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Transition metal-catalyzed fluorination of multi carbon–carbon bonds: new strategies for fluorinated heterocycles

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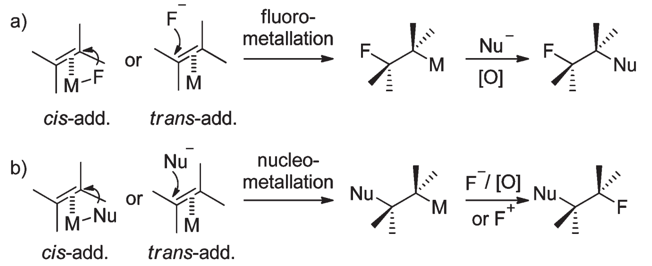
Transition metal catalysts have been developed for introducing fluorine into organic compounds. Recent progress in this area is reviewed with an emphasis on the selective fluorination of alkenes, alkynes and allenes. Regio- and stereoselective fluorination reactions are highlighted.

A. Introduction

Introducing fluorine into organic molecules significantly improves properties such as solubility, bioavailability and metabolic stability, which are of great importance in pharmaceuticals.[1] Despite the utilities of organofluorine compounds, relatively few methods exist for selective carbon–fluorine bond formation,[2] especially when compared to methods for other carbon–halogen bond formations. In recent years, transition metal-catalyzed fluorination of organic compounds has received much attention.[3] Pioneering studies from the Grushin group have demonstrated that the reductive elimination of aryl-Pd^{II}(F) intermediates is quite challenging.[4] In 2009, Buchwald and coworkers have reported a palladium-catalyzed cross-coupling reaction of aryl triflates with CsF to afford fluoroarenes.[5] In this reaction, the sterically hindered phosphine ligand (Brettphos) plays an important role in promoting the reductive elimination from $L_nPd^{II}(Aryl)F$. Meanwhile, several groups described methods for Pd-catalyzed fluorination of aromatic compounds,[6] in which the formation of C–F bonds were achieved *via* a Pd(II/IV) catalytic cycles in the presence of F^+ reagents (Scheme 1).[7] In addition, silver-catalyzed fluorination of aryl-metal reagent has also been reported for synthesis of arylfluoride.[8] For the alkyl C–F bond formation, Gouverneur and Brown reported a palladium-catalyzed allylic fluorination,[9] and the related enantioselective allylic fluorination was explored by Doyle and coworkers.[10] Quite recently, Nguyen and coworkers reported an Ir-catalyzed allylic fluorination reaction utilizing trichloroacetimidates, and the reaction relies on the $Et_3N·3HF$ reagent to provide branched allylic fluorides at room temperature.[11]

Tandem cyclization and fluorination of unsaturated carbon–carbon bonds also represents an efficient way to construct fluorinated heterocycles, which serve as important moieties in bioactive compounds. Herein, we review recent progress of transition metal-catalyzed fluorination of alkenes, alkynes and allenes. The fluorination of aromatic compounds, which has been well summarized in other reviews,[3] is beyond the scope of this review.



Scheme 1 Two approaches to the C–F bond formation in transition metal-catalyzed fluorination of alkenes.

It has been well-documented that C–Cl bond formation can be achieved *via* either chloropalladation of multi C–C bonds[12] or oxidative cleavage of C–M bond[13] in metal-catalyzed chlorination of alkenes. We reasoned that C–F bond formation might be carried out *via* similar approaches: (a) fluorometallation of alkenes; (b) reductive elimination of C–M(F) intermediates which are generated from nucleometallation[14] of alkenes (Scheme 1). The fluorination of alkynes and allenes are proposed to proceed *via* the same strategy as well. However, those two approaches are hindered either by high barriers associated with reductive elimination to form C–F bond, or unknown reactivity of metal fluoride toward unsaturated C–C bond.

