Tetrahedron Letters 75 (2021) 153182

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Digest paper

Recent advance in synthetic applications of difluoromethyl phenyl sulfone and its derivatives

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ARTICLE INFO

Article history:
Received 4 March 2021
Revised 28 April 2021
Accepted 11 May 2021
Available online 17 May 2021

Keywords:
Difluoromethyl phenyl sulfone
Nucleophilic (phenylsulfonyl) difluoromethylation
Electrophilic (phenylsulfonyl) difluoromethylation
Radical (phenylsulfonyl) difluoromethylation
Difluorocarbene

ABSTRACT

Organofluorine compounds often possess unique chemical, physical and biological properties and therefore, they play important roles in pharmaceuticals, agrochemicals, and advanced materials. Notably, the introduction of CF_2 motif as an oxygen surrogate could significantly improve the metabolic stability and bioavailability of the target molecules. Therefore, selective introduction of the CF_2 group into organic molecules is an appealing task. It has been realized that the (phenylsulfonyl)difluoromethyl group is a versatile CF_2 building block, which can be readily transformed into other useful fluorinated functionalities such as difluoromethyl (CF_2H), difluoromethylene ($-CF_2-$), and difluoromethylidene ($=CF_2$) groups. This article overviews the recent advance of (phenylsulfonyl)difluoromethylation reactions as well as their synthetic applications in organic synthesis within the past decade. Five modes of difluoroalkylation reactions have been developed, including nucleophilic (phenylsulfonyl)difluoromethylations, electrophilic (phenylsulfonyl)difluoromethylations, radical (phenylsulfonyl)difluoromethylations, difluorocarbene reactions, and transition-metal mediated (phenylsulfonyl)difluoromethylations.

Contents

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https://doi.org/10.1016/j.tetlet.2021.153182
0040-4039/

Introduction

Organofluorine compounds have found wide applications in pharmaceuticals, agrochemicals, and advanced materials [1]. Due to the unique properties of fluorine atom, selective introduction of fluorine atom and fluorinated groups into organic molecules can improve the lipophilicity, bioavailability, and metabolic stability of the target molecules [2]. In recent years, considerable attention has been paid to the selective incorporation of fluorine atom (s) or the CF_3 group; however, selective introduction of CF_2 moiety has been less explored [3]. Selective introduction of a CF_2 group into organic molecules is a very appealing task, since the CF_2 motif can be considered as an oxygen surrogate and significantly improve the metabolic stability and bioavailability of the molecules [4,5].

Difluoromethyl phenyl sulfones (**1**, $PhSO_2CF_2H$) is a commercially available compound. It can be readily transformed into other useful fluorinated functionalities such as difluoromethyl (CF_2H), difluoromethylene (–CF_2–), and difluoromethylidene (=CF_2) groups [6]. Five types of reactions of difluoromethyl phenyl sulfone **1** and its derivatives **2**–**8** are shown in Scheme 1: nucleophilic (phenylsulfonyl)difluoromethylations, electrophilic (phenylsulfonyl)difluoromethylations, radical (phenylsulfonyl)-difluoromethylations, difluorocarbene reactions, and transition-metal mediated (phenylsulfonyl)difluoromethylations. **1** was firstly synthesized by Hine and Porter in 1960 [7]. The value of $PhSO_2CF_2H$ as a nucleophilic (phenylsulfonyl)-difluoromethylation reagent was not recognized at that time, although they found that (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$) could be formed by deprotonation of $PhSO_2CF_2H$. Only four reports on (phenylsulfonyl)difluoromethylation reactions with $PhSO_2CF_2H$ were available before 2003 [8]. A summary of (phenylsulfonyl)difluoromethylation reactions was published in 2009 by one of us [6b]. Herein, we wish to highlight the recent advance in synthetic applications of $PhSO_2CF_2H$ (**1**) and its derivatives **2**–**8** since 2009. Representative (phenylsulfonyl)difluoromethylation reagents include $PhSO_2CF_2X$ (X = H, Cl, Br, I, $SiMe_3$, COOK), hypervalent iodine(III)-CF_2SO_2Ph, as well as S-((phenylsulfonyl)-difluoromethyl)thiophenium triflate (see Scheme 1).

Nucleophilic (phenylsulfonyl)difluoromethylation reaction

Using $PhSO_2CF_2H$ reagent

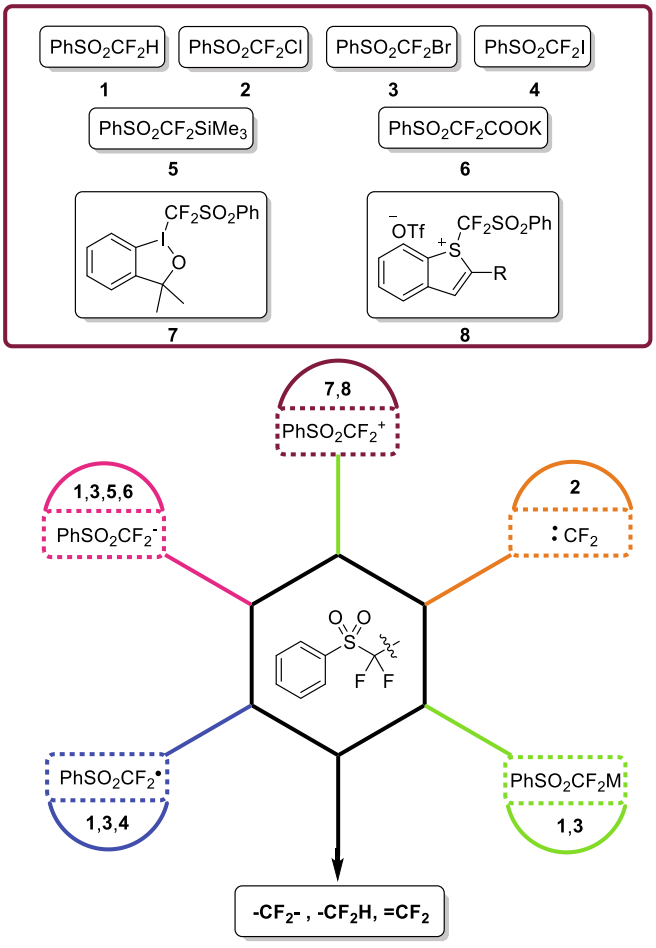
In 2010, the highly stereoselective difluoromethylation of *N-tert*-butanesulfinyl ketimines was achieved via in situ generated $PhSO_2CF_2^-$ anion (Scheme 2) [9]. This synthetic method enabled the preparation of structurally diverse homochiral α-difluoromethyl tertiary carbinamines, including α -difluoromethyl allylic amines and α -difluoromethyl propargylamines. Proposed reaction mechanism involved a cyclic six-membered transition state, which was different from other reported fluoroalkylations of *N-tert*-butylsulfinyl aldimines. Fortunately, the phenylsulfonyl group could be readily removed by the treatment of Mg^0 under acidic conditions.

In 2013, nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes was developed in the presence of substoichiometric amount of base in situ generated from $N(TMS)_3$ and catalytic amount of Me_4NF (Scheme 3) [10]. This work was inspired by the trifluoromethylation of carbonyls with CF_3H under similar reaction conditions reported by Langlois [11]. Notably, the reaction of $PhSO_2CF_2H$ with ketones was relatively slow, and the selective difluoromethylation of aldehydes over ketones became possible [11].

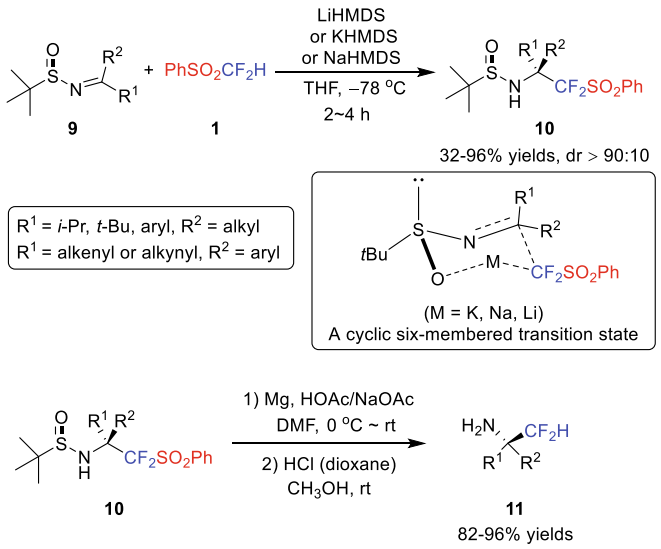
In 2014, the [3 + 2] cycloaddition reaction involving (phenylsulfonyl)difluoromethylated *N-tert*-butanesulfinyl ketimine (**15**) and benzyne was reported (Scheme 4) [12]. This reaction was facilitated by the presence of the electron-withdrawing $PhSO_2CF_2$ group in imine **15**. Furthermore, the phenylsulfonyl group could be removed by the treatment of Mg^0 under acidic conditions.

