liu have very recently presented a review article on methods for accessing \( \beta\)-fluoroamines.\(^{\text{93}}\) These \( \beta\)-fluoroamines constitute important structural motifs in a large array of biological important molecules. Figure 28 illustrates some relevant \( \beta\)-fluoroamine bioactive compounds: LY503430 \( \text{213} \); MK-0731 \( \text{214} \); antibacterial agent \( \text{215} \), and GABA-AT inactivator \( \text{216} \).
Figure 28. Relevant β-fluoroamines bioactive compounds 213-216

A general strategy to prepare β-fluoroamines using Selectfluor, is illustrated in Scheme 50.

Scheme 50. Ritter-type amino-fluorination of olefins

The reaction depicted in Scheme 50 belongs to a Ritter-type aminofluorination reaction or a fluoroamination reaction. In this reaction, 1-fluoro-4-hydroxy-1,4-diazeniabicyclo[2.2.2]octane bis(tetrafluoroborate) (NFTh, 13) was used as electrophilic fluorinating reagent (Figure 3), while the
solvent MeCN functions as nucleophile. Both tetramethylethene and styrenes successively gave vicinal fluoroamides in good yields.

Shibata and co-workers have used FP-T300 (compound 6 in Scheme 51) as a fluorinating reagent for the synthesis of bioactive fluorobrevianamide E 217 and fluorogypsetin 218.25,86

![Scheme 51. Synthesis of β-fluoroamines fluorobrevianamide E 217 and fluorogypsetin 218 employing FP-T300 6 (1-fluoro-2,4,6-trimethyl pyridinium triflate)](image)

The strategy was also employed for the synthesis of fluorinated α-carboline fragments.26 A carbocation is involved in the electrophilic fluorination process. These transformations rely on the electrophilic incorporation of fluorine atom and a subsequent cyclization process.
For transition metal-catalyzed formation of β-fluoramino compounds, the review from Chen and Liu is quite comprehensive. Thus, transition metals such as Pd, Ag, Au, Fe, and Cu, have been shown to catalyze aminofluorination reactions, enabling the syntheses of fluoro-piperidines, pyrrolidines, pyrroles, quinolones, isoquinolines, lactams, pyrazoles, oxazolidinones, and fluorinated indoles. The fluorinating agents employed in this fluorinating reaction were Selectfluor or NFSI.

More recently, Chen and Liu have accomplished the fluorination reaction of piperidine cores through an aminofluorination reaction with high stereoselectivity. They applied the methodology towards the synthesis of 6-((R)-fluoroswansonine 219 (an anticancer alkaloid with potential to treat glioma and gastric carcinoma, and also an adjuvant for other anticancer drugs) and 5-((R)-fluoroferifugine 220 (with antimalarial properties). The synthetic targets are depicted in Scheme 52.

Scheme 52. Fluorination reaction towards the synthesis of F-swansonine and F-ferifugine

7.-Fluorination of sp² Carbon Atoms

Gulder and co-workers have reported the synthesis of the pharmacologically interesting heterocycles 4-fluoro-1,3-benzoxazepines from o-styryl benzamides by employing a fluorination/aryl migration/cyclization cascade strategy. The protocol avoids the need for transition metal catalysts,
and uses a shelf-stable hypervalent fluoro iodane reagent as an electrophilic source of fluorine. This reagent is not only significantly more reactive than the well-established iodine(III)-based fluorinating reagent Selectfluor, but provides completely different chemoselectivity, providing seven-membered ring benzoxazepines instead of oxazines. Moreover, this strategy is used in the synthesis of 20 structurally distinct congeners and proceeds with complete regioselectivity under mild reaction conditions, according to Scheme 53. The reaction employs the shelf-stable crystalline fluoro-benzoiodoxole 14 and consists of a fluorination / aryl migration / cyclization steps.

Scheme 53. Fluorinated benzoxazepine derivatives 221

8.-Fluorination of sp Carbon Atoms

For the biological-relevant synthesis of fluorinated isoquinoline nuclei, the silver-catalyzed reaction of alkynes in the presence of NFSI is illustrated in Scheme 54.
In the reaction, a fluorinated isoquinolinium intermediate \(222\) (Scheme 54) is derived from the oxidative fluorination of an heteroaryl-silver complex. The \(t\)-butyl substituent is eliminated as iso-butene in the presence of weak base (Li\(_2\)CO\(_3\)).

When the \(t\)-butyl group was changed to a CH\(_2\)CO\(_2\)R group, a fluorinated isoquinolinium intermediate is obtained instead, which can act as a 1,3-dipolar reagent. In the presence of base, and together with an alkyne, a 3+2 cycloaddition can yield biologically-interesting nuclei, such as pyrrolo[2,1-a]isoquinolines (Scheme 54). When CF\(_3\) alkynes were used, the pyrrolo[α]isoquinoline products show remarkable regioselectivity and excellent yields.

