

# C–F Bond Activation in Organic Synthesis

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## Contents

1. Introduction	2119	4.1.3. Electroreductive C–F Bond Activation	2158
2. C–F Bond Activation in Aromatic Fluorides	2120	4.2. Low-Valent Metal-Promoted Reductive C–F Bond Cleavage	2160
2.1. Oxidative Addition of C–F Bond to Low-Valent Metals	2120	4.2.1. Low-Valent Metal-Promoted Reductive Dehalodefluorination	2162
2.1.1. Transition Metal-Mediated Activation of $sp^2$ -C–F Bonds: Stoichiometric Reactions	2121	4.2.2. Low-Valent Metal-Promoted Reductive Defluorination from Trifluoromethyl Group Attached to $\pi$ -Electron System	2163
2.1.2. Transition Metal-Mediated Activation of $sp^2$ -C–F Bonds: Catalytic Transformations	2124	4.3. Lewis Acid- and Cation-Promoted C–F Bond Activation	2168
2.1.3. Ni-Catalyzed Cross-Coupling Reactions of Aromatic Fluorides	2125	4.4. Ate Complex-Catalyzed Cross-Coupling	2173
2.1.4. Pd-Catalyzed Cross-Coupling Reactions of Aromatic Fluorides	2127	4.5. E2-type Dehydrofluorination	2174
2.1.5. Other Transition Metal Catalyzed Cross-Coupling Reactions	2129	4.5.1. Dehydrofluorination of Trifluoromethyl Compounds	2175
2.2. C–F Bond Activation Initiated by Electron Transfer to Fluoroaromatics	2130	4.5.2. Dehydrofluorination Leading to Quinodimethane Intermediates	2175
2.2.1. Catalytic Hydrogenolysis of Aromatic C–F Bonds	2130	4.5.3. Brook Rearrangement	2176
2.2.2. Reductive Transformations of Fluoroarenes	2132	5. Concluding Remarks	2177
2.3. Nucleophilic Substitution in Aromatic Fluorides	2136	6. Acknowledgments	2177
2.3.1. Nucleophilic Substitution in Monofluoroaromatics	2136	7. References	2177
2.3.2. Nucleophilic Substitution in Hexafluorobenzene	2141		
2.3.3. Nucleophilic Substitution in Pentafluoropyridine	2143		
2.4. Defluorination via Benzynes	2145		
3. C–F Bond Activation in Alkenyl Fluorides	2148		
3.1. General Aspect of Nucleophilic Substitution in <i>gem</i> -Difluoroalkenes	2148		
3.2. Structure and Reactivity of <i>gem</i> -Difluoroalkenes	2150		
3.3. Intramolecular Nucleophilic Substitution in <i>gem</i> -Difluoroalkenes	2151		
3.4. High Reactivity and Toxicity of Polyfluorinated Fluoroalkenes	2152		
3.5. Defluorinative Modification of Octafluorocyclopentene	2152		
4. C–F Bond Activation in Aliphatic Fluorides	2153		
4.1. C–F Bond Activation of Trifluoromethyl Group Attached to $\pi$ -Electron System	2153		
4.1.1. $S_N2'$ Type Reactions in Trifluoromethylalkenes	2153		
4.1.2. Fluoride-Ion Catalyzed Desilylative Defluorination	2156		

## 1. Introduction

Fluorine has received great attention in all fields of science. “Small atom with a big ego” was the title of the Symposium at the ACS meeting in San Francisco in 2000, where a number of the current scientific and industrial aspects of fluorine chemistry made possible by the small size and high electronegativity of the atom were discussed. This small atom has provided mankind with significant benefits in special products such as poly(tetrafluoroethylene) (PTFE), freon, fluoro-liquid crystals, optical fiber, pharmaceutical and agrochemical compounds, and so on, all of which have their own unique properties that are otherwise difficult to obtain.<sup>1</sup> For instance, at present, up to 30% of agrochemicals and 10% of pharmaceuticals currently used contain fluorine atoms. Therefore, organic fluorine compounds have received a great deal of interest and attention from the scientists involved in diverse fields of science and technology.

Now, not only C–F bond formation but also selective C–F bond activation have become current subjects of active investigation from the viewpoint of effective synthesis of fluoroorganic compounds. The former is highlighted by designing a sophisticated fluorinating reagent for regio- and stereocontrolled fluorination and developing versatile multifunctional and easily prepared building blocks. C–F bond formation has been treated extensively in several reviews<sup>2</sup> and books.<sup>3</sup> The latter is a subject that has been less explored but would be promising for selective defluorination of aliphatic fluorides, cross-coupling with aryl fluorides, and

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Hideki Amii was born in Hyogo in 1968. He graduated from Kyoto University, where he received his Doctorate degree in 1996 under the direction of Professor Yoshihiko Ito. During 1996–2003, he worked as Research Associate of the Department of Applied Chemistry, Faculty of Engineering, Okayama University (Prof. Kenji Uneyama's group). He carried out postdoctoral work in France with Dr. Guy Bertrand at Université Paul Sabatier during 2000–2001. He was the recipient of Inoue Research Award for Young Scientists (1998); Otsuka Award in Synthetic Organic Chemistry, Japan (1998); Award for Poster Contribution at the 13th European Symposium on Fluorine Chemistry, Bordeaux, France (2001); and the Chemical Society of Japan Award for Young Chemists (2002). In 2003, he was appointed to Associate Professor of Kobe University. His research interest is currently in the synthesis of organofluorine compounds by the use of metal reagents.



Kenji Uneyama was born in Osaka, Japan, in 1941. He studied chemistry at the Department of Applied Chemistry, Osaka City University, where he received B.Eng. in 1964 and M.Eng. in 1966. He obtained his doctorate of technology under the direction of Shigeru Oae concerning the chemistry of divalent sulfur-stabilized carbanions at the same university, in 1969. His professional academic career started as a lecturer at the Department of Applied Chemistry, Okayama University, in 1969, where he was promoted to an associate professor in 1970 and to a professor in 1984. He spent one year (1972–1973) at Ohio State University as a postdoctoral to study electrochemical molecular transformation of small aza-ring compounds with P. G. Gassman. He has been a visiting professor at the University of Paris (Chatenay-Malabry) and the University of Valencia. He served as the vice chair for the editorial board of *Chem. Lett.* and *Bull. Chem. Soc. Jpn.* and has been a member of the editorial board of *J. Fluorine Chem.* He enjoyed research works on synthesis of natural products and electrochemical molecular transformation in Sigeru Torii's group in Okayama for 14 years. Since 1985, he has been involved in study on organofluorine chemistry, which focuses on the synthetic methodology of organic fluorine compounds and covers particularly the chemistry of trifluoroacetimidoyl halides and the C–F bond activation for synthetic chemistry. He has received Award of the Society of Synthetic Organic Chemistry, Japan, and ACS Award for Creative Work in Fluorine Chemistry 2007.

transformation of poly- or perfluorinated compounds to partially fluorinated compounds.

This is a review of C–F bond activation chemistry from the perspective of synthetic organic chemistry. The strength of the carbon–fluorine bond<sup>4</sup> is exemplified by the unique property of organic perfluorocarbons such as PTFE polymer. A C–F bond is mostly thermally, photochemically, electrooxidatively, and often even chemically stable so that it is not easy, in general, to cleave for chemical modification of organic fluorocompounds. Nevertheless, it is potentially useful for synthetic chemistry to utilize effective C–F bond activation of aryl fluorides and trifluoromethyl and perfluoroalkyl compounds, all of which are readily available. The approach provides us an excellent opportunity to synthesize nonfluorinated coupling products and partially fluorinated compounds, which are otherwise difficult to be prepared. The aim of this review involves two aspects: one is to summarize the present state in C–F bond activation from the viewpoint of synthetic chemistry and the other is to develop this unexplored but potentially promising field of C–F bond activation for synthetic chemistry. Several excellent reviews<sup>5–14</sup> on mechanistic, structural, and, in some cases, synthetic aspects of C–F bond activation by metal complexes have been published: the transition metal-promoted activation of C–F bonds by Richmond,<sup>5</sup> Ni-complex mediated C–F bond activation by Braun and Perutz,<sup>6</sup> chemistry of transition metal fluoro-compounds by Hoffman and Doherty,<sup>7</sup> Cp\*<sub>2</sub>ZrH<sub>2</sub>-mediated hydrodefluorination by Jones,<sup>8</sup> chemistry of organometallic fluorides by Roesky,<sup>9</sup> chemistry of fluorine–metal coordination by Plenio,<sup>10</sup> and C–F bond activation by platinum group metal complexes by Torrens.<sup>11</sup> Encouraged by these well-documented reviews, the present review will focus on C–F bond activation for synthetic chemistry and will cover metal-catalyzed C–F bond activation leading to C–C formation, which was uncovered in the former reviews and will provide a systematic summary of chemistry on the effective replacement of fluorine with other elements feasible for synthetic chemistry.

## 2. C–F Bond Activation in Aromatic Fluorides

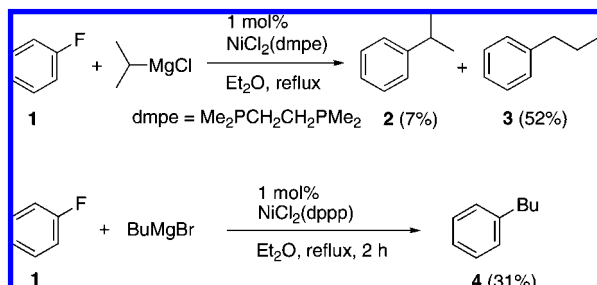
### 2.1. Oxidative Addition of C–F Bond to Low-Valent Metals

Transition metal catalyzed C–C bond-forming reactions are useful tools for wide fields of chemistry. Selective functionalization of sp<sup>2</sup>-carbon–halogen bonds, such as cross-coupling reaction, has found an important place in modern synthetic protocols for drug discovery, natural product synthesis, and material science. In the case of palladium-catalyzed cross-coupling reactions, the first step is oxidative addition of C–X bonds to Pd species. Although aryl iodides and bromides are most commonly employed, the use of aryl chlorides as cross-coupling participants has recently received increasing attention from the scientific and industrial viewpoints. Actually, there have been excellent reports on Stille and Suzuki–Miyaura reactions of aromatic chlorides by the use of bulky and electron-donating phosphine ligands on the palladium. However, the progress in cross-coupling of aromatic and vinylic fluorides has been much slower than that of chlorides. Hitherto, aryl fluorides were considered to be uncommon coupling partners for the cross-coupling reactions because of the low reactivity for oxidative addition attributed to the strength of carbon–fluorine bonds (154 kcal/mol for C<sub>6</sub>F<sub>6</sub>).

In 1973, Tamao and Kumada reported the nickel-catalyzed cross-coupling reactions of Grignard reagents with aryl and

alkenyl halides.<sup>15</sup> In these reports, aryl fluorides were found to be applicable to cross-coupling reactions by the use of nickel phosphine complexes (Scheme 1). At that time, the reaction conditions for fluorobenzene (**1**) were not fully optimized to improve the chemical yields. To the best of our knowledge, this is the first example of the catalytic C–C bond formation involving  $sp^2$ -carbon–fluorine bond cleavage.

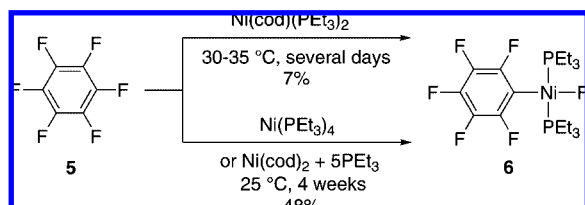
Scheme 1



### 2.1.1. Transition Metal-Mediated Activation of $sp^2$ -C–F Bonds: Stoichiometric Reactions

In 1977, Fahey and Mahan reported several examples of oxidative addition of aryl, vinyl, and acyl halides ( $X = \text{Br}, \text{Cl}, \text{and F}$ ) to triethylphosphine nickel(0) complexes.<sup>16</sup> They observed the oxidative addition of hexafluorobenzene (**5**) to  $\text{Ni}(\text{cod})(\text{PEt}_3)_2$  to afford the pentafluorophenyl fluoronickel(II) complex **6** (Scheme 2). However, the reaction is slow (at 30–35 °C for several days) with a yield of only 7%, and characterization of the product was limited to elemental analysis and IR spectroscopy.

Scheme 2

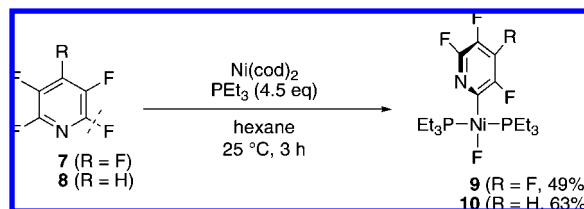


After 20 years, Perutz et al. succeeded in the full characterization of *trans*- $\text{Ni}(\text{PEt}_3)_2(\text{C}_6\text{F}_5)\text{F}$  (**6**), by the reaction of hexafluorobenzene with  $\text{Ni}(\text{PEt}_3)_4$ .<sup>17</sup> Although the reaction proceeded slowly at room temperature (rt) for 4 weeks, the fluoronickel(II) complex was isolated in 48% yield, and the structure of fluoronickel complex **6** was revealed by X-ray crystal structure analysis.

Furthermore, Perutz's group undertook the selective C–F bond activation of fluorinated heteroaromatics. The reactions

of pentafluoropyridine (**7**) and 2,3,5,6-tetrafluoropyridine (**8**) with triethylphosphine nickel(0) complexes take place much more rapidly than that of hexafluorobenzene (**5**) (Scheme 3).<sup>18</sup> In each case, a C–F bond at the 2-position of a pyridine ring is cleaved selectively at 25 °C for 2–3 h by the use of  $\text{Ni}(0)$  species.

Scheme 3



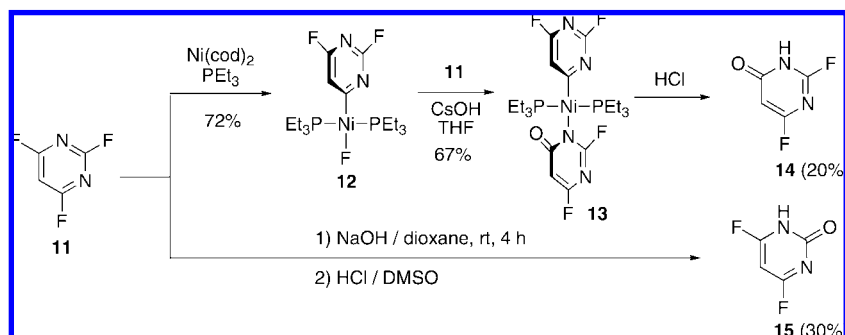
Toward the transformation of C–F bonds, the selective substitution of the 4-fluoro substituent of 2,4,6-trifluoropyrimidine (**11**) by a hydroxy group through the Ni-mediated reaction proceeds smoothly (Scheme 4).<sup>19</sup> The oxidative addition of C–F bond in trifluoropyrimidine **11**, the subsequent treatment with an excess amount of pyrimidine **11**, and the hydrolysis provide pyrimidin-4-one **14**. On the other hand, the reaction of 2,4,6-trifluoropyrimidine (**11**) with NaOH (in the absence of the Ni complex) yields pyrimidin-2-one **15**.

Braun et al. demonstrated that the discrete chemoselectivity in C–X bond cleavage was dictated by catalyst ligands.<sup>20</sup> The stepwise treatment of  $\text{Ni}(\text{cod})_2$  with  $\text{PEt}_3$  and 5-chloro-2,4,6-trifluoropyrimidine (**16**) results in the selective cleavage of the C–Cl bond to form chloronickel complex **17** (Scheme 5). In contrast, the use of  $\text{PCy}_3$  instead of  $\text{PEt}_3$  completely changes the reaction course. Exclusive activation of the C–F bond in the 4-position of the pyrimidine ring takes place to provide the fluoro complex **18**, which reacts with HCl and  $\text{I}_2$  to give fluoropyrimidine derivatives **19** and **20**, respectively.

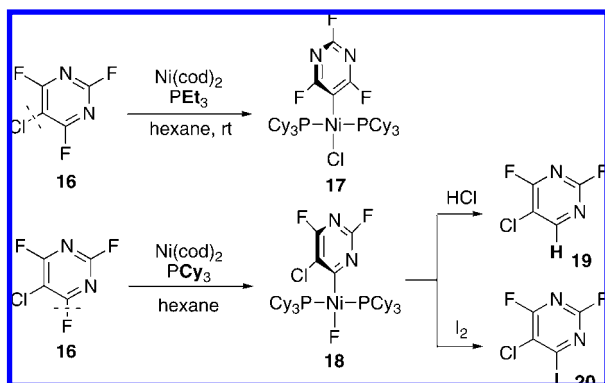
There are several plausible pathways for oxidative addition to the metal complexes involving three-centered transition states (**A**), tight ion-pairs via electron transfer from the electron-rich  $\text{Ni}(0)$  complexes (**B**), or Meisenheimer intermediates via  $\text{S}_{\text{N}}\text{Ar}$  reactions (**C**) (Scheme 6).

By the use of nickel complexes, the observed preference for C–F cleavage at the 2-position of pentafluoropyridine provides indirect evidence for concerted oxidative addition of the aza-heterocycles via a three-centered transition state **A**. On the contrary, the divergent behavior is revealed in the reactivity of  $\text{Pd}(0)$ ,  $\text{Pt}(0)$ , and  $\text{Rh}(I)$  toward pentafluoropyridine (**7**); the insertion of the metal into the C–F bond proceeds selectively at the 4-position of fluoropyridine **7** (Scheme 7).<sup>21</sup> The difference in regioselectivity of aromatic

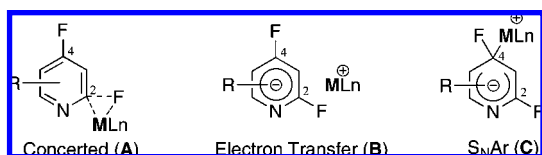
Scheme 4



Scheme 5

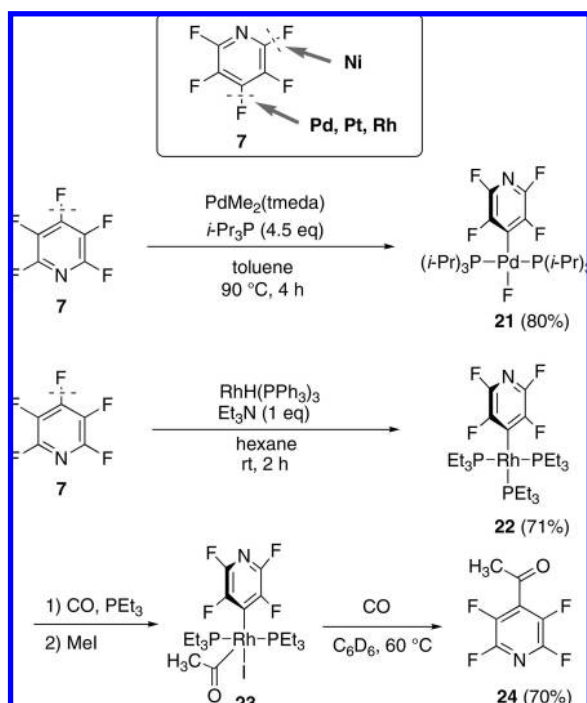


Scheme 6



C–F bond activation has been accounted for with differing mechanisms. Both electron-transfer reaction pathways and nucleophilic substitution pathways would lead to reactions in the 4-position of the aza-heterocycles as have been established for other such reactions. It is generalized that the aromatic C–F bond activation is kinetically favored by electronic and steric effects in the nucleophilic reaction of electron-rich metal to the electron-deficient and less-sterically hindered carbon attached to a fluorine atom.

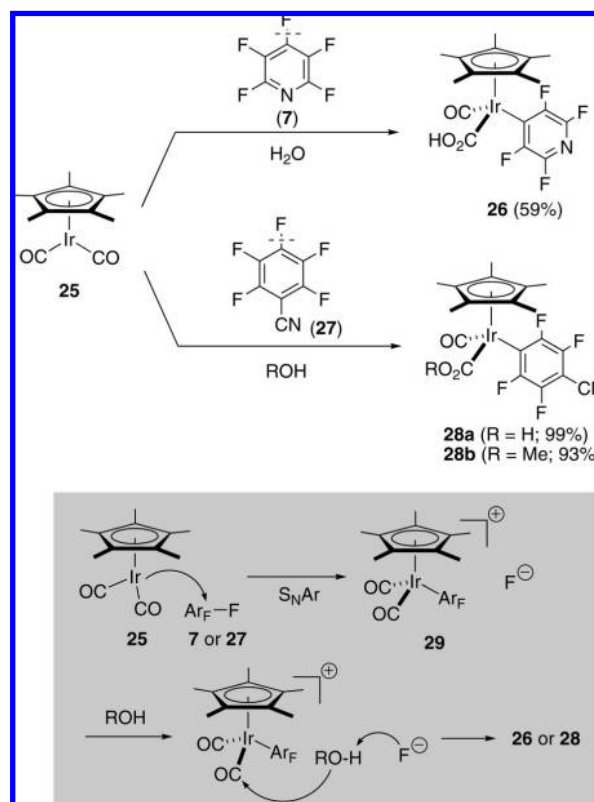
Scheme 7



As an example of transformations involving aromatic nucleophilic substitution by transition metals, Chan and Leong reported the reactions of  $\text{Cp}^*\text{Ir}(\text{CO})_2$  (**25**) with activated perfluoroaromatic compounds (Scheme 8).<sup>22</sup> In the presence of water or methanol, pentafluoropyridine (**7**) and pentafluorobenzonitrile (**27**) undergo C–F bond cleavage

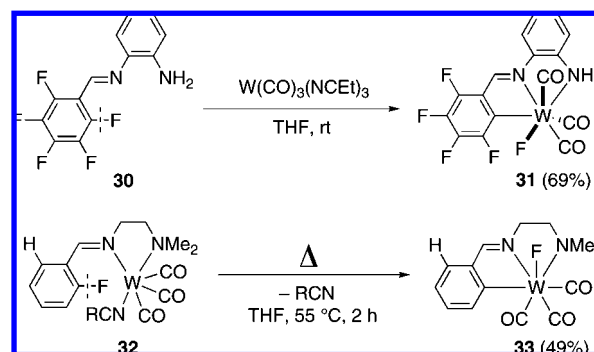
with high *para*-selectivity to produce the metallocarboxylic acids or esters **26** and **28**, respectively.

Scheme 8



Chelate-assisted oxidative addition is one of the potential methods to cleave strong C–F bonds. In 1987, Richmond reported the chelate-assisted oxidative addition of aromatic C–F bonds to tungsten(0) to afford seven-coordinate tungsten(II) fluoride complexes (Scheme 9).<sup>23,24</sup> Schiff's base **30**, which is prepared from pentafluorobenzaldehyde and diaminebenzene, is used as a suitable bidentate ligand; the reaction of aromatic C–F bond activation is completed in <10 min. It is noted that W(0) inserts into a C–F bond in the presence of a weaker C–H bond in **32**. The chelate-assisted C–F oxidative addition is applicable to substrates containing *ortho*-monofluorinated aromatic rings of Schiff's base ligands.

Scheme 9

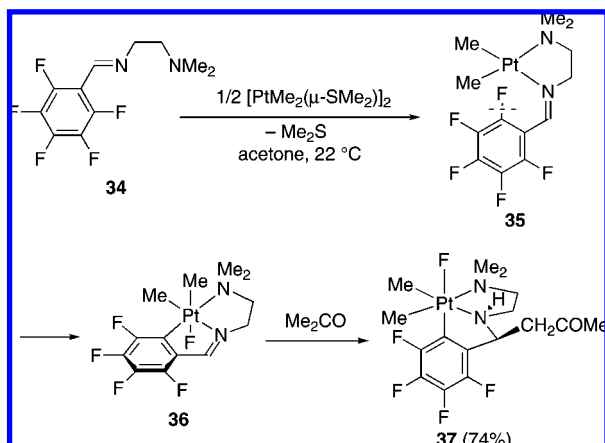


Chelate-assisted intramolecular oxidative addition reactions of aromatic fluorides take place also in the case of square planar  $d^8$  complexes. The C–F bond of the pentafluorophenyl group in the bidentate Schiff's base ligand **34** adds *trans* to the tetra-coordinated Pt(II) complex to provide the Pt(IV)



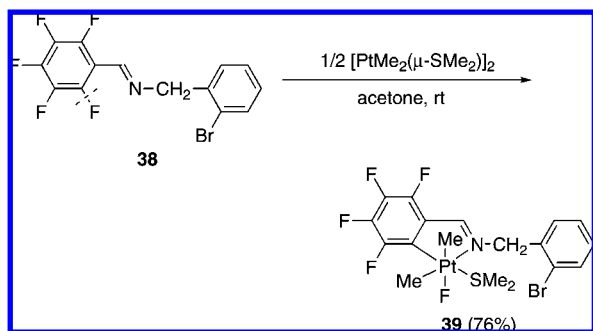
fluoro complex **36**, which reacts with acetone solvent by *cis*-addition of  $\text{H}-\text{CH}_2\text{COCH}_3$  across the imine bond with a change of the stereochemistry at Pt(IV) (Scheme 10).<sup>25</sup>

Scheme 10



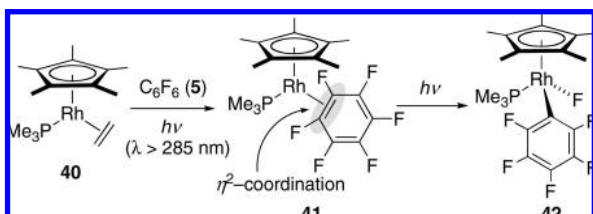
A key feature of the present Pt-mediated C–F bond activation is high chemoselectivity. Interestingly, even in the presence of a much weaker C–Br bond, selective intramolecular activation reaction of the C–F bond of bifunctional ligand **38** takes place by the action of  $[\text{PtMe}_2(\mu\text{-SMe}_2)_2]$  (Scheme 11).<sup>26</sup> The fluoroaromatic imine moiety in **38** is a pivotal ligand skeleton for *ortho*-selective C–F bond cleavage.

Scheme 11



Partial coordination of arenes to transition metals is regarded as a step toward oxidative addition. The photochemical reaction of  $\text{Cp}^*\text{Rh}(\text{PMe}_3)(\text{C}_2\text{H}_4)$  (**40**) with hexafluorobenzene (**5**) gives  $\text{Cp}^*\text{Rh}(\text{PMe}_3)(\eta^2\text{-C}_6\text{F}_6)$  (**41**), which followed by pyrolysis generates  $\text{Cp}^*\text{Rh}(\text{PMe}_3)(\text{C}_6\text{F}_5)\text{F}$  (**42**) via the reaction of the electronically unsaturated fragment  $\text{Cp}^*\text{Rh}(\text{PMe}_3)$  with free hexafluorobenzene (**5**) (Scheme 12).<sup>27</sup>

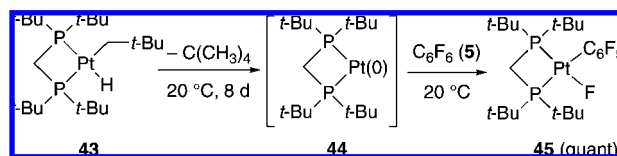
Scheme 12



Reductive elimination is one of the efficient methods to generate electronically unsaturated complexes. The 14-electron Pt(0) fragment **44**, which is generated by reductive elimination of neopentane from *cis*-hydrido(neopentyl)plati-

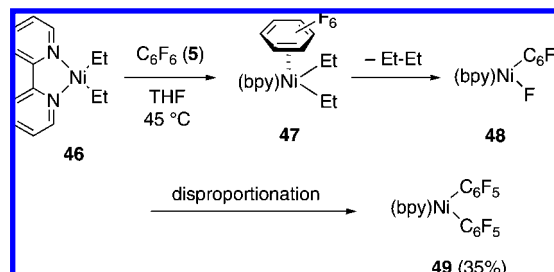
num(II) complex (**43**), is capable of oxidative addition of a C–F bond of hexafluorobenzene (**5**) (Scheme 13).<sup>28</sup>

Scheme 13



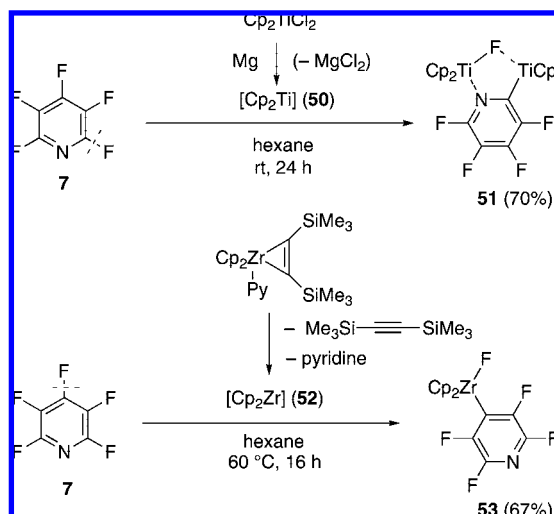
$\text{NiEt}_2(\text{bpy})$  (**46**) is a stable compound in various nonaromatic solvents and aromatic solvents without an electron-withdrawing group at room temperature. On the other hand, reductive elimination of Et–Et (butane) from diethylnickel(II) complex **46** is enhanced by the interaction with electron-accepting aromatics. The reaction of  $\text{NiEt}_2(\text{bpy})$  (**46**) with hexafluorobenzene (**5**) leads to the formation of  $\text{Ni}(\text{C}_6\text{F}_5)_2(\text{bpy})$  (**49**) with evolution of butane (Scheme 14).<sup>29</sup> Initially, oxidative addition of a C–F bond of  $\text{C}_6\text{F}_6$  to unsaturated  $\text{Ni}(0)(\text{bpy})$  complex gives  $\text{NiF}(\text{C}_6\text{F}_5)(\text{bpy})$  (**48**), which participates in disproportionation to yield bis(pentafluorophenyl)nickel(II) complex **49**.

Scheme 14

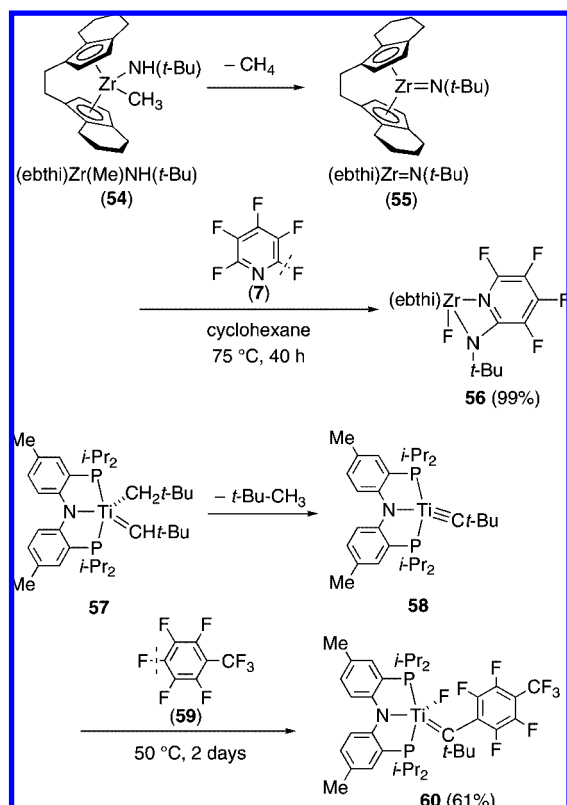


These protocols as mentioned above are also effective to generate coordinatively unsaturated species of early transition metals. By the use of highly reactive, transient low-valent intermediates such as  $\text{Cp}_2\text{Ti}$  (**50**)<sup>30</sup> and  $\text{Cp}_2\text{Zr}$  (**52**),<sup>31</sup> 2,3,4,5,6-pentafluoropyridine (**7**) undergoes selective C–F bond cleavage to provide the corresponding metal fluorides **51** and **53** in good yields (Scheme 15). Imidozirconocene **55**<sup>32</sup> and alkylidyne titanium **58**<sup>33</sup> engage regioselective 1,2-addition of a C–F bond across a multiple M–N or M–C bond (Scheme 16).

Scheme 15

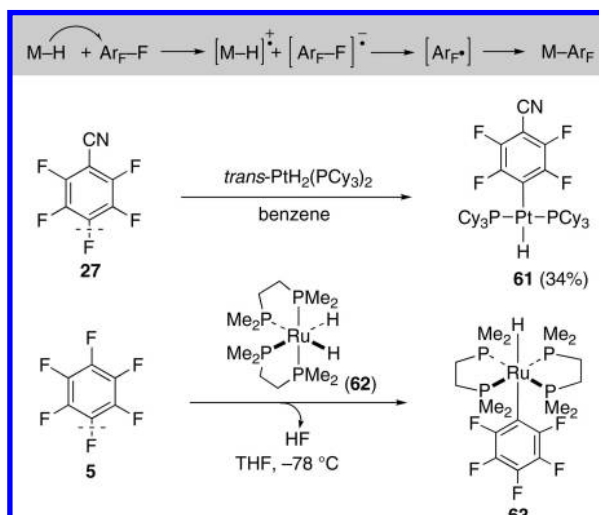


Scheme 16



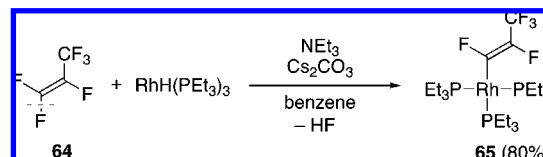
Single electron-transfer reactions from transition metal hydride complexes trigger C–F bond cleavage of fluoroarenes via formation of caged radical pairs (Scheme 17). *trans*-PtH<sub>2</sub>(PCy<sub>3</sub>)<sub>2</sub> reacts with fluorinated benzonitriles such as 4-RC<sub>6</sub>F<sub>4</sub>CN (R = H, F, CN, and OMe) to give the arylplatinum(II) complexes *trans*-[PtH{RC<sub>6</sub>F<sub>3</sub>CN}(PCy<sub>3</sub>)<sub>2</sub>].<sup>34</sup> Electron transfer from electron-rich dihydride complex [Ru(dmpe)<sub>2</sub>H<sub>2</sub>] (**62**) to hexafluorobenzene (**5**) provides the radical anion of C<sub>6</sub>F<sub>6</sub>, which readily eliminates fluoride anion.<sup>35</sup> Overall, HF is lost to yield monohydride complex [Ru(dmpe)<sub>2</sub>(C<sub>6</sub>F<sub>5</sub>)H] (**63**). Note that reactions also take place with C<sub>6</sub>F<sub>5</sub>H, C<sub>6</sub>F<sub>5</sub>CF<sub>3</sub>, C<sub>6</sub>F<sub>5</sub>OMe, 1,2,3,4-C<sub>6</sub>F<sub>4</sub>H<sub>2</sub>, and 1,2,3-C<sub>6</sub>F<sub>3</sub>H<sub>3</sub> to afford products formed from aromatic C–F bond insertion exclusively.

Scheme 17



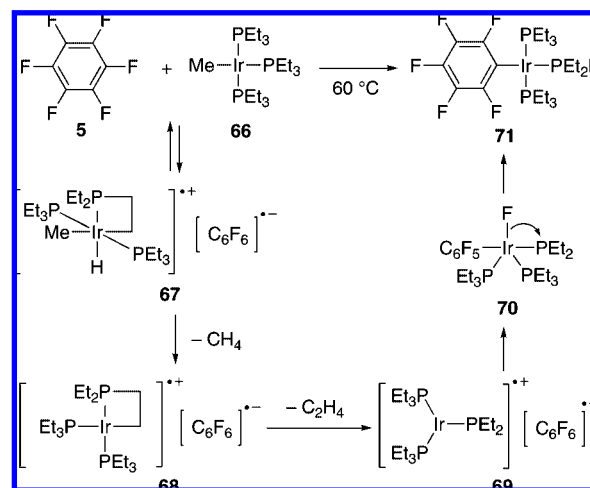
A rhodium hydrido complex such as RhH(PEt<sub>3</sub>)<sub>3</sub> works well for the C–F bond activation of hexafluoropropene (**64**) (Scheme 18).<sup>36</sup> The reaction proceeds in regioselective fashion to produce [Rh{(Z)-CF=CF(CF<sub>3</sub>)}(PEt<sub>3</sub>)<sub>3</sub>] (**65**) in 80% yield, and there is no indication of defluorination from the trifluoromethyl group of **64**.

Scheme 18



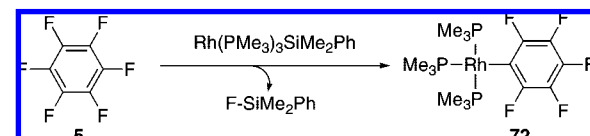
In 1991, Milstein et al. reported a unique process involving Ir-mediated cleavage of C–F and P–C bonds.<sup>37</sup> Methyl iridium(I) complex **66** is treated with hexafluorobenzene (**5**) at 60 °C to form pentafluorophenyl iridium(I) complex **71** with evolution of methane and ethylene (Scheme 19). The present reaction would proceed via (i) electron transfer from the electron-rich metallacycle generated by intramolecular activation of C–H bond in ligand PEt<sub>3</sub> to C<sub>6</sub>F<sub>6</sub> (**5**), (ii) subsequent extrusion of methane and ethylene to give a low-valent Ir complex **69**, and (iii) oxidative addition of C<sub>6</sub>F<sub>6</sub> (**5**) and fluoride migration to the phosphine atom.<sup>38,39</sup>

Scheme 19



In 1994, Aizenberg and Milstein demonstrated that silyl complex (Me<sub>3</sub>P)<sub>3</sub>RhSiMe<sub>2</sub>Ph reacts quantitatively with hexafluorobenzene (**5**) at room temperature (Scheme 20).<sup>40</sup> With loss of F–SiMe<sub>2</sub>Ph, the pentafluorophenyl rhodium(I) complex **72** with square-planar geometry is obtained. The silyl ligand would facilitate aromatic C–F bond cleavage by electron transfer from the electron-rich Rh complex to C<sub>6</sub>F<sub>6</sub> (**5**) as well as release of fluorosilane, which arises from the great affinity between silicon and fluorine atoms.

Scheme 20



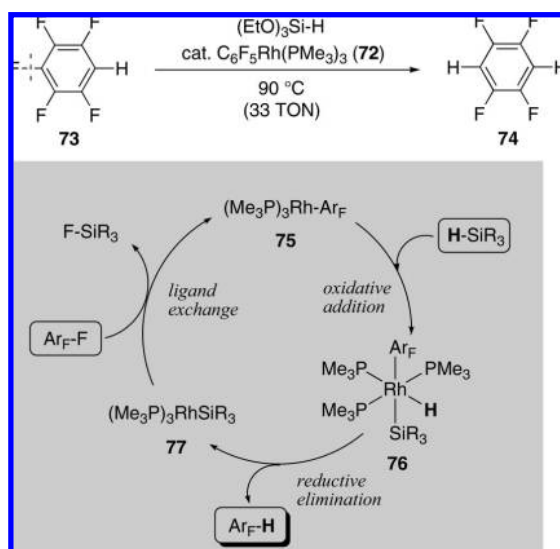
### 2.1.2. Transition Metal-Mediated Activation of *sp*<sup>2</sup>-C–F Bonds: Catalytic Transformations

From the viewpoint of organic synthesis, atom economy, chemo-, regio-, and stereoselective transformations, and

catalytic processes have become primary and most essential requirements. With the remarkable progress in C–F bond activation by the use of stoichiometric amounts of transition metal complexes, the number of reports on catalytic transformations has been increasing. Development of catalytic processes of C–F bond activation is of practical significance both for laboratory synthesis and for industrial production. Herein, several catalytic reactions under the principles of transition metal promoted C–F bond cleavage are highlighted.

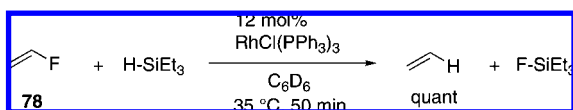
In 1994, Milstein et al. reported catalytic hydrodefluorination of aromatic C–F bonds. Rh(I)–silyl complexes can cleave C–F bonds of  $C_6F_6$  (**5**) and  $C_6F_5H$  (**73**).<sup>40</sup> Highly regioselective catalysis of  $C_6F_5H$  proceeds upon the treatment of  $(EtO)_3Si-H$  and  $C_6F_5Rh(PMe_3)_3$  to yield 1,4- $C_6F_4H_2$  (**74**) exclusively (Scheme 21). In combination with Si–H oxidative addition to arylrhodium(I) complex **75** and C–H reductive elimination, a catalytic cycle of Rh-mediated activation of aromatic C–F bonds is completed.

Scheme 21



McNeill et al. investigated the catalytic dehalogenation of fluoro- and chloroethylenes (Scheme 22).<sup>41</sup> Treatment of vinyl fluoride (**78**) with  $H-SiEt_3$  and a catalytic amount of  $RhCl(PPh_3)_3$  at 35 °C leads to complete defluorination in 50 min. Very interestingly, fluoride **78** is a more reactive substrate with a dehalogenation rate 6 times that of vinyl chloride.

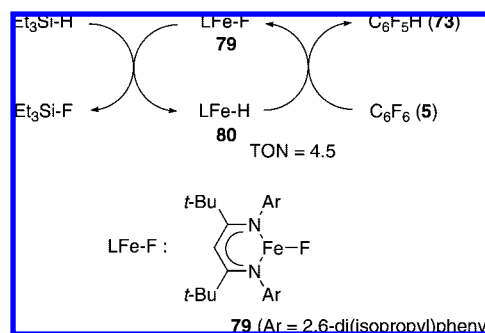
Scheme 22



Metal hydride complexes are effective catalysts for hydrodefluorination of organic fluorides. Iron–fluoride complex **79** reacts with  $Et_3Si-H$  to generate active iron–hydride complex **80**, which can readily undergo defluorination of hexafluorobenzene (**5**) to yield pentafluorobenzene (**73**) (Scheme 23).<sup>42</sup>

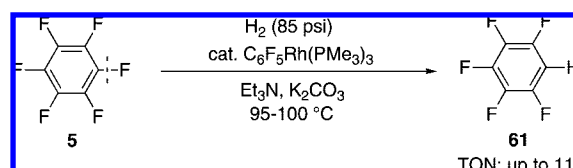
Instead of hydrosilanes, hydrogen ( $H_2$ ) gas is an attractive reagent for catalytic C–F transformations. Rh(I)-catalyzed hydrogenolysis of a C–F bond in  $C_6F_6$  (**5**) proceeds smoothly in the presence of bases (Scheme 24).<sup>43</sup> Electron-transfer type of C–F bond cleavage by the use of hydrido–Rh complex

Scheme 23

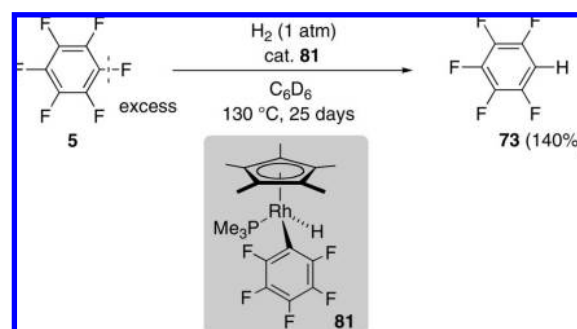


**81** is also applicable to a catalytic hydrogenation of hexafluorobenzene (**5**) (Scheme 25).<sup>44</sup>

Scheme 24

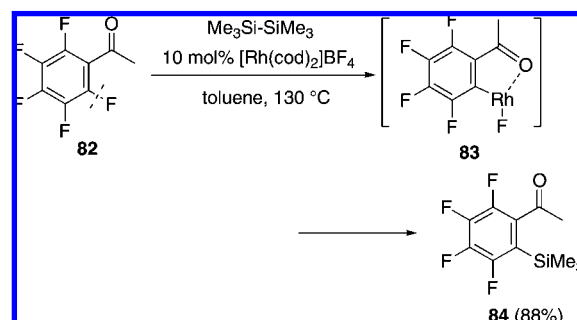


Scheme 25



Chatani and Murai et al. presented an example of catalytic functionalization of C–F bonds.<sup>45</sup> The reactions of fluoroacetophenones and (fluorophenyl)oxazolines, with hexamethyldisilane in the presence of a catalytic amount of cationic rhodium complex such as  $[Rh(cod)_2]BF_4$ , result in site-selective Si–F exchange to give *ortho*-(trimethylsilyl)acetophenones (Scheme 26). The existence of a coordination functionality such as a carbonyl group or an oxazoline unit is essential for the present F–Si exchange process at the *ortho*-position of the phenyl moiety.

Scheme 26



### 2.1.3. Ni-Catalyzed Cross-Coupling Reactions of Aromatic Fluorides

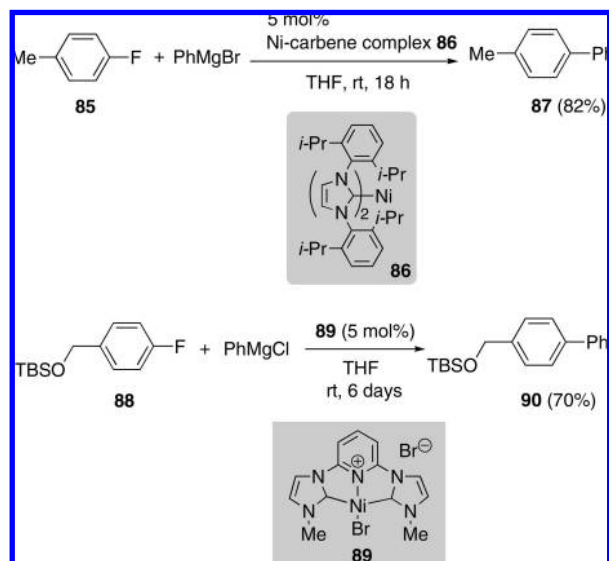
Catalytic conversion of a C–F bond to a C–C bond is one of the most challenging topics in organic synthesis. Ni-

catalyzed cross-coupling reactions of organic halides with Grignard reagents (so-called Kumada–Tamao–Corriu reaction) are general and quite useful tools for a wide repertoire of organic compounds. The catalytic cycle commences with oxidative addition of an aromatic halide (Ar–X), and the square planar ArNi(II)X complex is formed. Subsequently, by exposure of alkyl (or aryl) Grignard reagent (RMgX), displacement of the halide ligand (X) in the Ni complex with an alkyl (aryl) group, so-called transmetalation, gives the di(organo)nickel complex and magnesium dihalide. The third reaction is reductive elimination leading the cross-coupling product (Ar–R) with regeneration of the active Ni(0) complex.

Since the first report (Tamao and Kumada, 1973) on Ni-catalyzed  $sp^3$ –C– $sp^2$ –C cross-coupling reactions using alkyl Grignard reagents and aryl fluorides,<sup>15</sup> there existed a long absence. However, recently several excellent examples of Ni-catalyzed cross-coupling reactions involving C–F bond cleavage have been published.

