Synthesis X. Xiao et al. Short Review

Recent Advances in Difluoromethylthiolation

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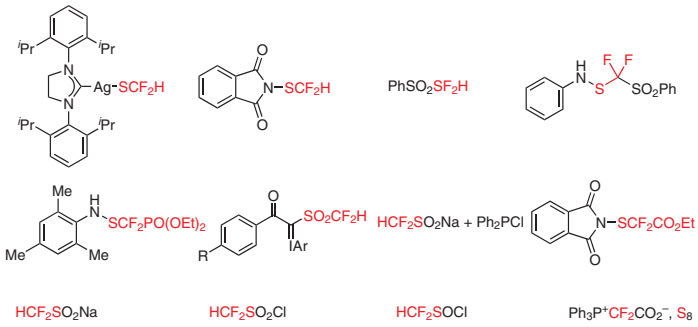

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Abstract The difluoromethylthio group (HCF_2S), which has been identified as a valuable functionality in drug and agrochemical discovery, has received increased attention recently. Two strategies, difluoromethylation and direct difluoromethylthiolation, have been well established for HCF_2S incorporation. The former strategy suffers from the need to prepare sulfur-containing substrates. In contrast, direct difluoromethylthiolation is straightforward and step-economic. This short review covers the recent advances in direct difluoromethylthiolation, including electrophilic, radical, and transition-metal-catalyzed or -promoted reactions.

Key words difluoromethylthio group, difluoromethylthiolation, electrophilic, radical, fluorine

1 Introduction

Fluorine, which has been called 'a magic atom',[1] 'fabulous fluorine',[2] and 'a small atom with a big ego',[3] exhibits unique properties such as high electronegativity, low polarizability, and small atomic radius. The incorporation of fluorinated groups into organic molecules would lead to profound changes in the latter's physicochemical properties.[4] Therefore, fluorine-containing compounds have found widespread application in various research areas, including pharmaceutical chemistry, agrochemistry, and material

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Jin-Hong Lin (right) obtained his Bachelor's degree from Donghua University in 2005. He received his Ph.D. from SIOC-CAS, under the supervision of Prof. Ji-Chang Xiao in January 2011. In March 2011, he joined the group of Prof. John T. Welch at State University of New York at Albany as a postdoctoral researcher. In February 2013, he left Welch's group and joined Prof. Xiao's group at SIOC as an associate professor. His current research interests focus on the development and the synthetic application of fluorinated salts.

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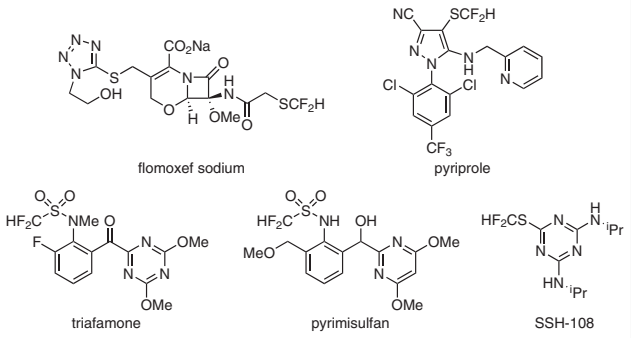


Scheme 1 HCF_2S-containing biologically active compounds

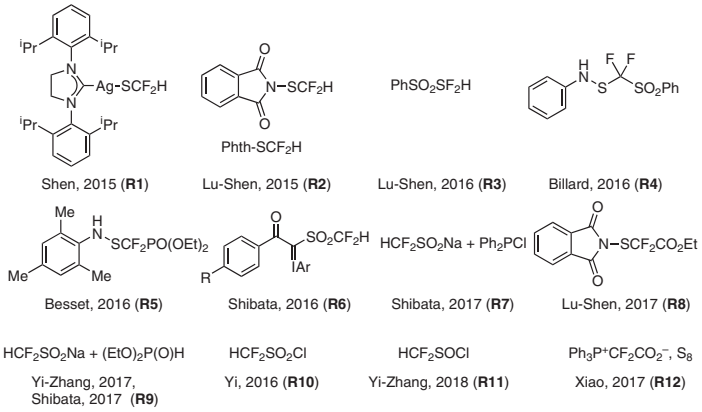
sciences.[4,5] Since the first approval of the steroid fludrocortisone in 1955 by the FDA (US Food and Drug Administration), a large number of fluorinated drugs have been developed. It was estimated in 2006 that approximately 20% of pharmaceuticals (over 150 drugs) and 30% of agrochemicals contain a fluorinated substituent.[2] The percentages have been increasing since then.[5c]

Many fluorinated substituents have been identified as valuable functionalities in drug and agrochemical discovery, and the difluoromethylthio group (HCF_2S) has received increasing attention recently[6] due to its intermediate lipophilicity (Hansch lipophilicity parameter π = 0.68),[7] electron-withdrawing nature (Hammett constants σ_p = 0.37, σ_m = 0.33),[8] and hydrogen bonding ability,[9] and also because of the possibility for further transformation of the HCF_2S group. Some HCF_2S-containing pharmaceuticals and agrochemicals have appeared (Scheme 1), such as flomoxef sodium,[10] pyriprole,[11] triafamone,[12] pyrimisulfan,[13] and SSH-108.[14] Consequently, significant efforts have been devoted to the development of efficient approaches for the incorporation of the HCF_2S into organic molecules.

Two strategies have been well-established for the installation of the HCF_2S group, difluoromethylation of sulfur-containing compounds and direct difluoromethylthiolation.[6] The difluoromethylation strategy suffers from a limited substrate scope and the need to prepare the sulfur-containing substrates. In contrast, direct difluoromethylthiolation is straightforward and step-economic, and thus has become an active research area in organofluorine chemistry. A variety of difluoromethylthiolation reagents (Scheme 2) and difluoromethylthiolation approaches have been developed over the past few years. The only example of a nucleophilic reagent is the Ag-SCF_2H type reagent **R1** developed by the Shen group,[15] and the other reagents exhibit good electrophilicity. The installation of the HCF_2S group was reviewed by Besset and co-workers in 2016,[6] but studies prior to 2016 were focused on difluoromethylation strategies and most difluoromethylthiolation approaches were developed subsequent to the publication of this review. In this review, we will discuss the recent advances in direct difluoromethylthiolation. The reactions are classified into three categories, electrophilic, radical, and transition-metal-catalyzed or -promoted reactions.

