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C–F Bond Formation for the Synthesis of Aryl Fluorides

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Abstract

A selection of carbon–fluorine bond-forming reactions is presented with particular focus on transition metal-mediated fluorination. A brief summary of conventional fluorination reactions is followed by a discussion of fluorination reactions mediated by palladium and silver. Investigations into the mechanism as well as the conceptual difficulty associated with transition metal-mediated carbon–fluorine bond formation are presented.

Keywords

carbon–fluorine bond formation; transition metals; palladium; silver; catalysis

1 Introduction

Fluorinated molecules are valuable as pharmaceuticals,[1] agrochemicals,[2] tracers for positron emission tomography (PET),[3] and new materials.[4] The introduction of fluorine into organic molecules can affect the basicity and acidity of proximal functional groups, the dipole moment, and hydrogen bonding ability.[5] In pharmaceuticals, fluorine is often introduced to increase lipophilicity, bioavailability, and metabolic stability.[3a,6] The size of fluorine as a substituent is similar to a hydroxyl group (van der Waals radii: F: 1.47 Å; OH 1.40 Å; compare to H: 1.20 Å). The radioisotope ^{18}F has a half-life of 110 minutes and is used in PET for the synthesis of ^{18}F-PET tracers. Despite the utility of fluorine substituents, relatively few methods are available for selective carbon–fluorine bond formation,[7] when compared to methods for other carbon–halogen bond formations.

Recently, much progress has been made in C_{sp^3}–F bond formation including the asymmertric α-fluorination of carbonyl compounds with organo-[8] and metal[9] catalysis. However, the general construction of C_{sp^2}–F bonds, especially aromatic carbon–fluorine bonds, in functionalized molecules remains an unsolved problem in organic chemistry. The transition metals copper, palladium, and silver have been used for aromatic carbon–fluorine bond formations.[10] This review discusses state-of-the-art aromatic carbon–fluorine bond formation reactions with particular focus on recently emerged transition metal-mediated approaches. A brief outline of classical methods of aromatic carbon–fluorine bond formation reactions is presented, followed by a discussion of novel fluorination reactions mediated by palladium and silver.

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2 Nucleophilic Fluorination

Nucleophilic aromatic substitution reactions can introduce fluorine atoms into electron-deficient arenes. A common method for the synthesis of fluorinated aromatics in industry is the Halex (halogen exchange) process, in which halogen atoms serve as leaving groups and inexpensive, inorganic fluoride sources such as spray-dried KF are used as nucleophiles.[11] The rate-determining step in nucleophilic aromatic fluorination by substitution, including the Halex process, is the addition of fluoride to form a Meisenheimer complex. Therefore, aryl chlorides are more suitable substrates in the Halex process than the corresponding aryl bromides and iodides, because chlorine is more electronegative than bromine and iodine. High reaction temperatures and phase transfer catalysts can increase the efficiency of the Halex process due to increased solubility of fluoride (Scheme 1).

A useful alternative to the Halex process is fluorodenitration, a process in which the nitro group functions as a leaving group.[11a,12] The nitro group is often displaced preferentially in the presence of chloride substituents, presumably because the Meisenheimer complex derived from attack at the carbon bearing the nitro group is more stabilized (Scheme 2).[13]

Ammonium substituents can also be appropriate leaving groups for nucleophilic fluorination reactions and are often used for the introduction of radio labeled fluoride ($^{18}F^-$). Trimethylammonium groups are typically more electron-withdrawing than nitro groups and undergo nucleophilic aromatic fluorination more efficiently than nitroarenes (Table 1).[14]

Fluorination of diaryliodonium salts[15] was reported by Beringer in 1953.[16] In 2007, Ross used aryl(2-thienyl)iodonium salts for nucleophilic introduction of fluorine-18 to control the regioselectivity of fluoride attack.[17] Notably, arenes that do not possess electron-withdrawing groups were also successfully fluorinated (Scheme 3).

Tetrabutylammonium fluoride (TBAF) is a common fluorinating reagent that is available as a trihydrate. Tetraalkylammonium counterions for fluoride reduce the ionic bond strength and increases the solubility of fluoride salts in organic solvents.[18] The presence of water reduces the nucleophilicity of fluoride by hydrogen bonding. Drying of most quaternary ammonium fluorides by heat is problematic due to competing E2-elimination (Hofmann elimination) with fluoride serving as a strong base under anhydrous conditions (Scheme 4, top).[19] In 2005, DiMagno reported the preparation of anhydrous tetrabutylammonium fluoride ($TBAF_{anh}$) from hexafluorobenzene and tetrabutylammonium cyanide (Scheme 4, bottom).[20]

The Halex processes and fluorodenitration reactions can proceed at lower temperatures with $TBAF_{anh}$ as the fluoride source. For example, a typical Halex fluorination of 2,6-dichloropyridine requires heating at 200 °C for 10 hr (Scheme 5, top).[21] In comparison, the same substrate is fluorinated within 1.5 hr upon exposure to $TBAF_{anh}$ at 20 °C (Scheme 5, bottom).[22]

In 2008, the synthesis of fluoroarenes from unactivated haloarenes upon treatment with tetramethylammonium fluoride (TMAF) was reported by Grushin.[23]

Fluorobenzene could be prepared in 65% yield from bromobenzene (Scheme 6). The fluorination of 2-bromonaphthalene resulted in a 3:2 mixture of 2-fluoronaphthalene and 1-fluoronaphthalene. The observed regioselectivity is consistent with the formation of an aryne intermediate. Elimination to form an aryne demonstrates the high basicity of fluoride in an anhydrous solvent ("naked" fluoride[24]). It has been shown that "naked" fluoride can deprotonate DMSO to form HF,[23] which can be problematic because the in situ generated HF quickly consumes another equivalent of fluoride to form bifluoride (FHF^-), which is less nucleophilic than fluoride.

3 Electrophilic Fluorination

Electron-rich arenes react with electrophilic fluorinating reagents but the regioselectivity is typically low (Scheme 7).[25] Common organometallic reagents such as organomagnesiums or organolithiums can afford regio-specific fluorination with electrophilic fluorinating reagents, though the fluorination yield is highly dependent on the substrate.[26]

In 2010, Beller reported improved reaction conditions for the electrophilic fluorination of Grignard reagents (Table 2).[27] The Beller conditions are especially useful for the fluorination of electron-rich aryl Grignard reagents.

In 2010, Knochel reported an improved procedure for the electrophilic fluorination of aryl- and heteroarylmagnesium reagents (Table 3).[28] Knochel's conditions are particularly convenient for the fluorination of a variety of heteroarenes including isoquinolines, pyrroles, pyridines, benzothiophenes, and furans.

Organometallics with lower basicity and therefore larger functional group tolerance than Grignard reagents such as arylzinc halides, arylsilanes, arylstannanes, arylgermaniums and arylboronic acids can be converted into fluorinated arenes. However, they usually require reactive electrophilic fluorinating reagents such as elemental fluorine, XeF_2, or AcOF for successful fluorination,[29] or are limited to electron-rich arenes (Table 4).[30]

Electrophilic fluorination of arylsilanes with *N*-fluoro reagents gives aryl fluorides in low yields (Table 5).[31] Therefore, the use of highly reactive electrophilic reagents is required. For example, XeF_2 can be used to fluorodesilylate aryltrimethylsilanes in C_6F_6 at 18 °C in 61–86% yield.[32]

A successful example of fluorodestannylation is the preparation of 6-fluoro-*L*-DOPA.[33] Treatment of the trimethylarylstannane with elemental fluorine allowed for the regioselective introduction of fluorine (Scheme 8). This strategy allows for the preparation of the [^{18}F]-analogue (25% radiochemical yield), which is a PET-tracer for Parkinson's disease[34a] and has been used in oncology.[34b]

4 Balz-Schiemann Reaction

A special class of nucleophilic aromatic fluorination reactions is the Balz-Schiemann reaction (Scheme 9).[35] In the Balz-Schiemann reaction, aryl fluorides are formed by pyrolysis (typically 110–170 °C) of aromatic diazonium tetrafluoroborates ($ArN_2^+BF_4^-$).

Diazotization of an aniline in the presence of hydrogen tetrafluoroborate (HBF_4) followed by either thermal or photochemical decomposition of the resulting diazonium tetrafluoroborate affords the aryl fluoride. Yields can often be improved when hexafluorophosphates (PF_6^-) or hexafluoroantimonates (SbF_6^-) are used instead of tetra-fluoroborates (Table 6).[36]

Alternative approaches include diazotization with $NOBF_4$ followed by in situ fluorodediazoniation, which provided improved yields and broader substrate scope (Table 7).[37]

Other variations involve fluorodediazoniation in HF/pyridine and in $BF_3{\cdot}Et_2O$,[38] the use of triazenes in HF/pyridine as precursors to aryldiazonium salts,[39] and fluorodediazoniation in ionic liquids.[40]

5 Palladium-Mediated C–X Bond Formation

Transition metals, especially palladium, have been widely used for carbon–heteroatom bond formation reactions including C–O, C–N, C–S, and C–P bonds.[41] Despite efforts in the last decades, only recently have successful transition metal-mediated C–F bond formations been achieved.[42] In this chapter, the general considerations for carbon–heteroatom bond formations are discussed. Chapter 5 introduces concepts regarding general features of C–X bond-forming reactions, with a focus on hypotheses on why C–F bond formation is difficult. We subsequently discuss transition metal-mediated nucleophilic and electrophilic fluorination reactions in chapters 6–9.

A series of studies from the Hartwig group, the Buchwald group, and others have shown that reductive elimination to form carbon–heteroatom bonds occurs more rapidly from complexes with more nucleophilic heteroatoms.[43] The rate of reductive eliminations to form C–X bonds from arylpalladium(II) amido, alkoxo, thiolato, and phosphido complexes that contain similar substituents on the heteroatoms occur in the order C–P > C–S > C–N > C–O as shown in Scheme 10.

Reductive elimination from the alkylamido complex shown is faster than reductive elimination from an analogous arylamido complex, which is faster than reductive elimination from the corresponding diarylamido complex.[44] Recently, it has been shown that arylpalladium amidate complexes undergo reductive elimination more slowly than the diarylamido complexes (Scheme 11).[45]

With increasing nucleophilicity of the heteroatom, reductive elimination becomes faster, presumably due to a more favorable attack of the electron pair onto the ipso carbon of the aryl group in the transition state (π effect).[46] Alternatively, faster reductive elimination may be attributed to a decrease in the polarity, and thereby bond strength, of the metal–heteroatom bond. In the absence of steric or mesomeric effects, increased polarity of a metal–heteroatom bond typically leads to increased bond strength due to stronger ionic contribution to the bond energy (σ effect). A comparison between the electronic effects on the rate of reductive elimination from arylpalladium amido and amidate complexes (Scheme 11) with those on the rate of reductive elimination from arylpalladium alkyl complexes (Scheme 12)[47] helps to elucidate the potential contributions of the σ and π effects.

Studies on the rates of reductive elimination from arylpalladium alkyl complexes containing varying functional groups on the carbon (R) are shown in Scheme 12. Reductive elimination from the arylpalladium alkyl complexes occurs more slowly from the alkyl complexes containing an electron-withdrawing group on the R carbon. Because the arylpalladium alkyl complexes lack lone pair electrons on the alkyl carbon bound to the metal, only the σ effect need be considered.

Fluorine is the most electronegative element, which should result in metal–fluorine bond energies with a large ionic contribution that lead to slower reductive elimination. Likewise, for the anions in the series C, N, O, F, fluorine is the least nucleophilic atom. Both properties of fluorine may explain why C–F reductive elimination is so challenging when compared to other carbon–heteroatom bond formations. In fact, despite significant research, a well-defined C–F reductive elimination reaction to form an aryl fluoride was reported only in 2008.[48] In 2009, Buchwald reported C–F reductive elimination from a palladium(II) complex utilizing a bulky monodentate phosphine ligand, BrettPhos.[49]

6 Palladium-Mediated Nucleophilic Fluorination

A general scheme of palladium-catalyzed nucleophilic fluorination is shown in Scheme 13. Oxidative addition of an aryl halide or triflate to palladium(0) followed by ligand exchange with fluoride (F^-) provides an arylpalladium(II) fluoride complex, which undergoes C–F bond formation via reductive elimination.

Oxidative addition of aryl halides and pseudohalides to palladium(0) is well established.[50] Grushin showed that halide to fluoride exchange is possible to make arylpalladium(II) fluoride complexes.[51] Spectroscopic evidence has been reported[52] for the formation of $[(Et_3P)_3Pd^{II}F]^+$ in solution, although the complex was never isolated, likely due to its rapid decomposition by an intramolecular redox process to produce $[(Et_3P)_nPd^0]$ and Et_3PF_2.[52b, 53] The redox reaction Pd(II)/P(III)→ Pd(0)/P(V)[53] may be the reason that complexes of the type $[(R_3P)_2Pd^{II}F_2]$ have not yet been prepared, while several corresponding chloro, bromo, and iodo analogues are stable and well-known.

Grushin has developed two methods for the preparation of palladium(II) fluoride complexes. The reaction of organopalladium hydroxides with $Et_3N{\cdot}(HF)_3$ (TREAT HF) in the presence of a free phosphine results in the formation of mononuclear fluoride complexes (Scheme 14, top).[54] Alternatively, palladium(II) fluoride complexes can be prepared by I/F ligand exchange with AgF in benzene[54] or toluene[55] in the presence of ArI (5–10 mol%) (Scheme 14, bottom).

The palladium fluoride $[(Ph_3P)_2Pd^{II}(Ph)(F)]$ is stable in the solid state and in anhydrous solution.[51] NMR analysis of wet solutions, however, suggested that water may facilitate cleavage of the Pd–F bond as shown in Scheme 15.[56] While reversible, ionization could be problematic for synchronous C–F reductive elimination.

The thermal decomposition of $[(Ph_3P)_2Pd^{II}(Ph)(F)]$ in anhydrous toluene at 110 °C was slow, and no C–F reductive elimination products were observed. Instead, P–F, P–P, and C–C bond formation products were formed (Scheme 16, top).[57] In addition, mechanistic studies of the thermal decomposition of $[(Ph_3P)_2Pd^{II}(Ph)(F)]$ and $[(Ph_3P)_2Pd^{II}(C_6D_5)(F)]$ established reversible C–P oxidative addition/reductive elimination that results in scrambling of the phenyl groups on the phosphine ligand and the aryl group on the palladium (Scheme 16, bottom).

Arylpalladium(II) fluoride complex **1** features a Xantphos ligand,[58] a bidentate phosphine ligand with a large bite angle that is known to facilitate reductive elimination.[59] The trifluoromethyl complex **2** successfully afforded C–CF_3 bond formation in quantitative yield upon heating in anhydrous benzene at 80 °C for 3 hr. However, thermolysis of the fluoride complex **1** in anhydrous benzene at 60 °C led only to P–F bond formation and no C–F reductive elimination (Scheme 17).

In an attempt to avoid competing P–F bond formation, arylpalladium(II) complex **3**, which lacks phosphine ligands, was synthesized.[60] Thermal decomposition of **3** and **4** in anhydrous benzene at 80 °C did not result in C–F bond formation. Palladium black and the C–C bond formation product biphenyl were produced instead, along with palladium(II) difluoride complex **4** (Scheme 18).

In 2007, Yandulov reported a computational analysis on C–F reductive elimination from arylpalladium(II) fluorides.[61] Yandulov explored *N*-heterocyclic carbenes (NHC)[62,63] and phosphines as auxiliary ligands.

Potential C–F reductive elimination from T-shaped $(PMe_3)Pd^{II}(Ph)F$ (**5**) was computed. The activation enthalpy for Ph–F bond formation was predicted to be $\Delta H^{\ddagger}$ = 25.1 kcal/mol; however, reversible migration of the phenyl group to the phosphine ligand, as observed by

Grushin, had a lower activation enthalpy of $\Delta H^{\ddagger}$ = 21.1 kcal/mol. Moreover, dimerization of **5** to form **6** was computed to be exothermic by ΔH° = 21.8 kcal/mol (Scheme 19).

A four-coordinate palladium fluoride complex would avoid dimer formation; however, the enthalpy of activation for C–F reductive elimination from four-coordinate complex [$(Me_3P)_2Pd^{II}(Ph)(F)$] (**7**) was predicted to be 38.8 kcal/mol, which is too high for practical synthetic applications (Scheme 20).

Yandulov's calculations predicted that in the related tricoordinate NHC complex **8** reductive elimination of Ar–F is more facile for electron-withdrawing substituents, similar to related carbon–heteroatom reductive elimination reactions[64] and nucleophilic aromatic substitution reactions (Scheme 21).[65]

Yandulov further performed calculations on the effect of the presence of a hydrogen bond donor and found that hydrogen bonding stabilized the starting material more than the transition state (Scheme 22).

Yandulov's calculations predicted that 1) NHC ligands would undergo unproductive C–C reductive elimination preferentially over C–F reductive elimination, 2) palladium complexes with phosphines would have lower activation barriers than those with NHC ligands, 3) C–F reductive elimination from a four-coordinate bisphosphine complex would have a high activation barrier, 4) electron-withdrawing groups on the aryl substituent would decrease the TS energy, and 5) presence of hydrogen bond donors would increase the activation barrier.

Yandulov proposed that destabilization of a palladium fluoride dimer such as **6** by bulky ligands should increase the concentration of the three-coordinate arylpalladium(II) fluoride complex that could undergo C–F reductive elimination. Arylpalladium(II) fluoride dimer **9** features an electron-withdrawing aryl group and a bulky phosphine ligand P(*t*-Bu)$_3$. Complex **9** did not afford any C–F bond formation product upon thermolysis at 60 °C for 160 hr; however, upon addition of the bulky phosphine ligand *t*-BuXPhos, developed by Buchwald and shown to mediated various carbon–heteroatom bond formations including C–O bonds,[66] circa 10% of C–F bond formation was observed after 22 hr at 60 °C (Scheme 23).

The first observation of Ar–F bond formation from an arylpalladium(II) fluoride complex was a significant and promising result. Conclusive evidence for concerted C–F reductive elimination was not obtained. In 2007, Grushin proposed the possibility of C–P reductive elimination with subsequent nucleophilic aromatic fluorination to account for Yandulov's observation of C–F bond formation in 10% yield (Scheme 24).[67] As of yet, the mechanism of Yandulov's C–F bond formation remains unknown.

In 2009, Buchwald communicated the first palladium-catalyzed nucleophilic aromatic fluorination as well as C–F reductive elimination from a palladium(II) complex.[49] Key to the successful reaction was the use of the recently developed bulky monodentate phosphine ligand BrettPhos[68] and its *t*-butyl derivative that afford mononuclear, tricoordinate Pd(II) complexes (Figure 1).

$ArPd^{II}(X)(L)$ (L = Buchwald's 2-biphenylphosphine ligand) are known to exist in a T-shaped three-coordinate structure where the fourth coordination site is occupied by the biphenyl moiety of the phosphine ligand (Scheme 25, left).[69] When monomeric three-coordinate palladium(II) bromide complex **10** was treated with AgF, the corresponding three-coordinate palladium(II) fluoride complex **11** was obtained and its solid state structure was confirmed by X-ray crystallography. Upon thermolysis of **11** in toluene at 100 °C for 2 hr, C–F bond formation occurred in 15 to 25% yield (Scheme 25, right).

