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Carbon–Fluorine Bond Formation

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Abstract

We present a selection of carbon–fluorine bond formations that have been developed in the recent past. An overview of the most common fluorination reagents is followed by fluorination reactions organized by reactivity. We have distinguished between nucleophilic and electrophilic fluorinations as well as aliphatic and aromatic fluorinations. Each section is divided into more specific reaction classes and examples for syntheses of pharmaceuticals, ^{18}F-radiolabeling, and mechanistic investigations are provided.

Keywords

Fluorination; carbon–fluorine bond formation; nucleophilic fluorination; electrophilic fluorination; fluorinating reagents, enantioselective fluorination

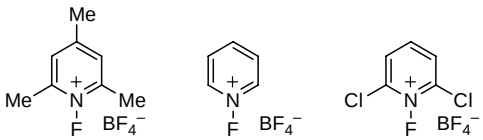
Abbreviations

Ac acetyl, **Boc** *tert*-butoxycarbonyl, ***n*-Bu** normal butyl, ***t*-Bu** *tert*-butyl, **Bn** benzyl, **Bz** benzoyl, **18-crown-6** 1,4,7,10,13,16-hexaoxacyclooctadecane, **Cy** cyclohexyl, **DAST** (diethylamino)sulfur trifluoride, **Deoxofluor** bis(2-methoxyethyl)aminosulfur trifluoride, **DMF** dimethylformamide, **DMSO** dimethylsulfoxide, **Et** ethyl, **Me** methyl, **MOST** 4-morpholinosulfur trifluoride, **Ms** methanesulfonyl, **NFSI** *N*-fluorobenzenesulfonimide, ***p*-Ns** 4-nitrobenzenesulfonyl, ***o*-Ns** 2-nitrobenzenesulfonyl, **Nu** nucleophile, **PET** positron-emission tomography, **Ph** phenyl, ***i*-Pr** isopropyl, **Py** pyridyl, **Selectfluor = F-TEDA-BF$_4$** 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), **TADDOL** $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol **TBAF** tetrabutylammonium fluoride, **TBAT** tetrabutylammonium (triphenylsilyl)difluorosilicate, **Tf** trifluoromethanesulfonyl, **TFA** trifluoroacetic acid, **THF** tetrahydrofurane, **TMAF** tetramethylammonium fluoride, **TMS** trimethylsilyl, ***o*-Tol** 2-tolyl, **Ts** 4-toluenesulfonyl, **Tr** trityl

Introduction

Fluorinated molecules have become increasingly important as pharmaceuticals [1–3], agrochemicals [4], tracers for positron-emission tomography (PET) [5,6], and new materials [7,8]. The introduction of fluorine into organic molecules can affect the basicity of nearby nitrogen atoms, the dipole moment, and hydrogen bonding [9]. In pharmaceuticals, fluorine is often introduced to increase lipophilicity, bioavailability and metabolic stability [5,10–16]. The fluorine substituent is often considered an isostere of hydrogen, but its size is similar to a hydroxyl group (van der Waals radii: F: 1.47 Å; OH 1.40 Å; compared to H: 1.20 Å). The radioisotope ^{18}F has a half-life of 109 minutes and is used in positron-emission tomography (PET) for the synthesis of ^{18}F-based PET tracers. Despite the utility of fluorine substituents, relatively few methods are available for general, selective carbon–fluorine bond formation [17], when compared to methods for other carbon–halogen bond formations. Interestingly, only 30 natural organofluorides have been identified to date [18], which may indicate the unavailability of suitable fluorination methods in nature. In this short review we provide a selection of reports from the last few years for carbon–fluorine bond formations, without giving a comprehensive collection of all new fluorination reactions [19–22].

1. Fluorinating reagents

Nucleophilic fluorinating agents (F^-)	Electrophilic fluorinating agents (F^+)
Alkali metal fluorides NaF KF CsF	*N*-Fluoropyridinium salts 

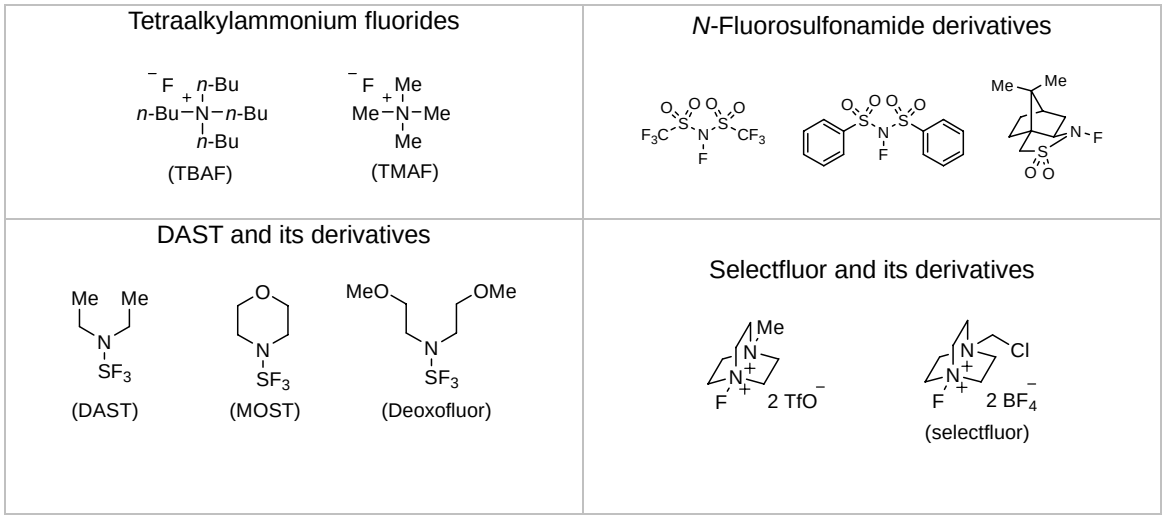


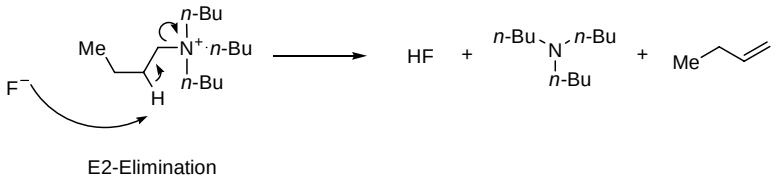
Chart 1. Overview of some of the most common fluorinating reagents.

1.1 Nucleophilic fluorinating reagents

Fluoride is the smallest of all anions. The high charge density renders unsolvated fluoride strongly basic. Fluoride can form strong hydrogen bonds [23] and its solvation can dramatically decrease the nucleophilicity by the formation of stable solvation shells. Common alkali fluorides such as LiF [24], NaF [25], KF [26, 27], and CsF [28] can be used as fluorination reagents [12,29–31]. Increasing ionic strength decreases the nucleophilicity and solubility of fluoride in organic solvents, which renders LiF the least reactive fluorination reagent among the alkali metal fluorides. Crown ethers in combination with alkali metal fluorides such as KF-18-crown-6 can be used to increase solubility and hence reactivity [32]. Nevertheless, the combination of high basicity and strong hydrogen bonding makes fluoride a challenging nucleophile for nucleophilic displacements.

