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Deoxyfluorination: A Detailed Overview Of Recent Developments

Jan Jelen, Gašper Tavčar.

Affiliations below.

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Corresponding Author:
Prof. Gašper Tavčar, Jožef Stefan Institute, Department of Inorganic chemistry and technology, Jamova 39, 1000 Ljubljana, Slovenia, gasper.tavcar@ijs.si

Affiliations:
Jan Jelen, Institut Jožef Stefan, Department of Inorganic Chemistry and Technology (K1), Ljubljana, Slovenia
Jan Jelen, Jožef Stefan International Postgraduate School, Department of Inorganic Chemistry and Technology (K1), Ljubljana, Slovenia
Gašper Tavčar, Jožef Stefan Institute, Department of Inorganic chemistry and technology, Ljubljana, Slovenia

Deoxyfluorination: A Detailed Overview Of Recent Developments

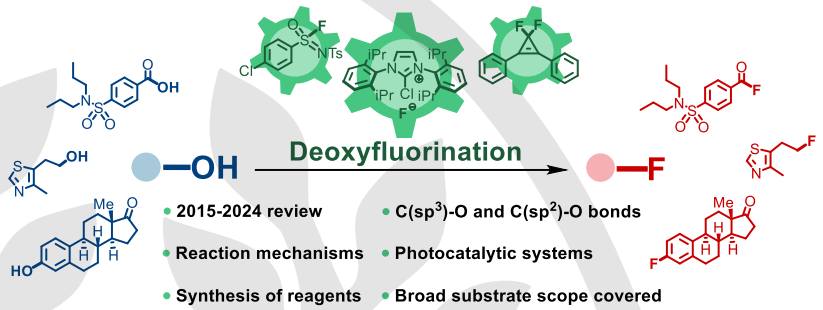
Jan Jelen[a,b]
Gašper Tavčar*[a,b]

[a] Jožef Stefan Institute, Department of Inorganic Chemistry and Technology, Jamova cesta 39, 1000 Ljubljana, Slovenia

[b] Jožef Stefan International Postgraduate School, Jamova cesta 39, 1000 Ljubljana, Slovenia

* indicates the corresponding author

gasper.tavcar@ijs.si



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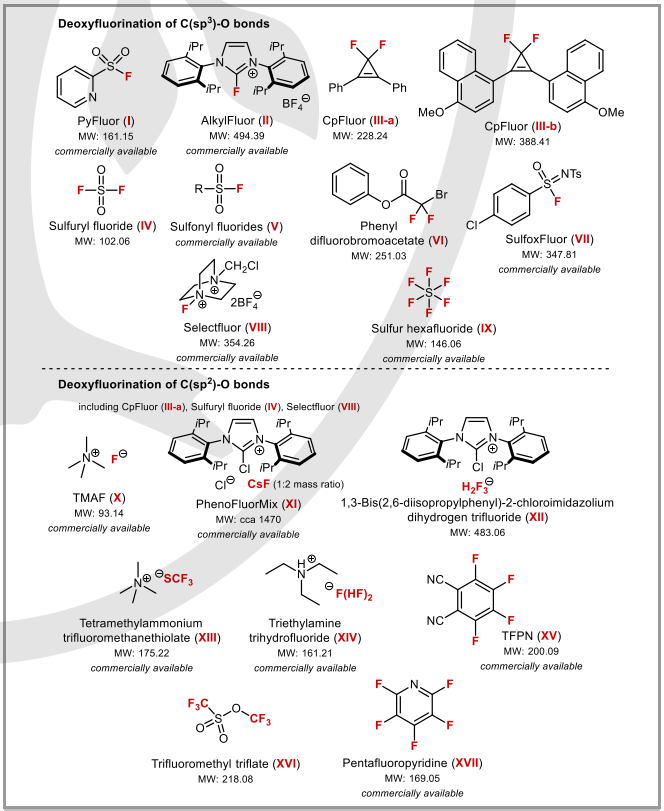
Abstract Fluorine organic compounds have been a predominant force of pharmaceutical chemistry for modern drug design with an increasing amount of fluorine-containing compounds entering the market. Methodologies for fluorine atom incorporation into organic molecules are still challenging to date and thus represent an important research area. Deoxyfluorination reaction serves as a useful tool for construction of carbon-fluorine bonds in biologically active molecules by converting a common hydroxyl group into corresponding fluoride. In this review we have summarized and categorized deoxyfluorination reaction protocols developed over the last decade (2015-2024) by the structural type of C-O bond deoxyfluorination including substrates like alcohols, phenols, ketones, aldehydes, and carboxylic acids.

Key words deoxyfluorination, photochemical conditions, alcohols, phenols, carboxylic acids

1 Introduction

The significance of carbon-fluorine bonds lies in their exceptional strength and effects on biological processes. These bonds play a pivotal role in enhancing the stability of molecules and have become indispensable in pharmaceuticals, where stability is the linchpin for drug safety and efficacy. However, the influence of C-F bonds is not limited to stability. Since they possess lipophilic character, they are adept at improving a compound's bioavailability, affecting its absorption, distribution, metabolism, and excretion—key factors in drug design. Furthermore, they bring an element of diastereoselectivity particularly useful in medicinal chemistry. [1–8] One of the perspective means of introducing carbon-fluorine bonds are deoxyfluorination reactions. In these one-step nucleophilic substitution reactions, oxygen atoms, often derived from hydroxyl groups, are displaced by fluoride anions.



Scheme 1 Deoxyfluorination reagents discussed in presented review article.

In this article, we explore the pivotal role of deoxyfluorination reactions developed over the last decade covering key literature findings published between January 2015 and March 2024. There are several previously published review articles that cover deoxyfluorination reactions [4,9,10]; in particular reviews by Hunter[11] in 2017 and Verma[12] in 2021 have discussed this topic in a great detail, however, many novel deoxyfluorination protocols have been developed since. While those reviews are mostly categorized by structural types of reagents, our goal is to address deoxyfluorination in a different systematic way of dividing sections by type of C-O bond participating in deoxyfluorination reaction and strategies used for achieving such a transformation providing more mechanistic insights. We place a particular attention to novel recently developed photochemical deoxyfluorination reactions as they often rely on milder reaction conditions. Deoxyfluorination reagents or nucleophilic fluoride sources discussed in the presented review are orderly listed in Scheme 1. Below each compound are listed molar masses (in *g mol*$^{-1}$) along with information on whether the compound is commercially available from common worldwide chemical suppliers.

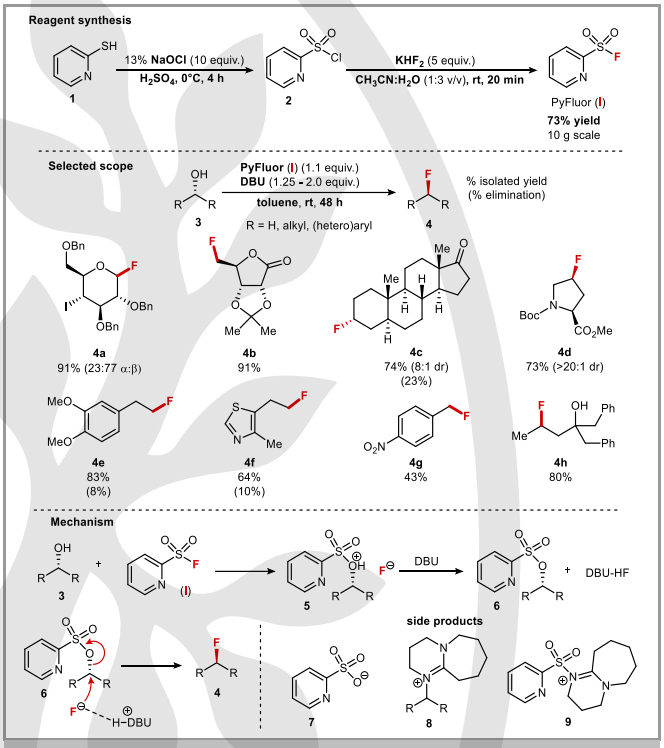
2 Deoxyfluorination of C(sp^3)-O bonds

2.1 Alcohols

The most abundant and cheapest starting materials containing C(sp^3)-O bonds are alcohols due to their extensive presence in nature. In the last decade, numerous reaction protocols using various structural types of reagents have been developed to convert alcohols into corresponding alkyl fluorides. In addition to the newly discovered strategies, a brief summary of reagents and methodologies already discussed in several other review articles is given below.

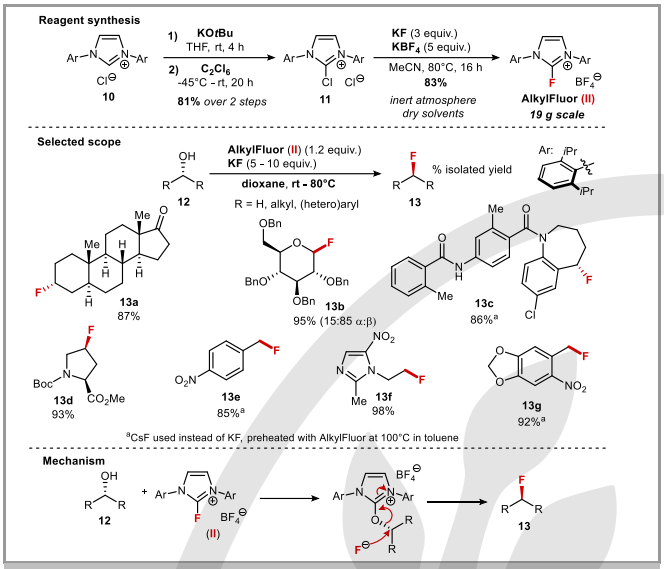
2.1.1 PyFluor, AlkylFluor and CpFluor

In 2015, Doyle's group reported a stable low-cost sulfonyl fluoride-based reagent PyFluor (**I**) that exhibits high chemical and thermal stability with excellent selectivity against elimination side product, allowing for straightforward purification. It is a low-melting solid (mp 23-26 °C) and can be readily prepared on a multigram scale via a 2-step synthesis from 2-mercaptopyridine (**1**) by aqueous sodium hypochlorite oxidation followed by fluoride anion exchange with potassium bifluoride in MeCN to afford PyFluor in 73% overall yield on 10 g scale. It acts as a deoxyfluorination agent for primary and secondary aliphatic or benzylic alcohols (**3**) with wide functional group tolerance and substrate scope including amino acid derivative (**4d**), carbohydrate (**4a**), and steroid derivative (**4c**) demonstrating a high yielding late-stage deoxyfluorination potential. [13] Reaction requires use of strong amidine or guanidine bases such as DBU and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) for high conversion to deoxyfluorination product and minimization of side product formation. Reaction mechanism involves rapid formation of a sulfonate ester intermediate (**6**), which is then gradually converted to alkyl fluoride product by base-assisted fluoride attack. The only side product detected by LC-MS was alkylated DBU cation (**8**) arising from DBU nucleophilic attack on the sulfonate ester intermediate and accounts for the mass balance. Blind experiment with PyFluor and DBU base showed observation of a complex (**9**), but it forms several orders of magnitude slower than the sulfonate ester intemerdiate (**8**) and is incompetent for deoxyfluorination reactions. Additionally, deoxyfluorination with PyFluor is not highly solvent dependent (toluene and cyclic ethers perform best) and proceeds with an inversion of stereochemistry (Scheme 2). [13]



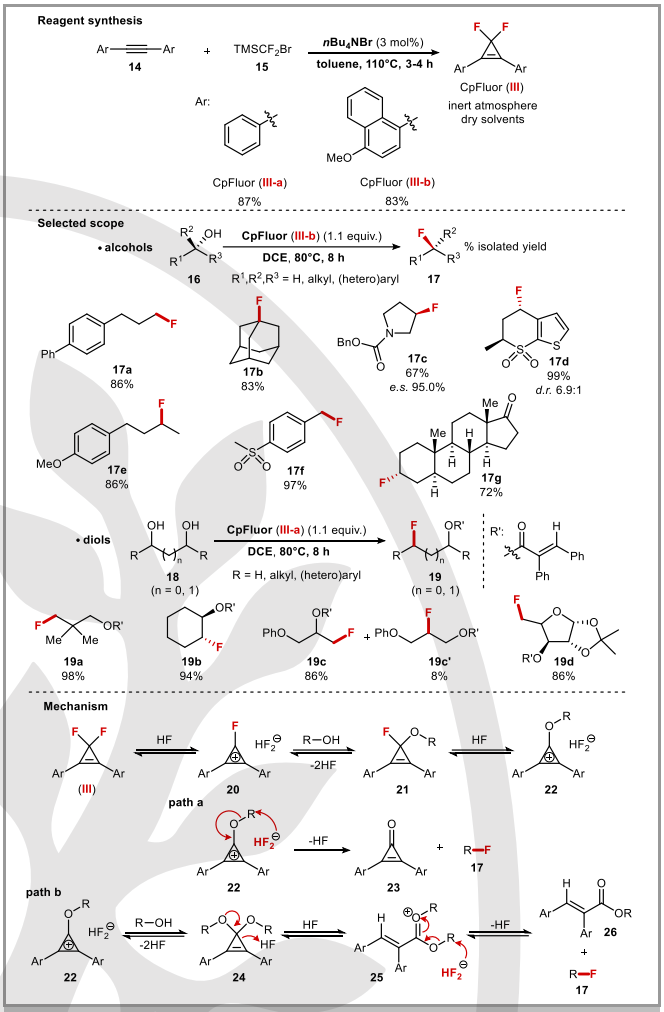
Scheme 2 Deoxyfluorination of primary and secondary alcohols with PyFluor.

