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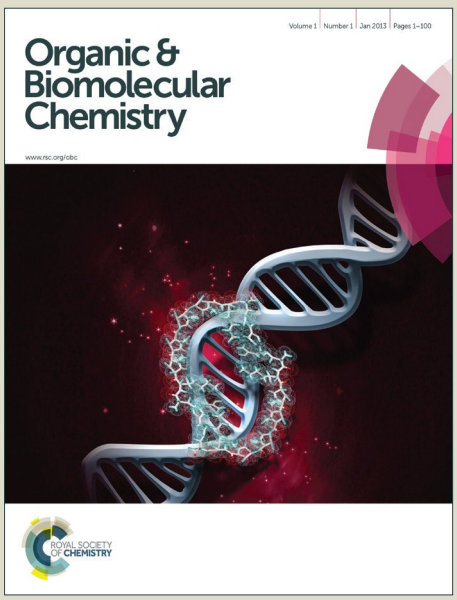

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FLUORINATION METHODS IN DRUG DISCOVERY

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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 [1] and comprehensive books [2] 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 [3] in reports dealing with fluorine in pharmaceuticals and in medicinal chemistry in general. [1b-o] A brief historical overview of fluorine in chemistry and medicinal chemistry has recently been described. [1b,c,e]

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 [4], 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.[1o,5,6]

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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) .

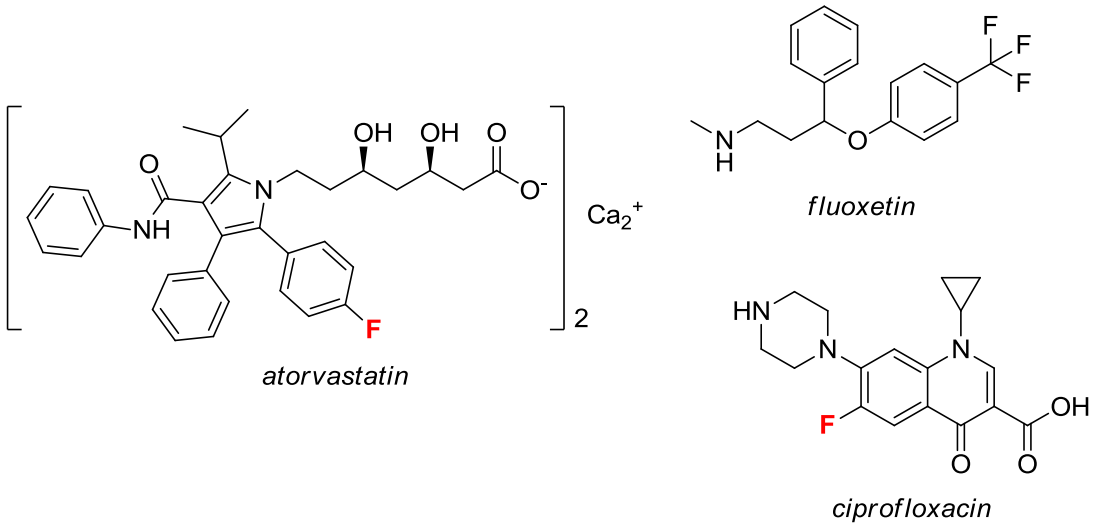

Figure 1. Structures of *atorvastatin*, *fluoxetin* and *ciprofloxaxin*

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

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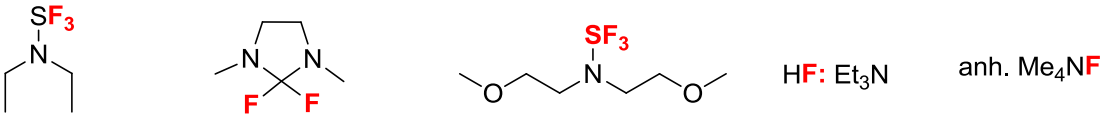
to describe, or enumerate fluorine-containing drugs and their mechanism of action.[1,10] Trifluoromethylation, trifluoromethoxylation, and trifluoromethylthiolation strategies will not be considered in this review.

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 *ipso* aromatic substitutions on phenyl and heteroaromatic rings, and substitutions at sp^3, sp^2 C-H bonds in aliphatic compounds.

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

2.-Fluorinating Reagents Used in Medicinal Chemistry [16]

Examples of nucleophilic reagents employed to construct C–F bonds (Figure 2) include diethylaminosulfur trifluoride **1** (DAST) [17], 2,2-difluoro-1,3-dimethylimidazolidine **2** (DFI) [18], and bis(2-methoxyethyl) aminosulfur trifluoride **3** (Deoxofluor).[19] Triethylamine trihydrofluoride **4** (TREAT-HF), [20] has been used as a highly polar fluorinating reagent. More classical fluorinating reagents include CsF used at elevated temperatures in S_NAr reactions or anhydrous tetramethyl ammonium fluoride [21], AgF, and AgF_2.



1, DAST **2, DFI** **3, DEOXOFLUOR** **4, TREAT-HF**

CsF **AgF** **AgF_2** Bu_4NF

Figure 2. Nucleophilic fluorinating reagents

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The development of electrophilic [22] fluorinating agents to tame the reactivity of elemental fluorine resulted in a great advancement. [23] A large array of electrophilic reagents [24] bearing a $R_2N–F$ or R_3N^{+-} 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[24b-d]), 2,4,6-trimethyl-1-fluoropyridinium triflate **6** (FP-T300,), introduced by Shibata. [25,26]. 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-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **7** (Selectfluor) [11], 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) **8** (FTEDA-PF_6), 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **9** (Selectfluor II), 1-methyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(hexafluorophosphate) **10** (Selectfluor II-PF_6), and *N*-fluorobenzenesulfonimide **11** (NFSI)[27], or the methyl analog Me-NFSI **12** [28], or 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) **13** (NFTh), developed by Stavber [29] and fluorobenziodoxole **14** (1-fluoro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxle), reported in 2013 by Togni and Stuart [30] (Figure 3).

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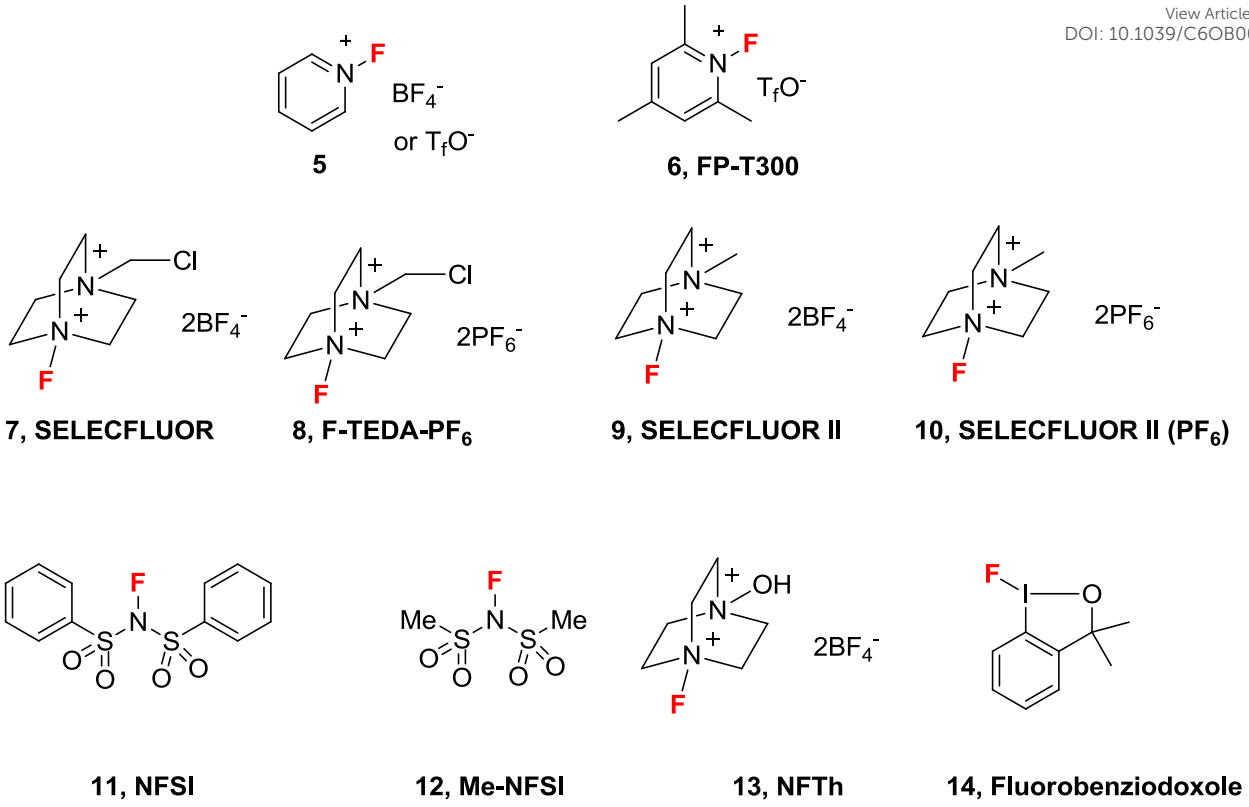

Figure 3. Electrophilic fluorinating reagents

Other recently introduced reagents, particularly for deoxyfluorination (Figure 4), include Phenofluor **15** [31], PyFluor **16**[32] and nickel-fluorido complexes **17a** and **17b** [33] together with (diethylamino)difluorosulfonium tetrafluoroborate **18** (XtalFluor-E). [34].

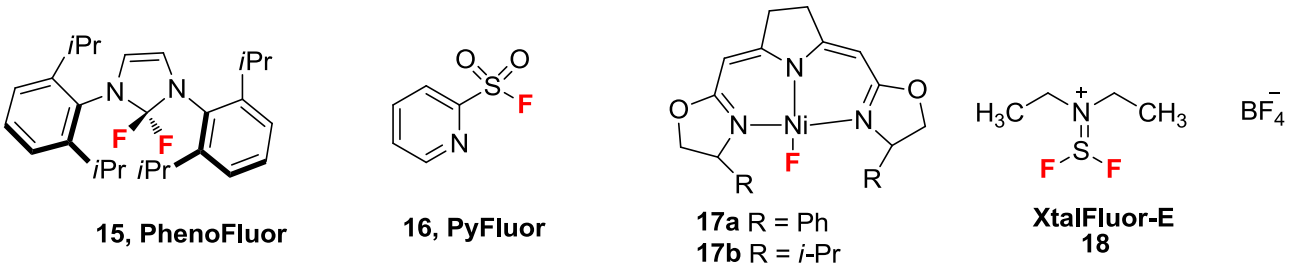

Figure 4. Deoxy-fluorinating reagent **15**, PyFluor **16**, nickel-fluorido complex **17**, and XtalFluor E, **18**

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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.[1c] 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).

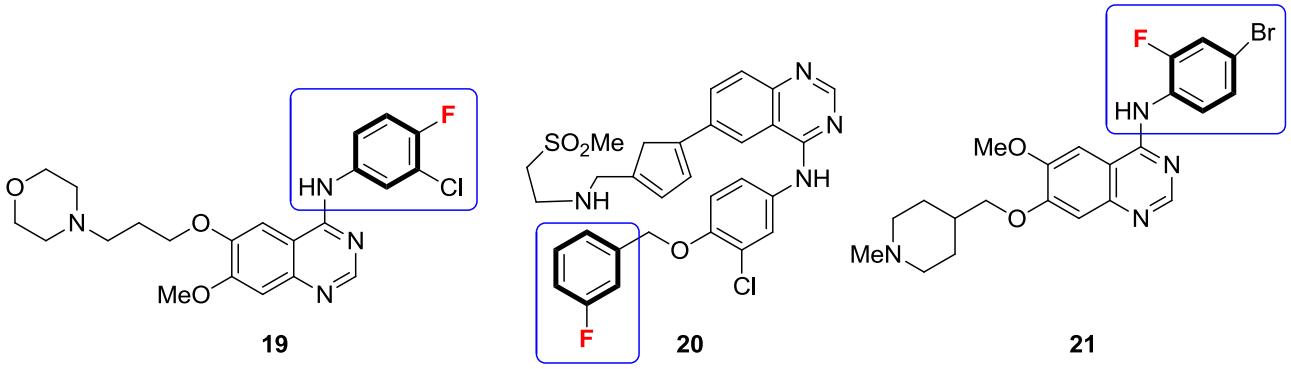

Figure 5. Structures of *Gefitinib* **19**, *Lapatanib* **20**, and *Vandetanib* **21**

While the vast majority of fluorinated pharmaceuticals are derived from fluoroaryl building blocks, the development of selective fluorination reactions or late-stage fluorination protocols [1b,37] would be beneficial to the syntheses.

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

Xu and co-workers [38] have developed an *ortho* C-H bond fluorination of 2-phenoxyl 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-phenoxyl nicotinic acid derivatives which are antagonists of the $P2Y_{12}$ receptor, an important target in antiplatelet therapies [39], Scheme 1.

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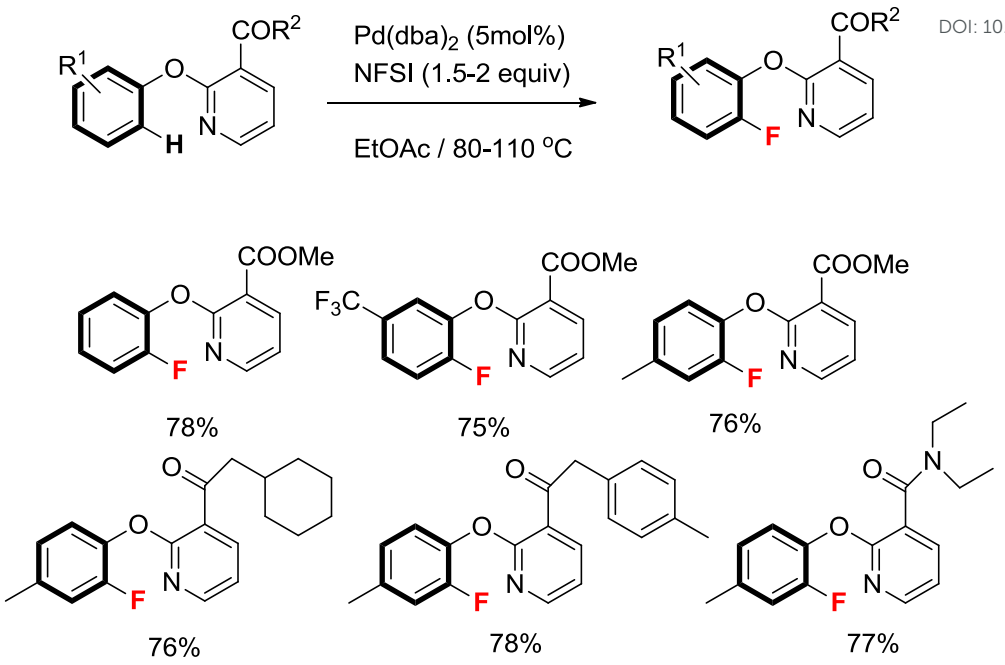
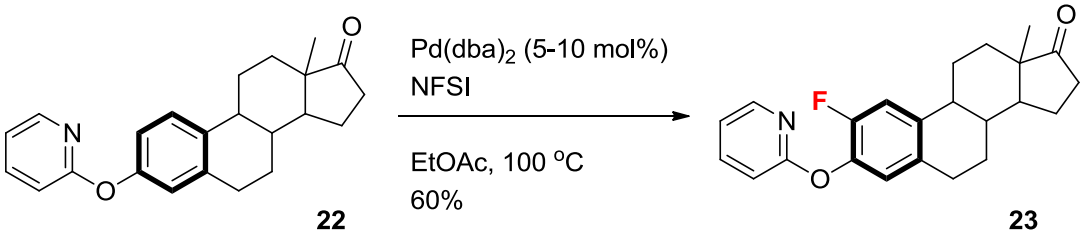


Scheme 1. *ortho* C-H bond fluorination of 2-phenoxyl pyridine derivatives through a palladium-catalysis

The strategy [38] utilizes 2-phenoxypyridines 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)

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Transition metal-complexes have been used to prepare fluoroarenes. [42,35]. For instance, the palladium-catalyzed fluorination of aryl triflates bearing electron-withdrawing groups has been undertaken.[43] The conversion of aryl stannanes [44,35,45a], trifluoroborates [44], boronic acids [45c], and silanes to aryl fluorides through silver or palladium catalysis and an electrophilic fluoride reagent has been reported. [45].

Ritter and co-workers [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.[46] Thus, treatment of the palladium complex **24** with KF affords the palladium fluoride complex **25** in 90% yield within 5 min (Figure 6). [46].

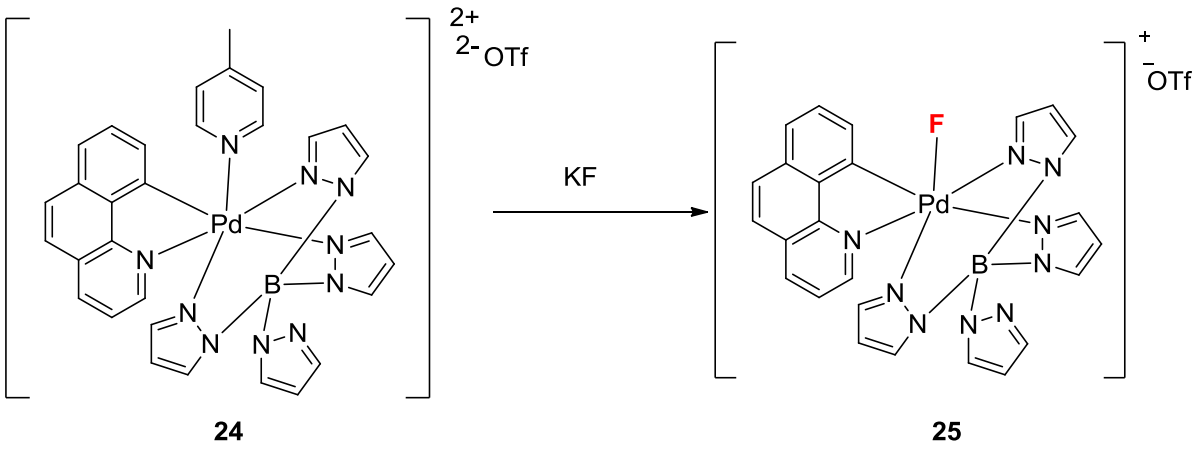
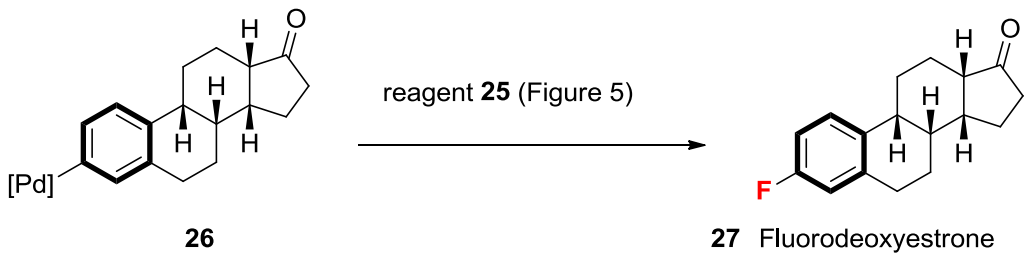


Figure 6. Synthesis of fluorinating reagent for late-stage fluorination

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)

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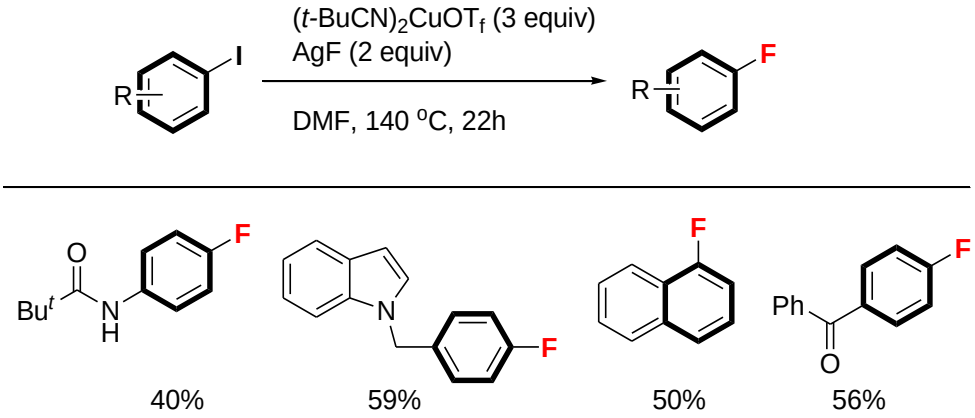
This reagent can easily be employed for fluorination with ^{18}F for PET (positron emission tomography) studies. [46]

Hartwig and collaborators [47,35] have reported the fluorination of aryl iodides with a simple copper reagent and fluoride source. Reactions of $(t\text{-BuCN})_2CuOT_f$ 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_2O, triflic acid and *t*-BuCN.



