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二氟甲基杂芳基砜作为二氟烷基化试剂的应用研究进展

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摘要 氟原子以及 C—F 键的独特性使得二氟亚甲基具有特殊的性质, 作为氧原子或羰基的生物电子等排体, 其在医药、农药与材料中起着有别于其他氟烷基的重要作用. 以二氟甲基 2-吡啶基砜(胡试剂)为代表的二氟甲基杂芳基砜, 是近几年开发的新型二氟烷基化试剂, 因其具有易制备、官能团耐受性良好及对多种羰基化合物具有普遍适用性等优点而广受合成化学工作者的关注. 该类含氟试剂主要通过亲核取代反应、亲核加成反应、Julia-Kocienski 烯化反应和自由基介导的双官能团化等反应, 将二氟甲基、二氟亚甲基、二氟烯基及其他二氟烷基引入醛、酮和杂环化合物的结构中. 首次从反应类型及其应用研究的角度综述了近十年来各种二氟甲基杂芳基砜参与的含氟有机化合物的合成研究.
关键词 二氟甲基杂芳基砜; 亲核反应; Julia-Kocienski 烯化反应; 自由基双官能团化反应

Progress of Difluoromethyl Heteroaryl Sulfones as Difluoroalkylation Reagents

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Abstract Due to the uniqueness of fluorine atom and C—F bond, difluoromethylene has special properties. As a bioisostere of an oxygen or a carbonyl group, it plays an important role in medicines, pesticides and materials. Difluoromethyl heteroaryl sulfones, represented by 2-$PySO_2CF_2H$ (Hu reagent), have been developed recently as difluoromethylation reagents, and widely recognized by synthetic chemists for their ease of preparation, good functional group tolerance and universal applicability to a wide range of carbonyl compounds. Through different types of reactions such as nucleophilic substitution, nucleophilic addition, Julia-Kocienski olefination reaction, and radical-mediated difunctionalization, they introduced difluoromethyl, difluoromethylene, *gem*-difluoroalkene and other fluorine-containing groups into aldehydes, ketones, and heterocyclic compounds. For the first time, the synthesis of fluorine-containing organic compounds involved in various difluoromethyl heteroaryl sulfones in the past decade is reviewed from the perspective of reaction types and their application studies.
Keywords difluoromethyl heteroaryl sulfones; nucleophilic reaction; Julia-Kocienski olefination; radical-mediated difunctionalization

1 Introduction

The selective introduction of a fluorine atom or a fluorine-containing group into a specific portion of an organic molecule can significantly change the original physical and chemical properties and biological activities of the parent molecule, due to the unique characteristics of fluorine, such as small atomic radius, maximum electronegativity, low polarizability, and strong C—F bond.[1,2]

Among all the fluorine-containing groups, difluoromethyl (or difluoromethylene) is the most special one. It is generally believed that difluoromethyl group is similar in volume and polarity with hydroxymethyl. It can functionalize as a bioisostere of an oxygen or a carbonyl group. And it can also act as a lipophilic hydrogen bond donor better than hydroxymethyl. Therefore, difluoromethyl groups are often introduced into many biologically active molecules, such as anti-infectives, protease inhibitors,

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herbicides and so on (Figure 1).[3~6]

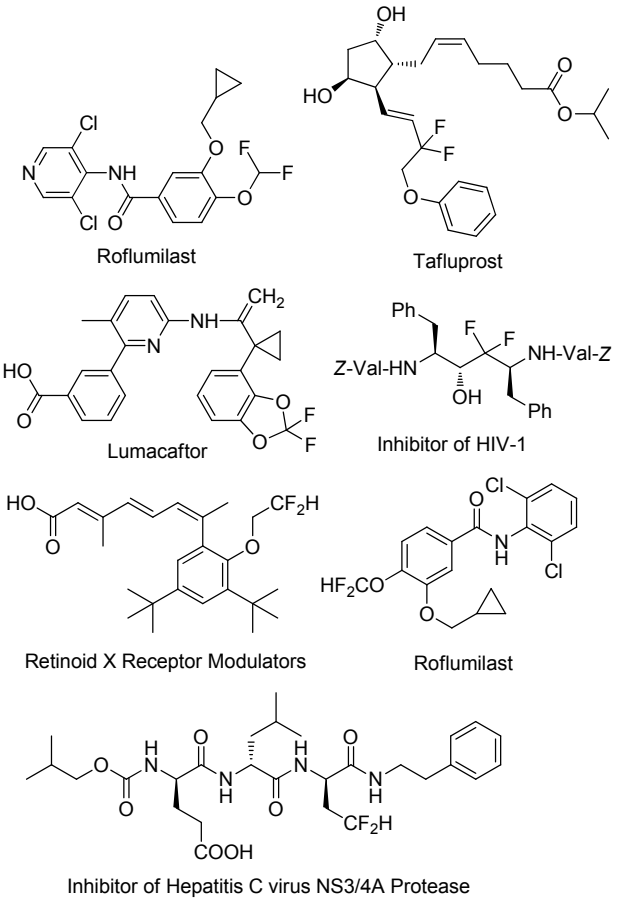


Figure 1 Biologically active molecules

Researching on difluoromethyl-containing organic compounds has become one of the most popular areas in organic chemistry. Many efforts have been focused on the development of efficient difluoromethylation reagents. Over the past decade, a variety of difluoromethyl heteroaryl sulfones have been developed and widely used by introducing difluoromethyl-containing groups into organic compounds through various types of reactions, due to their ease of preparation, good functional group tolerance and universal applicability to a wide range of carbonyl compounds. They not only facilitate the generation of the specific reactive species for fluoroalkylation, but also provide opportunities to achieve synthetic diversity.[7~10]

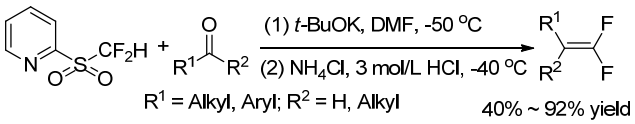
Although several reviews on the fluoroalkylating agents have been appeared,[11~13] however, to the best of our knowledge, there is no review focus specifically on the applications of difluoromethyl heteroaryl sulfones. In this paper, we aim to provide a full review on the synthetic applications of these difluoromethyl heteroaryl sulfones in recent ten years.