In 2006, it was reported that nucleophilic (phenylsulfonyl)difluoromethylation of epoxides with $PhSO_2CF_2H$ was unsuccessful (Scheme 5A) [13a]. Later, it was found that the pre-coordination of $BF_3{\cdot}Et_2O$ with $PhSO_2CF_2H$ and an epoxide, and the subsequent deprotonation of $PhSO_2CF_2H$ enabled the nucleophilic attack of $PhSO_2CF_2^-$ to the activated epoxides (Scheme 5B) [13b]. This preorganization strategy afforded the desired product **22** with 38% yield (Scheme 5B) [13b].

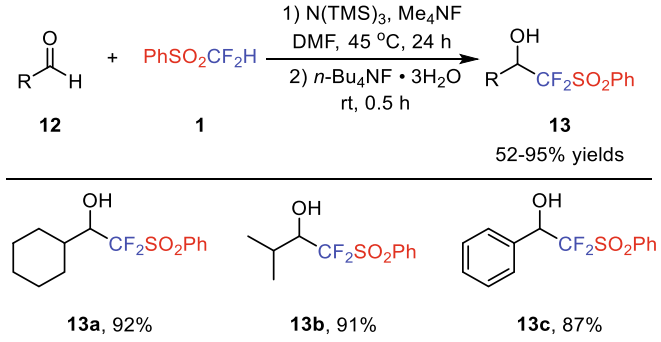
In 2016, the (phenylsulfonyl)difluoromethylation of arylboronic acids was realized by the in-situ formed "$PhSO_2CF_2Cu$" (Scheme 6) [14]. A wide range of difluromethyl arenes were obtained in moderate to good yields under air atmosphere. In 2018, a new protocol to synthesize 2,2-diaryl-1,1-difluoroethylenes was reported by palladium-catalyzed difluoroolefination of α-[(phenylsulfonyl)difluoromethyl]benzyl tosylates (**28**) and arylboronic acids (Scheme 7) [15]. The precursors **28** were generated by (phenylsulfonyl)difluoromethylation of aldehydes. Mechanistic investigations (Scheme 7, path a and path b) elaborated that the reaction was proceeded through the base-mediated dehydrosulfonylation reaction, followed by palladium-catalyzed $C(sp^2)$-$C(sp^2)$ cross-coupling reactions. This strategy was considered as a new synthetic application of $PhSO_2CF_2H$, providing an efficient method to prepare a series of 2,2-diaryl-1,1-difluoroethenes from commercially available starting materials.



Scheme 1. Transformations of difluoromethyl phenyl sulfone (**1**) and its derivatives **2**–**8**.



Scheme 2. Stereoselective difluoromethylation of *N-tert*-butane-sulfinyl ketimines.



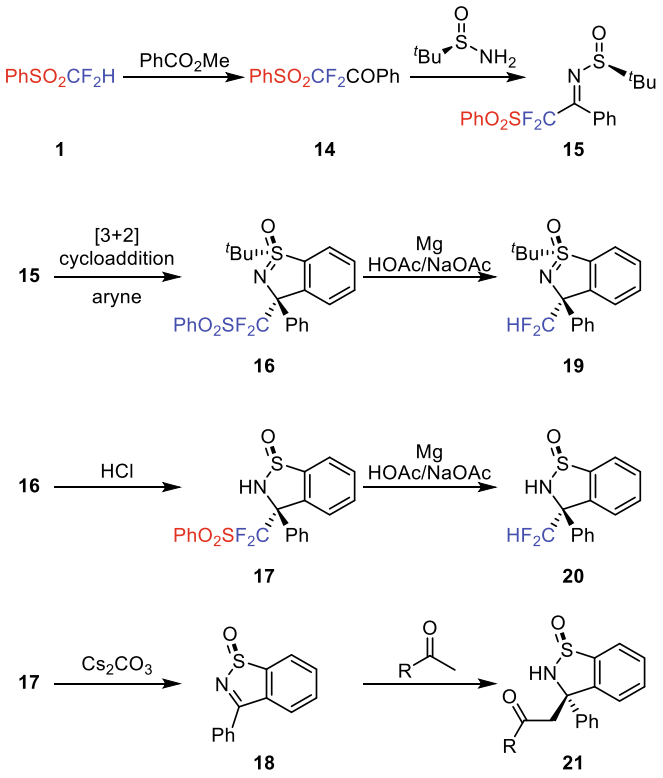
Scheme 3. Nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes.

Using $PhSO_2CF_2SiMe_3$ reagent

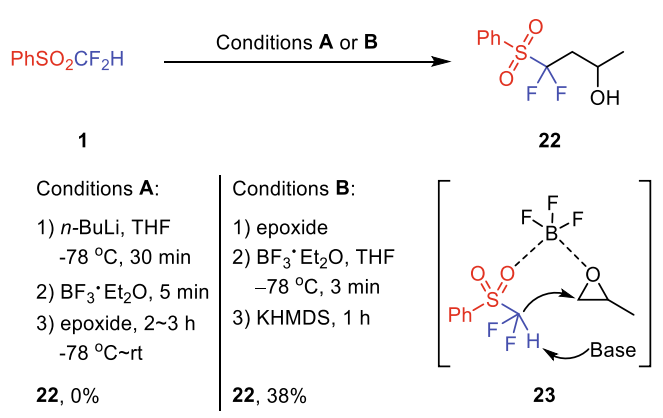
In nucleophilic difluoromethylation of electrophiles with $PhSO_2CF_2H$ [6b], strong bases such as *t*-BuOK and LiHMDS were required. Therefore, $PhSO_2CF_2H$ is not an ideal nucleophilic difluoromethylation reagent when substrates are sensitive to bases. [(Phenylsulfonyl)difluoromethyl]trimethylsilane (**5**, $PhSO_2CF_2SiMe_3$), the synthetic equivalent of $PhSO_2CF_2^-$, provides an alternative option for nucleophilic difluoromethylation of base-sensitive substrates.

In 2010, a new method for indirect preparation of *gem*-difluoroalkenes under the neutral reaction conditions via nucleophilic fluoroalkylation of alkyl iodides or allyl bromides was developed (Scheme 8) [16]. The *gem*-difluoroalkenes could be further converted into trifluoromethyl compounds (Scheme 8) [16].

In 2011, the "$PhSO_2CF_2Cu$" species was prepared from $PhSO_2CF_2SiMe_3$/CuI/CsF in DMF for the first time (Scheme 9) [17]. "$PhSO_2CF_2Cu$" was found to smoothly undergo cross-coupling reaction with propargyl chlorides or alkynyl halides, giving $PhSO_2CF_2$-containing allenes and alkynes, respectively. Compound **36** was desulfonylated to give difluoromethylated product **39** by using Mg/$HgCl_2$ system. Furthermore, compound **36a** was used as a nucleophilic fluoroalkylating agent to react with 4-methoxybenzaldehyde, giving **40** in 65% yield. It was found that $PhSO_2CF_2Cu$/CuI/DMF system could undergo oxidative coupling reaction to give $PhSO_2CF_2I$ (**37**) when air was present. A similar oxidative chlorination reaction occurred and $PhSO_2CF_2Cl$ (**38**) was obtained when $CuCl_2$ was used instead of CuI (Scheme 9) [17].



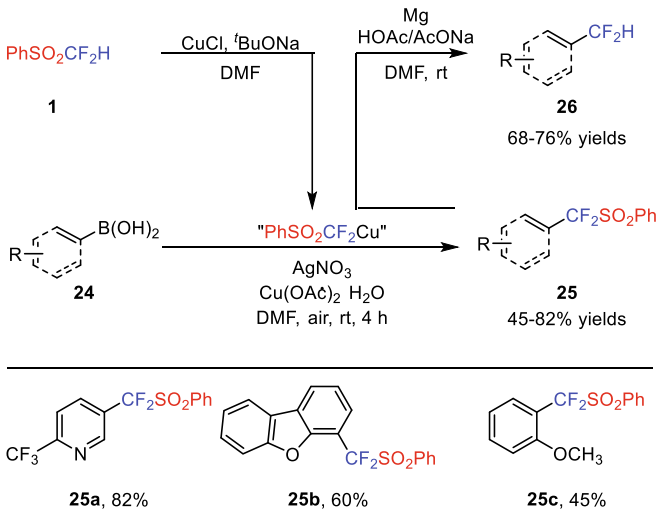
Scheme 4. Applications of $PhSO_2CF_2H$ in [3 + 2] cycloaddition reaction between ketimine and benzyne.



