3

Difluoromethylation and Difluoroalkylation in C(sp^3) Centers and C═O, C═C, and C═N Bonds

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3.1 Nucleophilic Difluoromethylation and Difluoroalkylation

3.1.1 By Means of $XCF_2PO(OEt)_2$

Due to the facile C─F bond cleavage in HCF_2Li or HCF_2MgX reagents, direct difluoroalkylation with these reagents is difficult. However, when the H atom of CF_2H group is substituted by a proper electron-withdrawing group or changing the hard Li or Mg to other soft metals, the corresponding RCF_2M can be synthetically useful. Burton et al. reported that the reaction between $BrCF_2PO(OEt)_2$ and Cd would generate a stable organocadmium reagent, which can react with allyl bromide (Scheme 3.1a) [1]. Allylation of [(diethoxyphosphinyl)difluoromethyl] zinc bromide can also be accomplished under copper catalysis [2]. Obayashi et al. reported that $LiCF_2PO(OEt)_2$, generated from $HCF_2PO(OEt)_2$ and lithium diisopropylamide (LDA) at −78 °C, could react with alkyl bromides, allylic bromides, aldehydes, and ketones, giving the corresponding difluoroalkylated products (Scheme 3.1b) [3]. An improved method for the synthesis of 1,1-difluoro-2-hydroxyalkylphosphates was demonstrated by Obayashi and Kondo using $Me_3SiCF_2PO(OEt)_2$/CsF [4]. Similar protocol was used by Prakash and coworkers to achieve difluoromethylenation of aldehydes and ketones [5].

3.1.2 By Means of $BrCF_2CO_2Et$ and $BrCF_2CH{=}CH_2$

In 1984, Fried and coworker reported that $BrCF_2CO_2Et$ could undergo facile Reformatsky addition to aldehydes and ketones (Scheme 3.2a) [6]. This method have found many applications for the incorporation of $–CF_2C(O)–$ group or its derivatives [7]. In 1989, Burton and coworker reported that the reaction of $BrCF_2CH{=}CH_2$, zinc powder, and aldehydes or ketones provides a useful route to *gem*-difluoro homoallylic alcohols (Scheme 3.2b) [8].

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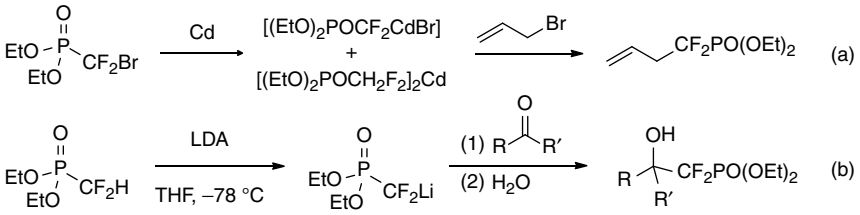
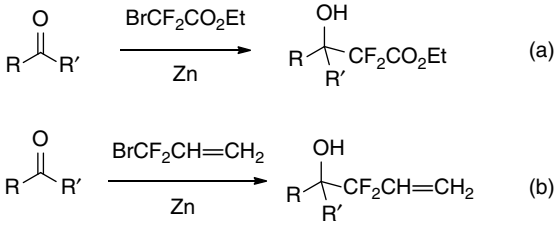


Scheme 3.1 Nucleophilic difluoroalkylation with $XCF_2PO(OEt)_2$. (a) for X = Br and (b) for X = H.



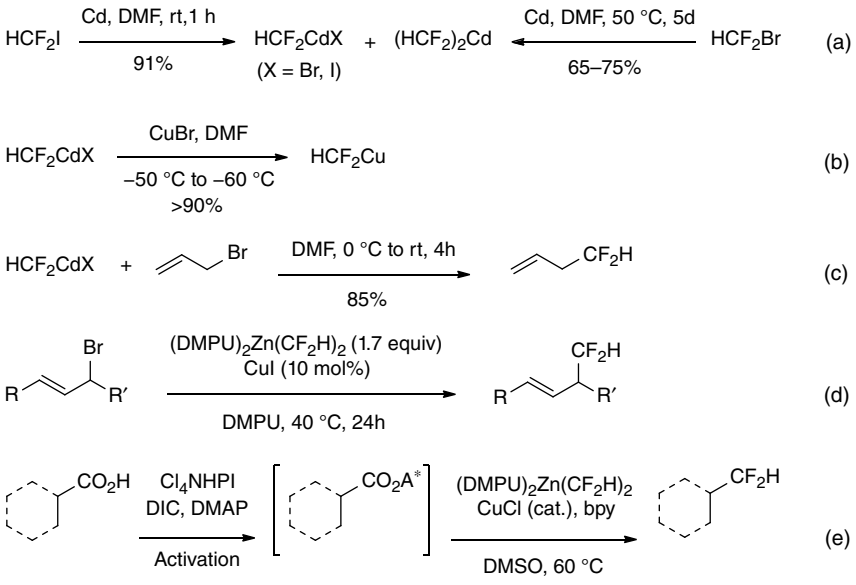
Scheme 3.2 Reformatsky-type nucleophilic difluoroalkylation with $BrCF_2CO_2Et$ and $BrCF_2CH{=}CH_2$.

3.1.3 By Means of Difluoromethylcadmium, Difluoromethylcopper, and Difluoromethylzinc Reagents

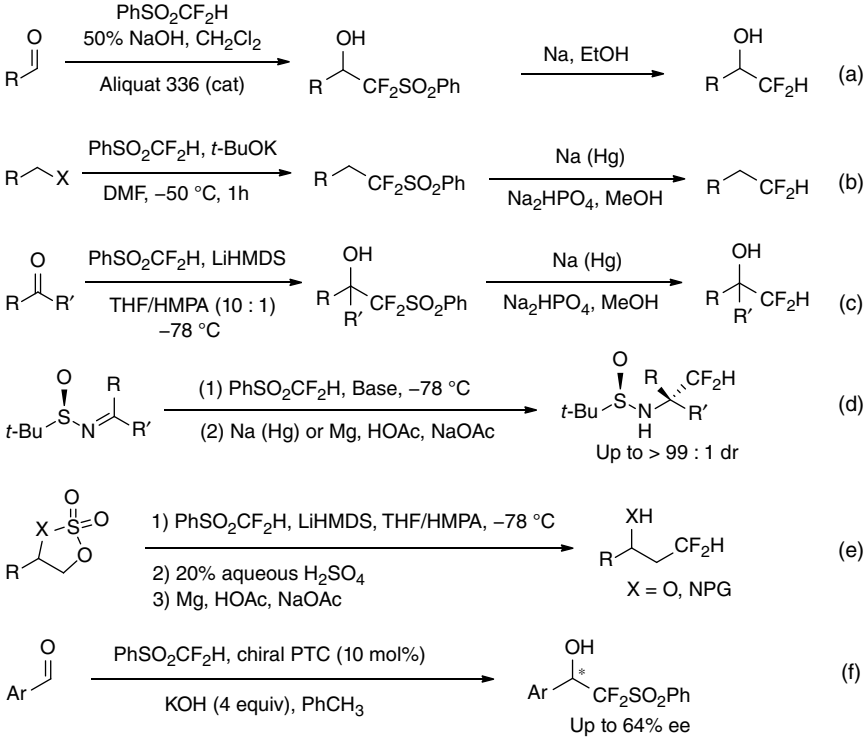
In 1988, Burton and coworker found that difluoromethylcadmium can be prepared from HCF_2I or HCF_2Br with acid-washed cadmium powder in *N,N*-dimethylformamide (DMF) (Scheme 3.3a) [9]. The formed difluoromethylcadmium is a mixture of mono- and bis-difluoromethylcadmium. Difluoromethylzinc can be prepared in a similar way. Difluoromethylcopper can be easily prepared from metathesis between difluoromethylcadmium and CuBr or CuCl at temperatures ranging from −50 to −60 °C (Scheme 3.3b) [10]. Both difluoromethylcadmium and difluoromethylcopper could undergo allylic difluoromethylation reaction (Scheme 3.3c) [9, 10]. Difluoromethylcopper could also react with strong alkylating reagents, such as benzyl bromide and chloromethyl ethyl ether [10]. In 2016, Mikami and coworkers reported that bis(difluoromethyl)zinc reagent $(DMPU)_2Zn(CF_2H)_2$ can be prepared by the reaction of $ZnEt_2$ and HCF_2I [11]. $(DMPU)_2Zn(CF_2H)_2$ was applied to the copper-catalyzed allylic difluoromethylation of allyl carbonates (Scheme 3.3d) [12] and copper-catalyzed decarboxylation difluoromethylation (Scheme 3.3e) [13].

3.1.4 By Means of Difluoroalkylated Sulfone Reagents (XCF_2SO_2Ar) and Difluoromethylated Sulfoxides

Difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) was first prepared by Hine and Porter [14], but its application as a difluoromethylation reagent was largely overlooked for about three decades. In 1989, Stahly reported nucleophilic addition of $PhSO_2CF_2H$ to aldehydes in a two-phase system, and the $PhSO_2$ group could be removed under Na/EtOH conditions (Scheme 3.4a) [15]. This seminal report



Scheme 3.3 Preparation and application of difluoromethylcadmium copper and zinc reagents.

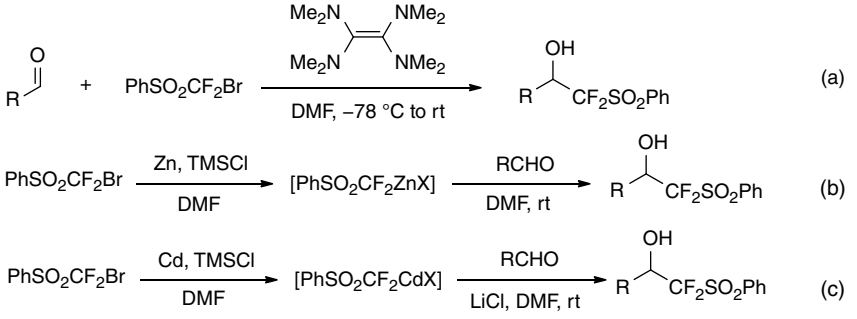


Scheme 3.4 Nucleophilic difluoromethylation with $PhSO_2CF_2H$.

showcased the difluoromethylating ability of $PhSO_2CF_2H$ but did not catch much attention until recently. Prakash et al. and Hu and coworkers made contributions to the synthetic application of $PhSO_2CF_2H$ as an efficient difluoromethylation reagent. In 2004, Prakash et al. reported a facile nucleophilic difluoromethylation of primary alkyl halides through a nucleophilic substitution-reductive desulfonation strategy (Scheme 3.4b) [16]. Later on, Hu et al. systematically studied the reaction of $PhSO_2CF_2H$ with various electrophiles. Aldehydes and ketones [17], imines [18], and cyclic sulfates and sulfamidates [19] are all amenable substrates, and the desired C(sp^3) phenylsulfonyldifluoromethylated products can be obtained in good yields (Scheme 3.4c–f). The $PhSO_2$ group can be successfully removed by either Na (Hg) or Mg/HOAc/NaOAc to give the difluoromethylated products. It should be noted that, although strong bases were required to generate the anion $PhSO_2CF_2^-$, both non-enolizable and enolizable carbonyl compounds and imines are tolerated (Scheme 3.4c,d) [17a]. High diastereoselectivity was observed in the reaction of *N-tert*-butylsulfinyl imines (Scheme 3.4d) [18], while only moderate ee values were achieved in the chiral quaternary ammonium salt-catalyzed enantioselective nucleophilic difluoromethylation of aromatic aldehydes with $PhSO_2CF_2H$ (Scheme 3.4f) [17b].

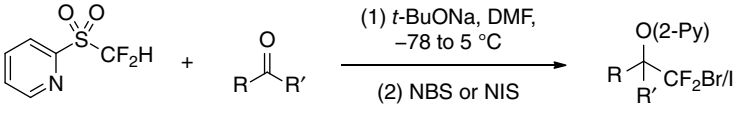
Since a strong base is required in the difluoromethylation with $PhSO_2CF_2H$, Hu and coworker developed a new difluoromethylating reagent, $PhSO_2CF_2SiMe_3$, which can readily undergo difluoromethylation reaction in the presence of catalytic amount of fluoride [20]. $PhSO_2CF_2SiMe_3$ showed similar reactivity with $PhSO_2CF_2H$, except that it gave better results in the reaction with enolizable aldehydes [20, 21]. $PhSO_2CF_2SiMe_3$ was also able to react with alkyl halides and *N,N*-acetals [22].

$PhSO_2CF_2Br$ can also be used as a nucleophilic difluoromethylation reagent. In 2005, Prakash et al. reported that tetrakis(dimethylamino)ethylene (TDAE) is an effective electron-transfer agent to promote the reaction of $PhSO_2CF_2Br$ with aldehydes (Scheme 3.5a) [23]. In 2017, Hu and coworkers reported that $PhSO_2CF_2Br$ can be transformed to the corresponding organozinc and cadmium reagents, which are efficient difluoromethylating reagents toward aldehydes (Scheme 3.5b,c) [24].



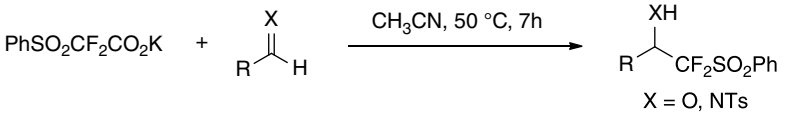
Scheme 3.5 Nucleophilic difluoromethylation with $PhSO_2CF_2Br$.

In 2010, Hu and coworkers reported that difluoromethyl 2-pyridyl sulfone, a previously unknown reagent, is an efficient gem-difluoroolefination reagent [25]. In 2012, by using difluoromethyl 2-pyridyl sulfone, Hu and coworkers realized the formal nucleophilic iodo- and bromodifluoromethylation of carbonyl compounds (Scheme 3.6) [26]. The key to success is the halogenation of *in situ* generated sulfinate intermediates from the Julia–Kocienski reaction to change the reaction pathway from the traditional olefination to alkylation.



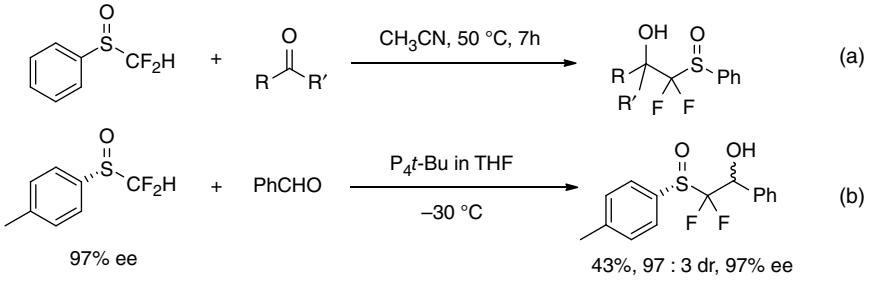
Scheme 3.6 Nucleophilic bromo- and iododifluoromethylation with difluoromethyl 2-pyridyl sulfone.

In 2018, Xiao and coworkers found that phenylsulfonyl difluoroacetate salt ($PhSO_2CF_2CO_2K$) could directly undergo decarboxylation upon mild heating to produce $PhSO_2CF_2^-$ without the need of any base or additive; therefore difluoromethylation of aldehydes and imines can be achieved using $PhSO_2CF_2CO_2K$ (Scheme 3.7) [27].



Scheme 3.7 Nucleophilic difluoromethylation with $PhSO_2CF_2CO_2K$.

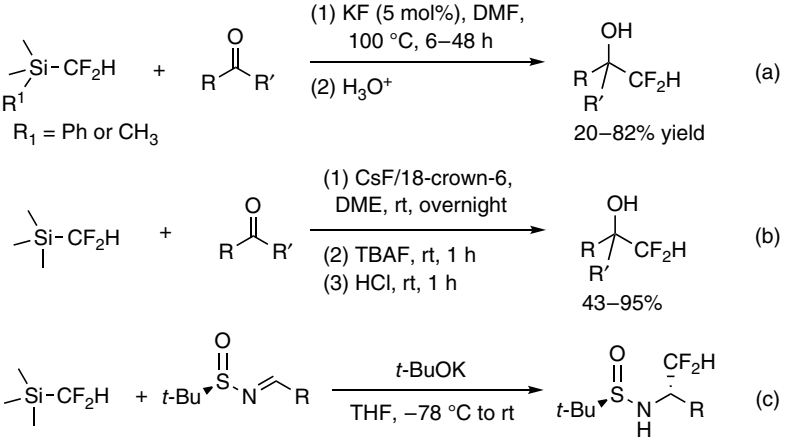
Difluoromethyl sulfoxides have also been used as difluoromethylation reagent. Hu and coworkers disclosed that difluoromethyl phenyl sulfoxide can undergo direct addition to aldehydes and ketones in the presence of *t*-BuOK (Scheme 3.8a) [28]. The yields are good, while the diastereoselectivity is poor (1 : 1.04–2.03). In 2018, Leroux and coworkers reported that chiral difluoromethyl sulfoxides can be prepared and used for the synthesis of highly enantioenriched α,α-difluoromethyl alcohols (Scheme 3.8b) [29].



Scheme 3.8 Nucleophilic difluoromethylation with difluoromethyl sulfoxides.

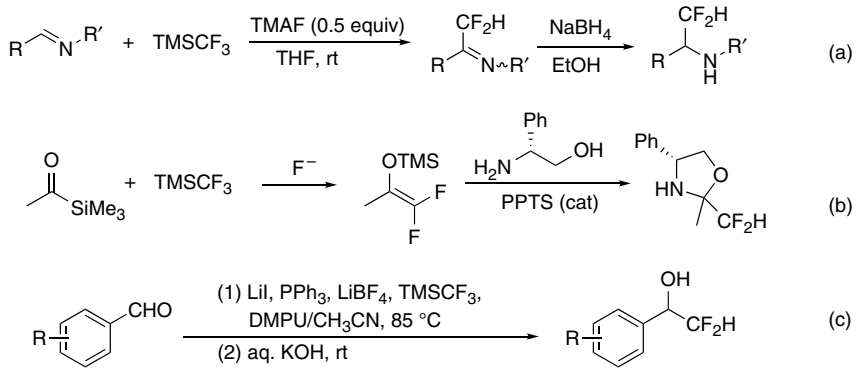
3.1.5 By Means of Difluoroalkylated Silanes and Trifluoromethylsilane Reagents

In 1995, Fuchikami and Hagiwara demonstrated that nucleophilic difluoromethylation of carbonyl compounds could be achieved using difluoromethyldimethylphenylsilane and difluoromethyltrimethylsilane ($TMSCF_2H$) at elevated temperatures (Scheme 3.9a) [30]. However, this method only works well for non-enolizable aldehydes, and the yields are generally low for ketones and enolizable aldehydes. Because of the harsh reaction conditions and narrow substrate scope, several modified methods were reported [31]. Remarkably, in 2016, Hu and coworkers disclosed an efficient protocol for the difluoromethylation of enolizable ketones using $TMSCF_2H$ (Scheme 3.9b) [31d]. The key to success is the formation of $[Me_3Si(CF_2H)_2]^-$, a key intermediate that acts as both the difluoromethanide anion source and difluoromethanide reservoir. $TMSCF_2H$ has also been used for the difluoromethylation of imines (Scheme 3.9c) [31b].