B. Fluorometallation of unsaturated C–C bonds

As we mentioned above, the halometallation of multi C–C bonds has been extensively studied. Meanwhile, the corresponding fluorometallation is less explored. Early examples of fluorination of alkynes have been investigated with gold catalysts. In 2007, Sadighi and coworkers reported the (NHC)gold-catalyzed

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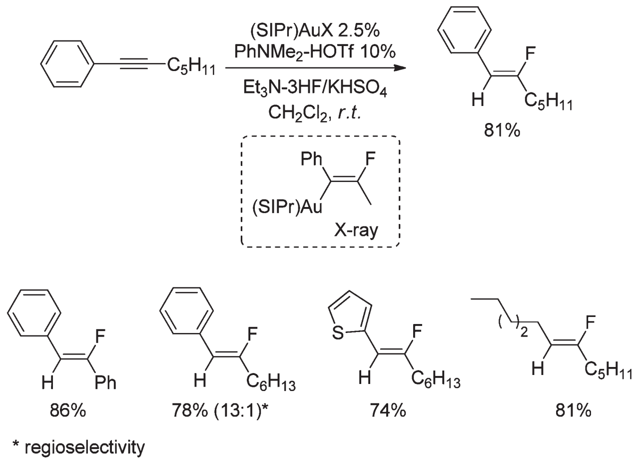
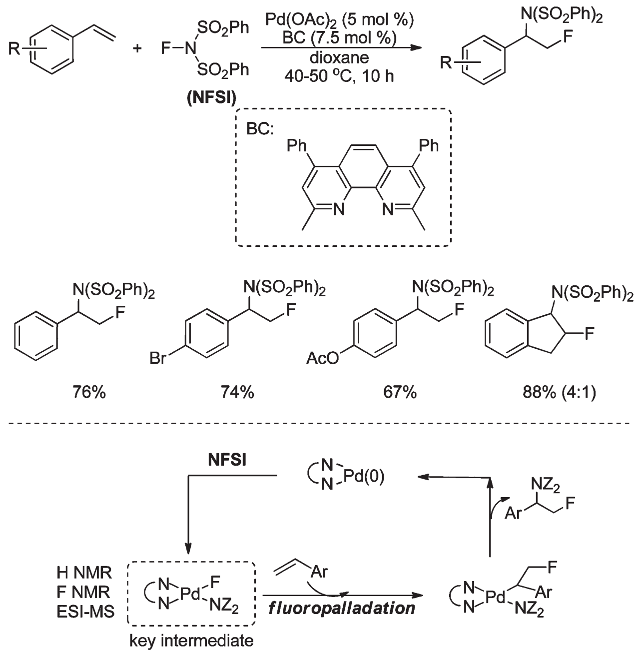
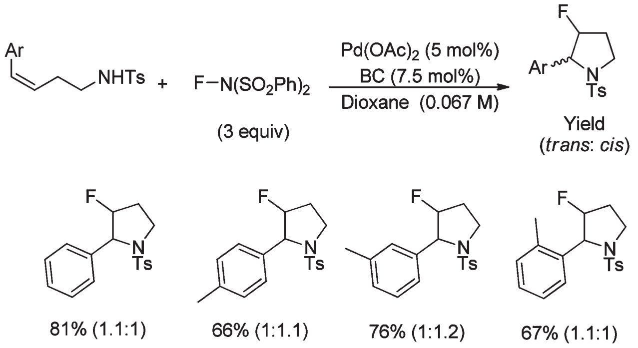


Scheme 2 Au-catalyzed fluorination of alkynes.



Scheme 3 Pd-catalyzed fluoroamination of styrenes.



Scheme 4 Palladium-catalyzed intramolecular aminofluorination.