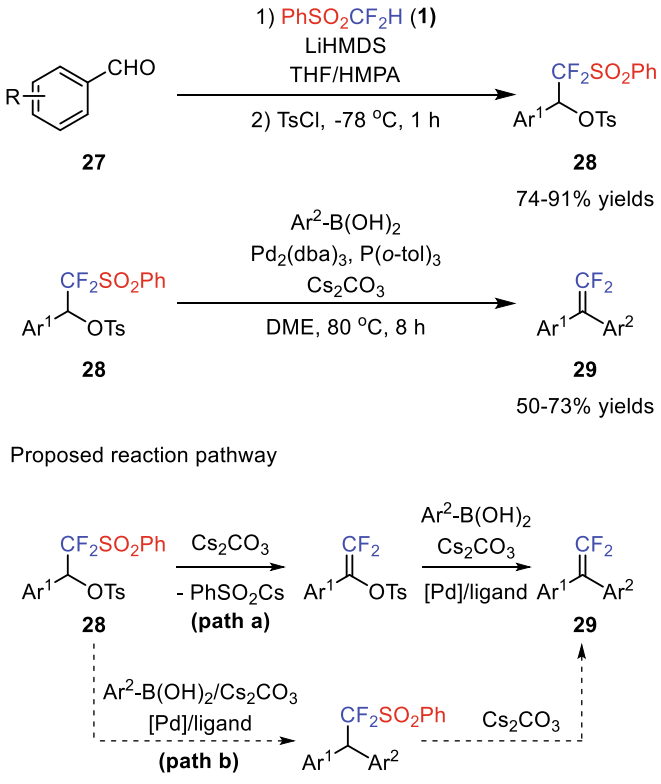
Scheme 5. Nucleophilic (phenylsulfonyl)difluoromethylation of epoxides.

In 2012, nucleophilic (phenylsulfonyl)difluoromethylation of iminium salts [prepared from quinoline derivatives, cyclic imines and *p*-methoxybenzyl bromide (PMBBr) or methyl triflate (MeOTf)] with $PhSO_2CF_2SiMe_3$ (**5**) was reported (Scheme 10) [18]. This work expanded the synthetic application of sulfur-based fluoroalkylsilanes and provided a new approach to prepare a series of nitrogen-containing heterocyclic compounds [18].

At the same year, a new protocol was developed to synthesize difluoromethylated tertiary amines by nucleophilic difluoromethylation of activated *N,N*-acetals (**47**) (Scheme 11) [19]. Iminium salts were in-situ formed with the assistance of Brønsted acid, which was the key factor to efficiently react with $PhSO_2CF_2SiMe_3$ reagent (Scheme 11) [19].



Scheme 6. Cu-mediated (phenylsulfonyl)difluoromethylation of arylboronic acids.

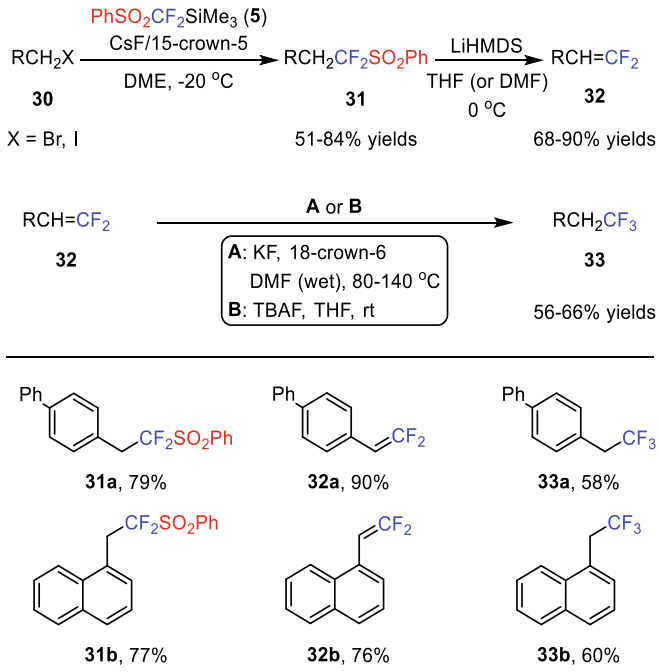


Scheme 7. Synthesis of 2,2-diaryl-1,1-difluoroethylenes.

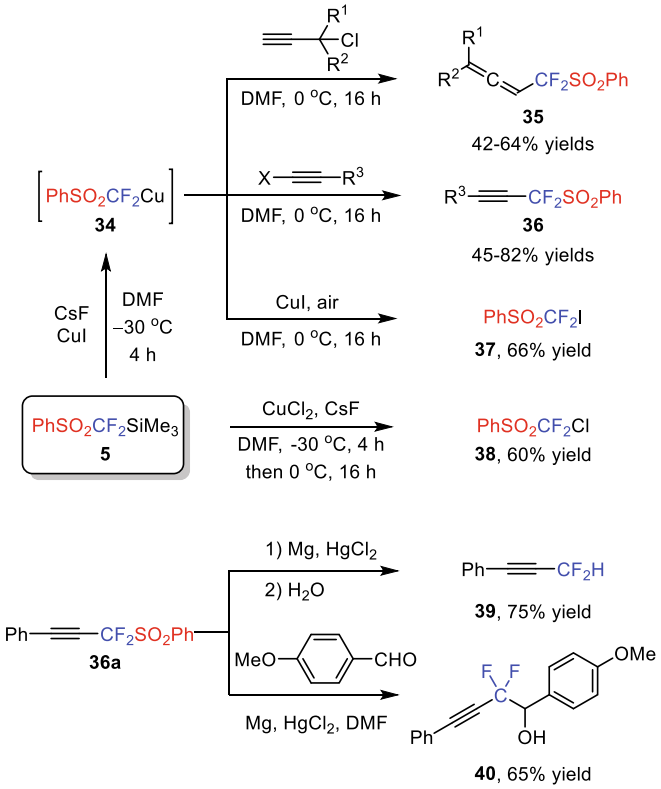
Meanwhile, Dilman and Hu reported nucleophilic difluoroalkylation of imines or enamines with α-phenylthio-, α-(phenylsulfonyl)- and α-diethylphosphoryl-substituted difluoromethylsilanes [20]. The results of the reactions between imines (or enamines) and $PhSO_2CF_2SiMe_3$ (**5**) are shown in Scheme 12.

In 2013, Dilman and co-workers reported one example of the reaction between $PhSO_2CF_2SiMe_3$ (**5**) and pinacolborane **53**, in which fluorine-substituted pinacolborane (**54**) was obtained in 55% yield (Scheme 13) [21].

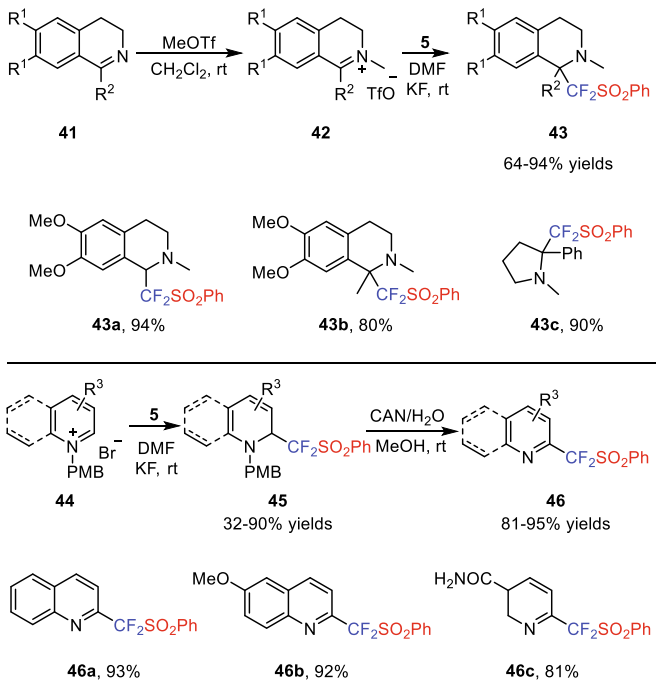
In addition, $PhSO_2CF_2SiMe_3$ (**5**) could be further transformed into another bench-stable (benzenesulfonyl)difluoromethane-sulfonamide in the presence of diethylaminosulfurtrifluoride (DAST) [22a]. This reagent could be applied in electrophilic aromatic substitution of arenes and electrophilic addition of alkenes or alkynes for the synthesis of fluoroalkylthiolated compounds [22b].



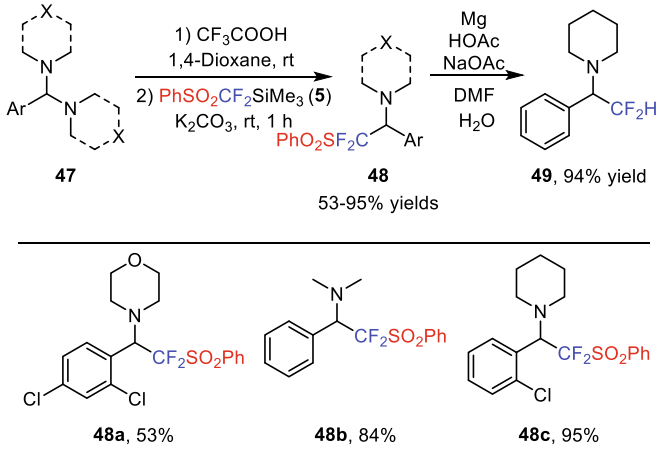
Scheme 8. Nucleophilic (phenylsulfonyl)difluoromethylation of **30** under neutral reaction conditions.



