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REVIEW

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Transition metal-mediated/catalyzed fluorination methodology developed in the 2000s

Dae Young Bae[1] and Eunsung Lee[1,2,3*]

[1] Department of Chemistry, Pohang University of Science and Technology, Pohang, 790–784, Republic of Korea [2] Division of Advanced Materials Science, Pohang University of Science and Technology, Pohang, 790–784, Republic of Korea [3] Department of Chemistry, Stanford University, Stanford, CA 94305-5080, United States

ABSTRACT

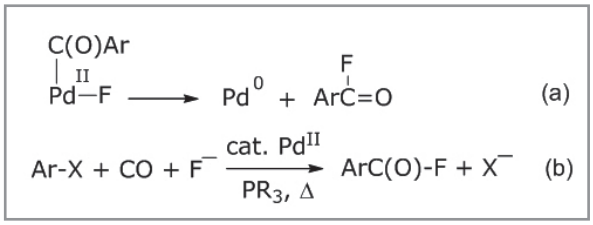
In the 2000s, there has been a significant advance on carbon–fluorine (C–F) bond formation reactions via transition metal mediated or catalyzed methods. Of course, for the past 10 years, transition metal catalysis improves C-F bond formation in terms of practicality and even can be applied to C-18F bond formation reaction. In this mini-review, we summarize various transition metal mediated or catalyzed fluorination reactions, which were developed in the mid-2000s.

Key Word: Fluorination, Carbon–fluorine, Transition metals, Catalysis

Introduction

Traditional carbon-fluorine bond formation reactions such as nucleophilic fluorination typically requires high reaction temperatures due to weak nucleophilicity of fluoride anion causing a huge activation energy. Thus, transition metal catalysis has been studied extensively because the catalyst can lower activation energy, as numerous transition metal catalyzed carbon-heteroatom formation reactions have been developed dramatically for the last half centry. A transition metal-mediated fluorination method was performed for the first time in the late 1980s by Tanaka, who found that catalytic carbonylative aromatic halide-exchange fluorination was possible using an organometallic complex (Scheme 1(a)) (1). Subsequent reactivity studies by Grushin (2) suggested reductive elimination of ArC(O)-F from PdII as the mechanism of C-F bond formation in this system, by analogy to the reductive elimination of other carboxylic acids derivatives mediating PdII catalysis of the many related carbonylative transformations of aryl halides (3).

Since then, Togni (4) have developed catalytic enantioselective fluorination methods utilizing asymmetric transition metal Lewis acids (chiral Ti^{IV}(TADDOLate)X_2 catalysts) (5) as well as aliphatic halide-exchange fluorination utilizing an Ru(II)/TlF system (Scheme 2) (6). Sodeoka (7) and Cahard (8) developed well-defined Pd^{II}, Cu^{II} and other metal-based catalytic systems, in all of which C-F bond



Scheme 1. The catalytic fluorocarbonylation process. (a) The formation of acyl fluoride on palladium center and (b) the first catalytic carbon-fluorine bond formation via transition metal catalysis.

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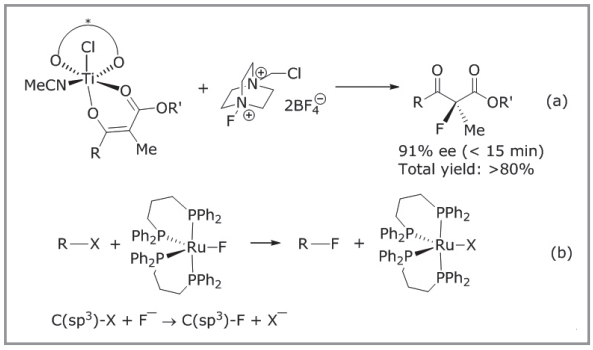
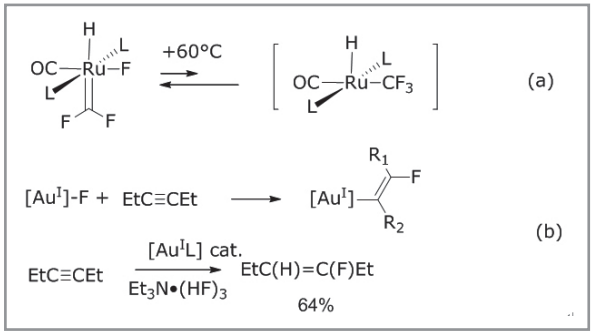
Correspnding Author : Eunsung Lee, Tel: +82-54-279-2111, Fax: +82-54-279-8129, E-mail: eslee@postech.ac.kr