In 2001, Herrmann et al. reported the successful results of  $sp^2$ –C– $sp^2$ –C bond-forming reactions by the use of *N*-heterocyclic carbene ligands (Scheme 27).<sup>46</sup> By the use of nickel carbene complex **86**, electronically nonactivated aryl fluorides undergo cross-coupling reactions affording a variety of biaryls. Thus, the choice of the catalyst ligands plays a pivotal role. Also, pincer-type bis(imidazolin-2-ylidene)nickel(II) complex **89** is an effective catalyst in the Kumada–Tamao–Corriu reaction.<sup>47</sup>

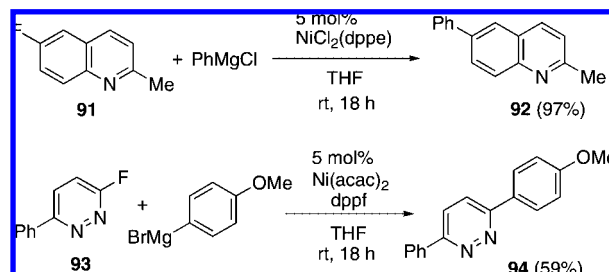
Scheme 27



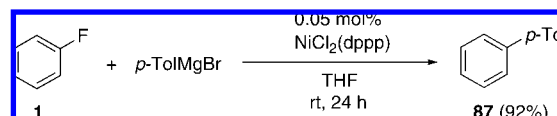
Bidentate phosphine ligands, such as dppe and dppp, are effective for the catalytic  $sp^2$ –C– $sp^2$ –C cross-coupling reactions to yield *N*-heterocyclic biaryls (Scheme 28).<sup>48</sup> With exposure of only 0.0005 equiv of NiCl<sub>2</sub>(dppp),  $sp^2$ –C–F bond-activation reactions proceed smoothly to provide the corresponding unsymmetrical biaryls in high yields (Scheme 29).<sup>49</sup>

Fluoropyridyl and pyrimidyl Ni complexes possessing monodentate phosphine ligands such as PEt<sub>3</sub> promote cross-coupling reactions.<sup>50</sup> For polyhalogenated pyrimidine **16** endowed with C–F and C–Cl bonds, the nickel complex **96** assists chemoselective activation of C–F bonds to afford 4,6-diphenylpyrimidine **97**, in which the C–Cl functionality is compatible (Scheme 30).

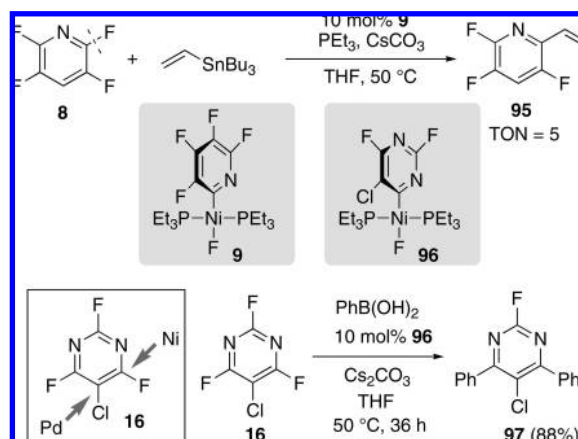
Scheme 28



Scheme 29



Scheme 30



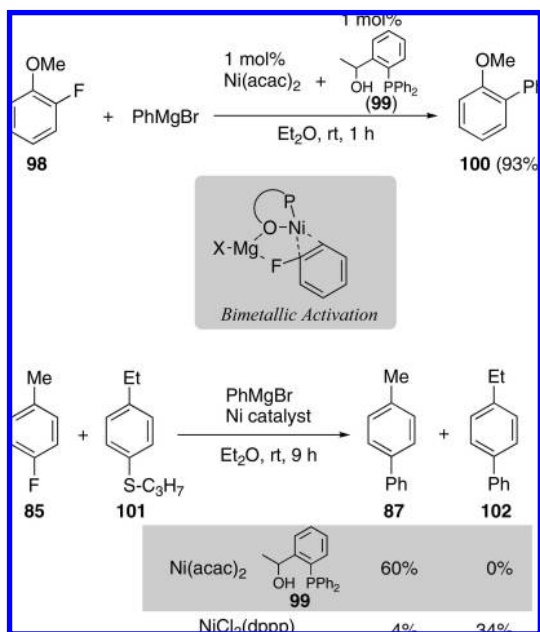
Design of phosphine ligands is quite important for improvement of catalytic activity. Nakamura designed a useful hydroxy phosphine ligand **99** that facilitated C–F bond activation of fluoroaromatics via nickel/magnesium bimetallic cooperation (Scheme 31).<sup>51</sup> On the basis of an assumption that C–F bond breaking is a turnover-limiting step in the catalytic cycle, the bidentate ligand **99** can hold nickel and magnesium atoms together to accelerate the Ni-catalyzed cross-coupling reactions of aromatic fluorides. Furthermore, the present catalysis shows intriguing chemoselectivity in which aryl fluorides react faster than sulfides and triflates.

Besides aryl and alkyl phosphines, bulky phosphites<sup>52</sup> and aminophosphine oxides<sup>53</sup> are effective ligands for Ni-catalyzed cross-coupling reactions (Schemes 32 and 33). Combined with Pd-catalyzed amination, the sequential transformation of 4-chlorofluorobenzene (**104**) proceeds in a highly chemoselective fashion.

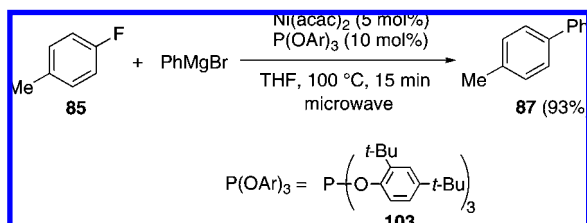
Several nickel complexes are able to catalyze cross-coupling reactions between organoboron compounds and organic halides.<sup>54</sup> In 2006, Radius et al. reported the first examples of Ni-catalyzed Suzuki–Miyaura coupling involving C–F bond activation of fluoroarenes (Scheme 34).<sup>55</sup> In the presence of the NHC (*N*-heterocyclic carbene)-stabilized nickel complex [Ni<sub>2</sub>(*i*-Pr<sub>2</sub>Im)<sub>4</sub>(cod)] (**109**) (*i*-Pr<sub>2</sub>Im: 1,3-di(isopropyl)imidazol-2-ylidene), the cross-coupling reactions of octafluorotoluene (**59**) and perfluorinated biphenyl (**111**) with phenylboronic acid proceed smoothly. In all cases, the fluoro-substituents in the *para*-position of the CF<sub>3</sub> or C<sub>6</sub>F<sub>5</sub> group are substituted with aryl groups.



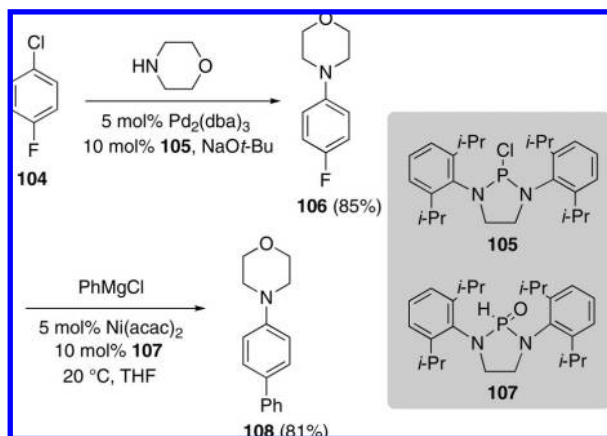
Scheme 31



Scheme 32



Scheme 33

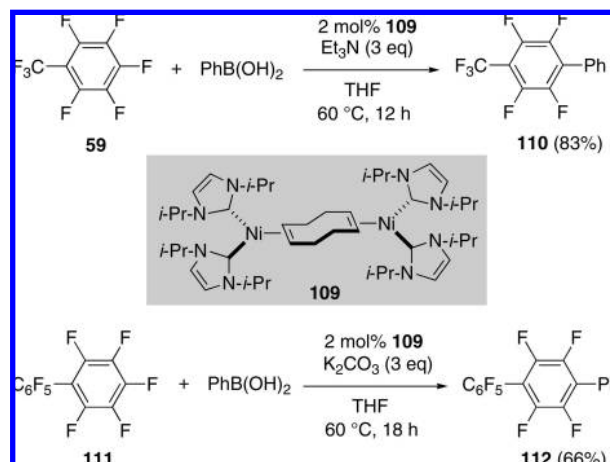


#### 2.1.4. Pd-Catalyzed Cross-Coupling Reactions of Aromatic Fluorides

In the previous section, we introduced Ni-catalyzed cross-coupling reactions of organic fluorides with Grignard reagents (RMgX). Generally in the Ni-catalyzed cross-coupling, the oxidative addition reactions of C–F, C–O, and C–S bonds to Ni(0) take place, followed by transmetalation due to the strong affinity of fluorine, oxygen, and sulfur atoms, respectively, with Mg in the Grignard reagents. Thus, cleavage reactions of these strong bonds are possible with Ni catalysts.

The palladium-catalyzed coupling of aryl and alkenyl halides and triflates with main group organometallics has been very broadly developed. These reactions also involve

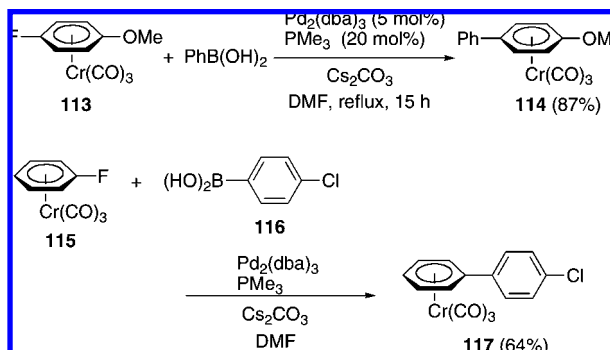
Scheme 34



oxidative addition/transmetalation/reductive elimination sequences. A very wide range of main group organometallics undergo transmetalation to Pd(II); that is, they transfer their R group to palladium in exchange for metal halides or triflates.<sup>56</sup> Transmetalation from Li, Mg, Zn, Zr, B, Al, Sn, Si, and others have been reported. Therefore, a key feature of Pd-catalyzed cross-coupling is functional group tolerance. Organometallic reagents such as tin and boron compounds have proved their usefulness in the synthesis of compounds containing functional groups (COOR, CN, etc.) that are not compatible with organomagnesium and -lithium compounds. Cross-couplings with boron compounds (the Suzuki–Miyaura reactions) and tin compounds (the Stille reactions) are especially useful in syntheses of structurally complicated molecules. In the oxidative addition of organic halides to a Pd center, the order of reactivity is I > OTf, Br >> Cl >> F. Actually, in the old days, aryl fluorides were considered to be inert for Pd-catalyzed cross-coupling reactions. How to activate aryl and alkenyl fluorides is strategically important.

Utilization of tricarbonylchromium complexes of fluoroarenes permits Suzuki and Stille cross-coupling reactions via nucleophilic aromatic substitution to form the corresponding biaryl and styrene Cr-complexes.<sup>57</sup> When *p*-chlorosubstituted phenylboronic acid (**116**) is used, the cross-coupling product **117** is isolated in 64% yield, which suggests that the reactivity of the C–F bond in Cr(0)–arene complex **115** is greater than that of the aromatic C–Cl bond under the present conditions (Scheme 35).

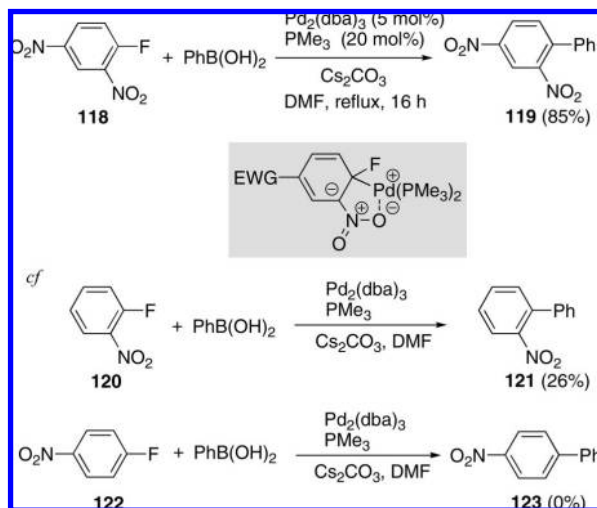
Scheme 35



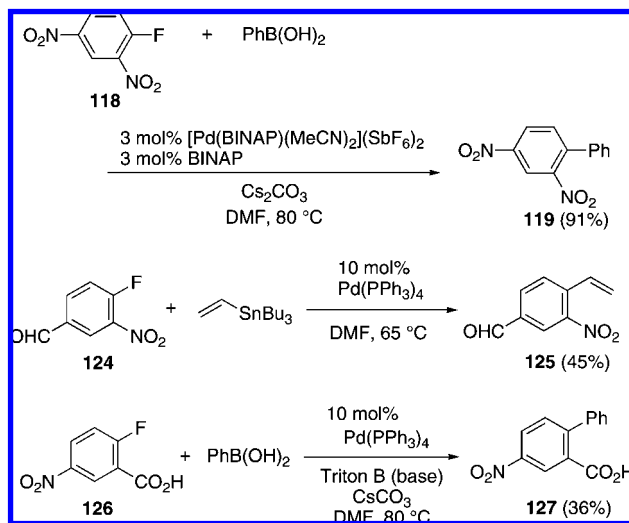
Introduction of electron-withdrawing groups such as nitro and carboxyl groups, which are sensitive to organomagnesium and -lithium reagents, into aryl groups of fluoroarenes is effective for Suzuki–Miyaura and Stille cross-coupling

reactions (Schemes 36 and 37).<sup>58–61</sup> The Pd-catalyzed coupling reactions proceed smoothly by the use of *ortho*-nitro-substituted fluoroarenes as substrates.<sup>58</sup> On the contrary, when 4-nitrofluorobenzene (**122**) is used, no trace of the cross-coupling product can be detected (Scheme 36). As obligate features of the coupling process, the *o*-nitro groups of fluoroarenes not only can function as electron-withdrawing groups but also can coordinate the incoming Pd atom to facilitate C–F bond activation.

Scheme 36

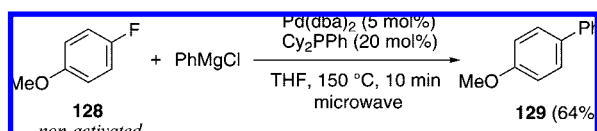


Scheme 37



For Pd-catalyzed cross-coupling, the use of organomagnesium reagents as main group organometallic reagents is efficient because of the large interaction between magnesium and fluorine atoms. The Pd-catalyzed cross-coupling reactions of nonactivated fluoroarenes such as **128** with Grignard reagents proceed under thermal or microwave-irradiation conditions (Scheme 38).<sup>52</sup>

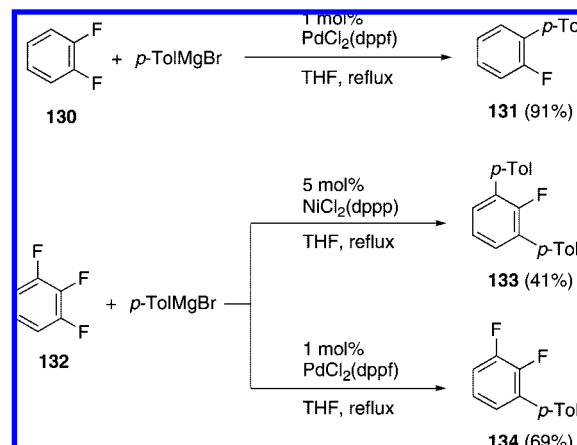
Scheme 38



Cross-coupling reactions containing selective C–F bond activation of polyfluoroarenes are useful tools for synthesis

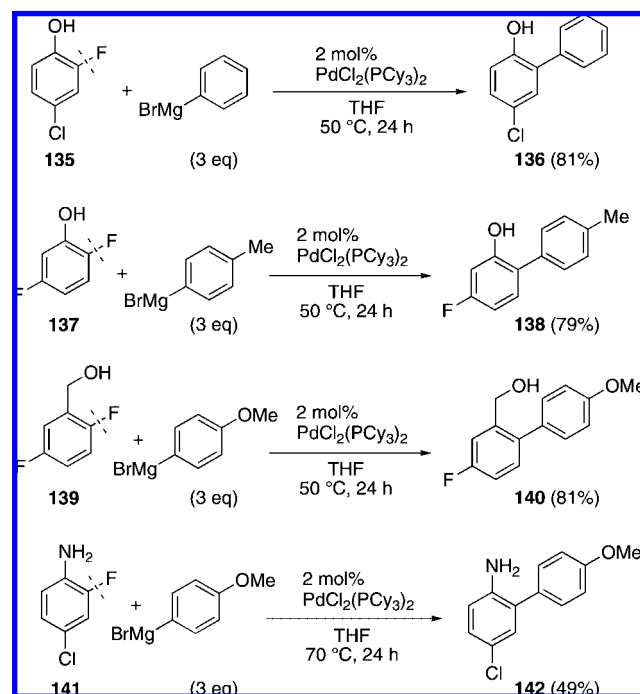
of partially fluorinated aromatics. PdCl<sub>2</sub>(dppf) is a quite effective catalyst for the cross-coupling of 1,2-difluorobenzene (**130**) to afford the monocoupling product **131** in high yield (Scheme 39).<sup>49</sup> From the finding that 1,3- and 1,4-difluorobenzenes give the cross-coupling products in poor yields, a chelating effect of the adjacent atom is expected to play an important role in promoting oxidative addition of the C–F bond. The reaction of 1,2,3-trifluorobenzene (**132**) using NiCl<sub>2</sub>(dppp) provides dicoupled product **133** exclusively, whereas the use of the Pd catalyst furnishes mono-coupled product **134**.

Scheme 39



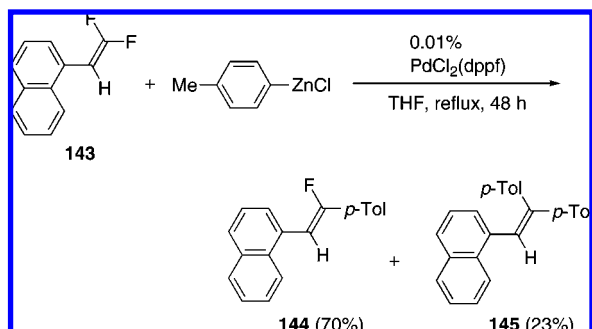
In 2008, Manabe and Ishikawa demonstrated interesting examples of *ortho*-selective cross-coupling of fluoroarene derivatives with Grignard reagents (Scheme 40).<sup>62</sup> Hydroxy, hydroxymethyl, and amino directing groups in aromatics such as **135**, **137**, **139**, and **141** accelerate the palladium-catalyzed cross-coupling reactions at the fluoro group *ortho* to the directing group. As a noteworthy event, fluoro- and chloro-groups at positions other than *ortho* to the directing groups survive under the reaction conditions.

Scheme 40



Alkenyl fluorides are applicable to Pd-catalyzed cross-coupling reactions. Selective cleavage of a C–F bond is observed in the cross-coupling reaction of *gem*-difluoroalkene **143** to form (*Z*)-fluoroalkene **144** as a major product; the fluorine atom *trans* to the naphthyl group is selectively replaced because of the steric hindrance of the naphthyl group at the vicinal *cis*-position in **143** (Scheme 41).<sup>49</sup>

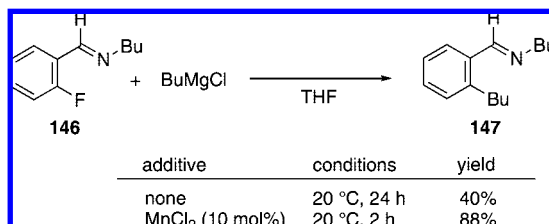
Scheme 41



### 2.1.5. Other Transition Metal Catalyzed Cross-Coupling Reactions

Several transition metal reagents including both early transition metal salts and late transition metal complexes are quite useful as catalysts for cross-coupling reactions of aromatic and vinylic fluorides. In 1999, Cahoez et al. reported the manganese-catalyzed cross-coupling between activated aryl halides and Grignard reagents (Scheme 42).<sup>63</sup> In the presence of  $\text{MnCl}_2$  (10 mol %),  $\text{BuMgCl}$  readily reacts in tetrahydrofuran (THF) with aryl fluoride **146** bearing an electron-withdrawing activating group ( $\text{CH}=\text{NR}$ ) in the *ortho*-position. The manganese-catalyzed procedure compares favorably to the aromatic nucleophilic substitution ( $\text{S}_{\text{N}}\text{Ar}$ ). From aldimine **146**, in the absence of  $\text{MnCl}_2$ , the substitution takes place at 20 °C for 24 h to give **147** in 40% yield. On the contrary, the beneficial influence of manganese chloride is obvious; the reaction proceeds faster (2 h instead 24 h) and leads to a much better yield (88% instead 40%), and no adduct of the Grignard reagent to the imino carbon of **146** is observed.

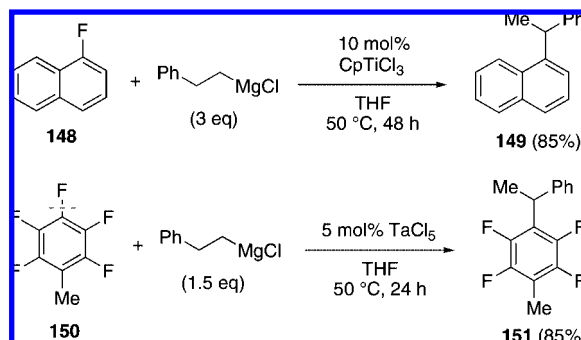
Scheme 42



Cross-coupling reactions of fluoroarenes are catalyzed by early transition metals. The reaction of 1-fluoronaphthalene (**148**) with 3 equiv of 2-phenylethylmagnesium chloride in the presence of a catalytic amount of  $\text{CpTiCl}_3$  affords 1-(1-phenylethyl)naphthalene (**149**) in good yield via isomerization of the 1-phenylethyl group (Scheme 43).<sup>64</sup> Similarly,  $\text{TaCl}_5$ -catalyzed coupling reactions of phenethylmagnesium chloride with substituted fluoroarenes proceed with high regioselectivity at the *para*-position to provide the corresponding 1-phenethylarenes in good yields.

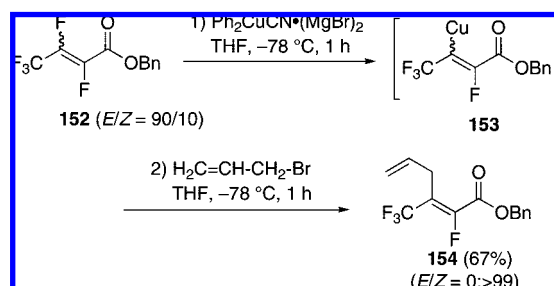
Copper(I) salts promote the fluorine–metal exchange reactions of fluoroalkenes with Grignard reagents.<sup>65</sup> Selective

Scheme 43



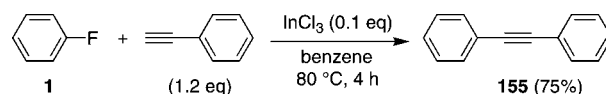
replacement of fluorine in 2,3,4,4,4-pentafluorocrotonate **152** by the organocuprate derived from Grignard reagent and  $\text{CuCN}$  takes place efficiently to generate the  $\beta$ -metalated tetrafluorocrotonate intermediate **153**, which reacts with allyl bromide to give  $\beta$ -substituted 2,4,4,4-tetrafluorocrotonate **154** in a highly stereoselective manner (Scheme 44).

Scheme 44



Indium salts engender copper-, phosphine ligand-, and palladium-free Sonogashira coupling reactions (Scheme 45).<sup>66</sup> In the presence of 10 mol % indium trichloride, the coupling of fluorobenzene (**1**) with phenylacetylene affords diphenylacetylene (**155**) in 75% yield.

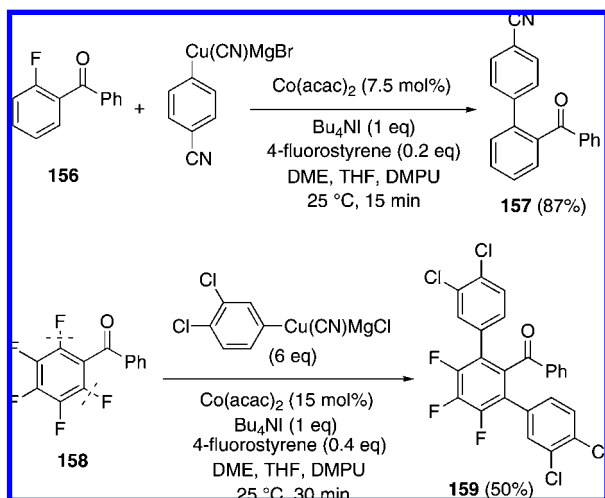
Scheme 45



Knochel et al. demonstrated cobalt(II)-catalyzed cross-coupling between aryl cuprates and aryl fluorides (Scheme 46).<sup>67</sup> In the presence of  $\text{Co}(\text{acac})_2$  (7.5 mol %),  $\text{Bu}_4\text{NI}$  (1 equiv), and 4-fluorostyrene (20 mol %) as promoters, organocopper compounds prepared by the transmetalation of functionalized arylmagnesium halides with  $\text{CuCN} \cdot 2\text{LiCl}$  undergo the cross-coupling reactions with aryl fluorides **156** and **158** bearing a carbonyl functionality in the *ortho*-position, leading to polyfunctional aromatics **157** and **159**, respectively.

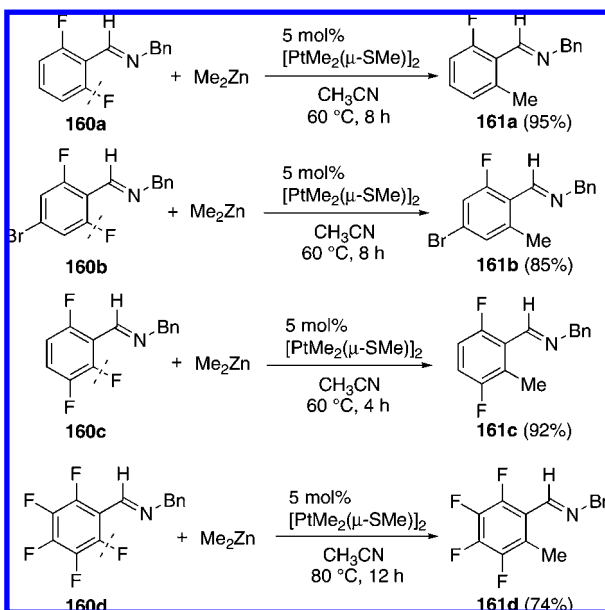
The first report on platinum-catalyzed cross-coupling of aryl fluorides was provided by Love et al. (Scheme 47).<sup>68</sup> Inspired by the reports on  $[\text{Me}_2\text{Pt}(\mu\text{-SMe}_2)]_2$ -mediated stoichiometric C–F activation of *ortho*-fluoroaryl imines,<sup>25,26</sup> they explored the catalytic version of these *ortho*-selective C–F transformations. Among the examined nucleophiles,  $\text{Me}_2\text{Zn}$  is a suitable reagent for the catalytic C–F cross-coupling reactions of fluoroarenes **160**. Of particular significance, fluorinated imine **160b** bearing a bromo group reacts exclusively at the 2-position to afford **161b** in 85% yield, the  $\text{C}=\text{N}$  directing group permits the cleavage of the

Scheme 46



strong C–F bond even in the presence of a considerably weaker C–Br bond.

Scheme 47



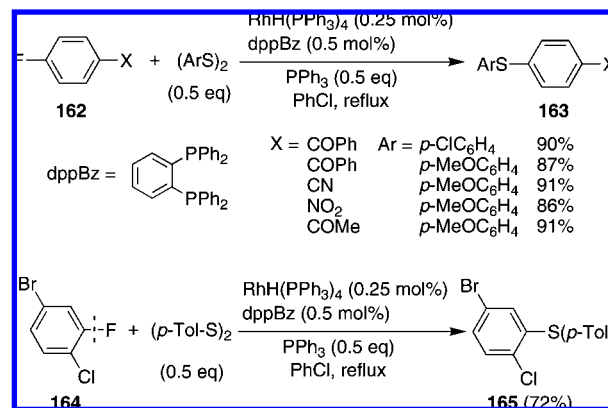
In 2008, Arisawa and Yamaguchi developed Rh-catalyzed single-bond metathesis of C–F and S–S bonds (Scheme 48).<sup>69</sup> Upon exposure to a catalytic amount of RhH(PPh<sub>3</sub>)<sub>4</sub> and 1,2-bis(diphenylphosphino)benzene (dppBz), aromatic fluorides **162**, disulfides (0.5 equiv), and triphenylphosphine (0.5 equiv) react in refluxing chlorobenzene to give aryl sulfides **163** in high yields. Triphenylphosphine traps fluoride atoms to form phosphine difluoride; both organothio groups of the disulfides react effectively. Interestingly, the fluorine substituent in **164** reacts more readily than the chlorine and bromine atoms.

## 2.2. C–F Bond Activation Initiated by Electron Transfer to Fluoroaromatics

### 2.2.1. Catalytic Hydrogenolysis of Aromatic C–F Bonds

Hydrodehalogenation of organohalogen compounds is a fundamental and important reaction for several fields of chemistry. Especially, catalytic hydrogenolysis of carbon–halogen

Scheme 48



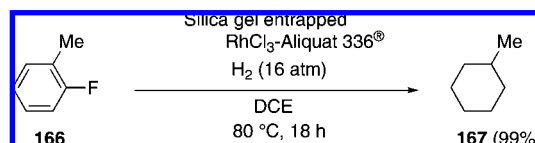
bonds is one of the most promising methods for detoxification of organohalogen pollutants, such as polychlorobiphenyls (PCBs), polychlorinated dibenzo-*p*-dioxins (PCDD), dibenzofurans (PCDF), and chlorofluorocarbons (CFCs).<sup>70</sup>

In 1920, Swarts reported the first example of catalytic hydrodefluorination of monofluoroarenes by hydrogen gas over a heterogeneous metal.<sup>71</sup> Pt black in water is the catalyst system for the transformations in which fluorobenzene, *p*-fluorobenzoic acid, and benzotrifluoride are converted to cyclohexane, cyclohexanecarboxylic acid, and trifluoromethylcyclohexane, respectively. In 1946, Renoll used nickel supported on kieselguhr for the reduction of 2-fluoro-4'-acetylbiaryl in methylcyclohexane at 125–150 °C and under 140 atm of H<sub>2</sub> to provide *p*-cyclohexylethylbenzene.<sup>72</sup> Raney nickel is also an active catalyst for the reductive transformation of *p*-fluorophenylacetic acid to ethyl cyclohexylacetate at 180–200 °C under 160–180 atm of H<sub>2</sub> gas in ethanol.<sup>73</sup>

Under catalytic hydrogenative conditions, fluoroarenes undergo not only hydrodefluorination but also hydrogenation of the aromatic rings to yield cyclohexane derivatives. Heterogeneous rhodium catalysts are effective for hydrodefluorination of aromatic fluorides under mild reaction conditions. The first example of the use of heterogeneous rhodium catalyst was reported in 1955. In the presence of Rh on alumina, the hydrodefluorination of *o*-fluorophenylphosphonic acid runs smoothly under 4 atm of H<sub>2</sub> at room temperature in 95% ethanol, affording cyclohexylphosphonic acid.<sup>74</sup>

The SiO<sub>2</sub> sol–gel entrapped ion pair [(*n*-C<sub>8</sub>H<sub>17</sub>)<sub>3</sub>NMe]<sup>+</sup>RhCl<sub>4</sub><sup>−</sup>·*n*H<sub>2</sub>O, generated from RhCl<sub>3</sub>·3H<sub>2</sub>O, methyltriocetylammmonium chloride (Aliquat 336), and Si(OMe)<sub>4</sub>, catalyzes the hydrodefluorination and hydrogenation of nonactivated fluoroarenes at 80 °C under 16 atm of hydrogen to provide the corresponding dehalogenated cyclohexanes (Scheme 49).<sup>75</sup>

Scheme 49

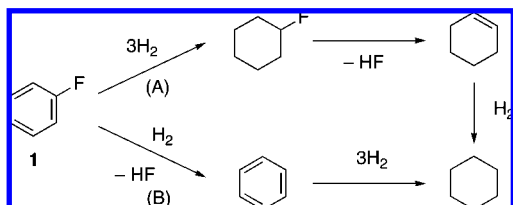


As introduced above, these catalytic transformations involve both hydrogenolysis of C–F bonds in fluoroarenes and hydrogenation of aromatic rings. In the net transformation from fluorobenzene to cyclohexane, there are two different pathways shown in Scheme 50: (A) fluorobenzene is first converted into thermally labile fluorocyclohexane,



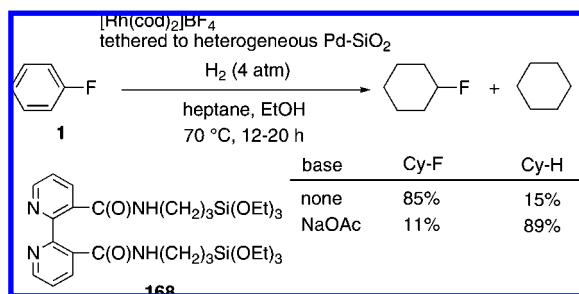
which eliminates HF at the reaction temperature (in a noncatalytic process) to form cyclohexene, followed by catalytic addition of H<sub>2</sub>, and (B) fluorobenzene is initially defluorinated to give benzene, which undergoes catalytic hydrogenation in the second step. Whether the reaction proceeds via path (A) or (B) is dependent on the reaction conditions (metal, solvent, pH, added base, temperature, hydrogen pressure, etc.).

Scheme 50



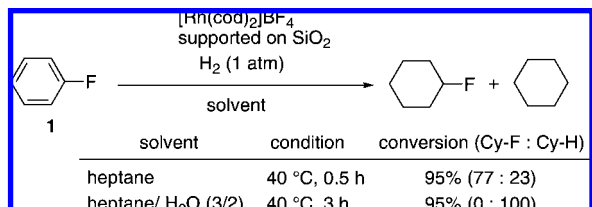
The bimetallic rhodium and palladium catalyst tethered on a silica gel, which is prepared from [Rh(cod)<sub>2</sub>]BF<sub>4</sub>, bipyridyl **168**, and silica-supported palladium (Pd–SiO<sub>2</sub>), works well for hydrodefluorination of fluorobenzene (**1**) under 4 atm of hydrogen at 70 °C to give a mixture of fluorocyclohexane (CyF) and cyclohexane (CyH) (Scheme 51).<sup>76</sup> The relative amounts of CyF and CyH are influenced by the base used.

Scheme 51



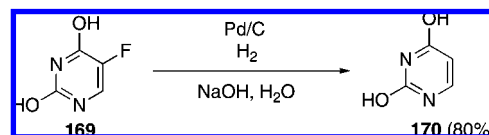
The rhodium metal supported on silica is a highly efficient catalyst for hydrodefluorination of fluorobenzene (**1**) under mild reaction conditions (1 atm of hydrogen at 40 °C) (Scheme 52).<sup>77</sup> The product distribution (Cy–F/Cy–H) is influenced by the solvent. In heptane, fluorocyclohexane (Cy–F) is the major product, whereas in heptane/water, benzene is formed initially but is subsequently hydrogenated to cyclohexane.

Scheme 52



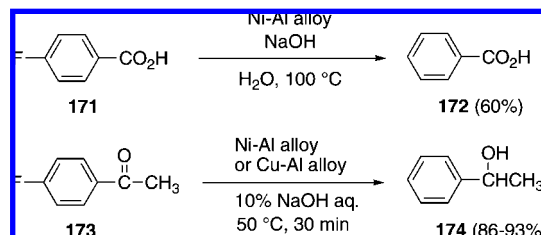
Next, we show the examples of selective hydrogenative removal of fluorides from fluoroarenes without accompanying hydrogenation of the aromatic rings.<sup>78,79</sup> Palladium charcoal works well for the selective hydrogenolysis of 5-fluorouracil (**169**) in an aqueous caustic solution to give uracil (**170**) in 80% yield (Scheme 53),<sup>78</sup> whereas heterogeneous Rh catalyst in acetic acid produces a mixture containing 6.5% of 5-fluorodihydrouracil.

Scheme 53



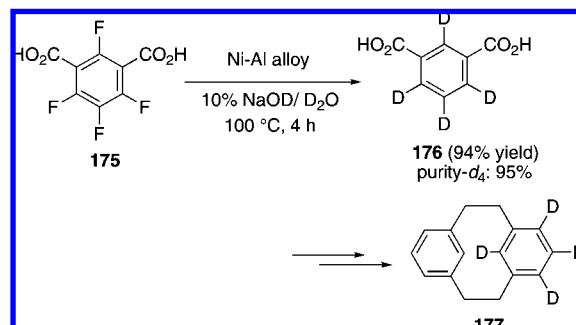
Raney alloys are able to catalyze the hydrodefluorination of aromatic fluorides upon the treatment of aqueous alkalis (with evolution of hydrogen gas).<sup>80,81</sup> To the solution of *p*-fluorobenzoic acid (**171**) in 10% NaOH (aq.) is added Raney Ni–Al alloy to afford benzoic acid selectively (Scheme 54). By the use of Raney Ni–Al and Raney Cu–Al alloys, *p*-fluoroacetophenone (**173**) undergoes hydrodefluorination and carbonyl reduction to provide 1-phenylethanol (**174**) in good yield.

Scheme 54



These protocols are applicable to deuterium labeling of aromatic rings. Toward the synthesis of deuteriated [2.2]metacyclopentane, 2,4,5,6-tetrafluoroisophthalic acid (**175**) is converted with Ni–Al alloy in 10% NaOD–D<sub>2</sub>O to [2,4,5,6-<sup>2</sup>H<sub>4</sub>]-isophthalic acid (**176**) in high chemical yield with high isotopic purity (Scheme 55).<sup>82</sup>

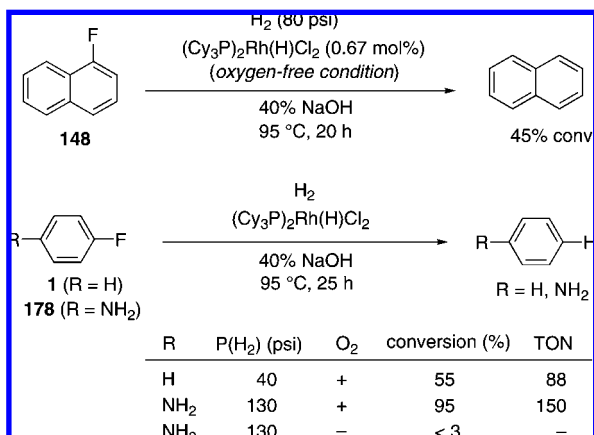
Scheme 55



In 1999, Young and Grushin reported selective hydrogenolysis of C–F bonds in nonactivated monofluoroarenes. A homogeneous rhodium catalyst, which is generated from [(Cy<sub>3</sub>P)<sub>2</sub>Rh(H)Cl<sub>2</sub>], H<sub>2</sub>, and aqueous alkali (in the absence of O<sub>2</sub>), promotes the hydrogenolysis of 1-fluoronaphthalene (**148**) to yield naphthalene (Scheme 56).<sup>83</sup> However, this homogeneous rhodium catalyst is incapable of hydrogenolysis of fluorobenzene under oxygen-free conditions. On the contrary, the presence of a trace amount of air causes the formation of the heterogeneous rhodium catalyst, which demonstrates a high activity for selective hydrogenolysis of fluorobenzene, 4-fluorotoluene, 3-fluoroanisole, and 4-fluoroaniline.

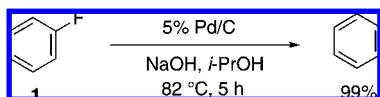
Next, we discuss examples of catalytic hydrogenolysis of fluoroaromatics without using hydrogen gas as the hydrogen atom donor. In conventional procedures, molecular hydrogen (H<sub>2</sub>) has been widely employed for the catalytic hydrodehalogenation of organic halides, in which high hydrogen

Scheme 56



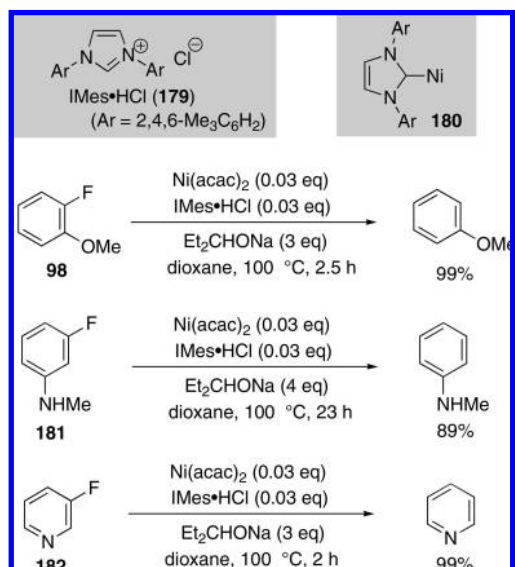
pressure is often required. Therefore, facile and convenient methods have been developed including hydrogen transfer from hydrogen donors such as formic acid, secondary alcohols, and their salts. Without using special apparatus for high pressure, catalytic hydrogen-transfer reactions usually proceed under mild conditions. Palladium on carbon (Pd/C) is applicable to hydrogen-transfer defluorination of aromatic fluorides. With exposure to aqueous NaOH, fluorobenzene undergoes hydrogen transfer from 2-propanol at 82 °C to afford benzene quantitatively (Scheme 57).<sup>84</sup>

Scheme 57



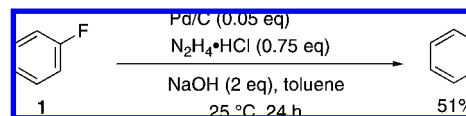
Not only heterogeneous but also homogeneous systems are able to catalyze hydrogen-transfer C–F bond activation of fluoroarenes. Ni(0)/N-heterocyclic carbene (NHC) complexes promote catalytic activation of aromatic C–F bonds. Using hydrogen-transfer reactions from Et<sub>2</sub>CHONa as a hydrogen source, various aryl fluorides are converted to the corresponding reduction products in the presence of a catalytic amount of the monocoordinate nickel–carbene complex **180**, which is prepared in situ from Ni(acac)<sub>2</sub> and IMes•HCl (**179**) (Scheme 58).<sup>85</sup>

Scheme 58



Hydrazine is an alternative hydrogen donor for catalytic dehalogenation of organic halides. Hydrazine hydrochloride is a good candidate since it is less dangerous and easier to handle than the anhydrous hydrazine or its hydrated form. At room temperature, treatment of fluorobenzene with catalytic amounts of Pd/C in the presence of hydrazine hydrochloride in basic medium leads to benzene (Scheme 59).<sup>86</sup>

Scheme 59



### 2.2.2. Reductive Transformations of Fluoroarenes

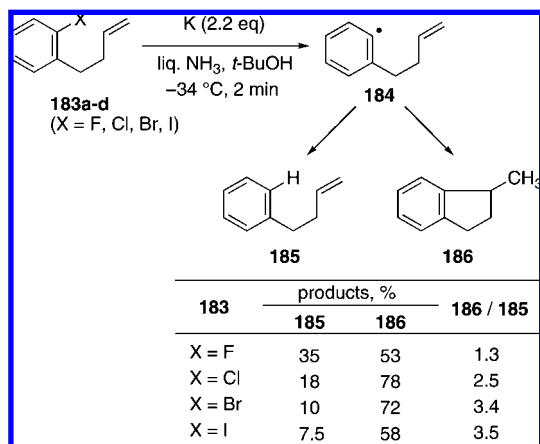
The paramount importance for reductive transformation of organic halides has attracted much attention from wide fields of chemists because of its application in practical organic synthesis.<sup>87</sup> Chemical methods by the use of low-valent metals for reductive cleavage of aromatic C–F bonds have been widely investigated, and various reducing systems have been developed hitherto. Herein, we show the powerful exemplars of reducing systems for selective transformations of fluoroarenes.

Solutions of Li, Na, or K in liquid ammonia (bp = –33 °C) contain solvated metal cations and electrons. These solutions are able to reduce organic molecules. Bunnet and co-workers reported both intra- and intermolecular addition reactions of aryl radicals, generated from haloarenes and solvated electrons in ammonia solution, with alkenes to form carbon–carbon bonds.<sup>88</sup> For instance, the reactions of *o*-(3-butenyl)halobenzenes **183a–d** (X = F, Cl, Br, I) with potassium in 67% ammonia/33% *tert*-butyl alcohol medium afford two principal products, 3-butenylbenzene (**185**) and 1-methylindan (**186**) (Scheme 60). One-electron reduction of halide **183** and subsequent fragmentation of the resultant anion radical give halide anions and aryl radical **184**. The radical **184** is considered to be a key intermediate, one that in part undergoes intramolecular addition of the aryl radical center to the C–C double bond en route to cyclized product **186**. Interestingly, the ratio of **186** to **185** increases as the atomic number of the halogen increases, from 1.3 with **183a** (X = F) to 3.5 with **183d** (X = I). The variation in **186**/**185** ratio with halogen identity is ascribed mainly to differences in the time interval between formation of the free radical **184** from halobenzenes **183a–d** and termination of its life by reaction with a solvated electron.

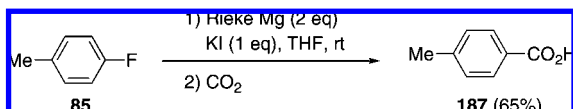
An activated magnesium powder (so-called Rieke magnesium), which is prepared by reduction of anhydrous magnesium chloride with potassium in refluxing THF, exhibits unusual reactivity toward organic halides. The reaction of *p*-fluorotoluene (**85**) with the activated magnesium (prepared from 2 equiv of MgCl<sub>2</sub> and 4 equiv of metallic potassium) leads to formation of the Grignard reagent, which reacts with CO<sub>2</sub> to afford *p*-toluic acid (**187**) in 65% yield (Scheme 61).<sup>89</sup> It is noted that the addition of potassium iodide (1 equiv) prior to the reduction of MgCl<sub>2</sub> yields the magnesium black powders of even greater reactivity.

Lithium naphthalene (also called lithium naphthalenide) is formulated as an ionic substance consisting of lithium cation and naphthalene anion radical, which can serve a soluble reducing agent. By dissolving metallic lithium with a stoichiometric amount of naphthalene in THF, the solution

Scheme 60

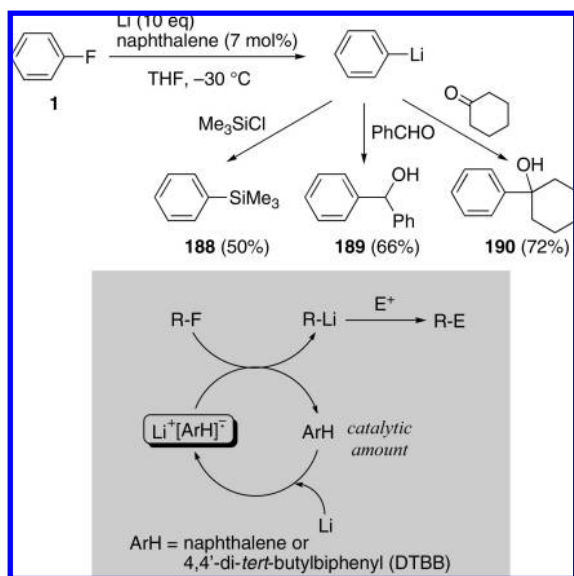


Scheme 61



of lithium naphthalenide is obtained. An anion radical of naphthalene acts as a one-electron donor to organic halides. In situ regeneration of lithium naphthalenide by the use of waste naphthalene with an excess amount of metallic lithium (coreductant) provides the reaction sequence catalytic in naphthalene. Yus et al. have systematically investigated the arene-catalyzed lithiation protocols; a combination of lithium powder and a catalytic amount of arene (naphthalene or 4,4'-di-*tert*-butylbiphenyl) is effective for reductive lithiation of organic halides at low temperature. The arene-catalyzed halogen–lithium exchange procedure works well for fluorobenzene (**1**) to generate phenyllithium, which readily reacts with a variety of electrophiles (Scheme 62).<sup>90</sup>

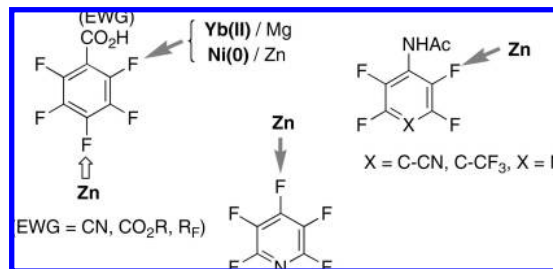
Scheme 62



Reductive defluorination of polyfluoroarenes has been a subject of great interest for synthetic organic chemistry. In particular, regioselective hydrodefluorination of readily available perfluoroarenes provides a promising route to partially fluorinated aromatics that are less accessible but act as versatile synthetic intermediates for the useful organofluorine

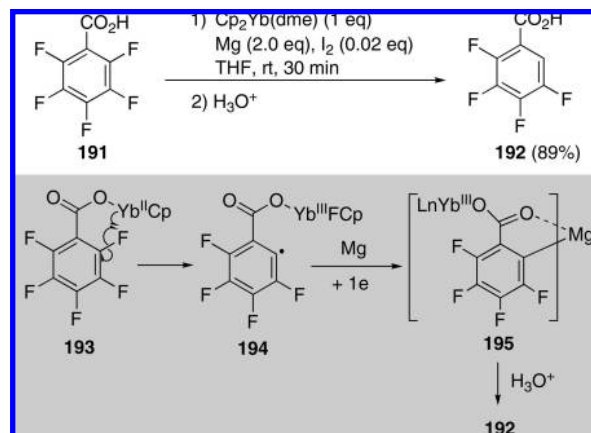
compounds. There have been specific examples of reductive hydrodefluorination of perfluoroarenes by the use of low-valent metals. Fascinatingly, the regioselectivities of C–F bond cleavage and the mechanisms are very different for the metals used. The observed tendency of regioselective hydrodefluorination of substituted perfluoroarenes is summarized in Scheme 63.