Scheme 4. Fluorination reaction of iodobenzenes with $(t\text{-BuCN})_2CuOT_f$ and AgF

The same combination of $(t\text{-BuCN})_2CuOT_f$ 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.

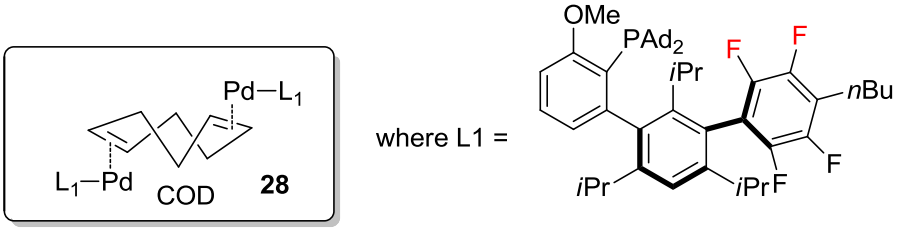


Figure 7. Structure of Pd-complex for effecting highly regioselective fluorination of aryl bromides and triflates

The scope of the transformation and application to some biologically- active compounds is illustrated in Scheme 5.[49]

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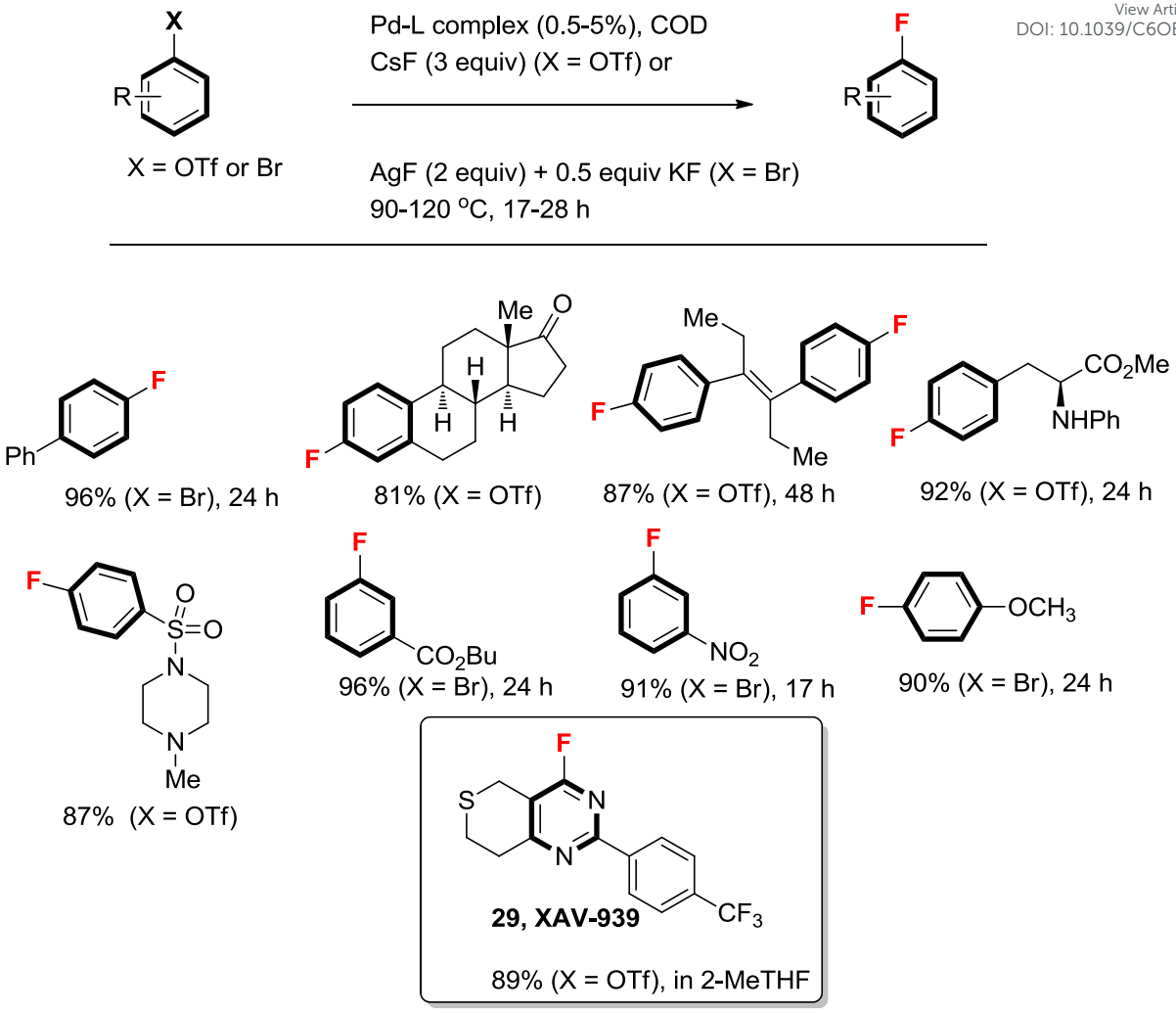

Scheme 5. Fluorination reaction of aryl triflates and bromides employing CsF or AgF in the presence of Pd-L COD complex (Figure 6) in 2-Me-THF or Toluene

Heteroaryl triflates were also suitable substrates. Notably, XAV939 **29** [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_NAr).[52] This involves the reaction of an electron-deficient (hetero)aryl halide or nitroarene with a nucleophilic fluoride source to generate the corresponding

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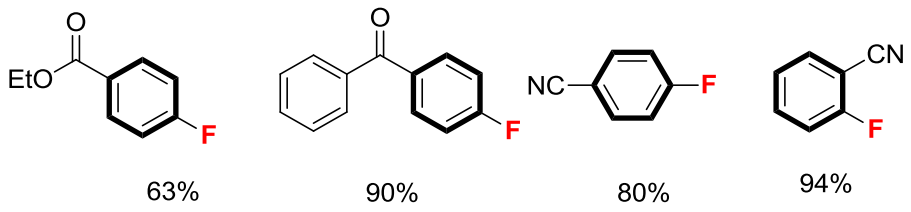
aryl fluoride. [53a] Anhydrous alkali metal fluorides (MF) are most typically employed as the fluoride source (usually CsF). However, these salts are poorly soluble in organic solvents. As a result, high temperatures and long reaction times are necessary to obtain high conversions. These forcing conditions often limit functional group tolerance and lead to the formation of undesired side products. [52]

Sanford and co-workers [53b] have recently introduced the use of anhydrous tetramethyl ammonium fluoride Me_4NF, as fluorinating reagent for halo(hetero)arenes in S_NAr reactions. The reactions are carried out in DMF as solvent, at room temperature, and the yields are superior to those obtained when CsF or Bu_4NF 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 Me_4NF in DMF at room temperature (24 h) through a S_NAr reaction

As opposed to the observed low reactivity of aryl bromides and iodides in S_NAr fluorination reactions[54], Sanford and co-workers showed [53b] that aryl halides (and nitro-arenes) can react with NMe_4F to afford comparable yields of the fluorinated product.[53b] The relative rates of substitution were found to be $NO_2 \gg Br > Cl > I \gg OT_f$.

Ritter and co-workers [31c] have accomplished the deoxy-fluorination of aromatic and heteroaromaticcompounds employing Phenofluor **14** as fluorinating reagent. The scope of the transformation is illustrated in Scheme 7.

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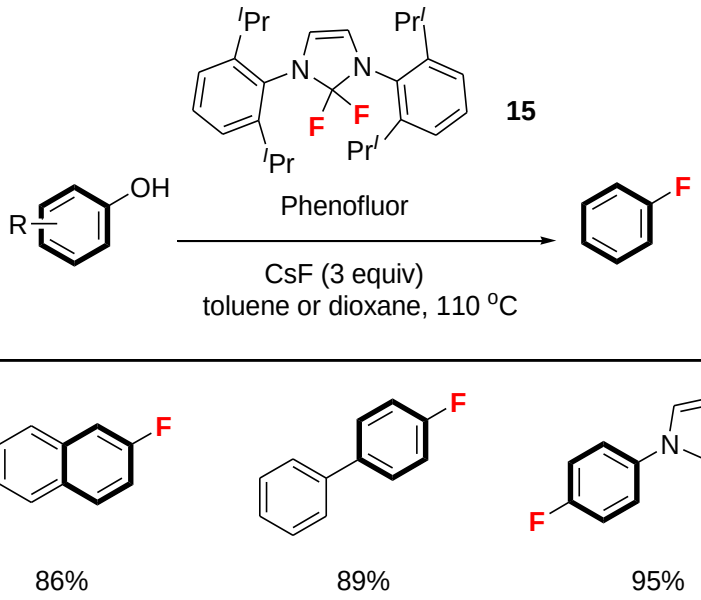
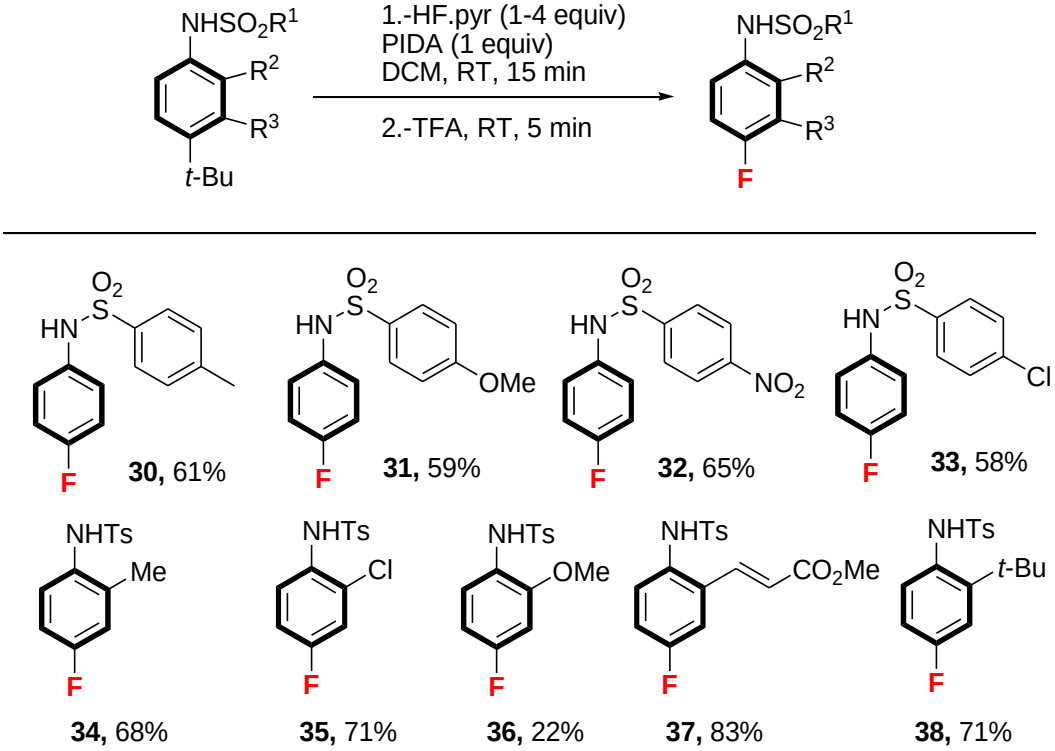


Scheme 7. Deoxy-fluorination of aromatic compounds

Sulfonamides are well represented in a number of antibacterial, antimigraine, antiinflammatory and antidiabetic agents as well as diuretics. [55] Gouverneur and colleagues [56] 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

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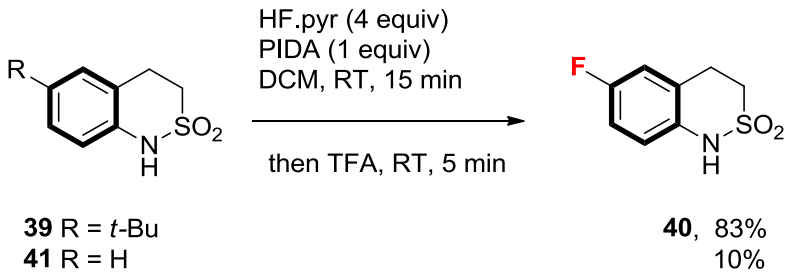
Arylsulfonamides substituted with either electron withdrawing or releasing groups, afford the respected fluorinated products in similar yields (products **30-33**). Aryl rings *ortho*-substituted with moderate releasing or attracting groups, afford fluorine substituted products in good yields (products **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.

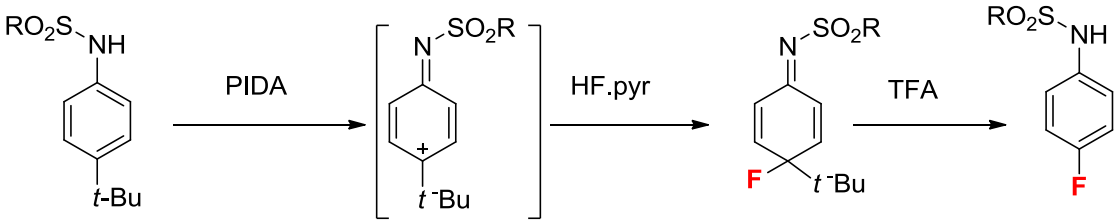


39 R = *t*-Bu
41 R = H

40, 83%
10%

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).[56]



Scheme 10. Proposed reaction mechanism for the oxidative fluorination of sulfonamides

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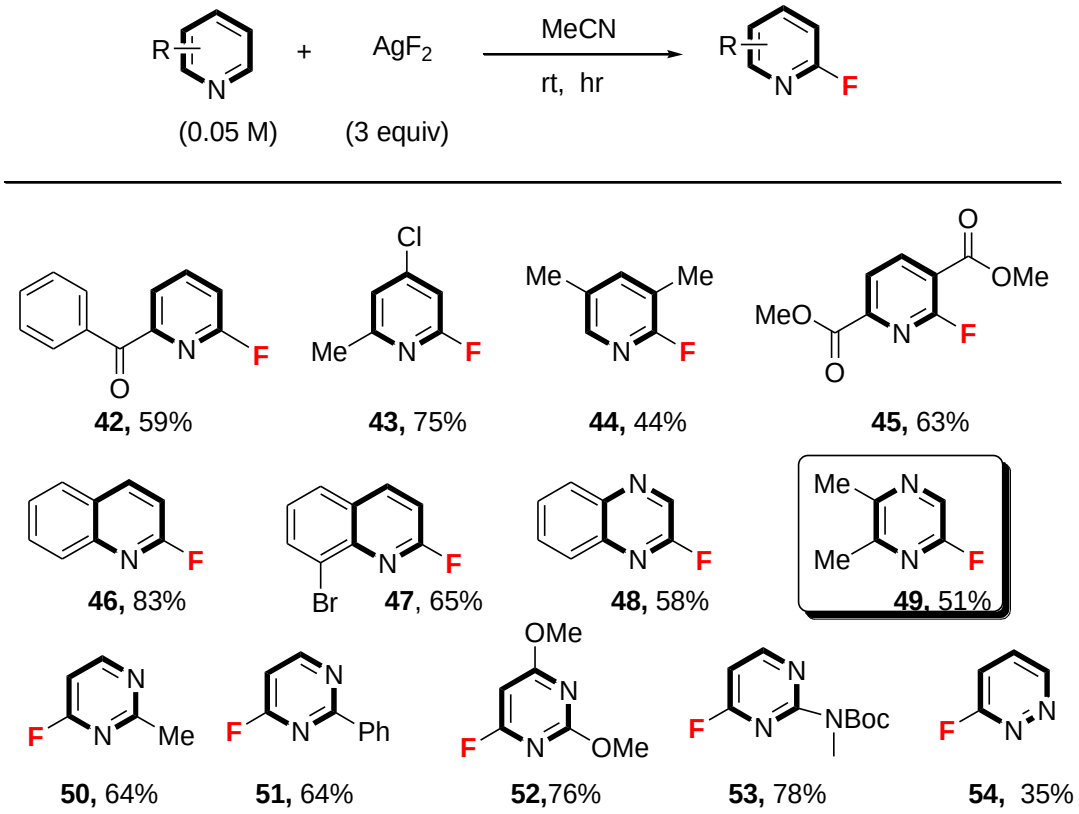
4.-Methods for Fluorination of Heteroaromatic Compounds

4.a.- Conversion of C_{Het}-H into C_{Het}-F Bonds

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

Hartwig and co-workers [57] have accomplished the late stage [36,37] C_{Het}-H fluorination of a broad range of pyridines, quinolines, pyrazines, pyrimidines, and pyridazines with AgF_2 to afford monofluorinated products (Scheme 11).



Scheme 11. Late stage fluorination reaction of pyridines, quinolines, pyrazines, pyrimidines, and pyridazines with AgF_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

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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. [58] 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.

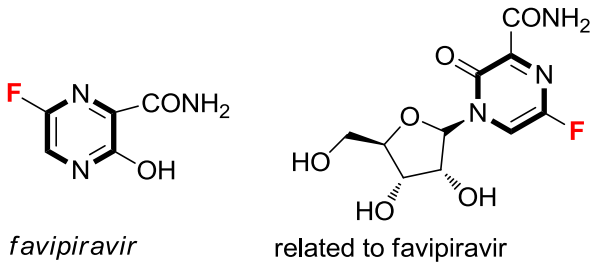
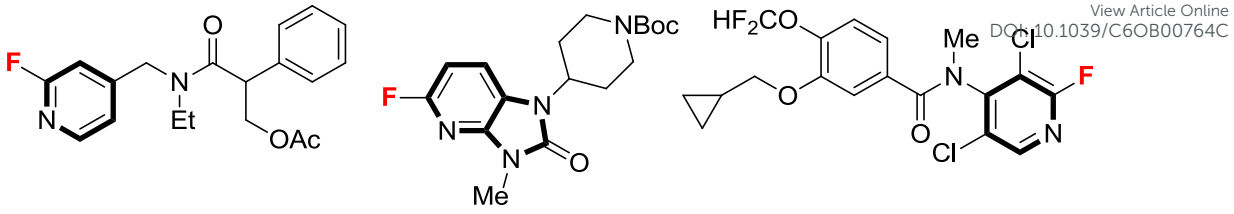


Figure 8. Structure of *favipiravir* and related active pyrazine analog

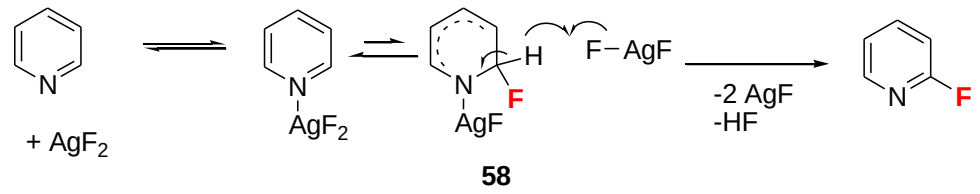
The authors [57] next examined the late-stage fluorination with representative drugs.[57] The fluorination of acetyl-protected *tropicamide*, an anticholinergic drug containing a base-sensitive acetate and an acidic α-phenyl amide, gave **55** in 70% isolated yield (Figure 9). *t*-Butyl 4-(3-methyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-1-yl)piperidine-1-carboxylate, (a 1-(piperidin-4-yl)-1*H*-imidazo[4,5-b]- pyridin-2-(3*H*)-one core found in more than 1000 calcitonin gene-related peptide (CGRP) receptor antagonists [59]), 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* **57**, a drug used to treat chronic obstructive pulmonary disease. [57]



55, 70% **56**, 82% **57** 69%

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 AgF_2 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 AgF_2 and the addition step are reversible.



