C–F bond activation under transition-metal-free conditions
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The unique properties of fluorine-containing organic compounds make fluorine substitution attractive for the development of pharmaceuticals and various specialty materials, which have inspired the evolution of diverse C–F bond activation techniques. Although many advances have been made in functionalizations of activated C–F bonds utilizing transition metal complexes, there are fewer approaches available for nonactivated C–F bonds due to the difficulty in oxidative addition of transition metals to the inert C–F bonds. In this regard, using Lewis acid to abstract the fluoride and light/radical initiator to generate the radical intermediate have emerged as powerful tools for activating those inert C–F bonds. Meanwhile, these transition-metal-free processes are greener, economical, and for the pharmaceutical industry, without heavy metal residues. This review provides an overview of recent C–F bond activations and functionalizations under transition-metal-free conditions. The key mechanisms involved are demonstrated and discussed in detail. Finally, a brief discussion on the existing limitations of this field and our perspective are presented.

transition-metal-free, fluorinated compounds, C–F activation, coupling

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1 Introduction

Fluorinated organic compounds are distinguished in diverse fields such as materials science, polymer chemistry, pesticides and pharmaceuticals [1–6]. This is mainly due to the unique nature of C–F bonds, which can dramatically change the reactivity and properties of parent molecules [7,8]. However, these features also make the C–F bond the strongest C-heteroatom bond linkages in nature [8]. Beyond that, the kinetic issues are also responsible for the inertness of the C–F bond, and thus in most cases, fluorine is not a good leaving group [9]. The above reasons lead to these molecules not easily modified, extraordinarily long-lived and potentially toxic. The study of processes that allow fluorine to be substituted by other atoms or functional groups is an academic challenge and has great promise for applications.

Realizing the importance of C–F bond activation, chemists have put great efforts into C–F bond conversion and functionalization to explore milder reaction conditions and more efficient transformations. This review will mainly discuss transition-metal-free C–F bond activations to form the C–H, C–C, C–Si, C–N, C–B, C–P, C–O, C–S bonds and so on. The numerous examples of transition-metal-catalyzed C–F bond activations have already been well documented and reviewed [10–20].
In general, the most obvious advantage of the transition-metal-free C–F bond activation methods is the cheapness and greenness, and in the field of drug development, without heavy metal residues. What is more, the approach of transition metals for C–F bond cleavage typically underwent oxidative addition of the C–F bond to an electron-rich metal center [21] or involves the homolytic splitting of C–F bonds via a single-electron transfer process [22]. However, the substrate scope is mainly limited to activated aromatic and vinyle C(sp^2)–F bond, or/and strong nucleophilic reagents; [10–20], the C–F bond transformations of nonactivated aliphatic fluorides have received less attention [23,24]. Contingent on the activation mode, three strategies might be distinguished for the C–F bond cleavage under transition-metal-free conditions: (1) using Lewis acid to directly abstract the fluoride; (2) in the presence of strong bases or/and strong nucleophilic reagents, fluoride are nucleophilically substituted; (3) through C–F bond homolysis, C–F bond activation via a radical-based pathway has emerged as a promising and conceptually novel strategy in recent years. Under transition-metal-free conditions, the C–F bond-breaking event proceeds gently and selectively with light or radical initiator.

It is necessary to understand the bond dissociation energies (BDE) of different C–F bonds to study the activation of C–F bonds. As shown in Scheme 1 [25–27], the greater the degree of unsaturation or the more substituents, the higher the BDEs (Scheme 1, left). The BDE of the C–F bond of alkyl fluorides is also related to the amount of fluorine on the carbon. For example, the BDE of CF_4 and CH_3F are 547 and 460 kJ/mol, respectively (Scheme 1, middle). In general, the BDEs of C(sp^3)–F bonds are higher than those of C(sp^2)–F bonds. However, the BDEs of C–F bonds of polyfluorinated are much lower (Scheme 1, right). This review will cover the activation of most of those C–F bonds, and the key mechanisms involved will be demonstrated and discussed in detail. The literature in this review is mostly from 2015 to the present and includes some selected examples during 2000–2015. A small amount of earlier literature is selected to demonstrate the historical advances of the related topics.

## 2 Hydrodefluorination

Catalytic hydrodefluorination (HDF) is an exciting process with great application potential. Not only because it offers a strategy for converting cheaply available perfluorinated or polyfluorinated hydrocarbon into more valuable fluorinated compounds, but also because it is considered as a solution to address the super long-lived greenhouse gas: chloro-fluorocarbons, hydrofluorocarbons, and perfluorocarbons (for example, the atmospheric lifetime of CF_4 can exceed 50,000 years) [28]. Therefore, the current trend in HDF is towards the use of milder solutions for the decomposition of stable C–F bonds and preparing more valuable products from readily available polyfluorinated compounds.

### 2.1 Silicon electrophiles

Under transition-metal-free conditions to break the high activation barrier of the C–F bond, an exceptionally potent Lewis acid with high fluoride affinity is normally required. The formation of more stable main-group element-fluorine bonds is thought to be the key driving force for this transition. The earliest work on the use of Lewis acid to seize fluoride from fluoroalkane was reported by Krause and Lampe [29] in 1977. They observed the redistribution of Si–H/C–F by mass spectrometry in the gas phase upon collision of SiH_3 with CF_4. Subsequently, the Ozerov’s group [30–32] further demonstrated that silicon cations (R_3Si^+), as the extremely strong Lewis acids, could readily abstract fluorides from fluorocarbons by reporting the catalytic HDF of C (sp^3)–F bonds at room temperature. Initially, they employed Et_3Si[B(C_6F_5)_3]^− as catalyst and Et_3SiH as the H source (Scheme 2). Under this catalytic system, silylium ions reacted with almost any C(sp^3)–F bond [30], while C(sp^2)–F bond was retained. They speculated that the inertness of 3 might be due to the relative difficulty of generating perfluoroalkyl cations. Moreover, the catalytic efficiency is highly dependent on the nature of the counter anion, and the authors identified that although [B(C_6F_5)_4]^− is experimentally compatible with triethylsilylium, it is ostensibly not resistant to carbocations and high levels of Brønsted acidity; however, decomposition of [B(C_6F_5)_4] by silylium ions limited the turnover numbers (TONs).

The choice of halogenated monocarboranes [33], which are compatible with the highest levels of Bronsted Lewis [34], as the supporting anions dramatically improved the longevity of the catalysis (Scheme 3) and allowed the TON of the catalytic HDF up to 2,700 [31]. The high efficiency of the process offers the possibility of large-scale restoration applications. In addition to this, although the metathesis of the Si–H/C–F is thermodynamically favorable, this article illustrates that maintaining the Lewis acidity in the reaction system is the key to the overall catalytic HDF reaction.
Similarly, Müller and co-workers [35] designed a hydride-bridged disilyl cation 10\(^+\) for HDF (Scheme 4). Trifluoromethyl benzene 1 could be converted entirely to toluene under mild conditions when a catalytic amount of 10\([\text{B(C}_6\text{F}_5\text{)}_4]^-\) was used. The success of this catalytic cycle is based on the fact that by treatment with an excess of Et\(_3\)SiH, 12\(^-\) can be converted to 10\(^+\).

Subsequently, Stephan and co-workers [36] reported F/H exchange between alkyl fluorides and Et\(_3\)SiH employing the commercially available strong organoborane Lewis acid B(C\(_6\)F\(_5\))\(_3\) [37,38] as the catalyst (Scheme 5). Through \(\eta^1\)-coordination to activate silane [39,40], primary (13, 14), secondary (15) and tertiary (16) alkyl fluorides can be successfully converted into the corresponding alkanes. Notably, due to the lower reactivity of the B(C\(_6\)F\(_5\))\(_3\)/Et\(_3\)SiH system compared with silylium ions, the CF\(_3\) group in 17 did not react, resulting in selective HDF of the fluoromethoxy fragment. The slower reaction in this case is attributed to the presence of the heteroatom, which often prevents the reaction by their nucleophilicity and the potential of donor-acceptor interactions.

Their subsequent research [41] shows that besides common Lewis acids, electrophilic P\(^{III}\) compounds can also achieve catalytic HDF reactions (Scheme 6). Quantitative reduction of C–F bonds was observed for primary (18), secondary (19), or tertiary fluoroalkanes (20). The CF\(_3\) group in PhCF\(_3\) (21) was converted to CH\(_3\) group. The CH\(_2\)F or CH\(_3\)F containing intermediates were not detected even when a limited amount of Et\(_3\)SiH was used. That is probably because the BDE of CHF\(_2\) and CH\(_2\)F are lower than CF\(_3\) (vide supra).

Recently, Ogoshi’s group [42] reported a pentacoordinated hydrosilicates (tetrabutylammonium difluorotriphenylsilicate, TBAT) catalyzed HDF reaction (Scheme 7). Employing hydrosilane as the H source, polyfluoroarenes were converted into the HDF or twofold-HDF products such as 22, 23, 24 and 25 with high regioselectivity. The higher the electron density, the lower the reactivity and regioselectivity of the substrates. (26). Notably, functional groups are generally incompatible with strong Lewis acids, such as nitro group (27), cyano groups (28), ester (29), amides (30), chloride (31) and pyridine (32) are tolerated in this cata-

Scheme 2 The first catalytic HDF of C(sp\(^3\))-F bonds (color online).