Scheme 63



First, we introduce *ortho*-selective hydrodefluorination of perfluoroarenes. A combination of the low-valent ytterbium complex Cp<sub>2</sub>Yb(dme) and coreductant metallic magnesium induces *ortho*-selective C–F bond activation of pentafluorobenzoic acid (**191**) to produce 2,3,4,5-tetrafluorobenzoic acid (**192**) after hydrolysis (Scheme 64).<sup>91</sup> The regioselectivity of defluorination would derive from the intramolecular electron transfer of the Yb(II)–pentafluorobenzoate intermediate **193**. The amount of the ytterbium complex can be reduced up to 0.2 equiv with addition of a cyclopentadiene source such as CpTi.

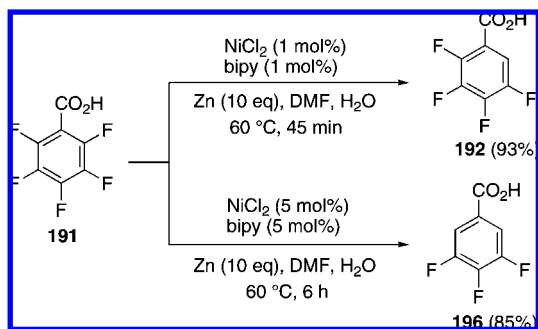
Scheme 64



Low-valent Ni complexes work well for *ortho*-hydrodefluorination of pentafluorobenzoic acid (**191**). In the presence of 0.01 equiv of NiCl<sub>2</sub>–2,2'-bipyridine complex and 10 equiv of Zn, *ortho*-monodefluorination of C<sub>6</sub>F<sub>5</sub>CO<sub>2</sub>H proceeds selectively to give 2,3,4,5-tetrafluorobenzoic acid (**192**) in 93% yield (Scheme 65).<sup>92</sup> The use of an increased amount of Ni catalyst (up to 5 mol %) and the increased reaction time lead to the further removal of *ortho*-fluorine atoms to afford 3,4,5-trifluorobenzoic acid (**196**).

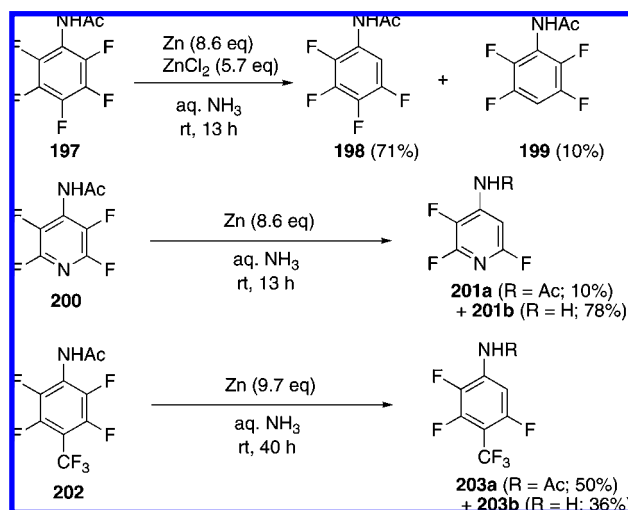
Selective removal of a fluoride from an accessible perfluoroaromatic amine at a position *ortho* to the amino group is a synthetically important and useful transformation. For their applications to medicines and materials, the polyfluorinated aromatic amines with an unsubstituted *ortho*-position are versatile building blocks for the synthesis of heterocycles through electrophilic cyclizations such as Skraup condensation and Fischer indole synthesis.<sup>93,94</sup> In 2001, Shteingarts

Scheme 65



and co-workers developed a new simple route to partially fluorinated (*ortho*-defluorinated) aromatic amines. *N*-Acetyl-protected polyfluoroaromatic amines such as **197**, **200**, and **202** undergo highly selective monodefluorination by zinc in aqueous ammonia at the position *ortho* to the acetamide group (Scheme 66).<sup>95</sup>

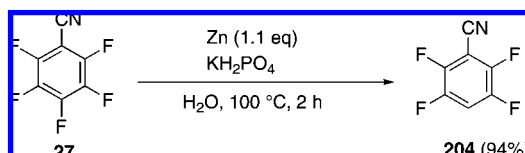
Scheme 66



Now, the examples of *para*-selective hydrodefluorination of perfluoroarenes are given. In different media, metallic zinc as a reducing agent plays a notable role for regioselective hydrodefluorination. The polyfluorinated arenes endowed with functional groups such as cyano and carboxyl groups show a great tendency to undergo selective defluorination at the position *para* to the functional groups. The regiochemical preference of reductive C–F bond cleavage is attributed to the mechanism involving electron transfer from zinc to the substrates, followed by fragmentation (site-selective fission) of the resulting radical anions.<sup>96</sup>

In 1990, Nippon Carbide Industries Co., Inc., reported the preparation of 2,3,5,6-tetrafluorobenzonitrile (**204**) from pentafluorobenzonitrile (**27**) (Scheme 67).<sup>97</sup> Treatment of **27** with Zn powder and aqueous  $\text{KH}_2\text{PO}_4$  at 100 °C for 2 h leads to 2,3,5,6-tetrafluorobenzonitrile (**204**) in 94% yield at 100% conversion.

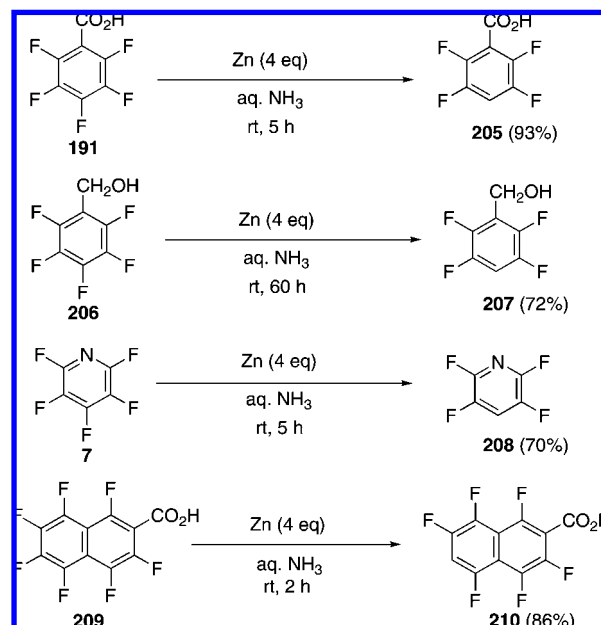
Scheme 67



Zn(Cu) in aqueous dimethylformamide (DMF)<sup>98</sup> and Zn in liquid ammonia<sup>99a</sup> allow the highly *para*-selective hydrodefluorination of various polyfluoroarenes. By the use of metallic Zn in liquid ammonia, the reduction of pentafluorobenzoic acid (**191**) provides selective formation of 2,3,5,6-tetrafluorobenzoic acid (**205**), whereas the use of sodium results in a mixture of several products in poor yields via the further defluorination with removal of three or more fluorine atoms.

In 1997, Laev and Shteingarts discovered that aqueous ammonia is a good and versatile medium for the reductive defluorination of polyfluoroarenes by zinc (Scheme 68).<sup>99b,c</sup> The present convenient protocol works well for *para*-hydrodefluorination of pentafluorobenzoic acid (**191**), 2,3,4,5,6-pentafluorobenzyl alcohol (**206**), and pentafluoropyridine (**7**). Heptafluoro-2-naphthoic acid (**209**) undergoes selective monodefluorination at the 6-position.

Scheme 68

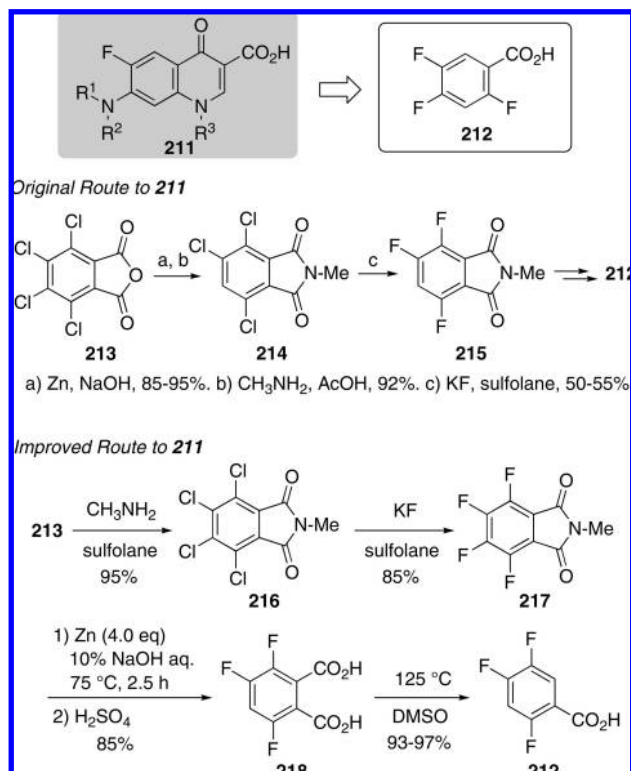


Zn-mediated selective hydrodefluorination provides process improvements in the synthesis of industrially key intermediate compounds. Fertel and co-workers (Occidental Chemical Corporation) developed a new route to 2,4,5-trifluorobenzoic acid (**212**) involving hydrodefluorination.<sup>100</sup> Trifluorobenzoic acid **212** is a valuable synthetic intermediate for a number of fluoroquinolone antibacterials **211**, which are a relatively new class of anti-infective agents and are effective against a number of bacteria strains.<sup>93,94</sup> The pivotal reaction steps in their original synthesis of **212** are Zn-promoted hydrodechlorination of commercially available tetrachlorophthalic anhydride (**213**) to 3,4,6-trichlorophthalic acid and nucleophilic halogen exchange of the trichlorophthalimide **215** with potassium fluoride (Scheme 69). However, despite the excellent yields for the hydrodechlorination, imidization/hydrolysis, and decarboxylation steps, the overall yield of the synthesis suffers because of the poor efficiency of the halogen-exchange step from trichlorophthalimide **214** to trifluorophthalimide **215** (50–55% yield). Admirably, the process improvement in the synthesis of 2,4,5-trifluorobenzoic acid (**212**) is accomplished in a 60% overall yield over five steps. Central to the success of this venture are the shift of the halogen-exchange reaction into



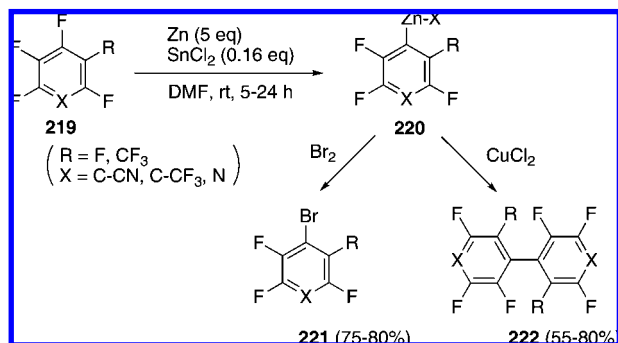
the former step to give 3,4,5,6-tetrafluoro-*N*-methylphthalimide (**217**) in high yield and also the development of an effective, high-yielding regioselective hydrodefluorination/hydrolysis reaction of **217** to **218**.

Scheme 69



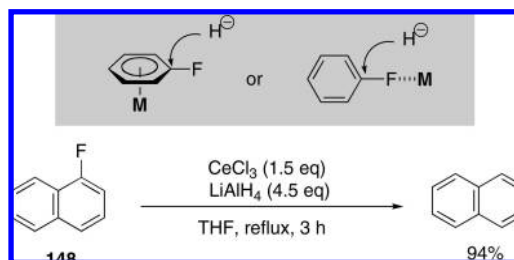
As mentioned above, use of a protic solvent such as DMF–H<sub>2</sub>O or aqueous ammonia is important for running the hydrodefluorination reactions smoothly under mild conditions. On the contrary, under anhydrous conditions, the reductive C–F bond activation reactions yield organozinc compounds, which are usable for further transformations. In the presence of SnCl<sub>2</sub> (0.16 equiv), direct insertion reactions of zinc into aromatic C–F bonds of the perfluoroarenes **219** take place to yield the corresponding organozinc compounds (**220**).<sup>101</sup> The subsequent transformations of **220** involving bromination and homocoupling afford diverse fluoroaromatics **221** and **222**.

Scheme 70



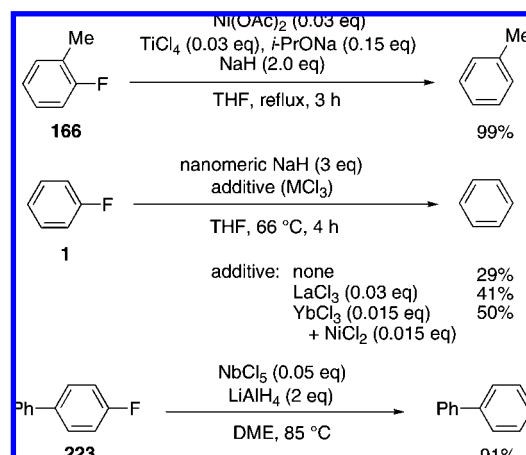
Hydrodefluorination of fluoroarenes is also attained via aromatic nucleophilic substitution with hydride. In 1985, Imamoto demonstrated the facile hydrodefluorination of monofluoroarenes upon the treatment of CeCl<sub>3</sub> (1.5 equiv) and LiAlH<sub>4</sub> (4.5 equiv) in THF (Scheme 71).<sup>102</sup>

Scheme 71



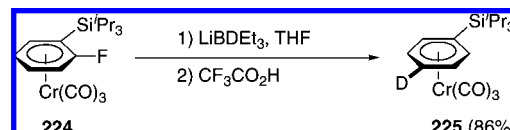
Because of the practical significance both for laboratory synthesis and for industrial production, it is desirable to reduce the quantity of transition metals employed in these transformations. There have been several splendid examples of reductive catalytic hydrodefluorination of monofluoroarenes by the action of a small amount of transition metal salts (Ni, La, Nb, etc.) and a stoichiometric amount of hydride sources such as NaH and LiAlH<sub>4</sub> (Scheme 72).<sup>103–105</sup>

Scheme 72



Rose and co-workers reported the hydride attack to  $\eta^6$ -fluoro(triisopropyl)benzene chromium tricarbonyl complex.<sup>106</sup> It is worth noting that the hydrodefluorination of the fluorobenzene ligands<sup>107</sup> does not proceed via ipso-substitution pathway. *o*-Fluoro(silyl)benzenechromium tricarbonyl complex **224** reacts with Et<sub>3</sub>BDLi to give deuterio(silyl)benzene–chromium complex **225** via *tele-meta* nucleophilic aromatic substitution (Scheme 73).

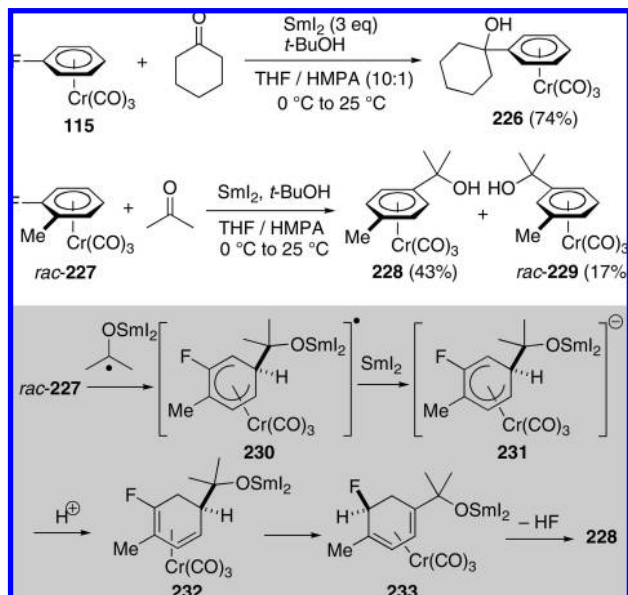
Scheme 73



Reductive transformations of haloarene–Cr(CO)<sub>3</sub> complexes would involve radical intermediate complexes of chromium. Fluoro-substituted  $\eta^6$ -arene tricarbonylchromium complexes react with aliphatic ketones in the presence of SmI<sub>2</sub> and *t*-BuOH under C–C bond formation to give the corresponding benzylic alcohols in good yields (Scheme 74).<sup>108</sup> Fluorotoluene complex *rac*-**227** is subjected to the reductive coupling with acetone under the standard conditions to afford a mixture of regioisomers **228** and *rac*-**229** in 60% combined yield. The reaction of *rac*-**227** proceeds likely through attack of the ketyl radical to the fluoroarene ligand in **227** followed by single-electron reduction of the 17-

electron Cr intermediate **230**.<sup>109</sup> The overall transformation is represented as a nucleophilic aromatic substitution of fluoride ( $S_NAr$ ), which preferentially takes place in a *tele-meta* fashion.

Scheme 74

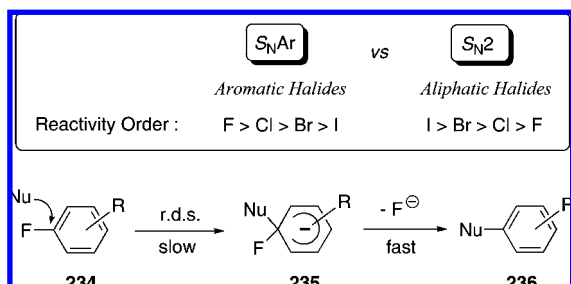


## 2.3. Nucleophilic Substitution in Aromatic Fluorides

### 2.3.1. Nucleophilic Substitution in Monofluoroaromatics

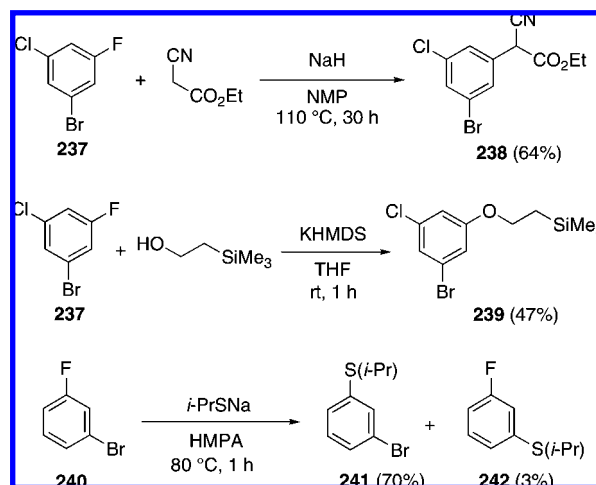
Electrophilic reagents are typically employed for substitution chemistry on aromatic rings. However, replacement of fluorine on an aromatic ring with nucleophiles by either nucleophilic substitution ( $S_NAr$ ) or transition metal catalyzed coupling with organometallics has seen increasing attention for the synthesis of functionalized aromatic compounds. The strong electron-withdrawing inductive effect exerted by fluorine makes nucleophilic substitutions on an aromatic ring possible. The reactivity of the aryl halides decreases in the order of fluoride > chloride > bromide > iodide, which is entirely opposite to that observed in the  $S_N2$  reactions of aliphatic halides. The big difference arises from the extent of bond breaking between carbon and halogen atoms at the transition state. Addition and elimination pathways (**234** → **235** → **236**) are involved in the mechanism of aromatic nucleophilic substitution, in which addition is rate-determining (Scheme 75). Therefore, the sterically small and strongly electron-withdrawing fluorine atom activates the addition step. Meanwhile, bond breaking between carbon and halogen atoms plays an important role in the transition state for the  $S_N2$  reaction so that aliphatic iodides react fastest among the aliphatic halides.

Scheme 75

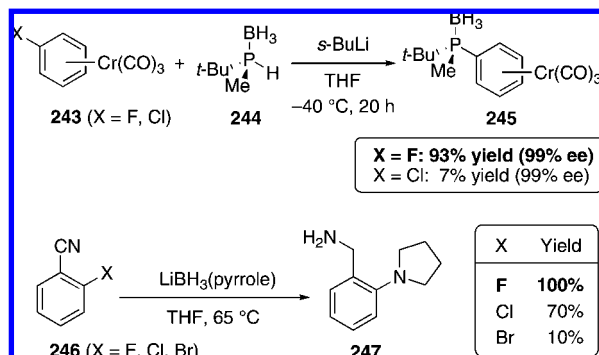


The higher reactivity of fluorine than those of chlorine and bromine is demonstrated by the reactions of 1-bromo-3-chloro-5-fluorobenzene (**237**) with carbon<sup>110</sup> and oxygen<sup>111</sup> nucleophiles, where only 2% of 3-chloro-5-fluorobenzene is obtained in the reaction of **237** with cyanoacetate (Scheme 76). Upon treatment with 1 equiv of *i*-PrSnA, 3-fluorobromobenzene (**240**) is converted to 3-bromo- (**241**) and 3-fluorophenyl isopropyl sulfide (**242**) in the ratio 70:3.<sup>112</sup> A big reactivity difference is also shown in the reaction of **243** with phosphorus<sup>113</sup> and nitrogen<sup>114</sup> nucleophiles (Scheme 77).

Scheme 76

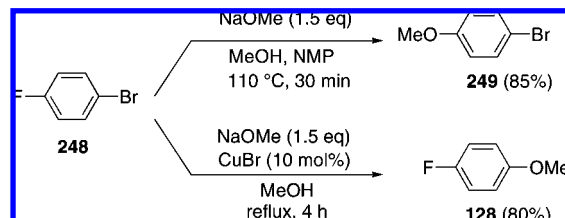


Scheme 77



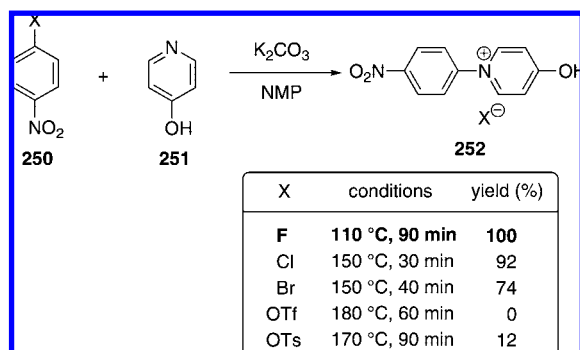
There is an interesting comparison between aromatic C–F and C–Br bonds. For  $S_NAr$  reactions of aryl halides, as mentioned above, the higher reactivity of fluorine than those of chlorine and bromine is observed. Actually, the noncatalyzed  $S_NAr$  reaction of 4-fluorobromobenzene (**248**) with sodium methoxide proceeds smoothly to afford 4-bromoanisole (**249**) in 85% yield (Scheme 78).<sup>115</sup> On the other hand, the selective replacement of a bromo group in **248** by a methoxide is accomplished in the presence of a catalytic amount of CuBr.

Scheme 78

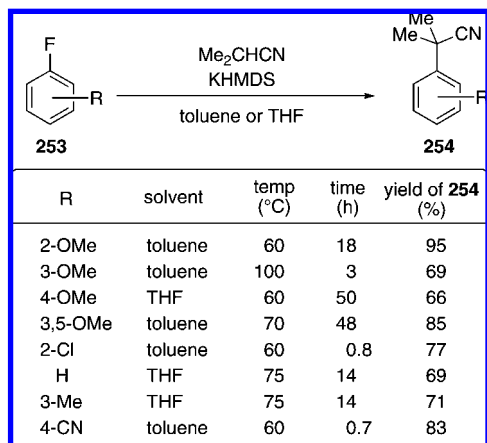


As shown in Scheme 79, it is noticeable that fluoride **250** ( $X = F$ ) is much more reactive than tosylate and even triflate, both of which are excellent leaving groups in  $S_N1$ ,  $S_N2$ , and  $E2$  reactions.<sup>116</sup> Aryl fluorides with an electron-donating group such as methoxy and methyl groups, which should deactivate the  $S_NAr$  reaction, can undergo nucleophilic substitution, although rather higher reaction temperature and prolonged reaction time are needed (Scheme 80).<sup>117</sup>

Scheme 79

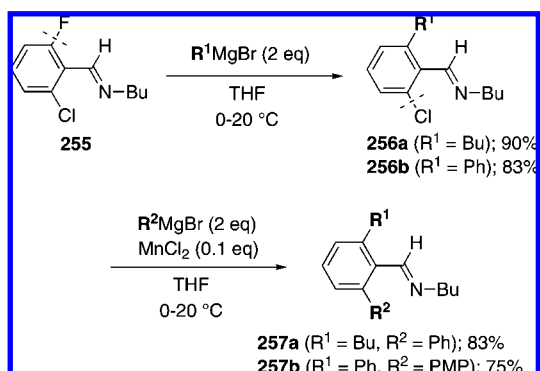


Scheme 80



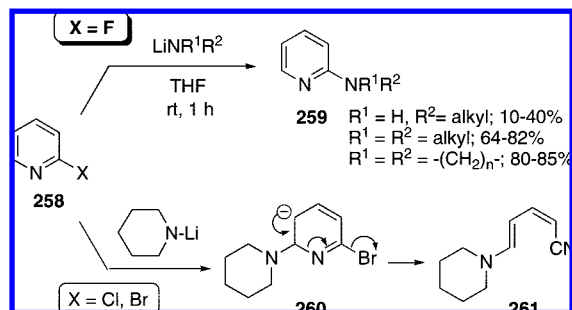
When two different leaving groups such as F and Cl are present at the *ortho*-position of the activating group, the chemoselective nucleophilic transformation produces a variety of *ortho*-disubstituted arenes. By combining the nucleophilic aromatic substitution and the subsequent manganese-catalyzed cross-coupling of **255**, it is possible to replace selectively the fluorine atom and then, in the presence of  $MnCl_2$  (0.1 equiv), the chlorine atom according to a two-step procedure (Scheme 81).<sup>63</sup>

Scheme 81



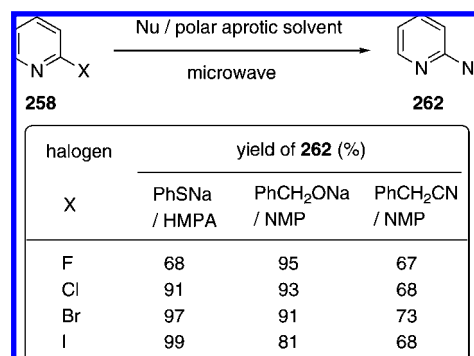
A similar priority of fluorine substituent for nucleophilic substitution on aromatic rings is observed in the pyridine ring. The lithium amides undergo nucleophilic substitution to 2-fluoropyridine, affording 2-aminopyridines **259** in reasonable yields (Scheme 82).<sup>118</sup> Quite in contrast, lithium amide attacks on the C-6 position rather than C-2 of **258** ( $X = Cl, Br$ ) to give the ring-opened product **261** as a final product via intermediate **260**.

Scheme 82



However, one report demonstrated that hardness or softness of a nucleophile sometimes governs the rate of the  $S_NAr$  reaction with 2-halopyridines (Scheme 83).<sup>119</sup> Of the four 2-halopyridines **258**, the relative reactivity toward sulfur nucleophiles, typical soft nucleophiles ( $PhSNa$ ,  $MeSNa$ ), appears to decrease in the order of  $I > Br > Cl > F$ , which is opposite to that expected as discussed above but is consistent with the order of polarizability of halogens. The rate-determining step in the addition–elimination sequence of  $S_NAr$  reaction of **258** would be the second step. On the other hand, reaction with benzyloxide, a hard nucleophile, in *N*-methylpyrrolidone (NMP) followed the reactivity order of  $F > Cl > Br > I$ . The rate-determining step in the present  $S_NAr$  reaction may vary when different nucleophiles are employed. The carbon nucleophiles, such as  $PhCH_2CN$ , show almost comparable reactivities among the four 2-halopyridines **258**.

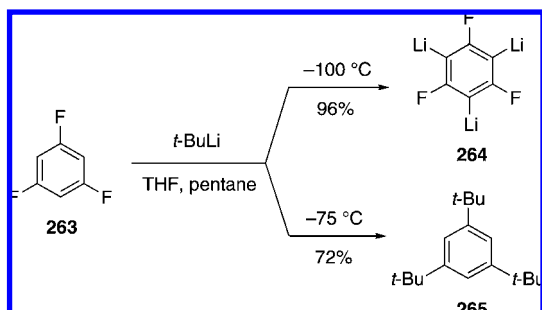
Scheme 83



Nucleophilic substitution of fluorine and deprotonation of the acidic proton on the *ortho*-position of aryl fluoride are sometimes competitive depending on the reaction conditions. A strongly basic nucleophile such as *tert*-butyllithium abstracts exclusively *ortho*-proton of **263** at the lower temperature (below –100 °C) while it replaces fluorine, providing 1,3,5-tri(*tert*-butyl)benzene (**265**) (Scheme 84).<sup>120</sup>

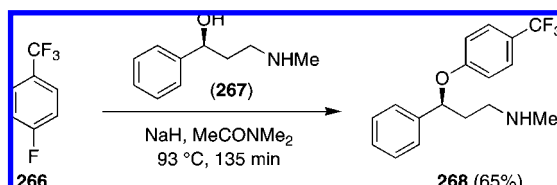
The fluorine-activated aromatic nucleophilic substitutions are highly useful for the syntheses of functionalized and multisubstituted aromatic compounds via both inter- and intramolecular substitutions. At first, several synthetically

Scheme 84

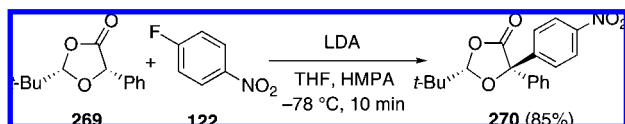


useful intermolecular  $S_NAr$  reactions are summarized. Nucleophilic replacement of fluorine is an important tool for pharmaceuticals, for example (*S*)-fluoxetine (**268**), an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class (Scheme 85).<sup>121</sup> Tertiary carbanion generated from **269** is alkylated with *p*-fluoronitrobenzene (**122**) to give **270** with chiral quaternary carbon in a high yield and an excellent stereoselectivity (Scheme 86).<sup>122</sup> 2-Pyridinylmethyl lithium couples with both 2- and 6-carbons of 2,6-difluoropyridine (**271**) to form tris(pyridine) product **272** in an excellent yield (Scheme 87).<sup>123</sup> Highly functionalized binaphthols **275** are prepared by stepwise replacement of fluorine from octafluorobinaphthol derivative **273** (Scheme 88).<sup>124</sup>

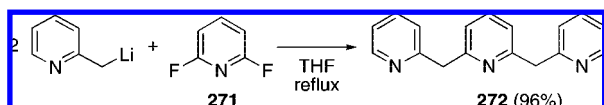
Scheme 85



Scheme 86



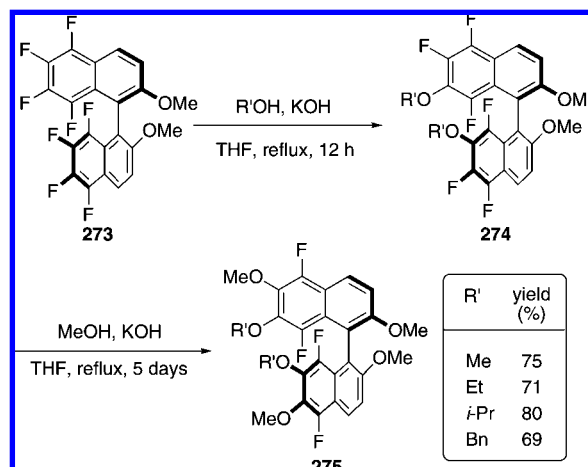
Scheme 87



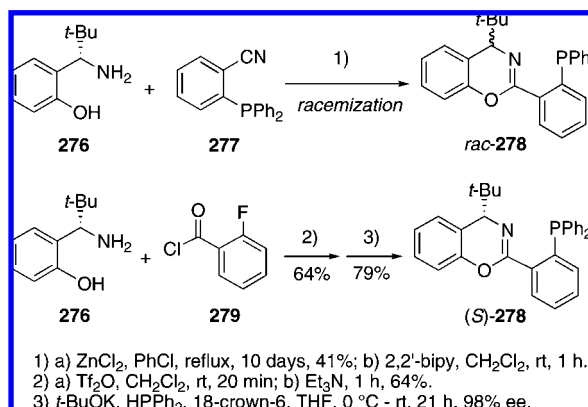
Chiral (phosphorophenyl)benzoxazine *P,N*-ligand (*S*)-**278** is prepared by a combination of **276** with acid chloride **279** followed by replacement of fluorine with diphenylphosphine (Scheme 89). In contrast, combination of **276** with nitrile **277** provides **278** in a racemic form.<sup>125</sup> Fluorine–phosphine exchange reaction on an aromatic ring is quite useful for nonracemized phosphorylation on an aromatic ring as shown in Scheme 90.<sup>126,127</sup> Anthrpos (**285**) is prepared by nucleophilic substitution of 1,8-difluoroanthracene (**284**) with 2 equiv of potassium di-*tert*-butylphosphide (*t*-Bu<sub>2</sub>PK) in 80% yield.<sup>128</sup>

Two fluorine atoms in 2,6-difluorocyanobenzene (**286**) play different roles in the preparation of liquid crystalline compound **289**. One fluorine acts as a leaving group for replacement with ethoxide and another acts as an activator for *ortho*-deprotonation and subsequent boration (Scheme 91).<sup>129</sup> 2,4-Difluorobromobenzene (**290**) is transformed el-

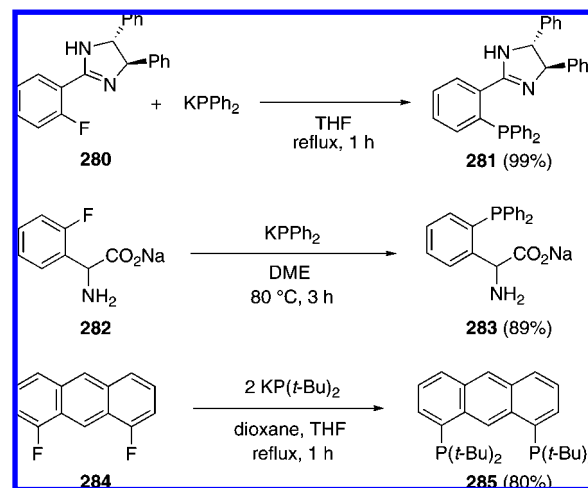
Scheme 88



Scheme 89



Scheme 90

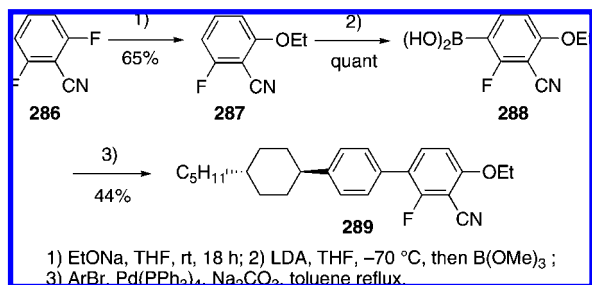


egantly to functionalized heterocycle **296**, a cyclooxygenase-2 (COX-2) inhibitor, by the well-designed choice of the electronic nature of the two halogen atoms; electrophilic nitration is controlled by the electron-donating nature of both 2- and 4-fluorine atoms and, thus, occurs regioselectively at C-5. The more reactive bromine toward oxidative addition of aryl bromide to palladium enables the cross-coupling with vinyl stannane to provide **292**. Intramolecular and subsequent intermolecular replacements of two fluorines via  $S_NAr$  reaction afford **296** as a final product (Scheme 92).<sup>130</sup>

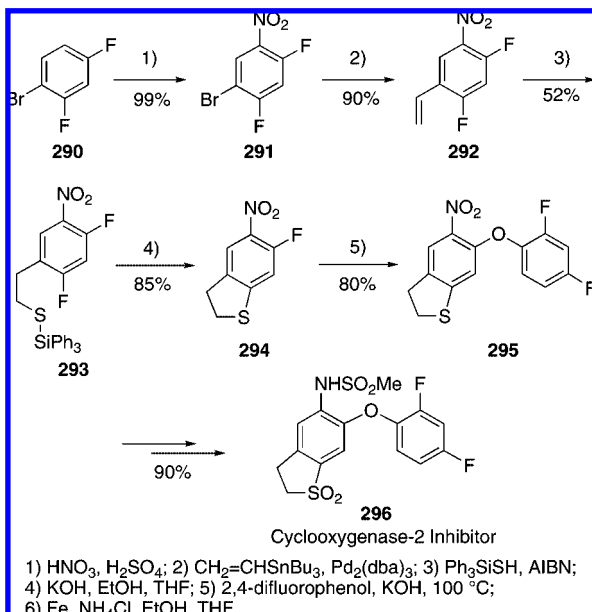
Takeda Pharmaceutical Company developed the practical method of producing **300**, an orally active CC chemokine



Scheme 91

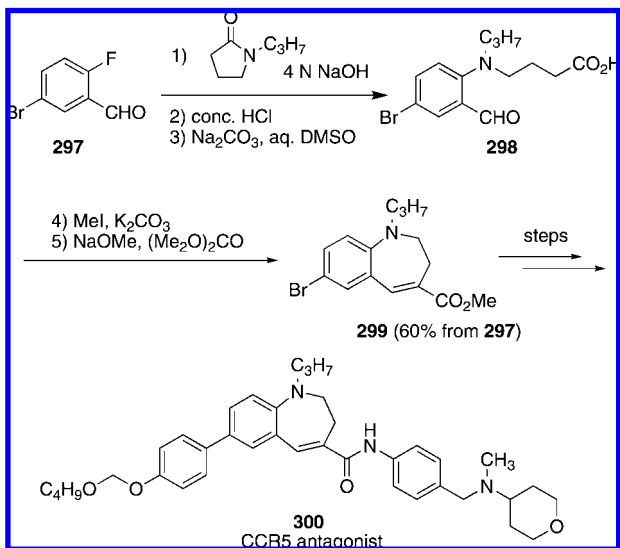


Scheme 92



receptor 5 (CCR5) antagonist (Scheme 93).<sup>131</sup> The reaction sequence involving nucleophilic displacement of the fluorine atom in **297**, intramolecular Claisen-type reaction, and Suzuki–Miyaura coupling reaction delivers **300** effectively without chromatographic purification.

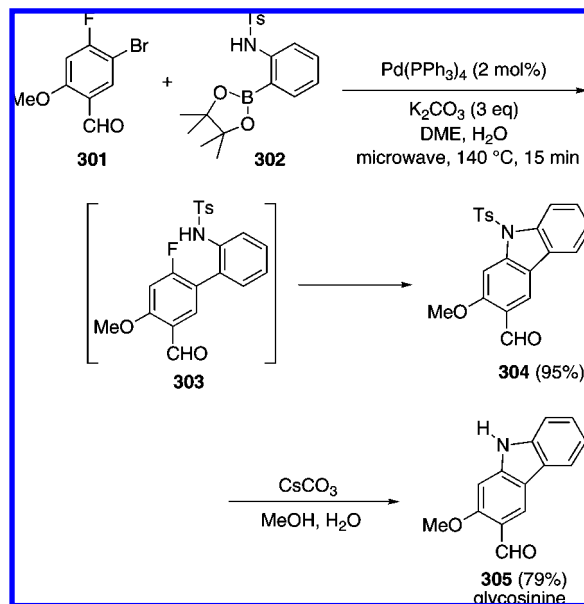
Scheme 93



The tandem Suzuki cross-coupling/ $\text{S}_\text{N}\text{Ar}$  protocol gives a facile route to carbazoles (Scheme 94).<sup>132</sup> Boronic ester **302** cleanly reacts with **301** using a one-pot procedure involving

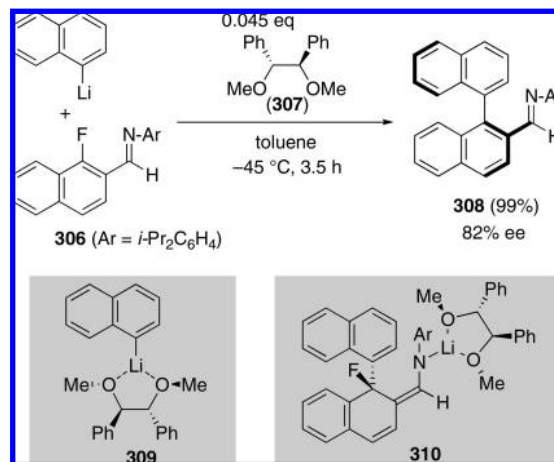
$\text{Pd}(\text{PPh}_3)_4$ -catalyzed cross-coupling and the subsequent intramolecular  $\text{S}_\text{N}\text{Ar}$  reaction of aryl fluoride to deliver *N*-tosylated carbazole **304** in near quantitative yield. Deprotection of the tosyl group from **304** using  $\text{Cs}_2\text{CO}_3$  produces the carbazole alkaloid glycosinine (**305**).

Scheme 94



In 1992, Shindo, Koga, and Tomioka demonstrated the catalytic asymmetric version of nucleophilic aromatic substitution leading to optically active binaphthyls (Scheme 95).<sup>133</sup> The reaction of naphthyllithium with naphthyl imine **306** is catalyzed by dimethyl ether of (*R,R*)-1,2-diphenylethane-1,2-diol to provide the corresponding binaphthyl **308** in high enantiomeric excess. The nucleophilic aromatic substitution leading to **308** proceeds via two successive stereoselective processes; the first is enantioselective conjugate addition of the naphthyllithium–diether complex **309** to imine **306** providing **310**, and the second involves elimination of the  $\text{LiF}$ –diether complex from **310** in which transfer of central chirality to axial chirality occurs. In addition, regeneration of the complex **309** through ligand exchange is essential for the propagation of the catalytic asymmetric process.