2 Nucleophilic reaction

2.1 Julia and Julia-Kocienski olefination reaction

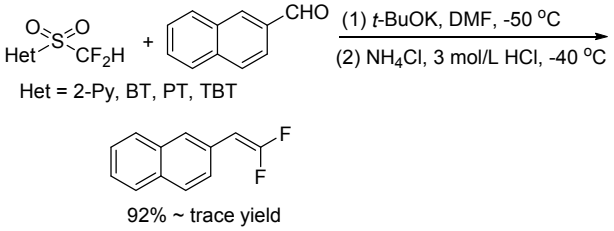
Julia-Kocienski olefination reaction is a typical cascade process that involves three sequential steps: (1) the nucleophilic addition of a sulfonyl carbanion to a carbonyl group, (2) the ipso-substitution of the addition adduct at the heteroaryl ring (also known as the Smiles rearrangement), and (3) the fragmentation of the resulting sulfinate salt to give an alkene.

In 2010, Hu group[14] reported the first Julia-Kocienski olefination reaction for the synthesis of 1,1-difluoroalkenes. Alkyl ketones, aromatic and aliphatic aldehydes were treated with heteroaryl sulfones in the presence of base, such as *t*-BuOK, then followed by the treatment with acid to result in *gem*-difluoroolefins (Scheme 1).



Scheme 1 Julia-Kocienski olefination reaction

They demonstrated that difluoromethyl 2-pyridyl sulfone (2-PySO_2CF_2H) showed higher reactivity in the difluoroolefination reaction with 2-naphthaldehyde than other heteroaryl sulfones, such as difluoromethyl 1,3-benzothiazol-2-yl sulfone (BTSO_2CF_2H), difluoromethyl 1-phenyl-1*H*-tetrazol-5-yl sulfone (PTSO_2-CF_2H), and difluoromethyl 1-*tert*-butyl-1*H*-tetrazol-5-yl sulfone (TBT-SO_2CF_2H) sulfone (Scheme 2). The yield of the reaction with BTSO_2CF_2H is 42%, while both PTSO_2CF_2H and TBTSO_2CF_2H gave almost no product.



Scheme 2 *gem*-Difluoroolefination reaction with different sulfones

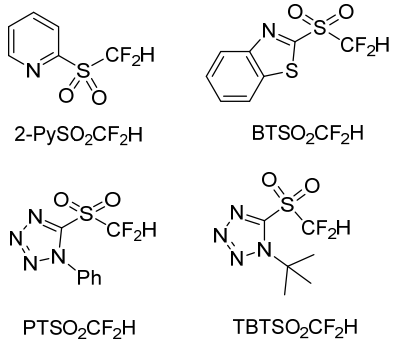
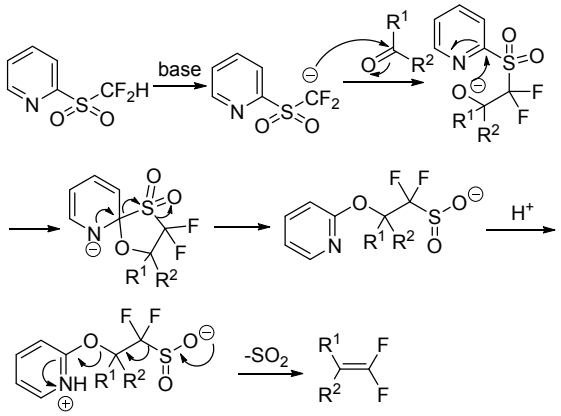


Figure 2 Difluoromethyl heteroaryl sulfones

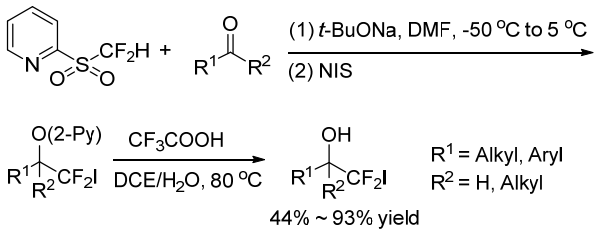
The olefination reaction involved the formation of a relatively stable difluorinated sulfinate salt (Scheme 3).

In 2012, Hu group[15] developed a formal nucleophilic iodo-, or bromo-difluoro-methylation for carbonyl com-



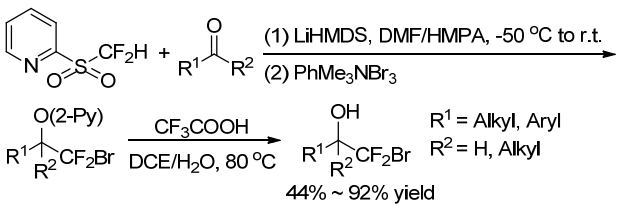
Scheme 3 Proposed mechansism of olefination reaction

pounds to obtain iodo- or bromo-difluoromethylated compounds via halogenation of the Julia-Kocienski intermediates and subsequent deprotection (Schemes 3, 4). The optimal reaction conditions for bromodifluoromethylation are using *N*,*N*-dimthylformamide (DMF) as solvent, sodium *tert*-butoxide (*t*-BuONa) as base to enhance the stability of the *in-situ* generated sulfinate intermediate, *N*-iodosuccinimide (NIS) as the iodinating reagent to inhibite the formation of the undesired difluoroalkene, and the reactant molar ratio of 2-$PySO_2CF_2H$/carbonyl compound/*t*-BuONa/NIS (n : n : n : n = 1 : 1.2 : 1.8 : 4). The reaction tolerates various substituents on the aryl aldehyde, aliphatic α,β-unsaturated aldehydes and ketones (Scheme 4).