Scheme 3 Silylium-carborane catalyzed HDF (color online).

Scheme 4 Hydride-bridged disilyl cation for catalytic HDF (color online).

Scheme 5 B(C\(_6\)F\(_5\))\(_3\)-catalyzed HDF of alkyl fluorides (color online).
lytic system. Furthermore, octafluorocyclopentene could be transformed, whereby only the HDF of the alkenyl fluoride proceeded to afford 33. Unlike the method which utilizes silylium cations as strong Lewis acids to abstract the fluoride (vide supra), this transformation underwent a pentacoordinated hydrosilicates-catalyzed concerted nucleophilic aromatic substitution (CS$_N$Ar) process. The key to this success is that the eliminated fluoride can be regenerated to the hydrosilicate and complete the catalytic cycle.

The heterogeneous catalytic C–F activation of fluoromethanes was achieved by Kemnitz and Braun’s group [43,44] with nanoscopic aluminium chlorofluoride (ACF) as the catalyst (Scheme 8). ACF is an amorphous chlorine-containing aluminum fluoride AlCl$_x$F$_{3-x}$ ($x \approx 0.05–0.3$) and is considered to be the strongest solid Lewis acid with acidity comparable to that of SbF$_5$ [45–47]. In a glass ampule under mild reaction conditions, CH$_3$F (34) yielded Et$_3$SiF and CH$_4$ with a TON up to 400. For CH$_2$F$_2$ (35), the TON can be increased to 112. The HDF of CH$_3$F (36) was also achieved, albeit at elevated temperatures and prolonged reaction time. A surface-bound silylium-ion-like species is considered as the crucial intermediate in the C–F bond cleavage step for this heterogeneous catalytic process.

2.2 Aluminum electrophiles

In addition to silylium ions, aluminium ions can also be applied to catalytic HDF reactions. For example, Rosenthal, Krossing and co-workers [48] reported the room-temperature HDF of 1-fluorohexane 37 with Ph$_3$C$^+$(B(C$_6$F$_5$)$_4$)$^-$ as the per-catalyst (Scheme 9). However, it is less efficient than the silylium ion-based protocols and limited to monofluorinated hydrocarbons. And choosing Reed’s halogenated carborane [CHB$_{11}$H$_7$Br$_6$]$^-$ as the supporting counteranion, the de-fluorinative alkylation competed strongly with the HDF reaction via the alkyl transfer from iBu$_2$AlH [49].

It is worthy of mention that Ehm and Lentz’s group [50] developed an organocatalytic HDF with alkanes as the electrophiles (Scheme 10). This research demonstrated that...
donor solvents activate the aluminium hydride bond, lower the barrier for HDF significantly, and switch the product preference from Z to E. Polyyluorinated compounds such as 41, 42, 43, 44 underwent HDF to deliver corresponding products when Bu₂AlH was employed as the H source.

In a practical contribution, Crimmin and co-workers [51] recently reported the selective HDF of hexafluoropropene 45 to industrially relevant hydrofluoroolefins (a new class of refrigerants) (Scheme 11). The use of AlH₃·NMe₃ leads to the efficient and highly selective formation of 46 (HFO-1234yf) under mild conditions. The mechanism experiment and the DFT calculations suggest that a concerted SNV mechanism occurs with high substrate bias for H/F-exchange at the terminal position of 45.

2.3 Germeylium electrophiles

In analogy to the HDF using silicon and aluminium electrophiles, it has been shown that germane can be employed as the hydrogen source or the per-catalyst. Different from Crimmin’s work to synthesize the HFO-1234yf, Kemnitz and Braun’s group [52] reported a consecutive transformation of it (46 or 47) with germane as the H source (Scheme 12). Treatment of 47 with Et₃GeH in the presence of ACF (vide supra) under photolytic condition, the HDF products 49 and 50 were generated. Note that the irradiation is for the hydrogermylation step of the double bond (48, 50), and the presence of ACF in the reaction mixture is for HDF.

Subsequently, Weinert’s group [53] reported a room-temperature HDF of acid fluorides (51, 52) and alkyl fluorides (53, 54). It postulated germylium cation Ph₃Ge⁺ as the active catalyst, generated in situ from germene Ph₃GeH and a trityl salt Ph₃[B(C₆F₅)₄]⁻ (Scheme 13). Interestingly, there is no decarbonylation or over-reduction of the acid fluorides.

2.4 Photoinduced HDF

In recent years, photocatalytic HDF has emerged as a promising, conceptually novel strategy to activate C–F bonds selectively. Unlike strong Lewis acid for C–F activation via fluoride abstraction, the photoredox protocol undergoes a single electron transfer (SET) process. Therefore, it’s compatible with more functional groups and atoms which are incompatible with strong Lewis acids.

In 2016, Zhang and co-workers [54] reported a polyfluoroarene-arene ("π-hole-π" [55]) interaction promoted photocatalytic HDF (Scheme 14). Using pyrene-based photocatalyst (PC1), N,N-diisopropylethylamine (DIPEA) as the base, common polyfluoroaromatics including hexafluorobenzene (HFB, 55), pentafluorobenzene (PFB, 56), pentafluoropyridine (57), and octafluoronaphthalene (58) could be successfully converted in good yields. And this catalytic system is compatible with an array of functional groups such as ester (59), CF₃ (60), ether (61), and aryl (62). Notably, the 1,2,4,5-TFB (56) is also possible to be synthesized directly from HFB via one-pot di-HDF when a two-fold base was used (see ref. for details). In addition to this, 24,250 TON was obtained when 0.002 mol% of PC1 was used for the HDF of HFB. The authors proposed a weak "π-hole-π" interaction promoted inner-sphere electron transfer (ET) reaction pathway based on the mechanism studies. Interestingly, the size and the shape of the photocatalyst for this conversion can be fine-tuned to enhance the overall catalytic

Scheme 9 Catalytic HDF with aluminium ions (color online).

Scheme 10 Organocatalytic HDF with alanes (color online).

Scheme 11 Selective HDF of hexafluoropropene (color online).

Scheme 12 Germane as the H source of ACF-catalyzed HDF (color online).

Scheme 13 Germane promoted catalytic HDF (color online).
activity.

Recently, Jui’s group [56] developed an elegant photo-induced selective HDF of unactivated trifluoromethylarenes (Scheme 15). The reaction conditions involved using cesium formate (3 equiv.) along with PC2 (2 mol%) as the photocatalyst delivering the mono-HDF product 63 in 75% yield, without detectable over-reduction products. Functional groups such as cyano, amino (64), ether, hydroxyl (65), triflate (67), and alkyl (68) are compatible. Trifluoromethyl substituted pyridines 69, 70 were also successfully transformed in this protocol, and the yields of pyridine-based substrates were bolstered by substituting electron-donating groups (EDG) at the ortho-position. The authors proposed that this strategy is achieved through an endergonic electron transfer event that provides access to arene radical anions that lie outside the catalyst reduction potential.

Subsequently, Gouverneur and co-workers’ research [57] on selective mono-HDF of trifluoromethylarenes with electron-withdrawing groups (EWG) further significantly expanded the application scope (Scheme 16). Functionalities on the aromatic ring, including cyano (71, 72), fluorine (72), ester (73), unprotected sulfonamide (74), were tolerated. The authors also examined complex molecules of biological relevance. For example, the doubly trifluoromethylated cannabinoid receptor agonist BAY 59-3074 reacted exclusively at the arene (75). Bicalutamide, a drug used to treat prostate cancer, underwent HDF affording 76 in 50% yield and high CF2H/CH2F selectivity. Remarkable, an analogue of Enobosarm, which has three trifluoromethylaryl groups, further demonstrated the chemoselectivity of the protocol. The HDF occurred at a single site with excellent CF2H/CH2F selectivity, leaving the 3,5-bis-trifluoromethylarene motif untouched (77). The mechanistic studies suggest that the photocatalyst is reduced by the hydrogen atom donors and returned to its native oxidation state by the trifluoromethylarene that acts as an oxidant.

2.5 Other electrophiles

In addition to the nucleophilic reagents mentioned above, there are some other interesting approaches to HDF. Simi-
larly, for the selective HDF of bis(trifluoromethyl)arenes, Prakash’s group [58] used Mg powder to activate the C–F bond. It is worth mentioning that no mixture of bis-CF$_2$H, CF$_2$H/CH$_2$F, or CF$_2$H/CH$_3$-containing compounds was detected in the reactions (78–80) (Scheme 17). The reason explains that those CF$_3$H-containing aromatics are less likely to accept an electron from Mg due to the lower electron-withdrawing ability than CF$_3$-containing aromatics. Therefore, bis(trifluoromethyl)arenes are prone to accept an electron for the HDF than the corresponding CF$_2$H/CF$_3$-containing analogues. Once a CF$_3$H/CF$_2$-containing compound accepts an electron, the CF$_2$H group preferentially undergoes HDF due to lower BDG than the CF$_3$ group. The scope also showed good compatibility with hydroxyl (81), aldehyde (82), and acetyl (83). However, the complete HDF products were delivered when extended π-system or nitrile-containing substrates were used (85, 86), reflecting some shortcomings of this protocol. The modifications of the drugs were successfully proceeded and provided mono-HDF products in moderate yields (86, 87).