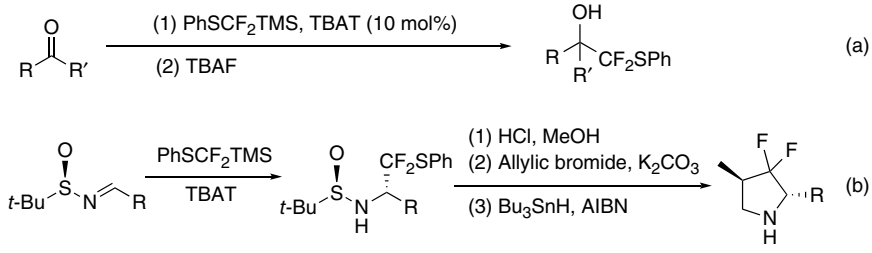
Scheme 3.9 Nucleophilic difluoromethylation with $TMSCF_2H$.

Trifluoromethyltrimethylsilane ($TMSCF_3$) is a well-known trifluoromethylation reagent. However, it can also be used as a formal difluoromethylation reagent. In 2006, Prakash et al. reported that the reaction of $TMSCF_3$ with unactivated imines in the presence of half a molar of tetramethylammonium fluoride and then reduction with $NaBH_4$ delivered the difluoromethylated amines (Scheme 3.10a) [32]. The mechanism involves the elimination of HF from trimethylsilyl (TMS)-protected trifluoromethylated amines to produce difluoromethylated imines, which can be reduced to difluoromethylated amines. Portella et al. reported that the reaction between acylsilanes and $TMSCF_3$ would produce difluoroenol silyl ethers, which can serve as electrophiles to react with amino alcohols to give difluoromethylated oxazolidines (Scheme 3.10b) [33]. Recently, Prakash and coworkers realized the difluoromethylation of aldehydes using a combination of $TMSCF_3$/LiI/PPh_3, in which difluoromethylene phosphonium ylide is the key intermediate (Scheme 3.10c) [34].



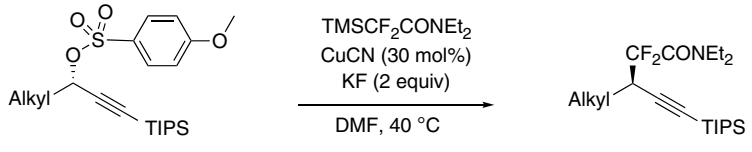
Scheme 3.10 Nucleophilic difluoromethylation with $TMSCF_3$.

Phenylthiodifluoromethyltrimethylsilane ($PhSCF_2TMS$) is also a widely studied difluoromethylation reagent. It was first prepared by Prakash et al. in 2005 for phenylthiodifluoromethylation of carbonyl compounds (Scheme 3.11a) [35]. Later on, Hu and coworker developed a new synthetic application of $PhSCF_2TMS$ as a difluoromethylene radical anion synthon for the synthesis of chiral 2,4-disubstituted 3,3-difluoropyrrolidines (Scheme 3.11b) [36]. Its reaction with alkyl halides was also explored [37]. Pohmakotr et al. also applied $PhSCF_2TMS$ for the synthesis of various difluoromethylene-containing molecules [38].



Scheme 3.11 Nucleophilic difluoromethylation with $PhSCF_2TMS$.

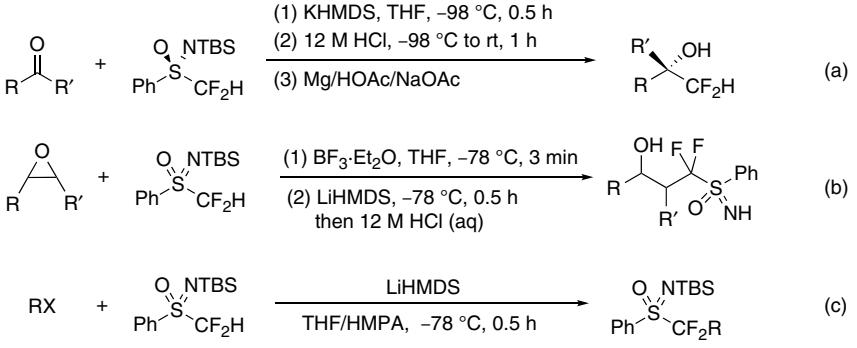
$PhSeCF_2TMS$ [39], heteroaryl-*N*-difluoromethyltrimethylsilanes [40], TMS CF_2CN [41], $TMSCF_2Cl$, and $TMSCF_2TMS$ [42] were also used for the difluoromethylation of carbonyl compounds. Recently, Zhang and coworkers developed the first example of copper-catalyzed stereospecific difluoroalkylation of secondary propargyl sulfonates with $TMSCF_2CONEt_2$ (Scheme 3.12) [43].



Scheme 3.12 Nucleophilic difluoromethylation with $TMSCF_2CONEt_2$.

3.1.6 By Means of Difluoromethyl Sulfoximine Reagent

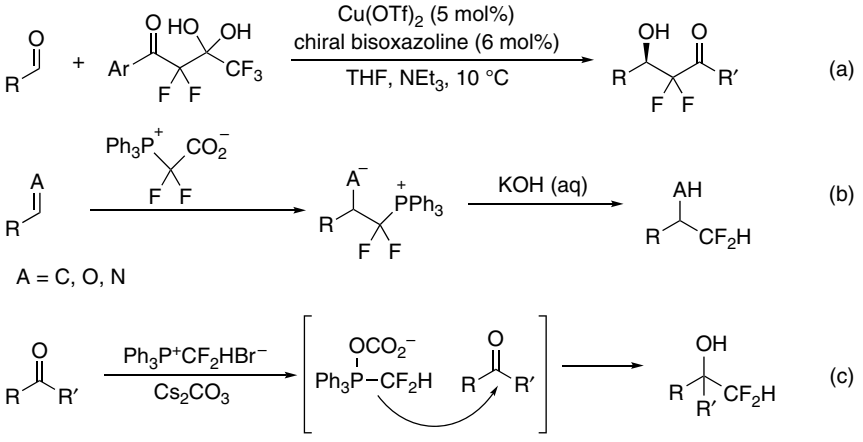
In 2012, Hu and coworkers developed a novel chiral difluoromethyl sulfoximine reagent, (*R*)-*N*-*tert*-butyldimethylsilyl-*S*-difluoromethyl-*S*-phenylsulfoximine, which can be readily used for the stereoselective difluoromethylation of aryl ketones (Scheme 3.13a) [44]. The nature of N-substituent was found to be crucial for the success of this reaction. Subsequently, nucleophilic substitution of epoxides and alkyl halides with PhSO(NTBS)CF_2H were also accomplished (Scheme 3.13b,c) [44].



Scheme 3.13 Nucleophilic difluoromethylation with PhSO(NTBS)CF_2H.

3.1.7 Miscellaneous Reagents

Apart from the abovementioned kinds of reagents, many others have also been used for nucleophilic difluoromethylation reaction. $ArCF_2Br$ [45], $PhXCF_2H$ (X = S, Se, Te) [46], $ArCF_2H$ [47], difluoroolefines [48], and $ArCOCF_2CO_2H$ [49] have been applied for the difluoroalkylation of carbonyl compounds. Difluoroenol silyl ethers were used to the oxidative difluoromethylation of tertiary amines [50]. Notably, trifluoromethyl α,α-difluorinated β-keto *gem*-diols were used for the asymmetric difluoroalkylation of aldehydes using copper(II) triflate as the catalyst and chiral bisoxazoline as the ligand (Scheme 3.14a) [51]. In 2014, Dilman and coworkers reported that difluoromethylene phosphabetaine can be used for the difluoromethylation of Michael acceptors, aldehydes, and azomethines (Scheme 3.14b) [52]. This reaction proceeds via the addition of *in situ* generated difluorinated phosphonium ylide to the electrophiles, followed by hydrolysis of the C—P bond. Interestingly, Xiao and coworkers found that DFPB ($[Ph_3P^+CF_2H]Br^-$) can undergo difluoromethylation of carbonyl compounds (Scheme 3.14c) [53]. This reaction proceeds via the direct transfer of CF_2H, not via phosphonium ylide intermediate. Recently, Mikami and coworkers succeeded in the copper-catalyzed enantioselective Michael-type difluoromethylation of arylidene Meldrum's acids with bis(difluoromethyl)zinc reagents to give the corresponding β-difluoromethylated carbonyl products in good yields and enantioselectivity [54].

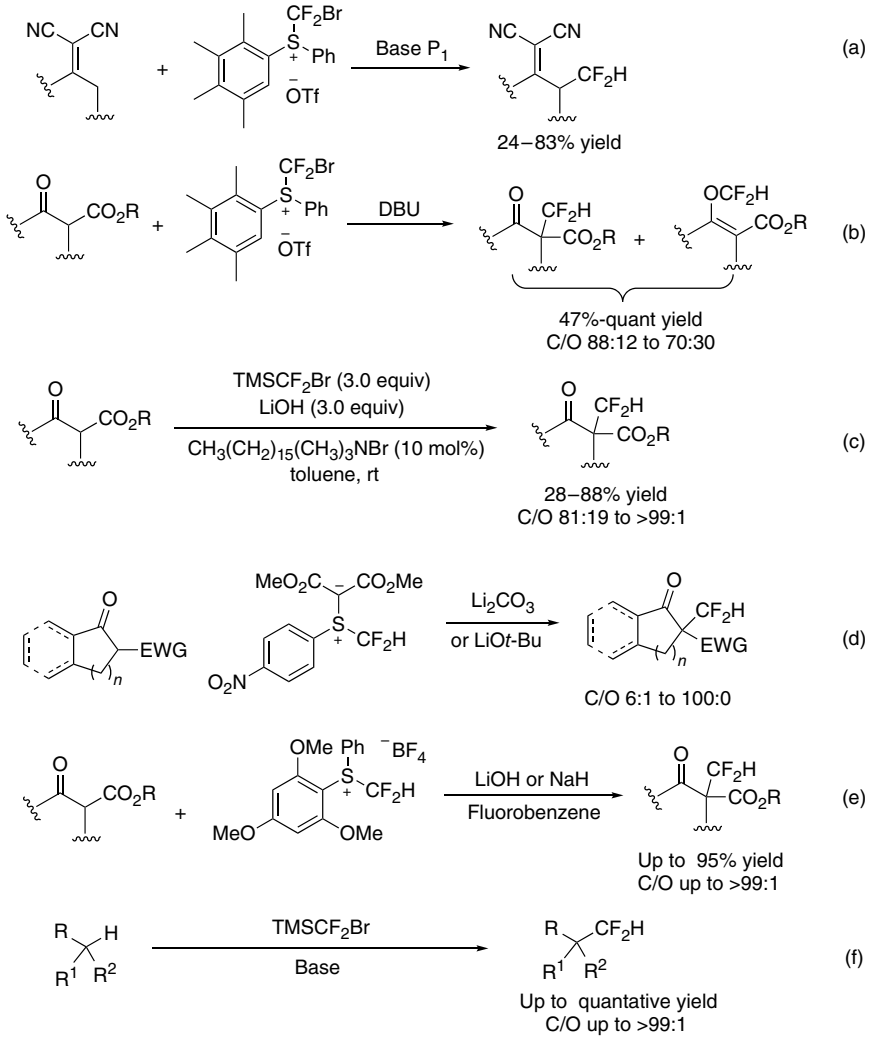


Scheme 3.14 Nucleophilic difluoromethylation with miscellaneous reagents.

3.2 Electrophilic Difluoromethylation and Difluoroalkylation

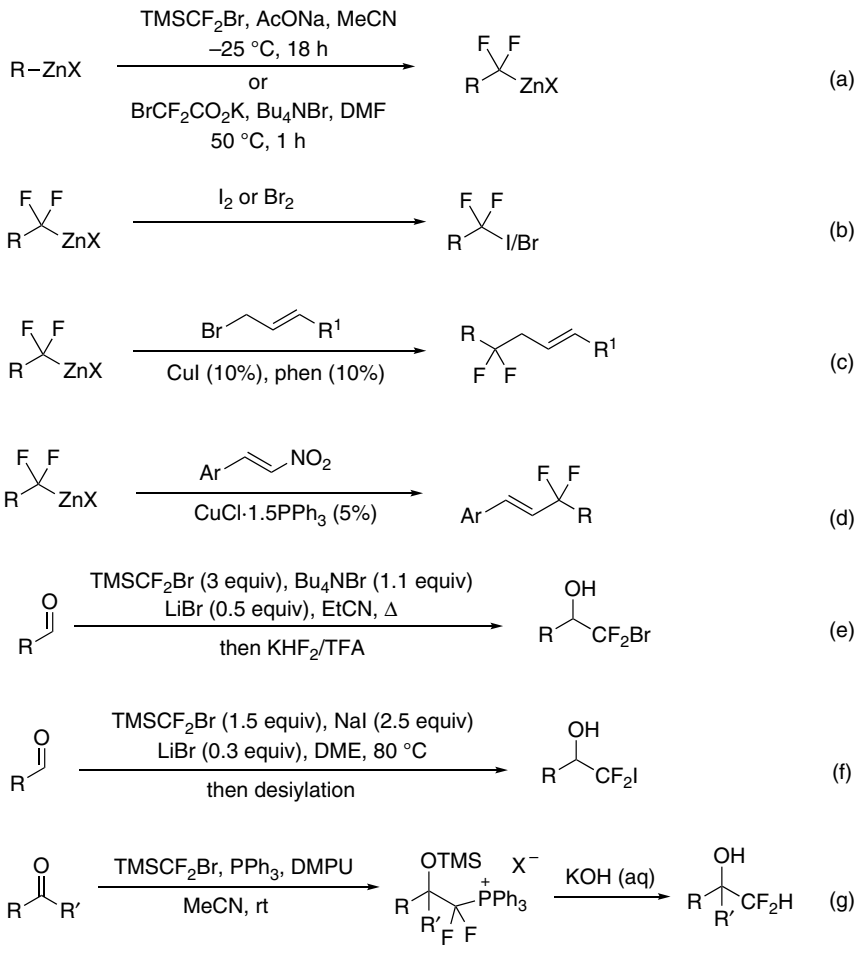
3.2.1 By Means of Difluorocarbene Reagents

Difluorocarbene is the most widely used electrophilic intermediate for the incorporation of difluoromethyl group into C(sp^3) center. HCF_2Cl can be used for the difluoromethylation of some carbon acids [55], while CF_2Br_2 has been used for the bromodifluoromethylation of lithium enolates [56]. However, these two reagents only work well for a few selected carbon nucleophiles. The reactivity of difluorocarbene with various carbon nucleophiles was largely unknown before 2009. In 2009, Jonczyk and coworker found that only the carbon acids with pK_a in the range 16.3–19.1 could be difluoromethylated in moderate yields using HCF_2Cl in the presence of concentrated aqueous NaOH [55b]. In 2012, Shibata and coworkers developed a new method for the difluoromethylation of sp^3 carbon nucleophiles using *S*-(bromodifluoromethyl)diarylsulfonium salts. This method is efficient for dicyanoalkylidene substrates (Scheme 3.15a), while when β-ketoesters were used, a mixture of C- and O-difluoromethylated products were formed with low selectivity (Scheme 3.15b) [57]. In 2018, Shibata and coworkers realized the highly selective C-difluoromethylation of β-ketoesters using $TMSCF_2Br$ (Scheme 3.15c) [58], a versatile difluorocarbene reagent developed by Hu and coworkers [59]. Shortly afterward, Shen and coworkers realized the difluoromethylation of soft carbon nucleophile using difluoromethylated sulfonium ylide (Scheme 3.15d) [60]; Liu and coworkers realized the selective C-difluoromethylation of β-ketoesters and malonates by developing new *S*-difluoromethylsulfonium salts as difluorocarbene sources (Scheme 3.15e) [61]. In early 2019, Hu and coworkers developed a general protocol for C—H difluoromethylation of carbon acids with $TMSCF_2Br$; a variety of carbon nucleophiles, such as esters, amides, fluorenes, terminal alkynes, β-ketoesters, malonates, and other activated C—H bonds, could be efficiently and selectively transformed to the C-difluoromethylated products (Scheme 3.15f) [62].



Scheme 3.15 Electrophilic difluoromethylation at Csp^3 center with difluorocarbene reagents.

Dilman and coworkers proposed a new concept for assembling gem-difluorinated molecules by using difluorocarbene as a building block for consecutive bond-forming reactions. Indeed, difluorocarbene can be considered as a bridge, connecting a nucleophile and an electrophile. Following this concept, Dilman and coworkers found that difluorocarbene can be easily inserted into alkylzinc reagents (RZnX) to give RCF_2ZnX (Scheme 3.16a) [63]. RCF_2ZnX can react with a variety of electrophiles, such as I_2, Br_2 (Scheme 3.16b), HOAc [63a], *n*-BuONO [64], R′SSR′ [65], allylic bromide (Scheme 3.16c) [66], propargyl bromide [67], alkynyl bromide [68], and nitrostyrene (Scheme 3.16d) [69], among others [70]. Difluorocarbene can also be trapped by halide anions. Although this process is reversible, using excess of halide anions should shift the equilibrium to XCF_2^-; therefore halodifluoromethylation of aldehydes can be realized



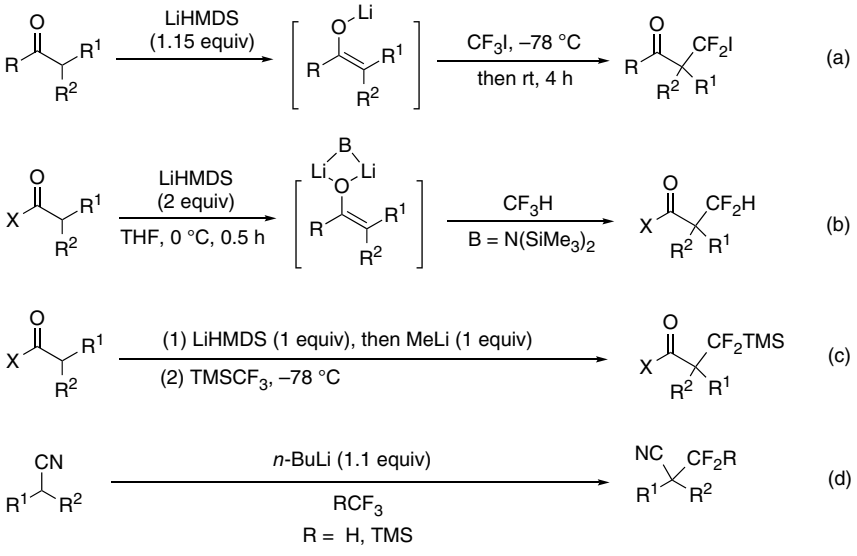
Scheme 3.16 Representative applications of difluorocarbene in consecutive bond-forming reactions.

(Scheme 3.16e,f) [71]. A combination of difluorocarbene with aldehydes and potassium dithiocarbamate could lead to the formation of difluoromethylated alcohols [72]. Triphenylphosphine was also applied as a nucleophile to capture difluorocarbene. The *in situ* generated phosphorous ylide, which was known to undergo Wittig reaction with aldehydes to give *gem*-difluoroolefins, was elegantly used for the difluoromethylation of aldehydes, ketones (Scheme 3.16g) [73], Michael acceptors [73], and acid chlorides [74].