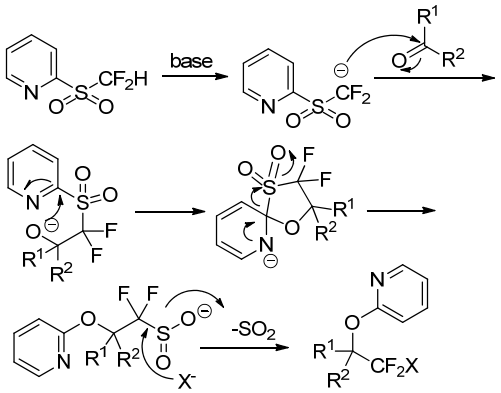
Scheme 4 Iododifluoromethlation of carbonyl compounds

By changing the base to LiHMDS, using phenyltrimethylammonium tribromide ($PhMe_3NBr_3$) as the halogenating reagent, and adjusting the reactant ratio of PY sulfone/carbonyl compound/LiHMDS/$PhMe_3NBr_3$ (n : n : n : n = 1 : 1.2 : 1.4 : 4), the bromodifluoromethylation of carbonyl compounds proceeded smoothly to afford the desired CF_2Br-containing products mostly in good yields (Scheme 5).



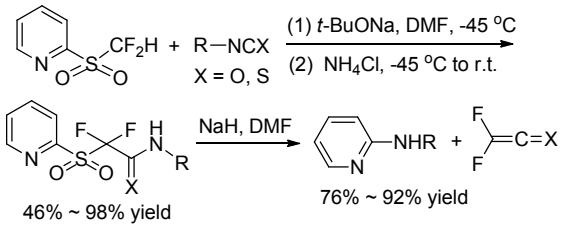
Scheme 5 Bromodifluoromethylation of carbonyl compounds

The proposed reaction mechanism of this nucleophilic halogen-difluoromethylation is shown as Scheme 6.

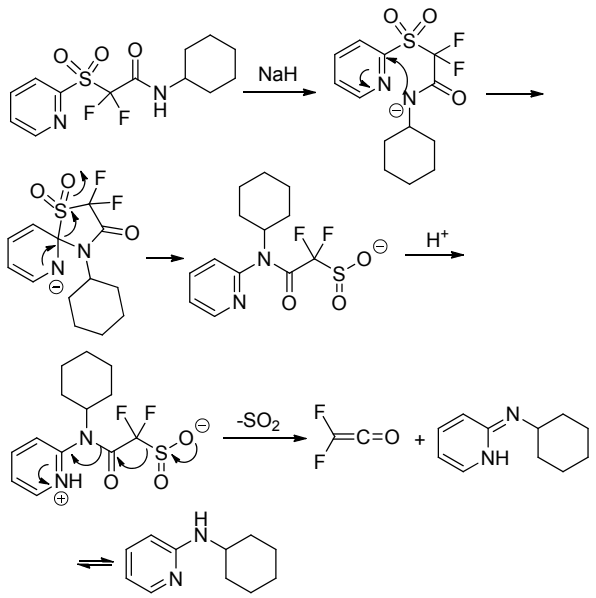


Scheme 6 Proposed mechanism of halogen-difluoromethylation

Sheng group[16] reported the first nucleophilic difluoroalkylation of isocyanates with difluoromethyl 2-pyridyl sulfone to get 2,2-difluoro-2-pyridinylsulfonylacetamides and declared that the substrate scope of this reaction was including phenyl isocyanates, phenyl thioisocyanates and aliphatic isocyanates. The addition products converted to difluoroacetamide sulfinate and iododifluoroacetamide easily in the presence of sodium hydride (NaH) (Scheme 7). A proposed mechanism showed that the reaction experienced an intramolecular Julia-Kocienski reaction (Scheme 8).