Gallium hydrides such as iBu$_2$GaH, LiGaH$_4$, and Me$_3$N·GaH$_3$ can also be used as the electrophiles of HDF reactions (Scheme 18), which are illustrated by Ehm and Lentz et al. [59]. Employing diglyme as the donor (vide supra), quantitative conversion to the HDF conversion to the HDF products could be observed for hexafluoropropene (88) and 1,1,3,3,3-pentafluoropropene (89), 94% conversion of pentafluoropyridine (90) and 49% of octafluorotoluene (91). Compared with their previous work (Scheme 10), the gallium hydrides are a better H source than aluminium hydrides.

An accidental example from García’s group [60] showed that phosphine Et$_3$P could act as a fluoride acceptor to promote the HDF reaction (Scheme 19). Note that the mechanism initially proposed was amended by their subsequent work [61]. In this conversion, the source of the hydrogen was the water in the reaction rather than Et$_3$P. Under the given system, polyfluoroarenes underwent single or di-HDF to quantitatively provide the relatively stable fluorinated arenes (92–95). EWGs such as trifluoromethyl, acetyl, and cyano were tolerated well (96–98). To achieve this transformation, Et$_3$P first nucleophilic attacks the polyfluoroaromatic ring with F-migration forming 99 and yielding intermediate 100. Then it reacts with water and produces ionic pair 102 via the transition state 101. The highest barrier corresponds to the first step; thus, it is considered the rate-determining step of the reaction.

In analogy to previous protocols which utilized iBu$_2$AlH or LiGaH$_4$ (vide supra), Weaver and co-workers [62] reported the HDF of perfluoroarenes with NaBH$_4$ (Scheme 20). The advantage of this reaction is that it is compatible with both EDG and EWG substituted substrates (103–114). Specifically, the use of NaBH$_4$ rather than more potent reductant LiAlH$_4$ allowed for the incorporation of ester (103) and amide (104). Both alkenyl (108) and alkynyl (109) sub-
stituents were sufficiently activated to facilitate HDF. Unsurprisingly, substrates such as hexafluorobenzene or octafluoronaphthalene underwent di-HDF in the expected reaction site (112, 113).

Very recently, Wang’s group [63] published their research on the sequential C–F functionalizations of trifluoroacetamides and acetates (Scheme 21). This breakthrough provides a straightforward manner for the selective formation of mono- and difluoroalkyl from readily accessible trifluoroacetic acid derivatives. They posited a discrete two-stage process with each stage involving a spin-center shift (SCS) [64–66] based on radical process, which involves 1,2-radical delocalization and leaving group elimination for the C–F bond cleavage. In this reaction system, 4-dimethylaminopyridine (DMAP)-BH$_2$ as a radical initiato generated by hydrogen atom abstraction from DMAP-BH$_3$ using di-tert-butyl hyponitrite (TBHN), to promote the defluorination. Thiophenol (PhSH) was used as a polarity reversal catalyst. And in the presence of NaH$_2$PO$_4$·2H$_2$O (1.2 equiv.) as the base, various mono-HDF products were obtained. When increased the amounts of DMAP-BH$_3$ (3 equiv.) and NaH$_2$PO$_4$·2H$_2$O (2.4 equiv.) in 1,4-dioxane, di-HDF products were selectively produced. Both methods showed broad substrates scope and good chemoselectivity (114–123). Tertiary amides and pentafluoropropanamides reacted well under both methods (124–131). Only the C–F bonds α to carbonyl group were selectively reduced, whereas the CF$_3$ group was inert, suggesting that cleavage of C–F bond might be assisted by the adjacent carbonyl moiety. Complex molecules containing β-estradiol or cholesterol framework were also successfully converted into corresponding products (132–134).

3 Defluorinative C–C bond formation

3.1 Aromatic C–F bond cleavage

The Grignard reagent is one of the most frequently used organometallic reagents to form C–C bonds and occupies an important position in synthetic chemistry. Since Kumada et al. [67] reported the first Ni-catalyzed cross-coupling of fluorobenzene with Grignard reagent, investigations into this type of reaction gradually emerged. In a transition-metal-free manner, Cao’s group [68,69] presented their studies of cross-coupling of polyfluoroarenes and gem-difluoroalkenes with Grignard reagents (Scheme 22). First, they utilized pyridine as the directed group. The C–F bond ortho to the pyridine nitrogen could be selective cleaved (136–139). Three years later, they found that the steric effect played a very important role in stereoselective alkylation of gem-difluoroalkenes. The tertiary and secondary alkylation proceeded smoothly, affording alkyl-substituted fluoroalkenes in good to excellent yields with excellent Z stereoselectivity (140–143).

Similarly, Li and co-workers [70,71] reported alkylation and arylation of fluorinated arenes with Grignard reagents (Scheme 23). By choosing the aldazine-N atom as the directing group, fluorinated aryl aldehydes were regioselectively synthesized (144–147). Subsequently, they described a simple method on direct nucleophilic substitution of polyfluoroarenes under mild conditions. Both alkyl and aryl Grignard reagents, as well as a variety of polyfluoroarenes, were amenable (148–151). It is worth noting that they ob-
served this reaction was dramatically suppressed in the presence of the Ni catalyst, which was distinct from other Grignard reactions.

The demand for transition-metal-free polymerization methods stimulated the development of innovative C–F functionalization protocols. Watson’s group [72,73] and Iyoda’s group [74] showed that Fluoride ion could activate the C–Si bond of silylalkynes, thereby allowing for the polymerization with polyfluoroarenes (Scheme 24). The high molecular weight poly(phenylene ethynylene)s (PPEs) can be obtained by the simple SNAr reaction and the only side product is fluorotrimethylsilane (TMSF, gas).

The direct cross-coupling of polyfluoroarenes and alkynes is usually required. For example, Cao’s group [75,76], Zhang’s group [77], and Kondo’s group [78] reported those base-assisted alkylnations of the polyfluoroarenes (Scheme 25). The key to this type of transformation is the generation of the acetylene anion. Thus, the strong base is indispensable under transition-metal-free conditions.

For intramolecular reactions, Siegel and co-workers [79,80] gave an impressive contribution (Scheme 26). They showed that phenyl cation, which is generated from otherwise unreactive aryl fluorides, allows extension of the Friedel-Crafts reaction to intramolecular aryl couplings. The reaction is activated by an intermediate silyl cation. The methodology allows the high-yield formation of a range of tailored polycyclic aromatic hydrocarbons and graphene fragments. This strategy could also lead to formal C–H activation and the new C(sp²)–C(sp³) bonds formation.

The intramolecular HF elimination reaction (cove-region closure process) is also the key transformation in the rational synthesis of bucky-bowl, nanographenes, and nanoribbons. Amsharov’s group [81–84] demonstrated this type of transformation by utilizing γ-Al₂O₃ (Scheme 27). Only when the hydrogen atoms in the precursor structure are spatially adjacent can fluorine promote the desired ring closure (156–159). The high efficiency of the approach provided the desired products with high purity without any additional purification procedures.
Interestingly, Ichikawa and co-workers [85] demonstrated that the construction of benzene-fused triphenylene frameworks is regioswitchable (Scheme 28). On treatment with AlCl₃ or γ-Al₂O₃, benzo[f]tetraphenes and benzo[g]chrysenes could be selectively synthesized via aromatic C–F bond cleavage of 2-(biphenyl-2-yl)-1-fluoronaphthalenes (cyclization precursors). The authors proposed that the high selectivity is due to the generation of fluorine-stabilized intermediary arenium ions.

Nelson’s group [86] presented that the arenium ions can be stabilized by β-silicon and inserted into sp² and sp³ C–H bond (Scheme 29). Phenyl halonium salt of undeca-chlorinated monocarba-closo-dodecaborate anion (160) as pre-catalyst, β-silylated aryl fluorides as phenyl cation precursors, the weaker C–X bonds that have less steric encumbrance than the C–F bond did not undergo ionization (161). The alkanes could also be phenylated in moderated yield (164). Remarkably, the methane gas functionalization was successful (165) under the conditions. The key to this success is the β-silicon group stabilization lowers the barrier for fluoro abstraction and temper the σ-electrophilicity of the resulting phenyl cations, thus generated the key reactive intermediate (β-silicon stabilized arenium).