3.2.2 By Means of CF_3X (X = H, I, TMS) Reagents

Fluoroform CF_3H can hardly undergo traditional S_N2 reaction with nucleophiles because the carbon center is largely shielded by the three fluorine atoms, which will have strong repulsion toward the incoming nucleophiles. Therefore, using CF_3H or its derivatives as CF_2X^+ equivalents in nucleophilic substitution,

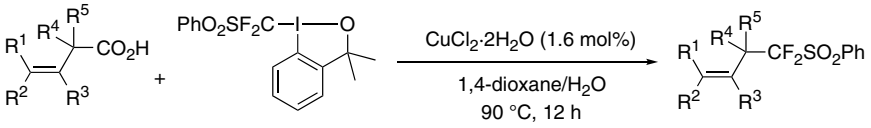
reactions are challenging. In 2011, Mikami et al. reported an unprecedented route to construct difluoromethyl-substituted all-carbon quaternary centers using lithium enolates and CF_3I through activation of C—F bond rather than C—I bond (Scheme 3.17a), and the lithium cation is found to play pivotal role in the C—F bond activation [75]. Later on, by using this C—F bond activation strategy, CF_3H and $TMSCF_3$ can be directly used as electrophilic difluoromethylating reagents with various nucleophiles (Scheme 3.17b–d) [76]. A mechanistic study for difluoromethylation of lithium enolates with CF_3H by density functional theory (DFT) calculation supports a S_N2-type C—C bond formation [77].



Scheme 3.17 Electrophilic difluoroalkylation with CF_3X (X = H, I, TMS) reagents.

3.2.3 By Means of I(III)–CF_2SO_2Ph Reagent

In 2012, Hu and coworkers developed a new strategy for regiospecific allylic difluoromethylation. By using I(III)–CF_2SO_2Ph as the difluoromethyl source, Lewis acid-catalyzed decarboxylative phenylsulfonyldifluoromethylation of β,γ-unsaturated carboxylic acids was realized in high yields (Scheme 3.18) [78].

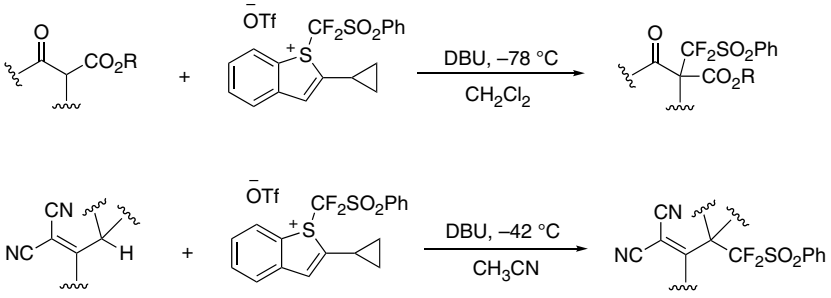


Scheme 3.18 Electrophilic difluoromethylation with a I(III)–CF_2SO_2Ph reagent.

3.2.4 By Means of *S*-((Phenylsulfonyl)difluoromethyl)thiophenium Salts

In 2014, Shibata and coworkers designed *S*-((phenylsulfonyl)difluoromethyl) thiophenium salts as novel difluoromethylation reagents. The thiophenium

salts can be efficient difluoromethylate sp^3-hybridized carbon nucleophiles such as in β-ketoesters and dicyanoalkylidenes with exclusive C selectivity (Scheme 3.19) [79].



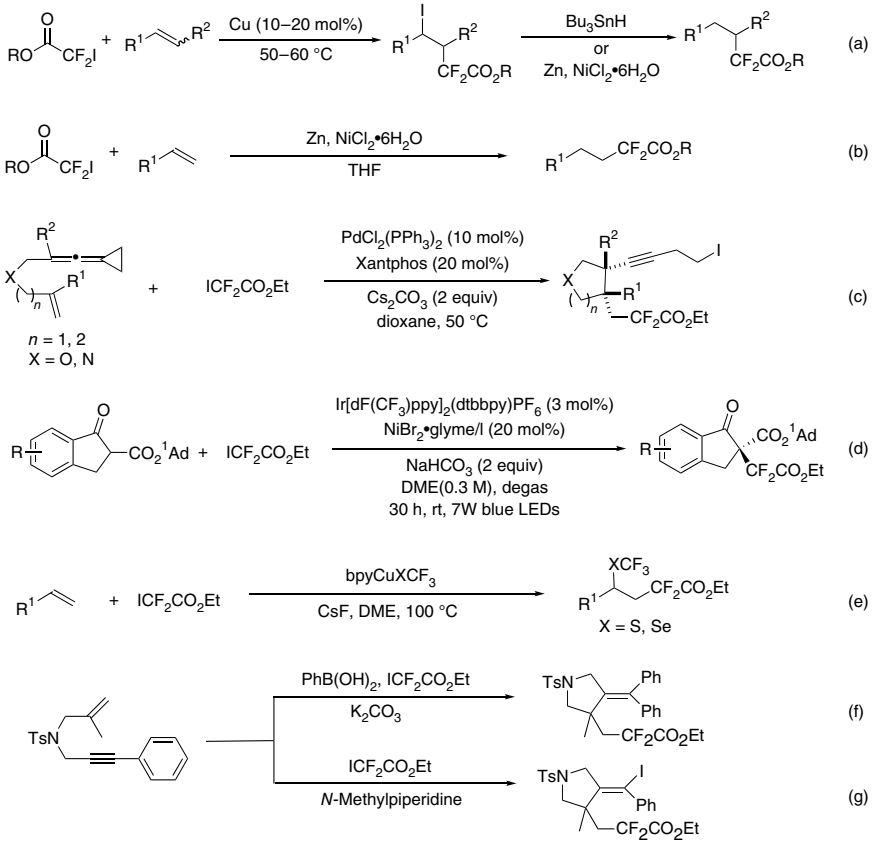
Scheme 3.19 Electrophilic difluoromethylation with *S*-((phenylsulfonyl)difluoromethyl) thiophenium salts.

3.3 Free Radical Difluoromethylation and Difluoroalkylation

Free radical difluoromethylation and difluoroalkylation are almost exclusively based on the addition of difluoroalkyl radicals into alkenes followed by various subsequent transformations, which were dependent on the alkene substrates and reaction conditions.

3.3.1 By Means of Iododifluoroacetates

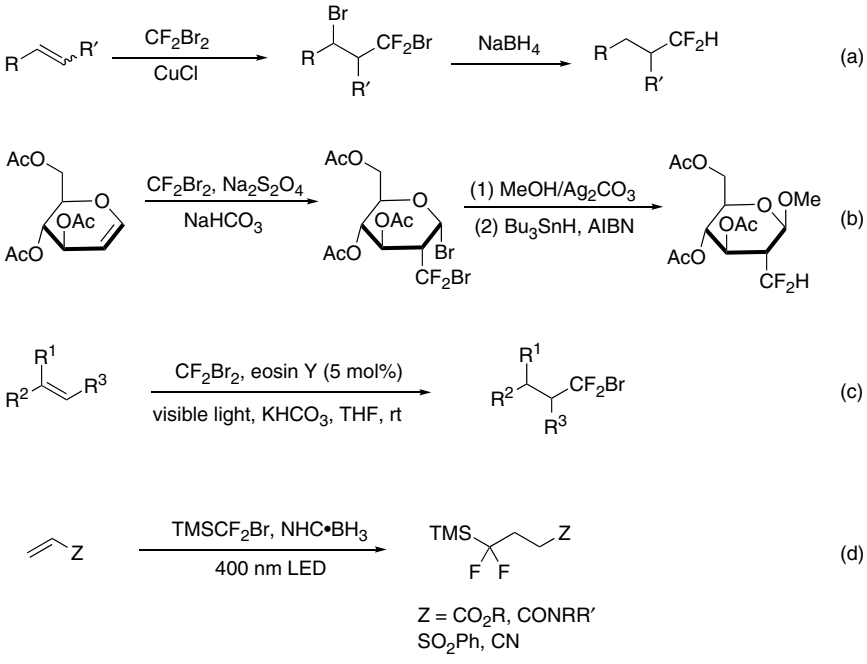
In 1989, Burton and coworker reported that iododifluoroacetates could undergo radical addition into alkenes under copper-catalyzed conditions [80]. Reduction of the adducts with Bu_3SnH or $Zn/NiCl_2{\cdot}6H_2O$ could provide α,α-difluoroacetates (Scheme 3.20a) [80, 81]. Later on, they found that α,α-difluoroacetates can be prepared directly by the reaction of iododifluoroacetates and alkenes under $Zn/NiCl_2{\cdot}6H_2O$ condition (Scheme 3.20b) [82]. In 2016, Shi and coworkers reported a novel palladium-initiated radical cascade stereoselective iododifluoroalkylation/cycloisomerization of ene-vinylidenecyclopropanes (Scheme 3.20c) [83]. In 2018, Xiao and coworkers carried out an enantioselective radical difluoromethylation of β-ketoesters through an asymmetric photoredox and nickel catalysis cascade (Scheme 3.20d) [84]. Good enantioselectivities were observed. In the same year, Liang and coworkers reported a three-component difluoroalkylation/trifluoromethylthiolation or trifluoromethylselenolation of alkenes, in which the air-stable SCF_3- and $SeCF_3$– containing reagents acted as the radical initiators (Scheme 3.20e) [85]. Shortly after, the same group demonstrated a base promoted direct difunctionalization/cascade cyclization of 1,6-enynes. By using different bases, two different difluoroalkylated cyclization products can be synthesized (Scheme 3.20f,g) [86]. Very recently, Liang and coworkers presented a general organic base-promoted difluoroalkylation of 1,4-enynes, and a radical 1,2-alkynyl migration process was involved [87].



Scheme 3.20 Radical difluoroalkylation with iododifluoroacetates.

3.3.2 By Means of CF_2Br_2, CF_2BrCl, or $TMSCF_2Br$

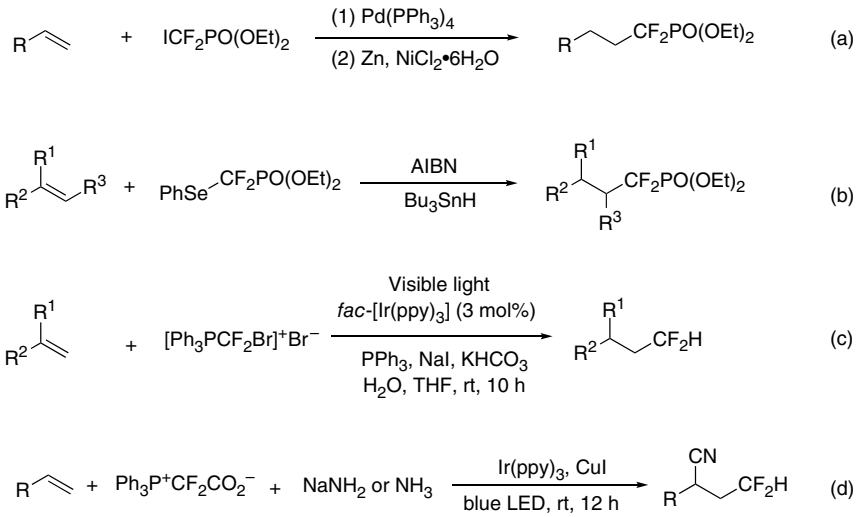
In 1991, Elsheimer and coworkers reported that CuCl-initiated radical addition of CF_2Br_2 to olefins followed by reduction with $NaBH_4$ provided a two-step method for introducing difluoromethyl group (Scheme 3.21a) [88]. In 1997, Miethchen et al. studied the addition of CF_2Br_2 to glucal under sodium dithionite-initiated conditions (Scheme 3.21b) [89]. CF_2BrCl was used to introduce CF_2Cl group into monosaccharide derivatives by using the same mean [90]. In 2015, Qing and coworkers developed an efficient method for the selective hydrobromodifluoromethylation of alkenes with CF_2Br_2 under visible light-induced conditions using eosin Y as the photoredox catalyst (Scheme 3.21c) [91]. In 2017, Dilman et al. reported that $TMSCF_2Br$, a versatile difluorocarbene reagent [59], can undergo radical coupling with electron-deficient alkenes using $NHC{\cdot}BH_3$ as the reductant, affording the products of hydrodifluoroalkylation (Scheme 3.21d) [92].



Scheme 3.21 Radical difluoromethylation with CF_2Br_2, CF_2BrCl, or $TMSCF_2Br$.

3.3.3 By Means of Phosphorus-containing Reagents

In 1992, Burton and coworker demonstrated addition of $ICF_2PO(OEt)_2$ to alkenes can be catalyzed by $Pd(PPh_3)_4$ or copper metal with good functional groups tolerance (Scheme 3.22a) [93]. The C—I bond of the adduct can be readily cleaved using $Zn/NiCl_2{\cdot}6H_2O$. In 2006, Piettre and coworkers prepared selanylated difluoromethylphosphonates as phosphonodifluoromethyl radical precursors. Using azodiisobutyronitrile (AIBN) as the radical initiator, Bu_3SnH as the hydrogen source, α,α-difluorinated alkylphosphonates can be prepared by the reaction of $PhSeCF_2PO(OEt)_2$ with alkenes (Scheme 3.22b) [94]. Phosphonium salts are also good radical precursors. In 2015, Qing and coworkers found that bromodifluoromethylphosphonium bromide, previously used as a difluorocarbene precursor [95], can be used as a difluoromethylation reagent for the synthesis of hydrodifluoromethylated alkanes (Scheme 3.22c) [96]. The *in situ* generated difluoromethylphosphonium salt and difluoromethyl radical are involved in this transformation. Interestingly, $Ph_3P^+CF_2CO_2^-$, a difluorocarbene reagent developed by Xiao and coworkers [97], was used for cyano-difluoromethylation of alkenes (Scheme 3.22d) [98]. $Ph_3P^+CF_2CO_2^-$ acts as both difluorocarbene source and difluoromethyl radical source. $Ph_3P^+CF_2CO_2^-$ generates difluorocarbene *in situ*, which was captured by $NaNH_2$ or NH_3 to form CN^-. It also generates difluoromethylphosphonium salt *in situ*, which affords difluoromethyl radical under photoredox conditions. The direct use of difluoromethylphosphonium salts as difluoromethyl radical has also be reported in ring expansion of 1-(1-arylvinyl)cyclobutanols [99].



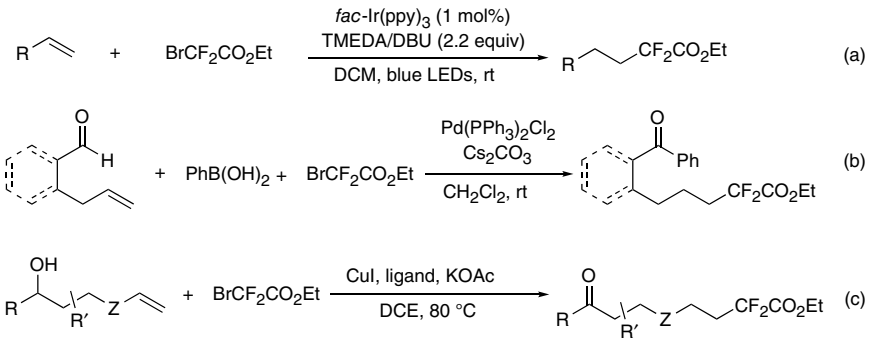
Scheme 3.22 Radical difluoromethylation with phosphorus-containing reagents.

3.3.4 By Means of $BrCF_2CO_2Et$

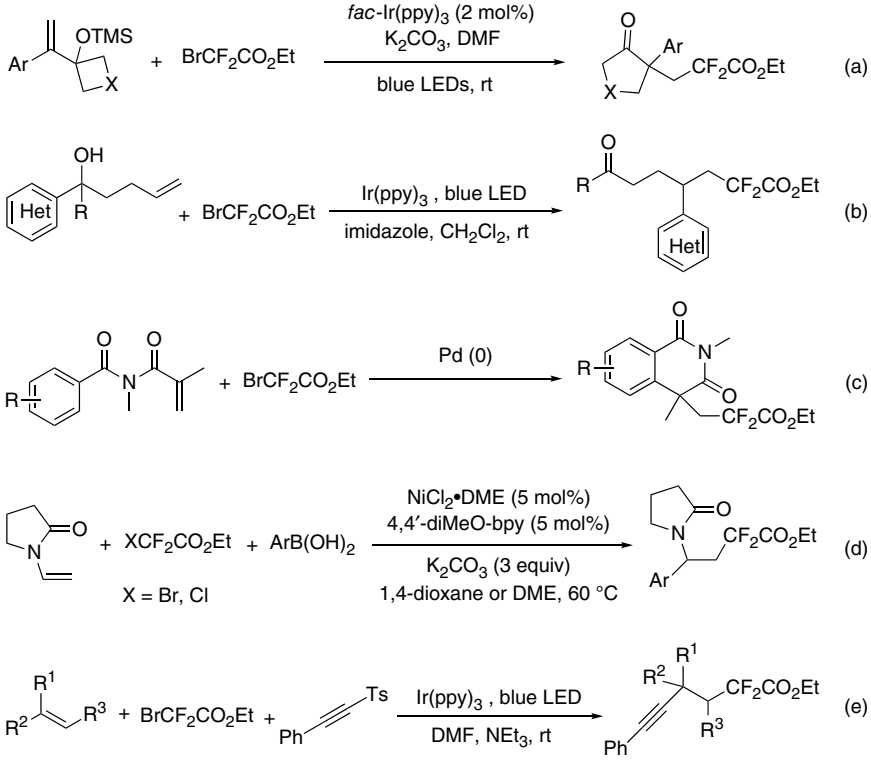
$BrCF_2CO_2Et$ is perhaps the most widely used radical difluoroalkylation reagent due to low cost and commercial availability. Almost all the radical reactions using $BrCF_2CO_2Et$ started with the addition of $^{\cdot}CF_2CO_2Et$ to alkene to form a new alkyl radical. The new radical can undergo diversified transformations to construct molecules with different complexity.

In 2014, Cho and coworkers reported that hydrodifluoroalkylation of aliphatic alkenes can be realized with $BrCF_2CO_2Et$ using photoredox catalysis, and the choice of base was found to be crucial (Scheme 3.23a) [100]. In 2017, Zhu and coworkers reported a palladium-catalyzed remote aryldifluoroalkylation of alkenyl aldehydes. The alkyl radical intermediate could abstract hydrogen from the remote CHO group, thereby enabling remote arylation (Scheme 3.23b) [101]. A similar remote hydrogen abstraction was also reported by Luo and coworkers (Scheme 3.23c) [102].

Carbodifluoroalkylation was also achieved. In 2015, Kim and coworker reported a photocatalytic difluoroalkylation/1,2-carbon migration sequence of 1-(1-arylvinyl)cyclobutanol derivatives (Scheme 3.24a), in which the alkyl migration was promoted by a cation intermediate [103]. The photocatalytic difluoroalkylation-induced 1,4-heteroaryl (Scheme 3.24b) [104], 1,2-heteroaryl [105], and 1,4-alkynyl [106] radical migration were achieved. In 2016, Wang and coworkers reported a palladium-catalyzed difluoroalkylation/cyclization of acrylamides (Scheme 3.24c) [107]. A similar sequence involving difluoroalkylation/ring opening/cyclization of α-cyclopropylstyrene substrates was also realized [108]. Intermolecular carbodifluoroalkylations have also been developed. In 2016, Zhang and coworkers demonstrated a nickel-catalyzed reaction for preparing difluoroalkylated compounds via tandem radical difluoroalkylation–cross-coupling arylation; both $BrCF_2CO_2Et$ and the "inert" $ClCF_2CO_2Et$ can



Scheme 3.23 Radical hydrodifluoroalkylation of alkenes with $BrCF_2CO_2Et$.