2 Electrophilic Difluoromethylthiolation

After the development of N-SCF_3-type trifluoromethylthiolation reagents (NBS analogues),[16] in 2017 Shen, Lu, and co-workers developed a new N-SCF_2H-type reagent **R2**.[17] This reagent is shelf-stable and easy-to-handle, but its preparation requires a four-step procedure and the use of Cl_2 gas. It was found to be quite electrophilic, and was able to directly difluoromethylthiolate amines and thiols to give the corresponding products **1** and **2** (Scheme 3). The presence of a base allowed for the difluoromethylthiolation of β-keto esters to give **3**. The Lewis acid, TMSCl, could activate reagent **R2** and heteroarenes would then undergo direct difluoromethylthiolation to give **4**. The difluoromethylthiolation of boronic acids and terminal alkynes catalyzed by a copper source also proceeded smoothly giving **5** and **6**, respectively.



Scheme 2 Difluoromethylthiolation reagents

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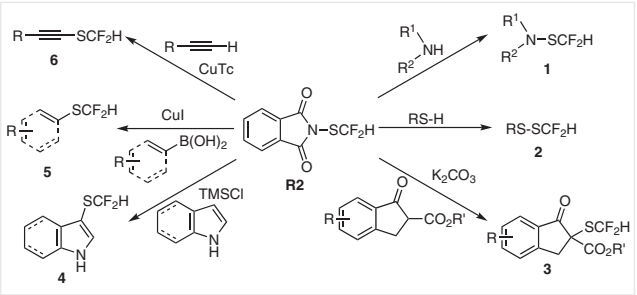
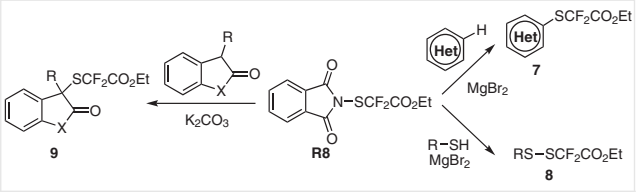


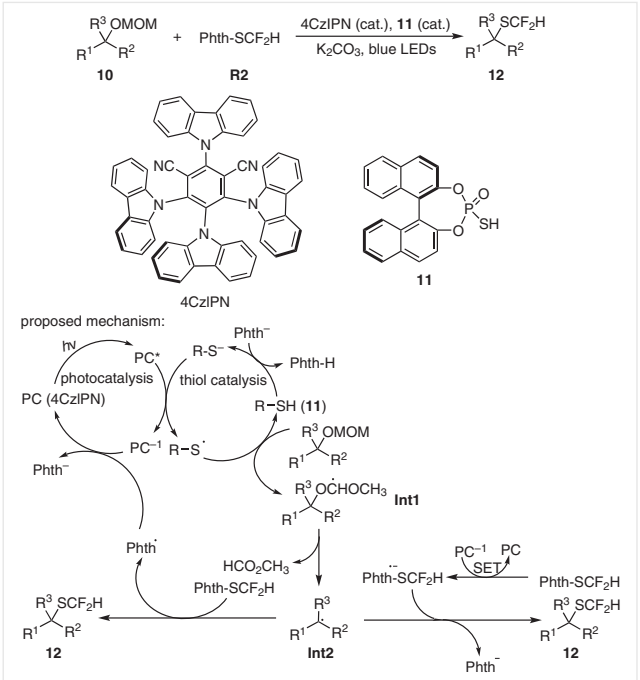
Scheme 3 Electrophilic difluoromethylthiolation with reagent Phth-SCF_2H (**R2**)

On the basis of the reliable practicability of the N-SCF_2H-type reagent **R2**, in 2017 Shen, Lu, and co-workers further designed a fluoroalkylthiolation reagent, **R8**.[18] It could be prepared either via sulfuration of phthalimide or via a substitution by potassium phthalimide. This reagent is also quite electrophilic and the difluoroalkylthiolation of heteroarenes and thiols was observed in the presence of a Lewis acid to give [(ethoxycarbonyl)difluoromethyl]thio derivatives **7** and **8**, respectively (Scheme 4). For active ketones, the α-positions were highly reactive towards this transformation using potassium carbonate as a base to give products such as **9**. The CO_2Et is a versatile functionality and could be transformed into other groups. Although a wide substrate scope was observed, the use of Cl_2 gas is also necessary for the preparation of reagent **R8**, which is a disadvantage of this difluoromethylthiolation protocol.



Scheme 4 Fluoroalkylthiolation with reagent Phth-$SCF_2(CO_2Et)$ (**R8**)

In 2018, Xie, Zhu, and co-workers used the N-SCF_2H-type reagent **R2** to achieve an umpolung difluoromethylthiolation of tertiary ethers (Scheme 5).[19] As shown in the proposed mechanism, two catalytic cycles are involved. Interestingly, even if a weaker benzylic C–H bond (BDE ≈ 90 kcal mol^{-1}) is present in the substrates, the selective abstraction of a hydrogen from the stronger C–H bond in the ether group (BDE ≈ 93 kcal mol^{-1}) by the RS$^{\bullet}$ radical was observed to generate intermediate **Int1**. This phenomenon was ascribed to a polarity-matching effect, i.e., an electrophilic radical should undergo selective hydrogen abstraction at the most hydridic C–H bond, owing to a lower kinetic barrier.[20] The homolytic cleavage of the C–O bond in **Int1** produces radical **Int2**, which is then converted into the desired product via an abstraction of the HCF_2S moiety from Phth-SCF_2H or [Phth-SCF_2H]$^{\bullet-}$.



Scheme 5 Umpolung difluoromethylthiolation of tertiary ethers with Phth-SCF_2H (**R2**)

The successful development of efficient electrophilic ArN-SCF_3-type trifluoromethylthiolation reagents **R13**[21] prompted Billard and co-workers in 2016 to further develop PhNH-$SCF_2(SO_2Ph)$ electrophilic difluoromethylthiolation reagent **R4**,[22] in which the SO_2Ph group is an auxiliary. For the preparation of this reagent, a good yield (60%) was obtained on a gram scale (10 g), but the use of a hazardous reagent, DAST (diethylaminosulfur trifluoride), is required. An acid such as TsOH or $BF_3{\cdot}Et_2O$ could increase the electrophilicity of reagent **R4** and therefore alkynes, alkenes, or arenes were well converted into the desired products such as **13** and **14** (Scheme 6). Many functional groups could be tolerated, such as hydroxyl or amino groups and carboxylic acids, and a wide substrate scope was observed. Reduction conditions led to the removal of the auxiliary SO_2Ph to give difluoromethylthiolated product **15**.