9.-Conclusions
The introduction of new and easy-to-handle commercial fluorinating reagents, either of nucleophilic or electrophilic in nature, has tamed the reactivity of fluorine gas for fluorination reactions and, therefore, made protocols more direct and less cumbersome. However, there still remains the need for fluorinating reagent strategies that could be easily prepared from inorganic fluoride salts as opposed from fluorine gas, as is the case with the majority of commercial electrophilic fluorinating reagents. Although the mechanism for fluorination with electrophilic fluorinating reagents remains a matter of some debate, with possibly both polar and radical components, the reactions have shown substantially improved yields over alternative processes, and opened-up an array of activity for the application of these reagents on diverse families of compounds. Thus, electrophilic fluorination strategies for aromatic compounds as well as for heteroaromatic compounds have been the subject of many literature reports. These strategies describe homolytic aromatic substitution reactions or replacement of groups such as halides, triflates, or boronic acids, with fluorine. Fluorination of aliphatic substrates has also been shown to proceed with electrophilic reagents, albeit through different mechanisms, on sp<sup>3</sup>, sp<sup>2</sup>, and sp carbon atoms. However, there still remains the challenge for stereoselective introduction of fluorine atoms into C<sub>sp</sub>3 centres.

Nucleophilic fluorination strategies with nucleophilic fluorinating reagents have been employed in the fluorination of (hetero)aromatic substrates, mainly through S<sub>N</sub>Ar reactions, and for the ipso substitution of hydroxy-substituted (hetero)aromatic compounds.

Table 1 summarizes the different applications of both electrophilic and nucleophilic reagents for the fluorination of different families of organic compounds. Denoted in red is the atom or group to be substituted by F, or position of addition of the fluorine moiety. As opposed to the reactions illustrated in the text above, Table 1 classifies the transformations according to fluorinating reagent for a quick reference guide to reagent applications.
Table 1. Different fluorination strategies most commonly employed for medicinal targets. In red is the group to be replaced by fluorine atom or position of addition of the fluorine atom

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Organic family</th>
<th>Additive</th>
<th>Conditions</th>
<th>Substrate</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>NFSI, 11</td>
<td>aryls</td>
<td>Pd(dba)$_2$</td>
<td>EtOAc, 80-110 $^\circ$C</td>
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<td>[38]</td>
</tr>
<tr>
<td>NFSI, 11</td>
<td>pyrroles</td>
<td>LHDMS</td>
<td>THF, -78 $^\circ$C</td>
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<td>[60]</td>
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<tr>
<td>NFSI, 11</td>
<td>imidazoles</td>
<td>LTMP</td>
<td>THF, -78 $^\circ$C</td>
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<td>[61]</td>
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<tr>
<td>NFSI, 11</td>
<td>isoxazolino-nes</td>
<td>bis-cinchona alkaloid (stereospecific fluorination)</td>
<td>K$_3$PO$_4$, CHCl$_3$, -50 $^\circ$C</td>
<td></td>
<td>[71]</td>
</tr>
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<td>NFSI, 11</td>
<td>pyrrolidinones</td>
<td>^3PrNH, BuLi</td>
<td>THF, -78 $^\circ$C</td>
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<td>[98]</td>
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<tr>
<td>NFSI, 11</td>
<td>nucleobases</td>
<td>LDA</td>
<td>Solid NFSI</td>
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<td>benzylic positions</td>
<td>tetrabutylammonium decatungstein (TBADC)</td>
<td>NaHCO$_3$, MeCN, $\lambda = 365$ nm, flow system</td>
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<td>[104]</td>
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<td>Position Type</td>
<td>Reagents</td>
<td>Solvent/Condition</td>
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<td>NFSI, 11</td>
<td>methine positions</td>
<td>Na$<em>4$W$</em>{10}$O$_{32}$ (cat.)</td>
<td>MeCN : H$_2$O (9 : 1) $\lambda = 365$ nm</td>
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<td>NFSI 11 or Me-NFSI 12</td>
<td>$\alpha$-carbonyl positions</td>
<td>LDA</td>
<td>THF, -78 °C – RT;</td>
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</tr>
<tr>
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<td>Pd(AcO)$_2$, Ag$_2$O Pivot</td>
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<td>NFSI, 11</td>
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<td>Selectfluor, 7</td>
<td>imidazoheterocyclic cores</td>
<td>DMAP</td>
<td>CH$_3$Cl: H$_2$O, 3:1 0 °C-RT</td>
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<td>methylene and methine carbon atoms</td>
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<td>MeCN, RT</td>
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<td>Reaction Conditions</td>
<td>Products</td>
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<td>14</td>
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<td>14</td>
<td>$\text{sp}^2$ carbon atoms</td>
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<td>aryl iodides</td>
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<td>phenols and hydroxyheteroaromatics</td>
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</tr>
</tbody>
</table>

10. References


100 Process and intermediates for preparing emtricitabine. US patent 7939660 B2.


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