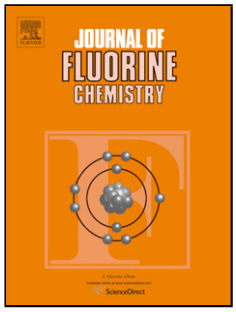

Title: Review of recent advances in C–F bond activation of aliphatic fluorides

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Review of recent advances in C–F bond activation of aliphatic fluorides

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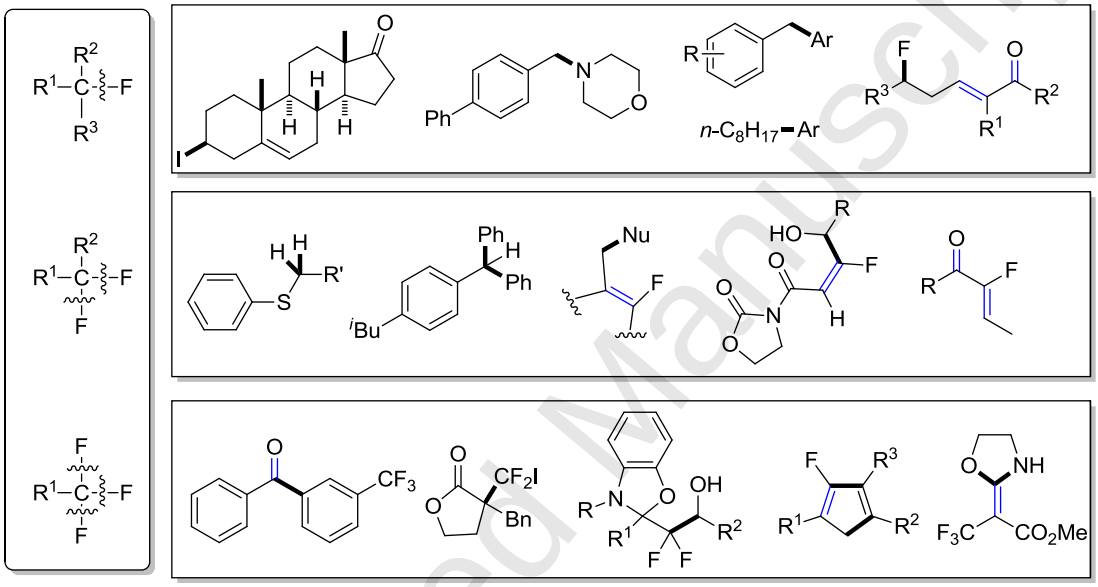
Graphic abstract



Review of recent advances in C–F bond activation of aliphatic fluorides

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Abstract

C-F bond activation of aliphatic fluoride provides new methodologies for synthesis of new fluorinated building blocks as well as versatile non-fluorinated products. This review covers recent C-F bond cleavage and further transformation of compounds bearing with an aliphatic fluoride, difluoromethylene group or trifluoromethyl groups. The methods to activate a C-F bond include activation by Lewis acid, Brønsted superacids and hydrogen bonding, and mediation by transition-metals and rare earth metals. Reduction through a single electron transfer can provide the compounds with less fluorine from trifluoromethyl compounds. Bases are often used for the elemination of hydrofluoride. S_N2' displacement is also an important method for transformation of α-fluorinated, difluorinated and trifluorinated olefins to various synthetically interesting molecules.

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Highlight

This review covers compounds with a C-F bond, CF_2 or CF_3.

Various organic compounds are synthesized through C-F bond activation.

Aliphatic fluorides could be activated by Lewis acid, Brønsted superacids or hydrogen bonding.

The cleavage of C-F bond could be mediated by transition-metal or rare earth metal.

Dehydrofluorination by a base or S_N2' displacement by a nucleophile could be a method for leaving of a fluoride.

Review of recent advances in C–F bond activation of aliphatic fluorides

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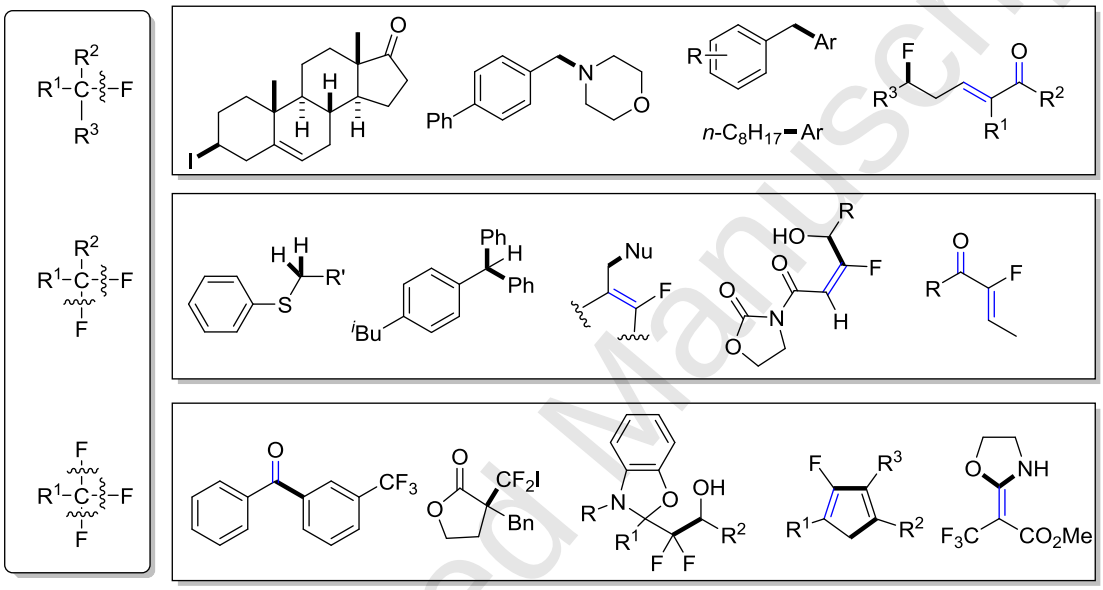
Graphic abstract



Abstract

C-F bond activation of aliphatic fluorides provides new methodologies for synthesis of new fluorinated building blocks as well as versatile non-fluorinated products. This review covers the recent C-F bond cleavage examples and further transformation of compounds bearing with an aliphatic fluoride, difluoromethylene group or trifluoromethyl groups. The methods to activate a C-F bond include activation by Lewis acid, Brønsted superacids and hydrogen bonding, and mediation by transition-metals and rare earth metals. Partial reduction of trifluoromethyl group through a single electron transfer (SET) process can provide the compounds with less fluorine. Bases are often used for the elimination of hydrofluoride. S_N2' displacement is also an important method for transformation of monofluorinated, difluorinated and trifluorinated olefins to various synthetically interesting molecules.

Introduction

Organofluorine chemistry has attracted much attention because introduction of fluorine to an agrochemical, pharmaceutical and material molecule can enhance multiple functions, such as bioavailability, metabolic stability and structure rigidity. Fluorides have been used as powerful and practical fluorinating reagents for constructing organic compounds [1, 2]. On the contrary to the C-F bond formation, the C-F cleavage and sequent functionalization is becoming more and more important with the increase of fluorinated compounds. Treating environmental persistent chlorofluorocarbons and fluorocarbons needs hydrodefluorination technique. Transformation of easily available perfluorinated compounds to those compounds with less fluorine atoms is a practical methodology for synthesis of versatile fluorinated molecules. Functionalization of C-F bond for the carbon-carbon formation fulfills the coupling mode of halides.

Aliphatic fluorides include compounds bearing with a monofluoro-substituent, a difluoromethylene group or a trifluoromethyl group. Although a C-F bond is strong and unreactive, many methods for C-F bond activation of aliphatic fluorides have been reported. In 2009, Amii and Uneyama fully summarized C-F bond activation in organic synthesis [3]. Several reviews related on C-F bonds activation have been reported recently [4-7]. Braun and coworkers have reviewed transition-metal-mediated activation of C-F bond and hydrodefluorination of polyfluorinated aromatics, heteroaromatics and olefins [4,6]. Oestreich and coworkers have reviewed the selective activation of C(sp^3)−F bond in saturated fluorocarbons by main-group Lewis acids [5]. The content of this review is selected from papers published after 2009 and focuses on C-F bond activation of aliphatic fluorides.

