Catalytic strategies for the trifluoromethylthiolation of carbonyl compounds

S. Rossi,*[a] A. Puglisi, L. Raimondi, M. Benaglia*[a]

Abstract: The role of fluorine atoms in drug discovery has become of fundamental importance, due to their ability to confer new and unprecedented therapeutic profiles on a molecule. In this framework, the trifluoromethylthio group (SCF_3) is attracting an increasing attention in pharmaceutical, agrochemical and material chemistry and it is commonly used to modulate and tune lipophilicity, bioavailability and metabolic stability of newly designed molecules. Actually, several drugs whose biological activity is strictly related to the presence of a SCF_3 residue in the molecular scaffold are already on the market. Despite trifluoromethylthiolated carbonyl derivatives present a high potential of application in medicinal chemistry, synthetic approaches to α-SCF_3-substituted carbonyl compounds are still limited, and catalytic strategies to access optically active functionalized carbonyl compounds are almost unexplored. The present review will discuss the use of radical, nucleophilic and electrophilic trifluoromethylthiolating reagents, to synthesize decorated trifluoromethylthio carbonyl derivatives, with a particular attention on catalytic methodologies and stereoselective methods affording enantiomerically enriched molecules.

1. Introduction

The exceptional high frequency of fluorinated molecules in the pharmaceutical pipeline is truly amazing, considering that only a relatively few fluorinated natural products have been identified so far. Due to the ability to confer to a molecule new and unprecedented therapeutic profiles, the role of fluorine atoms in drug discovery has become of fundamental importance; in fact fluorine is found in around 20% of all new chemical entities licensed each year for the clinical market, and is present in 30% of the leading blockbuster pharmaceuticals.[1] Enantiopure molecules featuring fluorinated groups are at the forefront of innovation in modern organofluorine chemistry, because of the increasing occurrence of this motif in a wide range of biologically active compounds, and also in chiral reagents/catalysts or in materials for optoelectronic devices.

Therefore it is not surprising that the trifluoromethylthio group (SCF_3) is attracting an increasing attention in pharmaceutical, agrochemical and material chemistry.[2] Thanks to its high lipophilicity (Hansch's hydrophobic parameter π = 1.44) and strong electron withdrawing properties (Hammett constant: σ_m = 0.40 and σ_p = 0.50),[3] the SCF_3 group may be used to modulate and tune lipophilicity, bioavailability and metabolic stability of newly designed molecules. Actually, several drugs whose biological activity is strictly related to the presence of a SCF_3 in the molecular scaffold are already on the market, demonstrating the appealing of this substitution in drug discovery (Figure 1).

As testimonial of this strategic interest, in the last five years, many methods for the introduction of a trifluoromethylthio group into organic compounds have been reported.[4] All these methodologies can be classified in two groups: the first one (indirect methods) involves the introduction of the SCF_3 moiety through a modification of a functionality already present in the molecule); this approach usually requires harsh reaction conditions and the formation of byproducts are often observed. The direct methods, on the other hand, exploit the introduction of the SCF_3 group on the precursor substrate by using a trifluoromethylthiolating reagent. The present review will focus on this second group of methods, which can be divided, in turn, into three classes, depending on the type of trifluoromethylthiolating reagent employed in the chemical transformation: a radical compound, a source of nucleophilic SCF_3 or a SCF_3-containing electrophilic compound.

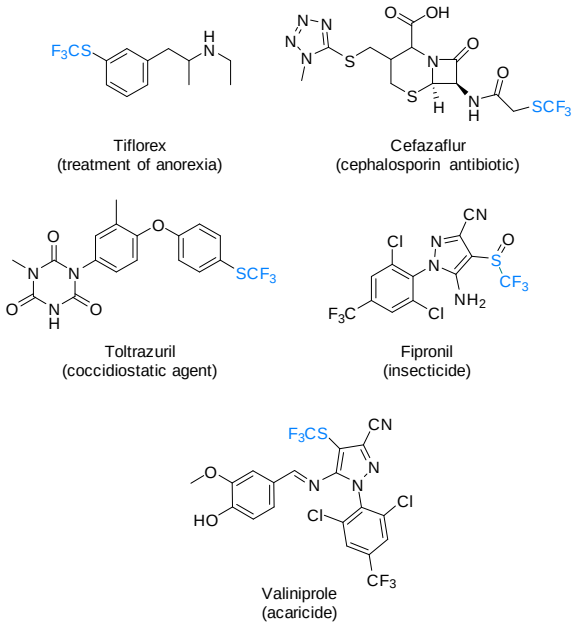

Figure 1. Pharmaceutical drugs containing a SCF_3 group.

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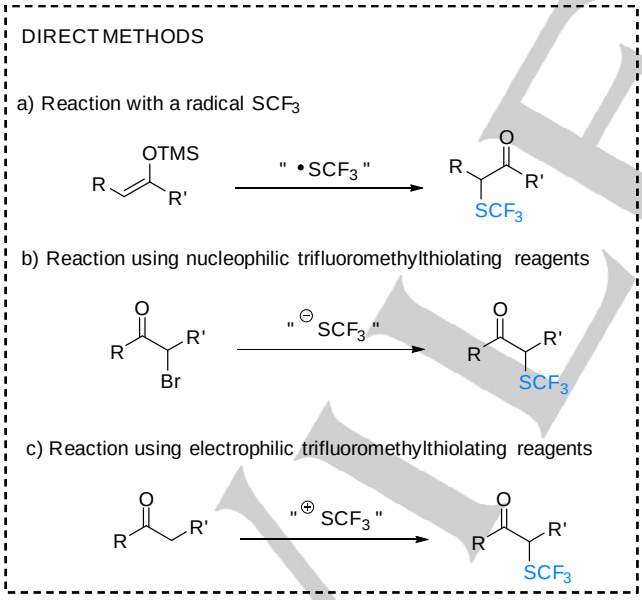
The direct introduction of the SCF_3 group into the desired molecule represents the more attractive approach. In this sense, in 1961, Harris[5] reported for the first time the free-radical trifluoromethylthiolation of olefins using the highly toxic trifluoromethanesulfenyl chloride (CF_3SCl), where the radical can be generated by the presence of light. Since then, further radical trifluoromethylthiolation reactions were reported by Wang,[6] Nevado,[7]Tang,[8] Liang[9] Liu and Chen[10] where the use of toxic reagents can be avoided. However, even if many radical approaches have been developed, their applications are generally limited to the functionalization of activated or inactivated C(sp3)-H bonds, and only few examples involves the functionalization of carbonyl compounds.

Carbonyl derivatives are found in a wide range of biologically active products and constitute a large family of interesting building blocks; therefore, trifluoromethylthiolated carbonyl derivatives present a high potential of application in medicinal chemistry. Despite this consideration, approaches to α-SCF_3-substituted carbonyl compounds are still limited, and catalytic strategies to access optically active functionalized carbonyls are almost unexplored. Only few examples of trifluorothio-functionalization are known and generally involve the use of nucleophilic[11] or electrophilic trifluoromethylthiolating reagents, where the SCF_3 ion can be generated starting from easy synthesizable precursors. These types of synthetic approaches will be described in the following sections of this review, with a particular attention on catalytic methodologies, which will be discussed in more details.

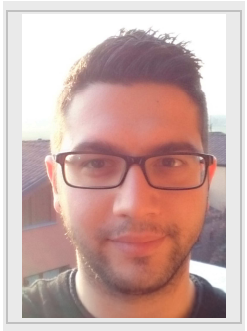


Scheme 1. Direct methods for the introduction of a SCF_3 group in a carbonyl derivative.

After his PhD with prof. M. Cinquini and F. Cozzi, **Maurizio Benaglia** joined in 1995 prof. J. S. Siegel group at UCSD (USA); then he moved back to the University of Milan, where in 2015 he was appointed as Full Professor of Organic Chemistry. His research activities focus on the development of novel synthetic methodologies, design of new chiral organocatalysts, study of stereoselective reactions in flow and catalytic reactors, synthesis of pharmaceutical products, taking advantage also of 3D-printing technologies and alternative reaction media.

Laura Raimondi received her PhD in Chemistry from the University of Milano in 1989, and joined prof. Ken N. Houk group at UCLA (Los Angeles - USA). She became Assistant Professor in the University of Milan in 1990, and Associate Professor in 1998. Experimental and theoretical studies on the origin of stereoselection in organic reactions are her main research field. She is also interested in the study of intermolecular interactions and in conformational analysis of biomolecules.

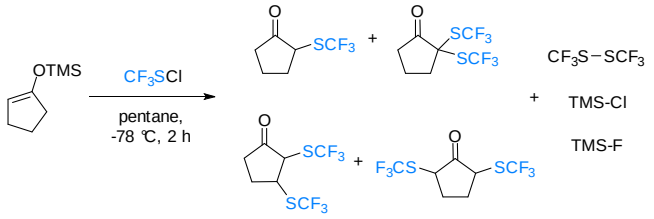
Alessandra Puglisi received her PhD from University of Milan, Italy in 2003. She spent her post-doctoral fellowship in the group of Prof. Amir H. Hoveyda (Boston College, USA) in 2004. In 2011 she became Assistant Professor the University of Milan. Her main scientific interests are in the field of stereoselective organocatalysis, in particular, the synthesis, characterization and synthetic applications of chiral supported catalysts and their applications in continuous-flow chemistry and 3D printing applications.



Sergio Rossi received his PhD from University of Milan, Italy in 2010. He joined the University of Illinois at Urbana Champaign (USA) in 2011 as a post-doctoral fellow, in the group of Prof. S.E. Denmark. In 2017 he obtained an Assistant Professor position at the University of Milan, where he is currently working in the stereoselective synthesis of chiral pharmaceutical products and in the development of new catalytic stereoselective metal-free methodologies, under continuous-flow conditions in micro- and 3D printed mesoreactors

2. 2. Reactions with radical SCF_3 species

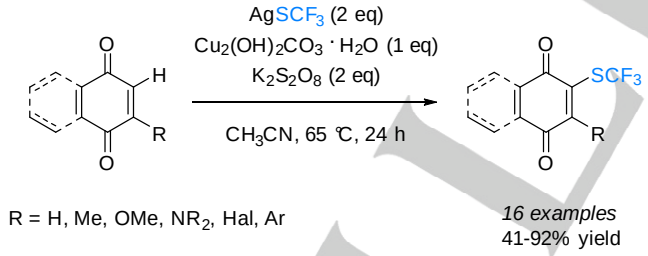
In 2001 Munavalli reported the only example known for the introduction of a SCF_3 moiety at the alpha position of a carbonyl function using radicals: α-trifluoromethylthiolated ketones were synthesized by reacting trimethylsilyl enol ethers with the reagent CF_3SCl (Scheme 2).[12]



Scheme 2. α-trifluoromethylthiolation of trimethylsilylenol ethers.

