Cornerstones in Chemistry

Chen's reagent, Trifluoromethylation, Difluoroalkylation, Fluorine, Copper

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Chen's Reagent: A Versatile Reagent for Trifluoromethylation, Difluoromethylenation, and Difluoroalkylation in Organic Synthesis†

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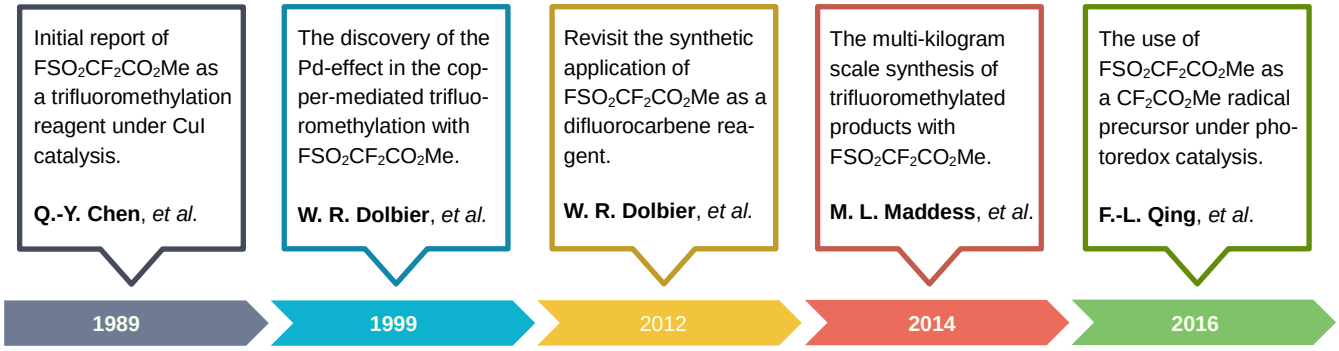
Summary Methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$ or MFSDA), often called "Chen's reagent", is commonly used to synthesize trifluoromethylated and difluoroalkylated compounds. This important reagent was initially developed as an efficient trifluoromethylating agent by Professor Qing-Yun Chen and co-workers at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences in 1989. Since then, this reagent has been widely used in academia and industry for the copper-mediated trifluoromethylation of aryl, alkenyl, and even some alkyl halides, among others. During the last decade, this reagent was further developed as a difluorocarbene precursor as well as a radical difluoroalkylating agent under visible light promoted redox catalysis. This review aims to briefly highlight the initial discovery, historical development, and synthetic applications of Chen's reagent, and provide some guidelines for readers to use Chen's reagent in their own synthesis.



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1. Introduction

Fluorine, lying in a unique position (Group VIIA and Period 2) in the periodic table of chemical elements, possesses unique properties such as high electron affinity and small atomic radius. As the most electronegative element, fluorine forms strong chemical bonds with other atoms; for instance, the C—F bond is the strongest single bond that carbon can form.[1] Therefore, introducing fluorine atom or fluorine-containing moieties into organic molecules can often lead to profound property changes, such as changing the electron distribution, increasing or decreasing the acidity of neighboring functionalities, enhancing the antioxidation ability, and improving the metabolic stability and lipophilicity of the target molecules.[2] As a consequence, fluorine has played a prominent role in the design and development of pharmaceuticals,[3] agrochemicals,[4] and functional materials.[5]

Among various fluorinated groups, the trifluoromethyl (CF_3) group is one of the most attractive functionalities, as witnessed by the fact that an increasing number of bioactive molecules and marketed drugs contain a CF_3 group.[3a,3c] Figure 1 shows some representative CF_3-containing drugs.

During the past half-century, a myriad of methods and reagents have been developed for the incorporation of CF_3 group into different types of substrates.[6] In this review, we intend to introduce one of the widely used trifluoromethylating reagents, methyl fluorosulfonyldifluoroacetate ($FSO_2CF_2CO_2Me$, MFSDA), which was initially developed by Chen and his student Wu in 1989.[7] This reagent is now known as Chen's reagent, which is perhaps the first well-recognized and widely used trifluoromethylation reagent developed in China. Several excellent reviews have put emphasis on the synthetic application of Chen's reagent,[8] including a recent one entitled "Methyl fluorosulfonyldi-

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† Dedicated to Professor Qing-Yun Chen on the occasion of his 90th birthday.

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fluoroacetate (MFSDA): An Underutilised Reagent for Trifluoromethylation".[9]

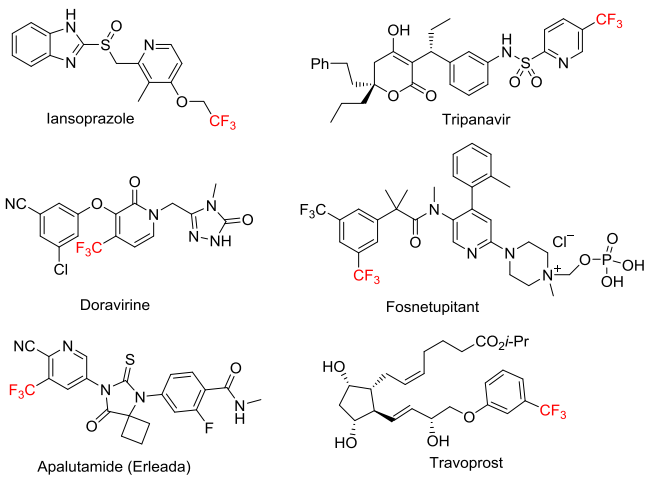


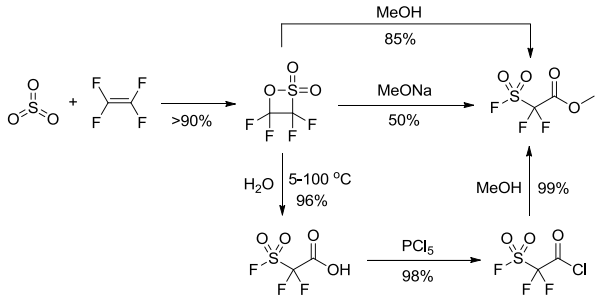
Figure 1 CF_3-containing drugs.

The aim of this review is not attempting to provide a comprehensive summary of every synthetic application of Chen's reagent. Instead, we would like to share with the readers a story about how Chen's reagent was initially discovered, and how this reagent/method was further developed over the years. We also provide the key applications as well as mechanistic insights into the trifluoromethylation and other fluoroalkylation reactions with Chen's reagent. Concurrently, we hope to provide some guidelines for readers to use Chen's reagent in their own synthesis.

2. Initial Discovery

$FSO_2CF_2CO_2Me$ can be easily prepared from tetrafluoroethylene β-sultone (TFES), which is the starting material for the industrial production of Nafion-H resin.[10] In 1955, the first preparation of TFES was recorded in two patents owned by 3M[11] and DuPont companies,[12] both using a [2+2] cycloaddition reaction between tetrafluoroethylene (TFE) and SO_3. Similarly, an analogous [2+2] cycloaddition between polyfluoroalkene and SO_3 was reported by Jiang in China two years later.[13] In 1956, England from DuPont patented the first preparation of $FSO_2CF_2CO_2Me$ by reacting TFES with sodium methoxide.[14a] Later on, in 1960, England *et al*. published a research paper to summarize their results in the synthesis of TFES, $FSO_2CF_2CO_2Me$, and other related compounds.[14b] During this period of time, Soviet chemists Dmitriev *et al.* also reported the preparation of TFES and $FSO_2CF_2CO_2Me$ using similar methods.[15a-b] Recently, Chen *et al*. described a more convenient method to access $FSO_2CF_2CO_2Me$ by the direct reaction of TFES and methanol.[15c] These three routes reported by England, Dmitriev and Chen to access $FSO_2CF_2CO_2Me$ are shown in Scheme 1, respectively.