Ritter's group later in 2016 developed AlkylFluor (**II**), a derivative of PhenoFluor type reagent suitable for deoxyfluorination of alcohols. It is a bench-stable reagent and can be prepared by treating 2-chloro-1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**11**) with potassium fluoride and potassium tetrafluoroborate in MeCN under inert atmosphere. It is capable of efficient and practical deoxyfluorination of primary and secondary aliphatic or benzylic alcohols including carbohydrates (**13b**), amino acids (**13d**), steroids (**13a**) and pharmaceutical compounds (**13c**). Reaction requires use of potassium fluoride as an additional fluoride source in 1,4-dioxane as a solvent and tolerates many useful functional groups including ketones, esters, amides, carbamates, protected or unprotected amines, acetals and heterocyclic compounds. Although deoxyfluorination with AlkylFluor generally proceeds cleanly with minor elimination side product, certain substrates required AlkylFluor to be converted into PhenoFluor *in situ* by preheating it with caesium fluoride at 100 °C in toluene beforehand (Scheme 3).[14]



Scheme 3 Deoxyfluorination of primary and secondary alcohols with AlkylFluor.

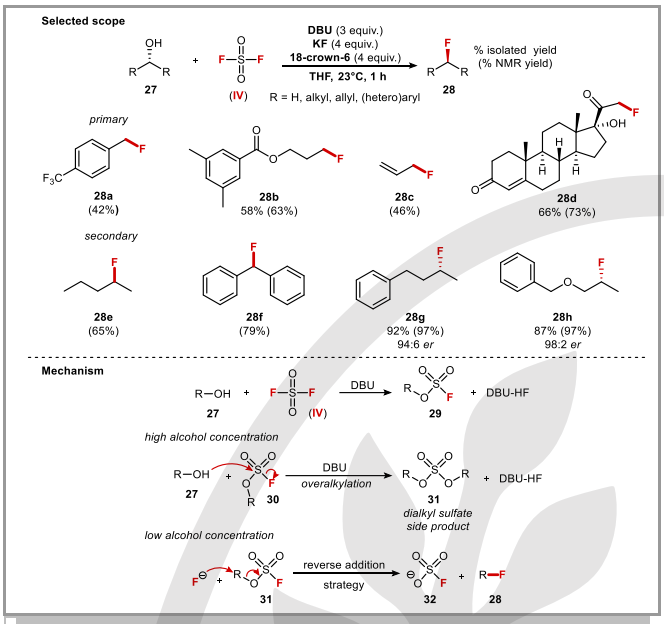
In 2016, Hu and coworkers reported 3,3-difluoro-1,2-diarylcyclopropenes, CpFluors (**III**) as usefull bench-stable deoxyfluorination reagents. CpFluor (**IIIb**) performed best at facilitating deoxyfluorination of primary, secondary, and tertiary aliphatic or benzylic alcohols (**16**), while CpFluor (**IIIa**) allowed for monodeoxyfluorination of 1,2- or 1,3-diols (**18**) due to unique sensitivity to the electronic character of the substrates. Deoxyfluorination proceeds through the formation of an alkoxycyclopropenium cation intermediate (**22**) stabilized by electron-rich aryl groups. Therefore, the electronic nature of the aryl substituents was a crucial selection factor to achieve high reaction yields with minimal formation of the by-product 2,3-diarylacrylate (**26**) alongside 2,3-diarylcyclopropanone (**23**). On the other hand, monodeoxyfluorination of diols occurs through formation of non-conjugated cyclopropenone acetals, which in turn makes them less sensitive to electronic effects of substituents. CpFluors react readily with glass and Lewis basic solvents such as THF and MeCN, consequently requiring PTFE reaction vessel and solvents like toluene, DCM, DCE or chlorobenzene. CpFluors can be prepared by a single-step synthesis from 1,2-di(aryl)acetylene and difluorocarbene generated *in situ* via $TMSCF_2Br$ in toluene at 110°C under an inert atmosphere (Scheme 4).[15]



Scheme 4 Deoxyfluorination of primary, secondary, and tertiary alcohols with CpFluors.

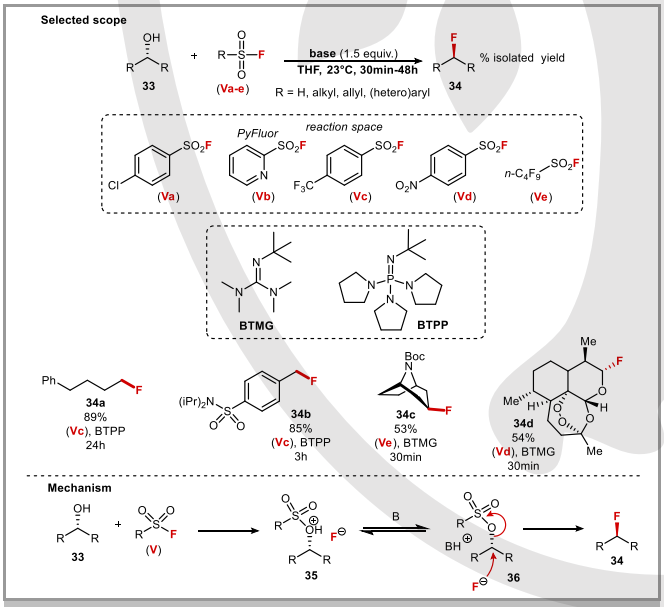
2.1.2 SO_2F_2 and other sulfonyl fluorides

Recently, a protocol for SO_2F_2-mediated deoxyfluorination of primary and secondary alcohols was developed by Sammis's group. The optimal reaction conditions required the use of an external fluoride source (KF in combination with 18-crown-6) together with a base DBU for efficient HF abstraction in THF at room temperature under an anhydrous inert atmosphere. The reaction protocol employs the reverse addition strategy, in which the alcohol solution is slowly added to the SO_2F_2 solution prepared *in situ* to prevent the formation of a dialkyl sulfate (**31**) side product. This effectively promoted the deoxyfluorination of many primary (**28a-d**) and some secondary aliphatic (**28e-h**) or allylic alcohols (**28c**) tolerating a handful of functional groups such as esters, olefins, halides, nitro group and phthalimide. Elimination side reaction was problematic for several substrates and required a reduction in the amount of base added to achieve higher yields. Benzylic alcohols were generally not effective under these reaction conditions, the only exception being 4-trifluoromethylbenzyl alcohol (**28a**). Finally, the method was applied to a steroid derivative (**28d**) in good yield and *dr* with inversion of the stereocenter (Scheme 5).[16]



Scheme 5 Deoxyfluorination of primary and secondary alcohols with SO_2F_2.

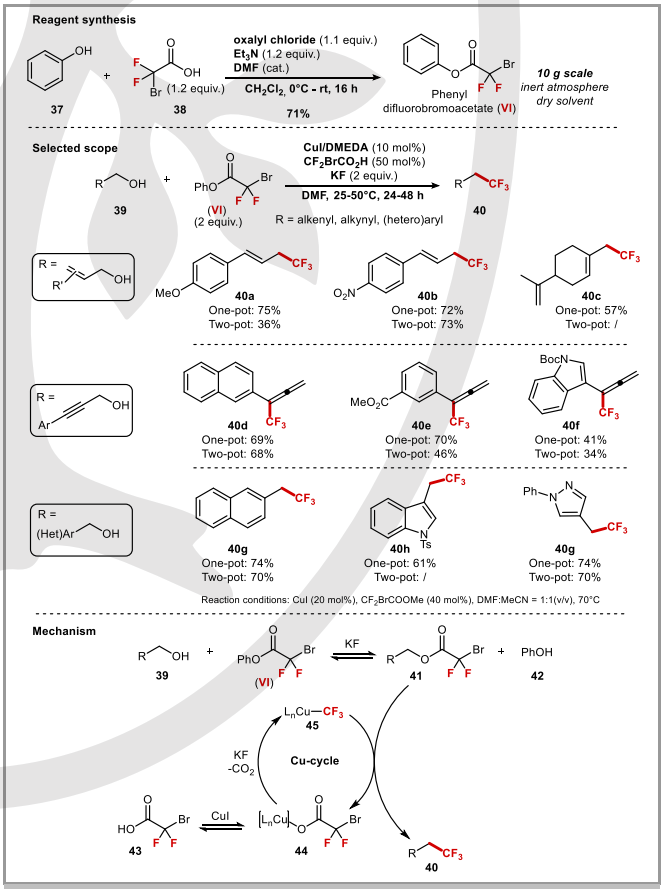
Doyle's group explored reaction space of deoxyfluorination with sulfonyl fluorides (**V**). They screened five structurally different sulfonyl fluorides (**Va-e**) with different electronic properties. They demonstrated that the flexibility of sulfonyl fluoride scaffolds allows for deoxyfluorination of wide range of alcohol substrates including cyclic alcohols (**34c**), unactivated (primary, secondary and tertiary) alcohols (**34a**), activated (benzylic and allylic) alcohols (**34b**), homobenzylic alcohols, hemiacetals (**34d**) and α/β-hydroxy carbonyl compounds. Furthermore, they employed a random forest model to accurately predict reaction outcomes and help assessing optimal reaction conditions for new alcohols (Scheme 6).[17]



Scheme 6 Deoxyfluorination of alcohols with different sulfonyl fluorides

2.1.3 Deoxytrifluoromethylation by bromodifluoroacetate

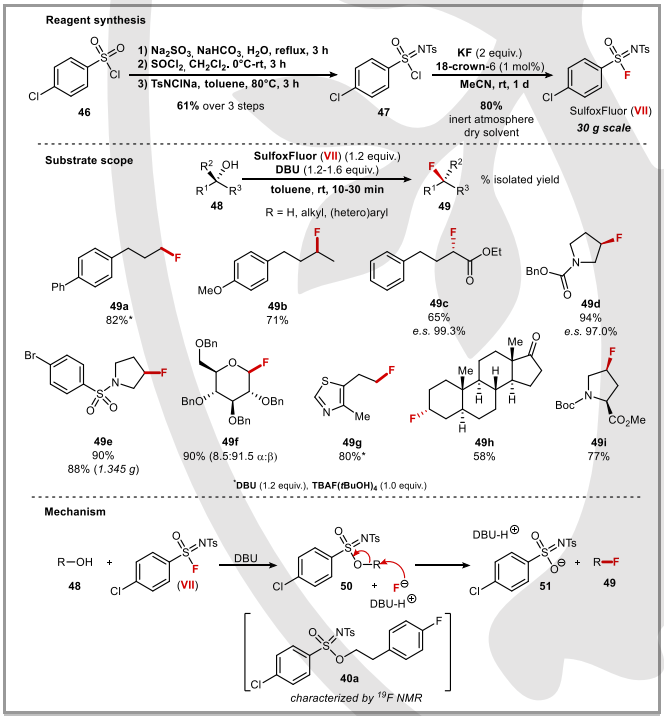
In 2019, R.A. Altman's group developed a rare example of catalytic one-step deoxytrifluoromethylation of alcohols. Using phenyl bromodifluoroacetate (**VI**) and Cu(I)-based catalyst, they were able to efficiently convert benzylic, allylic, and propargylic alcohols to their corresponding trifluoromethyl counterparts in moderate to good yields. The reaction mechanism involves the transesterification of phenyl bromodifluoroacetate (**VI**) with an alcohol that replaces the phenolate leaving group, leading to the formation of an active intermediate (**41**), that participates in the final decarboxylative copper catalytic trifluoromethylation cycle. The reaction can be carried out either as a one-pot synthesis or by a two-pot synthesis involving the formation and purification of intermediate bromodifluoroacetic esters (**41**). For most allylic and propargylic alcohols (**40a**, **40b**, **40c**, **40e**, **40f**), a one-pot deoxytrifluoromethylation gave higher yields, since many allylic and propargylic bromodifluoroacetates were unstable to basic conditions, silica gel, and even cold storage. A handful of (hetero)benzylic alcohols proved to be more challenging substrates requiring higher temperatures and copper catalyst loading to achieve useful yields. The reaction is compatible with many heterocycles and tolerates many useful functional groups including halides, olefins, esters, amides, tosylated amines and nitro group. In addition, it afforded synthetic intermediate of L-784,512 (COX-2 inhibitor) and fluorinated analogue of Tebufenpyrad in one step with comparable yields. The reagent aryl bromodifluoroacetate is synthesized by mixing the corresponding phenol (**37**) with bromodifluoroacetyl chloride prepared *in situ* from oxalyl chloride and bromodifluoroacetic acid (**38**) in DCM under an inert atmosphere (Scheme 7).[18]



Scheme 7 Deoxytrifluoromethylation of allylic, propargilyc and (hetero)benzylic alcohols with phenyl difluorobromoacetate and Cu(I) catalyst.

