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Review

Advances in Catalytic C–F Bond Activation and Transformation of Aromatic Fluorides

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Abstract: The activation and transformation of C–F bonds in fluoro-aromatics is a highly desirable process in organic chemistry. It provides synthetic methods/protocols for the generation of organic compounds possessing single or multiple C–F bonds, and effective catalytic systems for further study of the activation mode of inert chemical bonds. Due to the high polarity of the C–F bond and it having the highest bond energy in organics, C–F activation often faces considerable academic challenges. In this mini-review, the important research achievements in the activation and transformation of aromatic C–F bond, catalyzed by transition metal and metal-free systems, are presented.

Keywords: C–F bond; catalytic; activation; aromatics; transition metal; metal-free

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1. Introduction

Organic fluoride refers to a class of organic compounds in which one or more of the C–H bonds are replaced by C–F bonds. Due to the high electronegativity of the fluorine atom and the high C–F bond energy, the fluorine-containing organic molecules usually exhibit unique and interesting chemical and biological properties to a great extent [1] and have been widely used in pharmaceuticals, synthetic materials, agricultural chemicals and fine chemicals [2,3], which play indispensable roles in our daily life. The nonmetallic element fluorine atom with the highest electronegativity (Pauling's Electronegativity 3.98) in the periodic table of elements is indeed a small atom (Pauling's Van der Waals radius 135 pm)with increasing impact in organic and biochemistries [4–6].

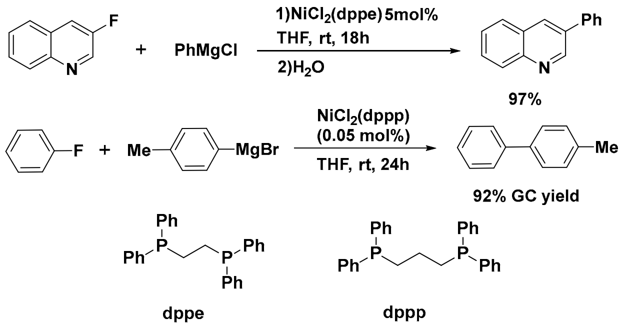
The activation of inert chemical bonds is an ineluctable task in general organic synthesis; however, compared with the rich chemistries of activation/transformation of various single bonds with high bonding energies, such as (E_b kJ/mol) C–H (E_b 414) [7–19], C–C (E_b 347) [20–30], C–N (E_b 308) [31–40] and C–O (E_b 358) [41–53], the activation of C–F bond (E_b 485)—which could be built efficiently following typical procedures [4,54–62]—is still scarce, due mainly to the abnormal strength of the bond energy and the shielding effect of fluorine atoms. Developing an efficient methodology for the functionalization of C–F bond is highly desirable for the following both academic and industrial reasons [63–65]: (1) It will enrich the catalytic toolbox for the activation of inert and polarized chemical bonds; (2) Selective C–F activation of multiple C–F bond containing compounds can provide attractive strategies for synthetic organic chemistry; (3) Regio-selective conversion of fluoride into various functional groups could provide novel molecular structures that are otherwise difficult to create. Therefore, catalytic C–F activations are receiving increased attention and significant progress has been made in the activation and transformation of C–F bonds in alkane fluorides [66–77]. This mini-review focuses on recent progress in the activation and functionalization of aromatic C–F bonds catalyzed by transition metal catalysts, as well some metal-free catalytic systems [78–80].

2. Transition Metal-Promoted Catalytic C–F Activation of Aromatic Hydrocarbons

Transition metals catalyst-promoted C–F bond activation and functionalization with high selectivity and activities represent effective ways to convert easily available and low-cost fluoro-aromatics into high value fluorine-containing or fluorine-free products via C–C (carbon–carbon coupling), C–H (hydro-defluorination, HDF) and carbon-hetero-atom bond formation processes [81]. Progress in recent years in aromatic C–F bond activation has accumulated steadily, and the newly developed methods could potentially also be applied to fluoro-containing organic waste degradation.

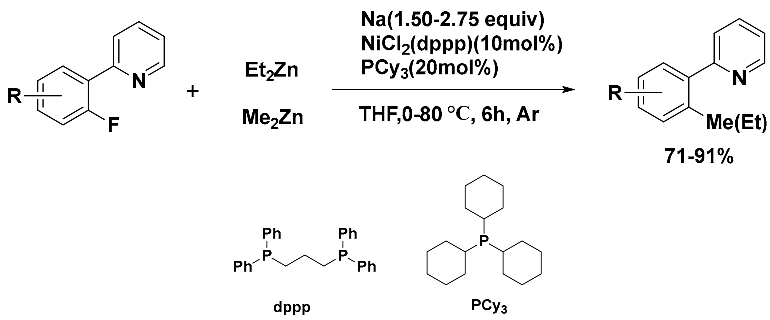
2.1. Ni-Catalyzed Activation of C–F Bonds in Fluoro-Aromatics

Nickle complexes are widely used in catalytic chemical transformations. The coupling reaction between the Grignard reagent and fluoro-aromatics catalyzed by Nickel (II) complexes containing bidentate phosphine ligands (1,2-diphenylphosphinoethane, DPPE, and 1,3-diphenyl phosphinopropane, DPPP) proved to be an efficient method for the defluoro-coupling reaction. Thus, in the presence of a DPPE-Ni(II) complex, Grignard reagent reacts with N-heterocyclic aryl fluorides to produce N-heterocyclic biphenyl compounds (TOF ca. 1.1 h^{-1},Scheme 1), whereas in the presence of DPPP-$NiCl_2$ under mild conditions, the reaction proceeded smoothly to generate the corresponding unsymmetrical biphenyl compounds with high yield and selectivity (TOF ca. 76 h^{-1}, Scheme 1) [82,83]. The structure of the bidentated phosphino-ligand plays a key role [84].



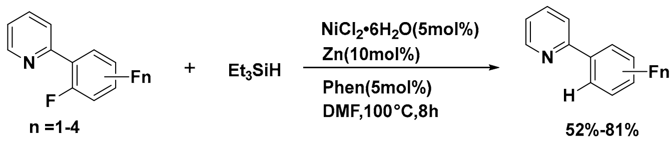
Scheme 1. Activation of C–F Bond catalyzed by nickel complexes with bidentate phosphine ligand.

Cao et al. reported a Na-assisted $NiCl_2$-dppp catalytic coupling reaction between fluoro-aromatics and alkyl zinc reagents. The pyridinyl ring was used as a guiding group to introduce a new C–C bond at the ortho position. The mechanistic study showed that there were free radical intermediates generated during the reaction [85]. The C–C coupling product can be obtained in high yield (TOF ca. 1.2–1.5 h^{-1}, Scheme 2).



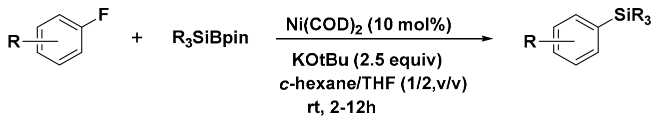
Scheme 2. $NiCl_2$ (dppp) catalyzed cross–coupling of fluoro–aromatics with organozinc reagents.

Zhang et al. reported the ortho-selective hydrodefluorination (HDF) of the similar fluoro-aromatics. In the presence of silane, using easily available inorganic Ni(II), $NiCl_2 \cdot 6H_2O$, *o*-2-pyridinyl-fluorobenzene derivatives underwent selective partial HDF reaction (TOF ca. 1.3–2.0 h^{-1}) [86]; this reaction can be applied to a variety of multifluoro-aromatic substrates, and a range of usually hard-to-access partial fluoro-aromatics can be effectively prepared (Scheme 3).