Scheme 1 The preparation of $FSO_2CF_2CO_2Me$



Although $FSO_2CF_2CO_2Me$ was known in late 1950s, its synthetic application in organic synthesis had been almost neglected. Almost nobody paid attention to this compound until Chen's seminal work on the trifluoromethylation of aryl halides by means of $FSO_2CF_2CO_2Me$ in 1989.[7] Indeed, Chen's discovery of $FSO_2CF_2CO_2Me$ as a trifluoromethylating agent was an excellent example of mission-driven academic research.[8b]

The story can be dated back to 1970s. In order to tackle a problem of chromic acid pollution in chromium plating industry, Chen's group devoted to the synthesis of perfluoroalkoxyalkanesulfonic acids using TFE as a starting material in late 1970s. After several years of hard work, Chen's group developed China's first novel and structurally unique chromic acid mist suppressant $CF_3(CF_2)_5OCF_2CF_2SO_3K$ (F-53), eventually.[8b] The success in the development of F-53 not only solved the chromic acid pollution problem in many chromium plating factories in China, but also provided many useful fluorinated intermediates (such as FSO_2CF_2COOH and fluoroalkyl iodides). These useful fluorinated intermediates became the starting materials of basic research in Chen's group.[8b] Subsequently, using these valuable intermediates, Chen's group carried out a systematic investigation on the reactivity of perfluoro- and polyfluorosulfonic acids and their derivatives.[16] They discovered several difluorocarbene precursors, which can generate difluorocarbene under acidic conditions or basic conditions or both, including $FSO_2CF_2CO_2Me$.[8c] In their initial studies, they found that many nucleophiles, for instance, X^- (Cl^-, Br^-, I^-), CNS^-, Et_3N and pyridine, can react with $FSO_2CF_2CO_2Me$ to produce difluorocarbene.[17] Serendipitously, they observed the formation of a side-product, HCF_3. This observation was so important that it finally changed the fate of $FSO_2CF_2CO_2Me$. Chen quickly realized that the generation of HCF_3 clearly suggests that there might be an equilibrium between trifluoromethyl anion (CF_3^-) and difluorocarbene ($:CF_2$) and fluoride ion (F^-). Therefore, he envisaged that $FSO_2CF_2CO_2Me$ might be able to serve as a trifluoromethylating agent.[18] Indeed, by taking advantage of this equilibrium, Chen and his graduate student Wu ultimately accomplished the trifluoromethylation of organohalides with $FSO_2CF_2CO_2Me$ in the presence of only catalytic amount (12 mol%) of CuI.[7] Since this pioneering work, $FSO_2CF_2CO_2Me$ has found wide use ever since.[8a,8c,9]

3. Reactivity, Scope and Application of $FSO_2CF_2CO_2Me$

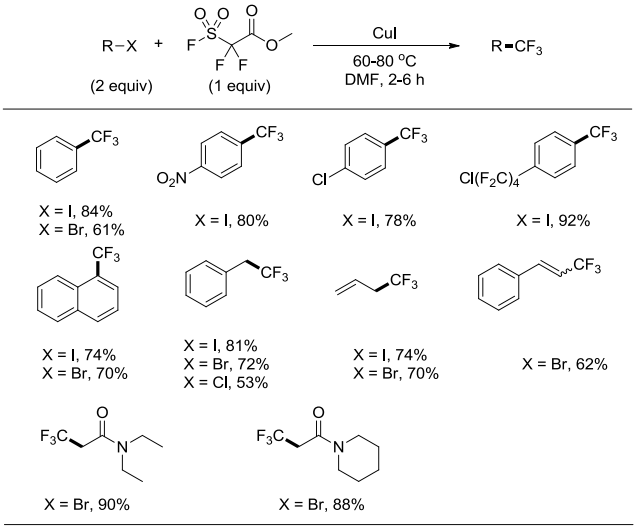
3.1. $FSO_2CF_2CO_2Me$ as a trifluoromethyl source

3.1.1. Seminal reports on $FSO_2CF_2CO_2Me$. In 1989, Chen *et al*. reported $FSO_2CF_2CO_2Me$ as a new trifluoromethylation reagent.[7] In their seminal report, they unraveled that aryl halides, alkenyl halides, and α-haloamides can be efficiently trifluoromethylated in the presence of catalytic amount of CuI (12 mol%). It must be emphasized that this was the first example of copper-catalyzed aromatic trifluoromethylation reaction, and the second example of aromatic trifluoromethylation under copper catalysis was reported nearly 20 years later.[6h,6k] DMF was used as the solvent, although DMSO is also a good alternative. The reaction proceeded at 60—80 °C, which was relatively milder than previous reports on copper-mediated trifluoromethylation. The reaction typically completed within 2—6 h. The substrate scope demonstrated in the seminal report is shown in Scheme 2.

From these preliminary results, Chen *et al*. uncovered that the reactivity order was RI > RBr > RCl. RBr was reactive enough to achieve high yields, while RCl showed low reactivity (for R = benzyl) or even no reactivity (for R = aryl) in trifluoromethylation.[7] In a subsequent report, they described that if aryl chlorides containing strong electron-withdrawing groups (such as NO_2), trifluoromethylation of aryl chloride can be achieved; the more NO_2 groups an

aryl chloride bears, the higher reactivity it has.[19]

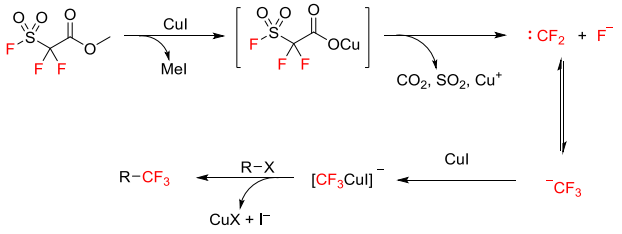
Scheme 2 Copper-catalyzed trifluoromethylation of organohalides with $FSO_2CF_2CO_2Me$



CuI is essential for this reaction. If KI was used instead of CuI under similar conditions, the substrate PhI was recovered completely, and only HCF_3 was obtained in 93% yield.[7]

One of the most interesting features of $FSO_2CF_2CO_2Me$ is that, although it is a trifluoromethylating agent, there is indeed no CF_3 group in the chemical structure of this reagent. During the copper-catalyzed trifluoromethylation reaction with $FSO_2CF_2CO_2Me$, the CF_3 group comes from the combination of difluorocarbene and fluoride anion, which are generated in situ from the decomposition of the $FSO_2CF_2CO_2Me$. This behavior is different from many other well-known trifluoromethylation reagents containing a CF_3 group, such as CF_3I, Ruppert-Prakash reagent ($TMSCF_3$) and Togni's reagent.[6h] Moreover, unlike some difluorocarbene reagents that require an extra addition of fluoride source[8a] or sacrifice of one molar of difluorocarbene to generate fluoride in situ[20] to implement trifluoromethylation, $FSO_2CF_2CO_2Me$ itself contains a latent fluoride, thus no extra fluoride ion is required. The mechanism of trifluoromethylation with $FSO_2CF_2CO_2Me$ is shown in Scheme 3.

