C–F Bond Activation in Organic Synthesis

Hideki Amii*† and Kenji Uneyama*‡

Department of Chemistry, Graduate School of Science, Kobe University, Kobe 657-8501, Japan, and Department of Applied Chemistry, Faculty of Engineering, Okayama University, Okayama 700-8530, Japan

Received June 27, 2008

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.\(^{1}\) 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\(^{2}\) and books.\(^{3}\) 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...
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 trifluoroaceticimidoyl 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.

This is a review of C–F bond activation chemistry from the perspective of synthetic organic chemistry. The strength of the carbon–fluorine bond 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 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,5 Ni-complex mediated C–F bond activation by Braun and Perutz,6 chemistry of transition metal fluoro-compounds by Hoffman and Doherty,7 Cp*2ZrH2-mediated hydrodefluorination by Jones,8 chemistry of organometallic fluorides by Roesky,9 chemistry of fluorine–metal coordination by Plenio,10 and C–F bond activation by platinum group metal complexes by Torrens.11 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 sp2-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 vinylclic 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_F3).

In 1973, Tamao and Kumada reported the nickel-catalyzed cross-coupling reactions of Grignard reagents with aryl and
alkenyl halides.\textsuperscript{15} In these reports, aryl fluorides were found to be applicable to cross-coupling reactions by the use of nickel phosphate 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\textsuperscript{2}-carbon–fluorine bond cleavage.

2.1.1. Transition Metal-Mediated Activation of sp\textsuperscript{2}-C–F Bonds: Stoichiometric Reactions

In 1977, Fahey and Mahan reported several examples of oxidative addition of aryl, vinyl, and acyl halides (X = Br, Cl, and F) to triethylphosphine nickel(0) complexes.\textsuperscript{16} They observed the oxidative addition of hexafluorobenzene (5) to Ni(cod)(PEt\textsubscript{3})\textsubscript{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.

After 20 years, Perutz et al. succeeded in the full characterization of trans-Ni(PEt\textsubscript{3})\textsubscript{2}(C\textsubscript{6}F\textsubscript{5})F (6), by the reaction of hexafluorobenzene with Ni(PEt\textsubscript{3})\textsubscript{4}.\textsuperscript{17} 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).\textsuperscript{18} 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 Ni(0) species.

Scheme 3

Towards 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).\textsuperscript{19} 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.\textsuperscript{20} The stepwise treatment of Ni(cod)\textsubscript{2} with PEt\textsubscript{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 PCy\textsubscript{3} instead of PEt\textsubscript{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 I\textsubscript{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 Ni(0) complexes (B), or Meisenheimer intermediates via SN\textsubscript{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 Pd(0), Pt(0), and 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).\textsuperscript{21} The difference in regioselectivity of aromatic
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.

As an example of transformations involving aromatic nucleophilic substitution by transition metals, Chan and Leong reported the reactions of Cp*Ir(CO)₂(25) with activated perfluoroaromatic compounds (Scheme 8). 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.

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). Schiff’s base 30, which is prepared from pentafluorobenzaldehyde and diaminobenzene, 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.

Chelate-assisted intramolecular oxidative addition reactions of aromatic fluorides take place also in the case of square planar d⁸ 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 H–CH\(_2\)COCH\(_3\) across the imine bond with a change of the stereochemistry at Pt(IV) (Scheme 10).

**Scheme 10**

![Scheme 10 Diagram]

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 [PtMe\(_2\)(µ-SMe\(_2\))]\(_2\) (Scheme 11). The fluoroaromatic imine moiety in 38 is a pivotal ligand skeleton for ortho-selective C–F bond cleavage.

**Scheme 11**

![Scheme 11 Diagram]

Partial coordination of arenes to transition metals is regarded as a step toward oxidative addition. The photochemical reaction of Cp\(^\ast\)Rh(PMe\(_3\))(C\(_2\)H\(_4\)) (40) with hexafluorobenzene (5) gives Cp\(^\ast\)Rh(PMe\(_3\))([η\(^2\)-C\(_6\)F\(_6\)]) (41), which followed by pyrolysis generates Cp\(^\ast\)Rh(PMe\(_3\))(C\(_6\)F\(_5\))F (42) via the reaction of the electronically unsaturated fragment Cp\(^\ast\)Rh(PMe\(_3\)) with free hexafluorobenzene (5) (Scheme 12).

**Scheme 12**

![Scheme 12 Diagram]

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)plat-
Single electron-transfer reactions from transition metal hydride complexes trigger C–F bond cleavage of fluoroarenes via formation of caged radical pairs (Scheme 17). \(\text{trans-PtH}_2(\text{PCy}_3)_2\) reacts with fluorinated benzonitriles such as 4-RC\(_6\text{F}_4\text{CN}\) (R = H, F, CN, and OMe) to give the arylplatinum(II) complexes \(\text{trans-}[\text{PtH}_{\text{RC}_6\text{F}_4\text{CN}}(\text{PCy}_3)_2]\).\(^{34}\) Electron transfer from electron-rich dihydride complex \([\text{Ru(dmpe)}_2\text{H}_2]\)\(^{62}\) to hexafluorobenzene (5) provides the radical anion of C\(_6\text{F}_6\), which readily eliminates fluoride anion.\(^{35}\) Overall, HF is lost to yield monohydride complex \([\text{Ru(dmpe)}_2(\text{C}_6\text{F}_5)\text{H}]\)\(^{63}\). Note that reactions also take place with C\(_6\text{F}_5\)H, C\(_6\text{F}_5\text{CF}_3\), C\(_6\text{F}_5\text{OMe}\), 1,2,3,4-C\(_6\text{F}_4\)H\(_2\), and 1,2,3-C\(_6\text{F}_3\)H\(_3\) to afford products formed from aromatic C–F bond insertion exclusively.

A rhodium hydrido complex such as \(\text{RhH(PEt}_3)_3\) works well for the C–F bond activation of hexafluoropropene (64) (Scheme 18).\(^{36}\) The reaction proceeds in regioselective fashion to produce \([\text{Rh}((Z)\text{-CF=CF(CF}_3)\text{]}(\text{PEt}_3)_2]\) (65) in 80% yield, and there is no indication of defluorination from the trifluoromethyl group of 64.

In 1991, Milstein et al. reported a unique process involving Ir-mediated cleavage of C–F and P–C bonds.\(^{37}\) 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 \(\text{PEt}_3\) to C\(_6\text{F}_6\) (5), (ii) subsequent extrusion of methane and ethylene to give a low-valent Ir complex 69, and (iii) oxidative addition of C\(_6\text{F}_6\) (5) and fluoride migration to the phosphine atom.\(^{38,39}\)

In 1994, Aizenberg and Milstein demonstrated that silyl complex (Me\(_3\text{P})_3\text{RhSiMe}_2\text{Ph}\) reacts quantitatively with hexafluorobenzene (5) at room temperature (Scheme 20).\(^{40}\) With loss of F–SiMe\(_2\)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\(_6\text{F}_6\) (5) as well as release of fluorosilane, which arises from the great affinity between silicon and fluorine atoms.

**2.1.2. Transition Metal-Mediated Activation of sp\(^2\)-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 C6F6 (5) and C6F5H (73). Highly regioselective catalysis of C6F5H proceeds upon the treatment of (EtO)3Si–H and C6F5Rh(PMe3)3 to yield 1,4-C6F4H2 (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.

McNeill et al. investigated the catalytic dehalogenation of fluoro- and chloroethylenes (Scheme 22). Treatment of vinyl fluoride (78) with H–SiEt3 and a catalytic amount of RhCl(PPh3)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.

Metal hydride complexes are effective catalysts for hydrodefluorination of organic fluorides. Iron–fluoride complex 79 reacts with Et3Si–H to generate active iron–hydride complex 80, which can readily undergo defluorination of hexafluorobenzene (5) to yield pentafluorobenzene (73) (Scheme 23).42

Instead of hydrosilanes, hydrogen (H2) gas is an attractive reagent for catalytic C–F transformations. Rh(I)-catalyzed hydrogenolysis of a C–F bond in C6F6 (5) proceeds smoothly in the presence of bases (Scheme 24).43 Electron-transfer type of C–F bond cleavage by the use of hydrido–Rh complex 81 is also applicable to a catalytic hydrogenation of hexafluorobenzene (5) (Scheme 25).44

Chatani and Murai et al. presented an example of catalytic functionalization of C–F bonds. 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]BF4, 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.

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 ($\text{ArX}$), and the square planar $\text{ArNi(II)X}$ complex is formed. Subsequently, by exposure of alkyl (or aryl) Grignard reagent ($\text{RgMgX}$), displacement of the halide ligand ($\text{X}$) in the Ni complex with an alkyl (aryl) group, so-called transmetalation, gives the $\text{d(organano)nichel}$ complex and magnesium dihalide. The third reaction is reductive elimination leading the cross-coupling product ($\text{Ar-R}$) 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, 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). 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.