### 3.2 Benzylic and allylic C–F bonds cleavage

The Friedel-Crafts type reaction, classical C–C bond formation reaction, is an important tool for building C–C bonds. Ozerov’s group [30–32] and Müller’s group [35] already noticed this type of reaction in their silylium ion-catalyzed HDF contributions (vide supra). When (3,3,3-trifluoropropyl)benzene 7 was treated with the silylium ion catalyst in benzene as the solvent, and no HDF product was observed (Scheme 3). Instead, the defluorinative Friedel-Crafts type C–C bond formation product 9 was obtained as the major product. A well-conceived approach on benzyla- tion and alkylation of aryl and alkyl CF₃ groups was then reported by Stephan et al. [87] (Scheme 30). This metal-free procedure involves sequential benzylation or alkylation and HDF reactions. The difluorocarbocation is generated by the Lewis acid catalyst [(C₆F₅)₃PF][B(C₆F₅)₄] and then undergoes Friedel-Crafts type electrophilic aromatic substitution. The resulting intermediate reacts with silane through HDF to deliver the target molecules and release H₂. With this protocol, various arenes or trifluoromethyl aryl species such as C₆D₆, 1,2,3,4,5-pentamethylbenzene, halobenzene, and naphthalene, were converted into diarenes in moderate to high yields (166–171). The alkyl CF₃ substrates have analogous reactivity and delivered the corresponding products 172–174 in good yields. The coordination of the pyrazole derivative to the phosphonium Lewis acid catalyst makes the
N atom incompatible under this catalytic system. However, the addition of 1 equivalent of B(C$_6$F$_5$)$_3$ to the reaction mixture, resulting in the clean formation of the benzylated product 175 in 74% yield. This observation suggests that coordination of the pyrazole to the more accessible borane allows C–F activation and electrophilic substitution.

Similarly, for converting the stable CF$_3$ group, Yoshida’s group [88] developed a boron tribromide-mediated Friedel-Crafts-type acylation of arenes with benzotrifluoride (Scheme 31). Through the three-times defluorobromination of benzotrifluoride to generate the tribromide, then reacted with methanol and arene, various diaryl ketones (176–178) and aromatic esters (179–182) were synthesized. This protocol provided an alternative method for the formation of diaryl ketone. The success of this transformation is consistent with the relative Lewis acid strengths of the boron halides, the order of catalyst activity is BI$_3$ > BBr$_3$ > BCl$_3$ > BF$_3$. Thus, complete bromodefluorination of C(sp$^3$)–F bonds can be achieved using stoichiometric amounts of BBr$_3$ [89,90].

The strategy for the formation of TMSF to break the C–F bond can be extended to trifluoromethylarenes. In 2016, Hosoya’s group [91] reported a single C–F bond cleavage of trifluoromethylarenes with an ortho-silyl group (Scheme 32). The activation of the hydrosilyl group with a trityl cation in the presence of nucleophiles allowed for selective C–F bond functionalization (183–189). The authors proposed that the reaction was triggered by hydride abstraction or underwent a concerted pathway involving hydride abstraction and C–F bond cleavage.

Subsequently, Bandar and co-workers [92] developed a fluoride-initiated coupling reaction between trifluoromethylarenes and allylsilanes to access allylated α,α-difluorobenzylc compounds (Scheme 33). This strategy employed fluoride ions as promoters to break the C–Si bond and then facilitated the cleavage of the C–F bond. The 1,3-bis(trifluoromethyl)arenes underwent allylation of one trifluoromethyl group in high yield (190). Heterocyclic substrates were similarly effective (191, 192). 2-Substituted allyltrimethylsilanes yielded disubstituted alkene product 193 in good yield. Unlike the Hosoya’s work, the initial mechanistic studies suggested a base-induced single electron transfer pathway is involved in this transformation. Thus, the allyl radical species that are generated only in the presence of a suitable trifluoromethylarene substrate (194–196). In addition to using fluoride ion, this transformation can actually be achieved with a hemilabile ligand coordinated P(III) complex developed by Stephan’s group [93] (not shown).

The radical-based process for C–F bond cleavage was reported by Jui’s group [56,94] (Scheme 34). They developed
photocatalytic selective functionalization of the C−F bonds in trifluoromethylaromatic systems. First, they choose N-phenylphenothiazine (PTH), introduced by Read de Alaniz and Hawker’s group [95], as the organic photoredox catalyst, which would generate the highly reducing excited state PTH* ($E_{1/2}^* = -2.10$ V vs. SCE). The catalytic system can activate the 1,3-bistrifluoromethylbenzene ($E_{0}^{1/2} = -2.07$ V vs. SCE) via single electron transfer (SET) and deliver the radicals, which are captured by the alkenes and provide the target molecule (T.M.) via HAT. Although the protocol is limited to substrates with EWG, it is a significant breakthrough in the field of transition-metal-free C−F bond cleavage. Subsequently, the authors found that the PC2, developed by Miyake’s group [96] for organic atom-transfer radical polymerization, was a more effective catalyst for this type of reaction. It enabled a wider range of substrates to be applied.

Activation of the allylic C−F bond could be accomplished through treatment with a Lewis acid (Scheme 35), which was demonstrated by Ichikawa’s group [97]. In the presence of stoichiometric EtAlCl2, the (trifluoromethyl)alkenes readily eliminated F− and underwent cationic substitution with arenes to produce 3,3-difluoroallylated arenes (197–202) in good yields. The silyl ether 202 was isolated after the quenching procedure. The regioselectivity showed in this reaction suggests a Friedel-Crafts-type mechanism for the C−C bond-forming step. The fluorine stabilized allylic CF2 cations might be the key intermediate in this transformation.

An example on enantioselective C−C bond formation via C−F bond cleavage was achieved by Shibata et al. [98–101] by using (DHQD)2PHAL, a bis(cinchona alkaloid), as the catalyst (Scheme 36). Their elegant and detailed research demonstrated that with the assistance of (DHQD)2PHAL, the allylic monofluorides could be kinetically split and reacted enantioselectively with the TMS reagents, such as Ruppert-Prakash reagent (TMSCF3), alkynylsilanes, and (tetrazolyl)methylsilanes.

### 3.3 Vinylic and aliphatic C−F bond cleavage

Ichikawa’s group [102–106] developed a series of Friedel-Crafts-type cyclization of 1,1-difluoroallenes to synthesize helicenes and polycyclic aromatic hydrocarbons (PAHs)
(Scheme 37). Utilizing highly acidic reagents such as magic acid (FSO$_3$H·SbF$_5$) and TFOH, or Lewis acid TiF$_4$, the 1,1-difluoroalkenes were successfully converted into desired products via the generation of the CF$_2$ cations. After the dehydrogenation step, PTHs were then obtained. The authors’ research suggested that the CF$_2$ cations can be accessed easier by introducing an electron-rich group (alkene) to 1,1-difluoroalkenes (Scheme 37, A and B). Remarkably, the catalytic process was also developed. With InBr$_3$ as the catalyst, the 1,1-difluoroallene (Scheme 37, D) was transformed into the allylic CF$_2$ cation, which undergoes Friedel-Crafts-type cyclization and 1,2-migration, ring expansion to provide the product.

Shibata’s group [107,108] developed another type of intramolecular ring-closure reaction (Scheme 38). They described the B(C$_6$F$_5$)$_3$-catalyzed intramolecular cascade Friedel-Crafts defluorinative cyclization of inert C(sp$^3$)–F bonds. It is worth noting that in the absence of a hydrogen-bonding donor solvent HFIP, the aliphatic gem-difluorides preferentially engage in a defluorination/elimination process that provides monofluorinated alkenes (not shown).

Aluminum as a Lewis acid could also facilitate the coupling of the silylalkynes with the C–F bonds [49]. Young’s group [109] demonstrated that ACF (vide supra) performed well in of catalytic incorporation of alkynes into allyl C–F positions (Scheme 39). This method applies to primary, secondary, and tertiary fluorides. The fluorophilicity of the Al catalyst gives rise to fluorine selectivity over other halogens.

Interestingly, Tobisu’s group [110] reported a phosphine-catalyzed intermolecular acylfluorination of alkynes using acyl fluorides as the fluorinating reagents (Scheme 40). Halogen groups (207) were compatible in the reactions. The ratio of isomers was determined under thermodynamic. However, when substrates with a 2-pyridine group were used, the products were obtained with high Z selectivity (208–210). Different electron-withdrawing groups (EWG) such as a tert-butyl ester (211), or benzoyl (212) were tolerated. The late-stage functionalization of pharmaceuticals containing a carboxylic acid functionality was successful and delivered corresponding monofluoroalkene derivative 213 in 51% yield.

The ring-fluorinated thiophene derivatives could be synthesized from CF$_3$-cyclopropanes via C–F bond activation under transition-metal-free conditions (Scheme 41), established by Ichikawa and co-workers [111]. With Lewis acid
Et₂AlCl as the promoter, the CF₃-cyclopropanes eliminated \( \text{F}^- \) to form CF₂ cations, which were stabilized by the vinyl or cyclopropyl group. In the presence of thioacetic acids or thiols, the CF₂ cations underwent sulfanylation. They provided the products, which could be transformed to fluorodihydrothiophene (without H⁺) or difluorinated tetrahydrothiophenes (with H⁺) under alkaline conditions via 5-endo-trig cyclization.

In an inspiring contribution, Wang and co-workers [63] recently reported the chemoselectivity-controllable C–F functionalizations via sequential generation of difluoro- and monofluoroalkyl radicals (vide supra). The coupling of trifluoroacetamides with alkenes could be step by step (stage A or stage B) toward the synthesis of difluorinated or monofluorinated molecules (Scheme 42). This example showcases the potential of radical-involved C–F bond activation to build up partially fluorinated complex molecules.