Scheme 2. (a) The catalytic enantioselective fluorination and (b) aliphatic halide-exchange fluorination.



Scheme 3. (a) Reversible transfer of coordinated fluoride to α-(Ru(II)/CF_2) and (b) selective catalytic hydrofluorination of alkyne.

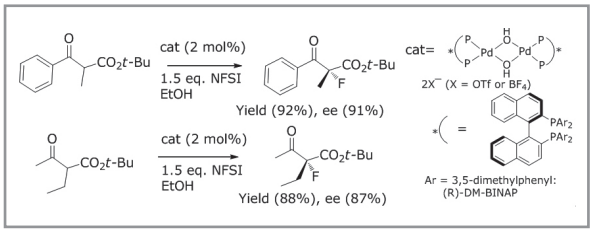
formation is believed to result from direct electrophilic attack at chiral metal-bound enolate intermediates by stoichiometric electrophilic fluorinating reagents. Caulton (9) and Sadighi (10) reported reversible transfer of coordinated fluoride to -(Ru(II)/CF_2) and ß-carbons (Au(I)/alkyne) of unsaturated substrates, respectively, the latter in the context of uniquely selective catalytic hydrofluorination of alkynes using triethylamine trihydrogen fluoride ($Et_3N{\cdot}(HF)_3$) as a fluorinating reagent (Scheme 3).

Most recently, Sanford et al (11) reported on directed oxidative fluorination of unactivated aromatic and aliphatic C-H bonds with electrophilic fluorinating reagents, utilizing a Pd(II/IV) catalytic system. In a following mechanistic study by Furuya and Ritter (12), aryl fluoride reductive elimination from Pd(IV) was conclusively demonstrated for the first time for any metal as an elementary C-F bond forming reaction that yields aryl fluorides at least in the related stoichiometric protocols.

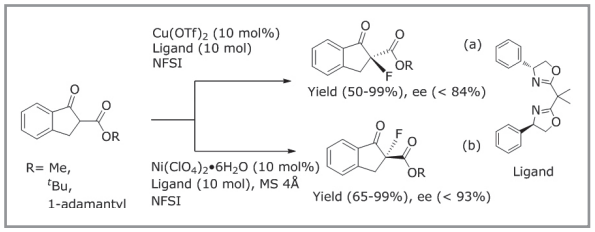
Buchwald and coworkers have accomplished the long-sought aryl fluoride reductive elimination from Pd(II) and successfully applied it to catalyze aromatic halide-exchange fluorination with CsF that features wide substrate scope (13). This work strongly supports the aryl fluoride bond formation from a well-defined Pd(II)ArF complex (14), which is the first example of aryl fluoride bond formation from Pd(II)ArF complex, that resulted from the reductive elimination pathway rather than a nucleophilic attack of fluoride anions formed from Pd(II)-F complex (15).

Transition Metal-mediated/catalyzed Asymmetric Fluorination

As described in the previous section, asymmetric fluorination has been studied by other groups seeking a better catalyst that utilizes organic catalysts or transition-metal catalysts in the presence of electrophilic fluorinating reagents (16). Sodeoka et al. achieved enantioselective fluorination of various ß-ketoesters with enantioselectivity over 87% ee (Scheme 4). Interestingly, the reaction proceeds well in ethanol and is not sensitive to water, broadening the selectivity of solvents. The Shibata group showed the formation of opposite enantiomers as a result of fluorination in different metal complexes with the same chiral ligand (Scheme 5). The mechanism for the formation of enantiomeric products is unclear, even though the



Scheme 4. The catalytic enantioselective fluorination using a chiral palladium complex with NFSI.