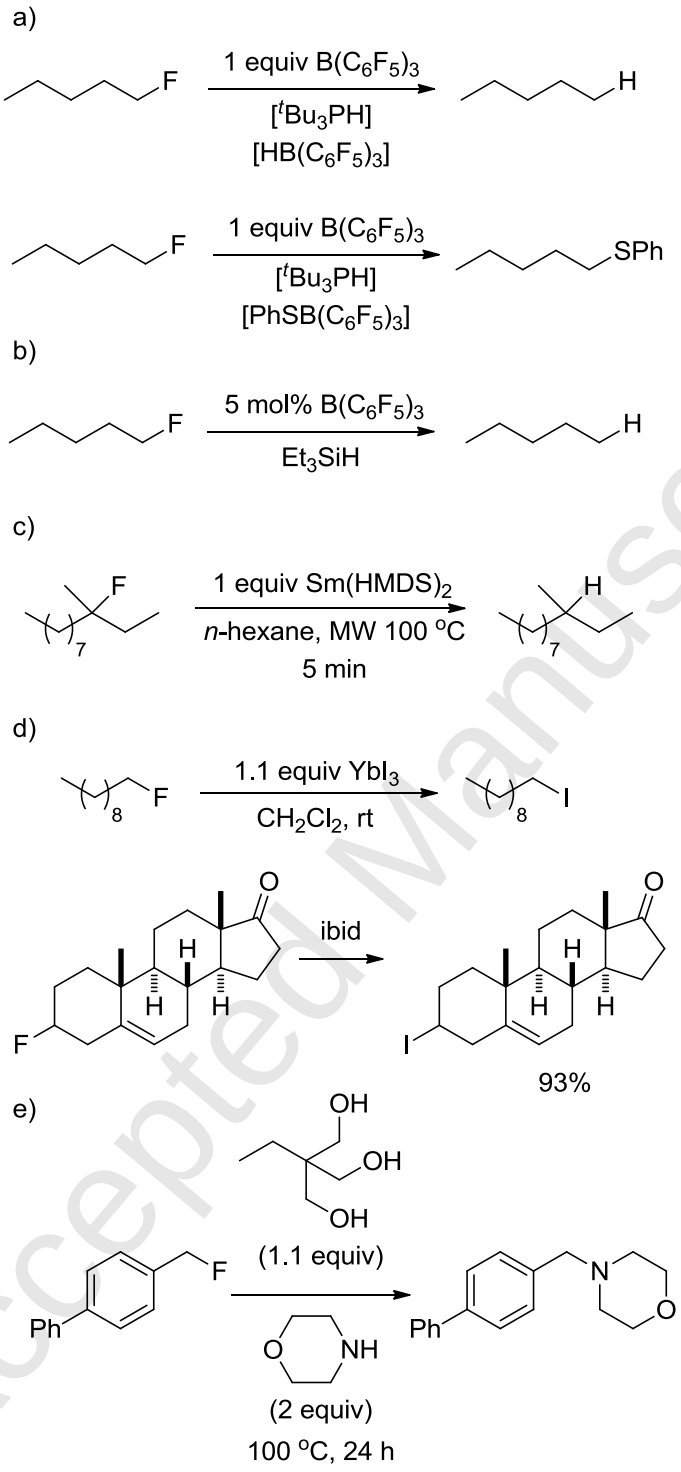
1. The C-F bond activation of compounds bearing with a monofluoro-substituent

The use of strong main-group Lewis acids has emerged as a powerful tool to selectively activate C(sp^3)−F bonds in saturated fluorocarbons [5]. In this approach, the broken of C−F bond proceeds through heterolytic abstraction of the fluoride anion by a strong Lewis acid instead of a redox process. In 2012, Stephan exploits the

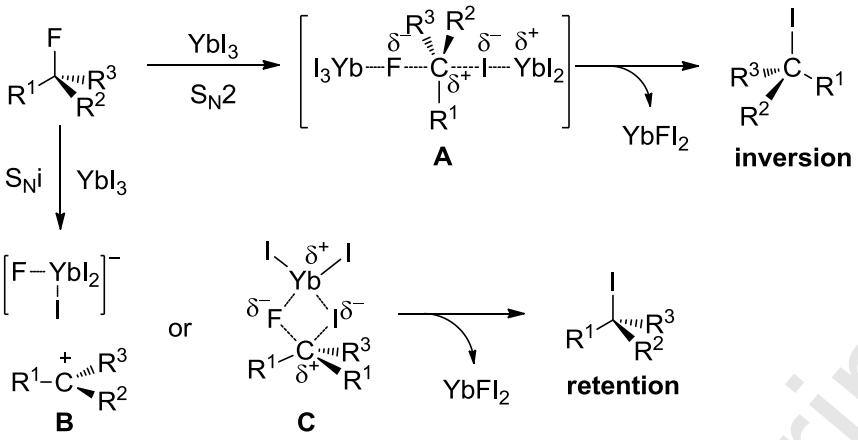
fluorophilicity of the borone based Lewis acid $B(C_6F_5)_3$ to activate C−F bonds [8]. By the use of stoichiometric amount of $B(C_6F_5)_3$, activation of alkyl fluorides gave alkane and thioester by an effective X-F exchange in the presence of borate anions of the form $[XB(C_6F_5)_3]^-$ (X = H, SPh) (Scheme 1a). Similarly, the activation of the C−F bonds by interaction with the Lewis acid $B(C_6F_5)_3$ can be used to catalytically effect hydride/fluoride exchange between alkyl fluorides and silanes (Scheme 1b). The reaction with silane can be applied to secondary fluorides, primary fluorides and difluorides to afford corresponding alkanes in excellent yields (> 95%).

Hilmersson reported that $Sm(HMDS)_2$ (HMDS=hexamethyldisilazide) can be used as a single electron transfer (SET) reagent, to promote the reductive defluorination of aliphatic C–F bonds (Scheme 1c) [9]. $Sm(HMDS)_2$ exhibits uniquely enhanced reductive ability towards the C–F bond in *n*-hexane compared to when using THF as solvent. Although cleavage of primary, secondary or tertiary alkyl fluorides mediated by $Sm(HMDS)_2$ in *n*-hexane undergoes quickly to give corresponding alkanes in good to excellent yields, tertiary fluoride is selectively reduced in the presence of primary and secondary fluorides.

In 2009, Deacon reported that the aromatic C-F bond can be activated through the formation of Lanthanoid-Fluoride cluster due to the strong interaction of Yb-F. [10] This Lanthanide catalyzed C-F bond activation is further applied in aliphatic C-F bonds by Hilmersson, in which alkyl fluorides can be selectively substituted with iodide by means of YbI_3 under mild condition (Scheme 1d) [11]. The substitution is stereospecific and proceeds by the S_N2 mechanism with a competing S_Ni pathway, with the ratio of products from either pathway being dependent on the substrate (Scheme 2). The reaction is compatible with a large range of common functional groups including alkyl chloride and bromide. Since C-I group is highly reactive and versatile, the F/I substitution with YbI_3 paves the way for the use of fluorine as a small, sterically unhindered protecting group which now is easy to remove. In addition, it is a direct and powerful route for late-stage incorporation of iodine into complex target molecules.

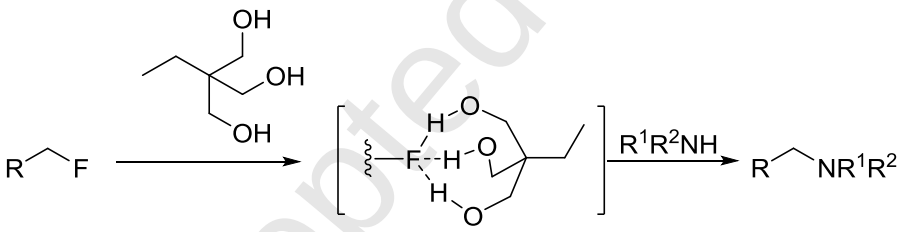


Scheme 1. Substitution of fluorides mediated by Lewis acids and hydrogen bonds.



Scheme 2. Mechanistic proposal for the F/I substitution

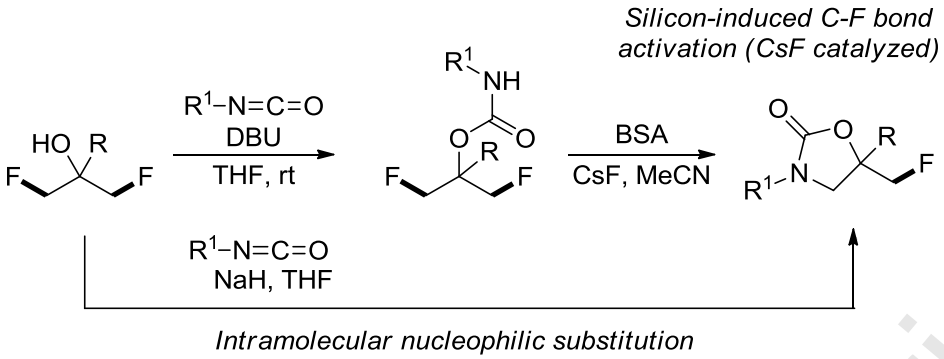
The nucleophilic substitution of benzylic fluorides by amines promoted by a hydrogen bond-donating agent (triol) was successfully achieved under neutral and solvent-free conditions by Paquin (Scheme 1e) [12]. Triol, 1,1,1-tris(hydroxymethyl)propane, is supposed to provide simultaneous coordination of the three lone pairs of fluorine. The reaction can be applied to a variety of secondary amines as nucleophiles (Scheme 3).