The palladium byproduct of the reaction shown in Scheme 25 was not identified, presumably due to its instability and high reactivity. However, when complex **11** was thermally decomposed in the presence of excess aryl bromide, formation of complex **10** was confirmed by ^{31}P NMR, which suggests the intermediacy of a Pd(0) complex upon C–F bond formation (Scheme 26). In the solid state structure of **11**, the phosphine ligand and the fluoride ligand occupy mutually *trans* coordination sites, likely due to the strong *trans*-influence of the σ-aryl ligand.[70] This *trans* relationship between the phosphine ligand and the fluoride might be responsible for the successful C–F reductive elimination over the competing P–F reductive elimination, which was observed for other palladium(II) fluoride phosphine complexes.[71]

Buchwald successfully extended the stoichiometric reaction to catalysis and used the stable palladium(0) precursor [(cinnamyl)Pd^{II}Cl]$_2$, the sterically demanding *t*-BuBrettPhos, and CsF. The substrate scope of the catalytic fluorination is shown in Scheme 27. Electron-rich, electron-poor, *ortho*, *ortho*-disubstituted arenes, as well as heterocycles were compatible with the reaction conditions. Substrates with protic functional groups were not demonstrated to undergo fluorination, presumably due to the high basicity of fluoride under anhydrous conditions. The reactions are carried out with rigorous exclusion of moisture.

For most of the substrates only small amounts (up to 4%) of protodetriflated products (Ar–H) were obtained, which is advantageous for purification because the protodetriflated products typically have similar physical properties (R_f value, boiling point) to the corresponding fluorinated products. The intriguing formation of regioisomers was observed when *para* electron-donating or *meta* electron-withdrawing groups were present (Scheme 28).

The mechanism for the formation of the regioisomers is not yet elucidated; however, it was rationalized that attack of a fluoride anion to the in situ formed benzyne is unlikely because the observed selectivities of regioisomers were distinct from those reported for the benzyne process reported by Grushin (Scheme 29).[23]

7 Palladium-Mediated Directed Electrophilic Fluorination

A general pathway for palladium-mediated directed electrophilic fluorination is shown in Scheme 30. A palladium(II) complex undergoes cyclometallation followed by electrophilic fluorination resulting in regiospecific fluorination of the arene.

In 2006, the first palladium-catalyzed fluorination of phenylpyridine derivatives was reported by Sanford.[72] Sanford pioneered palladium-catalyzed oxidative C–H functionalization of arenes that bear *ortho*-directing groups[73] and extended the methodology to electrophilic fluorination. Phenylpyridines with electron-donating and electron-withdrawing groups were fluorinated in the presence of 10 mol% of Pd(OAc)$_2$ and *N*-fluoropyridinium tetrafluoroborate in 33–75% yield under microwave irradiation (Table 8).

The development of the first palladium-catalyzed aromatic fluorination reaction was a significant advance in this research area. Challenges that remain are the harsh reaction conditions (microwave, reaction temperature of 150 °C), the necessity for *ortho*-directing groups, and the need for blocking groups in the *ortho*' or *meta*' position to avoid difluorination (Scheme 31).

In 2009, Yu reported a similar palladium-catalyzed directed electrophilic fluorination of C–H bonds of *N*-benzyltriflamide derivatives (Table 9).[74]

The use of *N*-fluoro-2,4,6-trimethylpyridinium triflate, Pd(OTf)$_2$·2H$_2$O, and NMP (*N*-methylpyrrolidinone) was important for obtaining the aryl fluorides in high yields. The reaction reported by Yu employed milder reaction conditions than those reported by Sanford, but the

necessity of an *ortho*-directing group and *ortho*' or *meta*' blocking groups remained. A major advantage of Yu's fluorination reaction is the identity of the directing group; the triflamide can be readily converted into other functional groups (Scheme 32).[75] The mechanism of the directed electrophilic fluorination has not been established and fluorination from Pd(II), Pd(III),[76] and Pd(IV)[77] intermediates are conceivable.

8 Pd-Mediated Electrophilic Fluorination

A general scheme of palladium-mediated electrophilic fluorination without directing groups is described in Scheme 33. The carbon–palladium bond is introduced by transmetalation rather than cyclopalladation as discussed above. The potential substrate scope is therefore significantly larger than for directed fluorination reactions because directing groups are not required. However, substrates need to be pre-functionalized to introduce appropriate functionality for transmetalation. Oxidation of an arylpalladium(II) complex with an electrophilic fluorinating reagent (F^+) can provide a high-valent arylpalladium complex that subsequently can afford C–F bond formation by reductive elimination.

In 2008, Vigalok reported a study on reactivity of arylpalladium(II) complexes toward electrophilic fluorinating reagents.[78] Vigalok observed a C–F bond forming reaction from a palladium(II) complex that possesses a monodentate aryl group. Upon treatment with the electrophilic fluorinating reagent *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate, aryl fluoride was obtained in circa. 10% yield (Scheme 34). Both electrophilic cleavage of the Pd–C bond with the electrophilic fluorinating reagent and a C–F reductive elimination from a Pd(IV) complex are potential mechanisms for this transformation.

In 2009, Sanford reported fluorination of arylpalladium(II) complex **12** upon treatment with the strong electrophilic fluorinating agent XeF_2 (Scheme 35).[79] When the reaction was stopped after 2.5 min, the intermediate arylpalladium(IV) trifluoride complex **13** was isolated. Complex **13** did not undergo C–F bond formation by reductive elimination, but gave C–F bond formation upon addition of oxidants such as XeF_2, $(PhSO_2)_2NF$, and *N*-bromosuccinimide in high yield. The mechanism of C–F bond formation has not yet been established.

In 2008, fluorination of arylboronic acids via stoichiometric palladium complexes was reported by our group.[80] An electron-poor sulfonamide ligand was introduced via nitrene insertion to benzo[*h*]quinoline palladium chloride dimer complex **18** (Scheme 36).[81] Chloro palladium complex **19** did not undergo transmetalation with arylboronic acids. The acetate analogue **20**, however, smoothly afforded the corresponding arylpalladium complex **21** in 65–91% yield when treated with a variety of functionalized arylboronic acids. The arylpalladium complexes derived from **21** are stable to moisture and air, and readily purified by column chromatography on silica gel.

Fluorination of arylpalladium complexes **21** using the electrophilic reagent F-TEDA-BF_4 (**22**) afforded the corresponding aryl fluorides **23a**–**h** regioselectively in 31–82% yield (Table 10). The scope of the reaction is large and a variety of functional groups can be tolerated; however, palladium is used in stoichiometric quantities.

Under the reaction conditions that afforded fluorination products **23a**–**h**, a high-valent palladium fluoride was not observed by NMR analysis. We sought to design an analogue of **23** that upon oxidation and formation of a putative high-valent palladium fluoride would exhibit higher stability than the presumed intermediate generated by fluorination of **21**. Rigid ligands have been shown to stabilize high-valent metal centers including palladium(IV) intermediates.[82] We therefore targeted the benzo[*h*]quinoline derivative **24** (Scheme 37). Treatment of benzo[*h*]quinoline palladium acetate dimer **25** with one equivalent of pyridine-sulfonamide ligand **26** in CH_2Cl_2 at 23 °C afforded arylpalladium complex **24** in 95% yield.[48]

Fluorination of **24** in acetonitrile at 50 °C afforded 10-fluorobenzo[*h*]quinoline (**30**) in 94% yield (Scheme 38). Moreover, a deep purple, well-defined intermediate **27** was spectroscopically observed at 23 °C. The pyridine complex **28** was significantly more stable than **27** and afforded C–F bond formation product in 90% yield. When **27** was treated with tetramethylammonium fluoride tetrahydrate (TMAF·4H_2O) at 23°C, palladium(IV) difluoride **29** was obtained. The neutral palladium di-fluoride **29** was more stable than monofluorides **27** and **28**, and the solid state structure of **29** was identified by X-ray crystallography. Complex **29** afforded **30** by reductive elimination in 97% yield when heated in DMSO at 150 °C for 10 min. Reductive elimination from compounds **27**–**29** were the first established examples of C–F reductive elimination to form aryl fluorides from transition metal complexes.

In 2010, the first mechanism study of C–F reductive elimination reactions from arylpalladium (IV) fluoride complexes was reported with particular focus on the C–F reductive elimination from **27**.[83] The C–F reductive elimination from **27** showed first-order kinetics. The proposed mechanism of C–F reductive elimination is shown in Scheme 39 and is based on activation parameters, rate dependence on the polarity of the reaction medium, Hammett analysis, and DFT calculations (Figure 2).

The mechanism study confirmed that C–F reductive elimination proceeds efficiently from arylpalladium(IV) fluoride complexes, supported by pyridyl-sulfonamide ancillary ligands. It was proposed that the pyridyl-sulfonamide ligand plays a crucial role for facile and efficient C–F bond formation. The ability of the pyridyl-sulfonamide ligand to function as a bidentate-tridentate-bidentate coordinating ligand during oxidation and reductive elimination, combined with the appropriate electronic requirements of the sulfonamide to position the aryl substituent *trans* to the sulfonamide ligand in the Pd(II) complex and the fluoride ligand *trans* to the sulfonamide ligand in the Pd(IV) complex, may be the reasons for facile C–F bond formation (Scheme 40).

9 Silver-Mediated Fluorination

Ag-catalyzed reactions have emerged as important synthetic methods for a variety of organic transformations[84] including halogenations of terminal alkynes, additions of OH or NH groups[85] across allenes, alkynes or alkenes, group transfer reactions[86] of carbenes, nitrenes, or silylenes, C–H insertion reactions,[87] enantioselective carbonyl/imine addition reactions such as Mukaiyama-Aldol reaction,[88] Mannich reaction,[89] or allylation reactions,[90] and decarboxylation reactions.[91]

In 2009, we reported silver-mediated C–F bond formation.[92] Encouraged by a literature report of facile transmetalation from arylstannanes to silver(I) nitrate, known for almost 100 years, [93] silver-mediated fluorination was developed. Arylstannanes afford the corresponding aryl fluorides when reacted with F-TEDA-PF_6 in the presence of 2.0 equiv of AgOTf in acetone within 20 min (Scheme 41). The silver-mediated fluorination tolerates electron-rich, electron-poor, *ortho*, *ortho*-disubstituted, and heterocyclic aromatics, as well as protic functional groups. The fluorination was applicable to functionalized biologically active molecules such as camptothecin and quinine, enabling access to complex aryl fluorides.

Nucleophilic functional groups such as amines and sulfides were not compatible with the fluorination reaction conditions because they react with F-TEDA-PF_6 to form *N*-fluoro or *S*-fluoro compounds which, if appropriately positioned β-hydrogen atoms are present, eliminate hydrogen fluoride (Scheme 42). Although the yields for this reaction are uniformly high, 10–20% of the corresponding protodestannylated products were observed. Recently, a catalytic version of the silver-mediated fluorination reaction has been developed by our group.[94]

In 2009, the silver-mediated fluorination reaction was extended to arylboronic acids and their derivatives.[95] Boronic acid derivatives are versatile, virtually non-toxic, commercially available in great diversity, and readily prepared.[96] Upon addition of NaOH in methanol, arylboronic acids underwent transmetalation to Ag(I) to afford the corresponding arylsilver complexes. After methanol evaporation and dissolving the reaction mixture in acetone, fluorination was achieved (Scheme 43).

The substrate scope of the silver-mediated one-pot fluorination of arylboronic acids is shown in Table 11. Electron-rich (**28a**, **28d**), electron-poor (**28c**, **28e**), protic (**28a**, **28b**), halogenated (**28e**), *ortho*, *ortho*-disubstituted (**28d**) arenes, as well as heterocycles (**28f**–**28h**) were fluorinated successfully. The stoichiometric accumulation of the thermally unstable arylsilver complex proved increasingly problematic for complex molecules, limiting the utility of the silver-mediated fluorination of boronic acids. Importantly, only trace amounts of proto-deborylation were observed during this process.

The postulated mechanism for the silver-mediate fluorination involves a high-valent silver species from which C–F reductive elimination can occur.

10 Conclusion

Carbon–fluorine bond formation for the synthesis of aryl fluorides is challenging by conventional synthesis and transition metal-mediated transformations. The properties of fluorine, such as high electronegativity, high reactivity of F_2, and the high basicity of naked fluoride are responsible for the difficulties associated with C–F bond formation. Carbon–fluorine reductive elimination from transition metal complexes is more challenging than C–C, C–N, and C–O reductive eliminations, presumably due to the strong ionic contribution of transition metal–fluorine bonds, which increase metal–fluorine bond strength and result in basic fluoride ligands that can form bifluorides.

Significant advances in transition metal-mediated fluorination reactions have been reported in the past five years. Palladium-catalyzed cross coupling chemistry was extended to C–F bond formation by the Buchwald group. Pd(0)/(II)-catalyzed nucleophilic fluorination has been a sought after reaction and can access fluoroarenes from aryl triflates. Current challenges include anhydrous reaction conditions that render the naked fluoride ion basic, which so far has prevented the fluorination of substrates with protic functional groups. The directed electrophilic palladium-catalyzed fluorination reactions developed by Sanford and Yu can fluorinate C–H bonds directly if appropriate directing groups are present. The palladium and silver-mediated fluorination reactions developed by our group have a broader substrate scope, likely due to the milder reaction conditions, but the palladium-mediated fluorination reaction currently requires stoichiometric amounts of transition metal.

Acknowledgments

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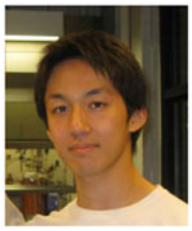
Biographies



Takeru Furuya was born in 1983 in Tokyo, Japan. He received his undergraduate chemistry degree in 2006 at Tokyo University where he conducted research on a total synthesis of (−)-Tetrodotoxin under Prof. Tohru Fukuyama. He then moved to Harvard University in 2006 for graduate study with Prof. Tobias Ritter, where he is currently pursuing graduate work on transition-metal-mediated aromatic C–F bond formation. He is expected to obtain a Ph.D. degree in 2010 and will join the Du Bois group at Stanford University.

Johannes Klein was born in 1985 in Wuppertal, Germany. He received his undergraduate degree in 2007 from the Dortmund University of Technology. He then moved to University College Dublin where he worked on heterocyclic chemistry under the guidance of Dr. P. Evans and obtained his M.Sc. in 2009. He then joined the Ritter lab as a visiting scholar and worked on silver-mediated fluorination reactions and mechanistic studies on bimetallic palladium catalysis for 6 months. He has now moved to the University of York where he started working towards his Ph.D. under the supervision of Prof. Taylor.

Tobias Ritter was born in 1975 in Lübeck, Germany. He received his undergraduate education in Braunschweig, Germany, Bordeaux, France, Lausanne, Switzerland, and Stanford, US, and received a master of science from Braunschweig University in 1999. He conducted undergraduate research with Prof. Barry M. Trost at Stanford, obtained his PhD with Prof. Erick M. Carreira at ETH Zurich in 2004, and was a postdoc with Prof. Robert H. Grubbs at Caltech. In 2006, Tobias was appointed as Assistant Professor in the Department of Chemistry and Chemical Biology at Harvard. His research program is based on synthetic organic and organometallic chemistry. The Ritter lab currently focuses on fluorination chemistry for late-stage functionalization of complex natural and unnatural products and bimetallic transition metal redox catalysis.

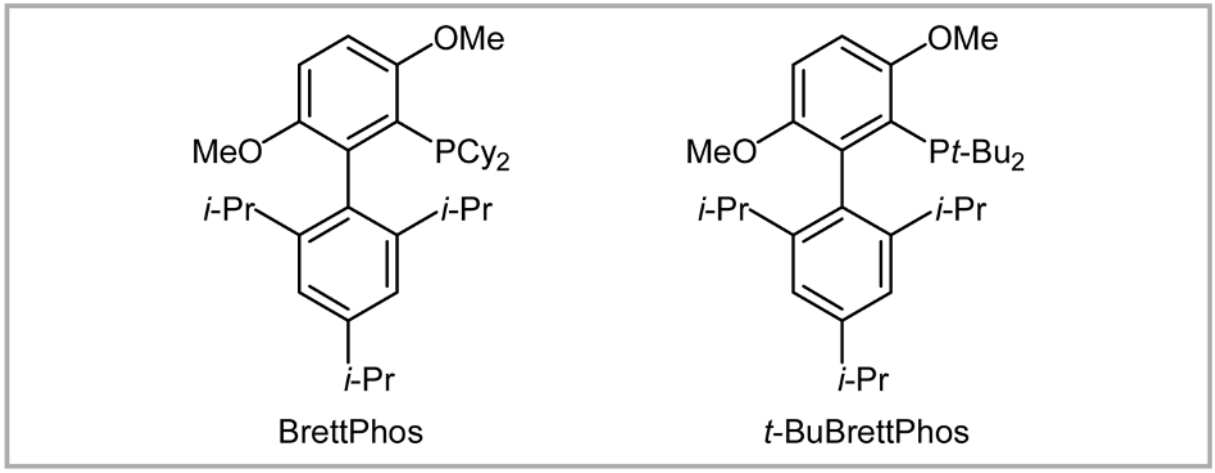


Figure 1.
Structure of BrettPhos and its *t*–butyl derivative.

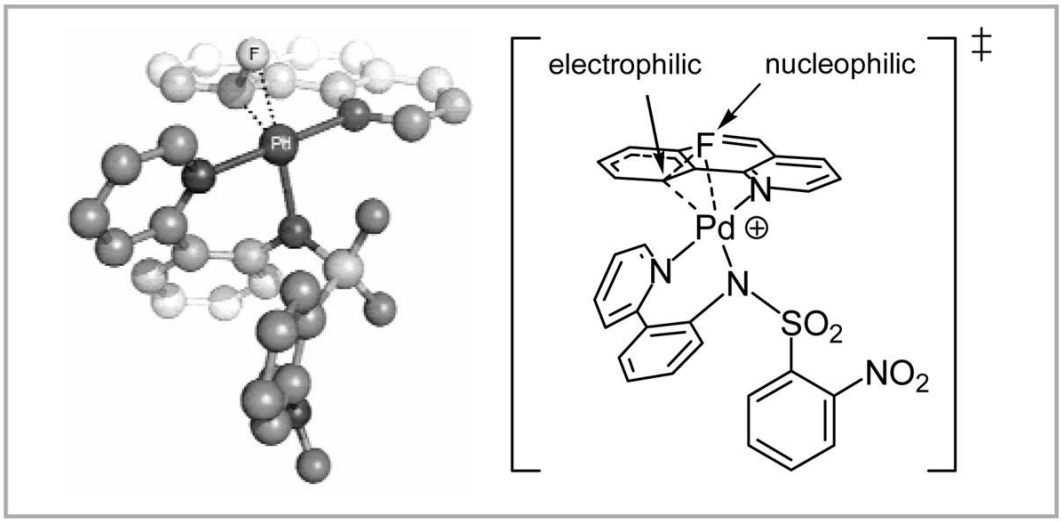
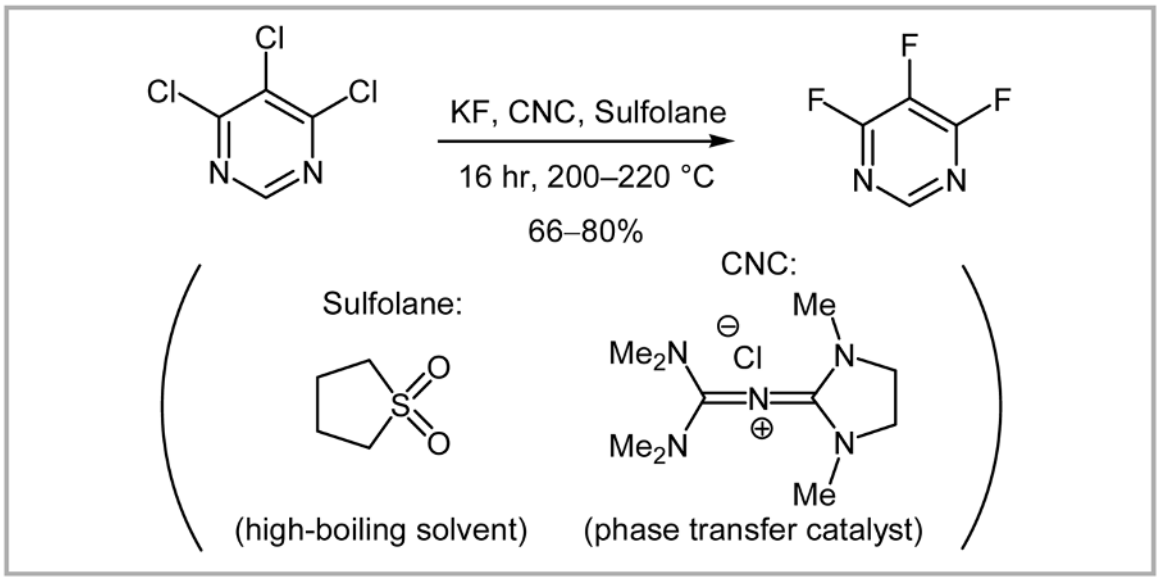
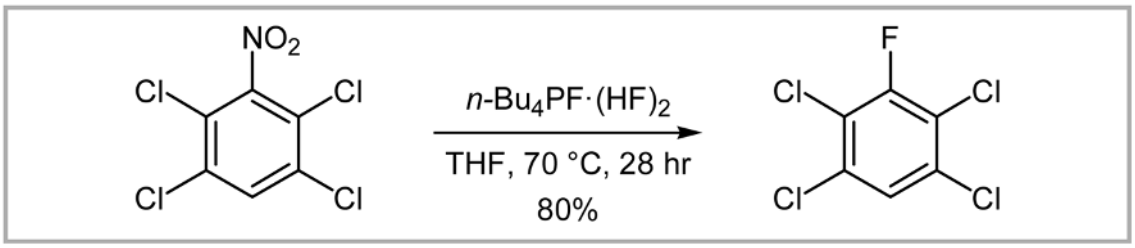


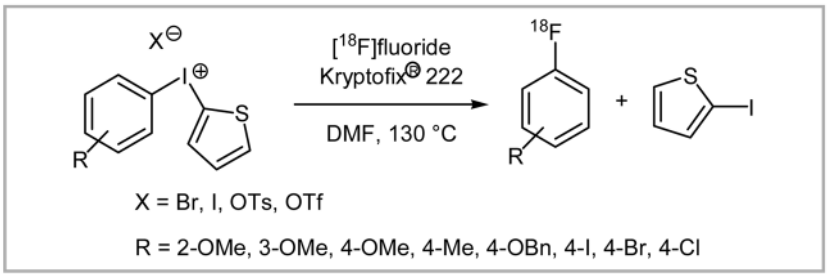
Figure 2.
Calculated structure of the transition state of C–F reductive elimination from **27**.