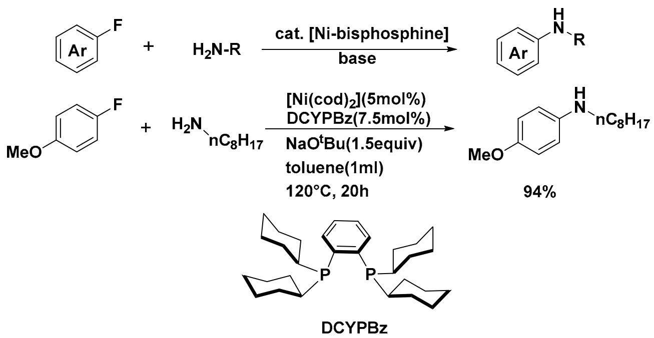
Scheme 3. $NiCl_2$ Catalyzed hydro–defluorination of fluoro–aromatics.

Shibata et al. developed an effective nickel(0)-based catalytic metathesis system for the defluoro-silylation reaction between fluoro-aromatics and R_3SiBpin, i.e., an aromatic C–F bond can be activated in the absence of additional ligands to obtain aryl silanes in high yield. This reaction is suitable for various inert fluoro-aromatics and a wide range of substrates [87]. Interestingly, it was further observed that the reaction can proceed under very similar conditions in the absence of a Ni(0) catalyst (Scheme 4).



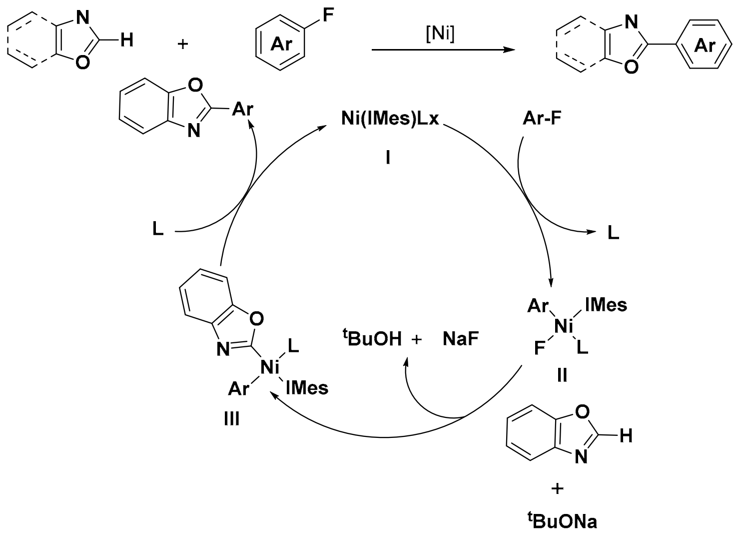
Scheme 4. Nickel(0)–catalyzed defluoro–silylation of fluoro–aromatics.

In 2018, Sawamura et al. reported the cross-coupling reaction between fluoro-aromatics and primary amines, mediated by Ni-complexes and producing secondary amines in high selectivity [88]. Electron-rich aryl fluoride 4-fluoroanisole reacted with alkyl-amine to give secondary amine products in up to 94% isolated yields (TOF ca. 0.9 h^{-1}). More importantly, no tertiary amine was detected in the crude product. Thus, this method has the potential for the synthesis of multifunctional aniline derivatives from diversified fluoro-aromatic substrates (Scheme 5).



Scheme 5. Nickel–catalyzed amination of fluoro–aromatics with primary amines.

Zhang et al. [89] developed a method for the nickel-catalyzed coupling of fluoro-aromatics with oxazole. Studies showed that the heteroaryl fluoride is a class of substrate that can tolerate various functional groups. The mechanism of the C–F/C–H metathesis coupling reaction was thusly proposed: fluoro-aromatics first coordinate with Ni(0), **I**, and then C–F is oxidatively added to the center of Ni(0) to obtain Ni(II) intermediate **II**. In the presence of the base, the deprotonation reaction of benzoxazole generates a benzoxazole anion, which undergoes the metal transformation with intermediate **II** to form diaryl intermediate **III**. Finally, the required product is obtained through reductive elimination and regeneration of active Ni(0) species **I** (Scheme 6).

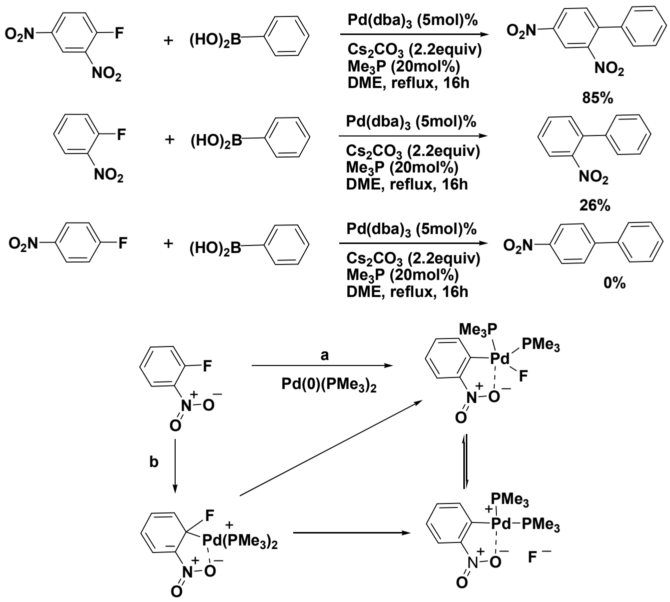


Scheme 6. Nickel–catalyzed cross–coupling of fluoro–aromatics with oxazole and the mechanistic pathway.

2.2. Pd-Catalyzed Activation of C–F Bonds in Fluoro-Aromatics

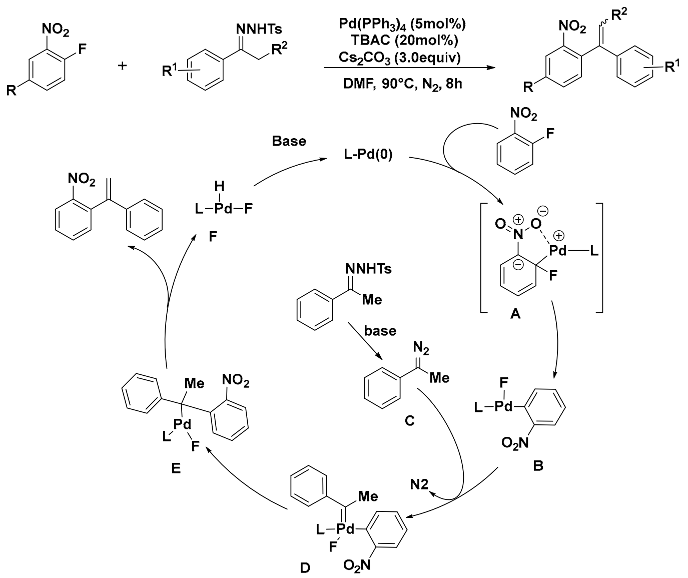
Other than nickel species, palladium complexes were also frequently utilized in the activation of C–F bonds.

Suzuki coupling is a heavily explored C–C formation reaction involving aryl groups [90–92]. Widdowson et al. carried out the first successful Suzuki coupling of fluoro-aromatics [93]; the ortho-substituted nitrofluorobenzene can proceed smoothly under Suzuki coupling conditions (TOF ca. 1.1 h^{-1}). However, no coupling product is detected when the ortho-position is substituted by –CF_3. Thus, the reaction clearly indicated that the ortho-nitro group is a necessary electron-withdrawing group for the catalytic activation of the C–F bond. Two possible reaction pathways may have operated in the products' formation: cooperative insertion (path **a**) or addition-elimination sequence (path **b**) (Scheme 7).



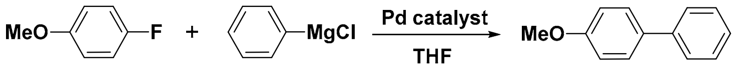
Scheme 7. Palladium–catalyzed C–F bond activation of nitrofluoro–aromatics and the reaction mechanism.