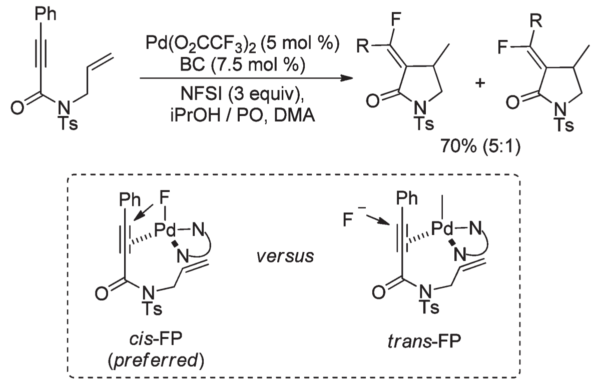
hydrofluorination of alkynes to afford a variety of vinylfluorides with Et$_3$N·3HF as the fluorine source (Scheme 2).[15a] The *trans*-addition of (NHC)gold(I) fluoride to alkynes results in reversible C$_{sp^2}$–F bonds formation. This reaction exhibits high regio-selectivity to afford vinylfluoride products in good to excellent yields. Recently, a modified gold catalytic system reported by Miller and coworkers allowed regio- and stereo-controlled addition of HF across functionalized alkynes.[15b]

In 2010, Liu and coworkers reported a palladium-catalyzed intermolecular aminofluorination of styrenes by using NFSI as the fluorine source. In this transformation, a bidentate-nitrogen ligand was shown to be crucial to promote the formation of aminofluorine product.[16a] Further study revealed that a Pd(II) fluoride complex, characterized by ^{19}F NMR, ^{1}H NMR and MS, was generated from the oxidation of Pd(0) by NFSI. The following fluoropalladation of styrenes and reductive elimination proceeded to afford desired products (Scheme 3). This catalytic system was demonstrated to be efficient for the intramolecular aminofluorination of styrenes, and led to a variety of five-membered fluorinated products in good yields but moderate diastereoselectivities (Scheme 4).[16b] In order to explore the stereochemistry in the fluoropalladation step, a palladium-catalyzed tandem fluorination and cyclization of an enyne was investigated. The reaction afforded a fluorinated 3-benzylidenyllactame with (*E*)-isomer as the major product.[16c] The result suggested that *cis*-aminopalladation of alkynes is the preferred pathway in the construction of C$_{sp^2}$–F bond (Scheme 5).

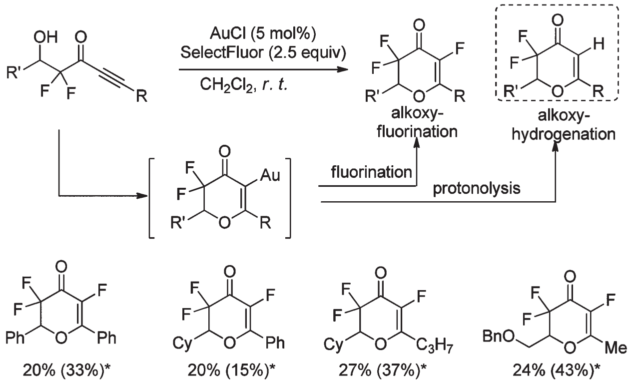
C. Transition metal-catalyzed oxidative fluorination of multi C–C bonds

In addition to fluorometallation of unsaturated C–C bonds, fluorination of a C–M bond is an alternative pathway to construct C–F bonds (Scheme 1B). In this way, the intramolecular reaction represents a good way to synthesize fluorinated heterocycles. Due to the scarcity of methods for the fluorination of C–M bonds, transition metal-catalyzed selective fluorination of multi C–C bond reactions have been less investigated until recently. So far, only three types of metals, Au, Pd and Ag, were applied in these transformations. In 2008, Gouverneur and coworkers reported a gold-catalyzed alkoxyfluorination of alkynes, which involves a sequential alkoxyauration reaction and oxidative fluorination of the vinyl–Au bond with SelectFluor as the fluorine source.[17] However, the protonolysis of vinyl–Au bond cannot be avoided, leading to significant amount alkoxyhydrogenation product (Scheme 6). It is worth noting that difluorine substitution at the α-position of carbonyl group is vital for this transformation. Only hydroalkoxylation is observed in the absence of the difluorine substitution.