Scheme 5. The catalytic enantioselective fluorination using chiral metal complexes with NFSI. (a) Copper catalyzed asymmetric carbon-fluorine bond formation and (b) nickel-catalyzed asymmetric carbon-fluorine bond formation. See Figure 1 for explanation of different chiral induction at each metal center.

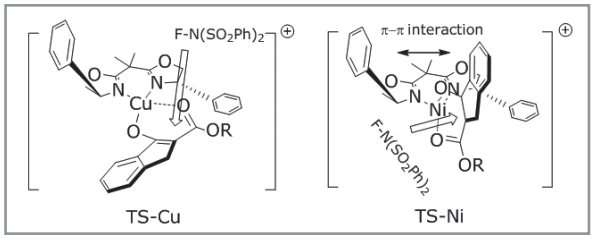
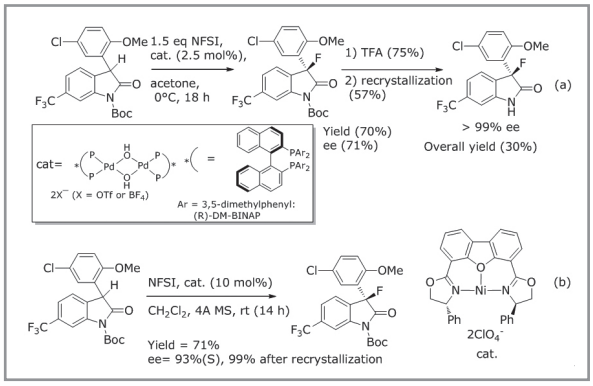


Figure 1. Proposed transition states of two different chiral transition metals complexes for enantioselective fluorination.

authors described possible transition states of two complexes that produce a different enantioselectivity (Figure 1). They proposed that the different results stem from a change in metal center geometry from (distorted) square planar (Figure 1, TS-Cu) or from square pyramidal (Figure 1, TS-Ni) in the transition states. Later, DFT optimization of a different chiral nickel complex revealed that the octahedral complex with water molecule formed with a ketoester substrate (17). Thus it is recommended that TS-Ni needs to be optimized to the octahedral geometry.

From the discovery of the protocols for enantioselective fluorination, the Sodeoka and Shibata groups extended their work to the preparation of Flindokalner, a Bristol-Myers Squibb drug candidate, for post-stroke neuroprotection (Scheme 6) (18, 19). These examples show how currently developed enantioselective fluorination could apply to the field of medicinal chemistry.



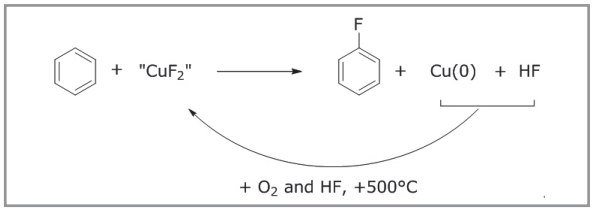
Scheme 6. The preparation of Flindokalner, a Bristol-Myers Squibb drug candidate, via catalytic enantioselective fluorination using chiral metal complexes with NFSI.

Transition Metal-mediated Fluorination

As mentioned above, previous asymmetric fluorination examples of C-F bond formation resulted from direct electrophilic attack at the substrates bonded to chiral metal intermediates. There was no example in which the transition metal plays a key role for a C-F bond formation such as reductive elimination on a metal center except for the Tanaka's catalytic fluorocarbonylation work. In this section, examples with such a key role of transition metal complexes will be discussed.