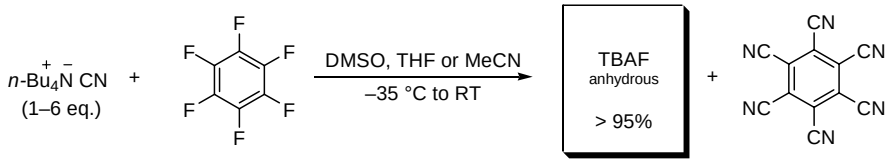
The use of tetraalkylammonium ions as counterions for fluoride reduces the ionic bond strength and increases the solubility in organic solvents [33]. Tetrabutylammonium fluoride (TBAF) is a common fluorinating agent that is available as a trihydrate. The presence of water reduces the nucleophilicity of fluoride by hydrogen bonding and is responsible for side reactions such as alcohol formation by serving as hydroxide source. Drying of most quaternary ammonium fluorides is difficult due to competing Hofmann elimination with fluoride serving as a strong base under anhydrous conditions

(Equation 1) [34].



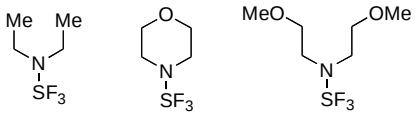
(1)

Hofmann elimination can be circumvented when using tetramethylammmonium fluoride (TMAF [35]), which lacks β-hydrogen atoms for elimination and can be obtained as an anhydrous salt. In 2005, the synthesis of anhydrous TBAF via nucleophilic aromatic substitution of hexafluorobenzene with cyanide was reported by DiMagno (Equation 2) [36]. TBAF produced by this procedure is highly nucleophilic due to the absence of water [37•].



(2)

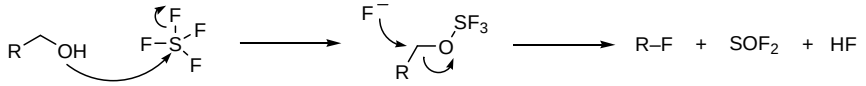
Sulfur fluorides can serve as nucleophilic fluorination sources. One of the most versatile fluorinating agents of this class is (diethylamino)sulfur trifluoride (DAST, **1**), a less toxic and less volatile analog of sulfur tetrafluoride SF_4 [38]. DAST can explode when shock-heated; thus, thermally more stable and, hence, safer derivatives with similar reactivity such as 4-morpholinosulfur trifluoride (MOST, **2**) and bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor, **3**) have been developed (Figure 1) [39].



1 **2** **3**

Figure 1. (Diethylamino)sulfurtrifluoride (DAST, 1) and its analogs 4-morpholinosulfur trifluoride (MOST, 2) and bis(2-methoxyethyl)aminosulfur trifluoride (Deoxofluor, 3).

SF_4, DAST, and their derivatives are useful for converting hydroxyl groups into fluorides. Upon nucleophilic attack of the alcohol onto sulfur, fluoride is released that, in turn, functions as a nucleophile to displace the activated hydroxyl group (Equation 3).



(3)

1.2 Electrophilic fluorinating reagents

N-Fluoropyridinium salts were first developed in the 1980s and have become an important source of electrophilic fluorine for fluorination [22]. *N*-fluoropyridinium salts allow the fluorination of a wide range of nucleophilic substrates and their reactivity can be adjusted by substitution of the pyridine heterocycle (Figure 2). One potential mechanism for fluorination using *N*-fluoropyridinium salts involves a single electron transfer process as shown in Scheme 1. Equations 4 [40] and 5 [41] provide examples for the fluorination reaction of silyl-enol ethers and enolates with *N*-fluoropyridinium triflate.

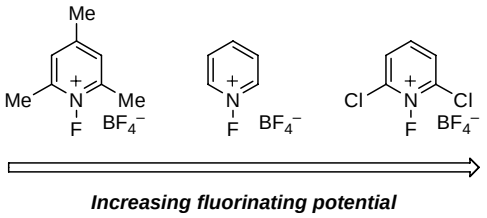
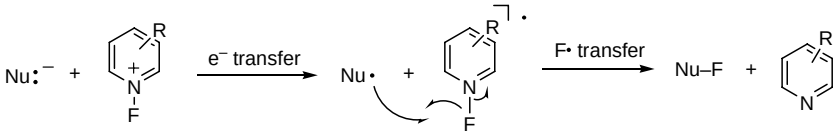
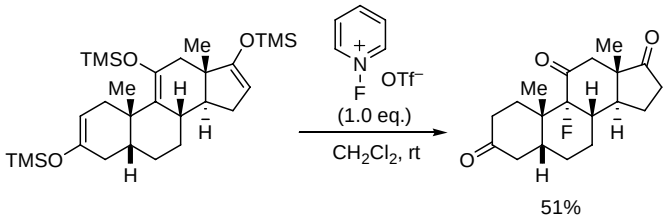


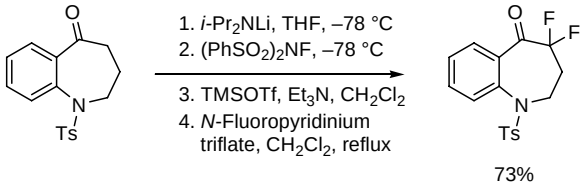
Figure 2. Effect of substituents on the oxidation potential of *N*-fluoropyridinium salts.



Scheme 1. Single electron transfer mechanism for the fluorination with *N*-fluoropyridinium salts.

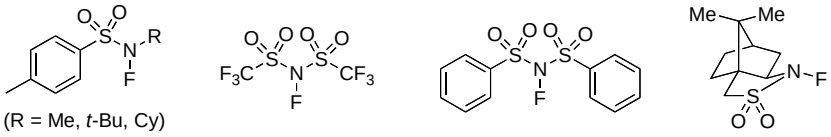


(4)



(5)

In 1984, Barnette reported the use of *N*-fluorosulfonamides **4** (Figure 3) as a new class of broadly applicable fluorinating reagents that were easily prepared by treatment of *N*-alkylsulfonamides with dilute elemental fluorine [42]. Subsequently, several research groups reported the syntheses and use of additional fluorinating reagents of this type such as *N*-fluorobis[(trifluoromethyl)sulfonyl]imide (**5**) [43] or *N*-fluorobenzenesulfonimide (NFSI, **6**) [44]. An enantioselective fluorination reaction has been achieved by Differding and Lang using chiral *N*-fluorosultam (**7**) [45].



4 **5** **6** **7**

Figure 3. Common sulfonamide- or sulfonimide-based fluorinating agents.

The development of the reagent Selectfluor (**8**) and its derivatives presented a major advance for electrophilic fluorination. F-TEDA-BF_4 or Selectfluor was developed by Banks and is a commercially available, stable, and effective source of electrophilic fluorine [46]. The oxidation potential of the F-TEDA-X reagents can be increased by nitrogen substitution with electron-withdrawing substituents (Figure 4) [47].