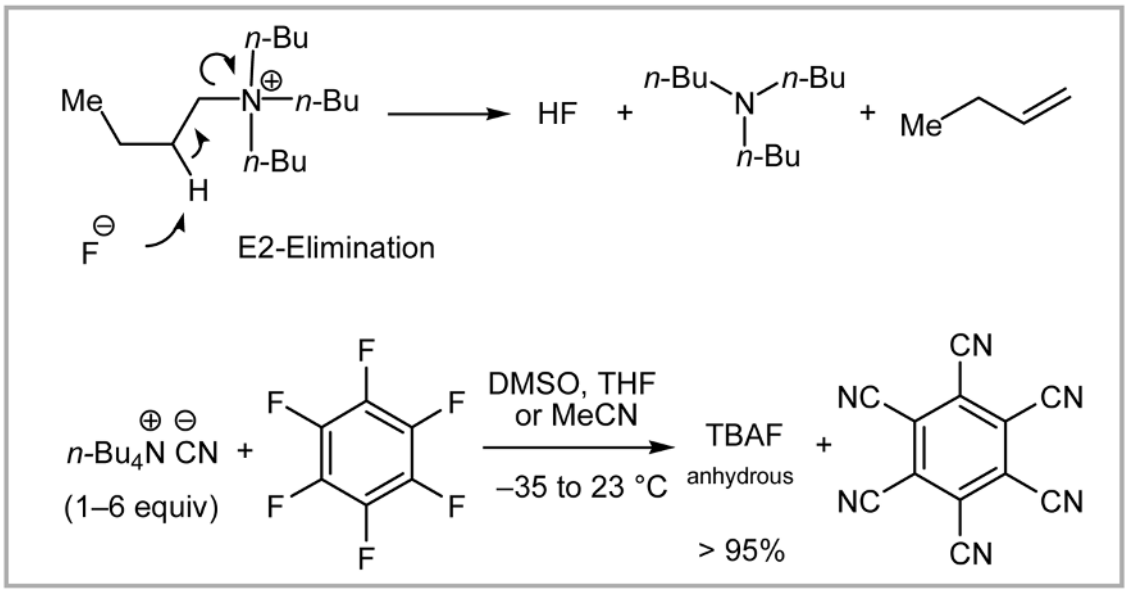
Scheme 1.
Example of the Halex process with high-boiling solvent and phase transfer catalyst.



Scheme 2.
Fluorodenitration. The nitro group is displaced selectively in the presence of chloride substituents.

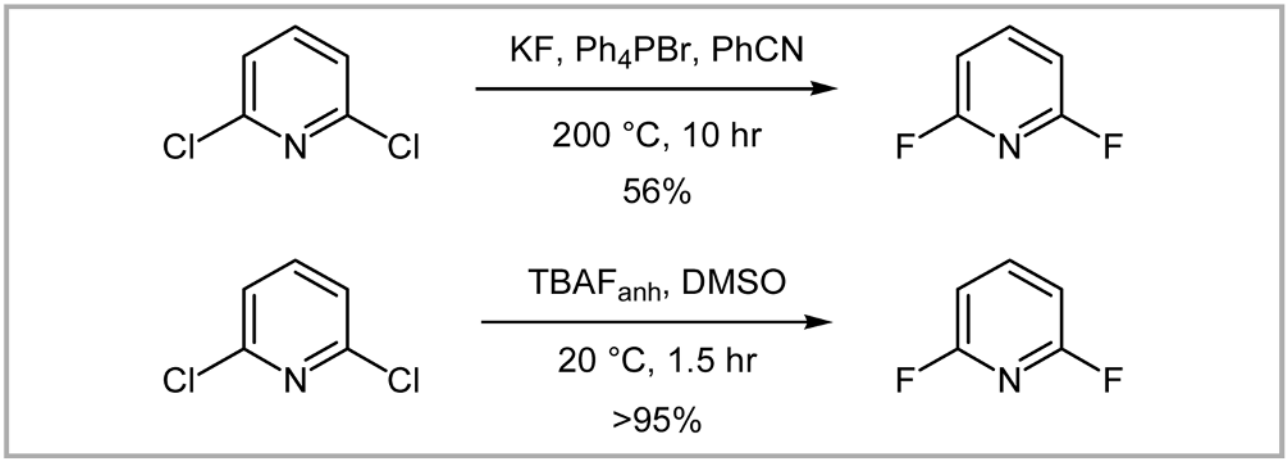


Scheme 3.
Fluorination of aryliodonium salts.

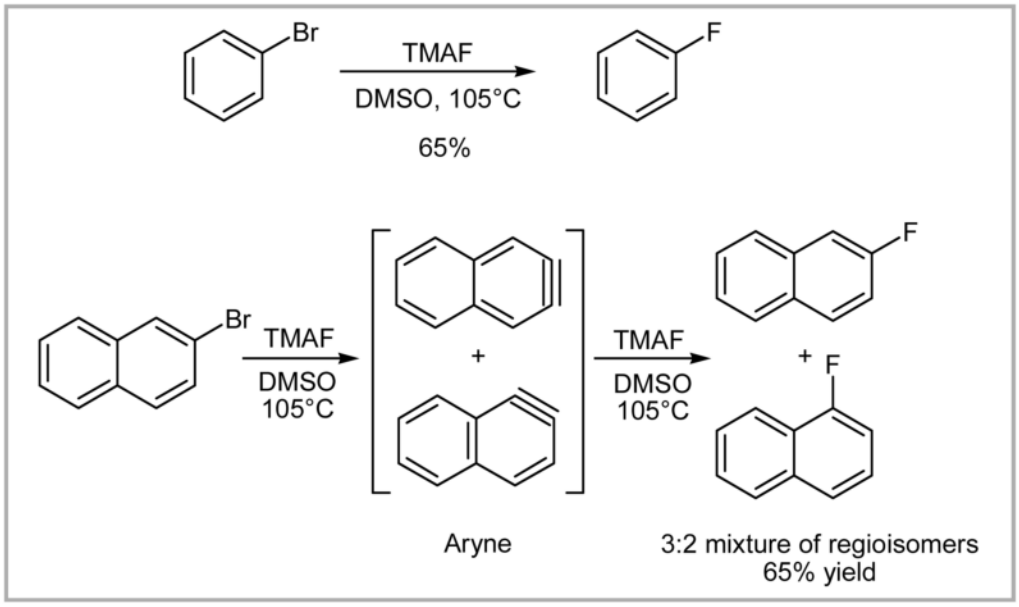


Scheme 4.

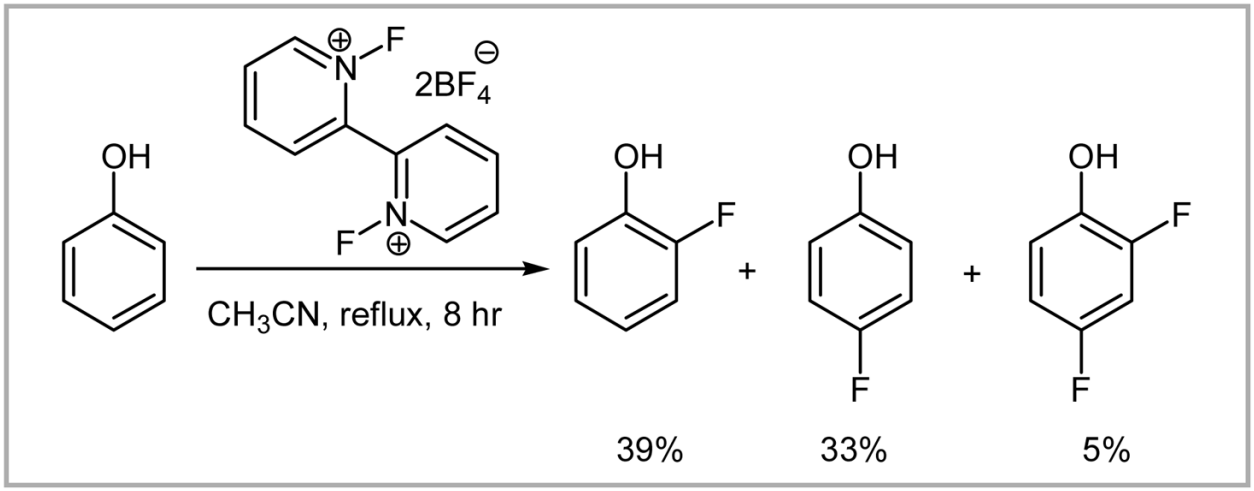
Preparation of anhydrous TBAF. Drying at high temperature results in Hofmann elimination but the reaction between hexafluorobenzene and tetrabutylammonium cyanide affords anhydrous TBAF at low temperature.



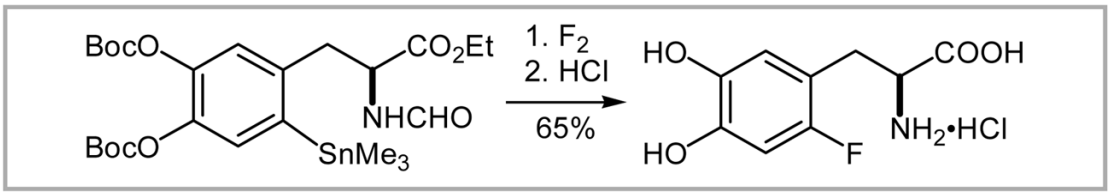
Scheme 5.
Efficient nucleophilic aromatic substitution with anhydrous TBAF in comparison to traditional conditions.



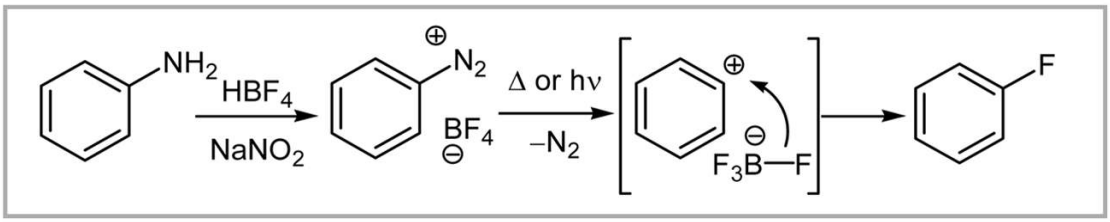
Scheme 6.
Fluorination of unactivated arenes via arynes using TMAF.



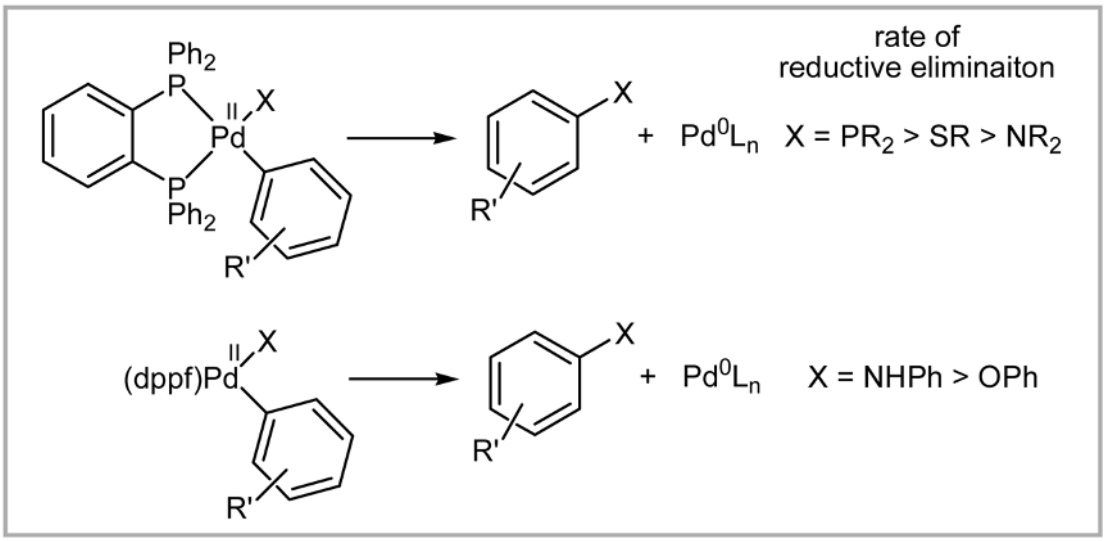
Scheme 7.
Unselective fluorination of phenol with an electrophilic fluorinating reagent.



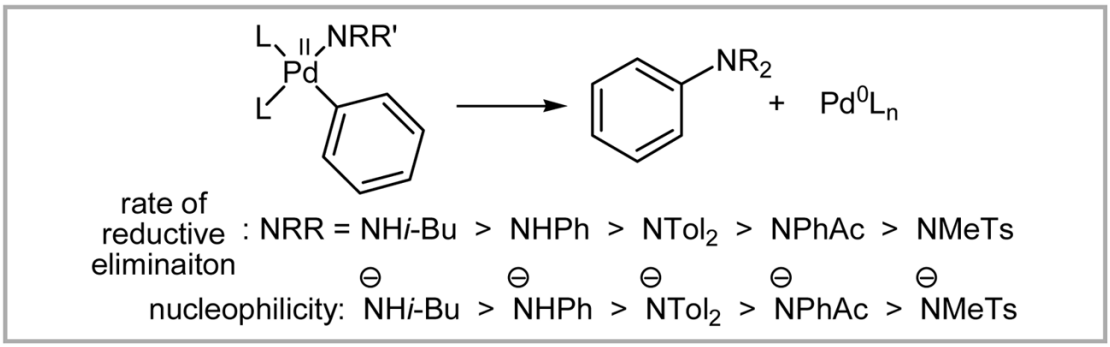
Scheme 8.
Fluorodestannylation in the preparation of 6-fluoro-*L*-DOPA.



Scheme 9.
The Balz-Schiemann reaction.

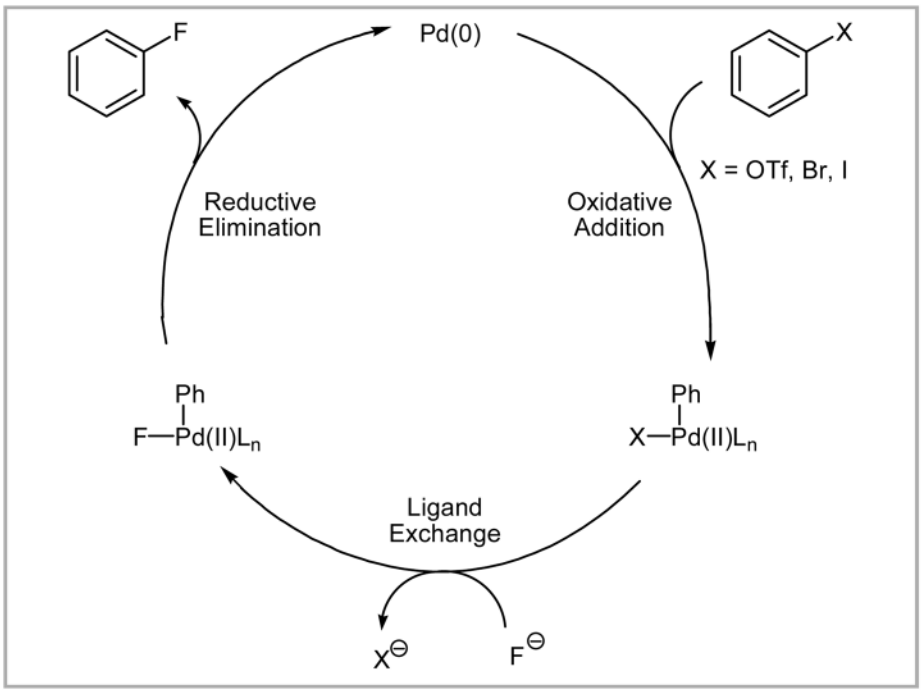


Scheme 10.
Rate of C–X reductive elimination as a function of the heteroatom.

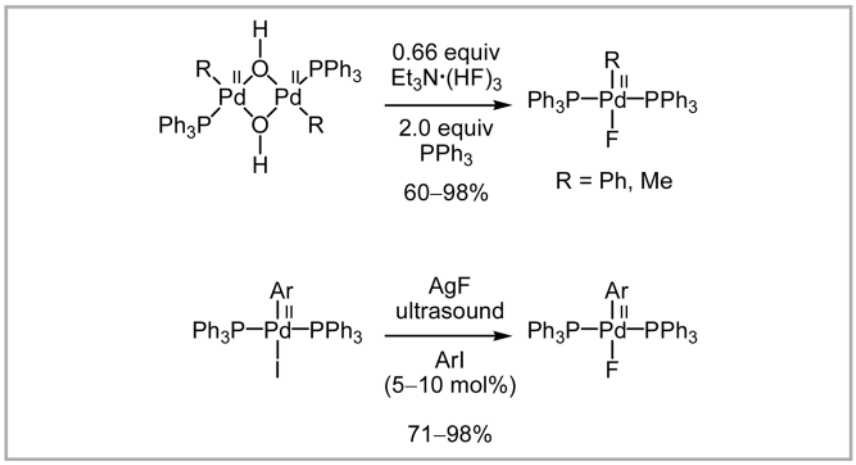


Scheme 11.
Electronic effect on the rate of C–N reductive elimination.