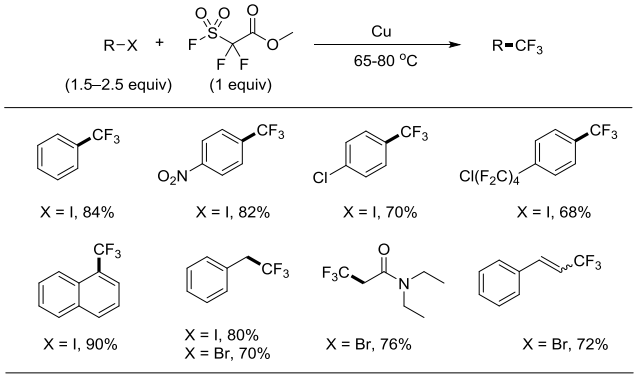
Scheme 3 The proposed mechanism of copper-catalyzed trifluoromethylation of organohalides with $FSO_2CF_2CO_2Me$



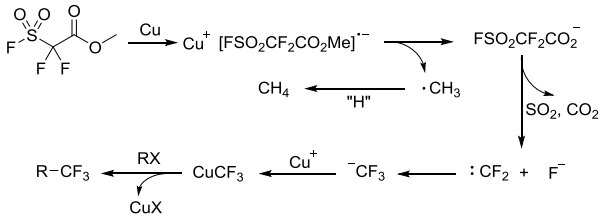
The reaction of $FSO_2CF_2CO_2Me$ with CuI generates $FSO_2CF_2CO_2Cu$ and MeI. The $FSO_2CF_2CO_2Cu$ species readily undergoes decarboxylation to give difluorocarbene and a fluoride ion, which are in equilibrium with a trifluoromethyl anion. In the presence of CuI, this equilibrium quickly shifts to CF_3^-, forming $[CF_3CuI]^-$ intermediate, which reacts with organohalides to afford the desired trifluoromethylated products.[7]

Chen *et al*. found that $FSO_2CF_2CO_2Me$ can also efficiently trifuoromethylate aryl and benzyl halides in the presence of catalytic amount of copper powder (Scheme 4).[19] The gases produced during the reaction was identified as CH_4 (~30%), CO_2 (quantitative), and SO_2 (quantitative). As the reaction could be partially suppressed by oxygen, *p*-dinitrobenzene or in darkness, they proposed a copper-induced single electron transfer (SET) mechanism, as described in Scheme 5.

Scheme 4 Cu(0)-induced trifluoromethylation of organohalides with $FSO_2CF_2CO_2Me$



Scheme 5 The proposed mechanism of Cu(0)-induced trifluoromethylation of organohalides with $FSO_2CF_2CO_2Me$



The single electron transfer (SET) from Cu to $FSO_2CF_2CO_2Me$ would generate Cu^+ and a radical anion, which readily undergoes fragmentation into methyl radical, difluorocarbene and fluoride ion. The combination of difluorocarbene and fluoride forms CF_3^-, which further delivers $CuCF_3$. The reaction of $CuCF_3$ with RX generates the desired products, liberating CuX. Methyl radical abstracts a hydrogen from solvent to give CH_4.[19] However, in the trifluoromethylation of RX using $FSO_2CF_2CO_2Me$/CuI system, no methane was produced.[7] It is apparent that Cu^0 plays an important role in the formation of methane. Since only 30 mol% of methane was collected during the reaction, the in situ generated CuX may also be involved in the trifluoromethylation as a catalyst via a mechanism shown in Scheme 3.

The mechanism shown in Scheme 5 gives a good rationale for the trifluoromethylation with $FSO_2CF_2CO_2Me/Cu^0$, and the formation of methane could support the presence of methyl radical; however, it is known that a methyl radical is generally difficult to generate and harsh conditions are usually required.[21] So it is particularly interesting that $FSO_2CF_2CO_2Me/Cu^0$ system is able to generate methyl radical in such an easy fashion.

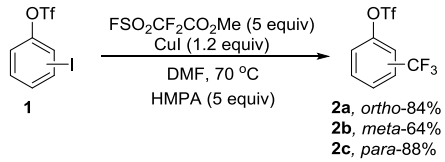
Another interesting reactivity of $FSO_2CF_2CO_2Me$ is, as will be introduced later, that its C—S bond can be homolytically cleaved under other SET processes.[22]

$FSO_2CF_2CO_2Me$ can also be used to achieve trifluoromethylthiolation of aryl halides in the presence of S_8. In this process, the in situ generated $[CuCF_3]$ species reacts with S_8 to give $[CuSCF_3]$, which serves as the key intermediate for the trifluoromethylthiolation.[23]

3.1.2. Representative applications of $FSO_2CF_2CO_2Me$. Considering that trifluoromethylated aryl triflates are potentially useful intermediates for the preparation of bioactive trifluoromethylated aromatic compounds via cross-coupling reactions, Qing *et al*. de-

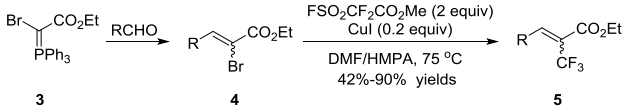
veloped an efficient method to access this type of molecules and *ortho*-trifluoromethylphenyl triflate was synthesized for the first time.[24] Reaction of iodophenol with trifluoromethanesulfonic anhydride gave high yields of triflates. A number of methods had been attempted to trifluoromethylate iodophenyl triflates. For instance, treatment of *ortho*-iodophenyl triflate with Me_3SiCF_3/CuI or CF_2Br_2/Cd/CuBr or $ClCF_2CO_2Me$/CuI/KF system was unsuccessful; no desired trifluoromethylated product was observed, with the starting material being recovered or decomposed. When employing Chen's method ($FSO_2CF_2CO_2Me$/CuI), they found that the reaction proceeded slowly, with low conversion of the starting materials. But when hexamethylphosphoric triamide (HMPA) was added, $FSO_2CF_2CO_2Me$ could efficiently trifluoromethylate *ortho*-iodophenyl triflate at 70 °C in 4 h in 84% yield (Scheme 6). HMPA might function as a stabilizer to stabilize the in situ formed $CuCF_3$ species.[20] With *ortho*-trifluoromethylphenyl triflate in hand, a concise synthesis of conformationally restricted retinoid containing a CF_3 group was achieved.[24]

Scheme 6 The trifluoromethylation of iodophenyl triflates with $FSO_2CF_2CO_2Me$



Qing *et al*. developed a new route for the synthesis of α-trifluoromethyl-α,β-unsaturated esters, which were the key intermediates to synthesize trifluoromethyl nucleosides, and $FSO_2CF_2CO_2Me$ was used as a trifluoromethylating agent (Scheme 7).[25] Several notifications should be pointed out in the trifluoromethylation step. (1) Excess of $FSO_2CF_2CO_2Me$ is required to fulfill full conversion of the alkenyl bromides, and the addition rate of $FSO_2CF_2CO_2Me$ has an influence on the reaction: the slower the addition rate is, the lower loadings of $FSO_2CF_2CO_2Me$ are required. (2) The reaction proceeds smoothly in the presence of either catalytic or stoichiometric amount of CuI, and the use of stoichiometric amount of CuI has no advantage over the catalytic version. (3) Alkene isomerization was observed during this process. One of α-trifluoromethyl-α,β-unsaturated esters was transformed to a variety of 2',3'-dideoxy-2'-trifluoromethylnucleosides.[25b]