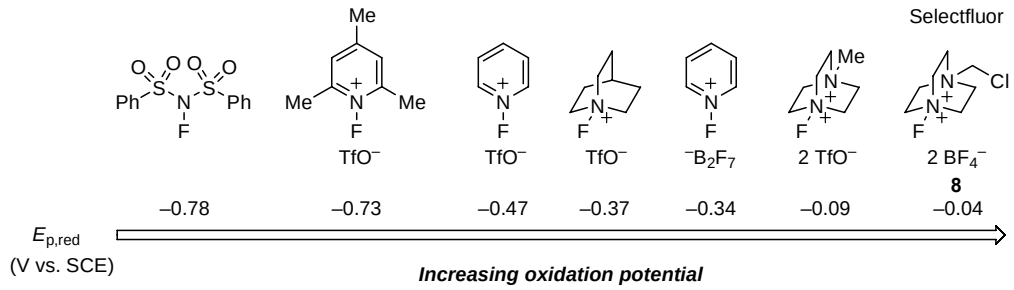
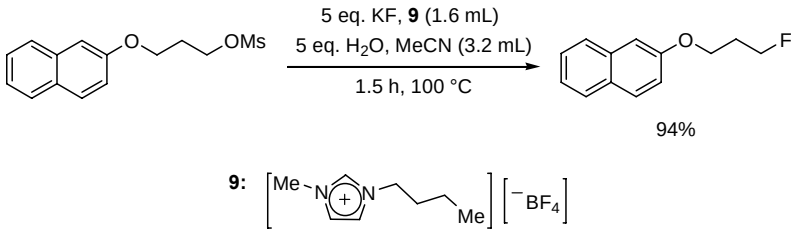


Figure 4. Reduction peak potentials of different electrophilic fluorination reagents: $E_{p,red}$ in V relative to the standard calomel electrode; 1–5 mM in MeCN/0.1 M Bu_4N^+ BF_4^- or $CF_3SO_3^-$ [47].

2. Fluorination Reactions

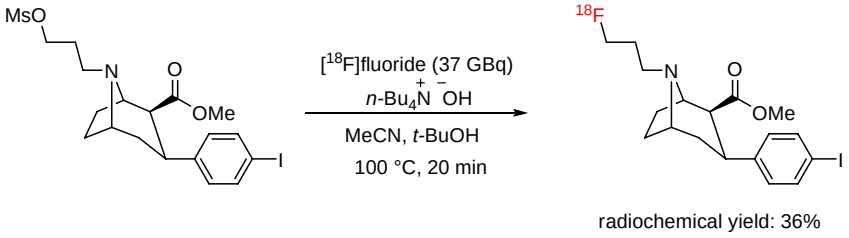
2.1 Nucleophilic Aliphatic Fluorinations

The choice of solvent is important for successful S_N2 fluorinations. Nucleophilic displacement of leaving groups by fluoride at sp^3 hybridized carbon atoms can be impaired by undesired side reactions such as β-elimination or hydroxylation when fluoride is too basic in uncoordinating solvents. In protic solvents, on the other hand, strong hydrogen bonds decrease the nucleophilicity of the fluoride anion and also render the solvent nucleophilic. In dipolar aprotic solvents such as dimethyl sulfoxide (DMSO) and *N,N*-dimethylformamide (DMF) hydrogen-bonding is minimized and the nucleophilicity of the fluoride is retained [48]. In 2002, Chi reported the use of ionic liquids such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmin][BF_4], **9**) as suitable solvents for fluorination [49]. Chi also demonstrated that the addition of small amounts of water to the ionic liquid reduced the formation of undesired by-products such as alkenes or alcohols (Equation 6).

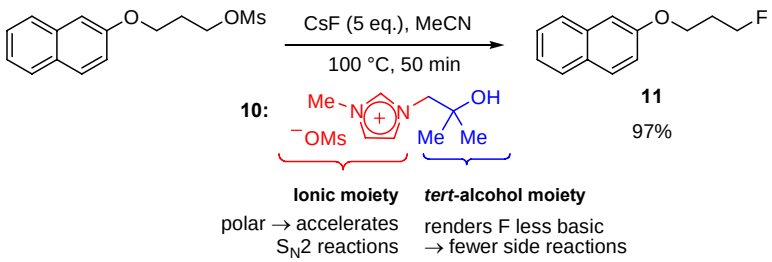


(6)

Fluoride is solvated less efficiently by tertiary alcohols than by primary alcohols and water [50]. Fluoride is hence more nucleophilic in tertiary alcohols as solvent and its basicity is sufficiently attenuated to avoid side reactions. Therefore, *tert*-butanol can increase the reaction rate of S_N2 fluorinations and can afford alkyl fluorides in high yield [51,52•]. Chi used *tert*-butanol as solvent for the synthesis of the ^{18}F-PET radiopharmaceutical [51] *N*-[^{18}F]fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane ([^{18}F]FP-CIT) (Equation 7) for PET imaging of dopamine transporters. While previous methods only afforded 1% of the desired product [53], *tert*-butanol increased the yield to 35.8 ± 5.2%. The combination of ionic liquid and a tertiary alcohol in a single molecule can function as bifunctional solvent for S_N2 displacements for fluorination. In 2008, Chi reported that the imidazolium ionic liquid **10** as solvent can afford the fluorination product **11** in 97% yield (Equation 7, Scheme 2) [54].

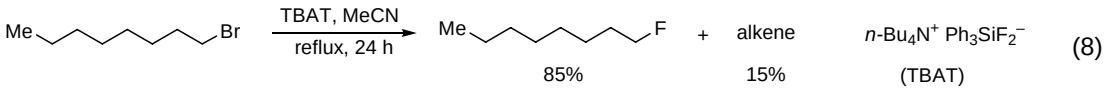


(7)



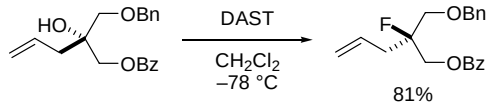
Scheme 2. Combined effect of ionic liquid and *tert*-alcohol on nucleophilic fluorination.

The nucleophilic fluorination source tetrabutylammonium (triphenylsilyl)difluorosilicate (TBAT) was introduced by DeShong [55]. The fluorine atoms of TBAT are coordinated to the complex silicate anion. While nucleophilicity is reduced compared to "naked" fluoride, TBAT is obtained as an anhydrous solid, less basic than other fluoride sources such as TBAF, and can displace halides in S_N2 reactions. Fluorination of octylbromide with TBAT afforded 15% elimination by-product together with 85% fluorination, while TBAF produced 48% fluorination and 40% octanol (Equation 8) [55].

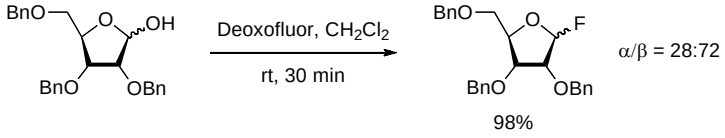


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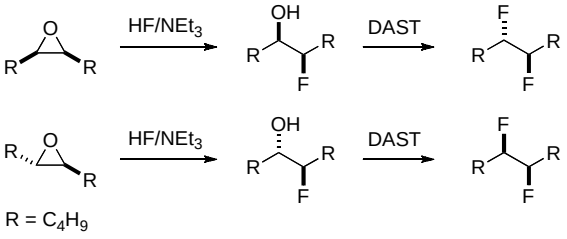
Aliphatic alcohols can be converted into the corresponding fluorides with the nucleophilic fluorination reagent DAST. Typically, fluorinations with DAST proceed with inversion. Two examples for such transformations are given in Equation 9 and 10 [38,39]. Schlosser developed a method to access vicinal difluoroalkanes stereoselectively by epoxide ring-opening with hydrogen fluoride and subsequent treatment with DAST (Scheme 3) [56]. A similar strategy has been applied by Hunter for a stereoselective synthesis of an all-*syn* four vicinal fluorine motif [57]. Key steps in their synthetic route (Scheme 4) included epoxide ring-opening by treatment with HF-triethylamine, ring opening of the cyclic sulfate with TBAF and introduction of the fourth fluorine atom by treatment with Deoxofluor.