58

Scheme 12. Proposed reaction mechanism for the synthesis of 2-fluoropyridines with AgF_2

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.

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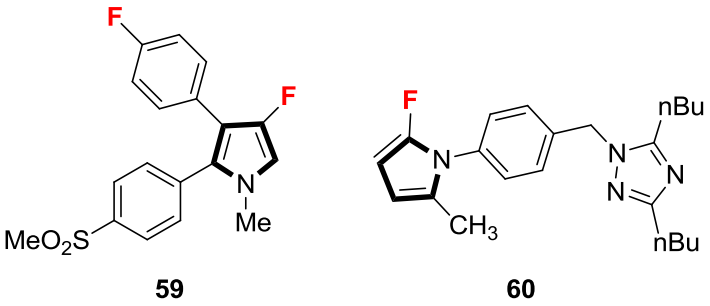
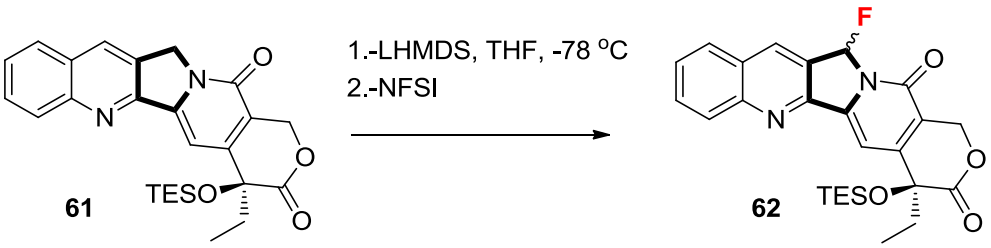


59 **60**

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 acuminate* (Scheme 13).[60]



61 **62**

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.

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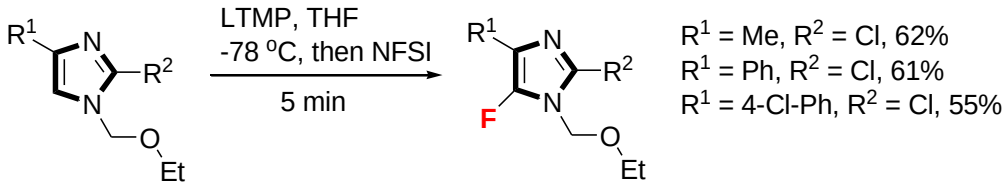

Scheme 14. Regioselective electrophilic fluorination of *N*-1-protected imidazolines

5.a.3.-Imidazoheterocyclic Derivatives

Imidazo[1,2-a]pyridines are important structural motifs in medicinal chemistry, such as *zolpidem* **63** [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]

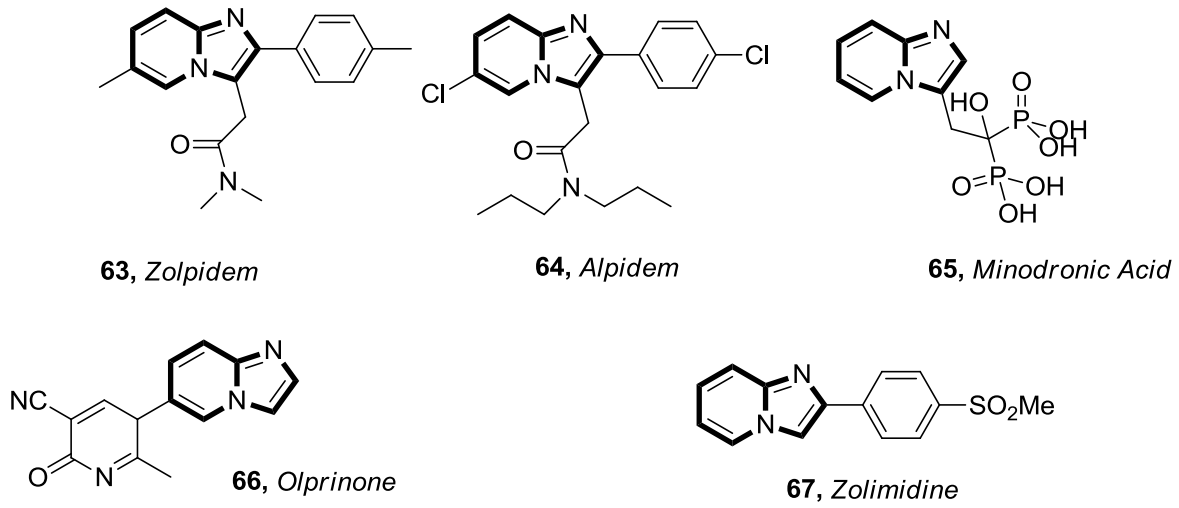

Figure 11. Therapeutic drugs containing the imidazo[1,2-a]pyridine nucleus

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 $CHCl_3$:H_2O (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.

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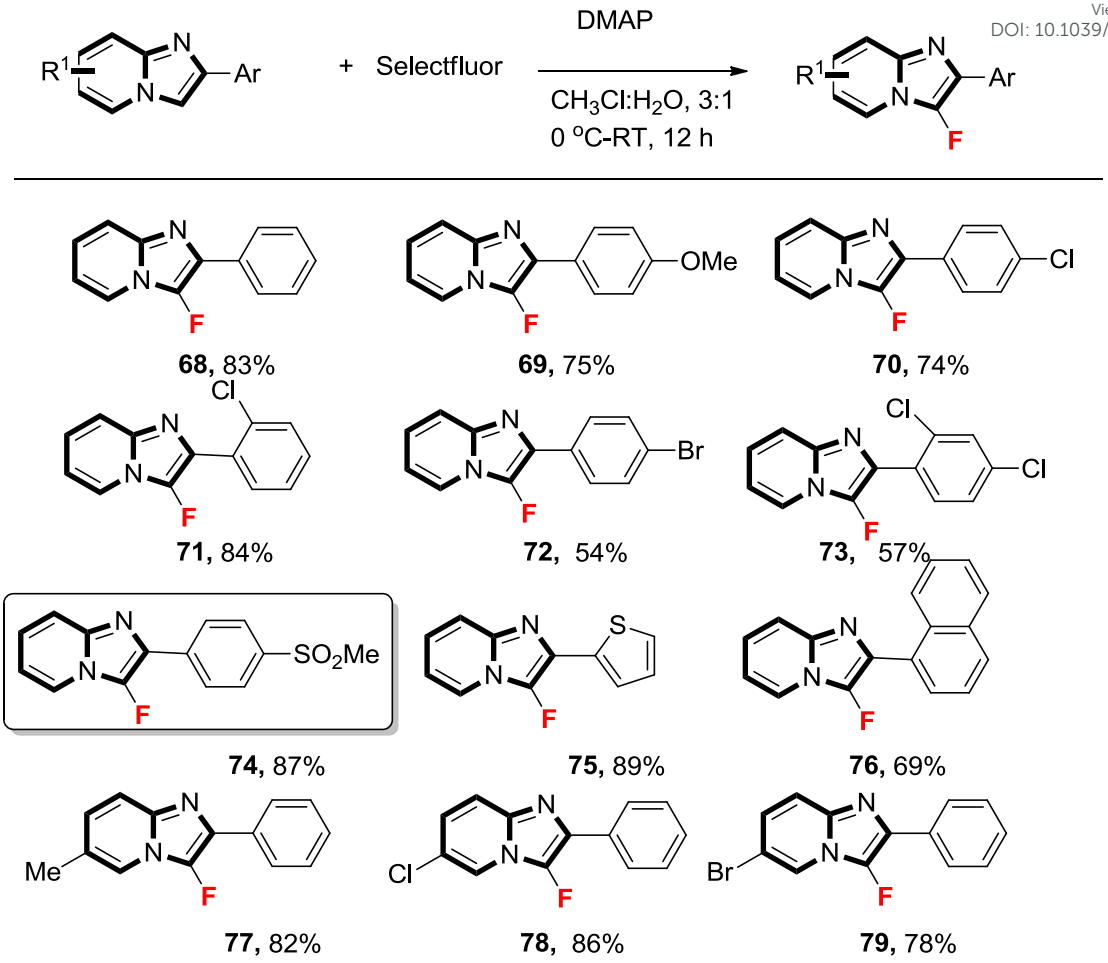
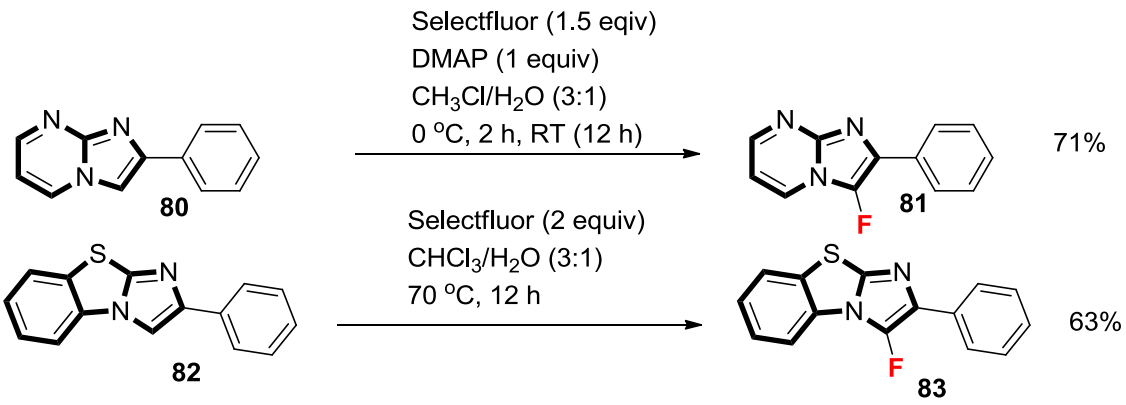


Scheme 15. Monofluorination of aryl-substituted imidazo[1,2-a]pyridines

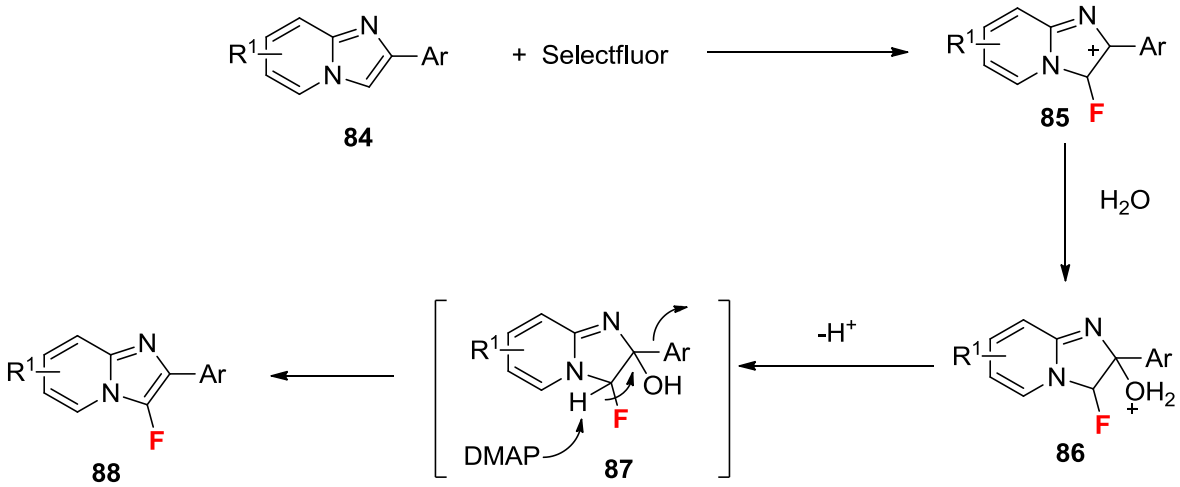
Imidazopyridines with electron releasing groups such as OMe proceeded in good yields (compound **69**). Aryl-substituted imidazopyridines with halogen atoms on the aryl ring, also gave good yields of 3-fluorinated imidazo[1,2-a]pyridine derivatives (compounds **70**-**73**). Notably, the antiulcer drug *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 [63] 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

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

Taking into account literature precedent [69], 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**.[63]

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4.a.4.-Isoxazolinone Cores

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

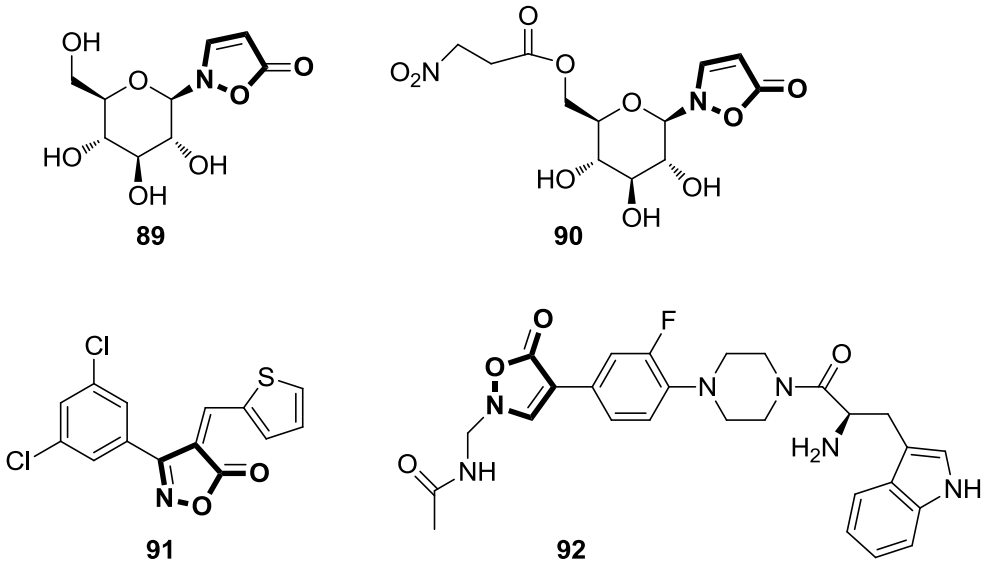
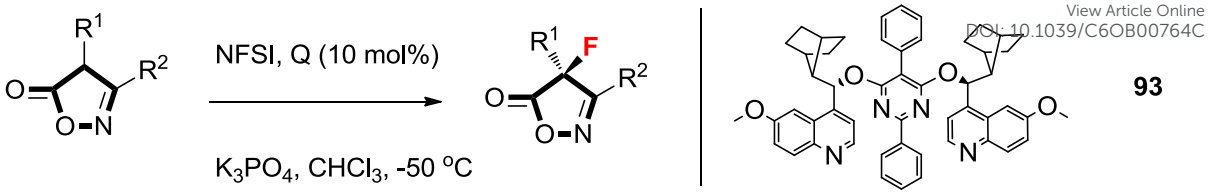


Figure 12. Representative isoxazolinone cores in pharmaceutical drugs **89** and **90** are of natural origin; **91** and **92** are of non-natural origin

The fluorination of isoxazolinone cores has recently been developed by Wang and co-workers. [71] The authors [71] have accomplished the stereoselective fluorination through the use of an asymmetric catalyst **93** (a *bis*-cinchona alkaloid [72]), NFSI as fluorinating agent, in the presence of K_3PO_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).

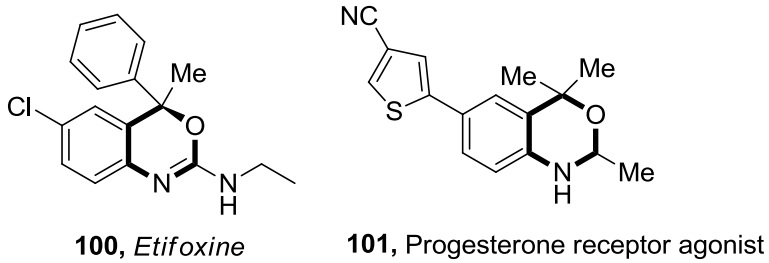


$R^1 = R^2 = Ph$	**94,** 78%, 83 % ee
$R^1 = p$MeOC_6H_4, $R^2 = Ph$	**95,** 87%, 80 % ee
$R^1 = p$FC_6H_4, $R^2 = Ph$	**96,** 79%, 76% ee
R^1=2-thienylmethyl, R^2=Ph	**97,** 89%, 73% ee
R^1 = naphthylmethyl, $R^2 = Ph$	**98,** 87%, 80% ee
R^1 =Bn, $R^2 = p$MeOC_6H_4	**99,** 93%, 82% ee

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).



100, *Etifoxine* **101,** Progesterone receptor agonist

Figure 13. Bioactive compounds **100** and **101** containing the 4*H*-3,1-benzoxazine core

The fluorination of 4*H*-3,1-benzoxazine core has been developed by Guo and co-workers, [73] through electrophilic fluorocyclization [75] 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.

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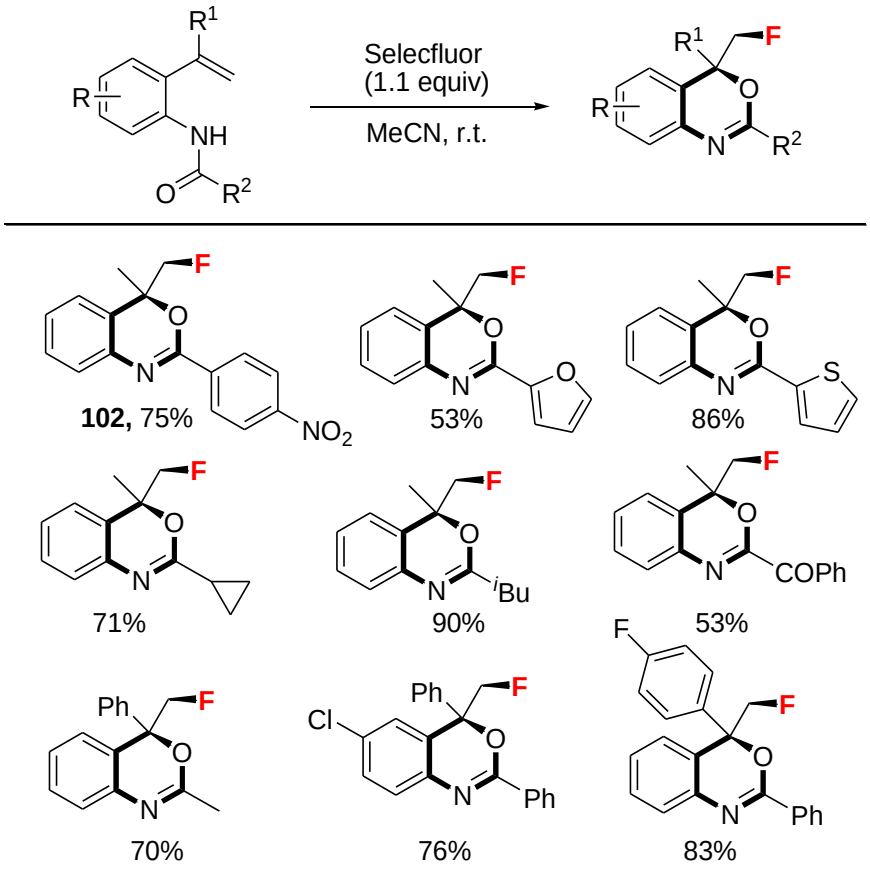

Scheme 19. Synthesis of fluorinated 4*H*-3,1-benzoxazine cores from styryl-amide precursors

4.b.-Conversion of C_{Het}-X into C_{Het}-F Bonds (X = Cl, Br, I, OH, OT_f, NO_2)

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

As mentioned in Section 3a, Sanford and co-workers [53b] developed anhydrous Me_4NF for S_NAr 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 **103-105** in good yields. Chloroquinoline, chloroisoquinoline, chloropyridazine and chloropyrazine substrates also undergo room-temperature fluorination to form fluorinated products **106-110,** respectively**,** in excellent yields. The high-yielding synthesis of 8-(benzyloxy)-2-fluoroquinoline **107** is particularly noteworthy, as ^{18}F-**107** has been used for the PET imaging of amyloid plaques. [76,77]