Scheme 9. Copper-mediated (phenylsulfonyl)difluoromethylation with $PhSO_2CF_2SiMe_3$ reagent.



Scheme 10. (Phenylsulfonyl)difluoromethylation of inactive imines.



Scheme 11. Nucleophilic difluoromethylation of activated acetals.

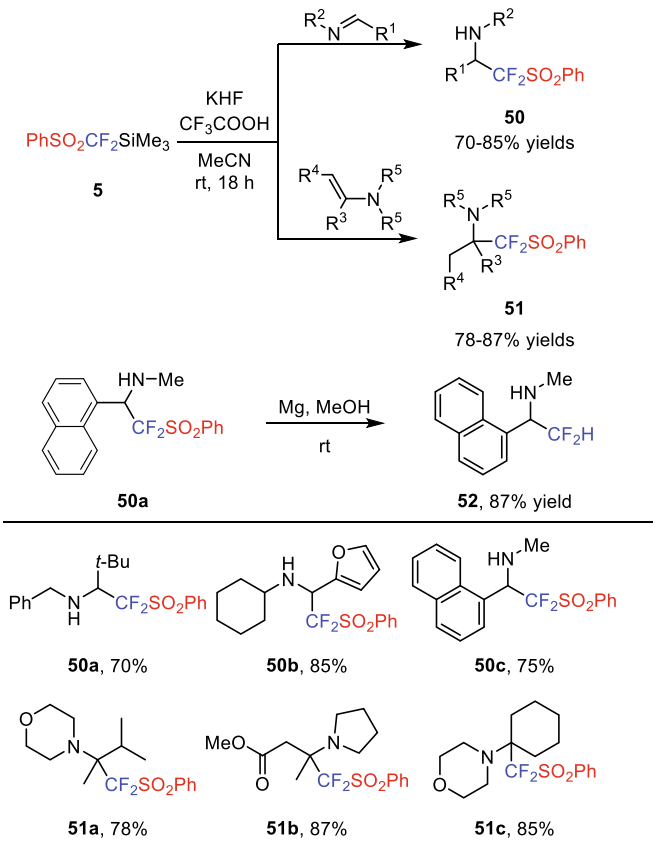
Using $PhSO_2CF_2COOK$ reagent

In 2018, it was reported that $PhSO_2CF_2COOK$ and aldehydes could undergo decarboxylative addition reaction without the use of transition metals and ligands (Scheme 14) [23]. This approach tolerated a variety of aldehydes under mild conditions, providing a simple and effective method to synthesize various difluoromethylated carbinols. In these reactions, no difluoroolefination products were observed.

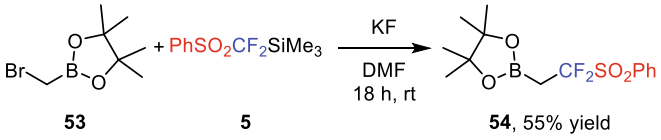
Electrophilic (phenylsulfonyl)difluoromethylation reactions

Using hypervalent iodine(III)-CF_2SO_2Ph reagent

In 2008, (phenylsulfonyl)difluoromethylated hypervalent iodine salt **7** was developed as an electrophilic (phenylsulfonyl)difluoromethylation reagent, which was able to react with S- and



Scheme 12. Difluoroalkylation of imines or enamines with $PhSO_2CF_2SiMe_3$.

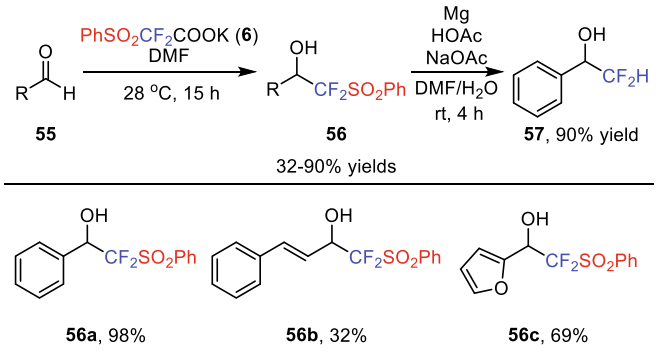


Scheme 13. Nucleophilic fluoroalkylation of pinacolborane **53**.

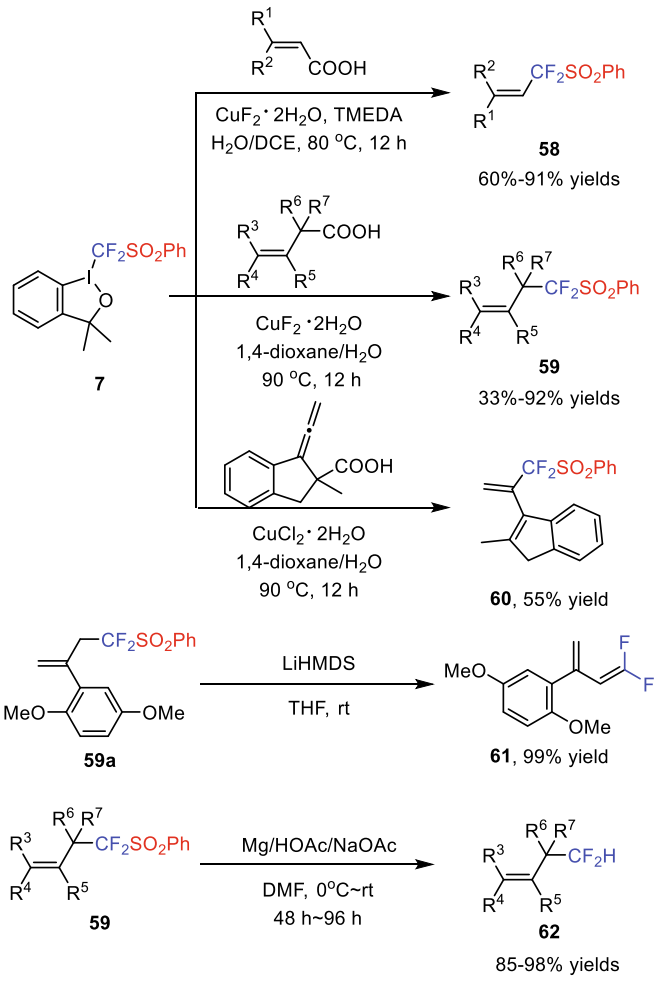
O-nucleophiles [24a]. In 2012, it was discovered that hypervalent iodine salt **7** could undergo decarboxylative (phenylsulfonyl)difluoromethylation with α,β- or β,γ-unsaturated carboxylic acids [24b,c]. Catalytic amount of copper salt was added as Lewis acid to both enhance the electrophilicity of **7** and promote the decarboxylation of the α,β- or β,γ-unsaturated carboxylic acids. The (phenylsulfonyl)difluoromethyl group in the products could be further transformed into difluoromethylidene (=CF_2) and difluoromethyl (CF_2H) groups (Scheme 15).

Using S-(phenylsulfonyl)difluoromethyl sulfonium salts

In 2014, Shibata and co-workers developed *S*-[(phenylsulfonyl)difluoromethyl]sulfonium salt **8** as a new electrophilic difluoromethylation reagent. Reagent **8** was effective in the difluoromethylation of sp^3 C-nucleophiles. Various β-ketoesters and 1,1-dicyanoalkenes could react with **8** to give C-difluoromethylated products in high yields under the mild reaction conditions (Scheme 16) [25]. In particular, there was no *O*-difluoromethylation products formed in the reactions with β-ketoesters. However, reagent **8** was not efficient in (phenylsulfonyl)difluoromethylation of acyclic β-ketoesters and 1,3-dicarbonyl substrates.



Scheme 14. Decarboxylative addition of $PhSO_2CF_2COOK$ to aldehydes.

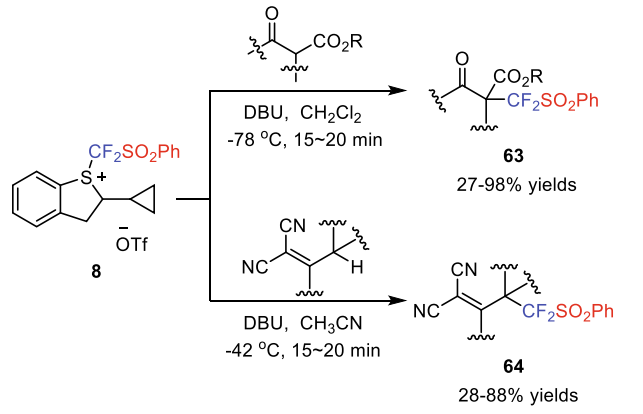


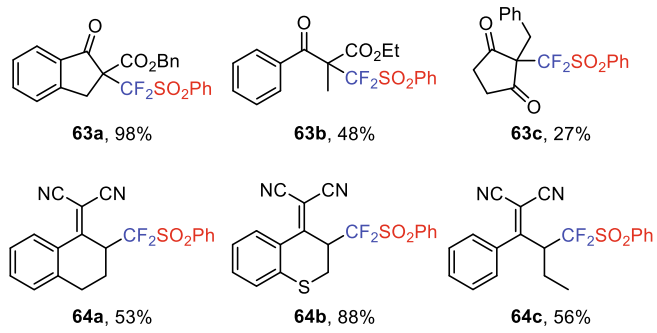
Scheme 15. Applications of hypervalent iodine(III)-CF_2SO_2Ph reagent.