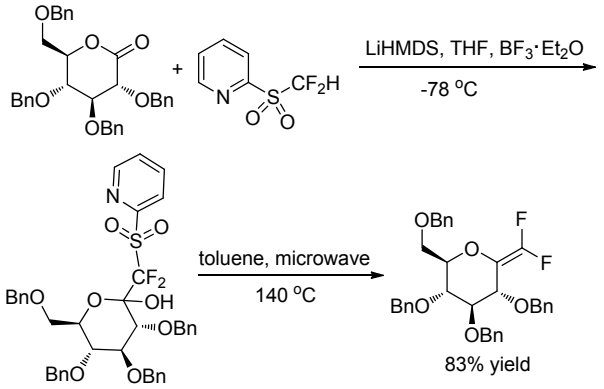


Scheme 7 Julia-Kocienski reaction of isocyanates

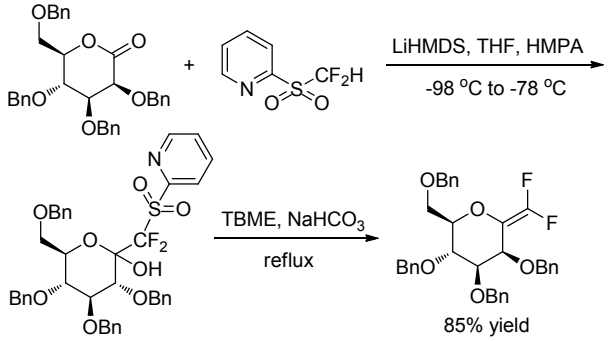


Scheme 8 Proposed mechanism of Julia-Kocienski reaction of isocyanates

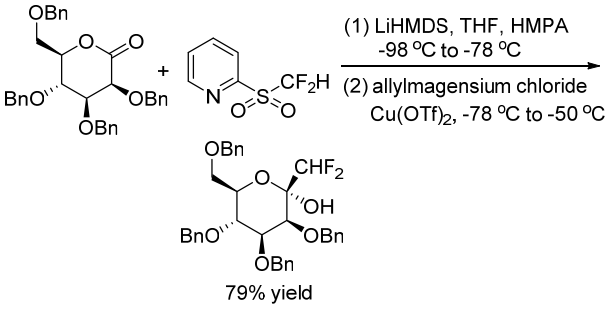
Gueyrard and Shen group[17,18] reported the *gem*-difluoroolefination of benzylated sugar-derived lactones by a modified Julia olefination with difluoromethyl-2-pyridyl sulfone separately (Schemes 9, 10). The reaction was shown to proceed efficiently in both pyranose (*D*-gluco, *D*-galacto, *D*-manno, 2-deoxy-*D*-gluco) and furanose (*D*-arabino) sugar series. Meanwhile, Shen group[18] carried out a one-pot reduction with Grignard reagent of sugar lactones for the preparation of fluorinated 2-ketoses (Scheme 11).



Scheme 9 Julia-Kocienski reaction of glycal

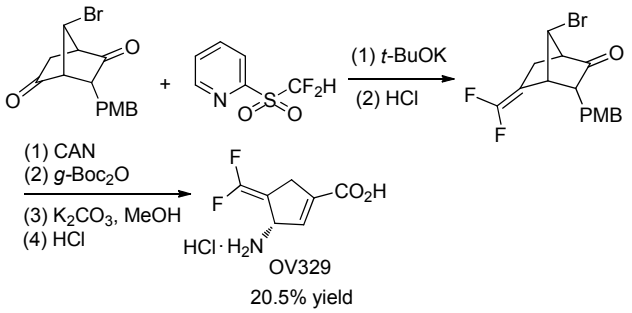


Scheme 10 Julia-Kocienski reaction of glycal



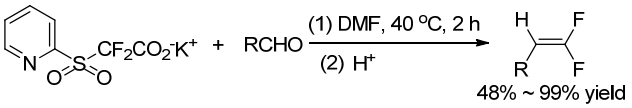
Scheme 11 One-pot Julia-Kocienski reaction of glycal

Later in 2018, Silverman and his coworker[19] optimized the synthesis of (*S*)-3-amino-4-(difluoromethylenyl)-cyclopent-1-en-1-carboxylic acid (OV329), a potent inactivator of GABA aminotransferase (GABA-AT) via Julia-Kocienski reaction (Scheme 12). Using Hu's reagent in the key step to furnish 1,1'-difluoroalkene followed by methanolysis and subsequent elimination, the number of synthetic steps was reduced from 14 to 9, and the overall yield doubled.



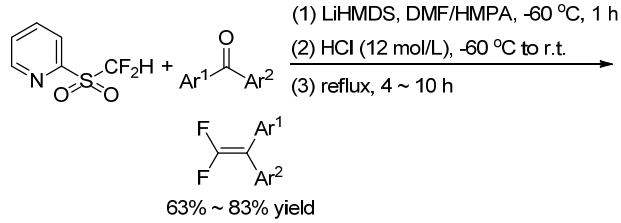
Scheme 12 Application of Julia-Kocienski reaction

Xiao group[20] reported an optimized Julia-Kocienski reaction which could be performed under mild conditions without additional base (Scheme 13). In this protocol the 2-$PySO_2CF_2^-$ was generated through the decarboxylation of potassium 2-pyridinyl sulfonyldifluoroacetate.



Scheme 13 H^+-mediated Julia-Kocienski reaction

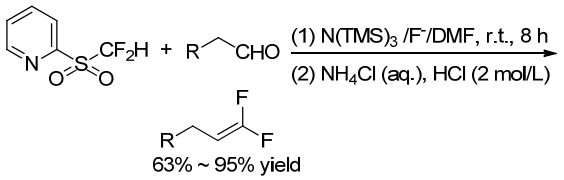
As for normal diaryl ketones, it is difficult to achieve efficient *gem*-difluoroolefination by typical Julia-Kocienski reaction under basic conditions. Hu group[21] further improved the classical Julia-Kocienski reaction and reported the acid-promoted Smiles rearrangement applying in Julia-Kocienski olefination reactions. Using LiHMDS as base and HMPA/DMF (V/V = 1/10) as solvent, the *gem*-difluoroolefination of diaryl ketones is improved. Quenching the alcoholate intermediate with concentrated HCl at low temperature, such as −60 ℃, followed by acid-promoted elimination of the carbinol intermediate, 2,2-diaryl-1,1-difluoroalkenes were obtained in good yields (Scheme 14). By this strategy, both symmetric and asymmetric diaryl ketones, even some heteroaryl ketones, smoothly gave *gem*-difluoroalkenes in moderate-to-good yields.



Scheme 14 Julia-Kocienski reaction of diaryl ketones

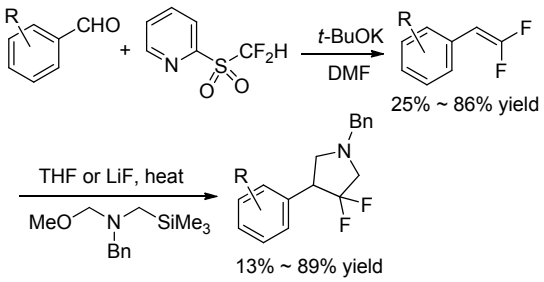
The advantages of this protocol are one-pot operation, good functional-group tolerance, and high efficiency. But there still remain some limitations. As for nitrogen-containing ketones, such as phenyl 2-pyridyl ketone, the Smiles rearrangement failed to take place.

Hu group also studied the application of Julia-Kocienski reaction in the aliphatic aldehydes to achieve *gem*-difluoroolefination depending on amide base generated *in situ* (Scheme 15). This method could not only avoid the enolization of aliphatic aldehydes, but also be chemoselective of multi-carbonyl compounds. It demonstrated that aldehyde preferentially underwent *gem*-difluoroolefination than ketone, and ketone preferentially than ester.