Nevado recently reported a gold-catalyzed tandem rearrangement and fluorination of propargyl acetate, which serves as an efficient method to synthesize α-fluoroenones.[18] This reaction is initiated by 1,3-migration of the acyloxy moiety to the triple bond to generate a vinyl–Au(I) intermediate. This intermediate is then oxidized by SelectFluor to Au(III) species, which undergoes reductive elimination to generate C$_{sp^2}$–F bonds (Scheme 7). This strategy has been applied to the synthesis of fluorinated pyrazoles. Xu and coworkers reported a gold-catalyzed

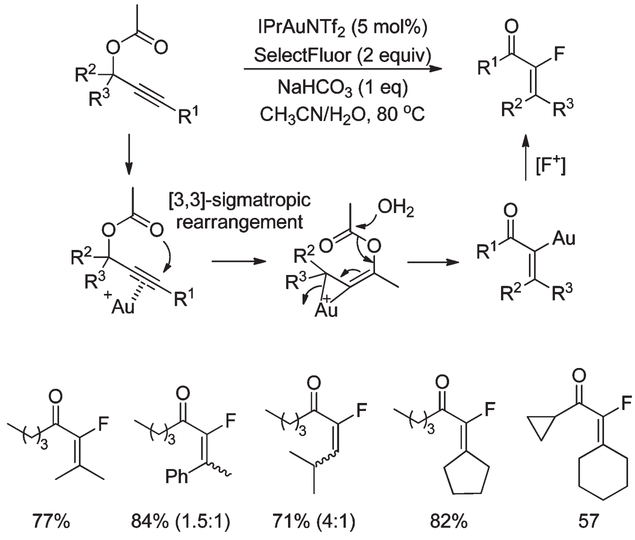


Scheme 5 Pd-catalyzed tandem fluoropalladation and enyne cyclization.



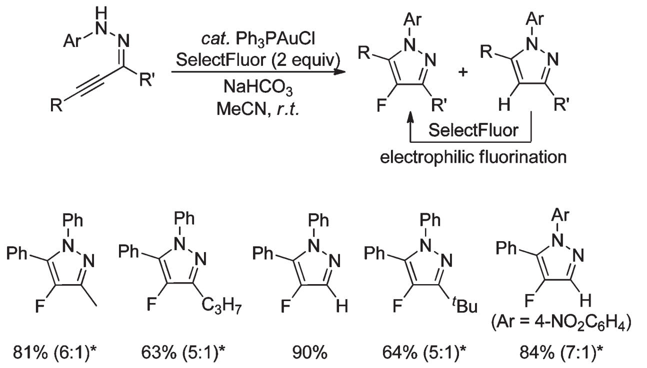
* The data in parentheses is the yield of alkoxyhydrogenation.

Scheme 6 Au-catalyzed alkoxyfluorination of alkynes.



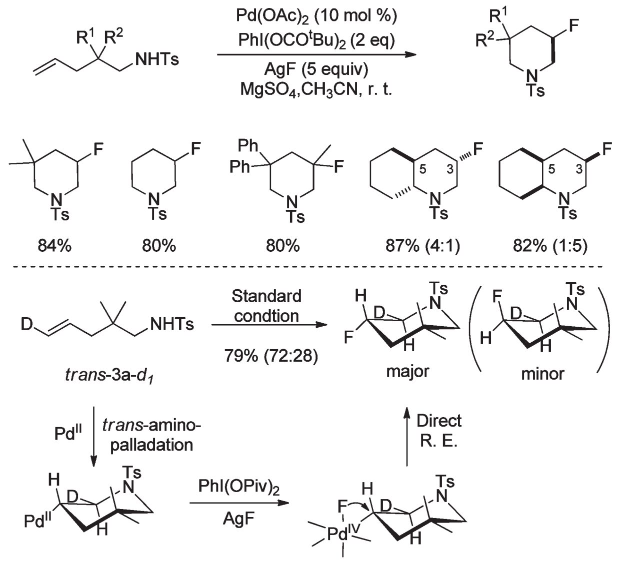
Scheme 7 Au-catalyzed fluorination of alkynes.

fluoroamination of alkyne by employing a similar catalytic system (Scheme 8).[19] In this transformation, a hydroamination product pyrazole formed simultaneously, which can further convert to the corresponding fluorinated pyrazole *via* electrophilic fluorination.