Wang et al. reported a palladium-catalyzed cross-coupling between electron-deficient fluoro-aromatics and N-tosylhydrazones; the reaction can tolerate variety of functionalities on the substrates [94]. Using a substrate with a strong electron-withdrawing CF_3 group, the coupling reaction proceeded smoothly with up to 70% yield (TOF ca. 1.8 h^{-1}). Mechanistic study showed the reaction path includes activation of C–F bond and migration insertion of palladium carbene as two key steps, which are useful in preparing 1,1-diaryl ethylene derivatives (Scheme 8).



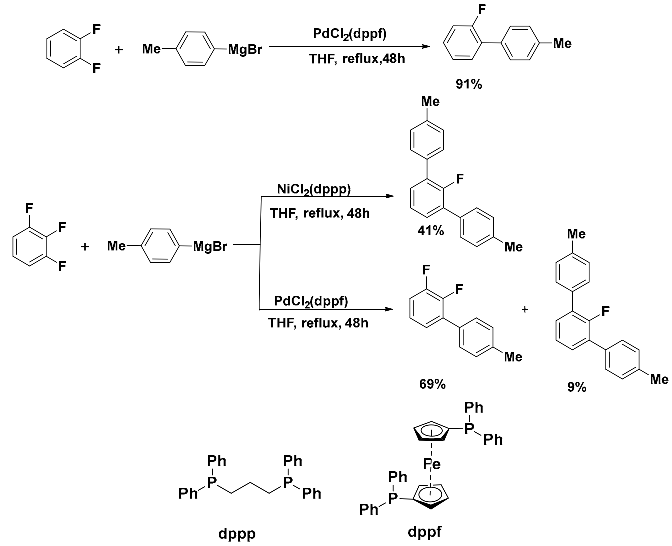
Scheme 8. Pd–catalyzed cross–coupling of electron–deficient fluoro–aromatics with N–tosylhydrazones and the reaction pathway.

In Suzuki-type cross-coupling reactions, direct cross-coupling of organometallic reagents with fluoro-aromatics is relatively rare. In 2005, Dankwardt et al. carried out a microwave-assisted reaction between fluoro-aromatics and Grignard reagent [84] (Scheme 9).



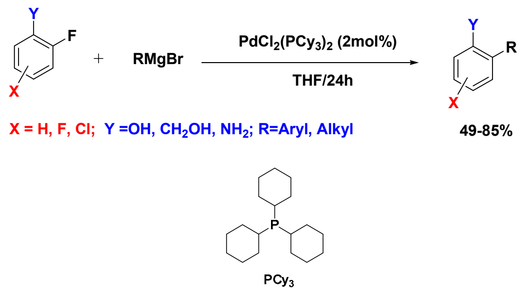
Scheme 9. Palladium–catalyzed cross–coupling of fluoro-aromatics with PhMgCl under microwave assistance.

Saeki et al. found that nickel and palladium complexes are complementary catalysts for the cross-coupling of Grignard reagent and C–F bond in fluoro-aromatics, but with different selectivity. The team used a DPPF-$PdCl_2$ system in the cross-coupling of difluorobenzene with aryl Grignard reagents [83]. The chelating effect of the adjacent F-atom may promote the oxidative addition and facilitate the C–F bond activation. Thus, the Pd (1 mol%) catalyzed reaction of *ortho*-difluorobenzene with aryl Grignard reagent can obtain a single substituted product with up to 91% yield (TOF ca. 1.9 h^{-1}), while the yield of cross-coupling products of *meta*-and *para*-difluorobenzene substrates is low. Subsequently, the study showed the reaction of 1,2,3-trifluorobenzene with Grignard reagent, using DPPP-$NiCl_2$ (5 mol%) to obtain mainly the double coupling product with low conversion, while the DPPF-$PdCl_2$ (1 mol%)-catalyzed reaction selectively received the single substitution product in high yields (Scheme 10).



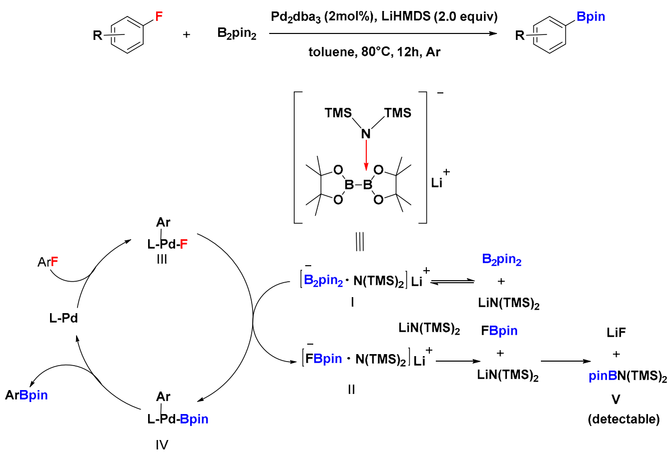
Scheme 10. Cross–coupling of fluoro–aromatic with Grignard reagents.

Manabe et al. reported a process of *ortho*-selective cross-coupling of fluorobenzene with Grignard reagents, and $PdCl_2$ $(PCy_3)_2$ was found to be an excellent catalyst for the reaction. Whereas, electron-donating groups such as hydroxyl, hydroxymethyl, and amino groups on the *ortho*-position of the fluoro-aromatics played a key role in accelerating the palladium-catalyzed cross-coupling [95] (TOF ca. 1.0–1.8 h^{-1}, Scheme 11).



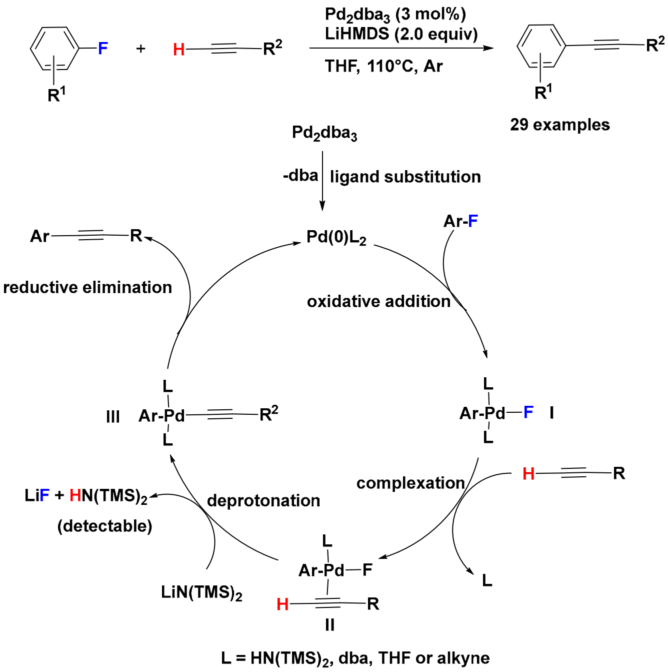
Scheme 11. Cross–coupling of fluoro–aromatics with Grignard reagent catalyzed by $PdCl_2(PCy_3)_2$.

Cao et al. showed a palladium-catalyzed cross-coupling of fluoro-aromatics with B_2pin_2 in the presence of LiHMDS, and proposed an efficient method for the synthesis of aryl borate pinacol ester [96]. In general, fluoro-aromatics containing electron-neutral groups, weak electron-donating groups, or strong electron-donating groups have a higher yield than substrates containing electron-withdrawing groups. Under optimal conditions, the expected boronates are obtained in moderate to good yields (R = Ph, TOF ca. 3.9 h^{-1}). In addition, the reaction tolerates wide range of functional groups, and no external ligand is needed. The plausible reaction pathway may be illustrated as such; at first, a boron atom of B_2pin_2 coordinates with a strong base LiN $(SiMe_3)_2$ to form a Lewis adduct of sp^2-sp^3 diborane species **I**. The B-B bond of the diborane species can be activated and then undergo heterolytic cleavage. The oxidative addition of the C-F bond in the fluoro-aromatics to the Pd(0) complex produces LArPd (II) F adduct **III**. Subsequently, the trans-metallization of intermediates **I** and **III** formed LArPd(II)Bpin **IV** and intermediate **II**. Finally, the reductive elimination from **IV** provides the required aryl borate esters, accompanied by the regeneration of the active catalytic Pd(0) species (Scheme 12). The LiHMDS played the role of binding and breaking up the B_2pin_2 unit to facilitate the activation and transformation of the C–F bond of fluoro-aromatics.