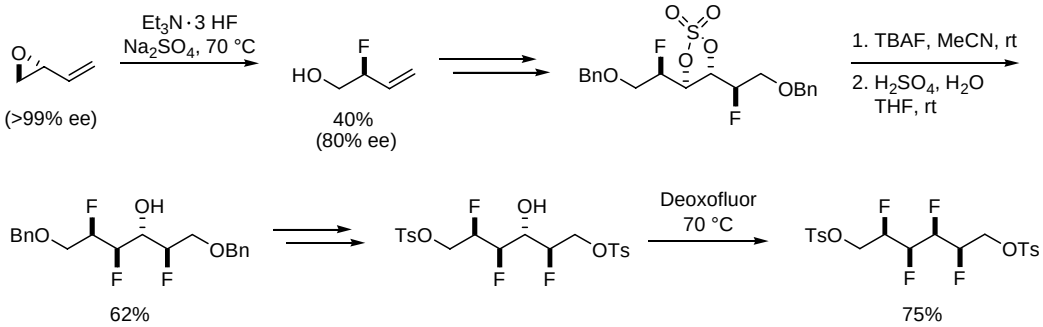
(9)



(10)



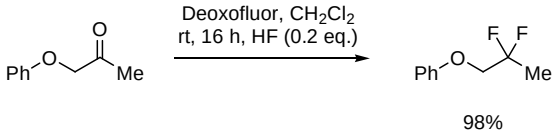
Scheme 3. Stereoselective synthesis of vicinal difluoroalkanes via epoxide opening with hydrogen fluoride and deoxyfluorination with DAST.



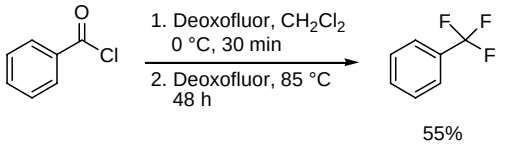
Scheme 4. Asymmetric synthesis of an all-*syn* four vicinal fluoride motif.

DAST and its derivatives are also suitable for the conversion of carbonyl groups into *gem*-difluoromethylene groups [58]. Examples include the conversions of ketones to difluoromethylene derivatives (Equation 11) and of carboxylic acid derivatives to the trifluoromethyl groups (Equation 12)

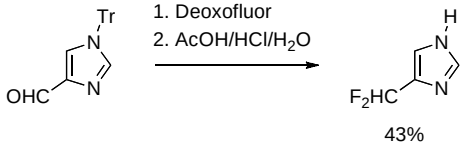
[59]. Aldehydes can be converted into the corresponding difluoromethyl groups as shown in Equation 13 [60].



(11)



(12)



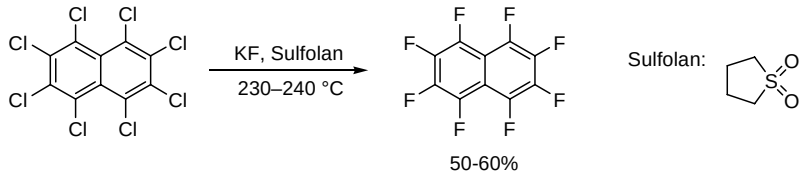
(13)

Enzymatic carbon–fluorine bond formation by *Streptomyces cattleya* is responsible for the synthesis of a variety of fluorometabolites [61–64]. Overexpression of the fluorinase enzyme that catalyzes the reaction of fluoride and (*S*)-adenosyl-L-methionine presumably by S_N2 displacement has made milligram quantities of this enzyme available. O'Hagan has employed the enzymatic reaction for the introduction of ^{18}F for PET [65].

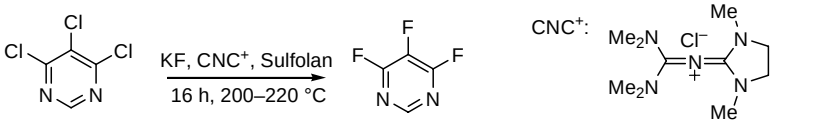
2.2 Nucleophilic Aromatic Fluorinations

Nucleophilic aromatic substitutions can be employed to introduce fluorine atoms into electron-deficient arenes. Elimination typically does not occur for arenes as it does for aliphatic compounds and strongly basic, nucleophilic fluoride can be used [27,66–72]. A common method for the synthesis of fluorinated aromatics in industry is the Halex (halogen exchange) process [27], in which halogens, typically chloride, serve as leaving groups and inexpensive, inorganic fluoride sources such as spray-dried KF are used as nucleophiles. High-boiling solvents and phase transfer catalysts to solubilize the

fluoride source can increase the efficiency of the Halex process (Equations 14 and 15). A useful alternative to the Halex process is fluorodenitration, a process in which the nitro-group functions as the leaving group (Equation 16) [66,73].

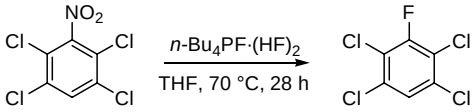


50-60% (14)



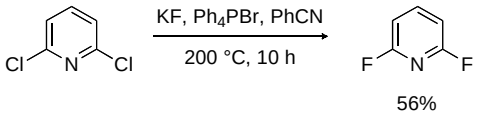
66-80%

(*N*,*N*-dimethylimidazolidino)-tetramethylguanidinium chloride (15)

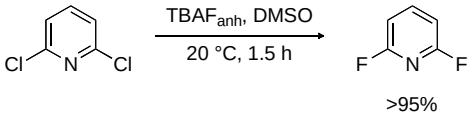


80% (16)

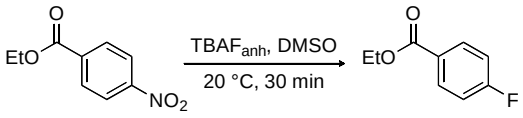
In 2005, DiMagno reported the preparation and use of anhydrous tetrabutylammonium fluoride ($TBAF_{anh}$) [36,37•]. When $TBAF_{anh}$ was used in halogen exchange and fluorodenitration reactions, these reactions could be run under mild conditions. For example, a typical Halex fluorination of 2,6-dichloropyridine requires heating at 200 °C for ten hours (Equation 17) [74]. In comparison, the same substrate is fluorinated within 90 minutes upon exposure to $TBAF_{anh}$ at room temperature (Equation 18). Aromatic fluorodenitration using $TBAF_{anh}$ occurs within minutes with electron-poor, weakly activated arenes (Equation 19).