Transition Metal-mediated/catalyzed Oxidative Fluorination

Electron-rich aromatic compounds can react with electrophilic fluorinating reagents (20), but the results show a low selectivity because the process could possibly occur by one electron transfer to make aromatic radicals, followed by fluorination. Thus, the methodology for selective aromatic fluorination has



Scheme 7. Oxidative fluorination of benzene by CuF2.

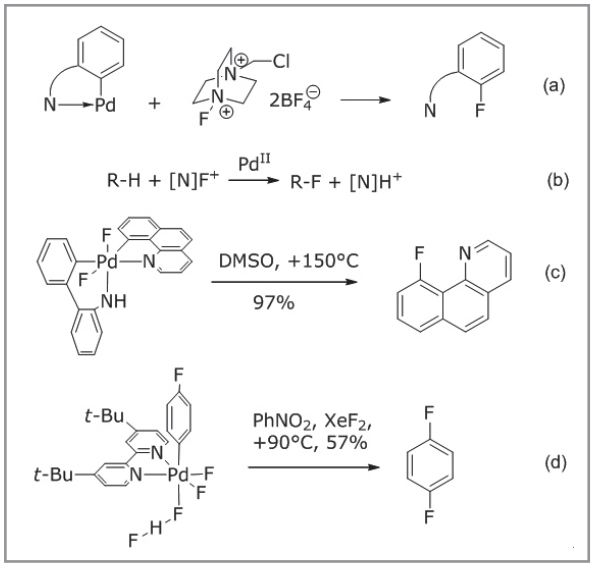
been sought by the chemists.

In 2002, Subramanian et al. reported that fluorobenzene can be prepared by copper(II) fluoride and the reduced copper can also be reoxidized to CuF_2 with HF and O_2 at 500°C (Scheme 7) (21). Further investigation was made by the Dolbier group focusing on oxidative fluorination of aromatic groups with $CuAl_2F_6$ (22).

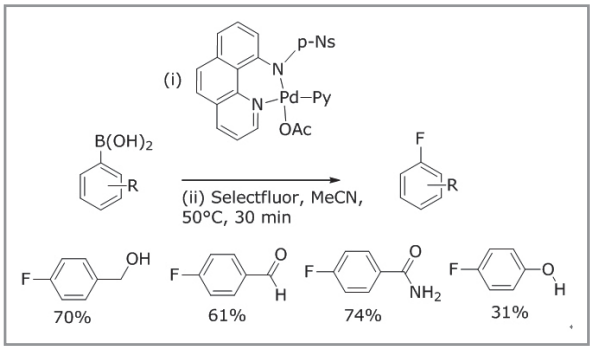
In 2006, Sanford reported catalytic oxidative fluorination of aryl and alkyl C-H bonds in quinoline substrates in the presence of $Pd(OAc)_2$ and N-fluoropyridinium salts (11), expanding on well-defined C-O bond-forming oxidative transformations developed with the same system (Scheme 8(a) and 8(b)) (23). From the protocol, various fluorinated quinolines were obtained with 33-75% yields. The mechanism was elucidated by the Ritter group, who reported aryl fluoride bond formation from a Pd(IV) fluoride complex directly (Scheme 8(c)) and by the Sanford group (Scheme 8(d)) (24). The Ritter work was also applied for preparing aryl fluorides with various functional groups from Pd(IV) fluoride complexes (Scheme 9) (12). With a similar approach, Yu et al. have established the preparation of ortho fluorination of aryl substrates with a directing group of triflamide in the presence of catalytic amount of $Pd(OTf)_2 \cdot 2H_2O$ (OTf= triflate) and *N*-fluoro-2,4,6-trimethylpyridinium triflate (25). The ortho-fluorination on aryl groups suggests that a five-membered palladacycle is an intermediate for the following fluorination. Vigalok et al. also reported aryl fluoride bond formation from well-defined palladium(II) complexes utilizing electrophilic fluorinating reagents (26).