Radical (phenylsulfonyl)difluoromethylation reactions

Using $PhSO_2CF_2H$ reagent

In 2016, the synthetic application of $PhSO_2CF_2H$ (**1**) as a radical fluoroalkylation reagent for isocyanides was reported for the first time under the transition-metal-free conditions (Scheme 17) [26a]. Notably, $PhSO_2CF_2H$ could produce $PhSO_2CF_2$ radical in the presence of $PhI(OAc)_2$, which enabled a facile method for the synthesis of desired products **65**. On the basis of this work, the substitution reaction between difluoroalkyl sulfones **65** and O- or C-nucleophiles (the phenylsulfonyl group as a leaving group), provides new carbon–heteroatom and carbon–carbon bond formation methods [26b].





Scheme 16. Electrophilic (phenylsulfonyl)difluoromethylation of C-nucleophiles.

Using $PhSO_2CF_2Br$ reagent

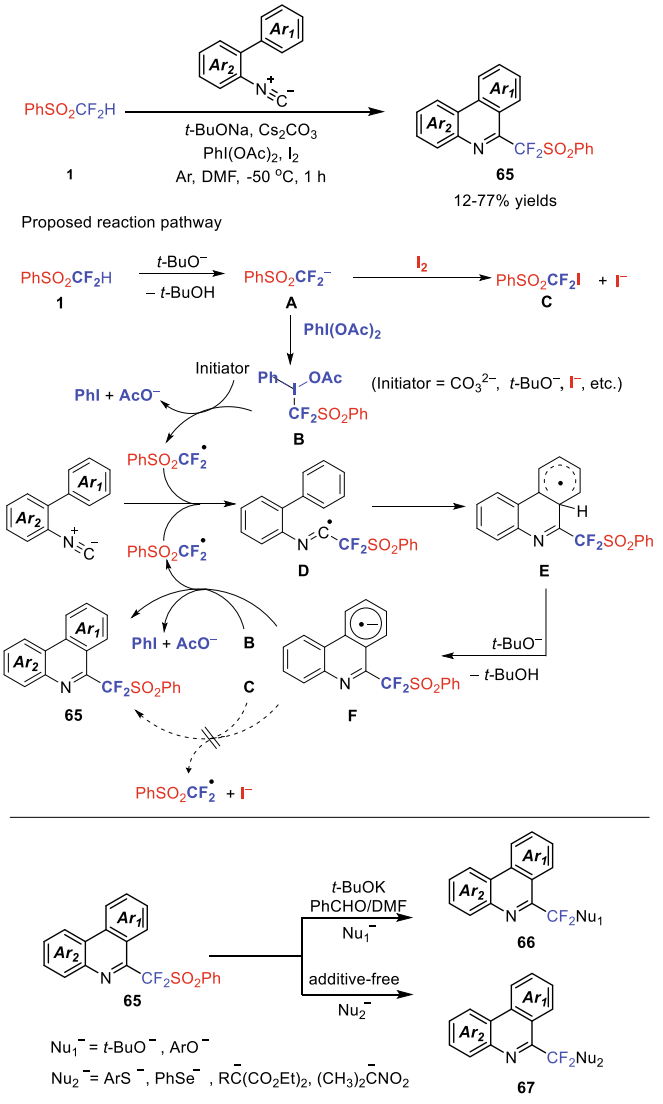
In 2015, it was reported that $PhSO_2CF_2Br$ (**3**) could be reduced by the excited photocatalyst *fac*-Ir(ppy)$_3$* to generate fluoroalkyl radical ($PhSO_2CF_2\cdot$), which was captured by vinyl isocyanide to form *ortho*-fluoroalkylated pyridines under visible light irradiation (Scheme 18) [27].

In 2016, Hashmi reported the first gold-catalyzed photoredox C (sp^2)-H difluoroalkylation of hydrazone (**70**) by using $PhSO_2CF_2Br$ reagent (Scheme 19) [28]. The EPR (electron paramagnetic resonance) spin trapping experiments showed that this reaction involved difluoroalkyl radical intermediates.

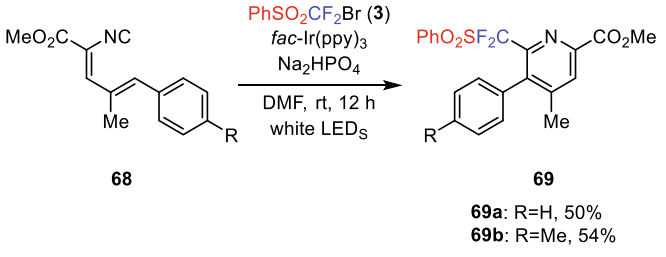
In recent years, carbon-difluoroalkylation of unactivated olefins was developed based on the combination of intramolecular functional group migration and visible light photocatalysis (Scheme 20). A series of functional groups including cyano, heteroaryl, imino, formyl and alkynyl showed excellent ability of migration. The combination of functional group migration and photo-redox catalysis opened up a new way for the radical-mediated difunctionalization of unactivated olefins [29,30].

Using $PhSO_2CF_2I$ reagent

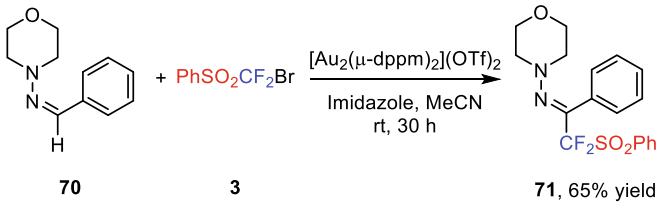
In 2007, Hu group reported the first free radical (phenylsulfonyl)difluoromethylation reaction with alkenes by using $PhSO_2CF_2I$ (**4**) [6b]. Wang and coworkers used $PhSO_2CF_2I$ (**4**) as a good precursor to form (phenylsulfonyl)difluoromethyl radical. In 2014, it was reported that the Pd(0)-catalyzed and Fe-catalyzed intramolecular aryl difluoromethylation of activated olefins with **4** for the synthesis of a variety of difluoromethylated indole derivatives (Scheme 21) [31a,31b]. A new approach was also developed to achieve the difluoromethylation of electron-rich N-, O- and S-heteroaromatics under visible-light photoredox catalysis



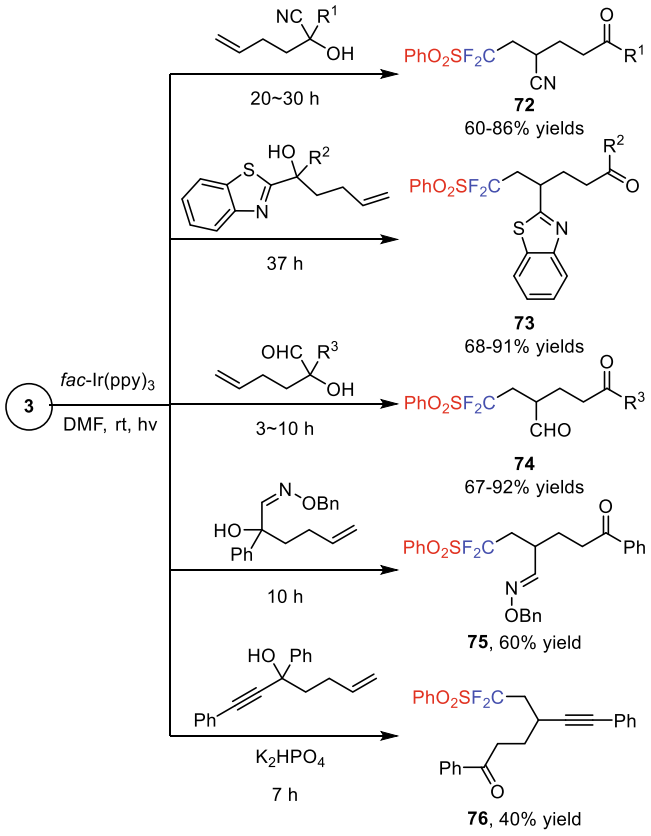
Scheme 17. Radical (phenylsulfonyl)difluoromethylation of isocyanides and their transformations.



