Carbon–Fluorine Bond Formation

Carbon–Fluorine Bond Formation

Takeru Furuya, Christian A. Kuttruff, and Tobias Ritter*

Department of Chemistry and Chemical Biology

Harvard University

12 Oxford Street

Cambridge, MA 02138

ritter@chemistry.harvard.edu

Phone 617 496 0750

Fax 617 496 4591

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

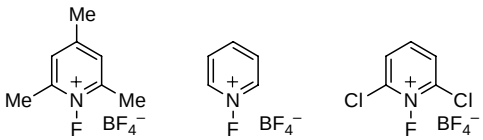
Abbreviations

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 

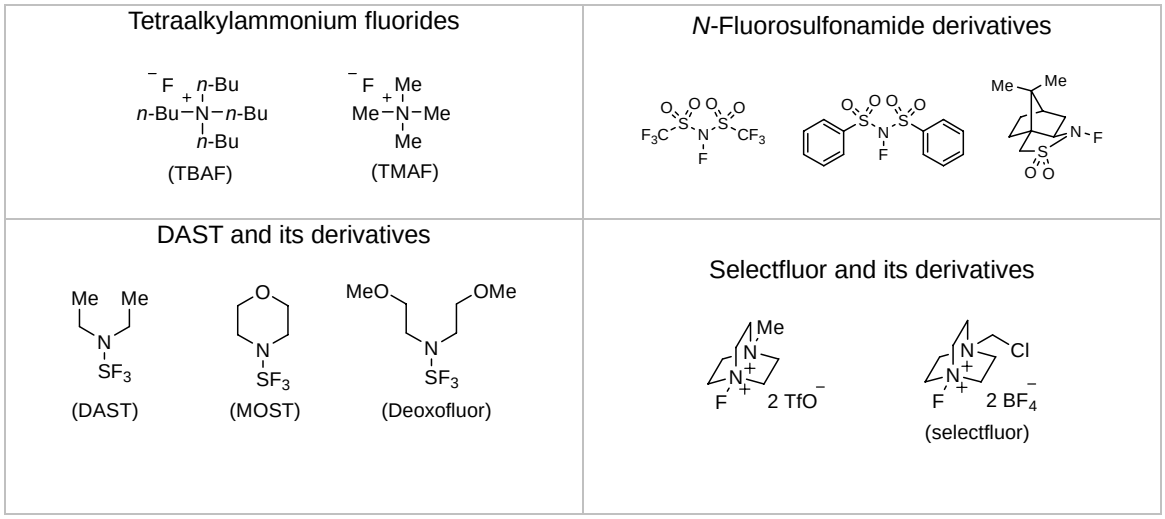


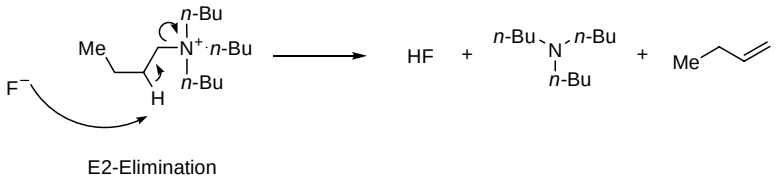
Chart 1. Overview of some of the most common fluorinating reagents.

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.

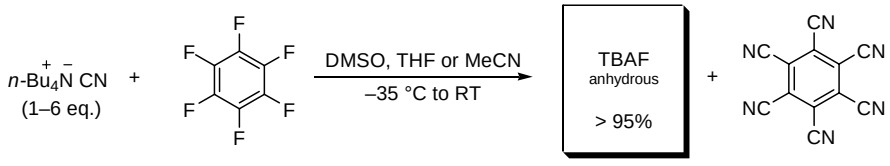
The use of tetraalkylammonium ions as counterions for fluoride reduces the ionic bond strength and increases the solubility in organic solvents [33]. Tetrabutylammonium fluoride (TBAF) is a common fluorinating agent that is available as a trihydrate. The presence of water reduces the nucleophilicity 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].



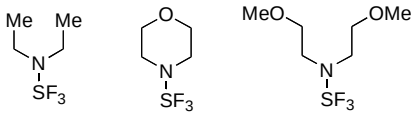
(1)

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)

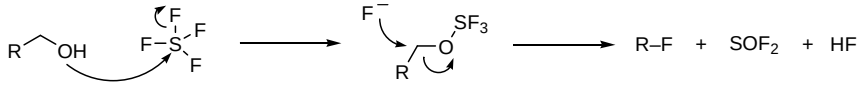
Sulfur fluorides can serve as nucleophilic fluorination sources. One of the most versatile fluorinating agents of this class is (diethylamino)sulfur trifluoride (DAST, **1**), a less toxic and less volatile analog of sulfur tetrafluoride SF_4 [38]. DAST can explode when shock-heated; thus, thermally 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.

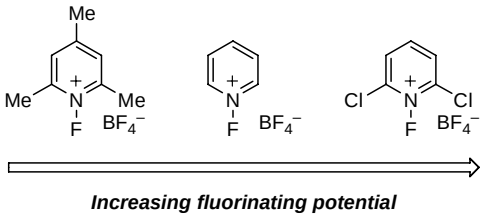
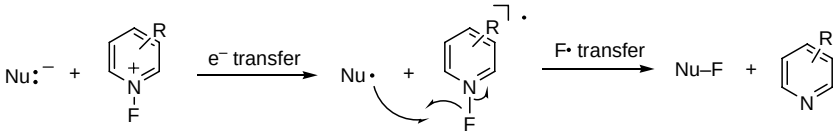
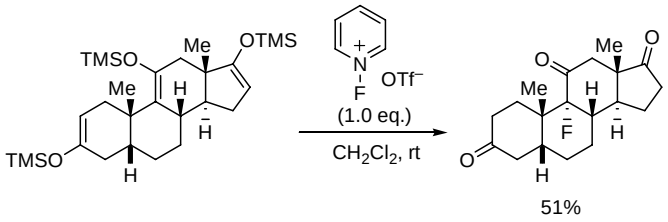


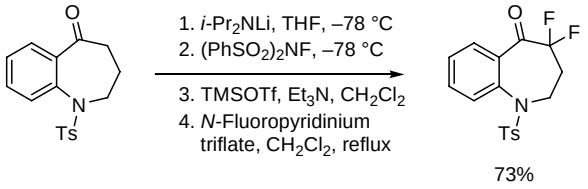
Figure 2. Effect of substituents on the oxidation potential of *N*-fluoropyridinium salts.



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

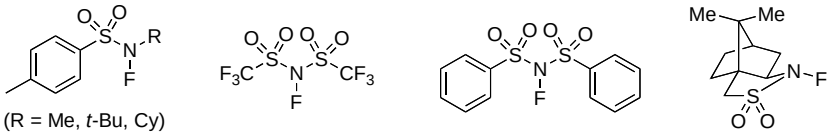


(4)



(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].

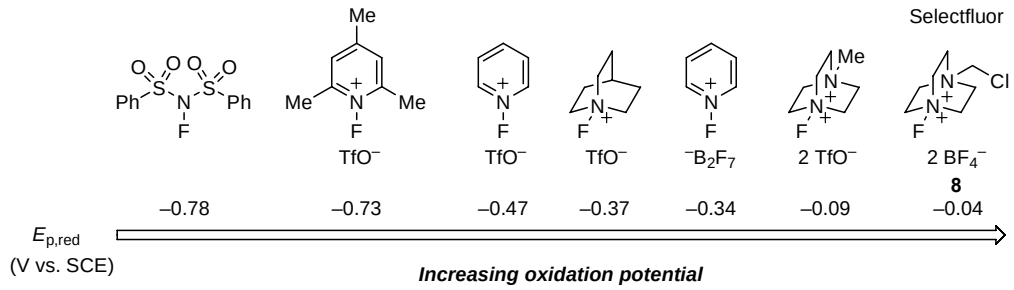
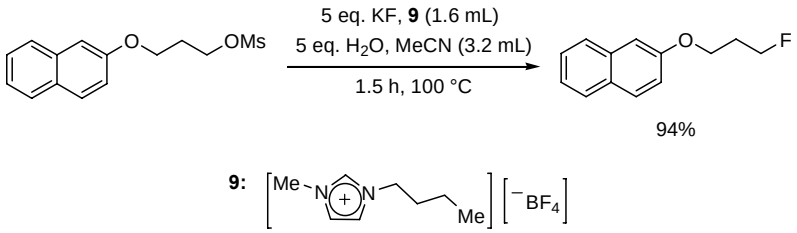


Figure 4. Reduction peak potentials of different electrophilic fluorination reagents: $E_{p,red}$ in V relative to the standard calomel electrode; 1–5 mM in MeCN/0.1 M Bu_4N^+ BF_4^- or $CF_3SO_3^-$ [47].