Also in 2016, Besset and co-workers developed a similar reagent **R5** and disclosed an effective method for the incorporation of the $SCF_2PO(OEt)_2$ group into molecules (Scheme 7).[23] **R5** could be prepared without the use of a hazardous reagent. The activation of **R5** by a Lewis acid was necessary to facilitate the difluoromethylthiolation of various nucleophiles, including ketones (**16**), electron-rich arenes and heteroarenes (**17**), aniline derivatives (**18**), and thiols (**19**). Hydrolysis of the $SCF_2PO(OEt)_2$-containing product by NaOH gave a difluoromethylthiolated product. The strong basic conditions for hydrolysis indicate that this protocol may not be quite suitable for the synthesis of functionalized HCF_2S-molecules.

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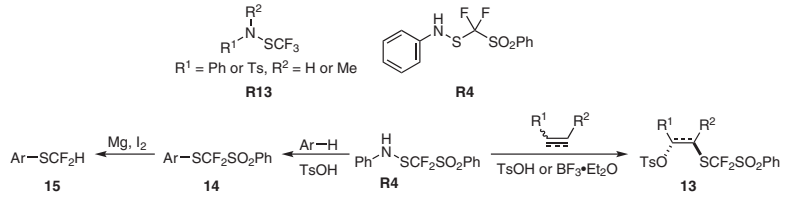
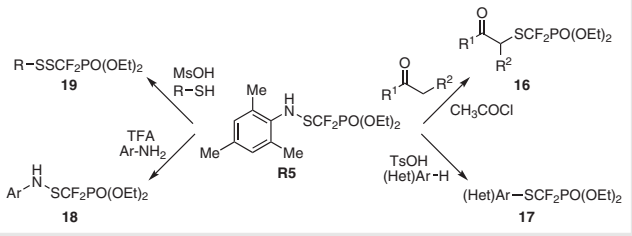


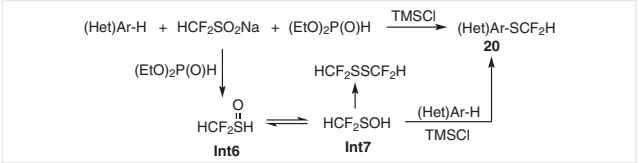
Scheme 6 Difluoromethylthiolation with PhNH-$SCF_2(SO_2Ph)$ (**R4**)



Scheme 7 The incorporation of $SCF_2PO(OEt)_2$ group by using MesNH-$SCF_2[PO(OEt)_2]$ (**R5**)

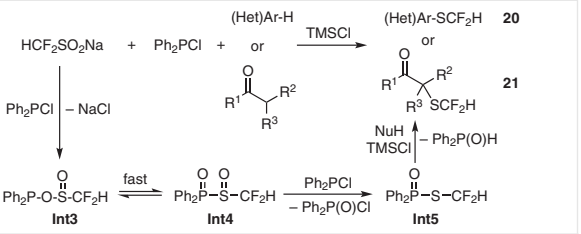
The Shibata group found, in 2017, that the HCF_2SO_2Na/Ph_2PCl (**R7**) system could act as an efficient electrophilic difluoromethylthiolation reagent (Scheme 8).[24] They propose that HCF_2SO_2Na first reacts with Ph_2PCl to generate intermediate **Int3**, which is in fast equilibrium with **Int4**. Intermediate **Int4** is reduced by a second Ph_2PCl to generate reactive species **Int5**. The electrophilicity of **Int5** is not high enough and therefore the activation by a Lewis acid is required. Final difluoromethylthiolation gives the desired products **20** or **21**. Interestingly, the reagent system could be used for the late-stage direct difluoromethylthiolation of a number of natural products and pharmaceutically attractive molecules, demonstrating the synthetic utility of this approach.

Zhang, Yi, and co-workers described, in 2017, the difluoromethylthiolation of heteroarenes and electron-rich arenes with the $HCF_2SO_2Na/(EtO)_2P(O)H$ (**R9**) system (Scheme 9).[25] Like Ph_2PCl,[24] $(EtO)_2P(O)H$ could also convert HCF_2SO_2Na into active HCF_2S species for electrophilic difluoromethylthiolation. Due to the high affinity of phosphorus towards oxygen, $(EtO)_2P(O)H$ would abstract oxygen from HCF_2SO_2Na to release $HCF_2S(O)H$ (**Int6**), which is in equilibrium with HCF_2SOH (**Int7**). Although HCF_2SSCF_2H could also be generated, they found that this species cannot difluoromethylthiolate electron-rich arenes such as indoles. Therefore, they propose that it is HCF_2SOH that generates HCF_2S^+ species via the activation of S–OH bond by TMSCl, allowing for the final difluoromethylthiolation to give products **20**. Compared with Shibata's method using Ph_2PCl, which is moisture sensitive,[24] this approach may be relatively more operationally convenient since $(EtO)_2P(O)H$ is not so sensitive to moisture.

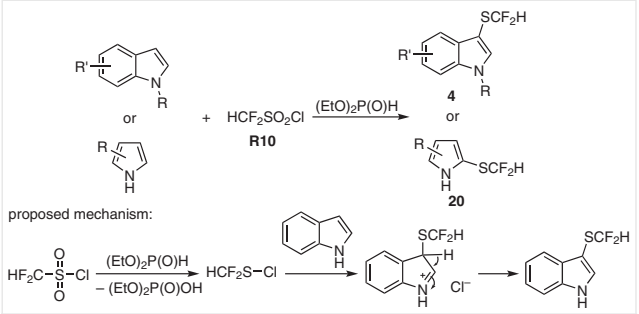


Scheme 9 Difluoromethylthiolation with $HCF_2SO_2Na/(EtO)_2P(O)H$ (**R9**)

Besides HCF_2SO_2Na, HCF_2SO_2Cl can also be considered as a HCF_2S^+ source. Yi and co-workers found that difluoromethylthiolation of indoles or pyrroles with HCF_2SO_2Cl (**R10**) proceeded smoothly by using $(EtO)_2P(O)H$ as a reducing agent (Scheme 10).[26] They proposed that HCF_2SO_2Cl is reduced to HCF_2S-Cl, which is the active difluoromethylthiolation species. Compared with the HCF_2SO_2Na/Ph_2PCl (**R7**) or $HCF_2SO_2Na/(EtO)_2P(O)H$ (**R9**) systems, the $HCF_2SO_2Cl/(EtO)_2P(O)H$ system could effectively difluoromethylthiolate the substrates without the need for a Lewis acid. However, the high volatility of HCF_2SO_2Cl (bp 95–99 °C) and the necessity of the toxic Cl_2 gas for its preparation[27] are disadvantages of this difluoromethylthiolation approach.