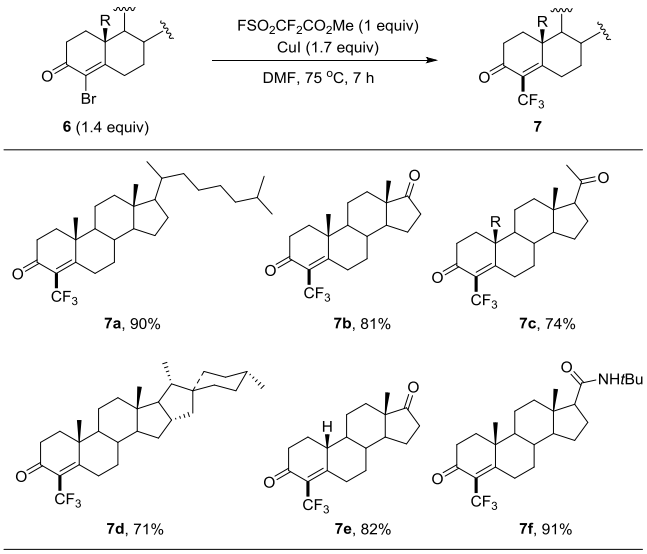
Scheme 7 Synthesis of α-trifluoromethyl-α,β-unsaturated esters with $FSO_2CF_2CO_2Me$



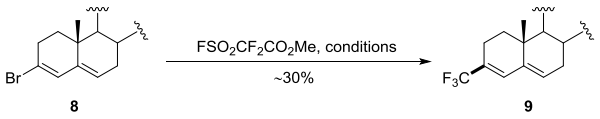
In 1997, Chen *et al*. investigated the reaction between steroid olefinic bromides and $FSO_2CF_2CO_2Me$,[26] considering the good bioactivity of steroids and the well-known benefit of introducing a CF_3 group into bioactive molecules. They found that 4-bromo-3-oxo-Δ^4-steroids **6** smoothly reacted with $FSO_2CF_2CO_2Me$ to give 4-trifluoromethylated products **7** in good yields (Scheme 8), whereas steroidal 3-bromo-$\Delta^{3,5}$-dienes **8** showed low reactivity towards $FSO_2CF_2CO_2Me$ (Scheme 9).[26b] It is remarkable that **7f** exhibited higher reactivity towards 5α-reductase in *in vitro* assay than Finasterides, which has been used as an effective cure for BPH.[26a]

In 1999, Dolbier *et al*. conducted a research for the preparation of ring-substituted derivatives of octafluoro[2.2]paracyclophane (OFP), which is a monomer for the Parylene VIPAF4 polymer.[27] A trifluoromethylated derivative of OFP was synthesized

Scheme 8 The synthesis of 4-trifluoromethyl-3-oxo-Δ^4-steroids with $FSO_2CF_2CO_2Me$

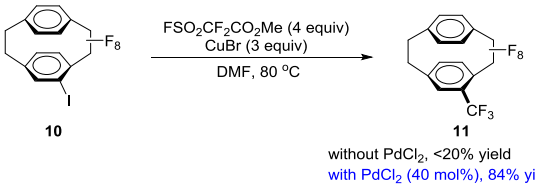


Scheme 9 The trifluoromethylation of steroidal 3-bromo-$\Delta^{3,5}$-diene with $FSO_2CF_2CO_2Me$



from the corresponding iodo derivative **10** with Chen's reagent. When they used Chen's standard procedure, a poor yield of **11** was obtained (< 20%), with hydrodeiodination product (the reduction product) being formed as the major one. However, the addition of $PdCl_2$ (40 mol%) dramatically increased the yield of **11** to 84%, and only 3% of reduction product was formed (Scheme 10). The intriguing effect of $PdCl_2$, yet in a much smaller amount (about 5%), was again observed in the double trifluoromethylation of diiodo-OFP.[28]

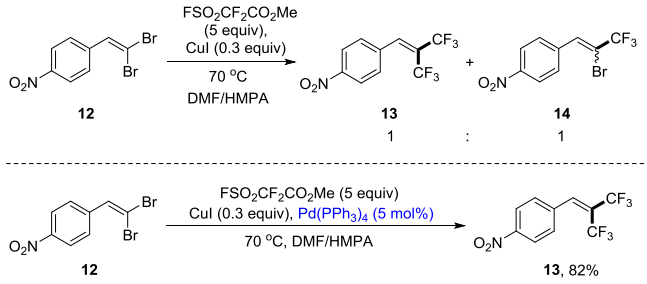
Scheme 10 The trifluoromethylation of **10** with $FSO_2CF_2CO_2Me$



Similarly, the Pd-effect was observed by Qing *et al.* in the trifluoromethylation of dibromoalkenes.[29] When 1,1-dibromo-2-(4-nitrophenyl)ethane **12** reacted with $FSO_2CF_2CO_2Me$/CuI in DMF/HMPA at 70 °C for 24 h, a mixture of bistrifluoromethylated product **13**, monotrifluoromethylated products **14** and unreacted **12** were observed (Scheme 11, top). Remarkably, when $Pd(PPh_3)_4$ was added as a cocatalyst, only the bistrifluoromethylated product **13** was obtained in 82% yield (Scheme 11, bottom). This comparison again demonstrates that the presence of a palladium catalyst can dramatically improve the efficiency of trifluoromethylation. The critical role of the palladium catalyst to promote aromatic trifluoromethylation was also observed in the trifluoromethylation of porphyrins with $FSO_2CF_2CO_2Me$/CuI by Chen and coworkers.[30]

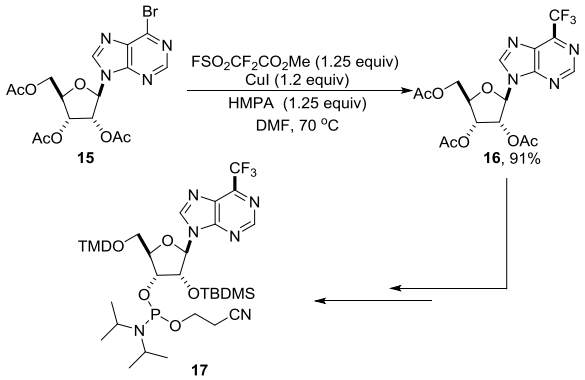
Beal *et al*. reported the synthesis of 6-trifluoromethylpurine ribonucleosides, which might be valuable in the study of RNA

Scheme 11 The trifluoromethylation of dibromoalkene **12** with $FSO_2CF_2CO_2Me$



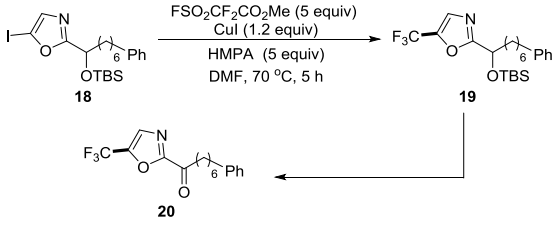
structure and the binding of RNA-modifying enzymes, particularly the RNA-editing adenosine deaminases.[31] The preparation of 6-trifluoromethylpurine ribonucleoside was studied first. Although this compound had been prepared previously by the reaction of 6-chloropurine ribonucleoside with CF_3I/Cu^0, the yield was low (29%) and the reaction time was long (60 h).[32] Beal *et al*. found two efficient routes for the synthesis of **16**. Starting from bromopurine derivative **15**, both $FSO_2CF_2CO_2Me$/CuI/DMF/HMPA and CF_3I/Zn/CuI/DMF systems led to high yield of **16**, and the former method was deemed to be more favorable owing to the ease of manipulation of liquid $FSO_2CF_2CO_2Me$ versus the gaseous CF_3I. **16** was then transformed to phosphoramide **17** (Scheme 12), which can be easily incorporated into RNA using a standard automated synthetic procedure.