56% (17)

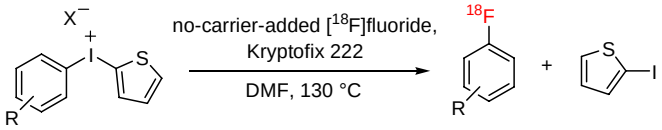


>95% (18)



>95% (19)

The hypervalency of iodine in diaryliodonium salts renders aryl iodide an excellent leaving group [75]. Beringer used diaryliodonium salts for the nucleophilic fluorination of arenes [76,77]. In 2007, Ross used aryl(2-thienyl)iodonium salts for nucleophilic no-carrier-added ^{18}F-labeling of arenes [78] to control the regioselectivity of fluoride attack (Equation 20).



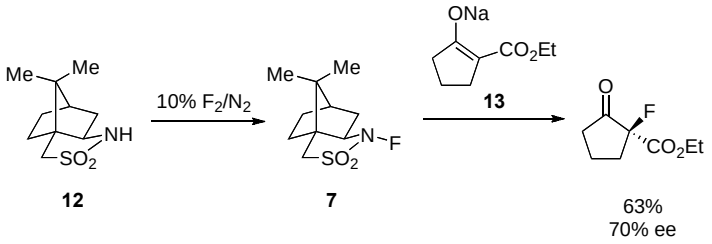
X = Br, I, OTs, OTf

R = 2-OMe, 3-OMe, 4-OMe, 4-Me, 4-OBn, 4-I, 4-Br, 4-Cl (20)

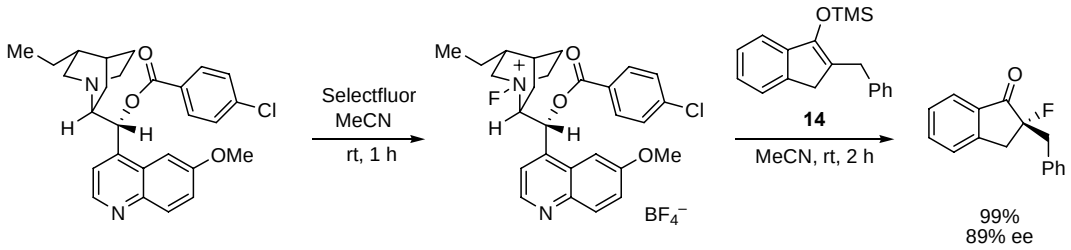
2.3 Electrophilic Aliphatic Fluorination

Reagents for electrophilic aliphatic fluorination can react with carbon nucleophiles such as enolates or allylsilanes [79]. Recent research has focused on asymmetric fluorination of carbon nucleophiles [22]. Differding has developed a chiral fluorinating agent for the enantioselective fluorination of enolates [45]. Davis prepared *N*-fluorosultam (**7**) by treatment of camphorsultam **12** with diluted fluorine for

fluorination of β-ketoester **13** in 70% ee. (Scheme 5) [80]. Fluorinated quinuclidine alkaloids such as *N*-fluoroquinine can also function as electrophilic fluorination sources. Fluorination of the alkaloid with Selectfluor generates the chiral *N*-fluoro reagent that can transfer its fluorine atom via fluorination to the silyl enol ether **14** in 99% yield and 89% ee (Scheme 6) [81]. A catalytic version of this reaction was reported by the same authors in 2008 [82•].

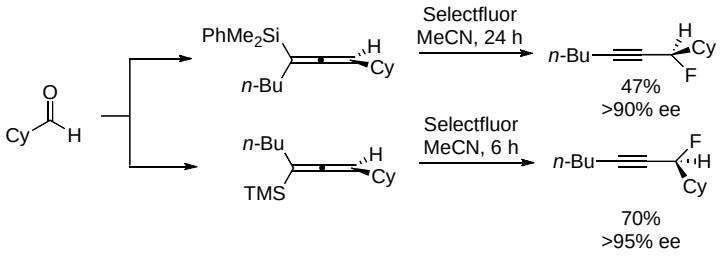


Scheme 5. Asymmetric fluorination of cyclic enolate 13 with (+)-*N*-fluoro-2,10-camphorsultam (7).



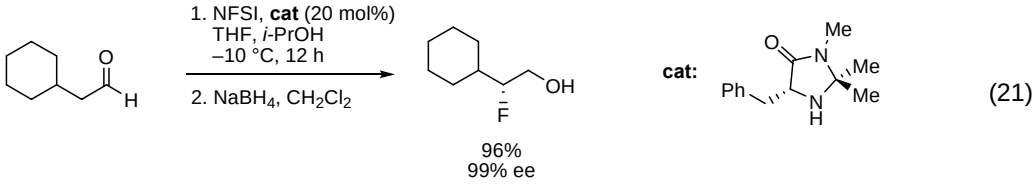
Scheme 6. Asymmetric electrophilic fluorination of a silyl enol ether with *N*-fluorodihydroquinine 4-chlorobenzoate [81].

An elegant fluorodesilylation protocol was reported by Gouverneur in 2008 (Scheme 7) [83]. Enantioenriched propargylic fluorides are generated in high ee upon treatment of chiral allenylsilanes with Selectfluor. The process complements the nucleophilic fluorination of propargylic alcohols by DAST developed in 2007 by Grée [84]. The enantioenriched propargylic alcohols can be obtained by Carreira alkynylation in both cases [85,86]. Gouverneur also pioneered the use of electrophilic [^{18}F]-radiolabeled *N*-fluorobenzenesulfonamide fluorinating agents for use in PET [87].

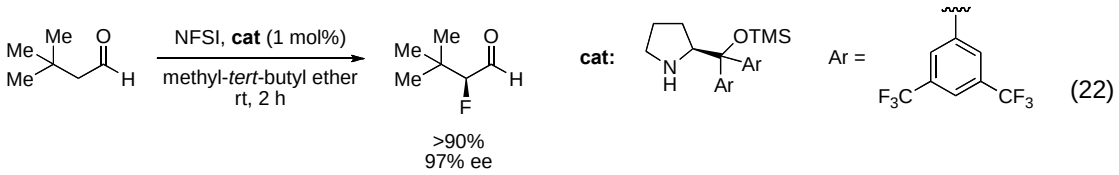


Scheme 7. Synthesis of enantioriched propargylic fluorides.

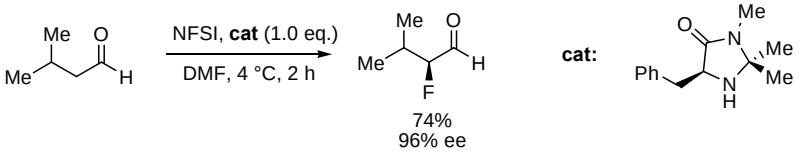
Chiral α-fluorination of aldehydes was reported by MacMillan (Equation 21) [88•], Jørgensen (Equation 22) [89•], and Barbas (Equation 23) [90•] in 2005. Chiral enamine catalysis provided enantioselectively enriched α-fluoroaldehydes in up to 99% ee. Isolation of the chiral fluoroalcohols after reduction can prevent the erosion of the stereocenter after fluorination. Enders reported the α-fluorination of ketones also in the year 2005 (Equation 24) [91].