Scheme 8 Difluoromethylthiolation of electron-rich compounds with HCF_2SO_2Na/Ph_2PCl (**R7**)



Scheme 10 Difluoromethylthiolation with HCF_2SO_2Cl (**R10**)/$(EtO)_2P(O)H$

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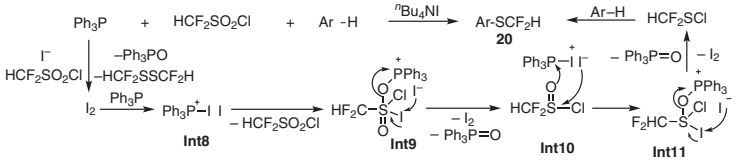
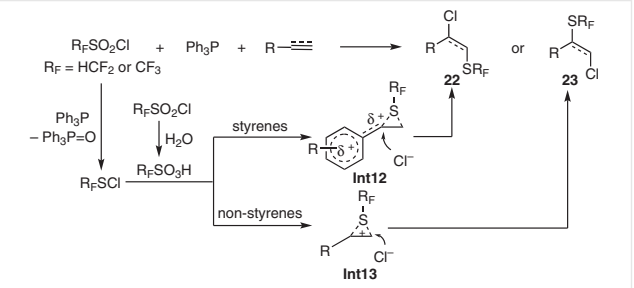


Scheme 11 Difluoromethylthiolation with HCF_2SO_2Cl (**R10**)/Ph_3P

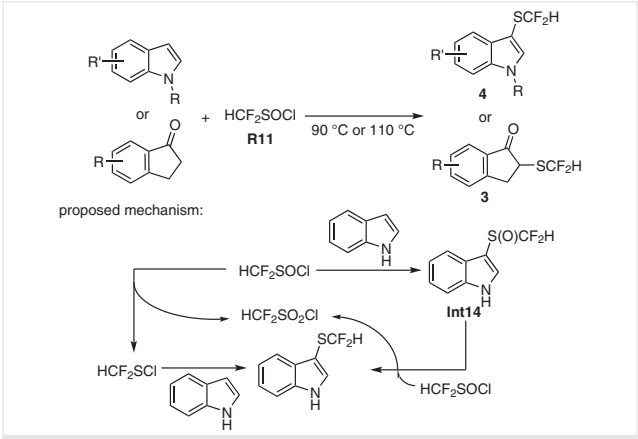
Triphenylphosphine could also activate HCF_2SO_2Cl (**R10**) for difluoromethylthiolation. In 2017, Lu and co-workers reported the difluoromethylthiolation of thiols[28] and electron-rich aromatics[29] with the HCF_2SO_2Cl (**R10**)/Ph_3P system in the presence of an iodide anion. The iodide anion would react with HCF_2SO_2Cl/Ph_3P to produce molecular iodine, which could be trapped by Ph_3P to generate iodophosphonium salt **Int8** (Scheme 11). **Int8** is an electrophilic species and would be attacked by the oxygen lone pair electrons in HCF_2SO_2Cl to afford **Int9**. The strong P=O bond drives the cleavage of S–O bond to give **Int10**. A second similar sequence affords difluoromethanesulfenyl chloride (HCF_2SCl).

The HCF_2SO_2Cl (**R10**)/Ph_3P system can be used to achieve not only difluoromethylthiolation,[28,29] but also chloro-difluoromethylthiolation.[30] Zhang, Yi, and co-workers disclosed the chloro-difluoromethylthiolation of alkenes and alkynes with this reagent system (Scheme 12).[30] Interestingly, iodide anion was not necessary in this conversion, and the regioselectivity depends on whether the unsaturated bond is conjugated with an aromatic ring or not. They propose that HCF_2SCl could be directly produced from HCF_2SO_2Cl via reduction by Ph_3P. HCF_2SO_3H, which is formed from HCF_2SO_2Cl by hydrolysis, serves as a catalyst for electrophilic addition. The conjugation of the double bond with a phenyl ring would favor the formation of Markovnikov products **22** via the generation of intermediate **Int12**. In the case of non-styrene-type alkenes, the steric hindrance of the R group is the dominant factor to control the regioselectivity, and therefore *anti*-Markovnikov adducts **23** would be formed.



Scheme 12 Difluoromethylthiolation of alkenes and alkynes with HCF_2SO_2Cl (**R10**)/Ph_3P

HCF_2SO_2Cl (**R10**) has to be activated by a reducing reagent, such as $(EtO)_2P(O)H$ or Ph_3P, for difluoromethylthiolation. In contrast, HCF_2SOCl (**R11**) could directly difluoromethylthiolate electron-rich substrates without the need for a reductant. Zhang, Yi, and co-workers found that difluoromethylthiolation of indoles or ketones with HCF_2SOCl occurred smoothly under heating conditions (Scheme 13).[31] They proposed that HCF_2SOCl could react with indole to generate **Int14**, which is reduced by HCF_2SOCl to afford the final product. HCF_2SOCl may also undergo disproportionation to form HCF_2SO_2Cl and HCF_2SCl, and the subsequent difluoromethylthiolation delivers the expected product.



Scheme 13 Difluoromethylthiolation with HCF_2SOCl (**R11**)

Our group has previously shown that the phosphobetaine salt ($Ph_3P^+CF_2CO_2^-$) **R12** could rapidly react with elemental sulfur (S_8) to generate thiocarbonyl fluoride (CF_2=S), a process which was used to achieve trifluoromethylthiolation and ^{18}F-trifluoromethylthiolation.[32] CF_2=S is an electrophilic species and would be readily trapped by nucleophiles. The use of vicinal hydroxyl (or amino) arylamines as nucleophiles could efficiently give difluoromethylthiolated heterocycles **20** (Scheme 14).[33] We propose that substrates undergo cyclization with CF_2=S to deliver thiourea **Int17** via the formation of phenylcarbamothioic fluoride **Int15** or isothiocyanate **Int16**; **Int17** is in equilibrium with thiol **Int18**. The insertion of difluorocarbene generated from phosphobetaine salt ($Ph_3P^+CF_2CO_2^-$)[34] into **Int18** affords the final products.