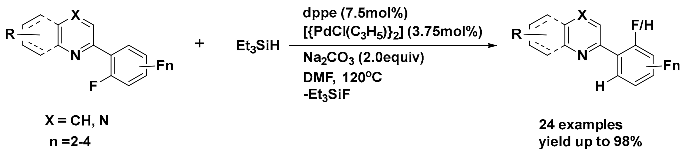
Scheme 12. LiHMDS–promoted palladium catalyzed defluoroborylation of fluoro–aromatics and reaction pathways.

Cao et al. created a catalytic system for the Sonogashira coupling of fluoro-aromatics with terminal alkynes, utilizing a Pd-catalyst. Thus, in the presence of LiHMDS, various electron-rich and/or electron-deficient fluoro-aromatics can be converted to aryl substituted alkynes (TOF ca. 2.2 h^{-1}) [97]. The scope of this transformation can also be extended to aryl chlorides and bromides, and a plausible reaction mechanism may be illustrated as such. The first step involves the oxidative addition of C-F bonds of fluoro-aromatics to the $Pd(0)L_2$ species to generate the intermediate $L_2ArPd(II)F$ complex **I**; subsequently, coordination of complex **I** with alkynes resulted in the formation of palladium alkynes transition state complex **II**; the coordinated alkynes **II** are deprotonated by LiHMDS to produce complex **III**; and finally, the product and the active catalyst $Pd(0)L_2$ species are generated by reductive elimination of intermediate **III** to complete the catalytic cycle (Scheme 13).



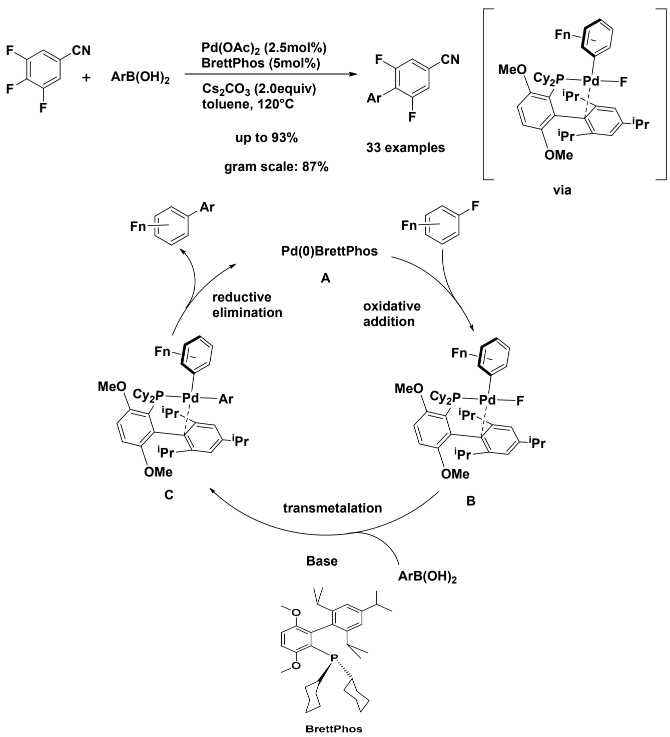
Scheme 13. Plausible mechanism of LiHMDS–promoted Sonogashira cross–coupling of fluoro–aromatics with terminal alkynes catalyzed with palladium.

In general, methods for the selective activation of C–F bonds in multifluoro-aromatics to obtain partially fluoro-substituted aromatics are highly desirable. Zhang et al. developed a practical method for activating the C–F bonds of multifluoro-aromatics [98]. Thus, utilizing a palladium catalytic system, multifluorophenyl-pyridine substrates and triethylsilane undergo *ortho*-selective hydro-defluorination (HDF) with yields up to 98%. This method has the characteristics of low cost, wide substrate range, mild operation conditions, high efficiency, good regio-selectivity, etc. (Scheme 14).



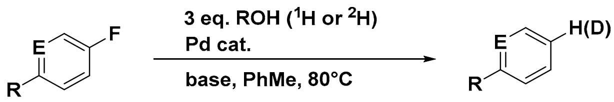
Scheme 14. Pd–catalyzed HDF of fluorophenyl–pyridine substrates with triethylsilane.

Recently, Zhang et al. developed a method for the palladium-catalyzed arylation of multifluoro-aromatics [99]. The catalytic system, $Pd(OAc)_2$/BrettPhos, is considered to be highly effective (TOF ca. 3.1 h^{-1}), and has the advantages of high efficiency, wide substrate range, high regio-selectivity, and toleration of nitrogen-containing heterocyclic groups. In order to further improve the scope of the process, selective activation of multifluoro-aromatic substrates was carried out, and cross-coupling of trifluoro-aromatic with aryl-boronic acid in a gram scale reaction demonstrated fairly good results, which confirms the generality of this Pd-catalytic system. Preliminary mechanism studies have shown that the high regio-selectivity of the current reaction may be attributed to the electron-rich palladium complex Pd(0)BrettPhos, which may facilitate the oxidative addition of the C–F bonds. The catalytic system opens up a new scheme for the activation of C–F bonds in multifluoro-aromatics for the organic synthesis and related chemistry (Scheme 15).



Scheme 15. $Pd(OAc)_2$/BrettPhos–catalyzed C–F bond activation of multifluoro–aromatics and plausible reaction pathway.

Differing from the Zhang's process [98], Grey and others studied Pd-catalyzed hydro-defluorination (HDF) of heterocyclic fluoro-aromatics (TOF ca. 1.3 h^{-1}) [100] and extended the scope of this reaction to a range of hetero-aromatic scaffolds commonly encountered in pharmaceutical chemistry (Scheme 16).

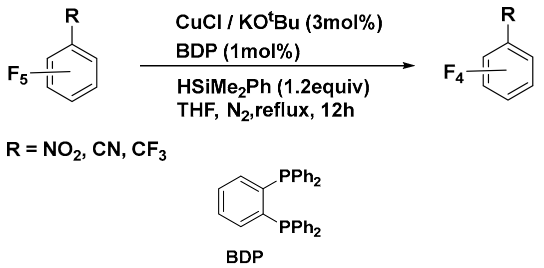


Scheme 16. Palladium–catalyzed HDF of heterocyclic fluoro–aromatics.

2.3. Other Transition Metal Complexes Catalyzed C–F Activation of Fluoro-Aromatics

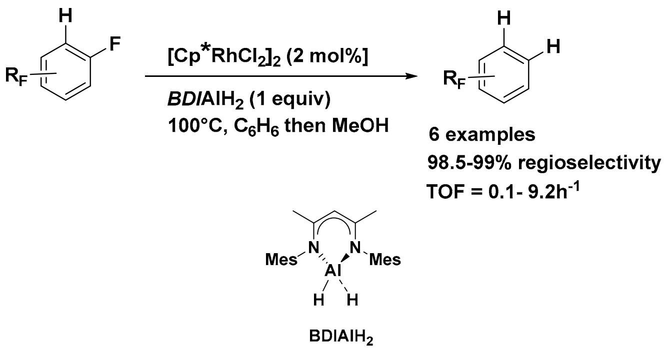
In comparison with nickel and palladium-catalyzed C–F bond activation, the same class of reaction, catalyzed with other transition metals, are less popular to date. In recent years, naturally abundant metals such as copper, cobalt, and iron have found increased application in the activation and functionalization of fluoro-aromatic C–F bonds.