2.1.4 SulfoxFluor

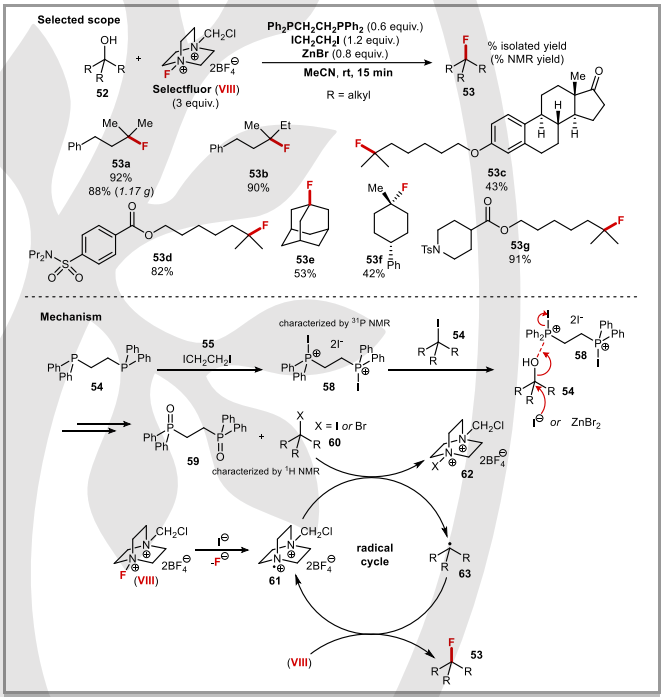
Hu and coworkers developed an alternative sulfonyl fluoride deoxyfluorination reagent called SulfoxFluor (**VII**) in 2019. Like its structural relative PyFluor, it is capable of converting primary, secondary and even tertiary alcohols to their corresponding alkyl fluorides in fair to excellent yields, with broad functional group tolerance including ketones, aldehydes, esters, amides, sulfonamides, carbamates, olefins, and heterocycles, including natural compounds such as carbohydrates (**49f**), steroids (**49h**) and amino acids (**49i**). It also exhibits a high selectivity against elimination reactions. For example, deoxyfluorination of primary alcohols rarely produces elimination side products even in case of homobenzylic alcohols (**49g**) that tend to undergo elimination. The deoxyfluorination reaction requires DBU as a base to effectively abstract HF similarly to PyFluor, however, in comparison usually proceeds much faster in order of minutes. Some difficult substrates (**49a**, **49g**) required the addition of TBAF(*t*BuOH)$_4$ (1.0 equiv.) to achieve higher yields. Deoxyfluorination with SulfoxFluor occurs with inversion of stereochemistry on chiral alcohols with high enantiospecificity. Monitoring of the reaction mechanism by ^{19}F NMR spectroscopy at various reaction conditions showed the formation of a sulfonimidate intermediate (**40a**), resulting from nucleophilic attack of alcohol (**48**) to Sulfoxfluor (**VII**), that slowly converted to corresponding alkyl fluoride (**49**) by DBU-HF (Scheme 8).[19,20]



Scheme 8 Deoxyfluorination of alcohols with SulfoxFluor.

2.1.5 Radical deoxyfluorination with Selectfluor

An alternative radical deoxyfluorination reaction of tertiary alcohols was discovered by Xiao and colleagues in 2020 using Selectfluor (**VIII**) as a fluorine source for efficient formation of tertiary C-F bonds under mild conditions. It relies on the activation of the hydroxyl group by the $Ph_2PCH_2CH_2PPh_2$/ICH_2CH_2I reagent system, which generates iodoposphonium salt (**58**) *in situ*, detected by ^{31}P NMR spectroscopy, and is capable of converting alcohols (**52**) to corresponding alkyl iodides (**54**). Under the reaction conditions, iodide anions (from **58**) promote a redox reaction with Selectfluor generating intermediate radical species (**61**) and alkyl radicals (**63**) by XAT (halogen atom transfer), which in turn capture electrophilic fluorine atom of Selectfluor closing a radical cycle. Nucleophilic fluoride substitution of tertiary alkyl iodides could be ruled out since no fluorination occurs when CsF is used as the fluorine source. The reaction is usually completed in less than 15 minutes and is carried out in MeCN as a solvent at room temperature. Various functional groups were tolerated such as carbonyl, esters, sulfonate, sulfonamide, aryl and primary alkyl halides including more complex molecules like steroids. Bulkier substituents on tertiary alcohols (**53e** and **53f**) resulted in lower yields indicating steric effects greatly affect reaction efficiency. Deoxyfluorination protocol was also applicable on a gram scale without a noticeable decrease in yield (**53a**) (Scheme 9).[21]

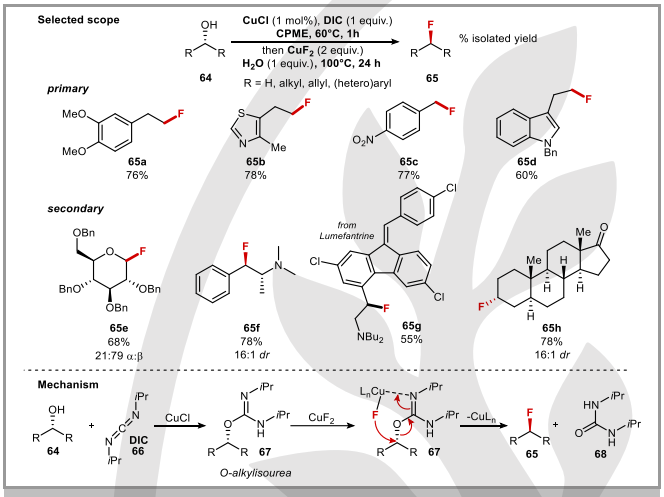


Scheme 9 Radical deoxyfluorination of tertiary alcohols using Selectfluor.

2.1.6 CuF_2/DIC system

In 2020, Watson and coworkers succeeded in deoxyfluorinating primary and secondary alkyl, benzyl, or allyl alcohols with CuF_2 and a Lewis base activating group, overcoming previous difficulties in using transition metal fluorides (MF_n) as fluorinating agents. The procedure utilizes the DIC-derived O-alkylisourea chelate (**67**) as an auxiliary that drives fluoride transfer from hydrated $Cu^{II}F$ species that displaces the urea (**68**) leaving group. The reaction required Cu^{I}-catalyzed formation of O-alkylisourea (**67**) prior to the addition of CuF_2. Furthermore, the addition of H_2O to anhydrous CuF_2 was essential since removal of H_2O or use of a hydrate salt resulted in lower yields. Powder XRD and solid-state NMR suggested a superposition of two phases different from hydrate form of CuF_2. The reaction was

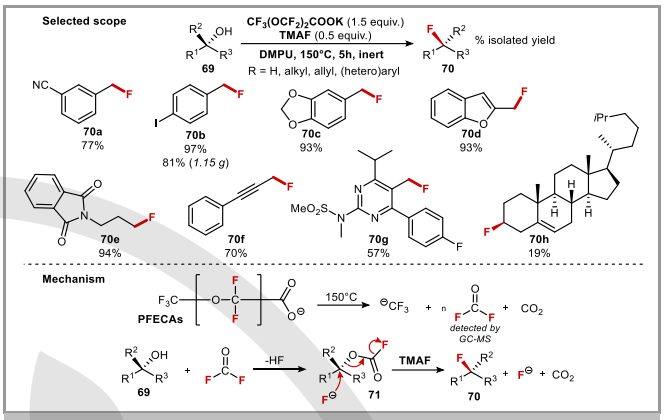
effective for both primary and secondary alcohols (**64**) in moderate to good yields tolerating a variety of common functional groups such as aryl or alkyl halides, amines, esters, heterocycles and even tertiary hydroxyl groups. This method also showed high stereospecificity for various substrates such as steroid compounds (**65h**), carbohydrates (**65e**) and other bioactive molecules (**65f** and **65g**) (Scheme 10). The method was also used to enable effective ^{18}F installation using $Cu(OTf)_2$ and the $[^{18}F]F^-/K222/K_2CO_3$ system.[22]



Scheme 10 Deoxyfluorination of primary and secondary alcohols with CuF_2/DIC.

2.1.7 Perfluoroalkyl ether carboxylic acids (PFECAs)

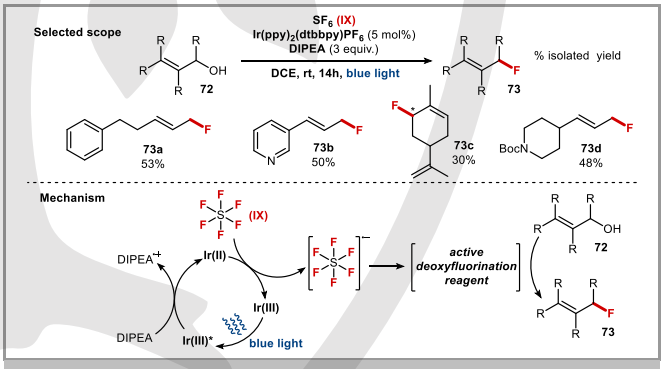
Chen and colleagues successfully used perfluoroalkyl substances (PFAS) to deoxyfluorinate primary, secondary and tertiary alcohols containing alkyl or (hetero)aryl substituents. They used thermal decomposition of perfluoroalkyl ether carboxylic acids (PFECAs), namely $CF_3(OCF_2)_2COOK$, to generate carbonyl fluoride (COF_2) *in situ* capable of mediating deoxyfluorination reactions. Addition of the external fluoride salt TMAF and heating to 150°C in DMPU as solvent under inert atmosphere were required to achieve optimal yields. Used reaction conditions tolerated many functional groups, including carbonyls, esters, nitriles, halides, sulfones, olefins, methoxy group and several heterocyclic systems and provided alkyl fluoride products in moderate to excellent yields (79%-94%). Substrate scope included bioactive compounds like steroid (**70h**) and rosuvastatin impurity derivative (**70g**). Investigation of the reaction mechanisms with GC-MS confirmed formation of COF_2. They proposed an intermediate (**71**) formation between alcohol (**69**) and carbonyl fluoride (COF_2), which is susceptible to nucleophilic attack by fluoride ion realising alkyl fluoride product and gaseous CO_2. Tracking of stereoselectivity showed an inversion of the configuration, suggesting an S_N2 reaction pathway of fluoride attack on intermediate (**71**) (Scheme 11).[23]



Scheme 11 Deoxyfluorination of alcohols with PFECAs.

2.1.8 Sulphur hexafluoride (SF_6)

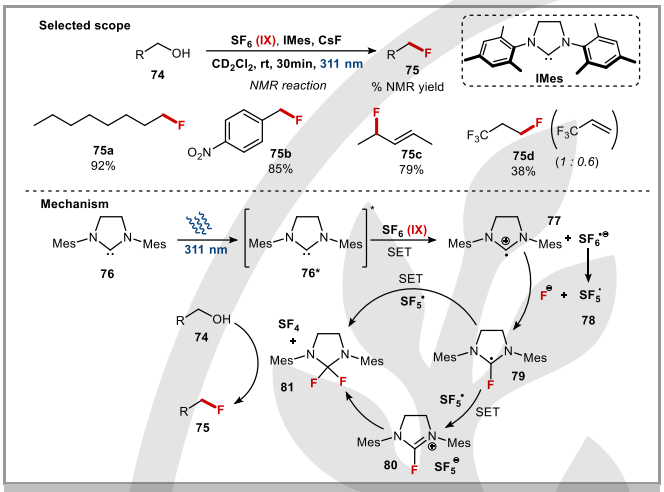
Sulphur hexafluoride (SF_6) is found as an important fluorinating agent for photocatalytic C-F bond construction of alcohols as suggested by recent findings in literature. Jamison's group used SF_6 for the deoxyfluorination of allylic alcohols (**81**). They utilized an Ir(III)-based photocatalyst together with a sacrificial electron-donor amine DIPEA to effectively reduce SF_6 under visible light. The resulting species act as a deoxyfluorinating agent that activates the alcohols by forming R-O-SF_x intermediates, in a manner similar to the chlorination of allyl alcohols by thionyl chloride. Moreover, this deoxyfluorination reaction proceeds with complete overall retention of stereochemistry. The presence of an adjacent π-bond enables unique reactivity under these conditions. Deoxyfluorination reaction tolerates a handful of functional groups, including amides, protected amines (**73d**), carbonyls or pyridine ring (**73b**), and gives moderate to good yields (Scheme 12a).[24]



Scheme 12a Photocatalyzed deoxyfluorination of allyl alcohols with SF_6 and Ir(III)-photocatalyst.

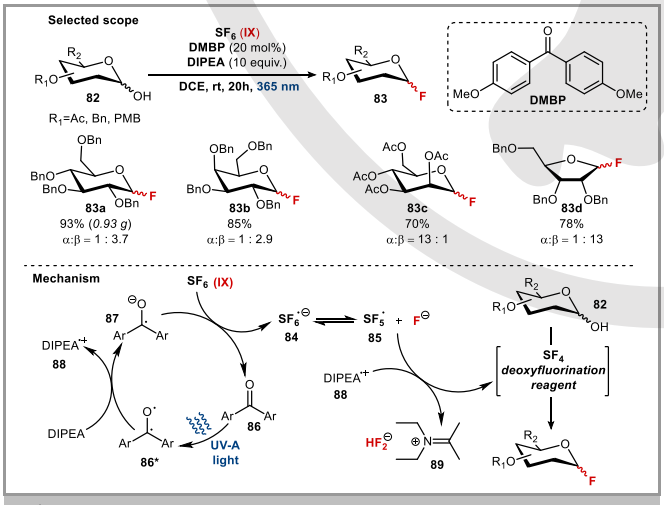
Kemnitz and coworkers discovered in 2018, that SF_6 could be successfully activated by N-heterocyclic carbenes (NHCs) to provide a deoxyfluorination reagent for alcohols by irradiation with UV light at 311 nm. Mechanistically, excited state NHC (**76***) enables a single electron transfer (SET) event reducing SF_6. Formed reactive sulphur pentafluoride radical species (**78**) oxidizes NHC radical cation (**77** and **79**) to the 2-fluoroimidazolidinium cation (**80**), producing PhenoFluor-type compound 2,2-difluoroimidazolidine (**81**) detected by ^1H, ^{13}C, ^{19}F NMR spectroscopy and LIFDI-MS. During the deoxyfluorination reaction, the formed active deoxyfluorination reagent 2,2-

difluoroimidazolidine (**81**) is able, in combination with CsF, to effectively convert aliphatic, benzylic, and allylic alcohols to their corresponding fluoride counterpart. Testing of three different NHCs (SIMes, IMes, and IPr) revealed that SIMes (**76**) performed the best and gave highest yield of 2,2-difluoroimidazolidine intermediate (**81**) (Scheme 12b).[25]



Scheme 12b Photocatalyzed deoxyfluorination of alcohols with SF_6 and NHC.