Scheme 3. Proposed activation of C-F bonds mediated by a triol.

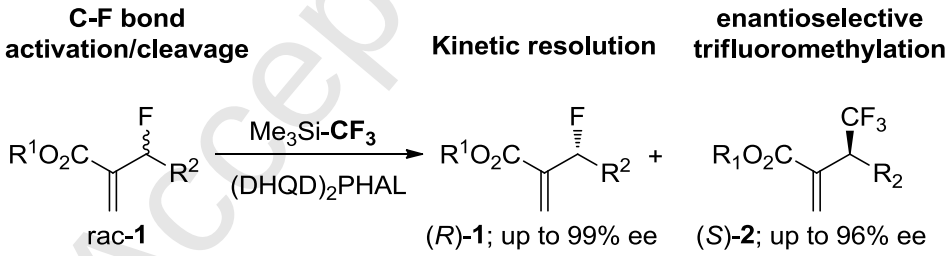
In 2012, Haufe, Shibata and coworkers reported the synthesis of biologically relevant fluoromethyl-3,5-diaryl-2-oxazolidinones by desymmetrization of 2-aryl-1,3-difluoropropan-2-ols (Scheme 4) [13]. The transformation was achieved in a mild, BSA/CsF catalytic system (BSA = bis(trimethylsilyl)acetamide). This catalytic C-F bond activation of unactivated aliphatic di-fluorides induced by silicon is conceptually new. Meanwhile, the fluoromethyl substituted oxazoline can also be formed directly from di-fluorides and isocyanates by cascade carbamoylation/cyclization, in which the cyclization is believed to occur through an

intramolecular nucleophilic substitution of sodium amide intermediate.



Scheme 4. Synthesis of 3,5-diaryl-2-fluoromethyl-oxazolidin-2-ones by the desymmetrization of unactivated aliphatic fluorides.

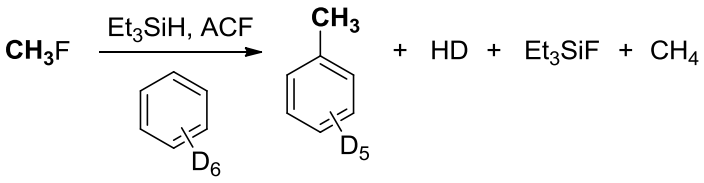
Silane coordination-assisted C-F activation [14] is applied to the kinetic resolution of MBH-type allyl fluorides by enantioselective allylic trifluoromethylation under organocatalysis (Scheme 5) [15]. The key for success is the cleavage of the strong C-F bond of **(S)-1** by a cooperative system that includes the bis(cinchona alkaloid) and the silicon atom of the trifluoromethylating reagent, while **(R)-1** remains intact. Interestingly, enantioselective allylic pentafluoroethylation and pentafluorophenylation were also achieved through the kinetic resolution of allyl fluoride under the same reaction condition.



Scheme 5. Kinetic resolution of MBH-type allyl fluorides by enantioselective fluoroalkylation through C-F bond activation/cleavage.

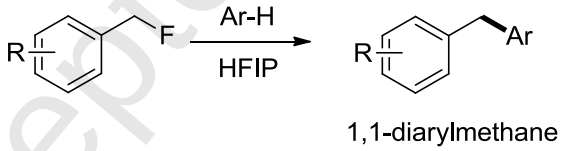
Carbon-carbon bond formation with fluoromethane as a starting material has been realized after C-F activation by Lewis acids [16]. The Lewis acid, aluminum chlorofluoride (ACF), can be used in an unprecedented heterogeneous catalytic process for the C-F activation of fluoromethane in the presence of Et_3SiH (Scheme 6).

The C-F bonds are either converted into C-H bonds by hydrodefluorination or into C-C bonds in the presence of benzene through a Friedel–Crafts-type reaction. The conversions are presumably mediated by a silylium-ion-like surface species which initiates the C-F activation step.



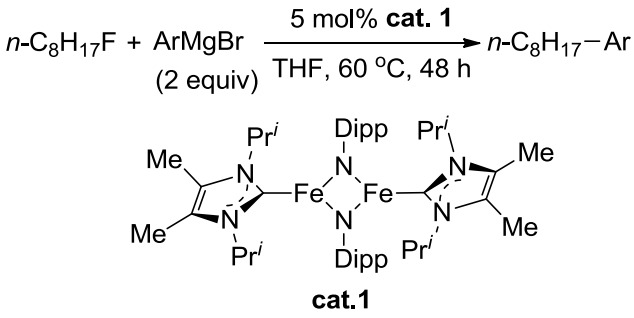
Scheme 6. ACF-catalyzed C-F activation reaction of fluoromethane.

The Friedel-Crafts reactions between benzyl fluorides and various arenes were then reported by Paquin in 2014 [17]. Selective activation of the benzylic C-F bond is realized by a hydrogen bond donating agent, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) (Scheme 7). The reaction proceeds at room temperature, however, α,α-difluorotoluene remains intact. This C-C bond formation reaction provides a facile access to 1,1-diaryl alkanes under mild conditions without the need for a transition metal or a strong Lewis acid. This mode of activation exploited a new type of reactivity of benzylic fluorides as building blocks in organic synthesis.



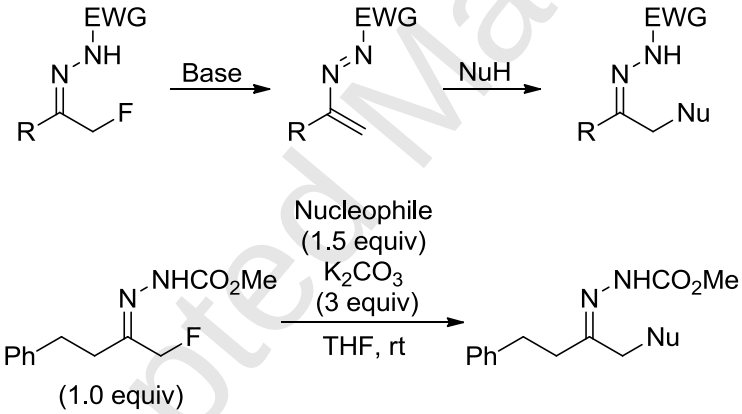
Scheme 7. Friedel-Crafts benzylation enabled by hydrogen bonding.

The first example of an iron-catalyzed cross-coupling reaction of primary alkyl fluoride with a variety of aryl Grignard reagents was reported by Deng (Scheme 8) [18]. A low-coordinate dinuclear iron(II) complex [(IPr_2Me_2)Fe(μ_2-NDipp)$_2$Fe(IPr_2Me_2)] is used as the catalyst, and a radical-type mechanism that is distinct from the known Ni- and Cu-catalyzed C(sp^3)–F bond functionalization reactions [19] may be involved.



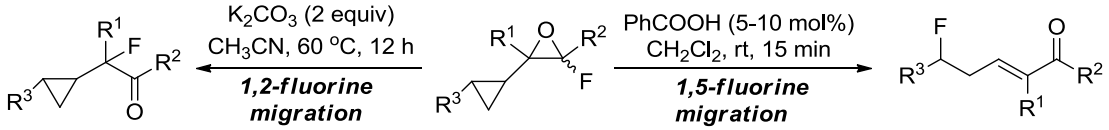
Scheme 8. Iron-catalyzed arylation of *n*-octyl fluoride.

Taniguchi revealed that α-fluorohydrazone derivatives are promising as useful building blocks which can be applied in nucleophilic substitution reactions under mild basic conditions to give various substituted products (Scheme 9) [20]. No expensive and toxic reagent is required, and the experimental procedure is very simple. The reaction is proposed through an elimination and addition process.



Scheme 9. Nucleophilic substitution of α-fluorohydrazone derivatives by elimination of a fluorine atom followed by the addition of nucleophiles.