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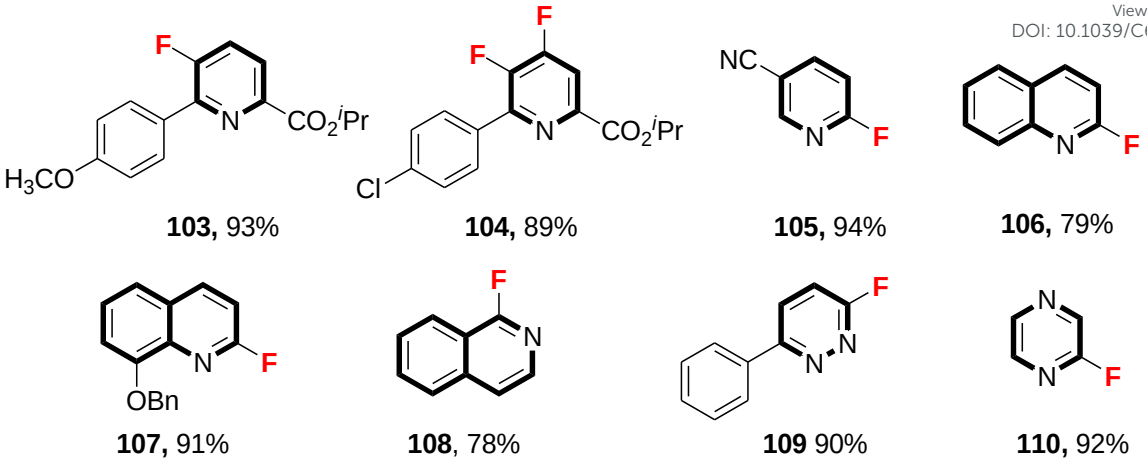
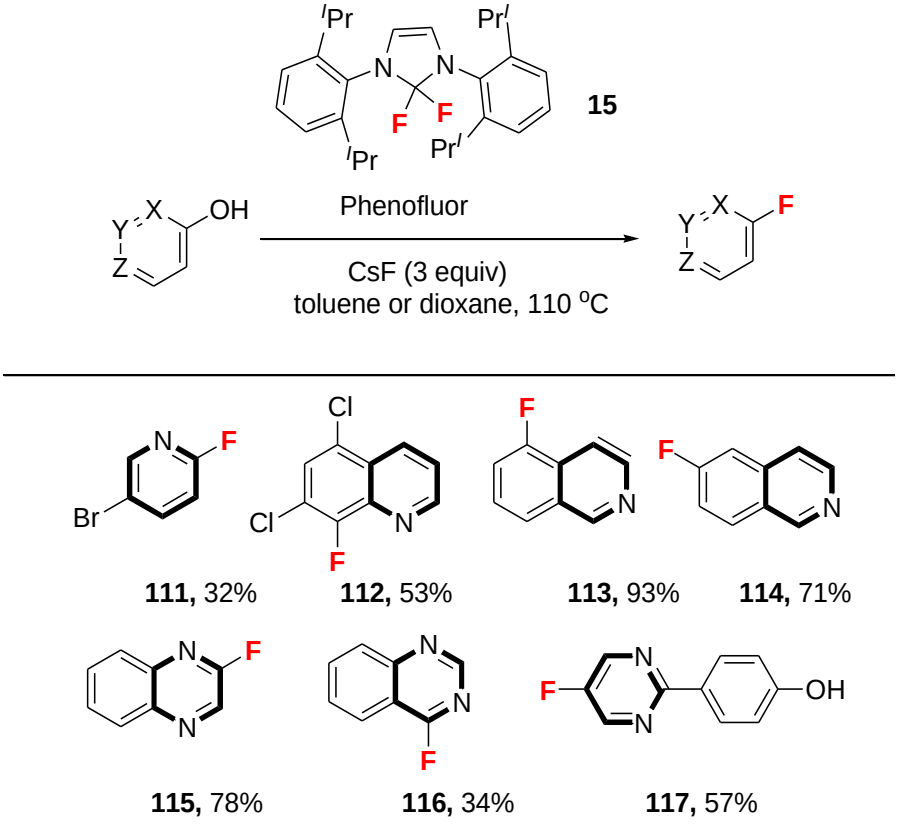


Figure 14. S_NAr fluorination of chloropyridine, isoquinoline, chloropyridazine and chloropyrazine substrates with Me_4NF

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.



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Scheme 20. Scope of the deoxyfluorination reaction of quinolines, isoquinolines, pyrazines and pyrimidine derivatives with Phenofluor

Quinolines, isoquinoline, 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]

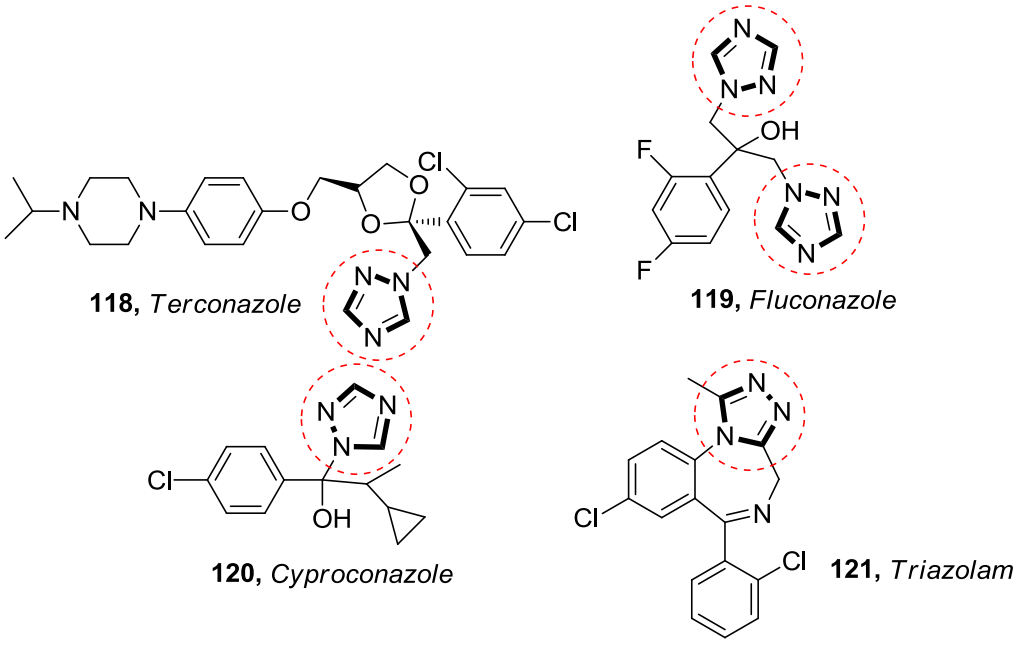

Figure 15. Triazoles in clinical use

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

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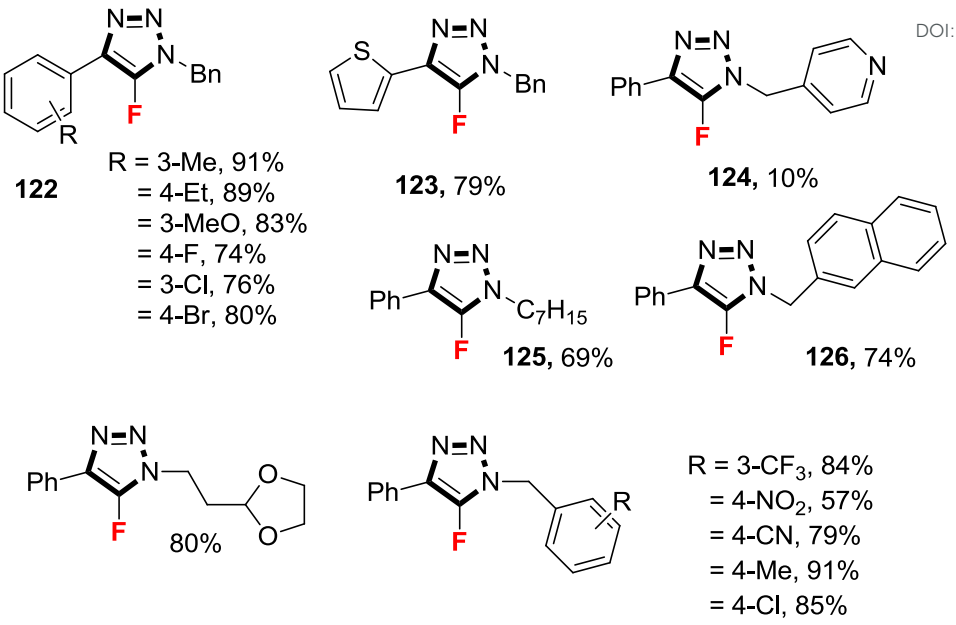

Figure 16. Scope of the fluorination of triazole derivatives

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 [80]

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. [81] 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. [82] Such dominating effects can control the conformational equilibria [5,6] and lock the sugar ring into either a North, **127** (C3′- endo pucker) or a South, **128** (C2′-endo pucker) conformation, [83] that can stabilize the glycosidic bond toward hydrolysis, [84] and can also modulate the octanol/water partition coefficient (Log P) (Figure 17). [85]

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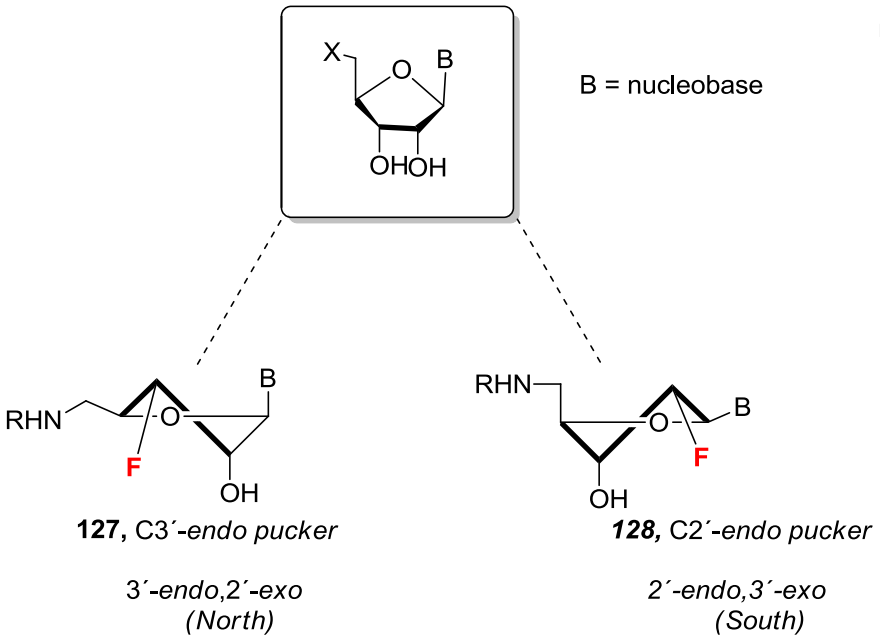
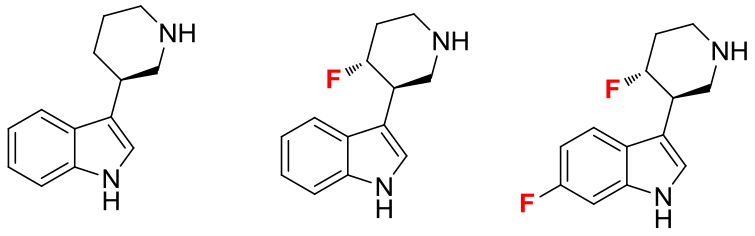


Figure 17. North **127** (C3′- endo pucker) or a South, **128** (C2′-endo pucker) conformations of carbohydrates

A recent finding [5] has shown that compounds that mimic the C3′-(F) endo pucker of the native acyl adenylate intermediate [6] exhibit greater biological activity than compounds that adopt the C2′-endo pucker, thus establishing a strong relationship between bioactivity and conformation for inhibitors of the nucleoside antibiotic 5′-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 **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 **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 (**130,** Figure 18), reducing the basicity of the secondary amine by nearly two orders of magnitude, resulting in a marked betterment

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]



	129	**130**	**131**
pK_a	10.4	8.5	8.5
5-HT_{2A} affinity	0.99 nM	0.43 nM	0.06 nM
bioavailability	poor	18%	80%

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.

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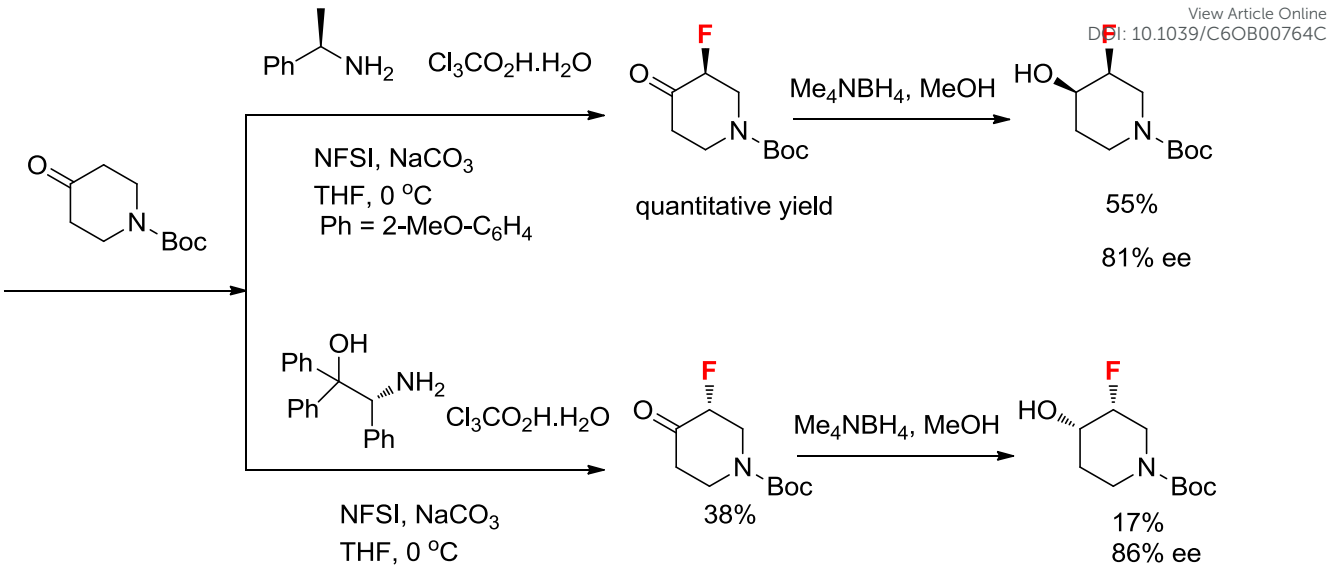

Scheme 21. Enantioselective fluorination of piperidinone

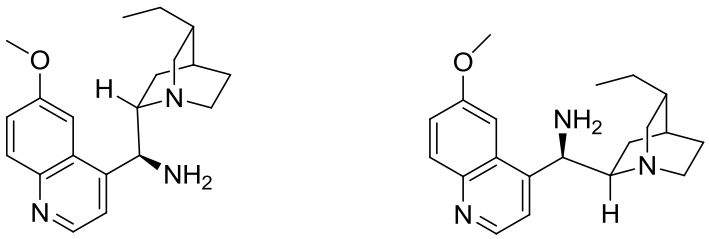

Figure 19. Structure of cinchona alkaloid-derived catalysts

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[30b] 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-3*S*-fluoro-4*R*-piperidinol.

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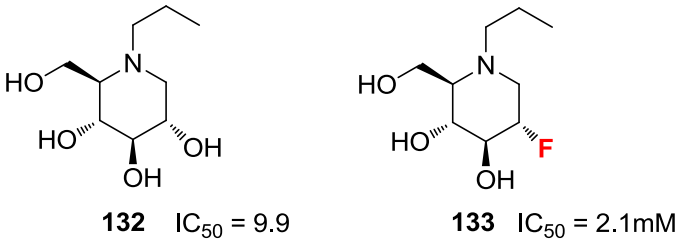
Iminosugars can competitively bind to glycosidase enzymes because of their structural resemblance to the terminal sugar moiety of natural substrates. As a consequence, iminosugars show great promise for the treatment of a variety of diseases including diabetes, viral infection, bacterial infection, and lysosomal storage disorders. [88]

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. [89]



132 IC_{50} = 9.9 **133** IC_{50} = 2.1mM

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.

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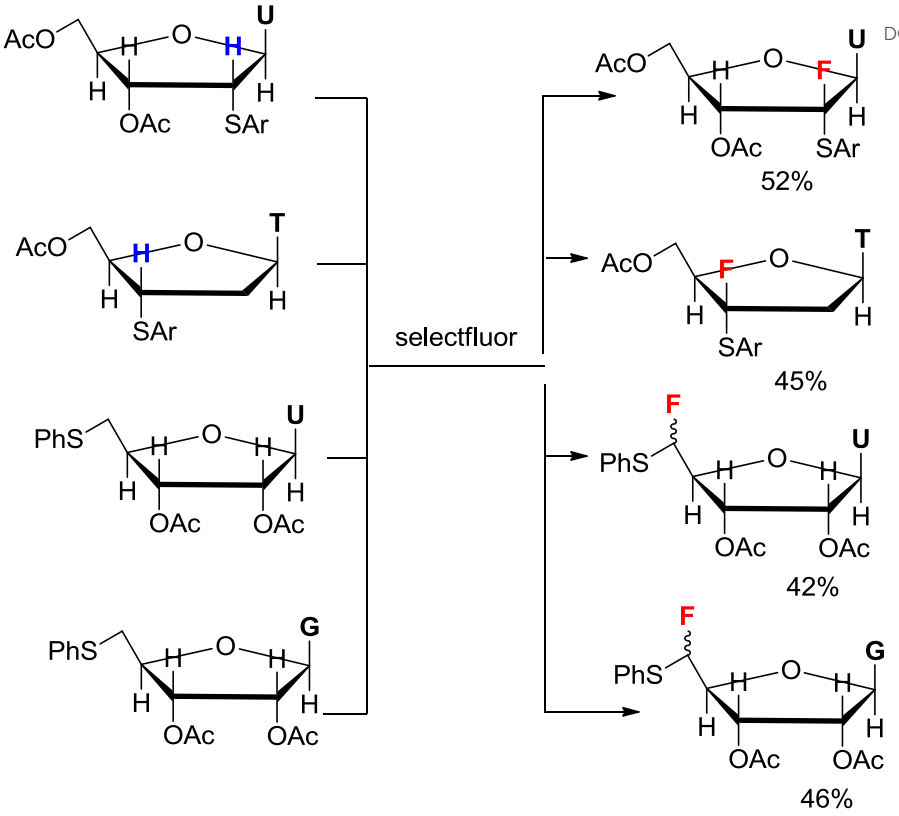
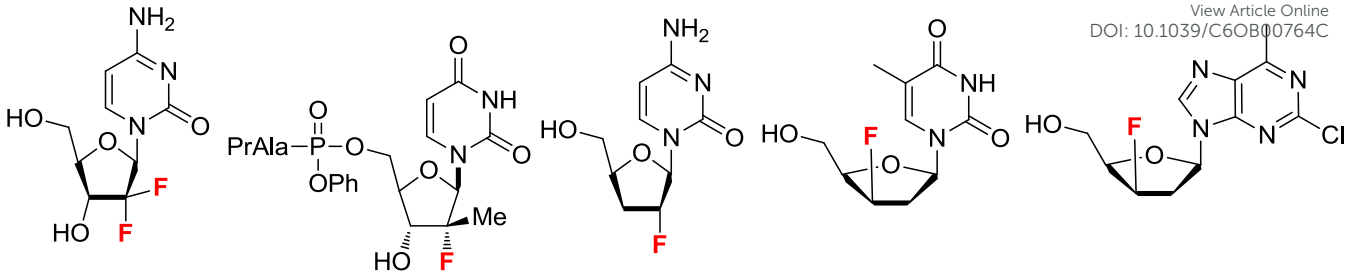


U = uracil, T = thymine, G = tribenzoyl guanidine

Scheme 22. Fluorination of nucleosides with Selectfluor

There has been a recent review article on the synthesis of fluorinated nucleoside derivatives [91], 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*) [92] belongs to the most widespread applied therapeutics in combination with radiotherapy, against a number of cancers (Figure 21).