## 4 Silyldefluorination

Organosilanes are valuable synthetic intermediates and are of great importance in medicine and materials science as well [112,113]. Compared with the classical methods for their synthesis which rely on stoichiometric aryl Grignard or aryl lithium compounds with chlorosilanes [114], greener protocols are highly desirable.

An early report by Roesky and co-workers [115] demonstrated that the Lewis base stabilized silylene (222, 224) reacted efficiently with polyfluoroarenes and delivered the corresponding C–Si bond formation products (Scheme 43). Their subsequent research [116] found that these two silylene were also applicable to PhN=C(CF₃)₂ (not shown). The discovery illustrates that the low valent silicon, a congener of carbon, mimics transition metal complexes.

A more general method of silyldefluorination of fluoroarenes was developed by Wgrthwein, Studer et al. [117] (Scheme 44). Utilized silyl lithium reagents, such as PhMe₂SiLi, Ph₂BuSiLi, and Ph₂HSiLi, the fluoroarenes could be successfully converted into the corresponding silylated products (226–228). The non-activated fluorobenzene afforded dimethyldiphenylsilane (229). The electron-rich para-phenoxy derivative provided desired product 230 along with 15% of its meta isomer, which was formed via the corresponding aryne intermediate. The pyrrole-substituted fluorobenzene and para-fluoro-2-methyl-

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**Scheme 41** C–F bond activation of CF₃-cyclopropanes (color online).

**Scheme 42** Sequential C–F functionalization via spin-center shifts (color online).

**Scheme 43** C–Si bond formation with three-coordinate silylene (color online).

**Scheme 44** Silyldefluorination of fluoroarenes by concerted S₅Ar (color online).
pyridine delivered 23, 232 in 72% and 25% yield, respectively. It is worth noting that the ortho-fluorobiphenyl directly provided the 9-silafluorene 235 under the standard conditions. Unlike the classical nucleophilic aromatic substitution, this transformation also occurred on more electron-rich aryl fluorides. Based on the experimental phenomena and DFT calculations, the authors proposed a concerted nucleophilic aromatic substitution mechanism.

Almost at the same time, Martin’s group [118] reported a base-mediated defluorosilylation of C(sp2)–F and C(sp3)–F bonds (Scheme 45). The choice of Et3SiBPin offered the opportunity to functionalize the resulting aryl-Si bond selectively. Notably, no ortho- or meta-silylation products were even observed in the crude reaction mixtures (236), thus arguing against an aryne intermediates-attended process. The countercation Li+ was critical for this transformation. With LiHMDS as the base, the defluorosilylation of unactivated C (sp2)–F bonds (236–240), C(sp3)–F bonds (241–242), and the late-stage functionalization (243–244) performed well, constituting a complementary approach to existing C–Si bond-forming protocols.

In industrially relevant research, Crimmin and co-workers [119] reported the silyldefluorination of the fluoroolefins HFO-1234yf, HFO-1234ze, and HFO-1336mzz (Scheme 46). The PhMe2Si-Li·THF was synthesized by direct metatation of PhMe2SiCl with Li metal and it contains 1.5 THF molecules per silicon atom. Under mild conditions, this lithium silyl reagent reacted with sp2 or sp3 C–F bonds to deliver the fluorinated organosilanes in high yield with good selectivity. This route holds promise to be the means of upgrading and recycling fourth-generation refrigerants.

5 Defluorinative C–N bond formation

Research on the catalytic formation of C–N bonds has been the topic with intensive studies [120]. The majority of C–N bond-forming transformations involve coupling aryl halides with nitrogen-containing compounds in the presence of a transition-metal catalyst, in which expensive catalysts and complicated ligands are usually required [121–125]. Despite a wealth of protocols for the formation of C–N bonds that have been developed, including Ullmann, Chan-Lam and Buchwald-Hartwig reactions etc. [126–129], cleavage of C–F bonds without the involvement of transition-metal to construct C–N bonds is still challenging due to the stability of the C–F bonds.

5.1 Aromatic nucleophilic substitution reaction (SNAr)

The aromatic nucleophilic substitution reaction (SNAr) of aryl halides with aliphatic amines is a straightforward protocol for the preparation of aromatic amines [130,131]. Besides, this method has been applied in the synthesis of drugs and natural products as well. In 1997, MacDonald’s group [132] utilized the diversomer technology to prepare Ciprofloxacin and several structurally related quinolones derivatives involving some SNAr of aryl fluorides with aliphatic amines (Scheme 47). And this is the first library of the quinolone antibacterial agents prepared by solid phase organic synthesis. First, the cyclization of the resin-bound enamide prepared by multi-step reaction in a solution of tetramethylquinuamide (TMG) and dichloromethane (DCM) provided the corresponding resin-bound quinolones. One C–F bond cleavage occurred, achieving aminodefluorination in the absence of transition-metal catalysis. The quinolones were then reacted with various solutions of piperazine compounds in N-methylpyrrolidinone (NMP). The crude products (250–255) were obtained with high purity via secondary C–N bonding.

In addition, Seto and co-workers [133] reported a protocol for total synthesis of 7-[4-[2-[butoxy]ethoxy]phenyl]-N-[4-[(methyl[tetrahydro-2H-pyran-4-yl]amino)methyl]phenyl]-1-propyl-2,3-dihydro-1H-1-benzazepine-4-carboxamide (259), an orally active CC chemokine receptor 5 (CCR5) antagonist (Scheme 48). The SNAr of aryl fluorides with
amines was involved in this transformation (Scheme 48, path 1). Detailly, the reaction of the 5-bromo-2-fluorobenzaldehyde 256 with amine 257 delivered the cyclization precursor 258 under basic conditions. Subsequently, compound 259 was prepared through a multi-step process. Furthermore, Ito’s group [134] developed an alternative strategy of producing 259 using inexpensive materials (Scheme 48, path 2). Hydrolysis of 1-propylpyrrolidin-2-one (258′) with 4 N NaOH yielded 4-(propylamino)butanoic acid with high conversion. Then the reaction mixture was neutralized with concentrated HCl and sodium carbonate and 5-bromo-2-fluorobenzaldehyde (256) was added. The resulting reaction mixture was refluxed to afford 258′ smoothly in a one-pot small-scale reaction. Eventually, the same product 259 could be obtained by a multi-step reaction as well.

With regard to fluoroquinolone antibacterial agents, in 2004, Choi and co-workers [135] disclosed a procedure for the synthesis of new fluoroquinolone antibacterial agents bearing pyrrolidine ring at the C-7 position (Scheme 49). Considering the importance of pyrrolidine ring in vitro antibacterial activities and pharmacokinetic profiles, optically inactive pyrrolidine derivative 260 was selected as the benchmark substrate to react with various fluoroquinolone compounds 261, 263, 265, 267 to provide the desired fluoroquinolone antibacterial agents 262, 264, 266, 268 in good to excellent yields by SNAr.

In addition to the biologically active molecules mentioned above, various heterocyclic aromatic compounds, such as pyridines and quinolines are ubiquitous in natural products, pharmaceuticals, and pesticides [136–138]. There are several aminopyridine-based drug molecules, which are used to treat disorders. For the construction of such compounds, nucleophilic aromatic substitution reaction of 2-fluoropyridine with amines through C–F bond activation is a straightforward and practical method. Singaram and co-workers [139] reported an efficacious lithium amides-promoted amination of 2-fluoropyridine in the absence of transition-metal (Scheme 50). A series of primary and secondary lithium amides could react with 2-fluoropyridine under mild reaction conditions to provide the corresponding aminopyridines (269–276) in moderate to good yields. Notably, this strategy could be successfully applied to synthesize enantiomerically pure aminopyridines (275), which might be utilized as potential ligands for asymmetric synthesis.

Additionally, Hevia and co-workers [140] reported an excellent methodology on amination of pyridine-containing fluoroarenes via magnesium-mediated C–F bond activation (Scheme 51). Various β-diketiminate stabilized mononuclear Mg-containing amines complex as nucleophilic reacted with fluoroarenes under mild reaction conditions to obtain a series...
of aryl amines (277–284) in excellent yield. This reaction promotes the synthetic utility of β-diketiminate stabilized magnesium complexes and provides a novel route for monofluorination via C–F bond activation of fluoroarenes.

Ding’s group [141] presented a LiH-stimulated C–F bond activation for the formation of the C–N bond (Scheme 52). Firstly, lithium-ion coordinates with the nitrogen atom of pyridine moiety. The C–F bond would be slightly elongated owing to the Li ion and F atom interaction. Subsequently, adding an amine to the benzene ring would result in the formation of a C–N bond. Finally, the cleavage of the C–F bond furnishes the corresponding product (285–296). This reaction features good substrate scope, high yields, mild reaction conditions as well as excellent regioselectivity for (difluorophenyl)pyridines.