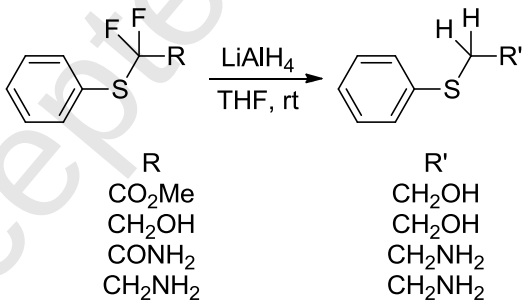
Hu and coworkers reported the divergent rearrangements of cyclopropyl-substituted fluoroepoxides involving C-F bond cleavage and formation (Scheme 10) [21]. In the presence of a catalytic amount of benzoic acid, cyclopropyl-substituted fluoroepoxides efficiently undergo 1,5-fluorine migration, giving δ-fluoro-α,β-unsaturated ketones. However, when the fluoroepoxides are heated with K_2CO_3 at 60 °C, 1,2-fluorine migration occurs to provide cyclopropyl-substituted α-fluoroketones. The 1,5-fluorine and 1,2-fluorine migrations are believed to proceed via a carbocation intermediate and a tight ion pair intermediate, respectively.



Scheme 10. Fluorine migration of cyclopropyl-substituted fluoroepoxides.

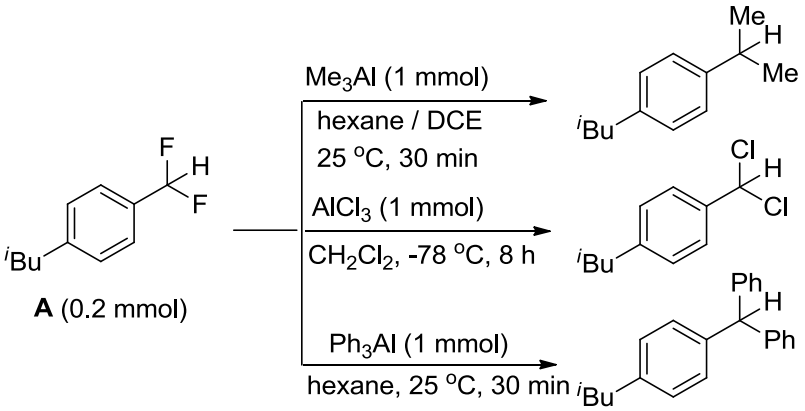
2. The C-F bond activation of compounds bearing with a difluoromethylene group

Usually, the C-F bond in aliphatic fluoride becomes shorter and stronger as the number of fluorine atoms attached to the same carbon atom increases [22, 23]. Consequently, thermal stability and chemical resistance of C-F bond in difluoromethylene group is higher than that of C-F bond in monofluoromethyl group, but lower than that of C-F bond in trifluoromethyl group. Hydrodefluorination of unactivated aliphatic C-F bonds of CF_2 derivatives with $LiAlH_4$ was reported by Cao (Scheme 11) [24]. The reaction condition is mild and no additional metal catalyst is needed. Deuterium-labeling experiments suggest that the hydrogens introduced into the products originated from $LiAlH_4$.



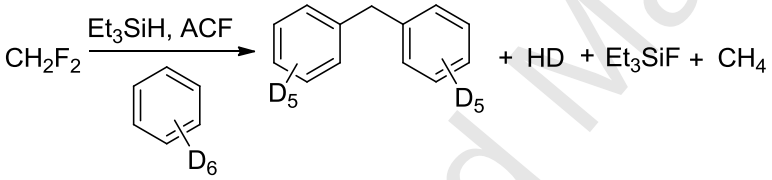
Scheme 11. Hydrodefluorination of difluoromethylene-containing derivatives.

Organoaluminium reagents are often used in the transformation of C-F bond. Terao reported that two C-F bonds of difluoromethylbenzene derivative **A** can be efficiently converted into C-Me, C-Cl and C-Ph bonds by using Me_3Al, $AlCl_3$ and Ph_3Al, respectively, as aluminium reagents in the absence of catalysts (Scheme 12) [25].



Scheme 12. Transformation of C-F bond of benzodifluoride.

Catalytic hydrodefluorination of difluoromethane at room temperature by silylium-ion-like surface species ACF is realized as mentioned for fluoromethane (Scheme 13) [16]. The formation of [D10]diphenylmethane is believed to proceed through two Friedel-Crafts reactions with benzyl fluoride as a key intermediate.

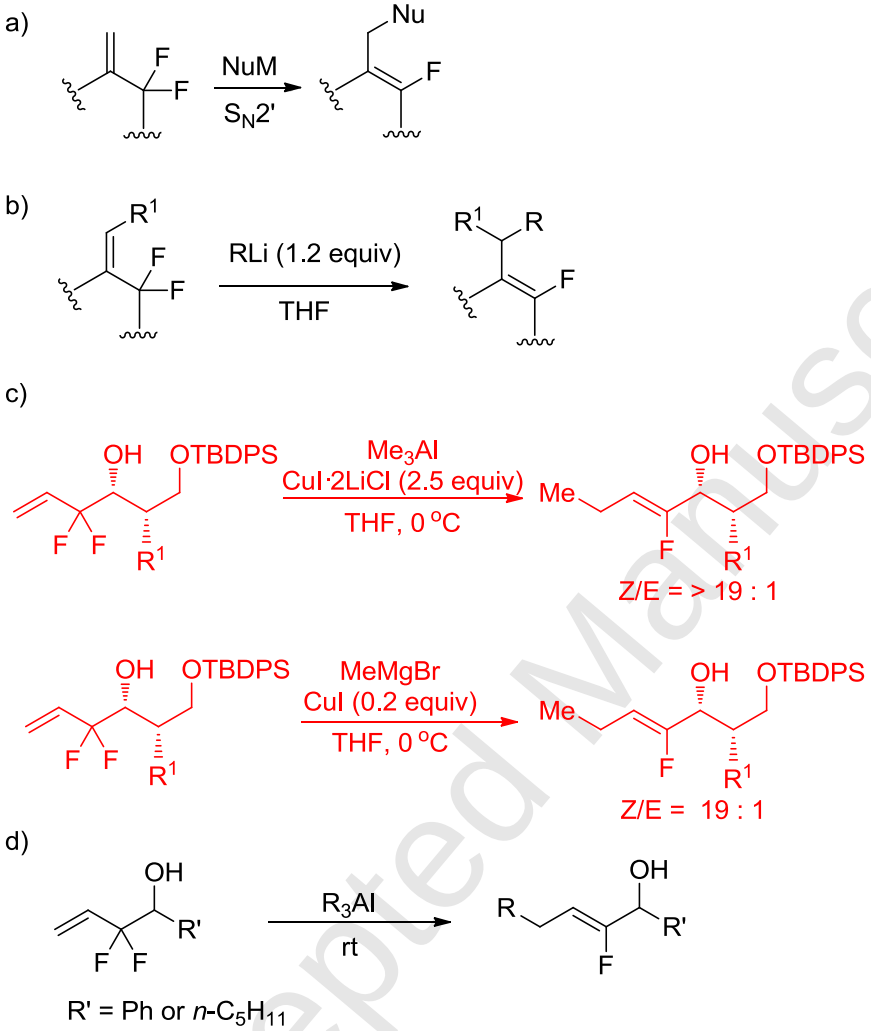


Scheme 13. ACF-catalyzed C-F activation reactions of difluoromethane.

By the use of fluoride as a leaving group, S_N2' displacement of a C-F bond on 3,3-difluoropropenes derivatives by a nucleophile has been researched extensively (Scheme 14a). Organolithium reagents gave direct access from 3,3-difluoropropene compounds to monofluoroalkenes (Scheme 14b) [26]. Organolithium reagent can be methyl lithium, *sec*-butyl lithium, *tert*-butyl lithium and 2-lithio-1,3-dithiane. A sp^2-based organolithium such as vinyllithium, phenyllithium, and (3-trifluoromethyl)-phenyllithium could also be used. Even less-nucleophilic lithiated alkynes could react although a higher temperature was required.

Copper mediated defluorinative allylic alkylation of difluorohomoallyl alcohol derivatives directed to an efficient synthetic method for (*Z*)-fluoroalkene dipeptide isosteres was reported by Taguchi (Scheme 14c) [27]. The reaction of each diastereoisomer of the difluorohomoallyl alcohol with trialkylaluminium and Cu(I)

system or Grignard reagent and a catalytic amount of CuI system in THF gave the fluorine-substituted allylic alcohol in an high yield and an excellent *Z* selective manner (Scheme 14c).