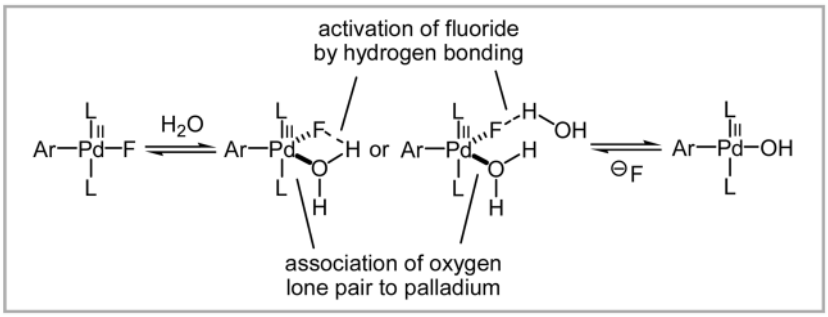
Scheme 12.
Electronic effect on the rate of C–C reductive elimination.



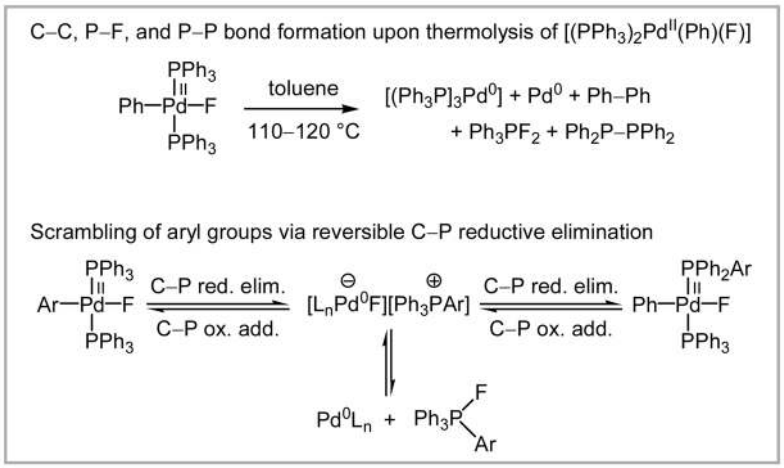
Scheme 13.
General scheme of Pd-mediated nucleophilic fluorination.



Scheme 14.
Preparation of Pd^{II} fluoride complexes by Grushin.

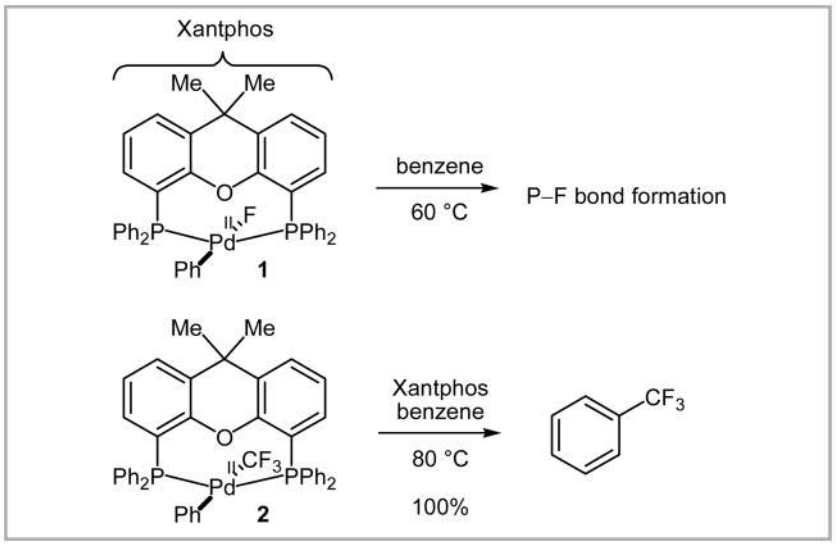


Scheme 15.
Water-induced ionization of a Pd–F bond.

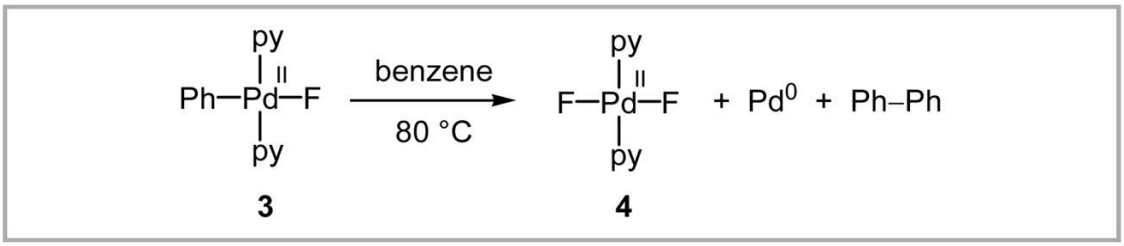


Scheme 16.

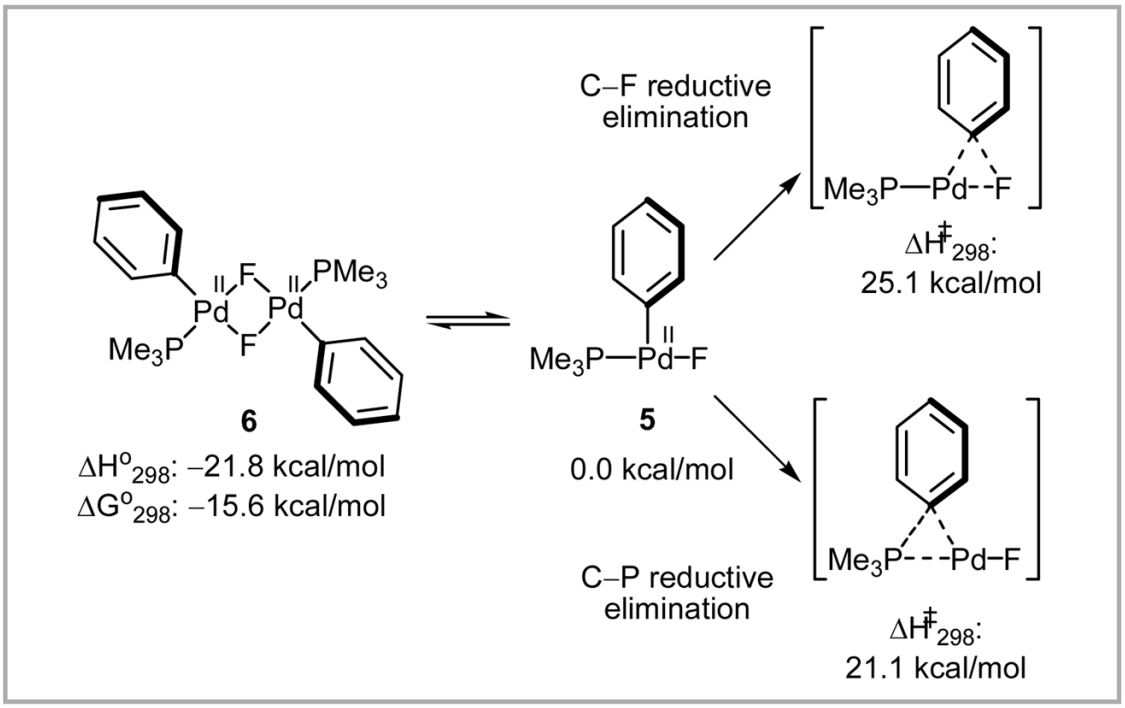
Unsuccessful C–F reductive elimination due to the competing P–F, P–P, C–C, and C–P bond formation.



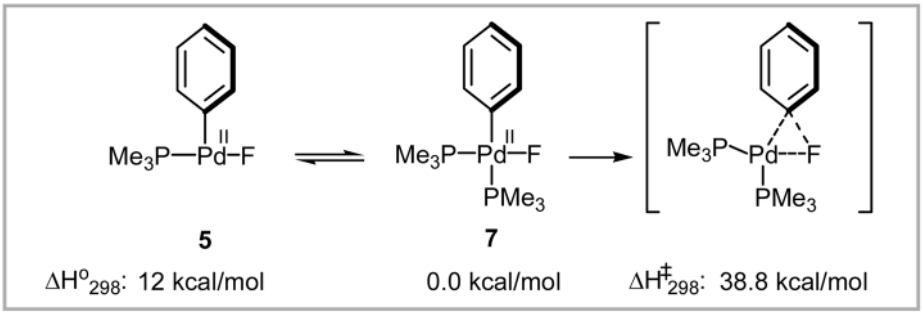
Scheme 17.
Unsuccessful C–F reductive elimination and successful C–CF_3 reductive elimination.



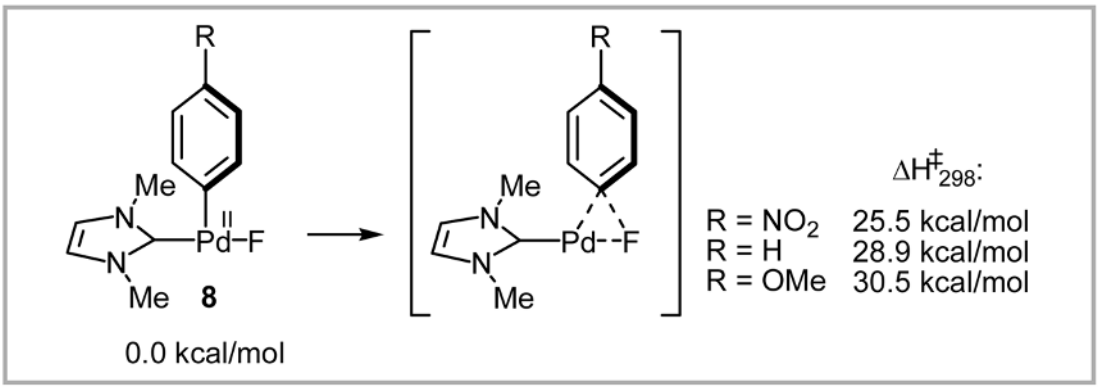
Scheme 18.
C–C bond formation from bis(pyridyl)phenylpalladium(II) fluoride complex (**3**).



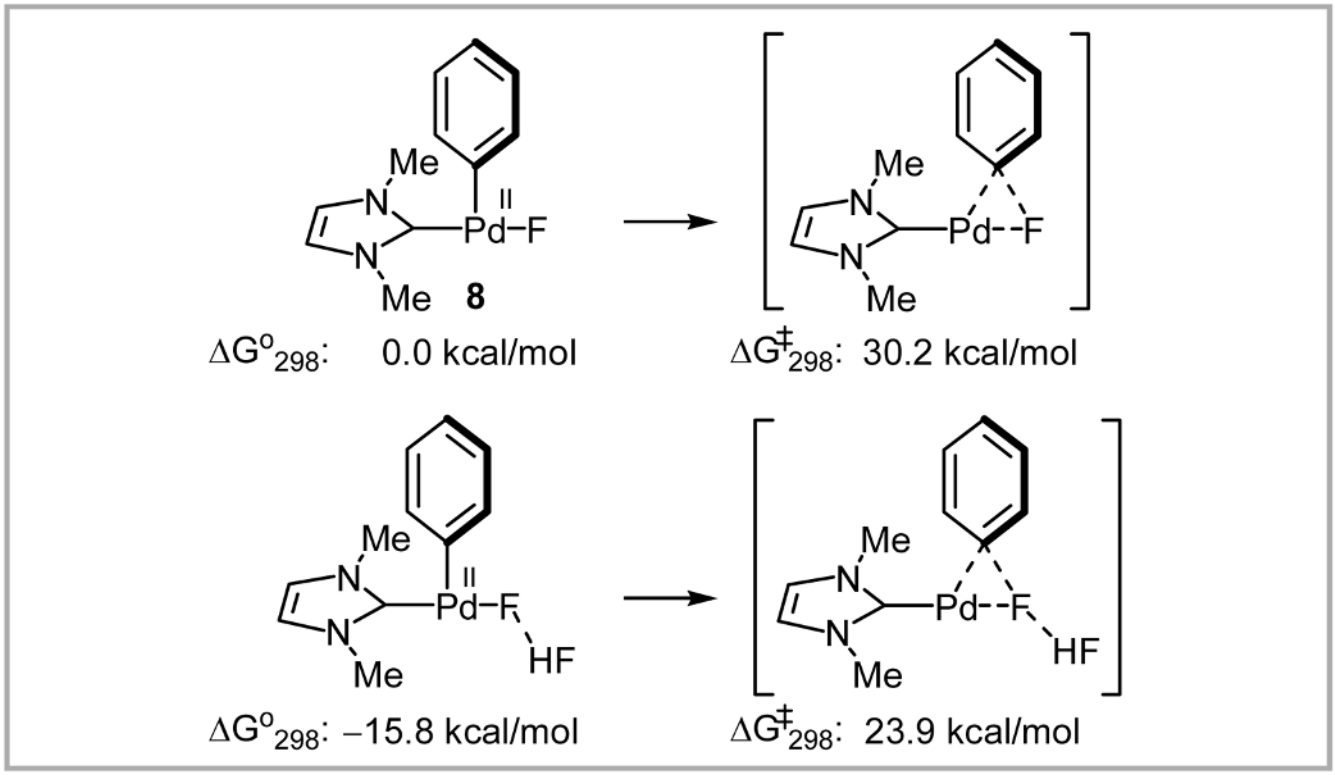
Scheme 19.
Computed C–F reductive elimination from the T-shaped three-coordinate PMe_3 palladium(II) fluoride complex **5**.



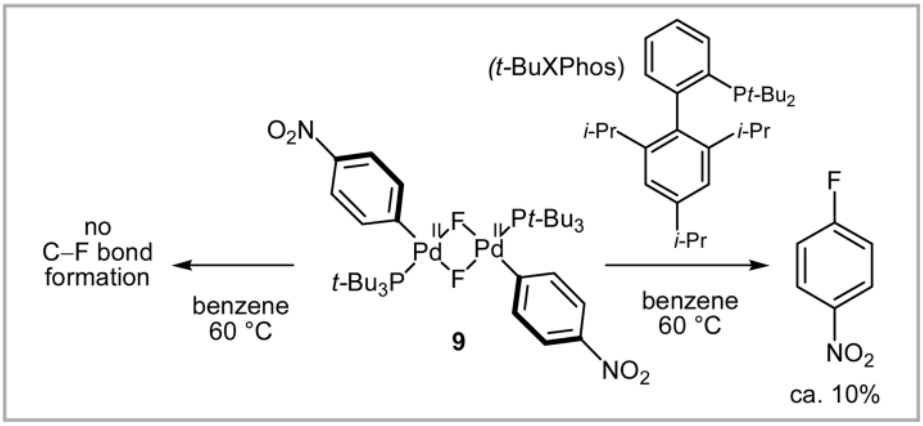
Scheme 20.
Computed C–F reductive elimination from four-coordinate PMe_3 palladium(II) fluoride complex.



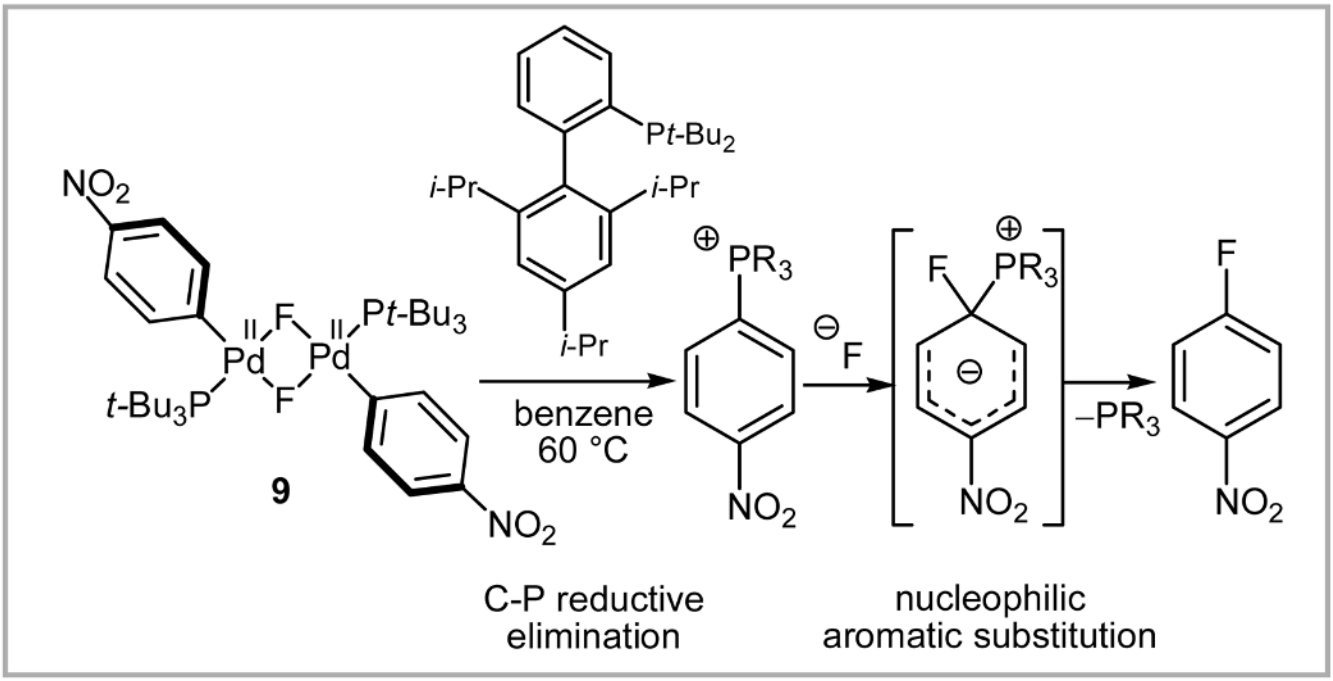
Scheme 21.
Computed effect of substituents on the aryl group on C–F reductive elimination.



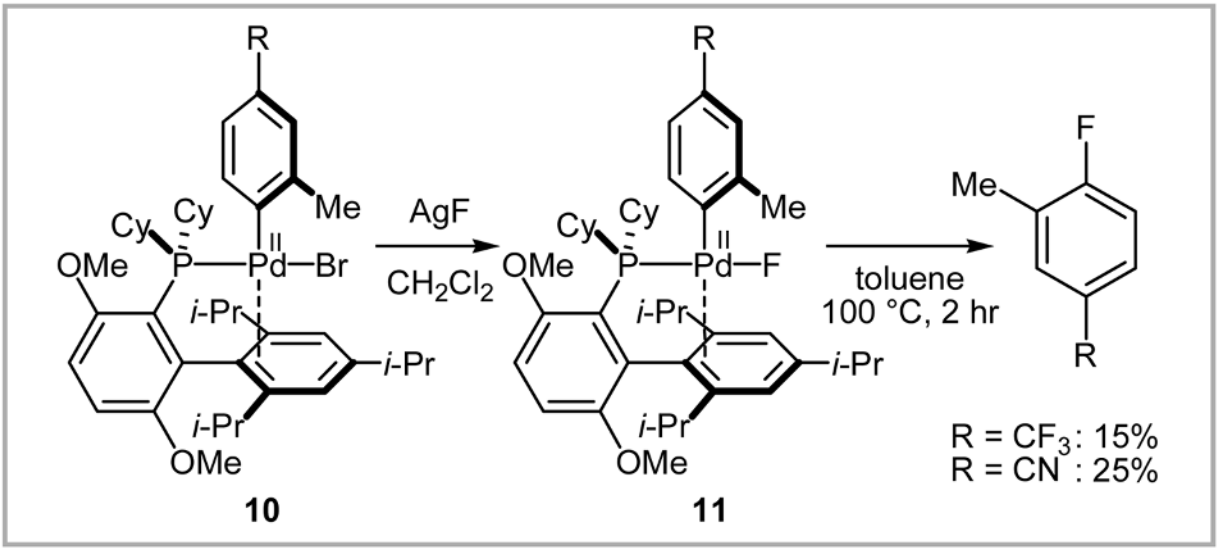
Scheme 22.
Computed effect of hydrogen bond donor on C–F reductive elimination.