In addition to aminopyridines, the aminoquinoline derivatives received much attention as important structural motifs in polyolefin catalyst families [142,143]. Transition-metal catalysis is involved in the most known methods for the assembly of aminoquinolines [144–146]. And the transition-metal-free synthesis of aminoquinoline is still yet to be addressed. Taking advantage of the above same strategy, Ding and co-workers [147] also reported an efficient and general method for the selective synthesis of 8-aminoquinoline derivatives, in which C–F bond on the 8-substituted position was broken in the presence of lithium salts (Scheme 53), and excellent chemo- and regioselectivity was detected for polyfluorquinolines. For the substrate scope, substituted amines, such as o-toluidine, 2,6-dimethylaniline, p-toluidine, as well as various polyfluorquinolines presented good reactivity to generate the corresponding products (297–303) in moderate to good yields in the presence of LiH. As for the reaction mechanism, firstly, lithium ion preferentially coordinates with the lone-pair electrons of the nitrogen atom. Meanwhile, the C–F bond is activated and the anilide as nucleophile attacks the benzene ring, leading to the formation of the C–N bond. Finally, the cleavage of the C–F bond furnishes the targeted product along with releasing LiF (Scheme 53, bottom).

With respect to lithium-assisted C–F bond activation, a novel tandem amination-reduction reaction has been reported by Singaram’s group [148] (Scheme 54), in which 2-(N,N-dialkylamino)benzylamines are generated from 2-halobenzonitriles and lithium N,N-dialkylaminoborohydride (LAB) reagents in the solution of THF. And the target products (N,N-dialkylamino)benzylamine (305–308) could be easily obtained in good to excellent yields after a simple aqueous workup procedure. This process is believed to proceed through a tandem S_NAr amination-reduction mechanism wherein the LAB reagent promotes the displacement of the fluorine substituents and the cyano groups. This one-pot procedure is an attractive synthetic tool for the nucleophilic aromatic substitution of halobenzenes with less...
Recently, Cao and co-workers [149] disclosed an efficient and mild strategy for the assembly of aromatic tertiary amines by the reactions of fluoroarenes with secondary amines in the presence of \( n \)-butyllithium at room temperature (Scheme 55). Both cyclic amines (piperidines, morpholines as well as piperazines) and acyclic amines (chain secondary amines) proceeded efficiently to afford a series of aromatic tertiary amines in good yields (309–317). This current methodology provides an alternative route to access valuable aromatic tertiary amines from readily available fluoroarenes.

For lithium salts-mediated C–F bond activation, Diness and co-workers [150] reported the amination-defluorination of (ploy)fluorobenzenes enabling transition-metal-free \( N \)-arylations of aliphatic amines (Scheme 56). The target products (318–325) were obtained in decent yields with high regio- and chemoselectivity. This reaction provided a prominent approach to forge polyfluorine-containing amines, enabling a valid transformation for late-stage functionalization of Vortioxetine.

Regio- and chemoselective amination of polyfluoroarenes has loomed as the popular and intriguing subject, beneficial to pharmaceuticals and agriculture chemistry [151–153]. Although the C–F bond activation of polyfluoroarenes has been flourishing, some challenges still exist for this type of transformation [23,154,155]. For example, selective mono-functionalization of polyfluorobenzene and preferentially activation of C–F bond over other C–X bonds (X=H, Cl, Br, I) are still not established. In addition to C–F bond activation of polyfluoroarenes mentioned above, in 2015, Pang’s group [156] developed a practical and effective aromatic nucleophilic monosubstitution reaction for the construction of various fluorine-containing aromatic amines (Scheme 57), in which selective cleavage of C–F bond of various fluoroar- enes (mono-, di-, tri-, tetra-, penta- and perfluorobenzene) proceeded under transition-metal free conditions. Fluoroarenes reacted with primary and secondary aromatic amines to generate target products in good to excellent yields in the presence of the base (t-BuOK). In this C–F bond activation, the solvents also controlled the reactivity of substrates. For instance, perfluorobenzene could work smoothly to render the desired products via selective C–F bond cleavage by using THF as a reaction medium (326–329), whereas, other substrates could be effectively transformed into target products in good yields in DMSO (330–331) or toluene (332–333).

Hevia’s group [140] also developed selective cleavage of C–F bond of perfluorobenzene under microwave radiation conditions, providing the expected products in higher yields.
with a better selectivity than that produced by conventional heating (Scheme 58). The β-diketiminate stabilized magnesium complex (334) served as a reaction baton to promote the reaction to proceed smoothly. This approach could be extended to piperidine, morpholine and pyrrolidine, affording the aminodefluorination products 335–338 in 65%, 67%, 73% and 91% yield, respectively (Scheme 58). Later, Zhou and co-workers[157] reported a facile and versatile defluorinative amination of fluorobenzenes under microwave irradiation without strong base and catalyst (Scheme 59). The process could proceed smoothly in N-methylpyrrolidinone (NMP), providing the target product (339–344) in good to excellent yields. Notably, the additional halogen atom(s) (F and Cl) installed on the aromatic ring could enhance the leaving ability of fluorine.

Despite substantial protocol for selective one C–F bond activation of polyfluoroarenes, the cleavage of two C–F bonds in a one-pot procedure are rarely reported. In 2013, Bunz and co-workers[158] disclosed a novel and intriguing transformation of ethynyl-substituted diaminophenazine with perfluorinated arenes to assemble partially fluorinated N-heteroacenes (Scheme 60). First, diaminophenazine (345) was employed as the starting material and reacted with hexafluorobenzene in the presence of an excess of NaH at 60 °C, rendering the desired coupling product (347) in 24% yield (Eq. (1)). Subsequently, N,N-dihydroacenes 349, 351, 353 were isolated in modest yields using a similar reaction system (Eqs. (2–4)). This reaction allowed the rapid assembly of N,N-dihydrotetraazapentacene and -heptacene cores in a simple one-step process without transition-metal catalyst. And the targeted products of this transformation have great potential applications in material science. Besides, Katz and co-workers[159] reported a transition-metal free one-step synthetic route to afford benzodipyroles via the successively cleavage of two C–F bonds (Scheme 61). p-Toluidine was utilized as a nucleophile to react with ((4,6-difluoro-1,3-phenylene)bis(ethyne-2,1-diyl))dibenzene (354) to obtain final product 357 through compounds 355 and 356. This transformation involved two S$_2$Ar reactions, leading to a double substitution-anionic cyclization cascade and four C–N bonds.
N-arylation of heteroaromatic compounds is an extremely significant C–N bond formation reaction in organic synthesis. For nucleophilic aromatic substitution (SNAr) mentioned above, most nucleophilic reagents are aniline and aliphatic amines. In addition, there are some protocols for aromatic nitrogen-containing heterocycles as nucleophilic reagents achieving C–F bond cleavage to form C–N bond. In 2012, Diness and Fairlie [160] developed a valuable and very simple catalyst-free N-arylation of azole and indole derivatives, which involved direct S_N Ar of fluorine on unactivated benzene derivatives (Scheme 62). The authors investigated numerous experiments for reaction condition optimization, and then studied the substrate scope under microwave featuring high conversion of reactants and good tolerance of functional groups (bromo and chloro etc.). As a result, a range of fluorobenzene with various substituents reacted with indole or benzimidazole to afford the defluorinative amination products (358–363) in good to excellent yield in the absence of transition metal.

Recently, Lambert and co-workers [161] developed an electrophotocatalytic S_N Ar reaction of unactivated aryl fluorides at ambient temperature without transition-metal catalyst (Scheme 63). This reaction presents a nascent area for the combination of electrical energy and light to promote redox neutral reactions. For substrate scope, various N-heterocyclic compounds, such as pyrazole, triazoles, tetrazoles, bioactive molecule derivatives, could react with fluorobenzene to provide the target products (364–369) in moderate to good yields.

5.2 Hydrogen bonds promote bimolecular nucleophilic substitution (HB-S_N 2)

As its known, fluorine atom can generate hydrogen bond with a hydrogen-bond donor (HBD) solvent, such as water or alcohols [162]. Numerous evidence suggests that the formation of hydrogen bond of organic fluorine is possible in an HBD solvent [163]. In this case, hydrogen bond would be considered as weak interaction of C–F bond. During the last decades, hydrogen bond-accelerated cleavage of the C–F bond has also drawn extensive attention from organic chemists. In 2013, Paquin and co-workers [163] reported a splendid water-stimulated C–F bonds activation, in which alkyl fluorides were also amenable to undergo the substitution reactions via defluorinative amination (Scheme 64, Eq. (1)). DFT calculation reveals that C–F bond activation proceeds via stabilization of the transition state by a stronger hydrogen bond between alkyl fluorine and water, making the C–F bond elongated. This finding presents a distinct and
novel strategy for C–F bond activation via hydrogen-bonding. Subsequently, the same group [164] reported a procedure using 1,1,1-tris(hydroxymethyl)propane as a hydrogen bond donating agent to achieve C–F bond cleavage of benzylic fluorides (Scheme 64, Eq. (2)). The benzylic fluorides with various functional groups could react with secondary amines or anilines to generate benzylic amines (370–377) in 56%–86% yields. Mechanism investigations demonstrated that hydrogen bond-donating solvent promotes the C–F bonds activation and hydrogen bond accepting one hinders the cleavage of C–F bonds.