2. Fluorination Reactions

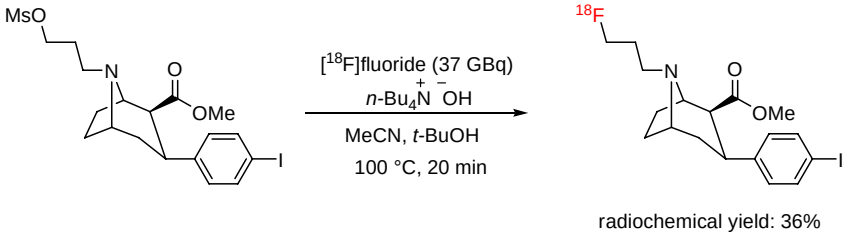
2.1 Nucleophilic Aliphatic Fluorinations

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).

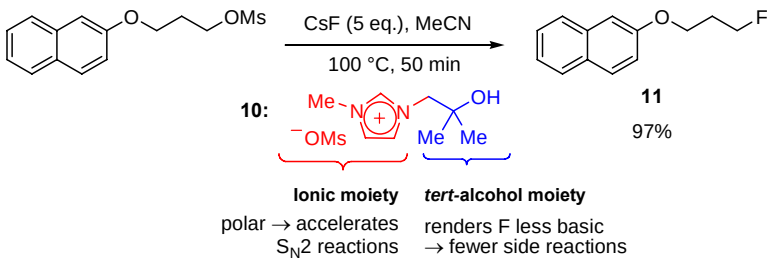


(6)

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].

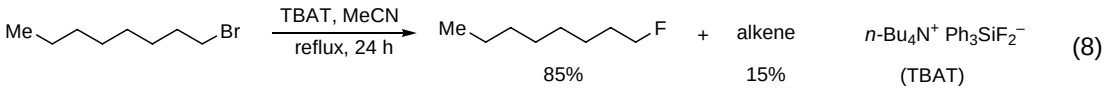


(7)



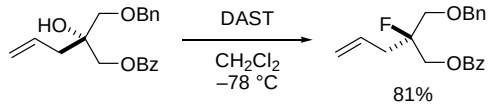
Scheme 2. Combined effect of ionic liquid and *tert*-alcohol on nucleophilic fluorination.

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].

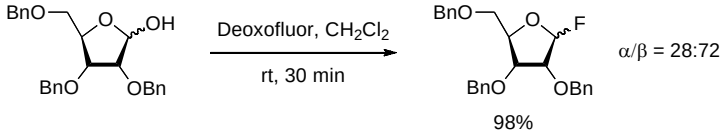


(8)

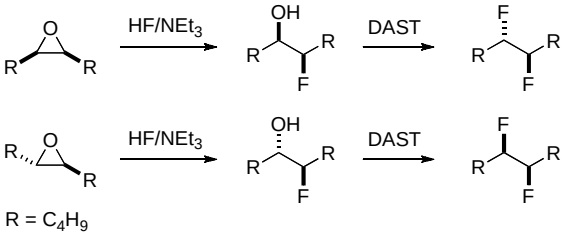
Aliphatic alcohols can be converted into the corresponding fluorides with the nucleophilic fluorination reagent DAST. Typically, fluorinations with DAST proceed with inversion. Two examples for such transformations are given in Equation 9 and 10 [38,39]. Schlosser developed a method to access vicinal 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.



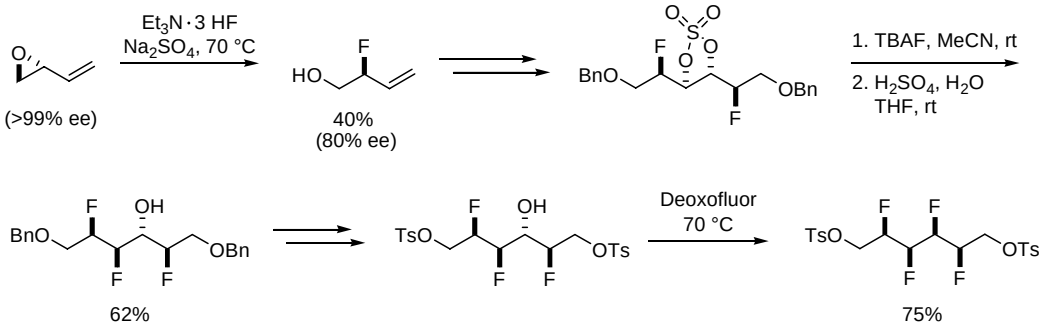
(9)



(10)



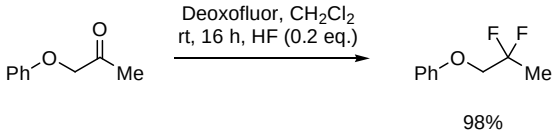
Scheme 3. Stereoselective synthesis of vicinal difluoroalkanes via epoxide opening with hydrogen fluoride and deoxyfluorination with DAST.



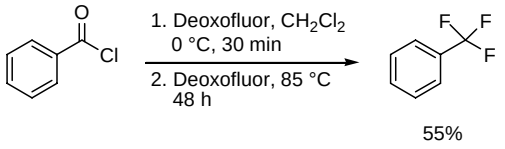
Scheme 4. Asymmetric synthesis of an all-*syn* four vicinal fluoride motif.

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)

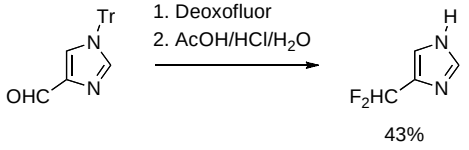
[59]. Aldehydes can be converted into the corresponding difluoromethyl groups as shown in Equation 13 [60].



(11)



(12)



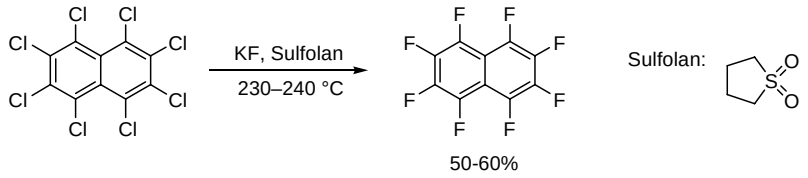
(13)

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].

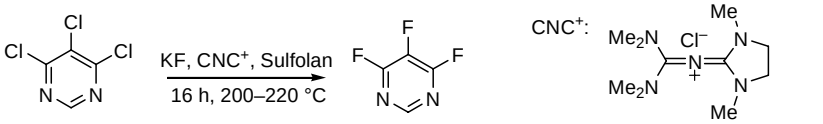
2.2 Nucleophilic Aromatic Fluorinations

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].

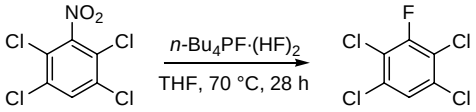


50-60% (14)



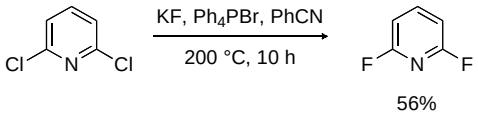
66-80%

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

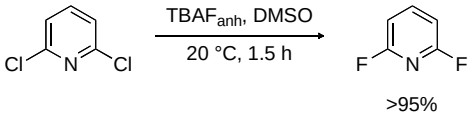


80% (16)

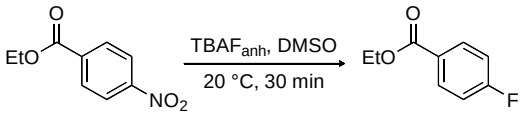
In 2005, DiMagno reported the preparation and use of anhydrous tetrabutylammonium fluoride ($TBAF_{anh}$) [36,37•]. When $TBAF_{anh}$ was used in halogen exchange and fluorodenitration reactions, these reactions could be run under mild conditions. For example, a typical Halex fluorination of 2,6-dichloropyridine 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)

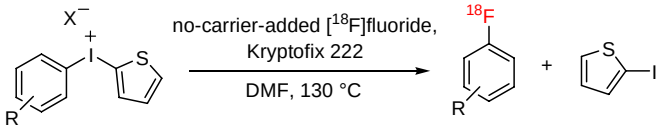


>95% (18)



>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).