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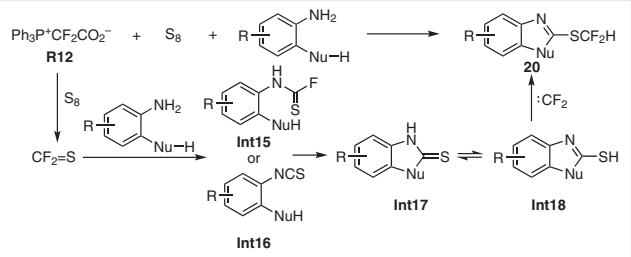
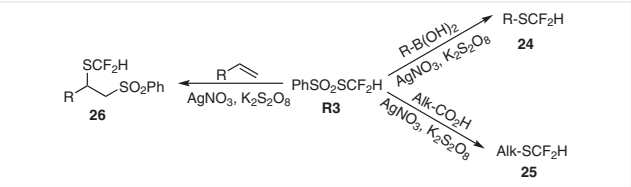


Scheme 14 The formation of HCF_2S-containing heterocycles using phosphobetaine salt ($Ph_3P^+CF_2CO_2^-$) **R12**

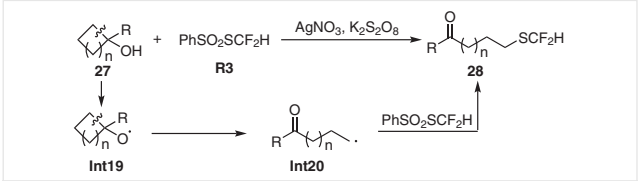
3 Radical Difluoromethylthiolation

$PhSO_2SCF_2H$ (**R3**), developed by Shen, Lu, and co-workers in 2016, is a mild electrophilic difluoromethylthiolation reagent which could be prepared by a two-step procedure.[35] It was found that the $AgNO_3/K_2S_2O_8$ system can promote the reaction of boronic acids and alkanoic acids with $PhSO_2SCF_2H$ to give difluoromethylthiolation products **24** and **25**, respectively (Scheme 15).[35] In the case of alkenes, phenylsulfonyl-difluoromethylthio difunctionalization was observed to give **26**. The mechanistic investigations revealed that a radical mechanism may be operative. $PhSO_2SCF_2H$ is a very efficient difluoromethylthiolation reagent, and has been used by other groups for radical reactions.



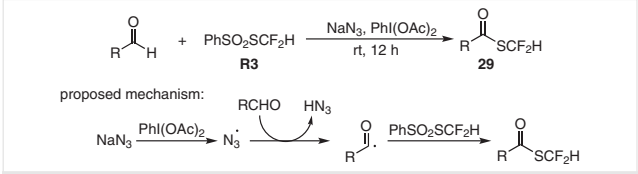
Scheme 15 Difluoromethylthiolation with $PhSO_2SCF_2H$ (**R3**)

In 2018, Shen and co-workers further used the $AgNO_3/K_2S_2O_8$-promoted strategy to achieve ring-opening difluoromethylthiolation of cycloalkanols **27** with $PhSO_2SCF_2H$ (**R3**) to deliver HCF_2S-containing ketones **28** (Scheme 16).[36] Various cycloalkanols, including cyclopropanols, cyclobutanols, cyclopentanols, cyclohexanols, and cycloheptanols, were all suitable for this conversion. Initial mechanistic studies indicate that a cycloalkoxy radical intermediate **Int19** is generated. The ring-opening of the alkoxy radical forms an alkyl radical **Int20**, which abstracts the HCF_2S group from $PhSO_2SCF_2H$ to afford the final products **28**. This is a very effective method for the synthesis of HCF_2S-substituted ketones.



Scheme 16 Ring-opening difluoromethylthiolation of cycloalkanols with $PhSO_2SCF_2H$ (**R3**)

Most difluoromethylthiolation methods focus on the synthesis of difluoromethyl thioethers. Difluoromethyl thioesters should also receive attention because they would predictably lead to new bioactive molecules, as indirectly demonstrated by the anti-inflammatory monofluoromethyl thioester drug fluticasone and its derivative fluticasone propionate.[37] Shen, Wang, and co-workers found that the $NaN_3/PhI(OAc)_2$ system was also a suitable radical initiator to enable the difluoromethylthiolation of aldehydes with $PhSO_2SCF_2H$ (**R3**) at room temperature to give *S*-difluoromethyl thioesters (Scheme 17).[38] Experimental evidence supports a radical pathway. The oxidation of NaN_3 by $PhI(OAc)_2$ generates an azide radical. The abstraction of H atom from an aldehyde by this azide radical forms a carbonyl radical, which reacts with $PhSO_2SCF_2H$ to provide the desired *S*-difluoromethyl thioester **29**.



Scheme 17 Difluoromethylthiolation of aldehydes with $PhSO_2SCF_2H$ (**R3**)

The Wang group also reported a radical difluoromethylthiolation of aldehydes with $PhSO_2SCF_2H$ (**R3**) (Scheme 18).[39] Various aryl, heteroaryl, alkyl, and alkenyl aldehydes could all be converted into the expected products, demonstrating a wide substrate scope. They proposed that *t*-BuOOH could directly abstract a hydrogen atom from aldehydes to generate a carbonyl radical. In the $NaN_3/PhI(OAc)_2$-promoted method,[38] room temperature was the reaction temperature but hazardous NaN_3 has to be used. In this method,[39] the operations are relatively more convenient, but a higher reaction temperature is necessary.