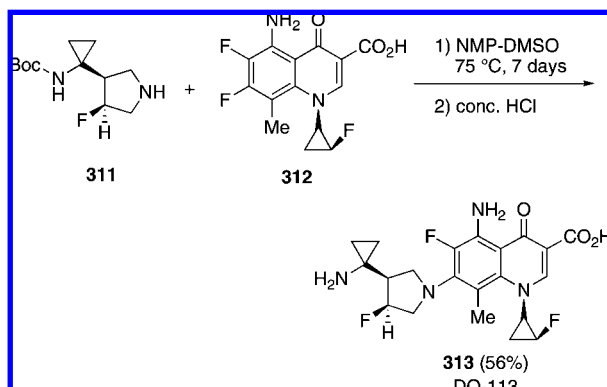
Scheme 95



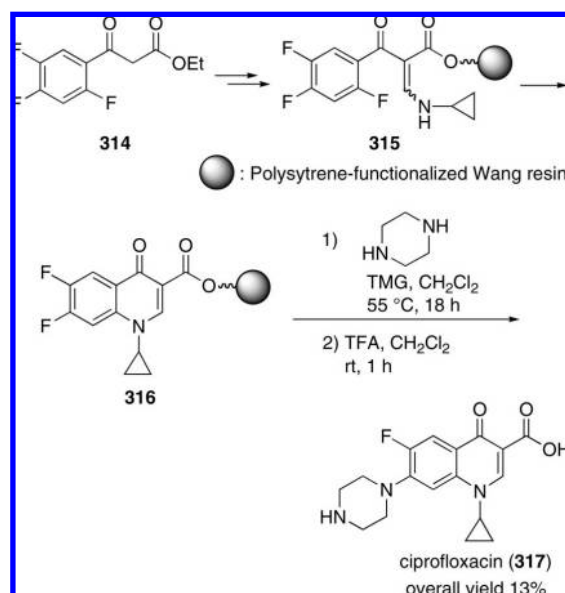
A number of quinolone carboxylic acid derivatives, useful antibacterial agents, have been prepared by nucleophilic

substitution of suitably designed aryl fluorides as a key reaction. Some of the related synthetic examples are shown in Schemes 96–98. Fluorine on C-7 is an important substituent to promote a smooth introduction of an amino group (Scheme 96).<sup>134</sup> Two of the three fluorine atoms in **314** can be employed in a stepwise manner to introduce amino functionalities (Scheme 97).<sup>135</sup> Several examples of the F-activated  $S_NAr$  protocol for the intramolecular ring closures between N-1 and C-8 related to quinolone derivatives have been reported.<sup>136–138</sup>

Scheme 96



Scheme 97

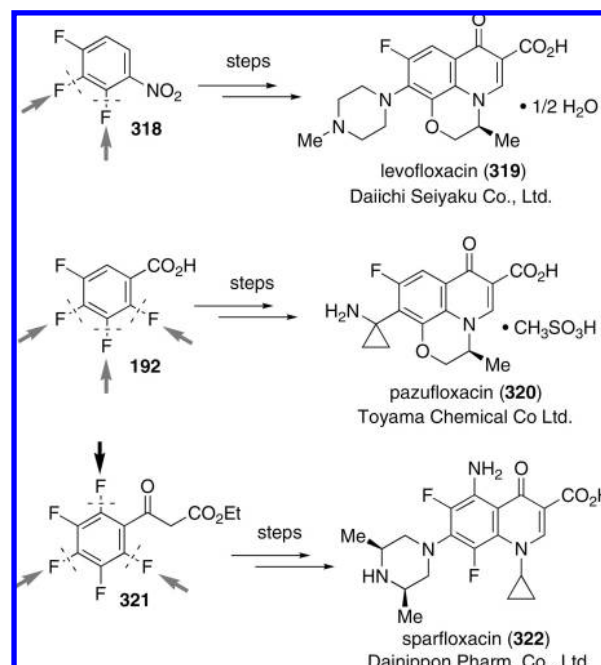


The reaction sequences involving regioselective nucleophilic displacement of polyfluorinated arenes are brilliant methodologies to produce quinolone carboxylic acid derivatives. Scheme 98 shows the summary of actual routes to quinolone antibacterial agents, levofloxacin (**319**),<sup>139</sup> pazufloxacin (**320**),<sup>140</sup> and sparfloxacin (**322**).<sup>141</sup>

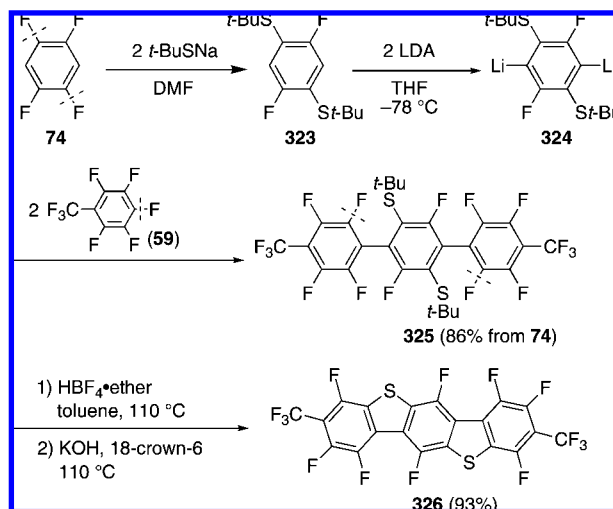
Nucleophilic aromatic substitution ( $S_NAr$ ) chemistry contributes to creating new materials with a  $\pi$ -conjugated system. Successive  $S_NAr$  transformations starting from tetrafluorobenzene **74** provide highly fluorinated benzobis-benzothiophene **326**, whose lower LUMO (lowest unoccupied molecular orbital) energy levels can facilitate electron injection and transport, leading to *n*-type semiconductor characteristics (Scheme 99).<sup>142</sup>

Fluorine is also an excellent leaving and accelerating group that is useful for extension of polymer chains with aryl

Scheme 98

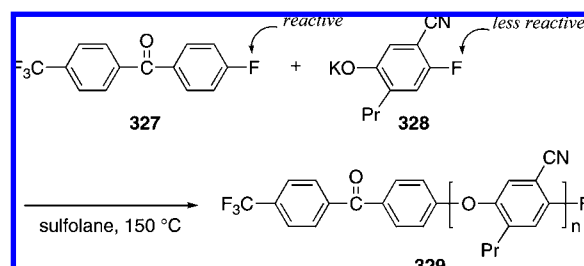


Scheme 99

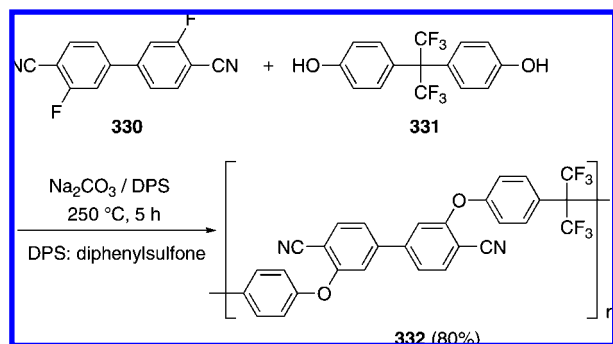


cores. Fluorine-promoted stepwise polymerization of 4-fluorophenol derivative **328** provides the polyaryl ether **329** where the fluorine atom plays an essential role for the activation of the reactive site in the chain-extension step (Scheme 100).<sup>143</sup> Two examples of polymeric materials **332** and **335** (electroluminescent containing hole-transporting and electron-transporting units) with an aryl ether chain are shown in Schemes 101 and 102.<sup>144,145</sup>

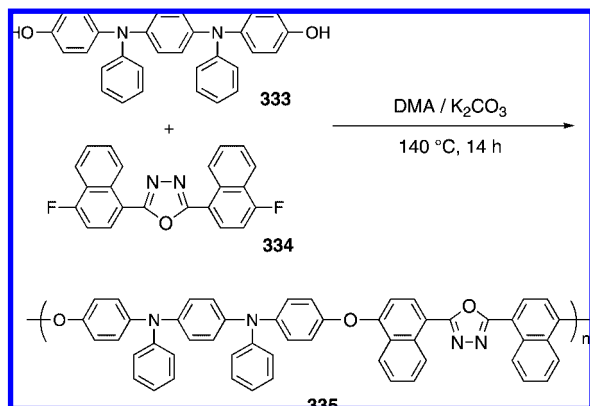
Scheme 100



Scheme 101

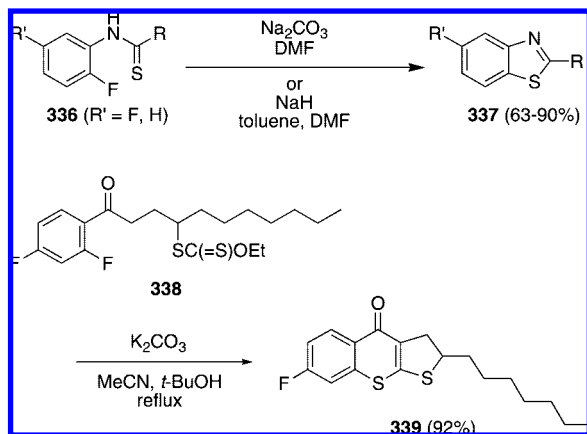


Scheme 102



The F-activated  $\text{S}_{\text{N}}\text{Ar}$  protocol has been used for the syntheses of a variety of heterocycles and macrocides.<sup>146</sup> One-pot synthesis of benzothiazoles **337**,<sup>147,148</sup> thiacycle **338**,<sup>149</sup> and macrocycle of aminoalcohol **340**<sup>150</sup> are excellent examples (Schemes 103 and 104). The preparation of cycloisodityrocine precursor **343** is achieved in a good yield by the intramolecular diarylether construction protocol using fluoroarene **342** (Scheme 105). In contrast, much higher temperature ( $130\text{ }^\circ\text{C}$ ) is required for the ring closure of the related **344**.<sup>151</sup> For the synthesis of the D–O–E segment of vancomycin, **346** undergoes  $\text{S}_{\text{N}}\text{Ar}$  macrocyclization to afford **347** as a mixture of atropisomers (Scheme 106).<sup>152</sup>

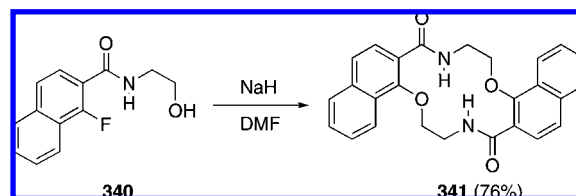
Scheme 103



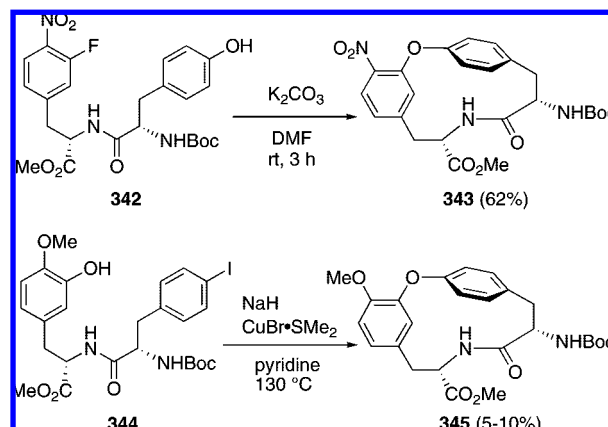
### 2.3.2. Nucleophilic Substitution in Hexafluorobenzene

Because of the strong electron-withdrawing nature of fluorine atom, perfluoro-substitution drastically lowers the energy of the  $\pi^*$  orbitals, making the aryl ring more

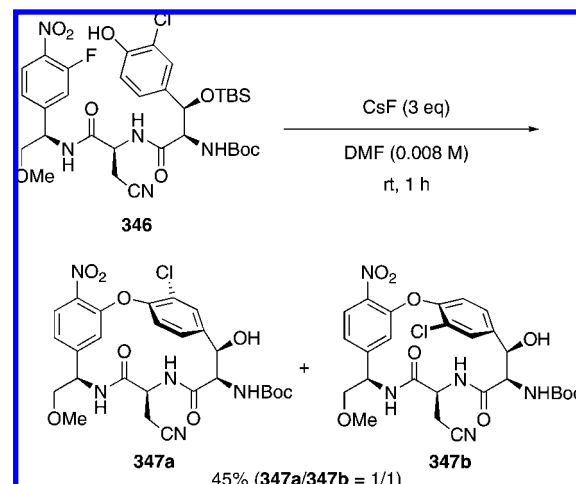
Scheme 104



Scheme 105



Scheme 106

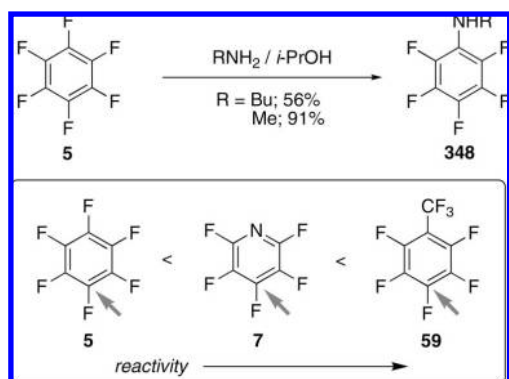


susceptible to nucleophilic attack (or toward reduction, for that matter). Therefore, **5** is remarkably reactive with nucleophiles. In fact, primary amines can attack the benzene ring without base catalysis, affording aminopentafluorobenzenes (Scheme 107).<sup>153</sup> The reactivity of the related perfluoroarenes in nucleophilic substitution with primary amines is in the order of perfluorotoluene > pentafluoropyridine > hexafluorobenzene. A wide repertoire of monosubstituted pentafluorobenzenes **349** are available. Table 1 shows some of the results of monosubstitution of hexafluorobenzene (**5**).

After monosubstitution, the second substitution of monosubstituted pentafluorobenzenes **350** occurs regioselectively at C-4 carbon, irrespective of the electronic nature of the first substituent, to give **351** as shown in Table 2. A simple calculation suggests that a highest spin density of a hypothetical anion radical intermediate is localized at carbon-4 in which substitution occurs.

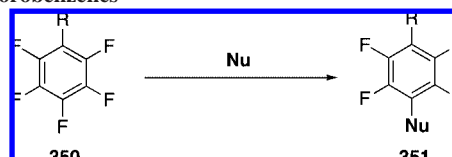
Ishihara and Yamamoto reported the functionalization of super Brønsted acid catalysts (Scheme 108).<sup>167</sup> Employing *para*-selective aromatic nucleophilic monosubstitution pro-

Scheme 107

Table 1. Nucleophilic Monosubstitution of Hexafluorobenzene (**5**)

entry	nucleophile and condition	product	yield	ref.
1	NaOH $\text{Bu}_4\text{NHSO}_4$ , 50 °C		71%	154
2	NaSH $\text{HO}(\text{CH}_2)_2\text{OH}$ , reflux		66%	155
3	$\text{H}_2\text{N}(\text{CH}_2)_3\text{NH}_2$ THF		80%	156
4	 1) $\text{K}_2\text{CO}_3$ , DMSO (83%) 2) Zr(IV), PhMe (88%)			157
5	 $\text{CsF}$ , THF		41%	158
6	1) $\text{Ph}_3\text{PCH}_2\text{CH}=\text{CH}_2$ $\text{BuLi}$ 2) RCHO		87–93%	159
7	$\text{R}_\text{F}\text{CH}_2\text{OTMS}$ $\text{CsF}$ , DME		$\text{R}_\text{F} = \text{C}_7\text{F}_{15}$ : 53% $= (\text{CF}_2)_2\text{CHF}_2$ : 74% $= \text{CF}_2\text{CHF}_2$ : 84% $= \text{CH}_2\text{F}$ : 66%	160
8	MeCN $\text{CsF}$ , MeCN		82%	161

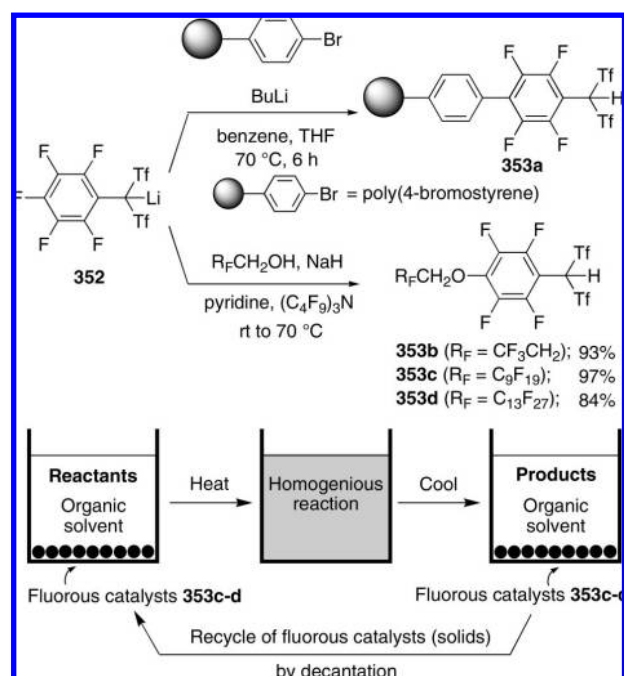
Table 2. Nucleophilic Substitution of Substituted Pentafluorobenzenes



entry	R	Nu (yield)	ref
1	Me	Bu	162
2	Me	SPh	162
3	Me	OMe (45%)	163
4	Me	$\text{NHC}_6\text{F}_5$ (58%)	164
5	Me	$\text{CHMePh}$ (81%)	64
6	$\text{CH}=\text{CH}_2$	$\text{NHOH}$ (80%)	165
7	$\text{C}\equiv\text{CH}$	OMe (73%)	166

ethers **353c–d** act as temperature-dependent organic solvent-miscible solid catalysts,<sup>167b</sup> and interestingly, perfluorocarbon solvents are not essential for fluororous biphasic catalyses such as acetalization, esterification, Mukaiyama aldol condensation, and Hosomi–Sakurai allylation. Furthermore, fluororous catalyst **353d** is perfectly recycled by using liquid/solid phase separation without fluororous solvents.

Scheme 108



The reactions of hexafluorobenzene (**5**) with 2 equiv of nucleophiles afford 1,4-disubstituted tetrafluorobenzenes **354** regioselectively in reasonable yields as shown in Table 3. The treatment with bidentate nucleophiles leads to the formation of 1,2-substituted tetrafluorobenzenes **355** (Table 4; see also Tables 5 and 6).

Sequential nucleophilic substitution of hexafluorobenzene (**5**) is applicable to supramolecular chemistry. Fujita et al. developed the pincer ligand **361** for molecular self-assembly systems (Scheme 109).<sup>186</sup> Successive ring extension starting from **359** and ring closure with Pt complex **362** provide the metal-centered macrocycle **363**,<sup>186b</sup> which is a key compound of catenane-based switching systems. Mayor and Lehn reported the synthesis and structural characterization of the macrobicyclic ligand **366** containing a reducible hexakis(phenylthio)benzene electron-acceptor site (Scheme 110).<sup>187</sup>

ocols provides a high-yielding route to polystyrene-bound and/or fluororous super Brønsted acids **353**. Highly fluorinated



Table 3. Preparation of 1,4-Disubstituted Tetrafluorobenzenes

entry	nucleophile and condition	product	yield	ref.
1	Ph <sub>2</sub> PH, BuLi THF, 0 °C		43%	168
2	 BuLi, THF –78 °C then reflux		R = H: 65% R = hexyl: 68%	169
3	 F <sub>5</sub> BuLi		85%	170
4	CF <sub>3</sub> CH <sub>2</sub> OSiMe <sub>3</sub> CsF, DMF		54%	158
5	(C <sub>6</sub> H <sub>5</sub> S) <sub>2</sub> Ni DMF		95%	171
6	 , Et <sub>2</sub> O		65%	172
7	 BuLi, TEMDA pentane		30%	173

Focusing attention on a fluoride ion as a leaving group, an interesting application of nucleophilic aromatic substitution of hexafluorobenzene was reported. Tetrabutylammonium fluoride (TBAF) is a versatile nucleophilic fluorination agent; however, it is quite difficult to obtain anhydrous TBAF because of its highly hygroscopic nature and to avoid decomposition by Hofmann elimination at room temperature while drying. Sun and DiMagno undertook the preparation of perfectly anhydrous TBAF (**369**) by nucleophilic substitution of hexafluorobenzene (**5**) with tetrabutylammonium cyanide (**367**).<sup>188</sup> Scheme 111 illustrates the synthetic utility of in situ generated anhydrous TBAF (**369**), an exceptionally nucleophilic, highly soluble fluoride ion source.

### 2.3.3. Nucleophilic Substitution in Pentafluoropyridine

Nucleophilic substitution of pentafluoropyridine occurs regioselectively in a stepwise manner, at first on carbon-4, then on carbon-2, and finally at carbon-3 (Scheme 112). Therefore, three kinds of different nucleophiles can be

Table 4. Reaction of **5** with Bidentate Nucleophiles

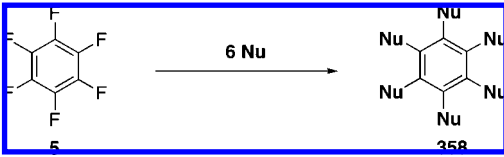
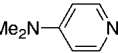
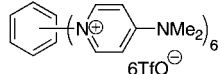
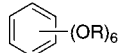
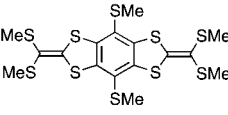
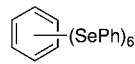
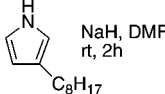
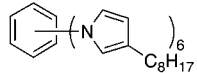
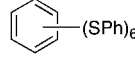
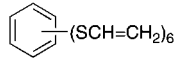
entry	nucleophile and condition	product	yield	ref.
1	 K <sub>2</sub> CO <sub>3</sub> , DMSO		85%	174
2	 BuLi (2 eq)		59%	175
3	 H <sub>2</sub> O		58%	176
4	PhCOMe		49%	177

Table 5. 1,2,4,5-Tetrasubstituted 3,6-Difluorobenzenes

entry	nucleophile and condition	product	yield	ref.
1	 Li, DMF		40% (5,6-difluoro isomer 10%)	178
2	S(CH=CH <sub>2</sub> ) <sub>2</sub> Na, NH <sub>3</sub>		30%	179
3	Sn(SPh) <sub>2</sub> DMF		54%	180
4	1) (Mes) <sub>2</sub> PH, BuLi (43%) 2) RLi, THF		R = Bu: 80% R = Ph: 54%	168

introduced stepwise.<sup>189</sup> The high reactivity of **7** to nucleophiles enables reactions with in situ generated unstable

Table 6. Hexasubstituted Benzenes

				
entry	nucleophile and condition	product	yield	ref.
1	 Me <sub>3</sub> SiOTf, MeCN		92%	181
2	ROSiMe <sub>3</sub> CsF, THF	 R = CH <sub>2</sub> CF <sub>3</sub> : 75% R = Ph: 72%		158
3	1) (MeS) <sub>2</sub> CHCS <sub>2</sub> Li, DMF 2) MeSH, LiOH, DMF		32%	182
4	PhSeNa, DMF 0 °C, 15 min		91%	183
5	 NaH, DMF rt, 2h		51%	184
6	PhSH DMI		39%	185
7	S(CH=CH <sub>2</sub> ) <sub>2</sub> Na, NH <sub>3</sub>		57%	179

nucleophiles under mild conditions, leading to preparation of 4-substituted 2,3,5,6-tetrafluoropyridines **370** (Table 7).<sup>190–199</sup>

A consecutive substitution with three different nucleophiles proceeds successfully at first on C-4, then on C-2, and finally on C-6, constructing macrocycle **374** as shown in Scheme 113.<sup>200</sup> A combination of CsF and ethylene glycol bistrimethylsilane is more useful for construction of crown ether **374** than a conventional sodium alkoxide of ethylene glycol, which provides mostly tar and a very poor yield of **374**.

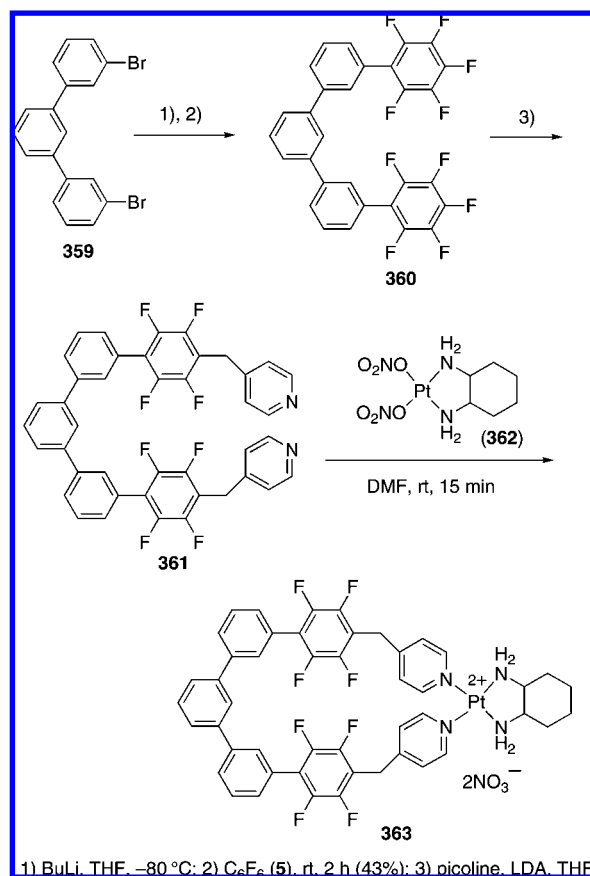
The preferred second substitution on C3 takes place only in the case of favorable medium-sized ring formation via intramolecular substitution (Scheme 114).<sup>176</sup> Initial nucleophilic attack of enamine **375** to the 4-position of pentafluoropyridine (**7**) and the subsequent intramolecular *N*-arylation afford tetrahydrocarbazole **376**.

Electron transfer from tetrakis(dimethylamino)ethane (TDAE) or triethylamine to highly fluorinated arenes such as pentafluoropyridine (**7**) induces generation of fluoride ion, which adds spontaneously to tetrafluoroethylene to form in situ pentafluoroethyl anion (**378**). The resultant anion **378** substitutes a fluorine atom in **7** to give perfluoro-4-ethylpyridine (**379**) and regenerates a fluoride ion (Scheme 115).<sup>191</sup>

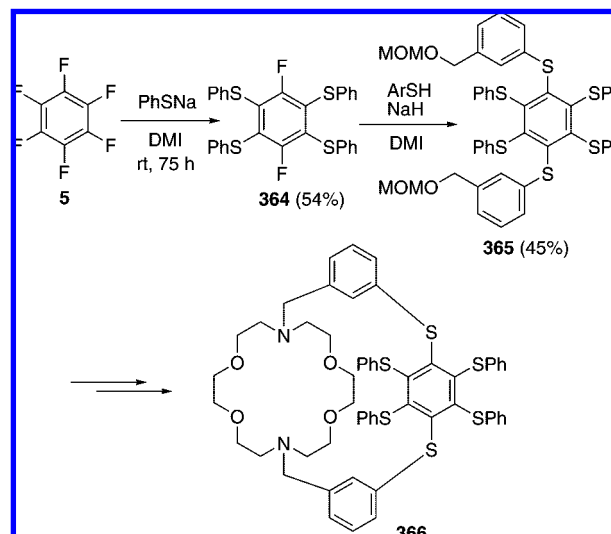
All of the five fluorine atoms in pentafluoropyridine can be replaced with nucleophiles as shown below. For instance, pentakis(phenylthio)pyridine (**380**) is formed quantitatively, while the formation of some byproduct from pentachloropyridine is observed (Scheme 116).<sup>201</sup>

Quite interesting is the fact that radical substitution of **7** also takes place exclusively at the 4-carbon, while that of

Scheme 109



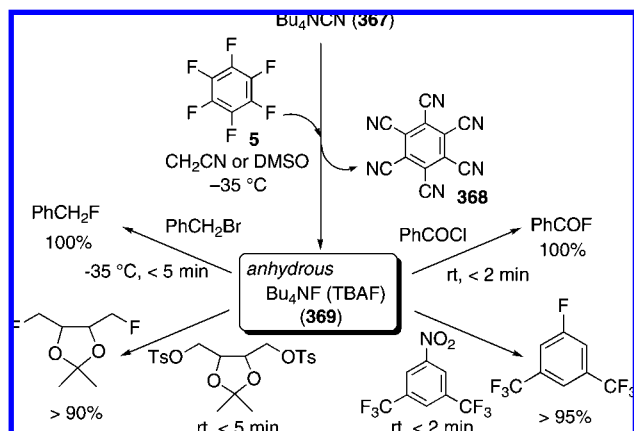
Scheme 110



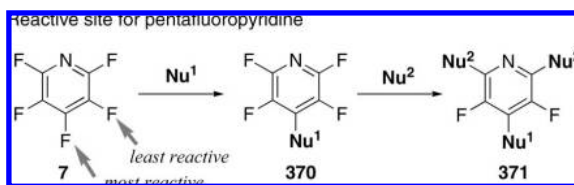
pentafluorobenzene or pentafluoroanisole provides a mixture of 2- and 4- or 2-, 3-, and 4-substituted products, respectively. Thus, irradiation of **7** in methanol in the presence of benzophenone produces 4-hydroxymethylpyridine **381** (Scheme 117).<sup>202</sup>

The behavior of perfluoroquinoline (**382**) toward nucleophiles is analogous to that of pentafluoropyridine (**7**) so that 2- and 4-positions in **382** are reactive sites (Scheme 118).<sup>203</sup> Meanwhile, the 6-position is the most reactive in perfluoroisquinoline **383**. However, the major reaction sites of displacement by the sulfur and the oxygen nucleophiles are significantly different: nucleophilic attacks take place at the

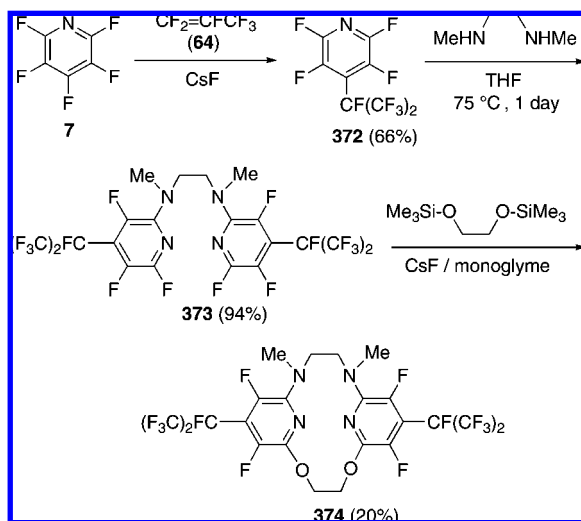
Scheme 111



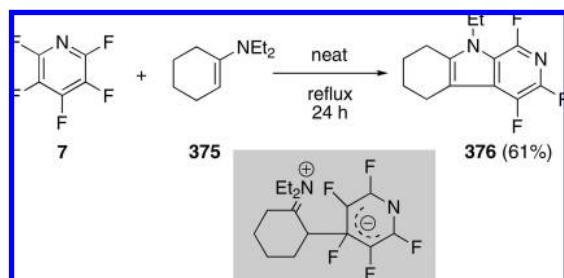
Scheme 112



Scheme 113



Scheme 114

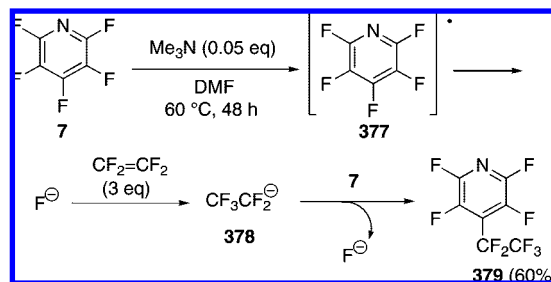


4-position by thiolates and at both the 2- and 4-positions by oxygen nucleophiles in quinoline **382**, as well as at the 6-position by sulfur and the 1-position by oxygen nucleophiles in isoquinoline **383**, irrespective of the relative reactivities. These results on regioselectivity are in agreement with the hard and soft acids and bases (HSAB) principle for the interaction between nucleophiles and reactive sites in heterocycles **382** and **383**.

Table 7. Nucleophilic Monosubstitution of Pentafluoropyridine (7)

entry	nucleophile and condition	product	yield	ref.
1	(XCF <sub>2</sub> ) <sub>2</sub> C=NH CsF, sulfolane		X = Cl: 64% X = F: 61%	190
2	CF <sub>2</sub> =CF <sub>2</sub> Me <sub>3</sub> N, DMF		60%	191
3	(C <sub>6</sub> F <sub>5</sub> ) <sub>3</sub> M CsF, MeCN M = P, Bi, As, Sb		75–82%	192
4	Ph Me <sub>3</sub> Si-N=P-CH <sub>2</sub> PPh <sub>2</sub> Ph		94%	193
5	PdMe <sub>2</sub> (TMEDA), THF H <sub>2</sub> O, Et <sub>3</sub> N, Me <sub>3</sub> SiCl		86%	194
6	(Ph) <sub>2</sub> S=NH THF, reflux, 5 h		84%	195
7	Me <sub>3</sub> Si-N=S=N-		85%	196
8	R <sub>2</sub> P-OSiMe <sub>3</sub> , benzene (R = Ph, <i>i</i> -Pr)		84–91%	197
9	PhSe-SnBu <sub>3</sub> CsF, CHCl <sub>3</sub>		98%	198
10	(H <sub>2</sub> N) <sub>2</sub> C=X, EtOH (X = S, O)		Y = S: 71% Y = NH: 93%	199

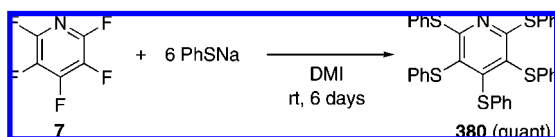
Scheme 115



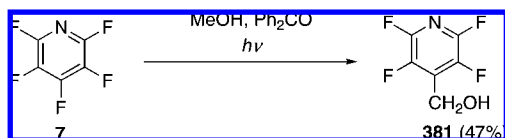
## 2.4. Defluorination via Benzyne

Aryl halides undergo several types of reactions such as halogen–metal exchange, substitution with nucleophiles, oxidative addition, and deprotonation of hydrogen *ortho* to

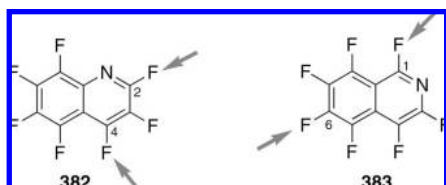
Scheme 116



Scheme 117

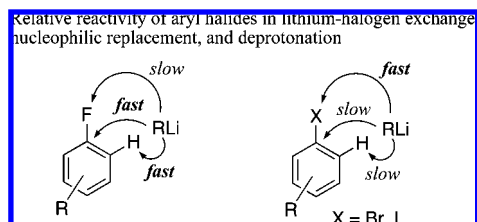


Scheme 118



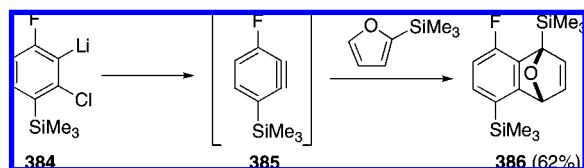
halogen on reacting with organometallics or low-valent metals. The chemical properties of the halogens profoundly affect what type of reaction does occur. As an example, reactions of aryl halides with alkyl lithium are schematically shown in Scheme 119.

Scheme 119



The relative stability of halogenated aryllithium toward elimination of LiX (X = halogen) follows the order of LiBr (−100 °C) < LiCl (−90 °C) < LiF (−60 °C), although other substituents will greatly affect the suitable temperature for elimination. Grignard reagents usually require elevated temperatures for both generation and elimination in comparison with the corresponding lithium reagents.<sup>204</sup> Thus, lithio species **384** undergoes elimination of chlorine chemoselectively, affording benzyne **385**, of which cycloaddition to 2-(trimethylsilyl)furan gives **386** regioselectively (Scheme 120).<sup>205</sup>

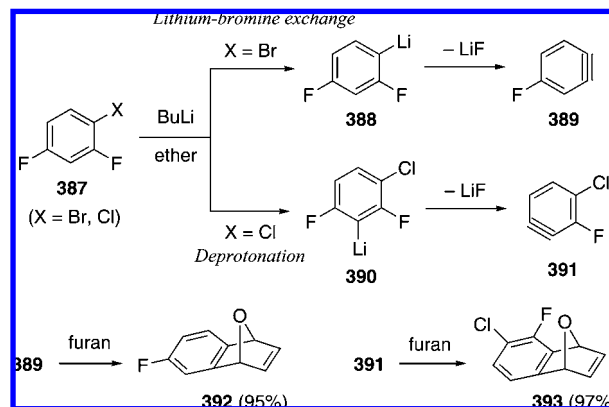
Scheme 120



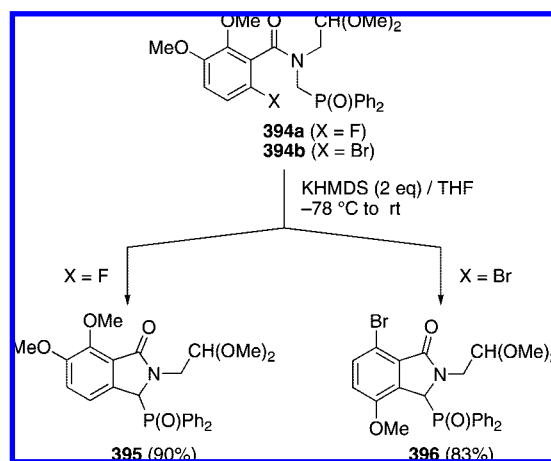
The *ortho*-position to fluorine substituent in fluoroarenes is generally more acidic<sup>206</sup> so that the fluorine atom on an aromatic ring activates *ortho*-hydrogen for deprotonation, while bromine or iodine mostly enhances the rate for halogen–lithium exchange on reacting with butyl lithium (Scheme 121).<sup>207</sup> The same type of selective benzyne formation was employed for the heterocycle synthesis of **396**,

in which a base, potassium bis(trimethylsilyl)amide (KHMDs), in THF deprotonates the *ortho*-hydrogen of aryl fluoride **394a** (X = F); in contrast, it does not deprotonate from bromo compound **394b** (X = Br) (Scheme 122).<sup>208</sup>

Scheme 121

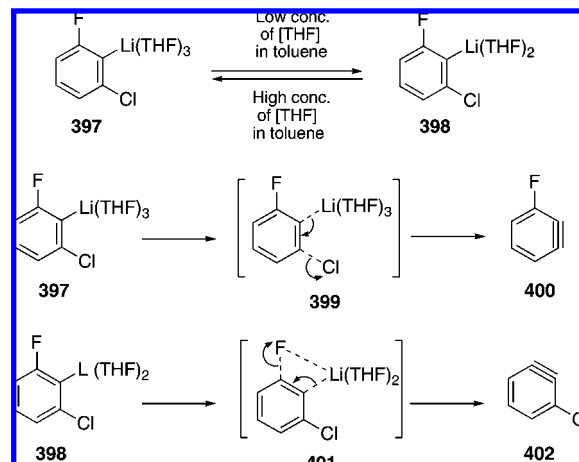


Scheme 122



The extent of solvent coordination (THF) around lithium sometimes governs the stability and reactivity of the lithium species (Scheme 123).<sup>209</sup> Lithium species **397** and **398** undergo benzyne formation either to 3-fluoro- or 3-chlorobenzyne depending on the concentration of THF in toluene. The less THF-coordinated lithium species **398** favors the additional interaction with *ortho*-fluorine and enhances LiF elimination to produce 3-chlorobenzyne **402**, while the fully

Scheme 123

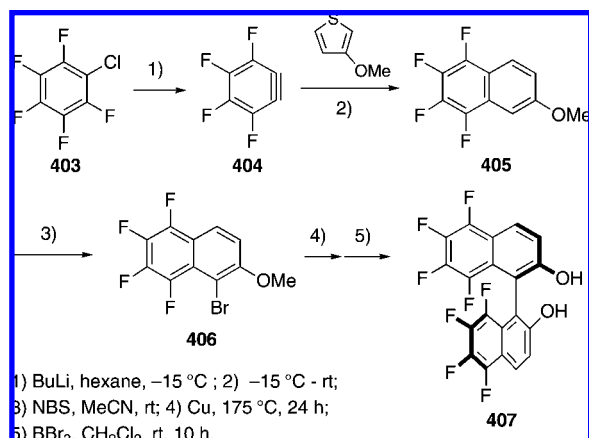




THF-coordinated lithium species **397** eliminates chlorine as a better leaving group to form 3-fluorobenzene **400**.

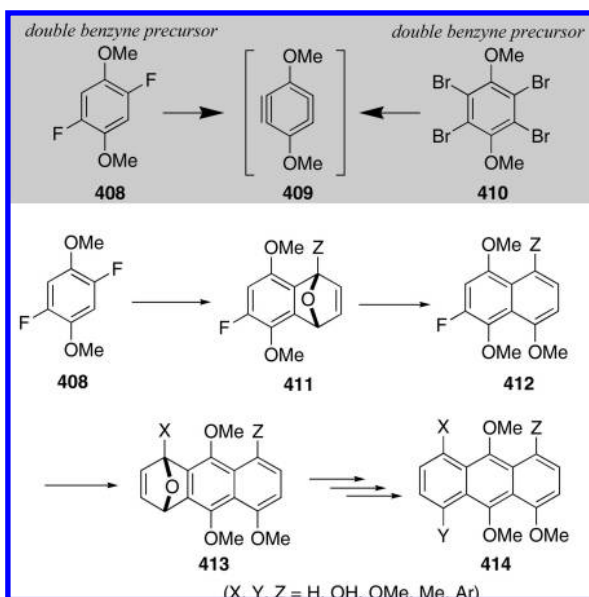
Aryl chlorides are mostly less reactive toward lithium–chlorine exchange, but highly electron-deficient aryl chloride like **403** provides benzyne **404** via pentafluorophenyl lithium, which undergoes cycloaddition with 3-methoxythiophene, producing **405**. OctafluoroBINOL **407** can be prepared from methoxynaphthalene **405** via bromide **406** (Scheme 124).<sup>210</sup>

Scheme 124



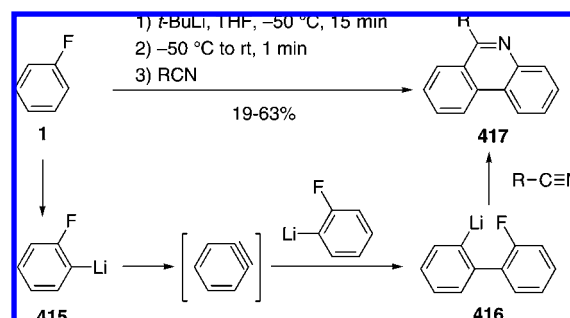
Benzynes from aryl fluorides have been employed for Diels–Alder cycloaddition with furans and thiophenes and coupling with aryl lithiums. With respect to the synthesis of unsymmetrical cycloadducts, 1,4-difluorobenzene **408** is a much more useful precursor of double benzyne **409**<sup>211</sup> than the original tetrabromo derivative **410**.<sup>212</sup> Sequential benzyne-formation and iterative cycloaddition from two sites of aryl fluoride **408** yield highly functionalized anthracenes **414** (Scheme 125).

Scheme 125



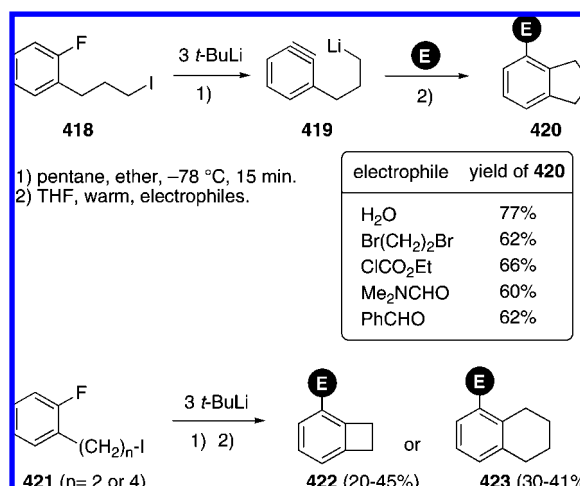
Addition of *ortho*-fluorophenyl lithium **415** to benzyne (in situ generated) gives 2-fluoro-2'-lithiobiphenyl (**416**), which then reacts with nitriles to provide 6-substituted phenanthridines **417**. The total process is a one-pot access to the phenanthridines (Scheme 126).<sup>213</sup>

Scheme 126



The intramolecular trapping of in situ generated arynes with nucleophiles is useful for the synthesis of heterocycles. Here again, many kinds of aryl fluorides have been employed for the generation of arynes. Lithium–iodine exchange and deprotonation–defluorination sequence from propyl iodide **418** generate lithiated aryne **419** in situ, and subsequent intramolecular addition and trapping newly generated aryl lithium produce substituted indanes **420** as final products (Scheme 127).<sup>214</sup> Both of cyclobutanation and cyclohexanation from **421** ( $n = 2$  or  $4$ ) are less effective in comparison with cyclopentanation.<sup>215</sup>

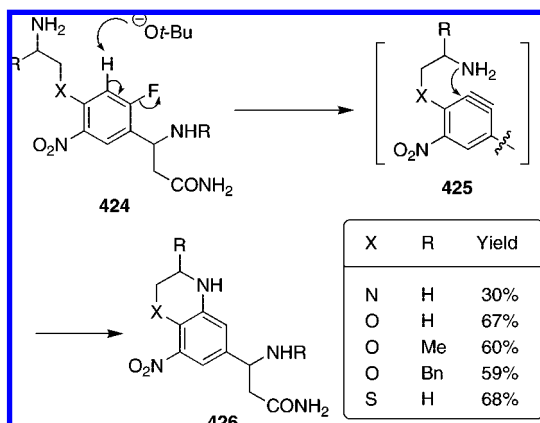
Scheme 127



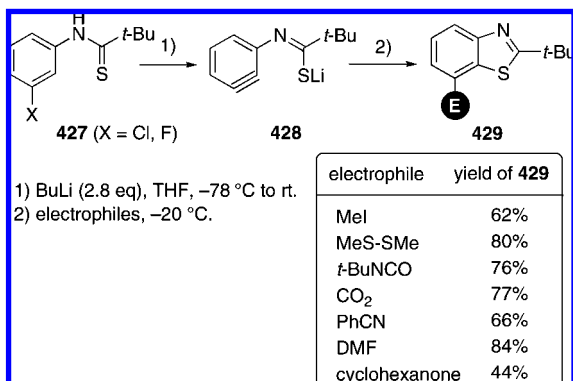
Some synthetic applications of the intramolecular benzyne-trapping protocol are shown in Scheme 128 for nitrogen nucleophile,<sup>216</sup> Scheme 129 for sulfur nucleophile,<sup>217</sup> and Schemes 130 and 131 for carbon nucleophiles.<sup>218,219</sup> The faster deprotonation and benzyne-formation of fluorocompound **436** result in successful preparation of indoles **437**. In contrast, carbon–nitrogen bond cleavage occurs predominantly from **442** rather than deprotonation–benzyne formation.<sup>219</sup>

In 2006, Barrett et al. reported the first total synthesis of (+)-clavilactone B (I), a potent antifungal agent via defluorinative benzyne formation.<sup>220</sup> The strategy employs a sophisticated three-component benzyne coupling with a methylallyl Grignard reagent and chiral epoxy-aldehyde **447** to generate two C–C bonds and install the carbon skeleton of clavilactone (Scheme 132). Furthermore, in 2008, they succeeded in the first total synthesis of dehydroaltenuene B by means of a four-component coupling reaction of 3,5-dimethoxybenzyne (**450**) with 2-methyl-2-cyclohexenylmagnesium chloride, carbon dioxide, and iodine (Scheme 133).<sup>221</sup>

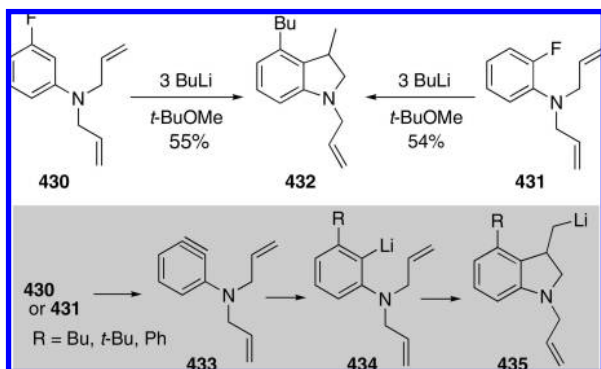
Scheme 128



Scheme 129



Scheme 130

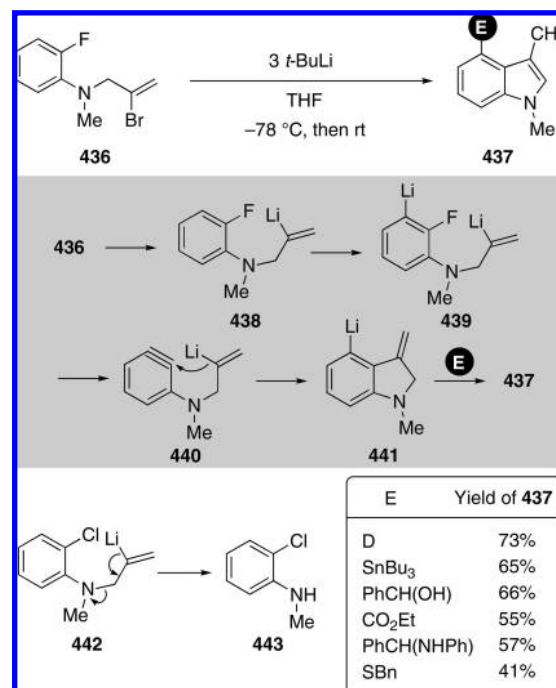


### 3. C–F Bond Activation in Alkenyl Fluorides

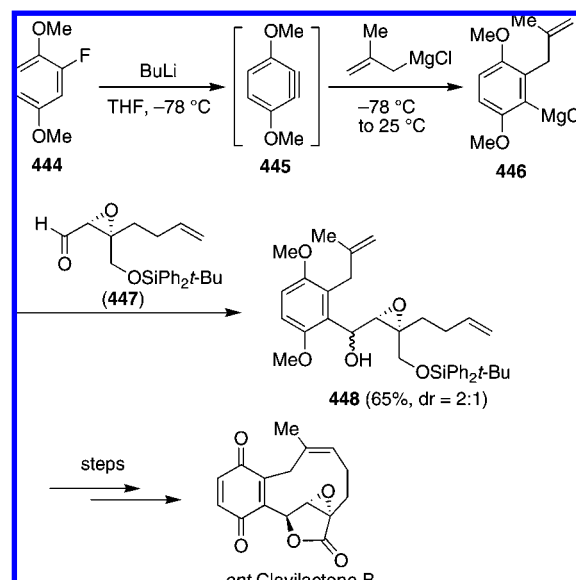
#### 3.1. General Aspect of Nucleophilic Substitution in *gem*-Difluoroalkenes

Activation of the  $sp^2$ -hybridized C–F bond mostly occurs via addition–elimination pathway since fluoroalkenes and *gem*-difluoroalkenes in particular are highly reactive toward nucleophilic attack at the fluorinated  $sp^2$ -carbon. The driving forces for the facile nucleophilic attack on *gem*-difluoromethylene carbon arise mostly from the following three factors: (i) high electron deficiency on *gem*-difluoromethylene carbon, (ii) thermodynamical instability of  $sp^2$ -hybridized fluoroalkenes **454**<sup>222,223</sup> in comparison with  $sp^3$ -hybridized fluoroalkanes, and (iii) stable  $sp^3$ -hybridized  $\beta$ -fluorocarbanions **455** (Scheme 134). The high reactivity of 1,1-difluoroalkenes to nucleophiles is dependent on the polar nature of the double bond. The <sup>13</sup>C NMR chemical shifts of difluoromethylene and methylene compounds (Scheme 135)<sup>223</sup> indicate a

Scheme 131



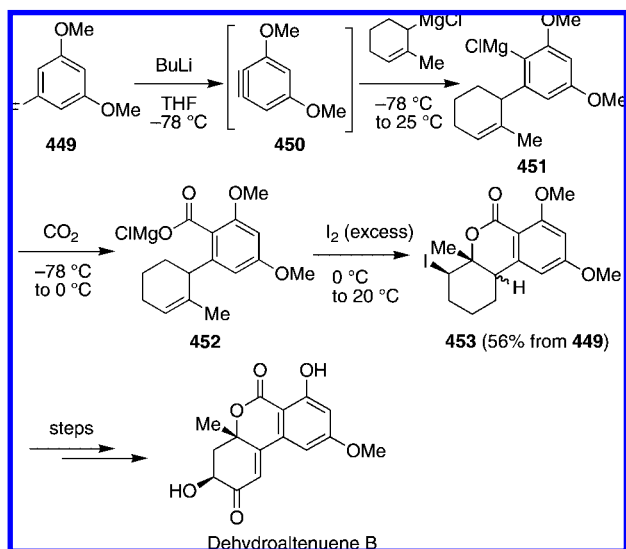
Scheme 132



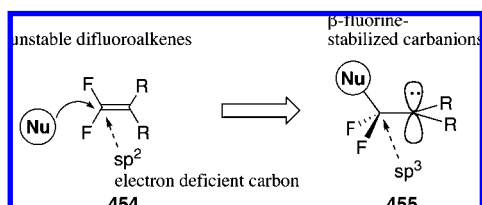
marked deshielding of  $\alpha$ -carbon and a large chemical shift difference between  $\alpha$ - and  $\beta$ -carbons for fluoroalkenes **454**, suggesting a low-lying LUMO with large coefficients at  $\alpha$ -carbon atom (high reactivity to nucleophiles).