Bidentate phosphine ligands, such as dppe and dppp, are effective for the catalytic sp$^3$-C–sp$^3$-C cross-coupling reactions to yield N-heterocyclic biaryls (Scheme 28). With exposure of only 0.0005 equiv of NiCl$_2$(dppp), sp$^3$-C–F bond-activation reactions proceed smoothly to provide the corresponding unsymmetrical biaryls in high yields (Scheme 29).

Fluoropyridyl and pyrimidyl Ni complexes possessing monodentate phosphine ligands such as PEt$_3$ promote cross-coupling reactions. 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).

Design of phosphate ligands is quite important for improvement of catalytic activity. Nakamura designed a useful hydroxy phosphate ligand 99 that facilitated C–F bond activation of fluoroaromatics via nickel/magnesium bimetallic cooperation (Scheme 31). 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 and aminophosphine oxides 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. In 2006, Radius et al. reported the first examples of Ni-catalyzed Suzuki–Miyaura coupling involving C–F bond activation of fluoroarenes (Scheme 34). In the presence of the NHC ($N$-heterocyclic carbene)-stabilized nickel complex [Ni$_2$(I-$Pr$-Im)$_4$(cod)] (109) (I-$Pr$-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$_3$ or C$_6$F$_5$ group are substituted with aryl groups.
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 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. 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. 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. When p-chloro substituted 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).
reactions (Schemes 36 and 37). The Pd-catalyzed coupling reactions proceed smoothly by the use of ortho-nitro-substituted fluoroarenes as substrates. 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 36 diagram]

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).

Scheme 38

![Scheme 38 diagram]

Cross-coupling reactions containing selective C–F bond activation of polyfluoroarenes are useful tools for synthesis of partially fluorinated aromatics. PdCl₂(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). From the finding that 1,3- and 1,4-difluorobenzences 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 NiCl₂(dppp) provides dicoupled product 133 exclusively, whereas the use of the Pd catalyst furnishes monocoupled product 134.

Scheme 39

![Scheme 39 diagram]

In 2008, Manabe and Ishikawa demonstrated interesting examples of ortho-selective cross-coupling of fluorobenzene derivatives with Grignard reagents (Scheme 40). 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

![Scheme 40 diagram]
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)-fluoroketene 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).49

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).63 In the presence of MnCl2 (10 mol %), BuMgCl readily reacts in tetrahydrofuran (THF) with aryl fluoride 146 bearing an electron-withdrawing activating group (CHdNR) in the ortho-position. The manganese-catalyzed procedure compares favorably to the aromatic nucleophilic substitution (SNAr). From aldimine 146, in the absence of MnCl2, 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 CpTiCl3 affords 1-(1-phenylethyl)naphthalene (149) in good yield via isomerization of the 1-phenylethyl group (Scheme 43).64 Similarly, TaCl5-catalyzed coupling reactions of phenylmagnesium chloride with substituted fluoroarenes proceed with high regioselectivity at the para-position to provide the corresponding 1-phenethylarenes in good yields.

Scheme 43

Knochel et al. demonstrated cobalt(II)-catalyzed cross-coupling between aryl cuprates and aryl fluorides (Scheme 46).67 In the presence of Co(acac)2 (7.5 mol %), Bu4NI (1 equiv), and 4-fluorostyrene (20 mol %) as promoters, organocopper compounds prepared by the transmetalation of functionalized arylmagnesium halides with CuCN·2LiCl 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.

Scheme 44

The first report on platinum-catalyzed cross-coupling of aryl fluorides was provided by Love et al. (Scheme 47).68 Inspired by the reports on [Me2Pt(μ-SMe2)]2-mediated stoichiometric C–F activation of ortho-fluoroaryl imines,25,26 they explored the catalytic version of these ortho-selective C–F transformations. Among the examined nucleophiles, Me2Zn 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 CdN directing group permits the cleavage of the
strong C–F bond even in the presence of a considerably weaker C–Br bond.

In 2008, Arisawa and Yamaguchi developed Rh-catalyzed single-bond metathesis of C–F and S–S bonds (Scheme 48). Upon exposure to a catalytic amount of RhH(PPh3)4 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 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). In 1920, Swarts reported the first example of catalytic hydrodefluorination of monofluoroarenes by hydrogen gas over a heterogeneous metal. In 1946, Renoll used nickel supported on kieselguhr for the reduction of 2-fluoro-4′-acetylbiphenyl in methylcyclohexane at 125–150 °C and under 140 atm of H2 to provide p-cyclohexylethylbenzene. 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 H2 gas in ethanol.

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 H2 at room temperature in 95% ethanol, affording cyclohexylphosphonic acid.

The SiO2-sol–gel entrapped ion pair [(n-C8H17)3NMe]+RhCl4–·nH2O, generated from RhCl3·3H2O, methyltrioctylammonium chloride (Aliquat 336), and Si-(OMe)4, catalyzes the hydrodefluorination and hydrogenation of nonactivated fluoroarenes at 80 °C under 16 atm of hydrogen to provide the corresponding dehalogenated cyclohexanes (Scheme 49).

As introduced above, these catalytic transformations involve both hydrog enolysis of C–F bonds in fluoroarenes and hydrogenation of aromatic rings. In the net transformation from fluoro benzene to cyclohexane, there are two different pathways shown in Scheme 50: (A) fluoro benzene 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 H₂, and (B) fluorenebenzene 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)₂]BF₄, bipyridyl 168, and silica-supported palladium (Pd-SiO₂), works well for hydrodefluorination of fluorenebenzene (I) under 4 atm of hydrogen at 70 °C to give a mixture of fluorocyclohexane (CyF) and cyclohexane (CyH) (Scheme 51). 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 fluorenebenzene (I) under mild reaction conditions (1 atm of hydrogen at 40 °C) (Scheme 52). 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 hydrogenation removal of fluorides from fluoroarenes without accompanying hydrogenation of the aromatic rings. 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), 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). To the solution of p-fluoroanisole (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-fluoracetanilide (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]methylcyclophan, 2,4,5,6-tetrafluoroorisophthalic acid (175) is converted with Ni-Al alloy in 10% NaOD-D₂O to [2,4,5,6-²H₄]-isophthalic acid (176) in high chemical yield with high isotopic purity (Scheme 55).

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 [(Cy₃P)₂Rh(H)Cl₂], H₂, and aqueous alkali (in the absence of O₂), promotes the hydrogenolysis of 1-fluoronaphthalene (148) to yield naphthalene (Scheme 56). However, this homogeneous rhodium catalyst is incapable of hydrogenolysis of fluorenebenzene 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 fluoroaromatics, 4-fluorotoluene, 3-fluoroanisole, and 4-fluoroaniline.

Next, we discuss examples of catalytic hydrogenolysis of fluoroaromatics without using hydrogen gas as the hydrogen donor. In conventional procedures, molecular hydrogen (H₂) has been widely employed for the catalytic hydrodehalogenation of organic halides, in which high hydrogen
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).84

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 Et₂CHONa 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)₂ and IMes·HCl (179) (Scheme 58).85

Scheme 57

Scheme 58

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.87 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.88 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 MgCl₂ and 4 equiv of metallic potassium) leads to formation of the Grignard reagent, which reacts with CO₂ to afford p-toluic acid (187) in 65% yield (Scheme 61).89 It is noted that the addition of potassium iodide (1 equiv) prior to the reduction of MgCl₂ 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 as a soluble reducing agent. By dissolving metallic lithium with a stoichiometric amount of naphthalene in THF, the solution
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 fluoroaromatics (Scheme 62).90

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.

First, we introduce ortho-selective hydrodefluorination of perfluoroarenes. A combination of the low-valent ytterbium complex Cp₂Yb(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).91 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 CpTl.

Low-valent Ni complexes work well for ortho-hydrodefluorination of pentafluorobenzoic acid (191). In the presence of 0.01 equiv of NiCl₂–2,2′-bipyridine complex and 10 equiv of Zn, ortho-monodefluorination of C₆F₅CO₂H proceeds selectively to give 2,3,4,5-tetrafluorobenzoic acid (192) in 93% yield (Scheme 65).92 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.93,94 In 2001, Shteingarts
and co-workers developed a new simple route to partially fluorinated (ortho-defluorinated) aromatic amines. 

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.96

In 1990, Nippon Carbide Industries Co., Inc., reported the preparation of 2,3,5,6-tetrafluorobenzonitrile (204) from pentafluorobenzonitrile (27) (Scheme 67).97 Treatment of 27 with Zn powder and aqueous KH2PO4 at 100 °C for 2 h leads to 2,3,5,6-C6F4CN (204) in 94% yield at 100% conversion.