Transition metal-mediated hydro-defluorination (HDF) of multifluoroaromatics is a fairly economic route for preparing partially fluorinated aromatics, and the methods' development has received increased attention. The selective conversion of C–F bonds in multifluoro-aromatics is considered a valuable practice [101]. Zhang et al. created a Cu-catalyzed HDF of muitifluoro-aromatics (TOF ca. 2.7 h^{-1}) [102]. Under optimal reaction conditions, pentafluoro-arenes with electron-withdrawing substituents (such as NO_2, CN, and CF_3) have fairly high reactivity, and the selective formation of tetrafluoroarene is also rapid (Scheme 17).



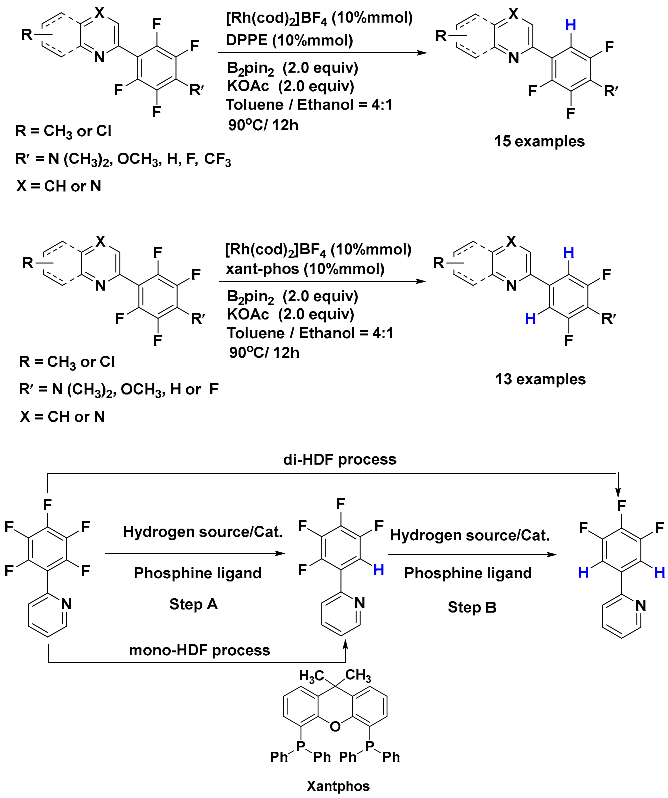
Scheme 17. Cu–catalyzed HDF of pentafluoroaromatics.

Crimmin et al. utilized a relatively rare example of Rh-mediated HDF of multifluoro-aromatics [103]; the catalytic system is highly selective, and the reaction directly activates C–F bonds adjacent to a C–H bond, with regio-selectivity up to 98.5–99% (Scheme 18).



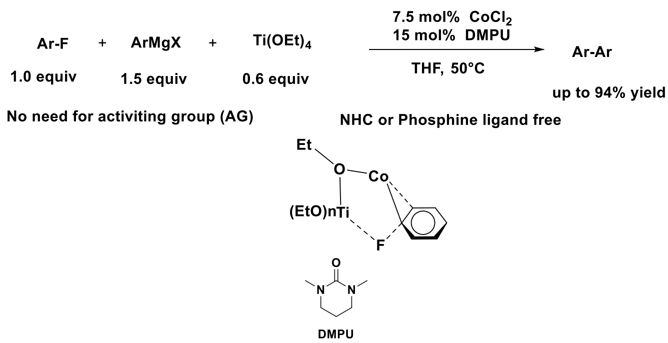
Scheme 18. Rh–catalyzed HDF of multifluoro–aromatics ($BDIAlH_2$, hydrocarbon-soluble aluminum dihydride).

Ding et al. also studied Rh-catalyzed HDF of heterocyclic multifluoro-aromatics via activation of C–F bonds in the *ortho* position of fluoro-aromatics [104]. Through the use of Rh-complexes and ethanol as hydride sources, the system can facilitate *ortho*-selective mono-HDF (TOF ca. 0.7 h^{-1}) or double-HDF (TOF ca. 0.8 h^{-1}) of multifluoro-aromatics. Mechanistic studies have shown that the phosphine ligands are crucial to catalytic performance, in which bidentate phosphine ligands are out-performing monodentate phosphine ligands in terms of product yields. In addition, phosphine ligands with higher steric hindrance are more favorable for producing mono-HDF products (Scheme 19).



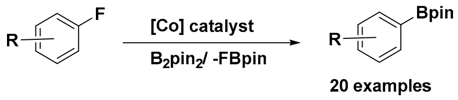
Scheme 19. Rh–catalyzed HDF of heterocyclic substituted multifluoro–aromatics and selectivity pathways for phosphine ligand control.

Differing from the HDF reaction of multifluoro-aromatics, Iwasaki et al. showed the activation of aliphatic C–F bond catalyzed by cobalt, and realized the catalytic cross-coupling reaction of alkyl fluoride with Grignard reagent obtained the corresponding coupling products in fairly high yields [105]. Duan et al. also studied a co-catalyzed coupling reaction of fluoro-aromatics with Grignard reagents, but in the absence of phosphine or NHC ligands [65]. The co-mediated 'easy-to-catalyze' biaryl cross-coupling reaction through the cleavage of C–F bond is unexpected, in sharp contrast to the Ni or Pd catalyzed reactions, in which the existence of activated group(s) on fluoro-aromatics are necessary. However, the current C–F activation reaction is only catalyzed by $CoCl_2$/DMPU; it is also noteworthy that in the coexisting of C–F, C–Cl and C–Br functionalities, highly selective C–F activation can be realized. Mechanistically, the assumption of the synergistic effect of Co–Ti bi-nuclear intermediate may play a key role in promoting the cleavage of the C–F bond. These findings will inspire further development of high-efficiency cobalt catalyst systems for C–F bond activation (Scheme 20).



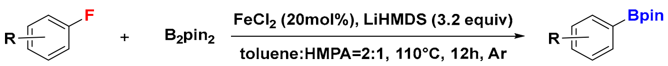
Scheme 20. Cobalt–catalyzed C–F bond activation and Co–Ti co–oxidative addition reaction transition state.

Lee et al. carried out a co-catalyzed boration of C–F bonds in fluoro-aromatics [106]. This was the first time that co-catalyzed defluoro-boration of fluoro-aromatics was carried out in mild and practical conditions; it exhibited high selectivity for C–F bonds, even exceeding the boration on C–H bonds in the same substrates. This method makes it possible to direct the functionalization of a series of fluoro-aromatics. In addition, the catalytic system can tolerate unprotected functional groups (e.g., alcohols and amines), and can also activate C–F bonds under aerobic conditions, while somewhat sacrificing productivity (Scheme 21).



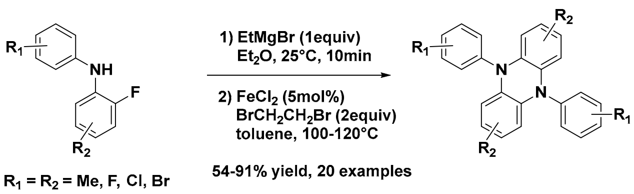
Scheme 21. Co–catalyzed boration of fluoro–aromatics.

Based on the palladium-catalyzed activation of C–F bond of fluoro-aromatics promoted by LiHMDS, Cao et al. extended the catalytic system to iron [96] complexes. At present, though the activity (R = Ph, TOF ca. 0.3 h^{-1}) of the catalyst is lower than that of Pd system, the Fe-catalyst has the advantages of low cost, low toxicity, environmentally friendliness and high availability (Scheme 22).