* The data in parentheses is the ratio of product C-F and C-H.

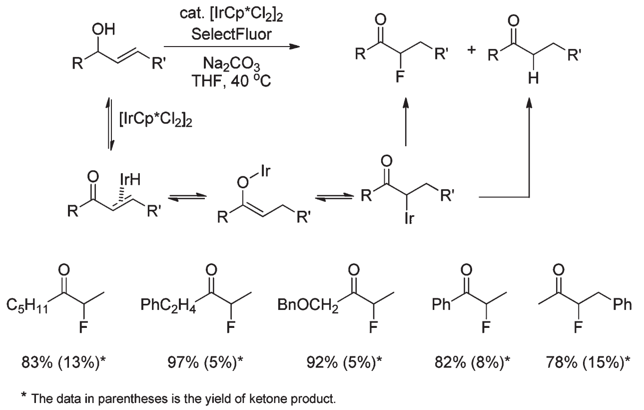
Scheme 8 Au-catalyzed aminofluorination of alkynes.



Scheme 9 Pd-catalyzed intramolecular aminofluorination of alkenes, and the related mechanism study.

All the successful examples of Au-catalyzed fluorination of alkynes involve a similar key vinyl–Au intermediate bearing an adjacent carbonyl group, which can be oxidatively fluorinated by SelectFluor. In contrast, the fluorination of normal vinyl–Au and other C–Au bonds remain unsuccessful.

Palladium catalysts have also been examined for fluorination of alkenes. Liu and coworkers disclosed a palladium-catalyzed oxidative fluoroamination of alkenes,[20] which is mechanistically similar to the Pd-catalyzed oxidative chlorination of alkenes.[21] A variety of fluorinated piperidine derivatives were obtained with high regio-selectivity. Preliminary mechanistic studies implied that the reaction involved (1) *trans*-aminopalladation of alkenes, (2) oxidation of C_{sp^3}–Pd^{II} intermediate to C_{sp^3}–Pd^{IV}(F), and (3) reductive elimination of the C_{sp^3}–Pd^{IV}(F) intermediate. The final C–F bond formation step predominantly proceeds *via* a direct reductive elimination pathway (Scheme 9). It is worth noting that, unlike previous generations of C–F bond by with F^+ reagent, this reaction represents the first oxidative fluorination of C–Pd bond by using inorganic fluoride salt and oxidant. Both AgF and hypervalent iodide reagent are crucial for this



* The data in parentheses is the yield of ketone product.

Scheme 10 Iridium-catalyzed fluorination of allylic alcohols.

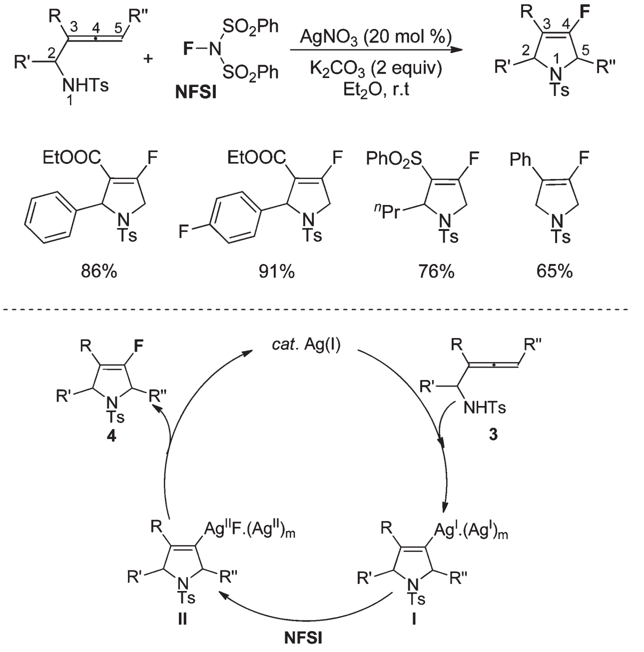
transformation. Further studies showed that the AgF/PhI(OPiv)$_2$ catalytic system could not afford the fluorination product in the reaction of *N*-Aryl acryamide at slightly higher temperatures. Instead, C–H bond activation of acetonitrile was observed, and AgF was shown to exhibit dual roles as both Lewis acid and base.[22]