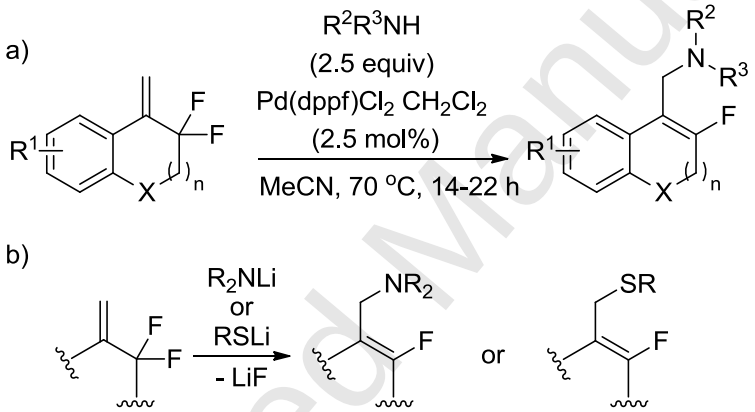


Scheme 14. C-C bond formation via S_N2' displacement of fluoride

At the same time, Taguchi also reported the copper-free defluorinative alkylation of allylic difluorides through Lewis acid-mediated C–F bond activation (Scheme 14d) [28]. The reactions of difluorohomoallyl alcohols with trialkylaluminiums smoothly proceeds in CH_2Cl_2 at room temperature in the absence of any Cu catalysts to give (*Z*)-fluoro-olefin products in excellent yields. On the basis of this chemistry, fluoro-olefinic dipeptide isostere of norvalinyl glycine is synthesized in stereoselective manner.

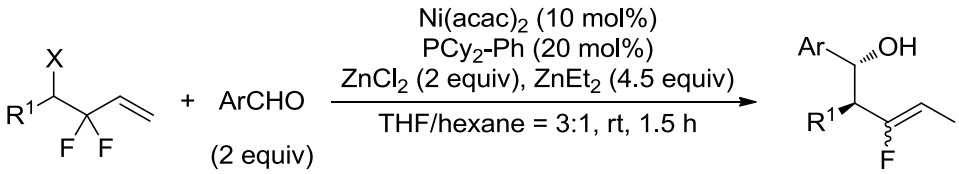
Allylic C–F bond could perform an oxidative addition with a palladium catalyst to

produce a palladium π-allyl complex [29-31]. Based on this key discovery, Paquin reported a novel route to *β*-aminofluoroalkenes using Pd-catalyzed allylic amination reactions of readily available 3,3-difluoropropenes (Scheme 15a) [32]. In this transformation, the key fluorinated palladium π-allyl intermediate is generated through an allylic C–F bond activation. Later, Paquin explored the syntheses of β-aminomonofluoroalkenes by a direct S_N2' reaction of lithium amides derived from aromatic amines with 3,3-difluoropropene derivatives (Scheme 15b) [33]. This transformation can be extended to S-based nucleophiles but not to O-based nucleophiles, and represents one of the rare cases where fluoride acts as a competent leaving group in a nucleophilic substitution reaction.



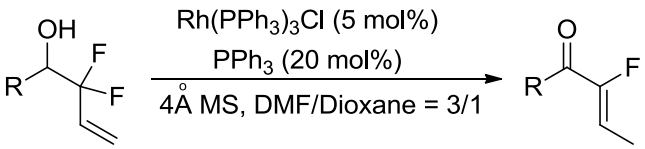
Scheme 15. Syntheses of *β*-aminomonofluoroalkenes and *β*-mercaptomonofluoroalkenes with 3,3-difluoropropene derivatives.

3,3-Difluoropropene derivatives can also be applied to a one-pot nickel-catalyzed allylation of aromatic aldehydes promoted by $Ni(acac)_2/PCy_2$-Ph/$ZnCl_2/ZnEt_2$ system (Scheme 16) [34]. The reaction displays moderate to good regio- and diastereoselectivity, tolerates a wide range of functional groups, and provides an efficient method for the synthesis of γ-fluorinated homoallylic alcohols.



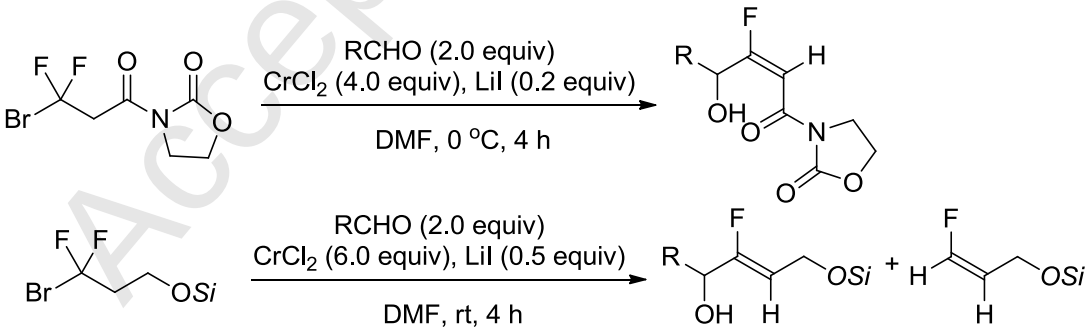
Scheme 16. Ni-catalyzed allylation of aromatic aldehydes with *α*-halo-*β*,*β*-difluorides.

Similar to the Ni, Pd-catalyzed allylic C-F bond activation, rhodium catalyst can also participate in the oxidative addition of allylic C-F bond. Based on this discovery, Xiao reported the efficient conversion of difluoro-homoallylic alcohols into *α*-fluoro-*α,β*-unsaturated ketones in good yields with excellent stereoselectivity (Scheme 17) [35]. The study of the mechanism shows that C–F bond activation via oxidative addition is involved and PPh_3 is responsible for the excellent stereoselectivity.



Scheme 17. Rh-catalyzed allylic C-F bond activation.

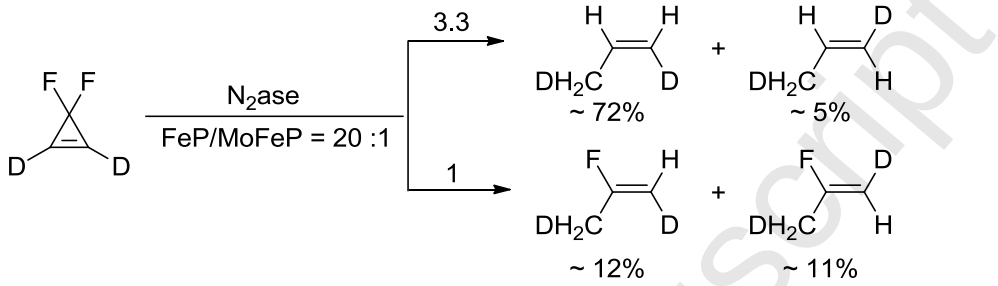
The early transition metal, Cr(II), was used by Konno to activate C-F bonds of CF_2Br-containing molecules [36]. Highly nucleophilic (*Z*)- or (*E*)-*α*-fluoroalkenylchromium species could be generated in a stereoselective manner for CF_2Br-containing molecules, and they reacted smoothly with various aldehydes to give (*E*)- or (*Z*)-*β*-fluoroallylic alcohol derivatives in high stereoselectivities (Scheme 18).



Scheme 18. Reductive coupling of CF_2Br-containing molecules with aldehydes.

Nitrogenase-catalyzed reduction of fluorinated substrates is of interest in relation to biological degradation of halogenated compounds [37, 38]. McKenna reported the reduction of 3,3-difluorocyclopropene by nitrogenase (Scheme 19) [39]. A reduction

mechanism, consistent with hydride transfer as a key step, is discussed. The enzyme catalyzed remarkable reductive C−F bond cleavage gave the $6e^-/6H^+$ and $4e^-/4H^+$ reduction products propene and 2-fluoropropene, respectively, consistent with a hydride-transfer step and C=C cleavage. This transformation demonstrates the unique and remarkable scope of catalytic process of nitrogenase.



Scheme 19. d_2-Propene and d_2-2-fluororpropene isomers produced by N_2ase-catalyzed reduction of d_2-DFCP (FEP/MoFeP = 20:1).