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.100 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.93,94 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 214 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\(_2\)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\(_2\) (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 (Scheme 70).\(^{101}\) 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\(_3\) (1.5 equiv) and LiAlH\(_4\) (4.5 equiv) in THF (Scheme 71).\(^ {102}\)

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\(_4\) (Scheme 72).\(^ {103–105}\)

Scheme 72

Rose and co-workers reported the hydride attack to \(\eta^6\)-fluoro(triisopropyl)benzene chromium tricarbonyl complex.\(^ {106}\) It is worth noting that the hydrodefluorination of the fluorobenzene ligands\(^ {107}\) does not proceed via ipso-substitution pathway. \(\alpha\)-Fluoro(silyl)benzene chromium tricarbonyl complex 224 reacts with Et\(_3\)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)\(_3\) complexes would involve radical intermediate complexes of chromium. Fluoro-substituted \(\eta^6\)-arene tricarbonylchromium complexes react with aliphatic ketones in the presence of SmI\(_2\) and \(t\)-BuOH under C–C bond formation to give the corresponding benzylic alcohols in good yields (Scheme 74).\(^ {108}\) 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-
The overall transformation is represented as a nucleophilic aromatic substitution of fluoride (SNAr), which preferentially takes place in a tele-meta fashion.

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 (SNAr) 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 SN2 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 SN2 reaction so that aliphatic iodides react fastest among the aliphatic halides.

There is an interesting comparison between aromatic C–F and C–Br bonds. For SNAr reactions of aryl halides, as mentioned above, the higher reactivity of fluorine than those of chlorine and bromine is observed. Actually, the noncatalyzed SNAr reaction of 4-fluorobromobenzene (248) with sodium methoxide proceeds smoothly to afford 4-bromoanisole (249) in 85% yield (Scheme 78).115 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.

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 carbon10 and oxygen11 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 70:3.112 A big reactivity difference is also shown in the reaction of 243 with phosphorus113 and nitrogen114 nucleophiles (Scheme 77).

There is an interesting comparison between aromatic C–F and C–Br bonds. For SNAr reactions of aryl halides, as mentioned above, the higher reactivity of fluorine than those of chlorine and bromine is observed. Actually, the noncatalyzed SNAr reaction of 4-fluorobromobenzene (248) with sodium methoxide proceeds smoothly to afford 4-bromoanisole (249) in 85% yield (Scheme 78).115 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.
As shown in Scheme 79, it is noticeable that fluoride (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. 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).

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-amino-pyridines in reasonable yields (Scheme 82). 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.

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). 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.

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-butyl lithium 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). 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
useful intermolecular $S_N$Ar 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). 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). 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). Highly functionalized binaphthols 275 are prepared by stepwise replacement of fluorine from octafluorobinaphthol derivative 273 (Scheme 88).

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. Fluorine—phosphine exchange reaction on an aromatic ring is quite useful for nonracemized phosphorylation on an aromatic ring as shown in Scheme 90. Anthraphos (285) is prepared by nucleophilic substitution of 1,8-difluoroanthracene (284) with 2 equiv of potassium di-$t$-tert-butylphosphide ($t$-Bu$_2$PK) in 80% yield.

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). 2,4-Difluorobromobenzene (290) is transformed elegantly 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 $S_N$Ar reaction afford 296 as a final product (Scheme 92).

Takeda Pharmaceutical Company developed the practical method of producing 300, an orally active CC chemokine
receptor 5 (CCR5) antagonist (Scheme 93). 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

![Scheme 93 Diagram]

The tandem Suzuki cross-coupling/S_NAr protocol gives a facile route to carbazoles (Scheme 94). Boronic ester 302 cleanly reacts with 301 using a one-pot procedure involving Pd(PPh_3)_4-catalyzed cross-coupling and the subsequent intramolecular S_NAr reaction of aryl fluoride to deliver N-tosylated carbazole 304 in near quantitative yield. Deprotection of the tosyl group from 304 using Cs_2CO_3 produces the carbazole alkaloid glycosinine (305).

Scheme 94

![Scheme 94 Diagram]

In 1992, Shindo, Koga, and Tomioka demonstrated the catalytic asymmetric version of nucleophilic aromatic substitution leading to optically active binaphthyls (Scheme 95). The reaction of naphtyllithium with naphthyl imine 306 is catalyzed by dimethyl ether of (R,R)-1,2-diphenylethane-1,2-diol (307) 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 naphtyllithium–diether complex 309 to imine 306 providing 310, and the second involves elimination of the 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

![Scheme 95 Diagram]

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). Two of the three fluorine atoms in 314 can be employed in a stepwise manner to introduce amino functionalities (Scheme 97). Several examples of the F-activated SNAr protocol for the intramolecular ring closures between N-1 and C-8 related to quinolone derivatives have been reported. 

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), pavalofloxacin (320), and sparfloxacin (322).

Nucleophilic aromatic substitution (SNAr) chemistry contributes to creating new materials with a π-conjugated system. Successive SNAr transformations starting from tetrafluorobenzene 74 provide highly fluorinated benzobisbenzothiophene 326, whose lower LUMO (lowest unoccupied molecular orbital) energy levels can facilitate electron injection and transport, leading to n-type semiconductor characteristics (Scheme 99).

Fluorine is also an excellent leaving and accelerating group that is useful for extension of polymer chains with aryl 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). 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.
The F-activated SNAr protocol has been used for the syntheses of a variety of heterocycles and macrolides. One-pot synthesis of benzothiazoles and macrocycle of aminoalcohol are excellent examples (Schemes 103 and 104). The preparation of cycloisodityrocine precursor is achieved in a good yield by the intramolecular diarylether construction protocol using fluoroarene (Scheme 105). In contrast, much higher temperature (130 °C) is required for the ring closure of the related. For the synthesis of the D-O-E segment of vancomycin, undergoes SNAr macrocyclization to afford as a mixture of atropisomers (Scheme 106).

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

After monosubstitution, the second substitution of mono-substituted pentafluorobenzenes occurs regioselectively at C-4 carbon, irrespective of the electronic nature of the first substituent, to give 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). Employing para-selective aromatic nucleophilic monosubstitution pro-
tocols provides a high-yielding route to polystyrene-bound and/or fluorous super Brønsted acids 353. Highly fluorinated ethers 353c–d act as temperature-dependent organic solvent-miscible solid catalysts,167 and interestingly, perfluorocarbon solvents are not essential for fluorous biphasic catalyses such as acetalization, esterification, Mukaiyama aldol condensation, and Hosomi–Sakurai allylation. Furthermore, fluorous catalyst 353d is perfectly recycled by using liquid/solid phase separation without fluorous solvents.

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).186 Successive ring extension starting from 359 and ring closure with Pt complex 362 provide the metal-centered macrocycle 363,186 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).187
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 \((367)\). Scheme 11 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 introduced stepwise.\(^{189}\) The high reactivity of 7 to nucleophiles enables reactions with in situ generated unstable

---

**Table 3. Preparation of 1,4-Disubstituted Tetrafluorobenzenes**

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile and condition</th>
<th>product</th>
<th>yield (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;PH, BuLi, THF; 0 °C</td>
<td>2 Nu</td>
<td>43% (168)</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
<td>BuLi, THF; -78 °C then reflux</td>
<td>R = H: 65%; R = hexyl: 68%</td>
</tr>
<tr>
<td>3</td>
<td>F6-BuLi</td>
<td>85% (170)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OSiMe&lt;sub&gt;3&lt;/sub&gt;, CsF, DMF</td>
<td>54% (158)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;S)&lt;sub&gt;2&lt;/sub&gt;Ni</td>
<td>95% (171)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>OMe-Li, Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>65% (172)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Fe&lt;sub&gt;2&lt;/sub&gt;, TEMDA, pentane</td>
<td>30% (173)</td>
<td></td>
</tr>
</tbody>
</table>

---

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

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile and condition</th>
<th>product</th>
<th>yield (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cl&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, DMSO</td>
<td>85% (174)</td>
</tr>
<tr>
<td>2</td>
<td>R&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td>BuLi (2 eq)</td>
<td>59% (175)</td>
</tr>
<tr>
<td>3</td>
<td>NEt&lt;sub&gt;2&lt;/sub&gt;, H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>58% (176)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PhCOMe</td>
<td>49% (177)</td>
<td></td>
</tr>
</tbody>
</table>

---

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

<table>
<thead>
<tr>
<th>entry</th>
<th>nucleophile and condition</th>
<th>product</th>
<th>yield (ref.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me-S-S-Me</td>
<td>Li, DMF</td>
<td>40% (5,6-difluoro isomer 10%)</td>
</tr>
<tr>
<td>2</td>
<td>S(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Na, NH&lt;sub&gt;3&lt;/sub&gt;, H&lt;sub&gt;2&lt;/sub&gt;C=CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30% (179)</td>
</tr>
<tr>
<td>3</td>
<td>Sn(SPh)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>DMF</td>
<td>54% (180)</td>
</tr>
<tr>
<td>4</td>
<td>1) (Mes)&lt;sub&gt;2&lt;/sub&gt;PH, BuLi (43%); 2) RLi, THF</td>
<td>R = Bu: 80%; R = Ph: 54%</td>
<td></td>
</tr>
</tbody>
</table>
nucleophiles under mild conditions, leading to preparation of 4-substituted 2,3,5,6-tetrafluoropyridines (Table 7). 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 as shown in Scheme 113. A combination of CsF and ethylene glycol bistrimethylsilane is more useful for construction of crown ether 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). Initial nucleophilic attack of enamine to the 4-position of pentafluoropyridine (7) and the subsequent intramolecular N-arylation afford tetrahydrocarbazole.