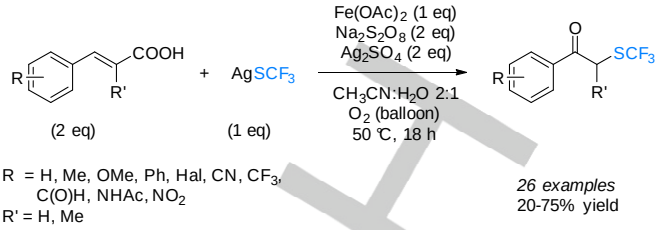
The use of different cyclic silylenol ethers were investigated and in each case, as a result of a radical mechanism, the formation of many byproducts in different ratios was observed. Since the gaseous trifluoromethylsulphenyl chloride is very toxic, and due to the complex mixture of products obtained, this methodology has not really found application in the synthesis of α-trifluoromethylthiolated ketones.

In 2015, Qing reported the synthesis of trifluoromethylthiolated quinones via the SCF_3 radical (Scheme 3).[13] Different quinone derivatives afforded the corresponding trifluoromethylthiolated products in moderate to excellent yields, although an excess of the trifluoromethylthiolating reagent needs to be used when quinones present electron-donating groups, in order to achieve high yields.



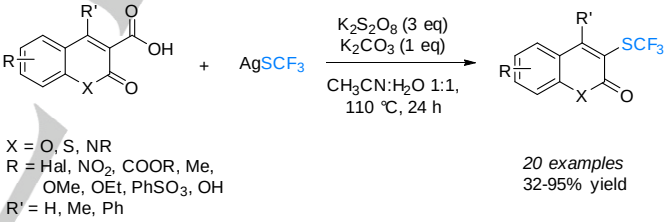
Scheme 3. Synthesis of trifluoromethylthiolated quinones.

One year later, Huang reported the synthesis of trifluoromethylthiolated ketones by radical decarboxylative functionalization of cinnamic acids using $AgSCF_3$ as trifluoromethylthiolating source, $Fe(OAc)_2$ and Ag_2SO_4 as initiator and $K_2S_2O_8$ as oxidant under oxygen atmosphere (Scheme 4).[14]



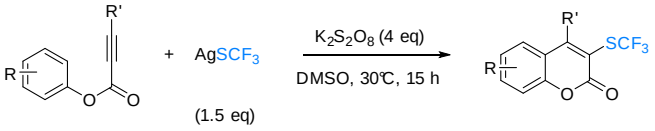
Scheme 4. Decarboxylative functionalization of cinnamic acids for the synthesis of α-trifluoromethylthiolated ketones.

A variety of α,β-unsaturated carboxylic acids could be efficiently converted to the desired α-SCF_3-substituted ketones in moderate to good yields. Electron-donating and withdrawing substituents are well tolerated and do not influence the chemical efficiency of the process. A decarboxylative approach was also employed in the synthesis of trifluoromethylthiolated coumarins, including analogues of natural products, in moderate to excellent yields (scheme 5).[15] Both electron-deficient and electron rich substrates undergo efficient trifluoromethylthiolation with electron-donating substituents providing slightly higher yields. Several experiments were also conducted in order to elucidate the mechanism of the reaction, clearly indicating the formation of a •SCF_3 specie.



Scheme 5. Synthesis of trifluoromethylthiolated coumarins by deacrboxylative approach.

3-Trifluoromethylthiolated coumarins can be synthesized also by direct radical trifluoromethylthiolation of aryl alkynoate esters, as reported by Wang (Scheme 6).[16] $AgSCF_3$ was employed in the presence of $K_2S_2O_8$ for the generation of the radical specie and many differently substituted substrates were investigated. Generally, the protocol is not affected by the electronic nature of the susbtituents on the aromatic ring, and lower yields were obtained only in the presence of aliphatic chains on the alkynyl moiety.

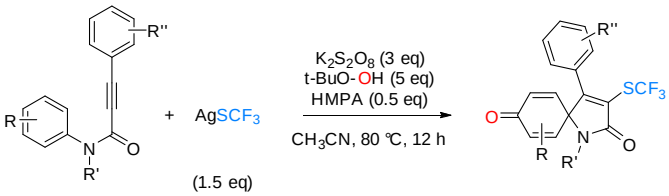


R = Me, ^{t}Bu, OMe, Hal, OCF_3, COOMe, Ac
R' = Ph, Ar, Het(Ar), ^{c}-Hexyl, pentyl-

24 examples
25-80% yield

Scheme 6. Synthesis of 3-Trifluoromethylthiolated coumarins.

Another interesting approach was reported by Liu where α-trifluoromethylthiolated spiro[4,5]trienones were synthesized starting from alkynes. This strategy consists in a cascade cyclization process with difunctionalization of alkynes and dearomatization (scheme 7).[17]



R = H, Me, Et, Cl
R' = Me, Bn
R'' = H, Me, OMe, ^{t}Bu, Hal-, CN, NO_2,

29 examples
52-95% yield

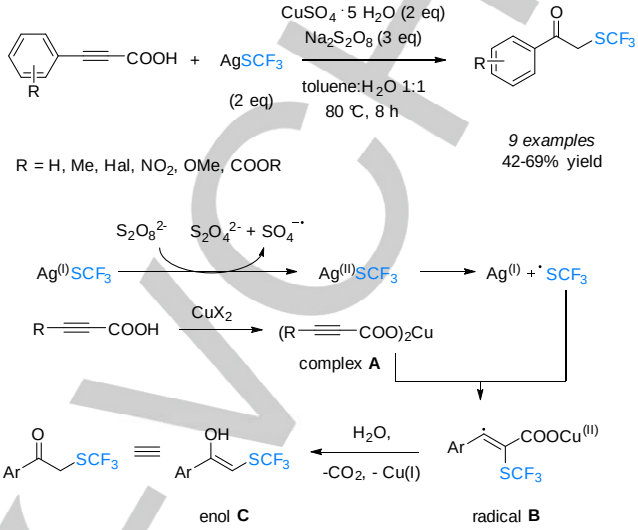
Scheme 7. Synthesis of α-trifluoromethylthiolated spiro[4,5]trienones starting from alkynes.

Different substitutions on the aromatic rings and at the nitrogen atom were investigated, and good to excellent yields were observed with most of the common electron donating or withdrawing groups. Only the presence of heteroaromatic rings on the alkynyl moiety causes a decrement of the yields.

Very recently, the decarboxylative approach was also employed for the synthesis of simple α-trifluoromethylthiolated ketones starting from α,β-unsaturated carboxylic acids (scheme 8).[18] The mechanism involves the oxidation of $AgSCF_3$ by $Na_2S_2O_8$ which triggers the SCF_3 radical. Contemporaneously, the interaction of the carboxylic acid with copper generates a Cu(II) carboxylate **A** that undergoes the SCF_3 radical attack at the α-position of the triple bond, thus generating the new radical **B**. Then the elimination of carbon dioxide and Cu(I) occurs, to afford the trifluoromethylthio enol **C** that rapidly converts to the corresponding trifluoromethylthiolated ketone. Moderate to good yields were observed, both with electron-withdrawing and electron-donating substituents on the starting compound, including CN and NO_2 groups; however, no reaction was observed when aliphatic propiolic acids were tested.

It is worth noting that none of the described methods is catalytic, and the use of stoichiometric amounts of reagents presents serious issues of sustainability, due to the waste disposal problems and, in some cases, the toxicity of the reagents.

The development of more environmentally friendly, catalytic approaches with radical trifluoromethylthiolation reagents would be therefore highly desirable.



R = H, Me, Hal, NO_2, OMe, COOR

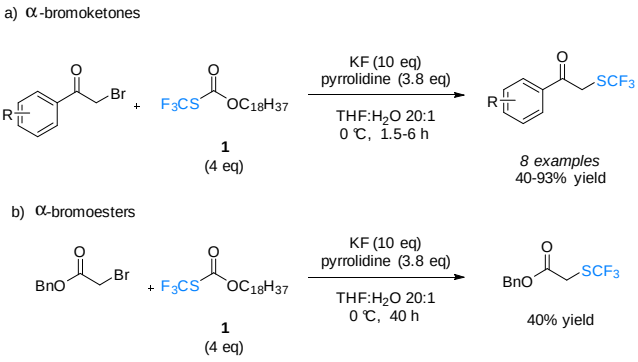
9 examples
42-69% yield

enol **C** radical **B**

Scheme 8. Cu(II)-Mediated decarboxylative trifluoromethylthiolation of α,β-unsaturated carboxylic acids.

3. Reactions with nucleophilic trifluoromethylthiolating reagents

One of the first examples of (non-catalytic) electrophilic trifluoromethylthiolation of carbonyl compounds was reported by Li and Zard in 2013; α-bromo ketones were reacted with *O*-octadecyl-*S*-trifluoromethylthiocarbonate **1** at 0 ℃ in the presence of pyrrolidine and KF and afforded the SCF_3- substituted derivatives in only 1.5 hours (scheme 9).[19]



8 examples
40-93% yield

40% yield

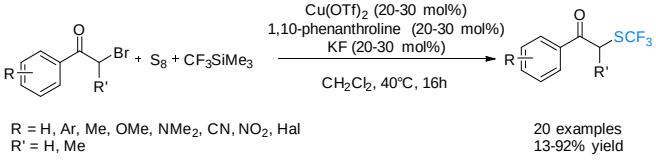
Scheme 9. *O*-octadecyl-*S*-trifluoromethylthiocarbonate as SCF_3 source in the synthesis of trifluoromethylthiolated carbonyl compounds.

The reaction could be applied also to α-bromo esters in modest yields; it was demonstrated that the presence of a base such as pyrrolidine is necessary to accelerate the generation of

the SCF_3 anion and the addition of high quantities of KF is fundamental for the stabilization of the SCF_3 anion, in order to avoid the formation of difluorothiophosgene by extrusion of a fluoride anion. Both electronpoor and neutral substituted α-bromo ketones gave corresponding products in high yields, but substrates bearing electrondonating substituents required longer reaction times to achieve the same level of conversion.