Nucleophiles therefore attack exclusively at the *gem*-difluoromethylene carbon atoms of difluoroalkenes to form  $\beta$ -fluorocarbanions **457**. The chemical fates of **457** are mostly dependent on the structures of the alkenes and the reaction conditions. The reaction pathways of **457** are typically classified into three categories (*a*, *b*, and *c*) as shown in Scheme 136: (*a*) *addition–elimination*: with metal-nucleophiles in aprotic solvents, the carbanions **457** undergo defluorination, producing  $\alpha$ -substituted monofluoroalkenes **458**; (*b*) *1,2-addition*: with any nucleophiles in protic solvents or with protic nucleophiles such as amines and alcohols or with electrophiles in aprotic solvents, the carbanions **457** can be trapped with a proton or an electrophile to give addition

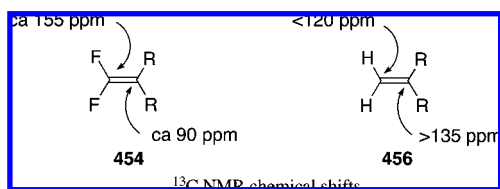
Scheme 133



Scheme 134

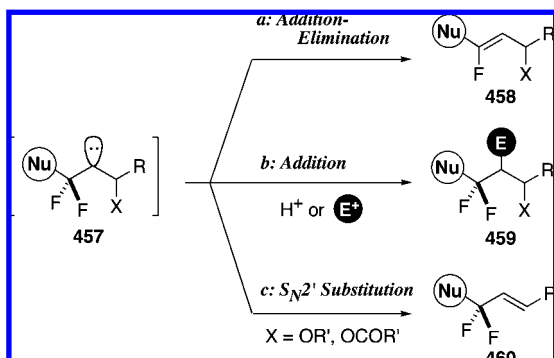


Scheme 135



products **459**; (c)  $S_N2'$  type substitution: the third case is  $S_N2'$  type substitution, where substrates must have a leaving group on  $\gamma$ -carbon of **457** such as alkoxy or acyloxy group and are transformed into substituted difluoromethyl alkenes **460**.

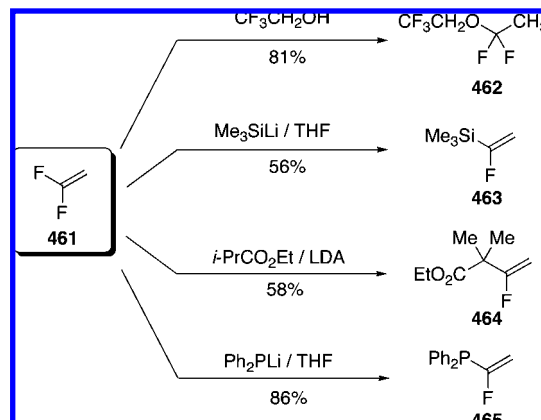
Scheme 136



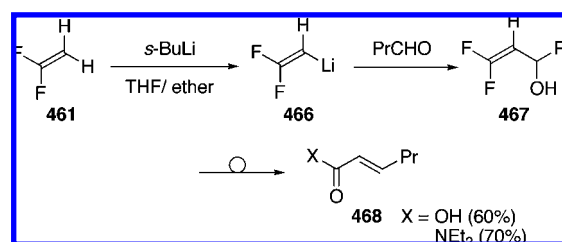
Some typical reactions of 1,1-difluoroethene (**461**) with nucleophiles are summarized in Scheme 137. Alkoxides,<sup>224</sup> silyl anions,<sup>225</sup> ester enolates,<sup>226</sup> and diphenylphosphinyl anion<sup>227</sup> attack the *gem*-difluorinated carbon of **461**. Addition and  $\beta$ -proton abstraction are competitive in some cases, and thus, a strong bulky base like *sec*-butyl lithium abstracts  $\beta$ -vinyllic proton to generate vinyl lithium rather than adds

to *gem*-difluorocarbon of **461**. The lithium species can be trapped with an aldehyde, providing difluoroallyl alcohol, which is rearranged and then hydrolyzed to  $\alpha,\beta$ -unsaturated carboxylic acid and amide **468** (Scheme 138).<sup>228</sup>

Scheme 137

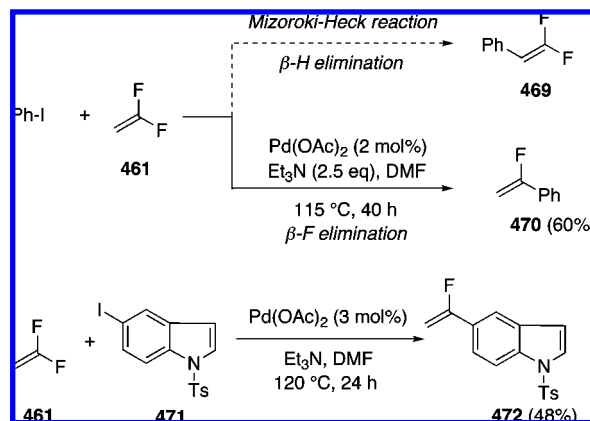


Scheme 138



The Mizoroki–Heck reaction is a general and convenient method for arylation of olefinic compounds involving oxidative addition of aromatic halides to Pd(0), carbopalladation to alkenes, and  $\beta$ -H elimination.<sup>56</sup> Under the Mizoroki–Heck reaction conditions, vinylidene fluoride **461** undergoes carbopalladation to give  $\alpha$ -fluorostyrene (**470**) as a main product instead of  $\beta,\beta$ -difluorostyrene (**469**; the Heck reaction product) as shown in Scheme 139.<sup>229</sup> In this transformation,  $\beta$ -fluorine elimination is the preferred type of elimination, even when a competing  $\beta$ -hydride elimination is possible. Also, an  $\alpha$ -fluorovinyl substituent is introduced into the 5-position of indole **471** using a catalytic amount of Pd(OAc)<sub>2</sub>.<sup>230</sup>

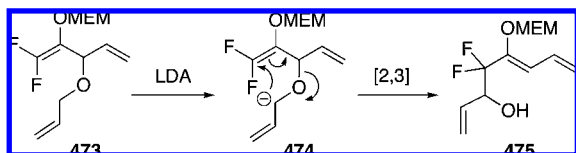
Scheme 139



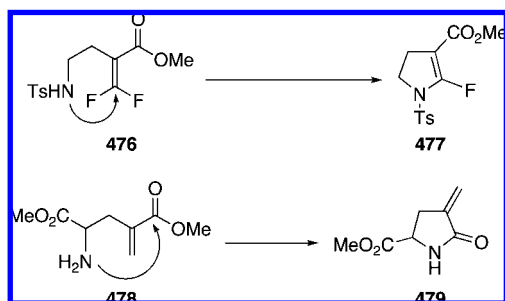
The much higher electrophilic reactivity of *gem*-difluoromethylene carbon versus methylene carbon is also demonstrated by [2,3]sigmatropic rearrangement of carbanion

**474**,<sup>231</sup> which exclusively attacks *gem*-difluoromethylene site rather than nonfluorinated methylene site (Scheme 140). Moreover, a remarkable chemoselectivity is observed for cyclization of  $\alpha$ -substituted  $\beta,\beta$ -difluoroacrylate **476** in contrast to nonfluorinated acrylate **478**.<sup>223</sup> Baldwin reported the cyclization of dimethyl 4-methyleneglutamate **478** to  $\gamma$ -lactam **479**, showing difficulty for 5-*endo**trig* cyclization of **478**.<sup>232</sup> In contrast, the difluorinated acrylate **476** undergoes facile intramolecular nucleophilic attack on difluoromethylene carbon, leading to the exclusive formation of dihydropyrrole ring **477** as shown in Scheme 141.<sup>223</sup>

Scheme 140



Scheme 141



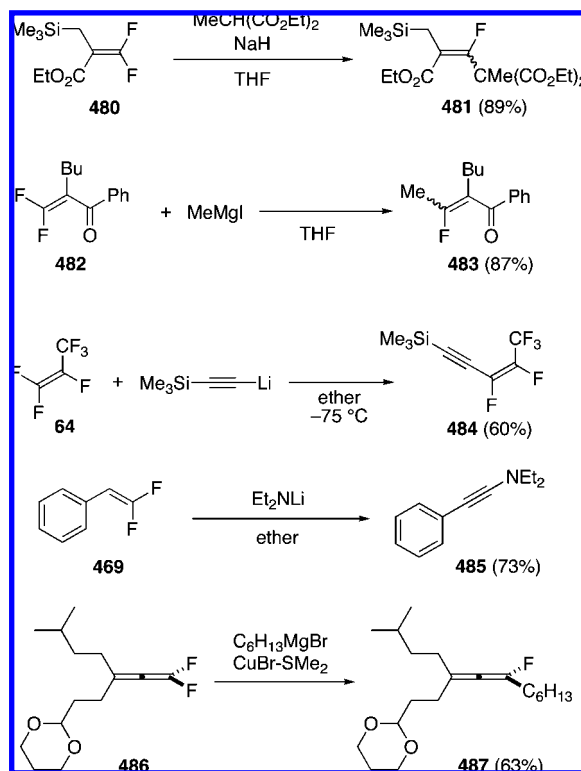
### 3.2. Structure and Reactivity of *gem*-Difluoroalkenes

Terminal *gem*-difluoroalkenes accept nucleophiles easily and undergo addition–elimination reaction to give  $\alpha$ -substituted fluoroalkenes. Some synthetically useful examples are shown in Scheme 142. Carbon nucleophiles such as metal enolates of dialkyl malonates,<sup>233</sup> Grignard reagents,<sup>234</sup> alkynyl lithiums,<sup>235</sup> and lithium amides<sup>236</sup> participate in smooth addition–elimination reactions to form the defluorinated products. Difluoroallene **486** behaves similarly, affording monofluoroallene **487** via addition–elimination.<sup>237</sup> The action of bidentate nucleophiles such as catechol<sup>238</sup> and thiocatechol<sup>239</sup> on fluoroalkenes **64** and **490** furnishes cyclized products **488** and **491**, respectively (Scheme 143).

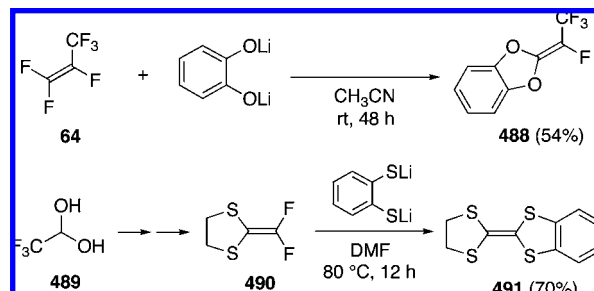
Two kinds of nucleophiles can be introduced stepwise to the *gem*-difluoromoiety to synthesize highly functionalized alkenes **494**<sup>240</sup> and **498**<sup>241</sup> (Scheme 144). The *gem*-difluoromethylene compounds are readily prepared from commercially available 2,2,2-trifluoroethanol for **492** and 2-bromopentafluoropropene for **495** so that the disubstitution protocol of the *gem*-CF<sub>2</sub> group is useful for the synthesis of highly substituted alkenes.

Difluoroenol ethers **499** and the corresponding enamines **500** are less reactive toward nucleophiles due to the electron-donating effect by alkoxy and amino groups (Scheme 145).<sup>242</sup> However, enol ethers and enamines with strong electron-withdrawing group R in **499** and **500** such as carboalkoxyl and trifluoromethyl groups are very reactive. Perfluorinated enolate **501** reacts with alkyl lithiums to afford substitution products **502**.<sup>243</sup> Reaction of enamine **503** with dimethylsulfoxonium methylide provides one carbon homologated vinyl fluoride **504** via **505**, which is formed as an intermediate by the addition–elimination pathway.<sup>244</sup>

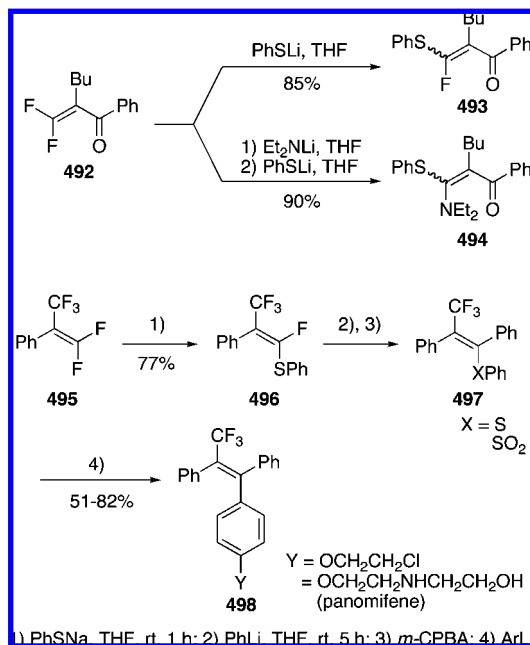
Scheme 142



Scheme 143

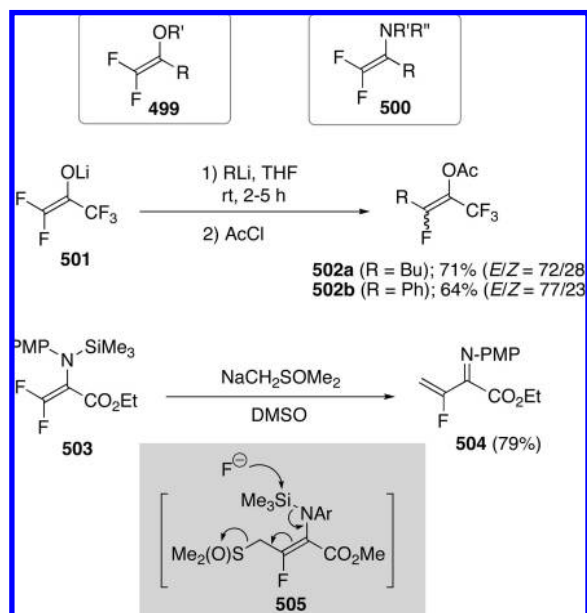


Scheme 144



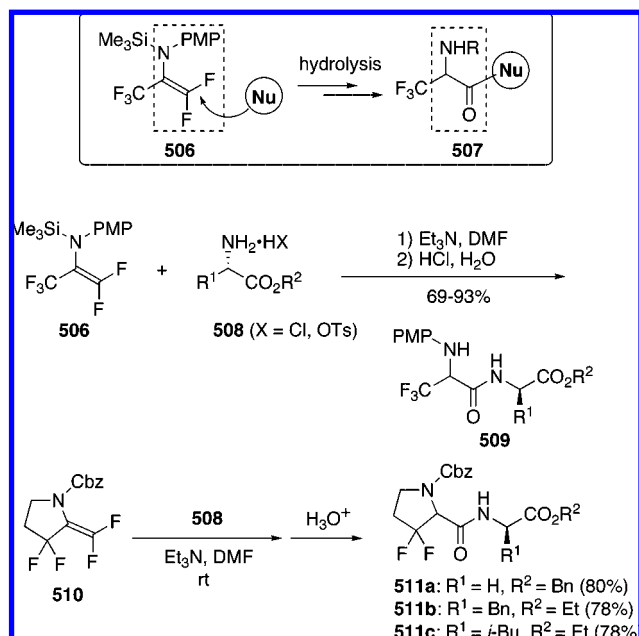


Scheme 145



*gem*-Difluoromethylene moiety is a potential precursor for carboxyl, alkoxy carbonyl, and carboamide groups since it can be transformed to these functional groups by reactions with water, alcohols, and amines followed by hydrolysis, respectively. A particularly interesting fact is that perfluoroenamine **506** reacts with a variety of amino esters **508** at 0 °C within 1 h, providing trifluoroalanine dipeptides **509** in good yields (Scheme 146).<sup>245</sup> Because of the higher nucleophilic reactivity of the amine group as compared with that of the hydroxyl group, serine reacts with **506** chemoselectively at the amino group rather than the hydroxyl group, even when serine is employed without protecting its hydroxyl group.<sup>245</sup> Furthermore, enamine **506** is readily converted to 3,3-difluoro-2-difluoromethylenepyrrolidine **510**, which acts as a source of 3,3-difluoroproline dipeptides **511** upon treatment with aminoesters.<sup>246</sup>

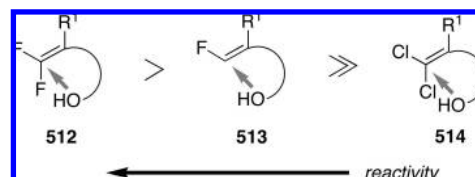
Scheme 146



### 3.3. Intramolecular Nucleophilic Substitution in *gem*-Difluoroalkenes

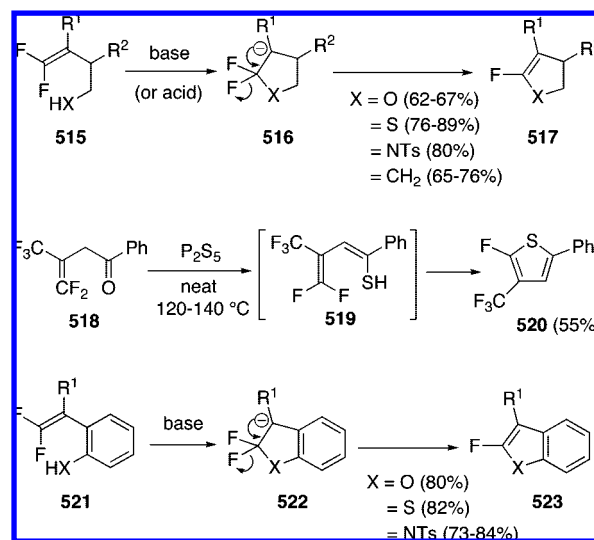
The defluorinative substitution of one of the fluorine atoms with other functional group on *gem*-difluorocarbon atom is so powerful that an intramolecular version of the addition–elimination protocol is useful for the synthesis of mono-fluorinated cyclic compounds. The striking feature in this cyclization is the fact that two fluorine substituents are essential; the corresponding monofluoro compound **513** (R<sup>1</sup> = Bu) reacts very slowly to furnish the desired benzofuran in only 17% yield (at 60 °C, 2 h for the difluoro compound, and at 80 °C, 43 h for the monofluoro compound) (Scheme 147). A large amount (80%) of the starting material is recovered without any desired cyclization product at 60 °C for 8 h in the case of chloro compound **514**.<sup>223</sup>

Scheme 147



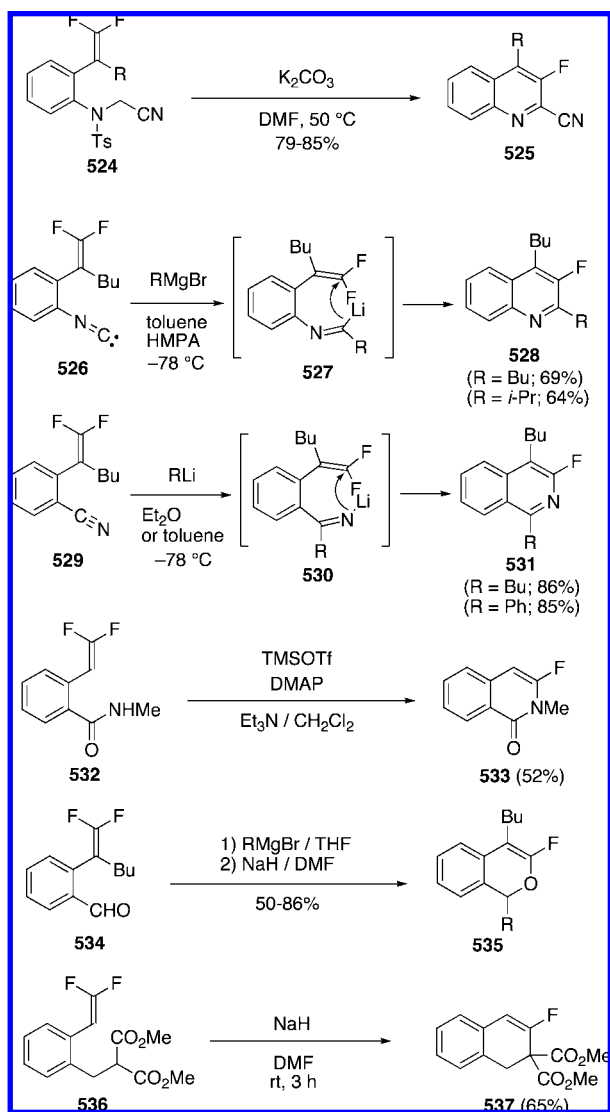
The cyclized products **517** and **520** include cyclopentenones,<sup>223,247,248</sup> dihydrofurans, dihydropyrroles,<sup>249</sup> dihydrothiophenes,<sup>249</sup> thiophenes,<sup>250</sup> and also corresponding benzo-derivatives **523** (Scheme 148).<sup>223,251</sup> As summarized in Scheme 149, the syntheses of the monofluorinated six-membered ring compounds such as 2-cyano,<sup>252</sup> 2-alkyl,<sup>253</sup> and 2-aryl-substituted<sup>254</sup> quinolines, isoquinolines,<sup>253</sup> dihydroisoquinolines,<sup>255</sup> cinnolines,<sup>256</sup> benzopyrans,<sup>257</sup> and dihydronaphthalenes<sup>247</sup> are accomplished by intramolecular addition–elimination protocols.

Scheme 148

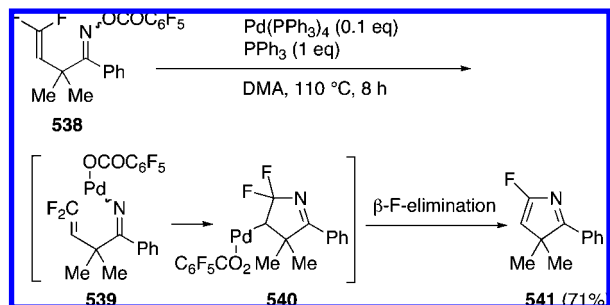


The intramolecular version of “atypical” Mizoroki–Heck reactions involving  $\beta$ -fluorine elimination<sup>229,230</sup> works well for the construction of fluorine-containing five-membered rings (Scheme 150).<sup>258</sup> In the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (0.1 equiv) and PPh<sub>3</sub> (1 equiv), a 5-*endo-trig*-alkene insertion proceeds smoothly via aminopalladium species **539** starting from 3,3-difluoroallyl ketone *O*-pentafluorobenzoyloxime **538**, providing a facile access to 5-fluoro-3H-pyrrole **541**.

Scheme 149



Scheme 150

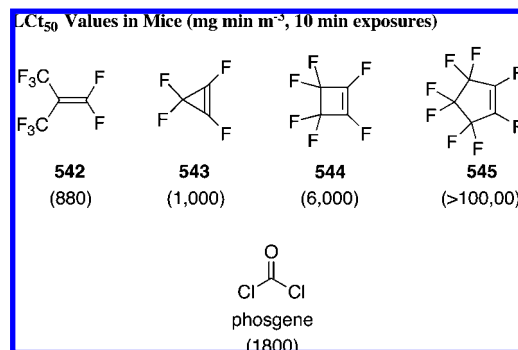


### 3.4. High Reactivity and Toxicity of Polyfluorinated Fluoroalkenes

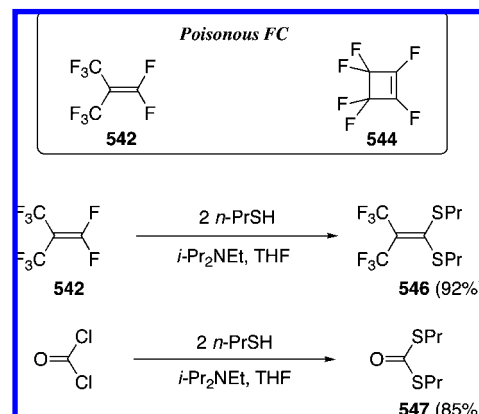
It is notable that some highly fluorinated alkenes are poisonous<sup>259</sup> because of their rapid reaction with cellular components. Perfluoroisobutene (PFIB, **542**), a byproduct of PTFE polymer manufacture, is one of the most toxic among them and is more toxic than phosgene. Other fluorinated alkenes such as tetrafluorocyclopentene (**543**) and hexafluorocyclobutene (HFCB, **544**) are toxic by inhalation. PFIB (**542**) has a high affinity for thiols in the lung. A rapid fall of cysteine and glutathione levels in lung is observed in rodents exposed to PFIB. The origin of the toxicity is

considered to be the rapid reaction between these perfluoroalkenes and cellular components such as cysteine via the addition–elimination pathway as described above. Some inhalation toxicities of fluorobutenes in mice are shown in Scheme 151.<sup>260</sup> Timperley demonstrated experimentally the relation between toxicity and reactivity toward thiols of these highly fluorinated alkenes. Both PFIB (**542**) and phosgene react rapidly with 2 mol of propane thiol to give dithiolated compounds **546** and **547**, respectively (Scheme 152). In connection with the similar reactivities, it is suggestive that the symptoms caused by inhalation of both PFIB and phosgene are quite similar and *N*-acetyl cysteine is effective for alleviating the symptoms of both PFIB and phosgene.<sup>261</sup>

Scheme 151



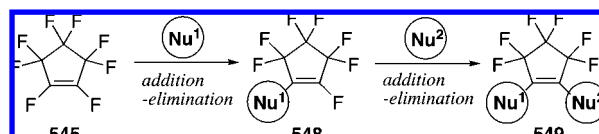
Scheme 152



### 3.5. Defluorinative Modification of Octafluorocyclopentene

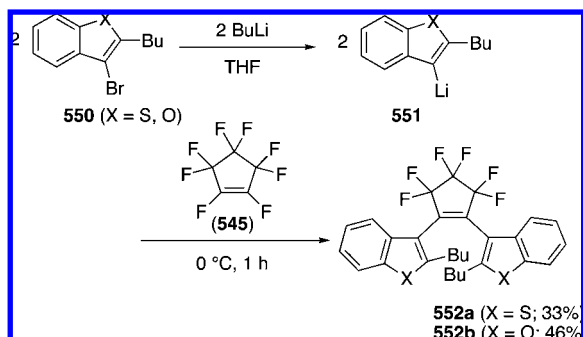
Reactions of octafluorocyclopentene (**545**) with nucleophiles take place very smoothly due to the extremely high electrophilicity of the double bond. The nucleophilic substitutions undergo via an addition–elimination pathway in a stepwise manner (Scheme 153). Two same nucleophiles are incorporated at the same time (Scheme 154)<sup>262</sup> or two different nucleophiles are introduced successively (Scheme 155).<sup>263</sup>

Scheme 153

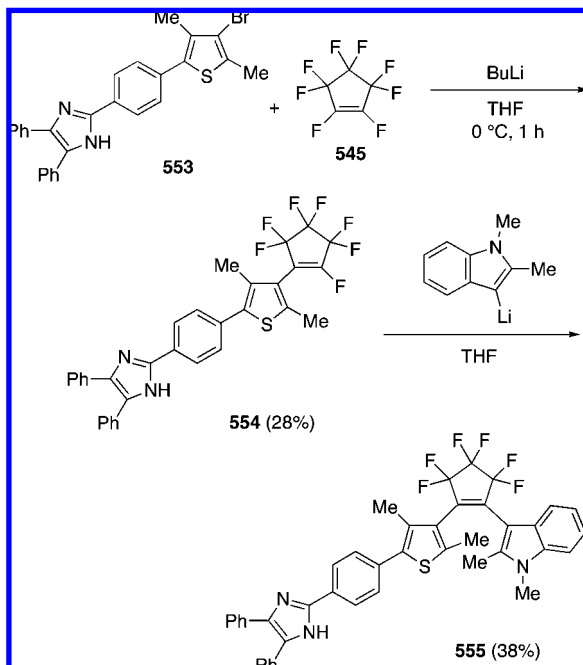


Diverse nucleophiles such as aryl and heteroaryl,<sup>262,264</sup> alkyl,<sup>265</sup> alkenyl,<sup>266</sup> and alkynyl<sup>267</sup> metals, anions of group

Scheme 154



Scheme 155



VI elements<sup>238,268</sup> have been employed for the substitution. In particular, a number of 1,2-bis(heteroaryl)-substituted perfluorocyclopentenes have been synthesized for the study on their photochromism.<sup>269</sup> As an exception, the  $S_N2'$  reaction takes place at the second substitution step depending on the nature of nucleophiles and stability of the products (Scheme 156).<sup>238</sup>

In the radical reactions, the intermediate alkylated perfluorocyclopentyl radicals do not eliminate fluorine from the  $\beta$ -position but mostly undergo either addition or hydrogen abstraction (Scheme 157). For instance, bis(trimethylsilyl)mercury adds to **545** to provide **559** on UV irradiation, which partakes in defluorodemercuration to give monosilyl cyclopentene **560**.<sup>270</sup> On  $\gamma$ -ray irradiation, the radicals derived from cyclic ethers **561** and octafluorocyclopentene **545** abstract hydrogen from ethers **561**, affording the addition products **562**.<sup>271</sup>

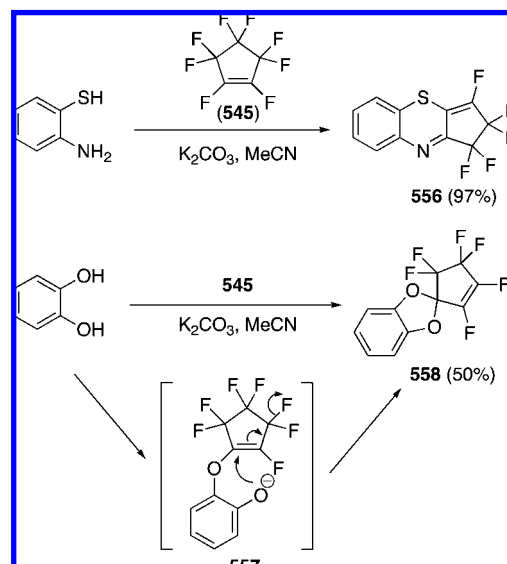
#### 4. C–F Bond Activation in Aliphatic Fluorides

##### 4.1. C–F Bond Activation of Trifluoromethyl Group Attached to $\pi$ -Electron System

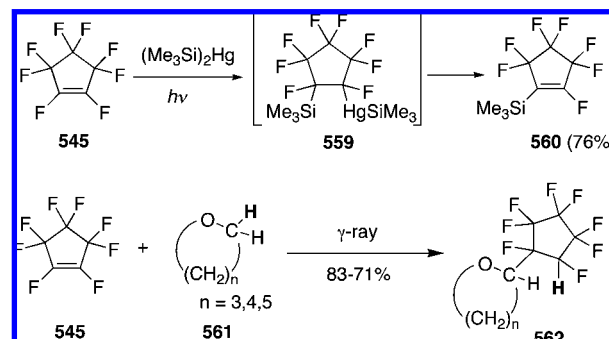
###### 4.1.1. $S_N2'$ Type Reactions in Trifluoromethylalkenes

The  $S_N2'$  reaction has been often employed for carbon–halogen bond cleavage. However, trifluoromethylated alkenes also

Scheme 156

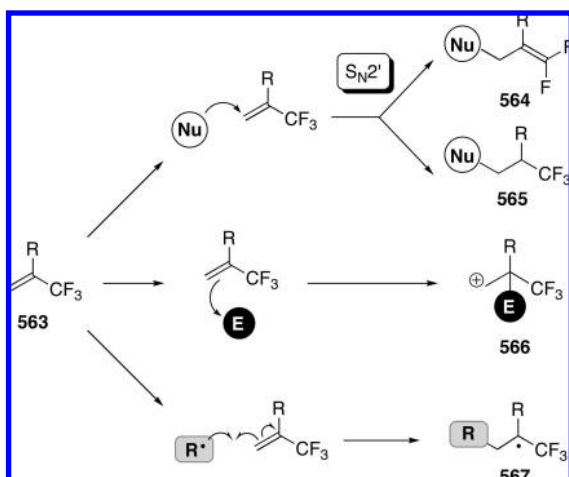


Scheme 157



are substrates that easily undergo the  $S_N2'$  reaction. Before discussing the  $S_N2'$  reaction, let us first consider the possible reactions of 3,3,3-trifluoropropene as a model substrate of trifluoromethylalkenes **563** with nucleophiles, electrophiles, and radicals as shown in Scheme 158. Reactions with nucleophiles are divided into two categories:  $S_N2'$  and addition. The former predominates in the reaction with metal nucleophiles such as alkyl and aryl metals and metal amides in aprotic solvents, while the latter occurs mainly in the reactions with protic nucleophiles such as amines and alcohols in protic solvents. The reactions of **563** with strong electrophiles occur slowly under rather severe conditions, providing addition products that arise from attacking electrophiles at  $\alpha$ -position via **566** (Scheme 159).<sup>272</sup> The reactions of 3,3,3-trifluoropropene (**568**) with radicals proceed mostly via radical addition at  $\beta$ -position followed by hydrogen abstraction (Scheme 160),<sup>273</sup> where no defluorination is observed.

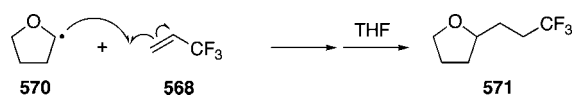
Now, let us return to the discussion of the  $S_N2'$  pathway. A trifluoromethyl group attached to a double bond lowers the LUMO of the bond and thus accelerates nucleophilic addition to the bond. The addition occurs mostly at the  $\beta$ -position due to the stabilization of the carbanions formed in the addition by both inductive and negative hyperconjugation effects,<sup>274</sup> which also apply to the carbanion-like transition states formed in concerted reactions. In aprotic solvents,  $S_N2'$  reactions proceed generally via defluorination to give functionalized 1,1-difluoroalkenes **564** (Scheme 158). Trifluoropropene derivatives **563** with either electron-

Scheme 158. Reaction Mode for  $\text{CF}_3\text{CR}=\text{CH}_2$  (563)

Scheme 159

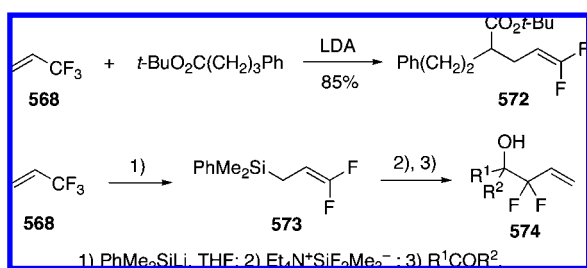


Scheme 160



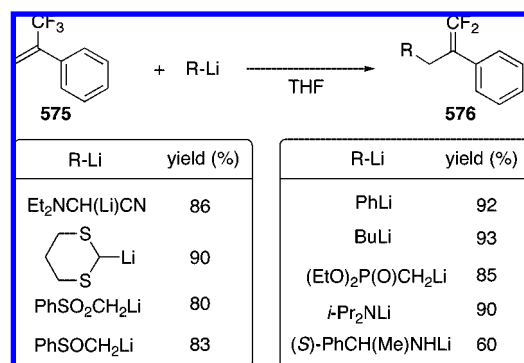
withdrawing or electron-donating substituents (R) at  $\alpha$ -carbon smoothly undergo  $\text{S}_{\text{N}}2'$  reactions on reacting with carbon and heteroatom nucleophiles. Reactions of trifluoropropene **568** with carbon<sup>275</sup> and silicon<sup>276</sup> nucleophiles provide **572** and **573**, respectively, in excellent yields (Scheme 161).  $\alpha$ -Trifluoromethylstyrene (**575**) is a good substrate that reacts with a variety of alkyl lithiums to yield  $\alpha$ -functionalized  $\beta,\beta$ -difluorostyrenes **576** (Scheme 162).<sup>277,278</sup>  $\alpha$ -Trifluoromethylstyrene (**575**) reacts with trimethylsilylated DMF (**577**), a synthon of iminium carbanion **579** under neutral conditions, affording **578** on heating in toluene (Scheme 163).<sup>279</sup> Bislithio nucleophile **580** couples with  $\text{CF}_3$ -styrene **575** at the carbon site rather than the amide-nitrogen site (Scheme 164).<sup>280</sup> Scheme 165 shows an intramolecular version of the  $\text{S}_{\text{N}}2'$  reaction of *ortho*-substituted  $\text{CF}_3$ -styrene derivatives where nitrogen nucleophile attacks  $\beta$ -carbon in  $\text{S}_{\text{N}}2'$  manner, forming isoquinoline skeleton **584** in DMF. However, notable is a fact that the same reaction of neutral imine nucleophile **586** provides trifluoromethylated dihydroisoquinoline **587**, a simple addition product rather than defluorinated product **584**.<sup>281</sup>

Scheme 161

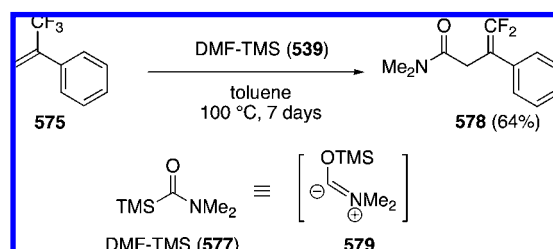


Silyl alkene **589**, which is readily prepared from commercially available **588**, undergoes facile  $\text{S}_{\text{N}}2'$  reactions with

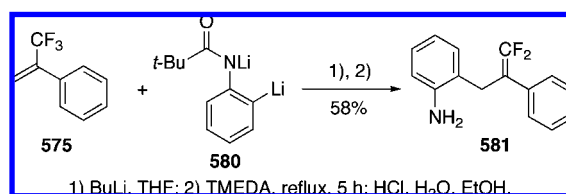
Scheme 162



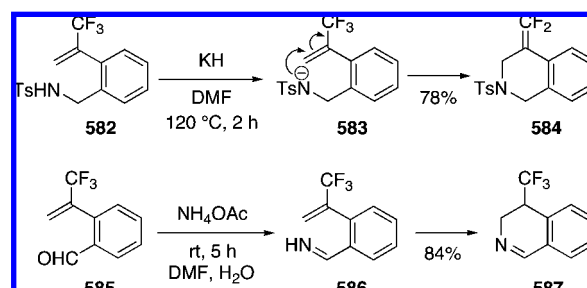
Scheme 163



Scheme 164



Scheme 165

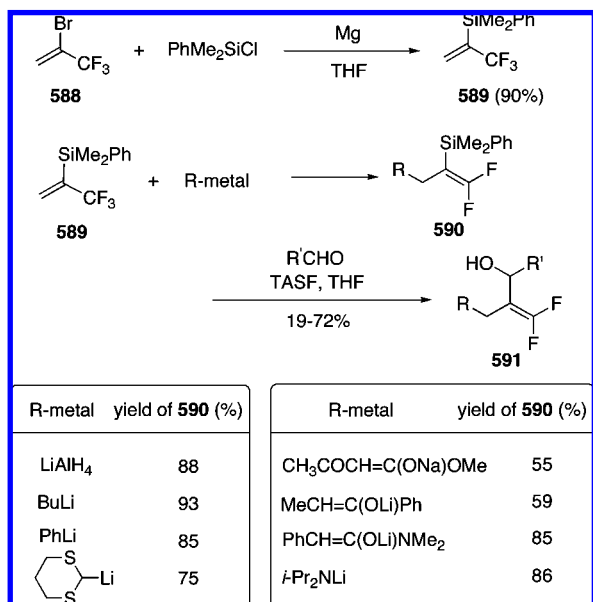


a variety of lithium nucleophiles to provide **590** (Scheme 166).<sup>282</sup> 3-Substituted 1,1-difluoro-2-silylalkenes **590** are useful difluoromethylene building blocks, which can be transformed to synthetically valuable compounds like **591** by fluoride-promoted desilylative alkylation on carbon 2.

Trifluoromethacrylic acid (**592**) and esters are extremely strong nucleophile acceptors so that they participate in facile  $\text{S}_{\text{N}}2'$  reaction even at low temperature in aprotic solvents. Some results are summarized in Scheme 167.<sup>223,283–285</sup> Grignard and alkyl lithium reagents provide  $\text{S}_{\text{N}}2'$  products in moderate yields. Excess use of nucleophiles induces sometimes further addition–elimination at *gem*-difluoromethylene carbon of initial products **593**, leading to the formation of  $\beta$ -substituted  $\beta$ -fluoroacrylic acids. However, it is noteworthy that protic nucleophiles such as amines<sup>286</sup> and alcohols<sup>287</sup> (Scheme 168) add simply to the double bond of **592** and do not induce the  $\text{S}_{\text{N}}2'$  reaction. In contrast to the facile  $\text{S}_{\text{N}}2'$  reaction of  $\text{CF}_3$ -alkenes,  $\text{CF}_3$ -alkynes undergo normal addition to the triple bond, as shown in

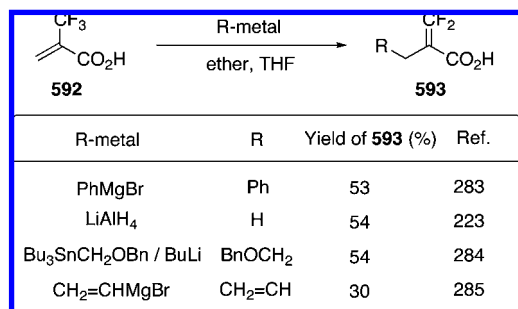


Scheme 166

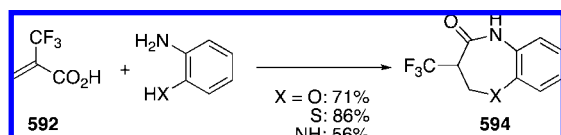


2-butynoic acid ester **595** in which addition occurs at the 3-position rather than the 2-position (Scheme 169).<sup>288</sup>

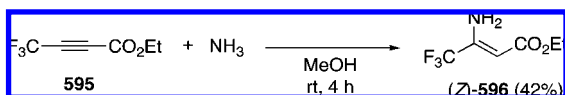
Scheme 167



Scheme 168



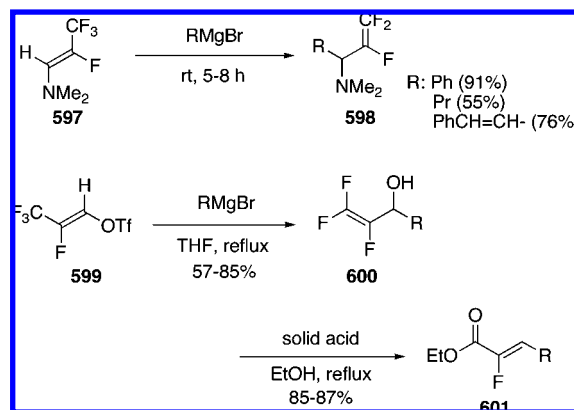
Scheme 169



Because of the high reactivity of trifluoromethylated alkenes, even 1-substituted-3,3,3-trifluoropropenes **597**<sup>289</sup> and **599**<sup>290</sup> undergo the S<sub>N</sub>2' reaction with Grignard reagents, although they need a higher temperature or longer reaction times as compared with H<sub>2</sub>C=CH–CF<sub>3</sub> (**568**), H<sub>2</sub>C=C(Ph)CF<sub>3</sub> (**575**), and H<sub>2</sub>C=C(SiMe<sub>2</sub>Ph)CF<sub>3</sub> (**589**), presumably because of the steric hindrance at the reaction sites (Scheme 170). Triflate **599** is transformed smoothly to α-fluoro-α,β-unsaturated esters **601** in good yields.<sup>290</sup>

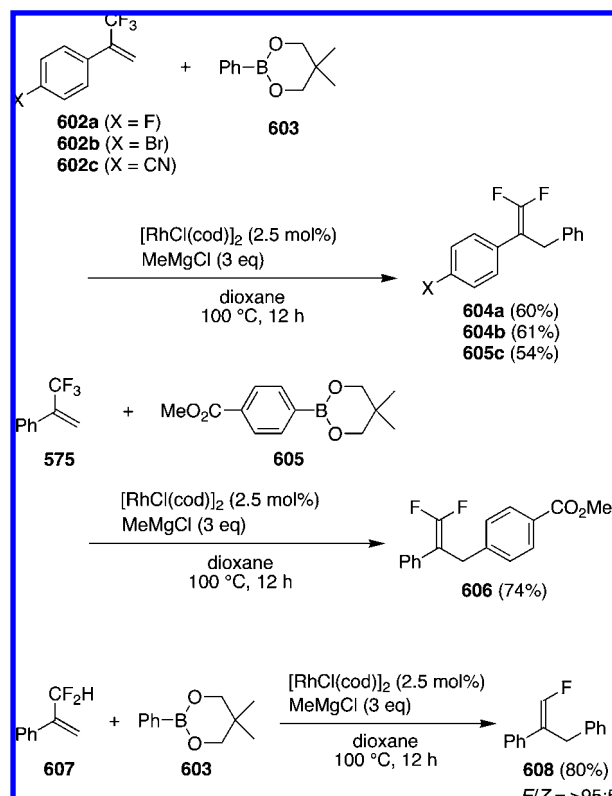
Besides strong nucleophilic reagents, organoboron compounds react with trifluoromethylated alkenes in the presence of Rh complexes. In 2008, Miura and Murakami reported the synthesis of *gem*-difluoroalkenes from the reactions of α-(trifluoromethyl)styrenes with arylboronic esters and

Scheme 170



MeMgCl (Scheme 171).<sup>291</sup> With a high level of functional group tolerance, the reaction proceeds through the addition of arylrhodium(I) species across the electron-deficient carbon–carbon double bonds and the subsequent β-fluoride elimination.

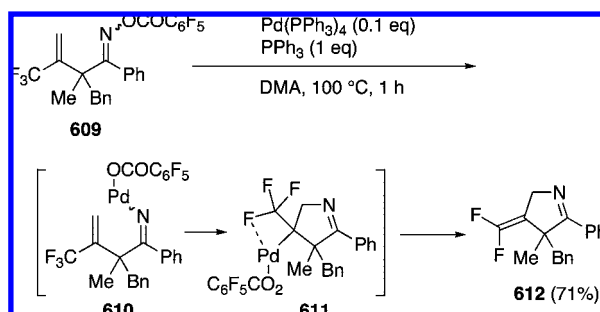
Scheme 171



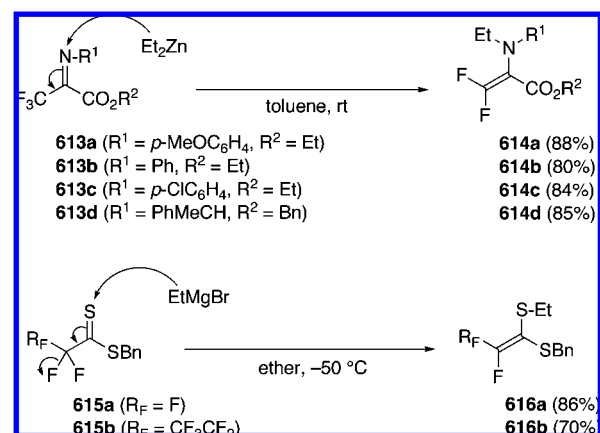
A catalytic version of the intramolecular S<sub>N</sub>2' reaction of trifluoromethylated alkenes was reported by Ichikawa (Scheme 172).<sup>292</sup> Upon exposure to a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub>, *O*-pentafluorobenzoyloxime **609** undergoes 5-*endo* mode of alkene insertion via oxidative addition of the N–O bond in **609**, followed by β-fluorine elimination to produce 4-difluoromethylene-1-pyrroline **612** in 71% yield.