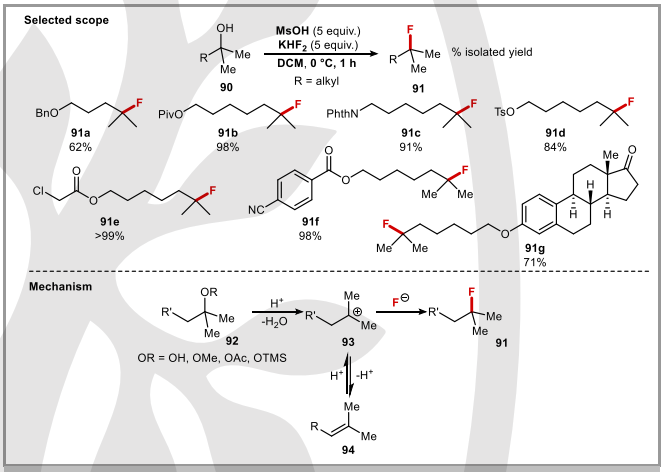
Another successful activation of SF_6 was achieved by Nagorny's group in 2021 using a benzophenone derivatives as photocatalysts, which facilitate deoxyfluorination of glycosylic hydroxyl groups to afford glycosyl fluorides. This photocatalytic reaction is similar to that of Jamison's group discussed earlier, relying on a sacrificial amine electron donor DIPEA using same reaction conditions, only with a UV-A light source (365 nm) and 4,4'-dimethoxybenzophenone (DMBP) as the optimal photocatalyst. Preliminary mechanistic studies suggested that the deoxyfluorination reaction proceeds through the formation of SF_4 active reagents They proposed that photoexcitation of DPMB (**86**) leads to the formation of a triplet state capable of oxidizing DIPEA to generate a ketyl radical (**87**), which in turn reduces SF_6 to a $SF_6^{\bullet-}$ radical anion (**84**), leading to the formation of SF_4 upon reaction with DIPEA radical cation (**88**). Substrate scope includes glycosyl fluorides such as glucose (**83a**), galactose (**83b**), mannose (**83c**), and ribose (**83d**) derivatives with various protecting groups (Scheme 12c).[26]



Scheme 12c Photocatalyzed deoxyfluorination of glycosides with SF_6.

2.1.9 MsOH/KHF_2 deoxyfluorination of tertiary alcohols

A novelty added by Paquin and coworkers in 2023 is deoxyfluorination of tertiary alcohols mediated by mesylic acid (MsOH) and potassium bifluoride (KHF_2) as a nucleophilic fluoride source. Reaction is performed in DCM as a solvent at 0°C, usually under an hour and averages 85% isolated yield on a broad scope of 23 substrate examples including a steroid derivative (**91g**). Reaction conditions tolerate many common functional groups such as protected primary alcohols (**91a**, **91b, 91d**), esters (**91e**, **91f**), amides (**91c**), olefins, (hetero)aromatics and more. Mechanistic investigation showed that deoxyfluorination reaction proceeds, in part, through an elimination/hydrofluorination pathway generating a carbocation intermediate (**93**) with no alkene elimination side product (**94**) observed after reaction, probably due to extreme acidic environment. Furthermore, they demonstrated examples of alkyl ether and alkyl acetate ester deoxyfluorination under the same reaction conditions (Scheme 13). [27]

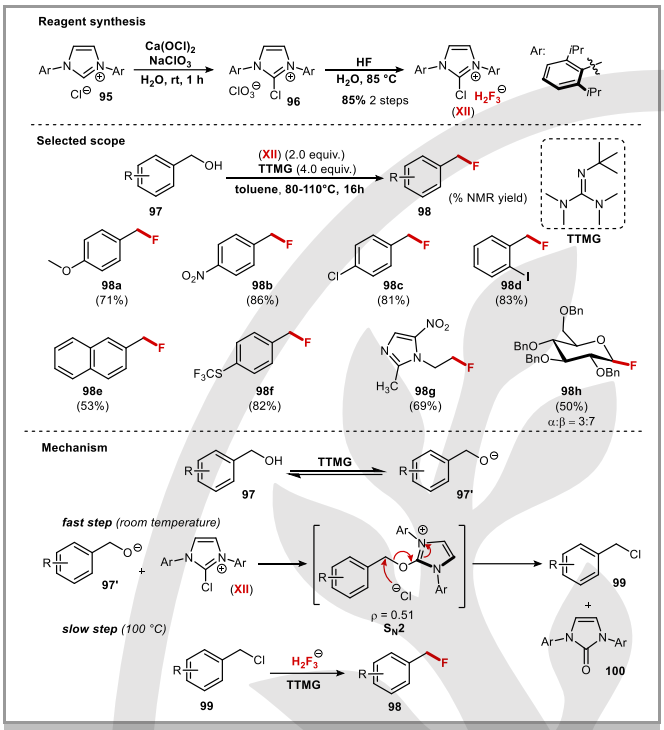


Scheme 13 Deoxyfluorination of tertiary alcohols with MsOH/KHF_2 system.

2.1.10 2-chloro-1,3-bis(aryl)imidazolium dihydrogen trifluoride

Tavčar's and Iskra's group recently developed a protocol for deoxyfluorination of benzylic and some aliphatic alcohols to corresponding alkyl fluorides using a benchtop stable, moisture-insensitive deoxyfluorination reagent, 2-chloro-1,3-bis(2,6-diisopropylphenyl)imidazolium dihydrogen trifluoride. It can be easily prepared in a two-step synthesis starting from readily accessible imidazolium chloride (**95**) by chlorination with hypochlorite in aqueous solution, followed by an anion exchange with an aqueous hydrofluoric acid. Deoxyfluorination requires TTMG as an appropriate base used for deprotonation of alcohol and activation of poly[hydrogen fluoride] anionic species in order to generate nucleophilic fluoride. Reaction is performed in an autoclave reactor at 100°C in MeCN as a solvent and usually proceeds within 3h. Benzylic alcohols provided moderate to excellent yields with good functional group tolerance including ethers (**98a**), nitro group (**98b**), halides (**98c** and **98d**), trifluoromethyl thioethers (**98f**) and (hetero)aromatics. The usefulness of described method was demonstrated on two

examples of bioactive aliphatic substrates, namely a metronidazole (**98g**) and glucose (**98h**) derivatives. [28]

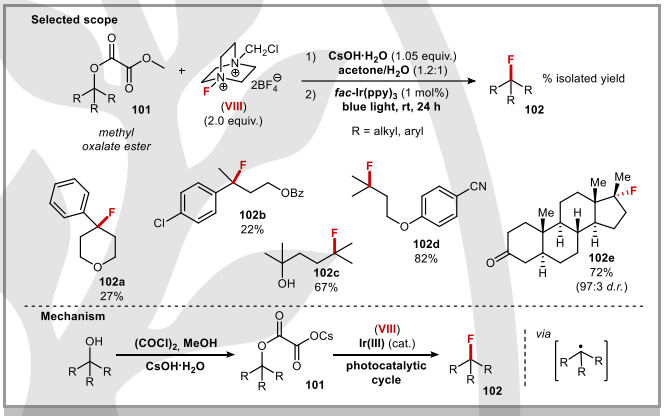


Scheme 14 Deoxyfluorination of benzylic alcohols with 1,3-bis(aryl)-2-chloroimidazolium dihydrogen trifluoride.

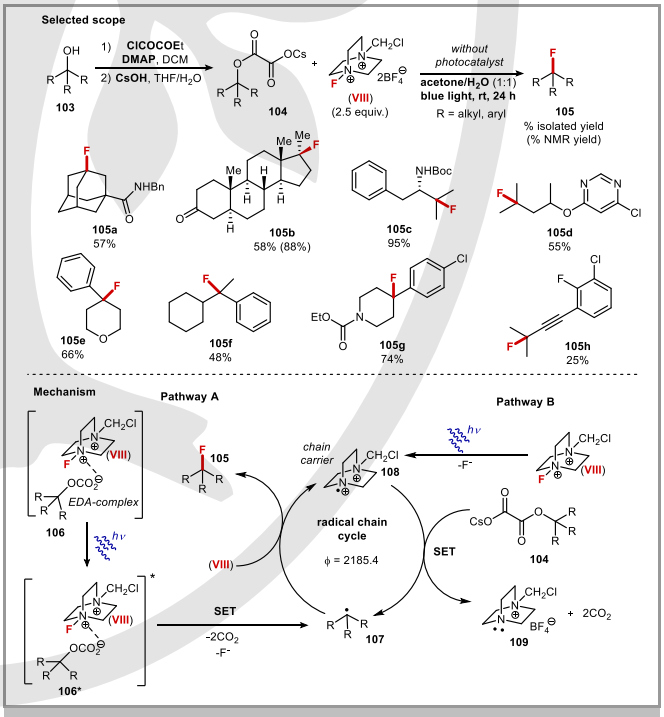
2.2 Alcohol derivatives

2.2.1 Photoredox deoxyfluorination of oxalate derivatives

In recent years, an increasing number of deoxyfluorination protocols have been developed utilizing photocatalysis as milder and more environmentally friendly conditions. They are mostly applicable to secondary, tertiary and allylic alcohol derived compounds that form stable radical species, which participate in the photocatalytic cycles. One such example was published by Brioche in 2018. They developed a photoredox deoxyfluorination of tertiary alcohol derived oxalate esters (**101**). This process is based on the preformation of caesium oxalate salt, followed by a photocatalytic cycle using an Ir(III)-based photocatalyst and Selectfluor in an acetone/H_2O solvent system. Although the substrate scope is predominantly limited to tertiary alcohols, deoxyfluorination reaction still shows very broad tolerance to different functional group such as esters, nitriles, tosylates, alcohols, carbonyls, halides and features compounds of biological interest such as steroid (**102e**) (Scheme 15a).[29] Interestingly, in 2019, Gómez-Suárez and coworkers independently discovered the same reaction protocol without using a photocatalyst. Under the same reaction conditions, they were able to convert aliphatic, (hetero)benzylic and propargylic tertiary alcohol oxalate esters (**104**) to the corresponding alkyl fluorides (**105**) under catalyst-free conditions exhibiting very similar tolerance to functional groups. Mechanistic studies shed some light on the photocatalyitic radical cycle, which showed two possible distinct reaction pathways. In both cases, $TEDA^{2+\bullet}$ radicals (**108**) are generated either by direct irradiation of Selectfluor (pathway B) or by formation of an EDA-complex (**106**) between Selectfluor and the corresponding oxalate derivative (**104**) followed by a subsequent excitation of the formed species. Quantum yield measurements (Φ = 2185.4) showed that a very efficient radical chain mechanism is in operation suggesting $TEDA^{2+\bullet}$ radicals (**106**) as chain carriers that convert several oxalate molecules (**104**) to corresponding alkyl radicals (**107**), which capture fluorine atom from Selectfluor closing the radical cycle (Scheme 15b). [30] Later, in 2021, Brioche's group developed a similar deoxyfluorination protocol by using silver(I) nitrate ($AgNO_3$) as an effective catalyst generating alkyl radical. Combination with Selectfluor as a fluorine source produces corresponding alkyl fluorides, showing similar preference for tertiary alcohol oxalate derivatives. [31]



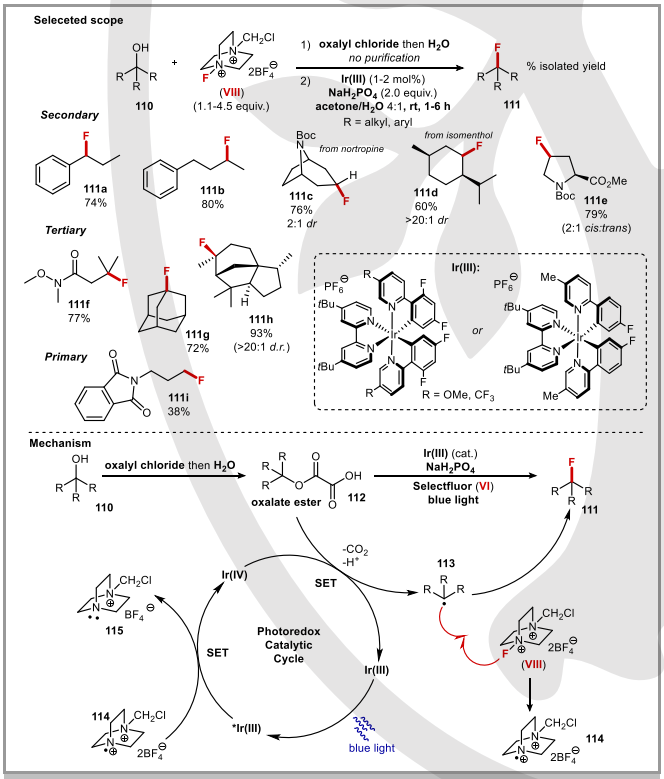
Scheme 15a Photochemical deoxyfluorination of methyl oxalate esters.