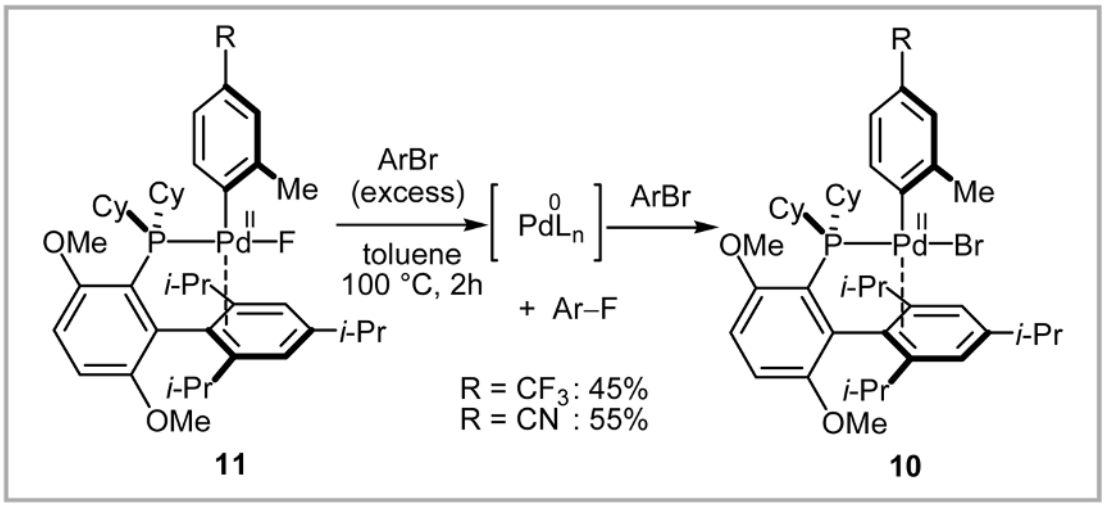
Scheme 23.
C–F bond formation from arylpalladium complex **9**.



Scheme 24.
C–P reductive elimination/nucleophilic aromatic substitution sequence for C–F bond formation proposed by Grushin.

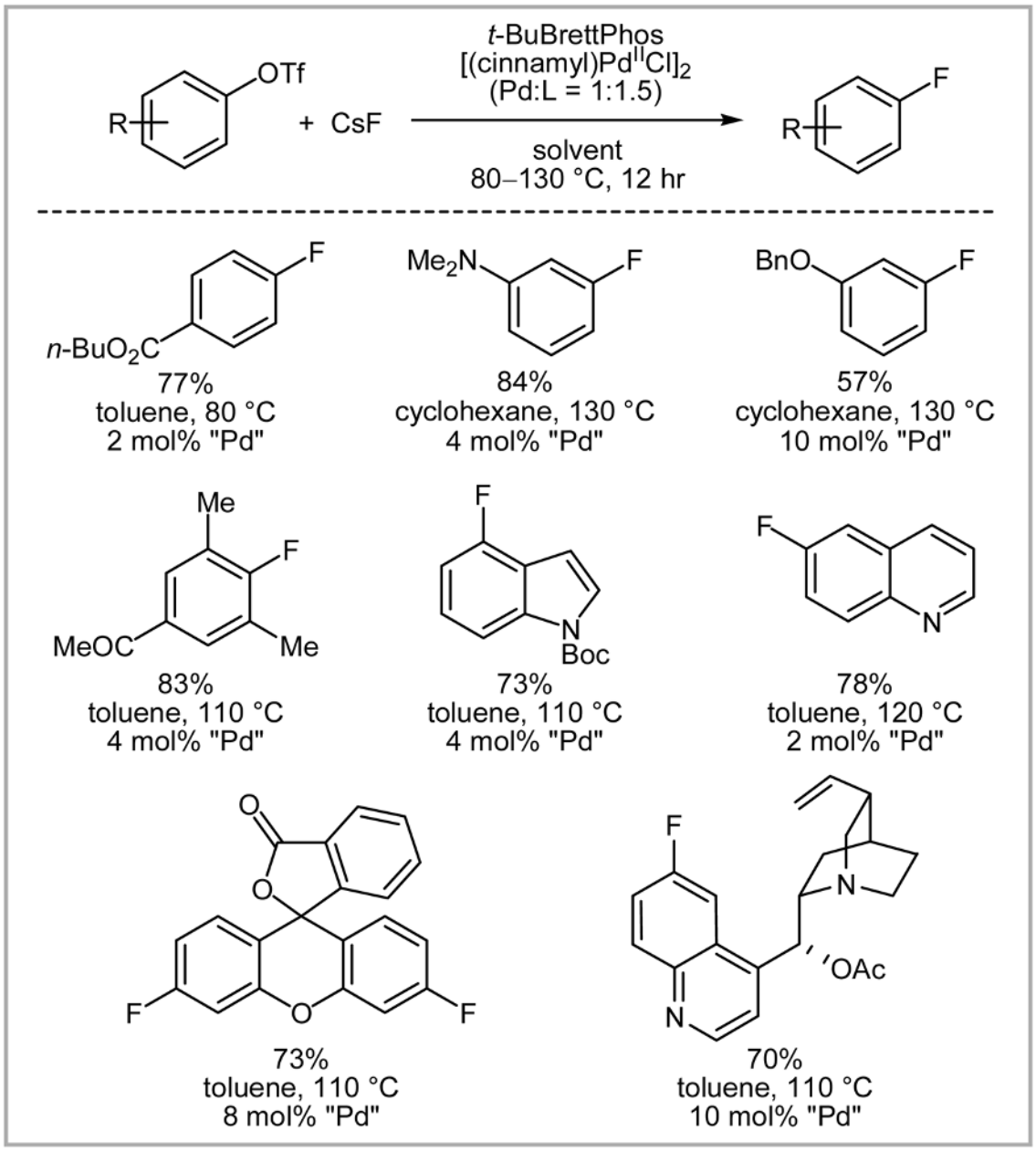


Scheme 25.
C–F bond formation from T-shape three-coordinate arylpalladium complex **11**.

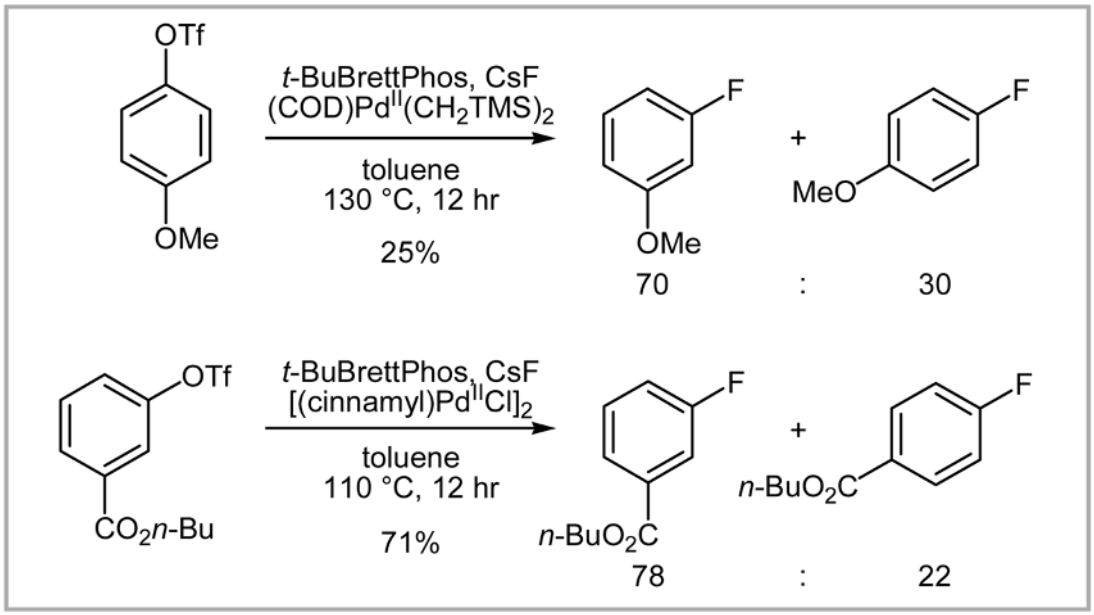


Scheme 26.

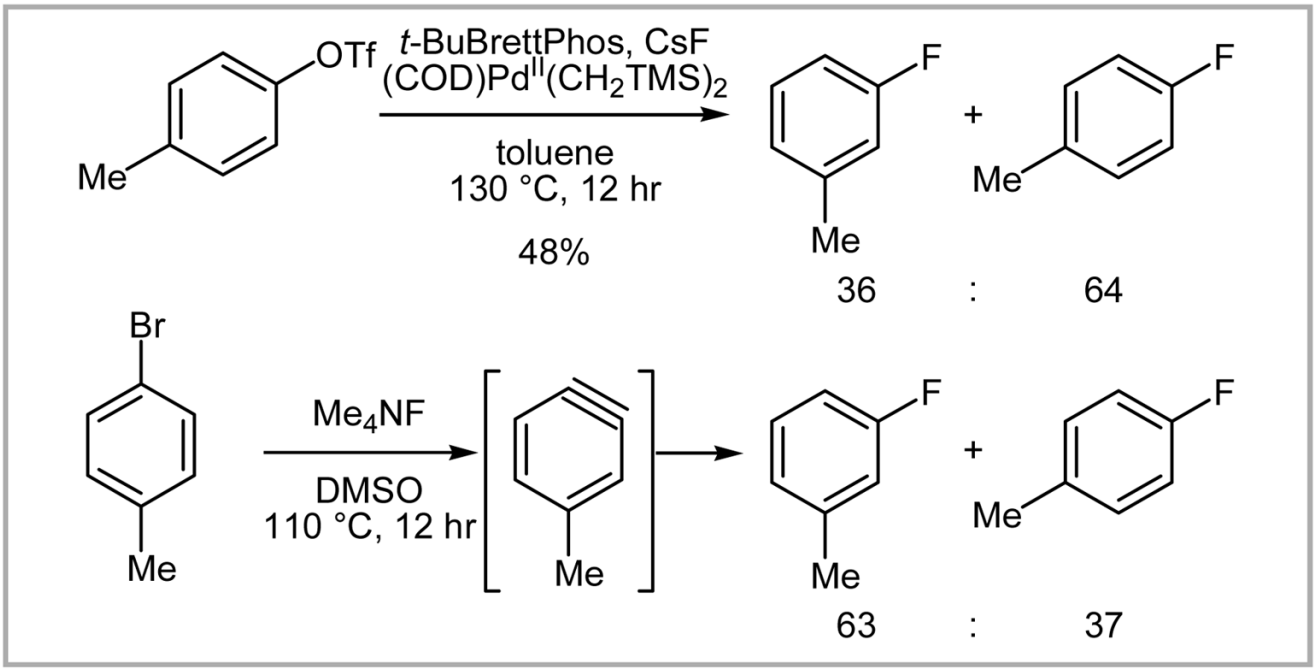
Proposed C–F reductive elimination. The presumed Pd(0) intermediate could not be observed but the Pd(II) complex after oxidative addition was characterized.



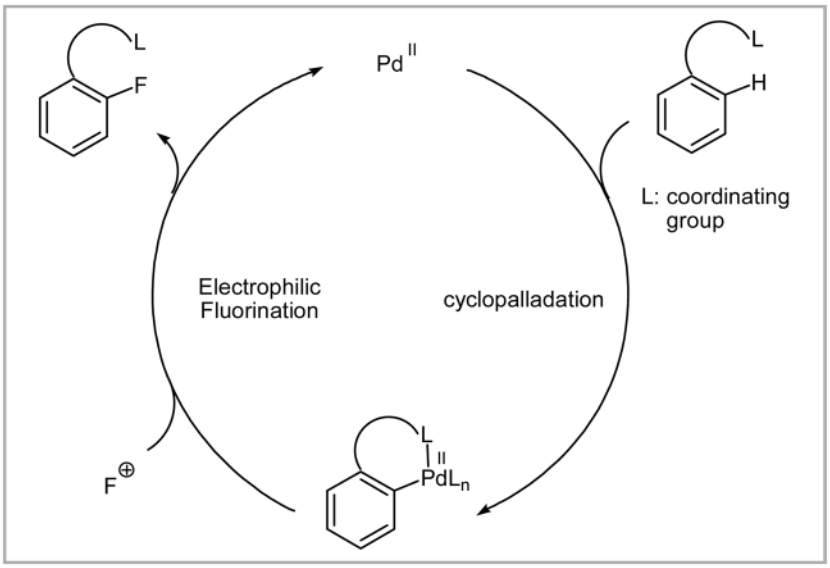
Scheme 27.
Substrate scope of palladium-catalyzed nucleophilic fluorination by Buchwald.



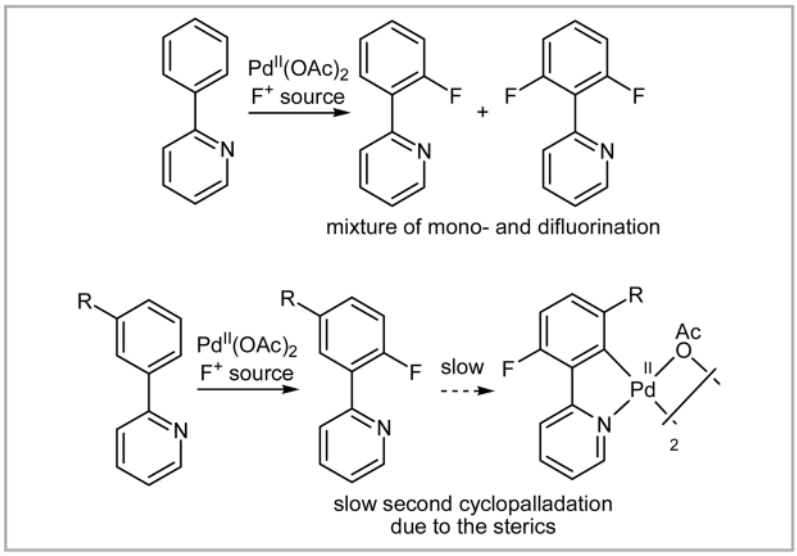
Scheme 28.
Formation of regioisomers.



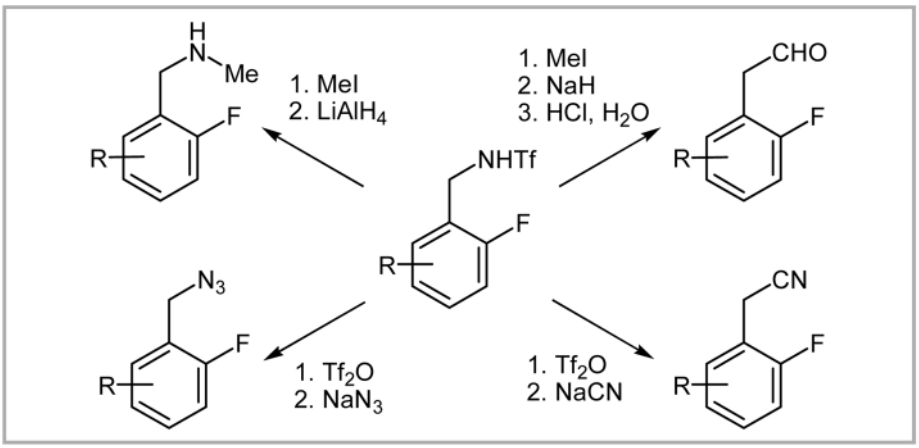
Scheme 29.
Comparison of the ratio of regioisomers with benzyne fluorination reported by Grushin.



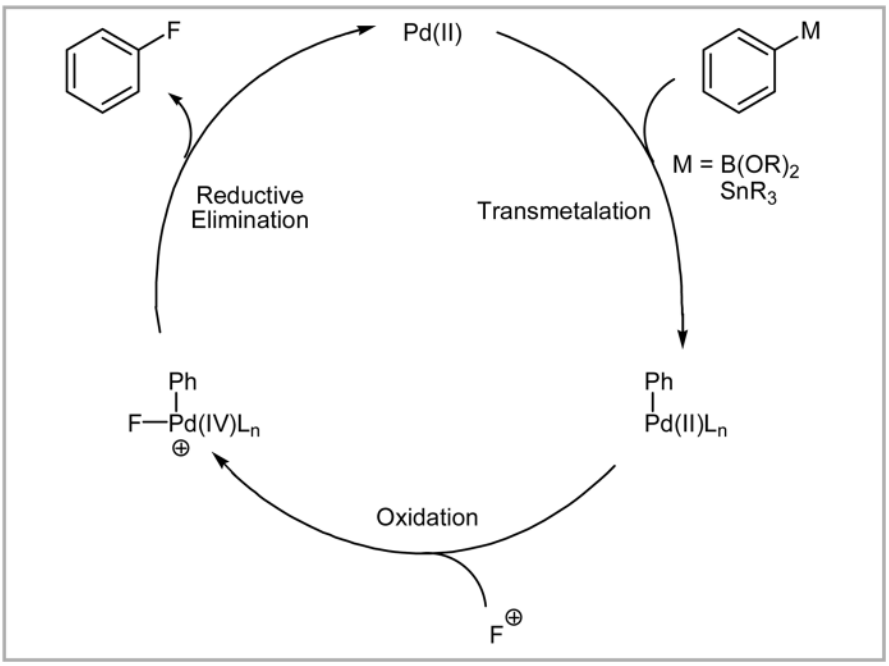
Scheme 30.
General scheme of Pd-mediated directed electrophilic fluorination.



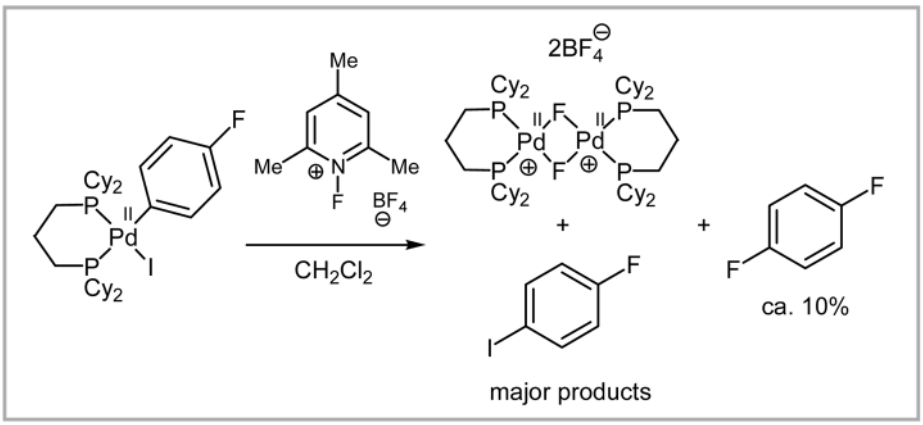
Scheme 31.
Problematic second fluorination event.