In 2011, Martín-Matute and coworkers disclosed an Ir-catalyzed conversion of allylic alcohols to α-fluoroketones, which is proposed to proceed through a tandem Ir-catalyzed isomerization of allylic alcohol and oxidative fluorination of C–Ir bond by SelectFluor (Scheme 10).[23]

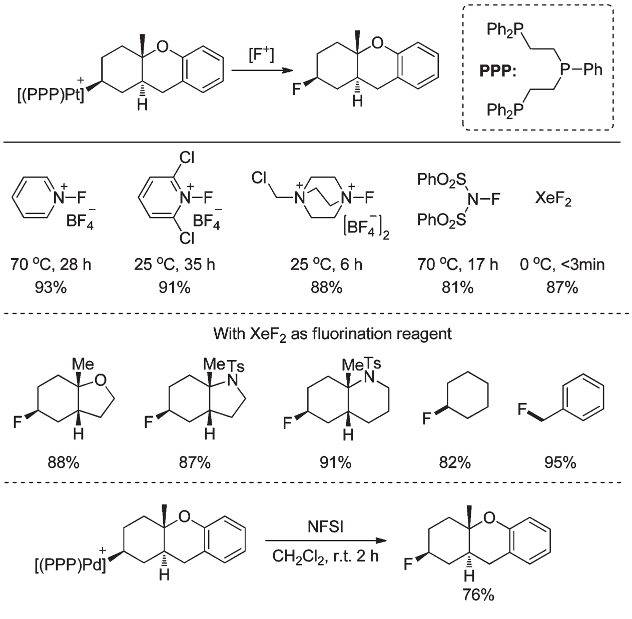
Finally, the fluorination of allenes has also been explored. Liu and coworkers recently reported a silver-catalyzed intramolecular aminofluorination of allenes, which provides an efficient synthetic route to a variety of 4-fluoro-dihydropyrrole derivatives. In this reaction, C–F bond formation was proposed to proceed *via* oxidative cleavage of vinyl–Ag bond.[24] Substrates bearing an electron-withdrawing group at the C-3 position exhibit excellent reactivities (Scheme 11). Those 4-fluoro-dihydropyrroles can be further converted to the corresponding 4-fluoropyrroles in a one-pot fashion in good yields.

D. Stoichiometric fluorination of sp^3 C–metal bond

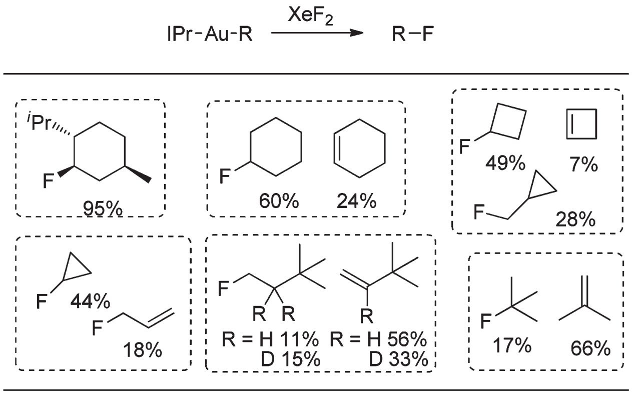
In the fluorination of alkenes, the fluorination of the sp^3 C–M bond is proposed as the key process for these transformations. In order to study the detailed mechanism, several stoichiometric fluorination reactions were performed. Sanford and coworkers have demonstrated that benzylic C–Pd bonds generated from C–H activation can be fluorinated by using F$^+$ reagent.[6a] Later on, Viagalok reported that complexes featuring benzylic C–Pt bonds react stoichiometrically with F$^+$ to form benzylic C–F bonds.[25] In 2011, Magne and coworkers reported the first example of an unactivated C–Pt bond fluorination, in which a secondary sp^3 C–Pt is oxidatively fluorinated to afford C–F bonds by using variety of electrophilic fluorinating reagents.[26] As shown in Scheme 12, XeF$_2$ exhibits excellent reactivity, and various secondary sp^3 C–Pt complexes could be successfully converted to fluoride products. It is quite interesting that the C–F bond formation proceeds *via* the direct reductive elimination of sp^3 C–Pt(IV) to retain the stereo-configuration at the carbon center. The reaction of the benzylic C–Pt compound proceed smoothly as well. In addition, palladium analogues of the Pt complexes show even better reactivity, which can be oxidized by using milder fluorinating reagent (*e.g.* NFSI) at room temperature. The fluorination of secondary sp^3 C–Au complexes was conducted by Toste and coworkers.[27] The sp^3 C–Au bonds exhibit lower reactivity than the related Pt and Pd complexes, and led to formation of byproducts *via* β-hydride elimination or rearrangement. The reductive elimination of sp^3 C–Au(III) intermediate shown same stereochemical outcome as the Pt complexes (Scheme 13). Overall, the above results indicated that secondary sp^3 C–M