Very interestingly, unusual reaction selectivities are observed in the nucleophilic transformations of fluorinated iminoesters **613** and dithioesters **615** as compared with that of the corresponding carbonyl compounds. The carbon–heteroatom double bonds bearing a CF<sub>3</sub> group accept nucleophiles at the heteroatom site, leading to fluoroalkenes via formal S<sub>N</sub>2' reactions (Scheme 173).<sup>293,294</sup>

Scheme 172



Scheme 173



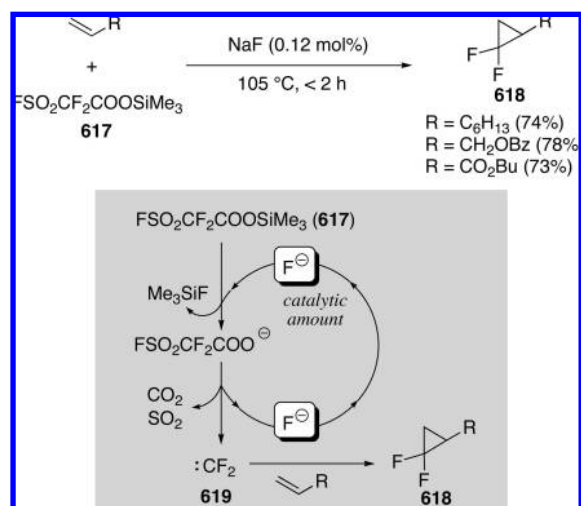
#### 4.1.2. Fluoride-Ion Catalyzed Desilylative Defluorination

Fluoride-ion-promoted reactions have been widely investigated in organic synthesis. A general, powerful strategy for activation of organosilicon compounds is the use of fluoride ( $\text{Bu}_4\text{NF}$ , TASF, CsF, KF/18-crown-6, etc.) endowed with the strong affinity to silicon. Generally, these reactions are in need of a stoichiometric amount of fluoride sources. From the practical viewpoint, the strong basic conditions occasionally cause side reactions, such as decomposition of the sensitive functional groups and decomposition of the desired products by side reactions involving further nucleophilic attack of fluoride ion. Thus, reaction conditions in which smaller amounts of fluoride can be employed are desirable for the development of more practical and useful protocols.

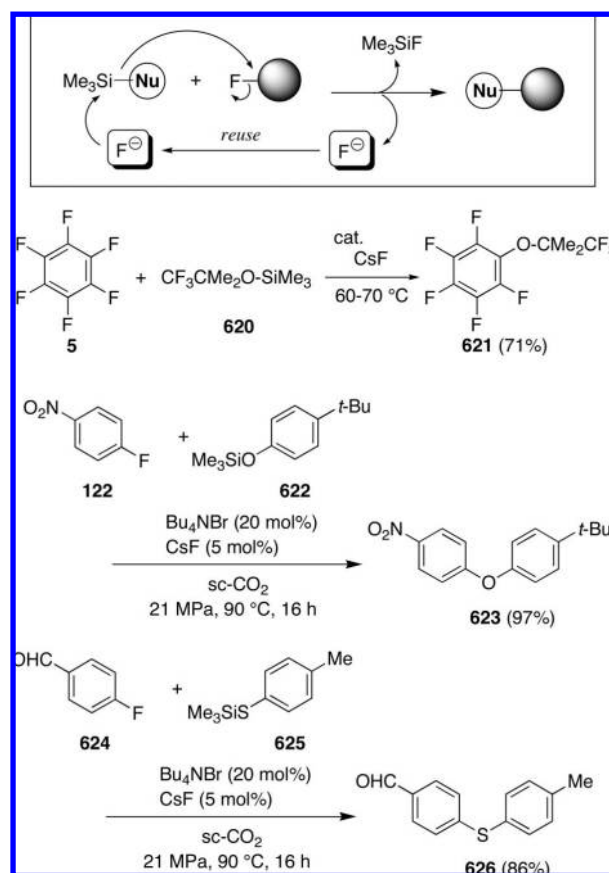
In 2000, Dolbier and Chen developed a general and highly efficient method to prepare *gem*-difluorocyclopropanes **618** by the use of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA, **617**), a versatile source of difluorocarbene (**619**) (Scheme 174).<sup>295</sup> In the presence of a catalytic amount of sodium fluoride, TFDA undergoes decomposition to afford difluorocarbene (**619**),  $\text{CO}_2$ ,  $\text{SO}_2$ , and fluoride, which can attack the starting silyl ester again to make the reaction a chain reaction catalytic in fluoride. The present protocol works well for a diverse group of alkene substrates that possess not only electron-donating but also electron-withdrawing groups.

Herein, the examples of C–F bond activation by the use of a catalytic amount of fluoride ion are presented (Scheme 175). As an intermolecular case, a fluoride ion reacts with an organosilicon compound to generate a nucleophile, followed by nucleophilic substitution to yield the desired product accompanied by fluoride elimination. Reuse of the resultant fluoride ion as a nucleophile completes the catalytic

Scheme 174



Scheme 175

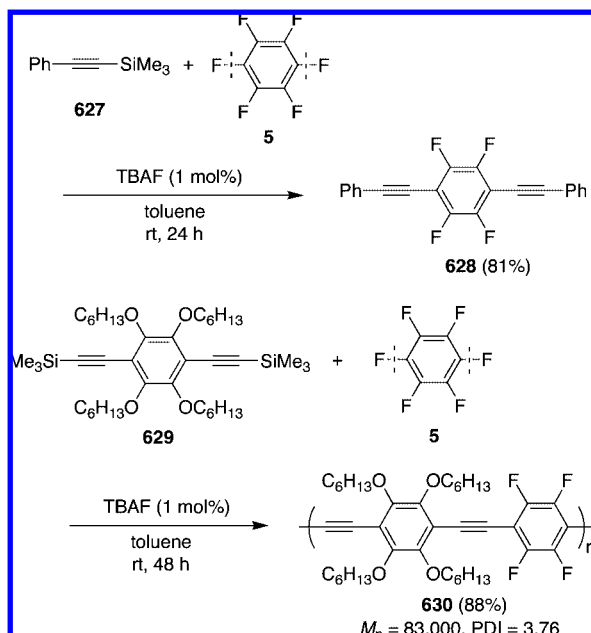


sequence of fluoride. By the use of a catalytic amount of CsF, the C–F bond activation reaction ( $\text{S}_\text{N}\text{Ar}$ ) of hexafluorobenzene (**5**) with silyl ether **620** affords the substitution product **621** in good yield.<sup>158,296</sup> In 2008, Holmes et al. developed a high yielding synthesis of diaryl ether **623** and sulfide **626** and by a fluoride-catalyzed  $\text{S}_\text{N}\text{Ar}$  process in  $\text{scCO}_2$ .<sup>297</sup>

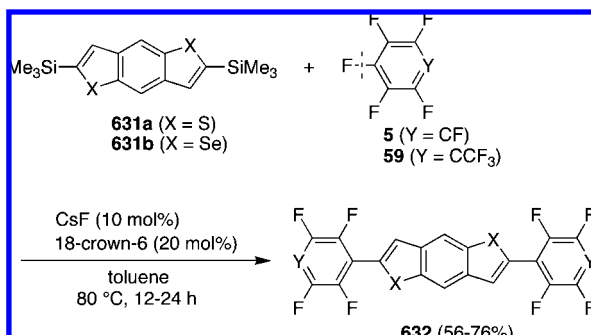
Upon treatment with a catalytic amount of TBAF, 2 equiv of alkynylsilane **627** reacts with hexafluorobenzene (**5**) smoothly to provide bis(alkynyl)benzene **628** in high yield (Scheme 176).<sup>298</sup> A small amount of fluoride salt promotes the condensation polymerization between silylacetylene-functionalized monomer **629** and  $\text{C}_6\text{F}_6$  to deliver high

molecular weight poly(phenylene ethynylene) **630**. Fluoride-induced  $S_NAr$  protocol is applicable to the synthesis of benzodichalcogenophenes **632** possessing polyfluoroarene moieties at their termini (Scheme 177).<sup>299</sup>

Scheme 176



Scheme 177

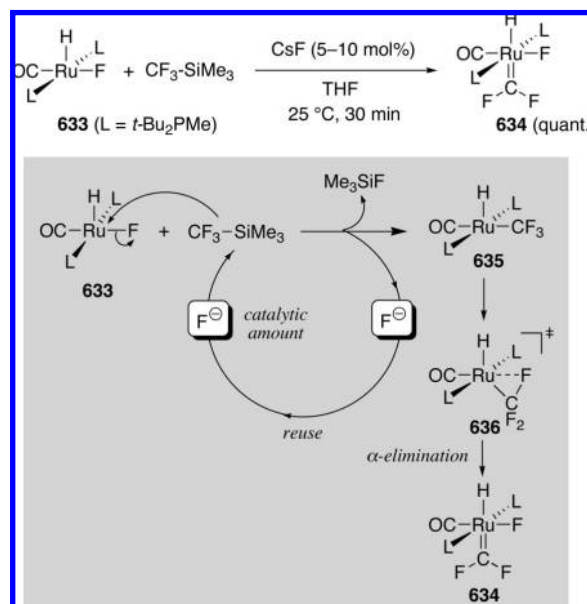


CsF-triggered C–F bond cleavage reactions are also applicable to the preparation of organometallic complexes. The nucleophilic reaction sequence combined with  $\alpha$ -fluoride elimination of trifluoromethyl ruthenium complex **635** provides the metal–difluorocarbene complex **634** (Scheme 178).<sup>300</sup>

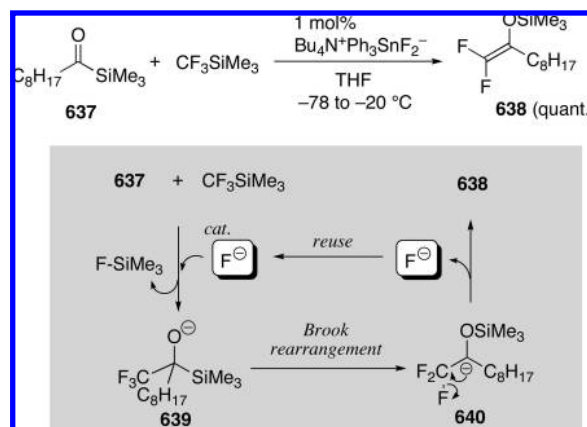
Fluoride-ion-catalyzed reaction sequences including  $\beta$ -fluoride elimination are also useful for the synthesis of  $\beta,\beta$ -difluoroenol silyl ethers (Scheme 179).<sup>301</sup> Fluoride-promoted trifluoromethylation of acylsilane **637** with trifluoromethylsilane and Brook-type rearrangement of the intermediate alkoxide **639** provide carbanion **640**, which readily eliminates a (reusable) fluoride ion to give difluoroenol silyl ether **638**.

Prakash et al. reported TBAF-catalyzed 1,2-fluoride elimination of 1,2-bis(trimethylsilyl)-1,1,2,2-tetrafluoroethane (**641**) acting as a convenient, in situ source of  $CF_2=CF^-$  (Scheme 180).<sup>302</sup> In the presence of 0.1 equiv of TBAF, the reactions of **641** with aldehydes and ketones give 2,3,3-trifluoroallylic alcohols **643** in good yields. A catalytic amount of TBAF is needed to convert **641** into (trifluorovinyl)trimethylsilane **645** via  $\beta$ -fluoride elimination and to initiate the reaction of vinylsilane **645** with carbonyl compounds **642**.

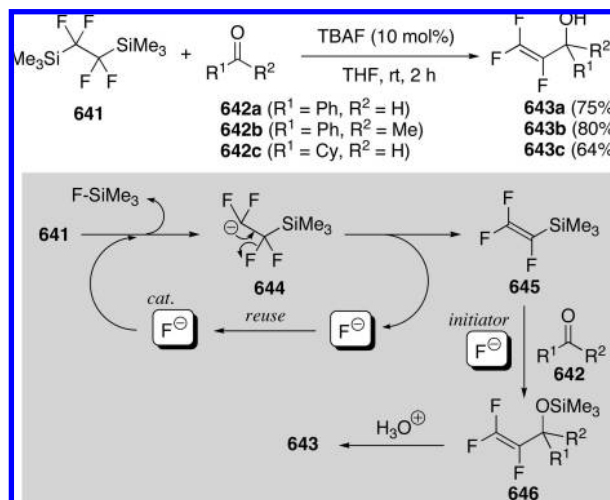
Scheme 178



Scheme 179



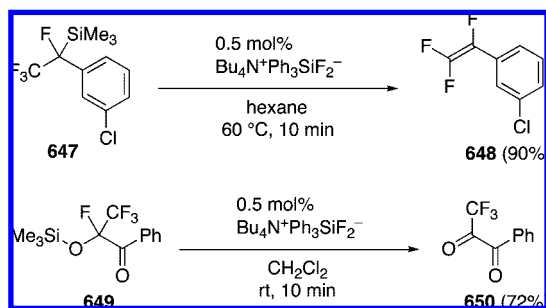
Scheme 180



In 2007, Nakamura and Uneyama reported the fluoride-ion-catalyzed 1,2-desilylative defluorination toward the synthesis of various 1-substituted 2,2-difluorostyrenes (Scheme 181).<sup>303</sup> When 1-(3'-chlorophenyl)-1-trimethylsilyl-1,2,2,2-tetrafluoroethane (**647**) is treated with a catalytic amount of [Bu<sub>4</sub>N][Ph<sub>3</sub>SiF<sub>2</sub>] (TBAT) in hexane at 60 °C for 10 min,

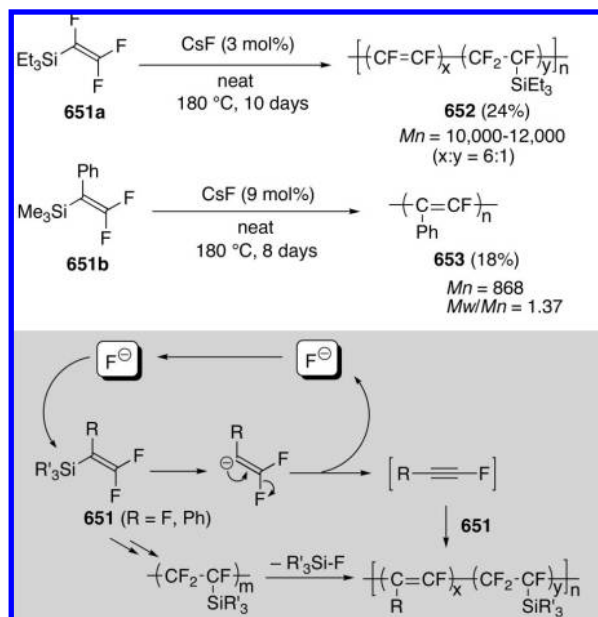
1,2-desilylative defluorination proceeds cleanly to afford 3'-chlorophenyl-1,2,2-trifluorostyrene (**648**) in excellent yield. In 2008, they demonstrated a good example of fluoride TBAT-catalyzed 1,2-desilylative defluorination from tetrafluoro-2-silyloxypropiophenone **649** leading to 1,2-diketone **650**.<sup>304</sup>

Scheme 181



CsF-catalyzed  $\beta$ -fluoride elimination of  $\beta,\beta$ -difluorovinylsilanes (**651**) is applicable to the generation of reactive fluoroalkynes, which readily undergo polymerization to yield the corresponding fluoropolyacetylenes (Scheme 182).<sup>305,306</sup> With exposure to a catalytic amount of CsF, defluorodesilylation of trifluorovinylsilane **651a** gives semiconductor polymer **652**, which shows conductivity of  $10^{-9}$  to  $10^{-10} \Omega^{-1} \text{cm}^{-1}$ .<sup>305</sup>

Scheme 182

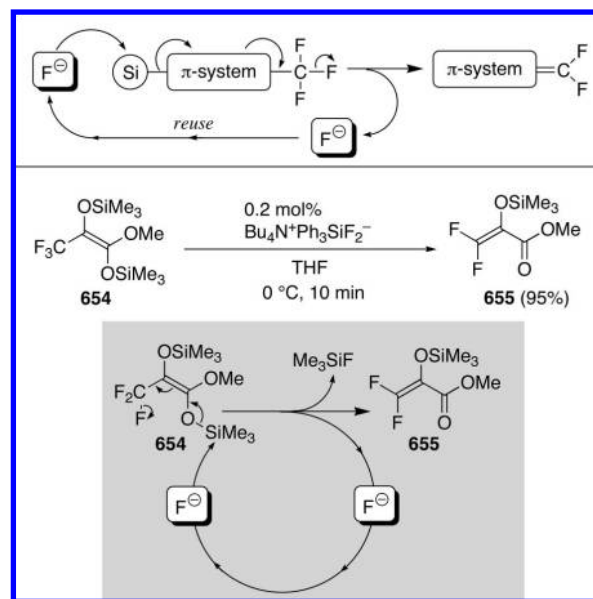


In the desilylative–defluorination reaction system, a catalytic amount of fluoride ion catalyzes at first desilylation and subsequently induces defluorination from a trifluoromethyl group, leading to the formation of difluoromethylene moiety and simultaneous regeneration of reusable fluoride ion.

Fluoride-catalyzed desilylative–defluorination reaction including conjugative fluoride elimination through  $\pi$ -electron system is a potential and suitable methodology for selective organic synthesis (Scheme 183), especially in the cases of the products possessing base- and/or nucleophile-sensitive functionalities that partake in further reactions in the presence of a large amount of base and/or nucleophile. As a good

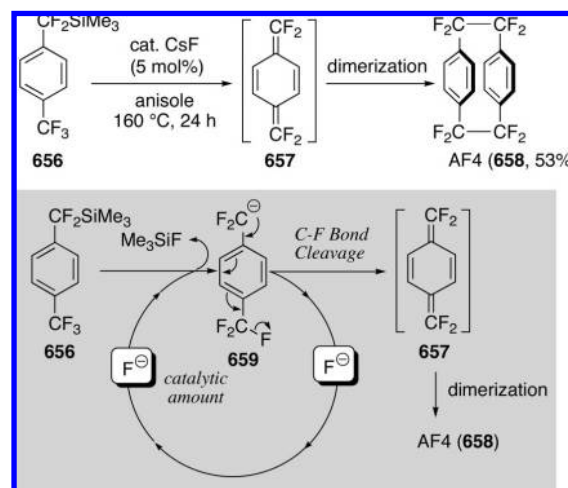
example of the basis of the desilylative–defluorination concept, a catalytic amount of TBAT (0.2 mol %) promoted 1,4-conjugative elimination of ketene silyl acetal of methyl *O*-trimethylsilyltrifluorolactate (**654**), affording methyl  $\beta,\beta$ -difluoro- $\alpha$ -trimethylsilyloxyacrylate (**655**).<sup>307</sup>

Scheme 183



In 2001, Amii and Uneyama explored the catalytic version of fluoride-induced 1,6-elimination to generate *p*-xylylene intermediate **657** (Scheme 184).<sup>308</sup> Heating the anisole solution of **656** containing a catalytic amount (0.05 equiv) of CsF at 160 °C provides octafluoro[2.2]paracyclophane (AF4, **658**) in 53% isolated yield, which is an excellent precursor of the insulating parylene polymer.<sup>309</sup> A higher reaction temperature is considered to be essential to the elimination of a fluoride ion, probably because the generation of tetrafluoroquinodimethane (**657**) is a thermodynamically unfavorable process to forfeit the stabilization energy of the aromatic 6 $\pi$ -system.

Scheme 184



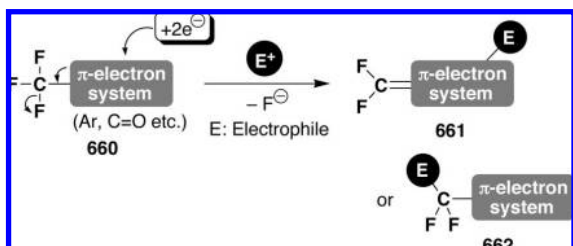
#### 4.1.3. Electroreductive C–F Bond Activation

In the previous section, we have introduced  $S_N2'$  reactions of organic fluorides. Allegorically, an electron is regarded as the smallest nucleophile. In general, C–F bonds in



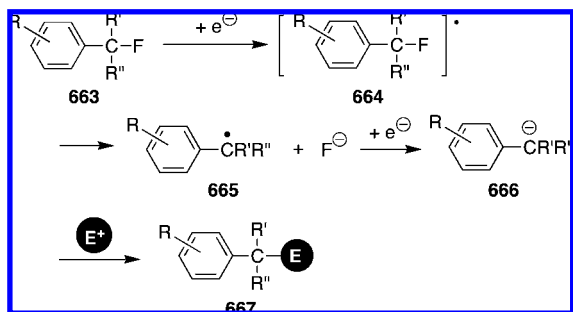
organofluorine compounds are inert. Under electroreductive conditions, however, the bond breaking does rather easily occur when a CF<sub>3</sub> group is attached to the  $\pi$ -electron system such as aryl and carbonyl groups, since electron acceptance into the  $\pi$ -system in **660** and subsequent extrusion of a fluoride ion may make large contributions to the net transformation (Scheme 185).

Scheme 185

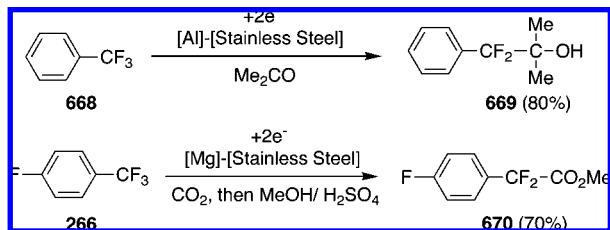


The reactivity and mechanism on electroreductive cleavage of C–F bonds in fluoromethylarenes (benzylic fluorides) **663** have been investigated by several groups (Scheme 186).<sup>310</sup> Two-electron reduction of fluoromethylarenes generates a fluoride ion and the corresponding carbanion intermediates, which are trapped by electrophiles. The electroreductive coupling of trifluoromethylarenes with electrophiles such as CO<sub>2</sub>, acetone, or DMF is achieved with good yields by electrolysis in an undivided cell fitted with Mg or Al sacrificial anode (Scheme 187).<sup>311</sup>

Scheme 186



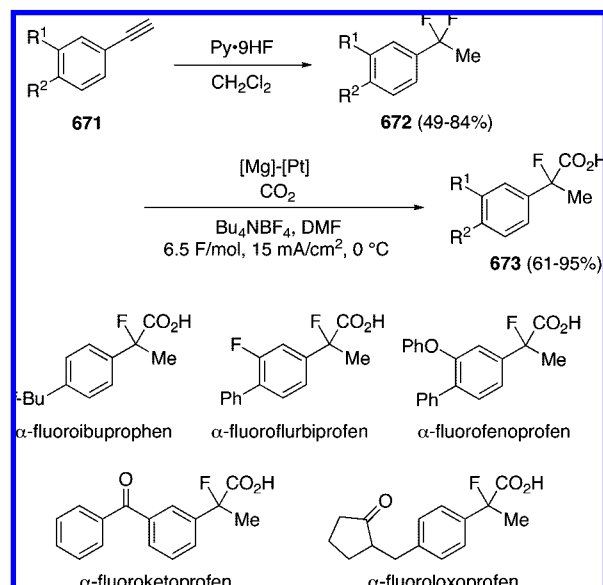
Scheme 187



In 2008, Senboku and Hara et al. reported the selective electrochemical carboxylation of  $\alpha,\alpha$ -difluoroalkyl aromatics **672**, providing the corresponding  $\alpha$ -fluorophenylacetic acids **673** in good yields (Scheme 188).<sup>312</sup> Interestingly enough, the present transformation is successfully applied to the synthesis of various  $\alpha$ -fluorinated nonsteroidal anti-inflammatory drugs (NSAIDs).

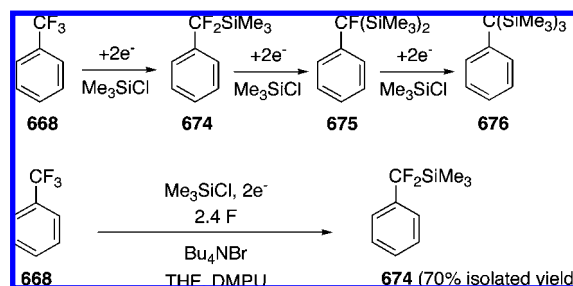
Chlorosilanes are good electrophiles for the present reductive defluorination to provide silicon-containing difluoromethylene building blocks. Defluorinative silylation of trifluoromethylbenzene (**668**) is one of the splendid methods for the preparation of PhCF<sub>2</sub>SiMe<sub>3</sub> (**674**), which acts as a difluorobenzyl carbanion synthon. The chemical metal reduc-

Scheme 188



tion methods are not available: the Me<sub>3</sub>SiCl/Li/THF system shows poor selectivity to lead to the trisilylated derivative **676** as a major product due to the close reduction potentials of **668**, **674**, and **675** (Scheme 189). The electrochemical route allows strict control of the silylation steps just by fine-tuning the charge passed. Selective monodefluorination of PhCF<sub>3</sub> (**668**) to furnish PhCF<sub>2</sub>SiMe<sub>3</sub> (**674**) is achieved by electroreduction.<sup>313</sup> Furthermore, the present protocol is applicable to a large-scale synthesis of **674** using a tubular flow cell.

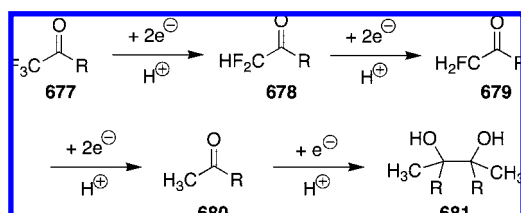
Scheme 189



Selective defluorination from readily available trifluoromethylated compounds are promising and highly efficient methods for the preparation of difluoromethylated compounds. Fluoromethylated ketones undergo electroreductive defluorination.<sup>314</sup> Stocker et al. reported electrochemical transformation of trifluoromethyl ketones **677** into methyl ketones **680** and/or pinacols **681** (Scheme 190).<sup>305</sup> In their reaction conditions, all fluorine atoms in the products are lost. Because of the small difference between the reduction potentials of CF<sub>3</sub>–, CF<sub>2</sub>H–, and CFH<sub>2</sub>–ketones (**677**–**679**), further reduction of the resultant fluoromethyl ketones takes place with low chemoselectivity, and it is very difficult to control the product distribution to provide the desired CF<sub>2</sub>H–ketones **678**.

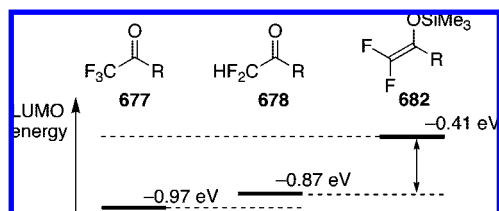
In order to avoid the overreduction and to execute selective monofluorination, one clever approach is the transformation of ketones **677** into difluoroenol silyl ethers **682** (silyl enolates of difluoroketones **678**), whose reduction potentials are much higher than those of the ketones **677** and/or **678**. As shown in Scheme 191, the LUMO energies of ketones

Scheme 190

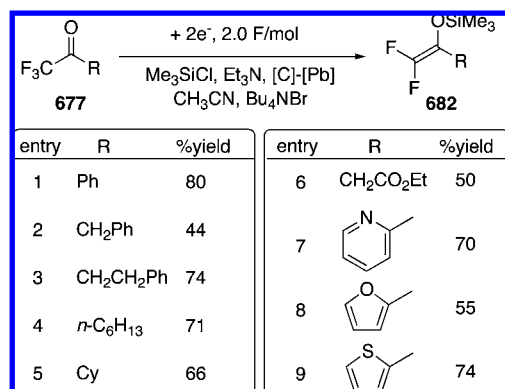


**677** and **678** and enol ethers **682** are  $-0.97$ ,  $-0.87$ ,  $-0.41$  eV, respectively.

Scheme 191

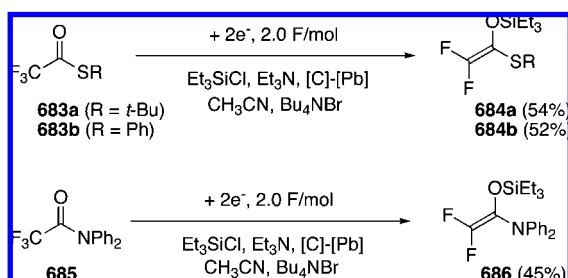


Electrochemical reductive defluorination of trifluoromethyl ketones **677** in the presence of  $\text{Me}_3\text{SiCl}$  affords the corresponding difluoroenol silyl ethers **682**. Combination of a lead cathode and  $\text{Bu}_4\text{NBr}$  as a supporting electrolyte gives a high yield of enol ethers **682**. A current density of  $\sim 10$  mA/cm<sup>2</sup> or less is effective for the selective monodefluorination of **677** (Scheme 192).<sup>316</sup>

Scheme 192. Electrochemical Synthesis of Difluoroenol Silyl Ethers **682**

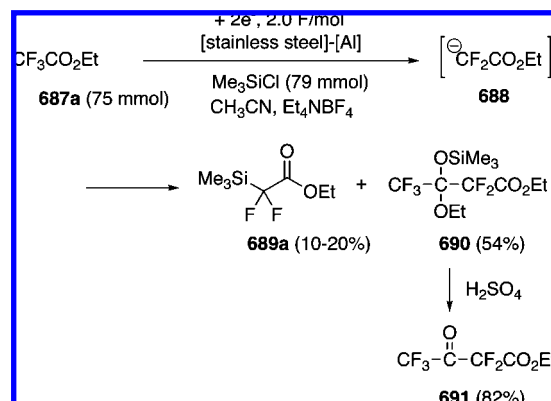
The similar electrolysis conditions are applicable for the preparation of ketene silyl (*O,S*- and *O,N*-) acetals.<sup>317</sup> As demonstrated in Scheme 193, the electrochemical reactions of thioesters **683** ( $\text{X} = \text{SR}$ ) and amide **685** ( $\text{X} = \text{NPh}_2$ ) afford the corresponding difluoro ketene silyl acetals **684** and **686** in good yields.

Scheme 193



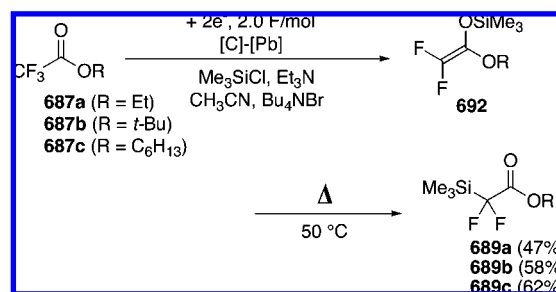
Reductive defluorination of trifluoroacetates is a very useful reaction because of the generation of difluoroacetate enolates. In 1999, Stepanov et al. reported the electroreduction of **687a** ( $\text{R} = \text{Et}$ ) to form a mixture of *C*-silyl difluoroacetate **689a** and acetal of ethyl pentafluoroacetoacetate (**691**, the Claisen condensation product) by the use of low equivalents of  $\text{Me}_3\text{SiCl}$  (Scheme 194).<sup>318</sup>

Scheme 194



Independently, from the viewpoint of the preparation of difluoroacetate building blocks, it was found that the use of a large excess of  $\text{Me}_3\text{SiCl}$  is quite effective to overcome self-condensation reactions. Furthermore, thermal silyl migration from oxygen to carbon in ketene silyl acetals **692** at  $50^\circ\text{C}$  affords *C*-silyl difluoroacetates **689** as a sole product (Scheme 195).<sup>319</sup>

Scheme 195



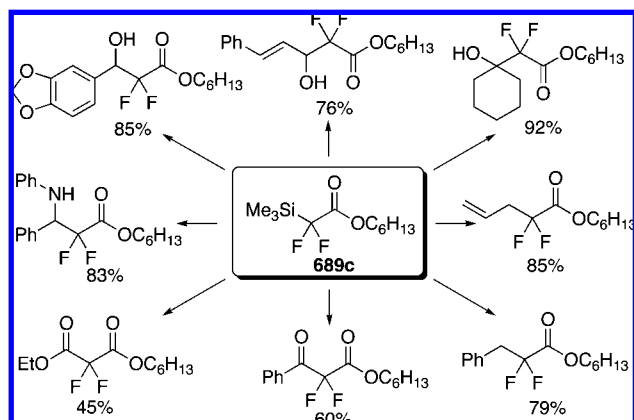
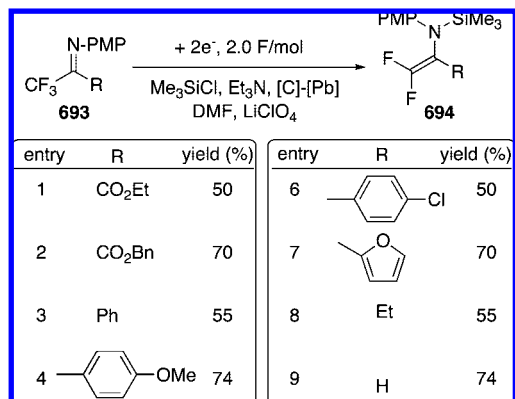
*C*-Silylated difluoroacetates **689** are versatile building blocks because they are readily available, distillable, stable enough to be stored for a long time, and highly reactive in the presence of a fluoride ion. The acetate **689c** is subjected to TBAF-promoted C–C bond formation with electrophiles such as aldehydes, ketones, acyl halides, imine, and alkyl halides, leading to a variety of difluorinated products in good yields (Scheme 196).<sup>317</sup>

The electroreductive protocol works well for selective monodefluorination of trifluoromethyl imines **693** to give the corresponding difluoroenamines **694** (Scheme 197).<sup>320</sup> In addition, *N*-silyl enamines **694** fulfill several important functions as difluoromethylated synthetic blocks.

## 4.2. Low-Valent Metal-Promoted Reductive C–F Bond Cleavage

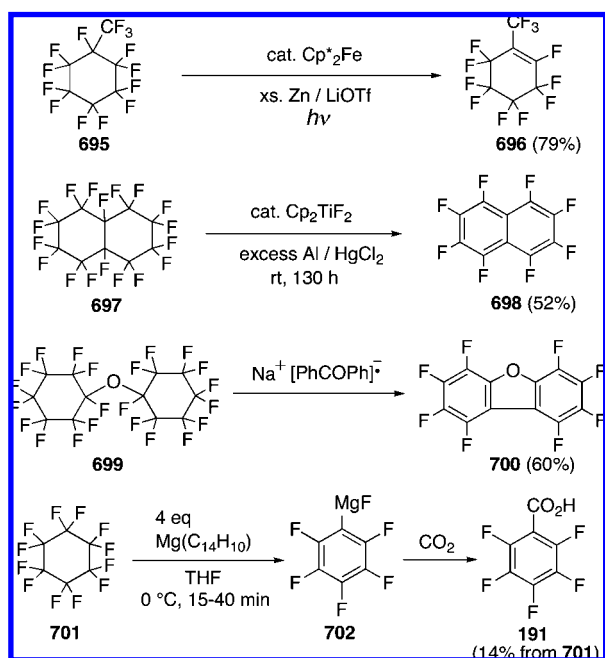
Generally, a C–F bond is the most inert and resistant to oxidative degradation. On the contrary, a C–F bond can be readily cleaved under the strong reducing conditions. There have been several reports on reductive defluorination of

Scheme 196

Scheme 197. Electroreductive Defluorination of Trifluoromethyl Imines **693**

perfluoroalkanes by using low-valent metals (reducing agents) or a combination of a catalytic amount of transition metal complexes and stoichiometric low-valent metals (Scheme 198).<sup>321–324</sup>

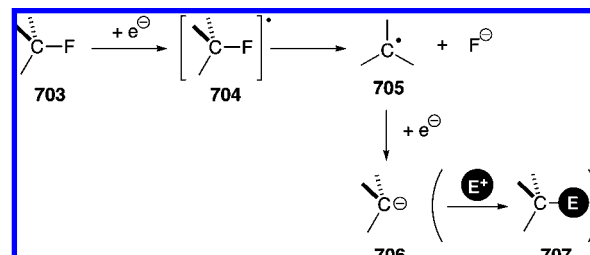
Scheme 198



The reductive cleavage of C–F bonds using low-valent metals can be explained by assuming the pathway pictured

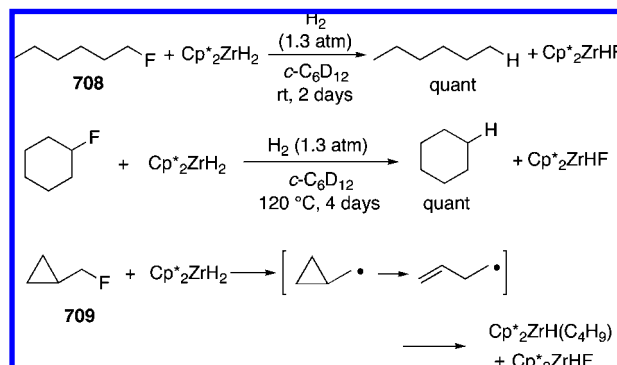
in Scheme 199. Initially, one-electron transfer to the alkyl fluorides **703** gives the radical anion intermediates **704**, which undergo decomposition to the radicals **705** and a fluoride anion. Next, further one-electron reduction of the radical intermediates **705** provides the corresponding anion species **706**.

Scheme 199



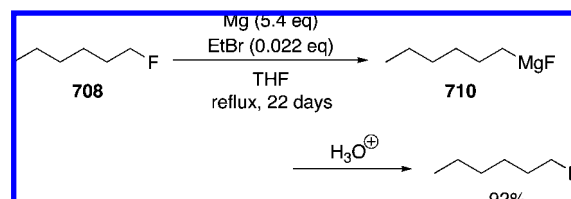
Jones et al. reported the first example of aliphatic  $\text{sp}^3$ -C–F bond activation by the use of the zirconium-complex (Scheme 200).<sup>325</sup> The reaction of 1-fluorohexane (**708**) with  $\text{Cp}^*_2\text{ZrH}_2$  at ambient temperature for 2 days produces hexane and  $\text{Cp}^*_2\text{ZrHF}$  in quantitative yields. Also, fluorocyclohexane undergoes hydrodefluorination at  $120^\circ\text{C}$ . The reaction of  $\text{Cp}^*_2\text{ZrH}_2$  with cyclopropylcarbonyl fluoride gives a definitive evidence for radical formation, in which the cyclopropylcarbonyl radical converts irreversibly into butenyl radical to provide the butylzirconium complex.

Scheme 200



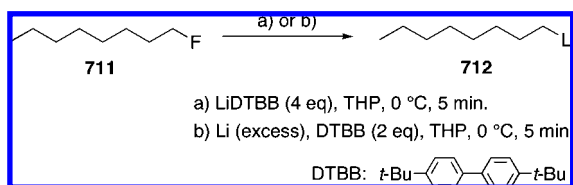
In 1971, Ashby et al. reported the first example of high yield preparation of alkylmagnesium fluorides by the direct reactions of alkyl fluorides and metallic magnesium (Scheme 201).<sup>326</sup> In the presence of a catalytic amount of ethyl bromide or iodine, the reactions proceed in ethereal solvents such as THF and 1,2-dimethoxyethane (DME) at reflux temperature.

Scheme 201



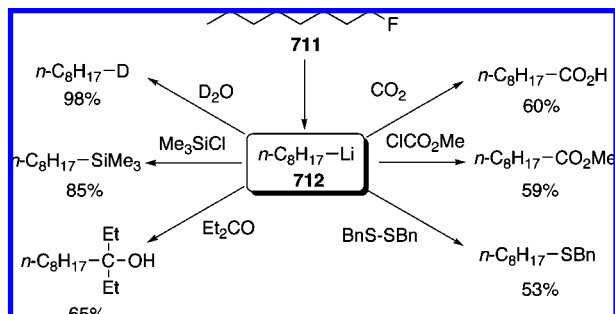
Yus et al. have systematically investigated arene-catalyzed lithiation of allylic, benzylic, and aromatic fluorides under mild conditions (Scheme 202).<sup>90a,327</sup> Primary aliphatic fluorides undergo fluorine–lithium exchange to form aliphatic organolithiums. The reaction of 1-fluorooctane (**711**) with

Scheme 202



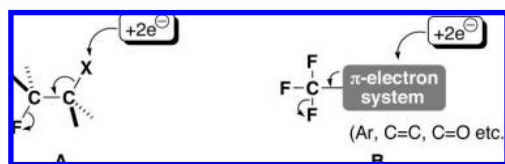
an excess amount of lithium powder (4–10 equiv) and 4,4'-di-*tert*-butylbiphenyl (DTBB, 2–4 equiv) at 0 °C for 5 min furnishes 1-octyllithium (**712**), which reacts with a wide repertoire of electrophiles (Scheme 203). On the contrary, the reaction with 2-fluorooctane gives 2-lithiooctane, which readily takes a proton from the solvent, affording octane as a sole product.

Scheme 203



Next, the following two topics are described (Scheme 204): (i) reductive dehalogenation of vicinal halides (**A**) and (ii) reductive demonofluorination from fluoromethyl groups attached to  $\pi$ -electron systems (**B**).

Scheme 204



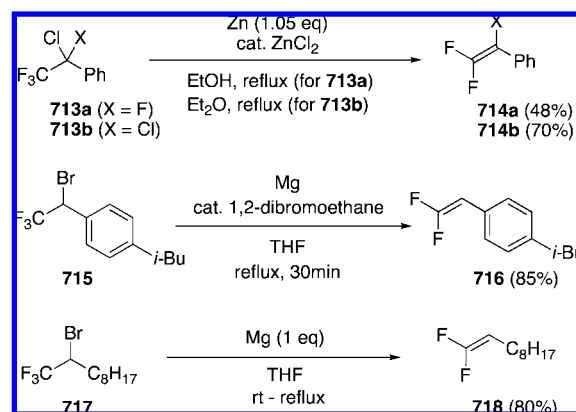
#### 4.2.1. Low-Valent Metal-Promoted Reductive Dehalodefluorination

Reductive dehalogenation of vicinal dihalides is one of the most versatile methods to prepare alkenes. Upon treatment with low-valent metals such as magnesium, zinc, and aluminum, chloro- and bromoalkanes endowed with a trifluoromethyl group at the  $\alpha$ -position partake in vicinal dehalodefluorination, resulting in the formation of *gem*-difluoroalkenes (Scheme 205).<sup>306,328–330</sup>

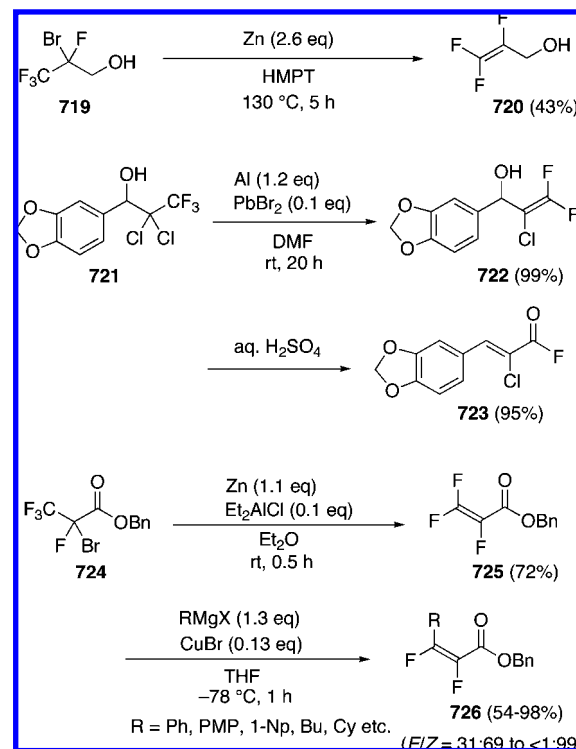
The scope of reductive  $\beta$ -elimination of vicinal halides is broad. It is noteworthy that alcohol and ester functionalities are compatible with the present reaction conditions to provide the corresponding fluoroalkenes (Scheme 206).<sup>331–333</sup>

Shi et al. reported Zn-promoted dechlorodefluorination of *O*,*Cl*-acetals of trifluoropyruvate to afford difluoroenol ethers, which are important precursors of useful fluorinated compounds (Scheme 207).<sup>334</sup> Claisen rearrangement of **728** leads to the formation of *C*-allylated ketoester **729**, and the subsequent transformations of the common precursor **729** provides racemic  $\beta,\beta$ -difluoroglutamic acid and  $\beta,\beta$ -difluoroproline (**730**).

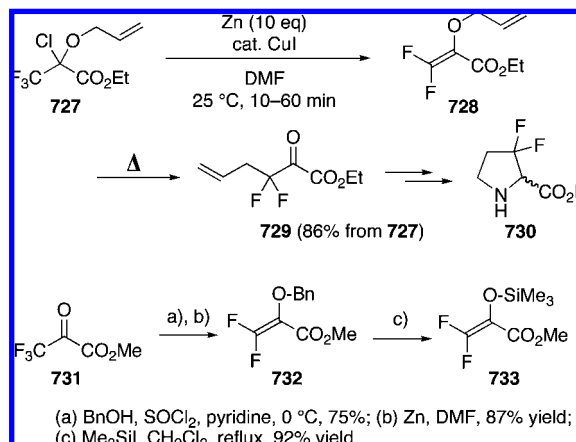
Scheme 205



Scheme 206



Scheme 207

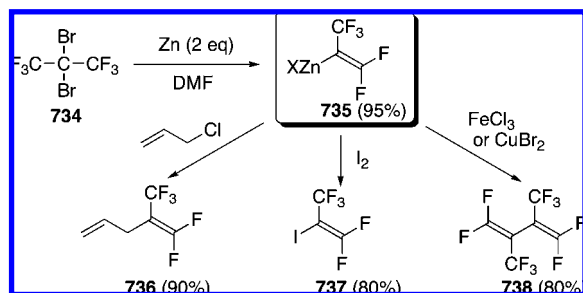


Reductive manipulations of  $\text{CF}_3\text{CX}_2$  moieties allow the formation of *gem*-difluorovinyl organometallic reagents. Treatment of 2,2-dibromohexafluoropropane (**734**) with 2 equiv of metallic zinc in DMF gives  $\text{CF}_3(\text{ZnX})\text{C}=\text{CF}_2$  (**735**),



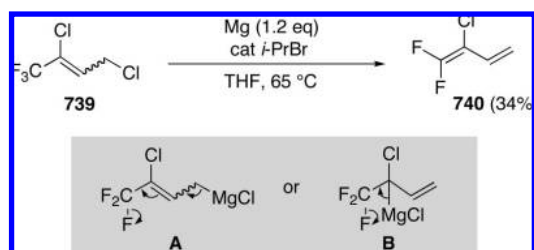
which participates in allylation, acylation, halogenation, and oxidative dimerization to afford a variety of  $\text{CF}_3(\text{R})\text{C}=\text{CF}_2$  compounds (Scheme 208).<sup>335</sup> In a competition experiment, Zn reacts faster with the intermediate  $\text{CF}_3\text{BrC}=\text{CF}_2$  than with  $\text{CF}_3\text{CBr}_2\text{CF}_3$  (**734**).