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 substitutes a fluorine atom in 7 to give perfluoro-4-ethylpyridine (379) and regenerates a fluoride ion (Scheme 115). 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).

Quite interesting is the fact that radical substitution of 7 also takes place exclusively at the 4-carbon, while that of 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 (Scheme 117).

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). Meanwhile, the 6-position is the most reactive in perfluoroisouquinoline. However, the major reaction sites of displacement by the sulfur and the oxygen nucleophiles are significantly different: nucleophilic attacks take place at the

---

### Table 6. Hexasubstituted Benzenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile and Condition</th>
<th>Product</th>
<th>Yield</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me3N=N=NMe, MeCN</td>
<td><img src="image1" alt="Product Image" /></td>
<td>92%</td>
<td>181</td>
</tr>
<tr>
<td>2</td>
<td>ROSiMe3, CsF, THF</td>
<td><img src="image2" alt="Product Image" /></td>
<td>75%</td>
<td>158</td>
</tr>
<tr>
<td>3</td>
<td>1) (Me2Si)2CHC6H4Li, DMF</td>
<td><img src="image3" alt="Product Image" /></td>
<td>32%</td>
<td>182</td>
</tr>
<tr>
<td>4</td>
<td>PhSeNa, DMF, 0 °C, 15 min</td>
<td><img src="image4" alt="Product Image" /></td>
<td>91%</td>
<td>183</td>
</tr>
<tr>
<td>5</td>
<td>H, NaH, C6H6, rt, 2 h</td>
<td><img src="image5" alt="Product Image" /></td>
<td>51%</td>
<td>184</td>
</tr>
<tr>
<td>6</td>
<td>PhSH, DMI</td>
<td><img src="image6" alt="Product Image" /></td>
<td>39%</td>
<td>185</td>
</tr>
<tr>
<td>7</td>
<td>S(CH=CH2)2, Na, NH3</td>
<td><img src="image7" alt="Product Image" /></td>
<td>57%</td>
<td>179</td>
</tr>
</tbody>
</table>
4-position by thiolates and at both the 2- and 4-positions by oxygen nucleophiles in quinoline \(^3\), as well as at the 6-position by sulfur and the 1-position by oxygen nucleophiles in isoquinoline \(^3\), 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 \(^3\) and \(^3\).

### 2.4. Defluorination via Benzynes

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

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. Thus, lithio species 384 undergoes elimination of chlorine chemoselectively, affording benzyne 385, of which cycloaddition to 2-(trimethylsilyl)furan gives 386 regioselectively (Scheme 120).

The ortho-position to fluorine substituent in fluoroarenes is generally more acidic 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). The same type of selective benzyne formation was employed for the heterocycle synthesis of 396, in which a base, potassium bis(trimethylsilyl)amide (KH-MDS), 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).

The extent of solvent coordination (THF) around lithium sometimes governs the stability and reactivity of the lithium species (Scheme 123). 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
THF-coordinated lithium species 397 eliminates chlorine as a better leaving group to form 3-fluorobenzyne 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).210

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 than the original tetrabromo derivative 410.211 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).211

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 arylene 419 in situ, and subsequent intramolecular addition and trapping newly generated aryl lithium produce substituted indanes 420 as final products (Scheme 127).214 Both of cyclobutanation and cyclohexanation from 421 (n = 2 or 4) are less effective in comparison with cyclopentanation.215

Scheme 127

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

In 2006, Barrett et al. reported the first total synthesis of (+)-clavilactone B (I), a potent antifungal agent via defluorinative benzyne formation.220 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).221
3. C–F Bond Activation in Alkenyl Fluorides

3.1. General Aspect of Nucleophilic Substitution in gem-Difluoroalkenes

Activation of the sp²-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 sp²-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 sp²-hybridized fluoroalkenes in comparison with sp³-hybridized fluoroalkanes, and (iii) stable sp³-hybridized β-fluorocarbanions (Scheme 134). The high reactivity of 1,1-difluoroalkenes to nucleophiles is dependent on the polar nature of the double bond. The ¹³C NMR chemical shifts of difluoromethylene and methylene compounds (Scheme 135) indicate a marked deshielding of α-carbon and a large chemical shift difference between α- and β-carbons for fluoroalkenes, suggesting a low-lying LUMO with large coefficients at α-carbon atom (high reactivity to nucleophiles).

Nucleophiles therefore attack exclusively at the gem-difluoromethylene carbon atoms of difluoroalkenes to form β-fluorocarbanions. 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 undergo defluorination, producing α-substituted monofluoroalkanes; (b) 1,2-addition: with any nucleophiles in protic solvents or with electrophiles in aprotic solvents, the carbanions can be trapped with a proton or an electrophile to give addition.
(c) $S_N2^\prime$ type substitution: the third case is $S_N2^\prime$ 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-difluoroethylene (461) with nucleophiles are summarized in Scheme 137. Alkoxides, silyl anions, ester enolates, and diphenylphosphinyl anion 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 $\beta$-vinylc proton to generate vinyllithium 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).

Scheme 137

The Mizoroki–Heck reaction is a general and convenient method for arylation of olefinic compounds involving oxidative addition of aromatic halides to Pd(0), carboxylation to alkenes, and $\beta$-H elimination. Under the Mizoroki–Heck reaction conditions, vinylidene fluoride 461 undergoes carboxylation to give $\alpha$-fluoroptyrene (470) as a main product instead of $\beta,\beta$-difluorostyrene (469; the Heck reaction product) as shown in Scheme 139. 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 using a catalytic amount of Pd(OAc)$_2$.

Scheme 139

The much higher electrophilic reactivity of gem-difluoromethylene carbon versus methylene carbon is also demonstrated by [2,3]sigmatropic rearrangement of carbanion...
which exclusively attacks gem-difluoromethylene site rather than nonfluorinated methylene site (Scheme 140). Moreover, a remarkable chemoselectivity is observed for cyclization of α-substituted β,β-difluoroacylate 476 in contrast to nonfluorinated acrylate 478. Baldwin reported the cyclization of dimethyl 4-methylene glutamate 478 to γ-lactam 479, showing difficulty for 5-endo-1,4-cyclization of 478. 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.

3.2. Structure and Reactivity of gem-Difluoroalkenes

Terminal gem-difluoroalkenes accept nucleophiles easily and undergo addition—elimination reaction to give α-substituted fluoroalkenes. Some synthetically useful examples are shown in Scheme 142. Carbon nucleophiles such as metal enolates of dialkyl malonates, Grignard reagents, alkynyl lithiums, and lithium amides participate in smooth addition—elimination reactions to form the defluorinated products. Difluoroallene 486 behaves similarly, affording monofluoroallene 487 via addition—elimination. The action of bidentate nucleophiles such as catechol and thiocatechol 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-difluoroalkenoyl to synthesize highly functionalized alkenes 494 and 498 (Scheme 144). The gem-difluoromethylene compounds are readily prepared from commercially available 2,2,2-trifluoroethanol for 492 and 2-bromo-pentafluoropropene for 495 so that the disubstitution protocol of the gem-CF₂ 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 alkoxyl and amino groups (Scheme 145). 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 lithiiums to afford substitution products 502. 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.
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 monofluorinated cyclic compounds. The striking feature in this cyclization is the fact that two fluorine substituents are essential; the corresponding monofluoro compound 513 (R1 = 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 514.223

The cyclized products 517 and 520 include cyclopentenes,232,247,248 dihydrofurans, dihydropyroles,249 dihydrothiophenes,249 thiophenes,250 and also corresponding benzo-derivatives 523 (Scheme 148).223,231 As summarized in Scheme 149, the syntheses of the monofluorinated six-membered ring compounds such as 2-cyano-,252 2-alkyl-,253 and 2-aryl-substituted254 quinolines, isoquinolines,253 dihydroisoquinolines,255 cinnolines,256 benzopyrans,257 and dihydronaphthalenes247 are accomplished by intramolecular addition–elimination protocols.