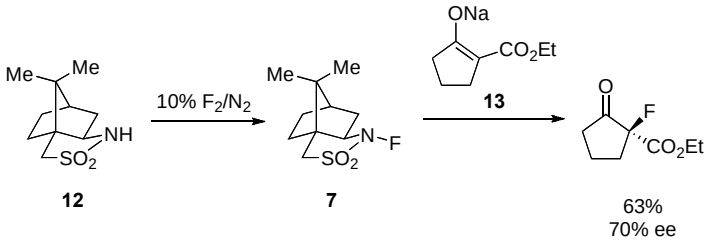
X = Br, I, OTs, OTf

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

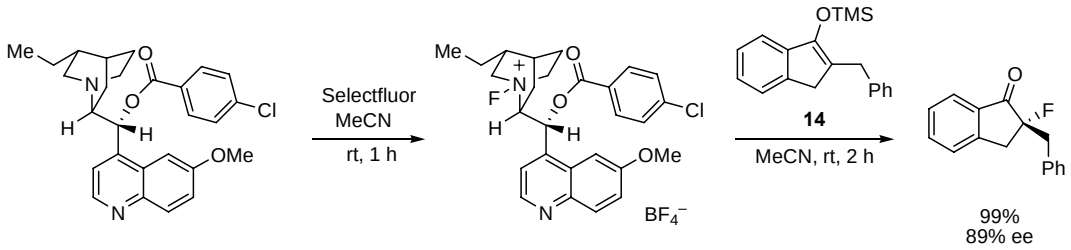
2.3 Electrophilic Aliphatic Fluorination

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•].

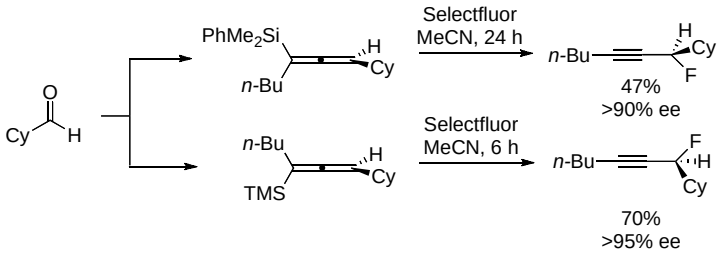


Scheme 5. Asymmetric fluorination of cyclic enolate 13 with (+)-*N*-fluoro-2,10-camphorsultam (7).



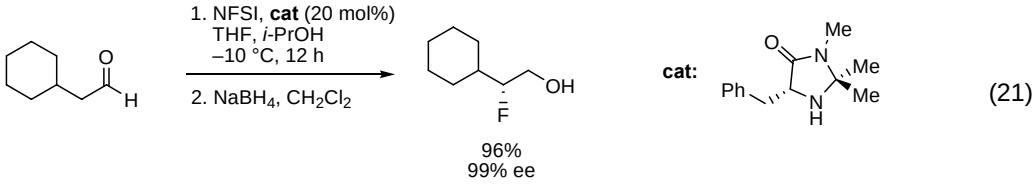
Scheme 6. Asymmetric electrophilic fluorination of a silyl enol ether with *N*-fluorodihydroquinine 4-chlorobenzoate [81].

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].

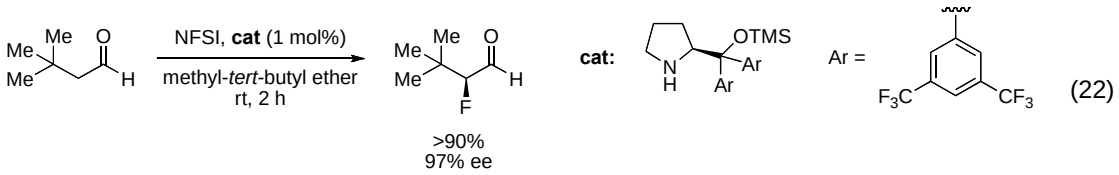


Scheme 7. Synthesis of enantioriched propargylic fluorides.

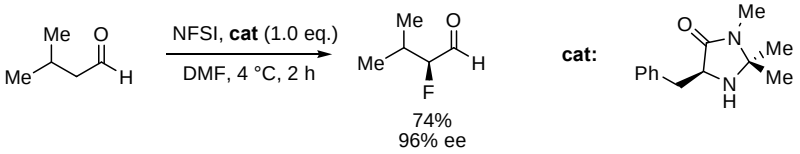
Chiral α-fluorination of aldehydes was reported by MacMillan (Equation 21) [88•], Jørgensen (Equation 22) [89•], and Barbas (Equation 23) [90•] in 2005. Chiral enamine catalysis provided enantioselectively enriched α-fluoroaldehydes in up to 99% ee. Isolation of the chiral fluoroalcohols after reduction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



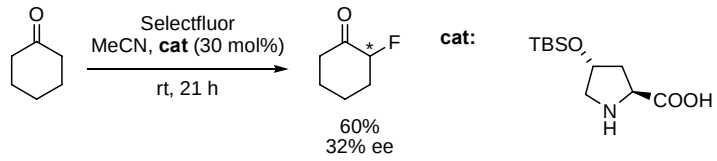
(21)



(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].

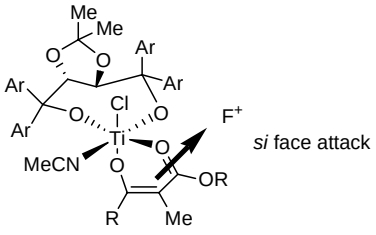
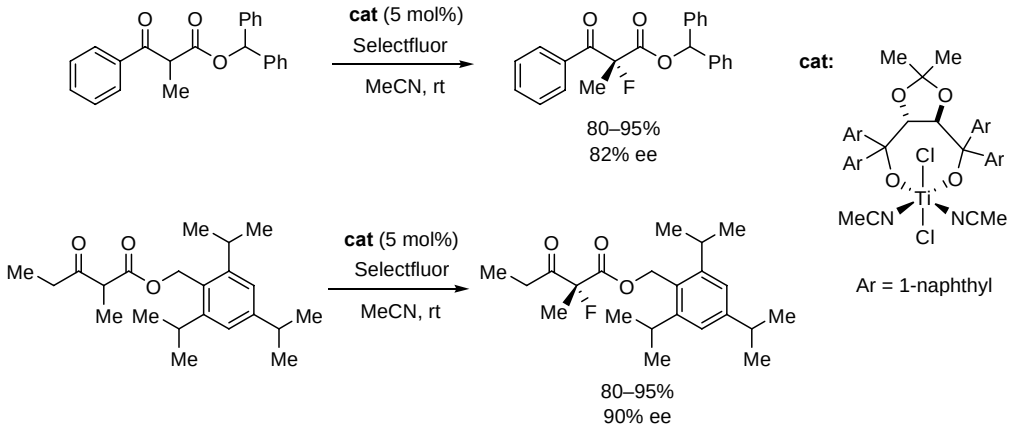
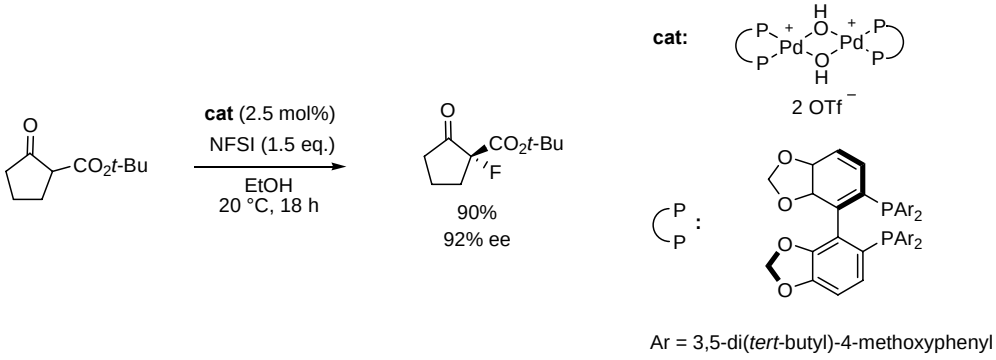