However, even if the trifluoromethylthiocarbonate is a cheap and stable compound that can be stored without problems, this metal-free protocol can be hardly considered of practical use, due to the large amount of reagent required.

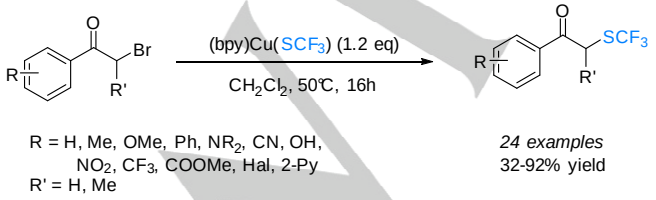
An improved version of this reaction was reported in 2014 by Weng,[20] who developed the first example of copper-catalyzed synthesis of α-trifluoromethylthio-substituted ketones. A large variety of α-bromoketones were converted in the corresponding trifluoromethylthiolated compounds using 20-30 mol% of the $Cu(OTf)_2$ complex with 1,10-phenanthroline, using CF_3SiMe_3 and elemental sulfur as precursors (Scheme 10).



Scheme 10. Copper-catalyzed synthesis of α-trifluoromethylthio-substituted ketones.

α-Bromo ketones bearing electron donating groups at the aromatic ring are transformed into α-SCF_3 ketones in high yields, whereas reduced yields are observed in the presence of cyano or nitro groups (typically < 20%). In these cases, the addition of SCF_3 group to carbonyl group takes place with consequent formation of the trifluoromethylated alcohols as side products. However, the trifluoromethylthiolation occurs in excellent yields on aliphatic ketones as well as on secondary α-bromoketones, albeit a higher catalyst loading is required.

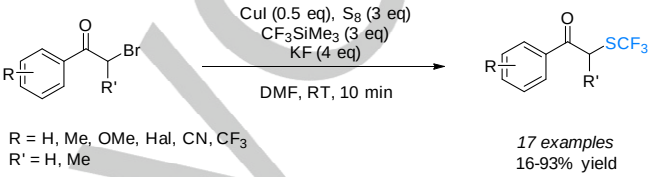
In order to successfully enlarge the scope of the reaction to all the aromatic ketones, the same group developed a new copper-mediated trifluoromethylthiolation methodology where the copper salt was replaced with (bpy)$CuSCF_3$ (scheme 11).[21]



Scheme 11. Copper-mediated trifluoromethylthiolation of α-bromoketones (bpy = 2,2'-Bipyridine).

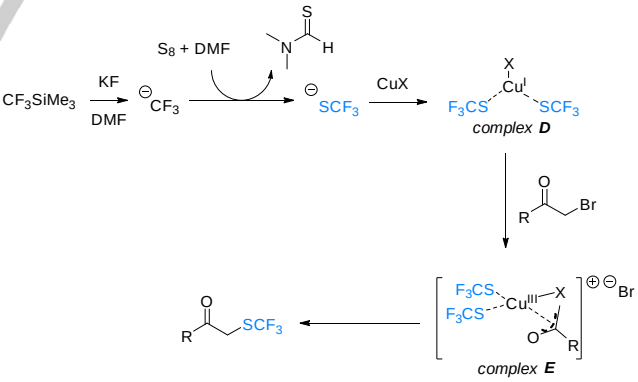
This methodology allowed to improve chemical yields and tolerance towards sensitive functionalities, as demonstrated by the large number of examples reported involving electron poor compounds; however, this process is not catalytic. Aliphatic α-bromo as well as α-chloro ketones react in good yields, in the presence of an excess of Bu_4NI.

One year later, Ren and Zeng reported a copper(I)-catalyzed α-trifluoromethylthiolation of both aromatic and aliphatic α-bromo ketones with elemental sulfur and CF_3SiMe_3 performed in the absence of ligand (scheme 12).



Scheme 12. α-trifluoromethylthiolation of α-bromo ketones promoted by CuI.

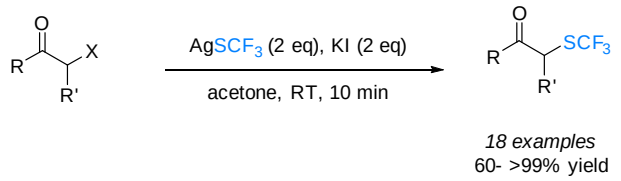
Compounds bearing electron donating substituents gave higher yields than those featuring electron withdrawing groups, but no product formation was observed when *o*-chloro and *p*-nitro groups were present on the aromatic ring. The same approach can be applied to α-bromo propiophenones and to aliphatic α-bromo ketones, affording the corresponding trifluoromethylthiolated products in moderate to good yields. A reaction mechanism was also proposed in analogy with the copper(I)-mediated direct trifluoromethylthiolation of allylic halides realized exploiting the same approach (scheme 13).[22]



Scheme 13. Proposed mechanism for copper-promoted α-trifluoromethylthiolation of α-bromo ketones.

Firstly, a SCF_3 anion is generated by interaction of CF_3SiMe_3 with KF, S_8 and DMF; then it reacts with the copper salt to generate complex **D**. The reaction of the α-bromo ketone with **D** generates the adduct **E** which rapidly evolves into the desired α-trifluoromethylthiolated product.

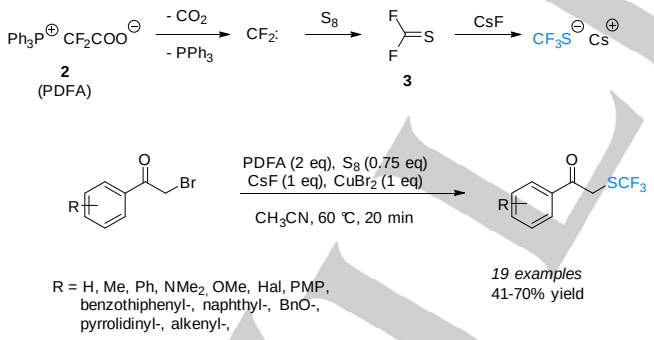
In the same year Yang reported another efficient approach to trifluoromethylthiolation of α-halo ketones, where $[Ag(SCF_3)I]^-{}^+K$ (the active trifluoromethylthiolating specie) is generated in situ from $AgSCF_3$ and KI.[23] The reaction proceeds under mild conditions, is insensible to moisture and allows to obtain desired products in almost quantitative yields using different α-halo ketones (Scheme 14).



X = Cl, Br, I
R = Me, Et, *c*-Pr, Ph, 4-MePh, 4-OMePh, 4-OHPh, 4-FPh, 3-ClPh, 4-BrPh, 4-SO_2MePh, 4-CNPh, 3-NO_2Ph, 2-naphthyl, 3-indolyl, furyl, thiophenyl, benzofuryl
R' = H, Me, Ph

Scheme 14. Trifluoromethylthiolation of α-halo ketones using $[Ag(SCF_3)I]^-{}^+K$

Very recently, Xiao and Liang, reported useful mechanistic information for the formation of trifluoromethylthio anion from difluorocarbene, sulfur, and fluoride, and the subsequent interactions between the generated SCF_3 anion and transition metals.[24] Difluoromethylene phosphobetaine **2** (Triphenylphosphoniodifluoroacetate, PDFA), in the presence of elemental sulfur, was found to generate thiocarbonyl fluoride **3**, that in turn, after interaction with CsF, promotes the α-trifluoromethylthiolation of carbonyl compounds (scheme 15).



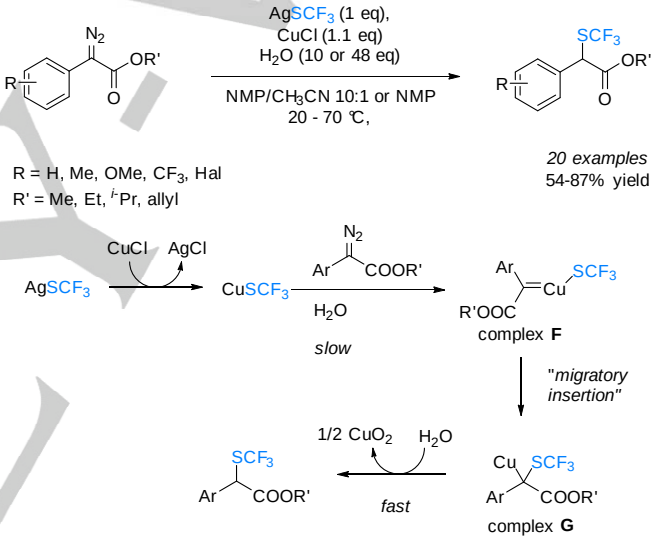
R = H, Me, Ph, NMe_2, OMe, Hal, PMP, benzothiophenyl-, naphthyl-, BnO-, pyrrolidinyl-, alkenyl-,

Scheme 15. α-trifluoromethylthiolation of carbonyl compounds performed with difluoromethylene phosphobetaine.

The addition of a copper source such as $CuBr_2$ allows to obtain products with yields up to 70%. The same approach was also successfully employed for synthetize radiochemical [^{18}F] trifluoromethylthiolated α-bromoketones. Electron-donating substituents on the aromatic ring are well tolerated while strong electron-withdrawing substituents (such as nitro) depressed the reaction.

Most of the protocols reported until now involves the use of α-halo ketones as starting material and this represents a limitations of this approach, due to the intrinsic problems of halogenation reaction, such as the formation of di-halogenated ketones or the halogenation of the aromatic ring. In addition, high amounts of sulfenylating reagents, combined with high catalysts loadings (20-50 mol%) contribute to make the above mentioned procedures less competitive from the atom-economy point of view and also less appealing for industrial applications.

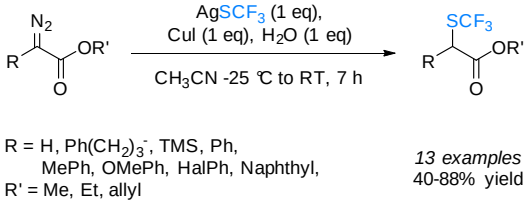
In 2014, with a completely new approach, Hu reported a copper-mediated trifluoromethylthiolation of α-diazoesters for the synthesis of the corresponding esters under mild reaction conditions.[25] In this case, $CuSCF_3$, the real trifluoromethylthiolating reagent, was generated in situ by reaction of $AgSCF_3$ with a stoichiometric amount of copper chloride for the synthesis of carboxylic esters (scheme 16).