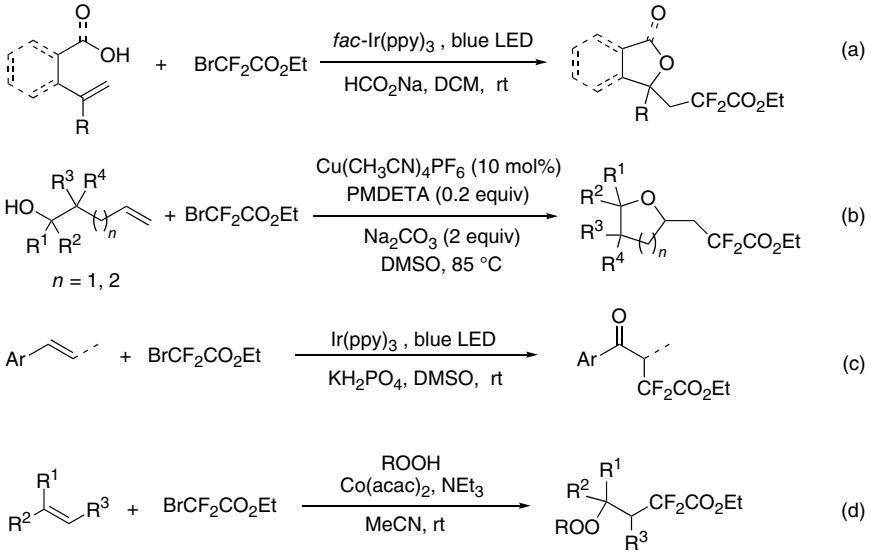


Scheme 3.24 Radical carbodifluoroalkylation of alkenes with $BrCF_2CO_2Et$.

be used as the difluoroalkyl radical source (Scheme 3.24d) [109]. Alkynyldifluoroalkylation was realized by the reaction of $BrCF_2CO_2Et$, unactivated alkenes, and alkynyl sulfones via photoredox catalysis (Scheme 3.24e) [110].

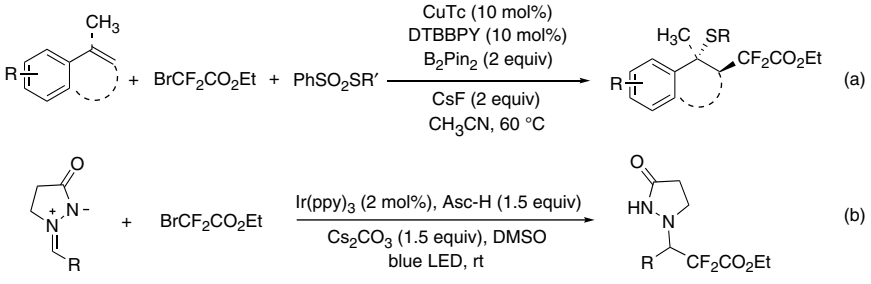
Oxodifluoroalkylation is well developed. The difluoroalkyl radical adds to alkene to generate a new alkyl radical, which can be oxidized to carbocation and then captured by an oxygen source either intramolecularly or intermolecularly.

By using this strategy, intramolecular cyclization for the construction of lactones (Scheme 3.25a) [111] and tetrahydrofurans (Scheme 3.25b) [112] has been reported. Intermolecular oxidation for the construction of α,α-difluoro-γ-ketoacetates (Scheme 3.25c) [113] and peroxidation (Scheme 3.25d) [114] were developed.



Scheme 3.25 Radical oxodifluoroalkylation of alkenes with $BrCF_2CO_2Et$.

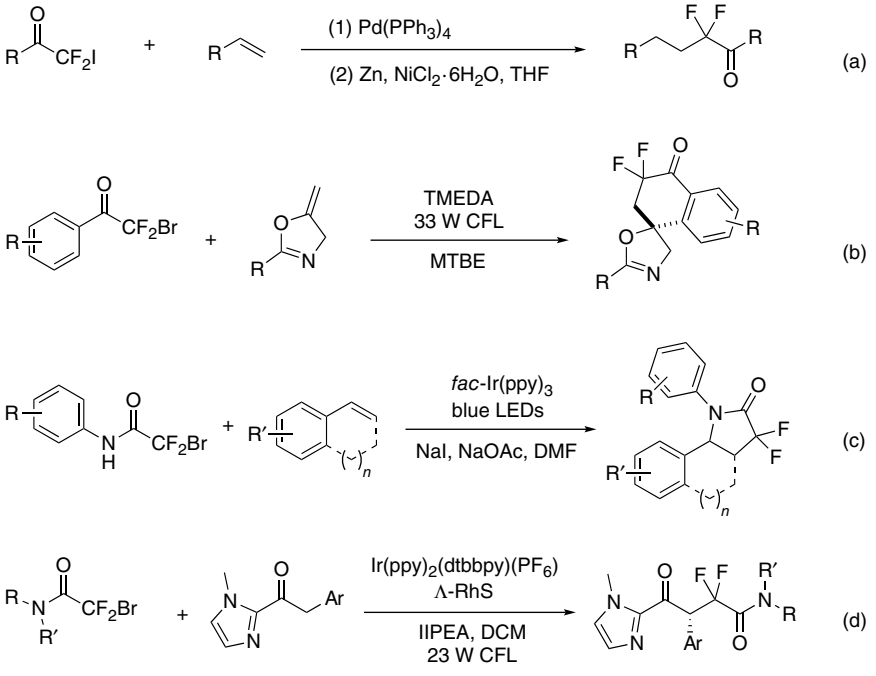
In 2018, Song and coworkers reported a copper-catalyzed intermolecular radical difluoroalkylation–thiolation reaction of aryl alkenes, and $PhSO_2SR$ was used as the S-source (Scheme 3.26a) [115]. A similar reaction was reported using RSH as the sulfur source by iron-facilitated photoredox catalysis [116]. Reductive radical–radical coupling of *N,N′*-cyclicazomethine imines with $BrCF_2CO_2Et$ was also accomplished (Scheme 3.26b) [117].



Scheme 3.26 Radical thiodifluoroalkylation of alkenes and difluoroalkylation *N,N′*-cyclicazomethine imines of with $BrCF_2CO_2Et$.

3.3.5 By Means of Halodifluoroketone or -Amide

In 1993, Burton and coworker found that iododifluoromethyl ketones could generate difluoroalkyl radicals using catalytic $Pd(PPh_3)_4$ [118]. The addition of iododifluoromethyl ketones to alkenes followed by reduction provides a general route to α,α-difluoroketones (Scheme 3.27a) [118, 119]. In 2017, Zhu and coworkers reported that bromodifluoromethyl ketones could undergo cascade difluoroalkylation/radical cyclization of methylene-2-oxazolines for the synthesis of difluoroalkyl substituted spiro compounds (Scheme 3.27b) [120]. In 2016, Zhu and coworkers reported that bromodifluoromethyl amides could realize the aminodifluoroalkylation of alkenes by cascade photoredox/iodide catalysis (Scheme 3.27c), and the iodide salts were found to play an important role for controlling reaction selectivity [121]. A tandem radical addition/cyclization for the construction of oxindoles was also achieved using bromodifluoromethyl amides [122]. Very recently, Xu and coworkers reported that difluoroalkyl radicals generated from bromodifluoromethyl amides could undergo addition to enols in high stereoselectivity by combining photoredox and chiral Lewis acid catalysis (Scheme 3.27d) [123].

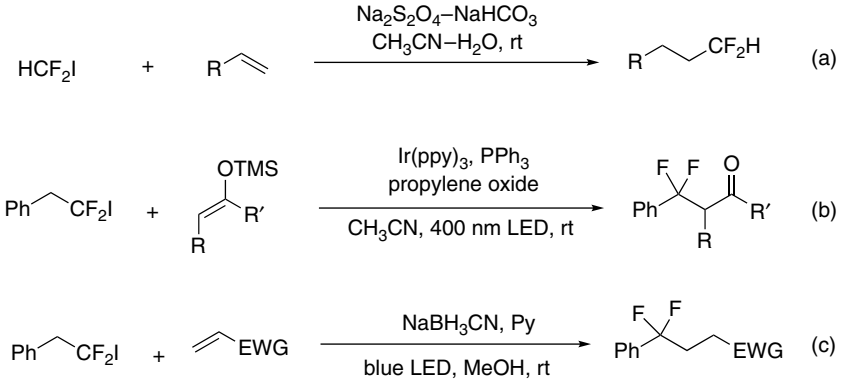


Scheme 3.27 Radical difluoroalkylation of alkenes or enols with halodifluoroketone or -amide.

3.3.6 By Means of HCF_2I and $PhCH_2CF_2I$

In 1994, Chen and coworkers reported that HCF_2I could readily undergo addition to alkenes using Huang's sulfinatodehalogenation (Scheme 3.28a) [124].

Recently, Dilman and coworkers reported the application of $PhCH_2CF_2I$, generated by difluorocarbene insertion into C—Zn bond followed by iodination [63a], as a difluoroalkyl radical precursor, which can undergo addition to silyl enol ethers for preparing gem-difluorinated ketones (Scheme 3.28b) [125]. Its addition to electron-deficient alkenes has also been demonstrated (Scheme 3.28c) [126].

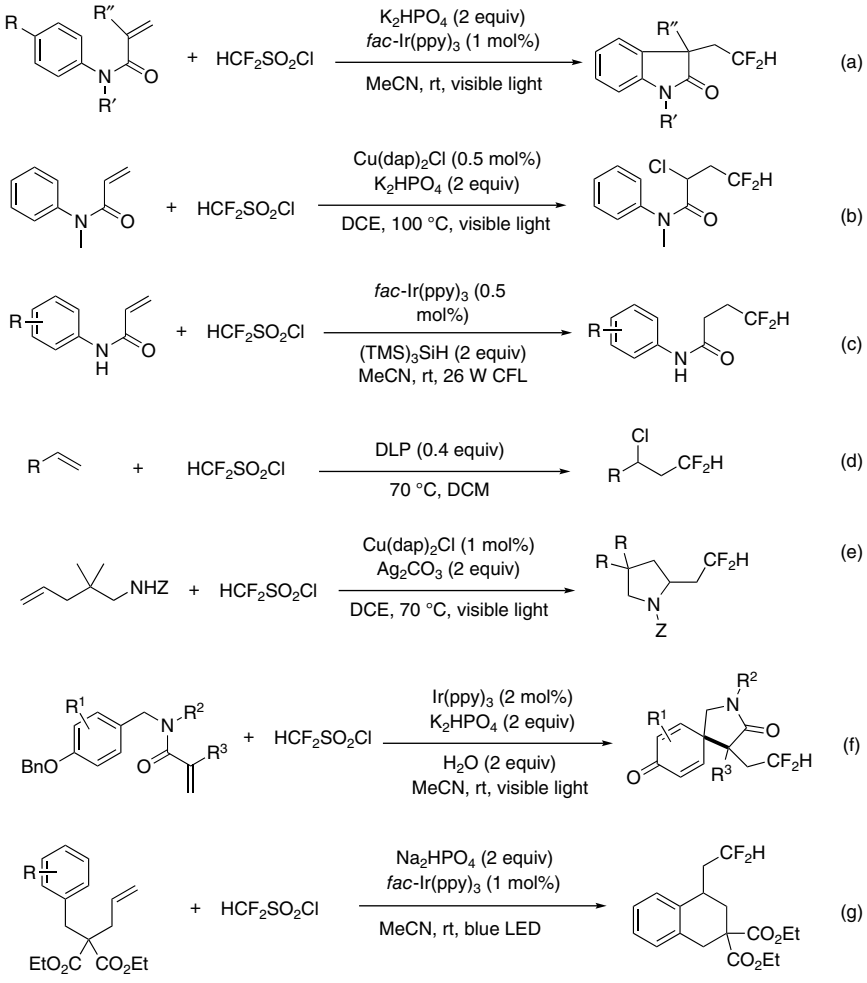


Scheme 3.28 Radical difluoroalkylation of alkenes with HCF_2I and $PhCH_2CF_2I$.

3.3.7 By Means of HCF_2SO_2Cl and HCF_2SO_2Na or $Zn(SO_2CF_2H)_2$

In 2014, Dolbier and coworkers reported that HCF_2SO_2Cl is a good difluoromethyl radical precursor by using photoredox catalysis [127]. A tandem radical cyclization of *N*-arylacrylamides to construct fluorinated 2-oxindoles was reported first, and the R″ group was found to be essential for this cyclization reaction (Scheme 3.29a) [127]. In the absence of R″ group, an atom transfer radical addition (ATRA) process was observed instead (Scheme 3.29b) [128]. If a H-donor was present, reductive difluoromethylation could be realized (Scheme 3.29c) [129]. The ATRA reaction between HCF_2SO_2Cl and unactivated alkene was possible under metal-free conditions (Scheme 3.29d) [130]. In addition, if an amino group is present in a proper position of the alkene substrate, intramolecular aminodifluoromethylation can be realized (Scheme 3.29e) [131]. When *N*-benzylacrylamides were used as substrates, the radical difluoromethylation was followed by a de-aromatizing spirocyclization (Scheme 3.29f) [132]. The presence of a nitrogen atom is not necessary for the cyclization reaction, as demonstrated that the tetralin skeleton can also be constructed (Scheme 3.29g) [133].

In 2014, Tan and coworkers reported that difluoromethylation/cyclization of *N*-arylacrylamides was realized using $Zn(SO_2CF_2H)_2$ as the difluoromethyl radical precursor under silver-catalyzed conditions (Scheme 3.30a) [134]. In 2015, Hu and coworkers developed an efficient method for the synthesis of fluorinated sulfinate salts by the $NaBH_4$-mediated reduction of the corresponding benzo[*d*]thiazol-2-yl sulfones and the application of HCF_2SO_2Na in the silver-catalyzed cascade difluoroalkylation/aryl migration/SO_2 extrusion of

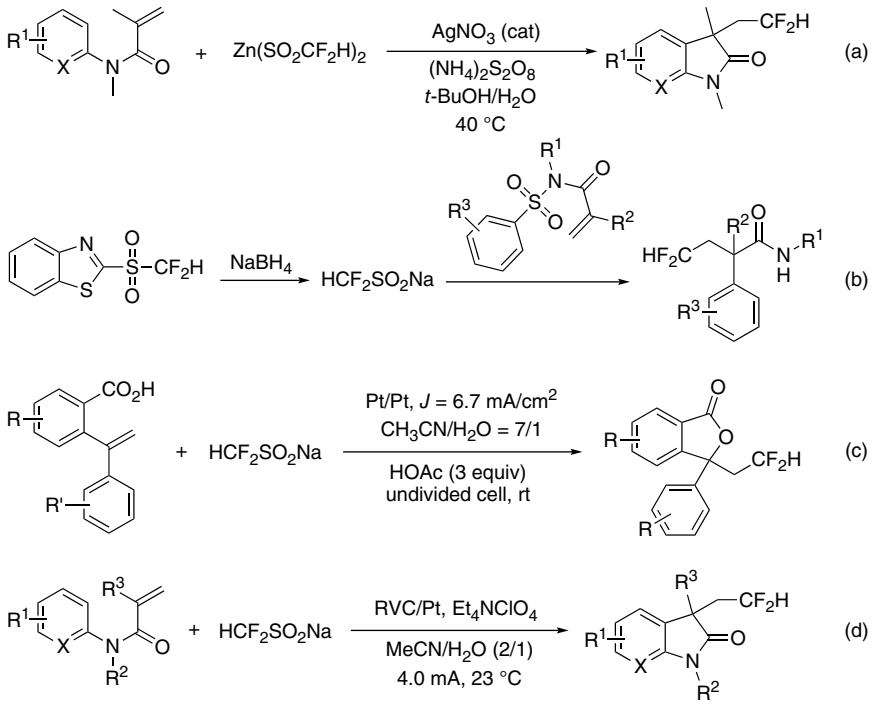


Scheme 3.29 Radical difluoromethylation of alkenes with HCF_2SO_2Cl.

conjugated N-arylsulfonated amides (Scheme 3.30b) [135]. In early 2019, Xu and coworkers and Ackermann and coworkers independently reported the use of HCF_2SO_2Na as the difluoromethyl radical source under electrochemical conditions [136]. Intramolecular oxodifluoromethylation of alkenes (Scheme 3.30c) [136a] and tandem difluoroalkylation/cyclization of N-substituted acrylamides (Scheme 3.30d) [136b] were accomplished.

3.3.8 By Means of Difluoromethylated Sulfones, Sulfoximines, Thioethers, and Sulfonium Salts

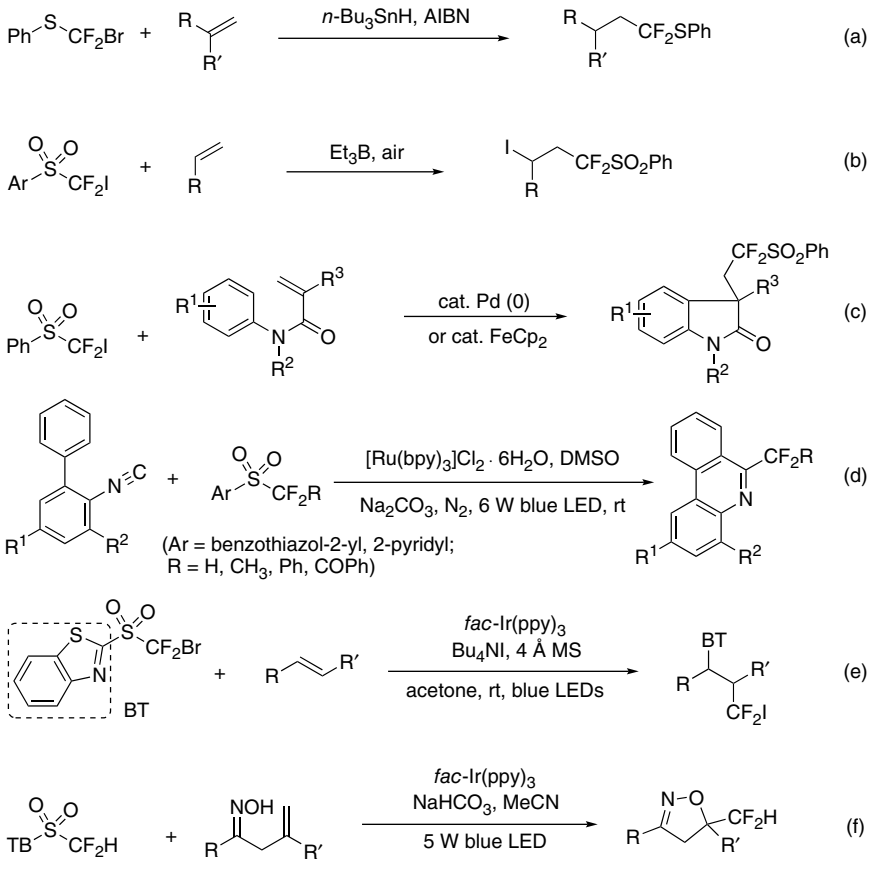
In 2004, Pohmakotr and coworkers reported the radical addition of $PhSCF_2Br$ to alkenes (Scheme 3.31a) [137]. Hu and coworkers reported that $PhSO_2CF_2I$ and $(2\text{-Py})SO_2CF_2I$ could be used for the radical difluoroalkylation of alkenes using



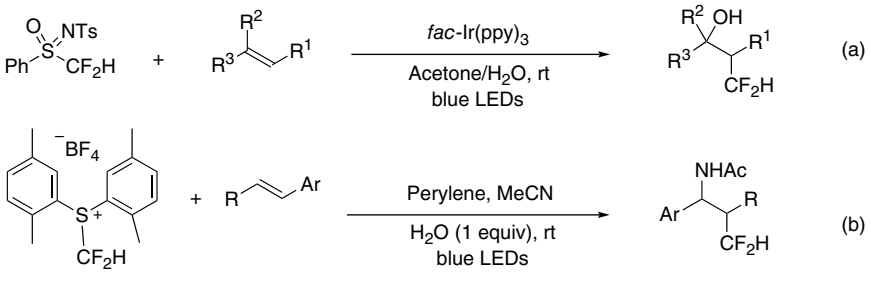
Scheme 3.30 Radical difluoromethylation of alkenes with HCF_2SO_2Na.