Scheme 15 Julia-Kocienski reaction of aliphatic aldehydes

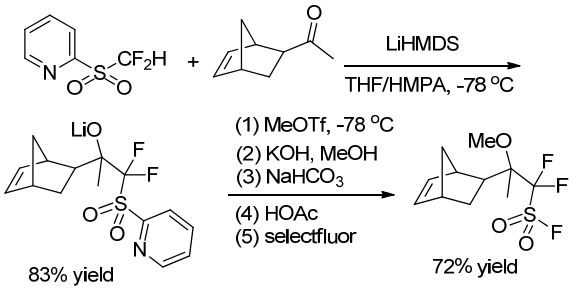
McAlpine group[22] showed that vinyl difluorides could participate in 1,3-dipolar cycloaddition with a simple azomethine ylide to generate *gem*-difluoropyrrolidines. They tried to synthesize 2,2-difluorostyrenes with benzaldehydes and Hu's reagent, then found out that benzaldehydes with electron deficient groups gave higher yields in [3+2] cycloaddition reactions (Scheme 16).



Scheme 16 Application of *gem*-difluoroalkene

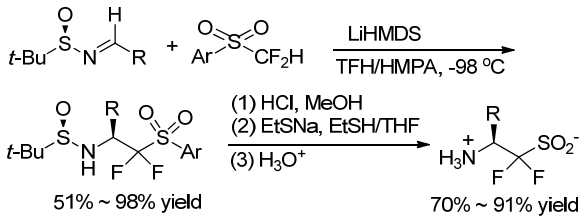
2.2 Nucleophilic addition

Difluoromethyl heteroaryl sulfones can be used to synthesize fluoropolymer. In 2011, Hu group[23] successfully synthesized the difluoroalkylsulfonyl chloride monomer for proton exchange membrane by nucleophilic addition (Scheme 17).



Scheme 17 Application of difluoromethyl heteroaryl sulfone

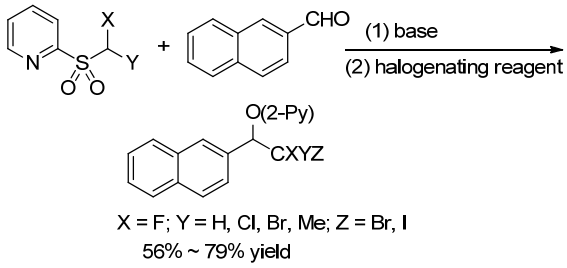
Taking 2-PySO_2CF_2H as a masked difluoro (sulfinato)-methylating agent, Prakash group[24] synthesized novel α,α-difluoro-β-amino sulfinics and sulfonic acids via nucleophilic difluoro(sulfinato)methylation of *N*-*tert*-butanesulfinyl imine, using 2-PySO_2CF_2H as a masked difluoro(sulfinato)-methylating agent (Scheme 18). The so-obtained sulfinics and sulfonic acids are potentially useful blocks to construct difluorinated peptidosulfonamides. The reaction was carried out by using excess LiHMDS as the base, HMPA as an additive in THF at a low temperature (such as −98 ℃) to obtain target product in a high yield (95%) with a good diastereoselectivity (*d.r.*＞99∶1).



Scheme 18 Nucleophilic addition to imines

By this protocol, the chiral optically active difluoro-β-amino sulfinic, sulfonic acids and complex fluorinated peptidosulfonamides were synthesized feasibly. The difluorinated β-amino sulfinates are expected to be suitable for constructing difluorinated peptidosulfonamides. The difluorinated β-amino sulfonic acids represent a novel class of functionalized fluoroalkyl sulfonic acids.

The key role that the traditional olefination changes to alkylation is the halogenation of *in situ*-generated sulfinate intermediates from Julia-Kocienski reaction. In addition, this method can also be extended to the introduction of other fluorinated groups, such as CFClBr, CFClI, $CFBr_2$, and CFMeI by using various 2-pyridyl sulfonates (Scheme 19).[15]

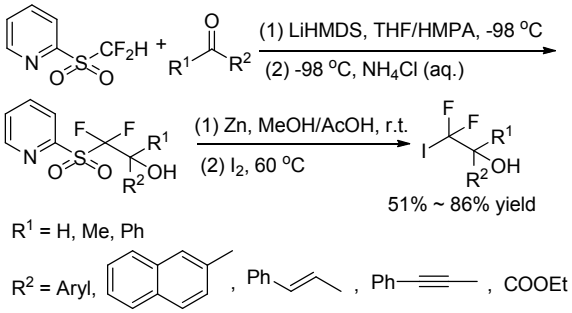


Scheme 19 Reaction of various 2-pyridyl sulfones

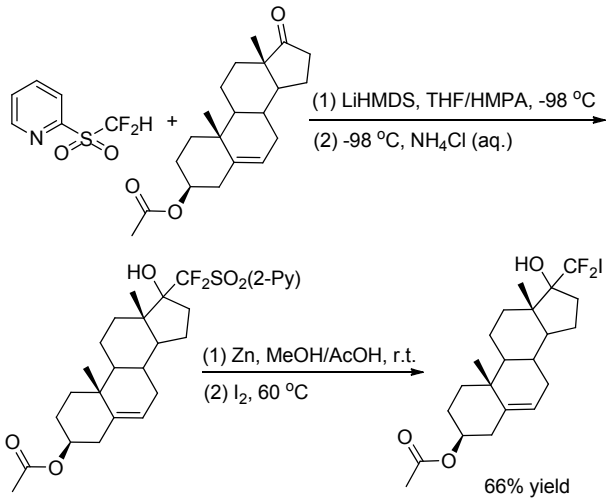
However, this protocol is limited by its difficulty in removing the pyridioxyl group on the substrates bearing electron withdrawing substituents. Moreover, this method is senstitive to steric hindrance. Thus, it is not compatible with the aliphatic system and diaryl ketones.