Scheme 22. LiHMDS–promoted Fe–catalyzed defluoroboration of fluoro–aromatics.

Recently, Nakamura et al. developed a new Fe-catalyzed *ortho*-C–F activation of diarylamine to synthesize DADHPs in one pot (TOF ca. 65–109 h^{-1}) [107]. The Fe-catalytic system has good regio-selectivity, and can selectively synthesize DADHPs with different halogen substituents (fluorine, chlorine, and bromine). Increasing the structural diversity and availability of DADHPs, will help further development of functional molecules in the fields of materials science and synthetic chemistry (Scheme 23).



Scheme 23. Ligand–free Fe–catalyzed C–F amination of diarylamine.

3. Activation of C–F Bond in Fluoro-Aromatics Promoted by Transition Metal-Free Processes

Most of the C–F bond activation in fluoro-aromatics is accomplished by transition metals [108–111]. However, the choice of different metal and/or ligands in the system will affect the outcoming products to somewhat unpredictable degrees. The activation of the C–F bond catalyzed by transition metal frequently requires harsh reaction conditions, and the transition metals may bring adverse effects to the working environment. Therefore, it is highly desirable to develop new, efficient and environmentally benign systems for chemical bond transformation reactions, and C–F bond activation/functionalization is one of the frontiers of inert chemical bonds activation [112]. In recent years, some efforts have also been made to explore the transition metal-free activation of C–F bonds in fluoro-aromatics.

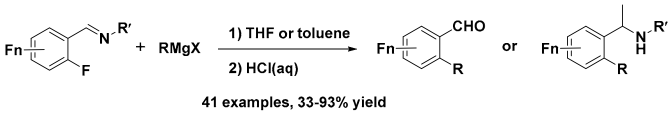
Li et al. reported a simple method for activation of C–F bonds [113] without transition metal mediation. Thus, perfluoropyridine and Grignard reagent can undergo cross-coupling under ambient temperature, and results showed that perfluorinated aromatics can react with aryl Grignards in general; alkyl Grignards are also suitable for the cross coupling (Scheme 24).

$$ArF_n + \text{aryl-MgBr} \xrightarrow[\text{r.t. 24h}]{\text{THF}} F_{n\text{-}1}\text{Ar-aryl}$$

$$ArF_n + \text{alkyl-MgBr} \xrightarrow[\text{r.t. 24h}]{\text{THF}} F_{n\text{-}1}\text{Ar-alkyl}$$

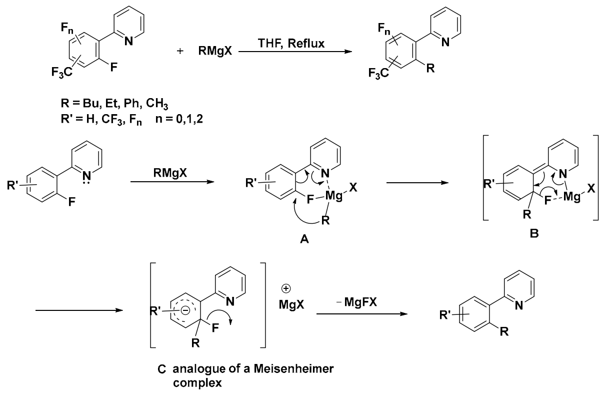
Scheme 24. Cross–coupling of perfluoropyridine and Grignard reagents.

Li et al. also showed the coupling reaction between multifluoro-aromatic imines and Grignard reagent without the participation of transition metal [114]. It was found that the electron-withdrawing effect of amino-functionality on the multifluoro-aromatic ring can weaken the bond energy of the *ortho*-C–F bond, which is beneficial to the activation of C–F bond in multifluoro-aromatic imines. This method is applicable to the coupling reaction between various fluoroarylimines and Grignard reagent, and can obtain *ortho*-substituted benzaldehyde derivatives with high yield (Scheme 25).



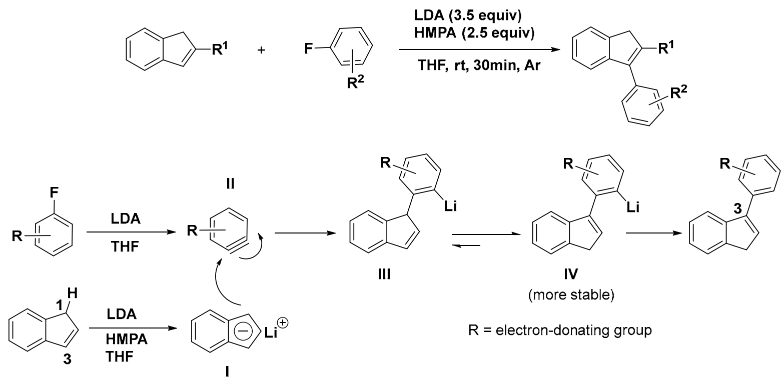
Scheme 25. Cross–coupling between multifluoroarylimine and Grignard reagent while excluding transition metal.

Cao et al. studied the metal-free cross-coupling of fluorinated phenyl pyridine with a variety of Grignard reagents [115]. The speculating mechanism indicates, at first, that the nitrogen atom on the pyridine ring coordinates with the magnesium ion of the Grignard reagent to form a magnesium complex. A; synergistic formation of a six-membered ring transition state, B; electrons' rearrangement in the aromatic ring to form a complex C; and finally, C–F bond cleavage which forms the coupling products (Scheme 26).



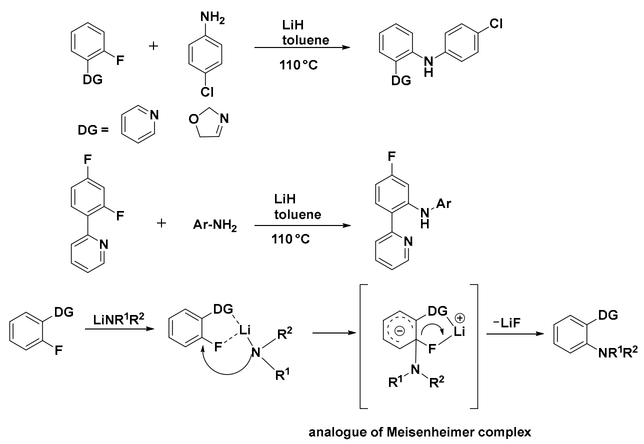
Scheme 26. The cross–coupling of multifluoro–arenes with Grignard reagents via pyridine–directed cleavage of the C–F bond in the absence of transition metal.

In 2018, Cao et al. showed that the 3-arylation of indene can be directly and conveniently prepared via HMPA-promoted cleavage of the C–F bond of fluoro-arene in the presence of LDA [116], and that the reaction can be completed in 30 min at ambient temperature. A plausible mechanism is proposed. First, indene deprotonates in the presence of LDA to generate indenyl lithium **I**. In the presence of LDA, the cleavage of the C–F bond provides a key intermediate aryne **II** (Scheme 27); subsequently, **I** is added to intermediate **II** to obtain lithiated 1- or 3-arylalkenes (**III** or **IV**), intermediate **III** is isomerized under alkaline conditions to form more stable intermediate **IV**, and finally, the desired compound is obtained by neutralizing **IV** with water. In addition, the coordination of HMPA/THF with lithium ions has a significant effect on the reaction. It is expected that further expanding the scope of the reaction is highly possible.



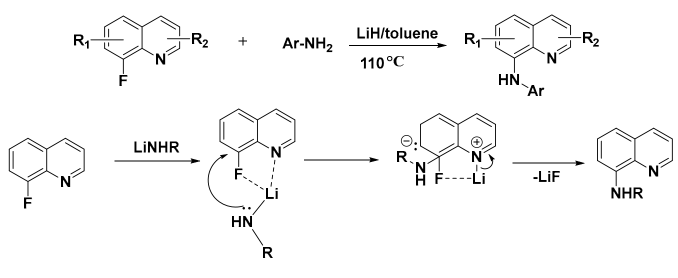
Scheme 27. HMPA–promoted direct arylation of indenes with aryl fluorides and plausible reaction pathway.