Scheme 12 The trifluoromethylation of bromopurine derivative **15** with $FSO_2CF_2CO_2Me$



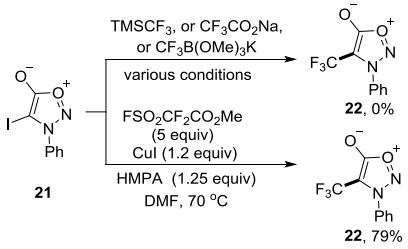
α-Ketoheterocycles belong to important fatty acid amide hydrolase (FAAH) inhibitors, exhibiting potent and selective enzyme inhibition and in vivo efficacy. Boger *et al*. synthesized a series of C5-substituted α-ketooxazoles to evaluate the substituent effect on the potency of inhibitors. Among them, 5-trifluoromethyl substituted α-ketooxazole **20** was prepared, which turned out to be a potent inhibitor, with K_i = 0.8 nM. **20** was readily prepared from the corresponding heteroaryl iodide **18**. The trifluoromethylation of **18** with $FSO_2CF_2CO_2Me$ afforded **19** in 55% yield under mild conditions (Scheme 13). **19** underwent a deprotection-oxidation sequence to deliver **20**.[33]

Scheme 13 The trifluoromethylation of **18** with $FSO_2CF_2CO_2Me$



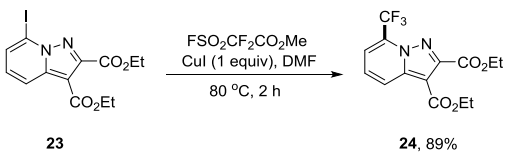
Fluorinated pyrazoles are prevalent targets in bioactive studies. Many bioactive trifluoromethylated pyrazoles have been known, such as celecoxib and fluazolate. In 2012, Harrity *et al*. developed a general protocol to construct 5-trifluoromethylpyrazoles through a regioselective cycloaddition reaction between 4-trifluoromethylsydnones and alkynes.[34] In this methodology, the preparation of a diversity of 4-trifluoromethylsydnones is a key issue. Although a linear and lengthy synthetic sequence was developed to forge 4-trifluoromethylsydnones, some serious limitations such as functional group incompatibility of this approach rendered them to develop a more convenient strategy to access 4-trifluoromethylsydnones.[34b] In this context, a late-stage trifluoromethylation met this criterion. Trifluoromethylation of 4-iodo-*N*-phenylsydnone **21** was tested. Surprisingly, Ruppert-Prakash reagent, a widely used trifluoromethylation reagent, failed to give the desired product **22** under a range of conditions. Analogously, using $CF_3B(OMe)_3K$ and CF_3CO_2Na as the CF_3 source all proved to be a failure. It should be underscored that only $FSO_2CF_2CO_2Me$ could successfully trifluoromethylate **21**, giving **22** in good yield (Scheme 14).[34a] These comparisons strongly highlight the superiority of Chen's reagent in trifluoromethylation of complex molecules. Combining the direct trifluoromethylation with $FSO_2CF_2CO_2Me$ and the cycloaddition methods, Harrity *et al*. accomplished the formal synthesis of fluazolate.[34a]

Scheme 14 The trifluoromethylation of 4-iodosydnone **21** with $FSO_2CF_2CO_2Me$



7-Trifluoromethylpyrazolo[1,5-*a*]pyridinedicarboxylate **24** was an important intermediate for a drug candidate in Liu's drug discovery program. They designed two new routes to overcome the restrictions of the previous one. One of the two new routes involves the trifluoromethylation of 7-iodopyrazolo[1,5-*a*]pyridinedicarboxylate **23** as a key step.[35] The trifluoromethylation of **23** turned out to be not trivial. Initial attempt using $TMSCF_3$ as the CF_3 source in the presence of CuI and CsF was able to transform **23** to **24**; however, other side products were also formed. A number of trifluoromethylation reagents and conditions were screened, and only $FSO_2CF_2CO_2Me$ could react cleanly with **23** in the presence of CuI (1 equiv) in DMF in 2 h, giving **24** in 89% yield (Scheme 15). Substoichiometric amount of CuI (0.75 equiv) is also applicable. Notably, pyrazolopyridine dicarboxylate (300 g) readily underwent zincation/iodination to give **23**, which was used for trifluoromethylation without isolation, giving **24** in 86% total yield (for two steps) on a 6-liter scale.

Scheme 15 The trifluoromethylation of **23** with $FSO_2CF_2CO_2Me$



Perhaps the power of Chen's reagent was best demonstrated according to a report from Maddess *et al*. in 2014.[36] Tetrahydrofluoroene **25** (Figure 2) was identified as a potent selective ER β agonist, which was selected for further development. In this re-

gard, two scalable approaches were described by them, both containing a trifluoromethylation step (Scheme 16).

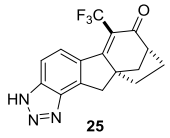
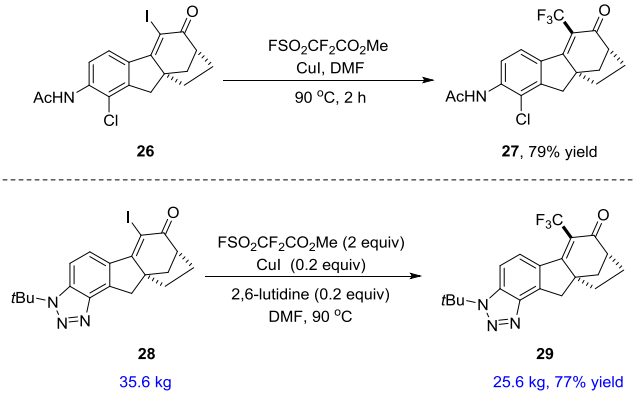


Figure 2 Tetrahydrofluoroene candidate **25**

Scheme 16 The trifluoromethylation of **26** and **28** with $FSO_2CF_2CO_2Me$

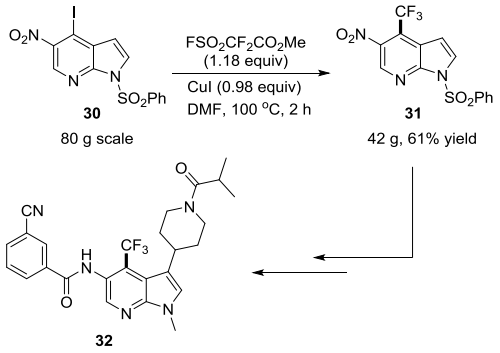


In the first approach, they introduced a CF_3 group into **26** (Scheme 16, top). After extensive optimizations, they revealed that $FSO_2CF_2CO_2Me$/CuI system provided the best result. It should be mentioned that a dropwise addition (over 3 h) of $FSO_2CF_2CO_2Me$ to the preheated reaction mixture (90 °C) was pivotal to a kilo-scale reaction by controlling the heat of reaction and ensuring safe processing. In this approach, product **27** was obtained in 79% yield. In the second approach, the installation of a CF_3 group into **28** was required (Scheme 16, bottom). For this substrate, the trifluoromethylation was particularly challenging because of the unproductive methylation of the product during the reaction process; the methyl group came from the in situ generated MeI, which was formed by the decomposition of $FSO_2CF_2CO_2Me$ (see Scheme 3). After numerous trials, they eventually identified good reaction conditions: adding 2,6-lutidine (0.2 equiv), keeping low concentration of reactants, and adding $FSO_2CF_2CO_2Me$ dropwise in a period of over 1 h. Under the optimized conditions, **28** was transformed into **29** in 77% isolated yield on up to 26 kg scale. Notably, in this case, CuI was used catalytically.