Scheme 15b Photochemical deoxyfluorination of oxalate esters.

Another example of radical photoredox deoxyfluorination of oxalate derivatives was independently reported in 2019 by MacMillan's group. They developed a photoredox-catalysed deoxyfluorination of secondary and tertiary alcohols via alcohol

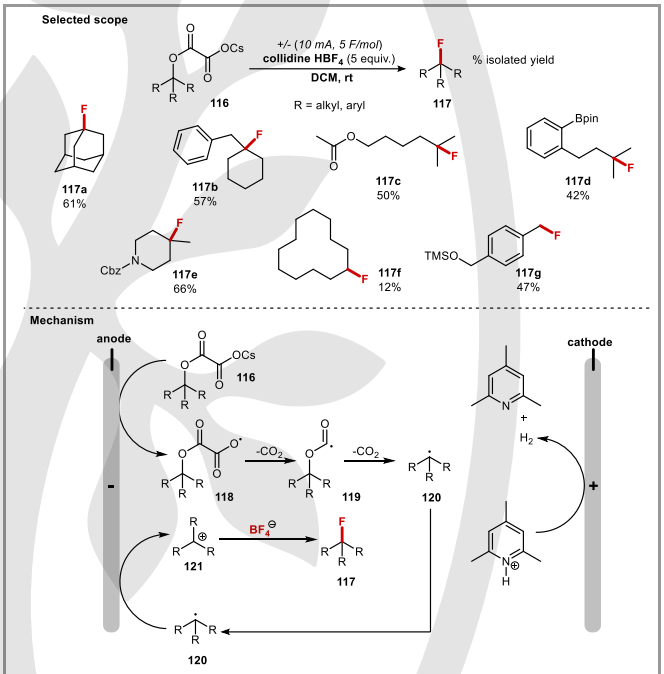
oxalate salt derivatives. Their catalytic system also relies on an Ir(III)-based photocatalyst and Selectfluor as an electrophilic fluorine source. Prior to the photocatalyzed fluorination reaction cycle, alcohols (**110**) are converted to their oxalate analogues (**112**) by reaction with oxalyl chloride and sequential hydrolysis without purification. Mechanism involves a SET reaction between photoexcited Ir(III) catalyst and oxalate derivative (**112**) generating alkyl radicals (**113**), which capture fluorine atom of Selectfluor in a similar fashion to previous findings of Brioche and Gómez-Suárez. Formed TEDA$^{2+\bullet}$ radicals (**114**) are responsible for reduction of Ir(IV) species regenerating Ir(III) photocatalyst A wide range of differentially substituted secondary and tertiary alcohols/oxalate derivatives were readily converted to their corresponding alkyl fluorides in good to excellent yields including motifs such as benzylic, homobenzylic, propargylic and β-benzyl-substituted alcohols. The reaction is compatible with many functional groups like amines, amides, phtalimides, olefins, halides, carbonyl, and cyanide group. Substrate scope includes steroidal compound and several natural compounds such as isomenthol (**111d**), nortropine (**111c**), cedrol and sclareolide Deoxyfluorination of primary alcohols resulted in lower yields (**111i**) due to the instability of the primary alkyl radicals. It should also be emphasised that the acetone/H_2O solvent system proved to be the most efficient. Organic cosolvents other than acetone resulted in poorer yields. (Scheme 16) [32,33].



Scheme 16 Photochemical deoxyfluorination of oxalic acids.

2.2.2 Electrochemical deoxyfluorination of oxalates

In 2023, Lam and coworkers developed a practical electrochemical deoxyfluorination method for accessing tertiary, secondary alkyl, and primary benzylic fluorides under mild reaction conditions from activated alcohol oxalate esters (**116**). This provides a useful green alternative to previous photochemical methods. Their protocol uses collidinium tetrafluoroborate as a fluoride source and a supporting electrolyte, together with a carbon graphite as both cathode and anode electrode material. Reaction proceeds in DCM as a solvent at room temperature and tolerates many useful functional groups such as esters, olefins, protected amines, boronic esters, aromatics, and even silyl ethers. Substrate scope includes several examples of tertiary and secondary oxalate derivatives with moderate yields. Reaction mechanism likely involves an anodic oxidation of oxalate derivatives (**116**) to afford hemioxalate radical (**118**), which undergoes two subsequent decarboxylation reactions (**119**) generating alkyl radical (**120**). Formed alkyl radicals rapidly undergo another anodic oxidation generating alkyl cations (**121**), which capture fluoride from tetrafluoroborate anion affording alkyl fluorides (**117**) (Scheme 17).[34]



Scheme 17 Electrochemical deoxyfluorination of oxalate esters.

3 Deoxyfluorination of C(sp^2)-O bonds

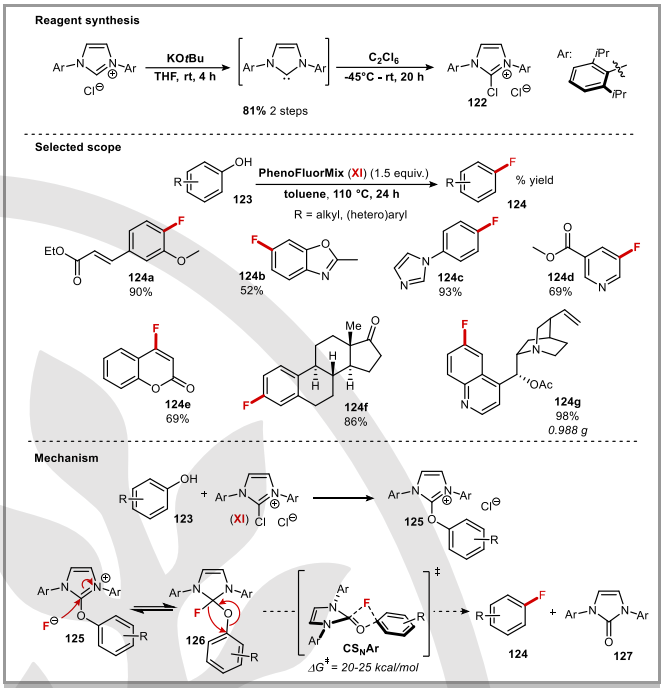
3.1 Phenols

Phenols are a great source of naturally occurring species containing a hydroxyl group at the C(sp^2) atom, whichmaking them prominent precursor for synthesis of aryl fluorides. In comparison to a deoxyfluorination reactions of alcohols, phenols usually require harsher reaction conditions. Reagents that facilitate deoxyfluorination of phenols often rely on concerted mechanisms of aromatic nucleophilic substitution reaction (CS_NAr) rather than typical nucleophilic aromatic substitution proceeding stepwise through Meisenheimer complex. This allows for lower reaction temperatures than for typical aromatic nucleophilic aromatic substitution with lesser solvent

dependence and wider substrate scope since substituent have marginal effect due to minor charge buildup during the transition state. [35–39]

3.1.1 PhenoFluor/PhenoFluorMix

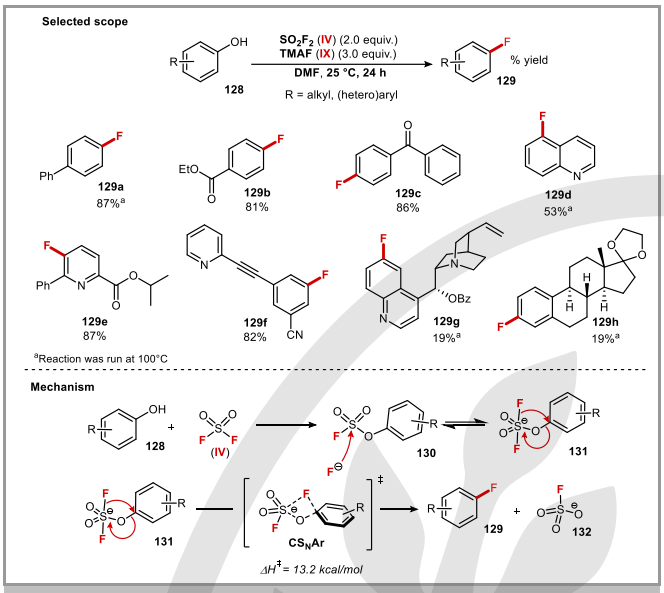
In 2015, Ritters group developed PhenoFluorMix reagent mixture, a bench-stable moisture-insensitive version of PhenoFluor, for deoxyfluorination of electron-poor and electron-rich phenols to corresponding aryl fluorides. PhenoFluorMix is based on 2-chloro-1,3-bis(aryl)imidazolium salt (**122**) that can be synthesized on a decagram scale from easily accessible imidazolium chloride through formation of NHC under inert atmosphere followed by chlorination with C_2Cl_6 as a chlorinating agent. Reaction conditions tolerate many synthetically useful functional groups (aldehydes, ketones, esters, olefins, sulphides, halides…) with broad substrate scope including heterocycles containing oxazole, pyridine, pyrimidine quinoline, or imidazole rings. Additionally, natural compounds such as estrone and a quinine derivative were successfully deoxyfluorinated in high isolated yields. Furthermore, the use of ruthenium complex allowed for ^{18}F-deoxyfluorination with high radiochemical (RCY) and activity (AY) yields on electron-deficient and electron-rich phenols with several representable biological compounds. ^{18}F-Deoxyfluorination of phenols barring electron-withdrawing groups or electron-poor ring systems was also feasible without the use of ruthenium catalyst with similar yields. Mechanistic investigations conducted by Ritter's group employing Eyring plot, Hammet plot and kinetic isotope effect showed that deoxyfluorination reaction proceeds through a concerted transition state (**CS$_N$Ar**), rather than classic two-step mechanism, with much lower activation energies due to minimal charge build-up during a transition state. This allows for nucleophilic displacement even on electron-rich arenes. Formation of tetrahedral intermediate (**126**) was evident from ^{19}F -^{13}C HSQC experiment of reaction mixture. On top of that, all was supported by DFT calculations (B3LYP/6-31G(d), toluene solvent model) of intermediates, transition state and intrinsic reaction coordinate (IRC) providing $\Delta G^{\ddagger}$ values of 20-25 kcal mol^{-1} in close agreement with experimental values (Scheme 18).[35,40,41]



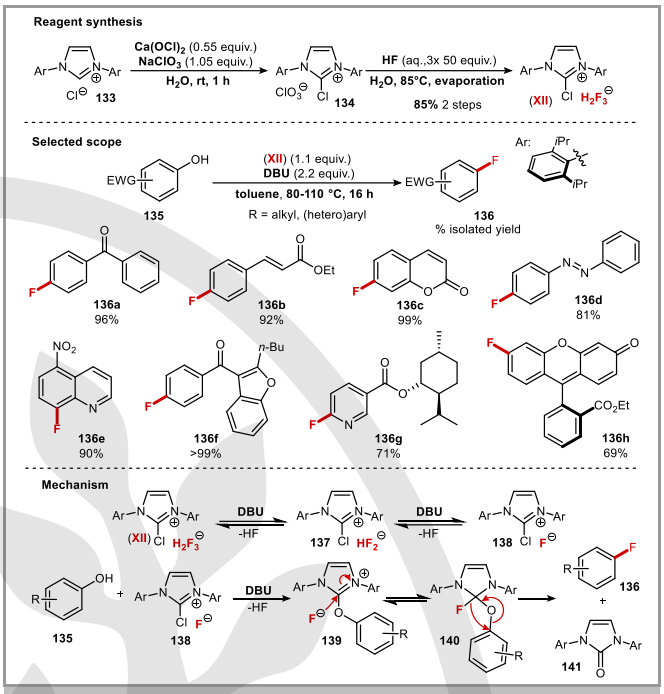
Scheme 18 Deoxyfluorination of phenols with PhenoFluorMix

3.1.2 SO_2F_2/TMAF system

Sanford and coworkers published in 2017 a promising alternative method for deoxyfluorination of phenols by using combination of sulfuryl fluoride (SO_2F_2) and tetramethylammonium fluoride (TMAF) as an additional nucleophilic fluoride source. Reaction proceeds via formation of aryl fluorosulphonate intermediates at room temperature for electron-poor phenols and requires heating to 80-100 °C for electron-neutral or electron-rich phenols. Reaction conditions display broad functional group tolerance including carbonyl, esters, amides, nitriles, tertiary amines and various heterocyclic compounds. Kinetic and computationally studies revealed a similar mechanistic feature as for deoxyfluorination with PhenoFluor reagent(s) – a concerted reaction pathway of a rate-determining step. Fluorosulphonate intermediate (**130**) formed by nucleophilic attack of phenol onto SO_2F_2 molecule sequesters fluoride anion forming anionic intermediate (**131**) and allowing for rearrangement via a concerted transition state. Low activation enthalpy ($\Delta H^{\ddagger}$) of 13.2 kcal/mol is consistent with a fast reaction rate measured experimentally (Scheme 19). Further mechanistic investigations revealed that reversible formation of diaryl sulphate side product accompanies deoxyfluorination reaction. While diaryl sulphates are capable of converting to aryl fluoride deoxyfluorination product by the action of SO_2F_2, their conversions are significantly lower and greatly impede the productive deoxyfluorination, especially with phenols barring electron-donating substituents. In order to prevent formation of diaryl sulphates, aryl triflate and aryl nonaflate derivatives were explored since these compounds are incapable of forming diaryl sulphates. They proved to be more efficient for electron-rich phenols. [36–38]



Scheme 19 Deoxyfluorination of phenols with SO_2F_2/TMAF.