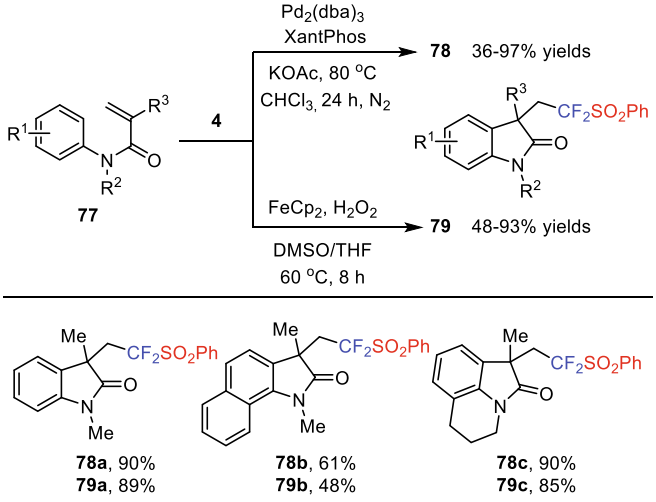
Scheme 18. Fluoroalkyl radicals generated from $PhSO_2CF_2Br$.



Scheme 19. Gold-catalyzed photoredox difluoroalkylation of hydrazine.



Scheme 20. Carbon-difluoroalkylation of unactivated olefins.

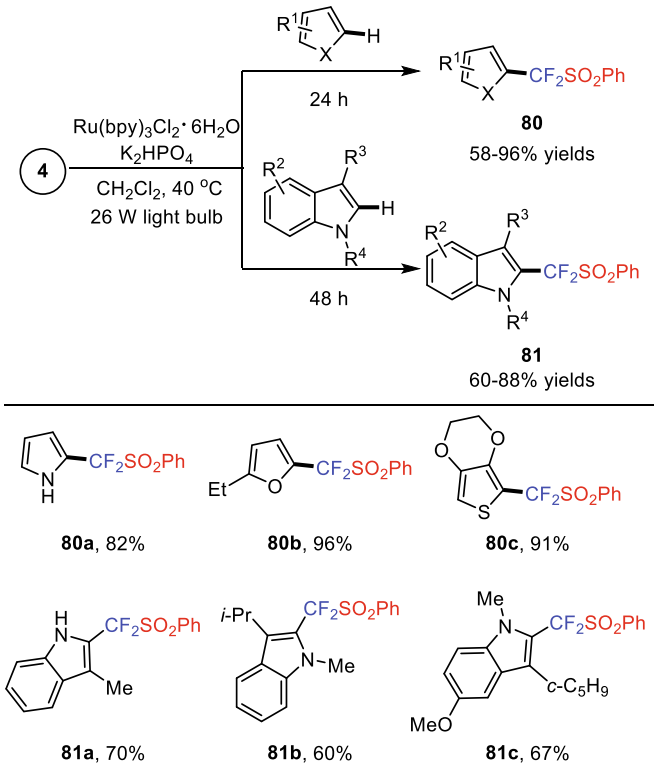


Scheme 21. Transition-metal-catalyzed intramolecular aryl (phenylsulfonyl)difluoromethylation of activated olefins.

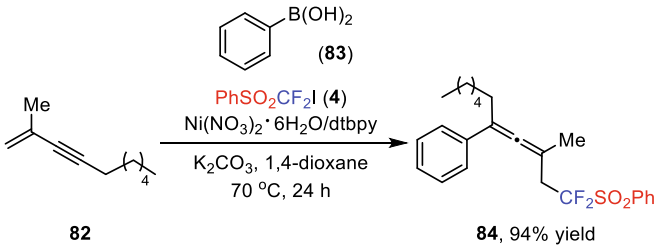
(Scheme 22) [31c]. Mechanistic investigations indicated that (phenylsulfonyl)difluoromethyl radical was involved in these reactions [6b,31a–31c].

In 2019, nickel-catalyzed 1,4-fluorocarbon alkylation reaction of 1,3-alkynes was reported, which could be used to synthesize fluoroalkyated allenes (such as **84**) (Scheme 23) [31d].

In 2020, atom-transfer radical addition (ATRA) reaction between (phenylsulfonyl)difluoromethyl iodide and styrene under visible-light promoted photoredox catalysis was reported (Scheme 24) [31e]. Surprisingly, ATRA and Heck reactions could be tuned by changing the organic or inorganic base in the



Scheme 22. Difluoromethylation of electron-rich N-, O- and S-heteroaromatics.



Scheme 23. Nickel-catalyzed 1,4-fluorocarbon alkylation reaction of 1,3-alkyne.

progress. This method provided a new solution for the difunctionalization of olefins.

Others have also studied the reactivity of $PhSO_2CF_2I$. In 2015, Mai group provided an example to construct fluorine-containing 3,3-disubstituted oxindole **89** by fluorinating/cyclization of activated olefin **88** without the metal catalysis (Scheme 25) [32]. It should be noted that this reaction was promoted by the introduction of a simple reducing agent under the metal-free conditions.

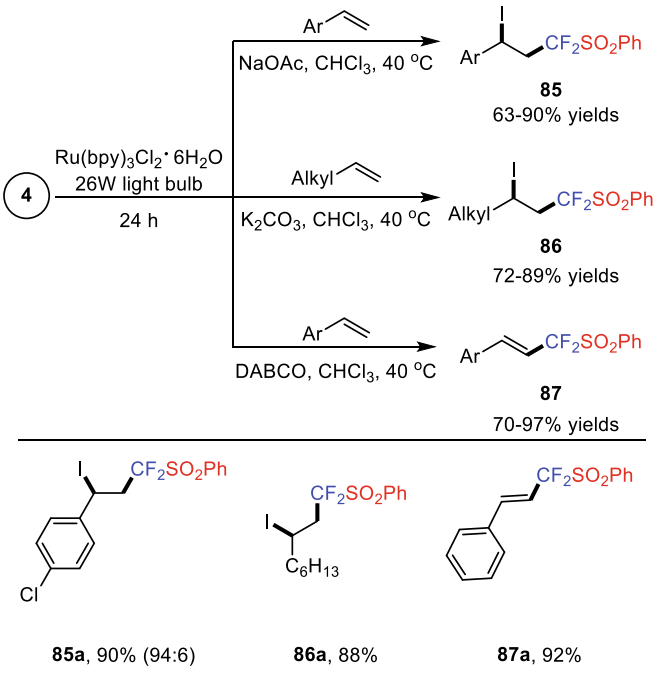
In 2016, a highly selective C3 difluoroalkylation of 2-pyridone (**90**) under visible light-promoted $Ir(ppy)_3$ photoredox catalysis was developed (Scheme 26) [33]. The introduction of $Na_2S_2O_3$ in the reaction was the key to facilitate direct C3 fluoroalkylation of *N*-methyl 2-pyridone with $PhSO_2CF_2I$ (**4**).

In 2017, Fu investigated visible light-promoted photoredox catalytic regioselective (phenylsulfonyl)difluoromethylation of imidazo[1,2-*a*]pyridine and benzo[*d*]-imidazo-[2,1-*b*]thiazole, which was supplemental to Wang's work (Scheme 27) [34].

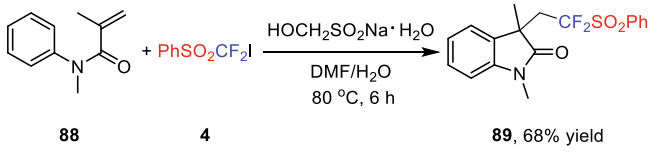
Difluorocarbene reactions

Using $PhSO_2CF_2Cl$ reagent

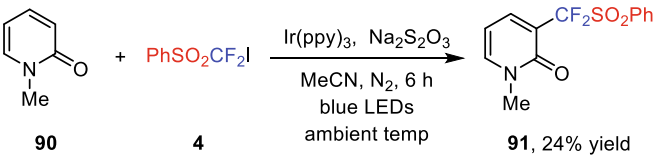
In 2007, the Hu group reported that chlorodifluoromethyl phenylsulfone ($PhSO_2CF_2Cl$, **2**) could be applied as a difluorocarbene reagent in *O*- and *N*-difluoromethylation [6b]. Later on, the different reactivities of chlorodifluoromethyl aryl ketone ($ArCOCF_2Cl$) and chlorodifluoromethyl aryl sulfone ($ArSO_2CF_2Cl$) as difluorocarbene precursors in O-difluoromethylation reaction were investigated (Scheme 28) [35]. It was found that *p*-chlorophenyl chlorodifluoromethyl sulfone and *p*-nitrophenyl chlorodifluoromethyl sulfone were effective difluorocarbene reagents. Furthermore, *p*-chlorophenyl chlorodifluoromethyl sulfone was also used for *N*-difluoromethylation of different *N*-heterocyclic compounds.



Scheme 24. Visible light-promoted ATRA and Heck reactions of $PhSO_2CF_2I$.