The nuclear hormone receptor retinoic acid receptor-related orphan C2 (RORC2) is a promising target for treating autoimmune diseases. Schnute *et al*. developed a strategy to optimize RORC2 inverse agonist.[37] During this process, a highly potent and orally bioavailable lead molecule **32**, which contains a CF_3 moiety, was cognized. **32** was able to reduce the levels of IL-17A and skin inflammation *in vivo* after oral dosing in mice. The 4-trifluoromethyl substituted intermediate was difficult to prepare, and the CF_3 group was finally introduced in the step of the conversion of **30** to **31** using Chen's reagent as the CF_3 source (Scheme 17). The corresponding chloro- and bromo-analogues of **30** could facilitate the incorporation of CF_3, but the iodide was the most efficient. Both NO_2 and $PhSO_2$ groups in **30** were found to play critical roles for the trifluoromethylation, as no desired products could be obtained without either of these two groups.

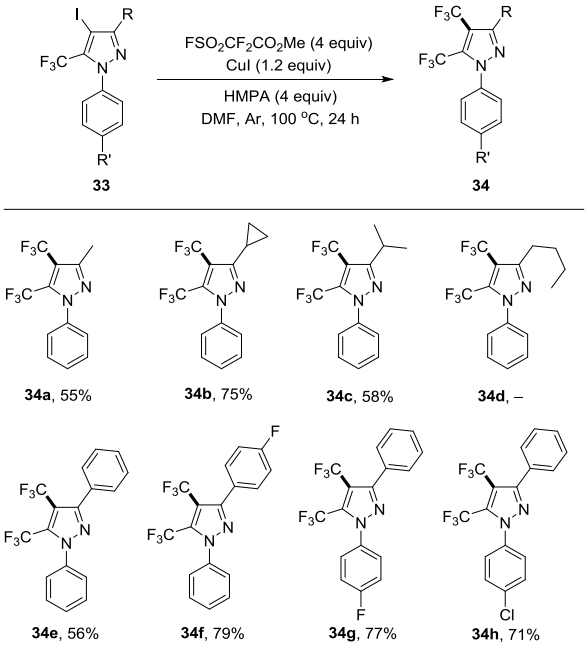
Very recently, Bonacorso *et al*. described a protocol for the assembly of novel 4,5-bis(trifluoromethyl)-1*H*-pyrazoles through a concise sequential iodination-trifluoromethylation.[38] The CF_3 group was introduced with $FSO_2CF_2CO_2Me$, and a number of

Scheme 17 The trifluoromethylation of **30** with $FSO_2CF_2CO_2Me$



1-aryl-3-alkyl(aryl)-4,5-bis(trifluoromethyl)-1*H*-pyrazoles **34** were smoothly obtained (Scheme 18). Notably, there are many interesting features that need to be mentioned in this trifluoromethylation reaction with $FSO_2CF_2CO_2Me$. When the reaction was carried out using **33a** as a model substrate under $FSO_2CF_2CO_2Me$/CuI/DMF/80 °C conditions, no desired product **34a** was observed. However, adding HMPA as a co-solvent led to 56% yield of **34a**. Raising the temperature to 100 °C or increasing the loadings of $FSO_2CF_2CO_2Me$ from 4 to 5 equivalents gave inferior results. Carrying out the reaction under argon atmosphere also had a beneficial effect.

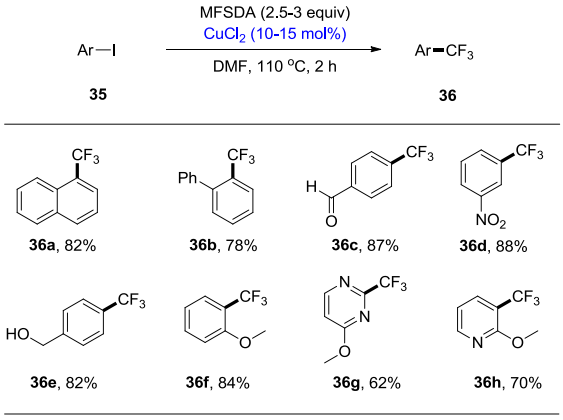
Scheme 18 The trifluoromethylation of **33** with $FSO_2CF_2CO_2Me$



There are many other elegant examples that applied Chen's regent ($FSO_2CF_2CO_2Me$) in the synthesis of biologically relevant scaffolds. One could refer to recent publications for more examples.[8c,9,39]

3.1.3. A revisit to Chen's reagent. Recently, a revisit to Chen's reagent was reported by Guo *et al*., and an improved catalytic trifluoromethylation was developed.[39a] They disclosed that using $FSO_2CF_2CO_2Me$ as the trifluoromethylation reagent, a myriad of structurally diverse (hetero)aryl iodides can be trifluoromethylated in a highly effective manner using $CuCl_2$ as a catalyst (Scheme 19).

Scheme 19 The trifluoromethylation of (hetero)aryl iodides **35** with $FSO_2CF_2CO_2Me$



3.1.4. An overview of Chen's reagent for trifluoromethylation. Since the seminal report by Chen et al. in 1989, the Chen's reagent ($FSO_2CF_2CO_2Me$) has undeniably received great attention in organic synthesis, as evidenced by the representative applications highlighted in section 3.1.2. Herein, we present some guidelines with respect to using Chen's reagent in trifluoromethylation as follows.

(1) $FSO_2CF_2CO_2Me$ was initially reported as a trifluoromethylation reagent for aryl halides ArX (X = I, Br), alkenyl halides, benzyl halides and α-bromocarbonyl compounds, among which the aryl or heteroaryl iodides are the most widely used substrates. A vast array of heterocycles, including but not limited to pyridine, pyrimidine, thiophene, oxazole, pyrazole, sydnone and purine, are amenable substrates.

(2) To date, three catalytic systems (using catalytic amount of CuI, Cu^0 or $CuCl_2$) have been known to achieve trifluoromethylation of ArI with $FSO_2CF_2CO_2Me$, and the CuI catalysis has been the most extensively used one.

(3) Although a catalytic amount of CuI was used in the seminal report and in some other cases, the stoichiometric amount of CuI is more often used in $FSO_2CF_2CO_2Me$-involved trifluoromethylation.

(4) DMF is a most commonly used solvent, and the reaction is typically carried out at 80±20 °C. However, in some cases, the addition of HMPA is required to ensure the reaction efficiency.

(5) CuI alone is enough to promote trifluoromethylation in most cases. Nevertheless, in some cases, the addition of an extra palladium catalyst is beneficial for the reaction efficiency.

(6) In many cases, large excess amounts of $FSO_2CF_2CO_2Me$ reagent are required. Notably, the slow addition of $FSO_2CF_2CO_2Me$ has been found to be helpful in reducing the loading of $FSO_2CF_2CO_2Me$.