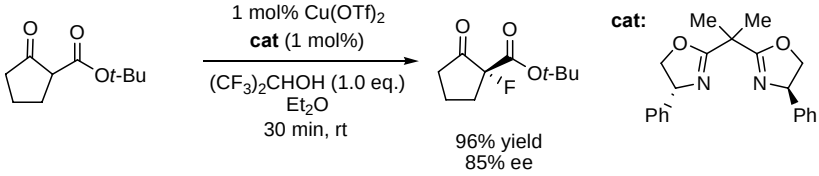
Figure 5. Proposed asymmetric induction mechanism for a titanium TADDOL complex.



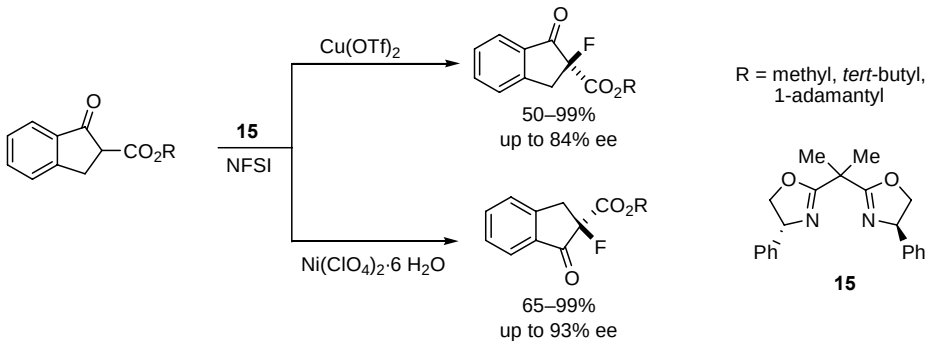
Scheme 8. Examples of catalytic asymmetric fluorination reaction with a [$TiCl_2$(TADDOLato)] complex.



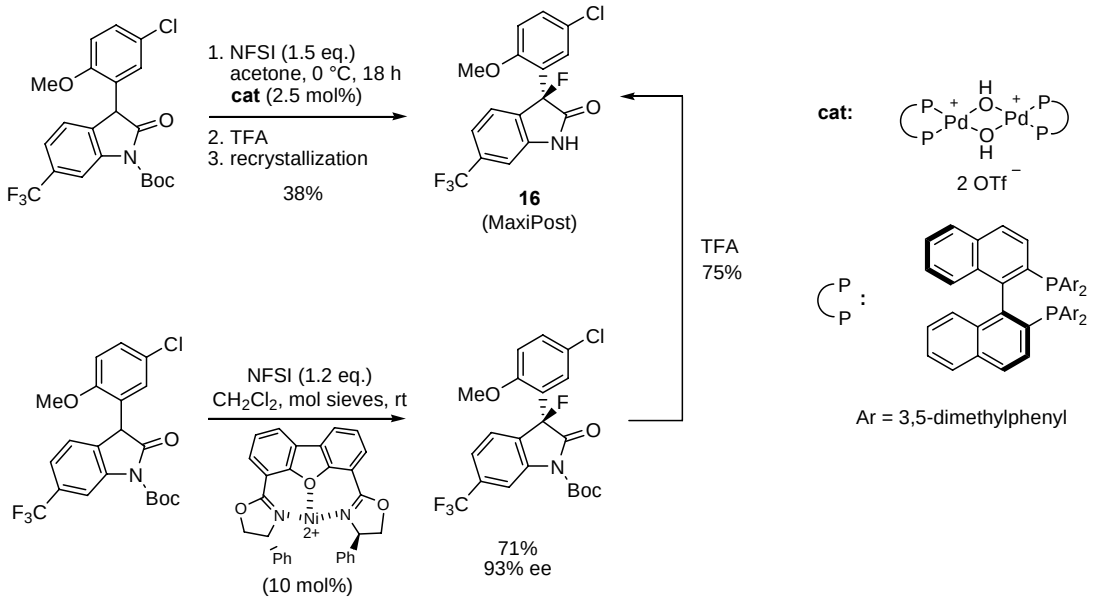
(25)



(26)



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

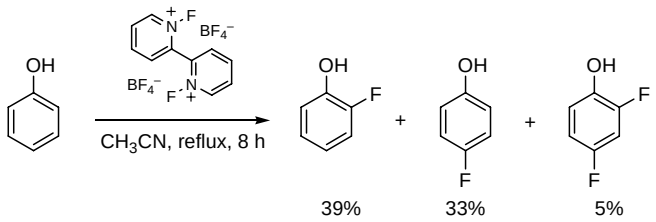


Scheme 10. Application of catalytic asymmetric fluorinations to the synthesis of MaxiPost.

2.4 Electrophilic Aromatic Fluorination

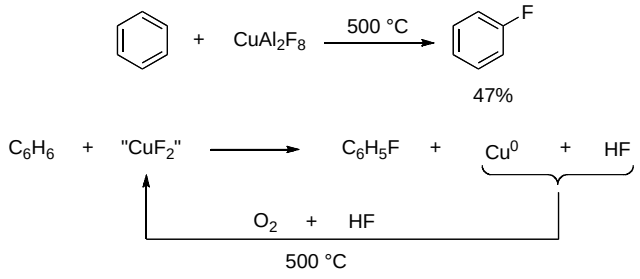
Electron rich arenes react with electrophilic fluorinating agents but the regioselectivity is usually low (Equation 27) [100]. Common organometallics such as organomagnesiums or organolithiums can afford regiospecific fluorination with electrophilic fluorinating reagents. However, many functional groups 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].

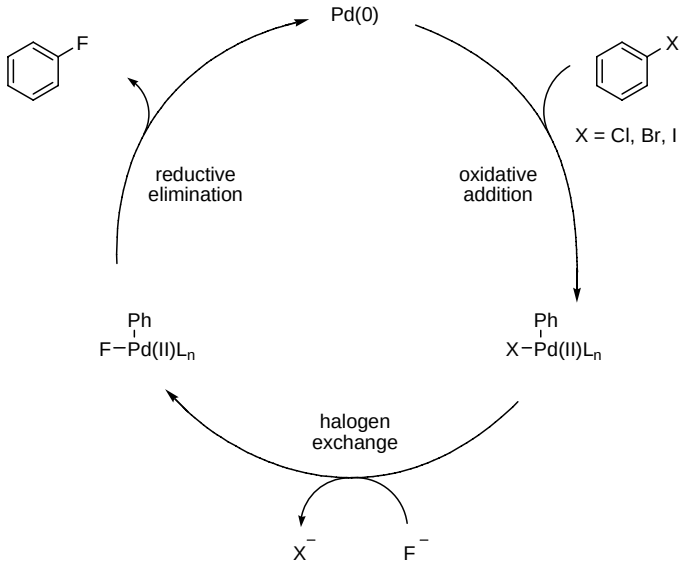
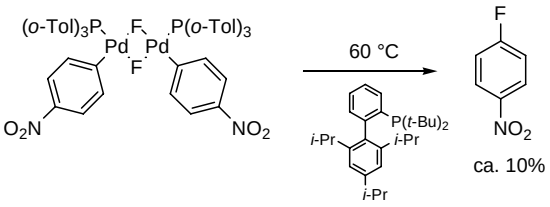
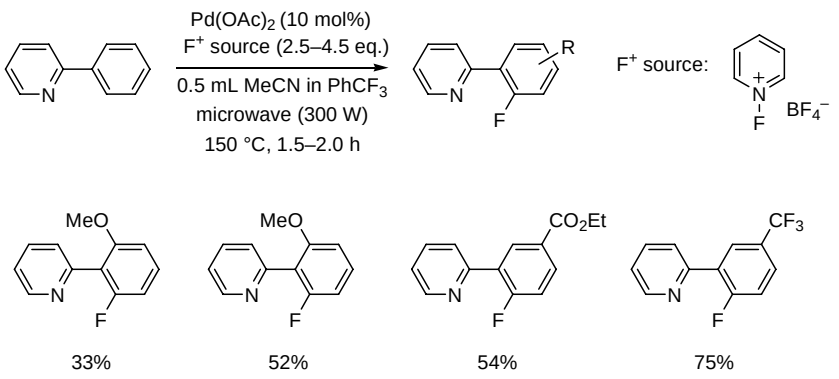


Figure 6. Proposed ideal catalytic cycle for transition-metal-catalyzed C–F bond formation.