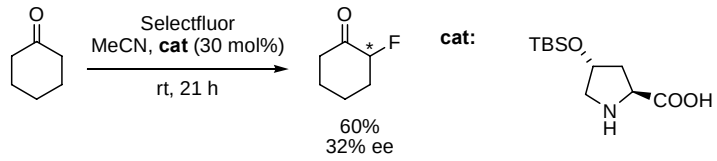
(21)



(22)



(23)



(24)

The successful use of metal-catalysts for enantioselective fluorination was first reported by Togni [92•,93]. They used a titanium TADDOL complex (TADDOL = α,α,α',α'-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) to catalyze the enantioselective fluorination of branched β-ketoesters. According to the authors, the steric bulk of the chiral titanium complex is responsible for the *si* facial attack of the F^+ source on the complexed β-ketoester (Figure 5, Scheme 8). Sodeoka used chiral phosphine palladium complexes to achieve enantioselective fluorination of various β-ketoesters. *N*-fluorobenzenesulfonimide was the most effective fluorinating source and afforded enantioselectivities of 92% (Equation 25) [94]. Following the pioneering work of Togni and Sodeoka, Cahard reported a catalytic enantioselective electrophilic fluorination of both cyclic and acyclic β-ketoesters catalyzed by copper (II) bis(oxazoline) (Phebox) complexes and NFSI (Equation 26) [95]. Shibata reported two fluorination reactions using the same ligand antipode **15** with copper (II) and nickel (II), respectively, to afford opposite fluorinated product enantiomers (Scheme 9) [96]. Both Sodeoka and Shibata applied their enantioselective fluorination approaches to the synthesis of MaxiPost™ (**16**) [97], a pharmaceutical developed by Bristol-Myers Squibb for the treatment of stroke (Scheme 10) [98,99].

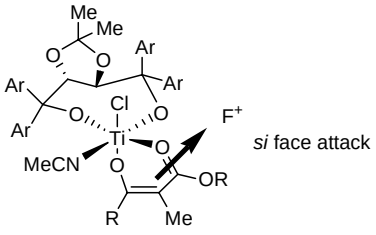
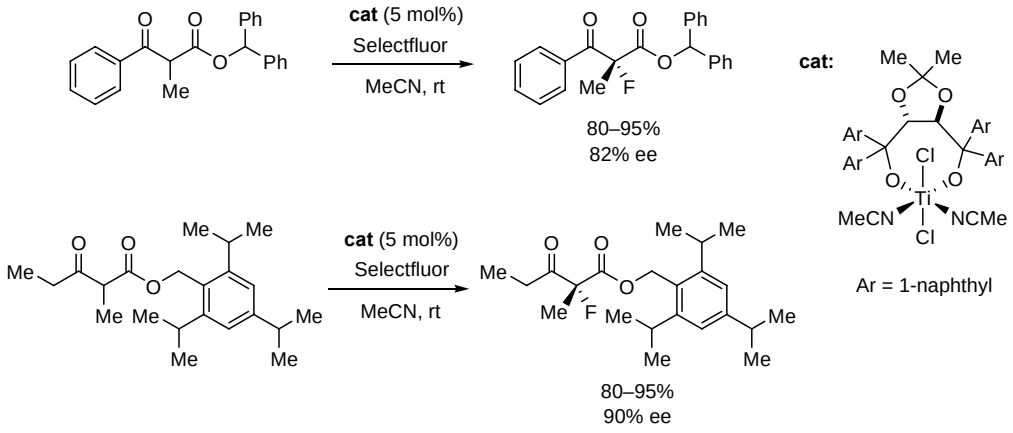
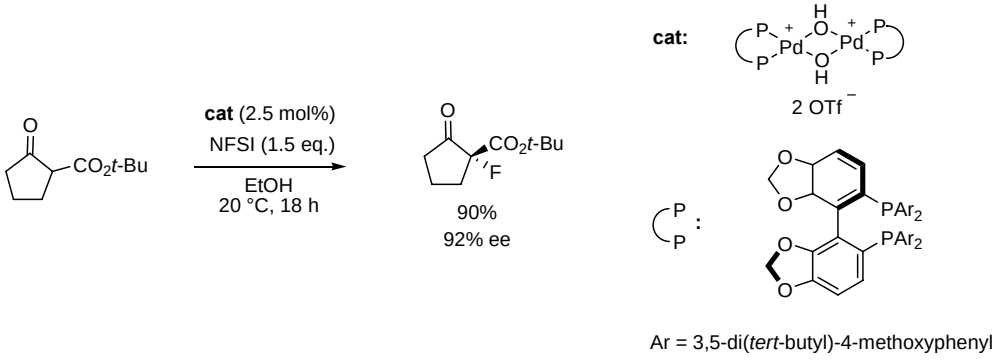


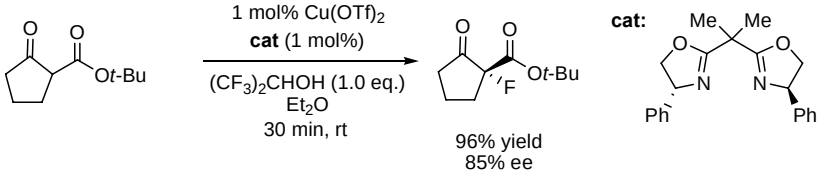
Figure 5. Proposed asymmetric induction mechanism for a titanium TADDOL complex.



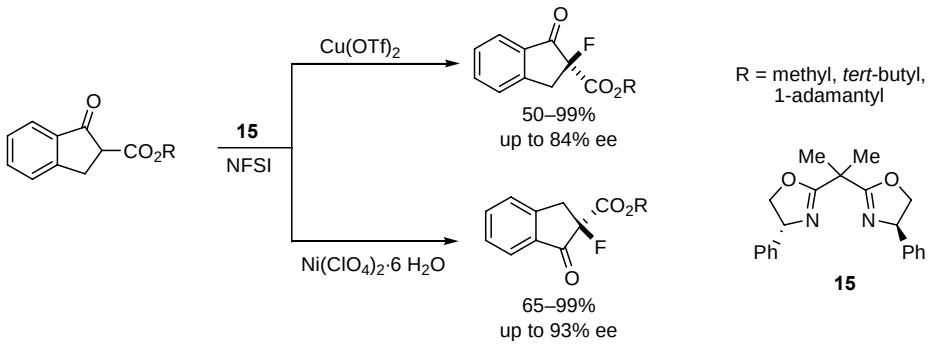
Scheme 8. Examples of catalytic asymmetric fluorination reaction with a [$TiCl_2$(TADDOLato)] complex.