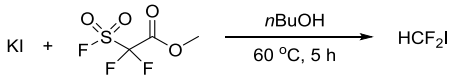
(7) The decomposition of $FSO_2CF_2CO_2Me$ releases MeI, CO_2, and SO_2. This process is highly exothermic; therefore, a close attention should be paid when $FSO_2CF_2CO_2Me$ is used in large scale reactions (for example, in multi-kilogram scale).

3.2. $FSO_2CF_2CO_2Me$ as a difluorocarbene source

As described in section 2, $FSO_2CF_2CO_2Me$ was initially identified as a difluorocarbene ($:CF_2$) precursor.[17] Despite this fact, $FSO_2CF_2CO_2Me$ was seldom used as a difluorocarbene source, and limited reports are known.

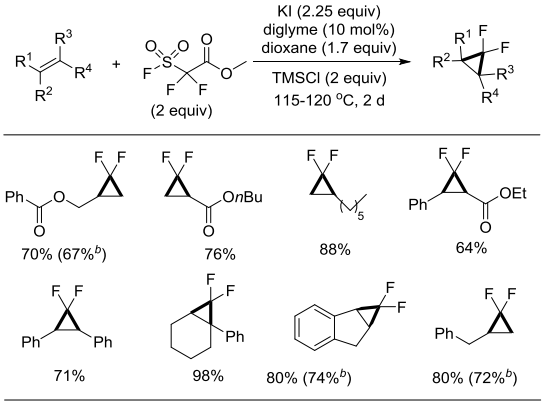
In 1994, Chen *et al*. reported that $FSO_2CF_2CO_2Me$ could be used as a $:CF_2$ source for the synthesis of HCF_2I (Scheme 20).[40] A possible mechanism was proposed: the difluorocarbene species (generated from $FSO_2CF_2CO_2Me$) reacts with iodide ion to form ICF_2^-, followed by protonation to give HCF_2I.[40]

Scheme 20 The preparation of HCF_2I with $FSO_2CF_2CO_2Me$



In attempts to seek an alternative difluorocarbene reagent that compensates the drawbacks of $FSO_2CF_2CO_2TMS$ while could still effectively react with electron-deficient alkenes, Dolbier *et al*. found that $FSO_2CF_2CO_2Me$ is the right choice.[41] By using KI as the iodide source to induce difluorocarbene generation from $FSO_2CF_2CO_2Me$, TMSCl as the fluoride scavenger and minimal mixed solvents (diglyme and dioxane), a broad selection of alkenes with varying reactivity could react with $FSO_2CF_2CO_2Me$ to give the desired *gem*-difluorocyclopropanes in good yields (Scheme 21). Remarkably, both high temperature and high concentration are critical to guarantee high reaction efficiency.

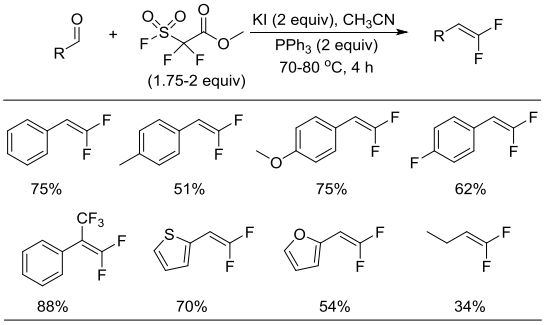
Scheme 21 The gem-difluorocyclopropanation of alkenes with $FSO_2CF_2CO_2Me$[a]



[a] NMR yield. [b] Isolated yield.

Shortly afterwards, Dolbier *et al*. applied $FSO_2CF_2CO_2Me$ for the difluoroolefination of carbonyl compounds.[42] KI was used as a demethylating agent to generate difluorocarbene from $FSO_2CF_2CO_2Me$. The *in situ* generated difluorocarbene was captured by PPh_3 to produce difluoromethylene triphenylphophonium ylide, $Ph_3P{=}CF_2$, which is the key intermediate to react with aldehydes or activated ketones, giving *gem*-difluoroolefins (Scheme 22).

Scheme 22 The gem-difluoroolefination of aldehydes and activated ketones with $FSO_2CF_2CO_2Me$[a]



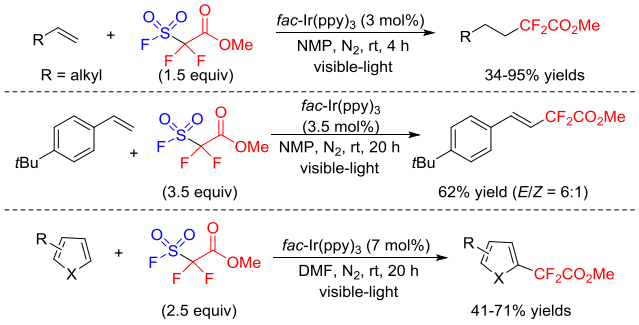
[a] Yields determined by ^{19}F NMR using trifluorotoluene as the internal standard.

3.3. $FSO_2CF_2CO_2Me$ as a difluoroalkyl source

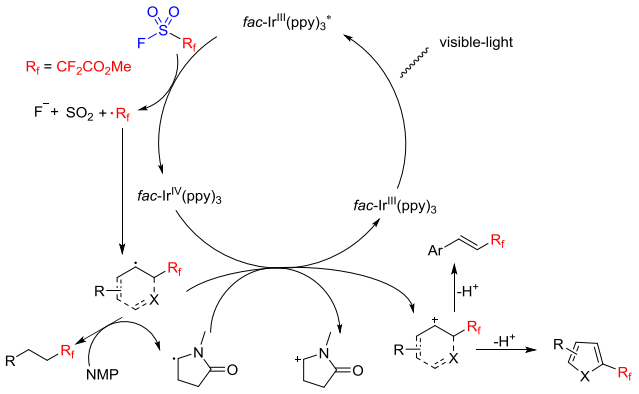
In the early report by Chen *et al*., they described that

$FSO_2CF_2CO_2Me$ could undergo C—O bond cleavage to generate methyl radical when a catalytic amount of Cu^0 was used (see Schemes 4 and 5).[19] In 2016, Qing *et al*. reported that $FSO_2CF_2CO_2Me$ can serve as a good CF_2CO_2Me radical precursor under photoredox catalysis.[22] Using *fac*-Ir(ppy)$_3$ as the photocatalyst, a series of unactivated alkenes, styrenes, and heteroarenes were efficiently carbomethoxyldifluoromethylated with good functional group tolerance (Scheme 23). A plausible mechanism is depicted in Scheme 24. The single electron transfer from *fac*-Ir(ppy)$_3$ to $FSO_2CF_2CO_2Me$ leads to the C—S bond cleavage, giving CF_2CO_2Me radical, and the latter species adds to the alkenes to give the final products (Scheme 24).