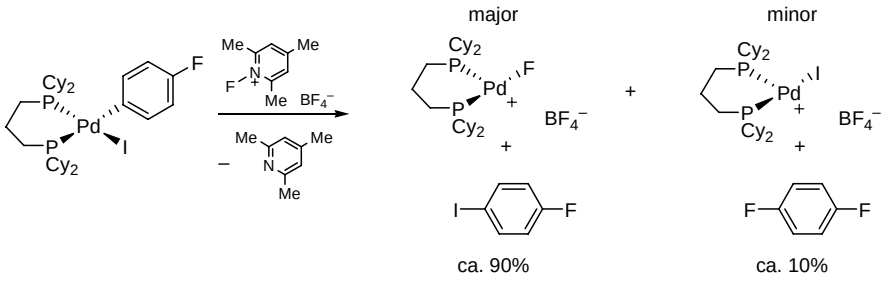
(28)

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.

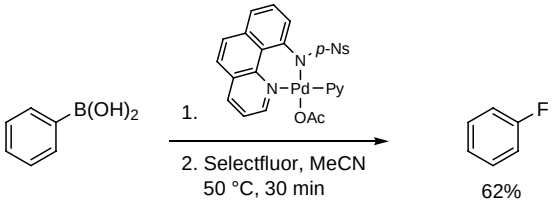
In 2008, Vigalok reported carbon–fluorine bond formation from a Pd (II) aryl complex upon treatment with an electrophilic fluorination reagent in 10% yield (Equation 29) [114]. Possible mechanistic pathways for this transformation include the involvement of a discrete palladium (IV) intermediate and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



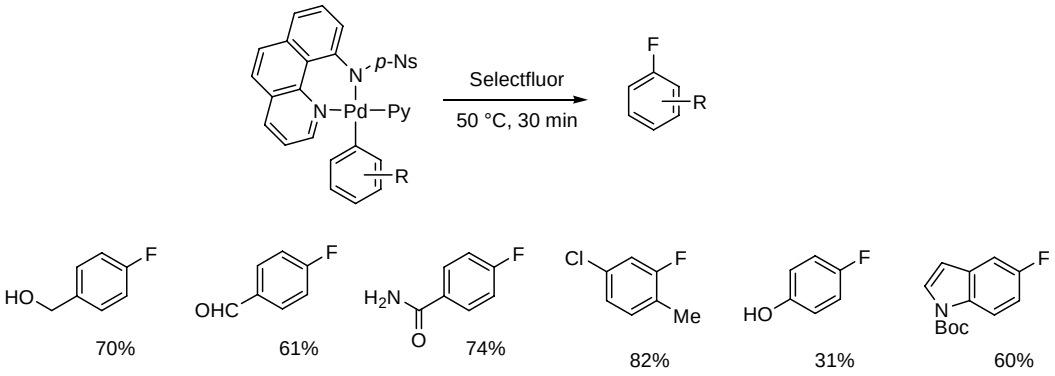
(29)

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

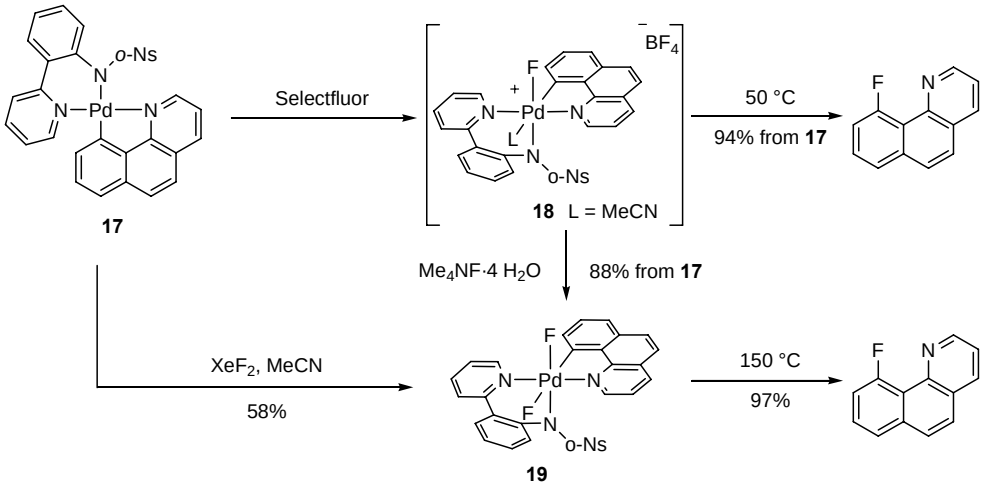
palladium (II) complex **17** was treated with Selectfluor and afforded the high-valent palladium (IV) aryl fluoride **18**. Thermolysis of **18** afforded carbon–fluorine reductive elimination. Similarly, the palladium (IV) difluoride **19** afforded carbon–fluorine bond formation in 97% yield (Scheme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

References

[1] Böhm HJ, Banner D, Bendels S, Kansy M, Kuhn B, Müller K, Obst-Sander U, Stahl M: **Fluorine in medicinal chemistry.** *ChemBioChem* (2004) **5**(5): 637–643.

[2] Müller K, Faeh C, Diederich F: **Fluorine in pharmaceuticals: looking beyond intuition.** *Science* (2007) **317**(5846): 1881–1886.

[3] Purser S, Moore PR, Swallow S, Gouverneur V: **Fluorine in medicinal chemistry.** *Chem Soc Rev* (2008) **37**(2): 320–330.

[4] Jeschke P: **The unique role of fluorine in the design of active ingredients for modern crop protection.** *ChemBioChem* (2004) **5**: 570–589.

[5] Phelps ME: **Positron emission tomography provides molecular imaging of biological processes.** *Proc. Natl. Acad. Sci. U. S. A.* (2000) **97**(16): 9226–9233.

[6] Ametamey SM, Honer M, Schubiger PA: **Molecular imaging with PET.** *Chem. Rev.* (2008) **108**(5): 1501–1516.

[7] Hung MH, Farnham WB, Feiring AE, Rozen S: *Functional Fluoromonomers and Fluoropolymers. In Fluoropolymers.* Plenum Publishing Co., New York, NY, USA (1999).

[8] Wei HC, Lagow RJ: **The synthesis of the largest perfluoro macrocycles; pPerfluoro [60]-crown-20 and perfluoro [30]-crown-10.** *Chem Commun.* (2000) (21): 2139–2141.

[9] O'Hagan D: **Understanding organofluorine chemistry. An introduction to the C–F bond.** *Chem Soc Rev* (2008) **37**(2): 308–319.

[10] Smart BE: **Fluorine substituent effects (on bioactivity).** *J Fluorine Chem* (2001) **109**(1): 3–11.

[11] Bondi A: **van der Waals volumes and radii.** *J Phys Chem* (1964) **68**(3): 441–451.

[12] Hudlicky M, Pavlath AE (Ed): *Chemistry of Organic Fluorine Compounds II*. American Chemical Society: Washington, DC, USA (1995).