In 2014, Paquin’s group [165] disclosed another hydrogen bond donating solvent promoted C–F bond cleavage (Scheme 65). The reaction mechanism is proposed via DFT calculation and structure-activity analysis. Tricoordination of the triol with the fluorne-containing substrate is disfavored due to conformational constraints. However, the existence of three hydrogen bonds provides an optimal activation of the S_N2 process. The author hypothesized that two OH groups from one triol molecule could coordinate with F- atom and another OH group from a neighboring triol leads to the triad of activator. This transformation proceeded in the presence of morpholine under highly concentrated conditions.

Similarly, in 2018, O’Hagan’s group [166] reported the enantioselective C–F activation reaction using an enantiopure isotopomer of benzyl fluoride in a mixed solvent of isopropanol and water (Scheme 66). In this transformation, hydrogen bond promoted C–F bond cleavage. Using water/isopropanol as the activator afforded the benzylated products 379–381 in moderate yields. The ee values of the two products were very close to that of the original benzyl fluoride ((R)-1, 95%), manifesting that a highly associative S_N2-like route was involved. And the additional nucleophile must have approached on a coordinate anti to the C–F bond leading to an inversion of the configuration. In addition, N-methylbenzylamine afforded a product 381 in 56% yields that did not resolve by 2H NMR, so the ee value could not be determined.

5.3 Other modes promote defluorinative amination/azidation

Although a number of methods have been disclosed for breaking C(sp^3)–F bonds in mono- and polyfluorinated aromatics as well as benzylic and allylic fluorides, the efficient cleavage of unactivated C(sp^3)–F bonds under transition-metal-free conditions remains challenging [167–174]. As an alternative approach, Lewis acid could also prompt the C–F bond activation. In 2016, Moran and co-workers [175] demonstrated an expedient B(C_6F_5)_3·H_2O-promoted C–F bond cleavage to achieve defluorinative azidation and defluorinative amination of tertiary aliphatic fluorides (Scheme 67). Trimethylsilyl azide (TMSN_3) was selected as the nitrogen source and nucleophile to form a new C–N bond in this reaction. Subsequently, various tertiary aliphatic fluorides were tested under this reaction system. Homobenzylic
tertiary aliphatic azides (381–386), cyclic aliphatic azide (386) as well as bisabolol-derived azide product (387) were smoothly prepared under the optimized conditions. Firstly, for the reaction mechanism, coordination of B(C₆F₅)₃·H₂O with tertiary aliphatic fluorides through hydrogen bond leads to the C–F bond cleavage, generating tertiary aliphatic carbocation and fluoride anion. Then, the fluoride anion is trapped by silicon, providing the target products with decent yields.

For unactivated C(sp³)–F bonds activation in the absence of transition metal, Terao and co-workers [176] reported a simple method for the cleavage of C(sp³)–F bonds of alkyl fluorides to obtain various C(sp³)–X (X = Cl, C, H, O, S, Se, Te, N) bonds using a hexane solution of organoaluminum reagents containing Al–X bonds (Scheme 68). There was one example that 1-fluoroocotane (388) reacted with (diethylamino)disobutylaluminum (389) to afford aminodefluorination product 390 in 71% yield.

As its known, 1,4-naphthoquinone derivatives have properties of antioxidant, anti-malarial and so on [177]. Polyfluorinated functionalized 1,4-naphthoquinones could act as inhibitors for the growth of cancer cells [178]. Moreover, 1,4-benzoquinone derivatives exhibit diverse biological activity as well. Similar reactions of polyfluorinated benzoquinones were not investigated. In 2015, Selivanova and co-workers [179] reported the reaction of 2-X-trifluoro-1,4-benzoquinones (X = F) with triphenylphosphine in various solvents (Scheme 69). An addition of a 0.6-equivalent of aniline 393 to a solution prepared by reaction of quinone 391 and PPh₃ (1:1) gave [4-fluoro-2-oxido-5-oxo-3-(phenylamino)-6-(phenyl- imino) cyclohexa-1,3-dien-1-yl]triphenylphosphonium 394 in 29% yield (Eq. (1)). Two C–F bonds were cleaved and two different C–N bonds were constructed (C–N single bond and C–N double bond). Subsequently, An addition of a 0.6-equivalent of aniline 393 to a solution prepared by reaction of quinone 391 and PPh₃ (1:1) gave the intermediates 395. The addition of an excess of 4-phenoxyaniline 396 to the reaction mixture rendered a new compound [4-fluoro-2-oxido-5-oxo-3-[(4-phenoxyphenyl)amino]-6-(phenylimino)cyclohexa-1,3-dien-1-yl]triphenylphosphonium (397, Eq. (2)). The addition of H₂O to a solution prepared by reaction of quinone 391 and PPh₃ (1:1) afforded the intermediates 398, whereas, the addition of an excess of 4-phenoxyaniline 396 to the reaction mixture delivered another new compound [4-fluoro-2-oxido-3,6-dioxo-5-[(4-phenoxyphenyl)amino]cyclohexa-1,4-dien-1-yl]triphenylphosphonium (399, Eq. (3)).

Intramolecular cyclization reactions have provided a powerful platform to forge cyclic molecules, which are
widely present in natural products, pharmaceuticals, etc. Obviously, incorporating fluorine atoms into the target products could improve both the pharmacokinetics and membrane permeability compared with their non-fluorinated congeners [180–183]. Thus, fluorine-containing cyclization products are more significant. Intramolecular selective C–F bond activation is a promising tactic for the construction of such compounds. In 2012, Shibata and co-workers [184] firstly disclosed the synthesis of a series of biologically relevant 3,5-diaryl-2-fluoromethyloxazolidin-2-ones scaffold by a conceptually new desymmetrization of unactivated aliphatic di-fluorides with silicon-induced catalytic C–F bond-cleavage as a key step to form C–N bond (Scheme 70). Various 2-aryl-1,3-difluoromethyl-2-carbamates with a variety of aromatic ring substituents, such as methyl, fluoro, and chloro, were converted into cyclization products (400–403) in good to excellent yields. For the reaction mechanism, firstly, BSA is activated by CsF to generate amido anion A, along with the release of TMSF. Next, anion A abstracts a proton from reactant to yield the carbamate anion B, along with the formation of Me3SiNHCOMe. Subsequently, the C–F bond of B is activated by interaction with the silicon atom of BSA, affording transition-state model C to induce intramolecular SN2-like reaction, which furnishes the target product and TMSF. The amido anion A, regenerated from C, is the true catalyst in this catalytic cycle.

6 Defluorinative borylation

Organoborane compounds are ubiquitous in various organic transformations, which are significant synthetic intermediates for the construction of pharmaceuticals, natural products, and organic materials [185–188]. Therefore, the development of simple and convenient methods for the assembly of organoborane compounds has received intensive attention [188]. Among them, direct borylation of non-activated aromatic hydrocarbon compounds has become the subject of a wealth of landmark studies over the past several decades, as it represents a straightforward conversion from inert raw materials to value-added chemical building blocks. A battery of transition metals has been dominantly employed as a catalyst for defluorinative borylation of arenes [188]. Despite the transition-metal-catalyzed borylations, transition-metal-free borylation reactions have attracted ongoing interest. At present, photocatalysis has witnessed dramatic advances which have enabled previously inaccessible synthetic transformations for defluorinative borylation [189].

In 2016, Larionov and co-workers [190] reported a photoinduced borylation of electron-rich fluoroarenes via defluorination (Scheme 71). This light-induced defluorinative borylation proceeded smoothly under transition-metal-free and additive-free conditions with good functional group tolerance. 4-Fluoroaniline readily produced potassium (4-aminophenyl)trifluoroborate (404) in 53% yield, indicating that certain Ar–F bonds can be harnessed to construct boronic acids without transition metal. Similarly, various electronic-rich fluoroarenes could yield the target product (404–409) in moderate yields under the viable reaction conditions.

Soon after, Li’s group [191] also developed a photocatalyzed C–B bond formation reaction via transition metal-free C–F bond activation of electron-rich aryl fluorides (Scheme 72). But only three examples were given in this study, and notably, electron-rich aryl chlorides and phenol derivatives were suitable substrates in this reaction as well. 4-Fluorophenol, 4-fluoroaniline as well as 4-fluoro-N,N-dimethylaniline were utilized as substrates under continuous-flow photolytic conditions, afforded the corresponding products (410–412) in 75%, 75% and 53% yields, respectively (Eqs. (1–3)).

Recently, Wu’s group [192] developed a photo-mediated hydrogen atom transfer (HAT) process with NHC-BH3 (Scheme 73). The boryl radical was generated in-situ under mild conditions, which could react with polyfluoroarenes and gem-difluoroalkenes to produce synthetically valuable fluorinated organic boranes. When various polyfluoroarenes with different functional groups were employed as reactants, defluorinative borylation products (415–417) could be isolated in moderate to good yields.

Boryl radical reactions with polyfluoroarenes have been developed in the presence of photocatalysis [192,193]. However, polyfluoroarenes as radical acceptors have been rarely explored under photocatalysis-free conditions. Very recently, Taniguchi and co-workers [194] reported a thermal
radical reaction of N-heterocyclic carbene boranes (NHC-boranes) by using polyfluoroarenes as good radical acceptors in the presence of di-tert-butyl peroxide (Scheme 74). In this process, the C–F bond of polyfluoroarenes was substituted with the NHC-boryl group to obtain B-aryl NHC-borane derivatives (418–421). The current synthetic strategy could also be applied to forge new borane-containing liquid crystalline molecules with high thermal stability.