134, *Gemcitabine* **135**, *Sofosbuvir* **136**, *F-ddc* **137**, *FLT* **138**, *Clofarabine*

Figure 21. Structures of fluorinated nucleobase and nucleosides currently employed in medicinal chemistry

The synthesis of *gemcitabine* **134** has been revisited and improved recently.[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) [95] and FLT **137** (3′-fluoro-3′-deoxythymidine) [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) which is used clinically for the treatment of leukemia in children. [97]

Ferrero and co-workers [98] have recently studied the synthesis of fluorinated azanucleosides and investigated their biological activity against HIV-1_{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.

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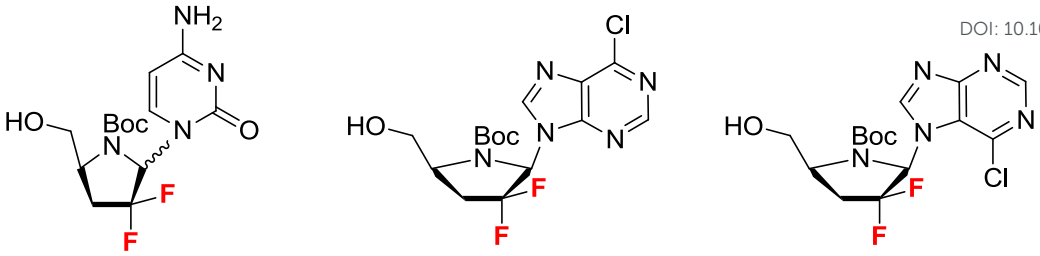

139 **140** **141**

Figure 22. Examples of azanucleosides investigated against HIV-1

Zajc and co-workers [99] have come up with a straightforward method for the introduction of a fluorine atom into the *8*-position of ribonucleosides via metalation-electrophilic fluorination under heterogeneous reaction conditions. The scope of the transformation is illustrated in Scheme 23.

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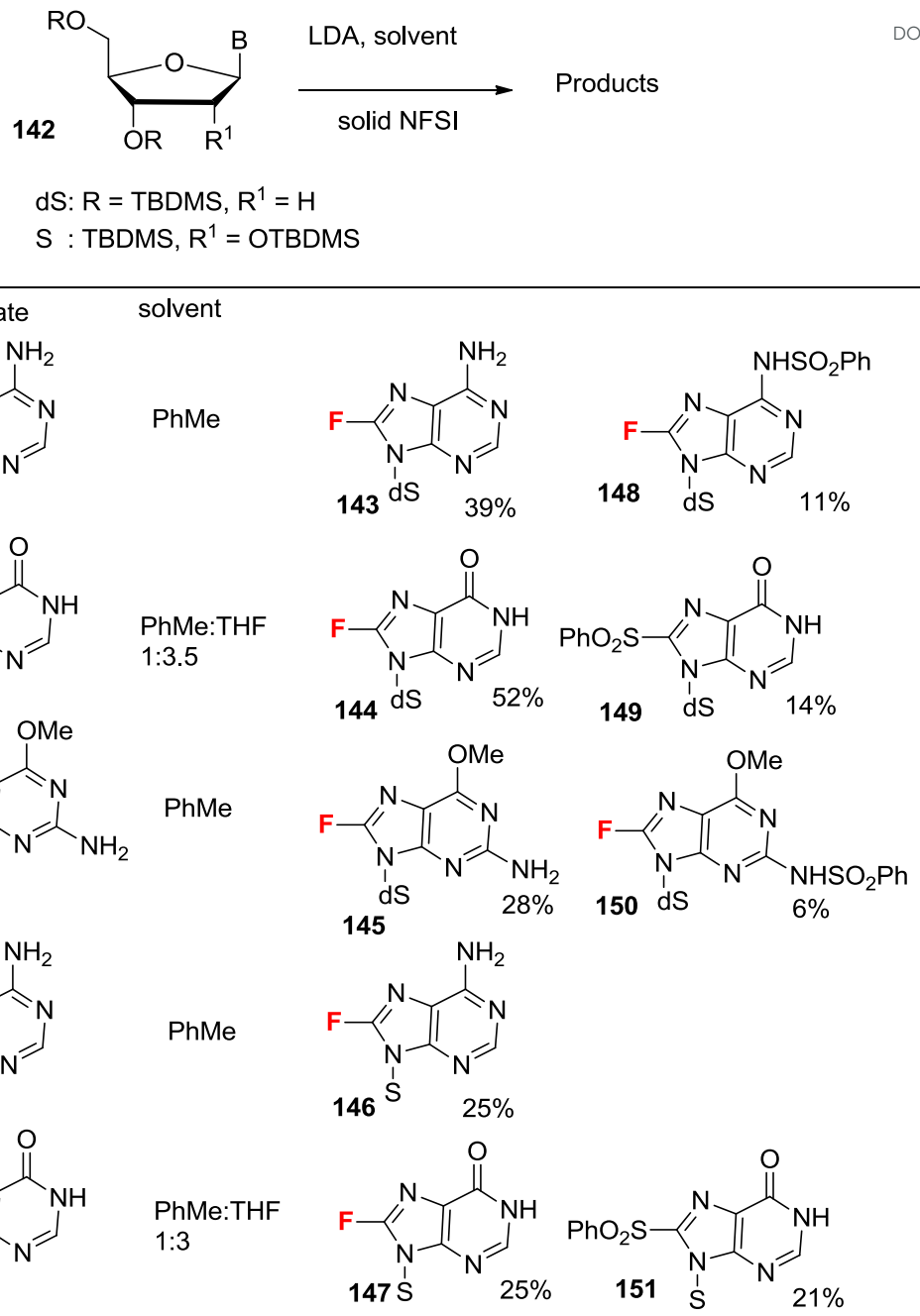
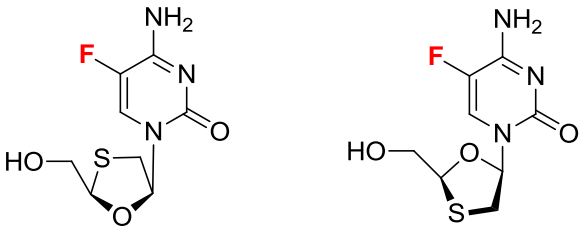


Scheme 23. Fluorination of ribonucleosides and 2´-deoxyribonucleodises

Fluorinated nucleosides **143-147** formed through a 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. [99] In the case of ribonucleosides, it is likely that the S_N reaction is slower due to steric reasons.

As a new family of anti-HIV compounds, *emtricitabine* FTC **152** (4-amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one) and *racivir* RCV **153** (4-amino-5-fluoro-1-[(2*S*,5*R*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one) (Phase II), contain a F atom. Figure 23 illustrates their structures.[100]



152, *Emtricitabine* **153,** *Racivir*

Figure 23. Structures *of Emtricitabine* and *Racivir*

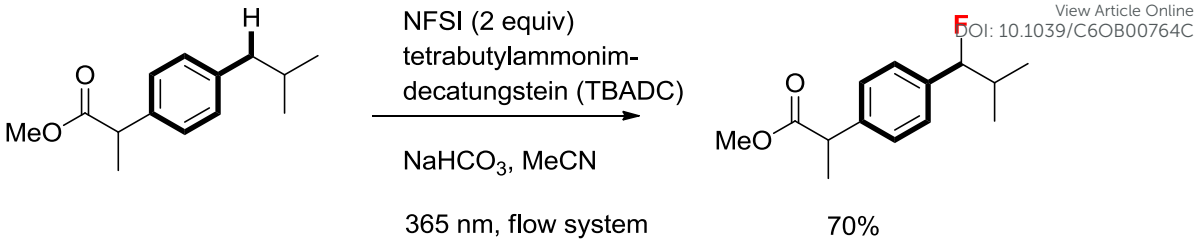
6.-Fluorination of sp^3 Carbon Atoms

6.a.-Fluorination of benzylic positions

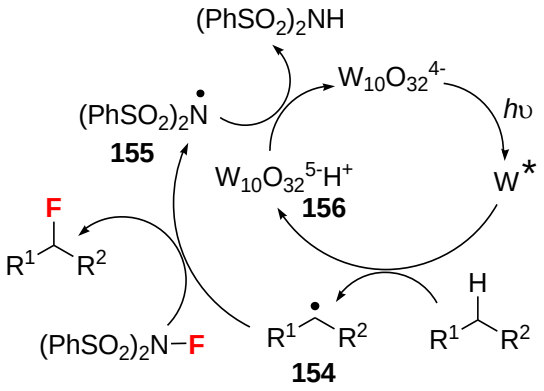
Methods for the fluorination of benzylic carbon atoms have been recently reviewed by Hurley and co-workers. [101]

The beneficial properties of benzyl fluorides in lead optimization [102,103] have motivated an intense research activity in late stage fluorination of benzylic positions. [101] Britton and colleagues [104] 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.



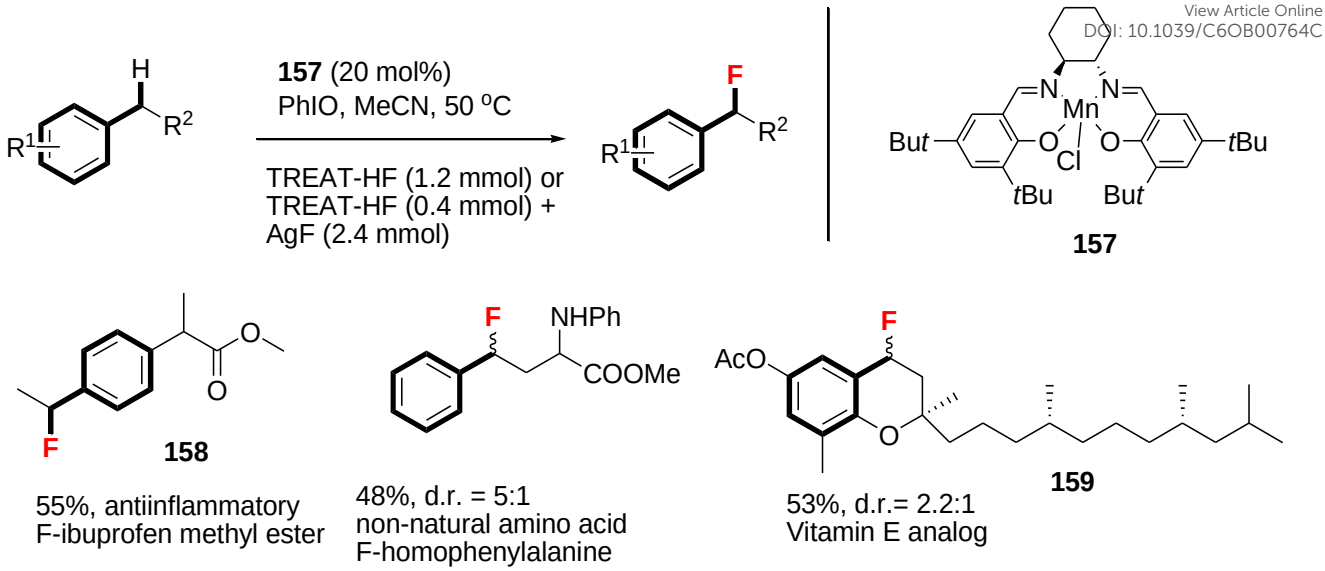
Scheme 24. Fluorination of ibuprofen methyl ester



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.



Scheme 26. Late-stage benzylic fluorination employing Mncatalyst A, AgF and TREAT-HF

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 [105] proposed a mechanism for the above reaction, as illustrated in Scheme 27. The starting $[Mn^{III}(salen)F]$ or $[Mn^{III}(salen)F_2]^-$ catalyst, formed in situ, is oxidized to $[Mn^{V}(O)(salen)F]$, 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 $[Mn^{IV}(salen)F_2]$ complex, yielding the fluorinated products, regenerating the Mn^{III} catalyst. An important kinetic isotope effect (5.6±0.6) was observed for a 1:1 mixture of ethylbenzene and ethylbenzene-d_{10} 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.

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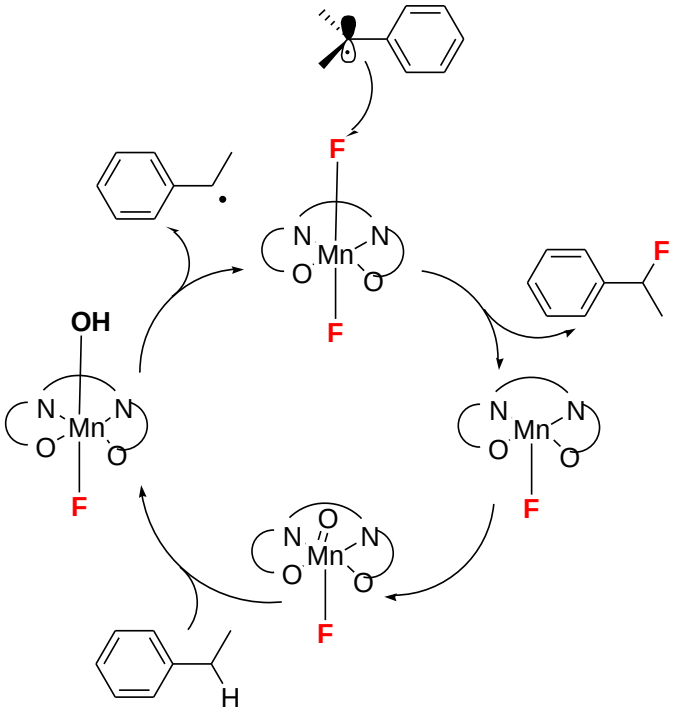
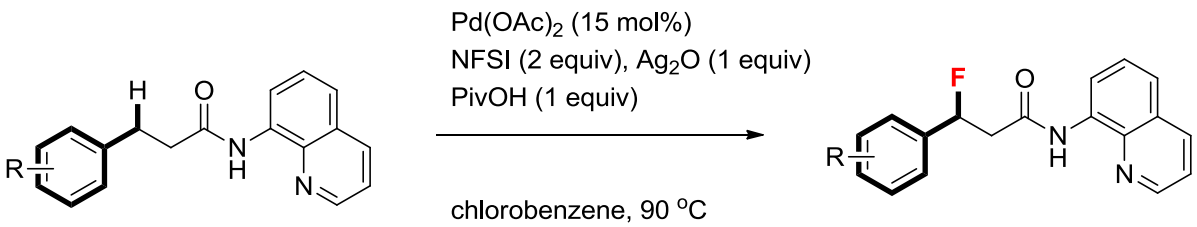


Scheme 27. Proposed mechanism for the catalyzed benzylic fluorination

Xu and co-workers [106a] have recently developed a fluorination method for benzylic positions (and β-carbonyl compounds, *vide infra*) employing 15 mol% of $Pd(OAc)_2$, NFSI as fluorinating agent, Ag_2O, and pivalic acid in chlorobenzene as solvent at 90 °C. The scope of the transformation is illustrated in Scheme 28.



R = H	**160,** 70%
= 2-Cl	**161,** 71%
= 4-F	**162,** 61%
= 2,4-Cl_2	**163,** 67%
= 3-NO_2	**164,** 75%
= 3-CF_3	**165,** 75%
= 3-OMe	**166,** 64%

Scheme 28. Palladium-mediated benzylic fluorination reaction

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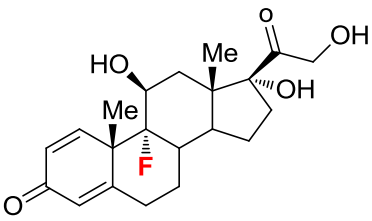
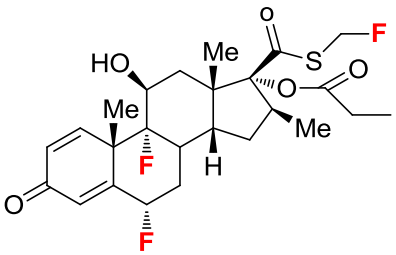
The 8-aminoquinoline-derived auxiliary is acting as a directing group for the β-fluorination of the amide group. [106a] Fluorination of benzenepropanamide derivative gave good yields of product **160** (Scheme 28). The authors [106a] examined additional substrates bearing halogen substituents such as *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*-NO_2, *m*-CF_3, or electron releasing *m*-OCH_3 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.



167 *Fludrocortisone*

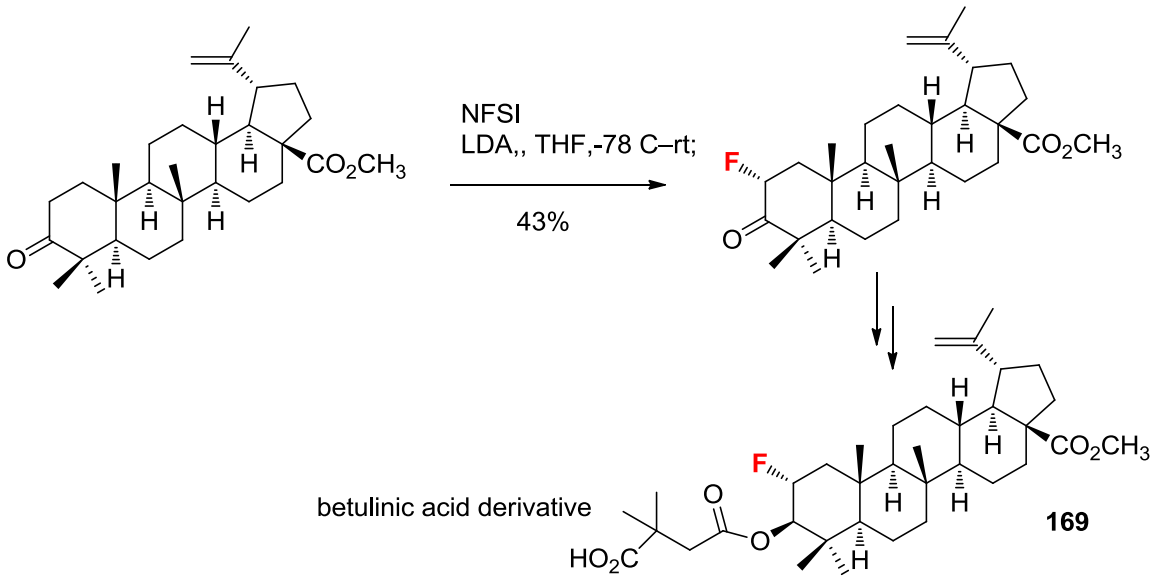


168 *Fluiticasone propionate*

Figure 24. **S**tructure of *fludrocortisone* **167**. Structure of *fluticasone propionate* **168**

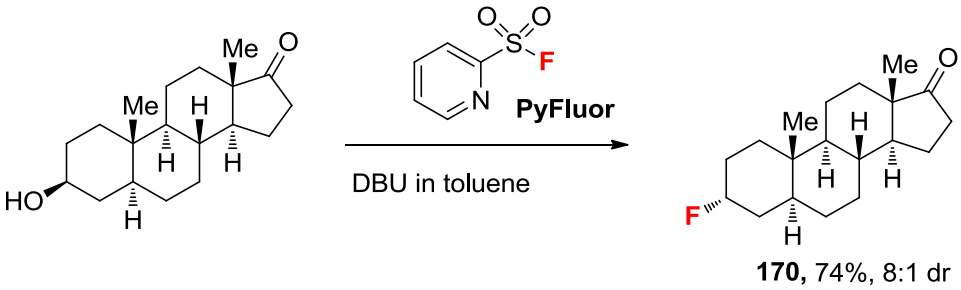
Fluticasone propionate **168** can be applied to treat inflammation associated with dermatoses and psoriasis. [108]

Lee and co-workers have recently employed NFSI for the fluorination pathway of *betulinic acid* derivative **169** [109], according to Scheme 29. *Betulinic acid* derivatives **169** possess potent anti HIV activity.