While complete mechanistic details of Pd(II/IV)-catalyzed aromatic oxidative fluorination protocols continue to evolve, Ritter has also developed a distinct Ag(I)-based oxidative fluorination of aryl stannanes and aryl boronic acids that now permits concise fluorodehydroxylation of complex aromatic substrates (Scheme 10) (27).

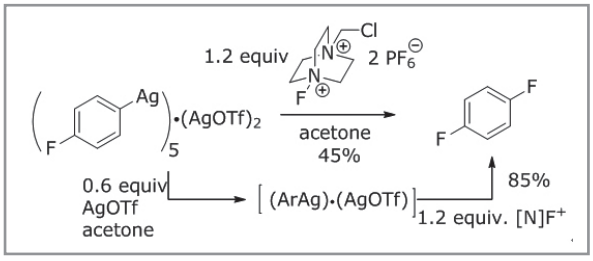
These discoveries are of a great importance because of they provide not only direct evidence for the C-F bond formation on the palladium complexes also but the protocols to prepare valuable fluorinated organic compounds. Nevertheless, the cost of the fluorination needs to be addressed due to a high cost of electrophilic



Scheme 8. (a) Proposed elementary step of aryl fluoride bond formation. (b) Catalytic Oxidative fluorination. (c) Elementary step of aryl fluoride bond formation a Pd(IV) fluoride complex. (d) Aryl fluoride bond formation from a Pd(IV) fluoride complex.



Scheme 9. The preparation of aryl fluoride with various functional groups.



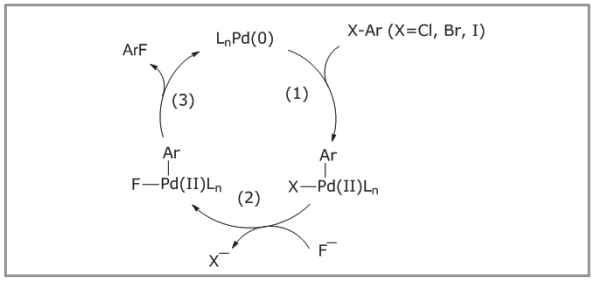
Scheme 10. The silver(I) catalyzed aryl fluoride bond formation.

fluorinating reagents and the palladium metal for the stoichiometric fluorination.

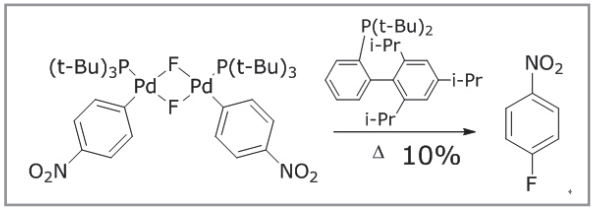
Transition Metal-catalyzed Fluorination

Distinct from previous approaches, attempts have been made to synthesize aryl fluoride from Pd(II)/Pd(0) system like C-C, C-N, or C-O coupling reactions on Pd(II) complexes (Scheme 11) (2). Grushin et al. patented the preparation of aryl fluoride from aryl halides in the presence of copper(II) fluoride, TMEDA (tetramethylethylene-diamine), and HMPA (hexamethylphosphoramide) or sulfolane at 180°C for 3 hours (28). In 2007, Yandulov et al. reported the formation of aryl fluoride from a well-defined palladium(II) aryl fluoride complex and the whole process was investigated with theoretical methods providing the fundamental insight of aryl fluoride bond formation on palladium(II) complexes (Scheme 12 and Figure 2).

DFT calculations suggest the feasibility of aryl fluoride bond formation from this palladium(II) aryl fluoride complex with electron withdrawing aryl group and sterically hindered phosphine ligand. The transition state is calculated to be + 18 kcal/mol. Even though



Scheme 11. Catalytic fluorination cycle via a Pd(II)/Pd(0) system.