The intramolecular version of “atypical” Mizoroki–Heck reactions involving β-fluorine elimination229,230 works well for the construction of fluorine-containing five-membered rings (Scheme 150).258 In the presence of Pd(PPh3)4 (0.1 equiv) and PPh3 (1 equiv), a 5-endo-trig-alkene insertion proceeds smoothly via aminopalladium species 539 starting from 3,3-difluorally ketone O-pentafluorobenzoyloxime 538, providing a facile access to 5-fluoro-3H-pyrrole 541.
3.4. High Reactivity and Toxicity of Polyfluorinated Fluoroalkenes

It is notable that some highly fluorinated alkenes are poisonous 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 tetrafluorocyclopropene (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 152.260 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.261

Scheme 150

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) or two different nucleophiles are introduced successively (Scheme 155).262

Scheme 153

Diverse nucleophiles such as aryl and heteroaryl, alkyl, alkenyl, and alkynyl metals, anions of group
VI elements\textsuperscript{238,268} 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.\textsuperscript{269} As an exception, the SN$_2^\prime$ reaction takes place at the second substitution step depending on the nature of nucleophiles and stability of the products (Scheme 156).\textsuperscript{238}

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 $\text{545}$ to provide $\text{559}$ on UV irradiation, which partakes in defluorodemercuration to give monosilyl cyclopentene $\text{560}$.\textsuperscript{270} On $\gamma$-ray irradiation, the radicals derived from cyclic ethers $\text{561}$ and octafluorocyclopentene $\text{545}$ abstract hydrogen from ethers $\text{561}$, affording the addition products $\text{562}$.\textsuperscript{271}

\section*{4. C–F Bond Activation in Aliphatic Fluorides}

\subsection*{4.1. C–F Bond Activation of Trifluoromethyl Group Attached to $\pi$-Electron System}

\subsubsection*{4.1.1. SN$_2^\prime$ Type Reactions in Trifluoromethylenalkenes}

The SN$_2^\prime$ reaction has been often employed for carbon–halogen bond cleavage. However, trifluoromethylated alkenes also are substrates that easily undergo the SN$_2^\prime$ reaction. Before discussing the SN$_2^\prime$ reaction, let us first consider the possible reactions of 3,3,3-trifluoropropene as a model substrate of trifluoromethylenalkenes $\text{563}$ with nucleophiles, electrophiles, and radicals as shown in Scheme 158. Reactions with nucleophiles are divided into two categories: SN$_2^\prime$ 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 $\text{563}$ with strong electrophiles occur slowly under rather severe conditions, providing addition products that arise from attacking electrophiles at $\alpha$-position via $\text{566}$ (Scheme 159).\textsuperscript{272} The reactions of 3,3,3-trifluoropropene ($\text{568}$) with radicals proceed mostly via radical addition at $\beta$-position followed by hydrogen abstraction (Scheme 160),\textsuperscript{273} where no defluorination is observed.

Now, let us return to the discussion of the SN$_2^\prime$ 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,\textsuperscript{274} which also apply to the carbanion-like transition states formed in concerted reactions. In aprotic solvents, SN$_2^\prime$ reactions proceed generally via defluorination to give functionalized 1,1-difluoroalkenes $\text{564}$ (Scheme 158). Trifluoropropene derivatives $\text{563}$ with either electron-
withdrawing or electron-donating substituents (R) at α-carbon smoothly undergo S_{N2}′ reactions on reacting with carbon and heteroatom nucleophiles. Reactions of trifluoropropene 568 with carbon and silicon nucleophiles provide 572 and 573, respectively, in excellent yields (Scheme 161). α-Trifluoromethylstyrene (575) is a good substrate that reacts with a variety of alkyl lithiums to yield α-functionalized β,β-difluorostyrenes 576 (Scheme 162). α-Trifluoromethylstyrene (575) reacts with trimethylsilylated DMF (577), a synthone of iminium carbanion 579 under neutral conditions, affording 578 on heating in toluene (Scheme 163).\textsuperscript{279} Bisolithio nucleophile 580 couples with CF3−styrene 575 at the carbon site rather than the amide-nitrogen site (Scheme 164).\textsuperscript{280} Scheme 165 shows an intramolecular version of the S_{N2}′ reaction of \textit{ortho}-substituted CF3−styrene derivatives where nitrogen nucleophile attacks β-carbon in S_{N2}′ 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.\textsuperscript{281}

Silyl alkene 589, which is readily prepared from commercially available 588, undergoes facile S_{N2}′ reactions with a variety of lithium nucleophiles to provide 590 (Scheme 166).\textsuperscript{282} 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.

Trifluoromethylacrylic acid (592) and esters are extremely strong nucleophile acceptors so that they participate in facile S_{N2}′ reaction even at low temperature in aprotic solvents. Some results are summarized in Scheme 167.\textsuperscript{223,283–285} Grignard and alkyl lithium reagents provide S_{N2}′ 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 β-substituted β-fluoroacrylic acids. However, it is noteworthy that protic nucleophiles such as amines\textsuperscript{286} and alcohols\textsuperscript{287} (Scheme 168) add simply to the double bond of 592 and do not induce the S_{N2}′ reaction. In contrast to the facile S_{N2}′ reaction of CF3−alkenes, CF3−alkynes undergo normal addition to the triple bond, as shown in...
2-butynoic acid ester 595 in which addition occurs at the 3-position rather than the 2-position (Scheme 169).288

Because of the high reactivity of trifluoromethylated alkenes, even 1-substituted-3,3,3-trifluoropropenes 597 and 599 undergo the SN2′ reaction with Grignard reagents, although they need a higher temperature or longer reaction times as compared with H₂C=C(CH₃)CF₃ (568), H₂C=C(Ph)CF₃ (575), and H₂C=C(SiMe₂Ph)CF₃ (589), presumably because of the steric hindrance at the reaction sites (Scheme 170). Triflate 599 is transformed smoothly to R-fluoro-R,beta-two-unsaturated esters 601 in good yields.290

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 R-(trifluoromethyl)styrenes with arylboronic esters and MeMgCl (Scheme 171).291 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.

A catalytic version of the intramolecular SN2′ reaction of trifluoromethylated alkenes was reported by Ichikawa (Scheme 172).292 Upon exposure to a catalytic amount of Pd(PPh₃)₄, 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 CF₃ group accept nucleophiles at the heteroatom site, leading to fluoroalkenes via formal SN2′ reactions (Scheme 173).293,294
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 (Bu$_4$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). In the presence of a catalytic amount of sodium fluoride, TFDA undergoes decomposition to afford difluorocarbene (619), CO$_2$, 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 sequence of fluoride. By the use of a catalytic amount of CsF, the C–F bond activation reaction (S$_N$Ar) of hexafluorobenzene (5) with silyl ether 620 affords the substitution product 621 in good yield. In 2008, Holmes et al. developed a high yielding synthesis of diaryl ether 623 and sulfide 626 and by a fluoride-catalyzed S$_N$Ar process in scCO$_2$. 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). A small amount of fluoride salt promotes the condensation polymerization between silylacetylene-functionalized monomer 629 and C$_6$F$_6$ to deliver high...
molecular weight poly(phenylene ethynylene) \( \text{630} \). Fluoride-induced \( \text{S}_\text{N} \text{Ar} \) protocol is applicable to the synthesis of benzodichalcogenophenes \( \text{632} \) possessing polyfluoroarene moieties at their termini (Scheme 177).\(^{299}\)

**Scheme 176**

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 \( \text{635} \) provides the metal—difluorocarbene complex \( \text{634} \) (Scheme 178).\(^{300}\)

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

Prakash et al. reported TBAF-catalyzed 1,2-fluoride elimination of 1,2-bis(trimethylsilyl)-1,1,2,2-tetrafluoroethane (\( \text{641} \)) acting as a convenient, in situ source of \( \text{CF}_2\text{CF}^- \) (Scheme 180).\(^{302}\) In the presence of 0.1 equiv of TBAF, the reactions of \( \text{641} \) with aldehydes and ketones give 2,3,3-trifluoroallylic alcohols \( \text{643} \) in good yields. A catalytic amount of TBAF is needed to convert \( \text{641} \) into (trifluorovinyl)trimethylsilane \( \text{645} \) via \( \beta \)-fluoride elimination and to initiate the reaction of vinylsilane \( \text{645} \) with carbonyl compounds \( \text{642} \).