Scheme 29. Fluorination step in the synthesis of *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. [32]



Scheme 30. Deoxyfluorination of steroid derivatives employing PyFluor

2

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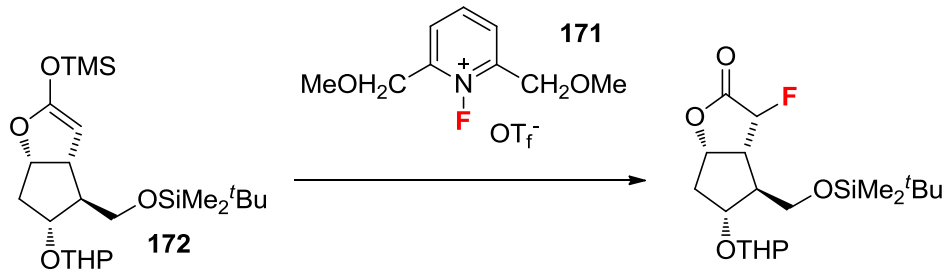
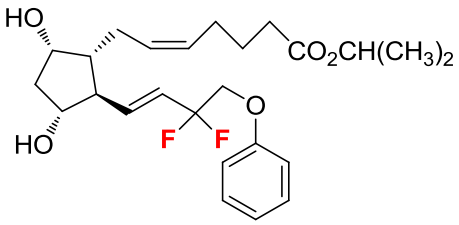
A laboratory-devised fluoro pyridinium **171** has been employed for the fluorination of an analog **172** of Corey lactone prostaglandin synthetic intermediate, as illustrated in Scheme 31.



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]



173, *Tafluprost*

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.

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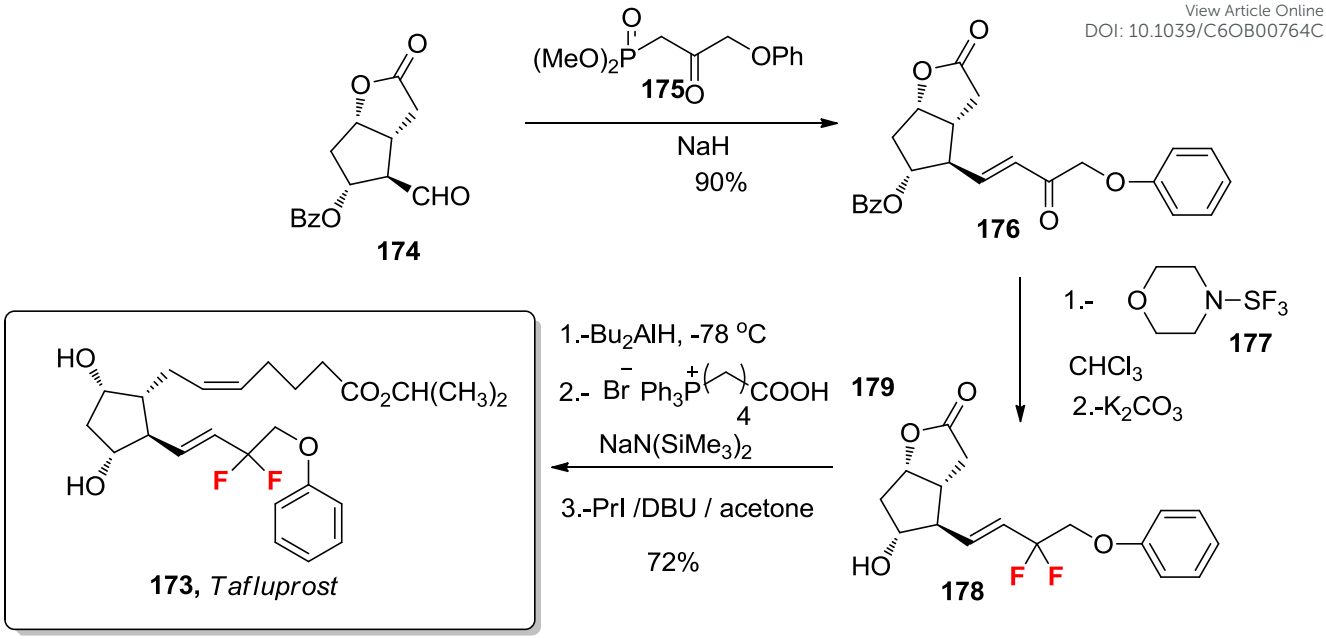

Scheme 32. Synthesis of *tafluprost*

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** [110] in $CHCl_3$ 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 $^{i}Bu_2AlH$ 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

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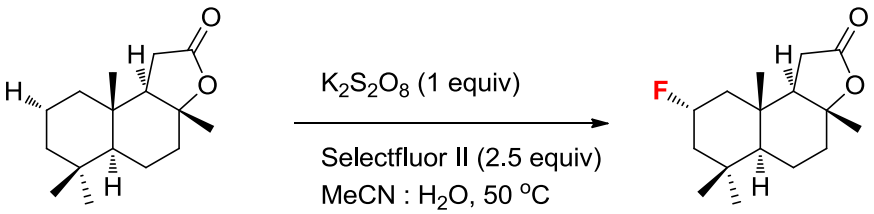
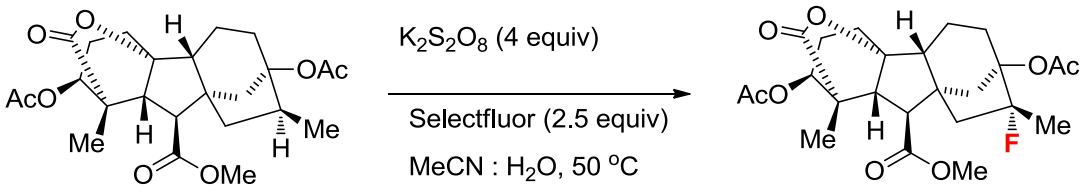
Tang and collaborators [112] have recently reported a new methodology to carry out the fluorination of sp^3 carbon atoms of biological relevant substrates. The fluorination of *sclareolide* **180**, a sesquiterpene lactone used as supplement in weight loss therapy, has been accomplished through the use of radical initiator $K_2S_2O_8$, Selectfluor II (Figure 3), in MeCN/H_2O 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.



180

Scheme 33. Late-stage fluorination of *sclareolide* **180**

Also, the fluorination of *gibberellic*-derivative GA **181** [112] (a diterpene, that stimulates the cells of germinating seeds to produce *m*RNA molecules that code for hydrolytic enzymes), can give 42% yield of fluorinated product **182** (Scheme 34).

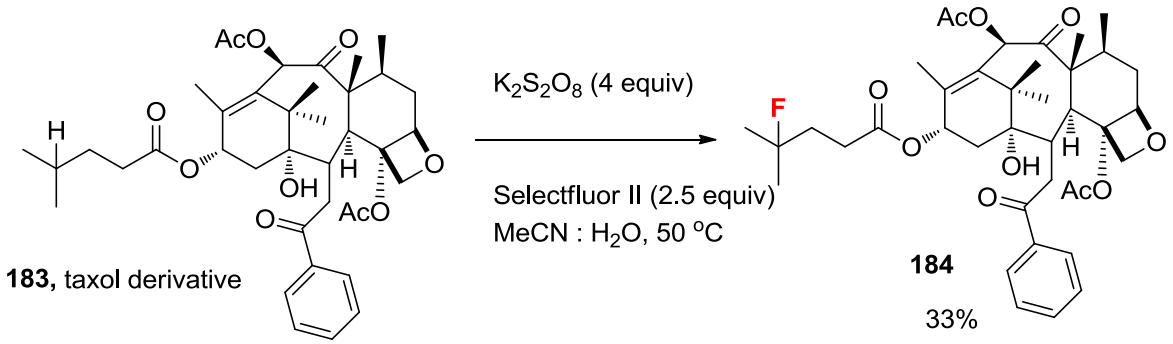


181, *Gibberellic* **182**

Scheme 34. Late stage fluorination of *gibberellic* **181** derivative

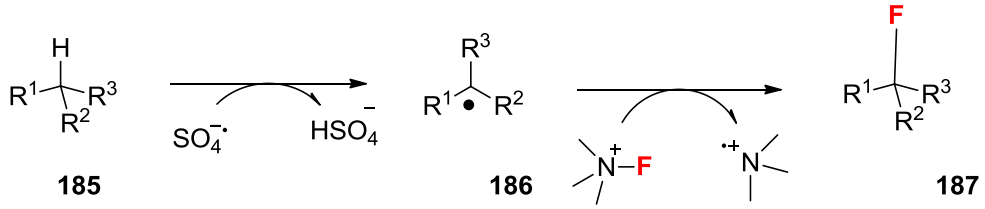
In *gibberellic* **181**, fluorination at the C16 methine position occurs as the major product due to a more electron-rich and less steric hindered site compared to the other tertiary C–H bonds. [112].

With an ester derivative of the anticancer drug *taxol* **183** (Scheme 35) [112], fluorination takes place with 4.0 equiv. of $K_2S_2O_8$ and 2.5 equiv. of Selectfluor II (PF_6) 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**

The proposed mechanism for all the transformations in Schemes 33-35 is depicted below in Scheme 36. [112]



Scheme 36. Proposed reaction mechanism for the radical fluorination of sp^3 C atoms with Selectfluor

It is accepted that peroxydisulfate anion decomposes into the sulfate radical anion [113] 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. [114].

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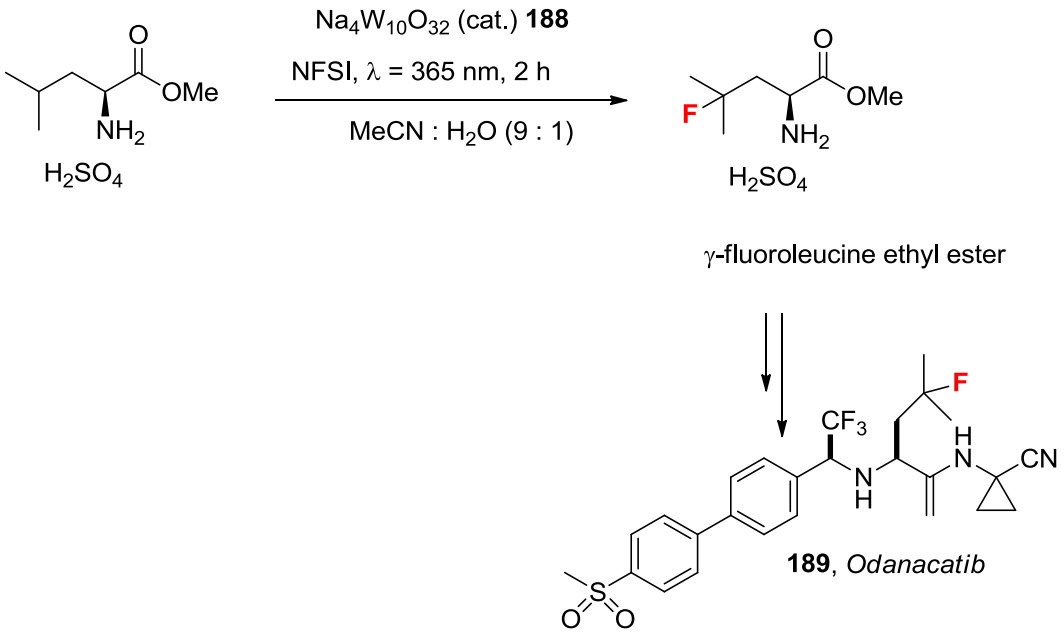
7.d.-Fluorination of sp^3 carbon atoms by photocatalysis

DiRocco and Britton [115] have reported the photocatalytic fluorination of sp^3 carbon atoms to be applied the methodology to the synthesis of *odanacatib* **189**, 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 **188** is able to catalyze the fluorination of salts of leucine methyl ester in the presence of NFSI. The large scale production of *odanacatib* **189** was carried out in a flow photoreactor while irradiating at 365 nm (Scheme 37). [116]



Scheme 37. Fluorination of leucine methyl ester towards the synthesis of *odanacatib* **189**

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

6.e.-Fluorination at the α-Carbonyl Positions [117] and β-Carbonyl Positions [106]

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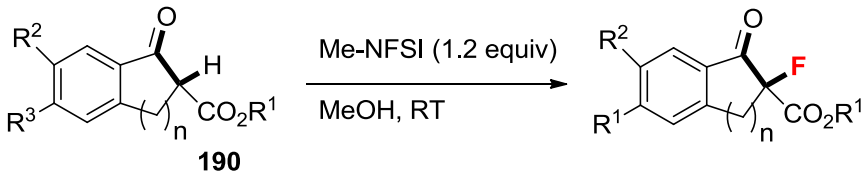
Shibata and colleagues [28] have recently shown that the fluorinating reagent *N*-fluoromethanesulfonimide ($F–N(SO_2Me)_2$, Me-NFSI, Figure 3) is a better fluorinating reagent for methane groups than NFSI. The authors compared a set of fluorination reactions of methane positions with Me-NFSI and NFSI and demonstrated improved scope and higher yields with the former. They have applied the new reagent to the fluorination reaction of β-keto-esters **190**, as illustrated in Scheme 38.



190

R^1= Me, R^2= R^3= H, n=1	92% (in THF)
R^1= R^2= Me, R^3= H, n=1	90%
R^1= Me, R^2= OMe, R^3= H, n=1	98%
R^1= Me, R^2= R^3= OMe, n= 1	66%
R^1= Me, R^2= R^3 = H, n= 2	91%
R^1 = Me, R^2 = H, R^3= OMe, n= 2	85%
R^1 =Me, R^2= R^3 = H, n= 3	35%

Scheme 38. Fluorination reaction of β-keto-esters with Me-NFSI

The enantioselective incorporation of fluorine atoms into organic substrates was pioneered by Shibata and co-workers. [118] The authors [118] 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 [119] have very recently employed the fluoromalonic acid

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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.

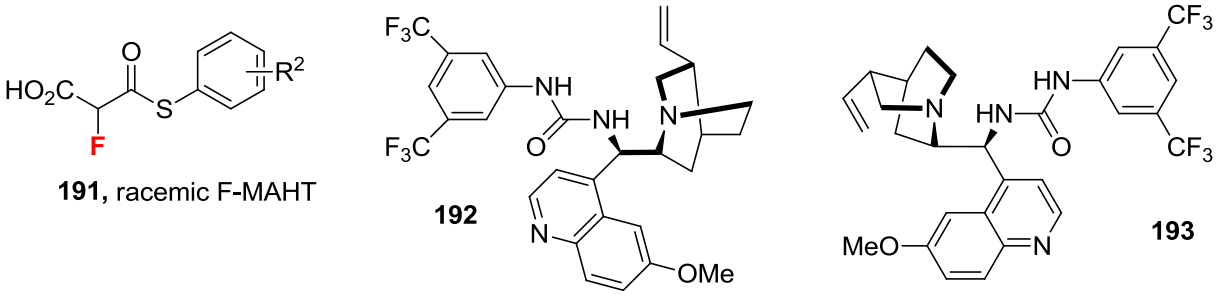
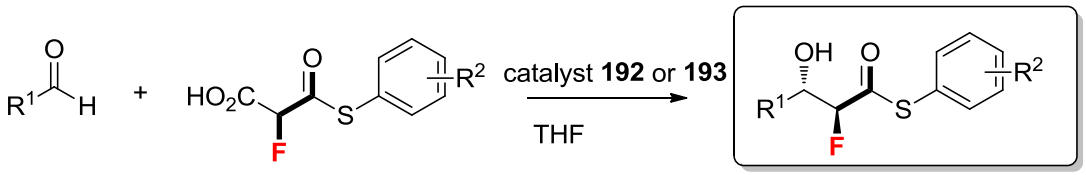


Figure 26. Structure of racemic fluoromalonic acid hemi-thioethers F-MAHTs **191**, and catalyst **192** (a quinidine-urea catalyst) and its enantiomer **193**

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.

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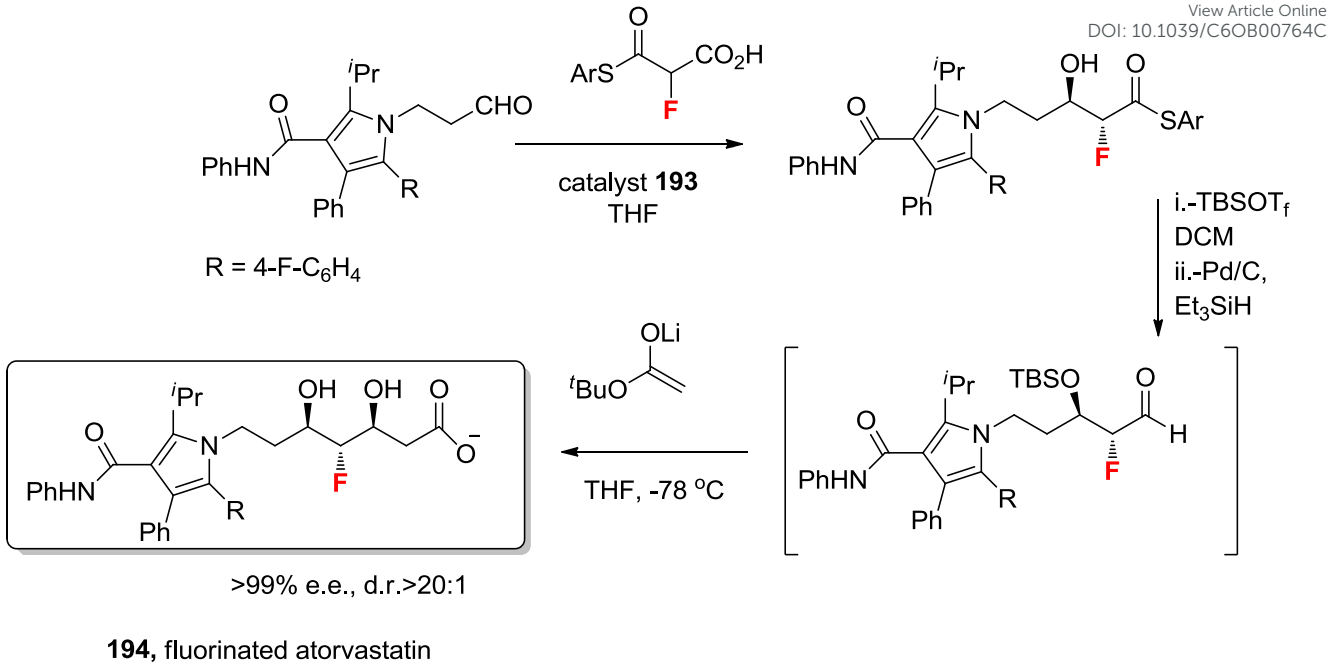


Scheme 40. Synthesis of enantioselective fluorinated atorvastatin **194**

Sanford and co-workers [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**. [122]

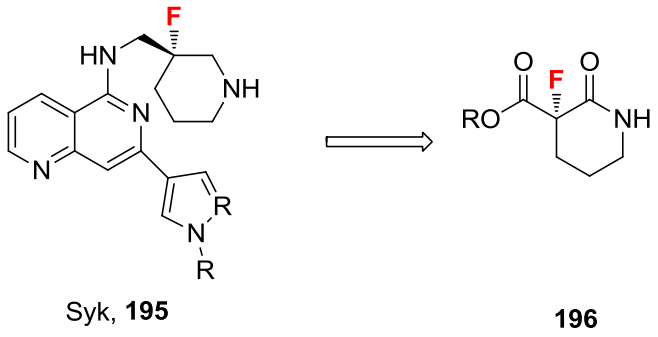
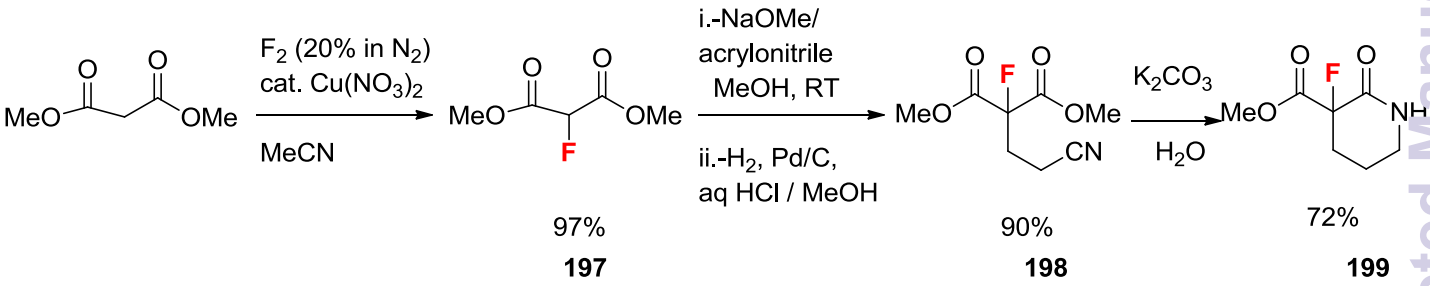


Figure 27. Spleen tyrosine kinase inhibitors Syk, and chiral fluorolactam building blocks **B**

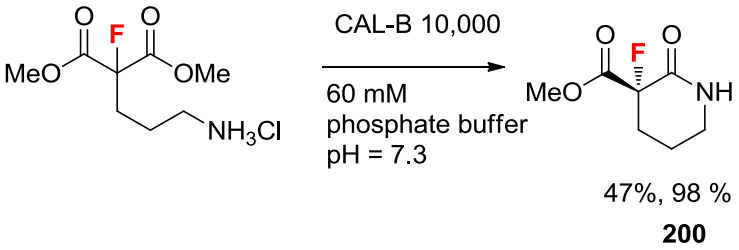
Fluoromalonate ester **197** (Scheme 41) is synthesized in high yield through direct fluorination reaction of dimethyl malonate ester using fluorine gas, catalyzed by copper nitrate in MeCN solution. Michael addition of acrylonitrile to fluoromalonate **197** affords the desired nitrile **198** in 90% 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**

The authors [121] 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

More recently, Stuart and co-workers [30] have come up with a fluorination method of 1,3-dicarbonyl compounds employing fluoroiodane **14**, according to Scheme 43.