R = H, Me, OMe, CF_3, Hal
R' = Me, Et, ^{i}Pr, allyl

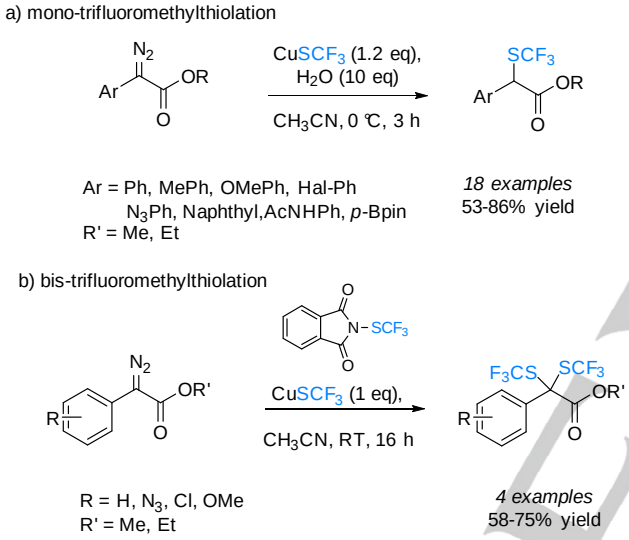
Scheme 16. Synthesis of α-trifluoromethylthioesters by Hu approach.

The reaction was performed using pure 1-methylpyrrolidin-2-one (NMP) as solvent or in mixture with CH_3CN, in the presence of water as promoter, necessary to guarantee high yields. Interestingly, the reaction is not influenced by the nature of substituents on the ortho- meta- or para- position of the phenyl ring. Heteroaromatic rings are tolerated, but alkyl substituted α-diazoesters are poorly reactive in this transformation and only traces of products formation were observed. Some experiments were also performed in order to elucidate the mechanism, and it was found that the reaction proceeds through the formation of a Cu-carbene intermediate **F** which quickly undergoes migratory insertion to give the complex **G** that is converted to the final product by reaction with water. Contemporaneously, Wang reported the same transformation using slightly different reaction conditions, obtaining the desired α-trifluoromethylthioesters in comparable results (Scheme 17).[26]



Scheme 17. Synthesis of α-trifluoromethylthioesters by Wang approach.

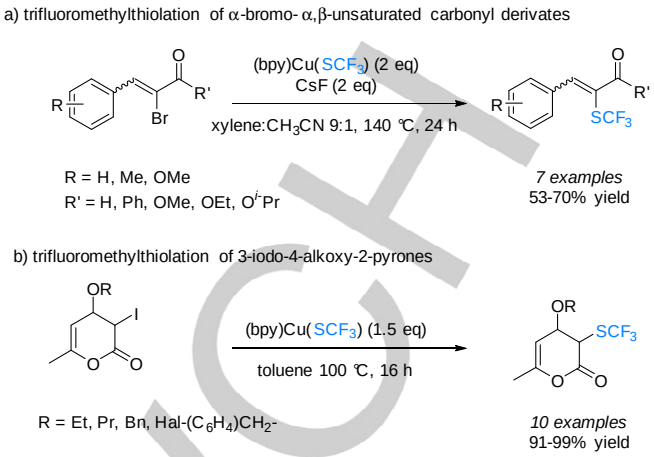
In the same year, Rueping independently reported a similar protocol for the mono and bis trifluoromethylthiolation of the same substrates using a combination of $CuSCF_3$ and water as additive (scheme 18).[27]



Scheme 18. Mono and bis trifluoromethylthiolation of α-diazoesters.

As for Hu approach, both electron donating and electron withdrawing substituents are well tolerated, with the exclusion of NO_2 group. Bis-trifluoromethylthiolation can be achieved by replacing water with *N*-SCF_3-pthalimide in order to generate the more reactive disulfide CF_3S-SCF_3 specie directly in situ which itself is a potent electrophilic SCF_3 source that reacts readily to give the ditrifluoromethylthiolated compounds in good yields.

In 2015 Weng reported also a route for the synthesis of α-trifluoromethylthio-α,β-unsaturated carbonyl compounds via a copper-mediated trifluoromethylthiolation of corresponding α-bromo-α,β-unsaturated carbonyl derivatives using the already menthioned (bpy)$CuSCF_3$ salt (Scheme 19a).[28] Under these reaction conditions, α-trifluoromethylthio-α,β-unsaturated aldehydes, ketones and esters were obtained in moderated yield with a E:Z ratio up to 10:1.



Scheme 19. Synthesis of α-trifluoromethylthio-α,β-unsaturated carbonyl compounds.

Last year, taking advantage of the high reactivity of (bpy)$CuSCF_3$, a trifluoromethylthiolation of 3-idodo-pyran-2-one derivatives was reported by Yang (scheme 19b).[29]

It should be remarked that the study of new synthetic stereoselective methodologies employing nucleophilic trifluoromethylthiolating reagents is clearly underdeveloped. Reliable, catalytic strategies are basically unknown and represent a challenge that calls for further researches in the future.

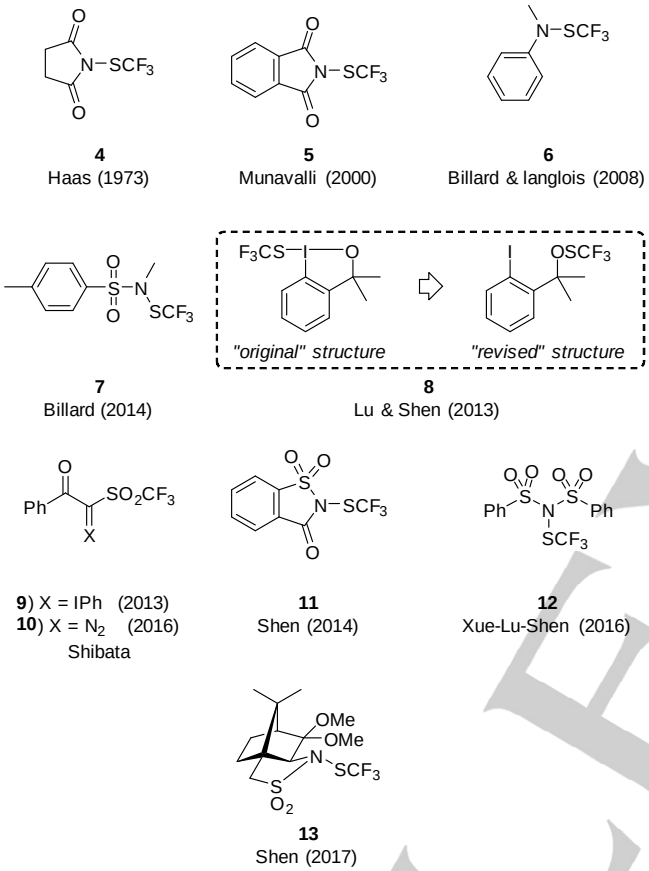
4. Reaction performed using electrophilic trifluoromethylthiolating reagents

Among the known direct methods, the use of electrophilic trifluoromethylthiolating reagents is the most widespread approach employed for the introduction of a SCF_3 group on a target molecule, and a lot of different reagents have been developed for this purpose during the last decade (see scheme 20).[30] Pioneer studies of α-trifluoromethylthiolation of ketones using electrophilic reagents were conducted by Bayreuther and Haas and by Kosala since 1973. These approaches involve the use of different metal precursors for mediated or catalyzed α-trifluoromethylthiolation of carbonyl, leading to the functionalization of ketones, esters, enamines, indoles, β-ketoesters and α-diazoesters. Electrophilic trifluoromethylthiolating reagents **4-13** of Scheme 20 have found application in metal-free and organocatalyzed processes, performed in some cases also stereoselectively.

Interesting, a scale of the SCF_3 cation-donating ability of many electrophilic trifluoromethylthiolating reagents was reported by Xue and Cheng.[31] Based on DFT calculations, it was possible to define the "trifluoromethylthiocation donating ability" (indicated with Tt^+DA) of many SCF_3 donating compounds. These parameters represent quantitative descriptors for the propensity of electrophilic trifluoromethylthiolating reagents to transfer a SCF_3 moiety in organic synthesis. A correlation between the new

$Tt^{+}DA$ parameter of the *N*-SCF_3-type reagent and the pKa of the corresponding acid was identified, offering a powerful tool for the rationalization of chemical processes and for the development of novel reagents.

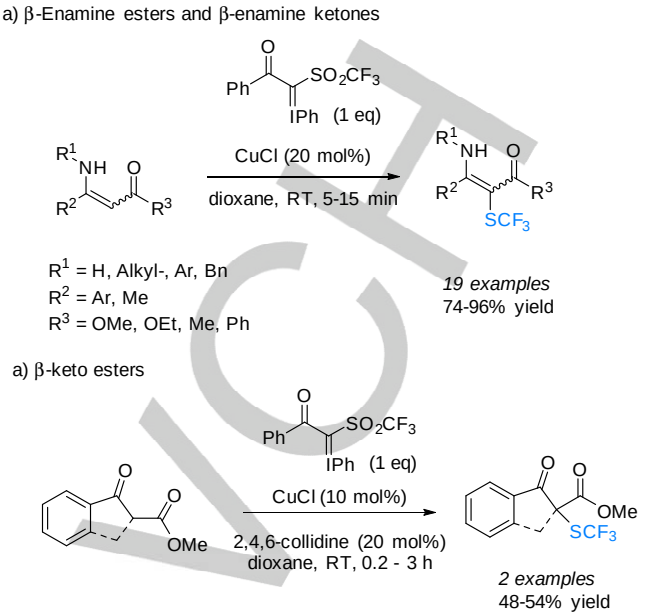
Furthermore, also the "trifluoromethylthio radical donating ability" (indicated with $Tt^{\bullet}DA$) of electrophilic SCF_3-transfer reagents has been developed using the same approach, where in this case the scale is based on *N*-SCF_3 bond dissociation energies obtained by density functional calculations.[32]



Scheme 20. Most common electrophilic trifluoromethylthiolating reagents.

3.1. Metal-based methods for the electrophilic α-trifluoromethylthiolation of carbonyl compounds

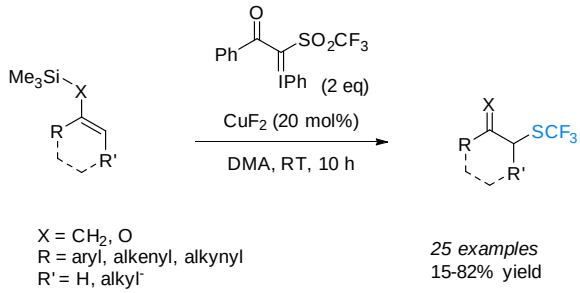
In 2013, Shibata reported the use of the novel electrophilic-type trifluoromethansulfonyl hypervalent iodonium ylide **9**, for the trifluoromethylthiolation of enamines, indoles and β-ketoesters catalyzed by copper(I)chloride (Scheme 21).[33]



Scheme 21. Trifluoromethylthiolation of enamines, indoles and β-ketoesters catalyzed by copper(I)chloride in the presence of Trifluoromethansulfonyl hypervalent iodonium ylide.