Scheme 208



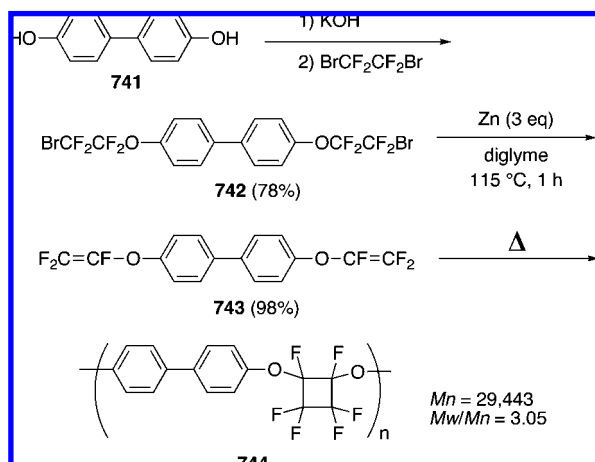
The reaction of 1,3-dichloro-4,4-trifluorobut-2-ene (**739**) with magnesium gives  $\text{CF}_2=\text{C}(\text{Cl})\text{CH}=\text{CH}_2$  (**740**) in 34% yield (Scheme 209).<sup>336</sup> The reaction would proceed via 1,4-elimination of allylic magnesium chloride **A** or 1,2-elimination of **B**, which is generated by 1,3-Mg migration of **A** due to the anion-stabilizing effect of the trifluoromethyl group.

Scheme 209



Reductive dehalodefluorination is applicable to the preparation of trifluorovinyl ethers (TFVE). The reactions of 2-bromotetrafluoroethyl ethers with metallic zinc lead to the formation of trifluorovinyl ethers in high yields (Scheme 210).<sup>337</sup> Multifunctional aromatic TFVE monomers undergo thermal [2 + 2]-cycloaddition polymerization to provide perfluorocyclobutane (PFCB) polymers, which have recently attracted enormous attention as versatile fluoropolymer materials for photonic applications such as optical fibers, polymer waveguides, and nonlinear optics; for electronic applications such as liquid crystalline polymers, micropho-

Scheme 210

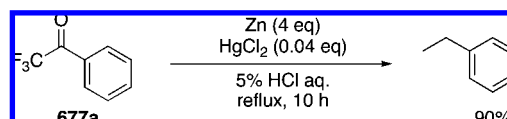


tonics, hole transporting layers in light-emitting diodes, and interlayer dielectrics; and for coating applications because of their low dielectric constants, high thermal and mechanical stability, facility of processing, and optical transparency.<sup>338</sup>

#### 4.2.2. Low-Valent Metal-Promoted Reductive Defluorination from Trifluoromethyl Group Attached to $\pi$ -Electron System

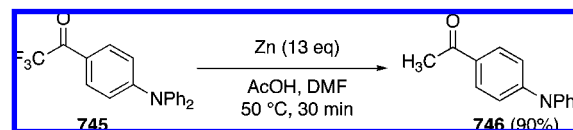
Chemical methods for reductive defluorination of a trifluoromethyl group (next to  $\pi$ -electron system) have been the subject of some of the earliest investigations of C–F bond cleavage. Under Clemmensen reduction conditions (Zn in hydrochloric acid), trifluoroacetophenone (**677a**) undergoes not only carbonyl reduction but also reductive substitution of all fluorine atoms of the trifluoromethyl group, leading to ethylbenzene in 90% yield (Scheme 211).<sup>339</sup>

Scheme 211



In 1996, Moskalev et al. succeeded in the exhaustive hydrodefluorination of aryl trifluoromethyl ketones under mild reaction conditions. With exposure to metallic Zn and acetic acid in DMF, aryl trifluoromethyl ketone **745** is converted into the corresponding (nonfluorinated) methyl ketone **746** in 90% yield (Scheme 212).<sup>340</sup>

Scheme 212

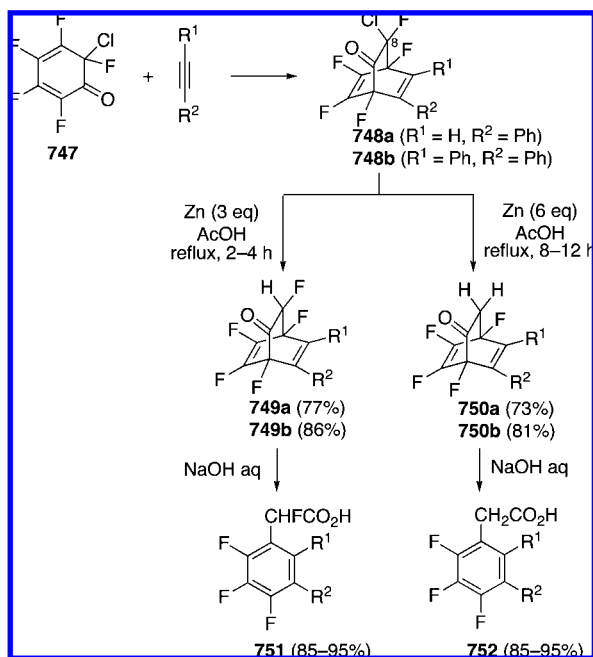


The reduction of 8-chloro-1,2,3,4,8-pentafluorobicyclo-[2.2.2]octa-2,5-dienones (**747**) with zinc in acetic acid leads to successive displacement of chlorine and fluorine atoms in position 8 by hydrogen regioselectively (Scheme 213).<sup>341</sup> Bicyclooctadienones **749** and **750** participate in ring-opening aromatization upon treatment with alkali to give the respective arylacetic acids **751** and **752** in high yields.

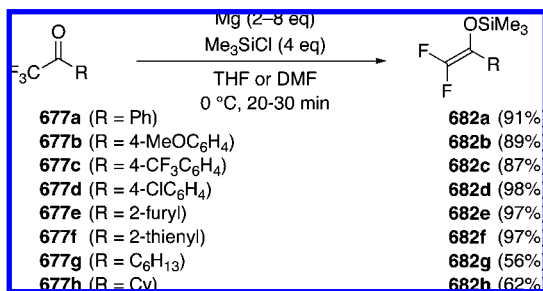
Thus, we have introduced the examples of exhaustive hydrodefluorination of fluoromethyl ketones. As mentioned before, the controlled partial defluorination of trifluoromethylated compounds is a splendid methodology from the viewpoint of synthetic organic chemistry. In the previous section, the electrochemical methods have hitherto been developed for reductive defluorination of a trifluoromethyl group, and they can be successfully applied to the preparation of difluoromethylene building blocks. In 1999, Amii and Uneyama reported that metallic magnesium, which serves as a more convenient electron source, proves useful for the C–F bond breaking process of trifluoromethyl ketones **677** to provide a practical route to 2,2-difluoroenol silyl ethers **682** (Scheme 214).<sup>242,342,343</sup>

The formation of **682** can be explained by assuming the pathway pictured in Scheme 215. Initially, the intermediate ketyl species **753** are generated in the reaction of  $\text{Mg}^0$  with ketones **677**, which are further reduced to anion species **754** by Mg. The resultant  $\beta$ -fluorinated organomagnesium species **754** readily undergo  $\beta$ -elimination to afford difluoroenol ethers **682**.

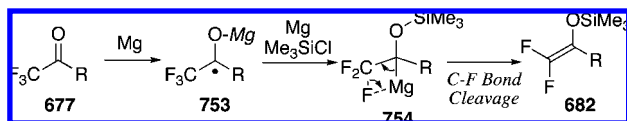
Scheme 213



Scheme 214



Scheme 215

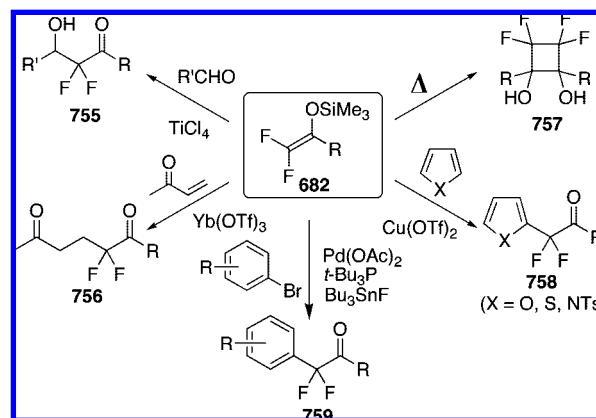


Compared to previously available methods, the present methodology has several advantages: (i) the starting trifluoromethyl ketones **677** are readily available directly from trifluoroacetates; (ii) Mg as a reducing agent is inexpensive and easy to handle and dispose; and (iii) selective formation of 2,2-difluoroenol silyl ethers **682** is achieved in a short reaction time (only 20–30 min) under mild reaction conditions. In light of operational simplicity and high efficiency, Mg(0)-promoted selective defluorination of **677** and the subsequent transformation of **682** provide a route reliable for preparing a diverse group of difluoro compounds (Scheme 216).<sup>301,344,347</sup>

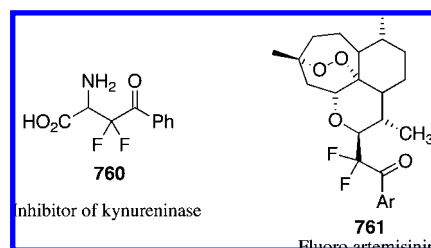
As an application of difluoroenol silyl ethers **682**, Lewis acid-promoted C–C bond-forming reaction gives the inhibitor of kynureninase **760** (Scheme 217).<sup>348</sup> Bonnet-Delpon and Bégué et al. reported fluoro artemisinins **761** by means of Lewis acid-catalyzed reactions of dihydroartemisinin acetate with difluoroenoxy silanes **682**,<sup>349</sup> which are prepared by Mg-promoted defluorination route.

Electrophilic halogenation of 2,2-difluoroenol silanes **682** is highly useful for the preparation of  $\alpha$ -halodifluoromethyl ketones. Prakash and Olah et al. presented the reaction of

Scheme 216

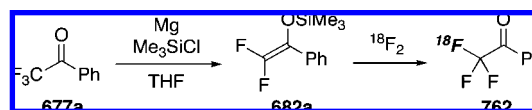


Scheme 217

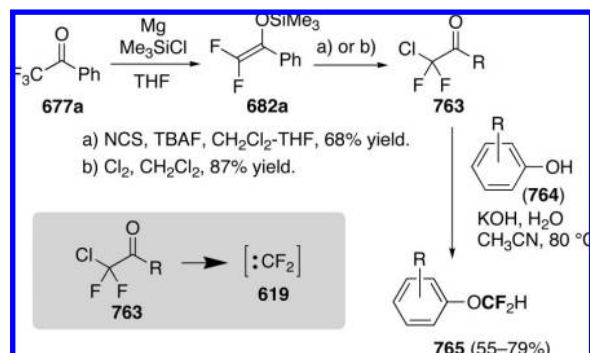


difluoro silyl enol ethers **682** with halogens at low temperature to produce a high yield of  $\alpha$ -halodifluoromethyl ketones and [ $^{18}F$ ]-labeled trifluoromethyl ketone **762** (Scheme 218).<sup>350</sup> In 2006, Hu et al. developed a non-ODS-based (ODS = ozone-depleting substance) preparation of chlorodifluoroacetophenone (**763**) via the Mg-mediated defluorination route and the use of **682a** as a novel and convenient difluorocarbene source for phenols **764**, providing aryl difluoromethyl ethers **765** in good yields (Scheme 219).<sup>351</sup>

Scheme 218



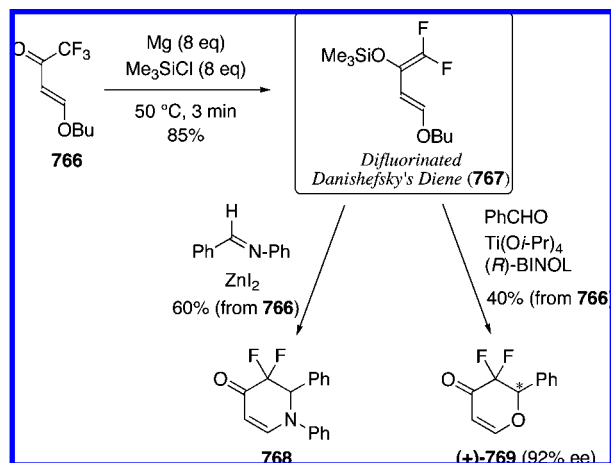
Scheme 219



To demonstrate further synthetic utility of our C–F bond cleavage reactions, we developed 1-butoxy-4,4-difluoro-3-(trimethylsiloxy)-1,3-butadiene **767**, a fluorinated analogue of Danishefsky's diene, acting as one of the most fascinating  $C_4$  building blocks.<sup>352</sup> The process shown in Scheme 220 provides access to Danishefsky's difluoro diene **767** in a simple and efficient fashion. The subsequent hetero Diels–Alder reactions of **767** give fluorinated six-membered heterocycles.

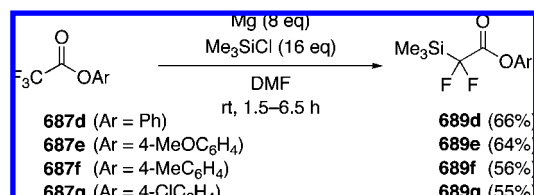
The reactions of diene **767** with aldehydes and aldimines in the presence of Lewis acid ( $\text{ZnBr}_2$  or  $\text{ZnI}_2$ ) yield the fluorinated dihydropyrones and difluoro dihydropyridones, respectively. Furthermore, the enantioselective heteroDiels–Alder reaction with benzaldehyde affords corresponding dihydropyrone (+)-**769** in 92% ee in the presence of chiral titanium(IV)–BINOL system.

Scheme 220



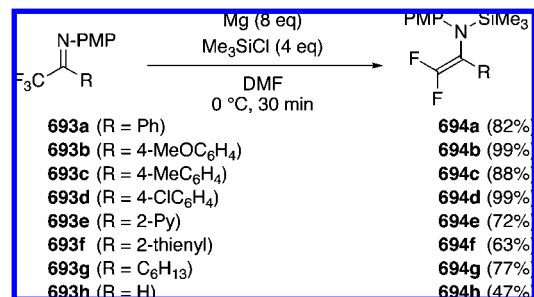
A magnesium(0)– $\text{Me}_3\text{SiCl}$  system is also effective for the selective defluorination reactions of trifluoroacetates, trifluoromethyl imines, and aromatics. Aryl trifluoroacetates (**687d–g**) are suitable substrates for Mg-promoted C–F bond cleavage reactions, to provide  $\alpha$ -silyldifluoroacetates **689d–g** in 55–66% isolated yields (Scheme 221).<sup>353</sup> In these reactions, the initial products must be the *O*-silylated compounds (difluoroketene silyl acetals), which then rearrange perfectly to *C*-silylated difluoroacetates **689** under the reaction conditions.

Scheme 221



The present protocol is also applicable for the selective defluorination of trifluoromethyl imines **693**, to yield the corresponding *N*-silylated difluoroenamines **694** (Scheme 222).<sup>354</sup> Notably, the Cl–arene functionality in **693d** is perfectly compatible under the present reaction conditions.

Scheme 222

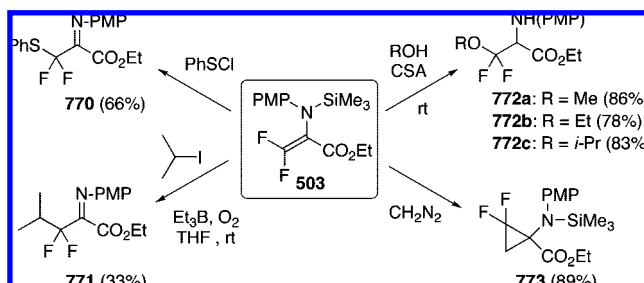


Trifluoromethyl iminoester **613a** is subjected to reductive defluorination upon treatment with metallic magnesium and trimethylsilyl chloride, leading to enaminoester **503** (Scheme 223).<sup>354</sup> Aminodifluoroacrylate **503** is a very interesting compound possessing both *N*-silyl-difluoroenamine and difluoroacrylate moieties. Because of the unique structure, enamine **503** is a useful precursor to a wide repertoire of difluorinated  $\alpha$ -amino acids, since it can react with not only electrophiles but also nucleophiles and radical species at the  $\beta$ -position, regioselectively (Scheme 224). Electrophilic introduction of a thiophenyl group is accomplished by the exposure of **503** to the action of phenylsulfenyl chloride, affording difluorinated cysteine derivative **770**.<sup>354</sup> Performing the reaction of **503** with isopropyl iodide under radical conditions gives difluorinated leucine derivative **771** without accompanying defluorination.<sup>320</sup> On the other hand, the difluoromethylene carbon of **503** is highly reactive even to a weak nucleophile like alcohols.<sup>354</sup> Thus, regioselective nucleophilic addition reactions of diverse alcohols to **503** proceed smoothly in the presence of 10-camphorsulfonic acid (CSA) to provide the corresponding 3,3-difluoroserine derivatives **772** in good yields. Moreover, nucleophilic attack of diazomethane to difluoroenamine **503** produces 1-amino-2,2-difluorocyclopropane-1-carboxylate **773** in 89% yield.

Scheme 223



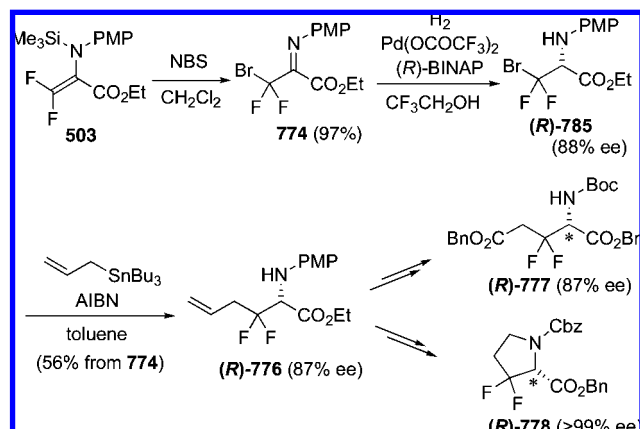
Scheme 224



More interesting and important is the asymmetric synthesis of difluorinated  $\alpha$ -amino acid derivatives (Scheme 225). Enaminoester **503** is treated with *N*-bromosuccinimide (NBS) to provide the corresponding bromodifluoromethyl iminoester **774** in excellent yield. When iminoester **774** is subjected to hydrogen pressure in the presence of a small amount of  $\text{Pd}(\text{OCOCF}_3)_2$  and (*R*)-BINAP in 2,2,2-trifluoroethanol (TFE),<sup>355</sup> the catalytic asymmetric hydrogenation of **774** proceeds smoothly at room temperature to yield aminoester (*R*)-**775** in 88% ee. Upon treatment with allyltributyltin and a catalytic amount of 2,2'-azobisisobutyronitrile (AIBN) as a radical initiator, (*R*)-**775** undergoes radical allylation to afford *C*-allylated aminoester (*R*)-**776**. By the use of chiral aminoester (*R*)-**776**, *N*- and *O*-protected  $\beta,\beta$ -difluoroglutamic acids (**777**) and  $\beta,\beta$ -difluoroproline (**778**) are obtained with high enantiopurity.<sup>356</sup>

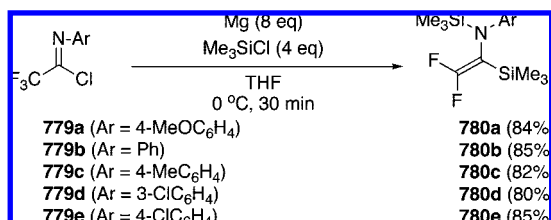
To demonstrate a synthetic virtuosity, reductive protocols using a magnesium(0)– $\text{Me}_3\text{SiCl}$  system deliver the fluorinated bifunctional building blocks **780**, which work as both an acyl anion synthon and an enolate synthon. A one-pot reaction sequence involving Mg(0)-promoted reductive C–F

Scheme 225



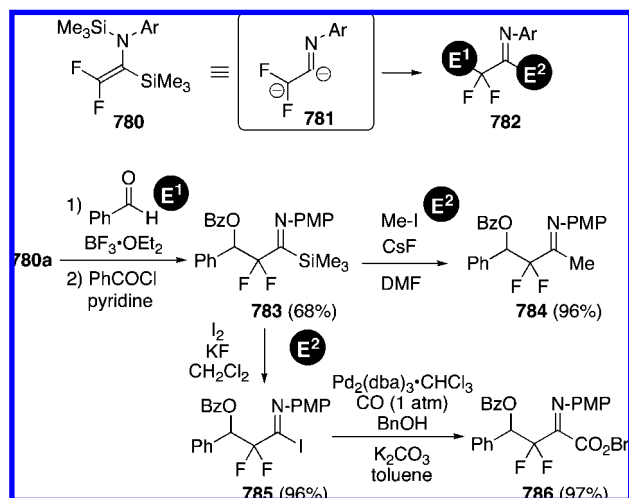
and C–Cl bond cleavage of trifluoroacetimidoyl chlorides **779** results in the selective formation of bis-silylated difluoroamines **780** (Scheme 226).<sup>357</sup> When imidoyl chlorides **779** are treated with Mg metal and chlorotrimethylsilane in THF at 0 °C for 30 min, the dehalogenative double silylation reactions proceed smoothly to afford bis-silylated difluoroamines **780** in high yields.

Scheme 226



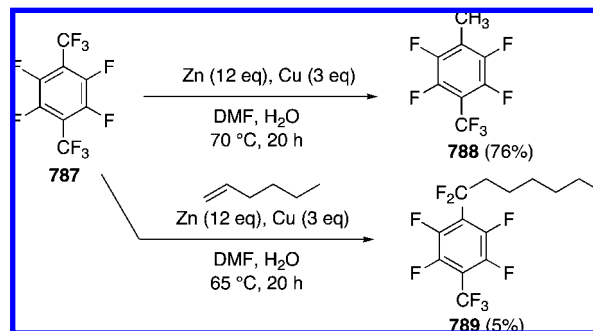
By means of the successive double dehalogenation reactions as shown above, the resultant bis-silylated difluoroamines **780** are very promising bifunctional synthetic blocks, which have not only *N*-silylenamine skeletons but also  $\alpha$ -aminovinylsilane skeletons. Subsequent transformations of the bis(silyl)enamines **780** with two kinds of electrophiles give a variety of difluorinated imines **782**. In Scheme 227, an application of **780** is represented by chemoselective sequential transformations with different electrophiles.

Scheme 227



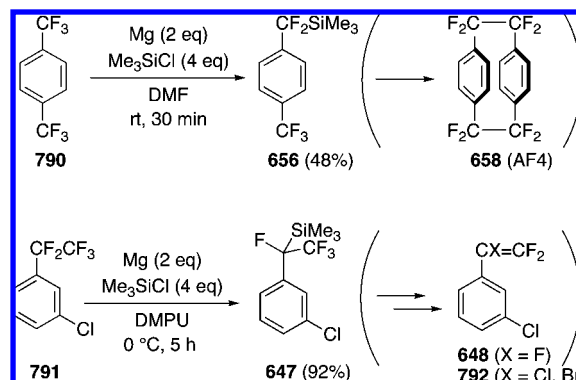
Next, we show the examples of reductive defluorination of trifluoromethylated aromatics. Perfluoro-*p*-xylene undergoes hydrodefluorination at the benzylic position using the Zn–Cu–DMF–H<sub>2</sub>O system (Scheme 228).<sup>98a,c</sup> Interestingly, when the reaction is performed with exposure to an excess amount of 1-hexene, the formation of adduct **789** is observed. The reaction would involve perfluoro-(4-methylphenyl)methyl radical, which is generated by one-electron reduction of perfluoro-*p*-xylene and the subsequent decomposition of the resultant anion radical intermediate.

Scheme 228



Metallic magnesium, which acts as a convenient electron source, proves useful for the C–F bond-breaking process of trifluoromethylated aromatics (Scheme 229). As a promising application for material science, the C–F bond-cleavage sequence for the synthesis of octafluoro[2.2]paracyclophane (AF4, **658**) is developed. Fluorocyclophane **658** is an excellent precursor of the insulating parylene polymer.<sup>309</sup> Mg(0)-promoted defluorinative silylation of 1,4-bis(trifluoromethyl)benzene (**790**) affords  $\alpha$ -silyl- $\alpha,\alpha,\alpha',\alpha',\alpha'$ -pentafluoroxylene (**656**) in 48% yield.<sup>308</sup> The subsequent conjugative 1,6-elimination from **656** induced by CsF provides fluorocyclophane AF4 (**658**). Furthermore, 3-chloropentafluoroethylbenzene (**791**) is subjected to the Mg-promoted defluorinative silylation to give 1-(3'-chlorophenyl)-1-trimethylsilyl-1,2,2,2-tetrafluoroethane (**647**), which is converted to *gem*-difluorostyrene derivatives **648** and **792** by fluoride ion-catalyzed 1,2-desilylative defluorination.<sup>303</sup>

Scheme 229

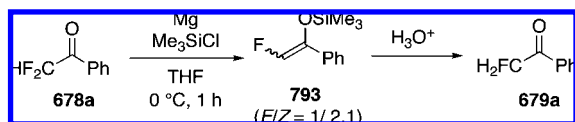


Selective defluorination from difluoromethylene compound serves as a practical synthetic route to monofluorinated compounds. In the same manner as trifluoromethyl ketones, difluoromethyl ketones undergo the selective defluorination reactions, providing the monofluorinated compounds. Prakash et al. presented a facile preparation of monofluoromethyl ketones (Scheme 230).<sup>358</sup> Metallic Mg-mediated reductive



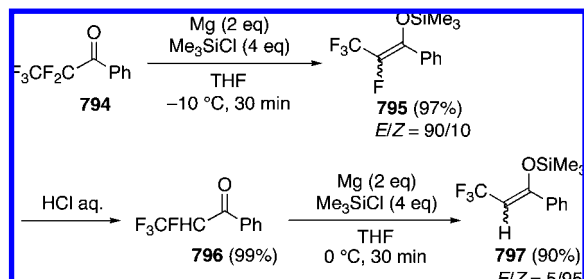
defluorination of difluoromethyl ketone **678a** readily generates monofluorinated enol silyl ether **793**, which is transformed into the respective ketone **679a** in good yield upon fluoride- or acid-assisted hydrolysis.

Scheme 230



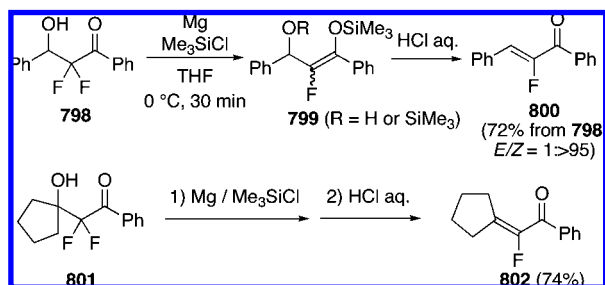
The similar successive defluorination–hydrolysis sequence of the difluoromethylene moiety in 2,2,3,3,3-pentafluoropropiophenone (**794**) to give  $\alpha$ -trifluoromethyl enol silyl ethers (Scheme 231).<sup>304</sup> The stereoselective formation of **795** and **797** can be explained by intramolecular C–F $\cdots$ Si coordinative interaction, which leads the *cis* relationship between  $\text{CF}_3$  and  $\text{OSiMe}_3$  groups in silyl enol ethers **795** and **797**.

Scheme 231



$\alpha$ -Fluoro- $\alpha,\beta$ -unsaturated carbonyl compounds are promising precursors for fluoroalkene oligopeptide isosteres, because of the interesting character of the fluoroolefin moieties. Replacement of the amide bond with a monofluorinated carbon–carbon double bond ( $\text{CF}=\text{C}$ ) has been recognized to provide conformationally fixed peptide bond isosteres.<sup>359</sup> The C–F bond cleavage protocols are used for the preparation of monofluoroenones (Scheme 232).<sup>360</sup> The action of  $\text{Mg}/\text{Me}_3\text{SiCl}$  in THF on difluoroaldol **798** causes the defluorinative silylation to afford monofluoroenol silyl ether **799**. The subsequent acid-catalyzed hydrolysis of the crude enol **799** yields  $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ketone **800**.

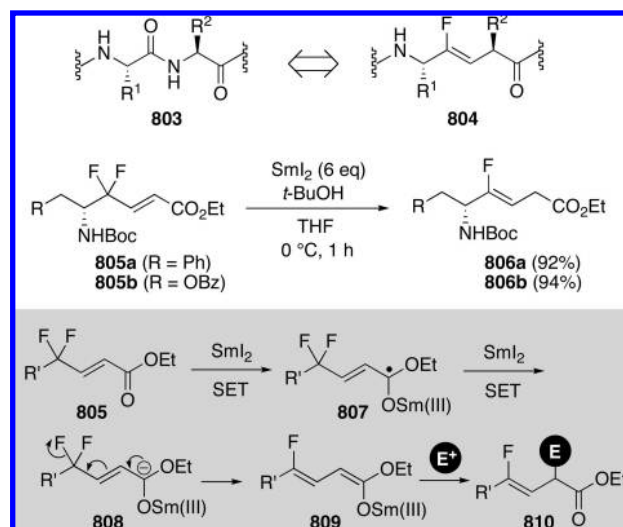
Scheme 232



Besides metallic zinc and magnesium, low-valent samarium reagents are effective for reductive C–F bond activation.  $\text{SmI}_2$ -mediated reductive defluorination of  $\gamma,\gamma$ -difluoro- $\alpha,\beta$ -enoates **805** is successfully applied to the synthesis of (*Z*)-fluoroalkene dipeptide isosteres **800** (Scheme 233).<sup>361</sup> In the presence of *t*-BuOH (a proton source), reduction of  $\gamma,\gamma$ -difluoro- $\alpha,\beta$ -enoates **805** proceeds smoothly to give monofluoroolefins in good yields. A plausible

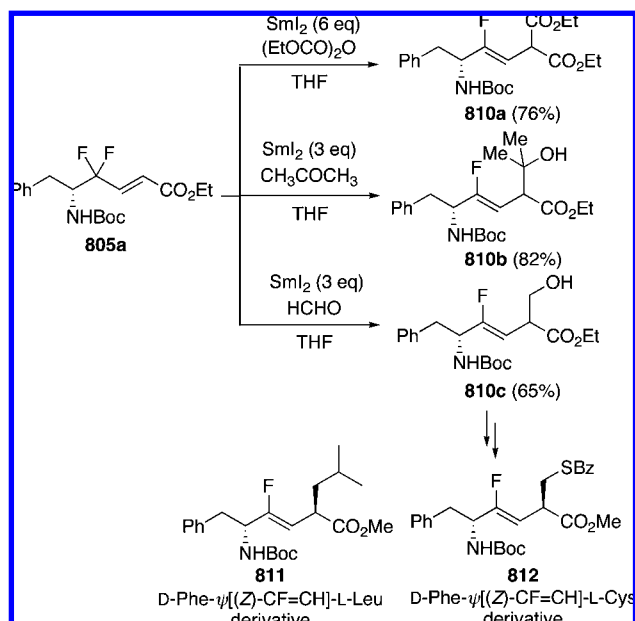
pathway involves dienolate intermediates **809** resulting from successive two-electron transfers of enoates **805**.

Scheme 233



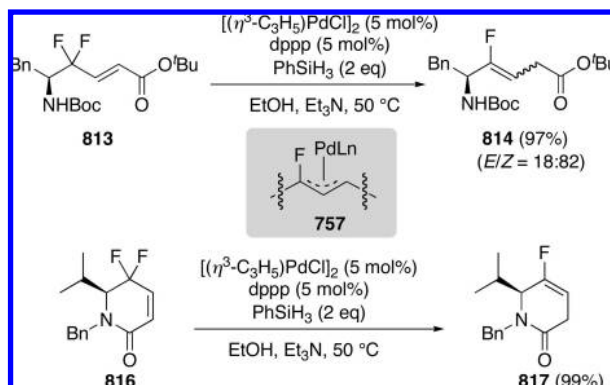
Replacement of the *t*-BuOH as a trapping agent with other electrophiles such as aldehydes or ketones provides access to various fluoroalkene isosteres through aldol reactions of Sm-dienolates with the carbonyl compounds (Scheme 234). Notably, the use of the  $\text{SmI}_2$ –HCHO reagent system with chiral enoate **810c** furnishes D-Phe- $\Psi[(Z)\text{-CF}=\text{CH}]$ -D/L-Ser isosteres, which is converted to enantiomerically pure isosteres such as D-Phe- $\Psi[(Z)\text{-CF}=\text{CH}]$ -D-Leu (**811**) and D-Phe- $\Psi[(Z)\text{-CF}=\text{CH}]$ -D-Cys (**812**) derivatives.<sup>361</sup>

Scheme 234



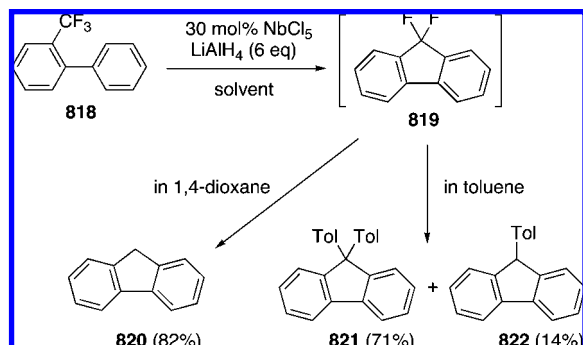
Palladium-catalyzed reductive defluorination of allylic *gem*-difluorides is also useful for the chemo- and stereoselective synthesis of fluoroalkenes (Scheme 235).<sup>362</sup> In the presence of a catalytic amount of  $[\eta^3\text{-C}_3\text{H}_5\text{PdCl}]_2$ , dppe, and  $\text{Et}_3\text{N}$ , allylic *gem*-difluorides **813** and **816** are treated with 2 equiv of  $\text{Ph}_3\text{SiH}$ , affording monofluoroalkenes **814** and **817**, respectively, in high yields.

Scheme 235



In 2006, low-valent niobium-mediated double activation of C–F/C–H bonds was reported (Scheme 236).<sup>363</sup> *o*-Phenyl trifluorotoluene **818** undergoes low-valent niobium-mediated dehydrodefluorination from both benzylic C–F bond and aromatic ortho C–H bond to form 9,9-difluorofluorene **819**, which is readily reduced under the conditions to produce parent fluorene **820**. When the reaction is carried out in toluene, **818** is converted into **821** and **822** via intermolecular dehydrodefluorination. One possible mechanism for the formation of difluorofluorene **819** is that difluorobenzyllic niobium species would be generated from **818** and the low-valent niobium. A generation of difluorobenzyllic niobium species might permit intramolecular coupling with ortho C–H bond, leading to **819**.

Scheme 236

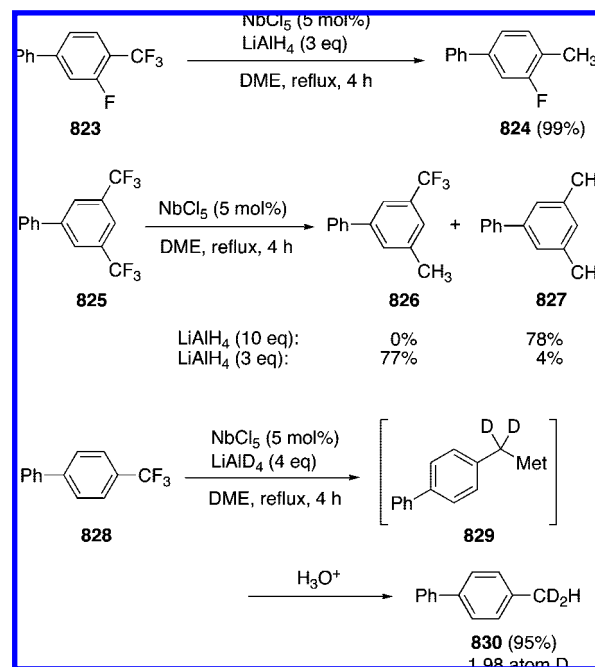


In the presence of a catalytic amount of niobium(V) chloride, trifluoromethylated aromatics are reduced with lithium aluminum hydride to provide toluene derivatives in good yields (Scheme 237). Stepwise, partial reduction of bis(trifluoromethyl)benzene derivatives proceeds by tuning of the amount of LiAlH<sub>4</sub>.<sup>364</sup> Deuterium labeling experiments suggests that the Nb-catalyzed hydrodefluorination of trifluoromethyl arenes does not proceed via a simple S<sub>N</sub>2 mechanism; two of the fluorines in **828** are replaced with deuteriums by LiAlD<sub>4</sub>, and (dideuterio)benzylic anion equivalent **829** is formed to give the product after hydrolysis.<sup>365</sup>

### 4.3. Lewis Acid- and Cation-Promoted C–F Bond Activation

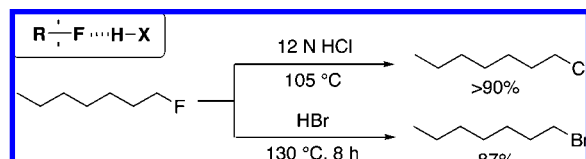
In general, alkyl fluorides are almost inert toward nucleophiles under neutral and basic reaction conditions (the order of reactivity: R–I > R–Br > R–Cl ≫ R–F). There have been a few reports on nucleophilic substitution using alkyl fluorides as substrates.<sup>366</sup> In marked contrast, the desired displacement of fluoroalkanes occurs efficiently under the

Scheme 237



acidic conditions. Upon the treatment of aqueous HX (X = Cl, Br, and I), alkyl fluorides are readily converted to the corresponding alkyl chlorides, bromides, and iodides, respectively. Probably because of the formation of the intermolecular hydrogen bond between the fluorine atom of alkyl fluorides and the protons of HX, halogen-exchange reactions proceed smoothly at 105–130 °C (Scheme 238).<sup>367,339</sup>

Scheme 238



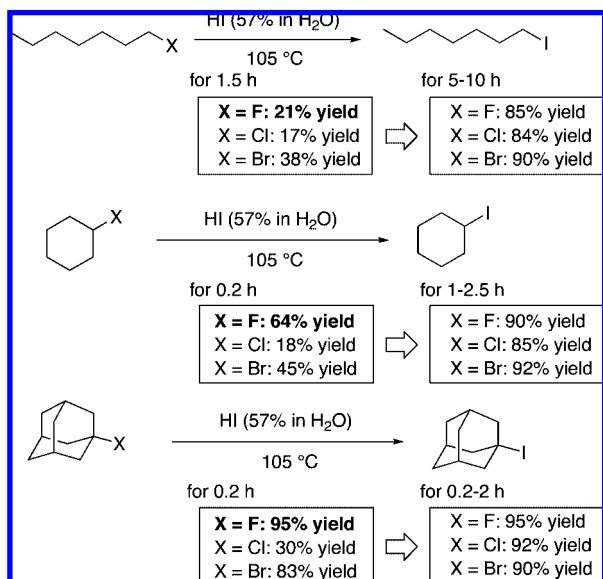
In each case, the substitution reaction of alkyl halides (X = F, Cl, Br) needs a longer reaction time. It is worth noting that the secondary or tertiary fluoride is more reactive than the corresponding chloride and bromide; when each reaction is quenched after several minutes, the conversion of the fluoride is larger than that of the corresponding chloride and bromide in aqueous media (Scheme 239).

In 1938, Henne and Newman initially attempted Friedel–Crafts reaction of benzotrifluoride with acetyl chloride; however, they discovered AlCl<sub>3</sub>-mediated halogen-exchange of benzotrifluoride to yield benzotrichloride.<sup>370</sup>

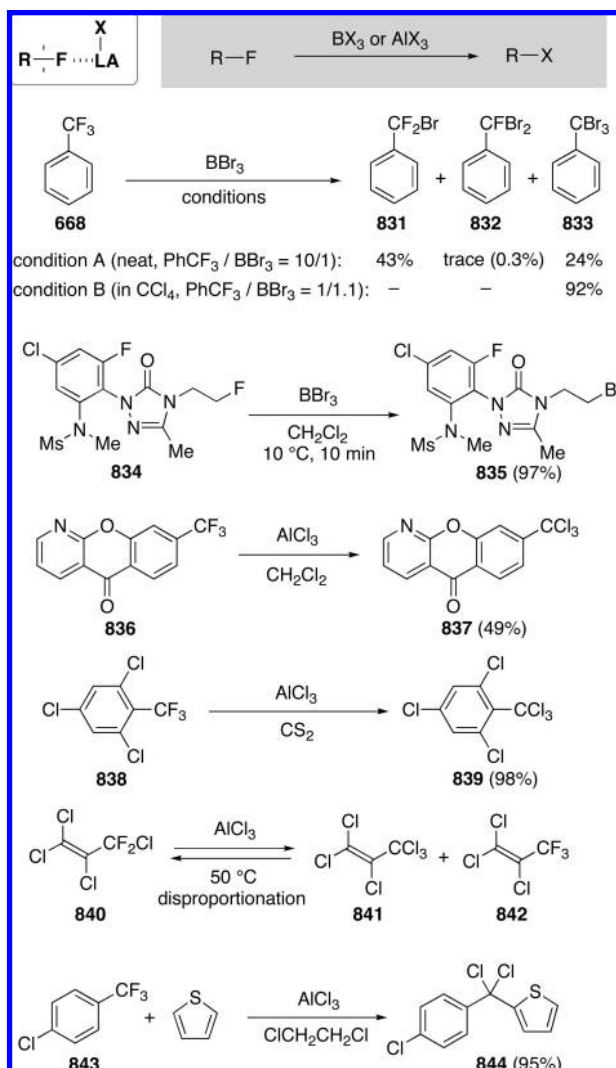
Boron and aluminum-containing Lewis acids such as BBr<sub>3</sub> and AlCl<sub>3</sub> promote the halogen-exchange reactions of a variety of fluoroalkanes to afford the corresponding halides (Scheme 240).<sup>368,371–376</sup> The halogen-exchange protocols work well for the trifluoromethyl compounds even possessing diverse functional groups.

Lewis acids are able to activate the C–F bonds of aliphatic organofluorine compounds effectively. Compared to the chlorine, bromine, and iodine atoms of haloalkanes, the fluorine atoms of alkyl fluorides can coordinate to the metal

Scheme 239



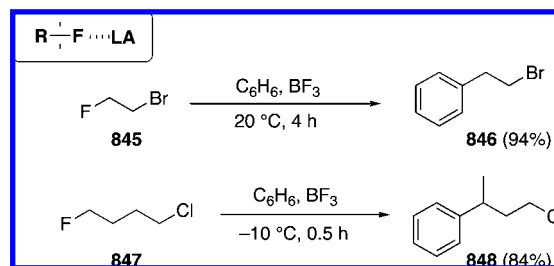
Scheme 240



centers of Lewis acids more strongly. The C–F bond cleavage reactions occur via abstraction of fluorides by Lewis acids. In 1964, Olah et al. reported Friedel–Crafts-type

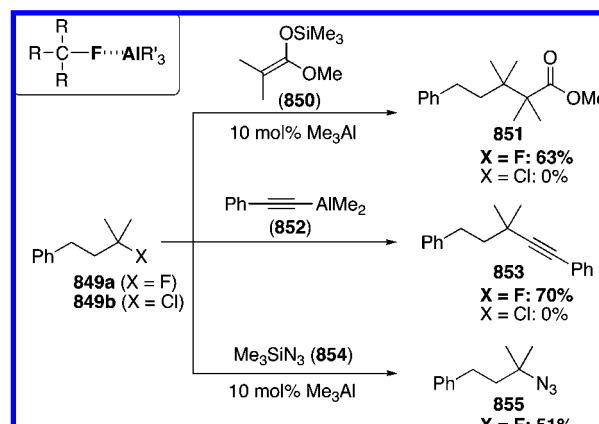
alkylation involving chemoselective transformation in which only fluorine atoms are displaced in S<sub>N</sub>1 mode (Scheme 241).<sup>377</sup>

Scheme 241



In 1997, Ooi and Maruoka et al. demonstrated a new synthetic utility of a strong Al–F interaction (Scheme 242).<sup>378</sup> *tert*-Alkyl fluorides are suitable alkylation agents for carbons of ketene silyl acetal **850**, alkynylaluminum **852**, and a nitrogen of silyl azide **854**. Notably, the reaction of chloro analogue **849b** with **850** under similar reaction conditions results in recovery of the starting chloride **849b**.

Scheme 242



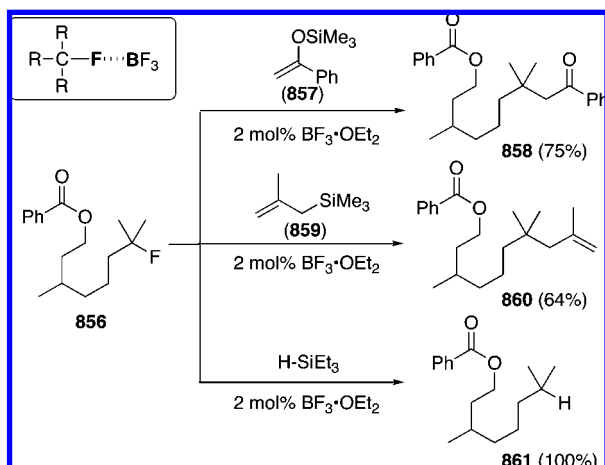
Oshima et al. reported the boron trifluoride-catalyzed transformations of alkyl fluorides with silyl enolate, allyl-silane, and hydrosilane (Scheme 243).<sup>379</sup> Alkylation reactions of silyl enolates with *tert*-alkyl or allylic fluorides proceed smoothly in the presence of a catalytic amount of boron trifluoride to afford the corresponding alkylation products in good yields. Interestingly, ether and ester functionalities are perfectly compatible under the reaction conditions.

Terao and Kambe et al. reported an interesting and general method for the conversion of sp<sup>3</sup>-C–F bonds of alkyl fluorides to sp<sup>3</sup>-C–X (X = Cl, C, H, O, S, Se, Te, and N) bonds by the use of various organoaluminum reagents endowed with Al–X bonds (Scheme 244).<sup>380</sup>

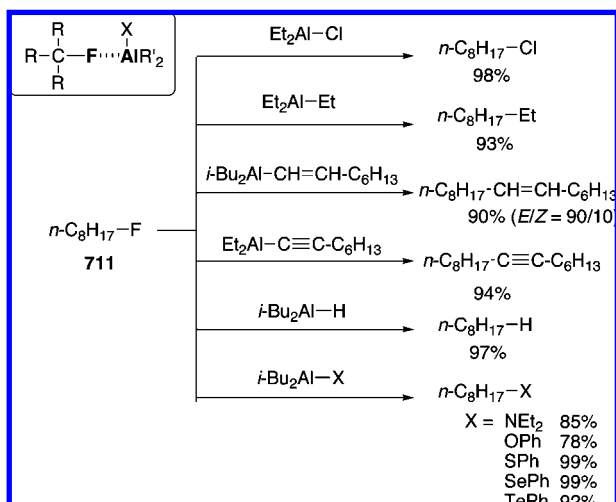
A key feature of these reactions is an excellent chemoselectivity; only alkyl fluorides react, and the corresponding alkyl bromides and iodides are tolerant under the standard reaction conditions. Furthermore, the competitive reaction using a mixture of *n*-octyl fluoride, cyclohexyl fluoride, and 1-adamantyl fluoride with Et<sub>2</sub>AlCl reveals that the order of reactivity for chlorination is tertiary > secondary > primary alkyl fluorides (Scheme 245).

Glycosyl fluorides are widely utilized for C-glycoside synthesis.<sup>381</sup> Several Lewis acids catalyze C–C bond formation at the anomeric position of glycosyl fluoride derivatives.