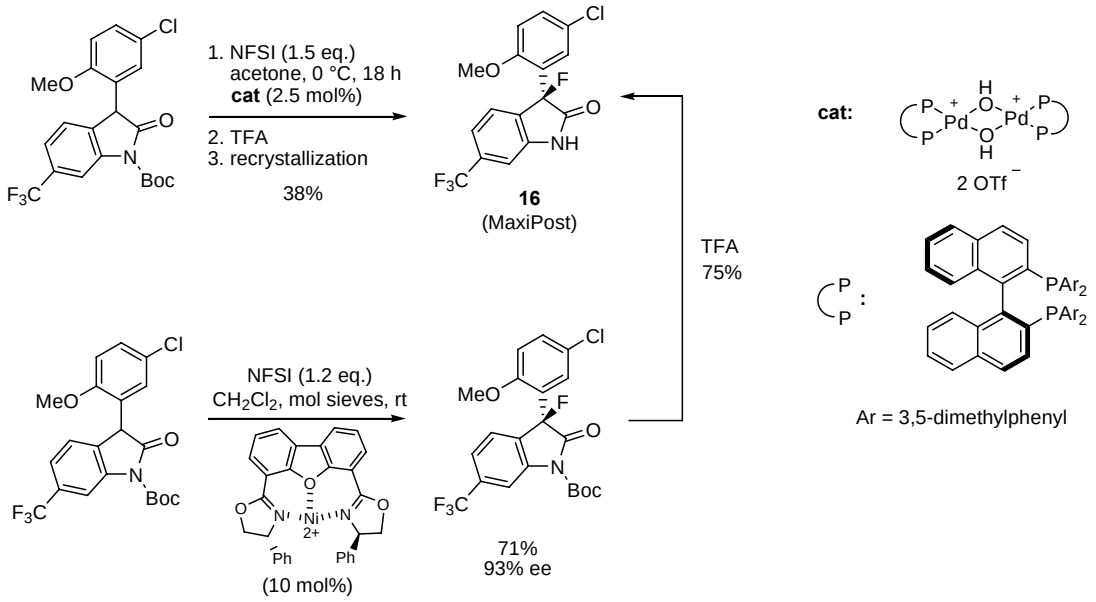
(25)



(26)



Scheme 9. Metal-dependent asymmetric fluorination for the synthesis of both enantiomers.

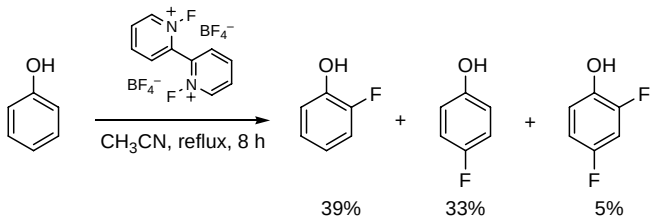


Scheme 10. Application of catalytic asymmetric fluorinations to the synthesis of MaxiPost.

2.4 Electrophilic Aromatic Fluorination

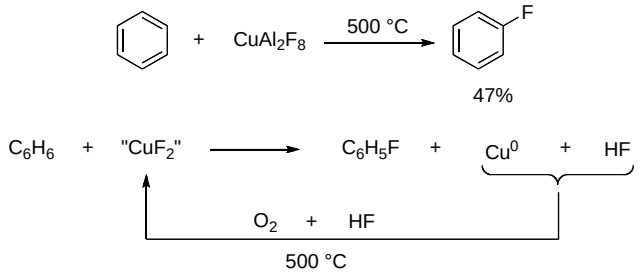
Electron rich arenes react with electrophilic fluorinating agents but the regioselectivity is usually low (Equation 27) [100]. Common organometallics such as organomagnesiums or organolithiums can afford regiospecific fluorination with electrophilic fluorinating reagents. However, many functional groups are not compatible with the strongly nucleophilic and basic Grignards or organolithiums [101].

Organometallics with lower basicity such as arylzinc halides, arylsilanes, arylstannanes, arylgermanium and arylboronic acids afford fluorinated products which typically require very reactive electrophilic fluorinating reagents such as elemental fluorine, XeF_2, or O-F reagents for successful fluorination [102,103].



(27)

Several organic compounds, including arenes, have been fluorinated employing transition metal fluorides such as CoF_3, $KCoF_4$, AgF_2, CeF_4, and MnF_3 [104–106]. Copper (II) fluoride was shown to function as catalyst for the fluorination of benzene in the gas phase at 500 °C [107]. In 2008, copper aluminum fluoride ($CuAl_2F_8$) was synthesized to exhibit reactivity towards direct oxidative fluorination of aromatic compounds as well. The $CuAl_2F_8$ reagent can be regenerated by treatment with O_2 and HF, and the fluorination process has been demonstrated to retain high conversions through 20 reaction cycles (Scheme 11) [108]. Transition-metal-catalyzed substitution of aryl halides by fluoride was reported in a patent in 2007 [109].



Scheme 11. Oxidative fluorination of benzene with $CuAl_2F_8$.

The palladium-catalyzed fluorination of aryl halides has been investigated by Grushin [110] over the

past two decades and, more recently, by Yandulov [111]. The proposed catalytic cycle involves oxidative addition of an arylhalide to palladium (0), ligand exchange to form a palladium (II) fluoride, followed by a carbon–fluorine reductive elimination. While oxidative addition and ligand exchange have been described, the carbon–fluorine reductive elimination has not yet been observed by Grushin. Yandulov reported the formation of fluorobenzene in 10% yield from a palladium (II) fluoride (Equation 28), but the mechanism of this formation has not yet been established (Figure 6) [112].

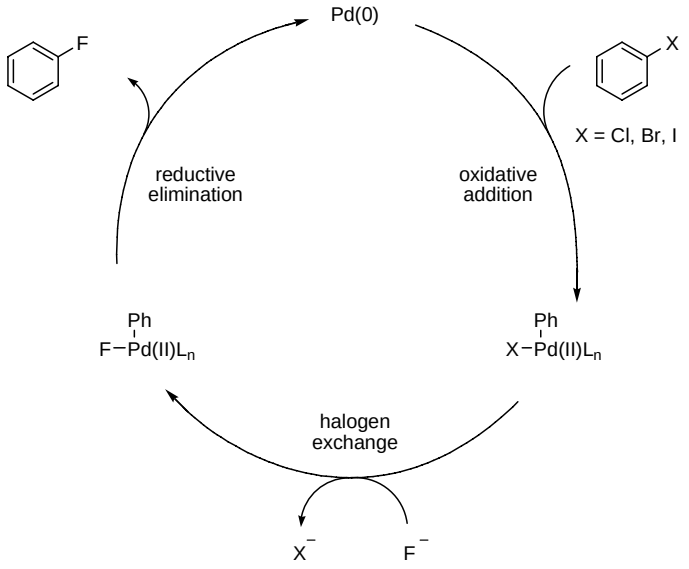
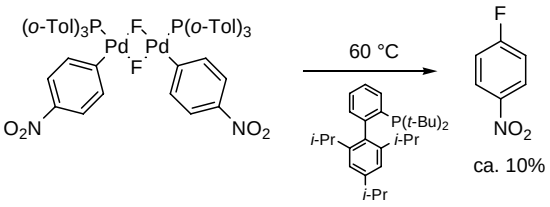
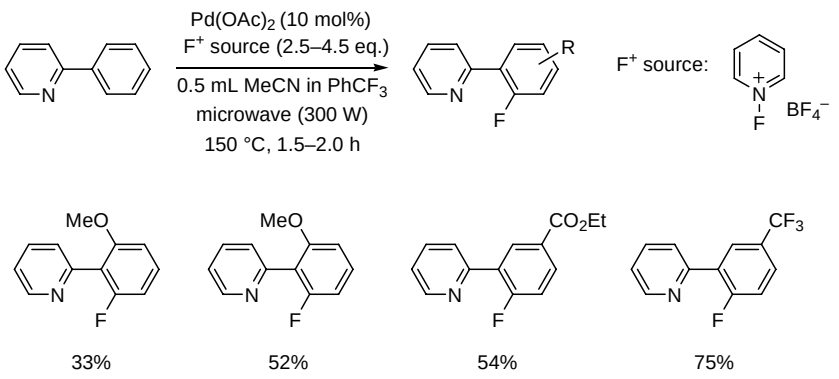


Figure 6. Proposed ideal catalytic cycle for transition-metal-catalyzed C–F bond formation.