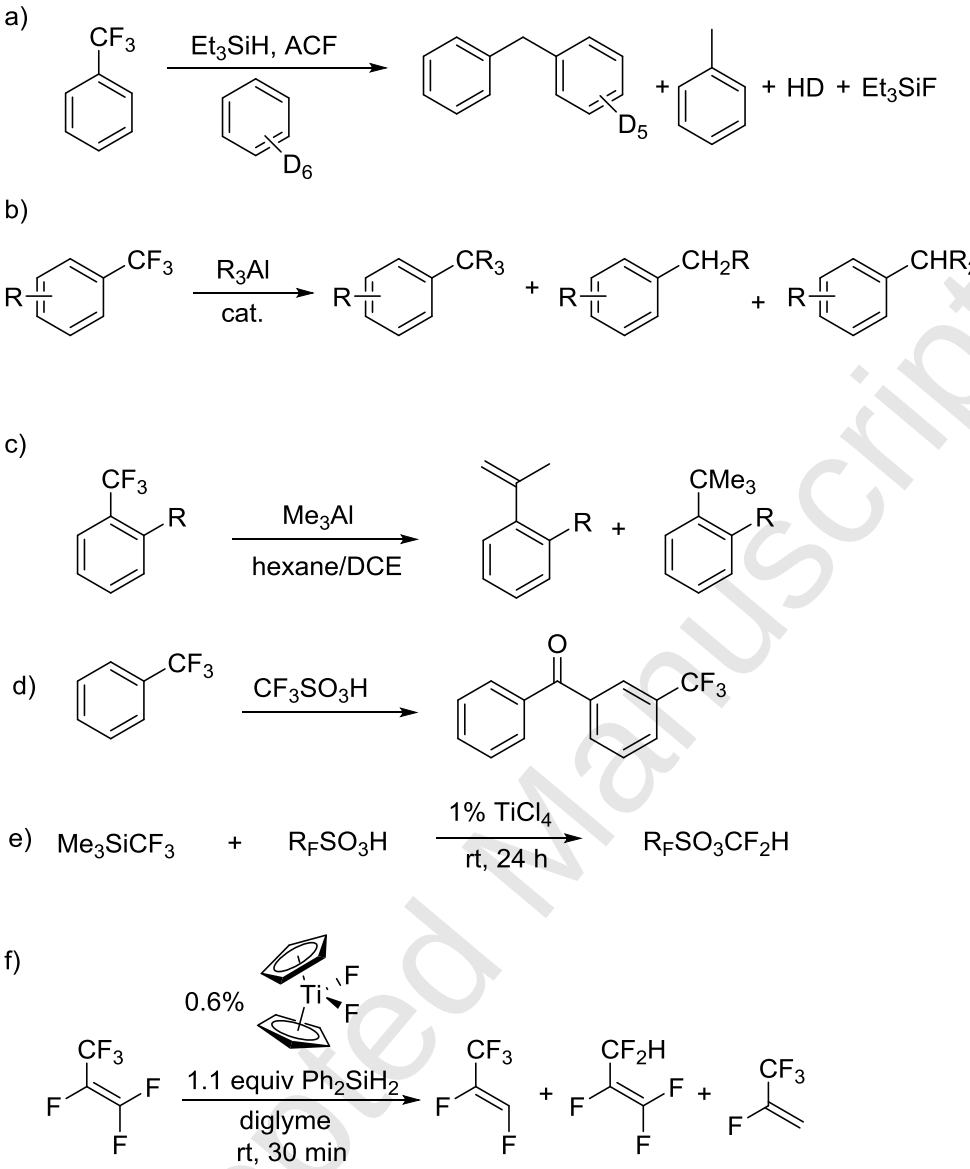
3. The C-F activation of compounds bearing with a trifluoromethyl group

Trifluoromethyl is the most common fluorinated functional group in organofluorines, and numerous methods exist to introduce this functionality. As mentioned before, aluminum chlorofluoride (ACF) is an effective catalyst of hydrodefluorination for not only fluoromethane but also benzotrifluoride in the presence of Et_3SiH (Scheme 20a) [16]. When running the reaction in deuterated benzene at room temperature, the Friedel-Crafts reaction product, [D5]diphenylmethane was detected. In 2013, Akiyama reported hydrodefluorination of benzotrifluoride by the catalysis of titanium tetrachloride in the precence of excess lithium aluminium hydride in refluxing dimethoxyethane [40].

The efficient alkylation of benzotrifluoride with alkylaluminum compounds is reported by Ozerov via using dialkylalumenium cation equivalents coupled with hexabromocarborane anion (eg. $Et_2Al[HCB_{11}H_5Br_6]$) as a catalyst (Scheme 20b) [41]. The catalytic system is specific, in which C(sp^3)-F bonds undergo alkylative defluorination while C(sp^2)-F bonds are unaffected. The conversion of C-F bonds of benzotrifluorides to C–C bonds can also be realized by using aluminium reagents in the absence of catalysts (Scheme 20c) [25]. Brønsted superacids can also promote

protolytic defluorination and Friedel–Crafts-type reactions of trifluoromethyl substituted arenes with benzene (Scheme 20d) [42]. The diaryl ketone products from these reactions suggest the formation of reactive electrophiles, such as carbocations, acylium cations or equivalent electrophilic species.

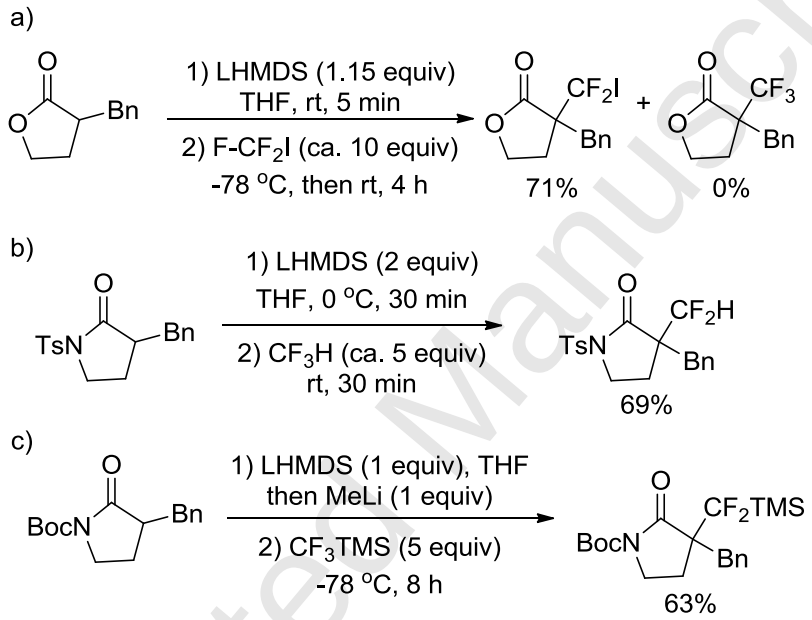
As a new property of trifluoromethyl trimethylsilane (CF_3TMS, Ruppert-Prakash reagent), C-F bond activation of CF_3TMS occurs upon interaction with perfluorosulfonic acids (Scheme 20e) [43]. The reaction is catalyzed by titanium tetrachloride and affords difluoromethyl perfluorosulfonate in good yield. The simultaneous C–F and C–Si bond activation by Lewis acid ($TiCl_4$) is believed to be the key feature responsible for the efficiency of the reaction. Then organotitanium catalyzed hydrodefluorination (HDF) of fluoroalkenes is reported by Lentz (Scheme 20f) [44]. The titanium catalyst requires low steric bulk and high electron density. Partially fluorinated alkenes can be synthesized stereoselectively from a broad range of substrates.



Scheme 20. Activation of C-F bonds of CF_3 by using Lewis acid and Brønsted superacids.

A conceptually different approach to the conversion C(sp^3)-F to C-C bonds with lithium enolates was reported by Mikami (Scheme 21). Cleavage of a C-F bond in preference to the weaker C-I bond of trifluoromethyl iodide provides a CF_2I-substituted compound rather than a CF_3-substituted compound (Scheme 21a) [45]. Fluoroform usually is employed as the nucleophilic trifluoromethyl carbanion equivalent for non-enolizable carbonyl compounds. However, by using polarity-inversion approach, namely, the umpolung of fluoroform by activation of an inert C-F bond, difluoromethyl group is introduced to α-position of various carbonyl

compounds by the reaction of cyclic lithium enolate with fluoroform (Scheme 21b) [46]. Direct α-siladifluoromethylation of lithium enolates with Ruppert-Prakash reagent via C-F bond activation was also realized (Scheme 21c) [47]. In the reaction, CF_3TMS works as an electrophile through polarity inversion to a siladifluoromethyl cation ($TMSCF_2^+$). This direct α-siladifluoromethylation of lithium enolate with CF_3TMS leads to construction of α-siladifluoromethyl-attached quaternary and tertiary carbon centers with high synthetical and biological potential.