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).\(^{303}\) When 1-(3′-chlorophenyl)-1-trimethylsilyl-1,2,2,2-tetrafluoroethane (\( \text{647} \)) is treated with a catalytic amount of \([\text{Bu}_4\text{N}]\text{[Ph}_3\text{SiF}_2] \) (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.\textsuperscript{304}

CsF-catalyzed β-fluoride elimination of β,β-difluoro vinylsilanes (651) is applicable to the generation of reactive fluoroalkynes, which readily undergo polymerization to yield the corresponding fluoropolyacetylenes (Scheme 182).\textsuperscript{305,306} With exposure to a catalytic amount of CsF, defluorodesilylation of trifluorovinylsilane 651a gives semiconductor polymer 652, which shows conductivity of 10\textsuperscript{-9} to 10\textsuperscript{-10} Ω\textsuperscript{-1} cm\textsuperscript{-1}.\textsuperscript{305}

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 π-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 β,β-difluoro-α-trimethylsilyloxyacrylate (655).\textsuperscript{307}

In 2001, Amii and Uneyama explored the catalytic version of fluoride-induced 1,6-elimination to generate p-xylylene intermediate 657 (Scheme 184).\textsuperscript{308} 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.\textsuperscript{309} A higher reaction temperature is considered to be essential to the elimination of a fluoride ion, probably because the generation of tetrafluorquinodimethane (657) is a thermodynamically unfavorable process to forfeit the stabilization energy of the aromatic 6π-system.

In the previous section, we have introduced SN2′ 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$_3$ 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).

The reactivity and mechanism on electroreductive cleavage of C–F bonds in fluoromethylarenes (benzylic fluorides) 663 have been investigated by several groups (Scheme 186).$^{310}$ 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$_2$, acetone, or DMF is achieved with good yields by electrolysis in an undivided cell fitted with Mg or Al sacrificial anode (Scheme 187).$^{311}$

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).$^{312}$ 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$_3$SiMe$_3$ (674), which acts as a difluorobenzyl carbanion synthon. The chemical metal reduction methods are not available: the Me$_3$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$_3$ (668) to furnish PhCF$_2$SiMe$_3$ (674) is achieved by electroreduction.$^{313}$ Furthermore, the present protocol is applicable to a large-scale synthesis of 674 using a tubular flow cell.

Selective defluorination from readily available trifluoromethylated compounds are promising and highly efficient methods for the preparation of difluoromethylated compounds. Fluoromethylated ketones undergo electroreductive defluorination.$^{314}$ Stocker et al. reported electrochemical transformation of trifluoromethyl ketones 677 into methyl ketones 680 and/or pinacols 681 (Scheme 190).$^{305}$ In their reaction conditions, all fluorine atoms in the products are lost. Because of the small difference between the reduction potentials of CF$_3$–, CF$_2$H–, and CFH$_2$–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$_2$H–ketones 678.

In order to avoid the overreduction and to execute selective demonofluorination, 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...
and 678 and enol ethers 682 are $-0.97$, $-0.87$, $-0.41$ eV, respectively.

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

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

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

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).$^{317}$

The electroreductive protocol works well for selective monodefluorination of trifluoromethyl imines 693 to give the corresponding difluoroamines 694 (Scheme 197).$^{320}$ 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...
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). 321–324

Scheme 196

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 sp³ C–F bond activation by the use of the zirconium complex (Scheme 200). 325 The reaction of 1-fluorohexane (708) with Cp*₂ZrH₂ at ambient temperature for 2 days produces hexane and Cp*₂ZrHF in quantitative yields. Also, fluorocyclohexane undergoes hydrodefluorination at 120 °C. The reaction of Cp*₂ZrH₂ with cyclopropylcarbinyl fluoride gives a definitive evidence for radical formation, in which the cyclopropylcarbinyl 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). 326 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). 90a,327 Primary aliphatic fluorides undergo fluorine–lithium exchange to form aliphatic organolithiums. The reaction of 1-fluoroctane (711) with
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.

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 π-electron systems (B).

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 α-position partake in vicinal dehalodefluorination, resulting in the formation of gem-difluoroalkenes (Scheme 205).306,328-330

The scope of reductive β-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).331-333

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).334 Claisen rearrangement of 728 leads to the formation of C-allylated keteester 729, and the subsequent transformations of the common precursor 729 provides racemic β,β-difluoroglutamic acid and β,β-difluoroproline (730).

Reductive manipulations of CF3CX2 moieties allow the formation of gem-difluorovinyl organometallic reagents. Treatment of 2,2-dibromohexafluoropropane (734) with 2 equiv of metallic zinc in DMF gives CF3(ZnX)C=CF2 (735),
which participates in allylation, acylation, halogenation, and oxidative dimerization to afford a variety of CF3(R)C==CF2 compounds (Scheme 208). In a competition experiment, Zn reacts faster with the intermediate CF3BrC==CF2 than with CF3CBr2CF3 (734).

Scheme 208

![Scheme 208](image)

The reaction of 1,3-dichloro-4,4,4-trifluorobut-2-ene (739) with magnesium gives CF2==C(Cl)CH==CH2 (740) in 34% yield (Scheme 209). 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

![Scheme 209](image)

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). 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, microphotonics, 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.

Scheme 210

![Scheme 210](image)

4.2.2. Low-Valent Metal-Promoted Reductive Defluorination from Trifluoromethyl Group Attached to π-Electron System

Chemical methods for reductive defluorination of a trifluoromethyl group (next to π-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) under- goes not only carbonyl reduction but also reductive substitution of all fluorine atoms of the trifluoromethyl group, leading to ethylbenzene in 90% yield (Scheme 211).

Scheme 211

![Scheme 211](image)

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).

Scheme 212

![Scheme 212](image)

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 fluoride atoms in position 8 by hydrogen regioselectively (Scheme 213). 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).

Scheme 214

![Scheme 214](image)

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 Mg0 with ketones 677, which are further reduced to anion species 754 by Mg. The resultant β-fluorinated organomagnesium species 754 readily undergo β-elimination to afford difluoroenol ethers 682.
Compared to previously available methods, the present methodology has several advantages: (i) the starting trifluoromethyl ketones 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 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 and the subsequent transformation of provide a route reliable for preparing a diverse group of difluoro compounds (Scheme 216).301,344,347

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

Electrophilic halogenation of 2,2-difluoroenol silanes is highly useful for the preparation of α-halodifluoromethyl ketones. Prakash and Olah et al. presented the reaction of difluoro silyl enol ethers with halogens at low temperature to produce a high yield of α-halodifluoromethyl ketones and [18F]-labeled trifluoromethyl ketone (Scheme 218).350

In 2006, Hu et al. developed a non-ODS-based (ODS = ozone-depleting substance) preparation of chlorodifluorocetophenone (763) via the Mg-mediated defluorination route and the use of as a novel and convenient difluorocarbene source for phenols (Scheme 219).351

To demonstrate further synthetic utility of our C–F bond cleavage reactions, we developed 1-butoxy-4,4-difluoro-3-(trimethylsiloxy)-1,3-butadiene, a fluorinated analogue of Danishefsky’s diene, acting as one of the most fascinating C4 building blocks. The process shown in Scheme 220 provides access to Danishefsky’s difluoro diene in a simple and efficient fashion. The subsequent hetero Diels–Alder reactions of give fluorinated six-membered heterocycles.
The reactions of diene 767 with aldehydes and aldimines in the presence of Lewis acid (ZnBr₂ or ZnI₂) yield the fluorinated dihydropyrones and difluoro dihydropyridones, respectively. Furthermore, the enantioselective hetero Diels−Alder reaction with benzaldehyde affords corresponding dihydropyrene (+)-769 in 92% ee in the presence of chiral titanium(IV)−BINOL system.

Scheme 220

A magnesium(0)−Me₃SiCl 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 α-silyldifluorocarboxylates 689d−g in 55−66% isolated yields (Scheme 221). 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 difluoroamines 694 (Scheme 222). 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). Aminodifluoroacrylate 503 is a very interesting compound possessing both N-silyl-difluoroamine and difluoroacrylate moieties. Because of the unique structure, enamine 503 is a useful precursor to a wide repertoire of difluorinated α-amino acids, since it can react with not only electrophiles but also nucleophiles and radical species at the β-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. Performing the reaction of 503 with isopropyl iodide under radical conditions gives difluorinated leucine derivative 771 without accompanying defluorination. On the other hand, the difluoromethylene carbon of 503 is highly reactive even to a weak nucleophile like alcohols. 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

More interesting and important is the asymmetric synthesis of difluorinated α-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 Pd(OCCF₃)₂ and (R)-BINAP in 2,2,2-trifluoroethanol (TFE), the catalytic asymmetric hydrogenation of 774 proceeds smoothly at room temperature to yield aminoester (R)-775 in 88% ee. Upon treatment with allylttributyltin 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 β,β-difluoroglutamic acids (777) and β,β-difluoroprolines (778) are obtained with high enantiopurity.