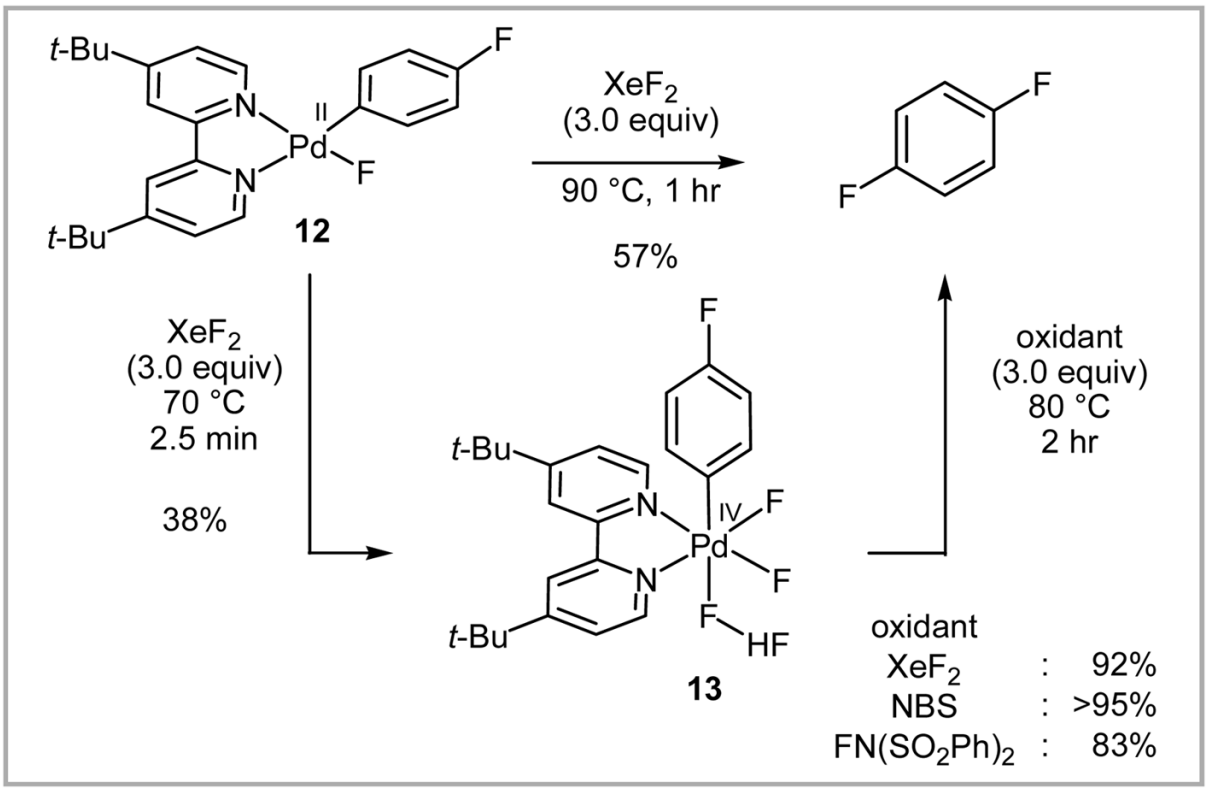
Scheme 32.
Interconversion of the triflamide directing group after fluorination.



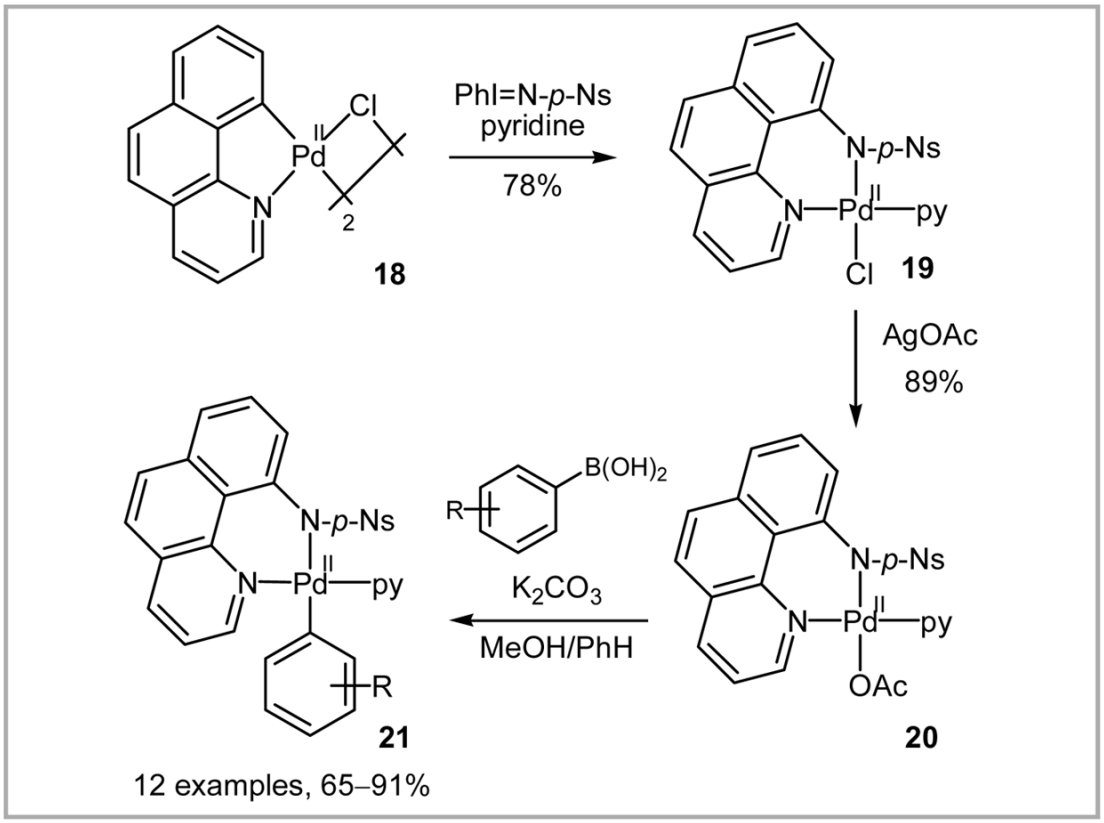
Scheme 33.
General scheme of Pd-mediated electrophilic fluorination.



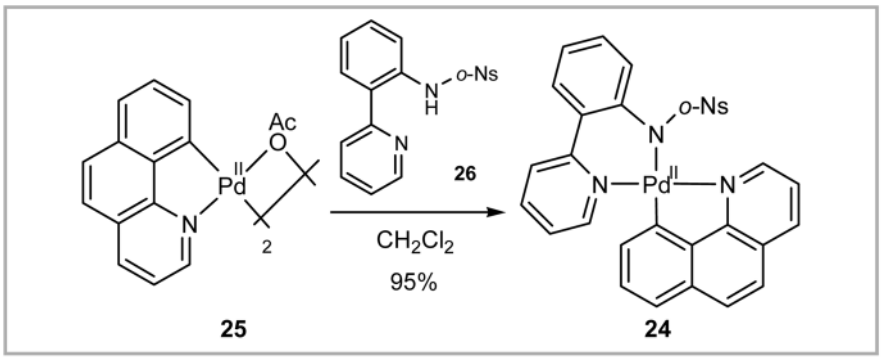
Scheme 34.
C–F bond formation from an arylpalladium(II) complex upon treatment with an electrophilic fluorinating reagent.



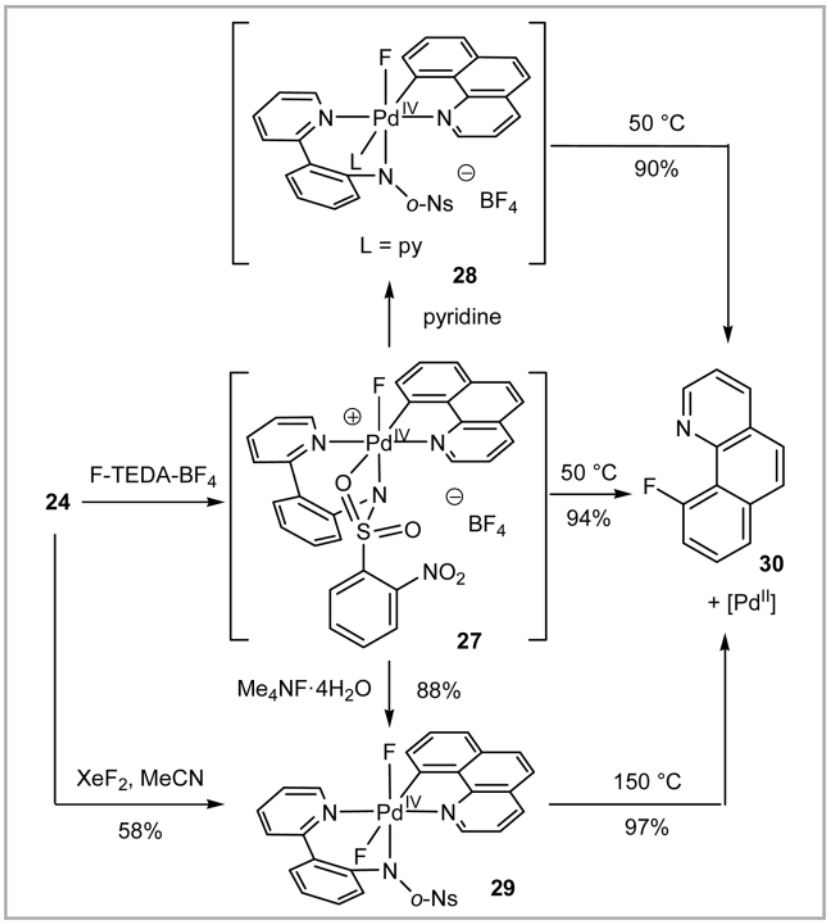
Scheme 35.
Oxidant-promoted C–F bond formation from palladium(IV) difluoride complex **13**.



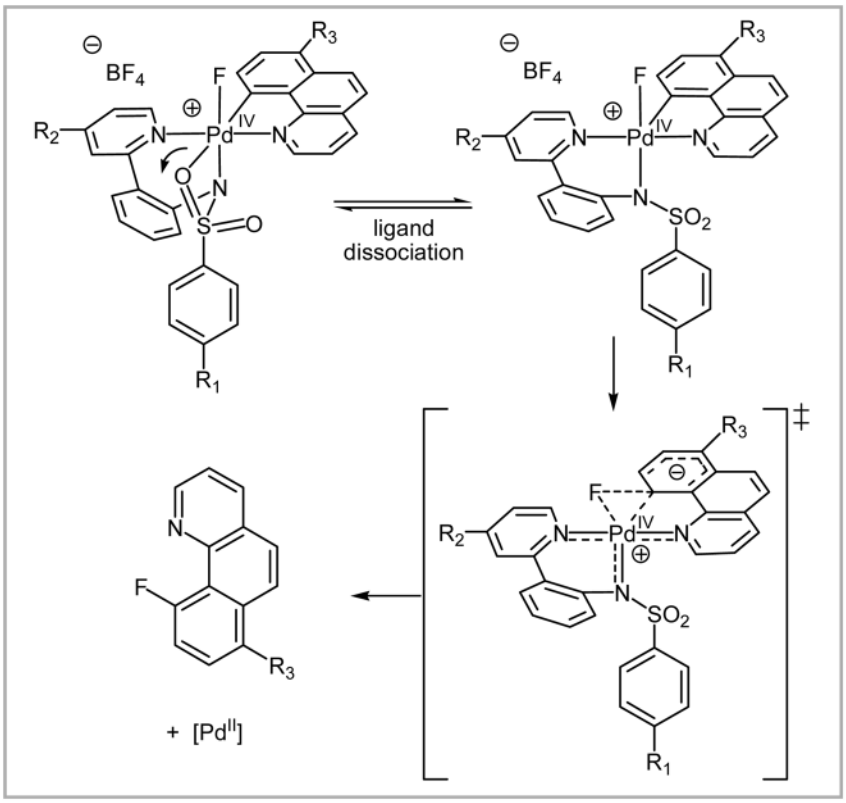
Scheme 36.
Synthesis of arylpalladium(II) pyridyl-sulfonamide complexes via transmetalation.



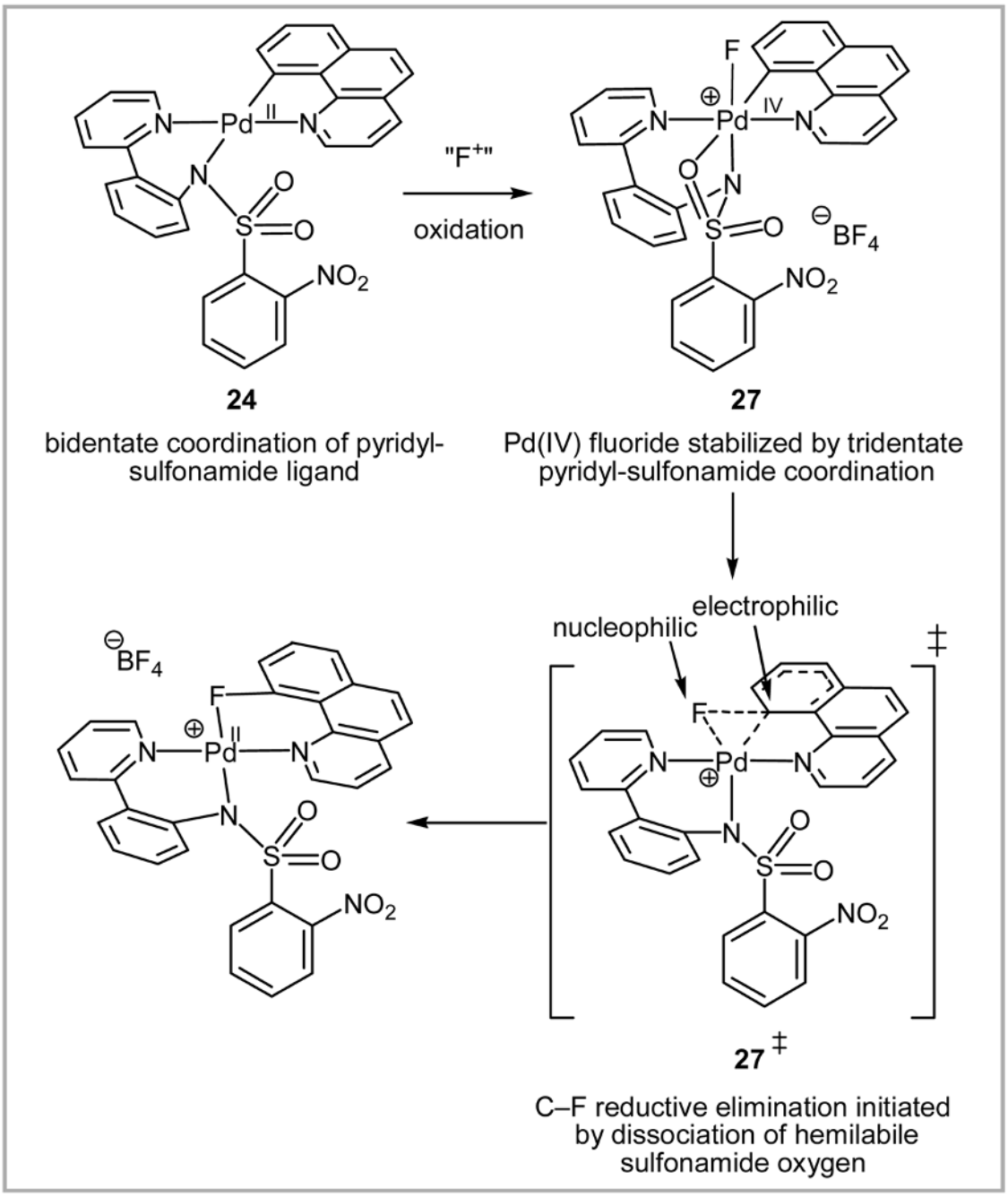
Scheme 37.
Synthesis of more rigid pyridyl-sulfonamido palladium(II) complex **24**.



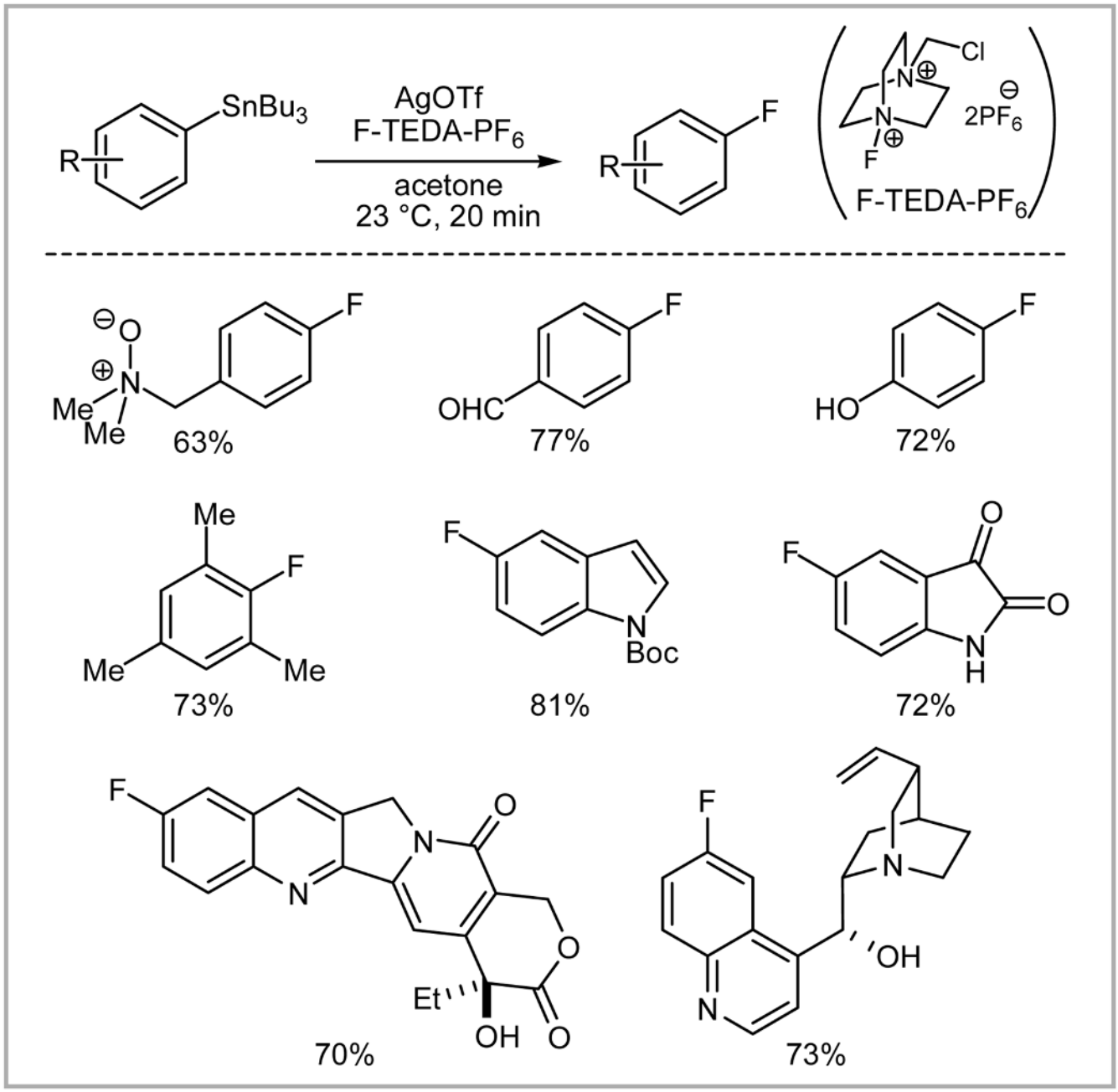
Scheme 38.
First synthesis of Pd(IV) fluoride complexes and establishment of Ar–F reductive elimination.