Et_3B/air as the initiator (Scheme 3.31b) [138a,b]. $PhSO_2CF_2I$ has also been used for the synthesis of CF_2H-containing oxindoles using palladium or iron catalysis (Scheme 3.31c) [139]. In 2016, Hu et al. reported that mono-, di-, and trifluorinated heteroaryl sulfones can be used as a new class of readily available, bench-stable, and reactivity-tunable radical fluoroalkylation reagents under visible light photoredox catalysis [138c]. $BTSO_2CF_2R$ (R = H, CH_3, Ph, benzoyl) were used to react with isocyanides to give fluoroalkylated phenanthridines (Scheme 3.31d) [138c]. Zhu and coworkers designed an efficient docking migration strategy for the difunctionalization of alkenes with $BTSO_2CF_2Br$ (Scheme 3.31e) [140]. The first example of $BTSO_2CF_2H$ was used for the direct difluoromethylation of β,γ-unsaturated oximes for the construction of difluoromethylated isoxazolines (Scheme 3.31f) [141].

Akita and coworkers found that $PhSO(NTs)CF_2H$, previously used as a difluorocarbene reagent by Hu and coworkers [142], could generate difluoromethyl radical using photoredox catalysis [143]. The application of $PhSO(NTs)CF_2H$ in oxodifluoromethylation of alkenes has been reported (Scheme 3.32a) [143, 144]. *S*-Difluoromethyl-*S*-di(*p*-xylyl)sulfonium tetrafluoroborate was developed by Akita and coworkers and its application in aminodifluoromethylation of alkenes was demonstrated using photoredox catalysis (Scheme 3.32b) [145].



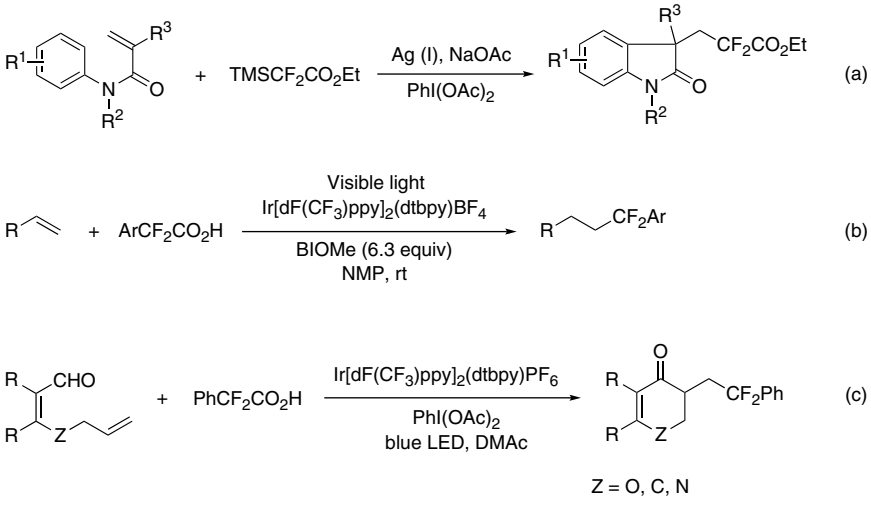
Scheme 3.31 Radical difluoromethylation of alkenes with $PhSCF_2Br$ or fluorinated sulfones.



Scheme 3.32 Radical difluoromethylation of alkenes with $PhSO(NTs)CF_2H$ and difluoromethylsulfonium salt.

3.3.9 By Means of $TMSCF_2CO_2Et$ and $ArCF_2CO_2H$

Nucleophilic difluoroalkylation reagents can also be used as radical difluoroalkylation reagents under oxidative conditions. In 2016, Hao and coworkers reported that $TMSCF_2CO_2Et$ can be used to the radical addition/cyclization sequence for the synthesis of difluoroalkylated oxindoles in good yields (Scheme 3.33a), and the combination of $AgNO_3$ and $PhI(OAc)_2$ is crucial for the generation of CF_2CO_2Et radical species [146]. Qing and coworkers reported a visible light-induced hydroaryldifluoromethylation of alkenes with $ArCF_2CO_2H$ (Scheme 3.33b) [147]. This reaction proceeds via hypervalent iodine reagent promoting decarboxylation and subsequent radical addition. Later on, $PhCF_2CO_2H$ was applied to acyldifluoroalkylation of unactivated alkenes by Zhu and coworkers (Scheme 3.33c) [148].



Scheme 3.33 Radical difluoromethylation of alkenes with $TMSCF_2CO_2Et$ and $ArCF_2CO_2H$.

References

1 Burton, D.J., Takei, R., and Shin-Ya, S. (1981). *J. Fluorine Chem.* 18: 197.
2 Burton, D.J. and Sprague, L.G. (1989). *J. Org. Chem.* 54: 613.
3 Obayashi, M., Ito, E., Matsui, K., and Kondo, K. (1982). *Tetrahedron Lett.* 23: 2323.
4 Obayashi, M. and Kondo, K. (1982). *Tetrahedron Lett.* 23: 2327.
5 Beier, P., Alexandrova, A.V., Zibinsky, M., and Prakash, G.K.S. (2008). *Tetrahedron* 64: 10977.
6 Hallinan, E.A. and Fried, J. (1984). *Tetrahedron Lett.* 25: 2301.
7 Burton, D.J. and Yang, Z.-Y. (1992). *Tetrahedron* 48: 189.
8 (a) Yang, Z.-Y. and Burton, D.J. (1989). *J. Fluorine Chem.* 44: 339. (b) Yang, Z.Y. and Burton, D.J. (1991). *J. Org. Chem.* 56: 1037.
9 Hartgraves, G.A. and Burton, D.J. (1988). *J. Fluorine Chem.* 39: 425.

10 Burton, D.J. and Hartgraves, G.A. (2007). *J. Fluorine Chem.* 128: 1198.
11 Serizawa, H., Ishii, K., Aikawa, K., and Mikami, K. (2016). *Org. Lett.* 18: 3686.
12 Aikawa, K., Ishii, K., Endo, Y., and Mikami, K. (2017). *J. Fluorine Chem.* 203: 122.
13 Zeng, X., Yan, W., Zacate, S.B. et al. (2019). *J. Am. Chem. Soc.* 141: 11398.
14 Hine, J. and Porter, J.J. (1960). *J. Am. Chem. Soc.* 82: 6178.
15 Stahly, G.P. (1989). *J. Fluorine Chem.* 43: 53.
16 Prakash, G.K.S., Hu, J., Wang, Y., and Olah, G.A. (2004). *Org. Lett.* 6: 4315.
17 (a) Prakash, G.K.S., Hu, J., Wang, Y., and Olah, G.A. (2005). *Eur. J. Org. Chem.* 2005: 2218. (b) Ni, C., Wang, F., and Hu, J. (2008). *Beilstein J. Org. Chem.* 4: 21. (c) Ni, C., Zhang, L., and Hu, J. (2008). *J. Org. Chem.* 73: 5699. (d) Hu, M., Gao, B., Ni, C. et al. (2013). *J. Fluorine Chem.* 155: 52.
18 (a) Li, Y. and Hu, J. (2005). *Angew. Chem. Int. Ed.* 44: 5882. (b) Liu, J., Li, Y., and Hu, J. (2007). *J. Org. Chem.* 72: 3119. (c) Liu, J. and Hu, J. (2010). *Chem. Eur. J.* 16: 11443.
19 Ni, C., Liu, J., Zhang, L., and Hu, J. (2007). *Angew. Chem. Int. Ed.* 46: 786.
20 Ni, C. and Hu, J. (2005). *Tetrahedron Lett.* 46: 8273.
21 Liu, J., Ni, C., Wang, F., and Hu, J. (2008). *Tetrahedron Lett.* 49: 1605.
22 (a) Zhu, L., Li, Y., Zhao, Y., and Hu, J. (2010). *Tetrahedron Lett.* 51: 6150. (b) Huang, W., Ni, C., Zhao, Y. et al. (2012). *J. Fluorine Chem.* 143: 161.
23 Prakash, G.K.S., Wang, Y., Hu, J., and Olah, G.A. (2005). *J. Fluorine Chem.* 126: 1361.
24 Jiang, F., Ni, C., and Hu, J. (2017). *J. Fluorine Chem.* 198: 67.
25 Zhao, Y., Huang, W., Zhu, L., and Hu, J. (2010). *Org. Lett.* 122: 1444.
26 Zhao, Y., Gao, B., and Hu, J. (2012). *J. Am. Chem. Soc.* 134: 5790.
27 Chen, J., Lin, J.-H., and Xiao, J.-C. (2018). *Tetrahedron* 74: 4295.
28 Zhu, L., Li, Y., Ni, C. et al. (2007). *J. Fluorine Chem.* 128: 1241.
29 Batisse, C., Panossian, A., Hanquet, G., and Leroux, F.R. (2018). *Chem. Commun.* 54: 10423.
30 Hagiwara, T. and Fuchikami, T. (1995). *Synlett*: 717.
31 (a) Tyutyunov, A.A., Boyko, V.E., and Igoumnov, S.M. (2011). *Fluorine Notes* 78: 1. (b) Zhao, Y., Huang, W., and Hu, J. (2011). *Org. Lett.* 13: 5342. (c) Du, G.-F., Wang, Y., Gu, C.-Z. et al. (2015). *RSC Adv.* 5: 35421. (d) Chen, D., Ni, C., Zhao, Y. et al. (2016). *Angew. Chem. Int. Ed.* 55: 12632. (e) Michurin, O.M., Radchenko, D.S., and Komarov, I.V. (2016). *Tetrahedron* 72: 1351.
32 Prakash, G.K.S., Mogi, R., and Olah, G.A. (2006). *Org. Lett.* 8: 3589.
33 Huguenot, F., Billac, A., Brigaud, T., and Portella, C. (2008). *J. Org. Chem.* 73: 2564.
34 Krishnamoorthy, S., Kar, S., Kothandaraman, J., and Prakash, G.K.S. (2018). *J. Fluorine Chem.* 208: 10.
35 Prakash, G.K.S., Hu, J., Wang, Y., and Olah, G.A. (2005). *J. Fluorine Chem.* 126: 527.
36 Li, Y. and Hu, J. (2007). *Angew. Chem. Int. Ed.* 46: 2489.
37 Li, Y. and Hu, J. (2008). *J. Fluorine Chem.* 129: 382.
38 (a) Pohmakotr, M., Panichakul, D., Tuchinda, P., and Reutrakul, V. (2007). *Tetrahedron* 63: 9429. (b) Bootwicha, T., Panichakul, D., Kuhakarn, C. et al. (2009). *J. Org. Chem.* 74: 3798. (c) Chatupheeraphat, A., Soorukram, D., Kuhakarn, C. et al. (2013). *Eur. J. Org. Chem.* 2013: 6844. (d) Punirun, T., Soorukram, D., Kuhakarn, C. et al. (2018). *J. Org. Chem.* 83: 765.

39 (a) Qin, Y.-Y., Qiu, X.-L., Yang, Y.-Y. et al. (2005). *J. Org. Chem.* 70: 9040. (b) Mizuta, S., Shibata, N., Ogawa, S. et al. (2006). *Chem. Commun.*: 2575. (c) Qing, F.-L., Qin, Y.-Y., Yang, Y.-Y., and Qiu, X.-L. (2006). *Synthesis* 2006: 1475.

40 Bissky, G., Staninets, V.I., Kolomeitsev, A.A., and Roschenthaler, G.-V. (2001). *Synlett*: 374.

41 Kosobokov, M.D., Dilman, A.D., Levin, V.V., and Struchkova, M.I. (2012). *J. Org. Chem.* 77: 5850.

42 Yudin, A.K., Prakash, G.K.S., Deffieux, D. et al. (1997). *J. Am. Chem. Soc.* 119: 1572.

43 Gao, X., Xiao, Y.L., Wan, X., and Zhang, X. (2018). *Angew. Chem. Int. Ed.* 57: 3187.

44 Shen, X., Zhang, W., Ni, C. et al. (2012). *J. Am. Chem. Soc.* 134: 16999.

45 Medebielle, M., Kato, K., and Dolbier, W.R. Jr. (2002). *Synlett*: 1541.

46 Hu, M., Wang, F., Zhao, Y. et al. (2012). *J. Fluorine Chem.* 135: 45.

47 Yang, X., Fang, X., Zhang, D. et al. (2013). *J. Fluorine Chem.* 145: 1.

48 Omote, M., Miake, T., Tarui, A. et al. (2013). *J. Fluorine Chem.* 147: 1.

49 Yuan, J.W., Liu, S.N., and Mai, W.P. (2017). *Org. Biomol. Chem.* 15: 7654.

50 Chu, L., Zhang, X., and Qing, F.L. (2009). *Org. Lett.* 11: 2197.

51 Zhang, P. and Wolf, C. (2013). *Angew. Chem. Int. Ed.* 52: 7869.

52 Levin, V.V., Trifonov, A.L., Zemtsov, A.A. et al. (2014). *Org. Lett.* 16: 6256.

53 Deng, Z., Lin, J.H., Cai, J., and Xiao, J.C. (2016). *Org. Lett.* 18: 3206.

54 Endo, Y., Ishii, K., and Mikami, K. (2019). *Tetrahedron* 75: 4099.

55 (a) Bey, P. and Schirlin, D. (1978). *Tetrahedron Lett.* 19: 5225. (b) Nawrot, E. and Jończyk, A. (2009). *J. Fluorine Chem.* 130: 466.

56 Iseki, K., Asada, D., Takahashi, M., and Kobayashi, Y. (1995). *Tetrahedron Lett.* 36: 3711.

57 Liu, G., Wang, X., Lu, X. et al. (2012). *ChemistryOpen* 1: 227.

58 Wang, J., Tokunaga, E., and Shibata, N. (2018). *Chem. Commun.* 54: 8881.

59 (a) Wang, F., Zhang, W., Zhu, J. et al. (2011). *Chem. Commun.* 47: 2411. (b) Li, L., Wang, F., Ni, C., and Hu, J. (2013). *Angew. Chem. Int. Ed.* 52: 12390.

60 Zhu, J., Zheng, H., Xue, X.-S. et al. (2018). *Chin. J. Chem.* 36: 1069.

61 Lu, S.L., Li, X., Qin, W.B. et al. (2018). *Org. Lett.* 20: 6925.

62 Xie, Q., Zhu, Z., Li, L. et al. (2019). *Angew. Chem. Int. Ed.* 58: 6405.

63 (a) Levin, V.V., Zemtsov, A.A., Struchkova, M.I., and Dilman, A.D. (2013). *Org. Lett.* 15: 917. (b) Levin, V.V., Zemtsov, A.A., Struchkova, M.I., and Dilman, A.D. (2015). *J. Fluorine Chem.* 171: 97.

64 Smirnov, V.O., Struchkova, M.I., Arkhipov, D.E. et al. (2014). *J. Org. Chem.* 79: 11819.

65 Ashirbaev, S.S., Levin, V.V., Struchkova, M.I., and Dilman, A.D. (2016). *J. Fluorine Chem.* 191: 143.

66 Zemtsov, A.A., Kondratyev, N.S., Levin, V.V. et al. (2014). *J. Org. Chem.* 79: 818.

67 zemtsov, A.A., Kondratyev, N.S., Levin, V.V. et al. (2016). *Russ. Chem. Bull. Int. Ed.* 65: 2760.

68 Zemtsov, A.A., Volodin, A.D., Levin, V.V. et al. (2015). *Beilstein J. Org. Chem.* 11: 2145.

69 Kondratyev, N.S., Levin, V.V., Zemtsov, A.A. et al. (2015). *J. Fluorine Chem.* 176: 89.

70 (a) Smirnov, V.O., Maslov, A.S., Levin, V.V. et al. (2014). *Russ. Chem. Bull. Int. Ed.* 63: 2564. (b) Levin, V.V., Struchkova, M.I., and Dilman, A.D. (2017). *Mendeleev Commun.* 27: 139. (c) Ashirbaev, S.S., Levin, V.V., Struchkova, M.I., and Dilman, A.D. (2018). *J. Org. Chem.* 83: 478.

71 (a) Kosobokov, M.D., Levin, V.V., Struchkova, M.I., and Dilman, A.D. (2014). *Org. Lett.* 16: 3784. (b) Levin, V.V., Smirnov, V.O., Struchkova, M.I., and Dilman, A.D. (2015). *J. Org. Chem.* 80: 9349.

72 Maslov, A.S., Smirnov, V.O., Struchkova, M.I. et al. (2015). *Tetrahedron Lett.* 56: 5048.

73 Trifonov, A.L., Zemtsov, A.A., Levin, V.V. et al. (2016). *Org. Lett.* 18: 3458.

74 Trifonov, A.L., Levin, V.V., Struchkova, M.I., and Dilman, A.D. (2017). *Org. Lett.* 19: 5304.

75 Mikami, K., Tomita, Y., and Itoh, Y. (2010). *Angew. Chem. Int. Ed.* 49: 3819.

76 (a) Iida, T., Hashimoto, R., Aikawa, K. et al. (2012). *Angew. Chem. Int. Ed.* 51: 9535. (b) Hashimoto, R., Iida, T., Aikawa, K. et al. (2014). *Chem. Eur. J.* 20: 2750. (c) Aikawa, K., Maruyama, K., Honda, K., and Mikami, K. (2015). *Org. Lett.* 17: 4882. (d) Aikawa, K., Maruyama, K., Nitta, J. et al. (2016). *Org. Lett.* 18: 3354.