[13] Rowley M, Hallett DJ, Goodacre S, Moyes C, Crawforth J, Sparey TJ, Patel S, Marwood TS, Hitzel L, O´Connor D, Szeto N, Castro JL, Hutson PH, MacLeod AM: **3-(4-Fluoropiperidin-3-yl)-2-phenylindoles as high affinity, selective, and orally bioavailable h5-HT_{2A} receptor antagonists.** *J Med Chem* (2001) **44**(10): 1603–1614.

[14] Berkowitz DB, Bose M: **(α-Monofluoroalkyl)phosphonates: a class of isoacidic and "tunable" mimics of biological phosphates.** *J Fluorine Chem* (2001) **112**(1): 13–33.

[15] Tanake F, Fukuse H, Wada H, Fukushima M: **The history, mechanism and clinical use of oral 5-fluorouracil derivative chemotherapeutic agents.** *Curr Pharm Biotechnol* (2000) **1**(2): 137–164.

[16] Couturier O, Luxen A, Chatal JF, Vuillez JP, Rigo P, Hustinx R: **Fluorinated tracers for imaging cancer with positron emission tomography.** *Eur J Nucl Med Mol Imaging* (2004) **31**(8): 1182–1206.

[17] Kirk KL: **Fluorination in medicinal chemistry: methods, strategies, and recent developments.** *Org Process Res Dev* (2008) **12**(2): 305–321.

[18] Gribble GW: **Natural organohalogens: a new frontier for medicinal agents?** *J Chem Ed* (2004) **81**(10):1441–1449.

[19] Chambers RD (Ed): *Fluorine in Organic Chemistry.* Blackwell Publishing Ltd., Oxford, UK (2004).

[20] Kirsch P (Ed): *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications.* Wiley-VCH: Weinheim, Germany (2004).

[21] Uneyama K (Ed): *Organofluorine Chemistry.* Blackwell Publishing Ltd.: Oxford, UK (2006).

[22] Brunet VA, O'Hagan D: **Catalytic asymmetric fluorination comes of age.** *Angew Chem Int Ed* (2008) **47**(7): 1179–1182.

[23] Emsley J: **Very strong hydrogen bonds.** *Chemical Society Reviews* (1980) **9**(1): 91–124.

[24] Manna S, Falck JR, Mioskowski C: **A convenient preparation of alkyl halides and cyanides**

from alcohols by modification of the Mitsunobu procedure. *Synth Commun* (1985) **15**(8): 663–668.

[25] Tullock CW, Coffman DD: **Synthesis of fluorides by metathesis with sodium fluoride.** *J Org Chem* (1960) **25**(11): 2016–2019.

[26] Shahak I, Bergmann ED: **Organic fluorine compounds. Part XXXVI. Preparation of N-substituted amides of α-fluoroacids.** *J Chem Soc C* (1967) 319–320.

[27] Finger GC, Kruse CW: **Aromatic fluorine compounds. VII. Replacement of aromatic –Cl and $-NO_2$ groups by –F.** *J Am Chem Soc* (1956) **78**(23): 6034–6037.

[28] Bram G, Loupy A, Pigeon P: **Easy and efficient heterogeneous nucleophilic fluorination without solvent.** *Synth Commun* (1988) **18**(14): 1661–1668.

[29] Collona S, Re A, Gelbard G, Cesarotti E: **Anionic activation in polymer supported reactions. Part 2. Stereochemical studies on the introduction of fluorine at chiral centers and in biologically significant molecules.** *J Chem Soc, Perkin Trans 1* (1979): 2248–2252.

[30] Ishikawa N, Kitazume T, Yamazaki T, Mochida Y, Tatsumo T: **Enhanced effect of spray-dried potassium fluoride on fluorination.** *Chem Lett* (1981) **10**(6): 761–764.

[31] Clark JH, Hyde A, Smith DK: **Calcium fluoride-supported alkali metal fluorides. New reagents for nucleophilic fluorine transfer reactions.** *J Chem Soc, Chem Commun* (1986) (10): 791–793.

[32] Liotta CL, Harris HP: **Chemistry of naked anions. I. Reactions of the 18-crown-6 complex of potassium fluoride with organic substrates in aprotic organic solvents.** *J Am Chem Soc* (1974) **96**(7): 2250–2252.

[33] Yoshida Y, Kimura Y: **A convenient synthesis of fluorobenzaldehydes by KF/Ph4PBr/18-crown-6 reagent system.** *Chem Lett* (1988) **17**(8): 1355–1358.

[34] Sharma RK, Fry JL: **Instability of anhydrous tetra-*n*-alkylammonium fluorides.** *J Org Chem* (1983) **48**(12): 2112–2114.

[35] Christe KO, Wilson WW, Wilson RD, Bau R, Feng JA: **Syntheses, properties, and structures of anhydrous tetramethylammonium fluoride and its 1:1 adduct with trans-3-amino-2-butenenitrile.** *J Am Chem Soc* (1990) **112**(21): 7619–7625

[36] Sun H, DiMagno SG: **Anhydrous tetrabutylammonium fluoride.** *J Am Chem Soc* (2005) **127**(7): 2050–2051.

[37•]DiMagno SG, Sun H: **Room-temperature nucleophilic aromatic fluorination: experimental and theoretical studies.** *Angew Chem Int Ed* (2006) **45**(17): 2720–2725.
The results of this paper indicate that nucleophilic aromatic substitution is feasible at significantly lower temperatures than previously observed, when anhydrous fluoride is used.

[38] Middleton WJ: **New fluorinating reagents. Dialkylaminosulfur fluorides.** *J Org Chem* (1975) **40**(5): 574–578.

[39] Lal GS, Pez GP, Pesaresi RJ, Prozonic FM, Cheng H: **Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability.** *J Org Chem* (1999) **64**(19): 7048–7054.

[40] Umemoto T, Fukami S, Tomizawa G, Harasawa K, Kawada K, Tomita K: **Power- and structure-variable fluorinating agents. The *N*-fluoropyridinium salt system.** *J Am Chem Soc* (1990) **112**(23): 8563–8575.

[41] Shimada Y, Taniguchi N, Matsuhisa A, Sakamoto K, Yatsu T, Tanaka A: **Highly potent and orally active non-peptide arginine vasopressin antagonists for both V1A and V2 receptors: synthesis and pharmacological properties of 4'-[(4,4-difluoro-5-methylidene-2,3,4,5-tetrahydro-1H-1-benzoazepin-1-yl)carbonyl]-2-phenylbenzanililde derivatives.** *Chem Pharm Bull* (2000) **48**(11): 1644–1651.

[42] Barnette WE: ***N*-Fluoro-*N*-alkylsulfonamides: useful reagents for the fluorination of carbanions.** *J Am Chem Soc* (1984) **106**(2): 452–454.

[43] Singh S, DesMarteau DD, Zuberi SS, Witz M, Huang HN: ***N*-Fluoroperfluoroalkylsulfonimides. Remarkable new fluorination reagents.** *J Am Chem Soc* (1987) **109**(23): 7194–7196.

[44] Differding E, Ofner H: ***N*-Fluorobenzenesulfonimide: a practical reagent for electrophilic fluorinations.** *Synlett* (1991) (3): 187–189.

[45] Differding E, Lang R: **New fluorinating reagents - I. The first enantioselective fluorination**

reaction. *Tetrahedron Lett* (1988) **29**(47): 6087–6090.

[46] Banks RE: **Selectfluor™ reagent F-TEDA-BF_4 in action: tamed fluorine at your service.** *J Fluorine Chem* (1998) **87**(1): 1–17.

[47] Gilicinski AG, Pez GP, Syvret RG, Lal GS: **On the relative power of electrophilic fluorinating reagents of the N–F class.** *J Fluorine Chem* (1992) **59**(1): 157–162.

[48] Clark JH: **Fluoride ion as a base in organic synthesis.** *Chem Rev* (1980) **80**(5): 429–452.

[49] Kim DW, Song CE, Chi DY: **New method of fluorination using potassium fluoride in ionic liquid: significantly enhanced reactivity of fluoride and improved selectivity.** *J Am Chem Soc* (2002) **124**(35): 10278–10279.

[50] Howard JAK, Hoy VJ, O'Hagan D, Smith GT: **How good is fluorine as a hydrogen bond acceptor?** *Tetrahedron* (1996) **52**(38): 12613–12622.