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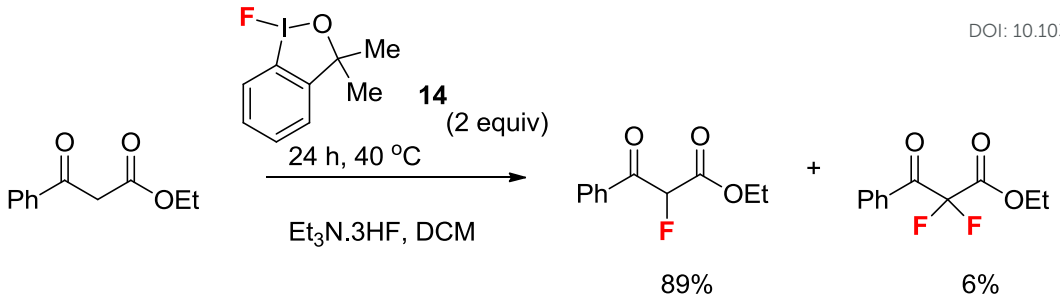
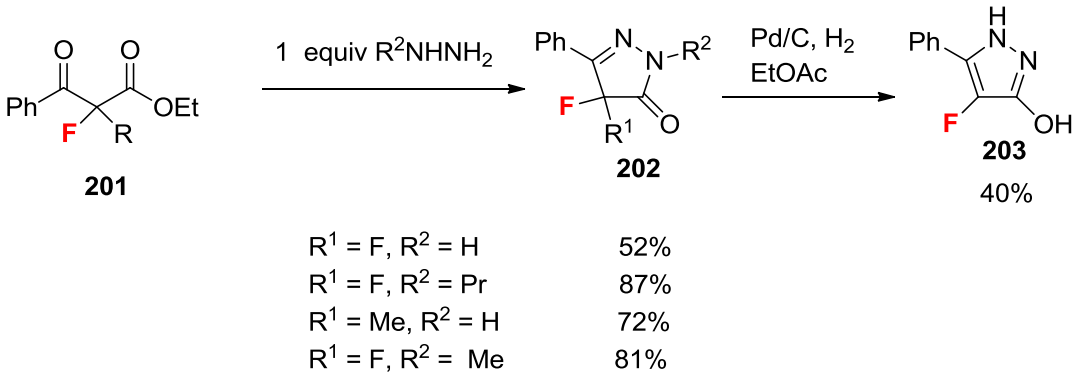


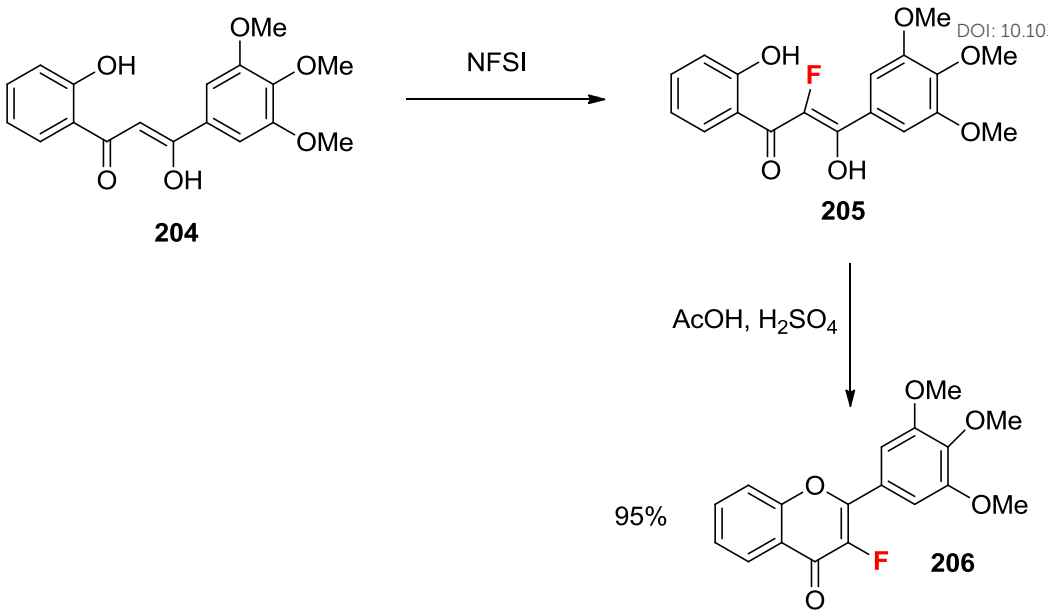
Scheme 43. Fluorination of 1,3-dicarbonyl compounds with 1-fluoro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole **14**

In a disconnected approach, De Kimpe and co-workers [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.



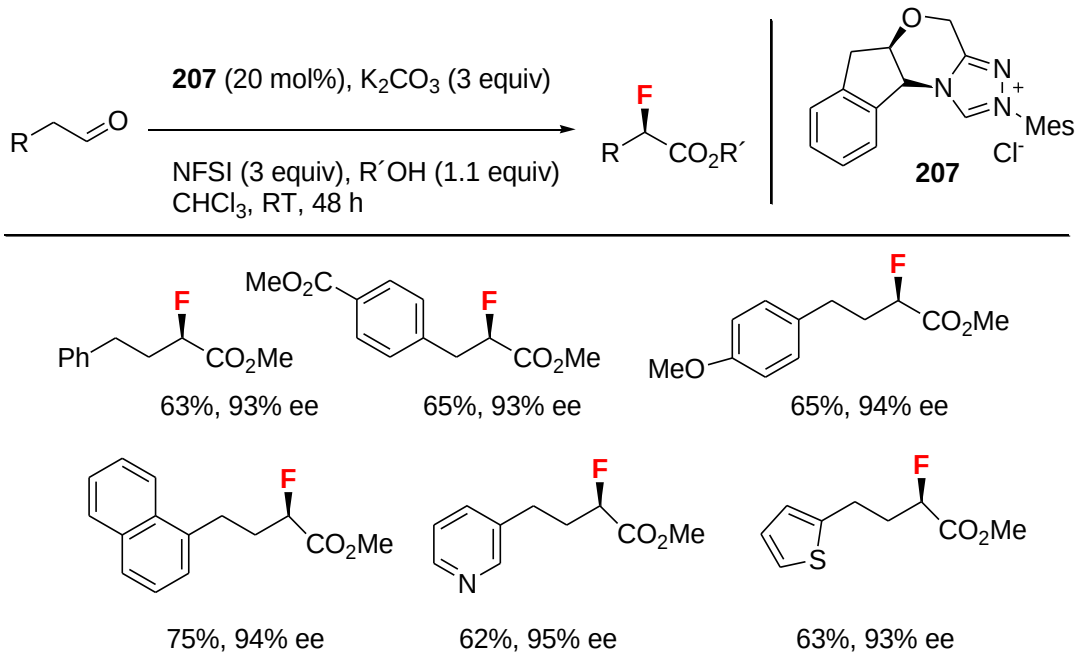
Scheme 44. Synthesis of 3-hydroxy-4-fluoropyrazole derivatives

Britton and co-workers have prepared a range of flavone derivatives in order to evaluate their potential as anti-prostate cancer agents [126] through α-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 α-fluorination of carbonyl compounds (aldehydes) has been developed by Sun and coworkers. [127] The authors [127] used the Bode catalyst **207** (Scheme 46), NFSI as both fluorinating and oxidizing agent, K_2CO_3 as the base, in $CHCl_3$ at room temperature.



Scheme 46. Scope of the enantioselective α-fluorination of aldehydes

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Heterocycles, such as the easily oxidizable pyridine and thiophene, were also compatible with the strongly oxidative reaction conditions. [127] The authors [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). [128] As a result, the synthesis of both natural statines and their analogues has been a subject of intense interest. Hunter and coworkers [129] have designed a diastereoselective synthesis of 2-(*R*) and 2-(*S*) fluorostatines represented in Scheme 47.

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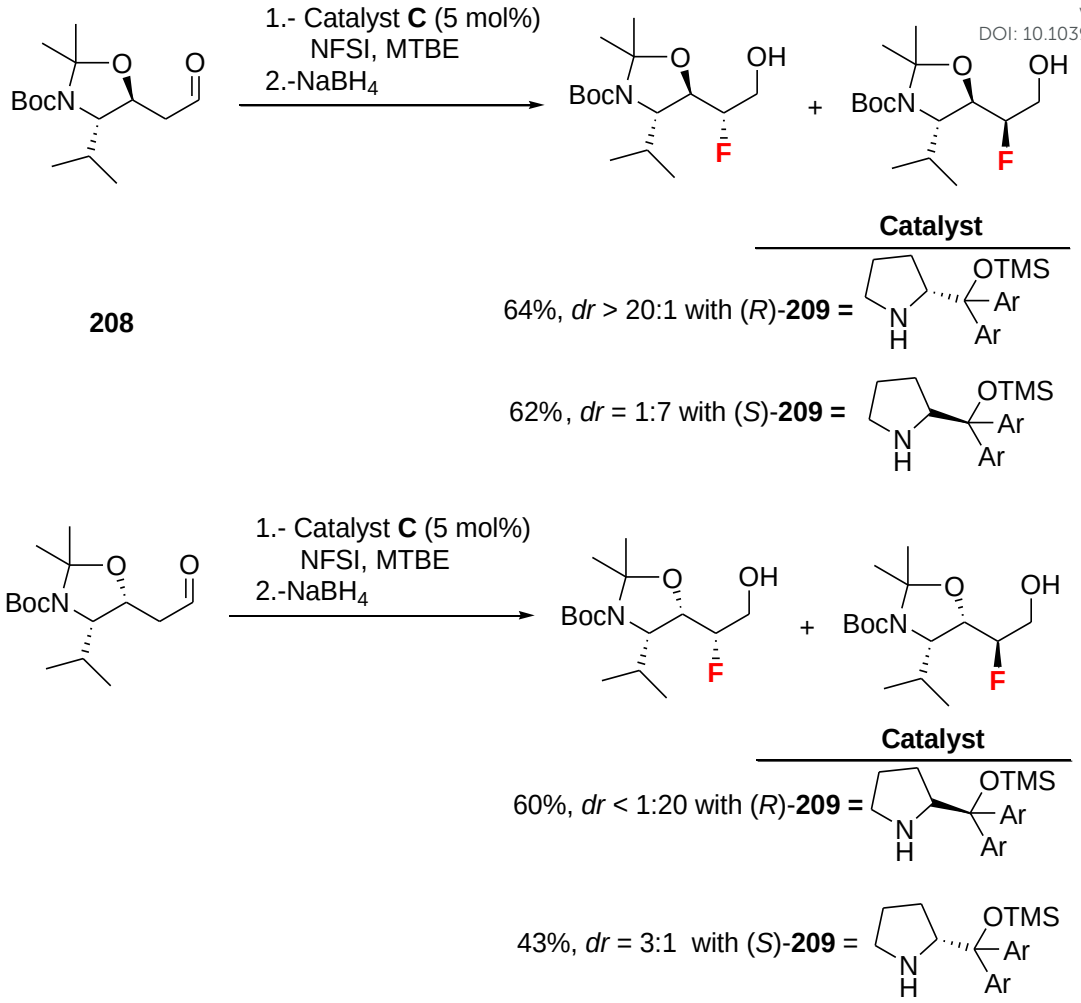
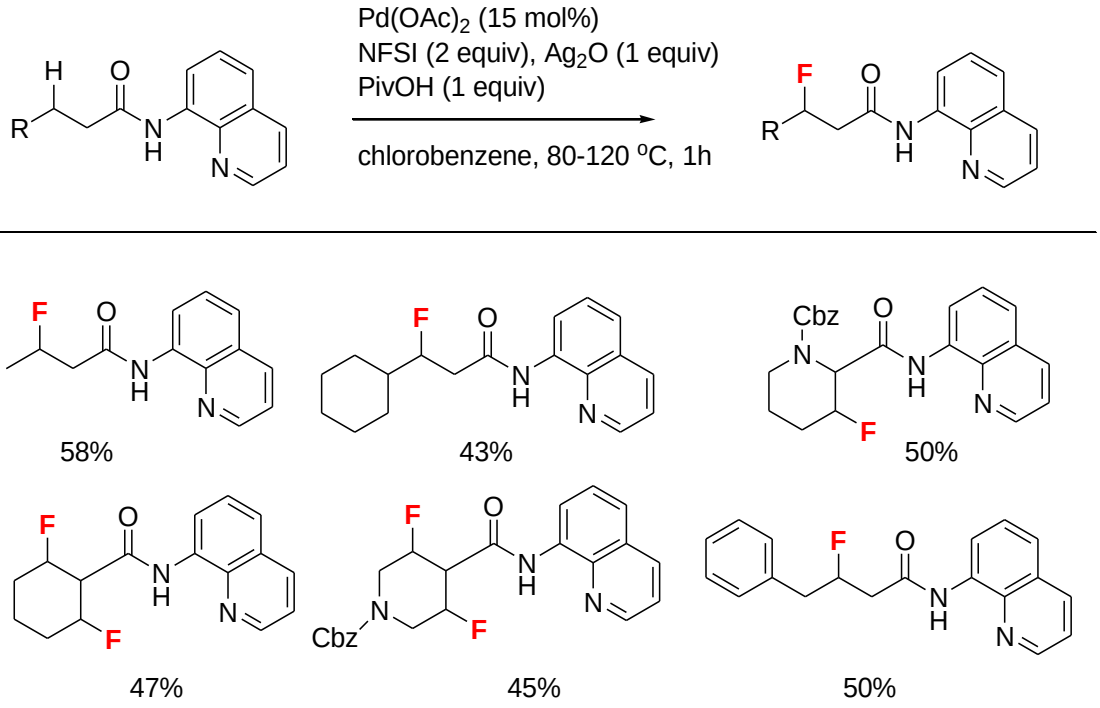


Scheme 47. Diastereoselective fluorination of protected *statines*

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 $NaBH_4$. The (*R*)-**209** organocatalyst afforded the highest diastereoselective ratios of protected fluoro-statine. Deprotection took place with HCl. [129]

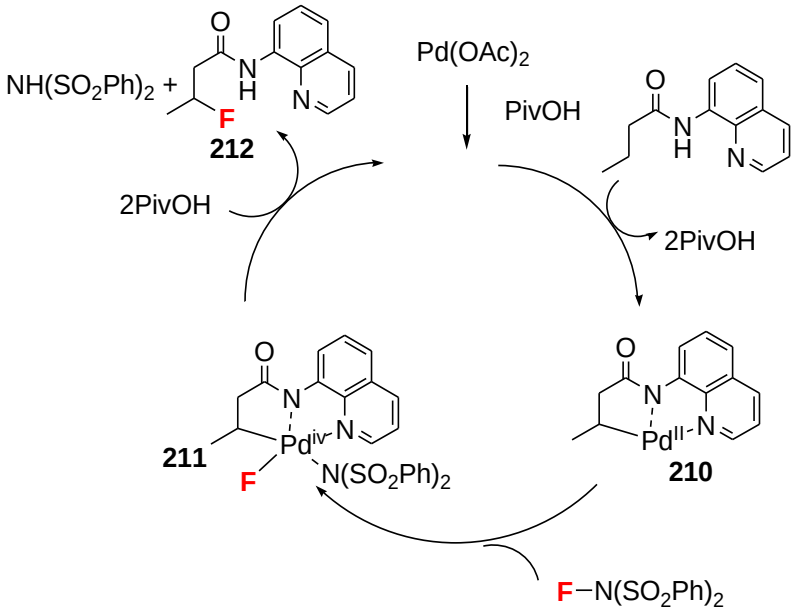
Xu and coworkers [106] have developed a protocol for introducing a fluorine atom into the β-position of carbonyl compounds. They employed catalyst $Pd(OAc)_2$, NFSI as fluorinating source,

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 [106] is illustrated in Scheme 49.



Scheme 49. Proposed reaction mechanism for the synthesis of fluorinated of β-carbonyl compounds

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The first step involves the formation of the cyclopalladated intermediate **210** (Scheme 49) to afford the [5,5]-fused bicyclic. Then, Pd^{II} is oxidized into a Pd^{IV} intermediate by NFSI and Ag_2O. The role of PivOH in this reaction is presumably to help reductive elimination of strong metal−fluorine bond by replacing the $N(SO_2Ph)_2$ ligand on Pd^{IV} complex or to help regenerate the active catalyst by replacing the $N(SO_2Ph)_2$ ligand on Pd^{II}. Finally, reductive elimination of **211** forms the fluorination product **212** with ulterior regeneration of Pd^{II}.

Thus this β-C(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.[1f,n]

6.f.-Synthesis of α- and β-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.[130].