Later in 2016, Hu group[25] revealed a new approach for incorporation of CF_2I group into organic molecules to achieve nucleophilic iododifluoromethylation of carbonyl compounds with 2-PySO_2CF_2H. In this method, the nucleophilic addition of 2-PySO_2CF_2H to carbonyl compounds was almost the same as previously reported, except that the reaction temperature was lowered to −98 ℃. The so-addition compounds went on depyridination smoothly by using a large excess of Zn in DMSO/AcOH

system to give sulfinate *in situ*, followed by treatment of I_2 at 60 ℃ to afford the corresponding iodinated products in high yield (Scheme 20). In this strategy, the Smiles rearrangement was avoided, and the substrate scope was rather broad. Benzaldehyde, 2-naphthaldehyde, aromatic aldehydes containing electron-donating and electron-withdrawing substituents, aliphatic and aromatic ketones were all well tolerated. Even some complex molecules such as steroidal ketones can result in excellent yields (Schemes 20, 21).



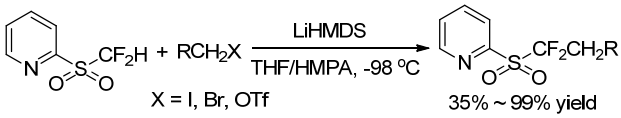
Scheme 20 Iododifluoromethylation



Scheme 21 Application of iododifluoromethylation

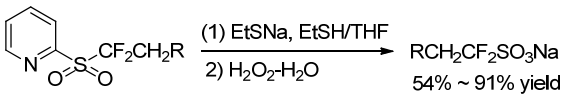
2.3 Nucleophilic substitution

In 2011, Prakash and George group[14] declared the first nucleophilic substitution of difluoromethyl heteroaryl sulfones with alkyl halogens. The reaction went in the presence of a base, such as lithium hexamethyldisilazide (LiHMDS), with tetrahydrofuran (THF) as solvent and hexamethylphosphoramide (HMPA) as an additive, the temperature lowered to −98 ℃, and finally afforded *α*,*α*-difluoroalkyl heteroaryl sulfones (Scheme 22). They also decalard that sulfones such as $BTSO_2CF_2H$, $PTSO_2CF_2H$, and $TBTSO_2CF_2H$ were not as significantly reactive as $2\text{-}PySO_2CF_2H$ (Hu's reagent). The substrate scope of this protocol was primary alkyl halides and primary alcohol triflates. The secondary alkyl iodide couldn't give anticipated product. It indicated that the reaction was very sensitive to steric hindrance.



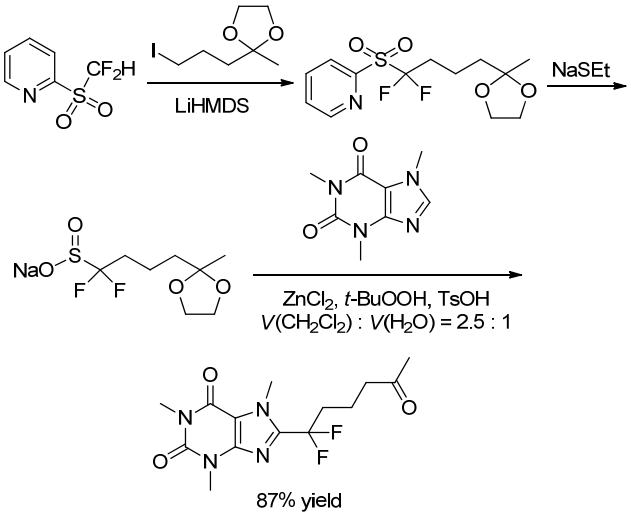
Scheme 22 Nucleophilic fluoroalkylation

By treating with a less basic nucleophile, such as sodium ethanethiolate (EtSNa) or sodium difluoroethylsulfinate (DFES-Na), the *α*,*α*-difluoroalkyl sulfonates definitely underwent an intermolecular and dearylation to result in alkyl 2,2-difluorosulfinate salts. Subsequently, oxidizing the so-obtained difluorosulfinate salts would give some efficient difluoroethylation agents (Scheme 23), which were difficult to prepare via direct nucleophilic difluoro (sulfonate)-methylation. This methodology was applicable for modification of functionalized molecules, such as carbohydrates, heterocycles and so on.[27,28]



Scheme 23 Synthesis of difluorinated sulfonates

Shabat group[29] developed new difluoroalkyl ketal sulfinate salt reagent which was suitable for introducing ketone functional group into heteroarene bioactive compounds via one-pot reaction (Scheme 24). This protocol provided a general approach to obtain taggable ketone analogs directly from bioactive heteroarene compounds with limited options for conjugation.



Scheme 24 Synthesis of difluoroalkyl ketal sulfinate salt and its application

3 Radical-mediated difunctionalization

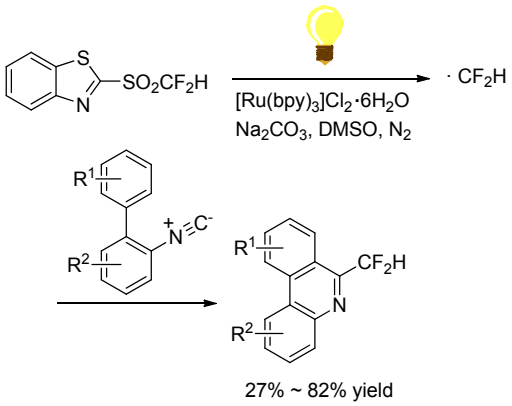
Radical mediated difunctionalization of alkenes provides a powerful tactic for olefin utilization. Through this route, both CF_2H and another functional group (H, C, N, O, Cl and Br) can be introduced into organic frameworks.[30~34]