[51] Kim DW, Ahn DS, Oh YH, Lee S, Kil HS, Oh SJ, Lee SJ, Kim JS, Ryu JS, Moon DH, Chi DY: **A new class of S_N2 reactions catalyzed by protic solvents: facile fluorination for isotopic labeling of diagnostic molecules.** *J Am Chem Soc* (2006) **128**(50): 16394–16397.

[52•]Kim DW, Jeong HJ, Lim ST, Sohn MH, Katzenellenbogen JA, Chi DY: **Facile nucleophilic fluorination reactions using *tert*-alcohols as reaction medium: significantly enhanced reactivity of alkali metal fluorides and improved selectivity.** *J Org Chem* (2008) **73**(3): 957–962.

This paper describes the use of tert-butyl alcohol as solvent for nucleophilic fluorination. Tert-butyl alcohol reduces the basicity of fluoride and therefore potential side reactions.

[53] Chaly T, Dhawan V, Kazumata K, Antonini A, Margouleff C, Dahl C, Belakhlef JR, Margouleff D, Yee A, Wang SY, Tamagnan G, Neumeyer JL, Eidelgerg D: **Radiosynthesis of [^{18}F] *N*-3-fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) nortropane and the first human study with positron emission tomography.** *Nucl Med Biol* (1996) **23**(8): 999–1004.

[54] Shinde SS, Lee BS, Chi DY: **Synergistic effect of two solvents *tert*-alcohol and ionic liquid, in one molecule in nucleophilic fluorination.** *Org Lett* (2008) **10**(5): 733–735.

[55] Pilcher AS, Ammon HL, DeShong P: **Utilization of tetrabutylammonium(triphenylsilyl)-difluorosilicate as a fluoride source for nucleophilic fluorination.** *J Am Chem Soc* (1995) **117**(18): 5166–5167.

[56] Hamatani T, Matsubara S, Matsuda H, Schlosser M: **A stereocontrolled access to vicinal difluoroalkenes**. *Tetrahedron* (1988) **44**(10): 2875–2881.

[57] Hunter L, O'Hagan D, Slawin AMZ: **Enantioselective synthesis of an all-*syn* four vicinal fluorine motif.** *J Am Chem Soc* (2006) **128**(51): 16422–16423.

[58] Tozer MJ, Herpin TF: **Methods for the synthesis of *gem*-difluoromethylene compounds.** *Tetrahedron* (1996) **52**(26): 8619–8683.

[59] Lal GS, Pez GP, Pesaresi RJ, Prozonic FM: **Bis(2-methoxyethyl)aminosulfur trifluoride: a new broad-spectrum deoxofluorinating agent with enhanced thermal stability.** *Chem Commun* (1999) (2): 215–216.

[60] Dolensky B, Kirk KL: **Preparation of (fluoromethyl)- and (difluoromethyl)imidazoles.** *Collect Czech Chem Commun* (2002) **67**(9): 1335–1344.

[61] O'Hagan D, Schaffrath C, Cobb SL, Hamilton JTG, Murphy CD: **Biosynthesis of an organofluorine molecule.** *Nature* (2002) **416**(6878): 279.

[62] Deng H, O'Hagan D, Schaffrath C: **Fluorometabolite biosynthesis and the fluorinase from *Streptomyces cattleya*.** *Nat. Prod. Rep.* (2004) **21**(6): 773–784.

[63] O'Hagan D: **Recent developments on the fluorinase from *Streptomyces cattleya*.** *J Fluorine Chem* (2006) **127**(11): 1479–1483.

[64] Fujimori DG, Walsh CT: **What's new in enzymatic halogenations.** *Current Opin Chem Biol* (2007) **11**(5): 553–560.

[65] Deng H, Cobb SL, Gee AD, Lockhart A, Martarello L, McGlinchey RP, O'Hagan D, Onega M: **Fluorinase mediated C–^{18}F bond formation, an enzymatic tool for PET labelling.** *Chem Commun* (2006) (6): 652–654.

[66] Adams DJ, Clark JH: **Nucleophilic routes to selectively fluorinated aromatics.** *Chem Soc*

Rev (1999) **28**(4): 225–231.

[67] Horwitz JP, Tomson AJ: **Some 6-substituted uracils.** *J Org Chem* (1961) **26**(9): 3392–3395.

[68] Kiburis J, Lister JH: **Syntheses of 6-fluoropurine and 6-fluoropurine-9-β-D-ribofuranoside.** *J Chem Soc, Chem Commun* (1969) (8): 381.

[69] Barlin GB, Young AC: **Useful preparations involving the reactions of nucleophiles with some trimethylammonio-derivatives of nitrogen heterocycles.** *J Chem Soc, Perkin Trans 1* (1972) 1269–1272.

[70] Pike VW, Aigbirhio FI: **Reactions of cyclotron-produced [^{18}F]fluoride with diaryliodonium salts—a novel single-step route to no-carrier-added [^{18}]fluoroarenes.** *J Chem Soc, Chem Commun* (1995) (21): 2215–2216.

[71] Shah A, Pike VW, Widdowson DA: **The synthesis of [^{18}F]fluoroarenes from the reaction of cyclotron-produced [^{18}F]fluoride ion with diaryliodonium salts.** *J Chem Soc, Perkin Trans 1* (1998) (13): 2043–2046.

[72] Ermert J, Hocke C, Ludwig T, Gail R, Coenen HH: **Comparison of pathways to the versatile synthon of no-carrier-added 1-bromo-4-[^{18}F]fluorobenzene.** *J Labelled Compd Radiopharm* (2004) **47**(7): 429–441.

[73] Adams DJ, Clark JH, McFarland H: **The formation of 4,4'-difluorobenzophenone from 4,4'-dinitrodiphenylmethane.** *J Fluorine Chem* (1998) **92**(2): 127–129.

[74] Asahi Glass Co (Kumai S, Seki T, Wada A): **Preparation of fluorinated pyridines.** JP 04164068 (1992).

[75] Zhdankin VV: **Recent developments in the chemistry of polyvalent iodine compounds.** *Chem Rev* (2002) **102**(7): 1179–1182.

[76] Beringer FM, Brierley A, Drexler M, Gindler EM, Lumpkin CC: **Diaryliodonium salts. II. The phenylation of organic and inorganic bases.** *J Am Chem Soc* (1953): **75**(11): 2708–2712.

[77] Angelini G, Speranza M, Wolf AP, Shiue CY: **Nucleophilic aromatic substitution of activated cationic groups by ^{18}F-labeled fluoride. A useful route to no-carrier-added (NCA) ^{18}F-labeled aryl fluorides.** *J Fluorine Chem* (1985) **27**(2): 177–191.

[78] Ross TL, Ermert J, Hocke C, Coenen HH: **Nucleophilic ^{18}F-fluorination of heteroaromatic iodonium salts with no-carrier-added [^{18}F]fluoride.** *J Am Chem Soc* (2007) **129**(25): 8018–8025.

[79] Lam Y, Bobbio C, Cooper IR, Gouverneur V: **A concise synthesis of enantioenriched fluorinated carbocycles,** *Angew Chem Int Ed* (2007) **46**(27): 5106–5110.

[80] Davis FA, Zhou P, Murphy CK, Sundarababu G, Qi H, Han W, Przeslawski RM, Chen BC, Carroll PJ: **Asymmetric fluorination of enolates with nonracemic *N*-fluoro-2,10-camphorsultams.** *J Org Chem* (1998) **63**(7): 2273–2280.

[81] Shibata N, Suzuki E, Takeuchi Y: **A fundamentally new approach to enantioselective fluorination based on cinchona alkaloid derivatives/Selectfluor combination.** *J Am Chem Soc* (2000) **122**(43): 10728–10729.

[82•] Ishimaru T, Shibata N, Horikawa T, Yasuda N, Nakamura S. Toru T, Shiro M: **Cinchona alkaloid catalyzed enantioselective fluorination of allyl silanes, silyl enol ethers, and oxindoles.** *Angew Chem Int Ed* (2008) **47**(22): 4157–4161.