77 Honda, K., Harris, T.V., Hatanaka, M. et al. (2016). *Chem. Eur. J.* 22: 8796.

78 He, Z., Hu, M., Luo, T. et al. (2012). *Angew. Chem. Int. Ed.* 51: 11545.

79 Wang, X., Liu, G., Xu, X.H. et al. (2014). *Angew. Chem. Int. Ed.* 53: 1827.

80 Yang, Z.-Y. and Burton, D.J. (1989). *J. Fluorine Chem.* 45: 435.

81 Yang, Z.-Y. (1991). *J. Org. Chem.* 56: 5125.

82 Yang, Z.-Y. and Burton, D.J. (1992). *J. Org. Chem.* 57: 5144.

83 Yang, S., Xu, Q., and Shi, M. (2016). *Chem. Eur. J.* 22: 10387.

84 Liu, J., Ding, W., Zhou, Q.Q. et al. (2018). *Org. Lett.* 20: 461.

85 Zhang, B.S., Gao, L.Y., Zhang, Z. et al. (2018). *Chem. Commun.* 54: 1185.

86 Li, M., Wang, C.T., Qiu, Y.F. et al. (2018). *Chem. Commun.* 54: 5334.

87 Li, M., Zhu, X.Y., Qiu, Y.F. et al. (2019). *Adv. Synth. Catal.* 361: 2945.

88 Gonzalez, J., Foti, C.J., and Elsheimer, S. (1991). *J. Org. Chem.* 56: 4322.

89 Miethchen, R., Hein, M., and Reinke, H. (1998). *Eur. J. Org. Chem.* 1998: 919.

90 Miethchen, R., Wegert, A., Hein, M., and Reinke, H. (2005). *Synthesis* 2005: 1850.

91 Lin, Q.Y., Xu, X.H., and Qing, F.L. (2015). *Org. Biomol. Chem.* 13: 8740.

92 Supranovich, V.I., Levin, V.V., Struchkova, M.I. et al. (2017). *Org. Lett.* 19: 3215.

93 Yang, Z.-Y. and Burton, D.J. (1992). *J. Org. Chem.* 57: 4676.

94 Pignard, S., Lopin, C., Gouhier, G., and Piettre, S.R. (2006). *J. Org. Chem.* 71: 31.

95 Burton, D.J. and Naae, D.G. (1973). *J. Am. Chem. Soc.* 95: 8467.

96 Lin, Q.-Y., Xu, X.-H., and Qing, F.-L. (2015). *Angew. Chem. Int. Ed.* 55: 1479.

97 Zheng, J., Cai, J., Lin, J.H. et al. (2013). *Chem. Commun.* 49: 7513.

98 Zhang, M., Lin, J.-H., and Xiao, J.-C. (2019). *Angew. Chem. Int. Ed.* 58: 6079.

99 Kim, Y.J. and Kim, D.Y. (2018). *J. Fluorine Chem.* 211: 119.

100 Yu, C., Iqbal, N., Park, S., and Cho, E.J. (2014). *Chem. Commun.* 50: 12884.

101 Nie, X., Cheng, C., and Zhu, G. (2017). *Angew. Chem. Int. Ed.* 56: 1898.

102 Zhang, J., Jin, W., Cheng, C., and Luo, F. (2018). *Org. Biomol. Chem.* 16: 3876.

103 Suh, C.W. and Kim, D.Y. (2015). *Tetrahedron Lett.* 56: 5661.

104 Yu, J., Wang, D., Xu, Y. et al. (2018). *Adv. Synth. Catal.* 360: 744.

105 Wei, X.J. and Noel, T. (2018). *J. Org. Chem.* 83: 11377.
106 Liu, J., Li, W., Xie, J., and Zhu, C. (2018). *Org. Chem. Front.* 5: 797.
107 Xia, X.-F., Zhu, S.-L., Li, Y., and Wang, H. (2016). *RSC Adv.* 6: 51703.
108 Li, J., Chen, J., Jiao, W. et al. (2016). *J. Org. Chem.* 81: 9992.
109 Gu, J.W., Min, Q.Q., Yu, L.C., and Zhang, X. (2016). *Angew. Chem. Int. Ed.* 55: 12270.
110 Jin, W., Wu, M., Xiong, Z., and Zhu, G. (2018). *Chem. Commun.* 54: 7924.
111 (a) Sha, W., Zhang, W., Ni, S. et al. (2017). *J. Org. Chem.* 82: 9824. (b) Da, Y., Han, S., Du, X. et al. (2018). *Org. Lett.* 20: 5149. (c) Yin, Z.B., Ye, J.H., Zhou, W.J. et al. (2018). *Org. Lett.* 20: 190. (d) Yuan, F., Zhou, S., Yang, Y. et al. (2018). *Org. Chem. Front.* 5: 3306.
112 Yang, Y., Yuan, F., Ren, X. et al. (2019). *J. Org. Chem.* 84: 4507.
113 Xia, Z.H., Gao, Z.H., Dai, L., and Ye, S. (2019). *J. Org. Chem.* 84: 7388.
114 Chen, Y., Li, L., Ma, Y., and Li, Z. (2019). *J. Org. Chem.* 84: 5328.
115 Kong, W., Yu, C., An, H., and Song, Q. (2018). *Org. Lett.* 20: 4975.
116 Xu, R. and Cai, C. (2019). *Chem. Commun.* 55: 4383.
117 Xia, P.J., Ye, Z.P., Song, D. et al. (2019). *Chem. Commun.* 55: 2712.
118 Qiu, Z.-M. and Burton, D.J. (1993). *Tetrahedron Lett.* 34: 3239.
119 Qiu, Z.-M. and Burton, D.J. (1995). *J. Org. Chem.* 60: 5570.
120 Qu, C., Wu, Z., Li, W. et al. (2017). *Adv. Synth. Catal.* 359: 1672.
121 Zhang, M., Li, W., Duan, Y. et al. (2016). *Org. Lett.* 18: 3266.
122 Ding, F., Fang, Y., Jiang, Y. et al. (2018). *Chem. Asian J.* 13: 636.
123 Liang, H., Xu, G.Q., Feng, Z.T. et al. (2019). *J. Org. Chem.* 84: 60.
124 Cao, P., Duan, J.-X., and Chen, Q.-Y. (1994). *J. Chem. Soc., Chem. Commun.* 737.
125 Chernov, G.N., Levin, V.V., Kokorekin, V.A. et al. (2017). *Adv. Synth. Catal.* 359: 3063.
126 Supranovich, V.I., Levin, V.V., Struchkova, M.I. et al. (2018). *Beilstein J. Org. Chem.* 14: 1637.
127 Tang, X.-J., Thomoson, C.S., and Dolbier, W.R. (2014). *Org. Lett.* 16: 4594.
128 Tang, X.-J. and Dolbier, W.R. Jr. (2015). *Angew. Chem. Int. Ed.* 54: 4246.
129 Tang, X.J., Zhang, Z., and Dolbier, W.R. Jr. (2015). *Chem. Eur. J.* 21: 18961.
130 Thomoson, C.S., Tang, X.J., and Dolbier, W.R. Jr. (2015). *J. Org. Chem.* 80: 1264.
131 Zhang, Z., Tang, X., Thomoson, C.S., and Dolbier, W.R. Jr. (2015). *Org. Lett.* 17: 3528.
132 Zhang, Z., Tang, X.J., and Dolbier, W.R. Jr. (2016). *Org. Lett.* 18: 1048.
133 Zhang, Z., Martinez, H., and Dolbier, W.R. (2017). *J. Org. Chem.* 82: 2589.
134 Liu, J., Zhuang, S., Gui, Q. et al. (2014). *Eur. J. Org. Chem.* 2014: 3196.
135 He, Z., Tan, P., Ni, C., and Hu, J. (2015). *Org. Lett.* 17: 1838.
136 (a) Zhang, S., Li, L., Zhang, J. et al. (2019). *Chem. Sci.* 10: 3181. (b) Ruan, Z., Huang, Z., Xu, Z. et al. (2019). *Org. Lett.* 21: 1237.
137 Reutrakul, V., Thongpaisanwong, T., Tuchinda, P. et al. (2004). *J. Org. Chem.* 69: 6913.
138 (a) Li, Y., Liu, J., Zhang, L. et al. (2007). *J. Org. Chem.* 72: 5824. (b) Miao, W., Ni, C., Zhao, Y., and Hu, J. (2014). *J. Fluorine Chem.* 167: 231. (c) Rong, J., Deng, L., Tan, P. et al. (2016). *Angew. Chem. Int. Ed.* 55: 2743.

139 (a) Wang, J.Y., Su, Y.M., Yin, F. et al. (2014). *Chem. Commun.* 50: 4108.
(b) Wang, J.Y., Zhang, X., Bao, Y. et al. (2014). *Org. Biomol. Chem.* 12: 5582.
140 Yu, J., Wu, Z., and Zhu, C. (2018). *Angew. Chem. Int. Ed.* 57: 17156.
141 Zhu, M., Fun, W., Guo, W. et al. (2019). *Eur. J. Org. Chem.* 2019: 1614.
142 Zhang, W., Wang, F., and Hu, J. (2009). *Org. Lett.* 11: 2109.
143 Arai, Y., Tomita, R., Ando, G. et al. (2016). *Chem. Eur. J.* 22: 1262.
144 Nakayama, Y., Ando, G., Abe, M. et al. (2019). *ACS Catal.* 9: 6555.
145 Noto, N., Koike, T., and Akita, M. (2017). *Chem. Sci.* 8: 6375.
146 Wang, X., Wan, W., Chen, Y. et al. (2016). *Eur. J. Org. Chem.* 2016: 3773.
147 Yang, B., Xu, X.-H., and Qing, F.-L. (2016). *Org. Lett.* 18: 5956.
148 Zhou, Y., Xiong, Z., Qiu, J. et al. (2019). *Org. Chem. Front.* 6: 1022.

4

Monofluoromethylation Reactions of Aliphatic Substrates and (Hetero)Arenes

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4.1 Nucleophilic Monofluoromethylation

4.1.1 By Means of Fluoromalonates

For many years, direct nucleophilic monofluoromethylation with FCH_2M was known as a very challenging task, owing to the instability (facile α-fluoride elimination) of FCH_2M (M = Li, MgX) species [1]. Therefore, functionalized fluoromethanes were developed as indirect monofluoromethylation reagents. Fluoromalonates have been known to act as nucleophilic monofluoroalkylation reagents over half a century [2]; however, these reagents were rarely used for the synthesis of CH_2F-containing molecules because decarboxylation of two carboxylate groups is very difficult. Palmer described a monofluoromethylation protocol for the synthesis of α-fluoroketone by a nucleophilic monofluoroalkylation–decarboxylation sequence (Scheme 4.1) [3]. The decarboxylation step is assisted by the carbonyl group from the carboxylic acid substrate; therefore, this method may only work for the synthesis of monofluoromethylketones. Indeed, although many catalytic enantioselective nucleophilic additions of fluoromalonates to various substrates were reported, the subsequent transformation of the addition products to CH_2F derivatives via decarboxylation was not demonstrated [4].

4.1.2 By Means of Fluoromethyl Phenyl Sulfone

In 2006, Hu and coworkers reported the first stereoselective nucleophilic monofluoromethylation of (*R*)-(*tert*-butanesulfinyl)imines with fluoromethyl phenyl sulfone in the presence of a base (Scheme 4.2) [5]. A variety of enantiomerically pure α-monofluoromethylamines could be obtained via a nonchelation-controlled stereoselectivity mode. By using tosylate-bearing (*R*)-(*tert*-butanesulfinyl)imine as the substrate, α-monofluoromethylated cyclic secondary amine can also be obtained. $PhSO_2CH_2F$ reagent was also applicable for the (benzenesulfonyl)monofluoromethylation of epoxides [6].

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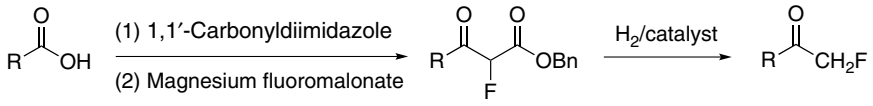
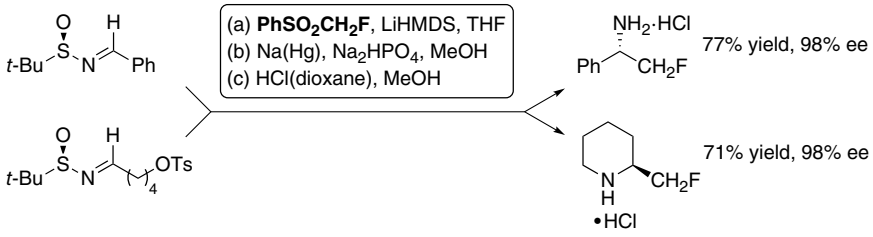
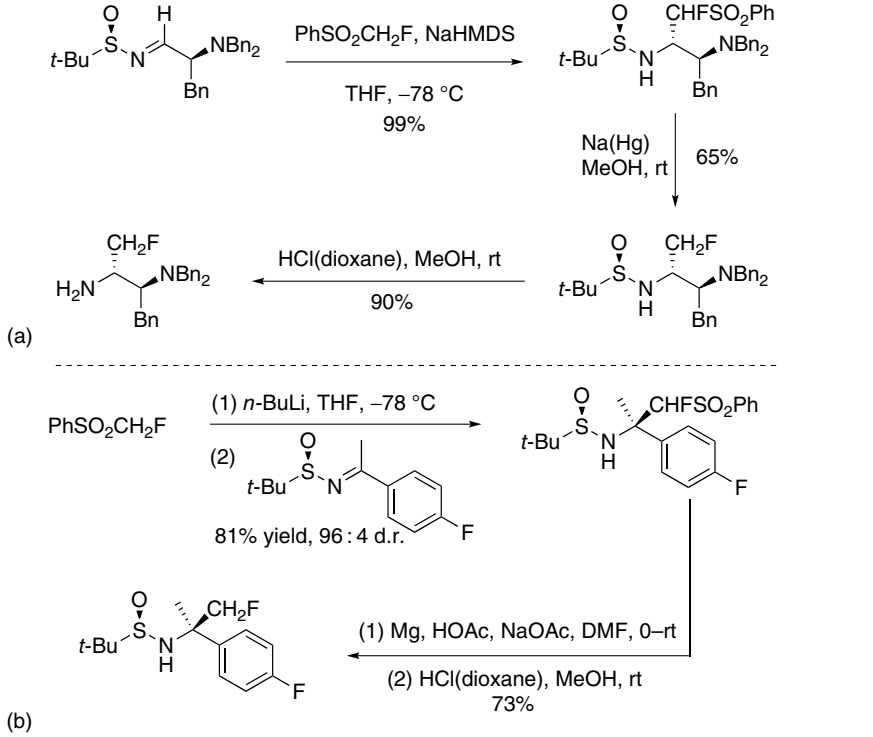


Scheme 4.1 Nucleophilic monofluoromethylation with fluoromalonates. CDI, 1,1′-carbonyldiimidazole.



Scheme 4.2 Nucleophilic monofluoromethylation of *N*-(*tert*-butanesulfinyl)imines with $PhSO_2CH_2F$.

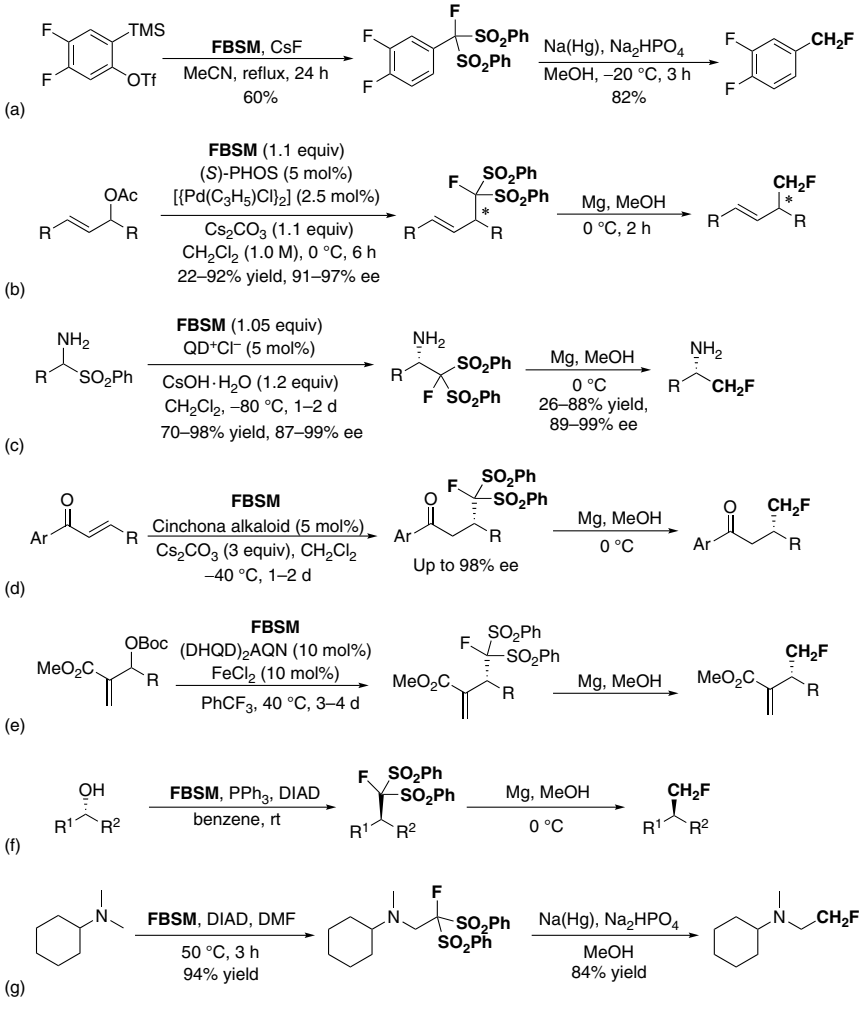
Later on, the Hu group extended the synthetic application of $PhSO_2CH_2F$ to the synthesis of chiral α-monofluoromethylated vicinal ethylenediamines (Scheme 4.3a) [7], the stereoselective monofluoromethylation of *N*-*tert*-butylsulfinyl ketimines via chelation-controlled mode [8], and monofluoromethylation of α,β-unsaturated compounds (Scheme 4.3b) [9].



Scheme 4.3 Nucleophilic monofluoromethylation of *N*-(*tert*-butanesulfinyl) aldimines and ketimines with $PhSO_2CH_2F$.

4.1.3 By Means of Fluorobis(phenylsulfonyl)methane

In 2006, Shibata and coworkers [10] and Hu and coworkers [6] demonstrated fluorobis(phenylsulfonyl)methane ($(PhSO_2)_2CHF$, FBSM) as a novel nucleophilic monofluoromethylation reagent. In Hu's work, the synthesis of FBSM was done by the reaction of bis(phenylsulfonyl)methane with Selectfluor [6]. FBSM turns out to be a good nucleophile, which can readily undergo addition to epoxides and aziridines [6], 1,4-addition to α,β-enones and activated alkynes [9], addition to arynes (Scheme 4.4a) [9], and allylation of simple alkynes under palladium/HOAc catalysis [11]. In Shibata's work, FBSM was applied in the palladium-catalyzed enantioselective allylic monofluoromethylation with allylic acetates (Scheme 4.4b) [10].



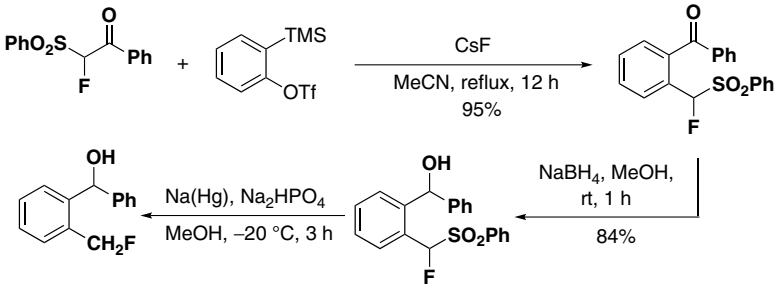
Scheme 4.4 Representative applications of FBSM as a monofluoromethylation reagent.