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

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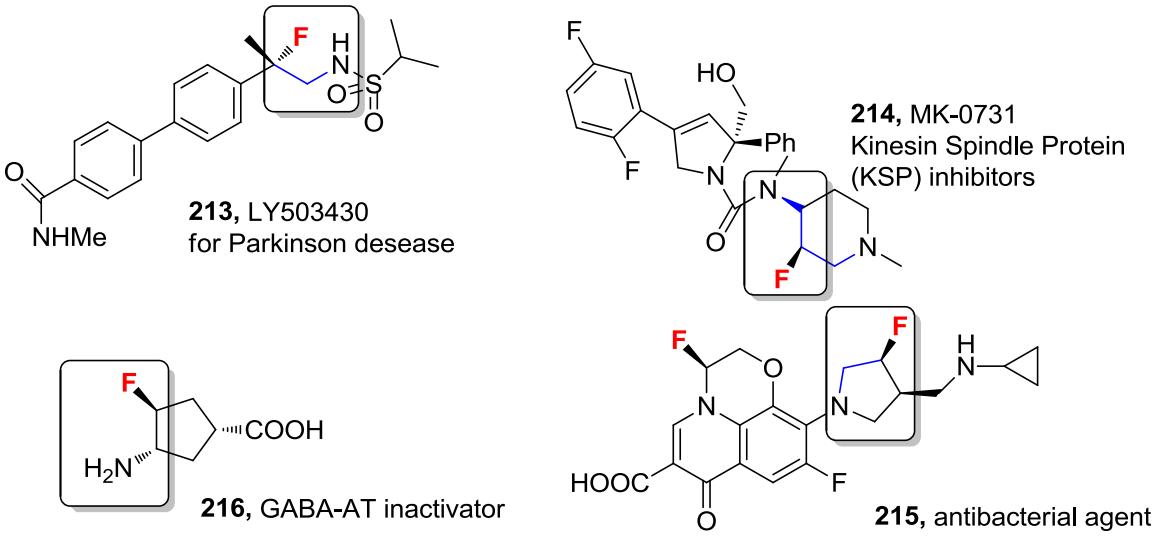
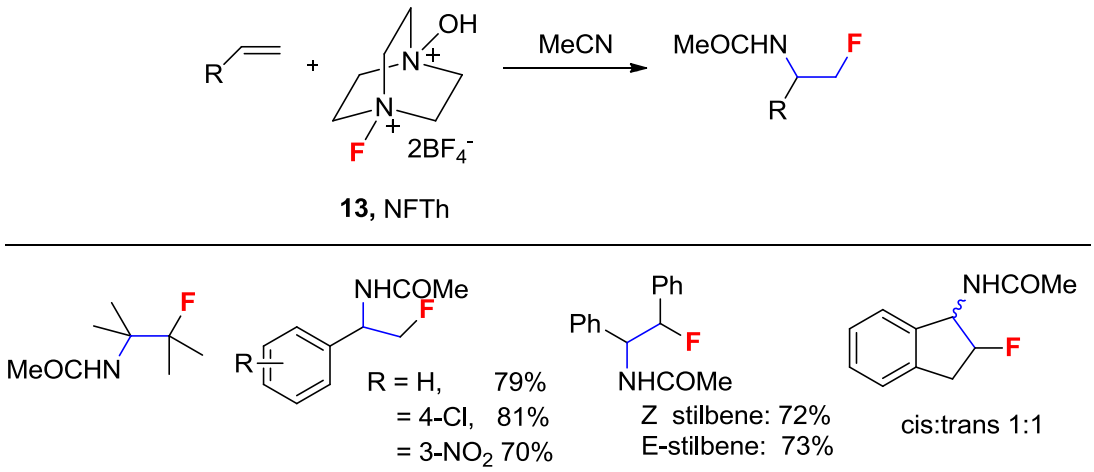


Figure 28. Relevant β-fluoroamines bioactive compounds **213-216**

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

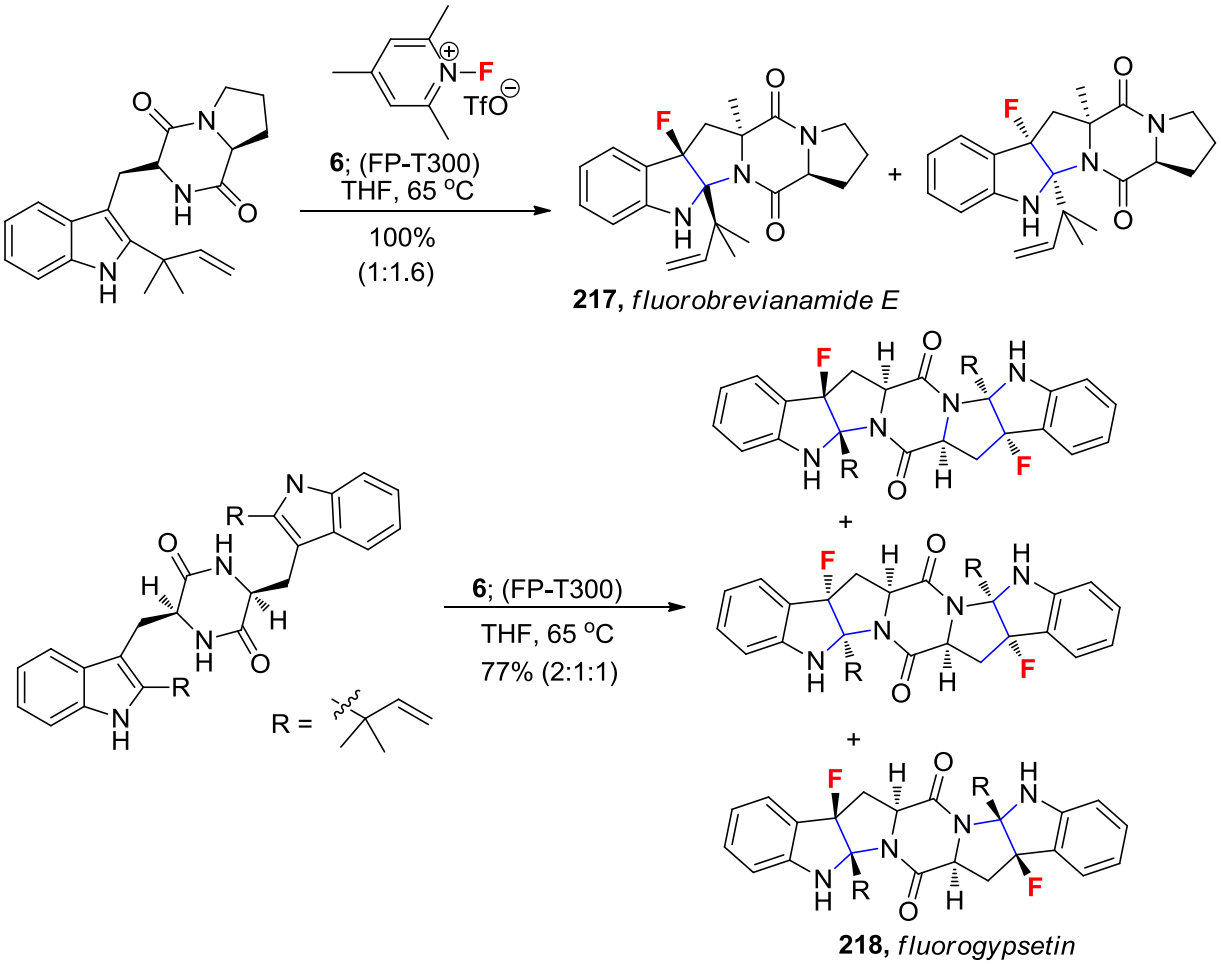


Scheme 50. Ritter-type amino-fluorination of olefins [131]

The reaction depicted in Scheme 50 belongs to a Ritter-type aminofluorination reaction or a fluoroamination reaction. [29] In this reaction, 1-fluoro-4-hydroxy-1,4-diazoniabicyclo[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]

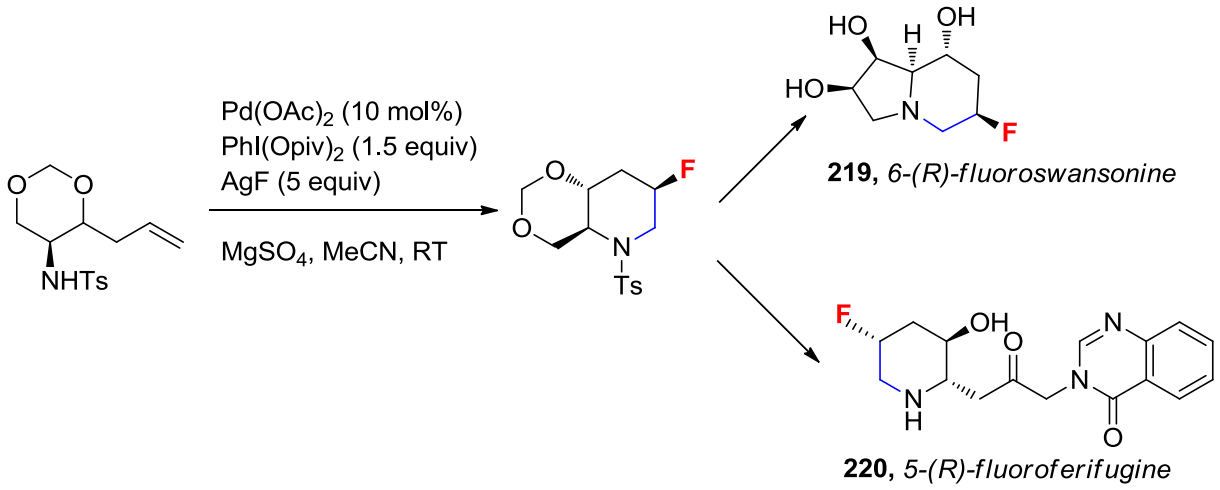


Scheme 51. Synthesis of β-fluoroamines *fluorobrevianamide E* **217** and *fluorogypsetin* **218** employing FP-T300 **6** (1-fluoro-2,4,6-trimethyl pyridinium triflate)

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. [93] Thus, transition metals such as Pd , Ag, Au, Fe and Cu, have been shown to catalyze aminofluorination reactions [93], 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 [132] have accomplished the fluorination reaction of piperidine cores through an aminofluorination reaction [75] 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*)-*fluorofebrifugine* **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 sp^2 Carbon Atoms

Gulder and co-workers [133] 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. [75] The protocol avoids the need for transition metal catalysts,

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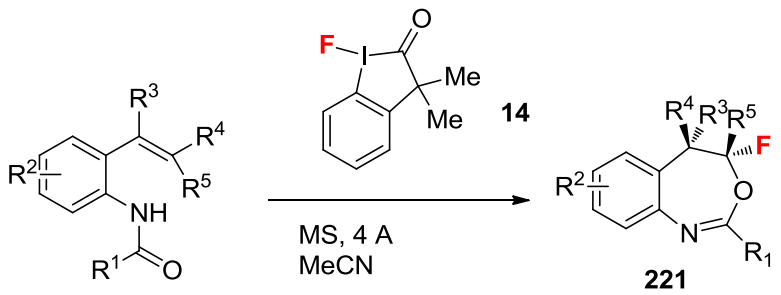
and uses a shelf-stable hypervalent fluoro iodane reagent as an electrophilic source of fluorine. This reagent is not only significantly more reactive than the well-established iodine(III)-based fluorinating reagent Selectfluor, but provides completely different chemoselectivity, providing seven-membered 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. [133] The reaction employs the shelf-stable crystalline fluoro-benzoiodoxole **14** and consists of a fluorination / aryl migration / cyclization steps.[75]



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 [134] of alkynes in the presence of NFSI is illustrated in Scheme 54.

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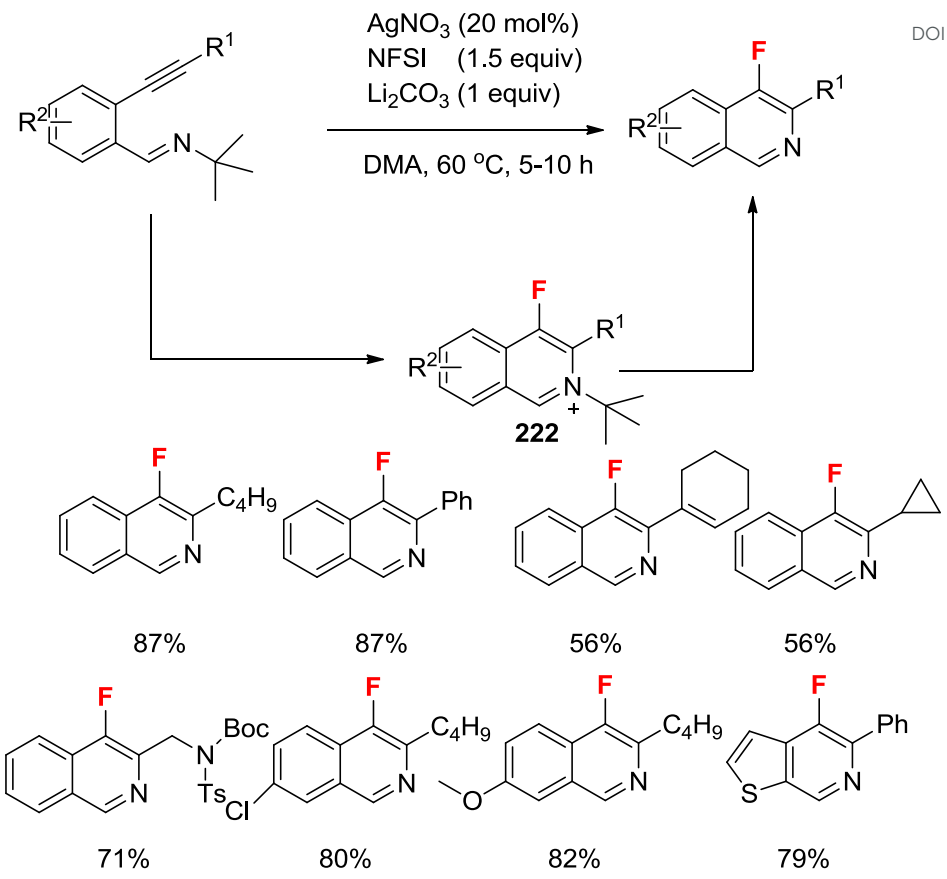

Scheme 54. Ag-catalyzed fluorination of alkynes by NFSI

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_2CO_3).

When the *t*-butyl group [134] was changed to a CH_2CO_2R 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

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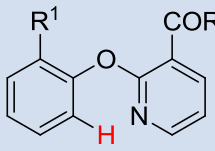
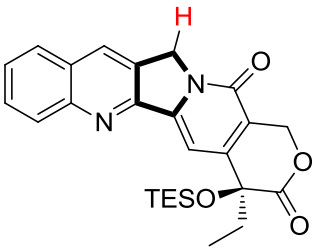
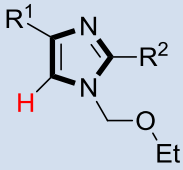
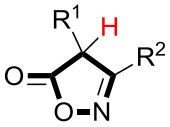
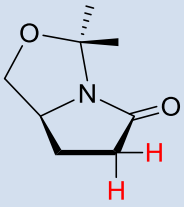
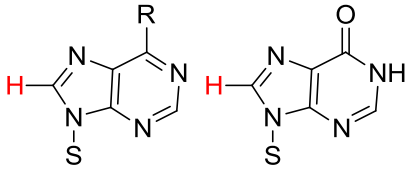
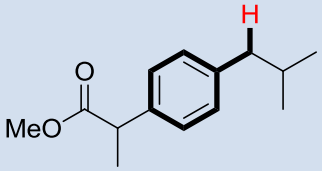
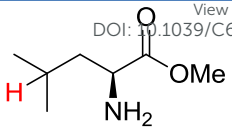
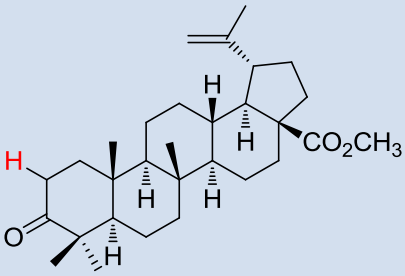
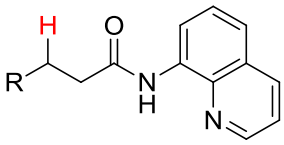
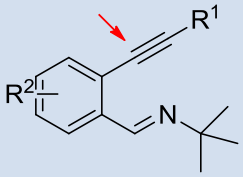
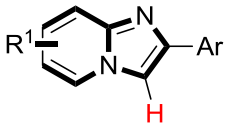
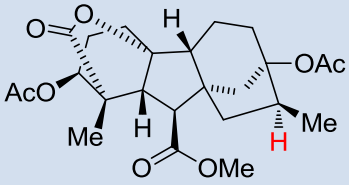
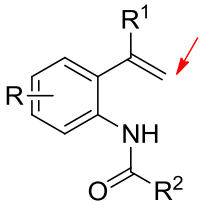
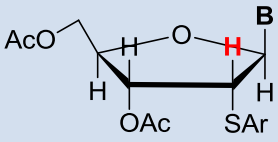
The introduction of new and easy-to-handle commercial fluorinating reagents, either of nucleophilic or electrophilic in nature, has tamed the reactivity of fluorine gas for fluorination reactions and, therefore, made protocols more direct and less cumbersome. However, there still remains the need for 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^3, sp^2, and sp carbon atoms. However, there still remains the challenge for stereoselective introduction of fluorine atoms into Csp^3 centres

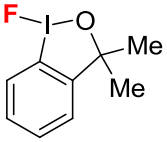
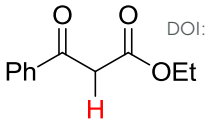
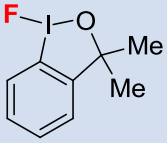
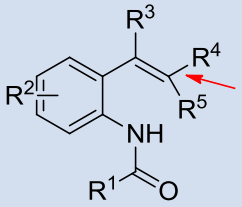
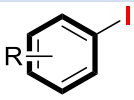
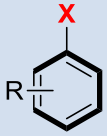
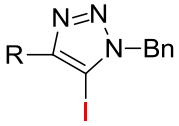
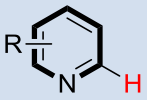
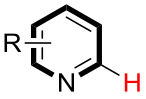
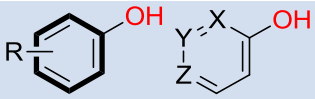
Nucleophilic fluorination strategies with nucleophilic fluorinating reagents have been employed in the fluorination of (hetero)aromatic substrates, mainly through S_NAr reactions, and for the ipso substitution of hydroxy-substituted (hetero)aromatic compounds.

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

reagent	Organic family	Additive	Conditions	Substrate	Ref.
NFSI, 11	aryls	$Pd(dba)_2$	EtOAc, 80-110 °C		[38]
NFSI, 11	pyrroles	LHDMS	THF, -78 °C		[60]
NFSI, 11	imidazoles	LTMP	THF, -78 °C		[61]
NFSI, 11	isoxazolino-nes	bis-cinchona alkaloid (stereospecific fluorination)	K_3PO_4, $CHCl_3$, -50 °C		[71]
NFSI, 11	pyrrolidinon-es	^{i}PrNH, BuLi	THF, -78 °C		[98]
NFSI, 11	nucleobases	LDA	Solid NFSI	 S = sugar and deoxysugar	[99]
NFSI, 11	benzylic positions	tetrabutylammonium-decatungstein (TBADC)	$NaHCO_3$, MeCN $\lambda = 365$ nm, flow system		[104]

NFSI, 11	methine positions	$Na_4W_{10}O_{32}$ (cat.)	MeCN : H2O (9 : 1) λ = 365 nm		[115]
NFSI 11 or Me-NFSI 12	α-carbonyl positions	LDA	THF,-78 °C–RT;		[109] [28] [127] [129] [120]
NFSI, 11	β-carbonyl positions	$Pd(AcO)_2$, Ag_2O Pivot	chlorobenzene, 80-120 oC		[106]
NFSI, 11	sp carbon atoms	$AgNO_3$, Li_2CO_3	DMA, 60 °C		[134]
SelectFluor, 7	imidazohete-rocyclic cores	DMAP	CH_3Cl:H_2O, 3:1 0 °C-RT		[63]
Selectfluor, 7	methylene and methine carbon atoms	$K_2S_2O_8$	MeCN : H_2O, 50 °C		[112]
Selectfluor, 7	sp^2 carbon atoms	-	MeCN, RT		[73]
Selectfluor, 7	carbohydrat-es	-	MeCN, RT		[90] [92] [93] [95]

 **14**	α-carbonyl positions	$Et_3N.3HF$	24 h, 40 °C DCM		[30]
 **14**	sp^2 carbon atoms	MS, 4 A	MeCN		[133]
AgF	aryl iodides	$(t\text{-BuCN})_2CuOTf$	DMF, 140 °C, 22h		[47] [35]
AgF	aryl triflates or bromides	Pd-L complex COD, KF or CsF	Me-THF	 X = OTf or Br	[49]
AgF	iodotriazoles	-	MeCN		[79]
AgF_2	pyridines, pyrazines, pyridazines and pyrimidines	-	MeCN		[57]
Me_4NF	pyridines, pyrazines, pyridazines and pyrimidines	-	MeCN		[53b]
Phenofluor 15	phenols and hydroxyheteroaromatics	CsF	toluene or dioxane, 110 °C		[31c]

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