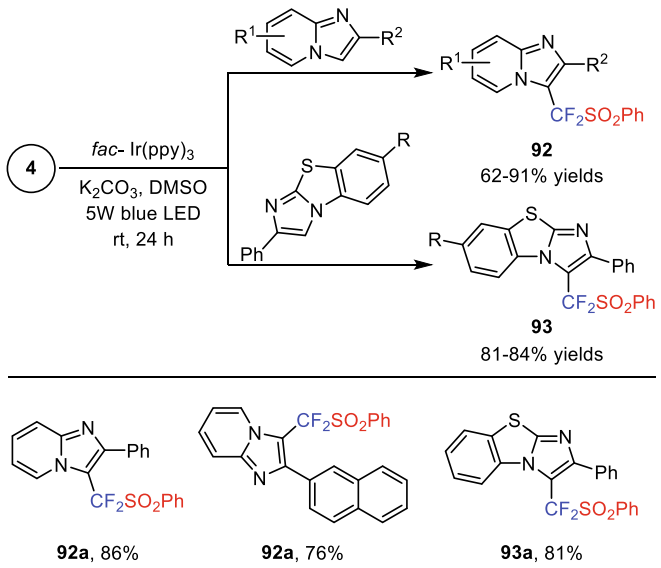
Scheme 25. Fluoroalkylative cyclization of activated olefins.



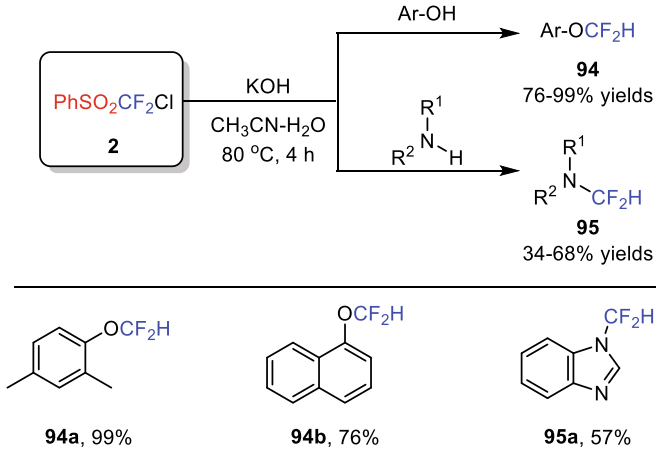
Scheme 26. Selective C3 difluoroalkylation of 2-pyridone.

Transition-metal-mediated (phenylsulfonyl) difluoromethylation reactions

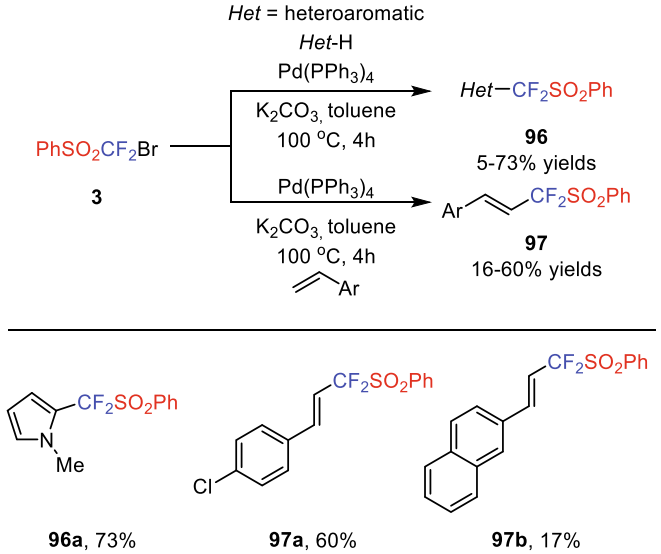
In 2010, Pd-catalyzed Heck-type reactions between [(bromodifluoromethyl)sulfonyl]benzene (**3**) and heteroaromatic compounds or styrene derivatives were reported, giving α-heteroaryl- or α-alkenyl α,α-difluoromethyl phenyl sulfones (Scheme 29) [36]. The strong electron-withdrawing ability and coordination (with



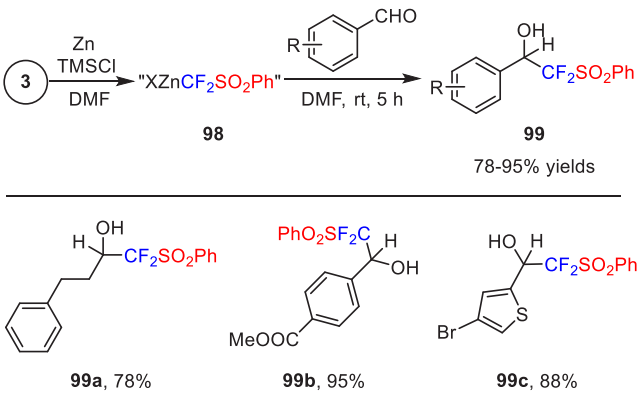
Scheme 27. Visible light-catalyzed regioselective (phenylsulfonyl) difluoromethylation.



Scheme 28. *O*-, *N*-difluoromethylation reactions with reagent **2**.



Scheme 29. Pd-catalyzed Heck-type reaction with $PhSO_2CF_2Br$.



Scheme 30. Nucleophilic (phenylsulfonyl)difluoromethylation of aldehydes with organometallic reagents.

lone pairs of electrons) of the sulfonyl group could stabilize the reaction intermediates, which might play an important role in the coupling reactions.

In 2016, the Hu group developed a nucleophilic difluoromethylation of aldehydes by using [(phenylsulfonyl)difluoromethyl]zinc ("$BrZnCF_2SO_2Ph$") and [(phenylsulfonyl)difluoromethyl]cadmium ("$BrCdCF_2SO_2Ph$") reagents (Scheme 30) [37]. The phenylsulfonyl group had great advantages in improving the stability of the difluoromethyl anion and activating the corresponding difluoromethylmetal reagents.

Conclusions

In this digest article, we have summarized recent advance in the (phenylsulfonyl)difluoromethylation reactions since 2009. Five modes of difluoroalkylation reactions have been classified: nucleophilic (phenylsulfonyl)difluoromethylation, electrophilic (phenylsulfonyl)difluoromethylation, radical (phenylsulfonyl)difluoromethylation, difluorocarbene reaction, and transition-metal mediated (phenylsulfonyl)difluoromethylation reactions. On the basis of these methods, the CF_2 group can be site-selectively introduced into organic molecules under mild reaction conditions to give difluoromethyl-, difluoromethylene-, and difluoromethylidene-containing organic molecules. On the other hand, the direct difluoromethylation using difluoromethyl phenyl sulfone in one-pot has been less studied. We believe that this digest article will inspire further development of innovative methods for the difluoroalkylation using difluoromethyl phenyl sulfone and its derivatives. Furthermore, difluoromethyl phenyl sulfone and its derivatives will find more applications in the synthesis of organofluorine compounds. Notably, the wide investigation of difluoromethyl phenyl sulfone and its derivatives was also greatly promoted the chemistry of difluoromethyl (hetero)aryl sulfone [38].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (2016YFB0101200), the National Natural Science Foundation of China (21632009), the Key Programs of the Chinese Academy of Sciences (KGZD-EW-T08), the Key

Research Program of Frontier Sciences of CAS (QYZDJ-SSW-SLH049), and Shanghai Science and Technology Program (18JC1410601).

References

[1] (a) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320;
(b) K. Müller, C. Faeh, F. Diederich, Science 2007 (1881) 317;
(c) J. Wang, M. Sanchez-Rosello, J.L. Acena, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Chem. Rev. 114 (2014) 2432;
(d) W.K. Hagmann, J. Med. Chem. 51 (2008) 4359;
(e) N.A. Meanwell, J. Med. Chem. 54 (2011) 2529;
(f) J. Wang, M. Sanchez-Rosello, J.L. Acena, C. del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Chem. Rev. 114 (2014) 2432;
(g) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J.L. Acena, V.A. Soloshonok, K. Izawa, H. Liu, Chem. Rev. 116 (2016) 422;
(h) Q. Liu, C. Ni, J. Hu, Natl. Sci. Rev. 4 (2017) 303;
(i) H. Mei, J. Han, S. Fustero, M. Medio-Simon, D.M. Sedgwick, C. Santi, R. Ruzziconi, V.A. Soloshonok, Chem. Eur. J. 25 (2019) 840.

[2] (a) D. O'Hagan, Chem. Soc. Rev. 37 (2008) 308;
(b) L.E. Zimmer, C. Sparr, R. Gilmour, Angew. Chem. Int. Ed. 50 (2011) 11860.

[3] (a) T. Furuya, A.S. Kamlet, T. Ritter, Nature 473 (2011) 470;
(b) O.A. Tomashenko, V.V. Grushin, Chem. Rev. 111 (2011) 4475;
(c) T. Besset, C. Schneider, D. Cahard, Angew. Chem. Int. Ed. 51 (2012) 5048;
(d) T. Liang, C.N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 52 (2013) 8214;
(e) S. Caron, Org. Process Res. Dev. 24 (2020) 470;
(f) J. Ma, D. Cahard, Chem. Rev. 108 (2008) PR1;
(g) J. Nie, H. Guo, D. Cahard, J. Ma, Chem. Rev. 111 (2011) 455;
(h) F. Zhang, X. Wang, Y. Zhou, H. Shi, Z. Feng, J. Ma, I. Marek, Chem. Eur. J. 26 (2020) 15378.