Since these two seminal reports on FBSM, the synthetic potential of FBSM has been extensively explored. Shibata and coworkers realized the first catalytic enantioselective monofluoromethylation of *in situ* generated imine from α-amido sul-

fone under cinchona alkaloid catalysis with FBSM (Scheme 4.4c) [12], the first asymmetric conjugate addition of FBSM to α,β-unsaturated ketones in high level of enantioselectivity (Scheme 4.4d) [13], the synthesis of monofluoromethylated allenes via palladium catalysis using FBSM [14], the asymmetric allylic monofluoromethylation of Morita–Baylis–Hillman carbonates by cooperative cinchona alkaloid/$FeCl_2$ catalysis (Scheme 4.4e) [15], and the PTC-catalyzed asymmetric monofluoromethylation of indole derivatives via *in situ* generated vinylogous imino intermediates [16]. Prakash et al. reported a stereoselective monofluoromethylation of alcohols with FBSM in a Mitsunobu reaction (Scheme 4.4f) [17], a 1,4-addition of FBSM to α,β-unsaturated compounds [18], and the nucleophilic substitution of alkyl halides with FBSM [19]. Cordova and coworkers and Wang and coworkers independently accomplished the organocatalyzed enantioselective conjugate addition of FBSM to enals [20]. Zhao et al. reported a highly regioselective Pd-catalyzed allylic monofluoromethylation reaction [21]. In 2011, Hu and coworkers realized the nucleophilic fluoromethylation of aldehydes with FBSM [22], which was thought to be unattainable [23]. They pointed out that both the strong Li–O coordination at low temperature and fluorine substitution play important roles. In 2013, a metal-free dehydrogenative cross-coupling between tertiary amines and FBSM was also achieved by Hu and coworkers, providing an efficient method for the synthesis of β-fluorinated amines (Scheme 4.4g) [24].

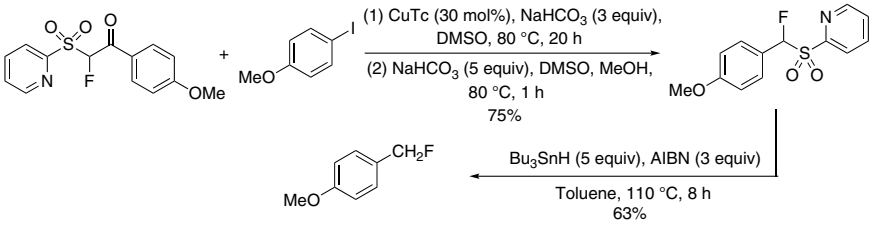
4.1.4 By Means of 2-Fluoro-2-Sulfonylketone

In 2008, the Hu group found that 2-fluoro-2-phenylsulfonylacetophenone is a good nucleophilic fluoroalkylation reagent for the bifunctionalization of arynes and activated alkynes enabling both C—R_f bond and CC(O)Ph bond formations in a single step (Scheme 4.5) [9]. The phenylsulfonyl group can be easily cleaved under reductive conditions to give the monofluoromethylated products.



Scheme 4.5 Nucleophilic monofluorome thylation of arynes with 2-fluoro-2-phenylsulfonylacetophenone.

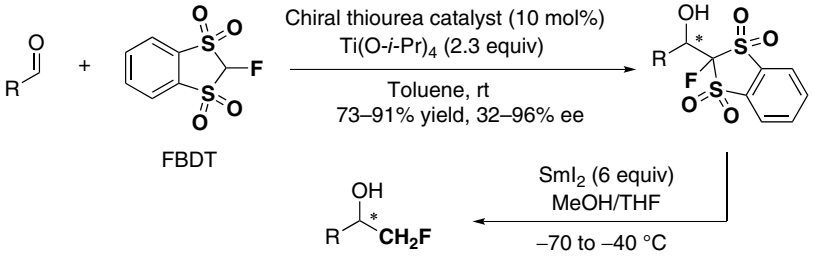
In 2013, Hu and coworkers developed a new method for aromatic monofluoromethylation with 2-$PySO_2CHFCOR$ (R = 4-methoxyphenyl) [25]. A variety of aryl iodides can be efficiently monofluoromethylated via a copper-catalyzed debenzoylative fluoroalkylation-reductive desulfonylation sequence (Scheme 4.6). They found that the pyridylsulfonyl group plays an important role in this Hurtley-type cross-coupling reaction.



Scheme 4.6 Copper-catalyzed monofluoromethylation of aryl iodides with 2-$PySO_2CHFCOR$.

4.1.5 By Means of 2-Fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT)

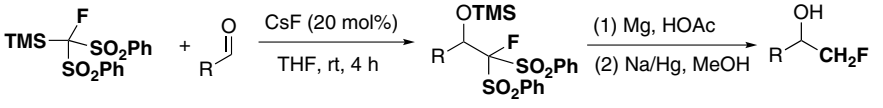
In 2010, as FBSM failed to undergo nucleophilic addition to aldehydes in Shibata's attempts, they designed a new reagent, 2-fluoro-1,3-benzodithiole-1,1,3,3-tetraoxide (FBDT), for nucleophilic monofluoromethylation of aldehydes [23]. Later on, by using a bifunctional cinchona alkaloid-derived thiourea–titanium complex, the enantioselective monofluoromethylation of aldehydes can be achieved with FBDT in good yields and high ee values (Scheme 4.7) [26].



Scheme 4.7 Enantioselective monofluoromethylation of aldehydes with FBDT.

4.1.6 By Means of $TMSCF(SO_2Ph)_2$ (TFBSM)

In 2012, Prakash et al. developed TFBSM as a novel monofluoromethylation reagent. Compared with FBSM, TFBSM can monofluoromethylate aldehydes under milder conditions (Scheme 4.8) [27].

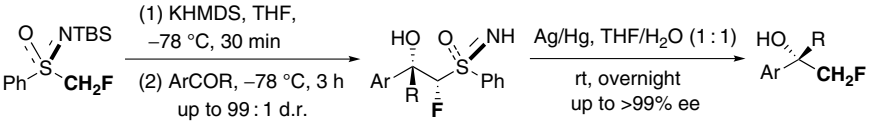


Scheme 4.8 Monofluoromethylation of aldehydes with TFBSM.

4.1.7 By Means of $PhSO(NTBS)CH_2F$

In 2014, to access chiral monofluoromethylated tertiary alcohols, Hu and coworkers developed a chiral monofluoromethylation reagent, (*R*)-PhSO(NTBS)CH_2F. This reagent can readily undergo stereoselective nucleophilic fluorometh-

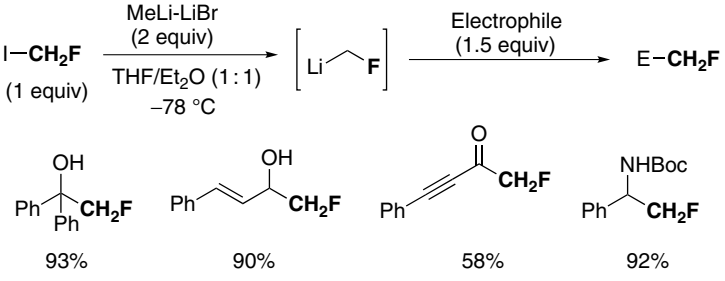
ylation of arylketones (Scheme 4.9), and the high stereoselectivity was believed to be facilitated by the kinetic resolution of the chiral α-fluorocarbanion [28].



Scheme 4.9 Enantioselective monofluoromethylation of aldehydes with chiral PhSO(NTBS)CH_2F.

4.1.8 By Means of CH_2FI

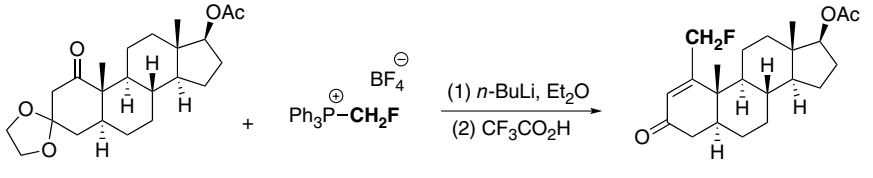
As mentioned earlier in the chapter, direct nucleophilic monofluoromethylation with FCH_2M (M = Li, MgX) is challenging. However, despite the known difficulties, in 2017, Luisi and coworkers demonstrated the first direct and straightforward nucleophilic monofluoromethylation with a "fleeting" lithium fluorocarbenoid ($LiCH_2F$) generated from commercially available CH_2FI [29]. This protocol overcomes the drawbacks associated with the use of auxiliary groups, where removal of the auxiliary is required to give the monofluoromethyl group. This strategy shows broad substrate scope, where a plethora of electrophiles such as aldehydes, ketones, Weinreb amides, and imines are suitable in monofluoromethylation (Scheme 4.10).



Scheme 4.10 Nucleophilic monofluoromethylation with CH_2FI via $LiCH_2F$ intermediate.

4.1.9 By Means of Monofluoromethyl Phosphonium Salts

Monofluoromethyl phosphonium salts can be used for the monofluoroolefination of carbonyl compounds, after which hydrogenation of the C=C bond would give the corresponding monofluoromethylated product (Scheme 4.11) [30].

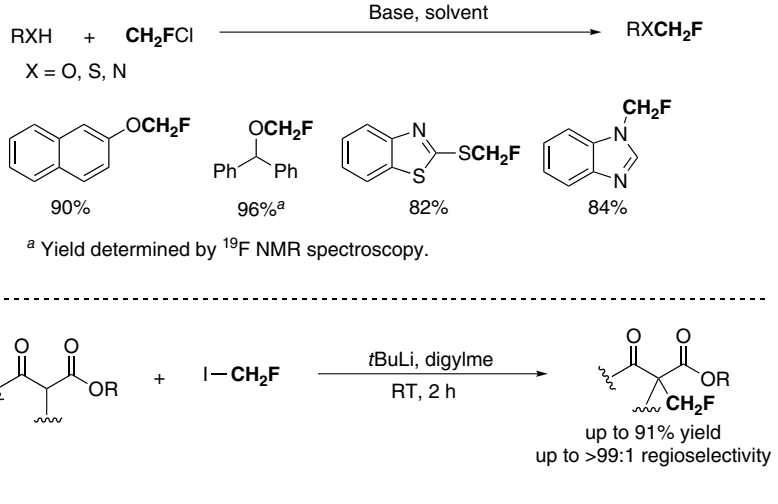


Scheme 4.11 Nucleophilic monofluoromethylation with monofluoromethyl phosphonium salt.

4.2 Electrophilic Monofluoromethylation

4.2.1 By Means of CH_2FX (X = Cl, Br, I, OTf, OTs, OMs)

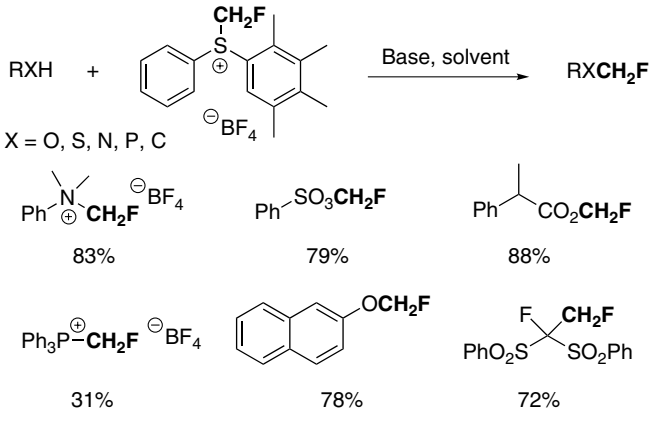
Compared with nucleophilic monofluoromethylation, electrophilic monofluoromethylation is less studied. In 1953, Olah and Pavlath reported the first electrophilic monofluoromethylation of benzene with monofluoromethanol in the presence of an acid [30]. The electrophilic monofluoromethylation was neglected until 1985 when several examples of electrophilic monofluoromethylation of O-, S-, N-, and C-nucleophiles have been reported using CH_2FX (X = Cl, Br, I, OTf, OTs, OMs) [31a]. In 2007, Hu and coworkers systematically explored the monofluoromethylation ability of CH_2FCl as an electrophilic monofluoromethylation reagent for a number of O-, S-, and N-nucleophiles, and the yields are typically good (Scheme 4.12a) [31a]. Very recently, Jiang and coworkers reported a highly carbon-selective electrophilic monofluoromethylation of β-ketoesters with CH_2FI under mild conditions (Scheme 4.12b) [31b]. The major feature of this reaction is that the use of lithium *tert*-butoxide as base and the diglyme as solvent leads to a high C/O regioselectivity [31b].



Scheme 4.12 Electrophilic monofluoromethylation with CH_2FX (X = Cl, I).

4.2.2 By Means of *S*-(monofluoromethyl)diarylsulfonium Tetrafluoroborate

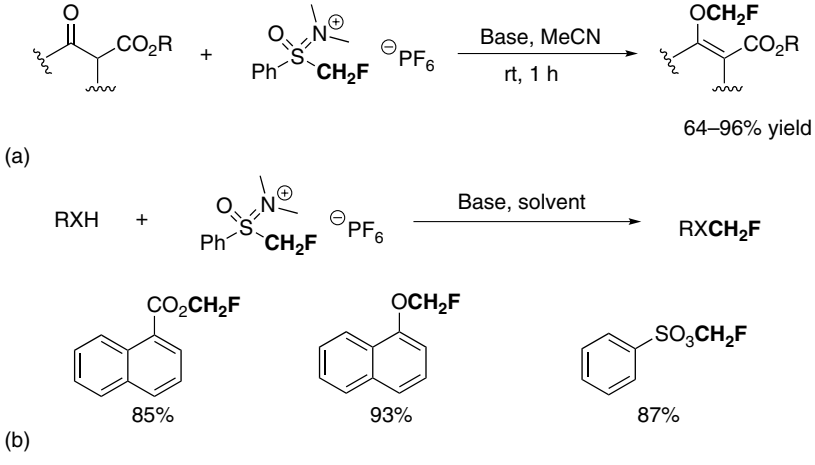
In 2008, Prakash et al. developed a novel electrophilic monofluoromethylation reagent, *S*-monofluoromethyl-*S*-phenyl-2,3,4,5-tetramethylphenylsulfonium tetrafluoroborate, which can be used for the direct FH_2C^+ transfer to a wide range of O-, S-, N-, P-, and C-nucleophiles (Scheme 4.13) [32].



Scheme 4.13 Electrophilic monofluoromethylation with *S*-(monofluoromethyl) diarylsulfonium tetrafluoroborate.

4.2.3 By Means of Monofluoromethylsulfoxinium Salts

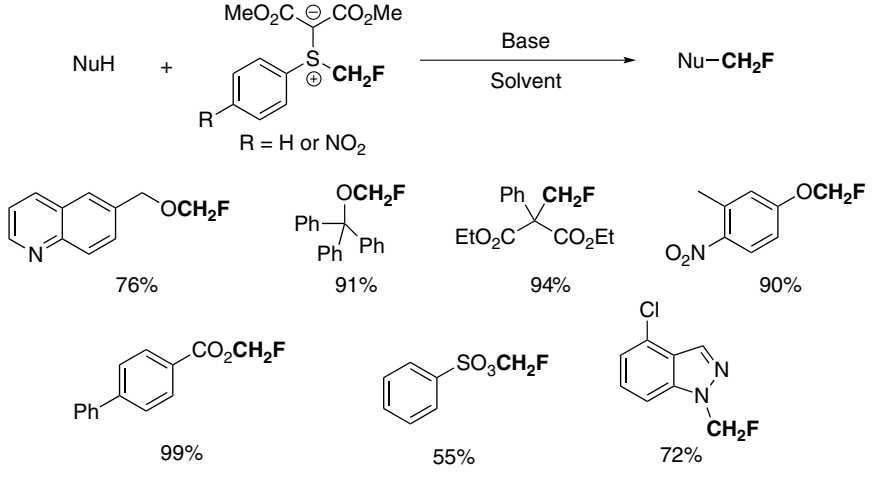
In 2011, Shibata and coworkers developed novel shelf-stable *N*,*N*-(dimethylamino)-*S*-phenyl-*S*-monofluoromethyloxosulfonium trifluoromethanesulfonate or hexafluorophosphate salts for electrophilic monofluoromethylation reaction [33]. When β-ketoesters were used as substrates, exclusive O-monofluoromethylation was observed in high yields (Scheme 4.14a). This reagent can also monofluoromethylate other O-nucleophiles, for instance, carboxylic acids, phenols, and sulfonic acids (Scheme 4.14b). A further mechanistic study revealed that monofluoromethylation of β-ketoesters with monofluoromethylsulfoxinium salt probably involves a radical-like species [34].



Scheme 4.14 Electrophilic monofluoromethylation with monofluoromethylsulfoxinium salts.

4.2.4 By Means of Monofluoromethylsulfonium Ylides

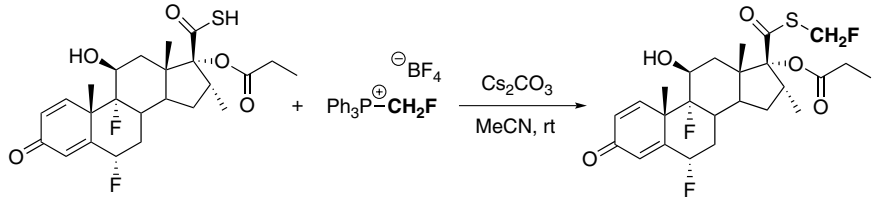
Very recently, Shen and coworkers synthesized two electrophilic monofluoromethylation reagents, monofluoromethyl(phenyl)sulfonium bis(carbomethoxy) methylide and monofluoromethyl(4-nitrophenyl)sulfonium bis(carbomethoxy) methylide [35]. Both reagents show much higher reactivity than those previously reported reagents. A variety of nucleophiles, such as alcohols, phenols, malonates, sulfonic acids, carboxylic acids, amides, and N-heteroarenes, could be monofluoromethylated in high yields under mild conditions (Scheme 4.15). Mechanistic investigations support an electrophilic substitution pathway.



Scheme 4.15 Electrophilic monofluoromethylation with monofluoromethylsulfonium ylides.

4.2.5 By Means of Monofluoromethyl Phosphonium Salts

In 2011, Leitao and Turner reported that monofluoromethyltriphenylphosphonium tetrafluoroborate can be used as a direct electrophilic monofluoromethylation reagent for monofluoromethylation of carbothioic acid (Scheme 4.16) [36].

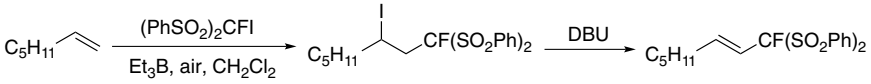


Scheme 4.16 Electrophilic monofluoromethylation with monofluoromethyl phosphonium salt.

4.3 Free Radical Monofluoromethylation

4.3.1 By Means of $(PhSO_2)_2CFI$

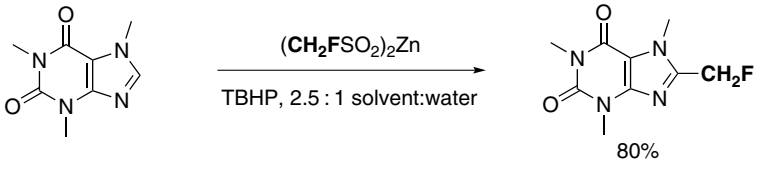
Radical monofluoromethylation is less studied than tri- and difluoromethylation. In 2008, Prakash et al. demonstrated the preparation of $(PhSO_2)_2CFI$ and its application as a radical precursor, which can undergo addition to terminal alkenes. The adduct can easily undergo dehydroiodination to give *E*-alkenes (Scheme 4.17) [37]. However, although desulfonation is easy and well documented, the products were not converted into the monofluoromethylated ones.