In 2017, Ding et al. reported an economical and environmentally friendly cross-coupling reaction between fluoro-aromatics and amines, which involved N-heterocyclic-assisted selective C–F bond cleavage without the need for transition metal catalysts [112]. The reaction selectively cleaves the *ortho*-C–F bond of the difluorophenyl pyridine, while the *para*-C–F bond remains intact. The mechanistic studies showed that the cross-coupling reaction is promoted by intra-molecular Li/F interaction (Scheme 28).



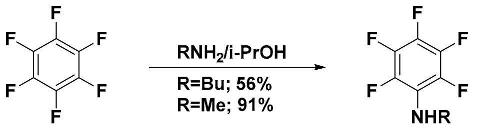
Scheme 28. Cross–coupling of fluoro–aromatics with amines under transition metal–free conditions.

Extending the scope of the heterocyclic-assisted C–F cleavage, Ding et al. created an efficient process for the activation of C–F bonds in polycyclic hetero-aromatics [117]. The reaction may proceed through the following route: lithium ions preferentially coordinate with a lone pair of polycyclic fluoro-aromatic nitrogen atoms, and through binding up the adjacent F atoms, the C–F bond energy is weakened. The incoming amine substrate nucleophilic attacks the carbon where the C–F is activated, and thereby forms the new C–N bond while simultaneously releasing LiF salt (Scheme 29).



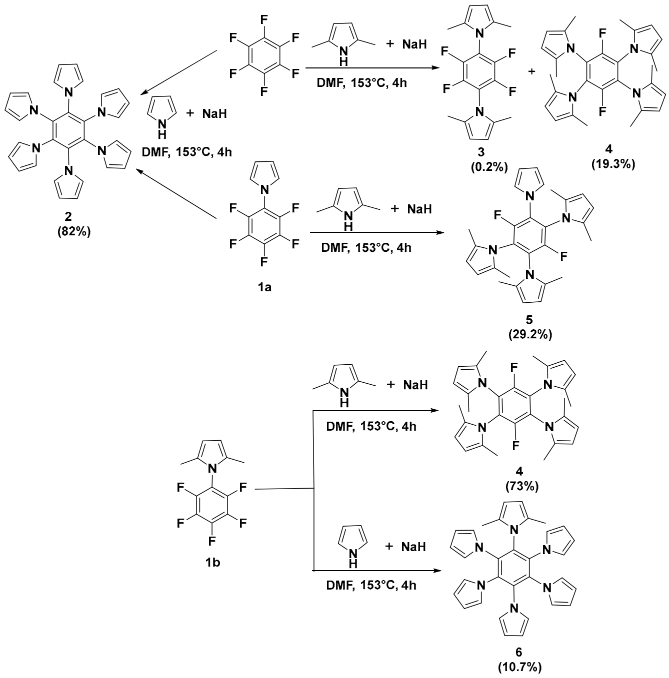
Scheme 29. Cross–coupling of heterocyclic fluoro–aromatics with amines under transition metal–free conditions.

It was found that multifluoro-benzenes can undergo a metathesis reaction with nucleophilic amines, and primary amines are easily reacted with multifluoro-aromatics to obtain aromatic amines [118] (Scheme 30).



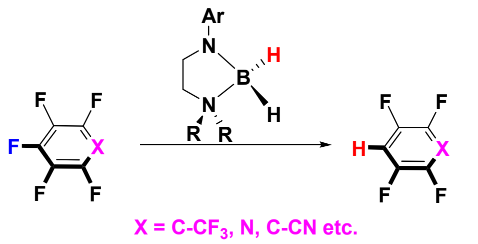
Scheme 30. Reaction of perfluorobenzene C–F bond with primary amines.

For activation of C-F bond in multifluoro-aromatics, Tokárová et al. demonstrated consecutive nucleophilic substitutions of hexafluorobenzene and 1-pentafluorophenyl-1H-pyrrole (**1a**) with pyrrole/NaH and 2,5-dimethylpyrrole/NaH [119]. Results showed that the substitution mode of stepwise defluorinating specific fluorine atoms depends on the nature and quantity of nucleophiles used (pyrrole/NaH and 2,5-dimethylpyrrole/NaH). The reaction of hexafluorobenzene with pyrrolidinyl sodium salt (generated in situ from equimolar amounts of pyrrole and sodium hydride) proceeded smoothly to fully substituted compound **2** in 82% yield (Scheme 31).



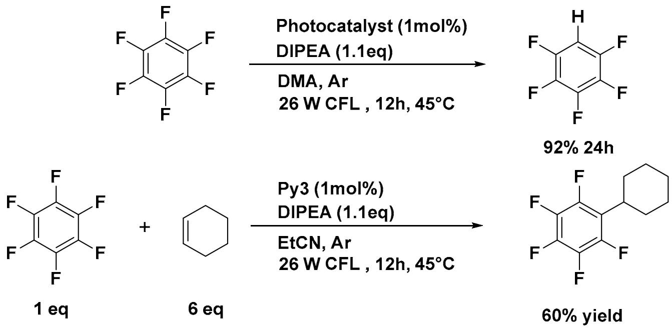
Scheme 31. Nucleophilic substitution of multifluoro–aromatics with pyrrole/NaH and 2,5–Dimethylpyrrole/NaH.

Crimmin et al. reported a transition metal-free hydro-defluorination (HDF) process [120], and it was believed that the boron hydrides may represent a new tool for the activation of C-F bonds in transition metal-free HDF systems (Scheme 32).



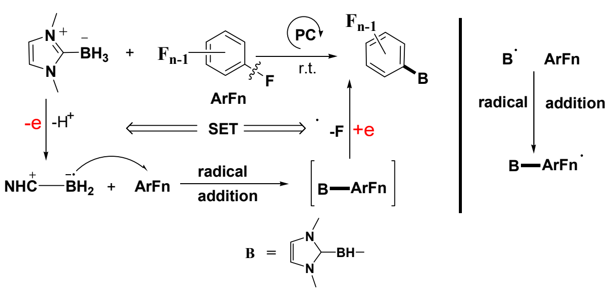
Scheme 32. Regio–selective HDF of fluoro–aromatics with dihydroboranes.

Due mainly to its environmentally friendly and economical characteristics, as well as the possibility of utilization in some sophisticate synthetic practices, photo-catalysis also appears to be a useful tool in C–F bond activation/transformations [121]. Compared with the previous studies on the activation of C–F bond by cross-coupling of fluoro-aromatics with Grignard reagents, Zhang et al. demonstrated a selective mono-HDF of hexafluorobenzene, under transition metal-free photocatalysis conditions, to yield pentafluorobenzene in fairly high yields [122]. The photo-catalytic method can be applied to HDF of multifluorobenzenes. Research has shown that the steric hindrance of the photocatalyst and the multifluoro-aromatics largely determine the HDF rate, pointing to an internal sphere electron transfer pathway. The study emphasized the importance of the size and shape of photocatalyst and substrates in controlling the electron transfer mechanism and rate law. To further prove the potential of the transition metal-free photocatalysis, hexafluorobenzene was reacted with cyclohexene, where Py_3 is used as a metal-free photocatalyst to generate hexafluorophenyl radicals, which are intercepted by 6.0 equivalents of cyclohexene, thus obtaining C–C coupling products with good yield. The study demonstrated the potential of obtaining partially fluorinated aromatics through photocatalytic HDF and the cross-coupling of multiflorophenyl with olefinic substrates (Scheme 33).



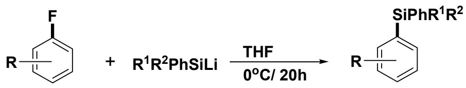
Scheme 33. Photocatalystic HDF of perfluorobenzene and cross–coupling of multifluorobenzene with olefinc substrate.