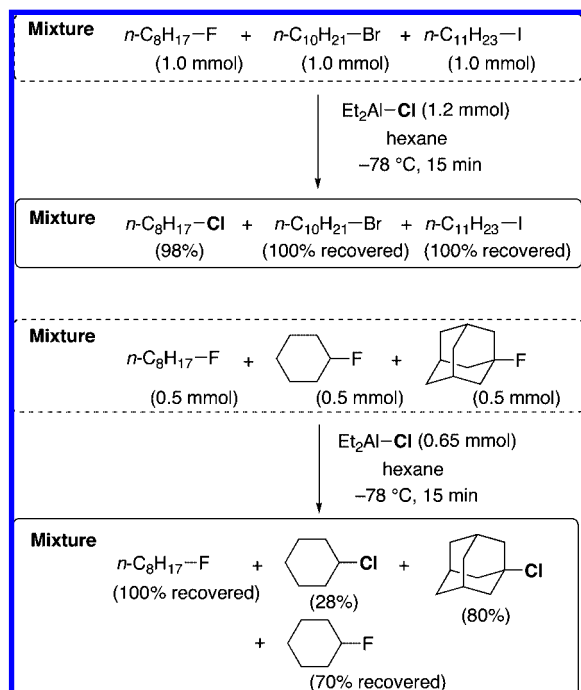
Scheme 243



Scheme 244



Scheme 245

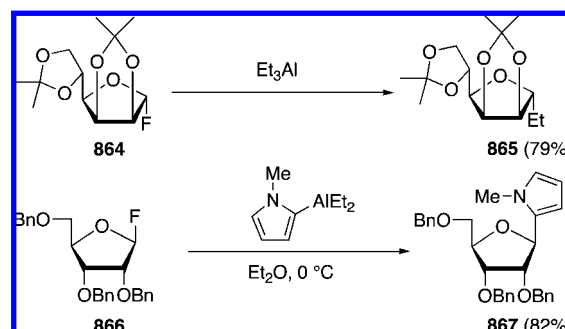


Tetra-*O*-benzyl-D-glycopyranosyl fluoride (**862**) undergoes the coupling reactions with trialkylaluminum reagents under

mild conditions with  $\alpha$ -preference at the anomeric positions of the resultant *C*-glycosides **863** (Table 8).<sup>382–387</sup>

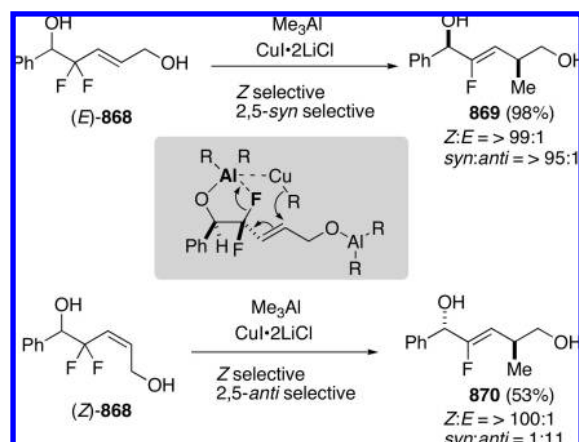
For furanosyl fluorides **864** and **866**, the coupling reactions proceed in good yields with the retention of the configuration at the starting anomeric center (Scheme 246).<sup>386,388</sup>

Scheme 246



The successful results of the regio- and stereoselective fluoride-displacement reaction using trialkylaluminum reagents (R<sub>3</sub>Al) were reported (Scheme 247).<sup>389</sup> In the presence of a Cu(I) salt, alkyl-transfer reactions from R<sub>3</sub>Al to (*E*)- and (*Z*)-4,4-difluoro-5-hydroxyallylic alcohol derivatives **868** proceed in S<sub>N</sub>2'-type manner to give the corresponding 2-alkylated (*Z*)-4-fluoro-5-hydroxyhomoallylic alcohol derivatives **869** and **870** with 2,5-*syn*- or 2,5-*anti* selectivity, respectively. The chelation of aluminum involving both oxygen and fluorine would make a great contribution to rate enhancement and stereocontrol.

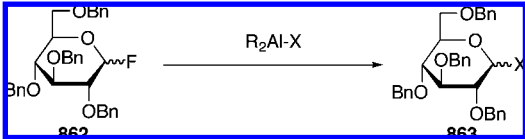
Scheme 247



Carbocations<sup>390,391</sup> and silyl cations<sup>392,393</sup> are electron-deficient species that can readily abstract fluorides from organofluorine compounds. In 1997, Lectka et al. described C–F bond activation induced by aryl carbocations in solution (Scheme 248).<sup>390</sup> The conclusive intramolecular fluoride shifts between carbon atoms are observed when aryl diazonium salts such as **871** are heated. The reaction of diazonium salt **871** in Et<sub>2</sub>O and 10% aqueous NaHCO<sub>3</sub>, fluoride transfer through six-membered ring, takes place to afford ethyl ester **874** as a major product. On the contrary, heating **871** at 40 °C in C<sub>6</sub>F<sub>6</sub> results intramolecular cyclization of the difluoromethyl cation intermediate to provide fluorofluorenone **875** and trifluorofluorene **876**. Furthermore, the authors disclosed the first example of intermolecular fluoride shift by heating diazonium salt **877** in C<sub>6</sub>F<sub>6</sub>.

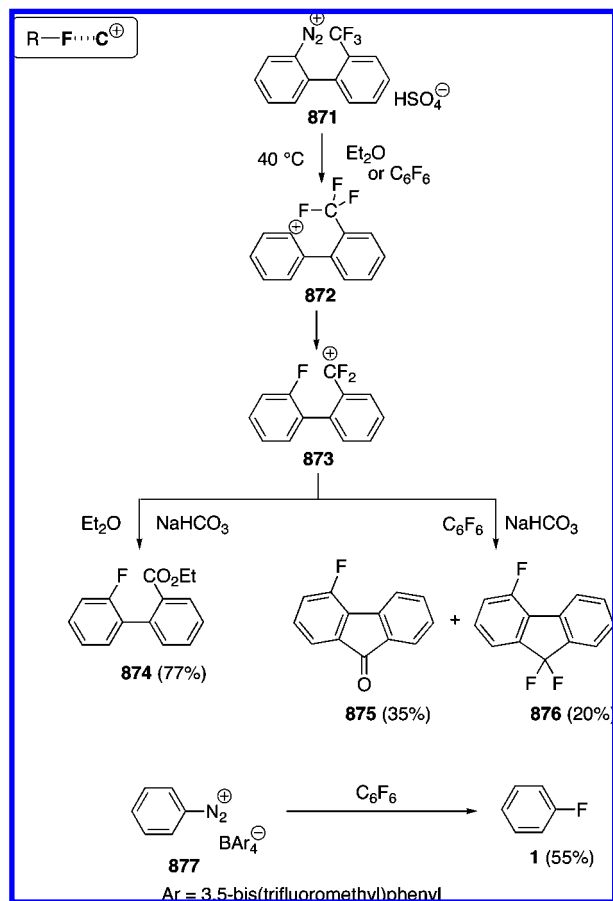


Table 8. Defluorinative C-Glycosidations with Aluminum Reagents



entry	R <sub>2</sub> Al–X	condition	X	% yield (α/β)
1	Me <sub>3</sub> Al	toluene, 0 °C	Me	95 (>20:1)
2	Me <sub>2</sub> AlCN	toluene, 0 °C	CN	96 (10:1)
3	Me <sub>2</sub> AlH	Et <sub>2</sub> O, 0 °C	H	90
4	<i>i</i> -Bu <sub>2</sub> AlCH=CHC <sub>6</sub> H <sub>13</sub>	toluene, 0 °C	CH=CHC <sub>6</sub> H <sub>13</sub>	85 (2.6:1)
5	Me <sub>2</sub> AlNHCH <sub>2</sub> CH=CH <sub>2</sub>	CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	NHCH <sub>2</sub> CH=CH <sub>2</sub>	99 (2:1)

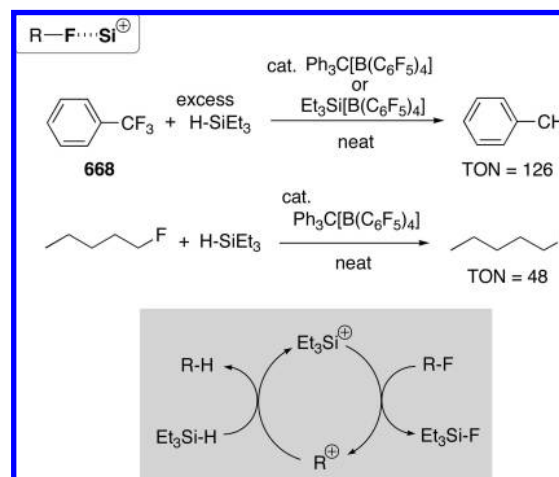
Scheme 248



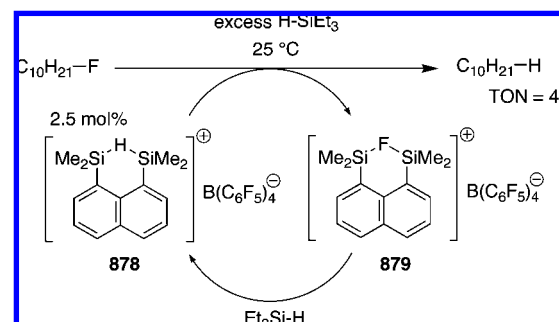
Because of the strong affinity for a fluorine atom, free X<sub>3</sub>Si<sup>+</sup> cations (silylium ions) are able to abstract fluorides from organofluorine compounds quite effectively. X<sub>3</sub>Si<sup>+</sup> salts of weakly coordinating anions such as tetraarylborates are extremely electrophilic. In 2005, Ozerov et al. presented the first catalytic examples of room-temperature hydrodefluorination of sp<sup>3</sup>-C–F bonds (Scheme 249).<sup>392</sup> The strategic features are (i) abstraction of a fluoride ion from a C–F bond in R–F by X<sub>3</sub>Si<sup>+</sup> salt, (ii) generation of a carbocation R<sup>+</sup>, which can abstract H<sup>+</sup> from hydrosilane X<sub>3</sub>Si–H, and (iii) regeneration of X<sub>3</sub>Si<sup>+</sup> species. The overall transformation is designed to be a Si–H/C–F σ-bond metathesis catalyzed by X<sub>3</sub>Si<sup>+</sup> salt. At 22 °C, benzotrifluoride (**668**) as well as 1-fluoropentane smoothly undergo hydrodefluorination in the presence of Et<sub>3</sub>SiH and a catalytic amount of Et<sub>3</sub>Si[B(C<sub>6</sub>F<sub>5</sub>)<sub>4</sub>] to yield the corresponding hydrocarbons. The hydrogen-bridged disilyl cation **878** possessing a 1,8-naphthalenediyl

backbone is also an effective catalyst for hydrodefluorination of fluorocarbons under mild reaction conditions (Scheme 250).<sup>393</sup>

Scheme 249



Scheme 250

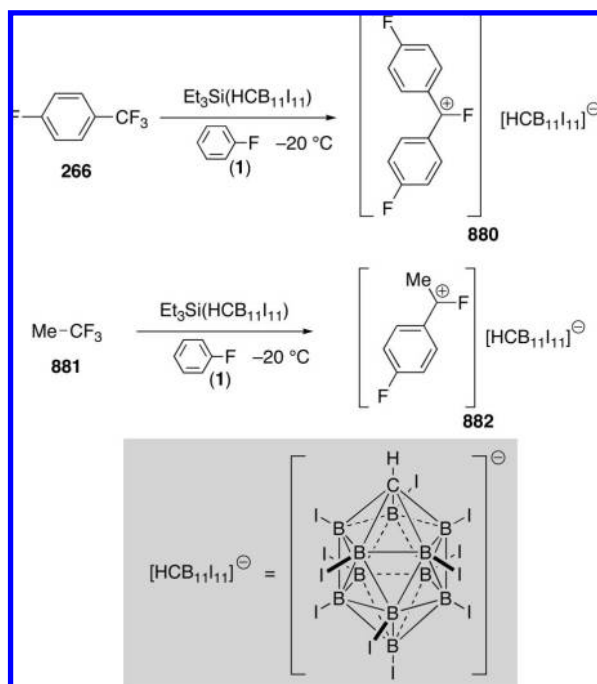


Using highly electrophilic silylium compounds endowed with carboranes as weakly coordinating counterions, fluorinated benzylic carbocations such as (*p*-FC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CF<sup>+</sup> (**880**), (*p*-FC<sub>6</sub>H<sub>4</sub>)(CH<sub>3</sub>)CF<sup>+</sup> (**882**), and fluorinated trityl ions are readily isolated (Scheme 251).<sup>394</sup>

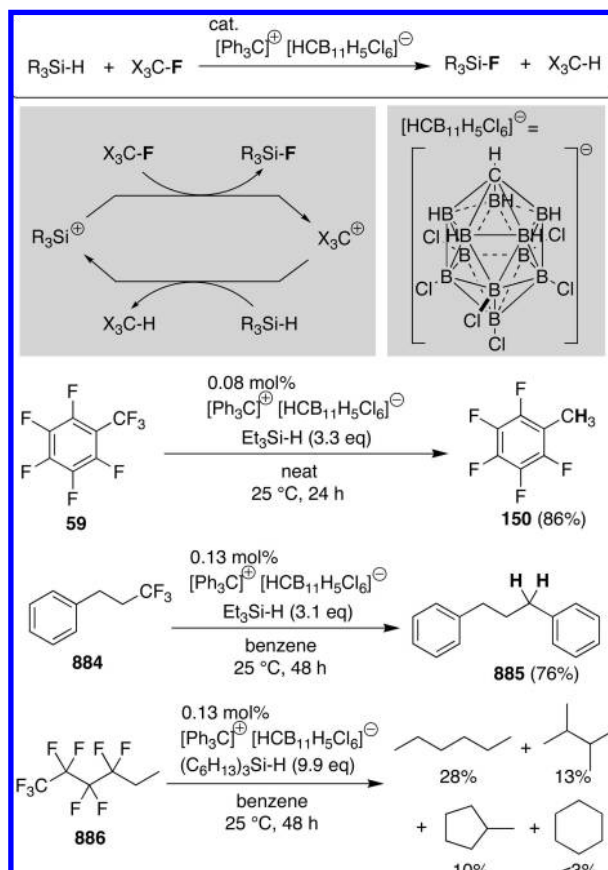
In 2008, Douvris and Ozerov developed a carborane-supported catalyst that can activate the carbon–fluorine bonds of saturated fluorocarbons (Scheme 252).<sup>395</sup> With high efficiency, these catalytic hydrodefluorination reactions are completely selective for aliphatic C–F bonds in preference to aromatic C–F bonds.

Not only cationic species but also neutral organosilicon compounds have potentials to activate C–F bonds. Yus et al. found that the organosilicon compounds such as bidentate compound **887** are excellent additives for reductive defluorination of fluoroalkanes (Scheme 253).<sup>396</sup> Fluorononane

Scheme 251



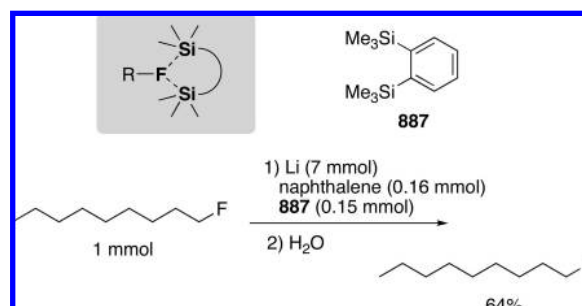
Scheme 252



is treated with an excess of lithium in the presence of a catalytic amount of naphthalene; however, no reaction takes place after several hours at  $20^\circ\text{C}$ . Very interestingly, in the presence of a substoichiometric amount of 1,2-bis(trimethylsilyl)benzene **887**, naphthalene-catalyzed fluorine–hydrogen-exchange reactions of primary, secondary, and tertiary

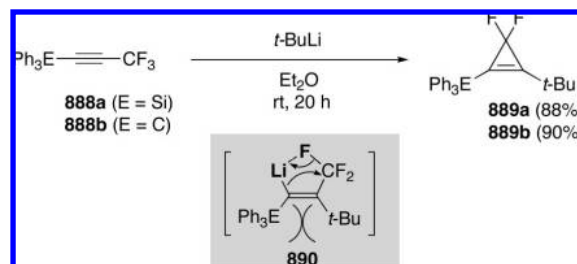
fluoroalkanes afford the corresponding alkanes, while monosilylbenzene is fruitless for the purpose.

Scheme 253



Intramolecular metal–fluorine (M–F) interaction can trigger an effective cyclization involving C–F bond cleavage. In 2003, Brisdon et al. reported the remarkable carbene-free synthesis of difluorocyclopropenes from trifluoropropynyls **888** (Scheme 254).<sup>397</sup> Treatment of **888a** with  $t\text{-BuLi}$  (as a sterically demanding organolithium reagent) at ambient temperature over 20 h results in a facile formation of difluorocyclopropene **889a** in 88% yield. The present interesting cyclization presumably occurs by elimination of  $\text{LiF}$  from the lithiated intermediate **890**, driven by the steric strain associated with the introduction of a  $t\text{-Bu}$  group *cis* to the  $\text{Ph}_3\text{E}$  fragment.

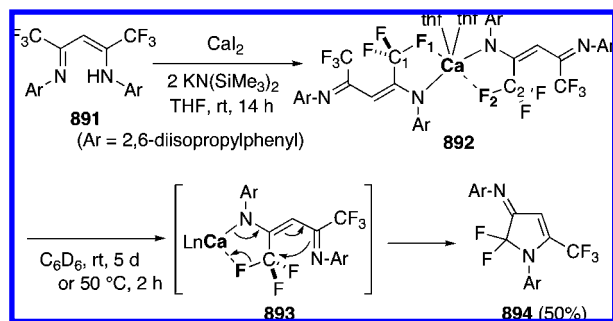
Scheme 254



The calcium  $\beta$ -diketiminate complex (**892**) not only exhibits an interesting interaction mode of a  $\text{CF}_3$  group, from which one fluorine atom coordinates to the  $\text{Ca}$  center, but also undergoes C–F bond breaking (Scheme 255).<sup>398</sup> From single-crystal X-ray diffraction analysis of the six-coordinate  $\text{Ca}$  complex **892**, examination of the C–F bond lengths of all four trifluoromethyl groups in **892** evidence a notable elongation of the C–F bonds to the coordinated fluorine atoms ( $\text{C}_1\text{-F}_1$ : 1.381(5) Å,  $\text{C}_2\text{-F}_2$ : 1.361(5) Å) in comparison to those of the uncoordinated fluorine atoms (average C–F: 1.328(5) Å), owing to the increased coordination number of these atoms. The  $\beta$ -diketiminate ligand in **892** undergoes intramolecular cyclization involving C–F bond cleavage to give the heterocycle **894** in 50% yield. The present anchimerically assisted cyclization would proceed via the following pathway; coordination of the  $\text{CF}_3$  group of the  $\beta$ -diketiminate ligand to the calcium center in **892** effectively polarizes one of the C–F bonds, resulting in an enhancement of the electrophilicity of the trifluoromethyl carbon atom, which is thus susceptible to intramolecular attack by the nucleophilic nitrogen atom of the uncoordinated imine moiety in **893**.

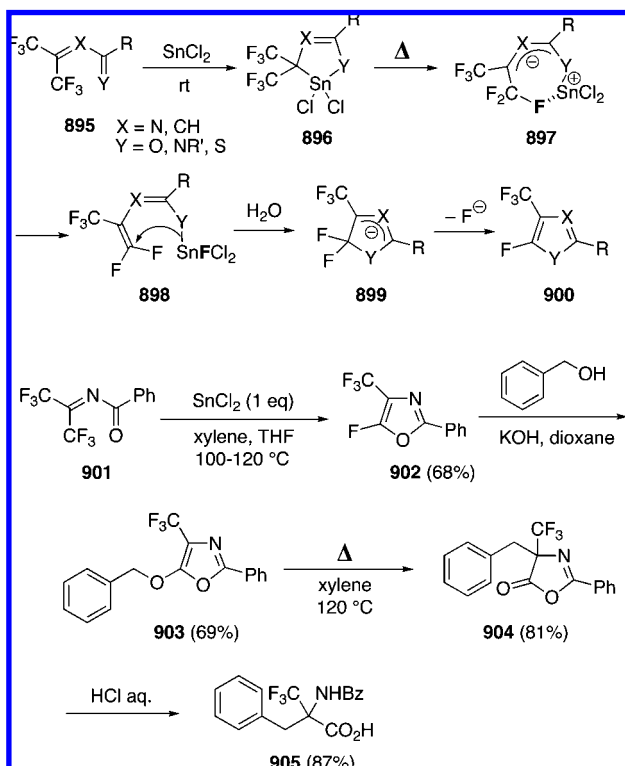
Burger et al. have been investigating various useful transformations involving C–F bond activation of bis(trimethylsilyl)-substituted hetero-1,3-dienes **895** to furnish

## Scheme 255



partially fluorinated five-membered heterocycles **900** (Scheme 256).<sup>399–401</sup> Initially, [4 + 1]-cycloaddition of  $\text{SnCl}_2$  to hetero-1,3-dienes **895** gives tin(IV)-containing five-membered rings **896**. On heating, **896** undergo heterolytic ring cleavage to provide dipolar species **897** with heteroaryl anion substructures and cationic tin(IV) moieties. Intramolecular fluoride migration to tin(IV) affording **898** and the subsequent nucleophilic cyclization and heteroaromatization with fluoride elimination from **899** yield fluorinated heteroaromatics **900**. Certain heterocyclic products act as versatile building blocks. For instance,  $\alpha$ -trifluoromethyl  $\alpha$ -amino acids are readily available via 5-fluoro-4-trifluoromethyloxazole **902**.<sup>401</sup>

## Scheme 256



## 4.4. Ate Complex-Catalyzed Cross-Coupling

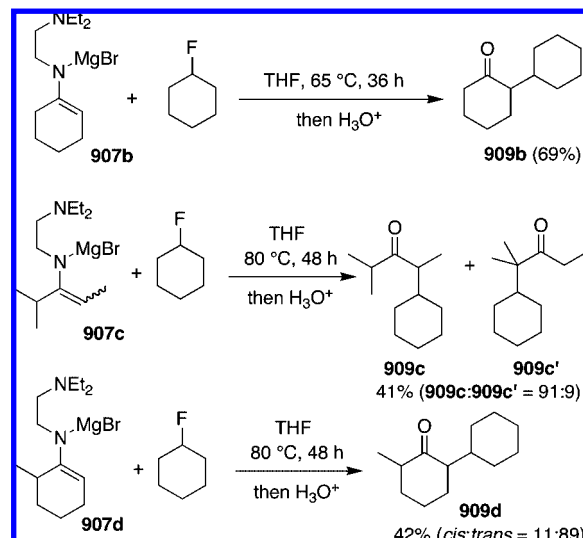
Alkyl bromides and iodides are generally more reactive and synthetically versatile than the corresponding chlorides and fluorides. Usually, Pd-, Ni-, and Cu-catalyzed alkylations require alkyl bromides and iodides as coupling partners for organometallics. Actually, toward enolates and enamides derived from ketones, the alkylating reagents that give synthetically useful yield and selectivity have been limited largely to alkyl iodides and bromides, as well as benzylic

and allylic halides. In recent studies on  $\alpha$ -alkylation of metal enamides done by Nakamura's group, primary alkyl fluorides are useful alkylating reagents for magnesium enamides of ketones (Table 9).<sup>402</sup> In some cases, the reactions using alkyl fluorides show better regio- and stereoselectivities than those of the corresponding chlorides (entries 3 and 4 in Table 9). Fluorocyclohexane, a secondary alkyl fluoride, also takes part in the alkylation reactions with magnesium enamides **907** to give the products **909** (Scheme 257).

Table 9. Alkylation of Magnesium Enamide with Alkyl Fluorides and Chlorides

entry	magnesium enamide	halodecane	product
1		(X = F)	 908a (97%)
2		(X = F)	 908b (75%)
3		(X = F) (X = Cl)	 908c (90%) 908c': 91:9 908c:908c' = 85:15
4		(X = F) (X = Cl)	 908d 93% (cis:trans = 72:28) 92% (cis:trans = 50:50)

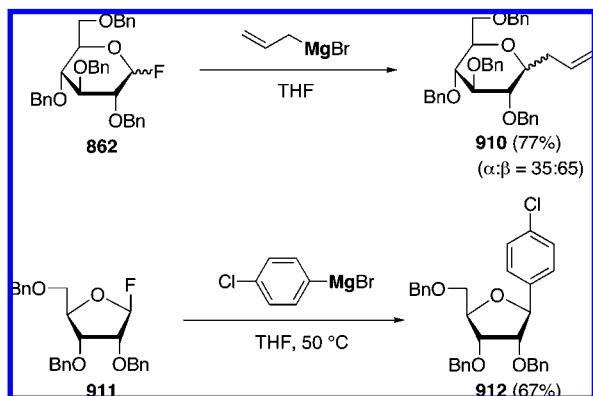
## Scheme 257



For nucleophilic transformation of organic fluorides, the choice of a counteranion of nucleophile is quite important.

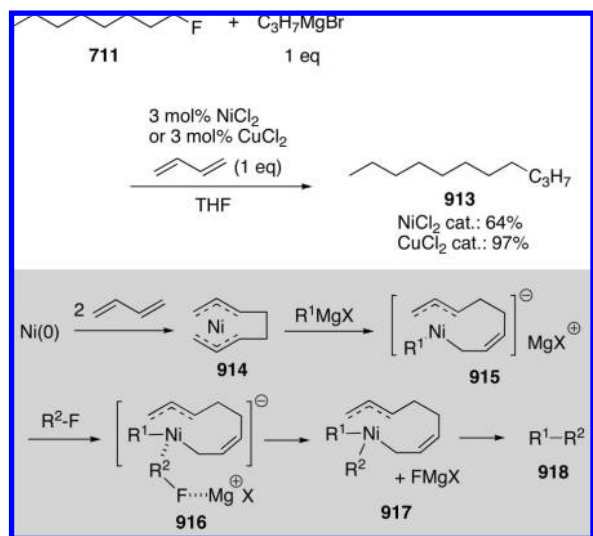
In general, Lewis acids are able to catalyze C–C bond-forming reactions of sugar fluorides that act as versatile sugar donors. In the absence of external Lewis acids, perbenzylated sugar fluorides **862** and **911** are allowed to react with diverse Grignard reagents to afford the corresponding  $\beta$ -C-glycoside derivatives **910** and **912** in moderate yields (Scheme 258).<sup>403</sup> The present finding implies that magnesium atoms of Grignard reagents or the resultant Mg(II) salts per se play the role of Lewis acid.

Scheme 258



Terao and Kambe et al. have investigated systematically the transition metal-catalyzed alkyl–alkyl cross-coupling reactions.<sup>404</sup> In 2003, they disclosed the first example of C–C bond formation using nonactivated alkyl fluorides. The cross-coupling reaction of *n*-octyl fluoride with *n*-propylmagnesium bromide proceeds smoothly at 25 °C in the presence of 1,3-butadiene as an additive. However, when no additive is employed, *n*-C<sub>8</sub>H<sub>17</sub>–F does not react at all, even in the presence of Ni catalyst (Scheme 259).<sup>405</sup>

Scheme 259

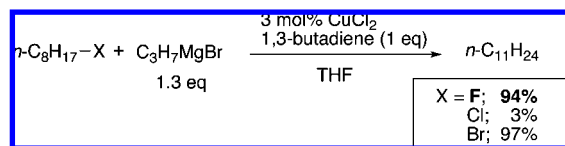


A plausible reaction pathway involves bis- $\pi$ -allyl nickel complex, which is generated by the reaction of Ni(0) with 2 equiv of 1,3-butadiene. Grignard reagents (R<sup>1</sup>MgX) react with ( $\eta^3$ -allyl)<sub>2</sub>nickel (**914**) to form  $\eta^1, \eta^3$ -octadienediynickelate (**915**). The cross-coupling products (R<sup>1</sup>–R<sup>2</sup>; **918**) would be formed via oxidative addition of alkyl fluorides (R<sup>2</sup>–F) to anionic Ni-complex **915**, providing di(alkyl)nickel complex **917**, followed by reductive elimination. In the oxidative addition step, magnesium (the counteraction of anionic

complex **916**) might play an important role (as a Lewis acid) to activate C–F bonds in fluoroalkanes by complexation.

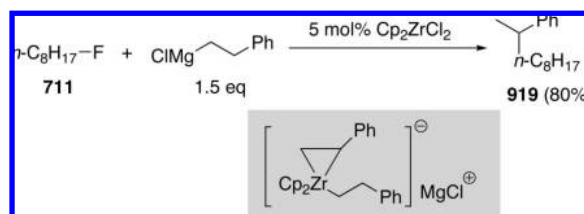
A CuCl<sub>2</sub>/butadiene system is quite effective for the cross-coupling reactions of fluoroalkanes with a variety of Grignard reagents (Scheme 260). It is noted that *n*-octyl fluoride is much more reactive than the corresponding chloride under the present reaction conditions.<sup>405</sup>

Scheme 260



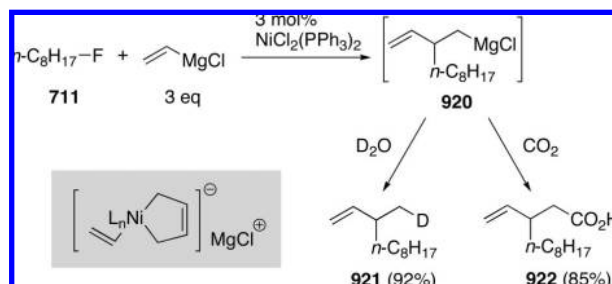
In the presence of a catalytic amount of Cp<sub>2</sub>ZrCl<sub>2</sub>, *n*-octyl fluoride (**711**) reacts with  $\beta$ -phenethylmagnesium chlorides to afford 2-phenyldecane (**919**) via alkylation of the styrene–zirconate intermediate at the benzylic position (Scheme 261).<sup>406</sup>

Scheme 261



Fascinatingly, Ni complexes catalyze the alkylative dimerization reaction of vinyl Grignard reagents using alkyl fluorides to give the 2-alkyl-3-butenyl Grignard reagent (**920**) (Scheme 262).<sup>407</sup> When the reaction of *n*-octyl fluoride (**711**) with 3 equiv of H<sub>2</sub>C=CH–MgCl in the presence of NiCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (3 mol %) is quenched with D<sub>2</sub>O, deuterated compound **921** is formed. When CO<sub>2</sub> is introduced to the mixture after the reaction, carboxylic acid **922** is obtained in 85% yield.

Scheme 262



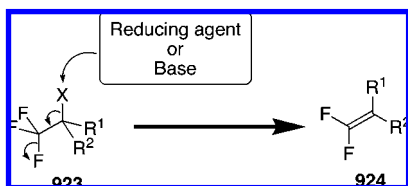
## 4.5. E2-type Dehydrofluorination

$\alpha$ -Substituted trifluoroethyl motifs shown in **923** are potential sources for difluoroalkenes **924**. Nucleophilic or reductive attack on X should induce, in principle, ionic cleavage of C–X bond, leading to elimination of XF and formation of *gem*-difluoroalkenes **924** (Scheme 263). When X is hydrogen, base-catalyzed dehydrofluorination is a choice for the desired reaction. Reductive cleavage of carbon–halogen bond (X = Cl, Br in **923**) with metal zinc is useful for eliminating both F and X as halides ions. Brook rearrangement is effective for cleavage of carbon–silicon bond (X = SiR<sub>3</sub>, trialkylsilyl group; and R<sup>1</sup> = O<sup>–</sup>, alkoxy anion).



Dehydrofluorination and the related defluorination reactions, Brook rearrangement, and other interesting defluorinative reactions are summarized in this section.

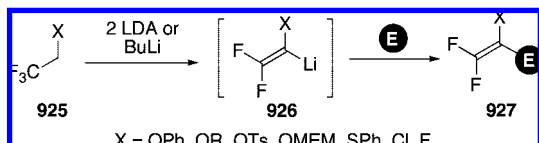
Scheme 263



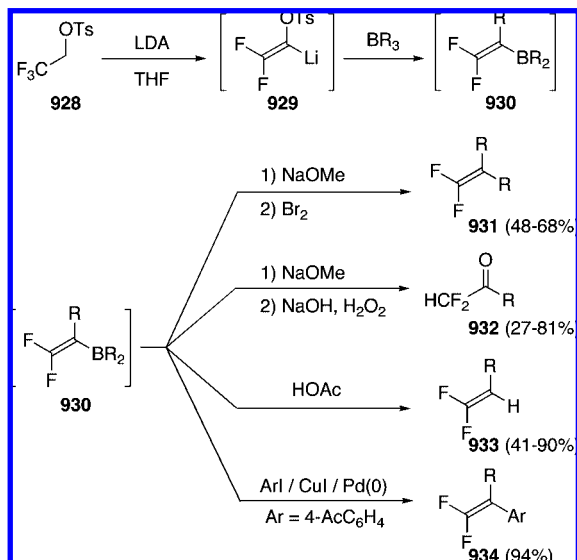
#### 4.5.1. Dehydrofluorination of Trifluoromethyl Compounds

Base-promoted dehydrofluorination from trifluoroethyl moiety often has been employed for the synthesis of difluoro compounds, since dehydrofluorination is easy because of the higher acidity of the  $\alpha$ -proton attached to the CF<sub>3</sub> group. Trifluoroethyl compounds such as phenyl ether,<sup>408</sup> alkyl ether,<sup>409</sup> tosylate,<sup>410</sup> 2-methoxyethoxymethyl (MEM)–ether,<sup>411</sup> phenyl sulfide,<sup>408</sup> chloride,<sup>412</sup> and fluoride<sup>413</sup> are known (Scheme 264).  $\alpha$ -Protons of *gem*-difluoroalkenes are acidic to be deprotonated in the presence of an excess amount of base, affording vinyl lithiums **926**. Vinyl lithium intermediates **926** are unstable so that they undergo either delithiumfluorination<sup>414</sup> or coupling reactions with reactive electrophiles. *gem*-Difluorovinyl dialkyl boranes **930** are available by a sequence of dehydrofluorination, boration, and alkylation of tosylate **928**. They are reactive and versatile building blocks for difluoro compounds (Scheme 265).<sup>410,415</sup> *gem*-Difluorovinyl phenyl sulfide **936** is so reactive to nucleophiles as to be aminated with lithium diisopropylamide (LDA), leading to alkynyl amine **938** as a final product (Scheme 266).<sup>408</sup>

Scheme 264

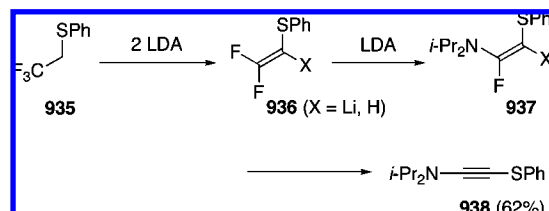


Scheme 265



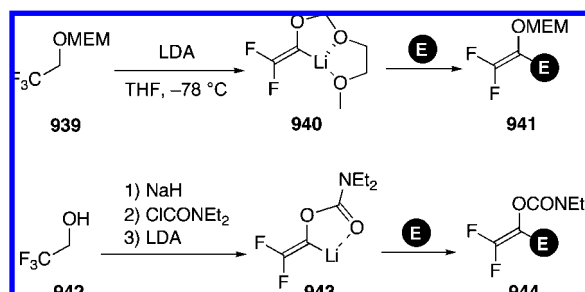
Stabilization of *gem*-difluorovinyl lithium is important for effective synthetic utilization. MEM and carbamate moieties

Scheme 266

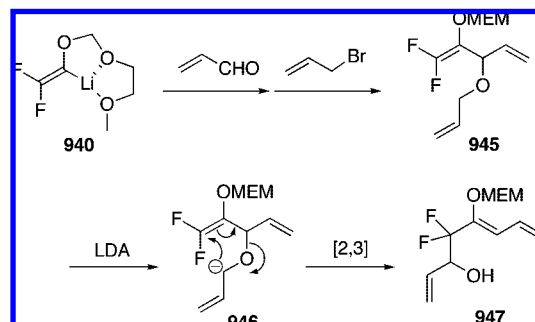


(in **940** and **943**, respectively) assist chelation for lithium species (Scheme 267).<sup>231,411d,416,417</sup> The same type of dehydrofluorination–lithiation chemistry for difluoroethanol is also effective for the synthesis of monofluoro derivatives.<sup>418</sup> A wealth of applications using this protocol have been developed by Percy;<sup>411,416,417</sup> as an example, a synthesis of difluoropolyene **947** via alkylation of **940** and chemoselective [2,3]sigmatropic rearrangement is shown in Scheme 268.

Scheme 267



Scheme 268

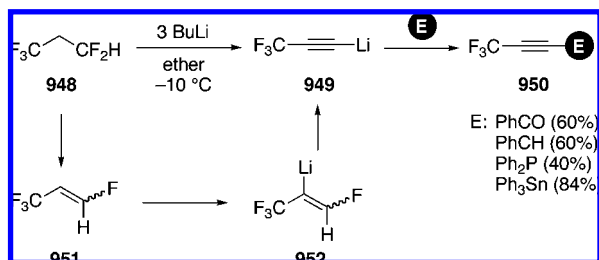


It is interesting to see whether trifluoromethyl or difluoromethylene group is more reactive under the base-catalyzed dehydrofluorination conditions. An example shown in Scheme 269 demonstrates that the CF<sub>2</sub> group is more susceptible to the base-catalyzed dehydrofluorination than the CF<sub>3</sub> group.<sup>419</sup> The preferred defluorination from the CF<sub>2</sub> group rather than the CF<sub>3</sub> group arises from the lower stability of the *gem*-difluorinated C–C double bond in comparison with that of the monofluorinated C–C double bond as discussed in section 3.1. Preferential formation of acetylide **949** suggests that the reaction proceeds via **951** and **952**.<sup>420</sup>

#### 4.5.2. Dehydrofluorination Leading to Quinodimethane Intermediates

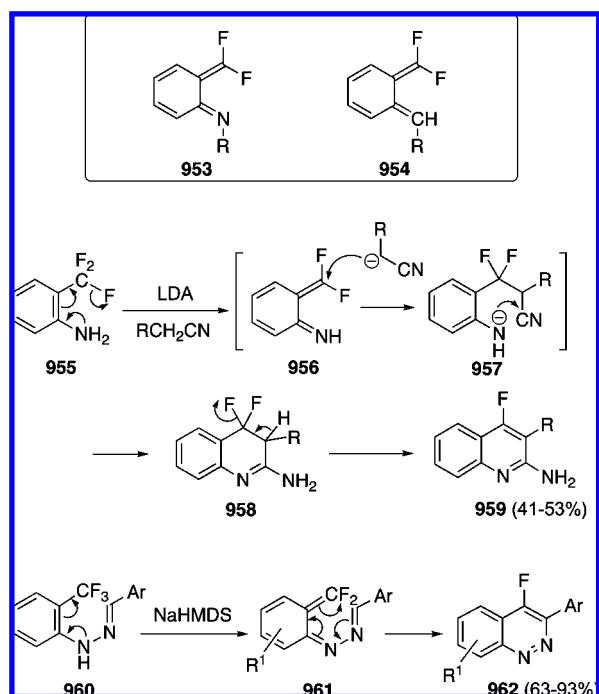
Difluorinated quinodimethane derivatives **953** and **954** are potential precursors for fluoroheterocycles. The base-catalyzed 1,4-dehydrofluorination of 2-trifluoromethyl aniline **955**<sup>421</sup> and its derivative **960**,<sup>422</sup> and 2-trifluoromethyl active methylene compounds **963**<sup>423</sup> proceeds smoothly and gener-

Scheme 269

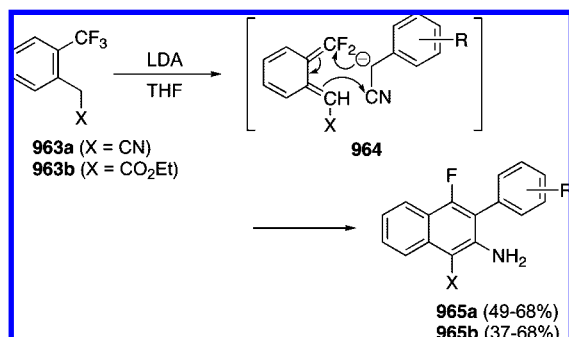


ates the difluorinated *ortho*-quinodimethane-type intermediates (Schemes 270 and 271). All of these intermediates **953** and **954** are very reactive toward nucleophilic alkylation at the difluoromethylene site, leading to fluoroaromatics via formal addition–elimination pathway (section 3.1). The overall chemical transformations provide a variety of highly functionalized fluoroheterocycles **959**, **962**, and **965**.

Scheme 270



Scheme 271

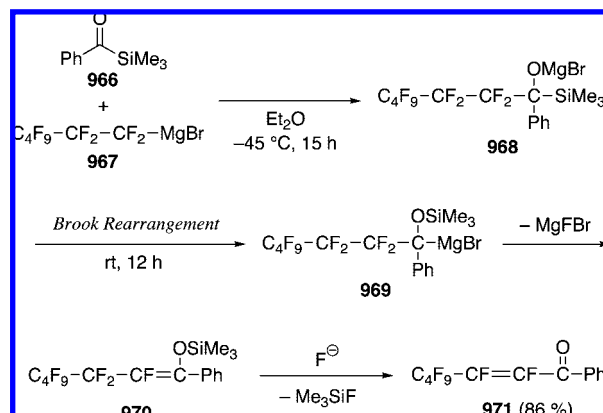


#### 4.5.3. Brook Rearrangement

The rearrangement of organosilyl groups from carbon to oxygen atoms (usually under the influence of a base) is called the Brook rearrangement.<sup>424</sup> A significant driving force for this transposition is the increased bond strength of the Si–O bond (110 kcal/mol) compared with the Si–C bond (76 kcal/mol).

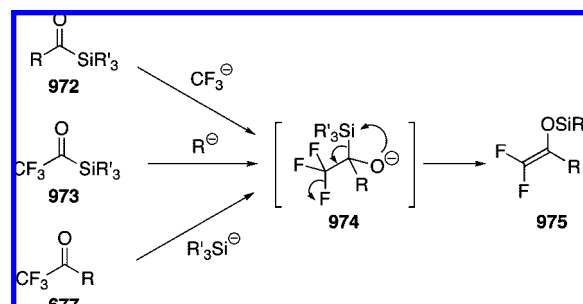
In 1991, Portella and Dondy found the formation of the defluorinated enone **971** by the reaction of benzoylsilane **966** with perfluoroorganometallic reagent **967** (Scheme 272).<sup>425</sup> It is considered that Brook rearrangement of the alkoxide **968** takes place to give the organometallic intermediate **969**, which readily participates in  $\beta$ -fluoride elimination to provide silyl enol ether **970**.<sup>426</sup>

Scheme 272

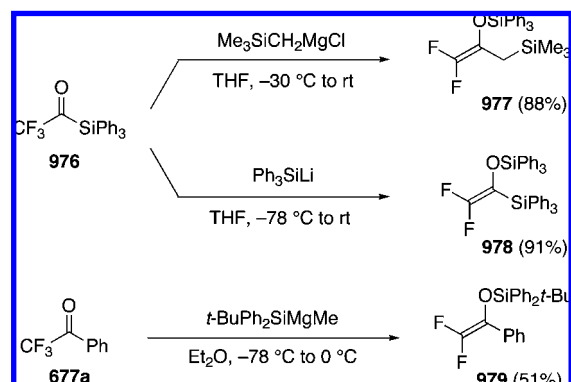


C–F bond activation triggered by Brook rearrangement is applicable to the preparation of 2,2-difluoroenol silyl ethers.<sup>242</sup>  $\alpha$ -Silyl- $\alpha$ -trifluoromethylalkoxylates **974** are generated in situ by one of the three possible reactions: reaction of acyl silanes **972** with  $\text{CF}_3\text{SiMe}_3$ ,<sup>301</sup> trifluoroacetyl silanes **973** with alkyl lithiums,<sup>427</sup> and trifluoromethyl ketones **677** with trialkylsilyl anions,<sup>428</sup> respectively (Scheme 273). They undergo desilylative defluorination via Brook rearrangement, providing difluoroenol silyl ethers in good yields (Scheme 274).

Scheme 273



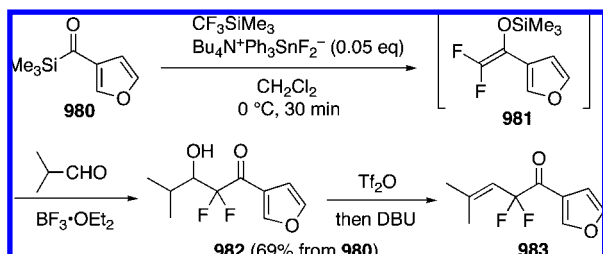
Scheme 274



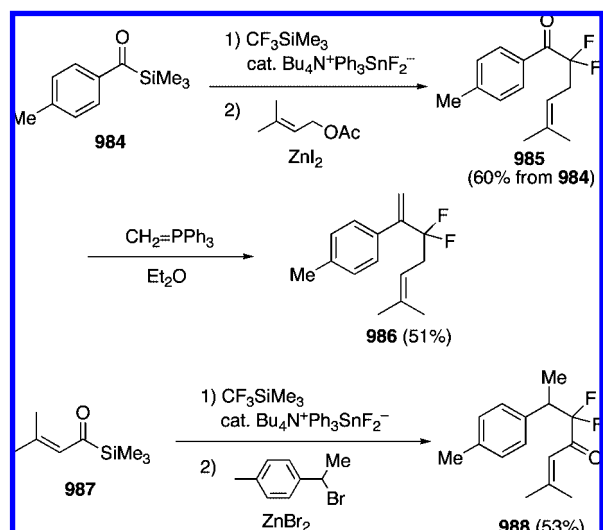
Portella et al. have continuously investigated the useful applications of 2,2-difluoroenol silyl ethers. Under fluoride

initiation, the reactions of acylsilanes with trifluoromethyltrimethylsilane give difluoroenoxyasilanes, which are used in situ for the subsequent Lewis acid-promoted C–C bond formation with electrophiles.<sup>344,429</sup> As depicted in Schemes 275 and 276, the present one-pot procedures are applicable to the synthesis of difluorinated monoterpenes such as difluoroegomaketone (**983**),<sup>430</sup> difluorodehydro-*ar*-curcumene (**986**),<sup>431</sup> and difluoro-*ar*-tumerone (**988**).<sup>431</sup> By employing this C–F bond-breakage protocol in sugar chemistry, xylose-derived acylsilane **989** is converted to the corresponding difluoroenoxyasilane **990**, which is glycosylated by glucal **991** to yield *gem*-difluoro-*C*-disaccharide **992** as an 80/20 mixture of  $\alpha$ - and  $\beta$ -isomers (Scheme 277).<sup>432</sup>

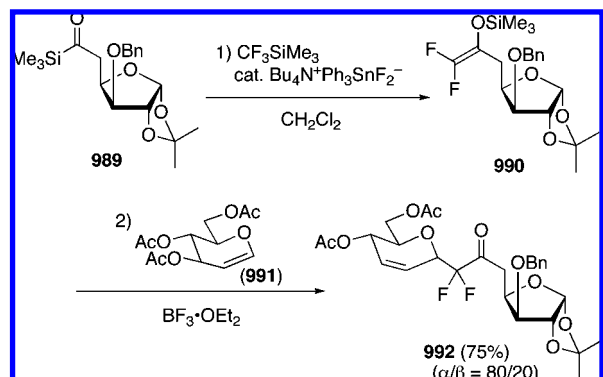
Scheme 275



Scheme 276



Scheme 277



## 5. Concluding Remarks

Development of organic transformations based on C–F bond activation is a highly challenging subject because it is necessary to overcome some of the most fundamental

concepts and theories such as classical reactivity and bond strength. As highlighted in this review, outstanding progress has been recently made in the development of useful reactions involving selective C–F bond activation in organic synthesis. For certain, the ingenious design of the reaction sequences expands remarkably the scope of organofluorine compounds in practical synthetic applications. Without question, each of these elegant C–F transformations sets an impressively high standard for future synthetic efforts targeting members of this growing class of important natural products, medicines, and organic intelligent materials.

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