[4] (a) J.A. Erickson, J.I. McLoughlin, J. Org. Chem. 60 (1995) 1626;
(b) C.D. Sessler, M. Rahm, S. Becker, J.M. Goldberg, F. Wang, S.J. Lippard, J. Am. Chem. Soc. 139 (2017) 9325;
(c) Y. Zafrani, D. Yeffet, G. Sod-Moriah, A. Berliner, D. Amir, D. Marciano, E. Gershonov, S. Saphier, J. Med. Chem. 60 (2017) 797.

[5] (a) C. Ni, L. Zhu, J. Hu, Acta Chim. Sinica 73 (2015) 90;
(b) M.-C. Belhomme, T. Besset, T. Poisson, X. Pannecoucke, Chem. Eur. J. 21 (2015) 12836;
(c) J. Rong, C. Ni, J. Hu, J. Asian, Org. Chem. 6 (2017) 139;
(d) D.E. Yerien, S. Barata-Vallejo, A. Postigo, Chem. Eur. J. 23 (2017) 14676.

[6] (a) G.K.S. Prakash, J. Hu, Acc. Chem. Res. 40 (2007) 921;
(b) J. Hu, J. Fluorine Chem. 130 (2009) 1130;
(c) C. Ni, M. Hu, J. Hu, Chem. Rev. 115 (2015) 765;
(d) C. Ni, J. Hu, Chem. Soc. Rev. 45 (2016) 5441;
(e) J. Hu, W. Zhang, F. Wang, Chem. Commun. (2009) 7465;
(f) W. Zhang, C. Ni, J. Hu, Top. Curr. Chem. 308 (2012) 25;
(g) B. Chen, D.A. Vicic, Top. Organomet. Chem. 52 (2014) 113;
(h) Y. Lu, C. Liu, Q. Chen, Curr. Org Chem. 19 (2015) 1638;
(i) D. Dong, H. Yang, J. Shi, W. Si, Z. Wang, X. Xu, Org. Chem. Front. 7 (2020) 2538.

[7] J. Hine, J.J. Porter, J. Am. Chem. Soc. 82 (1960) 6178.

[8] (a) G.P. Stahly, J. Fluorine Chem. 43 (1989) 53;
(b) J.S. Sabol, J.R. McCarthy, Tetrahedron Lett. 33 (1992) 3101;
(c) D.L. Boger, T.J. Jenkins, J. Am. Chem. Soc. 118 (1996) 8860;
(d) P.J. Serafifinowski, C.J. Barnes, Synthesis. (1997) 225.

[9] J. Liu, J. Hu, Chem. Eur. J. 16 (2010) 11443.

[10] M. Hu, B. Gao, C. Ni, L. Zhang, J. Hu, J. Fluorine Chem. 155 (2013) 52.

[11] (a) S. Large, N. Roques, B.R. Langlois, J. Org. Chem. 65 (2000) 8848;
(b) T. Billard, S. Bruns, B.R. Langlois, Org. Lett. 14 (2000) 2101.

[12] W. Ye, L. Zhang, C. Ni, J. Rong, J. Hu, Chem. Commun. 50 (2014) 10596.

[13] (a) C. Ni, Y. Li, J. Hu, J. Org. Chem. 71 (2006) 6829;
(b) X. Shen, Q. Liu, T. Luo, J. Hu, Chem. Eur. J. 20 (2014) 6795.

[14] X. Li, J. Zhao, M. Hu, D. Chen, C. Ni, L. Wang, J. Hu, Chem. Commun. 52 (2016) 3657.

[15] R. Zhang, C. Ni, Y. Zhao, J. Hu, Tetrahedron. 74 (2018) 5295.

[16] L. Zhu, Y. Li, Y. Zhao, J. Hu, Tetrahedron Lett. 51 (2010) 6150.

[17] J. Zhu, F. Wang, W. Huang, Y. Zhao, W. Ye, J. Hu, Synlett. 7 (2011) 899.

[18] W. Huang, C. Ni, Y. Zhao, W. Zhang, A.D. Dilman, J. Hu, Tetrahedron. 68 (2012) 5137.

[19] W. Huang, C. Ni, Y. Zhao, B. Gao, J. Hu, J. Fluorine Chem. 143 (2012) 161.

[20] M.D. Kosobokov, A.D. Dilman, M.I. Struchkova, P.A. Belyakov, J. Hu, J. Org. Chem. 77 (2012) 2080.

[21] V.V. Levin, P.K. Elkin, M.I. Struchkova, A.D. Dilman, J. Fluorine Chem. 154 (2013) 43.

[22] (a) E. Ismalaja, T. Billard, J. Fluorine Chem. 203 (2017) 215;
(b) E. Ismalaj, D.L. Bars, T. Billard, Angew. Chem. Int. Ed. 55 (2016) 4790.

[23] Y. Zhu, Z. Lei, D. Huang, B. Lian, Z. Liu, X. Hu, J. Liu, Tetrahedron Lett. 59 (2018) 3184.

[24] (a) W. Zhang, J. Zhu, J. Hu, Tetrahedron Lett. 49 (2008) 5006;
(b) Z. He, T. Luo, M. Hu, Y. Cao, J. Hu, Angew. Chem. Int. Ed. 51 (2012) 3944;
(c) Z. He, M. Hu, T. Luo, L. Li, J. Hu, Angew. Chem. Int. Ed. 51 (2012) 11545.

[25] X. Wang, G. Liu, X. Xu, N. Shibata, E. Tokunaga, N.A. Shibata, Chem. Int. Ed. (1827, 2014,) 53.

[26] (a) P. Xiao, J. Rong, C. Ni, J. Guo, X. Li, D. Chen, J. Hu, Org. Lett. 18 (2016) 5912;
(b) P. Xiao, C. Ni, W. Miao, M. Zhou, J. Hu, D. Chen, J. Hu, J. Org. Chem. 84 (2019) 8345.

[27] K. Tong, T. Zheng, Y. Zhang, S. Yu, Adv. Synth. Catal. 357 (2015) 3681.

[28] J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A.S.K. Hashmi, Angew., Chem. Int. Ed. 55 (2016) 2934.

[29] R. Ren, Z. Wu, L. Huan, C. Zhu, Adv. Synth. Catal. 359 (2017) 3052.

[30] J. Yu, D. Wang, Y. Xu, Z. Wu, C. Zhu, Adv. Synth. Catal. 360 (2018) 744.

[31] (a) J. Wang, Y. Su, F. Yin, Y. Bao, X. Zhang, Y. Xu, X. Wang, Chem. Commun. 50 (2014) 4108;
(b) J. Wang, X. Zhang, Y. Bao, Y. Xu, X. Cheng, X. Wang, Org. Biomol. Chem. 12 (2014) 5582;
(c) Y. Su, Y. Hou, F. Yin, Y. Xu, Y. Li, X. Zheng, X. Wang, Org. Lett. 16 (2014) 2958;
(d) K. Zhang, K. Bian, C. Li, J. Sheng, Y. Li, X. Wang, Angew. Chem. Int. Ed. 58 (2019) 5069;
(e) J. Sheng, K. Bian, Y. Su, G. Liao, R. Duan, C. Li, Z. Liu, X. Wang, Org. Chem. Front. 7 (2020) 617.

[32] W. Mai, B. Sun, G. Qian, J. Yuan, P. Mao, L. Yang, Y. Xiao, Tetrahedron. 71 (2015) 8416.

[33] A. Najib, S. Tabuchi, K. Hirano, M. Miura, Heterocycles. 92 (2016) 1187.

[34] G. Yin, M. Zhu, W. Fu, Heterocycl. Commun. 23 (2017) 275.

[35] F. Wang, L. Zhang, J. Zheng, J. Hu, J. Fluorine Chem. 132 (2011) 521.

[36] N. Surapanich, C. Kuhakarn, M. Pohmakotr, V. Reutrakul, Eur. J. Org. Chem. (2012) 5943.

[37] F. Jiang, C. Ni, J. Hu, J. Fluorine Chem. 198 (2017) 67.

[38] (a) X. Tao, R. Sheng, K. Bao, Y. Wang, Y. Jin, Chin. J. Org. Chem. 39 (2019) 2726;
(b) Y. Zhao, W. Huang, L. Zhu, J. Hu, Org. Lett. 12 (2010) 1444;
(c) W. Miao, Y. Zhao, C. Ni, B. Gao, W. Zhang, J. Hu, J. Am. Chem. Soc. 140 (2018) 880;
(d) R.R. Merchant, J.T. Edwards, T. Qin, M.M. Kruszyk, C. Bi, G. Che, D. Bao, W. Qiao, L. Sun, M.R. Collins, O.O. Fadeyi, G.M. Gallego, J.J. Mousseau, P. Nuhant, P. S. Baran, Science 360 (2018) 75;
(e) B. Josephson, C. Fehl, P.G. Isenegger, S. Nadal, T.H. Wright, A.W.J. Poh, B.J. Bower, A.M. Giltrap, L. Chen, C. Batchelor-McAuley, G. Roper, O. Arisa, J.B.I. Sap, A. Kawamura, A.J. Baldwin, S. Mohammed, R.G. Compton, V. Gouverneur, B.G. Davis, Nature 585 (2020) 530.