Scheme 224

To demonstrate a synthetic virtuosity, reductive protocols using a magnesium(0)−Me₃SiCl 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 activation.
and C–Cl bond cleavage of trifluoroacetimidoyl chlorides 779 results in the selective formation of bis-silylated difluoroenamines 780 (Scheme 226). 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 difluoroenamines 780 in high yields.

By means of the successive double dehalogenation reactions as shown above, the resultant bis-silylated difluoroenamines 780 are very promising bifunctional synthetic blocks, which have not only N-silylenamine skeletons but also α-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.

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. Mg(0)-promoted defluorinative silylation of 1,4-bis(trifluoromethyl)benzene (790) affords α-silyl-α,α′,α″-pentfluoroxylene (656) in 48% yield. The subsequent conjugative 1,6-elimination from 656 induced by CsF provides fluorocyclophane AF4 (658). Furthermore, 3-chloropentafluorobenzene (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.

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). 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 α-trifluoromethyl enol silyl ethers (Scheme 231).304 The stereoselective formation of 795 and 797 can be explained by intramolecular C–F···Si coordinative interaction, which leads the cis relationship between CF₃ and OSiMe₃ groups in silyl enol ethers 795 and 797.

Scheme 231

α-Fluoro-α,β-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 (CF=CH) has been recognized to provide conformationally fixed peptide bond isosteres.359 The C–F bond cleavage protocols are used for the preparation of monofluoroalkenes (Scheme 232).360 The action of Mg/Me₃SiCl in THF on difluoroaldol 798 causes the defluorinative silylation to afford monofluoroalkenyl silanyl ether 799. The subsequent acid-catalyzed hydrolysis of the crude enol 799 yields α-fluoro-α,β-unsaturated ketone 800.

Scheme 232

Besides metallic zinc and magnesium, low-valent samarium reagents are effective for reductive C–F bond activation. SmI₂-mediated reductive defluorination of γ,γ-difluoro-α,β-enoates 805 is successfully applied to the synthesis of (Z)-fluoroalkene dipeptide isosteres 800 (Scheme 233).361 In the presence of t-BuOH (a proton source), reduction of γ,γ-difluoro-α,β-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 SmI₂–HCHO reagent system with chiral enoate 810c furnishes D-Phe-Ψ[(Z)-CF=CH]-D-α,α-Ser isosteres, which is converted to enantiomerically pure isosteres such as D-Phe-Ψ[(Z)-CF=CH]-D-Leu (811) and D-Phe-Ψ[(Z)-CF=CH]-D-Cys (812) derivatives.361

Scheme 234

Palladium-catalyzed reductive defluorination of allylic gem-difluorides is also useful for the chemo- and stereoselective synthesis of fluoroalkanes (Scheme 235).362 In the presence of a catalytic amount of [η₃-C₃H₅PdCl]₂, dppe, and Et₃N, allylic gem-difluorides 813 and 816 are treated with 2 equiv of Ph₃SiH, affording monofluoroalkanes 814 and 817, respectively, in high yields.
In 2006, low-valent niobium-mediated double activation of C–F/C–H bonds was reported (Scheme 236). α-Phenyl trifluorotoluene \( \mathbf{818} \) undergoes low-valent niobium-mediated dehydrodefluorination from both benzylic C–F bond and aromatic ortho C–H bond to form 9,9-difluorofluorene \( \mathbf{819} \), which is readily reduced under the conditions to produce parent fluorene \( \mathbf{820} \). When the reaction is carried out in toluene, \( \mathbf{818} \) is converted into \( \mathbf{821} \) and \( \mathbf{822} \) via intermolecular dehydrodefluorination. One possible mechanism for the formation of difluorofluorene \( \mathbf{819} \) is that difluorobenzylic niobium species would be generated from \( \mathbf{818} \) and the low-valent niobium. A generation of difluorobenzylic niobium species might permit intramolecular coupling with ortho C–H bond, leading to \( \mathbf{819} \).

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\(_4\). Deuterium labeling experiments suggests that the Nb-catalyzed hydrodefluorination of trifluoromethyl arenes does not proceed via a simple S\(_\mathrm{N}\)2 mechanism; two of the fluorines in \( \mathbf{828} \) are replaced with deuteriums by LiAlD\(_4\), and (dideuterio)benzylic anion equivalent \( \mathbf{829} \) is formed to give the product after hydrolysis.

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: \( \text{R–I} > \text{R–Br} > \text{R–Cl} > \text{R–F} \)). There have been a few reports on nucleophilic substitution using alkyl fluorides as substrates. In marked contrast, the desired displacement of fluoroalkanes occurs efficiently under the 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). The halogen-exchange protocols work well for the trifluoromethyl compounds even possessing diverse functional groups.

In 1938, Henne and Newman initially attempted Friedel–Crafts reaction of benzotrifluoride with acetyl chloride; however, they discovered AlCl\(_3\)-mediated halogen-exchange of benzotrifluoride to yield benzotrichloride.

Boron and aluminum-containing Lewis acids such as BBr\(_3\) and AlCl\(_3\) promote the halogen-exchange reactions of a variety of fluoroalkanes to afford the corresponding halides (Scheme 240). 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...
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 alkylations involving chemoselective transformation in which only fluorine atoms are displaced in S_N1 mode (Scheme 241).

In 1997, Ooi and Maruoka et al. demonstrated a new synthetic utility of a strong Al–F interaction (Scheme 242). tert-Alkyl fluorides are suitable alkylation agents for carbons of ketene silyl acetal 850, alkylnylaluminum 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.

Oshima et al. reported the boron trifluoride-catalyzed transformations of alkyl fluorides with silyl enolate, allylsilane, and hydrosilane (Scheme 243). 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^3-C-F bonds of alkyl fluorides to sp^3-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). 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_3AlCl 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. Several Lewis acids catalyze C–C bond formation at the anomeric position of glycosyl fluoride derivatives.
Tetra-O-benzyl-D-glycopyranosyl fluoride (862) undergoes the coupling reactions with trialkylaluminum reagents under mild conditions with α-preference at the anomeric positions of the resultant C-glycosides 863 (Table 8). 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). The successful results of the regio- and stereoselective fluoride-displacement reaction using trialkylaluminum reagents (R3Al) were reported (Scheme 247). In the presence of a Cu(I) salt, alkyl-transfer reactions from R3Al to (E)- and (Z)-4,4-difluoro-5-hydroxyallylic alcohol derivatives 868 proceed in S_N2′-type manner to give the corresponding 2-alkylated (Z)-4-fluoro-5-hydroxyhomallylic 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.

Carbocations and silyl cations are electron-deficient species that can readily abstract fluorides from organofluorine compounds. In 1997, Lectka et al. described C–F bond activation induced by ary1 carbocations in solution (Scheme 248). 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 Et2O and 10% aqueous NaHCO3, 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 C6F6 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 C6F6.
Because of the strong affinity for a fluorine atom, free $\text{X}_3\text{Si}^+$ cations (silylium ions) are able to abstract fluorides from organofluorine compounds quite effectively. $\text{X}_3\text{Si}^+$ 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$^3$-$\text{C}$-$\text{F}$ bonds (Scheme 249). The strategic features are (i) abstraction of a fluoride ion from a $\text{C}$-$\text{F}$ bond in $\text{R}_2\text{F}$ by $\text{X}_3\text{Si}^+$ salt, (ii) generation of a carbocation $\text{R}^+$, which can abstract $\text{H}^-$ from hydrosilane $\text{X}_3\text{SiH}$, and (iii) regeneration of $\text{X}_3\text{Si}^+$ species. The overall transformation is designed to be a $\text{Si}$-$\text{H}/\text{C}$-$\text{F}$ σ-bond metathesis catalyzed by $\text{X}_3\text{Si}^+$ salt. At 22 °C, benzotrifluoride (668) smoothly undergo hydrodefluorination in the presence of $\text{Et}_3\text{SiH}$ and a catalytic amount of $\text{Et}_3\text{Si}[\text{B(C}_6\text{F}_5\text{)}_4]$ to yield the corresponding hydrocarbons. The hydrogen-bridged disilyl cation 878 possessing a 1,8-naphthalenediy1 backbone is also an effective catalyst for hydrodefluorination of fluorocarbons under mild reaction conditions (Scheme 250).

Using highly electrophilic silylium compounds endowed with carboranes as weakly coordinating counterions, fluorinated benzylic carbocations such as ($\text{p}$-$\text{FC}_6\text{H}_4$)$_2\text{CF}^+$ (880), ($\text{p}$-$\text{FC}_6\text{H}_4$)(CH$_3$)$_2\text{CF}^+$ (882), and fluorinated trityl ions are readily isolated (Scheme 251).