β-Enamino esters and β-enamino ketones were efficiently trifluoromethylthiolated in 5 minutes only; both electron rich and electron deficient substituents on the amino group gave high yields and a slight decrement was observed only when aliphatic substituents were employed. Unprotected enamines as well as disubstituted enamines can be employed, even if in the latter case 15 minutes were required in order to achieve full conversion. In similar reaction conditions β-keto esters were also tested, and desired products were obtained with modest yield only when 2,4,6-collidine was present as co-catalyst. Two different mechanisms involving the formation of two different carbene species were proposed by the authors, but further studies are required to elucidate the real pathway.

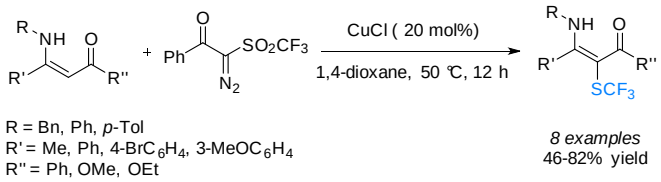
Two years later Shibata, using the same trifluoromethanesulfonyl hypervalent iodonium ylide **9**, reported the trifluoromethylthiolation of allylsilanes and silyl enol ethers in the presence of a catalytic amount of CuF_2 (scheme 22).[34]



Scheme 22. Cu-catalyzed trifluoromethylthiolation of silyl enol ethers (DMA = dimethyl acetamide).

It was demonstrated that the best reaction conditions developed for enamines failed when employed to silyl enol ethers. After a deep screening it was found that the replacement of CuCl with CuF with the concomitant increasing of ylide equivalents allowed to obtain the desired α- trifluoromethylthio ketones in modest to high yields. The presence of electron-donating as well as electron-withdrawing groups on the aromatic ring did not show a strong effect on the yield, and cyclic silyl enol ethers were also compatible with this system. Moreover, mono-trifluoromethylthiolated products were selectively obtained in all cases.

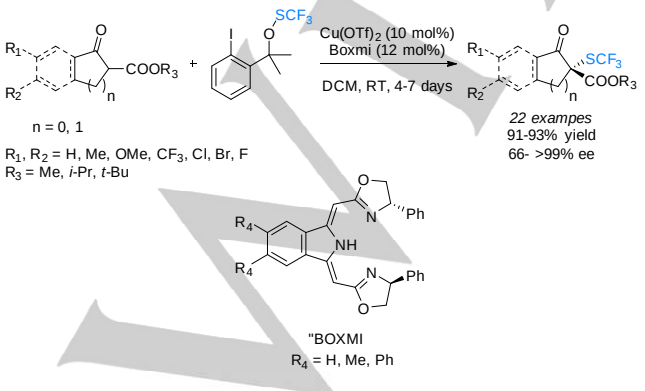
In 2016, Shibata developed diazo-triflone **10** (a second generation of the corresponding diazo-triflone **9**) for electrophilic trifluoromethylthiolation of enamines, indoles, β-keto esters, pyrroles and anilines in the presence of a catalytic amount of copper salt (scheme 23).[35]



Scheme 23. Trifluoromethylthiolation reaction promoted by diazo-triflone.

Under these reaction conditions, enamine substrates undergo α-trifluoromethylthiolation to provide corresponding SCF_3 products in moderate to good yields. Reaction performed using enamino esters is not influenced by the size of esters and by the substitution of the terminal aryl group, showing higher yields than those obtained using enamino ketones. Enamino esters with an enolizable proton (when R' = Me) reacted under the optimized reaction conditions, although in lower yields.

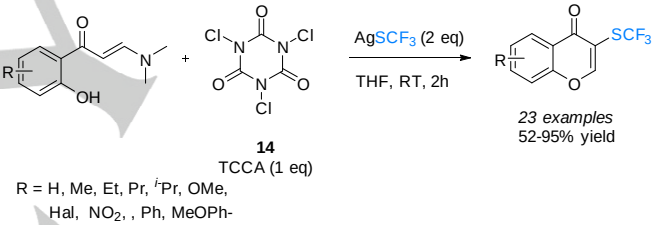
Despite impressive progresses in the development of α-trifluoromethylthiolating strategies, the first example of catalytic and stereoselective introduction of the SCF_3 group to organic compounds was reported only in 2014 by Gade, when chiral α-SCF_3-substituted cyclic β-ketoesters were synthesized using chiral copper–BOXMI complexes as catalysts (Scheme 24).[36]



Scheme 24. Catalytic and stereoselective a-trifluoromethylthiolation of cyclic β-ketoesters (BOXMI = bis(oxazolinylmethylidene)isoindolines).

Using Lu and Shen's reagent **8** as SCF_3 transfer,[37] α-SCF_3-substituted indanone-derived β-ketoesters were obtained in high yields and with up to >99% enantiomeric excess. The catalytic system is generated in situ from $Cu(OTf)_2$ and a "BOXMI" ligand and the reaction proceeds for 4-7 days at room temperature in CH_2Cl_2 as solvent. Among the many substrates investigated, it was found that the presence of bulky substituents at the alkoxy function is necessary for high enantioselectivities. Nevertheless, methyl esters reacted in a satisfactory combination of yields and enantioselectivities. Interestingly, this transformation is independent from by the presence of electron donating or electron withdrawing groups on the aromatic ring.

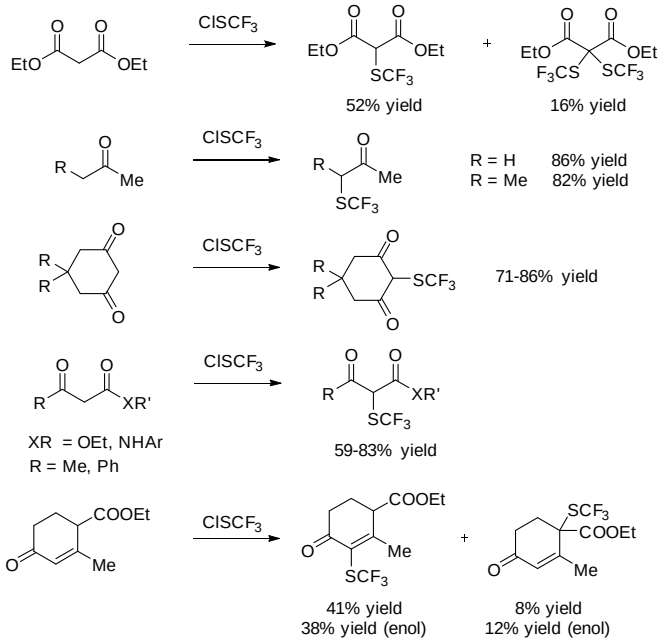
A facile and general synthetic route to 3-(trifluoromethyl)thio chromones, via in situ generation of electrophilic trifluoromethansulfanyl cation from trichloroisocianuric acid (TCCA) **14** and $AgSCF_3$, was reported in 2014 (scheme 25).[38] This practical reaction, which is insensitive to air and moisture, can occur under mild conditions in a short reaction time without any extra additive metal.



Scheme 25. Synthesis of 3-(trifluoromethyl)thio chromones.

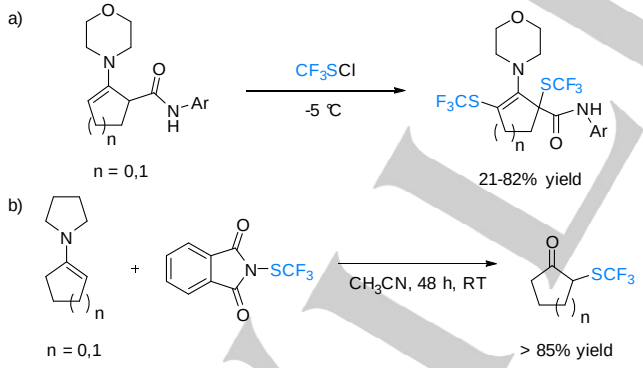
3.2. Metal-free approaches for the electrophilic α-trifluoromethylthiolation of carbonyl compounds

Contrary to other α-trifluoromethylthiolation reactions, the metal-free introduction of the SCF_3 moiety on a carbonyl compound is quite rare. In this field, the first example of SCF_3 electrophilic substitution was reported by Haas in 1980; diethyl malonate reacts with the toxic electrophilic CF_3SCl to form mono- and di-substituted products.[39] Few years later also the α-trifuoromethylthiolation of ketones,[40] cyclic β-diketones,[41] β-keto acids[42] and cyclohexanone esters[43] performed with CF_3SCl were reported in good yields (Scheme 26).



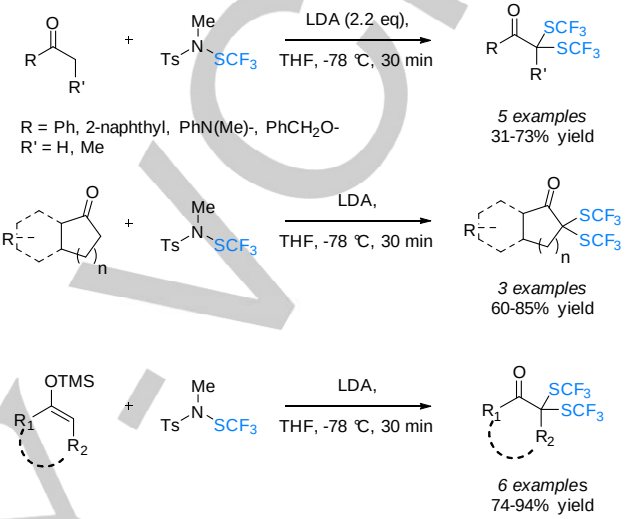
Scheme 26. α-trifluoromethylthiolation of diethyl malonate, ketones, cyclic β-diketones, β-keto acids and cyclohexanone esters performed with CF_3SCl.