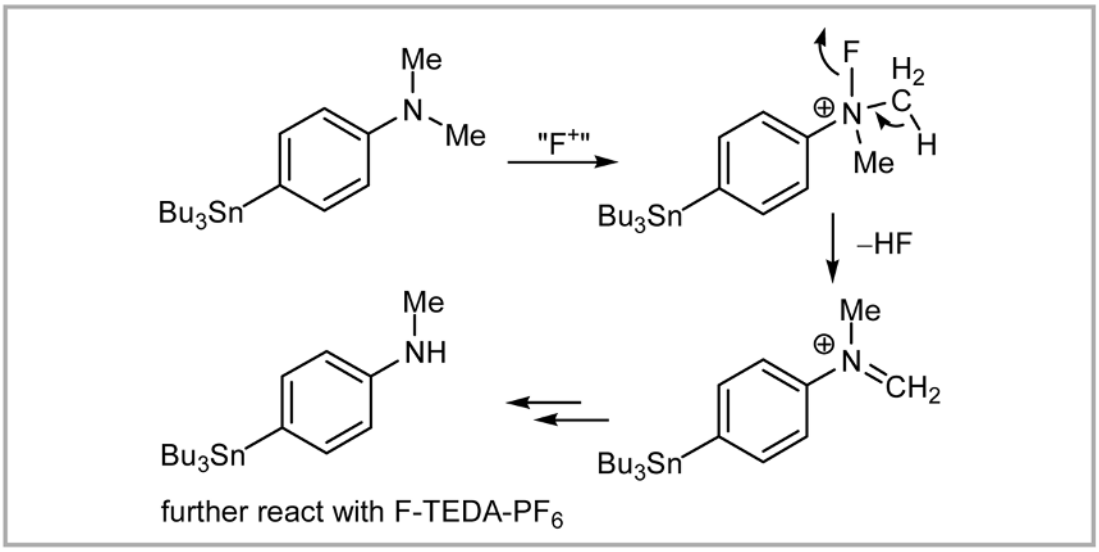
Scheme 39.
Proposed dissociative mechanism for C–F reductive elimination.



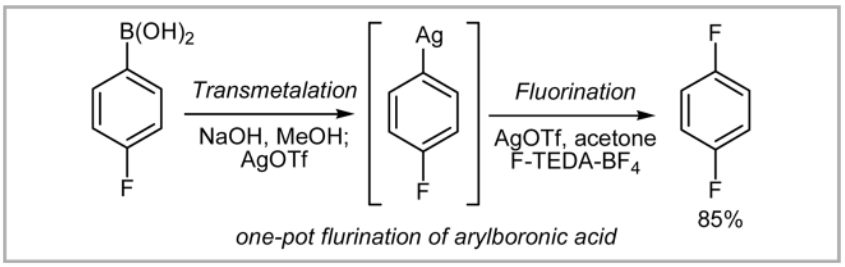
Scheme 40.
Oxidation and reductive elimination supported by the pyridyl-sulfonamide ligand.



Scheme 41.
Substrate scope of AgOTf-mediated fluorination of aryl-stannanes by our group.



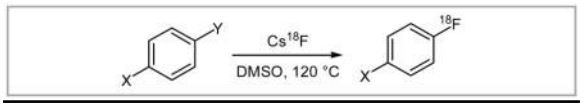
Scheme 42.
Decomposition of a tertiary amine with F-TEDA-PF_6.



Scheme 43.
One-pot fluorination of arylboronic acids.

Table 1

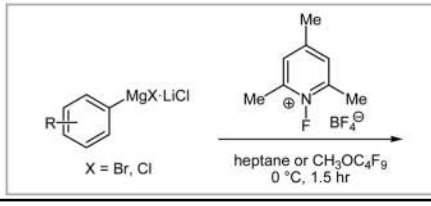
Effect of leaving groups (Y) and activating groups (X) on the rate of nucleophilic aromatic fluorination.

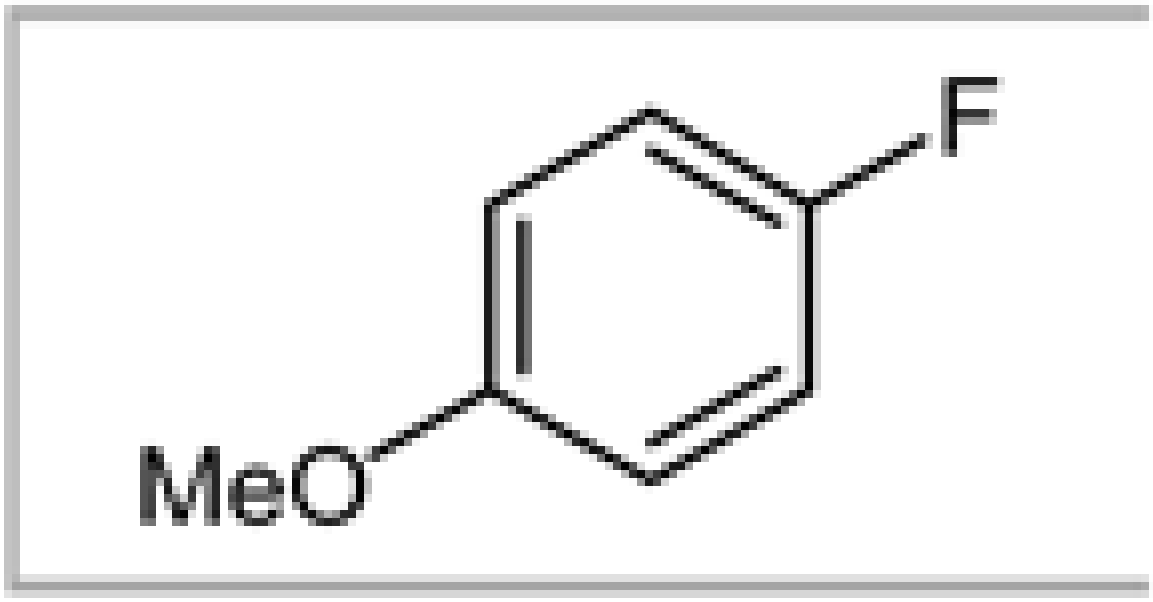


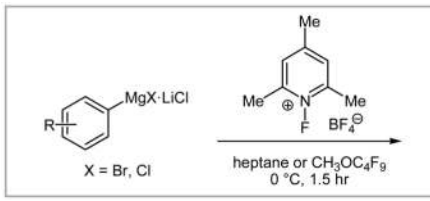
X	Y	k_{rel} (120 °C)	k_{rel} (80 °C)
NO_2	NMe_3ClO_4	400	30000
NO_2	NO_2	40	420
CN	NMe_3ClO_4	16	100
COMe	NMe_3ClO_4	8	33
CN	NO_2	1	1

Table 2

Electrophilic fluorination of arylmagnesium reagents by Beller.



Product	Yield
	81%



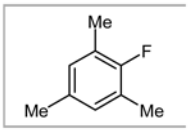
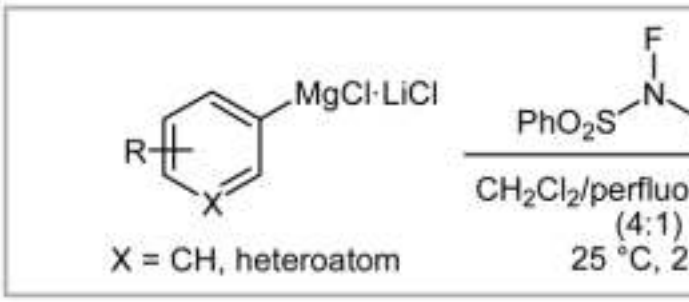
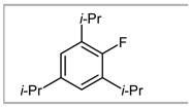
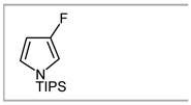
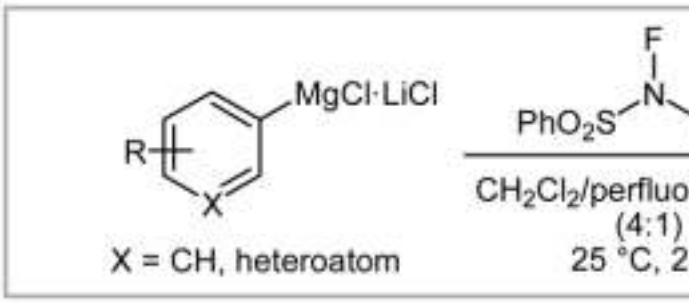
Product	Yield
	73%

Table 3

Electrophilic fluorination of arylmagnesium reagents by Knochel.



Product	Yield
	90%
	43%



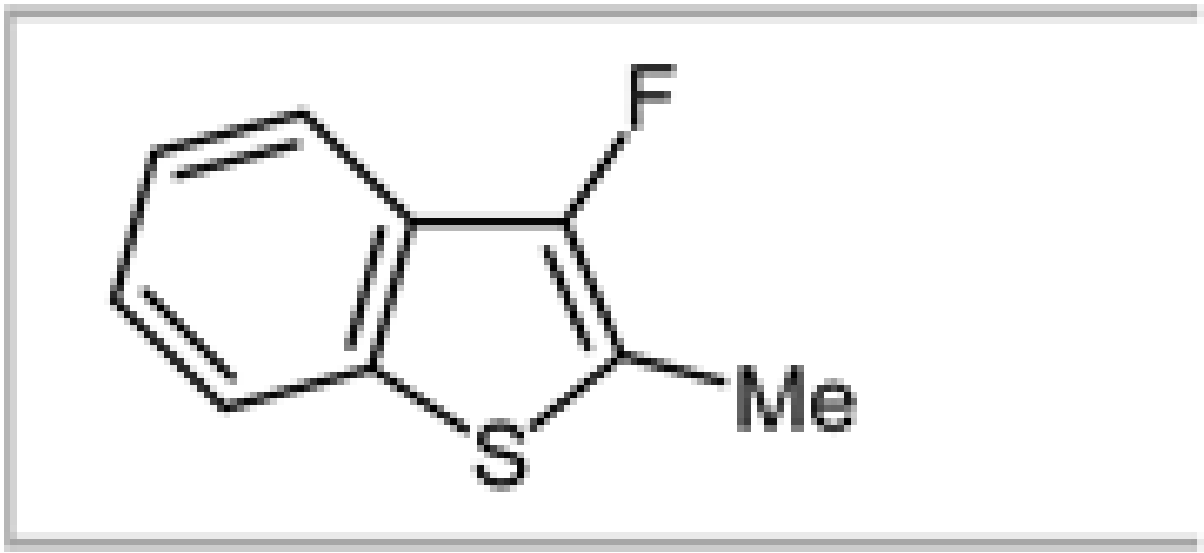
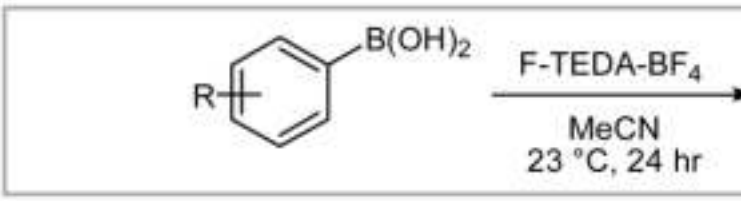
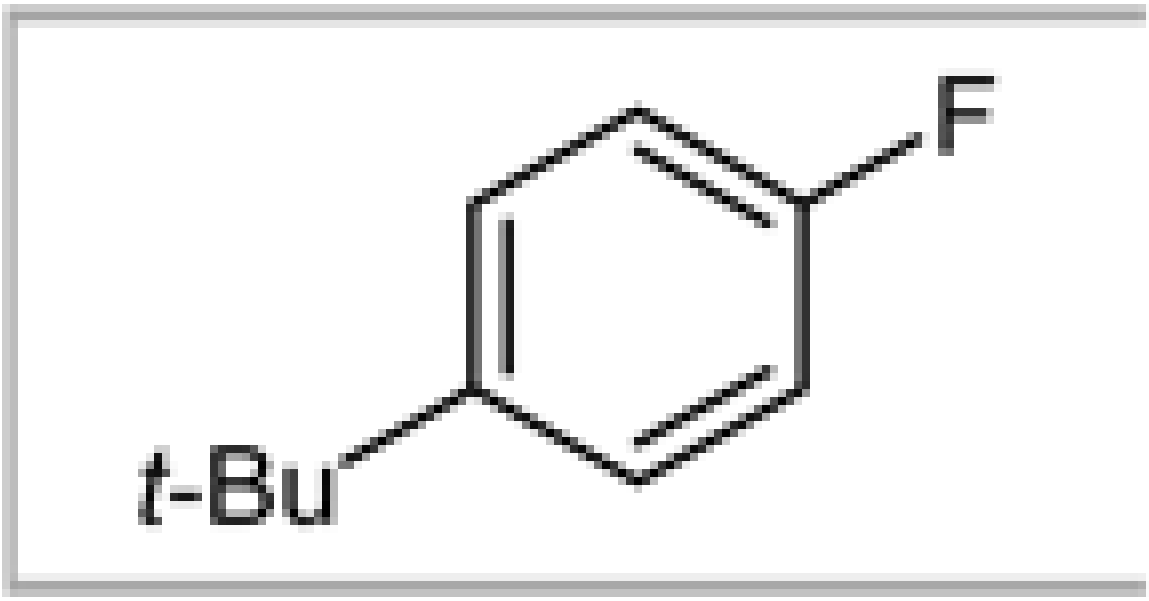
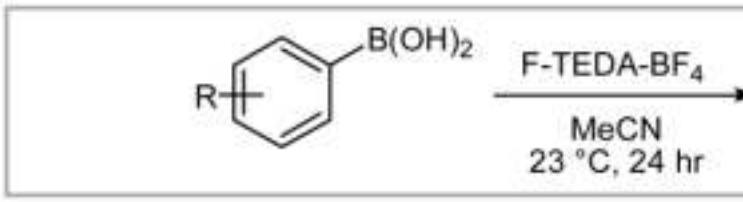
Product	Yield
	60%

Table 4

Electrophilic fluorination of arylboronic acids and aryl-trifluoroborate.



Product	Yield
	75%



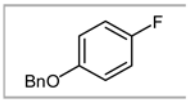
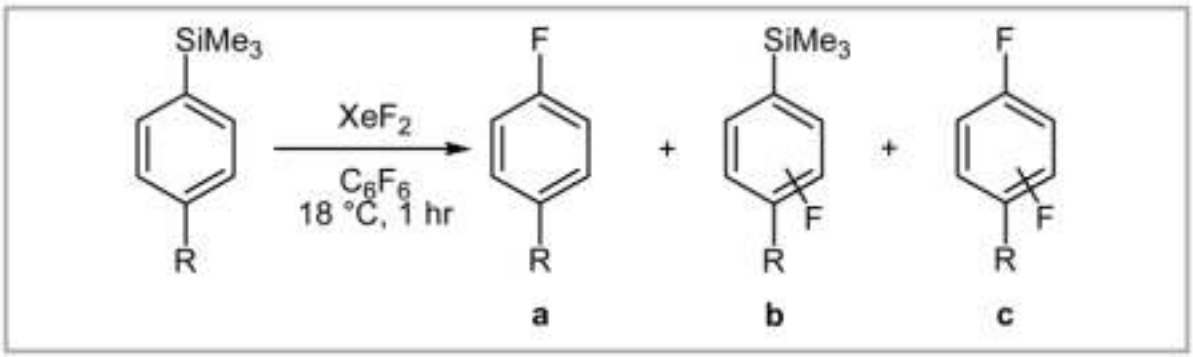
Product	Yield
	100%

Table 5

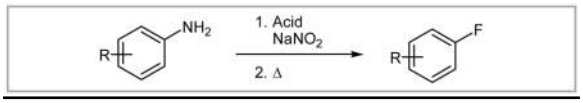
Fluorination of aryltrimethylsilanes.



R	a	b	c
t-Bu	86	8	6
Cl	82	12	6
OMe	61	39	0

Table 6

Substrate scope of the Balz-Schiemann reaction.

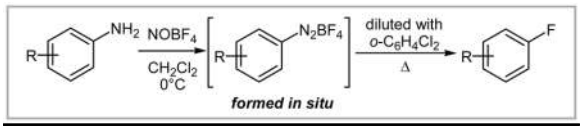


R	HBF_4 (%)	HPF_6 (%)	$HSbF_6$ (%)
p-CH_3	70	71	47
p-COOH	40	49	76
p-NO_2	40–58	63	60
p-OH	_[a]	10–20	trace
o-OCH_3	54–67	60	37
o-COOH	9	60	62

[a]Preparation of the diazonium salt failed.

Table 7

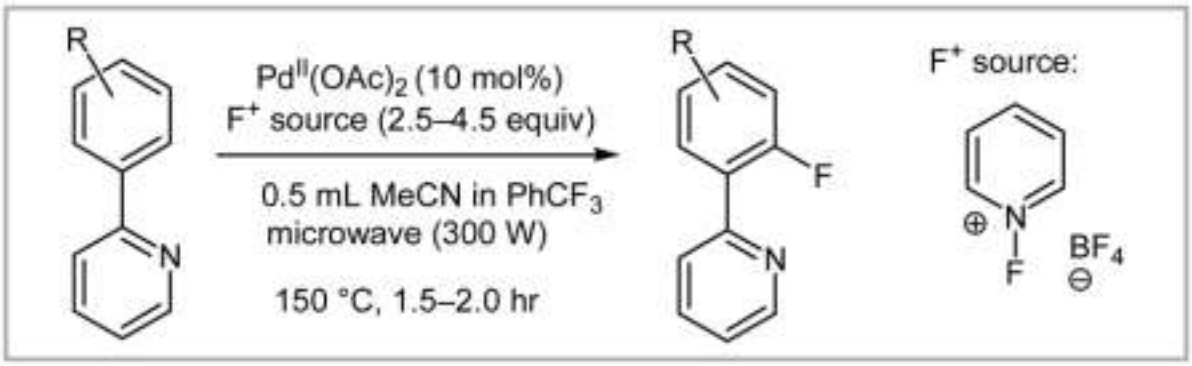
One-pot procedure for the Balz-Schiemann reaction.



R	$NOBF_4$ reaction (%)	Traditional method
H	72	60
2-Cl	90	40
2-COMe	56	47
4-CH_2COOH	73	failed
2-OH	58	failed

Table 8

Substrate scope of the palladium-catalyzed directed electrophilic fluorination by Sanford.