Scheme 20 Deoxyfluorination of electron-deficient phenols.

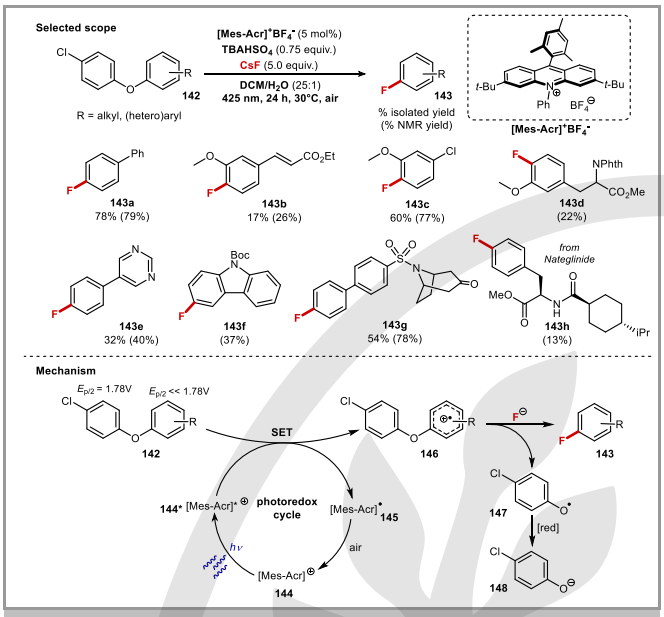
3.1.3 2-Chloro-1,3-bis(aryl)imidazolium poly[hydrogen fluorides]

Recently in 2023, Tavčar's group developed a derivative of PhenoFluorMix reagent based on dihydrogen trifluoride salt of 2-chloro-1,3-bis(aryl)imidazolium cation moiety. It can be easily prepared in a two-step synthesis from accessible 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (**133**) by using bleach solution as a chlorinating agent and hydrofluoric acid as a fluoride source without the need of organic solvents or inert conditions providing a far cheaper alternative with easier operation. This deoxyfluorination reagents is capable of converting electron-deficient phenols (**135**) to corresponding aryl fluorides (**136**) using similar reaction conditions and functional group tolerance. The use of external fluoride (CsF) is unnecessary since reagent already contains nucleophilic fluoride source. As previous research indicated poly[hydrogen fluoride] anion can be efficiently active by addition of base[13,42]; in this case amidine base DBU proved to be most effective. Substrate scope includes natural compounds (**136b**, **136c**), dyes (**136d**, **136h**) and compounds of pharmaceutical relevance (**136e**, **136f**, **136g**). Mechanistic studies revealed DBU acts as hydrogen fluoride abstraction agent generating nucleophilic fluoride anion (**137** and **138**). Formation of aryl fluoride product then proceeds similarly to deoxyfluorination with PhenoFluor reagents. (Scheme 20).[43]

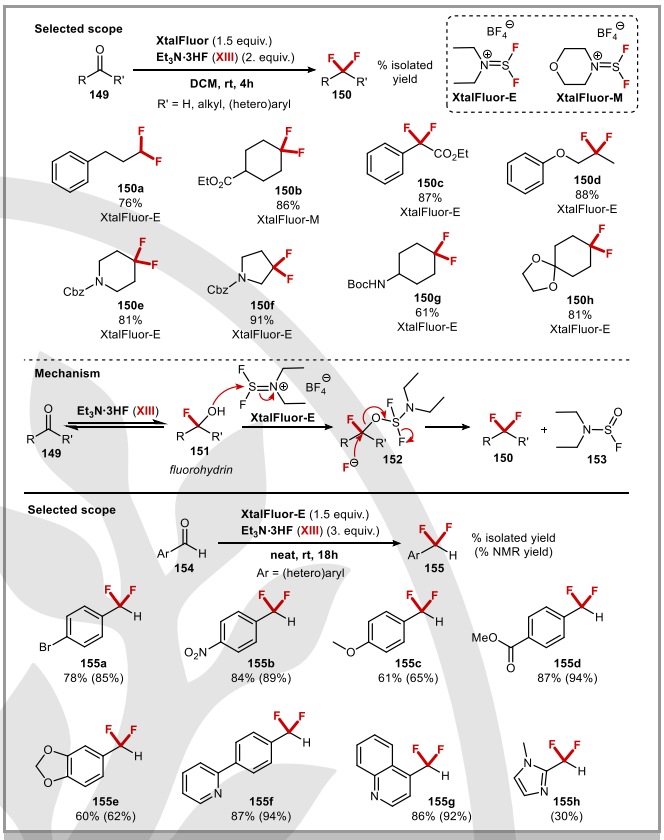
3.2 Phenol derivatives

3.2.1 Photochemical deoxyfluorination of aryl ethers

In 2020, Ritter's group demonstrated a polarity-reversed photoredox-catalysed deoxyfluorination, that operates via cation-radical-accelerated SNAr and enables deoxyfluorination of electron-rich aryl ethers with $^{19}F^-$ and $^{18}F^-$ under mild reaction conditions. This methodology thus complements the traditional arene polarity requirements (electron-withdrawing groups) necessary for S_NAr-based fluorination. After extensive optimization, it was found that using an acridinium-based photooxidant, CsF and $TBAHSO_4$ with a biphasic DCM/water solvent system provided optimized yields for most substrates. Reaction tolerates many useful functional groups such as esters, ethers, protected amines, amides, sulfonates, olefines, halides and several (hetero)aromatic compounds. Substrate scope includes natural (**143b**) and pharmaceutical compounds like nateglinide (**143h**) This reaction can be performed under air or N_2 without significant difference. At the outset, it was determined that light-emitting diodes (LEDs) with λ=427nm were interchangeable with 455nm LEDs. Reaction mechanism involves a SET reaction between excited acridinium photocatalyst (**144**) and aryl ether (**142**). This generates aryl cation radical (**146**) on a more oxidizable aromatic ring with lower reduction potential. By careful design of sacrificial aromatic ring (4-chlorophenyl, $E_{p/2}$ = 1.78 V) this process was made selective for most substrates Utility of presented method was furthermore complemented by application as radiofluorination strategy, which is highlighted with short reaction times, compatibility with multiple nucleofuges and high radiofluorination yields. (Scheme 21).[44]



Scheme 21 Photochemical deoxyfluorination of electron-rich aryl ethers.



Scheme 22. Deoxyfluorination of aldehydes and ketones with XtalFluor.

3.3 Aldehydes and ketones

A carbonyl group in aldehydes or ketones could also be subjected to deoxyfluorination reaction resulting in gem-difluoro compounds by displacement of carbon-oxygen double bond. In general, those type of deoxyfluorination reactions usually require use of unstable aminodifluorosulfinium salts as deoxyfluorination reagents like DAST or DeoxoFluor. More stable analogues like XtalFluor-E or XtalFluor-M were also explored in development of deoxyfluorination protocols. Typical reaction conditions involve stirring ketone or aldehyde substrate at room temperature in DCM with the addition of Et_3N 3HF and Et_3N under inert atmosphere and tolerate common functional groups such as protected amines and esters. Although not supported by conclusive experimental proof, the first step toward geminal difluorination is generally considered to be the addition of HF across the carbonyl group to provide a fluorohydrin (**151**), which then partakes in deoxyfluorination with the reagent. In the case of DAST and DeoxoFluor, the initial source of free HF arises by hydrolysis of the reagents with trace amounts of water or by the deliberate addition of ethanol. On the other hand, exogenous HF is required to initiate deoxyfluorination of carbonyls using dialkylaminodifluorosulfinium salts (Scheme 22).[45–47] Recently, in 2023, Paquin and coworkers developed a protocol for deoxyfluorination of aromatic aldehydes using XtalFluor-E as deoxyfluorination agent at room temperature and without added solvent. A wide range of gem-difluoride compounds was obtained in 21 to 87% isolated yields and broad functional group tolerance including nitro group, halides, esters and several (hetero)aromatic compounds (Scheme 16).[48]

3.4 Carboxylic acids

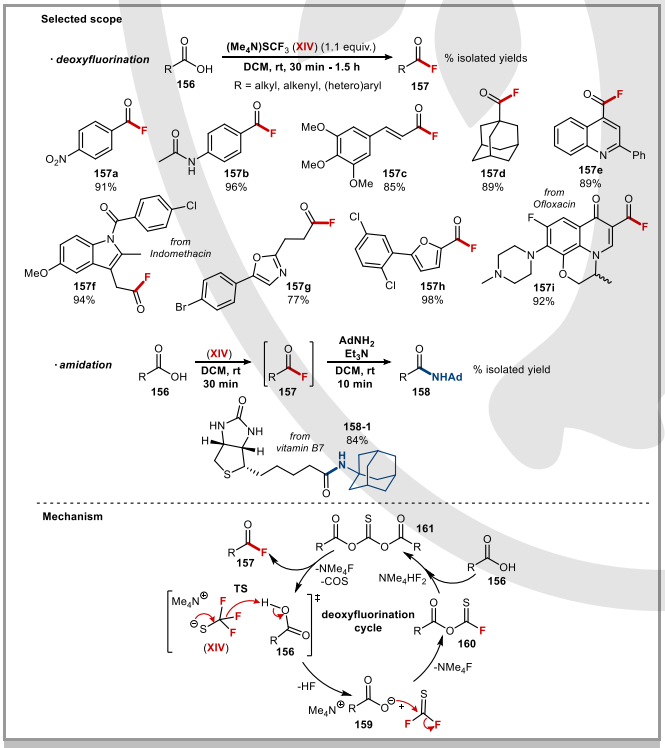
Carboxylic group (-COOH) is another example of functional motif possessing hydroxyl group on a C(sp^2)-atom and is abundantly present in naturally-occurring compounds. Deoxyfluorination derivatives of carboxylic acids most commonly involve acyl fluorides, however fluorine products such as trifluoromethyl ketones[49] or trifluoromethyl thioesters[50] can also be achieved. This provides a great platform for diversification of carboxylic group to other synthetically and biologically relevant functional groups. For example, acyl fluorides when reacted with various nucleophiles provide a straightforward access of high-value products such as esters, amides (peptides), or thioesters and exhibit reactivity toward a broad spectrum of nucleophiles with diverse electronic and steric properties. Compared to the traditionally used acyl chlorides, corresponding acyl fluorides demonstrate superior stability to reactivity ratio allowing for greater reaction yields. The former are notorious for their instability towards moisture and air, while the latter are sufficiently stable to be isolated and withstand column chromatography on silica gel and even wet solvents. Their reactivity is comparable to activated esters while not suffering from steric constraints.[51,52] Consequently, acyl fluorides provide good acyl synthons in acyl cross coupling reactions.[53,54]

3.4.1 Deoxyfluorination of carboxylic acids to acyl fluorides

Acyl fluorides can be prepared from carboxylic acids in the same mechanistic manner as their corresponding chlorides counterparts by using different deoxyfluorination reagents. Since

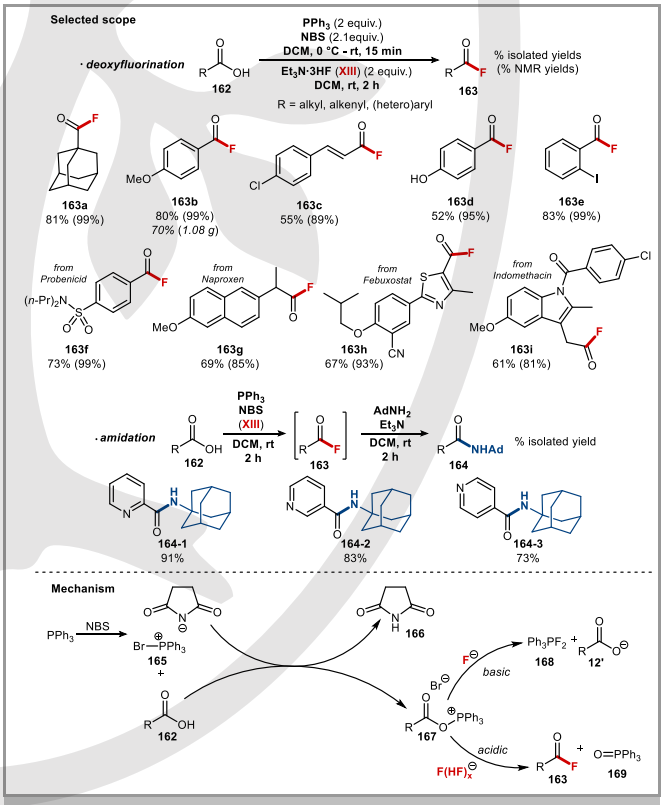
hydroxyl group (-OH) is attached to a significantly electron-deficient carbon atom of carbonyl group, deoxyfluorination (nucleophilic substitution with fluoride) proceeds rapidly, usually at room temperature in manner of minutes to few hours for a complete conversion. In the last decade an increasing amount of useful reaction protocols have been developed, generally relying on very mild ambient reaction conditions.