In 1987, Bogdanowicz-Szwed and Kawalwek[44] developed the reaction of trifluoromethanthiochloride with enamines of keto carboxylic acid anilides (Scheme 27a), but was only in 2000 that Munavalli reported an α-trifluoromethylthiolation of enamines with *N*-(trifluoromethylthio)phthalimide for the synthesis of carbonyl compounds (Scheme 27).[45]



Scheme 27. α-trifluoromethylthiolation of enamines performed with CF_3SCl.

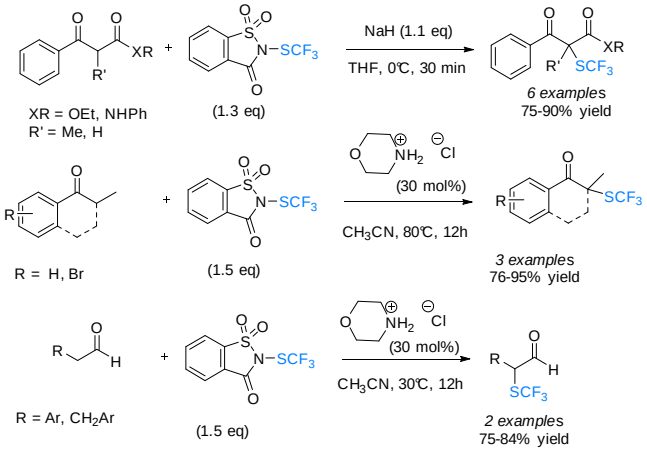
In 2014 Billard and coworkers[46] developed an electrophilic trifluoromethylthiolation of different carbonyl compounds based on the use of trifluoromethanesulfenamide in the presence of more than stoichiometric amounts of lithium diisoproylamide (LDA) (scheme 28). In these reaction conditions, and in the presence of primary compounds, the excess of LDA, as well as the presence of iPr_2NH byproduct generated from LDA, cause a second deprotonation of the α-trifluoromethanthiolated ketone with consequent addition of a second SCF_3 unit. With secondary compounds instead, monotrifluoromethylthiolated products are generally the major compounds formed. With the same protocol, also β-keto esters and silyl enol ethers were converted in the corresponding bis-trifluoromethylthiolated compounds in high yields.



Scheme 28. Electrophilic trifluoromethylthiolation of carbonyl compounds using trifluoromethanesulfenamide in the presence of more than stoichiometric amounts of LDA.

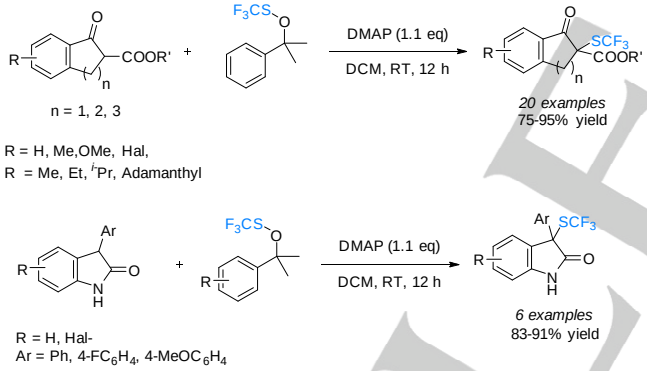
Another powerful trifluoromethylthiolating reagent, based on saccharine scaffold, was developed by Shen in 2014.[47] *N*-trifluoromethylthiosaccharin can be efficiently synthesized from commercially available *N*-chlorosaccharin or through a two-step process from saccharin. Its superior reactivity was further demonstrated by trifluoromethylthiolation of a variety of nucleophiles such as alcohols, amines, thiols, and electron-rich arenes, aldehydes, ketones, and acyclic β-ketoesters under mild reaction conditions (scheme 29).

It was found that reactions of acyclic β-keto esters with *N*-trifluoromethylthiosaccharin occurred to afford the mono-trifluoromethylthiolated β-keto esters after 0.5 hours at 0 °C when stoichiometric amounts of NaH was used as the base. Noteworthy, in the case of aldehydes and ketones, catalytic amounts of morpholine hydrochloride were sufficient to promote the reaction in high yields, even if high temperatures and longer reaction times were required.



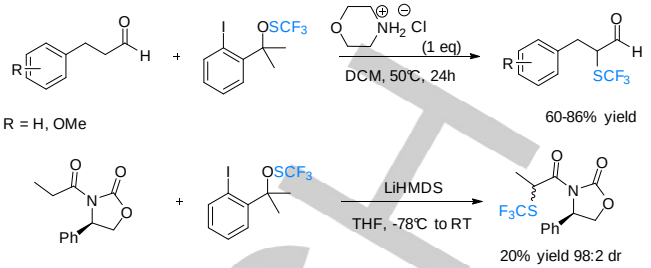
Scheme 29. *N*-trifluoromethylthiosaccharin as electrophilic source of SCF_3 in the α-trifluoromethylthiolation of carbonyl compounds.

Lu and Shen[37,48] reported also the possibility to use trifluoromethyl substituted arylthioperoxides as electrophilic sources of $^{+}SCF_3$, demonstrating the possibility to perform different trifluoromethylthiolation reactions with a wide range of nucleophiles such as Grignard reagents, arylboronic acids, alkynes, indoles, β-ketoesters, oxindoles, and sodium sulfinates under mild reaction conditions (scheme 30).



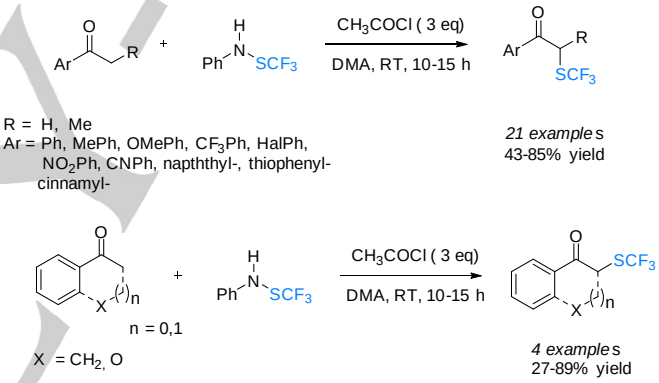
Scheme 30 Trifluoromethyl substituted arylthioperoxides as electrophilic source of SCF_3 in the α-trifluoromethylthiolation of β-ketoesters and oxindoles.

When 4-dimethylaminopyridine (DMAP) was used as the base for deprotonation, β-ketoesters reacted with trifluoromethyl phenylthioperoxide in CH_2Cl_2 at room temperature to give the corresponding α-trifluoromethylthiolated derivatives up to 95% yields. Under these reaction conditions however, the reaction of open-chain β-ketoesters was much slower, and 24 hours were necessary in order to achieve high yields. In the same paper,[37] examples of α-trifluoromethylthiolation of aldehydes and of a chiral amide enolate (derived from an Evans-type oxazolidinone auxiliary) were also reported, allowing to synthesized the desired α-trifluoromethylthiolated products in good yields (scheme 31).



Scheme 31. α-trifluoromethylthiolation of aldehydes and chiral amides promoted by

In the same year, Cao and co-workers reported that arylketones can undergo mild electrophilic trifluoromethylthiolation in the presence of *N*-trifluoromethanesulfenamide and acetyl chloride at room temperature.[49] The presence of CH_3COCl is necessary for the activation and the release of "$+SCF_3$" group (scheme 32).

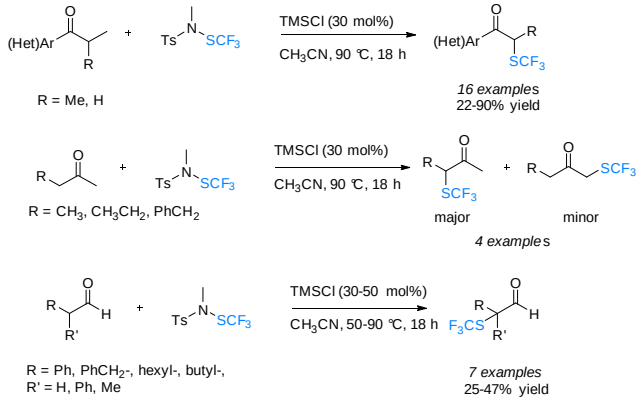


Scheme 32. *N*-trifluoromethanesulfenamide as SCF_3 source for a-trifluoromethylthiolation of ketones (DMA = *N,N*-dimethylacetamide).

Under these reaction conditions, a variety of aromatic and cyclic ketones with both electron-donating and electron withdrawing substituents afford the corresponding trifluoromethylthiolated products in moderate to good yields. Differently from the Billard approach showed in scheme 27, when primary ketones were employed, only traces of bistrifluoromethylthiolated products were observed.

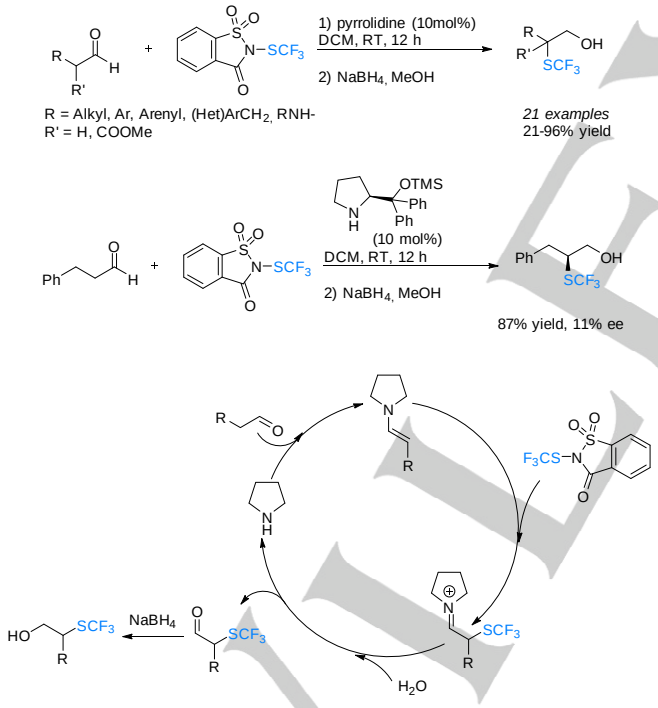
An acid-catalyzed synthesis of α-trifluoromethylthiolated carbonyl compounds was also developed by Billard in 2015 using a more electron rich *N*-trifluoromethylthiosulfenamide **7** and 30-50 mol% of Me_3SiCl (scheme 33).[50]

With this methodology, only mono-trifluoromethylthiolation was selectively observed and aliphatic aldehydes were also trifluoromethylthiolated with good yields. However, it must be noted that in the latter case the auto-aldol reaction competes with the trifluoromethylthiolation process.