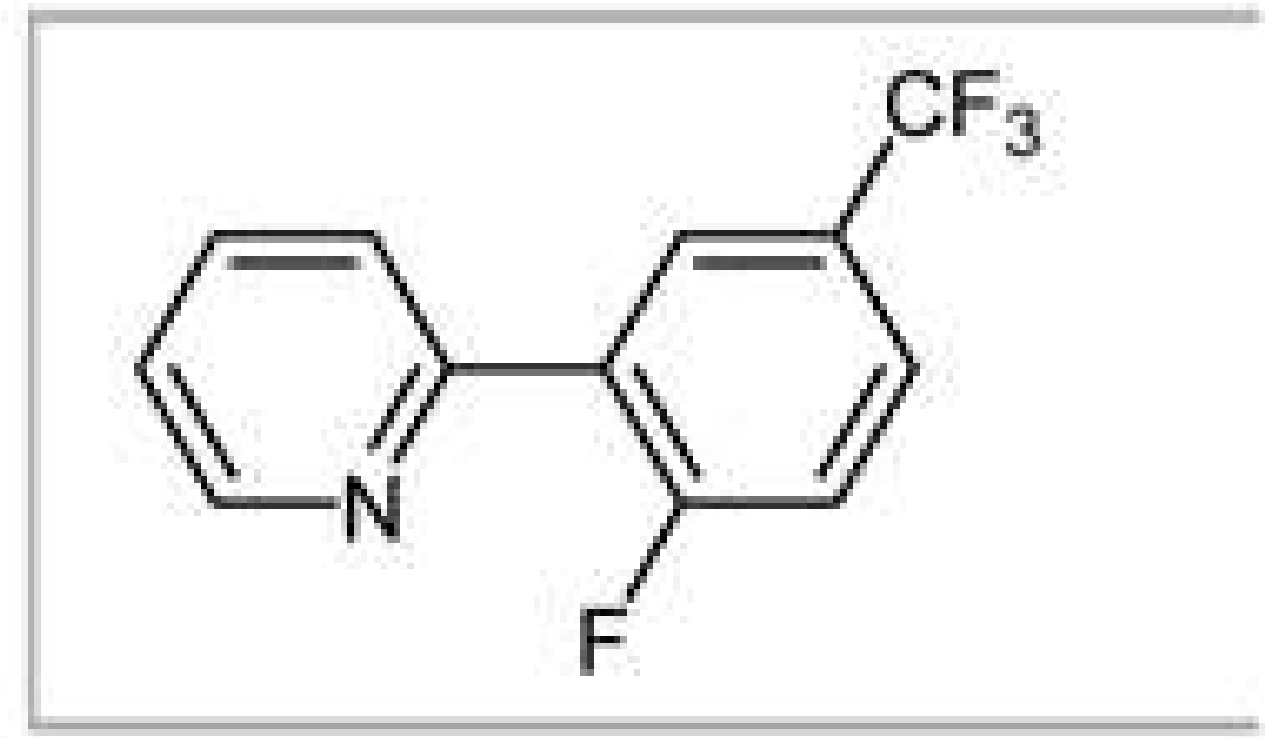
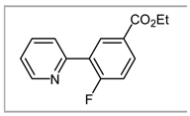
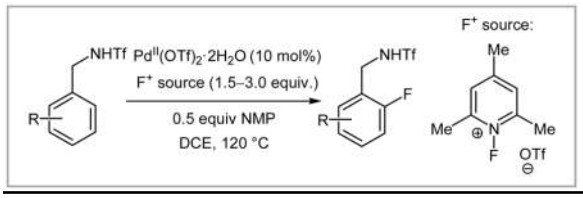
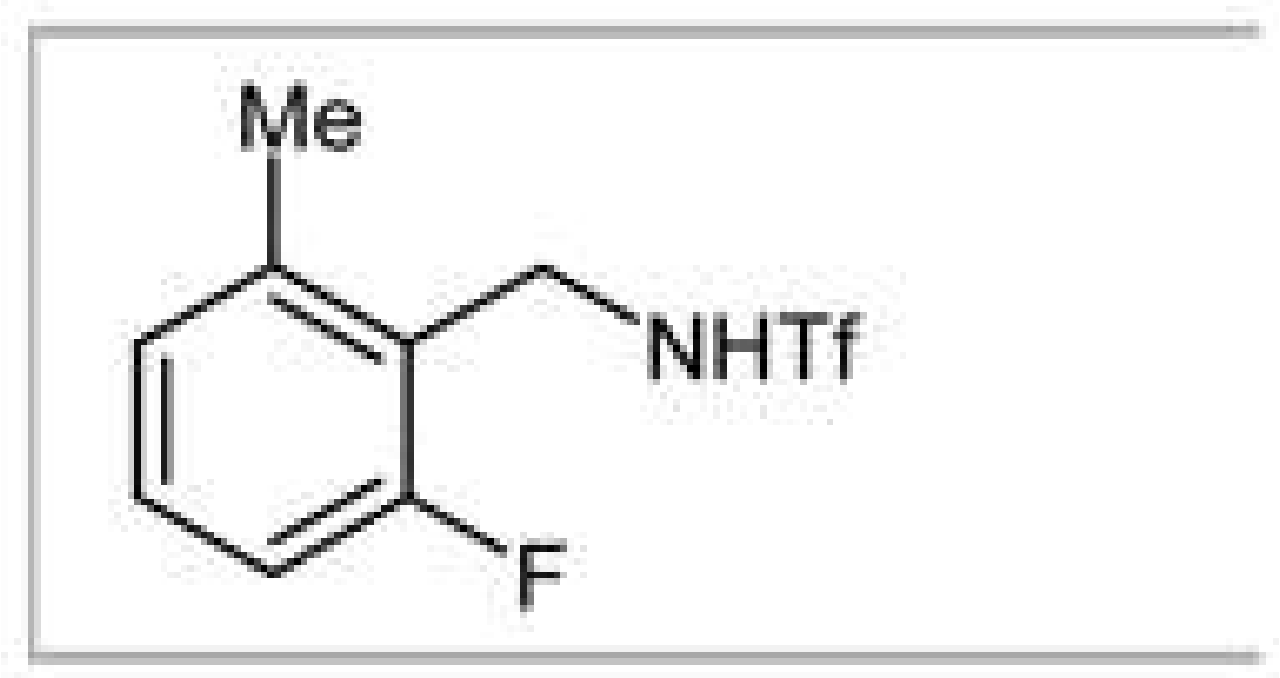
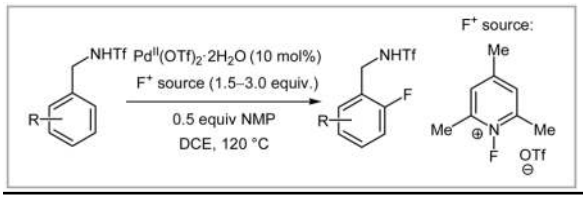
Product	Yield	Pro
	75%	
	67%	

Table 9

Substrate scope of the palladium-catalyzed directed electrophilic fluorination by Yu.



Product	Yield	Pro
	82%	



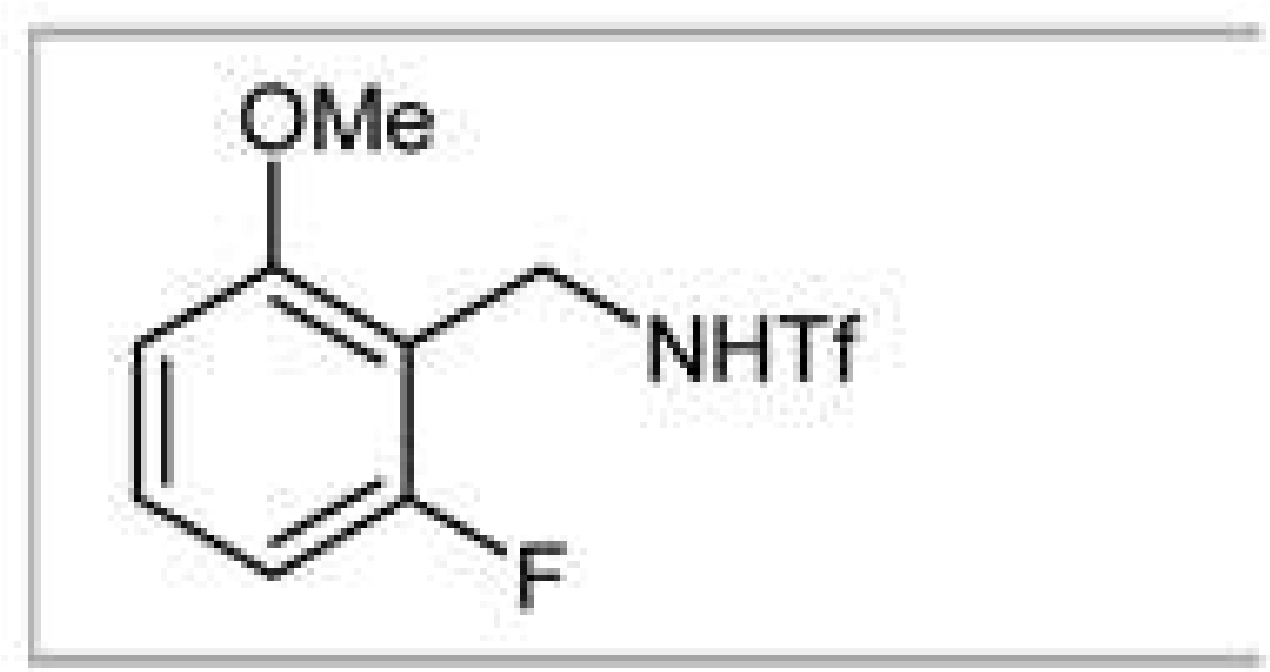
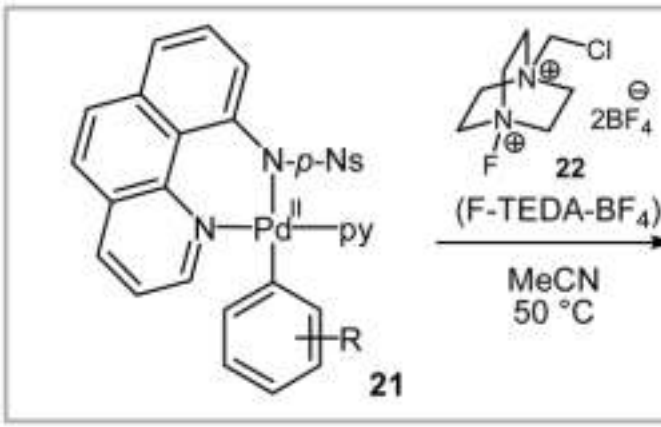
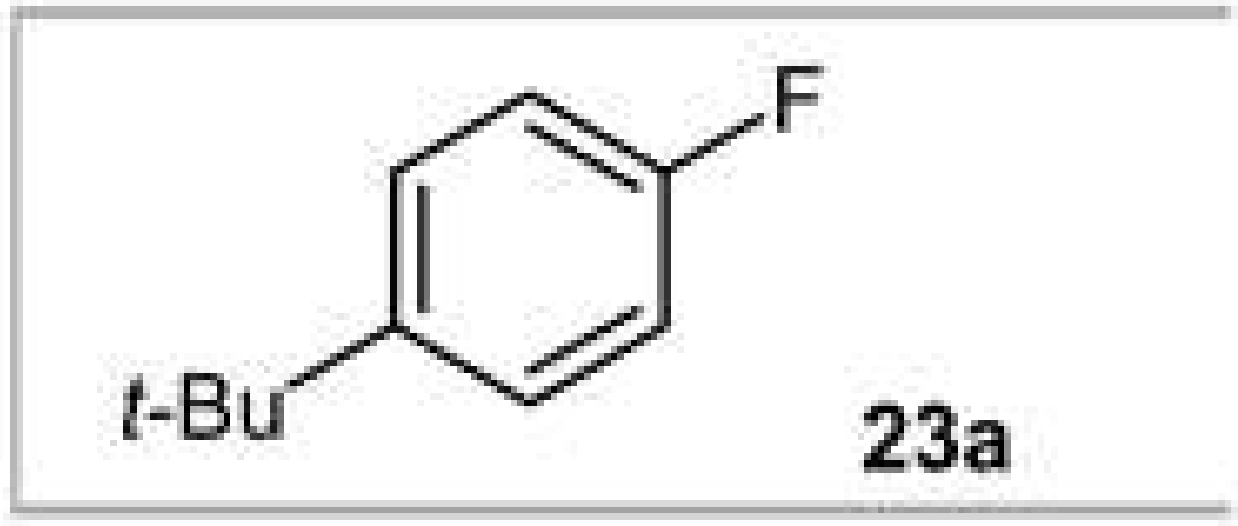
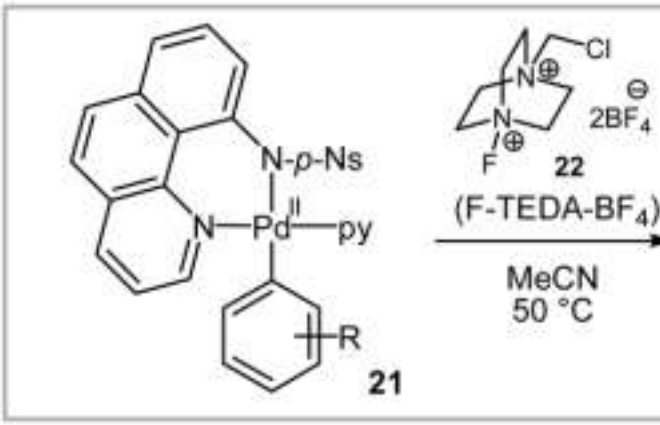
Product	Yield	Pro
	60%	

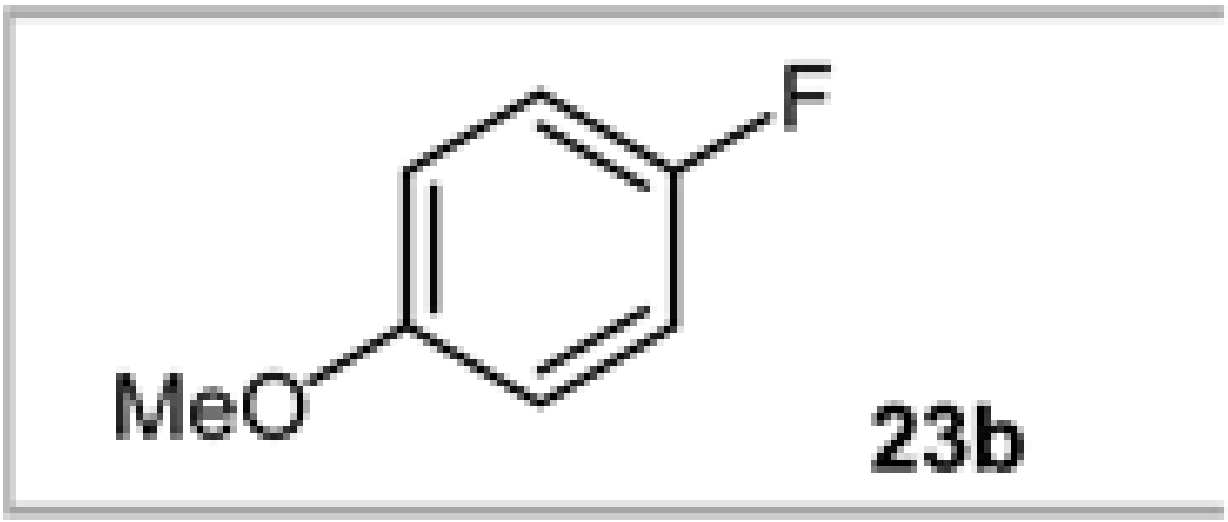
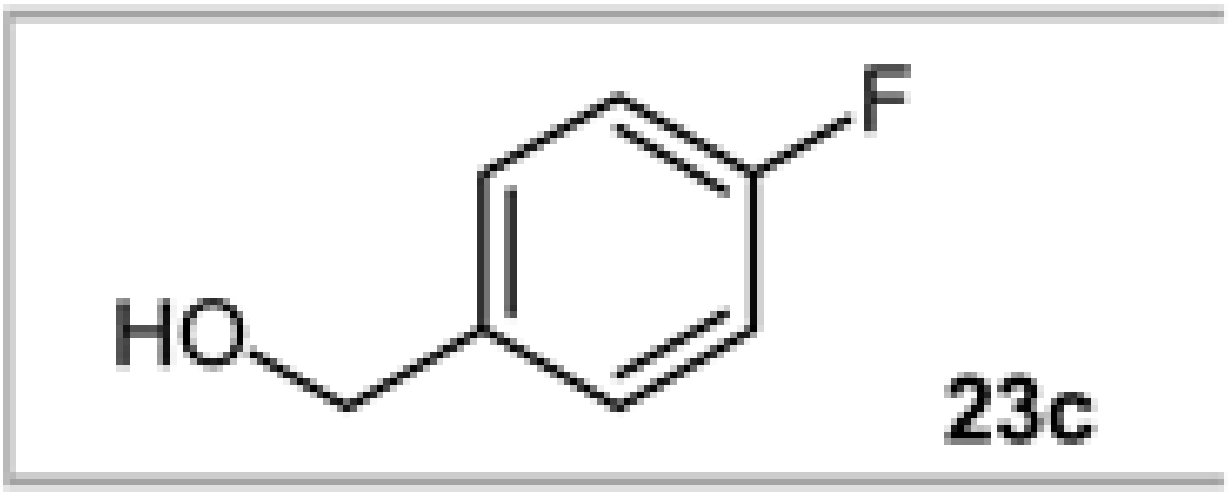
Table 10

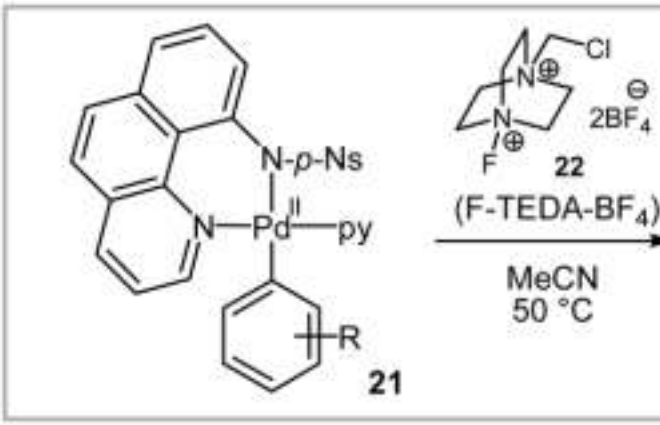
Substrate scope of the palladium-mediated electrophilic fluorination by our group



Product	Yield
	79%



Product	Yield
	46%
	70%



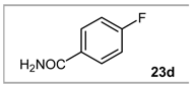
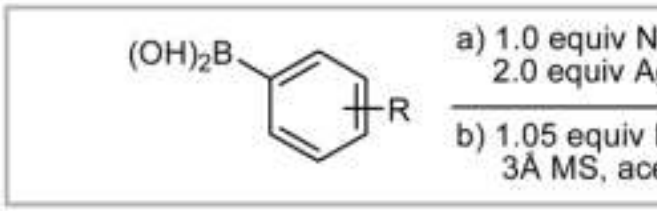
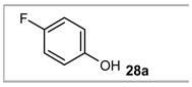
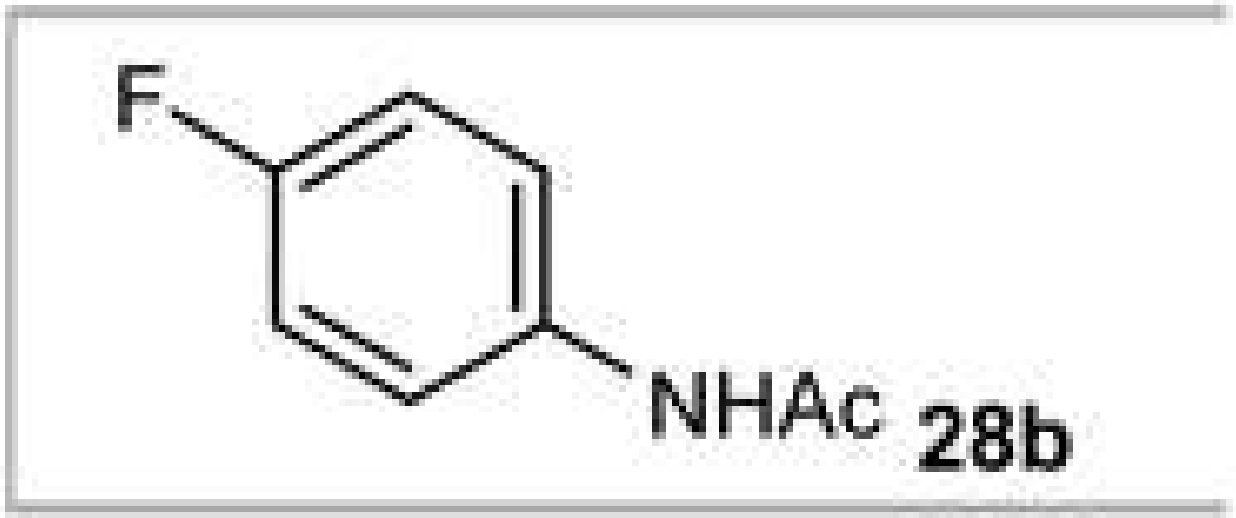
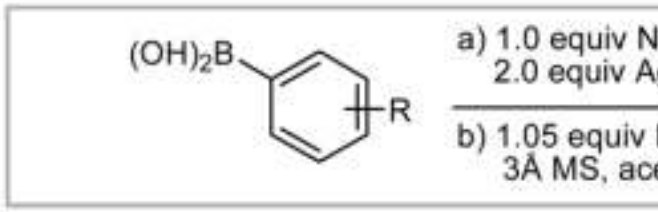
Product	Yield
	74%

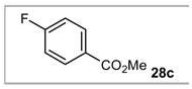
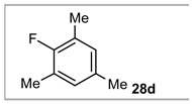
Table 11

Substrate scope of the silver-mediated fluorination of aryl-boronic acids reported by our group.



Product	Yield
 28a	70%
 28b	77%



Product	Yield
	76%
	73%