Scheme 4.17 Radical monofluoromethylation with $(PhSO_2)_2CFI$.

4.3.2 By Means of $(H_2FCSO_2)_2Zn$ (MFMS)

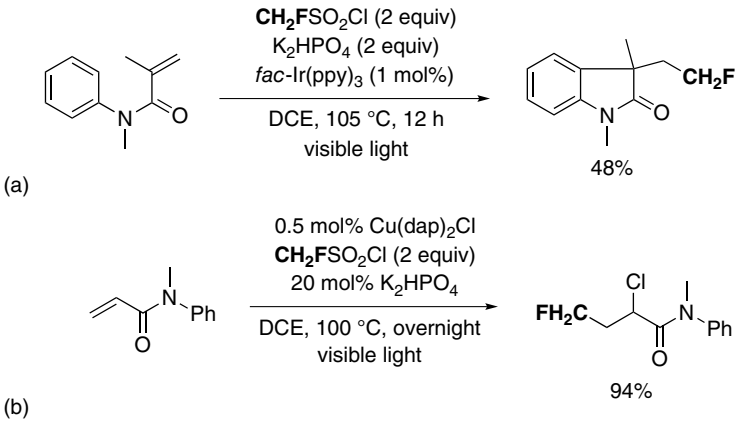
Direct $H_2FC^{\cdot}$ radical reagent with synthetic utility was unprecedented until 2012. In this year, Baran and coworkers designed a new direct $H_2FC^{\cdot}$ radical transfer reagent, zinc monofluoromethanesulfinate (MFMS), which can readily be used to functionalize innate carbon–hydrogen bond of heterocycles in good yields (Scheme 4.18) [38].



Scheme 4.18 Direct radical monofluoromethylation with MFMS.

4.3.3 By Means of CH_2FSO_2Cl

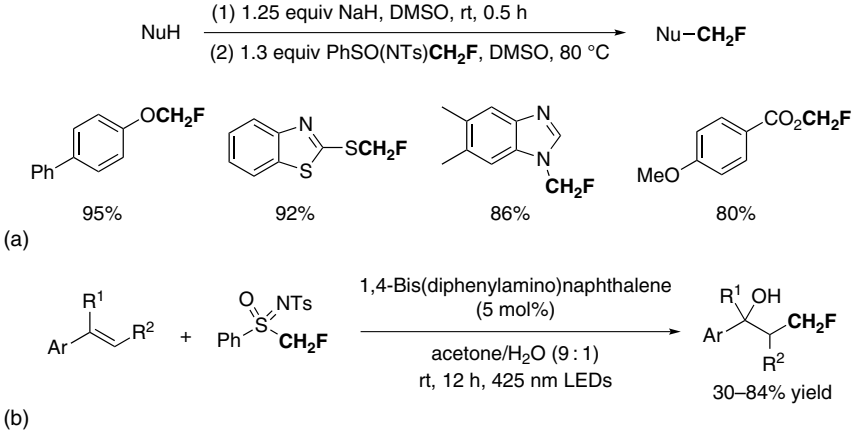
Inspired by Baran's work that $(R_fSO_2)_2Zn$, which can be prepared from R_fSO_2Cl, is good $R_f^{\cdot}$ radical precursor, Dolbier and coworkers presented that R_fSO_2Cl can act as radical precursor under photoredox catalysis. $H_2FC^{\cdot}$ radical can be generated from CH_2FSO_2Cl using *fac*-Ir(ppy)$_3$ as the photocatalyst, and its addition to *N*-arylacrylamides delivers monofluoromethylated 3,3-disubstituted 2-oxindoles in moderate yields (Scheme 4.19a) [39]. Later on, they also achieved copper-catalyzed atom transfer radical addition reaction of CH_2FSO_2Cl onto unsaturated carbonyl compounds to afford α-chloro-β-monofluoromethylcarbonyl products in excellent yields (Scheme 4.19b) [40].



Scheme 4.19 Direct radical monofluoromethylation with CH_2FSO_2Cl.

4.3.4 By Means of $PhSO(NTs)CH_2F$

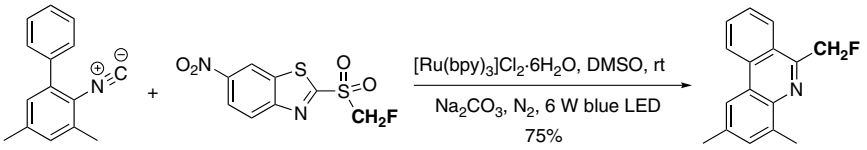
In 2014, Hu and coworkers revealed that $PhSO(NTs)CH_2F$ is a good monofluoromethylation reagent for the direct monofluoromethylation of O-, S-, N-, and P-nucleophiles (Scheme 4.20a) [41]. An accelerating effect is observed by the α-fluorine substitution, which is in sharp contrast with previously known detrimental impact of α-fluorine substitution on S_N2 reactions. Preliminary mechanistic studies suggest a radical mechanism. In 2019, Akita and coworkers presented that monofluoromethyl radical can be generated from $PhSO(NTs)CH_2F$ by using strongly reducing 1,4-bis(diphenylamino) naphthalene photoredox catalyst. The monofluoromethyl radical can add to alkenes, leading to facile synthesis of γ-fluoroalcohols (Scheme 4.20b) [42].



Scheme 4.20 Direct radical monofluoromethylation with $PhSO(NTs)CH_2F$.

4.3.5 By Means of Monofluoromethyl Sulfone

In 2016, Hu and coworkers reported that fluorinated sulfones can be used as radical precursors by photoredox catalysis. By using 2-((fluoromethyl)sulfonyl)-6-nitrobenzo[*d*]thiazole, monofluoromethyl radical can be produced smoothly and add to isocyanide for the construction of phenanthridine structure (Scheme 4.21) [43].

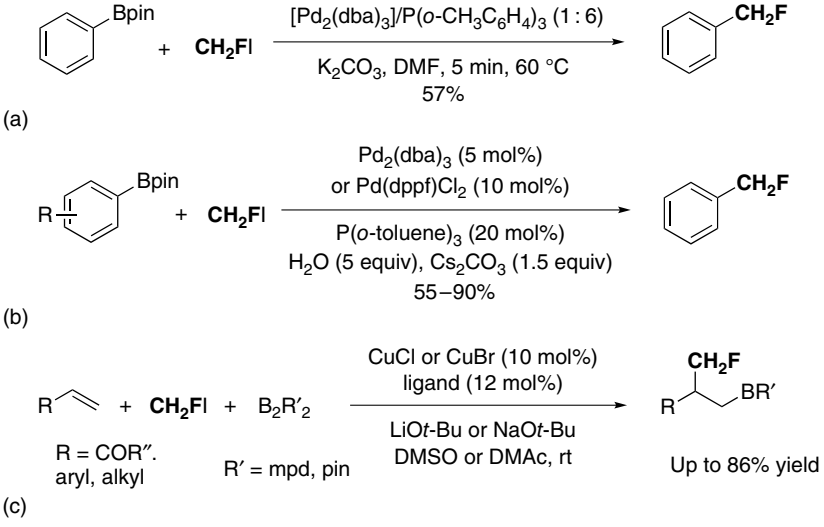


Scheme 4.21 Direct radical monofluoromethylation with monofluoromethyl sulfone.

4.4 Transition-Metal-Catalyzed/Mediated Monofluoromethylation

4.4.1 By Means of CH_2FI

Monofluoromethylation via transition-metal-catalyzed/mediated cross-coupling reactions is an emerging research area. The seminal report in this direction is the palladium(0)-mediated cross-coupling between pinacophenylborate and CH_2FI, demonstrated by Suzuki and coworkers in 2009 (Scheme 4.22a) [44]. However, according to Suzuik's report, stoichiometric amount of palladium and large excess of pinacophenylborate (40 equiv) are required, which restricted its application. In 2015, Hu et al. reported that a catalytic version using Pd(0) as the catalyst and P(*o*-toluene)$_3$ as the ligand, and a variety of electron-rich and electron-deficient arylborates could be monofluoromethylated in good yields under

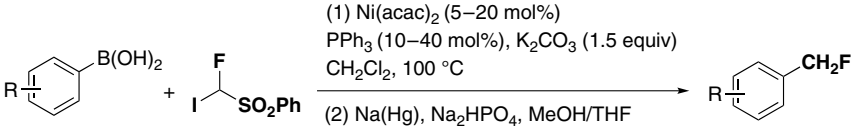


Scheme 4.22 Monofluoromethylation with CH_2FI.

mild conditions (Scheme 4.22b) [45]. In 2009, Qing and coworkers realized the regioselective borylmonofluoromethylation of alkenes with CH_2FI using copper catalysis (Scheme 4.22c), and the Bpin group in the products can be transformed into various functional groups [46].

4.4.2 By Means of $PhSO_2CHFI$

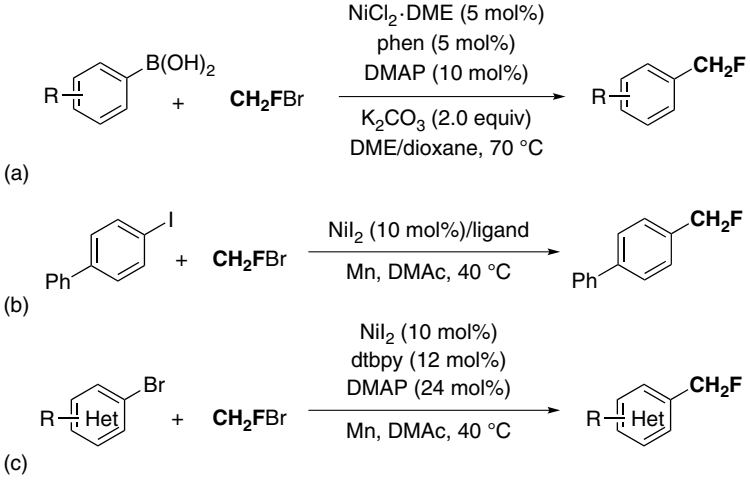
In 2015, Wang and coworkers reported a nickel-catalyzed monofluoromethylation of aryl boronic acids with $PhSO_2CHFI$. The sulfonyl group can be readily removed under reductive conditions to give the monofluoromethylated arenes (Scheme 4.23) [47].



Scheme 4.23 Monofluoromethylation with $PhSO_2CHFI$.

4.4.3 By Means of CH_2FBr

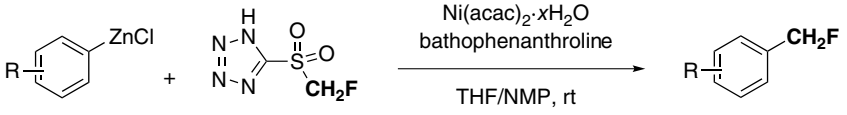
In 2015, Zhang and coworkers reported a nickel-catalyzed cross-coupling reaction between arylboronic acids and CH_2FBr for the facile access to monofluoromethylated arenes (Scheme 4.24a) [48]. Later on, in 2018, Wang and coworkers reported a nickel-catalyzed reductive cross-coupling of aryl halides with CH_2FBr for the preparation of monofluoromethyl-substituted arenes, and a combination of bidentate and monodentate pyridine-type nitrogen ligand is the key to success (Scheme 4.24b) [49]. Very recently, Wang and coworkers also achieved the reductive cross-coupling between (hetero)aryl bromides and CH_2FBr (Scheme 4.24c) [50].



Scheme 4.24 Monofluoromethylation with CH_2FBr.

4.4.4 By Means of $PTSO_2CH_2F$

In 2018, Baran and coworkers reported a modular radical cross-coupling with sulfones to access sp^3-riched (fluoro)alkylated scaffolds. Five specific sulfone reagents were developed; among them, monofluoromethyl phenyl-tetrazole (PT) sulfone is a good monofluoromethylation reagent, which can readily undergo cross-coupling reaction with arylzinc reagents by nickel catalysis (Scheme 4.25) [51].



Scheme 4.25 Monofluoromethylation with $PTSO_2CH_2F$.

References

1 Reeder, M.R. and Anderson, R.M. (2006). *Chem. Rev.* 106: 2828.
2 (a) Buchanan, R.L. and Pattison, F.L.M. (1965). *Can. J. Chem.* 43: 3466. (b) Ishikawa, N., Takaoka, A., and Ibrahim, M.K. (1984). *J. Fluorine Chem.* 25: 203.
3 Palmer, J.T., Reagents and methods for stereospecific fluoromethylation, (1991). EP0442754A2, filed 15 February 1991 and issued 21 August 1991.
4 (a) Kwon, B.K., Kim, S.M., and Kim, D.Y. (2009). *J. Fluorine Chem.* 130: 759. (b) Wang, W., Li, H., Zu, L., and Xie, H. (2009). *Synthesis* 2009: 1525.
5 Li, Y., Ni, C., Liu, J. et al. (2006). *Org. Lett.* 8: 1693.
6 Ni, C., Li, Y., and Hu, J. (2006). *J. Org. Chem.* 71: 6829.
7 Liu, J., Li, Y., and Hu, J. (2007). *J. Org. Chem.* 72: 3119.
8 Liu, J., Zhang, L., and Hu, J. (2008). *Org. Lett.* 10: 5377.
9 Ni, C., Zhang, L., and Hu, J. (2008). *J. Org. Chem.* 73: 5699.
10 Fukuzumi, T., Shibata, N., Sugiura, M. et al. (2006). *Angew. Chem. Int. Ed.* 45: 4973.
11 Ni, C. and Hu, J. (2009). *Tetrahedron Lett.* 50: 7252.
12 Mizuta, S., Shibata, N., Goto, Y. et al. (2007). *J. Am. Chem. Soc.* 129: 6394.
13 Furukawa, T., Shibata, N., Mizuta, S. et al. (2008). *Angew. Chem. Int. Ed.* 47: 8051.
14 Ogasawara, M., Murakami, H., Furukawa, T. et al. (2009). *Chem. Commun.*: 7366.
15 Furukawa, T., Kawazoe, J., Zhang, W. et al. (2011). *Angew. Chem. Int. Ed.* 50: 9684.
16 Matsuzaki, K., Furukawa, T., Tokunaga, E. et al. (2013). *Org. Lett.* 15: 3282.
17 Prakash, G.K.S., Chacko, S., Alconcel, S. et al. (2007). *Angew. Chem. Int. Ed.* 46: 4933.
18 Prakash, G.K.S., Zhao, X., Chacko, S. et al. (2008). *Beilstein J. Org. Chem.* 4: 17.
19 Prakash, G.K.S., Chacko, S., Vaghoo, H. et al. (2009). *Org. Lett.* 11: 1127.
20 (a) Ullah, F., Zhao, G.L., Deiana, L. et al. (2009). *Chemistry* 15: 10013.(b) Zhang, S., Zhang, Y., Ji, Y. et al. (2009). *Chem. Commun.*: 4886.
21 Zhao, X., Liu, D., Zheng, S., and Gao, N. (2011). *Tetrahedron Lett.* 52: 665.

22 Shen, X., Zhang, L., Zhao, Y. et al. (2011). *Angew. Chem. Int. Ed.* 50: 2588.
23 Furukawa, T., Goto, Y., Kawazoe, J. et al. (2010). *Angew. Chem. Int. Ed.* 49: 1642.
24 Huang, W., Ni, C., Zhao, Y., and Hu, J. (2013). *New J. Chem.* 37: 1684.
25 Zhao, Y., Ni, C., Jiang, F. et al. (2013). *ACS Catal.* 3: 631.
26 Ma, H., Matsuzaki, K., Yang, Y.-D. et al. (2013). *Chem. Commun.* 49: 11206.
27 Prakash, G.K.S., Shao, N., Zhang, Z. et al. (2012). *J. Fluorine Chem.* 133: 27.
28 Shen, X., Miao, W., Ni, C., and Hu, J. (2014). *Angew. Chem. Int. Ed.* 53: 775.
29 Parisi, G., Colella, M., Monticelli, S. et al. (2017). *J. Am. Chem. Soc.* 139: 13648.
30 Hu, J., Zhang, W., and Wang, F. (2009). *Chem. Commun.*: 7465.
31 (a) Zhang, W., Zhu, L., and Hu, J. (2007). *Tetrahedron* 63: 10569; and the references therein. (b) Ding, T., Jiang, L., Yang, J. et al. (2019). *Org. Lett.* 21: 6025.
32 Prakash, G.K.S., Ledneczki, I., Chacko, S., and Olah, G.A. (2008). *Org. Lett.* 10: 557.
33 Nomura, Y., Tokunaga, E., and Shibata, N. (2011). *Angew. Chem. Int. Ed.* 50: 1885.
34 Yang, Y.-D., Lu, X., Liu, G. et al. (2012). *ChemistryOpen* 1: 221.
35 Liu, Y., Lu, L., and Shen, Q. (2017). *Angew. Chem. Int. Ed.* 56: 9930.
36 Leitao, E.P.T. and Turner, C.R. (2011). Method for monofluoromethylation of organic substrates to prepare biologically active organic compounds, WO2011151624(A1), filed 01 June 2011 and issued 08 December 2011.
37 Prakash, G.K.S., Ledneczki, I., Chacko, S. et al. (2008). *J. Fluorine Chem.* 129: 1036.
38 Fujiwara, Y., Dixon, J.A., O'Hara, F. et al. (2012). *Nature* 492 (7427): 95–99.
39 Tang, X.-J., Thomoson, C.S., and Dolbier, W.R. (2014). *Org. Lett.* 16: 4594.
40 Tang, X.-J. and Dolbier, W.R. Jr. (2015). *Angew. Chem. Int. Ed.* 54: 4246.
41 Shen, X., Zhou, M., Ni, C. et al. (2014). *Chem. Sci.* 5: 117.
42 Noto, N., Koike, T., and Akita, M. (2019). *ACS Catal.* 9: 4382.
43 Rong, J., Deng, L., Tan, P. et al. (2016). *Angew. Chem. Int. Ed.* 55: 2743.
44 Doi, H., Ban, I., Nonoyama, A. et al. (2009). *Chem. Eur. J.* 15: 4165.
45 Hu, J., Gao, B., Li, L. et al. (2015). *Org. Lett.* 17: 3086.
46 Wu, N.-Y., Xu, X.-H., and Qing, F.-L. (2019). *ACS Catal.* 9: 5726.
47 Su, Y.-M., Feng, G.-S., Wang, Z.-Y. et al. (2015). *Angew. Chem. Int. Ed.* 54: 6003.
48 An, L., Xiao, Y.-L., Min, Q.-Q., and Zhang, X. (2015). *Angew. Chem. Int. Ed.* 54: 9079.
49 Sheng, J., Ni, H.-Q., Zhang, H.-R. et al. (2018). *Angew. Chem. Int. Ed.* 57: 7634.
50 Yin, H., Sheng, J., Zhang, K.F. et al. (2019). *Chem. Commun.* 55: 7635.
51 Merchant, R.R., Edwards, J.T., Qin, T. et al. (2018). *Science* 360: 75.