3.1 CF_2H radical

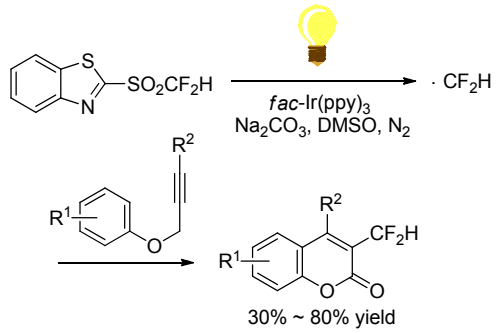
3.1.1 Visible-light photoredox catalysis

In recent years, visible-light photoredox catalysis has emerged as a powerful synthetic method for bond activation and construction processes that are usually difficult to achieve with conventional methods.[35~38]

Hu and Ni group[39] reported the use of mono-, di-, and tri-fluorinated heteroaryl sulfones as a new class of radical fluoroalkylation reagents under visible-light photoredox catalysis (Scheme 25). With various isocyanides as radical acceptors, the radical fluoroalkylation progressed smoothly to afford fluoroalkylatedphenanthridine derivatives. This protocol opened a new door for the synthetic application of fluorinated sulfones as fluoroalkyl radical precursors. Using difluoromethyl sulfones as CF_2H radical precursors, Fu group[40] realized an intramolecular difunctionalization of aryl alkynoates via radical initiating addition/cyclization (Scheme 26). This method provides a simple and efficient synthesis of 3-difluoromethylsubstituted coumarins in moderate to good yields. But the scope of alkynes was limited to alkynyl arenes. Later in 2016, Fu group[41] reported an efficient method for the synthesis of CF_2H-containing benzoxazines and oxazolines through radical oxydifluoromethylation reaction of various olefinic amides with difluoromethyl sulfones. It was carried out in the presence

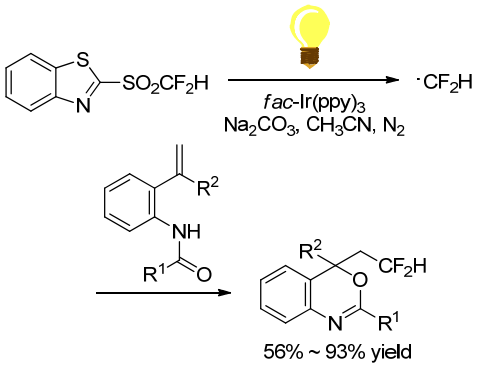


Scheme 25 Radical difluoromethylation

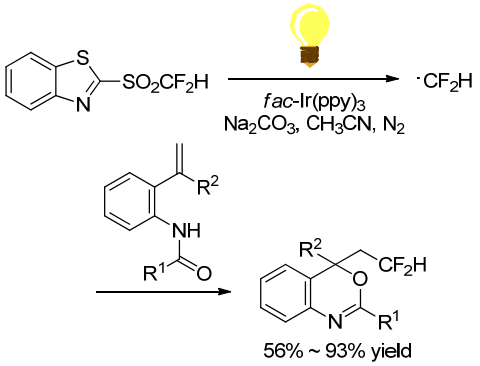


Scheme 26 Radical difluoromethylation

of [*fac*-Ir(III)(ppy)$_3$] excited by 5 W blue LED for several hours (Scheme 27). Zou and his coworker[42] declared a similar radical cyclization of *N*-methacryloyl benzamides by using difluoromethyl sulfone to give difluoromethylated coumarins or isoquinolinediones (Scheme 28). Among the difluoromethyl sulfones, $BTSO_2CF_2H$ was the best CF_2H-transfer reagents.



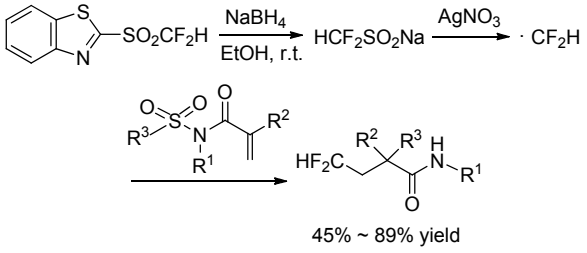
Scheme 27 Radical difluoromethylation



Scheme 28 Radical difluoromethylation

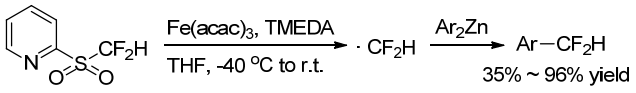
3.1.2 Metal-mediated

Hu group[43] developed a method for the straightforward introduction of CF_2H and CH_2F groups via a radical process (Scheme 29). The reaction went on in silver-catalyzed cascade fluoroalkylation/aryl migration/SO_2 extrusion of conjugated *N*-arylsulfonylated amides. By treating ethanol solution of $BTSO_2CF_2H$ with slight excess of $NaBH_4$, followed by precipitation of the resulting salt in hexanes and washing with ethanol/hexanes, afforded fluorinated sulfinate salts. The later was excited by silver and gave out CF_2H• radical, which reacted with conjugated *N*-arylsulfonylated amides to produce *α*-aryl-*β*-fluoroalkyl amides. This reaction had a wide range of scope for substrates.



Scheme 29 Difluoromethyl radicalization

The direct introduction of difluoromethyl group onto arenes was often suffered from harsh reaction conditions, and poor functional group compatibility. Transition-metal-mediated difluoromethylation reactions were demonstrated as a viable approach for direct difluoromethylation. Recently, Hu group[44] tested this new strategy of iron-catalyzed aromatic difluoromethylation by using 2-PySO_2CF_2H as a precursor to generate difluoromethyl radical (Scheme 30).