This paper describes the enantioselective fluorination of nucleophiles using a substoichiometric amount of chiral amine.

[83] Carroll L, McCullough S, Rees T, Claridge TDW, Gouverneur V: **Sterospecific *anti* S_E2' fluorination of allenylsilanes: synthesis of enantioenriched propargylic fluorides.** *Org Biomol Chem* (2008) **6**(10): 1731–1733.

[84] Grée D, Grée R: **A new strategy for the synthesis of optically active benzylic fluorides and corresponding five-membered heteroaromatic analogues.** *Tetrahedron Lett* (2007) **48**(31): 5435–5438.

[85] Frantz DE, Fassler, R, Carreira EM: **Facile enantioselective synthesis of propargylic alcohols by direct addition of terminal alkynes to aldehydes.** *J Am Chem Soc* (2000) **122**(8): 1806–1807.

[86] Anand NK, Carreira EM: **A simple, mild catalytic, enantioselective addition of terminal acetylenes to aldehydes.** *J Am Chem Soc* (2001) **123**(39): 9687–9688.

[87] Teare H, Robins EG, Årstad E, Luthra SK, Gouverneur V: **Synthesis and reactivity of [^{18}F]-*N*-fluorobenzenesulfonimide.** *Chem Commun* (2007) (23): 2330–2332.

[88•] Beeson TD, MacMillan DWC: **Enantioselective organocatalytic α-fluorination of aldehydes.** *J Am Chem Soc* (2005) **127**(24): 8826–8828.

This paper and ref 89 and 90 describe the enantioselective organocatalytic α-fluorination of aldehydes.

[89•] Marigo M, Fielenbach D, Braunton A, Kjærsgaard A, Jørgensen KA: **Enantioselective formation of stereogenic carbon–fluorine centers by a simple catalytic method.** *Angew Chem Int Ed* (2005) **44**(24): 3703–3706.

This paper and ref 88 and 90 describe the enantioselective organocatalytic α-fluorination of aldehydes.

[90•] Steiner DD, Mase N, Barbas III CF: **Direct asymmetric α-fluorination of aldehydes.** *Angew Chem Int Ed* (2005) **44**(24): 3706–3710.

This paper and ref 88 and 89 describe the enantioselective organocatalytic α-fluorination of aldehydes.

[91] Enders D, Hüttl MRM: **Direct organocatalytic α-fluorination of aldehydes and ketones.** *Synlett* (2005) (6): 991–993.

[92•] Hintermann L, Togni A: **Catalytic enantioselective fluorination of β-ketoesters**. *Angew Chem Int Ed* (2000) **39**(23): 4359–4362.

This paper describes the first transition-metal-catalyzed enantioselective electrophilic fluorination of carbonyl compounds.

[93] Pihko PM: **Enantioselective α-fluorination of carbonyl compounds: organocatalysis or metal catalysis?** *Angew Chem Int Ed* (2006) **45**(4): 544–547.

[94] Hamashima Y, Yagi K, Takano H, Tamas L, Sodeoka M: **An efficient enantioselective fluorination of various β-ketoesters catalyzed by chiral palladium complexes.** *J Am Chem Soc* (2002) **124**(49): 14530–14531.

[95] Ma JA, Cahard D: **Copper(II) triflate-bis(oxazoline)-catalysed enantioselective electrophilic fluorination of β-ketoesters.** *Tetrahedron: Asymmetry* (2004) **15**(6): 1007–1011.

[96] Shibata N, Ishimaru T, Nagai T, Kohno J, Toru T: **First enantio-flexible fluorination reaction using metal-bis(oxazoline) complexes.** *Synlett* (2004) (10): 1703–1706.

[97] Hewawasam P, Gribkoff VK, Pendri Y, Dworetzky SI, Meanwell NA, Martinez E, Boissard CG, Post-Munson DJ, Trojnacki JT, Yeleswaram K, Pajor LM, Knipe J, Gao Q, Perrone R, Starrett JE *Jr.*: **The synthesis and characterization of BMS-204352 (MaxiPost™) and related 3-fluorooxindoles as openers of maxi-K potassium channels.** *Bioorg Med Chem Lett* (2002) **12**(7): 1023–1026.

[98] Hamashima Y, Suzuki T, Takano H, Shimura Y, Sodeoka M: **Catalytic Enantioselective Fluorination of Oxindoles** . *J Am Chem Soc* (2005) **127**(29): 10164–10165.

[99] Shibata N, Kohno J, Takai K, Shimaru T, Nakmura S, Toru T, Kanemasa S: **Highly enantioselective catalytic fluorination and chlorination reactions of carbonyl compounds capable of two-point binding.** *Angew Chem Int Ed* (2005) **44**(27): 4204–4207.

[100] Adachi K, Ohira Y, Tomizawa G, Ishihara S, Oishi S: **Electrophilic fluorination with *N,N*'-**

difluoro-2,2'-bipyridinium salt and elemental fluorine. *J Fluorine Chem* (2003) **120**(2): 173–183.

[101] Davis FA, Han W, Murphy CK: **Selective, electrophilic fluorinations using *N*-fluoro-*o*-benzenedisulfonimide.** *J Org Chem* (1995) **60**(15): 4730–4737.

[102] Bryce MR, Chambers RD, Mullins ST, Parkin A: **Electrophilic fluorination of arylatrialkultin derivatives with caesium fluoroxysulphate.** *J Chem Soc, Chem Commun* (1986) (21): 1623–1624.

[103] Tius MA, Kawakami JK: **Vinyl fluorides from vinylstannanes.** *Synth Commun* (1992) **22**(10): 1461–1471.

[104] Stacey M, Tatlow JC, Sharpe AG (Ed): *Advances in Fluorine Chemistry*. Academic Pres, New York, NY, USA (1960).

[105] Banks RE, Tatlow JC: **A guide to Modern Organofluorine Chemistry.** *J Fluorine Chem* (1986) **33**(1-4): 227–346.

[106] Bailey J, Plevey RG, Tatlow JC: **Fluorinations with potassium tetrafluorocobaltate[III]. Part VIIII Fluorinations of toluene and of phenylacetic acid.** *J Fluorine Chem* (1988) **39**(1): 23–37.

[107] Subramanian MA, Manzer LE: **A greener synthetic route for fluoroaromatics via copper(II) fluoride.** *Science* (2002) **297**(5587): 1665.

[108] Janmanchi KM, Dolbier WR Jr: **Highly reactive and regenerable fluorinating agent for**

oxidative fluorination of aromatics. *Org Process Res Dev* (2008) **12**(2): 349–354.

[109] E.I.DU PONT DE NEMOURS AND COMPANY (Grushin V): **Processes for preparing fluoroarenes from haloarenes.** US-7202388 (2007).

[110] Grushin VV: **Palladium fluoride complexes: one more step toward metal-mediated C–F bond formation.** *Chem — Eur J* (2002) **8**(5): 1006–1014.

[111] Yandulov DV, Tran NT: **Aryl–fluoride reductive elimination from Pd(II): feasibility assessment from theory and experiment.** *J Am Chem Soc* (2007) **129**(5): 1342–1358.

[112] Grushin VV, Marshall WJ: **Ar–F reductive elimination from Palladium(II) revisited.** *Organometallics* (2007) **26**(20): 4997–5002.

[113•] Hull KL, Anani WQ, Sanford MS: **Palladium-catalyzed fluorination of carbon–hydrogen bonds.** *J Am Chem Soc* (2006) **128**(22): 7134–7135.

This paper describes the first palladium catalyzed fluorination of an arene.

[114] Kaspi AW, Yahav-Levi A, Goldberg I, Vigalok A: **Xenon difluoride induced aryl iodide reductive elimination: a simple access to difluoropalladium(II) complexes**. *Inorg Chem* (2008) **47**(1): 5–7.

[115•] Furuya T, Kaiser HM, Ritter T: **Transition-metal-mediated carbon–fluorine bond formation.** *Angew Chem Int Ed* (2008) *in press.*

This paper describes a general fluorination of boronic acids via stoichiometric palladium complexes.

[116] Furuya T, Ritter T: **Carbon–fluorine reductive elimination from high-valent palladium fluorides.** *Manuscript submitted*.