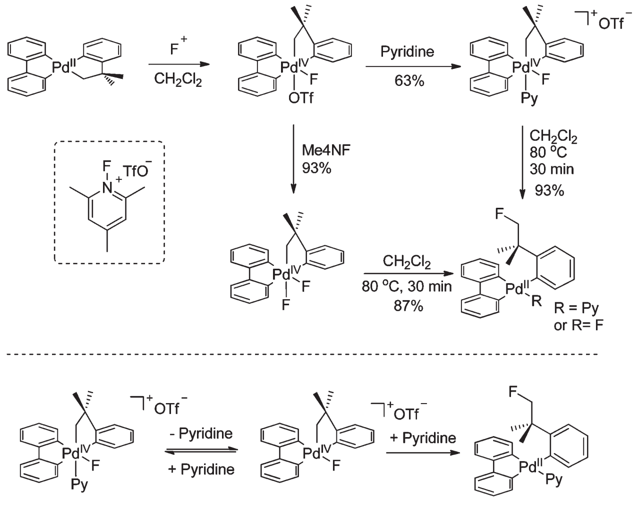
Scheme 11 Silver-catalyzed intramolecular aminofluorination of allenes.



Scheme 12 Fluorination of sp^3 C–Pt bonds.



Scheme 13 Fluorination of sp^3 C–Au bonds.



Scheme 14 Fluorination of sp^3 C–Pd bonds.

(M = Pt, Pd and Au) bonds can be efficiently fluorinated by electrophilic F$^+$ reagents *via* reductive elimination of hypervalent metal fluoride complexes. However, the fluorination of primary sp^3 C–Pt bonds is still challenging.

In 2012, Sanford and coworkers demonstrated that the reductive elimination of Pd(IV) complexes can be used as an efficient way to construct sp^3 C–F. The authors utilized a Pd complex bearing both sp^3 and sp^2 C–Pd bonds to examine the fluorination reaction, and found that the sp^3 C–F bond was selectively formed (Scheme 14).[28] The reductive elimination of the Pd(IV) complex is quite sensitive to the coordinated ligand, and the reaction rate is inhibited by an excess of ligand, such as pyridine or fluoride. The authors suggested that dissociation of the pyridine or fluoride ligand occurs prior to the rate-determining reductive elimination of Pd(IV).

Conclusions

Significant progress in the utilization of transition metal-catalyzed fluorination reactions to introduce fluorine into organic compounds has been achieved in recent years. These catalytic systems have been applied to synthesize a variety of fluorinated organofluorine compounds, especially fluoroheterocycles. The mechanistic studies provide important insights for deeply understanding of pathways of the fluorination, and also a rational basis for the development of new fluorination methodology. We envisage that applications of specified metal catalyst in synthesizing complex target molecules should be possible.

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