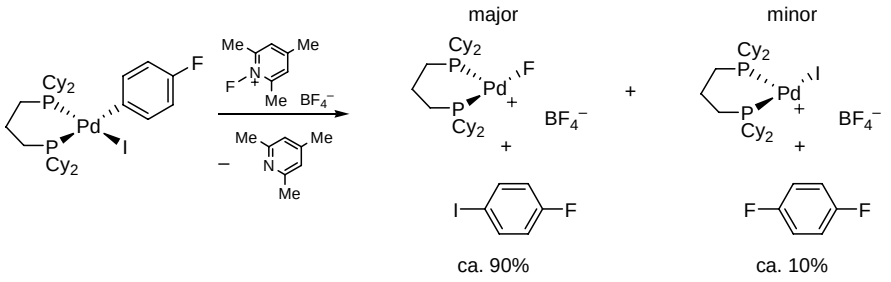
(28)

The electrophilic fluorination of specific carbon–hydrogen bonds of phenylpyridine derivatives and related structures was reported by Sanford in 2006 [113•]. The reaction takes advantage of a covalently attached pyridine directing group and affords fluorinated arylpyridine derivatives using microwave irradiation (100–150 °C, 1–4 h, 33–75% yield) by fluorination of carbon–hydrogen bonds proximal to the pyridine directing group (Scheme 12).



Scheme 12. Palladium-catalyzed fluorination of phenylpyridine derivatives.

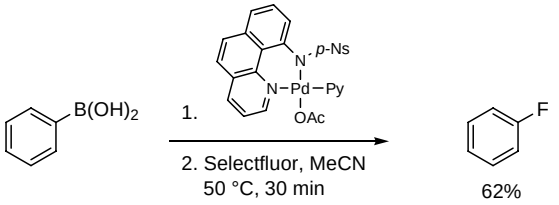
In 2008, Vigalok reported carbon–fluorine bond formation from a Pd (II) aryl complex upon treatment with an electrophilic fluorination reagent in 10% yield (Equation 29) [114]. Possible mechanistic pathways for this transformation include the involvement of a discrete palladium (IV) intermediate and electrophilic palladium–carbon bond cleavage.



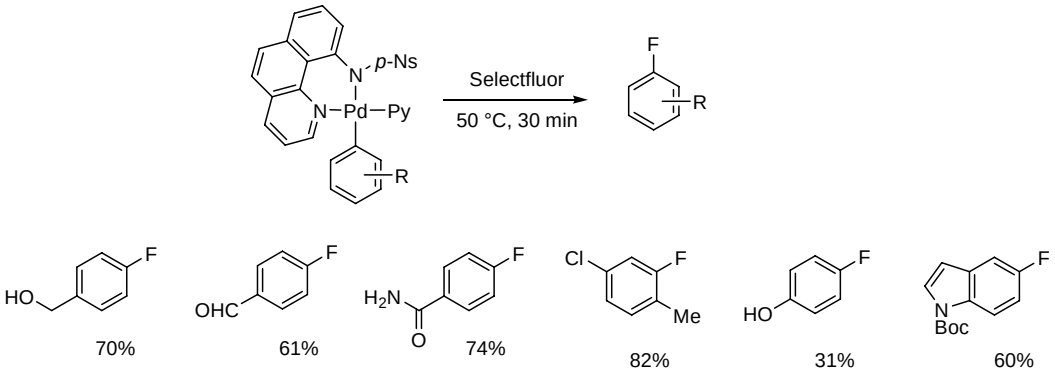
(29)

In 2008, our group developed a two-step fluorination reaction from arylboronic acids using stoichiometric amounts of a palladium (II) pyridyl-sulfonamide complex (Equation 30) [115•]. The fluorination reaction is regiospecific and functional-group-tolerant as illustrated in Scheme 13. In addition, the reaction conditions are attractive for the late-stage introduction of fluorine atom into functionalized molecules. Mechanistic investigations suggest the intermediacy of discrete palladium (IV) intermediates for this reaction. To stabilize a hypothetical palladium (IV) intermediate, the rigid

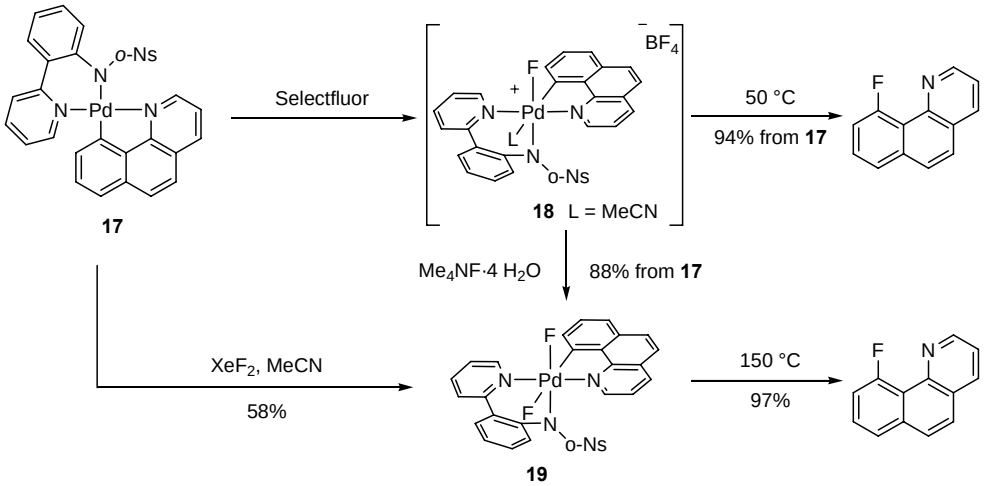
palladium (II) complex **17** was treated with Selectfluor and afforded the high-valent palladium (IV) aryl fluoride **18**. Thermolysis of **18** afforded carbon–fluorine reductive elimination. Similarly, the palladium (IV) difluoride **19** afforded carbon–fluorine bond formation in 97% yield (Scheme 14) [116].



(30)



Scheme 13. Functional-group-tolerant fluorination of aryl palladium complexes.



Scheme 12. C–F reductive elimination from palladium(IV) fluorides.

Conclusion

In the past decade, a number of new transformations for carbon–fluorine bond formations has been developed. Impressive advances in the fields of enantioselective fluorination, transition-metal-mediated fluorinations, and applications for positron-emission tomography provided a wealth of new reactivity for carbon–fluorine bond formation. Despite recent progress, controlled, general, and selective carbon–fluorine bond formation remains a major challenge in synthetic organic chemistry and due to the importance of fluorine in pharmaceuticals, agrochemicals, materials, and PET, we will witness a rapid development of new fluorination reactions in years to come.

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