Wu et al. demonstrated a visible light-catalyzed defluoro-boration of multifluoro-aromatics with high selectivity [121]. Subsequently, Yang et al. also showed the photocatalytic boration of multifluoro-aromatics with NHC borane [123]. This transition metal-free photocatalytic process can directly generate B–H bonds in the aromatic products. With good functional group tolerance and high regioselectivity characteristics, the method provided nonparallel advantages for the preparation of a large number of valuable multifluoroaryl borane compounds, which further enriches the photocatalytic defluoroboration (DFB) of multifluoro-aromatics (Scheme 34).



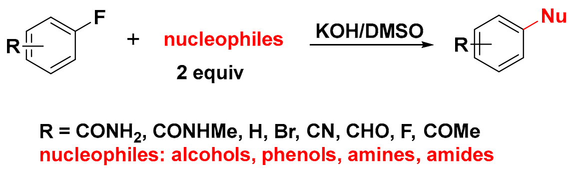
Scheme 34. Photocatalytic defluoro–boration of multifluoro–aromatics with NHC borane.

Studer et al. showed that fluoro-aromatics undergo cross-metathesis defluoro-silylation, through synergistic nucleophilic aromatic substitution similar to the nickel-catalyzed cross-coupling of C–Si bond, and provided a synthetic method for obtaining aryl-substituted silanes through C–F bond activation [124]. Studies have shown that silicon-based lithium reagents such as $PhMe_2SiLi$ or Ph_2t-BuSiLi, which are easily generated in situ from their hydrosilane analogs, react with various fluoro-aromatics to obtain corresponding highly substituted aromatic silanes. Compared with the classic nucleophilic aromatic substitutions, this transition metal-free, synergistic and nucleophilic aromatic substitution defluorosilylation reaction ais lso suitable for substrates bearing relatively electron-rich substituents (Scheme 35).



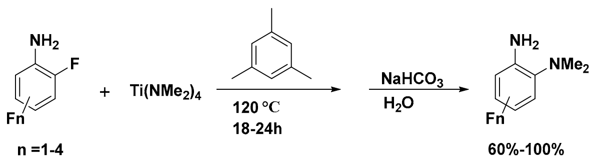
Scheme 35. Transition metal–free defluoro–silylation of fluoro–aromatics.

Hua et al. demonstrated a nucleophilic substitution of fluoro-aromatics with various nucleophiles (such as alcohols, phenols, amines, amides, and N-heterocyclic compounds) [125]. The nucleophilic substitution uses KOH/DMSO as a medium, under mild, transition metal-free conditions, and provides an alternative alkali-promoted C–F bond activation process. Studies have shown that fluoro-aromatics with either electron-withdrawing or electron-donating groups can undergo smooth nucleophilic substitution, and have made the activation of the fluoro-aromatics' C–F bond with electron donating functionalities, such as amide, bromine, cyano, aldehyde, acetyl, etc., possible. (Scheme 36).



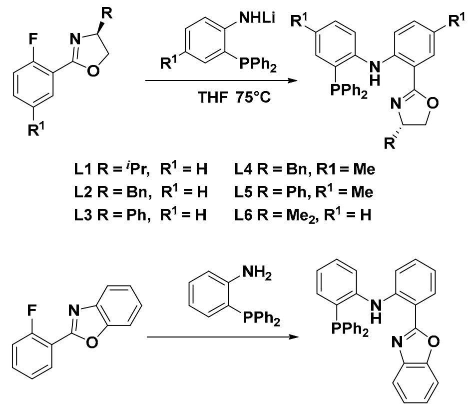
Scheme 36. Transition metal–free nucleophilic substitution of fluoro–aromatics with various nucle–ophiles.

In 2019, Deck et al. reported the nucleophilic activation of the C–F bond in *ortho*-fluoroaniline [126]. Fluorinated aniline reacts with stoichiometric $Ti(NMe_2)_4$ in 1,3,5-trimethylbenzene to obtain the *ortho*-defluoroamination products with good selectivity and yields (Scheme 37).



Scheme 37. Activation of C–F bond in *ortho*–fluoroaniline.

Shi et al. prepared a series of PNN-type tridentate coordination organic molecules through the metathesis of 2-diphenylphosphinyl arylamino-lithium salt with fluoro-aromatics [127]. This provided a transition metal-free protocol for the synthesis of PN-type tridentate ligands via activation of C–F bond in *ortho*-fluoroaniline. The method certainly enriched the PNN tridentate-ligated transition metal complexes toolbox, and the PNN tridentate-ligated transition metal catalytic chemistry (Scheme 38).



Scheme 38. Synthesis of PNN type tridentate ligands.

4. Conclusions and Outlook

Method development for the activation and conversion of inert C–F bonds in fluoro-aromatics is highly desirable for both routine organic synthesis and industrial and environmental applications. In recent years, effective and selective processes and systems developed for the activation and transformation of C–F bonds have seen remarkable signs of progress. However, in comparison with the activation of C–H and C–C bonds, the C–F bond activation fields still lack systematic concepts and theories.

As mentioned in this text, a good sign is that the activation and transformation of C–F bonds in fluoro-aromatics have seen increasing attention, and the advances made not only demonstrate new processes for the synthesis of novel fluorinated organic compounds, but also provide insight into theoretical perspectives, inspiring new concepts and methodologies in the search for more efficient C–F bond activation and transformation processes and systems.

The activation and functionalization of C–F bonds catalyzed by transition metal complexes are still the main focus of the subject. However, owing to the abnormal strength of the C-F bond energy and the shielding effects of the fluorine atom, currently, the transition metal-catalyzed sp^2 C–F bonds activated in fluorinated aromatics are generally suffering from low catalytic efficiency, the high loading of catalyst (1–10 mol%) and the forced reaction conditions (e.g., the prolonged reaction time or high reaction temperature needed to ensure sufficient substrate conversion) as well the disappointing TOF numbers. Moreover, the precious metals (Pd, Pt, Rh, etc.)-catalyzed reactions showed no advantageous catalytic performances from an economic point of view, and the metal-catalyzed C–F activation may draw attention to the first-row transition metals for future developments toward practical applications.

On the other hand, economic and environmentally friendly chemical bond activation processes/methods are attracting increased attention. The development of low-cost, environmentally benign, highly efficient C–F activation and conversion, especially the transition metal-free processes, has recently opened up a window for the stochiometric reaction of fluorinated aromatics with a variety of reactive substrates; this should generate sustainable and sufficient interest to warrant further research works. Metal-free C–F bond activation processes have the advantage of easy scale-up and fewer environmental concerns; therefore, they will be one of the focal spots of C–F bond activation research.

In addition, ever since it was first demonstrated in 2006 that Frustrate Lewis Pairs (FLP) can split H–H bonds, FLP-catalyzed reactions are exhibiting outstanding performances in the activation of a wide variety of high-bonding-energy species [128–130], including organic molecules possessing sp^3 and sp^2 C–F bonds [68]. FLP-catalyzed C–F bond activation paves a new avenue for efficient and selective functionalization of multifluoro organic species to yield desirable new products. It is believed that FLP-catalyzed C–F bond activation will provide new chemical processes for practical applications.

It is expected that this paper will be of some help to researchers working in the C–F activation fields. The literature in this text is up to date at the end of 2022, and the fast development in the field will certainly bring some outcomes which you may find valuable. We will stay alert to the field to announce the most exciting research news periodically.

Together with the rapid development of organic chemistry, C–F bonds activation/functionalization will be one of the frontiers of research, and it is expected that the activation/functionalization of the C–F bond in fluoro-aromatics will keep its fast-developing pace. Thus, more fundamental and general processes/methods will be available for routine synthetic chemistry and application in industry.

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