In 2017, Schoenebeck and coworkers developed a bench-stable solid reagent $(Me_4N)SCF_3$ capable of converting aliphatic or (hetero)aromatic carboxylic acids (**156**) to corresponding acyl fluorides (**157**) with up to excellent yields and broad functional group tolerance like ethers, esters, amides, protected amines, nitro group, halides, olefins, and (hetero)aromatics. Substrate scope includes biologically active compounds like pharmaceuticals indomethacin (**157**) and ofloxacin (**157i**). Reaction proceeds cleanly at room temperature with DCM or MeCN as a solvent. Products can be easily isolated by low-polarity solvent addition and separation of insoluble byproducts with simple filtration. Mechanistic studies based on *in situ* FTIR and NMR spectroscopy showed, that deoxyfluorination likely proceeds through *in situ* generated carbonyl fluoride COF_2, which rapidly reacts with carboxylic acids (**156**) forming two distinct active intermediates (**160**) and (**161**), which are transformed to acyl fluoride (**157**) under release of gaseous carbonyl sulphide (COS). The authors additionally managed to prepare a vitamin B7 amide deriviative (**158-1**) by subsequent one-pot deoxyfluorination/amidation strategy utilizing acyl fluoride as a synthetic intermediate, furthermore showing usefulness of acyl fluorides. The most problematic challenge presents synthesis of $(Me_4N)SCF_3$ reagent and accordingly its high price (Scheme 23).[51] Additionally, in 2023 Maruoka and Nagano developed a protocol for efficient one-pot amide/peptide synthesis via acyl fluorides utilizing $AgSCF_3$/KI system working similarly to$(Me_4N)SCF_3$.[55]



Scheme 23 Deoxyfluorination of carboxylic acids with $(Me_4N)SCF_3$.

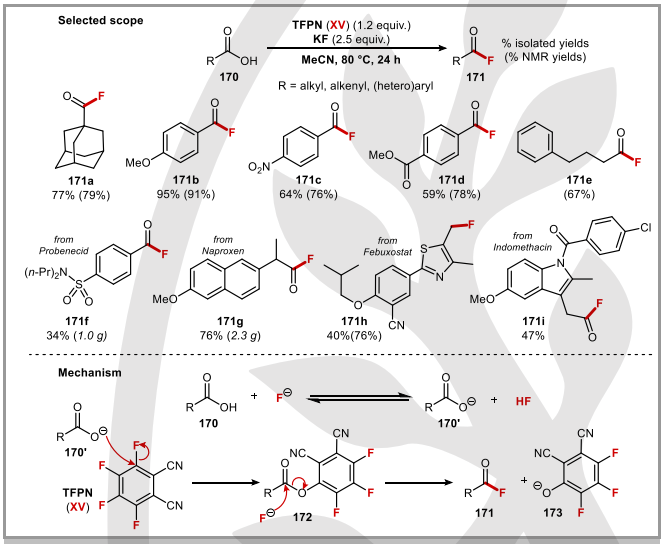
Prakash and colleagues developed in 2019 a convenient deoxyfluorination protocols using triphenylphosphine (PPh_3), NBS as an oxidant, and an acidic fluoride source such as triethylamine trifluoride ($Et_3N{\cdot}3HF$) or potassium bifluoride (KHF_2) with trifluoroacetic acid (TFA). Reaction proceeds at room temperature in DCM or MeCN as a solvent and requires premixing of PPh_3 and NBS with carboxylic acids (**162**) followed by fluoride addition. It demonstrates good functional group tolerance like esters, ethers, amides, sulphonamides, nitriles, halides, and even hydroxyl group with generally high reaction yields for both aliphatic and (hetero)aromatic carboxylic acids. Substrate scope includes several pharmaceutical compounds such as naproxen (**163g**), ibuprofen, indomethacin (**163f**), febuxostat (**163h**) and probenecid (**163i**). Notably, the reaction exhibits chemoselectivity towards carboxylic acid -OH group as shown by the example of 4-hydroxybenozic acid (**163d**) with 52% isolated yield. Furthermore, the authors managed to prepare three different amide derivatives of nicotinic acid (**164**) in a tandem deoxyfluorination/amidation reaction in good to high yields, furthermore demonstrating the utility of presented method. Mechanistic investigation by ^{31}P and ^{19}F NMR spectroscopy revealed reaction proceeds through bromophosphonium ion (**165**) reacting with carboxylic acid (**162**) and forming acyloxyphosphonium ion intermediate (**167**). Upon addition of fluoride, this intermediate quickly reacts forming acyl fluoride (**163**) under acidic conditions (HF) or Ph_3PF_2 (**168**) with basic fluoride anion (F^-) (Scheme 24).[56]



Scheme 24 Deoxyfluorination of carboxylic acids with PPh_3/NBS system.

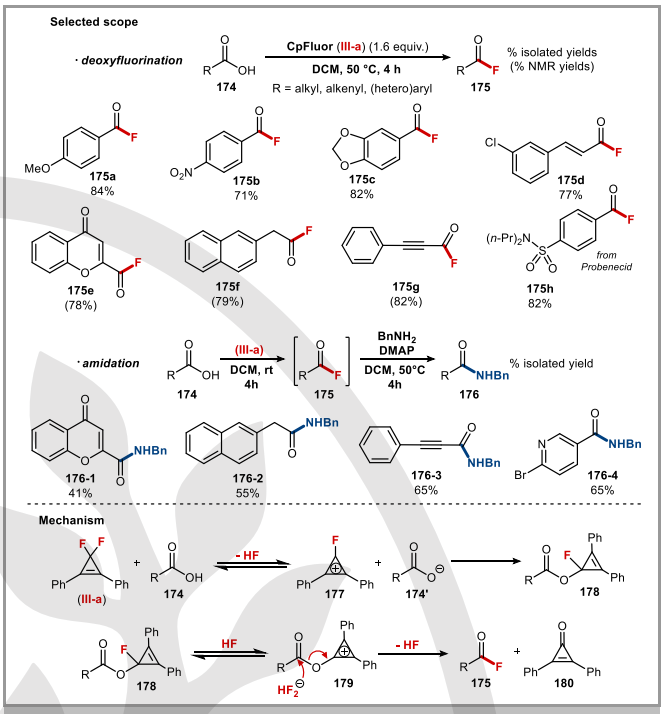
A year later Sun's group developed a deoxyfluorination protocol utilizing electron-deficient fluoroarenes, namely tetrafluorophtalonitrile (**TFPN**) and spray-dried potassium fluoride (KF) as an additional fluoride source. Reaction proceeds under heating to 80°C in anhydrous MeCN for both aliphatic and

aromatic carboxylic acids in moderate to excellent yields with good functional group tolerance including functionalities such as esters, ethers, nitro group, sulphonamides, and (hetero)aromatics. Substrate scope also includes several pharmaceutical compounds like probenecid (**171f**), naproxen (**171g**), febuxostat (**171h**), and indomethacin (**171i**) providing moderate to good isolated yields of corresponding acyl fluorides. NMR mechanistic and computational studies suggest formation of an ester intermediate (**172**) by nucleophilic substitution of carboxylate nucleophile (**170'**) onto TFPN. The strongly acidic phenol leaving group (**173**) is further easily displaced by fluoride nucleophile (Scheme 25).[57]



Scheme 25 Deoxyfluorination of carboxylic acids with TFPN/KF.

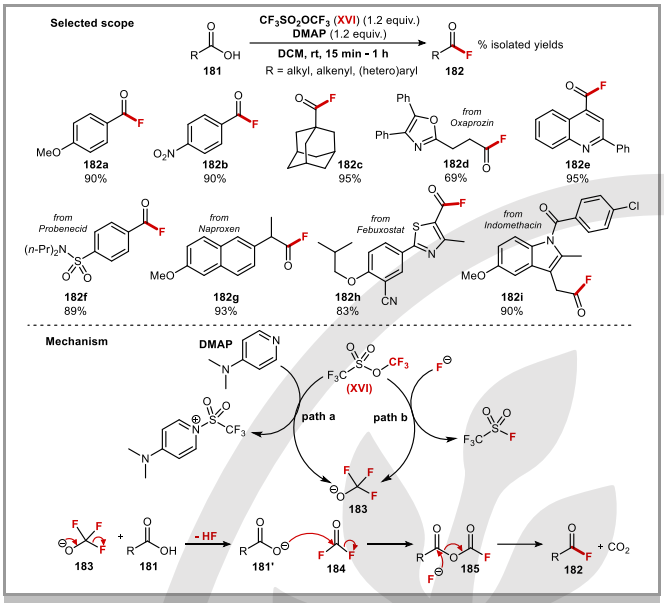
CpFluor can also be successfully employed for deoxyfluorination of aliphatic and (hetero)aromatic carboxylic acids as demonstrated by Hu's group in 2021. Reaction requires heating to 50°C for 4h in DCM as a solvent and slight excess of CpFluor (III-a) reagent (1.6 equiv.) affording moderate to excellent reaction yields of corresponding acyl fluorides. Deoxyfluorination displays good functional group tolerance on a broad substrate scope including natural compounds and pharmaceuticals like probenecid (**175h**). Additionally, a one-pot synthesis of amides (**176**) by deoxyfluorination/amidation strategy of several carboxylic acids with benzylamine was demonstrated in moderate to good yields. Reaction mechanistic studies showed formation of a carboxylate-cyclopropenium derived intermediate (**178**) and (**179**), which is susceptible to an acyl nucleophilic substitution reaction with fluoride nucleophile, providing acyl fluorides (**175**) and cyclopropenone (**180**) side product (Scheme 26). [58]



Scheme 26 Deoxyfluorination of carboxylic acids with CpFluor.

Deoxyfluorination of aliphatic and aromatic carboxylic acid with trifluoromethyl triflate ($CF_3SO_2OCF_3$) and DMAP as a tertiary amine base was achieved by Zhang and coworkers in 2020. Reaction proceeds at room temperature with slight excess of trifluoromethanesulfonate (1.2 equiv.) under inert atmosphere and is usually complete under an hour. For substrates barring electron-withdrawing substituents longer reaction times were required as this appears to slow down the transformation. This deoxyfluorination method affords high isolated yields and displays good functional group tolerance demonstrated on a broad substrate scope including pharmaceutical compounds such as oxaprozin (**182d**), probenecid (**182f**), naproxen (**182g**), febuxostat (**182h**), and indomethacin (**182i**). Reaction mechanism involves two possible distinct pathways of generating CF_3O^- anion (**183**), which rapidly decomposes under acidic environment to active carbonyl difluoride (**184**) capable of deoxyfluorination of carboxylic acids with release of CO_2 gas (Scheme 27).[59]

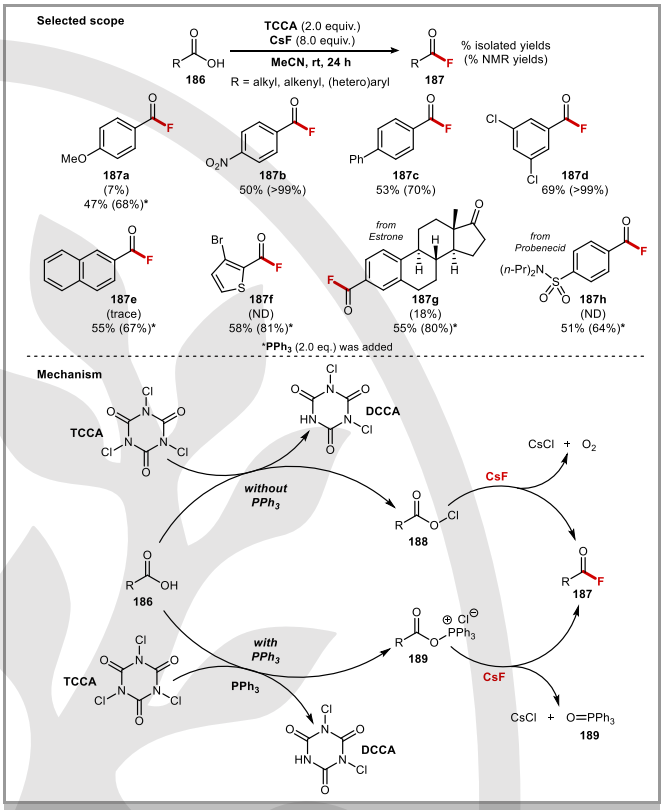
This year a comprehensive guide to synthesis of acyl fluoride by utilizing different CF_3-X^- anions has been reported by the Billard's group. They developed a novel reagent based on DMAP and $OCF3^-$ anion working similarly to Zhang's deoxyfluorination method. Additionally, they showed usefulness in synthesis of amides and esters via one-pot deoxyfluorination/amidation strategy with different amines or alcohols.[60]



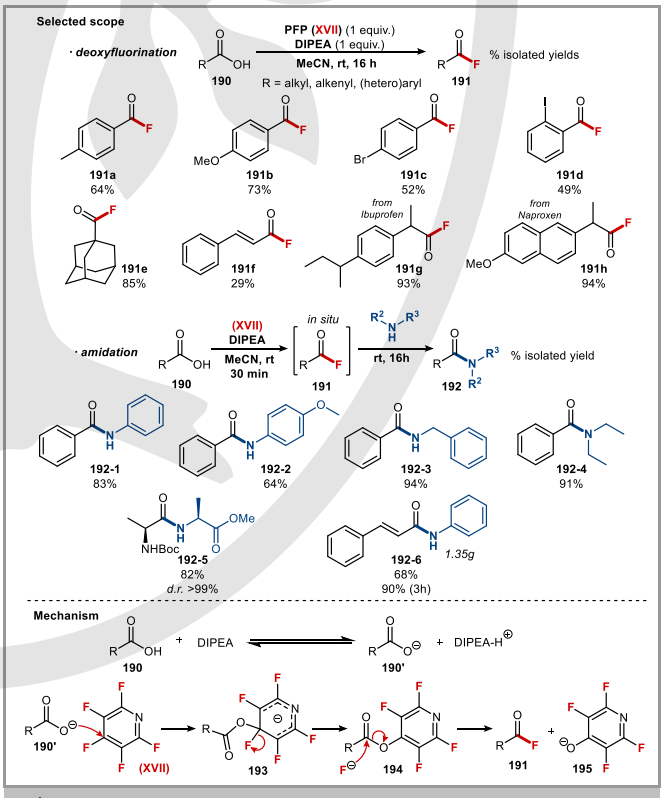
Scheme 27 Deoxyfluorination of carboxylic acids with trifluoromethyl triflate