Scheme 21. Defluorination of CF_3I, CF_3H and CF_3TMS and fluoroalkylations of cyclic lithium enolates

Trifluoroethanol is a good building block for the synthesis of fluorinated compounds. Protected trifluoroethanol can be defluorinated in basic condition to generated difluorovinyl lithium, and exchange of lithium to zinc allowed the subsequent Negishi reaction under mild reaction conditions to afford difluoroalkenes in moderate yields (Scheme 22a) [48].

Taguchi revealed that the reaction of trifluoroacetaldehyde N,O-acetals with more than 2 equiv of alkyllithiums at -78 °C resulted in regiospecific defluorinative alkylation to give α,α-difluoroketone N,O-acetals in excellent yield. In contrast, under similar conditions, trichloroacetaldehyde N,O-acetals gave simple

mono-dechlorinated product without the alkyl transfer reaction from alkyllithiums to the generated intermediates (Scheme 22b) [49, 50].

Magauer reported a transition-metal-free protocol for the conversion of simple 2-allyl-3-(trifluoromethyl)phenols into substituted 5-fluoronaphthalen-1-ols (Scheme 22c) [51]. The key events of this reaction include the selective activation of two C-F bonds and formation of an intermediate hexatriene system, which undergoes a 6π electrocyclization, followed by rearomatization. It is need to be pointed out that a free hydroxy group adjacent to the allyl unit is required for the reaction to occur.

Fluorine atoms in vinylic and allylic positions are easy to undergo substitution reactions [52, 53]. Based on this fact, Ichikawa reported the regioselective synthesis of 3-fluoropyrazoles by substitution of two fluorine atoms in an allylic trifluoromethyl group (Scheme 22d) [54]. This transformation includes the following two steps: 1) the S_N2'-type reaction of 2-trifluoromethyl-1-alkenes with lithio- or sodiohydrazines gives 1,1-difluoro-1-alkenes and 2) the cyclization of tosylated 1,1-difluoro-1-alkenes affords 3-fluoropyrazoles.

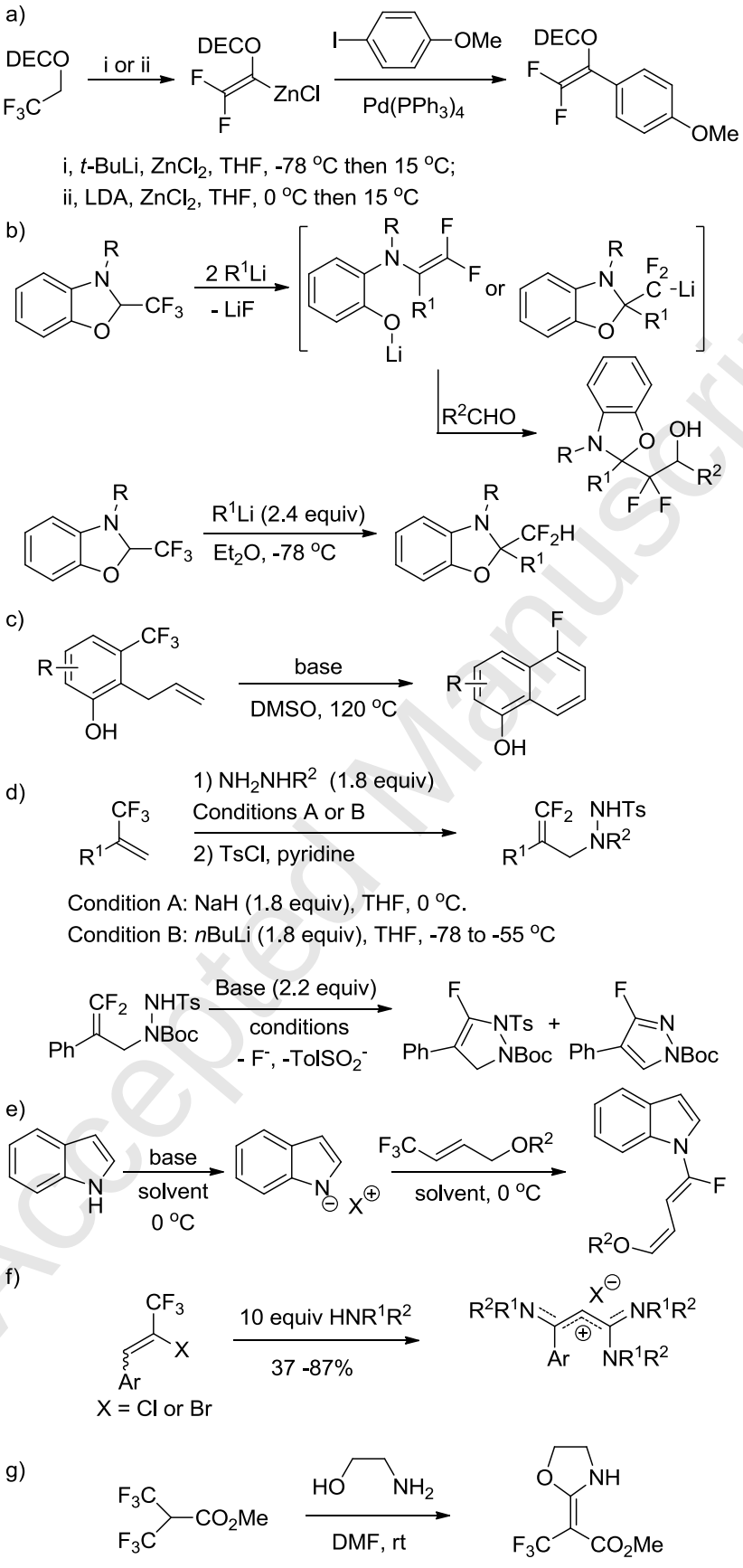
Marques found that fluorine in trifluoromethylated olefins can be a better leaving group than bromide, mesyl or tosyl [55]. Reactions of trifluoromethylated allylic methanesulfonate and toluene-4-sulfonate with indole sodium salt gave indole-substituted monofluoroolefins (Scheme 22e).

Selective synthesis of α-trifluoromethyl-β-aryl enamines or vinylogous guanidinium salts by treatment of β-halo-β-trifluoromethylstyrenes with secondary amines under different conditions were discovered by Nenajdenko (Scheme 22f) [56]. Two pathways were found depending on the electronic properties of the starting styrenes and the reaction parameters. Reactions of β-halo-β-trifluoromethylstyrenes with neat secondary amines afford a series of α-trifluoromethyl-β-aryl enamines in high yields. In contrast, the reactions of the mentioned styrenes with the same amines in polar solvent (ethanol) result in substitution of all halogen atoms to give vinylogous guanidinium salts in good yields.

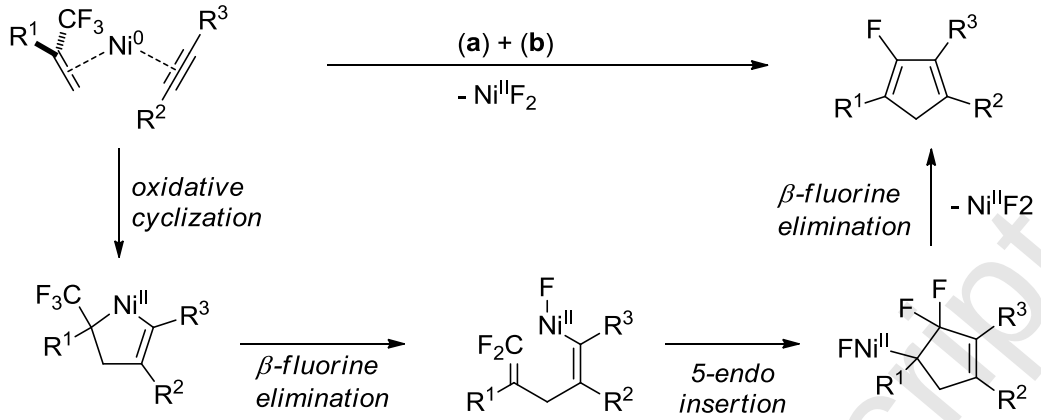
The defluorination of one of the trifluoromethyl group in methyl 3,3,3-trifluoro-2-trifluoromethylpropanoate is realized in the presence of

aminoalcohols to afford trifluoromethylated ketene aminoacetals (Scheme 22g) [57]. Palladium-catalyzed asymmetric allylation of the ketene aminoacetals is further investigated.

Ichikawa and coworkers reported palladium-catalyzed intramolecular Fridel-Crafts-type reaction of difluoroalkenes in 2007 [58] . In 2014, their group discovered that trifluoromethylated alkenes readily underwent [3+2] cycloaddition with alkynes mediated by nickel catalyst to afford fluorine-containing multi-substituted cyclopentadienes in a regioselective manner (Scheme 23) [59]. This reaction involves the consecutive two C-F bond cleavage of a trifluoromethyl group through allylic C-F activation via nickelcycles or intermoleculer vinylic C-F bond activation.