Scheme 33. Acid-catalyzed α-trifluoromethylthiolation promoted by TMSCl.

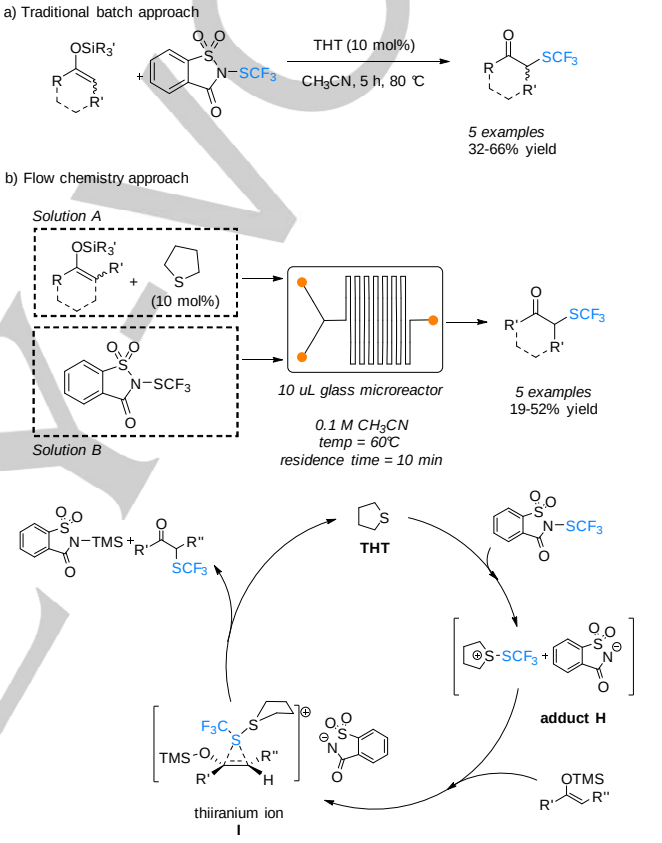
In 2016, Wu and Sun taking advantage of the enamine catalysis approach, reported an elegant and efficient catalytic method for the α-trifluoromethylthiolation of aldehydes promoted by catalytic amounts of pyrrolidine and using *N*-trifluoromethylthiosaccarin as sulfenylating reagent (Scheme 34).[51]



Scheme 34. Catalytic α-trifluoromethylthiolation of aldehydes by enamine catalysis.

Many different groups are well tolerated, but, due to the instability of the α-substituted aldehydes, the final products were isolated as alcohols. The authors reported also one example of α-trifluoromethylthiolation of aldehydes promoted by enantiopure diphenylprolinol (Hayashi-Jorgensen catalyst); unfortunately, in this case, only 11% ee value was achieved.

One year later, a Lewis base catalyzed α-trifluoromethylthiolation of simple silylenol ethers was reported by our group, using *N*-trifluoromethylthiosaccarin **11** as trifluoromethylthiolating reagent.[52] Tetrahydrothiophene (THT) was identified as the best organocatalyst and it was successfully employed to promote the synthesis of different α-trifluoromethylketones under a traditional batch methodology and, for the first time, under continuous flow conditions (scheme 35).

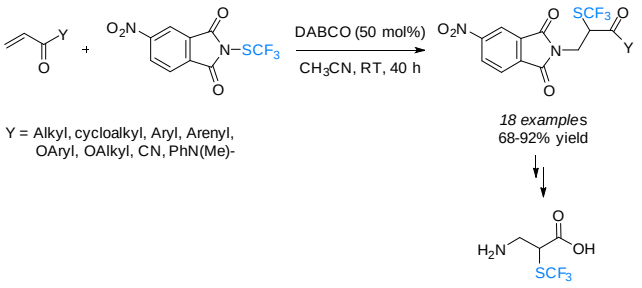


Scheme 35. Lewis base catalyzed α-trifluoromethylthiolation of silylenol ethers.

In general, yields obtained using the traditional batch process were higher than those observed when the reaction was performed under flow conditions. However, short reaction times, higher productivity and higher space time yields were observed when a flow system process was employed. Preliminary DFT calculations were also performed in order to elucidate the mechanism of the reaction, confirming the formation of the thiiranium ion **I.**

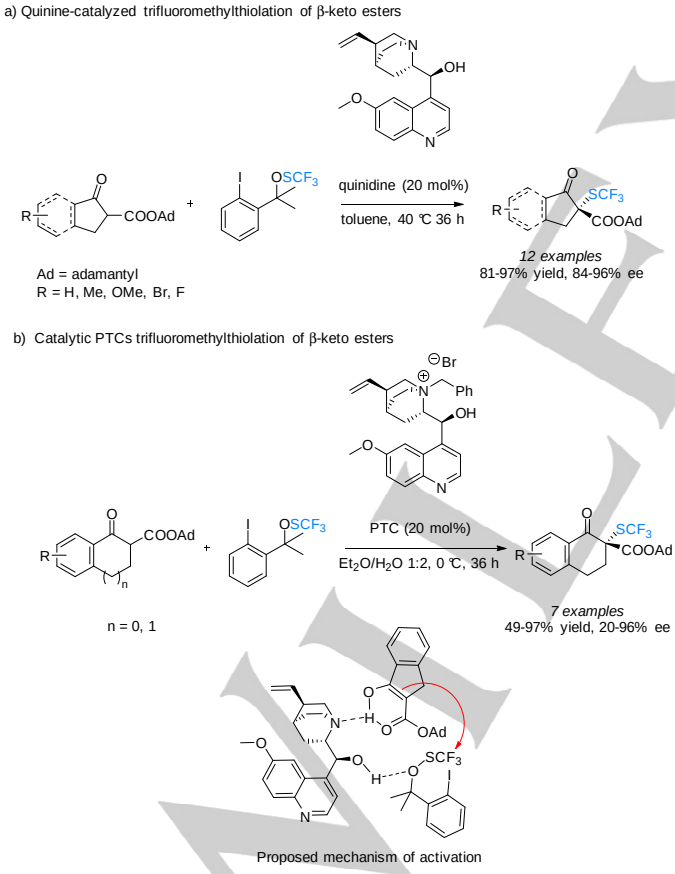
In 2016, Wang demonstrated that also α,β-unsaturated carbonyl compounds are suitable reagents for the introduction of the SCF_3 moiety using trifluoromethylthio-4-nitrophthalimide.[53] Using DABCO as promoter, both the nitrogen and SCF_3 groups can be incorporated into the final structure, leading to the formation of versatile β-amino ketones and esters in good yields

(scheme 36). It must be noted that with this methodology, α-SCF_3 amino acids became also accessible.



Scheme 36. DABCO-mediated a-trifluoromethylthiolation of α,β-unsaturated carbonyl compounds

In 2013 Shen reported the stereoselective Cinchona-catalyzed trifluoromethylthiolation of indanone-derived β-ketoesters using a phenyl trifluoromethylthioperoxide as SCF_3 source (Scheme 37).[54]



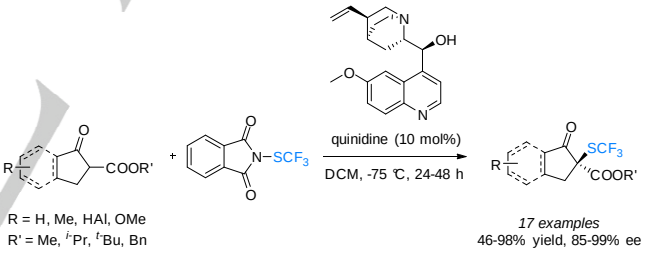
Scheme 37. Stereoselective Cinchona-catalyzed trifluoromethylthiolation of indanone-derived β-ketoesters using phenyl trifluoromethylthioperoxide .

In this case, indanone-derived β-ketoesters generated the corresponding products in high yields with excellent enantioselectivities (86-94% ee), regardless of the nature and position of the substituents on the β-keto ester derivatives (scheme 37). However, bulky substituents on the alkoxy position are required in order to reach high level of enantioselection. Other Cinchona alkaloids, such as cinchonidine, hydroquinine, quinidine, cinchonine and hydroquinidine were able to promote this type of transformation, but with lower enantioselectivities. Moreover, when more-enolizable tetralones or β-ketoesters with larger rings were subjected to this protocol, no desired product was formed. In these cases, only the use of cinchona alkaloid based chiral phase-transfer catalysts (PTC) afforded the desired products with good yields and high enantiomeric excess (up to 96% ee).

It was also proposed that the reaction proceeds through dual activation that involves the simultaneous activation of the ketoester and the trifluoromethylthiolating reagent through the formation of hydrogen bonds with quinine. The activated species is sterically congested and only one of the two enantiofaces of the ketoesters will be accessible for the transfer of the SCF_3 group.

Independently, in the same year, Rueping reported the catalytic and stereoselective trifluoromethylthiolation of indanone-derived β-ketoesters with *N*-trifluoromethylthiophthalimide as electrophilic SCF_3 source using Cinchona alkaloids as organic catalysts (scheme 38).[55]

Among the various Cinchona alkaloid derivatives evaluated, quinidine resulted to be the best catalysts for this transformation.

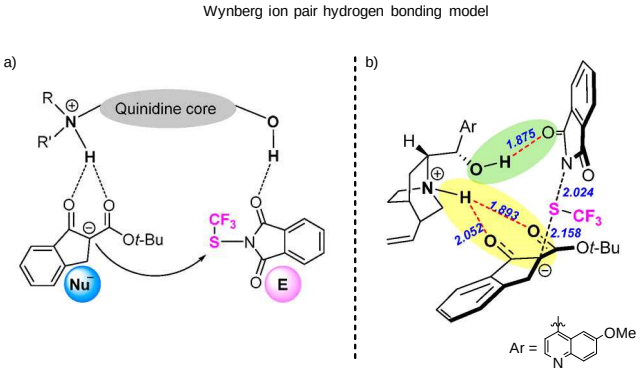


Scheme 38. Stereoselective Cinchona-catalyzed trifluoromethylthiolation of indanone-derived β-ketoesters using *N*-trifluoromethylthiophthalimide.

In general, independently by the substitution on the aromatic ring, the reactions of cyclic five-membered-ring β-ketoesters proceeded smoothly to provide the corresponding products in high yields (71-99%) and excellent enantioselectivities. Lower yields were observed when large membered systems were employed. Interestingly, this enantioselective method enables the construction of a quaternary carbon stereocenter bearing a SCF_3 group; in general, products are obtained in good yields and with excellent enantioselectivities.