In 2021, two additional deoxyfluorination strategies were developed. Shibata's group reported deoxyfluorination of aromatic and aliphatic carboxylic acids under oxidative fluorination conditions using TCCA as an oxidation/chlorination agent and CsF as a fluoride source. This method closely resembles Prakash's PPh_3/NBS/ $Et_3N{\cdot}3HF$ method. Reaction relies on oxidative activation of carboxylic acids (**186**) by chlorination with TCCA to generate reactive hypochlorous anhydrides (**188**). The formed hypochlorous anhydrides (**188**) react with CsF to afford acyl fluoride (**187**) and molecular oxygen. Evolution of gaseous oxygen was confirmed experimentally using $Fe(OH)_2$ test. This deoxyfluorination reaction proceeds at room temperature overnight with moderate yields and tolerates many useful functional groups. Substrate scope includes bioactive compounds like estrone derivative (**187g**) and pharmaceuticals like probenecid (**187h**). In some cases, evidently for substrates with electron-donating groups, reaction provides very poor conversions or no product at all (**187a, 187e, 187f, 187g, 187g**). Addition of PPh_3 (2.0 equiv.) was found to be very effective at improving reaction yields by changing reaction mechanism analogously to previous NBS method – with formation of acyloxyphosphonium ion intermediate (**189**) (Scheme 28).[61]

Cobb and colleagues managed to develop a method using cheap, commercially available and bench-stable pentafluoropyridine (PFP) as an active deoxyfluorination reagent together with DIPEA as a base. This deoxyfluorination reaction proceeds at room temperature in MeCN as a solvent of choice for both aliphatic and aromatic carboxylic acids providing acyl fluorides with moderate to excellent yields on a broad substrate scope and functional group tolerance. Additionally, a one-pot amide synthesis using deoxyfluorination/amidation protocol was developed by authors on a wide range of carboxylic acids and amines with generally high isolated yields. They concluded that a preactivation period of at least 30 min is required, for the *in situ* formation of acyl fluorides, before the addition of amines in order to achieve higher reaction yields. Mechanistic studies with LC-MS and NMR spectroscopy suggest, that reaction proceeds through nucleophilic attack of carboxylate (**190'**) on a electron-poor pyridine ring of PFP forming an acyloxypyridine intermediate (**194**). This intermediate rapidly reacts with fluoride anion in an aromatic nucleophillic substitution reaction displacing pyridone leaving group(**195**)and affording acyl fluorides (Scheme 29). [62]

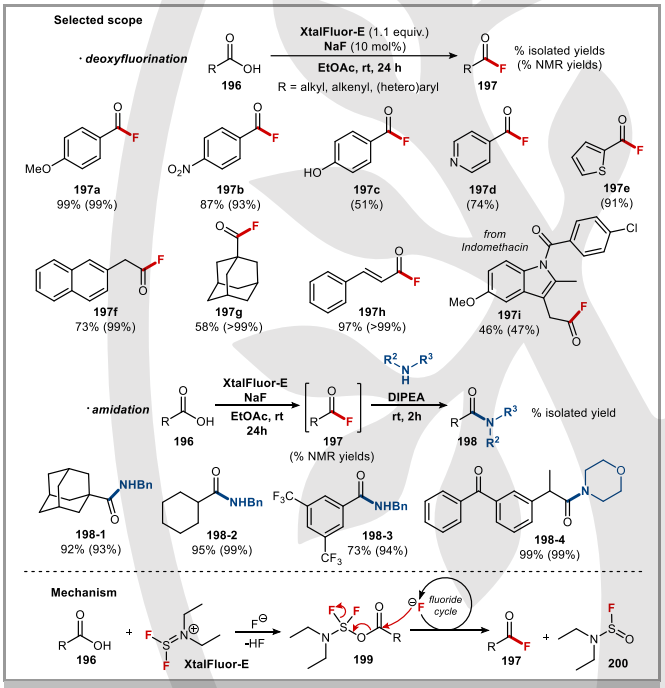


Scheme 28 Deoxyfluorination of carboxylic acids with TCCA/CsF system.



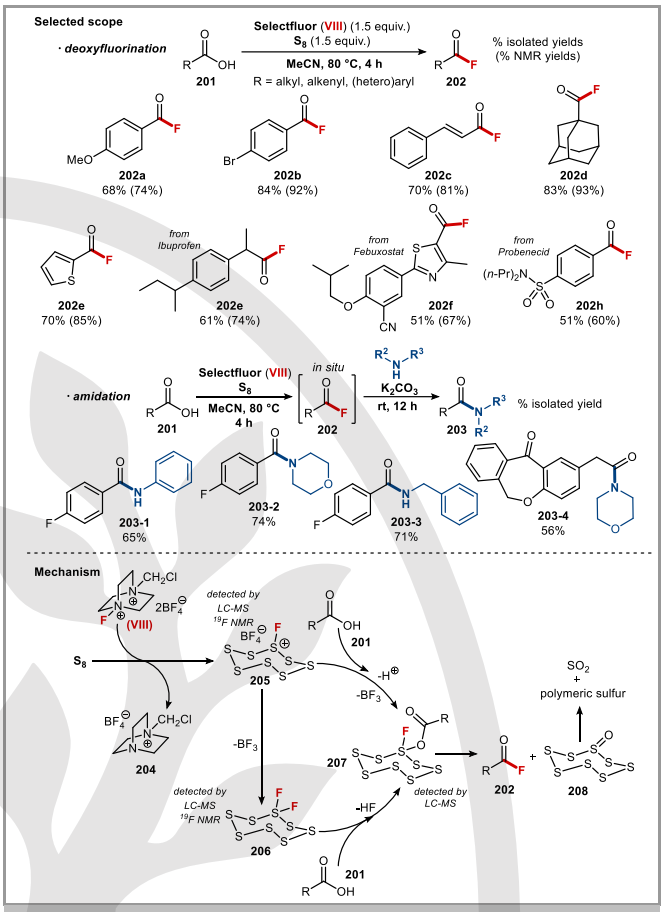
Scheme 29 Deoxyfluorination of carboxylic acids with pentafluoropyridine.

Paquin and coworkers developed in 2019 a deoxyfluorination protocol of carboxylic acids by utilizing a sulphur-based reagent XtalFluor-E with catalytic amount of added external fluoride. Reaction proceeds at room temperature in EtOAc as a solvent on a wide range of aliphatic or (hetero)aromatic carboxylic to afford corresponding acyl fluorides in moderate to excellent yields. Reaction tolerates many useful functionalities such as carbonyls, amides, ethers, halides, olefins, and even phenolic hydroxyl group. Substrate scope also includes a pharmaceutical compound indomethacin (**197i**). Reaction mechanism likely involves formation of an activated carboxylic acid intermediate (**199**) followed by fluoride acyl nucleophilic substitution reaction resulting in acyl fluoride (**197**) along with a fluoride ion, which re-enters the acyl nucleophilic substitution reaction forming a catalytic cycle. They additionally showed a one-pot sequential deoxyfluorination/amidation reaction protocol for amide (**198**) synthesis by addition of amine and DIPEA as a base providing amides (**198**) in good to excellent isolated yields (Scheme 30).[63]



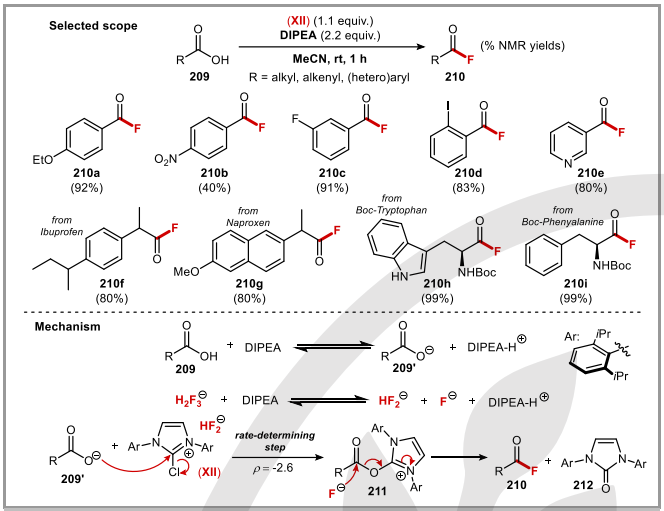
Scheme 30 Deoxyfluorinaation of carboxylic acids with XtalFluor-E.

Recently, in 2023, a new sulphur-based deoxyfluorination method to acyl fluorides via electrophilic fluorine source has been reported. Direct transformation of aliphatic and aromatic carboxylic acids is mediated with slight excess of Selectfluor (1.5 equiv.) and elemental sulphur (S_8). Reaction conditions involve heating to 80 °C for 4 h in MeCN as a solvent and tolerates a handful of functional groups shown on broad range of substrates including pharmaceuticals such as ibuprofen (**202e**), probenecid (**202h**) and febuxostat (**202f**) with moderate to excellent yields. Reaction mechanism involves *in-situ* generation of two types of sulphur-fluorine fluorination agents by action of Selectfluor; a S_8-fluoro-sulfonium species (**205**) and S_8-difluoride (**206**), where both facilitate direct formation of acyl fluoride products (**202**), SO_2 gas and polymeric sulphur (Scheme 31). [64]



Scheme 31 Deoxyfluorination of carboxylic acids with S_8/Selectfluor system.

Tavčar's and Iskra's group demonstrated that 2-chloro-1,3-bis(2,6-diisopropylphenyl)imidazolium dihydrogen trifluoride reagent is applicable not just for deoxyfluorination of electron-deficient phenols and benzylic alcohols, but also for deoxyfluorination of aliphatic and (hetero)aromatic carboxylic acids to corresponding acyl fluorides. Reaction proceeds under mild conditions (room temperature, 1 h) in MeCN as a solvent with good to excellent yields tolerating a wide variety of functional groups, similarly to previous findings.[43] Substrate scope includes several bioactive compounds such as amino acid derivatives (**210h** and **210i**), naproxen (**210g**), aspirin, ibuprofen (**210f**) and nicotinic acid. Mechanistic studies based on Hammett correlation (ρ =-2.6) revealed electron-donating groups present on carboxylic acid accelerate reaction rate, indicating a carboxylate (**209'**) attack on 2-chloroimadzolium ion of reagent as a rate-determining step. The resulting 2-acyloxyimidazolium intermediate (**211**) then undergoes a rapid fluoride nucleophilic acyl substitution reaction converting to corresponding acyl fluorides (**210**) and 2-imidazolone (**212**) side product. [28]



Scheme 32 Deoxyfluorination of carboxylic acids with 2-chloro-1,3-bis(aryl)imidazolium dihydrogen trifluoride reagent.

4 Conclusions

This review summarizes and emphasizes recent developments of deoxyfluorination methods in the previous decade. We delve deep into the topics of both C(sp^3)-O and C(sp^2)-O bond deoxyfluorination reactions categorized by different type of substrates. Review includes several different strategies for synthesis of aryl fluorides, alkyl fluorides, gem-difluorides, and acyl fluorides obtained from corresponding phenols, alcohols, ketones and carboxylic acids. Many discussed deoxyfluorination reactions lead to the formation of useful organofluorine compounds, which contribute to promising pharmaceutical applications. The described protocols are highly versatile and tolerate wide range of functional groups to afford diversely substituted fluorine products in up to excellent yields.

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Acknowledgment

Conflict of Interest

The authors declare no conflict of interest.

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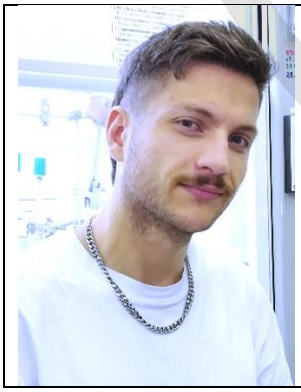
Biosketches

Gašper Tavčar studied chemistry at the University of Ljubljana, earning a B.Sc. in 2000. He then studied Inorganic chemistry with Professor Boris Žemva at the Jožef Stefan Institute in Ljubljana, graduating in 2005. He than did postdoctoral research with Professor Herbert Roesky at Georg August University in Goettingen, Germany and in 2010 returned to Slovenia to begin his independent career at Jožef Stefan Institute. In 2011 he was appointed head of the Department of Inorganic Chemistry and Technology. He habilitated at the Jožef Stefan International Postgraduate School and was appointed an associate professor in 2023.

His research interests include synthesis, fluorine chemistry, coordination chemistry and crystallography.



Jan Jelen was born in Ljubljana, Slovenia. He studied chemistry at the University of Ljubljana obtaining his master's degree (M.Sc.) in 2022 under the supervision of Gašper Tavčar working as a project student at Department of Inorganic Chemistry and Technology, Jožef Stefan Institute. He continued his postgraduate studies at Jožef Stefan International Postgraduate School working in the same department.

His research interests include organic chemistry, fluorine chemistry, synthetic strategies, catalysis and photocatalysis.