Although hydro-fluoroalkyl(thiol)ation of multiple bonds has proved to be effective methods for the incorporation of fluoroalkyl or fluoroalkylthio groups into organic molecules,[40] hydro-difluoromethylthiolation has not been reported until recently. In 2019, Shen, Lu, and co-workers described a Co-catalyzed radical hydro-difluoromethylthiolation of unactivated alkenes with $PhSO_2SCF_2H$ (**R3**) at room temperature (Scheme 19).[41] They proposed that hydro-

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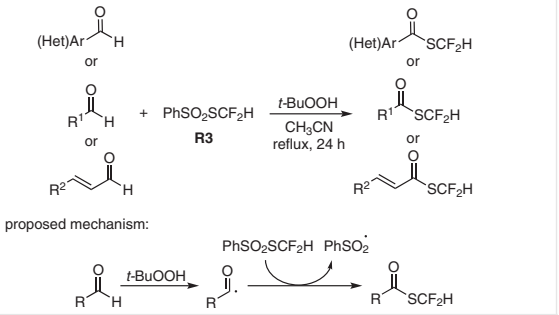
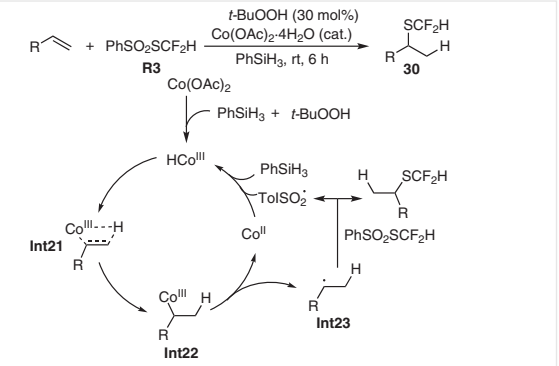


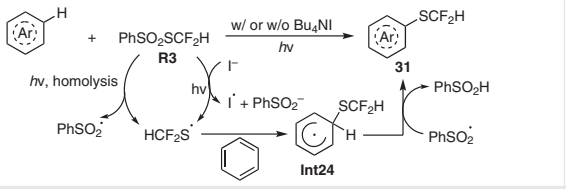
Scheme 18 *t*-BuOOH-promoted difluoromethylthiolation with $PhSO_2SCF_2H$ (**R3**)



Scheme 19 Hydro-difluoromethylthiolation of unactivated alkenes using $PhSO_2SCF_2H$ (**R3**)

metalation followed by a homolytic cleavage of the Co–C bond generates an alkyl radical **Int23**, which is trapped by $PhSO_2SCF_2H$ to afford the final product.

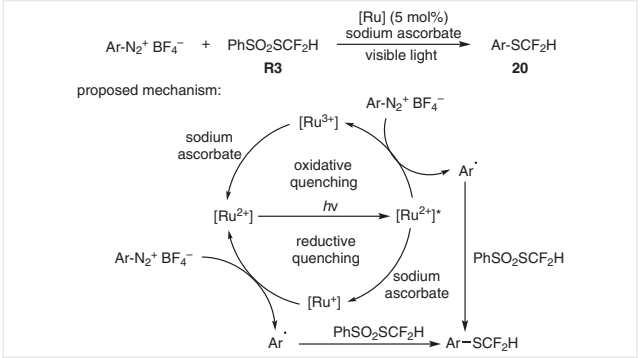
Visible-light-promoted reactions, a valuable synthetic tool for functionalization, usually proceed via the generation of radical intermediates.[42] Recently, the Li group developed a visible-light-promoted radical difluoromethylthiolation of arenes with $PhSO_2SCF_2H$ (**R3**) (Scheme 20).[43] Under CFL (compact fluorescent lamp) irradiation, a difluoromethylthio radical ($HCF_2S^{\bullet}$) is generated from $PhSO_2SCF_2H$ either by the homolysis of the S–SCF_2H bond or by the photoinduced electron transfer reaction between $PhSO_2SCF_2H$ and iodide. The capture of the $HCF_2S^{\bullet}$ radical by an arene produces radical intermediate **Int24**, and the subsequent hydrogen atom abstraction by the $PhSO_2^{\bullet}$ radical



Scheme 20 Visible-light-promoted difluoromethylthiolation of arenes with $PhSO_2SCF_2H$ (**R3**)

furnishes the target compound. Interestingly, irrespective of whether Bu_4NI was used or not, high yields could be obtained. Only electron-rich (hetero)arenes are suitable for this conversion.

Visible-light catalysis could also enable the radical difluoromethylthiolation of arenediazonium salts with $PhSO_2SCF_2H$ (**R3**) (Scheme 21).[44] In contrast to Li's case,[43] the visible light catalytic conditions generated an Ar• radical rather than the $HCF_2S^{\bullet}$ radical. Both an oxidative quenching pathway and a reductive quenching pathway are proposed. The $[Ru^{2+}]^*$ complex, generated from $[Ru^{2+}]$ by photoexcitation, reduces $[ArN_2^+ BF_4^-]$ to generate an Ar• radical (oxidative quenching), which is trapped by $PhSO_2SCF_2H$ to furnish the final products **20**. The $[Ru^{2+}]^*$ complex could also be reduced by sodium ascorbate to $[Ru^+]$ (reductive quenching), by which $[ArN_2^+ BF_4^-]$ is reduced to produce the Ar• radical. A wide substrate scope was observed, but the prefunctionalization of substrates is required.



Scheme 21 Visible-light-promoted difluoromethylthiolation of arenediazonium salts with $PhSO_2SCF_2H$ (**R3**)

Xu and co-workers described an atom-transfer radical addition of alkynes to give difunctionalized alkenes by the combination of visible-light photoredox catalysis and gold catalysis (Scheme 22).[45] The *E*/*Z* stereoselectivity is a challenging issue for atom-transfer radical addition to alkynes due to the low activation barriers for *E*/*Z* isomerization of the vinyl radicals generated in situ. In this work, high *E*/*Z* selectivity was observed due to the stabilization of the vinyl radical by the Au catalyst. They proposed that the Au catalyst interacts with the vinyl radical to form intermediate **Int25** or **Int26**. Radical **Int25** can then react with $PhSO_2SCF_2H$ to form the *trans*-difunctionalization product and regenerate a sulfonyl radical and the Au(I) catalyst. Intermediate **Int26** might react with $PhSO_2SCF_2H$ through single electron oxidation to generate the sulfonyl radical and a Au(III) intermediate **Int27**, the reductive elimination of which delivers the final product.