Scheme 23 The radical difluoroalkylation of alkenes and heteroarenes with $FSO_2CF_2CO_2Me$

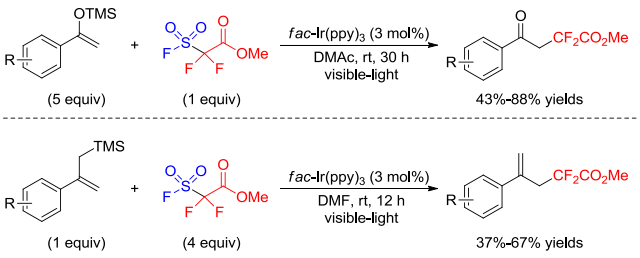


Scheme 24 The proposed mechanism for radical difluoroalkylation of alkenes and heteroarenes with $FSO_2CF_2CO_2Me$



Later, Qing *et al*. reported the difluoroalkylation of trimethylsilyl enol ethers and allyltrimethylsilanes with $FSO_2CF_2CO_2Me$ for the synthesis of α-CF_2CO_2R substituted aromatic ketones and allylic compounds, which are otherwise difficult to access by other means (Scheme 25).[43]

Scheme 25 The radical difluoroalkylation of trimethylsilyl enol ethers and allyltrimethylsilanes with $FSO_2CF_2CO_2Me$



Very recently, Chen, Xi and coworkers found that using Chen's reagent as the difluoroalkyl source, DMSO as the oxidant, keto-difluoroacetylation of styrenes for the preparation of α-CF_2CO_2R substituted aromatic ketones can be achieved under photoredox catalysis.[44]

4. Other related reagents

In addition to the widely used $FSO_2CF_2CO_2Me$ (Chen's reagent), Chen *et al*. have also developed many other reagents, such as $FSO_2CF_2CO_2H$,[45] FSO_2CF_2I,[46] CF_2I_2,[47] $FSO_2CF_2CF_2OCF_2CO_2X$ (X = Me or K),[48] $FSO_2CF_2CF_2OCF_2CF_2I$,[49] $FSO_2CF_2CO_2TMS$,[50] $Cu(O_2CCF_2SO_2F)_2$[15c], $Ag(O_2CCF_2SO_2F)$,[51] and XCF_2CO_2Me (X = Cl, Br or I; $BrCF_2CO_2K$).[52] These reagents have been used as trifluoromethylation, difluorocarbene or/and difluoroalkylation regents. For instance, $FSO_2CF_2CO_2H$ is a unique acidic difluorocarbene precursor that can implement the difluoromethylation of alcohols in high efficiency,[45a,53] as only limited reagents are known to achieve this goal;[54] $FSO_2CF_2CO_2TMS$ is a versatile difluorocarbene reagent, as it shows usual reactivity towards electron-deficient alkenes to give the corresponding difluorocyclopropanes;[50] $Cu(O_2CCF_2SO_2F)_2$ was found to be a more efficient trifluoromethylation reagent than $FSO_2CF_2CO_2Me$, since in the presence of Cu^0, it can easily trifluoromethylate a plethora of hetero(aryl) iodides and benzyl bromides in high yields even at room temperature;[15c] $Ag(O_2CCF_2SO_2F)$ is a very recently developed reagent that can fulfill the one-pot cascade trifluoromethylation-fluorosulfonylation of unactivated alkenes in the presence of *N*-fluorobenzenesulfonimide, where the byproduct SO_2 (generated during the decomposition of $Ag(O_2CCF_2SO_2F)$) can be utilized.[51]

5. Conclusions and Perspectives

Chen's reagent ($FSO_2CF_2CO_2Me$) has found wide applications in the trifluoromethylation of aromatic, herteroaromatic and alkenic compounds since its seminal report by Chen's group in 1989.[7] A diverse array of structurally unique and biologically active molecules containing CF_3 group have been prepared using Chen's reagent. In some cases, Chen's reagent showed significant advantages over other trifluoromethylation reagents, such as $TMSCF_3$, $CF_3B(OMe)_3K$ and CF_3CO_2Na.[24,34b,36] Recently, the ability of Chen's reagent to act as a difluorocarbene source was revisited, and its new reactivity to serve as a CF_2CO_2Me radical source was developed. Despite the versatility of Chen's reagent, it is still largely overlooked by the chemical community, and its application in organic synthesis is far less than that of $TMSCF_3$.[6h,6i,9] In light of the high reactivity of Chen's reagent in trifluoromethylation of various kinds of structurally diverse molecules and much cheaper price of Chen's reagent (28.5 USD/5 g) compared with $TMSCF_3$ (136 USD/5 mL, density 0.962 g/mL),[55] we call for more attention to this important reagent. We anticipate that Chen's reagent will continue to find more applications in life science and materials science, especially in the incorporation of CF_3 group(s) into complex molecules.

Acknowledgement

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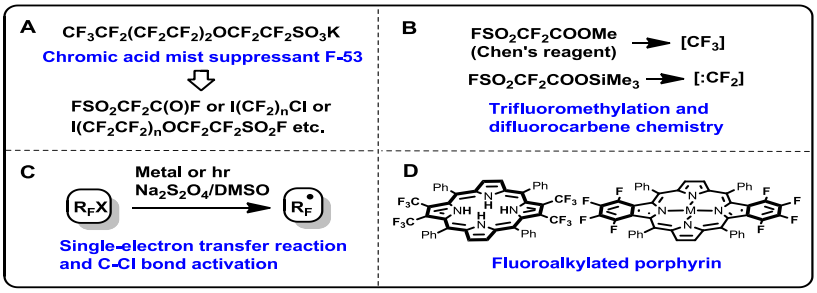
Profile of Professor Qing-Yun Chen

Professor Qing-Yun Chen was born in Yuanjiang, Hunan Province, China, on January 25, 1929. He received his B.S. degree in Chemistry from Peking University in 1952, and his Ph.D. from Institute of Elementoorganic Compounds, Soviet Academy of Sciences, Moscow in 1960. Professor Chen's research career began in Changchun Institute of Optics, Fine Mechanics and Physics, Chinese Academy of Sciences (1952–1955). Since 1960, he has been working at Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, where he was Research Associate (1963–1979), Associate Professor (1979–1986), Professor (1986–present), and elected as a member of the Chinese Academy of Sciences in 1993. Professor Chen received the National Natural Science Award (second class), the Prizes of Shanghai City for significant fruits of scientific research (first class), CAS Science & Technology Progress Award (second class), the National Innovation Award (third class), the Chinese Chemical Society W.-Y. Huang Fluorine Chemistry Prize, and the Ho Leung Ho Lee Prize for Science and Technology, Hongkong, *etc.*

Chemistry developed in his laboratory

Professor Chen's research work is focused on organofluorine chemistry, mainly including single-electron transfer reaction in organofluorine chemistry, trifluoromethylation, difluorocarbene chemistry, C—Cl bond activation of fluoroalkyl chlorides, fluoroalkylated porphyrins, *etc*. In order to meet the demands of the country, a new chromic acid mist suppressant potassium oxaperfluoroalkanesulfonate (named as F-53) was developed and has been widely used in more than 1000 electroplating factories in China, which has imposed an enormous influence on the development of organofluorine chemistry in China by providing several unique types of fluorine-containing starting material derived from the production of F-53 (Figure A).[1] Based on the preparation of F-53, the synthesis and reactions of perfluoroalkanesulfonic esters were investigated, and 14 new difluorocarbene precursors and 8 new trifluoromethylation reagents were developed. Among them, methyl fluorosulfonyldifluoroacetate (named as Chen's reagent) has been widely used in both academia and industry for many years (Figure B).[2] The single electron-transfer reaction of fluoroalkyl halides and the C—Cl bond activation of fluoroalkyl chlorides were studied systematically by many metal-catalyzed initiation systems and modified sulfinatodehalogenation system via single-electron transfer process (Figure C).[3] On the basis of the above work, the synthesis and application of fluoroalkylated porphyrins were performed (Figure D).[4]



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