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

Not only cationic species but also neutral organosilicon compounds have potentials to activate $\text{C}$-$\text{F}$ bonds. Yus et al. found that the organosilicon compounds such as bidentate compound 887 are excellent additives for reductive defluorination of fluoroalkanes (Scheme 253). Fluorononane
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 °C. Very interestingly, in the presence of a substoichiometric amount of 1,2-bis(trimethylsilyl)benzene, naphthalene-catalyzed fluorine–hydrogen-exchange reactions of primary, secondary, and tertiary fluoroalkanes afford the corresponding alkanes, while monosilylbenzene is fruitless for the purpose.

The calcium β-diketiminate complex 892 not only exhibits an interesting interaction mode of a CF₃ group, from which one fluorine atom coordinates to the Ca center, but also undergoes C–F bond breaking (Scheme 255). From single-crystal X-ray diffraction analysis of the six-coordinate 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 (C₁–F₁: 1.381(5) Å, C₂–F₂: 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 β-diketimine ligand in 892 undergoes intramolecular cyclization involving C–F bond cleavage to give the heterocycle 894 in 50% yield. The present anechimically assisted cyclization would proceed via the following pathway: coordination of the CF₃ group of the β-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(trifluoromethyl)-substituted hetero-1,3-dienes 895 to furnish
partially fluorinated five-membered heterocycles 900 (Scheme 256). Initially, [4 + 1]-cycloaddition of SnCl₂ 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 heteroallyl anion substructures and cationic tin(IV) moieties. Intramolecular fluoride migration to tin(IV) affording 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, α-trifluoromethyl α-amino acids are readily available via 5-fluoro-4-trifluoromethyloxazole 902.

### Scheme 256

**Scheme 255**

![Scheme 255 diagram]

**Scheme 256**

![Scheme 256 diagram]

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 α-alkylation of metal enamides done by Nakamura’s group, primary alkyl fluorides are useful alkylating reagents for magnesium enamides of ketones (Table 9). 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 alklylation reactions with magnesium enamides 907 to give the products 909 (Scheme 257).

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Magnesium Enamide</th>
<th>Halodecane</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N,N-dimethyl</td>
<td>X = F</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908a</td>
</tr>
<tr>
<td>2</td>
<td>N,N-dimethyl</td>
<td>X = F</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908b</td>
</tr>
<tr>
<td>3</td>
<td>N,N-dimethyl</td>
<td>X = F</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908c</td>
</tr>
<tr>
<td></td>
<td>N,N-dimethyl</td>
<td>X = Cl</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908c'</td>
</tr>
<tr>
<td></td>
<td>N,N-dimethyl</td>
<td>X = Cl</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td>4</td>
<td>N,N-dimethyl</td>
<td>X = F</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908d</td>
</tr>
<tr>
<td></td>
<td>N,N-dimethyl</td>
<td>X = Cl</td>
<td>C₁₀H₂₁</td>
</tr>
<tr>
<td></td>
<td>MesMgBr</td>
<td></td>
<td>908d'</td>
</tr>
</tbody>
</table>

For nucleophilic transformation of organic fluorides, the choice of a countercation 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 β-C-glycoside derivatives 910 and 912 in moderate yields (Scheme 258).403 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.404 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\(_8\)H\(_{17}\)-F does not react at all, even in the presence of Ni catalyst (Scheme 259).405

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\(^1\)MgX) react with (\( \eta^1 \)-allyl)\( \eta^1 \)nickel 914 to form \( \eta^1 \),\( \eta^1 \)-octadienylmagnesium 915. The cross-coupling products (R\(^1\)-R\(^2\); 918) would be formed via oxidative addition of alkyl fluorides (R\(^2\)-F) to anionic Ni-complex 915, providing di(alkyl)nickel complex 917, followed by reductive elimination. In the oxidative addition step, magnesium (the countercation of anionic complex 916) might play an important role (as a Lewis acid) to activate C–F bonds in fluoroalkanes by complexation.

A CuCl\(_2\)/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.405

Scheme 260

In the presence of a catalytic amount of Cp\(_2\)ZrCl\(_2\), \( n \)-octyl fluoride (711) reacts with \( \beta \)-phenethylmagnesium chloride to afford 2-phenyldecane (919) via alkylation of the styrene–zirconate intermediate at the benzylic position (Scheme 261).406

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).407 When the reaction of \( n \)-octyl fluoride (711) with 3 equiv of H\(_2\)C\( = \)CH–MgCl in the presence of NiCl\(_2\)(PPh\(_3\))\(_2\) (3 mol %) is quenched with D\(_2\)O, deuterated compound 921 is formed. When CO\(_2\) 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 halide ions. Brook rearrangement is effective for cleavage of carbon–silicon bond (X = SiR\(_3\), trialkysilyl group; and R\(^1\) = O\(^-\), alkoxyl anion).
Dehydrofluorination and the related defluorination reactions, Brook rearrangement, and other interesting defluorinative reactions are summarized in this section.

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$_3$ group. Trifluoroethyl compounds such as phenyl ether, alkyl ether, tosylate, 2-methoxyethoxymethyl (MEM)—ether, phenyl sulfide, chloride, and fluoride 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. Vinyl lithium intermediates are unstable so that they undergo either delithiumfluorination or coupling reactions with reactive electrophiles. gem-Difluorovinyl dialkyl boranes are available by a sequence of dehydrofluorination, boration, and alkylation of tosylate. They are reactive and versatile building blocks for difluoro compounds (Scheme 265). gem-Difluorovinyl phenyl sulfide is so reactive to nucleophiles as to be aminated with lithium diisopropylamide (LDA), leading to alkynyl amine as a final product (Scheme 266).

4.5.2. Dehydrofluorination Leading to Quinodimethane Intermediates

Difluorinated quinodimethane derivatives and are potential precursors for fluoroheterocycles. The preferred defluorination from the CF$_3$ group rather than the CF$_2$ 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 suggests that the reaction proceeds via and .

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$_3$ group is more susceptible to the base-catalyzed dehydrofluorination than the CF$_2$ group. The preferred defluorination from the CF$_3$ group rather than the CF$_2$ 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 suggests that the reaction proceeds via and .

4.5.2. Dehydrofluorination Leading to Quinodimethane Intermediates

Difluorinated quinodimethane derivatives and are potential precursors for fluoroheterocycles. The base-catalyzed 1,4-dehydrofluorination of 2-trifluoromethyl aniline and its derivative and 2-trifluoromethyl active methylene compounds proceed smoothly and gener-
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

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.424 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 benzylsilane 966 with perfluoroorganometallic reagent 967 (Scheme 272).425 It is considered that Brook rearrangement of the alkoxide 968 takes place to give the organometallic intermediate 969, which readily participates in β-fluoride elimination to provide silyl enol ether 970.426

Scheme 272

C–F bond activation triggered by Brook rearrangement is applicable to the preparation of 2,2-difluoroeno silyl ethers.422 α-Silyl-α-trifluormethylalkoxylates 974 are generated in situ by one of the three possible reactions: reaction of acyl silanes 972 with CF₃SiMe₃,301 trifluoroacetyl silanes 973 with alkyl lithiums,427 and trifluoromethyl ketones 677 with trialkysilyl anions,428 respectively (Scheme 273). They undergo desilylative defluorination via Brook rearrangement, providing difluoroenol silyl ethers in good yields (Scheme 274).

Scheme 273

Portella et al. have continuously investigated the useful applications of 2,2-difluoroeno silyl ethers. Under fluoride
initiation, the reactions of acylsilanes with trifluoromethyltrimethylsilane give difluoroenoxysilanes, which are used in situ for the subsequent Lewis acid-promoted C–F bond formation with electrophiles. As depicted in Schemes 275 and 276, the present one-pot procedures are applicable to the synthesis of difluorinated monoterpenes such as difluorogomaketone (983), and difluoro-dehydro-curcumene (988). By employing this C–F bond-breakage protocol in sugar chemistry, xylose-derived acylsilane 989 is converted to the corresponding difluoroenoxysilane 990, which is glycosylated by glacial 991 to yield gem-difluoro-C-disaccharide 992 as an 80/20 mixture of α- and β-isomers (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.

6. Acknowledgments

We thank the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant-in-Aid for Scientific Research (B), No. 18350054) for the financial support.

7. References


(a) Lucht, B. L.; Poss, M. J.; King, M. A.; Richmond, T. G.


(g) Anderson, C. M.; Puddephatt, R. J.; Ferguson, G.; Lough, A. J.; Richmond, T. G. Organometallics 1992, 11, 1177.