Organoboron compounds have served as valuable nucleophiles for a variety of reactions such as Suzuki coupling.[46] Recent studies (2010–2014) indicated that organoboron compounds can also act as radical precursors, but usually a

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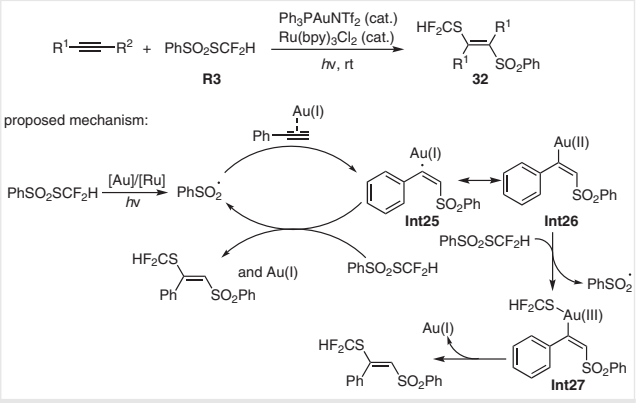
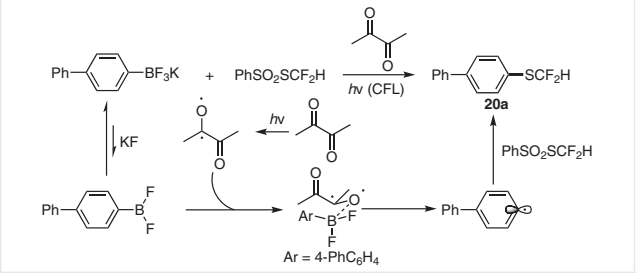


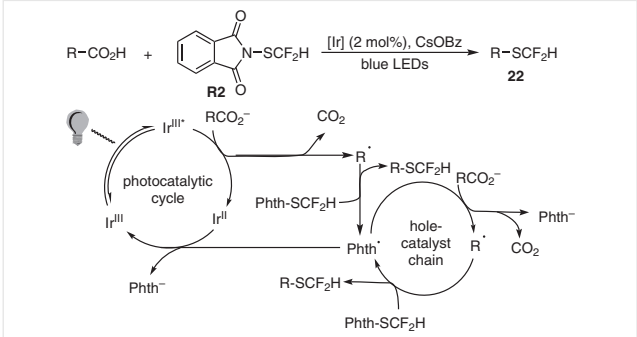
Scheme 22 Difluoromethylthiolation of alkynes with $PhSO_2SCF_2H$ (**R3**)

photoredox catalyst or strong oxidant is required.[47] In 2018, the Li group reported a distinct strategy for generating both aryl and alkyl radicals from organotrifluoroborates through an S_H2 (bimolecular homolytic substitution) process, and by using visible light as the energy input and diacetyl as the promoter in the absence of any metal catalyst or redox reagent.[48] This approach utilizes the triplet diacetyl to activate organotrifluoroborate and proceeds under mild reaction conditions. The use of $PhSO_2SCF_2H$ (**R3**) as the radical trapping reagent led to the difluoromethylthiolation product (Scheme 23).



Scheme 23 Radical difluoromethylthiolation of phenyltrifluoroborates using $PhSO_2SCF_2H$ (**R3**)

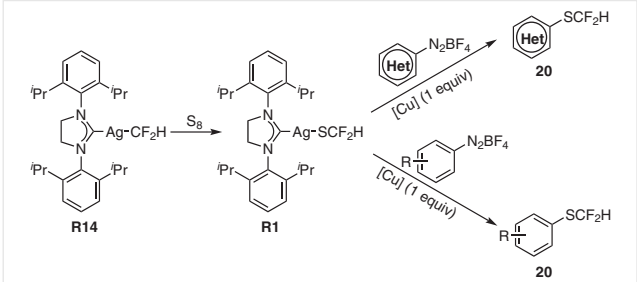
In 2016, the Glorius group developed a visible-light-promoted decarboxylative difluoromethylthiolation of alkanoic acids with reagent **R2** (Scheme 24).[49] Two catalytic cycles may be involved in this transformation. Photoexcitation of the Ir^{III} photocatalyst produces a strong oxidant, Ir^{III}*, which could oxidize the carboxylic acid to generate the R• radical (photocatalytic cycle). The abstraction of the HCF_2S group from **R2** by the radical affords the final product and the and the phthalimidyl radical (Phth•). A redox reaction between Ir^{II} and Phth• regenerates the catalyst Ir^{III} complex. Alternatively, the Phth• radical may also oxidize the carboxylic acid to form the R• radical (hole-catalyst chain). The cheap and abundant nature of alkanoic acids is an advantage of this protocol.



Scheme 24 Photocatalyzed difluoromethylthiolation with reagent Phth-SCF_2H (**R2**)

4 Transition-Metal-Catalyzed or -Promoted Difluoromethylthiolation

The nucleophilic difluoromethylthiolation reagent (SIPr)Ag(SCF_2H) (**R1**) was developed by Shen and co-workers in 2015.[15] It was prepared from a nucleophilic difluoromethylation reagent **R14**, which was also developed by Shen and co-workers.[50] Cu-mediated Sandmeyer-type difluoromethylthiolation of arene- and heteroarenediazonium salts with reagent **R1** occurred under mild reaction conditions and a variety of functional groups were compatible (Scheme 25).[15] A practical one-pot protocol for the synthesis of HCF_2S-substituted arenes from arylamines via direct diazotization followed by difluoromethylthiolation was developed. A series of biologically active HCF_2S-containing molecules was prepared via this Sandmeyer reaction, further demonstrating the synthetic utility of the protocol. Despite its relatively high cost, reagent **R1** shows wide applicability for various coupling reactions.



Scheme 25 Sandmeyer-type difluoromethylthiolation of diazonium salts with (SIPr)Ag(SCF_2H) (**R1**)

Although a reductive-elimination step may be problematic for the Pd-catalyzed difluoromethylthiolation of heteroaryl halides due to the electron-withdrawing nature of the HCF_2S group, Shen and co-workers found that Pd-catalyzed reactions by using (SIPr)Ag(SCF_2H) (**R1**) as the difluoromethylthiolation reagent proceeded smoothly (Scheme 26).[51] A variety of heteroaryl iodides, bromides and triflates

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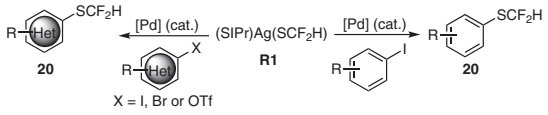
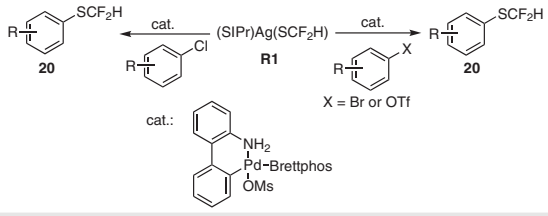
could all be converted into HCF_2S-substituted heteroarenes. Likewise, aryl iodides were transformed into the desired products in high yields. Medicinally important compounds were prepared by this Pd-catalyzed difluoromethylthiolation reaction, demonstrating the applicability of this protocol.