Scheme 22. Defluorination of a trifluoromethyl group in the presence of various bases

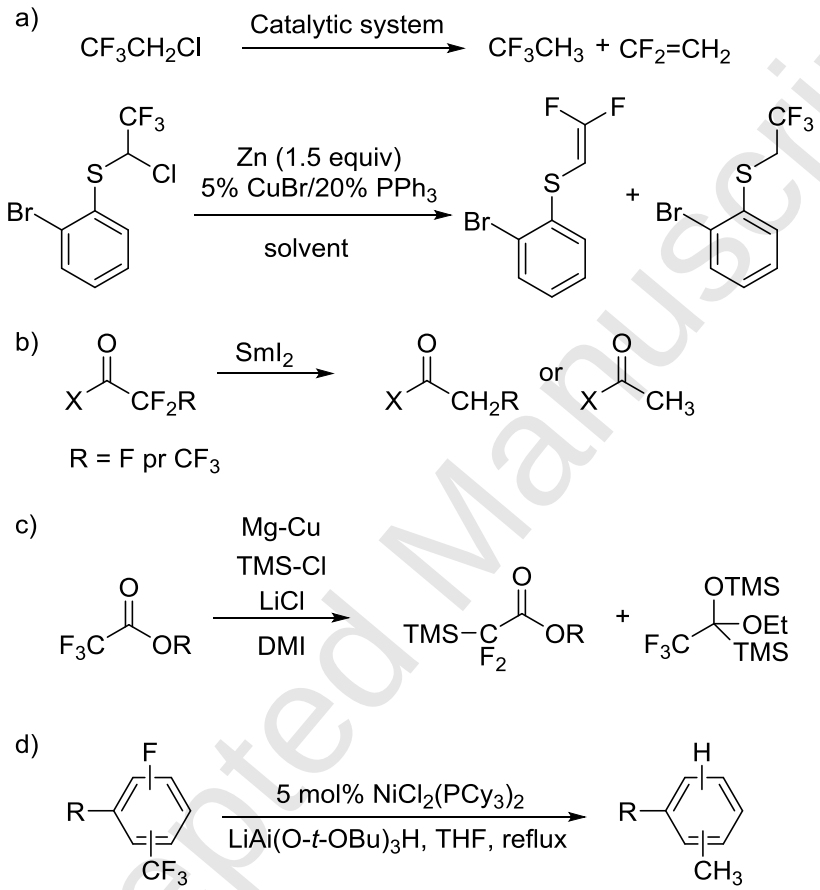


Scheme 23. Double C-F bond activation of a CF_3 group by a) allylic C-F bond activation via nickelcycles and b) intermoleculer vinylic C-F bond activation.

Instead of C-F bond activation, the reductive cleavage of the unactivated carbon–chlorine bond of 2-chloro-1,1,1-trifluoroethane (HCFC-133a) via a single electron transfer (SET) process catalyzed by transition-metal was achieved by Chen (Scheme 24a) [60]. Ni(0) or Cu(0) catalytic systems afford 1,1,1-trifluoroethane (HFC-143a) or 1,1-difluoroethylene (VDF) with excellent yields, respectively. The formation of VDF may be due to the elimination of the 1,1,1-trifluoroethyl anion generated by SET between the corresponding radical and a Cu(I) intermediate. A sulfur containing aryl bromide was further researched for the understanding the mechanism. The remaining of C–Br bond suggest that the process of Cu(0) or Cu(I) oxidative addition to the C–Cl bond may be excluded in this process due to the oxidative addition of aryl bromides being much faster than that of alkyl chlorides.

A reducing system containing $SmI_2/Et_3N/H_2O$ was used to selective α-defluorinated polyfluorinated esters and amides (Scheme 24b) [61]. It is noted that the degree of defluorination can be controlled by altering the temperature and amount of base. The reductive defluorination-silylation of various alkyl trifluoroacetates for preparation of alkyl 2,2-difluoro-2-(trimethylsilyl)acetates was also realized by copper-deposited magnesium (Scheme 24c) [62]. The deposition of copper metal on the surface of magnesium metal powder increases the reducing ability of magnesium.

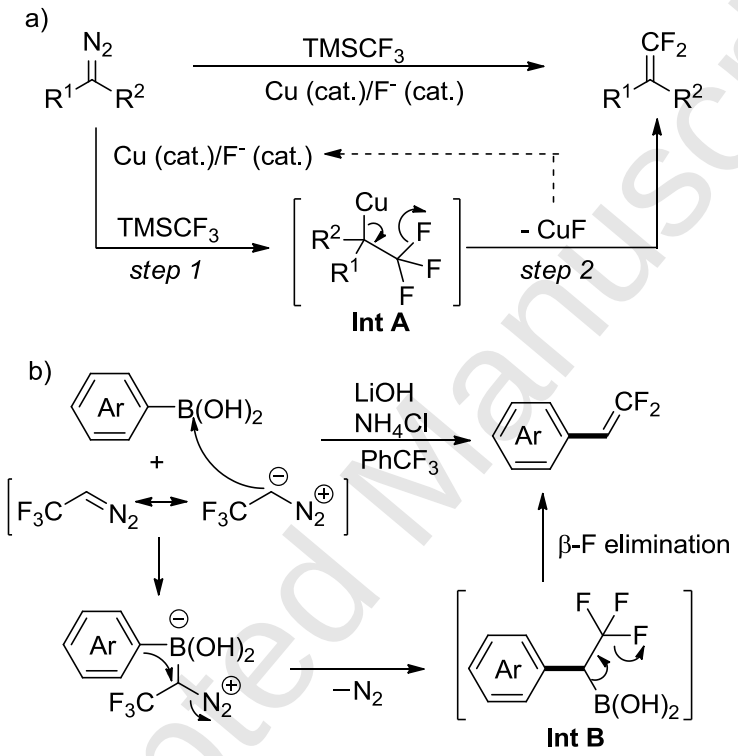
In continuation of the research on the hydrodefluorination reaction, Cao and coworkers reported various reaction conditions for different types of C-F bonds [24, 63-65]. They found that C–F bonds of fluoroarenes are more easily reduced with $LiAl(O^tBu)_3H$ than C–F bonds of α,α,α-trifluorotoluenes under the catalysis of $NiCl_2(PCy_3)_2$ (Scheme 24d) [66].



Scheme 24. Defluorination of perfluoroalkyl groups by reductive transition metal systems.

As an important class of fluorinated compounds, *gem*-difluoroalkenes can be achieved through defluorination of trifluoromethyl group. Cu-catalyzed gem-difluoroolefination of diazo compounds was described by Hu (Scheme 25a) [67]. This transformation starts from $TMSCF_3$ and diazo compounds, via trifluoromethylation followed by β-fluoride elimination of the key intermediate **A**, to afford a variety of structurally diverse 1,1-difluoroalkene products. *Gem*-difluoroalkenes can also be synthesized by using trifluorodiazoethane as the

fluorinating agent under transition-metal-free conditions (Scheme 25b) [68]. In this transformation, the electron-rich diazo carbon atom is coordinated to the electron-deficient boron center, which is followed by a 1,2-shift of the carbon ligand from boron to carbon to form intermediate **B**. The subsequent β-fluoride elimination of **B** achieve *gem*-difluorovinylation products in good to excellent yields.



Scheme 25. Preparation of *gem*-difluoroalkenes from diazo compounds.

Conclusion

In summary, we have classified the recent methodologies for the C-F bond activation of three kinds of substrates, namely, the compounds with a monofluoro-substituent, a difluoromethylene group and a trifluoromethyl group. Similar reactions illustrated with a representive example or a general formula are collected into the same schemes (Scheme 1, 14, 15, 20, 21, 22 and 24). The methods to activate a C-F bond include activation by Lewis acid, Brønsted superacids and hydrogen bonding, and mediation by transition-metals and rare earth metals. Partial

reduction of trifluoromethyl group through a single electron transfer process can provide less fluorine-containing compounds. Bases are often used for the elimination of hydrofluoride. S_N2' displacement is also an important method for transformation of α-fluorinated, difluorinated and trifluorinated olefins to various synthetically interesting molecules. We believe that many new methods for C-F activation of alphatic fluorides will be developed with the increase of fluorinated compounds disclosed in organic synthesis for multiple purposes, such as agrochemical, medicinal and material usage.

Acknowledgements

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