In late 2017, Xue and Cheng perform an in-depth DFT computational analysis in order to clarify the real action mechanism and the origins of stereocontrol in natural Cinchona alkaloid-catalyzed asymmetric electrophilic trifluoromethyl-thiolation of β-keto esters with *N*-Trifluoromethylthiophthalimide as electrophilic SCF_3 source.[56] Three different possible mechanisms were investigated, and it was found that the

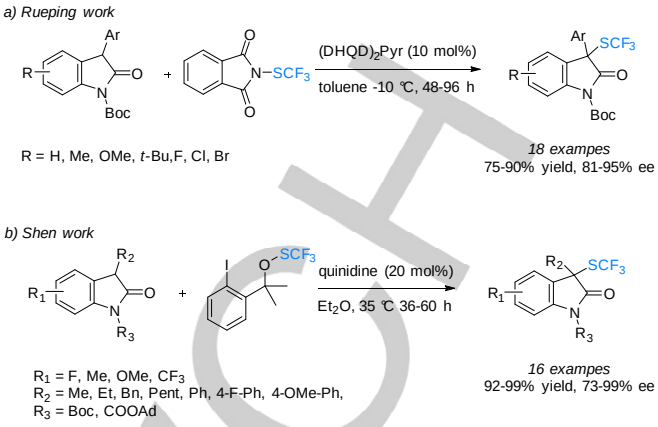
Wynberg ion pair-hydrogen bonding model[57] (dual activation of trifluoromethylthiolating reagent and β-keto ester by the catalyst's hydroxyl group and the quinuclidine nitrogen, respectively) is the most preferred mode of activation, as previously hypothesized by Shen (scheme 39).



Scheme 39. Wynberg ion pair hydrogen bonding model. a) general mechanism activation of quinidine; b) calculated lowest TS for the C-SCF_3 bond formation calculated calculated at the (SMD)-B3LYP-D3(BJ)/6-311++G(2d,p)//(SMD)-M06-2X/6-31G(d) level of theory. Bond lengths are in Å. Reproduced with permission from Xue, Cheng et al.[56]

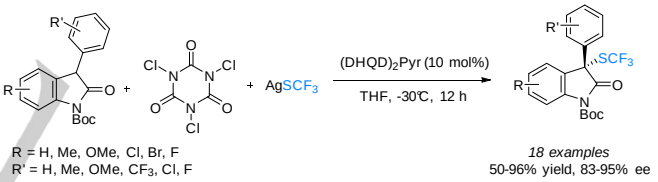
According to this mechanism, the SCF_3 transfer from trifluoromethylthiolating reagent to β-keto esters proceeds via an SN2 like approach, and it was found that the Cinchona alkaloid catalyst employs a combination of multiple weak noncovalent interactions to achieve the high levels of enantioselectivities.

Chincona alkaloids are also able to catalyze the enantioselective trifluoromethylthiolation of other classes of compounds such as oxindoles. In this sense, two different versions have been reported. The first one, developed by Rueping and co-workers (scheme 40-a) involves the use of *N*-trifluoromethylthio phthalimide as "$^+SCF_3$" source and $(DHQD)_2Pyr$ as organocatalyst;[58] the second one instead, requires the presence of a trifluoromethyl-substituted thioperoxide activated by catalytic amounts of quinidine (scheme 40-b).[59] Even if in the latter case the catalyst loading is higher, products are obtained in higher yields and short reaction times. Also in these cases, a series of optically active oxindoles bearing a SCF_3-substituted quaternary stereogenic center were obtained in excellent yields with good to excellent enantioselectivities, without influence of the substitutions on the aromatic ring.



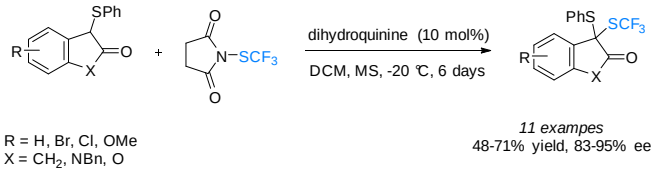
Scheme 40. trifluoromethylthiolation of oxindoles.

In 2014, Liu and Tan reported another version of enantioselective trifluoromethylthiolation of oxindoles performed with an in situ generation of a electrophilic trifluoromethylthio reagent involving as precursors trichloroisocyanuric acid (TCCA) and $AgSCF_3$.[60] This one-pot strategy in the presence of a catalytic amounts of and $(DHQD)_2Pyr$ leads to the formation of enantiopure oxindoles bearing a SCF_3-substituted quaternary stereocenter in good yields and excellent stereoselectivities (scheme 41).



Scheme 41. Synthesis of oxindoles bearing a SCF_3-substituted quaternary stereocenter

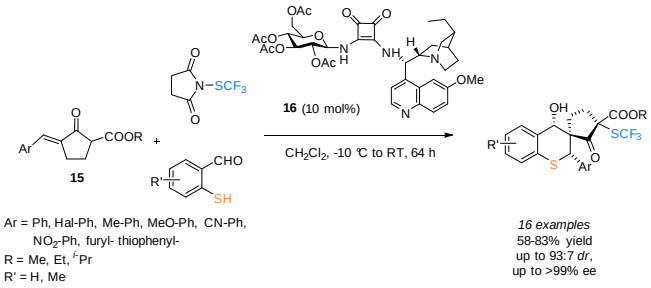
One year later, Zhou and co-workers reported an example of enantioselective synthesis of chiral dithioketals accomplished by a stereoselective trifluoromethylthiolation of different thio-based nucleophiles catalyzed by dihydroquinine in the presence of the Haas thiolating reagent (scheme 42).[61]



Scheme 42. enantioselective synthesis of trifluoromethylthio- functionalized chiral dithioketals

However, in this case, products were obtained in moderate yields, and long reaction times are required.

In 2017, taking advantage of a squaramide-catalyzed cascade reaction, Du reported an enantioselective synthesis of trifluoromethylthiolated spiro cyclopentanone-thiochromanes with the one-pot formation of four stereocenters.[62] In the first step, the SCF_3 group was enantiomerically and organocatalytically introduced on a cyclic β-keto ester which undergoes a catalyzed sulfur-Michael aldol reaction in the presence of 2-mercaptobenzaldehydes, with consequent formation of the corresponding high fuctionalized spiro compounds (scheme 43).

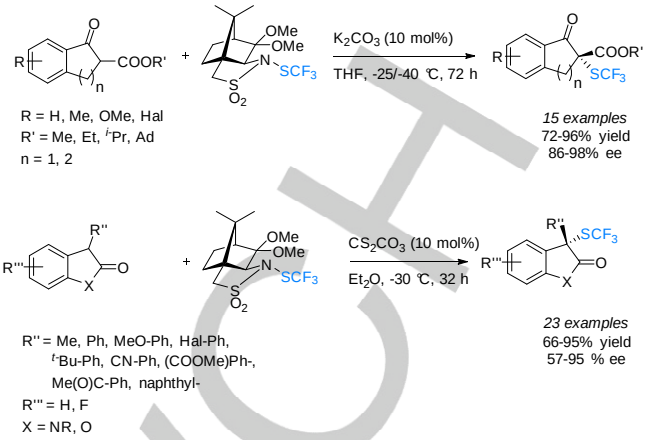


Scheme 43. Enantioselective synthesis of trifluoromethylthiolated spiro cyclopenanone-thiochromanes

The presence of squaramide organocatalyst is necessary for both processes to take place. Different aryliden β-ketoesters bearing electron-donating or electron-withdrawing groups on the aryl rings reacted with mercaptoaldehydes smoothly, affording the corresponding products in moderate-to-good yields and diastereoselectivities, with excellent enantioselectivities. Decrement on yields was observed only when the substituent on the aromatic ring was in the ortho or meta position.

Finally, in 2017 Shen and co workers developed the first example of chiral electrophilic trifluormethylthiolating reagent derived from commercially available (1S)-(-)-*N*-2,10-camphorsultam and its use in the stereoselective α-trifluoromethylthiolation of β-ketoesters, oxindoles and benzofuranones employing K_2CO_3 as catalytic base (scheme 44)[63]

β-Ketoesters derived from tetralone react with higher yields and enantioselectivities (94-98% ee) than those derived from indanone (79-92% ee), although the presence of electron-withdrawing groups lowers the reaction rate. Switching the base from K_2CO_3 to Cs_2CO_3 and the solvent from THF to Et_2O was necessary in order to perform the α-trifluoroethylthiolation of oxidones and benzofuran-2(3H)-ones with high enantioselectivity.



Scheme 44. α-trifluoromethylthiolation of β-ketoesters, oxindoles and benzofuranones in the presence of a chiral source of $^+SCF_3$.

5. Conclusions

In conclusion, an overview on the α-trifluoromethylthiolation of carbonyl compounds using radical, nucleophilic or electrophilic trifluoromethylthiolating reagents was highlighted. The survey has evidenced how in the last decade several methods have been developed, demonstrating a real and continuously increasing interest for the topic. At the same time, it was clearly highlighted that the field lacks of efficient catalytic methods, of wide general applicability. And enantioselective catalytic processes are even more rare and very limited as scope of reaction. Under organocatalytic approaches, high enantioselectivities were obtained using carbonyl compounds as the starting substrates. However, the substrate scope is almost exclusively limited to activated bifunctional substrates, such as to β-ketoesters and oxindoles.

The development of novel catalytic methods and of enantioselective catalytic trifluoromethylthiolation reactions, of wide general applicability represent the challenge for the future.

Acknowledgements

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Keywords: trifluoromethylthiolation • carbonyl compounds • organocatalysis • fluorinated products • electrophilic reagents • metal catalysts

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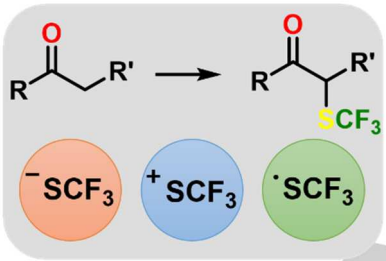
Entry for the Table of Contents

Layout 1:

MINIREVIEW

The use of radical, nucleophilic or electrophilic trifluoromethylthiolating reagents, to synthesize decorated trifluoromethylthio carbonyl derivatives is discussed, with a particular attention on the catalytic (in a few cases stereoselective) methodologies.



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Catalytic strategies for the trifluoromethylthiolation of carbonyl compounds