In addition to radical transformations of organoborane compounds to achieve defluorinative borylation, Finze and co-workers [195] developed borylation of fluorinated arenes using the boron-centered nucleophile B(CN)\(_3\)\(^{2−}\), a unique entry to aryltricyanoborates (Scheme 75). The potassium salt of the boron-centered nucleophile B(CN)\(_3\)\(^{2−}\) readily reacted with perfluorinated arenes under mild reaction conditions, such as hexafluorobenzene, decafluorobiphenyl, octafluoronaphthalene and pentafluoropyridine, leading KF and the K+ salts of the respective borate anions with one B(CN)\(_3\) unit bonded to the (hetero)arene. Pentafluorobenzenes R-C\(_6\)F\(_5\) (R = –CN, –OMe, –Me, or –CF\(_3\)) react with boron-centered nucleophile B(CN)\(_3\)\(^{2−}\) to obtain the corresponding products in good yields.

Tetracoordinate triarylboranes have a wide range of applications in organic photoelectronic materials due to their intriguing and unique properties. Song’s group [187,196,197] has developed abundant protocols for accessing such compounds and has used such reagents to disclose various transformations. In 2019, Kinjo and co-workers [198] reported a metal-free selective borylation of arenes to afford tetracoordinate boranes via C–H/C–F bond activation and dearomatization (Scheme 76). Intriguingly, when partially fluorinated arene derivatives were employed as the substrates, chemoselective C–F bond activation was detected. Thus, the treatment of 422 with various fluorinated arene derivatives at 80 °C for 12 h afforded tetracoordinate boranes (423–425) in moderate to good yields.

7 Other C–X (X = P, O, S, Cl, Br, I) bonds formation reactions

In addition to the above discussed examples, some innovative C–F functionalization protocols such as C–P bond,
C–O bond, C–S bond, and C–halogen (Br or Cl) bond formation were also studied. The Lewis acids (via abstraction of fluorides) and appropriate bases (via nucleophilic substitution) were shown to activate the C–F bond successfully, thereby allowing for the coupling with nucleophiles or exchange with halogens.

Recently, Iwai and Sawamura et al. [199] reported a phosphinylation of non-activated aryl fluorides (Scheme 77). Employing LiHMDS as the base, most of the electron-neutral and electron-rich aryl fluorides could participate in the reaction with substantially stabilized anionic P nucleophiles to form the corresponding tertiary phosphine oxides (426–431). However, fluorobenzene was not reactive under the conditions (429). The present protocol, noteworthy, applies to the synthesis of P-chiral tertiary phosphine oxides (432, 434). The quantum chemical calculations in the paper suggested a nucleophile-dependent mechanism that involves both concerted and stepwise SNAr reaction pathways.

Another successful C–P bond formation protocol was developed by Young’s group [200,201]. Utilizing P(o-Tol)3 and B(C6F5)3 (BCF) as the frustrated Lewis pair, substrates bearing gem-difluoromethyl groups underwent highly selective monodefluorination, and the resulting products were subject to Wittig reaction protocols to provide a variety of monofluoroalkenes (Scheme 78, A). Based on this achievement, they subsequently developed a frustrating Lewis-pair-mediated selective single fluoride substitution in trifluoromethyl groups (Scheme 78, B). Treatment of trifluoromethyl arenes with 2,4,6-triphenylpyridine (TPPy) and Me3SiNTf2 allowed for catalytic quantities of BCF (20 mol%) to be used. In addition, the resulting pyridinium salts could be further functionalized via nucleophilic substitution, photoredox coupling, and electrophilic transfer reactions, delivering a range of difluoromethylene derivatives from such starting materials (438–445).

Based on the previous work (Scheme 70), Shibata’s group [202] reported a phosphazene base-catalyzed C–O bond formation to synthesize monofluoromethyl-substituted epoxides (Scheme 79). The proposed mechanism shows that the sterically demanding base P4-tBu first reacts with the alcohol 446 to afford reactive alkoxide ion pair A. Then, with the assistance of the silicon-based trapping reagent N(TMS)3, complex B provides the product 447 via C–F bond cleavage and generates the true catalyst C. The key to this catalytic cycle is the choice of the huge size superbase P4-tBu (500 Å3) [203], which prohibits the intermolecular silylation side reactions to silyl ethers.
The defluorinative C–Nu bond formation reactions can also be achieved with Lewis acid, as demonstrated by Moran and co-workers [175] (Scheme 80). With B(C₆F₅)₃·H₂O as the catalyst, the tertiary aliphatic fluorides were efficiently converted into the corresponding C(sp³)–Nu (Nu = N₃, SR, OR, NHR, and CH₂R) compounds (448−455). The protocol is remarkably general, and only alkyl fluorides reacted chemoselectively in the presence of other halides.

Zhu and Jiang’s group [204] developed a defluorinative ipso-functionalization reaction of (trifluoromethyl)alkenes with oximes through an anionic SN₂-type substitution pathway (Scheme 81). Under the base conditions, various O-(1,1-difluoroallyl)oxime ethers (456−461) were synthesized. The interesting aspect of this work is that the gem-difluoroalkene products it obtained contain two C(sp³)–F bonds rather than C(sp²)–F bonds.

Nucleophilic substitution reactions of pentafluoroarenes occurred firstly on the C4 position, then on the C2/C6 and C3/C5 positions if the nucleophilic reagents are overloading. This pattern was demonstrated by Ouyang and Yang’s work [205]. As shown in Scheme 82, a DMF solution of sodium thiophenolate (462) and pentafluorobenzene (463) (1:1) were stirred overnight, generating 1-phenylthio-2,3,5,6-tetrafluorobenzene in 65% yield; the employment of excess 462, however, giving product 1,2,4-tris(phenylthio)-3,6-difluorobenzene (465).

The aluminum-based Lewis acids have shown to activate the C–F bond (vide supra), and it can also be served as alklylation reagents to convert C(sp³)–F bond into C–Nu (Nu = Cl, C, H, O, S, Se, Te, N) bonds by Terao’s group [176] (Scheme 83). In the competitive experiments designed by the authors, only alkyl fluorides reacted chemoselectively in the presence of other alkyl halides.

In a similar manner, Young and co-workers [206] reported a catalytic halodefluorination of aliphatic C–F bonds (Scheme 84). The halosilanes, in conjunction with aluminum catalysts, can convert alkyl fluorides into alkyl halides (466−

\[ \text{Scheme 79} \] Phosphazene base-catalyzed C–O bond formation (color online).

\[ \text{Scheme 80} \] Defluorinative functionalization of tertiary aliphatic fluorides (color online).

\[ \text{Scheme 81} \] Defluorooxidation of (trifluoromethyl)alkenes with oximes (color online).

\[ \text{Scheme 82} \] Thiolation of pentafluorobenzene (color online).

\[ \text{Scheme 83} \] Competitive reaction of alkyl halides with Et₂AlCl (color online).

\[ \text{Scheme 84} \] Catalytic halodefluorination of aliphatic C–F bonds (color online).

474) under mild conditions.

A o-hydrosilyl-assisted C–F transformation was developed by Yoshida’s group [207] (Scheme 85). Utilizing in-situ generated trityl cation as the activator and the counter cation as the nucleophile, various transformations from C–F to C–Cl, C–Br, C–OTs, and C–SCN were achieved (475–480).
The o-hydrosilyl makes this transformation selectively (480). In addition to that, various ortho-functionalized difluorobenzyl chlorides and ortho-bromo-substituted difluorobenzyl chlorides were synthesized by the authors (not shown).

8 Summary and outlooks

Overall, the past decades have witnessed the significant advances in transition-metal-free C–F bond activation of fluorine molecules. Most of the strategies used in the process are the capture of fluorine atoms with Lewis acid and the nucleophilic substitution reactions with strong bases. Some other approaches, such as the generation of radical intermediates by light or free radical initiators, have also been developed as alternatives to these strategies. There are also various types of reactions in which the C–F bonds have been successfully converted into C–H, C–C, C–B, C–N, C–Si, C–O, C–S bonds etc. under transition-metal-free conditions. Meanwhile, research on selective C–F bond activation is even more exciting and will certainly receive more attention in the near future.

The efficiency of these reactions is remarkable. However, from the substrate point of view, there is a high preference for C(sp^3)–F bonds. In addition to this, most of the articles published to date involving C(sp^3)–F bond are basic nucleophilic substitution reactions or activation of polyfluorocarbons, which are limited by the restricted substrates and/or harsh reaction conditions. This is attributed to the excessive BDE of the C(sp^3)–F bond. In this regard, light or electricity might be able to play a key role to achieve the expected breakthrough. Undoubtedly, selective C–F bond functionalization continues to be an attractive yet challenging topic. Selective activation of trifluoromethyl and polyfluorinated compounds remains one of the key research directions in this field. With continuing efforts, we expect to see the development of more useful approaches in this rapidly evolving research area.

Conflict of interest The authors declare no conflict of interest.

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