Scheme 12. Formation of aryl fluoride from a well-defined palladium(II) aryl fluoride complex.

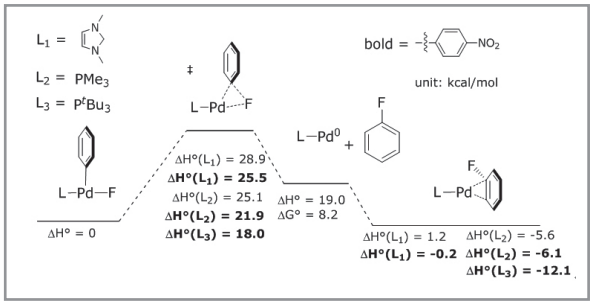
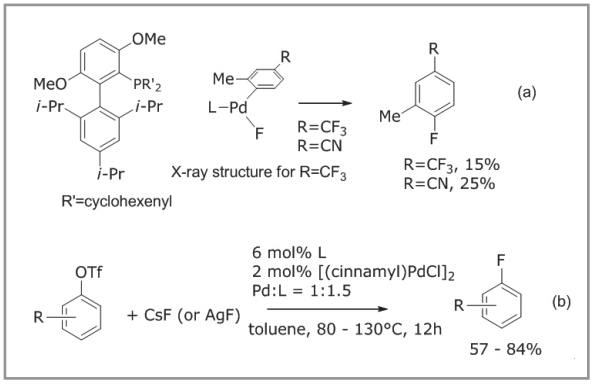


Figure 2. DFT calculation of aryl fluoride bond reductive elimination on Pd(II) complexes: computed reactivity profile of Pd(Ph)F(L) and related analogs.

the mechanistic issue on the (net) reductive elimination of aryl fluoride was questioned by Grushin (29), the subsequent Buchwald work supports the feasibility of aryl fluoride formation on the metal center.

First catalytic fluorination accommodating Pd(II)/Pd(0) system in the presence of CsF, a benign fluorinating source, or AgF, was reported by the Buchwald group. From an elementary aryl fluoride bond formation from a three-coordinate palladium aryl fluoride complex, whose structure was elucidated by X-ray crystallography, the catalytic fluorination was developed for the first time for a direct transformation of aryl bromides and aryl triflates into the aryl fluorides in the presence of F^-, finally completing the catalytic cycle (Scheme 13). The key for the success is a sterically hindered ligands, which was also demonstrated by Yandulov who showed the thermodynamic advantage (4 kcal/mol) by replacing the trimethylphosphine



Scheme 13. (a) Elementary aryl fluoride bond formation from three-coordinate palladium aryl fluoride complex and (b) catalytic aryl fluoride formation.

ligand with the sterically hindered phoshpine ligand (Figure 2) and the thermodynamic disadvantage from the dimerization of three coordinate palladium aryl fluoride complex, which did not occur in Buchwald's work.

Conclusions

In the 2000s, numerous new fluorination methodologies have been developed by focusing on fluorinating reagents and transition metal catalysts on the demands of current applications on pharmaceuticals, agrochemicals, ^{18}F radiotracers and materials. Nevertheless, beyond great discoveries that discussed in the main, there still remain several limitations in the scope of catalytic fluorination. As of now, no facile, mild, benign, reactive, and, so-called versatile yet low-pricing, fluorinating reagents are available, thus large scale preparation of fluorinated compounds is infeasible. Also, there is a limit for choosing the substrates because triflate or halogenated compounds are relatively expensive. The ideal fluorination could be oxidative catalytic fluorination with a cheap fluorinating sources such as alkali metal fluoride (KF or NaF) and cheap oxidants utilizing transition metal catalysts under mild conditions. Thus one research direction has been focused on (i) the synthesis of well-defined metal fluoride complexes and (ii) a C-H activation of a wide variety of substrates and (iii) a fluorination of activated substrates, and finally (iv) reoxidation of reduced metal complex for completing a catalytic cycle.

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