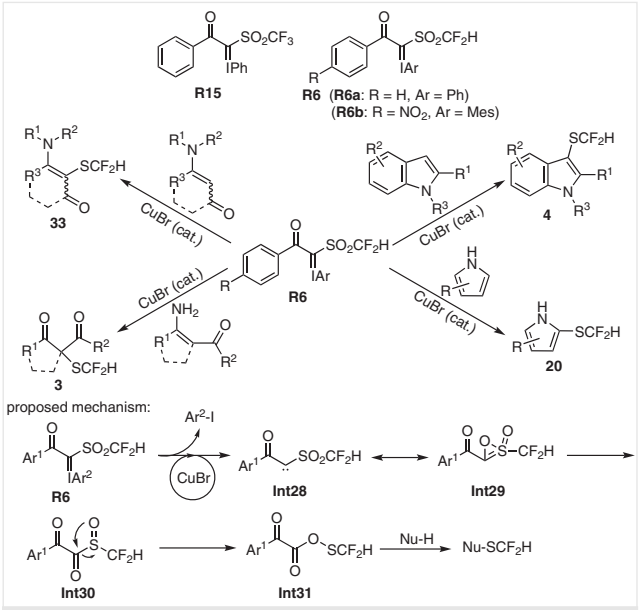
Scheme 26 Pd-catalyzed difluoromethylthiolation of aryl halides with (SIPr)Ag(SCF_2H) (**R1**)

Apparently, the C–Cl bond is much stronger than C–I and C–Br bonds, and therefore it would be more difficult to achieve the Pd-catalyzed coupling reaction of aryl chlorides with (SIPr)Ag(SCF_2H) (**R1**). However, Shen and co-workers disclosed that the use of an electron-rich and sterically bulky alkylphosphine as a ligand could enable the coupling reaction (Scheme 27).[52] Besides aryl chlorides, both aryl bromides and aryl triflates could also be converted smoothly. The functionalization of biologically active molecules and material molecules were achieved by this Pd-catalyzed coupling reaction.



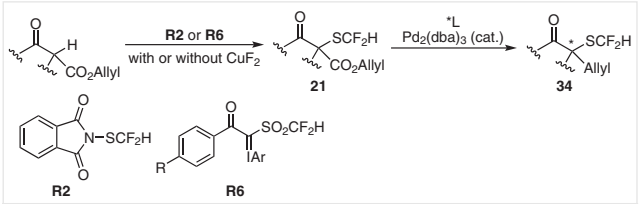
Scheme 27 Pd-catalyzed difluoromethylthiolation aryl chlorides, bromides, and triflates with (SIPr)Ag(SCF_2H) (**R1**)

In 2013, the Shibata group developed an effective trifluoromethanesulfonyl hypervalent iodonium ylide reagent **R15** for trifluoromethylthiolation.[53] On the basis of this work, they further developed (2016) difluoromethanesulfonyl hypervalent iodonium ylide reagents **R6**.[54] These reagents were very effective for the Cu-catalyzed difluoromethylthiolation of a variety of nucleophiles, such as enamines, indoles, β-keto esters, silyl enol ethers, and pyrroles (Scheme 28). The difluoromethylthiolation of enamines is particularly effective with wide generality, and a series of HCF_2S-containing cyclic and acyclic β-keto esters, and 1,3-diketones could be synthesized by this approach. They propose that the copper source is a catalyst for the generation of the carbene intermediate **Int28**. The subsequent formation of oxathiirene 2-oxide **Int29**, rearrangement to sulfoxide **Int30**, and the further collapse produces thioperoxoate **Int31**. Intermediate **Int31** is likely to be the real species for the difluoromethylthiolation of nucleophiles.



Scheme 28 Cu-catalyzed difluoromethylthiolation of nucleophiles with reagent **R6**

In 2018, the Shibata group further used reagents Phth-SF_2H (**R2**) and **R6** to synthesize racemic α-SCF_2H-β-keto-substituted allyl esters **21** (Scheme 29).[55] Interestingly, a Pd-catalyzed Tsuji decarboxylative asymmetric allylation of racemic β-keto allyl esters **21** gave chiral α-allyl-α-SCF_2H ketones **34** with high enantiopurity. The electron-withdrawing properties of the HCF_2S group presumably accelerate the decarboxylation process by stabilizing the resulting anion. This is the first report of the construction of a HCF_2S-containing tetrasubstituted stereogenic center.



Scheme 29 The synthesis of chiral α-allyl-α-SCF_2H ketones using Phth-SF_2H (**R2**) or **R6**

Intensive research efforts have been devoted to the development of difluoromethylthiolation methods, but asymmetric difluoromethylthiolation remains challenging. Although the above work provides a method for constructing HCF_2S-containing stereogenic centers,[55] a tedious two-step procedure is required. In 2019, the Shibata group further used their reagent **R6b** to achieve the asymmetric difluoromethylthiolation of indanone-based β-keto esters to deliver chiral HCF_2S-containing β-keto esters **35** (Scheme 30).[56] In this reaction, high enantioselectivity was obtained, but

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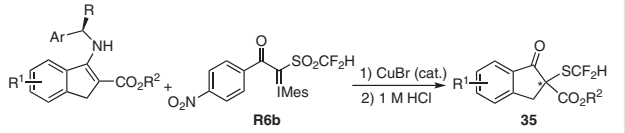

Scheme 30 Asymmetric difluoromethylthiolation using **R6b**

stoichiometric chiral amines have to be used as chiral auxiliaries.

5 Conclusions and Perspectives

As emphasized in this review, the incorporation of the HCF_2S group into organic compounds can drastically change their biological and physicochemical properties. The emergence of HCF_2S-containing pharmaceuticals and agrochemicals have prompted research into the development of efficient approaches for direct difluoromethylthiolation, including electrophilic, radical, and transition-metal-catalyzed or -promoted reactions. Although significant accomplishments have been made in the past two years, further developments are still necessary. The C–H difluoromethylthiolation and asymmetric catalyzed difluoromethylthiolation have rarely been reported. It is our hope that this review will encourage organic chemists to develop new and exciting methods for direct difluoromethylthiolation.

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