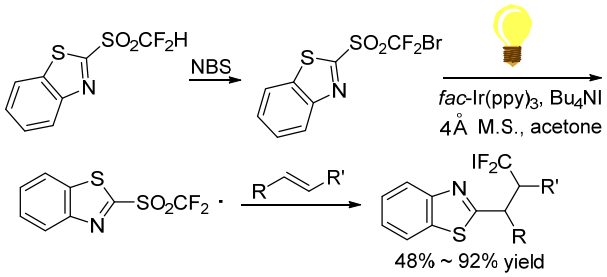


Scheme 30 Difluoromethyl radicalization

3.2 Sulfonyl carbon radical

Zhu group[45] described a strategy for radical difunctionalization of alkenes. The heteroaryl and difluoromethyl incorporated into alkenes simultaneously by this process. After turning difluoromethyl heteroaryl sulfones into bromide difluoromethyl ones, the C—Br bond could readily promote by visible-light photoredox catalysis to form the difluoromethyl sulfonyl carbon radical species. The iododifluoromethylheteroarylation of alkenes promoted in the presence of tetrabutylammonium iodide (TBAI) and 4 Å molecular sieves (Scheme 31). The reaction demonstrated a highly broad substrate scope and functional group tolerance. The versatile adducts afforded by this protocol can be conveniently converted into a variety of valuable fluorine-containing compounds. The proposed reaction mechanism of radical difunctionalization is as shown in Scheme 32.

In 2014, Hu group[46] reported an Et_3B/air-initiated radical (2-pyridylsulfonyl) difluoromethylation of terminal alkenes with iododifluoromethyl 2-pyridyl sulfone (2-Py-SO_2CF_2I). This synthetic methodology could also be extended to synthesize of (2-pyridylsulfonyl) difluoromethylated alkanes and alkenes (Scheme 33).

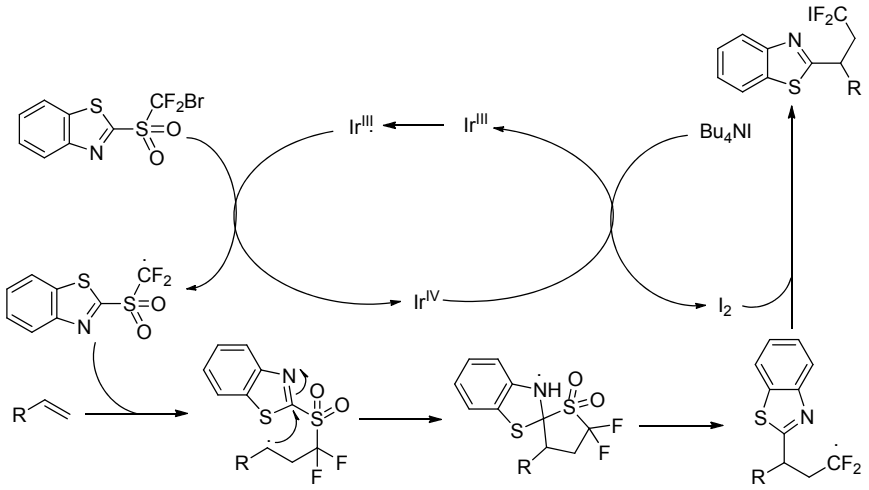


Scheme 31 Radical difunctionalization of alkenes

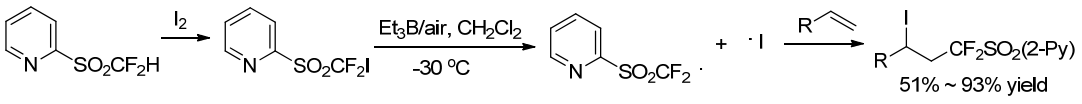
3.3 $ArSCF_2$ radical

Using 2-PySO_2CF_2SAr as $ArSCF_2$ radical precursor, Sheng group[47] first reported an efficient radical arylthiodifluoromethylation of various isocyanides to form phenanthridines and isoquinolines in good to excellent yields (Scheme 34). The optimal conditions for this protocol were taking $[Ru(bpy)_3Cl_2]•6H_2O$ (2 mol%) as photocatalyst, DMSO as solvent, Na_2CO_3 (3.0 equiv.) as base and under 6 W blue LED irradiation. It was proposed that 2-PySO_2CF_2SAr was reduced by $[Ru]^+$ through a SET process to release highly reactive radical species $ArSCF_2$•.

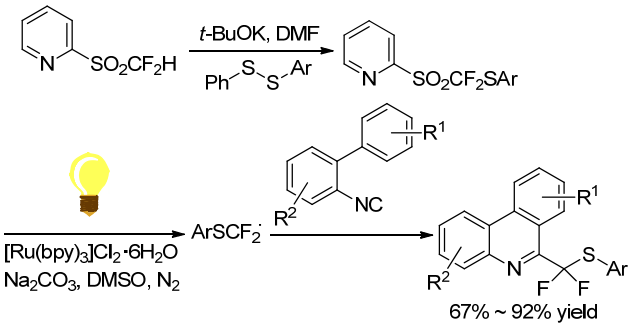
This strategy gave a method for introducing an arylthiodifluoromethyl moiety into nitrogen containing heterocycles. The substrate scope of this radical reaction was wide. The ArSCF2 group could be introduced into both electron-rich and electron-deficient isocyanides under mild conditions. It demonstrated excellent functional group compatibility except the methyl-thiodifluoroalkyl sulfone.



Scheme 32 Proposed mechanism of radical difunctionalization of alkenes



Scheme 33 Et_3B/air initiated radical reaction



Scheme 34 $ArSCF_2$ radical-triggered cyclization

4 Conclusion

Difluoromethyl heteroaryl sulfones are the newly developed nucleophilic difluoromethylation reagents. Among them, 2-PySO_2CF_2H is a bench-stable, crystalline solid that is now commercially available. It was widely used in nucleophilic reaction. 2-BTSO_2CF_2H is also a worthwhile novel reagent in addition. It opens up a straightforward access to difluoromethyl compounds. The substrate scope of these reagents has extended to carbonyl, alkyl halide, alkyne, imine derivatives, isocyanates and so on. There still are some unexplored applications worth studying. Finally, we hope that this review can provide new thoughts for the synthesis of difluoroalkyl compounds.

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